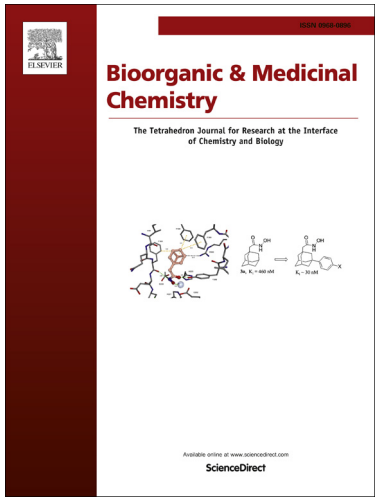

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Discovery of Inhibitors of the Mitotic Kinase TTK Based on N-(3-(3-Sulfamoylphenyl)-1H-indazol-5-yl)-Acetamides and Carboxamides

*Radoslaw Laufer**,[a] Grace Ng,[a] Yong Liu,[a] Narendra Kumar B. Patel,[a] Louise G. Edwards,[a] Yunhui Lang,[a] Sze-Wan Li,[a] Miklos Feher,[a] Don E. Awrey,[a] Genie Leung,[a] Irina Beletskaya,[a] Olga Plotnikova,[a] Jacqueline M. Mason,[a] Richard Hodgson,[a] Xin Wei,[a] Guodong Mao,[a] Xunyi Luo,[a] Ping Huang,[a] Erin Green,[a] Reza Kiarash, Dan Chi-Chia Lin,[a] Marees Harris-Brandts,[a] Fuqiang Ban,[a] Vincent Nadeem,[a] Tak W. Mak,[a] Guohua J. Pan,[a] Wei Qiu,[b] Nicolay Y. Chirgadze,[b] Henry W. Pauls*[a]*

[a]*Campbell Family Institute for Breast Cancer Research, Therapeutics Group, University Health Network, 101 College St. W, Toronto, Ontario, M5G 1L7, Canada*

[b]*Campbell Family Cancer Research Institute, Ontario Cancer Institute, Princess Margaret Hospital, University Health Network, 610 University Ave, Toronto, Ontario M5G 2C4, Canada*

Corresponding authors. e-mail: rlaufer@uhnresearch.ca, Tel.: +1-416-581-7572; e-mail: hpauls@uhnresearch.ca, Tel.: 416-581-7620.

Abstract

TTK kinase was identified by in-house siRNA screen and validated as a tractable, novel target for cancer treatment. A screening campaign and systematic optimization, supported by computer modeling led to indazole core with key sulfamoylphenyl and acetamido moieties at positions 3 and 5, respectively, establishing a novel chemical class culminating in identification of **72** (CFI-400936). This potent inhibitor of TTK (IC_{50} = 3.6 nM) demonstrated good potency in cell based assay and selectivity against a panel of

human kinases. A co-complex TTK X-ray crystal structure and results of a xenograft study with the TTK inhibitor are described.

Keywords

Anticancer, antimitotic agents; indazolyl benzenesulfonamide; mitotic kinase; Monopolar Spindle 1 kinase; Mps1; Tyrosine Threonine Kinase ,TTK.

1. Introduction

Tyrosine Threonine Kinase (TTK) also known as Monopolar Spindle 1 (Mps1),[1] or Phosphotyrosine-Picked Threonine Kinase (PYT) is a conserved dual-specificity, cell cycle-regulated kinase, essential for genomic integrity during cell division through establishment and maintenance of the mitotic checkpoint.[2] TTK is overexpressed in a variety of solid cancers[3-12], and elevated levels of TTK correlate with high histological grade in tumors[10] and poor patient outcome.[7,8,9] Overexpression of TTK may promote tumor initiation, and survival of genomically unstable and aneuploid cancer cells.[10,13,14] Beyond mitosis, TTK has roles in development and several signaling pathways, including Hedgehog/Gli1[15] and EGFR.[16] Also, several lines of evidence implicate TTK in DNA damage signaling. TTK controls DNA damage responses and genome stability by phosphorylating the Bloom syndrome helicase (BLM)[17], CHK2 in the G2/M checkpoint[18,19] and c-ABL after oxidative stress.[20] Taken together, these observations point to TTK as a potential target for therapeutics for solid tumors. In efforts to validate this hypothesis we have performed a series of in vitro and in vivo experiments: RNAi-mediated depletion of TTK in cancer cells disabled the mitotic checkpoint, caused gross chromosome segregation errors resulting in aneuploidy, induced cell death, and suppressed the growth of tumor xenografts in mice.[21]

The interest in TTK as a potential target for the discovery of novel therapeutics is underscored by the number of TTK inhibitors that have been disclosed since the commencement of our study. Small molecule TTK inhibitors (Chart 1) include reversine[22,23], its analog MPI-0479605,[24] NMS-P715,[25,26] MPS1-IN-1,[27] AZ 3146[28,29] , the Genentech and Cancer Research UK inhibitors (CCT251455).[30,31] The

striking feature in all of these inhibitors is the common occurrence of a key N-phenylpyrimidin-2-amine motif highlighted in blue in Chart 1. The Shionogi-1[32,33] inhibitor incorporates a variation on this theme.

Reversine is also an inhibitor of Aurora B; analoging efforts demonstrated that the inclusion of a substituent on the aniline ring (R = Me) served to abrogate this activity. It's notable that the subsequent analogs with the N-phenylpyrimidin-2-amine motif all incorporate a substituent at this position. After completion of the research presented in this manuscript,[34] Kusakabe et al. have disclosed a unique series of indazole-based inhibitors.[35] The work, stimulated by the structure of a nonselective kinase inhibitor, SP600125,[36] explored a set of C5 and C6 substitutions of the indazole ring and culminated in the synthesis of potent TTK inhibitors exemplified by the structure of Shionogi-2 (
Chart **1**) with undisclosed in vivo activities. Despite the plethora of reports on TTK inhibitors, apparently, none as yet, has advanced to the clinic, and the discovery of new efficacious TTK inhibitors presents a challenge and the promise of new approaches to cancer therapy.

The results of our lead generation and subsequent optimization efforts are described in the body of this publication. We began with a focused screening approach that included virtual hits from commercial collections and our in-house library of kinase inhibitors. One chemotype that was identified by our medium throughput assay was indazole, a well precedented class of ATP-competitive protein kinase inhibitors. The initial synthetic work was driven by two objectives, namely, a desire to identify new chemotypes for subsequent elaboration, and to increase the potency of the series. Subsequent lead optimization efforts on the C-3 sulfamoylphenyl compounds that resulted, established the acetamido moiety at position 5 but not 6, as being distinctive and pivotal to potent TTK inhibition. Further optimization of this novel series, together with structural work, corroborated the binding hypothesis and gave potent and selective TTK inhibitors, with the desired in vitro and in vivo anticancer activity.

2. Results and discussion

2.1 Screening and Lead Finding.

Our lead finding strategy began with an internal library of focused kinase inhibitors whose assembly was previously described[37] and supplemented by a series of PLK4 inhibitors and intermediates.[37] In addition, virtual screening hits against a TTK model, based on the known TTK X-ray structure (PDB 3CEK *vide infra*),[27] were obtained. The combined collection (~13,000 compounds) was screened on a medium throughput robotics workstation using an indirect ELISA TTK assay. Hits from several chemical series (over 75% inhibition at the screening dose of 10 μM) were validated as follows: the active compounds were clustered into chemical series; their purity was checked by LCMS and IC_{50} values were determined. Selected compounds from series of interests were subjected to a modeling exercise in the TTK active site.

2.1.2 Molecular modeling.

The first publicly available TTK X-ray structure appeared during our initial lead finding efforts (2.3 Å resolution, PDB code 3CEK)[27] which we modified to render it suitable for molecular modeling. The structure is characterized by a bound pentaethyleneglycol (PEG) unit wound around Lys553 with hydrogen bonds to the positively charged side chain amino group. This PEG is situated in a volume where it would prevent ligands from binding into the kinase active site. The X-ray structure was modified by removing the PEG; molecular dynamics simulations of the active site indicated that it remained largely unchanged. This result implied that the PEG unit did not significantly influence the conformation of the TTK binding site. Hence, this modified X-ray structure was utilized for the virtual screen of available commercial collections and modeling new synthetic targets going forward. This model was later superseded by a co-crystal structure with a ligand from this series (*vida infra*). The modified 3CEK structure was useful in describing the binding pose of our ligands but had limitations: a somewhat flat SAR was predicted for structural changes in the region close to the putative activation loop.

2.1.3. Lead Finding

Of the series identified by these exercises, 3- substituted-indazoles, represented by compounds **1-3** (**Scheme 1**), held the most promise based on such criteria as: micromolar TTK inhibition, acceptable ligand efficiency, predictable binding mode and ease of chemical synthesis. This particular motif could also be recognized in the Jun N-terminal kinases inhibitor, SP600125;[36]an anthrapyrazole, and at the time, the only known inhibitor of TTK**.**[38] Besides improving TTK binding, the challenge presented was to generate a previously unexplored chemotype. Given the propensity of 3-vinylic indazoles **1** to inhibit PLK4,[37] we felt that 3-aryl indazoles **3** represented a better opportunity for the development of novel and selective inhibitors of TTK. We conducted molecular docking exercises, based on the known 3CEK crystal structure,[27] to overlay indazole hit **3** and a previously described VEGFR inhibitor, GW-786034 (pazopanib). The latter was reported as a low submicromolar inhibitor of TTK in a large kinase panel screen study reported by Karaman *et al*.[39] From the results of the overlay presented in Figure 1 it is clear that the sulfonamide group in GW-786034 is engaged in a bonding interaction with the hinge residue Gly605. We hypothesized that a similar interaction would be maintained if a sulfonamide group was grafted to the meta position of 3-phenyl group to yield indazoles **4** and **5**. In our model, the indazole core makes two anticipated H-bonds to the hinge region and the sulfonamide group captures additional interactions with polar functions of the TTK active site.

We were pleased to see that the *meta*-benzenesulfonamides **4** and **5** inhibited TTK in the single digit micromolar range, about 5-7 fold more potent than the unsubstituted parent, compound **3** (Table 1). In contrast, the *para*-substituted regioisomer (**6**) was an order of magnitude less active than the meta isomer. Bioisosteric replacement of the 3-benzensulfonamide with a *meta*-benzamide or *meta*-benzylic amine (Table 1, compounds **7** and **8**), reduced potency by up to an order of magnitude, underscoring the importance of the meta sulfonamide group for optimal binding. Our interest in this chemotype was enhanced by the paucity of literature reports on the indazole-based benzenesulfonamides, the later patent by Kusakabe *et al*[40] notwithstanding.

2.2 Inhibitor Design. To corroborate the nature of the binding of 3-(1H-indazol-3-yl)benzenesulfonamides, a kinetic analysis of compound **4** was performed (Supplementary material). This study showed that compound **4** displays kinetics consistent with direct competition for ATP binding in the active site of TTK with an apparent K_i of 3 μM. Inspection of the binding modes of compound **4** and analogs with various substituents on the indazole ring convinced us that substitution at position C7 of the indazole ring would not be tolerated. On the other hand, capturing additional interaction with the enzyme should be possible by substituting positions C4, C5 and C6. Accordingly, a limited SAR study of C4-C6 substitutions of the indazole core was undertaken; the data is summarized in Table 2. Soon after we initiated this work the substrate used in the TTK assay was changed from MBP to a recombinantly produced protein construct containing residues 1-275 of TTK[42b] (referred to herein as TTK-N) and the data in Tables 2-6 was obtained using the latter condition. In head to head comparison, this change improved the robustness of the assay and the absolute value of the TTK inhibition was effected but the relative potency was not.

Although phenyl rings are tolerated at all three positions there was no advantage to substitution with these hydrophobes (compounds **9**-**11**). In stark contrast, there was a discernible trend favoring C-5 substitutions involving polar linkers. For the C5 and C6 amide matched pairs; it was observed that C5-isomers were markedly more active against TTK (**14/15**, and **16/17**). For example, compound **16** was an order of magnitude more potent than the parent sulfonamide, **4**, whereas the C6 regioisomer **17** was significantly less active. These results focused the subsequent lead optimization work around the C5 substitution.

2.3 Chemical Synthesis. Halogenation of indazoles followed by a palladium-catalyzed cross coupling reaction comprise the key events in the synthesis of all of the indazolyl benzenesulfonamides described herein (Scheme 2). For example 1H-indazol-5-amine (**19**) was, after incorporation of N-Boc group, subjected to a halogenation followed by Suzuki-Miyaura arylation and a deprotection step to provide aniline **21**. This versatile intermediate was used in reactions with a variety of electrophiles in preparation of ureas, sulfonamides, sulfamides, amides and carbamates (**23**). In the same way, indazole carboxamides

26 were synthesized from methyl 1H-indazole-5-carboxylate **24** in a sequence consisting of halogenation followed by Pd-catalyzed cross-coupling reaction and an amide formation**.** Alternatively, alkylations of 1H-indazol-5-ol (**27**) followed by halogenation and arylation steps allowed for preparation of ethers of type **29**. α Amino acids used in the preparation of acetamides **22** were most conveniently prepared via a Petasis borono-Mannich reaction utilizing a mixture of arylboronic acid, dialkyl amine and glyoxylic acid.[41] In most cases, the α-substituted amides were tested as racemates. In selected cases, optical resolution by chiral HPLC, distereomeric recrystallization, or chiral synthesis provided the required optically active materials.

2.5 Lead optimization. Lead optimization efforts were focused on appending hydrophobic, aryl terminal groups to the C5 position of the indazole via a variety of linkers Table 3. To this end, a comprehensive set of compounds was synthesized consisting of ethers (**30**, **31**), acetamides (**32**, **33**), sulfonamides (**34**, **35**), ureas (**36**, **37**, **38)**, sulfamides (**39**, **40**) and carboxamides (**41**, **42**, **43**). Acetamides, ureas and carboxamides proved to be potent TTK inhibitors and the most active analogs in each class i.e. **33**, **37** and **42**, respectively, inhibited HCT116 cell growth in the single digit micromolar range. To gauge the suitability of these series for extensive lead optimization efforts we measured their plasma exposure in mice upon IP dosing at 25 mg/kg. Acetamide **33** attained micromolar levels ($AUC_{0\text{-}last}$ 0.72 μg·h/mL) whereas urea **37** could not be detected; this was attributed to the compounded effects of reduced solubility and permeability of the latter (Table 6).

The SAR (Tables 2 & 3) points to the importance of the linker in conferring optimal activity. To better understand these effects, we masked the potential hydrogen bond donors by introducing an N-methyl group in the urea linker (**38**) and amide linker (**43).** This modification resulted in a loss in enzymatic activity as illustrated by the matched pairs **41** and **37** and was especially significant for the urea. A loss of activity was also observed on replacement of the proximal nitrogen in the urea **36** with carbon (entry **45**) and by isomeric displacement of the amide linker (entry **44**). *In toto*, these observations pointed to the significance of the presence and position of the amide and/or urea functionality, perhaps in the formation of an H-bond interaction or by enforcing a binding conformation.

Based on these results, subsequent efforts focused exclusively on the two types of the amide-linked compounds (Table 4). Carboxamide and acetamide congeners were effective inhibitors of TTK; in many cases the activities for the matched pairs **33/42** (Table 3); **50/49** and **61/62** were remarkably similar. In other matched sets one or other of these linkers was more effective: acetamide **51** was about 4-fold more potent than carboxamide **52** whereas carboxamide **55** was appreciably more active than acetamide **54**. We noted that the optimal distance from the hydrophobe to the indazole attachment was 4 bonds (e.g. acetamides **32**, **33** and carboxamide **42**). Shorter distances of 3 bonds (**16**) and longer distances of 5 bonds (**46**) were less effective. The nature of the terminal hydrophobe was also probed; the pyridines were less effective than phenyl, whereas thiophenes was generally more active (entries **47**, **48**, **32** and **33**). Ortho mono and *o*,*o*-disubstitutions of the terminal ring were found to be greatly advantageous in terms of the biochemical as well as antiproliferative properties, as exemplified by compounds **49**, **50** and **51**.

With the exception of α-gem-disubstitution (examples **53**, **54**), α-substitution by small side chains such as alkyls, alkoxides, and amines led to a significant improvement in cellular GI_{50}'s and also to lesser extent in enzyme IC_{50}'s (examples **32** and **56**, **63**, **67** in Table 5). An α-amino modification was particularly beneficial as illustrated by the results for matched pairs: *i*-Pr/NMe_2, (**57/67**) c-pentyl/pyrrolidinyl (**60 /70**) and c-hexyl/piperidinyl (**61 /71**). The 2-ethylphenyl (**72**) and thiophen-3-yl (**73**) alpha-amines emerged as the two most potent molecules from this group with IC_{50}'s of 3.6 and 2.9 nM and GI_{50}'s of 0.1 and 0.07 μM respectively. The sense of chirality of the α-substituent did not appear to have great significance as illustrated by matched racemates and enantio-enriched pairs: **63 /64 /65** and **67 /68 /69** (Table 5). These results were consistent with the molecular modeling findings that aromatic and alkylamino groups occupy a large hydrophobic pocket and engage in relatively non-specific interactions.

2.6 X-ray structure

During the course of this work we obtained an X-ray co-complex crystal structure of the potent TTK inhibitor **32** and the TTK kinase domain at 2.2 Å resolution (PDB 4JT3, Figure 2). The kinase is in a DFG-in conformation with the inhibitor binding into the ATP binding site of the enzyme. Only part of the activation loop is resolved and a PEG unit is not seen in the electron density (Figure 4 supplementary material). It should be noted that the published TTK structures available during the course of this work were characterized by the presence of a PEG unit in the ATP binding site.[42] More recently, TTK/small molecule co-complex structures have been reported wherein the PEG unit is absent.[31,33,35] The salient features of our co-complex X-ray structure (Figure 2) include extensive hydrophobic contacts between ligand and protein (Val539, Met602, Ile531), two hydrogen bonds to hinge residues (Glu603 and Gly605), as well as two hydrogen bonds of the sulfonamide nitrogen to the backbone carbonyls of Gly605 and Asn606. The carbonyl of the acetamido group of inhibitor **32** makes a hydrogen bond to Lys553 (N-O 2.83 Å); this result explains the preference for amide linkers at this position. This interaction was not always seen in the models based on the 3CEK structure (wherein a bound PEG unit was wound around Lys553) and represented a significant advance in our understanding of the SAR. However, no direct H-bond to the amide NH is observed suggesting that the N-Me capping of the nitrogen reduces potency through a conformational or steric effect. Inspection of the co-complex X-ray structure (Figure 2) reveals a larger packet at the position alpha to the amide carbonyl. Modeling indicated that α-substituents would result in compounds with increased hydrophobic interactions as represented by the more potent inhibitors of Tables 4 and 5.

2.7 In vitro profile and kinase selectivity. Selected TTK inhibitors, **32**, **63** and **73** were profiled against a panel of 55 kinases (Millipore, Dundee, Scotland) at a screening concentration of 1 μM. This data is presented as a heat map (Figure 3) and of the 55 kinases tested only a handful are appreciably inhibited at the screening concentration of 1 μM (Supplementary Material). In this panel, our TTK inhibitors display a selectivity profile somewhat more selective than sorafenib and less than imatinib, two

clinically useful kinase inhibitors. In addition, IC_{50}s were determined for compounds **72** and **73** against a panel of mitotic kinases (Table 6). Four kinases were inhibited at the sub-micromolar level namely PLK4, AuroraA, Aurora B and CHK2 with IC_{50}'s of 0.083, 0.40, 0.48, and 0.42 μM and 0.089, 0.9, 0.72, and 0.1 μM for compounds **72** and **73**, respectively. Thus, **72** and **73** are selective inhibitors of TTK being at least 1.5 orders of magnitude more potent against the target vis a vis relevant mitotic kinases. The compounds also exhibited a desirable cytochrome P450 inhibition profile with IC_{50} values approximately 3 orders of magnitude greater than the TTK IC_{50} (Table 6).

Three cancer cell lines (HCT116, MDA-MB-468, A549) were chosen to monitor the growth inhibitory effects of these compounds. These lines are well-characterized, encompass some of the major human cancer types (breast, colon, lung) and thus demonstrate the spectrum of cellular activities achievable with our inhibitors. TTK is overexpressed in each of these cancer cell lines relative to their normal tissue counterparts.[3] As a group these compounds had variable effects on cell growth inhibition; GI_{50}s were in the sub-micromolar range for the HCT116, MDA-MB-468 and A549 cell lines (Table 5). In particular, compound **72**, attenuates cell growth of HCT116 cells with GI_{50} of 0.10 μM. Compound **72** also inhibits the cell growth of A549, MD-MB-468, OVCAR-3 andSW620 cancer cell lines with GI_{50}'s of 0.16, 0.66, 1.3, and 0.21, respectively.

A correlation between TTK inhibition and GI_{50} values is presented in Figure 4; there is a clear relationship between the two values (pGI_{50} vs pIC_{50} slope = 0.81, R^2 = 0.59). In an attempt to improve the correlation a limited subset of physicochemical parameters were evaluated; of these, logP (a surrogate for cell permeability) had the greatest effect and improved the correlation to an R^2 of 0.72. Note that the outliers present in the direct correlation (compounds **32**, **33** and **39**) are eliminated by the introduction of the second variable, logP. Besides statistical variation, the remaining variance observed may indicate that additional unrecognized factors such as for example, binding kinetics and transporter affinity, contribute to the observed cell growth inhibition. The results support the hypothesis that TTK inhibition is a driver of cell growth inhibition. The graph also allows us to estimate the average shift between the two values (TTK IC_{50} and HCT116 GI_{50}) which is about 1.5 log units. A shift of this kind

is often seen for anti-proliferative kinase inhibitors including TTK inhibitors,[31,35] although the magnitude is variable, depending not only on the compound properties but also the specific methods used to determine the two values. That being said, it would appear that the inhibitors from this series are less permeable than compounds with more drug-like properties.

2.8 Cell cycle analysis. To verify the mechanism of action of inhibitors **72** and **73**, we examined their ability to override the mitotic checkpoint in nocodazole-arrested cells, and analyzed their effect on cell cycle progression. Similarly to TTK silencing by RNAi,[43] inhibitors **72** and **73** promoted mitotic checkpoint bypass with phospho-histone H3 EC_{50} values of 0.52 μM and 0.42 μM, respectively. Cell cycle analysis showed that both inhibitors caused massive aneuploidization of cells at 1 μM and cell death as indicated by sub-G1 cells (Figure 5) recapitulating the TTK RNAi phenotype in HCT116 cells. The polyploidy phenotype, typical of Aurora B inhibitors, was not observed. On the other hand, a much weaker TTK inhibitor **74** (TTK IC_{50} 0.054 μM, HCT116 GI_{50} 0.78 μM) did not induce any change in the cell cycle up profile to the concentration of 2.5 μM. These data support that TKK inhibitors **72** and **73** are acting on target in the HCT116 cell line.

2.9 In vivo efficacy. In anticipation of an *in vivo* efficacy experiment, the plasma levels of compound **72** were determined in mice at 25 mg/kg IP and PO dosing. Upon IP dosing a C_{max} of 4.8 μg/mL and AUC of 3.0 μg·h/mL were obtained as compared to a C_{max} of 0.13 μg/mL and AUC of 0.14 μg·h/mL for PO dosing. The result for IP dosing corresponds to a plasma level of about 6 μM, well above the GI_{50} in HCT116 cell line and accordingly IP was selected as the preferred route of administration. Figure 6 shows the results of the xenograft experiment using an HCT116 mouse xenograft model. At 15 mg/kg daily IP dose, 5-fluorouracil (5-FU), a literature standard,[44] achieved a 46 % reduction in tumor volume compared to the negative control. Upon IP dosing of the TTK inhibitor **72** at 12.5 and 25 mg/kg QD, the compound demonstrated a dose dependent tumor growth inhibition (TGI) of 10 % and 66 %, respectively. In the 12.5 mg/kg BID arm we observed a TGI of 46% i.e. comparable to the positive control 5-FU. One mouse was lost at 25 mg/kg QD but there was no significant weight loss in the remaining animals or in any of the other arms of the study.

3 Conclusions

TTK was identified by an in-house siRNA screen and supporting in-house and literature validation efforts as a novel target for anti-cancer drug discovery. A screening campaign led to identification of the 3-arylindazole core for subsequent validation work. Substitution of the indazole core with key sulfamoylphenyl and amide moieties at positions 3 and 5 respectively established a novel class of TTK inhibitors. Systematic optimization of the 3-(1H-indazol-3-yl)benzenesulfonamide series, supported by computer modeling and X-ray co-crystal structure, yielded inhibitors with nanomolar activity against TTK. Selected inhibitors from this series recapitulate the phenotype of TTK silencing RNAi on HCT116 colon cancer cells.

Representative inhibitors were selected for additional studies. Compounds **72** and **73** are potent against TTK (IC_{50} = 3.6 and 2.9 nM respectively); the later shows selectivity against a broad panel of kinases. TTK inhibitor **72** demonstrated a dose dependent inhibition of HCT116 tumor growth, comparable to the standard of care 5-fluorouracil. The data reported herein, on this new class of antimitotic agents, illustrates the potential of these novel TTK inhibitors for cancer therapy. However the series suffers from some shortcomings; lack of oral exposure being among them. Further efforts detailing the optimization of physicochemical properties and in vivo performance, culminating in and the identification of a development candidate, will be disclosed in due course.

4 Experimental

4.1 Computational Methods.

Modified 3CEK Structure: The 3CEK structure was modified prior to use in virtual screening experiments. The bound PEG ligand of the first chain was removed and the active site of the resulting structure was subjected to molecular dynamics simulations. In a 10 ns simulation the binding site remained largely unchanged; this version was subsequently handled as an apo-structure and used for virtual screening experiments. Limited molecular dynamics simulation of the 3CEK structure was performed using MOE with the OPLS-AA force field,[45] using the GB/VI continuum solvation model.[46] Subsequently, the conformation of Lys553 was modified by using the Rotamer Explorer in MOE,

followed by the local energy minimization of the side chain, the rest of the structure being held frozen in place.

Docking Experiments: Most of the molecule handling was performed from within the MOE software.[47] First ligand pKa values were determined using ADMET Predictor.[48] Molecules were protonated, deprotonated according to their predicted predominant protonation state at pH 7 and if predicted pKa values fell between 6-8, all relevant protonation states were simultaneously considered. All relevant stereoisomers were generated using the stergen setting in Corina.[49] This was followed by a conformational analysis using the Conformation Import in MOE (up to 20 conformers in a 1 kcal/mol energy window) to generate multiple input copies in agreement with our previous docking recommendation[50,51] followed by the minimization of these structures using the MMFF94x forcefield in MOE The modified protein structures were first prepared using the Protonate3D process in MOE, which assigns relevant ionization states for the residues and finds the most favorable positions for hydrogens. For the purposes of Glide docking, the Protein Preparation wizard in the Schrodinger suite[52] was utilized next. Molecules were docked using the Glide XP software.[53] Hinge hydrogen bond constraints to Glu603 and Gly605 were applied in all cases to ensure correct top-scoring ligand poses.

4.2 Chemistry

4.2.1 General Experimental Methods. Commercially available starting materials, reagents, and solvents were used as received. In general, anhydrous reactions were performed under an inert atmosphere such as nitrogen or Ar. Microwave reactions were performed with a Biotage Initiator microwave reactor. In most cases, the yields were not optimized. Reaction progress was generally monitored by TLC using Merck SiO_2 plates with visualization by UV at 254 nm, by analytical HPLC or by LCMS (Bruker Exquire 4000). Flash column chromatographic purification of intermediates or final products was performed using 230-400 mesh SiO_2 60 from EMD chemicals. Preparative TLC SiO_2 plates with l mm thickness were purchased from SiliCycle Inc. Final products were also purified by preparative reverse-phase HPLC on a Varian PrepStar model SD-1HPLC system with a Varian MonoChrom 10u C-18 reverse-phase column using a gradient of about 5-30 % MeCN/ H_2O + 0.05 % TFA to 70-100%

MeCN/H_2O + 0.05% TFA over a 20-40-min period at a flow rate of 30-50 mL/min. Fractions containing the desired material were concentrated and lyophilized to obtain the final products. Nuclear magnetic resonance spectra were recorded on a Bruker AV 400 spectrometer using Bruker 5 mm probe PABBO BB-1H/D Z-GRD Z108618/0004. Chemical shifts were reported in parts per million (ppm) from tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low resolution mass spectra (MS ESI) were obtained using a Bruker Esquire 4000 spectrometer under electric spray ionization conditions. High resolution mass spectra (HRMS) were obtained by a Waters Acquity UPLC coupled with a Waters Synapt G2 time-of-flight mass spec, using an ESI source. Compounds in DMSO solutions (5 mg/mL) were diluted to 0.01 mg/mL; 5uL was injected on to a Waters BEH C18 1.7 um 2.1x100 mm column equilibrated at 10% MeCN (solvent B) in H_2O (solvent A) spiked with 0.1 % formic acid at a flow rate of 0.5 mL/min. Bound analytes were eluted by a linear gradient of 10 to 95 % B, between 1 and 8 min. The mass spectrometer was calibrated using formate clusters; leucine enkephalin was used as a"lock mass" for additional, real-time, accurate- mass correction. The purity of all compounds was determined by (A) LCMS (Phenomenex Gemini C18 column, 50 mm x 4.6 mm, 3μm), with gradient of 10-90% MeCN in H_2O (with 0.1% formic acid in each mobile phases), with UV detection at λ = 254 or 214 with an Agilent 1100 Series; or (B) analytical HPLC (Varian MonoChrom C18 column, 100 mm x 4.6 mm, 10 μm), with gradient of 10-90% MeCN in H_2O (with 0.1% TFA in each mobile phases), with UV detection at λ = 254 and 214 or 325 nm with a Varian ProStar 335 LC detector. PorapPak® Rxn CX refers to a commercial cation-exchange resin available from Waters.

Optical Rotations were measured at the sodium D-line (589.44 nm) using an AA-55 Polarimeter from Optical Activity Ltd with a 2.5x100 mm unjacketed stainless steel tube at given sample concentrations (c, units of g/100mL). Chiral supercritical fluid chromatography (SFC) analyses were performed at Lotus Separations, LLC, using Chiralpak AS-H (25 x 0.46 cm) 30% *i*-BuOH(0.1% DEA)/CO_2, 100 bar 3 mL/min, detecting at 220 and 254 nm. Compound names were generated using the software built into ChemBioDraw Ultra version 12.0.

Method A (amide coupling)

A DMF solution of 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (1.0 equiv), DIPEA (N,N-diisopropylethylamine, 3 equiv) and RCO_2H (1.05 equiv) at 0 ^oC was treated with TBTU (O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate) (1.05 equiv) added in one portion. The reaction was stirred allowing slowly to warm to rt. After several hours or overnight stirring the crude reaction was purified directly by preparative HPLC.

Alternatively, a DMF solution of 3-(3-sulfamoylphenyl)-1H-indazole-5-carboxylic acid (1.0 equiv), DIPEA (3 equiv) and RR'NH (1.05 equiv) at 0 ^oC or rt was treated with TBTU (1.05 equiv) added in one portion. The reaction was stirred allowing slowly to warm to rt. After several hours or overnight stirring the crude reaction was purified directly by prepHPLC.

Method B (iodination)

To a cooled (0 ^oC) DMF solution indazole (1.0 equiv) and K_2CO_3 or KOH (~3 equiv) was added I_2 (2-4 equiv) in one portion. The reaction was stirred with cooling or rt for several h and then was treated with xs 10 % aq $NaHSO_3$ and subsequently diluted with H_2O. In the majority of examples a filtration and washing (H_2O) of the precipitate provided the desired material with the required purity.

Method C (Suzuki-Miyaura cross coupling)

A mixture of 3-iodo-1H-indazole (1.0 equiv), $ArB(OH)_2$ or $ArB(OR')_2$ (1.2 equiv), xs base (typically 3-4 equiv, Na_2CO_3, K_2CO_3, $NaHCO_3$, Cs_2CO_3 or KF) and palladium catalyst (0.05 equiv, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ or $PdCl_2$(dppf)) in solvents (DME/H_2O, DME/H_2O/EtOH, PhMe/EtOH/H_2O or DMF/H_2O) was degassed with Ar and heated sealed in a microwave reactor (110-130 ^oC, 1 h). The crude material after passing through Celite using MeOH to rinse the pad was purified by preparative HPLC or flash chromatography on SiO_2.

