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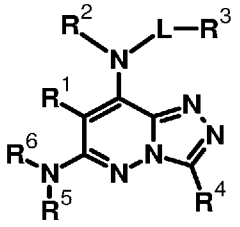
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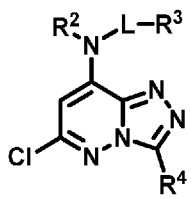
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(54) Title: [1,2,4]-TRIAZOLO[4,3-B]PYRIDAZINE DERIVATIVES USEFUL AS A MEDICAMENT



(I)



(II)

(57) Abstract: The present invention relates to a compound of formula (I) or any of its pharmaceutically acceptable salt. The present invention further relates to a synthesis process for manufacturing compound of formula (I) or any of its pharmaceutically acceptable salts, comprising at least a step of reacting a compound of formula (II) with an amine of formula (IV) NHR^5R^6 for example in a molar ratio ranging from 1 to 20 eq, with respect to the compound of formula (II), in an aprotic solvent or without solvent or else in a protic solvent.

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[1,2,4]-TRIAZOLO[4,3-B]PYRIDAZINE DERIVATIVES USEFUL AS A MEDICAMENT

FIELD OF THE INVENTION

The present invention relates to [1,2,4]-triazolo[4,3-b]pyridazine derivatives useful in treating pathologies mediated by adenosine A3 receptor (A_3AR). It further relates to their manufacturing process and to pharmaceutical compositions containing them.

BACKGROUND

Adenosine interacts with four types of G-protein-coupled receptors (GPCRs), the adenosine receptors (AR): A_1AR, $A_{2A}AR$, $A_{2B}AR$, A_3AR as described in IJzerman, A. P. et al., International Union of Basic and Clinical Pharmacology, CXII: Adenosine Receptors: A Further Update, *Pharmacol Rev* **2022**, *74* (2), 340–372. $A_{2A}AR$ has been most extensively studied while A_3AR is the least studied AR.

A large number of sub-type specific AR agonists and antagonists have been developed in the last few decades and evaluated in clinical trials for numerous indications as described in IJzerman, A. P. *et al.*, International Union of Basic and Clinical Pharmacology, CXII: Adenosine Receptors: A Further Update, *Pharmacol Rev* **2022**, *74*, 340–372; and described in Jacobson, K. A. *et al.* Medicinal Chemistry of P2 and Adenosine Receptors: Common Scaffolds Adapted for Multiple Targets, *Biochem Pharmacol* **2021**, *187*, 114311. The approved AR drugs are the A_1AR agonist adenosine (paroxysmal supraventricular tachycardia), the $A_{2A}AR$ agonist Regadenoson (used for myocardial perfusion imaging), the A_1AR antagonist Bamifylline (asthma) and the $A_{2A}AR$ antagonist Istradefylline (Parkinson's disease).

A_3AR (P0DMS8) (gene located on human chromosome 1 (1p13.2); 318 amino acids in human) was discovered in the early nineties as described in Borea, P. A. *et al.*, The A3 Adenosine Receptor: History and Perspectives, *Pharmacol Rev* **2015**, *67*, 74–102. A_3AR is coupled to Gi proteins, leading to inhibition of adenylate cyclase, and to Go proteins, leading to activation of phospholipase C and Ca^{++} release. A_3AR is also coupled to PI3K/Akt, MAPKs and NF-κB signaling pathways. The biodistribution of A_3AR is rather species-dependent. In man, A_3AR is expressed in lung, liver, kidney, pancreas, brain, testis and cells of the immune system. A_3AR knock-out mice have been generated to

investigate the functions of A_3AR. $A_3AR^{-/-}$ mice are viable, fertile and apparently morphologically indistinguishable from wild-type mice, suggesting that inhibition of this receptor is unlikely to lead to gross toxicity.

Although A_1AR, $A_{2A}AR$ and $A_{2B}AR$ are well conserved throughout evolution, there are rather important differences in the A_3AR sequences of rodents and man (72% and 73% sequence identity between human A_3AR and rat or mouse A_3AR, respectively). Many human A_3AR antagonists are very poorly active or even inactive on rat and mouse orthologs. This complicates translational investigations on the action of A_3AR agonists and antagonists in rodent models of human diseases. A_3AR-humanized ($A_3AR^{h/h}$) and human/mouse chimeric A_3AR ($A_3AR^{c/c}$) mice have been constructed which are sensitive to the agonists developed against human A_3AR.

In cerebral ischemia A_3AR may play both a protective role, by inhibiting excitatory synaptic transmission in synergy with $A_{1A}R$, and a deleterious effect, by favoring excitotoxicity. A_3AR agonists may regulate pain signaling, in particular in the case of anticancer drugs-induced neuropathic pain. A_3AR is overexpressed in several tumors and has anti-proliferative and pro-proliferative effects. A_3AR agonists and antagonists display antitumor activity. A_3AR appears to play a key role in the modulation of inflammation by adenosine. A_3AR agonists have therefore been evaluated in clinical trials to treat various inflammatory diseases such as osteoarthritis of the knee, asthma, lung fibrosis. A_3AR agonists have been investigated for induction of hypothermia as well as for potential cardioprotective activity, yet the deletion of A_3AR appears to confer some resistance to myocardial ischemic injury.

Several potent and selective A_3AR agonists have been described, Piclidenoson (IB-MECA, N^6-iodobenzyl-substituted methylcarboxamidoadenosine, CF101, Can-Fite BioPharma) and Namodenoson (2-Cl-IB-MECA, CF102) being the most advanced drug candidates. Piclidenoson is in clinical trials against in rheumatoid arthritis and psoriasis, while Namodenoson is in clinical trials against hepatocellular carcinoma and non-alcoholic steatohepatitis (NASH).

Several A_3AR antagonists have also been described, such as KF2677, PSB-10, DPTN (N-[4-(3,5-dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]nicotinamide), MRS1523, SSR161421, LJ-1888, pyrazolo-triazolo-pyrimidines, ISVY-130 analogs, 2-chloro-N6-phenylethyladenosine as described in Borea, P. A. *et al.* previously mentioned,

7-Amino-pyrazolo[3,4-d]pyridazine 10a (dual A1/A3AR antagonist), as described in Gao, Z.-G. *et al.* Species Dependence of A3 Adenosine Receptor Pharmacology and Function, *Purinergic Signal* **2022**, 1–28, as illustrated in **figure 1**.

In prior art, only the compounds PBF-677 and PBF-1650, (undisclosed structures) have entered clinical trials, for ulcerative colitis (phase 2) and atopic dermatitis (phase 1), respectively (https://www.palobiofarma.com/pipeline-2/). A_3AR antagonists are evaluated for the treatment of glaucoma as they lower intraocular pressure (IOP) in animal models of glaucoma. A_3AR antagonists have been evaluated as treatment of asthma, ulcerative colitis, liver fibrosis, kidney diseases in particular kidney fibrosis, nephropathy, nephrotoxicity, atherosclerosis and hypercholestemia. Stimulation of A_3AR by adenosine, under hypoxia, contributes to the migration, invasiveness and chemoresistance of glioblastoma stem-like cells and probably in other cancer types under hypoxic conditions. A_3AR antagonists inhibit the proliferation of glioblastoma cell lines.

Hearing loss (HL) originates from exposure to ototoxic agents (such as platinum-based anticancer drugs or aminoglycoside antibiotics – there are over 600 ototoxic agents described, among which over 200 marketed drugs), from noise, from acoustic trauma (high intensity noise) or from aging. These aggressions trigger irreversible death of ear hair cells located in the organ of Corti (cochlea). The function of these cells is to capture sound vibrations and transduce them as neuronal signals sent to the brain auditory structures. There is considerable interest in the development of otoprotective compounds.

Cisplatin is a highly effective anticancer drug widely used for the treatment of cancers. Cisplatin's side effects include nephrotoxicity and ototoxicity. Cisplatin-induced ototoxicity occurs in 23-50% of adults and up to 60% in children. Elevated hearing thresholds may occur in up to 100% of cisplatin-treated cancer patients. Otoprotection would allow the use of these highly effective drugs for life threatening diseases at reduced risk of HL, thereby addressing a significant unmet clinical need. Similarly addressing cisplatin-induced nephrotoxicity would be beneficial. The same applies for the potent but HL-inducing antibiotics, in particular ototoxicity is observed in up to 47% of patients treated with gentamycin, and other products such as neomycin, tobramycin, kanamycin. Noise-induced HL occurs when the ear is exposed to unsafe levels of sounds. The industries where workers often experience noise exposure include agriculture, mining,

construction, manufacturing and utilities, transportation, and the military. Globally, some 1.1 billion teenagers and young adults are at risk of HL due to the unsafe use of personal audio devices and exposure to damaging levels of sound at noisy entertainment venues. In all these situations, external protective ear coverings are either insufficient or inappropriate. Moreover, A_3R is in particular present in the rat cochlea and is predominantly expressed in the organ of Corti (inner and outer hair cells, Deiter's cells, Claudius cells, pillar cells). Furthermore, adenosine plays a protective role in nephrotoxicity induced by various drug agents. In particular, there is data available in the litterature suggesting that A_2AR and A_3AR antagonism may have some protective effects in kidneys exposed to nephrotoxic agents as described in Dewaeles *et al.* Istradefylline protects from cisplatin-induced nephrotoxicity and peripheral neuropathy while preserving cisplatin antitumor effects, *J. Clin. Invest.* **2022**, *132*, e152924; Lee *et al.* A3 adenosine receptor knockout mice are protected against ischemia- and myoglobinuria-induced renal failure, *Am. J. Physiol. Renal Physiol.* **2003**, *284*, 267-273; and Min *et al.* Renopprotective effects of a highly selective A3 adenosine receptor antagonist in a mouse model of adriamycin-induced nephropathy, *J. Korean Med. Sci.* **2016**, *31*, 1403-1412.

There is a thus a need to find therapeutic agents to target specific inhibition of A_3R.

SUMMARY OF THE INVENTION

It has now been found that the compounds as defined in formula (I) hereinafter are useful in the treatment and/or prevention of diseases mediated by A_3R.

FIGURES

Figure 1 depicts two agonists and a few reported antagonists of A3AR.

Figure 2 depicts the results of an evaluation of the potential agonist or antagonist activity of compound (175) on 168 GPCRs and being illustrated in example 10.2.

Figure 3 depicts the results of a study evaluating the selectivity of compound (175) towards various ARs being illustrated in example 10.3.

Figure 4 depicts the results of an A_3AR functional assay being illustrated in exemple 10.3.

Figure 5 depicts the effects of compound (175) on ciliated cells in *ex vivo* cultured mice organs of Corti exposed to either cisplatin (5A), gentamycin (5B) or neomycin (5C), and being illustrated in example 10.4.

Figure 6 depicts the effects of compound (175) on the antiproliferative activity of cisplatin evaluated for various cancer cell lines: A549 (human lung carcinoma) (figure 6-A), PANC-1 (human pancreatic cancer) (figure 6-B), and MDA-435 (human breast cancer) (figure 6-C), being illustrated in example 10.5.

Figure 7 depicts the results of antibiogram assays obtained with *Pseudomonas aeruginosa* PA-19660 without preincubation (A) or after an incubation with vehicle (DMSO) (B) or compound (175) (C), wherein G: Gentamicin; K: Kanamycin; N: Neomycin; S: Streptomycin; T: Tobramycin and W: Water, being illustrated in example 10.6.

Figure 8 depicts diameters of the inhibition zones determined with *Pseudomonas aeruginosa* PA-19660 (figure 8 left) and *Staphylococcus aureus* Newman strains (figure 8 right) preincubated with vehicle (0.1% DMSO), compound (175) or compound (147) prior to exposure to paper disks containing Gentamicin, Kanamycin, Neomycin, Streptomycin or Tobramycin, being illustrated in example 10.6.

DEFINITIONS

As used herein, the term "*patient*" refers to either an animal, such as a valuable animal for breeding, company or preservation purposes, or preferably a human or a human child, which is afflicted with, or has the potential to be afflicted with one or more diseases and conditions described herein.

In particular, as used in the present application, the term "*patient*" refers to a mammal such as a rodent, cat, dog, primate or human, preferably said subject is a human.

The identification of those patients who are in need of treatment of herein-described diseases and conditions is well within the ability and knowledge of one skilled in the art. A veterinarian or a physician skilled in the art can readily identify, by the use of clinical tests, physical examination, medical/family history or biological and diagnostic tests, those patients who are in need of such treatment.

In the context of the invention, the term "*treating*" or "*treatment*", as used herein, means preventing, reversing, alleviating, inhibiting the progress of, or preventing the diseases as described herein after in the paragraph "PATHOLOGIES".

Therefore, the term "*treating*" or "*treatment*" encompasses within the framework of the present invention the improvement of medical conditions of patients suffering from the diseases as described herein after in the paragraph "PATHOLOGIES", mediated by the A_3AR receptor.

As used herein, an "A_3AR *inhibitor*" or "A_3AR *antagonist*" is a compound able to inhibit A_3AR in the assays displayed in example 10.1 in biological activity part described hereafter. In one embodiment, the IC_{50} value from the compounds of formula (I) according to the invention may be less than or equal to 1000 nM, in particular less than or equal to 100 nM, and more particularly less than or equal to 10 nM, and even more particularly less than or equal to 1 nM, said IC_{50} values all attesting the inhibitory activity of the compounds.

As used herein, an "*effective amount*" refers to an amount of a compound of the present invention which is effective in preventing, reducing, eliminating, treating or controlling the symptoms of the herein-described diseases and conditions. An "*effective amount*" also refers to an amount of a compound of the present invention which is effective in inhibiting A_3AR.

The term "*controlling*" is intended to refer to all processes wherein there may be a slowing, interrupting, arresting, or stopping of the progression of the diseases and conditions described herein, but does not necessarily indicate a total elimination of all disease and condition symptoms, and is intended to include prophylactic treatment.

The term "*effective amount*" includes "*prophylaxis-effective amount*" as well as "treatment-effective amount".

The term "*preventing*", as used herein, means reducing the risk of onset or slowing the occurrence of a given phenomenon, namely in the present invention, a disease mediated by ADORA3.

As used herein, "*preventing*" also encompasses "*reducing the likelihood of occurrence*" or "*reducing the likelihood of reoccurrence*".

The term "*prophylaxis-effective amount*" refers to a concentration of compound of this invention that is effective in inhibiting, preventing, decreasing the likelihood of anyone of the hereabove described diseases.

Likewise, the term "*treatment-effective amount*" refers to a concentration of compound that is effective in treating the hereabove described diseases.

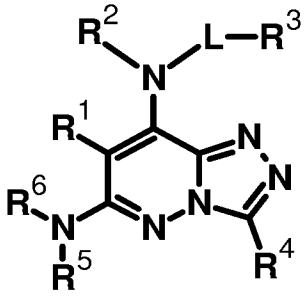
As used herein, the term "*pharmaceutically acceptable*" refers to those compounds, materials, excipients, compositions or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response or other problem complications commensurate with a reasonable benefit/risk ratio.

DETAILED DESCRIPTION OF THE INVENTION

The inventors have surprisingly found that the compounds of formula (I) as disclosed herein after, present inhibition activity of A_3AR.

This assertion is based on data as illustrated in the following examples and more detailed herein after.

Herein is further describes a compound of formula (I) or any of its pharmaceutically acceptable salt



(I)

wherein

R^1 represents a hydrogen atom or a (C_1-C_6)alkyl group;

R^2 represents a hydrogen atom;

R^3 represents

- a linear or branched (C_1-C_6)alkyl group, optionally substituted by
  - one phenyl group, optionally substituted by at least one substituent selected from a -OR^7 group, a -NH_2 group, a halogen atom, a phenyl group and a (C_5-C_6)heteroaryl group,
  - one (C_6-C_{10})heteroaryl group, or
  - one -OR^7 group,
- a phenyl group or a phenyl group fused with a (C_4-C_6)cycloalkyl group; or
- a (C_5-C_6)heteroaryl group, optionally substituted by one to three substituents selected from a (C_1-C_4)alkyl group, a deuterated (C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a

deuterated (C_1-C_4)alkoxy group and a halogen atom, in particular a fluorine atom or a chlorine atom;

L represents a bond, a -CO- group or a -C(O)O- group;

or alternately **L** is a bond and $\mathbf{R^2}$ and $\mathbf{R^3}$ form together with the nitrogen atom bearing them a (C_5-C_6)heterocycloalkyl group containing at least a nitrogen atom fused with a phenyl group;

$\mathbf{R^4}$ represents a hydrogen atom, a linear or branched (C_1-C_6)alkyl group, a (C_3-C_6)cycloalkyl group, a (C_1-C_4)alkoxy group, a (C_5-C_6)heterocyclocalkyl group, a phenyl group, a (C_5-C_6)heteroaryl group or a -CF_3 group;

$\mathbf{R^5}$ represents a hydrogen atom or a (C_1-C_4)alkyl group;

$\mathbf{R^6}$ represents

- a linear or branched (C_1-C_6)alkyl group, optionally interrupted by one or two oxygen atoms and optionally substituted by
  - one phenyl group, optionally substituted by one or two substituents selected from a (C_1-C_4)alkyl group and a (C_1-C_4)alkoxy group,
  - one (C_3-C_8)cycloalkyl group, optionally substituted by one or two substituents selected from a halogen atom, a (C_1-C_4)alkyl group and a -OR^7 group,
  - one (C_5-C_6)heterocycloalkyl,
  - one (C_5-C_6)heteroaryl group, optionally substituted by one or two (C_1-C_6)alkyl group,
  - one or two -OR^7 groups,
  - one -SR^7 group,
  - one -C(O)NR^8R^9 group,
  - one -C(O)OR^{10} group, or
  - one -NHR^{11} group,
- a (C_3-C_7)cycloalkyl group, optionally substituted by one or two substituents selected from a halogen atom, a (C_1-C_4)alkyl group and a -OR^7 group,
- one bridged (C_6-C_{10})cycloalkyl group,
- one spiro(C_5-C_{11})bicyclic ring,
- a (C_5-C_6)heteroaryl group,
- a (C_5-C_6)heterocycloalkyl group, or

- a phenyl group fused with a (C_4-C_6)cycloalkyl group;

or **R^5** and **R^6** form together with the nitrogen atom bearing them a (C_5-C_6)heterocycloalkyl group;

R^7 represents a hydrogen atom, a (C_1-C_4)alkyl group or a deuterated (C_1-C_4)alkyl group;

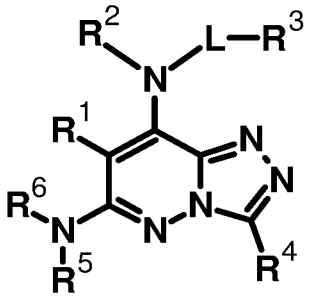
R^8 and **R^9** independently represent a hydrogen atom or a (C_1-C_6)alkyl group;

R^{10} represents a (C_1-C_4)alkyl group; and

R^{11} represents a hydrogen atom or a -CO-(C_1-C_6)alkyl group;

provided that when NR^2LR^3 represents a benzylamino group, then R^4 does not represent a hydrogen atom.

According to a first aspect, a subject-matter of the present invention relates to a compound of formula (I) or any of its pharmaceutically acceptable salt



(I)

wherein

R^1 represents a hydrogen atom or a (C_1-C_6)alkyl group;

R^2 represents a hydrogen atom;

R^3 represents

- a linear or branched (C_1-C_6)alkyl group, substituted by
  - one phenyl group, optionally substituted by at least one substituent selected from a -OR^7 group, a -NH_2 group, a halogen atom, a phenyl group and a (C_5-C_6)heteroaryl group,
  - one (C_6-C_{10})heteroaryl group, or
  - one -OR^7 group,
- a phenyl group or a phenyl group fused with a (C_4-C_6)cycloalkyl group; or
- a (C_5-C_6)heteroaryl group, optionally substituted by one to three substituents selected from a (C_1-C_4)alkyl group, a deuterated (C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a

deuterated (C_1-C_4)alkoxy group and a halogen atom, in particular a fluorine atom or a chlorine atom;

L represents a bond or a -CO- group;

or alternately **L** is a bond and $\mathbf{R^2}$ and $\mathbf{R^3}$ form together with the nitrogen atom bearing them a (C_5-C_6)heterocycloalkyl group containing at least a nitrogen atom fused with a phenyl group;

$\mathbf{R^4}$ represents a hydrogen atom, a linear or branched (C_1-C_6)alkyl group, a (C_3-C_6)cycloalkyl group, a (C_1-C_4)alkoxy group, a (C_5-C_6)heterocyclocalkyl group, a phenyl group, a (C_5-C_6)heteroaryl group or a -CF_3 group;

$\mathbf{R^5}$ represents a hydrogen atom or a (C_1-C_4)alkyl group;

$\mathbf{R^6}$ represents

- a linear or branched (C_1-C_8)alkyl group, optionally interrupted by one or two oxygen atoms and optionally substituted by
  - one phenyl group, optionally substituted by one or two substituents selected from a (C_1-C_4)alkyl group and a (C_1-C_4)alkoxy group,
  - one (C_3-C_8)cycloalkyl group, optionally substituted by one or two substituents selected from a halogen atom, a (C_1-C_4)alkyl group and a -OR^7 group,
  - one (C_5-C_6)heterocycloalkyl,
  - one (C_5-C_6)heteroaryl group, optionally substituted by one or two (C_1-C_6)alkyl group,
  - one or two -OR^7 groups,
  - one -SR^7 group,
  - one -$C(O)NR^8R^9$ group,
  - one -$C(O)OR^{10}$ group, or
  - one -NHR^{11} group,
- a (C_3-C_7)cycloalkyl group, optionally substituted by one or two substituents selected from a halogen atom, a (C_1-C_4)alkyl group and a -OR^7 group,
- one bridged (C_6-C_{10})cycloalkyl group,
- one spiro(C_5-C_{11})bicyclic ring,
- a (C_5-C_6)heteroaryl group,
- a (C_5-C_6)heterocycloalkyl group, or

- a phenyl group fused with a (C_4-C_6)cycloalkyl group;

or **R^5** and **R^6** form together with the nitrogen atom bearing them a (C_5-C_6)heterocycloalkyl group;

R^7 represents a hydrogen atom, a (C_1-C_4)alkyl group or a deuterated (C_1-C_4)alkyl group;

R^8 and **R^9** independently represent a hydrogen atom or a (C_1-C_6)alkyl group;

R^{10} represents a (C_1-C_4)alkyl group; and

R^{11} represents a hydrogen atom or a -CO-(C_1-C_6)alkyl group;

provided that when NR^2LR^3 represents a benzylamino group, then R^4 does not represent a hydrogen atom.

The inventors have surprisingly discovered that compounds of formula (I) present an inhibitory activity specific to the Adenosine receptor A3 (A_3AR) and that some of them even present a powerful inhibitory activity.

According to another particular embodiment, herein is further provided a compound of formula (I) as defined herein above, wherein **R^1** represents a hydrogen atom or a methyl group.

According to another particular embodiment, herein is further provided a compound of formula (I) as defined herein above, wherein

R^2 represents a hydrogen atom;

R^3 represents

- a linear or branched (C_1-C_6)alkyl group, substituted by
  - one phenyl group, optionally substituted by one substituent selected from a hydroxy group, a methoxy group, an amino group, a halogen atom, a phenyl group and a pyridyl group,
  - one pyridyl, one pyrazinyl, one pyrimidinyl or one pyridazinyl group, in particular one pyridyl, pyridazinyl or pyrimidinyl group, or one indolyl or isoindolyl group, in particular an indolyl group,
  - one hydroxy group,
  - one methoxy group, one deuterated methoxy group, or
  - a halogen atom, in particular a fluorine atom or a chlorine atom,
- a phenyl group or an indanyl group; or

- a pyridyl, a pyrazinyl, a pyrimidinyl or a pyridazinyl group, optionally substituted by one methoxy group or deuterated methoxy group, in particular a pyridyl group;

L represents a bond or a -CO- group;

or alternately **L** is a bond and $\mathbf{R^2}$ and $\mathbf{R^3}$ form together with the nitrogen atom bearing them an indolinyl, an isoindolinyl, a tetrahydroquinolinyl or a tetrahydroisoquinolinyl group, in particular an isoindolinyl or a tetrahydroisoquinolinyl group.

According to another particular embodiment, herein is further provided a compound of formula (I) as defined herein above, wherein $\mathbf{R^4}$ represents a hydrogen atom, a linear or branched (C_1-C_5)alkyl group, a (C_3-C_6)cycloalkyl group, a phenyl group, a pyridyl group or a -CF_3 group.

According to another particular embodiment, herein is further provided a compound of formula (I) as defined herein above, wherein

$\mathbf{R^5}$ represents a hydrogen atom or a (C_1-C_4) alkyl group, in particular a methyl group;

$\mathbf{R^6}$ represents

- a linear or branched (C_1-C_8)alkyl group, optionally interrupted by one or two oxygen atoms and optionally substituted by
  - one phenyl group, optionally substituted by one or two substituents selected from a methyl group and a methoxy group,
  - one (C_3-C_6)cycloalkyl group, optionally substituted by a methyl group,
  - one tetrahydropyranyl or one tetrahydrofuranyl group,
  - one pyrazolyl, imidazolyl, pyrimidinyl, pyrazinyl, pyridyl, furanyl or thienyl group, optionally substituted by one or two methyl group,
  - one or two hydroxy group or methoxy group,
  - one methylthio group,
  - one -$CONH_2$ group, one –$CONHCH_3$ group or one -$CON(CH_3)_2$ group,
  - one -$COOCH_3$ or one -$COOCH_2CH_3$ group, or
  - one -NH_2 group or one -$NCOCH_3$ group,
- a (C_3-C_7)cycloalkyl group, optionally substituted by one or two substituents selected from a halogen atom, a hydroxy group or a methoxy group,
- an adamantyl group,

- a spiro[3.3]heptanyl group,
- an imidazolyl group, optionally substituted by one or two methyl group,
- a morpholinyl group, a tetrahydropyranyl or a tetrahydrofuranyl group, or
- an indanyl group;

or $\mathbf{R^5}$ and $\mathbf{R^6}$ form together with the nitrogen atom bearing them a morpholinyl group or a piperidinyl group.

Herein is further provided a pharmaceutical composition comprising a compound of formula (I) as defined herein after, or at least any of compounds **(1)** to **(234)** as defined hereinafter or any of their pharmaceutically acceptable salts.

As illustrated in example 10.1, the compounds of formula (I) have been tested as A_3AR antagonists. It has been observed that the compounds of formula (I) exert an inhibitory activity on A_3AR and thus may be useful in the treatment of pathologies mediated by A_3AR.

As illustrated in example 10.2, a compound of formula (I) has been tested with respect to 168 GPCR receptors. It has been surprisingly observed that this compound of formula (I) is only active on one of them.

As illustrated in example 10.3, a compound of formula (I) has been additionnaly tested with respect to other adenosine receptors A_1AR, $A_{2A}AR$ and $A_{2B}AR$ for selectivity study. It has been surprisingly observed that this compound of formula (I) is only active on A_3AR. Moreover, a compound of formula (I) has been additionnaly tested in A_3AR functional assay. It has been observed that this compound of formula (I) is an antagonist inhibitor of A_3AR.

The unusal and unexpected specificity and functionality highligted in examples 10.2 and 10.3 calls for the development of potent and selective A_3AR antagonists with clinical applications.

In other terms, as illustrated in examples 10.1, 10.2 and 10.3 the compounds of formula (I) are potent and selective A_3AR antagonists.

Additionaly, the inventors have suprisingly found that compounds of formula (I) display protective activity towards inner ear hair cells of the organ of Corti exposed to ototoxic agents, in particular platin-based anticancer drugs such as cisplatin, or antibiotics

aminoglycosides such as gentamicin or neomycin. Typically, as illustrated in example 10.4, the inventors have shown that the compounds of the present invention display otoprotective activity on *ex vivo* models of ototoxicity (cultured organs of Corti) induced by ototoxic agents, in particular platin-based anticancer drugs such as cisplatin, or antibiotics aminoglycosides such as gentamicin or neomycin.

At last, as illustrated in example 10.5, it has been demonstrated that compounds of formula (I), in particular compound (175), have modest effects on the sensitivity of three cancer cell lines to cisplatin and as illustrated in example 10.6, compounds of formula (I) do not modify the susceptibility of bacterial strains, in particular *Pseudomonas aeruginosa* and *Staphylococcus aureus*, to antibiotics, in particular aminoglycosides and more particularly Gentamicin, Kanamycin, Neomycin, Streptomycin and Tobramycin.

In the context of the present invention, the term:

- "halogen" is understood to mean chlorine, fluorine, bromine, or iodine, and in particular denotes chlorine, fluorine or bromine,

- "(C_1-C_x)alkyl", as used herein, respectively refers to a C_1-C_x normal, secondary or tertiary monovalent saturated hydrocarbon radical, for example (C_1-C_8)alkyl. Examples are, but are not limited to, methyl, ethyl, propyl, *n*-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, hexyl,ethylbutyl, isohexyl, heptyl, ethylpentyl and octyl groups, and the like.

- "(C_1-C_x)alkoxy", as used herein, refers to a -O-(C_1-C_x)alkyl or -O-(C_3-C_x)cycloalkyl moiety, wherein alkyl and cycloalkyl are as defined above, for example (C_1-C_6)alkoxy. Examples are, but are not limited to, methoxy, ethoxy, 1-propoxy, 2-propoxy, cyclopropoxy, butoxy, *tert*-butoxy and pentoxy.

- a (C_1-C_4)alkylthio group also named a (C_1-C_4)alkylsulfanyl group: a -S-alkyl group where the alkyl group is as previously defined. By way of examples, mention may be made of, but not limited to: methylthio, ethylthio, propylthio, isopropylthio, linear, secondary or tertiary butylthio, isobutylthio, and the like;

- "(C_3-C_8)cycloalkyl", as used herein, refers to a monocyclic saturated hydrocarbon, from 3 to 8 carbon atoms, saturated or partially unsaturated and unsubstituted or substituted. Examples of monocyclic rings are, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

- a "bridged (C_6-C_{10})cycloalkyl" group, as used herein, refers to a bi- or tricyclic compound where the cycles are cycloalkyls, the rings share three or more atoms and the bridge contains at least one atom, for example 1, 2 or 3 atoms. Such bridged cycloalkyl groups may be substituted by one or more C_1-C_3 alkyl. Examples are, but not limited to adamantyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, 6,6-dimethylbicyclo[3.1.1]heptyl, bicyclo[3.1.1]heptyl, 1,6,6-trimethylbicyclo[3.1.1]heptyl.

- "spiro(C_5-C_{11})bicyclic ring" refers to two rings connected through a defining single common atom. Such spiro bicyclic alkyl generally comprises 5 to 11 carbon atoms referring to a "spiro(C_5-C_{11})bicyclic alkyl group". Such spirobicyclic ring may be unsubstituted or substituted, in particular by at least one (C_1-C_3)alkyl group such as methyl. Examples are, but are not limited to spiro[3.3]heptanyl, spiro[2.5]octanyl, in particular a spiro[3.3]heptanyl.

- "(C_5-C_6)heterocycloalkyl group", as used herein, refers to a (C_5-C_6)cycloalkyl group wherein one or two of the carbon atoms are replaced with a heteroatom such as oxygen, nitrogen or sulphur, and more particularly with at least one nitrogen atom. Such heterocycloalkyl group may be saturated or partially saturated and unsubstituted or substituted. Examples are, but are not limited to piperazinyl, piperidinyl, pyrrolidinyl, aziridinyl, oxanyl, oxetanyl, tetrahydropyranyl, morpholinyl, tetrahydrofuranyl, oxazolidinyl, oxepanyl, diazepanyl, dioxanyl and tetrahydrothiopyranyl, and more particularly pyrrolidinyl, piperidinyl, morpholinyl, tetrahydropyranyl or one tetrahydrofuranyl group.

- a (C_5-C_{10})heteroaryl group, as used herein, refers to a monocyclic aromatic or a bicyclic group wherein one to three carbon atom is replaced by a heteroatom, such as nitrogen, oxygen or sulphur. By way of examples of monocyclic aromatic ring of heteroaryl groups, more particulary as a (C_5-C_6)heteroaryl group, mention may be made of, but not limited to: oxazolyl, isoxazolyl, pyridyl, pyrimidinyl, pyridazinyl, triazinyl, pyrazinyl, oxadiazolyl, furanyl, pyrazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, triazolyl and the like. In the framework of the present invention, the heteroaryl is advantageously pyridyl, imidazolyl, pyrazinyl, furanyl, thiazolyl, pyrazolyl, thiadiazolyl, pyridazinyl and pyrimidinyl, and in particular pyridyl, pyrazinyl, pyrimidinyl or pyridazinyl. By way of examples of bicyclic aromatic ring of heteroaryl groups, mention may be made of indolyl, isoindolyl, indolinyl, isoindolinyl, quinolinyl or isoquinolinyl.

- an aromatic ring means, according to Hückel's rule, that a molecule has $4n + 2$ π-electrons.

- "deuterated" refers to a group wherein at least one hydrogen atom is replaced by a deuterium atom, such as perdeuterated group wherein all hydrogen atoms are replaced by deuterium atoms. In other terms, a deuterated group may be partially or totally deuterated. By way of examples of deuterated group, more particularly as deuterated (C_1-C_4)alkyl group, mention may be made of, but not limited to: -CH_2D group, -CHD_2 group or -CD_3 group. By way of other examples of deuterated group, more particularly as deuterated (C_1-C_4)alkoxy group, mention may be made of, but not limited to: deuterated methoxy group such as -OCH_2D group, -$OCHD_2$ group or -OCD_3 group.

In the context of the present invention, the terms "aromatic ring", and "heteroaryl" include all the positional isomers.

The nomenclature of the following compounds (1) to (234) was generated according to the principles of the International Union of Pure and Applied Chemistry, using ChemDraw® Professional v22.0.022. To avoid any confusion, the "(±)" symbol added to designate a racemic mixture; "*cis*" and "*trans*" prefixes were also used to assign the relative stereochemistry of two adjacent chiral centers.

Specific compounds of the present invention are listed herein after:

(1) (2*R*)-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(2) (2*S*)-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(3) 2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propane-1,3-diol,

(4) (2*R*,3*R*)-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol,

(5) (2*S*,3*S*)-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol,

(6) *N*-benzyl-3-isopropyl-6-morpholino-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine

(7) (2*S*)-3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propane-1,2-diol,

(8) *N*6-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-*N8*-benzyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(9) 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propan-1-ol,

(10) *N8*-benzyl-3-isopropyl-*N6*-(3-methoxypropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(11) 2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]ethanol,

(12) *N8*-benzyl-3-isopropyl-*N6*-(2-methoxyethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(13) 4-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(14) *N8*-benzyl-3-isopropyl-*N6*-(4-methoxybutyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(15) 5-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]pentan-1-ol,

(16) *N8*-benzyl-3-isopropyl-*N6*-(5-methoxypentyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(17) *N8*-benzyl-3-isopropyl-*N6*-(3-methylsulfanylpropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(18) *N8*-benzyl-*N6*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(19) *N8*-benzyl-3-isopropyl-*N6*-[(3*R*)-tetrahydrofuran-3-yl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(20) *N8*-benzyl-3-cyclopentyl-*N6*-[(3*R*)-tetrahydrofuran-3-yl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(21) *N8*-benzyl-3-isopropyl-*N6*-[(3*R*)-tetrahydropyran-3-yl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(22) *N8*-benzyl-3-isopropyl-*N6*-[(3*S*)-tetrahydropyran-3-yl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(23) *N8*-benzyl-3-isopropyl-*N6*-tetrahydropyran-4-yl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(24) *N*-[3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propyl]acetamide,

(25) 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propanamide,

(26) 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]-*N*-methyl-propanamide,

(27) 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]-*N*,*N*-dimethyl-propanamide,

(28) Methyl 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propanoate,

(29) ethyl 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propanoate,

(30) (*2R*)-2-[[8-(benzylamino)-3-cyclopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(31) *N8*-benzyl-3-cyclopropyl-*N6*-(3-methoxypropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(32) *N8*-benzyl-*N6*-(3-methoxypropyl)-3-methyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(33) (*2R*)-2-[[8-(benzylamino)-3-methyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(34) *N8*-benzyl-*N6*-(3-methoxypropyl)-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(35) (*2R*)-2-[[8-(benzylamino)-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(36) *N8*-benzyl-*N6*-(3-methoxypropyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(37) (*2R*)-2-[[8-(benzylamino)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(38) 2-[[[6-[[(*1R*)-1-(hydroxymethyl)propyl]amino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(39) 2-[[[3-isopropyl-6-(3-methoxypropylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(40) 2-[[[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(41) 3-[[[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(42) 4-[[[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(43) 2-[[[3-isopropyl-6-[[(3*R*)-tetrahydropyran-3-yl]amino]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(44) 2-[[[3-isopropyl-6-(tetrahydropyran-4-ylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(45) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(46) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(2-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(47) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(3-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(48) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(4-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(49) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(4-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(50) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(3-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(51) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(52) *N6*-tert-butyl-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(53) 3-isopropyl-*N8*-(2-pyridylmethyl)-*N6*-spiro[3.3]heptan-2-yl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(54) *N6*-(3,3-difluorocyclobutyl)-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(55) *N6*-(4,4-difluorocyclohexyl)-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(56) *N6*-benzyl-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(57) *N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(58) *N6*-(1-ethylpropyl)-3-methyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(59) 3-ethyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(60) *N6*-(1-ethylpropyl)-3-propyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(61) 3-tert-butyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(62) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(63) 3-cyclobutyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(64) 3-cyclopentyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(65) 3-cyclohexyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(66) *N6*-(1-ethylpropyl)-3-phenyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(67) *N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-3-sec-butyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(68) *N6*,3-bis(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(69) *N6*-(1-ethylpropyl)-3-isobutyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(70) *N6*-(1-ethylpropyl)-3-(2-pyridyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(71) *N6*-(1-ethylpropyl)-3-(3-pyridyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(72) *N6*-(1-ethylpropyl)-3-(4-pyridyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(73) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[(2-methoxyphenyl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(74) (*2R*)-2-[[8-[(4-aminophenyl)methylamino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(75) *N8*-[(4-aminophenyl)methyl]-*N6*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(76) *N8*-[(3-aminophenyl)methyl]-*N6*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(77) *N8*-[(2-aminophenyl)methyl]-*N6*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(78) *N6*-(1-ethylpropyl)-*N8*-(*1H*-indol-2-ylmethyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(79) *N*-(1-ethylpropyl)-8-isoindolin-2-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-amine,

(80) 8-(3,4-dihydro-*1H*-isoquinolin-2-yl)-*N*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-amine,

(81) *N6*-(1-ethylpropyl)-*N8*-indan-1-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(82) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(2-phenylethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(83) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(84) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[2-(3-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(85) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[2-(4-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(86) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(87) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-[2-(3-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(88) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-[2-(4-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(89) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[3-(2-pyridyl)propyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(90) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[3-(3-pyridyl)propyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(91) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[3-(4-pyridyl)propyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine

(92) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(pyrimidin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(93) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(pyrimidin-5-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(94) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(pyrazin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(95) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(pyridazin-3-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(96) *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]benzamide,

(97) *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]pyridine-2-carboxamide,

(98) *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]-2-phenyl-acetamide,

(99) ethyl *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]carbamate,

(100) phenyl *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]carbamate,

(101) (2*S*)-2-[[8-[(4-bromophenyl)methylamino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(102) (2*S*)-2-[[3-isopropyl-8-[(4-phenylphenyl)methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(103) (2*S*)-2-[[3-isopropyl-8-[[4-(4-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(104) (2*S*)-2-[[3-isopropyl-8-[[4-(3-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(105) (2*S*)-2-[[3-isopropyl-8-[[4-(2-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(106) (2*R*,3*R*)-2-[[8-[(4-bromophenyl)methylamino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol,

(107) (2*R*,3*R*)-2-[[3-isopropyl-8-[[4-(2-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol,

(108) (2*R*,3*R*)-2-[[3-isopropyl-8-[[4-(4-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol,

(109) *N6,N8*-bis(3-methoxypropyl)-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(110) 3-cyclopropyl-*N6,N8*-bis(3-methoxypropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(111) *N6,N8*-bis(3-methoxypropyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(112) 3-isopropyl-*N6,N8*-bis(2-methoxyethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(113) (2*R*)-2-[[6-[[(1*R*)-1-(hydroxymethyl)propyl]amino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]butan-1-ol,

(114) *N6,N8*-bis(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(115) (2*R*)-2-[[8-(benzylamino)-3-isopropyl-7-methyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(116) *N8*-[(4-bromophenyl)methyl]-3-isopropyl-*N6*-methyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(117) *N8*-benzyl-*N6*-cyclobutyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(118) *N8*-benzyl-*N6*-cyclopentyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(119) *N8*-benzyl-*N6*-cyclohexyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(120) *N8*-benzyl-3-isopropyl-*N6*-(4-methoxycyclohexyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(121) *N8*-benzyl-*N6*-cycloheptyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(122) *N8*-benzyl-*N6*-(cyclopropylmethyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(123) *N8*-benzyl-*N6*-(cyclobutylmethyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(124) *N8*-benzyl-*N6*-(cyclohexylmethyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(125) *N8*-benzyl-3-isopropyl-*N6*-(tetrahydropyran-4-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(126) *N8*-benzyl-*N6*-(2-ethylbutyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(127) *N8*-benzyl-3-isopropyl-*N6*-(2-phenylethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(128) *N8*-benzyl-3-isopropyl-*N6*-(2-phenoxyethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(129) *N8*-benzyl-3-isopropyl-*N6*-[(1-methylimidazol-2-yl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(130) *N6*,*N8*-dibenzyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(131) *N8*-benzyl-3-isopropyl-*N6*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(132) *N8*-benzyl-3-isopropyl-*N6*-(3-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(133) *N8*-benzyl-3-isopropyl-*N6*-(4-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(134) racemic trans-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]cyclohexanol,

(135) racemic trans-4-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]cyclohexanol,

(136) *N8*-benzyl-3-isopropyl-*N6*-[(1-methylcyclohexyl)methyl]-[1,2,4]triazolo[4,3-

b]pyridazine-6,8-diamine,

(137) *N6*-(1-adamantyl)-*N8*-benzyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(138) *N8*-benzyl-*N6*-indan-2-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(139) *N8*-benzyl-3-isopropyl-*N6*-[(5-methylpyrazin-2-yl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(140) *N8*-benzyl-3-isopropyl-*N6*-[(1-methylpyrazol-4-yl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(141) *N8*-benzyl-*N6*-[(3,5-dimethylphenyl)methyl]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(142) *N8*-benzyl-3-isopropyl-*N6*-(tetrahydrofuran-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(143) *N8*-benzyl-3-isopropyl-*N6*-(2-methylsulfanylethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(144) *N8*-benzyl-3-isopropyl-*N6*-(1-methylimidazol-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(145) *N8*-benzyl-*N6*-[(4,6-dimethylpyrimidin-2-yl)methyl]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(146) *N8*-benzyl-*N6*-indan-1-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(147) *N6*-(2-ethylbutyl)-3-isopropyl-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(148) 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(149) 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(150) 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(151) 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-5-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(152) 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-2-yl)-[1,2,4]triazolo[4,3-

b]pyridazine-6,8-diamine,

(153) 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrazin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(154) 3-isopropyl-*N8*-(6-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(155) 3-isopropyl-*N8*-(5-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(156) 3-isopropyl-*N8*-(4-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(157) 3-isopropyl-*N8*-(3-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(158) 3-isopropyl-*N8*-(2-methoxypyridin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(159) 3-isopropyl-*N8*-(6-methoxypyridin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(160) isopropyl-*N8*-(5-methoxypyridin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(161) 3-isopropyl-*N*8-(4-methoxypyridin-3-yl)-*N*6-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(162) 3-isopropyl-*N8*-(5-methoxypyridazin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(163) (2*R*)-2-[[3-isopropyl-8-(2-pyridylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(164) *N6*-(2-ethylbutyl)-3-isopropyl-*N8*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(165) *N6*-cyclopentyl-3-isopropyl-*N8*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(166) *N6*-(2-ethylbutyl)-3-isopropyl-*N8*-[2-(3-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(167) *N6*,*N8*-bis(2-ethylbutyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine

(168) *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]-2-(3-pyridyl)acetamide,

(169) (*2R*)-2-[[3-isopropyl-8-(2-pyridylmethylamino)imidazo[1,2-*b*]pyridazin-6-yl]amino]butan-1-ol,

(170) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(3-phenylpropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(171) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(172) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(173) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-(3-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(174) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-(4-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(175) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(176) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(177) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(178) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-pyrimidin-5-yl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(179) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(180) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrazin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(181) (*R*)-2-((3-cyclopropyl-8-(pyridazin-3-ylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino)butan-1-ol,

(182) (*S*)-2-((3-cyclopropyl-8-(pyridazin-3-ylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino)butan-1-ol,

(183) 3-cyclopropyl-*N8*-(6-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(184) 3-cyclopropyl-*N8*-(2-methoxypyridin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(185) (2*R*)-2-[[3-cyclopropyl-8-[2-(2-pyridyl)ethylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(186) *N6*-benzyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(187) 3-cyclopropyl-*N6*-(4-methoxybenzyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(188) 3-cyclopropyl-*N6*-(4-methoxybenzyl)-*N6*-methyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(189) 3-cyclopropyl-*N6*-ethyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(190) 3-cyclopropyl-*N6*-propyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(191) *N6*-butyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(192) 3-cyclopropyl-*N6*-isopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(193) *N6*-(sec-butyl)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(194) 3-cyclopropyl-*N6*-isobutyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(195) *N6*-(tert-butyl)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(196) 3-cyclopropyl-*N6*-(2-ethylbutyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(197) *N6*,3-dicyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(198) *N6*-cyclobutyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(199) *N6*-cyclopentyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(200) *N6*-cyclohexyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(201) *N6*-cycloheptyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(202) *N6*-((3s,5s,7s)-adamantan-1-yl)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(203) 3-cyclopropyl-*N6*-(cyclopropylmethyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(204) *N6*-(cyclobutylmethyl)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(205) 3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(spiro[3.3]heptan-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(206) 3-cyclopropyl-*N6*-((1-methylcyclobutyl)methyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(207) 3-cyclopropyl-6-(1-piperidyl)-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine,

(208) 3-cyclopropyl-*N6*-(furan-2-ylmethyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(209) 3-cyclopropyl-*N6*-(furan-3-ylmethyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(210) 3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(thiophen-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(211) (*R*)-2-((3-cyclopropyl-8-((pyridin-2-ylmethyl)amino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino)butan-1-ol,

(212) (*S*)-2-((3-cyclopropyl-8-((pyridin-2-ylmethyl)amino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino)butan-1-ol,

(213) (*R*)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(tetrahydrofuran -3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(214) (*R*)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(tetrahydro-*2H*-pyran-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(215) 3-cyclopropyl-*N8*-(6-methoxypyridazin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(216) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-3-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(217) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-phenethyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(218) 3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(thiophen-3-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(219) 3-cyclopropyl-*N6*-methyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(220) 3-cyclopropyl-*N*-(pyridin-2-ylmethyl)-6-(pyrrolidin-1-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine,

(221) 3-isopropyl-*N8*-(2-methoxypyrimidin-4-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(222) 3-isopropyl-*N8*-(5-methoxypyrimidin-4-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(223) 3-isopropyl-*N8*-(6-methoxypyrimidin-4-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(224) 3-isopropyl-*N8*-(6-methoxypyridazin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(225) 3-cyclopropyl-*N6*-(2-ethylbutyl)-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(226) 3-cyclopropyl-*N6*-(2-ethylbutyl)-*N8*-(6-methoxypyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(227) *N8*-(6-chloropyridazin-3-yl)-3-isopropyl-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(228) *N8*-(2-chloropyrimidin-4-yl)-3-isopropyl-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(229) *N6*-(2-ethylbutyl)-3-isopropyl-*N8*-(6-methoxypyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(230) *N6*-(3-ethylpentyl)-3-isopropyl-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(231) 3-isopropyl-*N8*-(6-(methoxy-*d3*)pyridazin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(232) *N8*-(6-chloropyridazin-3-yl)-*N6*-(2-ethylbutyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(233) *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]-2-(2-pyridyl)acetamide,

(234) *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]-2-(4-pyridyl)acetamide

and their pharmaceutically acceptable salts.

Thus, herein is provided anyone of the compounds (1) to (234) as defined above or any of their pharmaceutically acceptable salts.

According to an even more preferred embodiment of the present invention, the compound is chosen from the group consisting of compounds (1), (2), (10), (13), (14), (17) to (19), (21) to (23), (26), (28), (29), (31), (35) to (56), (58) to (64), (66) to (69), (71) to (78), (80) to (105), (107), (110), (111), (114), (117) to (119), (121) to (124), (126), (127), (130) to (132), (134), (136), (138), (140), (143), (146) to (160), (162) to (187), (189) to (206), (208) to (212), (215) to (218), (221) and (223) to (234) and their pharmaceutically acceptable salts.

According to an even more preferred embodiment of the present invention, the compound is chosen from the group consisting of compounds (18), (38), (40) to (42), (45) to (53), (56), (59), (62), (63), (67), (68), (73), (75), (76), (80), (82) to (88), (90), (91), (93) to (95), (98) to (100), (114), (118), (126), (130), (147) to (151), (153) to (156), (158) to (160), (162), (164) to (168), (170) to (178), (180) to (183), (186), (187), (191) to (193), (195), (196), (198) to (202), (204) to (206), (208) to (210), (215) to (218), (221) and (223) to (234) and their pharmaceutically acceptable salts.

According to an even more particularly preferred embodiment of the present invention, the compound is chosen from the group consisting of compounds (46), (47), (83), (86), (87), (98), (147), (148), (150), (151), (153) to (155), (158), (159), (162), (164), (168), (171) to (175), (177), (178), (180) to (183), (215), (221), (223) to (232) and (234) and their pharmaceutically acceptable salts.

According to another aspect, a subject-matter of the present invention relates to a compound of formula (I) as defined above or any of its pharmaceutically acceptable salts, or at least any of compounds (1) to (234) or any of their pharmaceutically acceptable salts, for use as a medicament.

"Pharmaceutically acceptable salt thereof" refers to salts which are formed from acid addition salts formed with inorganic acids (*e.g.* hydrochloric acid, hydrobromic acid,), as well as salts formed with organic acids such as acetic acid, tartaric acid, succinic acid.

Suitable physiologically acceptable acid addition salts of compounds of formula (I) include hydrobromide, tartrate, hydrochloride, mesylate, succinate and acetate.

The compounds of formula (I), and any of compounds (1) to (234) or any of their pharmaceutically acceptable salts may form solvates or hydrates and the invention includes all such solvates and hydrates.

The terms "hydrates" and "solvates" simply mean that the compounds (I) according to the invention can be in the form of a hydrate or solvate, *i.e.* combined or associated with one or more water or solvent molecules. This is only a chemical characteristic of such compounds, which can be applied for all organic compounds of this type.

The compounds of formula (I) can comprise one or more asymmetric carbon atoms. They can thus exist in the form of enantiomers or of diastereoisomers. These enantiomers, diastereoisomers and their mixtures, including the racemic mixtures, are encompassed within the scope of the present invention.

The compounds of the present invention can be prepared by conventional methods of organic synthesis practiced by those skilled in the art. The general reaction sequences outlined below represent a general method useful for preparing the compounds of the present invention and are not meant to be limiting in scope or utility.

List of abbreviations:

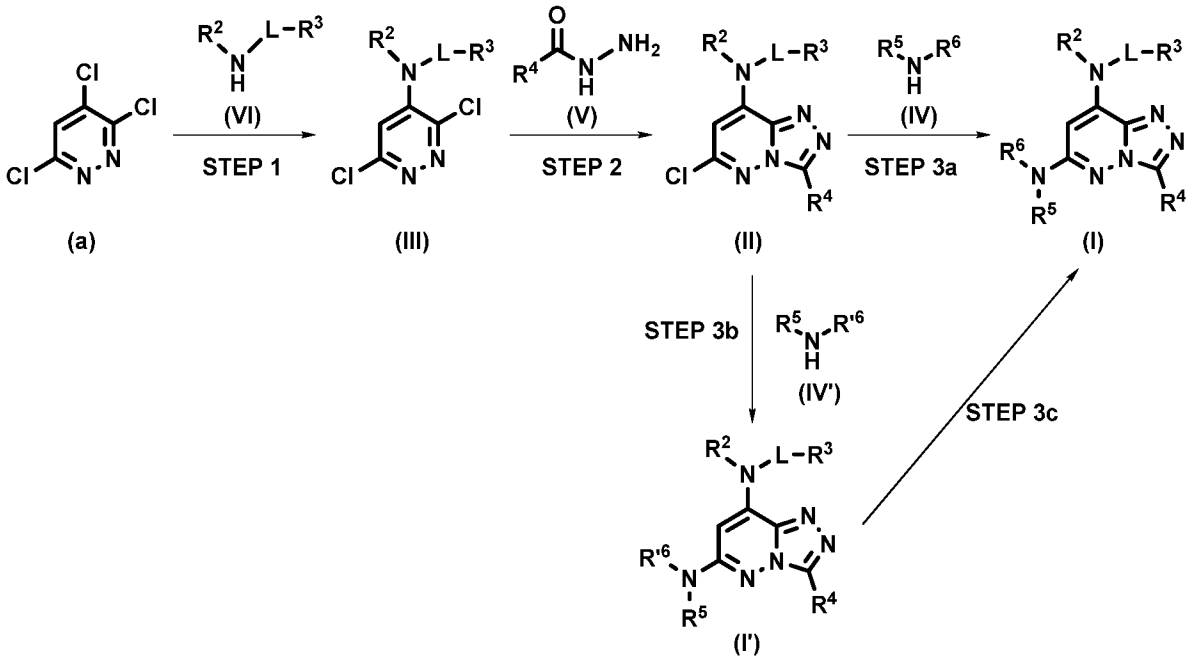
Abbreviation/acronym	**Name**
A_1AR	Adenosine receptor A_1
A_{2A}AR	Adenosine receptor A_{2A}
A_{2B}AR	Adenosine receptor A_{2B}
A_3AR	Adenosine receptor A_3
ACN	Acetonitrile
AcOH	Acetic acid
Alk	Alkyl
ATP	Adenosine triphosphate
br s	Broad singlet

Abbreviation/acronym	Name
nBuOH	Butan-1-ol
C	Molar concentration
cHex	Cyclohexane
Cpd N°	Compound number
d	Doublet
DCM	Methylene chloride
dd	Doublet of doublets
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
eq	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EtOAc	Ethyl Acetate
GP	General protocol
Hal	Halogen
HPLC	High pressure liquid chromatography
IC_{50}	Half maximal inhibitory concentration
iPr	isopropyl
iPrOH	Isopropanol
KHMDS	Potassium bis(trimethylsilyl)amide
m	Multiplet
M	Molarity
Me	Methyl
2MePrOH	2-Methylpropan-1-ol
MS	Mass spectroscopy
MW	Molecular weight
NBS	*N*-Bromosuccinimide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
N/A	Not applicable
n.t.	Not tested
Phe	phenyl
PIDA	phenyliodine(III) diacetate
nPrOH	Propan-1-ol

Abbreviation/acronym	Name
PTLC	Preparative thin layer chromatography
PTSA.H_2O or APTS.H_2O	p-Toluenesulfonic acid monohydrate
Rac	Racemic
r.t.	Room temperature
s	Singlet
t	Triplet
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	Tosyl
T °C	Temperature in degrees Celsius
UV	Ultraviolet
v/v	Volume per volume
w/v	Weight per volume
Δ	chemical shift
μw	Microwave irradiation

The compounds of general formula (I) can be prepared according to **Route 1** depicted in scheme 1 below.

Scheme 1



According to Route 1, the synthesis of compounds according to the invention is based on a functionalization of a compound of formula (II) wherein L, R^2, R^3 and R^4 are as defined above by an amine of formula (IV) wherein R^5 and R^6 are as defined above. The compound of formula (II) may be placed in STEP 3a in an aprotic solvent such as Et_3N, THF, 2-MeTHF, dioxane, cineol or NMP or a mixture of both or without solvent or else in a protic solvent such as ethylene glycol. The amine of formula (IV) may be added, for example in a molar ratio ranging from 1 to 20 eq, in particular of 10 eq, with respect to the compound of formula (II). The reaction mixture may be heated at a temperature between 150 to 180°C. Upon completion of the reaction, the mixture may be brought back to room temperature.

The compound of formula (II) may be placed in STEP 3b in an aprotic solvent such as Et_3N, THF, 2-MeTHF, dioxane, cineol or NMP or a mixture of both or without solvent or else in a protic solvent such as ethylene glycol. The amine of formula (IV'), wherein R'^6 comprises a -COOH group, may be added, for example in a molar ratio ranging from 1 to 20 eq, in particular of 10 eq, with respect to the compound of formula (II). The reaction mixture may be heated at a temperature between 150 to 180°C. Upon completion of the reaction, the mixture may be brought back to room temperature.

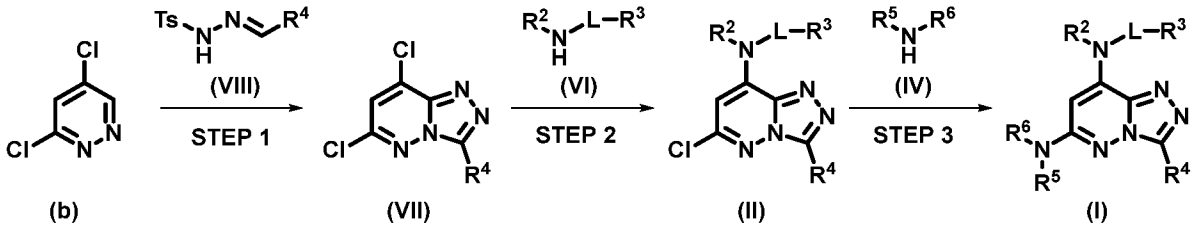
STEP 3c may be implemented according to known procedures for obtaining the corresponding amide or ester compound of formula (I).

A compound of formula (II) as defined above may be obtained in STEP 2 by reaction of a compound of formula (III) wherein L, R^2 and R^3 are as defined above, in an aprotic solvent such as dioxane. The hydrazide of formula (V) may be added, for example in a molar ratio ranging from 1 to 3 eq, in particular of 1.2 eq, with respect to the compound of formula (III). The resulting mixture may then be stirred, for example from 1 to 36 hours, in particular for 16 hours at a temperature between 100 °C to 115 °C by refluxing or in a sealed tube.

A compound of formula (III) as defined above may be obtained in STEP 1 by reaction of a compound of formula (a) with a compound of formula (VI) wherein L, R^2 and R^3 are as defined above, in an aprotic solvent such as DCM, THF, 2-MeTHF or dioxane, or a mixture thereof. The reaction mixture may be stirred at room temperature or reflux temperature or in sealed tube with DCM at 50 °C for a duration ranging from 1 to 24 hours, for example for 16 hours.

The compounds of general formula (I) can alternatively be prepared according to **Route 2**, depicted in scheme 2 below.

Scheme 2



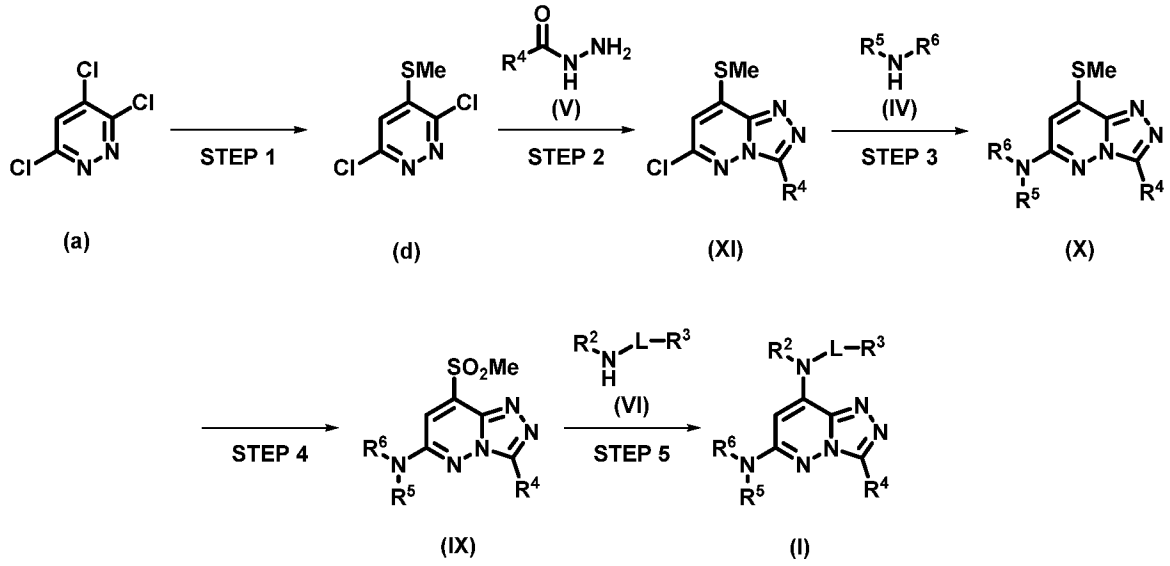
According to Route 2, the synthesis of compounds according to the invention is based on a functionalization of a compound of formula (II) wherein L, R^2, R^3, R^4 and R^5 are as defined above by an amine of formula (IV) wherein R^5 and R^6 are as defined above. The compound of formula (II) may be placed in STEP 3 in an aprotic solvent such as Et_3N, THF, 2-MeTHF, dioxane, cineol or NMP or a mixture of both or without solvent or else in a protic solvent such as ethylene glycol. The amine of formula (IV) may be added, for

example in a molar ratio ranging from 1 to 20 eq, in particular of 10 eq, with respect to the compound of formula (II). The reaction mixture may be heated at a temperature between 150 to 180°C. Upon completion of the reaction, the mixture may be brought back to room temperature.A compound of formula (II) as defined above may be obtained in STEP 2 by reaction of a compound of formula (VII) wherein R^4 is as defined above by an amine of formula (VI) wherein L, R^2 and R^3 are as defined above, in an aprotic solvent such as DCM, THF or 2Me-THF. The amine of formula (VI) may be added, for example in a molar ratio ranging from 1 to 5 eq, in particular of 1.2 eq, with respect to the compound of formula (VII). The resulting mixture may then be stirred, for example from 1 to 24 hours, in particular for 3 hours at a temperature between room temperature to solvent refluxing.

A compound of formula (VII) as defined above may be obtained in STEP 1 by reaction of a compound of formula (b) with a compound of formula (VIII) wherein R^4 is as defined above, in an aprotic solvent such as THF, 2-MeTHF or dioxane. The reaction mixture may be stirred at room temperature for a duration ranging from 1 to 24 hours, for example for 16 hours.

The compounds of general formula (I) can alternatively be prepared according to **Routes 3**, depicted in scheme 3 below.

Scheme 3



According to Route 3, the synthesis of compounds according to the invention is based on a functionalization of a compound of formula (IX) wherein R^4, R^5 and R^6 are as defined above by an amine of formula (VI) wherein L, R^2 and R^3 are as defined above. The

compound of formula (IX) may be placed in STEP 5 in an aprotic solvent such as dioxane. The amine of formula (VI) may be added, for example in a molar ratio ranging from 1 to 10 eq, in particular of 6 eq, with respect to the compound of formula (IX). The reaction mixture may be heated at a temperature between 100 to 130°C, in particular 110°C in a sealed tube. Upon completion of the reaction, the mixture may be brought back to room temperature.

