RIGA TECHNICAL UNIVERSITY

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SYNTHESIS OF BACTERIAL TWO-COMPONENT SYSTEM INHIBITORS

Doctoral Thesis

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RIGA TECHNICAL UNIVERSITY
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Scientific supervisor
Professor *Dr. chem.* Aigars Jirgensons

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ABSTRACT

Synthesis of bacterial two-component system inhibitors. Solomin V., scientific supervisor Prof., *Dr. chem.* Jirgensons A. Doctoral thesis, 134 pages, 17 figures, 76 schemes, 20 tables, 101 references, 3 appendices. In English.

ANTIBIOTIC RESISTANCE, HISTIDINE KINASE INHIBITORS, AMINOQUINAZOLINES, INDAZOLES, PHENYLAZOLES

Research, presented in the thesis, dedicated to the development of a new histidine kinase two-component systems inhibitors. To find putative inhibitors, fragment-based drug design approach was used. Resolved crystal structures of protein-ligand complexes were analyzed using computer-aided drug design software technics to define modifications which can increase affinity of the ligand to protein (done by Marco Albanese, Oxford Drug Design). Most perspective inhibitors were synthesized and subjected to *in vitro* studies on bacterial cell lines (Blanca Fernandez, Wageningen University) and proteins of interest (done by Anmol Adhav, Institut de Biomedicina de Valencia CSIC). This research resulted in discovery of a new 2-aminoquinazoline-based inhibitors of histidine kinases two-component systems with high nanomolar affinity. In addition, perspective phenylazole-based antibacterials active against *S. Aureus Newman* were studied and described. During the synthesis of the series of perspective inhibitors, a new methods dedicated to the synthesis of 2-aminoquinazoline and indazole heterocyclic cores were described.

ABBREVIATIONS

NMP – *N*-Methyl-2-pyrrolidone

DMA – Dimethylacetamide

DIPEA – *N*,*N*-Diisopropylethylamine

S-Phos – Dicyclohexyl(2′,6′-dimethoxy[1,1′-biphenyl]-2-yl)phosphane

TFA – Trifluoroacetic acid

TEA – Triethylamine

DMEDA – 1,2-Dimethylethylenediamine

DME – Dimethoxyethane

BINAP – 2,2′-*bis*(diphenylphosphino)-1,1′-binaphthyl

NBS – *N*-Bromosuccinimide

DMF – Dimethylformamide

THF – Tetrahydrofuran

TBAI – Tetra-*n*-butylammonium iodide

TBAF – Tetra-*n*-butylammonium iodide

p-TSA – *p*-Toluenesulfonic acid

HFIP – Hexafluoroisopropanol

DCE – 1,2-Dichloroethane

DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene

BOP – Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate

TBHP – *tert*-Butyl hydroperoxide

MTBE – *tert*-Butyl methyl ether

CHP – Cumene hydroperoxide

DMSO – Dimethyl sulfoxide

EDC – 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

HOBt – Hydroxybenzotriazole

CDI – 1,1'-Carbonyldiimidazole

DCM – Dichloromethane

X-Phos – Dicyclohexyl[2′,4′,6′-tris(propan-2-yl)[1,1′-biphenyl]-2-yl]phosphane

ATP – Adenosine triphosphate

TMEDA - *N,N,N′,N′*-Tetramethylethylenediamine

DEAD – Diethyl azodicarboxylate

DIAD – Diisopropyl azodicarboxylate

Dppf – 1,1′-Bis(diphenylphosphino)-ferrocene

All – Allyl

tBuBrettPhos – 2-(Di-tert-butylphosphino)-2′,4′,6′- triisopropyl-3,6-dimethoxy-1,1′-biphenyl

Diox – 1,4-Dioxane

[OMIm]Cl – 1-Methyl-3-octylimidazolium chloride

TES – Triethylsilane

EtNCO – Ethyl isocyanate

CONTENTS

INTRODUCTION

Bacterial infections have a great impact on public health.[1] Starting from the middle of the 20th century a lot of deaths were prevented by introducing the antibiotics, and average life expectancy at birth rose almost to 79 years.[2] A number of antibiotic classes were established between 1930th and 1960th, while only few of them were discovered in recent decades.[3] The long term use of the same lifesaving antimicrobials was the strong evolutionary factor for bacterial species - bacteria developed mechanisms that helps them to neutralize antibiotics.[4] A bacteria can develop mechanisms of resistance to several types of antimicrobial drugs, which makes it a multidrug resistant bacteria. Such mechanisms can occur either by accumulation of the multiple genes, responsible for resistance to a particular drug, or by overexpression of genes coding efflux pumps of bacteria.[5] Clinical therapy of infections, caused by resistant bacteria, usually require higher doses of medicines, or the use of more efficient but also more toxic drugs.[2,6]

The above-mentioned reasons have motivated a research to discover new perspective antimicrobials which are able to target antibiotic-resistant strains. Primary task of such a research is the definition of potential target for a new drug. Most of the traditional antibiotics are targeting cell wall synthesis (penicillines, cephalosporines, polypeptides) and bacterial protein synthesis (tetracyclines, amphenicols, macrolides).[7] All of these drugs induce bacterial death, which is a significant factor to the bacteria for adaptation to such therapeutics.[8] Prospectively, compounds which are targeting bacterial systems involved in the adaptation to antibiotics can be a solution to the problem of multidrug resistant bacteria. One group of such possible targets are histidine kinase two-component systems (HK TCs).[9]

HK TCs of bacteria are responsible for the signal transduction pathways, including regulation of virulence, secretion systems and antibiotic resistance. Additionally, HK TCs are ubiquitous among bacteria and absent in mammalian cells.[10]

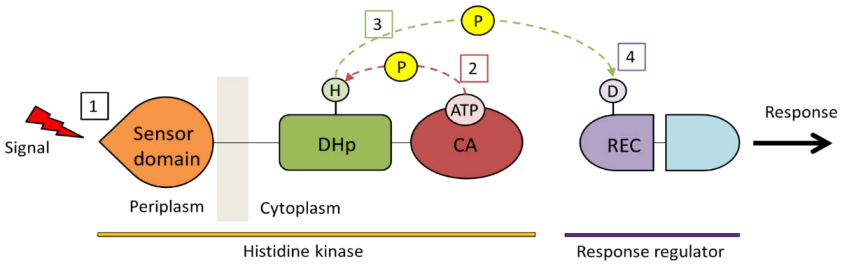


Figure 1. Histidine kinase two component system signaling pathway.
Abbreviations: DHp – dimerization and histidine phosphotransfer domain (DHp); CA – catalytic domain; REC – receiver domain; H – histidine residue; D – aspartate residue; ATP – adenosine triphosphate; P – phosphate. Numbers in the scheme corresponds to the order of signal transduction pathway: 1 – receiving of extracellular signal; 2 – ATP binding and phosphate transfer to histidine; 3 – phosphate transfer to aspartate residue on receiver domain; 4 – structural change of receiver domain.

Signal cascade in TCs starts from a sensor domain (1), located in periplasmic or extracellular media.[11] Then ATP binds to catalytic domain (CA) followed by transfer of a γ-phosphate group to a conserved histidine at histidine phosphotransfer domain (DHp). Subsequently the high-energy phosphoryl group is transferred to a conserved aspartate at the receiver domain (REC) of the response regulator. The response regulator, in turn, undergoes conformational change which leads to a specific response.[12]

The most attractive point for targeting in the TCs signaling pathway is the catalytic domain (CA) as this domain is already evolved to bind the small ATP molecule. Using properly designed inhibitors, specifically targeting CA, the transduction pathway can be interrupted leading to reduced bacterial fitness or inducing a bactericidal effect.[13]

Our work was directed to the design and synthesis of novel HK TCs inhibitors starting from hit molecules identified by X-ray crystallography of the corresponding protein-ligand structures. Perspective for the further modification scaffolds then were subjected to computer-aided drug design (CADD) studies to reveal possible structure modifications which can enhance the potency of compounds. After CADD modelling the most perspective compounds were selected for synthesis. Newly synthesized compounds were subjected to the variety of tests to see whether predictions were accurate enough. To measure biological activity of the compounds, both enzymatic assays on bacterial proteins and *in vitro* tests on bacterial cultures were performed.

Several types of proteins, belongs to the family of HK TCs were selected. One of the proteins used in the enzymatic tests was CheA domain. This protein is the central regulator of bacterial chemotaxis. It belongs to proteins that control gene expression in

response to changing environmental conditions. The CheA binds ATP and catalyzes the phosphorylation of one of its own histidine residues.[14] The second used in the assays protein - PhoR. It is the sensor kinase in PhoRB two component signal transduction pathway. In live cell PhoR indirectly senses and responds to the level of extracellular inorganic phosphate by phosphorylating and dephosphorylating its cognate response regulator PhoB.[15] Also HK853 protein was applied for the tests. HK853 is the *C*-terminal catalytic and ATP-binding domain[16] which was shown to possess an ATP-dependent autokinase activity *in vitro* and to support phosphotransfer to PhoP response regulator.[17] The last member of this protein family used in the assays – EnvZ, playing the key role in phosphorylation of the activator protein OmpR. Phosphorotransfer between EnvZ and OmpR in *E. coli* regulates adaptation to changes in environmental osmotic pressure.[18]

For the *in vitro* bacterial growth inhibition assays were used Gram positive bacterial strains: *S Aureus Newman*,[19] and *E. Faecalis.*[20] Gram negative strains were represented by *E Coli*.[21] Additionally, antibiotic resistant strains were used, such as Methicillin-resistant (MRSA) *S. Aureus*,[21] and Vancomycin-resistant *E. Faecalis*.[22]

The research was performed in collaboration with the group of Dr. A. Marina from Instituto de Biomedicina de Valencia, CSIC (X-ray crystallography, screening of fragment library, enzymatic and biophysical binding assays), group of Prof. J. Wells from University of Wageningen (antibacterial cell based assays), and with the team of Prof. P. Finn from company Oxford Drug Design (CADD).

Our main contribution to the discovery of HK TCs inhibitors was the synthetic development of hit compounds resulting from screening libraries. This included the generation of focused libraries based on a defined core of a hit compound as well as fragment merging and fragment growth. To enable access of certain compound classes such as quinazolines and indazoles with expanded functionalization pattern, we also developed new synthetic methods to construct these heterocycles.

Aims and objectives

The aim of the thesis is to develop new potent inhibitors of HK TCs utilizing the fragment-based lead discovery approach and virtual screening hits. Concomitantly a new methods of synthesis of the most potent heterocyclic motifs may be explored. The following tasks were set:

1) to synthesize putative HK TCs inhibitors, virtually designed by project partners – derivatives of pyrazole, quinazoline and indazole heterocyclic motifs and analyze their structure-activity relaitionship (SAR), using the data, provided by collaboration institutions;
2) to explore novel milder ways of assembling of the most perspective 2-aminoquinazoline and indazole scaffolds, starting from readily available 2-formylphenylboronic acids;
3) to synthesize 3,4-diphenylpyrazole derivatives with proved antimicrobial activity, possibly connected with inhibition of HK TCs and analyze their SAR regarding inhibition of growth of *S. Aureus Newman*;

Scientific novelty and main results

As the result of the thesis, new chemotypes of the HK TCS inhibitors were proposed: 1) indazole derivatives, modified with aryl substituent on the 4th position of heterocyclic ring; 2) 2-aminoquinazoline derivatives, modified on the 7th position with aryl substituents. Additionally, antimicrobial efficiency of arylazoles against *S. Aureus Newman* and their structure-activity relationship were described. New synthesis methods of heterocycles of interest were discovered: 1) convenient and mild copper-catalyzed synthesis of 2-aminoquinazolines from 2-formylphenylboronic acids and guanidines; 2) copper-mediated synthesis of indazoles from 2-formylphenylboronic acids and azodicarboxylates or hydrazine dicarboxylates.

Publications and aprobation of the thesis

Scientific publications:

1. **V. V. Solomin**, A. Seins, and A. Jirgensons. 2-Aminoquinazolines by Chan–Evans–Lam coupling of guanidines with (2-formylphenyl)boronic acids. *Synlett*, 31, **2020**, 1507-10 (IF(2020): 2.454)
2. **V. V. Solomin**, A. Seins, and A. Jirgensons. Synthesis of indazoles from 2-formylphenylboronic acids. *RSC Advances*, 11, **2021**, 22710-14 (IF(2021): 4.036)
3. **V. V. Solomin**, B. Fernandez Ciruelos, N. Velikova, J. Wells, M. Albanese, A. Adhav and A. Jirgensons. Synthesis and SAR of phenylazoles, active against Staphylococcus Aureus Newman. *Chemistry of Heterocyclic Compounds*, 58 (12), **2022**, 737-748 (IF(2021): 1.490)

Results of the thesis were presented at the following conferences:

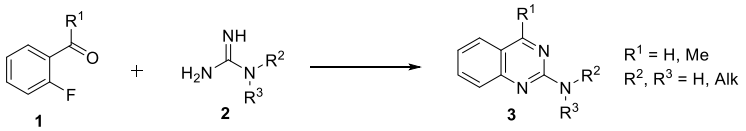
1. **V. V. Solomin**, A. Jirgensons. Synthesis of 2-Aminoquinazolines and Indazoles from 2-Formylphenylboronic Acids. 80th International Scientific Conference of the University of Latvia, February 11, **2022**, Riga, Latvia.
2. **V. V. Solomin**, A. Jirgensons. Synthesis of 2-Aminoquinazolines and Indazoles from 2-Formylphenylboronic Acids. Balticum Organicum Syntheticum (BOS 2022), July 3 - 6, **2022**, Vilnius, Lithuania.
3. **V. V. Solomin**, A. Jirgensons. Chan-Evans-Lam reaction inspired synthesis of 2-Aminoquinazolines and N-protected indazoles. SPRINGBOARD project Summer School: Major milestones in design and development of novel antimicrobials, August 23 – 25, **2022**, Apšuciems, Latvia.
4. **V. V. Solomin**, D. Zaharova. Synthesis of Quinazolines and Indazoles from 2-formylphenylboronic acids. 81th International Scientific Conference of the University of Latvia, March 17, **2023**, Riga, Latvia

LITERATURE REVIEW: Methods of 2-aminoquinazoline synthesis and their application for drug discovery

Since main part of the experimental work in the theses was devoted to the synthesis of 2-aminoquinazoline derivatives, the literature review was focused on the methods for their synthesis together with the application of 2-aminoquinazolines as enzyme inhibitors.

1. Nucleophilic addition of guanidines to 2-fluorobenzaldehydes

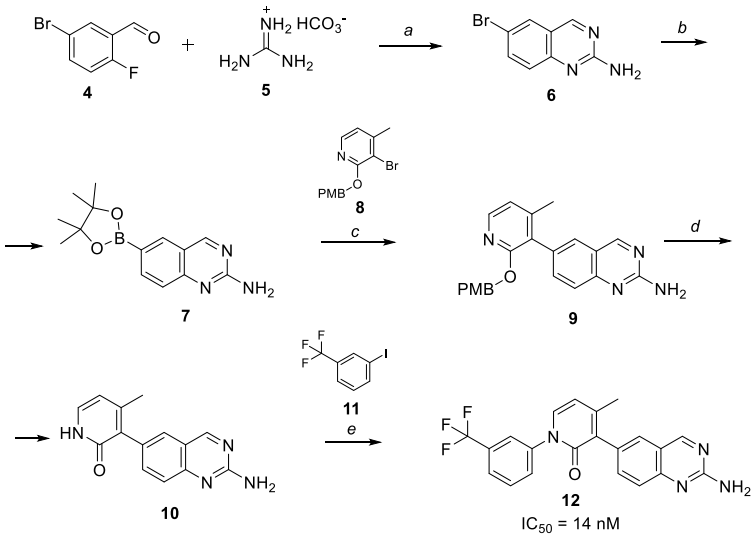
One of the most used starting materials for the synthesis of 2-aminoquinazolines are 2-fluorobenzaldehydes[23] and 2-fluoroacetophenones[24] **1**. Upon coupling with guanidines **2** at elevated temperatures they can be transformed to the target heterocycle **3** (Scheme 1).



Scheme 1. Synthesis of 2-aminoquinazolines from *ortho*-fluorobenzaldehydes and acetophenones. Reaction conditions: NMP or DMA, 100 to 150 °C.

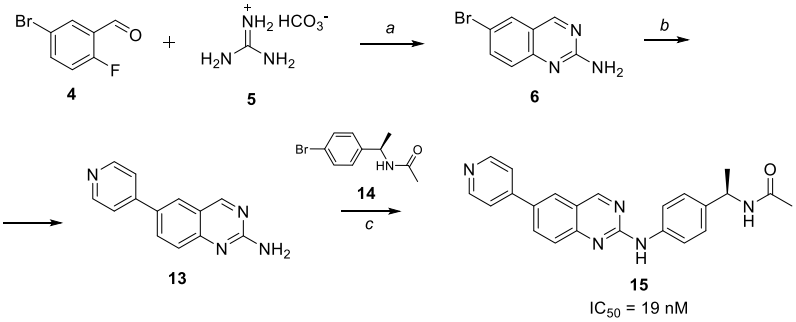
This approach has been described in a number of publications, dedicated to the development of perspective 2-aminoquinazoline-based kinase inhibitors.

Inhibitors of c-Kit tyrosine kinase - mast/stem cell growth factor receptor were developed based on 2-aminoquinazoline core by Hu's group.[25] Inhibition of this type of kinases can potentially be used for the treatment of the mast cell associated fibrotic diseases. Compound **12** was declared to have a great selectivity to c-Kit against other structurally similar kinases. The synthesis of **12** started from 4-bromo-2-fluorobenzaldehyde **4**, which was cyclized to 2-aminoquinazoline **6** in the presence of guanidine carbonate at elevated temperature. Following transformations included replacement of bromine in 2-aminoquinazoline with boron pinacolate to achieve compound **7** and subsequent Suzuki-Miyaura coupling with pyridine **8** to form compound **9**. Finally, after the PMB group deprotection, followed by Buchwald-Hartwig amination reaction with 2-aminoquinazoline **10**, compound **12** was obtained (Scheme 2).



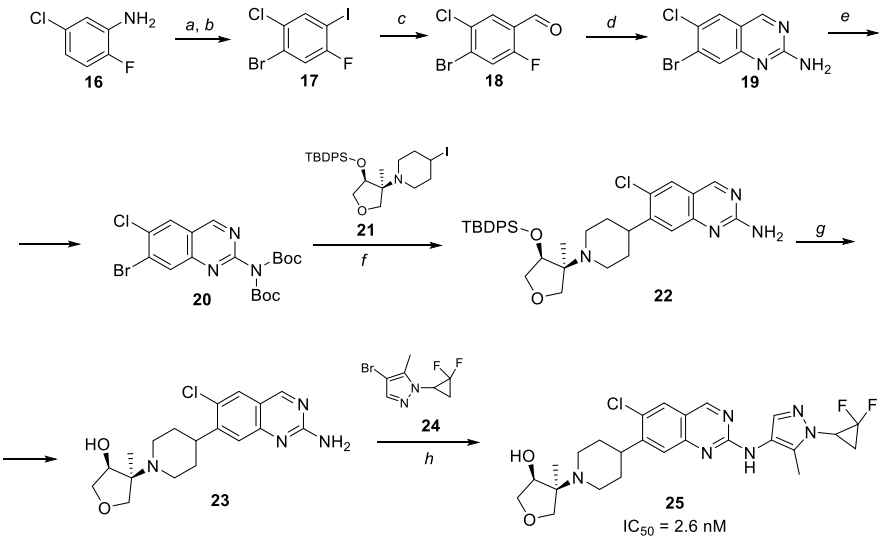
Scheme 2. Synthesis of 2-aminoquinazoline inhibitor of c-Kit.
Reaction conditions: *a*) DIPEA, NMP, 160°C, 48%; *b*) bis(pinacolato)diboron, KOAc, $PdCl_2(dppf)\cdot CH_2Cl_2$, 85°C, 50%; *c*) $Pd(OAc)_2$, S-phos, K_3PO_4, 90%; *d*) TFA; *e*) CuI, K_3PO_4, DMEDA, NMP, 85°C, 60−80% two steps.

Similar approach for the synthesis of a potential anticancer agent was presented by Vasbinder and co-authors.[26] Assembly of 2-aminoquinazoline **6** from aldehyde **4** and guanidine **5** was followed by Suzuki-Miyaura coupling with 4-pyridine boronic acid to give compound **13**. Subsequent Buchwald-Hartwig reaction with aryl bromide **14** produced 2-aminoquinazoline **15**. Compound **15** selectively inhibited mutant B-Raf^{V600E} (Rapidly Accelerated Fibrosarcoma) kinases, which are involved in metastatic melanoma growth (Scheme 3).



Scheme 3. Synthesis of B-Raf inhibitor.
Reaction conditions: *a*) DMA, 140 °C; *b*) 20 mol % $Pd(PPh_3)_4$, K_2CO_3, 4-Py-$B(OH)_2$, DME/water, 90 °C; *c*) 5 mol % $Pd_2(dba)_3$, 10 mol% BINAP , Cs_2CO_3, dioxane, 100 °C.

Another type of kinase inhibitor, based on 2-aminoquinazoline scaffold was reported in recent article.[27] Leucine rich repeat kinase 2 (LRRK2), linked to progression of the Parkinson's disease, was successfully targeted by compound **25**. The key intermediate, 2-aminoquinazoline **19** was made from densely decorated 2-fluorobenzaldehyde **18**. Following steps included Boc-protection of 2-aminoquinazoline **19** to give compound **20**, which was further subjected to the Ni-mediated coupling with alkyl iodide **21**. After hydroxyl group deprotection from newly formed **22** and Buchwald-Hartwig reaction with pyrazole bromide **24**, an inhibitor **25** was obtained. The inhibitor **25** possessed high potency against LRRK2. According to *in vivo* tests compound **25** had a good potential for further drug development (Scheme 4).

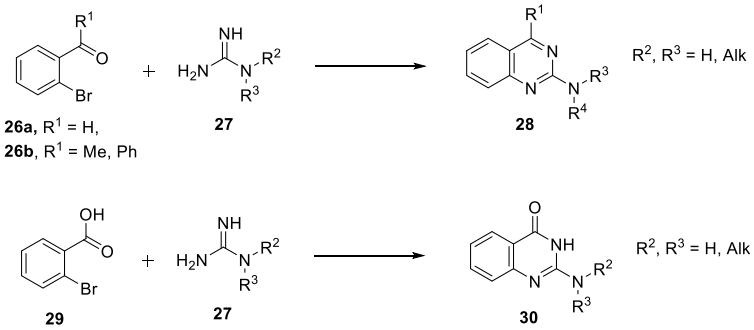


Scheme 4. Synthesis of LRRK2 inhibitor.
Reaction conditions: *a)* NBS, MeCN, 84%; *b)* KI, $NaNO_2$, 6 N HCl, -20 °C, 81%; *c)* DMF, *i*-PrMgCl, THF, -78 °C, 67%; *d)* guanidine carbonate, Cs_2CO_3, DMA, 120 °C, 76%; *e)* Boc_2O, DMAP, MeCN, 45 °C, 37%; *f)* $NiCl_2$·dme, picolinamidine, TBAI, Zn, DMF, 55 °C, 63%; *g)* TBAF, then TFA, 70% in two steps; *h)* $PdCl_2(all)_2$, *t*BuBrettPhos, Cs_2CO_3, Diox, 100 °C.

2. Copper-catalyzed addition of guanidines to 2-bromobenzaldehydes and 2-bromobenzoic acids

2-Aminoquinazolines **28** can be readily accessed from 2-bromobenzaldehydes **26a** and corresponding 2-bromoaryl ketones **26b** using CuI catalysis.[28] This type of transformation

can also be used to obtain 2-amino-4-quinazolinones from 2-bromobenzoic acid **29** (Scheme 5). [28-29]

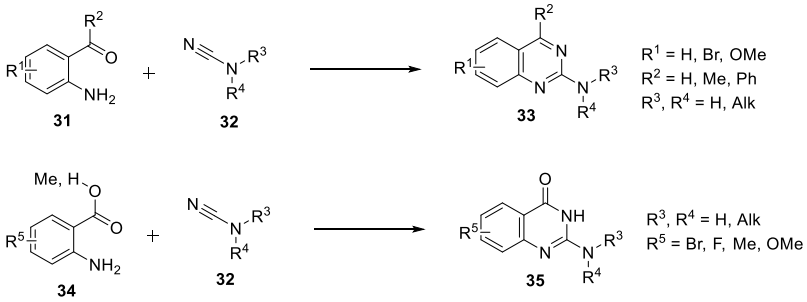


Scheme 5 Synthesis of 2-aminoquinazolines and 2-amino-4-quinazolinone, catalyzed by copper. Reaction conditions: CuI, Cs_2CO_3, L-proline, DMF, 110 °C.

For the transformation of 2-bromobenzoic acid **29** to 2-amino-4-quinazolinones **30** Cu_2O[30] and $CuCl_2$[31] were also reported to be efficient catalysts.

3. Condensation of 2-aminobenzaldehydes and anthranilic acids with cyanamides and guanidines

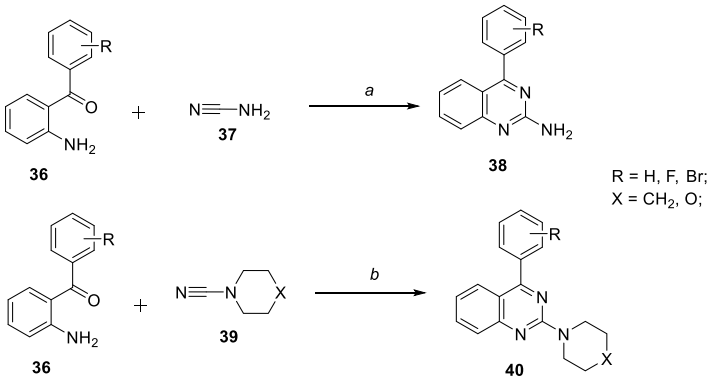
Although 2-aminobenzaldehydes and related ketones **31** have limited commercial availability, they represent good starting materials for the construction of 2-aminoquinazoline derivatives in the reaction with cyanamides **32**.[32] Similarly, 2-amino-4-quinazolinones **35** can be obtained from anthranilic acids **34** and their esters (Scheme 6).[33]



Scheme 6. Synthesis of 2-aminoquinazolines **33** and 2-amino-4-quinazolinones **35** from 2-aminobenzaldehydes **31** and anthranilic acids **34**.
Reaction conditions: HCl_{aq}, EtOH, 90 °C.

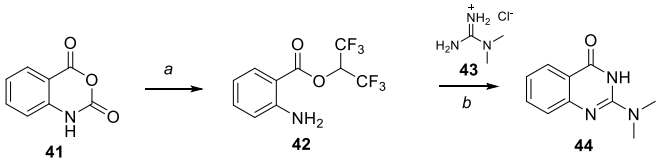
Pandya *et al.* reported synthesis of 2-aminoquinazolines **38, 40** from 2-aminobenzophenones **36** in aprotic media.[34] According to the published data, both acidic

(*p*-TSA) and basic (KO*t*Bu) conditions-promoted cyclization is possible in DMF at elevated temperatures (Scheme 7).



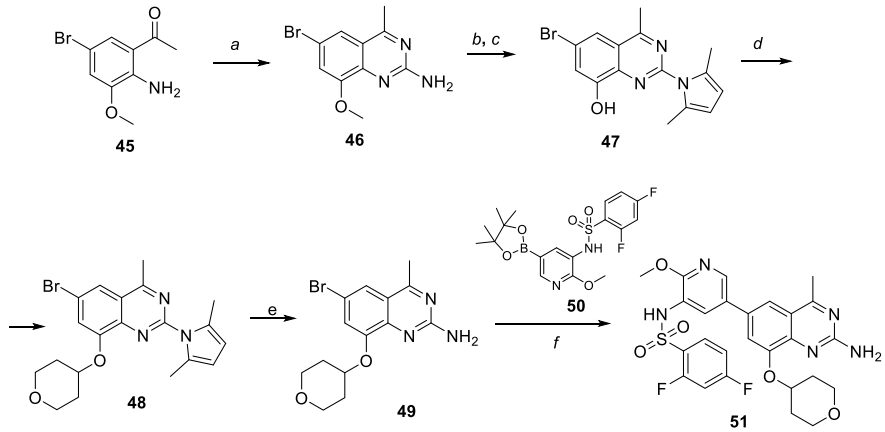
Scheme 7. Synthesis of aminoquiazolines from 2-aminobenzophenones.
Reaction conditions: *a) p*-TSA, DMF, 110 °C, 75-78%; *b)* KO*t*Bu, DMF, 110 °C, 75-81%.

Mild and efficient protocol of 2-amino-4-quinazolinones synthesis was introduced by Chen *et al*.[35] They describe a stepwise process, which includes initial formation of hexfluoroisopropyl (HFIP) ester of anthranilic acid **42** followed by the reaction with guanidine **43** at room temperature to afford 2-amino-4-quinazolinone **44** (Scheme 8).



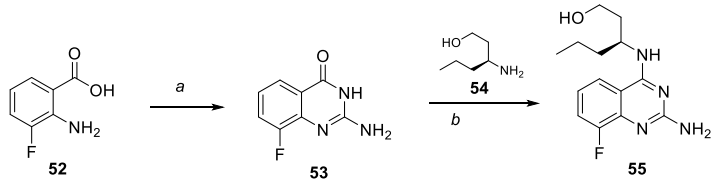
Scheme 8. Synthesis of 2-amino-4-quinazolinone **44**.
Reaction conditions: a) HFIP, NEt_3, 25 °C, 1 h; b) K_3PO_4, DMF, 25 °C, 10 h.

2-Aminoacetophenone **45** has been used by Lin and co-workers[36] to prepare perspective 2-aminoquinazoline-based inhibitor **51** of phosphatidylinositol 3-kinase (PI3K) (Scheme 9). The reaction of acetophenone **45** with cyanamide in acidic conditions provided 2-aminoquinazoline **46**. After the protection of amino group as a 2,5-dimethylpyrrole to achieve compound **47**, phenolic oxygen was alkylated with 4-bromopyran to obtain compound **48**. Further 2,5-dimethylpyrrole protection was cleaved to obtain unprotected compound **49**, and 2-aminoquinazoline **49** was reacted with arylboronic acid pinacolate **50** to give compound **51**. The inhibitor **51** was proposed as potential anti-cancer agent.



Scheme 9. The synthesis of PI3K inhibitor **51**.
Reaction conditions: *a)* conc. HCl, 50% cyanamide in water, 120 °C, 15 min, 98%; *b)* 2,5-hexanedione, *p*-toluenesulfonic acid, NMP, toluene, 160 °C, 6 h, 87%; *c)* $AlCl_3$, DCE, 80 °C, 1.5 h, 77%; *d)* alkyl bromide, K_2CO_3, acetonitrile, sealed tube, reflux, overnight, 58%; *e)* hydroxylamine hydrochloride, EtOH, H_2O, reflux, overnight, 85%; *f)* $PdCl_2$(dppf), 2 M K_2CO_3, dioxane, 100 °C, Ar, 4 h, 45%.

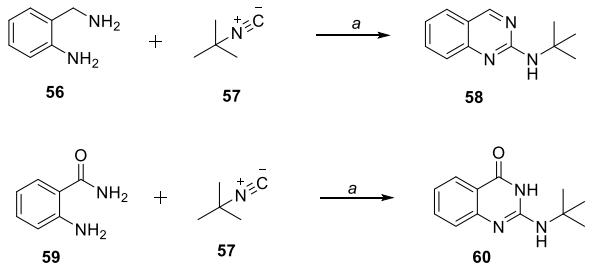
In the publication by Embrechts *et al.*[37] the cyclization of anthranilic acid with cyanamide have been used for the preparation of a potent toll-like receptor (TLR) modulator **55** which could be used for the treatment of Hepatitis B virus infection (Scheme 10).



Scheme 10. Synthesis of TLR modulator **55**.
Reaction conditions: *a)* HCl, NH_2CN, EtOH, 100 °C, 16 h, pressure vessel; *b)* DBU, BOP, anhydrous DMF, rt, 16 h.

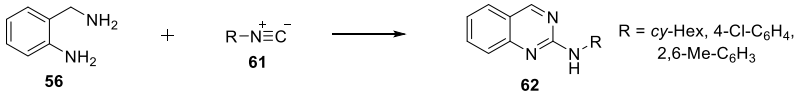
4. Cyclization of 2-aminobenzyl amines and 2-aminobenzamides with isonitriles

An example of assembling 2-aminoquinazoline **58** and 2-amino-4-quinazolinone **60** from 2-aminobenzyl amine **56** or 2-aminobenzamide **59** was described by Vlaar and co-workers.[38] Compounds **56** and **59** were subjected to the reaction with tert-butyl isonitrile **57** in palladium-catalyzed aerobic oxidation process, leading to heterocycles of interest **58** and **60** respectively (Scheme 11).



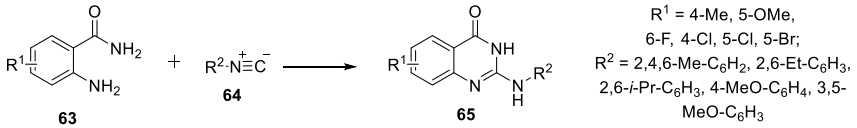
Scheme 11. Synthesis of 2-aminoquinazoline **58** and 2-amino-4-quinazolinone **60** from isonitriles using Pd catalysed oxidation.
Reaction conditions: *a)* 1 mol % $Pd(OAc)_2$, MeTHF, 75 °C, 1 atm O_2, 4 Å MS, 79-85%.

Similar approach was reported by Wang.[39] In this case, the reaction of 2-aminobenzyl amine **56** with isonitriles **61** was perfomed in the presence of I_2-tert-butyl hydroperoxide (TBHP) system as an oxidant. In contrast to the previous example, this process proceeds under metal-free conditions. Remarkably, different types of isonitriles **61** were compatible with the reaction conditions (Scheme 12).



Scheme 12. Synthesis of 2-aminoquinazolines **62** from isonitrile using I_2/TBHP oxidation.
Reaction conditions: 10 mol% I_2, 2 equiv TBHP, MTBE, 50 °C, 12 h, 40-83%.

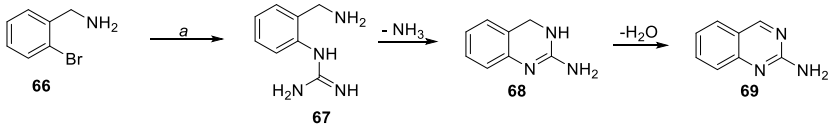
Another oxidation, leading to formation of 2-amino-4-quinazolinones **65** from 2-aminobenzamides **63** was also described.[40] Herein, cumene hydroperoxide (CHP) acted as a stoichiometric oxidant while iodine was added in catalytic amount (Scheme 13).



Scheme 13. Synthesis of 2-amino-4-quinazolinones **65** using I_2/CHP.
Reaction conditions: 10 mol% I_2, 2 equiv CHP, MTBE, 80 °C, 2 h, 76-93%.

5. Copper-catalyzed addition of guanidines to 2-bromobenzyl amines

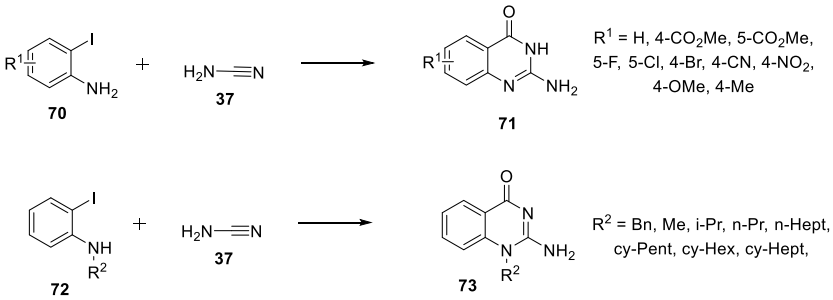
Liu *et al.* reported synthesis of quinazoline derivatives, including 2-aminoquinazoline **69**, from 2-bromobenzyl amine **66** and guanidine.[41] According to the proposed mechanism, an initially formed arylguanidine **67** further undergoes cyclization to 3,4-dihydroquinazolin-2-amine **68** followed by aerobic oxidation providing 2-aminoquinazoline **69** (Scheme 14).



Scheme 14. Synthesis of 2-aminoquinazolines **69** from 2-bromobenzylamine **66**.
Reaction conditions: *a)* 20 mol% CuBr, 2 equiv. guanidine hydrochloride, 3 equiv. K_2CO_3, DMSO, air, 120 °C, 24 h, 68-86%.

6. Pd-catalyzed condensation of 2-iodoanilines with cyanamide and carbon monooxide

2-Iodoanilines **70**, **72** could be used as starting materials in a process of carbonylative coupling with cyanamide **37**, which results in formation of 2-amino-4-quinazolinones **71**, **73**.[42] The reaction works both for the non-substituted and substituted anilines **70**. *N*-alkyl 2-iodoanilines **72** also can be used as starting materials leading to *N*-substituted 2-amino-4-quinazolinones **73** (Scheme 15).

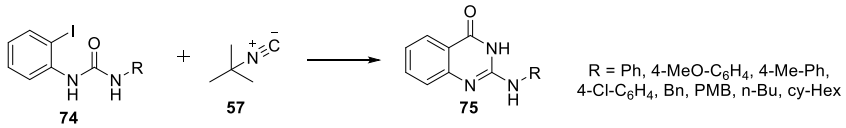


Scheme 15. Synthesis of 2-amino-4-quinazolinones **71**, **73** from 2-iodoanilines **70**, **72**.
Reaction conditions: 5 mol% $Pd(PPh_3)_4$, 3 equiv. cyanamide, 2 equiv. Et_3N, 1,4-dioxane, 65 °C, 20 h, MW 20 min; separate CO generation vessel: 1 equiv. $Mo(CO)_6$, 3 equiv. DBU, 1,4-dioxane, 65 °C, 20 h.

In this case, $Mo(CO)_6$ which decomposes in separate vessel, acts as a source of CO for the reaction. For the complete conversion of the formed intermediates, microwave irradiation was used as the last step of the transformation.

7. Pd-catalyzed addition of isonitriles to *N*-alkyl-*N′*-(2-iodophenyl)ureas

Sharma *et al*[43] reported ligand-free palladium assisted insertion of isonitriles **57** to urea derivatives **74** that leads to 2-amino-4-quinazolinones **75**. Reaction proceeded in aprotic media (DMF) with cesium carbonate as a base and palladium (II) acetate as a catalyst (Scheme 16).



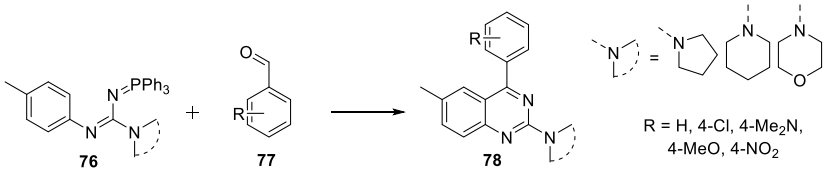
74 57 75

Scheme 16. Synthesis of 2-amino-4-quinazolinones **75** from *N*-alkyl-*N′*-(2-iodophenyl)ureas **74**.
Reaction conditions: 10 mol% $Pd(OAc)_2$, 2 equiv. Cs_2CO_3, DMF, 120 °C, 12 h, 45-71%.

The same research group also described a modified approach,[44] where the flow reactor and solid-supported NHC-Pd catalyst were used leading to increased yields of products **75** (up to 88%).

8. Cyclization of phenylguanidine derivatives

Microwave-assisted solvent-free approach to access 2-aminoquinazolines was reported by Kumar and co-workers.[45] *N*-Imidoyliminophosphoranes **76** were reacted with benzaldehydes **77** giving the corresponding 2-aminoquinazolines **78** (Scheme 17).

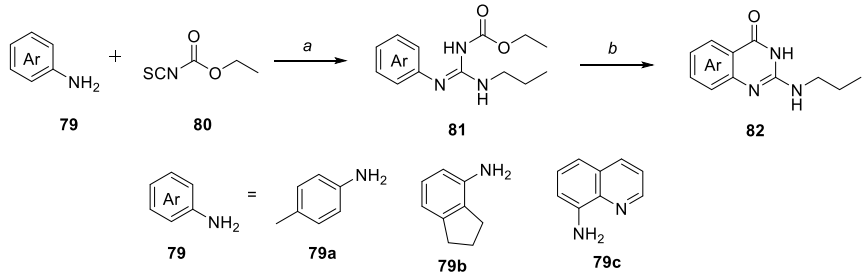


76 77 78

Scheme 17. Synthesis of 2-amino-4-phenylquinazolines **78** from imidoyliminophosphoranes **76**. Reaction conditions: MW 300 W, 4 min, 65-80%.

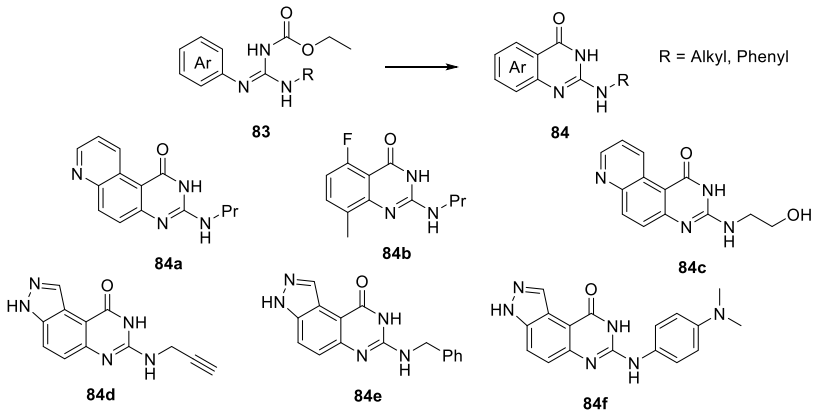
Perspective anxiolytic and anti-convulse activity was claimed for the compound **78** series.[45b]

2-Amino-4-quinazolinones **82** can be obtained by the cyclization of ethoxycarbonyl-protected guanidines **81**.[46] Reaction proceeds in DMF at 80 °C using excess TMSCl. Corresponding ethoxycarbonyl guanidines **81** can be accessed from anilines **79a-d** using one-pot protocol, which involves initial reaction of aniline with ethyl isothiocyanatoformate **80** followed by a subsequent reaction of intermediate thioureas with n-propylamine (Scheme 18).



Scheme 18. Synthesis of 2-amino-4-quinazolinones **82** from anilines **79**.
Reaction conditions: *a)* 1.2 equiv. EDCI, 2 equiv. *n*-propylamine, 3 equiv. Et_3N, 6 h; *b)* 10 equiv. TMSCl, DMF, 80 °C.

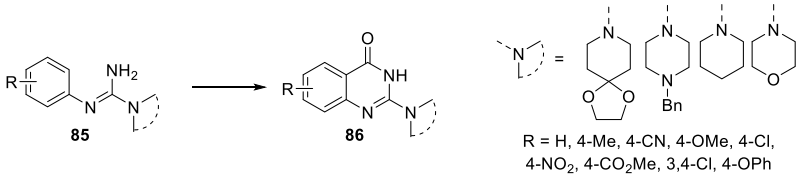
Similar approach has been used by Debray *at al*[47] – who showed that ethoxycarbonyl-protected guanidines **83** can be transformed to 2-amino-4-quinazolinones **84** without catalyst just by heating the starting material suspended in water under microwave irradiation (Scheme 19).



Scheme 19. Synthesis of 2-amino-4-quinazolinones from ethoxycarbonyl protected guanidines **83**. Reaction conditions: *a)* H_2O, MW, 130 °C, 20 min, 70-97%.

Compounds **84a**, **84c**, and **84d** exhibited low micromolar potency as DYRK1A kinase inhibitors.[47] Polymorphism of DYRK1A kinase was associated with HIV-1 replication in monocyte-derived macrophages.[48] Mutations in this type of kinase are also associated with autism disorder.[49]

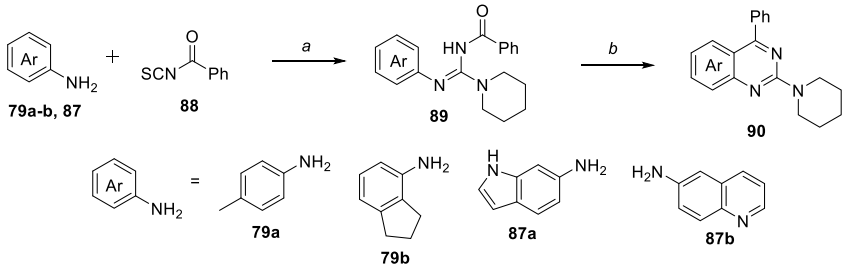
Simple route to 2-amino-4-quinazolineones was introduced by Sales and co-workers.[50] In their method, carbonyldiimidazole (CDI) was used as a source of carbonyl group to cyclize phenylguanidines **85** into 2-aminoquinazolinones **86** (Scheme 20).



Scheme 20. Synthesis of 2-amino-4-quinazolinones **86** from phenylguanidines **85** and CDI. Reaction conditions: 1.5 equiv. CDI, MeCN, 80 °C, 5 h, 52-91%.

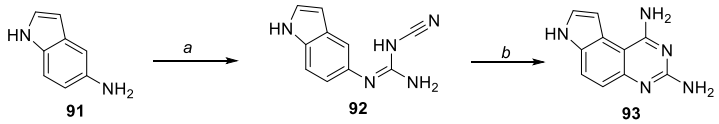
This type of reaction required no additional catalyst - just heating the components in MeCN was performed. An additional advantage of the method – large variety of functional groups were shown to tolerate the reaction conditions.

Ionic liquid-assisted cyclization of guanidine derivative **89** to give 2-alkylamino-4-phenylquinazolines **90** was reported by Debray.[51] Corresponding guanidines can be obtained from anilines **79a-b, 87** using one-pot protocol of transformation with benzoyl isothiocyanate **88** and piperidine. [OMIm]Cl was used as an ionic liquid, and the reaction was facilitated by a MW irradiation. Despite the fact that only limited number of examples of such a cyclization was presented in the paper, this approach could offer very mild conditions for the Bishler-Napieralski type transformation (Scheme 21).



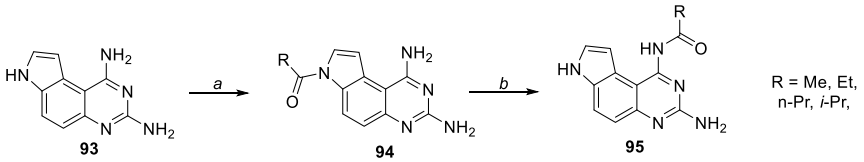
Scheme 21. Synthesis of 2-amino-4-phenylquinazolines **95**.
Reaction conditions: *a)* 2 equiv. piperidine, 1.2 equiv. EDCI, 3 equiv. Et_3N, DCM, 6 h, 91-95%; *b)* [OMim]Cl, MW, 110 °C, 10 min, 62-81%.

2,4-Diaminoquinazoline **93** was obtained from an electron-rich aniline **91** using *N*-cyano guanidine **92** as a suitable intermediate.[52] The corresponding guanidine **92** was cyclized in presence of Lewis acid (boron trifluoride diethyl etherate) to give the target quinazoline **93** (Scheme 22).



Scheme 22. Synthesis of 2,4-diaminoquinazoline **93**.
Reaction conditions: *a)* 2.5 equiv. $NaN(CN)_2$, DMF, 40 °C, 3 h, 90%; *b)* 5 equiv. $BF_3 \cdot Et_2O$, 60 °C, 2 h, 76%.

Chen and co-workers described synthesis of compound **93** derivatives and described their anti-tumor activity.[53] Using the above-mentioned approach for the construction, 2,4-diaminoquinazoline **93** was obtained, and the indole core was further selectively acylated to give compounds **94**. Curiously, using sodium hydride in DMF, the acyl group was shifted to the nitrogen of aminoquinazoline substructure, resulting in compounds **95** (Scheme 23).

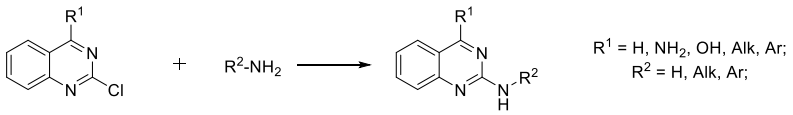


Scheme 23. Synthesis of 2,4-aminoquinazoline derivatives **95**.
Reaction conditions: *a)* 1.1 equiv. $(RCO)_2O$, 1.1 equiv. NaH, DMF, 25 °C, 1 h, 73-78%; *b)* 1.1 equiv. NaH, DMF, 1 h, 25 °C, 24-32%.

Compounds **95** exhibited potency against breast cancer cell lines MDA-MB-231 and MDA-MB-468 at micromolar concentrations.[53]

9. Amination of 2-chloroquinazolines

Nucleophilic substitution of halogens at the second position of quinazolines **96** has proven as a powerful and one of the most used methods for the synthesis of various 2-aminoquinazoline derivatives **98**. 2-Aminoquinazolines[54], 2-amino-4-quinazolinones[55] and 2,4-diaminoquinazoline[56] can be easily accessed with this approach (Scheme 24).

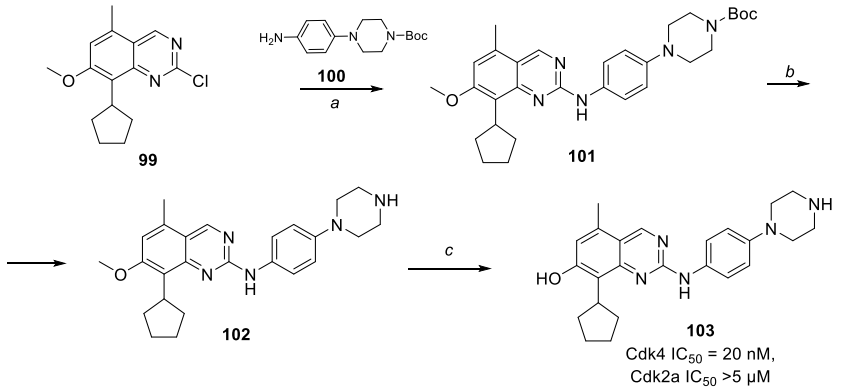


Scheme 24. Synthesis of 2-aminoquinazolines **98** from 2-haloquinazolines **96**.

2-Chloroquinazoline derivatives can be transformed to the corresponding amino derivatives by the reaction with ammonia, primary or secondary amines.[57] The substitution with amines can be facilitated by organic (triethylamine,[58] diisopropylethylamine,[54b] pyridine[59]) or inorganic (potassium carbonate,[54a] sodium hydride[60]) bases.

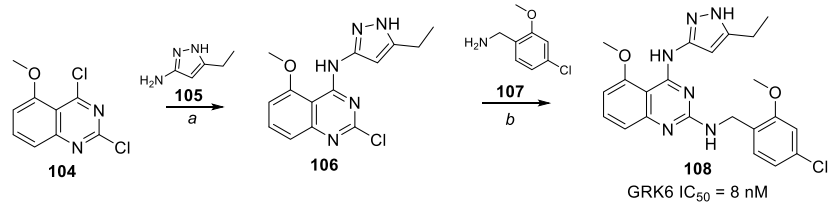
To illustrate the application of such type of transformation for the synthesis of biologically active compounds, some selected examples shall be mentioned. One of such

examples is the synthesis of a new inhibitor series of cyclin-dependent kinase 4 (Cdk4) by Bathini and co-workers.[61] This kinase is playing key role in cell division mechanism, therefore molecules targeting Cdk4 are potential anti-proliferative agents. Synthesis starts from 2-chloroquinazoline **99**, which undergoes amination at elevated temperatures with aniline **100** to produce 2-aminoquinazoline **101**. This aminoquinazoline was sequentially deprotected from Boc on piperazine moiety (**102**) and from methyl group on phenolic moiety to obtain 2-aminoquinazoline **103**. Compound **103** showed high inhibitory potency of Cdk4 and was selective Cdk4 inhibitor over the structurally-related kinase Cdk2a (Scheme 25).



Scheme 25. Synthesis of Cdk4 inhibitor **103**.
Reaction conditions: *a)* MeCN, 110 °C; *b)* TFA; *c)* EtSNa.

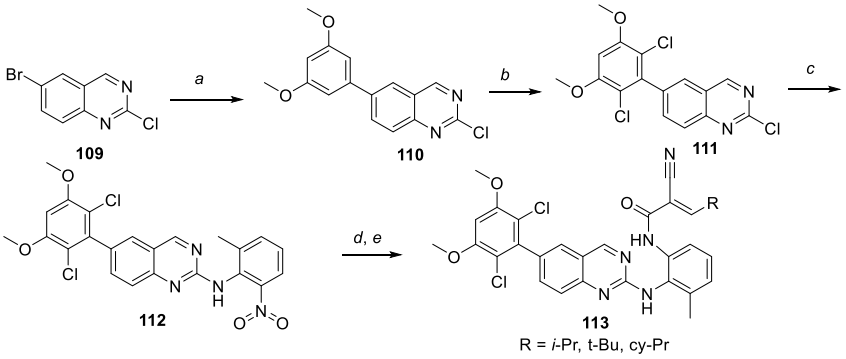
Recent research dedicated to the development of G protein-coupled receptor kinase 6 (GRK6) inhibitors resulted in compound **108** based on 2,4-aminoquinazoline scaffold.[62] GRK6 was found to be crucial for the surviving of multiple myeloma cells, so selective inhibitor of this enzyme would be applicable for therapy of such a cancer type. In this article, a modular approach was shown for assembling 2,4-diaminoquinazoline-based structure. A chlorine atom at the 4th position of 2,4-dichloroquinazoline building block **104** was replaced with an amine **105** under mild conditions. Using elevated temperatures, the chlorine atom in 2nd position of the intermediate heterocycle **106** could be replaced with an amine nucleophile **107** to give the product **108** (Scheme 26).



Scheme 26. Synthesis of 2,4-aminoquinazoline-based GRK6 inhibitor **108**.
Reaction conditions: *a)* 3 equiv. TEA, EtOH, 25 °C, 76%; *b)* butan-1-ol, MW, 200 °C, 2 h, 63%.

2-Chloroquinazoline derivatives can be subjected for amination to give 2-aminoquinazolines by using the Buchwald-Hartwig reaction protocol. Usually such a reaction can be catalyzed with tris(dibenzylideneacetone)dipalladium in pair with a phosphine ligand.

Wenwen *et al* presented a novel class of inhibitors of fibroplast growth factor receptor 4 (FGFR4) which is associated with development of Hepatocellular Carcinoma.[63] One of the key steps of the transformations towards the active compounds **113** was palladium-catalyzed amination of 2-chloroquinazoline **109** with 2-methyl-6-nitroaniline. On the first stage of transformation compound **109** reacted with (3,5-dimethoxyphenyl)boronic acid under the Suzuki-Miyaura reaction conditions to form quinazoline **110**, which was further chlorinated to obtain compound **111**.

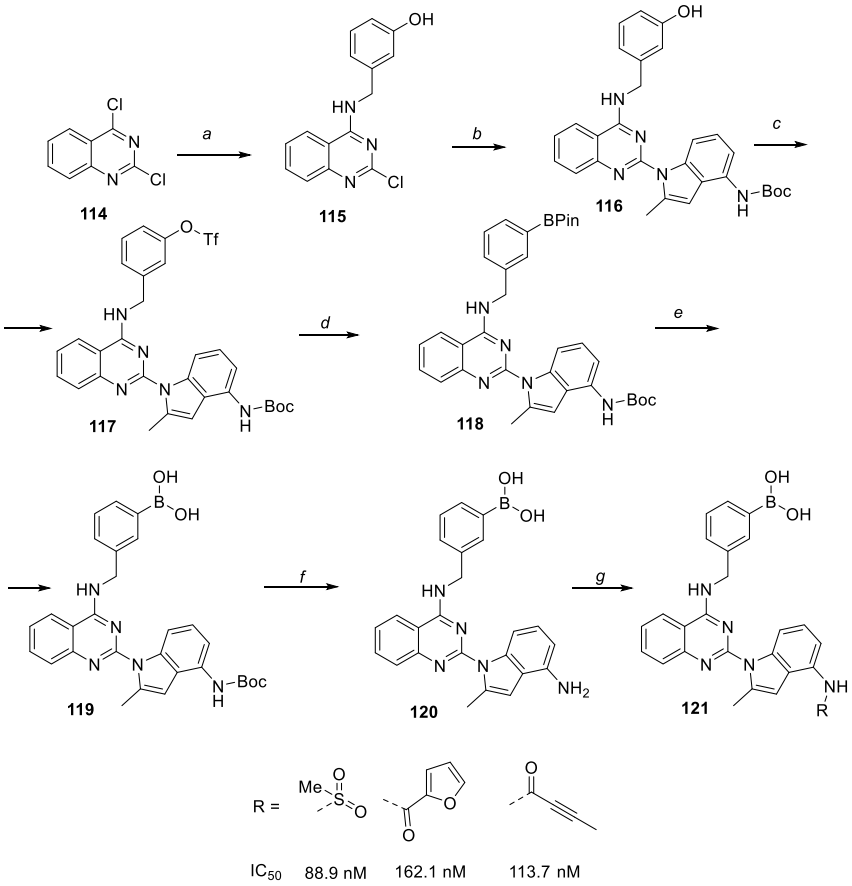


Scheme 27. Synthesis of FGFR4 inhibitor **113**.
Reaction conditions: *a)* $Pd(PPh_3)_2Cl_2$, Cs_2CO_3, THF/Dioxane/H_2O, 100 °C, 3 h; *b)* SO_2Cl_2, THF, -20 °C, 1 h; *c)* 2-methyl-6-nitroaniline, $Pd_2(dba)_3$, X-Phos, Cs_2CO_3, DMA, 100 °C, 3 h; *d)* H_2, Pd/C, MeOH, r.t. 4 h; *e)* EDCI, DCM, r.t. 4 h.

Buchwald-Hartwig reaction between quinazoline **111** and 2-methyl-6-nitroaniline provided 2-aminoquinazoline **112**. This compound was reduced and transformed to amides with general formula **113** (Scheme 27).

Catalytic amination of 2-chloroquinazoline was also used in recently reported putative pyrimidine-based inhibitors of valine-containing proteins VCP/p97[64]. This

protein associated with maintaining protein homeostasis and mediation of degradation of misfolded polypeptides. In the reaction sequence, chlorine atom in the 4th position of 2,4-dichloroquinazoline **114** was replaced with 3-(aminomethyl)phenol to produce compound **115**.



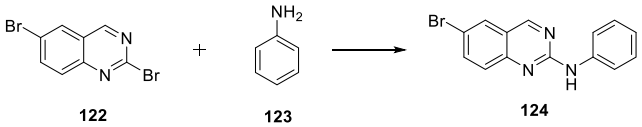
Scheme 28. Synthesis of VCP/p97 inhibitors **121**.
Reaction conditions: *a)* IPA, TEA, 80 °C; *b)* Cs_2CO_3, $Pd_2(dba)_3$, X-Phos, dioxane, 105 °C; *c)* $PhNTf_2$, TEA, THF, 50 °C; *d)* $(BPin)_2$, $Pd(dppf)_2Cl_2$, KOAc, dioxane, 110 °C; *e)* $NaIO_4$, NH_4OAc, THF, H_2O, rt; *f)* TFA, DCM, rt; *g)* carboxylic acid, *N*,*N*′-dicyclohexylcarbodiimide, DCM; or carboxylic acid, *N*-ethyl-N′-(3-dimethylaminopropyl)carbodiimide, 1-hydroxybenzotriazole, DIPEA, DMF; or acid chloride, TEA, DCM.

Further chlorine in 2nd position was replaced with indole using Buchwald-Hartwig reaction to obtain 2,4-diaminoquinazoline **116**. Then, free hydroxyl group of compound **116** was transformed to triflate. Triflate **117**, in turn, was transformed to phenylboronic acid pinacolate **118**. Pinacol protection cleaved to obtain phenylboronic acid **119**, which

after acidic cleavage of Boc group provided compound **120**. Amino group in intermediate **120** was acylated using EDCI to obtain final amides **121** (Scheme 28).

10. Amination of 2-bromo, iodo and fluoroquinazolines

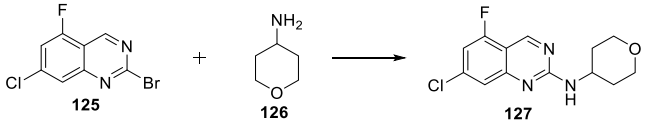
A nucleophilic replacement of bromine or iodine is not so frequently used for 2-aminoquinazoline formation in comparison with replacement of chlorine. Huang *at al* reported replacement of bromine at the 2nd position of quinazoline ring with aniline when heating a mixture of reagents **122** and **123** in dioxane in the presence of acetic acid.[65] (Scheme 29).



122 123 124

Scheme 29. Synthesis of 2-aminoquinazoline **124** from 2-bromoquinazoline **122**.
Reaction conditions: 1.5 equiv. $PhNH_2$, 1 equiv. AcOH, dioxane, 110 °C, 22 h, 70%.