Method D (Petasis borono-Mannich reaction)

To a mixture of arylboronic acid (5 mmol) and glyoxylic acid monohydrate (460 mg, 5 mmol) in CH_2Cl_2 (25 mL) was added dialkylamine (5 mmol). The resulting mixture was stirred overnight at rt. After evaporation of solvents, it was used as crude or purified by column chromatography.

4.2.2 Synthesis of 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide (21). *tert-Butyl 1H-indazol-5-ylcarbamate.* A DMF (15 mL) solution of 1H-indazol-5-amine (1.0 g, 7.5 mmol) and DIPEA (2.0 mL, 11 mmol) was treated with Boc_2O (1.7 g, 7.7 mmol) (50 % added in one portion as a solid, and 50 % as a solution in anh DMF (1 mL)) at 0 °C. The reaction was stirred with the cooling for 1.5 h and then allowed to warm slowly to rt overnight. Later it was diluted with H_2O to ~ 100 mL. A tan precipitate was collected by filtration, washed with H_2O and dried to afford the product as a light tan solid (1.7 g, 94 %). ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 12.90 (s., 1 H), 9.27 (s, 1 H), 7.94 (s, 1 H), 7.87 (br.s, 1 H), 7.41 (d, *J* = 8.80 Hz,1 H), 7.33 (d, *J* = 9.2Hz, 1 H), 1.47 (s, 9 H). MS ESI 233.9 $[M + H]^+$, calcd for $[C_{12}H_{15}N_3O_2 + H]^+$ 234.1 .

tert-Butyl 3-iodo-1H-indazol-5-ylcarbamate. To a cooled (0 ° C) DMF (30 mL) solution t-butyl 1H-indazol-5-ylcarbamate (1.6 g, 6.9 mmol) and K_2CO_3 (3.8 g, 27.6 mmol) was added I_2 (1.8 g, 7.1 mmol) in one portion. The reaction was stirred with cooling for 3 h and then treated with 10 % aq $NaHSO_3$ (50 mL) and subsequently with H_2O (150 mL). A filtration and washing (H_2O) of the precipitate provided crude material which after purification by flash chromatography (SiO_2, 70 g, 0 to 6 % MeOH in DCM) and recrystallization from EtOAc/hexanes yielded tert-butyl 3-iodo-1H-indazol-5-ylcarbamate as an off-white solid (1.9 g, 78 %). ^{1}H NMR (400 MHz, *acetone-d_6*) δ ppm 12.54 (br. s., 1 H), 8.51 (br. s., 1 H), 7.87 (br.s., 1 H), 7.24 - 7.66 (m, 2 H), 1.51 (s, 9 H); MS ESI $[M + H]^+$ 359.9, calcd for $[C_{12}H_{14}IN_3O_2 + H]^+$ 360.0.

tert-butyl 3-(3-sulfamoylphenyl)-1H-indazol-5-ylcarbamate

t-Butyl 3-iodo-1H-indazol-5-ylcarbamate (100 mg, 0.28 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (118 mg, 0.42 mmol) and KF (50 mg, 0.86 mmol) in DMF (2 mL) and H_2O (0.7 mL) were degassed by evacuation and refill with Ar (3x). $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) was then added and the degassing was repeated. The reaction mixture was heated (sealed, microwave reactor) at 120 °C for 1.5 h. The crude material was concentrated under reduced pressure and then purified by flash chromatography (SiO_2, 50 g, 0 to 10 % MeOH in DCM) to provide tert-butyl 3-(3-sulfamoylphenyl)-1H-indazol-5-ylcarbamate as a white solid (76 mg, 70 %). ^{1}H NMR (400 MHz,

CD_3OD) δ ppm 8.48 (s, 1 H), 8.21-8.14 (m, 2 H), 7.94 (d, *J* =8.0 Hz, 1 H), 7.72 (t, *J* =7.8 Hz, 1 H), 7.52 (d, *J*=9.2 Hz,1 H), 7.42 (d, *J*=9.2 Hz, 1 H), 1.55 (s, 9H); MS ESI $[M + H]^+$ 389.2 (100), calcd for $[C_{18}H_{20}N_4O_4S + H]^+$ 389.2.

3-(5-Amino-1H-indazol-3-yl)benzenesulfonamide. A suspension of tert-butyl 3-(3-sulfamoylphenyl)-1H-indazol-5-ylcarbamate (0.56 g, 1.4 mmol) in DCM (30 mL) was treated with TFA (10 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and then at rt for 1 h. Concentration under reduced pressure and drying in vacuo afforded the title compound as a light beige solid (TFA salt, 0.58 g, quant). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.47 (s, 1 H), 8.17 (d, *J* = 8.28 Hz, 1 H), 8.02 (s, 1 H), 7.98 (d, *J* = 7.53Hz, 1 H), 7.70 - 7.78 (m, 2 H), 7.42 (d, *J* = 9.29 Hz, 1 H). MS ESI $[M + H]^+$ 288.9, calcd for $[C_{13}H_{12}N_4O_2S + H]^+$ 289.1. HPLC: 95A% at 254 nm.

4.2.3 (E)-3-(2-(Pyridin-4-yl)vinyl)-1H-indazole-6-carbonitrile (1). To a suspension of 4-(chloromethyl)pyridine hydrochloride (3.28 g, 20 mmol) in PhH (50 mL) was added 40 % aq NaOH (1.35 mL). The resulting mixture was sonicated for 10 min and filtered. The residue was treated with additional PhH (10 mL), sonicated and filtered. The combined PhH layers were dried (Na_2SO_4) to give a solution of 4-(chloromethyl)pyridine in PhH.

To a solution of diethyl phosphate (3.03 g, 22 mmol) in PhH (35 mL) was added freshly cut Na (510 mg, 22 mmol). The resulting mixture was refluxed (oil temp. 90 °C) for 30 min then cooled to 0 °C. The solution of 4-(chloromethyl)pyridine in PhH obtained above was added dropwise to this solution via dropping funnel over 10 min. After addition, the resulting mixture was refluxed for 3 h (oil temp. 100 °C) and LC-MS indicated the completion of reaction. After cooling to rt, the insoluble white precipitate (NaCl) was filtered off and rinsed with PhH (20 mL). The filtrate was concentrated and dried under high vacuum to give 3.50 g colorless oil which was redissolved in DMF (25 mL). It was cooled to 0 °C and treated with *t*-BuOK (3.36 g, 30 mmol) portion wise over 2 min; the reaction turned dark reddish brown. After stirring for 2 min at 0 °C, a solution of 3-formyl-1H-indazole-6-carbonitrile[54] (1.71 g, 10 mmol) in DMF (15 mL) was added dropwise by pipette over 5 min. After addition, the resulting mixture was stirred for 40 min at 0 °C before quenching with ice, 2 M aq HCl, H_2O and adjusted pH to about 8 using

$NaHCO_3$. The resulting precipitate was collected by filtration and rinsed with H_2O, then dried under high vacuum to give the title compound (2.016 g, 82%) as a beige solid. ^{1}H NMR (400 MHz, *DMSO-d_6*) δ 13.90 (s, 1 H), 8.60- 8.54 (m, 2 H), 8.43 (d, *J* = 8.0 Hz, 1 H), 8.20 (s, 1 H), 7.88 (d, *J* = 16.8 Hz, 1 H), 7.73-7.67 (m, 2 H), 7.60-7.52 (m, 2 H); MS ESI 247.0 $[M + H]^+$, calcd for $[C_{15}H_{10}N_4 + H]^+$ 247.1. HRMS (ESI) *m/z* calcd for $[C_{15}H_{10}N_4 + H]^+$ 247.0984 , found 247.0985; HPLC: >99A% at 214 nm.

4.2.4 Synthesis of 3-(Pyridin-3-yl)-1H-indazole-6-carbaldehyde (2). *3-Iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde and 3-iodo-2-(2-(trimethylsilyl)ethyl)-2H-indazole-6-carbaldehyde.* To a stirred suspension of 3-iodo-1H-indazole-6-carbaldehyde (3.01 g, 11.1 mmol) and TBAB (36 mg, 0.11 mmol) in CH_2Cl_2 (70 mL) and 50 % aq. KOH (20 mL) was added, dropwise, (2-(chloromethoxy)ethyl)trimethylsilane (2.3 mL, 13.3 mmol) at 0 °C. The stirring was continued at 0 °C for 3 h. The solution was then diluted with CH_2Cl_2 (200 mL), the layers were separated and the organic phase was washed with brine (2 x 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 100 % CH_2Cl_2) to give of the N-1 isomer (higher eluting spot, 2.88 g, 65 %) and the N-2 isomer (lower eluting spot, 757 mg, 17 %). ^{1}H NMR N-1 isomer: (400 MHz, *$CDCl_3$*) δ 10.18 (s, 1 H), 8.11 (s, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 5.82 (s, 2 H), 3.60 (m, 2 H), 0.91 (m, 2 H), -0.042 (s, 9 H); MS ESI 425.0 $[M + Na]^+$, calcd for $[C_{14}H_{19}IN_2O_2Si + Na]^+$ 425.02. N-2 isomer : (400 MHz, *CD_3OD*) 10.09 (s, 1 H), 8.31 (s, 1 H), 7.62 (m, 2 H), 5.91 (s, 2 H), 3.71 (m, 2 H), 0.92 (m, 2 H), -0.039 (s, 9 H); MS ESI 425.0 $[M + Na]^+$, calcd for $[C_{14}H_{19}IN_2O_2Si + Na]^+$ 425.0.

3-(Pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde. A mixture of 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (100 mg, 0.25 mmol), pyridin-3-ylboronic acid (37 mg, 0.30 mmol), $PdCl_2(PPh_3)_2$ (17 mg, 0.025 mmol) and 2 M aq Na_2CO_3 (0.13 mL, 0.25 mmol) in DME/H_2O/EtOH (1.4 mL/0.4 mL/0.2 mL) was degassed by evacuation and refilling with Ar. The reaction mixture was sealed and heated with stirring under microwave irradiation at 125 °C for 2 h. The crude reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography on SiO_2 using 20-40% EtOAc/hexanes as eluent to give the desired product as a

white solid (70 mg, 79 %). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 10.16 (s, 1 H), 9.22 (d, *J* =1.8 Hz, 1 H), 8.67 (dd, *J* =4.8, 1.5 Hz, 1 H), 8.25 (ddd, *J* = 7.9, 1.9, 1.8 Hz, 1 H), 8.16 (s, 1 H), 8.10 (d, *J* = 8.3Hz, 1 H), 7.81 (dd, *J* = 8.3, 1.0 Hz, 1 H), 7.45 (dd, *J* = 7.9, 4.9 Hz, 1 H), 5.87 (s, 2 H), 3.64 (t, *J* = 8.5 Hz, 2 H), 0.92 (t, *J* = 8.3Hz, 2 H), -0.07 (s, 9 H).

3-(Pyridin-3-yl)-1H-indazole-6-carbaldehyde. A solution of 3-(pyridin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole-6-carbaldehyde (70 mg, 0.20 mmol) in THF (10 mL) was treated with TBAF (1.0 mL of a 1 M in THF) and refluxed for 24 h. The solvent was removed and the residue re-dissolved into EtOAc. The organics were washed with H_2O (2x), brine (2x) and then dried ($MgSO_4$). The solvent was removed and the solid was triturated with EtOAc to give the title compound as a pale yellow powder (5 mg, 11 %). ^{1}H NMR (400 MHz, *CD$_3$OD*) δ ppm 10.15 (s, 1 H), 9.19 (d, *J* =1.8 Hz, 1 H), 8.61 (dd, *J* =4.8, 1.5 Hz, 1 H), 8.47 (dt, *J* = 8.0, 2.3Hz, 1 H), 8.19 - 8.24 (m, 2 H), 7.81 (d, *J* = 9.5 Hz, 1 H), 7.63 (dd, *J* = 8.2, 5.1Hz, 1 H); MS ESI 224.0 $[M + H]^+$, calcd for $[C_{13}H_9N_3O + H]^+$ 224.07. HPLC: > 99A% at 214 nm.

4.2.5 3-Phenyl-1H-indazole (3). The title compound was synthesized according to the General Method C, utilizing iodo-1H-indazole (Sinova Inc., 40 mg, 0.16 mmol), phenylboronic acid (31 mg, 0.25 mmol), Na_2CO_3 (106 mg, 1.0 mmol), $PdCl_2$dppf*CH_2Cl_2 (12 mg, 0.015 mmol) in EtOH (5 mL) and H_2O (1 mL). After heating, sealed in microwave reactor for 3 h at 120 ^{o}C under Ar the reaction was filtered using MeOH to rinse the vial and the filter. The filtrate was concentrated and purified by flash chromatography (SiO_2, 0-40 % EtOAc in hexanes) to afford the desired product as a pale yellow solid (22.7 mg, 71 %). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 10.65 (br. s., 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 8.00-8.40 (m, 2 H), 7.52-7.58 (m, 2 H), 7.40-7.48 (m, 3 H), 7.22-7.28 (m, 1 H); MS ESI 195.2 $[M + H]^+$, calcd for $[C_{13}H_{10}N_2 + H]^+$ 195.1. HPLC: 97.3 A% at 254 nm, 98.3 A% at 300 nm.

4.2.6 3-(1H-indazol-3-yl)benzenesulfonamide (4). The title compound was synthesized according to the General Method C, utilizing iodo-1H-indazole (Sinova Inc., 30 mg, 0.12 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (42 mg, 0.15 mmol), K_2CO_3 (34 mg, 0.25 mmol), DME (1 mL), EtOH (1 mL), H_2O (0.5 mL) and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol). The degassed

solution was sealed and heated in a microwave reactor at 120 °C for 1 h. Purification by preparative HPLC provided the title compound as a white solid (21 mg, 63 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.51 (s, 1 H), 8.20 (d, *J* = 7.8 Hz, 1 H) 8.09 (d, *J* = 8.3Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.70 (t, *J* = 7.8 Hz, 1 H), 7.60 (d, *J* = 8.5 Hz, 1 H), 7.46 (t, *J* = 7.4 Hz, 1 H), 7.27 (t, *J* = 7.2Hz, 1 H); MS ESI 274.0 $[M + H]^+$, calcd for $[C_{13}H_{11}N_3O_2S + H]^+$ 274.1. HPLC: 98A% at 254 nm.

4.2.6 3-(4-Chloro-1H-indazol-3-yl)benzenesulfonamide (5). To a stirred mixture of 4-chloro-3-iodo-1H-indazole (0.18 g, 0.65 mmol) and TBAB (4 mg, 0.01 mmol) in CH_2Cl_2 (20 mL) and 50 % aq. KOH (20 mL) was added, dropwise, (2-(chloromethoxy)ethyl)trimethylsilane (0.13 g, 0.78 mmol) at 0 °C. The stirring was continued at 0 °C for 70 min and then at rt for 3 h. The solution was then diluted with CH_2Cl_2 and brine. The layers were separated and the organic phase was washed (H_2O, brine) , dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-6 % EtOAc in hexanes) to give of 2:1 mixture of 4-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole and 4-chloro-3-iodo-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-indazole as a pale yellow gum (0.23g, 85 %). MS ESI 408.9 $[M + H]^+$, calcd for $[C_{13}H_{18}ClIN_2OSi+H]^+$ 409.0. The mixture of isomers (100 mg, 0.24 mmol) was subjected to Suzuki-Miyaura coupling following the method described for 3-(1H-indazol-3-yl)benzenesulfonamide (**4**) using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (76 mg, 0.27 mmol), Cs_2CO_3 (0.16 g, 0.50 mmol), $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) in H_2O (1 mL) and DME (4 mL). After 40 min of microwave heating at 100 °C under Ar, the reaction was portioned between EtOAc and H_2O, the organic layer was washed (satd aq $NaHCO_3$, brine), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by preparative TLC (SiO_2, using 5:1 hexanes:EtOAc) to afford 3-(4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-3-yl)benzenesulfonamide as colorless gum (69 mg, 64 %), ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 8.29 (t, *J* =1.50 Hz, 1 H), 7.99 (dq, *J* = 8.00, 0.80 Hz, 1 H), 7.94 (dt, *J* = 7.50, 1.50 Hz, 1 H), 7.61 (t, *J* = 7.80 Hz, 1 H), 7.56 (dd, *J* = 8.53, 0.75 Hz, 1 H), 7.38 (dd, *J* = 8.41, 7.40 Hz, 1 H), 7.23 (dd, *J* = 7.53, 0.75 Hz, 1 H), 5.78 (s, 2 H), 4.97 (br. s. 2 H), 3.61 (dd, *J* = 8.78, 7.78 Hz, 2 H), 0.91 (t, *J* = 8.30 Hz, 2 H), -0.05 (s, 9 H).; MS ESI 438.1 $[M + H]^+$, calcd for

$[C_{19}H_{24}ClN_3O_3SSi+ H]^+$ 438.1 An oven-dried round bottom was charged with 3-(4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-3-yl)benzenesulfonamide (34 mg, 0.078 mmol), and CH_2Cl_2 (5 mL) under an atmosphere of N_2. $BF_3{\cdot}OEt_2$ (0.1 mL, 0.8 mmol) was added dropwise and the reaction was stirred at rt for 2.5 h. The CH_2Cl_2 was removed under reduced pressure. A mixture of EtOH (4 mL) and 2 M aq HCl (1 mL) was added and the reaction was heated at 50 °C for 1 h. The reaction was cooled to rt and concentrated under reduced pressure. The residue was purified by preparative HPLC to give 3-(4-chloro-1H-indazol-3-yl)benzenesulfonamide as a white powder (15 mg, 63 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.23 (t, *J* =1.50 Hz, 1 H), 7.99 (dq, *J* = 7.80, 1.10 Hz, 1 H), 7.90 (dq, *J* = 7.80, 1.00 Hz, 1 H), 7.65 (t, *J* = 7.80 Hz, 1 H), 7.55 (dq, *J* = 8.30, 0.70 Hz, 1 H), 7.39 (dd, *J* = 8.30, 7.30 Hz, 1 H), 7.20 (dd, *J* = 7.30, 0.70 Hz, 1 H); MS ESI 308.0 $[M + H]^+$, calcd for $[C_{13}H_{10}ClN_3O_2S+ H]^+$ 308.0.. HRMS (ESI) *m/z* calcd for $[C_{13}H_{10}ClN_3O_2S+ H]^+$ 308.0261, found 308.0263; HPLC: 98A% at 254 nm.

4.2.7 4-(4-Chloro-1H-indazol-3-yl)benzenesulfonamide (6). 4-chloro-3-iodo-1H-indazole (30 mg, 0.12 mmol) was subjected to Suzuki-Miyaura coupling following the method described for 3-(1H-indazol-3-yl)benzenesulfonamide (**4**) using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (Frontier Scientific, 46 mg, 0.16 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.010 mmol) in aq Na_2CO_3 (1M, 0.2 mL) and DMF (0.8 mL). After heating in a microwave reactor for 1 h at 120 °C, the reaction mixture was cooled to rt, diluted with MeOH and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure and purified by preparative HPLC to afford the title compound as a white powder (14.4 mg, 29 %).^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.00 (d, *J* = 8.53Hz, 2 H), 7.85 (d, *J* = 8.50 Hz, 2 H), 7.55 (dd, *J* = 8.30, 0.50 Hz, 1 H), 7.39 (dd, *J* = 8.41, 7.40 Hz, 1 H), 7.20 (dd, *J* = 7.30, 0.75 Hz, 1 H); MS ESI 308.1 $[M + H]^+$, calcd for $[C_{13}H_{10}ClN_3O_2S + H]^+$ 308.0. HPLC: 99A% at 254 nm.

4.2.8 3-(4-Chloro-1H-indazol-3-yl)benzamide (7). 4-Chloro-3-iodo-1H-indazole (30 mg, 0.12 mmol) was subjected to Suzuki-Miyaura coupling following the method described for 3-(1H-indazol-3-yl)benzenesulfonamide (**4**) using (3-carbamoylphenyl)boronic acid (26 mg, 0.16 mmol) and $Pd(PPh_3)_4$ (12

mg, 0.010 mmol) in aq Na_2CO_3 (1 M, 0.2 mL) and DMF (0.8 mL). After heating in a microwave reactor for 1 h at 120 °C, the reaction mixture was cooled to rt, diluted with MeOH and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure and purified by preparative HPLC to afford the title compound as a white powder (13 mg, 44 %).^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.21 (t, *J* =1.50 Hz, 1 H), 7.97 (dq, *J* = 8.00, 1.00 Hz, 1 H), 7.86 (dq, *J* = 7.50, 0.80 Hz, 1 H), 7.58 (t, *J* = 7.50 Hz, 1 H), 7.54 (dd, *J* = 8.30, 0.50 Hz, 1 H), 7.38 (dd, *J* = 8.30, 7.30 Hz, 1 H), 7.19 (dd, *J* = 7.30, 0.50 Hz, 1 H);MS ESI 272.0 $[M + H]^+$, calcd for $[C_{14}H_{10}ClN_3O + H]^+$ 272.0. HPLC: 98A% at 254 nm.

4.2.9 (3-(4-Chloro-1H-indazol-3-yl)phenyl)methanamine (8). 4-Chloro-3-iodo-1H-indazole (30 mg, 0.12 mmol) was subjected to Suzuki-Miyaura coupling following the method described for 3-(1H-indazol-3-yl)benzenesulfonamide (**4**) using (3-(aminomethyl)phenyl)boronic acid hydrochloride (Frontier Scientific, 30 mg, 0.14 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.01 mmol), K_2CO_3 (50 mg, 0.36 mmol) in EtOH (1 mL), DME (1 mL) and H_2O (0.5 mL). After heating in a microwave reactor for 1 h at 120 °C, the reaction mixture was cooled to rt, diluted with MeOH and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure and purified by preparative HPLC to afford the title compound as a white powder (TFA salt, 22 mg, 49 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.76 (m, 2 H), 7.53 - 7.58 (m, 3 H), 7.39 (dd, *J* = 8.30, 7.30 Hz, 1 H), 7.19 (dd, *J* = 7.40, 0.63Hz, 1 H), 4.21 (s, 2 H);MS ESI 241.0 $[M - NH_2]^+$, calcd for $[C_{14}H_{12}ClN_3 - NH_2]^+$ 241.0. HPLC: 99A% at 254 nm.

4.2.10 Synthesis of 3-(4-(2,6-Difluorophenyl)-1H-indazol-3-yl)benzenesulfonamide (9). *4-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole*. SEMCl (0.65 mL, 3.6 mmol) was added dropwise at 0 °C to mixture of 4-chloro-1H-indazole (0.50 g, 3.3 mmol) and TBAB (10.5 mg, 0.03 mmol) in aq KOH (50 %, 40 mL) and DCM (60 mL). The reaction was stirred with cooling for 2 h and at rt for another 2 h before it was diluted with DCM. The layers were separated and the organic phase washed (H_2O, brine), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 0-6 % EtOAc in hexanes) to afford 4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole as a pale yellow oil (0.69 g, 75 %). ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 8.10 (d, *J* =1.00 Hz, 1 H), 7.48 (d, *J* = 8.28 Hz, 1 H), 7.33 (dd, *J* = 8.28, 7.53 Hz, 1 H), 7.18 (dd, *J* = 7.53, 0.50 Hz, 1 H),

5.74 (s, 2 H), 3.52 (s, 2 H), 0.85 - 0.91 (m, 2 H), -0.07 (s, 9 H); MS ESI 282.9 $[M + H]^+$, calcd for $[C_{13}H_{19}ClN_2OSi + H]^+$ 283.1.

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole. A mixture of 4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (107 mg, 0.38 mmol), KOAc (110 mg, 1.1 mmol), B_2pin_2 (286 mg, 1.1 mmol) and Pd_2dba_3 (6.8 mg, 0.007 mmol) in anh. dioxane (2mL) was degassed with Ar. S-Phos (6.2 mg, 0.02 mmol) was added and the degassing was repeated. The reaction mixture was heated sealed under microwave irradiation at 110 °C for 90 min. The reaction was then concentrated under reduced pressure filtered through a plug of two equal layers: one of SiO_2 and one of Celite using hexanes then 5:1 hexanes:EtOAc. The filtrate was concentrated under reduced pressure to afford 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole as an off white solid (130 mg, 75 %).^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.32 (d, *J* =1.00 Hz, 1 H), 7.79 (d, *J* = 8.50 Hz, 1 H), 7.66 (dd, *J* =6.80, 0.80 Hz, 1 H), 7.47 (dd, *J* = 8.50, 7.00 Hz, 1 H), 5.77 (s, 2 H), 3.54 (t, *J* = 7.80 Hz, 2 H), 1.42 (s, 12 H), 0.84 (t, *J* = 7.80 Hz, 2 H), -0.09 (s, 9 H); MS ESI 375.1 $[M + H]^+$, calcd for $[C_{19}H_{31}BN_2O_3Si + H]^+$ 375.2.

4-(2,6-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole. 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (130 mg, 0.35 mmol) was subjected to Suzuki-Miyaura coupling following the method described for 3-(1H-indazol-3-yl)benzenesulfonamide (**4**) using 2-bromo-1,3-difluorobenzene (81 mg, 0.42 mmol) and $Pd(PPh_3)_4$ (40 mg, 0.038 mmol) in Cs_2CO_3 (342 mg, 1.0 mmol), H_2O (1 mL) and DME (4 mL). After heating in a microwave reactor for 1 h at 100 °C, the reaction mixture was cooled to rt, diluted with EtOAc and washed (2 M aq NaOH, H_2O, H_2O-brine 1:1, brine). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 0-10 % EtOAc in hexanes) afforded 4-(2,6-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole as a pale yellow gum (121 mg, 97 %).^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 7.85 (d, *J* =1.00 Hz, 1 H), 7.66 (d, *J* = 8.53 Hz, 1 H), 7.53 (dd, *J* = 8.41, 7.15 Hz, 1 H), 7.35 - 7.46 (m, 1 H), 7.29 (d, *J* = 7.03 Hz, 1 H), 7.05 -

7.10 (m, 2 H), 5.80 (s, 2 H), 3.57 - 3.63 (m, 2 H), 0.88 - 0.94 (m, 2 H), -0.05 (s, 9 H); MS ESI 361.0 $[M + H]^+$, calcd for $[C_{19}H_{22}F_2N_2OSi + H]^+$ 361.1.

4-(2,6-Difluorophenyl)-1H-indazole. 4-(2,6-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (121 mg, 0.34 mmol) in anh DCM (5mL) was treated with $BF_3{\cdot}OEt_2$ (0.4 mL, 3.2 mmol) at rt. The reaction was sealed and stirred at for 2.5 h before being concentrated under reduced pressure. The residue was heated in EtOH (4 mL) and aq HCl (2 M, 1 mL) at 50 ^oC overnight. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (SiO_2, 0-2 % MeOH in DCM) and later preparative TLC (SiO_2 1 mm, 2 % MeOH in DCM, 2x) to afford 4-(2,6-difluorophenyl)-1H-indazole as a white solid (55 mg, 70 %);MS ESI 231.0 $[M + H]^+$, calcd for $[C_{13}H_8F_2N_2 + H]^+$ 231.1.

4-(2,6-Difluorophenyl)-3-iodo-1H-indazole

4-(2,6-difluorophenyl)-1H-indazole (48 mg, 0.21 mmol) was iodinated following method B using powdered KOH (44 mg, 0.8 mmol), I_2 (106 mg, 0.4 mmol) in DMF (5mL) to afford 4-(2,6-difluorophenyl)-3-iodo-1H-indazole as a white solid (57 mg, 77 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.11 (d, *J* = 8.53 Hz, 1 H), 6.90 - 6.99 (m, 2 H), 6.45 - 6.55 (m, 3 H);MS ESI 357.0 $[M + H]^+$, calcd for $[C_{13}H_7F_2IN_2 + H]^+$ 357.0.

3-(4-(2,6-Difluorophenyl)-1H-indazol-3-yl)benzenesulfonamide. 4-(2,6-difluorophenyl)-3-iodo-1H-indazole (20 mg, 0.06 mmol) was subjected to Suzuki-Miyaura coupling following General Method C using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (Frontier Scientific, 33 mg, 0.1 mmol), DME (1.3 mL), H_2O (0.3 mL), $NaHCO_3$ (20 mg, 0.24 mmol) and $Pd(PPh_3)_4$ (6.8 mg, 0.006 mmol). Purification by prep TLC (SiO_2 1 mm, 10 % MeOH-DCM) followed by prep HPLC afforded 3-(4-(2,6-difluorophenyl)-1H-indazol-3-yl)benzenesulfonamide as a white solid (3 mg, 14 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.80 (s, 1 H), 7.71 - 7.74 (m, 1 H), 7.69 (dd, *J* = 8.50, 0.50 Hz, 1 H), 7.55 (dd, *J* = 8.50, 7.00 Hz, 1 H), 7.18 - 7.25 (m, 3 H), 7.15 (d, *J* = 7.00 Hz, 1 H), 6.73 (dd, *J* = 8.30, 7.80 Hz, 2 H); MS ESI 386.2 $[M + H]^+$, calcd for $[C_{19}H_{13}F_2N_3O_2S + H]^+$ 386.1. HPLC: 95A% at 254 nm.

4.2.11 Synthesis of 3-(5-Phenyl-1H-indazol-3-yl)benzenesulfonamide (10). *5-Phenyl-1H-indazole*

Following General Method C, tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole-1-carboxylate (Ryan Scientific, 110 mg, 0.32 mmol), PhBr (50 mg, 0.32 mmol), Cs_2CO_3 (291 mg, 0.89 mmol) and $Pd(PPh_3)_4$ (17 mg, 0.016 mmol) in DME (3 mL), H_2O (0.75 mL) was heated sealed in a microwave reactor at 120 °C for 1.5 h. The reaction was concentrated and purified by prep TLC (SiO_2, 10 % MeOH in DCM). The material was stirred than with TFA (0.5 mL) in DCM (6 mL) at rt for 2.5 h. The reaction concentrated under reduced pressure and the crude 5-phenyl-1H-indazole was used directly in following step. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 13.08 (br. s., 1 H), 8.52 (s, 1 H), 8.07 (s, 1 H), 8.00 (dd, *J* = 9.00, 1.50 Hz, 1 H), 7.90 (d, *J* = 9.00 Hz, 1 H), 7.61 - 7.67 (m, 2 H), 7.52 (t, *J* = 7.53Hz, 2 H), 7.38 - 7.48 (m, 1 H); MS ESI 194.9 $[M + H]^+$, calcd for $[C_{13}H_{10}N_2 + H]^+$ 195.1.

3-Iodo-5-Phenyl-1H-indazole. 5-Phenyl-1H-indazole (59 mg, 0.30 mmol) was iodinated following General method B to afford purification by prep TLC (SiO_2, 2 % MeOH in DCM) 3-iodo-5-phenyl-1H-indazole as a light beige solid (81 mg, 83 %). ^{1}H NMR (400 MHz, *CD$_3$OD*) δ ppm 7.67 (dd, *J* = 8.66, 1.63Hz, 1 H), 7.59 - 7.64 (m, 3 H), 7.52 (dd, *J* = 8.66, 0.63Hz, 1 H), 7.43 (t, *J* = 7.65 Hz, 2 H), 7.32 (t, *J* = 7.28 Hz, 1 H); MS ESI 320.9 $[M + H]^+$, calcd for $[C_{13}H_9IN_2 + H]^+$ 321.0.

3-(5-Phenyl-1H-indazol-3-yl)benzenesulfonamide. 3-Iodo-5-phenyl-1H-indazole (40 mg, 0.12 mmol) was subjected to Suzuki-Miyaura coupling following General Method C using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (Frontier Scientific, 53 mg, 0.18 mmol), DMF (1.0 mL), H_2O (0.4 mL), Cs_2CO_3 (122 mg, 0.37 mmol) and $Pd(PPh_3)_4$ (7.2 mg, 0.0068 mmol). Purification by prep HPLC afforded 3-(5-phenyl-1H-indazol-3-yl)benzenesulfonamide as a white solid (10 mg, 24 %). ^{1}H NMR (400 MHz, *CD$_3$OD*) δ ppm 8.54 (s, 1 H), 8.23 (d, *J* = 7.78 Hz, 1 H), 8.20 (s, 1 H), 7.96 (d, *J* = 7.53Hz, 1 H), 7.65 - 7.77 (m, 5 H), 7.46 (t, *J* = 7.65 Hz, 2 H), 7.34 (t, *J* =6.80 Hz, 1 H); MS ESI 350.1 $[M + H]^+$, calcd for $[C_{19}H_{15}N_3O_2S + H]^+$ 350.1. HPLC: 99A% at 254 nm.

