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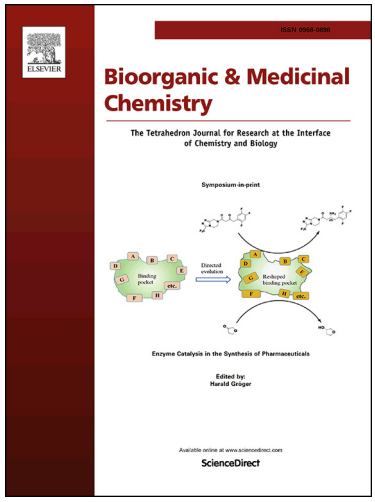

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Discovery of tetrahydroindazoles as a novel class of potent and in vivo efficacious gamma secretase modulators

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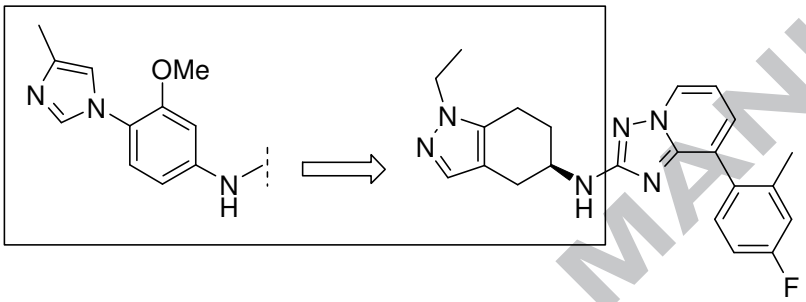
ABSTRACT:

The identification and optimization of a novel series of centrally efficacious gamma secretase modulators (GSMs) offering an alternative to the privileged aryl imidazole motif is described. Chiral bicyclic tetrahydroindazolyl amine substituted triazolopyridines were identified as structurally distinct novel series of GSMs. Representative compound **BI-1408** (***(R)*-42**) was demonstrated to be centrally efficacious in rats at a 30 mg/kg oral dose.



BI-1408
Aβ42 IC_{50} = 0.04 μM

Key words: Gamma secretase modulators; Tetrahydroindazols; Alzheimer's disease; Aβ42 reduction;

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid peptide; APP, amyloid precursor protein; BACE1, β-amyloid cleavage enzyme 1, β-secretase 1; GSM, gamma secretase modulator; LHS, left hand side; NSAID, non-steroidal anti-inflammatory drug; SAR, structure

activity relationships; HLM, human liver microsomes; RLM, rat liver microsomes; PPB, plasma protein binding, MDCK cells Madin-Darby canine kidney epithelial cells; pgp,p-glycoprotein; MDR1, multidrug resistance protein 1; MRT, mean residence time; psi pounds per square inch.

1. INTRODUCTION

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disease resulting in cognitive decline and memory loss. One of the hallmarks of this disease is the deposition of extracellular senile plaques comprised of amyloid-beta (Aβ) peptides.[1] The Aβ peptide derives from the sequential proteolytic cleavage of the amyloid precursor protein (APP) by BACE1, yielding a short membrane-bound C-terminal fragment (C99). Subsequently, C99 is cleaved via γ-secretase. While cleavage by γ-secretase yields Aβ peptides ranging from 37-43 amino acids long,[2] the hydrophobic Aβ 42 peptide ($A\beta_{42}$) appears most prone to aggregation. These aggregates form not only the nucleus of the senile plaques,[3] but also soluble oligomers, which are considered to be the primary neurotoxic agent in AD and have been proposed to play a central role in both the cause and progression of the disease.[4] Supporting this, mutations in presenilin 1 or 2, the catalytic subunits of γ-secretase, are associated with increased production of $A\beta_{42}$ and result in early onset AD.[5] Therefore, therapeutic approaches aimed at lowering the production of $A\beta_{42}$ represent an attractive pharmacological strategy to slow the progression of the disease. Gamma secretase modulators (GSMs), *i.e.* compounds that do not block gamma secretase cleavage but specifically lower $A\beta_{42}$ production while leaving total Aβ levels unchanged, were first identified in 2001.[6] Since then, GSMs have been demonstrated to lower $A\beta_{42}$ levels in both in vitro as well as in vivo studies. Furthermore, GSMs have been demonstrated to lower plaque load as well as rescue cognitive behavior in transgenic mice.[7]

From a chemistry perspective, GSMs can be divided into two main series: 1) NSAID-derived lipophilic carboxylic acids and 2) aryl imidazole compounds. In addition, Satori has reported natural product derived triterpenoid GSMs as an independent third chemical class.[8] Several reviews have been published on that matter and cover work of research teams in the GSM field of an entire decade.[9] The beginnings of aryl imidazole type GSMs can be traced back to an early report by Neurogenetics in 2004,[10] claiming compounds of a general structure represented by the molecule in Figure 1. The compounds show four consecutively arranged (hetero)aromatic rings that became known as the A-B-C-D ring motif.[11] Later, Eisai described a similar, more elaborated compound E-2012 (**1**),[12] the first aryl imidazole type GSM to reach clinical trials.[13]

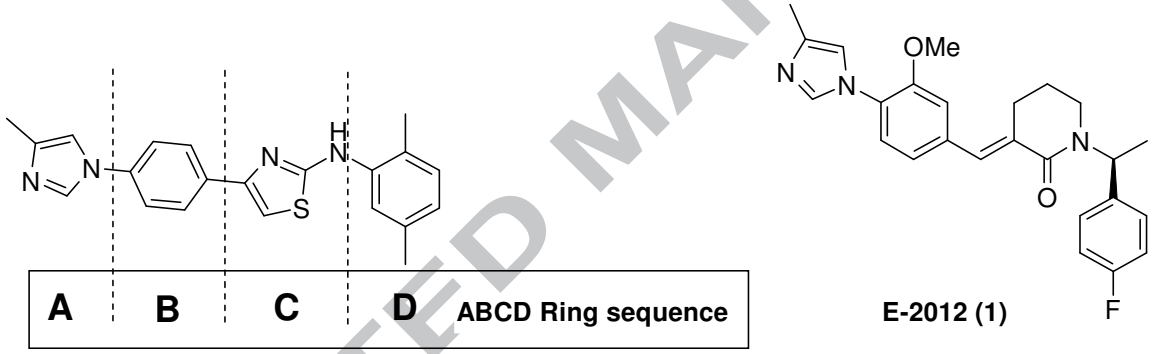


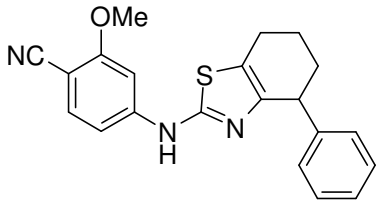
Figure 1. Generic structure of aryl imidazole type GSMs.

However, almost all non-NSAID-derived GSMs reported to date - including our own initial GSMs[14] - still share the same general characteristics such as a very high degree of aromaticity and the presence of an aryl imidazole left-hand side (LHS) moiety, which was often incorporated as aniline substructure into the compounds. While the privileged aryl imidazole A-B ring sequence seems to be particularly necessary to achieve good potency, we thought that a structural element lacking (*a*) the imidazole and (*b*) the electron rich aniline substructures would

be desirable in order to avoid both CYP inhibition and potential formation of reactive metabolites.[15,16]

Several efforts have therefore been directed at reducing electron density of the B-ring by the introduction of electron-withdrawing groups, replacing the central aniline with heteroaromatics or more recently using benzoic acids and their conjugates as more polar B-C ring fragments.[17,18,19,20]

Researchers at Merck reported on benzoazepinones where the imidazole was replaced by other heterocycles and the B-ring aromatic moity was substituted or replaced by other aromatics or a triple bond linker.[21] A small number of patent applications deal with compounds that demonstrated the successful replacement of the A-Ring imidazole by a nitrile moiety (Figure 2). First introduced by Roche[22] in 2009 (compound **2**), the research team at Bristol-Myers Squibb[23] highlighted amino benzonitriles (e.g. **3**) as a specific structural class of GSMs in two patent applications in 2012. Additionally, cyano indoles (e.g. **4**) were claimed as even further advanced analogues of the original motif by the research team at Janssen with C-linked connectivity towards the C-D fragment.[24] Sekioka *et al.* recently reported the identification of isoindolinone **5** as replacement for the aryl imidazole motif on an imidazopyridine scaffold as weakly active GSM.[25]



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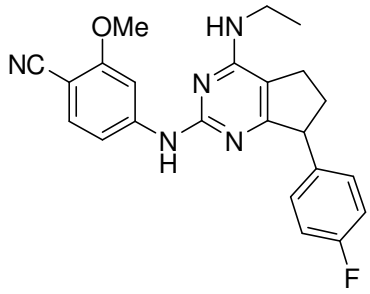

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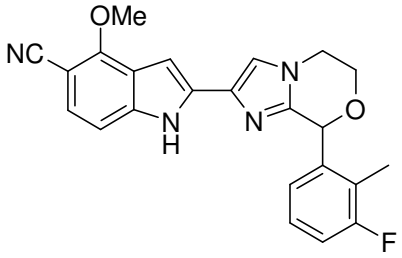
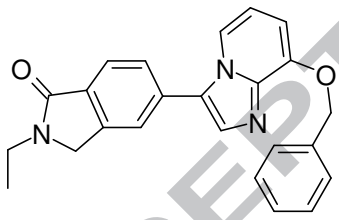


4 (Johnson&Johnson)



5 (Astellas)

Figure 2. Literature-known structural alternatives to the aryl imidazole moiety: benzonitriles and conjugates.

However, only a handful of reports dealt with finding non-aromatic B ring replacements, which in turn highlights the difficulties in identifying novel GSMs showing a lower degree of aromaticity: methoxyphenyl piperazines (e.g. **6**) were reported first by Merck & Co[26] and

subsequently utilized on a different core by the research team from Janssen,[27] whereas heteroaromatic piperidinyl amines were published in 2011 and 2012 by Roche[28] (e.g. **7** and **8**) (Figure 3).

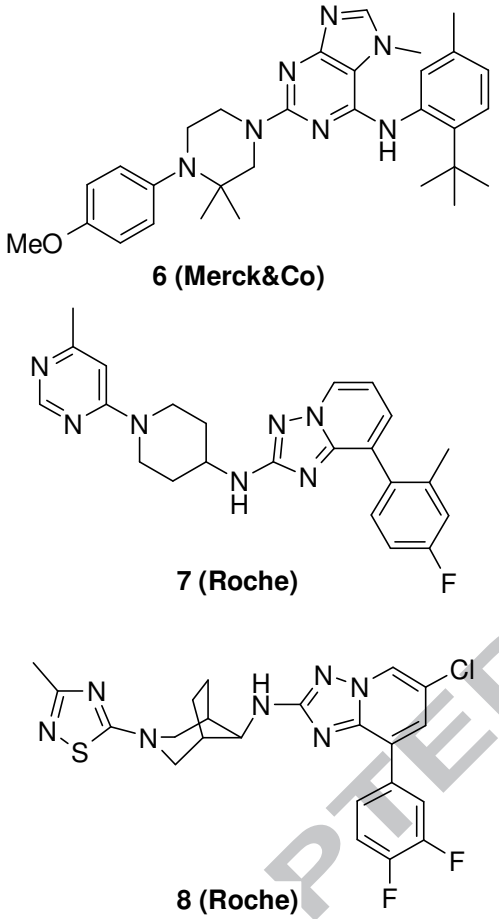


Figure 3. Literature-known alternatives to the aryl imidazole moiety: non-aromatic B-ring replacements.

While there is structural freedom to annellate the B-C ring sequence[29] as well as using bicyclic core systems as C-ring elements there is yet no evidence in literature that more flexible, partially saturated bicyclic amines can be used as A-B ring system.[30]

Herein, we report our work leading to a novel class of potent and *in vivo* efficacious gamma secretase modulators that comprise tetrahydroindazolyl amines as a replacement of the prominent aryl imidazole motif. To our best knowledge, this is the first disclosure of highly potent GSMs with partially saturated bicyclic amines as A-B ring fragments.

2. Design and Synthesis

2.1. Design

When looking for promising starting points to identify such novel A-B entities we recognized[31] the marked tolerance of the [1,2,4]triazolo[1,5-a]pyridine core to non-aromatic B ring modifications (e.g. compound **7**, Figure 4). We therefore hypothesized the triazolopyridine core to be a good probe for the identification of novel A-B structures. To this end, we chose a diverse set of primary and secondary amines of commercial and internal origin including numerous bicyclic amines as left-hand side elements for combination with a suitable triazolopyridine scaffold.

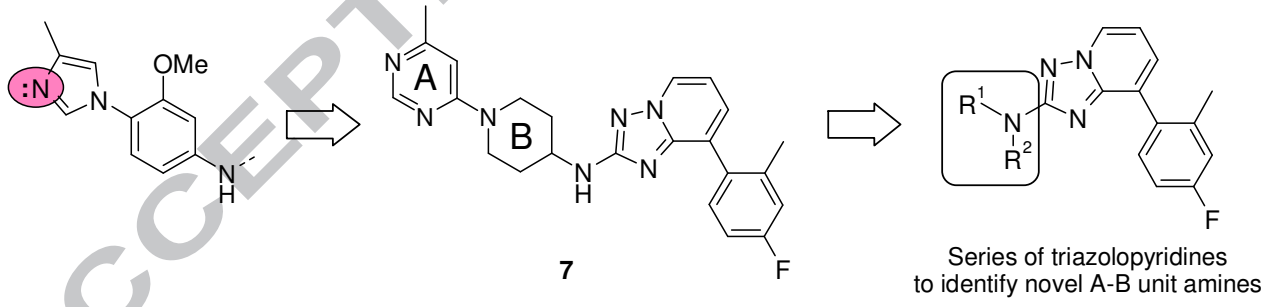


Figure 4. Design of an arylimidazole replacement series using the triazolopyridine scaffold.

In the amine selection process, we acknowledged the necessity of keeping a terminal hydrogen bond acceptor as a key pharmacophore (see Figure 4, pink ellipse) as well as the presence of at

least one ring system to limit conformational flexibility. Apart from that, we allowed all kinds of mono- or bicyclic aromatic, saturated, or partially saturated ring systems.

Applying these hypotheses we selected around 30 amines for synthesis and screened the products for GSM activity (data not shown). Compounds with an $A\beta_{42}$ IC_{50}<10 µM were defined as active from this exercise. Within this subset, we became particularly interested into two compounds: triazolopyridine **9** with an indazolyl amine moiety as bicyclic A-B ring motif, which was complemented by identification of compound **10**, which can be regarded as its partially hydrogenated analogue. Both indazolyl and 1-alkyl-4,5,6,7-tetrahydro-1*H*-indazolyl amines are - to the best of our knowledge - unprecedented as aryl imidazole replacement options (Figure 5).

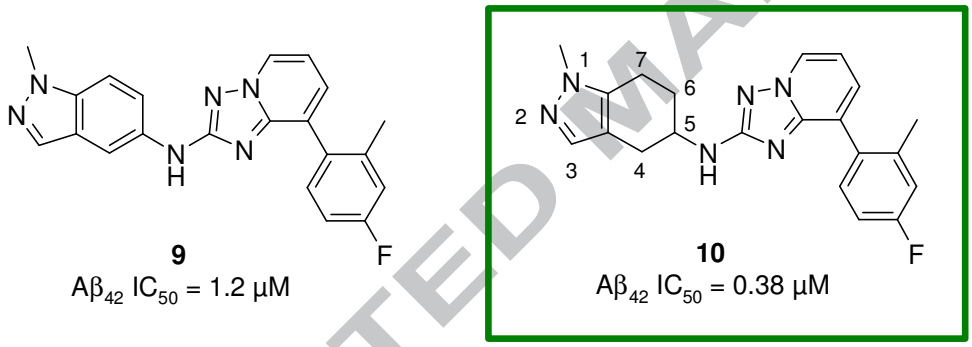


Figure 5. (Tetrahydro)indazolyl amine hits **9** and **10**.

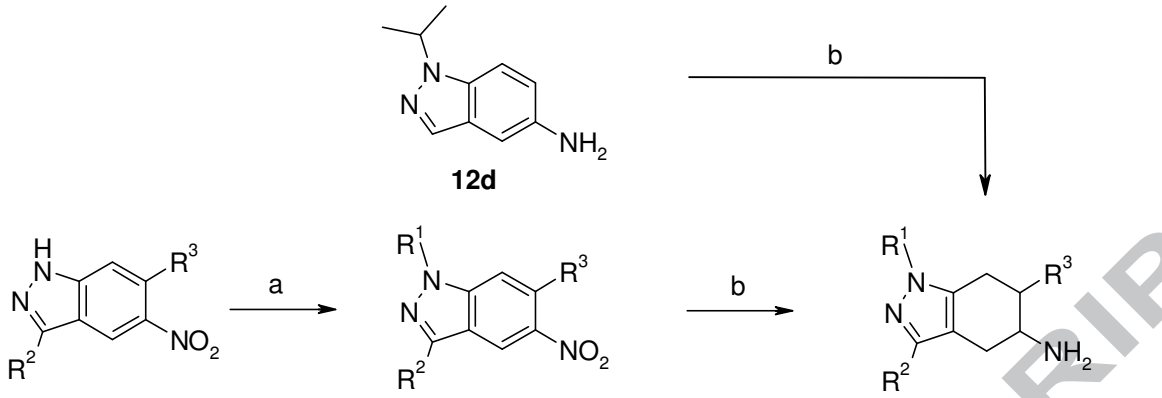
While compound **10** is not only more potent than compound **9**, it also contained the desired non-aromatic amine motif. We therefore decided to thoroughly investigate tetrahydroindazole substituted triazolopyridines as a novel series of GSMs.

2.2. Synthesis

Preparation of tetrahydroindazolyl amine intermediates: At the time of the discovery of compound **10** the respective 1-methyl-tetrahydroindazolyl amine building block was available

from one commercial vendor[32] only and no synthesis was described in literature. In order to explore tetrahydroindazole SAR we needed to find a robust and scalable synthetic approach to obtain sufficient material and to allow the synthesis of analogues. Initially we intended to alkylate 5-nitro-1*H*-indazole **11a** in the presence of potassium carbonate (Scheme 1). The reaction proceeded in high chemical yield, but the regioselectivity of the alkylation was rather modest with only a 1.7:1 ratio in favor of the desired 1-ethylated product **12a** over its 2-ethyl regioisomer. The desired regioisomer **12a** was chromatographically separated from the undesired isomer and hydrogenated using Nishimura's catalyst to give first access to initial quantities of 1-ethyl-4,5,6,7-tetrahydro-1*H*-indazol-5-ylamine **13a**.

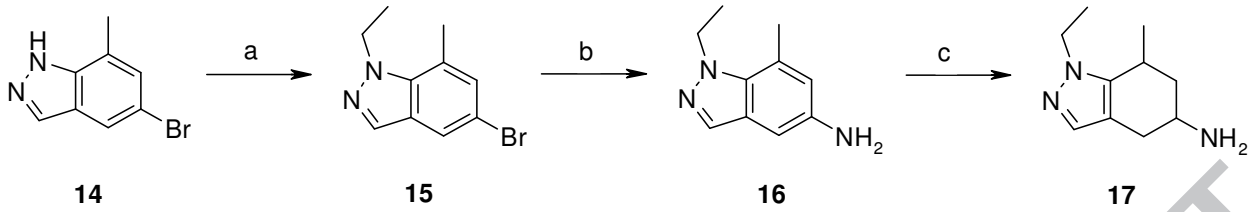
Alkylation regioselectivity was significantly improved upon switching to 3-halo-5-nitro-1*H*-indazoles **11b-c** as starting materials. 3-Chloro substitution favorably tuned the pyrazole reactivity in the alkylation reaction in such a way that now a 7:1 ratio of alkylated regioisomers was obtained. Moreover, the major product **12b** was easily separated by recrystallization. Almost complete regiospecificity was obtained for analogues containing either 3-bromo or 3-chloro substitution as in **12c-g**. Hydrogenation using Nishimura's catalyst followed by palladium on charcoal to completely remove remaining halide provided tetrahydroindazolyl amine **13a** in gram quantities. Chlorinated analogue **13b** was obtained as additional intermediate by stopping the hydrogenation at an earlier timepoint. Intermediates **13c**-**h** were synthesized using the same alkylation-hydrogenation sequence starting from nitro indazoles **11b-d**.



Scheme 1. Synthesis of tetrahydroindazolyl amine building blocks 13a-h[a]

[a]Reagents and conditions: (a) **12a**: ethyl iodide, K_2CO_3, DMF, 70°C, 57%; **12b**: ethyl iodide, K_2CO_3, DMF, 70°C, 83%; **12c**: *n*-propyl iodide, K_2CO_3, DMF, 70°C, 79%; **12e**: 3-bromo-2-methyl-propene, K_2CO_3, DMF, 70°C, 90%; **12f**: 1-bromo-but-2-yne, K_2CO_3, DMF, 70°C, 96%; **12g**: 1-bromo-pent-2-yne, K_2CO_3, DMF, 70°C, 93%; **12h**: ethyl iodide, K_2CO_3, DMF, 70°C, 56%; (b) H_2, 3 bar, Nishimura's catalyst, MeOH, 11-99%.

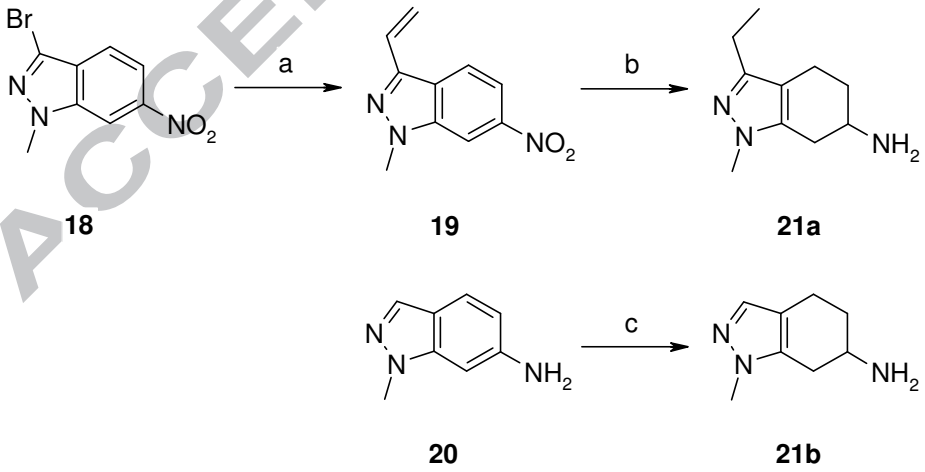
Introduction of a methyl group at position 7 warranted a different synthetic approach (Scheme 2): commercially available 5-bromo-7-methyl-1*H*-indazole **14** was alkylated (with poor regioselectivity of 1:1.6 in favor of the undesired 2-alkylated isomer) using sodium hydride as base and ethyl iodide to give intermediate **15** which was converted into the indazolyl amine **16** by a palladium-catalyzed amination with benzophenone imine as nitrogen source and subsequent acidic hydrolysis of the intermediate imine. The indazole amine **16** was hydrogenated to give the 7-methylated precursor **17** as mixture of diastereomers.



Scheme 2. Synthesis of 7-methyl substituted tetrahydroindazolyl amine 17[a]

[a]Reagents and conditions: (a) ethyl iodide, NaH, DMF, 0°C, 31%; (b) (i) benzophenone imine, Xantphos, $Pd_2(dba)_3$, NaO^tBu, toluene, 130°C, (ii) TFA/water, 39% over two steps; (c) H_2, 3 bar, Nishimura's catalyst, MeOH, 94%.

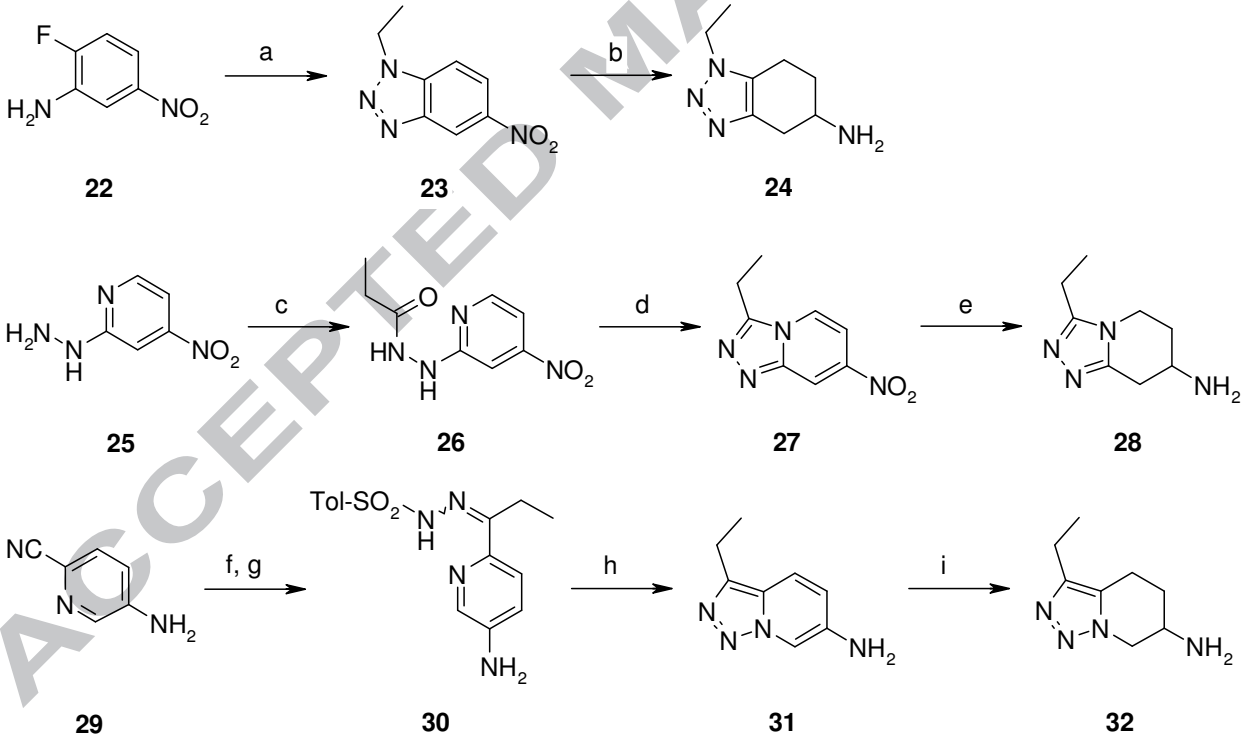
Regioisomeric tetrahydroindazol-6-yl amines **21a-b** were obtained using 3-bromo-1-methyl-1*H*-indazole **18** and 1-methyl-indazol-6-yl amine **20** as starting materials. In order to introduce an ethyl group at position 3 Suzuki-Miyaura cross coupling of **18** with vinyl boronic acid pinacole ester followed by hydrogenation of intermediate 3-vinyl-6-nitroindazole **19** gave the desired 3-ethyl analogue **21a** in a two-step sequence. Indazole amine **20** was directly hydrogenated to give **21b**.



Scheme 3. Synthesis of regiosomeric tetrahydroindazolyl amines 21a and 21b[a]

[a]Reagents and conditions: (a) vinyl boronic acid pinacol ester, $Pd(Ph_3P)_2Cl_2$, aq. Na_2CO_3 (2M), 1,4-dioxane/MeOH, 90°C, 81%; (b) H_2, 3→50 bar, Nishimura's catalyst, MeOH, 50°C, 38%; (c) H_2, 50 bar, Pd/C, MeOH, conc. aq. HCl, 50°C, 29%.

Scheme 4 outlines the preparation of additional analogues to the tetrahydroindazole core: the introduction of an extra nitrogen atom in the aromatic part gives rise to three possible types of bicyclic triazole building blocks: tetrahydro-1*H*-benzotriazol-5-ylamine **24**, tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-7-ylamine **28** and tetrahydro-[1,2,3]triazolo[1,5-a]pyridin-6-ylamine **32**.



Scheme 4: Preparation of variations of the original tetrahydroindazole core[a]

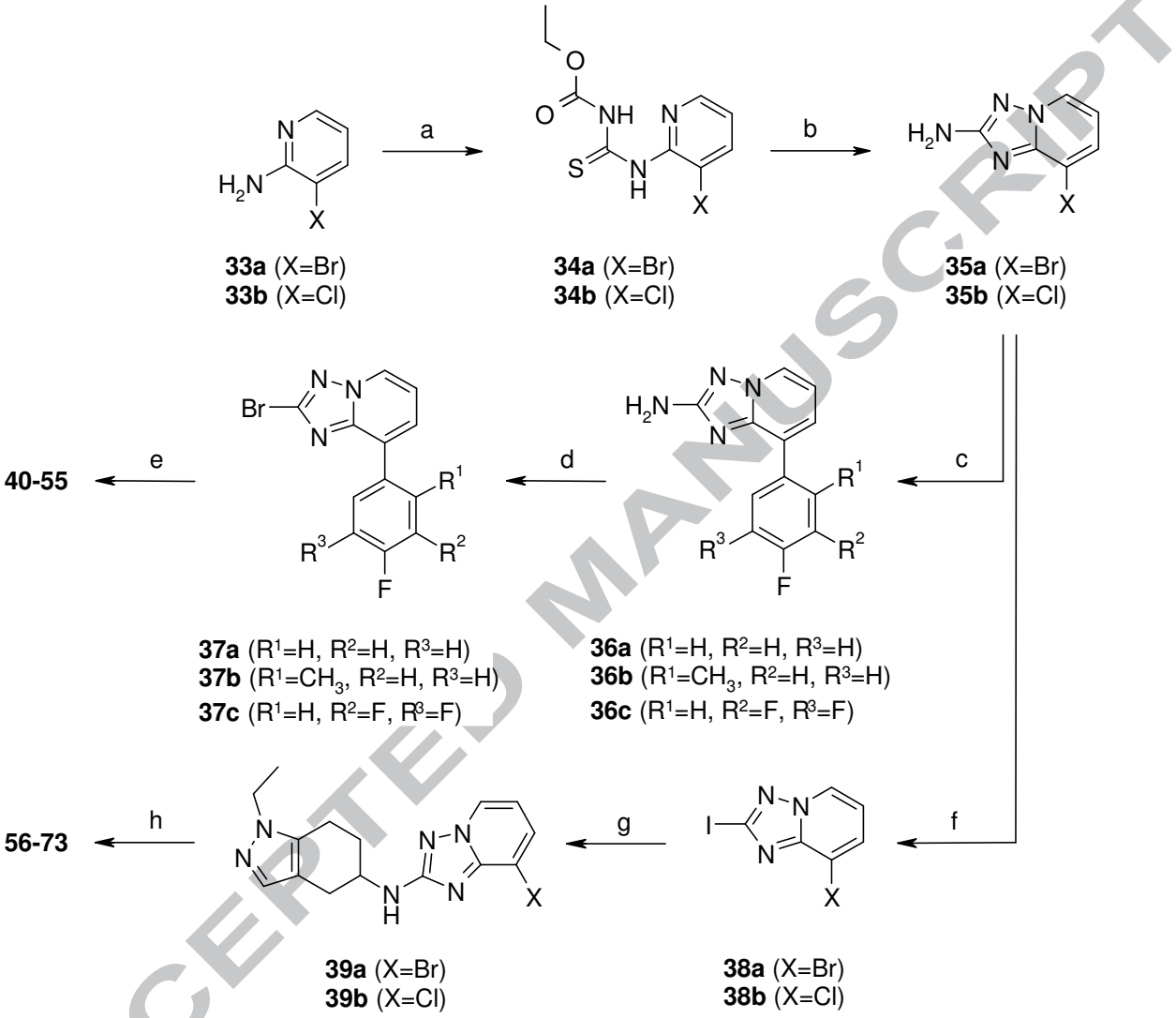
[a]Reagents and conditions: (a) (i) ethyl amine (2M THF solution), DMSO, 120°C, sealed tube, (ii) AcOH, $NaNO_2$ (2M aq. solution), 47% over two steps; (b) H_2, 3 bar, Nishimura's catalyst, MeOH, 66%; (c) propionyl chloride, DIPEA, THF, quant.; (d) Burgess' reagent, THF, 65°C, 61%; (e) H_2, 3 bar, Nishimura's catalyst, MeOH, 54%; (f) (i) ethyl magnesium bromide (3M in Et_2O), Et_2O, reflux→rt, (ii) aq. HCl, rt→40°C, 16%; (g) *para*-toluene sulfonyl hydrazide, MeOH, quant. (mixture of isomers); (h) (*Z*)-**30**, morpholine, 100°C, 69%; (i) H_2, 0.5 bar, Pd/C 10%, MeOH, 23%.

The benzotriazole scaffold was synthesized in a two-step sequence starting from 2-fluoro-5-nitro aniline. Ethyl amine was introduced by nucleophilic aromatic substitution to give an intermediate phenylene diamine, which was cyclized with sodium nitrite in aqueous acetic acid to directly afford 1-ethyl-5-nitro-1*H*-benzotriazole **23**.[33] Subsequent hydrogenation using Nishimura's catalyst provided desired tetrahydrobenzotriazol-5-ylamine **24**.

The synthesis of isomeric 3-ethyl-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl amine **28** commenced with the propionylation of 4-nitropyridin-2-ylhydrazine **25**. The acylated product **26** was condensed with the aid of Burgess reagent[34] to form the corresponding triazolopyridine **27**, which was hydrogenated to give the desired amine precursor **28**.

Addition of ethyl magnesium bromide to cyano pyridine **29** converted the nitrile moiety into intermediate ethyl ketone, which was condensed with tosyl hydrazide to furnish the corresponding tosyl hydrazones **30** as a mixture of *E*- and *Z*-isomers. The Z-isomer of **30** was taken forward and heated in morpholine to construct [1,2,3]triazolo[1,5-a]pyridine amine **31**,[35] which was finally hydrogenated to yield building block amine **32**.

The core framework of triazolopyridines was constructed starting from commercially available 2-amino 3-halo pyridines **33a-b** (scheme 5).



Scheme 5: Syntheses of central intermediates 37a-c, 39a-b and final compounds 40-73[a]

[a]Reagents and conditions: (a) ethoxycarbonyl isothiocyanate, DCM, rt, 87-96%; (b) hydroxylamine hydrochloride, DIPEA, EtOH/MeOH, reflux, 74-75%; (c) aryl boronic acid, $Pd(dppf)Cl_2$, aq. Na_2CO_3 (2M), 1,4-dioxane, 110°C, 45-80%; (d) **37a**: $^tBuNO_2$, $CuBr_2$, 60°C, 59%, **37b**: aq. HBr (47%), $NaNO_2$, CuBr, 0°C, 53%, **37c**: aq. HBr (47%), $NaNO_2$, 0°C, 42%;

(e) (i) amine, $Pd_2(dba)_3$, Johnphos, NaOtBu, 1,4-dioxane, 80°C, or (ii) amine, CsF, DMSO, 160°C, microwave irradiation; (f) **38a**: HI, $NaNO_2$, DMSO, 50°C, 57%, **38b**: KI, *p*-toluene sulfonic acid monohydrate, $NaNO_2$, MeCN/water, 50°C, 85%; (g) **39a**: **13a**, CsF, DMSO, 140°C, microwave irradiation, 29%; **39b**: **13a**, Pd-PEPPSI-IPent Cl, NaO^{t}Bu, 1,4-dioxane, 100°C, 51%; (h) (i) (hetero)aryl boronic acid or pinacole ester, SPhos palladacycle, K_3PO_4, toluene, 80°C or THF/water, 120°C, sealed tube or (ii) aryl boronic acid, $Pd(Ph_3P)_2Cl_2$, aq. Na_2CO_3 (2M), 1,4-dioxane/MeOH, 90°C or (iii) (hetero)aryl boronic acid or pinacole ester, $Pd(dppf)_2Cl_2$*DCM complex, 1,4-dioxane/MeOH, 70°C.

Treatment of **33a-b** with ethoxycarbonyl isothiocyanate provided the corresponding thiourea derivatives **34a-b**, which were readily cyclized upon heating with hydroxylamine hydrochloride in presence of a base to form the halogenated amino triazolopyridines **35a-b**.[36] Intermediates **35a-b** enabled flexible synthesis of building blocks **39a-c** and **37a-b**. These two types of functionalized building blocks would set the stage to either explore the nature of the distant aryl ring or the LHS amine's SAR.

Amino triazolopyridines **35a-b** were converted into iodo triazolopyridines **38a-b** using Sandmeyer conditions, which were reacted with tetrahydroindazolyl amine **13a** by heating in presence of cesium fluoride or using chemoselective palladium-catalyzed Buchwald-Hartwig conditions with Organ's catalyst system[37] to give precursors **39a-b** ready for aryl ring exploration. Finally, Suzuki-Miyaura cross coupling reactions with bromo amino triazolopyridine **35a** and the appropriate phenyl boronic acids provided intermediates **36a-c**,

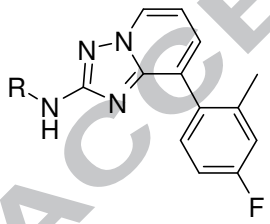
which were converted employing Sandmeyer conditions to yield bromo triazolopyridine building blocks **37a-c**.

The final compounds were synthesized by the two different approaches described already above depending on SAR purposes (Scheme 5): *i*) to evaluate the LHS area, 2-bromo triazolopyridine building blocks **37a-c** were reacted with the required amines **13a-h**, **17**, **21a-b**, **24** and **32** under conditions similar (*vide supra*) to those that were used to prepare intermediates **39a-b** to give the final compounds **40**-**54** (see Table 1) and **56** (see Table 2); *ii*) to explore SAR of the phenyl substituent, Suzuki-Miyaura cross coupling reactions with boronic acids and building blocks **39a-b** were used to successfully introduce various phenyl and pyridinyl substituents furnishing final compounds **55** and **57**-**73** (see Table 2).

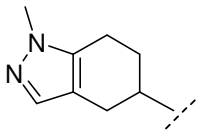
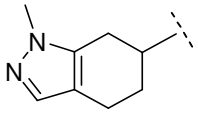
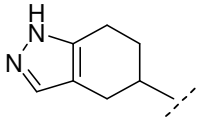
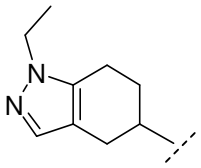
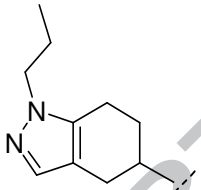
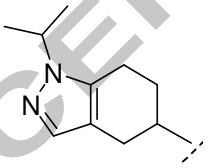
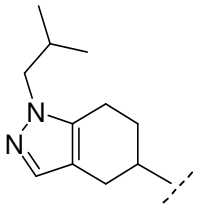
3. Results and discussion

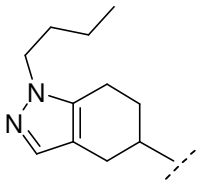
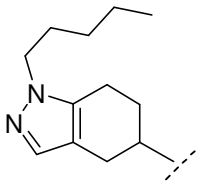
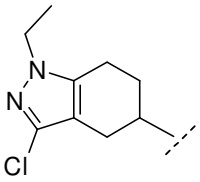
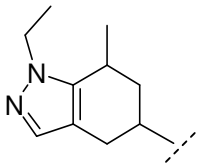
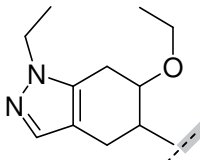
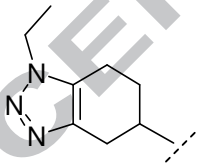
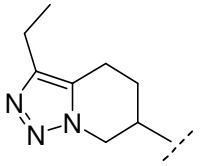
3.1. Left-hand side SAR analysis

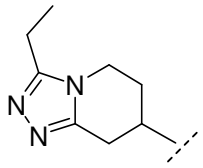
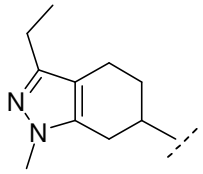
Excited by the already submicromolar activity of the initial hit **10** (IC_{50} = 0.38 μM), we explored the SAR of this novel LHS systematically (Table 1).



Cpd.	R	$A\beta_{42}$ IC_{50} [μM][a]

10		0.38 (5)
40		>30 (1)
41		4.57 (2)
42		0.07 (5)
43		0.06 (2)
44		0.43 (2)
45		3.40 (1)

46		2.77 (2)
47		>30 (2)
48		0.75 (1)
49[a]		0.95 (3)
50[b]		21.70 (1)
51		2.20 (1)
52		0.74 (2)

53		1.39 (1)
54		3.13 (1)

[a]For multiple determinations, values are reported as geometric mean. Number of experiments is given in parentheses. [b]Compound was prepared as 3,4,5-trifluoro-phenyl derivative.

Table 1. LHS SAR Analysis

The regioisomeric 6-amino tetrahydroindazolyl derivative **40** did not modulate gamma secretase up to a concentration of 30 μM and served to illustrate the importance of exactly positioning the acceptor atom in the pyrazole unit relative to the attachment point to the core. Also demethylated tetrahydroindazole derivative **41** (IC_{50} = 4.57 μM) was significantly less active, which may in part be attributed to tautomerism of the pyrazole unit leading to a less confined electron density. Next, we turned our attention to the pyrazole substituent itself and attached alkyl chains of varying length and steric bulk (Table 1). Extension of the original *N*-methyl group to an ethyl (compound **42** (IC_{50} = 0.07 μM)) or an *n*-propyl group (compound **43**(IC_{50} = 0.06 μM)) improved activity 4-5-fold compared to the parent compound **10** and lead to derivatives with $A\beta_{42}$ IC_{50} <100 nM. The significant increase in activity achieved by simply switching from methyl to ethyl substitution can be seen as the SAR key finding in retrospect and spurred our efforts in further optimizing this series of GSMs. Branching of the alkyl chain as in compound **44** (IC_{50} = 0.43 μM)reduced potency slightly. Further substitutions of increasing size and chain length with *iso*butyl, *n*-butyl and *n*-pentyl groups (derivatives **45-47**) revealed very steep, but reliable and

robust SAR: just a simple one carbon atom chain extension from the most potent *n*-propyl residue to its higher homologue (compound **46** (IC_{50} = 2.77 μM)) lead to a significant drop in activity, which was completely abolished upon further extension to the *n*-pentyl homologue **47** (IC_{50} > 30 μM).