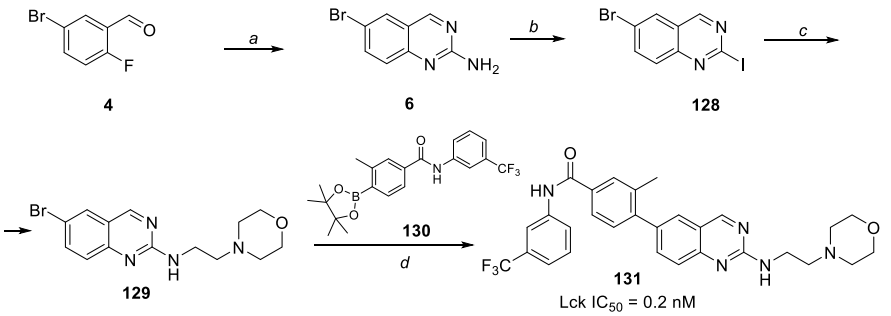
Relatively mild conditions for bromine substitution at 2-bromoquinazoline **125** with amine **126** to give the product **132** were also reported (Scheme 30).[66]



125 126 127

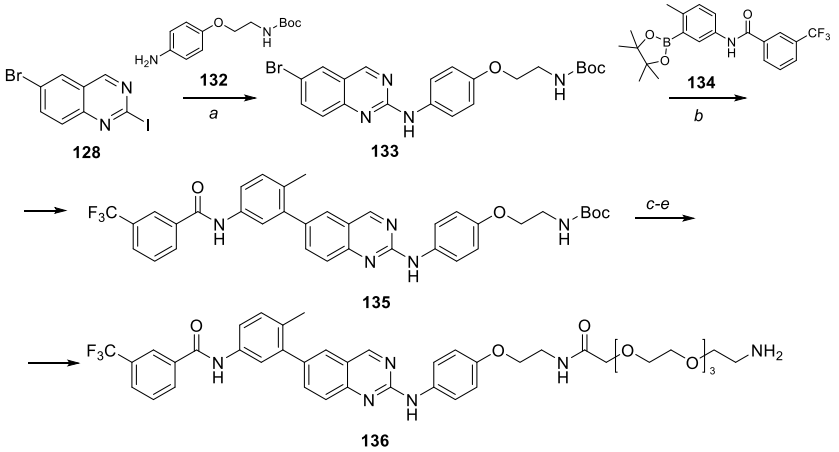
Scheme 30. 2-Bromoquinazoline **125** amination.
Reaction conditions: 3 equiv. TEA, i-PrOH, 85 °C, 2 h, 100%.

Perspective quinazoline-based inhibitor **138** of lymphocyte-specific kinase (Lck) were synthesized, using nucleophilic replacement of iodine in 2-iodoquinazoline building block **135**.[67] The corresponding 2-iodoquinazoline **135** was made from non-substituted 2-aminoquinazoline **134** which in turn was synthesized from 2-fluorobenzaldehyde **133** 2-Aminoquinazoline **136**, obtained from 2-iodoquinazoline **135**, further reacted with phenylboronic acid pinacolate **137** to give the target inhibitor **138** (Scheme 31).



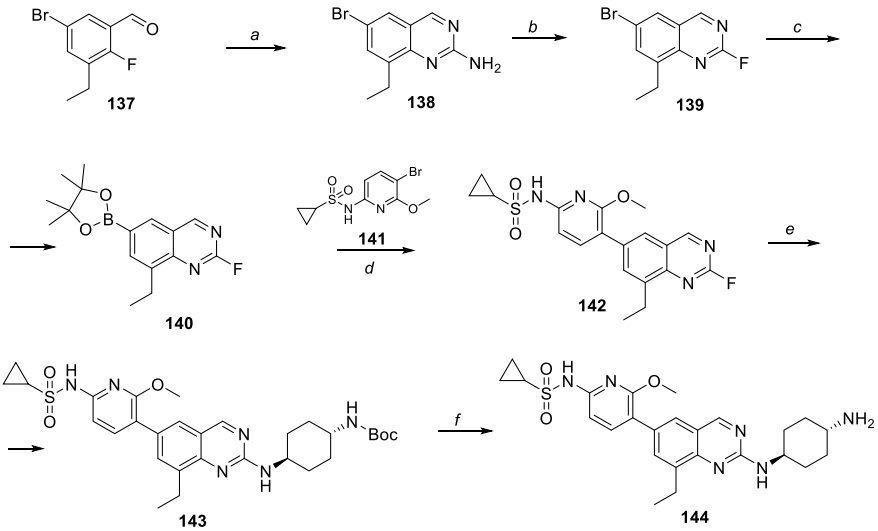
Scheme 31. Synthesis of Lck inhibitor **131**.
Reaction conditions: *a)* 1.3 equiv. guanidine carbonate, 2.6 equiv. DIPEA, NMP, 160 °C, 3 h, 48%; *b)* 1 equiv. CuI, 5 equiv. CH_2I_2, 3 equiv. *i*-amyl nitrite, THF, 70 °C, 2 h, 35%; *c)* 5 equiv. 2-morpholinoethanamine, 1.5 equiv. DIPEA, *i*-PrOH, 80 °C, 2 h, 95%; *d)* 10 mol% $Pd(dppf)_2Cl_2 \cdot CH_2Cl_2$, 5 equiv. K_2CO_3, MeCN:H_2O 3:1, 60 °C, 3 h, 17%.

The same 2-iodoquinazoline **128** was used for the construction of a non-covalent bonding probes for protein kinases **136**. 2-Iodoquinazoline **128** was aminated with substituted aniline **132**, and further reacted with phenylboronic acid pinacolate **134** to produce compound **135**. Compound **135** was further decorated with polyethoxyl chain to obtain product **136** (Scheme 32). Compound **136** was capable to interact with ATP-binding sites of the corresponding protein kinases and hold them in inactive conformation.[68]



Scheme 32. Synthesis of a non-covalent ATP inhibitor **136**.
Reaction conditions: *a)* 2 equiv. TFA, i-PrOH, 70 °C, 12 h, 47%; *b)* 5 mol% $Pd(PPh_3)_4$, 2 equiv. Na_2CO_3, DME:H_2O 3:1, 85 °C, 77%; *c)* TFA:DCM 1:2, 3 h, 25 °C, 58%; *d)* 1.3 equiv. EDCI, 1.3 equiv. HOBt, 3 equiv. DIPEA, 12 h, 25 °C, 12 h; *e)* TFA:DCM 1:2, 5 h, 25 °C, 20%.

Limited amount of data in the literature describes nucleophilic substitution of fluorine at the 2nd position of a quinazoline ring. One of such examples is a construction of IRE1-α inhibitor **144**. Inhibitors of this type are claimed to be perspective drugs against cell degenerative diseases, such as diabetes and Alzheimer disease.[69] In the synthetic scheme, 2-aminoquinazoline **138**, obtained from 2-fluorobenzaldehyde **137**, was subjected to Balz-Schiemann reaction to obtain 2-fluoroquinazoline **139**. This further was transformed to phenyl boronic acid pinacolate **140**, which was reacted in Suzuki-Miyaura coupling with aryl bromide **141**. Fluorine atom in the second position of quinazoline ring in compound **142** was replaced with substituted cyclohexylamine to obtain 2-aminoquinazoline **143**, which was deprotected from Boc group to obtain final structure **144** (Scheme 33).



Scheme 33. Synthesis of IRE1-α inhibitor **144**.
Reaction conditions: *a)* 1.5 equiv. guanidine carbonate, 3 equiv. K_2CO_3, DMF, 160 °C, 2 h, 30%; *b)* 2 equiv. *t*-$BuNO_2$, HF·Py, Py, -40 °C, 1 h, 33%; *c)* 10 mol% $Pd(dppf)Cl_2$, 1.2 equiv. $(BPin)_2$, 1.5 equiv. KOAc, dioxane, 90 °C, 18 h; *d)* 10 mol% $Pd(dppf)Cl_2$, 4 equiv. K_2CO_3, dioxane, 90 °C, 18 h, 73%; *e)* 4 equiv. *tert*-butyl ((1*R*,4*R*)-4-aminocyclohexyl) carbamate, 5 equiv. DIPEA, *n*-butanol, 100 °C, 18 h, 33%; *f)* 4 M HCl in dioxane, 2 h, 2 h, 25 °C, 30%.

11. Literature review summary

Currently existing methods for assembling 2-aminoquinazolines mostly start from benzaldehydes, phenylketones or benzoic acids with halogen (or amino group) in the *ortho*- position to carbonyl group. In the case of halogen-substituted benzaldehydes, phenylketones, or benzoic acids, the commonly used reaction partners are guanidines or guanidine derivatives. The process in such case proceeds via a nucleophilic aromatic substitution of a halogen with guanidine, with subsequent formation of quinazoline cycle. Usually process of cyclization proceeds at an elevated temperature higher than 100 °C and requires presence of a strong base. Reaction partners for 2-aminosubstituted phenylcarbonyl derivatives are mostly cyanamide derivatives. Cyclization of 2-aminoquinazoline core in this case usually posess milder conditions, but frequently required temperatures up to 100°C and acid catalysis.

Substitution of halogen of 2-haloquinazolines can be achieved either via nucleophilic mechanism or using palladium-catalyzed Buchwald-Hartwig type amination. These are the mildest ways of 2-aminoquinazoline synthesis, described in literature at the date. Large variety of functional and protective groups can tolerate these conditions. However, most of such substitution protocols involves elevated temperature and presence of a strong base.

The reasons, mentioned above, promoted our interest for a search of a new methods of 2-aminoquinazoline assembling (see Results and Discussion, section 3).

RESULTS AND DISCUSSION

1. Synthetic evolution of HK fragment hits

To find a perspective inhibitor of HK TCs we pursued the fragment-based drug discovery approach starting from the fragments hits which were identified by crystallography screening of the fragment library (project partners: group of Dr. A. Marina, Instituto de Biomedicina de Valencia CSIC). Computational studies of the ligand-protein structures and proposed possible structure modifications to increase potency of initial hits were performed by M. Albanese (Oxford Drug Design, Oxford). Blanca Fernandez (Prof. Jerry Wells group, Wageningen University) studied the effect of synthesized compounds on different bacterial strains. Synthesis of target compounds together with SAR analysis were made by V. Solomin.

1.1. Pyrazole amide series of compounds

Ethyl 1*H*-pyrazole-4-carboxylate **145** was one of the fragment hits which was co-crystallized with CA domain of CheA (Figure 2).

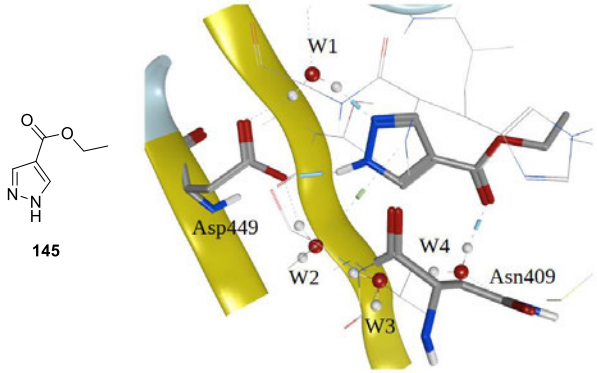
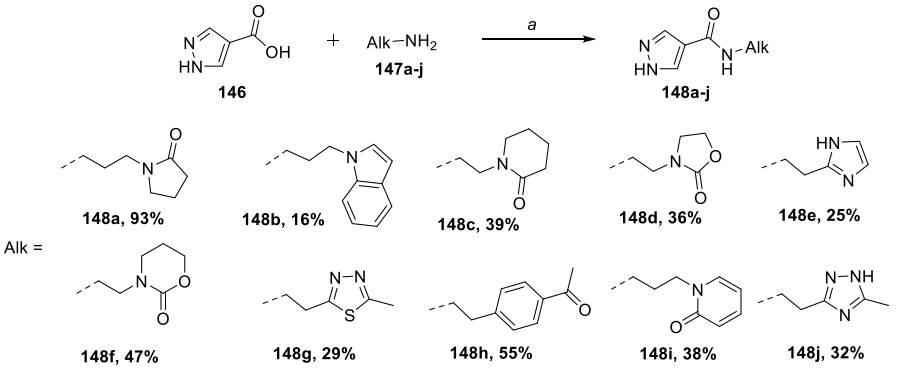


Figure 2. Crystal structure of CA domain of CheA from *T. Maritima* in a complex with compound **145**.

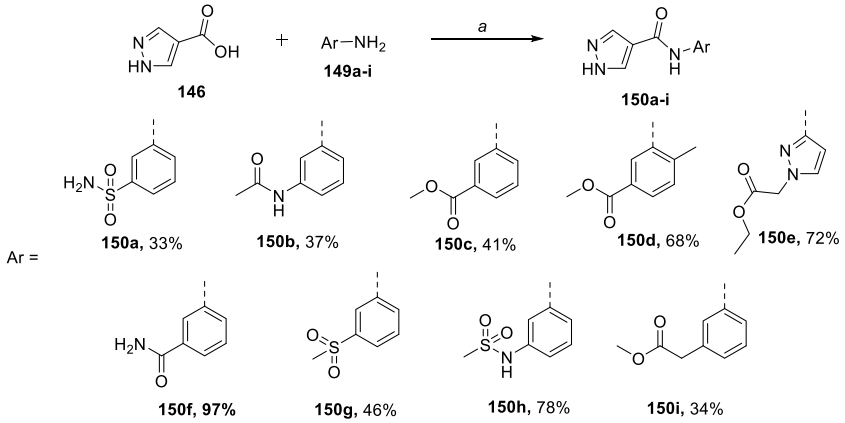
Compound **145** was particularly attractive for further modifications because of accessibility of modifications which can be made with the carboxyl group of the molecule. A virtual library of amides **148a-j** was created in collaboration with Marco Albanese (Oxford Drug Design) which was subjected to the docking studies, using computer-aided drug design (CADD). After several refinements of the results, the most promising compounds **148a-j** were selected for the synthesis. Amides **148a-j** were

prepared from pyrazole-4-carboxylic acid **146** and corresponding amines **147a-j** by using EDCI in pair with HOBt as coupling agents (Scheme 34).



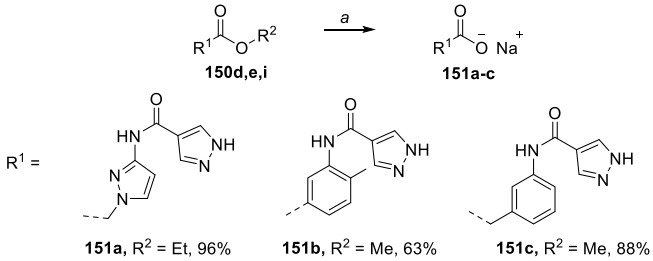
Scheme 34 Synthesis of amides **148**.
Reaction conditions: *a)* 1.1 equiv. HOBt, 2 equiv. EDC, 4 equiv. TEA, MeCN, 25 °C, 14 h.

The amides **148a-j** were subjected to enzymatic assay and bacterial growth assay. Unfortunately, the compounds **148a-j** showed no detectable activity in any of the assays. The initial unsuccessful results promted to propose more rigid compounds without flexible chain between structural elements of the molecule. Using CADD, another series of pyrazole amides **150a-i** was designed as potential inhibitors for histidine kinases. Using EDCl as a coupling reagent and pyridine as a solvent, anilines **149a-i** were converted to the corresponding amides **150a-i** (Scheme 35).



Scheme 35. Synthesis of anilides **150a-i**.
Reaction conditions: *a)* 1.6 equiv. EDCI, pyridine, 25 °C, 16 h.

Several anilides were made by hydrolysis of ester groups in amides **150d,e,i** to give carboxylic acid derivatives **151a-c** (Scheme 36).



Scheme 36. Hydrolysis of compounds **150d,e,i** to carboxylic acid salts **151a-c**. Reaction conditions: *a)* 2.2 equiv. NaOH, MeOH/H_2O, 70 °C, 12 h.

Compounds **150a-i** and **151a-c** showed weak inhibitory potency in the case of target proteins PhoR and EnvZ. Autophosphorylation inhibition assay in pair with these proteins revealed that all of the compounds **150a-i** and **151a-c** have IC_{50} less than 1 mM.

Another type of assays was performed with proteins CheA and Hsp90. In the case of CheA TNP-ATP displacement assay[70] showed that K_D for all of the compounds is less than 500 μM. Radicicol replacement assay[71] in the case of Hsp90 protein indicated that K_D of the compounds **150a-i** and **151a-c** is lower than 100 μM.

Upon crystallography studies in IBV CSIC X-Ray crystal structure of compound **148f** with CheA protein was revealed (Figure 3, A). Generally, this structure confirmed predictions made by CADD. Real structure position (in red) and predicted binding mode (in green) are almost identical (Figure 3, B).

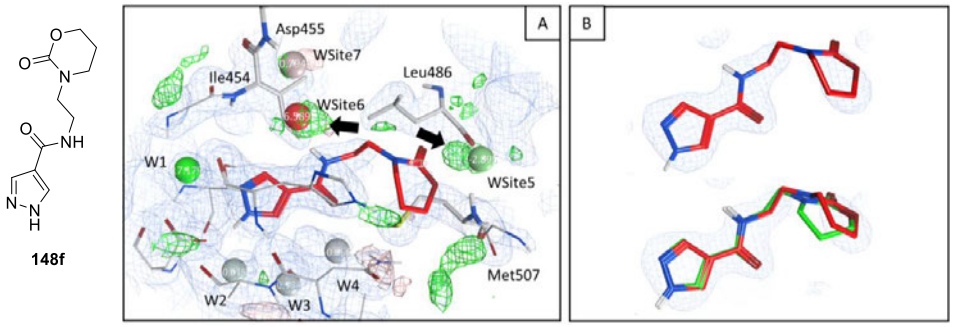


Figure 3. X-ray crystal structure of **148f** in complex with CheA.

A) Crystal binding mode of **148f** (red tubes) in complex with CheA. Water sites are shown as solid spheres coloured by free energy (green: negative free energy, red: positive free energy). Black arrows indicate the regions of positive energy in the proximity of the ligand.
B) Top - Crystal bound conformation of **148f** (in red tubes). Bottom – an overlay of the crystal-bound conformation (red tubes) onto the energy minimized crystal bound conformation (green tubes).

However, none of the pyrazole amide derivatives **150a-i** and **151a-c**, derived from the second fragment **145** development series, did not show any activity to inhibit the growth of Gram positive and Gram negative bacterial cultures.

1.2. 2-Aminopyrimidine-5-carboxamide and structurally related derivatives

Another fragment hit **152** identified by X-ray screening of fragment library (group of Dr. A. Marina at CSIC) was analysed by CADD (M. Albanese at Oxford Drug Design). These studies suggested 8-amino-1,7-naphtyridine **153**, 2-aminopyrimidine **154** and 3,4-dihydroisoquinolin-1(2*H*)-one **155** as putative HK ligands (Figure 4).

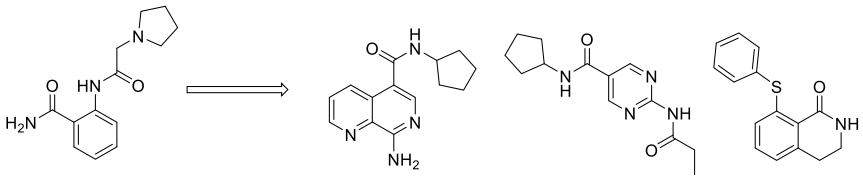
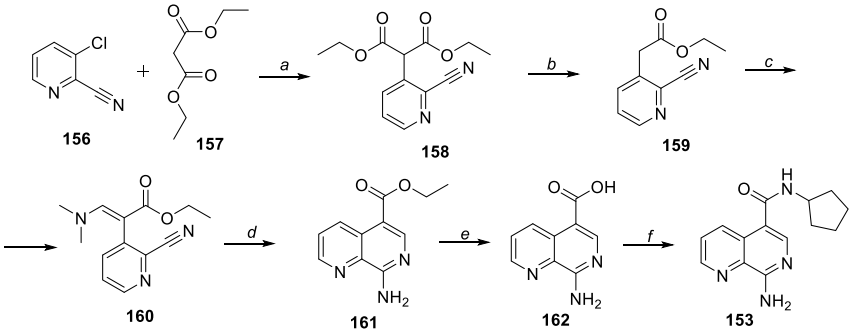


Figure 4. Proposed as analogues of a fragment hit **152** compounds **153-155**.

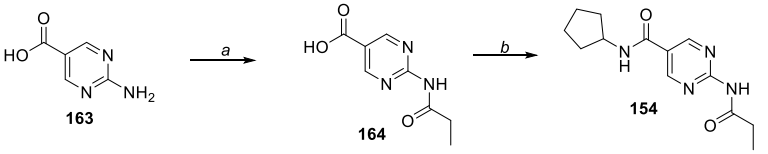
Following the literature procedure,[72] 1,7-naphtyridine **161** was synthesized starting from 3-chloropicolinonitrile **156** (Scheme 37). After arylation of diethyl malonate obtained ester **158** was de-carboxylated to obtain ester **159**. Ester **159** was subjected to the reaction with DMF-DMA to obtain enamine **160**, which further was cyclized to 1,7-naphtyridine **161**. Ethyl ester **161** was hydrolysed to carboxylic acid **162** using aqueous sodium hydroxide. The carboxylic acid **162** was converted to cyclopentylamide **153** using EDCI in pair with HOBt as coupling reagents (Scheme 37).

2-Aminopyrimidine derivative **154** was made starting from 2-aminopyrimidine-5-carboxylic acid **163** (Scheme 38). This was *N*-acylated with propionic anhydride at elevated temperature to receive compound **164** and then coupled with cyclopentylamine using EDCI to give the target compound **154**.

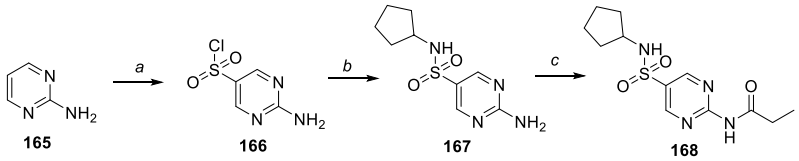
Additionally, an analogues aminopyrimidine **168** containing sulphonamide instead of carboxamide moiety was prepared. 2-Aminopyrimidine **165** was converted to sufonyl chloride **166**, using chlorosulfonic acid mixture with thionyl chloride. Newly formed sulfonyl chloride **166** reacted with cyclopentylamine to produce sulfonamide **167**. This was acylated using propionic anhydride to obtain amide **168** (Scheme 39).



Scheme 37. Synthesis of 1,7-naphtyridine **153**.
Reaction conditions: *a)* 2 equiv. NaH, 0.2 equiv. KF, DMF, 130 °C, 14 h, 69%; *b)* 2 equiv. LiCl, 2 equiv H_2O, DMSO, 140 °C, 3 h, 86%; *c)* 3 equiv. DMF-DMA, neat, 100 °C, 6 h; *d)* 18 equiv. NH_4OAc, AcOH, 100 °C, 14 h, 39% over 2 st; *e)* 2 equiv. NaOH, H_2O, 100 °C, 2 h, 77%; *f)* 1.5 equiv. *cy*-Pent-NH_2, 1.5 equiv. EDCl, 1.2 equiv. HOBt, 4 equiv. Et_3N, DMF, 25 °C, 14 h, 84%.

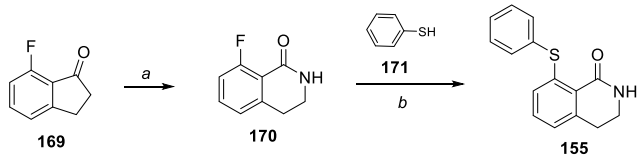


Scheme 38. Synthesis of 2-aminopyrimidine **154**.
Reaction conditions: *a)* 6 equiv. propionic anhydride, neat, 140 °C, 1 h, 49%; *b)* 1.5 equiv. EDCI, 1.2 equiv. HOBt, 2 equiv. *cy*-Pent-NH_2, DMF, 25 °C, 14 h, 55%.



Scheme 39. Synthesis of sulphonamide **168**.
Reaction conditions: *a)* 8.5 equiv. HSO_3Cl, 4 equiv. $SOCl_2$, 0 to 150 °C, 16 h, 30%; *b)* 1.5 equiv. *cy*-Pent-NH_2, 2 equiv. Et_3N, MeCN, 25 °C, 1 h, 76%; *c)* 12 equiv. propionic anhydride, neat, 140 °C, 2 h, 48%.

3,4-Dihydroisoquinolin-1(2*H*)-one **155** was synthesized starting from 7-fluoro-2,3-dihydro-1H-inden-1-one **169** (Scheme 40). The Schmidt rearrangement[73] was applied to transform the ketone **169** to lactam **170**. This was subjected to S_NAr reaction with thiophenol **171** to give the target product **155**.



Scheme 40. Synthesis of 3,4-dihydroisoquinolin-1(2*H*)-one **155**.

Reaction conditions: *a)* 2 equiv. NaN_3, 23 equiv. $MeSO_3H$, DCM, 0 °C, 14 h, 35%; *b)* 1.5 equiv. K_2CO_3, DMF, 120 °C, 14 h, 62%.

Unfortunately, compounds **153-155**, **168** showed no measurable biological activity in *in vitro* tests with different bacterial cell lines. Compounds were not inhibiting growth of *S. Aureus Newman*, *E. Coli D21F2*, *E. Coli 25922*, *E. Faecium* and *E. Faecalis* up to concentrations of 250 μg/mL.

1.3. Indazole series of compounds

Structural information of the binding for fragment hits ethyl 1*H*-pyrazole-4-carboxylate **145** and 4-[4-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]benzene-1,3-diol **172** was available from crystallography studies (group of prof. A. Marina at CSIC, Figure 5).

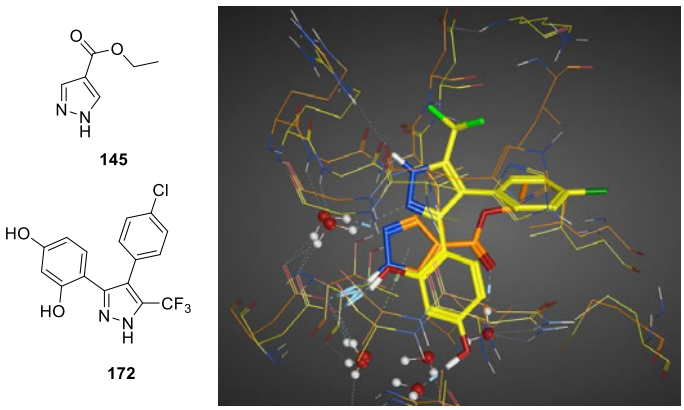


Figure 5 Ligands **145** (in orange) and **172** (in yellow) superposition of X-Ray crystal structures with CheA protein.

The two hits were virtually combined using CADD software resulting in indazole based compound **173** (Figure 6, on the top). Analysis of possible options for modification of virtual fragment **173** was made and it was proposed to introduce an aryl substituent at the 4th position of the indazole. Preferably aryl group at 4th position shall contain hydrogen bond acceptor, such as pyridine nitrogen (additional interaction showed with arrows). In this way indazole **174** was determined as perspective compound (Figure 6, on the bottom).

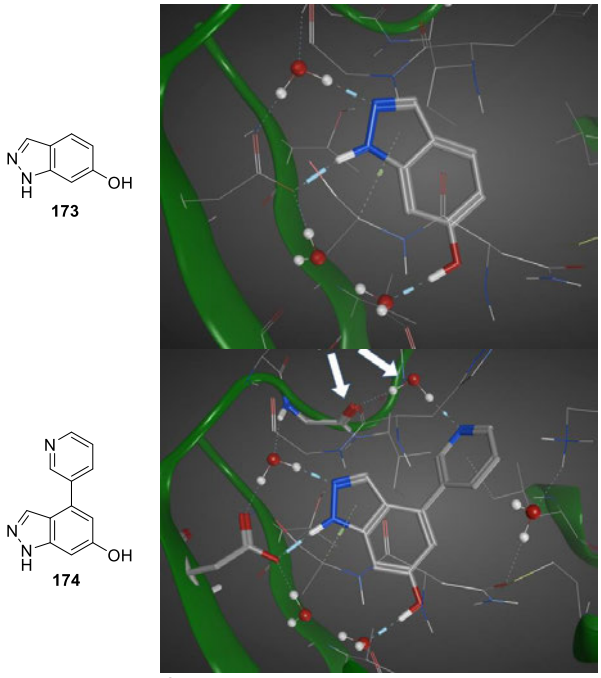
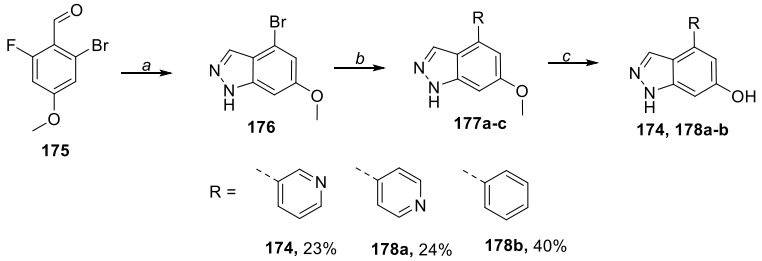


Figure 6. A predicted binding mode of 1*H*-indazol-6-ol **173** (on the top) and 4-(pyridin-3-yl)-1*H*-indazol-6-ol **174** (on the bottom) with CheA.

Suzuki reaction of bromoindazole **176** with aryl boronic acids was chosen to introduce an aryl group at the indazole ring (Scheme 41). The synthesis of the key intermediate bromoindazole **176** was performed starting from 2-fluorobenzaldehyde **175** which was cyclized with hydrazine at elevated temperature.[74]

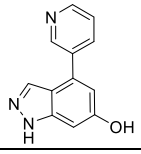
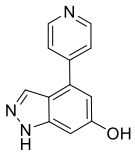
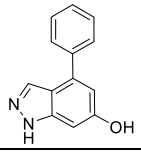


Scheme 41. Synthesis of indazoles **174**, **178a-b**.
Reaction conditions: *a)* 22 equiv. $N_2H_4 \cdot H_2O$, Dioxane, 110 °C, 12 h, 93%; *b)* 1.4 equiv. R-B$(OH)_2$, 7 mol% Pd(dppf)Cl_2, 4 equiv. K_2CO_3, dioxane:H_2O 4:1. 100 °C, 12 h; *c)* 5 equiv. BBr_3, DCM, 0 °C to r.t., 15 h.

Further compound **176** was subjected to Suzuki reaction with arylboronic acids to obtain compounds **177a-c**, followed by deprotection of hydroxy group using boron tribromide to obtain indazoles **174**, **178a-b**.

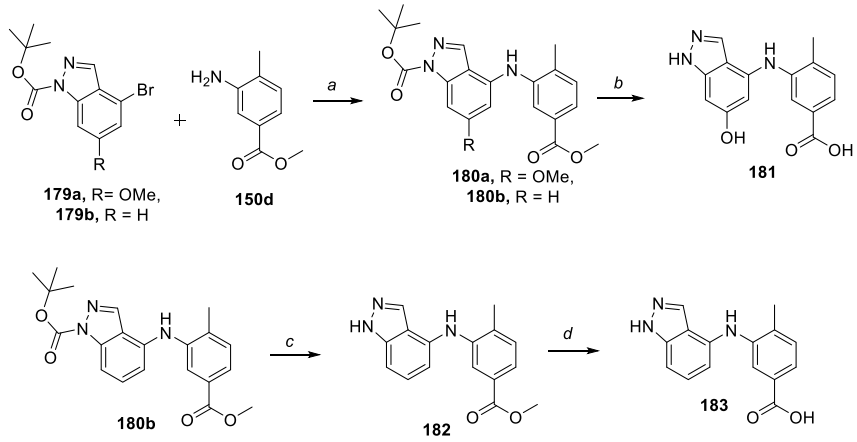
The indazoles **174**, **178a-b** were subjected to bacterial growth assays. Compounds **174**, **178a-b** showed no inhibition of growth of *S. Aureus* representing Gram-positive bacteria. Nevertheless, indazoles **174**, **178a-b** were found to be weak inhibitors of growth of *E. Coli* representing gram-negative bacteria (Table 1).

Table 1. The growth inhibition of *E.Coli* by indazoles **174**, **178a-b**

Number	Indazole	MIC (*E. Coli*, μg/mL)
174		250
178a		250
178b		62.5

Unfortunately, indazoles **174**, **178a-b** showed no inhibition of target PhoR activity (IC_{50} was higher than 2 mM). It is known that this type of protein belongs to the family of highly structurally conserved proteins,[75] and most likely other proteins of this type could not be inhibited too. This fact implies that the antibacterial activity of these indazoles is linked to other mechanism of action not involving inhibition of HK TCs.

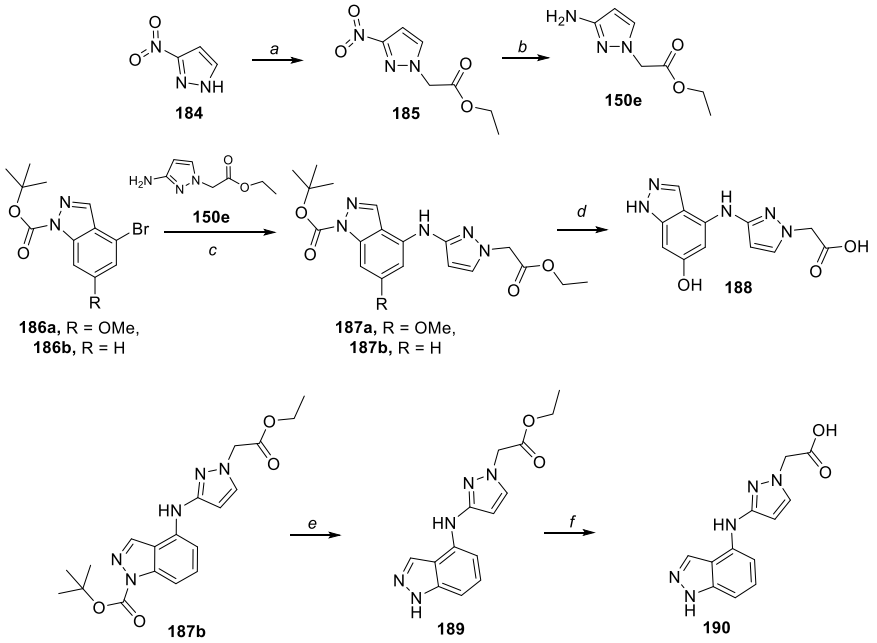
Second series of indazole-based compounds retained the main scaffold, but were modified at 4th position using Buchwald-Hartwig amination reaction with aniline using Boc-protected indazoles **179a-b** as a starting materials (Scheme 42). At the final step, Boc group was cleaved from the compound **180a** together with methyl ester to produce compound **181**. A simplified analog **183** was made lacking OH group at the 6th position of the indazole ring. For this purpose, bromoindazole **179b** was used as a starting material. This was coupled with aniline **150d** in amination reaction to obtain intermediate **180b**. Then, protection groups were sequentially removed. After Boc deprotection with TFA, compound **182** was obtained; further hydrolysis of ester with sodium hydroxide provided compound **183** (Scheme 42):



Scheme 42. Synthesis of indazoles **181**, **183**.
Reaction conditions: *a)* 3 mol % $Pd_2(dba)_3$, 6 mol% Xantphos, 1.5 equiv. K_3PO_4, PhMe, 100 °C, 48 h; *b)* 48% HBr_{aq}, neat, 100 °C, 3 h, 20%; *c)* 30 equiv. TFA, DCM, 25 °C, 18 h, 80%; *d)* 3 equiv. NaOH, MeOH/H_2O, 70 °C, 16 h, 84%.

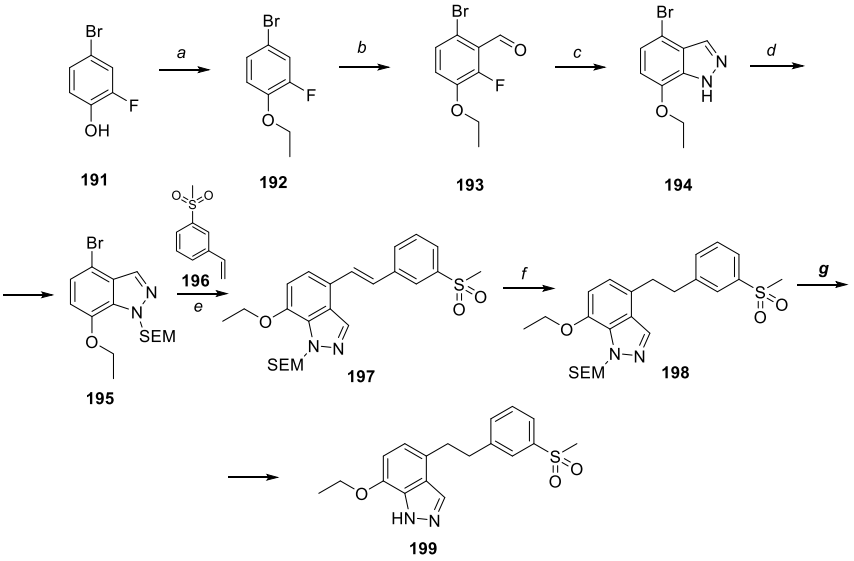
Compound **188** was synthesized in a similar way, using aminopyrazole **150e** as a building block for the coupling with bromoindazoles **186a-b** (Scheme 43). Aminopyrazole **150e** was prepared by reduction of nitropyrazole **185**, which, in turn, was synthesized by alkylation of 3-nitropyrazole **184**. Deprotection of all of three protecting groups of compound **187a** was done in one step using aqueous HBr to obtain compound **188**.

A simplified analog **190** lacking OH group at the 6th position of the indazole ring was synthesized as well. After the Pd-catalyzed amination reaction between **186b** and **150e**, compound **187b** was deprotected with TFA to obtain compound **189**. Ester group was further hydrolyzed to obtain compound **190** (Scheme 43).



Scheme 43. Synthesis of indazoles **188**-**190**.
Reaction conditions: *a)* 1.2 equiv. ethyl bromoacetate, 2 equiv. K_2CO_3, DMF, 80 °C, 16 h, 80%; *b)* 1 atm H_2, 10% Pd/C, EtOH, 25 °C, 3 h, quant; *c)* 3 mol % $Pd_2(dba)_3$, 6 mol% Xantphos, 1.5 equiv. K_3PO_4, PhMe, 100 °C, 48 h; *d)* 48% HBr_{aq}, neat, 100 °C, 3 h, 49%; *e)* 30 equiv. TFA, DCM, 25 °C, 18 h, 71%; *f)* 3 equiv. NaOH, MeOH/H_2O, 70 °C, 16 h, 44%.

The third type of indazole based compound **199** was made with with ethoxy substituent in 7th position and phenylethyl substituent in the 4th position as suggested by the CADD studies. The synthesis of compound started from phenol **191**, which was alkylated with ethyl bromide to obtain compound **192**. Ortho-lithiation with LDA leaded to fluorobenzaldehyde **193** in an excellent yield. Further this was converted towards indazole **194**, which was protected with trimethylsilylethoxymethyl (SEM) group to obtain compound **195**. Heck reaction of indazole **195** with styrene **196** leaded to alkene **197**, which was further reduced to produce compound **198**. SEM group was cleaved in acidic media to obtain final indazole **199** (Scheme 44).



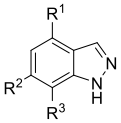
Scheme 44. Synthesis of indazole **199**.
Reaction conditions: *a)* 2 equiv. EtBr, 2 equiv. K_2CO_3, DMF, 25 °C, 16 h, 91%; *b)* 1.3 equiv. LDA, 2 equiv. DMF, THF, -78 °C, 2 h, 94%; *c)* 18 equiv. $N_2H_4 \cdot H_2O$, DMSO, 120 °C, 16 h, 88%; *d)* 1.3 equiv. SEM-Cl, 1.1 equiv. NaH 60%, THF, 0 °C to 25 °C, 1 h, 37%; *e)* 10 mol% $Pd(OAc)_2$, 20 mol% P(o-Tol)$_3$, 10 equiv. TEA, DMF, 100 °C, 18 h, 98%; *f)* 5 mol% 10% Pd/C, 6 equiv. TES, MeOH, 25 °C, 18 h, 57%; *g)* 12 M HCl, MeOH, 25 °C, 24 h, 49%.

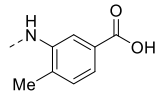
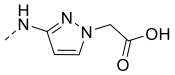
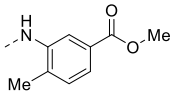
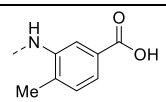
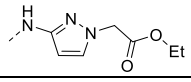
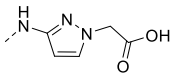
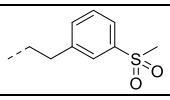
The compounds **181-183**, **188-190**, **199** were investigated for their ability to bind bacterial protein PhoR from *E. Coli* and *S. Aureus* strains, and a structurally similar human protein Hsp90 using microscale thermophoresis (MST) assay.[76] Results of the MST experiments are summarized in Table 2.

Compounds **182** and **188** bearing hydroxy group at 6th position of indazole ring showed no measurable binding to *S. Aureus* PhoR and *E.Coli* PhoR – in both cases tests indicated that activity level was higher than 1 mM. Nevertheless, K_d data in tests with Hsp90 revealed nanomolar affinity levels for these compounds – 241 nM for **181** and 187 nM for **188**.

Simplified compounds without hydroxy group in 6th position of indazole **182**, **183**, **189**, **190** and **199** also exhibited affinity to Hsp90 in range 300-700 nM. But only compounds **189** and **190** showed activity with tests in pair with *S. Aureus* PhoR and *E.Coli* PhoR. Remarkably, higher potency was exhibited in the case of *S. aureus* PhoR protein (67 μM for **189** and 86 μM for **190**), and slightly lower in the case of *E. Coli* PhoR (162 μM for **189** and 143 μM for **190**). Compound **199** showed weak results in pair with *S. Aureus* PhoR (486 μM), but in pair with *E. Coli* PhoR no binding was detected.

Table 2. IC_{50} data for the synthesized indazoles **181-183**, **188-190**, **199**



Number	R^1	R^2	R^3	*S.Aureus* PhoR	*E. Coli* PhoR	Hsp90 K_d
181		OH	H	>1 mM	> 1 mM	241 nM
188		OH	H	>1 mM	> 1 mM	187 nM
182		H	H	>500 μM	>500 μM	474 nM
183		H	H	>500 μM	>500 μM	327 nM
189		H	H	67 uM	162 uM	457 nM
190		H	H	86 uM	143 uM	689 nM
199		H	OEt	486 uM	>1 mM	547 nM

1.4. Development of 2-aminoquinazoline based bacterial HK inhibitors

Screening of fragment library by X-ray chrystallography using CheA as a HK TCs protein revealed 2-aminoquinazoline bound to ATP binding domain (Figure 7).

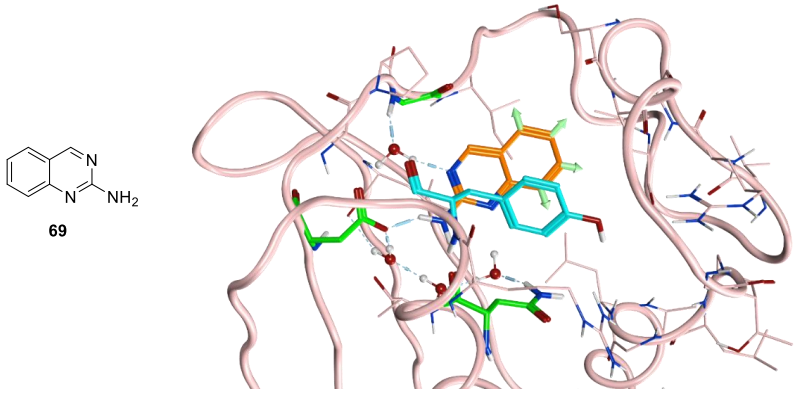
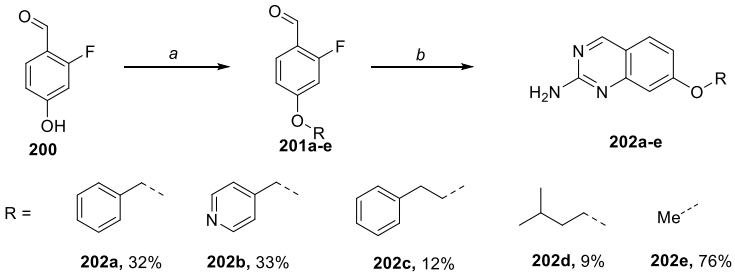


Figure 7. 2-Aminoquinazoline **69** in the complex with CheA protein. Tyrosine residue showed in blue, growth vectors are showed in green.

Analysis of the crystal structure of the ligand-protein complex suggested several fragment **69** growth vectors for the improvement of the molecule affinity (green arrows on Figure 7). From these the 7th position of 2-aminoquinazoline was prioritized as the best attachment point for an additional structural element according to CADD modelling data. The first set of aminoquinazoline analogues were targeted bearing the substituents attached to the heterocycle at the 7th position via oxygen as a linker. Starting from commercially available 2-fluoro-4-hydroxybenzaldehyde **200**, small set of compounds **201a-e** was synthesized. On the second stage 2-fluorobenzaldehyde moiety was converted to 2-aminoquinazoline, using cyclization with guanidine at 150 °C to achieve compounds **202a-e** (Scheme 45).



Scheme 45. Alkylation and cyclization cascade towards 2-aminoquinazolines **202a-e**. Reaction conditions: *a)* 1.2 equiv. R-Hal, 1.5 equiv. K_2CO_3, DMF, 25 °C; *b)* 1.4 equiv. guanidine carbonate, 1.4 equiv. Na_2CO_3, DMA, 150 °C.

Some of the synthesized compounds (**202a-b**) were crystallized together with CheA protein and obtained protein-ligand complexes were analysed using X-Ray

crystallography (group of prof. A. Marina) (Figure 8). This showing general tendency that compounds shall contain aryl groups as substituents to show better affinity towards protein of interest.

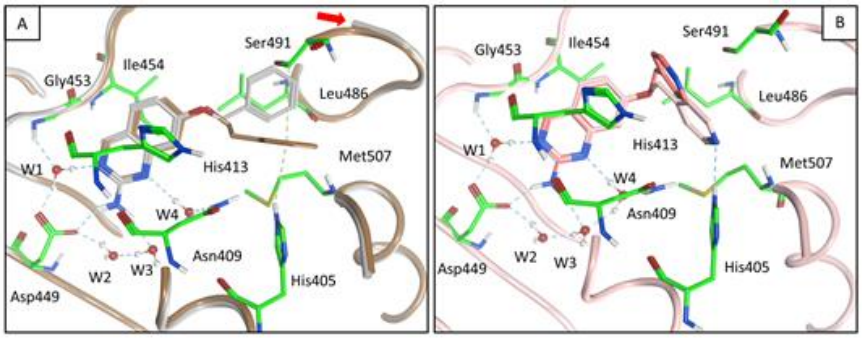
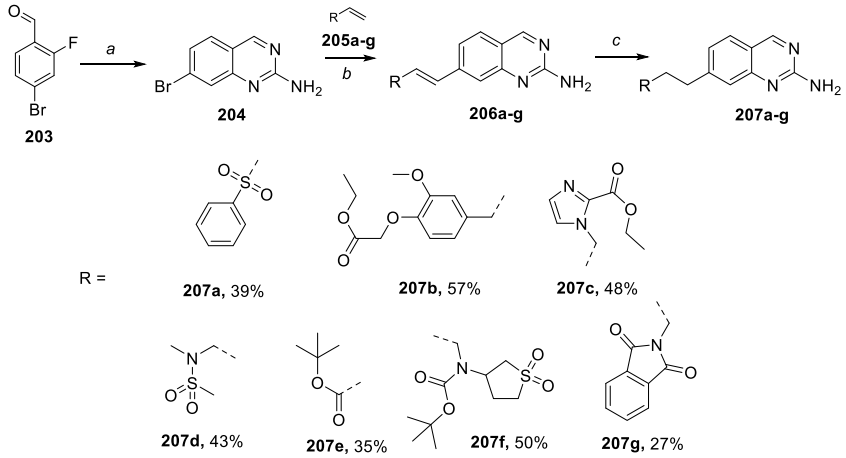


Figure 8. X-ray crystal structures of CheA in complex with **202a** (A) and **202b** (B). Two alternate positions of **202b** were built in the crystal model: alternate one in dark pink tubes and alternate two in pink. Key residues are shown in green tubes.

Unfortunately, aminoquinazolines **202a-e** showed no inhibitory potency for PhoR (*S. Aureus*) and EnvZ (*E. Coli*) histidine kinases. Negative results were obtained also for the growth inhibition of *S.Aureus* and *E.Coli* cells.

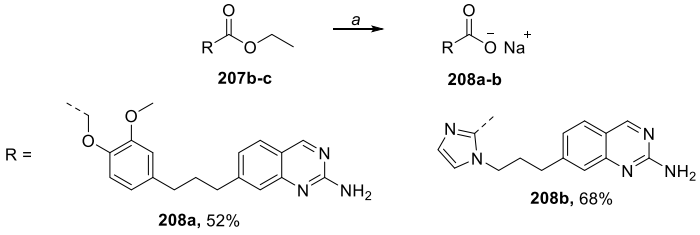
According to CADD results (M. Albanese, Oxford Drug Design), putative HK TCS inhibitors should contain an additional structural element attached at 7th position of quinazoline ring via a flexible linker. For such type of compounds the Heck reaction was chosen as the most feasible way to connect the building blocks. For this purpose, 7-bromoquinazolin-2-amine **204** was synthesized from 4-bromo-2-fluorobenzaldehyde **203** in the reaction with guanidine.[77]

The Heck reaction of bromoquinazoline **204** with terminal alkenes **205a-g** provided disubstituted alkenes **206a-g**. On the next step, alkene was reduced to form compounds **207a-g** with alkyl linker. Precise amount of equivalents of reducing agents was essential to avoid concomitant reduction of 2-aminoquinazoline heterocyclic core (Scheme 46).

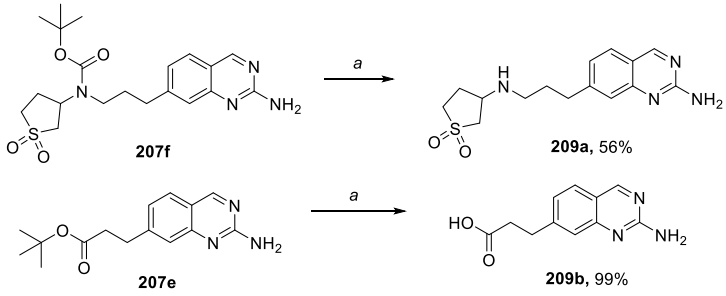


Scheme 46. Synthesis of 2-aminoquinazolines **207a-g** using the Heck reaction.
Reaction conditions: *a)* 1.4 equiv. guanidine carbonate, 1.4 equiv. Na_2CO_3, DMA, 150 °C, 69%; *b)* 10 mol% tris-(*o*-tolyl)P, 5mol% $Pd(OAc)_2$, 3 equiv. TEA, DMF, 100 °C, 8 h; *c)* 10 mol% $Pd(OAc)_2$, 3 equiv. TEA, 2.5 equiv. HCOOH, DMF, 60 °C, 2 h.

Compounds **207b** and **207c**, bearing an ester group, were hydrolyzed under basic conditions to obtain carboxylic acids sodium salts **208a** and **208b** (Scheme 47). Compounds **209a** and **209b** were obtained by acidic cleavage of Boc and t-Bu groups from the **207f** and **207e**, respectively (Scheme 48).



Scheme 47. Synthesis of 2-aminoquinazolines **208a-b** using basic hydrolysis of esters. Reaction conditions: *a)* 1.8 equiv NaOH, $EtOH/H_2O$, 50 °C.



Scheme 48. Synthesis of 2-aminoquinazolines **209a-b** using acidic cleavage of protecting groups.
Reaction conditions: *a)* 20 equiv. TFA, DCM, 16 h.

The structural investigations of the compounds **207a-g**, **208a-b**, **209a-b** binding to the CheA protein were attempted by X-ray crystallography (group of prof. A. Marina). However, it appeared that the density maps of ligand-protein complexes were too hard to resolve. 2-Aminoquinazoline core was located properly in the area predicted by CADD while the location of "tail" part of the compound inside the crystal structure was unclear. This was assumed to be the result of several energetically similar conformations of the molecule inside the crystal pocket. For one of the compounds (**207c**) was possible to distinguish two possible way of binding inside the pocket. CheA protein consist of two similar, but not identical, assymetric parts. Compound **207c** has different conformation of the flexible part in each of these two structural units (Figure 9).

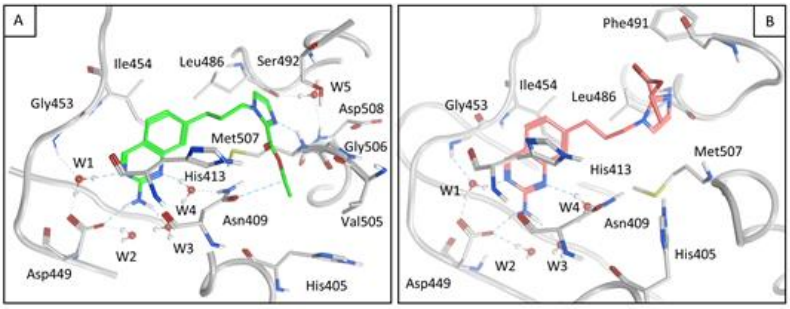
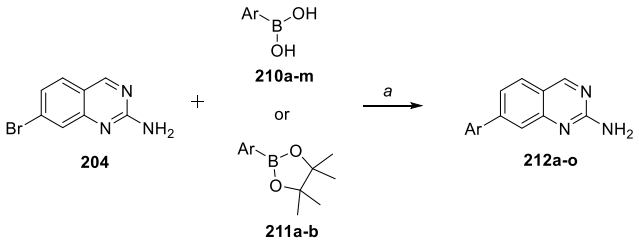


Figure 9. X-ray crystal structure of two structural elements of CheA in complex with **207c**.

Facing these problems, the 3rd series of 2-aminoquinazoline derivatives was designed bearing aryl substituents, attached to the 7th position of quinazoline ring. According to the CADD predictions the aryl substituent should contain hydrogen bond acceptor group such as ketone, amide or sulphonamide. To prepare such analogues, Suzuki-Miyaura reaction of 7-bromoquinazolin-2-amine **204** with arylboronic acids **210** or the corresponding pinacolates **211** were used to attach the arylgroup at the required position of 2-aminoquinazoline (Scheme 49). Using this approach, small library of the compounds **212a-o** was synthesized (Table 3).



Scheme 49. Synthesis of 7-aryl 2-aminoquinazolines from 7-bromoquinazolin-2-amine **204**. Reaction conditions: *a)* 5 mol% $PdCl_2(dppf)$, 2.5 equiv. Na_2CO_3, dioxane:H_2O 5:1, 100 °C, 16 h.

Table 3. Starting boronic acids and products **212a-o** of the Suzuki-Miyaura reaction

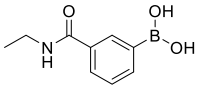
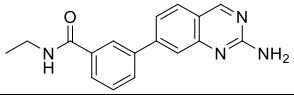
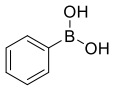
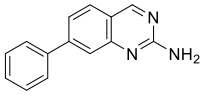
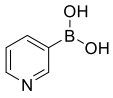
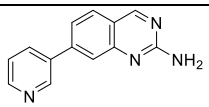
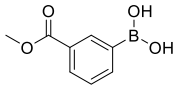
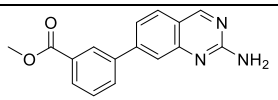
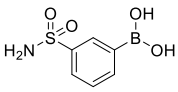
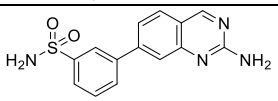
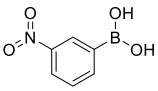
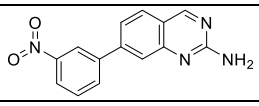
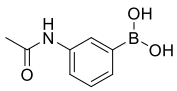
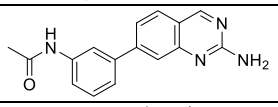
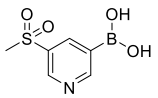
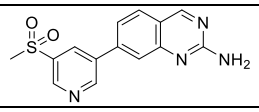
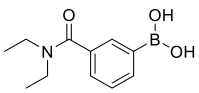
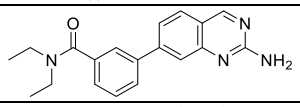
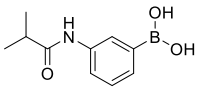
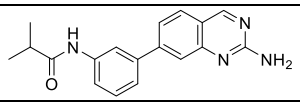
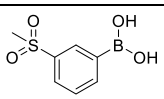
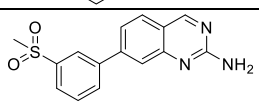
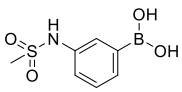
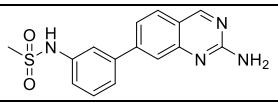
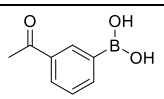
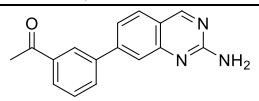
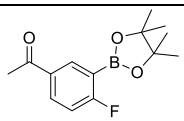
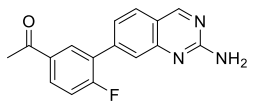
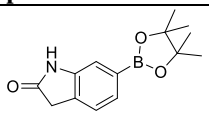
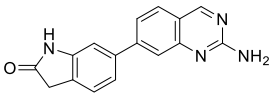
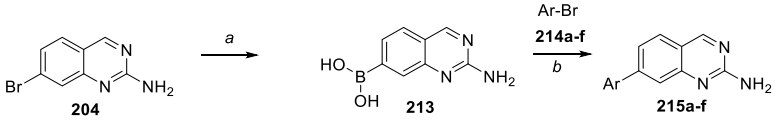
Number	Boronic acid 210a-m, or pinacolate 211a-b	Product	Yield, %
212a			quant.
212b			64
212c			46
212d			82
212e			76
212f			77
212g			78
212h			91
212i			60
212j			55
212k			67
212l			40
212m			30
212n			52

Table 3 (continuous)

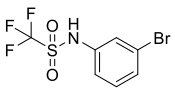
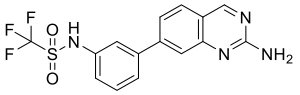
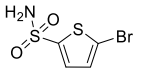
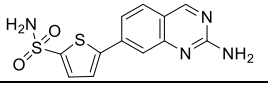
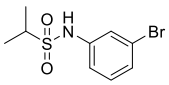
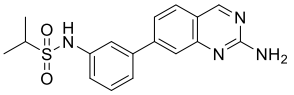
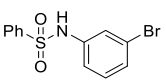
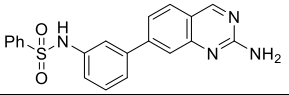
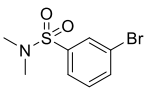
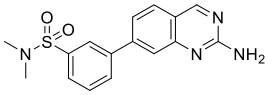
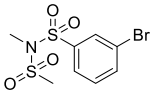
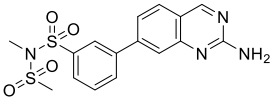
Number	Boronic acid 219a-m, or pinacolate 220a-b	Product	Yield, %
212o			52

To expand the range of synthesized compounds, a boronic acid building block **213** was prepared from 7-bromoquinazolin-2-amine **204**. Then it was used to prepare aryl-substituted 2-aminoquinazolines by the coupling with wide variety of readily available aryl bromides (Scheme 50, Table 4).



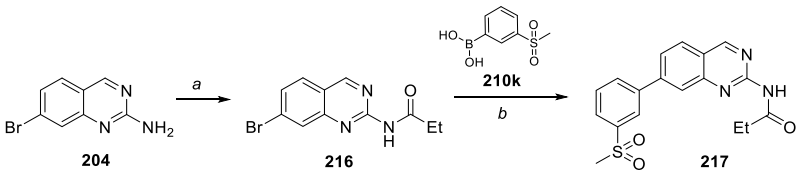
Scheme 50 Synthesis and Suzuki-Miyaura reaction with (2-aminoquinazolin-7-yl)boronic acid **213**.
Reaction conditios: *a)* 3 mol% $PdCl_2$(dppf), 1.5 equiv. $(BPin)_2$, 3 equiv. KOAc, dioxane, 100 °C, 12 h, 76%; *b)* 5 mol% $PdCl_2$(dppf), 2.5 equiv. Na_2CO_3, dioxane:H_2O 5:1, 100 °C, 16 h.