A compound of formula (IX) as defined above may be obtained in STEP 4 by oxydation of a compound of formula (X) wherein R^4, R^5 and R^6 are as defined above, in a mixture of THF and water. The oxidazing reagent may be added, for example in a molar ratio ranging from 2 to 5 eq, in particular of 3.3 eq, with respect to the compound of formula (IX). The resulting mixture may then be stirred, for example from 1 to 24 hours, in particular for 18 hours at room temperature.

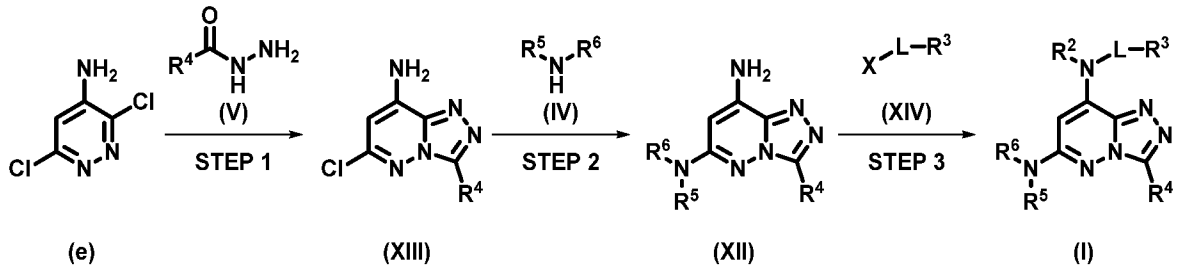
A compound of formula (X) as defined above may be obtained in STEP 3 by an amine of formula (V) wherein R^1 and R^2 are as defined above. The compound of formula (X) may be placed in STEP 3 in an aprotic solvent such as Et_3N, DIPEA, THF, 2-MeTHF, dioxane, cineol or NMP or a mixture of both or without solvent. The amine reagent may be added, for example in a molar ratio ranging from 2 to 20 eq, in particular of 15 eq, with respect to the compound of formula (IX). The resulting mixture may then be stirred, for example from 0.5 to 24 hours, in particular for 18 hours at a temperature between 100 to 150°C, in particular 120°C in a sealed tube.

A compound of formula (XI) as defined above may be obtained in STEP 2 by reaction of a compound of formula (d) with a compound of formula (V) wherein R^4 is as defined above, in an aprotic solvent such as THF, 2-MeTHF or dioxane. The reaction mixture may be stirred for a duration ranging from 1 to 24 hours, for example for 16 hours at a temperature ranging between 100 to 150°C, in particular 110°C in a sealed tube.

A compound of formula (d) as defined above may be obtained in STEP 2 by reaction of a compound of formula (a) with methylsulfanylsodium in an aprotic solvent such as THF or 2-MeTH. The reaction mixture may be stirred for a duration ranging from 1 to 6 hours, for example for 3 hours at room temperature or solvent refluxing.

The compounds of general formula (I) can alternatively be prepared according to **Routes 4**, depicted in scheme 4 below.

Scheme 4



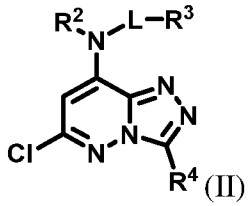
According to Route 4, the synthesis of compounds according to the invention is based on a functionalization of a compound of formula (XII) wherein R^4, R^5 and R^6 are as defined above by a reagent of formula (XIV) wherein L and R^3 are as defined above and X represents a hydroxy group, a chlorine atom, a bromine atom, an (C_1-C_3)alkyl sulfonate group or a phenyl sulfonate group . The compound of formula (XII) may be placed in STEP 3 in an aprotic solvent such as THF, 2-MeTHF, dioxane, DMSO or DMF. The reagent of formula (XIV) may be added, for example in a molar ratio ranging from 1 to 10 eq, in particular of 2 eq, with respect to the compound of formula (XII). The reaction mixture may be stirred for a duration ranging from 1 to 24 hours, for example for 3 hours at room temperature or solvent refluxing.

A compound of formula (XII) as defined above may be obtained in STEP 2 by reacting a compound of formula (XIII) wherein R^4 is as defined above with an amine of formula (IV) wherein R^5 and R^6 are as defined above. The compound of formula (XIII) may be placed in STEP 2 in an aprotic solvent such as Et_3N, DIPEA, THF, 2-MeTHF, dioxane, cineol or NMP or a mixture of both or without solvent. The amine reagent may be added, for example in a molar ratio ranging from 2 to 20 eq, in particular of 10 eq, with respect to the compound of formula (XIII). The resulting mixture may then be stirred, for example from 0.5 to 72 hours, in particular for 24 hours at a temperature between 150 to 220 °C, in particular 180°C in a sealed tube or under microwave irradiation system.

A compound of formula (XIII) as defined above may be obtained in STEP 1 by reaction of a compound (e) with a compound of formula (V) wherein R^4 is as defined above, in an aprotic solvent such as THF, 2-MeTHF or dioxane or an protic solvent such as iPrOH, nPrOH, 2-MePrOH or nBuOH. The reaction mixture may be stirred for a duration

ranging from 1 to 24 hours, for example for 18 hours at a temperature ranging between 100 to 150°C, in particular 110°C in a sealed tube or solvent refluxing.

Accordingly, herein is further provided a synthesis process for manufacturing a compound of formula (I) as defined above or any of its pharmaceutically acceptable salts, or at least any of compounds (1) to (234) as defined above or any of their pharmaceutically acceptable salts, comprising at least a step of reacting a compound of formula (II)

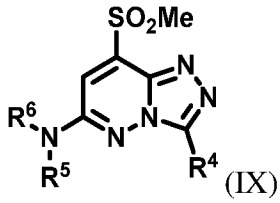

(II)

wherein L, R^2, R^3 and R^4 are as defined above, with an amine of formula (IV)

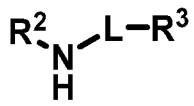
NHR^5R^6 (IV)

wherein R^5 and R^6 are as defined above, for example in a molar ratio ranging from 1 to 20 eq, with respect to the compound of formula (II), in an aprotic solvent or without solvent or else in a protic solvent.

Herein is further provided a synthesis process for manufacturing a compound of formula (I) as defined above or any of its pharmaceutically acceptable salts, or at least any of compounds (1) to (234) as defined above or any of their pharmaceutically acceptable salts, comprising at least a step of reacting a compound of formula (IX)

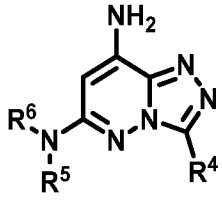

(IX)

wherein R^4, R^5 and R^6 are as defined above, with a compound of formula (VI)

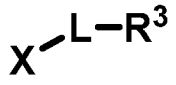

(VI)

wherein R^2 and R^3 are as defined above, in an aprotic solvent, for example in a molar ratio ranging from 1 to 10 eq, with respect to the compound of formula (IX).

Herein is further provided a synthesis process for manufacturing a compound of formula (I) as defined above or any of its pharmaceutically acceptable salts, or at least any of compounds (1) to (234) as defined above or any of their pharmaceutically acceptable salts, comprising at least a step of reacting a compound of formula (XII)

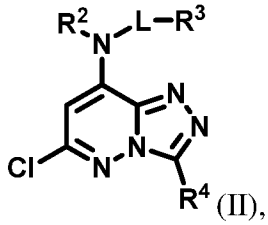
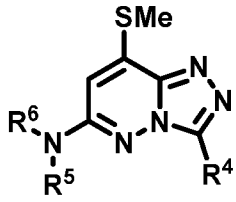
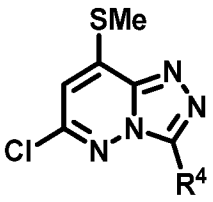
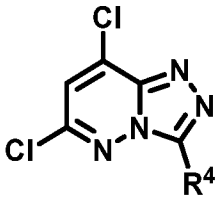

(XII)

wherein R^5 and R^6 are as defined above, with a compound of formula (XIV)


(XIV)

wherein L and R^3 are as defined above and X represents a hydroxy group, a chlorine atom, a bromine atom, an (C_1-C_3)alkyl sulfonate group or a phenyl sulfonate group, in an aprotic solvent for example in a molar ratio ranging from 1 to 10 eq, with respect to the compound of formula (XII).

Herein is further provided a compound of formula (II), (X), (XI) or (VII), in particular as an intermediate compound


(II),

(X),

(XI) or

(VII)

wherein R^4, R^5 and R^6 are as defined above, provided that R^4 is not a methyl group in formula (XI).

The intermediate products (a), (b) and (e) may be obtained commercially or according to methods known to the man skilled in the art.

The chemical structures, the analytical and spectroscopic data of some compounds of formula (I) of the invention are illustrated respectively in the following **Table 1** and **Table 2**.

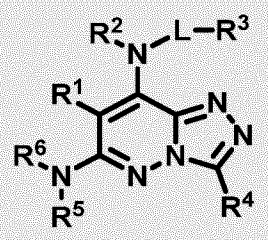
Reactions were performed using glassware or oven-dried glassware under inert atmosphere of argon or not. Unless otherwise noted, all reagent-grade chemicals and solvents were obtained from commercial suppliers and were used as received. Reactions were monitored by thin-layer chromatography with silica gel 60 F254 pre-coated aluminum plates (0.25 mm). Visualization was performed under UV light and 254 or 365 nm, or with appropriate TLC stains including, but not limited to: phosphomolybdic acid, $KMnO_4$, ninhydrin, CAM, vanillin, *p*-anisaldehyde.

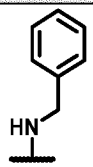
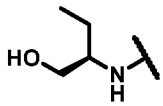
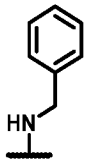
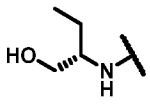
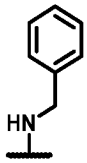
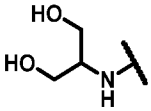
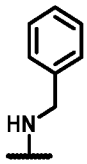
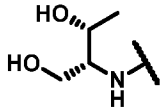
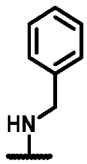
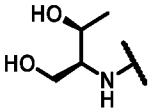
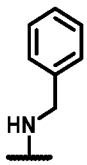
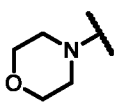
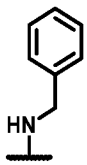
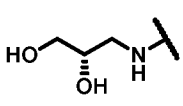
Chromatographic purifications of compounds were achieved on an automated Interchim Puriflash XS420 equipped with 30 µm spherical silica-filled prepacked columns as stationary phase (normal phase) or with C18 silica prepacked columns as stationary phase (reversed phase). Nevertheless, a second purification could be achieved with preparative thin layer chromatography with standard silica. Purifications work with various solvent as pur or mixed such as ethyl acetate, cyclohexane, methanol, methanol with ammonia 7N, dichloromethane, triethylamine and tetrahydrofuran on a normal phase then ACN, MeOH, H_2O and NH_4OH on a reversed phase.

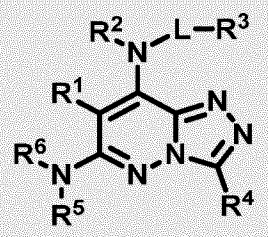
Mixtures possibilities: cHex/EtOAc, cHex/DCM, cHex/DCM/EtOAc, DCM/EtOAc, DCM/MeOH, DCM/MeOH NH_3 7N, DCM/MeOH/Et_3N, DCM/MeOH/THF, EtOAc/MeOH, EtOAc/MeOH NH_3 7N, EtOAc/THF, ACN/H_2O, ACN/NH_4OH, MeOH/H_2O, MeOH/NH_4OH.

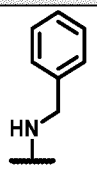
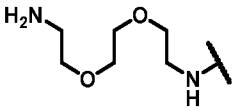
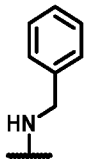
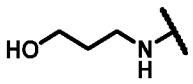
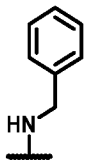
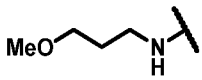
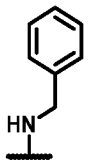
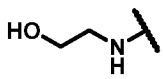
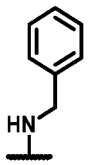
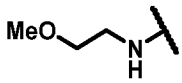
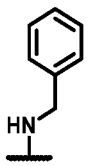
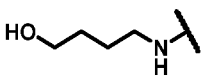
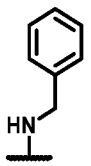
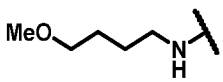
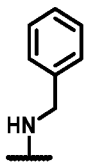
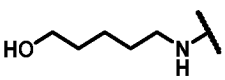
Some compounds of the invention are described with their structure in the below **Table 1**, which is merely illustrative and does not limit the scope of the present invention.

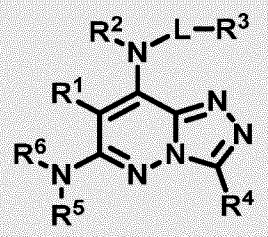
Table 1: Structure of compounds (1) to (234). Formulas and molecular weights were generated using Perkin Elmer's ChemDraw® Professional v22.0.022.


(I)

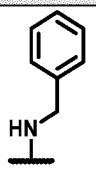
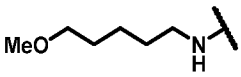
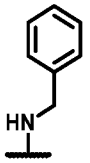
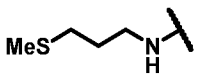
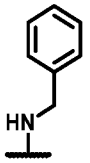
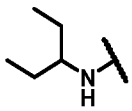
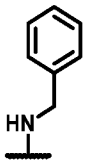
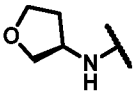
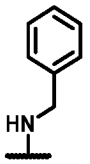
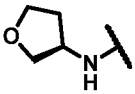
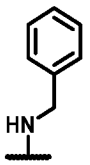
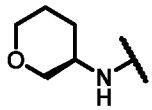
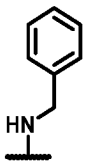
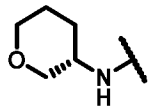
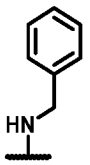
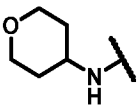
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(1)					$C_{19}H_{26}N_6O$	354.46	(R)
(2)					$C_{19}H_{26}N_6O$	354.46	(S)
(3)					$C_{18}H_{24}N_6O_2$	356.43	-
(4)					$C_{19}H_{26}N_6O_2$	370.46	(2R,3R)
(5)					$C_{19}H_{26}N_6O_2$	370.46	(2S,3S)
(6)					$C_{19}H_{24}N_6O$	352.44	-
(7)					$C_{18}H_{24}N_6O_2$	356.43	(S)

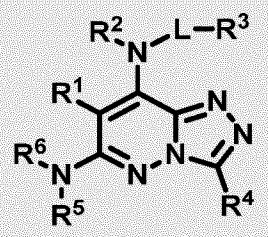

(I)

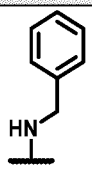
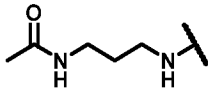
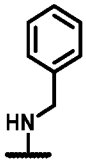
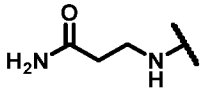
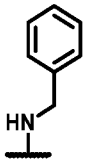
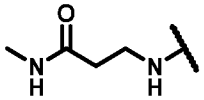
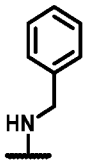
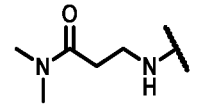
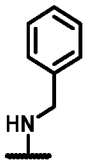
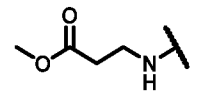
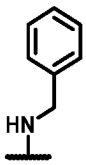
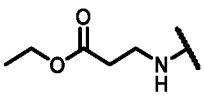
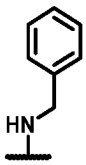
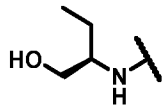
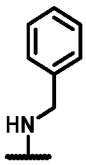
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(8)					$C_{21}H_{31}N_7O_2$	413.53	-
(9)					$C_{18}H_{24}N_6O$	340.43	-
(10)					$C_{19}H_{26}N_6O$	354.46	-
(11)					$C_{17}H_{22}N_6O$	326.40	-
(12)					$C_{18}H_{24}N_6O$	340.43	-
(13)					$C_{19}H_{26}N_6O$	354.46	-
(14)					$C_{20}H_{28}N_6O$	368.49	-
(15)					$C_{20}H_{28}N_6O$	368.49	-

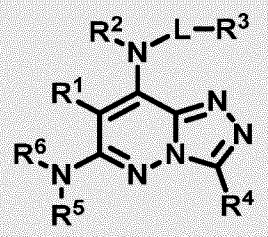


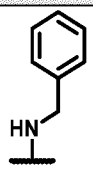
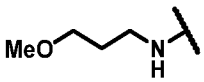
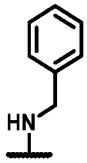
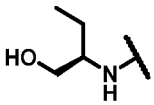
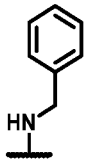
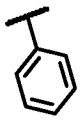
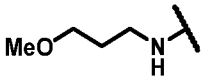
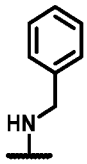
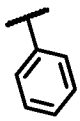
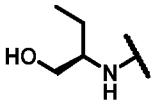
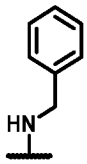
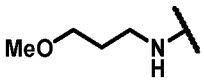
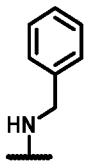
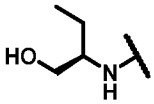
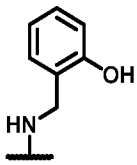
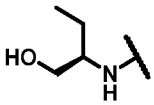
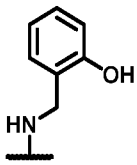
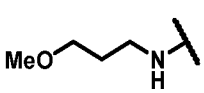
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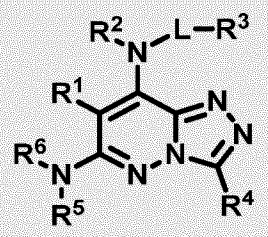
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(16)					$C_{21}H_{30}N_6O$	382.51	-
(17)					$C_{19}H_{26}N_6S$	370.52	-
(18)					$C_{20}H_{28}N_6$	352.49	-
(19)					$C_{19}H_{24}N_6O$	352.44	(R)
(20)					$C_{21}H_{26}N_6O$	378.48	(R)
(21)					$C_{20}H_{26}N_6O$	366.47	(R)
(22)					$C_{20}H_{26}N_6O$	366.47	(S)
(23)					$C_{20}H_{26}N_6O$	366.47	-

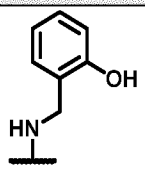
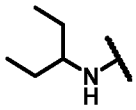
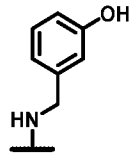
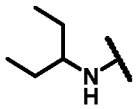
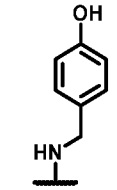
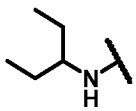
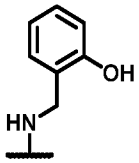
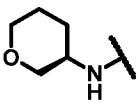
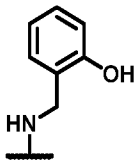
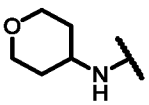
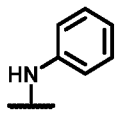
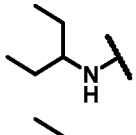
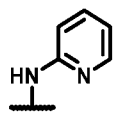
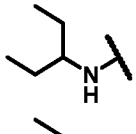
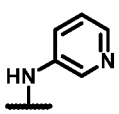
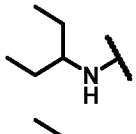
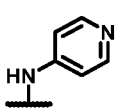
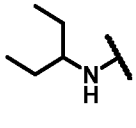

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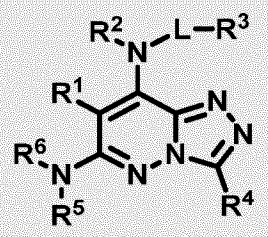
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(24)					$C_{20}H_{27}N_7O$	381.48	-
(25)					$C_{18}H_{23}N_7O$	353.43	-
(26)					$C_{19}H_{25}N_7O$	367.46	-
(27)					$C_{20}H_{27}N_7O$	381.48	-
(28)					$C_{19}H_{24}N_6O_2$	368.44	-
(29)					$C_{20}H_{26}N_6O_2$	382.47	-
(30)					$C_{19}H_{24}N_6O$	352.44	(R)
(31)					$C_{19}H_{24}N_6O$	352.44	-


(I)

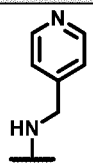
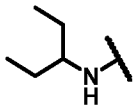
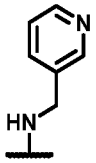
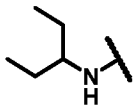
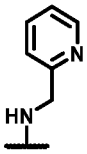
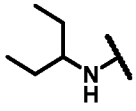
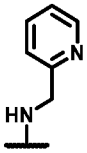
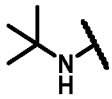
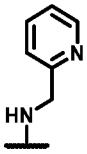
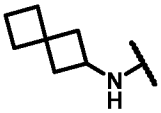
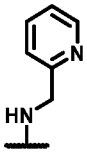
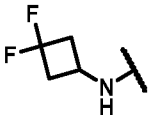
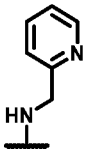
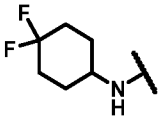
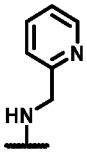
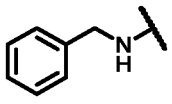
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(32)					$C_{17}H_{22}N_6O$	326.40	-
(33)					$C_{17}H_{22}N_6O$	326.40	(R)
(34)					$C_{22}H_{24}N_6O$	388.48	-
(35)					$C_{22}H_{24}N_6O$	388.48	(R)
(36)					$C_{17}H_{19}F_3N_6O$	380.38	-
(37)					$C_{17}H_{19}F_3N_6O$	380.38	(R)
(38)					$C_{19}H_{26}N_6O_2$	370.46	(R)
(39)					$C_{19}H_{26}N_6O_2$	370.46	-

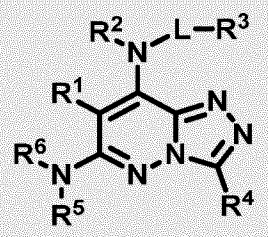

(I)

Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(40)					$C_{20}H_{28}N_6O$	368.49	-
(41)					$C_{20}H_{28}N_6O$	368.49	-
(42)					$C_{20}H_{28}N_6O$	368.49	-
(43)					$C_{20}H_{26}N_6O_2$	382.47	(R)
(44)					$C_{20}H_{26}N_6O_2$	382.47	-
(45)					$C_{19}H_{26}N_6$	338.46	-
(46)					$C_{18}H_{25}N_7$	339.45	-
(47)					$C_{18}H_{25}N_7$	339.45	-
(48)					$C_{18}H_{25}N_7$	339.45	-

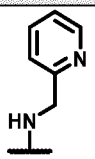
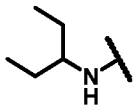
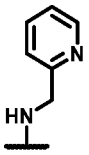
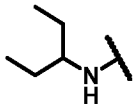
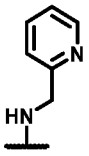
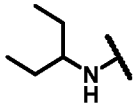
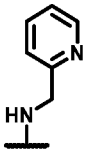
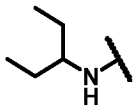
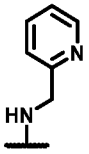
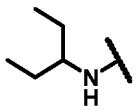
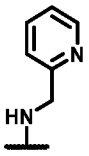
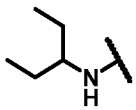
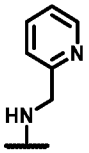
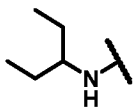
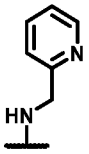
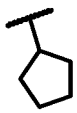
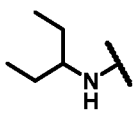


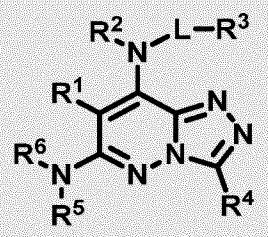
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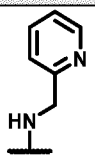
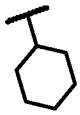
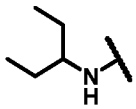
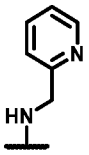
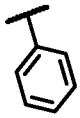
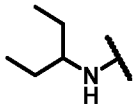
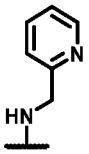
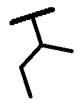
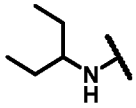
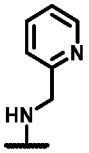
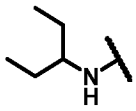
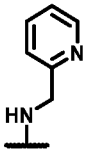
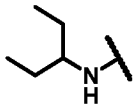
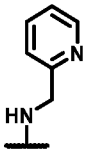
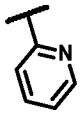
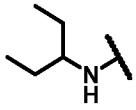
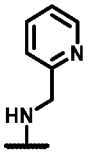
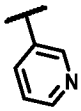
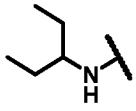
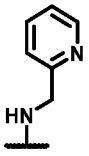
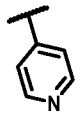
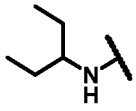
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(49)					$C_{19}H_{27}N_7$	353.47	-
(50)					$C_{19}H_{27}N_7$	353.47	-
(51)					$C_{19}H_{27}N_7$	353.47	-
(52)					$C_{19}H_{27}N_7$	339.45	-
(53)					$C_{21}H_{27}N_7$	377.50	-
(54)					$C_{18}H_{21}F_2N_7$	373.41	-
(55)					$C_{20}H_{25}F_2N_7$	401.47	-
(56)					$C_{21}H_{23}N_7$	373.46	-

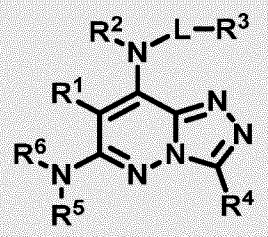


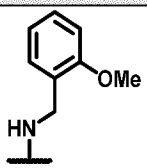
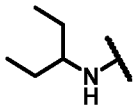
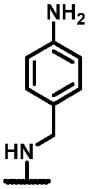
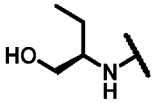
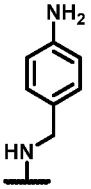
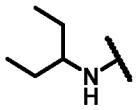
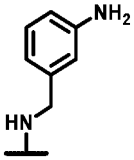
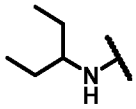
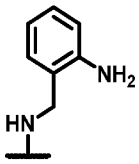
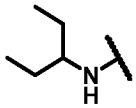
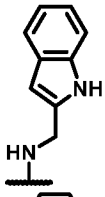
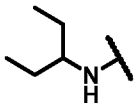
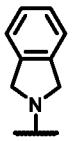
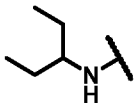
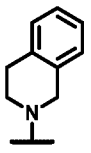
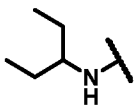
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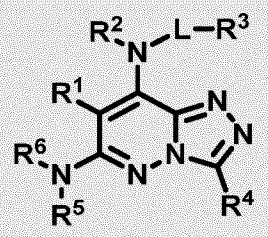
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(57)					$C_{16}H_{21}N_7$	311.39	-
(58)					$C_{17}H_{23}N_7$	325.42	-
(59)					$C_{18}H_{25}N_7$	339.45	-
(60)					$C_{19}H_{27}N_7$	353.47	-
(61)					$C_{20}H_{29}N_7$	367.50	-
(62)					$C_{19}H_{25}N_7$	351.46	-
(63)					$C_{20}H_{27}N_7$	365.49	-
(64)					$C_{21}H_{29}N_7$	379.51	-


(I)

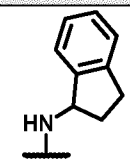
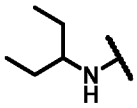
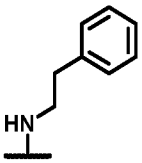
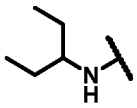
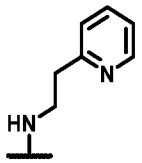
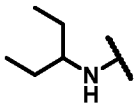
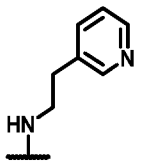
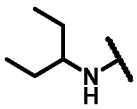
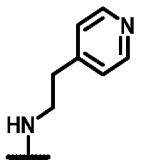
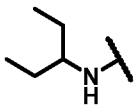
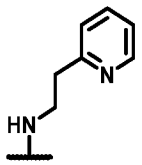
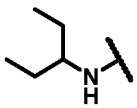
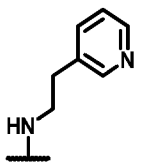
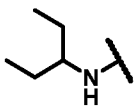
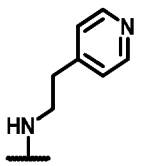
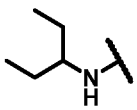
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(65)					$C_{22}H_{31}N_7$	393.54	-
(66)					$C_{22}H_{25}N_7$	387.49	-
(67)					$C_{20}H_{29}N_7$	367.50	-
(68)					$C_{21}H_{31}N_7$	381.53	-
(69)					$C_{20}H_{29}N_7$	367.50	-
(70)					$C_{21}H_{24}N_8$	388.48	-
(71)					$C_{21}H_{24}N_8$	388.48	-
(72)					$C_{21}H_{24}N_8$	388.48	-

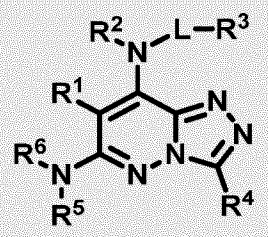

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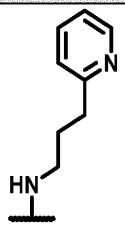
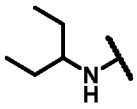
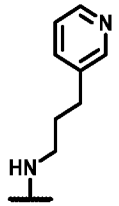
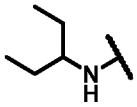
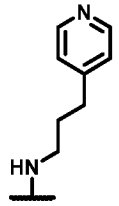
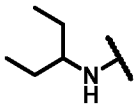
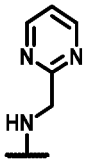
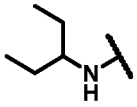
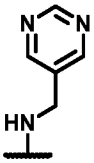
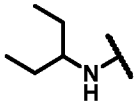
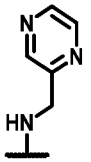
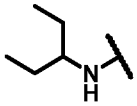
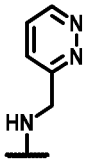
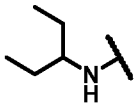
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(73)					$C_{21}H_{30}N_6O$	382.51	-
(74)					$C_{19}H_{27}N_7O$	369.47	(R)
(75)					$C_{20}H_{29}N_7$	367.50	-
(76)					$C_{20}H_{29}N_7$	367.50	-
(77)					$C_{20}H_{29}N_7$	367.50	-
(78)					$C_{22}H_{29}N_7$	391.52	-
(79)					$C_{21}H_{28}N_6$	360.50	-
(80)					$C_{22}H_{30}N_6$	378.52	-

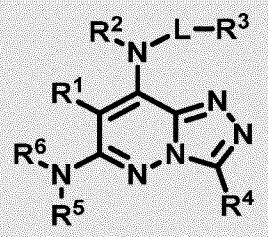


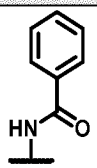
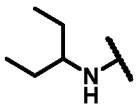
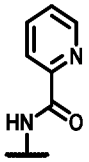
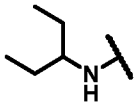
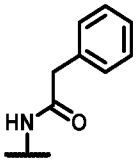
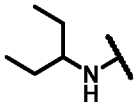
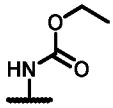
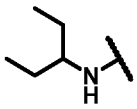
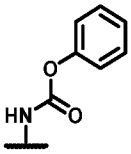
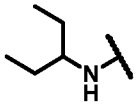
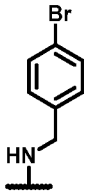
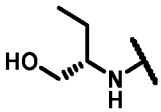
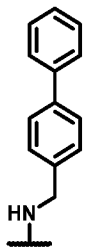
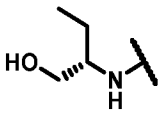
(I)

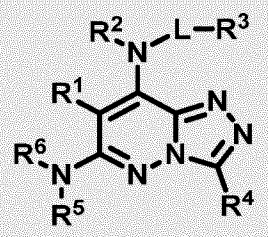
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(81)					$C_{22}H_{30}N_6$	378.52	Rac
(82)					$C_{21}H_{30}N_6$	366.51	-
(83)					$C_{20}H_{29}N_7$	367.50	-
(84)					$C_{20}H_{29}N_7$	367.50	-
(85)					$C_{20}H_{29}N_7$	367.50	-
(86)					$C_{20}H_{27}N_7$	365.49	-
(87)					$C_{20}H_{27}N_7$	365.49	-
(88)					$C_{20}H_{27}N_7$	365.49	-


(I)

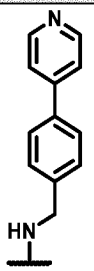
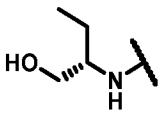
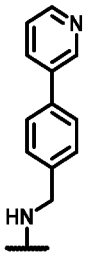
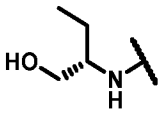
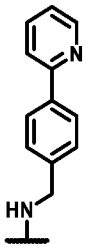
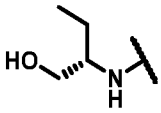
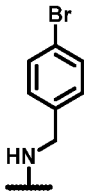
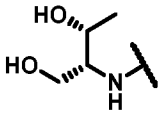
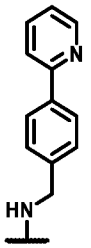
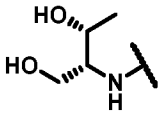
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(89)					$C_{21}H_{31}N_7$	381.53	-
(90)					$C_{21}H_{31}N_7$	381.53	-
(91)					$C_{21}H_{31}N_7$	381.53	-
(92)					$C_{18}H_{26}N_8$	354.46	-
(93)					$C_{18}H_{26}N_8$	354.46	-
(94)					$C_{18}H_{26}N_8$	354.46	-
(95)					$C_{18}H_{26}N_8$	354.46	-

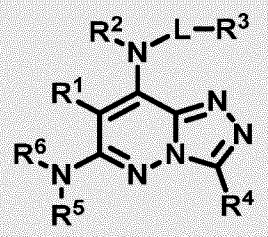

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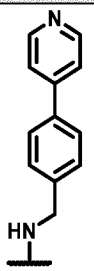
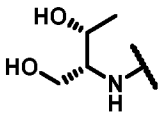
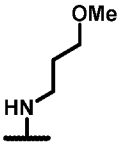
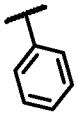
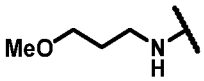
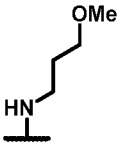
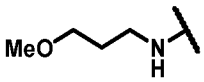
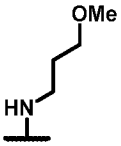
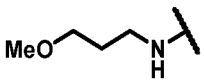
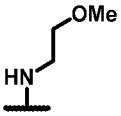
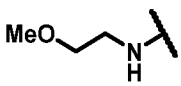
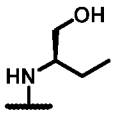
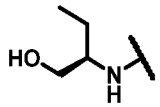
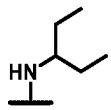
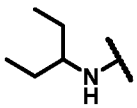
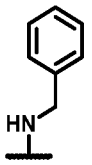
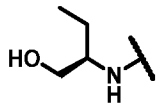
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(96)					$C_{20}H_{26}N_6O$	366.47	-
(97)					$C_{19}H_{25}N_7O$	367.46	-
(98)					$C_{21}H_{28}N_6O$	380.50	-
(99)					$C_{16}H_{26}N_6O_2$	334.42	-
(100)					$C_{20}H_{26}N_6O_2$	382.47	-
(101)					$C_{19}H_{25}BrN_6O$	433.35	(S)
(102)					$C_{25}H_{30}N_6O$	430.56	(S)

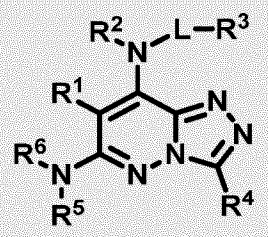


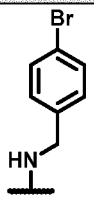
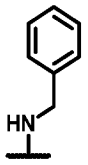
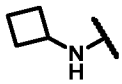
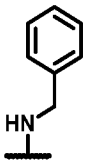
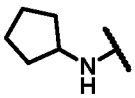
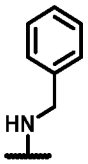
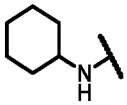
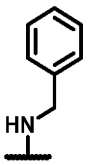
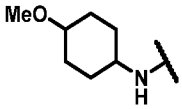
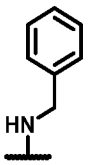
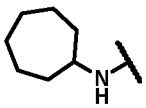
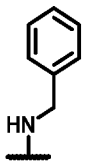
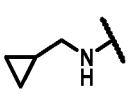
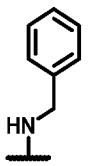
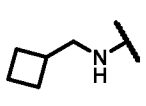
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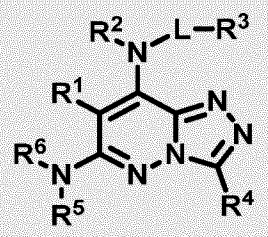
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(103)					$C_{24}H_{29}N_7O$	431.54	(S)
(104)					$C_{24}H_{29}N_7O$	431.54	(S)
(105)					$C_{24}H_{29}N_7O$	431.54	(S)
(106)					$C_{19}H_{25}BrN_6O_2$	449.35	(S)
(107)					$C_{24}H_{29}N_7O_2$	447.54	(2R,3R)


(I)

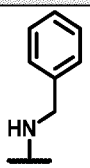
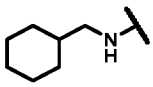
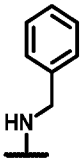
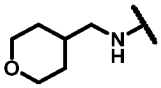
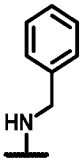
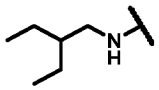
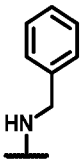
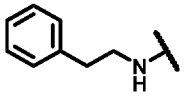
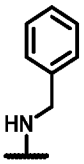
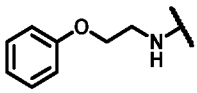
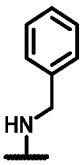
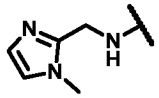
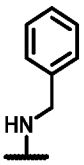
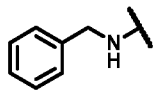
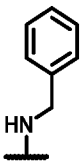
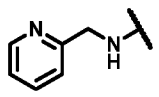
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(108)					$C_{24}H_{29}N_7O_2$	447.54	(2R,3R)
(109)					$C_{19}H_{26}N_6O_2$	370.46	-
(110)					$C_{16}H_{26}N_6O_2$	334.42	-
(111)					$C_{14}H_{21}F_3N_6O_2$	362.36	-
(112)					$C_{14}H_{24}N_6O_2$	308.39	-
(113)					$C_{16}H_{28}N_6O_2$	336.44	(R), (R)
(114)					$C_{18}H_{32}N_6$	332.50	-
(115)					$C_{20}H_{28}N_6O$	368.49	(R)

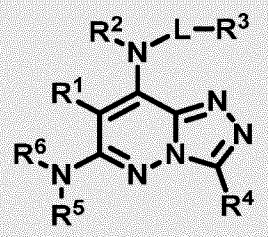

(I)

Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(116)					$C_{16}H_{19}BrN_6$	375.27	-
(117)					$C_{19}H_{24}N_6$	336.44	-
(118)					$C_{20}H_{26}N_6$	350.47	-
(119)					$C_{21}H_{28}N_6$	364.50	-
(120)					$C_{22}H_{30}N_6O$	394.52	Z/E, rac.
(121)					$C_{22}H_{30}N_6$	378.52	-
(122)					$C_{19}H_{24}N_6$	336.44	-
(123)					$C_{20}H_{26}N_6$	350.47	-

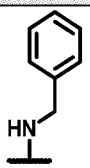
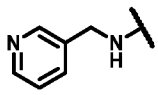
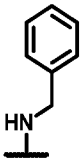
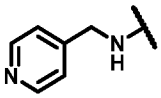
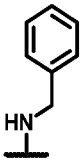
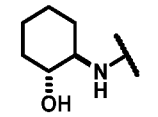
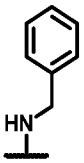
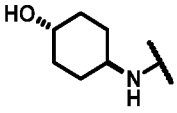
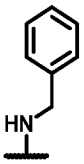
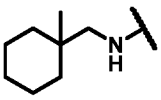
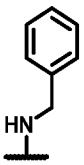
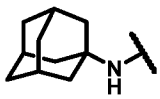
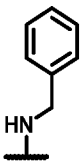
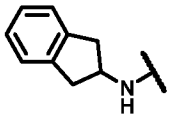
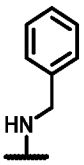
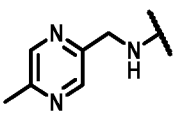


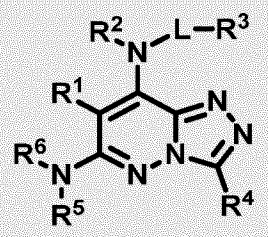
(I)

Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(124)					$C_{22}H_{30}N_6$	378.52	-
(125)					$C_{21}H_{28}N_6O$	380.50	-
(126)					$C_{21}H_{30}N_6$	366.51	-
(127)					$C_{23}H_{26}N_6$	386.50	-
(128)					$C_{23}H_{26}N_6O$	402.50	-
(129)					$C_{20}H_{24}N_8$	376.47	-
(130)					$C_{22}H_{24}N_6$	372.48	-
(131)					$C_{21}H_{23}N_7$	373.46	-

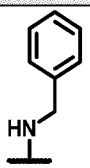
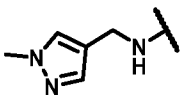
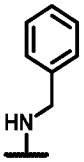
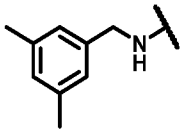
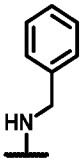
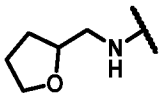
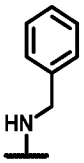
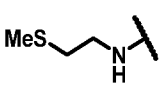
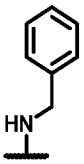
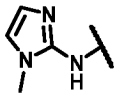
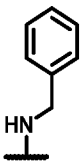
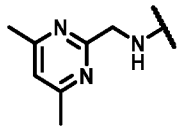
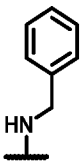
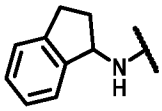
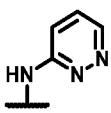
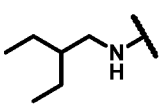
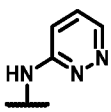
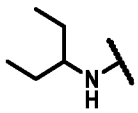


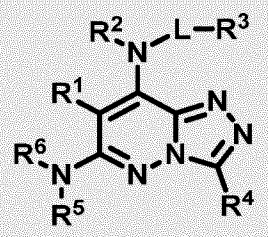
(I)

Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(132)					$C_{21}H_{23}N_7$	373.46	-
(133)					$C_{21}H_{23}N_7$	372.48	-
(134)					$C_{21}H_{28}N_6O$	380.50	Z, rac.
(135)					$C_{21}H_{28}N_6O$	380.50	Z, rac.
(136)					$C_{23}H_{32}N_6$	379.51	-
(137)					$C_{25}H_{32}N_6$	380.50	-
(138)					$C_{24}H_{26}N_6$	380.50	-
(139)					$C_{21}H_{24}N_8$	392.35	-

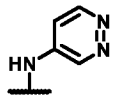
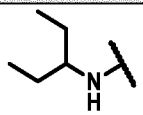
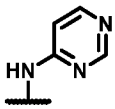
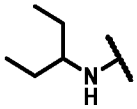
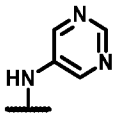
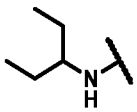
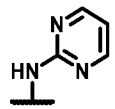
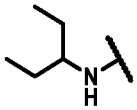
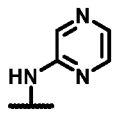
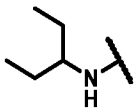
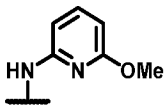
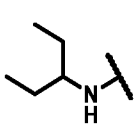
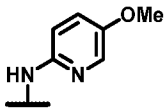
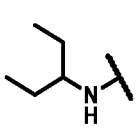
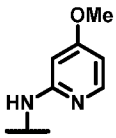
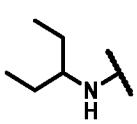
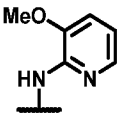
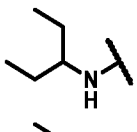
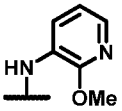
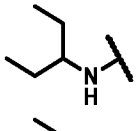


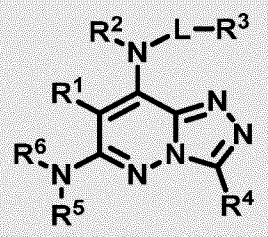
(I)

Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(140)					$C_{20}H_{24}N_8$	393.54	-
(141)					$C_{24}H_{28}N_6$	416.57	-
(142)					$C_{20}H_{26}N_6O$	366.47	Rac.
(143)					$C_{18}H_{24}N_6S$	356.49	-
(144)					$C_{19}H_{22}N_8$	362.44	-
(145)					$C_{22}H_{26}N_8$	402.51	-
(146)					$C_{24}H_{26}N_6$	398.51	rac.
(147)					$C_{18}H_{26}N_8$	354.46	
(148)					$C_{17}H_{24}N_8$	340.44	-

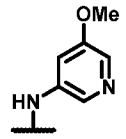
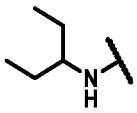
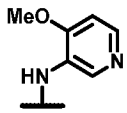
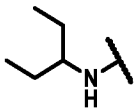
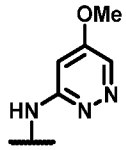
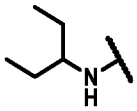
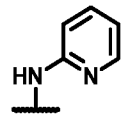
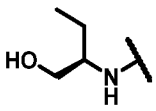
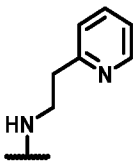
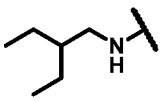
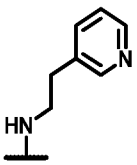
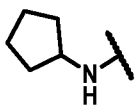
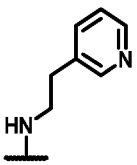
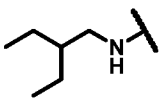
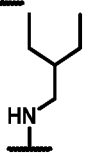
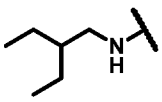


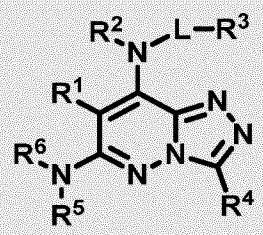
(I)

Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(149)					$C_{17}H_{24}N_8$	340.44	-
(150)					$C_{17}H_{24}N_8$	340.44	-
(151)					$C_{17}H_{24}N_8$	340.44	-
(152)					$C_{17}H_{24}N_8$	340.44	-
(153)					$C_{17}H_{24}N_8$	340.44	-
(154)					$C_{19}H_{27}N_7O$	369.47	-
(155)					$C_{19}H_{27}N_7O$	369.47	-
(156)					$C_{19}H_{27}N_7O$	369.47	-
(157)					$C_{19}H_{27}N_7O$	369.47	-
(158)					$C_{19}H_{27}N_7O$	369.47	-
(159)					$C_{19}H_{27}N_7O$	369.47	-

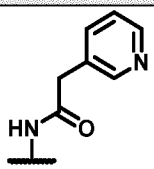
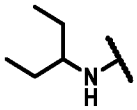
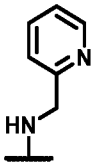
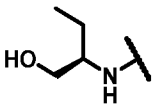
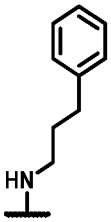
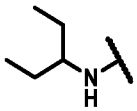
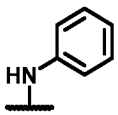
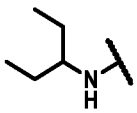
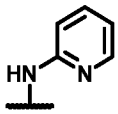
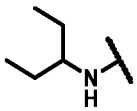
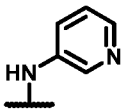
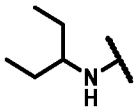
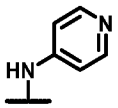
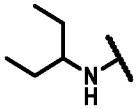
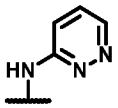
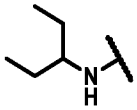
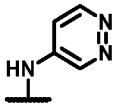
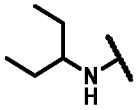
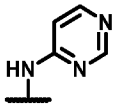
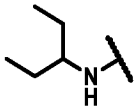


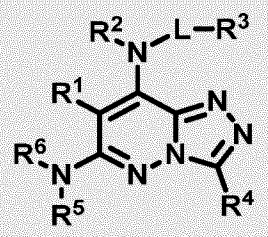
(I)

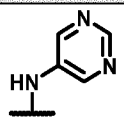
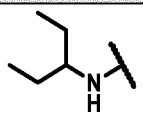
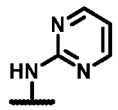
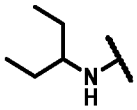
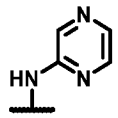
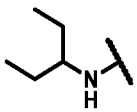
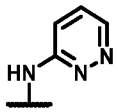
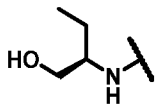
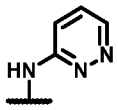
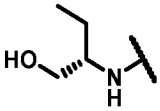
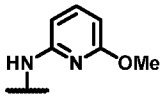
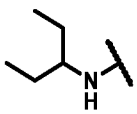
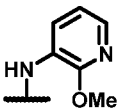
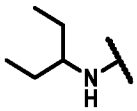
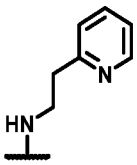
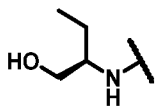
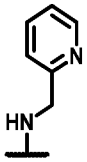
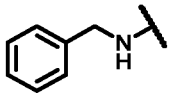
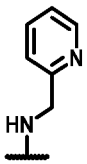
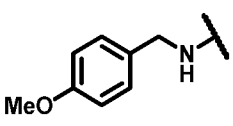
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(160)					$C_{19}H_{27}N_7O$	369.47	-
(161)					$C_{19}H_{27}N_7O$	369.47	-
(162)					$C_{18}H_{26}N_8O$	370.46	-
(163)					$C_{17}H_{23}N_7O$	341.42	(R)
(164)					$C_{21}H_{31}N_7$	381.53	-
(165)					$C_{20}H_{27}N_7$	365.49	-
(166)					$C_{21}H_{31}N_7$	381.53	-
(167)					$C_{20}H_{36}N_6$	360.55	-

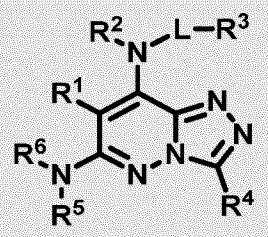


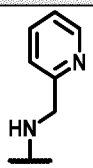
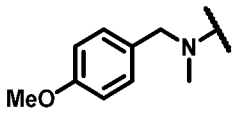
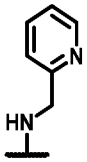
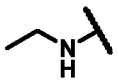
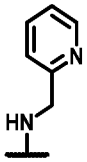
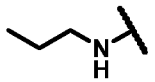
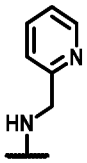
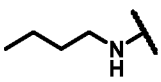
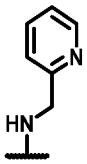
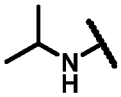
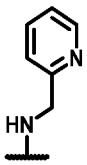
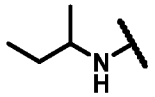
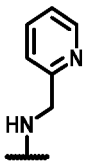
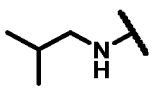
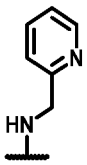
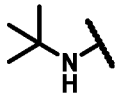
(I)

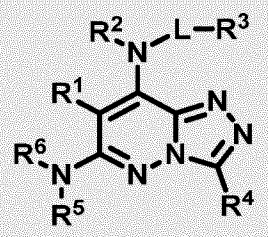
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(168)					$C_{20}H_{27}N_7O$	381.48	-
(169)					$C_{18}H_{25}N_7O$	355.45	(R)
(170)					$C_{22}H_{32}N_6$	380.54	-
(171)					$C_{19}H_{24}N_6$	336.44	-
(172)					$C_{18}H_{23}N_7$	337.43	-
(173)					$C_{18}H_{23}N_7$	337.43	-
(174)					$C_{18}H_{23}N_7$	337.43	-
(175)					$C_{17}H_{22}N_8$	338.42	-
(176)					$C_{17}H_{22}N_8$	338.42	-
(177)					$C_{17}H_{22}N_8$	338.42	-


(I)

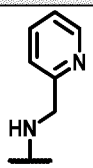
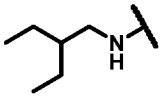
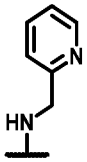
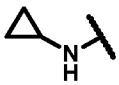
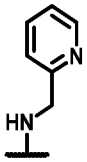
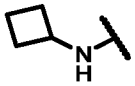
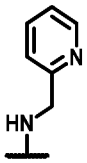
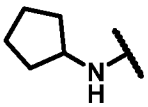
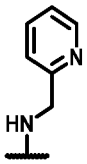
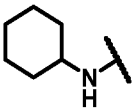
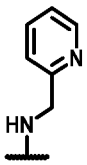
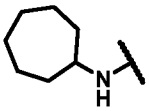
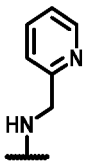
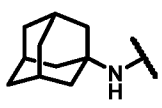
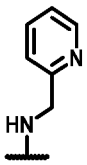
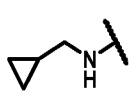
Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(178)					$C_{17}H_{22}N_8$	338.42	-
(179)					$C_{17}H_{22}N_8$	338.42	-
(180)					$C_{17}H_{22}N_8$	338.42	-
(181)					$C_{16}H_{20}N_8O$	340.39	(R)
(182)					$C_{16}H_{20}N_8O$	340.39	(S)
(183)					$C_{19}H_{25}N_7O$	367.46	-
(184)					$C_{19}H_{25}N_7O$	367.46	-
(185)					$C_{19}H_{25}N_7O$	367.46	(R)
(186)					$C_{21}H_{21}N_7$	371.45	-
(187)					$C_{22}H_{23}N_7O$	401.47	-

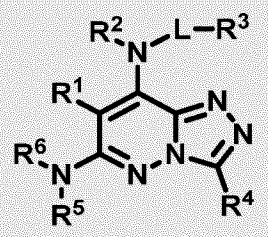

(I)

Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(188)					$C_{23}H_{25}N_7O$	415.50	-
(189)					$C_{16}H_{19}N_7$	309.38	-
(190)					$C_{17}H_{21}N_7$	323.40	-
(191)					$C_{18}H_{23}N_7$	337.43	-
(192)					$C_{17}H_{21}N_7$	323.40	-
(193)					$C_{18}H_{23}N_7$	337.43	Rac.
(194)					$C_{17}H_{21}N_7$	337.43	-
(195)					$C_{18}H_{23}N_7$	337.43	-

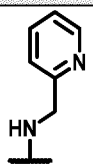
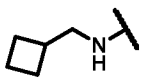
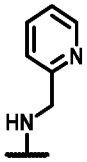
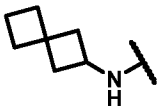
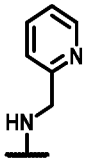
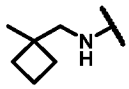
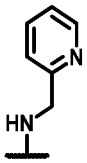
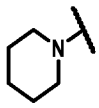
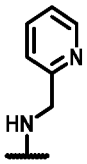
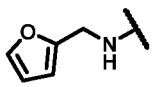
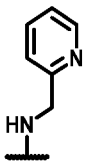
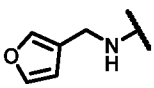
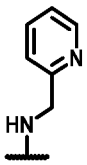
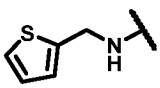
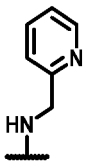
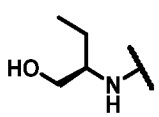


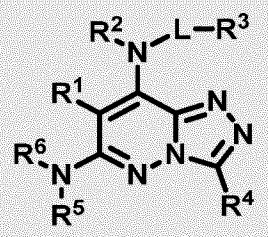
(I)

Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(196)					$C_{20}H_{27}N_7$	365.49	-
(197)					$C_{17}H_{19}N_7$	321.39	-
(198)					$C_{18}H_{21}N_7$	335.42	-
(199)					$C_{19}H_{23}N_7$	349.44	-
(200)					$C_{20}H_{25}N_7$	363.47	-
(201)					$C_{21}H_{27}N_7$	377.50	-
(202)					$C_{24}H_{29}N_7$	415.55	-
(203)					$C_{18}H_{21}N_7$	335.42	-

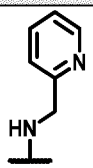
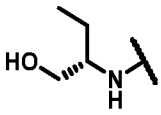
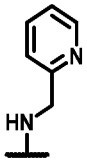
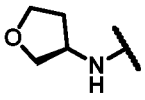
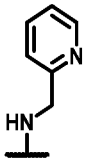
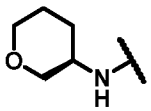
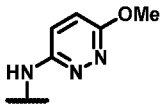
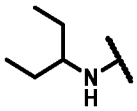
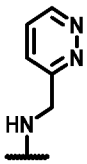
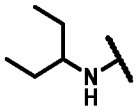
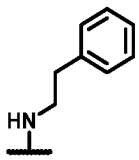
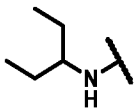
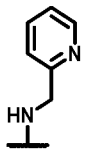
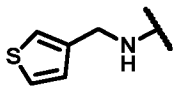
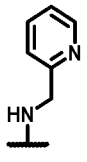


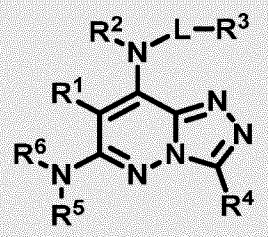
(I)

Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(204)					$C_{16}H_{23}N_7$	349.44	-
(205)					$C_{21}H_{25}N_7$	375.45	-
(206)					$C_{20}H_{25}N_7$	363.47	-
(207)					$C_{19}H_{23}N_7$	349.44	-
(208)					$C_{19}H_{19}N_7O$	361.41	-
(209)					$C_{19}H_{19}N_7O$	361.41	-
(210)					$C_{19}H_{19}N_7S$	377.47	-
(211)					$C_{18}H_{23}N_7O$	353.43	(R)

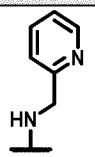
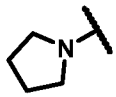
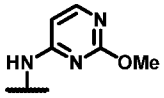
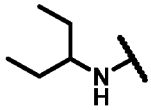
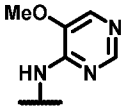
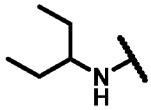
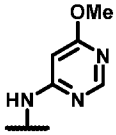
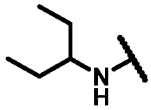
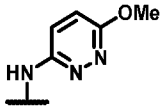
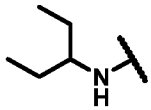
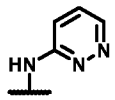
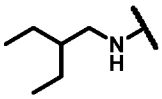
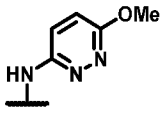
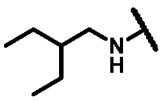
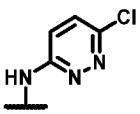
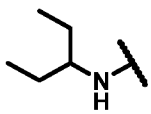
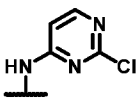
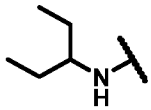
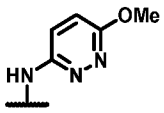
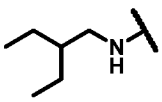


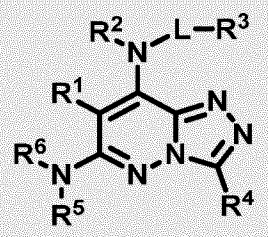
(I)

Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(212)					$C_{18}H_{23}N_7O$	353.43	(S)
(213)					$C_{18}H_{21}N_7O$	351.41	(R)
(214)					$C_{19}H_{23}N_7O$	365.44	(R)
(215)					$C_{18}H_{24}N_8O$	368.45	-
(216)					$C_{18}H_{24}N_8$	352.45	-
(217)					$C_{21}H_{28}N_6$	364.50	-
(218)					$C_{19}H_{19}N_7S$	377.47	-
(219)					$C_{15}H_{17}N_7$	295.35	-

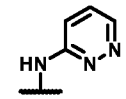
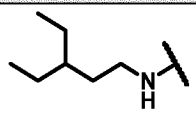
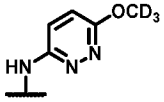
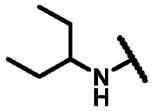
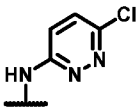
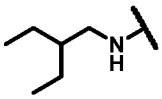
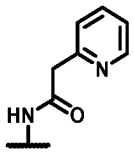
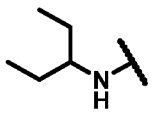
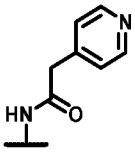
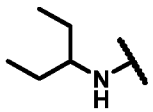


(I)

Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(220)					$C_{18}H_{21}N_7$	335.42	-
(221)					$C_{18}H_{26}N_8O$	370,46	-
(222)					$C_{18}H_{26}N_8O$	370,46	-
(223)					$C_{18}H_{26}N_8O$	370,46	-
(224)					$C_{18}H_{26}N_8O$	370,46	-
(225)					$C_{18}H_{24}N_8$	352,45	-
(226)					$C_{19}H_{26}N_8O$	382,47	-
(227)					$C_{17}H_{23}ClN_8$	374,88	-
(228)					$C_{17}H_{23}ClN_8$	374,88	-
(229)					$C_{19}H_{28}N_8O$	384,49	-



(I)

Cpd N°	NR^2LR^3	R^4	NR^5R^6	R^1	Formula	MW	Stereo-chemistry
(230)					$C_{19}H_{28}N_8$	368,49	-
(231)					$C_{18}H_{23}D_3N_8O$	373,48	-
(232)					$C_{18}H_{25}ClN_8$	388,90	-
(233)					$C_{20}H_{27}N_7O$	381.48	-
(234)					$C_{20}H_{27}N_7O$	381.48	-

The below **Table 2** describes the analytical and spectroscopic data of the compounds introduced in **Table 1**.