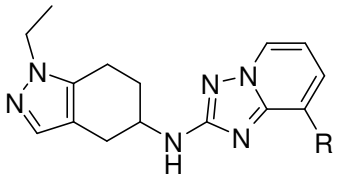
SAR on other positions of the bicycle appears to be even more limited: 3-substitution at the pyrazole ring with chlorine (compound **48** (IC_{50} = 0.75 μM)) lead to reduction of activity. Taking into consideration that methylation at position 7 (compound **49** (IC_{50} = 0.95 μM)) or ethoxylation at position 6 (compound **50** (IC_{50} = 21.7 μM)) of the saturated part of the bicycle installed a second stereogenic center and thus gave rise to diastereomeric mixtures of micromolar activity, none of the single isomers – if there was a eutomer - could potentially provide a superior compound over parent derivative **42** (IC_{50} = 0.07 μM). Therefore no attempts were undertaken to synthesize the pure diastereomers.

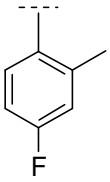
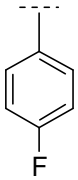
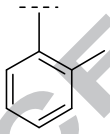
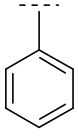
We investigated other closely related heterobicyclic systems as isosteric replacement of the tetrahydroindazole element. However, all of the variations synthesized were significantly less potent (Table 1, compounds **51**-**54**). Interestingly, attaching an ethyl group at position 3 of inactive regioisomeric tetrahydroindazol-6-yl amine derivative **40** (IC_{50} > 30 μM) restored activity to some degree. Therefore, although being a tetrahydroindazole derivative, **54** (IC_{50} = 3.13 μM) may technically also be envisioned as additional isostere.

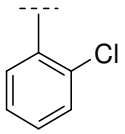
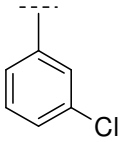
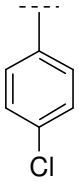
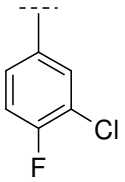
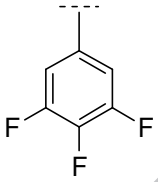
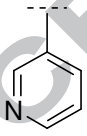
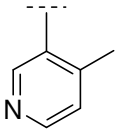
3.2. Aryl head group SAR

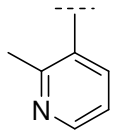
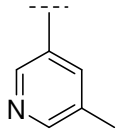
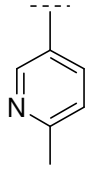
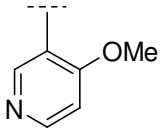
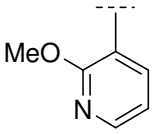
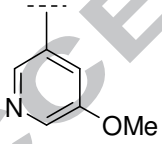
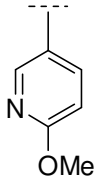
Next, we turned towards exploration of the distal aryl group (Table 2). In order to interpret the individual contribution of the aryl substituents of our original hit to compound activity, we synthesized mono-substituted *o*-CH_3- and *p*-fluoro analogues **55** (IC_{50} = 0.18 μM) and **56** (IC_{50} =

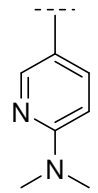
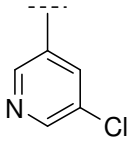
0.16 μM). Interestingly, both derivatives appeared to be less active compared to the parent molecule, however in comparison to the unsubstituted phenyl analogue **57** (IC_{50} = 0.07 μM) the individual activity spread was rather small.



Cpd.	R	$A\beta_{42}$ IC_{50} [μM][a]
42		0.07 (5)
55		0.18 (2)
56		0.16 (2)
57		0.07 (2)

58		0.06 (2)
59		0.04 (2)
60		0.06 (2)
61		0.02 (3)
62		0.03 (2)
63		0.35 (2)
64		0.73 (1)

65		0.68 (1)
66		0.20 (1)
67		0.67 (2)
68		0.12 (2)
69		0.50 (2)
70		0.20 (1)
71		0.09 (1)

72		0.05 (1)
73		0.04 (1)

[a]For multiple determinations, values are reported as geometric mean. Number of experiments is given in parentheses.

Table 2. Aryl head group SAR

We followed up by synthesizing all three mono-chloro analogues (compounds **58**-**60**). Within this subset of compounds the *meta*-substituted derivative **59** (IC_{50} = 0.04 μM) appeared to be more active than its regioisomers. An additional fluorine substituent at the *para* position (compound **61** (IC_{50} = 0.02 μM)) helped to further increase potency by a factor of two and resulted in preparation of the most potent racemic compound within this structural class. This effect was further substantiated by the 3,4,5-trifluoro derivative **62** (IC_{50} = 0.03 μM), which was also more potent than its 4-fluoro analogue **55** (IC_{50} = 0.18 μM).

Since the individual substituent effect on potency was rather limited, the increase in activity presumably is mainly lipophilicity-driven. Therefore, in order not to compromise the beneficial contribution of our tetrahydroindazole residue to the overall molecular polarity, we incorporated 3-pyridines as replacement for the phenyl group. When comparing parent compounds **57** (IC_{50} = 0.07 μM) and **63** (IC_{50} = 0.35 μM), this bioisosteric replacement initially seemed to result in activity reduction, which is in line with the increased polarity of the basic pyridyl group.

We revisited the substituent pattern by scanning with a neutral methyl substituent in order to retain the pyridine basicity (entries **64**-**67**): Addition of a methyl group in position 2 and 4 as well as in the 6-position of the pyridine lead to a reduction of activity, whereas the 5-methyl substitution in **66** (IC_{50} = 0.20 μM) increased activity relative to the other methyl analogues, but also in comparison to parent pyridine derivative **63** (IC_{50} = 0.35 μM), confirming the previously observed phenyl group substituent effect pattern.

We hypothesized that modulating pyridine basicity could influence activity. To this end, we prepared methoxy analogues **68**-**71**. Alkoxy substitution in the *alpha* position relative to a pyridine nitrogen atom is known to significantly reduce basicity[38]. Indeed, 6-methoxy pyridine **71** (IC_{50} = 0.09 μM) ($pKa_{calc.}$ = 4.55)[39] showed improved activity, but not its 2-methoxy analogue **69** (IC_{50} = 0.50 μM) ($pKa_{calc.}$ = 4.55), indicating a potential negative interaction with the GS binding site in the case of **69**. Interestingly, the 4-methoxy analogue **68** (IC_{50} = 0.12 μM, $pKa_{calc.}$ = 7.16), which should be more basic than its regioisomer **69** (IC_{50} = 0.50 μM) ($pKa_{calc.}$ = 4.55) is about 4-fold more potent. Also, 6-dimethylamino pyridine **72** (IC_{50} = 0.05 μM) is surprisingly potent in light of its high calculated pKa value ($pKa_{calc.}$ = 6.67). For the latter two compounds, **68** and **72**, basicity is increased in a way that could potentially provide a favorable balance between solubility at low pH and permeability at physiological pH. Overall, there was no clear correlation of basicity alone with potency of the pyridine derivatives.

The most potent compound of the pyridine subseries was the more lipophilic 5-chloro pyridine **73** with an $A\beta_{42}$ IC_{50} of 37 nM, which is equal to the activity of 3-chloro phenyl derivative **59** (IC_{50} = 0.04 μM), although it is more polar.

3.3. Influence of stereochemistry on biological activity

Since the tetrahydroindazole compounds were obtained as racemates we sought to obtain their pure enantiomers and investigate potential enantiomer effects with representatives (Figure 6).

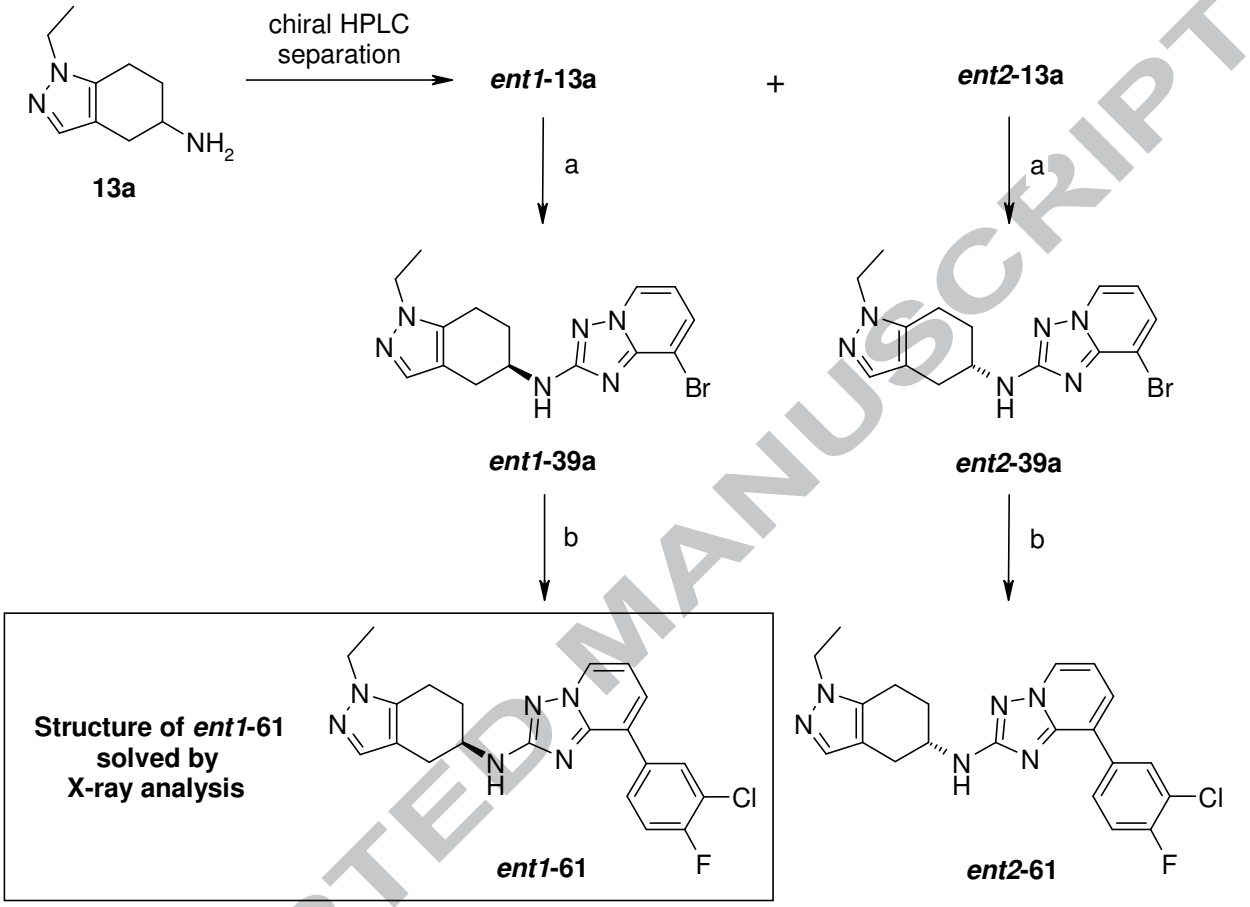


Figure 6: Determination of the absolute stereochemistry of tetrahydroindazole GSMs[a]

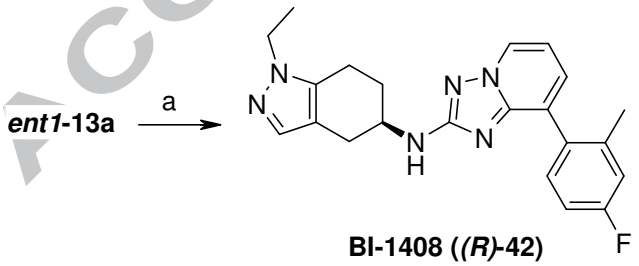
[a]Reagents and conditions: (a) **38a**, CsF, DMSO, 130°C, microwave irradiation, ***ent1*-39a**: 46%, ***ent2*-39a**: 62%; (b) 3-chloro-4-fluoro-phenylboronic acid, aq. K_2CO_3 (2M), $Pd(dppf)_2Cl_2$*DCM complex, 1,4-dioxane/MeOH, 90°C, ***ent1*-61**: 57%, ***ent2*-61**: 71%.

In order to determine the absolute stereochemistry of the enantiomers the racemic amine building block **13a** was resolved into its enantiomers by chiral HPLC and served to prepare chiral intermediates ***ent1*-39a** and ***ent2*-39a** (with at this stage still undetermined absolute

stereochemistry). We then synthesized chloride containing analogues to determine the absolute stereochemistry by analysis of anomalous scattering in X-ray analysis of single-crystals. From intermediate ***ent1*-39a** we synthesized chiral tetrahydroindazole ***ent1*-61**, one enantiomer of our most potent racemic compound **61** ($A\beta_{42}$ IC_{50} = 0.02 µM). The corresponding enantiomer ***ent2*-61** was prepared from the antipode building block ***ent2*-39a**.

We were delighted to discover a pronounced enantiomer effect for our tetrahydroindazolyl amine moiety: ***ent1*-61** ($A\beta_{42}$ IC_{50} = 0.009 µM) was approximately two-fold more active than racemic **61** and over 20-fold more active compared to its corresponding enantiomer ***ent2*-61** ($A\beta_{42}$ IC_{50} = 0.194 µM) when measured within the same assay run. A crystalline batch of ***ent1*-61**, obtained by recrystallization from methanol, was used in X-ray analysis (for details see Supporting Information) to unambiguously determine the absolute stereochemistry of the more active tetrahydroindazole enantiomer to be (*5R)*.

With this information in hand, we now readily matched the stereochemistry to both chiral batches of **13a** and prepared additional chiral tetrahydroindazole derivatives. In particular, based on its overall profile, we chose to synthesize the more active ingredient of compound **42** (Scheme 6).



Scheme 6: Preparation of chiral tetrahydroindazole BI-1408 ((*R*)-42)[a]

[a]Reagents and conditions: (a) **37b**, CsF, DMSO, 160°C, microwave irradiation, 80%.

3.4. *In vitro* and rat *in vivo* profile of BI-1408

While most of the described compounds suffer from poor metabolic stability in rodents, the overall profile (Table 3-1 and 3-2) of **BI-1408** (***(R)*-42**) led us to the conclusion that this compound might be an appropriate tool to asses in vivo activity of the series.

In accordance with our expectations, tetrahydroindazole ***(R)*-42** was also approximately two-fold more active compared to the racemate **42**. Furthermore, ***(R)*-42** was equipotent in rat primary cortical neurons, but affected neither total Aβ concentration (ratio $A\beta_{total}$ / $A\beta_{42}$ = 254) nor Notch receptor processing, which is in line with the proposed mode of action for gamma secretase modulation.

***In vitro* profile**	**BI-1408 (*(R)*-42)**
$A\beta_{42}$ IC_{50} [μM] (no. of experiments)	0.04 (6)
Ratio $A\beta_{total}$ / $A\beta_{42}$ (no. of experiments)	254 (6)
Rat primary cortical neurons $A\beta_{42}$ IC_{50} [μM]	0.04
Notch IC_{50} [μM]	>30
HLM / RLM [mL/min*kg]	12.6/57
PPB rat (%)	98.8
MDCK P_{a-b} [10^{-6} cm/s] (efflux ratio)	78 (0.7)
hERG inhibition [% inhibition at 1 and 10 μM]	8/39

CYP450 IC_{50} (3A4/2D6/2C9/2C8/2C19) [μM]	>50/>50/25/9.5/36

Table 3-1. *In vitro* profile of BI-1408 (*(R)*-42)

Metabolic stability of ***(R)*-42** was at best borderline in rat, but acceptable in human microsomes. Permeability was tested in MDR1-expressing cells: ***(R)*-42** showed excellent permeability with no indication for pgp-mediated efflux. The plasma protein binding in rats was high, but with a reasonable fraction unbound of approximately 1%.

A basic *in vitro* safety profile (Table 3-1) was also assessed and highlights the advantages of the novel tetrahydroindazole motif over many (hetero)aryl imidazole based γ-secretase modulators: **BI-1408** (***(R)*-42**) showed no indication for relevant interaction with the hERG channel and demonstrated a very clean cytochrome P450 profile with 2C8 being the only isoform that was moderately inhibited (IC_{50} = 9.5 μM).

In rat i.v. PK studies (1μmol/kg dose, Table 3-2) tetrahydroindazole ***(R)*-42** was cleared only moderately fast with 40 mL/min*kg despite high clearance observed in rat microsomes. **BI-1408** (***(R)*-42**) was then administered orally to rats at a 10 μmol/kg dose to evaluate its distribution into different tissues. We were delighted to see that the compound showed no indication of *in vivo* efflux as judged by the ratio of muscle to brain concentrations which was in line with the MDCK assay prediction. Furthermore, the compound was distributed equally between plasma and brain; this result encouraged us to advance the compound into acute pharmacodynamic studies.

***In vivo* PK profile (rat)**	**BI-1408 (*(R)*-42)**

i.v. bolus (1µmol/kg)	
Clearance [mL/min*kg]	40
MRT [h]	0.6
V_{ss} [L/kg]	1.5
p.o. tissue distribution (10 µmol/kg, 3h p.a.)	
C_{plasma} [nM]	2677
C_{brain} [nM]	2990
C_{muscle} [nM]	2595
C_{Muscle} / C_{Brain}	0.9
C_{Brain} / C_{Plasma}	1.1

Table 3-2. *In vivo* PK profile of BI-1408 (*(R)*-42)

3.5. Ab42 lowering

In the acute PD experiment, **BI-1408** (***(R)*-42**) was dosed at 30 mg/kg to rats and compound **1** ($A\beta_{42}$ IC_{50} = 0.1 µM), as a positive control, was dosed at 25 mg/kg (this dose for the positive control was chosen since it reliably led to about 50% reduction in $A\beta_{42}$ in our hands). Three hours post p.o. application, blood was sampled to determine plasma exposure and brains were extracted to measure $A\beta_{42}$ and $A\beta_{total}$ levels. With no indication for *in vivo* efflux and equal drug distribution across measured tissue compartments, the free brain concentration of **(*R*)-42** was estimated from the unbound plasma exposure to be about 30 nM, in the range the *in vitro* $A\beta_{42}$

IC_{50}. Brain $A\beta_{42}$ levels were lowered by approximately 50% while total levels of $A\beta_{total}$ levels remained unchanged (Figure 7).

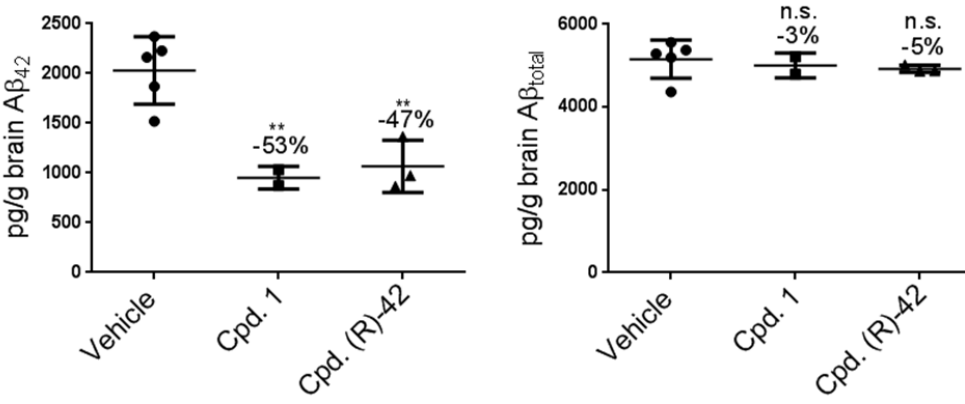


Figure 7. Effects of GSM treatment on rat brain Aβ species. A) Measurement of brain $A\beta_{42}$ levels 3 hrs. after a single p.o. application of 25 mg/kg compound **1** and 30 mg/kg **BI-1408** (**(*R*)-42**). B) Measurement of brain $A\beta_{total}$ levels 3 hrs. after a single p.o. application of 25 mg/kg compound **1** and 30 mg/kg **BI-1408** (**(*R*)-42**). (** = $p < 0.01$)

4. Summary and conclusion

In summary, we have identified two novel bicyclic elements, indazole and tetrahydroindazolyl amines as replacement option for the frequently described (hetero)aryl imidazole moiety of non-NSAID gamma secretase modulators. Starting from our initial weakly active hit **10** we were able to improve potencies more than 40-fold. The key SAR achievement was the discovery of *N*-ethyl and *N*-*n*-propyl substitutions at the tetrahydroindazole moiety, where both modifications boosted potency about 4-5-fold compared to the original *N*-methyl starting point. In addition, we

discovered a prominent enantiomer effect and were able to unambiguously determine the absolute stereochemistry of the more active enantiomer by X-ray analysis.

Finally, we profiled representative tetrahydroindazole **BI-1408** (***(R)*-42**) both *in vitro* and *in vivo* and demonstrated efficacy at 30 mg/kg oral dose in an acute pharmacodynamic setting in naïve rats. Tetrahydroindazoles show favorable CYP and hERG parameters, which could potentially translate into an improved safety profile.

Taken together, we succeeded in identification and optimization of a hitherto unprecedented series of gamma secretase modulators, which no longer contain obvious risk-associated structural elements such as imidazole or electron-rich aniline substructures.

5. Experimental section

Methods

Animals: Procedures involving animals and their care were in conformity with institutional and European Union guidelines (EEC Council Directive 86/609) and approved by the regional Ethical Committee. The rats used in these experiments were purchased from Janvier.

Cellular measurements:

$A\beta_{42}$ measurements: H4 cells overexpressing human APPwt were used for $A\beta_{42}$ and $A\beta_{total}$ measurements. For these measurements, 10,000 cells /well were aliquoted using a Multidrop into a 384-well cell culture plate in which 5 µL of the various compound (or vehicle) solutions had previously been applied. The cell culture plate was then incubated for 22 hrs. at 37°C, 5% CO_2.

For measurement of $A\beta_{42}$ levels, an MSD® Human Anti-Abeta-42 Peptide 96-well plate was blocked according to the manufacturer's protocol and subsequently5 µL/well of the supernatant from the treated H4 APPwt cells (see above) were pipetted into the wells of the anti-Abeta-42 plate. 20µL cell culture media was added into each well containing 5µL treated cell culture supernatant, such that the final volume in each of these wells was 25µL. After incubation and washing, each well was incubated with 1:50 diluted S-tag 6E10 for 1 hr. After subsequent washing, 1x read buffer was added to each well and the electrochemiluminescence was detected with the MSD® -reader.

$A\beta_{total}$ measurements: The measurement of $A\beta_{total}$ was performed identical to the $A\beta_{42}$ measurement with the exception that an MSD 96-well plate pre-coated with the 4G8 antibody was used.

Notch assay: Notch cleavage was measured using a luciferase complementation based reporter assay using the HeLaTetON-NotchΔE-NLuc/CLuc-RBP cell line E6 that was licensed from R. Kopan/Washington University.[40] Briefly, the cells were seeded out at 10,000 cells /well in a 96well plate in DOX-containing media. The cells were then incubated in presence of compound for 16 hr. After the incubation, the media was aspirated, imaging buffer with 150µg/mL D-luciferin was incubated for 15 min. and the bioluminescence was measured.

Primary neurons: Primary cortical neurons were isolated from E18 rat embryos, where 70,000 cells/well were plated into a 96 well plate. Cortical primary neurons were treated 5 days after preparation. The cell culture media from the 96-well plate containing the primary neurons was completely aspirated and 180 µL of the diluted compound or vehicle (0.5% DMSO in neurobasal media with 2% B-27 Supplement) were transferred onto the primary neurons. The 96-well plate

was then incubated at 37°C, 10% CO_2 for 22 hours. Measurement of $A\beta_{42}$ was as listed above with the exception that an S-tag 4G8 labeled antibody was used for detection instead of 6E10.

Treatment and sampling:

All compounds were formulated in 0.5% Natrosol and 0.01% Tween 80 (w/v) and were applied p.o. After the indicated treatment period, the mice were anesthetized by a 0.75 mL/kg i.p. injection of 100 mg/mL Ketavet® followed by a 0.85 mL/kg i.p. injection of 100 mg/mL Inactin® hydrate. The rat was subsequently decapitated and the brain was removed. The brain was sectioned to remove the cerebellum and the two hemispheres were separated and two approximately 3 mm coronal slides were prepared. The brain samples were then individually weighed, frozen in liquid nitrogen and stored at -80°C.

Homogenate preparation:

The individual frozen brain tissues were briefly thawed on ice, then subsequently 5 fold v/w 20 mM Tris pH 8.5 + 0.2% Triton X-100 as added to each sample. This was then transferred to an ice cold douncer and the brain tissue was dounced 12 times with the loose pestle and subsequently 12 times with the tight pestle. The homogenate was then transferred into centrifuge tubes and centrifuged for 1 hr. at 210,000 x g at 4°C. The supernatant was transferred back into ice cold Eppendorf tubes prior to Aβ measurement.

Rat brain homogenate $A\beta_{42}/A\beta_{total}$ measurement:

Measurement of $A\beta_{42}$ was performed as listed above with the exception that an S-tag 4G8 labeled antibody was used for detection instead of 6E10. For $A\beta_{total}$ from rat brain homogenates, measurements were as listed above with the exception that an MSD streptavidin plate was coated

with a biotinylated, rodent Aβ specific antibody (Covance Sig39156) and detection was via an S-tag 4G8 antibody.

in vivo PK: For the i.v. PK the drug was administered as solution intravenously to female fed HanWistar rats. For p.o. dosing, the compound is administered per gavage as a Natrosol suspension to 16 hour fasted female Han Wistar rats. Blood samples were taken at several time points post administration and EDTA plasma was prepared by centrifugation. PK parameters were calculated using non compartment methods.

For the p.o. tissue distribution study the compound was administered orally to fasted female HanWistar rats. 3 hours post administration the animals were sacrificed, tissue samples were collected and stored frozen until concentrations were quantified.

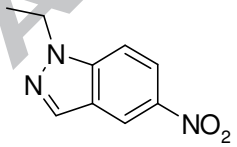
Bioanalytics: Plasma and tissue concentrations were quantified by LC/MS/MS. Plasma and tissue homogenate sample preparation was carried out via acetonitrile precipitation on a Hamilton Star (Hamilton Bonaduz Switzerland) robot system. The precipitation was kept in the freezer for 15 min and centrifuged at 3000 rpm for 3 min. The supernatant was diluted 1:100 with 25% acetonitrile 75% of a 0.1% formic acid and injected for analysis by LC–ESI-MS/MS. The analytical instrumentation consisted of a CTC HTX PAL (CTC Analytics, Switzerland) autosampling system coupled to an Agilent 1100 series liquid chromatography device (Agilent Technologies, Palo Alto, CA, USA) interfaced with an Applied Biosystems/MDS Sciex API 5000 triple quadrupole mass spectrometer (ABISciex, Concord, Canada).

General Analytics. All reactions were carried out using commercial grade reagents and solvents. NMR spectra were recorded on a Bruker AVANCE IIIHD 400 MHz instrument using TopSpin 3.2 pl6 software. Chemical shifts are given in parts per million (ppm) downfield from internal reference trimethylsilane in units. Selected data are reported in the following manner: chemical

shift, multiplicity, coupling constants (*J*), integration. Analytical thin-layer chromatography (TLC) was carried out using Merck silica gel 60 F254 plates. All compounds were visualized as single spots using short wave UV light. Low resolution mass spectra were obtained using a liquid chromatography mass spectrometer (LCMS) that consisted of an Agilent 1100 series LC coupled to a Agilent 6130 quadrupole mass spectrometer (electrospray positive ionization). High resolution masses were determined on a Waters QTOF G2-Si spectrometer. Unless otherwise specified the purity of all intermediates and final compounds was determined to be >95% by LCMS using one of the methods (1-12), which are described in detail in the Supporting information. Enantiomeric purity was determined by supercritical fluid chromatography on Agilent 1260 SFC with DA- and ELS detection using one of the methods (13-15), which are described in detail in the Supporting information. Optical rotation was determined by a Perkin Elmer 343 polarimeter. Specific rotations $[\ ]_D^{20}$ are given in deg $cm^3\ g^{-1}\ dm^{-1}$.

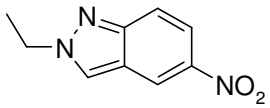
Synthesis Procedures

General procedure A: preparation of intermediates 12a-c and 12e-h. A mixture of the respective nitro indazole **11a-d** (1.0 equiv), alkyl halide (1.0 equiv) and K_2CO_3 (2 equiv) in DMF was stirred for 3h at 60°C. After cooling to RT the reaction mixture was poured into water and extracted 3x with ethyl acetate. The combined organic phases were dried and concentrated under reduced pressure. The crude residue was purified by preparative reverse-phase HPLC.

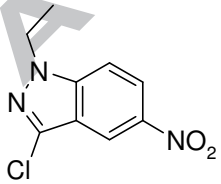


*1-Ethyl-5-nitro-1H-indazole (**12a**)*. Prepared according to general procedure A using nitro indazole **11a** and ethyl iodide. Ratio of **12a** vs. regioisomeric 2-ethyl-5-nitro-*2H*-indazole (HPLC analysis, method 1): 2:1.

12a precipitated during work-up and was collected by filtration. Yield: 332 mg (57%). LCMS (ESI^+) calculated for $C_9H_8N_3O_2$ $[M + H]^+$ *m/z* 192.0773, found 192.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.83 (d, J = 2.2 Hz, 1H), 8.40 (s, 1H), 8.22 (dd, J =9.3, 2.2 Hz, 1H), 4.53 (q, J = 7.3 Hz, 2H), 1.43 (t, J = 7.3 Hz, 3H). HPLC (Method 1): R_t = 0.89 min.

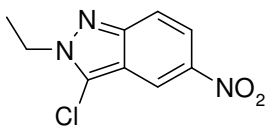


2-Ethyl-5-nitro-2H-indazole. Regioisomeric byproduct 2-ethyl-5-nitro-*2H*-indazole was isolated by preparative HPLC from the remaining mother liquor. Yield: 193 mg (33%). LCMS (ESI^+) calculated for $C_9H_8N_3O_2$ $[M + H]^+$ *m/z* 192.0773, found 192.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.87 (d, J = 2.2 Hz, 1H), 8.82 (s, 1H), 8.01 (dd, J = 9.4, 2.3 Hz, 1H), 7.78 (d, J = 9.4 Hz, 1H), 4.54 (q, J = 7.3 Hz, 2H), 1.54 (t, J = 7.3 Hz, 3H).



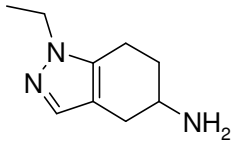
*3-Chloro-1-ethyl-5-nitro-1H-indazole (**12b**)*. Prepared according to general procedure A using nitro indazole **11b** and ethyl iodide. Ratio of **12b** vs. regioisomeric 3-chloro-2-ethyl-5-nitro-*2H*-indazole (HPLC analysis, method 11): 87:13.

12b. Yield: 5.68 g (83%). LCMS (ESI^+) calculated for $C_9H_8ClN_3O_2$ $[M + H]^+$ *m/z* 226.0383, found 226.1.^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.60 (dd, J = 2.2, 0.5 Hz), 8.31 (dd, J = 9.3, 2.2 Hz, 1H), 8.00 (dd, J = 9.3, 0.5 Hz, 1H), 4.51 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H). HPLC (Method 1): R_t = 0.95 min.



3-Chloro-2-ethyl-5-nitro-2H-indazole. Yield: 0.78 g (11%). LCMS (ESI^+) calculated for $C_9H_8ClN_3O_2$ $[M + H]^+$ *m/z* 226.0383, found 226.1.^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.65 (dd, J = 2.3, 0.6 Hz, 1H), 8.07 (dd, J = 9.5, 2.2 Hz, 1H), 7.85 (dd, J = 9.5, 0.6 Hz, 1H), 4.55 (q, J = 7.3 Hz, 2H), 1.51 (t, J = 7.3 Hz, 3H). HPLC (Method 1): R_t = 0.87 min.

General procedure B: preparation of intermediates 13a-h. To a solution of the respective nitro/amino indazole **12a-h** (1.0 equiv) in MeOH was added Nishimura's catalyst.[41] The mixture was hydrogenated (4 bar hydrogen atmosphere) for 6-53h at RT, filtered and concentrated under reduced pressure. The crude product was purified by preparative reverse-phase HPLC.

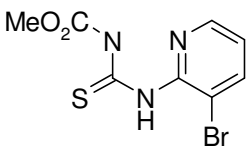


*1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-ylamine (**13a**)*. Prepared according to general procedure B from nitro indazole **12b** (reaction time 11h). To achieve complete dehalogenation the catalyst was switched to palladium on charcoal (additional reaction time 1h at 4 bar hydrogen atmosphere and RT).Yield: 2.85 g (69%). LCMS (ESI^+) calculated for $C_9H_{15}N_3$ $[M + H]^+$ *m/z* 166.1344, found 166.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.08 (s, 1H), 3.93 (q, J = 7.3 Hz, 2H), 2.90-2.98 (m, 1H), 2.50-2.71 (m, 3H), 2.05-2.12 (m, 1H), 1.82-1.90 (m, 1H),1.54 (br s, 2H), 1.44-1.55 (m, 1H), 1.25 (t, J = 7.3 Hz, 3H). Note: NH_2 protons not visible. HPLC (Method 4): R_t = 0.64 min.

Preparative chiral separation: Racemic amine **13a** (27 g, 163 mmol) was submitted to preparative chiral SFC separation (Thar SFC-80, Chiralpak AD-H, 25x 3 cm, 5 µm, mobile phase: eluent A: supercritical CO_2, eluent B: isopropanol containing 0.1% conc aq ammonia, gradient A:B 75:25, flow rate 65 g/min, wavelength 220 nm, system back pressure 100 bar). ***ent1*-13a**: R_t = 2.19 min. ***ent2*-13a**: R_t = 2.84 min.

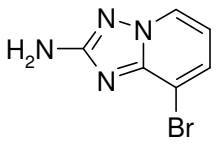
***ent1*-13a**: Yield: 9.21 g (34%). Enantiomeric purity (method 13): 98.7% ee.

***ent2*-13a**: Yield: 8.37 g (31%). Enantiomeric purity (method 13): 97.8% ee.



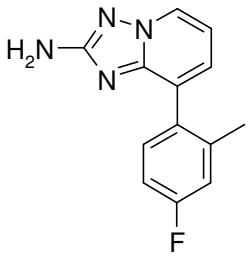
34a

*1-(3-Bromo-pyridin-2-yl)-3-carboethoxy-thiourea (**34a**)*. Ethyl isocyanatoformate (52.5 g, 397 mmol) is added dropwise at 5°C to a solution of 2-amino-3-bromopyridine (**33a**) (66 g, 378 mmol) in DCM (660 mL). After stirring for 16h at RT the reaction mixture is concentrated under reduced pressure to give crude product, which is washed with PE and dried. Yield: 105 g (87%). LCMS (ESI^+) calculated for $C_9H_{10}BrN_3O_2S$ $[M + H]^+$ *m/z* 303.9755, found 304.0. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 11.43 (br s, 2H), 8.49 (dd, J = 4.6, 1.5 Hz, 1H), 8.17 (dd, J = 7.9, 1.5 Hz, 1H), 7.33 (dd, J =7.9, 4.7 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1Hz, 3H). TLC (silica gel, PE/EE 3:1): R_f = 0.4.



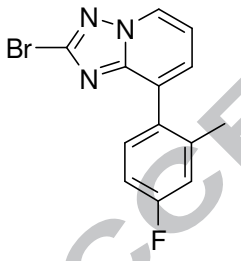
35a

*8-Bromo-[1,2,4]triazolo[1,5-a]pyridine-2-ylamine (**35a**)*. To a suspension of DIPEA (128.2 g, 984 mmol) and hydroxylamine hydrochloride (115.1 g, 1.64 mol) in a mixture of ethanol/methanol (400 mL/400 mL) is added 1-(3-bromo-pyridin-2-yl)-3-carboethoxy-thiourea (**34a**) (105.0 g, 328 mmol). After stirring for 2h at RT, the reaction mixture is heated under reflux for 18h. After cooling to RT the precipitate is collected, washed with water and EE and dried to give the product (**35a**). Yield: 55 g (75%). LCMS (ESI^+) calculated for $C_6H_5BrN_4$ $[M + H]^+$ *m/z* 212.9776, found 213.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.58 (dd, J = 6.6, 0.7 Hz, 1H), 7.73 (dd, J = 7.6, 0.7 Hz, 1H), 6.81 (dd, J = 7.5, 6.7 Hz, 1H), 6.24 (br s, 2H). TLC (silica gel, DCM/MeOH 10:1): R_f = 0.5.



36b

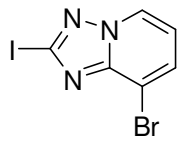
*8-(4-Fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-ylamine (**36b**)*. Prepared by a procedure similar to that described for the synthesis of **36a** starting from 4-fluoro-2-methyl-phenyl boronic acid (27.74 g, 178 mmol) and 8-bromo-[1,2,4]triazolo[1,5-a]pyridine-2-ylamine (**35a**) (20 g, 89 mmol). Yield: 17 g (75%). LCMS (ESI^+) calculated for $C_{13}H_{11}FN_4$ $[M + H]^+$ *m/z* 243.1046, found 243.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.56 (dd, J = 6.7, 1.0 Hz, 1H), 7.31-7.36 (m, 1H), 7.30 (dd, J = 7.3, 1.0 Hz, 1H), 7.17 (m, 1H), 7.09 (m, 1H), 6.94 (dd, J = 7.3, 6.7 Hz, 1H), 6.00 (s, 2H), 2.17 (s, 3H). TLC (silica gel, PE/ethyl acetate 4:1): R_f = 0.5. HPLC (method 3) R_t = 0.43 min.



37b

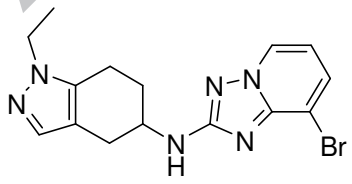
*2-Bromo-8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine (**37b**)*. To a mixture of 8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-ylamine (**36b**) (15 g, 62 mmol) in hydrobromic acid (47% in water, 70.8 mL, 62 mmol) at 0°C was added an aqueous solution of sodium nitrite (10.68 g in 150 mL water, 155 mmol). After stirring for 2h copper(I) bromide

(8.88 g, 62 mmol) was added. After stirring for 4h at 0°C the reaction mixture was diluted with ethyl acetate (50 mL) and water (20 mL). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude material which was purified by MPLC (silica gel, PE/ethyl acetate 9:1) to obtain the product (**37b**). Yield: 10.0 g (53%). LCMS (ESI^+) calculated for $C_{13}H_9BrFN_3$ $[M + H]^+$ *m/z* 306.0042, found 306.0. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.98 (dd, J = 6.9, 0.8 Hz, 1H), 7.65 (dd, J = 7.2, 0.8 Hz, 1H), 7.39 (m, 1H), 7.34 (dd, J = 7.2, 6.9 Hz, 1H), 7.24 (m, 1H), 7.15 (m, 1H), 2.16 (s, 3H). TLC (silica gel, PE/ethyl acetate 1:1): R_f = 0.6.



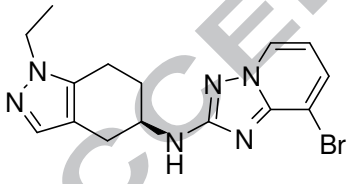
38a

*8-Bromo-2-iodo-[1,2,4]triazolo[1,5-a]pyridine (**38a**)*. Prepared according to literature procedure[42] starting from 8-bromo-[1,2,4]triazolo[1,5-a]pyridine-2-ylamine (**35a**) (5.0 g, 23.47 mmol). Yield: 4.35 g (57%). LCMS (ESI^+) calculated for $C_6H_3BrIN_3$ $[M + H]^+$ *m/z* 323.8633, found 323.9. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.96 (dd, J = 6.8, 0.8 Hz, 1H), 8.01 (dd, J = 7.6, 0.8 Hz, 1H), 7.12 (dd, J = 7.5, 6.9 Hz, 1H). HPLC (method 5): Rt = 0.52 min.



39a

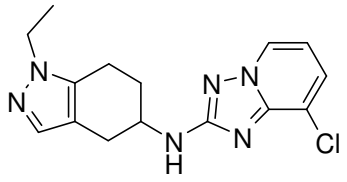
*(8-Bromo-[1,2,4]triazolo[1,5-a]pyridine-2-yl)-(1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**39a**)*. A mixture of 8-bromo-2-iodo-[1,2,4]triazolo[1,5-a]pyridine (**38a**) (200 mg, 617 µmol), 1-ethyl-4,5,6,7-tetrahydro-*1H*-indazol-5-ylamine (**13a**) (245 mg, 1.48 mmol) and cesium fluoride (131 mg, 864 µmol) in DMSO (2.5 mL) was heated at 130-160°C for 10h with microwave irradiation. After cooling to RT the precipitates were filtered off and discarded. The filtrate was taken up in ethyl acetate and water and was extracted 3x with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative reversed-phase HPLC to give the product (**39a**). Yield: 86 mg, TFA salt (29%). LCMS (ESI^+) calculated for $C_{15}H_{17}BrN_6$ $[M + H]^+$ *m/z* 361.0776, found 361.1. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.64 (dd, J =6.6, 0.8 Hz, 1H), 7.75 (dd, J = 7.7, 0.8 Hz, 1H), 7.18 (s, 1H), 6.94 (very br s, 1H), 6.81 (dd, J = 7.7, 6.6 Hz, 1H), 3.98 (q, J = 7.2 Hz, 2H), 3.81-3.90 (m, 1H), 2.76-2.91 m, 2H), 2.61-2.72 (m, 1H), 2.41-2.51 (m, 1H, partially obscured by DMSO signal), 2.10-2.18 (m, 1H), 1.75-1.87 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H). HPLC (Method 6): R_t = 0.91 min.



ent1-**39a**

*(R)-(8-Bromo-[1,2,4]triazolo[1,5-a]pyridine-2-yl)-(1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**ent1-39a**)*. Prepared in analogy to the preparation of racemic **39a** starting from chiral ***ent1*-13a** and **38a**. Yield: 550 mg (46%). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.64 (dd, J =6.6, 0.8 Hz, 1H), 7.75 (dd, J = 7.7, 0.8 Hz, 1H), 7.18 (s, 1H), 6.94 (very br s, 1H), 6.81 (dd, J = 7.7, 6.6

Hz, 1H), 3.98 (q, *J* = 7.2 Hz, 2H), 3.81-3.90 (m, 1H), 2.76-2.91 m, 2H), 2.61-2.72 (m, 1H), 2.41-2.51 (m, 1H, partially obscured by DMSO signal), 2.10-2.18 (m, 1H), 1.75-1.87 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H). HPLC (Method 4): R_t = 0.91 min.