Table 4. Starting aryl bromides and products of the Suzuki-Miyaura coupling reaction

Number	Aryl bromides 214a-f	Product	Yield, %
215a			22
215b			73
215c			29
215d			45
215e			37
215f			41

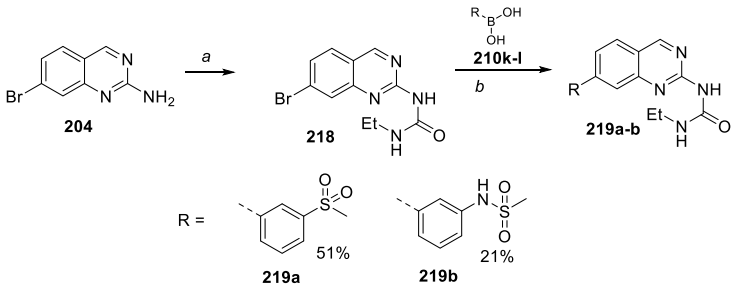
An additional modifications of 2-aminoquinazoline scaffold were performed based on CADD predictions which revealed possibility to increase the affinity of the compounds through the acylation of amino group of 2-aminoquinazoline. To check the hypothesis, the

corresponding *N*-acylated derivative of 7-bromoquinazolin-2-amine **216** was obtained (Scheme 51). Amide **216** was further subjected to the Suzuki-Miyaura coupling providing the target compound **217**.



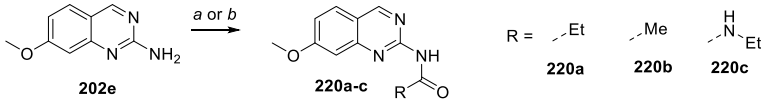
Scheme 51. Acylation of 7-bromoquinazolin-2-amine **204** and Suzuki-Miyaura reaction towards **217**.
Reaction conditions: *a)* 6 equiv. propionic anhydride, pyridine, 80 °C, 2 h, 74%; *b)* 3 mol% $PdCl_2$(dppf), 2 equiv. Na_2CO_3, dioxane:H_2O 5:1, 100 °C, 12 h, 37%.

In a similar way the reaction with ethyl isocyanate was used to prepare the corresponding ethylcarbamate **218** (Scheme 52). This was coupled with arylboronic acids **210k-l** to give the target compounds **219a-b**.



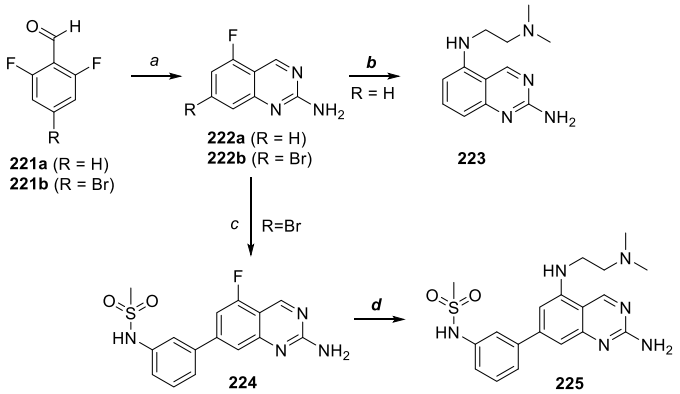
Scheme 52. Synthesis of ethylcarbamates **219a-b**.
Reaction conditions: *a)* 3 equiv. EtNCO, DMF, 100 °C, 12 h, quant.; *b)* 3 mol% $PdCl_2$(dppf), 2 equiv. Na_2CO_3, dioxane:H_2O 5:1, 100 °C, 12 h.

To have more clear picture of the influence of acylation of free NH_2 group of aminoquinazoline on its properties, one of the simplest compounds **202e** was acylated as well. Using propionic anhydride compound **220a** was made, and reaction with acetic anhydride leaded to compound **220b**. Analogously to compound **218**, ethylcarbamate **220c** was made using ethylisocyanate (Scheme 53).



Scheme 53. Synthesis of amides **220a-b** (procedure a) and ethylcarbamate **220c** (procedure b).
Reaction conditions: *a)* 4 equiv. acid anhydride, pyridine, 80 °C, 2 h, 36% for **220a** and 58% for **220b**; *b)* 6 equiv. EtNCO, DMF, 100 °C, 12 h, 90%.

In order to increase the solubility of aminoquinazoline type of compounds, *N*,*N*-dimethyl-1,2-ethanediamine was attached as a solubilizing group (Scheme 54). This particular derivatisation was chosen due to the fact that this is one of the smallest groups whish should not significantly influence binding of the compound. 5-Fluoroquinazolin-2-amines **222a-b** were made from 2,6-difluorobenzaldehydes **221a-b**. Nucleophilic aromatic replacement of fluorine in the condensation product **222a** with *N*,*N*-dimethyl-1,2-ethanediamine provided target compound **223**. More complex 2-aminoquinazoline **225** with aryl substituent on 7th position was prepared by coupling of bromoquinazoline **222b** with boronic acid **210l** followed by replacement of fluorine in intermediate **224**.



Scheme 54. Synthesis of 2-aminoquinazolines **223** and **225**.
Reaction conditions: *a)* 1.6 equiv. guanidine carbonate, 1.6 equiv Na_2CO_3, NMP, 145 °C, 12 h, 23% for **222a** and 14% for **222b**; *b) N*,*N*-dimethyl-1,2-ethanediamine, neat, 120 °C, 24 h, 70%; *c)* 1.2 equiv. **210l**, 3 mol% $PdCl_2$(dppf), 2 equiv. Na_2CO_3, dioxane:H_2O 5:1, 100 °C, 12 h, 58%; *d) N*,*N*-dimethyl-1,2-ethanediamine, neat, 120 °C, 24 h, 27%.

Crystallography studies showed that polar substituent on phenyl ring points towards proper point of the protein pocket to find additional interactions. Both of the structural units of CheA protein can effectively interact with **212k** by formation of additional hydrogen bonds with methylsulfone moiety (shown in superposition on Figure 10, A). Compounds **212l** and **212m** could form the same type of interactions (Figure 10, B).

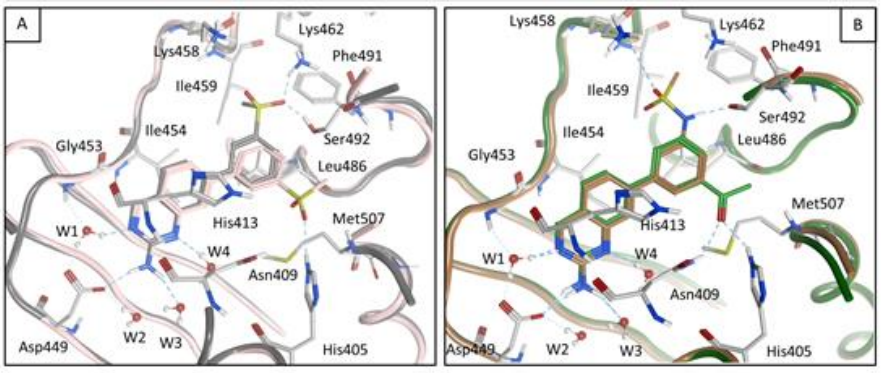


Figure 10. X-ray crystal structures of CheA in complex with **212k** (A) and **212l-m** (B).

The synthesized compounds **202a-e**, **207a-g**, **208a-b**, **209a-b**, **212a-o**, **215a-f**, **217**, **219a-b**, **223**, **225** were tested for their binding to bacterial proteins CheA, PhoR and HK853 using MST.[76] Again, as in the case of indazoles **181-183**, **188-190**, **199** compounds tests, human protein Hsp90 was used as the control. Results of the in vitro tests are depicted in Table 5 (the results are provided Anmol Adhav from IBV CSIC).

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2. Diphenylpyrazoles as antibacterials active against *S. Aureus*

In line with the search of new HK TCS inhibitors our attention was attracted by 3,4-diarylpyrazole based antibacterial compound series which was repurposed from compounds with anticancer activity acting as a heat shock protein 90 (Hsp90) inhibitors (Figure 17).[81] The antibacterial activity was proposed to be linked to the inhibition of bacterial histidine kinases by the binding of 3,4-diarylpyrazoles to ATP binding domain which share high similarity to the ATPase domain of eukaryotic Hsp90. The representative compound **226** displayed micromolar inhibition of histidine kinases *C. crescentus* CckA and *Salmonella* PhoQ and medium activity against certain Gram-negative and Gram-positive bacterial strains. Structurally similar hit **227** with good potency against *S. Aureus* was revealed in prof. J. Wells lab by screening of compounds libraries in antibacterial susceptibility tests.[82]

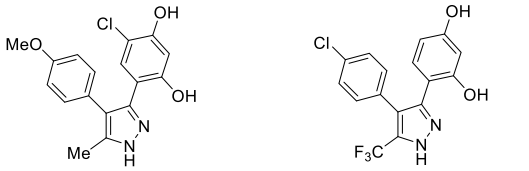
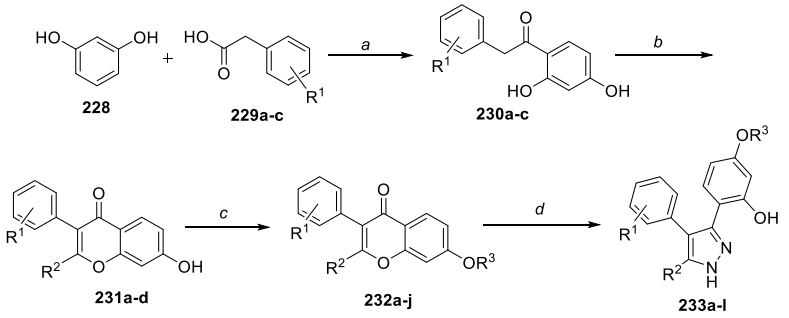


Figure 17. Pyrazole-based antimicrobials **226** and **227**.

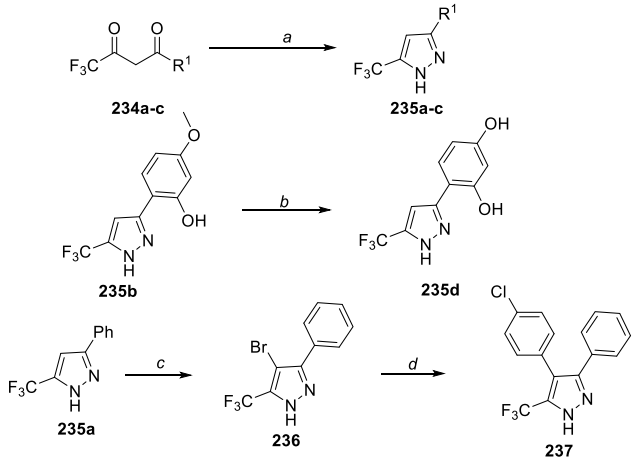
To explore the potential of 3,4-diarylpyrazoles as antibacterial compounds series of compounds were made according to the general Scheme 55. The key intermediates for the synthesis of 3,4-diarylpyrazoles **233a-l** were isoflavones **232a-j**.[83] These were synthesized form readily available resorcinol **228** and phenylacetic acid derivatives **229a-c** in two steps.[83b,84] The first step included Friedel-Crafts acylation of resorcinol **228**, catalysed by boron trifluoride diethyl etherate. The resulting acylresorcinols **230a-c** underwent condensation with acid anhydride followed by the cyclization to give isoflavones **231a-d**. O-Alkylation provided isoflavone derivatives **232a-j** which were condensed with hydrazine to provide the novel target compounds **233a-l**.



Scheme 55. Synthesis of 3,4-diarylpyrazoles **233a-l**.
Reaction conditions: *a)* 3 equiv. $BF_3 \cdot Et_2O$, PhMe, 100 °C, 2 h, 55-78%; *b)* 4 equiv. $(R^2CO)_2O$, pyridine, 25 °C, 16 h, 19-79%; *c)* 1.5-4 equiv. R^3Hal, 2 equiv. K_2CO_3, DMF, 25- 60 °C, 25-98%; *d)* $N_2H_4 \cdot H_2O$, EtOH, 90 °C, 3 h, 62-97%.

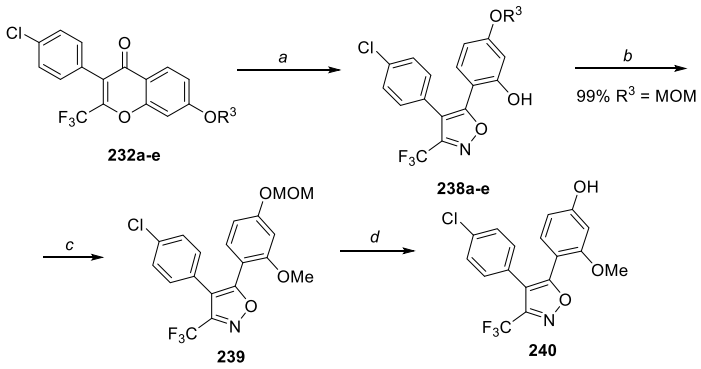
Furthermore, to check importance of each part of the molecule, series of derivatives with changed or removed substructures were synthesized.

Synthesis of previously reported monoaryl pyrazoles **235a,c** and novel **235b,d** was achieved by the condensation of diketones **234a-c** with hydrazine (Scheme 56). One of the monoaryl pyrazoles, compound **235a**, was further brominated to obtain bromo derivative **236** which was subjected to Suzuki-Miyaura coupling to provide the novel diaryl pyrazole **237** (Scheme 56).



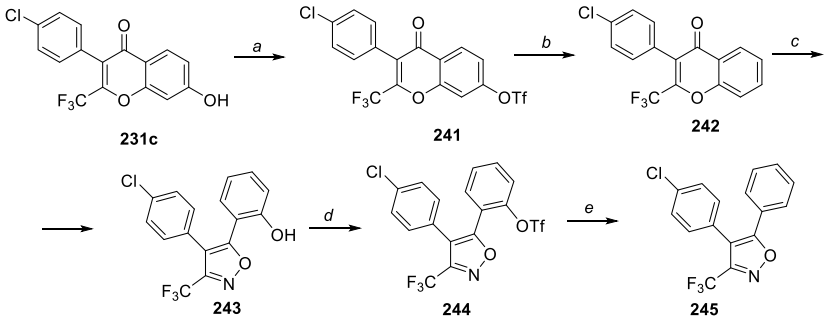
Scheme 56. Synthesis 3-aryl and 3,4-diarylpyrazoles **235a-d**, **237**.
Reaction conditions: *a)* $N_2H_4 \cdot H_2O$, EtOH, 90 °C, 3 h, 65-91%; *b)* 4 equiv. BBr_3, DCM, 0 °C, 1 h, 14%; *c)* 2 equiv. NBS, DMF, 75 °C, 5 h, 50%; *d)* 6 mol% $PdCl_2(PPh_3)_2$, 1.3 equiv. 4-chlorophenylboronic acid, 2.6 equiv. Cs_2CO_3, dioxane:H_2O 4:1, 100 °C, 16 h, 26%.

Additionally, a possibility to replace the pyrazole core with isoxazole moiety was explored. Novel isoxazole based analogues **247a-e**, **248**, and **249** were obtained from isoflavone derivatives **232a-e** (Scheme 57). Their reaction with hydroxylamine provided isoxazoles **238a-e**.[85] *O*-MOM protected product **238c** was methylated at the free phenolic OH group and the resulting derivative **239** was subjected to MOM deprotection in acid media to obtain isoxazole **240**.



Scheme 57. Synthesis of 4,5-diarylisoxazoles **238a-e**, **239**, **240**.
Reaction conditions: *a)* 2 equiv. $NH_2OH{\cdot}HCl$, pyridine, 100 °C, 16 h, 63-97%; *b)* 3 equiv. MeI, 2.5 equiv. K_2CO_3, DMF, 2 h, 99%; *c)* 4 equiv. 12 M HCl, MeOH, 60 °C, 3 h, 96%.

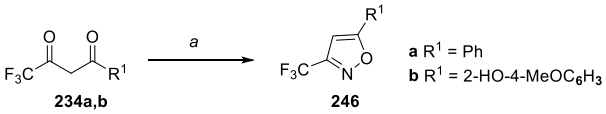
New de-oxygenated diaryloxazole analogues **243** and **245** were prepared starting from isoflavone derivative **231c** (Scheme 58). This was transformed to triflate **241** in which the C-O bond was cleaved under palladium-catalyzed hydrogenolysis conditions using triethylsilane as a hydrogen transfer reagent.



Scheme 58. Synthesis of 4,5-diarylisoxazoles **243** and **245**.
Reaction conditions: *a)* 1.1 equiv. trifluoromethanesulfonic anhydride, 2 equiv. TEA, DCM, 0 °C, 2 h, 95%; *b)* 5 mol% $PdCl_2(PPh_3)_2$, 2.5 equiv. Et_3SiH, DMF, 60 °C, 30 min, 58%; *c)* 2 equiv. $NH_2OH{\cdot}HCl$, Pyridine, 100 °C, 16 h, 99%; *d)* 1.4 equiv. trifluoromethanesulfonic anhydride, 2 equiv. TEA, DCM, 0 °C, 30 min, 97%; *e)* 5 mol% $PdCl_2(PPh_3)_2$, 2.5 equiv. Et_3SiH, DMF, 60 °C, 30 min, 72%.

The resulting isoflavone derivative **242** was converted to isoxazole **243**. It was then transformed to the triflate **244** which was reduced to give the product **245**.

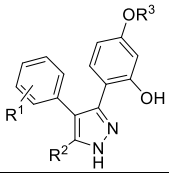
Previously reported isoxazole **246a**[86] and the novel isoxazole **246b** without a substituent at the 4th position of the heterocycle were prepared starting from diketones **234a,b** (Scheme 59).



Scheme 59. Synthesis of 4,5-diarylisoxazoles **246a,b**.
Reaction conditions: *a)* 2 equiv. $NH_2OH \cdot HCl$, EtOH, 90 °C, 16 h, then 4 equiv. H_2SO_4, AcOH, 2 h, 100 °C, 38-63%.

All of the synthesized compounds **233a-l**, **235a-d**, **237**, **238a-e**, **240**, **243**, **245**, **246a,b** were subjected to *in vitro* growth inhibition tests of *S. aureus* str. Newman. The results of these tests are summarized in Tables 7-11.

Table 7. Antibacterial activity of the compounds **233a-l**



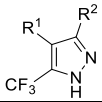
Entry	Number	R^1	R^2	R^3	MIC[a], µg/mL
1	**233a**	4-Cl	Me	H	25
2	**233b**	4-Cl	CF_3	Me	3.12
3	**233c**	H	CF_3	Me	12.5
4	**233d**	4-OMe	CF_3	Me	12.5
5	**233e**	4-Cl	CF_3	Bn	1.56
6	**233f**	H	CF_3	Bn	1.56
7	**233g**	4-Cl	CF_3	MOM	3.12
8	**233h**	4-Cl	CF_3	2,5-Cl-$C_6H_3CH_2$	1.56
9	**233i**	4-Cl	CF_3	4-Br- $C_6H_4CH_2$	1.56
10	**233j**	4-Cl	CF_3	$PhSO_2$-	1.56
11	**233k**	4-Cl	CF_3	*i*-Pr	0.78
12	**233l**	4-Cl	CF_3	*i*-Amyl	<0.39

[a]*Staphylococcus aureus Newman*

Compound with methyl group as R^2 substituent (**233a**; Table 7, entry 1) exhibited fourfold lower potency compared to the original hit **227**. An improvement of the antibacterial potency was achieved by addition of methyl group as R^3 substituent` (**233b**; Table 7, entry 3). Replacement of 4-chlorophenyl with phenyl group as R^1 substituent

(**233c**; Table 7, entry 4) or 4-methoxyphenyl group (**233d**; Table 7, entry 4) slightly decreased the antibacterial potency. However, *O*-benzyl group as R^3 substituent had a positive effect to antibacterial potency (**233e**, **233f**; Table 7, entries 5,6). Curiously, in the case of compounds **233e** and **233f**, the difference in R^1 substitution did not affect MIC values which were retained around 1.56 µg/mL for both of the compounds. MOM group as R^3 substituent (**233g**; Table 7, entry 7) only slightly increased activity in comparison with hit compound **227**. Substitution of benzyl group with 2,5-dichlorobenzyl (**233h**; Table 7, entry 8), 4-bromobenzyl (**233i**; Table 7, entry 9) and phenylsulfonyl (**233j**; Table 7, entry 10) group did not change the activity of the compounds in comparison with the benzyl analogue **233e**. The best antimicrobial activity in this series was exhibited by the compounds bearing lipophilic R^3 substituents such as *iso*-propyl group (**233k,** Table 7, entry 11) and *iso*-amyl group (**233l** Table 7, entry 12).

Table 8. Antibacterial activity of the compounds **235a-d**, **237**

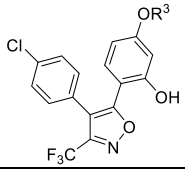


Entry	Number	R^1	R^2	MIC[a], µg/mL
1	**235a**	H	Ph	50
2	**235b**	H	2-HO-4-MeO-C_6H_3	25
3	**235c**	H	2-HO-C_6H_4	125
4	**235d**	H	2,4-di-HO-C_6H_3	250
5	**237**	4-ClC_6H_4	Ph	1.56

[a]*Staphylococcus aureus Newman*

Derivatives **235a-d** lacking substituents at the 4th position of pyrazole showed significantly worse results in comparison with the hit compound **227** (Table 8, entries 1-4). However, compound **237** with 4-chlorophenyl group as R^1 substituent and phenyl group as R^2 substituent exhibited activity four times higher than compound **227** (Table 8, entry 5). These results point to the importance of the two aryl substituents at the pyrazole to ensure high antimicrobial potency. In addition, the high antimicrobial potency of compound **237** implies that hydroxyl groups at the phenyl group as the R^1 substituent are not essential.

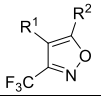
Table 9. Antibacterial activity of isoxazole-based compounds **238a-e**



Entry	Number	R^3	MIC[a], μg/mL
1	**238a**	H	3.12
2	**238b**	Bn	0.78
3	**238c**	MOM	3.12
4	**238d**	*i*-Pr	0.78
5	**238e**	*i*-Amyl	<0.39

[a]*Staphylococcus aureus Newman*

Table 10. Antibacterial activity of simplified isoxazole-based compounds **240**, **243**, **245**, **246a,b**



Entry	Number	R^1	R^2	MIC[a], μg/mL
1	**246a**	H	Ph	*inactive*
2	**246b**	H	2-HO-4-MeO-C_6H_3	6.25
3	**240**	4-ClC_6H_4	2-MeO-4-HO-C_6H_3	3.12
4	**243**	4-ClC_6H_4	2-HO-C_6H_4	3.12
5	**245**	4-ClC_6H_4	Ph	*inactive*

[a]*Staphylococcus aureus Newman*

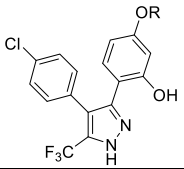
The isoxazole analogues **238a-d** (Table 9) showed similar potency and structure activity relationships to their pyrazole peers **227, 233e, 233g, 233k, 233l**, respectively (Table 7). An interesting deviation was observed for isoxazoles **240**, **243**, **245** and **246a,b** (Table 10) Compound **246a**, contrary to its pyrazole-based analogue **235a**, completely lost activity against *S. Aureus*. Compound **246b** increased activity level in comparison with **235b**. Surprisingly, methylation of ortho hydroxy group in R^2 substituent (compound **240**, Table 10, entry 3) did not affected MIC value - it was retained at 3.12 μg/mL. Finally, compound **245** totally lost the antimicrobial potency (Table10, entry 5) in comparison with pyrazole derivative **237** with the same substitution pattern (Table 8).

The SAR of the compounds provides the directions for further structural improvements to achieve more potent phenylazole based antimicrobials. Thus, introduction of the lipophilic groups at the 5th position of phenolic ring of the molecule increased the potency of the compounds (**233k**, **233l**). Further increase of lipophilicity in these positions could increase the potency. Additionally, further work should explore

another suitable 5-membered cycles such as imidazole, 1,2,3-triazole or isothiazole as scaffolds to improve the potency of the compounds. Nevertheless, the SAR of the pairs of the compounds **243** and **245**, or **237** and **245** implies that at least one NH or OH group shall be retained in the inhibitor to preserve its potency.

Autophosphorylation inhibition assay in pair with PhoR and EnvZ proteins revealed that only diarylpyrazole **233b** with small substituents had high micromolar IC_{50} values (Table 11, Entry 1). For the most active in bacterial growth inhibition tests compounds **233e,k,l** IC_{50} range lays above 2 mM (Table 11, Entries 2-4).

Table 11. IC_{50} values of the compounds **233b,e,k,l**



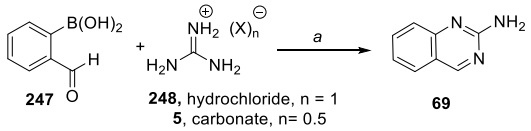
Entry	Number	R	IC_{50} PhoR, μM	IC_{50} EnvZ, μM
1	**233b**	Me	55	98
2	**233e**	Bn	>2000	>2000
3	**233k**	*i*-Pr	>2000	>2000
4	**233l**	*i*-Amyl	>2000	>2000

This data convincing that antibacterial activity of the diarylpyrazoles connected with mechanism different from inhibition of two-component systems.

3. New method for synthesis of 2-aminoquinazoline from 2-formylphenylboronic acids and guanidines

Facing with problems during the synthesis of proposed by CADD 2-aminoquinazoline-based structures, we looked for possibilities to find a mild and an efficient process to assemble 2-aminoquinazoline core.

The Chan-Evans-Lam coupling[87] is an attractive C-N bond forming reaction as it can be done under relatively mild copper catalyzed conditions and tolerates alcoholic solvents. We explored if the Chan-Evans-Lam coupling can be applied also for the synthesis of aminoquinazolines at mild reaction conditions using readily available reagents (Table 12). The screening of the reaction conditions was performed for the synthesis of unsubstituted 2-aminoquinazoline **69** from boronic acid **247** and guanidine hydrochloride **248**. The representative results are given in Table 12. Due to the polarity of the product **69**, its purification by chromatography was difficult. Therefore, it was purified by trituration from ethyl acetate. Identical scale and the workup was applied for all experiments in order to compare the efficiency of other reaction parameters. Methanol as a reaction solvent, CuI as a catalyst, and KOH as a base were found to be productive conditions for 2-aminoquinazoline **69** formation from boronic acid **247** and



247 **248,** hydrochloride, n = 1
5, carbonate, n= 0.5 **69**

Scheme 60. Synthesis of aminoquinazoline **69**. Reaction conditions: *a)* see conditions in Table 12.

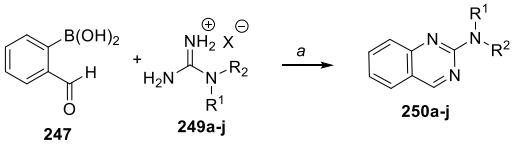
Table 12 Chan-Evans-Lam conditions for the synthesis of 2-aminoquinazoline **69**

Entry	Solvent[a], t°	248 or 5, equiv.	Catalyst, mol%	Base, eq	Yield, %
1	MeOH, 70 °C	**248**, 1.5	CuI, 15	K_2CO_3, 2.5	31
2	MeOH, 70 °C	**248**, 2.5	CuI, 15	K_2CO_3, 3	44
3	MeOH, 70 °C	**248**, 2.5	$Cu(OAc)_2$, 15	K_2CO_3, 3	35
4	MeOH, 70 °C	**248**, 2.5	CuCl,15	K_2CO_3, 3	23
5	MeOH, 70 °C	**248**, 1.5	CuI, 15	KOH, 1.5	34
6	MeOH, 70 °C	**248**,3	CuI,15	KOH, 3	**51 (65)**[c]
7	EtOH, 90 °C	**248**, 3	CuI,15	KOH, 3	52
8	MeOH, 70 °C	**5**, 3	CuI, 15	-	13
9	MeOH, 70 °C	**5**,1.5	CuI,15	KOH, 3	17

[a]Reactions were performed open to air, reaction time 12-17 h; [b]The product **69** purified by trituration with EtOAc to reach purity 98+% [c]NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

guanidine hydrochloride **248** (Table 12, entries 1,2). Excess of base and guanidine was beneficial to improve the yield of product **69** (Table 12, entry 2). Other copper catalysts

such as CuCl and $Cu(OAc)_2$ were found to be less efficient (Table 12, entries 3,4). The use of KOH as base improved the yield of product **69** when excess of guanidine was used (Table 12, entries 5,6). EtOH could also be successfully used as the reaction solvent (Table 12, entry 7). Guanidine carbonate **5** was explored as the reaction partner, however, this provided reduced yield of quinazoline **69** (Table 12, Entries 8,9). 2-Formylphenylboronic acid **247** was subjected to the reaction with the range of guanidines under the most productive reaction conditions (Table 12, entry 6). Both *N*-monosubstituted guanidines **249a-g** and *N*,*N*-disubstituted guanidines **249h-j** provided 2-aminoquinazolines **250a-j** in fair yields (Table 13).

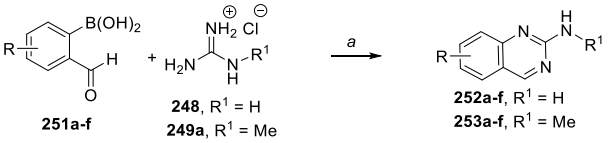


Scheme 61. Synthesis of aminoquinazolines **250a-j**.
Reaction conditions: *a)* 15 mol% CuI, 3 equiv. KOH, MeOH, 70 °C, 12 h.

Table 13. Guanidine scope for the synthesis of aminoquinazolines

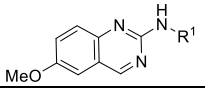
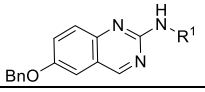
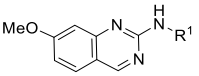
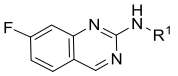
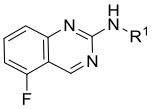
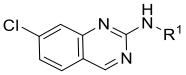
Entry	249[a]	R^1	R^2	250, yield %[b]
1	**249a**	H	Me	**250a**, 63
2	**249b**	H	Ph	**250b**, 56
3	**249c**	H	$PhCH_2$	**250c**, 66[c]
4	**249d**	H	$Ph(CH_2)_2$	**250d**, 52
5	**249e**	H	*n*-Pent	**250e**, 54
6	**249f**	H	*cy*-Pent	**250f**, 55
7	**249g**	H	*cy*-Hex	**250g**, 37
8	**249h**	Me	Me	**250h**, 43
9	**249i**	$-(CH_2)_4-$		**250i**, 47
10	**249j**	$-(CH_2)_2-O-(CH_2)_2-$		**250j**, 39

[a]Guanidines **249a,c-g, i,j** used as hydrochlorides, **249b** as carbonate, **249h** as sulphate [b]Purified by column chromatography if not stated otherwise. [c]Purified by trituration with EtOAc.



Scheme 62. Synthesis of aminoquinazolines **252a-f**, **253a-f**.
Reaction conditions: *a)* 15 mol% CuI, 3 equiv. KOH, MeOH, 70 °C, 12 h.

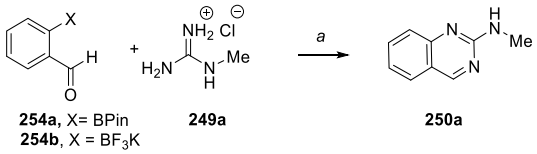
Table 14. Boronic acid scope for the synthesis of aminoquinazolines

Entry	Boronic acid 251	Product	252 or 253, Yield, %[a]
1	**251a**, R = 4-MeO		**252a**, 55
2			**253a**, 59[b]
3	**251b**, R = 4-BnO		**252b**, 32 (53)[c]
4			**253b**, 57[b]
5	**251c**, R = 5-MeO		**252c**, 17 (53)[c]
6			**253c**, 48[b]
7	**251d**, R = 5-F		**252d**, 36 (45)[c]
8			**253d**, 52[b]
9	**251e**, R = 3-F		**252e**, 52
10			**253e**, 46[b]
11	**251f**, R = 5-Cl		**252f**, 35
12			**253f**, 55[b]

[a]Purified by trituration with EtOAc if not stated otherwise. [b]Purified by column chromatography. [c]NMR yield using 1,3,5-trimethoxy benzene as an internal standard.

Several 2-formylphenylboronic acids **251a-f** were explored as substrates for the synthesis of amino quinazolines **252a-f** and **253a-f** (Table 14). Both guanidines **248** and **249a** gave the expected products, however the isolated yields in most cases were somewhat higher in the case of *N*-methylsubtituted guanidine **249a** (Table 14, entries 3 *vs* 4, 5 *vs* 6, 7 *vs* 8).

Boronic acid derivatives such as pinacolate ester **254a** and trifluoroborate **254b** were also competent substrates providing aminoquinazoline derivative **250a** in yields comparable to boronic acid **247** (Scheme 63). These results complement relatively few cases of the use of boronic acid derivatives as partners for Chan-Evans-Lam coupling.[88]

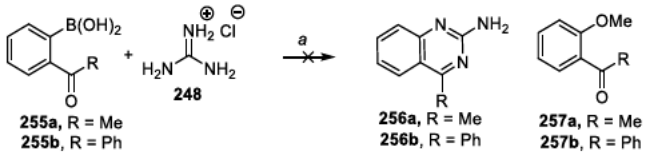


254a, X= BPin
254b, X = BF_3K **249a** **250a**

Scheme 63 Synthesis of 2-aminoquinazoline **250a** from boronic acid ester **254a** and trifluoroborate **254b**.
Reaction conditions: *a)* 15 mol% CuI, 3 equiv. KOH, MeOH, 70 °C, 12 h, 58% from pinacolate **254a**, 51% from trifluoroborate **254b**.

In contrast, boronic acids **255a,b** bearing a keto group were found to be unsuitable reaction partners for the synthesis of quinazolines **256a,b** (Scheme 64). In the case of

these substrates, complex mixtures were obtained with *O*-arylation products **257a,b** as the only identified by-products. The failure of 2-acyl-phenyl boronic acids **255a,b** to give the expected products imply that, for the synthesis of aminoquinozolines **69, 250, 252, 253** arylidene guanidine formation is the first step followed by intramolecular arylation



255a, R = Me
255b, R = Ph

256a, R = Me
256b, R = Ph

257a, R = Me
257b, R = Ph

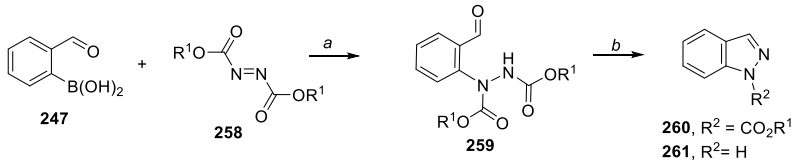
Scheme 64 An attempt to condense the keto group containing boronic acids **255a,b** with guanidine **248**.
Reaction conditions: *a)* 15 mol% CuI, 3 equiv. KOH, MeOH, 70 °C, 12 h.

In summary, the method of synthesis of 2-aminoquinazolines we proposed, is much more attractive than the traditional ones. Relatively mild reaction conditions enable the use of this method for the synthesis of pharmacologically relevant compounds bearing 2-aminoquinozaline scaffold. The drawback of such approach is relatively low availability of 2-formylphenyl-boronic acids from the commercial sources.

4. New method for synthesis of indazoles from 2-formylphenylboronic acids and azodicarboxylates or hydrazine dicarboxylates

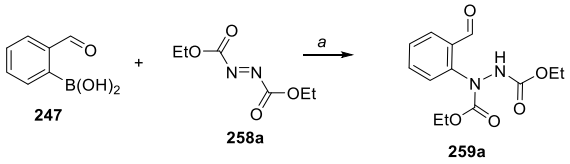
Inspired by the application of 2-formylphenylboronic acids for the construction of 2-aminoquinazolines we aimed to expand the use of these building blocks for assembly of indazole core.

Initial attempts to synthesize indazole starting from 2-formylphenylboronic acid and hydrazine hydrate under copper-catalyzed conditions failed. Next, we tried a stepwise protocol based on the work of Uemura and Chatani[89] who have reported that phenylboronic acids undergo smooth reaction with azodicarboxylates providing arylhydrazine derivatives. Using 2-formylphenylboronic acid **247** as substrate, the addition to N=N bond in azadicarboxylates **258** would give *N*-arylhydrazine intermediate **259** which could be further transformed to indazoles **260** and **261** (Scheme 65).



Scheme 65. Indazole synthesis from 2-formylphenylboronic acid **247**.
Reaction conditions: *a)* Cu (II) catalyst; *b)* acid ($R^2 = CO_2R^1$) or base ($R^2 = H$).

The investigation of the arylation conditions was performed for the reaction of 2-formylphenylboronic acid **247** with diethylazodicarboxylate (DEAD, **258a**) using $Cu(OAc)_2$ as a catalyst in a range of solvents (Table 15, entries 1-9). Solvents such as MeCN, DMF and DMA were found to be appropriate to obtain the product **259** in a good yield (Table 15, entries 5-6). Decreased catalyst loading was also possible using DMA as a solvent without affecting the product **259a** yield (Table 15, entries 7-9). Range of other copper sources was investigated (Table 15, entries 10-14). $CuCl_2$ $Cu(OTf)_2$ $Cu(acac)_2$ performed as efficient catalysts for C-N bond formation giving the product **259a** in high yield (Table 15, entries 10-12). Copper (I) source such as CuCl proved to be ineffective catalyst, while catalytic amount of CuI enabled product **259a** formation in good yield (Table 15, entries 13,14).



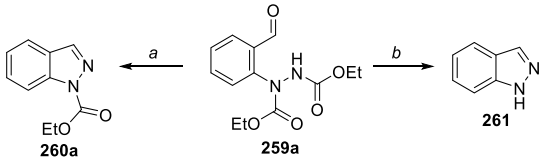
Scheme 66: Synthesis of hydrazine dicarboxylate **259a**.
Reaction conditions: *a)* see conditions in Table 15.

Table 15 Conditions for the arylation of DEAD **258a**

Entry	Copper catalyst	Solvent	Yield, %
1	20 mol% $Cu(OAc)_2$	MeOH[a]	0
2	20 mol% $Cu(OAc)_2$	PhMe	0
3	20 mol% $Cu(OAc)_2$	THF	64
4	20 mol% $Cu(OAc)_2$	MeCN	80
5	20 mol% $Cu(OAc)_2$	DMF	83
6	20 mol% $Cu(OAc)_2$	DMA	98
7	15 mol% $Cu(OAc)_2$	DMA	98
8	10 mol% $Cu(OAc)_2$	DMA	98
9	5 mol% $Cu(OAc)_2$	DMA	96
10	10 mol% $CuCl_2$	DMA	94
11	10 mol% $Cu(OTf)_2$	DMA	99
12	10 mol% $Cu(acac)_2$	DMA	97
13	10 mol% CuCl	DMA	25
14	10 mol% CuI	DMA	93

[a]Violent DEAD decomposition observed;

Next, the conditions were investigated for the indazole ring closure using arylhydrazine **259a** (Table 16). Acidic reaction conditions enabled the condensation of arylhydrazine **259a** to 1*N*-etoxycarbonyl indazole **260a** (Table 16, entries 1-5). TFA in DCM and in MeCN gave the expected product **260a** in good yield (Table 16, entries 1, 2). Neat AcOH at r.t. did not enable the cyclization of arylhydrazine **259a**, while heating in a solution of MeCN induced formation of indazole **260a** (Table 16, entries 3, 4). Formic acid was strong enough to enable the formation of indazole **260a** at room temperature in a solution of MeCN (Table 16, entry 5).



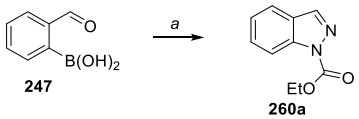
Scheme 67. Synthesis of indazoles **260a** and **261**.
Reaction conditions: *a)* acid-promoted cyclization (Table 16, entries 1-5); *b)* base-promoted cyclization (Table 16, entries 6-8)

Table 16. Cyclization of arylhydrazine **259a** to indazoles **260a** and **261**

Entry	Reagent	Solvent	Temp., time	Product	Yield, %
1	5 equiv. TFA	DCM	25 °C, 12 h	**260a**	63
2	5 equiv. TFA	MeCN	25 °C, 12 h	**260a**	64
3	AcOH	neat	r.t., 12 h	**260a**	0
4	30 equiv. AcOH	MeCN	70 °C, 12 h	**260a**	56
5	30 equiv HCOOH	MeCN	r.t., 12 h	**260a**	56
6	3 equiv. K_2CO_3	MeOH	70 °C, 1 h	**261**	67
7	3 equiv. K_2CO_3	MeOH	25 °C, 12 h	**261**	67
8	4 equiv. KOH	EtOH	r.t., 12 h	**261**	59

The use of a base in alcoholic solvent provided unprotected indazole **261** (Table 16, entries 6-8). Both K_2CO_3 and KOH could be efficiently used for the ring closure – deacylation reaction of arylhydrazine **259a**.

Next, the one pot formation of 1*N*-etoxycarbonyl indazole **260a** from 2-formylphenylboronic acid **247** was investigated (Table 17). Unfortunately, DMA which was the solvent of choice for high yielding arylation of DEAD was not suitable for the ring closure step in the presence of TFA (Table 17, entry 1). In this case, the arylhydrazine **259a** intermediate was not transformed to product **260a**, according to LC-MS. In turn, the addition of TFA in DCM in an amount to sufficiently dilute DMA, enabled the formation of expected product **260a** in a good yield (Table 17, entry 2). The use of DCM as a solvent for both steps was less productive (Table 17, entry 3). However, MeCN was found as an appropriate solvent for both arylation and ring closure in the presence of TFA to give 1*N*-protected indazole **260a** in a good overall yield (Table 17, entry 4).



247 **260a**

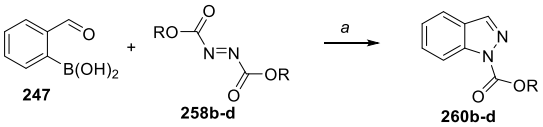
Scheme 68. Synthesis of indazole **260a**.
Reaction conditions: *a)* 1) 10 mol% $Cu(OAc)_2$, 1.5 equiv. DEAD, 25 °C, 18 h; 2) see Table 17 conditions.

Table 17. One-pot conversion of boronic acid **247** to indazole **260a**

Entry	Solvent	Conditions, step 2	Yield, %
1	DMA	10 equiv. TFA, 25 °C, 2 h	0
2	DMA	TFA:DCM 1:4[a], 25 °C, 2 h	73
3	DCM	5 equiv. TFA, 25 °C, 1 h	48
4	MeCN	5 equiv.TFA, 25 °C, 1 h	78

[a]3 mL of TFA/DCM mixture added per 1 mL of DMA

With one-pot conditions in hand, the synthesis of other alkoxycarbonylindazoles **260b-d** was performed by the reaction of boronic acid **247** with azodicarboxylates **258b-d** (Table 18). The best yield of product **260b** was obtained with diisopropyl azodicarboxylate (DIAD, **258b**, Table 4, entry 1).

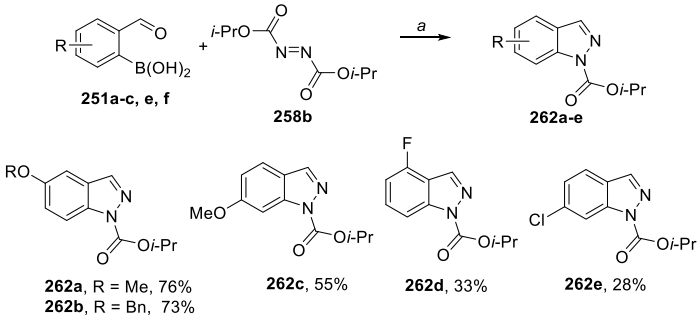


Scheme 69. Synthesis of indazoles **260b-d**.
Reaction conditions: *a)* 1) 20 mol% $Cu(OAc)_2$, MeCN, r.t., 18 h; 2) 5 equiv.TFA, r.t. 2 h.

Table 18. Azodicarboxylate **258b-d** scope for the synthesis of indazoles **260b-d**

Entry	R	Yield, %
1	*i*-Pr	**260b**, 86
2	Bn	**260c**, 60
3	*i*-Bu	**260d**, 45

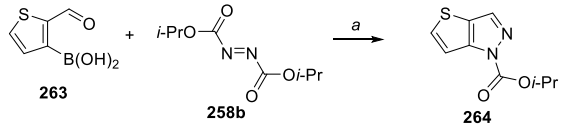
The scope of boronic acid substitution was investigated in the reaction of a range of formylboronic acids **251a-c,e,f** with DIAD **258b** followed by cyclization (Scheme 70). Substrates **251a-c** bearing methoxy and benzyloxy groups provided indazoles **262a-c** in a good to moderate yield. In the case of substrates **251e,f** bearing electron-withdrawing substituents, yields of products **262d,e** were decreased.



Scheme 70. The reaction of substituted formylboronic acids **251a-c,e,f** with DIAD **258b**.
Reaction conditions: *a)* 1) 20 mol% $Cu(OAc)_2$, MeCN, r.t., 18 h; 2) 5 equiv. TFA, r.t. 2 h.

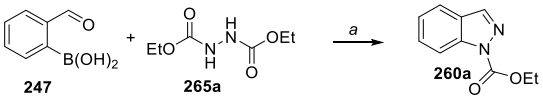
Thiophene boronic acid **263** was found a suitable substrate to obtain thienopyrazole derivative **264** in a good yield (Scheme 71).

Hydrazine dicarboxylate **265a** was also explored as a reagent for the synthesis of indazoles instead of azodicarboxylate **258a** (Table 19). 2-Formylphenylboronic acid **247**



Scheme 71. The reaction of tiophene boronic acid **263** with DIAD **258b**.
Reaction conditions: *a)* 1) 20 mol% $Cu(OAc)_2$, MeCN, r.t., 18 h; 2) 5 equiv. TFA, r.t. 2 h, 69%.

was subjected to the reaction with diethyl hydrazine dicarboxylate **265a** using the two-step one-pot procedure for the formation of indazole **260a**. A catalytic amount of $Cu(OAc)_2$ together with excess of triethylamine was not sufficient to achieve good yield of product **260a** formation (Table 19, entry 1). The use of equimolar amount of $Cu(OAc)_2$ and an excess of triethylamine for the first step enabled good yield of product **260a** over two steps, while increasing the amount of $Cu(OAc)_2$ reduced the yield of product **260a** (Table 19, entries 2,3). The transformation of 2-formylphenylboronic acid **247** to indazole **260a** was not efficient in the absence of base for the first step, however, TEA could be replaced by TMEDA and DIPEA without significantly reducing the product **260a** yield (Table 19, entries 5, 6). Several other Cu salts were tried for the first step of indazole **260a** formation, however, were found to be ineffective (Table 19, entries 7, 8). The need for an equimolar amount of $Cu(OAc)_2$ for successful synthesis of indazole **260a** using hydrazine dicarboxylate **265a** implies *in situ* oxidation of reagent **265a** to azodicarboxylate **258a**. However, *C-N* bond formation with hydrazine dicarboxylate **265a** in the Chan–Evans–Lam reaction cannot be excluded.[90]



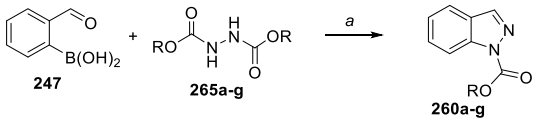
Scheme 72. Synthesis of indazole **260a** from hydrazine dicarboxylate **265a**.
Reaction conditions: *a)* 1) 2 equiv **265a**, MeCN, 25 °C, conditions Table 19; 2) 30 equiv TFA, 25 °C, 4 h.

Table 19. Synthesis of indazole using of hydrazine dicarboxylate **265a**

Entry	Catalyst	Additive	Yield[a], %
1	20 mol% $Cu(OAc)_2$	3 equiv. TEA	25
2	1 equiv. $Cu(OAc)_2$	3 equiv. TEA	66
3	1.5 equiv. $Cu(OAc)_2$	3 equiv. TEA	50
4	1 equiv. $Cu(OAc)_2$	none	26
5	1 equiv.$Cu(OAc)_2$	2 equiv. TMEDA	67
6	1 equiv. $Cu(OAc)_2$	3 equiv. DIPEA	60
7	1 equiv. CuCl	3 equiv. TEA	35
8	1 equiv.$CuCl_2$	3 equiv. TEA	25

[a]NMR yield, using 1,3,5-trimethoxybenzene as internal standard

Next, a range of hydrazine dicarboxylates **265a-g** was explored as reaction components for a one-pot two-step synthesis of indazoles **260a-g** (Table 20). TFA was a suitable acid for the cyclization step to give the corresponding products **260a-f** from the reaction of boronic acid **247** with hydrazine dicarboxylates **265a-f** (Table 20, entries 1-6). For the synthesis of product **265g** bearing acid labile t-Bu group, acetic acid at elevated temperature was used instead of TFA (Table 20, entry 7). This approach successfully provided product **260g** in a very good yield (Table 20, entry 7).



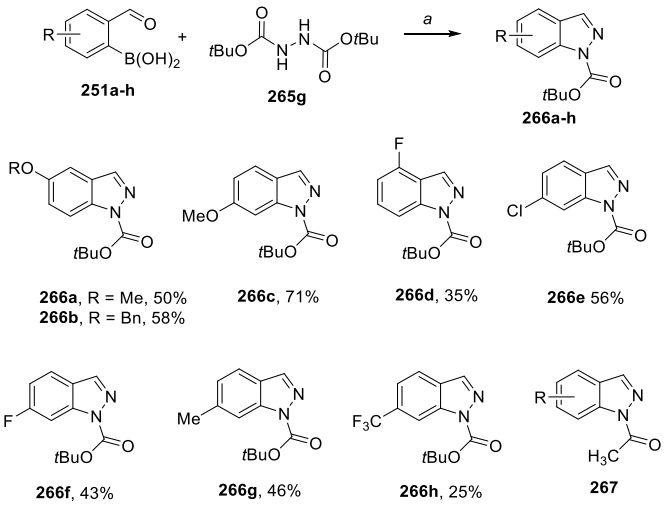
Scheme 73. Synthesis of indazoles **260a-g**.
Reaction conditions: *a)* 1) 1 equiv. $Cu(OAc)_2$, 3 equiv. TMEDA, 18 h, 25 °C; 2) 30 equiv. TFA, 25 °C, 4 h (**260a-f**) or 30 equiv. AcOH, 50 °C, 2 h (**260g**).

Table 20. Hydrazine dicarboxylate **265a-g** scope for the synthesis of indazoles **260a-g**

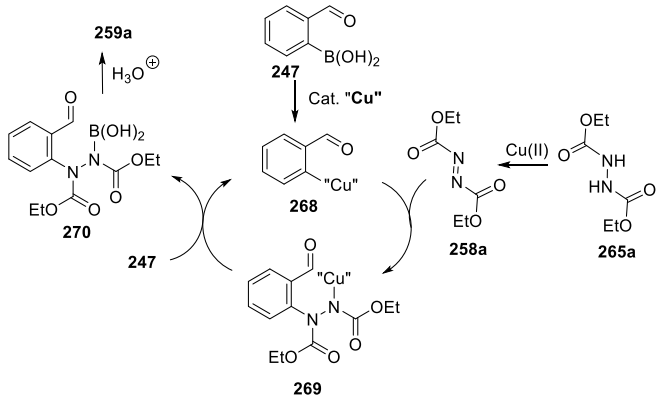
Entry	265, R	Acid	Yield, %
1	**265a**, Et	TFA	**260a,** 63
2	**265b**, i-Pr	TFA	**260b**, 47
3	**265c**, Bn	TFA	**260c**, 46
4	**265d**, i-Bu	TFA	**260d**, 61
5	**265e**, Me	TFA	**260e**, 63
6	**265f**, Allyl	TFA	**260f**, 40
7	**265g**, t-Bu	AcOH	**260g**, 73

The scope of phenyl boronic acids **251a-h** was explored with di-tert-butyl hydrazine dicarboxylate **265g** as a reaction component for the synthesis of 1*N*-Boc indazoles **266a-h** (Scheme 74). The major reason for the yields reduction was formation of *N*-acetyl indazoles **267** as by-products.

The mechanism for the C-N bond formation in the copper catalysed reaction of arylboronic acids with diazadicarboxylates has been proposed by Uemura and Chatani.[89] According to this, the transmetalation reaction of arylboronic acid **247** with a copper catalyst would form an arylcopper species **268** (Scheme 75). Addition of intermediate **268** to N=N double bond gives an arylhydrazine **269** which undergoes the transmetalation with boronic acid **247** to give intermediate **270** and return arylcopper species **268** into catalytic cycle. Work-up would produce arylhydrazine **259a**. Noteworthy, it was shown by Uemura and Chatani that dialkoxycarbonyl hydrazines are not competent substrates for this reaction unless additional oxidant is added. This implies that hydrazine **265a** is likely oxidised to diazadicarboxylate **258a** by stoichiometric amount of copper source.

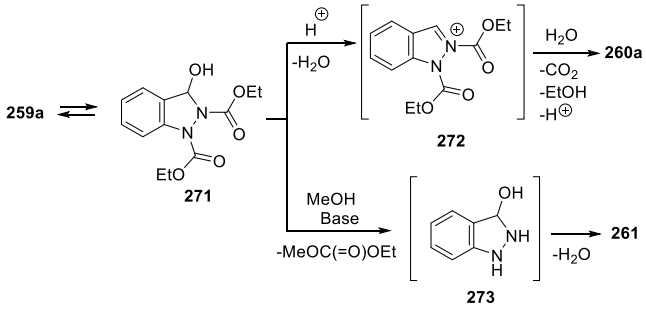


Scheme 74. Synthesis of indazoles **266a-h**.
Reaction conditions: *a)* 1) 1 equiv. $Cu(OAc)_2$, 3 equiv. TMEDA, 18 h, 25 °C; 2) 30 equiv. AcOH, 50 °C, 2 h.



Scheme 75. Proposed mechanism for the C-N bond forming step.

The proposed mechanism for the condensation of arylhydrazine intermediate into indazole is given in Scheme 76. In the presence of acid, *N*-acyliminium ion **272** is formed. Selective hydrolytic cleavage of one ethoxycarbonyl group in intermediate **272** gives 1*N*-ethoxycarbonyl indazole **260a**. In turn, basic conditions would enable cleavage of both ethoxycarbonyl groups leading to intermediate **273** which eliminates water to give indazole **261.**



Scheme 76. Proposed mechanism for the condensation step.

In summary, copper catalysed reaction of 2-formylphenylboronic acids with diazadicaboxylates followed by acid or base induced ring closure is a convenient method for the synthesis of 1*N*-alkoxycarbonyl indazole derivatives. The indazole synthesis can also be performed using hydrazine dicarboxylates as reaction partners for the synthesis of indazoles, however, required a stoichiometric amount of copper (II) acetate for the *C*-*N* bond formation step. The method is based on readily available building blocks and can be performed at relatively mild reaction conditions which enables its application for the synthesis of indazole motif containing compounds.

EXPERIMENTAL SECTION

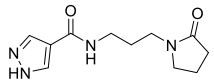
1. General information

Reagents and starting materials were obtained from commercial sources and used as received. The solvents were purified and dried by standard procedures prior to use. Flash chromatography was carried out using silica gel (230−400 mesh). NMR spectra were recorded on 300 and 400 MHz spectrometers with chemical shift values (δ) in parts per million using the residual chloroform, dimethylsulfoxide signal as the internal standard. LCMS spectra were recorded on UPLC Waters Acquity, column: Acquity UPLC BEH-C18, 1.7 μm, 2.1mm x 50 mm, column temperature (30.0±5.0) °C, gradient: 0.01% TFA in water/CH_3CN 90%/10% – 5%/95%; flow: 0.500 mL/min; time: 8 min; detector: PDA, 220 – 320 nm, SQ detector with an electrospray ion source (ESI/APCI). Exact molecular masses (HRMS) were determined on a hybrid quadrupole time-of-flight mass spectrometer equipped with an electrospray ion source.

2. Synthetic procedures and characterization data for the compounds 227-246 described in Annex I, compounds 250-253 - in Annex II, compounds 260-266 - in Annex III.

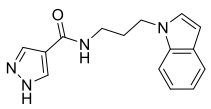
3. Synthetic procedures for compounds 148a-j, 150a-i, 151a-c, 153-170, 174, 176, 177a-c, 178a-b, 179a-b, 181a-b, 181-186, 187a-b, 188-199, 201a-d, 202a-d, 204, 206a-h, 208a-b, 209a-b, 212a-o, 213, 215a-f, 216-218, 219a-b, 220a-c, 222a-b, 223-225.

***N*-[3-(2-Oxopyrrolidin-1-yl)propyl]-1*H*-pyrazole-4-carboxamide (148a)**



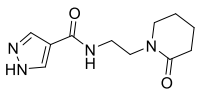
To a stirred solution of 1-(3-aminopropyl)pyrrolidin-2-one (279 mg, 1.1 equiv.) in dry MeCN (6 mL), 1*H*-pyrazole-4-carboxylic acid (200 mg, 1 equiv.) was added in one portion at 25 °C. At the same temperature were added TEA (497 μL, 2 equiv.) and HOBt (300 mg, 1.1 equiv.), followed by EDCI (513 mg, 1.5 equiv.). Resulting mixture was stirred for 16 h. After indicated time, product precipitated from MeCN. Precipitate was filtered, washed with two portions of MeCN (2×2 mL) and dried on air to give **148a** (393 mg, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (br. s, 1H), 8.10 (t, J = 5.7 Hz, 1H), 8.00 (s, 2H), 3.33 (t, J = 6.8 Hz, 2H), 3.18 (dt, J = 12.7, 6.5 Hz, 4H), 2.22 (t, J = 7.9 Hz, 2H), 2.00 – 1.82 (m, 2H), 1.72 – 1.56 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.6, 162.5, 138.7, 130.0, 118.1, 46.7, 36.4, 30.8, 27.2, 17.7 (one carbon is missing due to overlap with DMSO signal). HR-MS (ESI/TOF) calcd for $C_{11}H_{17}N_4O_2$ $[M+H]^+$ 237.1352, found 237.1353.

***N*-[3-(1*H*-Indol-1-yl)propyl]-1*H*-pyrazole-4-carboxamide (148b)**



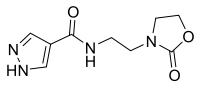
To a stirred solution of 3-(1*H*-indol-1-yl)propan-1-amine (200 mg, 1.1 equiv.) in dry MeCN (6 mL), 1*H*-pyrazole-4-carboxylic acid (141 mg, 1 equiv.) was added in one portion at 25 °C. At the same temperature were added TEA (320 µL, 2 equiv) and HOBt (211 mg, 1.1 equiv.), followed by EDCI (440 mg, 1.5 equiv.). Resulting mixture was stirred for 16 h. After indicated time, reaction mixture evaporated, partitioned between EtOAc (15 mL) and water (10 mL), organic layer washed with brine (10 mL) and dried over anhydrous Na_2SO_4 followed by evaporation in *vacuo*. Compound was purified by silica gel column chromatography using 5% MeOH in DCM to obtain product **155b** as a yellowish oil (50 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 3.1 Hz, 1H), 6.60 (t, *J* = 5.4 Hz, 1H), 6.41 (d, *J* = 3.1 Hz, 1H), 4.03 (t, *J* = 6.6 Hz, 2H), 3.21 (q, *J* = 6.4 Hz, 2H), 1.93 (p, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 135.7, 134.2, 128.7, 127.9, 121.7, 121.1, 119.6, 117.7, 109.4, 101.5, 50.4, 44.2, 37.4, 29.7. HR-MS (ESI/TOF) calcd for $C_{15}H_{17}N_4O$ $[M+H]^+$ 269.1402, found 269.1400.

***N*-[2-(2-Oxopiperidin-1-yl)ethyl]-1*H*-pyrazole-4-carboxamide (148c)**



Compound was prepared in analogues way as **148a** starting from 1-(2-aminoethyl)piperidin-2-one (250 mg, 1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (138 mg, 1.1 equiv.). Coupling reaction performed using TEA (624 µL, 4 equiv.), HOBt (206 mg, 1.2 equiv.) and EDCI (429 mg, 2 equiv.). Yield 103 mg (39%), white solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.99 (d, *J* = 39.0 Hz, 2H), 3.54 (s, 4H), 3.41 (t, *J* = 5.2 Hz, 2H), 2.30 (t, *J* = 5.9 Hz, 2H), 1.79 (s, 4H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 173.1, 165.6, 139.7, 131.1, 118.9, 38.0, 32.9, 24.0, 22.0 (two aliphatic carbons missing due to interference with CD_3OD signal). HR-MS (ESI/TOF) calcd for $C_{11}H_{17}N_4O_2$ $[M+H]^+$ 237.1352, found 237.1353.