^1H NMR analyses (400 or 500 MHz) and ^{13}C NMR spectra (101 MHz) were recorded with a Bruker ULTRASHIELD 500 or 400 spectrometer. Processing and analyses of the spectra were performed with MestReNova. Data appear in the following order: chemical shifts in ppm which were referenced to the internal solvent signal, multiplicity, number of protons, and coupling constant *J* in Hertz.

Synthetic intermediates: reversed-phase UPLC/MS analyses were carried out with a UPLC Acquity (Waters) with an UV-DAD detector and a mass detector (SQD2). Compounds (0.2 to 0.6 mg) were solubilized in a mixture of DMSO/H_2O (1/1) and filtered on syringe filter 0.2 µm.

- Acidic conditions:

Acquity BEH C18 column, 2.1 x 50 mm, 1.7 µm. Flow rate: 0.65 mL/min. Gradient: (H_2O + 0.1% HCOOH v/v)/(CAN + 0.1% HCOOH v/v) from 95/5 to 5/95 in 4.0 min.

Final compounds: Reversed-phase HPLC/MS analyses were carried out with a HPLC Ultimate 3000 (ThermoScientific) with an UV-DAD detector. Mass detection processing with direct infusion in mass detector (SQD2) from UPLC Acquity (Waters). Compounds (0.2 to 0.6 mg) were solubilized in a mixture of DMSO/H_2O (1/1) and filtered on syringe filter 0.2 µm.

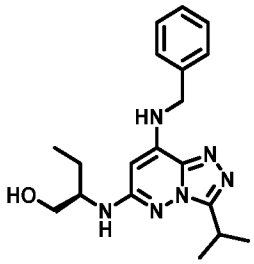
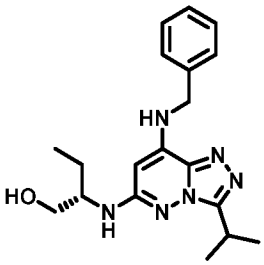
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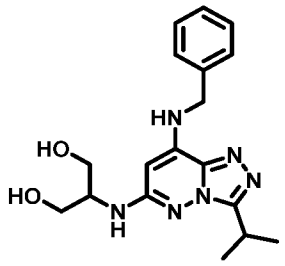
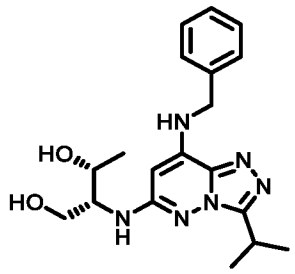
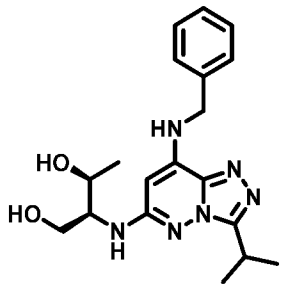
Thermo Scientific Syncronis C18 column, 150 x 4.6 mm, 5 µm. Flow rate: 1 mL/min. Gradient: (H_2O + 0.1% HCOOH v/v)/(ACN + 0.1% HCOOH v/v) from 95/5 to 5/95 in 19.0 min.

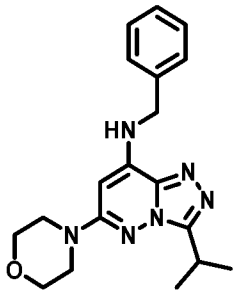
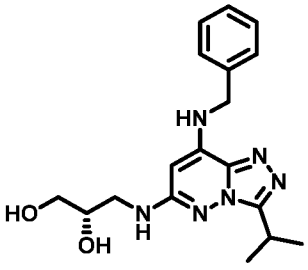
- Alkaline conditions:

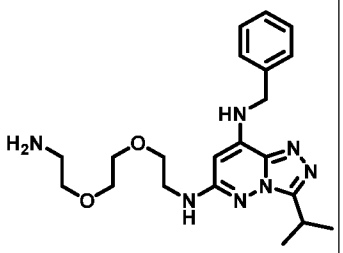
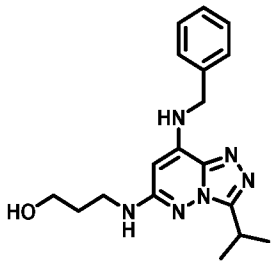
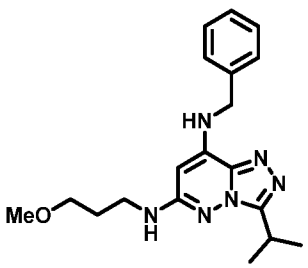
Thermo Scientific Syncronis C18 column, 150 x 4.6 mm, 5 µm or XTERRA RP18, 150x4.6mm, 3.5µm. Flow rate: 1 mL/min. Gradient: ($HCOONH_4$ 10mM + NH_4OH 25% aq. to ajust pH = 10)/ACN from 95/5 to 5/95 in 19.0 min.

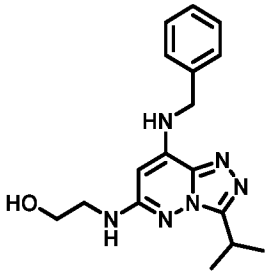
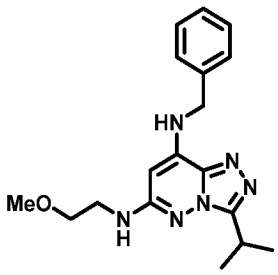
Table 2: Spectroscopic and analytical characterization of compounds **(1)** to **(234)**

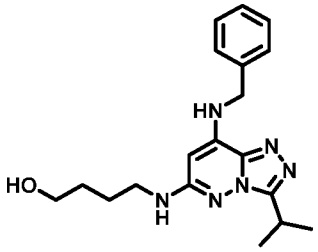
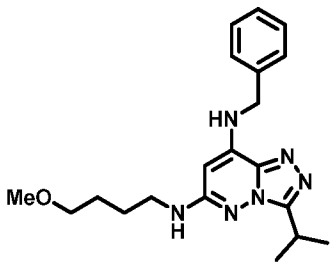
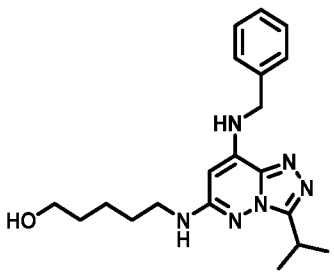
Cpd N°	Structure	HPLC	Description
(1)		> 98% [a]	Pale yellow solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.85 (t, J = 7.4 Hz, 3H, CH_3), 1.35 (d, J = 6.9 Hz, 6H, 2xCH_3), 1.37 – 1.66 (m, 2H, CH_2), 3.25 – 3.31 (m, 1H, CH_{Alk}), 3.41 (dq, J = 18.6, 5.3 Hz, 2H, CH_2), 3.62 (h, J = 5.9 Hz, 1H, CH_{Alk}), 4.37 – 4.48 (m, 2H, CH_2), 4.57 (t, J = 5.4 Hz, 1H, OH), 5.47 (s, 1H, H_{Ar}), 6.29 (d, J = 7.7 Hz, 1H, NH_{Alk}), 7.24 (td, J = 6.2, 2.6 Hz, 1H, H_{Ar}), 7.31 – 7.38 (m, 4H, 4xH_{Ar}), 7.86 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.5 (CH_3), 19.6 (CH_3), 23.6 (CH_2), 24.7 (CH), 45.2 (CH_2), 53.8 (CH), 61.9 (CH_2), 84.4 (CH), 126.8 (CH_{Ar}), 126.9 (CH_{Ar}), 128.4 (CH_{Ar}), 138.4 (C_q), 139.7 (C_q), 139.8 (C_q), 152.7 (C_q), 155.8 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{26}N_6O$:** 355.2 [M+H]+, **found :** 355.3.
(2)		> 98% [a]	White Solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.85 (t, J = 7.4 Hz, 3H, $CH_{3\ Alk}$), 1.35 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.67 (m, 2H, $CH_{2\text{-}CH3}$), 3.27 – 3.34 (m, 1H, H_{Alk}), 3.41 (dq, J = 18.5, 5.4 Hz, 2H, $CH_{2\text{-}OH}$), 3.62 (h, J = 6.0 Hz, 1H, $H_{Alk\ iPr}$), 4.34 – 4.52 (m, 2H, $CH_{2\ Bn}$), 4.57 (t, J = 5.4 Hz, 1H, OH), 5.47 (s, 1H, H_{Ar}), 6.29 (d, J = 7.8 Hz, 1H, NH), 7.17 – 7.45 (m, 5H, 5xH_{Ar}), 7.86 (t, J = 6.3 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.5 ($CH_{3\ Alk}$), 19.6 (2x$CH_{3\ iPr}$), 23.6 ($CH_{2\text{-}CH3}$), 24.7 (CH_{Alk}), 45.2 ($CH_{2\ Bn}$), 53.8 ($CH_{Alk\ iPr}$), 61.9 ($CH_{2\text{-}OH}$), 84.4 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.4 (C_q), 139.7 (C_q), 139.8 (C_q), 152.7 (C_q), 155.8 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{26}N_6O$:** 355.2 [M+H]+, **found :** 355.3.

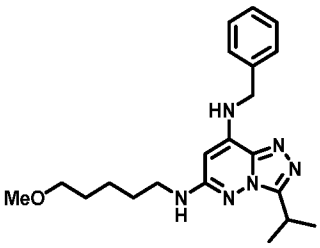
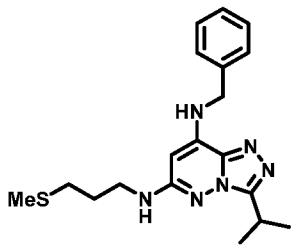
(3)		> 96 % [a]	White Solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (d, J = 7.0 Hz, 6H, 2xCH_3), 3.27 – 3.38 (m, 1H, H_{Alk}), 3.50 (t, J = 5.4 Hz, 4H, 2x$CH_{2\ Alk}$), 3.74 (h, J = 5.4 Hz, 1H, $H_{Alk\ iPr}$), 4.42 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 4.56 (t, J = 5.4 Hz, 2H, 2xOH), 5.53 (s, 1H, H_{Ar}), 6.28 (d, J = 7.5 Hz, 1H, NH), 7.21 – 7.44 (m, 5H, 5xH_{Ar}), 7.90 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.7 (2xCH_3), 24.7 (CH_{Alk}), 45.2 ($CH_{2\ Bn}$), 54.3 ($CH_{Alk\ iPr}$), 59.7 (2xCH_2), 84.5 (CH_{Ar}), 126.9 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.5 (C_q), 139.7 (C_q), 139.8 (C_q), 152.8 (C_q), 155.7 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{26}N_6O$:** 357.2 [M+H]+, **found :** 327.35.
(4)		> 96 % [a]	White Solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.04 (d, J = 6.4 Hz, 3H, $CH_{3\ Alk}$), 1.35 (dd, J = 7.0, 4.5 Hz, 6H, 2x$CH_{3\ iPr}$), 3.27 – 3.36 (m, 1H, H_{iPr}), 3.48 (ddt, J = 36.1, 10.5, 5.7 Hz, 2H, $CH_{2\text{-}OH}$), 3.73 (q, J = 7.6, 7.1 Hz, 1H, $H_{Alk\text{-}NH}$), 3.93 – 4.04 (m, 1H, $H_{Alk\text{-}OH}$), 4.42 (d, J = 6.4 Hz, 2H, $CH_{2\ Bn}$), 4.54 (t, J = 5.6 Hz, 2H, 2xOH), 5.65 (s, 1H, H_{Ar}), 6.12 (d, J = 8.3 Hz, 1H, NH), 7.20 – 7.41 (m, 5H, 5xH_{Ar}), 7.86 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.7 ($CH_{3\ iPr}$), 19.7 ($CH_{3\ iPr}$), 20.3 ($CH_{3\ Alk}$), 24.6 (CH_{iPr}), 45.2 ($CH_{2\ Bn}$), 56.9 (CH_{Alk}), 60.1 (CH_{Alk}), 64.5 ($CH_{2\text{-}OH}$), 84.5 (CH_{Ar}), 126.9 (CH_{Ar}), 127.0 (2xCH_{Ar}), 128.4 (2xCH_{Ar}), 138.5 (C_q), 139.7 (C_q), 139.7 (C_q), 152.7 (C_q), 156.3 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{26}N_6O_2$:** 371.22 [M+H]+, **found :** 371.36.
(5)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.03 (d, J = 6.4 Hz, 3H, $CH_{3\ Alk}$), 1.35 (dd, J = 7.0, 4.4 Hz, 6H, 2x$CH_{3\ iPr}$), 3.24 – 3.38 (m, 1H, H_{iPr}), 3.47 (ddt, J = 36.1, 10.5, 5.6 Hz, 2H, $CH_{2\text{-}OH}$), 3.73 (qt, J = 6.2, 2.8 Hz, 1H, $H_{Alk\text{-}NH}$), 3.97 (dq, J = 9.6, 6.2 Hz, 1H, $H_{Alk\text{-}OH}$), 4.41 (d, J = 6.4 Hz, 2H, $CH_{2\ Bn}$), 4.53 (t, J = 5.6 Hz, 2H, 2xOH), 5.64 (s, 1H, H_{Ar}), 6.11 (d, J = 8.3 Hz, 1H, NH), 7.20 – 7.41 (m, 5H, 5xH_{Ar}), 7.86 (t, J = 6.4

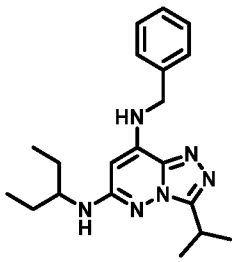
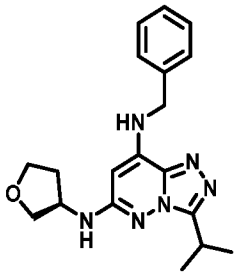
			Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.7 ($CH_{3\ iPr}$), 19.7 ($CH_{3\ iPr}$), 20.3 ($CH_{3\ Alk}$), 24.6 (CH_{iPr}), 45.2 ($CH_{2\ Bn}$), 56.9 (CH_{Alk}), 60.1 (CH_{Alk}), 64.5 ($CH_{2\text{-}OH}$), 84.5 (CH_{Ar}), 126.9 (CH_{Ar}), 127.0 ($2xCH_{Ar}$), 128.4 ($2xCH_{Ar}$), 138.5 (C_q), 139.7 (C_q), 139.7 (C_q), 152.7 (C_q), 156.3 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{26}N_6O_2$:** 371.22 [M+H]+, **found :** 371.36.
(6)		> 96% [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (d, J = 6.9 Hz, 6H, $2xCH_3$), 3.28 – 3.41 (m, 5H, $2xCH_{2\text{-}N}$ & CH_{iPr}), 3.62 – 3.73 (m, 4H, $2xCH_{2\text{-}O}$), 4.56 (d, J = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.83 (s, 1H, H_{Ar}), 7.23 (t, J = 7.3 Hz, 1H, H_{Ar}), 7.32 (t, J = 7.5 Hz, 2H, $2xH_{Ar}$), 7.40 (d, J = 7.5 Hz, 2H, $2xH_{Ar}$), 8.15 (t, J = 6.4 Hz, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.7 ($2xCH_{3\ iPr}$), 24.7 (CH_{iPr}), 44.9 ($CH_{2\ Bn}$), 46.1 ($2xCH_{2\text{-}N}$), 65.7 ($2xCH_{2\text{-}O}$), 82.4 (CH_{Ar}), 127.0 (CH_{Ar}), 127.3 ($2xCH_{Ar}$), 128.4 ($2xCH_{Ar}$), 138.5 (C_q), 139.4 (C_q), 140.9 (C_q), 153.1 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{26}N_6O$:** 353.21 [M+H]+, **found :** 353.26.
(7)		> 97 % [a]	White Solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.35 (d, J = 6.9 Hz, 6H, $2xCH_{3\ iPr}$), 2.99 – 3.11 (m, 1H, $H_{Alk(CH2\text{-}NH)}$), 3.25 – 3.36 (m, 4H, $H_{Alk\ iPr}$ & $CH_{2\text{-}OH}$ & $H_{Alk(CH2\text{-}NH)}$), 3.64 (h, J = 5.4 Hz, 1H, $H_{Alk\text{-}OH}$), 4.42 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 4.53 (t, J = 5.6 Hz, 1H, $OH\text{-}_{CH2}$), 4.71 (d, J = 5.0 Hz, 1H, $OH\text{-}_{HAlk}$), 5.51 (s, 1H, H_{Ar}), 6.47 (t, J = 5.4 Hz, 1H, NH_{Alk}), 7.21 – 7.41 (m, 5H, $5xH_{Ar}$), 7.90 (t, J = 6.5 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.7 ($2xCH_{3\ iPr}$), 24.6 (CH_{iPr}), 44.3 ($CH_{2\text{-}NH}$), 45.2 ($CH_{2\ Bn}$), 64.0 ($CH_{2\text{-}OH}$), 70.0 (CH_{Alk}), 84.3 (CH_{Ar}), 126.9 (CH_{Ar}), 126.9 ($2xCH_{Ar}$), 128.4 ($2xCH_{Ar}$), 138.4 (C_q), 139.7 (C_q), 139.8 (C_q), 152.9 (C_q), 156.2 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{24}N_6O_2$:** 357.20 [M+H]+, **found :**. 357.35.

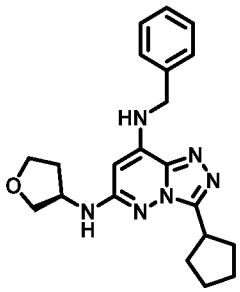
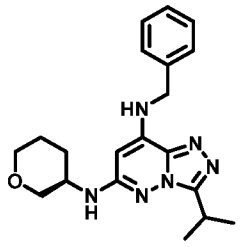
(8)		> 99 % [b]	White crystalline solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 2.63 (t, J = 5.7 Hz, 2H, CH_2), 3.29 – 3.36 (m, 5H, 2xCH_2 & H_{iPr}), 3.46 – 3.58 (m, 6H, 3xCH_2), 4.43 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.43 (s, 1H, H_{Ar}), 6.62 (t, J = 5.5 Hz, 1H, NH_{Bn}), 7.20 – 7.38 (m, 5H, 5xH_{Ar}), 7.93 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.7 (2xCH_3), 24.7 (CH_{iPr}), 40.6 (CH_2), 41.1 (CH_2), 45.2 ($CH_{2\ Bn}$), 68.6 (CH_2), 69.5 (CH_2), 69.6 (CH_2), 72.6 (CH_2), 84.1 (CH_{Ar}), 126.9 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.7 (C_q), 139.9 (C_q), 152.9 (C_q), 155.8 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{31}N_7O_2$:** 414.26 [M+H]+, **found :** 414.40.
(9)		> 99 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.66 (p, J = 6.6 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.17 (q, J = 6.6 Hz, 2H, $CH_{2\text{-}NH\ Alk}$), 3.29 – 3.37 (m, 1H, H_{iPr}), 3.45 (q, J = 6.0 Hz, 2H, $CH_{2\text{-}OH}$), 4.43 (dd, J = 6.2, 3.4 Hz, 3H, $CH_{2\ Bn}$ & OH), 5.38 (s, 1H, H_{Ar}), 6.50 (t, J = 5.3 Hz, 1H, NH_{Alk}), 7.20 – 7.40 (m, 5H, 5xH_{Ar}), 7.90 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.7 (2x$CH_{3\ iPr}$), 24.7 (CH_{iPr}), 31.8 ($CH_{2\text{-}CH2\text{-}NH}$), 38.0 ($CH_{2\text{-}NH\ Alk}$), 45.2 ($CH_{2\ Bn}$), 58.6 ($CH_{2\text{-}OH}$), 84.2 ($CH_{Ar}$), 126.8 (2x$CH_{Ar}$), 126.9 ($CH_{Ar}$), 128.4 (2x$CH_{Ar}$), 138.4 ($C_q$), 139.7 ($C_q$), 139.8 ($C_q$), 152.9 ($C_q$), 156.0 ($C_q$). **MS (ESI+) : m/z calcd for $C_{18}H_{24}N_6O$:** 341.21 [M+H]+, **found :** 341.36
(10)		> 98 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.75 (p, J = 6.6 Hz, 2H, $CH_{2\text{-}CH2}$), 3.17 (q, J = 6.5 Hz, 2H, $CH_{2\text{-}NH\ Alk}$), 3.22 (s, 3H, OCH_3), 3.29 – 3.39 (m, 3H, CH_{iPr} & $CH_{2\text{-}OCH3}$), 4.44 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.54 (t, J = 5.4 Hz, 1H, NH_{Alk}), 7.19 – 7.41 (m, 5H, 5xH_{Ar}), 7.91 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.7

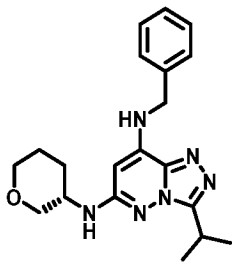
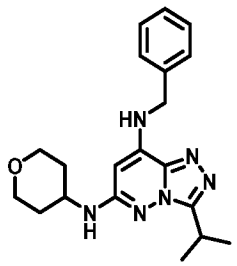
			(2xCH$_{3\ iPr}$), 24.7 (CH$_{iPr}$), 28.5 (CH$_{2\text{-}CH2}$), 38.0 (CH$_{2\text{-}NH\ Alk}$), 45.2 (CH$_{2\ Bn}$), 57.8 (OCH$_3$), 69.8 (CH$_{2\text{-}OCH3}$), 84.1 (CH$_{Ar}$), 126.8 (2xCH$_{Ar}$), 126.9 (CH$_{Ar}$), 128.4 (2xCH$_{Ar}$), 138.3 (C$_q$), 139.7 (C$_q$), 139.8 (C$_q$), 152.9 (C$_q$), 155.9 (C$_q$). **MS (ESI+) : m/z calcd for C$_{19}$H$_{26}$N$_6$O :** 355.2 [M+H]+, **found :** 355.3.
(11)		> 99 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.35 (d, *J* = 6.9 Hz, 6H, 2xCH$_3$), 3.21 (q, *J* = 5.7 Hz, 2H, CH$_{2\text{-}NH\ Alk}$), 3.28 – 3.36 (m, 1H, H$_{iPr}$), 3.52 (q, *J* = 5.7 Hz, 2H, CH$_{2\text{-}OH}$), 4.42 (d, *J* = 6.3 Hz, 2H, CH$_{2\ Bn}$), 4.63 (t, *J* = 5.3 Hz, 1H, OH), 5.44 (s, 1H, H$_{Ar}$), 6.55 (t, *J* = 5.5 Hz, 1H, NH$_{Alk}$), 7.19 – 7.39 (m, 5H, 5xH$_{Ar}$), 7.91 (t, *J* = 6.4 Hz, 1H, NH$_{Bn}$). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 19.7 (2xCH$_3$), 24.6 (CH$_{iPr}$), 43.6 (CH$_{2\text{-}NH}$), 45.2 (CH$_{2\ Bn}$), 59.3 (CH$_{2\text{-}OH}$), 84.3 (CH$_{Ar}$), 126.9 (2xCH$_{Ar}$), 126.9 (CH$_{Ar}$), 128.4 (2xCH$_{Ar}$), 138.4 (C$_q$), 139.7 (C$_q$), 139.8 (C$_q$), 152.8 (C$_q$), 156.0 (C$_q$). **MS (ESI+) : m/z calcd for C$_{17}$H$_{22}$N$_6$O :** 327.19 [M+H]+, **found :** 327.35.
(12)		> 95 % [a a]	White crystalline solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.35 (d, *J* = 6.9 Hz, 6H, 2xCH$_{3\ iPr}$), 3.24 (s, 3H, OCH$_3$), 3.27 – 3.37 (m, 3H, H$_{iPr}$ & CH$_{2\text{-}NH\ Alk}$), 3.45 (t, *J* = 5.6 Hz, 2H, CH$_{2\text{-}OCH3}$), 4.42 (d, *J* = 6.3 Hz, 2H, CH$_{2\ Bn}$), 5.44 (s, 1H, H$_{Ar}$), 6.62 (t, *J* = 5.5 Hz, 1H, NH$_{Alk}$), 7.19 – 7.41 (m, 5H, 5xH$_{Ar}$), 7.93 (t, *J* = 6.4 Hz, 1H, NH$_{Bn}$). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 19.6 (2xCH$_{3\ iPr}$), 24.7 (CH$_{iPr}$), 40.4 (CH$_{2\text{-}NH\ Alk}$), 45.2 (CH$_{2\text{-}OCH3}$), 57.9 (OCH$_3$), 70.1 (CH$_{2\ Bn}$), 84.1 (CH$_{Ar}$), 126.9 (2xCH$_{Ar}$), 126.9 (CH$_{Ar}$), 128.4 (2xCH$_{Ar}$), 138.3 (C$_q$), 139.7 (C$_q$), 139.9 (C$_q$), 152.8 (C$_q$), 155.8 (C$_q$). **MS (ESI+) : m/z calcd for C$_{18}$H$_{24}$N$_6$O :** 341.21 [M+H]+, **found :** 341.33.

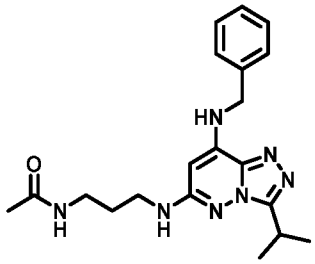
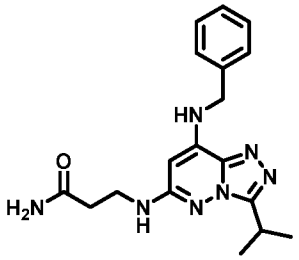
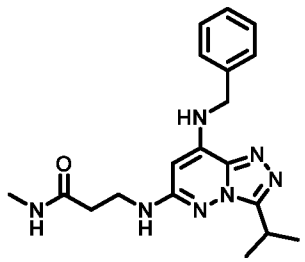
(13)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.37 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.41 – 1.49 (m, 2H, $CH_{2\text{-}CH2\text{-}OH}$), 1.49 – 1.59 (m, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.13 (q, J = 6.3 Hz, 2H, $CH_{2\text{-}NH}$), 3.27 – 3.37 (m, 1H, H_{iPr}), 3.39 (q, J = 6.1 Hz, 2H, $CH_{2\text{-}OH}$), 4.37 (t, J = 5.1 Hz, 1H, OH), 4.43 (d, J = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.38 (s, 1H, H_{Ar}), 6.52 (t, J = 5.4 Hz, 1H, NH_{Alk}), 7.18 – 7.41 (m, 5H, 5xH_{Ar}), 7.89 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6 (2x $CH_{3\ iPr}$), 24.7 (CH_{iPr}), 25.1 ($CH_{2\text{-}CH2\text{-}NH}$), 30.2 ($CH_{2\text{-}CH2\text{-}OH}$), 40.6 ($CH_{2\text{-}NH}$), 45.2 ($CH_{2\ Bn}$), 60.5 ($CH_{2\text{-}OH}$), 84.1 ($CH_{Ar}$), 126.8 (2x$CH_{Ar}$), 126.9 ($CH_{Ar}$), 128.4 (2x$CH_{Ar}$), 138.4 ($C_q$), 139.7 ($C_q$), 139.8 ($C_q$), 152.8 ($C_q$), 155.9 ($C_q$). **MS (ESI+) : m/z calcd for $C_{19}H_{26}N_6O$:** 355.22 [M+H]+, **found :** 355.34.
(14)		> 96 % [a]	White crystalline solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.53 (p, J = 3.5 Hz, 4H, 2xCH_2), 3.09 – 3.17 (m, 2H, CH_2), 3.20 (s, 3H, $CH_{3\text{-}O}$), 3.26 – 3.38 (m, 3H, CH_2 & H_{iPr}), 4.43 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.53 (t, J = 5.4 Hz, 1H, NH), 7.19 – 7.40 (m, 5H, 5xH_{Ar}), 7.88 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6 (2x$CH_{3\ iPr}$), 24.7 (CH_{iPr}), 25.2 (CH_2), 26.7 (CH_2), 40.5 (CH_2), 45.2 ($CH_{2\ Bn}$), 57.8 ($CH_{3\text{-}O}$), 71.6 (CH_2), 84.1 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.7 (C_q), 139.8 (C_q), 152.8 (C_q), 155.9 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{28}N_6O$:** 369.24 [M+H]+, **found :** 369.45.
(15)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.26 – 1.34 (m, 2H, $CH_{2\text{-}CH2\text{-}CH2}$), 1.36 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.42 (p, J = 6.6 Hz, 2H, $CH_{2\text{-}CH2\text{-}OH}$), 1.51 (p, J = 7.3 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.11 (q, J = 6.5 Hz, 2H, $CH_{2\text{-}NH\ Alk}$), 3.32 (s, 1H, H_{iPr}), 3.37 (q, J = 6.1 Hz, 2H, $CH_{2\text{-}OH}$), 4.33 (t, J = 5.1 Hz, 1H, OH), 4.43 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.51 (t, J = 5.4 Hz, 1H, NH_{Alk}),

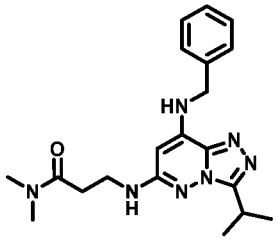
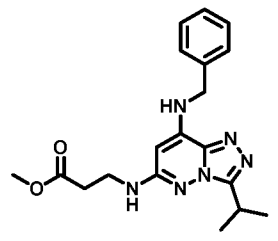
			7.19 – 7.40 (m, 5H, 5xH_{Ar}), 7.88 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 19.6 (2x$CH_{3\ iPr}$), 23.2 ($CH_{2\text{-}CH2\text{-}CH2}$), 24.7 ($CH_{iPr}$), 28.4 ($CH_{2\text{-}CH2\text{-}NH}$), 32.3 ($CH_{2\text{-}CH2\text{-}OH}$), 40.8 ($CH_{2\text{-}NH\ Alk}$), 45.2 ($CH_{2\ Bn}$), 60.7 ($CH_{2\text{-}OH}$), 84.1 ($CH_{Ar}$), 126.8 (2x$CH_{Ar}$), 126.9 ($CH_{Ar}$), 128.4 (2x$CH_{Ar}$), 138.4 ($C_q$), 139.7 ($C_q$), 139.8 ($C_q$), 152.8 ($C_q$), 155.9 ($C_q$). **MS (ESI+) : m/z calcd for $C_{20}H_{28}N_6O$:** 369.24 [M+H]+, **found :** 369.38.
(16)		> 95 % [a]	Light yellow solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.30 (dt, *J* = 10.2, 7.0 Hz, 2H, CH_2), 1.36 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.45 – 1.55 (m, 4H, 2xCH_2), 3.11 (q, *J* = 6.7 Hz, 2H, CH_2), 3.19 (s, 3H, $CH_{3\text{-}O}$), 3.28 (t, *J* = 6.5 Hz, 2H, CH_2), 3.31 – 3.39 (m, 1H, H_{iPr}), 4.43 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.52 (t, *J* = 5.4 Hz, 1H, NH), 7.19 – 7.38 (m, 5H, 5xH_{Ar}), 7.89 (t, *J* = 6.3 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 19.6 (2x$CH_{3\ iPr}$), 23.4 (CH_2), 24.7 (CH_{iPr}), 28.3 (CH_2), 28.8 (CH_2), 40.7 (CH_2), 45.2 ($CH_{2\ Bn}$), 57.8 ($CH_{3\text{-}O}$), 71.8 (CH_2), 84.2 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.4 (C_q), 139.7 (C_q), 139.8 (C_q), 152.8 (C_q), 155.9 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{30}N_6O$:** 383.26 [M+H]+, **found** : 383.45.
(17)		Unstable [a]	Brown solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.36 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.79 (h, *J* = 7.0 Hz, 2H, CH_2), 2.02 (s, 3H, $CH_{3\text{-}S}$), 3.21 (q, *J* = 6.4 Hz, 2H, CH_2), 3.34 (d, *J* = 6.9 Hz, 1H, H_{iPr}), 4.43 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.36 (s, 1H, H_{Ar}), 6.58 (q, *J* = 5.5, 4.5 Hz, 1H, NH), 7.18 – 7.42 (m, 5H, 5xH_{Ar}), 7.91 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** N.D. **MS (ESI+) : m/z calcd for $C_{19}H_{26}N_6S$:** 371.20 [M+H]+, **found :** 371.27.

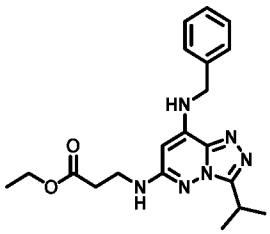
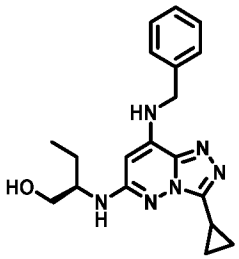
(18)		> 97 % [a]	White crystalline solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.82 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.35 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.47 (dtt, J = 32.1, 14.4, 7.4 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 3.30 (h, J = 6.8 Hz, 1H, H_{iPr}), 3.54 (hept, J = 6.0, 5.4 Hz, 1H, $H_{Alk\text{-}NH}$), 4.43 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.43 (s, 1H, H_{Ar}), 6.30 (d, J = 7.9 Hz, 1H, NH_{Alk}), 7.19 – 7.41 (m, 5H, 5xH_{Ar}), 7.84 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.1 (2x$CH_{2\text{-}CH3}$), 45.2 ($CH_{2\ Bn}$), 53.0 ($CH_{Alk\text{-}NH}$), 84.2 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.4 (C_q), 139.7 (C_q), 139.8 (C_q), 152.7 (C_q), 155.9 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{28}N_6$:** 353.24 [M+H]+, **found :** 353.29.
(19)		> 99 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (dd, J = 7.1, 2.8 Hz, 6H, 2x$CH_{3\ iPr}$), 1.78 (dq, J = 12.3, 6.2 Hz, 1H, $H_{(CH2)\text{-}CH2\text{-}O}$), 2.13 (dq, J = 14.5, 7.4 Hz, 1H, $H_{(CH2)\text{-}CH2\text{-}O}$), 3.26 – 3.37 (m, 1H, H_{iPr}), 3.51 (dd, J = 8.9, 3.9 Hz, 1H, $_{CH}$-$H_{(CH2)\text{-}O}$), 3.67 (td, J = 8.1, 5.5 Hz, 1H, $_{CH2}$-$H_{(CH2)\text{-}O}$), 3.77 (q, J = 7.6 Hz, 1H, $_{CH2}$-$H_{(CH2)\text{-}O}$), 3.85 (dd, J = 8.9, 5.8 Hz, 1H, $_{CH}$-$H_{(CH2)\text{-}O}$), 4.16 (q, J = 6.6, 6.0 Hz, 1H, H_{THF}), 4.43 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.81 (d, J = 5.5 Hz, 1H, NH_{Alk}), 7.20 – 7.42 (m, 5H, 5xH_{Ar}), 7.98 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.5 ($CH_{3\ iPr}$), 19.6 ($CH_{3\ iPr}$), 24.8 (CH_{iPr}), 32.1 ($CH_{2\text{-}CH2\text{-}O}$), 45.2 ($CH_{2\ Bn}$), 51.5 ($CH_{THF}$), 66.3 ($_{CH2}$-$CH_{2\text{-}O}$), 72.7 ($_{CH}$-$CH_{2\text{-}O}$), 84.0 ($CH_{Ar}$), 126.8 (2x$CH_{Ar}$), 126.9 ($CH_{Ar}$), 128.5 (2x$CH_{Ar}$), 138.3 ($C_q$), 139.6 ($C_q$), 140.0 ($C_q$), 152.9 ($C_q$), 155.5 ($C_q$). **MS (ESI+) : m/z calcd for $C_{19}H_{24}N_6O$:** 353.21 [M+H]+, **found :** 353.26.

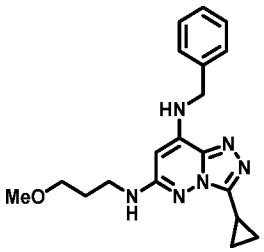
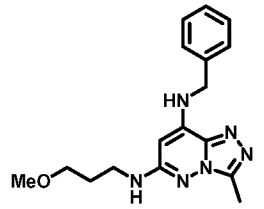
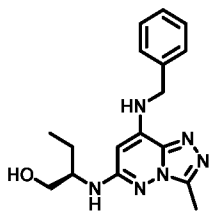
(20)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.59 – 1.84 (m, 5H, $H_{(CH2)\ THF}$ 2x$CH_{2\ cPent}$), 1.99 (dddd, *J* = 27.3, 12.3, 7.7, 4.3 Hz, 4H, $CH_{2\ THF}$ & $CH_{2\ cPent}$), 2.13 (dq, *J* = 15.0, 7.6 Hz, 1H, $H_{(CH2)\ THF}$), 3.44 (p, *J* = 8.2 Hz, 1H, H_{cPent}), 3.51 (dd, *J* = 8.9, 3.8 Hz, 1H, $H_{(CH2)\ THF}$), 3.67 (td, *J* = 8.1, 5.6 Hz, 1H, $H_{(CH2)\ THF}$), 3.76 (q, *J* = 7.6 Hz, 1H, $H_{(CH2)\ THF}$), 3.83 (dd, *J* = 8.9, 5.8 Hz, 1H, $H_{(CH2)\ THF}$), 4.14 (dq, *J* = 9.9, 4.9 Hz, 1H, H_{THF}), 4.43 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.80 (d, *J* = 5.5 Hz, 1H, NH_{THF}), 7.17 – 7.45 (m, 5H, 5xH_{Ar}), 7.96 (t, *J* = 6.3 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 25.3 (2x$CH_{2\ cPent}$), 29.6 ($CH_{2\ cPent}$), 29.7 ($CH_{2\ cPent}$), 32.0 ($CH_{2\ THF}$), 34.9 ($CH_{2\ cPent}$), 45.3 ($CH_{2\ Bn}$), 51.5 (CH_{THF}), 66.3 ($CH_{2\ THF}$), 72.7 ($CH_{2\ THF}$), 84.0 (CH_{Ar}), 126.7 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.7 (C_q), 140.0 (C_q), 151.8 (C_q), 155.4 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{26}N_6O$:** 379.22 [M+H]+, **found :** 379.29.
(21)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.35 (dd, *J* = 7.2, 4.2 Hz, 6H, 2x$CH_{3\ iPr}$), 1.42 – 1.58 (m, 2H, $H_{(CH2)-CH2-O}$ & $H_{(CH2)-CH\ THP}$), 1.61 – 1.75 (m, 1H, $H_{(CH2)-CH\ THP}$), 1.85 – 2.00 (m, 1H, $H_{(CH2)-CH2-O}$), 3.08 (dd, *J* = 10.6, 8.2 Hz, 1H, $_{O-}H_{(CH2)-CH\ THP}$), 3.33 (m, 2H, H_{iPr} & $_{CH2-}H_{(CH2)-O}$), 3.62 – 3.72 (m, 2H, H_{THP} & $_{CH2-}H_{(CH2)-O}$), 3.91 (dd, *J* = 11.0, 3.8 Hz, 1H, $_{O-}H_{(CH2)-CH\ THP}$), 4.42 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.42 (s, 1H, H_{Ar}), 6.50 (d, *J* = 7.1 Hz, 1H, NH_{Alk}), 7.16 – 7.38 (m, 5H, 5xH_{Ar}), 7.94 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6 ($CH_{3\ iPr}$), 19.7 ($CH_{3\ iPr}$), 24.2 ($CH_{2-CH\ THP}$), 24.7 (CH_{iPr}), 28.7 ($CH_{2-CH2-O}$), 45.2 ($CH_{2\ Bn}$), 46.6 (CH_{THP}), 67.1 ($_{CH2-}CH_{2-O}$), 70.3 ($_{CH-}CH_{2-O}$), 84.1 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.5 (2xCH_{Ar}), 138.3 (C_q), 139.7 (C_q), 140.0 (C_q), 152.8 (C_q), 155.2 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{26}N_6O$:**

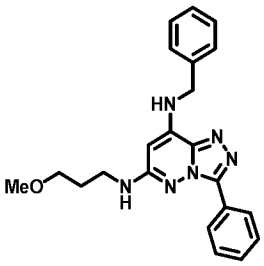
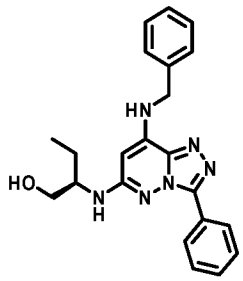
			367.22 [M+H]+, **found :** 367.30.
(22)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.35 (dd, *J* = 7.0, 4.4 Hz, 6H, 2x$CH_{3\ iPr}$), 1.43 – 1.59 (m, 2H, $H_{(CH2)-CH2-O}$ & $H_{(CH2)-CH\ THP}$), 1.64 – 1.74 (m, 1H, $H_{(CH2)-CH\ THP}$), 1.84 – 1.96 (m, 1H, $H_{(CH2)-CH2-O}$), 3.08 (dd, *J* = 10.7, 8.1 Hz, 1H, $_{O}$-$H_{(CH2)-CH\ THP}$), 3.26 – 3.38 (m, 2H, H_{iPr} & $_{CH2}$-$H_{(CH2)-O}$), 3.61 – 3.76 (m, 2H, H_{THP} & $_{CH2}$-$H_{(CH2)-O}$), 3.91 (dd, *J* = 11.2, 3.8 Hz, 1H, $_{O}$-$H_{(CH2)-CH\ THP}$), 4.42 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.42 (s, 1H, H_{Ar}), 6.50 (d, *J* = 7.1 Hz, 1H, NH_{Alk}), 7.21 – 7.36 (m, 5H, 5xH_{Ar}), 7.94 (t, *J* = 6.3 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6 ($CH_{3\ iPr}$), 19.7 ($CH_{3\ iPr}$), 24.2 ($CH_{2-CH\ THP}$), 24.7 (CH_{iPr}), 28.6 ($CH_{2-CH2-O}$), 45.2 ($CH_{2\ Bn}$), 46.6 (CH_{THP}), 67.1 ($CH_{2-CH2-O}$), 70.3 ($_{CH}$-CH_{2-O}), 84.1 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.6 (C_q), 140.0 (C_q), 152.8 (C_q), 155.2 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{26}N_6O$:** 367.22 [M+H]+, **found :** 367.30.
(23)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.35 (d, *J* = 7.0 Hz, 8H, 2xCH3 iPr & $CH_{2-CH\ THP}$), 1.90 (d, *J* = 12.5 Hz, 2H, $CH_{2-CH\ THP}$), 3.32 (s, 1H, H_{iPr}), 3.37 (td, *J* = 10.2, 9.0, 2.7 Hz, 2H, CH_{2-O}), 3.64 – 3.79 (m, 1H, H_{THP}), 3.83 (dt, *J* = 11.7, 3.7 Hz, 2H,CH_{2-O}), 4.43 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.52 (d, *J* = 6.9 Hz, 1H, NH_{THP}), 7.19 – 7.39 (m, 5H, 5xH_{Ar}), 7.93 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6 (2x$CH_{3\ iPr}$), 24.7 (CH_{iPr}), 32.3 (2x$CH_{2-CH\ THP}$), 45.2 ($CH_{2\ Bn}$), 46.8 (CH_{THP}), 65.9 (2xCH_{2-O}), 84.1 (CH_{Ar}), 126.7 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.5 (2xCH_{Ar}), 138.3 (C_q), 139.6 (C_q), 140.0 (C_q), 152.8 (C_q), 155.0 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{26}N_6O$:** 367.22 [M+H]+, **found :** 367.27.

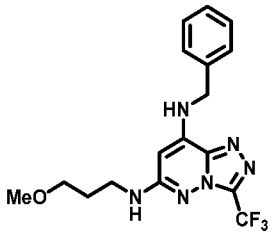
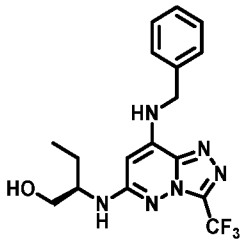
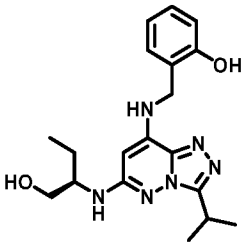
(24)		> 96 % [a]	White solid **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.37 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.65 (p, *J* = 6.9 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 1.78 (s, 3H, $CH_{3\text{-}CO}$), 3.08 (q, *J* = 6.6 Hz, 2H, $CH_{2\text{-}NH}$), 3.15 (q, *J* = 6.5 Hz, 2H, $CH_{2\text{-}NH}$), 3.33 (q, *J* = 7.0 Hz, 1H, H_{iPr}), 4.46 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.39 (s, 1H, H_{Ar}), 6.55 (t, *J* = 5.4 Hz, 1H, NH_{Alk}), 7.19 – 7.41 (m, 5H, 5xH_{Ar}), 7.83 (t, *J* = 5.6 Hz, 1H, $NH_{\text{-}CO}$), 7.95 (t, *J* = 6.3 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.7 (2x$CH_{3\ iPr}$), 22.6 ($CH_{3\text{-}CO}$), 24.7 (CH_{iPr}), 28.6 ($CH_{2\text{-}CH2\text{-}NH}$), 36.7 ($CH_{2\text{-}NH}$), 38.58 ($CH_{2\text{-}NH}$), 45.2 ($CH_{2\ Bn}$), 84.2 ($CH_{Ar}$), 126.8 (2x$CH_{Ar}$), 126.9 ($CH_{Ar}$), 128.4 (2x$CH_{Ar}$), 138.3 ($C_q$), 139.7 ($C_q$), 139.9 ($C_q$), 152.9 ($C_q$), 155.9 ($C_q$), 169.0 ($C_q$). **MS (ESI+) : m/z calcd for $C_{20}H_{27}N_7O$:** 382.23 [M+H]+, **found :** 382.32.
(25)		> 99 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 2.33 (t, *J* = 6.9 Hz, 2H, $CH_{2\text{-}CO}$), 3.27 – 3.42 (m, 3H, H_{iPr} & $CH_{2\text{-}NH}$), 4.42 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.41 (s, 1H, H_{Ar}), 6.55 (t, *J* = 5.5 Hz, 1H, NH), 6.78 (s, 1H, H_{amide}), 7.23 (tt, *J* = 5.7, 2.6 Hz, 1H, H_{Ar}), 7.27 (s, 1H, H_{amide}), 7.30 – 7.37 (m, 4H, 4xH_{Ar}), 7.90 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.7 (2x$CH_{3\ iPr}$), 24.6 (CH_{iPr}), 34.3 ($CH_{2\text{-}NH}$), 37.2 ($CH_{2\text{-}CO}$), 45.2 ($CH_{2\ Bn}$), 84.2 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.7 (C_q), 139.8 (C_q), 152.9 (C_q), 155.8 (C_q), 172.8 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{23}N_7O$:** 354.20 [M+H]+, **found :** 354.30.
(26)		> 99 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 2.34 (t, *J* = 6.8 Hz, 2H, $CH_{2\text{-}CO}$), 2.54 (d, *J* = 4.6 Hz, 3H, $CH_{3\text{-}NH}$), 3.28 – 3.39 (m, 3H, H_{iPr} & $CH_{2\text{-}NH}$), 4.42 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.40 (s, 1H, H_{Ar}), 6.56 (t, *J* = 5.6 Hz, 1H, NH), 7.19 – 7.39 (m, 5H, 5xH_{Ar}), 7.73 (d, *J* = 4.9 Hz, 1H, $NH_{\text{-}CO}$), 7.90 (t, *J* = 6.3 Hz, 1H, NH_{Bn}).

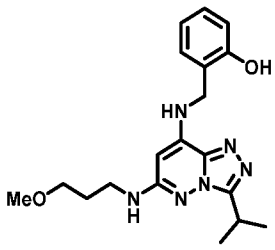
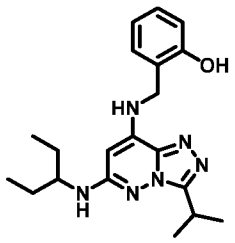
			^{13}C NMR (101 MHz, DMSO-d_6) δ : 19.7 ($2xCH_{3\ iPr}$), 24.6 (CH_{iPr}), 25.4 ($CH_{3\text{-}NH}$), 34.6 ($CH_{2\text{-}CO}$), 37.3 ($CH_{2\text{-}NH}$), 45.2 ($CH_{2\ Bn}$), 84.2 (CH_{Ar}), 126.8 ($2xCH_{Ar}$), 126.9 (CH_{Ar}), 128.4 ($2xCH_{Ar}$), 138.3 (C_q), 139.7 (C_q), 139.9 (C_q), 152.9 (C_q), 155.7 (C_q), 171.0 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{25}N_7O$:** 368.46 [M+H]+, **found :** 368.31.
(27)		> 99 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (d, J = 6.9 Hz, 6H, $2xCH_{3\ iPr}$), 2.56 (t, J = 7.0 Hz, 2H, $CH_{2\text{-}CO}$), 2.80 (s, 3H, $CH_{3\text{-}N}$), 2.92 (s, 3H, $CH_{3\text{-}N}$), 3.29 – 3.38 (m, 3H, H_{iPr} & $CH_{2\text{-}NH}$), 4.42 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.39 (s, 1H, H_{Ar}), 6.57 (t, J = 5.6 Hz, 1H, NH), 7.18 – 7.39 (m, 5H, $5xH_{Ar}$), 7.92 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.7 ($2xCH_{3\ iPr}$), 24.6 (CH_{iPr}), 32.0 ($CH_{2\text{-}CO}$), 34.6 ($CH_{3\text{-}N}$), 36.6 ($CH_{3\text{-}N}$), 37.1 ($CH_{2\text{-}NH}$), 45.2 ($CH_{2\ Bn}$), 84.2 (CH_{Ar}), 126.8 ($2xCH_{Ar}$), 126.9 (CH_{Ar}), 128.4 (CH_{Ar}), 138.3 (C_q), 139.7 (C_q), 139.9 (C_q), 152.9 (C_q), 155.8 (C_q), 170.6 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{27}N_7O$:** 382.23 [M+H]+, **found :** 382.32.
(28)		> 98 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.37 (d, J = 6.9 Hz, 6H, $2xCH_{3\ iPr}$), 2.60 (t, J = 6.6 Hz, 2H, $CH_{2\text{-}CO}$), 3.35 (m, 3H, H_{iPr} & $CH_{2\text{-}NH}$), 3.58 (s, 3H, OCH_3), 4.43 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.39 (s, 1H, H_{Ar}), 6.72 (d, J = 5.6 Hz, 1H, NH), 7.19 – 7.38 (m, 5H, $5xH_{Ar}$), 7.98 (t, J = 6.3 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.5 ($2xCH_{3\ iPr}$), 24.7 (CH_{iPr}), 33.0 ($CH_{2\text{-}CO}$), 36.8 ($CH_{2\text{-}NH}$), 45.2 ($CH_{2\ Bn}$), 51.3 ($CH_{3\text{-}O}$), 84.3 (CH_{Ar}), 126.8 ($2xCH_{Ar}$), 126.9 (CH_{Ar}), 128.4 ($2xCH_{Ar}$), 138.2 (C_q), 139.6 (C_q), 139.9 (C_q), 152.8 (C_q), 155.8 (C_q), 172.0 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{24}N_6O_2$:** 369.20 [M+H]+, **found :** 369.38.

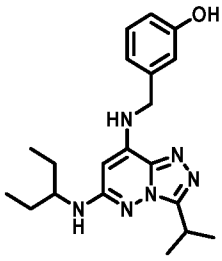
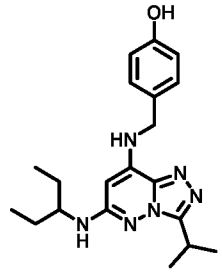
(29)		> 98 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.14 (t, J = 7.1 Hz, 3H, $CH_{3\text{-}CH2}$), 1.36 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 2.57 (t, J = 6.7 Hz, 2H, $CH_{2\text{-}CO}$), 3.29 – 3.41 (m, 3H, H_{iPr} & $CH_{2\text{-}NH}$), 4.03 (q, J = 7.1 Hz, 2H, $CH_{2\text{-}CH3}$), 4.43 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.67 (t, J = 5.5 Hz, 1H, NH), 7.19 – 7.38 (m, 5H, 5xH_{Ar}), 7.96 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 14.1 ($CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 24.7 (CH_{iPr}), 33.2 ($CH_{2\text{-}CO}$), 36.8 ($CH_{2\text{-}NH}$), 45.2 ($CH_{2\ Bn}$), 59.8 ($CH_{2\text{-}CH3}$), 84.0 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.7 (C_q), 140.0 (C_q), 152.9 (C_q), 155.7 (C_q), 171.6 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{26}N_6O_2$:** 383.22 [M+H]+, **found :** 383.30
(30)		> 97 % [a]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.85 (t, J = 7.4 Hz, 3H, $CH_{3\ Alk}$), 1.03 (dt, J = 8.7, 3.1 Hz, 2H, $CH_{2\ cPr}$), 1.11 (dq, J = 5.2, 3.2, 2.6 Hz, 2H, $CH_{2\ cPr}$), 1.51 (ddq, J = 79.0, 14.1, 7.3, 6.7 Hz, 2H, $CH_{2\ Alk}$), 2.24 (tt, J = 8.3, 5.1 Hz, 1H, H_{cPr}), 3.40 (ddt, J = 22.1, 11.0, 5.6 Hz, 2H, $CH_{2\ Alk}$), 3.64 (ddt, J = 13.0, 7.5, 5.4 Hz, 1H, H_{Alk}), 4.42 (dd, J = 6.3, 2.2 Hz, 2H, $CH_{2\ Bn}$), 4.58 (t, J = 5.4 Hz, 1H, OH), 5.46 (s, 1H, H_{Ar}), 6.28 (d, J = 7.9 Hz, 1H, NH_{Alk}), 7.24 (td, J = 5.9, 2.7 Hz, 1H, H_{Ar}), 7.29 – 7.39 (m, 4H, 4xH_{Ar}), 7.83 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.5 ($CH_{2\ cPr}$), 6.5 ($CH_{2\ cPr}$), 10.5 ($CH_{3\ Alk}$), 23.7 ($CH_{2\ Alk}$), 45.2 ($CH_{2\ Bn}$), 53.6 (CH_{Alk}), 62.1 ($CH_{2\ Alk}$), 84.4 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.4 (C_q), 139.6 (C_q), 139.7 (C_q), 149.9 (C_q), 156.1 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{24}N_6O$:** 353.21 [M+H]+, **found :** 353.36.

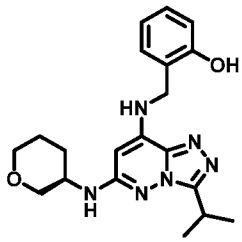
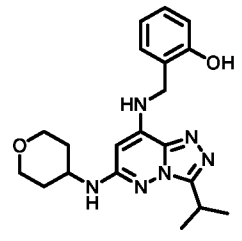
(31)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.00 – 1.12 (m, 4H, 2x$CH_{2\ iPr}$), 1.74 (p, *J* = 6.7 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 2.25 (tt, *J* = 9.1, 5.3 Hz, 1H, H_{cPr}), 3.17 (q, *J* = 6.5 Hz, 2H, $CH_{2\text{-}NH}$), 3.21 (s, 3H, OCH_3), 3.36 (t, *J* = 6.4 Hz, 2H, $CH_{2\text{-}OCH3}$), 4.42 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.36 (s, 1H, H_{Ar}), 6.52 (t, *J* = 5.4 Hz, 1H, NH_{Alk}), 7.24 (q, *J* = 4.5 Hz, 1H, H_{Ar}), 7.33 (d, *J* = 4.4 Hz, 4H, 4xH_{Ar}), 7.87 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.2 (CH_{cPr}), 6.6 (2c$CH_{2\ cPr}$), 28.6 ($CH_{2\text{-}CH2\text{-}NH}$), 38.0 ($CH_{2\text{-}NH}$), 45.2 ($CH_{2\ Bn}$), 57.8 ($OCH_3$), 69.8 ($CH_{2\text{-}OCH3}$), 84.1 ($CH_{Ar}$), 126.8 (2x$CH_{Ar}$), 126.9 ($CH_{Ar}$), 128.4 (2x$CH_{Ar}$), 138.3 ($C_q$), 139.6 ($C_q$), 139.8 ($C_q$), 150.1 ($C_q$), 156.2 ($C_q$). **MS (ESI+) : m/z calcd for $C_{19}H_{24}N_6O$:** 353.21 [M+H]+, **found :** 353.32.
(32)		> 98 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.74 (p, *J* = 6.6 Hz, 2H, $CH_{2\text{-}CH2}$), 2.46 (s, 3H, CH_3), 3.17 (q, *J* = 6.5 Hz, 2H, $CH_{2\text{-}NH}$), 3.21 (s, 3H, OCH_3), 3.36 (t, *J* = 6.3 Hz, 2H, $CH_{2\text{-}OCH3}$), 4.44 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.38 (s, 1H, H_{Ar}), 6.53 (t, *J* = 5.3 Hz, 1H, NH_{Alk}), 7.21 – 7.39 (m, 5H, 5xH_{Ar}), 7.88 (t, *J* = 6.3 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 9.4 (CH_3), 28.6 ($CH_{2\text{-}CH2}$), 38.0 ($CH_{2\text{-}NH}$), 45.2 ($CH_{2\ Bn}$), 57.8 (OCH_3), 69.8 ($CH_{2\text{-}OCH3}$), 84.1 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.4 (C_q), 139.8 (C_q), 145.6 (C_q), 156.3 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{22}N_6O$:** 327.19 [M+H]+, **found :** 327.32.
(33)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.85 (t, *J* = 7.4 Hz, 3H, $CH_{3\ Alk}$), 1.50 (dtt, *J* = 91.5, 14.5, 7.2 Hz, 2H, $CH_{2\text{-}CH3}$), 2.45 (s, 3H, CH_3), 3.35 – 3.47 (m, 2H, $CH_{2\text{-}OH}$), 3.66 (h, *J* = 6.0 Hz, 1H, $H_{Alk\text{-}NH}$), 4.36 – 4.50 (m, 2H, $CH_{2\ Bn}$), 4.58 (t, *J* = 5.4 Hz, 1H, OH), 5.48 (s, 1H, H_{Ar}), 6.29 (d, *J* = 7.9 Hz, 1H, NH_{Alk}), 7.19 – 7.41 (m, 5H, 5xH_{Ar}), 7.84 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 9.4

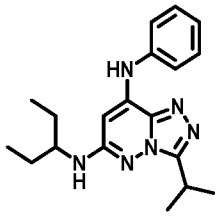
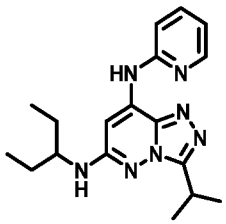
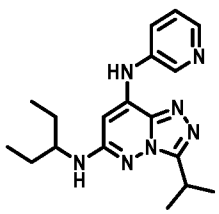
			(CH_3), 10.6 ($CH_{3\ Alk}$), 23.7 (CH_2), 45.3 ($CH_{2\ Bn}$), 53.6 (CH_{Alk}), 62.1 (CH_2), 84.4 (H_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.4 (C_q), 139.4 (C_q), 139.8 (C_q), 145.5 (C_q), 156.2 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{22}N_6O$:** 327.19 [M+H]+, **found :** 327.32.
(34)		> 99 % [a]	Pale yellow solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.79 (p, *J* = 6.6 Hz, 2H, $CH_{2\text{-}CH2}$), 3.20 – 3.29 (m, 5H, $CH_{2\text{-}NH}$ & CH_3), 3.39 (t, *J* = 6.3 Hz, 2H, $CH_{2\text{-}OCH3}$), 4.48 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.48 (s, 1H, H_{Ar}), 6.75 (t, *J* = 5.4 Hz, 1H, NH_{Alk}), 7.22 – 7.28 (m, 1H, H_{Ar}), 7.32 – 7.40 (m, 4H, 4xH_{Ar}), 7.44 – 7.50 (m, 1H, H_{Ar}), 7.53 (dd, *J* = 8.3, 6.6 Hz, 2H, 2xH_{Ar}), 8.07 (t, *J* = 6.3 Hz, 1H, NH_{Bn}), 8.43 – 8.56 (m, 2H, 2xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 28.5 ($CH_{2\text{-}CH2}$), 38.1 ($CH_{2\text{-}NH}$), 45.3 ($CH_{2\ Bn}$), 57.9 (OCH_3), 69.8 ($CH_{2\text{-}OCH3}$), 84.3 (CH_{Ar}), 126.5 (2xCH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 127.5 (C_q), 128.5 (2xCH_{Ar}), 128.5 (2xCH_{Ar}), 129.1 (CH_{Ar}), 138.2 (C_q), 139.9 (C_q), 140.6 (C_q), 146.3 (C_q), 156.5 (C_q). **MS (ESI+) : m/z calcd for $C_{22}H_{24}N_6O$:** 389.48 [M+H]+, **found :** 389.34.
(35)		> 99 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, *J* = 7.4 Hz, 3H, CH_3), 1.56 (ddq, *J* = 50.3, 14.0, 7.0 Hz, 2H, $CH_{2\text{-}CH3}$), 3.47 (dq, *J* = 14.3, 5.4 Hz, 2H, $CH_{2\text{-}OH}$), 3.67 (h, *J* = 5.7 Hz, 1H, H_{Alk}), 4.48 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 4.64 (t, *J* = 5.4 Hz, 1H, OH), 5.60 (s, 1H, H_{Ar}), 6.52 (d, *J* = 7.6 Hz, 1H, NH_{Alk}), 7.26 (t, *J* = 7.0 Hz, 1H, H_{Ar}), 7.33 – 7.43 (m, 4H, 4xH_{Ar}), 7.47 (t, *J* = 7.3 Hz, 1H, H_{Ar}), 7.54 (dd, *J* = 8.4, 6.7 Hz, 2H, 2xH_{Ar}), 8.04 (t, *J* = 6.4 Hz, 1H, NH_{Bn}), 8.41 – 8.54 (m, 2H, 2xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.7 (CH_3), 23.6 (CH_2), 45.3 ($CH_{2\ Bn}$), 54.3 (CH_{Alk}), 61.9 (CH_2), 84.6 (CH_{Ar}), 126.5 (2xCH_{Ar}), 126.9 (2xCH_{Ar}), 127.0 (CH_{Ar}), 127.5 (C_q), 128.5 (2xCH_{Ar}), 128.5 (2xCH_{Ar}), 129.1 (CH_{Ar}), 138.3 (C_q), 139.8 (C_q), 140.6 (C_q), 146.3 (C_q), 156.4 (C_q).