39b

*(8-Chloro-[1,2,4]triazolo[1,5-a]pyridine-2-yl)-(1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**39b**)*. A mixture of 1-ethyl-4,5,6,7-tetrahydro-*1H*-indazol-5-ylamine (**13a**) (1.57 g, 9.48 mmol), 8-chloro-2-iodo-[1,2,4]triazolo[1,5-a]pyridine (**38b**) (2.65 g, 9.48 mmol), dichloro[1,3-bis(2,6-di-3-pentylphenyl)imidazole-2-ylidene](3-chloropyridyl)palladium(II) (280.0 mg, 325.0 µmol) and sodium *tert*-butoxide (3.65 g, 37.93 mmol) in 1,4-dioxane (40 mL) was stirred at 100°C under argon atmosphere for 3 h. After cooling the reaction mixture was poured into ice water and extracted 3x with ethyl acetate. The combined organic phases were dried over sodium sulphate and concentrated under reduced pressure. The remainder was triturated with diethyl ether to give the product (**39b**). Yield: 1.55 g (51%). LCMS (ESI^+) calculated for $C_{15}H_{17}ClN_6$ $[M + H]^+$ *m/z* 317.1281, found 317.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.61 (dd, *J* = 6.7, 0.8 Hz, 1H), 7.61 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.14 (s, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.87 (dd, *J* = 7.7, 6.7 Hz, 1H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.80-3.92 (m, 1H), 2.75-2.91 (m, 2H), 2.60-2.73 (m, 1H), 2.41-2.51 (m, 1H), 2.10-2.19 (m, 1H), 1.75-1.87 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H). HPLC (Method 1): R_t = 0.85 min.

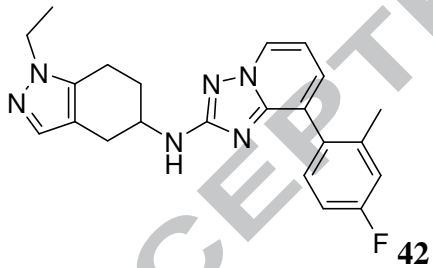
General procedure C-1: preparation of final compounds 42-45, 47, 48, 50, 51, 53-55: To a mixture of 2-halo-triazolopyridine **37a-c** (1 equiv), amine **13a-g**, **21a**, **24** or **28** (2 equiv) and sodium *tert*-butoxide (4 equiv) in degassed 1,4-dioxane (0.2 M) under Argon atmosphere was added Johnphos (0.1 equiv) and tris-(dibenzylidene acetone)dipalladium(0) (0.1 equiv). The reaction mixture was degassed, put again under argon atmosphere and stirred for 4-16 h at 80°C. After cooling to RT the reaction mixture was filtered and purified by preparative reverse-phase HPLC to furnish the desired products.

General procedure C-2: preparation of final compounds 40, *(R)*-42, 46, 49 and 52: A mixture of 2-halo triazolopyridine **38b or 37c** (1 equiv), amine ***ent1*-13a**, **13f**, **17**, **21b** or **32** (1 equiv) and cesium fluoride (5 equiv) in DMSO (0.1-0.3M) was heated at 130-160°C for 10h with microwave irradiation. After cooling to RT the precipitates were filtered off and discarded. The filtrate was taken up in ethyl acetate and water and was extracted 3x with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative reversed-phase HPLC to give the desired products.

General procedure D-1: preparation of final compounds 56-63, 65, 68-69: To a mixture of chloro triazolopyridine **39b** (1 equiv), the respective aryl boronic acid (2 equiv) and K_3PO_4 (2 equiv) in THF/water mixture (0.1 M, *v*/*v* 10:1) was added chloro-(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)-[2-(2'amino-1,1'-biphenyl)]palladium(II) (0.1 equiv) under argon atmosphere. The reaction mixture was degassed, put under argon atmosphere again and

heated at 120°C for 16h. After cooling to RT the mixture was filtered and purified by preparative reverse-phase HPLC to give the products.

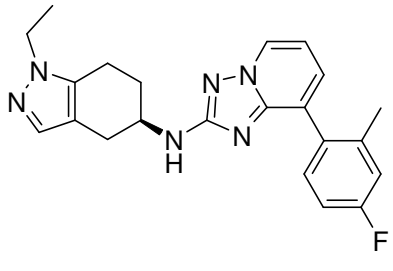
General procedure D-2: preparation of final compounds *ent1*-61, *ent2*-61, 64, 66 and 70-73: To a mixture of bromo triazolopyridine **39a** (1 equiv), the respective (hetero)aryl boronic acid or ester (1.1 equiv) in 1,4-dioxane/methanol mixture (0.05 M, *v*/*v* 2:1) were added aqueous sodium carbonate solution (2 M, 4 equiv) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (0.03 equiv) under argon atmosphere. The reaction mixture was heated at 90°C for 16h. After cooling to RT the mixture was filtered and purified by preparative reverse-phase HPLC to give the products.



42

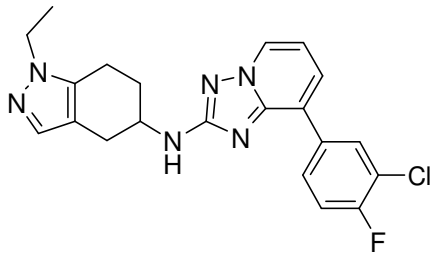
*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**42**)*. Prepared according to general procedure C-1 using triazolopyridine **37b** and amine **13a**. Yield: 35 mg (50%). LCMS (ESI^+) calculated for $C_{22}H_{23}FN_6$ $[M + H]^+$ *m/z* 391.2046, found 391.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.63 (dd, J = 6.7, 1.1 Hz, 1H), 7.31-7.36 (m, 2H), 7.17 (m, 1H), 7.12 (s, 1H), 7.09 (m, 1H), 6.95 (dd, J = 7.3, 6.7 Hz, 1H), 6.67 (d, J

= 7.5 Hz, 1H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.75-3.86 (m, 1H), 2.73-2.88 (m, 2H), 2.57-2.68 (m, 1H), 2.38-2.46 (m, 1H), 2.18 (s, 3H), 2.08-2.17 (m, 1H), 1.70-1.82 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H). HPLC (Method 1): R_t = 1.01 min. Chemical purity > 95%.



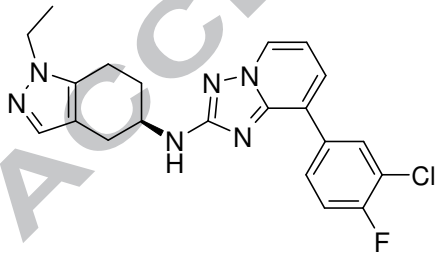
***(R)*-42**

*(R)-(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**(R)-42**)*. Prepared according to general procedure C-2 using triazolopyridine **37b** and chiral amine ***ent1*-13a**. Yield: 508 mg (80%). HRMS (ESI^+) calculated for $C_{22}H_{23}FN_6$ $[M+H]^+$ *m/z* 391.2046, found 391.2050. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.63 (dd, *J* = 6.7, 1.1 Hz, 1H), 7.31-7.36 (m, 2H), 7.17 (m, 1H), 7.12 (s, 1H), 7.09 (m, 1H), 6.95 (dd, *J* = 7.3, 6.7 Hz, 1H), 6.67 (d, *J* = 7.5 Hz, 1H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.75-3.86 (m, 1H), 2.73-2.88 (m, 2H), 2.57-2.68 (m, 1H), 2.38-2.46 (m, 1H), 2.18 (s, 3H), 2.08-2.17 (m, 1H), 1.70-1.82 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 165.4, 162.0 (d, *J* = 240 Hz), 149.2, 139.4 (d, *J* = 8 Hz), 136.7, 135.6, 132.4 (d, *J* = 3 Hz), 132.1 (d, *J* = 9 Hz), 129.7, 127.3, 125.0, 116.6 (d, *J* = 21 Hz), 113.9, 112.5 (d, *J* = 21 Hz), 111.4, 48.8, 43.2, 28.6, 27.2, 20.1, 19.1, 15.4. HPLC (Method 5): R_t = 0.56 min. Enantiomeric purity (method 15): 97.0% ee. Specific optical rotation: $[\alpha]^{20}_D$ = +5.1° (*c* 0.396, MeOH). Chemical purity > 95%.



61

*[8-(3-Chloro-4-fluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**61**)*. Prepared according to general procedure D-1 using halo triazolopyridine **39b** and 3-chloro-4-fluoro-phenylboronic acid. Yield: 16 mg (38%). LCMS (ESI^+) calculated for $C_{21}H_{20}ClFN_6$ $[M + H]^+$ *m/z* 411.1500, found 411.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.65 (dd, J = 6.6, 1.0 Hz, 1H), 8.48 (dd, J = 7.4, 2.3 Hz, 1H), 8.14 (m, 1H), 7.82 (dd, J = 7.5, 1.0 Hz, 1H), 7.55 (m, 1H), 7.15 (s, 1H), 6.99 (dd, J = 7.5, 6.6 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 3.81-3.91 (m, 1H), 2.85-2.93 (m, 1H), 2.76-2.85 (m , 1H), 2.60-2.71 (m, 1H), 2.44-2.52 (m, 1H, partially obscured by DMSO signal), 2.14-2.23 (m, 1H), 1.75-1.86 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H). HPLC (Method 8): R_t = 0.94 min. Chemical purity 95%.



***ent1*-61**

*(R)-[8-(3-Chloro-4-fluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**ent1-61**)*. Prepared according to general procedure D-2

using chiral halo triazolopyridine ***ent1*-39a** and 3-chloro-4-fluoro-phenylboronic acid. Yield: 232 mg (57%). HRMS (ESI^+) calculated for $C_{21}H_{20}ClFN_6$ $[M+H]^+$ *m/z* 411.1500, found 411.1500. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.65 (dd, J = 6.6, 1.0 Hz, 1H), 8.48 (dd, J = 7.4, 2.3 Hz, 1H), 8.14 (m, 1H), 7.82 (dd, J = 7.5, 1.0 Hz, 1H), 7.55 (m, 1H), 7.15 (s, 1H), 6.99 (dd, J = 7.5, 6.6 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 3.81-3.91 (m, 1H), 2.85-2.93 (m, 1H), 2.76-2.85 (m , 1H), 2.60-2.71 (m, 1H), 2.44-2.52 (m, 1H, partially obscured by DMSO signal), 2.14-2.23 (m, 1H), 1.75-1.86 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 165.7, 156.6 (d, J = 240 Hz), 148.9, 136.3, 135.8, 133.2 (d, J = 3 Hz), 130.3, 128.8 (d, J = 7 Hz), 127.6, 127.3, 121.7, 119.6 (d, J = 18 Hz), 117.0 (d, J = 21 Hz), 113.8, 111.5, 49.1, 43.2, 28.7, 27.2, 19.2, 15.4. HPLC (Method 4): R_t = 1.22 min. Enantiomeric purity (method 14): 97.4% ee. Specific optical rotation: $[\alpha]^{20}_D$ = +6.5° (*c* 0.4, MeOH). Chemical purity > 95%.

6. Achnowledgements

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8. **Supporting information**

Discovery of tetrahydroindazoles as a novel class of potent and in vivo efficacious gamma secretase modulators

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Assay method description

Microsomal stability:

The metabolic degradation of the test compound is assayed at 37°C with rat or human pooled liver microsomes. The final incubation volume of 100 µl per time point contains TRIS buffer pH 7.6 at RT (0.1 M), magnesium chloride (5 mM), microsomal protein (1 mg/ml) and the test

compound at a final concentration of 1 µM. Following a short pre-incubation period at 37°C, the reactions were initiated by addition of beta-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH, 1 mM) and terminated by transferring an aliquot into solvent after different time points. Additionally, the NADPH-independent degradation was monitored in incubations without NADPH, terminated at the last time point. The [%] remaining test compound after NADPH independent incubation is reflected by the parameter c (control). The quenched incubations are pelleted by centrifugation (10000 g, 5 min). An aliquot of the supernatant is assayed by LC-MS/MS for the amount of parent compound. The half-life is determined by the slope of the semi-logarithmic plot of the concentration-time profile. The intrinsic clearance is calculated by considering the amount of protein in the incubation: CL_INTRINSIC [µl/min/mg protein] = (Ln 2 / (half-life [min] * protein content [mg/ml])) * 1000.

CYP inhibition:

The inhibition of cytochrome P450 iso-enzymes is assayed at 37°C with human pooled liver microsomes. The final incubation volume contains TRIS buffer (0.1 M), MgCl2 (5 mM), human liver microsomes (0.1 mg/ml), the CYP substrates (CYP1A2 - Phenacetin 10 µm; CYP2D6 – Dextromethorphan 7 µM; CYP2C9 - Diclofenac 4 µM; CYP2C19 - (S)-Mephenytoin 30 µM; CYP3A4 - Testosterone 60 µM) and the test compound at five different concentrations. Following a short pre-incubation period, reactions are started by adding the cofactor NADPH (1mM) and stopped by cooling the incubation down to 8°C and subsequent addition of one volume of acetonitrile. As internal standard the stable isotope of the formed metabolite is added after quenching of incubations. Peak area analyte and internal standard is determined by LC-

MS/MS. The resulting peak area ratio of analyte to internal standard in these incubations is compared to a control activity containing no test compound.

Plasma protein binding:

Equilibrium dialysis technique is used to determine the approximate in vitro fractional binding of test compounds to rat plasma proteins. Incubation: Teflon dialysis cells or RED-devices are used. Each cell consists of a donor and an acceptor chamber, separated by an ultrathin semipermeable membrane (cutoff 5 - 10 kDa, high permeability). Rat EDTA plasma is spiked with test compound, 1 µM final concentration and then transferred into the donor chamber, while dialysis buffer (PBS containing Dextran, pH 7.4) is dispensed into the acceptor chamber. Incubation was carried out for 5 hours at 37°C. After the dialysis period aliquots of both dialysates are analyzed using HPLC-MS/MS.

MDCK permeability and efflux:

The assay provides information on the potential of a compound to pass the blood brain barrier. Permeability measurements across polarized, confluent MDCK-MDR1 cell monolayers (MDCK cells overexpression human MDR1) grown on permeable filter supports are used as the in vitro absorption model. Apparent permeability coefficients of the compounds across the MDCK-MDR1 cell monolayers are measured (pH 7.4, 37°C) in apical-to-basal (AB) and basal-to-apical (BA) transport direction using a1 µM initial donor compartment concentration. AB permeability represents drug absorption from the blood into the brain and BA permeability drug efflux from the brain back into the blood via both passive permeability as well as active transport

mechanisms mediated by efflux and uptake transporters that are expressed on the MDCK-MDR1 cells.

hERG Assay:

The assay was conducted as described by Rast *et al.* (*Rast G and Guth BD, Solubility assessment and on-line exposure confirmation in a patch-clamp assay for hERG (human ether-a-go-go-related gene) potassium channel inhibition; J Pharmacol Toxicol Methods. 2014 Sep-Oct;70(2):182-7*) http://www.ncbi.nlm.nih.gov/pubmed/25117629

Analytical HPLC-Methods

The following eluents were used: water containing 0.1% NH_3 (eluent A), acetonitrile (eluent B) and water containing 0.1% trifluoro acetic acid (eluent C). The mobile phase "water 0.1% TFA" is prepared by adding 1 mL of a commercially available TFA solution to 999 mL water. Analogously, the mobile phase "water 0.1% NH_3" is prepared by adding 4 mL of a commercially available concentrated ammonium hydroxide solution (25 wt%) to 996 mL water.

Method 1: Agilent 1200 with DA- and MS-detector, Waters Xbridge C18, 3.0 x 30 mm, 2.5 µm, 60°C, gradient 0.00 – 0.20 min 97% eluent A in eluent B (flow 2.2 mL/min), 0.20 – 1.20 min 3% to 100% eluent B (flow 2.2 mL/min), 1.20 – 1.25 min 100% eluent B (flow 2.2 mL/min), 1.25 – 1.40 min 100% eluent B (flow 3.0 mL/min).

Method 2: Agilent 1200 with DA- and MS-detector, Sunfire C18, 3.0 x 30 mm, 2.5 µm, 60°C, gradient 0.00 – 0.20 min 97% eluent C in eluent B (flow 2.2 mL/min), 0.20 – 1.20 min 3% to 100% eluent B (flow 2.2 mL/min), 1.20 – 1.25 min 100% eluent B (flow 2.2 mL/min), 1.25 – 1.40 min 100% eluent B (flow 3.0 mL/min).

Method 3: Waters Acquity with DA- and MS-detector, Waters XBridge BEH C18, 2.1 x 30 mm, 1.7 µm, 60°C, gradient 0.00 – 0.20 min 95% eluent A in eluent B (flow 1.3 mL/min), 0.02 – 1.00 min 5% to 100% eluent B (flow 1.3 mL/min), 1.00 – 1.10 min 100% eluent B (flow 1.3 mL/min).

Method 4: Waters Alliance with DA- and MS-detector, Waters XBridge C18, 4.6 x 30 mm, 3.5 µm, 60°C, gradient 0.00 – 0.20 min 97% eluent A in eluent B (flow 5.0 mL/min), 0.20 – 1.60 min 3% to 100% eluent B (flow 5.0 mL/min), 1.60 – 1.70 min 100% eluent B (flow 5.0 mL/min).

Method 5: Waters Acquity with DA- and MS-detector, Sunfire C18, 2.1 x 30 mm, 2.5 µm, 60°C, gradient 0.00 – 0.02 min 99% eluent C in eluent B (flow 1.3 mL/min), 0.02 – 1.00 min 1% to 100% eluent B (flow 1.3 mL/min), 1.00 – 1.10 min 100% eluent B (flow 1.3 mL/min), 1.10 – 1.15 min 99% eluent C in eluent B (flow 1.3 mL/min), 1.15 – 2.00 min 99% eluent C in eluent B (flow 1.3 mL/min).

Method 6: Waters Acquity with DA- and MS-detector, Sunfire C18, 2.1 x 30 mm, 2.5 µm, 60°C, gradient 0.00 – 0.02 min 99% eluent C in eluent B (flow 1.5 mL/min), 0.02 – 1.00 min 1% to 100% eluent B (flow 1.5 mL/min), 1.00 – 1.10 min 100% eluent B (flow 1.5 mL/min).

Method 7: Waters Acquity with DA- and MS-detector, Waters XBridge BEH C18, 2.1 x 30 mm, 1.7 µm, 60°C, gradient 0.00 – 0.02 min 99% eluent C in eluent B (flow 1.6 mL/min), 0.02 – 1.00 min 1% to 100% eluent B (flow 1.6 mL/min), 1.00 – 1.10 min 100% eluent B (flow 1.6 mL/min).

Method 8: Waters Acquity with 3100 MS detector, Waters Xbridge C18, 3.0 x 30 mm, 2.5 µm, 60°C, gradient 0.00 – 1.30 min 97% eluent A in eluent B (flow 1.5 mL/min), 1.30 – 1.50 min 1% eluent A in eluent B (flow 1.5 mL/min), 1.50 – 1.60 min 0.1% to 95% eluent A in eluent B (flow 1.5 mL/min).

Method 9: Agilent 1100 with DA- and MS-detector, Sunfire C18, 3.0 x 30 mm, 2.5 µm, 60°C, gradient 0.00 – 1.20 min 98% eluent C in eluent B (flow 2.0 mL/min), 1.20 – 1.40 min 2% to 100% eluent B (flow 2.0 mL/min).

Method 10: Agilent 1100 with DAD, CTC Autosampler and Waters MS-Detector, Waters Sunfire C18, 3.0 x 30 mm, 3.5 µm, 60°C, gradient 0.00 – 0.30 min 98% eluent C in eluent B (flow 2.0 mL/min), 0.30 – 1.50 min 2% to 100% eluent B (flow 2.0 mL/min), 1.50 – 1.60 min 100% eluent B (flow (2.0 mL/min).

Method 11: Waters Acquity with DA- and MS-Detector, Waters Sunfire C18, 3.0 x 30 mm, 2.5 µm, 60°C, gradient 0.00 – 1.30 min 95% eluent C in eluent B (flow 1.5 mL/min), 1.30 – 1.50 min 5% to 100% eluent B (flow 1.5 mL/min).

Method 12: Waters Acquity with DA- and MS-Detector , Waters XBridge C18, 3.0 x 30mm, 2.5µm, 60°C, gradient 0.00 – 1.20 min 95% eluent A in eluent B (flow 1.5 mL/min), 1.20 – 1.40

min 5% to 100% eluent B (flow 1.5 mL/min), 1.40 - 1.45 min 98% A in eluent B (flow 1.5 mL/min).

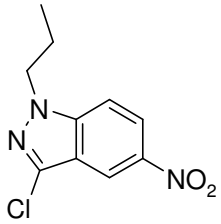
Method 13: Agilent 1260 SFC with DAD and ELSD, Daicel Chiralpak® AY-H, 4.6 x 250 mm, 5 µm, 40°C, mobile phase: eluent A: supercritical CO_2, eluent B: ethanol containing 20 mM ammonia, 0.00-10.00 min, gradient A:B 85:15, flow rate 4 mL/min, system back pressure 2175 psi.

Method 14: Agilent 1260 SFC with DAD and ELSD, Daicel Chiralpak® IF, 4.6 x 250 mm, 5 µm, 40°C, mobile phase: eluent A: supercritical CO_2, eluent B: ethanol containing 20 mM ammonia, 0.00-10.00 min, gradient A:B 60:40, flow rate 4 mL/min, system back pressure 2175 psi.

Method 15: Agilent 1260 SFC with DA- and MS-Detector, Daicel Chiralpak® IA, 4.6 x 250 mm, 5 µm, 40°C, mobile phase: eluent A: supercritical CO_2, eluent B: ethanol containing 20 mM ammonia, 0.00-10.00 min, gradient A:B 75:25, flow rate 4 mL/min, system back pressure 2175 psi.

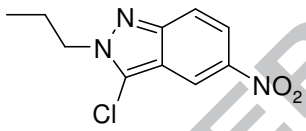
Synthesis procedures

General procedure A: preparation of intermediates 12a-c and 12e-g. A mixture of the respective nitro indazole **11a-d** (1.0 equiv), alkyl halide (1.0 equiv) and K_2CO_3 (2 equiv) in DMF was stirred for 3h at 60°C. After cooling to RT the reaction mixture was poured into water and extracted 3x with ethyl acetate. The combined organic phases were dried and concentrated under reduced pressure. The crude residue was purified by preparative reverse-phase HPLC.

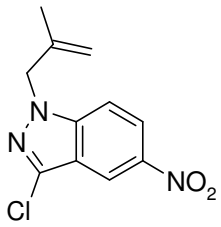


*3-Chloro-1-propyl-5-nitro-1H-indazole (**12c**)*. Prepared according to general procedure A using nitro indazole **11b** and *n*-propyl iodide. Ratio of **12c** *vs*. regioisomeric 3-chloro-2-*n*-propyl-5-nitro-*2H*-indazole (HPLC analysis, method 2): 88:12.

12c. Yield: 960 mg (79%). LCMS (ESI^+) calculated for $C_{10}H_{10}ClN_3O_2$ $[M + H]^+$ *m/z* 240.0540, found 240.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.60 (d, J = 2.2 Hz, 1H), 8.31 (dd, J = 9.4, 2.2 Hz, 1H), 8.01 (d, J = 9.4 Hz, 1H), 4.45 (t, J = 6.9 Hz, 2H), 1.86 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H). HPLC (Method 2): R_t = 1.15 min.

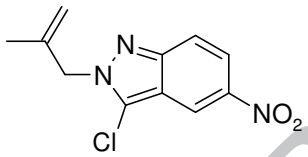


3-Chloro-2-n-propyl-5-nitro-2H-indazole. This minor regioisomer was not isolated. HPLC (Method 2): R_t = 1.10 min.

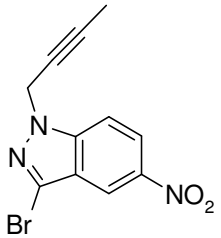


*3-Chloro-1-(2-methyl-allyl)-5-nitro-1H-indazole (**12e**)*. Prepared according to general procedure A using nitro indazole **11b** and 3-bromo-2-methyl propene. Ratio of **12e** *vs*. regioisomeric 3-chloro-2-(2-methyl-allyl)-5-nitro-*2H*-indazole (HPLC analysis, method 1): 92:8.

12e. Yield: 1.14 g (90%). LCMS (ESI$^+$) calculated for $C_{11}H_{10}ClN_3O_2$ $[M + H]^+$ *m/z* 252.0540, found 252.0. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.61 (d, J = 2.0 Hz, 1H), 8.32 (dd, J = 9.3, 2.0 Hz, 1H), 7.95 (d, J = 9.3 Hz, 1H), 5.10 (s, 2H), 4.93 (s, 1H), 4.71 (s, 1H), 1.63 (s, 3H). HPLC (Method 1): R_t = 1.09 min.

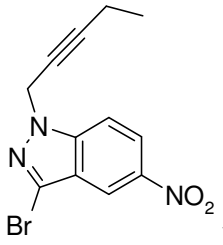


3-Chloro-2-(2-methyl-allyl)-5-nitro-2H-indazole. This minor regioisomer was not isolated. HPLC (Method 1): R_t = 1.04 min.



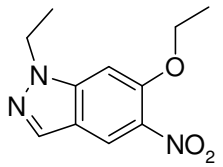
12f

*3-Bromo-1-but-2-ynyl-5-nitro-1H-indazole (**12f**)*. Prepared according to general procedure A using nitro indazole **11c** and 1-bromo-2-butyne. Only one regioisomer was observed. Yield: 1.17 g (96%). LCMS (ESI$^+$) calculated for $C_{11}H_9BrN_3O_2$ $[M + H]^+$ *m/z* 293.9878, found 294.0. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.50 (dd, J = 2.1, 0.4 Hz, 1H), 8.37 (dd, J = 9.3, 2.2 Hz, 1H), 8.02 (dd, J = 9.3, 0.4 Hz, 1H), 5.40 (q, J = 2.4 Hz, 2H), 1.80 (t, J = 2.4 Hz, 3H). HPLC (Method 11): R_t = 0.97 min.



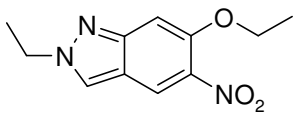
12g

*3-Bromo-1-pent-2-ynyl-5-nitro-1H-indazole (**12g**)*. Prepared according to general procedure A using nitro indazole **11c** and 1-bromo-2-pentyne. Only one regioisomer was observed. Yield: 1.18 g (93%). LCMS (ESI$^+$) calculated for $C_{11}H_9BrN_3O_2$ $[M + H]^+$ *m/z* 308.0035, found 308.0. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.50 (d, J = 2.0 Hz, 1H), 8.37 (dd, J = 9.3, 2.1 Hz, 1H), 8.02 (d, J = 9.3 Hz, 1H), 5.42 (t, J = 2.2 Hz, 2H), 2.15-2.23 (m, 2H), 1.03 (t, J = 7.5 Hz, 3H). HPLC (Method 11): R_t = 1.04 min.



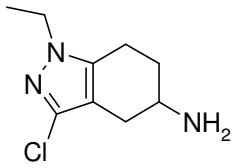
*6-Ethoxy-1-ethyl-5-nitro-1H-indazole (**12h**)*. Prepared according to general procedure A using nitro indazole **11d** and ethyl iodide. Ratio of **12h** *vs*. regioisomeric 6-ethoxy-2-ethyl-5-nitro-*2H*-indazole (HPLC analysis, method 3): 1.7:1.

12h. Yield: 255 mg (56%). LCMS (ESI$^+$) calculated for $C_{11}H_{13}N_3O_3$ $[M + H]^+$ *m/z* 236.1035, found 236.1. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.37 (s, 1H), 8.16 (s, 1H), 7.46 (s, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* =7.2 Hz, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). HPLC (Method 3): R_t = 0.55 min.

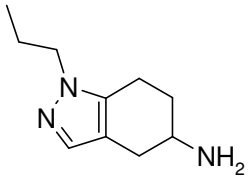


6-Ethoxy-2-ethyl-5-nitro-2H-indazole. Yield: 126 mg (28%). LCMS (ESI$^+$) calculated for $C_{11}H_{13}N_3O_3$ $[M + H]^+$ *m/z* 236.1035, found 236.1. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.57 (s, 1H), 8.36 (s, 1H), 7.24 (s, 1H), 4.45 (q, *J* = 7.3 Hz, 2H), 4.18 (q, *J* = 7.0 Hz, 2H), 1.50 (t, *J* =7.3 Hz, 3H), 1.35 (t, *J* = 7.0 Hz, 3H). HPLC (Method 3): R_t = 0.50 min.

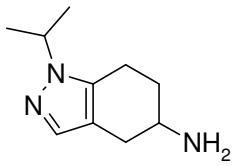
General procedure B: preparation of intermediates 13a-h. To a solution of the respective nitro/amino indazole **12a-h** (1.0 equiv) in MeOH was added Nishimura's catalyst.[42] The mixture was hydrogenated (4 bar hydrogen atmosphere) for 6-53h at RT, filtered and concentrated under reduced pressure. The crude product was purified by preparative reverse-phase HPLC.



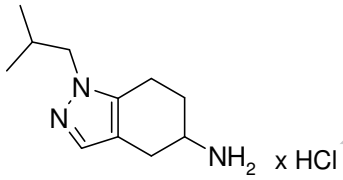
*3-Chloro-1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-ylamine (**13b**)*. Prepared according to general procedure B from nitro indazole **12b** (reaction time 24h). Yield: 140 mg (18%). LCMS (ESI^+) calculated for $C_9H_{14}ClN_3$ $[M + H]^+$ *m/z* 200.0955, found 200.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 3.92 (q, J = 7.2 Hz, 2H), 2.95-3.03 (m, 1H), 2.64-2.74 (m, 1H), 2.50-2.58 (m, 2H), 1.96-2.04 (m, 1H), 1.80-1.88 (m, 1H), 1.45-1.57 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H). Note: NH_2 signals not visible. HPLC (Method 1): R_t = 0.74 min.



*1-Propyl-4,5,6,7-tetrahydro-1H-indazol-5-ylamine (**13c**)*. Prepared according to general procedure B from nitro indazole **12c** (reaction time 7h). Yield: 250 mg (35%). LCMS (ESI^+) calculated for $C_{10}H_{17}N_3$ $[M + H]^+$ *m/z* 180.1501, found 180.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.09 (s, 1H), 3.85 (t, J = 7.2 Hz, 2H), 2.90-2.98 (m, 1H), 2.50-2.70 (m, 3H), 2.05-2.12 (m, 1H), 1.82-1.90 (m, 1H), 1.69 (m, 2H), 1.66 (br s, 2H), 1.44-1.54 (m, 1H), 0.81 (t, J = 7.4 Hz, 3H). HPLC (Method 1): R_t = 0.74 min.

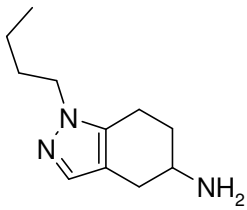


*1-Isopropyl-4,5,6,7-tetrahydro-1H-indazol-5-ylamine (**13d**)*. Prepared according to general procedure B from amino indazole **12d** (reaction time 6h). Yield: 540 mg (56%). LCMS (ESI^+) calculated for $C_{10}H_{17}N_3$ $[M + H]^+$ *m/z* 180.1501, found 180.3. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.10 (s, 1H), 4.33 (sept, J = 6.6 Hz, 1H), 2.90-2.98 (m, 1H), 2.51-2.73 (m, 3H), 2.04-2.12 (m, 1H), 1.82-1.91 (m, 1H), 1.44-1.55 (m, 1H), 1.33 (d, J = 6.6 Hz, 3H), 1.30 (d, J = 6.6 Hz, 3H). Note: NH_2 signals not visible. HPLC (Method 1): R_t = 0.70 min.



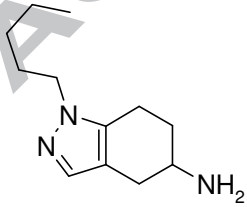
*1-Isobutyl-4,5,6,7-tetrahydro-1H-indazol-5-ylamine (**13e**)*. Prepared according to general procedure B from nitro indazole **12e** (reaction time 4h). However, to achieve complete dehalogenation the catalyst was switched to palladium on charcoal (additional reaction time 16h at 4 bar hydrogen atmosphere and RT). Yield: 1.07 g, HCl salt (quant.). LCMS (ESI^+) calculated for $C_{11}H_{19}N_3$ $[M + H]^+$ *m/z* 194.1657, found 194.3. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.08 (br s, 3H, NH_3^+), 7.22 (s, 1H), 3.73 (d, J = 7.3 Hz, 2H), 3.29-3.40 (m, 1H, partially obscured by water signal), 2.82-2.90 (m, 1H), 2.72-2.80 (m, 1H), 2.56-2.69 (m, 1H), 2.43-2.51 (m, 1H, partially

obscured by DMSO signal), 2.08-2.16 (m, 1H), 2.06 (m, 1H), 1.74-1.86 (m, 1H), 0.833 (d, J = 6.6 Hz, 3H), 0.831 (d, J = 6.6 Hz, 3H). HPLC (Method 1): R_t = 0.77 min.



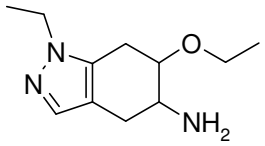
13f

*1-Butyl-4,5,6,7-tetrahydro-1H-indazol-5-ylamine (**13f**)*. Prepared according to general procedure B from nitro indazole **12f** (reaction time 45 min). To achieve complete dehalogenation the catalyst was switched to palladium on charcoal (additional reaction time 1h at 4 bar hydrogen atmosphere and 50°C). Yield: 505 mg, (66%). LCMS (ESI^+) calculated for $C_{11}H_{19}N_3$ $[M + H]^+$ *m/z* 194.1657, found 194.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.09 (s, 1H), 3.89 (t, J = 7.1 Hz, 2H), 2.89-2.98 (m, 1H), 2.57-2.71 (m, 2H), 2.45-2.56 (m, 1H), 2.04-2.13 (m, 1H), 1.82-1.90 (m, 1H), 1.60-1.70 (m, 2H), 1.44-1.55 (m, 1H), 1.18-1.29 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). Note: NH_2 signals not visible. HPLC (Method 4): R_t = 0.76 min.

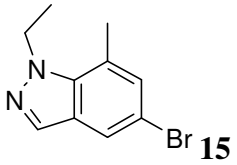


13g

*1-Pentyl-4,5,6,7-tetrahydro-1H-indazol-5-ylamine (**13g**)*. Prepared according to general procedure B from nitro indazole **12g** (reaction time 4h). Yield: 465 mg, (59%). LCMS (ESI^+) calculated for $C_{12}H_{21}N_3$ $[M + H]^+$ *m/z* 208.1814, found 208.0. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.09 (s, 1H), 3.88 (t, J = 7.1 Hz, 2H), 2.89-2.98 (m, 1H), 2.57-2.70 (m, 2H), 2.45-2.56 (m, 1H, mainly obscured by DMSO signal), 2.04-2.13 (m, 1H), 1.81-1.90 (m, 1H), 1.61-1.71 (m, 2H), 1.43-1.55 (m, 1H), 1.15-1.33 (m, 4H), 0.85 (t, J = 7.1 Hz, 3H). Note: NH_2 signals not visible. HPLC (Method 3): R_t = 0.46 min.

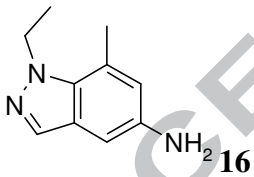


*6-Ethoxy-1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-ylamine (**13h**)*. Prepared according to general procedure B from nitro indazole **12h** (reaction time 24h). Yield: 31 mg (11%). LCMS (ESI^+) calculated for $C_{11}H_{19}N_3O$ $[M + H]^+$ *m/z* 210.1606, found 210.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.01 (s, 1H), 3.95 (q, J = 7.3 Hz, 2H), 3.62-3.67 (m, 1H), 3.45-3.62 (m, 2H), 3.06-3.11 (m, 1H), 2.67-2.79 (m, 2H), 2.48-2.56 (m, 1H, partially obscured by DMSO signal), 2.27-2.35 (m, 1H), 1.44 (broad s, 2H), 1.26 (t, J = 7.3 Hz, 3H), 1.12 (t, J = 7.0 Hz, 3H). HPLC (Method 3): R_t = 0.33 min.



15

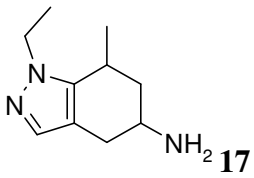
*5-Bromo-1-ethyl-7-methyl-1H-indazole (**15**)*. To a mixture of 5-bromo-7-methyl-1H-indazole **14** (2.4 g, 10.9 mmol) in DMF (25 mL) was added sodium hydride (525.0 mg, 55% in mineral oil, 12.0 mmol) at 0°-5°C. After stirring for 20 min ethyl iodide (874.8 µL, 10.9 mmol) was added. After stirring for 30 min, the reaction mixture was poured into water and extracted 3x with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The remainder was purified by preparative reverse-phase HPLC to give **15**. Yield: 800 mg (31%). LCMS (ESI^+) calculated for $C_{10}H_{11}BrN_2$ $[M + H]^+$ *m/z* 239.01839, found 239.0. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.00 (s, 1H), 7.80 (m, 1H), 7.28 (m, 1H), 4.58 (q, J = 7.2 Hz, 2H), 2.70 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H). HPLC (Method 4) : R_t = 1.23 min.



16

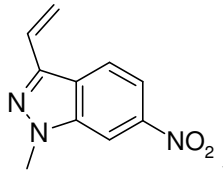
*1-Ethyl-7-methyl-1H-indazol-5-ylamine (**16**)*. To a mixture of bromo indazole **15** (800.0 mg, 3.3 mmol), benzophenone imine (673.7 µL, 4.0 mmol) and sodium *tert*.-butoxide (643.1 mg, 6.7 mmol) in toluene (15 mL) under an atmosphere of argon was added Xantphos (38.7 mg, 67 µmol) and tris(dibenzylidene acetone)palladium(0) (61.3 mg, 67 µmol). The reaction mixture was stirred for 1d at 130°C. After cooling to RT, TFA was added to acidify the reaction mixture.

Stirring was continued for 1h, then water was added and the organic phase was separated. The aqueous phase was subsequently made alkaline and extracted 3x with ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The remainder was purified by preparative reverse-phase HPLC to obtain **16**. Yield: 374 mg, TFA salt (39%). LCMS (ESI^+) calculated for $C_{10}H_{13}N_3$ $[M + H]^+$ *m/z* 176.1188, found 176.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.65 (s, 1H), 6.55 (m, 2H), 4.66 (br s, 2H), 4.46 (q, J = 7.1 Hz, 2H), 2.57 (s, 3H), 1.31 (t, J =7.1 Hz, 3H). Note: ^1H NMR spectrum was obtained from a sample of the free base. HPLC (Method 5) : Retention time = 0.30 min.



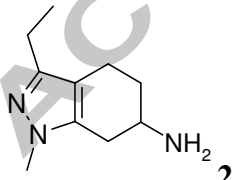
17

*1-Ethyl-7-methyl-4,5,6,7-tetrahydro-1H-indazol-5-ylamine (**17**)*. To a mixture of amino indazole **16** (obtained as TFA salt, 374 mg, 1.3 mmol) in methanol (15 mL) was added PL-HCO_3 MP ion exchanger resin (1.96 mmol/g loading, 150-300 μm particle size) until pH was alkaline. The mixture was filtered and concentrated under reduce pressure to give **16** as free base, which was directly hydrogenated according to general procedure B (reaction time 2d) to give **17**. Yield: 230 mg (94%). LCMS (ESI^+) calculated for $C_{10}H_{17}N_3$ $[M + H]^+$ *m/z* 180.1501, found 180.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.09 (s, 1H), 4.02 (q, J = 7.2 Hz, 1H), 4.01 (q, J = 7.2 Hz, 1H), 2.86-2.97 (m, 1H), 2.75-2.84 (m, 1H), 2.53-2.60 (m, 1H), 1.96-2.04 (m, 2H), 1.15-1.23 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.24 (d, J = 6.6 Hz, 3H). Notes: NH_2 signals not visible. Only the major *cis* diasteromer was interpreted. HPLC (Method 4): R_t = 0.67 min.



19

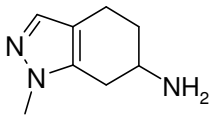
*1-Methyl-6-nitro-3-vinyl-1H-indazole (**19**)*. A mixture of 3-bromo-1-methyl-6-nitro-*1H*-indazole **18** (100.0 mg, 391 µmol), vinylboronic acid pinacol ester (72.9 µL, 430 µmol), sodium carbonate solution (2N in water, 0.39 mL, 781 µmol) and bis(triphenylphosphine)palladium(II) chloride (8.2 mg, 12 µmol) in a mixture of 1,4-dioxane/methanol (4mL/2 mL) was stirred at 90°C under an argon atmosphere for 4h. After cooling to RT the reaction mixture was poured into water. Precipitated product **19** was collected by filtration and dried under reduced pressure. Yield: 64 mg (81%). LCMS (ESI^+) calculated for $C_{10}H_9N_3O_2$ $[M + H]^+$ *m/z* 204.0773, found 204.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.71 (m, 1H), 8.24 (m, 1H), 7.98 (dd, J = 8.9, 2.0 Hz, 1H), 7.06 (dd, J = 18.0, 11.5 Hz, 1H), 6.15 (dd, J = 18.0, 1.0 Hz, 1H), 5.56 (dd, J = 11.5, 1.0 Hz, 1H), 4.18 (s, 3H). HPLC (Method 1): Retention time = 0.97 min.