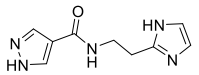
***N*-[2-(2-Oxooxazolidin-3-yl)ethyl]-1*H*-pyrazole-4-carboxamide (148d)**



Compound was prepared in analogues way as **148a** starting from 3-(2-aminoethyl)oxazolidin-2-one (250 mg, 1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (185 mg, 1.1 equiv.). Coupling reaction performed using TEA (837 µL, 4 equiv.), HOBt (275.74 mg, 1.2 equiv.) and EDCI (575 mg, 2 equiv.). Yield 121 mg (36%), white solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.01 (d, *J* = 66.1 Hz, 2H), 4.56 – 4.11 (m, 2H), 3.91 – 3.62 (m, 2H), 3.53 (t, *J* = 5.6 Hz, 2H),

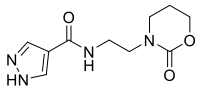
3.44 (t, *J* = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 165.7, 161.3, 139.75, 131.2, 118.8, 63.8, 45.9, 45.0, 37.9. HR-MS (ESI/TOF) calcd for $C_9H_{13}N_4O_2$ $[M+H]^+$ 225.0988, found 225.0979.

_N_-(2-(1_H_-Imidazol-2-yl)ethyl)-1_H_-pyrazole-4-carboxamide (148e)



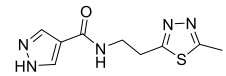
Compound was prepared in analogues way as **148a** starting from 2-(1*H*-imidazol-2-yl)ethan-1-amine dihydrochloride (255 mg, 1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (155 mg, 1 equiv.). Coupling reaction performed using TEA (965 μL, 5 equiv.), HOBt (254 mg, 1.2 equiv.) and EDCI (398 mg, 1.5 equiv.). Yield 72 mg (25%), white solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.03 (s, 2H), 6.96 (s, 2H), 3.66 (t, *J* = 7.2 Hz, 2H), 3.00 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 165.5, 147.2, 122.4, 118.9, 39.5, 29.3. HR-MS (ESI/TOF) calcd for $C_9H_{12}N_5O$ $[M+H]^+$ 206.1042, found 206.1044.

_N_-[2-(2-Oxo-1,3-oxazinan-3-yl)ethyl]-1_H_-pyrazole-4-carboxamide (148f)



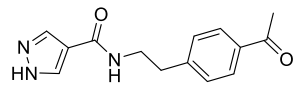
Compound was prepared in analogues way as **148a** starting from 3-(2-aminoethyl)-1,3-oxazinan-2-one hydrochloride (203 mg, 0.9 equiv.) and 1*H*-pyrazole-4-carboxylic acid (140 mg, 1 equiv.). Coupling reaction performed using TEA (696 μL, 4 equiv.), HOBt (229 mg, 1.2 equiv.) and EDCI (479 mg, 2 equiv.). Yield 139 mg (47%), white solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.02 (s, 2H), 4.24 (s, 2H), 3.75 – 3.28 (m, 6H), 2.03 (s, 2H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 165.7, 156.7, 139.7, 131.1, 118.9, 68.2, 50.0, 46.9, 37.9, 23.1. HR-MS (ESI/TOF) calcd for $C_{10}H_{15}N_4O_3$ $[M+H]^+$ 239.1144, found 239.1146.

_N_-[2-(5-Methyl-1,3,4-thiadiazol-2-yl)ethyl]-1_H_-pyrazole-4-carboxamide (148g)



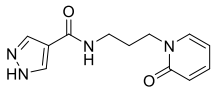
Compound was prepared in analogues way as **148a** starting from 2-(5-methyl-1,3,4-thiadiazol-2-yl)ethan-1-amine dihydrochloride (212 mg, 1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (110 mg, 1 equiv.). Coupling reaction performed using TEA (684 μL, 5 equiv.), HOBt (159 mg, 1.2 equiv.) and EDCI (376 mg, 2 equiv.). Yield 67 mg (29%), white yellow solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.01 (s, 2H), 3.72 (t, *J* = 6.7 Hz, 2H), 3.44 – 3.28 (m, 2H), 2.72 (s, 3H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 170.0, 168.3, 165.6, 139.8, 131.4, 118.8, 39.8, 30.8, 15.2. HR-MS (ESI/TOF) calcd for $C_9H_{12}N_5OS$ $[M+H]^+$ 238.0763, found 238.0767.

***N*-(4-Acetylphenethyl)-1*H*-pyrazole-4-carboxamide (148h)**



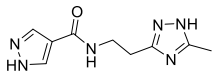
Compound was prepared in analogues way as **148a** starting from 1-(3-aminopropyl)pyridin-2(1*H*)-one (250 mg, 1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (140 mg, 1 equiv). Coupling reaction performed using TEA (698 µL, 4 equiv.), HOBt (230 mg, 1.2 equiv.) and EDCI (480 mg, 2 equiv.). Yield 177 mg (55%), white solid. ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.97 (d, J = 8.3 Hz, 2H), 7.89 (s, 2H), 7.41 (d, J = 8.3 Hz, 2H), 3.24 – 3.09 (m, 2H), 3.08 – 2.92 (m, 2H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.6, 166.0, 144.9, 135.5 (2C), 135.1, 129.0, 128.4, 118.7, 41.3, 36.4, 26.7. HR-MS (ESI/TOF) calcd for $C_{14}H_{16}N_3O_2$ $[M+H]^+$ 258.1243, found 258.1243.

***N*-[3-(2-Oxopyridin-1(2*H*)-yl)propyl]-1*H*-pyrazole-4-carboxamide (148i)**



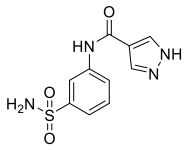
Compound was prepared in analogues way as **148a** starting from 1-(3-aminopropyl)pyridin-2(1*H*)-one hydrochloride (250 mg, 0.95 equiv.) and 1*H*-pyrazole-4-carboxylic acid (157 mg, 1 equiv.). Coupling reaction performed using TEA (780 µL, 4 equiv.), HOBt (257 mg, 1.2 equiv.) and EDCI (536 mg, 2 equiv.). Yield 130 mg (38%), white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (s, 1H), 8.18 (t, J = 5.3 Hz, 1H), 8.03 (s, 2H), 7.74 (dd, J = 6.7, 2.0 Hz, 1H), 7.55 – 7.29 (m, 1H), 6.51 – 6.32 (m, 1H), 6.22 (td, J = 6.7, 1.4 Hz, 1H), 3.92 (t, J = 7.0 Hz, 2H), 3.21 (q, J = 6.8 Hz, 2H), 1.84 (p, J = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2, 161.5, 139.9, 139.3, 134.3, 119.6, 117.9, 105.3, 46.6, 35.8, 29.1. HR-MS (ESI/TOF) calcd for $C_{12}H_{15}N_4O_2$ $[M+H]^+$ 247.1195, found 247.1198.

***N*-(2-(5-Methyl-1*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-pyrazole-4-carboxamide (148j)**



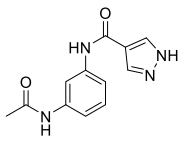
Compound was prepared in analogues way as **148a** starting from 2-(5-methyl-1H-1,2,4-triazol-3-yl)ethan-1-amine hydrochloride (255 mg, 1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (176 mg, 1 equiv.). Coupling reaction performed using TEA (874 µL, 4 equiv.), HOBt (288 mg, 1.2 equiv.) and EDCI (451 mg, 1.5 equiv). Yield 72 mg (32%), white solid. ^{1}H NMR (400 MHz, D_2O) δ 7.94 (s, 2H), 3.60 (t, J = 6.7 Hz, 2H), 2.92 (t, J = 6.7 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, D_2O) δ 165.2, 158.1, 155.8, 134.5, 116.5, 37.7, 26.6, 10.8. HR-MS (ESI/TOF) calcd for $C_9H_{13}N_6O$ $[M+H]^+$ 221.1151, found 221.1153.

***N*-(3-Sulfamoylphenyl)-1*H*-pyrazole-4-carboxamide (150a)**



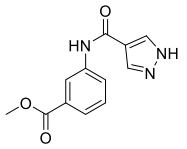
To a stirred solution of 3-aminobenzenesulfonamide (203 mg, 1.1 equiv.) in dry pyridine (5 mL), 1*H*-pyrazole-4-carboxylic acid (120 mg, 1 equiv.) was added in one portion at 25 °C. At the same temperature was added EDCI (328 mg, 1.6 equiv.). Resulting mixture was stirred for 16 h. After indicated time, reaction mixture diluted with EtOAc (25 mL) and water (10 mL), organic layer separated, washed with brine (10 mL), dried over anhydrous Na_2SO_4 and evaporated in *vacuo*. Compound purified by trituration with hot EtOH (2 mL) to obtain product **150a** as a white powder (93 mg, 32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.31 (br. s, 1H), 10.09 (s, 1H), 8.39 (br. s, 1H), 8.24 (s, 1H), 8.11 (br. s, 1H), 8.00 – 7.86 (m, 1H), 7.58 – 7.47 (m, 2H), 7.37 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.1, 144.5, 139.6, 139.1, 130.8, 129.4, 122.7, 120.2, 117.6, 116.9. LC-MS (ESI/APCI) $[M+H]^+$ 267.36.

***N*-(3-Acetamidophenyl)-1*H*-pyrazole-4-carboxamide (150b)**



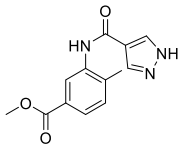
Compound was prepared in analogues way as **150a** starting from *N*-(3-aminophenyl)acetamide (221 mg, 1.1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (150 mg, 1 equiv.). Coupling reaction performed using EDCI (359 mg, 1.4 equiv). Yield 120 mg (37%), yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.24 (br. s, 1H), 9.93 (s, 1H), 9.79 (s, 1H), 8.38 (s, 1H), 8.06 (s, 1H), 8.02 (s, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.23 (dt, J = 15.8, 8.0 Hz, 2H), 2.04 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.3, 160.9, 139.5, 139.0, 130.3 (2C), 128.6, 118.0, 115.0, 114.1, 111.0, 24.0. LC-MS (ESI/APCI) $[M+H]^+$ 245.37.

Methyl 3-(1*H*-pyrazole-4-carboxamido)benzoate (150c)



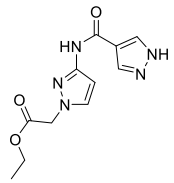
Compound was prepared in analogues way as **150a** starting from methyl 3-aminobenzoate (150 mg, 1.1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (144 mg, 1.3 equiv.). Coupling reaction performed using EDCI (304 mg, 1.6 equiv.). Yield 99 mg (41%), beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (br.s., 1H), 10.03 (s, 1H), 8.35 (t, J = 1.8 Hz, 1H), 8.23 (s, 2H), 8.04 (dd, J = 8.7, 1.6 Hz, 1H), 7.65 (dt, J = 7.7, 1.1 Hz, 1H), 7.48 (t, J = 7.9 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 161.2, 139.7, 134.9, 130.1 (2C), 129.2, 124.4, 123.9, 120.4, 117.8, 52.3. LC-MS (ESI/APCI) $[M+H]^+$ 246.39.

Methyl 4-methyl-3-(1*H*-pyrazole-4-carboxamido)benzoate (150d)



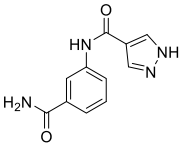
Compound was prepared in analogues way as **150a** starting from methyl 3-amino-4-methylbenzoate (230 mg, 1.1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (120 mg, 1.3 equiv). Coupling reaction performed using EDCI (308 mg, 1.5 equiv). Yield 188 mg (68%), beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.28 (br. s, 1H), 9.60 (s, 1H), 8.20 (s, 2H), 7.95 (d, J = 1.8 Hz, 1H), 7.73 (dd, J = 7.9, 1.8 Hz, 1H), 7.41 (d, J = 7.9 Hz, 1H), 3.84 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0, 161.0, 139.2, 136.6, 130.9 (2C), 127.6, 126.9, 126.2, 117.4, 52.1, 18.2. LC-MS (ESI/APCI) $[M+H]^+$ 260.37.

Ethyl 2-[3-(1*H*-pyrazole-4-carboxamido)-1*H*-pyrazol-1-yl]acetate (150e)



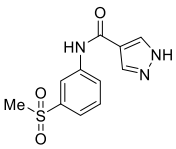
Compound was prepared in analogues way as **150a** starting from ethyl 2-(3-amino-1*H*-pyrazol-1-yl)acetate (199 mg, 1.1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (120 mg, 1 equiv.). Coupling reaction performed using EDCI (308 mg, 1.5 equiv.). Yield 202 mg (72%), white beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H), 10.52 (s, 1H), 8.23 (br. s, 2H), 7.65 (s, 1H), 6.62 (s, 1H), 4.96 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.3, 160.0, 147.8, 139.4, 131.9, 130.2, 117.5, 97.8, 61.0, 52.4, 14.1. LC-MS (ESI/APCI) $[M+H]^+$ 264.36.

***N*-(3-Carbamoylphenyl)-1*H*-pyrazole-4-carboxamide (150f)**



Compound was prepared in analogues way as **150a** starting from 3-aminobenzamide (160 mg, 1.1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (120 mg, 1 equiv.). Coupling reaction performed using EDCI (328 mg, 1.6 equiv). Yield 238 mg (97%), orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (br. s, 1H), 9.99 (br. s, 1H), 8.40 (s, 1H), 8.15 (s, 1H), 8.09 (s, 1H), 8.02 – 7.83 (m, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.34 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.0, 161.0, 139.3, 139.0, 134.9, 130.4, 128.5, 122.8, 122.0, 119.7, 117.8. LC-MS (ESI/APCI) $[M+H]^+$ 231.34.

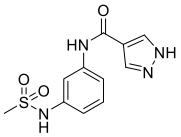
***N*-[3-(Methylsulfonyl)phenyl]-1*H*-pyrazole-4-carboxamide (150g)**



Compound was prepared in analogues way as **150a** starting from 3-(methylsulfonyl)aniline (336 mg, 1.1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (200 mg, 1 equiv.). Coupling reaction performed using EDCI (513 mg, 1.5 equiv.). Yield 216 mg (46%), beige solid. ^{1}H NMR

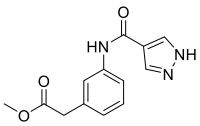
(400 MHz, DMSO-d_6) δ 13.76 (br. s, 1H), 10.54 (s, 1H), 9.29 (s, 1H), 8.68 (br. s, 1H), 8.35 – 8.25 (m, 1H), 8.19 – 8.03 (m, 1H), 7.80 – 7.46 (m, 2H), 3.22 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.8, 143.9, 141.3, 139.6, 130.1, 124.2, 121.9, 120.8, 117.7, 112.7, 43.6. LC-MS (ESI/APCI) $[M+H]^+$ 266.30.

_N_-[3-(Methylsulfonamido)phenyl]-1_H_-pyrazole-4-carboxamide (150h)



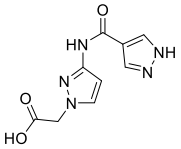
Compound was prepared in analogues way as **150a** starting from N-(3-aminophenyl)methanesulfonamide (150 mg, 1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (117 mg, 1.3 equiv.). Coupling reaction performed using EDCI (247 mg, 1.4 equiv.). Yield 175 mg (78%), white beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.26 (br. s, 1H), 9.86 (s, 1H), 9.76 (s, 1H), 8.38 (s, 1H), 8.06 (s, 1H), 7.66 (s, 1H), 7.49 (d, J = 9.2 Hz, 1H), 7.26 (t, J = 8.1 Hz, 1H), 6.90 (dd, J = 7.6, 1.7 Hz, 1H), 3.00 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.9, 140.1, 139.1, 138.7, 130.4, 129.4, 117.9, 115.6, 114.7, 111.3, 39.2. LC-MS (ESI/APCI) $[M+H]^+$ 281.35.

Methyl 2-[3-(1_H_-pyrazole-4-carboxamido)phenyl]acetate (150i)



Compound was prepared in analogues way as **150a** starting from methyl 2-(3-aminophenyl)acetate (194 mg, 1.1 equiv.) and 1*H*-pyrazole-4-carboxylic acid (120 mg, 1 equiv.). Coupling reaction performed using EDCI (246 mg, 1.2 equiv). Yield 94 mg (34%), white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (br. s, 1H), 9.79 (s, 1H), 8.36 (s, 1H), 8.05 (s, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.59 (t, J = 1.9 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 6.96 (dt, J = 7.8, 1.2 Hz, 1H), 3.66 (s, 2H), 3.62 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.6, 160.9, 139.3, 139.0, 134.7, 130.3, 128.6, 124.2, 120.7, 118.6, 117.9, 51.7, 40.4. LC-MS (ESI/APCI) $[M+H]^+$ 260.35.

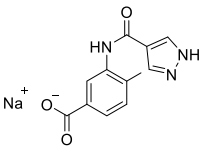
2-[3-(1_H_-Pyrazole-4-carboxamido)-1_H_-pyrazol-1-yl]acetic acid (151a)



To a stirred solution of ethyl 2-(3-(1*H*-pyrazole-4-carboxamido)-1*H*-pyrazol-1-yl)acetate **150e** (110 mg, 1 equiv.) dissolved in EtOH (7 mL), sodium hydroxide (50 mg, 3 equiv.) dissolved in H_2O (0.5 mL) was added in one portion. Resulting solution was stirred at 70 °C for 16 h, before evaporated to dryness. The residue was dissolved in water and acidified with 1 M HCl to obtain white precipitate. Precipitate filtered and washed with

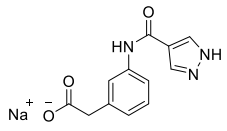
distilled water (2×3 mL) to obtain product as a white powder. Yield 94 mg (96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (br. s, 2H), 10.51 (s, 1H), 8.23 (s, 2H), 7.62 (s, 1H), 6.60 (s, 1H), 4.85 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.8, 160.0, 147.6, 134.7 (2C), 131.7, 117.5, 97.7, 52.5. LC-MS (ESI/APCI) $[M+H]^+$ 236.30.

Sodium 4-methyl-3-(1*H*-pyrazole-4-carboxamido)benzoate (151b)



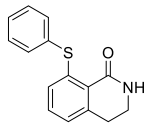
To a stirred solution of methyl 4-methyl-3-(1*H*-pyrazole-4-carboxamido)benzoate **150d** (135 mg, 1 equiv.) dissolved in MeOH (7 mL), sodium hydroxide (41 mg, 2 equiv.) dissolved in H_2O (0.5 mL) was added in one portion. Resulting solution was stirred at 70 °C for 16 h, before evaporated to dryness. The residue triturated with small amount of cold MeOH (1 mL) to obtain white crystalline solid. Precipitate filtered and washed with MeOH (2×0.5 mL) to obtain product as a white powder. Yield 88 mg (63%). ^{1}H NMR (400 MHz, D_2O) δ 8.18 (s, 2H), 7.74 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 7.40 (dt, *J* = 7.9, 0.6 Hz, 1H), 2.27 (s, 3H). 13C NMR (101 MHz, D_2O) δ 174.9, 165.9, 139.0, 137.9 (2C), 134.8, 134.5, 130.6, 127.9, 127.7, 115.3, 17.0. LC-MS (ESI/APCI) $[M+H]^+$ 246.34.

Sodium 2-(3-(1*H*-pyrazole-4-carboxamido)phenyl)acetate (151c)



Compound was prepared in analogues way as **151b** starting from methyl 2-(3-(1*H*-pyrazole-4-carboxamido)phenyl)acetate **150i** (74 mg, 1 equiv.) and NaOH (91 mg, 8 equiv.). Yield 67 mg (88%), white solid. ^{1}H NMR (400 MHz, D_2O) δ 8.13 (s, 2H), 7.41 – 7.30 (m, 2H), 7.28 (s, 1H), 7.11 (d, *J* = 6.7 Hz, 1H), 3.51 (s, 2H). ^{13}C NMR (101 MHz, D_2O) δ 180.7, 164.2, 138.2, 136.7, 135.7 (2C), 129.2, 126.3, 123.1, 120.6, 116.7, 44.3. LC-MS (ESI/APCI) $[M+H]^+$ 246.31.

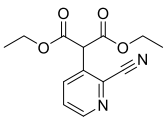
8-(Phenylthio)-3,4-dihydroisoquinolin-1(2*H*)-one (155)



8-Fluoro-3,4-dihydroisoquinolin-1(2*H*)-one **170 (**170 mg, 1 equiv.) was dissolved in anhydrous DMF (5 mL) and thiophenol (100 μL, 1 equiv.) together with K_2CO_3 (213 mg, 1.5 equiv.) was added thereto. Resulting solution heated at 115 °C for 16 h. After cooling down to room temperature reaction was diluted with EtOAc (30 mL) and extracted consequently with 1 M NaOH solution (15 mL) and brine (2×20 mL). Organic extract dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product, which was purified by trituration with the

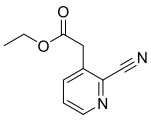
2:1 mixture of petroleum ether and EtOAc (10 mL) to obtain product as a solid. Yield 163 mg (62%), light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.52 (m, 2H), 7.52 – 7.33 (m, 3H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.48 (s, 1H), 3.54 (td, *J* = 6.5, 3.1 Hz, 2H), 2.97 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 144.2, 140.5, 136.3, 133.4, 131.3, 129.8, 129.2, 125.6, 124.5, 123.4, 39.9, 29.7. HR-MS (ESI/TOF) calcd for $C_{15}H_{14}NOS$ $[M+H]^+$ 256.0796, found 256.0799.

Diethyl 2-(2-cyanopyridin-3-yl)malonate (158)



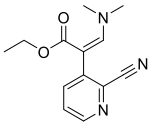
To a stirred solution of 3-chloropicolinonitrile (10 g, 1 equiv.), dissolved in DMF (40 mL), diethyl malonate (21.94 mL, 2 equiv.) was added, followed by careful portionwise addition of 60% NaH (5.77 g, 2 equiv.). Resulting solution slowly warmed up to 130 °C and stirred at this temperature for 16 h. Reaction mixture cooled down to room temperature and brine (100 mL) added thereto. Reaction mixture extracted with EtOAc (200 mL), and EtOAc layer washed with brine (2×100 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo. Crude residue was purified by silica gel chromatography using 20% EtOAc in petroleum ether to obtain product as a yellowish oil. Yield 13 g (69%). Spectral data consistent with previously reported.[72]

Ethyl 2-(2-cyanopyridin-3-yl)acetate (159)



To a stirred solution of diethyl 2-(2-cyanopyridin-3-yl)malonate **158** (12.6 g, 1 equiv.), dissolved in DMSO (50 mL), H_2O (1.73 mL, 2 equiv.) and LiCl (4.07 g, 2 equiv.) were added. Resulting solution warmed up to 140 °C and stirred at this temperature for 3 h. Reaction mixture cooled down to room temperature and brine (100 mL) added thereto Reaction mixture extracted with EtOAc (200 mL), and EtOAc layer washed with brine (4×70 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo. Crude residue used in the next step without further purification. Yield 7.85 g (86%), brown oil. Spectral data consistent with previously reported.[72]

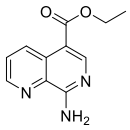
Ethyl 2-(2-cyanopyridin-3-yl)-3-(dimethylamino)acrylate (160)



Ethyl 2-(2-cyanopyridin-3-yl)acetate **159** (8.2 g, 1 equiv.) was dissolved in DMF-DMA (17.2 mL, 3 equiv.) Resulting solution warmed up to 100 °C and stirred at this temperature for 6 h. Reaction mixture cooled

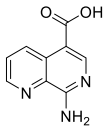
down to room temperature and evaporated in vacuo. Crude residue used in the next step without further purification. Yield 10.4 g (98%), black oil.[72]

Ethyl 8-amino-1,7-naphthyridine-5-carboxylate (161)



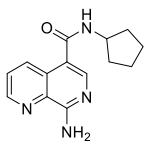
Ethyl 2-(2-cyanopyridin-3-yl)-3-(dimethylamino)acrylate **160** (10.4 g, 1 equiv.) was dissolved in glacial AcOH (130 mL) and ammonium acetate was added thereto (58.83 g, 18 equiv). Resulting solution warmed up to 100 °C and stirred at this temperature for 16 h. Reaction mixture cooled down to room temperature and evaporated in vacuo. Crude residue triturated with water to obtain solid, which was separated and washed with water (2×100 mL). Yield 3.58 g (39%), brown solid. Spectral data consistent with previously reported.[72]

8-Amino-1,7-naphthyridine-5-carboxylic acid (162)



Ethyl 8-amino-1,7-naphthyridine-5-carboxylate **161** (3 g, 1 equiv.) was suspended in aqueous solution (50 mL) of NaOH (1.1 g, 2 eqiuv.). Resulting suspension warmed up to 100 °C and stirred until clear solution was obtained. Reaction mixture cooled down to room temperature, acidified with 1 M HCl and evaporated in vacuo. Crude residue triturated with MeOH to obtain solid, which was separated and washed with MeOH (2×4 mL). Yield 1.03 g (39%), light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (br.s, 2H), 9.32 (dd, J = 8.6, 1.6 Hz, 1H), 9.02 (dd, J = 4.3, 1.6 Hz, 1H), 8.47 (s, 1H), 8.03 (dd, J = 8.7, 4.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.4, 155.7, 150.6, 136.4, 134.2, 134.1, 130.9, 129.4, 110.0. LC-MS (ESI/APCI) $[M+H]^+$ 190.26.

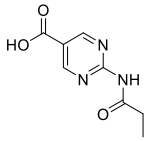
8-Amino-*N*-cyclopentyl-1,7-naphthyridine-5-carboxamide (153)



8-Amino-1,7-naphthyridine-5-carboxylic acid **169** (165 mg, 1 equiv.) was dissolved in dry DMF (5 mL) and cyclopentylamine (129 µL, 1.2 equiv.) was added thereto, followed by TEA (486 µL, 4 equiv.), EDCI (251 mg, 1.5 equiv.) and HOBt (160 mg, 1.2 equiv.). Resulting solution stirred at room temperature for 16 h. Reaction mixture diluted with water to obtain solid, which was separated and washed with water (2×10 mL). Yield 188 mg (84%), beige solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 9.33 (d, J = 7.4 Hz, 1H), 8.77 (d, J = 2.7 Hz, 1H), 8.46 (s, 1H), 7.66 (dd, J = 8.6, 4.2 Hz, 1H), 3.58 (p, J = 6.4 Hz, 1H), 2.21 – 1.92 (m, 2H), 1.92 – 1.73 (m, 2H), 1.74 – 1.51 (m, 4H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 174.3, 160.4, 149.5,

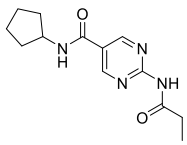
146.0, 136.0, 134.2, 132.4, 126.9, 118.6, 53.3, 32.1, 24.9. HR-MS (ESI/TOF) calcd for $C_{14}H_{17}N_4O$ $[M+H]^+$ 257.1402, found 257.1405.

2-Propionamidopyrimidine-5-carboxylic acid (164)



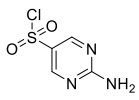
2-Aminopyrimidine-5-carboxylic acid **163** (1 g, 1 equiv.) was suspended in propionic anhydride (3.7 mL, 4 equiv.) and the resulting solution heated at 130 °C for 1 h. Reaction mixture cooled down to room temperature and diluted with water (60 mL) to obtain solid, which was filtered and discarded (bis-acylated impurity). Filtrate was evaporated to dryness in vacuo to obtain target product **160**. Yield 347 mg (25%), yellowish solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 9.03 (s, 2H), 2.55 (q, J = 7.6 Hz, 2H), 1.06 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.6, 164.8, 159.6, 159.5, 119.4, 30.0, 9.0. LC-MS (ESI/APCI) $[M+H]^+$ 196.30.

2-Propionamidopyrimidine-5-carboxylic acid (154)



2-Propionamidopyrimidine-5-carboxylic acid **164 (**150 mg, 1 equiv.) was dissolved in dry DMF (4 mL) and cyclopentylamine (114 µL, 1.5 equiv.) was added thereto, followed by TEA (214 µL, 2 equiv.), EDCI (221 mg, 1.5 equiv.) and HOBt (141 mg, 1.2 equiv.). Resulting solution stirred at room temperature for 16 h. Reaction mixture diluted with water to obtain solid, which was separated and washed with water (2×5 mL). Yield 112 mg (55%), light beige solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 9.04 (s, 2H), 3.60 (dt, J = 8.0, 6.1 Hz, 1H), 2.56 (q, J = 7.5 Hz, 2H), 2.26 – 1.94 (m, 2H), 1.92 – 1.48 (m, 6H), 1.20 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 175.5, 170.3, 160.6, 159.6, 126.9, 53.3, 32.1, 31.3, 24.9, 9.5. HR-MS (ESI/TOF) calcd for $C_{13}H_{19}N_4O_2$ $[M+H]^+$ 263.1508, found 263.1504.

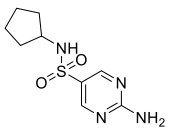
2-Aminopyrimidine-5-sulfonyl chloride (166)



2-Aminopyrimidine **165 (**2.64 g, 1 equiv.) was carefully dissolved portionwise in HSO_3Cl (15.7 mL, 8.5 equiv.) and thionyl chloride (8.55 mL, 4.25 equiv.) was added dropwise to the reaction mixture at room temperature. Resulting solution heated at 150 °C for 16 h. After cooling down to room temperature reaction was carefully added to crushed ice (400 g) and formed solution was saturated with NaCl and extracted with EtOAc (150 mL). Organic layer washed with brine (2×30 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain product

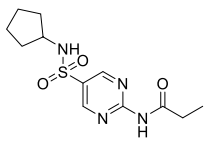
as a solid. Yield 1.614 g (30%), light beige solid. Spectral data consistent with previously reported.[91]

2-Amino-*N*-cyclopentylpyrimidine-5-sulfonamide (167)



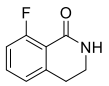
2-Aminopyrimidine-5-sulfonyl chloride **166 (**250 mg, 1 equiv.) was added portionwise to a stirred solution of cyclopentylamine (191 µL, 1.5 equiv.) and triethyl amine (360 µL, 2 equiv.) in dry MeCN (5 mL) under ice cooling. Resulting solution stirred at room temperature for 1 h. Reaction mixture evaporated in vacuo and triturated with water (5 mL) to obtain product as a solid. Yield 238 mg (76%), light beige solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.58 (s, 2H), 4.59 (s, 3H), 3.52 (p, J = 6.9 Hz, 1H), 1.88 – 1.71 (m, 2H), 1.72 – 1.59 (m, 2H), 1.57 – 1.47 (m, 2H), 1.46 – 1.31 (m, 2H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 165.7, 158.8, 125.9, 56.1, 34.1, 24.3. HR-MS (ESI/TOF) calcd for $C_9H_{15}N_4O_2S$ $[M+H]^+$ 243.0916, found 243.0914.

***N*-(5-(*N*-cyclopentylsulfamoyl)pyrimidin-2-yl)propionamide (168)**



2-Amino-N-cyclopentylpyrimidine-5-sulfonamide **167 (**150 mg, 1 equiv.) was suspended in propionic anhydride (955 µL, 12 equiv.) and the resulting solution heated at 150 °C for 2 h. Reaction cooled down to room temperature and neutralized with saturated aqueous K_2CO_3. Formed precipitate was filtered and washed with water (2×3 mL) to obtain product as a solid. Yield 88 mg (48%), light beige solid. ^{1}H NMR (400 MHz, MeCN-d_3) δ 9.00 (s, 1H), 8.90 (s, 2H), 5.84 (d, J = 7.2 Hz, 1H), 3.58 (q, J = 6.9 Hz, 1H), 2.64 (q, J = 7.4 Hz, 2H), 1.77 (dq, J = 12.5, 6.3 Hz, 2H), 1.61 (tt, J = 11.7, 7.1 Hz, 2H), 1.49 (qd, J = 8.9, 7.4, 5.0 Hz, 2H), 1.37 (dq, J = 13.8, 7.3, 6.9 Hz, 2H), 1.14 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, MeCN-d_3) δ 173.8, 164.0, 158.2, 131.4, 56.1, 33.8, 31.3, 23.9, 9.2. HR-MS (ESI/TOF) calcd for $C_{12}H_{19}N_4O_3S$ $[M+H]^+$ 299.1178, found 299.1176.

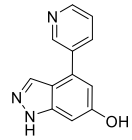
8-Fluoro-3,4-dihydroisoquinolin-1(2*H*)-one (170)



5-Fluoro-indan-1-one **169** (1 g, 1 equiv.) was dissolved in dichloromethane (10 ml) and methanesulfonic acid (10 ml). This solution was cooled to 0°C and sodium azide (866 mg, 2 equiv.) was added. After 2 hours, the solution was made basic by slow addition of 20% aqueous sodium hydroxide. The resulting mixture was partitioned between dichloromethane and water. The dichloromethane layer was dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by trituration with the 1:1

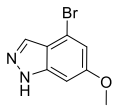
mixture of petroleum ether and EtOAc (10 mL) to obtain product as a solid. Yield 347 mg (31%), white yellow solid. Spectral data consistent with previously reported.[92]

4-(Pyridin-3-yl)-1*H*-indazol-6-ol (174)



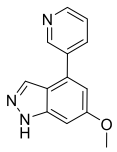
Compound was prepared in analogues way as **178a** starting from 6-methoxy-4-(pyridin-3-yl)-1*H*-indazole **177a** (150 mg, 1 equiv.) and 1 M BBr_3 (2.67 mL, 4 equiv.). Purified by reversed phase chromatography using gradient of MeCN in water to obtain product as a white solid. Yield 33 mg (23%). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.88 (br. s, 1H), 8.62 (br. s, 1H), 8.25 (dt, J = 8.0, 1.7 Hz, 1H), 8.00 (s, 1H), 7.66 (dd, J = 7.7, 5.1 Hz, 1H), 6.91 (dd, J = 1.8, 1.0 Hz, 1H), 6.87 (d, J = 1.9 Hz, 1H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 158.7, 148.3, 143.9, 138.8, 133.4, 132.3, 126.0, 116.9, 113.8, 94.8. LC-MS (ESI/APCI) $[M+H]^+$ 212.40.

4-Bromo-6-methoxy-1*H*-indazole (176)



2-Bromo-6-fluoro-4-methoxybenzaldehyde **175** (1.2 g, 1 equiv.), synthesized according to literature described procedure,[93] was dissolved in ethylene glycol (15 mL) and hydrazine hydrate (5.52 mL, 22 equiv.) was added thereto. Resulting solution heated at 110 °C for 16 h. After cooling down to room temperature reaction mixture evaporated in vacuo to dryness and water (20 mL) added thereto. Formed precipitate was filtered and washed with water (2×10 mL) to obtain product as a solid. Yield 952 mg (81%), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 7.98 (s, 1H), 7.02 (d, J = 1.9 Hz, 1H), 6.80 (s, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 141.5, 135.1, 119.7, 116.2, 114.9, 90.3, 56.0. LC-MS (ESI/APCI) $[M+H]^+$ 227.27/229.30.

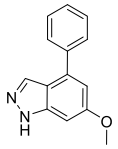
6-Methoxy-4-(pyridin-3-yl)-1*H*-indazole (177a)



4-Bromo-6-methoxy-1*H*-indazole **176** (300 mg, 1 equiv.) was dissolved in dioxane:water 3:1 mixture **(**10 mL) and pyridin-3-yl boronic acid (487 mg, 3 equiv.) was added thereto, followed by K_2CO_3 (213 mg, 1.5 equiv.) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (75.5 mg, 7 mol%). Resulting solution heated at 100 °C for 16 h. After cooling down to room temperature reaction mixture evaporated in vacuo to dryness and water (10 mL) added thereto. Then reaction extracted with EtOAc (30 mL). Organic extract washed with brine (2×30 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product. Purified by silica gel column chromatography using gradient from 0 to 2% MeOH in EtOAc to obtain product as a

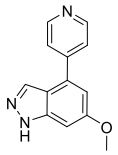
yellowish sticky oil. Yield 150 mg (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 9.09 – 8.89 (m, 1H), 8.68 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.08 (s, 1H), 7.99 (ddd, *J* = 7.9, 2.3, 1.6 Hz, 1H), 7.45 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 6.98 – 6.85 (m, 2H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 149.3, 149.2, 142.1, 135.8, 135.2, 134.1, 132.5, 123.9, 116.8, 113.0, 90.6, 55.8. LC-MS (ESI/APCI) $[M+H]^+$ 226.41.

6-Methoxy-4-phenyl-1*H*-indazole (177b)



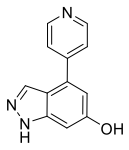
Compound was prepared in analogues way as **177a** starting from 4-bromo-6-methoxy-1*H*-indazole **176** (300 mg, 1 equiv.) and phenylboronic acid (225 mg, 1.4 equiv.). Coupling reaction performed using K_2CO_3 (730 mg, 4 equiv.) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (75.5 mg, 7 mol%). Purified by silica gel column chromatography using gradient from 10 to 50% EtOAc in petroleum ether to obtain product as a colourless oil. Yield 212 mg (72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (br. s, 1H), 8.12 (s, 1H), 7.77 – 7.65 (m, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 2.7 Hz, 1H), 6.89 (dd, *J* = 29.5, 2.1 Hz, 2H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 142.1, 139.4, 136.3, 134.7, 129.0, 128.5, 128.2, 117.0, 112.5, 89.9, 55.8. LC-MS (ESI/APCI) $[M+H]^+$ 225.31.

6-Methoxy-4-(pyridin-4-yl)-1*H*-indazole (177c)



Compound was prepared in analogues way as **177a** starting from 4-bromo-6-methoxy-1*H*-indazole **176** (300 mg, 1 equiv.) and 4-pyridineboronic acid hydrochloride (1.053 g, 5 equiv.). Coupling reaction performed using K_2CO_3 (1.46 g, 8 equiv.) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (75.5 mg, 7 mol%). Purified by trituration with methanol (2 mL) to obtain product as a beige solid. Yield 180 mg (60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (br. s, 1H), 8.70 (d, *J* = 5.4 Hz, 2H), 8.13 (s, 1H), 7.75 (d, *J* = 5.8 Hz, 2H), 7.15 – 6.84 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.7, 150.2, 146.0, 141.8, 132.3, 131.7, 122.8, 115.5, 111.8, 91.8, 55.5. LC-MS (ESI/APCI) $[M+H]^+$ 226.38.

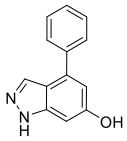
4-(Pyridin-4-yl)-1*H*-indazol-6-ol (178a)



6-Methoxy-4-(pyridin-4-yl)-1*H*-indazole **177c** (70 mg, 1 equiv.)**,** was dissolved in dry DCM **(**5 mL) and 1M BBr_3 solution in DCM (1.68 mL, 5.4 equiv.) was added thereto under ice cooling, Resulting solution stuirred at room temperature for 3 h. Then reaction neutralized with saturated aqueous $NaHCO_3$ and extracted with DCM (20 mL). Organic extract dried over

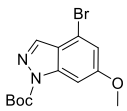
anhydrous Na_2SO_4 and evaporated in vacuo to obtain product as a brown solid. Yield 16 mg (24%). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.66 (d, J = 5.0 Hz, 2H), 8.06 (d, J = 0.9 Hz, 1H), 7.85 (d, J = 6.3 Hz, 2H), 6.96 (d, J = 1.9 Hz, 1H), 6.92 (dd, J = 1.9, 1.0 Hz, 1H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 158.6, 151.4, 149.1, 144.0, 133.4, 132.8, 125.1, 116.5, 114.1, 95.9. LC-MS (ESI/APCI) $[M+H]^+$ 212.38.

4-Phenyl-1*H*-indazol-6-ol (178b)



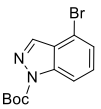
Compound was prepared in analogues way as **178a** starting from 6-methoxy-4-phenyl-1*H*-indazole **177b** (320 mg, 1 equiv.) and 1 M BBr_3 (7.13 mL, 5 equiv.). Purified by silica gel column chromatography using gradient from 20 to 50% EtOAc in petroleum ether to obtain product as a white solid. Yield 120 mg (40%).^{1}H NMR (400 MHz, MeOH-d_4) δ 8.17 (d, J = 0.9 Hz, 1H), 7.89 (s, 1H), 7.72 – 7.61 (m, 2H), 7.56 – 7.47 (m, 2H), 7.47 – 7.37 (m, 1H), 6.88 (d, J = 1.9 Hz, 1H), 6.86 – 6.81 (m, 1H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 159.9, 143.8, 140.4, 137.9, 133.4, 130.0, 129.3, 129.2, 116.8, 114.3, 93.3. LC-MS (ESI/APCI) $[M+H]^+$ 211.34.

***tert*-Butyl 4-bromo-6-methoxy-1*H*-indazole-1-carboxylate (179a)**



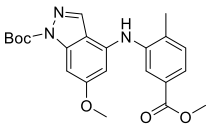
4-Bromo-6-methoxy-1*H*-indazole **176** (950 mg, 1 equiv.) was dissolved in dry MeCN **(**20 mL) and Boc_2O (1.15 mL, 1.2 equiv.) was added thereto, followed by DMAP (51 mg, 0.1 equiv.). Resulting solution stirred at room temperature for 16 h. Reaction mixture evaporated in vacuo and purified by silica gel column chromatography using gradient from 3 to 10% EtOAc in petroleum ether to obtain product as a white solid. Yield 552 mg (40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 3.90 (s, 3H), 1.72 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 149.4, 141.8, 139.1, 121.4, 118.0, 114.8, 96.2, 85.4, 56.1, 28.3. LC-MS (ESI/APCI) $[M+H]^+$ 271.20/273.20.

***tert*-Butyl 4-bromo-1*H*-indazole-1-carboxylate (179b)**



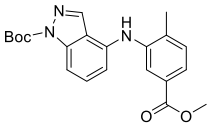
Compound was prepared in analogues way as **179a** starting from 4-bromo-1*H*-indazole (1.2 g, 1 equiv.), Boc_2O (1.15 mL, 1.2 equiv.) and DMAP (74.4 mg, 0.1 equiv.). Purified by silica gel column chromatography using gradient from 3 to 10% EtOAc in petroleum ether to obtain product as a yellowish oil. Yield 1184 mg (65%). Spectral data consistent with previously reported.[94]

***tert*-Butyl 6-methoxy-4-((5-(methoxycarbonyl)-2-methylphenyl)amino)-1*H*-indazole-1-carboxylate (180a)**



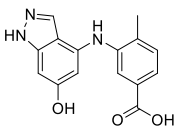
tert-Butyl 4-bromo-6-methoxy-1*H*-indazole-1-carboxylate **179a** (150 mg, 1 equiv.) was dissolved in toluene **(**8 mL) and methyl 3-amino-4-methylbenzoate **150d** (152 mg, 2 equiv.) was added thereto, followed by K_3PO_4 (146 mg, 1.5 equiv.), Xanthphos (16 mg, 6 mol%) and $Pd_2(dba)_3$ (12 mg, 3 mol%). Resulting solution heated at 100 °C for 16 h. After cooling down to room temperature reaction evaporated in vacuo to dryness and water (10 mL) added thereto. Then reaction extracted with EtOAc (20 mL). Organic extract washed with brine (2×10 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product. Purified by silica gel column chromatography using gradient from 10 to 50% EtOAc in petroleum ether to obtain product as a yellow oil. Yield 165 mg (87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.7 Hz, 1H), 7.83 (d, *J* = 0.8 Hz, 1H), 7.74 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 6.22 (d, *J* = 2.0 Hz, 1H), 5.79 (br. s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.33 (m, 3H), 1.72 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 162.8, 149.7, 142.9, 139.9, 138.7, 137.0, 136.6, 131.4, 129.4, 125.6, 123.9, 111.9, 99.4, 89.5, 84.8, 55.7, 52.2, 28.3, 18.3. LC-MS (ESI/APCI) $[M+H]^+$ 412.54.

***tert*-Butyl 4-((5-(methoxycarbonyl)-2-methylphenyl)amino)-1*H*-indazole-1-carboxylate (180b)**



Compound was prepared in analogues way as **180a** starting from tert-*butyl* 4-bromo-1*H*-indazole-1-carboxylate **179b** (200 mg, 1 equiv.), methyl 3-amino-4-methylbenzoate **150d** (222 mg, 2 equiv.), K_3PO_4 (146 mg, 1.5 equiv.), Xanthphos (58 mg, 15 mol%) and $Pd_2(dba)_3$ (43 mg, 7 mol%). After aqueous workup used in the next step without further purification. Yield 142 mg (55%). LC-MS (ESI/APCI) $[M+H]^+$ 382.49.

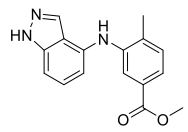
3-[(6-Hydroxy-1*H*-indazol-4-yl)amino]-4-methylbenzoic acid (181)



tert-Butyl 6-methoxy-4-((5-(methoxycarbonyl)-2-methylphenyl)amino)-1*H*-indazole-1-carboxylate **180a** (142 mg, 1 equiv.) was dissolved in 3 mL of 48% aqueous HBr. Resulting solution stirred at 100 °C for 3 h. After cooling down to room temperature reaction mixture evaporated in vacuo to dryness and water (3 mL) added thereto and evaporated to remove residual HBr. Purified by reversed phase column

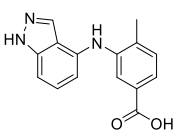
chromatography using gradient of MeCN in water to obtain product as a beige solid. Yield 20 mg (20%). ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.95 – 7.80 (m, 3H), 7.71 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 5.88 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 170.0, 159.6, 144.5, 142.2, 141.1, 141.0, 139.6, 139.5, 133.0, 132.1, 130.6, 126.3, 110.9, 96.3, 18.4. LC-MS (ESI/APCI) $[M+H]^+$ 284.38.

Methyl 3-[(1*H*-indazol-4-yl)amino]-4-methylbenzoate (182)



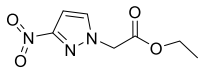
tert-Butyl 4-((5-(methoxycarbonyl)-2-methylphenyl)amino)-1*H*-indazole-1-carboxylate **180b** (141 mg, 1 equiv.) was dissolved in DCM (3 mL) and TFA (852 μL, 30 equiv.) was added thereto. Resulting solution stirred at room temperature for 6 h. Then reaction mixture diluted with saturated $NaHCO_3$ (30 mL) and brine (10 mL). Organic extract dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product. Purified by silica gel column chromatography using gradient from 10 to 50% EtOAc in petroleum ether to obtain product as a white yellow solid. Yield 83 mg (80%). ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.92 (s, 1H), 7.81 (d, *J* = 1.7 Hz, 1H), 7.66 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.18 (dd, *J* = 8.3, 7.4 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.35 (d, *J* = 7.3 Hz, 1H), 3.83 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 168.6, 143.3, 142.9, 140.0, 138.7, 133.1, 132.1, 129.8, 129.1, 125.3, 124.5, 116.3, 105.7, 102.3, 52.5, 18.4. LC-MS (ESI/APCI) $[M+H]^+$ 282.38.

3-[(1*H*-Indazol-4-yl)amino]-4-methylbenzoic acid (183)



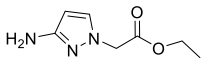
Methyl 3-((1*H*-indazol-4-yl)amino)-4-methylbenzoate **182** (66 mg, 1 equiv.) was dissolved in MeOH:H_2O mixture 4:1 (5 mL) and NaOH (28 mg, 3 equiv.) was added thereto. Resulting solution stirred at 70 °C for 16 h. Then reaction mixture evaporated in vacuo and the residue triturated with 1 M HCl (2 mL). Obtained precipitate was filtered and washed with water (2×1 mL) to obtain product as a beige-purple solid. Yield 53 mg (84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (br. s, 2H), 7.97 (s, 1H), 7.91 (s, 1H), 7.71 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.27 (d, *J* = 7.4 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.2, 141.6, 141.2, 138.2, 136.4, 131.9, 131.0, 129.2, 127.1, 123.8, 122.9, 114.8, 103.5, 100.9, 18.1. LC-MS (ESI/APCI) $[M+H]^+$ 268.34.

Ethyl 2-(3-nitro-1*H*-pyrazol-1-yl)acetate (185)



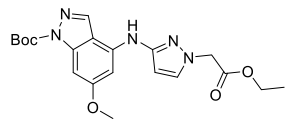
3-Nitro-1*H*-pyrazole **184** (1 g, 1 equiv.) was dissolved in DMF (25 mL) and ethyl bromoacetate (1.17 mL, 1.2 equiv.) was added thereto, followed by K_2CO_3 (2.44 g, 2 equiv.). Resulting mixtire heated at 80 °C for 16 h. After cooling down to room temperature reaction diluted with brine (50 mL) and extracted with EtOAc (80 mL). Organic extract washed with brine (2×30 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product. Purified by trituration with hot 10% EtOAc in petroleum ether to obtain product as a white beige solid. Yield 1.4 g (80%). Spectral data consistent with previously reported.[95]

Ethyl 2-(3-amino-1*H*-pyrazol-1-yl)acetate (150e)



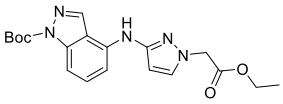
Ethyl 2-(3-nitro-1*H*-pyrazol-1-yl)acetate **185** (1.3 g, 1 equiv.) was dissolved in EtOH (30 mL) and 10% Pd on carbon (300 mg, 4 mol%) was added thereto, Resulting mixtire hydrogenated at 1 atm of H_2 for 6 h at room temperature. After consumption of starting material, reaction ventilated from hydrogen, catalyst filtered off and ethanolic solution evaporated in vacuo to obtain pure product as a yellow viscous oil. Yield 1.1 g (99%). Spectral data consistent with previously reported.[96]

***tert*-Butyl 4-((1-(2-ethoxy-2-oxoethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxy-1*H*-indazole-1-carboxylate (187a)**



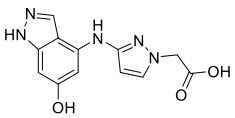
Compound was prepared in analogues way as **180a** starting from tert-butyl 4-bromo-6-methoxy-1*H*-indazole-1-carboxylate **179a** (250 mg, 1 equiv.), ethyl 2-(3-amino-1*H*-pyrazol-1-yl)acetate **150e** (194 mg, 1.5 equiv.), K_3PO_4 (243 mg, 1.5 equiv.), Xanthphos (35 mg, 8 mol%) and $Pd_2(dba)_3$ (28 mg, 4 mol%). Purified by silica gel column chromatography using gradient from 10 to 100% EtOAc in petroleum ether to obtain product as a yellow solid. Yield 206 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 0.9 Hz, 1H), 7.39 (d, *J* = 2.5 Hz, 1H), 7.20 (s, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.50 (br. s, 1H), 6.14 (d, *J* = 2.4 Hz, 1H), 4.80 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 1.71 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 163.0, 150.5, 149.7, 142.6, 137.2, 136.3, 132.1, 111.2, 98.3, 97.3, 89.0, 84.7, 62.1, 55.7, 53.2, 28.3, 14.3. LC-MS (ESI/APCI) $[M+H]^+$ 416.51.

***tert*-Butyl 4-{[1-(2-ethoxy-2-oxoethyl)-1*H*-pyrazol-3-yl)]amino}-1*H*-indazole-1-carboxylate (187b)**



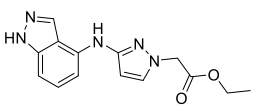
Compound was prepared in analogues way as **180a** starting from tert-butyl 4-bromo-1*H*-indazole-1-carboxylate **179b** (200 mg, 1 equiv.), ethyl 2-(3-amino-1H-pyrazol-1-yl)acetate **150e** (137 mg, 1.2 equiv.), K_3PO_4 (285 mg, 2 equiv.), Xanthphos (58 mg, 15 mol%) and $Pd_2(dba)_3$ (43 mg, 7 mol%). Purified by silica gel column chromatography using gradient from 10 to 100% EtOAc in petroleum ether to obtain product as a yellow oil. Yield 99 mg (38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 0.9 Hz, 1H), 7.65 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.21 (dd, *J* = 7.8, 0.7 Hz, 1H), 6.48 (br. s, 1H), 6.14 (d, *J* = 2.4 Hz, 1H), 4.81 (s, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.72 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 150.9, 149.5, 141.2, 136.9, 136.5, 132.1, 130.6, 116.3, 107.7, 106.2, 97.2, 84.9, 62.1, 53.2, 28.3, 14.3. LC-MS (ESI/APCI) $[M+H]^+$ 386.54.

2-{3-[(6-Hydroxy-1*H*-indazol-4-yl)amino]-1*H*-pyrazol-1-yl}acetic acid (188)



Compound was prepared in analogues way as **181** starting from tert-butyl 4-((1-(2-ethoxy-2-oxoethyl)-1*H*-pyrazol-3-yl)amino)-6-methoxy-1*H*-indazole-1-carboxylate **187a** (195 mg, 1 equiv.). Purified by reversed phase column chromatography using gradient of MeCN in water to obtain product as a beige solid. Yield 71 mg (49%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (br. s, 2H), 9.18 (br. s, 1H), 8.62 (s, 1H), 8.12 (s, 1H), 7.60 (d, *J* = 2.3 Hz, 1H), 6.92 (d, *J* = 1.8 Hz, 1H), 6.16 (s, 1H), 5.98 (d, *J* = 2.4 Hz, 1H), 4.84 (s, 2H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 171.77, 162.06, 152.49, 152.43, 144.17, 139.47, 133.71, 133.64, 131.50, 109.96, 97.81, 53.34. LC-MS (ESI/APCI) $[M+H]^+$ 274.34.

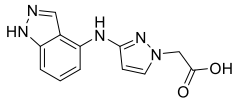
Ethyl 2-{3-[(1*H*-indazol-4-yl)amino]-1*H*-pyrazol-1-yl}acetate (189)



Compound was prepared in analogues way as **182** starting from tert-butyl 4-((1-(2-ethoxy-2-oxoethyl)-1*H*-pyrazol-3-yl)amino)-1*H*-indazole-1-carboxylate **187b** (97 mg, 1 equiv.) and TFA (386 µL, 20 equiv.). Purified by trituration with hot EtOAc:petroleum ether 1:2 to obtain product as a beige solid. Yield 51 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.10 (br. s, 1H), 9.27 (s, 1H), 9.03 – 8.67 (m, 1H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.27 – 7.20 (m, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.35 (d, *J* = 2.4 Hz, 1H), 4.82 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ

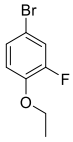
168.2, 152.3, 141.5, 137.1, 132.1, 128.2, 115.3, 101.9, 101.1, 96.1, 62.1, 53.0, 14.1. LC-MS (ESI/APCI) $[M+H]^+$ 286.43.

2-{3-[(1*H*-Indazol-4-yl)amino]-1*H*-pyrazol-1-yl}acetic acid (190)



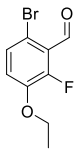
Compound was prepared in analogues way as **183** starting from ethyl 2-(3-((1*H*-indazol-4-yl)amino)-1*H*-pyrazol-1-yl)acetate **189** (50 mg, 1 equiv.) and NaOH (28 mg, 4 equiv.). White beige solid. Yield 51 mg (71%). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.18 (d, J = 1.0 Hz, 1H), 7.55 (d, J = 2.5 Hz, 1H), 7.29 – 7.10 (m, 2H), 6.94 (dt, J = 8.0, 1.0 Hz, 1H), 6.09 (d, J = 2.5 Hz, 1H), 4.87 (s, 2H). ^{13}C NMR (101 MHz, MeOH-d_4) δ 171.8, 153.2, 143.1, 138.5, 133.6, 132.8, 129.3, 115.5, 104.6, 101.6, 97.7, 53.3. LC-MS (ESI/APCI) $[M+H]^+$ 258.29.

4-Bromo-1-ethoxy-2-fluorobenzene (192)



4-Bromo-2-fluorophenol **191** (2.62 g, 1 equiv.) was dissolved in DMF (25 mL) and K_2CO_3 (3.78 g, 2 equiv.) was added thereto, followed by bromoethane (2.98 g, 2 equiv.). Resulting mixtire stirred at room temperature for 16 h. Then reaction mixture diluted with brine (50 mL) and extracted with pertroleum ether (100 mL). Organic extract washed with brine (2×25 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain product as a white yellow oil. Yield 2.737 g (91%). Spectral data consistent with previously reported.[97]

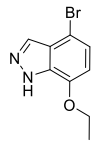
6-Bromo-3-ethoxy-2-fluorobenzaldehyde (193)



2.4 M solution of n-BuLi in hexane (7.34 mL, 1.3 equiv.) was added dropwise to a stirred solition of diisopropylamine (2.485 mL, 1.3 equiv.) in THF under Ar atmosphere at 0 °C. After stirring for 20 min, freshly prepared LDA solution was cooled to -78 ° and 4-bromo-1-ethoxy-2-fluorobenzene **192** (2.62 g, 1 equiv.), dissolved in dry THF (8 mL) was slowly added dropwise. Resulting mixtire stirred at -78 °C for 1 h. After indicated time, DMF (2.1 mL, 2 equiv.) was added dropwise to the reaction mixture. Then reaction allowed to warm to room temperature, diluted with brine (70 mL) and extracted with EtOAc (150 mL). Organic extract washed with brine (3×40 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain product as a white yellow solid. Yield 3.1 g (93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 7.36 (dd, J = 8.8, 2.0 Hz, 1H), 7.03 (t, J = 8.6 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 1.46 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.8, 153.7 (d, J = 266.9 Hz), 147.4 (d, J = 10.5 Hz), 129.3 (d, J = 4.7 Hz), 123.2 (d, J = 6.9 Hz), 120.1 (d, J = 3.8 Hz),

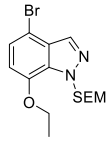
114.1 (d, *J* = 1.8 Hz), 65.8, 14.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -135.45 (d, *J* = 8.0 Hz). LC-MS (ESI/APCI) $[M+H]^+$ 247.16/249.25.

4-Bromo-7-ethoxy-1*H*-indazole (194)



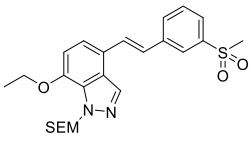
6-Bromo-3-ethoxy-2-fluorobenzaldehyde **193** (3.1 g, 1 equiv.)**,** was dissolved in DMSO **(**15 mL) and hydrazine hydrate (12.23 mL, 20 equiv.) was added thereto. Resulting solution heated at 110 °C for 16 h. After cooling down to room temperature reaction mixture diluted with water (70 mL). Formed precipitate was filtered and washed with water (2×15 mL) to precipitate the product. Yield 2.75 g (81%), yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (br. s, 1H), 8.09 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 1.54 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4, 135.1, 133.1, 125.5, 124.1, 106.9, 104.3, 64.4, 14.9. LC-MS (ESI/APCI) $[M+H]^+$ 241.21/243.19.

4-Bromo-7-ethoxy-1-[(2-(trimethylsilyl)ethoxy)methyl]-1*H*-indazole (195)



4-Bromo-7-ethoxy-1*H*-indazole **194** (946 mg, 1 equiv.) was dissolved in THF (20 mL) and 60% NaH in mineral oil (188 mg, 1.2 equiv.) was added portionwise under ice cooling. After stirring for 30 min at 0 °C, SEM chloride (900 μL, 1.3 equiv.) was added dropwise. Resulting mixtire gradually warmed up to room temperature for 1 h. Then reaction mixture neutralized with brine (30 mL) and extracted with EtOAc (70 mL). Organic extract washed with brine (2×20 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product. Compound purified by silica gel column chromatography using EtOAc gradient in petroleum ehter from 5 to 25% to obtain product as a slightly yellow oil. Yield 1.308 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 5.93 (s, 2H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.68 – 3.49 (m, 2H), 1.53 (t, *J* = 7.0 Hz, 3H), 0.93 – 0.80 (m, 2H), -0.07 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 134.7, 131.9, 127.3, 124.5, 108.0, 104.5, 79.7, 66.4, 64.5, 17.9, 14.8, -1.3. LC-MS (ESI/APCI) $[M+H]^+$ 371.42/373.40.

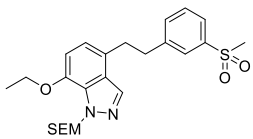
7-Ethoxy-4-(3-(methylsulfonyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (197)



4-Bromo-7-ethoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole **195** (150 mg, 1 equiv.) was dissolved in DMF (7 mL) and 1-(methylsulfonyl)-3-vinylbenzene (88 mg, 1.2 equiv.) was

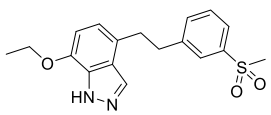
added thereto, followed by TEA (563 μL, 10 equiv.), tri-*o*-tolylphosphine (25 mg, 20 mol%) and $Pd(OAc)_2$ (9 mg, 10 mol%). Resulting solution heated at 100 °C for 16 h. After cooling down to room temperature reaction nixture evaporated in vacuo to dryness and water (15 mL) added thereto. Then reaction extracted with EtOAc (30 mL). Organic extract washed with brine (2×10 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product. Purified by silica gel column chromatography using gradient from 5 to 50% EtOAc in petroleum ether to obtain product as a yellowish oil. Yield 187 mg (98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.11 (t, *J* = 1.8 Hz, 1H), 7.84 – 7.73 (m, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 16.5 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 5.82 (s, 2H), 4.32 (q, *J* = 7.0 Hz, 2H), 3.73 – 3.63 (m, 2H), 3.10 (s, 3H), 1.58 (t, *J* = 7.0 Hz, 3H), 1.05 – 0.92 (m, 2H), -0.01 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 142.6, 141.3, 139.7, 131.3, 131.2, 130.6, 130.3, 129.9, 125.6, 125.5, 124.7, 122.2, 121.6, 104.0, 82.2, 67.8, 64.2, 44.7, 18.1, 14.8, -1.2. LC-MS (ESI/APCI) $[M+H]^+$ 473.58.