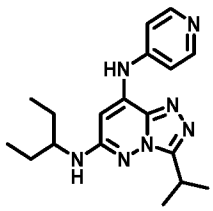
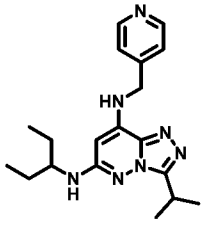
			MS (ESI+) : m/z calcd for $C_{22}H_{24}N_6O$: 389.48 [M+H]+, [M+H]+, **found :** 389.34.
(36)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.73 (p, *J* = 6.6 Hz, 2H, $CH_{2\text{-}CH2}$), 3.15 (q, *J* = 6.6 Hz, 2H, $CH_{2\text{-}NH}$), 3.20 (s, 3H, OCH_3), 3.35 (t, *J* = 6.3 Hz, 2H, $CH_{2\text{-}OCH3}$), 4.47 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.55 (s, 1H, H_{Ar}), 6.94 (t, *J* = 5.3 Hz, 1H, NH_{Alk}), 7.22 – 7.40 (m, 5H, 5xH_{Ar}), 8.31 (t, *J* = 6.3 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 28.3 ($CH_{2\text{-}CH2}$), 37.9 ($CH_{2\text{-}NH}$), 45.3 ($CH_{2\ Bn}$), 57.8 (OCH_3), 69.6 ($CH_{2\text{-}OCH3}$), 85.5 (CH_{Ar}), 118.7 (q, *J* = 269.1 Hz, CF_3), 126.8 (2xCH_{Ar}), 127.0 (CH_{Ar}), 128.5 (2xCH_{Ar}), 137.8 (C_q), 137.8 (q, *J* = 39.3, 38.3 Hz, $C_{q\text{-}CF3}$), 139.3 (C_q), 141.7 (C_q), 157.3 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{19}F_3N_6O$:** 381.16 [M+H]+, **found :** 381.31.
(37)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.84 (t, *J* = 7.4 Hz, 3H, CH_3), 1.50 (ddq, *J* = 66.5, 14.1, 7.0 Hz, 2H, $CH_{2\text{-}CH3}$), 3.42 (t, *J* = 5.3 Hz, 2H, $CH_{2\text{-}OH}$), 3.60 (h, *J* = 6.3, 5.9 Hz, 1H, H_{Alk}), 4.40 – 4.55 (m, 2H, $CH_{2\ Bn}$), 4.62 (t, *J* = 5.3 Hz, 1H, OH), 5.67 (s, 1H, H_{Ar}), 6.74 (d, *J* = 7.8 Hz, 1H, NH_{Alk}), 7.23 – 7.43 (m, 5H, 5xH_{Ar}), 8.28 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (CH_3), 23.5 ($CH_{2\text{-}CH3}$), 45.3 ($CH_{2\ Bn}$), 53.9 (CH_{Alk}), 61.7 ($CH_{2\text{-}OH}$), 85.8 (CH_{Ar}), 118.8 (d, *J* = 269.1 Hz, CF_3), 126.9 (2xCH_{Ar}), 127.0 (CH_{Ar}), 128.5 (2xCH_{Ar}), 137.7 (d, *J* = 39.5 Hz, $C_{q\text{-}CF3}$), 137.9 (C_q), 139.2 (C_q), 141.7 (C_q), 157.3 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{19}F_3N_6O$:** 381.16 [M+H]+, **found :** 381.31.
(38)		> 96 % [a]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.85 (t, *J* = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.36 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.68 (m, 2H, $CH_{2\text{-}CH3}$), 3.24 – 3.48 (m, 3H, H_{iPr} & $CH_{2\text{-}OH}$), 3.63 (dp, *J* = 9.4, 5.7 Hz, 1H, H_{Alk}), 4.36 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 4.55 (d, *J* = 5.6 Hz, 1H, $OH_{\text{-}CH2}$), 5.44 (s, 1H, H_{Ar}), 6.29 (d, *J* = 7.7 Hz, 1H, NH_{Alk}), 6.73 (t, *J* =

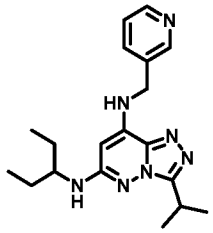
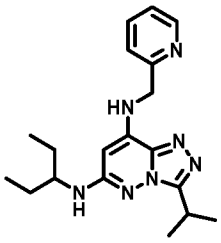
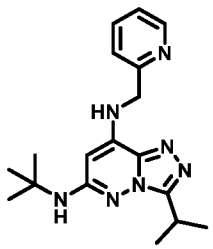
			7.4 Hz, 1H, H_{Ar}), 6.84 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.00 – 7.17 (m, 2H, 2xH_{Ar}), 7.48 (t, *J* = 6.3 Hz, 1H, NH_{Bn}), 9.65 (s, 1H, OH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.5 ($CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.6 ($CH_{2\text{-}CH3}$), 24.8 (CH_{Alk}), 40.8 ($CH_{2\ Bn}$), 53.8 (CH_{iPr}), 62.0 ($CH_{2\text{-}OH}$), 84.2 (CH_{Ar}), 114.9 (CH_{Ar}), 118.8 (CH_{Ar}), 123.8 (C_q), 127.0 (CH_{Ar}), 127.7 (CH_{Ar}), 139.7 (C_q), 140.0 (C_q), 152.8 (C_q), 154.8 (C_q), 155.9 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{26}N_6O_2$:** 371.46 [M+H]+, **found :** 371.36.
(39)		92 % [a]	Pale yellow solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.37 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.75 (p, *J* = 6.6 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH\ Alk}$), 3.17 (q, *J* = 6.6 Hz, 2H, $CH_{2\text{-}NH\ Alk}$), 3.22 (s, 3H, OCH_3), 3.30 – 3.39 (m, 3H, $H_{iPr\ \&}$ $CH_{2\text{-}OCH3}$), 4.37 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.35 (s, 1H, H_{Ar}), 6.55 (t, *J* = 5.3 Hz, 1H, NH_{Alk}), 6.73 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 6.84 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.06 (t, *J* = 7.5 Hz, 2H, 2xH_{Ar}), 7.55 (t, *J* = 6.3 Hz, 1H, NH_{Bn}), 9.66 (s, 1H, OH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 19.7 (2x$CH_{3\ iPr}$), 24.7 (CH_{iPr}), 28.5 ($CH_{2\text{-}CH2\text{-}NH\ Alk}$), 38.0 ($CH_{2\text{-}NH\ Alk}$), 40.7 ($CH_{2\ Bn}$), 57.8 ($OCH_3$), 69.8 ($CH_{2\text{-}OCH3}$), 83.9 ($CH_{Ar}$), 114.9 ($CH_{Ar}$), 118.8 ($CH_{Ar}$), 123.7 ($C_q$), 127.0 ($CH_{Ar}$), 127.7 ($CH_{Ar}$), 139.7 ($C_q$), 140.1 ($C_q$), 152.9 ($C_q$), 154.8 ($C_q$), 156.0 ($C_q$). **MS (ESI+) : m/z calcd for $C_{19}H_{26}N_6O_2$:** 371.46 [M+H]+, **found :** 371.26.
(40)		88 % [a]	White crystalline solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.84 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.36 – 1.38 (m, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.57 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.29 (d, *J* = 7.1 Hz, 1H, H_{iPr}), 3.56 (q, *J* = 6.7 Hz, 1H, H_{iPent}), 4.37 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.42 (s, 1H, H_{Ar}), 6.32 (d, *J* = 8.0 Hz, 1H, $NH_{\text{-}CH}$), 6.69 – 6.80 (m, 1H, H_{Ar}), 6.85 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.08 (t, *J* = 8.2 Hz, 2H, 2xH_{Ar}), 7.47 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 9.64 (s, 1H, OH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.1 (2x$CH_{2\text{-}CH3}$), 40.8 ($CH_{2\ Bn}$), 53.0 (CH-

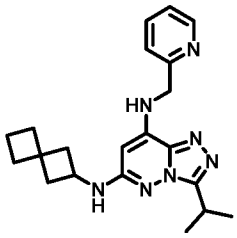
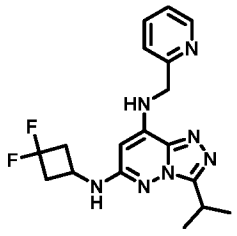
			$_{NH}$), 84.0 (CH_{Ar}), 114.9 (CH_{Ar}), 118.8 (CH_{Ar}), 123.8 (C_q), 127.0 (CH_{Ar}), 127.7 (CH_{Ar}), 139.7 (C_q), 140.0 (C_q), 152.7 (C_q), 154.8 (C_q), 156.0 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{28}N_6O$:** 369.24 [M+H]+, **found :** 369.35.
(41)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.84 (t, J = 7.4 Hz, 6H, 2x$CH_{3\ iPent}$), 1.37 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.58 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.31 (q, J = 6.9 Hz, 1H, H_{iPr}), 3.56 (h, J = 6.5 Hz, 1H, H_{iPent}), 4.36 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.41 (s, 1H, H_{Ar}), 6.32 (d, J = 8.0 Hz, 1H, NH_{iPent}), 6.63 (ddd, J = 8.1, 2.5, 1.0 Hz, 1H, H_{Ar}), 6.74 (t, J = 2.0 Hz, 1H, H_{Ar}), 6.77 (dt, J = 7.6, 1.2 Hz, 1H, H_{Ar}), 7.12 (t, J = 7.8 Hz, 1H, H_{Ar}), 7.79 (t, J = 6.3 Hz, 1H, NH_{Bn}), 9.33 (s, 1H, OH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.9 (2x$CH_{3\ iPent}$), 20.0 (2x$CH_{3\ iPr}$), 25.3 (CH_{iPr}), 26.6 (2x$CH_{2\text{-}CH3}$) , 45.6 ($CH_{2\ Bn}$), 53.4 (H_{iPent}), 84.7 (CH_{Ar}), 113.7 (CH_{Ar}), 114.3 (CH_{Ar}), 117.7 (CH_{Ar}), 129.8 (CH_{Ar}), 140.2 (C_q), 140.3 (C_q), 140.3 (C_q), 153.2 (C_q), 156.4 (C_q), 158.0 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{28}N_6O$:** 369.24 [M+H]+, **found :** 369.38.
(42)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.84 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.35 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.38 – 1.57 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.25 – 3.31 (m, 1H, H_{iPr}), 3.55 (h, J = 6.8 Hz, 1H, H_{iPent}), 4.29 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.45 (s, 1H, H_{Ar}), 6.29 (d, J = 8.0 Hz, 1H, NH), 6.65 – 6.79 (m, 2H, 2xH_{Ar}), 7.10 – 7.23 (m, 2H, 2xH_{Ar}), 7.68 (t, J = 6.3 Hz, 1H, NH_{Bn}), 9.28 (s, 1H, OH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.2 (2x$CH_{2\text{-}CH3}$), 44.8 ($CH_{2\ Bn}$), 53.0 (CH_{iPr}), 84.1 (CH_{Ar}), 115.1 (2xCH_{Ar}), 128.2 (2xCH_{Ar}), 128.4 (C_q), 139.7 (C_q), 139.7 (C_q), 152.6 (C_q), 156.0 (C_q), 156.3 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{28}N_6O$:** 369.24 [M+H]+, **found :** 369.30.

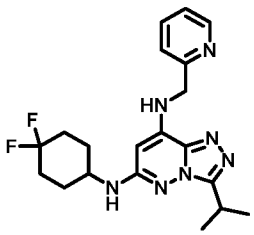
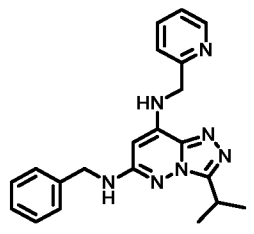
(43)		93 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (dd, *J* = 6.9, 4.4 Hz, 6H, 2x$CH_{3\ iPr}$), 1.43 – 1.58 (m, 2H, $H_{(CH2)-CH2-O}$ & $H_{(CH2)-CH\ THP}$), 1.64 – 1.72 (m, 1H, $H_{(CH2)-CH\ THP}$), 1.92 (dt, *J* = 8.1, 4.0 Hz, 1H, $H_{(CH2)-CH2-O}$), 3.07 (dd, *J* = 10.5, 8.4 Hz, 1H, $_{O}$-$H_{(CH2)-CH\ THP}$), 3.32 (m, 2H, H_{iPr} & $_{CH2}$-$H_{(CH2)-O}$), 3.68 (dt, *J* = 11.3, 3.8 Hz, 2H, H_{THP} & $_{CH2}$-$H_{(CH2)-O}$), 3.92 (dd, *J* = 10.7, 3.1 Hz, 1H, $_{O}$-$H_{(CH2)-CH\ THP}$), 4.36 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.39 (s, 1H, H_{Ar}), 6.50 (d, *J* = 7.1 Hz, 1H, NH_{THP}), 6.73 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 6.83 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.06 (m, 2H, 2xH_{Ar}), 7.58 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 9.63 (s, 1H, OH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6 ($CH_{3\ iPr}$), 19.7 ($CH_{3\ iPr}$), 24.2 ($CH_{2\ THP}$), 24.7 ($CH_{2\ THP}$), 28.7 (CH_{iPr}), 40.7 ($CH_{2\ Bn}$), 46.6 (CH_{THP}), 67.1 ($CH_{2\ THP}$), 70.3 ($CH_{2\ THP}$), 83.9 (CH_{Ar}), 114.8 (CH_{Ar}), 118.8 (CH_{Ar}), 123.6 (C_q), 126.9 (CH_{Ar}), 127.7 (CH_{Ar}), 139.7 (C_q), 140.3 (C_q), 152.8 (C_q), 154.8 (C_q), 155.3 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{26}N_6O_2$:** 383.22 [M+H]+, **found :** 383.26.
(44)		94 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.32 – 1.45 (m, 8H, 2x$CH_{3\ iPr}$ & $CH_{2-CH\ THP}$), 1.90 (dd, *J* = 13.0, 3.6 Hz, 2H, $CH_{2-CH\ THP}$), 3.36 (dp, *J* = 14.7, 7.0, 4.6 Hz, 3H, , CH_{2-O} & HiPr), 3.71 (qd, *J* = 10.4, 9.8, 4.7 Hz, 1H, H_{THP}), 3.83 (dt, *J* = 11.6, 3.7 Hz, 2H, CH_{2-O}), 4.37 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.36 (s, 1H, H_{Ar}), 6.54 (d, *J* = 6.9 Hz, 1H, NH_{THP}), 6.73 (td, *J* = 7.5, 1.2 Hz, 1H, H_{Ar}), 6.84 (dd, *J* = 8.5, 1.2 Hz, 1H, H_{Ar}), 7.06 (ddd, *J* = 7.6, 6.3, 1.8 Hz, 2H, 2xH_{Ar}), 7.59 (t, *J* = 6.3 Hz, 1H, NH_{Bn}), 9.64 (s, 1H, OH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 32.3 (2x$CH_{2-CH\ THP}$), 40.7 (CH_{iPr}), 46.8 (CH_{THP}), 65.8 (2xCH_{2-O}), 83.9 (CH_{Ar}), 114.9 (CH_{Ar}), 118.9 (CH_{Ar}), 123.7 (C_q), 126.9 (CH_{Ar}), 127.7 (CH_{Ar}), 139.7 (C_q), 140.2 (C_q), 152.8 (C_q), 154.8 (C_q), 155.1 (C_q).

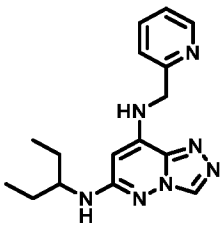
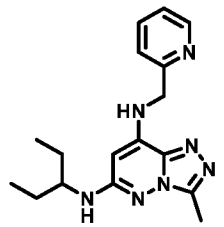
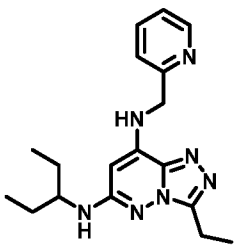
			MS (ESI+) : m/z calcd for $C_{20}H_{26}N_6O_2$: 383.22 [M+H]+, **found** : 383.29.
(45)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.86 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.39 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.41 – 1.61 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.36 (q, J = 6.6 Hz, 1H, H_{iPr}), 3.61 (q, J = 6.6 Hz, 1H, H_{iPent}), 6.20 (s, 1H, H_{Ar}), 6.49 (d, J = 7.9 Hz, 1H, NH_{iPent}), 7.14 (tt, J = 5.8, 2.4 Hz, 1H, H_{Ar}), 7.32 – 7.52 (m, 4H, 4xH_{Ar}), 9.23 (s, 1H, $NH_{\text{-}Ph}$). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.3 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.1 (2x$CH_{2\text{-}CH3}$), 53.0 (CH_{iPent}), 86.7 (CH_{Ar}), 122.3 (2xCH_{Ar}), 123.7 (CH_{Ar}), 129.2 (2xCH_{Ar}), 137.1 (C_q), 139.5 (C_q), 139.7 (C_q), 153.0 (C_q), 155.9 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{26}N_5$:** 339.23 [M+H]+, **found :** 339.32.
(46)		> 96 % [a]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.89 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.39 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.45 – 1.67 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.36 (p, J = 7.1 Hz, 1H, H_{iPr}), 3.66 (dtd, J = 12.8, 7.5, 5.4 Hz, 1H, H_{iPent}), 6.81 (d, J = 8.0 Hz, 1H, NH_{iPent}), 6.99 (ddd, J = 7.4, 5.0, 1.0 Hz, 1H, H_{Ar}), 7.48 (d, J = 8.4 Hz, 1H, H_{Ar}), 7.72 (ddd, J = 8.8, 7.2, 2.0 Hz, 1H, H_{Ar}), 7.82 (s, 1H, H_{Ar}), 8.33 (dd, J = 5.2, 1.9 Hz, 1H, H_{Ar}), 9.85 (s, 1H, NH_{Ph}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.5 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.1 (2x$CH_{2\text{-}CH3}$), 53.2 (CH_{iPent}), 94.0 (CH_{Ar}), 113.7 (CH_{Ar}), 117.0 (CH_{Ar}), 133.6 (C_q), 137.6 (C_q), 139.4 (C_q), 146.9 (CH_{Ar}), 153.0 (C_q), 154.9 (C_q), 155.9 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{25}N_7$:** 340.22 [M+H]+, **found :** 340.32.
(47)		> 98 % [b]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.87 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.39 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.41 – 1.62 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.37 (q, J = 7.0 Hz, 1H, CH_{iPr}), 3.61 (qd, J = 7.3, 3.6 Hz, 1H, CH_{iPent}), 6.24 (s, 1H, CH_{Ar}), 6.53 (d, J = 7.9 Hz, 1H, NH_{iPent}), 7.44 (dd, J = 8.3, 4.7 Hz, 1H, CH_{Ar}), 7.80 (ddd, J = 8.3, 2.7, 1.5

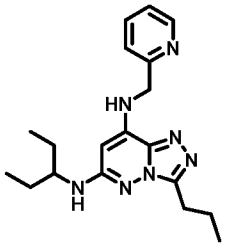
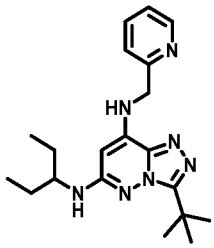
			Hz, 1H, CH_{Ar}), 8.34 (dd, *J* = 4.7, 1.5 Hz, 1H, CH_{Ar}), 8.67 (d, *J* = 2.6 Hz, 1H, CH_{Ar}), 9.44 (s, 1H, NH_{Pyr}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.3 ($2xCH_{3\text{-}CH2}$), 19.5 ($2xCH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.0 ($2xCH_{2\text{-}CH3}$), 53.0 (CH_{iPent}), 87.5 (CH_{Ar}), 123.9 (CH_{Ar}), 129.2 (CH_{Ar}), 136.4 (C_q), 136.8 (C_q), 139.5 (C_q), 143.9 (CH_{Ar}), 144.5 (CH_{Ar}), 153.0 (C_q), 155.8 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{25}N_7$:** 340.22 [M+H]+, **found :** 340.32.
(48)		> 98 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.89 (t, *J* = 7.4 Hz, 6H, $2xCH_{3\text{-}CH2}$), 1.39 (d, *J* = 7.0 Hz, 6H, $2xCH_{3\ iPr}$), 1.42 – 1.66 (m, 4H, $2xCH_{2\text{-}CH3}$), 3.36 (p, *J* = 6.8 Hz, 1H, H_{iPr}), 3.64 (h, *J* = 6.9 Hz, 1H, H_{iPent}), 6.61 (s, 1H, H_{Ar}), 6.68 (d, *J* = 7.9 Hz, 1H, NH_{iPent}), 7.26 – 7.51 (m, 2H, $2xH_{Ar}$), 8.37 – 8.58 (m, 2H, $2xH_{Ar}$), 9.75 (s, 1H, NH_{Pyr}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.3 ($2xCH_{3\text{-}CH2}$), 19.4 ($2xCH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.0 ($2xCH_{2\text{-}CH3}$), 53.1 (CH_{iPent}), 91.6 (CH_{Ar}), 113.8 (CH_{Ar}), 134.7 (C_q), 139.4 (C_q), 147.2 (C_q), 150.4 (CH_{Ar}), 153.2 (C_q), 155.4 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{25}N_7$:** 340.22 [M+H]+, **found :** 340.32.
(49)		> 98 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.82 (t, *J* = 7.4 Hz, 6H, $2xCH_{3\text{-}CH2}$), 1.36 (d, *J* = 6.9 Hz, 6H, $2xCH_{3\ iPr}$), 1.38 – 1.58 (m, 4H, $2xCH_{2\text{-}CH3}$), 3.24 - 3.33 (m, 1H, H_{iPr}), 3.54 (h, *J* = 6.6 Hz, 1H, H_{iPent}), 4.47 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.34 (s, 1H, H_{Ar}), 6.30 (d, *J* = 7.9 Hz, 1H, NH_{iPent}), 7.24 – 7.39 (m, 2H, $2xH_{Ar}$), 7.91 (t, *J* = 6.4 Hz, 1H, NH_{Bn}), 8.44 – 8.61 (m, 2H, $2xH_{Ar}$). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.4 ($2xCH_{3\text{-}CH2}$), 19.5 ($2xCH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.1 ($2xCH_{2\text{-}CH3}$), 44.4 ($CH_{2\ Bn}$), 53.0 (CH_{iPent}), 84.5 (CH_{Ar}), 121.8 ($2xCH_{Ar}$), 139.5 (C_q), 139.7 (C_q), 147.5 (C_q), 149.7 ($2xCH_{Ar}$), 152.7 (C_q), 155.8 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{27}N_7$:** 354.24 [M+H]+, **found :** 354.30.

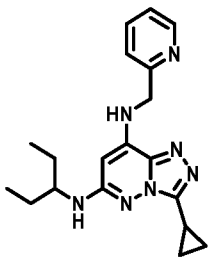
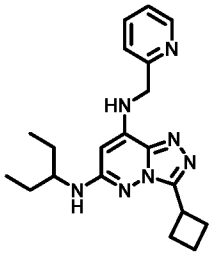
(50)		> 97 % [a]	Light pink solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.83 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.35 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.38 – 1.58 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.24 – 3.31 (m, 1H, H_{iPr}), 3.55 (h, *J* = 6.2 Hz, 1H, H_{iPent}), 4.45 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.47 (s, 1H, H_{Ar}), 6.31 (d, *J* = 8.0 Hz, 1H, $NH_{\text{-}CH}$), 7.37 (dd, *J* = 7.9, 4.8 Hz, 1H, H_{Ar}), 7.75 (dt, *J* = 7.9, 2.0 Hz, 1H, H_{Ar}), 7.90 (t, *J* = 6.4 Hz, 1H, NH_{Bn}), 8.41 – 8.51 (m, 1H, H_{Ar}), 8.60 (s, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.1 (2x$CH_{2\text{-}CH3}$), 43.0 ($CH_{2\ Bn}$), 53.0 (CH_{iPent}), 84.4 (CH_{Ar}), 123.6 (CH_{Ar}), 133.9 (C_q), 134.8 (CH_{Ar}), 139.5 (C_q), 139.6 (C_q), 148.3 (CH_{Ar}), 148.6 (CH_{Ar}), 152.7 (C_q), 155.8 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{27}N_7$:** 354.24 [M+H]+, **found :** 354.33.
(51)		> 98 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.82 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.38 – 1.55 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.25 – 3.32 (m, 1H, H_{iPr}), 3.55 (h, *J* = 6.4 Hz, 1H, H_{iPent}), 4.52 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.42 (s, 1H, H_{Ar}), 6.35 (d, *J* = 7.9 Hz, 1H, NH_{iPent}), 7.28 (dd, *J* = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.34 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.71 – 7.86 (m, 2H, H_{Ar} & NH_{Bn}), 8.49 – 8.62 (m, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.1 (2x$CH_{2\text{-}CH3}$), 47.2, 53.0 (CH_{iPent}), 84.50 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.7 (C_q), 139.8 (C_q), 149.0 (CH_{Ar}), 152.7 (C_q), 155.9 (C_q), 157.7 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{27}N_7$:** 354.24 [M+H]+, **found :** 354.30.
(52)		93 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.35 (s, 9H, 3x$CH_{3\ tBu}$), 1.38 (d, *J* = 6.9 Hz, 6H, 2xCH_{iPr}), 3.36 (dd, *J* = 13.5, 6.8 Hz, 1H, H_{iPr}), 4.49 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.42 (s, 1H, H_{Ar}), 6.25 (s, 1H, NH), 7.28 (ddd, *J* = 6.3, 5.0, 1.2 Hz, 1H, H_{Ar}), 7.31 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.76 (ddd, *J* = 9.5, 5.3, 1.8 Hz, 2H, NH_{Bn} & H_{Ar}), 8.50 – 8.61 (m,

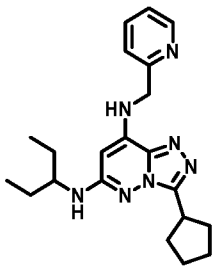
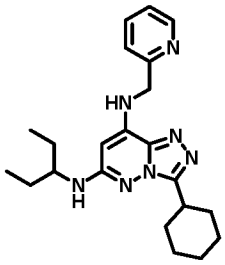
			1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6 ($2xCH_{3\ iPr}$), 24.9 (CH_{iPr}), 28.5 ($3xCH_{3\ tBu}$), 47.1 ($CH_{2\ Bn}$), 50.6 (C_q), 85.5 (CH_{Ar}), 120.5 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.2 (C_q), 139.6 (C_q), 149.0 (CH_{Ar}), 152.8 (C_q), 155.2 (C_q), 157.7 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{27}N_7$:** 340.22 [M+H]+, **found :** 340.39.
(53)		93 % [a]	Grey solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (d, J = 6.9 Hz, 6H, $2xCH_{3\ iPr}$), 1.79 (dtd, J = 12.5, 8.3, 7.4, 2.7 Hz, 4H, $2xCH_{2\ spiro}$), 1.87 (dd, J = 8.4, 5.7 Hz, 2H, $CH_{2\ spiro}$), 2.00 (t, J = 7.2 Hz, 2H, $CH_{2\ spiro}$), 2.34 (ddd, J = 11.6, 6.1, 2.4 Hz, 2H, $CH_{2\ spiro}$), 3.23 – 3.38 (m, 1H, H_{iPr}), 3.90 (h, J = 7.9 Hz, 1H, H_{spiro}), 4.51 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.29 (s, 1H, H_{Ar}), 6.78 (d, J = 6.2 Hz, 1H, NH_{spiro}), 7.28 (dd, J = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.32 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.76 (td, J = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.87 (t, J = 6.2 Hz, 1H, NH_{Bn}), 8.54 (dd, J = 4.8, 1.7 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 16.4 ($CH_{2\ spiro}$), 19.6 ($2xCH_{3\ iPr}$), 24.7 (CH_{iPr}), 34.1 ($CH_{2\ spiro}$), 34.8 ($CH_{2\ spiro}$), 37.2 (C_q), 41.6 (CH_{spiro}), 42.5 ($2xCH_{2\ spiro}$), 47.2 ($CH_{2\ Bn}$), 84.2 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.6 (C_q), 140.0 (C_q), 149.0 (CH_{Ar}), 152.8 (C_q), 155.0 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{27}N_7$:** 378.24 [M+H]+, **found :** 378.29.
(54)		> 98 % [a]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (d, J = 6.9 Hz, 6H, $2xCH_{3\ iPr}$), 2.54 (dd, J = 15.3, 6.1 Hz, 2H, $CH_{2\ cBut}$), 2.92 (tt, J = 14.1, 7.6 Hz, 2H, $CH_{2\ cBut}$), 3.39 (d, J = 9.3 Hz, 1H, H_{iPr}), 3.95 (dq, J = 14.0, 7.2 Hz, 1H, H_{cBut}), 4.54 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.32 (s, 1H, H_{Ar}), 7.14 (d, J = 5.4 Hz, 1H, NH_{cBut}), 7.28 (dd, J = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.33 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.76 (td, J = 7.7, 1.8 Hz, 1H, H_{Ar}), 8.01 (t, J = 6.2 Hz, 1H, NH_{Bn}), 8.49 – 8.59 (m, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6

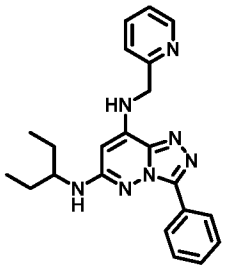
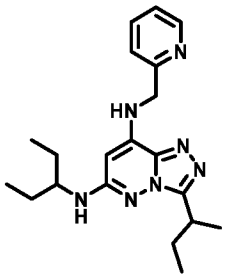
			(2x$CH_{3\ iPr}$), 24.7 (CH_{iPr}), 35.8 (dd, *J* = 17.9, 6.5 Hz, CH_{cBut}), 42.0 (d, *J* = 21.4 Hz, $CH_{2\ cBut}$), 42.2 (d, *J* = 21.0 Hz, $CH_{2\ cBut}$), 47.3 ($CH_{2\ Bn}$), 83.9 (CH_{Ar}), 120.1 (t, *J* = 277.4 Hz, CF_2), 120.8 (CH_{Ar}), 122.4 (CH_{Ar}), 137.0 (CH_{Ar}), 139.6 (C_q), 140.4 (C_q), 149.0 (CH_{Ar}), 153.0 (C_q), 155.0 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{21}F_2N_7$:** 374.19 [M+H]+, **found :** 374.35.
(55)		> 99 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.38 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.56 (dd, *J* = 12.2, 8.5 Hz, 2H, $CH_{2\ cHex}$), 1.82 – 2.10 (m, 6H, 3x$CH_{2\ cHex}$), 3.36 (d, *J* = 7.5 Hz, 1H, H_{iPr}), 3.75 (d, *J* = 4.9 Hz, 1H, H_{cHex}), 4.53 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.40 (s, 1H, H_{Ar}), 6.61 (d, *J* = 6.9 Hz, 1H, NH), 7.29 (dd, *J* = 7.5, 4.8 Hz, 1H, H_{Ar}), 7.33 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.77 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.91 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 8.48 – 8.63 (m, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 19.6 (2x$CH_{3\ iPr}$), 24.7 (CH_{iPr}), 27.4 (t, *J* = 4.7 Hz, 2x$CH_{2\ cHex}$), 31.0 (t, *J* = 23.8 Hz, 2x$CH_{2\ cHex}$), 46.5 (CH_{cHex}), 47.2 ($CH_{2\ Bn}$), 84.3 (CH_{Ar}), 120.6 (CH_{Ar}), 122.3 (CH_{Ar}), 123.8 (t, *J* = 240.4 Hz, CF_2), 137.0 (CH_{Ar}), 139.6 (C_q), 140.0 (C_q), 149.0 (CH_{Ar}), 152.9 (C_q), 155.2 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{25}F_2N_7$:** 402.22 [M+H]+, **found :** 402.40
(56)		> 98 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.30 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.25 – 3.31 (m, 1H, H_{iPr}), 4.32 (d, *J* = 5.8 Hz, 2H, $CH_{2\ Bn}$), 4.53 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.45 (s, 1H, H_{Ar}), 7.16 (t, *J* = 5.9 Hz, 1H, NH), 7.17 – 7.22 (m, 1H, H_{Ar}), 7.25 – 7.37 (m, 6H, 6xH_{Ar}), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.89 (t, *J* = 6.2 Hz, 1H, NH), 8.54 (dt, *J* = 4.8, 1.5 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 19.6 (2x$CH_{3\ iPr}$), 24.7 (CH_{iPr}), 44.5 ($CH_{2\ Bn}$), 47.2 ($CH_{2\ Bn}$), 84.3 (CH_{Ar}), 120.8 (CH_{Ar}), 122.3 (CH_{Ar}), 126.6 (CH_{Ar}), 127.6 (2xCH_{Ar}), 128.1 (2xCH_{Ar}), 136.9 (CH_{Ar}), 139.6 (C_q), 139.8 (C_q), 140.0 (C_q), 149.0

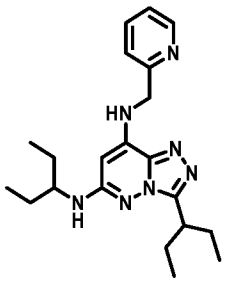
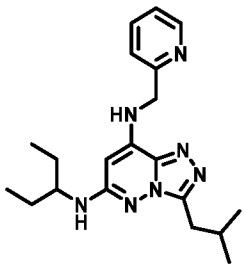
			(CH_{Ar}), 152.9 (C_q), 155.6 (C_q), 157.5 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{23}F_2N_7$:** 374.21 [M+H]+, **found :** 374.35.
(57)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.81 (t, J = 7.4 Hz, 6H, 2x$CH_{3\ iPent}$), 1.30 – 1.58 (m, 4H, 2x$CH_{2\ iPent}$), 3.56 (h, J = 6.4 Hz, 1H, H_{iPent}), 4.54 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.47 (s, 1H, H_{Ar}), 6.39 (d, J = 8.3 Hz, 1H, NH_{iPent}), 7.29 (dd, J = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.35 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.77 (td, J = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.85 (t, J = 6.2 Hz, 1H, NH_{Bn}), 8.56 (d, J = 4.7 Hz, 1H, H_{Ar}), 8.94 (s, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.2 (2x$CH_{3\ iPent}$), 25.9 (2x$CH_{2\ iPent}$), 47.2 ($CH_{2\ Bn}$), 52.5 (CH_{iPent}), 85.2 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 138.7 (CH_{Ar}), 139.2 (C_q), 139.5 (C_q), 149.0 (CH_{Ar}), 156.7 (C_q), 157.5 (C_q). **MS (ESI+) : m/z calcd for $C_{16}H_{21}N_7$:** 312.19 [M+H]+, **found :** 312.27.
(58)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.82 (t, J = 7.4 Hz, 6H, 2x$CH_{3\ iPent}$), 1.44 (ddp, J = 35.5, 14.4, 7.0 Hz, 4H, 2x$CH_{2\ iPent}$), 2.45 (s, 3H, CH_3), 3.58 (h, J = 6.6 Hz, 1H, H_{iPent}), 4.53 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.44 (s, 1H, H_{Ar}), 6.35 (d, J = 8.1 Hz, 1H, NH_{Bn}), 7.29 (dd, J = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.33 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.68 – 7.83 (m, 2H, H_{Ar} & NH_{iPent}), 8.55 (d, J = 4.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 9.3 (CH_3), 10.3 (2x$CH_{3\ iPent}$), 26.1 (2x$CH_{2\ iPent}$), 47.2 ($CH_{2\ Bn}$), 52.7 (CH_{iPent}), 84.5 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.3 (C_q), 139.8 (C_q), 145.4 (C_q), 149.0 (CH_{Ar}), 156.3 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{23}N_7$:** 326.21 [M+H]+, **found :** 326.35.
(59)		81 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.82 (t, J = 7.4 Hz, 6H, $_{2xCH3\ iPent}$), 1.30 (t, J = 7.5 Hz, 3H, $CH_{3\text{-}CH2}$), 1.35 – 1.62 (m, 4H, 2x$CH_{2\ iPent}$), 2.88 (q, J = 7.5 Hz, 2H, $CH_{2\text{-}CH3}$), 3.57 (p, J = 6.8 Hz, 1H, H_{iPent}), 4.53 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.44 (s, 1H,

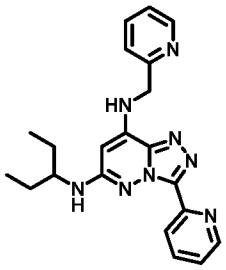
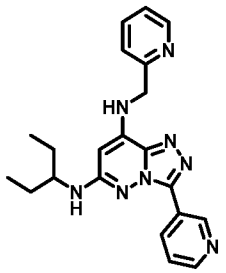
			H_{Ar}), 6.35 (d, *J* = 7.9 Hz, 1H, NH_{iPent}), 7.29 (dd, *J* = 7.5, 4.8 Hz, 1H, H_{Ar}), 7.34 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.77 (ddt, *J* = 7.7, 5.5, 2.1 Hz, 2H, H_{Ar} & NH_{Bn}), 8.55 (d, *J* = 4.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.3 ($CH_{3\ iPent}$), 10.9 ($CH_{3\text{-}CH2}$), 17.5 ($CH_{2\text{-}CH3}$), 26.1 ($CH_{2\ iPent}$), 47.2 ($CH_{2\ Bn}$), 52.8 (CH_{iPent}), 84.5 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.5 (C_q), 139.8 (C_q), 149.0 (C_q), 149.7 (C_q), 156.1 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{25}N_7$:** 340.22 [M+H]+, **found :** 340.41.
(60)		> 98 % [a]	Beige solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.83 (t, *J* = 7.4 Hz, 6H, $2xCH_{3\text{-}CH2}$), 0.93 (t, *J* = 7.4 Hz, 3H, CH_3), 1.46 (ddq, *J* = 28.4, 13.9, 7.1, 6.5 Hz, 4H, $2xCH_{2\text{-}CH3}$), 1.78 (h, *J* = 7.5 Hz, 2H, CH_2), 2.86 (t, *J* = 7.4 Hz, 2H, CH_2), 3.55 (td, *J* = 12.8, 6.3 Hz, 2H, H_{iPent}), 4.53 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.44 (s, 1H, H_{Ar}), 6.36 (d, *J* = 7.9 Hz, 1H, NH), 7.26 – 7.32 (m, 1H, H_{Ar}), 7.35 (d, *J* = 7.9 Hz, 1H), 7.78 (td, *J* = 7.4, 1.8 Hz, 2H), 8.56 (d, *J* = 4.9 Hz, 1H). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.4 ($2xCH_{3\text{-}CH2}$), 13.7 (CH_3), 19.5 (CH_2), 25.7 (CH_2), 26.1 ($2xCH_{2\text{-}CH3}$), 47.2 ($CH_{2\ Bn}$), 52.9 (CH_{iPent}), 84.5 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.4 (C_q), 139.8 (C_q), 148.7 (C_q), 149.0 (CH_{Ar}), 156.1 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{27}N_7$:** 354.24 [M+H]+, **found :** 354.40.
(61)		91 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.83 (t, *J* = 7.4 Hz, 6H, $2xCH_{3\text{-}CH2}$), 1.37 – 1.58 (m, 13H, $2xCH_{2\text{-}CH3}$ & $3xCH_{3\ tBu}$), 3.52 (h, *J* = 6.5 Hz, 1H, H_{iPent}), 4.51 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.42 (s, 1H, H_{Ar}), 6.35 (d, *J* = 7.8 Hz, 1H, NH_{iPent}), 7.28 (dd, *J* = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.34 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.70 – 7.84 (m, 2H, NH_{Bn} & H_{Ar}), 8.47 – 8.60 (m, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.4 ($2xCH_{3\text{-}CH2}$), 26.0 ($2xCH_{2\text{-}CH3}$), 26.9 ($3xCH_{3\ tBu}$), 32.1 (C_q), 47.2 ($CH_{2\ Bn}$), 53.3

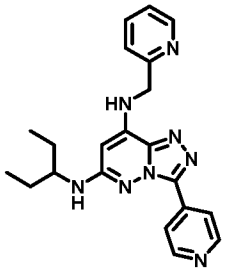
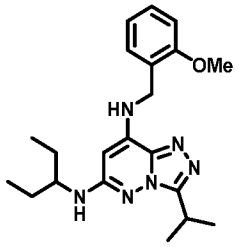
			(CH_{iPent}), 84.2 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.8 (C_q), 140.3 (C_q), 149.0 (CH_{Ar}), 154.1 (C_q), 155.3 (C_q), 157.7 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{29}N_7$:** 368.26 [M+H]+, **found :** 368.37.
(62)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.83 (t, J = 7.4 Hz, 6H, 2x$CH_{3\ iPent}$), 1.08 (ddq, J = 43.6, 7.1, 4.2 Hz, 4H, 2x$CH_{2\ cPr}$), 1.45 (ddt, J = 40.6, 13.9, 6.8 Hz, 4H, 2x$CH_{2\ iPent}$), 2.24 (tt, J = 8.8, 5.1 Hz, 1H, H_{cPr}), 3.55 (h, J = 6.4 Hz, 1H, H_{iPent}), 4.52 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.42 (s, 1H, H_{Ar}), 6.35 (d, J = 8.0 Hz, 1H, NH_{iPent}), 7.28 (dd, J = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.33 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.76 (q, J = 5.4, 3.7 Hz, 2H, H_{Ar} & NH_{Bn}), 8.55 (d, J = 4.8 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.4 (CH_{cPr}), 6.3 (2x$CH_{2\ cPr}$), 10.3 (2x$CH_{3\ iPent}$), 26.1 (2x$CH_{2\ iPent}$), 47.2 ($CH_{2\ Bn}$), 52.8 (CH_{iPent}), 84.5 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.5 (C_q), 139.7 (C_q), 149.0 (CH_{Ar}), 149.9 (C_q), 156.1 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{25}N_7$:** 352.22 [M+H]+, **found :** 352.32.
(63)		> 95 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.82 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.45 (ddq, J = 28.0, 13.9, 7.0 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 1.87 – 2.16 (m, 2H, $CH_{2\text{-}CH2\text{-}CH}$), 2.33 (dtd, J = 12.1, 8.6, 3.1 Hz, 2H, $_{CH2}$-$CH2_{\text{-}CH}$), 2.52 – 2.59 (m, 2H, $_{CH2}$-$CH2_{\text{-}CH}$), 3.54 (h, J = 6.6, 6.2 Hz, 1H, H_{iPent}), 3.86 (p, J = 8.7 Hz, 1H, H_{cBut}), 4.52 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.43 (s, 1H, H_{Ar}), 6.34 (d, J = 7.8 Hz, 1H, NH_{iPent}), 7.28 (dd, J = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.33 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.72 – 7.86 (m, 2H, H_{Ar} & NH_{Bn}), 8.55 (d, J = 4.8 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 18.6 ($CH_{2\text{-}CH2\text{-}CH}$), 25.9 (2x$_{CH2}$-$CH_{2\text{-}CH}$), 26.0 (2x$CH_{2\text{-}CH3}$), 29.7 ($CH_{cBut}$), 47.2 ($CH_{2\ Bn}$), 53.0 ($CH_{iPent}$), 84.6 ($CH_{Ar}$), 120.7 ($CH_{Ar}$), 122.3 ($CH_{Ar}$), 136.9 ($CH_{Ar}$), 139.6 ($C_q$), 139.8 ($C_q$), 149.0 ($CH_{Ar}$), 150.9 ($C_q$), 156.0 ($C_q$), 157.6 ($C_q$).

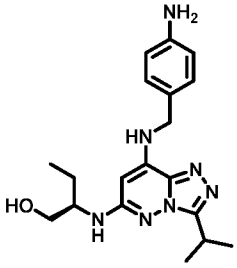
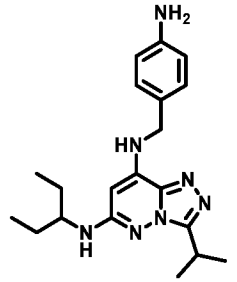
			MS (ESI+) : m/z calcd for $C_{20}H_{27}N_7$: 366.24 [M+H]+, **found :** 366.33.
(64)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.82 (t, *J* = 7.3 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.44 (ddp, *J* = 28.3, 14.4, 7.4, 6.9 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 1.60 – 1.84 (m, 4H, 2x$CH_{2\text{-}CH2\text{-}CH}$), 1.90 – 2.10 (m, 4H, 2x$_{CH2\text{-}}CH_{2\text{-}CH}$), 3.42 (p, *J* = 8.2 Hz, 1H, H_{cPent}), 3.54 (h, *J* = 6.4, 5.9 Hz, 1H, H_{iPent}), 4.52 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.43 (s, 1H, H_{Ar}), 6.34 (d, *J* = 7.9 Hz, 1H, NH_{iPent}), 7.28 (dd, *J* = 7.4, 4.9 Hz, 1H, H_{Ar}), 7.34 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.77 (t, *J* = 7.2 Hz, 2H, H_{Ar} & NH_{Bn}), 8.55 (d, *J* = 4.8 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 25.3 (2x$CH_{2\text{-}CH3}$), 26.0 (2x$CH_{2\text{-}CH2\text{-}CH}$), 29.6 (2x$_{CH2\text{-}}CH_{2\text{-}CH}$), 35.0 ($CH_{cPent}$), 47.2 ($CH_{2\ Bn}$), 53.0 ($CH_{iPent}$), 84.5 ($CH_{Ar}$), 120.7 ($CH_{Ar}$), 122.3 ($CH_{Ar}$), 137.0 ($CH_{Ar}$), 139.8 ($C_q$), 139.8 ($C_q$), 149.0 ($CH_{Ar}$), 151.6 ($C_q$), 155.9 ($C_q$), 157.7 ($C_q$). **MS (ESI+) : m/z calcd for $C_{21}H_{29}N_7$:** 380.26 [M+H]+, **found :** 380.30.
(65)		87 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.83 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.22 – 1.55 (m, 7H, 2x$CH_{2\text{-}CH3}$ & $CH_{2\ cHex}$ & $H_{(CH2)\ cHex}$), 1.70 (qd, *J* = 12.4, 12.0, 3.3 Hz, 3H, $CH_{2\ cHex}$ & $H_{(CH2)\ cHex}$), 1.77 – 1.86 (m, 2H, $CH_{2\ cHex}$), 1.93 – 2.06 (m, 2H, $CH_{2\ cHex}$), 3.04 (tt, *J* = 11.4, 3.6 Hz, 1H, H_{cHex}), 3.48 (hept, *J* = 5.7, 5.2 Hz, 1H, H_{iPent}), 4.52 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.42 (s, 1H, H_{Ar}), 6.35 (d, *J* = 7.7 Hz, 1H, NH_{iPent}), 7.28 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H, H_{Ar}), 7.34 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.68 – 7.88 (m, 2H, H_{Ar} & NH_{Bn}), 8.55 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.5 (2x$CH_{3\text{-}CH2}$), 25.6 (2x$CH_{2\ cHex}$), 25.7 ($CH_{2\ cHex}$), 26.1 (2x$CH_{2\text{-}CH3}$), 29.2 (2x$CH_{2\ cHex}$), 34.0 (CH_{cHex}), 47.2 ($CH_{2\ Bn}$), 53.3 (CH_{iPent}), 84.5 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.4 (C_q), 139.8 (C_q), 149.0 (CH_{Ar}), 152.0 (C_q), 155.8 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{22}H_{31}N_7$:**

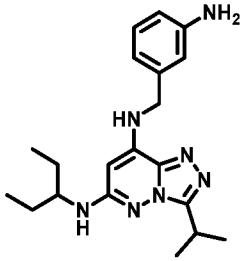
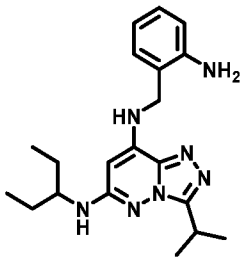
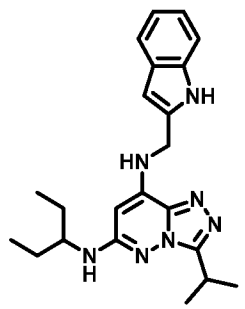
			394.27 [M+H]+, **found :** 394.41.
(66)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.87 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.43 – 1.63 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.55 (h, *J* = 6.4 Hz, 1H, H_{iPent}), 4.57 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.55 (s, 1H, H_{Ar}), 6.57 (d, *J* = 7.7 Hz, 1H, NH_{iPent}), 7.30 (dd, *J* = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.38 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.43 – 7.50 (m, 1H, H_{Ar}), 7.53 (dd, *J* = 8.3, 6.6 Hz, 2H, 2xH_{Ar}), 7.78 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.96 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 8.44 – 8.51 (m, 2H, 2xH_{Ar}), 8.57 (dd, *J* = 5.1, 1.7 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.5 (2x$CH_{3\text{-}CH2}$), 26.0 (2x$CH_{2\text{-}CH3}$), 47.2 (CH_2), 53.6 (CH_{iPent}), 84.7 (CH_{Ar}), 120.8 (CH_{Ar}), 122.4 (CH_{Ar}), 126.5 (2xCH_{Ar}), 127.5 (C_q), 128.5 (2xCH_{Ar}), 129.1 (CH_{Ar}), 137.0 (CH_{Ar}), 139.9 (C_q), 140.5 (C_q), 146.2 (C_q), 149.0 (CH_{Ar}), 156.5 (C_q), 157.5 (C_q). **MS (ESI+) : m/z calcd for $C_{22}H_{25}N_7$:** 388.22 [M+H]+, **found :** 388.33.
(67)		> 95 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.82 (t, *J* = 7.4 Hz, 9H, 3x$CH_{3\text{-}CH2}$), 1.34 (d, *J* = 7.0 Hz, 3H, $CH_{3\text{-}CH}$), 1.37 – 1.54 (m, 4H, 2x$CH_{2\text{-}CH3\ iPent}$), 1.81 (ddt, *J* = 94.8, 13.7, 7.1 Hz, 2H, $CH_{2\text{-}CH3\ sec\text{-}but}$), 3.16 (h, *J* = 7.0 Hz, 1H, $H_{C\text{-}CH3}$), 3.53 (h, *J* = 6.0 Hz, 1H, H_{iPent}), 4.52 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.43 (s, 1H, H_{Ar}), 6.34 (d, *J* = 7.9 Hz, 1H, NH_{iPent}), 7.29 (dd, *J* = 7.4, 4.9 Hz, 1H, H_{Ar}), 7.35 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.71 – 7.83 (m, 2H, H_{Ar} & NH_{Bn}), 8.55 (d, *J* = 4.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.8 ($CH_{3\text{-}CH2\ iPent}$), 10.9 ($CH_{3\text{-}CH2\ iPent}$), 12.2 ($CH_{3\text{-}CH2\ sec\text{-}but}$), 17.7 ($CH_{3\text{-}CH}$), 26.5 ($CH_{2\text{-}CH3\ iPent}$), 26.6 ($CH_{2\text{-}CH3\ iPent}$), 27.0 ($CH_{2\text{-}CH3\ sec\text{-}but}$), 31.9 ($CH_{sec\text{-}but}$), 47.7 ($CH_{2\ Bn}$), 53.5 ($CH_{iPent}$), 85.0 ($CH_{Ar}$), 121.2 ($CH_{Ar}$), 122.8 ($CH_{Ar}$), 137.4 ($CH_{Ar}$), 140.0 ($C_q$), 140.3 ($C_q$), 149.5 ($CH_{Ar}$), 152.4 ($C_q$), 156.3 ($C_q$), 158.1 ($C_q$). **MS (ESI+) : m/z calcd for $C_{20}H_{29}N_7$:** 368.26 [M+H]+, **found :** 368.37.

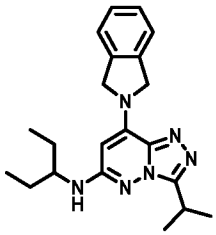
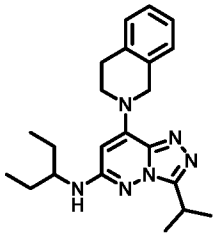
(68)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.76 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 0.82 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.33 – 1.57 (m, 4H, 2x$CH_{2\text{-}CH3}$), 1.68 – 2.01 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.04 (tt, J = 8.8, 5.5 Hz, 1H, H_{iPent}), 3.52 (h, J = 6.6 Hz, 1H, H_{iPent}), 4.52 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.43 (s, 1H, H_{Ar}), 6.33 (d, J = 7.8 Hz, 1H, NH_{iPent}), 7.29 (dd, J = 7.5, 4.8 Hz, 1H, H_{Ar}), 7.36 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.71 – 7.86 (m, 2H, NH_{Bn} & H_{Ar}), 8.51 – 8.64 (m, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 11.8 (2x$CH_{3\text{-}CH2}$), 24.7 (2x$CH_{2\text{-}CH3}$), 26.0 (2x$CH_{2\text{-}CH3}$), 38.7 (CH_{iPent}), 47.2 ($CH_{2\ Bn}$), 53.0 (CH_{iPent}), 84.5 (CH_{Ar}), 120.8 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.4 (C_q), 139.8 (C_q), 149.0 (CH_{Ar}), 150.8 (C_q), 155.8 (C_q), 157.7 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{31}N_7$:** 382.27 [M+H]+, **found :** 382.35.
(69)		82 % [a]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.82 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 0.92 (d, J = 6.7 Hz, 6H, 2x$CH_{3\ iPr}$), 1.34 – 1.57 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.19 (hept, J = 6.8 Hz, 1H, H_{iPr}), 2.77 (d, J = 7.0 Hz, 2H, $CH_{2\text{-}CH}$), 3.53 (h, J = 6.5 Hz, 1H, H_{iPent}), 4.53 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.44 (s, 1H, H_{Ar}), 6.35 (d, J = 7.9 Hz, 1H, $NH_{\text{-}CH}$), 7.26 – 7.31 (m, 1H, H_{Ar}), 7.35 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.72 – 7.81 (m, 2H, NH_{Bn} & H_{Ar}), 8.46 – 8.61 (m, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 22.3 (2xCH_{iPr}), 26.1 (2x$CH_{2\text{-}CH3}$), 26.4 (CH_{iPr}), 32.4 ($CH_{2\text{-}CH}$), 47.2 ($CH_{2\ Bn}$), 53.1 (CH_{iPent}), 84.5 (CH_{Ar}), 120.8 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.2 (C_q), 139.8 (C_q), 148.1 (C_q), 149.0 (CH_{Ar}), 156.0 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{29}N_7$:** 368.26 [M+H]+, **found :** 368.34.

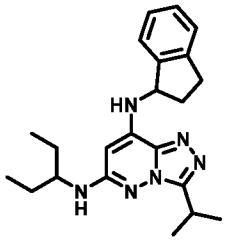
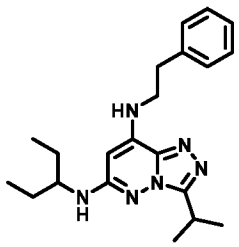
(70)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.85 (t, *J* = 7.3 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.48 (dhept, *J* = 14.0, 6.8 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 3.52 (h, *J* = 6.5 Hz, 1H, H_{iPent}), 4.58 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.58 (s, 1H, H_{Ar}), 6.58 (d, *J* = 7.7 Hz, 1H, NH_{iPent}), 7.30 (dd, *J* = 7.4, 4.9 Hz, 1H, H_{Ar}), 7.39 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.48 (dd, *J* = 7.6, 4.8 Hz, 1H, H_{Ar}), 7.79 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.94 – 8.06 (m, 2H, H_{Ar} & NH_{Bn}), 8.51 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 8.57 (d, *J* = 4.8 Hz, 1H, H_{Ar}), 8.75 (d, *J* = 4.7 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 11.0 (2x$CH_{3\text{-}CH2}$), 26.5 (2x$CH_{2\text{-}CH3}$), 47.7 ($CH_{2\ Bn}$), 54.0 (CH_{iPent}), 85.4 (CH_{Ar}), 121.3 (CH_{Ar}), 122.9 (CH_{Ar}), 123.3 (CH_{Ar}), 124.4 (CH_{Ar}), 137.0 (CH_{Ar}), 137.5 (CH_{Ar}), 140.3 (C_q), 140.8 (C_q), 146.7 (C_q), 147.0 (C_q), 149.5 (CH_{Ar}), 150.3 (CH_{Ar}), 157.1 (C_q), 158.0 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{24}N_8$:** 389.22 [M+H]+, **found :** 389.30.
(71)		> 97 % [a]	Grey solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.86 (t, *J* = 7.3 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.50 (ddp, *J* = 21.0, 14.2, 6.9 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 3.56 (h, *J* = 6.4 Hz, 1H, H_{iPent}), 4.58 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.58 (s, 1H, H_{Ar}), 6.65 (d, *J* = 7.8 Hz, 1H, NH_{iPent}), 7.30 (dd, *J* = 7.4, 4.9 Hz, 1H, H_{Ar}), 7.38 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.58 (dd, *J* = 8.1, 4.8 Hz, 1H, H_{Ar}), 7.75 – 7.86 (m, 1H, H_{Ar}), 8.03 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 8.57 (d, *J* = 4.8 Hz, 1H, H_{Ar}), 8.66 (d, *J* = 4.8 Hz, 1H, H_{Ar}), 8.76 (dd, *J* = 8.1, 2.5 Hz, 1H, H_{Ar}), 9.62 (d, *J* = 2.1 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.5 (2x$CH_{3\text{-}CH2}$), 26.0 (2x$CH_{2\text{-}CH3}$), 47.2 ($CH_{2\ Bn}$), 53.6 (CH_{iPent}), 85.0 (CH_{Ar}), 120.8 (CH_{Ar}), 122.4 (CH_{Ar}), 123.6 (CH_{Ar}), 123.7 (C_q), 133.5 (CH_{Ar}), 137.0 (CH_{Ar}), 139.9 (C_q), 140.7 (C_q), 144.3 (C_q), 147.2 (CH_{Ar}), 149.1 (CH_{Ar}), 149.8 (CH_{Ar}), 156.7 (C_q), 157.5 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{24}N_8$:** 389.22 [M+H]+, **found :** 389.30.

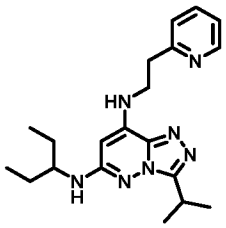
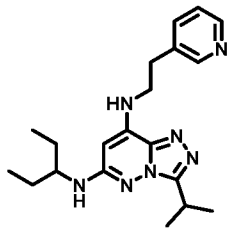
(72)		> 97 % [a]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.88 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.52 (dq, J = 18.3, 7.0 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 3.60 (h, J = 6.4 Hz, 1H, H_{iPent}), 4.58 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.60 (s, 1H, H_{Ar}), 6.70 (d, J = 7.7 Hz, 1H, NH_{iPent}), 7.30 (dd, J = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.38 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.78 (td, J = 7.7, 1.8 Hz, 1H, H_{Ar}), 8.07 (t, J = 6.2 Hz, 1H, NH_{Bn}), 8.42 (d, J = 5.6 Hz, 2H, 2xH_{Ar}), 8.57 (d, J = 4.8 Hz, 1H, H_{Ar}), 8.74 (d, J = 5.3 Hz, 2H, 2xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.5 (2x$CH_{3\text{-}CH2}$), 26.0 (2x$CH_{2\text{-}CH3}$), 47.2 ($CH_{2\ Bn}$), 53.7 (CH_{iPent}), 85.1 (CH_{Ar}), 119.9 (CH_{Ar}), 120.8 (CH_{Ar}), 122.4 (CH_{Ar}), 134.3 (C_q), 137.0 (CH_{Ar}), 139.8 (C_q), 141.2 (C_q), 144.2 (C_q), 149.1 (CH_{Ar}), 150.1 (CH_{Ar}), 156.9 (C_q), 157.4 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{24}N_8$:** 389.22 [M+H]+, **found :** 389.30.
(73)		91 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.82 (t, J = 7.4 Hz, 6H, 2x$CH_{3\ iPent}$), 1.36 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.38 – 1.56 (m, 4H, 2x$CH_{2\ iPent}$), 3.30 (d, J = 6.8 Hz, 1H, H_{iPr}), 3.55 (h, J = 6.8 Hz, 1H, H_{iPent}), 3.85 (s, 3H, OCH_3), 4.39 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.36 (s, 1H, H_{Ar}), 6.29 (d, J = 8.0 Hz, 1H, NH_{iPent}), 6.89 (td, J = 7.5, 1.1 Hz, 1H, H_{Ar}), 7.02 (dd, J = 8.3, 1.1 Hz, 1H, H_{Ar}), 7.13 (dd, J = 7.5, 1.7 Hz, 1H, H_{Ar}), 7.24 (td, J = 7.9, 1.7 Hz, 1H, H_{Ar}), 7.55 (t, J = 6.2 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\ iPent}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.1 (2x$CH_{2\ iPent}$), 40.6 ($CH_{2\ Bn}$), 52.9 (CH_{iPent}), 55.3 (OCH_3), 84.1 (CH_{Ar}), 110.5 (CH_{Ar}), 120.2 (CH_{Ar}), 125.3 (C_q), 126.5 (CH_{Ar}), 128.1 (CH_{Ar}), 139.7 (C_q), 140.0 (C_q), 152.7 (C_q), 156.0 (C_q), 156.6 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{30}N_5$:** 383.26 [M+H]+, **found :** 383.31.

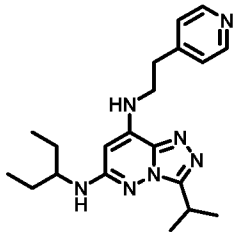
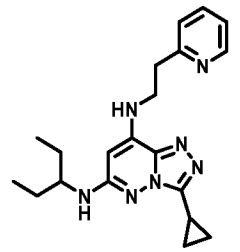
(74)		> 95 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.86 (t, J = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.35 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.71 (m, 2H, $CH_{2\text{-}CH3}$), 3.25 – 3.32 (m, 1H, H_{iPr}), 3.44 (ddt, J = 20.8, 10.6, 5.1 Hz, 2H, $CH_{2\text{-}OH}$), 3.63 (q, J = 6.8 Hz, 1H, H_{Alk}), 4.12 – 4.30 (m, 2H, $CH_{2\ Bn}$), 4.58 (t, J = 5.4 Hz, 1H, OH), 4.95 (s, 2H, NH_2), 5.50 (s, 1H, H_{Ar}), 6.29 (d, J = 7.8 Hz, 1H, NH_{Alk}), 6.47 – 6.58 (m, 2H, 2xH_{Ar}), 7.02 (d, J = 8.1 Hz, 2H, 2xH_{Ar}), 7.61 (t, J = 6.2 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.6 ($CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.6 ($CH_{2\text{-}CH3}$), 24.7 (CH_{iPr}), 45.0 ($CH_{2\ Bn}$), 53.8 ($CH_{\text{-}NH}$), 62.0 ($CH_{3\text{-}CH2}$), 84.2 (CH_{Ar}), 113.8 (2xCH_{Ar}), 125.1 (C_q), 127.9 (2xCH_{Ar}), 139.7 (C_q), 139.7 (C_q), 147.6 (C_q), 152.6 (C_q), 155.9 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{27}N_7O$:** 370.23 [M+H]+, **found :** 370.36.
(75)		> 96 % [a]	Yellow solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.84 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.35 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.47 (ddt, J = 28.5, 13.9, 7.0 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 3.25 – 3.30 (m, 1H, H_{iPr}), 3.56 (dd, J = 13.6, 6.7 Hz, 1H, H_{iPent}), 4.22 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 4.96 (s, 2H, NH_2), 5.46 (s, 1H, H_{Ar}), 6.29 (d, J = 8.0 Hz, 1H, NH), 6.51 (d, J = 8.1 Hz, 2H, 2xH_{Ar}), 7.02 (d, J = 8.1 Hz, 2H, 2xH_{Ar}), 7.56 (t, J = 6.2 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\ iPr}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.2 (2x$CH_{2\text{-}CH3}$), 45.0 ($CH_{2\ Bn}$), 53.0 (CH_{iPent}), 84.0 (CH_{Ar}), 113.8 (2xCH_{Ar}), 125.0 (C_q), 127.9 (2xCH_{Ar}), 139.7 (C_q), 139.7 (C_q), 147.6 (C_q), 152.6 (C_q), 156.0 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{29}N_7$:** 368.26 [M+H]+, **found :** 368.41.