21a

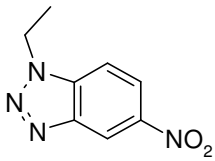
*3-Ethyl-1-methyl-4,5,6,7-tetrahydro-1H-indazol-6-ylamine (**21a**)*. Prepared according to general procedure B from nitro indazole **19** (reaction time 7h at 50-80°C, then 18h at 50°C under 50 bar

hydrogen atmosphere). Yield: 10 mg (38%). LCMS (ESI$^+$) calculated for $C_{10}H_{17}N_3$ [M + H]$^+$ *m/z* 180.1501, found 180.2. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 3.54 (s, 3H), 2.97-3.05 (m, 1H), 2.40 (q, J =7.5 Hz, 2H), 2.33-2.46 (m, 2H), 2.24-2.35 (m, 1H), 2.10-2.19 (m, 1H), 1.73-1.83 (m, 1H), 1.33-1.44 (m, 1H), 1.09 (t, J = 7.5 Hz, 3H). HPLC (Method 1) : R_t = 0.70 min.



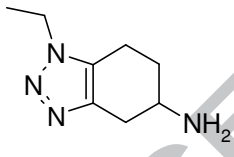
21b

*1-Methyl-4,5,6,7-tetrahydro-1H-indazol-6-ylamine (**21b**)*. To a solution of 1-methyl-*1H*-indazol-6-ylamine **20** (200 mg, 1.4 mmol) in methanol (10 mL) was added conc. aq. HCl (186 µL, 1.6 mmol) and palladium (10% on charcoal, 20 mg). The mixture was hydrogenated at 50 bar for 16h at 50°C. After cooling to RT the reaction mixture was filtered and concentrated under reduced pressure. The remainder was taken up in DMF and was purified by preparative reverse-phase HPLC to give product **21b**. Yield: 59 mg (29%). LCMS (ESI$^+$) calculated for $C_8H_{13}N_3$ [M + H]$^+$ *m/z* 152.1188, found 152.1. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.14 (s, 1H), 3.64 (s, 3H), 2.90-2.99 (m, 1H), 2.38-2.60 (m, 4H, partially obscured by DMSO signal), 1.90-1.98 (m, 1H), 1.56-1.68 (m, 1H). Note: NH_2 signals not visible. HPLC (Method 4): R_t = 0.57 min.



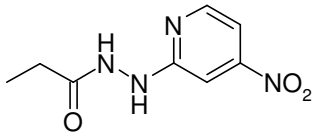
23

*1-Ethyl-5-nitro-1H-benzotriazole (**23**)*. 2-Fluoro-5-nitro-aniline **22** (5.0 g, 32.03 mmol) was dissolved in dry DMSO (50 mL), treated with ethylamine (2M in THF, 56 mL, 112.10 mmol) in a sealed flask and heated at 120°C. After 2 days the reaction mixture was cooled to RT and acetic acid (20 mL) was added followed by addition of $NaNO_2$ (2 M aq solution, 19.2 mL, 38.4 mmol). Stirring was continued for 20 min, then the reaction mixture was acidified to pH=2 with HCl (1M aq solution), water was added and the mixture was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The remainder was purified by preparative MPLC (silica gel, cyclohexane/ethyl acetate, gradient 0-45% ethyl acetate over 40 min) to afford product **23**. Yield: 2.87 g (47%). LCMS (ESI^+) calculated for $C_8H_8N_4O_2$ $[M + H]^+$ *m/z* 193.0726, found 193.0. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 9.03 (m, 1H), 8.40 (dd, J = 9.2, 2.0 Hz, 1H), 8.16 (m, 1H), 4.84 (q, J = 7.4 Hz, 2H), 1.55 (t, J = 7.4 Hz, 3H). HPLC (Method 3): R_t = 0.44 min.



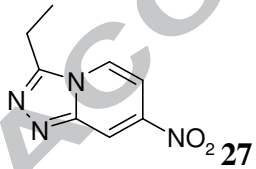
24

*1-Ethyl-4,5,6,7-tetrahydro-1H-benzotriazol-5-ylamine (**24**)*. Prepared according to general procedure B from nitro benzotriazole **23** (reaction time 2d). Yield: 800 mg (66%). LCMS (ESI^+) calculated for $C_8H_{14}N_4$ $[M + H]^+$ *m/z* 167.1297, found 167.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 4.14-4.23 (m, 2H), 3.05-3.13 (m, 1H), 2.77-2.84 (m, 1H), 2.67-2.76 (m, 1H), 2.53-2.63 (m, 1H), 2.25-2.33 (m, 1H), 1.83-1.92 (m, 1H), 1.50-1.62 (m, 1H), 1.35 (t, J = 7.2 Hz, 3H). HPLC (Method 3): R_t = 0.22 min.



26

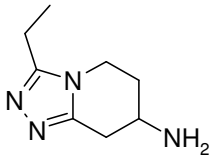
*Propionic acid N'-(4-nitro-pyridin-2-yl)-hydrazide (**26**)*. To a mixture of (4-nitro-pyridin-2-yl)-hydrazine **25** (2.31 g, 8.14 mmol) and DIPEA (5.39 mL, 32.56 mmol) in THF was dropwise added a solution of propionyl chloride (0.78 mL, 8.95 mmol) in THF. After stirring for 15 min at RT, few drops of water were added and the reaction mixture was concentrated under reduced pressure. The remainder was suspended in water and acidified with TFA. The suspension was filtered and purified by preparative HPLC to give product **26**. Yield: 1.7 g (quant.). LCMS (ESI^+) calculated for $C_8H_{10}N_4O_3$ $[M + H]^+$ *m/z* 211.0831, found 211.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 9.87 (s, 1H), 9.05 (br s, 1H), 8.37 (dd, J = 5.4, 0.4 Hz, 1H), 7.34 (dd, J = 5.4, 2.0 Hz, 1H), 7.14 (dd, J = 2.0, 0.4 Hz, 1H), 2.22 (q, J = 7.6 Hz, 2H), 1.07 (t, J = 7.6 Hz, 3H). HPLC (Method 6): R_t = 0.31 min.



27

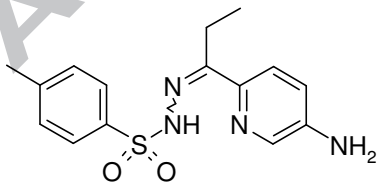
*3-Ethyl-7-nitro-[1,2,4]triazolo[4,3-a]pyridine (**27**)*. To a mixture of **26** (1.70 g, 8.09 mmol) in THF (30 mL) was added Burgess' reagent (5.78 g, 24.26 mmol). After stirring for 3d at 65°C the mixture was concentrated under reduced pressure. The remainder was taken up in a mixture of

MeOH/water, acidified with TFA and purified by preparative reverse-phase HPLC. Yield: 954 mg (61%). LCMS (ESI^+) calculated for $C_8H_8N_4O_2$ $[M + H]^+$ *m/z* 193.0726, found 193.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.78 (dd, J =2.2, 0.8 Hz, 1H), 8.64 (dd, J = 7.6, 0.8 Hz, 1H), 7.63 (dd, J = 7.6, 2.2 Hz, 1H), 3.18 (q, J =7.5 Hz, 2H), 1.40 (t, J = 7.5 Hz, 3H). HPLC (Method 6): R_t = 0.32 min.



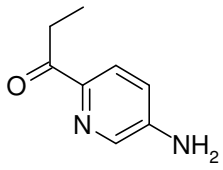
28

*3-Ethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-7-ylamine (**28**)*. Prepared according to general procedure B from nitro triazolopyridine **27** (reaction time 16h). Yield: 185 mg (54%). LCMS (ESI^+) calculated for $C_8H_{14}N_4$ $[M + H]^+$ *m/z* 167.1297, found 167.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 3.89-3.97 (m, 1H), 3.73-3.80 (m, 1H), 3.22-3.28 (m, 1H), 2.87-2.94 (m, 1H), 2.63 (q, J = 7.5 Hz, 1H), 2.49 (q, J = 7.5 Hz, 1H), 1.90-1.99 (m, 1H), 1.69-1.79 (m, 2H), 1.21 (t, J = 7.5 Hz, 3H). HPLC (Method 3): R_t = 0.10 min.



30

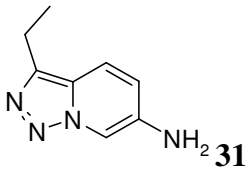
*p-tolylsulfonic acid [1-(5-amino-pyridin-2-yl)-(propylidene]-hydrazide (**30**), E/Z-isomers*.



i) *1-(5-Amino-pyridin-2-yl)-propan-1-one*. To a solution of ethyl magnesium bromide in diethyl ether (3M, 13.8 mL, 41.4 mmol) was added slowly a mixture of 5-aminopyridine-2-carbonitrile **29** (1.0 g, 8.4 mmol) in diethyl ether (192 mL) under argon atmosphere. The mixture was stirred under reflux for 6h, then for 16h at RT. The reaction mixture was poured onto ice (77 g) mixed with conc HCl (15 mL), stirred at RT for 90 min and 16h at 40°C. The reaction mixture was then made alkaline until pH 9 with aq NaOH (4N) and was extracted 3x with diethyl ether. The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified by preparative reverse-phase HPLC to afford the product. Yield: 206 mg (16%). LCMS (ESI^+) calculated for $C_8H_{10}N_2O$ $[M + H]^+$ *m/z* 151.0871, found 151.0. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.95 (d, J = 2.7 Hz, 1H), 7.70 (d, J = 8.6 Hz, 1H), 6.94 (dd, J = 8.6, 2.7 Hz, 1H), 6.20 (br s, 2H), 3.00 (q, J = 7.4 Hz, 2H), 1.04 (t, J = 7.4 Hz, 3H). HPLC (Method 3): R_t = 0.29 min.

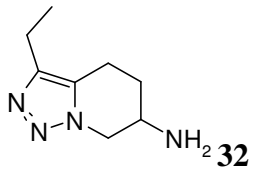
ii) *p-tolylsulfonic acid [1-(5-amino-pyridin-2-yl)-(propylidene]-hydrazide (**30**), E/Z-isomers*. To a mixture of *p*-tolylsulfonohydrazide (272.8 mg, 1.5 mmol) in MeOH (3 mL) was added portionswise 1-(5-amino-pyridin-2-yl)-propan-1-one (200.0 mg, 1.3 mmol) at RT. Another portion of *p*-tolylsulfonohydrazide (173.6 mg, 0.9 mmol) was added and stirring was continued for 6h. The reaction mixture was purified by preparative reverse-phase HPLC to obtain product **30** as separable *E*- and *Z*-isomers. Yield: ***E*-30**: 212 mg (50%). LCMS (ESI^-) calculated for $C_{15}H_{18}N_4O_2S$ $[M - H]^-$ *m/z* 317.1072, found 317.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 10.40 (s, 1H),

7.85 (d, *J* = 2.7 Hz, 1H), 7.77-7.81 (m, 2H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.38-7.42 (m, 2H), 6.88 (dd, *J* = 8.6, 2.7 Hz, 1H), 5.62 (br s, 2H), 2.75 (q, *J* = 7.5 Hz, 2H), 2.37 (s, 3H), 0.93 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 158.4, 145.5, 143.1, 141.4, 136.3, 134.2, 129.4, 127.4, 120.8, 120.1, 21.0, 18.3, 10.4. HPLC (Method 3): R_t = 0.26 min. Yield: **Z-30**: 212 mg (50%). LCMS (ESI^+) calculated for $C_{15}H_{18}N_4O_2S$ $[M + H]^+$ *m/z* 319,1229, found 319.1. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 14.2 (s, 1H), 7.99 (d, *J* = 2.8 Hz, 1H), 7.70-7.73 (m, 2H), 7.42 (d, *J* = 8.9 Hz, 1H), 7.35-7.40 (m, 2H), 7.03 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.10 (br s, 2H), 2.51 (q, *J* = 7.3 Hz, 2H), 2.36 (s, 3H), 0.97 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 147.5, 145.8, 143.1, 139.3, 136.5, 132.9, 129.5, 127.0, 125.0, 120.0, 27.4, 21.0, 11.9. HPLC (Method 3): R_t = 0.53 min.



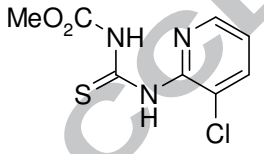
31

*3-Ethyl-[1,2,3]triazolo[1,5-a]pyridine-6-ylamine (**31**)*. Hydrazide **Z-30** (240 mg, 0.75 mmol) was dissolved in morpholine (0.66 mL, 7.54 mmol) and stirred for 4h at 100°C. After cooling to RT the reaction mixture was directly purified by preparative reverse-phase HPLC to obtain product **31**. Yield: 84 mg (69%). LCMS (ESI^+) calculated for $C_8H_{10}N_4$ $[M + H]^+$ *m/z* 163.0984, found 163.0. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.99 (dd, *J* =1.7, 0.7 Hz, 1H), 7.62 (dd, *J* = 9.3, 0.7 Hz, 1H), 6.87 (dd, *J* = 9.4, 1.7 Hz, 1H), 5.36 (br s, 2H), 2.84 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H). HPLC (Method 3): R_t = 0.30 min.



32

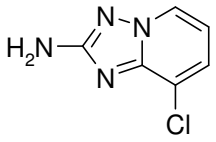
*3-Ethyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-6-ylamine (**32**)*. To a solution of amino triazolopyridine **31** (84 mg, 518 μmol) in methanol (5 mL) was added palladium (10% on charcoal, 25 mg). The mixture was hydrogenated at 0.5 bar for 16h at RT, then filtered and concentrated under reduced pressure. The remainder was taken up in DMF and purified by preparative reverse-phase HPLC to give product **32**. Yield: 20 mg (23%). LCMS (ESI^+) calculated for $C_8H_{14}N_4$ $[M + H]^+$ *m/z* 167.1297, found 167.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 4.32 (m, 1H), 3.84 (m, 1H), 3.27-3.33 (m, 1H, largely obscured by water signal), 2.81 (m, 1H), 2.58-2.67 (m, 1H), 2.53 (q, *J* =7.6 Hz, 2H), 1.86-1.94 (m, 1H), 1.77 (br s, 2H), 1.60-1.70 (m, 1H), 1.15 (t, *J* = 7.6 Hz, 3H). HPLC (Method 3): R_t = 0.25 min.



34b

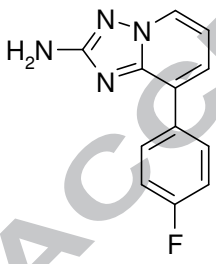
*1-(3-Chloro-pyridin-2-yl)-3-carboethoxy-thiourea (**34b**)*. Prepared by a procedure similar to that described for the synthesis of **34a** starting from 2-amino-3-chloropyridine (**33b**) (3.16 g, 25 mmol) in DMF. Yield: 6.11 g (96%). LCMS (ESI^+) calculated for $C_9H_{10}ClN_3O_2S$ $[M + H]^+$ *m/z* 260.0261, found 260.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 11.45 (br s, 1H), 11.42 (br s, 1H), 8.45

(dd, *J* = 4.7, 1.4 Hz, 1H), 8.04 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.42 (dd, *J* = 8.0, 4.7 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.27, (t, *J* = 7.1 Hz, 3H). HPLC (method 1) R_t = 0.64 min.



35b

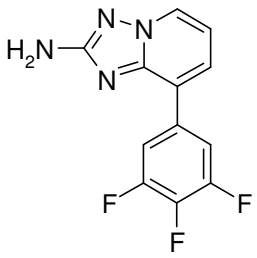
*8-Chloro-[1,2,4]triazolo[1,5-a]pyridine-2-ylamine (**35b**)*. Prepared by a procedure similar to that described for the synthesis of **35a** starting from 1-(3-chloro-pyridin-2-yl)-3-carboethoxy-thiourea (**34b**) (6.1 g, 23.5 mmol). Yield: 2.95 g (74%). LCMS (ESI^+) calculated for $C_6H_5ClN_4$ $[M + H]^+$ *m/z* 169.0281, found 169.0. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.54 (dd, *J* = 6.7, 0.8 Hz, 1H), 7.59 (d, *J* = 7.7, 0.8 Hz, 1H), 6.86 (dd, *J* = 7.7, 6.7 Hz, 1H), 6.22 (br s, 2H). HPLC (method 1) R_t = 0.57 min.



36a

*8-(4-Fluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-ylamine (**36a**)*. A mixture of 8-bromo-[1,2,4]triazolo[1,5-a]pyridine-2-ylamine (**35a**) (10 g, 45 mmol), 4-fluoro-phenylboronic acid (12.61 g, 89 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloro palladium(II) (2.93 g, 4

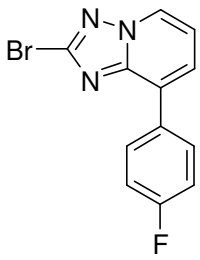
mmol) and sodium carbonate solution (2N in water, 44.6 mL, 89 mmol) in 1,4-dioxane (200 mL) was stirred at 110°C under nitrogen atmosphere for 12h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The remainder was purified by preparative MPLC (silica gel, PE/ethyl acetate 20:1) to afford the product (**36a**). Yield: 8.6 g (80%). LCMS (ESI^+) calculated for $C_{12}H_9FN_4$ $[M + H]^+$ *m/z* 229.0889, found 229.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.54 (dd, J = 6.7, 1.0 Hz, 1H), 8.14-8.21 (m, 2H), 7.70 (dd, J = 7.3, 1.0 Hz, 1H), 7.29-7.37 (m, 2H), 6.97 (dd, J = 7.3, 6.7 Hz, 1H), 6.12 (s, 2H). TLC (silica gel, PE/ethyl acetate 10:1): R_f = 0.5. HPLC (method 3) R_t = 0.43 min.



36c

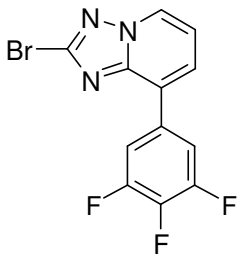
*8-(3,4,5-Trifluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-ylamine (**36c**)*. Prepared by a procedure similar to that described for the synthesis of **36a** starting from 3,4,5-trifluoro-phenyl boronic acid (1.5 g, 8.5 mmol), 8-bromo-[1,2,4]triazolo[1,5-a]pyridine-2-ylamine (**35a**) (1.8 g, 8.5 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloro palladium(II), complex with dichloromethane (1:1) (0.7 g, 0.85 mmol). Yield: 1.03 g (45%). LCMS (ESI^+) calculated for $C_{12}H_7F_3N_4$ $[M + H]^+$ *m/z* 265.0701, found 265.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.61 (dd, J =

6.6, 0.8 Hz, 1H), 8.23-8.32 (m, 2H), 7.90 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.00 (dd, *J* = 7.5, 6.8 Hz, 1H), 6.24 (br s, 2H). HPLC (method 6): R_t = 0.51 min.



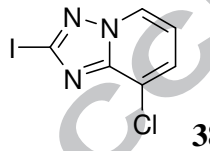
37a

*2-Bromo-8-(4-fluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine (**37a**).* A mixture of *tert*-nitrobutane (8.35 g,78.76 mmol) and copper(II) bromide (17.77 g, 78.76 mmol) in acetonitrile (180 mL) was heated to 60°C, 8-(4-fluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-ylamine (**36a**) (8.60 g, 35.8 mmol) was added in small portions. After complete addition, the mixture was heated to 75°C for 1h. Further portions of *tert*-nitrobutane and copper(II) bromide were added and the mixture heated to 75°C for an additional hour. The mixture was cooled to RT, water was added and extracted with DCM. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain crude material which was purified by MPLC (silica gel, PE/ethyl acetate 8:1) to obtain the product (**37a**). Yield: 6.17 g (59%). LCMS (ESI^+) calculated for $C_{12}H_7BrFN_3$ $[M + H]^+$ *m/z* 291.9886, found 292.0. ^1H NMR (400 MHz, $(CD_3)_2SO$) 8.95 (dd, *J* = 6.7, 1.0 Hz, 1H), 8.11-8.17 (m, 2H), 7.99 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.34-7.43 (m, 2H), 7.36 (dd, *J* = 7.4, 6.7 Hz, 1H). TLC (silica gel, PE/ethyl acetate 4:1): R_f = 0.5.



37c

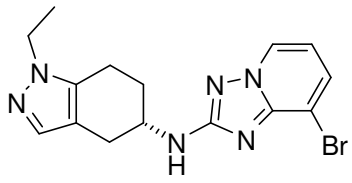
*2-Bromo-8-(3,4,5-trifluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine (**37c**)*. To a mixture of 8-(3,4,5-Trifluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-ylamine (**36c**) (1.22 g, 4.6 mmol) and $NaNO_2$ (955 mg, 4.31 mmol) in ice water (~1 mL) hydrobromic acid (48% in water, 11.2 mL, 99 mmol) was added dropwise at -5°C. After complete addition the reaction mixture was slowly warmed up to RT, then refluxed for 1d. After cooling to RT the precipitate was filtered off and purified by preparative reverse-phase HPLC to afford the product (**37c**). Yield: 627 mg (42%). LCMS (ESI^+) calculated for $C_{12}H_5BrF_3N_3$ $[M + H]^+$ *m/z* 327.9697, found 328.0. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 9.02 (dd, J = 6.8, 0.8 Hz, 1H), 8.11-8.20 (m, 3H), 7.39 (m, 1H). HPLC (method 6): R_t = 0.75 min.



38b

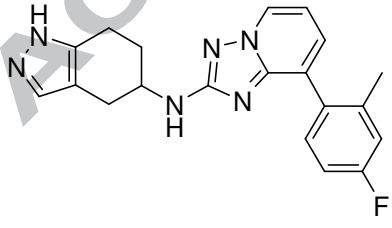
*8-Chloro-2-iodo-[1,2,4]triazolo[1,5-a]pyridine (**38b**)*. To a mixture of sodium nitrite (7.8 g, 112.7 mmol) and potassium iodide (23.4 g, 140.9 mmol) in water (30 mL) was added a mixture of *para*-toluene sulfonic acid monohydrate (42.9 g, 225.4 mmol) in acetonitrile (500 mL) at RT followed by addition of 8-chloro-[1,2,4]triazolo[1,5-a]pyridine-2-ylamine (**35b**) (9.5 g, 56.4

mmol). After stirring at 50°C for 2h the reaction mixture was diluted with water and sodium thiosulfate was added until color change persisted. The mixture was extracted twice with DCM and the combined organic phases were concentrated under reduced pressure. The remainder was triturated with water, filtered and dried to give the product (**38b**). Yield: 13.34 g (85%). LCMS (ESI$^+$) calculated for $C_6H_3ClIN_3$ $[M + H]^+$ *m/z* 279.9138, found 279.9. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.94 (dd, J = 6.8, 0.9 Hz, 1H), 7.88 (dd, J = 7.7, 0.9 Hz, 1H), 7.19 (dd, J = 7.7, 6.8 Hz, 1H). HPLC (Method 1): R_t = 0.77 min.



ent2-**39a**

*(S)-(8-Bromo-[1,2,4]triazolo[1,5-a]pyridine-2-yl)-(1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**ent2-39a**)*. Prepared in analogy to the preparation of racemic **39a** starting from chiral ***ent2*-13a** and **38a**. Yield: 206 mg (62%). HPLC (Method 5): R_t = 0.91 min.



41

*[8-(4-Fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**41**)*. To a mixture of 4,5,6,7-tetrahydro-*1H*-indazol-5-amine dihydrochloride (52 mg, 245 µmol), 2-bromo-8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine (**37b**) (50 mg, 163 µmol) and Cs_2CO_3 (213 mg, 653 µmol) in toluene (2 mL) was added dichloro[1,3-bis(2,6-di-3-pentylphenyl)imidazole-2-ylidene](3-chloropyridyl)palladium(II) (6.5 mg, 8 µmol). The reaction mixture was stirred at 110°C for 5d. To the reaction mixture was added 1,4-dioxane (1 mL) and water (0.1 mL) and stirring was continued for 16h at 120°C. After cooling to RT the reaction mixture was concentrated under reduced pressure, taken up in 1,4-dioxane, filtered over Alox and purified by preparative reverse-phase HPLC to afford the product (**41**). Yield: 3 mg (5%). LCMS (ESI^+) calculated for $C_{20}H_{19}FN_6$ $[M + H]^+$ *m/z* 363.1733, found 363.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.99 (dd, J = 6.8, 1.1 Hz, 1H), 7.64 (dd, J = 7.3, 1.1 Hz, 1H), 7.53 (s, 1H), 7.44 (m, 1H), 7.32 (m, 1H), 7.26 (m, 1H), 7.16 (m, 1H), 2.99-3.17 (m, 2H), 2.83-2.94 (m, 1H), 2.66-2.73 (m, 1H), 2.22 (s, 3H), 2.14-2.21 (m, 1H), 1.85-1.94 (m, 1H), 1.51-1.62 (m, 1H). Note: Both NH signals were not visible. HPLC (Method 1): R_t = 0.94 min.

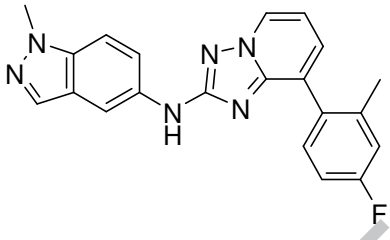
General procedure C-1: preparation of final compounds 42-45, 47, 48, 50, 51, 53-55: To a mixture of 2-halo-triazolopyridine **37a-c** (1 equiv), amine **13a-g**, **21a**, **24** or **28** (2 equiv) and sodium *tert*-butoxide (4 equiv) in degassed 1,4-dioxane (0.2 M) under Argon atmosphere was added Johnphos (0.1 equiv) and tris-(dibenzylidene acetone)dipalladium(0) (0.1 equiv). The reaction mixture was degassed, put again under argon atmosphere and stirred for 4-16 h at 80°C.

After cooling to RT the reaction mixture was filtered and purified by preparative reverse-phase HPLC to furnish the desired products.

General procedure C-2: preparation of final compounds 40, *(R)*-42, 46, 49 and 52: A mixture of 2-halo triazolopyridine **38b or 37c** (1 equiv), amine ***ent1*-13a**, **13f**, **17**, **21b** or **32** (1 equiv) and cesium fluoride (5 equiv) in DMSO (0.1-0.3M) was heated at 130-160°C for 10h with microwave irradiation. After cooling to RT the precipitates were filtered off and discarded. The filtrate was taken up in ethyl acetate and water and was extracted 3x with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by preparative reversed-phase HPLC to give the desired products.

General procedure D-1: preparation of final compounds 56-63, 65, 68-69: To a mixture of chloro triazolopyridine **39b** (1 equiv), the respective aryl boronic acid (2 equiv) and K_3PO_4 (2 equiv) in THF/water mixture (0.1 M, *v*/*v* 10:1) was added chloro-(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)-[2-(2'amino-1,1'-biphenyl)]palladium(II) (0.1 equiv) under argon atmosphere. The reaction mixture was degassed, put under argon atmosphere again and heated at 120°C for 16h. After cooling to RT the mixture was filtered and purified by preparative reverse-phase HPLC to give the products.

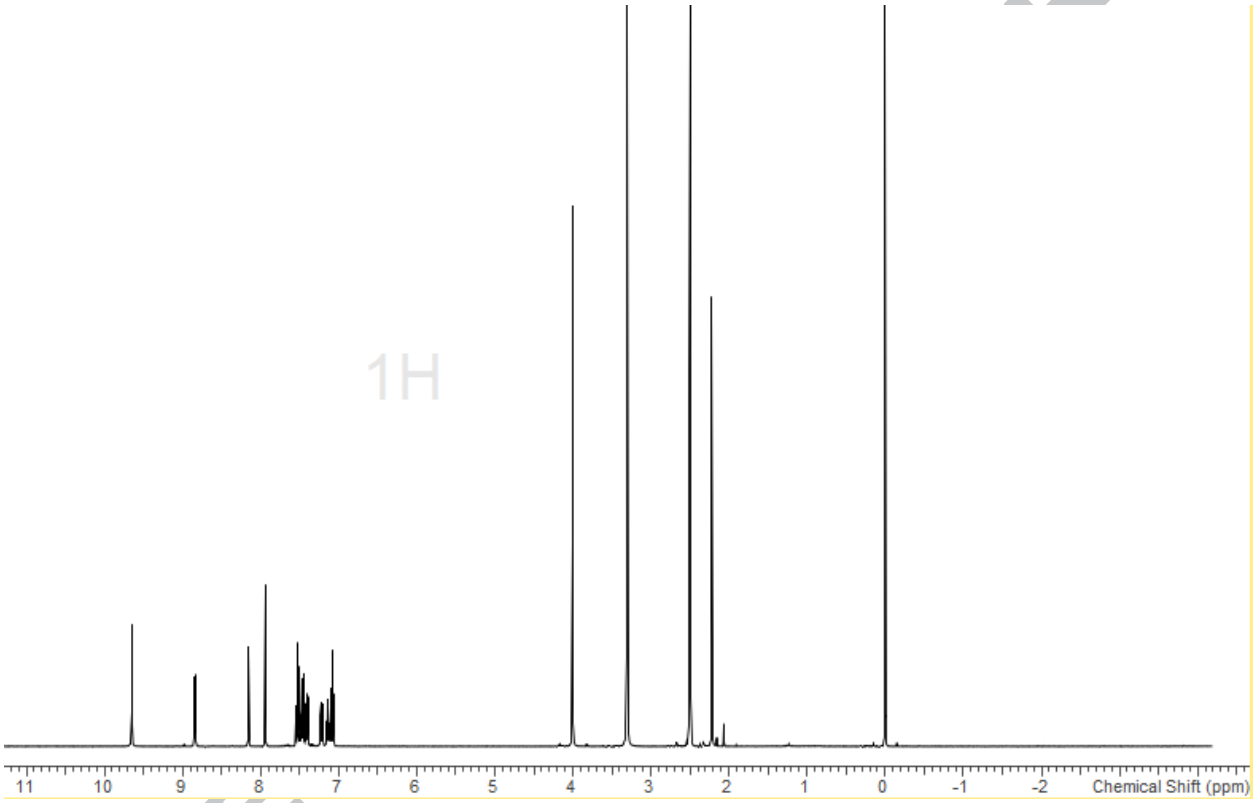
General procedure D-2: preparation of final compounds *ent1*-61, *ent2*-61, 64, 66 and 70-73: To a mixture of bromo triazolopyridine **39a** (1 equiv), the respective (hetero)aryl boronic acid or ester (1.1 equiv) in 1,4-dioxane/methanol mixture (0.05 M, *v*/*v* 2:1) were added aqueous sodium carbonate solution (2 M, 4 equiv) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (0.03 equiv) under argon atmosphere. The reaction mixture was heated at 90°C for 16h. After cooling to RT the mixture was filtered and purified by preparative reverse-phase HPLC to give the products.

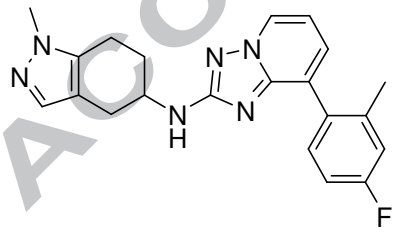


9

*[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-methyl-1H-indazol-5-yl)-amine (**9**)*. Palladium acetate (8 mg, 36 µmol) and X-Phos (17 mg, 36 µmol) were added to a mixture of 2-halo-triazolopyridine **37b** (110 mg, 359 µmol) and 1-methyl-*1H*-indazol-5-ylamine (58 mg, 395 µmol) in 1,4-dioxane (5 mL) under an argon atmosphere. After 45 min at 140°C (microwave irradiation), the mixture was cooled to RT and an additional portion of 1-methyl-*1H*-indazol-5-ylamine (15 mg, 102 µmol) was added. The reaction mixture was heated for another 45 min at 140°C under microwave irradiation, then cooled to RT and acidified with TFA. The mixture was filtered and concentrated under reduced pressure. The remainder was purified by preparative reverse-phase HPLC to obtain compound **9**. Yield: 87 mg, TFA salt (50%). LCMS

(ESI$^+$) calculated for $C_{21}H_{17}FN_6$ $[M + H]^+$ *m/z* 373.1577, found 373.1. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.65 (s, 1H), 8.84 (dd, J = 6.6, 0.9 Hz, 1H), 8.16 (m, 1H), 7.94 (s, 1H), 7.38-7.56 (m, 4H), 7.22 (m, 1H), 7.13 (m, 1H), 7.08 (dd, J = 7.3, 6.6 Hz, 1H), 4.00 (s, 3H), 2.22 (s, 3H). HPLC (Method 5): R_t = 0.70 min. Chemical purity > 95%.

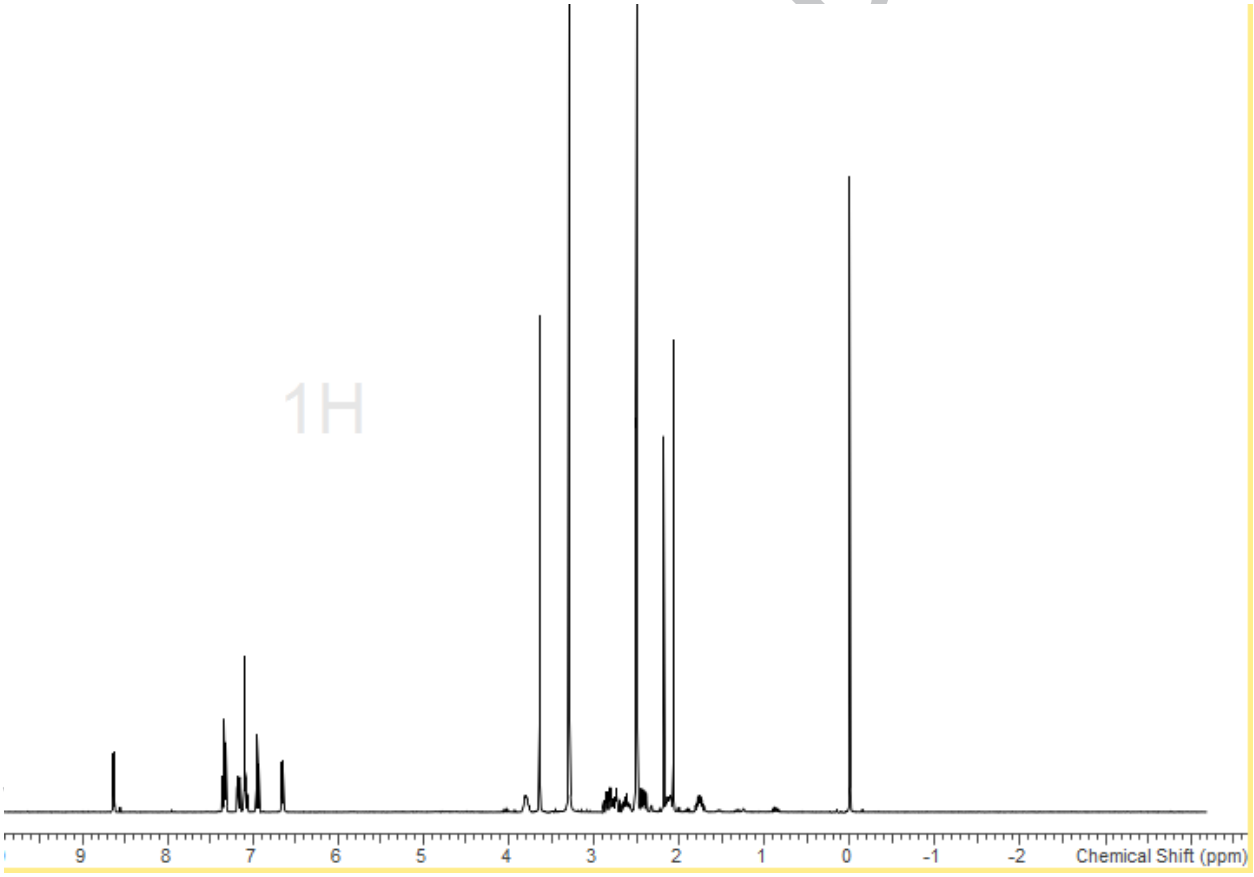


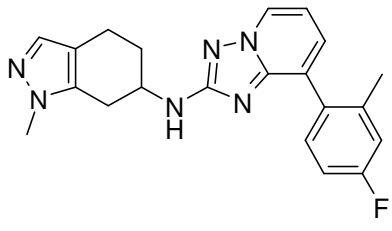


10

*[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-methyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**10**)*. Prepared according to general procedure C-1 using triazolopyridine

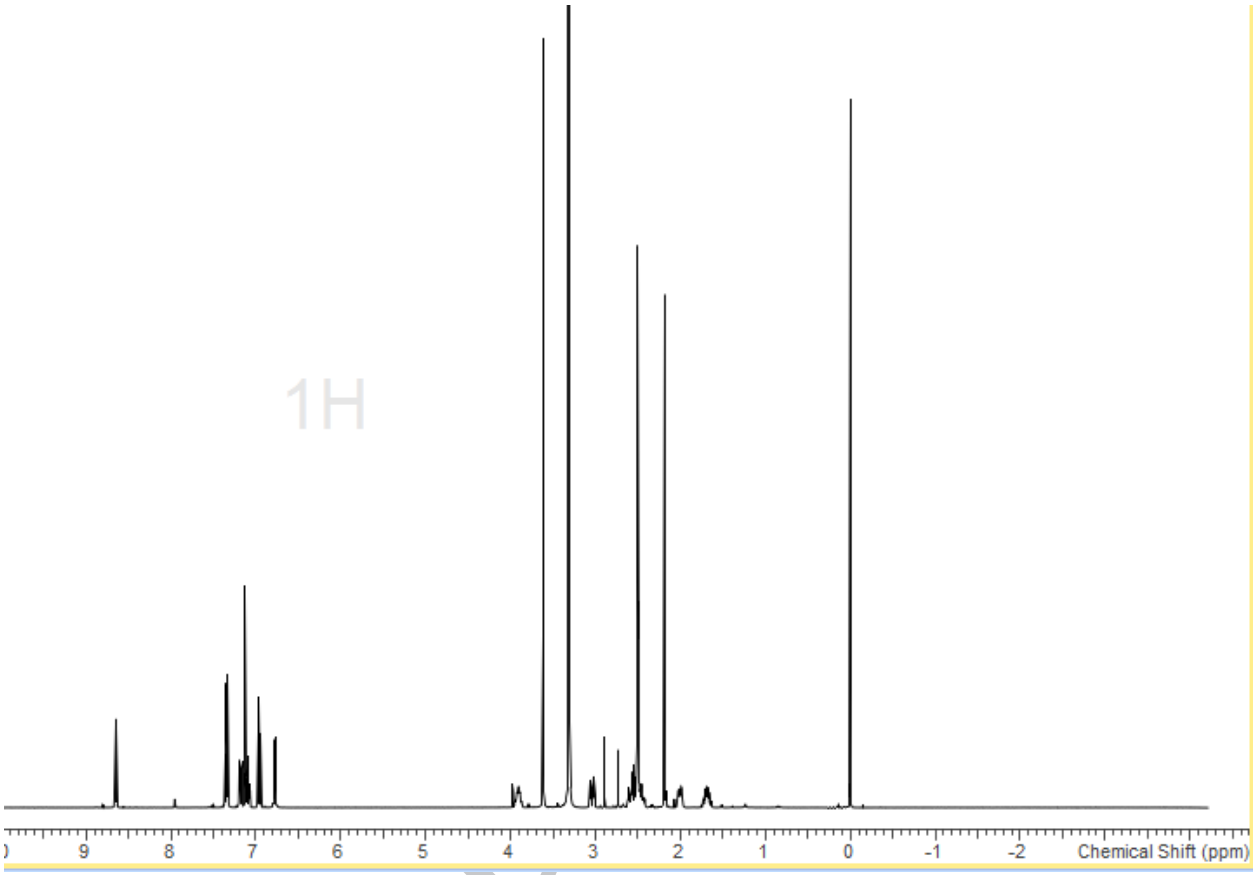
37b and 1-methyl-4,5,6,7-tetrahydro-*1H*-indazol-5-ylamine (as dihydrochloride salt, source: Chemizon, order no. 006-002, CAS no. 1228878-82-7). Yield: 100 mg (41%). HRMS (ESI^+) calculated for $C_{21}H_{21}FN_6$ $[M+H]^+$ *m/z* 377.1890, found 377.1892. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.63 (dd, J = 6.7, 1.1 Hz, 1H), 7.30-7.37 (m, 1H), 7.32 (dd, J = 7.3, 1.1 Hz, 1H), 7.17 (m, 1H), 7.10 (s, 1H), 7.05-7.12 (m, 1H), 6.95 (dd, J =7.3, 6.7 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 3.74-3.85 (m, 1H), 3.64 (s, 3H), 2.68-2.87 (m, 2H), 2.56-2.68 (m, 1H), 2.37-2.46 (m, 1H), 2.18 (s, 3H), 2.07-2.17 (m, 1H), 1.70-1.82 (m, 1H). HPLC (Method 1): R_t = 0.98 min. Chemical purity: 95%.