4.2.12 Synthesis of 3-(6-Phenyl-1H-indazol-3-yl)benzenesulfonamide (11). *3-(6-bromo-1H-indazol-3-yl)benzenesulfonamide.* 6-bromo-3-iodo-1H-indazole (70 mg, 0.22 mmol), was subjected to Suzuki-Miyaura coupling following General Method C using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (Frontier Scientific, 64 mg, 0.23 mmol), DME (1.2 mL), H_2O (0.3 mL),

$NaHCO_3$ (55 mg, 0.65 mmol) and $Pd(PPh_3)_4$ (25 mg, 0.02 mmol). After heating sealed under Ar in a microwave reactor at 120o for 1 h, the reaction was cooled to rt, diluted with MeOH and filtered through Celite. The filtrate was concentrated and purified by preparative HPLC to afford 3-(6-bromo-1H-indazol-3-yl)benzenesulfonamide as a white solid (19 mg, 25 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.48 (t, *J* =1.50 Hz, 1 H), 8.18 (dt, *J* = 7.91, 1.19 Hz, 1 H), 8.00 (d, *J* = 8.53Hz, 1 H), 7.95 (dq, *J* = 7.78, 1.00 Hz, 1 H), 7.80 (d, *J* =1.00 Hz, 1 H), 7.70 (t, *J* = 7.91Hz, 1 H), 7.38 (dd, *J* = 8.78, 1.76 Hz, 1 H); MS ESI 351.9/353.9 $[M + H]^+$, calcd for $[C_{13}H_{10}BrN_3O_2S + H]^+$ 352.0/354.0.

3-(6-Phenyl-1H-indazol-3-yl)benzenesulfonamide. 3-(6-bromo-1H-indazol-3-yl)benzenesulfonamide (19 mg, 0.053 mmol), was subjected to Suzuki-Miyaura coupling following General Method C using $PhB(OH)_2$ (10 mg, 0.082 mmol), DMF (1.6 mL), H_2O (0.3 mL), Cs_2CO_3 (54 mg, 0.16 mmol) and $Pd(PPh_3)_4$ (8 mg, 0.008 mmol). After heating sealed under Ar in a microwave reactor at 120 °C for 3 h, the reaction was diluted with DMSO, filtered and purified by preparative HPLC to afford 3-(6-phenyl-1H-indazol-3-yl)benzenesulfonamide as a white solid (7 mg, 37 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.54 (t, *J* =1.60 Hz, 1 H), 8.22 (ddd, *J* = 7.80, 1.80, 1.30 Hz, 1 H), 8.14 (dd, *J* = 8.50, 0.50 Hz, 1 H), 7.95 (ddd, *J* = 7.80, 1.76, 1.00 Hz, 1 H), 7.78 (q, *J* =0.80 Hz, 1 H), 7.70 - 7.74 (m, 3 H), 7.56 (dd, *J* = 8.53, 1.51Hz, 1 H), 7.48 (t, *J* = 7.30 Hz, 2 H), 7.38 (tt, *J* = 7.30, 1.30 Hz, 1 H); MS ESI 350.1 $[M + H]^+$, calcd for $[C_{19}H_{15}N_3O_2S + H]^+$ 350.1. HRMS (ESI) *m/z* calcd for $[C_{19}H_{15}N_3O_2S+ H]^+$ 350.0963, found 350.0959;HPLC: 99A% at 254 nm

4.2.13 Synthesis of 3-(4-Methoxy-1H-indazol-3-yl)benzenesulfonamide (12). *3-Iodo-4-methoxy-1H-indazole.* 4-Methoxy-1H-indazole (Sinova Inc., 60 mg, 0.40 mmol) was iodinated following General Method B, using powdered KOH (91 mg, 1.6 mmol) and I_2 (206 mg, 0.81 mmol) in DMF (1 mL). A standard work up followed by purification by flash chromatography (SiO_2, 0-2 % MeOH in DCM) afforded 3-iodo-4-methoxy-1H-indazole as a off white solid (100 mg, 90 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.29 (t, *J* = 8.03Hz, 1 H), 7.07 (d, *J* = 8.53Hz, 1 H), 6.52 (d, *J* = 7.53Hz, 1 H), 3.93 (s, 3 H); MS ESI 274.8 $[M + H]^+$, calcd for $[C_8H_7IN_2O + H]^+$ 275.0.

3-(4-Methoxy-1H-indazol-3-yl)benzenesulfonamide. 3-iodo-4-methoxy-1H-indazole (70 mg, 0.25 mmol), was subjected to Suzuki-Miyaura coupling following General Method C using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (Frontier Scientific, 86 mg, 0.30 mmol), DMF (1.5 mL), H_2O (0.4 mL), Cs_2CO_3 (165 mg, 0.51 mmol) and $Pd(PPh_3)_4$ (15 mg, 0.014 mmol). After heating sealed under Ar in a microwave reactor at 120 °C for 2 h, the reaction was diluted with DMSO, filtered and purified by preparative HPLC to 3-(4-methoxy-1H-indazol-3-yl)benzenesulfonamide as a white solid (14 mg, 18 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.53 (s, 1 H), 8.09 (d, *J* = 7.78 Hz, 1 H), 7.91 (d, *J* = 7.78 Hz, 1 H), 7.60 (t, *J* = 7.78 Hz, 1 H), 7.35 (t, *J* = 8.00 Hz, 1 H), 7.13 (d, *J* = 8.28 Hz, 1 H), 6.62 (d, *J* = 7.53Hz, 1 H), 3.92 (s, 3 H); MS ESI 304.0 $[M + H]^+$, calcd for $[C_{14}H_{13}N_3O_3S + H]^+$ 304.1. HPLC: 99A% at 254 nm.

4.2.14 3-(5-Methoxy-1H-indazol-3-yl)benzenesulfonamide (13). The title compound was synthesized according to the General Method C, utilizing 3-iodo-5-methoxy-1H-indazole (Sinova Inc., 40 mg, 0.15 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (54 mg, 0.19 mmol), Cs_2CO_3 (143 mg, 0.44 mmol), DMF (1mL), H_2O (0.25 mL) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol). The degassed solution was sealed and heated in a microwave reactor at 120 °C for 1.5 h. Purification by preparative HPLC provided the title compound as a white solid (12 mg, 27 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.46 (s, 1 H), 8.15 (d, *J* = 7.78 Hz, 1 H), 7.93 (d, *J* = 7.78 Hz, 1 H), 7.70 (d, *J* = 8.03Hz 1 H), 7.50 (d, *J* = 9.03Hz, 1 H), 7.38 (d, *J* =1.76 Hz, 1 H), 7.13 (dd, *J* = 9.03, 2.26 Hz, 1 H), 3.89 (s, 3 H); MS ESI 304.0 $[M + H]^+$, calcd for $[C_{14}H_{13}N_3O_3S + H]^+$ 304.1. HRMS (ESI) *m/z* calcd for $[C_{14}H_{13}N_3O_3S+ H]^+$ 304.0756, found 304.0756; HPLC: 99A% at 254 nm.

4.2.15 Synthesis of N-(3-(3-Sulfamoylphenyl)-1H-indazol-5-yl)acetamide (14). *N-(1H-indazol-5-yl)acetamide.* A DMF (2 mL) solution of Ac_2O (82 mg, 0.80 mmol) *N,N*-dimethylpyridin-4-amine (5.5 mg, 0.045 mmol) and DIPEA (0.26 mL, 1.5 mmol) was treated 1H-indazol-5-amine (0.10 g, 0.75 mmol) added in one portion at 0 °C. The reaction was stirred with cooling for 3 h then treated with H_2O (10 mL) and concentrated under reduced pressure and then quenched by addition of xs H_2O. Trituration with DCM provided the title compound as a red solid (0.11 g, 84 %). ^{1}H NMR (400 MHz, *DMSO-d_6*) δ

ppm 12.94 (br. s., 1 H), 9.91 (s, 1 H), 8.11 (s, 1 H), 8.00 (s, 1 H), 7.45 (d, *J* = 9.00 Hz, 1 H), 7.37 (d, *J* = 8.53Hz, 1 H), 2.05 (s, 3 H); MS ESI 175.8 $[M + H]^+$, calcd for $[C_9H_9N_3O + H]^+$ 176.1.

N-(3-Iodo-1H-indazol-5-yl)acetamide. The title compound was synthesized according to the General Method B, utilizing *N-(1H-indazol-5-yl)acetamide* (105 mg, 0.60 mmol), I_2 (304 mg, 1.2 mmol) and K_2CO_3 (330 mg, 2.4 mmol) in DMF (2 mL). A red solid (124 mg, 69 %). ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 13.41 (s, 1 H), 10.03 (s, 1 H), 7.89 (s, 1 H), 7.42 - 7.50 (m, 2 H), 2.06 (s, 3 H).

(3-(3-Sulfamoylphenyl)-1H-indazol-5-yl)acetamide. The title compound was synthesized according to the General Method C, utilizing N-(3-iodo-1H-indazol-5-yl)acetamide (62 mg, 0.20 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (73 mg, 0.26 mmol), KF (23 mg, 0.40 mmol), DMF (1.5mL), H_2O (0.37 mL) and $Pd(PPh_3)_4$ (12 mg, 0.010 mmol). The degassed solution was sealed and heated in a microwave reactor at 120 °C for 2 h. Purification by preparative HPLC provided the title compound as an off-white solid (29 mg, 44 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 10.03 (s, 1 H), 8.47 (s, 1 H), 8.35 (br. s., 1 H), 8.16 (d, *J* = 7.03Hz, 1 H), 7.94 (d, *J* = 8.28 Hz, 1 H), 7.70 (t, *J* = 7.78 Hz, 1 H), 7.56 (d, *J* = 8.50 Hz, 1 H), 7.51 (d, *J* = 9.00 Hz, 1 H), 2.17 (s, 3 H); MS ESI 331.2 $[M + H]^+$, calcd for $[C_{15}H_{14}N_4O_3S + H]^+$ 331.1. HPLC: 99A% at 254 nm.

4.2.16 Synthesis of N-(3-(3-sulfamoylphenyl)-1H-indazol-6-yl)acetamide (15). *N-(3-iodo-1H-indazol-6-yl)acetamide*. To a cold (0 °C) DMF (10 mL) solution of DIPEA (1.3 mL, 7.5 mmol) and Ac_2O (0.40 g, 3.9 mmol) and DMAP (14 mg, 0.11 mmol) was added 1H-indazol-6-amine (0.50 g, 3.7 mmol) in one portion. The reaction was stirred at the temperature for 3.5 h then aq NaOH (2 M, 2 mL) was added and stirring was continued at rt for 1 h. The solvent was removed under reduced pressure, the residue was taken into DCM, filtered, rinsed with DCM and subsequently with H_2O (10 mL) to afford N-(1H-indazol-6-yl)acetamide as a white solid (0.56 g, 87 %); MS ESI 175.8 $[M + H]^+$, calcd for $[C_9H_9N_3O + H]^+$ 176.1. N-(1H-indazol-6-yl)acetamide (0.56 g, 3.2 mmol) was iodinated using General Method B using I_2 (0.97 g, 3.8 mmol) and K_2CO_3 (0.88 g, 6.4 mmol) in DMF (10 mL) to afford after filtration, N-(3-iodo-1H-indazol-6-yl)acetamide as a light yellow solid (0.37 g, 38 %). MS ESI 301.8 $[M + H]^+$, calcd for $[C_9H_8IN_3O + H]^+$ 302.0.

N-(3-(3-Sulfamoylphenyl)-1H-indazol-6-yl)acetamide. N-(3-iodo-1H-indazol-6-yl)acetamide (62 mg, 0.21 mmol) was subjected to Suzuki-Miyaura coupling following the General Method C using *3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide* (70 mg, 0.24 mmol), KF (35 mg, 0.60 mmol), DMF (1 mL), H_2O (0.25 mL) and $Pd(PPh_3)_4$ (12 mg, 0.010 mmol). The degassed solution was sealed and heated in a microwave reactor at 120 ^oC for 2 h. Purification by preparative HPLC provided the title compound as a white solid (27 mg, 39 %). ^1H NMR (400 MHz, *CD_3OD*) δ ppm 10.12 (br. s., 1 H), 8.52 (s, 1 H), 8.22 (s, 1 H), 8.18 (d, *J* = 7.03Hz, 1 H), 8.00 (d, *J* = 8.53Hz, 1 H), 7.94 (d, *J* = 7.78 Hz, 1 H), 7.70 (t, *J* = 8.00 Hz, 1 H), 7.19 (d, *J* = 8.03Hz, 1 H), 2.20 (s, 3 H); MS ESI 331.0 $[M + H]^+$, calcd for $[C_{15}H_{14}N_4O_3S + H]^+$ 331.1. HPLC: 95A% at 254 nm.

4.2.17 Synthesis of N-(3-(3-Sulfamoylphenyl)-1H-indazol-5-yl)thiophene-2-carboxamide (16). *A. N-(1H-Indazol-5-yl)thiophene-2-carboxamide.* A DMF (5 mL) solution of 1H-indazol-5-amine (0.67 g, 5.0 mmol) and Et_3N (0.84 mL, 6.0 mmol) an 0^oC was treated dropwise with thiophene-2-carbonyl chloride (0.53 mL, 5.0 mmol) in DMF (1 mL). The reaction was stirred with cooling for 1 h and then quenched by addition of xs H_2O. The collected by filtration solid was washed with H_2O to provide the title compound as a yellow solid (0.73 g, 57 %). ^1H NMR (400 MHz, *CD_3OD*) δ ppm 8.11 (s, 1 H), 8.04 (s, 1 H), 7.92 (d, *J* =3.51Hz, 1 H), 7.73 (d, *J* =5.02Hz, 1 H), 7.61 (d, *J* = 8.50 Hz, 1 H), 7.55 (d, *J* = 9.00 Hz, 1 H), 7.20 (t, *J* =5.00 Hz, 1 H); MS ESI 243.9 $[M + H]^+$, calcd for $[C_{12}H_9N_3OS + H]^+$ 244.0.

N-(3-Iodo-1H-indazol-5-yl)thiophene-2-carboxamide was synthesized according to the General Method B, utilizing N-(1H-indazol-5-yl)thiophene-2-carboxamide (0.75 g, 3.1 mmol), I_2 (1.6 g, 6.2 mmol) and K_2CO_3 (1.3 g, 9.3 mmol) in DMF (11 mL). An off-white solid (0.31 g, 27 %). ^1H NMR (400 MHz, *CD_3OD*) δ ppm 7.94 (d, *J* =3.76 Hz, 1 H), 7.91 (s, 1 H), 7.75 (d, *J* =4.77 Hz, 1 H), 7.71 (dd, *J* =2.01, 9.03 Hz, 1 H), 7.53 (d, *J* = 9.03 Hz, 1 H), 7.21 (t, *J* =4.39 Hz, 1 H); MS ESI 369.9 $[M + H]^+$, calcd for $[C_{12}H_8IN_3OS + H]^+$ 370.0.

N-(3-(3-Sulfamoylphenyl)-1H-indazol-5-yl)thiophene-2-carboxamide. The title compound was synthesized according to the General Method C, utilizing N-(3-iodo-1H-indazol-5-yl)thiophene-2-

carboxamide (63 mg, 0.17 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (58 mg, 0.20 mmol), Cs_2CO_3 (167 mg, 0.51 mmol), DMF (1.6 mL), H_2O (0.4 mL) and $Pd(PPh_3)_4$ (10 mg, 0.008 mmol). The degassed solution was sealed and heated in a microwave reactor at 120 ^oC for 2 h. Purification by column chromatography (SiO_2, 3-10 % MeOH/DCM) provided the title compound as a yellow solid (4.6 mg, 7 ^1H NMR (400 MHz, *CD_3OD*) δ ppm 8.51 (s, 1 H), 8.44 (s, 1 H), 8.20 (d, *J* = 8.53Hz, 1 H), 7.93 - 7.97 (m, 2 H), 7.68 - 7.76 (m, 3 H), 7.61 (d, *J* = 9.00 Hz, 1 H), 7.21 (t, *J* =4.50 Hz, 1 H); MS ESI 399.1 $[M + H]^+$, calcd for $[C_{18}H_{14}N_4O_3S_2 + H]^+$ 399.1. HPLC: 95A% at 254 nm (LCMS).

4.2.18 Synthesis of N-(3-(3-sulfamoylphenyl)-1H-indazol-6-yl)thiophene-2-carboxamide (17). A. *N-(1H-indazol-6-yl)thiophene-2-carboxamide.* The solution of 1H-indazol-6-amine (266 mg, 2 mmol), Et_3N (0.42 mL, 3 mmol) in DMF (5 mL) was added the solution of thiophene-2-carbonyl chloride (0.21 mL, 2 mmol) in DMF (1 mL) dropwise over 2 min at rt. The resulting reaction mixture was stirred at 0 ^oC for 30 min before cooled down to 0 ^oC and quenched with H_2O and filtered. The filter cake was rinsed with H_2O, collected and dried to give N-(1H-indazol-6-yl)thiophene-2-carboxamide compound as a yellow solid (460 mg, 95%). ^1H NMR (400 MHz, *DMSO-d_6*) δ ppm 12.96 (s, 1 H), 10.32 (s, 1 H), 8.17 (s, 1 H), 8.06 (d, *J* =3.8 Hz, 1 H), 7.98 - 8.00 (m, 1 H), 7.87 (d, *J* =5.0 Hz, 1 H), 7.70 (d, *J* = 8.5 Hz, 1 H), 7.32 - 7.37 (m, 1 H), 7.23 (dd, *J* =4.6, 3.9 Hz, 1 H); MS ESI 244.1 $[M + H]^+$, calcd for $[C_{12}H_9N_3OS+H]^+$ 244.0.

N-(3-iodo-1H-indazol-6-yl)thiophene-2-carboxamide. To the solution of N-(1H-indazol-6-yl)thiophene-2-carboxamide (100 mg, 0.41 mmol) in DMF (2 mL) was added K_2CO_3 (215 mg, 1.56 mmol), and I_2 (230 mg, 0.91 mmol) in portions. The resulting reaction mixture was stirred at rt for 1 hour before quenched with 10% $Na_2S_2O_3$ aq. solution at 0^oC and filtered. The filter cake was collected and dried to give N-(3-iodo-1H-indazol-6-yl)thiophene-2-carboxamide as a light brown solid (106 mg, 70 %). ^1H NMR (400 MHz, *CD_3OD*) δ ppm 8.22 (s, 1 H), 7.96 (d, *J* =3.8 Hz, 1 H), 7.76 (d, *J* =5.0 Hz, 1 H), 7.41 - 7.45 (m, 1 H), 7.36-7.39 (m, 1 H), 7.21 (t, *J* = 4.4. Hz, 1 H); MS ESI 369.9 $[M + H]^+$, calcd for $[C_{12}H_8N_3IOS + H]^+$ 369.9.

N-(3-(3-sulfamoylphenyl)-1H-indazol-6-yl)thiophene-2-carboxamide. The title compound was synthesized according to the General Method C, utilizing N-(3-iodo-1H-indazol-6-yl)thiophene-2-carboxamide (53 mg, 0.14 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (49 mg, 0.179 mmol), Cs_2CO_3 (140 mg, 0.43 mmol), DMF (0.8 mL), H_2O (0.2 mL) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol). The degassed solution was sealed and heated in a microwave reactor at 120 ^oC for 2 h. Purification by preparative HPLC provided an off-white solid (2.7 mg, 5% yield). ^1H NMR (400 MHz, *CD_3OD*) δ ppm 10.26 (s, 1 H), 8.51 (s, 1 H), 8.26 (s, 1 H), 8.20 (d, *J* = 7.5 Hz, 1 H), 8.05 (d, *J* = 8.8 Hz, 1 H), 7.98-7.94 (m, 2 H), 7.76 (d, *J* =5.3Hz, 1 H), 7.70 (t, *J* = 7.7 Hz, 1 H), 7.44 (d, *J* = 8.8 Hz, 1 H), 7.22 (t, *J* =4.4 Hz, 1 H); MS ESI 399.1 $[M + H]^+$, calcd for $[C_{18}H_{14}N_4O_3S_2 + H]^+$ 399.1. HPLC: 95A% at 254 nm.

4.2.19 Synthesis of N-methyl-3-(3-sulfamoylphenyl)-1H-indazole-6-carboxamide (18). *A. N-methyl-1H-indazole-6-carboxamide.* 1H-indazole-6-carboxylic acid (Tyger Scientific, 51 mg, 0.31 mmol) was reacted according to General Method A using $MeNH_2$ (2 M in MeOH, 0.18 mL, 0.36 mmol), TBTU (120 mg, 0.37 mmol) and DIPEA (0.1 mL, 0.57 mmol) in anh DMF (2.5 mL). The crude reaction mixture was filtered and purified directly by preparative HPLC to afford N-methyl-1H-indazole-6-carboxamide as a white solid (54 mg, 99 %); MS ESI 175.8 $[M + H]^+$, calcd for $[C_9H_9N_3O+ H]^+$ 176.1.

3-Iodo-N-methyl-1H-indazole-6-carboxamide. N-methyl-1H-indazole-6-carboxamide (54 mg, 0.31 mmol) was iodinated following General Method B, using K_2CO_3 (180 mg, 1.3 mmol) and I_2 (170 mg, 0.67 mmol) in DMF (1 mL). A standard work up followed by filtration afforded 3-iodo-N-methyl-1H-indazole-6-carboxamide as a off white solid (54 mg, 58 %). ^1H NMR (400 MHz, *CD_3OD*) δ ppm 8.02 (s, 1 H), 7.62 (d, *J* = 8.53Hz, 1 H), 7.54 (d, *J* = 8.80 Hz, 1 H), 2.96 (s, 3 H); MS ESI 301.8 $[M + H]^+$, calcd for $[C_9H_8IN_3O + H]^+$ 302.0.

Methyl-3-(3-sulfamoylphenyl)-1H-indazole-6-carboxamide. 3-iodo-N-methyl-1H-indazole-6-carboxamide (40 mg, 0.13 mmol), was subjected to Suzuki-Miyaura coupling following General Method C using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (Frontier

Scientific, 44 mg, 0.15 mmol), DMF (1.5 mL), H_2O (0.3 mL), Cs_2CO_3 (128 mg, 0.39 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol). After heating sealed under Ar in a microwave reactor at 120 °C for 2.5 h, the reaction was diluted with DMSO, filtered and purified by preparative HPLC to afford N-methyl-3-(3-? sulfamoylphenyl)-1H-indazole-6-carboxamide as a white solid (8 mg, 19 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.52 (s, 1 H), 8.22 (d, *J* = 7.80 Hz, 1 H), 8.15 (d, *J* = 8.53Hz, 1 H), 8.09 (s, 1 H), 7.95 (d, *J* = 8.03Hz, 1 H), 7.72 (d, *J* = 8.00 Hz, 1 H), 7.68 (d, *J* = 8.00 Hz, 1 H), 2.98 (s, 3 H); MS ESI 331.0 $[M + H]^+$, calcd for $[C_{15}H_{14}N_4O_3S + H]^+$ 331.1. HPLC: >99A% at 254 nm.

4.2.20 Synthesis of 3-(3-sulfamoylphenyl)-1H-indazole-5-carboxylic acid (25). *Methyl 3-iodo-1H-indazole-5-carboxylate.* was synthesized according to the General Method B utilizing methyl 1H-indazole-5-carboxylate (300 mg, 1.70 mmol), K_2CO_3 (704 mg, 5.10 mmol), I_2 (864 mg, 3.40 mmol) and DMF (8 mL) as an orange solid (415 mg, 81%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.18 (s, 1 H), 8.07 (d, *J* = 8.78 Hz, 1 H), 7.58 (d, *J* = 8.78 Hz, 1 H), 3.95 (s, 3 H); MS ESI 302.8 $[M + H]^+$, calcd for $[C_9H_7IN_2O_2 + H]^+$ 303.0.

3-(3-Sulfamoylphenyl)-1H-indazole-5-carboxylic acid. A sealed degassed mixture of methyl 3-iodo-1H-indazole-5-carboxylate (800 mg, 2.65 mmol), benzenesulfonamide-3-boronic acid pinacol ester (896 mg, 3.18 mmol), $Pd(dppf)Cl_2$ (108 mg, 0.130 mmol), saturated aqueous Na_2CO_3 (2 mL) in PhMe / EtOH (8 mL / 8 mL) under Ar was heated under microwave irradiation at 125 ºC for 3 h. The reaction mixture was filtered, diluted with 20 mL of H_2O and then acidified with 2 M aq HCl. The solid was filtered out and triturated with MeOH to give the title compound at 90% purity (780 mg, 93%). ^{1}H NMR (400 MHz, *DMSO-d_6*) δ 13.76 (s, 1 H), 12.95 (bs, 1 H), 8.68 (s, 1 H), 8.44 (s, 1 H), 8.21 (d, *J* = 8.78 Hz, 1 H), 8.00 (d, *J* = 9.03Hz, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H), 7.78 (t, *J* = 7.65 Hz, 1 H), 7.70 (d, *J* = 9.03Hz, 1 H), 7.52 (s, 2 H); MS ESI 318.0 $[M + H]^+$, calcd for $[C_{14}H_{11}N_3O_4S + H]^+$ 318.0.

4.2.20 Synthesis of 3-(5-(benzyloxy)-1H-indazol-3-yl)benzenesulfonamide (30). *5-(Benzyloxy)-1H-indazole.* A degassed DMF (30 mL) suspension of *1H*-indazol-5-ol (1.0 g, 7.5 mmol) and K_2CO_3 (2.0 g, 15 mmol) was treated with benzylbromide (0.98 mL, 8.20 mmol) at 0 °C. The reaction was stirred with cooling for 2 h and then allowed slowly to warm to rt overnight. Later the reaction mixture

was diluted with H_2O (100 mL). A precipitate was collected filtration, rinsed with H_2O then suspended in Et_2O and isolated by a filtration to provide the title compound as white solid (0.77 g, 46 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.93 (s, 1 H), 7.43 - 7.50 (m, 3 H), 7.36 - 7.42 (m, 2 H), 7.33 (d, *J* = 7.03Hz, 1 H), 7.26 (s, 1 H), 7.15 (d, *J* = 8.78 Hz, 1 H), 5.12 (s, 2 H); MS ESI 225.0 $[M + H]^+$, calc for $[C_{14}H_{12}N_2O+H]^+$ 225.1.

5-(Benzyloxy)-3-iodo-1H-indazole. The title compound was synthesized according to the General Method B, utilizing *5-(benzyloxy)-1H-indazole* (0.77 g, 3.4 mmol), K_2CO_3 (1.4 g, 10 mmol) and I_2 (1.7 g, 6.9 mmol) in DMF (10 mL). An off-white solid (0.88 g, 73 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.52-7.36 (m, 5 H), 7.34 (d, *J* = 7.28 Hz, 1 H), 7.21 (d, *J* = 8.78 Hz, 1 H), 6.91 (s, 1 H), 5.15 (s, 2 H); MS ESI 351.2 $[M + H]^+$, calcd for $[C_{14}H_{11}IN_2O + H]^+$ 351.0.

3-(5-(Benzyloxy)-1H-indazol-3-yl)benzenesulfonamide. The title compound was synthesized according to the General Method C, utilizing 5-(benzyloxy)-3-iodo-1H-indazole (0.50 g, 1.4 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (0.53 mg, 1.9 mmol), satd aq Na_2CO_3 (3 mL), PhMe (9 mL), EtOH (9 mL) and $Pd(dppf)Cl_2$ (52 mg, 0.071 mmol). The crude material was in sequence taken into MeOH and then H_2O and filtered through Celite using MeOH and subsequently to transfer the crude material. The filtrate was concentrated to dryness affording a solid which was then suspended into H_2O. Filtration and rinsing with MeCN yielded the title compound to as a light tan solid (0.5 g, 92 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.46 (s, 1 H), 8.12 (d, *J* = 8.53Hz, 1 H), 7.94 (d, *J* =6.78 Hz, 1 H), 7.70 (t, *J* = 7.53Hz, 1 H), 7.46 - 7.55 (m, 4 H), 7.40 (m, 2 H), 7.32 (t, *J* = 7.30 Hz, 1 H), 7.22 (d, *J* = 8.53Hz, 1 H), 5.18 (s, 2 H); MS ESI 380.2 $[M + H]^+$, calcd for $[C_{20}H_{17}N_3O_3S + H]^+$ 380.1. HRMS (ESI) *m/z* calcd for $[C_{20}H_{17}N_3O_3S+ H]^+$ 380.1069, found 380.1066; HPLC: 96A% at 254 nm (HRMS).

4.2.21 Synthesis of 3-(5-(2-(thiophen-2-yl)ethoxy)-1H-indazol-3-yl)benzenesulfonamide (31). *A. 5-(2-(Thiophen-2-yl)ethoxy)-1H-indazole.* DIAD (0.09 mL, 0.47 mmol) was added dropwise to a solution of 1H-indazol-5-ol (50 mg, 0.37 mmol), 2-(thiophen-2-yl)ethanol (Alfa Aeasar, 58 mg, 0.47 mmol) and PPh_3 (0.12 g, 0.47 mmol) and) in anh THF (2 mL) and PhMe (2 mL) at 0 °C. The reaction

was stirred with cooling for 4 h and then concentrated under reduced pressure and purified by column chromatography twice (SiO_2, 0-12 % MeOH/DCM) and (SiO_2, 20-50 % EtOAc/hexanes) to provide the title compound a white solid (0.047 g, 52 %). MS ESI 244.9 $[M + H]^+$, calcd for $[C_{13}H_{12}N_2OS + H]^+$ 245.1.

3-Iodo-5-(2-(thiophen-2-yl)ethoxy)-1H-indazole. The title compound was synthesized according to the General Method B, utilizing 5-(2-(thiophen-2-yl)ethoxy)-1H-indazole (0.049 g, 0.20 mmol), KOH (47 mg, 0.84 mmol) and I_2 (0.078 g, 0.31 mmol) in DMF (10 mL) as a white solid (0.059 g, 81 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.32 (d, *J* = 9.03Hz, 1 H), 7.23 (d, *J* =4.77 Hz, 1 H), 6.92 - 6.99 (m, 3 H), 6.89 (dd, *J* = 8.91, 1.88 Hz, 1 H), 4.26 (t, *J* =6.40 Hz, 2 H), 3.35 (t, *J* =6.40 Hz, 2 H); MS ESI 370.9 $[M + H]^+$, calcd for $[C_{13}H_{11}IN_2OS + H]^+$ 371.0.

3-(5-(2-(Thiophen-2-yl)ethoxy)-1H-indazol-3-yl)benzenesulfonamide. The title compound was synthesized according to the General Method C, utilizing a degassed mixture of 3-iodo-5-(2-(thiophen-2-yl)ethoxy)-1H-indazole (0.030 g, 0.081 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (0.030 mg, 0.11 mmol) KF (14 mg, 0.24 mmol) and $Pd(PPh_3)_4$ (5 mg, 0.008 mmol) in DMF (1.5 mL)/H_2O (0.5 mL). The reaction mixture was heated sealed in a microwave reactor at 120 °C for 2 h. The crude material filtered through Celite (MeOH), concentrated under reduced pressure and subsequently purified by column chromatography (SiO_2, 0-9 % MeOH/DCM) and later by preparative TLC (SiO_2, 10 % MeOH/DCM). The material was triturated with hexanes, then dissolved in 2 % MeOH/DCM and filtered to afford the title compound as a white powder (10 mg, 32 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.46 (s, 1 H), 8.14 (d, *J* = 7.78 Hz, 1 H), 7.93 (d, *J* = 8.03Hz, 1 H), 7.70 (t, *J* = 7.78 Hz 1 H), 7.51 (d, *J* = 9.03Hz, 1 H), 7.40 (s, 1 H), 7.22 (d, *J* =5.02Hz, 1 H), 7.17 (dd, *J* = 9.03, 2.01Hz, 1 H), 6.91 - 7.00 (m, 2 H), 4.29 (t, *J* =6.40 Hz, 2 H), 3.34 (t, *J* =6.40 Hz, 2 H); MS ESI 400.0 $[M + H]^+$, calcd for $[C_{19}H_{17}N_3O_3S_2 + H]^+$ 400.1. HPLC: 95A% at 254 nm (LCMS).