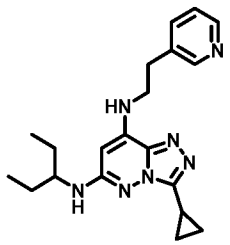
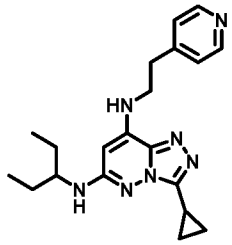
(76)		> 96 % [a]	Light brown solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.83 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.36 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.40 – 1.57 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.28 – 3.31 (m, 1H, H_{iPr}), 3.55 (q, J = 6.6 Hz, 1H, H_{iPent}), 4.29 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.02 (s, 2H, NH_2), 5.39 (s, 1H, H_{Ar}), 6.31 (d, J = 7.9 Hz, 1H, NH), 6.38 – 6.44 (m, 1H, H_{Ar}), 6.47 (d, J = 7.5 Hz, 1H, H_{Ar}), 6.51 (t, J = 2.0 Hz, 1H, H_{Ar}), 6.96 (t, J = 7.7 Hz, 1H, H_{Ar}), 7.67 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** N.D. **MS (ESI+) : m/z calcd for $C_{20}H_{29}N_7$:** 368.26 [M+H]+, **found :** 368.47.
(77)		> 93 % [a]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.83 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.36 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.38 – 1.57 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.35 (s, 1H, H_{iPr}), 3.56 (h, J = 6.8, 6.3 Hz, 1H, H_{iPent}), 4.23 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.13 (s, 2H, NH_2), 5.45 (s, 1H, H_{Ar}), 6.35 (d, J = 8.0 Hz, 1H, NH_{iPent}), 6.49 (td, J = 7.4, 1.2 Hz, 1H, H_{Ar}), 6.63 (dd, J = 8.0, 1.2 Hz, 1H, H_{Ar}), 6.95 (ddd, J = 8.5, 7.4, 1.6 Hz, 1H, H_{Ar}), 7.02 (dd, J = 7.5, 1.6 Hz, 1H, H_{Ar}), 7.63 (t, J = 6.1 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.2 (2x$CH_{2\text{-}CH3}$), 42.6 ($CH_{2\ Bn}$), 53.0 (CH_{iPent}), 84.1 (CH_{Ar}), 114.7 (CH_{Ar}), 115.6 (CH_{Ar}), 120.2 (C_q), 127.5 (CH_{Ar}), 127.6 (CH_{Ar}), 139.7 (C_q), 139.9 (C_q), 146.2 (C_q), 152.7 (C_q), 156.0 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{29}N_7$:** 368.26 [M+H]+, **found :** 368.42.
(78)		> 95 % [a]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.82 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.36 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.57 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.22 – 3.46 (m, 1H, H_{iPr}), 3.56 (q, J = 6.5 Hz, 1H, H_{iPent}), 4.59 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.58 (s, 1H, H_{Ar}), 6.33 (d, J = 9.1 Hz, 2H, NH_{Alk} & H_{Indole}), 6.94 (t, J = 7.4 Hz, 1H, H_{Indole}), 7.02 (t, J = 7.8 Hz, 1H, H_{Indole}), 7.32 (d, J = 8.1 Hz, 1H, H_{Indole}), 7.43 (d, J = 7.8 Hz, 1H, H_{Indole}),

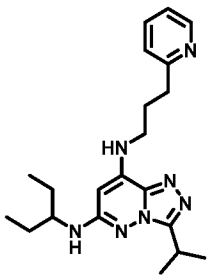
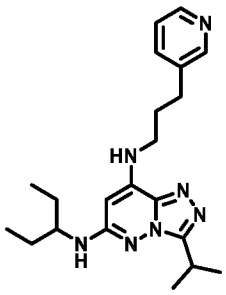
			7.56 (t, J = 6.2 Hz, 1H, NH_{Bn}), 10.96 (s, 1H, NH_{Indole}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 ($2xCH_{3\text{-}CH2}$), 19.5 ($2xCH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.2 ($2xCH_{2\text{-}CH3}$), 39.7 ($CH_{2\ Bn}$), 53.0 (CH_{Ar}), 84.7 (CH_{Indole}), 99.2 (CH_{Indole}), 111.1 (CH_{Indole}), 118.9 (CH_{Indole}), 119.6 (CH_{Indole}), 120.7 (CH_{Indole}), 127.9 (C_q), 136.1 (C_q), 136.2 (C_q), 139.7 (C_q), 139.9 (C_q), 152.7 (C_q), 155.9 (C_q). **MS (ESI+) : m/z calcd for $C_{22}H_{29}N_7$:** 392.26 [M+H]+, **found :** 392.33.
(79)		> 97 % [a]	Solid beige. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.89 (t, J = 7.4 Hz, 6H, $2xCH_{3\text{-}CH2}$), 1.38 (d, J = 6.9 Hz, 6H, $2xCH_{3\ iPr}$), 1.44 – 1.63 (m, 4H, $2xCH_{2\text{-}CH3}$), 3.28 – 3.35 (m, 1H, H_{iPr}), 3.58 – 3.70 (m, 1H, H_{iPent}), 5.07 (s, 4H, $2xCH_{2\text{-}N}$), 5.50 (s, 1H, H_{Ar}), 6.39 (d, J = 8.0 Hz, 1H, NH), 7.34 (dd, J = 5.6, 3.1 Hz, 2H, $2xH_{Ar}$), 7.45 (dt, J = 7.5, 3.6 Hz, 2H, $2xH_{Ar}$). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 ($2xCH_{3\text{-}CH2}$), 19.4 ($2xCH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.3 ($2xCH_{2\text{-}CH3}$), 53.0 (CH_{iPent}), 55.4 ($2xCH_{2\text{-}N}$), 86.3 (CH_{Ar}), 122.7 ($2xCH_{Ar}$), 127.4 ($2xCH_{Ar}$), 136.6 ($2xC_q$), 139.5 (C_q), 140.4 (C_q), 152.5 (C_q), 155.9 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{28}N_6$:** 365.24 [M+H]+, **found :** 365.42.
(80)		92 % [a]	Light brown oil. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.88 (t, J = 7.4 Hz, 6H, $2xCH_{3\text{-}CH2}$), 1.36 (d, J = 6.9 Hz, 6H, $2xCH_{3\ iPr}$), 1.41 – 1.62 (m, 4H, $2xCH_{2\text{-}CH3}$), 2.97 (t, J = 5.9 Hz, 2H, $CH_{2\text{-}CH2}$), 3.28 – 3.36 (m, 1H, H_{iPr}), 3.61 (h, J = 6.5 Hz, 1H, H_{iPent}), 4.22 (t, J = 5.9 Hz, 2H, $CH_{2\text{-}CH2}$), 4.89 (s, 2H, $CH_{2\ THQ}$), 5.83 (s, 1H, H_{Ar}), 6.43 (d, J = 8.0 Hz, 1H, NH), 7.21 (s, 4H, $4xH_{Ar}$). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.3 ($2xCH_{3\text{-}CH2}$), 19.4 ($2xCH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.2 ($2xCH_{2\text{-}CH3}$), 27.7 ($CH_{2\text{-}CH2}$), 45.3 ($CH_{2\text{-}CH2}$), 49.1 ($CH_{2\ THQ}$), 53.0 (CH_{iPent}), 88.9 (CH_{Ar}), 126.1 (CH_{Ar}), 126.3 (CH_{Ar}), 126.5 (CH_{Ar}), 128.5 (CH_{Ar}), 133.4 (C_q), 134.4 (C_q), 140.6 (C_q), 141.4 (C_q), 152.4 (C_q), 155.7 (C_q).

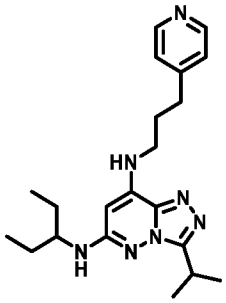
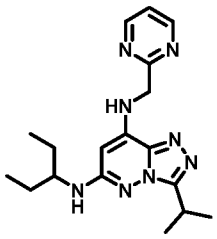
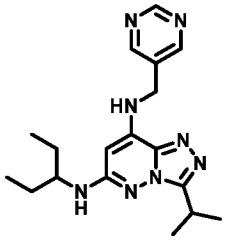
			MS (ESI+) : m/z calcd for $C_{22}H_{30}N_6$: 379.26 [M+H]+, **found :** 379.46.
(81)		> 97 % [a]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.88 (td, J = 7.4, 4.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.37 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.40 – 1.65 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.14 (dq, J = 12.5, 8.4 Hz, 1H, $H_{(CH2)indane}$), 2.46 (dt, J = 7.7, 3.9 Hz, 1H, $H_{(CH2)indane}$), 2.85 (dt, J = 16.0, 8.2 Hz, 1H, $H_{(CH2)indane}$), 3.02 (ddd, J = 15.9, 8.8, 3.4 Hz, 1H, $H_{(CH2)indane}$), 3.26 – 3.42 (m, 1H, H_{iPr}), 3.53 – 3.69 (m, 1H, H_{iPent}), 5.22 (s, 1H, H_{indane}), 5.80 (s, 1H, H_{Ar}), 6.33 (d, J = 8.0 Hz, 1H, NH_{iPent}), 7.12 – 7.38 (m, 5H, NH_{indane} & 4xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 ($CH_{3\text{-}CH2}$), 10.4 ($CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.2 (2x$CH_{2\text{-}CH3}$), 29.7 ($CH_{2\ indane}$), 32.1 ($CH_{2\ indane}$), 53.0 (CH_{iPent}), 57.3 (CH_{indane}), 84.6 (CH_{Ar}), 123.9 (CH_{Ar}), 124.7 (CH_{Ar}), 126.4 (CH_{Ar}), 127.6 (CH_{Ar}), 139.7 (C_q), 139.8 (C_q), 143.0 (C_q), 143.6 (C_q), 152.7 (C_q), 156.1 (C_q). **MS (ESI+) : m/z calcd for $C_{22}H_{30}N_6$:** 379.26 [M+H]+, **found :** 379.33.
(82)		> 97 % [a]	White amorphous solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.88 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.36 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.42 – 1.64 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.92 (dd, J = 8.8, 6.5 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.25 – 2.27 (m, 1H, H_{iPr}), 3.40 (q, J = 6.8 Hz, 2H, $CH_{2\text{-}NH}$), 3.61 (h, J = 6.5 Hz, 1H, H_{iPent}), 5.63 (s, 1H, H_{Ar}), 6.31 (d, J = 8.0 Hz, 1H, NH_{iPent}), 7.19 – 7.38 (m, 6H, 5xH_{Ar} & $NH_{\text{-}CH2}$). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\text{-}CH2}$), 24.8 (CH_{iPr}), 26.3 (2x$CH_{2\text{-}CH3}$), 33.8 ($CH_{2\text{-}CH2\text{-}NH}$), 43.6 ($CH_{2\text{-}NH}$), 52.9 ($CH_{iPent}$), 83.6 ($CH_{Ar}$), 126.2 ($CH_{Ar}$), 128.4 (2x$CH_{Ar}$), 128.7 (2x$CH_{Ar}$), 139.2 ($C_q$), 139.7 ($C_q$), 139.7 ($C_q$), 152.6 ($C_q$), 156.1 ($C_q$). **MS (ESI+) : m/z calcd for $C_{21}H_{30}N_6$:** 367.26 [M+H]+, **found :** 367.33.

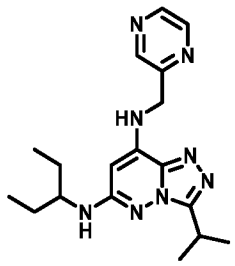
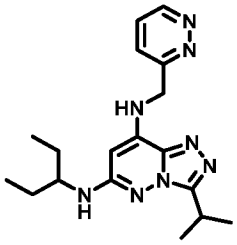
(83)		> 95 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.87 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.35 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.64 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.09 (t, *J* = 7.3 Hz, 2H, CH_2), 3.27 – 3.32 (m, 1H, H_{iPr}), 3.51 – 3.66 (m, 3H, CH_2 & H_{iPent}), 5.61 (s, 1H, H_{Ar}), 6.34 (d, *J* = 8.0 Hz, 1H, $NH_{\text{-}CH}$), 7.17 – 7.28 (m, 2H, NH_{Bn} & H_{Ar}), 7.34 (dt, *J* = 7.7, 1.1 Hz, 1H, H_{Ar}), 7.72 (td, *J* = 7.6, 1.9 Hz, 1H, H_{Ar}), 8.45 – 8.56 (m, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.3 (2x$CH_{2\text{-}CH3}$), 35.9 (CH_2), 41.7 (CH_2), 52.9 (CH_{iPent}), 83.7 (CH_{Ar}), 121.6 (CH_{Ar}), 123.3 (CH_{Ar}), 136.6 (CH_{Ar}), 139.7 (C_q), 139.8 (C_q), 149.1 (CH_{Ar}), 152.7 (C_q), 156.1 (C_q), 159.0 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{29}N_7$:** 368.26 [M+H]+, **found :** 368.34.
(84)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.89 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.36 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.41 – 1.64 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.95 (t, *J* = 7.3 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.33 (s, 1H, H_{iPr}), 3.44 (q, *J* = 6.8 Hz, 2H, $CH_{2\text{-}NH}$), 3.57 – 3.68 (m, 1H, H_{iPent}), 5.62 (s, 1H, H_{Ar}), 6.31 (d, *J* = 8.0 Hz, 1H, $NH_{\text{-}CH}$), 7.30 (t, *J* = 5.9 Hz, 1H, $NH_{\text{-}CH2\text{-}CH2}$), 7.34 (dd, *J* = 7.7, 4.7 Hz, 1H, H_{Ar}), 7.72 (dt, *J* = 7.9, 2.0 Hz, 1H, H_{Ar}), 8.44 (dd, *J* = 4.8, 1.6 Hz, 1H, H_{Ar}), 8.53 (d, *J* = 2.2 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.3 (2x$CH_{2\text{-}CH3}$), 30.8 ($CH_{2\text{-}CH2\text{-}NH}$), 43.2 ($CH_{2\text{-}NH}$), 52.9 ($CH_{iPent}$), 83.8 ($CH_{Ar}$), 123.4 ($CH_{Ar}$), 134.7 ($C_q$), 136.2 ($CH_{Ar}$), 139.6 ($C_q$), 139.7 ($C_q$), 147.5 ($CH_{Ar}$), 149.9 ($CH_{Ar}$), 152.6 ($C_q$), 156.1 ($C_q$). **MS (ESI+) : m/z calcd for $C_{20}H_{29}N_7$:** 368.26 [M+H]+, **found :** 368.34.

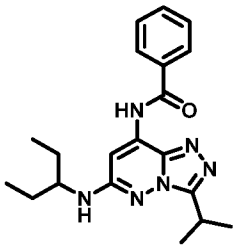
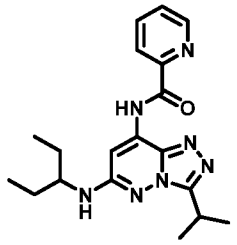
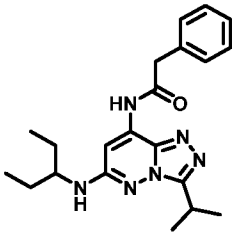
(85)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.88 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.35 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.41 – 1.64 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.95 (t, J = 7.3 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.23 – 3.37 (m, 1H, H_{iPr}), 3.45 (q, J = 6.8 Hz, 2H, $CH_{2\text{-}NH}$), 3.61 (h, J = 6.6 Hz, 1H, H_{iPent}), 5.62 (s, 1H, H_{Ar}), 6.30 (d, J = 8.0 Hz, 1H, NH_{iPent}), 7.28 (t, J = 5.8 Hz, 1H, $NH_{\text{-}CH2}$), 7.30 – 7.34 (m, 2H, 2xH_{Ar}), 8.39 – 8.57 (m, 2H, 2xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.2 (2x$CH_{2\text{-}CH3}$), 32.9 ($CH_{2\text{-}CH2\text{-}NH}$), 42.4 ($CH_{2\text{-}NH}$), 52.9 ($CH_{iPent}$), 83.8 ($CH_{Ar}$), 124.2 (2x$CH_{Ar}$), 139.6 ($C_q$), 139.7 ($C_q$), 148.2 ($C_q$), 149.5 (2x$CH_{Ar}$), 152.6 ($C_q$), 156.0 ($C_q$). **MS (ESI+) : m/z calcd for $C_{20}H_{29}N_7$:** 368.26 [M+H]+, **found :** 368.34.
(86)		> 97 % [a]	Yellow solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.87 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.02 (dt, J = 8.6, 3.1 Hz, 2H, $CH_{2\ cPr}$), 1.11 (dt, J = 5.6, 2.9 Hz, 2H, $CH_{2\ cPr}$), 1.50 (dtq, J = 42.5, 14.4, 7.3, 6.5 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 2.24 (tt, J = 8.5, 5.1 Hz, 1H, H_{cPr}), 3.08 (t, J = 7.3 Hz, 2H, CH_2), 3.50 – 3.66 (m, 3H, H_{iPent} & CH_2), 5.60 (s, 1H, H_{Ar}), 6.33 (d, J = 8.1 Hz, 1H, NH_{iPent}), 7.18 – 7.26 (m, 2H, NH & H_{Ar}), 7.32 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.71 (td, J = 7.6, 1.9 Hz, 1H, H_{Ar}), 8.51 (dd, J = 4.9, 1.8 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.4 (CH_{cPr}), 6.3 (2x$CH_{2\ cPr}$), 10.3 (2x$CH_{3\text{-}CH2}$), 26.2 (2x$CH_{2\text{-}CH3}$), 35.9 (CH_2), 41.7 (CH_2), 52.8 (CH_{iPent}), 83.7 (CH_{Ar}), 121.6 (CH_{Ar}), 123.3 (CH_{Ar}), 136.5 (CH_{Ar}), 139.5 (C_q), 139.7 (C_q), 149.0 (CH_{Ar}), 149.8 (C_q), 156.3 (C_q), 158.9 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{27}N_7$:** 366.24 [M+H]+, **found :** 366.42.

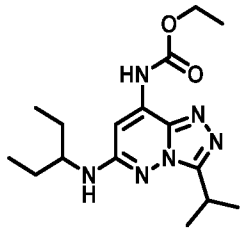
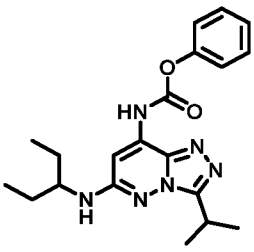
(87)		> 98 % [a]	Beige solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.88 (t, *J* = 7.4 Hz, 6H, 2xCH$_{3\text{-}CH2}$), 0.98 – 1.16 (m, 4H, 2xCH$_{2\ cPr}$), 1.40 – 1.63 (m, 4H, 2xCH$_{2\text{-}CH3}$), 2.24 (tt, *J* = 8.5, 5.2 Hz, 1H, H$_{cPr}$), 2.94 (t, *J* = 7.4 Hz, 2H, CH$_2$), 3.38 – 3.48 (m, 2H, CH$_2$), 3.56 – 3.68 (m, 1H, H$_{iPent}$), 5.60 (s, 1H, H$_{Ar}$), 6.30 (d, *J* = 8.1 Hz, 1H, NH$_{iPent}$), 7.28 (t, *J* = 5.8 Hz, 1H, NH), 7.32 (dd, *J* = 7.8, 4.7 Hz, 1H, H$_{Ar}$), 7.70 (dt, *J* = 7.9, 2.0 Hz, 1H, H$_{Ar}$), 8.42 (d, *J* = 4.0 Hz, 1H, H$_{Ar}$), 8.47 – 8.56 (m, 1H, H$_{Ar}$). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.4 (CH$_{cPr}$), 6.4 (CH$_{2\ cPr}$), 10.3 (2xCH$_{3\text{-}CH2}$), 26.2 (2xCH$_{2\text{-}CH3}$), 30.8 (CH$_2$), 43.2 (CH$_2$), 52.8 (CH$_{iPent}$), 83.8 (CH$_{Ar}$), 123.4 (CH$_{Ar}$), 134.7 (C$_q$), 136.3 (CH$_{Ar}$), 139.5 (C$_q$), 139.6 (C$_q$), 147.5 (CH$_{Ar}$), 149.8 (C$_q$), 149.9 (CH$_{Ar}$), 156.3 (C$_q$). **MS (ESI+) : m/z calcd for C$_{20}$H$_{27}$N$_7$:** 366.24 [M+H]+, **found :** 366.39.
(88)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.88 (t, *J* = 7.4 Hz, 6H, 2xCH$_{3\text{-}CH2}$), 0.99 – 1.15 (m, 4H, 2xCH$_{2\ cPr}$), 1.40 – 1.63 (m, 4H, 2xCH$_{2\text{-}CH3}$), 2.24 (tt, *J* = 8.5, 5.1 Hz, 1H, H$_{cPr}$), 2.95 (t, *J* = 7.3 Hz, 2H, CH$_2$), 3.45 (q, *J* = 6.8 Hz, 2H, CH$_2$), 3.61 (q, *J* = 6.2 Hz, 1H, H$_{iPent}$), 5.60 (s, 1H, H$_{Ar}$), 6.30 (d, *J* = 8.1 Hz, 1H, NH$_{iPent}$), 7.25 (t, *J* = 5.8 Hz, 1H, NH), 7.28 – 7.36 (m, 2H, 2xH$_{Ar}$), 8.42 – 8.54 (m, 2H, 2xH$_{Ar}$). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.4 (CH$_{cPr}$), 6.4 (2xCH$_{2\ cPr}$), 10.3 (2xCH$_{3\text{-}CH2}$), 26.2 (2xCH$_{2\text{-}CH3}$), 32.9 (CH$_2$), 42.4 (CH$_2$), 52.8 (CH$_{Ar}$), 83.8 (C$_q$), 124.2 (2xCH$_{Ar}$), 139.5 (C$_q$), 139.6 (C$_q$), 148.2 (C$_q$), 149.5 (2xCH$_{Ar}$), 149.8 (C$_q$), 156.3 (C$_q$). **MS (ESI+) : m/z calcd for C$_{20}$H$_{27}$N$_7$:** 366.24 [M+H]+, **found :** 366.39.

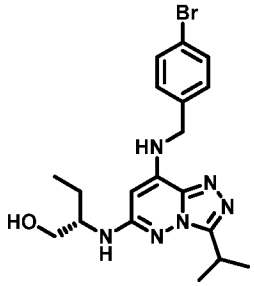
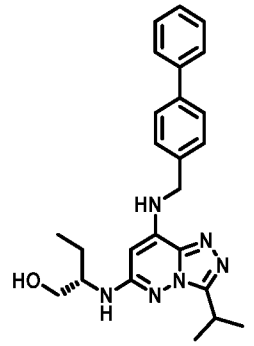
(89)		> 95 % [a]	Yellow solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.87 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.35 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.40 – 1.62 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.03 (p, J = 7.3 Hz, 2H, CH_2), 2.82 (t, J = 7.7 Hz, 2H, CH_2), 3.23 (q, J = 6.6 Hz, 2H, CH_2), 3.30 (q, J = 6.9 Hz, 1H, H_{iPr}), 3.61 (qd, J = 7.5, 3.7 Hz, 1H, H_{iPent}), 5.52 (s, 1H, H_{Ar}), 6.28 (d, J = 8.0 Hz, 1H, NH), 7.19 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H, H_{Ar}), 7.28 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.33 (t, J = 5.7 Hz, 1H, NH), 7.68 (td, J = 7.7, 1.9 Hz, 1H, H_{Ar}), 8.48 (dd, J = 5.1, 1.7 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.2 (2x$CH_{2\text{-}CH3}$), 27.5 (CH_2), 35.0 (CH_2), 41.8 (CH_2), 52.9 (CH_{iPent}), 83.4 (CH_{Ar}), 121.2 (CH_{Ar}), 122.7 (CH_{Ar}), 136.4 (CH_{Ar}), 139.7 (C_q), 140.0 (C_q), 148.9 (CH_{Ar}), 152.6 (C_q), 156.1 (C_q), 161.0 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{31}N_7$:** 382.27 [M+H]+, **found :** 382.32.
(90)		> 95 % [a]	Yellow solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.80 – 0.98 (m, 6H, 2x$CH_{3\text{-}CH2}$), 1.36 (dd, J = 7.0, 1.3 Hz, 6H, 2x$CH_{3\ iPr}$), 1.51 (ddt, J = 33.1, 13.9, 6.9 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 1.95 (p, J = 7.3 Hz, 2H, CH_2), 2.70 (t, J = 7.9 Hz, 2H, CH_2), 3.19 (q, J = 6.7 Hz, 2H, CH_2), 3.29 (s, 1H, H_{iPr}), 3.60 (td, J = 12.9, 6.3 Hz, 1H, H_{iPent}), 5.51 (s, 1H, H_{Ar}), 6.28 (d, J = 8.0 Hz, 1H, NH_{iPent}), 7.27 (t, J = 5.7 Hz, 1H, NH), 7.31 (dd, J = 7.8, 4.8 Hz, 1H, H_{Ar}), 7.56 – 7.78 (m, 1H, H_{Ar}), 8.40 (d, J = 4.7 Hz, 1H, H_{Ar}), 8.47 (s, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.2 (2x$CH_{2\text{-}CH3}$), 29.0 (CH_2), 29.7 (CH_2), 41.6 (CH_2), 52.9 (CH_{iPent}), 83.5 (CH_{Ar}), 123.4 (CH_{Ar}), 135.8 (CH_{Ar}), 137.0 (C_q), 139.7 (C_q), 140.0 (C_q), 147.2 (CH_{Ar}), 149.6 (CH_{Ar}), 152.6 (C_q), 156.1 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{31}N_7$:** 382.27 [M+H]+, **found :** 382.32.

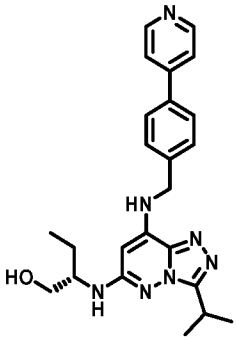
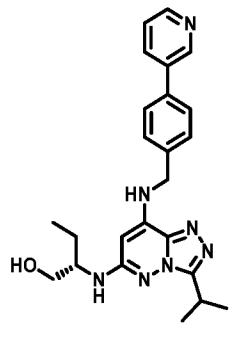
(91)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.87 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.36 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.54 (tdd, J = 12.3, 7.3, 5.4 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 1.87 – 2.06 (m, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 2.65 – 2.77 (m, 2H, $CH_{2\text{-}CH2\text{-}CH2\text{-}NH}$), 3.19 (q, J = 6.5 Hz, 2H, $CH_{2\text{-}NH}$), 3.26 – 3.32 (m, 1H, H_{iPr}), 3.60 (hept, J = 5.9, 5.4 Hz, 1H, H_{iPent}), 5.51 (s, 1H, H_{Ar}), 6.28 (d, J = 8.0 Hz, 1H, NH_{iPent}), 7.22 – 7.35 (m, 3H, NH_{Bn} & 2xH_{Ar}), 8.45 (d, J = 5.0 Hz, 2H, 2xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.2 (2x$CH_{2\text{-}CH3}$), 28.2 ($CH_{2\text{-}CH2\text{-}CH2\text{-}NH}$), 31.8 ($CH_{2\text{-}CH2\text{-}NH}$), 41.5 ($CH_{2\text{-}NH}$), 52.9 ($CH_{iPent}$), 83.5 ($CH_{Ar}$), 123.9 ($CH_{Ar}$), 139.7 ($C_q$), 140.0 ($C_q$), 149.5 ($CH_{Ar}$), 150.5 ($C_q$), 152.6 ($C_q$), 156.1 ($C_q$). **MS (ESI+) : m/z calcd for $C_{21}H_{31}N_7$:** 382.27 [M+H]+, **found :** 382.35.
(92)		> 95 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.83 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.36 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.57 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.26 – 3.33 (m, 1H, H_{iPr}), 3.50 – 3.64 (m, 1H, H_{iPent}), 4.64 (d, J = 5.9 Hz, 2H, $CH_{2\ Bn}$), 5.46 (s, 1H, H_{Ar}), 6.33 (d, J = 8.0 Hz, 1H, NH_{iPent}), 7.44 (t, J = 4.9 Hz, 1H, H_{Ar}), 7.49 (t, J = 6.0 Hz, 1H, NH_{Bn}), 8.81 (d, J = 4.9 Hz, 2H, 2xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.2 (2x$CH_{2\text{-}CH3}$), 47.6 ($CH_{2\ Bn}$), 53.0 (CH_{iPent}), 84.7 (CH_{Ar}), 120.1 (CH_{Ar}), 139.7 (C_q), 139.9 (C_q), 152.7 (C_q), 156.0 (C_q), 157.5 (2xCH_{Ar}), 166.0 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{26}N_8$:** 355.24 [M+H]+, **found :** 355.34.
(93)		> 96 % [a]	Pale yellow solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.84 (t, J = 7.4 Hz, 6H, 2xCH_3), 1.35 (d, J = 7.0 Hz, 6H, 2xCH_3), 1.38 – 1.57 (m, 4H, 2xCH_2), 3.27 (d, J = 6.9 Hz, 1H, H_{iPr}), 3.55 (p, J = 6.6 Hz, 1H, H_{iPent}), 4.48 (d, J = 6.2 Hz, 2H, CH_2), 5.51 (s, 1H, H_{Ar}), 6.31 (d, J = 7.9 Hz, 1H, NH), 7.90 (t, J = 6.2 Hz, 1H, NH), 8.82 (s, 2H, 2xH_{Ar}), 9.10 (s, 1H, H_{Ar}).

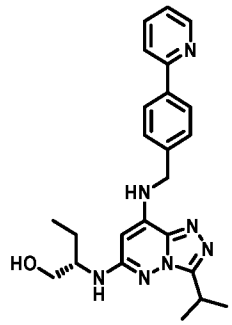
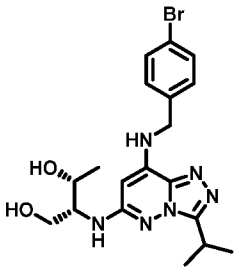
			^{13}C NMR (101 MHz, DMSO-d_6) δ : N.D. **MS (ESI+) : m/z calcd for $C_{18}H_{26}N_8$:** 355.24 [M+H]+, **found :** 355.34.
(94)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.83 (t, J = 7.3 Hz, 6H, 2x$CH_{3\ iPr}$), 1.36 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.47 (ddt, J = 32.1, 14.0, 6.8 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 3.26 – 3.35 (m, 1H, H_{iPr}), 3.56 (q, J = 6.6 Hz, 1H, H_{iPent}), 4.60 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.47 (s, 1H, H_{Ar}), 6.35 (d, J = 7.9 Hz, 1H, NH_{iPent}), 7.82 (t, J = 6.2 Hz, 1H, NH_{Bn}), 8.56 (d, J = 2.5 Hz, 1H, H_{Ar}), 8.63 (d, J = 6.4 Hz, 2H, 2xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.1 (2x$CH_{2\text{-}CH3}$), 45.4 ($CH_{2\ Bn}$), 53.0 (CH_{iPent}), 84.7 (CH_{Ar}), 139.6 (C_q), 139.7 (C_q), 143.3 (CH_{Ar}), 143.4 (CH_{Ar}), 144.1 (CH_{Ar}), 152.7 (C_q), 153.4 (C_q), 155.8 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{26}N_8$:** 355.24 [M+H]+, **found :** 355.31.
(95)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.82 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.35 (d, J = 7.0 Hz, 6H; 2x$CH_{3\ iPr}$), 1.46 (ddt, J = 31.0, 14.0, 7.3 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 3.25 – 3.33 (m, 1H, H_{iPr}), 3.54 (q, J = 6.7 Hz, 1H, H_{iPent}), 4.73 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.47 (s, 1H, H_{Ar}), 6.40 (d, J = 7.9 Hz, 1H, NH_{iPent}), 7.58 – 7.75 (m, 2H, 2xH_{Ar}), 7.94 (t, J = 6.4 Hz, 1H, NH_{Bn}), 9.16 (dd, J = 4.7, 1.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.1 (2x$CH_{2\text{-}CH3}$), 45.7 ($CH_{2\ Bn}$), 53.0 (CH_{iPent}), 84.8 (CH_{Ar}), 125.0 (CH_{Ar}), 127.5 (CH_{Ar}), 139.6 (C_q), 139.6 (C_q), 150.8 (CH_{Ar}), 152.7 (C_q), 155.8 (C_q), 160.3 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{26}N_8$:** 355.24 [M+H]+, **found :** 355.31.

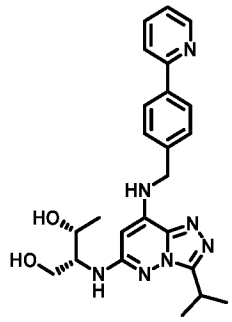
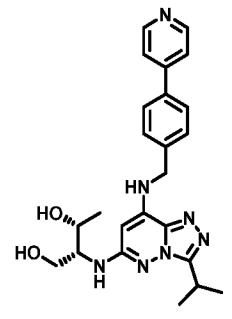
(96)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.90 (t, *J* = 7.4 Hz, 6H, 2xCH$_{3\text{-}CH2}$), 1.40 (d, *J* = 6.9 Hz, 6H, 2xCH$_{3\ iPr}$), 1.46 – 1.68 (m, 4H, 2xCH$_{2\text{-}CH3}$), 3.38 (p, *J* = 7.0 Hz, 1H, H$_{iPr}$), 3.67 (h, *J* = 6.7 Hz, 1H, H$_{iPent}$), 7.12 (d, *J* = 7.9 Hz, 1H, NH$_{Alk}$), 7.57 (dd, *J* = 8.3, 6.9 Hz, 2H, 2xH$_{Ar}$), 7.65 (d, *J* = 7.9 Hz, 2H, 2xH$_{Ar}$), 7.99 (dd, *J* = 7.2, 1.8 Hz, 2H, 2xH$_{Ar}$), 10.46 (s, 1H, NH$_{\text{-}CO}$). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.4 (2xCH$_{3\text{-}CH2}$), 19.4 (2xCH$_{3\ iPr}$), 24.8 (CH$_{iPr}$), 25.9 (2xCH$_{2\text{-}CH3}$), 53.4 (CH$_{iPent}$), 100.9 (CH$_{Ar}$), 128.1 (2xCH$_{Ar}$), 128.5 (2xCH$_{Ar}$), 131.9 (C$_q$), 132.5 (CH$_{Ar}$), 133.4 (C$_q$), 138.9 (C$_q$), 153.3 (C$_q$), 155.1 (C$_q$), 167.0 (C$_q$). **MS (ESI+) : m/z calcd for C$_{20}$H$_{26}$N$_6$O :** 367.22 [M+H]+, **found :** 367.30.
(97)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.90 (t, *J* = 7.3 Hz, 6H, 2xCH$_{3\ iPent}$), 1.40 (d, *J* = 6.9 Hz, 6H, 2xCH$_{3\ iPr}$), 1.46 – 1.66 (m, 4H, 2xCH$_{2\ iPent}$), 3.34 – 3.43 (m, 1H, H$_{iPr}$), 3.67 (h, *J* = 6.4 Hz, 1H, H$_{iPent}$), 7.20 (d, *J* = 7.9 Hz, 1H, NH$_{iPent}$), 7.73 (s, 1H, H$_{Ar}$), 7.80 (dd, *J* = 7.6, 4.8 Hz, 1H, H$_{Ar}$), 8.16 (t, *J* = 7.8 Hz, 1H, H$_{Ar}$), 8.25 (d, *J* = 7.8 Hz, 1H, H$_{Ar}$), 8.84 (d, *J* = 4.7 Hz, 1H, H$_{Ar}$), 10.85 (s, 1H, NH$_{\text{-}CO}$). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.4 (2xCH$_{3\ iPent}$), 19.4 (2xCH$_{3\ iPr}$), 24.8 (CH$_{iPr}$), 25.9 (2xCH$_{2\ iPent}$), 53.4 (CH$_{iPent}$), 98.8 (CH$_{Ar}$), 122.5 (CH$_{Ar}$), 128.2 (CH$_{Ar}$), 130.5 (C$_q$), 138.5 (C$_q$), 138.8 (CH$_{Ar}$), 147.6 (C$_q$), 149.0 (CH$_{Ar}$), 153.5 (C$_q$), 155.2 (C$_q$), 163.0 (C$_q$). **MS (ESI+) : m/z calcd for C$_{19}$H$_{25}$N$_7$O :** 368.22 [M+H]+, **found :** 368.31.
(98)		> 97 % [a]	Pale yellow solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.86 (t, *J* = 7.4 Hz, 6H, 2xCH$_{3\text{-}CH2}$), 1.37 (d, *J* = 7.0 Hz, 6H, 2xCH$_{3\ iPr}$), 1.52 (dtt, *J* = 38.9, 14.0, 6.5 Hz, 4H, 2xCH$_{2\text{-}CH3}$), 3.33 – 3.39 (m, 1H, H$_{iPr}$), 3.61 (hept, *J* = 5.9, 5.4 Hz, 1H, H$_{iPent}$), 3.92 (s, 2H, CH$_{2\text{-}CO}$), 6.98 (d, *J* = 7.9 Hz, 1H, NH$_{iPent}$), 7.21 – 7.29 (m, 1H, H$_{Ar}$), 7.29 – 7.41 (m, 4H, 4xH$_{Ar}$), 7.59 (s, 1H, H$_{Ar}$), 10.89 (s, 1H, NH$_{\text{-}CO}$).

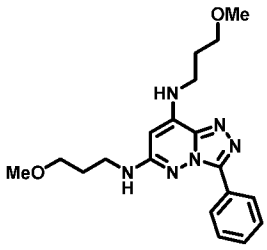
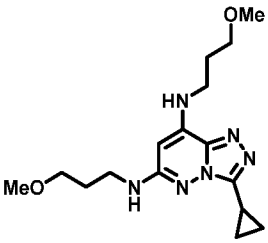
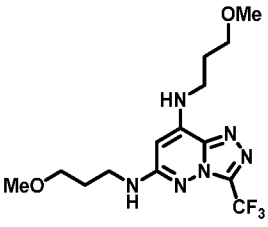
			^{13}C NMR (101 MHz, DMSO-d_6) δ : 10.3 ($2xCH_{3\text{-}CH2}$), 19.4 ($2xCH_{3\ iPr}$), 24.8 (CH_{iPr}), 25.9 ($2xCH_{2\text{-}CH3}$), 42.7 ($CH_{2\text{-}CO}$), 53.3 (CH_{iPent}), 99.4 (CH_{Ar}), 126.7 (CH_{Ar}), 128.3 ($2xCH_{Ar}$), 129.1 ($2xCH_{Ar}$), 131.8 (C_q), 135.5 (C_q), 138.5 (C_q), 153.2 (C_q), 155.2 (C_q), 171.9 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{28}N_6O$:** 381.24 [M+H]+, **found :** 381.41.
(99)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.88 (t, J = 7.4 Hz, 6H, $2xCH_{3\ iPent}$), 1.26 (t, J = 7.1 Hz, 3H, $CH_{3\text{-}CH2\text{-}O}$), 1.37 (d, J = 6.9 Hz, 6H, $2xCH_{3\ iPr}$), 1.43 – 1.66 (m, 4H, $2xCH_{2\ iPent}$), 3.34 – 3.41 (m, 1H, H_{iPr}), 3.63 (h, J = 6.6, 6.1 Hz, 1H, H_{iPent}), 4.20 (q, J = 7.1 Hz, 2H, $CH_{2\text{-}O}$), 6.99 (d, J = 7.9 Hz, 1H, NH_{iPent}), 7.26 (s, 1H, H_{Ar}), 10.07 (s, 1H, $NH_{\text{-}CO}$). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.3 ($2xCH_{3\ iPent}$), 14.3 ($CH_{3\text{-}CH2\text{-}O}$), 19.4 ($2xCH_{3\ iPr}$), 24.8 ($CH_{iPr}$), 25.9 ($2xCH_{2\ iPent}$), 53.3 ($CH_{iPent}$), 61.3 ($CH_{2\text{-}O}$), 97.9 ($CH_{Ar}$), 132.5 ($C_q$), 138.7 ($C_q$), 153.1 ($C_q$), 153.5 ($C_q$), 155.2 ($C_q$). **MS (ESI+) : m/z calcd for $C_{16}H_{26}N_6O_2$:** 335.22 [M+H]+, **found** : 335.32.
(100)		Unstable [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.88 (t, J = 7.4 Hz, 6H, $2xCH_{3\ iPent}$), 1.39 (d, J = 7.0 Hz, 6H, $2xCH_{3\ iPr}$), 1.42 – 1.65 (m, 4H, $2xCH_{2\ iPent}$), 3.37 (q, J = 7.0 Hz, 1H, H_{iPr}), 3.63 (hept, J = 5.9, 5.2 Hz, 1H, H_{iPent}), 7.03 (d, J = 7.9 Hz, 1H, NH_{iPent}), 7.22 – 7.34 (m, 4H, $4xH_{Ar}$), 7.42 – 7.50 (m, 2H, $2xH_{Ar}$), 10.87 (s, 1H, $NH_{\text{-}CO}$). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 ($2xCH_{3\ iPent}$), 19.4 ($2xCH_{3\ iPr}$), 24.8 (CH_{iPr}), 25.9 ($2xCH_{2\ iPent}$), 53.3 (CH_{iPent}), 98.9 (CH_{Ar}), 121.8 ($2xCH_{Ar}$), 125.9 (CH_{Ar}), 129.5 ($2xCH_{Ar}$), 132.4 (C_q), 138.7 (C_q), 150.3 (C_q), 151.9 (C_q), 153.2 (C_q), 155.1 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{26}N_6O_2$:** 383.22 [M+H]+, **found** : 383.32.

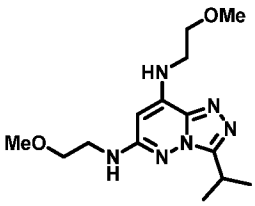
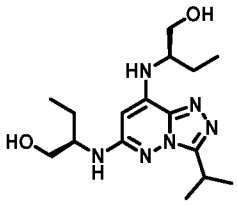
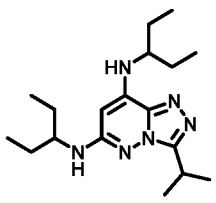
(101)		> 98 % [a]	White crystalline solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, J = 7.4 Hz, 3H), 1.35 (d, J = 6.9 Hz, 6H), 1.37 – 1.69 (m, 2H), 3.30 (q, J = 6.8 Hz, 1H), 3.42 (dq, J = 18.4, 5.4 Hz, 2H), 3.57 – 3.69 (m, 1H), 4.39 (d, J = 6.3 Hz, 2H), 4.58 (t, J = 5.4 Hz, 1H), 5.43 (s, 1H), 6.29 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.91 (t, J = 6.4 Hz, 1H). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.5 (CH_3), 19.6 (2xCH_3), 23.6 (CH_2), 24.7 (CH_{iPr}), 44.7 (CH_2), 53.8 (CH_{Alk}), 61.9 (CH_2), 84.6 (CH_{Ar}), 119.9 (C_q), 129.0 (CH_{Ar}), 131.3 (CH_{Ar}), 137.9 (C_q), 139.6 (C_q), 139.6 (C_q), 152.7 (C_q), 155.8 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{25}BrN_6O$:** 433.13 [M+H]+, **found :** 433.28.
(102)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.85 (t, J = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.33 – 1.39 (m, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.68 (m, 2H, $CH_{2\text{-}CH3}$), 3.28 – 3.32 (m, 1H, H_{iPr}), 3.37 – 3.48 (m, 2H, $CH_{2\text{-}OH}$), 3.62 (dt, J = 12.6, 6.5 Hz, 1H, $H_{C\text{-}NH}$), 4.41 – 4.55 (m, 2H, $CH_{2\ Bn}$), 4.58 (t, J = 5.4 Hz, 1H, OH), 5.51 (s, 1H, H_{Ar}), 6.31 (d, J = 7.7 Hz, 1H, NH_{Bn}), 7.31 – 7.38 (m, 1H, H_{Ar}), 7.40 – 7.50 (m, 4H, 4xH_{Ar}), 7.57 – 7.69 (m, 4H, 4xH_{Ar}), 7.92 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.6 ($CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.6 ($CH_{2\text{-}CH3}$), 24.8 (CH_{iPr}), 44.9 ($CH_{2\ Bn}$), 53.8 ($CH_{\text{-}NH}$), 61.9 ($CH_{2\text{-}OH}$), 84.5 (CH_{Ar}), 126.6 (2xCH_{Ar}), 126.8 (2xCH_{Ar}), 127.3 (CH_{Ar}), 127.4 (2xCH_{Ar}), 128.9 (2xCH_{Ar}), 137.7 (C_q), 138.9 (C_q), 139.7 (C_q), 139.8 (C_q), 139.9 (C_q), 152.8 (C_q), 155.9 (C_q). **MS (ESI+) : m/z calcd for $C_{25}H_{30}N_6O$:** 431.26 [M+H]+, **found :** 431.43.

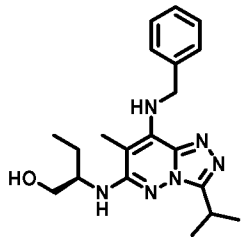
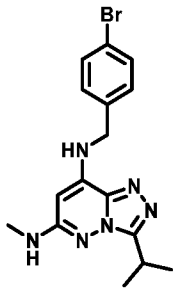
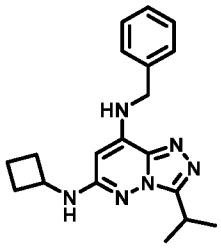
(103)		> 96 % [a]	Yellow solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.84 (t, *J* = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.36 (d, *J* = 6.8 Hz, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.68 (m, 2H, $CH_{2\text{-}CH3}$), 3.27 – 3.31 (m, 1H, H_{iPr}), 3.41 (dq, *J* = 18.5, 5.4 Hz, 2H, $CH_{2\text{-}OH}$), 3.62 (tt, *J* = 7.2, 3.5 Hz, 1H, $H_{C\text{-}NH}$), 4.42 – 4.55 (m, 2H, $CH_{2\ Bn}$), 4.57 (t, *J* = 5.4 Hz, 1H, OH), 5.49 (s, 1H, H_{Ar}), 6.30 (d, *J* = 7.8 Hz, 1H, $NH_{\text{-}CH}$), 7.50 (d, *J* = 8.2 Hz, 2H, 2xH_{Ar}), 7.64 – 7.73 (m, 2H, 2xH_{Ar}), 7.79 (d, *J* = 8.3 Hz, 2H, 2xH_{Ar}), 7.95 (t, *J* = 6.4 Hz, 1H, NH_{Bn}), 8.54 – 8.69 (m, 2H, 2xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.5 ($CH_{3\text{-}CH2}$), 19.6 (2xCH_{iPr}), 23.6 ($CH_{2\text{-}CH3}$), 24.7 (CH_{iPr}), 44.9 ($CH_{2\ Bn}$), 53.8 ($CH_{\text{-}NH}$), 61.9 ($CH_{2\text{-}OH}$), 84.5 (CH_{Ar}), 121.1 (2xCH_{Ar}), 126.9 (2xCH_{Ar}), 127.6 (2xCH_{Ar}), 135.8 (C_q), 139.7 (C_q), 139.8 (C_q), 139.8 (C_q), 146.7 (C_q), 150.2 (2xCH_{Ar}), 152.7 (C_q), 155.8 (C_q). **MS (ESI+) : m/z calcd for $C_{24}H_{29}N_7O$:** 432.25 [M+H]+, **found :** 432.40.
(104)		> 95 % [a]	Yellow solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.85 (t, *J* = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.36 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.68 (m, 2H, $CH_{2\text{-}CH3}$), 3.30 (s, 1H, H_{iPr}), 3.37 – 3.47 (m, 2H, $CH_{2\text{-}OH}$), 3.63 (h, *J* = 5.9 Hz, 1H, $H_{C\text{-}NH}$), 4.49 (d, *J* = 6.5 Hz, 2H, $CH_{2\ Bn}$), 4.57 (d, *J* = 5.5 Hz, 1H, OH), 5.51 (s, 1H, H_{Ar}), 6.31 (d, *J* = 7.7 Hz, 1H, $NH_{\text{-}CH}$), 7.44 – 7.51 (m, 3H, 3xH_{Ar}), 7.71 (d, *J* = 8.2 Hz, 2H, 2xH_{Ar}), 7.94 (t, *J* = 6.4 Hz, 1H, NH_{Bn}), 8.05 (dt, *J* = 8.1, 2.0 Hz, 1H), 8.55 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.88 (d, *J* = 2.4 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.5 ($CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.6 ($CH_{2\text{-}CH3}$), 24.7 (CH_{iPr}), 44.9 ($CH_{2\ Bn}$), 53.8 ($CH_{\text{-}NH}$), 61.9 ($CH_{2\text{-}OH}$), 84.5 (CH_{Ar}), 123.9 (CH_{Ar}), 127.0 (2xCH_{Ar}), 127.6 (2xCH_{Ar}), 134.0 (CH_{Ar}), 135.3 (C_q), 135.7 (C_q), 138.5 (C_q), 139.7 (C_q), 139.8 (C_q), 147.5 (CH_{Ar}), 148.4 (CH_{Ar}), 152.7 (C_q), 155.8 (C_q). **MS (ESI+) : m/z calcd for $C_{24}H_{29}N_7O$:** 432.25 [M+H]+, **found :** 432.40.

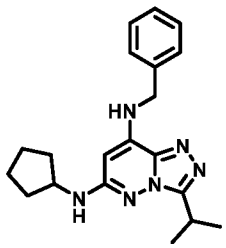
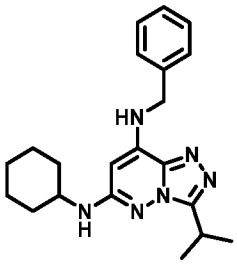
(105)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.84 (t, J = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.36 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.67 (m, 2H, $CH_{2\text{-}CH3}$), 3.32 (s, 1H, H_{iPr}), 3.42 (ddd, J = 19.6, 10.7, 5.2 Hz, 2H, $CH_{2\text{-}OH}$), 3.56 – 3.70 (m, 1H, $H_{C\text{-}NH}$), 4.49 (d, J = 6.4 Hz, 2H, NH_{Bn}), 4.56 (t, J = 5.4 Hz, 1H, OH), 5.49 (s, 1H, H_{Ar}), 6.30 (d, J = 7.7 Hz, 1H, $NH_{\text{-}CH}$), 7.33 (dd, J = 7.4, 4.8 Hz, 1H, H_{Ar}), 7.47 (d, J = 8.0 Hz, 2H, 2xH_{Ar}), 7.86 (td, J = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.90 – 7.96 (m, 2H, NH_{Bn} & H_{Ar}), 8.05 (d, J = 8.0 Hz, 2H, 2xH_{Ar}), 8.65 (d, J = 4.4 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.5 ($CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.6 ($CH_{2\text{-}CH3}$), 24.7 (CH_{iPr}), 45.0 ($CH_{2\ Bn}$), 53.8 ($CH_{\text{-}NH}$), 61.9 ($CH_{2\text{-}OH}$), 84.5 (CH_{Ar}), 120.1 (CH_{Ar}), 122.5 (CH_{Ar}), 126.6 (CH_{Ar}), 127.2 (CH_{Ar}), 137.2 (CH_{Ar}), 137.5 (C_q), 139.4 (C_q), 139.7 (C_q), 139.8 (C_q), 148.3 (C_q), 149.5 (CH_{Ar}), 152.7 (C_q), 155.8 (C_q). **MS (ESI+) : m/z calcd for $C_{24}H_{29}N_7O$:** 432.25 [M+H]+, **found :** 432.40.
(106)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.03 (d, J = 6.4 Hz, 3H, CH_3), 1.35 (dd, J = 7.0, 4.4 Hz, 6H, 2x$CH_{3\ iPr}$), 3.23 – 3.36 (m, 1H, H_{iPr}), 3.37 – 3.57 (m, 2H, CH_2), 3.72 (dtd, J = 8.5, 5.9, 2.8 Hz, 1H, H_{Alk}), 3.97 (ddd, J = 6.5, 4.9, 3.1 Hz, 1H, H_{Alk}), 4.38 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 4.54 (dd, J = 5.0, 3.5 Hz, 2H, 2xOH), 5.61 (s, 1H, H_{Ar}), 6.11 (d, J = 8.4 Hz, 1H, NH), 7.29 – 7.36 (m, 2H, 2xH_{Ar}), 7.46 – 7.58 (m, 2H, 2xH_{Ar}), 7.89 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6 ($CH_{3\ iPr}$), 19.7 ($CH_{3\ iPr}$), 20.3 (CH_3), 24.6 (CH_{iPr}), 44.6 ($CH_{2\ Bn}$), 56.9 (CH_{Alk}), 60.1 (CH_2), 64.5 (CH_{Alk}), 84.7 (CH_{Ar}), 119.9 (C_q), 129.2 (2xCH_{Ar}), 131.2 (2xCH_{Ar}), 138.0 (C_q), 139.6 (C_q), 139.6 (C_q), 152.7 (C_q), 156.2 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{25}N_6O_2$:** 449.13 [M+H]+, **found :** 449.19.

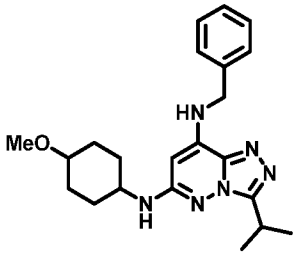
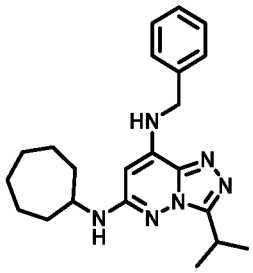
(107)		> 98 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.03 (d, J = 6.3 Hz, 3H, $CH_{3\text{-}CH}$), 1.35 (dd, J = 6.9, 4.4 Hz, 6H, 2x$CH_{3\ iPr}$), 3.27 – 3.37 (m, 1H, H_{iPr}), 3.46 (ddt, J = 35.1, 10.6, 5.6 Hz, 2H, $CH_{2\text{-}OH}$), 3.73 (q, J = 7.9 Hz, 1H, $CH_{\text{-}NH}$), 3.97 (d, J = 7.4 Hz, 1H, $CH_{\text{-}OH}$), 4.44 – 4.58 (m, 4H, $CH_{2\ Bn}$ & 2xOH), 5.68 (s, 1H, H_{Ar}), 6.13 (d, J = 8.3 Hz, 1H, $NH_{\text{-}CH}$), 7.33 (dd, J = 7.3, 4.8 Hz, 1H, H_{Ar}), 7.49 (d, J = 8.0 Hz, 2H, 2xH_{Ar}), 7.86 (td, J = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.89 – 7.96 (m, 2H, H_{Ar} & NH_{Bn}), 8.05 (d, J = 8.0 Hz, 2H, 2xH_{Ar}), 8.64 (d, J = 4.7 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6 ($CH_{3\ iPr}$), 19.7 ($CH_{3\ iPr}$), 20.3 ($CH_{3\text{-}CH}$), 24.6 (CH_{iPr}), 45.0 ($CH_{2\ Bn}$), 56.9 ($CH_{\text{-}NH}$), 60.1 ($CH_{\text{-}OH}$), 64.6 ($CH_{\text{-}OH}$), 84.6 (CH_{Ar}), 120.1 (CH_{Ar}), 122.5 (CH_{Ar}), 126.6 (2xCH_{Ar}), 127.3 (2xCH_{Ar}), 137.2 (CH_{Ar}), 137.4 (C_q), 139.5 (C_q), 139.7 (C_q), 139.7 (C_q), 149.5 (CH_{Ar}), 152.7 (C_q), 155.8 (C_q), 156.3 (C_q). **MS (ESI+) : m/z calcd for $C_{24}H_{29}N_7O_2$:** 448.25 [M+H]+, **found :** 448.36.
(108)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.03 (d, J = 6.3 Hz, 3H, CH_3), 1.35 (dd, J = 6.9, 4.3 Hz, 6H, 2x$CH_{3\ iPr}$), 3.32 (m, 1H, H_{iPr}), 3.47 (ddt, J = 35.1, 10.5, 5.7 Hz, 2H, $CH_{2\text{-}OH}$), 3.68 – 3.78 (m, 1H, H_{Alk}), 3.97 (dq, J = 9.2, 6.1 Hz, 1H, H_{Alk}), 4.48 (d, J = 6.4 Hz, 2H, $CH_{2\ Bn}$), 4.51 – 4.57 (m, 2xOH), 5.67 (s, 1H, H_{Ar}), 6.13 (d, J = 8.3 Hz, 1H, NH), 7.52 (d, J = 8.0 Hz, 2H, 2xH_{Ar}), 7.65 – 7.73 (m, 2H, 2xH_{Ar}), 7.78 (d, J = 8.1 Hz, 2H, 2xH_{Ar}), 7.94 (t, J = 6.4 Hz, 1H, NH_{Bn}), 8.55 – 8.68 (m, 2H, 2xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6 ($CH_{3\ iPr}$), 19.7 ($CH_{3\ iPr}$), 20.3 (CH_3), 24.6 (CH_{iPr}), 44.9 ($CH_{2\ Bn}$), 56.9 (CH), 60.1 (CH_2), 64.5 (CH), 84.7 (CH_{Ar}), 121.1 (2xCH_{Ar}), 126.9 (2xCH_{Ar}), 127.8 (2xCH_{Ar}), 135.8 (C_q), 139.7 (C_q), 139.7 (C_q), 139.9 (C_q), 146.7 (C_q), 150.2 (2xCH_{Ar}), 152.7 (C_q), 156.3 (C_q). **MS (ESI+) : m/z calcd for $C_{24}H_{29}N_7O_2$:** 448.25 [M+H]+, **found :** 448.33.

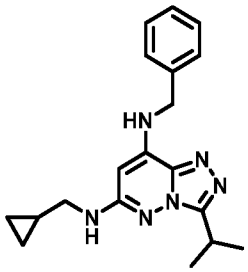
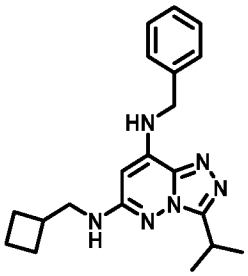
(109)		> 98 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.86 (dp, *J* = 13.4, 6.6 Hz, 4H, 2x$CH_{2\text{-}CH2}$), 3.24 – 3.32 (m, 10H, 2xOCH_3 & 2x$CH_{2\text{-}NH}$), 3.43 (td, *J* = 6.2, 2.9 Hz, 4H, 2x$CH_{2\text{-}OCH3}$), 5.58 (s, 1H, H_{Ar}), 6.77 (t, *J* = 5.5 Hz, 1H, NH_{Alk}), 7.37 (t, *J* = 5.7 Hz, 1H, NH_{Alk}), 7.44 – 7.49 (m, 1H, H_{Ar}), 7.53 (dd, *J* = 8.3, 6.6 Hz, 2H, 2xH_{Ar}), 8.49 (d, *J* = 7.1 Hz, 2H, 2xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 27.9 ($CH_{2\text{-}CH2}$), 28.6 ($CH_{2\text{-}CH2}$), 38.1 ($CH_{2\text{-}NH}$), 39.4 ($CH_{2\text{-}NH}$), 58.0 (OCH_3), 58.0 (OCH_3), 69.7 ($CH_{2\text{-}OCH3}$), 69.8 ($CH_{2\text{-}OCH3}$), 83.4 (CH_{Ar}), 126.5 (2xCH_{Ar}), 127.5 (C_q), 128.5 (2xCH_{Ar}), 129.1 (CH_{Ar}), 140.1 (C_q), 140.6 (C_q), 146.3 (C_q), 156.7 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{26}N_6O_2$:** 371.22 [M+H]+, **found :** 371.36.
(110)		> 97 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.99 – 1.14 (m, 4H, 2x$CH_{2\ cPr}$), 1.81 (dp, *J* = 20.1, 6.5 Hz, 4H, 2x$CH_{2\text{-}CH2}$), 2.22 – 2.31 (m, 1H, H_{cPr}), 3.18 – 3.26 (m, 10H, 2xOCH_3 & 2x$CH_{2\text{-}NH}$), 3.40 (td, *J* = 6.2, 4.2 Hz, 4H, 2x$CH_{2\text{-}OCH3}$), 5.46 (s, 1H, H_{Ar}), 6.54 (t, *J* = 5.4 Hz, 1H, NH), 7.17 (t, *J* = 5.7 Hz, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.6 (2x$CH_{2\ cPr}$), 28.0 ($CH_{2\text{-}CH2\text{-}NH}$), 28.7 ($CH_{2\text{-}CH2\text{-}NH}$), 38.0 ($CH_{2\text{-}NH}$), 39.3 ($CH_{2\text{-}NH}$), 57.9 ($OCH_3$), 58.0 ($OCH_3$), 69.7 ($CH_{2\text{-}OCH3}$), 69.8 ($CH_{2\text{-}OCH3}$), 83.2 ($CH_{Ar}$), 139.6 ($C_q$), 140.0 ($C_q$), 150.0 ($C_q$), 156.4 ($C_q$). **MS (ESI+) : m/z calcd for $C_{16}H_{26}N_6O_2$:** 335.43 [M+H]+, **found :** 335.35.
(111)		> 98 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.78 (p, *J* = 6.7 Hz, 2H, $CH_{2\text{-}CH2\text{-}O}$), 1.86 (p, *J* = 6.5 Hz, 2H, $CH_{2\text{-}CH2\text{-}O}$), 3.17 – 3.29 (m, 10H, , 2x$CH_{2\text{-}NH}$ & 2x$CH_{3\text{-}NH}$), 3.40 (dt, *J* = 6.3 Hz, 4H, 2x$CH_{2\text{-}O}$), 5.66 (s, 1H, H_{Ar}), 6.95 (t, *J* = 5.3 Hz, 1H, NH), 7.62 (t, *J* = 5.5 Hz, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** N.D. **MS (ESI+) : m/z calcd for $C_{14}H_{21}N_6O_2$:** 363.18 [M+H]+, **found :** 363.30.