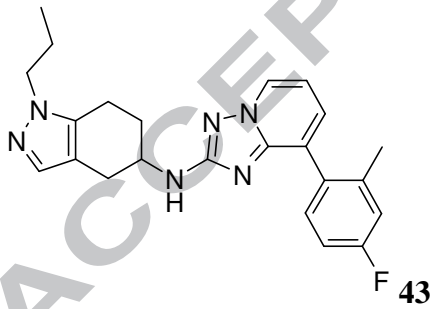




40

*[8-(4-Fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-methyl-4,5,6,7-tetrahydro-1H-indazol-6-yl)-amine (**40**)*. Prepared according to general procedure C-2 using triazolopyridine **37b** and amine **21b** (1 equiv) by heating at 160°C for 6h under microwave irradiation. Yield: 29 mg, TFA salt (20%). LCMS (ESI^+) calculated for $C_{21}H_{21}FN_6$ $[M + H]^+$ *m/z* 377.1890, found 377.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.65 (dd, J = 6.6, 1.0 Hz, 1H), 7.35 (dd, J = 7.3, 1.1 Hz, 1H), 7.32-7.37 (m, 1H), 7.18 (m, 1H), 7.16 (s, 1H), 7.09 (m, 1H), 6.98 (dd, J = 7.3, 6.6 Hz, 1H), 6.78 (br s, 1H), 3.87-3.96 (m, 1H), 3.63 (s, 3H, partially obscured by water signal), 3.01-3.08 (m, 1H), 2.41-2.63 (m, 3H, partially obscured by DMSO signal), 2.19 (s, 3H), 1.96-2.05 (m, 1H), 1.64-1.76 (m, 1H). HPLC (Method 5): R_t = 0.57 min. Chemical purity > 95%.

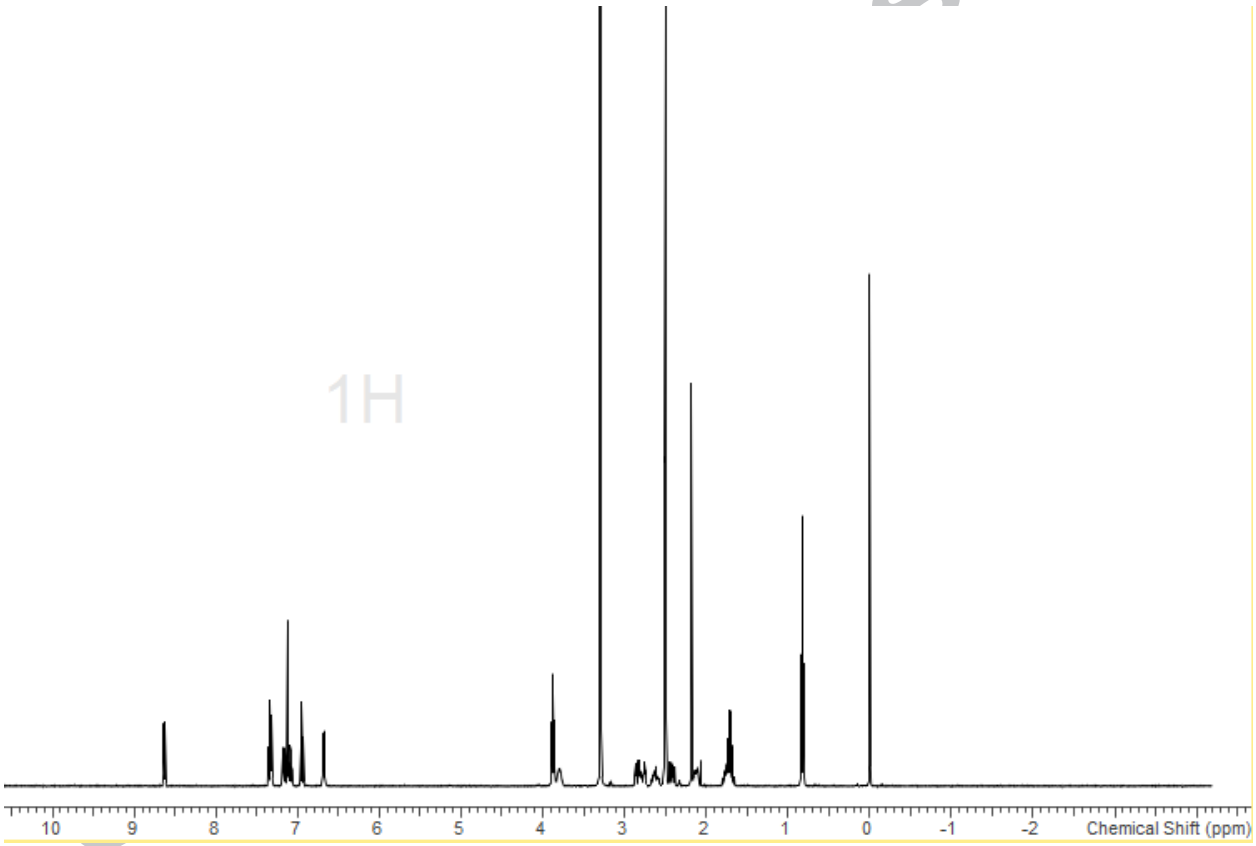


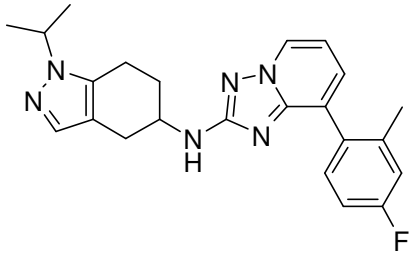


43

*[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-propyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**43**)*. Prepared according to general procedure C-1 using triazolopyridine **37b** and amine **13c**. Yield: 29 mg (48%). LCMS (ESI^+) calculated for $C_{23}H_{25}FN_6$ $[M + H]^+$ *m/z*

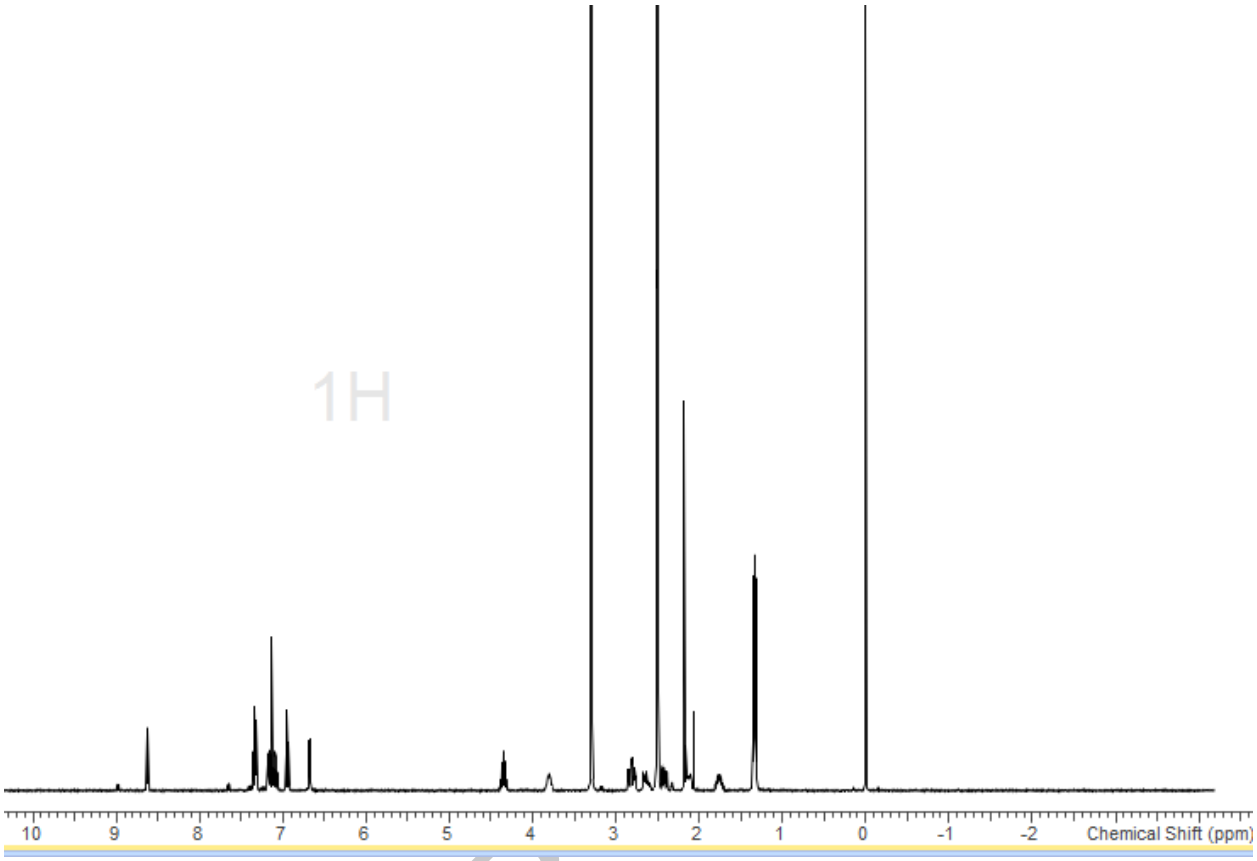
405.2203, found 405.3. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.63 (dd, J = 6.6, 1.0 Hz, 1H), 7.30-7.36 (m, 1H), 7.32 (dd, J = 7.3, 1.0 Hz, 1H), 7.17 (m, 1H), 7.13 (s, 1H), 7.06-7.12 (m, 1H), 6.95 (dd, J = 7.3, 6.6 Hz, 1H), 6.68 (d, J = 7.6 Hz, 1H), 3.87 (t, J = 7.1 Hz, 2H), 3.74-3.84 (m, 1H), 2.73-2.88 (m, 2H), 2.56-2.68 (m, 1H), 2.37-2.47 (m, 1H), 2.08-2.17 (m, 1H), 2.18 (s, 3H), 1.65-1.75 (m, 1H), 1.70 (sext, J = 7.2 Hz, 2H), 0.83 (t, J = 7.4 Hz, 3H). HPLC (Method 1): R_t = 1.05 min. Chemical purity > 95%.

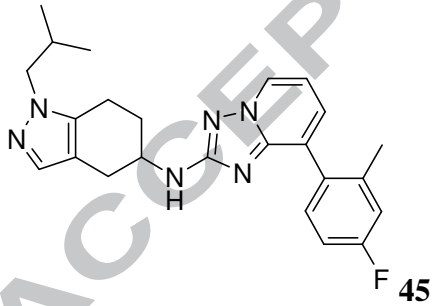




44

*[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-isopropyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**44**)*. Prepared according to general procedure C-1 using triazolopyridine **37b** and amine **13d**. Yield: 28 mg (45%). LCMS (ESI^+) calculated for $C_{23}H_{25}FN_6$ $[M + H]^+$ *m/z* 405.2203, found 405.3. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.62 (dd, J = 6.6, 1.0 Hz, 1H), 7.30-7.36 (m, 1H), 7.32 (dd, J = 7.3, 1.0 Hz, 1H), 7.17 (m, 1H), 7.13 (s, 1H), 7.06-7.12 (m, 1H), 6.95 (dd, J = 7.3, 6.6 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 4,35 (sept, J = 6.6 Hz, 1H), 3.75-3.86 (m, 1H), 2.74-2.87 (m, 2H), 2.58-2.69 (m, 1H), 2.37-2.46 (m, 1H), 2.18 (s, 3H), 2.08-2.17 (m, 1H), 1.70-1.82 (m, 1H), 1.34 (d, J = 6.6 Hz, 3H), 1.32 (d, J = 6.6 Hz, 3H). HPLC (Method 1): R_t = 1.04 min. Chemical purity 90%.

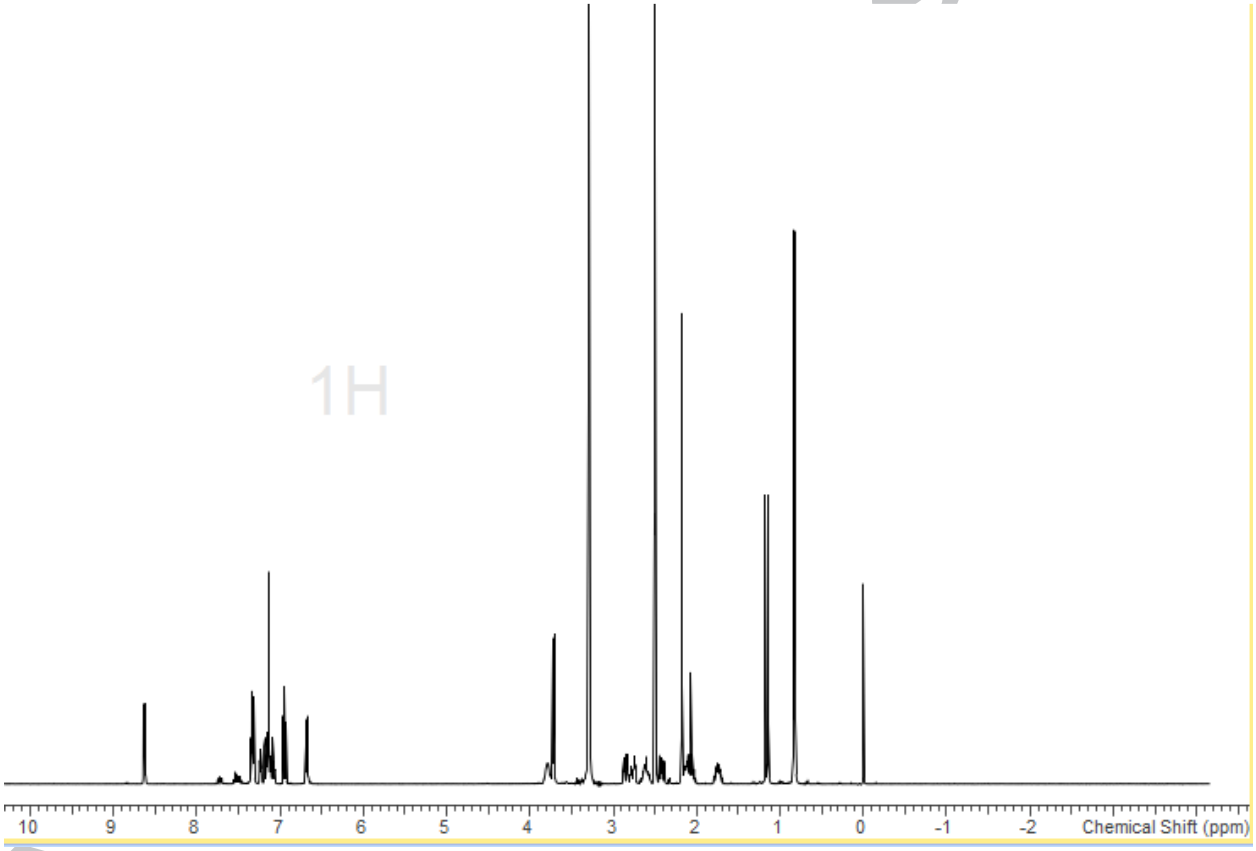


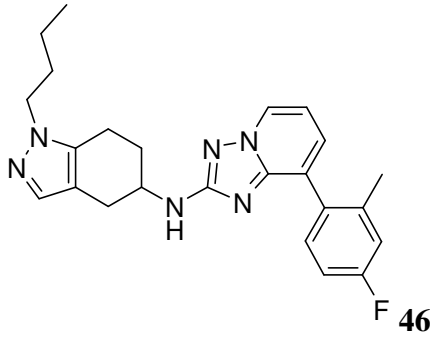


45

*[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-isobutyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**45**)*. Prepared according to general procedure C-1 using triazolopyridine **37b** and amine **13e**. Yield: 27 mg (42%). LCMS (ESI^+) calculated for $C_{25}H_{29}FN_6$

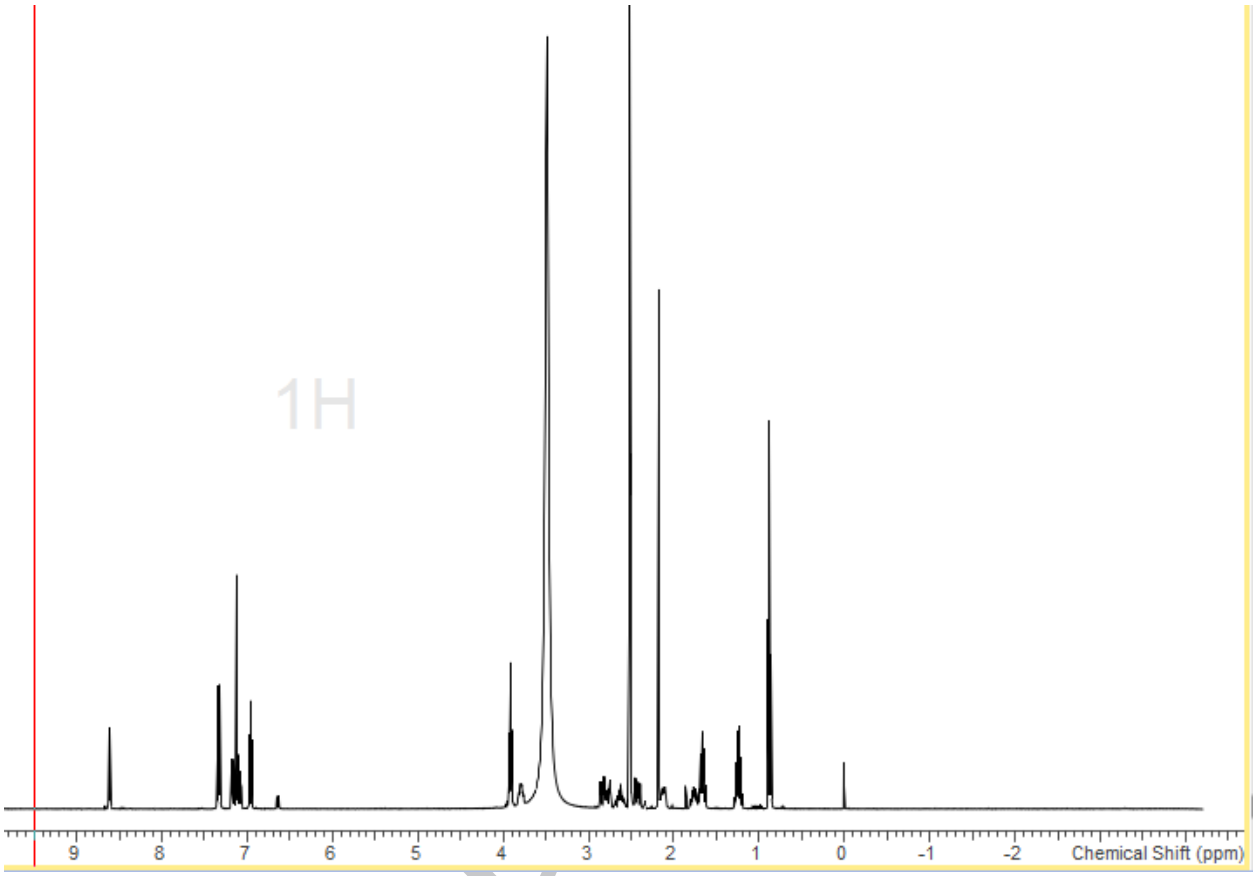
$[M + H]^+$ *m/z* 433.2516, found 419.3. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.63 (dd, J = 6.7, 1.2 Hz, 1H), 7.30-7.36 (m, 1H), 7.32 (dd, J = 7.3, 1.2 Hz, 1H), 7.17 (m, 1H), 7.14 (s, 1H), 7.09 (m, 1H), 6.95 (dd, J = 7.3, 6.7 Hz, 1H), 6.67 (d, J = 7.5 Hz, 1H), 3.75-3.85 (m, 1H), 3.72 (d, J = 7.2 Hz, 2H), 2.81-2.89 (m, 1H), 2.71-2.81 (m, 1H), 2.55-2.65 (m, 1H), 2.37-2.47 (m, 1H), 2.18 (s, 3H), 2.00-2.16 (m, 2H), 1.68-1.81 (m, 1H), 0.83 (d, J = 6.8 Hz, 6H). HPLC (Method 12): R_t = 0.85 min. Chemical purity 90%

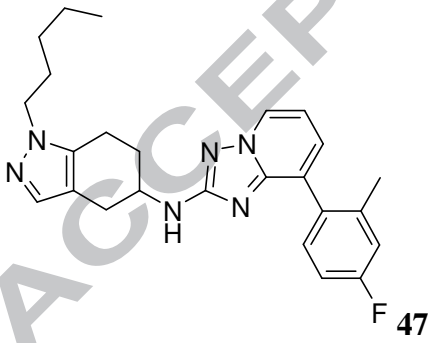




46

*[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-butyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**46**)*. Prepared according to general procedure C-2 using triazolopyridine **37b** and amine **13f**. Yield: 109 mg (80%). LCMS (ESI^+) calculated for $C_{24}H_{27}FN_6$ $[M + H]^+$ *m/z* 419.2359, found 419.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.64 (dd, J = 6.6, 1.1 Hz, 1H), 7.32-7.37 (m, 2H), 7.17 (m, 1H), 7.17 (s, 1H), 7.06-7.12 (m, 1H), 6.98 (dd, J = 7.2, 6.6 Hz, 1H), 6.72 (br s, 1H, poor integration), 3.93 (t, J = 7.1 Hz, 2H), 3.76-3.86 (m, 1H), 2.73-2.88 (m, 2H), 2.57-2.68 (m, 1H), 2.39-2.47 (m, 1H), 2.18 (s, 3H), 2.08-2.18 (m, 1H), 1.72-1.83 (m, 1H), 1.62-1.72 (m, 1H), 1.20-1.30 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H). HPLC (Method 11): R_t = 0.80 min. Chemical purity > 95%.

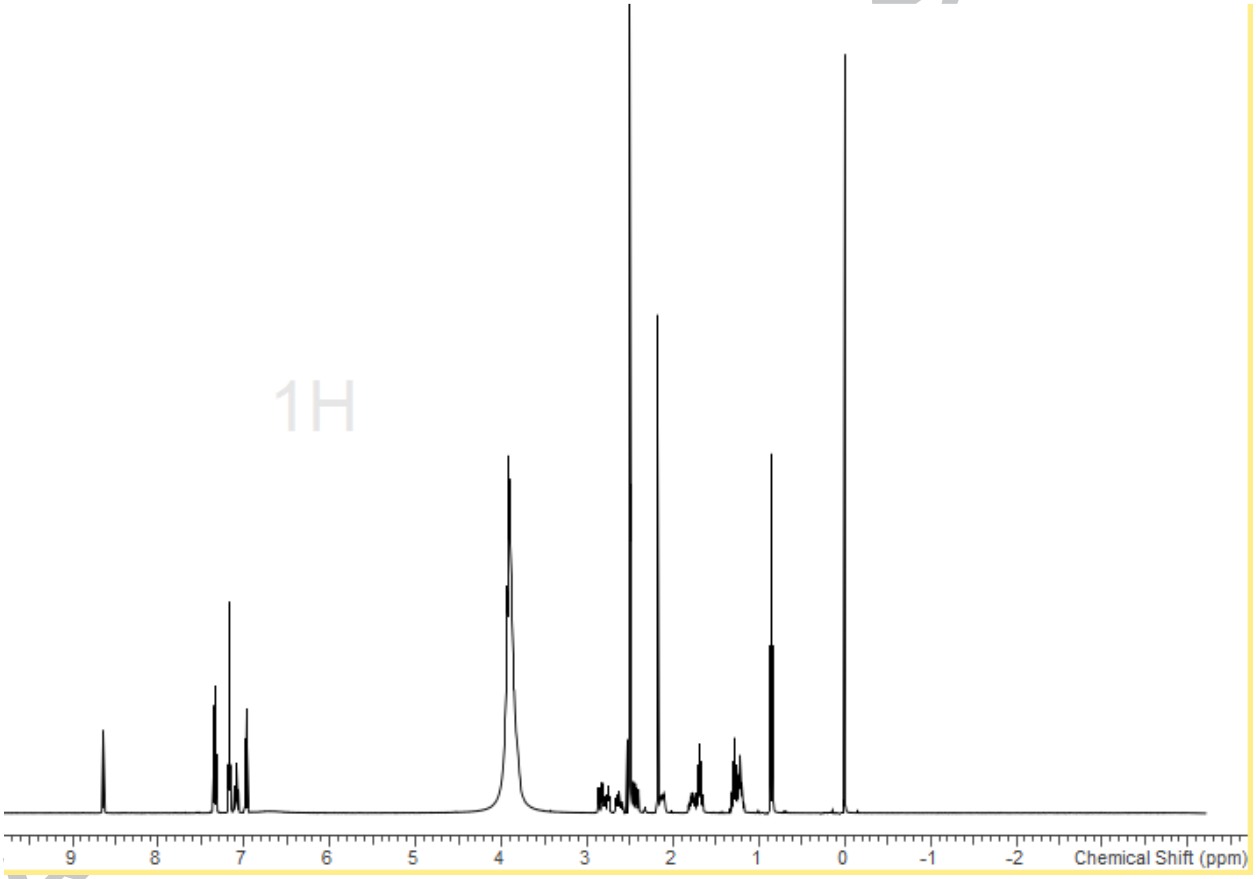


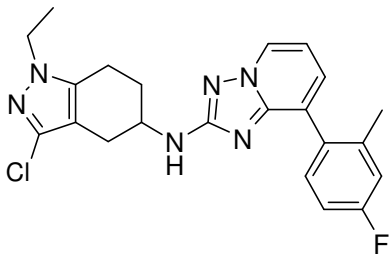


47

*[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-pentyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**47**)*. Prepared according to general procedure C-2 using triazolopyridine **37b** and amine **13g**. Yield: 101 mg (71%). LCMS (ESI^+) calculated for $C_{24}H_{27}FN_6$ $[M + H]^+$ *m/z*

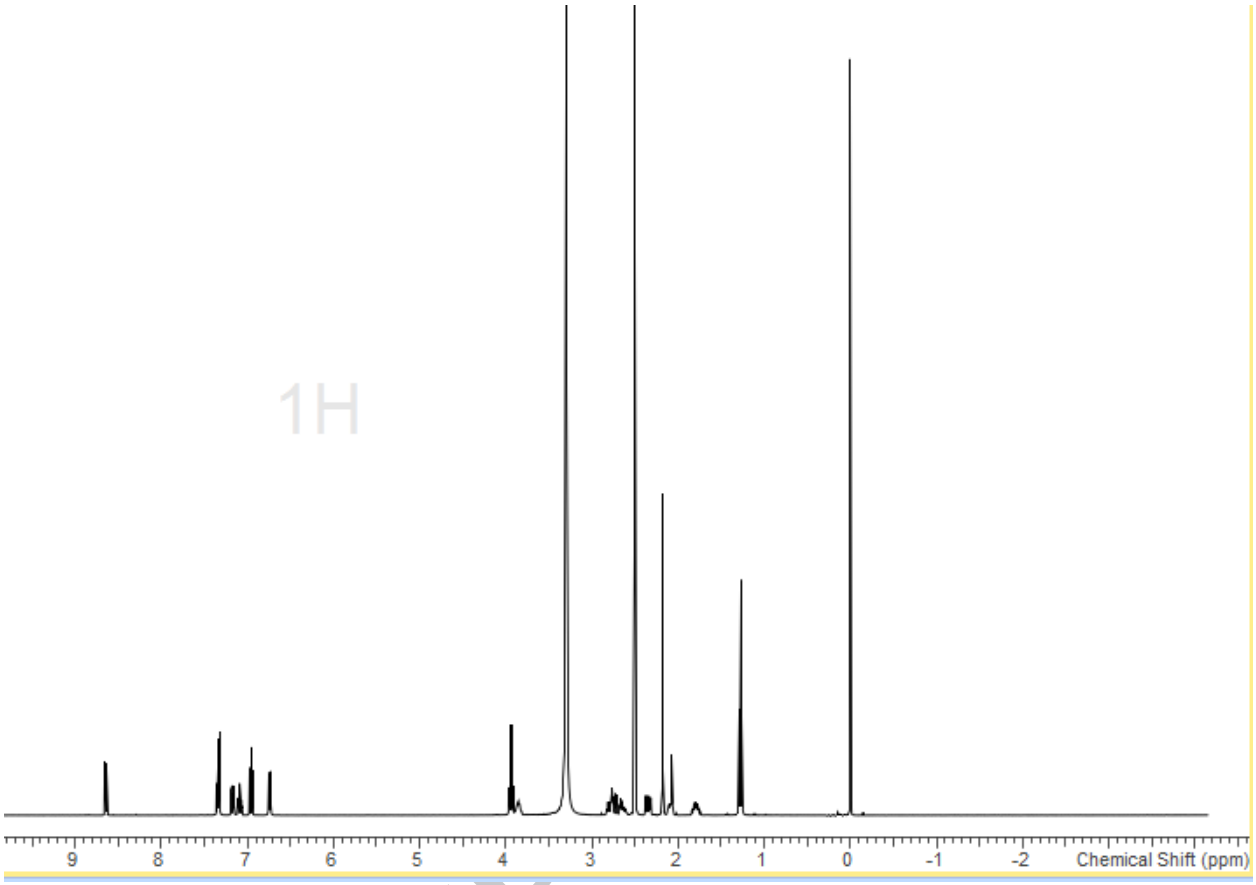
433.25160, found 433.3. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.64 (dd, J = 6.6, 1.2 Hz, 1H), 7.35 (dd, J = 7.2, 1.2 Hz, 1H), 7.31-7.37 (m, 1H), 7.15-7.20 (m, 1H), 7.17 (s, 1H), 7-06-7.12 (m, 1H), 6.97 (dd, J = 7.2, 6.6 Hz, 1H), 6.71 (br s, 1H, poor integration), 3.92 (t, J = 7.1 Hz, 2H, partially obscured by water signal), 2.81-2.88 (m, 1H), 2.73-2.81 (m, 1H), 2.57-2.68 (m, 1H), 2.39-2.47 (m, 1H), 2.18 (s, 3H), 2.08-2.17 m, 1H), 2.73-2.83 (m, 1H), 1.64-1.73 (m, 2H), 1.17-1.35 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H). HPLC (Method 11): R_t = 0.86 min. Chemical purity > 95%.

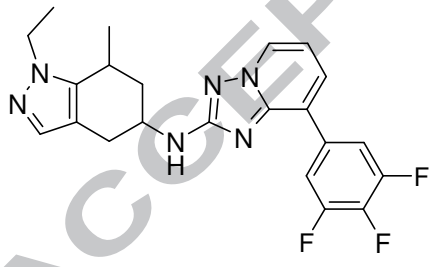




48

*(3-Chloro-1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**48**)*. Prepared according to general procedure C-1 using triazolopyridine **37b** and amine **13b** (1 equiv). Yield: 16 mg (15%). LCMS (ESI^+) calculated for $C_{22}H_{22}ClFN_6$ $[M + H]^+$ *m/z* 425.1657, found 425.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.64 (dd, J = 6.6, 1.0 Hz, 1H), 7.31-7.36 (m, 2H), 7.17 (m, 1H), 7.05-7.12 (m, 1H), 6.96 (dd, J = 7.4, 6.6 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 3.94 (q, J = 7.2 Hz, 2H), 3.80-3.90 (m, 1H), 2.70-2.84 (m, 2H), 2.58-2.70 (m, 1H), 2.31-2.39 (m, 1H), 2.18 (s, 3H), 2.05-2.13 (m, 1H), 1.73-1.85 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H). HPLC (Method 1): R_t = 1.09 min. Chemical purity > 95%.

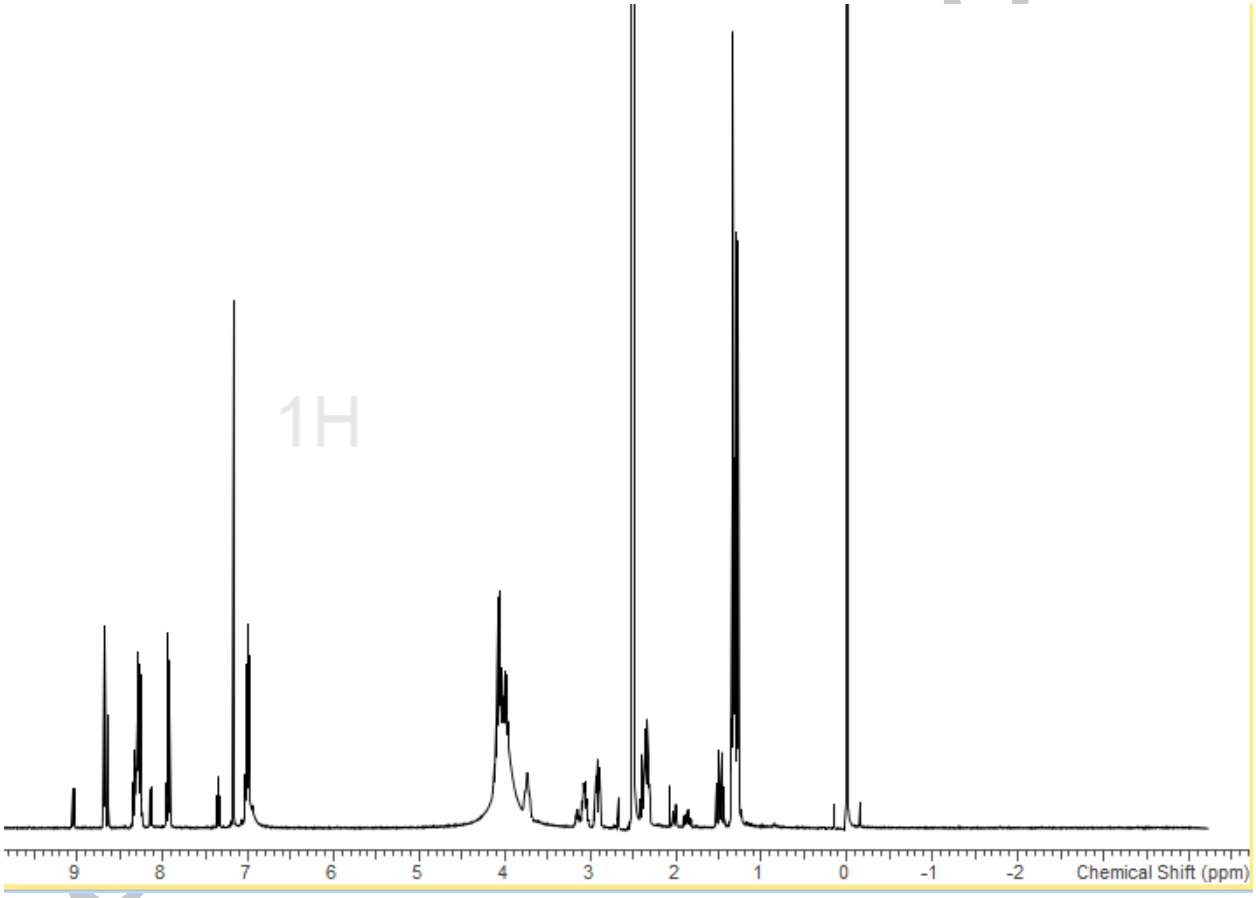


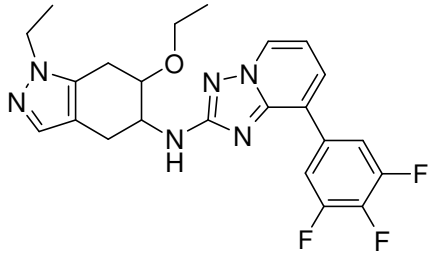


49

*(1-Ethyl-7-methyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(3,4,5-trifluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**49**)*. Prepared according to general procedure C-2 using triazolopyridine **37c** and amine **17** (1 equiv) by heating at 160°C for 6h under microwave irradation. Yield: 18 mg (9%). LCMS (ESI^+) calculated for $C_{22}H_{21}F_3N_6$ $[M + H]^+$ *m/z* 427.1858,

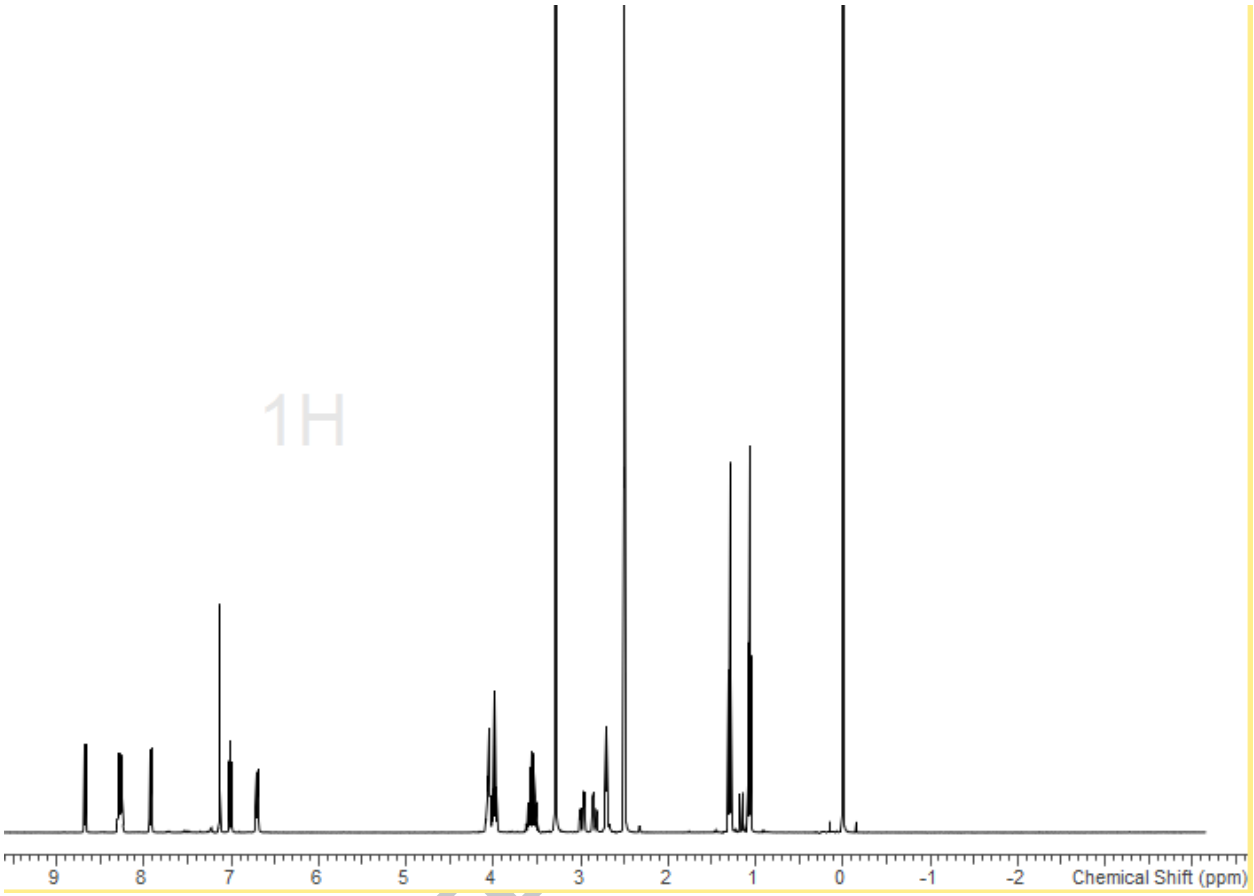
found 427.1. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.67 (m, 1H), 8.23-8.32 (m, 2H), 7.92 (m, 1H), 7.16 (s, 1H), 6.95-7.03 (m, 2H), 4.07 (q, J = 7.2 Hz, 1H), 4.06 (q, J = 7.2 Hz, 1H), 3.68-3.79 (m, 1H), 3.02-3.11 (m, 1H), 2.87-2.95 (m, 1H), 2.29-2.43 (m, 2H), 1.43-1.53 (m, 1H), 1.33 (t, J = 7.2 Hz, 3H), 1.28 (d, J = 6.7 Hz, 3H). Note: Only the major *cis* diastereomer was assigned. HPLC (Method 4): R_t = 1.25 min. Chemical purity >95%. cis/trans ratio 85:15.

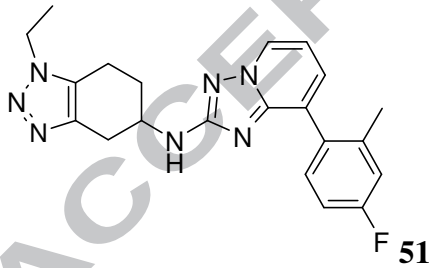




50

*(6-Ethoxy-1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(3,4,5-trifluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**50**)*. Prepared according to general procedure C-1 using triazolopyridine **37c** and amine **13h** (1 equiv). Yield: 11 mg (17%). LCMS (ESI^+) calculated for $C_{23}H_{22}F_3N_6O$ $[M + H]^+$ *m/z* 457.1964, found 457.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.68 (dd, J = 6.7, 0.9 Hz, 1H), 8.23-8.32 (m, 2H), 7.92 (dd, J = 7.5, 0.9 Hz, 1H), 7.14 (s, 1H), 7.01 (dd, J = 7.5, 6.7 Hz, 1H), 6.70 (d, J = 7.7 Hz, 1H), 4.02-4.09 (m, 2H), 3.98 (q, J = 7.4 Hz, 2H), 3.48-3.63 (m, 2H), 2.93-3.03 (m, 1H), 2.79-2.89 (m, 1H), 2.70 (m, 2H), 1.29 (t, J = 7.3 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H). Note: Only the major diastereomer was assigned. HPLC (Method 3): R_t = 0.70 min. Chemical purity > 95%.