4.2.22 2-Phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (32). 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate(51 mg, 0.127 mmol), 2-phenylacetic acid (17 mg, 0.127 mmol), and DIPEA (66 µL, 0.381 mmol) was dissolved in 2 mL of DMF and cooled to 0 ºC.

TBTU (41 mg, 0.127 mmol) was added and the reaction was stirred at 0 ºC for 90 min. Purification by preparative HPLC gave the title compound as a white solid (24 mg, 47%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.46 (s, 1 H), 8.39 (s, 1 H), 8.14 (d, *J* = 8.03Hz, 1 H), 7.93 (d, *J* = 8.03Hz, 1 H), 7.68 (t, *J* = 7.91Hz, 1 H), 7.54 (m, 2 H), 7.36 (m, 4 H), 7.26 (t, *J* = 7.03Hz, 1 H), 3.73 (s, 2 H)); MS ESI 407.2 $[M + H]^+$, calcd for $[C_{21}H_{18}N_4O_3S + H]^+$ 407.1. HRMS (ESI) *m/z* calcd for $[C_{21}H_{18}N_4O_3S+ H]^+$ 407.1178, found 407.1182; HPLC: 97A% at 254 nm (HRMS).

4.2.23 Synthesis of N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)-2-(thiophen-2-yl)acetamide (33). *N-(1H-Indazol-5-yl)-2-(thiophen-2-yl)acetamide.* A DMF (5 mL) solution of 1H-indazol-5-amine (0.67 g, 5.0 mmol) and Et_3N (0.84 mL, 6.0 mmol) an 0 ^{o}C was treated dropwise with 2-(thiophen-2-yl)acetyl chloride (Sigma-Aldrich, 0.62 mL g, 5.0 mmol) in DMF (1 mL). The reaction was stirred with cooling for 1 h and then quenched by addition of xs H_2O. The collected by filtration solid was washed with H_2O and then purified by column chromatography (SiO_2, 50-100 % EtOAc/hexanes) to provide the title compound as a light brown solid (0.73 g, 57 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.07 (s, 1 H), 8.01 (s, 1 H), 7.50 (d, *J* = 9.03Hz, 1 H), 7.47 (d, *J* = 8.78 Hz, 1 H), 7.30 (d, *J* =5.02Hz, 1 H), 7.02 - 7.05 (m, 1 H), 6.99 (t, *J* =4.10 Hz, 1 H), 3.92 (s, 2 H); MS ESI 257.9 $[M + H]^+$, calcd for $[C_{13}H_{11}N_3OS + H]^+$ 258.1.

N-(3-Iodo-1H-indazol-5-yl)-2-(thiophen-2-yl)acetamide. The title compound was synthesized according to the General Method B, utilizing *N-(1H-indazol-5-yl)-2-(thiophen-2-yl)acetamide* (0.51 g, 2.0 mmol), I_2 (1.0 g, 3.9 mmol) and K_2CO_3 (0.83 g, 6.0 mmol) in DMF (7 mL). A gray-yellow solid (0.32 g, 42 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.86 (s, 1 H), 7.52 (d, *J* = 8.41Hz, 1 H), 7.50 (d d, *J* = 8.78 Hz, 1 H), 7.31 (d, *J* = 4.99 Hz, 1 H), 7.02 - 7.05 (m, 1 H), 6.99 (t, *J* =4.10 Hz, 1 H), 3.94 (s, 2 H); MS ESI 384.0 $[M + H]^+$, calcd for $[C_{13}H_{10}IN_3OS + H]^+$ 384.0.

N-(3-(3-Sulfamoylphenyl)-1H-indazol-5-yl)-2-(thiophen-2-yl)acetamide. The title compound was synthesized according to the General Method C, utilizing N-(3-iodo-1H-indazol-5-yl)-2-(thiophen-2-yl)acetamide (100 mg, 0.26 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (96 mg, 0.34 mmol), KF (45 mg, 0.78 mmol), DMF (4 mL), H_2O (1 mL) and $Pd(PPh_3)_4$ (15 mg, 0.013

mmol). The degassed solution was sealed and heated in a microwave reactor at 120 °C for 2 h. Purification by preparative HPLC followed by preparative TLC (SiO_2, 10 % MeOH/DCM) and trituration (DCM, 2 % MeOH, DCM) provided the title compound as an off-white solid (35 mg, 32 ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.47 (s, 1 H), 8.40 (s, 1 H), 8.16 (d, *J* = 7.53Hz, 1 H), 7.94 (d, *J* = 8.03Hz, 1 H), 7.71 (t, *J* = 7.80 Hz, 1 H), 7.55 (d, *J* =6.78 Hz, 2 H), 7.30 (d, *J* =4.52Hz, 1 H), 7.05 (d., *J* =3.26 Hz, 1 H), 6.99 (dd, *J* =3.63Hz, 4.77 Hz 1 H), 3.95 (s, 3 H); MS ESI 413.2 $[M + H]^+$, calcd for $[C_{19}H_{16}N_4O_3S_2 + H]^+$ 413.1. HRMS (ESI) *m/z* calcd for $[C_{19}H_{16}N_4O_3S_2 + H]^+$ 413.0742, found 413.0739;HPLC: 97A% at 254 nm (HRMS).

4.2.24 N-(3-(3-Sulfamoylphenyl)-1H-indazol-5-yl)thiophene-2-sulfonamide (34). A DMF (2 mL) solution of 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (39 mg, 0.098 mmol) and DIPEA (0.05 mL, 0.3 mmol) was treated with a DMF (0.5 mL) solution of thiophene-2-sulfonyl chloride (Sigma-Aldrich, 18 mg, 0.10 mmol) at 0 °C. The reaction mixture was stirred for 3 h before being stirring at rt overnight. The reaction was quenched by an addition of $MeNH_2$ (2 M in MeOH, 0.3 mL, 0.6 mmol) at rt. Purification by preparative HPLC provided the title compound as a white powder (19 mg, 45 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.40 (s, 1 H), 8.05 (d, *J* = 8.03Hz, 1 H), 7.95 (d, *J* = 8.28 Hz, 1 H), 7.67 - 7.74 (m, 3 H), 7.51 (d, *J* = 8.78 Hz, 1 H), 7.47 (dd, *J* =1.25, 3.76 Hz, 1 H), 7.26 (dd, *J* =1.76, 8.78 Hz, 1 H), 7.05 (t, *J* =4.52Hz, 1 H); MS ESI 435.1 $[M + H]^+$, calcd for $[C_{17}H_{14}N_4O_4S_3 + H]^+$ 435.0. HRMS (ESI) *m/z* calcd for $[C_{17}H_{14}N_4O_4S_3 + H]^+$ 435.0255, found 435.0249;HPLC: >99A% at 254 nm.

4.2.25 e 3-{5-[(m-tolylmethylsulfonyl)amino]-1H-indazol-3-yl}benzenesulfonamide (35). The title compound was prepared as white powder (40 mg) according to the method for. N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)thiophene-2-sulfonamide. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 8.36 (s., 1 H), 8.00 (d, *J* = 7.30 Hz, 1 H), 7.86 (d, *J* = 7.90 Hz, 1 H), 7.69 (s, 1 H), 7.62 (t, *J* = 7.60 Hz, 1 H), 7.45 (d, *J* = 8.83Hz, 1 H), 7.23 (d, *J* = 9.10 Hz, 1 H), 7.06 (t, *J* = 7.60 Hz, 1 H), 7.01 (d, *J* =6.30 Hz, 1 H), 6.93 - 6.98 (m, 2 H), 4.27 (s, 2 H), 2.08 (s, 3 H); MS ESI 457.2 $[M + H]^+$, calcd for $[C_{21}H_{20}N_4O_4S_2 + H]^+$ 457.1. HPLC: >99A% at 254 nm.

4.2.26 3-(5-(3-Phenylureido)-1H-indazol-3-yl)benzenesulfonamide (36). A DMF (2 mL) solution of 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (50 mg, 0.12 mmol) and DIPEA (0.1 mL, 0.6 mmol) was treated with a DMF (0.5 mL) solution of isocyanatobenzene (16 mg, 0.13 mmol) at -20 °C. The reaction mixture was stirred with cooling for 2 h before being allowed to warm to 0 °C for 1 h and later to rt. The reaction was quenched by an addition of $MeNH_2$ (2 M in MeOH, 0.3 mL, 0.6 mmol) at rt. Purification by preparative HPLC provided the title compound as a white powder (15 mg, 30 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.50 (s, 1 H), 8.23 (s, 1 H), 8.20 (d, *J* = 8.03Hz, 1 H), 7.95 (d, *J* = 7.78 Hz, 1 H), 7.72 (t, *J* = 7.91Hz, 1 H), 7.57 (d, *J* = 8.78 Hz, 1 H), 7.41 - 7.49 (m, 3 H), 7.31 (t, *J* = 7.65 Hz, 2 H), 7.04 (t, *J* = 7.15 Hz, 1 H); MS ESI 408.1 $[M + H]^+$, calcd for $[C_{20}H_{17}N_5O_3S+ H]^+$ 408.1. HPLC: 95A% at 254 nm.

4.2.27 3-(5-(3-(2,6-Diethylphenyl)ureido)-1H-indazol-3-yl)benzenesulfonamide (37). A DMF (2 mL) solution of 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (50 mg, 0.12 mmol) and DIPEA (0.1 mL, 0.6 mmol) was treated with a DMF (0.5 mL) solution of 1,3-diethyl-2-isocyanatobenzene (Sigma-Aldrich, 23 mg, 0.13 mmol) at 0 °C. The reaction mixture was stirred with cooling for 2 h before being allowed to warm to rt overnight. The reaction was quenched by an addition of $MeNH_2$ (2 M in MeOH, 0.3 mL, 0.6 mmol) at rt. Purification by preparative HPLC provided the title compound as a white powder (18 mg, 31 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.47 (s, 1 H), 8.22 (br. s, 1 H), 8.17 (d, *J* = 7.28 Hz, 1 H), 7.93 (d, *J* = 7.80 Hz, 1 H), 7.69 (t, *J* = 7.78 Hz, 1 H), 7.55 (d, *J* = 8.03 Hz, 1 H), 7.35 - 7.50 (m, 1 H), 7.11 - 7.28 (m, 3 H), 2.72 (q, *J* = 7.53 Hz, 4 H), 1.24 (t, *J* = 7.53Hz, 6 H); MS ESI 464.2 $[M + H]^+$, calcd for $[C_{24}H_{25}N_5O_3S + H]^+$ 464.2. HPLC: 97A% at 254 nm. HRMS (ESI) *m/z* calcd for $[C_{24}H_{25}N_5O_3S+ H]^+$ 464.1756, found 464.1745;HPLC: 98A% at 254 nm.

4.2.28 Synthesis of 3-(5-(3-(2,6-diethylphenyl)-1-methylureido)-1H-indazol-3-yl)benzenesulfonamide (38). *3-(5-(Methylamino)-1H-indazol-3-yl)benzenesulfonamide.* $LiAlH_4$ (1.0 M in THF, 4.5 mL, 4.5 mmol) was added slowly at 0°C to a stirred solution of tert-butyl (3-(3-sulfamoylphenyl)-1H-indazol-5-yl)carbamate_(0.35 g, 0.90 mmol) in anh. THF (22 mL) under Ar.

Later, after 5 min at 0 °C, the cooling bath was removed and after stirring at rt for 20 min, the reaction was heated at reflux for 5.5 h. The reaction was then cooled to rt and quenced by a slow addition of xs $Na_2SO_4*10H_2O$. The crude mixture was filtered through Celite, rinsing the plug with MeOH. The filtrate was concentrated under reduced pressure to afford 3-(5-(methylamino)-1H-indazol-3-yl)benzenesulfonamide as a white solid (0.26 g,96 %) which was used without further purification. ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.49 (s, 1 H), 8.16 - 8.24 (m, 2 H), 7.99 (d, *J* = 7.53Hz, 1 H), 7.82 (d, *J* = 9.03Hz, 1 H), 7.74 (t, *J* = 8.03Hz, 1 H), 7.56 (d, *J* = 8.78 Hz, 1 H), 3.18 (s, 3 H); MS ESI 303.0 $[M + H]^+$, calcd for $[C_{14}H_{14}N_4O_2S + H]^+$ 303.1.

3-(5-(3-(2,6-diethylphenyl)-1-methylureido)-1H-indazol-3-yl)benzenesulfonamide. An anh DMF (2 mL) solution of 3-(5-(methylamino)-1H-indazol-3-yl)benzenesulfonamide (66 mg, 0.22 mmol) from the preceeding step and DIPEA (0.10 mL, 0.57 mmol) under Ar was treated with 1,3-diethyl-2-isocyanatobenzene (0.04 mL, 0.2 mmol) at 0 °C. The reaction was stirred at 0 °C for 1 h and then at rt for 5 h. At this point, by LCMS analysis, N-(2,6-diethylphenyl)-5-(3-(2,6-diethylphenyl)-1-methylureido)-3-(3-sulfamoylphenyl)-1H-indazole-1-carboxamide was a signifiant byproduct in the reaction mixture. The reaction was treated with $MeNH_2$ (1 M in MeOH, 0.5 mL), stirred for 10 min and concentrated under reduced pressure. The residue was suspended in MeOH (5 mL) and treated with MeONa (25 %wt in MeOH, 0.4 mL, 1.7 mmol). After stirring for 3 h at 55 °C and then overnight at rt, the reaction was concentrated under reduced pressure and purified by preparative HPLC to afford 3-(5-(3-(2,6-diethylphenyl)-1-methylureido)-1H-indazol-3-yl)benzenesulfonamide as an off-white solid (14.8 mg, 14 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.71 (s, 1 H), 8.30 (d, *J* = 7.50 Hz, 1 H), 8.26 (s, 1 H), 8.10 (d, *J* = 7.78 Hz, 1 H), 7.81 (d, *J* = 7.80 Hz, 1 H), 7.77 (d, *J* = 9.54 Hz, 1 H), 7.47 (d, *J* = 9.03Hz, 1 H), 7.16 (t, *J* = 7.80 Hz, 1 H), 7.04 (d, *J* = 7.53Hz, 2 H), 2.79 (s, 3 H), 2.40 (q, *J* = 7.50 Hz, 4 H), 0.95 (t, *J* = 7.53Hz, 6 H); MS ESI 478.3 $[M + H]^+$, calcd for $[C_{25}H_{27}N_5O_3S + H]^+$ 478.2. HPLC: 97A% at 254 nm.

4.2.29 3-(5-((N-phenylsulfamoyl)amino)-1H-indazol-3-yl)benzenesulfonamide (39). To a mixture of 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide trifluoroacetate (101 mg, 0.25 mmol) and 2-

chloroethyl N-phenylsulfamoylcarbamate ($PhNH(SO_2)NH(C=O)OCH_2CH_2Cl$) [55] (70 mg, 0.25 mmol in CH_3CN (30 mL) was added Et_3N (0.11 mL, 0.75 mmol). The resulting mixture was refluxed (oil temp. 90 °C) for 2 h. It was concentrated to dryness, redissolved in DMF (4 mL), filtered through microfilter and purified by preparative HPLC. The title compound was obtained as a white solid (33 mg, 30 %) after trituration with MeOH. ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.43 (s, 1 H), 7.96 (t, *J* = 8.8 Hz, 2 H), 7.68 (pseudo t, *J* = 7.8 Hz, 2 H), 7.48 (d, *J* = 8.8 Hz, 1 H), 7.27-7.21 (m, 3 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 7.04 (t, *J* = 7.2Hz, 1 H); MS ESI 444.2 $[M + H]^+$, calcd for $[C_{19}H_{17}N_5O_4S_2 + H]^+$ 444.1. HRMS (ESI) *m/z* calcd for $[C_{19}H_{17}N_5O_4S_2 + H]^+$ 444.0800, found 444.0804; HPLC: >99A% at 214 nm.

4.2.30 Synthesis of 3-(5-((N-(2,6-diethylphenyl)sulfamoyl)amino)-1H-indazol-3-yl)benzenesulfonamide (40). *2-Chloroethyl N-(2,6-diethylphenyl)sulfamoylcarbamate.* To a solution of chlorosulfonyl isocyanate (2.83 g, 20 mmol) in CH_2Cl_2 (10 mL) was added 2-chloroethanol (1.34 mL, 20 mmol) dropwise over 2 min (exothermic). The resulting mixture was stirred for 5 min at rt, then cooled to 0 °C and added dropwise to a round bottom flask charged with 2,6-diethylaniline (2.98 g, 20 mmol) and Et_3N (3.08 mL, 22 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After addition, the resulting mixture was stirred for2h at 0 °C then quenched with H_2O and extracted with CH_2Cl_2. The combined extracts were concentrated to give a white solid, which was triturated with H_2O (100 mL) to give the title compound as a white solid (6.66 g, 100%) after drying. Analysis by ^{1}H NMR indicated the presence of trace amount of Et_3N*HCl. ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 11.49 (s, 1 H), 9.63 (s, 1 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 4.37 (t, *J* = 4.8 Hz, 2 H), 3.84 (t, *J* =5.0 Hz, 2 H), 2.67 (q, *J* = 7.5 Hz, 4 H), 1.14 (t, *J* = 8.0 Hz, 6 H).

3-(5-(N-(2,6-Diethylphenyl)sulfamoylamino)-1H-indazol-3-yl)benzene sulfonamide. To a mixture of 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide trifluoroacetate (101 mg, 0.25 mmol) and 2-chloroethyl N-(2,6-diethylphenyl)sulfamoylcarbamate (100 mg, 0.3 mmol) in CH_3CN (10 mL) was added Et_3N (0.11 mL, 0.75 mmol). The resulting mixture was refluxed (oil temp. 90 °C) for 2h. It was concentrated to dryness, redissolved in DMF (4 mL), filtered through microfilter and purified by preparative HPLC. The title compound was obtained as a light gray solid (24 mg, 19%) after trituration

with CH_2Cl_2. ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.48 (s, 1 H), 8.07 (d, *J* = 7.2 Hz, 1 H), 7.94 (d, *J* = 7.6 Hz, 1 H), 7.90 (s, 1 H), 7.70 (t, *J* = 7.4 Hz, 1 H), 7.55 (d, *J* = 9.2 Hz, 1 H), 7.36 (d, *J* = 8.4 Hz, 1 H), 7.13 (t, *J* = 7.4 Hz, 1 H), 7.04 (d, *J* = 7.2 Hz, 2 H), 2.68 (q, *J* = 7.2Hz, 4 H), 1.03 (t, *J* = 7.6 Hz, 6 H); MS ESI 500.3 $[M + H]^+$, calcd for $[C_{23}H_{25}N_5O_4S_2 + H]^+$ 500.1. HPLC: >99A% at 214 nm.

4.2.31 Synthesis of benzyl-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide (41). *N-Benzyl-1H-indazole-5-carboxamide.* Benzylamine (150 mg, 1.40 mmol), 1H-indazole-5-carboxylic acid (227 mg, 1.40 mmol), and DIPEA (293 µL, 1.68 mmol) was dissolved in 5 mL of DMF and cooled to 0 ºC. TBTU (297 mg, 0.925 mmol) was added and the reaction was stirred at 0 ºC for 120 min. Completion of the reaction was monitored by LC-MS and purification by flash chromatography (50% EtOAc/hexanes to 100% EtOAc) gave the title compound as a white solid (31 mg, 9%) ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.35 (s, 1 H), 8.16 (s, 1 H), 7.91 (d, *J* = 8.78 Hz, 1 H), 7.60 (d, *J* = 9.03 Hz, 1 H), 7.38 (d, *J* = 7.28 Hz, 2 H), 7.33 (t, *J* = 7.30 Hz, 2 H), 7.25 (t, *J* = 7.00 Hz, 1 H), 4.61 (s, 2 H); MS ESI 251.9 $[M + H]^+$, calcd for $[C_{15}H_{13}N_3O + H]^+$ 252.1.

N-Benzyl-3-iodo-1H-indazole-5-carboxamide. The title compound was synthesized according to the General Method B utilizing N-benzyl-1H-indazole-5-carboxamide (30 mg, 0.120 mmol), K_2CO_3 (50 mg, 0.358 mmol), I_2 (60 mg, 0.240 mmol) and DMF (2 mL). An orange solid (32 mg, 71%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.08 (s, 1 H), 7.96 (d, *J* = 9.03 Hz, 1 H), 7.58 (d, *J* = 9.03 Hz, 1 H), 7.38 (d, *J* = 7.30 Hz, 2 H), 7.33 (t, *J* = 7.30 Hz, 2 H), 7.21-7.28 (m, 1 H), 4.61 (s, 2 H); MS ESI 377.9 $[M + H]^+$, calcd for $[C_{15}H_{12}IN_3O + H]^+$ 378.0.

N-benzyl-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide. A sealed degassed mixture of N-benzyl-3-iodo-1H-indazole-5-carboxamide (30 mg, 0.080 mmol), benzenesulfonamide-3-boronic acid pinacol ester (27 mg, 0.095 mmol), $PdCl_2$dppf (4 mg, 0.0040 mmol), saturated aq. Na_2CO_3 (400 µL) in PhMe / EtOH (0.8 mL / 0.8 mL) under Ar was heated under microwave irradiation at 125 ºC for 120 min. The reaction mixture was purified by preparative HPLC to give the title compound as a white solid (3.4 mg, 10%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.64 (s, 1 H), 8.53 (s, 1 H), 8.25 (d, *J* = 7.03Hz, 1 H), 7.97 (d, *J* = 7.78 Hz, 2 H), 7.72 (t, *J* = 7.78 Hz, 1 H), 7.66 (d, *J* = 9.54 Hz, 1 H), 7.39 (d, *J* = 8.00 Hz, 2 H),

7.34 (t, *J* = 7.40 Hz, 2 H), 7.25 (t, *J* = 7.30 Hz, 1 H), 4.63 (s, 2 H); MS ESI 407.1 $[M + H]^+$, calcd for $[C_{21}H_{18}N_4O_3S + H]^+$ 407.1. HRMS (ESI) *m/z* calcd for $[C_{21}H_{18}N_4O_3S+ H]^+$ 407.1178, found 407.1182;HPLC: 96A% at 254 nm (HRMS).

4.2.32 3-(3-sulfamoylphenyl)-N-(thiophen-2-ylmethyl)-1H-indazole-5-carboxamide (42). The title compound was synthesized according to the General Method A utilizing 3-(3-sulfamoylphenyl)-1H-indazole-5-carboxylic acid (100 mg, 0.32 mmol), 2-thiophenemethylamine (36 mg, 0.32 mmol), DIPEA (83 µL, 0.48 mmol), TBTU (103 mg, 0.32 mmol) and DMF (4 mL). The reaction mixture was purified by preparative HPLC, and then triturated with Et_2O and acetone to give the title compound as a white solid (65 mg, 49%). ^{1}H NMR (400 MHz, *DMSO-d$_6$*) δ ppm 13.67 (s, 1 H), 9.27 (t, *J* =5.65 Hz, 1 H), 8.62 (s, 1 H), 8.47 (s, 1 H), 8.28 (d, *J* =6.27 Hz, 1 H), 7.97 (d, *J* = 9.03 Hz, 1 H), 7.88 (d, *J* =6.78 Hz, 1 H), 7.77 (t, *J* = 7.30 Hz, 1 H), 7.68 (d, *J* = 8.53 Hz, 1 H), 7.50 (s, 2 H), 7.38 (d, *J* =4.77 Hz, 1 H), 7.02 - 7.07 (m, 1 H), 6.95 - 6.99 (m, 1 H), 4.69 (d, *J* = 5.77 Hz, 2 H); MS ESI 413.2 $[M + H]^+$, calcd for $[C_{19}H_{16}N_4O_3S_2 + H]^+$ 413.1; HPLC: 98A% at 254 nm (LCMS).

4.2.33 N-Benzyl-N-methyl-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide (43). The title compound was synthesized according to the General Method A utilizing 3-(3-sulfamoylphenyl)-1H-indazole-5-carboxylic acid (60 mg, 0.189 mmol), N-methyl-1-phenylmethanamine (23 mg, 0.189 mmol), DIPEA (49 µL, 0.284 mmol), TBTU (61 mg, 0.189 mmol) and DMF (4 mL). The reaction mixture was purified by preparative HPLC, and triturating with Et_2O to give the title compound as a white solid (43 mg, 54%). ^{1}H NMR (400 MHz, *CD$_3$OD*) δ ppm 8.47 (br. s., 1 H), 8.04 - 8.29 (m, 1 H), 7.94 (br. s., 1 H), 7.77 - 7.87 (m, 1 H), 7.53 - 7.77 (m, 3 H), 7.09 - 7.51 (m, 5 H), 4.81 (br. s., 1 H), 4.65 (br. s., 1 H), 3.11 (br. s., 1 H), 2.99 (br. s., 1 H); MS ESI 421.3 $[M + H]^+$, calcd for $[C_{22}H_{20}N_4O_3S + H]^+$ 421.1. HPLC: >99A% at 254 nm (LCMS).

4.2.34 Synthesis of N-((3-(3-sulfamoylphenyl)-1H-indazol-5-yl)methyl)benzamide (44). *N-((3-Iodo-1H-indazol-5-yl)methyl)benzamide.* TFA (0.075 mL, 1.0 mmol) was added dropwise to a solution of 1H-indazole-5-carbaldehyde (50 mg, 0.34 mmol), benzamide (124 mg, 1.0 mmol) and Et_3SiH (0.16 mL, 1.0 mmol) in anh MeCN (6 mL) at rt. The reaction was stirred at rt for 1.5 h and then heated at

50-65 °C for 4 d. The reaction was later concentrated under reduced pressure and purified by column chromatography (SiO_2, 0-8 % MeOH/DCM) to afford N-((1H-indazol-5-yl)methyl)benzamide; MS ESI 251.9 $[M + H]^+$, calcd for $[C_{15}H_{13}N_3O+ H]^+$ 252.1. The material was subjected to condition described by the general method for iodination using K_2CO_3 (190 mg, 1.4 mmol), I2 (117 mg, 2.2 mmol) and DMF (2 mL) to afford the title compound as pale yellow solid (66 mg, 51 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.88 (d, *J* = 7.53 Hz, 2 H), 7.41 - 7.59 (m, 6 H), 4.71 (s, 2 H).

N-((3-(3-sulfamoylphenyl)-1H-indazol-5-yl)methyl)benzamide. The title compound was synthesized according to the General Method C utilizing N-((3-iodo-1H-indazol-5-yl)methyl)benzamide (40 mg, 0.11 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide (39 mg, 0.14 mmol), satd aq Na_2CO_3 (0.5 mL), PhMe (1.5 mL), EtOH (1.5 mL) and $Pd(dppf)Cl_2$ (4 mg, 0.005 mmol). Purification by preparative HPLC provided the title compound to as a white powder (20 mg, 28 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.51 (s, 1 H), 8.19 (d, *J* = 7.78 Hz, 1 H), 8.07 (s, 1 H), 7.94 (d, *J* = 8.03Hz, 1 H), 7.86 (d, *J* = 7.28 Hz, 2 H), 7.69 (t, *J* = 7.91Hz, 1 H), 7.42 - 7.62 (m, 5 H), 4.73 (s, 2 H); MS ESI 407.1 $[M + H]^+$, calcd for $[C_{21}H_{18}N_4O_3S + H]^+$ 407.1. HRMS (ESI) *m/z* calcd for $[C_{21}H_{18}N_4O_3S+ H]^+$ 407.1178, found 407.1172;HPLC: 96A% at 254 nm (HRMS).

4.2.35 Synthesis of 2-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)-N-(o-tolyl)acetamide (45). *2-(1H-indazol-5-yl)acetic acid.* A sealed degassed mixture of 5-bromo-1H-indazole (2.0 g, 10 mmol), *tert*-butyl acetate (1.6 mL, 12 mmol), $Pd(dba)_2$ (288 mg, 0.5 mmol), 1,3-bis(2,6-diisopropylphenyl)-imidazolium chloride (238 mg, 0.5 mmol), and LiHMDS (1 M in hexanes, 30 mL) in PhMe (40 mL) under Ar was stirred at 50 ºC for 2 d. The reaction mixture was quenched with saturated aq. NH_4Cl (20 mL) and then acidified using 2 M aq HCl. The reaction mixture was extracted with EtOAC, dried ($MgSO_4$), and then concentrated under reduced pressure to give the title compound: as a yellow solid (460 mg, 26 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.00 (s, 1 H), 7.67 (s, 1 H), 7.49 (d, *J* = 8.5 Hz, 1 H), 7.34 (d, *J* = 8.5 Hz, 1 H), 3.71 (s, 2 H). MS ESI 177.0 $[M + H]^+$, calcd for $[C_9H_8N_2O_2 + H]^+$ 177.1.

2-(1H-indazol-5-yl)-N-(o-tolyl)acetamide. The title compound was synthesized according to General Method A utilizing 2-(1H-indazol-5-yl)acetic acid (60 mg, 0.34 mmol), o-toluidine (36 mg, 0.34 mmol),

TBTU (109 mg, 0.34 mmol), DIPEA (66 mg, 0.51 mmol), and DMF (3 mL) to give the title compound as a pale yellow solid (36 mg, 40%); MS ESI 266.1 $[M + H]^+$, calcd for $[C_{16}H_{15}N_3O + H]^+$ 266.1.

2-(3-Iodo-1H-indazol-5-yl)-N-(o-tolyl)acetamide. The title compound was synthesized according to General Method B utilizing 2-(1H-indazol-5-yl)-N-(o-tolyl)acetamide (36 mg, 0.14 mmol), I_2 (70 mg, 0.27 mmol), K_2CO_3 (57 mg, 0.41 mmol), and DMF (3 mL) to give the product as a beige solid (50 mg, 93%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.48 - 7.54 (m, 3 H), 7.30 (d, *J* = 7.3Hz, 1 H), 7.09 - 7.23 (m, 3 H), 3.85 (s, 2 H), 2.17 (s, 3 H).

2-(3-(3-Sulfamoylphenyl)-1H-indazol-5-yl)-N-(o-tolyl)acetamide. The title compound was synthesized according to General Method C utilizing 2-(3-iodo-1H-indazol-5-yl)-N-(o-tolyl)acetamide (50 mg, 0.13 mmol), (3-sulfamoylphenyl)boronic acid (43 mg, 0.15 mmol), $PdCl_2$dppf (5.2 mg, 0.006 mmol), satd. aq. Na_2CO_3 (0.5 mL), PhMe (0.75 mL), EtOH (0.75 mL) to give the title compound as a white solid (11 mg, 20%). ^{1}H NMR (400 MHz, *acetone-d_6*) δ ppm 12.61 (br. s., 1 H), 8.62 (br. s., 1 H), 8.59 (s, 1 H), 8.29 (d, *J* = 7.5 Hz, 1 H), 8.18 (s, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.71 (t, *J* = 7.5 Hz, 1 H), 7.64 (t, *J* = 8.4 Hz, 2 H), 7.55 (d, *J* = 8.5 Hz, 1 H), 7.07 - 7.19 (m, 2 H), 7.02 (br. s., 1 H), 6.74 (br. s., 2 H), 3.92 (s, 2 H), 2.15 (s, 3 H); MS ESI 421.3 $[M + H]^+$, calcd for $[C_{22}H_{20}N_4O_3S + H]^+$ 421.1. HRMS (ESI) *m/z* calcd for $[C_{22}H_{20}N_4O_3S+ H]^+$ 421.1334, found 421.1327;HPLC: 96A% at 254 nm (LCMS).