7-Ethoxy-4-[3-(methylsulfonyl)phenethyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indazole (198)



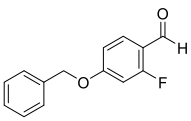
7-Ethoxy-4-(3-(methylsulfonyl)styryl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole **197** (174 mg, 1 equiv.) was dissolved in MeOH **(**8 mL) and 10% Pd on carbon (20 mg, 5 mol%) was added thereto, followed by triethylsilane (353 μL, 6 equiv.). Resulting mixtire stirred for 16 h at room temperature. Then catalyst filtered off and methanolic solution evaporated in vacuo to obtain crude product. Purified by silica gel column chromatography using gradient from 5 to 50% EtOAc in petroleum ether to obtain product as an oil. Yield 101 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.80 (dt, *J* = 7.4, 1.8 Hz, 1H), 7.75 (t, *J* = 1.6 Hz, 1H), 7.49 – 7.45 (m, 2H), 6.71 (d, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 7.5 Hz, 1H), 5.79 (s, 2H), 4.28 (q, *J* = 7.0 Hz, 2H), 3.77 – 3.61 (m, 2H), 3.15 (s, 3H), 3.02 (s, 2H), 2.54 (s, 2H), 1.58 (t, *J* = 7.0 Hz, 3H), 1.11 – 0.89 (m, 2H), 0.03 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3, 143.5, 142.2, 140.4, 133.8, 131.1, 130.1, 129.2, 127.1, 124.8, 124.4, 124.2, 103.4, 81.8, 67.4, 63.6, 44.3, 36.2, 34.8, 17.8, 14.7, -1.41. LC-MS (ESI/APCI) $[M+H]^+$ 475.57.

7-Ethoxy-4-(3-(methylsulfonyl)phenethyl)-1*H*-indazole (199)



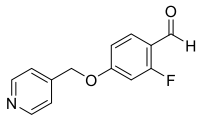
7-Ethoxy-4-(3-(methylsulfonyl)phenethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole **198** (101 mg, 1 equiv.) was dissolved in MeOH **(**8 mL) and 37% aqueous HCl (1.5 mL, excess) was added thereto. Resulting mixtire stirred for 16 h at room temperature. Then reaction mixture evaporated in vacuo, neutralized with $NaHCO_3$ (10 mL) and extracted with EtOAc (20 mL). Organic extract washed with brine (2×5 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product. Compound purified by silica gel column chromatography using EtOAc gradient in petroleum ehter from 20 to 70% to obtain product as a colorless oil. Yield 36 mg (49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (br. s, 1H), 7.93 (s, 1H), 7.73 (d, *J* = 6.8 Hz, 1H), 7.62 (d, *J* = 1.8 Hz, 1H), 7.47 – 7.37 (m, 2H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.22 – 3.04 (m, 4H), 2.91 (s, 3H), 1.49 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 143.3, 140.4, 134.0, 133.2, 132.4, 129.4, 127.3, 125.3, 125.0, 124.5, 120.8, 105.8, 64.0, 44.4, 37.0, 34.5, 14.9. LC-MS (ESI/APCI) $[M+H]^+$ 345.42.

4-(Benzyloxy)-2-fluorobenzaldehyde (201a)



2-Fluoro-4-hydroxybenzaldehyde **200** (2 g, 1 equiv.) was dissolved in DMF (30 mL) and K_2CO_3 (2.96 g, 1.5 equiv.) was added thereto, followed by benzyl bromide (2.03 mL, 1.5 equiv.). Resulting mixture stirred at room temperature for 16 h. Then reaction mixture diluted with brine (80 mL) and extracted EtOAc (100 mL). Organic extract washed with brine (2×40 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product. Purified by crystallization from EtOAc:petroleum ether 1:10 to obtain product as a slightly pink solid Yield 2.22 g (67%). Spectral data consistent with previously reported.[98]

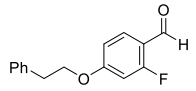
2-Fluoro-4-(pyridin-4-ylmethoxy)benzaldehyde (201b)



Compound was prepared in analogues way as **201a**, starting from 2-fluoro-4-hydroxybenzaldehyde **200** (500 mg, 1 equiv.), K_2CO_3 (1.23 g, 2.5 equiv.) and 4-(chloromethyl)pyridine hydrochloride (819 mg, 1.4 equiv.). Purified by trituration with Et_2O to obtain product as a slightly yellow solid. Yield 176 mg (21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.65 (d, *J* = 6.0 Hz, 2H), 7.84 (dd, *J* = 8.8, 8.1 Hz, 1H), 7.34 (d, *J* = 6.0 Hz, 2H), 6.85 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.71 (dd, *J* = 12.1, 2.3 Hz, 1H), 5.16 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ

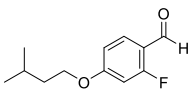
185.9, 166.2 (d, *J* = 259.2 Hz), 164.5 (d, *J* = 11.8 Hz), 150.4, 144.6, 130.5 (d, *J* = 3.8 Hz), 121.5, 118.6 (d, *J* = 8.4 Hz), 111.8 (d, *J* = 3.0 Hz), 102.6 (d, *J* = 24.3 Hz), 68.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.64 (dd, *J* = 12.0, 8.1 Hz). LC-MS (ESI/APCI) $[M+H]^+$ 232.37.

2-Fluoro-4-phenethoxybenzaldehyde (201c)



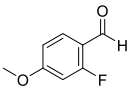
Compound was prepared in analogues way as **201a**, starting from 2-fluoro-4-hydroxybenzaldehyde **200** (400 mg, 1 equiv.), K_2CO_3 (789 mg, 2 equiv.) and 2-phenylethylbromide (507 μL, 1.3 equiv.). Purified by trituration with petrolleum ether to obtain product as a yellow solid. Yield 445 mg (64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.73 (dd, *J* = 8.8, 8.2 Hz, 1H), 7.31 – 7.23 (m, 2H), 7.23 – 7.15 (m, 3H), 6.69 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.55 (dd, *J* = 12.4, 2.3 Hz, 1H), 4.16 (t, *J* = 7.0 Hz, 2H), 3.05 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.0 (d, *J* = 6.0 Hz), 166.4 (d, *J* = 258.5 Hz), 165.5 (d, J = 11.9 Hz), 137.5, 130.2 (d, *J* = 4.0 Hz), 129.1, 128.8, 126.9, 118.0 (d, *J* = 8.4 Hz), 111.7 (d, *J* = 2.7 Hz), 102.0 (d, *J* = 24.0 Hz), 69.6, 35.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -119.17 (dd, *J* = 12.4, 8.2 Hz). LC-MS (ESI/APCI) $[M+H]^+$ 245.39.

2-Fluoro-4-(isopentyloxy)benzaldehyde (201d)



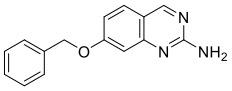
Compound was prepared in analogues way as **201a**, starting from 2-fluoro-4-hydroxybenzaldehyde **200** (400 mg, 1 equiv.), K_2CO_3 (789 mg, 2 equiv.) and 1-bromo-3-methylbutane (536 μL, 1.5 equiv.). Yellowish oil, yield 527 mg (88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.79 (dd, *J* = 8.7, 8.2 Hz, 1H), 6.76 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.61 (dd, *J* = 12.5, 2.3 Hz, 1H), 4.04 (t, *J* = 6.6 Hz, 2H), 1.81 (sept, *J* = 6.6 Hz, 1H), 1.69 (q, *J* = 6.7 Hz, 2H), 0.96 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.0 (d, *J* = 5.9 Hz), 166.4 (d, *J* = 258.3 Hz), 165.9 (d, J = 11.9 Hz), 130.2 (d, *J* = 4.0 Hz), 117.8 (d, *J* = 8.4 Hz), 111.8 (d, *J* = 2.8 Hz), 101.9 (d, *J* = 23.9 Hz), 67.5, 37.7, 25.1, 22.6. LC-MS (ESI/APCI) $[M+H]^+$ 211.36.

2-Fluoro-4-methoxybenzaldehyde (201e)



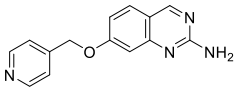
Compound was prepared in analogues way as **201a**, starting from 2-fluoro-4-hydroxybenzaldehyde **200** (2 g, 1 equiv.), K_2CO_3 (2.96 g, 1.5 equiv.) and methyl iodide (1.78 mL, 2 equiv.). Slightly orange solid, yield 2.02 g (92%). Spectral data consistent with previously reported.[99]

7-(Benzyloxy)quinazolin-2-amine (202a)



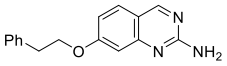
4-(Benzyloxy)-2-fluorobenzaldehyde **201a** (2.22 g, 1 equiv.) was dissolved in DMA (45 mL) and Na_2CO_3 (1.43 g, 1.4 equiv.) was added thereto, followed by guanidine carbonate (1.63 g, 1.4 equiv.). Resulting mixture heated at 140 °C for 16 h. Then reaction mixture cooled down to room temperature, diluted with water (100 mL) and extracted EtOAc (100 mL). Organic extract washed with brine (2×30 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product. Purified by trituration with EtOAc to obtain product as an off-white solid. Yield 771 mg (32%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.54 – 7.22 (m, 5H), 6.90 (d, J = 8.9 Hz, 1H), 6.86 (s, 1H), 6.71 (br. s, 2H), 5.22 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.8, 161.2, 160.9, 154.0, 136.6, 129.3, 128.5, 128.0, 127.8, 115.0, 114.5, 104.7, 69.5. LC-MS (ESI/APCI) $[M+H]^+$ 252.43.

7-(Pyridin-4-ylmethoxy)quinazolin-2-amine (202b)



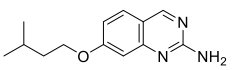
Compound was prepared in analogues way as **202a**, starting from 2-fluoro-4-(pyridin-4-ylmethoxy)benzaldehyde **201b** (166 mg, 1 equiv.), Na_2CO_3 (122 mg, 1.6 equiv.) and guanidine carbonate (139 mg, 1.6 equiv.). Purified by trituration with EtOAc to obtain product as a slightly yellow solid. Yield 59 mg (33%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (d, J = 0.7 Hz, 1H), 8.59 (d, J = 6.0 Hz, 2H), 7.71 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 6.0 Hz, 2H), 6.94 (dd, J = 8.8, 2.4 Hz, 2H), 6.82 (d, J = 2.3 Hz, 1H), 6.72 (br. s, 2H), 5.31 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.3, 161.2, 161.0, 153.9, 149.8, 145.7, 129.5, 121.9, 115.1, 114.3, 104.9, 67.7. HR-MS (ESI/TOF) calcd for $C_{14}H_{13}N_4O$ $[M+H]^+$ 253.1089, found 253.1098.

7-Phenethoxyquinazolin-2-amine (202c)



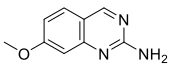
Compound was prepared in analogues way as **202a**, starting from 2-fluoro-4-phenethoxybenzaldehyde **201c** (430 mg, 1 equiv.), Na_2CO_3 (298 mg, 1.6 equiv.) and guanidine carbonate (341 mg, 1.6 equiv.). Purified by trituration with MeCN to obtain product as a slightly yellow solid. Yield 55 mg (12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.56 (d, J = 9.2 Hz, 1H), 7.42 – 7.14 (m, 5H), 6.91 (d, J = 2.3 Hz, 1H), 6.88 (s, 1H), 5.24 (br. s, 2H), 4.30 (t, J = 6.9 Hz, 2H), 3.15 (t, J = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 161.0, 160.7, 154.5, 138.0, 129.1, 129.0, 128.7, 126.8, 116.7, 115.9, 104.6, 68.9, 35.5. LC-MS (ESI/APCI) $[M+H]^+$ 266.46.

7-(Isopentyloxy)quinazolin-2-amine (202d)



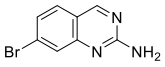
Compound was prepared in analogues way as **202a**, starting from 2-fluoro-4-(isopentyloxy)benzaldehyde **201d** (512 mg, 1 equiv.), Na_2CO_3 (413 mg, 1.6 equiv.) and guanidine carbonate (472 mg, 1.6 equiv.). Purified by trituration with Et_2O to obtain product as an off-white solid. Yield 48 mg (9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.55 (d, *J* = 8.9 Hz, 1H), 6.90 (d, *J* = 2.3 Hz, 1H), 6.87 (s, 1H), 5.25 (br. s, 2H), 4.09 (t, *J* = 6.7 Hz, 2H), 1.85 (sept, *J* = 6.7 Hz, 1H), 1.73 (q, *J* = 6.7 Hz, 2H), 0.97 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 161.0, 160.7, 154.5, 128.9, 116.8, 115.8, 104.3, 66.93, 37.7, 25.2, 22.7. LC-MS (ESI/APCI) $[M+H]^+$ 232.43.

7-Methoxyquinazolin-2-amine (202e)



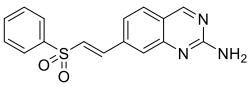
Compound was prepared in analogues way as **202a**, starting from 2-fluoro-4-methoxybenzaldehyde **201e** (1.58 g, 1 equiv.), Na_2CO_3 (1.74 g, 1.6 equiv.) and guanidine carbonate (1.98 g, 1.6 equiv.). Mustard-colored powder, yield 1.37 g (76%). Spectral data consistent with previously reported.[100]

7-Bromoquinazolin-2-amine (204)



Compound was prepared in analogues way as **211a**, starting from 4-bromo-2-fluorobenzaldehyde **212** (10 g, 1 equiv.), Na_2CO_3 (8.35 g, 1.6 equiv.) and guanidine carbonate (9.54 g, 1.6 equiv.). Purified by trituration with hot EtOH to obtain product as a white beige solid. Yield 1.37 g (76%). Spectral data consistent with previously reported.[101]

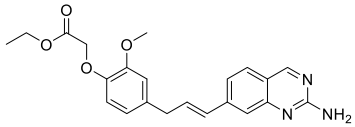
7-[2-(Phenylsulfonyl)vinyl]quinazolin-2-amine (206a)



7-Bromoquinazolin-2-amine **204** (536 mg, 1 equiv.) was dissolved in DMF (15 mL) and (vinylsulfonyl)benzene (805 mg, 2 equiv.) was added thereto, followed by TEA (1 mL, 3 equiv.), tri-*o*-tolylphosphine (73 mg, 10 mol%) and $Pd(OAc)_2$ (27 mg, 10 mol%). Resulting solution heated at 100 °C for 16 h. After cooling down to room temperature reaction mixture evaporated in vacuo to dryness and water (40 mL) added thereto. Then reaction extracted with EtOAc (100 mL). Organic extract washed with brine (2×30 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product. Purified by trituration with EtOAc to obtain product as a brown solid. Yield 520 mg (70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.01 – 7.91 (m, 2H), 7.83 – 7.71 (m, 5H), 7.71 – 7.64 (m, 2H), 7.58 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.98 (br. s, 2H). ^{13}C NMR (101 MHz,

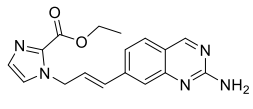
DMSO-d_6) δ 162.2, 161.3, 152.0, 141.4, 140.4, 137.5, 133.8, 130.6, 129.7, 128.5, 127.3, 127.0, 120.3, 120.2. LC-MS (ESI/APCI) $[M+H]^+$ 312.41.

Ethyl 2-{4-[3-(2-aminoquinazolin-7-yl)allyl]-2-methoxyphenoxy}acetate (206b)



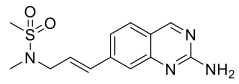
Compound was prepared in analogues way as **206a**, starting from 7-bromoquinazolin-2-amine **204** (358 mg, 1 equiv.) and ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (400 mg, 1 equiv.). Coupling stage performed using TEA (668 µL, 3 equiv.), tri-o-tolylphosphine (58 mg, 12 mol%) and $Pd(OAc)_2$ (21 mg, 6 mol%). Purified by trituration with Et_2O to obtain product as a light brown solid. Yield 470 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 0.4H, minor isomer), 8.93 (s, 0.6H, major isomer), 7.62 (dd, *J* = 12.7, 8.3 Hz, 1H), 7.44 (s, 1H), 7.34 (dd, *J* = 8.4, 1.5 Hz, 0.6H, major isomer), 7.18 (dd, *J* = 8.2, 1.5 Hz, 0.4H, minor isomer), 6.92 (d, *J* = 2.0 Hz, 0.4H, minor isomer), 6.85 (dd, *J* = 8.4, 2.0 Hz, 0.6H, major isomer). 6.82 – 6.70 (m, 2H), 6.58 – 6.52 (m, 1H), 6.43 (d, *J* = 15.7 Hz, 0.6H, major isomer), 6.31 – 6.19 (m, 0.4H, minor isomer) 5.32 (br. s, 2H), 4.66 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 3.65 (d, *J* = 6.8 Hz, 0.8H, minor isomer), 3.54 (d, *J* = 4.0 Hz, 1.2H, major isomer), 1.28 (t, *J* = 7.1 Hz, 3H). Complicated ^{13}C NMR due to presence of both E and Z isomers. LC-MS (ESI/APCI) $[M+H]^+$ 394.52.

Ethyl 1-[3-(2-aminoquinazolin-7-yl)allyl]-1*H*-imidazole-2-carboxylate (206c)



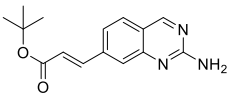
Compound was prepared in analogues way as **206a**, starting from 7-bromoquinazolin-2-amine **204** (447 mg, 1 equiv.) and ethyl 1-allyl-1*H*-imidazole-2-carboxylate (396 mg, 1.1 equiv.). Coupling stage performed using TEA (835 µL, 3 equiv.), tri-*o*-tolylphosphine (91 mg, 15 mol%) and $Pd(OAc)_2$ (31 mg, 7 mol%). Purified by trituration with EtOH to obtain product as a brown solid. Yield 297 mg (46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 1.1 Hz, 1H), 7.37 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.32 (s, 1H), 7.14 (d, *J* = 1.0 Hz, 1H), 6.83 (br. s, 2H), 6.68 (dt, *J* = 15.9, 5.8 Hz, 1H), 6.55 (d, *J* = 16.0 Hz, 1H), 5.22 (dd, *J* = 5.9, 1.3 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.73, 161.15, 158.63, 152.28, 141.26, 135.56, 131.57, 129.12, 128.63, 128.11, 126.16, 122.75, 119.52, 118.94, 60.71, 49.41, 14.09. LC-MS (ESI/APCI) $[M+H]^+$ 324.49.

***N*-[3-(2-aminoquinazolin-7-yl)allyl]-*N*-methylmethanesulfonamide (206d)**



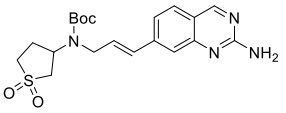
Compound was prepared in analogues way as **206a**, starting from 7-bromoquinazolin-2-amine **204** (600 mg, 1 equiv.) and *N*-allyl-*N*-methylmethanesulfonamide (479 mg, 1.2 equiv.). Coupling stage performed using TEA (1.12 mL, 3 equiv.), tri-*o*-tolylphosphine (122 mg, 15 mol%) and $Pd(OAc)_2$ (42 mg, 7 mol%). Purified by trituration with EtOAc:petroleum ether 1:1 to obtain product as a brown solid. Yield 655 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.64 (t, *J* = 8.1 Hz, 1H), 7.47 (s, 1H), 7.40 – 7.31 (m, 1H), 6.82 – 6.63 (m, 1H), 6.38 (dt, *J* = 15.8, 6.5 Hz, 1H), 5.36 (br. s, 2H), 3.99 (dd, *J* = 6.5, 1.4 Hz, 2H), 2.89 (s, 3H), 2.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 160.6, 152.5, 142.0, 133.7, 128.0, 127.3, 123.6, 121.2, 120.0, 52.3, 36.5, 34.6. LC-MS (ESI/APCI) $[M+H]^+$ 293.43.

***tert*-Butyl 3-(2-aminoquinazolin-7-yl)acrylate (206e)**



Compound was prepared in analogues way as **206a**, starting from 7-bromoquinazolin-2-amine **204** (600 mg, 1 equiv.) and tert-butyl acrylate (510 µL, 1.3 equiv.). Coupling stage performed using TEA (1.12 mL, 3 equiv.), tri-o-tolylphosphine (163 mg, 20 mol%) and $Pd(OAc)_2$ (60 mg, 10 mol%). Purified by trituration with EtOAc:petroleum ether 1:1 to obtain product as a yellow-green solid. Yield 581 mg (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.77 – 7.55 (m, 3H), 7.43 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 5.40 (br. s, 2H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 162.2, 160.7, 152.4, 142.6, 140.5, 128.1, 126.1, 123.4, 121.5, 120.8, 81.1, 28.3. LC-MS (ESI/APCI) $[M+H]^+$ 272.49.

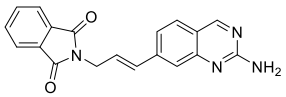
***tert*-Butyl [3-(2-aminoquinazolin-7-yl)allyl](1,1-dioxidotetrahydrothiophen-3-yl)carbamate (206f)**



Compound was prepared in analogues way as **206a**, starting from 7-bromoquinazolin-2-amine **204** (400 mg, 1 equiv.) and *tert*-butyl allyl(1,1-dioxidotetrahydrothiophen-3-yl)-carbamate (589 mg, 1.2 equiv.). Coupling stage performed using TEA (746 µL, 3 equiv.), tri-o-tolylphosphine (81 mg, 15 mol%) and $Pd(OAc)_2$ (28 mg, 7 mol%). Purified by crystallization from EtOH to obtain product as a yellow-brown solid. Yield 413 mg (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 1.4 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.59 (dd, *J* = 15.9, 1.6 Hz, 1H), 6.33 (dt, *J* = 15.9, 5.8 Hz, 1H), 5.27 (br. s, 2H), 4.64 (s, 1H), 4.05 (d, *J* = 5.7 Hz, 2H), 3.43 – 3.19 (m, 3H), 3.01 (dt, *J* = 13.2, 9.1 Hz, 1H), 2.58 – 2.30 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (101

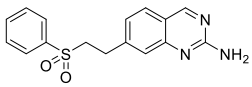
MHz, $CDCl_3$) δ 162.1, 160.6, 154.6, 152.5, 142.2, 131.7, 129.3, 128.0, 123.3, 121.4, 120.0, 81.7, 52.9, 51.9, 51.6, 47.8, 28.5, 27.5. LC-MS (ESI/APCI) $[M+H]^+$ 419.54.

2-[3-(2-Aminoquinazolin-7-yl)allyl]isoindoline-1,3-dione (206g)



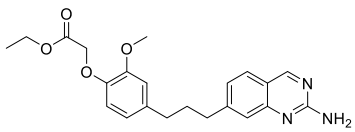
Compound was prepared in analogues way as **206a**, starting from 7-bromoquinazolin-2-amine **204** (511 mg, 1 equiv.) and 2-allylisoindoline-1,3-dione (470 mg, 1.1 equiv.). Coupling stage performed using TEA (955 µL, 3 equiv.), tri-o-tolylphosphine (69 mg, 10 mol%) and $Pd(OAc)_2$ (26 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a light brown solid. Yield 120 mg (16%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 7.95 – 7.78 (m, 4H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.34 (s, 1H), 6.76 (s, 1H), 6.69 (d, *J* = 16.1 Hz, 1H). 6.53 (dt, *J* = 16.1, 5.5 Hz, 1H), 4.40 (dd, *J* = 5.5, 1.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.79, 161.87, 161.13, 152.35, 141.72, 134.60, 131.85, 130.92, 128.18, 127.57, 123.28, 122.65, 119.76, 118.97 (one carbon is missing due to overlap with DMSO signal). LC-MS (ESI/APCI) $[M+H]^+$ 331.48.

7-[2-(Phenylsulfonyl)ethyl]quinazolin-2-amine (207a)



7-(2-(Phenylsulfonyl)vinyl)quinazolin-2-amine **206a** (300 mg, 1 equiv.) was dissolved in DMF (5 mL) and formic acid (109 µL, 3 equiv.) was added thereto, followed by TEA (403 µL, 3 equiv.) and $Pd(OAc)_2$ (22 mg, 10 mol%). Resulting solution heated at 60 °C for 1 h. After cooling down to room temperature reaction mixture diluted with water (30 mL) and extracted with EtOAc (60 mL). Organic extract washed with brine (2×10 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product. Purified by trituration with EtOAc to obtain product as a light brown solid. Yield 119 mg (39%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.00 – 7.89 (m, 2H), 7.82 – 7.60 (m, 4H), 7.22 (s, 1H), 7.07 (dd, *J* = 8.3, 1.5 Hz, 1H), 6.79 (br. s, 2H), 3.82 – 3.64 (m, 2H), 3.12 – 2.90 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.8, 161.0, 152.0, 144.2, 138.9, 133.8, 129.4, 127.8, 127.7, 123.6, 122.9, 118.2, 54.6, 28.7. LC-MS (ESI/APCI) $[M+H]^+$ 314.44.

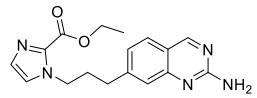
Ethyl 2-{4-[3-(2-Aminoquinazolin-7-yl)propyl]-2-methoxyphenoxy}acetate (207b)



Compound was prepared in analogues way as **207a**, starting from ethyl 2-(4-(3-(2-aminoquinazolin-7-yl)allyl)-2-methoxy-phenoxy)acetate **206b** (250 mg,

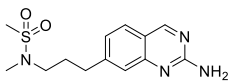
1 equiv.), formic acid (59 µL, 2.5 equiv.), TEA (266 µL, 3 equiv.) and $Pd(OAc)_2$ (14 mg, 10 mol%). Purified by trituration with EtOAc:petroleum ether 1:1 to obtain product as a light brown solid. Yield 143 mg (57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 1.4 Hz, 1H), 7.12 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.73 – 6.61 (m, 2H), 5.27 (br. s, 2H), 4.65 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.61 (t, *J* = 7.7 Hz, 2H), 2.00 (p, *J* = 7.7 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 162.0, 160.4, 152.4, 149.8, 149.6, 145.6, 136.5, 127.5, 125.0, 124.1, 120.3, 119.0, 114.7, 112.5, 66.9, 61.3, 56.0, 36.0, 35.1, 32.4, 14.3. LC-MS (ESI/APCI) $[M+H]^+$ 396.53.

Ethyl 1-[3-(2-Aminoquinazolin-7-yl)propyl]-1*H*-imidazole-2-carboxylate (207c)



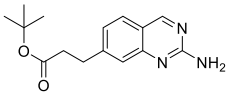
Compound was prepared in analogues way as **207a**, starting from ethyl 1-[3-(2-aminoquinazolin-7-yl)allyl]-1*H*-imidazole-2-carboxylate **206c** (250 mg, 1 equiv.), formic acid (73 µL, 2.5 equiv.), TEA (323 µL, 3 equiv.) and $Pd(OAc)_2$ (17 mg, 10 mol%). Purified by trituration with EtOAc:petroleum ether 1:1 to obtain product as a light brown solid. Yield 121 mg (48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.62 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.35 (dt, *J* = 1.7, 0.8 Hz, 1H), 7.15 (d, *J* = 1.0 Hz, 1H), 7.09 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.04 (d, *J* = 1.1 Hz, 1H), 5.36 (br. s, 2H), 4.45 (t, *J* = 7.2 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.82 – 2.74 (m, 2H), 2.21 (p, *J* = 7.6 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 160.5, 159.2, 152.4, 147.9, 136.3, 129.7, 127.8, 125.3, 124.4, 124.1, 119.1, 61.6, 48.0, 33.3, 32.0, 14.4. HR-MS (ESI/TOF) calcd for $C_{17}H_{20}N_5O_2$ $[M+H]^+$ 326.1617, found 326.1618.

***N*-[3-(2-Aminoquinazolin-7-yl)propyl]-*N*-methylmethanesulfonamide (207d)**



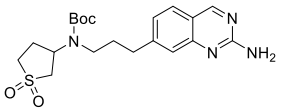
Compound was prepared in analogues way as **207a**, starting from *N*-(3-(2-aminoquinazolin-7-yl)allyl)-*N*-methylmethane-sulfonamide **206d** (300 mg, 1 equiv.), formic acid (97 µL, 2.5 equiv.), TEA (429 µL, 3 equiv.) and $Pd(OAc)_2$ (23 mg, 10 mol%). Purified by trituration with EtOAc to obtain product as a grey-brown solid. Yield 129 mg (43%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 1.5 Hz, 1H), 7.12 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.74 (br. s, 2H), 3.08 (t, *J* = 7.1 Hz, 2H), 2.84 (s, 3H), 2.75 (s, 3H), 2.72 – 2.64 (m, 2H), 1.87 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.8, 161.0, 152.1, 148.2, 127.8, 123.4, 123.2, 118.1, 49.1, 34.6, 34.5, 32.7, 28.5. LC-MS (ESI/APCI) $[M+H]^+$ 295.42.

***tert*-Butyl 3-(2-aminoquinazolin-7-yl)propanoate (207e)**



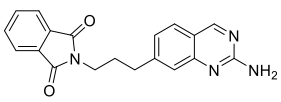
Compound was prepared in analogues way as **207a**, starting from *tert*-butyl 3-(2-aminoquinazolin-7-yl)acrylate **206e** (400 mg, 1 equiv.), formic acid (139 µL, 2.5 equiv.), TEA (616 µL, 3 equiv.) and $Pd(OAc)_2$ (33 mg, 10 mol%). Purified by trituration with EtOAc:petroleum ether 1:1 to obtain product as a yellow solid. Yield 140 mg (35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 0.8 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.37 (dt, *J* = 1.8, 0.8 Hz, 1H), 7.15 (dd, *J* = 8.2, 1.6 Hz, 1H), 5.32 (br. s, 2H), 3.04 (t, *J* = 7.7 Hz, 2H), 2.61 (t, *J* = 7.8 Hz, 2H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 162.0, 160.5, 152.4, 148.2, 127.6, 124.7, 124.1, 119.1, 80.8, 36.4, 31.7, 28.2. LC-MS (ESI/APCI) $[M+H]^+$ 274.52.

***tert*-Butyl [3-(2-aminoquinazolin-7-yl)propyl](1,1-dioxidotetrahydrothiophen-3-yl)carbamate (207f)**



Compound was prepared in analogues way as **207a**, starting from tert-butyl [3-(2-aminoquinazolin-7-yl)allyl](1,1-dioxidotetrahydrothiophen-3-yl)-carbamate **206f** (300 mg, 1 equiv.), formic acid (68 µL, 2.5 equiv.), TEA (300 µL, 3 equiv.) and $Pd(OAc)_2$ (16 mg, 10 mol%). Purified by trituration with EtOAc:petroleum ether 1:1 to obtain product as a grey solid. Yield 151 mg (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.34 (s, 1H), 7.10 (dd, *J* = 8.3, 1.6 Hz, 1H), 5.32 (br. s, 2H), 4.40 (br. s, 1H), 3.43 – 3.14 (m, 5H), 3.09 – 2.93 (m, 1H), 2.73 (t, J = 7.7 Hz, 2H), 2.45 – 2.28 (m, 2H), 2.00 – 1.79 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 160.5, 154.6, 152.4, 148.4, 127.9, 124.4, 124.0, 119.1, 81.2, 60.5, 53.5, 51.6, 46.4, 33.9, 31.0, 28.5, 27.5. LC-MS (ESI/APCI) $[M+H]^+$ 421.59.

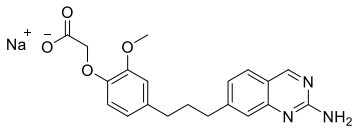
2-[3-(2-Aminoquinazolin-7-yl)propyl]isoindoline-1,3-dione (207g)



Compound was prepared in analogues way as **207a**, starting from 2-(3-(2-aminoquinazolin-7-yl)allyl)isoindoline-1,3-dione **206g** (122 mg, 1 equiv.), formic acid (35 µL, 2.5 equiv.), TEA (156 µL, 3 equiv.) and $Pd(OAc)_2$ (8 mg, 10 mol%). Purified by trituration with EtOAc:petroleum ether 1:1 to obtain product as a light brown solid. Yield 34 mg (27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.79 (qd, *J* = 4.4, 2.1 Hz, 4H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.22 (s, 1H), 7.07 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.71 (br. s, 2H), 3.62 (t, *J* = 6.9 Hz, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 1.98 (p, *J* = 7.1 Hz, 2H). ^{13}C NMR (101

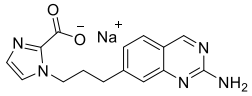
MHz, $CDCl_3$) δ 168.0, 161.7, 160.9, 152.0, 147.9, 134.3, 131.6, 127.7, 123.2, 123.1, 122.9, 118.0, 37.2, 33.1, 28.7. LC-MS (ESI/APCI) $[M+H]^+$ 333.49.

Sodium 2-{4-[3-(2-aminoquinazolin-7-yl)propyl]-2-methoxyphenoxy}acetate (208a)



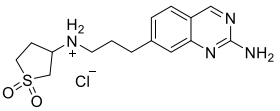
To a stirred solution of ethyl 2-(4-(3-(2-aminoquinazolin-7-yl)propyl)-2-methoxyphenoxy)-acetate **207b** (96 mg, 1 equiv.) dissolved in EtOH (5 mL), sodium hydroxide (10 mg, 1 equiv.) dissolved in H_2O (0.5 mL) was added in one portion. Resulting solution was stirred at 70 °C for 16 h, before evaporated to dryness. The residue triturated with small amount of EtOH (1 mL) to obtain crystalline solid. Precipitate filtered and washed with EtOH (0.5 mL) to obtain product as a white brown solid. Yield 49 mg (52%). ^{1}H NMR (400 MHz, D_2O) δ 8.67 (s, 1H), 7.32 (d, J = 8.6 Hz, 1H), 6.93 (s, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.67 – 6.53 (m, 2H), 6.50 (d, J = 8.5 Hz, 1H), 4.34 (s, 2H), 3.69 (s, 3H), 2.44 (br. s, 2H), 2.31 (t, J = 7.4 Hz, 2H), 1.81 – 1.56 (m, 2H). ^{13}C NMR (101 MHz, D_2O) δ 176.4, 162.2, 159.2, 151.0, 150.5, 147.6, 144.9, 135.4, 127.7, 124.8, 122.1, 120.6, 117.7, 112.2, 112.1, 67.1, 55.4, 35.2, 34.0, 31.2. LC-MS (ESI/APCI) $[M+H]^+$ 368.49.

Sodium 1-[3-(2-aminoquinazolin-7-yl)propyl]-1*H*-imidazole-2-carboxylate (208b)



Compound was prepared in analogues way as **208a**, starting from ethyl 1-[3-(2-aminoquinazolin-7-yl)propyl]-1*H*-imidazole-2-carboxylate **207c** (70 mg, 1 equiv.) and NaOH (15 mg, 1.8 equiv.). Purified by crystallization from EtOH to obtain product as a white beige solid. Yield 47 mg (68%). ^{1}H NMR (400 MHz, D_2O) δ 8.67 (s, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.09 (s, 1H), 6.95 (s, 1H), 6.91 – 6.83 (m, 2H), 4.34 (t, J = 6.8 Hz, 2H), 2.57 – 2.40 (m, 2H), 2.00 (p, J = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, D_2O) δ 165.7, 162.4, 159.0, 150.3, 149.8, 142.9, 127.9, 126.5, 124.7, 123.3, 121.6, 117.7, 47.1, 32.5, 31.3. LC-MS (ESI/APCI) $[M(decarbox)+H]^+$ 254.42.

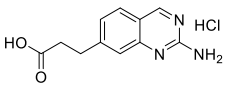
3-{[3-(2-Aminoquinazolin-7-yl)propyl]amino}tetrahydro-thiophene 1,1-dioxide hydrochloride (209a)



tert-Butyl (3-(2-aminoquinazolin-7-yl)propyl)(1,1-dioxido-tetrahydrothiophen-3-yl)carbamate **207f** (117 mg, 1 equiv.) was dissolved in DCM (8 mL) and TFA (427 µL, 20 equiv.)

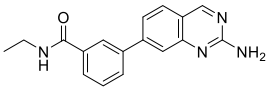
was added thereto. Resulting solution stirred at room temperature for 6 h. Then reaction evaporated in vacuo, dissolved in 5 mL of 1 M aqueous HCl and evaporated to dryness to obtain product as a yellowish oil, which solidifies on standing. Yield 61 mg (56%). ^{1}H NMR (400 MHz, D_2O) δ 8.86 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.17 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.15 (s, 1H), 4.11 (p, *J* = 8.3 Hz, 1H), 3.74 (dd, *J* = 14.1, 8.4 Hz, 1H), 3.52 (dddd, *J* = 13.4, 8.0, 3.8, 1.4 Hz, 1H), 3.40 – 3.25 (m, 2H), 3.07 (qt, *J* = 12.2, 7.7 Hz, 2H), 2.90 – 2.69 (m, 3H), 2.30 (dddd, *J* = 13.7, 10.7, 9.2, 8.1 Hz, 1H), 2.05 (p, *J* = 7.9 Hz, 2H). ^{13}C NMR (101 MHz, D_2O) δ 163.2, 159.0, 149.8, 149.4, 128.5, 124.9, 121.5, 117.9, 52.9, 52.1, 50.0, 45.9, 32.5, 27.0, 25.9. LC-MS (ESI/APCI) $[M+H]^+$ 321.45.

3-(2-Aminoquinazolin-7-yl)propanoic acid hydrochloride (209b)



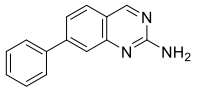
Compound was prepared in analogues way as **209a**, starting from *tert*-butyl 3-(2-aminoquinazolin-7-yl)propanoate **207e** (400 mg, 1 equiv.) and TFA (562 µL, 20 equiv.). Light yellow powder, yield 140 mg (35%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (s, 1H), 8.56 (br. s, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 1.4 Hz, 1H), 7.47 (dd, *J* = 8.2, 1.5 Hz, 1H), 3.02 (t, *J* = 7.3 Hz, 2H), 2.65 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.3, 168.9, 155.4, 152.4, 139.5, 129.4, 126.4, 116.7, 115.8, 34.2, 30.9. LC-MS (ESI/APCI) $[M+H]^+$ 218.34.

3-(2-Aminoquinazolin-7-yl)-*N*-ethylbenzamide (212a)



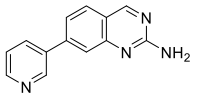
7-Bromoquinazolin-2-amine **204** (150 mg, 1 equiv.) was dissolved under Ar atmosphere in dioxane:H_2O 5:1 (10 mL) and (3-(ethylcarbamoyl)phenyl)-boronic acid **210a** (155 mg, 1.2 equiv.) was added thereto, followed by Na_2CO_3 (142 mg, 2 equiv.) and $PdCl_2$(dppf)·DCM (27 mg, 5 mol%). Resulting solution heated at 100 °C for 16 h. After cooling down to room temperature reaction mixture evaporated in vacuo to dryness and water (30 mL) added thereto. Then reaction mixture extracted with EtOAc (75 mL). Organic extract washed with brine (2×20 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product. Purified by trituration with EtOAc to obtain product as a white beige solid. Yield 196 mg (quant.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.67 (t, *J* = 5.5 Hz, 1H), 8.22 (s, 1H), 7.91 (td, *J* = 8.9, 7.7, 2.7 Hz, 3H), 7.74 (d, *J* = 1.7 Hz, 1H), 7.60 (ddd, *J* = 7.8, 4.5, 2.8 Hz, 2H), 6.86 (br. s, 2H), 3.40 – 3.24 (m, 2H)., 1.15 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.8, 162.3, 161.2, 152.3, 145.0, 139.5, 135.4, 129.9, 129.3, 128.7, 127.4, 125.8, 122.2, 121.3, 118.9, 34.3, 14.9. LC-MS (ESI/APCI) $[M+H]^+$ 293.48.

7-Phenylquinazolin-2-amine (212b)



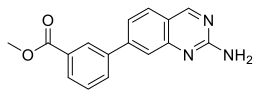
Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **204** (150 mg, 1 equiv.) and phenylboronic acid **210b** (106 mg, 1.3 equiv.). Coupling stage performed using Na_2CO_3 (177 mg, 2.5 equiv.) and $PdCl_2(dppf)\cdot DCM$ (27 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a beige solid. Yield 95 mg (64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.82 – 7.73 (m, 2H), 7.63 (s, 1H), 7.58 – 7.48 (m, 3H), 7.47 – 7.37 (m, 1H), 6.85 (br. s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2, 161.2, 152.3, 145.7, 139.5, 129.2, 128.6, 128.5, 127.3, 121.8, 121.4, 118.7. LC-MS (ESI/APCI) $[M+H]^+$ 222.36.

7-(Pyridin-3-yl)quinazolin-2-amine (212c)



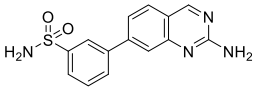
Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **204** (150 mg, 1 equiv.) and pyridin-3-ylboronic acid **210c** (123 mg, 1.5 equiv.). Coupling stage performed using Na_2CO_3 (177 mg, 2.5 equiv.) and $PdCl_2(dppf)\cdot DCM$ (27 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a beige solid. Yield 68 mg (46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.98 (d, J = 2.4 Hz, 1H), 8.63 (dd, J = 4.8, 1.6 Hz, 1H), 8.19 (dt, J = 8.1, 2.0 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.70 (s, 1H), 7.61 – 7.45 (m, 2H), 6.90 (br. s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.4, 161.2, 152.2, 149.4, 148.1, 142.6, 135.1, 134.9, 128.9, 124.1, 122.3, 121.1, 119.0. LC-MS (ESI/APCI) $[M+H]^+$ 223.34.

Methyl 3-(2-aminoquinazolin-7-yl)benzoate (212d)



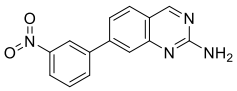
Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **204** (500 mg, 1 equiv.) and (3-(methoxycarbonyl)phenyl)boronic acid **210d** (481 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (473 mg, 2 equiv.) and $PdCl_2(dppf)\cdot DCM$ (73 mg, 4 mol%). Purified by trituration with EtOAc to obtain product as a white beige solid. Yield 509 mg (82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.26 (t, J = 1.8 Hz, 1H), 8.03 (ddt, J = 17.6, 7.7, 1.3 Hz, 2H), 7.90 (d, J = 8.3 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.54 (dd, J = 8.3, 1.8 Hz, 1H), 6.89 (br. s, 2H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.2, 162.3, 161.3, 152.2, 144.5, 140.1, 132.1, 130.5, 129.8, 129.0, 128.9, 127.7, 122.2, 121.2, 118.9, 52.5. LC-MS (ESI/APCI) $[M+H]^+$ 280.41

3-(2-Aminoquinazolin-7-yl)benzenesulfonamide (212e)



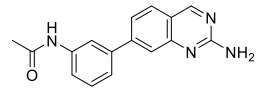
Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **204** (90 mg, 1 equiv.) and (3-sulfamoylphenyl)boronic acid **210e** (97 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (85 mg, 2 equiv.) and $PdCl_2$(dppf)·DCM (16 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a beige solid. Yield 92 mg (76%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.22 (d, J = 1.9 Hz, 1H), 8.02 (d, J = 7.7 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.91 – 7.83 (m, 1H), 7.76 – 7.66 (m, 2H), 7.56 (dd, J = 8.3, 1.7 Hz, 1H), 7.47 (s, 2H), 6.90 (br. s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.4, 161.3, 152.3, 145.0, 144.2, 140.3, 130.6, 130.0, 129.0, 125.3, 124.4, 122.3, 121.0, 119.0. LC-MS (ESI/APCI) $[M+H]^+$ 301.39.

7-(3-Nitrophenyl)quinazolin-2-amine (212f)



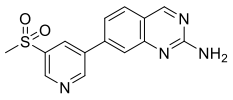
Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **204** (150 mg, 1 equiv.) and (3-nitrophenyl)boronic acid **210f** (134 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (177 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (27 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a white beige solid. Yield 138 mg (77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.51 (t, J = 2.0 Hz, 1H), 8.34 – 8.19 (m, 2H), 7.94 (d, J = 8.3 Hz, 1H), 7.80 (t, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.61 (dd, J = 8.3, 1.8 Hz, 1H), 6.92 (br. s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.4, 161.3, 152.2, 148.5, 143.3, 141.2, 134.0, 130.8, 129.0, 123.1, 122.7, 121.8, 121.1, 119.1. LC-MS (ESI/APCI) $[M+H]^+$ 267.38.

***N*-(3-(2-Aminoquinazolin-7-yl)phenyl)acetamide (212g)**



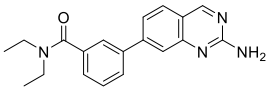
Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **204** (150 mg, 1 equiv.) and (3-acetamidophenyl)boronic acid **210g** (144 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (177 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (27 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a yellow beige solid. Yield 138 mg (77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 9.12 (s, 1H), 8.00 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.61 (td, J = 4.5, 2.0 Hz, 1H), 7.57 (s, 1H), 7.46 (dd, J = 8.4, 1.7 Hz, 1H), 7.43 (d, J = 5.1 Hz, 2H), 6.86 (br. s, 2H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.8, 162.2, 161.2, 152.2, 145.7, 140.1, 140.0, 129.6, 128.7, 122.0, 121.8, 121.2, 119.0, 118.8, 117.8, 24.2. LC-MS (ESI/APCI) $[M+H]^+$ 279.43.

7-(5-(Methylsulfonyl)pyridin-3-yl)quinazolin-2-amine (212h)



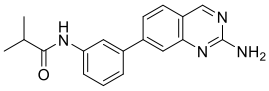
Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **204** (150 mg, 1 equiv.) and (5-(methylsulfonyl)pyridin-3-yl)boronic acid **210h** (161 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (177 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (27 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a beige solid. Yield 184 mg (91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (d, J = 2.2 Hz, 1H), 9.18 (s, 1H), 9.10 (d, J = 2.1 Hz, 1H), 8.64 (t, J = 2.2 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 1.7 Hz, 1H), 7.67 (dd, J = 8.3, 1.8 Hz, 1H), 6.94 (br. s, 2H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.5, 161.3, 152.6, 152.2, 147.0, 140.8, 137.4, 135.5, 133.7, 129.1, 123.2, 121.1, 119.3, 43.7. LC-MS (ESI/APCI) $[M+H]^+$ 301.40.

3-(2-Aminoquinazolin-7-yl)-*N*,*N*-diethylbenzamide (212i)



Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **204** (150 mg, 1 equiv.) and (3-(diethylcarbamoyl)phenyl)boronic acid **210i** (177 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (177 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (27 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a beige solid. Yield 130 mg (60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.61 – 7.51 (m, 2H), 7.39 (d, J = 7.6 Hz, 1H), 6.87 (br. s, 2H), 3.22 (br. s, 4H), 1.31 – 0.95 (m, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.8, 162.3, 161.2, 152.2, 144.9, 139.7, 138.2, 129.4, 128.8, 127.9, 126.2, 124.8, 122.1, 121.3, 118.9, 43.0, 14.2. LC-MS (ESI/APCI) $[M+H]^+$ 321.52.

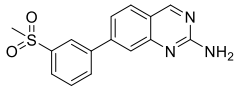
***N*-(3-(2-Aminoquinazolin-7-yl)phenyl)isobutyramide (212j)**



Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **204** (140 mg, 1 equiv.) and (3(3-isobutyramidophenyl)boronic acid **210j** (155 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (165 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (25 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a beige solid. Yield 105 mg (55%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (br. s, 1H), 9.12 (s, 1H), 8.04 (s, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.70 – 7.62 (m, 1H), 7.58 (s, 1H), 7.47 (dd, J = 8.3, 1.8 Hz, 1H), 7.44 – 7.40 (m, 2H), 6.85 (br. s, 2H), 2.61 (hept, J = 6.6 Hz, 1H), 1.12 (d, J = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.7, 162.2, 161.2, 152.2, 145.7, 140.2, 140.0, 129.6,

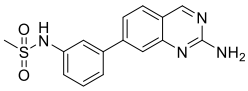
128.7, 121.9, 121.8, 121.2, 119.2, 118.8, 117.9, 35.2, 19.6. LC-MS (ESI/APCI) $[M+H]^+$ 307.50.

7-(3-(Methylsulfonyl)phenyl)quinazolin-2-amine (212k)



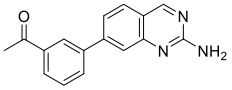
Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **204** (200 mg, 1 equiv.) and (3-(methylsulfonyl)phenyl)boronic acid **210k** (196 mg, 1.1 equiv.). Coupling stage performed using Na_2CO_3 (189 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (22 mg, 5 mol%). Purified by trituration with hot EtOH to obtain product as a white beige solid. Yield 180 mg (67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.27 (s, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.96 (dd, J = 20.6, 8.0 Hz, 2H), 7.87 – 7.70 (m, 2H), 7.61 (d, J = 8.3 Hz, 1H), 6.92 (br. s, 2H), 3.33 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.3, 161.2, 152.2, 143.7, 141.7, 140.7, 132.3, 130.2, 128.8, 126.6, 125.6, 122.6, 121.1, 119.0, 43.4. HR-MS (ESI/TOF) calcd for $C_{15}H_{14}N_3O_2S$ $[M+H]^+$ 300.0807, found 300.0814.

***N*-[3-(2-Aminoquinazolin-7-yl)phenyl]methanesulfonamide (212l)**



Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **213** (250 mg, 1 equiv.) and (3-(methylsulfonamido)phenyl)boronic acid **210l** (264 mg, 1.1 equiv.). Coupling stage performed using Na_2CO_3 (236 mg, 2 equiv.) and $PdCl_2$(dppf)·DCM (27 mg, 3 mol%). Purified by silica gel column chromatography using gradient from 0 to 5% MeOH in DCM to obtain product as a white solid. Yield 141 mg (40%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (br. s, 1H), 9.13 (s, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.53 – 7.43 (m, 3H), 7.28 (dt, J = 7.5, 1.8 Hz, 1H), 6.90 (br. s, 2H), 3.06 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 161.2, 152.2, 145.1, 140.7, 139.1, 130.1, 128.6, 122.7, 121.9, 121.1, 119.5, 118.8, 118.2 (one carbon is missing due to interference with DMSO signal). HR-MS (ESI/TOF) calcd for $C_{15}H_{15}N_4O_2S$ $[M+H]^+$ 315.0916, found 315.0919.

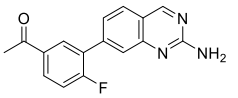
1-[3-(2-Aminoquinazolin-7-yl)phenyl]ethan-1-one (212m)



Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **204** (200 mg, 1 equiv.) and (3-acetylphenyl)boronic acid **210m** (175 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (236 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (36 mg, 5 mol%). Purified by silica gel column chromatography using gradient from 50 to 100%

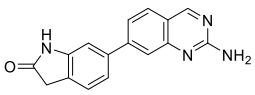
EtOAc in petroleum ether to obtain product as a creamy solid. Yield 71 mg (30%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.28 (t, *J* = 1.8 Hz, 1H), 8.04 (ddd, *J* = 7.7, 2.0, 1.1 Hz, 1H), 8.02 – 7.99 (m, 1H), 7.96 – 7.86 (m, 1H), 7.71 (s, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.59 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.90 (br. s, 2H), 2.68 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 198.0, 162.2, 161.2, 152.2, 144.7, 140.0, 137.6, 131.8, 129.5, 128.7, 127.9, 127.0, 122.2, 121.2, 118.8, 27.0. HR-MS (ESI/TOF) calcd for $C_{16}H_{14}N_3O$ $[M+H]^+$ 264.1137, found 264.1144.

1-[3-(2-Aminoquinazolin-7-yl)-4-fluorophenyl]ethan-1-one (212n)



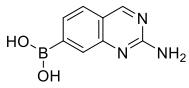
Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **204** (150 mg, 1 equiv.) and 1-(4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-ethan-1-one **211a** (212 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (177 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (27 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a beige solid. Yield 97 mg (52%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.16 (dd, *J* = 7.6, 2.3 Hz, 1H), 8.06 (ddd, *J* = 8.6, 4.9, 2.3 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.60 (s, 1H), 7.51 (dd, *J* = 10.5, 8.6 Hz, 1H), 7.43 (dt, *J* = 8.3, 1.8 Hz, 1H), 6.91 (br. s, 2H), 2.64 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.8, 162.4, 162.0 (d, J = 254.5 Hz), 161.2, 151.8, 139.8, 134.0 (d, *J* = 3.2 Hz), 131.6 (d, *J* = 4.6 Hz), 130.7 (d, *J* = 9.8 Hz), 128.4, 128.0 (d, *J* = 13.8 Hz), 124.7 (d, *J* = 3.0 Hz), 122.8, 118.9, 117.0 (d, *J* = 23.5 Hz), 27.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.72. LC-MS (ESI/APCI) $[M+H]^+$ 282.40.

6-(2-Aminoquinazolin-7-yl)indolin-2-one (212o)



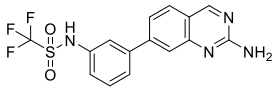
Compound was prepared in analogues way as **212a**, starting from 7-bromoquinazolin-2-amine **204** (150 mg, 1 equiv.) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one **211b** (208 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (177 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (27 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a beige solid. Yield 97 mg (52%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 9.11 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.55 (s, 1H), 7.47 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.33 (s, 2H), 7.14 (s, 1H), 6.83 (br. s, 2H), 3.53 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.7, 162.2, 161.2, 152.2, 145.9, 144.6, 139.2, 128.6, 126.4, 125.1, 121.7, 121.4, 120.5, 118.7, 107.8, 35.8. LC-MS (ESI/APCI) $[M+H]^+$ 277.42.

(2-Aminoquinazolin-7-yl)boronic acid (213)



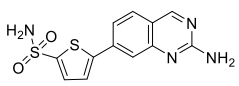
7-Bromoquinazolin-2-amine **204** (1.5 g, 1 equiv.) was dissolved under Ar atmosphere in Dioxane (90 mL) and *bis*(pinacolato)diboron (2.04 g, 1.2 equiv.) was added thereto, followed by KOAc (1.97 g, 3 equiv.) and $PdCl_2$(dppf)·DCM (164 mg, 3 mol%). Resulting solution heated at 100 °C for 16 h. After cooling down to room temperature reaction mixture evaporated in vacuo to dryness and 1 M HCl (80 mL) added thereto. Then reaction mixture extracted with EtOAc (2×70 mL). Organic extract discarded, and water layer evaporated in vacuo to obtain crude product. Purified by trituration with cold H_2O (5 mL) to obtain product as a brown solid. Yield 960 mg (76%). ^{1}H NMR (400 MHz, D_2O) δ 8.91 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, D_2O) δ 162.7, 159.1, 150.1, 128.3, 126.2, 124.7, 118.5 (one carbon is missing due to proton exchange). LC-MS (ESI/APCI) $[M+H]^+$ 190.35.

***N*-[3-(2-Aminoquinazolin-7-yl)phenyl]-1,1,1-trifluoro-methanesulfonamide (215a)**



(2-Aminoquinazolin-7-yl)boronic acid **213** (120 mg, 1 equiv.) was dissolved under Ar atmosphere in dioxane:H_2O 5:1 (8 mL) and *N*-(3-bromophenyl)-1,1,1-trifluoromethanesulfonamide **214a** (155 mg, 1.2 equiv.) was added thereto, followed by Na_2CO_3 (168 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (26 mg, 5 mol%). Resulting solution heated at 100 °C for 2 h. After cooling down to room temperature reaction mixture evaporated in vacuo to dryness and water (30 mL) added thereto. Then reaction mixture extracted with EtOAc (2×30 mL). Organic extract washed with brine (2×10 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuo to obtain crude product. Purified by trituration with MeCN to obtain product as a beige solid. Yield 52 mg (22%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.59 (br.s., 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.44 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.33 (t, *J* = 2.0 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.12 (dt, *J* = 7.6, 1.5 Hz, 1H), 6.99 (dt, *J* = 7.8, 1.8 Hz, 1H), 6.81 (br. s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1, 161.2, 152.2, 148.7, 146.7, 139.5, 129.9, 129.2, 128.9, 128.4, 124.1, 123.2, 121.4, 120.1 (d, *J* = 308.0 Hz), 118.5. ^{19}F NMR (376 MHz, DMSO-d_6) δ -75.55. LC-MS (ESI/APCI) $[M+H]^+$ 369.43.

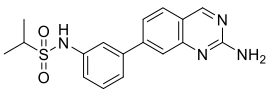
5-(2-Aminoquinazolin-7-yl)thiophene-2-sulfonamide (215b)



Compound was prepared in analogues way as **215a**, starting from (2-aminoquinazolin-7-yl)boronic acid **213** (120 mg,

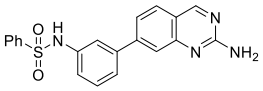
1 equiv.) and 5-bromothiophene-2-sulfonamide **214b** (169 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (168 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (26 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a beige solid. Yield 142 mg (73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 2H), 7.72 (d, *J* = 3.9 Hz, 1H), 7.65 (s, 1H), 7.59 (d, *J* = 3.9 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 6.94 (br. s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.5, 162.3, 161.4, 152.2, 146.8, 145.6, 137.5, 131.3, 129.3, 125.6, 120.7, 119.9. LC-MS (ESI/APCI) $[M+H]^+$ 307.38.

***N*-(3-(2-Aminoquinazolin-7-yl)phenyl)propane-2-sulfonamide (215c)**



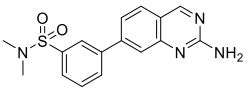
Compound was prepared in analogues way as **215a**, starting from (2-aminoquinazolin-7-yl)boronic acid **213** (80 mg, 1 equiv.) and *N*-(3-bromophenyl)propane-2-sulfonamide **214c** (129 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (112 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (17 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a beige solid. Yield 42 mg (29%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (br. s, 1H), 9.13 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.65 – 7.51 (m, 2H), 7.51 – 7.43 (m, 3H), 7.29 (dt, *J* = 6.4, 2.3 Hz, 1H), 6.86 (br. s, 2H), 3.30 (p, *J* = 6.8 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 162.3, 161.2, 152.2, 145.1, 140.7, 139.5, 130.2, 128.8, 122.5, 121.9, 121.2, 119.2, 118.9, 117.8, 51.6, 16.2. LC-MS (ESI/APCI) $[M+H]^+$ 343.47.

***N*-[3-(2-Aminoquinazolin-7-yl)phenyl]benzenesulfonamide (215d)**



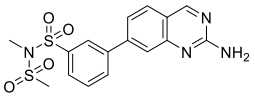
Compound was prepared in analogues way as **215a**, starting from (2-aminoquinazolin-7-yl)boronic acid **213** (80 mg, 1 equiv.) and *N*-(3-bromophenyl)-benzenesulfonamide **214d** (159 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (112 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (17 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a beige solid. Yield 71 mg (45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (br. s, 1H), 9.11 (s, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.80 (dd, *J* = 7.1, 1.9 Hz, 2H), 7.67 – 7.51 (m, 3H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.42 (dd, *J* = 4.3, 2.3 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 1H), 6.87 (br. s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.3, 161.2, 152.2, 145.0, 140.5, 139.4, 138.5, 133.2, 130.1, 129.5, 128.8, 126.8, 123.1, 121.8, 121.0, 119.9, 118.8, 118.6. LC-MS (ESI/APCI) $[M+H]^+$ 377.46.

3-(2-Aminoquinazolin-7-yl)-*N*,*N*-dimethylbenzenesulfonamide (215e)



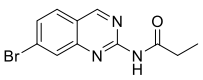
Compound was prepared in analogues way as **215a**, starting from (2-aminoquinazolin-7-yl)boronic acid **213** (80 mg, 1 equiv.) and 3-bromo-*N*,*N*-dimethylbenzenesulfonamide **214e** (145 mg, 1.3 equiv.). Coupling stage performed using Na_2CO_3 (112 mg, 2.5 equiv.) and $PdCl_2$(dppf)·DCM (17 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a brown solid. Yield 52 mg (37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.20 – 8.08 (m, 1H), 7.99 (s, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.85 – 7.77 (m, 2H), 7.70 – 7.65 (m, 1H), 7.57 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.90 (br. s, 2H), 2.67 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.4, 161.3, 152.2, 143.9, 140.8, 135.7, 132.0, 130.5, 129.0, 127.4, 125.7, 122.6, 121.3, 119.1, 37.8. LC-MS (ESI/APCI) $[M+H]^+$ 329.44.