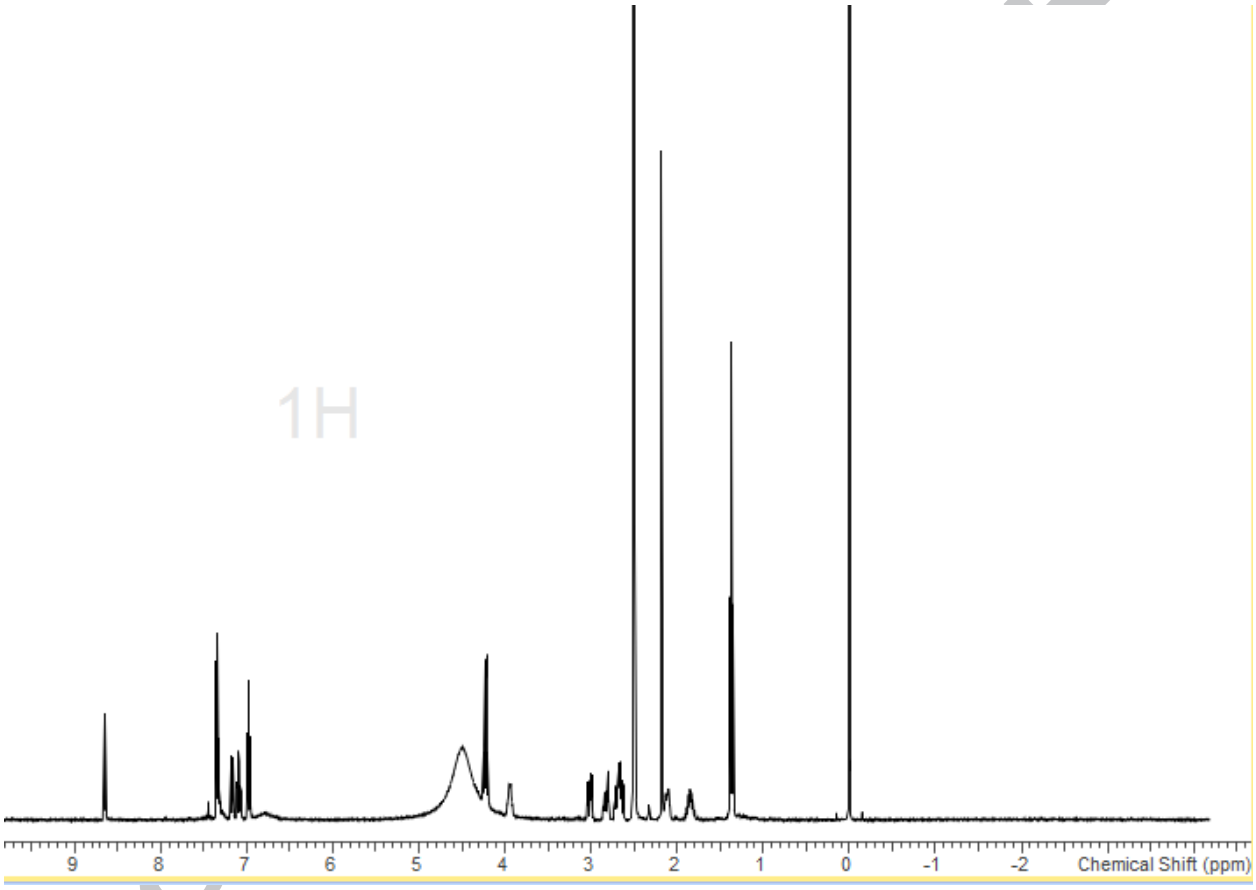


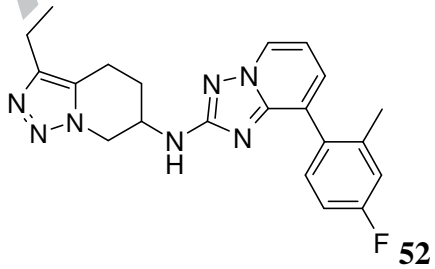


51

*(1-Ethyl-4,5,6,7-tetrahydro-1H-benzotriazol-5-yl)-[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**51**)*. Prepared according to general procedure C-1 using triazolopyridine **37b** and amine **24** (1 equiv). Yield: 90 mg (59%). LCMS (ESI^+) calculated for $C_{21}H_{22}FN_7$ $[M + H]^+$ *m/z* 392.1999, found 392.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.65 (dd, *J*

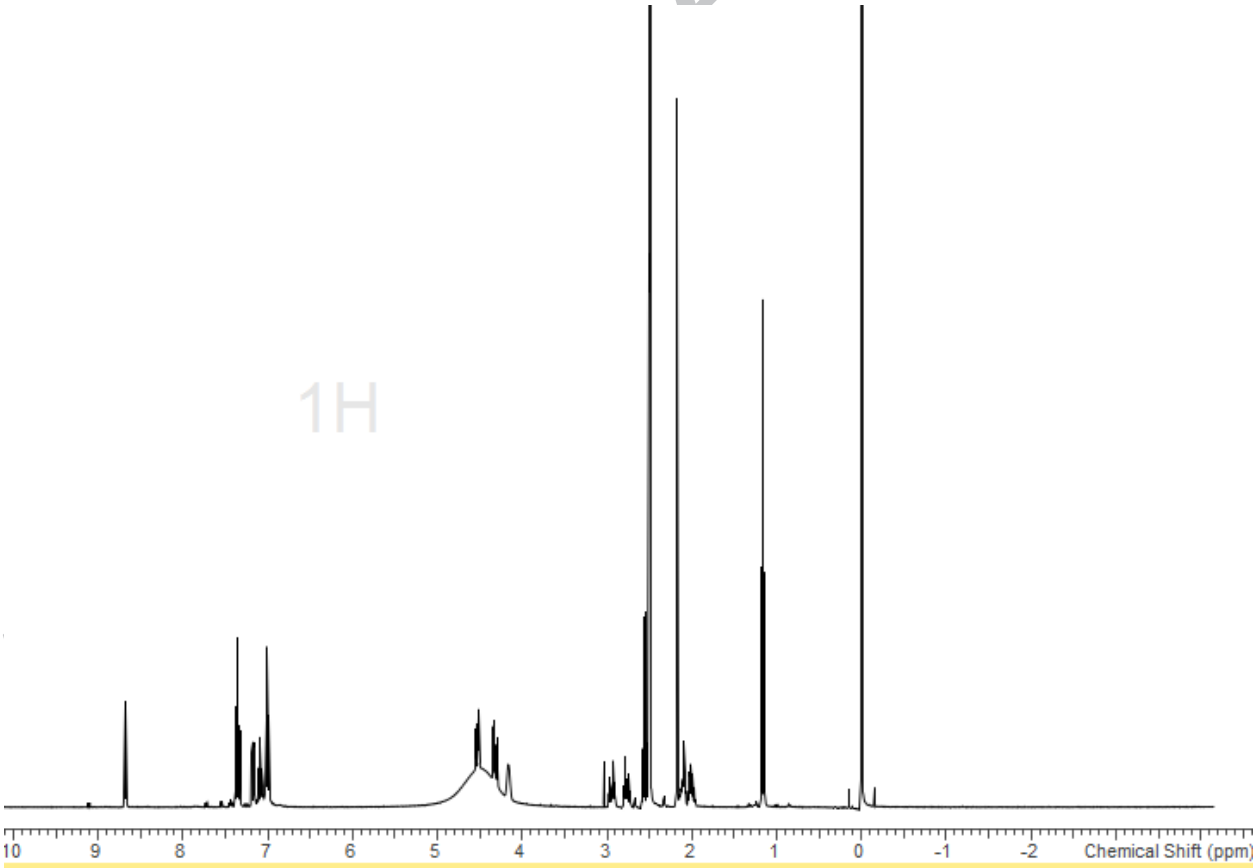
= 6.7, 1.0 Hz, 1H), 7.30-7.37 (m, 2H), 7.17 (m, 1H), 7.09 (m, 1H), 6.98 (dd, *J* = 7.3, 6.7 Hz, 1H), 6.80 (br s, 1H), 4.22 (q, *J* = 7.3 Hz, 2H), 3.90-3.98 (m, 1H), 2.97-3.06 (m, 1H), 2.78-2.88 (m, 1H), 2.61-2.74 (m, 2H), 2.18 (s, 3H), 2.07-2.16 (m, 1H), 1.79-1.91 (m, 1H), 1.37 (t, *J* = 7.3 Hz, 3H). HPLC (Method 7): R_t = 0.50 min. Chemical purity 90%.

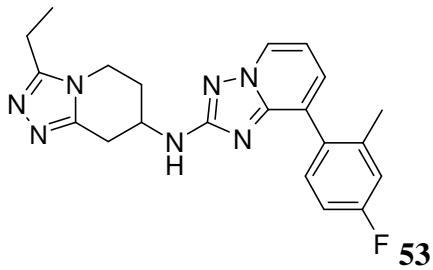




52

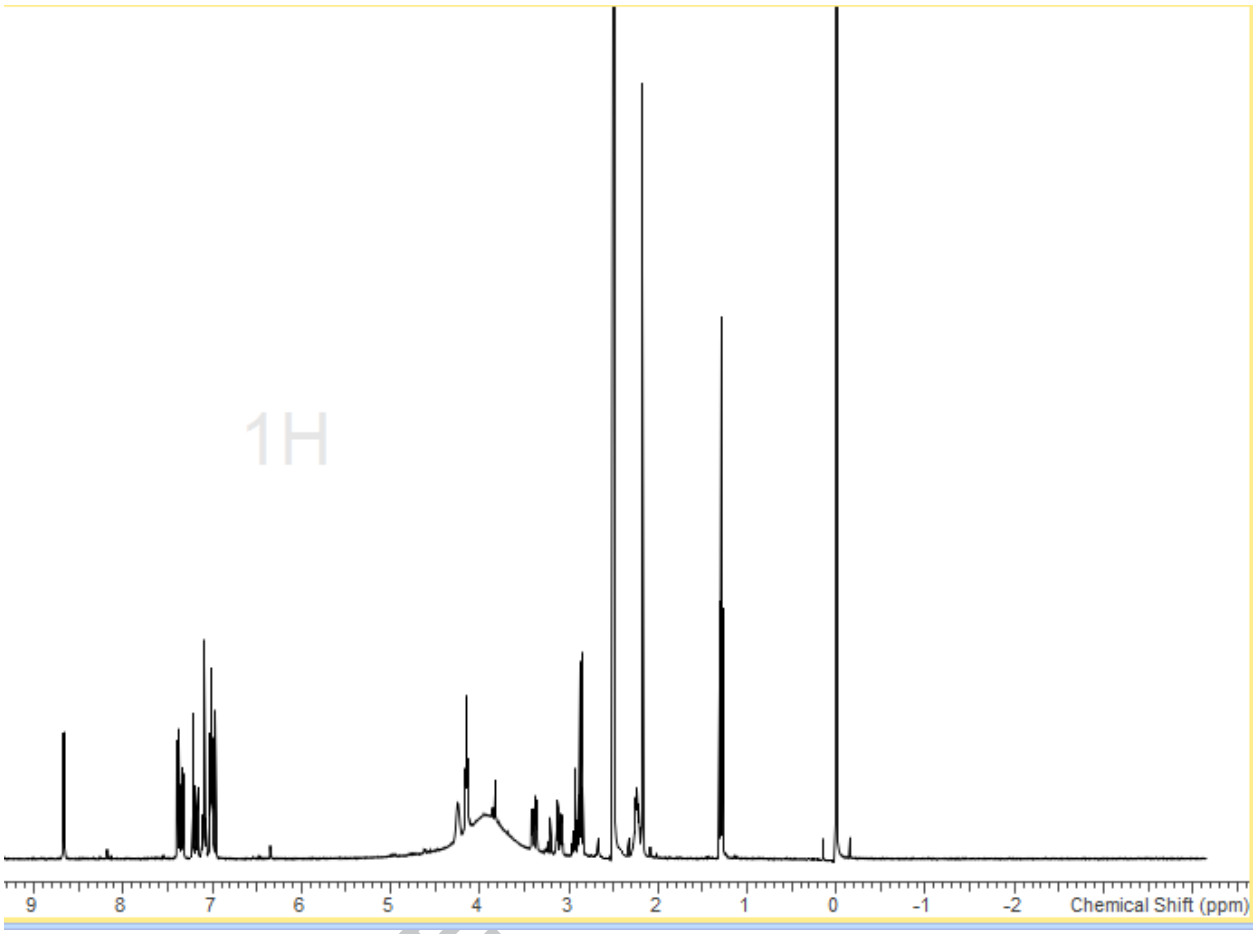
*(3-Ethyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine-6-yl)-[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**52**)*. Prepared according to general procedure C-2 using triazolopyridine **37b** and amine **32** (1 equiv) by heating at 160°C for 3h under microwave irradiation. Yield: 9 mg, TFA salt (16%). LCMS (ESI^+) calculated for $C_{21}H_{22}FN_7$ $[M + H]^+$ *m/z* 392.1999, found 392.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.68 (dd, J = 6.7, 1.0 Hz, 1H), 7.37 (dd, J = 7.3, 1.0 Hz, 1H), 7.32-7.36 (m, 1H), 7.17 (m, 1H), 7.09 (m, 1H), 7.00 (dd, J = 7.3, 6.7 Hz, 1H), 4.53 (dd, J = 12.2, 4.3 Hz, 1H), 4.32 (dd, J = 12.6, 6.2 Hz, 1H), 4.12-4.20 (m, 1H), 2.89-2.99 (m, 1H), 2.71-2.81 (m, 1H), 2.55 (q, J = 7.7 Hz, 2H), 2.18 (s, 3H), 2.06-2.15 (m, 1H), 1.95-2.05 (m, 1H), 1.16 (t, J = 7.7 Hz, 3H). HPLC (Method 3): R_t = 0.59 min. Chemical purity 90%.

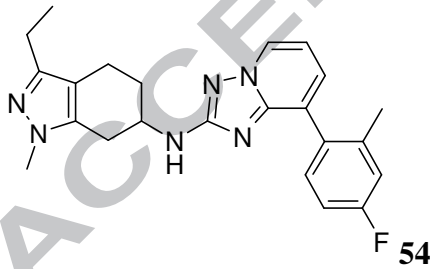




53

*(3-Ethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridine-7-yl)-[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**53**)*. Prepared according to general procedure C-1 using triazolopyridine **37b** and amine **28** (1 equiv). Yield: 15 mg (26%). LCMS (ESI^+) calculated for $C_{21}H_{22}FN_7$ $[M + H]^+$ *m/z* 392.1999, found 392.3. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.66 (dd, *J* = 6.6, 1.1 Hz, 1H), 7.35 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.32-7.37 (m, 1H), 7.17 (m, 1H), 7.09 (m, 1H), 6.98 (dd, *J* = 7.3, 6.7 Hz, 1H), 6.91 (d, *J* = 6.8 Hz, 1H), 3.98-4.11 (m, 2H), 3.84-3.93 (m, 1H), 3.15 (dd, *J* = 16.4, 5.0 Hz, 1H), 2.87 (dd, *J* = 16.4, 7.5 Hz, 1H), 2.63 (q, *J* = 7.5 Hz, 2H), 2.18-2.27 (m, 1H), 2.18 (s, 3H), 1.97-2.09 (m, 1H), 1.22 (t, *J* = 7.5 Hz, 3H). HPLC (Method 6): R_t = 0.46 min. Chemical purity 80%.

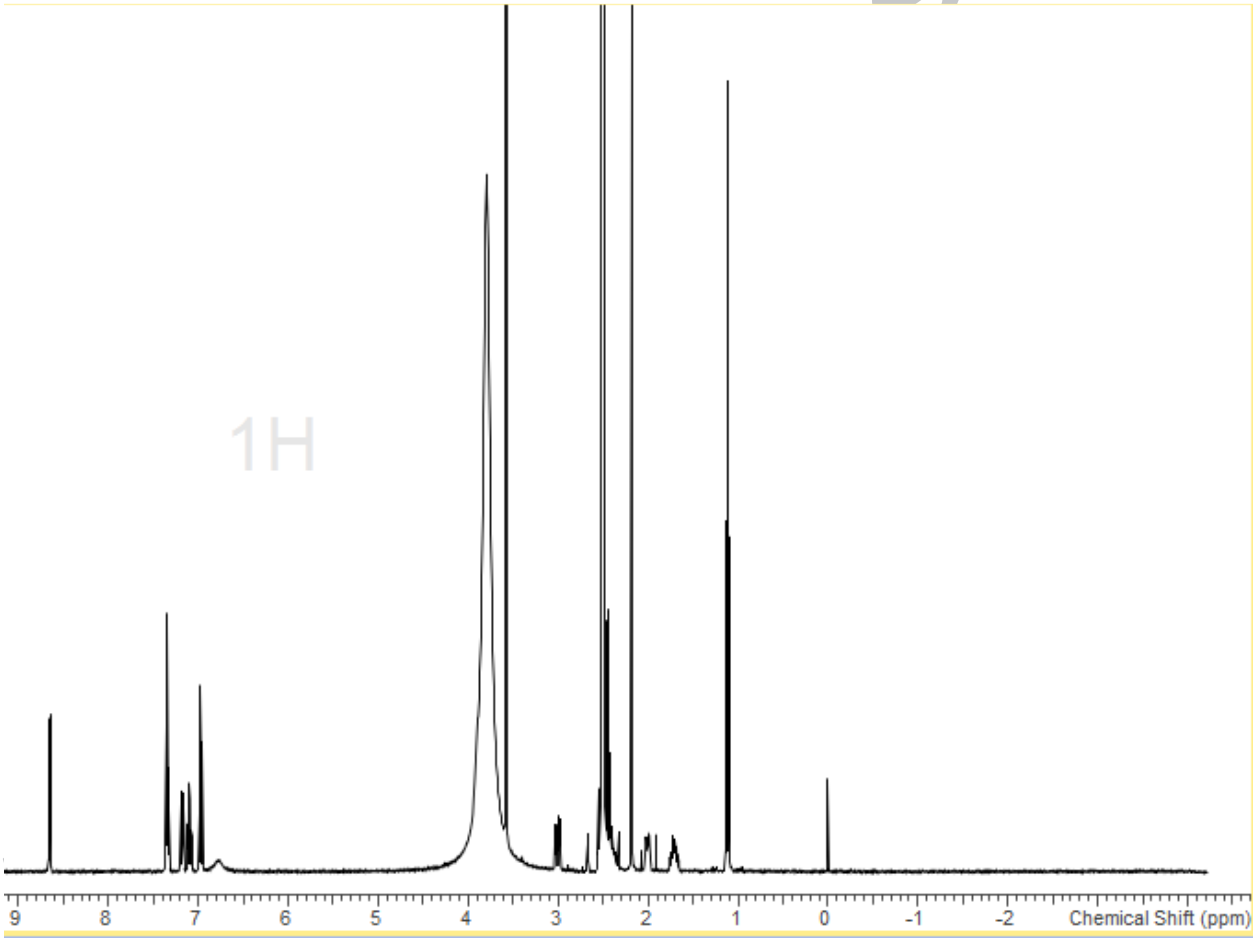


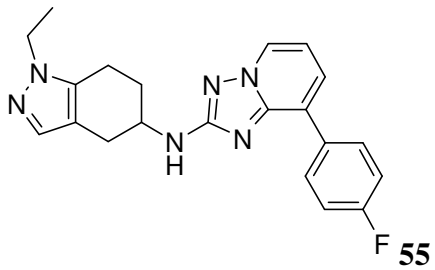


54

*(3-Ethyl-1-methyl-4,5,6,7-tetrahydro-1H-indazol-6-yl)-[8-(4-fluoro-2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**54**)*. Prepared according to general procedure C-1 using triazolopyridine **37b** and amine **21a** (1 equiv). Yield: 77 mg (58%). LCMS (ESI^+)

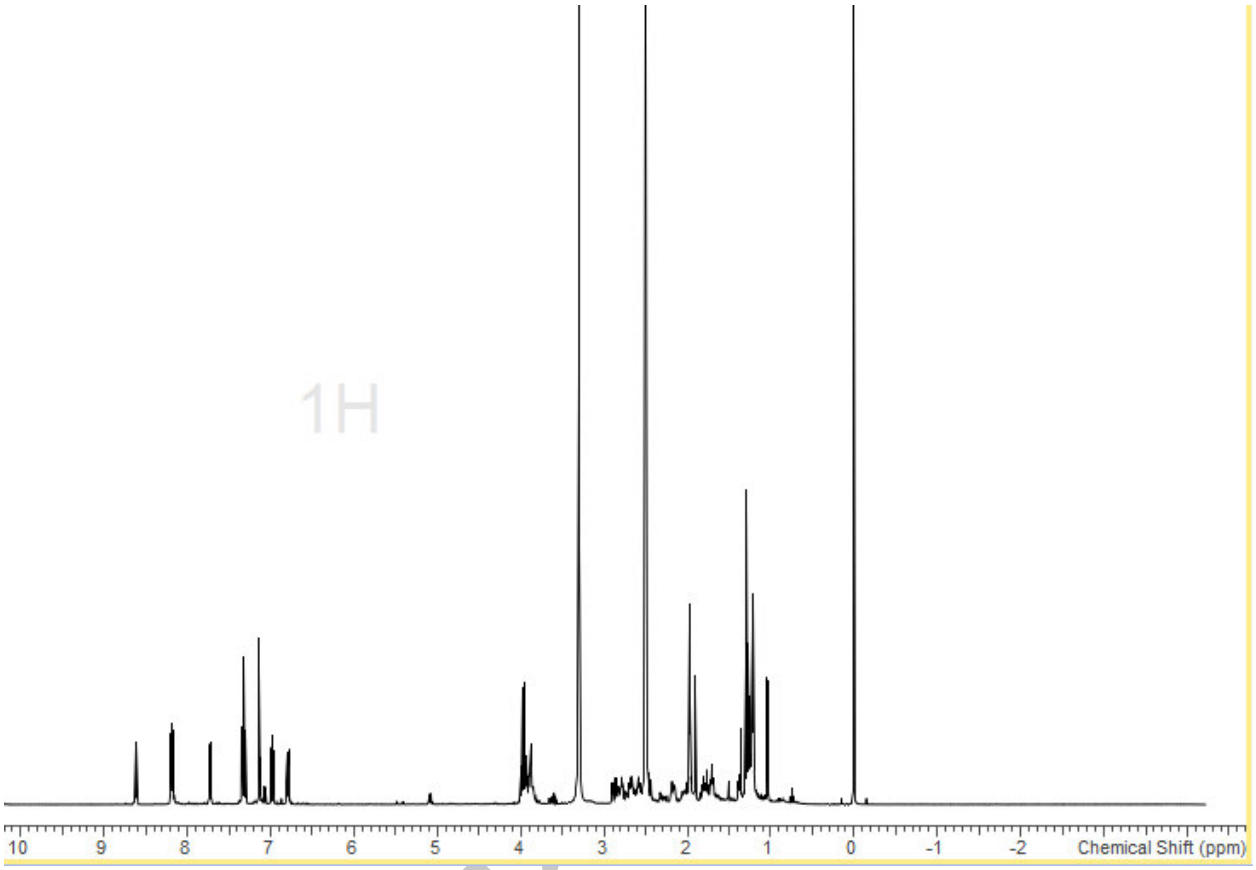
calculated for $C_{23}H_{25}FN_6$ $[M + H]^+$ *m/z* 405.2203, found 405.3. ^{1}H NMR (400 MHz, (CD3)2SO) 8.65 (dd, *J* = 6.7, 1.2 Hz, 1H), 7.35 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.32-7.37 (m, 1H), 7.18 (m, 1H), 6.97 (dd, *J* = 7.2, 6.7 Hz, 1H), 6.78 (br, 1H), 3.84-3.94 (m, 1H, largely obscured by water signal), 3.58 (s, 3H), 2.96-3.05 (m, 1H), 2.35-2.57 (m, 3H, partially obscured by DMSO signal), 2.45 (q, *J* = 7.6 Hz, 2H), 2.19 (s, 3H), 1.96-2.05 (m, 1H), 1.65-1.76 (m, 1H), 1.15 (t, *J* = 7.6 Hz, 3H). HPLC (Method 1): R_t = 1.04 min. Chemical purity > 95%.

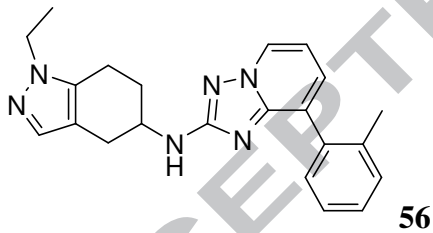




55

*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(4-fluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**55**)*. Prepared according to general procedure C-2 using triazolopyridine **37a** and amine **13a** (1 equiv) by heating at 120-160°C for 9h under microwave irradiation. Yield: 115 mg (obtained as TFA salt, 69%). LCMS (ESI^+) calculated for $C_{21}H_{21}FN_6$ $[M + H]^+$ *m/z* 377.1890, found 377.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) 8.62 (dd, *J* = 6.6, 1.1 Hz, 1H), 8.14-8.20 (m, 2H), 7.73 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.29-7.36 (m, 2H), 7.22 (s, 1H), 6.99 (dd, *J* = 7.4, 6.6 Hz, 1H), 3.99 (q, *J* = 7.3 Hz, 2H), 3.85-3.93 (m, 1H), 2.77-2.93 (m, 2H), 2.62-2.73 (m, 1H), 2.45-2.52 (m, 1H, largely obscured by DMSO signal), 2.13-2.22 (m, 1H), 1.76-1.88 (m, 1H), 1.30 (t, *J* = 7.3 Hz, 3H). HPLC (Method 5): R_t = 0.61 min. Chemical purity 80%.

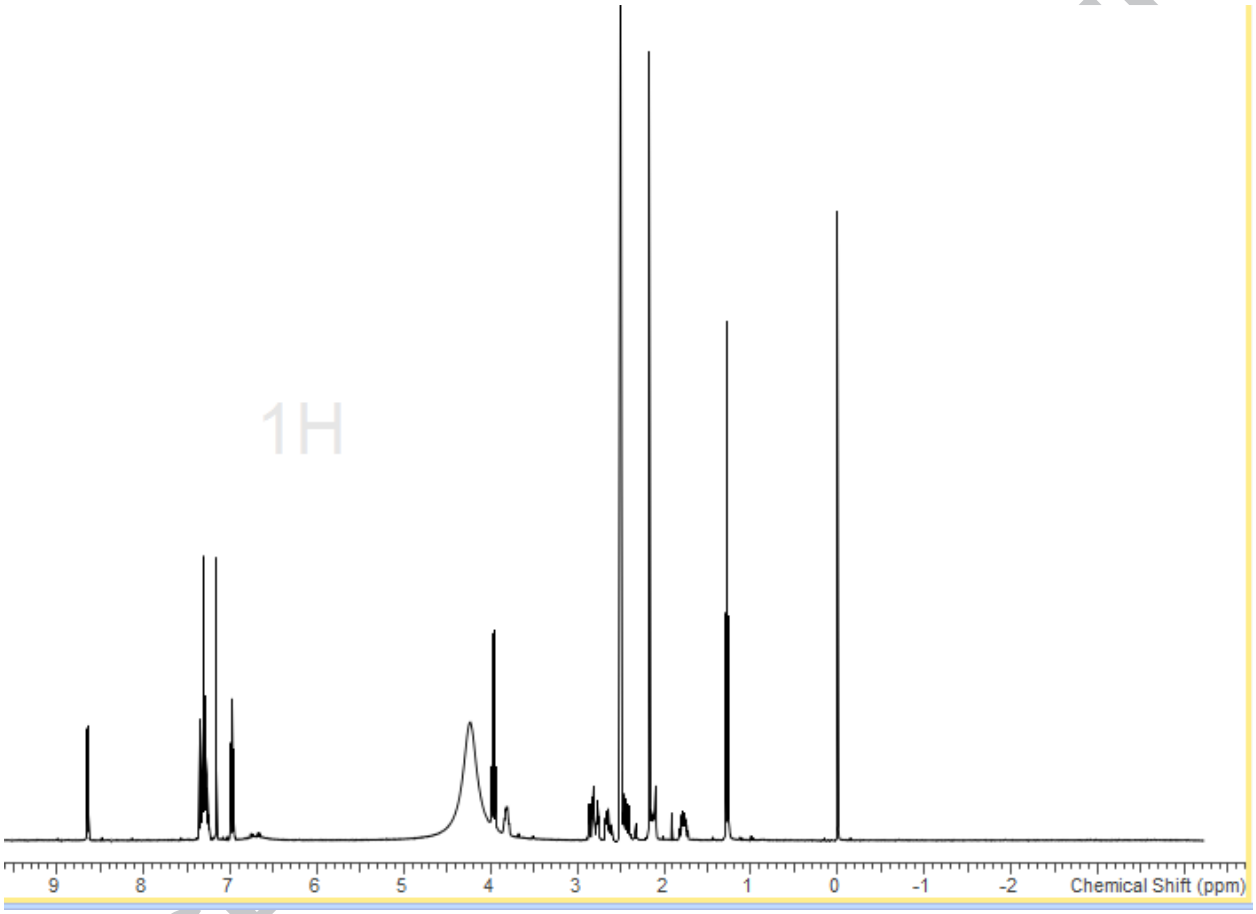


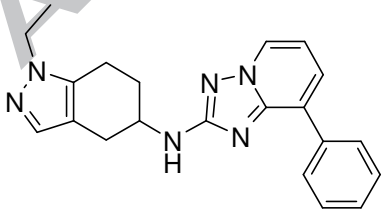


56

*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(2-methyl-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**56**)*. Prepared according to general procedure D-1 using triazolopyridine **39b** and 2-methyl-phenylboronic acid (1.5 equiv) by heating at 80°C for 3h in toluene. Yield: 22 mg (59%). LCMS (ESI^+) calculated for $C_{22}H_{24}N_6$ $[M + H]^+$ *m/z* 373.2141, found 373.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.64 (dd, J = 6.6, 1.1 Hz, 1H), 7.35 (dd, J = 7.3, 1.1 Hz, 1H), 7.23-7.33 (m, 4H), 7.16 (s, 1H), 6.98 (dd, J = 7.3, 6.6 Hz, 1H), 6.69 (br s, 1H), 3.96 (q, J = 7.2 Hz, 2H),

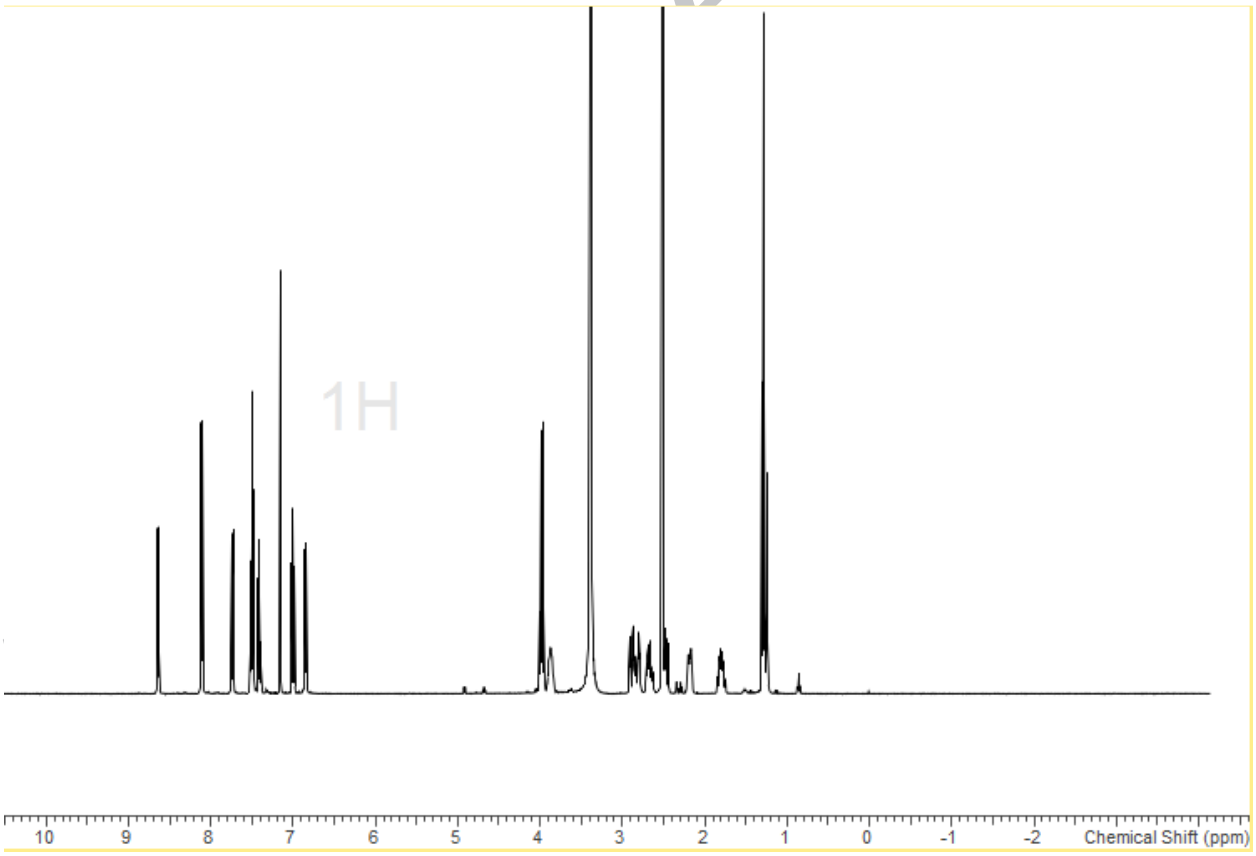
3.77-3.86 (m, 1H), 2.73-2.87 (m, 2H), 2.58-2.69 (m, 1H), 2.39-2.47 (m, 1H), 2.17 (s, 3H), 2.08-2.17 (m, 1H), 1.71-1.83 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H). HPLC (Method 2): R_t = 0.89 min. Chemical purity 95%.

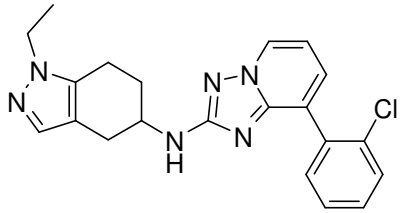




57

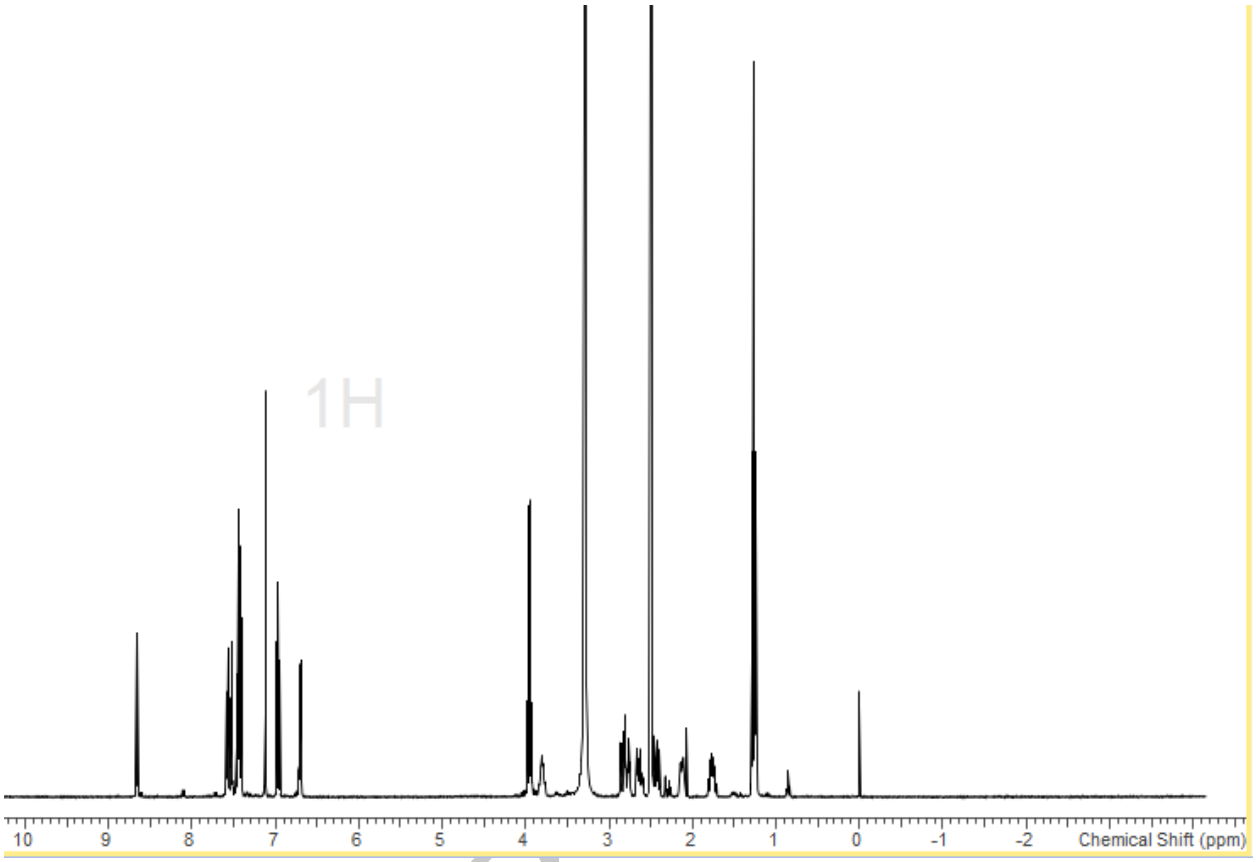
*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-(8-phenyl-[1,2,4]triazolo[1,5-a]pyridine-2-yl)-amine (**57**)*. Prepared according to general procedure D-1 using halo triazolopyridine **39b** and phenylboronic acid. Yield: 26 mg (72%). LCMS (ESI^+) calculated for $C_{21}H_{22}N_6$ $[M + H]^+$ *m/z* 359.1984, found 359.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.64 (dd, J = 6.6, 1.0 Hz, 1H), 8.09-8.13 (m, 2H), 7.74 (dd, J = 7.5, 1.0 Hz, 1H), 7.47-7.53 (m, 2H), 7.38-7.44 (m, 1H), 7.16 (s, 1H), 7.00 (dd, J = 7.5, 6.6 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 3.98 (q, J = 7.2 Hz, 2H), 3.82-3.92 (m, 1H), 2.77-2.93 (m, 2H), 2.60-2.72 (m, 1H), 2.43-2.51 (m, 1H, partially obscured by DMSO signal), 2.13-2.23 (m, 1H), 1.73-1.87 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H). HPLC (Method 9): R_t = 0.64 min. Chemical purity > 95%.

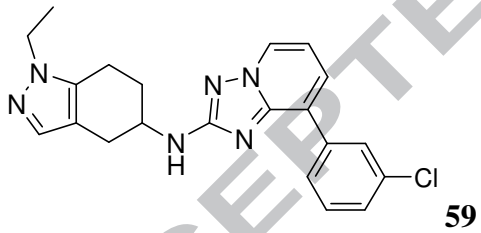




58

*[8-(2-Chloro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**58**)*. Prepared according to general procedure D-1 using halo triazolopyridine **39b** and 2-chloro-phenylboronic acid. Yield: 12 mg (30%). LCMS (ESI^+) calculated for $C_{21}H_{21}ClN_6$ $[M + H]^+$ *m/z* 393.1594, found 393.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.66 (dd, *J* = 6.6, 1.1 Hz, 1H), 7.56-7.60 (m, 1H), 7.55-7.51 (m, 1H), 7.41-7.47 (m, 2H), 7.41 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.12 (s, 1H), 6.97 (dd, *J* =7.3, 6.7 Hz, 1H), 6.70 (d, *J* = 7.4 Hz, 1H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.75-3.85 (m, 1H), 2.73-2.88 (m, 2H), 2.58-2.69 (m, 1H), 2.38-2.47 (m, 1H), 2.08-2.18 (m, 1H), 1.70-1.83 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H). HPLC (Method 8): R_t = 0.83 min. Chemical purity 95%.

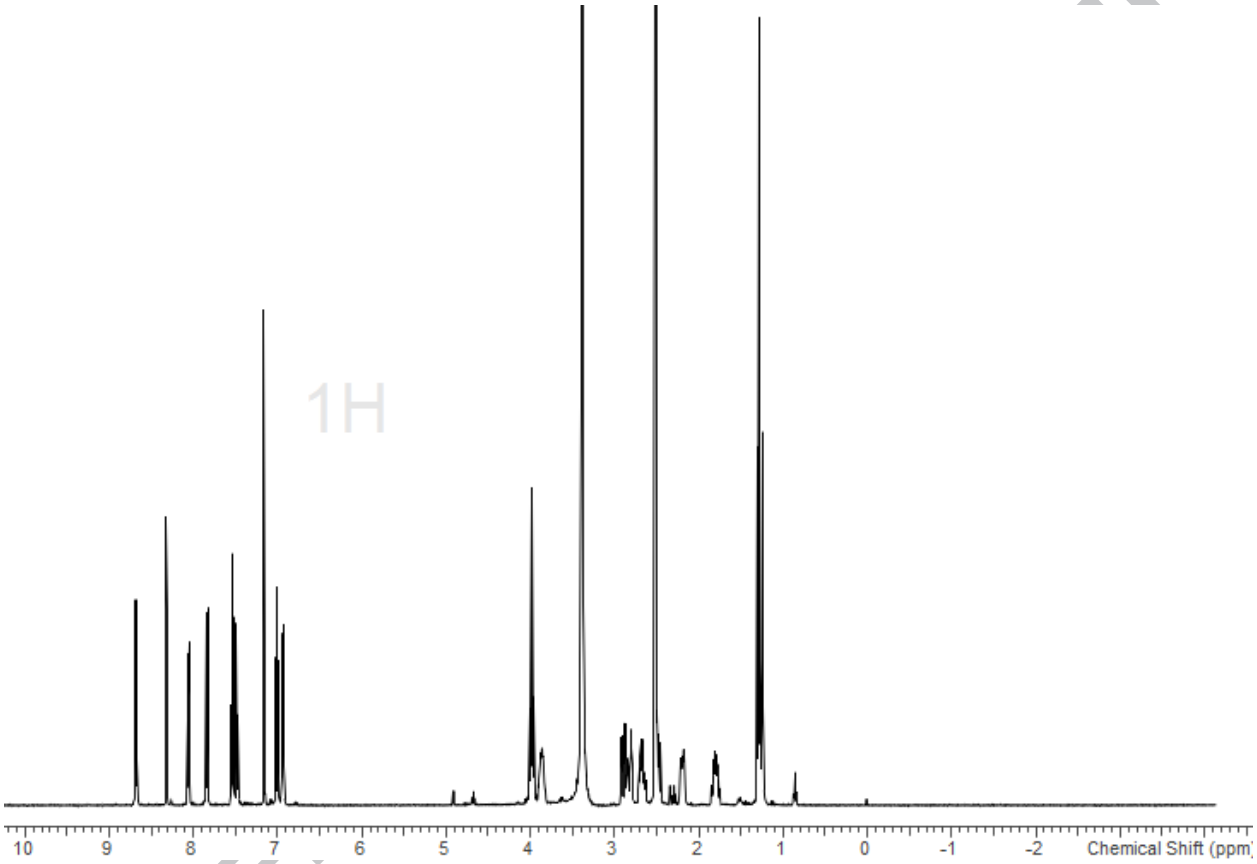


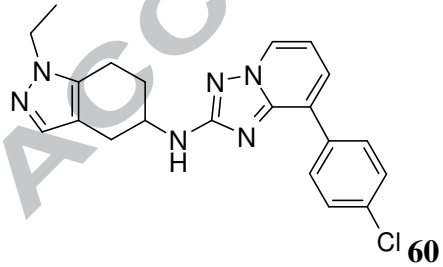


59

*[8-(3-Chloro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**59**)*. Prepared according to general procedure D-1 using halo triazolopyridine **39b** and 3-chloro-phenylboronic acid. Yield: 21 mg (53%). LCMS (ESI^+) calculated for $C_{21}H_{21}ClN_6$ $[M + H]^+$ *m/z* 393.1594, found 393.3. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.68 (d, J = 6.7, 0.9 Hz, 1H), 8.31 (m, 1H), 8.06 (m, 1H), 7.83 (dd, J = 7.5, 0.9 Hz, 1H), 7.54 (m, 1H), 7.46-7.50 (m, 1H), 7.15 (s, 1H), 7.00 (t, J = 7.5, 6.7 Hz, 1H), 6.93 (d, J = 7.4 Hz,

1H),3.97 (q, *J* = 7.1 Hz, 2H), 3.80-3.91 (m, 1H), 2.76-2.93 (m, 2H), 2.60-2.71 (m, 1H), 2.43-2.50 (m, 1H), 2.14-2.23 (m, 1H), 1.73-1.86 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). HPLC (Method 9): R_t = 0.75 min. Chemical purity > 95%.