4.2.36 3-Phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)propanamide (46). The title compound was synthesized according the General Method A, utilizing 3-phenylpropanoic acid (11 mg, 0.075 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (30 mg, 0.075 mmol), DIPEA (39 µL, 0.224 mmol), TBTU (24 mg, 0.075 mmol) and 2 mL of DMF. The majority of impurities were removed by an application of preparative HPLC, however some di-acetylated byproduct co-eluted with the title compound. The mixture was then dissolved in 2 mL of MeOH and MeONa(2 M in MeOH, 0.10 mL) was added. The mixture was stirred at 40 ºC overnight and then triturated with Et_2O to give the title compound as a white solid (4.9 mg, 16%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.48 (s, 1 H), 8.25 (s, 1 H), 8.08 (d, *J* = 7.78 Hz, 1 H), 7.94 (d, *J* = 7.78 Hz, 1 H), 7.65

(t, *J* = 7.78 Hz, 1 H), 7.53 (s, 2 H), 7.26 - 7.33 (m, 4 H), 7.16 - 7.24 (m, 1 H), 3.04 (t, *J* = 7.78 Hz, 2 H), 2.72 (t, *J* = 7.28 Hz, 2 H); MS ESI 421.2 $[M + H]^+$, calcd for $[C_{22}H_{20}N_4O_3S + H]^+$ 421.1. HPLC: >99A% at 254 nm.(HPLC).

4.2.37 2-(Pyridin-2-yl)-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (47). The title compound was synthesized according to the General Method A, utilizing 2-pyridylacetic acid (26 mg, 0.19 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate(75 mg, 0.19 mmol), DIPEA (97 µL, 0.56 mmol), TBTU (60 mg, 0.19 mmol) and 4 mL of DMF. The reaction mixture was purified using preparative HPLC, followed by triturating with CH_2Cl_2 to give the title compound as a white solid (33 mg, 43%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.77 (d, *J* =6.27 Hz, 1 H), 8.46 (s, 1 H), 8.44 (s, 1 H), 8.40 (t, *J* = 8.66 Hz, 1 H), 8.14 (d, *J* = 8.53Hz, 1 H), 7.93 (br. d, *J* =6.80 Hz, 2 H), 7.84 (t, *J* =6.30 Hz, 1 H), 7.69 (t, *J* = 8.03Hz, 1 H), 7.52 - 7.61 (m, 2 H), 4.21 (s, 2 H); MS ESI 408.1 $[M + H]^+$, calcd for $[C_{20}H_{17}N_5O_3S + H]^+$ 408.1. HPLC: >99A% at 254 nm (HPLC).

4.2.38 2-(Pyridin-4-yl)-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (48). The title compound was synthesized according to the General Method A, utilizing 4-pyridylacetic acid*HCl (22 mg, 0.124 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (50 mg, 0.124 mmol), DIPEA (108 µL, 0.622 mmol), TBTU (40 mg, 0.124 mmol) and 2 mL of DMF. The reaction mixture was purified using preparative HPLC, followed by triturating with CH_2Cl_2 to give the title compound as a white solid (40 mg, 79%). ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 13.43 (br. s., 1 H), 10.47 (s, 1 H), 8.72 (d, *J* = 6.02Hz, 2 H), 8.42 (s, 1 H), 8.39 (s, 1 H), 8.07 (d, *J* = 7.28 Hz, 1 H), 7.83 (d, *J* = 8.03 Hz, 1 H), 7.69 - 7.78 (m, 3 H), 7.62 - 7.54 (m, 2 H), 7.47 (s, 2 H), 3.96 (s, 2 H); MS ESI 408.1 $[M + H]^+$, calcd for $[C_{20}H_{17}N_5O_3S + H]^+$ 408.1. HPLC: >99A% at 254 nm (HPLC).

4.2.29 N-(2-methylbenzyl)-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide (49). The title compound was synthesized according to the General Method A utilizing 3-(3-sulfamoylphenyl)-1H-indazole-5-carboxylic acid (200 mg, 0.63 mmol), 2-methylbenzylamine (76 mg, 0.63 mmol), DIPEA (164 µL, 0.95 mmol), TBTU (202 mg, 0.63 mmol) and DMF (6 mL). The reaction mixture was purified by preparative HPLC, and then triturated with Et_2O and acetone to give the title compound as a beige

solid (157 mg, 59%). ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 13.65 (s, 1 H), 9.03 (t, *J* =5.40 Hz, 1 H), 8.65 (s, 1 H), 8.47 (s, 1 H), 8.28 (d, *J* = 6.53Hz, 1 H), 7.99 (d, *J* = 9.03Hz, 1 H), 7.87 (d, *J* = 8.28 Hz, 1 H), 7.77 (t, *J* = 8.00 Hz, 1 H), 7.68 (d, *J* = 9.03Hz, 1 H), 7.49 (s, 2 H), 7.26 - 7.30 (m, 1 H), 7.13 - 7.20 (m, 3 H), 4.51 (d, *J* =4.77 Hz, 2 H), 2.35 (s, 3 H); MS ESI 421.2 $[M + H]^+$, calcd for $[C_{22}H_{20}N_4O_3S + H]^+$ 421.1. HPLC: >99A% at 254 nm (LCMS).

4.2.30 N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)-2-(o-tolyl)acetamide (50). The title compound was synthesized according to the General Method A, utilizing 2-tolylacetic acid (12 mg, 0.075 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (30 mg, 0.075 mmol), DIPEA (39 µL, 0.225 mmol), TBTU (24 mg, 0.075 mmol) and 3 mL of DMF. The reaction mixture was purified using preparative HPLC and triturated with CH_2Cl_2 to give the title compound as a white solid (10 mg, 32 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.46 (s, 1 H), 8.39 (s, 1 H), 8.14 (d, *J* = 7.53Hz, 1 H), 7.92 (d, *J* = 7.53Hz, 1 H), 7.68 (t, *J* = 7.78 Hz, 1 H), 7.50 - 7.52 (m, 2 H), 7.25 - 7.30 (m, 1 H), 7.13 - 7.22 (m, 3 H), 3.79 (s, 2 H), 2.38 (s, 3 H); MS ESI 421.2 $[M + H]^+$, calcd for $[C_{22}H_{20}N_4O_3S + H]^+$ 421.1. HPLC: 97A% at 254 nm (HPLC).

4.2.31 Synthesis of 2-(2,6-diethylphenyl)-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (51). t*ert-Butyl 2-(2,6-diethylphenyl)acetate.* A sealed degassed mixture of 2-bromo-1,3-diethylbenzene (400 mg, 1.89 mmol), *tert*-butyl acetate (280 µL, 2.08 mmol), $Pd(dba)_2$ (54 mg, 0.09 mmol), 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (40 mg, 0.09 mmol) and LiHMDS (1 M in hexanes, 4.3 mL, 4.3 mmol) in PhMe (8 mL) under Ar was stirred at rt for 16 h. The reaction mixture was diluted with 20 mL of Et_2O and then quenched with satd aq. NH_4Cl (20 mL). The reaction mixture was washed with brine, dried over $MgSO_4$ and then under reduced pressure to give *tert*-butyl 2-(2,6-diethylphenyl)acetate as a yellow liquid (322 mg, 69 %). ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 7.13 (t, *J* = 7.5 Hz, 1 H),7.08 (d, *J* = 7.5 Hz, 2 H), 3.67 (s, 2 H), 2.68 (q, *J* = 7.5 Hz, 4 H), 1.43 (s, 9 H), 1.23 (t, *J* = 7.5 Hz, 6 H).

2-(2,6-Diethylphenyl)acetic acid. A solution of *tert*-butyl 2-(2,6-diethylphenyl)acetate (161 mg, 0. 65 mmol) in CH_2Cl_2 (5 mL) and cooled to 0 ºC. Et_3SiH (255 µL, 1.6 mmol) was added, followed by TFA

(550 μL, 8.4 mmol) and the mixture was stirred at 0 ºC for 3 h. The reaction mixture was dried under reduced pressure to give the title compound as a yellow solid (124 mg, 100 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.13 (t, *J* = 7.3Hz, 1 H), 7.04 (d, *J* = 7.8 Hz, 2 H), 3.74 (s, 2 H), 2.65 (q, *J* = 7.6 Hz, 4 H), 1.19 (t, *J* = 7.5 Hz, 6 H).

2-(2,6-Diethylphenyl)-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide. The title compound was synthesized according to the General Method A, utilizing 2-(2,6-diethylphenyl)acetic acid (20 mg, 0.104 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (42 mg, 0.104 mmol), DIPEA (55 μL, 0.313 mmol), TBTU (34 mg, 0.104 mmol) and 3 mL of DMF. The reaction mixture was purified using preparative HPLC and triturated with CH_2Cl_2 to give the title compound as a white solid (11 mg, 23 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.45 (s, 1 H), 8.37 (s, 1 H), 8.14 (d, *J* = 7.53Hz, 1 H), 7.91 (d, *J* = 8.28 Hz, 1 H), 7.67 (t, *J* = 8.03Hz, 1 H), 7.47 - 7.59 (m, 2 H), 7.16 (t, *J* = 7.00 Hz, 1 H), 7.08 (d, *J* = 8.03Hz, 2 H), 3.92 (s, 2 H), 2.73 (q, *J* = 7.53Hz, 4 H), 1.23 (t, *J* = 7.53Hz, 6 H); MS ESI 463.3 $[M + H]^+$, calcd for $[C_{25}H_{26}N_4O_3S + H]^+$ 463.2. HRMS (ESI) *m/z* calcd for $[C_{25}H_{26}N_4O_3S + H]^+$ 463.1804, found 463.1803; HPLC: >99A% at 254 nm (HPLC).

4.2.32 N-(2,6-diethylbenzyl)-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide (52). The title compound was synthesized according to the General Method A utilizing 3-(3-sulfamoylphenyl)-1H-indazole-5-carboxylic acid (25 mg, 0.079 mmol), (2,6-diethylphenyl)methanamine[56] (13 mg, 0.079 mmol), DIPEA (20 μL, 0.118 mmol), TBTU (25 mg, 0.079 mmol) and DMF (3 mL). The reaction mixture was purified by preparative HPLC, redissolved in a small amount of MeOH and precipitated out of H_2O to give the title compound as a white solid (7.5 mg, 21 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.58 (s, 1 H), 8.51 (s, 1 H), 8.22 (d, *J* = 7.53Hz, 1 H), 7.94 (t, *J* = 9.16 Hz, 2 H), 7.69 (t, *J* = 7.65 Hz, 1 H), 7.62 (d, *J* = 8.53Hz, 1 H), 7.20 (t, *J* = 7.80 Hz, 1 H), 7.11 (d, *J* = 7.78 Hz, 2 H), 4.69 (s, 2 H), 2.79 (q, *J* = 7.53Hz, 4 H), 1.25 (t, *J* = 7.53Hz, 6 H); MS ESI 463.3 $[M + H]^+$, calcd for $[C_{25}H_{26}N_4O_3S + H]^+$ 463.2. HPLC: >99A% at 254 nm (HPLC).

4.2.33 Synthesis of 4-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)piperidine-4-carboxamide (53). *1-(tert-Butoxycarbonyl)-4-phenylpiperidine-4-carboxylic acid.* Solution of 4-

phenylpiperidine-4-carboxylic acid hydrochloride (Tyger Scientific, 0.30 g, 1.2 mmol) and DIPEA (0.65 mL, 3.7 mmol) in DCM (10 mL) and DMF (4 mL) was treated with di-tert-butyl dicarbonate (0.34 g, 1.6 mmol) and stirred at rt for 3 h. Later the reaction was concentrated under reduced pressure and triturated with hexanes to afford 1-(tert-butoxycarbonyl)-4-phenylpiperidine-4-carboxylic acid (0.2g) containing 1 equiv of DIPEA . The material was used in the following step without further purification.

4-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)piperidine-4-carboxamide. The title compound was synthesized according the General Method A., utilizing 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (80 mg, 0.20 mmol), crude *1-(tert-butoxycarbonyl)-4-phenylpiperidine-4-carboxylic acid* (153 mg, 0.22 mmol), DIPEA (0.1 mL, 0.6 mmol) and TBTU (70 mg, 0.22 mmol) in DMF (2 mL). The crude material was purified by preparative HPLC to provide tert-butyl 4-phenyl-4-(3-(3-sulfamoylphenyl)-1H-indazol-5-ylcarbamoyl)piperidine-1-carboxylate (MS ESI 576.2 $[M + H]^+$, calcd for $[C_{30}H_{33}N_5O_5S + H]^+$ 576.2) as a pale red solid. The material was then taken in DCM (10 mL), treated with Et_3SiH (0.07 mL, 0.44 mmol) and TFA (2 mL) at 0 ^oC allowing after 1 h to warm to rt (2h). Later the reaction mixture was concentrated and purified by preparative HPLC. A single trituration with Et_2O provided the title compound as an off-white solid (TFA salt, 30 mg, 26 %). ^1H NMR (400 MHz, *CD_3OD*) δ ppm 8.47 (s, 1 H), 8.23 (s, 1 H), 8.15 (d, *J* = 7.78 Hz, 1 H), 7.95 (d, *J* = 7.78 Hz, 1 H), 7.70 (t, *J* = 7.78 Hz, 1 H), 7.51 - 7.57 (m, 3 H), 7.50 - 7.57 (m, 3 H), 7.36 (t, *J* = 7.16 Hz, 1 H), 3.34 - 3.51 (m, 4 H), 2.79 - 2.92 (m, 2 H), 2.25 - 2.37 (m, 2 H); MS ESI 476.3 $[M + H]^+$, calcd for $[C_{25}H_{25}N_5O_3S + H]^+$ 476.2. HPLC: >99A% at 254 nm.

4.2.34 1-Phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)cyclopropanecarboxamide (54). The title compound was synthesized according to the General Method A, utilizing 1-phenylcyclopropanecarboxylic acid (Alfa Aeasar, 22 mg, 0.124 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (50 mg, 0.124 mmol), DIPEA (65 µL, 0.373 mmol), TBTU (40 mg, 0.124 mmol) and 3 mL of DMF. The reaction mixture was purified using preparative HPLC and triturated with Et_2O to give the title compound as a white solid (50 mg, 93%). ^1H NMR (400

MHz, *acetone-d_6*) δ ppm 12.50 (br. s, 2 H), 8.51 (s, 1 H), 8.35 (s, 1 H), 8.14 (d, *J* = 7.53Hz, 1 H), 8.09 (br. s., 1 H), 7.89 (d, *J* = 7.78 Hz, 1 H), 7.70 (t, *J* = 7.65 Hz, 1 H), 7.54 (t, *J* = 8.03Hz, 3 H), 7.42 (t, *J* = 7.30 Hz, 3 H), 7.35 (t, *J* = 7.30 Hz, 1 H), 6.71 (br. s., 1 H), 1.59 (s, 2 H), 1.13 (s, 2 H); MS ESI 433.3 $[M + H]^+$, calcd for $[C_{23}H_{20}N_4O_3S + H]^+$ 433.1. HPLC: 95A% at 254 nm.(LCMS)

4.2.35 Synthesis of N-(1-phenylcyclopropyl)-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide (55). *1-Phenylcyclopropanamine.* A sealed degassed mixture of 1-phenylcyclopropane carboxylic acid (500 mg, 3.09 mmol), triethylamine (429 µL, 3.09 mmol), and PhMe (2 mL) was charged with Ar. Diphenylphosphoryl azide (668 µL, 3.09 mmol) was slowly added and then the reaction mixture was heated to 80 ºC and stirred for 120 min. *tert*-Butanol (586 µL, 6.2 mmol) was added and the reaction was continued to stir at 80 ºC for 6 h. The reaction mixture was diluted with Et_2O (20 mL) and washed with 0.33 M aq NaOH, dried ($MgSO_4$) and concentrated under reduced pressure to give tert-butyl 1-phenylcyclopropylcarbamate as a white solid (448 mg, 62%). This material was dissolved in CH_2Cl_2 (5 mL), cooled to 0 ºC and treated with TFA (1 mL). The reaction was stirred at 0 ºC for 30 min and then at rt for 1 h. The reaction mixture was then dried under reduced pressure to give the title compound (TFA salt) as a white solid (475 mg, 62%). ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 7.95 (br. s., 2 H), 7.28 - 7.49 (m, 5 H), 1.35 (br. s., 2 H), 1.13 (br. s, 2 H).

N-(1-phenylcyclopropyl)-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide. The title compound was synthesized according to the General Method A utilizing 3-(3-sulfamoylphenyl)-1H-indazole-5-carboxylic acid (40 mg, 0.126 mmol), 1-phenylcyclopropanamine*TFA (31 mg, 0.126 mmol), DIPEA (66 µL, 0.378 mmol), TBTU (41 mg, 0.126 mmol) and DMF (3 mL). The reaction mixture was purified by preparative HPLC, and triturating with Et_2O to give the title compound as a white solid (14 mg, 26%). ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 13.66 (s, 1 H), 9.32 (s, 1 H), 8.66 (s, 1 H), 8.48 (s, 1 H), 8.31 (d, *J* = 8.53Hz, 1 H), 7.97 (d, *J* = 8.03Hz, 1 H), 7.88 (d, *J* = 7.28 Hz, 1 H), 7.78 (t, *J* = 7.78 Hz, 1 H), 7.68 (d, *J* = 8.28 Hz, 1 H), 7.50 (s, 2 H), 7.20 - 7.31 (m, 4 H), 7.15 (t, *J* =6.80 Hz, 1 H), 1.25 - 1.35 (m, 4 H); MS ESI 433.2 $[M + H]^+$, calcd for $[C_{23}H_{20}N_4O_3S + H]^+$ 433.1. HPLC:95A% at 254 nm (LCMS).

4.2.36 (±)-**2-Phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)butanamide (56).** The title compound was synthesized according to the General Method A, utilizing (±)-2-phenylbutanoic acid (Alfa Aeasar, 16 mg, 0.10 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate(40 mg, 0.10 mmol), DIPEA (52 μL, 0.30 mmol), TBTU (32 mg, 0.10 mmol) and 3 mL of DMF. The reaction mixture was purified using preparative HPLC and triturated with CH_2Cl_2 to give the title compound as a white solid (19 mg, 44%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.46 (s, 1 H), 8.37 (s, 1 H), 8.15 (d, *J* = 8.03Hz, 1 H), 7.93 (d, *J* = 7.53Hz, 1 H), 7.69 (t, *J* = 7.91Hz, 1 H), 7.52 (m, 2 H), 7.44 (d, *J* = 7.28 Hz, 2 H), 7.33 (t, *J* = 7.50 Hz, 2 H), 7.24 (t, *J* = 7.50 Hz, 1 H), 3.58 (t, *J* = 7.40 Hz, 1 H), 2.12 - 2.24 (m, 1 H), 1.78 - 1.90 (m, 1 H), 0.98 (t, *J* = 7.28 Hz, 3 H); MS ESI 435.2 $[M + H]^+$, calcd for $[C_{23}H_{22}N_4O_3S + H]^+$ 435.1. HPLC: >99A% at 254 nm (HPLC).

4.2.37 3-Methyl-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)butanamide (57). The title compound was synthesized according to the General Method A, utilizing (±)-3-methyl-2-phenylbutanoic acid (Alfa Aeasar, 22 mg, 0.124 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (50 mg, 0.124 mmol), DIPEA (65 μL, 0.372 mmol), TBTU (40 mg, 0.124 mmol) and 2 mL of DMF. The reaction mixture was purified using preparative HPLC to give the desired product and some di-acetylated byproduct. The di-acetylated byproduct was then dissolved in 2 mL of MeOH and then 2 M of MeONa in MeOH (100 μL) was added and then stirred at 45ºC for 4 h. This was purified by preparative HPLC, combined with the pure product from the first HPLC run and triturated with CH_2Cl_2 to give the title compound as a white solid (5.8 mg, 10 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.45 (s, 1 H), 8.36 (s, 1 H), 8.15 (d, *J* = 7.03Hz, 1 H), 7.93 (d, *J* = 8.28 Hz, 1 H), 7.67 - 7.73 (m, 1 H), 7.49 - 7.56 (m, 2 H), 7.44 - 7.48 (m, 2 H), 7.33 (t, *J* = 7.10 Hz, 2 H), 7.25 (t, *J* = 8.00 Hz, 1 H), 3.23 (d, *J* =10.79 Hz, 1 H), 2.42 - 2.52 (m, 1 H), 1.13 (d, *J* =6.27 Hz, 3 H), 0.75 (d, *J* =6.27 Hz, 3 H); MS ESI 449.2 $[M + H]^+$, calcd for $[C_{24}H_{24}N_4O_3S + H]^+$ 449.2. HPLC: >99A%at 254 nm (HPLC).

4.2.38 N-(cyclopropyl(phenyl)methyl)-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide (58). The title compound was synthesized according to the General Method A utilizing 3-(3-

sulfamoylphenyl)-1H-indazole-5-carboxylic acid (40 mg, 0.13 mmol), cyclopropyl(phenyl)methanamine (AlfaAeasar, 23 mg, 0.13 mmol), DIPEA (66 μL, 0.38 mmol), TBTU (41 mg, 0.13 mmol) and DMF (3 mL). The reaction mixture was purified by preparative HPLC, and triturating with Et_2O to give the title compound as a white solid (21 mg, 37%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.65 (s, 1 H), 8.55 (s, 1 H), 8.27 (d, *J* = 8.28 Hz, 1 H), 7.98 (d, *J* = 8.03Hz, 2 H), 7.73 (t, *J* = 7.50 Hz, 1 H), 7.66 (d, *J* = 9.29 Hz, 1 H), 7.49 (d, *J* = 7.28 Hz, 2 H), 7.34 (t, *J* = 7.65 Hz, 2 H), 7.24 (t, *J* = 8.00 Hz, 1 H), 4.48 (d, *J* = 8.78 Hz, 1 H), 1.36 - 1.45 (m, 1 H), 0.64 - 0.70 (m, 2 H), 0.45 - 0.52 (m, 2 H); MS ESI 447.3 $[M + H]^+$, calcd for $[C_{24}H_{22}N_4O_3S + H]^+$ 447.1. HRMS (ESI) *m/z* calcd for $[C_{24}H_{22}N_4O_3S+ H]^+$ 447.1491, found 447.1492;HPLC: 96A% at 254 nm (HRMS).

4.2.39 Synthesis of N-(cyclopropyl(thiophen-3-yl)methyl)-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide (59). *Cyclopropyl(thiophen-3-yl)methanamine.* The title compound was synthesized according to the method described for N-(cyclohexyl(phenyl)methyl)-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide (**62**) step A, utilizing cyclopropyl(thiophen-3-yl)methanone (Rieke Metals, 500 mg, 3.29 mmol), MeOH (15 mL), NH_4OAc (3.04 g, 40 mmol), and $NaCNBH_3$ (829 mg, 13 mmol) to give the title compound as a clear oil (460 mg, 91%); MS ESI 154.2 $[M + H]^+$, calcd for $[C_8H_{11}NS + H]^+$ 154.1

N-(cyclopropyl(thiophen-3-yl)methyl)-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide. The title compound was synthesized according to the General method A utilizing 3-(3-sulfamoylphenyl)-1H-indazole-5-carboxylic acid (100 mg, 0.32 mmol), cyclopropyl(thiophen-3-yl)methanamine (48 mg, 0.32 mmol), DIPEA (111 μL, 0.64 mmol), TBTU (103 mg, 0.32 mmol) and DMF (4 mL). The reaction mixture was purified by preparative HPLC, and then triturated with Et_2O to give the title compound as a white solid (70 mg, 48%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.64 (s, 1 H), 8.54 (s, 1 H), 8.26 (d, *J* = 7.78 Hz, 1 H), 7.94 - 8.00 (m, 2 H), 7.73 (t, *J* = 7.78 Hz, 1 H), 7.66 (d, *J* = 9.03 Hz, 1 H), 7.34 - 7.39 (m, 2 H), 7.20 (m, *J* =3.26 Hz, 1 H), 4.59 - 4.66 (m, 1 H), 1.38 - 1.49 (m, 1 H), 0.68 - 0.76 (m, 1 H), 0.60 - 0.68 (m, 1 H), 0.44 - 0.54 (m, 2 H); MS ESI 453.2 $[M + H]^+$, calcd for $[C_{22}H_{20}N_4O_3S_2 + H]^+$

453.1. HRMS (ESI) *m/z* calcd for $[C_{22}H_{20}N_4O_3S_2 + H]^+$ 453.1055, found 453.1053;HPLC: 98A% at 254 nm (HRMS).

4.2.40 2-Cyclopentyl-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (60). The title compound was synthesized the General Method A, utilizing 2-cyclopentyl-2-phenylacetic acid (TCI America, 51 mg, 0.25 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide*TFA (100 mg, 0.25 mmol), DIPEA (130 µL, 0.75 mmol), TBTU (80 mg, 0.25 mmol) and 4 mL of DMF. The reaction mixture was purified using preparative HPLC and triturated with Et_2O to give the title compound as a white solid (33 mg, 28%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.46 (s, 1 H), 8.35 (s, 1 H), 8.15 (d, *J* = 8.53Hz, 1 H), 7.93 (d, *J* = 7.28 Hz, 1 H), 7.70 (t, *J* = 7.53Hz, 1 H), 7.45 - 7.56 (m, 4 H), 7.32 (t, *J* = 7.78 Hz, 2 H), 7.25 (t, *J* =6.80 Hz, 1 H), 3.37 (t, *J* =11.30 Hz, 1 H), 2.72 (br. s, 1 H), 1.98 (br. s, 1 H), 1.33 - 1.80 (m, 6 H), 1.08 (br. s, 1 H); MS ESI 475.3 $[M + H]^+$, calcd for $[C_{26}H_{26}N_4O_3S + H]^+$ 475.2. HPLC: >96A% at 254 nm (LCMS).

4.2.41 2-Cyclohexyl-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (61). The title compound was synthesized according to General Method A utilizing cyclohexylphenylacetic acid (55 mg, 0.25 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide*TFA (100 mg, 0.25 mmol), DIPEA (130 µL, 0.75 mmol), TBTU (80 mg, 0.25 mmol) and 4 mL of DMF. The reaction mixture was purified using preparative HPLC and triturated with Et_2O to give the title compound as a white solid (71 mg, 58%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.45 (s, 1 H), 8.35 (s, 1 H), 8.15 (d, *J* = 7.53Hz, 1 H), 7.93 (d, *J* = 7.28 Hz, 1 H), 7.70 (t, *J* = 7.91Hz, 1 H), 7.47 - 7.55 (m, 2 H), 7.45 (d, *J* = 7.03Hz, 2 H), 7.32 (t, *J* =6.90 Hz, 2 H), 7.24 (t, *J* = 7.30 Hz, 1 H), 3.33 - 3.37 (m, 1 H), 2.10 - 2.22 (m, 1 H), 1.97 (d, *J* =11.80 Hz, 1 H), 1.79 (d, *J* =13.55 Hz, 1 H), 1.67 (br. s., 2 H), 1.30 - 1.42 (m, 2 H), 1.10 - 1.27 (m, 3 H), 0.76 - 0.91 (m, 1 H); MS ESI 489.3 $[M + H]^+$, calcd for $[C_{27}H_{28}N_4O_3S + H]^+$ 489.2. HPLC: >99A%at 254 nm (LCMS).

4.2.42 Synthesis of N-(cyclohexyl(phenyl)methyl)-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide (62). *Cyclohexyl(phenyl)methanamine*. Cyclohexyl(phenyl)methanone (940 mg, 5 mmol) was dissolved in MeOH (15mL) and then NH_4OAc (4.62 g, 60 mmol) was added. Reaction was

stirred for 10 min at 25 ºC. $NaBH_3CN$ (1.26 g, 20 mmol) was added and the reaction was heated to 60 ºC and stirred at that temperature for 16 h. The solvent was removed under reduced pressure and the reaction mixture was suspended in 0.5 M aq NaOH (75 mL), extracted with EtOAc (3 x 20 mL), dried ($MgSO_4$) and then under reduced pressure to give the title compound as a clear oil (868 mg, 92%). ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 7.20 - 7.41 (m, 5 H), 3.61 (d, *J*=7.78 Hz, 1 H), 2.77 (br. s., 2 H), 1.96 (d, *J*=12.80 Hz, 1 H), 1.78 (d, *J*=13.05 Hz, 1 H), 1.47 - 1.70 (m, 3 H), 1.38 (d, *J*=12.30 Hz, 1 H), 0.78 - 1.33 (m, 5 H).

N-(cyclohexyl(phenyl)methyl)-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide. The title compound was synthesized according to General Method A utilizing 3-(3-sulfamoylphenyl)-1H-indazole-5-carboxylic acid (100 mg, 0.32 mmol), cyclohexyl(phenyl)methanamine (60 mg, 0.32 mmol), DIPEA (111 µL, 0.64 mmol), TBTU (103mg, 0.32 mmol) and DMF (4 mL). The reaction mixture was purified by preparative HPLC, and then triturated with Et_2O to give the title compound as white solid (60 mg, 38%). ^{1}H NMR (400 MHz, *CD_3OD* δ ppm 8.57 (br. s., 1 H), 8.53 (br. s., 1 H), 8.23 (d, *J*=6.78 Hz, 1 H), 7.96 (d, *J*=7.78 Hz, 1 H), 7.90 (d, *J*=8.78 Hz, 1 H), 7.67-7.76 (m., 1 H), 7.63 (d, *J*=9.03 Hz, 1 H), 7.14 - 7.43 (m, 5 H), 4.80 (d, *J*=9.54 Hz, 1 H), 2.09 (br. s., 1 H), 1.75 - 1.98 (m, 2 H), 1.66 (br. s., 2 H), 1.06 - 1.45 (m, 5 H), 0.80 - 1.02 (m, 1 H); MS ESI 489.3 $[M + H]^+$, calcd for $[C_{27}H_{28}N_4O_3S + H]^+$ 489.2. HPLC: 99A% at 254 nm (LCMS).

4.2.43 2-Methoxy-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (63). The title compound was synthesized according to General Method A utilizing 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (0.050 g, 0.12 mmol), rac-2-methoxy-2-phenylacetic acid (Sigma-Aldrich, 0.021 g, 0.12 mmol), DIPEA (0.1 mL, 0.6 mmol) and TBTU (0.042 g, 0.13 mmol) in DMF (2 mL). Purification by preparative HPLC provided the title compound as a white powder (13 mg, 24 ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 10.00 (s, 1 H), 8.47 (s, 1 H), 8.37 (s, 1 H), 8.16 (d, *J* = 7.78 Hz, 1 H), 7.94 (d, *J* = 7.28 Hz, 1 H), 7.69 (t, *J* = 7.91Hz, 1 H), 7.62 (dd, *J* =1.51, 9.03Hz, 1 H), 7.50 - 7.59 (m, 3 H), 7.29 - 7.46 (m, 3 H), 4.85 (s, 1 H), 3.47 (s, 3 H); MS ESI 437.2 $[M + H]^+$, calcd

for $[C_{22}H_{20}N_4O_4S+ H]^+$ 437.1. HRMS (ESI) *m/z* calcd for $[C_{22}H_{20}N_4O_4S+ H]^+$ 437.1284, found 437.1274 ;HPLC: >99A% at 254 nm.

4.2.44 (S)-2-Methoxy-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (64). The title compound was synthesized according to the General Method A, utilizing (S)-2-methoxy-2-phenylacetic acid (Alfa Aeasar, 83 mg, 0.50 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (200 mg, 0.50 mmol), DIPEA (260 µL, 1.50 mmol), TBTU (160 mg, 0.50 mmol) and 64 mL of DMF. The reaction mixture was purified using preparative HPLC and triturated with Et_2O to give the title compound as a white solid (129 mg, 59%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.46 (s, 1 H), 8.37 (s, 1 H), 8.15 (d, *J* = 8.28 Hz, 1 H), 7.93 (d, *J* = 8.03Hz, 1 H), 7.68 (t, *J* = 7.78 Hz, 1 H), 7.62 (d, *J* = 9.03Hz, 1 H), 7.49 - 7.58 (m, 3 H), 7.40 (d, *J* = 7.28 Hz, 3 H), 4.84 (s, 1 H), 3.46 (s, 3 H); MS ESI 437.3 $[M + H]^+$, calcd for $[C_{22}H_{20}N_4O_4S + H]^+$ 437.1 HPLC: >99A%at 254 nm (LCMS).