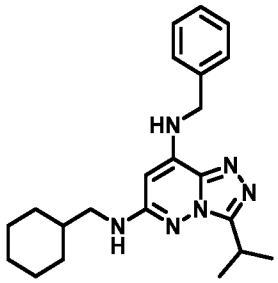
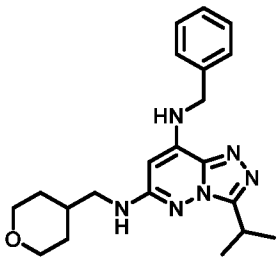
(112)		> 96 % [a]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.28 (s, 6H, 2xOCH_3), 3.31 – 3.39 (m, 5H, 2x$CH_{2\text{-}NH}$ & H_{iPr}), 3.52 (dt, J = 13.4, 5.7 Hz, 4H, 2x$CH_{2\text{-}OCH3}$), 5.60 (s, 1H, H_{Ar}), 6.62 (t, J = 5.5 Hz, 1H, NH), 7.08 (t, J = 5.8 Hz, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6 (2x$CH_{3\ iPr}$), 24.7 (CH_{iPr}), 40.4 ($CH_{2\text{-}NH}$), 41.6 ($CH_{2\text{-}NH}$), 57.9 (OCH_3), 58.1 (OCH_3), 69.6 ($CH_{2\text{-}OCH3}$), 70.2 ($CH_{2\text{-}OCH3}$), 83.5 (CH_{Ar}), 139.7 (C_q), 140.2 (C_q), 152.8 (C_q), 156.0 (C_q). **MS (ESI+) : m/z calcd for $C_{14}H_{24}N_6O_2$:** 309.20 [M+H]+, **found :** 309.25.
(113)		> 96 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.91 (td, J = 7.4, 4.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.36 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.40 – 1.62 (m, 2H, $CH_{2\text{-}CH3}$), 1.67 (dddd, J = 13.3, 9.6, 7.5, 5.7 Hz, 2H, $CH_{2\text{-}CH3}$), 3.34 (s, 1H, H_{iPr}), 3.39 – 3.58 (m, 5H, 2x$CH_{2\text{-}OH}$ & H_{Alk}), 3.62 – 3.74 (m, 1H, H_{Alk}), 4.62 (t, J = 5.4 Hz, 1H, OH), 4.83 (t, J = 5.5 Hz, 1H, OH), 5.64 (s, 1H, H_{Ar}), 6.27 (d, J = 7.8 Hz, 1H, NH), 6.57 (d, J = 8.6 Hz, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.6 ($CH_{3\text{-}CH2}$), 10.6 ($CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.3 ($CH_{2\text{-}CH3}$), 23.7 ($CH_{2\text{-}CH3}$), 24.8 (CH_{iPr}), 53.8 (CH_{Alk}), 55.7 (CH_{Alk}), 62.1 ($CH_{2\text{-}OH}$), 62.2 ($CH_{2\text{-}OH}$), 83.8 (CH_{Ar}), 139.8 (C_q), 140.0 (C_q), 152.7 (C_q), 156.1 (C_q). **MS (ESI+) : m/z calcd for $C_{16}H_{28}N_6O_2$:** 337.23 [M+H]+, **found :** 337.30.
(114)		> 95 % [a]	White crystalline solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.88 (td, J = 7.4, 4.8 Hz, 12H, 4x$CH_{3\ iPent}$), 1.36 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.43 – 1.63 (m, 8H, 4x$CH_{2\ iPent}$), 3.23 – 3.38 (m, 2H, H_{iPr} & H_{iPent}), 3.54 – 3.66 (m, 1H, H_{iPent}), 5.54 (s, 1H, H_{Ar}), 6.23 (d, J = 8.0 Hz, 1H, NH_{iPent}), 6.75 (d, J = 8.7 Hz, 1H, NH_{iPent}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\ iPent}$), 10.6 (2x$CH_{3\ iPent}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.1 (2x$CH_{2\ iPent}$), 26.2 (2x$CH_{2\ iPent}$), 52.9 (CH_{iPent}), 55.2

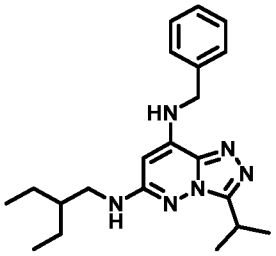
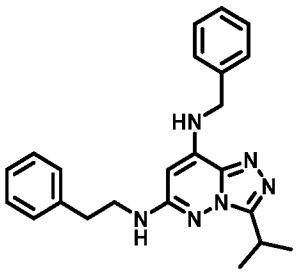
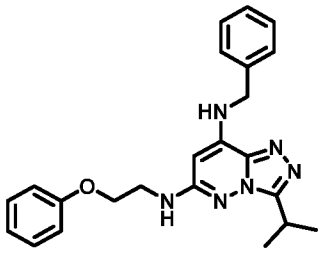
			(CH_{iPent}), 83.2 (CH_{Ar}), 139.7 (C_q), 140.1 (C_q), 152.7 (C_q), 156.2 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{32}N_6$:** 333.28 [M+H]+, **found :** 333.37.
(115)		91 % [a]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.89 (t, J = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.34 (dd, J = 7.0, 2.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.50 – 1.74 (m, 2H, $CH_{2\text{-}CH3}$), 2.02 (s, 3H, CH_3), 3.26 – 3.37 (m, 1H, H_{iPr}), 3.51 (dq, J = 18.5, 5.3 Hz, 2H, $CH_{2\text{-}OH}$), 3.78 (h, J = 6.2 Hz, 1H, H_{Alk}), 4.61 (t, J = 5.6 Hz, 1H, OH), 5.26 – 5.39 (m, 2H, $CH_{2\ Bn}$), 5.40 (d, J = 7.7 Hz, 1H, NH_{Alk}), 6.81 (t, J = 6.9 Hz, 1H, NH_{Bn}), 7.14 – 7.35 (m, 5H, 5xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.1 (CH_3), 10.8 ($CH_{3\text{-}CH2}$), 19.4 ($CH_{3\ iPr}$), 19.4 ($CH_{3\ iPr}$), 23.5 ($CH_{2\text{-}CH3}$), 24.7 (CH_{iPr}), 47.4 ($CH_{2\ Bn}$), 54.5 (CH_{Alk}), 62.1 ($CH_{2\text{-}OH}$), 94.1 (C_q), 126.4 (CH_{Ar}), 126.8 (2xCH_{Ar}), 128.2 (2xCH_{Ar}), 138.2 (C_q), 139.9 (C_q), 141.7 (C_q), 151.4 (C_q), 154.2 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{28}N_6O$:** 369.24 [M+H]+, **found :** 369.31.
(116)		94 % [a]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 2.68 (d, J = 4.8 Hz, 3H, $CH_{3\text{-}NH}$), 3.35 (d, J = 6.9 Hz, 1H, H_{iPr}), 4.41 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.29 (s, 1H, H_{Ar}), 6.52 (q, J = 4.8 Hz, 1H, $NH_{\text{-}CH3}$), 7.29 (d, J = 8.2 Hz, 2H, 2xH_{Ar}), 7.48 – 7.60 (m, 2H, 2xH_{Ar}), 7.93 (t, J = 6.3 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** N.D. **MS (ESI+) : m/z calcd for $C_{16}H_{19}BrN_6$:** 375.09 [M+H]+, **found :** 375.15.
(117)		> 95 % [b]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.36 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.62 – 1.71 (m, 2H, $CH_{2\ cBut}$), 1.76 – 1.88 (m, 2H, $CH_{2\ cBut}$), 2.18 – 2.29 (m, 2H, $CH_{2\ cBut}$), 3.32 – 3.36 (m, 1H, H_{iPr}), 4.04 – 4.13 (m, 1H, H_{cBut}), 4.43 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.31 (s, 1H, H_{Ar}), 6.79 (d, J = 6.7 Hz, 1H, NH), 7.24 (dt, J = 7.7, 4.0 Hz, 1H, H_{Ar}), 7.34 (d, J = 4.4 Hz, 4H, 4xH_{Ar}), 7.90 (t, J = 6.8 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : N.D.

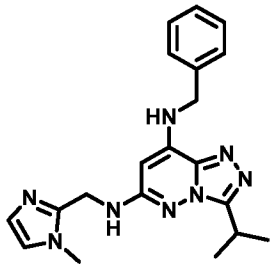
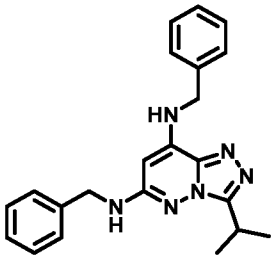
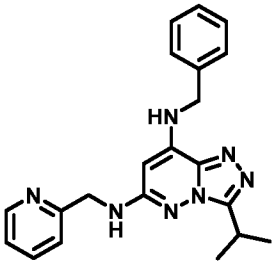
			MS (ESI+) : m/z calcd for $C_{19}H_{24}N_6$: 337.2 [M+H]+, **found :** 337.2. LogD (HPLC): 3.47
(118)		> 95 % [b]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.37 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.54 (m, 4H, CH_2), 1.61 (d, J = 7.1 Hz, 2H, CH_2), 1.89 (dt, J = 12.6, 6.0 Hz, 2H, CH_2), 3.32 – 3.37 (m, 1H, H_{iPr}), 3.93 (q, J = 6.5 Hz, 1H, H_{cPent}), 4.42 (d, J = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.52 (d, J = 6.1 Hz, 1H, NH), 7.24 (dt, J = 8.6, 4.4 Hz, 1H, H_{Ar}), 7.30 – 7.36 (m, 4H, 4xH_{Ar}), 7.85 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : 19.6 (2x$CH_{3\ iPr}$), 23.6 (2xCH_2), 24.8 (CH_{iPr}), 32.3 (2xCH_2), 45.2 ($CH_{2\ Bn}$), 52.3 (CH_{cPent}), 84.3 (CH_{Ar}), 126.7 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (CH_{Ar}), 138.4 (C_q), 139.6 (C_q), 139.7 (C_q), 152.8 (C_q), 155.5 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{26}N_6$:** 351.2 [M+H]+, **found :** 351.1. LogD (HPLC): 3.84
(119)		> 95 % [b]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.15 (q, J = 10.9, 10.2 Hz, 3H, CH_2 & $H_{(CH2)}$), 1.22 – 1.30 (m, 2H, CH_2), 1.36 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.56 (d, J = 12.3 Hz, 1H, $H_{(CH2)}$), 1.64 – 1.72 (m, 2H, CH_2), 1.92 (d, J = 12.1 Hz, 2H, CH_2), 3.26 – 3.35 (m, 1H, H_{iPr}), 3.51 (dt, J = 6.9, 3.5 Hz, 1H, H_{cHex}), 4.42 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.39 (s, 1H, H_{Ar}), 6.37 (d, J = 7.2 Hz, 1H, NH), 7.20 – 7.29 (m, 1H, H_{Ar}), 7.29 – 7.37 (m, 4H, 4xH_{Ar}), 7.85 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : 19.5 (2x$CH_{3\ iPr}$), 24.5 (2xCH_2), 24.8 (CH_{iPr}), 25.5 (CH_2), 32.1 (2xCH_2), 45.2 ($CH_{2\ Bn}$), 49.3 (CH_{cHex}), 84.3 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.4 (C_q), 139.6 (C_q), 139.8 (C_q), 152.7 (C_q), 155.0 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{28}N_6$:** 365.2 $[M+H]^+$, found : 365.1. LogD (HPLC): 4.17

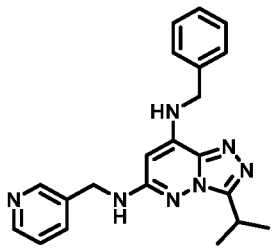
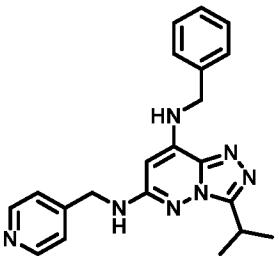
(120)		> 95 % [b]	Beige solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** : 1.12 – 1.22 (m, 4H, 2xCH_2), 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.93 – 2.04 (m, 4H, 2xCH_2), 3.10 (d, *J* = 4.0 Hz, 1H, $CH_{\text{-O}}$), 3.22 (s, 3H, $CH_{3\text{-O}}$), 3.27 – 3.35 (m, 1H, H_{iPr}), 3.48 (s, 1H, $CH_{\text{-NH}}$), 4.42 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.36 (s, 1H, H_{Ar}), 6.40 (d, *J* = 7.0 Hz, 1H, NH), 7.24 (td, *J* = 4.9, 2.7 Hz, 1H, H_{Ar}), 7.29 – 7.37 (m, 4H, 4xH_{Ar}), 7.88 (t, *J* = 6.3 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ** : 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 29.4 (2xCH_2), 29.8 (2xCH_2), 45.2 ($CH_{2\ Bn}$), 49.0 (CH_{cHex}), 55.0 (CH_2), 77.7 ($CH_{3\text{-O}}$), 84.2 (CH_{Ar}), 126.7 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.4 (C_q), 139.6 (C_q), 139.9 (C_q), 152.7 (C_q), 155.2 (C_q). **MS (ESI+) : m/z calcd for $C_{22}H_{30}N_6O$:** 395.3 [M+H]+, **found :** 395.1. LogD (HPLC): 3.09
(121)		> 95 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** : 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.67 (m, 10H, 5xCH_2), 1.81 – 1.94 (m, 2H, CH_2), 3.26 – 3.38 (m, 1H, H_{iPr}), 3.70 (d, *J* = 8.5 Hz, 1H, H_{cHept}), 4.42 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.39 (s, 1H, H_{Ar}), 6.42 (d, *J* = 7.1 Hz, 1H, NH), 7.24 (td, *J* = 5.3, 3.0 Hz, 1H, H_{Ar}), 7.29 – 7.37 (m, 4H, 2xH_{Ar}), 7.84 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ** : 19.5 (2x$CH_{3\ iPr}$), 24.1 (2xCH_2), 24.9 (CH_{iPr}), 28.0 (2xCH_2), 33.6 (2xCH_2), 45.2 ($CH_{2\ Bn}$), 51.3 (CH_{cHept}), 84.3 (CH_{Ar}), 126.7 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.4 (C_q), 139.6 (C_q), 139.8 (C_q), 152.7 (C_q), 154.8 (C_q). **MS (ESI+) : m/z calcd for $C_{22}H_{30}N_6$:** 379.3 [M+H]+, **found :** 379.2. LogD (HPLC): 4.57

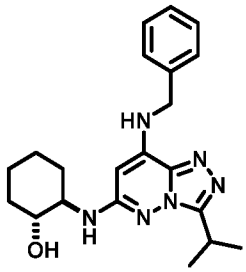
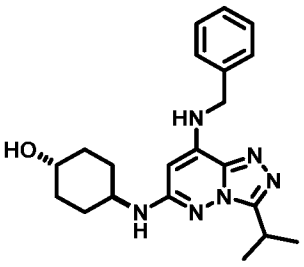
(122)		91% [b]	Beige solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** : 0.14 – 0.21 (m, 2H, CH_2), 0.37 – 0.45 (m, 2H, CH_2), 0.98 – 1.07 (m, 1H, H_{cPr}), 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.00 (dd, *J* = 6.9, 5.2 Hz, 2H, $CH_{2\text{-}NH}$), 3.33 (p, *J* = 7.0 Hz, 1H, H_{iPr}), 4.43 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.43 (s, 1H, H_{Ar}), 6.66 (t, *J* = 5.3 Hz, 1H, NH), 7.24 (dq, *J* = 6.0, 2.8 Hz, 1H, H_{Ar}), 7.30 – 7.41 (m, 4H, 4xH_{Ar}), 7.89 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ** : 3.5 (2x$CH_{2\ cPr}$), 10.5 (CH_{cPr}), 19.6 (2x$CH_{3\ iPr}$), 24.6 (CH_{iPr}), 45.2 ($CH_{2\ Bn}$), 45.4 (CH_2), 84.3 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.8 (C_q), 141.2 (C_q), 152.8 (C_q), 155.9 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{24}N_6$:** 337.2 [M+H]+, **found :** 337.2. LogD (HPLC): 3.33
(123)		87% [b]	Beige solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** : 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.67 (tt, *J* = 10.2, 7.8 Hz, 2H, CH_2), 1.78 – 1.86 (m, 2H, CH_2), 1.93 – 2.07 (m, 2H, CH_2), 2.51 - 2.55 (m, 1H, H_{cBut}), 3.16 (dd, *J* = 7.1, 5.3 Hz, 2H, CH_2), 3.32 – 3.38 (m, 1H, H_{iPr}), 4.43 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.39 (s, 1H, H_{Ar}), 6.48 (t, *J* = 5.5 Hz, 1H, NH), 7.24 (td, *J* = 5.2, 2.7 Hz, 1H, H_{Ar}), 7.30 – 7.36 (m, 4H, 4xH_{Ar}), 7.86 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ** : 17.9 (CH_{cBut}), 19.6 (2x$CH_{3\ iPr}$), 24.6 (CH_{iPr}), 25.6 (2xCH_2), 34.3 (CH_2), 45.2 ($CH_{2\ Bn}$), 46.2 (CH_2), 84.1 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.6 (C_q), 139.8 (C_q), 152.8 (C_q), 156.0 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{26}N_6$:** 351.2 [M+H]+, **found :** 351.1. LogD (HPLC): 3.86

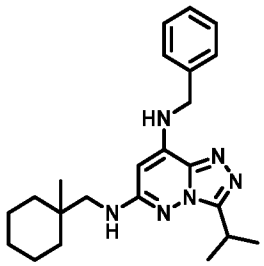
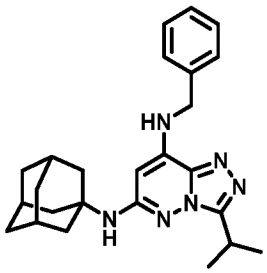
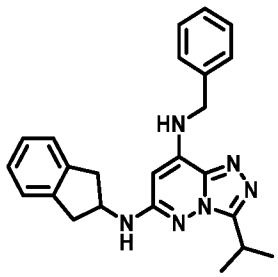
(124)		> 96 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 0.90 (q, *J* = 11.1, 10.0 Hz, 2H, CH_2), 1.15 (t, *J* = 11.1 Hz, 3H, $H_{(CH2)}$ & CH_2), 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.47 – 1.56 (m, 1H, H_{cHex}), 1.59 – 1.73 (m, 5H, 2xCH_2 &$H_{(CH2)}$), 2.97 (t, *J* = 6.1 Hz, 2H, CH_2), 3.27 – 3.36 (m, 1H, H_{iPr}), 4.43 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.41 (s, 1H, H_{Ar}), 6.52 (t, *J* = 5.5 Hz, 1H, NH), 7.21 – 7.28 (m, 1H, H_{Ar}), 7.29 – 7.39 (m, 4H, 4xH_{Ar}), 7.85 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : 19.5 (2x$CH_{3\ iPr}$), 24.7 (CH_{iPr}), 25.5 (2xCH_2), 26.0 (CH_{cHex}), 30.7 (2xCH_2), 36.9 (CH_2), 45.2 ($CH_{2\ Bn}$), 47.3 (CH_2), 84.1 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.7 (C_q), 139.8 (C_q), 139.8 (C_q), 156.1 (C_q). **MS (ESI$^+$) : m/z calcd for $C_{22}H_{30}N_6$:** 379.3 [M+H]+, **found :** 379.2. LogD (HPLC): 4.60
(125)		> 98 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.18 (qd, *J* = 12.1, 4.6 Hz, 2H, CH_2), 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.58 (d, *J* = 13.1 Hz, 2H, CH_2), 1.78 (dtq, *J* = 15.6, 7.5, 4.6, 3.8 Hz, 1H, H_{THP}), 3.03 (t, *J* = 6.1 Hz, 2H, CH_2), 3.23 (td, *J* = 11.7, 2.1 Hz, 2H, CH_2), 3.28 – 3.38 (m, 1H, H_{iPr}), 3.82 (dt, *J* = 9.5, 2.7 Hz, 2H, CH_2), 4.43 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.40 (s, 1H, H_{Ar}), 6.58 (t, *J* = 5.6 Hz, 1H, NH), 7.25 (dt, *J* = 5.6, 2.9 Hz, 1H, H_{Ar}), 7.29 – 7.38 (m, 4H, 4xH_{Ar}), 7.88 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : 19.6 (2x$CH_{3\ iPr}$) , 24.7 (CH_{iPr}), 30.7 (2xCH_2), 34.3 (CH_{THP}), 45.2 ($CH_{2\ Bn}$), 46.7 (CH_2), 66.8 (2xCH_2), 84.0 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.6 (C_q), 139.8 (C_q), 152.8 (C_q), 156.0 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{28}N_6O$:** 381.2 [M+H]+, **found :** 381.1. LogD (HPLC): 2.74

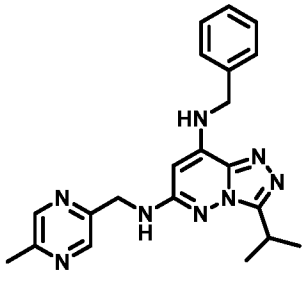
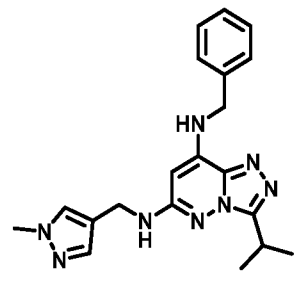
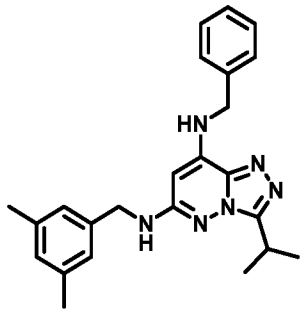
(126)		> 95 % [b]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 0.85 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.22 – 1.33 (m, 4H, 2x$CH_{2\text{-}CH3}$), 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.42 – 1.52 (m, 1H, H_{Alk}), 3.07 (t, *J* = 6.0 Hz, 2H, CH_2), 3.31 – 3.36 (m, 1H, H_{iPr}), 4.43 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.42 (s, 1H, H_{Ar}), 6.50 (t, *J* = 5.7 Hz, 1H, NH), 7.25 (dt, *J* = 5.8, 2.9 Hz, 1H, H_{Ar}), 7.29 – 7.37 (m, 4H, 4xH_{Ar}), 7.84 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : 10.9 (2x$CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.5 (2x$CH_{2\text{-}CH3}$), 24.7 (CH_{iPr}), 39.8 (CH_{Alk}), 43.3 (CH_2), 45.2 ($CH_{2\ Bn}$), 84.2 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.4 (C_q), 139.7 (C_q), 139.8 (C_q), 152.8 (C_q), 156.1 (C_q). **MS (ESI$^+$) : m/z calcd for $C_{21}H_{30}N_6$:** 367.3 [M+H]+, **found :** 367.1. LogD (HPLC): 4.42
(127)		94% [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.38 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 2.78 – 2.88 (m, 2H, CH_2), 3.36 (td, *J* = 8.5, 7.7, 5.1 Hz, 3H, H_{iPr} & CH_2), 4.44 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.38 (s, 1H, H_{Ar}), 6.68 (t, *J* = 5.5 Hz, 1H, NH), 7.16 – 7.36 (m, 10H, 10xH_{Ar}), 7.91 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : N.D. **MS (ESI+) : m/z calcd for $C_{23}H_{26}N_6$:** 387.2 [M+H]+, **found :** 387.1. LogD (HPLC): 3.78
(128)		88% [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.32 – 3.40 (m, 1H, H_{iPr}), 3.52 (q, *J* = 5.7 Hz, 2H, CH_2), 4.11 (t, *J* = 5.8 Hz, 2H, CH_2), 4.44 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.45 (s, 1H, H_{Ar}), 6.81 (t, *J* = 5.6 Hz, 1H, NH), 6.90 – 6.97 (m, 3H, 3xH_{Ar}), 7.21 – 7.38 (m, 7H, 7xH_{Ar}), 7.95 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : N.D. **MS (ESI+) : m/z calcd for $C_{23}H_{26}N_6O$:** 403.2 [M+H]+, **found :** 403.1. LogD (HPLC): 3.68

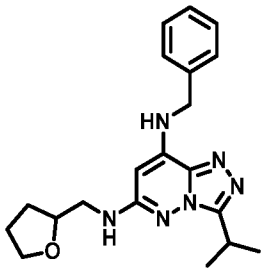
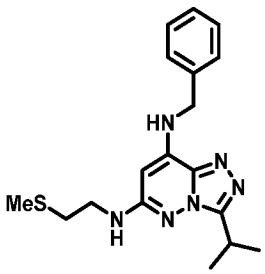
(129)		> 99 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.34 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.31 – 3.39 (m, 1H, H_{iPr}), 3.63 (s, 3H, $CH_{3\text{-}N}$), 4.35 (d, J = 5.3 Hz, 2H, CH_2), 4.42 (d, J = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.53 (s, 1H, H_{Ar}), 6.76 (d, J = 1.2 Hz, 1H, H_{Ar}), 7.00 (t, J = 5.4 Hz, 1H, NH), 7.04 (d, J = 1.2 Hz, 1H, H_{Ar}), 7.21 – 7.26 (m, 1H, H_{Ar}), 7.29 – 7.38 (m, 4H, 4xH_{Ar}), 7.96 (t, J = 6.3 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : 19.7 (2x$CH_{3\ iPr}$), 24.5 (CH_{iPr}), 32.3 ($CH_{3\text{-}N}$), 36.8 (CH_2), 45.2 ($CH_{2\ Bn}$), 84.0 (CH_{Ar}), 121.5 (CH_{Ar}), 126.3 (CH_{Ar}), 126.9 (CH_{Ar}), 126.9 (2xCH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.6 (C_q), 140.0 (C_q), 144.9 (C_q), 152.9 (C_q), 155.5 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{24}N_8$:** 377.2 [M+H]+, **found :** 377.1. LogD (HPLC): 1.95
(130)		> 96 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.30 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.25 – 3.33 (m, 1H, H_{iPr}), 4.32 (d, J = 5.7 Hz, 2H, $CH_{2\ Bn}$), 4.43 (d, J = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.46 (s, 1H, H_{Ar}), 7.09 (t, J = 5.8 Hz, 1H, NH_{Bn}), 7.18 – 7.36 (m, 10H, 10xH_{Ar}), 7.93 (t, J = 6.3 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : 19.6 (2x$CH_{3\ iPr}$), 24.6 (CH_{iPr}), 44.5 ($CH_{2\ Bn}$), 45.2 ($CH_{2\ Bn}$), 84.0 (CH_{Ar}), 126.6 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 127.7 (2xCH_{Ar}), 128.1 (2xCH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.6 (C_q), 139.8 (C_q), 140.0 (C_q), 152.9 (C_q), 155.6 (C_q). **MS (ESI+) : m/z calcd for $C_{22}H_{24}N_6$:** 373.2 [M+H]+, **found :** 373.1. LogD (HPLC): 3.50
(131)		> 97 % [b]	Brown solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.22 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.22 (q, J = 7.1 Hz, 1H, H_{iPr}), 4.38 – 4.50 (m, 4H, 2x$CH_{2\ Bn}$), 5.54 (s, 1H, H_{Ar}), 7.19 – 7.27 (m, 3H, 2xH_{Ar} & NH), 7.30 – 7.38 (m, 5H, 5xH_{Ar}), 7.69 (td, J = 7.6, 1.8 Hz, 1H, H_{Ar}), 7.95 (t, J = 6.4 Hz, 1H, NH_{Bn}), 8.47 (d, J = 4.5 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : 19.4

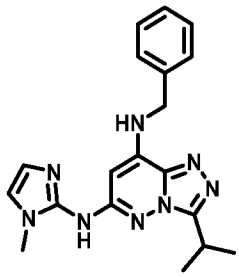
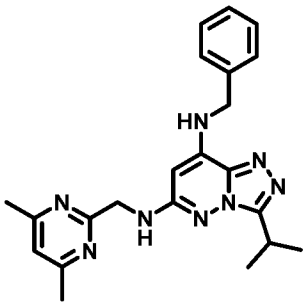
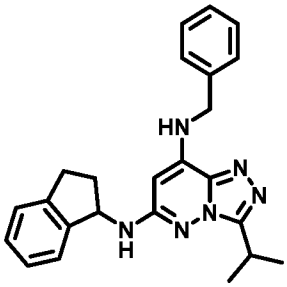
			($2xCH_{3\ iPr}$), 24.6 (CH_{iPr}), 45.2 ($CH_{2\ Bn}$), 46.4 (CH_2), 84.0 (CH_{Ar}), 121.2 (CH_{Ar}), 121.8 (CH_{Ar}), 126.9 ($2xCH_{Ar}$), 127.0 (CH_{Ar}), 128.4 ($2xCH_{Ar}$), 136.4 (CH_{Ar}), 138.3 (C_q), 139.6 (C_q), 140.1 (C_q), 148.7 (C_q), 152.8 (C_q), 155.6 (C_q), 159.0 (C_q). **MS (ESI+) : m/z calcd for C21H23N7 :** 374.2 [M+H]+, **found :** 374.1. LogD (HPLC): 2.51
(132)		> 97 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** : 1.28 (d, *J* = 6.9 Hz, 6H, $2xCH_{3\ iPr}$), 3.22 – 3.30 (m, 1H, H_{iPr}), 4.34 (d, *J* = 5.7 Hz, 2H, CH_2), 4.44 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.43 (s, 1H, H_{Ar}), 7.18 (t, *J* = 5.8 Hz, 1H, NH), 7.24 (dq, *J* = 5.7, 2.8 Hz, 1H, H_{Ar}), 7.27 – 7.37 (m, 5H, $5xH_{Ar}$), 7.70 (dt, *J* = 7.8, 2.0 Hz, 1H, H_{Ar}), 7.98 (t, *J* = 6.4 Hz, 1H, NH_{Bn}), 8.41 (dd, *J* = 4.8, 1.7 Hz, 1H, H_{Ar}), 8.54 (d, *J* = 2.3 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ** : 19.5 ($2xCH_{3\ iPr}$), 24.6 (CH_{iPr}), 42.2 (CH_2), 45.2 ($CH_{2\ Bn}$), 83.8 (CH_{Ar}), 123.3 (CH_{Ar}), 126.8 ($2xCH_{Ar}$), 126.9 (CH_{Ar}), 128.4 ($2xCH_{Ar}$), 135.2 (C_q), 135.3 (CH_{Ar}), 138.2 (C_q), 139.6 (C_q), 140.1 (C_q), 147.9 (CH_{Ar}), 149.1 (CH_{Ar}), 152.9 (C_q), 155.5 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{23}N_7$:** 374.2 [M+H]+, **found :** 374.1. LogD (HPLC): 2.36
(133)		> 99 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** : 1.21 (d, *J* = 7.0 Hz, 6H, $2xCH_{3\ iPr}$), 3.20 (p, *J* = 7.0 Hz, 1H, H_{iPr}), 4.35 (d, *J* = 5.8 Hz, 2H, CH_2), 4.46 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.47 (s, 1H, H_{Ar}), 7.21 – 7.29 (m, 4H, NH & $3xH_{Ar}$), 7.29 – 7.38 (m, 4H, $4xH_{Ar}$), 7.99 (t, *J* = 6.4 Hz, 1H, NH_{Bn}), 8.42 – 8.47 (m, 2H, $2xH_{Ar}$). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ** : N.D. **MS (ESI+) : m/z calcd for $C_{21}H_{23}N_7$:** 374.2 [M+H]+, found : 374.1. LogD (HPLC): 2.36

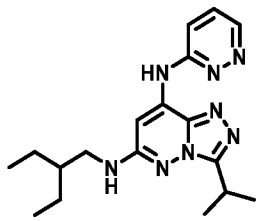
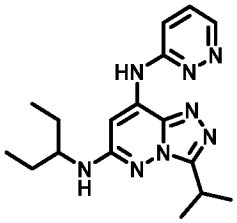
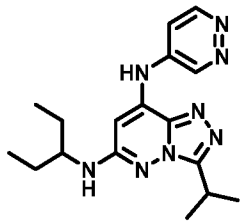
(134)		> 98 % [b]	Brown solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** : 1.03 (q, *J* = 10.2 Hz, 1H, $H_{(CH2)}$), 1.20 (dq, *J* = 19.6, 10.7, 9.2 Hz, 3H, 3x$H_{(CH2)}$), 1.36 (dd, *J* = 7.0, 5.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.52 – 1.67 (m, 2H, 2x$H_{(CH2)}$), 1.86 (d, *J* = 10.9 Hz, 1H, $H_{(CH2)}$), 2.10 (d, *J* = 12.7 Hz, 1H, $H_{(CH2)}$), 3.25 - 3.44 (s, 3H, H_{iPr} & $H_{C\text{-}O}$ & $H_{C\text{-}NH}$), 4.43 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 4.53 (d, *J* = 4.8 Hz, 1H, OH), 5.46 (s, 1H, H_{Ar}), 6.34 (d, *J* = 6.2 Hz, 1H, NH), 7.24 (ddt, *J* = 8.6, 5.7, 2.3 Hz, 1H, H_{Ar}), 7.29 – 7.41 (m, 4H, 4xH_{Ar}), 7.86 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ** : 19.5 ($CH_{3\ iPr}$), 19.6 ($CH_{3\ iPr}$), 23.7 (CH_2), 23.9 (CH_2), 24.8 (CH_{iPr}), 30.1 (CH_2), 34.0 (CH_2), 45.2 ($CH_{2\ Bn}$), 56.2 ($CH_{\text{-}NH}$), 71.0 ($CH_{\text{-}OH}$), 84.5 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.4 (C_q), 139.6 (C_q), 139.8 (C_q), 152.7 (C_q), 155.9 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{28}N_6O$:** 381.2 [M+H]+, **found :** 381.2. LogD (HPLC): 2.73
(135)		> 98 % [b]	Light brown solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ** : 1.06 – 1.30 (m, 4H, 2xCH_2), 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.73 – 2.03 (m, 4H, 2xCH_2), 3.26 – 3.36 (m, 1H, H_{iPr}), 3.41 (ddt, *J* = 18.5, 9.3, 4.3 Hz, 2H, $H_{C\text{-}O}$ & $H_{C\text{-}NH}$), 4.42 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 4.48 (d, *J* = 4.5 Hz, 1H, OH), 5.36 (s, 1H, H_{Ar}), 6.36 (d, *J* = 7.1 Hz, 1H, NH), 7.23 (tt, *J* = 4.9, 3.1 Hz, 1H, H_{Ar}), 7.29 – 7.39 (m, 4H, 4xH_{Ar}), 7.87 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ** : 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 29.9 (2xCH_2), 34.0 (2xCH_2), 45.2 ($CH_{2\ Bn}$), 49.2 ($CH_{\text{-}NH}$), 68.3 ($CH_{\text{-}OH}$), 84.2 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.4 (C_q), 139.6 (C_q), 139.8 (C_q), 152.7 (C_q), 155.2 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{28}N_6O$:** 381.2 [M+H]+, **found :** 381.2. LogD (HPLC): 2.22

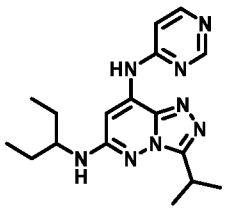
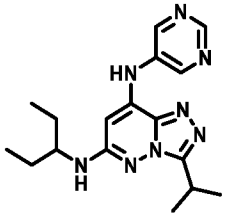
(136)		> 95 % [b]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 0.86 (s, 3H, $CH_{3\text{-}C}$), 1.16 – 1.34 (m, 6H, 3xCH_2), 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.38 – 1.51 (m, 4H, 2xCH_2), 3.08 (d, *J* = 6.0 Hz, 2H, $CH_{2\text{-}C}$), 3.25 – 3.37 (m, 1H, H_{iPr}), 4.43 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.55 (s, 1H, H_{Ar}), 6.35 (t, *J* = 6.0 Hz, 1H, NH), 7.24 (ddd, *J* = 8.5, 5.5, 2.4 Hz, 1H, H_{Ar}), 7.29 – 7.40 (m, 4H, 4xH_{Ar}), 7.82 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : N.D. **MS (ESI+) : m/z calcd for $C_{23}H_{32}N_6$:** 393.3 [M+H]+, **found :** 393.3. LogD (HPLC): 4.88
(137)		> 96 % [b]	Brown solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.39 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.64 (s, 6H, 3x$CH_{2\ ada}$), 2.05 (s, 9H, 3x$CH_{2\ ada}$ & 3xH_{ada}), 3.32 – 3.35 (m, 1H, H_{iPr}), 4.40 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.44 (s, 1H, H_{Ar}), 6.09 (s, 1H, NH), 7.20 – 7.27 (m, 1H, H_{Ar}), 7.30 – 7.36 (m, 4H, 4xH_{Ar}), 7.79 (t, *J* = 6.6 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : N.D. **MS (ESI+) : m/z calcd for $C_{25}H_{32}N_6$:** 417.3 [M+H]+, **found :** 417.3. LogD (HPLC): 5.02
(138)		> 97 % [b]	Light brown solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.39 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 2.81 (dd, *J* = 16.0, 5.6 Hz, 2H, CH_2), 3.25 (dd, *J* = 16.1, 7.3 Hz, 2H, CH_2), 3.36 (p, *J* = 7.0 Hz, 1H, H_{iPr}), 4.42 (t, *J* = 6.0 Hz, 3H, H_{indane} & $CH_{2\ Bn}$), 5.38 (s, 1H, H_{Ar}), 6.86 (d, *J* = 6.1 Hz, 1H, NH), 7.13 (dd, *J* = 5.5, 3.2 Hz, 2H, 2xH_{Ar}), 7.17 – 7.27 (m, 3H, 3xH_{Ar}), 7.27 – 7.35 (m, 4H, 4xH_{Ar}), 7.92 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : N.D. **MS (ESI+) : m/z calcd for $C_{24}H_{26}N_6$:** 399.2 [M+H]+, **found :** 399.2. LogD (HPLC): 4.08

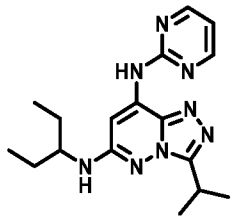
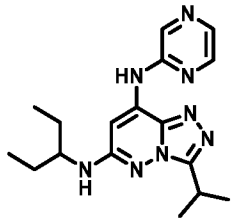
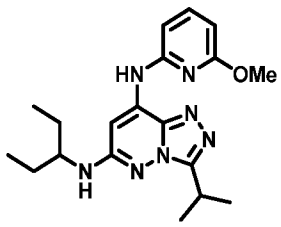
(139)		> 98 % [b]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.23 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 2.43 (s, 3H, CH_3), 3.22 (p, J = 7.0 Hz, 1H, H_{iPr}), 4.42 (d, J = 5.8 Hz, 2H, $CH_{2\ Bn}$), 4.45 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.49 (s, 1H, H_{Ar}), 7.11 – 7.48 (m, 6H, 5xH_{Ar} & NH), 7.99 (t, J = 6.4 Hz, 1H, NH_{Bn}), 8.43 (d, J = 1.4 Hz, 1H, H_{Ar}), 8.47 (d, J = 1.4 Hz, 1H, H_{Ar}). **^{13}C NMR (100 MHz, DMSO-d_6) δ** : 19.4 (2x$CH_{3\ iPr}$), 20.6 (CH_3), 24.6 (CH_{iPr}), 44.1 ($CH_{2\ Bn}$), 45.2 ($CH_{2\ Bn}$), 83.8 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.2 (C_q), 139.6 (C_q), 140.1 (C_q), 142.4 (CH_{Ar}), 143.2 (CH_{Ar}), 151.3 (C_q), 151.4 (C_q), 152.8 (C_q), 155.4 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{24}N_8$:** 389.2 [M+H]+, **found :** 389.2. LogD (HPLC): 2.30
(140)		> 99 % [b]	Pale yellow solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.37 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.37 (p, J = 6.9 Hz, 1H, H_{iPr}), 3.76 (s, 3H, $CH_{3\text{-}N}$), 4.14 (d, J = 5.3 Hz, 2H, CH_2), 4.41 (d, J = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.42 (s, 1H, H_{Ar}), 6.75 (t, J = 5.3 Hz, 1H, NH), 7.23 (ddd, J = 8.6, 5.5, 2.5 Hz, 1H, H_{Ar}), 7.28 – 7.36 (m, 5H, 5xH_{Ar}), 7.57 (s, 1H, H_{Ar}), 7.91 (t, J = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : 19.7 (2x$CH_{3\ iPr}$), 24.6 (CH_{iPr}), 35.1 (CH_2), 38.3 ($CH_{3\text{-}N}$), 45.2 ($CH_{2\ Bn}$), 84.1 (CH_{Ar}), 118.7 (C_q), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 129.6 (CH_{Ar}), 138.2 (CH_{Ar}), 138.3 (C_q), 139.7 (C_q), 139.9 (C_q), 152.9 (C_q), 155.6 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{24}N_8$:** 377.2 [M+H]+, **found :** 377.2. LogD (HPLC): 2.30
(141)		> 97 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.33 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 2.21 (s, 6H, 2xCH_3), 3.32 – 3.36 (m, 1H, H_{iPr}), 4.23 (d, J = 5.7 Hz, 2H, CH_2), 4.42 (d, J = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.44 (s, 1H, H_{Ar}), 6.84 (s, 1H, H_{Ar}), 6.93 (s, 2H, 2xH_{Ar}), 7.02 (t, J = 5.7 Hz, 1H, NH), 7.20 – 7.27 (m, 1H, H_{Ar}), 7.29 – 7.37 (m, 4H, 4xH_{Ar}), 7.91 (t, J = 6.3

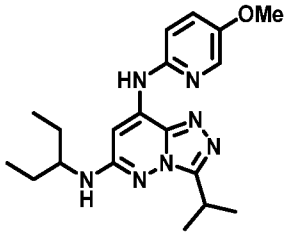
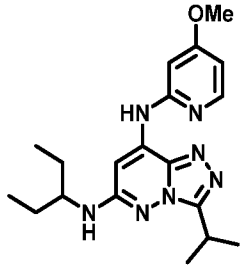
			Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : N.D. **MS (ESI+) : m/z calcd for $C_{24}H_{28}N_6$:** 401.2 [M+H]+, **found :** 401.2. LogD (HPLC): 4.20
(142)		> 97% [b]	Colorless oil. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.35 (dd, *J* = 7.0, 1.2 Hz, 6H, $2xCH_{3\ iPr}$), 1.54 (dt, *J* = 11.2, 7.3 Hz, 1H, $H_{(CH2)}$), 1.84 (dq, *J* = 32.3, 7.3, 6.5 Hz, 3H, CH_2 & $H_{(CH2)}$), 3.15 – 3.23 (m, 2H, CH_2), 3.28 – 3.37 (m, 1H, H_{iPr}), 3.60 (q, *J* = 7.4 Hz, 1H, $H_{(CH2)}$), 3.71 – 3.80 (m, 1H, $H_{(CH2)}$), 3.97 (p, *J* = 6.5 Hz, 1H, H_{C-O}), 4.42 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.48 (s, 1H, H_{Ar}), 6.61 (t, *J* = 5.6 Hz, 1H, NH), 7.24 (t, *J* = 6.5 Hz, 1H, H_{Ar}), 7.29 – 7.38 (m, 4H, $4xH_{Ar}$), 7.90 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : 19.6 ($2xCH_{3\ iPr}$), 24.6 (CH_{iPr}), 25.1 (CH_2), 28.8 (CH_2), 44.9 (CH_2), 45.2 (CH_{Bn}), 67.0 (CH_2), 76.7 (CH_{-O}), 84.1 (CH_{Ar}), 126.9 ($3xCH_{Ar}$), 128.4 (CH_{Ar}), 138.3 (C_q), 139.7 (C_q), 139.8 (C_q), 152.8 (C_q), 156.0 (C_q). **MS (ESI+): m/z calcd for $C_{20}H_{26}N_6O$:** 367.2 [M+H]+, **found :** 367.2. LogD (HPLC): 2.87
(143)		> 96% [b]	Colorless oil. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.36 (d, *J* = 6.9 Hz, 6H, $2xCH_{3\ iPr}$), 2.08 (s, 3H, CH_{3-S}), 2.64 (dd, *J* = 7.9, 6.3 Hz, 2H, CH_2), 3.28 – 3.38 (m, 3H, CH_2 & H_{iPr}), 4.44 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.38 (s, 1H, H_{Ar}), 6.73 (t, *J* = 5.7 Hz, 1H, NH), 7.24 (td, *J* = 5.9, 2.7 Hz, 1H, H_{Ar}), 7.28 – 7.37 (m, 4H, $4xH_{Ar}$), 7.94 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : 14.6 (CH_{3-S}), 19.6 ($2xCH_{3\ iPr}$), 24.7 (CH_{iPr}), 32.1 (CH_2), 40.3 (CH_2), 45.2 ($CH_{2\ Bn}$), 84.0 (CH_{Ar}), 126.8 ($2xCH_{Ar}$), 126.9 (CH_{Ar}), 128.4 ($2xCH_{Ar}$), 138.3 (C_q), 139.6 (C_q), 140.0 (C_q), 152.8 (C_q), 155.6 (C_q). **MS (ESI+): m/z calcd for $C_{18}H_{26}N_6S$:** 357.2 [M+H]+, **found :** 357.2. LogD (HPLC): 3.07

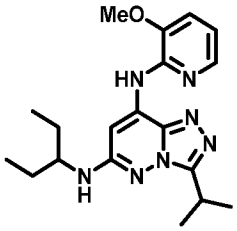
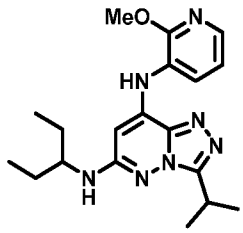
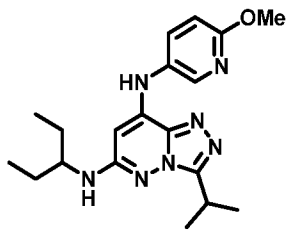
(144)		> 95% [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.40 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 2.86 (d, *J* = 4.9 Hz, 3H, $CH_{3\text{-}N}$), 3.55 (p, *J* = 7.0 Hz, 1H, H_{iPr}), 4.67 (s, 2H, $CH_{2\ Bn}$), 6.21 (s, 1H, H_{Ar}), 6.55 (q, *J* = 5.2, 4.8 Hz, 1H, NH), 6.63 (d, *J* = 1.8 Hz, 1H, H_{Ar}), 7.20 (s, 1H, H_{Ar}), 7.24 (t, *J* = 7.2 Hz, 1H, H_{Ar}), 7.33 (t, *J* = 7.5 Hz, 2H, 2xH_{Ar}), 7.42 (d, *J* = 7.5 Hz, 2H, 2xH_{Ar}), 8.96 (s, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : N.D. **MS (ESI+): m/z calcd for $C_{19}H_{22}N_8$:** 363.2 [M+H]+, **found :** 363.2. LogD (HPLC): 2.27
(145)		> 95% [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.23 (d, *J* = 7.0 Hz, 6H), 2.36 (s, 6H), 3.21 (h, *J* = 7.0 Hz, 1H), 4.44 (m, 4H), 5.62 (s, 1H), 7.08 (m, 2H), 7.25 (m, 1H), 7.31 – 7.40 (m, 4H), 7.92 (t, *J* = 6.4 Hz, 1H). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : N.D. **MS (ESI+): m/z calcd for $C_{22}H_{26}N_8$:** 403.2 [M+H]+, **found :** 403.2. LogD (HPLC): 2.52
(146)		> 99% [b]	Colorless oil. **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.83 (dq, *J* = 12.6, 8.1 Hz, 1H, $H_{(CH2)}$), 2.42 – 2.49 (m, 1H, $H_{(CH2)}$), 2.81 (dt, *J* = 15.9, 8.0 Hz, 1H, $H_{(CH2)}$), 2.94 (ddd, *J* = 15.8, 8.7, 4.0 Hz, 1H, $H_{(CH2)}$), 3.36 (q, *J* = 6.9 Hz, 1H, H_{iPr}), 4.43 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.27 (q, *J* = 7.4 Hz, 1H, H_{indane}), 5.47 (s, 1H, H_{Ar}), 6.93 (d, *J* = 7.6 Hz, 1H, NH), 7.12 (t, *J* = 7.1 Hz, 1H, H_{Ar}), 7.16 – 7.21 (m, 1H, H_{Ar}), 7.21 – 7.26 (m, 2H, 2xH_{Ar}), 7.33 (h, *J* = 6.6 Hz, 5H, 5xH_{Ar}), 7.95 (t, *J* = 6.4 Hz, 1H, NH_{Bn}). **^{13}C NMR (101 MHz, DMSO-d_6) δ** : N.D. **MS (ESI+): m/z calcd for $C_{24}H_{26}N_6$:** 399.2 [M+H]+, **found :** 399.2. LogD (HPLC): 4.10

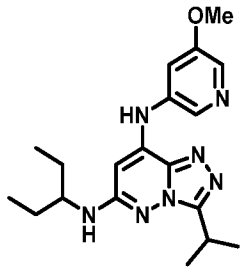
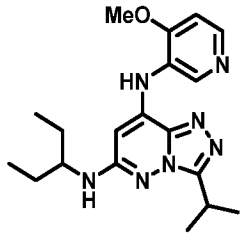
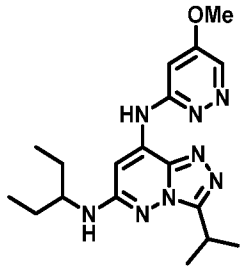
(147)		-	Beige solid. **Rf** (DCM/MeOH, 94/6) : 0.31 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.29 – 1.39 (m, 4H, 2x$CH_{2\text{-}CH3}$), 1.41 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.59 (hept, *J* = 6.1 Hz, 1H, $H_{c\text{-}CH2\text{-}NH}$), 3.18 (t, *J* = 6.0 Hz, 2H, $CH_{2\text{-}NH}$), 3.40 (h, *J* = 7.0 Hz, 1H, H_{iPr}), 7.29 (t, *J* = 5.6 Hz, 1H, $NH_{\text{-}CH2}$), 7.62 (dd, *J* = 9.0, 4.5 Hz, 1H, H_{Ar}), 7.80 (dd, *J* = 9.0, 1.5 Hz, 1H, H_{Ar}), 7.97 (s, 1H, H_{Ar}), 8.89 (dd, *J* = 4.5, 1.4 Hz, 1H, H_{Ar}), 10.15 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.9 (2x$CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.6 (2x$CH_{2\text{-}CH3}$), 24.8 (CH_{iPr}), 39.60 ($CH_{\text{-}CH2\text{-}NH}$), 43.6 ($CH_{2\text{-}NH}$), 95.9 ($CH_{Ar}$), 118.7 ($CH_{Ar}$), 128.1 ($CH_{Ar}$), 132.9 ($C_q$), 139.3 ($C_q$), 146.8 ($CH_{Ar}$), 153.3 ($C_q$), 156.1 ($C_q$), 157.6 ($C_q$).
(148)		> 97 % [b]	White solide. **Rf** (DCM/MeOH, 95/5) : 0.52 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, *J* = 7.3 Hz, 6H), 1.40 (d, *J* = 7.0 Hz, 6H), 1.44 – 1.66 (m, 4H), 3.39 (h, *J* = 7.1 Hz, 1H), 3.67 (h, *J* = 6.7 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 7.62 (dd, *J* = 9.0, 4.5 Hz, 1H), 7.79 (dd, *J* = 9.0, 1.4 Hz, 1H), 7.97 (s, 1H), 8.89 (dd, *J* = 4.5, 1.3 Hz, 1H), 10.14 (s, 1H). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.44 (2x$CH_{3\ iPent}$), 19.48 (2x$CH_{3\ iPr}$), 24.86 (CH_{iPr}), 26.02 (2x$CH_{2\ iPent}$), 53.26 (CH_{iPent}), 96.06 (CH_{Ar}), 118.65 (CH_{Ar}), 128.07 (CH_{Ar}), 132.89 (C_q), 139.30 (C_q), 146.77 (CH_{Ar}), 153.15 (C_q), 155.89 (C_q), 157.61 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{24}N_8$:** 341.22 [M+H]+, **found :** 341.40.
(149)		> 97 % [b]	Pale pink solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, *J* = 7.3 Hz, 6H, 2x$CH_{3\ iPent}$), 1.39 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.55 (ddt, *J* = 45.4, 13.9, 6.9 Hz, 4H, 2x$CH_{2\ iPent}$), 3.36 – 3.42 (m, 1H, H_{iPr}), 3.59 – 3.70 (m, 1H, H_{iPent}), 6.69 (s, 1H, H_{Ar}), 6.72 (d, *J* = 7.6 Hz, 1H, NH_{iPent}), 7.55 (dd, *J* = 6.1, 3.0 Hz, 1H, H_{Ar}), 9.01 (d, *J* = 6.0 Hz, 1H, H_{Ar}), 9.34 (d, *J* = 2.8 Hz, 1H, H_{Ar}), 10.07 (s, 1H, NH).

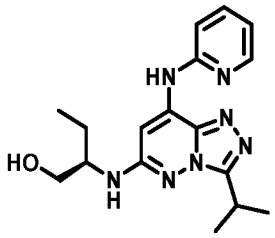
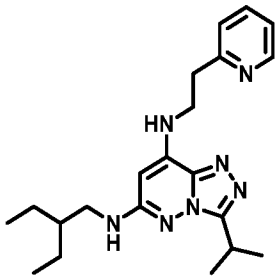
			^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 10.3 ($2xCH_{3\text{-}CH2}$), 19.4 ($2xCH_{3\ iPr}$), 24.9 (CH_{iPr}), 26.0 ($2xCH_{2\text{-}CH3}$), 53.2 (CH_{iPent}), 93.7 (CH_{Ar}), 112.8 (CH_{Ar}), 134.0 (C_q), 139.3 (C_q), 139.8 (C_q), 144.3 (CH_{Ar}), 150.8 (CH_{Ar}), 153.3 (C_q), 155.2 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{24}N_8$:** 341.22 [M+H]+, **found :** 341.36.
(150)		> 95 % [b]	Yellow solid. **Rf** (DCM/MeOH, 95/5) : 0.42 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.90 (t, *J* = 7.4 Hz, 6H, $2xCH_{3\ iPent}$), 1.40 (d, *J* = 7.0 Hz, 6H, $2xCH_{3\ iPr}$), 1.44 – 1.67 (m, 4H, $2xCH_{2\ iPent}$), 3.33 – 3.42 (m, 1H, H_{iPr}), 3.63 – 3.71 (m, 1H, H_{iPent}), 7.00 (d, *J* = 8.0 Hz, 1H, NH), 7.49 (d, *J* = 5.9, 1.3 Hz, 1H, H_{Ar}), 7.89 (s, 1H, H_{Ar}), 8.50 (d, *J* = 5.8 Hz, 1H, H_{Ar}), 8.86 (s, 1H, H_{Ar}), 10.41 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.45 ($2xCH_{3\ iPent}$), 19.46 ($2xCH_{3\ iPr}$), 24.83 (CH_{iPr}), 26.02 ($2xCH_{2\ iPent}$), 53.32 (CH_{iPent}), 97.64 (CH_{Ar}), 110.11 (CH_{Ar}), 132.53 (C_q), 139.13 (C_q), 153.18 (C_q), 155.51 (C_q), 156.15 (CH_{Ar}), 157.53 (CH_{Ar}), 160.17 (C_q).
(151)		> 97 % [b]	White solid. **Rf** (DCM/MeOH, 95/5) : 0.32 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.88 (t, *J* = 7.4 Hz, 6H, $2xCH_{3\ iPent}$), 1.39 (d, *J* = 7.0 Hz, 6H, $2xCH_{3\ iPr}$), 1.42 – 1.49 (m, 2H, $CH_{2\ iPent}$), 1.51 – 1.63 (m, 2H, $CH_{2\ iPent}$), 3.33 – 3.41 (m, 1H, H_{iPr}), 3.62 (h, *J* = 6.7 Hz, 1H, H_{iPent}), 6.35 (s, 1H, H_{Ar}), 6.56 (d, *J* = 7.8 Hz, 1H, NH_{iPent}), 8.90 (s, 2H, $2xH_{Ar}$), 8.94 (s, 1H, H_{Ar}), 9.62 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.26 ($2xCH_{3\ iPent}$), 19.46 ($2xCH_{3\ iPr}$), 24.86 (CH_{iPr}), 26.01 ($2xCH_{2\ iPent}$), 53.04 (CH_{iPent}), 88.78 (CH_{Ar}), 135.45 (C_q), 135.93 (C_q), 139.36 (C_q), 149.74 ($2xCH_{Ar}$), 152.89 (CH_{Ar}), 153.13 (C_q), 155.60 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{24}N_8$:** 341.22 [M+H]+, **found :** 341.36.

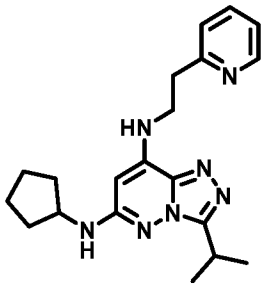
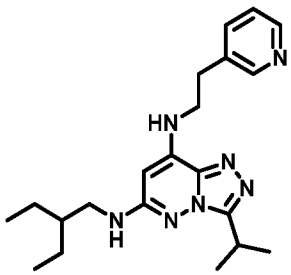
(152)		> 98 % [b]	Beige solid. **Rf** (DCM/MeOH, 95/5) : 0.35 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, J = 7.4 Hz, 6H, 2x$CH_{3\ iPent}$), 1.39 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.45 – 1.66 (m, 4H, 2x$CH_{2\ iPent}$), 3.32 – 3.42 (m, 1H, H_{iPr}), 3.60 – 3.73 (m, 1H, H_{iPent}), 7.00 (d, J = 8.0 Hz, 1H, NH_{iPent}), 7.16 (t, J = 4.8 Hz, 1H, H_{Ar}), 7.65 (s, 1H, H_{Ar}), 8.70 (d, J = 4.9 Hz, 2H, 2xH_{Ar}), 8.92 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.44 (2x$CH_{3\ iPent}$), 19.45 (2x$CH_{3\ iPr}$), 24.84 (CH_{iPr}), 26.02 (2x$CH_{2\ iPent}$), 53.30 (CH_{iPent}), 96.05 (CH_{Ar}), 115.25 (CH_{Ar}), 132.40 (C_q), 139.05 (C_q), 153.26 (C_q), 155.58 (C_q), 158.47 (2xCH_{Ar}), 158.91 (C_q). **MS (ESI+) : m/z calcd for $C_{12}H_{24}N_8$:** 341.22 [M+H]+, **found :** 341.40.
(153)		> 98 % [b]	White solid. **Rf** (DCM/MeOH, 95/5) : 0.27 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.89 (t, J = 7.3 Hz, 6H, 2x$CH_{3\ iPent}$), 1.40 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.45 – 1.67 (m, 4H, 2x$CH_{2\ iPent}$), 3.33 – 3.43 (m, 1H, H_{iPr}), 3.66 (q, J = 6.3 Hz, 1H, H_{iPent}), 6.91 (d, J = 8.0 Hz, 1H, NH_{iPent}), 7.75 (s, 1H), 8.19 (d, J = 2.8 Hz, 1H, H_{Ar}), 8.32 (t, J = 2.1 Hz, 1H, H_{Ar}), 8.84 (d, J = 1.5 Hz, 1H, H_{Ar}), 10.37 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.45 (2x$CH_{3\ iPent}$), 19.47 (2x$CH_{3\ iPr}$), 24.84 (CH_{iPr}), 26.06 (2x$CH_{2\ iPent}$), 53.27 (CH_{iPent}), 95.07 (CH_{Ar}), 133.08 (C_q), 136.31 (CH_{Ar}), 137.25 (CH_{Ar}), 139.24 (C_q), 140.77 (CH_{Ar}), 151.55 (C_q), 153.14 (C_q), 155.69 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{24}N_8$:** 341.22 [M+H]+, **found :** 341.36.
(154)		> 96 % [b]	White solid. **Rf** (DCM/MeOH, 96/4) : 0.28 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.89 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.39 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.45 – 1.66 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.36 – 3.41 (m, 1H, H_{iPr}), 3.66 (q, J = 6.3 Hz, 1H, H_{iPent}), 3.94 (s, 3H, $CH_{3\text{-}O}$), 6.37 – 6.48 (m, 1H, H_{Ar}), 6.64 (d, J = 8.1 Hz, 1H, NH_{iPent}), 6.92 – 7.09 (m, 1H, H_{Ar}), 7.45 (s, 1H, H_{Ar}), 7.63 (t, J = 7.9 Hz, 1H, H_{Ar}), 9.79 (s, 1H, NH).

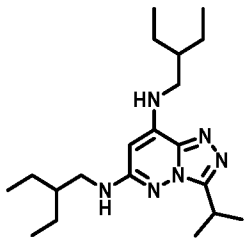
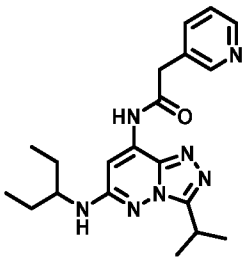
			^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 10.6 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.9 (CH_{iPr}), 26.2 (2x$CH_{2\text{-}CH3}$), 53.5 (CH_{iPent}), 54.0 ($CH_{3\text{-}O}$), 93.6 (CH_{Ar}), 101.8 (CH_{Ar}), 105.3 (CH_{Ar}), 133.7 (C_q), 139.5 (C_q), 140.5 (CH_{Ar}), 152.9 (C_q), 153.1 (C_q), 155.9 (C_q), 162.6 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{27}N_7O$:** 370.24 [M+H]+, **found :** 370.33.
(155)		> 96 % [b]	White solid. **Rf** (DCM/MeOH, 96/4) : 0.47 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.89 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.39 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.44 – 1.65 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.28 – 3.41 (m, 1H, H_{iPr}), 3.65 (q, *J* = 6.5 Hz, 1H, H_{iPent}), 3.81 (s, 3H, $CH_{3\text{-}O}$), 6.73 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.44 (s, 1H, H_{Ar}), 7.45 (s, 1H, H_{Ar}), 7.64 (s, 1H, H_{Ar}), 8.02 (t, *J* = 1.9 Hz, 1H, H_{Ar}), 9.72 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.5 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.9 (CH_{iPr}), 26.2 (2x$CH_{2\text{-}CH3}$), 53.2 (CH_{iPent}), 55.8 ($CH_{3\text{-}O}$), 92.2 (CH_{Ar}), 114.7 (CH_{Ar}), 124.7 (CH_{Ar}), 132.2 (CH_{Ar}), 133.9 (C_q), 139.5 (C_q), 148.6 (C_q), 150.8 (C_q), 153.0 (C_q), 156.1 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{27}N_7O$:** 370.24 [M+H]+, **found :** 370.33.
(156)		> 97 % [b]	White solid. **Rf** (DCM/MeOH, 96/4) : 0.47 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.89 (t, *J* = 7.3 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.39 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.54 (ddq, *J* = 28.3, 13.9, 7.0 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 3.28 – 3.40 (m, 1H, H_{iPr}), 3.65 (hept, *J* = 5.9, 5.2 Hz, 1H, H_{iPent}), 3.81 (s, 3H, $CH_{3\text{-}O}$), 6.63 (dd, *J* = 6.1, 2.2 Hz, 1H, H_{Ar}), 6.80 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.13 (d, *J* = 2.3 Hz, 1H, H_{Ar}), 7.79 (s, 1H, H_{Ar}), 8.14 (d, *J* = 5.9 Hz, 1H, H_{Ar}), 9.68 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.5 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.9 (CH_{iPr}), 26.1 (2x$CH_{2\text{-}CH3}$), 53.2 (CH_{iPent}), 55.2 ($CH_{3\text{-}O}$), 94.2 (CH_{Ar}), 97.7 (CH_{Ar}), 105.6 (CH_{Ar}), 133.7 (C_q), 139.5 (C_q), 148.1 (CH_{Ar}), 153.0 (C_q), 156.0 (C_q), 156.6 (C_q), 166.3 (C_q).