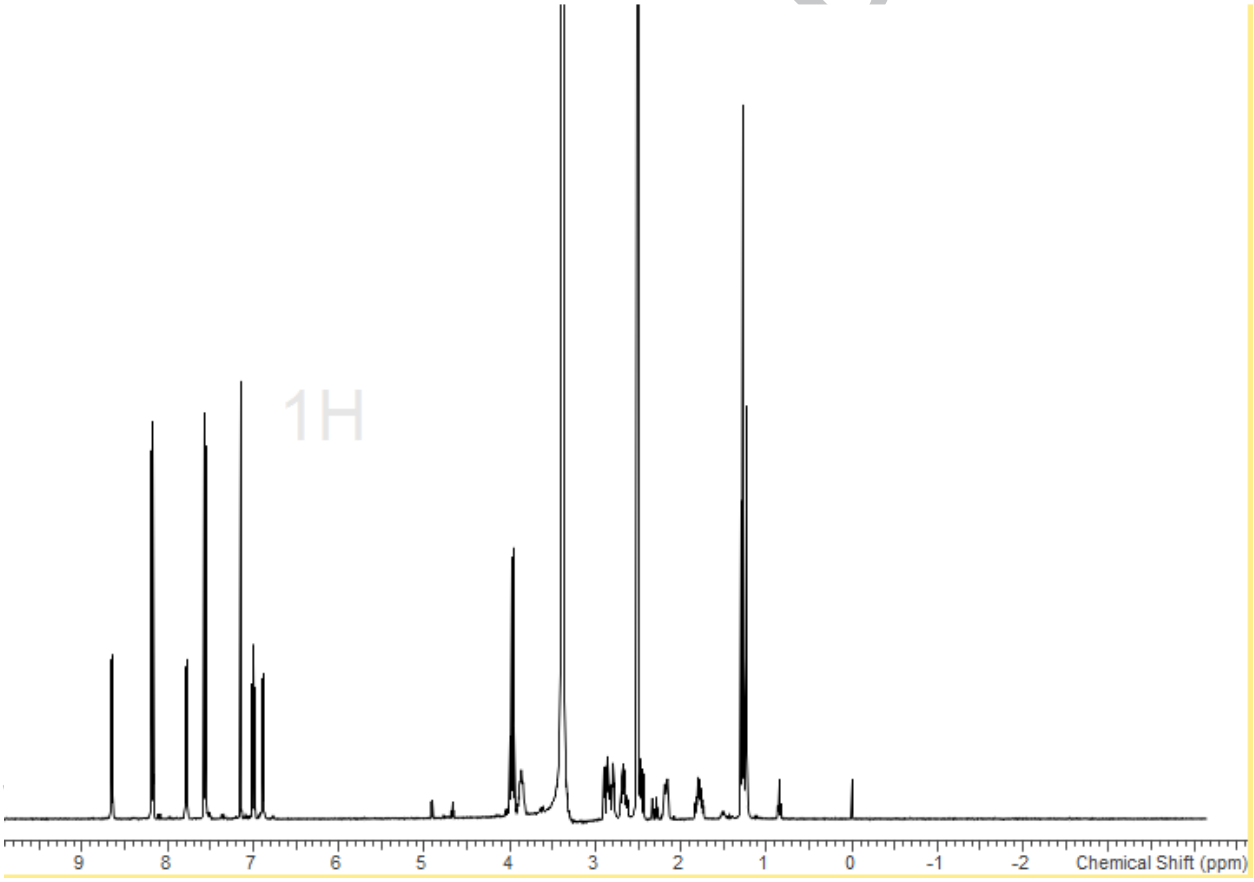


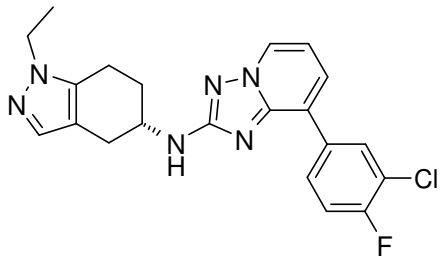


60

*[8-(4-Chloro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**60**)*. Prepared according to general procedure D-1 using halo

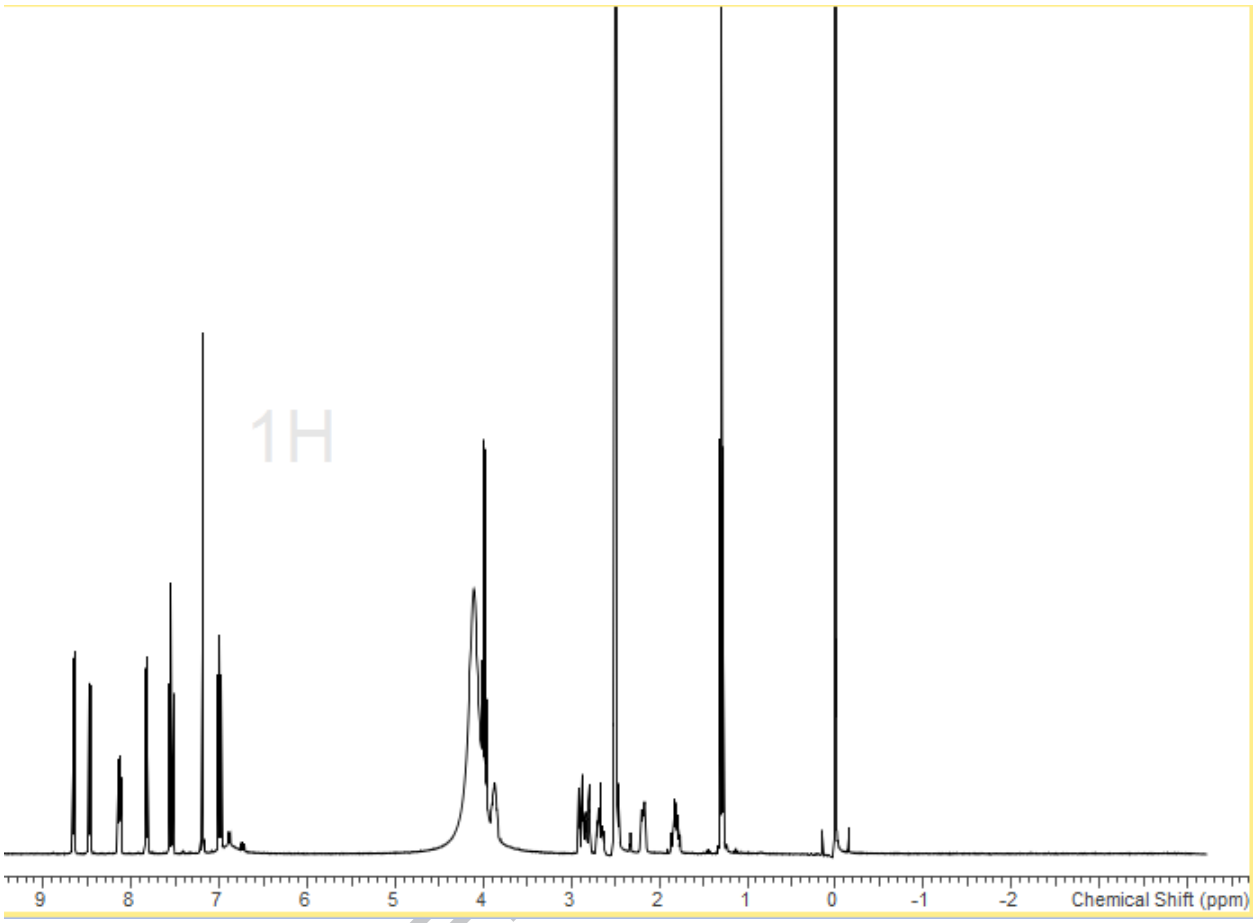
triazolopyridine **39b** and 4-chloro-phenylboronic acid. Yield: 16 mg (41%). LCMS (ESI^+) calculated for $C_{21}H_{21}ClN_6$ $[M + H]^+$ *m/z* 393.1594, found 393.3. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.65 (dd, J = 6.6, 1.0 Hz, 1H), 8.16-8.20 (m, 2H), 7.78 (dd, J = 7.5, 1.0 Hz, 1H), 7.54-7.58 (m, 2H), 7.15 (s, 1H), 7.00 (dd, J = 7.5, 6.6, 1H), 6.89 (d, J = 7.6 Hz, 1H), 3.97 (q, J = 7.3 Hz, 2H), 3.81-3.92 (m, 1H), 2.76-2.91 (m, 2H), 2.61-2.72 (m, 1H), 2.42-2.49 (m, 1H), 2.13-2.22 (m, 1H), 1.72-1.84 (m, 1H), 1.28 (t, J = 7.3 Hz, 3H). HPLC (Method 9): R_t = 0.75 min. Chemical purity > 95%.

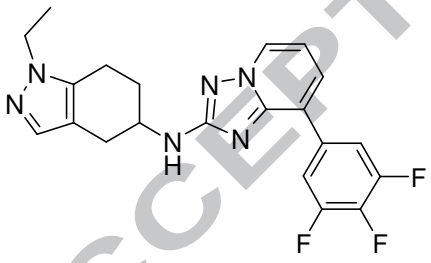




ent2-61

*(S)-[8-(3-Chloro-4-fluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**ent2-61**)*. Prepared according to general procedure D-2 using chiral halo triazolopyridine ***ent2*-39a** and 3-chloro-4-fluoro-phenylboronic acid. Yield: 108 mg (71%). HRMS (ESI^+) calculated for $C_{21}H_{20}ClFN_6$ $[M+H]^+$ *m/z* 411.1500, found 411.1502. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.65 (dd, J = 6.6, 1.0 Hz, 1H), 8.47 (dd, J = 7.4, 2.3 Hz, 1H), 8.14 (m, 1H), 7.82 (dd, J = 7.5, 1.0 Hz, 1H), 7.54 (m, 1H), 7.14 (s, 1H), 6.99 (dd, J = 7.5, 6.6 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 3.81-3.91 (m, 1H), 2.85-2.93 (m, 1H), 2.76-2.85 (m , 1H), 2.60-2.71 (m, 1H), 2.44-2.52 (m, 1H, partially obscured by DMSO signal), 2.14-2.23 (m, 1H), 1.75-1.86 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H). HPLC (Method 5): R_t = 0.65 min. Enantiomeric purity (method 14): 97.9% ee. Specific optical rotation: $[\alpha]^{20}_D$ = -7.5° (*c* 0.4, MeOH). Chemical purity 95%.

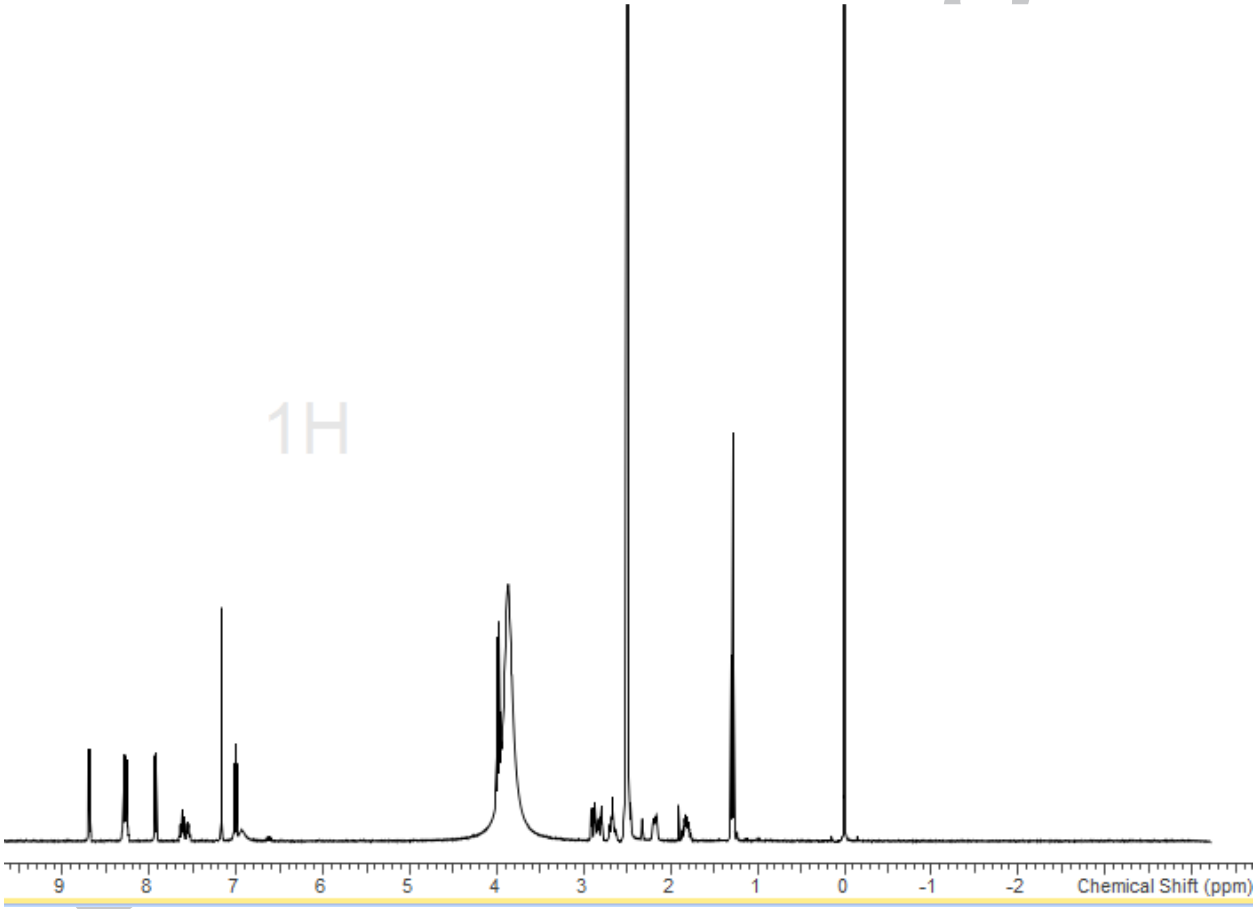


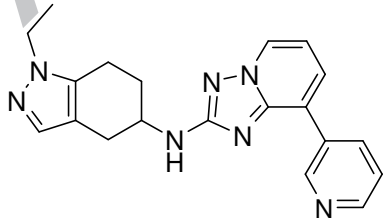


62

*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(3,4,5-trifluoro-phenyl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**62**)*. Prepared according to general procedure D-2 using halo triazolopyridine **39a** and 3,4,5-trifluoro-phenylboronic acid using bis(triphenylphosphine)palladium(II) chloride as catalyst. Yield: 14 mg (19%). LCMS (ESI^+) calculated for $C_{21}H_{19}F_3N_6$ $[M + H]^+$ *m/z* 413.1702, found 413.1. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ

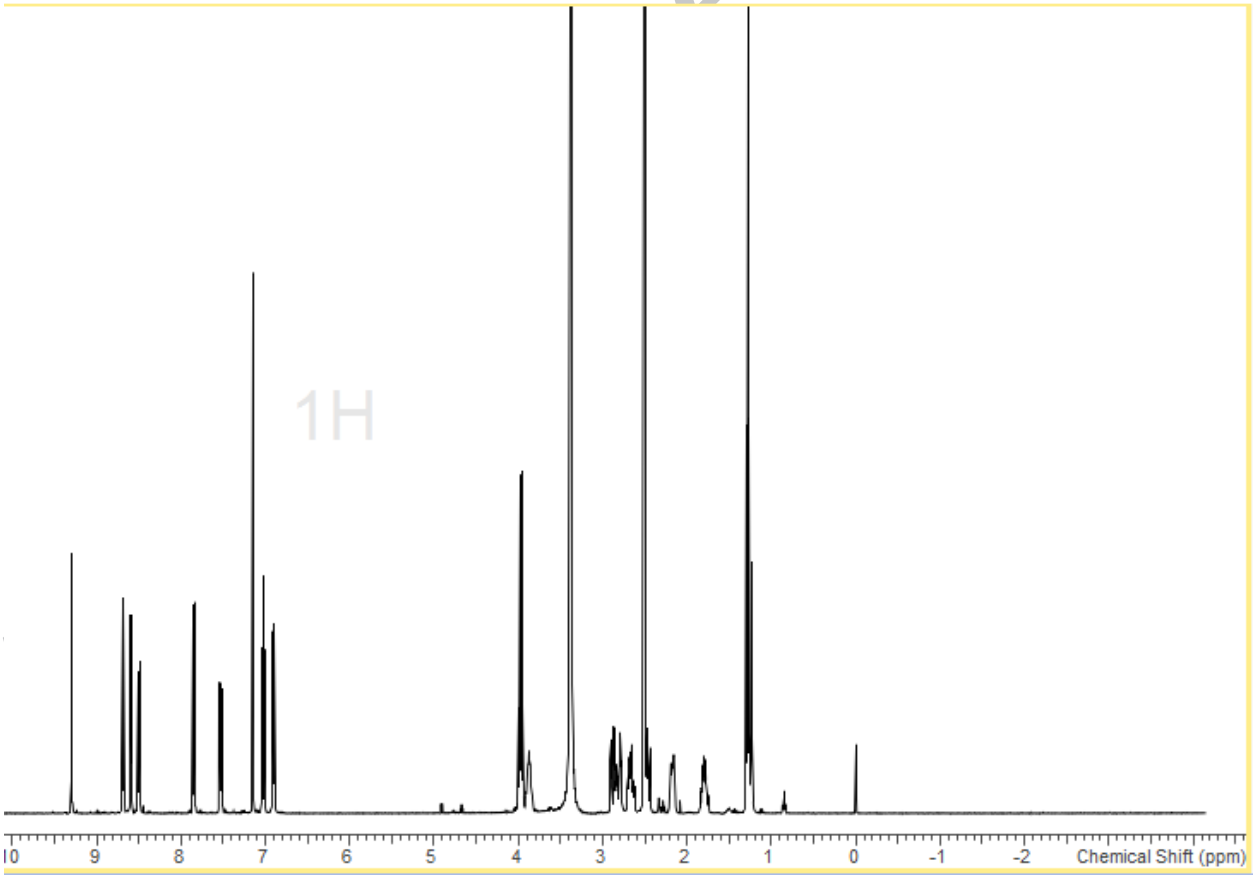
8.69 (dd, *J* = 6.6, 0.9 Hz, 1H), 8.23-8.32 (m, 2H), 7.92 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.15 (s, 1H), 7.01 (dd, *J* = 7.4, 6.8 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.82-3.92 (m, 1H), 2.85-2.92 (m, 1H), 2.77-2.85 (m, 1H), 2.61-2.71 (m, 1H), 2.44-2.54 (m, 1H), 2.14-2.22 (m, 1H), 1.76-1.87 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H). HPLC (Method 3): R_t = 0.67 min. Chemical purity > 95%.

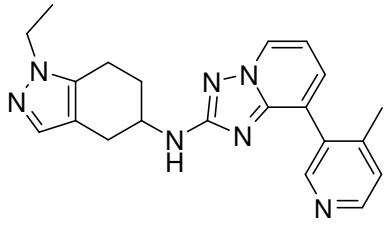




63

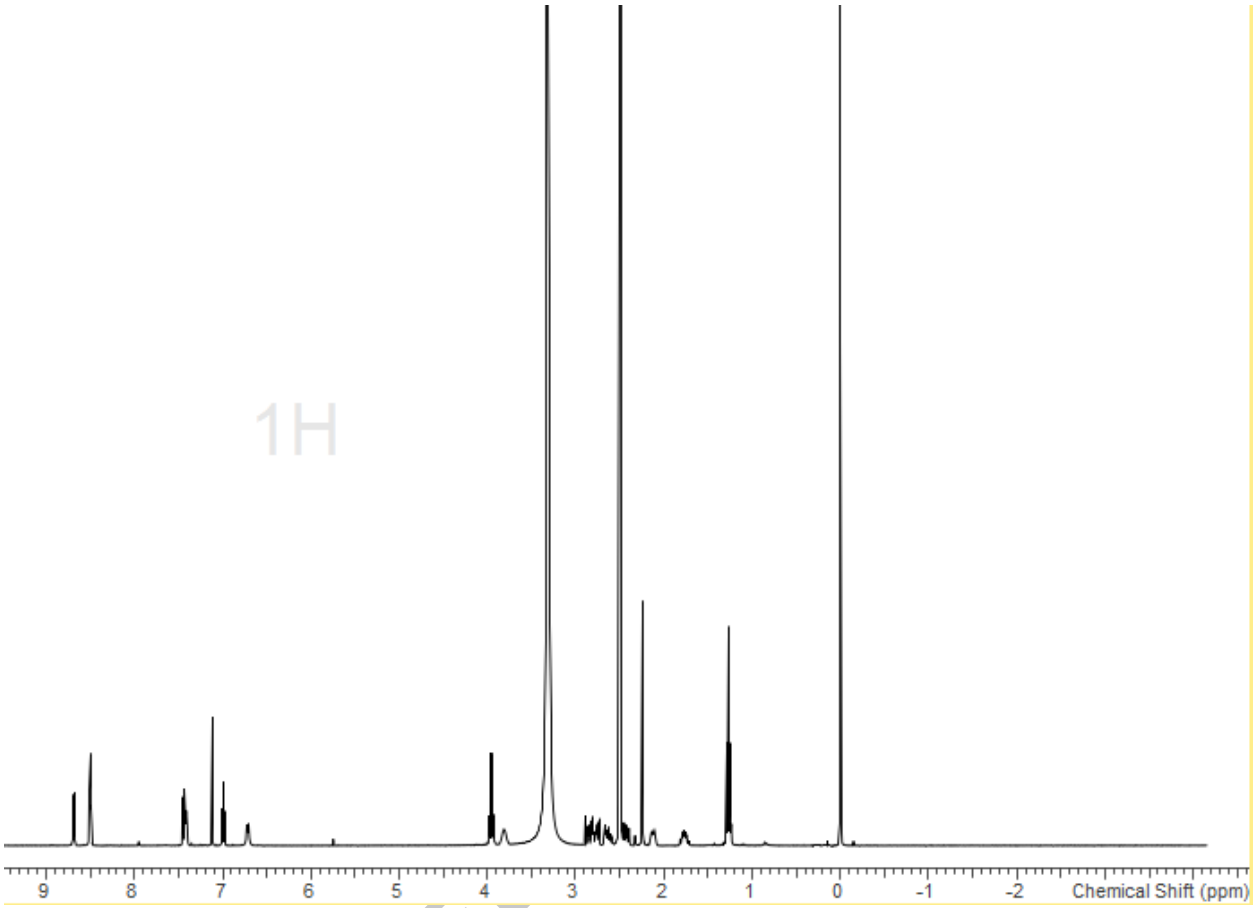
*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-(8-pyridin-3-yl-[1,2,4]triazolo[1,5-a]pyridine-2-yl)-amine (**63**)*. Prepared according to general procedure D-1 using halo triazolopyridine **39b** and pyridine-3-ylboronic acid. Yield: 26 mg (72%). LCMS (ESI^+) calculated for $C_{20}H_{21}N_7$ $[M + H]^+$ *m/z* 360.1937, found 360.3. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 9.30 (d, J = 2.1 Hz, 1H), 8.69 (dd, J = 6.6, 0.9 Hz, 1H), 8.59 (dd, J = 4.8, 1.7 Hz, 1H), 8.50 (m, 1H), 7.85 (dd, J = 7.4, 0.9 Hz, 1H), 7.53 (dd, J = 8.0, 4.8 Hz, 1H), 7.15 (s, 1H), 7.03 (dd, J = 7.4, 6.6 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 3.97 (q, J = 7.3 Hz, 2H), 3.82-3.92 (m, 1H), 2.76-2.92 (m, 2H), 2.61-2.71 (m, 1H), 2.44-2.50 (m, 1H), 2.12-2.20 (m, 1H), 1.73-1.86 (m, 1H), 1.28 (t, J = 7.3 Hz, 3H). HPLC (Method 9): R_t = 0.39 min. Chemical purity > 95%.

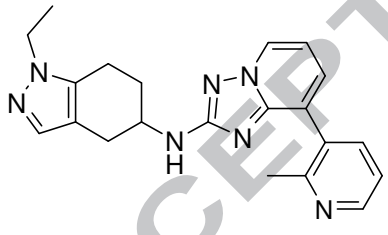




64

*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(4-methyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**64**)*. Prepared according to general procedure D-2 using halo triazolopyridine **39a** and 4-methyl-pyridin-3-ylboronic acid pinacol ester. Yield: 12 mg (12%). LCMS (ESI^+) calculated for $C_{21}H_{23}N_7$ $[M + H]^+$ *m/z* 374.2, found 374.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.69 (dd, J = 6.7, 1.0 Hz, 1H), 8.48-8.52 (m, 2H), 7.44 (dd, J = 7.3, 1.0 Hz, 1H), 7.39-7.43 (m, 1H), 7.12 (s, 1H), 6.99 (dd, J = 7.3, 6.7 Hz, 1H), 6.72 (d, J = 7.3 Hz, 1H), 3.95 (q, J = 7.2 Hz, 2H), 3.75-3.87 (m, 1H), 2.72-2.90 (m, 2H), 2.56-2.69 (m, 1H), 2.38-2.47 (m, 1H), 2.24 (s, 3H), 2.07-2.17 (m, 1H), 1.71-1.83 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H). HPLC (Method 5): R_t = 0.35 min. Chemical purity > 95%.

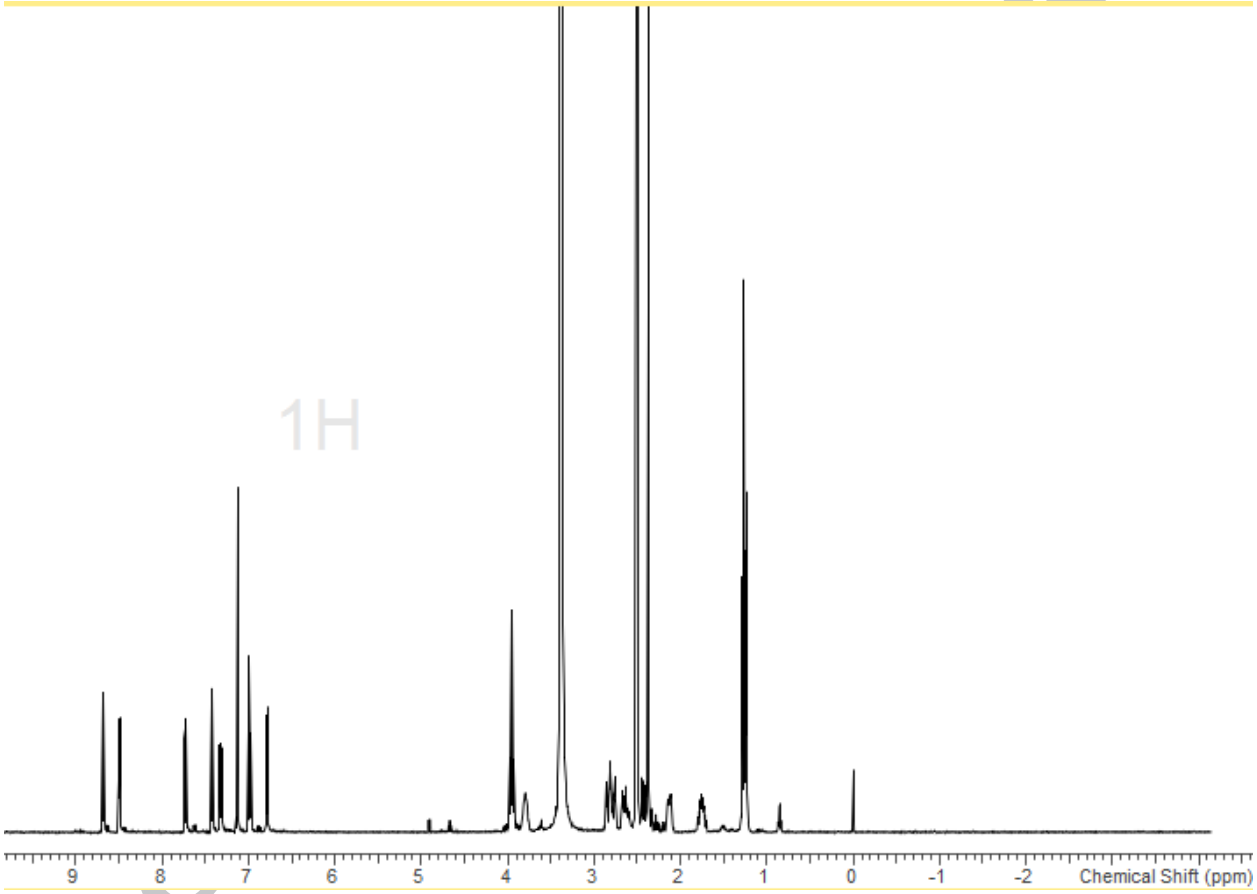


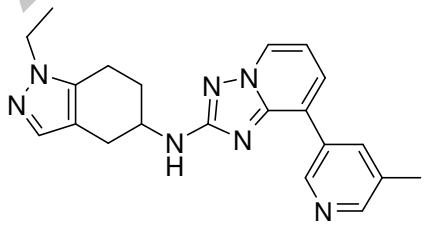


65

*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(2-methyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**65**)*. Prepared according to general procedure D-1 using halo triazolopyridine **39b** and 2-methyl-pyridine-3-ylboronic acid. Yield: 13 mg (34%). LCMS (ESI^+) calculated for $C_{21}H_{23}N_7$ $[M + H]^+$ *m/z* 374.2093, found 374.3. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.68 (d, J = 6.7, 1.0 Hz, 1H), 8.50 (dd, J = 4.8, 1.6 Hz, 1H), 7.73 (dd, J = 7.7, 1.6 Hz, 1H), 7.43

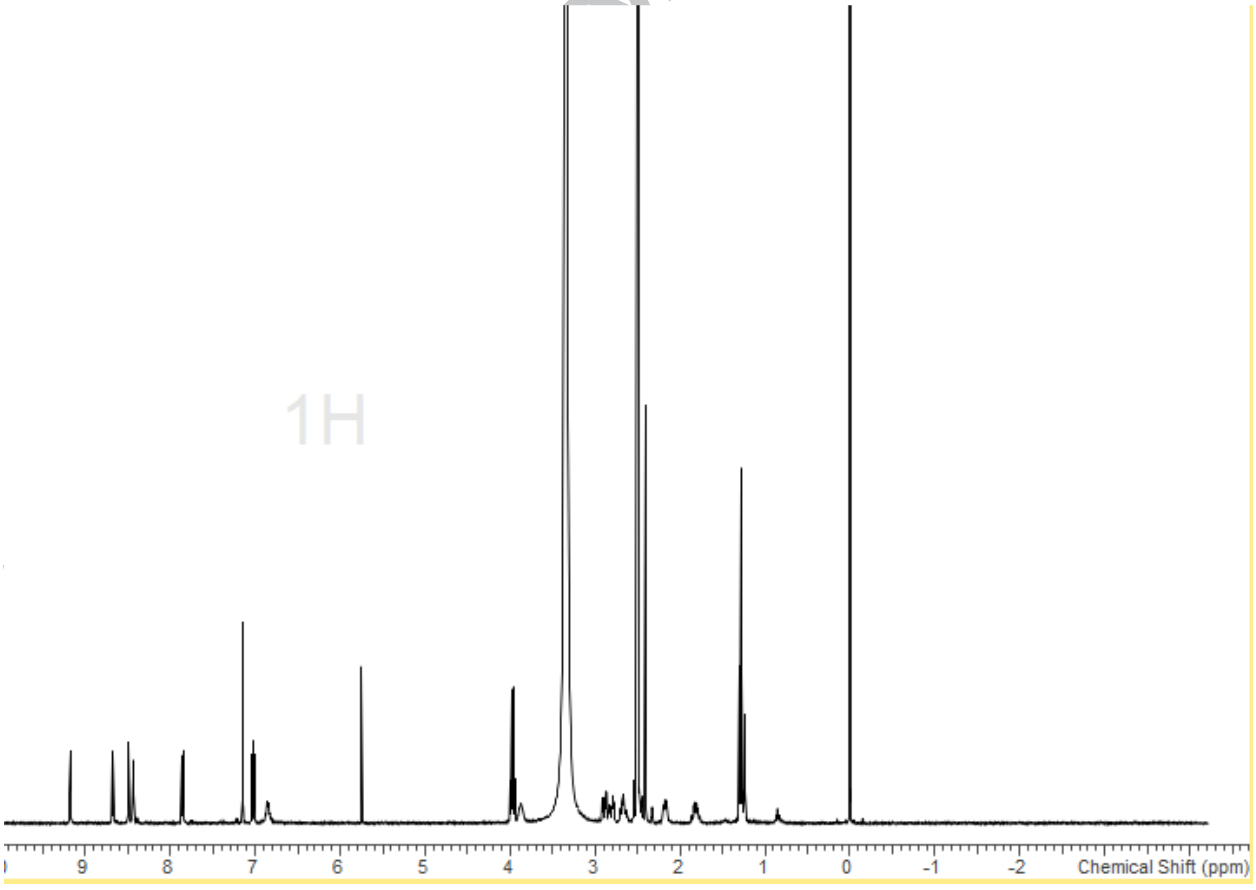
(dd, *J* =7.3, 1.0, 1H), 7.32 (dd, *J* = 7.7, 4.9 Hz, 1H), 7.13 (s, 1H), 6.99 (dd, *J* = 7.7.3, 6.7 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.74-3.85 (m, 1H), 2.73-2.87 (m, 2H), 2.57-2.69 (m, 1H), 2.38-2.46 (m, 1H), 2.37 (s, 3H), 2.08-2.18 (m, 1H), 1.69-1.81 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). HPLC (Method 9): R_t = 0.38 min. Chemical purity 90%.

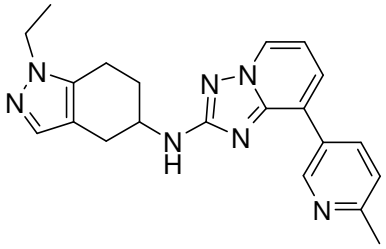




66

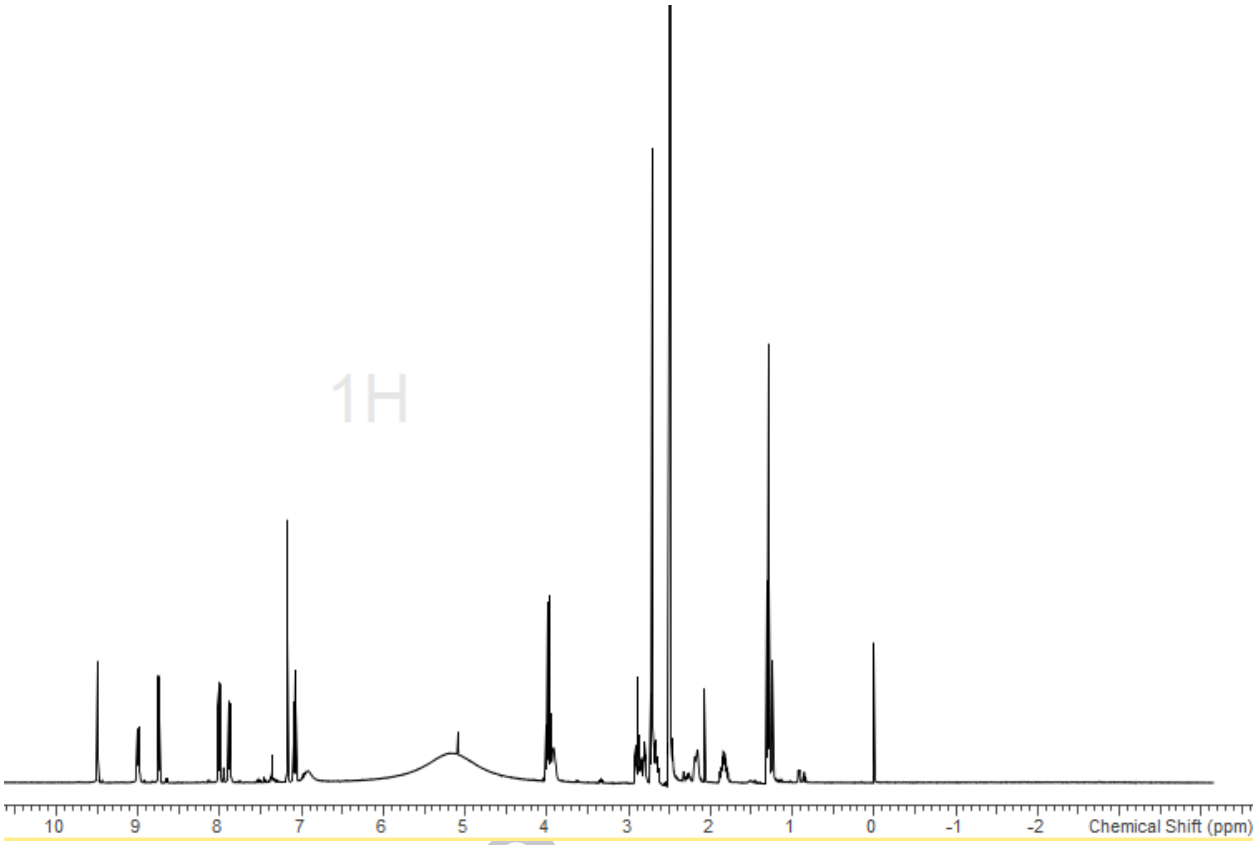
*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(5-methyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**66**)*. Prepared according to general procedure D-2 using halo triazolopyridine **39a** and 5-methyl-pyridin-3-ylboronic acid (1.5 equiv). Yield: 4 mg (11%). LCMS (ESI$^+$) calculated for $C_{21}H_{23}N_7$ $[M + H]^+$ *m/z* 374.2093, found 374.2. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.18 (d, J = 1.8 Hz, 1H), 8.68 (dd, J = 6.6, 1.0 Hz, 1H), 8.50-8.48 (m, 1H), 8.45-8.43 (m, 1H), 7.85 (dd, J = 7.5, 1.1 Hz, 1H), 7.15 (s, 1H), 7.02 (dd, J = 7.5, 6.7 Hz, 1H), 6.85 (br s, 1H), 3.97 (q, J = 7.3 Hz, 2H), 3.92-3.82 (m, 1H), 2.85-2.92 (m, 1H), 2.76-2.85 (m, 1H), 2.61-2.72 (m, 1H), 2.45-2.55 (m, 1H, partially obscured by DMSO signal), 2.41 (s, 3H), 2.13-2.21 (m, 1H), 1.75-1.87 (m, 1H), 1.29 (t, J = 7.3 Hz, 3H). HPLC (Method 5): R_t = 0.36 min. Chemical purity 95%.

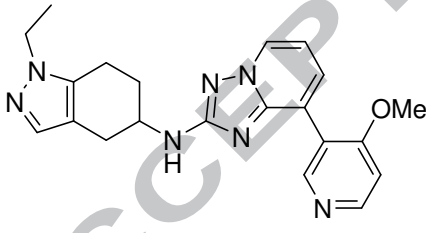




67

*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(6-methyl-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**67**)*. Prepared according to general procedure D-1 using chloro triazolopyridine **39b** and 6-methyl-pyridin-3-ylboronic acid (1.5 equiv). Yield: 36 mg (98%). LCMS (ESI^+) calculated for $C_{21}H_{23}N_7$ $[M + H]^+$ *m/z* 374.2093, found 374.3. ^1H NMR (400 MHz, $(CD_3)_2SO$) 9.50 (d, J = 1.5 Hz, 1H), 9.00 (m, 1H), 8.74 (dd, J = 6.6, 0.9 Hz, 1H), 8.00 (dd, J = 7.6, 0.8 Hz, 1H), 7.88 (m, 1H), 7.17 (s, 1H), 7.08 (dd, J = 7.4, 6.6 Hz, 1H), 6.92 (br, 1H), 3.98 (q, J = 7.2 Hz, 2H), 3.87-3.96 (m, 1H), 2.78-2.94 (m, 2H), 2.62-2.73 (m, 1H), 2.71 (s, 3H), 2.44-2.52 (m, 1H, largely obscured by DMSO signal), 2.13-2.33 (m, 1H), 1.78-1.89 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H). HPLC (Method 10): R_t = 0.74 min. Chemical purity 90%.