4.2.45 (R)-2-Methoxy-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (65). The title compound was synthesized according to the General Method A utilizing 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (0.10 g, 0.26 mmol), (R)-2-methoxy-2-phenylacetic acid (Alfa Aeasar, 0.044 g, 0.27 mmol), DIPEA (0.1 mL, 0.6 mmol) and TBTU (0.086 g, 0.27 mmol) in DMF (2 mL). Purification by preparative HPLC provided the title compound as a white powder (67 mg, 60 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 9.99 (s, 1 H), 8.47 (s, 1 H), 8.38 (s, 1 H), 8.15 (d, *J* = 7.78 Hz, 1 H), 7.93 (d, *J* = 8.03Hz, 1 H), 7.68 (t, *J* = 7.78 Hz, 1 H), 7.62 (d, *J* = 9.03Hz, 1 H), 7.50 - 7.58 (m, 3 H), 7.31 - 7.46 (m, 3 H), 4.85 (s, 1 H), 3.47 (s, 3 H); MS ESI 437.3 $[M + H]^+$, calcd for $[C_{22}H_{20}N_4O_4S+ H]^+$ 437.1. HPLC: 98A% at 254 nm.

4.2.46 2-Ethoxy-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (66). The title compound was synthesized according the General Method A, utilizing 2-ethoxy-2-phenylacetic acid (47 mg, 0.26 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (100 mg, 0.25 mmol), DIPEA (0.12 mL, 0.74 mmol), TBTU (81 mg, 0.25 mmol) and 3 mL of DMF. The reaction mixture was purified using preparative HPLC to give the title compound as a white solid (43 mg, 38%).

^{1}H NMR (400 MHz, *CD_3OD-d_4*) δ ppm 8.46 (s, 1 H), 8.37 (s, 1 H), 8.14 (d, *J*=7.78 Hz, 1 H), 7.93 (d, *J*=7.78 Hz, 1 H), 7.67 (t, *J*=7.50 Hz, 1 H), 7.51 - 7.63 (m, 4 H), 7.30 - 7.46 (m, 3 H), 4.95 (s, 1 H), 3.54 - 3.72 (m, 2 H), 1.33 (t, *J*=7.03 Hz, 3 H); MS ESI 451.3 $[M + H]^+$, calcd for $[C_{23}H_{22}N_4O_4S + H]^+$ 451.1. HPLC: >99A% at 254 nm.

4.2.47 Synthesis of 2-(dimethylamino)-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (67). *2-(Dimethylamino)-2-phenylacetic acid hydrochloride.* A sealed degassed mixture of PhBr (200 μL, 1.92 mmol), *N,N*-dimethylglycine ethyl ester (300 μL, 2.11 mmol), $Pd[P(t\text{-}Bu)_3]_2$ (49 mg, 0.096 mmol), K_3PO_4 (937 mg, 4.42 mmol), PhMe (6 mL) under Ar was heated at 120 ºC for 20 h. The reaction mixture was diluted with 20 mL of Et_2O, washed with brine, and then dried under reduced pressure to give ethyl 2-(dimethylamino)-2-phenylacetate as a yellow liquid (386 mg, 95%). ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 7.44 (d, *J* = 7.28 Hz, 2 H), 7.30 - 7.38 (m, 3 H), 4.08 - 4.26 (m, 2 H), 3.85 (s, 1 H), 2.26 (s, 6 H), 1.22 (t, *J* = 7.15 Hz, 3 H)

A sealed mixture of ethyl 2-(dimethylamino)-2-phenylacetate (130 mg, 0.63 mmol) and 6 M aq HCl (2 mL) was heated under microwave irradiation for 120 min at 120 ºC. The reaction mixture was dried under reduced pressure to give the title compound as a yellow solid (135 mg, 100 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.49 - 7.59 (m, 5 H), 5.11 (s, 1 H), 3.07 (s, 3 H), 2.60 (s, 3 H).

2-(Dimethylamino)-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide. The title compound was synthesized according to the General Method A, utilizing 2-(dimethylamino)-2-phenylacetic acid*HCl (32 mg, 0.15 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (60 mg, 0.15 mmol), DIPEA (130 μL, 0.75 mmol), TBTU (48 mg, 0.15 mmol) and 5 mL of DMF. The reaction mixture was purified using preparative HPLC and triturated with Et_2O to give the title compound as a white solid (TFA salt, 38 mg, 45%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.48 (s, 1 H), 8.41 (s, 1 H), 8.15 (d, *J* = 7.53Hz, 1 H), 7.95 (d, *J* = 8.03Hz, 1 H), 7.65 - 7.73 (m, 3 H), 7.50 - 7.60 (m, 5 H), 5.04 (s, 1 H), 3.10 (br. s, 3 H), 2.65 (br. s, 3 H); MS ESI 450.2 $[M + H]^+$, calcd for $[C_{23}H_{23}N_5O_3S + H]^+$ 450.1. HPLC: >99A% at 254 nm (HPLC).

4.2.48 Synthesis of (S)-2-(dimethylamino)-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (68). *A. Ethyl 2-bromo-2-phenylacetate.* To a solution of α-bromophenylacetic acid (5.0 g, 0.023 mol) in EtOH (50 mL) at was added conc. H_2SO_4 (0.5 g, 0.005 mol) dropwise over 15 min at rt. The resulting mixture was stirred at 75 °C for 18 h. The solvent was removed under reduced pressure and dissolved residue in EtOAc (50 mL) and washed with aq Na_2CO_3 (1 M, 50 mL). The phases were separated and dried (Na_2SO_4), filtered and concentrated to give the title compound as a colorless oil (5.25 g, 93 %).^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.56 (dd, *J* = 7.7, 1.9 Hz, 2 H), 7.4-7.34 (m, 3 H), 5.35 (s, 1 H),4.29-4.20 (m, 2 H), 1.29 (t, *J* = 7.2 Hz, 3 H).

Ethyl 2-(dimethylamino)-2-phenylacetate To a solution of ethyl 2-bromo-2-phenylacetate (5.25 g, 0.021 mol) in THF (26 mL) at rt was added Na_2CO_3 (2.29 g, 0.021 mol) followed by Me_2NH (1 M in THF, 24 mL) dropwise in 15 min at rt. After addition, the resulting mixture was stirred at the same temperature for 18 h, filtered the insoluble salt and washed with EtOAc (10 mL, 2x). The combined filtrate concentrated under reduced pressure to give a thick oil. The oily product was dissolved in DCM (25 mL) and washed it with H_2O (15 mL) and dried (Na_2SO_4), filtered and concentrated to give the title compound as a yellowish oil (4.25 g, 95%). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.56 (dd, *J* = 7.7, 1.9 Hz, 2 H), 7.4-7.34 (m, 3 H), 5.35 (s, 1 H),4.29-4.20 (m, 2 H), 2.26(s, 6H), 1.29 (t, *J* = 7.2 Hz, 3 H); MS ESI 208.0 $[M + H]^+$, calcd for $[C_{12}H_{17}NO_2 + H]^+$ 208.1.

(S)-2-(dimethylamino)-2-phenylacetic acid hydrochloride. To a solution of ethyl 2-(dimethylamino)-2-phenylacetate (1.5 g, 0.007 mol) in EtOH (15 mL) at rt was added (+)-dibenzoyl-D-tartaric acid (1.84 g, 0.005 mol). the solution was heated to 75°C for 1 h. after stirring 1 h at rt cooled to 5°C and agitated for 1 h. the precipitated insoluble salt was filtered, well pressed and washed it with EtOH (2x1.5 mL) and dried under vacuum at rt for 24 h to give (-)-ethyl 2-(dimethylamino)-2-phenylacetate*(+)-dibenzoyl-D-tartaric acid salt (1.87 g). The filtrate and washings were combined and to that another portion of (+)-dibenzoyl-D-tartaric acid (0.62 g, 0.0017 mol) and H_2O (25 mL) were added at rt. The solution was heated to 75 °C for 1 h and kept overnight at 0°C. The solid was filtered and washed it with EtOH (2x1.5 mL) and dried under vacuum at rt for 24 h to give a white solid as (+)-ethyl 2-

(dimethylamino)-2-phenylacetate*(+)-dibenzoyl-D-tartaric acid salt 1.67 g. Optical Rotation: $[\alpha]^{22}_{D}$ = 124 ^{o} (c 0.5, MeOH). Dissolved 1.67 g of above crude salt in a mixture of EtOH (5.85 mL) and H_2O (2.5 mL) at 65°C.then gradually cooled to rt and stirred at 0°C for 1 h. the solid was filtered and air-dried with suction to give pure white solid 1.08 g. Optical Rotation: $[\alpha]^{22}_{D}$ = 125.4^{o} (c 0.63, MeOH). ^{1}H NMR (400 MHz, *CD_3OD*) δ 8.14 (d, *J* = 7.2Hz, 4H), 7.64-7.60 (m, 2 H), 7.51-7.47 (m, 9 H), 5.93 (s, 2 H), 4.28-4.20 (m, 2 H), 2.68 (s, 6H), 1.18 (t, *J* =6.8 Hz, 3 H), 1H merged with solvent peak. The solid (1.08 g) was stirred with conc aq HCl (30 mL) at rt for 15 min and then extracted with DCM (40 mL). The aqueous layer was separated and refluxed for 32 h at 95 °C. Removal of solvents under high vacuum (35°C/2 mbar) gave the title compound as a white solid 300 mg. After trituration of 300 mg salt with MeCN (6 mL) at rt for 15 min to give title compound as a white hydrochloride salt (127 mg, 8 %). Optical Rotation: $[\alpha]^{22}_{D}$ = 107.8^{o}(c 0.51, H_2O). (lit. value for (*R*)-enatiomer: -117.1 °(c 0.99, H_2O)).[57] ^{1}H NMR (400 MHz, *DMSO-d_6*) δ 7.55-7.49 (m, 5 H), 5.21 (s, 1 H), 2.68 (s, 6 H); MS ESI 180.0 $[M + H]^+$, calcd for $[C_{10}H_{13}NO_2 + H]^+$ 180.1.

(S)-2-(dimethylamino)-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide

The title compound was synthesized according to the General Method A, utilizing (S)-2-(dimethylamino)-2-phenylaceticacid hydrochloride (91 % op, 30 mg, 0.139 mmol), 3-(5-amino-1H-indazol-3-yl) benzenesulfonamide hydrochloride (45 mg, 0.139 mmol), DIPEA (0.12 mL, 0.695 mmol) and TBTU (45 mg, 0.139 mmol) in DMF (1.2 mL). The reaction mixture was purified by flash chromatography (25 g SiO_2, gradient 0-10% MeOH in DCM) and repurified by reverse phase preparative HPLC (Biotage $C_{18,}$ 50 g column, gradient 90:10-20:80 % 0.1% TFA- H_2O: MeOH) to give the title compound as a white solid (TFA salt, 15 mg, 19 %, 86.2 % ee by chiral HPLC Rt = 9.8 min, Chiralpak AS-H (25 x 0.46 cm), 3.0 mL/min, isocratic 30% *i*-BuOH (0.1% DEA)/CO_2, 100 bar). ^{1}H NMR (400 MHz, *CD_3OD*) δ 8.48 (s, 1 H), 8.41 (s, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 7.94 (d, *J* = 7.6 Hz, 1 H), 7.28-7.68 (m, 3 H), 7.58-7.52 (m, 5H), 5.01 (s, 1 H), 3.13 (br.s, 3 H), 2.70-2.64 (br.m, 3 H); MS ESI 450.3. $[M + H]^+$, calcd for $[C_{23}H_{23}N_5O_3S + H]^+$ 450.1. HPLC: 95A% at 254 nm.

4.2.49 Synthesis of (R)-2-(dimethylamino)-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (69). *(R)-2-(Dimethylamino)-2-phenylacetic acid.* To a suspension of (D)-phenylglycine (4.53 g, 30 mmol, TCI America, specific rotation $[\alpha]_{20}D$ -155.0 to -159.0 ^{o} (c=1.1 mol/L HCl)) in MeOH (60 mL) was added 6 M aq HCl (5.5 mL, 33 mmol) dropwise, followed by 37 % aq formalin (20.7 mL, 270 mmol, 9 equiv). The resulting colorless clear solution was treated with 10 % Pd/C (272 mg, 6 wt. %). It was evacuated and refilled with H_2 twice. The resulting mixture was stirred for 1 d under H_2 (1 atm). After filtering through Celite and rinsing with MeOH, the filtrate was concentrated to dryness to give a white solid. Recrystallization from *i*-PrOH/MeOH (60 mL/5 mL) in at -20 ^{o}C gave (R)-2-(dimethylamino)-2-phenylacetic acid hydrochloride as white pellets (2.01 g, 33%). ^{1}H NMR (400 MHz, *DMSO-d_6*) δ 14.10 (s, br, 1 H), 11.00 (s, br, 1 H), 7.58-7.45 (m, 5H), 5.25 (s, 1 H), 2.69 (s, 6H). $[\alpha]_{24}D$= +116.4^{o} (c = 1.52, H_2O).

(R)-2-(dimethylamino)-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide.

To .a mixture of 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide hydrochloride (163 mg, 0.5 mmol), (*R*)-2-(dimethylamino)-2-phenylacetic acid hydrochloride (108 mg, 0.5 mmol) and TBTU (161 mg, 0.5 mmol) in DMF (6 mL) at 0 ^{o}C was added DIPEA (0.35 mL, 2. mmol). After addition, the resulting mixture was stirred for 1 h at 0 ^{o}C. The reaction mixture was purified directly by preparative HPLC followed by trituration with Et_2O to give the title compound as a light beige solid (TFA salt, 173 mg, 61%, 94.7% ee, Rt = 8.3 min, by chiral HPLC using Chiralpak AS-H (25 x 0.46 cm), 3.0 mL/min, isocratic 30% *i*-BuOH(0.1% DEA)/CO_2, 100 bar). ^{1}H NMR (400 MHz, *CD_3OD*) δ 8.49 (t, *J* = 1.8 Hz, 1 H), 8.42 (s, 1 H), 8.16 (d, *J* = 7.6 Hz, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 7.74-7.67 (m, 3 H), 7.61-7.56 (m, 4H), 7.54 (dd, *J* = 9.0, 1.8 Hz, 1 H), 5.03 (s, 1 H), 3.20-2.60 (br. m, 6H); MS ESI. $[M + H]^+$ 450.2, calcd for $[C_{23}H_{23}N_5O_3S + H]^+$ 450.2. HPLC: 95A% at 254 nm.

4.2.50 Synthesis of 2-Phenyl-2-(pyrrolidin-1-yl)-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (70). *tert-Butyl 2-phenyl-2-(pyrrolidin-1-yl)acetate*. tert-Butyl 2-phenyl-2-(pyrrolidin-1-yl)acetate was synthesized according to the method described for 2-(dimethylamino)-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (**67**) step A utilizing PhBr (200 µL, 1.9 mmol), *tert*-butyl

2-(pyrrolidin-1-yl)acetate (390 μL, 2.1 mmol), $Pd[P(t\text{-}Bu)_3]_2$ (49 mg, 0.096 mmol), K_3PO_4 (937 mg, 4.42 mmol) and PhMe (5 mL) to give tert-butyl 2-phenyl-2-(pyrrolidin-1-yl)acetate as a brown liquid (480 mg, 96 %). ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 7.48 (d, *J* = 7.5 Hz, 2 H), 7.30 - 7.37 (m, 3 H), 3.83 (s, 1 H), 2.56 - 2.64 (m, 2 H), 2.43 - 2.51 (m, 2 H), 1.77 - 1.85 (m, 4 H), 1.41 (s, 9 H).

1-(Carboxy(phenyl)methyl)pyrrolidinium 2,2,2-trifluoroacetate. The title compound was synthesized according to the method described for 2-(2,6-diethylphenyl)-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (**51**) in step B utilizing tert-butyl 2-phenyl-2-(pyrrolidin-1-yl)acetate (175 mg, 0.67 mmol) to give the title compound as a yellow solid (223 mg, 100 %). ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 12.68 (br. s, 1 H), 10.84 (br. s., 1 H), 6.95 - 7.81 (m, 5 H), 4.96 (s, 1 H), 3.86 (br. s., 1 H), 3.25 (br. m., 2 H), 2.85 (br. s., 1 H), 1.97 (br. s., 4 H).

2-Phenyl-2-(pyrrolidin-1-yl)-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide. The title compound was synthesized according to the General Method A, utilizing 2-phenyl-2-(pyrrolidin-1-yl)acetic acid*TFA (48 mg, 0.15 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (60 mg, 0.15 mmol), DIPEA (130 μL, 0.75 mmol), TBTU (48 mg, 0.15 mmol) and 4 mL of DMF. The reaction mixture was purified using preparative HPLC and triturated with Et_2O to give the title compound as a white solid (TFA salt, 21 mg, 24%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.48 (s, 1 H), 8.42 (s, 1 H), 8.14 (d, *J* = 7.53Hz, 1 H), 7.95 (d, *J* = 7.53Hz, 1 H), 7.66 - 7.73 (m, 3 H), 7.49 - 7.59 (m, 5 H), 5.06 (s, 1 H), 3.92 (br. s, 1 H), 2.86 - 3.21 (m, 2 H), 1.86 - 2.31 (m, 5 H); MS ESI 476.2 $[M + H]^+$, calcd for $[C_{25}H_{25}N_5O_3S + H]^+$ 476.2. HPLC: 95% at 254 nm.(LCMS)

4.2.51 Synthesis of 2-Phenyl-2-(piperidin-1-yl)-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (71). *2-Phenyl-2-(piperidin-1-yl)acetic acid*. Ethyl 2-phenyl-2-piperidinoacetate (Matirx Scientific, 247 mg, 1 mmol), and 6 M aq HCl (2 mL) were combined, sealed and heated under microwave irradiation for 120 min at 120 ºC. The reaction mixture was dried under reduced pressure to give 2-phenyl-2-(piperidin-1-yl)acetic acid compound as a yellow solid (HCl salt, 254 mg, 100 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.49 - 7.60 (m, 5 H), 5.13 (s, 1 H), 3.71 - 3.85 (m, 1 H), 3.15 (t, *J* =11.8 Hz, 1 H), 2.95 - 3.04 (m, 1 H), 2.75 - 2.89 (m, 1 H), 1.66 - 2.06 (m, 5 H), 1.41 - 1.58 (m, 1 H)

2-Phenyl-2-(piperidin-1-yl)-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide. The title compound was synthesized according to General Method A utilizing 2-phenyl-2-(piperidin-1-yl)acetic acid (55 mg, 0.25 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide TFA (100 mg, 0.25 mmol), DIPEA (130 μL, 0.75 mmol), TBTU (80 mg, 0.25 mmol) and 4 mL of DMF. The reaction mixture was purified using preparative HPLC and triturated with Et_2O to give a TFA salt of the title compound as a white solid (96 mg, 64%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.48 (s, 1 H), 8.43 (s, 1 H), 8.15 (d, *J* = 7.28 Hz, 1 H), 7.95 (d, *J* = 7.78 Hz, 1 H), 7.67 - 7.74 (m, 3 H), 7.48 - 7.60 (m, 5 H), 4.97 (s, 1 H), 3.73 - 3.91 (m, 1 H), 3.08 - 3.25 (m, 1 H), 2.81 - 3.04 (m, 2 H), 1.71 - 2.07 (m, 5 H), 1.38 - 1.69 (m, 1 H); MS ESI 490.2 $[M + H]^+$, calcd for $[C_{26}H_{27}N_5O_3S + H]^+$ 490.2. HPLC: >99A%at 254 nm (LCMS).

4.2.52 2-(Dimethylamino)-2-(2-ethylphenyl)-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (72). *2-(Dimethylamino)-2-(2-ethylphenyl)acetic acid hydrochloride*. Ethyl 2-(dimethylamino)-2-(2-ethylphenyl)acetate was synthesized according to method described for 2-(dimethylamino)-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (**67**) step A utilizing 1-bromo-2-ethylbenzene (239 mg, 1.9 mmol), *N,N*-dimethylglycine ethyl ester (300 μL, 2.1 mmol), $Pd[P(t\text{-}Bu)_3]_2$ (49 mg, 0.096 mmol), K_3PO_4 (937 mg, 4.42 mmol) and PhMe (4 mL) to give ethyl 2-(dimethylamino)-2-(2-ethylphenyl)acetate as a yellow oil (306 mg, 68%). ^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 7.60 (d, *J* = 7.53Hz, 1 H), 7.15 - 7.25 (m, 3 H), 4.18 (s, 1 H), 4.06 - 4.23 (m, 2 H), 2.80 (q, *J* = 7.50 Hz, 2 H), 2.27 (s, 6 H), 1.26 (t, *J* = 7.65 Hz, 3 H), 1.20 (t, *J* = 7.15 Hz, 3 H).

2-(Dimethylamino)-2-(2-ethylphenyl)acetic acid hydrochloride was synthesized according to the according to method described for 2-(dimethylamino)-2-phenyl-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide (**67)** step A utilizing ethyl 2-(dimethylamino)-2-(2-ethylphenyl)acetate (55 mg, 0.23 mmol). A yellow solid (54 mg, 95%). ^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 7.50 (d, *J* = 7.8 Hz, 1 H), 7.40 - 7.48 (m, 2 H), 7.36 (t, *J* = 7.3 Hz, 1 H), 5.35 (s, 1 H), 3.20 (s, 3 H), 2.92 - 3.03 (m, 1 H), 2.76 - 2.88 (m, 1 H), 2.60 (s, 3 H), 1.31 (t, *J* = 7.5 Hz, 3 H).

2-(Dimethylamino)-2-(2-ethylphenyl)-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)acetamide.

The title compound was synthesized according to the General Method A, utilizing 2-(dimethylamino)-2-(2-ethylphenyl)acetic acid•HCl (30 mg, 0.124 mmol), 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide 2,2,2-trifluoroacetate (50 mg, 0.124 mmol), DIPEA (108 μL, 0.621 mmol), TBTU (40 mg, 0.124 mmol) and 4 mL of DMF. The reaction mixture was purified using preparative HPLC and triturated with Et_2O and CH_2Cl_2 to give the title compound as a white solid (TFA salt, 15 mg, 20%).^{1}H NMR (400 MHz, *CD_3OD*) δ ppm 8.47 (s, 1 H), 8.38 (s, 1 H), 8.14 (d, *J* = 7.28 Hz, 1 H), 7.95 (d, *J* = 7.78 Hz, 1 H), 7.77 (d, *J* = 8.03Hz, 1 H), 7.70 (t, *J* = 8.16 Hz, 1 H), 7.56 (s, 2 H), 7.50 (d, *J* =4.02 Hz, 2 H), 7.35 - 7.42 (m, 1 H), 5.36 (s, 1 H), 2.91 - 3.10 (m, 2 H), 3.07 (br. s, 3 H), 2.65 (br. s, 3 H), 1.39 (t, *J* = 7.40 Hz, 3 H); MS ESI 478.3 $[M + H]^+$, calcd for $[C_{25}H_{27}N_5O_3S + H]^+$ 478.2. HRMS (ESI) *m/z* calcd for $[C_{25}H_{27}N_5O_3S+ H]^+$ 478.1913, found 478.1919; HPLC: 99A% at 254 nm (HRMS).

4.2.53 2-(Pyrrolidin-1-yl)-N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)-2-(thiophen-3-yl)acetamide (73). To a mixture of 3-(5-amino-1H-indazol-3-yl)benzenesulfonamide trifluoroacetate (100 mg, 0.25 mmol), 2-(pyrrolidin-1-yl)-2-(thiophen-3-yl)acetic acid[58] (55 mg, 0.25 mmol) and TBTU (80 mg, 0.25 mmol) in DMF (4 mL) at 0 °C was added DIPEA (0.22 mL, 1.25 mmol). After addition, the resulting mixture was stirred for 1h at 0 °C. After removal of DMF, the residue was diluted with H_2O (20 mL), satd. $NaHCO_3$ (5 mL) and extracted with EtOAc (30 mL x 2). Combined extracts were washed with H_2O (20 mL x 2) and concentrated to dryness. It was purified by preparative HPLC to give the title compound as an off white solid (TFA salt, 58 mg, 39 %). ^{1}H NMR (400 MHz, *CD_3OD*) δ 8.49 (s, 1 H), 8.42 (s, 1 H), 8.13 (d, *J* = 7.6 Hz, 1 H), 7.94 (d, *J* = 7.6 Hz, 1 H), 7.88 (s, 1 H), 7.68 (t, *J* = 7.8 Hz, 1 H), 7.65-7.61 (m, 1 H), 7.55 (pseudo t, 2 H), 7.38 (d, *J* =5.2Hz, 1 H), 5.31 (s, 1 H), 3.88 (br.s, 1 H), 3.40-3.05 (m, 3 H), 2.30-1.95 (m, 4H); MS ESI 482.2. $[M + H]^+$, calcd for $[C_{23}H_{23}N_5O_3S_2 + H]^+$ 482.1. HRMS (ESI) *m/z* calcd for $[C_{23}H_{23}N_5O_3S_2+ H]^+$ 482.1321 , found 482.1319 ;HPLC: 98A% at 214 nm.

4.2.54_____(*S*)-N-(2,3-dihydro-1H-inden-1-yl)-3-(3-sulfamoylphenyl)-1H-indazole-5-carboxamide (**74**).The title compound was synthesized according to the General Method A utilizing 3-(3-sulfamoylphenyl)-1H-indazole-5-carboxylic acid (50 mg, 0.16 mmol), (S)-1-aminoindane (21 mg, 0.16

mmol), DIPEA (55 µL, 0.32 mmol), TBTU (51 mg, 0.079 mmol) and DMF (4 mL). The reaction mixture was purified by preparative HPLC and Subsequently, triturated with MeOH followed by acetone to give the title compound as a white solid (8 mg, 12 %). ^{1}H NMR (400 MHz, *DMSO-d_6*) δ ppm 13.65 (s, 1 H), 8.91 (d, *J*=8.03 Hz, 1 H), 8.64 (s, 1 H), 8.48 (s, 1 H), 8.28 (d, *J*=7.78 Hz, 1 H), 8.02 (d, *J*=8.28 Hz, 1 H), 7.86 (d, *J*=7.78 Hz, 1 H), 7.75 (t, *J*=7.80 Hz, 1 H), 7.68 (d, *J*=8.78 Hz, 1 H), 7.49 (s, 2 H), 7.16 - 7.31 (m, 4 H), 5.63 (q, *J*=7.78 Hz, 1 H), 2.97 - 3.06 (m, 1 H), 2.82 - 2.93 (m, 1 H), 1.96 - 2.07 (m, 1 H) *a signal corresponding to one proton is obscured by the solvent peak. MS ESI $[M + H]^+$ 433.2, calcd for $[C_{23}H_{20}N_4O_3S + H]^+$ 433.1. HPLC: 95A% at 254 nm.

4.3 Biochemical assays:

4.3.1 TTK inhibition assay

Active TTK was purchased from Invitrogen as an amino terminal GST fusion of full length human TTK. Amino terminal 6 histidine, SUMO-tagged human TTK (TTK-N; residues 1-275) was expressed in *E. coli*, and purified to >95% homogeneity by Ni^{2+} agarose, gel filtration, and ion exchange chromatography.

TTK activity was measured using an indirect ELISA detection system. GST-TTK (0.15 nM) was incubated in the presence of 3 M or 10 µM ATP for TTK-N and MBP-based assays, respectively.(Sigma cat# A7699), 50 mM Hepes pH 7.5, 1mM EGTA, 10 mM $MgCl_2$, and 0.1% Pluronic in a 96 well microtitre plate pre-coated with amino terminal 6 histidine, SUMO-tagged TTK (amino acid residues 1-275) (TTK-N based assay). Alternatively, in the MBP-based assay, 96-well, MBP-coated plates were used (Upstate/Cedarlane Microplates Cat# 30-011). The reaction was allowed to proceed for 30 minutes, followed by 5 washes of the plate with Wash Buffer (phosphate buffered saline supplemented with 0.2% Tween 20), and incubation for 30 minutes with a 1:3000 dilution of primary antibody (Cell Signaling cat# 9381). The plate was washed 5 times with Wash Buffer, incubated for 30 minutes in the presence of secondary antibody coupled to horse radish peroxidase (BioRad cat# 1721019, 1:3000 concentration), washed an additional 5 times with Wash Buffer, and

incubated in the presence of TMB substrate (Sigma cat# T0440). The colourimetric reaction was allowed to continue for 5 minutes, followed by addition of stop solution (0.5 N H2SO4), and quantified by detection at 450 nm with either a monochromatic or filter based plate reader (Molecular Devices M5 or Beckman DTX880, respectively).

Compound inhibition was determined at either a fixed concentration (10 □M) or at a variable inhibitor concentration (typically 50 □M to 0.1 □M in a 10 point dose response titration). Compounds were pre-incubated in the presence of enzyme for 15 minutes prior to addition of ATP and the activity remaining quantified using the above described activity assay. The % Inhibition of a compound was determined using the following formula; % Inhibition = 100 x (1 – (experimental value – background value)/(high activity control – background value)). The IC_{50} value was determined using a non-linear 4 point logistic curve fit (XLfit4, IDBS) with the formula; (A+(B/(1+((x/C)^D)))), where A = background value, B = range, C = inflection point, D = curve fit parameter.

4.3.2 PLK4 inhibition assay

Active PLK4 was purified from an *E. coli* expression system as an amino terminal GST fusion of residues 1-391 of human PLK4. The protein was purified from clarified cell extracts after induction at 15 ^{o}C overnight using glutathione sepharose, gel permeation chromatography, and ion exchange (Resource Q). The resulting protein was dephosphorylated with lambda phosphatase (NEB cat# P0753), and resolved from the phosphatase using gluthione sepharose. The dephosphorylated GST-PLK4 was stored in aliquots at -80^{o}C until use.

PLK4 activity was measured using an indirect ELISA detection system. Dephosphorylated GST-PLK4 (4 nM) was incubated in the presence of 15 □M ATP (Sigma cat# A7699), 50 mM HEPES-Na^{2+} pH 7.4, 10 mM $MgCl_2$, 0.01% Brij 35 (Sigma cat# 03-3170), in a 96 well microtitre plate pre-coated with MBP (Millipore cat# 30-011). The reaction was allowed to proceed for 30 minutes, followed by 5 washes of the plate with Wash Buffer (50 mM TRIS-Cl pH 7.4 and 0.2% Tween 20), and incubation for 30 minutes with a 1:3000 dilution of primary antibody (Cell Signaling cat# 9381). The plate was washed 5 times with Wash Buffer, incubated for 30 minutes in the presence of secondary antibody

coupled to horse radish peroxidase (BioRad cat# 1721019, 1:3000 concentration), washed an additional 5 times with Wash Buffer, and incubated in the presence of TMB substrate (Sigma cat# T0440). The colorimetric reaction was allowed to continue for 5 minutes, followed by addition of stop solution (0.5 N H_2SO_4), and quantified by detection at 450 nm with either a monochromatic or filter based plate reader (Molecular Devices M5 or Beckman DTX880, respectively).

4.3.3 Assays for PLK1, PLK2, PLK3, Aurora A, Aurora B, FLT-3, and KDR

PLK1, PLK2, PLK3, Aurora A, Aurora B, FLT-3, and KDR compound inhibition were determined using FRET based homogenous assay kits from Invitrogen (Burlington, Ontario, Canada). The assays were performed according to the manufacturer's specifications with ATP concentrations of 25, 60, and 80 □M, respectively for PLK1, PLK2, and PLK3 and ATP concentrations of 20, 128, 940, and 156 □M, respectively for Aurora A, Aurora B, FLT3, and KDR.

Compound inhibition was determined at either a fixed concentration (10 □M) or at a variable inhibitor concentration (typically 50 □M to 0.1 □M in a 10 point dose response titration). Compounds were pre-incubated in the presence of enzyme for 15 minutes prior to addition of ATP and the activity remaining quantified using the above described activity assay. The % Inhibition of a compound was determined using the following formula; % Inhibition = 100 x (1 – (experimental value – background value)/(high activity control – background value)). The IC_{50} value was determined using a non-linear 4 point logistic curve fit (XLfit4, IDBS) with the formula; (A+(B/(1+((x/C)^D)))), where A = background value, B = range, C = inflection point, D = curve fit parameter.

The apparent K_i for compounds **4**,**32** and **37** was estimated by varying the [ATP] in a series of TTK inhibition experiments at 0-, 1-, 3- and 5-fold IC_{50} concentrations of each inhibitor and applying nonlinear regression analysis (see Supplementary material).