3-(2-Aminoquinazolin-7-yl)-*N*-methyl-*N*-(methylsulfonyl)benzenesulfonamide (215f)



Compound was prepared in analogues way as **226a**, starting from (2-aminoquinazolin-7-yl)boronic acid **213** (80 mg, 1 equiv.) and 3-bromo-*N*-methyl-*N*-(methylsulfonyl)-benzenesulfonamide **214f** (278 mg, 2 equiv.). Coupling stage performed using Na_2CO_3 (135 mg, 3 equiv.) and $PdCl_2$(dppf)·DCM (17 mg, 5 mol%). Purified by trituration with EtOAc to obtain product as a beige solid. Yield 68 mg (41%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.24 (t, *J* = 1.9 Hz, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.82 (t, *J* = 7.9 Hz, 1H), 7.68 (s, 1H), 7.56 (dd, *J* = 8.3, 1.5 Hz, 1H), 6.92 (br. s, 2H), 3.29 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.5, 161.3, 152.2, 143.6, 140.8, 139.4, 133.1, 130.6, 129.1, 127.3, 126.1, 122.6, 121.1, 119.1, 42.5, 34.6. LC-MS (ESI/APCI) $[M+H]^+$ 393.46.

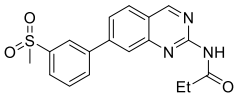
***N*-(7-Bromoquinazolin-2-yl)propionamide (216)**



7-Bromoquinazolin-2-amine **204 (**500 mg, 1 equiv.) was suspended in pyridine (10 mL) and propionic anhydride (1.73 mL, 6 equiv.) was added dropwise at room temperature. Resulting solution heated at 80 °C for 2 h. Reaction cooled down to room temperature and water (40 mL) added thereto. Formed precipitate was filtered and washed with water (2×10 mL) to obtain product as a solid. Purified by trituration with MeCN to obtain product as a white beige solid. Yield 463 mg (74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (br. s, 1H), 9.49 (s, 1H), 8.07 – 7.95 (m, 2H), 7.73 (dd, *J* = 8.6, 1.9 Hz, 1H), 2.59 (q, *J* = 7.5 Hz, 2H), 1.08 (t, *J* = 7.5 Hz, 3H).

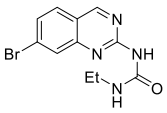
^{13}C NMR (101 MHz, DMSO-d_6) δ 172.7, 162.7, 155.2, 151.0, 129.8, 129.0, 128.7, 128.4, 120.5, 29.8, 9.2. LC-MS (ESI/APCI) $[M+H]^+$ 280.28/282.29.

***N*-{7-[3-(Methylsulfonyl)phenyl]quinazolin-2-yl}propionamide (217)**



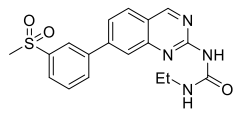
Compound was prepared in analogues way as **212a**, starting from *N*-(7-bromoquinazolin-2-yl)propionamide **216** (150 mg, 1 equiv.) and (3-(methylsulfonyl)phenyl)boronic acid **210k** (139 mg, 1.3 equiv.). Coupling stage performed using Na_2CO_3 (113 mg, 2 equiv.) and $PdCl_2$(dppf)·DCM (31 mg, 7 mol%). Purified by trituration with EtOAc to obtain product as a white beige solid. Yield 70 mg (37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (br. s, 1H), 9.53 (s, 1H), 8.36 (t, *J* = 1.9 Hz, 1H), 8.24 (d, *J* = 7.7 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.15 (s, 1H), 8.08 – 7.94 (m, 2H), 7.83 (t, *J* = 7.8 Hz, 1H), 3.33 (s, 3H), 2.63 (q, *J* = 7.5 Hz, 2H), 1.11 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.7, 162.4, 155.0, 150.7, 144.4, 141.8, 140.0, 132.5, 130.3, 128.8, 126.9, 125.9, 125.0, 124.3, 121.2, 43.4, 29.8, 9.2. HR-MS (ESI/TOF) calcd for $C_{18}H_{18}N_3O_3S$ $[M+H]^+$ 356.1069, found 356.1067.

1-(7-Bromoquinazolin-2-yl)-3-ethylurea (218)



7-Bromoquinazolin-2-amine **204** (600 mg, 1 equiv.) was suspended in DMF (15 mL) and ethyl isocyanate (636 μL, 3 equiv.) was added dropwise at room temperature. Resulting solution heated at 100 °C for 16 h. Reaction mixture cooled down to room temperature and water (40 mL) added thereto. Formed precipitate was filtered and washed with water (2×10 mL) to obtain product as a solid. Light brown crystals, yield 463 mg (74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (br. s, 1H), 9.39 (s, 1H), 9.36 (t, *J* = 5.7 Hz, 1H), 8.17 (d, *J* = 1.8 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.65 (dd, *J* = 8.6, 1.9 Hz, 1H), 3.29 (qd, *J* = 7.2, 5.6 Hz, 2H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.6, 156.0, 154.1, 149.9, 130.2, 129.3, 128.6, 128.1, 119.7, 34.4, 15.5. LC-MS (ESI/APCI) $[M+H]^+$ 295.31/297.33.

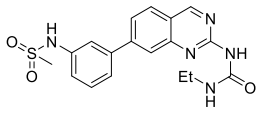
1-Ethyl-3-{7-[3-(methylsulfonyl)phenyl]quinazolin-2-yl}urea (219a)



Compound was prepared in analogues way as **212a**, starting from 1-(7-bromoquinazolin-2-yl)-3-ethylurea **218** (150 mg, 1 equiv.) and (3-(methylsulfonyl)phenyl)boronic acid **210k** (102 mg, 1 equiv.). Coupling stage performed using Na_2CO_3 (108 mg, 2 equiv.) and

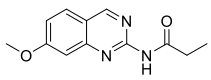
$PdCl_2$(dppf)·DCM (41 mg, 10 mol%). Purified by trituration with hot EtOH to obtain product as a white beige solid. Yield 96 mg (51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 9.50 (t, *J* = 5.6 Hz, 1H), 9.47 (s, 1H), 8.35 (t, *J* = 1.7 Hz, 1H), 8.29 – 8.22 (m, 2H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.94 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.84 (t, *J* = 7.8 Hz, 1H), 3.33 (q, *J* = 7.2 Hz, 2H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.1, 155.8, 153.9, 149.3, 144.7, 141.8, 140.0, 132.6, 130.3, 128.9, 126.9, 125.7, 124.3, 123.6, 120.2, 43.4, 34.1, 15.4. HR-MS (ESI/TOF) calcd for $C_{18}H_{19}N_4O_3S$ $[M+H]^+$ 371.1178, found 371.1189.

***N*-(3-(2-(3-Ethylureido)quinazolin-7-yl)phenyl)methanesulfonamide (219b)**



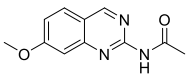
Compound was prepared in analogues way as **212a**, starting from 1-(7-bromoquinazolin-2-yl)-3-ethylurea **218** (150 mg, 1 equiv.) and (3-(methylsulfonamido)-phenyl)boronic acid **210l** (131 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (108 mg, 2 equiv.) and $PdCl_2$(dppf)·DCM (29 mg, 7 mol%). Purified by trituration with hot EtOH to obtain product as a grey solid. Yield 41 mg (21%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (br. s, 2H), 9.49 (t, *J* = 5.5 Hz, 1H), 9.43 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.05 (s, 1H), 7.77 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.65 – 7.55 (m, 2H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 3.44 (q, *J* = 7.0 Hz, 2H), 3.05 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.9, 155.7, 153.9, 149.3, 146.2, 140.0, 139.7, 130.1, 128.8, 124.2, 123.0, 122.6, 120.0, 119.9, 118.6, 39.4, 34.1, 15.4. HR-MS (ESI/TOF) calcd for $C_{18}H_{20}N_5O_3S$ $[M+H]^+$ 386.1287, found 386.1299.

***N*-(7-Methoxyquinazolin-2-yl)propionamide (220a)**



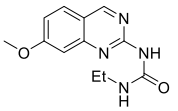
Compound was prepared in analogues way as **216**, starting from 7-methoxyquinazolin-2-amine **202e** (150 mg, 1 equiv.) and propionic anhydride (440 µL, 4 equiv.). Purified by crystallization from EtOH to obtain product as a white beige solid. Yield 71 mg (36%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (br. s, 1H), 9.26 (s, 1H), 7.93 (d, *J* = 8.9 Hz, 1H), 7.18 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.11 (d, *J* = 2.5 Hz, 1H), 3.94 (s, 3H), 2.59 (q, *J* = 7.5 Hz, 2H), 1.08 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.6, 164.3, 160.8, 155.0, 152.8, 129.2, 118.4, 117.2, 104.9, 55.8, 29.8, 9.3. HR-MS (ESI/TOF) calcd for $C_{12}H_{14}N_3O_2$ $[M+H]^+$ 232.1086, found 232.1096.

_N_-(7-Methoxyquinazolin-2-yl)acetamide (220b)



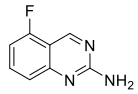
Compound was prepared in analogues way as **216**, starting from 7-methoxyquinazolin-2-amine **202e** (150 mg, 1 equiv.) and acetic anhydride (323 μL, 4 equiv.). Purified by crystallization from EtOH to obtain product as a white solid. Yield 108 mg (58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (br. s, 1H), 9.26 (s, 1H), 7.93 (d, J = 8.9 Hz, 1H), 7.18 (dd, J = 8.9, 2.4 Hz, 1H), 7.12 (s, 1H), 3.94 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.3, 164.3, 160.8, 155.0, 152.8, 129.2, 118.5, 117.2, 105.0, 55.8, 24.8. HR-MS (ESI/TOF) calcd for $C_{11}H_{12}N_3O_2$ $[M+H]^+$ 218.0930, found 218.0940.

1-Ethyl-3-(7-methoxyquinazolin-2-yl)urea (220c)



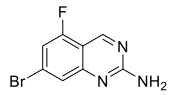
Compound was prepared in analogues way as **216**, starting from 7-methoxyquinazolin-2-amine **202e** (150 mg, 1 equiv.) and ethyl isocyanate (407 μL, 6 equiv.). White yellow solid, yield 189 mg (90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (br. s, 1H), 9.48 (t, J = 5.6 Hz, 1H), 9.20 (s, 1H), 7.89 (d, J = 8.9 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 7.11 (dd, J = 8.9, 2.4 Hz, 1H), 3.95 (s, 3H), 3.31 (q, J = 7.0 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.7, 161.4, 155.8, 154.0, 151.6, 129.4, 117.5, 116.2, 104.6, 55.9, 34.1, 15.4. HR-MS (ESI/TOF) calcd for $C_{12}H_{15}N_4O_2$ $[M+H]^+$ 247.1195, found 247.1207.

5-Fluoroquinazolin-2-amine (222a)



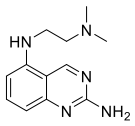
Compound was prepared in analogues way as **204**, starting from 2,6-difluorobenzaldehyde **221a** (1.17 g, 1 equiv.), guanidine carbonate (1.59 g, 1.6 equiv.) and Na_2CO_3 (1.39 g, 1.6 equiv.). Purified by trituration with EtOAc to obtain yellow solid. Yield 314 mg (23%). Spectral data consistent with previously reported.[100]

7-Bromo-5-fluoroquinazolin-2-amine (222b)



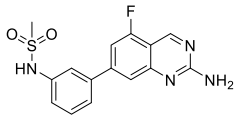
Compound was prepared in analogues way as **204**, starting from 4-bromo-2,6-difluorobenzaldehyde **221b** (3.28 g, 1 equiv.), guanidine carbonate (2.88 g, 1.6 equiv.) and Na_2CO_3 (2.52 g, 1.6 equiv.). Purified by crystallization from EtOH to white beige solid. Yield 495 mg (14%). Spectral data consistent with previously reported.[66]

***N*5-[2-(Dimethylamino)ethyl]quinazoline-2,5-diamine (223)**



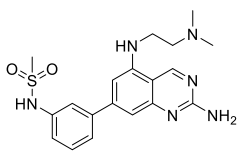
5-Fluoroquinazolin-2-amine **222a** (55 mg, 1 equiv.) was dissolved in *N*,*N*-dimethyl-1,2-ethanediamine (1 mL, 27 equiv.) and resulting solution heated at 110 °C for 48 h. After cooling down to room temperature, reaction mixture directly purified by reverse phase column chromatography using gradient of MeCN in water to obtain product as a yellow solid. Yield 55 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.51 (t, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.30 (d, *J* = 7.8 Hz, 1H), 5.51 (br. s, 1H), 5.28 (br. s, 2H), 3.27 – 3.15 (m, 2H), 2.71 – 2.61 (m, 2H), 2.28 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 156.1, 153.2, 146.0, 136.3, 113.5, 110.7, 102.2, 57.5, 45.2, 40.7. HR-MS (ESI/TOF) calcd for $C_{12}H_{18}N_5$ $[M+H]^+$ 232.1562, found 232.1568.

***N*-[3-(2-Amino-5-fluoroquinazolin-7-yl)phenyl]-methanesulfonamide (224)**



Compound was prepared in analogues way as **212a**, starting from 7-bromo-5-fluoroquinazolin-2-amine **222b** (180 mg, 1 equiv.) and (3-(methylsulfonamido)phenyl)boronic acid **210l** (192 mg, 1.2 equiv.). Coupling stage performed using Na_2CO_3 (158 mg, 2 equiv.) and $PdCl_2$(dppf)·DCM (42 mg, 7 mol%). Purified by trituration with $CHCl_3$ to obtain product as a white brown solid. Yield 144 mg (58%).^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 7.58 – 7.44 (m, 3H), 7.42 (s, 1H), 7.31 – 7.23 (m, 2H), 7.10 (br. s, 2H), 3.04 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.7, 159.2 (d, *J* = 255.1 Hz), 156.3 (d, *J* = 2.9 Hz), 153.4 (d, *J* = 3.2 Hz), 146.1 (d, *J* = 9.9 Hz), 139.8, 139.4, 130.5, 122.9, 120.3, 118.4, 118.3 (d, *J* = 3.5 Hz), 108.9 (d, *J* = 16.1 Hz), 105.4 (d, *J* = 20.0 Hz), 39.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ -123.02 (d, *J* = 10.8 Hz). LC-MS (ESI/APCI) $[M+H]^+$ 333.43.

***N*-(3-(2-Amino-5-((2-(dimethylamino)ethyl)amino)quinazolin-7-yl)phenyl)methanesulfonamide (225)**



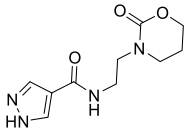
N-(3-(2-Amino-5-fluoroquinazolin-7-yl)phenyl)-methanesulfonamide **224** (100 mg, 1 equiv.) was dissolved in *N*,*N*-dimethyl-1,2-ethanediamine (1 mL, 30 equiv.) and resulting solution heated at 110 °C for 48 h. After cooling down to room temperature, reaction mixture directly purified by reverse phase column chromatography using gradient of MeCN in water to obtain product as a yellow solid. Yield 32 mg (27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.44 – 7.36 (m, 3H), 7.32 (td, *J* = 4.7, 4.2, 2.3 Hz, 1H), 6.92 (s, 1H), 6.41 (s, 1H), 5.63 (br. s, 1H), 5.39 (br. s, 2H), 3.25 (hept, *J* =

3.8, 2.9 Hz, 2H), 3.06 (s, 3H), 2.67 (dd, *J* = 6.6, 4.9 Hz, 2H), 2.28 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 156.1, 153.2, 147.9, 146.2, 143.1, 137.5, 130.2, 124.4, 120.8, 120.3, 111.8, 109.9, 101.6, 57.4, 45.2, 40.7, 39.8. HR-MS (ESI/TOF) calcd for $C_{19}H_{25}N_6O_2S$ $[M+H]^+$ 401.1760, found 401.1754.

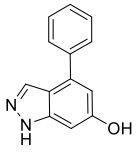
CONCLUSIONS

1. Four series of perspective HK TCs inhibitors were synthesized for biological activity evaluation: derivatives of pyrazole-4-carboxamide, 2-aminoquinazoline, indazole and 3,4-diphenylpyrazole.

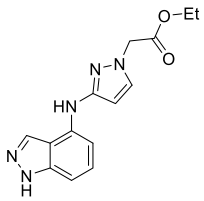
2. Library of pyrazole-4-carboxamides was made by coupling of pyrazole-4-carboxylic acid with various alkyl and aryl amines. Unfortunately, this library showed no potential for the further development: enzymatic and *in vitro* antibacterial assays revealed no significant activity. On the other hand, X-Ray crystallography of CheA protein-ligand complex with the amide, bearing cyclic carbamate moiety, showed interaction of the compound exactly as predicted in CADD models. Such a discrepancy can be explained by weak interactions of the mentioned ligand with the protein.



3. Indazole based library was made starting from substituted 4-bromoindazoles using different types of palladium couplings. The compound with phenyl substituent possessed weak antibacterial activity against *E. Coli*, but its mechanism of antibacterial action remained unclear. Indazole bearing 3-aminopyrazole substituent, and its structural analogues, revealed moderate potency in enzymatic assay but showed no antibacterial activity.



E. Coli MIC = 62.5 μg/mL

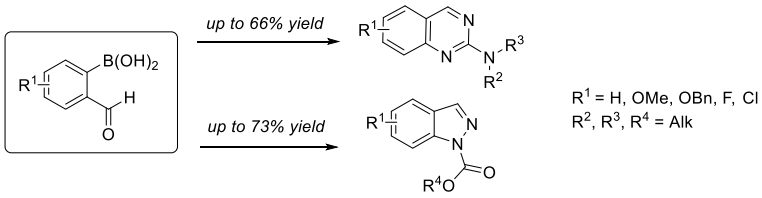


S. Aureus PhoR IC_{50} = 67 μM

4. Library of 2-aminoquinazolines was made using Heck reaction between 7-bromoquinazoline-2-amine and various alkenes. Newly formed alkenes were selectively reduced to form an alkyl linker. Additional compounds were derived from Suzuki-Miyaura reaction between 7-bromoquinazoline-2-amine and arylboronic acids or between (2-aminoquinazolin-7-yl)boronic acid and aryl bromides. All compounds from these series were tested for their ability to bind to CheA protein (MST assay) and two compounds displayed the best binding affinity in their series.

6. A range of 3-phenylpyrazole derivatives were synthesized by reaction of isoflavones and β-diketones with hydrazine hydrate. Cyclization of the same starting materials with hydroxylamine allowed to obtain isoxazoles with identical to pyrazoles substitution pattern. Moreover, compounds with cleaved hydroxyl groups were synthesized by transformation of OH group to triflate with subsequent Pd-catalyzed reduction. SAR studies revealed the crucial parts of the molecules for antibacterial activity. Pyrazole core can be replaced with isoxazole without change in activity, however at least one polar group shall be retained in molecule to preserve an antibacterial potency. The mechanism of the antibacterial effect for these type of compounds remained unclear, but most probably is not connected with HK TCs inhibition.

7. New methods for the synthesis of 2-aminoquinazolines and *N*-protected indazoles were developed by usage of copper catalysed Chen-Evans-Lam reaction starting from 2-formylphenylboronic acids. Reaction with guanidines proceeds to 2-aminoquinazolines, when the reaction with azodicarboxylates and hydrazine dicarboxylates delivering *N*-protected indazoles. The reaction can be done in milder conditions compared to the known coupling reactions using 2-halobenzaldehydes.



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Annex I

Synthesis and SAR of phenylazoles, active against Staphylococcus aureus Newman

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Химия гетероциклических соединений

Synthesis and SAR of phenylazoles, active against *Staphylococcus aureus* Newman

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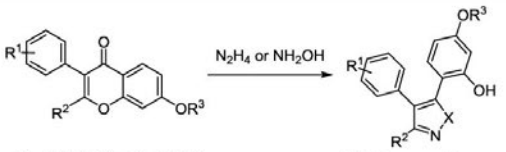


X = NH, O; R^1 = H, Cl, OMe
R^2 = Me, CF_3; R^3 = Alk

MIC *S. aureus* Newman up to 390 ng/ml

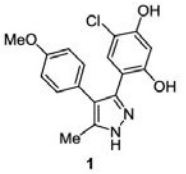
Series of new potent inhibitors of growth of *Staphylococcus aureus* Newman, based on 3,4-diphenylpyrazole and 4,5-diphenylisoxazole derivatives were discovered. Structures of interest were selectively modified to check their structure–activity relationship. Studies revealed the most essential groups in the molecule for the antimicrobial activity retention. Active compounds with good MIC range should contain both nonpolar aromatic residues and hydrogen bond donating groups. The best MIC results in selected cases were lower than 1 μg/ml.

Keywords: diphenylazole, isoflavone, isoxazole, pyrazole, antimicrobial activity, *Staphylococcus aureus* Newman.

The antibiotic resistance is one of the greatest health challenges requiring efficient solutions to prevent the increased number of lethal outcomes caused by bacterial infections.[1] The control of antimicrobial infections in hospitals is already complicated due to so-called ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) which are resistant to virtually all marketed antibiotics.[2] The new antimicrobial drugs acting by yet unexploited mechanism are therefore urgently needed.

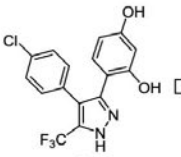
Recently Vo et al. reported 3,4-diarylpyrazole-based antibacterial compound series which was repurposed from compounds with anticancer activity acting as a heat shock protein 90 (HSP90) inhibitors (Fig. 1).[3] The antibacterial activity was linked to the inhibition of bacterial histidine kinases by binding to ATP-binding domain which share high similarity to the ATPase domain of eukaryotic HSP90. The representative compound **1** displayed micromolar inhibition of histidine kinases *C. crescentus* CckA and *Salmonella* PhoQ and medium activity against certain Gram negative and Gram positive bacterial strains. Structurally similar hit **2** with good potency against *S. aureus* was revealed in Wells lab by screening of compound libraries in antibacterial susceptibility tests. In this paper, we describe systematic investigation of SAR of diarylpyrazole-based compounds as well as scaffold hopping studies for the replacement of the pyrazole heterocycle with isoxazole.

The key intermediates for the synthesis of 3,4-diarylpyrazoles **8a–l** were isoflavones **7a–k** (Scheme 1).[4] These were synthesized from readily available resorcinol (**3**) and



1

MIC (*B. subtilis*) 50–74 μg/ml
MIC (*E. coli*) 12–25 μg/ml



2

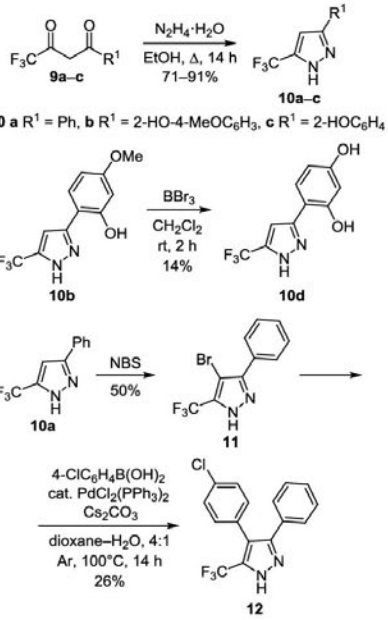
MIC (*S. aureus*) 6.25 μg/ml

Figure 1. 3,4-Diarylpyrazoles with antibacterial activity.

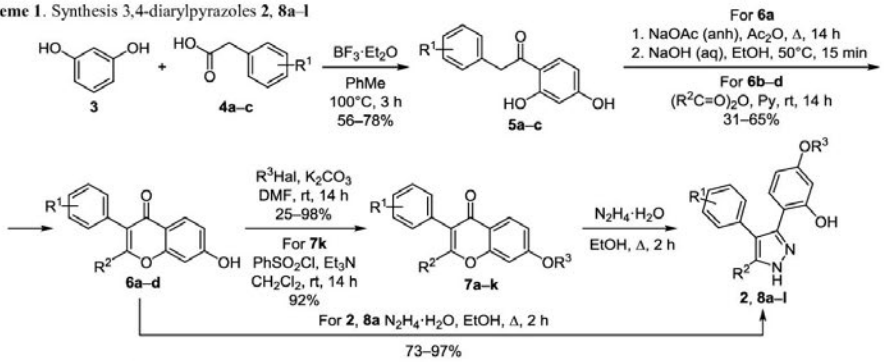
phenylacetic acid derivatives **4a**–**c** in two steps.[4b,5] The first step included Friedel–Crafts acylation of resorcinol (**3**), catalyzed by $BF_3 \cdot Et_2O$. The resulting acylresorcinols **5a**–**c** underwent condensation with acid anhydride followed by the cyclization to give isoflavones **6a**–**d**. *O*-Alkylation provided isoflavone derivatives **7a**–**k** which were condensed with hydrazine to provide the novel target compounds **8a**–**l**.

Synthesis of previously reported monoaryl pyrazoles **10a**,**c** and novel pyrazoles **10b**,**d** was achieved by the condensation of diketones **9a**–**c** with hydrazine (Scheme 2). One of the monoarylpyrazoles, compound **10a**, was further brominated to obtain bromo derivative **11** which was subjected to Suzuki–Miyaura coupling to provide the novel diarylpyrazole **12** (Scheme 2).

Scheme 2. Synthesis 3-aryl- and 3,4-diarylpyrazoles **10a**–**d**, **12**

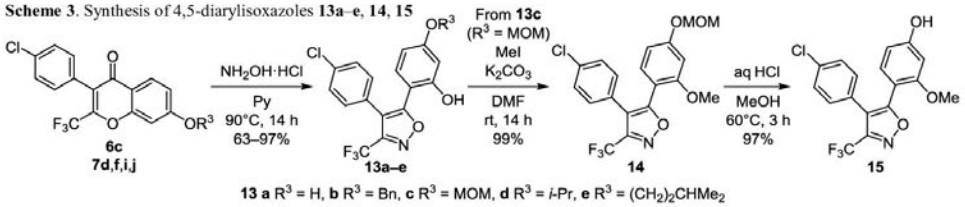


Scheme 1. Synthesis 3,4-diarylpyrazoles **2**, **8a**–**l**



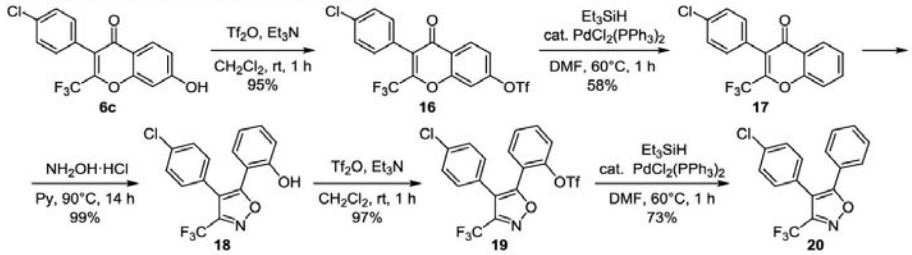
4, **5 a** R^1 = H, **b** R^1 = 4-Cl, **c** R^1 = 4-MeO
6 a R^1 = 4-Cl, R^2 = Me; **b** R^1 = H, R^2 = CF_3; **c** R^1 = 4-Cl, R^2 = CF_3; **d** R^1 = 4-MeO, R^2 = CF_3
7 a R^1 = 4-Cl, R^2 = CF_3, R^3 = Me; **b** R^1 = H, R^2 = CF_3, R^3 = Me; **c** R^1 = 4-MeO, R^2 = CF_3, R^3 = Me; **d** R^1 = 4-Cl, R^2 = CF_3, R^3 = Bn; **e** R^1 = H, R^2 = CF_3, R^3 = Bn; **f** R^1 = 4-Cl, R^2 = CF_3, R^3 = MOM; **g** R^1 = 4-Cl, R^2 = CF_3, R^3 = 2,6-$Cl_2C_6H_3CH_2$; **h** R^1 = 4-Cl, R^2 = CF_3, R^3 = 4-$BrC_6H_4CH_2$; **i** R^1 = 4-Cl, R^2 = CF_3, R^3 = *i*-Pr; **j** R^1 = 4-Cl, R^2 = CF_3, R^3 = $Me_2CH(CH_2)_2$; **k** R^1 = 4-Cl, R^2 = CF_3, R^3 = $PhSO_2$
2 R^1 = 4-Cl, R^2 = CF_3, R^3 = H; **8 a** R^1 = 4-Cl, R^2 = Me, R^3 = H; **b** R^1 = 4-Cl, R^2 = CF_3, R^3 = Me; **c** R^1 = H, R^2 = CF_3, R^3 = Me; **d** R^1 = 4-MeO, R^2 = CF_3, R^3 = Me; **e** R^1 = 4-Cl, R^2 = CF_3, R^3 = Bn; **f** R^1 = H, R^2 = CF_3, R^3 = Bn; **g** R^1 = 4-Cl, R^2 = CF_3, R^3 = MOM; **h** R^1 = 4-Cl, R^2 = CF_3, R^3 = 2,6-$Cl_2C_6H_3CH_2$; **i** R^1 = 4-Cl, R^2 = CF_3, R^3 = 4-$BrC_6H_4CH_2$; **j** R^1 = 4-Cl, R^2 = CF_3, R^3 = $PhSO_2$; **k** R^1 = 4-Cl, R^2 = CF_3, R^3 = *i*-Pr; **l** R^1 = 4-Cl, R^2 = CF_3, R^3 = $Me_2CH(CH_2)_2$

Scheme 3. Synthesis of 4,5-diarylisoxazoles **13a–e**, **14**, **15**



13 a R^3 = H, **b** R^3 = Bn, **c** R^3 = MOM, **d** R^3 = *i*-Pr, **e** R^3 = $(CH_2)_2CHMe_2$

Scheme 4. Synthesis of 4,5-diarylisoxazoles **18** and **20**

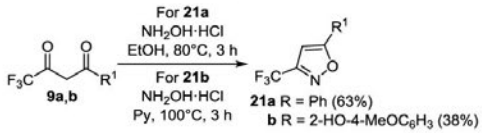


Novel isoxazole-based analogs **13a–e**, **14**, and **15** were obtained from isoflavone derivatives **6c**, **7d**,**f**,**i**,**j** (Scheme 3). Their reaction with hydroxylamine provided isoxazoles **13a–e**.[6] *O*-MOM-protected product **13c** was methylated at the free phenolic OH group, and the resulting derivative **14** was subjected to MOM deprotection in acid media to obtain isoxazole **15**.

Not previously described deoxygenated diarylisoxazole analogs **18** and **20** were prepared starting from isoflavone derivative **6c** (Scheme 4). Triflate formation with subsequent reduction has been tried. First, isoflavone **6c** transformed to triflate **16** in which the C–O bond was cleaved under Pd-catalyzed hydrogenolysis conditions using triethylsilane as hydrogen transfer reagent. The resulting isoflavone derivative **17** was converted to isoxazole **18**. It was then transformed to triflate **19** which was reduced to give product **20**.

Previously reported isoxazole **21a** and the novel isoxazole **21b** without a substituent in position 4 of heterocycle were prepared starting from diketones **9a**,**b** (Scheme 5).

Scheme 5. Synthesis of 4,5-diarylisoxazoles **21**

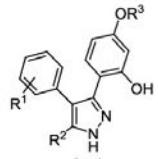


All synthesized compounds **8a–l**, **10a–d**, **12**, **13a–e**, **15**, **18**, **20**, **21a**,**b** were subjected to *in vitro* growth inhibiton tests of *Staphylococcus aureus* Newman.[7] The results of these tests are summarized in Tables 1–4.

Compound with methyl group as R^2 substituent (compound **8a**, Table 1) exhibited fourfold lower potency compared to the original hit **2**.

An improvement of the antibacterial potency was achieved by addition of methyl group as R^3 substituent (compound **8b**, Table 1). Replacement of 4-chlorophenyl with phenyl group as $R^1C_6H_4$ substituent (compound **8c**) or 4-methoxyphenyl group (compound **8d**) slightly decreased the antibacterial potency. However, *O*-benzyl group as R^3 substituent had a positive effect to antibacterial potency (compounds **8e**,**f**). Curiously, in the case of compounds **8e**,**f**, the difference in R^1 substitution did not affect MIC values which were retained around 1.56 μg/ml for both of

Table 1. Antibacterial activity of compounds **8a–l**

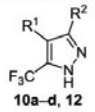


8a–l

Compound	R^1	R^2	R^3	MIC,* μg/ml
8a	4-Cl	Me	H	25
8b	4-Cl	CF_3	Me	3.12
8c	H	CF_3	Me	12.5
8d	4-OMe	CF_3	Me	12.5
8e	4-Cl	CF_3	Bn	1.56
8f	H	CF_3	Bn	1.56
8g	4-Cl	CF_3	MOM	3.12
8h	4-Cl	CF_3	2,6-Cl_2Bn	1.56
8i	4-Cl	CF_3	4-BrBn	1.56
8j	4-Cl	CF_3	$PhSO_2$	1.56
8k	4-Cl	CF_3	*i*-Pr	0.78
8l	4-Cl	CF_3	*i*-Amyl	<0.39

* *Staphylococcus aureus* Newman.

Table 2. Antibacterial activity of compounds **10a–d**, **12**



10a–d, 12

Compound	R^1	R^2	MIC,* μg/ml
10a	H	Ph	50
10b	H	2-(HO)-4-(MeO)C_6H_3	25
10c	H	2-(HO)C_6H_4	125
10d	H	2,4-di(HO)C_6H_3	250
12	4-ClC_6H_5	Ph	1.56

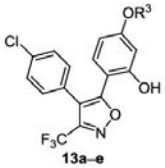
* *Staphylococcus aureus* Newman.

the compounds. MOM group as R^3 substituent (compound **8g**) only slightly increased activity in comparison with hit compound **2**. Substitution of benzyl group with 2,5-dichlorobenzyl (compound **8h**), 4-bromobenzyl (compound **8i**), and phenylsulfonyl (compound **8j**) group did not change the activity of the compounds in comparison with benzyl analog **8e**. The best antimicrobial activity in this series was exhibited by the compounds bearing lipophilic R^3 substituents such as isopropyl group (compound **8k**) and isoamyl group (compound **8l**).

Derivatives **10a–d** lacking substituents at position 4 of pyrazole ring showed significantly worse results in comparison with the hit compound **2** (Table 2). However, compound **12** with 4-chlorophenyl group as R^1 substituent and phenyl group as R^2 substituent exhibited activity four times higher than compound **2** (Table 2). These results point to the importance of the two aryl substituents at the pyrazole ring to ensure high antimicrobial potency. In addition, the high antimicrobial potency of compound **12** implies that hydroxyl groups at the phenyl group as the R^1 substituent are not essential.

Isoxazole analogs **13a–e** (Table 3) showed similar potency and SAR to their pyrazole peers **8e**,**g**,**k**,**l**, (Table 1). An interesting deviation was observed for isoxazoles **15**, **18**, **20**, and **21a**,**b** (Table 4). Compound **21a**, contrary to its pyrazole-based analog **10a**, completely lost activity against *S. aureus*. Compound **21b** possesses increased activity level in comparison with compound **10b**. Surprisingly, methylation of *o*-hydroxy group in R^2 substituent (compound **15**, Table 4) did not affect MIC value – it was retained at 3.12 μg/ml. Finally, compound **20** totally lost the antimicrobial potency (Table 4) in comparison with pyrazole derivative **12** having the same substitution pattern (Table 2).

Table 3. Activity of isoxazole-based compounds **13a–e**

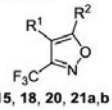


13a–e

Compound	R^3	MIC,* μg/ml
13a	H	3.12
13b	Bn	0.78
13c	MOM	3.12
13d	*i*-Pr	0.78
13e	*i*-Amyl	<0.39

* *Staphylococcus aureus* Newman.

Table 4. Activity of simplified isoxazole-based compounds **15**, **18**, **20**, **21a**,**b**



15, 18, 20, 21a,b

Compound	R^1	R^2	MIC,* μg/ml
21a	H	Ph	Inactive
21b	H	2-(HO)-4-(MeO)C_6H_3	6.25
15	4-ClC_6H_5	2-(MeO)-4-(HO)C_6H_3	3.12
18	4-ClC_6H_5	2-(HO)C_6H_4	3.12
20	4-ClC_6H_5	Ph	Inactive

* *Staphylococcus aureus* Newman.

The most efficient compounds, such as **8k**,**l** were exhibiting activity level against *Staphylococcus aureus* Newman comparable with well-known antibiotics such as ampicillin (MIC 1.0 μg/ml), ciprofloxacin (MIC 0.5 μg/ml), and vancomycin (MIC 1.0 μg/ml).

The SAR of the compounds provides the directions for further structural improvements to achieve more potent phenylazole-based antimicrobials. Thus, introduction of the lipophilic groups at position 5 of phenolic ring of the molecule increased the potency of compounds **8e**,**k**. Further increase of lipophilicity in this position could increase the potency. Additionally, further work should explore another suitable 5-membered cycles such as imidazole, 1,2,3-triazole, or isothiazole as scaffolds to improve the potency of the compounds. Nevertheless, the SAR of the pairs of compounds **12** and **20**, or **18** and **20** implies that at least one NH or OH group should be retained in the inhibitor to preserve its potency.

Our investigation of growth inhibition of *S. aureus* Newman by 3,4-diphenylpyrazole and 4,5-diphenylisoxazole derivatives lead to several very potent antibacterial compounds. The most potent growth inhibitors were pyrazole-based compounds **8k**,**l** and their isoxazole analogs **13d**,**e** with MIC <1 μg/ml. The studies revealed the most crucial elements for their antimicrobial activity. The structure should contain at least one hydrogen bond donor either in heterocycle or at aryl groups. Pyrazole replacement with isoxazole in most cases did not affect activity, however, several differences were found. For example, both aryl groups were needed at positions 3 and 4 for pyrazole-based compounds to exhibit high potency, however, relatively potent compound **21b** was found in

isoxazole series lacking aryl group at position 3 of isoxazole. The mechanism of action for pyrazole- and isoxazole-based *S. aureus* growth inhibitors needs further investigation.

Experimental

^{1}H NMR spectra were recorded on 300, 400, or 600 MHz Bruker spectrometers. ^{13}C and ^{19}F NMR spectra were recorded on 400 (101 and 376 MHz, respectively) or 600 MHz Bruker spectrometers (151 and 564 MHz, respectively) using the residual solvent peak as internal reference ($CDCl_3$: 7.26 ppm for ^{1}H nuclei and 77.2 ppm for ^{13}C nuclei; DMSO-d_6: 2.50 ppm for ^{1}H nuclei and 39.5 ppm for ^{13}C nuclei; $(CD_3)_2CO$: 2.05 ppm for ^{1}H nuclei and 29.8 and 206.3 ppm for ^{13}C nuclei). HRMS were determined on a Waters Synapt G2-Si hybrid quadrupole time-of-flight (TOF) mass spectrometer equipped with an electron spray ion source (ESI). Melting points were detected with an OptiMelt MPA100 melting point apparatus, with a heating rate of 3°C/min. When necessary, compounds were purified by crystallization or by column chromatography on silica gel (petroleum ether – EtOAc gradient).

Reagents were purchased from commercial sources and used as received. Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of moisture.

Synthesis of 1-(2,4-dihydroxyphenyl)-2-phenylethan-1-ones 5a–c (General method). Procedure described in literature have been used.[8] $BF_3{\cdot}Et_2O$ (15.46 ml, 17.47 g, 123 mmol) was added slowly to a solution of resorcinol (**3**) (4.52 g, 41 mmol) and phenylacetic acid **4a**–**c** (41 mmol) in anhydrous PhMe (120 ml). Resulting solution was heated at 100°C for 3 h and cooled down to room temperature. The mixture was poured into saturated NaOAc solution (300 ml) and then partitioned with EtOAc (300 ml). The EtOAc extract was washed with brine (2 × 200 ml). The extract was dried over Na_2SO_4 and concentrated *in vacuo*. Thus obtained crude product was triturated with PhMe or purified by column chromatography on silica gel using gradient EtOAc in petroleum ether.

1-(2,4-Dihydroxyphenyl)-2-phenylethan-1-one (5a) was synthesized from phenylacetic acid (**4a**) (1.1 g). Yield 1.23 g (66%), yellowish sticky oil. Spectral data was in accordance with the previously reported.[9]

2-(4-Chlorophenyl)-1-(2,4-dihydroxyphenyl)ethan-1-one (5b) was synthesized from 4-chlorophenylacetic acid (**4b**) (7.0 g). Yield 6.0 g (56%), slightly pink solid. Spectral data was in accordance with the previously reported.[10]

1-(2,4-Dihydroxyphenyl)-2-(4-methoxyphenyl)ethan-1-one (5c) was synthesized from 4-methoxyphenylacetic acid (**4c**) (350 mg). Yield 640 mg (78%), yellowish solid. Spectral data was in accordance with the previously reported.[11]

3-(4-Chlorophenyl)-7-hydroxy-2-methyl-4*H*-chromen-4-one (6a). Procedure, described in literature, have been used.[12] 2-(4-Chlorophenyl)-1-(2,4-dihydroxyphenyl)ethan-1-one (**5b**) (700 mg, 2.7 mmol) and anhydrous NaOAc (437 mg, 5.4 mmol) were dissolved in Ac_2O (4 ml, 42.6 mmol). The mixture was refluxed for 14 h, cooled, and poured into H_2O. The precipitate was filtered off, dried, and recrystallized from EtOH to obtain acylated intermediate as a slightly yellow solid (594 mg, 1.8 mmol). This material was suspended in EtOH (5 ml), and aqueous NaOH (86.7 mg, 2.2 mmol) was added thereto. After heating at 50°C for 15 min, solvent was distilled off under reduced pressure, residue was dissolved in H_2O and acidified by 1 M HCl. Formed precipitate was filtered off and dried. Yield 496 mg (65% over 2 steps), white-beige solid. Spectral data was in accordance with the previously reported.[12]

Synthesis of 7-hydroxy-3-phenyl-2-(trifluoromethyl)-4*H*-chromen-4-ones 6b–d (General method). Procedure, described in literature, have been used.[13] Trifluoroacetic acid anhydride (9 ml, 13.6 g, 64.8 mmol) was added dropwise to an ice-cooled solution of deoxybenzoin (16.2 mmol) in pyridine (20 ml). The resulting solution was stirred for 14 h at room temperature. Reaction mixture was diluted with EtOAc (200 ml), washed with 1 M HCl (3 × 150 ml), brine (150 ml), and dried over anhydrous Na_2SO_4, followed by evaporation *in vacuo*. Crude product was triturated with EtOH–H_2O, 1:1 (for compounds **6b**,**c**) or EtOAc – petroleum ether, 1:3 (for compound **6d**) mixture.

7-Hydroxy-3-phenyl-2-(trifluoromethyl)-4*H*-chromen-4-one (6b) was synthesized from compound **5a** (570 mg). Yield 497 mg (65%), white-beige solid. Spectral data was in accordance with the previously reported.[14]

3-(4-Chlorophenyl)-7-hydroxy-2-(trifluoromethyl)-4*H*-chromen-4-one (6c) was synthesized from compound **5b** (4.25 g). Yield 3.47 g (63%), white-yellow solid, mp 248–250°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 11.18 (1H, s, OH); 7.93 (1H, d, *J* = 8.8, H-5); 7.52 (2H, d, *J* = 8.5 C_6H_4Cl); 7.31 (2H, d, *J* = 8.5, C_6H_4Cl); 7.02 (1H, dd, *J* = 8.8, *J* = 2.2, H-8); 6.96 (1H, d, *J* = 2.2, H-6). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 175.1; 164.1; 156.6; 146.8 (q, *J* = 35.5); 133.6; 131.9; 128.6; 128.2; 127.6; 124.0; 119.4 (q, *J* = 276.4); 116.6; 115.5; 102.4. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –62.86. Found, *m*/*z*: 341.0198 $[M+H]^+$. $C_{16}H_9ClF_3O_3$. Calculated, *m*/*z*: 341.0192.

7-Hydroxy-3-(4-methoxyphenyl)-2-(trifluoromethyl)-4*H*-chromen-4-one (6d) was synthesized from compound **5c** (640 mg). Yield 258 mg (31%), light-brown solid. Spectral data was in accordance with the previously reported.[13]

Synthesis of 7-(alkyloxy)-3-(4-chlorophenyl)-2-(trifluoromethyl)-4*H*-chromen-4-ones 7a–j (General method). Alkyl chloride, iodide, or bromide (0.6 mmol) was added to a stirred solution of compound **6b**–**d** (0.45 mmol) and K_2CO_3 (1 mmol) in DMF (3 ml). The resulting solution was stirred for 14 h at room temperature. Reaction mixture was diluted with EtOAc (50 ml), washed with brine (3 × 50 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Crude product was crystallized from EtOH.

3-(4-Chlorophenyl)-7-methoxy-2-(trifluoromethyl)-4*H*-chromen-4-one (7a) was synthesized from compound **6c** (300 mg), using MeI as alkylating agent. Yield 258 mg (83%), white solid, mp 162–164°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.12 (1H, d, *J* = 8.9,

H-5); 7.42 (2H, d, J = 8.5, C_6H_4Cl); 7.20 (2H, d, J = 8.4, C_6H_4Cl); 7.05 (1H, dd, J = 8.9, J = 2.4, H-8); 6.95 (1H, d, J = 2.3, H-6); 3.95 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (J, Hz): 175.9; 165.3; 157.1; 148.3 (q, J = 36.5); 135.1; 131.4; 128.7; 128.0; 127.7; 124.6; 119.4 (q, J = 276.7); 117.1; 116.2; 100.3; 56.2. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.56. Found, m/z: 355.0360 $[M+H]^+$. $C_{17}H_{11}ClF_3O_3$. Calculated, m/z: 355.0349.

7-Methoxy-3-phenyl-2-(trifluoromethyl)-4*H*-chromen-4-one (7b) was synthesized from compound **6b** (200 mg) using MeI as alkylating agent. Yield 98 mg (47%), yellowish solid. Spectral data was in accordance with the previously reported.[15]

7-Methoxy-3-(4-methoxyphenyl)-2-(trifluoromethyl)-4*H*-chromen-4-one (7c) was synthesized from compound **6d** (138 mg) using MeI as alkylating agent. Yield 114 mg (79%), beige solid, mp 135–138°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.13 (1H, d, J = 8.9, H-5); 7.19 (2H, d, J = 8.7, $C_6\underline{H}_4OMe$); 7.03 (1H, dd, J = 8.9, J = 2.4, H-8); 6.97 (2H, d, J = 8.8, H Ar, $C_6\underline{H}_4OMe$); 6.94 (1H, d, J = 2.4, H-6); 3.95 (3H, s, OCH_3); 3.85 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (J, Hz): 176.5; 165.1; 160.1; 157.1; 148.1 (q, J = 35.6); 131.2; 128.0; 125.5; 121.2; 119.6 (q, J = 275.8); 117.3; 116.0, 113.9, 100.2, 56.2, 55.4. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –62.58. Found, m/z: 351.0857 $[M+H]^+$. $C_{18}H_{14}F_3O_4$. Calculated, m/z: 351.0844.

7-(Benzyloxy)-3-(4-chlorophenyl)-2-(trifluoromethyl)-4*H*-chromen-4-one (7d) was synthesized from compound **6c** (500 mg) using BnBr as alkylating agent. Yield 585 mg (92%), white solid, mp 160–162°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.14 (1H, d, J = 8.9, H-5); 7.49–7.35 (7H, m, C_6H_4Cl, $OCH_2C_6\underline{H}_5$); 7.20 (2H, d, J = 8.4, C_6H_4Cl); 7.13 (1H, dd, J = 8.9, J = 2.4, H-8); 7.03 (1H, d, J = 2.3, H-6); 5.20 (2H, s, $OC\underline{H}_2Ph$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (J, Hz): 175.9; 164.3; 156.9; 148.3 (q, J = 36.2); 135.4; 135.1; 131.4; 129.0; 128.7 (2C); 128.1; 127.7; 127.6; 124.6; 119.4 (q, J = 276.8); 117.3; 116.7; 101.4; 70.9. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –62.74. Found, m/z: 431.0672 $[M+H]^+$. $C_{23}H_{15}ClF_3O_3$. Calculated, m/z: 431.0662.

7-(Benzyloxy)-3-phenyl-2-(trifluoromethyl)-4*H*-chromen-4-one (7e) was synthesized from compound **6b** (180 mg) using BnBr as alkylating agent. Yield 60 mg (26%), white solid, mp 123–125°C. ^1H NMR spectrum (400 MHz, $(CD_3)_2CO$), δ, ppm (J, Hz): 8.02 (1H, d, J = 9.1, H-5); 7.53–7.49 (2H, m, H Ph); 7.44–7.37 (5H, m, H Ph); 7.37–7.32 (1H, m, H Ph); 7.32–7.27 (2H, m, H Ph); 7.26 (1H, d, J = 2.2, H-8); 7.20 (1H, dd, J = 8.9, J = 2.4, H-6); 5.34 (2H, s, $OC\underline{H}_2C_6H_5$). ^{13}C NMR spectrum (101 MHz, $(CD_3)_2CO$), δ, ppm (J, Hz): 176.1; 165.1; 157.8; 148.3 (q, J = 35.7); 137.1; 130.9 (q, J = 1.4); 130.7; 129.5; 129.3; 129.1; 128.7; 128.6; 128.2; 126.6; 120.6 (q, J = 275.6); 118.1; 117.3; 102.3; 71.5. ^{19}F NMR spectrum (376 MHz, $(CD_3)_2CO$), δ, ppm: –64.31. Found, m/z: 397.1057 $[M+H]^+$. $C_{23}H_{16}F_3O_3$. Calculated, m/z: 397.1052.

3-(4-Chlorophenyl)-7-(methoxymethoxy)-2-(trifluoromethyl)-4*H*-chromen-4-one (7f) was synthesized from compound **6c** (400 mg) using MOMCl as alkylating agent. Yield 262 mg (58%), off-white solid, mp 125–127°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.14 (1H, d, J = 8.9, H-5); 7.42 (2H, d, J = 8.5, C_6H_4Cl); 7.23–7.17 (3H, m, H Ar); 7.13 (1H, dd, J = 8.9, J = 2.3, H-6); 5.31 (2H, s, $OC\underline{H}_2OCH_3$), 3.52 (3H, s, $OCH_2OC\underline{H}_3$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (J, Hz): 176.0; 162.7; 156.7; 148.5 (q, J = 36.2); 135.2; 131.4; 128.7; 128.0; 127.7; 124.6; 119.4 (q, J = 276.4); 117.9; 117.0; 103.3; 94.6; 56.7. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.57. Found, m/z: 385.0465 $[M+H]^+$. $C_{18}H_{13}ClF_3O_4$. Calculated, m/z: 385.0454.

3-(4-Chlorophenyl)-7-[(2,6-dichlorobenzyl)oxy]-2-(trifluoromethyl)-4*H*-chromen-4-one (7g) was synthesized from compound **6c** (150 mg) using 2-(bromomethyl)-1,3-dichlorobenzene as alkylating agent. Yield 172 mg (78%), light-yellow solid, mp 196–197°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.16 (1H, d, J = 9.4, H-5); 7.46–7.39 (4H, m, H Ar); 7.31 (1H, dd, J = 8.8, J = 7.2, H Ar); 7.21 (2H, d, J = 8.4, C_6H_4Cl); 7.16–7.10 (2H, m, H Ar); 5.42 (2H, s, $OC\underline{H}_2C_6H_3Cl_2$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (J, Hz): 175.9; 164.3; 156.9; 137.2; 135.2; 131.4; 131.2; 130.9; 128.8; 128.7; 128.1; 127.7; 124.7; 119.4 (d, J = 276.6) 117.5; 116.6; 101.3; 100.1; 65.9. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.55. Found, m/z: 498.9877 $[M+H]^+$. $C_{23}H_{13}Cl_3F_3O_3$. Calculated, m/z: 498.9882.

7-[(4-Bromobenzyl)oxy]-3-(4-chlorophenyl)-2-(trifluoromethyl)-4*H*-chromen-4-one (7h) was synthesized from compound **6c** (150 mg) using 1-bromo-4-(bromomethyl)-benzene as alkylating agent. Yield 114 mg (51%), pink solid, mp 153–155°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.14 (1H, d, J = 8.9, H-5); 7.56 (2H, d, J = 8.4, C_6H_4Br); 7.42 (2H, d, J = 8.5, C_6H_4Cl); 7.33 (2H, d, J = 8.4, C_6H_4Br); 7.20 (2H, d, J = 8.4, C_6H_4Cl); 7.11 (1H, dd, J = 8.9, J = 2.4, H-8); 7.00 (1H, d, J = 2.3, H-6); 5.15 (2H, s, $OC\underline{H}_2C_6H_4Br$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (J, Hz): 175.9; 164.0; 156.9; 148.4 (q, J = 36.0); 135.2; 134.4; 132.2; 131.3; 129.2; 128.7; 128.2; 127.6; 124.7; 122.7; 120.8; 119.4 (q, J = 276.7); 116.6; 101.4; 70.1. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.53. Found, m/z: 508.9775 $[M+H]^+$. $C_{23}H_{14}BrClF_3O_3$. Calculated, m/z: 508.9767.

3-(4-Chlorophenyl)-7-isopropoxy-2-(trifluoromethyl)-4*H*-chromen-4-one (7i) was synthesized from compound **6c** (250 mg) using *i*-PrI as alkylating agent. Yield 275 mg (98%), yellowish solid, mp 128–130°C. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.11 (1H, d, J = 8.9, H-5); 7.42 (2H, d, J = 8.6, C_6H_4Cl); 7.20 (2H, d, J = 8.4, C_6H_4Cl); 7.00 (1H, dd, J = 8.9, J = 2.3, H-8); 6.91 (1H, d, J = 2.3, H-6); 4.70 (1H, hept, J = 5.8, $OC\underline{H}(CH_3)_2$), 1.43 (6H, d, J = 6.1, $OCH(C\underline{H}_3)_2$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (J, Hz): 175.9; 163.8; 157.1; 148.2 (q, J = 36.3); 135.1; 131.4; 128.7; 128.0; 127.8; 124.6; 119.5 (q, J = 276.7); 117.2; 116.8; 101.5; 71.3; 21.9. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.58. Found, m/z: 383.0656 $[M+H]^+$. $C_{19}H_{15}ClF_3O_3$. Calculated, m/z: 383.0662.

3-(4-Chlorophenyl)-7-(isopentyloxy)-2-(trifluoromethyl)-4*H*-chromen-4-one (7j) was synthesized from compound **6c** (250 mg) using isoamyl bromide as alkylating agent.

Yield 297 mg (98%), yellow solid, mp 80–82°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.11 (1H, d, *J* = 8.9, H-5); 7.42 (2H, d, *J* = 8.5, C_6H_4Cl); 7.20 (2H, d, *J* = 8.4, C_6H_4Cl); 7.03 (1H, dd, *J* = 8.9, *J* = 2.3, H-8); 6.94 (1H, d, *J* = 2.3, H-6); 4.12 (2H, t, *J* = 6.6, $OC\underline{H}_2CH_2CH(CH_3)_2$); 1.95–1.80 (1H, m, $OCH_2CH_2C\underline{H}(CH_3)_2$); 1.77 (2H, t, *J* = 6.5, $OCH_2C\underline{H}_2CH(CH_3)_2$); 1.00 (6H, d, *J* = 6.5, $OCH_2CH_2CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 175.9; 164.8; 157.1; 148.3 (q, *J* = 36.3); 135.1; 131.4; 128.6; 127.9; 124.6; 119.5 (q, *J* = 276.7); 116.9; 116.6; 110.2; 100.7; 67.6; 37.7; 25.2; 22.7. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.59. Found, *m*/*z*: 411.0981 $[M+H]^+$. $C_{21}H_{19}ClF_3O_3$. Calculated, *m*/*z*: 411.0975.

3-(4-Chlorophenyl)-4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl benzenesulfonate (7k). Phenylsulfonyl chloride (233 mg, 1.33 mmol) was added to a stirred solution of compound **6c** (300 mg, 0.88 mmol) and Et_3N (245 μl, 1.76 mmol) in CH_2Cl_2 (5 ml). Resulting solution was stirred for 14 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (15 ml), washed with brine (3 × 50 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Crude product was purified by silica gel column chromatography, using gradient from 5 to 20% EtOAc in petroleum ether. Yield 390 mg (92%), brown oil. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.16 (1H, d, *J* = 8.8, H-5); 7.91 (2H, d, *J* = 7.3, H Ar); 7.74 (1H, t, *J* = 7.5, H Ar); 7.60 (2H, t, *J* = 7.9, H Ar); 7.49–7.35 (3H, m, H Ar); 7.18 (2H, d, *J* = 8.4, C_6H_4Cl); 7.07 (1H, dd, *J* = 8.8, *J* = 2.2, H-6). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 175.9; 155.4; 154.1; 149.1 (q, *J* = 36.6); 135.5; 135.1; 135.0; 131.2; 129.7; 128.8; 128.6; 128.5; 127.0; 125.0; 121.9; 121.0; 119.2 (q, *J* = 277.2); 112.4. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.56. Found, *m*/*z*: 481.0128 $[M+H]^+$. $C_{22}H_{13}ClF_3O_5S$. Calculated, *m*/*z*: 481.0124.

Synthesis of pyrazoles 2, 8a–l (General method). Hydrazine hydrate (1.3 ml, 27.6 mmol) was added to a stirred solution of compound **6a**,**c**, **7a**–**k** (0.67 mmol) in EtOH (5 ml). Resulting solution was stirred for 2 h at reflux. Reaction mixture was evaporated to dryness and triturated with cold H_2O.

4-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]benzene-1,3-diol (2) was synthesized from compound **6c** (258 mg). Yield 208 mg (77%), white solid. Spectral data was in accordance with the previously reported.[16]

4-[4-(4-Chlorophenyl)-5-methyl-1*H*-pyrazol-3-yl]-benzene-1,3-diol (8a) was synthesized from compound **6a** (183 mg). Yield 158 mg (94%), white solid, mp 231–234°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 12.52 (1H, s, NH); 10.58 (1H, s, OH), 9.38 (1H, s, OH); 7.37–7.20 (4H, m, C_6H_4Cl); 6.76 (1H, d, *J* = 7.8, H Ar); 6.29–6.11 (2H, m, H Ar); 2.19 (3H, s, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 157.9; 157.0; 147.0; 137.6; 131.4; 130.3; 128.8; 128.5; 128.1; 115.1; 109.7; 106.3; 102.8; 12.9. Found, *m*/*z*: 301.0752 $[M+H]^+$. $C_{16}H_{14}ClN_2O_2$. Calculated, *m*/*z*: 301.0744.

2-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-5-methoxyphenol (8b) was synthesized from compound **7a** (600 mg). Yield 600 mg (96%), white-beige solid, mp 178–180°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.39 (2H, d, *J* = 8.4, C_6H_4Cl); 7.19 (2H, d, *J* = 8.4, C_6H_4Cl); 6.85 (1H, d, *J* = 8.5, H-5); 6.42 (1H, d, *J* = 2.4, H-2); 6.29 (1H, dd, *J* = 8.5, *J* = 2.4, H-6); 3.68 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 161.2; 156.8; 139.8; 138.1 (q, *J* = 36.0); 132.2; 131.9; 131.4; 130.6; 128.4; 122.2 (q, *J* = 269.2); 116.9; 107.8; 105.0; 101.5; 55.2. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.88. Found, *m*/*z*: 369.0628 $[M+H]^+$. $C_{17}H_{13}ClF_3N_2O_2$. Calculated, *m*/*z*: 369.0618.

5-Methoxy-2-[4-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]phenol (8c) was synthesized from compound **7b** (91 mg). Yield 82 mg (86%), white solid, mp 145–147°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.35–7.24 (3H, m, H Ar); 7.21–7.14 (2H, m, H Ar); 6.85 (1H, d, *J* = 8.5, H-3); 6.45 (1H, d, *J* = 2.5, H-6); 6.31 (1H, dd, *J* = 8.6, *J* = 2.5, H-4); 3.68 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.9; 156.7; 139.3; 138.1 (q, *J* = 34.8); 131.8; 131.5; 129.6; 128.1; 127.1; 122.2 (q, *J* = 269.2); 118.0; 108.0; 104.7; 101.3; 55.0. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.80. Found, *m*/*z*: 335.1021 $[M+H]^+$. $C_{17}H_{14}F_3N_2O_2$. Calculated, *m*/*z*: 335.1007.

5-Methoxy-2-[4-(4-methoxyphenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]phenol (8d) was synthesized from compound **7c** (102 mg). Yield 77 mg (73%), beige powder, mp 75–79°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.09 (2H, d, *J* = 8.2, $C_6\underline{H}_4OMe$); 6.87 (3H, t, *J* = 8.2, H Ar); 6.45 (1H, s, H-6); 6.32 (1H, d, *J* = 9.9, H-4); 3.73 (3H, s, OCH_3); 3.68 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.7; 158.3; 156.7; 139.2; 138.1 (q, *J* = 36.0); 131.7; 130.7; 123.5; 122.3 (q, *J* = 270.1); 117.6; 113.6; 108.2; 104.7; 101.3; 55.0 (q, *J* = 4.4). ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.84. Found, *m*/*z*: 365.1121 $[M+H]^+$. $C_{18}H_{16}F_3N_2O_3$. Calculated, *m*/*z*: 365.1113.