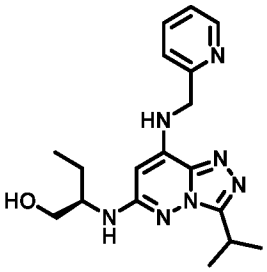
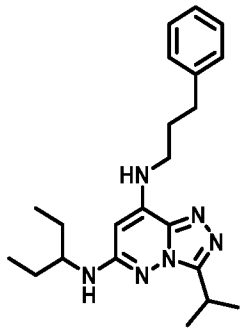
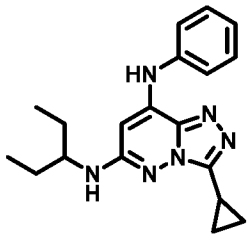
			MS (ESI+) : m/z calcd for $C_{19}H_{27}N_7O$: 370.24 [M+H]+, **found :** 370.33.
(157)		-	White solid. **Rf** (DCM/MeOH, 96/4) : 0.45 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.89 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.39 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.45 – 1.67 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.35 – 3.40 (m, 1H, H_{iPr}), 3.66 (h, *J* = 6.4 Hz, 1H, H_{iPent}), 3.99 (s, 3H, $CH_{3\text{-}O}$), 6.97 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.06 (dd, *J* = 8.0, 5.0 Hz, 1H, H_{Ar}), 7.45 (dd, *J* = 8.1, 1.4 Hz, 1H, H_{Ar}), 7.77 (s, 1H, H_{Ar}), 7.94 (dd, *J* = 5.0, 1.4 Hz, 1H, H_{Ar}), 8.27 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.5 (2x$CH_{3\text{-}CH2}$), 19.4 (2x$CH_{3\ iPr}$), 24.9 (CH_{iPr}), 26.0 (2x$CH_{2\text{-}CH3}$), 53.3 (CH_{iPent}), 56.2 ($CH_{3\text{-}O}$), 94.0 (CH_{Ar}), 117.0 (CH_{Ar}), 117.6 (CH_{Ar}), 132.1 (C_q), 137.9 (CH_{Ar}), 139.2 (C_q), 143.2 (C_q), 144.0 (C_q), 153.3 (C_q), 155.8 (C_q).
(158)		-	Pale grey solid. **^{1}H NMR (400 MHz, DMSO) δ** : 8.52 (s, 1H), 8.06 (d, *J* = 4.7 Hz, 1H), 7.71 (d, *J* = 7.1 Hz, 1H), 7.09 (dd, *J* = 7.6, 5.0 Hz, 1H), 6.46 (d, *J* = 7.9 Hz, 1H), 5.71 (s, 1H), 3.93 (d, *J* = 0.8 Hz, 3H), 3.66 – 3.53 (m, 1H), 3.41 – 3.34 (m, 1H), 1.61 – 1.49 (m, 2H), 1.49 – 1.41 (m, 2H), 1.38 (d, *J* = 7.0 Hz, 6H), 0.85 (t, *J* = 7.3 Hz, 6H). **^{13}C NMR (101 MHz, DMSO) δ** : 157.1, 155.8, 153.0, 142.6, 139.5, 136.8, 132.6, 122.6, 117.3, 88.1, 53.4, 53.0, 26.0, 24.9, 19.5, 10.3.
(159)		-	Brown viscous oil. **^{1}H NMR (400 MHz, DMSO) δ** : 9.12 (s, 1H), 8.20 (d, *J* = 2.7 Hz, 1H), 7.73 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.43 (d, *J* = 7.9 Hz, 1H), 5.90 (s, 1H), 3.87 (s, 3H), 3.59 (p, *J* = 6.5 Hz, 1H), 3.39 – 3.34 (m, 1H), 1.60 – 1.48 (m, 2H), 1.48 – 1.40 (m, 2H), 1.38 (d, *J* = 7.0 Hz, 6H), 0.85 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR (101 MHz, DMSO) δ** : 160.6, 155.9, 152.9, 142.1, 139.6, 138.3, 135.8, 130.0, 110.8, 86.2, 53.3, 52.3, 26.1, 24.9, 19.5, 10.3.

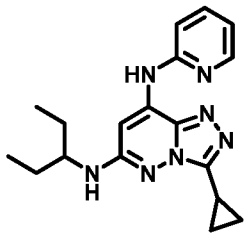
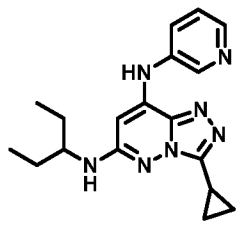
(160)		-	Pale beige solid. **^{1}H NMR (400 MHz, DMSO) δ** : 9.41 (s, 1H), 8.30 (s, 1H), 8.08 (s, 1H), 7.41 (s, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 6.32 (s, 1H), 3.85 (s, 3H), 3.66 – 3.56 (m, 1H), 3.42 – 3.35 (m, 1H), 1.64 – 1.51 (m, 2H), 1.50 – 1.41 (m, 2H), 1.39 (d, *J* = 6.9 Hz, 6H), 0.87 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR (101 MHz, DMSO) δ** : 156.2, 156.1, 153.6, 140.0, 137.6, 137.0, 136.1, 132.3, 114.4, 88.6, 56.1, 53.5, 26.5, 25.3, 20.0, 10.8.
(161)		-	Brown solid. **^{1}H NMR (400 MHz, DMSO) δ** : 0.84 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.38 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.40 – 1.58 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.36 – 3.40 (m, 1H, H_{iPr}), 3.57 (dt, *J* = 12.6, 6.8 Hz, 1H, H_{iPent}), 3.89 (s, 3H, $CH_{3\text{-}O}$), 5.53 (s, 1H, H_{Ar}), 6.41 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.23 (d, *J* = 5.7 Hz, 1H, H_{Ar}), 8.40 (d, *J* = 5.4 Hz, 1H, H_{Ar}), 8.41 (s, 1H, H_{Ar}), 8.67 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO) δ** : N.D.
(162)		> 97 % [b]	Light yellow solid. **Rf** (DCM/MeOH, 94/6) : 0.30 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.89 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.40 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.45 – 1.66 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.37 (p, *J* = 7.0 Hz, 1H, H_{iPr}), 3.67 (qt, *J* = 7.5, 5.3 Hz, 1H, H_{iPent}), 3.87 (s, 3H, $CH_{3\text{-}O}$), 7.06 (d, *J* = 7.9 Hz, 1H, NH_{iPent}), 7.43 (d, *J* = 2.6 Hz, 1H, H_{Ar}), 7.95 (s, 1H, H_{Ar}), 8.67 (d, *J* = 2.6 Hz, 1H, H_{Ar}), 9.94 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.9 (CH_{iPr}), 26.0 (2x$CH_{2\text{-}CH3}$), 53.2 (CH_{iPent}), 55.4 ($CH_{3\text{-}O}$), 96.1 (CH_{Ar}), 99.1 (CH_{Ar}), 133.0 (C_q), 139.3 (C_q), 139.8 (CH_{Ar}), 153.1 (C_q), 155.9 (C_q), 158.1 (C_q), 158.3 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{26}N_8O$:** 371.23 [M+H]+, **found :** 317.33.

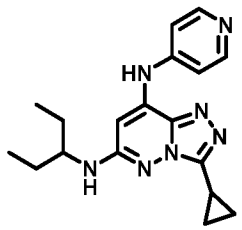
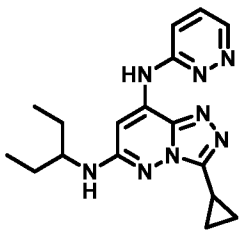
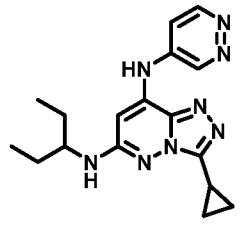
(163)		> 98 % [b]	White solid. **Rf** (DCM/MeOH, 94/6) : 0.23 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.91 (t, *J* = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.40 (dd, *J* = 6.9, 1.5 Hz, 6H, 2x$CH_{3\ iPr}$), 1.44 – 1.77 (m, 2H, $CH_{2\text{-}CH3}$), 3.37 (p, *J* = 7.2 Hz, 1H, H_{iPr}), 3.50 (dp, *J* = 19.4, 5.2 Hz, 2H, $CH_{2\text{-}OH}$), 3.73 (tq, *J* = 10.2, 5.6 Hz, 1H, $H_{C\text{-}NH}$), 4.62 (t, *J* = 5.5 Hz, 1H, OH), 6.79 (d, *J* = 7.8 Hz, 1H, $NH_{\text{-}CH}$), 6.99 (dd, *J* = 7.2, 5.0 Hz, 1H, H_{Ar}), 7.48 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 7.72 (td, *J* = 7.8, 7.3, 2.0 Hz, 1H, H_{Ar}), 7.84 (s, 1H, H_{Ar}), 8.32 (dd, *J* = 5.0, 1.9 Hz, 1H, H_{Ar}), 9.87 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.6 ($CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.5 ($CH_{2\text{-}CH3}$), 24.8 (CH_{iPr}), 54.1 ($CH_{\text{-}NH}$), 62.0 ($CH_{2\text{-}OH}$), 94.2 (CH_{Ar}), 113.7 (CH_{Ar}), 117.0 (CH_{Ar}), 133.6 (C_q), 137.7 (CH_{Ar}), 139.4 (C_q), 146.9 (CH_{Ar}), 153.1 (C_q), 154.9 (C_q), 155.9 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{23}N_7O$:** 342.20 [M+H]+, **found :** 342.42.
(164)		94 % [b]	Light brown solid. **Rf** (DCM/MeOH, 94/6) : 0.19 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.88 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.29 – 1.39 (m, 10H, 2x$CH_{3\ iPr}$ & 2x$CH_{2\text{-}CH3}$), 1.52 (p, *J* = 6.2 Hz, 1H, $H_{C\text{-}CH2\text{-}NH}$), 3.09 (t, *J* = 7.3 Hz, 2H, CH_2), 3.13 (t, *J* = 5.9 Hz, 2H, CH_2), 3.27 – 3.37 (m, 1H, H_{iPr}), 3.55 (q, *J* = 6.8 Hz, 2H, CH_2), 5.60 (s, 1H, H_{Ar}), 6.55 (t, *J* = 5.6 Hz, 1H, NH), 7.18 – 7.29 (m, 2H, NH & H_{Ar}), 7.33 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.72 (td, *J* = 7.7, 1.9 Hz, 1H, H_{Ar}), 8.52 (dd, *J* = 5.0, 1.8 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.9 (2x$CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.5 (2x$CH_{2\text{-}CH3}$), 24.7 (CH_{iPr}), 35.9 (CH_2), 39.9 ($CH_{\text{-}CH2\text{-}NH}$), 41.7 ($CH_2$), 43.3 ($CH_2$), 83.5 ($CH_{Ar}$), 121.6 ($CH_{Ar}$), 123.3 ($CH_{Ar}$), 136.5 ($CH_{Ar}$), 139.7 ($C_q$), 139.8 ($C_q$), 149.1 ($CH_{Ar}$), 152.8 ($C_q$), 156.3 ($C_q$), 158.9 ($C_q$). **MS (ESI+) : m/z calcd for $C_{21}H_{31}N_7$:** 382.27 [M+H]+, **found :** 382.45.

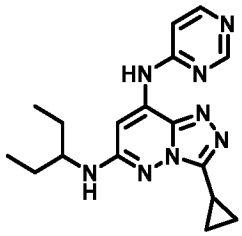
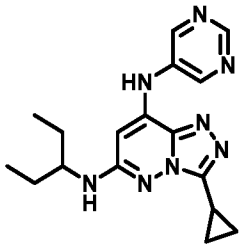
(165)		> 95 % [b]	Light brown solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.36 (dd, J = 7.0, 1.3 Hz, 6H, 2x$CH_{3\ iPr}$), 1.42 – 1.59 (m, 4H, 2xCH_2), 1.67 (dd, J = 9.2, 5.3 Hz, 2H, CH_2), 1.94 (dt, J = 12.9, 6.4 Hz, 2H, CH_2), 3.08 (t, J = 7.4 Hz, 2H, CH_2), 3.28 – 3.38 (m, 1H, H_{iPr}), 3.54 (q, J = 6.8 Hz, 2H, CH_2), 3.99 (p, J = 6.3 Hz, 1H, H_{cPent}), 5.56 (s, 1H, H_{Ar}), 6.58 (d, J = 6.1 Hz, 1H, NH_{cPent}), 7.17 – 7.30 (m, 2H, NH-$_{CH2}$ & H_{Ar}), 7.33 (d, J = 7.7 Hz, 1H, H_{Ar}), 7.72 (tt, J = 7.6, 1.6 Hz, 1H, H_{Ar}), 8.51 (dd, J = 4.7, 1.5 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 19.6 (2x$CH_{3\ iPr}$), 23.6 (2xCH_2), 24.8 (CH_{iPr}), 32.4 (2xCH_2), 35.8 ($CH_{2\text{-}CH2\text{-}NH}$), 41.7 ($CH_{2\text{-}NH}$), 52.3 ($CH_{cPent}$), 83.6 ($CH_{Ar}$), 121.6 ($CH_{Ar}$), 123.3 ($CH_{Ar}$), 136.5 ($CH_{Ar}$), 139.6 ($C_q$), 139.8 ($C_q$), 149.1 ($CH_{Ar}$), 152.8 ($C_q$), 155.7 ($C_q$), 158.9 ($C_q$). **MS (ESI+) : m/z calcd for $C_{20}H_{27}N_7$:** 366.24 [M+H]+, **found :** 366.42.
(166)		> 96 % [b]	Light brown solid. **Rf** (DCM/MeOH, 94/6) : 0.17 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.89 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.34 (dd, J = 15.9, 6.9 Hz, 10H, 2x$CH_{3\ iPr}$ & 2x$CH_{2\text{-}CH3}$), 1.52 (hept, J = 6.3 Hz, 1H, $H_{C\text{-}CH2\text{-}NH}$), 2.94 (t, J = 7.3 Hz, 2H, CH_2), 3.14 (t, J = 5.9 Hz, 2H, CH_2), 3.27 – 3.39 (m, 1H, H_{iPr}), 3.43 (q, J = 6.8 Hz, 2H, CH_2), 5.61 (s, 1H, H_{Ar}), 6.52 (t, J = 5.8 Hz, 1H, NH), 7.24 – 7.39 (m, 2H, NH & H_{Ar}), 7.71 (dt, J = 7.9, 2.0 Hz, 1H, H_{Ar}), 8.43 (dd, J = 4.8, 1.6 Hz, 1H, H_{Ar}), 8.52 (d, J = 2.2 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.9 (2x$CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.5 (2x$CH_{2\text{-}CH3}$), 24.7 (CH_{iPr}), 30.8 (CH_2), 39.9 ($CH_{\text{-}CH2\text{-}NH}$), 43.1 ($CH_2$), 43.3 ($CH_2$), 83.7 ($CH_{Ar}$), 123.4 ($CH_{Ar}$), 134.7 ($C_q$), 136.3 ($CH_{Ar}$), 139.6 ($C_q$), 139.7 ($C_q$), 147.5 ($CH_{Ar}$), 149.9 ($CH_{Ar}$), 152.8 ($C_q$), 156.3 ($C_q$). **MS (ESI+) : m/z calcd for $C_{21}H_{31}N_7$:** 382.27 [M+H]+, **found :** 380.40.

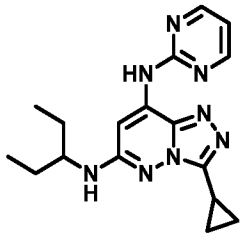
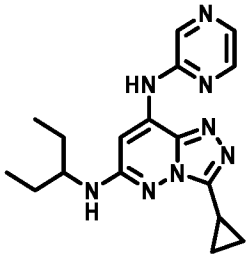
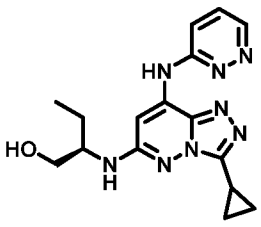
(167)		95 % [b]	Light brown solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.88 (t, *J* = 7.5 Hz, 6H, 2xCH$_{3\text{-}CH2}$), 0.89 (t, *J* = 7.4 Hz, 6H, 2xCH$_{3\text{-}CH2}$), 1.35 (dd, *J* = 14.2, 7.0 Hz, 14H, 2xCH$_{3\ iPr}$ & 4xCH$_{2\text{-}CH3}$), 1.52 (dq, *J* = 11.4, 5.6, 5.1 Hz, 1H, H$_{C\text{-}CH2\text{-}NH}$), 1.68 (hept, *J* = 6.6 Hz, 1H, H$_{C\text{-}CH2\text{-}NH}$), 3.07 (t, *J* = 6.5 Hz, 2H, CH$_{2\text{-}NH}$), 3.13 (t, *J* = 6.0 Hz, 2H, CH$_{2\text{-}NH}$), 3.28 – 3.40 (m, 1H, H$_{iPr}$), 5.50 (s, 1H, H$_{Ar}$), 6.54 (t, *J* = 5.7 Hz, 1H, NH), 7.18 (t, *J* = 5.8 Hz, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.5 (2xCH$_{3\text{-}CH2}$), 10.9 (2xCH$_{3CH2}$), 19.6 (2xCH$_{3\ iPr}$), 23.1 (2xCH$_{2\text{-}CH3}$), 23.5 (2xCH$_{2\text{-}CH3}$), 24.7 (CH$_{iPr}$), 38.3 (CH$_{\text{-}CH2}$), 39.9 (CH$_{\text{-}CH2}$), 43.3 (CH$_{2\text{-}NH}$), 45.3 (CH$_{2\text{-}NH}$), 83.1 (CH$_{Ar}$), 139.7 (C$_q$), 140.1 (C$_q$), 152.8 (C$_q$), 156.3 (C$_q$). **MS (ESI+) : m/z calcd for C$_{20}$H$_{36}$N$_6$:** 361.31 [M+H]+, **found :** 361.50.
(168)		> 96 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.86 (t, *J* = 7.3 Hz, 6H, 2xCH$_{3\text{-}CH2}$), 1.38 (d, *J* = 6.9 Hz, 6H, 2xCH$_{3\ iPr}$), 1.52 (dtt, *J* = 38.8, 14.0, 6.6 Hz, 4H, 2xCH$_{2\text{-}CH3}$), 3.29 – 3.41 (m, 1H, H$_{iPr}$), 3.57 – 3.69 (m, 1H, H$_{iPent}$), 3.98 (s, 2H, CH$_{2\text{-}CO}$), 6.98 (d, *J* = 7.9 Hz, 1H, NH$_{iPent}$), 7.36 (dd, *J* = 7.8, 4.8 Hz, 1H, H$_{Ar}$), 7.58 (s, 1H, H$_{Ar}$), 7.76 (dt, *J* = 7.9, 2.0 Hz, 1H, H$_{Ar}$), 8.47 (dd, *J* = 4.8, 1.7 Hz, 1H, H$_{Ar}$), 8.55 (d, *J* = 2.2 Hz, 1H, H$_{Ar}$), 11.01 (s, 1H, NH$_{\text{-}CO}$). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.3 (2xCH$_{3\text{-}CH2}$), 19.4 (2xCH$_{3\ iPr}$), 24.8 (CH$_{iPr}$), 25.9 (2xCH$_{2\text{-}CH3}$), 39.8 (CH$_{2\text{-}CO}$), 53.3 (CH$_{iPent}$), 99.6 (CH$_{Ar}$), 123.4 (CH$_{Ar}$), 131.2 (C$_q$), 131.8 (C$_q$), 136.8 (CH$_{Ar}$), 138.5 (C$_q$), 147.9 (CH$_{Ar}$), 150.3 (CH$_{Ar}$), 153.2 (C$_q$), 155.2 (C$_q$), 171.4 (C$_q$). **MS (ESI+) : m/z calcd for C$_{20}$H$_{27}$N$_7$O :** 382.23 [M+H]+, **found :** 382.44.

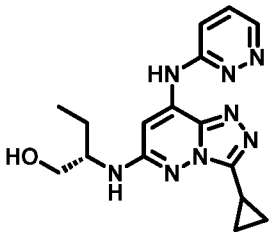
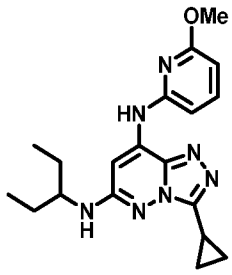
(169)		> 96 % [b]	White solid. **Rf** (DCM/MeOH, 92/8) : 0.29 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.85 (t, *J* = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.36 (dd, *J* = 6.9, 1.2 Hz, 6H, 2x$CH_{3\ iPr}$), 1.38 – 1.67 (m, 2H, $CH_{2\text{-}CH3}$), 3.24 - 3.37 (m, 1H, H_{iPr}), 3.41 (dq, *J* = 22.0, 5.2 Hz, 2H, $CH_{2\text{-}OH}$), 3.62 (h, *J* = 5.9 Hz, 1H, $H_{c\text{-}NH}$), 4.52 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 4.55 (t, *J* = 5.4 Hz, 1H, OH), 5.46 (s, 1H, H_{Ar}), 6.33 (d, *J* = 7.7 Hz, 1H, $NH_{\text{-}CH}$), 7.28 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H, H_{Ar}), 7.33 (dt, *J* = 7.9, 1.1 Hz, 1H, H_{Ar}), 7.75 (td, *J* = 7.8, 1.9 Hz, 1H, H_{Ar}), 7.80 (t, *J* = 6.5 Hz, 1H, NH_{Bn}), 8.55 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.5 ($CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.5 ($CH_{2\text{-}CH3}$), 24.7 (CH_{iPr}), 47.2 ($CH_{2\ Bn}$), 53.8 ($CH_{\text{-}NH}$), 62.0 ($CH_{2\text{-}OH}$), 84.6 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.6 (C_q), 139.8 (C_q), 149.0 (CH_{Ar}), 152.8 (C_q), 155.8 (C_q), 157.7 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{25}N_7O$:** 356.22 [M+H]+, **found :** 356.41.
(170)		84 % [b]	Brown oil. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.87 (t, *J* = 7.2 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.36 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.51 (ddq, *J* = 40.2, 13.9, 7.3 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 1.93 (p, *J* = 7.3 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 2.67 (t, *J* = 7.8 Hz, 2H, $CH_{2\text{-}Ph}$), 3.18 (q, *J* = 6.6 Hz, 2H, $CH_{2\text{-}NH}$), 3.30 (d, *J* = 7.6 Hz, 1H, H_{iPr}), 3.60 (h, *J* = 7.0 Hz, 1H, H_{iPent}), 5.50 (s, 1H, H_{Ar}), 6.28 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.23 (td, *J* = 18.1, 17.7, 7.2 Hz, 6H, NH_{Bn} & 5xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** N.D. **MS (ESI+) : m/z calcd for $C_{22}H_{21}N_6$:** 381.28 [M+H]+, **found :** 381.47.
(171)		> 96 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.86 (t, *J* = 7.3 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.02 – 1.19 (m, 4H, 2x$CH_{2\ cPr}$), 1.38 – 1.63 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.24 – 2.33 (m, 1H, H_{cPr}), 3.61 (h, *J* = 6.4 Hz, 1H, H_{iPent}), 6.20 (s, 1H, H_{Ar}), 6.49 (d, *J* = 7.9 Hz, 1H, NH_{iPent}), 7.13 (ddd, *J* = 8.6, 6.1, 2.2 Hz, 1H, H_{Ar}), 7.30 – 7.48 (m, 4H, 4xH_{Ar}), 9.19 (s, 1H, NH).

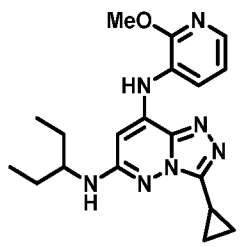
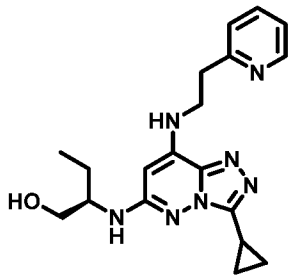
			^{13}C NMR (101 MHz, DMSO-d_6) δ : 5.4 (CH_{cPr}), 6.4 ($2xCH_{2\ cPr}$), 10.3 ($2xCH_{3\text{-}CH2}$), 26.1 ($2xCH_{2\text{-}CH3}$), 52.9 (CH_{iPent}), 86.8 (CH_{Ar}), 122.3 ($2xCH_{Ar}$), 123.7 (CH_{Ar}), 129.2 ($2xCH_{Ar}$), 137.0 (C_q), 139.5 (C_q), 139.6 (C_q), 150.2 (C_q), 156.1 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{24}N_6$:** 337.21 [M+H]+, **found :** 337.41.
(172)		> 96 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.91 (t, *J* = 7.4 Hz, 6H, $2xCH_{3\text{-}CH2}$), 1.02 – 1.23 (m, 4H, $2xCH_{2\ cPr}$), 1.41 – 1.68 (m, 4H, $2xCH_{2\text{-}CH3}$), 2.30 (ddd, *J* = 13.6, 8.4, 5.0 Hz, 1H, H_{cPr}), 3.60 – 3.75 (m, 1H, H_{iPent}), 6.82 (d, *J* = 8.1 Hz, 1H, NH_{iPent}), 7.00 (ddd, *J* = 7.2, 5.0, 1.0 Hz, 1H, H_{Ar}), 7.48 (dt, *J* = 8.5, 1.0 Hz, 1H, H_{Ar}), 7.72 (ddd, *J* = 9.0, 7.3, 2.0 Hz, 1H, H_{Ar}), 7.81 (s, 1H, H_{Ar}), 8.28 – 8.40 (m, 1H, H_{Ar}), 9.83 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.4 (CH_{cPr}), 6.4 ($2xCH_{2\ cPr}$), 10.4 ($CH_{3\text{-}CH2}$), 26.1 ($2xCH_{2\text{-}CH3}$), 53.1 (CH_{iPent}), 94.1 (CH_{Ar}), 113.7 (CH_{Ar}), 117.0 (CH_{Ar}), 133.5 (C_q), 137.7 (CH_{Ar}), 139.3 (C_q), 146.9 (CH_{Ar}), 150.2 (C_q), 154.9 (C_q), 156.2 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{23}N_7$:** 338.21 [M+H]+, **found :** 338.37.
(173)		93 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.87 (t, *J* = 7.4 Hz, 6H, $2xCH_{3\text{-}CH2}$), 1.03 – 1.19 (m, 4H, $2xCH_{2\ cPr}$), 1.39 – 1.62 (m, 4H, $2xCH_{2\text{-}CH3}$), 2.29 (tt, *J* = 8.5, 5.1 Hz, 1H, H_{cPr}), 3.54 – 3.69 (m, 1H, H_{iPent}), 6.23 (s, 1H, H_{Ar}), 6.53 (d, *J* = 7.9 Hz, 1H, NH_{iPent}), 7.44 (dd, *J* = 8.2, 4.7 Hz, 1H, H_{Ar}), 7.80 (ddd, *J* = 8.3, 2.7, 1.5 Hz, 1H, H_{Ar}), 8.34 (dd, *J* = 4.7, 1.5 Hz, 1H, H_{Ar}), 8.66 (d, *J* = 2.6 Hz, 1H, H_{Ar}), 9.41 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.4 (CH_{cPr}), 6.4 ($2xCH_{2\ cPr}$), 10.2 ($2xCH_{3\text{-}CH2}$), 26.0 ($2xCH_{2\text{-}CH3}$), 52.8 (CH_{iPent}), 87.6 (CH_{Ar}), 123.9 (CH_{Ar}), 129.1 (CH_{Ar}), 136.4 (C_q), 136.6 (C_q), 139.4 (C_q), 143.8 (CH_{Ar}), 144.4 (CH_{Ar}), 150.3 (C_q), 156.0 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{23}N_7$:** 338.21 [M+H]+, **found :** 338.37.

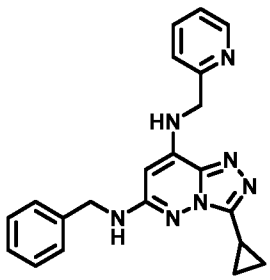
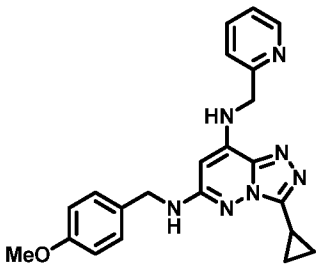
(174)		> 97 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.03 – 1.20 (m, 4H, 2x$CH_{2\ cPr}$), 1.40 – 1.69 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.29 (tt, *J* = 8.5, 5.0 Hz, 1H, H_{cPr}), 3.65 (h, *J* = 6.1, 5.7 Hz, 1H, H_{iPent}), 6.60 (s, 1H, H_{Ar}), 6.68 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.29 – 7.40 (m, 2H, 2xH_{Ar}), 8.35 – 8.48 (m, 2H, 2xH_{Ar}), 9.71 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.4 (CH_{cPr}), 6.5 (2x$CH_{2\ cPr}$), 10.3 (2x$CH_{3\text{-}CH2}$), 26.0 (2x$CH_{2\text{-}CH3}$), 53.0 (CH_{iPent}), 91.7 (CH_{Ar}), 113.8 (2xCH_{Ar}), 134.6 (C_q), 139.3 (C_q), 147.2 (C_q), 150.4 (CH_{Ar}), 150.4 (C_q), 155.7 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{23}N_7$:** 338.21 [M+H]+, **found :** 338.37.
(175)		> 98 % [b]	White solid. **Rf** (DCM/MeOH, 95/5) : 0.38 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.03 – 1.20 (m, 4H, 2x$CH_{2\ cPr}$), 1.43 – 1.65 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.30 (td, *J* = 8.6, 4.3 Hz, 1H, H_{cPr}), 3.62 – 3.72 (m, 1H, H_{iPent}), 7.06 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.61 (dd, *J* = 9.0, 4.5 Hz, 1H, H_{Ar}), 7.78 (d, *J* = 9.1, 1.3 Hz, 1H, H_{Ar}), 7.95 (s, 1H, H_{Ar}), 8.89 (d, *J* = 4.5, 1.2 Hz, 1H, H_{Ar}), 10.10 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.40 (CH_{cPr}), 6.47 (2x$CH_{2\ cPr}$), 10.40 (2x$CH_{3\text{-}CH2}$), 25.99 (2x$CH_{2\text{-}CH3}$), 53.12 (CH_{iPent}), 96.09 (CH_{Ar}), 118.64 (CH_{Ar}), 128.08 (CH_{Ar}), 132.81 (C_q), 139.16 (C_q), 146.78 (CH_{Ar}), 150.34 (C_q), 156.11 (C_q), 157.60 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{22}N_8$:** 339.20 [M+H]+, **found :** 339.38.
(176)		> 97 % [b]	White solid. **Rf** (DCM/MeOH, 94/6) : 0.11 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.12 (ddt, *J* = 32.5, 7.3, 2.8 Hz, 4H, 2x$CH_{2\ cPr}$), 1.55 (ddt, *J* = 47.4, 13.9, 6.8 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 2.30 (dd, *J* = 9.7, 4.7 Hz, 1H, H_{cPr}), 3.66 (dq, *J* = 12.1, 6.2, 5.3 Hz, 1H, H_{iPent}), 6.68 (s, 1H, H_{Ar}), 6.72 (d, *J* = 7.9 Hz, 1H, NH_{iPent}), 7.54 (dd, *J* = 6.0, 3.0 Hz, 1H, H_{Ar}), 9.00 (d, *J* = 6.0 Hz, 1H, H_{Ar}), 9.33 (d,

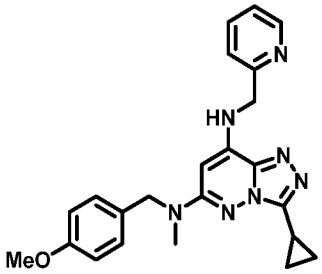
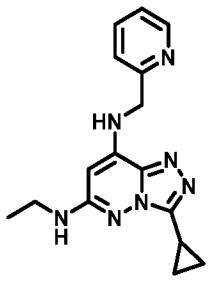
			J = 2.9 Hz, 1H, H_{Ar}), 10.04 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.5 (2x$CH_{2\ cPr}$), 10.2 (2x$CH_{3\text{-}CH2}$), 25.9 (2x$CH_{2\text{-}CH3}$), 53.0 (CH_{iPent}), 93.7 (CH_{Ar}), 112.8 (CH_{Ar}), 133.9 (C_q), 139.1 (C_q), 139.8 (C_q), 144.3 (CH_{Ar}), 150.5 (C_q), 150.8 (CH_{Ar}), 155.4 (C_q).
(177)		> 97 % [b]	Beige solid. **Rf** (DCM/MeOH, 95/5) : 0.25 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.05 – 1.20 (m, 4H, 2x$CH_{2\ cPr}$), 1.55 (ddt, J = 47.4, 13.9, 6.8 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 2.26 – 2.33 (m, 1H, H_{cPr}), 3.66 (h, J = 8.1, 7.6 Hz, 1H, H_{iPent}), 6.68 (s, 1H, H_{Ar}), 6.72 (d, J = 8.0 Hz, 1H, NH_{iPent}), 7.54 (dd, J = 6.0, 3.0 Hz, 1H, H_{Ar}), 9.00 (d, J = 6.0 Hz, 1H, H_{Ar}), 9.33 (d, J = 2.9 Hz, 1H, H_{Ar}), 10.04 (s, 1H, $NH_{Pyrimid}$). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.5 (2x$CH_{2\ cPr}$), 10.4 (2x$CH_{3\text{-}CH2}$), 26.0 (2x$CH_{2\text{-}CH3}$), 53.2 (CH_{iPent}), 97.7 (CH_{Ar}), 110.1 (CH_{Ar}), 132.5 (C_q), 139.0 (C_q), 150.4 (C_q), 155.7 (C_q), 156.2 (CH_{Ar}), 157.5 (CH_{Ar}), 160.2 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{22}N_8$:** 339.20 [M+H]+, **found :** 339.36.
(178)		> 97 % [b]	Orange solid. **Rf** (DCM/MeOH, 98/2) : 0.37 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.88 (t, J = 7.3 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.07 (dt, J = 8.5, 3.2 Hz, 2H, $CH_{2\ cPr}$), 1.16 (dt, J = 5.6, 3.0 Hz, 2H, $CH_{2\ cPr}$), 1.51 (ddq, J = 40.5, 14.0, 6.9 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 2.24 – 2.32 (m, 1H, H_{cPr}), 3.63 (q, J = 6.5 Hz, 1H, H_{iPent}), 6.35 (s, 1H, H_{Ar}), 6.56 (d, J = 8.0 Hz, 1H, NH_{iPent}), 8.89 (s, 2H, 2xH_{Ar}), 8.93 (s, 1H, H_{Ar}), 9.59 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.38 (CH_{cPr}), 6.50 (2x$CH_{2\ cPr}$), 10.21 (2x$CH_{3\text{-}CH2}$), 25.97 (2x$CH_{2\text{-}CH3}$), 52.88 (CH_{iPent}), 88.84 (CH_{Ar}), 135.45 (C_q), 135.81 (C_q), 139.20 (C_q), 149.67 (2xCH_{Ar}), 150.35 (C_q), 152.85 (CH_{Ar}), 155.79 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{22}N_8$:** 339.20 [M+H]+, **found :** 339.36.

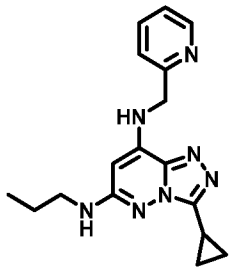
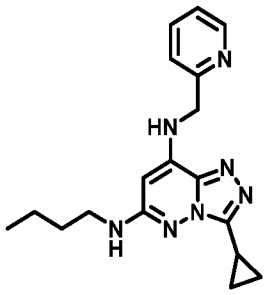
(179)		> 97 % [b]	White solid. **Rf** (DCM/MeOH, 95/5) : 0.4 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.02 – 1.21 (m, 4H, 2x$CH_{2\ cPr}$), 1.43 – 1.67 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.24 – 2.33 (m, 1H, H_{cPr}), 3.67 (q, *J* = 6.6 Hz, 1H, H_{iPent}), 6.99 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.15 (t, *J* = 4.8 Hz, 1H, H_{Ar}), 7.63 (s, 1H, H_{Ar}), 8.69 (d, *J* = 4.8 Hz, 2H, 2xH_{Ar}), 8.90 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.36 (CH_{cPr}), 6.49 (2x$CH_{2\ cPr}$), 10.40 (2x$CH_{3\text{-}CH2}$), 25.99 (2x$CH_{2\text{-}CH3}$), 53.15 (CH_{iPent}), 96.06 (CH_{Ar}), 115.24 (CH_{Ar}), 132.32 (C_q), 138.89 (C_q), 150.45 (C_q), 155.78 (C_q), 158.46 (2xCH_{Ar}), 158.91 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{22}N_8$:** 339.20 [M+H]+, **found :** 339.38.
(180)		> 98 %	White solid. **Rf** (DCM/MeOH, 95/5) : 0.36 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.89 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.07 (dt, *J* = 8.7, 3.2 Hz, 2H, $CH_{2\ cPr}$), 1.17 (dt, *J* = 5.6, 3.0 Hz, 2H, $CH_{2\ cPr}$), 1.42 – 1.66 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.25 – 2.33 (m, 1H, H_{cPr}), 3.61 – 3.71 (m, 1H, H_{iPent}), 6.91 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.73 (s, 1H, H_{Ar}), 8.18 (d, *J* = 2.8 Hz, 1H, H_{Ar}), 8.32 (d, *J* = 2.3 Hz, 1H, H_{Ar}), 8.82 (s, 1H, H_{Ar}), 10.33 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.37 (CH_{cPr}), 6.49(2x$CH_{2\ cPr}$), 10.42 (2x$CH_{3\text{-}CH2}$), 26.03 (2x$CH_{2\text{-}CH3}$), 53.13 (CH_{iPent}), 95.10 (CH_{Ar}), 133.00 (C_q), 136.33 (CH_{Ar}), 137.23 (CH_{Ar}), 139.10 (C_q), 140.78 (CH_{Ar}), 150.35 (C_q), 151.54 (C_q), 155.90 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{22}N_8$:** 339.20 [M+H]+, **found :** 339.38.
(181)		> 99 %	White solid. **Rf** (DCM/MeOH, 91/9) : 0.42 **^{1}H NMR (400 MHz, DMSO-d_6) δ** : 0.92 (t, *J* = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.03 – 1.12 (m, 2H, $CH_{2\ cPr}$), 1.12 – 1.21 (m, 2H, $CH_{2\ cPr}$), 1.42 – 1.54 (m, 1H, 0.5x$CH_{2\text{-}CH3}$), 1.63 – 1.78 (m, 1H, 0.5x$CH_{2\text{-}CH3}$), 2.26 – 2.38 (m, 1H, H_{cPr}), 3.44 (dt, *J* = 10.6, 5.9 Hz, 1H, 0.5x$CH_{2\text{-}OH}$), 3.52 (dt, *J* = 10.6, 5.3 Hz, 1H, 0.5x$CH_{2\text{-}OH}$), 3.76 (ddt, *J* = 13.1, 7.8, 5.5 Hz, 1H, $H_{\text{-butanol}}$), 4.62 (t, *J* = 5.6

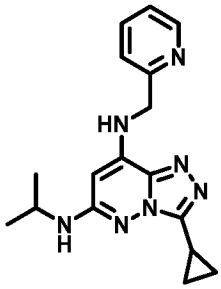
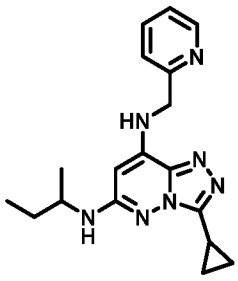
			Hz, 1H, OH), 7.04 (d, *J* = 7.9 Hz, 1H, NH-butanol), 7.61 (dd, *J* = 9.0, 4.5 Hz, 1H, H_{Ar}), 7.78 (dd, *J* = 9.0, 1.4 Hz, 1H, H_{Ar}), 7.96 (s, 1H, H_{Ar}), 8.89 (dd, *J* = 4.5, 1.4 Hz, 1H, H_{Ar}), 10.11 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.32 (CH_{cPr}), 6.64 ($CH_{2\ cPr}$), 6.67 ($CH_{2\ cPr}$), 10.53 ($CH_{3\text{-}CH2}$), 23.52 ($CH_{2\text{-}CH3}$), 54.05 ($CH_{\text{-butanol}}$), 62.09 ($CH_{2\text{-}OH}$), 96.24 (CH_{Ar}), 118.62 (CH_{Ar}), 128.07 (CH_{Ar}), 132.82 (C_q), 139.17 (C_q), 146.78 (CH_{Ar}), 150.42 (C_q), 156.10 (C_q), 157.57 (C_q). **MS (ESI+) : m/z calcd for $C_{16}H_{20}N_8O$:** 341.18 [M+H]+, **found :** 341.36.
(182)		> 99 %	White solid. **Rf** (DCM/MeOH, 90/10) : 0.41 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.92 (t, *J* = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.04 – 1.21 (m, 4H, 2x$CH_{2\ cPr}$), 1.40 – 1.56 (m, 1H, 0.5x$CH_{2\text{-}CH3}$), 1.63 – 1.76 (m, 1H, 0.5x$CH_{2\text{-}CH3}$), 2.32 (ddd, *J* = 13.7, 8.5, 5.1 Hz, 1H, H_{cPr}), 3.44 (dt, *J* = 11.0, 5.9 Hz, 1H, 0.5x$CH_{2\text{-}OH}$), 3.52 (dt, *J* = 10.5, 5.2 Hz, 1H, 0.5x$CH_{2\text{-}OH}$)), 3.71 – 3.80 (m, 1H, $H_{\text{-butanol}}$), 4.62 (t, *J* = 5.6 Hz, 1H, OH), 7.04 (d, *J* = 7.9 Hz, 1H, $NH_{\text{-butanol}}$), 7.61 (dd, *J* = 9.0, 4.5 Hz, 1H, H_{Ar}), 7.78 (dd, *J* = 9.0, 1.5 Hz, 1H, H_{Ar}), 7.96 (s, 1H, H_{Ar}), 8.89 (dd, *J* = 4.6, 1.4 Hz, 1H, H_{Ar}), 10.12 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.32 (CH_{cPr}), 6.64 ($CH_{2\ cPr}$), 6.67 ($CH_{2\ cPr}$), 10.53 ($CH_{3\text{-}CH2}$), 23.52 ($CH_{2\text{-}CH3}$), 54.05 ($CH_{\text{-butanol}}$), 62.09 ($CH_{2\text{-}OH}$), 96.23 (CH_{Ar}), 118.62 (CH_{Ar}), 128.07 (CH_{Ar}), 132.82 (C_q), 139.17 (C_q), 146.78 (CH_{Ar}), 150.41 (C_q), 156.10 (C_q), 157.57 (C_q). **MS (ESI+) : m/z calcd for $C_{16}H_{20}N_8O$:** 341.18 [M+H]+, **found :** 341.37.
(183)		> 95 %	White solid. **Rf** (DCM/MeOH, 96/4) : 0.28 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.90 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.03 – 1.20 (m, 4H, 2x$CH_{2\ cPr}$), 1.43 – 1.67 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.29 (tt, *J* = 8.5, 5.0 Hz, 1H, H_{cPr}), 3.59 – 3.72 (m, 1H, H_{iPent}), 3.94 (s, 3H, OCH_3), 6.40 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 6.63 (d, *J* = 8.2 Hz, 1H, NH_{iPent}), 7.00 (d, *J*

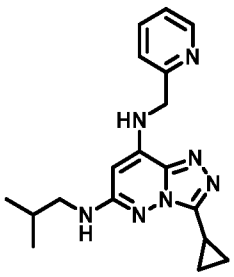
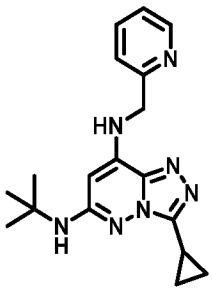
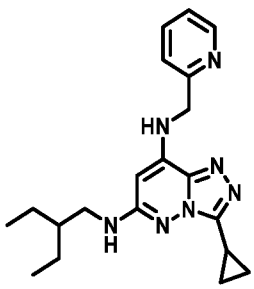
			= 7.9 Hz, 1H, H_{Ar}), 7.44 (s, 1H, H_{Ar}), 7.63 (t, *J* = 7.9 Hz, 1H, H_{Ar}), 9.76 (s, 1H, NH_{Pyr}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.4 (CH_{cPr}), 6.4 ($2xCH_{2\ cPr}$), 10.5 ($2xCH_{3\text{-}CH2}$), 26.2 ($2xCH_{2\text{-}CH3}$), 53.3 (CH_{iPent}), 53.9 (OCH_3), 93.6 (CH_{Ar}), 101.8 (CH_{Ar}), 105.3 (CH_{Ar}), 133.6 (C_q), 139.3 (C_q), 140.5 (CH_{Ar}), 150.2 (C_q), 152.9 (C_q), 156.1 (C_q), 162.6 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{25}N_7O$:** 368.22 [M+H]+, **found :** 368.37.
(184)		94 % [b]	**Rf** (DCM/MeOH, 96/4) : 0.21 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.86 (t, *J* = 7.4 Hz, 6H, $2xCH_{3\text{-}CH2}$), 1.02 – 1.19 (m, 4H, $2xCH_{2\ cPr}$), 1.37 – 1.60 (m, 4H, $2xCH_{2\text{-}CH3}$), 2.28 (tt, *J* = 8.5, 5.1 Hz, 1H, H_{cPr}), 3.61 (dt, *J* = 13.4, 6.8 Hz, 1H, H_{iPent}), 3.92 (s, 3H, $CH_{3\text{-}O}$), 5.72 (s, 1H, H_{Ar}), 6.47 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.09 (dd, *J* = 7.6, 4.9 Hz, 1H, H_{Ar}), 7.71 (dd, *J* = 7.6, 1.7 Hz, 1H, H_{Ar}), 8.05 (dd, *J* = 4.9, 1.7 Hz, 1H, H_{Ar}), 8.48 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.4 (CH_{cPr}), 6.4 ($2xCH_{2\ cPr}$), 10.2 ($2xCH_{3\text{-}CH2}$), 26.0 ($2xCH_{2\text{-}CH3}$), 52.8 (CH_{iPent}), 53.4 ($CH_{3\text{-}O}$), 88.1 (CH_{Ar}), 117.3 (CH_{Ar}), 122.6 (C_q), 132.3 (CH_{Ar}), 136.7 (C_q), 139.4 (C_q), 142.5 (CH_{Ar}), 150.1 (C_q), 156.0 (C_q), 157.0 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{25}N_7O$:** 368.22 [M+H]+, **found :** 368.37.
(185)		-	Light yellow solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.90 (t, *J* = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.07 (ddt, *J* = 29.3, 8.8, 3.5 Hz, 4H, $2xCH_{2\ cPr}$), 1.38 – 1.74 (m, 2H, $CH_{2\text{-}CH3}$), 2.24 (td, *J* = 8.4, 4.3 Hz, 1H, H_{cPr}), 3.08 (t, *J* = 7.4 Hz, 2H, $CH_{2\text{-}CH2}$), 3.45 (dq, *J* = 27.1, 5.3 Hz, 2H, $CH_{2\text{-}OH}$), 3.54 (q, *J* = 7.0 Hz, 2H, $CH_{2\text{-}NH}$), 3.68 (tt, *J* = 8.0, 3.9 Hz, 1H, $H_{C\text{-}NH}$), 4.62 (t, *J* = 5.4 Hz, 1H, OH), 5.64 (s, 1H, H_{Ar}), 6.31 (d, *J* = 8.0 Hz, 1H, $NH_{\text{-}CH}$), 7.17 – 7.27 (m, 2H, $NH_{\text{-}CH2}$ & H_{Ar}), 7.33 (d, *J* = 7.7 Hz, 1H, H_{Ar}), 7.72 (td, *J* = 7.6, 1.8 Hz, 1H, H_{Ar}), 8.51 (dd, *J* = 5.1, 1.8 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.3

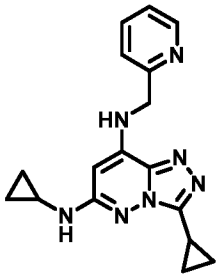
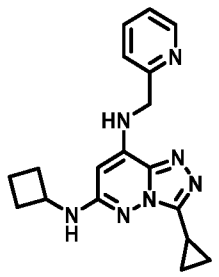
			(CH_{cPr}), 6.5 ($CH_{2\ cPr}$), 6.6 ($CH_{2\ cPr}$), 10.5 ($CH_{3\text{-}CH2}$), 23.7 ($CH_{2\text{-}CH3}$), 35.9 ($CH_{2\text{-}CH2}$), 41.8 ($CH_{2\text{-}CH2}$), 53.6 ($CH_{\text{-}NH}$), 62.2 ($CH_{2\text{-}OH}$), 83.8 (CH_{Ar}), 121.6 (CH_{Ar}), 123.3 (CH_{Ar}), 136.5 (CH_{Ar}), 139.5 (C_q), 139.8 (C_q), 149.1 (CH_{Ar}), 149.9 (C_q), 156.3 (C_q), 158.9 (C_q).
(186)		-	Light yellow solid. **Rf** (DCM/MeOH, 94/6) : 0.36 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.96 – 1.14 (m, 4H, 2x$CH_{2\ cPr}$), 2.25 (tt, *J* = 8.3, 5.1 Hz, 1H, H_{cPr}), 4.34 (d, *J* = 5.7 Hz, 2H, $CH_{2\text{-}Ph}$), 4.52 (d, *J* = 6.1 Hz, 2H, $CH_{2\text{-}Pyr}$), 5.45 (s, 1H, H_{Ar}), 7.12 (t, *J* = 5.8 Hz, 1H, $NH_{\text{-}CH2\text{-}Ph}$), 7.18 – 7.24 (m, 1H, H_{Ar}), 7.26 – 7.36 (m, 6H, 6xH_{Ar}), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.85 (t, *J* = 6.2 Hz, 1H, $NH_{\text{-}CH2\text{-}Pyr}$), 8.54 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.3 (CH_{cPr}), 6.5 (2x$CH_{2\ cPr}$), 44.5 ($CH_{2\text{-}Ph}$), 47.2 ($CH_{2\text{-}Pyr}$), 84.3 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 126.7 (CH_{Ar}), 127.7 (2xCH_{Ar}), 128.1 (2xCH_{Ar}), 136.9 (CH_{Ar}), 139.5 (C_q), 139.7 (C_q), 140.0 (C_q), 149.0 (CH_{Ar}), 150.1 (C_q), 155.9 (C_q), 157.5 (C_q).
(187)		-	White solid. **Rf** (DCM/MeOH, 95/5) : 0.46 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.01 – 1.12 (m, 4H, 2x$CH_{2\ cPr}$), 2.27 (td, *J* = 8.3, 4.1 Hz, 1H, H_{cPr}), 3.71 (s, 3H, OCH_3), 4.26 (d, *J* = 5.6 Hz, 2H, $CH_{2\ PMB}$), 4.51 (d, *J* = 6.0 Hz, 2H, $CH_{2\ Bn}$), 5.43 (s, 1H, H_{Ar}), 6.85 (d, *J* = 8.3 Hz, 2H, 2xH_{Ar}), 7.03 (t, *J* = 5.7 Hz, 1H, NH_{PMB}), 7.27 (t, *J* = 8.4 Hz, 3H, 3xH_{Ar}), 7.31 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.75 (td, *J* = 7.6, 1.8 Hz, 1H, H_{Ar}), 7.84 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 8.54 (dd, *J* = 5.1, 1.6 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.3 (CH_{cPr}), 6.6 (2x$CH_{2\ cPr}$), 43.9 ($CH_{2\ PMB}$), 47.2 ($CH_{2\ Bn}$), 55.0 (OCH_3), 84.4 (CH_{Ar}), 113.5 (2xCH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 129.1 (2xCH_{Ar}), 131.6 (C_q), 136.9 (CH_{Ar}), 139.5 (C_q), 139.9 (C_q), 149.0 (CH_{Ar}), 150.1 (C_q), 155.8 (C_q), 157.5 (C_q), 158.2 (C_q).

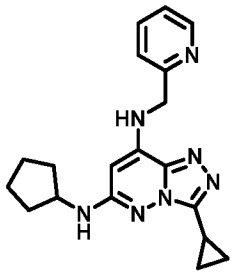
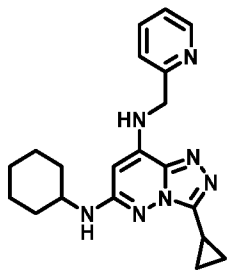
(188)		> 97 % [b]	White solid. **Rf** (DCM/MeOH, 95/5) : 0.36 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.00 – 1.15 (m, 4H, 2x$CH_{2\ cPr}$), 2.29 (tt, *J* = 8.4, 5.1 Hz, 1H, H_{cPr}), 2.94 (s, 3H, $CH_{3\text{-}N}$), 3.71 (s, 3H, OCH_3), 4.52 (s, 2H, $CH_{2\ PMB}$), 4.60 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.75 (s, 1H, H_{Ar}), 6.76 – 6.86 (m, 2H, 2xH_{Ar}), 7.04 – 7.13 (m, 2H, 2xH_{Ar}), 7.26 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H, H_{Ar}), 7.31 (dt, *J* = 7.9, 1.1 Hz, 1H, H_{Ar}), 7.73 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.98 (t, *J* = 6.1 Hz, 1H, NH_{Bn}), 8.49 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.6 (2x$CH_{2\ cPr}$), 36.3 ($CH_{3\text{-}N}$), 47.2 ($CH_{2\ Bn}$), 52.7 ($CH_{2\ PMB}$), 55.0 (OCH_3), 82.5 (CH_{Ar}), 113.8 (2xCH_{Ar}), 121.3 (CH_{Ar}), 122.3 (CH_{Ar}), 128.6 (2xCH_{Ar}), 130.0 (C_q), 136.9 (CH_{Ar}), 138.9 (C_q), 140.5 (C_q), 148.9 (CH_{Ar}), 150.1 (C_q), 156.6 (C_q), 157.5 (C_q), 158.3 (C_q). **MS (ESI+) : m/z calcd for $C_{23}H_{25}N_7O$:** 416.22 [M+H]+, **found :** 416.51.
(189)		> 96 % [b]	White solid. **Rf** (DCM/MeOH, 94/6) : 0.15 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.00 – 1.16 (m, 7H, $CH_{3\text{-}CH2}$ & 2x$CH_{2\ cPr}$), 2.26 (tt, *J* = 8.4, 5.1 Hz, 1H, H_{cPr}), 3.11 – 3.21 (m, 2H, $CH_{2\text{-}CH3}$), 4.51 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.34 (s, 1H, H_{Ar}), 6.55 (t, *J* = 5.2 Hz, 1H, NH_{Et}), 7.26 – 7.30 (m, 1H, H_{Ar}), 7.32 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.76 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.81 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 8.50 – 8.61 (m, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.6 (2x$CH_{2\ cPr}$), 14.2 ($CH_{3\text{-}CH2}$), 35.5 ($CH_{2\text{-}CH3}$), 47.2 ($CH_{2\ Bn}$), 84.4 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.5 (C_q), 139.8 (C_q), 149.0 (CH_{Ar}), 150.1 (C_q), 156.0 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{16}H_{19}N_7$:** 310.18 [M+H]+, **found :** 310.32.

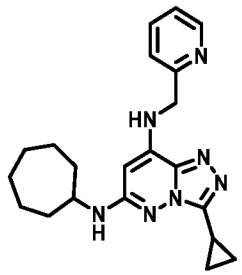
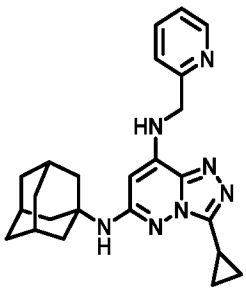
(190)		> 97 % [b]	Light yellow solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.88 (t, J = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.01 – 1.14 (m, 4H, 2x$CH_{2\ cPr}$), 1.51 (h, J = 7.3 Hz, 2H, $CH_{2\text{-}CH3}$), 2.26 (td, J = 8.5, 4.3 Hz, 1H, H_{cPr}), 3.09 (q, J = 6.5 Hz, 2H, $CH_{2\text{-}NH}$), 4.52 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.56 (t, J = 5.3 Hz, 1H, $NH_{\text{-}CH2\text{-}CH2}$), 7.28 (dd, J = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.32 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.76 (td, J = 7.7, 1.9 Hz, 1H, H_{Ar}), 7.80 (t, J = 6.1 Hz, 1H, NH_{Bn}), 8.55 (d, J = 4.8 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.6 (2x$CH_{2\ cPr}$), 11.7 ($CH_{3\text{-}CH2}$), 21.7 ($CH_{2\text{-}CH3}$), 42.7 ($CH_{2\text{-}NH}$), 47.2 ($CH_{2\ Bn}$), 84.4 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.5 (C_q), 139.8 (C_q), 149.0 (CH_{Ar}), 150.1 (C_q), 156.2 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{21}N_7$:** 324.19 [M+H]+, **found :** 324.39.
(191)		> 97 % [b]	White solid. **Rf** (DCM/MeOH, 95/5) : 0.46 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.83 – 0.92 (m, 3H, $CH_{3\text{-}CH2}$), 0.99 – 1.16 (m, 4H, 2x$CH_{2\ cPr}$), 1.32 (h, J = 7.3 Hz, 2H, $CH_{2\text{-}CH3}$), 1.48 (p, J = 7.1 Hz, 2H, $CH_{2\text{-}CH2\text{-}CH3}$), 2.26 (tt, J = 9.0, 5.1 Hz, 1H, H_{cPr}), 3.06 – 3.22 (m, 2H, , $CH_{2\text{-}NH\ nBut}$), 4.51 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.53 (t, J = 5.3 Hz, 1H, NH_{nBu}), 7.26 – 7.30 (m, 1H, H_{Ar}), 7.31 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.76 (tt, J = 7.7, 1.6 Hz, 1H, H_{Ar}), 7.80 (t, J = 6.2 Hz, 1H, NH_{Bn}), 8.54 (dd, J = 4.8, 1.4 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.6 (2x$CH_{2\ cPr}$), 13.7 ($CH_{3\text{-}CH2}$), 19.8 ($CH_{2\text{-}CH3}$), 30.6 ($CH_{2\text{-}CH2\text{-}CH3}$), 40.4 ($CH_{2\text{-}NH\ nBut}$), 47.2 ($CH_{2\ Bn}$), 84.4 ($CH_{Ar}$), 120.7 ($CH_{Ar}$), 122.3 ($CH_{Ar}$), 136.9 ($CH_{Ar}$), 139.5 ($C_q$), 139.7 ($C_q$), 149.0 ($CH_{Ar}$), 150.1 ($C_q$), 156.2 ($C_q$), 157.6 ($C_q$). **MS (ESI+) : m/z calcd for $C_{18}H_{23}N_7$:** 338.21 [M+H]+, **found :** 338.37.