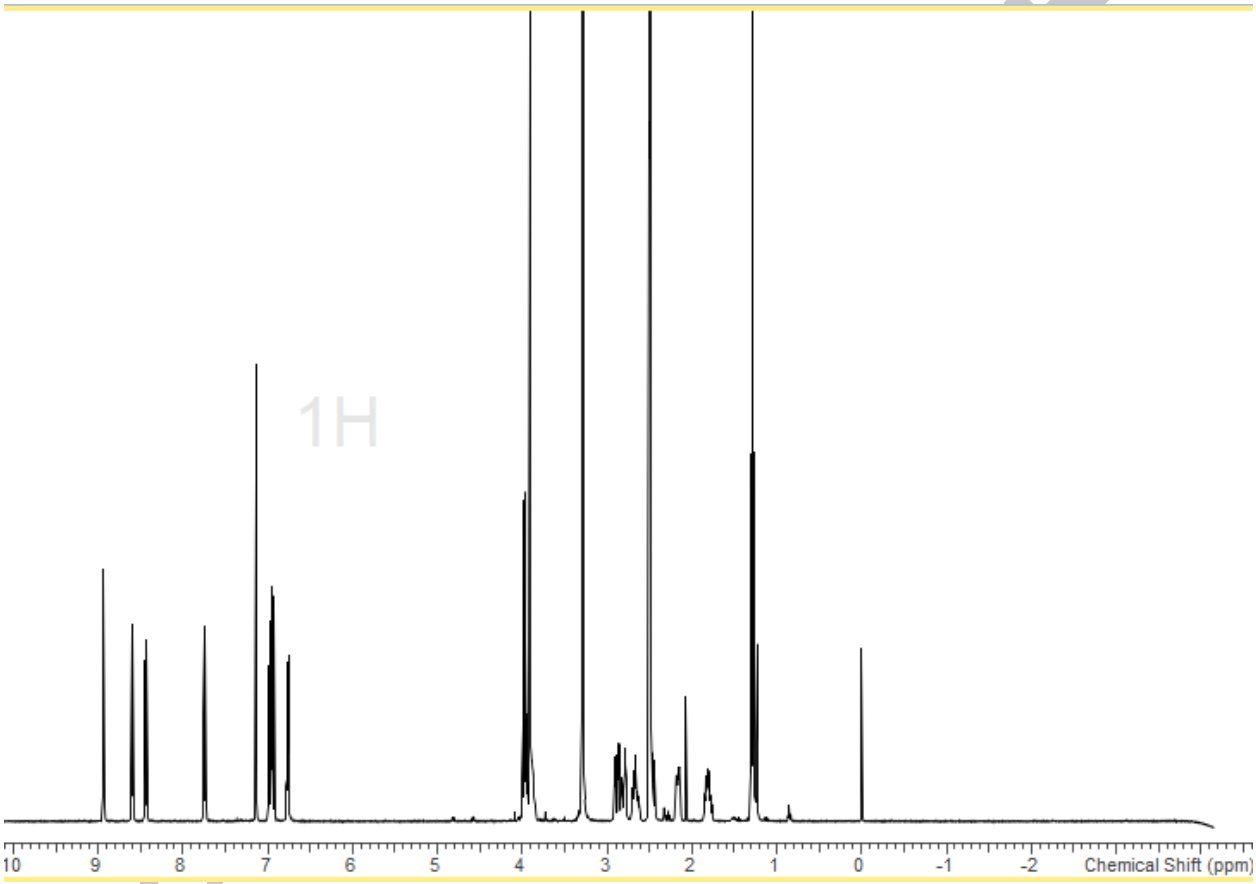


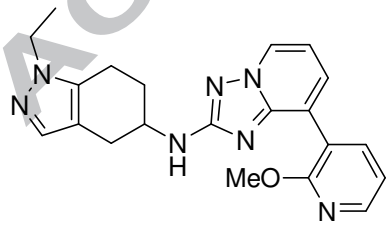


68

*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(4-methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**68**)*. Prepared according to general procedure D-1 using halo triazolopyridine **39b** and 4-methoxy-pyridine-3-ylboronic acid. Yield: 26 mg (66%). LCMS (ESI^+) calculated for $C_{21}H_{23}N_7O$ $[M + H]^+$ *m/z* 390.2042, found 390.123. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.94 (dd, J = 2.4, 0.6 Hz, 1H), 8.60 (dd, J = 6.7, 1.1 Hz, 1H), 8.44 (dd, J = 8.7, 2.4

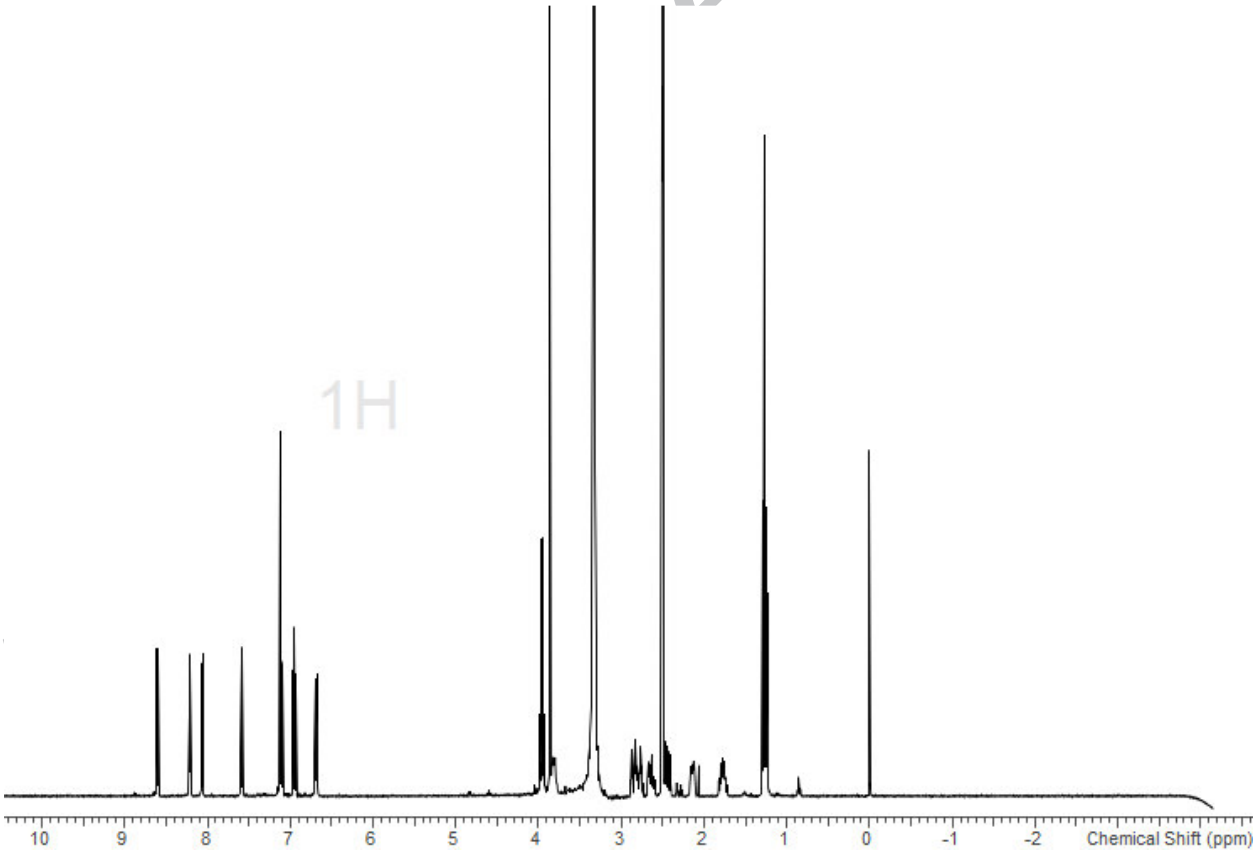
Hz, 1H), 7.74 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.14 (s, 1H), 6.98 (dd, *J* = 7.4, 6.7 Hz, 1H), 6.94 (dd, *J* = 8.7, 0.6 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 3.97 (q, *J* = 7.3 Hz, 2H), 3.84-3.93 (m, 1H), 3.91 (s, 3H), 2.76-2.92 (m, 2H), 2.60-2.72 (m, 1H), 2.43-2.49 (m, 1H), 2.12-2.21 (m, 1H), 1.75-1.87 (m, 1H), 1.29 (t, *J* = 7.3 Hz, 3H). HPLC (Method 10): R_t = 0.96 min. Chemical purity > 95%.

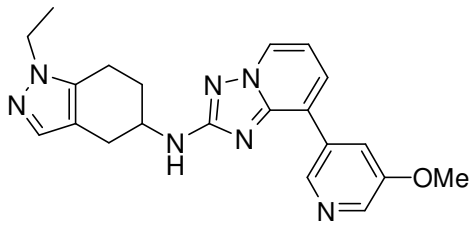




69

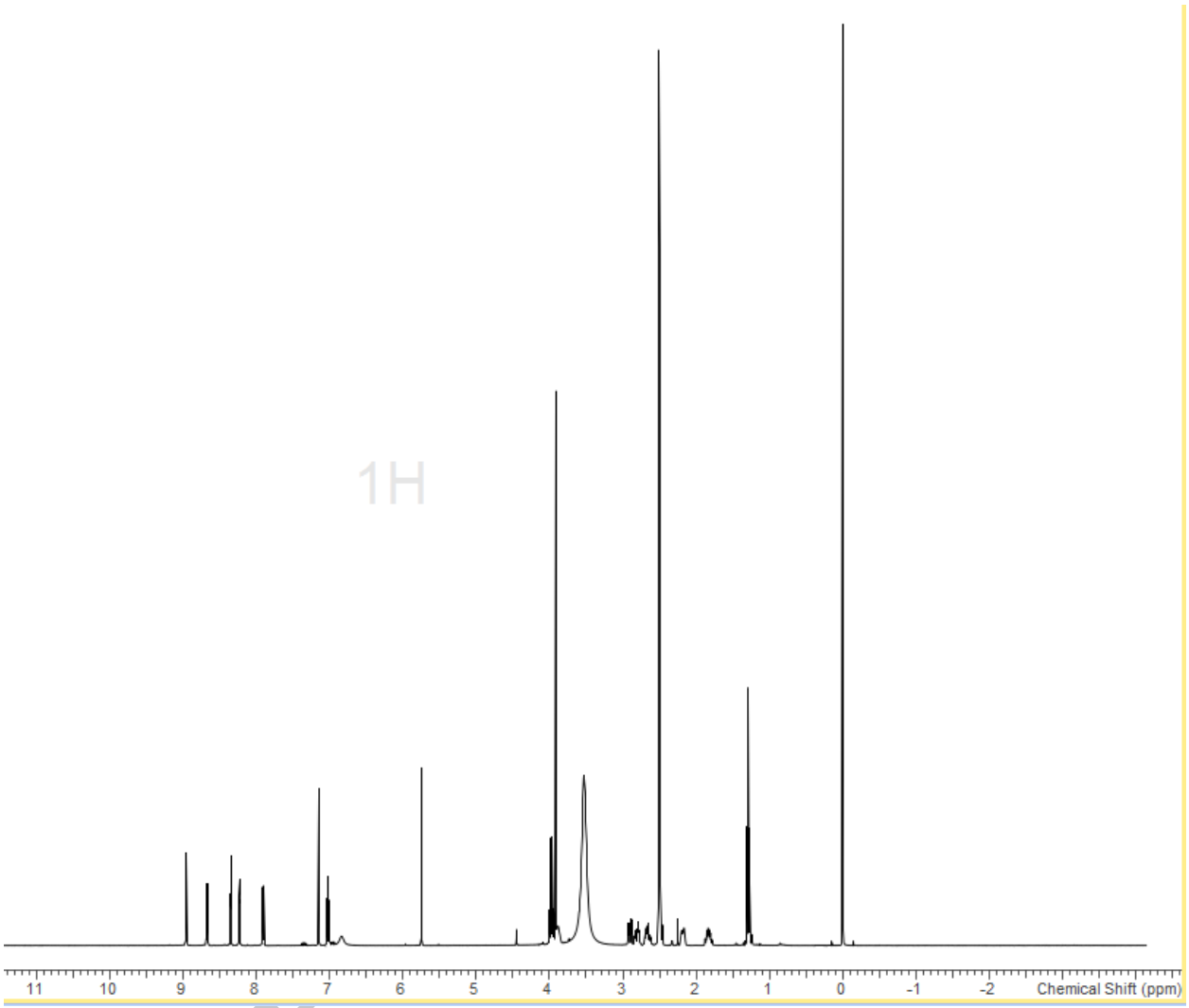
*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(2-methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**69**)*. Prepared according to general procedure D-1 using halo triazolopyridine **39b** and 2-methoxy-pyridine-3-ylboronic acid. Yield: 21 mg (53%). LCMS (ESI^+) calculated for $C_{21}H_{23}N_7O$ $[M + H]^+$ *m/z* 390.2042, found 390.1278. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.60 (dd, J = 6.7, 1.1 Hz, 1H), 8.21 (dd, J = 4.9, 1.9 Hz, 1H), 8.06 (dd, J = 7.4, 1.9 Hz, 1H), 7.58 (dd, J = 7.4, 1.1 Hz, 1H), 7.13 (s, 1H), 7.10 (dd, J = 7.4, 4.9 Hz, 1H), 6.95 (dd, J = 7.4, 6.7 Hz, 1H), 6.69 (d, J = 7.3 Hz, 1H), 3.96 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 3.78-3.85 (m, 1H), 2.73-2.90 (m, 2H), 2.58-2.69 (m, 1H), 2.39-2.48 (m, 1H), 2.09-2.19 (m, 1H), 1.71-1.83 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H). HPLC (Method 10): R_t = 0.96 min. Chemical purity 90%.

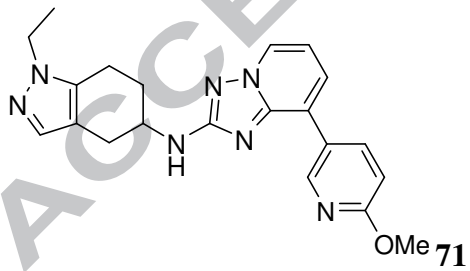




70

*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(5-methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**70**)*. Prepared according to general procedure D-2 using halo triazolopyridine **39a** and 5-methoxy-pyridin-3-ylboronic acid (1.7 equiv). Yield: 43 mg (65%). LCMS (ESI^+) calculated for $C_{21}H_{23}N_7O$ $[M + H]^+$ *m/z* 390.2042, found 390.2. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.96 (d, J = 1.6 Hz, 1H), 8.68 (dd, J = 6.7, 0.6 Hz, 1H), 8.35 (m, 1H), 8.23 (m, 1H), 7.92 (dd, J = 7.5, 0.6 Hz, 1H), 7.15 (s, 1H), 7.02 (dd, J = 7.5, 6.7 Hz, 1H), 6.84 (br s, 1H), 3.97 (q, J = 7.3 Hz, 2H), 3.92 (s, 3H), 3.84-3.92 (m, 1H), 2.86-2.94 (m, 1H), 2.76-2.86 (m, 1H), 2.60-2.72 (m, 1H), 2.45-2.52 (m, 1H, partially obscured by DMSO signal), 2.13-2.22 (m, 1H), 1.77-1.88 (m, 1H), 1.29 (t, J = 7.3 Hz, 3H). HPLC (Method 5): R_t = 0.40 min. Chemical purity 95%.

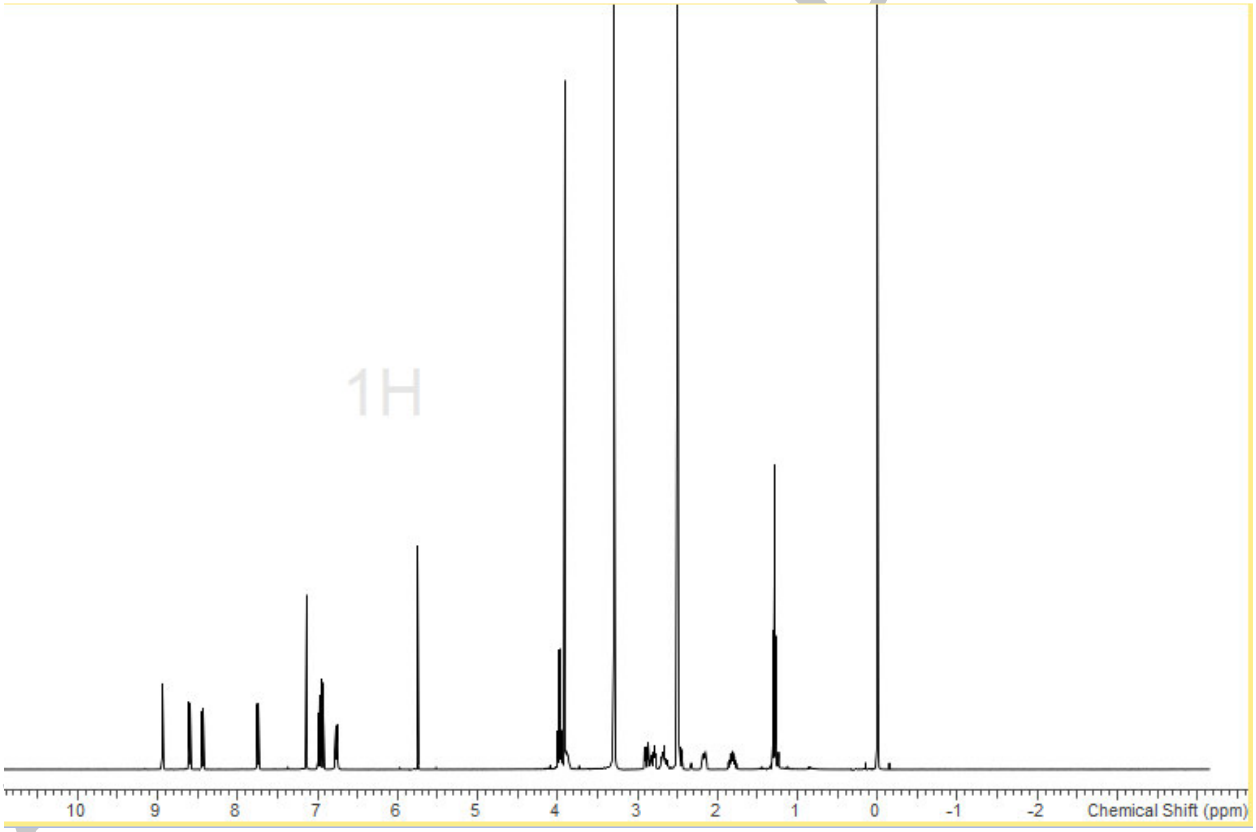


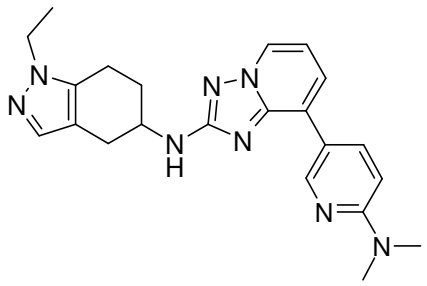


71

*(1-Ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-[8-(6-methoxy-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-amine (**71**)*. Prepared according to general procedure D-2 using halo triazolopyridine **39a** and 6-methoxy-pyridin-3-ylboronic acid (1.7 equiv). Yield: 29 mg (56%).

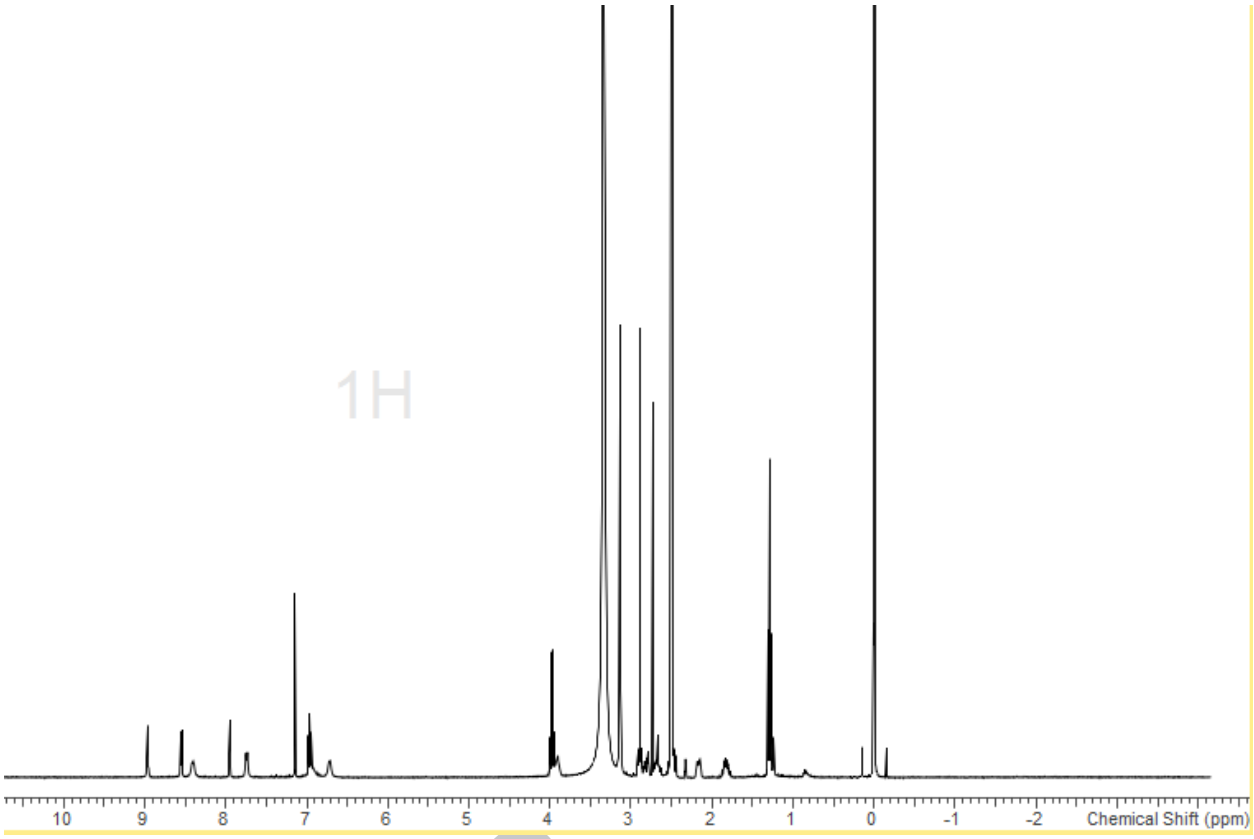
LCMS (ESI$^+$) calculated for $C_{21}H_{23}N_7O$ $[M + H]^+$ *m/z* 390.2042, found 390.3. ^{1}H NMR (400 MHz, (CD3)2SO) δ 8.94 (d, *J* = 2.4 Hz, 1H), 8.60 (dd, *J* = 6.6, 1.0 Hz, 1H), 8.44 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.74 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.14 (s, 1H), 6.98 (dd, *J* = 7.4, 6.6 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.91 (s, 3H), 3.84-3.93 (m, 1H), 2.85-2.93 (m, 1H), 2.76-2.85 (m, 1H), 2.61-2.72 (m, 1H), 2.43-2.52 (m, 1H, partly obscured by DMSO signal), 2.12-2.21 (m, 1H), 1.75-1.87 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H). HPLC (Method 5): R_t = 0.53 min. Chemical purity > 95%.

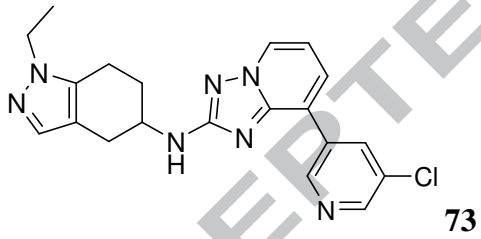




72

*[8-(6-Dimethylamino-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**72**)*. Prepared according to general procedure D-2 using halo triazolopyridine **39a** and 6-dimethylamino-pyridin-3-ylboronic acid. Yield: 8 mg (9%). LCMS (ESI^+) calculated for $C_{22}H_{26}N_8$ $[M + H]^+$ *m/z* 403.2359, found 403.3. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.96 (m, 1H), 8.55 (d, J = 6.5 Hz, 1H), 8.37-8.44 (m, 1H), 7.95 (s, 1H), 7.74 (m, 1H), 7.15 (s, 1H), 6.97 (m, 1H), 6.72 (br, 1H), 3.97 (q, J = 7.2 Hz, 2H), 3.86-3.94 (m, 1H), 3.14 (s, 6H), 2.85-2.93 (m, 1H), 2.76-2.85 (m, 1H), 2.43-2.51 (m, 1H), 2.15-2.21 (m, 1H), 1.77-1.88 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H). HPLC (Method 5): R_t = 0.39 min. Chemical purity 95%.

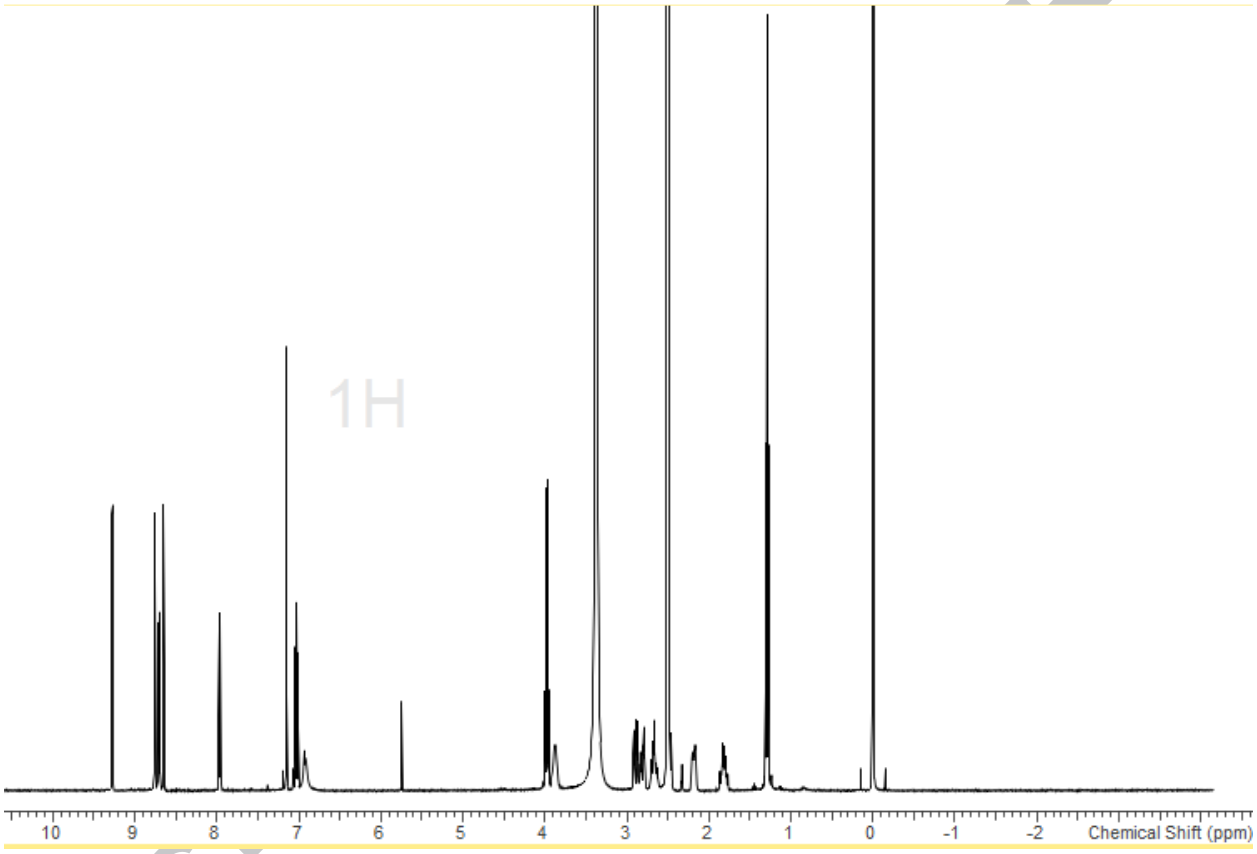




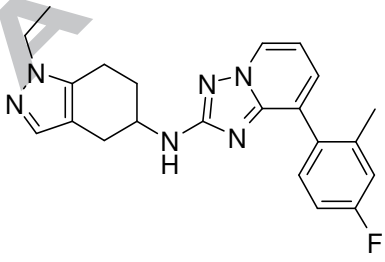
73

*[8-(5-Chloro-pyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridine-2-yl]-(1-ethyl-4,5,6,7-tetrahydro-1H-indazol-5-yl)-amine (**73**).* Prepared according to general procedure D-2 using halo triazolopyridine **39a** and 5-chloro-pyridin-3-ylboronic acid (1.6 equiv). Yield: 54 mg (81%). LCMS (ESI$^+$) calculated for $C_{20}H_{20}ClN_7$ $[M + H]^+$ *m/z* 394.1546, found 394.2. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.28 (d, J = 1.9 Hz, 1H), 8.75 (dd, J = 2.3, 2.3 Hz, 1H), 8.71 (dd, J = 6.7, 0.9 Hz, 1H), 8.64 (d, J = 2.3 Hz, 1H), 7.96 (dd, J = 7.5, 0.9 Hz, 1H), 7.15 (s, 1H), 7.03 (dd, J = 7.5,

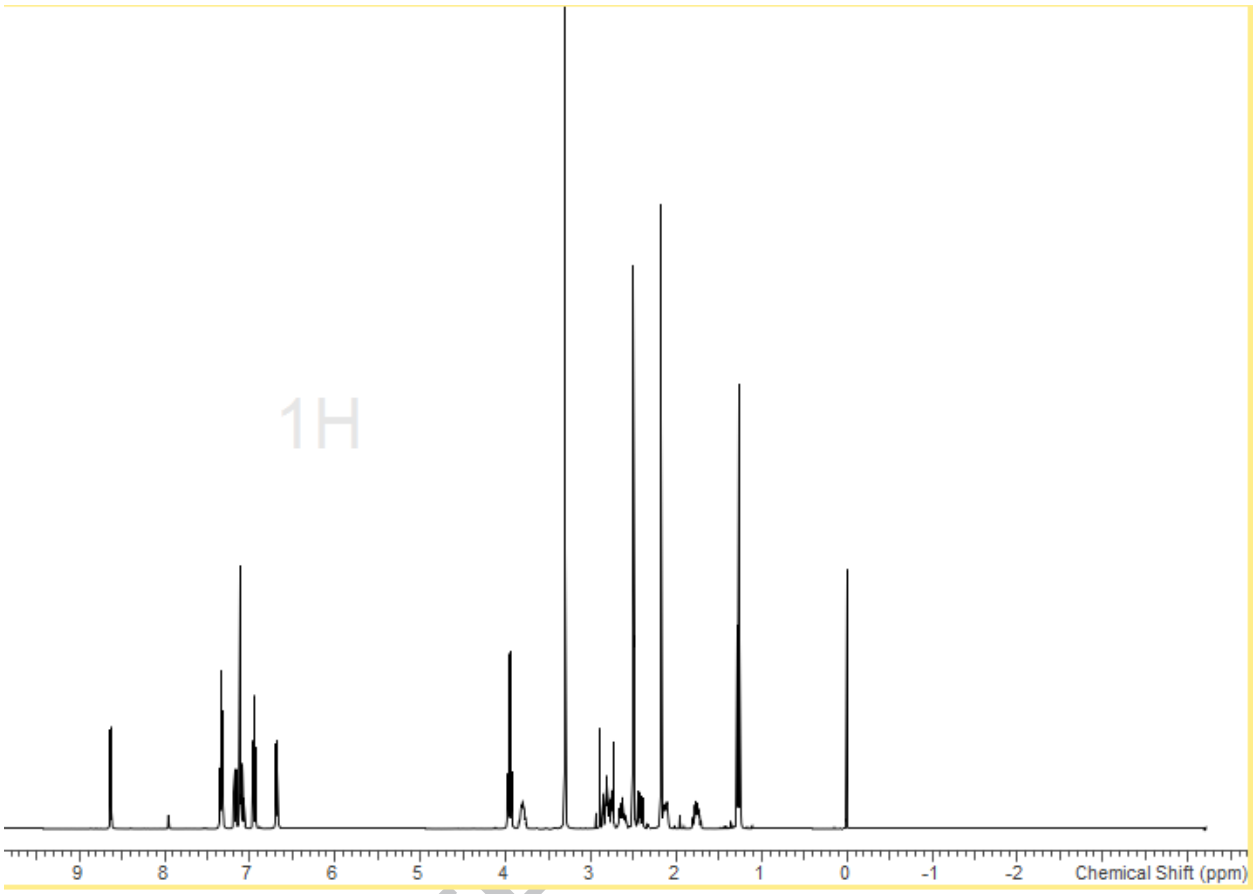
6.7 Hz, 1H), 6.92 (br s, 1H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.91-3.83 (m, 1H), 2.85-2.93 (m, 1H), 2.77-2.85 (m, 1H), 2.71-2.61 (m, 1H), 2.52-2.45 (m, 1H, partially obscured by DSMO signal), 2.22-2.14 (m, 1H), 1.87-1.76 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H). HPLC (Method 5): R_t = 0.56 min. Chemical purity > 95%.

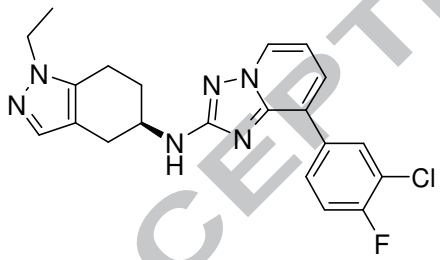


NMR-spectra of compounds described in main publication:

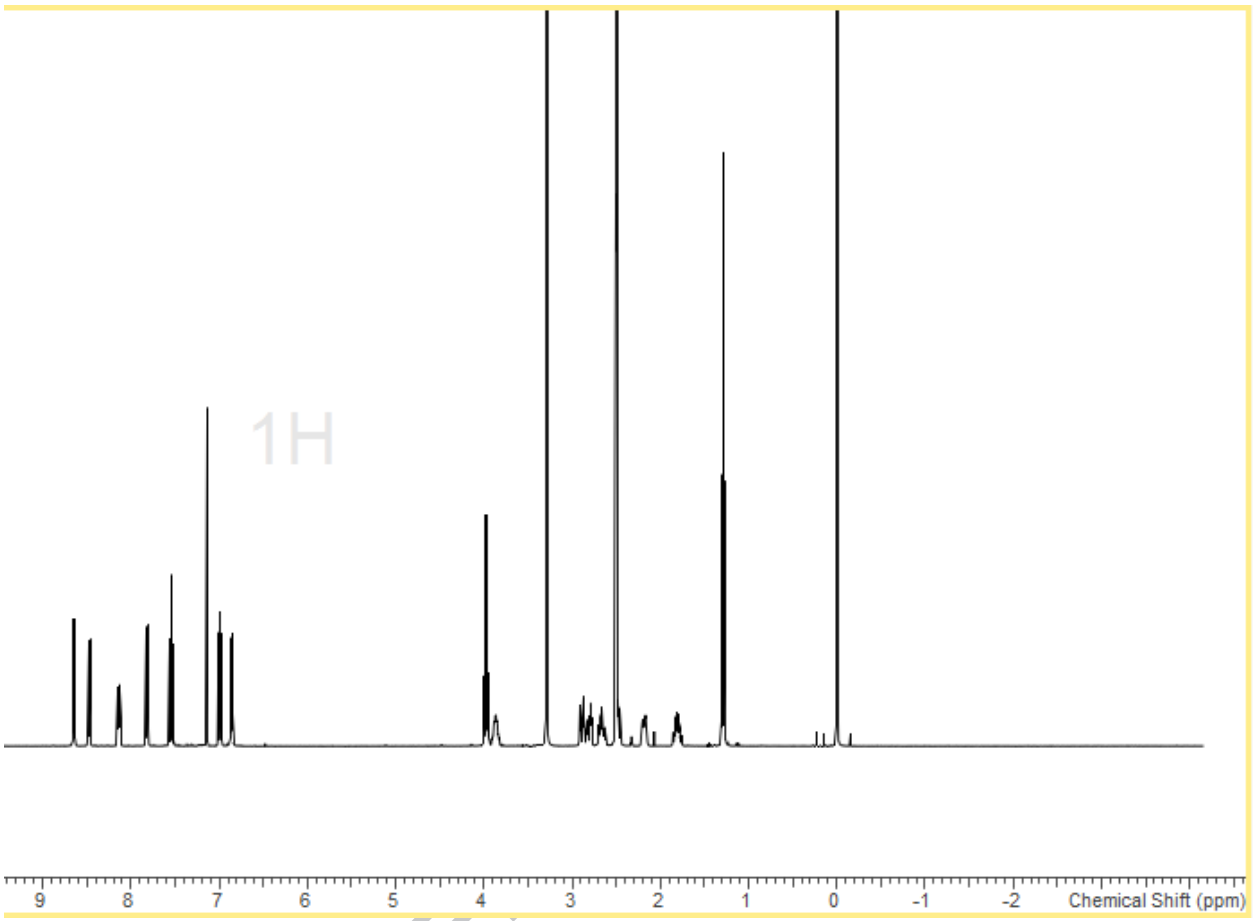


(R)-42





ent1-61



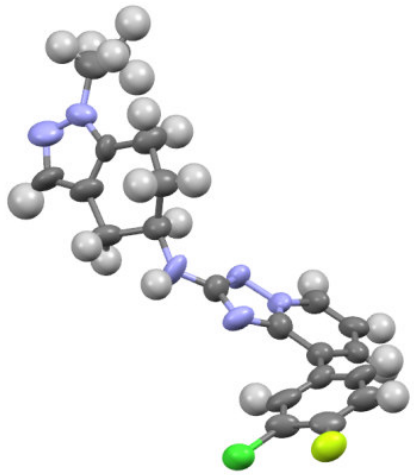
Crystal data of compound *ent1*-61

Single crystals of compound ***ent1*-61** ($C_{21}H_{20}ClFN_6$ *0.5 CH_3OH) were grown in methanol. A suitable crystal was coated with Paratone N oil, suspended in a small fiber loop and placed in a cooled N_2 gas stream at 100 K on a Rigaku AFC11R Cu K (1.5418 Å) diffractometer. The crystal was kept at 100 K during data collection. Using Olex2,[42] the structure was solved with the ShelXT[42] structure solution program using Direct Methods and refined with the ShelXL[42] refinement package using Least Squares minimization. CCDC [1578256] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Additional details of data collection and structure refinement are given in Table 1.

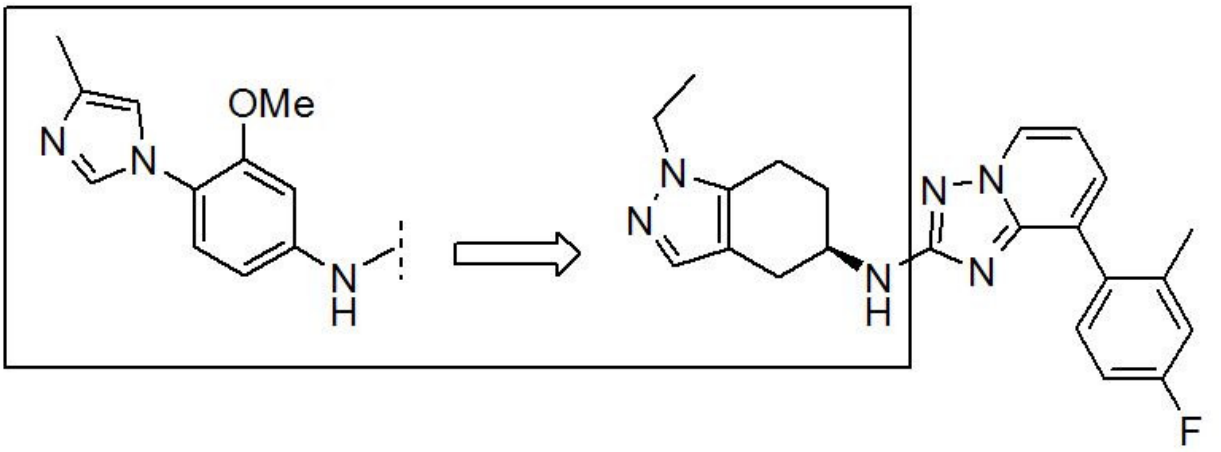
Identification code	CCDC [1578256]
Empirical formula	$C_{21.5}H_{22}ClFN_6O_{0.5}$
Formula weight	426.90
Temperature/K	100.15
Crystal system	monoclinic
Space group	P21
a/Å	7.10926(16)
b/Å	15.4984(2)
c/Å	18.5987(3)
/°	90
/°	94.4689(19)
/°	90
Volume/Å3	2043.01(6)
Z	4
calcg/cm3	1.388
μ/mm 1	1.933
F(000)	892.0
Radiation	CuK (= 1.54184)
2 range for data collection/°	7.434 to 129.036
Index ranges	-8 • h • 8, -17 • k • 18, -21 • l • 21
Reflections collected	43736
Independent reflections	6072 [Rint = 0.0775, Rsigma = 0.0339]
Data/restraints/parameters	6072/1/546
Goodness-of-fit on F2	1.113
Final R indexes [I>=2 (I)]	R1 = 0.0845, wR2 = 0.2256
Final R indexes [all data]	R1 = 0.0863, wR2 = 0.2317

Largest diff. peak/hole / e Å-3	0.71/-0.63
Flack parameter	0.02(3)

Supporting Information - Table 1. Data collection and structure refinement details of crystal structure of compound ***ent1*-61**.



Supporting information - Figure 1. X-Ray structure of compound ***ent1*-61**



BI-1408
Aβ42 IC_{50} = 0.04 μM