5-(Benzyloxy)-2-[4-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]phenol (8e) was synthesized from compound **7d** (289 mg). Yield 274 mg (92%), white solid, mp 78–81°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.46–7.28 (7H, m, C_6H_4Cl, $OCH_2C_6\underline{H}_5$); 7.18 (2H, d, *J* = 8.4, C_6H_4Cl); 6.89 (1H, d, *J* = 8.5, H-3); 6.50 (1H, d, *J* = 2.3, H-6); 6.43 (1H, dd, *J* = 8.5, *J* = 2.3, H-4); 5.03 (2H, s, $OC\underline{H}_2C_6H_5$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.2; 156.7; 139.8; 138.2 (q, *J* = 34.7); 136.9; 132.2; 131.9; 131.4; 130.6; 128.6; 128.4; 128.1; 127.9; 122.2 (q, *J* = 269.2); 117.0; 108.0; 105.8; 102.4; 69.3. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.59. Found, *m*/*z*: 445.0934 $[M+H]^+$. $C_{23}H_{17}ClF_3N_2O_2$. Calculated, *m*/*z*: 445.0931.

5-(Benzyloxy)-2-[4-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]phenol (8f) was synthesized from compound **7e** (48 mg). Yield 46 mg (92%), white solid, mp 84–88°C. ^{1}H NMR spectrum (400 MHz, $(CD_3)_2CO$), δ, ppm (*J*, Hz): 7.46–7.26 (9H, m, H Ar, $OCH_2C_6\underline{H}_5$); 6.90 (1H, d, *J* = 8.6, H-3); 6.63 (1H, d, *J* = 2.4, H-6); 6.40 (1H, dd, *J* = 8.6, *J* = 2.4, H-4), 5.06 (2H, s, $OC\underline{H}_2C_6H_5$). ^{13}C NMR spectrum (101 MHz, $(CD_3)_2CO$), δ, ppm (*J*, Hz): 161.4; 157.3; 140.3; 138.1; 132.9; 132.2; 131.1; 129.3; 129.1; 128.7; 128.5; 128.2; 122.3 (q, *J* = 268.8); 119.0; 109.4; 107.0; 103.5; 70.5. ^{19}F NMR spectrum (376 MHz, $(CD_3)_2CO$), δ, ppm: –59.66.

Found, *m/z*: 411.1344 $[M+H]^+$. $C_{23}H_{18}F_3N_2O_2$. Calculated, *m/z*: 411.1320.

2-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-5-(methoxymethoxy)phenol (8g) was synthesized from compound **7f** (136 mg). Yield 117 mg (83%), white-gray powder, mp 190–193°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.00 (2H, br. s, NH, OH); 7.39 (2H, d, *J* = 8.3, C_6H_4Cl); 7.19 (2H, d, *J* = 8.3, C_6H_4Cl); 6.91 (1H, d, *J* = 8.5, H-3); 6.57 (1H, d, *J* = 2.0, H-6); 6.43 (1H, dd, *J* = 8.5, *J* = 2.0, H-4); 5.13 (2H, s, $OC\underline{H}_2OCH_3$); 3.35 (3H, s, $OCH_2OC\underline{H}_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 158.5; 156.6; 139.5; 138.1 (q, *J* = 34.3); 132.0; 131.7; 131.3; 130.5; 128.3; 122.1 (q, *J* = 269.0); 116.9; 108.6; 106.9; 103.3; 93.6; 55.6. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.84. Found, *m/z*: 399.0735 $[M+H]^+$. $C_{18}H_{15}ClF_3N_2O_3$. Calculated, *m/z*: 399.0723.

2-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-5-[(2,6-dichlorobenzyl)oxy]phenol (8h) was synthesized from compound **7g** (161 mg). Yield 138 mg (83%), white solid, mp 92–94°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.60–7.52 (2H, m, H Ar); 7.46 (1H, dd, *J* = 8.9, *J* = 7.1, H Ar); 7.40 (2H, d, *J* = 8.5, C_6H_4Cl); 7.21 (2H, d, *J* = 8.4, C_6H_4Cl); 6.95 (1H, d, *J* = 8.3, H-3); 6.59–6.47 (2H, m, H Ar); 5.16 (2H, s, $OC\underline{H}_2C_6H_3Cl_2$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.3; 156.8; 139.8; 138.3 (q, *J* = 34.4); 136.2; 132.2; 132.1; 131.8; 131.6; 131.5; 130.6; 128.9; 128.4; 122.2 (q, *J* = 269.1); 117.0; 108.6; 105.3; 102.3; 65.0. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.83. Found, *m/z*: 513.0157 $[M+H]^+$. $C_{23}H_{15}Cl_3F_3N_2O_2$. Calculated, *m/z*: 513.0151.

5-[(4-Bromobenzyl)oxy]-2-[4-(4-chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]phenol (8i) was synthesized from compound **7h** (114 mg). Yield 93 mg (79%), beige solid, mp 83–85°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.58 (2H, d, *J* = 8.4, C_6H_4Br); 7.44–7.30 (4H, m, C_6H_4Cl, C_6H_4Br); 7.18 (2H, d, *J* = 8.4, C_6H_4Cl); 6.86 (1H, d, *J* = 8.5, H-3); 6.47 (1H, d, *J* = 2.4, H-6); 6.37 (1H, dd, *J* = 8.6, *J* = 2.4, H-4); 5.01 (2H, s, $OC\underline{H}_2C_6H_4Br$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.0; 156.8; 139.7; 138.2 (q, *J* = 33.3); 136.4; 132.2; 131.9; 131.5; 131.4; 130.6; 130.0; 128.4; 122.2 (q, *J* = 269.1); 121.1; 117.0; 108.2; 105.7; 102.4; 68.5. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.84. Found, *m/z*: 525.0023 $[M+H]^+$. $C_{23}H_{16}BrClF_3N_2O_2$. Calculated, *m/z*: 525.0040.

4-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-3-hydroxyphenyl benzenesulfonate (8j) was synthesized from compound **7k** (250 mg). Yield 228 mg (89%), beige solid, mp 193–196°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.87–7.79 (3H, m, H Ar); 7.66 (2H, t, *J* = 7.8, H Ar); 7.40 (2H, d, *J* = 8.5, C_6H_4Cl); 7.15 (2H, d, *J* = 8.4, C_6H_4Cl); 6.90 (1H, d, *J* = 8.5, H-2); 6.51 (1H, d, *J* = 2.4, H-5); 6.28 (1H, dd, *J* = 8.5, *J* = 2.4, H-6). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 158.0 (d, *J* = 16.5); 149.4 (d, *J* = 4.1); 140.3 (d, *J* = 14.2); 138.2 (d, *J* = 34.3); 134.9; 134.4; 132.0; 131.4; 131.0 (d, *J* = 8.6); 130.1 (d, *J* = 13.6); 129.8; 128.3; 128.1; 122.4 (d, *J* = 272.6); 116.3 (d, *J* = 9.0); 115.3 (d, *J* = 4.6); 111.2 (d, *J* = 9.9); 109.6. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –57.30. Found, *m/z*: 495.0407 $[M+H]^+$. $C_{22}H_{15}ClF_3N_2O_4S$. Calculated, *m/z*: 495.0393

2-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-5-isopropoxyphenol (8k) was synthesized from compound **7i** (130 mg). Yield 129 mg (95%), white solid, mp 176–178°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.38 (2H, d, *J* = 8.1, C_6H_4Cl); 7.18 (2H, d, *J* = 8.1, C_6H_4Cl); 6.86 (1H, d, *J* = 8.5, H-3); 6.41 (1H, s, H-6); 6.32 (1H, d, *J* = 8.4, H-4); 4.49 (1H, sept, *J* = 5.7, $OC\underline{H}(CH_3)_2$); 1.22 (6H, d, *J* = 5.9, $OCH(C\underline{H}_3)_2$). ^{13}C NMR spectrum (151 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 159.2; 156.8; 139.8; 138.0 (q, *J* = 34.6); 131.9; 131.6; 131.3; 130.7; 128.2; 122.2 (q, *J* = 269.0); 116.6; 107.4; 106.1; 102.8; 69.2; 21.8. ^{19}F NMR spectrum (564 MHz, $CDCl_3$), δ, ppm: –53.02. Found, *m/z*: 397.0932 $[M+H]^+$. $C_{19}H_{17}ClF_3N_2O_2$. Calculated, *m/z*: 397.0931.

2-[4-(4-Chlorophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-5-(isopentyloxy)phenol (8l) was synthesized from compound **7j** (140 mg). Yield 141 mg (97%), light-yellow solid, mp 73–75°C. ^{1}H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.38 (2H, d, *J* = 8.4, C_6H_4Cl); 7.24 (2H, d, *J* = 8.3, C_6H_4Cl); 6.82 (1H, d, *J* = 8.8, H-3); 6.49 (1H, s, H-6); 6.27 (1H, dd, *J* = 8.8, *J* = 1.9, H-4); 3.92 (2H, t, *J* = 6.7, $OC\underline{H}_2CH_2CH(CH_3)_2$); 1.77 (1H, sept, *J* = 6.7, $OCH_2CH_2C\underline{H}(CH_3)_2$); 1.63 (2H, q, *J* = 6.7, $OCH_2C\underline{H}_2CH(CH_3)_2$); 0.93 (6H, d, *J* = 6.6, $OCH_2CH_2CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.6; 156.7; 139.8; 138.3 (q, *J* = 32.9); 132.2; 131.9; 131.5; 130.7; 128.4; 122.2 (q, *J* = 269.1); 116.9; 107.7; 105.5; 102.0; 66.0; 37.5; 24.7; 22.5. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –59.35. Found, *m/z*: 425.1240 $[M+H]^+$. $C_{21}H_{21}ClF_3N_2O_2$. Calculated, *m/z*: 425.1244.

Synthesis of pyrazoles 10a–c (General method). Hydrazine hydrate (1.86 ml, 38 mmol) was added to a stirred solution of diketone **9a–c** (1.9 mmol) in EtOH (15 ml). The resulting solution was stirred for 14 h at reflux. Reaction mixture was evaporated to dryness and triturated with cold H_2O.

3-Phenyl-5-(trifluoromethyl)-1*H*-pyrazole (10a) was synthesized from 4,4,4-trifluoro-1-phenylbutane-1,3-dione (**9a**) (1.7 g). Yield 1.52 g (91%), white solid. Spectral data was in accordance with the previously reported.[17]

5-Methoxy-2-[5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-phenol (10b) was synthesized from 4,4,4-trifluoro-1-(2-hydroxy-4-methoxyphenyl)butane-1,3-dione (**9b**) (500 mg) (synthesized analogously to literature-described procedure[18] from 1-(2-hydroxy-4-methoxyphenyl)ethan-1-one). Yield 397 mg (80%), white solid, mp 149–151°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.59 (1H, d, *J* = 8.5, H-3); 6.97 (1H, s, H-6); 6.61–6.44 (2H, m, H-4 pyrazol, H-5); 3.74 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 160.6; 155.6; 141.4; 140.9 (q, *J* = 39.0); 128.6; 122.1 (q, *J* = 268.0); 108.1; 105.5; 101.6; 101.4; 55.1. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –60.28. Found, *m/z*: 259.0698 $[M+H]^+$. $C_{11}H_{10}F_3N_2O_2$. Calculated, *m/z*: 259.0694.

2-[5-(Trifluoromethyl)-1*H*-pyrazol-3-yl]phenol (10c) was synthesized from 4,4,4-trifluoro-1-(2-hydroxyphenyl)-

butane-1,3-dione (**9c**) (390 mg) according to the literature-described procedure.[19] Yield 271 mg (71%), white-beige solid. Spectral data was in accordance with the previously reported.[20]

4-[5-(Trifluoromethyl)-1*H*-pyrazol-3-yl]benzene-1,3-diol (10d). Boron tribromide (1 M in CH_2Cl_2, 3.65 ml, 3.65 mmol) was added dropwise to an ice-cooled solution of compound **10b** (236 mg, 0.91 mmol) in CH_2Cl_2 (5 ml). After stirring for 2 h at 25°C, the reaction mixture was poured into ice water, and neutralized with addition of saturated aqueous $NaHCO_3$, followed by extraction with CH_2Cl_2 (2 × 15 ml). Organic extracts were combined, dried over Na_2SO_4, and evaporated *in vacuo*. Pure product was obtained by trituration with EtOAc – petroleum ether. Yield 31 mg (14%), white solid, mp >220°C (decomp.). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 13.32 (1H, br. s, NH); 10.22 (1H, br. s, OH); 9.65 (1H, br. s, OH); 7.45 (1H, d, *J* = 8.5, H-5); 6.90 (1H, s, H-4 pyrazol); 6.44 (1H, d, *J* = 2.2, H-6); 6.31 (1H, dd, *J* = 8.5, *J* = 2.3, H-2). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 159.0; 155.6; 141.7; 128.6; 107.2; 106.6; 102.9; 100.9 (CF_3 and C–CF_3 carbons can not be observed due to proton exchange process). ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –60.24. Found, *m/z*: 245.0550 $[M+H]^+$. $C_{10}H_8F_3N_2O_2$. Calculated, *m/z*: 245.0538.

4-(4-Chlorophenyl)-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazole (12). 4-Bromo-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazole **11** (405 mg, 1.39 mmol) (synthesized by literature-described procedure[21]) was dissolved in dioxane–H_2O, 4:1 mixture (20 ml) under argon, followed by addition of 4-chlorophenylboronic acid (282 mg, 1.8 mmol), caesium carbonate (1.18 g, 3.62 mmol), and $PdCl_2(PPh_3)_2$ (59 mg, 0.08 mmol). Resulting mixture was heated for 14 h at 100°C. After cooling to room temperature, the reaction mixture was diluted with EtOAc (60 ml), washed with brine (3 × 60 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Crude product was purified by silica gel column chromatography, using gradient from 5 to 20% EtOAc in petroleum ether to obtain product. Yield 118 mg (26%), white solid, mp 187–190°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 11.02 (1H, br. s, NH); 7.45–7.37 (4H, m, H Ar); 7.35–7.21 (5H, m, H Ar). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 142.0; 139.6 (q, *J* = 35.0); 132.9; 132.1; 129.8; 129.2; 129.0; 128.8; 127.9; 125.7; 121.9 (q, *J* = 269.4); 116.3. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –58.19. Found, *m/z*: 323.0571 $[M+H]^+$. $C_{16}H_{11}ClF_3N_2$. Calculated, *m/z*: 323.0563.

Synthesis of isoxazoles 13a–e (General method). Hydroxylamine hydrochloride (42 mg, 0.6 mmol) was added to a stirred solution of compound **6c**, **7e**,**f**,**i**,**j** (0.3 mmol) in pyridine (2 ml). The resulting solution was stirred for 14 h at 90°C. After cooling to room temperature, the reaction mixture was poured into H_2O (70 ml) which was acidified with 1 M HCl. Product further was extracted with EtOAc (40 ml), organic layer was washed with brine (3 × 30 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Obtained isoxazoles **13a**,**b**,**d**,**e** were analytically pure and no further purification needed. Isoxazole **13c** was purified by column chromatography on silica gel, using 5 to 30% gradient of EtOAc in petroleum ether.

4-[4-(4-Chlorophenyl)-3-(trifluoromethyl)isoxazol-5-yl]-benzene-1,3-diol (13a) was synthesized from compound **6c** (130 mg). Yield 115 mg (85%), slightly gray solid, mp 165–168°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 9.95 (2H, d, *J* = 3.7, 2OH); 7.51–7.45 (2H, m, C_6H_4Cl); 7.30–7.25 (2H, m, C_6H_4Cl); 7.09 (1H, d, *J* = 8.5, H-5); 6.33 (1H, d, *J* = 2.2, H-2); 6.28 (1H, dd, *J* = 8.5, *J* = 2.3, H-6). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 169.3; 161.4; 157.1; 152.6 (d, *J* = 35.2); 133.3; 131.6; 131.1; 128.7; 127.0; 120.0 (q, *J* = 271.8); 113.4; 107.4; 103.6; 102.8. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –60.58. Found, *m/z*: 356.0302 $[M+H]^+$. $C_{16}H_{10}ClF_3NO_3$. Calculated, *m/z*: 356.0301.

5-(Benzyloxy)-2-[4-(4-chlorophenyl)-3-(trifluoromethyl)-isoxazol-5-yl]phenol (13b) was synthesized from compound **7d** (130 mg). Yield 129 mg (96%), white solid, mp 141–143°C. ^{1}H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.26 (1H, s, OH); 8.64 (1H, s, H Ar); 7.54–7.27 (9H, m, C_6H_4Cl, $OCH_2C_6\underline{H}_5$); 6.62 (1H, dd, *J* = 8.6, *J* = 2.2, H-6); 6.55 (1H, d, *J* = 2.1, H-4); 5.12 (2H, s, $OC\underline{H}_2C_6H_5$). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 168.8; 161.9; 157.1; 152.7 (q, *J* = 35.2); 149.4; 136.5; 136.4; 133.4; 131.7; 131.2; 128.7; 128.5; 128.0; 127.8; 126.7; 124.0; 119.9 (q, *J* = 271.8); 114.0; 106.4; 105.4; 102.3; 69.3. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –60.58. Found, *m/z*: 446.0767 $[M+H]^+$. $C_{23}H_{16}ClF_3NO_3$. Calculated, *m/z*: 446.0771.

2-[4-(4-Chlorophenyl)-3-(trifluoromethyl)isoxazol-5-yl]-5-(methoxymethoxy)phenol (13c) was synthesized from compound **7f** (190 mg). Yield 124 mg (63%), white solid, mp 119–121°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.40 (2H, d, *J* = 8.6, C_6H_4Cl); 7.25 (2H, d, *J* = 8.5, C_6H_4Cl); 7.00 (1H, d, *J* = 8.8, H-3); 6.65 (1H, d, *J* = 2.4, H-6); 6.53 (1H, dd, *J* = 8.8, *J* = 2.4, H-4); 6.23 (1H, br. s, OH); 5.16 (2H, s, $OC\underline{H}_2OCH_3$); 3.47 (3H, s, $OCH_2OC\underline{H}_3$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 167.5; 161.1; 155.8; 154.6 (q, *J* = 36.4); 135.4; 131.3; 130.5; 129.6; 126.0; 119.9 (q, *J* = 272.4); 113.4; 109.7; 106.4; 105.1; 94.3; 56.5. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.51. Found, *m/z*: 400.0550 $[M+H]^+$. $C_{18}H_{14}ClF_3NO_4$. Calculated, *m/z*: 400.0563.

2-[4-(4-Chlorophenyl)-3-(trifluoromethyl)isoxazol-5-yl]-5-isopropoxyphenol (13d) was synthesized from compound **7i** (124 mg). Yield 125 mg (97%), white solid, mp 111–113°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.40 (2H, d, *J* = 8.6, C_6H_4Cl); 7.25 (2H, d, *J* = 8.4, C_6H_4Cl); 6.95 (1H, d, *J* = 8.8, H-3); 6.46 (1H, d, *J* = 2.4, H-6); 6.36 (1H, dd, *J* = 8.8, *J* = 2.4, H-4); 6.31 (1H, br. s, OH); 4.53 (1H, septet, *J* = 6.0, $OC\underline{H}(CH_3)_2$); 1.33 (6H, d, *J* = 6.1, $OCH(C\underline{H}_3)_2$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 167.8; 162.0; 156.1; 154.6 (q, *J* = 36.2); 135.4; 131.3; 130.4; 129.6; 126.1; 119.9 (q, *J* = 272.3); 112.3; 109.4; 104.9; 104.0; 70.4; 22.1. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.54. Found, *m/z*: 398.0768 $[M+H]^+$. $C_{19}H_{16}ClF_3NO_3$. Calculated, *m/z*: 398.0771.

2-[4-(4-Chlorophenyl)-3-(trifluoromethyl)isoxazol-5-yl]-5-(isopentyloxy)phenol (13e) was synthesized from compound **7j** (140 mg). Yield 132 mg (91%), white-yellow solid, mp 112–114°C. ^{1}H NMR spectrum (600 MHz,

$CDCl_3$), δ, ppm (*J*, Hz): 7.40 (2H, d, *J* = 8.5, C_6H_4Cl); 7.25 (2H, d, *J* = 8.6, C_6H_4Cl); 6.96 (1H, d, *J* = 8.8, H-3); 6.48 (1H, d, *J* = 2.4, H-6); 6.39 (1H, dd, *J* = 8.8, *J* = 2.4, H-4); 6.32 (1H, br. s, OH); 3.97 (2H, t, *J* = 6.7, $OC\underline{H}_2CH_2CH(CH_3)_2$); 1.80 (1H, dsept, *J* = 13.4, *J* = 6.7, $OCH_2CH_2C\underline{H}(CH_3)_2$); 1.66 (2H, q, *J* = 6.7, $OCH_2C\underline{H}_2CH(CH_3)_2$); 0.95 (6H, d, *J* = 6.7, $OCH_2CH_2CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum (151 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 167.8; 163.1; 156.0; 154.6 (q, *J* = 36.1); 135.4; 131.3; 130.3; 129.6; 126.1; 119.9 (q, *J* = 272.4); 112.9; 108.7; 105.0; 103.1; 66.9; 37.8; 25.2; 22.7. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.54. Found, *m/z*: 426.1085 $[M+H]^+$. $C_{21}H_{20}ClF_3NO_3$. Calculated, *m/z*: 426.1084.

4-(4-Chlorophenyl)-5-[2-methoxy-4-(methoxymethoxy)-phenyl]-3-(trifluoromethyl)isoxazole (14). Methyl iodide (53 μl, 0.85 mmol) was added to a stirred solution of compound **13c** (114 mg, 0.285 mmol) with K_2CO_3 (98 mg, 0.71 mmol) in DMF (2 ml) at room temperature. The reaction mixture was stirred for 14 h and then partitioned between EtOAc (20 ml) and brine (10 ml). Organic layer was separated, washed with brine (2 × 20 ml), dried over anhydrous Na_2SO_4 to obtain pure product. Yield 117 mg (99%), colorless oil. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.36 (1H, d, *J* = 8.6, H-6); 7.32 (2H, d, *J* = 8.6, C_6H_4Cl); 7.17 (2H, d, *J* = 8.4, C_6H_4Cl); 6.69 (1H, dd, *J* = 8.6, *J* = 2.2, H-5); 6.53 (1H, d, *J* = 2.2, H-3); 5.20 (2H, s, $OC\underline{H}_2OCH_3$); 3.49 (3H, s, $OCH_2OC\underline{H}_3$); 3.40 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 167.7; 161.3; 158.1; 153.8 (q, *J* = 36.1); 134.4; 131.8; 130.6; 128.8; 127.6; 120.2 (q, *J* = 272.2); 114.6; 109.1; 108.1; 100.5; 94.5; 56.5; 55.1. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.32 Found, *m/z*: 414.0734 $[M+H]^+$. $C_{19}H_{16}ClF_3NO_4$. Calculated, *m/z*: 414.0720.

4-[4-(4-Chlorophenyl)-3-(trifluoromethyl)-isoxazol-5-yl]-3-methoxyphenol (15). 12 M HCl (30 μl, 0.97 mmol) was added to a stirred solution of isoxazole **14** (88 mg, 0.21 mmol) in MeOH (3 ml), and the reaction mixture was heated at 60°C for 3 h. After cooling to room temperature, reaction mixture was evaporated to dryness, partitioned between EtOAc (10 ml) and brine (10 ml). Organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to obtain pure product. Yield 76 mg (97%), white-yellow solid, mp 148–150°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.35–7.28 (3H, m, H Ar); 7.16 (2H, d, *J* = 8.4, C_6H_4Cl); 6.47 (1H, dd, *J* = 8.4, *J* = 2.3, H-6); 6.37 (1H, d, *J* = 2.3, H-2); 5.38 (1H, br. s, OH); 3.39 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 167.8; 159.8; 158.4; 153.8 (q, *J* = 36.1); 134.4; 132.1; 130.6; 128.8; 127.6; 120.1 (q, *J* = 272.1); 114.5; 108.2; 108.0; 99.7; 55.1. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.32. Found, *m/z*: 370.0457 $[M+H]^+$. $C_{17}H_{12}ClF_3NO_3$. Calculated, *m/z*: 370.0458.

3-(4-Chlorophenyl)-4-oxo-2-(trifluoromethyl)-4*H*-chromen-7-yl trifluoromethanesulfonate (16). Trifluoromethanesulfonic anhydride (530 μl, 3.22 mmol) was added dropwise under ice cooling to a stirred solution of compound **6c** (1 g, 2.93 mmol) and Et_3N (818 μl, 5.87 mmol) in dry CH_2Cl_2 (40 ml). After 1 h of stirring at room temperature, reaction mixture was poured into H_2O, oganic layer was washed with brine (20 ml), separated, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Product was purified by silica gel column chromatography using 5% EtOAc in petroleum ether. Yield 1.32 g (95%), light-yellow oil. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.35 (1H, d, *J* = 8.9, H-5); 7.58 (1H, d, *J* = 2.3, H-8); 7.51–7.35 (3H, m, H Ar); 7.20 (2H, d, *J* = 8.4, C_6H_4Cl). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 175.6; 155.4; 153.2; 149.4 (q, *J* = 36.5); 135.7; 131.2; 129.4; 128.9; 126.7; 125.4; 122.9; 120.5; 120.4; 120.1; 117.7; 117.2; 112.0. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.60; –72.50. Found, *m/z*: 472.9687 $[M+H]^+$. $C_{17}H_8ClF_6O_5S$. Calculated, *m/z*: 472.9685.

3-(4-Chlorophenyl)-2-(trifluoromethyl)-4*H*-chromen-4-one (17). Triethylsilane (1.12 ml, 7 mmol) and $PdCl_2(PPh_3)_2$ (98 mg, 0.14 mmol) were added to a stirred solution of compound **16** (1.32 g, 2.8 mmol) in DMF (15 ml) at room temperature. The reaction mixture was allowed to heat at 60°C for 1 h. After cooling to room temperature, reaction mixture was partitioned between EtOAc (30 ml) and brine (20 ml). Organic layer was separated, washed with brine (2 × 20 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Crude residue was crystallized from petroleum ether to obtain pure product. Yield 530 mg (58%), yellow solid, mp 107–109°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.24 (1H, dd, *J* = 8.0, *J* = 1.6, H-5); 7.80 (1H, ddd, *J* = 8.6, *J* = 7.2, *J* = 1.7, H-7); 7.59 (1H, d, *J* = 8.5, H-8); 7.50 (1H, t, *J* = 7.6, H-6); 7.44 (2H, d, *J* = 8.4, C_6H_4Cl); 7.21 (2H, d, *J* = 8.4, C_6H_4Cl). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 176.8; 155.2; 148.8 (q, *J* = 36.3); 135.3; 135.2; 131.4; 128.7; 127.6; 126.6; 126.5; 124.6; 123.3; 119.4 (q, *J* = 277.0); 118.5. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –63.60. Found, *m/z*: 325.0249 $[M+H]^+$. $C_{16}H_9ClF_3O_2$. Calculated, *m/z*: 325.0243.

2-[4-(4-Chlorophenyl)-3-(trifluoromethyl)isoxazol-5-yl]-phenol (18). Hydroxylamine hydrochloride (227 mg, 3.26 mmol) was added to a stirred solution of compound **17** (530 mg, 1.63 mmol) in pyridine (5 ml). The resulting solution was stirred for 14 h at 90°C. After cooling to room temperature, the reaction mixture was poured into H_2O (100 ml) which was acidified with 1 M HCl. Product further was extracted with EtOAc (60 ml), organic layer was washed with brine (3 × 30 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Yield 550 mg (99%), pink solid, mp 147–150°C. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.40–7.33 (3H, m, C_6H_4Cl, H Ar); 7.27–7.22 (2H, m, C_6H_4Cl); 7.14 (1H, dd, *J* = 7.9, *J* = 1.7, H-3); 6.96 (1H, dd, *J* = 8.3, *J* = 1.1, H-4); 6.88 (1H, ddd, *J* = 7.8, *J* = 7.3, *J* = 1.1, H-6); 6.04 (1H, br. s, OH). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 167.4; 154.5 (q, *J* = 36.4); 154.2; 135.5; 133.1; 131.1; 129.8; 129.5; 125.9; 121.1; 119.9 (q, *J* = 272.4); 117.9; 114.7; 112.7. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.42. Found, *m/z*: 340.0341 $[M+H]^+$. $C_{16}H_{10}ClF_3NO_2$. Calculated, *m/z*: 340.0352.

2-[4-(4-Chlorophenyl)-3-(trifluoromethyl)isoxazol-5-yl]-phenyl trifluoromethanesulfonate (19). Trifluoromethanesulfonic anhydride (200 μl, 1.22 mmol) was added dropwise under ice cooling to a stirred solution of compound **18** (295 mg, 0.87 mmol) and triethylamine (242 μl, 1.74 mmol) in

dry CH_2Cl_2 (10 ml). After 1 h of stirring at room temperature, the reaction mixture was poured into H_2O, oganic layer was washed with brine (15 ml), separated, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Product was purified by silica gel column chromatography, using 5% EtOAc in petroleum ether. Yield 399 mg (97%), light-yellow oil. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.60 (1H, ddd, *J* = 8.3, *J* = 6.8, *J* = 2.5, H-6); 7.44–7.33 (5H, m, C_6H_4Cl, H Ar); 7.18 (2H, d, *J* = 8.4, C_6H_4Cl). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 164.3; 154.2 (q, *J* = 36.7); 146.6; 135.7; 133.2; 131.8; 130.9; 129.5; 129.0; 125.0; 123.2; 120.5; 118.6 (q, *J* = 320.9); 119.8 (q, *J* = 272.4); 117.1. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.36, –73.40. Found, *m/z*: 471.9847 $[M+H]^+$. $C_{17}H_9ClF_6NO_4S$. Calculated, *m/z*: 471.9845.

4-(4-Chlorophenyl)-5-phenyl-3-(trifluoromethyl)-isoxazole (20). Triethylsilane (772 µl, 4.83 mmol) and $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol) were added to a stirred solution of compound **19** (380 mg, 0.8 mmol) in DMF (7 ml) at room temperature. Reaction mixture was allowed to heat at 60°C for 1 h. After cooling to room temperature, the reaction mixture was partitioned between EtOAc (20 ml) and brine (20 ml). Organic layer was separated, washed with brine (2 × 10 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Product was purified by silica gel column chromatography, using gradient from 1 to 5% EtOAc in petroleum ether. Yield 190 mg (73%), white solid, mp 88–90°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.54–7.47 (2H, m, H-2,6); 7.47–7.41 (3H, m, H Ar); 7.41–7.34 (2H, m, H Ar); 7.29 (2H, d, *J* = 8.4, C_6H_4Cl). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 168.2; 154.8 (q, *J* = 36.1); 135.5; 131.6; 131.1; 129.6; 129.2; 127.2; 126.3; 126.1; 119.9 (q, *J* = 272.2); 113.2. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: –61.64. Found, *m/z*: 324.0398 $[M+H]^+$. $C_{16}H_{10}ClF_3NO$. Calculated, *m/z*: 324.0403.

5-Phenyl-3-(trifluoromethyl)isoxazole (21a). Hydroxylamine hydrochloride (1.74 g, 25 mmol) was added to a stirred solution of 4,4,4-trifluoro-1-phenyl-1,3-butanedione (**9a**) (1.8 g, 8.33 mmol) in EtOH (50 ml) at room temperature. The reaction mixture was allowed to heat at 80°C for 3 h. After cooling to room temperature, the reaction mixture was partitioned between CH_2Cl_2 (50 ml) and 1 M HCl (20 ml). Organic layer was separated, washed with brine (2 × 20 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Obtained residue then was dissolved in glacial AcOH (25 ml), and 98% H_2SO_4 (2 ml, 37.5 mmol) was added dropwise. The resulting mixture was heated at 100°C for 1 h and cooled down to room temperature followed by evaporation *in vacuo*. After trituration of crude residue with cold H_2O, solid precipitated from the solution. This solid was filtered off, the filter cake was washed several times with distilled H_2O and dried in air. Yield 1.125 g (63%), beige crystals. Spectral data was in accordance with those previously reported.[22]

5-Methoxy-2-[3-(trifluoromethyl)isoxazol-5-yl]phenol (21b). Hydroxylamine hydrochloride (341 mg, 4.91 mmol) was added to a stirred solution of 4,4,4-trifluoro-1-(2-hydroxy-4-methoxyphenyl)butane-1,3-dione (**9b**) (600 mg, 2.3 mmol) in pyridine (7 ml) at room temperature. The reaction mixture was allowed to heat at 100°C for 3 h. After cooling to room temperature, reaction mixture was partitioned between EtOAc (30 ml) and 1 M HCl (30 ml). Organic layer was separated, washed with brine (2 × 30 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Obtained residue then was dissolved in glacial AcOH (10 ml), and 98% H_2SO_4 (500 µl, 9.38 mmol) was added dropwise. The resulting mixture was heated at 100°C for 1 h and cooled down to room temperature followed by evaporation *in vacuo*. After trituration of crude residue with cold H_2O, solid precipitated from the solution. This solid was filtered off, filter cake was washed several times with distilled H_2O and dried in air. Crude compound was purified by trituration with hot EtOAc – petroleum ether 1:3 mixture to obtain pure product. Yield 242 mg (38%), beige crystals, mp >150°C (decomp.). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 10.98 (1H, s, OH); 7.76 (1H, d, *J* = 9.5, H-3); 7.12 (1H, s, H-4 isoxazole); 6.63–6.58 (2H, m, H-4,6); 3.78 (3H, s, OCH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 169.5; 162.8; 156.9; 155.0 (q, *J* = 37.0); 128.2; 120.0 (q, *J* = 270.9); 106.4; 105.8; 101.4; 98.0; 55.3. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: –62.25. Found, *m/z*: 260.0530 $[M+H]^+$. $C_{11}H_9F_3NO_3$. Calculated, *m/z*: 260.0535.

MIC assay. All of the compounds for the MIC tests had the purity level not lower than 95%. *Staphylococcus aureus* strain Newman was cultured overnight at 37°C in Mueller Hinton broth (MHB) (Oxoid). The MIC was determined using the microdilution method according to guidelines of the Clinical Laboratory Standards Institute.[7] In a 96-well plate, a series of twofold dilutions of each compound were added to a 1:100 dilution of an overnight culture of *S. aureus* in a final volume of 100 µl and incubated overnight at 37°C. The final concentration of the compounds was in a range 50–0.39 µg/ml. MIC was determined as the lowest concentration where no growth was detected by measurement of optical density at 600 nm (OD600). Compounds that did not inhibit growth were retested at higher concentrations (250–1.95 µg/ml). Wells containing bacteria with or without 1% DMSO and medium alone were included as controls in every plate.

Supplementary information file containing ^{1}H, ^{13}C, ^{19}F NMR spectra and HRMS data of all synthesized compounds is available at the journal website http://hgs.osi.lv.

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Annex II

2-Aminoquinazolines by Chan–Evans–Lam Coupling of Guanidines with (2-Formylphenyl)boronic Acids

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Abstract A new method is presented for the synthesis of 2-aminoquinazolines, which is based on a Chan–Evans–Lam coupling of (2-formylphenyl)boronic acids with guanidines. Relatively mild conditions involving the use of inexpensive CuI as a catalyst and methanol as a solvent permit the application of the method to a wide range of substrates. Nonsubstituted, N-monosubstituted, and N,N-disubstituted guanidines can be used as reactants to give the corresponding 2-aminoquinazolines in moderate yields from readily available (2-formylphenyl)boronic acids.

Key words guanidines, Chan–Evans–Lam coupling, quinazolines, copper catalysis, formylphenylboronic acids

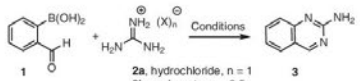
2-Aminoquinazoline is an important substructure for the development of pharmaceutically relevant compounds, especially for the discovery of kinase inhibitors.[1–6] A number of methods for the construction of 2-aminoquinazolines are know;[7–16] However, there are only a few approaches that exploit guanidines as reaction components. *ortho*-Halobenzaldehydes and aryl ketones can be condensed with guanidines in most cases if they contain an additional electron-withdrawing group that facilitates an S_NAr reaction.[3,6,13,14,17,18] For nonactivated substrates, a copper-catalyzed arylation of guanidines with aryl bromides has been described as a useful method for accessing 2-aminoquinazolines.[19] However, the reaction conditions are very harsh (DMF, 120 °C), which limits the scope of this approach.

The Chan–Evans–Lam coupling[20–24] is an attractive C–N bond-forming reaction that proceeds under relatively mild copper-catalyzed conditions and tolerates alcoholic solvents. To our knowledge, the only precedent for accessing quinazoline derivatives by using Chan–Evans–Lam coupling is a synthesis of quinazolonimines by arylation of N,N-disubstituted guanidines, formed in situ, with (2-cyanophenyl)boronic acids.[25] To facilitate our kinase-inhibitor-development program, we examined whether the Chan–Evans–Lam coupling might also be applicable to the synthesis of aminoquinazolines under mild conditions by using readily available reagents.

A screening of the reaction conditions was performed for the synthesis of unsubstituted quinazoline-2-amine (**3**). Representative results are reported in Table 1 [see Supporting Information (SI) for the full set of experiments]. Due to the polarity of the product **3**, its purification by chromatography was difficult, and it was therefore purified by trituration from ethyl acetate. An identical scale and workup were applied in all experiments to permit comparison of the effects of other reaction parameters. Methanol as a reaction solvent, CuI as a catalyst, and K_2CO_3 as a base were found to be productive conditions for the formation of quinazoline-2-amine (**3**) from (2-formylphenyl)boronic acid (**1**) and guanidine hydrochloride (**2a**) (Table 1, entries 1 and 2).

Excess amounts of the base and guanidine were beneficial in improving the yield of product **3** (Table 1, entry 2). Other copper catalysts [CuCl and $Cu(OAc)_2$] were found to be less efficient than CuI (entries 3 and 4). The use of KOH as base improved the yield of product **3** when an excess of guanidine was used (entries 5 and 6). EtOH could also be successfully used as the reaction solvent (entry 7). Guanidine carbonate (**2b**) as a reactant gave a reduced yield of quinazoline **3** (entries 8 and 9). All the experiments listed in Table 1 were performed open to air to ensure reoxidation

Table 1 Chan–Evans–Lam Conditions for the Synthesis of 2-Aminoquinazoline (**3**)[a]



Entry	Solvent	Temp (°C)	Reactant (equiv)	Catalyst	Base (equiv)	Yield[b] (%)
1	MeOH	70	**2a** (1.5)	CuI	K_2CO_3 (2.5)	31
2	MeOH	70	**2a** (2.5)	CuI	K_2CO_3 (3)	**44**
3	MeOH	70	**2a** (2.5)	$Cu(OAc)_2$	K_2CO_3 (3)	35
4	MeOH	70	**2a** (2.5)	CuCl	K_2CO_3 (3)	23
5	MeOH	70	**2a** (1.5)	CuI	KOH (1.5)	34
6	MeOH	70	**2a** (3)	CuI	K_2CO_3 (3)	**51 (65)**[c]
7	EtOH	90	**2a** (3)	CuI	K_2CO_3 (3)	**52**
8	MeOH	70	**2b** (3)	CuI	–	13
9	MeOH	70	**2b** (1.5)	CuI	KOH (3)	17

[a] Reactions were performed open to the air, reaction time: 12–17 h.
[b] Purified by trituration with EtOAc to a purity of >98%.
[c] NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

of the copper catalyst. Performing the reaction under an oxygen atmosphere or adding hydrogen peroxide did not substantially improve the yield of product **3** (see SI).

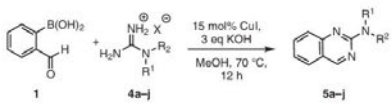
Next, (2-formylphenyl)boronic acid (**1**) was treated with a range of guanidines under the most productive reaction conditions (Table 1, entry 6).[26] Both N-monosubstituted guanidines **4a–g** and N,N-disubstituted guanidines (**4h–j**) provided the corresponding 2-aminoquinazolines **5a–j** in fairly good yields (Table 2).

Several (2-formylphenyl)boronic acids **6a–f** were next explored as substrates for the synthesis of aminoquinazolines **7a–f** and **8a–f** (Table 3). Both guanidines **2a** and **4a** gave the expected products but the isolated yields were generally somewhat higher in the case of the *N*-methyl-substituted guanidine **4a** (Table 3; entries 3 and 4, 5 and 6, 7 and 8).

Boronic acid derivatives such as the pinacolate ester **9a** and the trifluoroborate **9b** were also competent substrates, providing aminoquinazoline derivative **5a** in yields comparable to those from boronic acid **1** (Scheme 1). These results complement the relatively few reported cases of the use of boronic acid derivatives as partners for Chan–Evans–Lam coupling.[27,28]

In contrast, the boronic acids **10a** and **10b** bearing a keto group were found to be unsuitable reaction partners for the synthesis of the corresponding quinazolines **11a** and **11b** (Scheme 2). In the case of these substrates, complex mixtures were obtained containing the O-arylation products **12a** and **12b** as the only identifiable byproducts. The failure of (2-acylphenyl)boronic acids **10a** and **10b** to give the expected products implies that the formation of an arylidene guanidine is the first step in the synthesis of aminoquinazolines **3**, **5**, **7**, and **8**, followed by intramolecular arylation

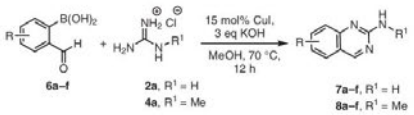
Table 2 Guanidine Scope for the Synthesis of Aminoquinazolines



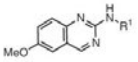
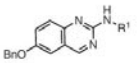
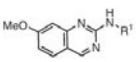
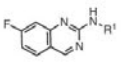
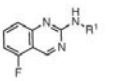
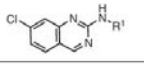
Entry	Guanidine	R^1	R^2	Product	Yield[a] (%)
1	**4a**[b]	H	Me	**5a**	63
2	**4b**[c]	H	Ph	**5b**	56
3	**4c**[b]	H	Bn	**5c**	66[d]
4	**4d**[b]	H	$Ph(CH_2)_2$	**5d**	52
5	**4e**[b]	H	$Me(CH_2)_4$	**5e**	54
6	**4f**[b]	H	cyclopentyl	**5f**	55
7	**4g**[b]	H	Cy	**5g**	37
8	**4h**[e]	Me	Me	**5h**	43
9	**4i**[b]	$(CH_2)_4$		**5i**	47
10	**4j**[b]	$(CH_2)_2O(CH_2)_2$		**5j**	39

[a] Purified by column chromatography unless stated otherwise.
[b] Hydrochloride salt.
[c] Carbonate salt.
[d] Purified by trituration with EtOAc.
[e] Sulfate salt.

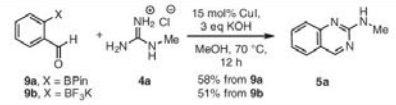
Table 3 Boronic Acid Scope for the Synthesis of Aminoquinazolines



6a–f **2a**, R^1 = H; **4a**, R^1 = Me **7a–f**, R^1 = H; **8a–f**, R^1 = Me

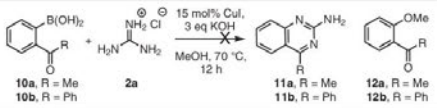
Entry	Boronic acid	Guanidine	Product		Yield[a] (%)
1	**6a**, R^1 = 4-MeO	**2a** (R^2 = H)		**7a**	55
2		**4a** (R^2 = Me)		**8a**	59[b]
3	**6b**, R = 4-BnO	**2a** (R^2 = H)		**7b**	32 (53)[c]
4		**4a** (R^2 = Me)		**8b**	57[b]
5	**6c**, R = 5-MeO	**2a** (R^2 = H)		**7c**	17 (53)[c]
6		**4a** (R^2 = Me)		**8c**	48[b]
7	**6d**, R = 5-F	**2a** (R^2 = H)		**7d**	36 (45)[c]
8		**4a** (R^2 = Me)		**8d**	52[b]
9	**6e**, R = 3-F	**2a** (R^2 = H)		**7e**	52
10		**4a** (R^2 = Me)		**8e**	46[b]
11	**6f**, R = 5-Cl	**2a** (R^2 = H)		**7f**	35
12		**4a** (R^2 = Me)		**8f**	55[b]

[a] Purified by trituration with EtOAc unless stated otherwise.
[b] Purified by column chromatography.
[c] NMR yield with 1,3,5-trimethoxybenzene as an internal standard.



9a, X = BPin; **9b**, X = BF_3K **4a** 58% from **9a**; 51% from **9b** **5a**

Scheme 1 Synthesis 2-aminoquinazoline from a boronic acid ester and trifluoroborate



10a, R = Me; **10b**, R = Ph **2a** **11a**, R = Me; **11b**, R = Ph **12a**, R = Me; **12b**, R = Ph

Scheme 2 Attempt to condense keto-group-containing boronic acids with guanidine

In summary, 2-aminoquinazolines can be obtained by Chan–Evans–Lam coupling of (2-formylphenyl)boronic acids with guanidines. The relatively mild reaction conditions permit the use of this method for the synthesis of pharmacologically relevant compounds bearing a 2-aminoquinazoline scaffold.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707080.

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(26) **Quinazolin-2-amine (3); Typical Procedure**
A mixture of guanidine hydrochloride (**2a**; 765 mg, 8 mmol) and KOH (441 mg, 8 mmol) was dissolved in MeOH (30 mL) and the mixture was stirred for 10 min at r.t. (2-Formylphenyl)boronic acid (**1**; 400 mg, 2.67 mmol) was added in one portion followed by CuI (76 mg, 0.4 mmol), and the resulting mixture was heated at 70 °C overnight. The mixture was then concentrated under reduced pressure and partitioned between aq NH_3 (30 mL) and EtOAc (120 mL). The organic layer washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by trituration with EtOAc (3 mL) to give a slightly beige solid; yield: 198 mg (51%); mp 194–196 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.10 (s, 1 H), 7.78 (d, *J* = 8.9 Hz, 1 H), 7.67 (t, *J* = 8.5 Hz, 1 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 7.21 (t, *J* = 7.9 Hz, 1 H), 6.82 (s, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.4, 160.9, 151.2, 134.1, 127.9, 124.5, 122.0, 119.5. LC/MS: *m/z* [M + H]$^+$ calcd for $C_8H_8N_3$: 146.17; found: 146.16. The spectral data correspond to the reported values (see Ref. 10).
***N*-Methylquinazolin-2-amine (5a)**
Prepared from (2-Formylphenyl)boronic acid (**1**) and *N*-methylguanidine hydrochloride (**4a**), and purified by column chromatography [silica gel, EtOAc–PE (20 to 50% gradient)] as a yellowish solid: yield: 134 mg (63%); mp 81–83 °C; R_f = 0.63 (EtOAc).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.03 (s, 1 H), 7.72–7.56 (m, 3 H), 7.22 (t, *J* = 7.9 Hz, 1 H), 5.43 (br s, 1 H), 3.12 (d, *J* = 4.0 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.01, 160.50, 152.44, 134.37, 127.79, 125.83, 122.72, 120.75, 28.77. HRMS: *m/z* [M + H]$^+$ calcd for $C_9H_{10}N_3$: 160.0875; found: 160.0881.
6-(Benzyloxy)-*N*-methylquinazolin-2-amine (8b)
Prepared from boronic acid **6b** and *N*-methylguanidine hydrochloride (**4a**), and purified by column chromatography [silica gel, EtOAc–PE (20 to 60% gradient)] as a yellowish solid; yield: 150 mg (57%); mp 130–132 °C, R_f = 0.38 (50% EtOAc–PE).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (s, 1 H), 7.58 (d, *J* = 9.2 Hz, 1 H), 7.51–7.32 (m, 6 H), 7.05 (d, *J* = 2.8 Hz, 1 H), 5.23 (s, 1 H), 5.12 (s, 2 H), 3.10 (d, *J* = 5.1 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.67, 159.78, 154.12, 148.30, 136.70, 128.80, 128.28, 127.67, 127.23, 127.13, 120.32, 106.82, 70.55, 28.76. HRMS: *m/z* [M + H]$^+$ calcd for $C_{16}H_{16}N_3O$: 266.1293; found: 266.1292.
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SUPPORTING INFORMATION

2-Aminoquinazolines by Chan-Evans-Lam coupling of guanidines with 2-formylphenylboronic acids

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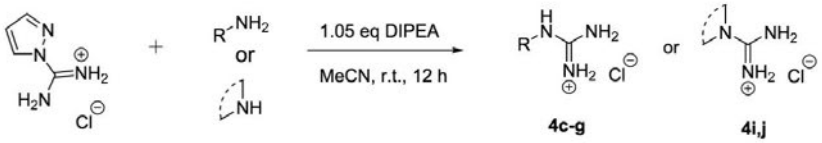
Contents

1. General information

All reagents were purchased from commercial source and used without further purification. Melting points were determined using a digital melting point apparatus and uncorrected. ^{1}H NMR spectra were recorded at 400 MHz using TMS as internal standard, ^{13}C NMR spectra were recorded at 101 MHz using TMS as internal standard. All chemical shifts were reported as δ values (ppm) relative to TMS and observed coupling constants (J) are given in Hertz (Hz). High resolution molecular masses (HRMS) were determined on a hybrid quadrupole time-of-flight (TOF) mass spectrometer Waters Synapt G2-Si equipped with an electron spray ion source (ESI). PE refers to light petroleum ether.

2. Synthesis of substituted guanidine hydrochlorides 4c-g, 4i,j

Guanidines **4c-g, 4i,j** were prepared according to the Scheme 1

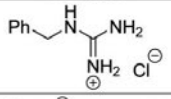
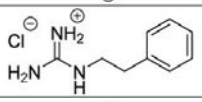
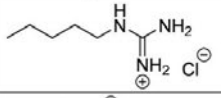
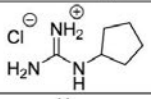
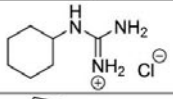
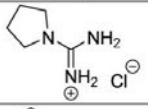
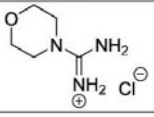


Scheme 1

General procedure. Subsituted guanidines were prepared according to the literature procedure.[1] To a stirred solution of 1H-pyrazole-1-carboxamidine hydrochloride (1.00 g; 6.8 mmol; 1.00 equiv.) and DIPEA (1.24 mL; 7.2 mmol; 1.05 equiv.) in MeCN (25 mL), benzylamine (782 µL; 7.2 mmol; 1.05 equiv.) was added. The reaction mixture was stirred at ambient temperature overnight and precipitated solid filtered and washed with MeCN and Et_2O to obtain pure product **4c** as an off-white solid.

The guanidines prepared are shown in the Table 1.

Table 1

Entry	R or Amine	Product	Yield
4c	Bn		85%
4d	Phenethyl		69%
4e	*n*-Pentyl		89%
4f	*cy*-Pentyl		81%
4g	*cy*-Hexy		80%
4i			72%
4j			75%

[1] An T.; Kang B.; Kang S.; Pac J.; Youk J.; Lin D.; Lee Y. *Chem. Commun.* **2019**, *55*, 10222.

3. Synthesis of 2-aminoquinazolines (3, 5a-j, 7a-f, 8a-f)

3.1. General procedure for the synthesis of 2-aminoquinazolines

A mixture of guanidine hydrochloride **2a** (765 mg, 8 mmol) and potassium hydroxide (441mg, 8 mmol) was dissolved in MeOH (30 mL) and stirred for 10 min at room temperature. Then 2-formylbenzeneboronic acid (400 mg, 2.67 mmol) was added to the mixture in one portion, followed by CuI (76 mg, 0.4 mmol). Then the mixture heated at 70 °C overnight. The reaction mixture evaporated under reduced pressure and partitioned between of aqueous ammonia (30 mL) and of ethyl acetate (120 mL). The organic layer washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by trituration with ethyl acetate (3 mL) to afford 2-aminoquinazoline **3** (198 mg, 51%) as slightly beige solid.

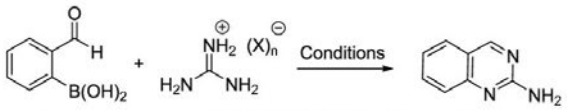
3.2. Preparation of aminoquinazoline 5a from 2-(4,4,5,5-tetramethyl-[1,3,2]dioxoborolan-2-yl)-benzaldehyde (9a)

Prepared according to general procedure using *N*-methylguanidine hydrochloride **4a** to obtain *N*-methylquinazoline-2-amine **5a.** Purified by silica gel column chromatography eluting with EtOAc in PE (gradient from 20 to 50%) to obtain 109 mg of product **5a**, 58% yield.

3.3. Preparation of aminoquinazoline 5a from potassium 2-formylphenyl-trifluoroborate (9b)

A mixture of *N*-methylguanidine hydrochloride **4a** (310 mg, 2.83 mmol) and potassium hydroxide (260 mg, 4.72 mmol) was dissolved in MeOH (20 mL) and stirred for 10 min at room temperature. Then, potassium 2-formylphenyl trifluoroborate (200 mg, 0.95 mmol) was added in one portion, followed by CuI (27 mg, 0.14 mmol). Then the mixture heated at 70 °C overnight. The reaction mixture evaporated under reduced pressure and partitioned between of aqueous ammonia (20 mL) and of ethyl acetate (40 mL). The organic layer washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography eluting with EtOAc in PE (gradient from 20 to 50%) to obtain 76 mg of the product **5a** as yellowish solid, 50% yield.

3.4. Reaction conditions screened for the synthesis of quinazoline 3



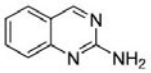
1 **2a**, hydrochloride, n = 1; **2b**, carbonate, n= 0.5 **3**

Entry[a]	Solvent, t°, time	2	Catalyst/oxidant system	Base	Additive	Yield of 3
1	MeOH, 70 °C, 17 h	**2a** 1.5 eq	CuI 15 mol%, air	Cs_2CO_3 2.5 eq	-	30%
2	MeOH, 70 °C, 17 h	**2a** 1.5 eq	CuI 15 mol%, air	Cs_2CO_3 2.5 eq	TMEDA, 30 mol%	23%
3	MeOH, 70 °C, 17 h	**2a** 1.5 eq	CuI 15 mol%, air	K_2CO_3 2.5 eq	-	31%
4	MeOH, 70 °C, 17 h	**2a** 2.5 eq	CuI 15 mol%, air	K_2CO_3 3 eq	-	44%
5	MeOH, 70 °C, 17 h	**2a** 3.5 eq	CuI 15 mol%, air	K_2CO_3 3.5 eq	-	46%
6	MeOH, 70 °C, 17 h	**2a** 5 eq	CuI 15 mol%, air	K_2CO_3 5 eq	-	14%
7	MeOH, 70 °C, 17 h	**2b** 3 eq	CuI 15 mol%, air	-	-	13%
8	MeOH, 70 °C, 17 h	**2b** 3 eq	CuI 15 mol%, air	KOH 3 eq	-	17%
9	MeOH, 70 °C, 17 h	**2a** 3 eq	CuI 15 mol%, air	KOH, 3 eq	-	51% (65%)[b]
10	MeOH, 70 °C, 17 h	**2a** 3 eq	CuI 5 mol%, air	KOH, 3 eq	-	11%
11	MeOH, 70 °C, 17 h	**2a** 3 eq	CuI 30 mol%, air	KOH, 3 eq		41%
12	MeOH, 70 °C, 17 h	**2a** 1.5 eq	CuI 15 mol%, air	KOH, 1.5 eq	-	34%
13	EtOH, 90 °C, 17 h	**2a** 3 eq	CuI 15 mol%, air	KOH 3 eq		52%
14	i-PrOH, 90 °C, 17 h	**2a** 3 eq	CuI 15 mol%, air	KOH 3 eq	-	n.r.
15	MeOH, 70 °C, 17 h	**2a** 2.5 eq	$Cu(OAc)_2$ 15 mol%, air	K_2CO_3, 3 eq	-	35%
16	DMF, 60 °C, 17 h	**2a** 1.5 eq	$Cu(OAc)_2$ 20 mol%, air	Cs_2CO_3 2.5 eq	2,2'-BiPy, 2 eq	n.r.
17	MeOH, 70 °C, 17 h	**2a** 2.5 eq	CuCl 15 mol%, air	K_2CO_3 3 eq	-	23%
18	MeOH, 70 °C, 17 h	**2a** 3 eq	CuI 15 mol%, O_2[c]	KOH, 3 eq	-	56%
19	MeOH, 70 °C, 17 h	**2a** 3 eq	CuI 15 mol%; 4 eq 35% aq H_2O_2	KOH, 3 eq	-	40%

[a]Reaction was performed in open flask, until otherwise noted; [b]The yield was determined by NMR using 1,3,5-trimethoxybenzene as internal standard; [c]1 atm of O_2.

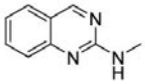
4. Characterization data of 2-aminoquinazolines 3, 5a-j, 7a-f, 8a-f.

2-Aminoquinazoline (3)



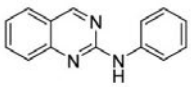
Prepared according to general procedure. Purified by trituration with EtOAc, white beige solid, 51% (198 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 7.78 (d, J = 8.9 Hz, 1H), 7.67 (t, J = 8.5 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 6.82 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.4, 160.9, 151.2, 134.1, 127.9, 124.5, 122.0, 119.5. LCMS: $C_8H_8N_3$ $[M+H]^+$; calculated 146.17, found 146.16. Corresponds to the reported data.[2]

***N*-Methylquinazolin-2-amine (5a)**



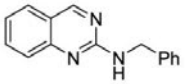
Prepared according to general procedure using commercially available *N*-methylguanidine hydrochloride (**4a**). Purified by silica gel column chromatography (gradient 20% to 50% EtOAc in PE), Rf 0.63 (EtOAc), yellowish solid; m.p. 81-83 °C, 63% (134 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.03 (s, 1H), 7.72 – 7.56 (m, 3H), 7.22 (t, J = 7.9 Hz, 1H), 5.43 (br. s, 1H), 3.12 (d, J = 4.0 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.01, 160.50, 152.44, 134.37, 127.79, 125.83, 122.72, 120.75, 28.77; HRMS: $C_9H_{10}N_3$ $[M+H^+]$; calculated 160.0875, found 160.0881

***N*-phenylquinazolin-2-amine (5b)**



Prepared according to general procedure using commercially available phenylguanidine carbonate (**4b**).The crude product was purified by silica gel column chromatography using EtOAc: PE (1:3), Rf 0.68 (EtOAc:PE, 1:3) to obtain 168 mg of the slightly beige solid, 56%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.09 (s, 1H), 7.84 (d, J = 7.6 Hz, 2H), 7.80 – 7.71 (m, 3H), 7.44 (s, 1H), 7.41 – 7.30 (m, 3H), 7.08 (t, J = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.99, 156.96, 151.68, 139.77, 134.52, 129.11, 127.57, 126.50, 123.93, 122.69, 121.02, 119.15. LCMS $C_{14}H_{12}N_3$ $[M+H]^+$; calculated 222.26, found 222.35. Corresponds to the reported data.[3]

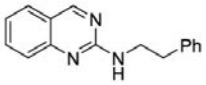
***N*-Benzylquinazolin-2-amine (5c)**



[2] Liu, Q.; Zhao, U.; Fu, H.; Cheng, C. *Synlett* **2013**, *24*, 2089-2094.
[3] Leitch J. A.; McMullin C. L.; Paterson A. J.; Mahon M. F; Bhonoah Y.; Frost C. G. *Angew. Chem. Int. Ed.* **2017**, *56*, 15131.

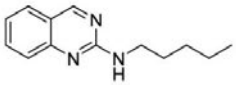
Prepared according to general procedure, using *N*-benzylguanidine hydrochloride (**4c**). Crude material dissolved in EtOAc:PE 1:1 and undissolved materials discarded. After evaporation of organic phase residue crystallized from EtOAc:PE (1:10) to obtain pure product as a beige solid, Rf 0.56 (EtOAc:PE 1:3), 66% (210 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.87 (s, 1H), 7.87 – 7.57 (m, 3H), 7.56 – 7.20 (m, 6H), 6.03 (s, 1H), 4.83 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.17, 159.63, 152.28, 139.33, 134.33, 127.90, 127.69, 127.41, 125.81, 122.77, 120.51, 45.85, 45.73. LCMS $C_{15}H_{14}N_3$ $[M+H]^+$; calculated 236.29, found 236.37. Corresponds to the reported data.[4]

_N_-Phenethylquinazolin-2-amine (5d)



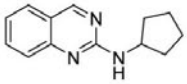
Prepared according to general procedure, using *N*-phenethylguanidine hydrochloride (**4d**). Purified by silica gel column chromatography using 10 to 40% EtOAc in PE gradient, Rf 0.46 (EtOAc:PE 1:3), slightly yellow solid, 52% (175 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.92 (s, 1H), 7.79 – 7.54 (m, 3H), 7.36 – 7.17 (m, 6H), 5.37 (s, 1H), 3.81 (q, *J* = 7.0 Hz, 2H), 2.97 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.06, 159.67, 152.34, 139.45, 134.28, 129.02, 128.72, 127.67, 126.52, 122.66, 120.39, 42.93, 35.82. LCMS $C_{16}H_{16}N_3$ $[M+H]^+$; calculated 250.32, found 250.43. Corresponds to the reported data.[4]

_N_-Pentylquinazolin-2-amine (5e)



Prepared according to general procedure, using *N*-(n-pentyl)guanidine hydrochloride (**4e**). Purified by silica gel column chromatography using 10 to 40% EtOAc in PE gradient, Rf 0.55 (EtOAc:PE 1:3), light yellow crystalline solid; m.p. 76-78 °C, 54% (187 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 7.74 – 7.52 (m, 3H), 7.21 (t, *J* = 8.0 Hz, 1H), 5.27 (s, 1H), 3.65 – 3.46 (m, 2H), 1.67 (p, *J* = 7.4 Hz, 2H), 1.40 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.87, 152.38, 134.27, 127.68, 125.65, 122.51, 120.29, 41.75, 29.44, 29.30, 22.59, 14.17. HRMS: $C_{13}H_{18}N_3$ $[M+H]^+$; calculated 216.1501, found 216.1508.