The selectivity of inhibitors **32**, **63** and **73** against 55 protein kinases was assessed by Millipore (Dundee, Scotland) using a radiometric assay. Inhibition was determined at 1 μM inhibitor concentration with [ATP] at Km; % inhibition was determined as stated in the preceding paragraph (see Supplementary material).

4.3.4 Cytochrome P450

Fluorogenic Cytochrome P450 (CYP) inhibition studies were conducted at 37 °C in 96-well, round-bottom, white polystyrene plates. Supersome mixtures containing CYP protein, insect control Supersomes , substrate, and potassium phosphate buffer (pH 7.4) were prepared with the following final concentrations: CYP 3A4, 4 nM 3A4+OR+*b*5 Supersomes + 40 µM BFC in 160 mM buffer; CYP 3A4, 0.8 nM 3A4+OR+*b*5 Supersomes + 0.8 µM DBF in 160 mM buffer; CYP 2D6, 6 nM 2D6+OR Supersomes + 1.2 µM AMMC in 40 mM buffer; CYP 2C9, 4 nM CYP 2C9+OR+ *b*5 + 8 µM MFC in 40 mM buffer; CYP 2C19, 4 nM CYP 2C19+OR+ *b*5 + 20 µM CEC in 40 mM buffer; and CYP 1A2, 2 nM CYP 1A2+OR + 4 µM CEC in 40 mM buffer. Reaction times were verified to be within the limits of kinetic linearity (data not shown). All probe substrate concentrations selected for these determinations were approximately equal to the Km. The final cofactor concentrations were 1.3 mM NADP, 3.3 mM glucose-6-phosphate and 0.4 U/mL glucose-6-phosphate dehydrogenase for all enzymes. The final incubation volume was 0.2 mL. Buffer, cofactors and inhibitor were added to the wells, and the plates prewarmed at 37°C for 10 min. The solvent concentration was constant (• 0.2% DMSO for test articles, • 2% CH_3CN for positive control inhibitors) for all conditions within an experiment. Incubations were initiated by the addition of pre-warmed enzyme/substrate mix. After the specified incubation times (10 min for CYP 3A4/DBF; 15 min for CYP 1A2/ CEC; 30 min for CYP 2D6/ AMMC, CYP 2C19/ MFC and CYP 3A4/ BFC; 45 min for CYP 2C9/ MFC) reactions were stopped by the addition of 75 µL of 80% acetonitrile/20% 0.5 M Tris base, with the exception of 3A4/DBF, which was stopped by addition of 75 µL of 2N NaOH. At the final reaction times, fluorescence was determined using the following excitation/emission wavelengths: 3A4 (485/535 nm), 2D6 (390/465 nm), and 2C9 (409/535 nm).

The fluorescence signals within a dilution series were normalized to 0% and 100% inhibition, using the range defined by the positive and negative control inhibitors for each isoform/substrate. The % inhibition of a compound was determined using the following formula; % inhibition = 100 x (1 – (experimental value – background value)/(high activity control – background value)). The IC_{50} value

was determined using a non-linear 4 point logistic curve fit (XLfit4, IDBS) with the formula; (A+(B/(1+((x/C)^D)))), where A = background value, B = range, C = inflection point, D = curve fit parameter.

4.4 Structural biology

4.4.1 Protein purification

Cell pellets were re-suspended (on ice) into lysis buffer, 25 mM HEPES pH 7.5 in 0.5 M NaCl, supplemented with 5 % glycerol, 1 mM imidazole, 2 protease inhibitor tablets, 1 mM PMSF and 2 mM DTT, and 20 µL Benzonase, DNAse. Cell suspension was stirred for 30 minutes on ice and kept at 4 ^{o}C for DNAse cleavage. Cells were then lysed by 3x passage using EmulsiFlex C5 (Avestin). The lysed cells were centrifuged 50,000 G, 45 min, 4 ^{o}C. Cell lysate supernatant was decanted and treated with 1 g DE52 resin, which had been pre-swollen, pre-equilibrated to pH 7.5 in lysis buffer. Lysate was allowed to contact resin for 20 min (on ice) to bind and remove DNA. Lysate was vacuum filtered to remove DE52 resin beads. Ni-NTA FPLC Chromatography. Filtered, cleared lysate was loaded onto 2 tandem 5ml Ni-NTA- HiTrap chelating columns (GE Healthcare) for FPLC purification of His tag binding proteins. Columns were pre-equilibrated with binding buffer after being charged with Ni^{2+} using 0.1 M $NiSO_4$ as per manufacturer's instructions. Binding buffer contained 50 mM HEPES pH 7.5, 0.5M NaCl, with 5 % glycerol, 1 mM imidazole. After lysate was loaded, the Ni-NTA column was washed with 10 CV binding buffer supplemented with 5 mM imidazole followed by a step wash of 10 CV binding buffer supplemented with 50 mM imidazole. Protein was eluted with a linear gradient of 50 mM-0.5 M imidazole in binding buffer. Fractions were collected and SDS-PAGE (Novex) used to determine purified TTK-B4-His peak elution. TTK-containing fractions were pooled for further purification on gel filtration Superdex 75 column. Gel filtration Superdex S75. Eluted pool of TTK-B4-His from Ni-NTA step was concentrated using Millipore 50 mL spin concentrators 10K MWCO and applied in two batches for large scale gel filtration chromatography SD 16 Superdex S75 column equilibrated with 10 mM Tris pH 8.0, 250 mM NaCl, 2 mM DTT supplemented with 2.5% glycerol. Elution of TTK-B4-His was monitored by SDS PAGE and 2 mL fractions were monitored and collected which showed a large peak of purified

TTK at expected MW 37 kDa. Pooled fractions of TTK were concentrated in spin concentrators for ion exchange chromatography. IEX Source Q FPLC. Pooled, concentrated TTK-B4-His fractions from gel filtration were diluted 20x volume with IEX buffer 50 mM Tris pH 8.0, 25 mM NaCl. 2.5mM DTT, 2.5% glycerol and loaded onto FPLC IEX Source Q column. Elution with a gradient 50 mM NaCl-1 M NaCl was monitored by SDS-PAGE and TTK-B4-His peak which eluted at approximately 125 mM NaCl was pooled and concentrated. The final yield of 75mg of TTK-B4-His (approximately 98% purity) was carried forward for crystallization trials. This material was concentrated (Millipore UFV 5K MWCO) to 27 mg/mL batch 1 and 31 mg/mL batch 2, flash frozen and stored -80 ^{o}C.

4.4.2 Crystallization

Purified TTK-B4-His was set up for crystal trials at 23 ^{o}C using the hanging drop-vapor diffusion method. Crystallization conditions initially yielded small crystals which were used to seed. TTK-B4-His stock was diluted immediately prior to use to a concentration of approximately 12.8 mg/mL as follows: 12 µL TTK-B4-His protein at 31 mg/mL, 4 µL **72** [10mM] in DMSO, 15 µL GF buffer, (aliquots kept frozen): 10 mM Tris pH 8.0, 250mM NaCl, 2 mM DTT. Drops were set up on siliconized coverslips at a varying ratio of 1:1, 1:2, 1:3 microliters of TTK-B4-His protein stock and screened against precipitant well solutions (Hampton). Panels of various additives were screened and it was determined that freshly thawed protein and the addition of fresh 2 mM DTT to well stocks at setup were conducive to obtaining good crystals. Ligand **72**, 10 mM in DMSO was used to obtain co-crystals with TTK-B4-His. Crystals were obtained at 23 ^{o}C using a 1 µL:2 µL drop ratio protein to precipitant well solutions of 6 % PEG 5000 MME, 0.2 M NaCl, 0.1 M Na/K phosphate pH 5.53, supplemented with additives 2 mM DTT, 2.5% glycerol, 3% ethylene glycol, $MgCl_2$ (10 mM) and ligand **72** (10 mM) in DMSO to final (0.8 mM). To obtain larger crystals drops were hair-seeded with a few small crystals from analogous compound obtained under similar conditions. Large crystals which had been growing undisturbed for 2 weeks were harvested by teasing away the surface precipitant film and adding cryoprotectant solution cryo 1 in 3:1 ratio to the drop. Crystals were cryoprotected by sequentially transfer passage through the solutions cryo

2 and cryo3 containing ligand **72** Cryo 1: A small Eppendorf tube containing cryo solution was prepared as follows: 160 µL well, 8 µL ethylene glycol (100%), 16 µL glycerol(95%) 24 µL PEG 5K MME. Cryo2: A second tube was prepared using 25 µL of cryo-1 supplemented with 3 µL ligand **72** (10mM in DMSO) and 6 µL PEG 5k MME Cryo3: A third tube was prepared 10 µL of cryo 2 supplemented by 2 µL more ethylene glycol for final cryo soak and mounting on cryo loops. Crystals were frozen mounted on goniometer head at 100 ^{o}K nitrogen stream, tested for X-ray diffraction at Beam1, Mar345 and stored frozen in a liquid nitrogen prior to high resolution synchrotron data collection.

4.4.3 X-ray Data Collection and Processing. X-ray data sets of TTK-inhibitor complexes were collected at temperature of 100 ^{o}K using beamlines 17-ID at the Advanced Photon Source, Argonne National Laboratory. The diffraction data were reduced and scaled with the program XDS.[59]

4.4.4 Structure Determination and Crystallographic Refinement. The crystal of TTK complex belongs to I222 space group. The initial phase of TTK-inhibitor complex was determined by molecular replacement using Phaser from Phenix package.[60] Following the initial rigid body refinement, interactive cycles of model building and refinement were carried out using COOT[61] and phenix.refine[60] or buster-TNT[62]. The coordinates and topologies of the ligands from this study were generated using phenix.elbow[60]. Ligands were introduced in the later stages of refinement after most of the protein models were built. Water molecules as well as other solvent ligands were added based on $2mF_o$-DF_c map in COOT and refined with phenix.refine or buster-TNT. The final structure was refined to 2.2 Å resolution with an R_{work}, of 23.81 % and an R_{free} of 25.14 % and deposited in PDB as 4JT3; additional crystallographic data and refinement statistics are presented in Table 2 of the Supporting Information.

4.5 In vitro cell-based assays

4.5.1 Cancer Cell Lines. All cell lines were obtained from American Type Culture Collection (ATCC, Manassas, VA), and maintained according to the supplier's instructions. Short tandem repeat (STR) profiling was used to verify authenticity of the cell lines. Sixteen STR loci were simultaneously amplified in a multiplex PCR reaction (The Hospital for Sick Children, Toronto, Canada), and the ATCC database

was used for comparison. Cell lines were routinely tested for mycoplasma, and used at low passage numbers (<15). Primary cultures of normal human mammary epithelial cells (HMEC) were obtained from Lonza (Anaheim, CA), and maintained according to the supplier's instructions. Cell doubling times were as follows: A549 = 22 h, OVCAR-3= 69 h; SW620 =26 h; MDA-MB-468=52 h, HCT116 = 21 h.

4.5.2 Cell Cycle Analysis. Human HCT 116 colon cancer cells in 6-well plates were treated with either DMSO or TTK inhibitor **72**, **73** or **74** at the indicated concentrations and cultured at 37° C and 5 % CO_2. After 2 d, the cells were trypsinized, washed in phosphate-buffered saline and centrifuged. Cell pellets were resuspended with propidium iodide in HEPES buffer, mixed and incubated at rt in the dark. Samples were read in a FACSCalibur flow cytometer (Becton, Dickinson and Company) and data analyzed using FloJo software (Tree Star, Inc.).

4.5.3 Phospho-Histone H3 (Ser10) EC_{50} Assay

HCT116 cells were seeded at 5000/well in growth medium (DMEM with 10% FBS) in a 96-well plate and cultured at 37°C and 5% CO_2. Twenty-four hours later, 200 ng/mL nocodazole (Sigma, St. Louis, MO) was added for 18 hours to induce unattached chromosomes and activation of the spindle assembly checkpoint. Compound **72** was added to the cells in triplicate in final concentrations ranging from 5 nM to 50 μM for 4 hours. Cells were fixed with 4% paraformaldehyde for 20 min at rt, permeabilized in 0.1% Triton-X 100 for 30 min at rt, incubated with anti-phospho-histone H3 (Ser10) antibody (rabbit polyclonal #9701; Cell Signaling Technology Inc., Danvers, MA) overnight at 4 °C followed by an 1 hour incubation with IRDye 800CW-labeled secondary antibody (LI-COR, Lincoln, NE) at rt. Cells were subsequently stained with DRAQ5 (BioStatus Limited, Leicestershire, UK). The percentage of phospho-histone H3 (Ser10)-positive cells was quantified by image analysis and compared to DMSO-treated cells (Odyssey LI-COR imaging system, Lincoln, NE). EC50s were calculated using GraphPad PRISM software (GraphPad Software Inc., San Diego, CA).

4.5.4 Cell viability assay (GI_{50}).

A549, OVCAR-3, SW620, MDA-MB-468, HCT116 cancer cells were seeded into 96-well plates at 1000, 6000, 1500, 3000 and 800 cells per 80 μL, respectively, 24 h before compound overlay and

cultured at 37°C and 5% CO_2. Compounds were prepared as 10 mM stocks in 100% DMSO. Each 10 mM stock was diluted with DMEM (Dulbecco's Modified Eagle's Medium) cell growth medium (Invitrogen, Burlington, ON, Canada) containing 10% FBS (fetal bovine serum) such that the final concentrations ranged from 50 nM to 250 μM. Aliquots (20 μL) from each concentration were overlaid to 80 μL of pre-seeded cells to achieve final concentrations of 10 nM to 50 μM. After 5 d, the cells were fixed in situ by gently removing the culture media and adding 50 μL of ice cold 10% trichloroacetic Acid (TCA) per well and incubation at 4°C for 30 min. The plates were washed with water five times and allowed to air dry for 5 min. 50 μL of 0.4% (w/v) sulforhodamine B (SRB) (Sigma, Oakville, ON, Canada) solution in 1% (v/v) acetic acid was added to each well followed by incubation for 30 min at rt. The plates were washed four times with 1% acetic acid to remove unbound SRB and air dried for 5 min. The SRB was solubilized with 100 μL of 10 mM Tris pH 10.5 per well, and absorbance was read at 570 nm using a SpectraPlus microplate reader (Molecular Devices Corporation). The percentage (%) of relative inhibition of cell viability was calculated by comparing to DMSO treated only cells. GI_{50}s were calculated using GraphPad PRISM software (GraphPad Software, Inc., San Diego, CA, USA).

4.6. In vivo experiments

4.6.1 Mouse plasma levels:

Adult female SCID mice (PMH Animal Facility) were used in the experiments. All animal experiments were approved by UHN IACUC. Nine mice were dosed at with compound **72** at 50 mg/kg (free base equivalents) via intraperitoneal injection (water with final pH adjusted to pH 4 with 1 M NaOH) using a volume of 200 μL. Saphenous vein blood was collected from 3 mice per time point over an 8 h period. The plasma samples were analyzed for drug and internal standard via LCMS/MS protocol using a Waters (Millford, MA, USA) UPLC coupled to either a Q-ToF Premier, or a XevoTQ mass spectrometer. The pharmacokinetic parameters were calculated using Microsoft Excel with pharmacokinetic add-in functions from Usansky et al.[63] Parameters were calculated using plasma concentration time data for composite averages.

4.6.2 Xenograft model

HCT116 colon cancer cells were purchased from ATCC (American Type Culture Collections) and cultured in DMEM (Dulbecco's Modified eagle medium- purchased from GIBCO) supplemented with 10% fetal calf serum. Five million cells were injected subcutaneously in the right flank of 6-8 week old male CB-17 SCID mice supplied by UHN animal facility. When the mean tumor volume reached 80-120 mm^3, mice were randomized into 5 groups (n = 5) and received either vehicle or compound at the doses indicated. Compound **72** was weighed and suspended in 0.1 % CMC+0.08 % TWEEN 80 and sonicated at rt for 30 min. The compound was dispensed in aliquots and stored at -20 ^oC for duration of the study and each aliquot was thawed at rt before each dose. The mice were dosed via intraperitoneal injection at indicated doses daily for 18 d; compound **72**: 12.5 mg/kg, 25 mg/kg QD and 12.5 mg/kg BID. 5-FU was dosed at 15 mg/kg IP, QDX5 in PBS.

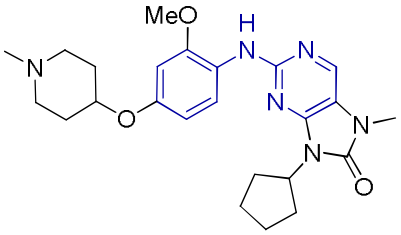
Tumor volume and body weight were measured three times weekly. Efficacy data were graphically represented as the mean tumor volume. Tumor volume was calculated by the following formula: $x^2y/2$. Percent tumor growth inhibition after initiation of treatment with compound was calculated by: TGI = 100 X 1- (tumor $volume_{final}$ – tumor $volume_{initial}$ for compound treated group) / (tumor $volume_{final}$ – tumor $volume_{initial}$ for compound control group).

5.0 Supplementary material

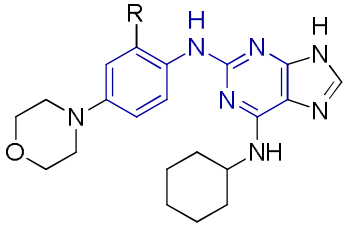
Inhibition data of 55-member kinase panel for compounds **32**, **63** and **73**. Steady State kinetics results for compounds **4, 32** and **37**. Summary of crystallographic data and refinement statistics. PDB structure file is available for download from http://www.rcsb.org/pdb/home/home.do with PDB accession code: 4JT3. This material is available free of charge via the Internet at http://.....

Acknowledgments: We thank Dr. Homer Pearce for helpful discussion during the course of the work. Amgen, the PMH Foundation, and the Canadian Foundation for Innovation are acknowledged for financial support.

Chart 1. Examples of literature inhibitors of TTK with reported TTK inhibitory activities. N-phenylpyrimidin-2-amine, hinge-binding motif is highlighted in blue.

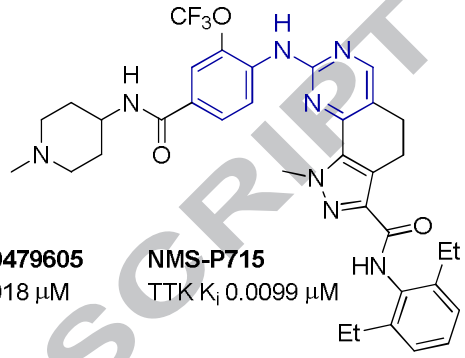


AZ3146
TTK IC_{50} 0.035 μM

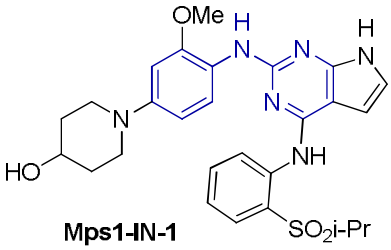


R = H, **Reversine**
TTK IC_{50} 0.0028 μM

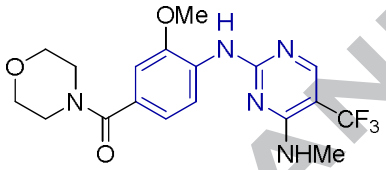
R = Me, **MPI-0479605**
TTK IC_{50} 0.0018 μM



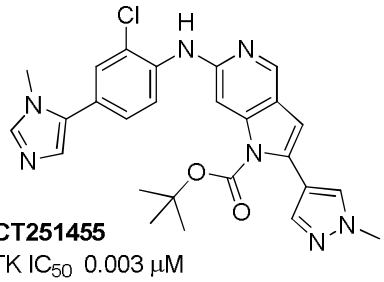
NMS-P715
TTK K_i 0.0099 μM



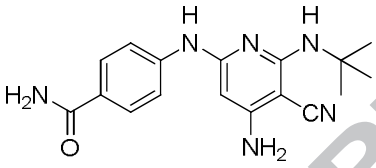
Mps1-IN-1
TTK IC_{50} 0.37 μM



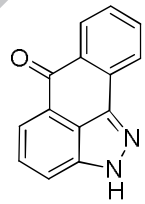
Genentech
TTK Ki 0.025 μM



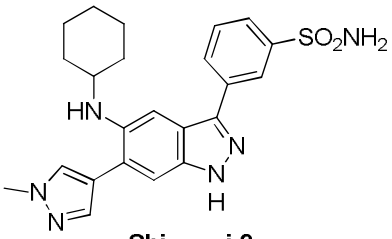
CCT251455
TTK IC_{50} 0.003 μM



Shionogi-1
TTK IC_{50} 0.0064 μM



SP600125
TTK IC_{50} 2.5 μM; LE 0.46



Shionogi-2
TTK IC_{50} 0.010 μM

Scheme 1. Progression sequence from initial screening hits to indazolyl benzenesulfonamides. GW-786034 was used in molecular overlay exercise resulting in incorporation of the sulfonamide headgroup.

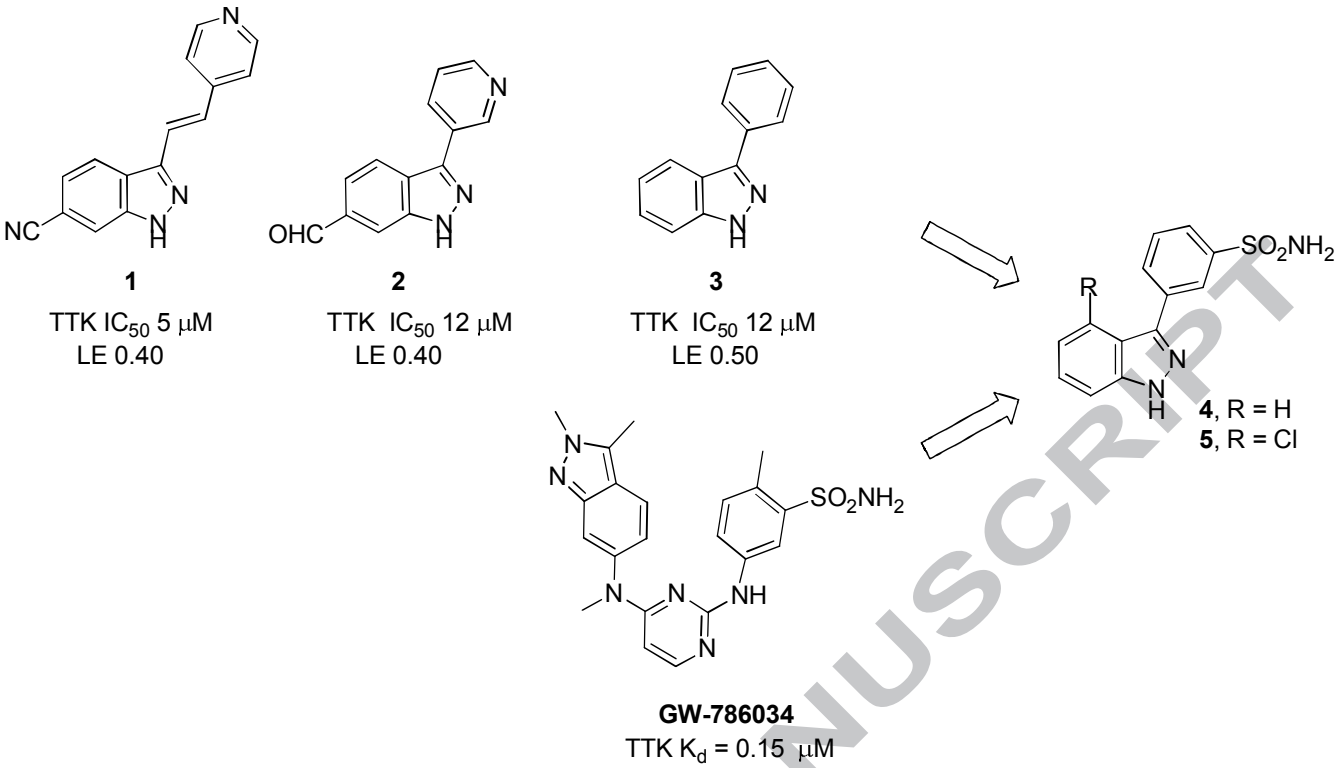
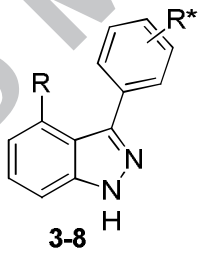


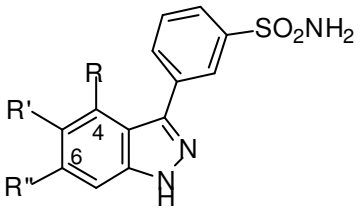
Table 1. SAR for 3-Phenyl-1H-indazoles: effect of phenyl substitution on inhibition of TTK.



cpd	R*	R	TTK IC_{50}* (μM)
3	H	H	12
4	3-SO_2NH_2	H	2.6
5	3-SO_2NH_2	Cl	1.8
6	4-SO_2NH_2	Cl	18
7	3-$CONH_2$	Cl	17
8	3-CH_2NH_2	Cl	>50

*MBP TTK assay

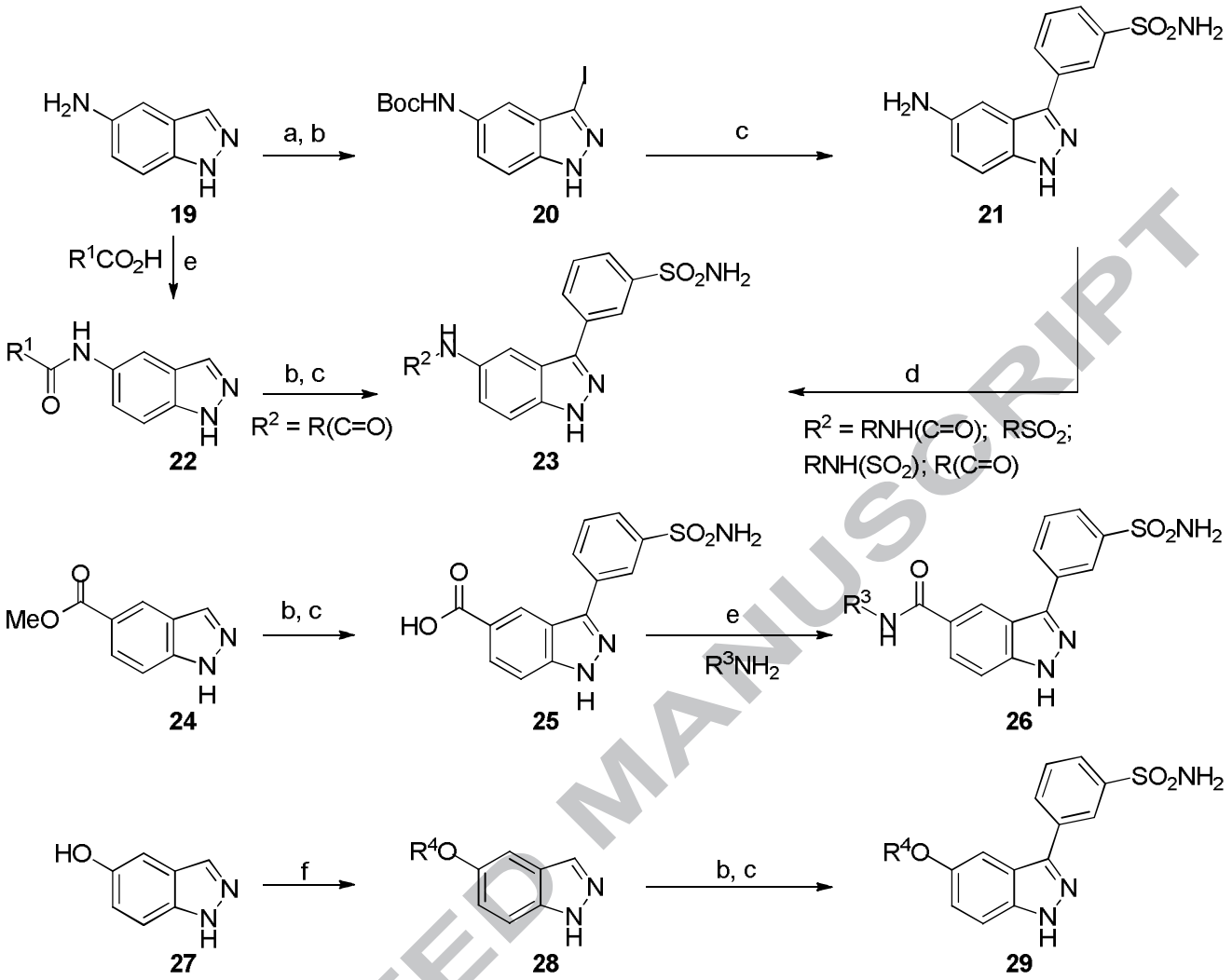
Table 2. Effects of C4, C5 and C6 substitutions of 3-(1H-indazol-3-yl)benzenesulfonamide on inhibition of TTK



4,5, 9-18

cpd	R	R’	R”	TTK IC_{50} (μM)	cpd	R	R’	R”	TTK IC_{50} (μM)
4	H	H	H	1.6	**5**	Cl	H	H	1.9
9	2,6-$F_2C_6H_3$	H	H	1.4	**14**	H	MeCONH-	H	0.64
10	H	Ph-	H	4.3	**15**	H	H	MeCONH-	18
11	H	H	Ph-	5.4	**16**	H	thien-2-yl-CONH-	H	0.28
12	MeO-	H	H	2.3	**17**	H	H	thien-2-yl-CONH-	4.3
13	H	MeO-	H	0.6	**18**	H	H	MeNHCO-	11

Scheme 2. Synthetic approach to 5-substituted indazolyl benzenesulfonamides



a. 1. Boc_2O, DIPEA, DMF, 0 °C; b. I_2, K_2CO_3, DMF, 0 °C to rt; c. 1. 3-NH_2SO_2-C_6H_4-Bpin, Pd cat., DMF/H_2O or DME/H_2O, or PhMe/EtOH/H_2O, KF or Na_2CO_3 or Cs_2CO_3, μw, Δ; 2. TFA, DCM (the two steps in c. can be interchanged) d. for R^2 = RNH(C=O): RNCO, DIPEA, DMF or RNH_2, $(Cl_3CO)_2C=O$, DCM, TEA then **21**; for R^2 = RSO_2: RSO_2Cl, DIPEA, DMF; for R^2= RNH(SO_2) 1. $ClSO_2NCO$, $ClCH_2CH_2OH$, DCM 2. RNH_2, Et_3N, DCM 3. **21**, MeCN, Δ; for R^2 = R(C=O): RCO_2H, TBTU, DIPEA, DMF; e. TBTU, DIPEA, DMF; f. a. R^4OH, DIAD, PPh_3, THF, PhMe; or R^4Br, K_2CO_3, DMF.

Figure 1. Binding modes of two inhibitors in the modified X-ray structure of TTK (PDB 3CEK). Compounds **4** and GW-786034 are shown in salmon and green colors, respectively. H-bonds from compound **4** to Glu603 and Gly605 and from sulfonamide to Gly605 shown as dashed lines.