_N_-cyclopentylquinazolin-2-amine (5f)

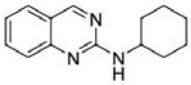


Prepared according to general procedure, using *N*-cyclopentylguanidine hydrochloride (**4f**). Purified by silica gel column chromatography using 10 to 40% EtOAc in PE gradient, Rf 0.46 (EtOAc:PE 1:3), yellow solid; m.p. 75-77 °C, 55% (198 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 7.73 – 7.52 (m, 3H), 7.20 (t, *J* = 8.0 Hz, 1H), 5.27 (d, *J* = 6.0 Hz, 1H), 4.44 (h, *J* = 6.8 Hz, 1H), 2.12 (m, 2H), 1.84 – 1.60 (m, 4H), 1.53 (m, 2H). ^{13}C NMR

[4] Li, F.; Chen, L.; Kang, Q.; Cai, J.; Zhu, G. *New J. Chem.*, **2013**,*37*, 624.

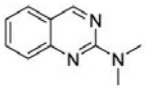
(101 MHz, Chloroform-*d*) δ 161.95, 159.54, 152.42, 127.64, 125.67, 122.42, 120.22, 53.11, 33.47, 23.82. HRMS: $C_{13}H_{16}N_3$ $[M+H]^+$; calculated 214.1344, found 214.1347.

_N_-Cyclohexylquinazolin-2-amine (5g)



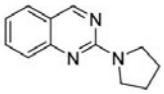
Prepared according to general procedure using *N*-cyclohexylguanidine hydrochloride (**4g**) (prepared from cyclohexylamine according to exemplary procedure B). Purified by silica gel column chromatography using 20 to 50% EtOAc in PE gradient, Rf 0.56 (EtOAc:PE 1:3), slightly yellow solid, 37% (113 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.94 (s, 1H), 7.64 (m, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.19 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 5.20 (d, *J* = 7.6 Hz, 1H), 4.01 (dtd, *J* = 14.4, 7.3, 6.4, 4.1 Hz, 1H), 2.11 (m, 2H), 1.77 (m, 2H), 1.65 (m, 1H), 1.54 – 1.35 (m, 2H), 1.34 – 1.16 (m, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.07, 152.49, 134.19, 127.64, 125.62, 122.38, 120.24, 49.75, 33.37, 25.93, 25.00. LCMS $C_{14}H_{18}N_3$ $[M+H]^+$; calculated 228.31, found 228.42. Corresponds to the reported data.[5]

_N,N_-Dimethylquinazolin-2-amine (5h)



Prepared according to general procedure using commercially available 1,1-dimethylguanidine sulphate (**4h**). The crude product was purified by silica gel column chromatography using 1:3 EtOAc:PE, Rf 0.79 (EtOAc:PE 1:3) to obtain 100 mg of the white solid, 43%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.99 (s, 1H), 7.66 – 7.60 (m, 2H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.20 – 7.14 (m, 1H), 3.31 (s, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.38, 160.06, 152.60, 134.08, 127.57, 125.66, 122.12, 119.24, 37.43. LCMS $C_{10}H_{12}N_3$ $[M+H]^+$; calculated 174.22, found 174.28. Corresponds to the reported data.[6]

2-(Pyrrolidin-1-yl)quinazoline (5i)



Prepared according to general procedure using pyrrolidine-1-carboximidamide hydrochloride (**4i**). Purified by silica gel column chromatography using 10 to 40% EtOAc in PE gradient, Rf 0.17 (EtOAc:PE 1:10), light yellow solid, 47% (108 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.99 (s, 1H), 7.67 – 7.55 (m, 3H), 7.19 – 7.12 (m, 1H), 3.77 – 3.65 (m, 4H), 2.08 – 1.98 (m, 4H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.53, 158.22, 152.76, 134.09, 127.68, 125.55, 121.88, 119.43, 47.01, 25.71. LCMS $C_{12}H_{14}N_3$ $[M+H]^+$; calculated 200.26, found 200.33. Corresponds to the reported data.[7]

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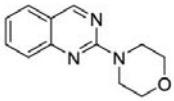
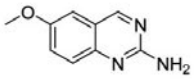
[5] Wang H. X.; Wei T. Q.; Xu P.; Wang S. Y.; Ji S. J. *J. Org. Chem.* **2018**, *83*, 21, 13491.
[6] Suzuki, Y.; Takemura, Y.; Iwamoto, K.; Higashino, T.; Miyashita, A. *Chem. Pharm. Bull.* **1998**, *46*, 199.
[7] Huang, X.; Yang, H.; Fu, H.; Qiao, R.; Zhao, Y. *Synthesis* **2009**, *16*, 2679.

4-(Quinazolin-2-yl)morpholine (5j)



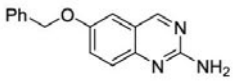
Prepared according to general procedure using morpholine-1-carboximidamide hydrochloride (**4j**). Purified by silica gel column chromatography using 10 to 30% EtOAc in PE gradient, Rf 0.26 (EtOAc:PE 1:10), yellow crystalline solid, 39% (114 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.01 (s, 1H), 7.71 – 7.63 (m, 2H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.26 – 7.20 (m, 1H), 4.01 – 3.92 (m, 4H), 3.85 – 3.78 (m, 4H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.60, 159.38, 152.32, 134.29, 127.55, 125.86, 122.89, 119.95, 67.11, 44.72. LCMS $C_{12}H_{14}N_3O$ $[M+H]^+$; calculated 216.26, found 216.35. Corresponds to the reported data.[8]

6-Methoxyquinazolin-2-amine (7a)



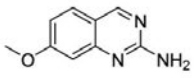
Prepared according to general procedure from boronic acid **6a** and guanidine hydrochloride (**2a**). Purified by trituration with EtOAc, beige solid, 55% (27 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 7.37 (s, 2H), 7.23 (s, 1H), 6.57 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.8, 160.0, 154.0, 147.6, 126.2, 126.1, 119.7, 105.7, 55.4. LCMS: $C_9H_{10}N_3O$ $[M+H]^+$; calculated 176.19, found 176.26. Corresponds to the reported data.[9]

6-(Benzyloxy)quinazolin-2-amine (7b)



Prepared according to general procedure from boronic acid **6b** and guanidine hydrochloride (**2a**). Purified by trituration with EtOH, beige solid; m.p. 149-150 °C, 32% (79 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 7.66 – 7.21 (m, 8H), 6.61 (s, 2H), 5.15 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.84, 160.07, 153.01, 147.70, 136.80, 128.45, 127.93, 127.84, 126.53, 126.17, 119.61, 107.13, 69.62; HRMS: $C_{15}H_{14}N_3O$ $[M+H]^+$; calculated 252.1137, found 252.1136.

7-Methoxyquinazolin-2-amine (7c)

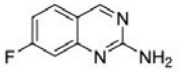


Prepared according to general procedure from boronic acid **6c** and guanidine hydrochloride (**2a**). Re-crystallized from EtOH, beige solid; m.p. 222-224 °C, 17% (26 mg); ^{1}H NMR (400 MHz, DMSO-d6) δ 8.90 (s, 1H), 7.67 (d, J = 8.8 Hz, 1H), 6.83 (dd, J = 8.8, 2.4 Hz, 1H), 6.78 (d, J = 2.4 Hz, 1H), 6.70 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.84,

[8] Huang, X.; Yang, H.; Fu, H.; Qiao, R.; Zhao, Y. *Synthesis* **2009**, *16*, 2679.
[9] Liu, Q.; Zhao, U.; Fu, H.; Cheng, C. *Synlett* **2013**, *24*, 2089-2094.

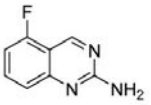
161.21, 160.83, 154.14, 129.20, 114.91, 114.18, 103.44, 55.41. HRMS: $C_9H_{10}N_3O$ $[M+H]^+$; calculated 176.0824, found 176.0820

7-Fluoroquinazolin-2-amine (7d)



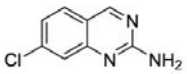
Prepared according to general procedure from boronic acid **6d** and guanidine hydrochloride (**2a**). Re-crystallized from EtOH, white beige solid, 36% (52 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.93 – 7.84 (m, 1H), 7.14 – 7.06 (m, 2H), 6.99 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.71 (d, J = 250.4 Hz), 162.08, 161.29, 153.55 (d, J = 14.5 Hz), 131.03 (d, J = 11.7 Hz), 116.89, 111.68 (d, J = 25.2 Hz), 108.18 (d, J = 20.6 Hz);^{19}F NMR (376 MHz, DMSO-d_6) δ -104.1. LCMS $C_8H_7FN_3$ $[M+H]^+$; calculated 164.16, found 164.30. Corresponds to the reported data.[10]

5-Fluoroquinazolin-2-amine (7e)



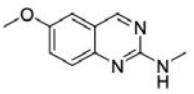
Prepared according to general procedure from boronic acid **6e** and guanidine hydrochloride (**2a**). Re-crystallized from EtOH, white yellow solid; m.p. 223-225 °C, 52% (76 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 7.72 – 7.60 (m, 1H), 7.23 (d, J = 10 Hz, 1H), 7.10 (s, 2H), 6.96 (d, J = 10 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.22, 158.54 (d, J = 255.2 Hz), 156.06, 153.11, 134.45 (d, J = 10.1 Hz), 120.94, 109.50 (d, J = 15.7 Hz), 105.85 (d, J = 18.7 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ -124.16. HRMS: $C_8H_7FN_3$ $[M+H]^+$; calculated 164.0624, found 164.0621.

7-Chloroquinazolin-2-amine (7f)



Prepared according to general procedure from boronic acid **6f** and guanidine hydrochloride (**2a**). Re-crystallized from EtOH, beige solid; decomp. >275 °C, 35% (52 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (s, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 2.0 Hz, 1H), 7.22 (dd, J = 8.5, 2.0 Hz, 1H), 7.05 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.40, 161.31, 152.53, 138.71, 129.93, 123.22, 122.34, 117.97, 40.19; HRMS: $C_8H_7ClN_3$ $[M+H]^+$; calculated 180.0328, found 180.0331.

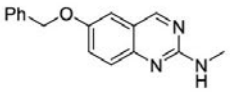
6-Methoxy-N-methylquinazolin-2-amine (8a)



[10] Taylor N. J.; Emer E.; Preshlock S.; Schedler M.; Tredwell M.; Verhoog S.; Mercier J.; Genicot C.; Gouverneur V. *J. Am. Chem. Soc.* **2017**, *139*, 8267.

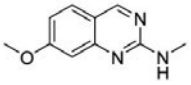
Prepared according to general procedure from boronic acid **6a** and *N*-methylguanidine hydrochloride **4a**. Purified by silica gel column chromatography eluting with EtOAc, Rf 0.54 (EtOAc), yellow solid; m.p. 144-145 °C, 59% (94 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.89 (s, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.35 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.96 (d, *J* = 2.8 Hz, 1H), 5.23 (s, 1H), 3.87 (s, 3H), 3.09 (d, *J* = 4.9 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.54, 159.78, 155.00, 148.31, 127.21, 126.70, 120.37, 105.25, 55.68, 28.75; HRMS: $C_{10}H_{12}N_3O$ $[M+H]^+$; calculated 190.0980, found 190.0983.

6-(benzyloxy)-*N*-methylquinazolin-2-amine (8b)



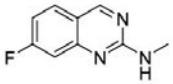
Prepared according to general procedure from boronic acid **6b** and *N*-methylguanidine hydrochloride (**4a**). Purified by silica gel column chromatography using 20% to 60% EtOAc in PE gradient, Rf 0.38 (EtOAc:PE 1:1), yellowish solid; m.p. 130-132 °C, 57% (150 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.88 (s, 1H), 7.58 (d, *J* = 9.2 Hz, 1H), 7.51 – 7.32 (m, 6H), 7.05 (d, *J* = 2.8 Hz, 1H), 5.23 (s, 1H), 5.12 (s, 2H), 3.10 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.67, 159.78, 154.12, 148.30, 136.70, 128.80, 128.28, 127.67, 127.23, 127.13, 120.32, 70.55, 28.76. HRMS: $C_{16}H_{16}N_3O$ $[M+H]^+$; calculated 266.1293, found 266.1292.

7-Methoxy-*N*-methylquinazolin-2-amine (8c)



Prepared according to general procedure from boronic acid **6c** and *N*-methylguanidine hydrochloride (**4a**). Purified by silica gel column chromatography eluting with EtOAc, Rf 0.54 (EtOAc), slightly yellow solid; m.p. 105-107 °C, 48% (77 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.81 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 6.94 (s, 1H), 6.84 (dd, *J* = 8.8, 2.3 Hz, 1H), 5.24 (s, 1H), 3.92 (s, 3H), 3.11 (d, *J* = 4.5 Hz, 3H);^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.72, 160.92, 160.43, 154.70, 128.97, 115.84, 115.51, 104.21, 55.68, 28.66. HRMS: $C_{10}H_{12}N_3O$ $[M+H]^+$; calculated 190.0980, found 190.0981.

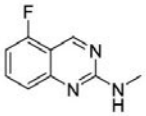
7-Fluoro-*N*-methylquinazolin-2-amine (8d)



Prepared according to general procedure from boronic acid **6d** and *N*-methylguanidine hydrochloride (**4a**). Purified by silica gel column chromatography eluting with EtOAc, Rf 0.65 (EtOAc), white solid; m.p. 135-137 °C, 52% (83 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.91 (s, 1H), 7.64 (dd, *J* = 8.8, 6.2 Hz, 1H), 7.22 (d, *J* = 9.7 Hz, 1H), 6.96 (td, *J* = 8.7, 2.4 Hz, 1H), 5.46 (s, 1H), 3.11 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.95, 165.42, 161.37, 160.73, 154.23, 154.09, 130.20, 130.09, 112.86, 112.61, 109.95,

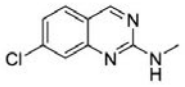
109.75; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -103.00. HRMS: $C_9H_9FN_3$ $[M+H]^+$; calculated 178.0781, found: 178.0782.

5-Fluoro-*N*-methylquinazolin-2-amine (8e)



Prepared according to general procedure from boronic acid **6e** and N-methylguanidine hydrochloride (**4a**). Purified by silica gel column chromatography using 10% to 40% EtOAc in PE gradient, Rf 0.41 (EtOAc:PE 1:3), white beige solid; m.p. 142-144 °C, 46% (74 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.37 (s, 1H), 7.58 (q, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 6.88 – 6.76 (m, 1H), 5.55 (s, 1H), 3.12 (s, 3H);^{13}C NMR (101 MHz, DMSO-d_6) δ 160.67, 158.12, 153.45, 134.39, 134.29, 121.73, 106.48, 28.60; ^{19}F NMR (376 MHz, DMSO-d_6) δ -128.79. HRMS: $C_9H_9FN_3$ $[M+H]^+$; calculated 178.0781, found: 178.0779.

7-Chloro-*N*-methylquinazolin-2-amine (8f)



Prepared according to general procedure from boronic acid **6f** and *N*-methylguanidine hydrochloride (**4a**). Purified by silica gel column chromatography in EtOAc, Rf 0.69 (EtOAc), white yellow solid; decomp. >80 °C, 55% (86 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.54 (s, 1H), 7.48 (s, 1H), 7.20 (dd, *J* = 8.5, 1.9 Hz, 1H), 2.88 (d, *J* = 4.7 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.88, 160.41, 152.33, 129.92, 123.62, 122.21, 118.01, 27.92. HRMS:$C_9H_9ClN_3$ $[M+H]^+$; calculated 194.0485, found: 194.0484.

Annex III

Synthesis of indazoles from 2-formylphenylboronic acids

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Synthesis of indazoles from 2-formylphenylboronic acids†

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A method for the synthesis of indazoles was developed which involves a copper(II) acetate catalysed reaction of 2-formylboronic acids with diazadicaboxylates followed by acid or base induced ring closure. Hydrazine dicarboxylates were also shown as competent reaction partners for the synthesis of indazoles, however, they required a stoichiometric amount of copper(II) acetate for the C–N bond formation step. The transformation can be efficiently performed as a two step-one pot procedure to give a range of 1*N*-alkoxycarbonyl indazoles.

Introduction

The indazole motif plays an important role in pharmaceutically relevant compounds including drugs and candidate drugs *e.g.* Lonidamine, Gamendazole, Bendazac, Pazopanib, Axitinib (Fig. 1).[1–4] A number of approaches have been developed to assemble indazole from 2-aminotoluenes,[5] 2-acyl-halobenzenes,[6–8] 2-aminophenyloximes,[9] and 2-nitrobenzaldehydes,[10,11] and by [3 + 2] annulations of *in situ* generated arynes.[12–14] Most of the above mentioned methods lead to the defined 1*N* or 2*N* indazole substitution pattern, however, they require harsh conditions or long routes to the key intermediates limiting their application. Selective *N*-functionalization of indazoles has been reported for alkylation reactions[15–17] and few reports can be found on selective *N*-acylation of indazoles.[18]

Previously, we demonstrated the construction of aminoquinazolines from 2-formylphenylboronic acids.[19] This method involved the Chan–Evans–Lam reaction for the C–N bond formation. To extend this approach for the synthesis of indazoles, we turned our attention to copper catalysed addition of phenyl boronic acids to azodicarboxylates reported by Uemura and Chatani.[20] Using 2-formylphenylboronic acids **1** as substrates, the addition to N=N bond in azadicarboxylates **2** would give *N*-arylhydrazine intermediates **3** which could be further transformed to indazoles **4** and **5** (Scheme 1).

Results and discussion

The initial investigation of the arylation conditions was performed for the reaction of 2-formylphenylboronic acid (**1a**) with diethylazodicarboxylate (DEAD, **2a**) using $Cu(OAc)_2$ as a catalyst in a range of solvents (Table 1, entries 1–9). Solvents such as MeCN, DMF and DMA were found to be appropriate to obtain the product **3a** together with its cyclic tautomer **6a** in a good yield (Table 1, entries 5 and 6). Decreased catalyst loading was also possible using DMA as a solvent without affecting the product **6a** yield (Table 1, entries 7–9). Range of other copper sources was investigated (Table 1, entries 10–14). $CuCl_2$ $Cu(OTf)_2$ $Cu(acac)_2$ performed as efficient catalysts for C–N bond formation giving the product **3a** in high yield (Table 1, entries 10–12). Copper(I) source such as CuCl proved to be ineffective catalyst, while catalytic amount of CuI enabled product **3a** formation in good yield (Table 1, entries 13 and 14).

Next, the conditions were investigated for the indazole ring closure using arylhydrazine **3a** (Table 2). Acidic reaction conditions enabled the condensation of arylhydrazine **3a** to 1*N*-etoxycarbonyl indazole (**4a**) (Table 2, entries 1–5). TFA in DCM and in MeCN gave the expected product **4a** in good yield (Table 2, entries 1 and 2). Neat AcOH at r. t. did not enable the cyclization of arylhydrazine **3a**, while heating in a solution of MeCN induced formation of indazole **4a** (Table 2, entries 3 and 4).

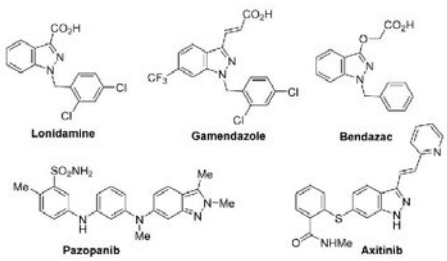

Fig. 1 Indazole containing drugs (Lonidamine, Gamendazole, Bendazac, Pazopanib) and candidate drug (Axitinib).

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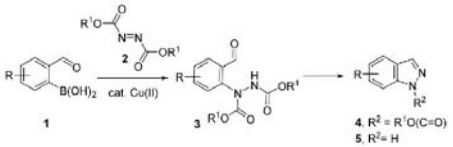
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra04056a



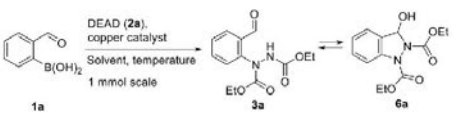
Scheme 1 Indazole synthesis from 2-formylphenylboronic acids.

Formic acid was strong enough to enable the formation of indazole **4a** at room temperature in a solution of MeCN (Table 2, entry 5).

The use of a base in alcoholic solvent provided unprotected indazole **5a** (Table 2, entries 6–8). Both K_2CO_3 and KOH could be efficiently used for the ring closure – deacylation reaction of arylhydrazine **3a**.

Next, the one pot formation of 1*N*-etoxycarbonyl indazole (**4a**) from 2-formylphenylboronic acid (**1a**) was investigated (Table 3). Unfortunately, DMA which was the solvent of choice for high yielding arylation of DEAD was not suitable for the ring closure step in the presence of TFA (Table 3, entry 1). In this case, the arylhydrazine **3a** intermediate was not transformed to product **4a**, according to LC-MS. In turn, the addition of TFA in DCM in an amount to sufficiently dilute DMA, enabled the formation of expected product **4a** in a good yield (Table 3, entry 2). The use of DCM as a solvent for both steps was less productive (Table 3, entry 3). However, MeCN was found as an appropriate solvent for both arylation and ring closure in the presence of TFA to give 1*N*-protected indazole **4a** in a good overall yield (Table 3, entry 4).

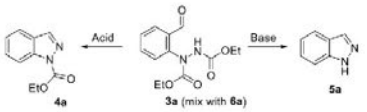
Table 1 Conditions for the arylation of DEAD (**2a**)



Entry	Copper catalyst	Solvent	Isolated yield
1	20 mol% $Cu(OAc)_2$	MeOH[a]	0%
2	20 mol% $Cu(OAc)_2$	PhMe	0%
3	20 mol% $Cu(OAc)_2$	THF	64%
4	20 mol% $Cu(OAc)_2$	MeCN	80%
5	20 mol% $Cu(OAc)_2$	DMF[b]	83%
6	20 mol% $Cu(OAc)_2$	DMA[c]	98%
7	15 mol% $Cu(OAc)_2$	DMA[c]	98%
8	10 mol% $Cu(OAc)_2$	DMA[c]	98%
9	5 mol% $Cu(OAc)_2$	DMA[c]	96%
10	10 mol% $CuCl_2$	DMAc	94%
11	10 mol% $Cu(OTf)_2$	DMAc	99%
12	10 mol% $Cu(acac)_2$	DMAc	97%
13	10 mol% CuCl	DMAc	25%
14	10 mol% CuI	DMAc	93%

[a] Violent DEAD decomposition observed. [b] *N*,*N*-Dimethylformamide. [c] *N*,*N*-Dimethylacetamide.

Table 2 Cyclization of arylhydrazone **3a** to indazoles **4a** and **5a**



Entry	Reagent	Solvent	Temp., time	Product	Yield
1	5 equiv. TFA	DCM	25 °C, 12 h	**4a**	63%
2	5 equiv. TFA	MeCN	25 °C, 12 h	**4a**	64%
3	AcOH	Neat	r. t., 12 h	**4a**	0%
4	30 equiv. AcOH	MeCN	70 °C, 12 h	**4a**	56%
5	30 equiv HCOOH	MeCN	r. t., 12 h	**4a**	56%
6	3 equiv. K_2CO_3	MeOH	70 °C, 1 h	**5a**	67%
7	3 equiv. K_2CO_3	MeOH	25 °C, 12 h	**5a**	67%
8	4 equiv. KOH	EtOH	r. t., 12 h	**5a**	59%

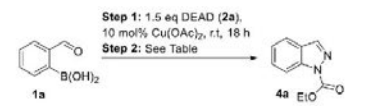
With one-pot conditions in hand, the synthesis of other alkoxycarbonylindazoles **4b–d** was performed by the reaction of boronic acid **1a** with azodicarboxylates **2b–d** (Table 4). The best yield of product **4b** was obtained with diisopropyl azodicarboxylate (DIAD, **2b**, Table 4, entry 1).

The scope of boronic acid substitution was investigated in the reaction of a range of formylboronic acids **1b–f** with DIAD (**2b**) followed by cyclization (Scheme 2). Substrates **1b–d** bearing methoxy and benzyloxy groups provided indazoles **4e–g** in a good to moderate yield. In the case of substrates **1e,f** bearing electron-withdrawing substituents, yields of products **4h, i** were decreased.

Thiophene boronic acid **8** was found a suitable substrate to obtain thienopyrazole derivative **9** in a good yield (Scheme 3).

Hydrazine dicarboxylate **7a** was also explored as a reagent for the synthesis of indazoles instead of azodicarboxylate **2a** (Table 5). 2-Formylphenylboronic acid (**1a**) was subjected to the reaction with diethyl hydrazine dicarboxylate (**7a**) using the two-step one-pot procedure for the formation of indazole **4a**. The catalytic amount of $Cu(OAc)_2$ and excess of triethylamine was not sufficient to achieve good yield of product **4a** formation (Table 5, entry 1). The use of equimolar amount of $Cu(OAc)_2$ and an

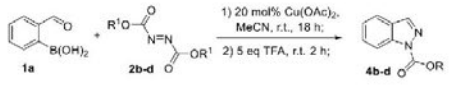
Table 3 One-pot conversion of boronic acid **1a** to indazole **4a**



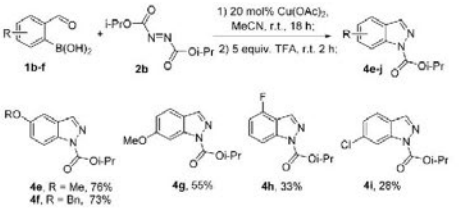
Entry	Solvent	Conditions, step 2	3a, isolated yield
1	DMA	10 equiv. TFA, 25 °C, 2 h	0%
2	DMA	TFA : DCM 1 : 4[a], 25 °C, 2 h	73%
3	DCM	5 equiv. TFA, 25 °C, 1 h	48%
4	MeCN	5 equiv. TFA, 25 °C, 1 h	78%

[a] 3 mL of TFA/DCM mixture added per 1 mL of DMA.

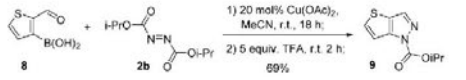
Table 4 Azodicarboxylate **2** scope for the synthesis of indazoles **4**



Entry	R	4, isolated yield
1	*i*-Pr	**4b**, 86%
2	Bn	**4c**, 60%
3	*i*-Bu	**4d**, 45%



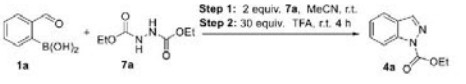
Scheme 2 The reaction of substituted formylboronic acids with DIAD (**2b**).



Scheme 3 The reaction of substituted formylboronic acids with DIAD (**2b**).

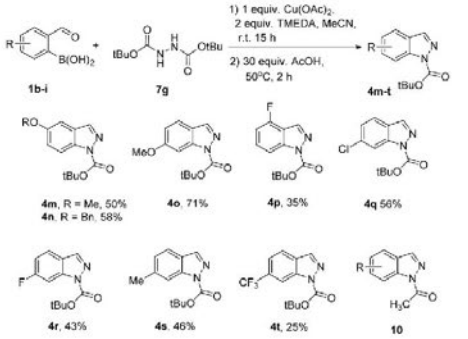
excess of triethylamine for the first step enabled good yield of product **4a** over two steps, while increasing the amount of $Cu(OAc)_2$ reduced the yield of product **4a** (Table 5, entries 2 and

Table 5 Synthesis of indazole using of hydrazine dicarboxylate **7a**



Entry	Catalyst	Solvent	Additive	NMR yield[a]
1	20 mol% $Cu(OAc)_2$	MeCN	3 equiv. TEA	25%
2	1 equiv. $Cu(OAc)_2$	MeCN	3 equiv. TEA	66%
3	1.5 equiv. $Cu(OAc)_2$	MeCN	3 equiv. TEA	50%
4	1 equiv. $Cu(OAc)_2$	MeCN	None	26%
5	1 equiv. $Cu(OAc)_2$	MeCN	2 equiv. TMEDA	67%
6	1 equiv. $Cu(OAc)_2$	MeCN	3 equiv. DIPEA	60%
7	1 equiv. CuCl	MeCN	3 equiv. TEA	35%
8	1 equiv. $CuCl_2$	MeCN	3 equiv. TEA	25%

[a] NMR yield, using 1,3,5-trimethoxybenzene as internal standard.

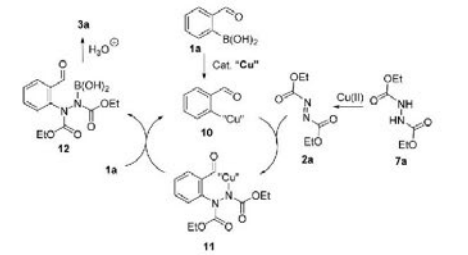


Scheme 4 Scope of boronic acids **1** in the reaction with diazadicarboxylate **7g**.

3). The transformation of 2-formylphenylboronic (**1a**) to indazole **4a** was not efficient in the absence of base for the first step, however, TEA could be replaced by TMEDA and DIPEA without significantly reducing the product **4b** yield (Table 5, entries 5 and 6). Several other Cu salts were tried for the first step of indazole **4b** formation, however, were found to be ineffective (Table 5, entries 7 and 8). The need for an equimolar amount of $Cu(OAc)_2$ for successful synthesis of indazole **4a** using hydrazine dicarboxylate **7a** implies *in situ* oxidation of reagent **7a** to azodicarboxylate **2a** (see also Scheme 5). However, C–N bond formation with hydrazine dicarboxylate **7a** in the Chan–Evans–Lam reaction cannot be excluded.[21]

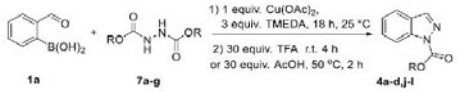
Next, a range of hydrazine dicarboxylates **7a–g** was explored as reaction components for a one-pot two-step synthesis of indazoles **4a–d**, **j–l** (Table 6). TFA was a suitable acid for the cyclization step to give the corresponding products **4a–d**, **j**, **k** from the reaction of boronic acid **1a** with hydrazine dicarboxylates **7a–f** (Table 6, entries 1–6). For the synthesis of product **4l** bearing acid labile *t*-Bu group, acetic acid at elevated temperature was used instead of TFA (Table 6, entry 7). This approach successfully provided product **4l** in a very good yield (Table 6, entry 8).

The scope of phenyl boronic acids **1b–i** was explored with di-*tert*-butyl hydrazine dicarboxylate **7g** as a reaction component

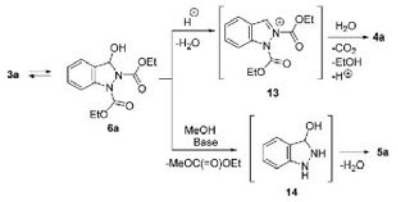


Scheme 5 Proposed mechanism for the C–N bond forming step.

Table 6 Hydrazine dicarboxylate **7** scope for the synthesis of indazoles **4**



Entry	7, R	Acid	4, isolated yield
1	**7a**, Et	TFA	**4a**, 63%
2	**7b**, *i*-Pr	TFA	**4b**, 47%
3	**7c**, Bn	TFA	**4c**, 46%
4	**7d**, *i*-Bu	TFA	**4d**, 61%
5	**7e**, Me	TFA	**4j**, 63%
6	**7f**, allyl	TFA	**4k**, 40%
7	**7g**, *t*-Bu	AcOH	**4l**, 73%



Scheme 6 Proposed mechanism for the condensation step.

for the synthesis of 1*N*-Boc indazoles **4m–t** (Scheme 4). The major reason for reduction was formation of *N*-acetyl indazoles **10** as by-products (see ESI† for the characterization of **10a**, R = H).

The mechanism for the C–N bond formation in the copper catalysed reaction of arylboronic acids with diazadicarboxylates has been proposed by Uemura and Chatani.[20] According to this, the transmetalation reaction of arylboronic acid **1a** with a copper catalyst would form an arylcopper species **10** (Scheme 5). Addition of intermediate **10** to N=N double bond gives an arylhydrazine **11** which undergoes the transmetalation with boronic acid **1a** to give intermediate **12** and return arylcopper species **10** into catalytic cycle. Work-up would produce arylhydrazine **3a**. Noteworthy, it was shown by Uemura and Chatani that dialkoxycarbonyl hydrazines are not competent substrates for this reaction unless additional oxidant is added.[20] This implies that hydrazine **7a** is likely oxidised to diazadicarboxylate **2a** by stoichiometric amount of copper source.

The proposed mechanism for the condensation of arylhydrazine intermediate into indazole is given in Scheme 6. In the presence of acid, *N*-acyliminium ion **13** is formed. Selective hydrolytic cleavage of one ethoxycarbonyl group in intermediate **13** gives 1*N*-ethoxycarbonyl indazole **4a**. In turn, basic conditions would enable cleavage of both ethoxycarbonyl groups leading to intermediate **14** which eliminates water to give indazole **5a**.

Conclusions

In summary, copper catalysed reaction of 2-formylboronic acids with diazadicaboxylates followed by acid or base induced ring closure is a convenient method for the synthesis of 1*N*-alkoxycarbonyl indazole derivatives. The indazole synthesis can also be performed using hydrazine dicarboxylates as reaction partners for the synthesis of indazoles, however, required a stoichiometric amount of copper(II) acetate for the C–N bond formation step. The method is based on readily available building blocks and can be performed at relatively mild reaction conditions which enables its application for the synthesis of indazole motif containing compounds.

Author contributions

V. S. and A. S performed the synthesis. A. J. wrote the paper.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Supporting Information

Synthesis of indazoles from 2-formylphenylboronic acids

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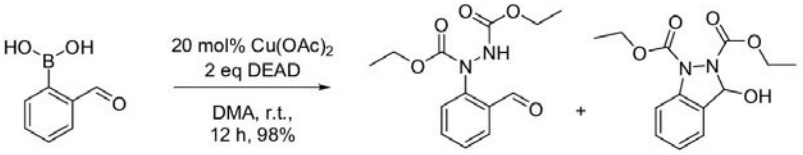
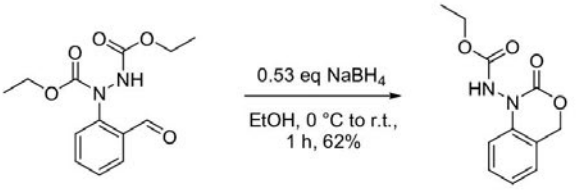
Procedure of synthesis of diethyl 1-(2-formylphenyl)hydrazine-1,2-dicarboxylate (3a) from (2-formylphenyl)boronic acid (1a)



To a stirred solution of (2-formylphenyl)boronic acid (150 mg, 1 mmol), N,N-Dimethylacetamide (5 mL) and DEAD (315 µL, 2 eq), catalytic $Cu(OAc)_2$ was added (20 mol%, 37 mg). Reaction sealed under air, and stirred overnight at room temperature. Then r.m. partitioned between EtOAc (20 mL) and brine (20 mL) washed with brine (3x15 mL), dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to obtain crude material. Compound was purified on silica gel, using EtOAc in PE gradient to obtain product **3a** (as a mixture with the cyclic tautomer) as colourless oil (283 mg, 98%).

Compound **3a** was difficult to characterize due to the mixture of tautomers. Therefore it was transformed to product **S1**, using reduction with $NaBH_4$.

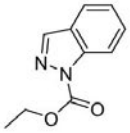


To a stirred solution of **3a** (120 mg, 0.43 mmol) in 2 ml EtOH, cooled to 0 °C, $NaBH_4$ (8.6 mg, 0.53 eq) added in one portion. After warming up to room temperature, reaction stirred for 1 h and quenched with 1 M aqueous HCl (5 mL) and stirred for additional 15 min. Reaction mixture partitioned between EtOAc (20 mL) and brine (10 mL), washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 ml), dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to obtain crude material. Compound purified using reverse phase chromatography to obtain product **S1** as viscous oil (63 mg, 62%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 (ddd, J = 8.3, 6.6, 2.3 Hz, 1H), 7.19 – 7.08 (m, 3H), 7.03 (s, 1H), 5.40 – 5.20 (m, 2H), 4.26 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 18.5 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.9, 152.4, 138.4, 129.5, 124.3, 124.0, 119.1, 112.7, 68.1, 63.0, 14.5. HRMS $C_{11}H_{13}N_2O_4$ $[M+H]^+$, calculated 237.0875, found 237.0886.

General Procedure A for the synthesis of alkoxycarbonyl-protected indazoles.

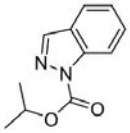
To a stirred solution of (2-formylphenyl)boronic acid (150 mg, 1 mmol), MeCN (5 mL) and DIAD (296 µL, 1.5 eq), catalytic $Cu(OAc)_2$ was added (20 mol%, 37 mg). Reaction sealed under air, and stirred overnight at room temperature. Then TFA (384 µL, 5 eq) added at room temperature, and reaction stirred for 2 h before evaporated to dryness. Resulting residue partitioned between EtOAc (20 mL) and saturated $NaHCO_3$ solution (30 mL), washed with brine (2x15 mL), dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to obtain crude material. Compound purified on silica, using EtOAc in PE gradient to obtain product **4b** as yellowish oil (176 mg, 86%).

Ethyl 1H-indazole-1-carboxylate (**4a**) (Reported in literature[1])



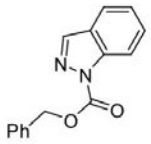
Prepared according to the General Procedure A, replacing DIAD with DEAD. Purified by silica gel column chromatography (gradient 5% to 20% EtOAc in PE), Rf 0.76 (EtOAc:PE 1:1), white yellow oil; 78% (150 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (d, *J* = 8.5 Hz, 1H), 8.18 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.4 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 4.59 (q, *J* = 7.1 Hz, 2H), 1.52 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.8, 140.2, 139.9, 129.3, 125.9, 124.1, 121.2, 114.6, 64.1, 14.5. HRMS: $C_{10}H_{11}N_2O_2Na$ $[M+Na]^+$; calculated 191.0821, found 191.0826.

Isopropyl 1H-indazole-1-carboxylate (**4b**) (Reported in literature[1])



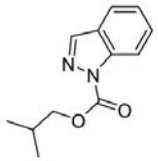
Prepared according to the General Procedure A. Purified by silica gel column chromatography (gradient 5 to 15% EtOAc in PE), Rf 0.48 (EtOAc:PE 1:4), yellowish oil; 86% (176 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (d, *J* = 8.5 Hz, 1H), 8.19 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.4 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 5.38 (hept, *J* = 6.3 Hz, 1H), 1.52 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.4, 140.1, 140.0, 129.2, 126.0, 124.0, 121.3, 114.7, 72.5, 22.1. HRMS: $C_{11}H_{12}N_2O_2Na$ $[M+Na]^+$; calculated 227.0796, found 227.0803.

Benzyl 1H-indazole-1-carboxylate (**4c**) (Reported in literature[2])



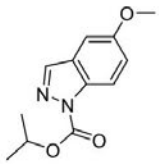
Prepared according to the General Procedure A, replacing DIAD with di-benzyl azodicaboxylate. Purified by silica gel column chromatography (gradient 5% to 20% EtOAc in PE), Rf 0.55 (EtOAc:PE 1:3), white solid; m.p.78-80 °C, 60% (76 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (d, *J* = 8.5 Hz, 1H), 8.20 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.59 – 7.51 (m, 3H), 7.44 – 7.30 (m, 4H), 5.55 (s, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.8, 140.5, 140.0, 135.0, 129.4, 128.9, 128.9, 128.9, 126.0, 124.2, 121.3, 114.7, 69.5.

Isobutyl 1H-indazole-1-carboxylate (**4d**)



Prepared according to the General Procedure A, replacing DIAD with di-isobutyl azodicaboxylate. Purified by silica gel column chromatography (gradient 5% to 10% EtOAc in PE), Rf 0.23 (EtOAc:PE 1:10), yellow oil; 45% (99 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 9.0 Hz, 1H), 8.18 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 8.3 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 4.30 (d, *J* = 6.9 Hz, 2H), 2.21 (dh, *J* = 13.5, 6.8 Hz, 1H), 1.06 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.9, 140.2, 139.8, 129.2, 126.0, 124.0, 121.2, 114.5, 73.9, 28.0, 19.2. HRMS: $C_{12}H_{14}N_2O_2Na$ $[M+Na]^+$; calculated 241.0953, found 241.0962.

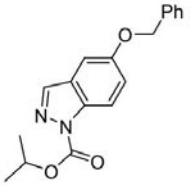
Isopropyl 5-methoxy-1H-indazole-1-carboxylate (**4e**)



Prepared according to the General Procedure A. Purified by silica gel column chromatography (gradient 5% to 35% EtOAc in PE), Rf 0.38 (EtOAc:PE 1:3), white oil, solidifies on standing; m.p. 73-75 °C, 76% (99 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 9.5 Hz, 2H), 7.18 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 5.35 (hept, *J* = 6.3 Hz, 1H), 3.86 (s, 3H), 1.51 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ

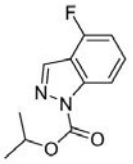
156.7, 150.4, 139.7, 135.3, 126.7, 120.0, 115.5, 101.4, 72.5, 55.8, 22.1. HRMS: $C_{12}H_{14}N_2O_3Na$ $[M+Na]^+$; calculated 257.0902, found 257.0911.

Isopropyl 5-(benzyloxy)-1H-indazole-1-carboxylate (**4f**)



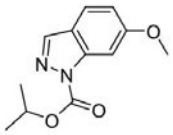
Prepared according to the General Procedure A. Purified by silica gel column chromatography (gradient 5% to 20% EtOAc in PE), Rf 0.45 (EtOAc:PE 1:3), white solid; m.p. 110-111 °C, 74% (89.5 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 9.1 Hz, 1H), 8.09 (s, 1H), 7.50 – 7.43 (m, 2H), 7.43 – 7.37 (m, 2H), 7.37 – 7.31 (m, 1H), 7.27 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.17 (d, *J* = 2.1 Hz, 1H), 5.36 (hept, *J* = 6.3 Hz, 1H), 5.12 (s, 2H), 1.51 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.8, 150.3, 139.7, 136.8, 135.4, 128.8, 128.3, 127.6, 126.7, 120.5, 115.6, 103.0, 72.5, 70.7, 22.1. HRMS: $C_{18}H_{19}N_2O_3$ $[M+H]^+$; calculated 311.1396, found 311.1400.

Isopropyl 4-fluoro-1H-indazole-1-carboxylate (**4g**)



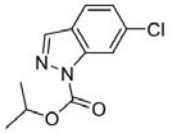
Prepared according to the General Procedure A. Purified by silica gel column chromatography (gradient 5% to 15% EtOAc in PE), Rf 0.85 (EtOAc:PE 1:3), white yellow solid; m.p. 80-82 °C, 33% (44 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.46 (td, *J* = 8.2, 5.2 Hz, 1H), 6.95 (ddd, *J* = 9.4, 7.9, 0.5 Hz, 1H), 5.35 (hept, *J* = 6.3 Hz, 1H), 1.50 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-d) δ 155.4 (d, J = 253.5 Hz), 150.2, 142.1 (d, J = 7.6 Hz), 135.9 (d, J = 1.6 Hz), 130.4 (d, J = 7.5 Hz), 115.9 (d, J = 22.7 Hz), 110.7 (d, J = 4.4 Hz), 108.8 (d, J = 18.0 Hz), 72.9, 22.0. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -117.70. HRMS: $C_{11}H_{11}N_2O_2NaF$ $[M+Na]^+$; calculated 245.0702, found 245.0707.

Isopropyl 6-methoxy-1H-indazole-1-carboxylate (**4h**)



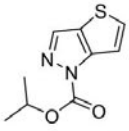
Prepared according to the General Procedure A. Purified by silica gel column chromatography (gradient 5% to 35% EtOAc in PE), Rf 0.36 (EtOAc:PE 1:4), white crystalline solid; m.p. 69-70 °C, 55% (72 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (s, 1H), 7.69 (d, *J* = 1.9 Hz, 1H), 7.55 (dd, *J* = 8.7, 0.4 Hz, 1H), 6.92 (dd, *J* = 8.7, 2.2 Hz, 1H), 5.33 (hept, *J* = 6.3 Hz, 1H), 3.89 (s, 3H), 1.49 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.4, 150.6, 141.7, 139.9, 121.7, 120.0, 115.2, 96.7, 72.4, 55.7, 22.0. HRMS: $C_{12}H_{14}N_2O_3Na$ $[M+Na]^+$; calculated 257.0902, found 257.0909.

Isopropyl 6-chloro-1H-indazole-1-carboxylate (**4i**)



Prepared according to the General Procedure A. Purified by silica gel column chromatography (gradient 5% to 15% EtOAc in PE), Rf 0.55 (EtOAc:PE 1:4), white yellow solid; m.p. 76-78 °C, 28% (36 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.25 (s, 1H), 8.13 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 8.5, 1.8 Hz, 1H), 5.36 (hept, *J* = 6.3 Hz, 1H), 1.51 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.1, 140.4, 139.7, 135.7, 125.0, 124.5, 122.0, 114.8, 73.0, 22.0. HRMS: $C_{11}H_{11}N_2O_2NaCl$ $[M+Na]^+$; calculated 261.0407, found 261.0410.

Isopropyl 1H-thieno[3,2-c]pyrazole-1-carboxylate (**9**)

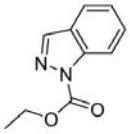


Prepared according to the General Procedure A. Purified by silica gel column chromatography (gradient 5% to 20% EtOAc in PE), Rf 0.29 (EtOAc:PE 1:10), yellow oil; 69% (112 mg).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 (s, 1H), 7.55 (d, *J* = 5.2 Hz, 1H), 7.37 (d, *J* = 5.2 Hz, 1H), 5.33 (hept, *J* = 6.3 Hz, 1H), 1.49 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.1, 148.7, 135.9, 134.2, 125.3, 113.4, 73.0, 22.0. HRMS: $C_9H_{10}N_2O_2SNa$ $[M+Na]^+$; calculated 233.0361, found 233.0368.

General Procedure B for the synthesis of alkoxycarbonyl-protected indazoles from dialkyl hydrazine-1,2-dicarboxylates.

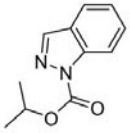
To a stirred solution of (2-formylphenyl)boronic acid (100 mg, 0.67 mmol), MeCN (5 mL), diethyl hydrazine-1,2-dicarboxylate (235 mg, 2 eq) and $Cu(OAc)_2$ (121 mg, 1 eq), TMEDA was added (200 µL, 2 eq). Reaction sealed under air, and stirred overnight at room temperature. Then TFA (768 µL, 15 eq) added dropwise at room temperature, and reaction stirred for 4 h before evaporated to dryness. Resulting residue partitioned between EtOAc (20 mL) and saturated $NaHCO_3$ solution (20 mL), washed with brine (2x15 mL), dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to obtain crude material. Compound purified on silica, using EtOAc in PE gradient to obtain product **4a** as a light yellow oil (80.2 mg, 63%).

Ethyl 1H-indazole-1-carboxylate (**4a**)



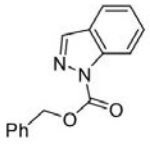
Prepared according to the General Procedure B. Purified by silica gel column chromatography (gradient 5% to 25% EtOAc in PE); 63% (80.2 mg). Analytical data corresponds to the previously described compound **4a**.

Isopropyl 1H-indazole-1-carboxylate (4**b**)



Prepared according to the General Procedure B, using diisopropyl hydrazine-1,2-dicarboxylate instead of diethyl hydrazine-1,2-dicarboxylate. Purified by silica gel column chromatography (gradient 5% to 15% EtOAc in PE); 46% (76 mg). Analytical data corresponds to the previously described compound **4b**.

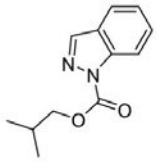
Benzyl 1H-indazole-1-carboxylate (**4c**)



Prepared according to the General Procedure B, using dibenzyl hydrazine-1,2-dicarboxylate instead of diethyl hydrazine-1,2-dicarboxylate. Purified by silica gel column chromatography

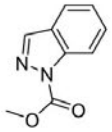
(gradient 5% to 20% EtOAc in PE); 46% (54 mg). Analytical data corresponds to the previously described compound **4c**.

Isobutyl 1H-indazole-1-carboxylate (**4d**)



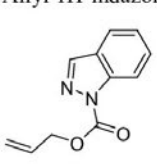
Prepared according to the General Procedure B, using diisobutyl hydrazine-1,2-dicarboxylate instead of diethyl hydrazine-1,2-dicarboxylate. Purified by silica gel column chromatography (gradient 5% to 10% EtOAc in PE); 61% (107 mg). Analytical data corresponds to the previously described compound **4d**.

Methyl 1H-indazole-1-carboxylate (**4j**) (Reported in literature[3])



Prepared according to the General Procedure B, using dimethyl hydrazine-1,2-dicarboxylate instead of diethyl hydrazine-1,2-dicarboxylate. Purified by silica gel column chromatography (gradient 5% to 25% EtOAc in PE), Rf 0.3 (EtOAc:PE 1:4), white crystalline solid; m.p. 56-57 °C, 64% (75 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (d, *J* = 8.5 Hz, 1H), 8.19 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.3 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 4.14 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.0, 140.1, 139.7, 129.1, 125.7, 123.9, 121.0, 114.3, 54.3. HRMS: $C_9H_9N_2O_2Na$ $[M+Na]^+$; calculated 177.0664, found 177.0688.

Allyl 1H-indazole-1-carboxylate (**4k**)



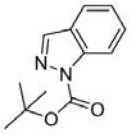
Prepared according to the General Procedure B, using diallyl hydrazine-1,2-dicarboxylate instead of diethyl hydrazine-1,2-dicarboxylate. Purified by silica gel column chromatography (gradient 5% to 20% EtOAc in PE), Rf 0.42 (EtOAc:PE 1:4), yellow oil; 40% (64 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 8.5 Hz, 1H), 8.16 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.4 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 6.20 – 6.02 (m, 1H), 5.49 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.35 (dq, *J* = 10.4, 1.1 Hz, 1H), 4.99 (dt, *J* = 6.0, 1.3 Hz, 2H); ^{13}C NMR (101

MHz, Chloroform-*d*) δ 150.5, 140.3, 139.9, 131.2, 129.3, 125.9, 124.1, 121.2, 120.2, 114.5, 68.4. HRMS: $C_{11}H_{10}N_2O_2Na$ $[M+Na]^+$; calculated 225.0640, found 225.0647

General Procedure C for the synthesis of 1*N*-Boc-protected indazoles from di-tert-butyl hydrazine-1,2-dicarboxylate.

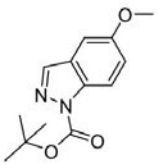
To a stirred solution of (2-formylphenyl)boronic acid (120 mg, 0.8 mmol), MeCN (7 mL), di-tert-butyl hydrazine-1,2-dicarboxylate (372 mg, 2 eq) and $Cu(OAc)_2$ (145 mg, 1 eq), TMEDA was added (240 µL, 2 eq). Reaction sealed under air, and stirred overnight at room temperature. Then AcOH (916µL, 20 eq) added dropwise at room temperature, and reaction heated at 50 °C for 2 h before evaporated to dryness. Resulting residue partitioned between EtOAc (20 mL) and saturated $NaHCO_3$ solution (30 mL), washed with brine (2x20 mL), dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to obtain crude material. Compound purified on silica, using EtOAc in PE gradient to obtain product **4l** as a yellow oil (128 mg, 73%). Major isolated by-product identified as 1-(1H-indazol-1-yl)ethan-1-one **10a**, which ^1H and ^{13}C NMR data are consistent with those previously reported in literature[4].

Tert-butyl 1H-indazole-1-carboxylate (**4l**) (Reported in literature[5])



Prepared according to the General Procedure C. Purified by silica gel column chromatography (gradient 5% to 12% EtOAc in PE), Rf 0.47 (EtOAc:PE 1:4), yellow oil; 73% (128 mg). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.19 (d, J = 9.1 Hz, 1H), 8.17 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.53 (t, J = 8.3 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 1.73 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.4, 139.8, 139.7, 129.0, 126.0, 123.8, 121.2, 114.7, 85.0, 28.3. HRMS: $C_{12}H_{14}N_2O_2Na$ $[M+Na]^+$; calculated 241.0953, found 241.0953.

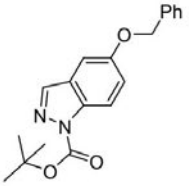
Tert-butyl 5-methoxy-1H-indazole-1-carboxylate (**4m**)



Prepared according to the General Procedure C. Purified by silica gel column chromatography (gradient 5% to 15% EtOAc in PE), Rf 0.28 (EtOAc:PE 1:4), white oil; 50% (69 mg). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.10 – 8.02 (m, 2H), 7.15 (dd, J = 9.0, 2.5 Hz, 1H), 7.08 (d, J = 2.3 Hz, 1H), 3.85 (s, 3H), 1.71 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*)

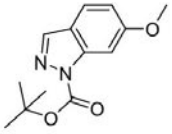
δ 156.5, 149.3, 139.2, 135.2, 126.6, 119.8, 115.6, 101.2, 84.8, 55.8, 28.3. HRMS: $C_{13}H_{16}N_2O_3Na$ $[M+Na]^+$; calculated 271.1059, found 271.1070.

Tert-butyl 5-(benzyloxy)-1H-indazole-1-carboxylate (**4n**)



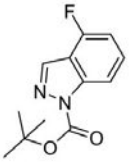
Prepared according to the General Procedure C. Purified by silica gel column chromatography (gradient 5% to 20% EtOAc in PE), Rf 0.31 (EtOAc:PE 1:4), white solid; m.p. 92-94 °C, 58% (74 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (s, 1H), 8.07 (s, 1H), 7.49 – 7.44 (m, 2H), 7.44 – 7.37 (m, 2H), 7.37 – 7.31 (m, 1H), 7.25 (d, J = 9.1 Hz, 1H), 7.16 (d, J = 2.2 Hz, 1H), 5.12 (s, 2H), 1.72 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.6, 149.3, 139.2, 136.8, 135.3, 128.8, 128.2, 127.6, 126.6, 120.4, 115.6, 102.9, 84.9, 70.7, 28.3. HRMS: $C_{19}H_{20}N_2O_3Na$ $[M+Na]^+$; calculated 347.1372, found 347.1373.

Tert-butyl 6-methoxy-1H-indazole-1-carboxylate (**4o**)



Prepared according to the General Procedure C. Purified by reverse phase chromatography (gradient 5% to 60% MeCN in H_2O), slightly yellow viscous oil; 71% (98 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (s, 1H), 7.68 (s, 1H), 7.57 (d, J = 8.7 Hz, 1H), 6.94 (dd, J = 8.7, 2.2 Hz, 1H), 3.91 (s, 3H), 1.72 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.3, 149.7, 141.6, 139.6, 121.8, 120.1, 115.2, 96.8, 84.9, 55.8, 28.3. HRMS: $C_{13}H_{16}N_2O_3Na$ $[M+Na]^+$; calculated 271.1059, found 271.1062.

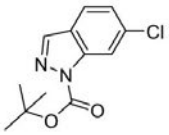
Tert-butyl 4-fluoro-1H-indazole-1-carboxylate (**4p**)



Prepared according to the General Procedure C. Purified by silica gel column chromatography (gradient 5% to 15% EtOAc in PE), Rf 0.69 (EtOAc:PE 1:4), yellow oil;

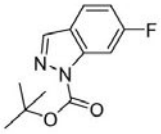
35% (49 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.49 – 7.41 (m, 1H), 6.95 (t, *J* = 9.1 Hz, 1H), 1.72 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.4 (d, *J* = 253.3 Hz), 149.1, 142.0 (d, *J* = 7.6 Hz), 135.5, 130.2 (d, *J* = 7.5 Hz), 115.9 (d, *J* = 22.7 Hz), 110.8 (d, *J* = 4.3 Hz), 108.5 (d, *J* = 18.0 Hz), 85.5, 28.2; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -117.89. HRMS: $C_{12}H_{13}N_2O_2FNa$ $[M+Na]^+$; calculated 259.0859, found 259.0858.

Tert-butyl 6-chloro-1H-indazole-1-carboxylate (**4q**)



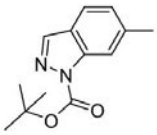
Prepared according to the General Procedure C. Purified by silica gel column chromatography (gradient 5% to 30% EtOAc in PE), Rf 0.38 (EtOAc:PE 1:4), white yellow oil; 56% (77 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (s, 1H), 8.13 (s, 1H), 7.64 (dd, *J* = 8.5, 0.6 Hz, 1H), 7.29 (dd, *J* = 8.5, 1.8 Hz, 1H), 1.72 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.1, 140.3, 139.3, 135.6, 124.8, 124.4, 121.9, 114.9, 85.6, 28.3. HRMS: $C_{12}H_{13}N_2O_2NaCl$ $[M+Na]^+$; calculated 275.0563, found 275.0567.

Tert-butyl 6-fluoro-1H-indazole-1-carboxylate (**4r**)



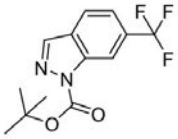
Prepared according to the General Procedure C. Purified by silica gel column chromatography (gradient 5% to 12% EtOAc in PE), Rf 0.34 (EtOAc:PE 1:4), white yellow oil; 43% (60 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 (s, 1H), 7.88 (d, *J* = 9.6 Hz, 1H), 7.67 (dd, *J* = 8.7, 5.2 Hz, 1H), 7.08 (td, *J* = 8.8, 2.3 Hz, 1H), 1.72 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.6 (d, *J* = 247.5 Hz), 149.1, 140.5 (d, *J* = 13.3 Hz), 139.4, 122.5, 122.4 (d, *J* = 10.9 Hz), 113.2 (d, *J* = 25.7 Hz), 101.6 (d, *J* = 28.6 Hz), 85.4, 28.3; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -110.49. HRMS: $C_{12}H_{13}N_2O_2FNa$ $[M+Na]^+$; calculated 259.0859, found 259.0859.

Tert-butyl 6-methyl-1H-indazole-1-carboxylate (**4s**) (Reported in literature[6])



Prepared according to the General Procedure C. Purified by silica gel column chromatography (gradient 5% to 15% EtOAc in PE), Rf 0.53 (EtOAc:PE 1:4), yellow oil; 46% (66 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (s, 1H), 8.03 (s, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 2.52 (s, 3H), 1.72 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.6, 140.5, 139.7, 139.6, 125.7, 124.0, 120.7, 114.6, 84.8, 28.3, 22.3. HRMS: $C_{13}H_{16}N_2O_2Na$ $[M+Na]^+$; calculated 255.1109, found 255.1115.

Tert-butyl 6-(trifluoromethyl)-1H-indazole-1-carboxylate (**4t**) (Reported in literature[7])



Prepared according to the General Procedure C. Purified by silica gel column chromatography (gradient 5% to 20% EtOAc in PE), Rf 0.46 (EtOAc:PE 1:4), white solid; m.p. 63-65 °C, 25% (32 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 8.24 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 1.74 (s, 9H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.9, 139.2, 139.1, 131.0 (q, *J* = 32.3 Hz), 127.8, 124.3 (q, *J* = 272.7 Hz), 122.0, 120.5 (q, *J* = 3.3 Hz), 112.6 (q, *J* = 4.7 Hz), 85.9, 28.2; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -61.82. LCMS: $C_9H_6N_2O_2F_3$ $[M-(t\text{-}Bu)+H]^+$ 231.27.

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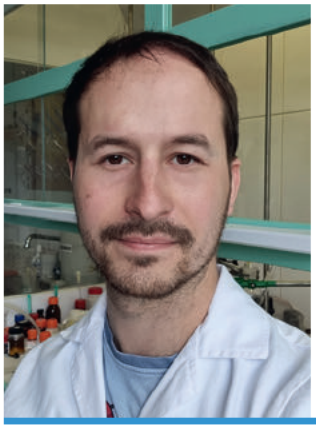

Vitalii Solomin was born in 1993 in Kharkiv, Ukraine. He obtained a Bachelor's degree in Chemistry from Taras Shevchenko National University of Kyiv in 2014 and a Master's degree from the Institute of High Technologies in 2016. From 2011 to 2018 he was working as a Synthetic Chemist at Enamine Ltd in Kyiv. In 2018, V. Solomin was awarded the Marie Sklodowska-Curie scholarship and started his career at the Latvian Institute of Organic Synthesis under the supervision of Professor Dr. chem. Aigars Jirgensons. In 2019, Vitalii performed a secondment to Oxford Drug Design company to master his skills in the field of computer-aided drug design (CADD). The results of V. Solomin's Doctoral Thesis are published in three international scientific journals. V. Solomin's main research interests are connected with the synthesis of heterocyclic compounds and their medicinal chemistry research.