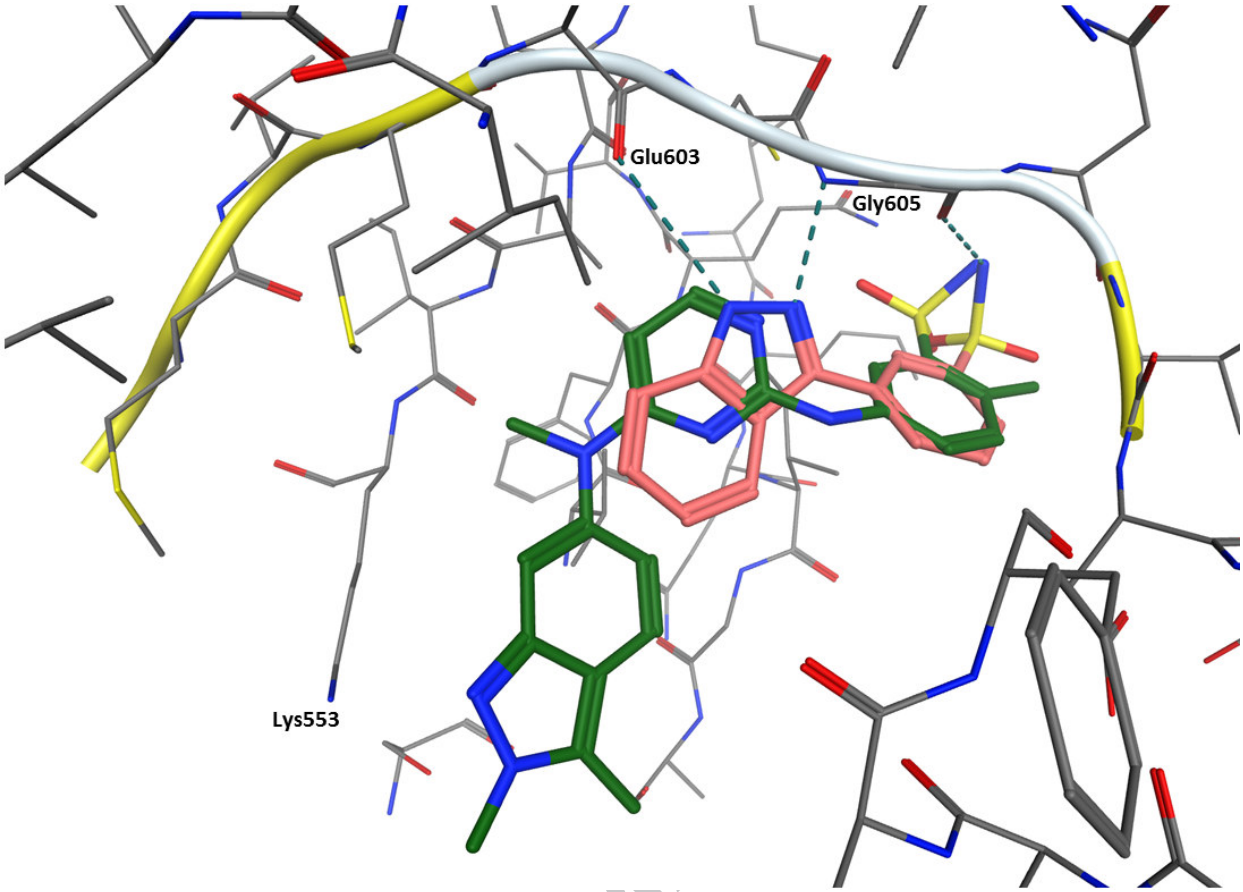


Figure 2. Co-crystal X-ray structure of TTK and **32** (PDB 4JT3) A. Left Panel shows compound **32** with a surface of TTK active site illustrating close contacts with hydrophobic residues between the benzenesulfonamide ring and Ile531, indazole core nestling against hydrophobic residues Val539, Ile663 and Met602, the phenylacetamide ring fills up a hydrophobic pocket lined with Gln672 and Val539. B. Right panel shows compound **32** with the indazole engaged in H-bonds to the hinge region (Glu603 and Gly605), carboxamide oxygen interacting with Lys553 and sulfonamide involved in a network of H-bond interactions at the solvent interface with residues Asn606 and Gln541.

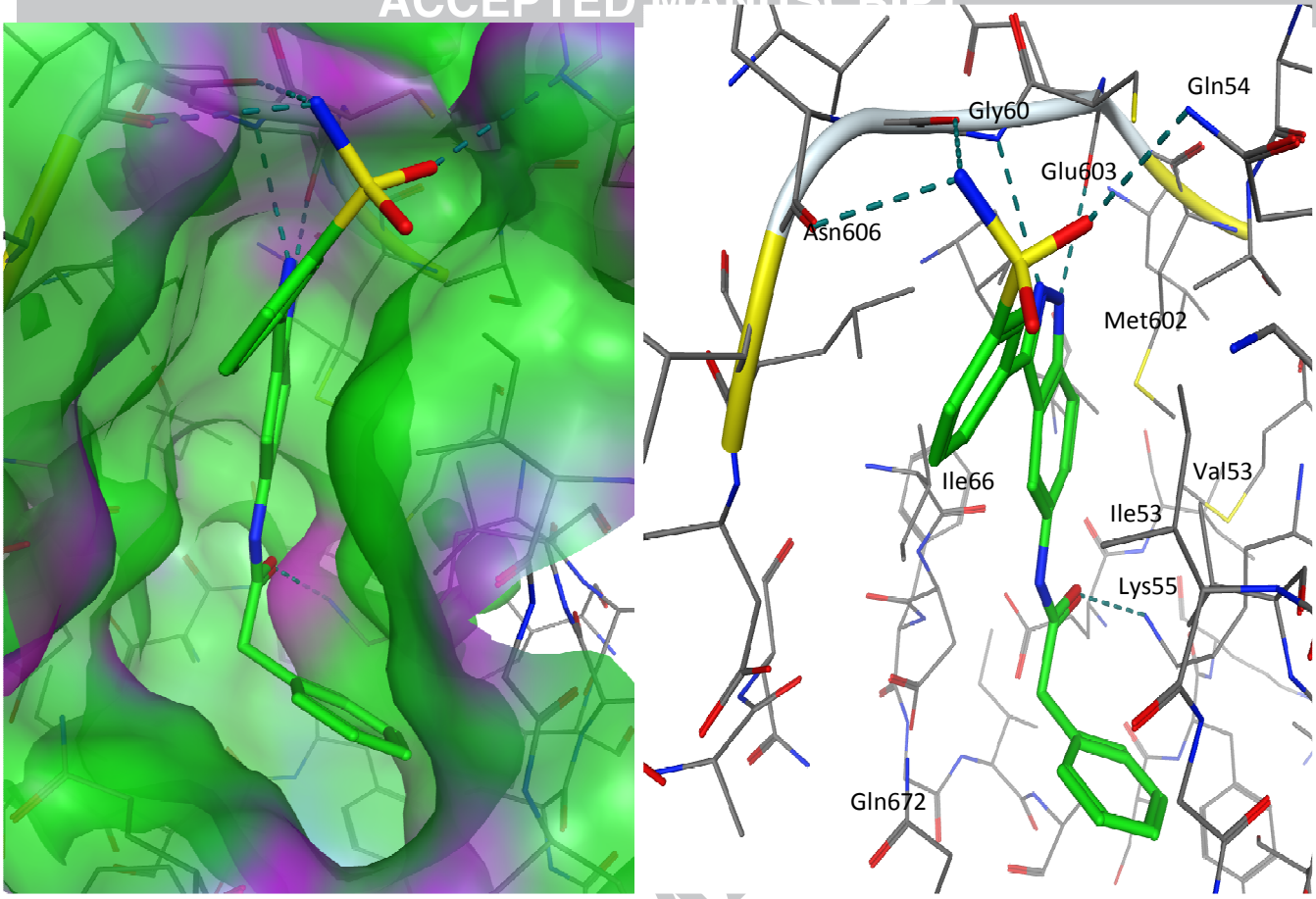
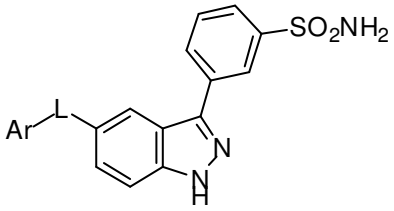


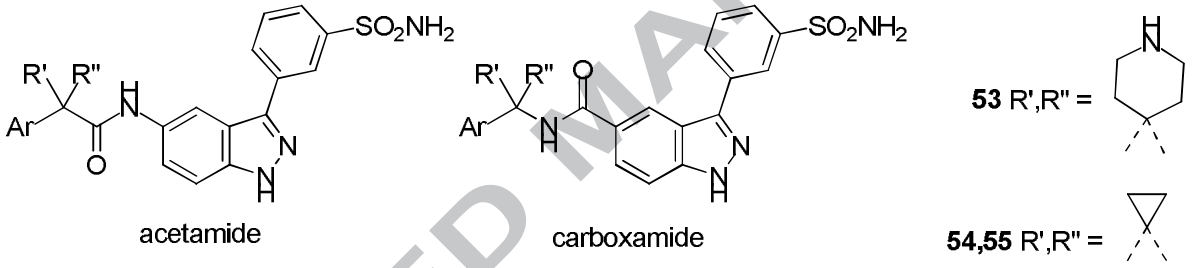
Table 3. SAR for 3-(1H-indazol-3-yl)benzenesulfonamides: Effects of various linkers at C5 of indazole on the inhibition of TTK and HCT116 cell proliferation.



30-45

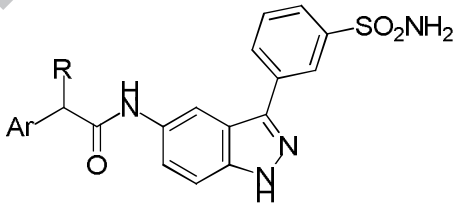
#	Ar	-L-	TTK IC_{50} (μM)	HCT116 GI_{50} (μM)	#	Ar	-L-	TTK IC_{50} (μM)	HCT116 GI_{50} (μM)
30	Ph-	CH_2O	0.58	4.8	**38**	2,6-$Et_2C_6H_3$	NH(C=O)N(Me)	>50	ND
31	thien-2-yl	CH_2CH_2O	0.38	2.7	**39**	Ph	$NHSO_2NH$	0.71	0.75
32	Ph	CH_2(C=O)NH	0.039	20	**40**	2,6-$Et_2C_6H_3$	$NHSO_2NH$	2.6	21
33	thien-2-yl	CH_2(C=O)NH	0.016	5.8	**41**	Ph	CH_2NH(C=O)	0.09	2.9
34	thien-2-yl	SO_2NH	0.34	26	**42**	thien-2-yl	CH_2NH(C=O)	0.033	3.4
35	3-MeC_6H_4	CH_2SO_2NH	0.33	15	**43**	Ph	CH_2N(Me)(C=O)	0.25	28
36	Ph-	HN(C=O)NH	0.39	>50	**44**	Ph	(C=O)$NHCH_2$	0.55	41
37	2,6-$Et_2C_6H_3$	NH(C=O)NH	0.0035	0.36	**45**	2-MeC_6H_4	HN(C=O)CH_2	>5	>50

Table 4. SAR for 3-(1H-indazol-3-yl)benzenesulfonamides: Comparing C5 substitutions: acetamides vs carboxamides



cpd	Ar	R'	R"	Linker	TTK IC_{50} (μM)	HCT116 GI_{50} (μM)
46	$PhCH_2$	H	H	acetamide	0.98	>50
47	2-pyridyl	H	H	acetamide	0.09	6.89
48	4-pyridyl	H	H	acetamide	0.34	50
49	o-tolyl	H	H	carboxamide	0.018	1.8
50	o-tolyl	H	H	acetamide	0.025	1.8
51	2,6-$Et_2C_6H_3$	H	H	acetamide	0.017	0.18
52	2,6-$Et_2C_6H_3$	H	H	carboxamide	0.08	0.70
53	Ph	4,4-piperidine		carboxamide	0.058	> 50
54	Ph	1,1-c-Pr		acetamide	0.31	7.3
55	Ph	1,1-c-Pr		carboxamide	0.035	3.3
56	Ph	H	Et	(±)-acetamide	0.024	1.3
57	Ph-	H	*i*-Pr	(±)-acetamide	0.046	ND
58	Ph	H	c-Pr	(±)-carboxamide	0.016	0.55
59	thien-3-yl	H	c-Pr	(±)-carboxamide	0.004	0.61
60	Ph	H	c-pentyl	(±)-acetamide	0.053	0.63
61	Ph	H	c-hexyl	(±)-acetamide	0.061	0.43
62	Ph	H	c-hexyl	(±)-carboxamide	0.047	0.81

Table 5. SAR for N-(1H-indazol-5-yl)acetamides: Effects of α-substitution on inhibition and TTK and proliferation of three different cell lines



63-73

cpd	Ar	R	stereo-chem	TTK IC_{50} (μM)	GI_{50} (μM)		
					HCT116	MDA-MB-468	A549
63	Ph	MeO	±	0.026	1.06	2.2	2.5
64	Ph	MeO	S	0.026	0.80	2.2	3.6
65	Ph	MeO	R	0.030	0.85	3.2	2.4
66	Ph	EtO	±	0.014	0.40	1.4	0.8
67	Ph	Me_2N	±	0.012	0.66	1.4	1.7
68	Ph	Me_2N	S	0.011	0.52	0.84	0.83
69	Ph	Me_2N	R	0.015	1.10	1.3	3.4
70	Ph	pyrrolidin-1-yl	±	0.0089	0.11	0.35	0.23
71	Ph	piperidin-1-yl	±	0.01	0.27	0.69	0.4
72	*o*-EtC_6H_4	Me_2N-	±	0.0036	0.10	0.66	0.16
73	thien-3-yl-	pyrrolidin-1-yl	±	0.0029	0.07	0.09	0.09

Table 6. Kinase, cytochrome P450 IC_{50}s and physicochemical properties (pION PAMPA and μSol) for compounds **37**, **72** and **73**.

		37	**72**	**73**			**37**	**72**	**73**
kinase IC_{50} (μM)	TTK	0.0035	0.0036	0.0029	CYP IC_{50} (μM)	3A4 (DBF)	~10	2.9	>1
	PLK1	ND	>50	>50		3A4 (BFC)	~1	0.7	4.0
	PLK2	ND	ND	10		2C19	>1	2.3	5.3
	PLK3	ND	ND	>50		2C9	1.7	2.5	0.9
	PLK4	0.13	0.083	0.089		1A2	>10	>10	>10
	AURA	ND	0.40	0.9		2D6	>10	~5	~10
	AURB	2.4	0.48	0.72	physico-chemical properties	PAMPA pH 7.4 (10^{-6}cm/s)	< 21	19	4.2
	CHK2	0.41	0.42	0.10		Solubility pH 7.4 (μg/mL)	< 0.1	1.4	9.0

Figure 3. Heat map showing % inhibition of 54 human kinases at a screening concentration of 1μM for compounds **32**, **63** and **73** in comparison to imatinib and sorafinib. Compounds were individually sorted.

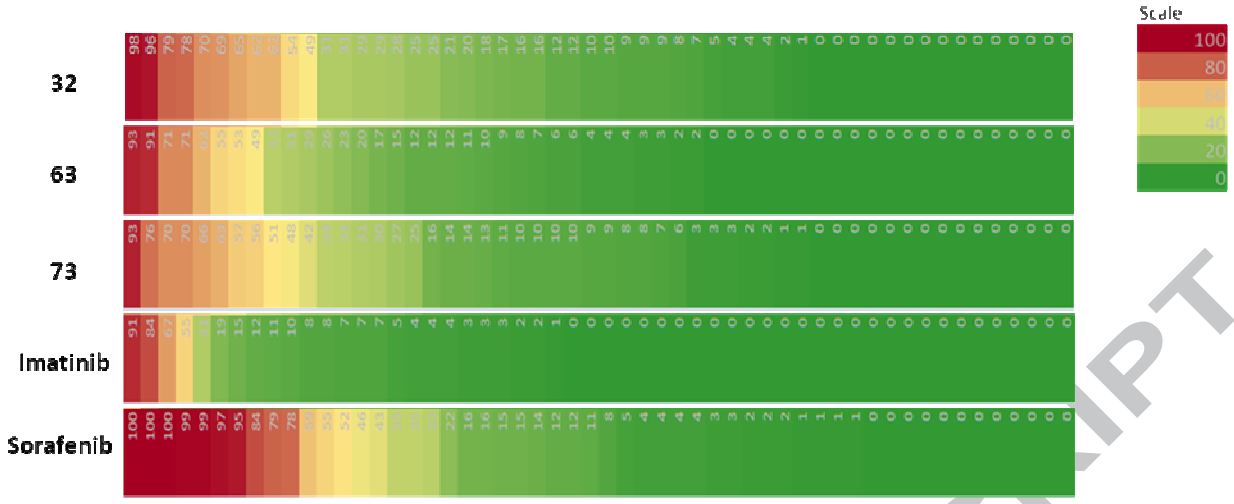


Figure 4. Correlation of measured HCT116 pGI_{50} with biochemical TTK pIC_{50} for TTK inhibitors for all the compounds with well defined GI_{50} values (n = 40). Linear regression of pGI_{50} vs pIC_{50} (n = 40) yields the following parameters: slope = 0.80, intercept = -0.14, R^2 = 0.59.[64] pGI_{50} values, measured and calculated from multiple linear regression utilizing both pIC_{50} and logP terms (intercept: -0.625, coefficients: pIC_{50}: 0.756, logP: 0.297), are represented by diamonds (♦) and triangles (▼), respectively. The labels correspond to the compound numbers.

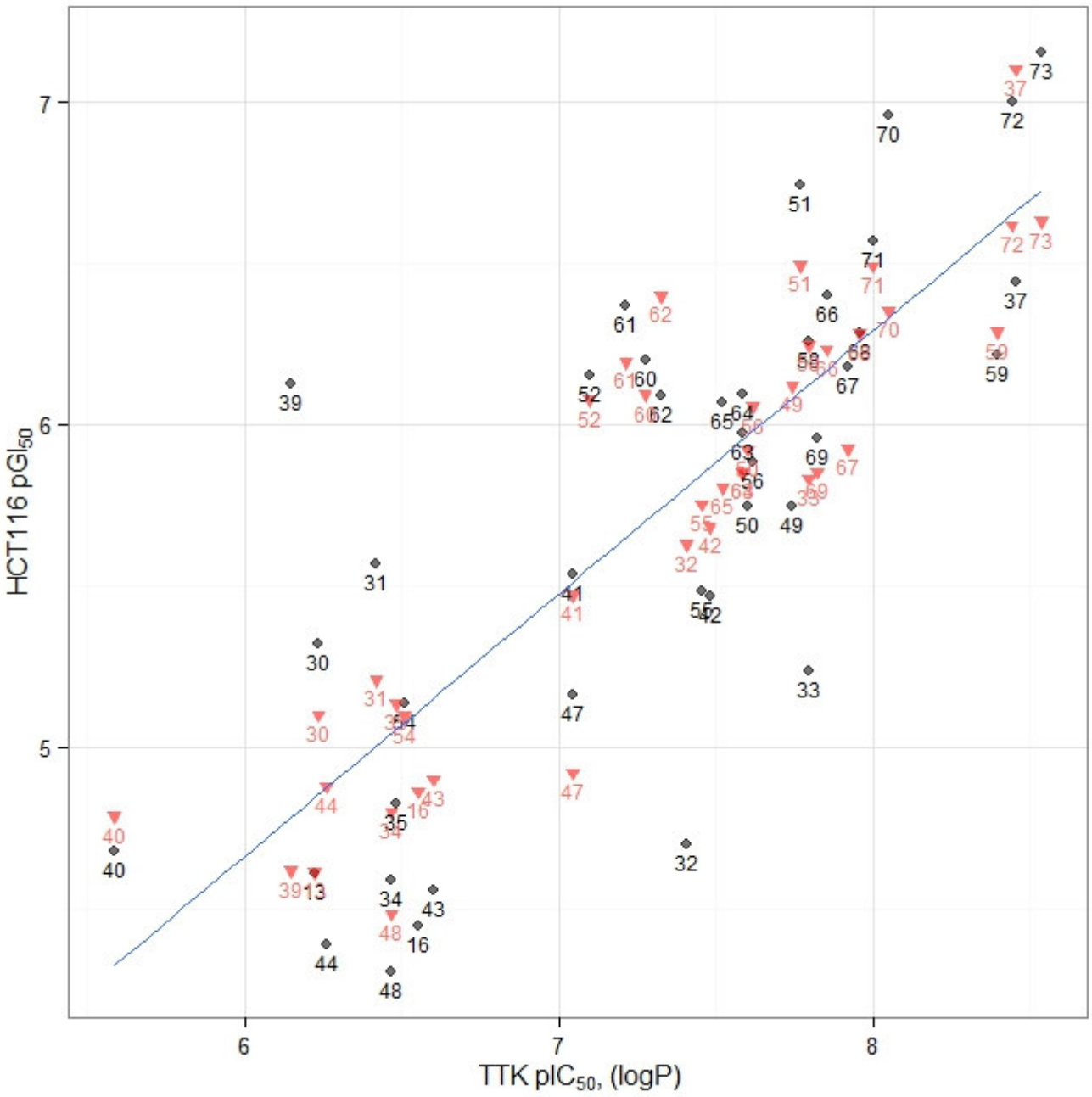


Figure 5. Effects of TTK inhibitors **72**, **73** and **74** on Cell Cycle analysis of HCT116 cells

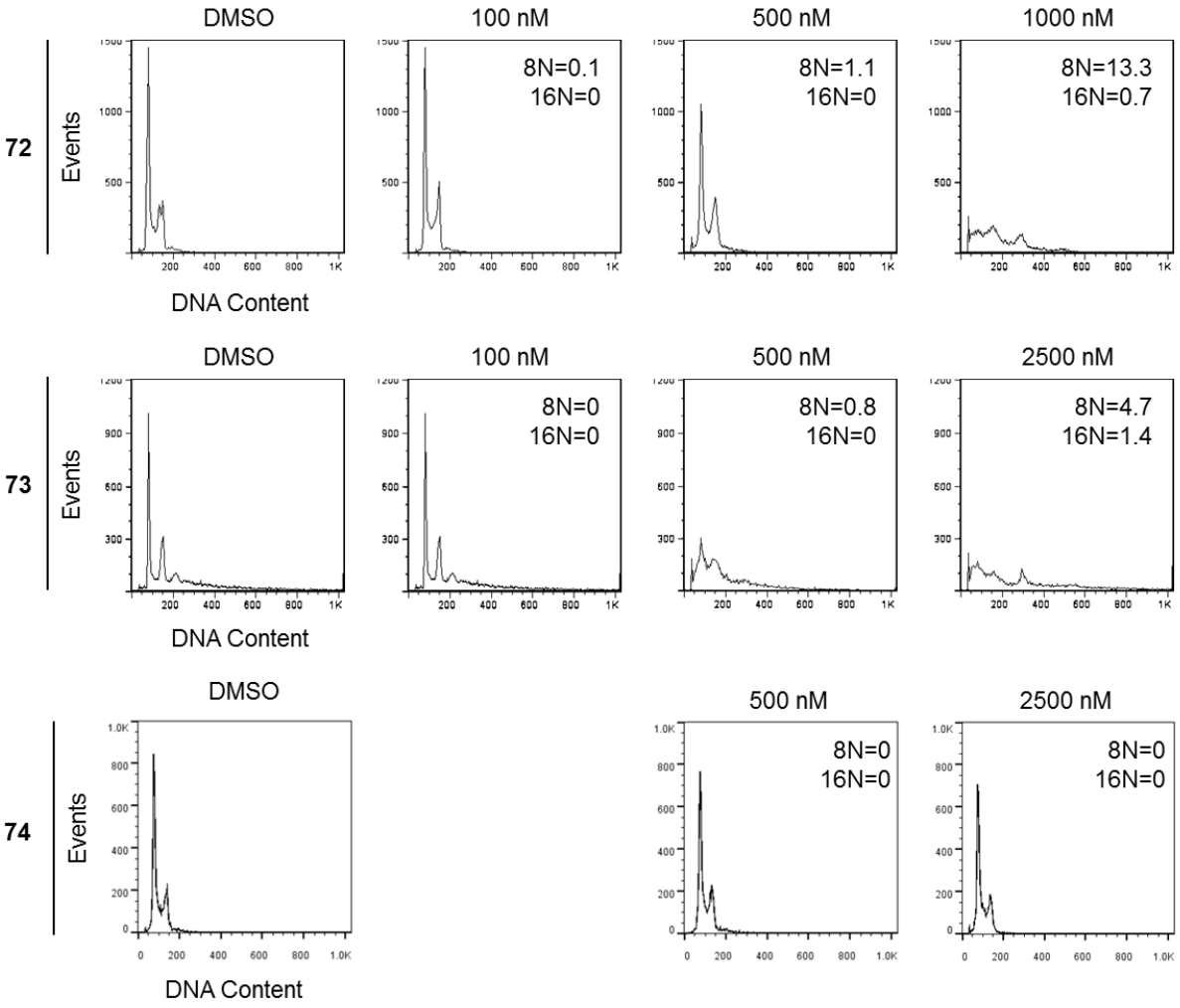
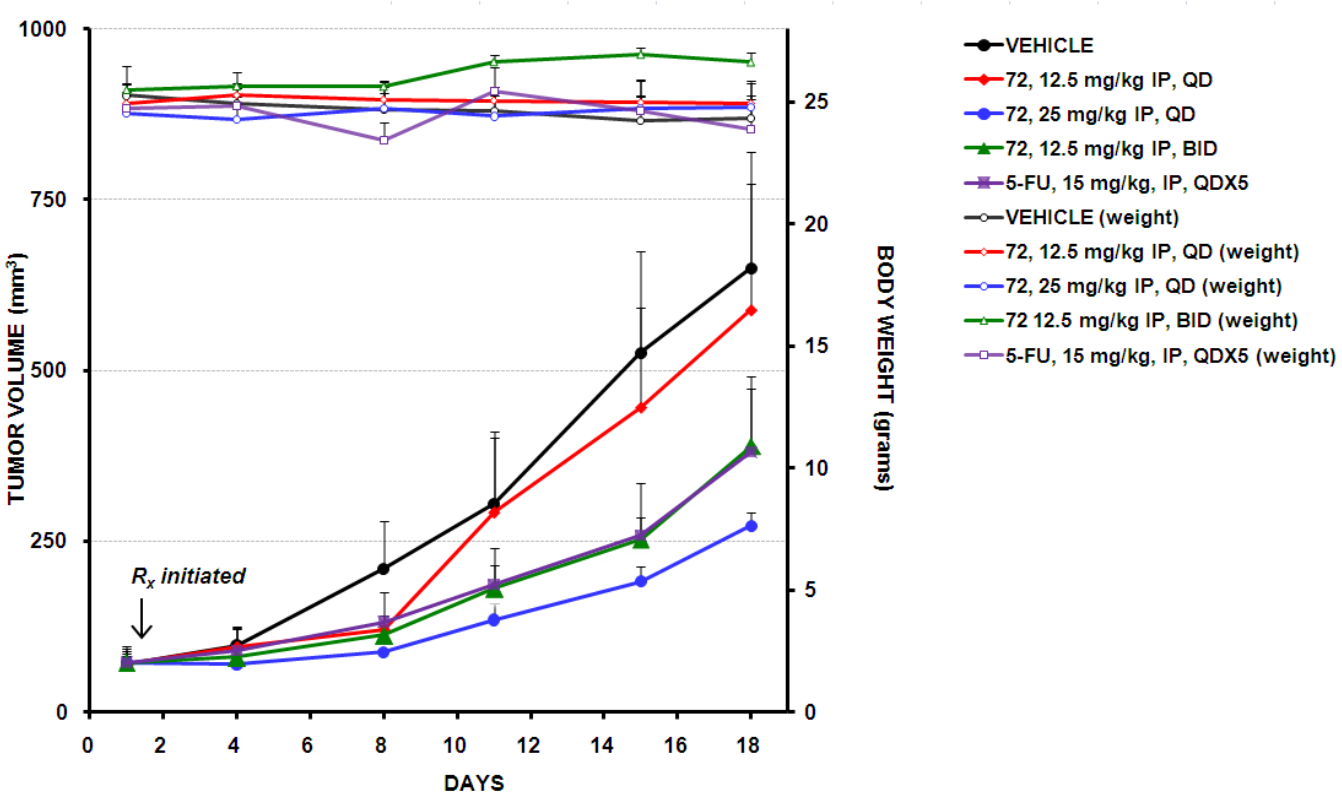
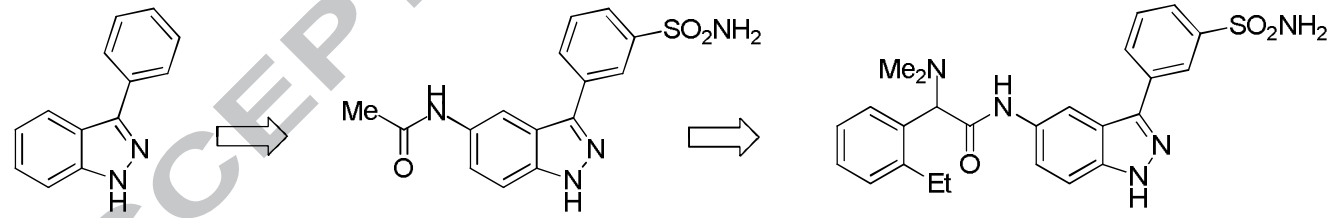


Figure 6. In vivo response of HCT116 xenografts in SCID mice to IP treatment with compounds **72** and 5-FU: **72** QD: 12.5 mg/kg and 25 mg/kg TGI = 10 %, and TGI = 66 %, respectively; **72** BID 12.5 mg/kg: TGI = 46 %; 5-FU QDX5 15 mg/kg TGI = 47 %.



Graphical Abstract



Screening Hit **3**
TTK IC_{50} 12 μM

New Chemotype **14**
TTK IC_{50} 0.64 μM

Potent TTK Inhibitor **72**
TTK IC_{50} 0.0036 μM

Abbreviations used

A%, area percent; aq, aqueous; anh, anhydrous; Ar, argon; ATP, Adenosine-5'-triphosphate; Boc, *tert*-butoxycarbonyl; br, broad; calcd, calculated; CMC, ;CYP; Cytochrome P450; d, doublet; dba, dibenzylideneacetone; DBU, 1,8-diazabicycloundec-7-ene; DCM, dichloromethane; DIAD, diisopropyl

azodicarboxylate; DIPEA, diisopropylethylamine; Δ ,heat; DMAP, 4-dimethyl-aminopyridine; DME, dimethoxyethane; DMF, *N,N*-dimethylformamide; DMSO, dimethyl sulfoxide; dppf, 1,1'- bis(diphenylphosphino) ferrocene; FLT3, fms-related tyrosine kinase 3; GI_{50}, half maximal cell growth inhibitory concentration; GST, glutathione S-transferase; h, hour; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HMDS, hexamethyldisilazane; HOBt, Hydroxybenzotriazole; HPLC, high performance liquid chromatography; HRMS, high-resolution mass spectrometry; IP, intraperitoneal; KDR, kinase insert domain receptor; LCMS, LE –ligand efficiency; liquid chromatography coupled to mass spectrometry; LE, ligand efficiency; MBP, Myelin basic protein; min, minute; m, multiplet; MS ESI, Electrospray Ionization mass spectrometry; µw microwave irradiation; NMR, nuclear magnetic resonance; NBS, *N*-bromosuccinimide; op, optical rotation; PAMPA, Parallel Artificial Membrane Permeability Assay; PBS, phosphate buffered saline; PCR polymerase chain reaction; PDB, protein data bank; PEG, polyethylene glycol; PEG400, polyethylene glycol 400; pIC50 - log (IC_{50}); pGI50, - log (GI_{50});, pin, pinacol; PMB, p-methoxybenzyl; PPB, plasma protein binding; prep, preparative; QSAR, Quantitative structure–activity relationship; Ra-Ni, Raney nickel; RBF, round bottomed flask; rt, room temperature; rmse, root-mean-square error; RP, reverse phase; s, singlet; satd, saturated; SEM, 2-(trimethylsilyl)ethoxy]methyl; siRNA, Small interfering RNA; SMs, starting materials; S-Phos, 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl; t, triplet; TBAB, tetra-n-butylammonium bromide; TBAF, tetra-n-butylammonium fluoride; TBTU, O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate; TEA, triethylamine; temp, temperature; TFA, trifluoroacetic acid; TGI, tumor growth inhibition; THF, tetrahydrofuran; TLC, thin layer chromatography; TWEEN, Polysorbate 80; q, quartet. UPLC, ultra performance liquid chromatography; UHN IACUC, University Health Network Institutional Animal Care and Use Committee; Δ, heat; µw microwave irradiation

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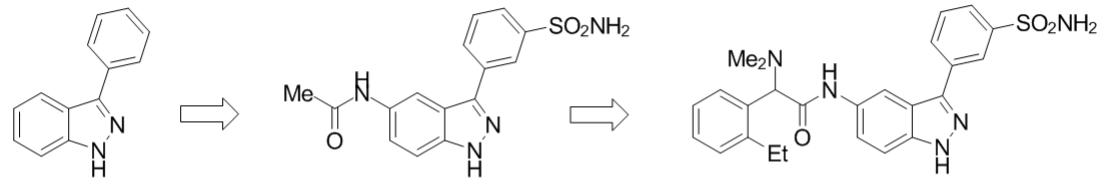
Graphical abstract



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