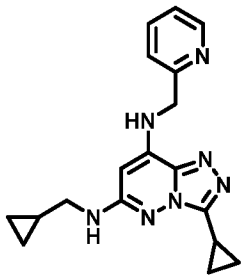
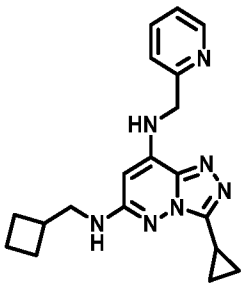
(192)		92 % [b]	White solid. **Rf** (DCM/MeOH, 95/5) : 0.24 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.00 – 1.18 (m, 10H, 2x$CH_{3\ iPr}$ & 2x$CH_{2\ cPr}$), 2.26 (tt, *J* = 8.8, 5.0 Hz, 1H, H_{cPr}), 3.83 (h, *J* = 6.5 Hz, 1H, H_{iPr}), 4.51 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.34 (s, 1H, H_{Ar}), 6.43 (d, *J* = 7.2 Hz, 1H, NH_{iPr}), 7.28 (dd, *J* = 7.4, 4.9 Hz, 1H, H_{Ar}), 7.32 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.73 – 7.78 (m, 1H, H_{Ar}), 7.79 (t, *J* = 5.3 Hz, 1H, NH_{Bn}), 8.55 (dd, *J* = 4.9, 1.6 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.4 (2x$CH_{2\ cPr}$), 22.3 (2x$CH_{3\ iPr}$), 41.9 (CH_{iPr}), 47.2 ($CH_{2\ Bn}$), 84.6 (CH_{Ar}), 120.6 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.5 (C_q), 139.8 (C_q), 149.0 (CH_{Ar}), 150.0 (C_q), 155.4 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{21}N_7$:** 324.19 [M+H]+, **found :** 324.37
(193)		> 97 % [b]	White solid. **Rf** (DCM/MeOH, 94/6) : 0.33 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.85 (t, *J* = 7.5 Hz, 3H, $CH_{3\text{-}CH2}$), 0.99 – 1.06 (m, 2H, $CH_{2\ cPr}$), 1.08 (d, *J* = 6.5 Hz, 3H, $CH_{3\text{-}CH}$), 1.13 (tt, *J* = 5.5, 3.0 Hz, 2H, $CH_{2\ cPr}$), 1.36 – 1.57 (m, 2H, $CH_{2\text{-}CH3}$), 2.25 (tt, *J* = 8.4, 5.1 Hz, 1H, H_{cPr}), 3.66 (hept, *J* = 6.2 Hz, 1H, $H_{C\text{-}CH3}$), 4.51 (d, *J* = 6.2 Hz, 2H, H_2, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.39 (d, *J* = 7.6 Hz, 1H, $NH_{\text{-}CH2\text{-}CH}$), 7.28 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H, H_{Ar}), 7.32 (dt, *J* = 7.8, 1.1 Hz, 1H, H_{Ar}), 7.73 – 7.80 (m, 2H, NH_{Bn} & H_{Ar}), 8.55 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.4 (CH_{cPr}), 6.4 (2x$CH_{2\ cPr}$), 10.4 ($CH_{3\text{-}CH2}$), 19.7 ($CH_{3\text{-}CH}$), 28.6 ($CH_{2\text{-}CH3}$), 47.2 ($CH_{2\ Bn}$), 47.3 ($CH_{\text{-}CH3}$), 84.6 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.5 (C_q), 139.8 (C_q), 149.0 (CH_{Ar}), 149.9 (C_q), 155.6 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{23}N_7$:** 338.21 [M+H]+, **found :** 338.41

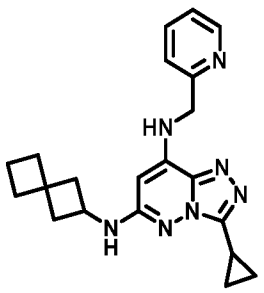
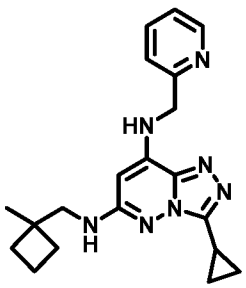
(194)		> 96 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.88 (d, J = 6.7 Hz, 6H, 2x$CH_{3\ iBut}$), 0.98 – 1.17 (m, 4H, 2x$CH_{2\ cPr}$), 1.82 (hept, J = 6.7 Hz, 1H, H_{iBut}), 2.26 (tt, J = 8.4, 5.1 Hz, 1H, H_{cPr}), 2.96 (dd, J = 6.8, 5.5 Hz, 2H, $CH_{2\text{-}CH}$), 4.52 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.42 (s, 1H, H_{Ar}), 6.57 (t, J = 5.5 Hz, 1H, NH_{iBut}), 7.28 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H, H_{Ar}), 7.32 (dt, J = 8.0, 1.1 Hz, 1H, H_{Ar}), 7.76 (td, J = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.79 (t, J = 6.2 Hz, 1H, NH_{Bn}), 8.55 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.6 (2x$CH_{2\ cPr}$), 20.4 (2x$CH_{3\ iBut}$), 27.4 (CH_{iBut}), 47.2 ($CH_{2\ Bn}$), 48.6 ($CH_{2\ iBut}$), 84.4 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.5 (C_q), 139.7 (C_q), 149.0 (CH_{Ar}), 150.1 (C_q), 156.3 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{23}N_7$:** 338.21 [M+H]+, **found :** 338.38
(195)		93 % [b]	Light brown solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.98 – 1.16 (m, 4H, 2x$CH_{2\ cPr}$), 1.35 (s, 9H, 3x$CH_{3\ tBu}$), 2.27 (tt, J = 8.4, 5.1 Hz, 1H, H_{cPr}), 4.49 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.41 (s, 1H, NH_{tBu}), 6.24 (s, 1H, H_{Ar}), 7.24 – 7.35 (m, 2H, 2xH_{Ar}), 7.71 (t, J = 6.2 Hz, 1H, NH_{Bn}), 7.76 (td, J = 7.7, 1.8 Hz, 1H, H_{Ar}), 8.52 – 8.58 (m, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.5 (CH_{cPr}), 6.2 (2x$CH_{2\ cPr}$), 28.6 (3x$CH_{3\ tBu}$), 47.1 ($CH_{2\ Bn}$), 50.6 (C_q), 85.5 (CH_{Ar}), 120.5 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.1 (C_q), 139.6 (C_q), 149.1 (CH_{Ar}), 149.9 (C_q), 155.4 (C_q), 157.7 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{23}N_7$:** 338.21 [M+H]+, **found :** 338.37.
(196)		> 99 % [b]	White solid. **Rf** (DCM/MeOH, 94/6) : 0.20 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.85 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 0.99 – 1.15 (m, 4H, 2x$CH_{2\ cPr}$), 1.21 – 1.37 (m, 4H, 2x$CH_{2\text{-}CH3}$), 1.44 (hept, J = 6.3 Hz, 1H, $H_{C\text{-}CH2\text{-}NH}$), 2.25 (tt, J = 8.4, 5.1 Hz, 1H, H_{cPr}), 3.07 (t, J = 5.9 Hz, 2H, $CH_{2\text{-}NH}$), 4.52 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.43 (s, 1H, H_{Ar}),

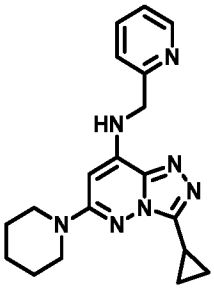
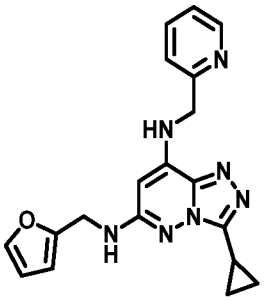
			6.52 (t, J = 5.6 Hz, 1H, $NH_{-CH2-CH}$), 7.28 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H, H_{Ar}), 7.32 (dt, J = 7.9, 1.1 Hz, 1H, H_{Ar}), 7.75 (dd, J = 7.7, 1.9 Hz, 1H, H_{Ar}), 7.76 – 7.81 (m, 1H, NH_{Bn}), 8.55 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.5 ($2xCH_{2\ cPr}$), 10.9 ($2xCH_{3-CH2}$), 23.5 ($2xCH_{2-CH3}$), 39.9 ($CH_{-CH2-NH}$), 43.3 (CH_{2-NH}), 47.2 ($CH_{2\ Bn}$), 84.5 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.5 (C_q), 139.7 (C_q), 149.0 (CH_{Ar}), 150.0 (C_q), 156.4 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{27}N_7$:** 366.24 [M+H]+, **found :** 366.39.
(197)		88 % [b] (unstable)	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.27 – 0.42 (m, 2H, $CH_{2\ cPr}$), 0.61 (td, J = 6.8, 4.6 Hz, 2H, $CH_{2\ cPr}$), 1.00 – 1.17 (m, 4H, $2xCH_{2\ cPr}$), 2.28 (tt, J = 8.4, 5.1 Hz, 1H, H_{cPr}), 2.52 – 2.52 (m, 1H, $H_{cPr\ (DEPT135\ observed)}$), 4.52 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.38 (s, 1H, H_{Ar}), 6.83 (d, J = 2.9 Hz, 1H, NH_{cPr}), 7.28 (dd, J = 7.5, 5.0 Hz, 1H, H_{Ar}), 7.32 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.76 (td, J = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.90 (t, J = 6.2 Hz, 1H, NH_{Bn}), 8.49 – 8.61 (m, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.5 ($2xCH_{2\ cPr}$), 6.7 ($2xCH_{2\ cPr}$), 23.5 (CH_{cPr-N}), 47.3 ($CH_{2\ Bn}$), 83.9 (CH_{Ar}), 120.8 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.6 (C_q), 139.9 (C_q), 149.0 (CH_{Ar}), 150.1 (C_q), 157.2 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{19}N_7$:** 322.18 [M+H]+, **found :** 322.32.
(198)		> 97 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.00 – 1.16 (m, 4H, $2xCH_{2\ cPr}$), 1.65 (tdd, J = 11.1, 7.7, 5.8 Hz, 2H, $CH_{2\ cBut}$), 1.82 (dddd, J = 12.0, 9.4, 7.2, 5.3 Hz, 2H, $CH_{2\ cBut}$), 2.19 – 2.31 (m, 3H, $CH_{2\ cBut}$ &H_{cPr}), 4.11 (hept, J = 7.3 Hz, 1H, H_{cBut}), 4.51 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.30 (s, 1H, H_{Ar}), 6.85 (d, J = 6.8 Hz, 1H, NH_{cBut}), 7.28 (ddd, J = 7.5, 4.9, 1.3 Hz, 1H, H_{Ar}), 7.30 – 7.33 (m, 1H, H_{Ar}), 7.76 (td, J = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.84 (t, J = 6.2 Hz, 1H, NH_{Bn}), 8.55 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H, H_{Ar}).

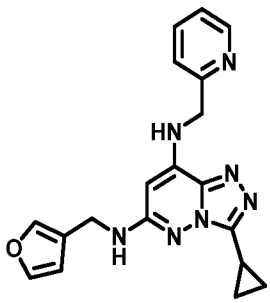
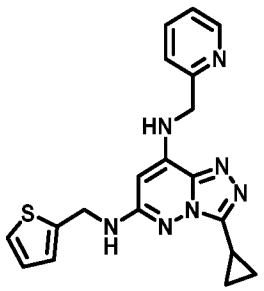
			^{13}C NMR (101 MHz, DMSO-d_6) δ : 5.3 (CH_{cPr}), 6.5 ($2xCH_{2\ cPr}$), 14.9 ($CH_{2\ cBut}$), 30.3 ($2xCH_{2\ cBut}$), 46.1 (CH_{cBut}), 47.2 ($CH_{2\ Bn}$), 84.1 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.5 (C_q), 140.0 (C_q), 149.0 (CH_{Ar}), 150.0 (C_q), 155.1 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{21}N_7$:** 336.19 [M+H]+, **found :** 336.33
(199)		> 96 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.09 (ddt, J = 41.4, 8.6, 3.6 Hz, 4H, $2xCH_{2\ cPr}$), 1.41 (tt, J = 13.6, 6.0 Hz, 2H, $CH_{2\ cPent}$), 1.51 (dtd, J = 11.6, 7.2, 3.0 Hz, 2H, $CH_{2\ cPent}$), 1.56 – 1.67 (m, 2H, $CH_{2\ cPent}$), 1.90 (dq, J = 12.5, 6.4 Hz, 2H, $CH_{2\ cPent}$), 2.27 (tt, J = 8.4, 5.1 Hz, 1H, H_{cPr}), 3.94 (h, J = 6.5 Hz, 1H, H_{cPent}), 4.51 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.35 (s, 1H, H_{Ar}), 6.58 (d, J = 6.3 Hz, 1H, NH_{cPent}), 7.28 (dd, J = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.31 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.76 (td, J = 7.6, 1.8 Hz, 1H, H_{Ar}), 7.79 (t, J = 6.6 Hz, 1H, NH_{Bn}), 8.54 (d, J = 4.5 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.4 (CH_{cPr}), 6.4 ($2xCH_{2\ cPr}$), 23.5 ($2xCH_{2\ cPent}$), 32.3 ($2xCH_{2\ cPent}$), 47.2 ($CH_{2\ Bn}$), 52.2 (CH_{cPent}), 84.5 (CH_{Ar}), 120.6 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.5 (C_q), 139.7 (C_q), 149.0 (CH_{Ar}), 150.0 (C_q), 155.8 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{23}N_7$:** 350.21 [M+H]+, **found :** 350.37.
(200)		> 98 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.98 – 1.06 (m, 2H, $CH_{2\ cPr}$), 1.07 – 1.21 (m, 5H, $CH_{2\ cPr}$ &$CH_{2\ cHex}$ & $H_{(CH2\ cHex)}$), 1.21 – 1.35 (m, 2H, $CH_{2\ cHex}$), 1.55 (dd, J = 12.3, 4.7 Hz, 1H, $H_{(CH2\ cHex)}$), 1.68 (dt, J = 12.1, 4.3 Hz, 2H, $CH_{2\ cHex}$), 1.90 (dd, J = 12.5, 3.7 Hz, 2H, $CH_{2\ cHex}$), 2.25 (tt, J = 8.5, 5.1 Hz, 1H, H_{cPr}), 3.45 – 3.64 (m, 1H, H_{cHex}), 4.51 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.43 (d, J = 7.3 Hz, 1H, NH_{cHex}), 7.28 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H, H_{Ar}), 7.31 (dd, J = 7.9, 1.1 Hz, 1H, H_{Ar}), 7.67 – 7.86 (m, 2H, NH_{Bn} & H_{Ar}), 8.55 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H, H_{Ar}).

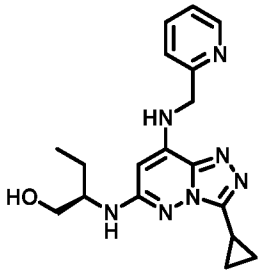
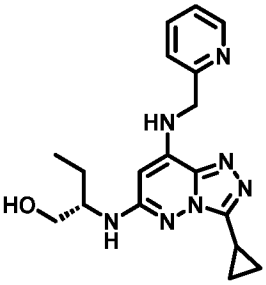
			^{13}C NMR (101 MHz, DMSO-d_6) δ : 5.3 (CH_{cPr}), 6.5 ($2xCH_{2\ cPr}$), 24.5 ($2xCH_{2\ cHex}$), 25.5 ($CH_{2\ cHex}$), 32.2 ($2xCH_{2\ cHex}$), 47.2 ($CH_{2\ Bn}$), 49.1 (CH_{cHex}), 84.5 (CH_{Ar}), 120.6 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.5 (C_q), 139.8 (C_q), 149.0 (CH_{Ar}), 149.9 (C_q), 155.3 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{25}N_7$:** 364.22 [M+H]+, **found :** 364.34
(201)		> 97 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.99 – 1.20 (m, 4H, $2xCH_{2\ cPr}$), 1.38 – 1.63 (m, 10H, $5xCH_{2\ cHept}$), 1.86 (ddd, J = 9.9, 6.5, 4.3 Hz, 2H, $CH_{2\ cHept}$), 2.25 (tt, J = 8.5, 5.1 Hz, 1H, H_{cPr}), 3.71 (q, J = 7.0, 5.5 Hz, 1H, H_{cHept}), 4.51 (d, J = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.37 (s, 1H, H_{Ar}), 6.48 (d, J = 7.3 Hz, 1H, NH_{cHept}), 7.28 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H, H_{Ar}), 7.30 – 7.34 (m, 1H, H_{Ar}), 7.73 – 7.80 (m, 2H, NH_{Bn} & H_{Ar}), 8.55 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.4 (CH_{cPr}), 6.3 ($2xCH_{2\ cPr}$), 24.0 ($2xCH_{2\ cHept}$), 28.0 ($2xCH_{2\ cHept}$), 33.7 ($2xCH_{2\ cHept}$), 47.2 ($CH_{2\ Bn}$), 51.1 (CH_{cHept}), 84.6 (CH_{Ar}), 120.6 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.5 (C_q), 139.7 (C_q), 149.0 (CH_{Ar}), 149.9 (C_q), 155.1 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{21}H_{27}N_7$:** 378.24 [M+H]+, **found :** 378.38
(202)		93 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.02 – 1.08 (m, 2H, $CH_{2\ cPr}$), 1.17 (dt, J = 5.9, 2.9 Hz, 2H, $CH_{2\ cPr}$), 1.63 (s, 6H, $3xCH_{2\ Ada}$), 2.03 (s, 9H, $3xH_{Ada}$ &$3xCH_{2\ Ada}$), 2.26 (tt, J = 8.5, 5.2 Hz, 1H, H_{cPr}), 4.49 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.42 (s, 1H, H_{Ar}), 6.14 (s, 1H, NH_{Ada}), 7.24 – 7.33 (m, 2H, $2xH_{Ar}$), 7.71 (t, J = 6.2 Hz, 1H, NH_{Bn}), 7.76 (td, J = 7.7, 1.8 Hz, 1H, H_{Ar}), 8.55 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.7 (CH_{cPr}), 6.0 ($2xCH_{2\ cPr}$), 28.9 ($3xCH_{Ada}$), 36.2 ($3xCH_{2\ Ada}$), 40.9 ($3xCH_{2\ Ada}$), 47.1 ($CH_{2\ Bn}$), 51.1 ($C_{q\ Ada}$), 85.5 (CH_{Ar}), 120.5 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.1 (C_q), 139.6 (C_q), 149.0 (CH_{Ar}), 149.7 (C_q), 155.2 (C_q), 157.6 (C_q).

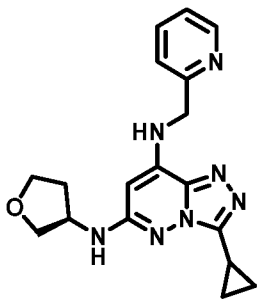
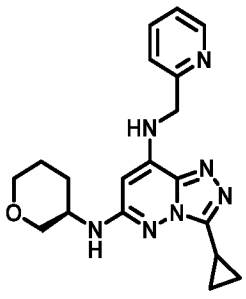
			MS (ESI+) : m/z calcd for $C_{24}H_{29}N_7$: 416.26 [M+H]+, **found :** 416.44.
(203)		> 96 % [b]	White solid. **Rf** (DCM/MeOH, 94/6) : 0.16 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.18 (q, *J* = 5.0 Hz, 2H, $CH_{2\ cPr}$), 0.37 – 0.50 (m, 2H, $CH_{2\ cPr}$), 0.97 – 1.14 (m, 5H, H_{cPr} & 2x$CH_{2\ cPr}$), 2.26 (ddd, *J* = 13.9, 8.5, 5.1 Hz, 1H, H_{cPr}), 3.00 (t, *J* = 6.1 Hz, 2H, $CH_{2\text{-}NH}$), 4.52 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.41 (s, 1H, H_{Ar}), 6.69 (t, *J* = 5.3 Hz, 1H, $NH_{\text{-}CH2}$), 7.28 (dd, *J* = 7.4, 4.9 Hz, 1H, H_{Ar}), 7.32 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.76 (td, *J* = 7.8, 1.8 Hz, 1H, H_{Ar}), 7.81 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 8.55 (d, *J* = 4.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** N.D. **MS (ESI+) : m/z calcd for $C_{18}H_{21}N_7$:** 336.19 [M+H]+, **found :** 336.38
(204)		> 97 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.01 – 1.15 (m, 4H, 2x$CH_{2\ cPr}$), 1.61 – 1.73 (m, 2H, $CH_{2\ But}$), 1.75 – 1.87 (m, 2H, $CH_{2\ cBut}$), 1.94 – 2.06 (m, 2H, $CH_{2\ cBut}$), 2.22 – 2.31 (m, 1H, H_{cPt}), 2.43 – 2.48 (m, 1H, H_{cBut}), 3.17 (dd, *J* = 7.2, 5.3 Hz, 2H, $CH_{2\text{-}CH\ cBut}$), 4.51 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.39 (s, 1H, H_{Ar}), 6.52 (t, *J* = 5.3 Hz, 1H, NH_{cBut}), 7.28 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H, H_{Ar}), 7.31 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.79 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 8.47 – 8.62 (m, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.2 (CH_{cPr}), 6.7 (2x$CH_{2\ cPr}$), 17.9 ($CH_{2\ cBut}$), 25.6 (2x$CH_{2\ cBut}$), 34.3 (CH_{cBut}), 46.3 ($CH_{2\text{-}CH\ cBut}$), 47.2 ($CH_{2\ Bn}$), 84.4 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.5 (C_q), 139.7 (C_q), 149.0 (CH_{Ar}), 150.1 (C_q), 156.3 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{23}N_7$:** 350.21 [M+H]+, **found :** 350.40

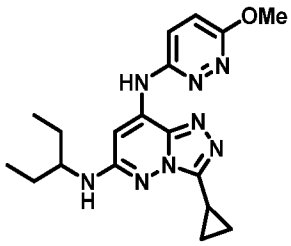
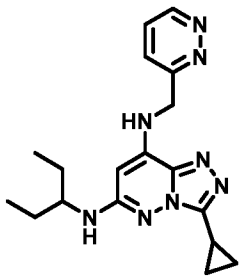
(205)		-	White solid. **Rf** (DCM/MeOH, 94/6) : 0.19 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.00 – 1.16 (m, 4H, 2x$CH_{2\ cPr}$), 1.74 – 1.83 (m, 4H, 2xCH_2), 1.87 (dd, *J* = 8.3, 5.6 Hz, 2H, CH_2), 1.96 – 2.03 (m, 2H, CH_2), 2.26 (tt, *J* = 8.4, 5.1 Hz, 1H, H_{cPr}), 2.35 (ddt, *J* = 12.0, 8.0, 2.2 Hz, 2H, CH_2), 3.93 (h, *J* = 7.8 Hz, 1H, $H_{C\text{-}NH}$), 4.50 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.28 (s, 1H, H_{Ar}), 6.77 (d, *J* = 6.4 Hz, 1H, $NH_{\text{-}CH}$), 7.23 – 7.36 (m, 2H, 2xH_{Ar}), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.83 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 8.54 (dt, *J* = 4.8, 1.5 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.3 (CH_{cPr}), 6.6 (2x$CH_{2\ cPr}$), 16.4 (CH_2), 34.0 (CH_2), 34.8 (CH_2), 37.1 (C_q), 41.4 ($CH_{\text{-}NH}$), 42.6 (2xCH_2), 47.2 ($CH_{2\ Bn}$), 84.2 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.5 (C_q), 139.9 (C_q), 149.0 (CH_{Ar}), 150.0 (C_q), 155.2 (C_q), 157.6 (C_q).
(206)		> 98 % [b]	White solid. **Rf** (DCM/MeOH, 94/6) : 0.29 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.99 – 1.15 (m, 7H, 2x$CH_{2\ cPr}$ & $CH_{3\text{-}Cq}$), 1.61 (ddt, *J* = 12.0, 6.1, 3.2 Hz, 2H, $CH_{2\ cBut}$), 1.75 – 1.92 (m, 4H, 2x$CH_{2\ cBut}$), 2.27 (tt, *J* = 8.4, 5.1 Hz, 1H, H_{cPr}), 3.18 (d, *J* = 5.6 Hz, 2H, $CH_{2\text{-}Cq}$), 4.52 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.52 (s, 1H, H_{Ar}), 6.47 (t, *J* = 5.7 Hz, 1H, $NH_{\text{-}CH2\text{-}Cq}$), 7.28 (ddd, *J* = 7.5, 4.9, 1.3 Hz, 1H, H_{Ar}), 7.31 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.73 – 7.81 (m, 2H, NH_{Bn} & H_{Ar}), 8.55 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.3 (CH_{cPr}), 6.6 (2x$CH_{2\ cPr}$), 14.6 ($CH_{2\ cBut}$), 25.3 ($CH_{3\text{-}Cq}$), 30.8 (2x$CH_{2\ cBut}$), 38.8 ($C_{q\text{-}CH3}$), 47.1 ($CH_{2\ Bn}$), 50.0 ($CH_{2\text{-}Cq}$), 84.5 (CH_{Ar}), 120.6 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.6 (C_q), 139.7 (C_q), 149.0 (CH_{Ar}), 150.1 (C_q), 156.8 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{25}N_7$:** 364.22 [M+H]+, **found :** 364.41.

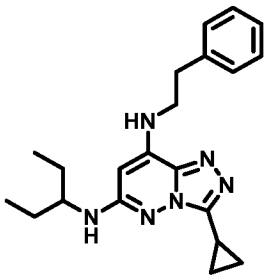
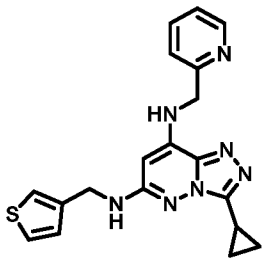
(207)		> 99 % [b]	Light grey solid. **Rf** (DCM/MeOH, 94/6) : 0.38 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.99 – 1.16 (m, 4H, 2x$CH_{2\ cPr}$), 1.46 – 1.59 (m, 6H, 3x$CH_{2\ pip}$), 2.28 (dq, *J* = 9.0, 5.2, 4.2 Hz, 1H, H_{cPr}), 3.36 – 3.39 (m, 4H, 2x$CH_{2\ pip}$), 4.64 (d, *J* = 6.0 Hz, 2H, $CH_{2\ Bn}$), 5.84 (s, 1H, H_{Ar}), 7.25 – 7.34 (m, 1H, H_{Ar}), 7.36 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.77 (t, *J* = 7.7 Hz, 1H, H_{Ar}), 7.90 (t, *J* = 5.9 Hz, 1H, NH_{Bn}), 8.54 (d, *J* = 4.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.3 (CH_{cPr}), 6.6 (2x$CH_{2\ cPr}$), 24.1 ($CH_{2\ pip}$), 24.9 (2x$CH_{2\ pip}$), 46.7 (2x$CH_{2\ pip}$), 47.1 ($CH_{2\ Bn}$), 83.3 (CH_{Ar}), 121.4 (CH_{Ar}), 122.4 (CH_{Ar}), 137.0 (CH_{Ar}), 139.1 (C_q), 140.6 (C_q), 148.9 (CH_{Ar}), 150.3 (C_q), 157.4 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{23}N_7$:** 350.21 [M+H]+, **found :** 350.40
(208)		> 96 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.01 – 1.15 (m, 4H, 2x$CH_{2\ cPr}$), 2.26 – 2.33 (m, 1H, H_{cPr}), 4.33 (d, *J* = 5.5 Hz, 2H, $CH_{2\ Bn}$), 4.52 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.43 (s, 1H, H_{Ar}), 6.28 (dd, *J* = 3.2, 0.9 Hz, 1H, H_{Ar}), 6.37 (dd, *J* = 3.2, 1.9 Hz, 1H, H_{Ar}), 7.04 (t, *J* = 5.6 Hz, 1H, NH), 7.28 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H, H_{Ar}), 7.31 (dt, *J* = 7.9, 1.1 Hz, 1H, H_{Ar}), 7.55 (dd, *J* = 1.9, 0.9 Hz, 1H, H_{Ar}), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.88 (t, *J* = 6.2 Hz, 1H, NH), 8.54 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.3 (CH_{cPr}), 6.6 (2xCH_{cPr}), 37.5 ($CH_{2\ Bn}$), 47.2 ($CH_{2\ Bn}$), 84.2 (CH_{Ar}), 107.1 (CH_{Ar}), 110.4 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.5 (C_q), 140.1 (C_q), 141.9 (CH_{Ar}), 149.0 (CH_{Ar}), 150.2 (C_q), 152.5 (C_q), 155.6 (C_q), 157.5 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{19}N_7O$:** 362.42 [M+H]+, **found :** 362.33.

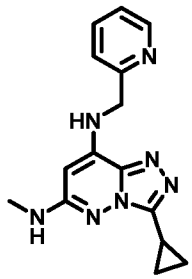
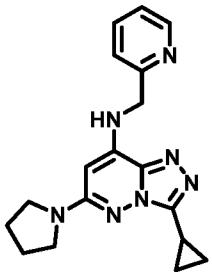
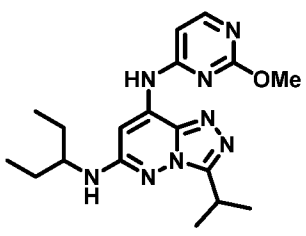
(209)		> 95 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.95 – 1.20 (m, 4H, 2x$CH_{2\ cPr}$), 2.30 (tt, *J* = 8.3, 5.2 Hz, 1H, H_{cPr}), 4.17 (d, *J* = 5.4 Hz, 2H, $CH_{2\ Fur}$), 4.52 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.43 (s, 1H, H_{Ar}), 6.48 (dd, *J* = 1.9, 0.9 Hz, 1H, H_{Ar}), 6.86 (t, *J* = 5.5 Hz, 1H, $NH_{\text{-}CH2\ Fur}$), 7.27 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, H_{Ar}), 7.31 (dd, *J* = 7.9, 1.1 Hz, 1H, H_{Ar}), 7.57 (t, *J* = 1.7 Hz, 1H, H_{Ar}), 7.59 (dd, *J* = 1.7, 0.9 Hz, 1H, H_{Ar}), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.86 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 8.54 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.2 (CH_{cPr}), 6.7 (2x$CH_{2\ cPr}$), 35.5 ($CH_{2\ Fur}$), 47.2 ($CH_{2\ Bn}$), 84.4 (CH_{Ar}), 111.0 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 122.9 (C_q), 136.9 (CH_{Ar}), 139.6 (C_q), 140.0 (C_q), 140.2 (CH_{Ar}), 143.1 (CH_{Ar}), 149.0 (CH_{Ar}), 150.2 (C_q), 155.9 (C_q), 157.5 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{19}N_7O$:** 362.17 [M+H]+, **found :** 362.31.
(210)		> 98 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.00 – 1.17 (m, 4H, 2x$CH_{2\ cPr}$), 2.29 – 2.37 (m, 1H, H_{cPr}), 4.52 (d, *J* = 5.3 Hz, 4H, 2x$CH_{2\text{-}NH}$), 5.40 (s, 1H, H_{Ar}), 6.93 (dd, *J* = 5.1, 3.4 Hz, 1H, H_{Ar}), 7.02 (dd, *J* = 3.4, 1.2 Hz, 1H, H_{Ar}), 7.17 (t, *J* = 5.9 Hz, 1H, NH_{Bn}), 7.27 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, H_{Ar}), 7.32 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.34 (dd, *J* = 5.1, 1.3 Hz, 1H, H_{Ar}), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.90 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 8.54 (dt, *J* = 4.7, 1.6 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.3 (CH_{cPr}), 6.7 (2x$CH_{2\ cPr}$), 39.2 ($CH_{2\text{-}NH}$), 47.2 ($CH_{2\text{-}NH}$), 84.2 (CH_{Ar}), 120.8 (CH_{Ar}), 122.3 (CH_{Ar}), 125.0 (CH_{Ar}), 125.8 (CH_{Ar}), 126.4 (CH_{Ar}), 136.9 (CH_{Ar}), 139.5 (C_q), 140.1 (C_q), 142.6 (C_q), 149.0 (CH_{Ar}), 150.3 (C_q), 155.5 (C_q), 157.5 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{19}N_7S$:** 378.15 [M+H]+, **found :** 378.28.

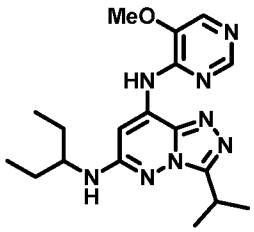
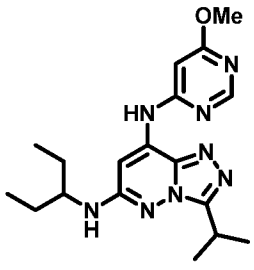
(211)		> 99 % [b]	Light yellow solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.85 (t, J = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.01 – 1.15 (m, 4H, 2x$CH_{2\ cPr}$), 1.32 – 1.69 (m, 2H, $CH_{2\text{-}CH3}$), 2.25 (tt, J = 8.5, 5.1 Hz, 1H, H_{cPr}), 3.33 – 3.47 (m, 2H, $CH_{2\text{-}OH}$), 3.63 (dtt, J = 10.6, 7.6, 3.8 Hz, 1H, $H_{c\text{-}NH}$), 4.51 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 4.56 (t, J = 5.5 Hz, 1H, OH), 5.45 (s, 1H, H_{Ar}), 6.33 (d, J = 7.9 Hz, 1H, $NH_{\text{-}CH}$), 7.28 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H, H_{Ar}), 7.32 (dt, J = 7.9, 1.1 Hz, 1H, H_{Ar}), 7.74 – 7.80 (m, 2H, NH_{Bn} & H_{Ar}), 8.55 (ddd, J = 4.8, 1.9, 0.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.5 ($CH_{2\ cPr}$), 6.5 ($CH_{2\ cPr}$), 10.5 ($CH_{3\text{-}CH2}$), 23.6 ($CH_{2\text{-}CH3}$), 47.2 ($CH_{2\ Bn}$), 53.7 ($CH_{\text{-}NH}$), 62.1 ($CH_{2\text{-}OH}$), 84.6 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.5 (C_q), 139.8 (C_q), 149.0 (CH_{Ar}), 150.0 (C_q), 156.1 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{23}N_7O$:** 354.20 [M+H]+, **found :** 354.36.
(212)		> 98 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.85 (t, J = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.00 – 1.15 (m, 4H, 2x$CH_{2\ cPr}$), 1.33 – 1.69 (m, 2H, $CH_{2\text{-}CH3}$), 2.25 (tt, J = 8.4, 5.1 Hz, 1H, H_{cPr}), 3.33 – 3.48 (m, 2H, $CH_{2\text{-}CH3}$), 3.64 (tq, J = 7.5, 5.3 Hz, 1H, $H_{C\text{-}NH}$), 4.51 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 4.56 (t, J = 5.4 Hz, 1H, OH), 5.45 (s, 1H, H_{Ar}), 6.32 (d, J = 7.9 Hz, 1H, $NH_{\text{-}CH}$), 7.28 (ddd, J = 7.7, 4.8, 1.1 Hz, 1H, H_{Ar}), 7.32 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.73 – 7.81 (m, 2H, NH_{Bn} & H_{Ar}), 8.55 (dt, J = 4.7, 1.4 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.5 ($CH_{2\ cPr}$), 6.5 ($CH_{2\ cPr}$), 10.5 ($CH_{3\text{-}CH2}$), 23.6 ($CH_{2\text{-}CH3}$), 47.2 ($CH_{2\ Bn}$), 53.7 ($CH_{\text{-}NH}$), 62.1 ($CH_{2\text{-}OH}$), 84.6 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.5 (C_q), 139.8 (C_q), 149.0 (CH_{Ar}), 150.0 (C_q), 156.1 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{23}N_7O$:** 354.20 [M+H]+, **found :** 354.36.

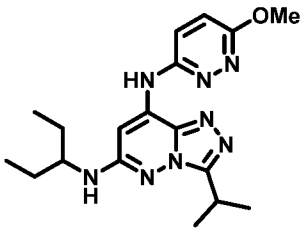
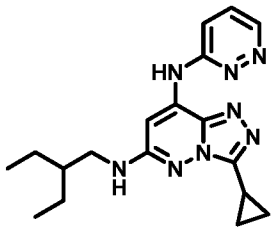
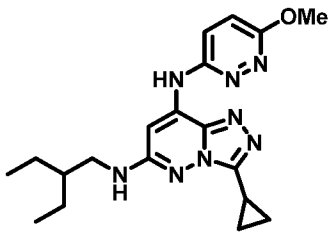
(213)		> 98 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.01 – 1.18 (m, 4H, 2x$CH_{2\ cPr}$), 1.71 – 1.82 (m, 1H, $H_{(CH2)}$), 2.13 (dq, *J* = 12.6, 7.6 Hz, 1H, $H_{(CH2)}$), 2.28 (tt, *J* = 8.5, 5.1 Hz, 1H, H_{cPr}), 3.50 (dd, *J* = 8.9, 4.0 Hz, 1H, $H_{(CH2)}$), 3.62 – 3.81 (m, 2H, CH_2), 3.86 (dd, *J* = 8.9, 5.9 Hz, 1H, $H_{(CH2)}$), 4.17 (dtt, *J* = 8.1, 5.8, 4.2 Hz, 1H, $H_{C\text{-}NH}$), 4.51 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.36 (s, 1H, H_{Ar}), 6.85 (d, *J* = 5.6 Hz, 1H, NH_{THF}), 7.28 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, H_{Ar}), 7.31 (dd, *J* = 7.8, 1.1 Hz, 1H, H_{Ar}), 7.76 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.88 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 8.55 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.3 (CH_{cPr}), 6.4 ($CH_{2\ cPr}$), 6.5 ($CH_{2\ cPr}$), 32.1 ($CH_{2\ THF}$), 47.2 ($CH_{2\ Bn}$), 51.4 (CH_{THF}), 66.3 ($CH_{2\ THF}$), 72.7 ($CH_{2\ THF}$), 84.2 (CH_{Ar}), 120.7 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.5 (C_q), 140.0 (C_q), 149.0 (CH_{Ar}), 150.1 (C_q), 155.7 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{21}N_7O$:** 352.19 [M+H]+, **found :** 352.82.
(214)		> 97 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 1.01 – 1.15 (m, 4H, 2x$CH_{2\ cPr}$), 1.37 – 1.59 (m, 2H, 2x$H_{(CH2)\ THP}$), 1.68 (dd, *J* = 13.5, 4.8 Hz, 1H, $H_{(CH2)\ THP}$), 1.91 (dd, *J* = 10.5, 5.8 Hz, 1H, $H_{(CH2)\ THP}$), 2.25 (tt, *J* = 8.4, 5.1 Hz, 1H, H_{cPr}), 3.06 (dd, *J* = 10.8, 8.3 Hz, 1H, $H_{(CH2)\ THP}$), 3.29 (d, *J* = 2.9 Hz, 1H, $H_{(CH2)\ THP}$), 3.68 (dt, *J* = 11.1, 4.1 Hz, 2H, $H_{(CH2)\ THP}$ & H_{THP}), 3.90 (ddd, *J* = 10.7, 4.0, 1.5 Hz, 1H, $H_{(CH2)\ THP}$), 4.51 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.41 (s, 1H, H_{Ar}), 6.53 (d, *J* = 7.3 Hz, 1H, NH_{THP}), 7.28 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H, H_{Ar}), 7.31 (dt, *J* = 7.8, 1.1 Hz, 1H, H_{Ar}), 7.76 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.85 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 8.55 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.3 (CH_{cPr}), 6.5 ($CH_{2\ cPr}$), 6.7 ($CH_{2\ cPr}$), 24.3 ($CH_{2\ THP}$), 28.8 ($CH_{2\ THP}$), 46.5 (CH_{THP}), 47.2 ($CH_{2\ Bn}$), 67.1 ($CH_{2\ THP}$), 70.3 ($CH_{2\ THP}$), 84.4 (CH_{Ar}), 120.6 (CH_{Ar}), 122.3 (CH_{Ar}), 137.0 (CH_{Ar}), 139.5 (C_q), 140.0 (C_q), 149.1 (CH_{Ar}), 150.1 (C_q), 155.4 (C_q),

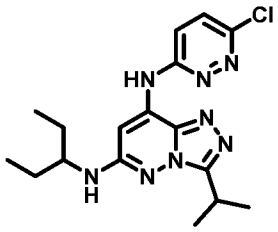
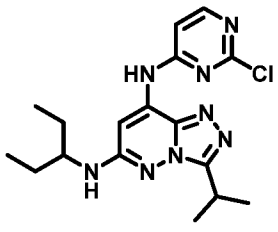
			157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{23}N_7O$:** 366.20 [M+H]+, **found :** 366.34.
(215)		-	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.03 – 1.11 (m, 2H, $CH_{2\ cPr}$), 1.17 (dt, *J* = 5.7, 2.9 Hz, 2H, $CH_{2\ cPr}$), 1.42 – 1.66 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.27 – 2.32 (m, 1H, H_{cPr}), 3.67 (dq, *J* = 13.2, 7.4, 6.8 Hz, 1H, H_{iPent}), 3.98 (s, 3H, $CH_{3\text{-}O}$), 7.02 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.24 (d, *J* = 9.4 Hz, 1H, H_{Ar}), 7.78 (d, *J* = 9.5 Hz, 1H, H_{Ar}), 7.90 (s, 1H, H_{Ar}), 10.00 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.4 (CH_{cPr}), 6.5 (2x$CH_{2\ cPr}$), 10.4 (2x$CH_{3\text{-}CH2}$), 26.0 (2x$CH_{2\text{-}CH3}$), 53.1 (CH_{iPent}), 54.1 ($CH_{3\text{-}O}$), 95.2 (CH_{Ar}), 119.6 (CH_{Ar}), 123.5 (CH_{Ar}), 133.0 (C_q), 139.2 (C_q), 150.3 (C_q), 154.2 (C_q), 156.2 (C_q), 160.9 (C_q).
(216)		> 97 % [b]	Light brown solid. **Rf** (DCM/MeOH, 96/4) : 0.19 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.82 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 0.99 – 1.16 (m, 4H, 2x$CH_{2\ cPr}$), 1.33 – 1.58 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.24 (tt, *J* = 8.4, 5.1 Hz, 1H, H_{cPr}), 3.54 (hept, *J* = 5.8, 5.1 Hz, 1H, H_{iPent}), 4.73 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.46 (s, 1H, H_{Ar}), 6.39 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.63 (dd, *J* = 8.5, 1.8 Hz, 1H, H_{Ar}), 7.68 (dd, *J* = 8.5, 4.8 Hz, 1H, H_{Ar}), 7.90 (t, *J* = 6.4 Hz, 1H, NH_{Bn}), 9.16 (dd, *J* = 4.8, 1.8 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.4 (CH_{cPr}), 6.4 (2x$CH_{2\ cPr}$), 10.3 (2x$CH_{3\text{-}CH2}$), 26.0 (2x$CH_{2\text{-}CH3}$), 45.7 ($CH_{2\ Bn}$), 52.8 (CH_{iPent}), 84.8 (CH_{Ar}), 125.0 (CH_{Ar}), 127.5 (CH_{Ar}), 139.4 (C_q), 139.6 (C_q), 149.9 (C_q), 150.9 (CH_{Ar}), 156.0 (C_q), 160.3 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{24}N_8$:** 353.22 [M+H]+, **found :** 353.32.

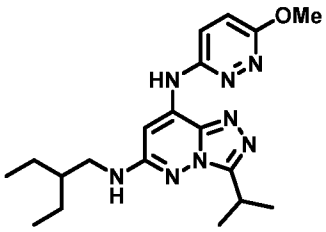
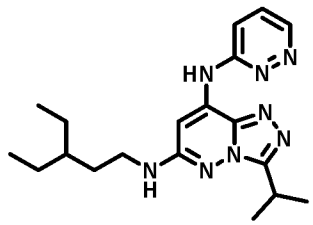
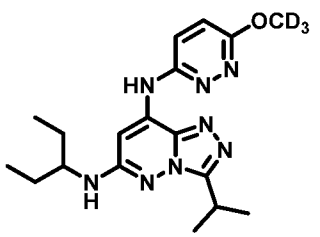
(217)		-	White cloudy oil. **Rf** (DCM/MeOH, 96/4) : 0.47 **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.88 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 0.99 – 1.15 (m, 4H, 2x$CH_{2\ cPr}$), 1.40 – 1.62 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.24 (tt, *J* = 8.4, 5.1 Hz, 1H, H_{cPr}), 2.91 (dd, *J* = 8.8, 6.4 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.40 (q, *J* = 6.8 Hz, 2H, $CH_{2\text{-}NH}$), 3.62 (h, *J* = 6.6 Hz, 1H, H_{iPent}), 5.61 (s, 1H, H_{Ar}), 6.30 (d, *J* = 8.1 Hz, 1H, NH_{iPent}), 7.15 – 7.25 (m, 2H, H_{Ar} & $NH_{\text{-}CH2}$), 7.27 – 7.37 (m, 4H, 4xH_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.4 (CH_{cPr}), 6.4 (2x$CH_{2\ cPr}$), 10.4 (2x$CH_{3\text{-}CH2}$), 26.2 (2x$CH_{2\text{-}CH3}$), 33.8 ($CH_{2\text{-}CH2\text{-}NH}$), 43.6 ($CH_{2\text{-}NH}$), 52.8 ($CH_{iPent}$), 83.6 ($CH_{Ar}$), 126.2 ($CH_{Ar}$), 128.4 (2x$CH_{Ar}$), 128.7 (2x$CH_{Ar}$), 139.2 ($C_q$), 139.5 ($C_q$), 139.7 ($C_q$), 149.8 ($C_q$), 156.3 ($C_q$).
(218)		> 97 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.98 – 1.18 (m, 4H, 2x$CH_{2\ cPr}$), 2.30 (tt, *J* = 8.4, 5.2 Hz, 1H, H_{cPr}), 4.35 (d, *J* = 5.5 Hz, 2H, $CH_{2\text{-}NH}$), 4.53 (d, *J* = 6.2 Hz, 2H, $CH_{2\text{-}NH}$), 5.46 (s, 1H, H_{Ar}), 7.01 (t, *J* = 5.7 Hz, 1H), 7.10 (dd, *J* = 4.9, 1.3 Hz, 1H, $NH_{\text{-}CH2}$), 7.28 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H, H_{Ar}), 7.32 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.35 (dd, *J* = 2.9, 1.2 Hz, 1H, H_{Ar}), 7.46 (dd, *J* = 5.0, 2.9 Hz, 1H, H_{Ar}), 7.76 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.87 (t, *J* = 6.2 Hz, 1H, $NH_{\text{-}CH2}$), 8.55 (dt, *J* = 4.7, 1.5 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 5.3 (CH_{cPr}), 6.6 (2x$CH_{2\ cPr}$), 39.8 ($CH_{2\text{-}NH}$), 47.2 ($CH_{2\text{-}NH}$), 84.4 (CH_{Ar}), 120.7 (CH_{Ar}), 122.1 (CH_{Ar}), 122.3 (CH_{Ar}), 126.0 (CH_{Ar}), 128.0 (CH_{Ar}), 136.9 (CH_{Ar}), 139.6 (C_q), 140.0 (C_q), 140.3 (C_q), 149.0 (CH_{Ar}), 150.2 (C_q), 155.9 (C_q), 157.5 (C_q). **MS (ESI+) : m/z calcd for $C_{19}H_{19}N_7S$:** 378.15 [M+H]+, **found :** 378.29.

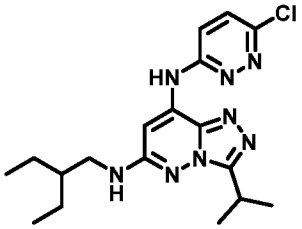
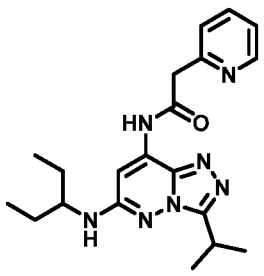
(219)		> 98 % [b]	White solid **Rf** (DCM/MeOH, 94/6) : 0.15 **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.02 – 1.13 (m, 4H, 2x$CH_{2\ cPr}$), 2.28 (tt, *J* = 8.4, 5.2 Hz, 1H, H_{cPr}), 2.70 (d, *J* = 4.8 Hz, 3H, $CH_{3\text{-}NH}$), 4.52 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.34 (s, 1H, H_{Ar}), 6.56 (q, *J* = 4.7 Hz, 1H, $NH_{\text{-}CH3}$), 7.28 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H, H_{Ar}), 7.32 (dd, *J* = 7.8, 1.1 Hz, 1H, H_{Ar}), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.81 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 8.54 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.2 (CH_{cPr}), 6.8 (2x$CH_{2\ cPr}$), 27.6 ($CH_{3\text{-}NH}$), 47.2 ($CH_{2\ Bn}$), 84.4 (CH_{Ar}), 120.8 (CH_{Ar}), 122.3 (CH_{Ar}), 136.9 (CH_{Ar}), 139.5 (C_q), 139.7 (C_q), 149.0 (CH_{Ar}), 150.2 (C_q), 156.7 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{15}H_{17}N_7$:** 296.16 [M+H]+, **found :** 296.31.
(220)		> 98 % [b]	White solid **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 1.01 – 1.15 (m, 4H, 2x$CH_{2\ cPr}$), 1.86 – 1.91 (m, 4H, 2x$CH_{2\text{-}CH2\text{-}N}$), 2.28 (tt, *J* = 8.5, 5.1 Hz, 1H, H_{cPr}), 3.29 (d, *J* = 6.7 Hz, 4H, 2x$CH_{2\text{-}N}$), 4.62 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 5.51 (s, 1H, H_{Ar}), 7.23 – 7.33 (m, 1H, H_{Ar}), 7.38 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.76 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.93 (t, *J* = 6.1 Hz, 1H, NH_{Bn}), 8.48 – 8.65 (m, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.6 (2x$CH_{2\ cPr}$), 24.8 (2x$CH_{2\text{-}CH2\text{-}N}$), 46.6 (2x$CH_{2\text{-}N}$), 47.3 ($CH_{2\ Bn}$), 82.9 ($CH_{Ar}$), 121.4 ($CH_{Ar}$), 122.4 ($CH_{Ar}$), 136.9 ($CH_{Ar}$), 139.1 ($C_q$), 140.3 ($C_q$), 148.9 ($CH_{Ar}$), 149.9 ($C_q$), 155.0 ($C_q$), 157.6 ($C_q$). **MS (ESI+) : m/z calcd for $C_{18}H_{21}N_7$:** 336.19 [M+H]+, **found :** 336.36
(221)		> 99 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.39 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.47 – 1.67 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.34 – 3.41 (m, 1H, H_{iPr}), 3.67 (h, *J* = 6.6 Hz, 1H, H_{iPent}), 3.94 (s, 3H, $CH_{3\text{-}O}$), 7.00 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.12 (d, *J* = 5.7 Hz, 1H, H_{Ar}), 7.70 (s, 1H, H_{Ar}), 8.28 (d, *J* = 5.7 Hz, 1H, H_{Ar}), 10.37

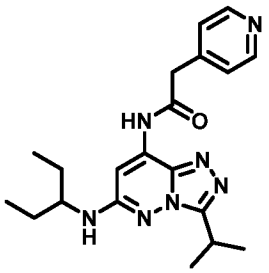
			(s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.5 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.1 (2x$CH_{2\text{-}CH3}$), 53.5 (CH_{iPent}), 54.4 ($CH_{3\text{-}O}$), 97.9 (CH_{Ar}), 103.9 (CH_{Ar}), 132.5 (C_q), 139.1 (C_q), 153.2 (C_q), 155.4 (C_q), 157.7 (CH_{Ar}), 162.2 (C_q), 164.5 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{26}N_8O$:** 371.23 [M+H]+, **found :** 371.42.
(222)		> 98 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.90 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.39 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.46 – 1.67 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.34 – 3.43 (m, 1H, H_{iPr}), 3.61 – 3.74 (m, 1H, H_{iPent}), 4.07 (s, 3H, $CH_{3\text{-}O}$), 7.14 (d, *J* = 7.9 Hz, 1H, NH_{iPent}), 7.80 (s, 1H, H_{Ar}), 8.36 (s, 1H, NH), 8.38 (s, 1H, H_{Ar}), 8.55 (s, 1H, H_{Ar}). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.4 (2x$CH_{3\ iPr}$), 24.9 (CH_{iPr}), 25.9 (2x$CH_{2\text{-}CH3}$), 53.4 (CH_{iPent}), 56.7 ($CH_{3\text{-}O}$), 97.1 (CH_{Ar}), 131.2 (C_q), 136.1 (CH_{Ar}), 138.9 (C_q), 141.0 (C_q), 149.4 (CH_{Ar}), 149.5 (C_q), 153.4 (C_q), 155.4 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{26}N_8O$:** 371.23 [M+H]+, **found :** 371.41.
(223)		> 98 % [b]	Light brown solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.89 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.39 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.43 – 1.69 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.35 – 3.41 (m, 1H, H_{iPr}), 3.65 (h, *J* = 6.5 Hz, 1H, H_{iPent}), 3.90 (s, 3H, $CH_{3\text{-}O}$), 6.87 (d, *J* = 1.0 Hz, 1H, H_{Ar}), 6.95 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 7.79 (s, 1H, H_{Ar}), 8.58 (d, *J* = 0.9 Hz, 1H, H_{Ar}), 10.18 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.5 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.0 (2x$CH_{2\text{-}CH3}$), 53.3 (CH_{iPent}), 53.7 ($CH_{3\text{-}O}$), 92.3 (CH_{Ar}), 96.9 (CH_{Ar}), 132.9 (C_q), 139.2 (C_q), 153.2 (C_q), 155.6 (C_q), 157.4 (CH_{Ar}), 161.8 (C_q), 169.6 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{26}N_8O$:** 371.23 [M+H]+, **found :** 371.40.

(224)		> 99 % [b]	Light yellow solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.89 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.40 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.44 – 1.67 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.28 – 3.41 (m, 1H, H_{iPr}), 3.66 (h, J = 6.6 Hz, 1H, H_{iPent}), 3.98 (s, 3H, $CH_{3\text{-}O}$), 7.02 (d, J = 7.9 Hz, 1H, NH_{iPent}), 7.24 (d, J = 9.5 Hz, 1H, H_{Ar}), 7.79 (d, J = 9.5 Hz, 1H, H_{Ar}), 7.92 (s, 1H, H_{Ar}), 10.03 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.9 (CH_{iPr}), 26.0 (2x$CH_{2\text{-}CH3}$), 53.2 (CH_{iPent}), 54.1 ($CH_{3\text{-}O}$), 95.1 (CH_{Ar}), 119.6 (CH_{Ar}), 123.5 (CH_{Ar}), 133.0 (C_q), 139.3 (C_q), 153.1 (C_q), 154.2 (C_q), 156.0 (C_q), 160.8 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{26}N_8O$:** 371.23 [M+H]+, **found :** 371.40.
(225)		> 99 % [b]	Beige solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.05 – 1.20 (m, 4H, 2x$CH_{2\ cPr}$), 1.28 – 1.46 (m, 4H, 2x$CH_{2\text{-}CH3}$), 1.56 (hept, J = 6.0 Hz, 1H, $H_{C\text{-}CH2\text{-}NH}$), 2.31 (tt, J = 8.4, 5.1 Hz, 1H, H_{cPr}), 3.18 (t, J = 5.9 Hz, 2H, $CH_{2\text{-}NH}$), 7.25 (t, J = 5.5 Hz, 1H, $NH_{\text{-}CH2}$), 7.61 (dd, J = 9.0, 4.5 Hz, 1H, H_{Ar}), 7.78 (dd, J = 9.0, 1.4 Hz, 1H, H_{Ar}), 7.96 (s, 1H, H_{Ar}), 8.89 (dd, J = 4.6, 1.4 Hz, 1H, H_{Ar}), 10.12 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 5.3 (CH_{cPr}), 6.6 (2x$CH_{2\ cPr}$), 10.9 (2x$CH_{3\text{-}CH2}$), 23.6 (2x$CH_{2\text{-}CH3}$), 43.5 ($CH_{2\text{-}NH}$), 96.0 (CH_{Ar}), 118.6 (CH_{Ar}), 128.1 (CH_{Ar}), 132.8 (C_q), 139.2 (C_q), 146.8 (CH_{Ar}), 150.5 (C_q), 156.3 (C_q), 157.6 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{24}N_8$:** 353.45 [M+H]+, **found :** 353.41.
(226)		> 98 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.89 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.03 – 1.20 (m, 4H, 2x$CH_{2\ cPr}$), 1.27 – 1.44 (m, 4H, 2x$CH_{2\text{-}CH3}$), 1.54 (hept, J = 6.3 Hz, 1H, $H_{C\text{-}CH2\text{-}NH}$), 2.31 (tt, J = 8.4, 5.1 Hz, 1H, H_{cPr}), 3.17 (t, J = 5.9 Hz, 2H, $CH_{2\text{-}NH}$), 3.97 (s, 3H, $CH_{3\text{-}O}$), 7.19 (t, J = 5.5 Hz, 1H, $NH\text{-}CH2$), 7.22 (d, J = 9.5 Hz, 1H, H_{Ar}), 7.77 (d, J = 9.4 Hz, 1H, H_{Ar}), 7.91 (s, 1H, H_{Ar}), 10.00 (s, 1H, NH).

			^{13}C NMR (101 MHz, DMSO-d_6) δ : 5.3 (CH_{cPr}), 6.6 ($2xCH_{2\ cPr}$), 11.0 ($2xCH_{3\text{-}CH2}$), 23.6 ($2xCH_{2\text{-}CH3}$), 39.8 ($CH_{\text{-}CH2\text{-}NH}$), 43.5 ($CH_{2\text{-}NH}$), 54.2 ($CH_{3\text{-}O}$), 95.1 ($CH_{Ar}$), 119.6 ($CH_{Ar}$), 123.5 ($CH_{Ar}$), 133.0 ($C_q$), 139.2 ($C_q$), 150.5 ($C_q$), 154.2 ($C_q$), 156.5 ($C_q$), 160.9 ($C_q$). **MS (ESI+) : m/z calcd for $C_{19}H_{26}N_8O$:** 383.23 [M+H]+, **found :** 383.40.
(227)		> 98 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.89 (t, J = 7.4 Hz, 6H, $2xCH_{3\text{-}CH2}$), 1.40 (d, J = 7.0 Hz, 6H, $2xCH_{3\ iPr}$), 1.44 – 1.67 (m, 4H, $2xCH_{2\text{-}CH3}$), 3.38 (q, J = 7.0 Hz, 1H, H_{iPr}), 3.66 (hept, J = 5.8, 5.2 Hz, 1H, H_{iPent}), 7.07 (d, J = 7.9 Hz, 1H, NH_{iPent}), 7.80 (d, J = 9.3 Hz, 1H, H_{Ar}), 7.87 (d, J = 9.4 Hz, 1H, H_{Ar}), 7.88 (s, 1H, H_{Ar}), 10.38 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 ($2xCH_{3\text{-}CH2}$), 19.5 ($2xCH_{3\ iPr}$), 24.9 (CH_{iPr}), 26.0 ($2xCH_{2\text{-}CH3}$), 53.3 (CH_{iPent}), 96.7 (CH_{Ar}), 122.4 (CH_{Ar}), 129.8 (CH_{Ar}), 132.5 (C_q), 139.2 (C_q), 149.7 (C_q), 153.2 (C_q), 155.8 (C_q), 157.1 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{23}ClN_8$:** 375.18 [M+H]+, **found :** 375.36.
(228)		> 96 % [b]	Light yellow solid. **Rf** (DCM/MeOH, 95/5): 0.35. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.91 (t, J = 7.4 Hz, 6H, $2xCH_{3\text{-}CH2}$), 1.39 (d, J = 7.0 Hz, 6H, $2xCH_{3\ iPr}$), 1.48 – 1.68 (m, 4H, $2xCH_{2\text{-}CH3}$), 3.35 – 3.43 (m, 1H, H_{iPr}), 3.67 (h, J = 6.5 Hz, 1H, H_{iPent}), 7.12 (d, J = 8.0 Hz, 1H, NH_{iPent}), 7.46 (d, J = 5.8 Hz, 1H, H_{Ar}), 7.60 (s, 1H, H_{Ar}), 8.40 (d, J = 5.8 Hz, 1H, H_{Ar}), 10.76 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.6 ($2xCH_{3\text{-}CH2}$), 19.5 ($2xCH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.1 ($2xCH_{2\text{-}CH3}$), 53.6 (CH_{iPent}), 98.5 (CH_{Ar}), 108.8 (CH_{Ar}), 132.0 (C_q), 139.0 (C_q), 153.3 (C_q), 155.3 (C_q), 158.2 (CH_{Ar}), 158.8 (C_q), 161.9 (C_q). **MS (ESI+) : m/z calcd for $C_{17}H_{23}ClN_8$:** 375.18 [M+H]+, **found :** 375.35.

(229)		> 98 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.90 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.30 – 1.39 (m, 4H, 2x$CH_{2\text{-}CH3}$), 1.40 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.58 (p, J = 6.2 Hz, 1H, $H_{C\text{-}CH2\text{-}NH}$), 3.17 (t, J = 5.9 Hz, 2H, $CH_{2\text{-}NH}$), 3.36 – 3.43 (m, 1H, H_{iPr}), 3.98 (s, 3H, $CH_{3\text{-}O}$), 7.20 – 7.28 (m, 2H, $NH_{\text{-}CH2}$ & H_{Ar}), 7.80 (d, J = 9.5 Hz, 1H, H_{Ar}), 7.92 (s, 1H, H_{Ar}), 10.04 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.9 (2x$CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.6 (2x$CH_{2\text{-}CH3}$), 24.8 (CH_{iPr}), 39.6 ($CH_{\text{-}CH2\text{-}NH}$), 43.5 ($CH_{2\text{-}NH}$), 54.1 ($CH_{3\text{-}O}$), 95.0 ($CH_{Ar}$), 119.6 ($CH_{Ar}$), 123.5 ($CH_{Ar}$), 133.0 ($C_q$), 139.3 ($C_q$), 153.2 ($C_q$), 154.2 ($C_q$), 156.2 ($C_q$), 160.9 ($C_q$). **MS (ESI+) : m/z calcd for $C_{19}H_{28}N_8O$:** 385.25 [M+H]+, **found :** 385.51.
(230)		> 93 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.85 (t, J = 6.9 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.32 (q, J = 6.3 Hz, 5H, $H_{C\text{-}CH2\text{-}CH3}$ & 2x$CH_{2\text{-}CH3}$), 1.41 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.57 (dd, J = 7.2, 4.2 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.24 (dt, J = 8.4, 5.7 Hz, 2H, $CH_{2\text{-}NH}$), 3.36 – 3.45 (m, 1H, H_{iPr}), 7.27 (t, J = 5.4 Hz, 1H, $NH_{\text{-}CH2}$), 7.61 (dd, J = 9.0, 4.5 Hz, 1H, H_{Ar}), 7.79 (dd, J = 9.1, 1.4 Hz, 1H, H_{Ar}), 7.93 (s, 1H, H_{Ar}), 8.88 (dd, J = 4.6, 1.4 Hz, 1H, H_{Ar}), 10.16 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.7 (2x$CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 24.9 (2x$CH_{2\text{-}CH3}$), 31.3 ($CH_{2\text{-}CH2\text{-}NH}$), 37.6 ($CH_{\text{-}CH2\text{-}CH3}$), 38.91 ($CH_{2\text{-}NH}$), 96.0 ($CH_{Ar}$), 118.7 ($CH_{Ar}$), 128.1 ($CH_{Ar}$), 132.9 ($C_q$), 139.3 ($C_q$), 146.8 ($CH_{Ar}$), 153.3 ($C_q$), 155.9 ($C_q$), 157.6 ($C_q$). **MS (ESI+) : m/z calcd for $C_{19}H_{28}N_8$:** 369.25 [M+H]+, **found :** 369.43.
(231)		> 98 % [b]	White solid. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.89 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.40 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.44 – 1.64 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.36 – 3.41 (m, 1H, H_{iPr}), 3.66 (hept, J = 5.9, 5.3 Hz, 1H, H_{iPent}), 7.02 (d, J = 7.9 Hz, 1H, NH_{iPent}), 7.23 (t, J = 4.7 Hz, 1H, H_{Ar}), 7.79 (t, J = 4.7 Hz, 1H, H_{Ar}),

			7.92 (s, 1H, H_{Ar}), 10.03 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.42 (2x$CH_{3\text{-}CH2}$), 19.50 (2x$CH_{3\ iPr}$), 24.87 (CH_{iPr}), 26.02 (2x$CH_{2\text{-}CH3}$), 53.20 (CH_{iPent}), 95.14 (CH_{Ar}), 119.58 (d, *J* = 11.3 Hz, CH_{Ar}), 123.49 (d, *J* = 10.6 Hz (CH_{Ar}), 132.96 (C_q), 133.05 (C_q), 139.32 (C_q), 153.12 (C_q), 154.22 (d, *J* = 2.1 Hz , C_q), 156.01 (d, *J* = 2.7 Hz, C_q), 160.86 (C_q). **MS (ESI+) : m/z calcd for $C_{18}H_{23}D_3N_8O$:** 374.25 [M+H]+, **found :** 374.50.
(232)		> 99 % [b]	Light yellow solid. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.90 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.29 – 1.39 (m, 4H, 2x$CH_{2\text{-}CH3}$), 1.40 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.58 (p, *J* = 6.2 Hz, 1H, $H_{C\text{-}CH2\text{-}NH}$), 3.18 (t, *J* = 6.0 Hz, 2H, $CH_{2\text{-}NH}$), 3.39 (p, *J* = 6.9 Hz, 1H, H_{iPr}), 7.28 (t, *J* = 5.7 Hz, 1H, $NH_{\text{-}CH2}$), 7.80 (d, *J* = 9.3 Hz, 1H, H_{Ar}), 7.87 (d, *J* = 9.3 Hz, 1H, H_{Ar}), 7.88 (s, 1H, H_{Ar}), 10.40 (s, 1H, NH). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.9 (2x$CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.6 (2x$CH_{2\text{-}CH3}$), 24.8 (CH_{iPr}), 39.6 ($CH_{\text{-}CH2\text{-}NH}$), 43.6 ($CH_{2\text{-}NH}$), 96.6 ($CH_{Ar}$), 122.4 ($CH_{Ar}$), 129.8 ($CH_{Ar}$), 132.5 ($C_q$), 139.2 ($C_q$), 149.8 ($C_q$), 153.3 ($C_q$), 156.0 ($C_q$), 157.1 ($C_q$). **MS (ESI+) : m/z calcd for $C_{18}H_{25}ClN_8$:** 389.20 [M+H]+, **found :** 389.46.
(233)		> 98 % [b]	Beige solid. **Rf** (DCM/MeOH, 94/6) : 0.29. **^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ :** 0.87 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.38 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.42 – 1.64 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.32 – 3.41 (m, 1H, H_{iPr}), 3.63 (h, *J* = 6.9 Hz, 1H, H_{iPent}), 4.12 (s, 2H, $CH_{2\text{-}CO}$), 7.00 (d, *J* = 7.9 Hz, 1H, NH_{iPent}), 7.30 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H, H_{Ar}), 7.41 (dt, *J* = 7.9, 1.1 Hz, 1H, H_{Ar}), 7.59 (s, 1H, H_{Ar}), 7.78 (td, *J* = 7.6, 1.9 Hz, 1H, H_{Ar}), 8.52 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H, H_{Ar}), 11.06 (s, 1H, $NH_{\text{-}CO}$). **^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.4 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.0 (2x$CH_{2\text{-}CH3}$), 45.2 ($CH_{2\text{-}CO}$), 53.3 (CH_{iPent}), 99.3 (CH_{Ar}), 122.1 (CH_{Ar}), 124.1 (CH_{Ar}), 131.7 (C_q), 136.9 (CH_{Ar}), 138.6

			(C_q), 149.0 (CH_{Ar}), 153.2 (C_q), 155.3 (C_q), 155.5 (C_q), 170.6 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{27}N_7O$:** 382.24 [M+H]+, **found :** 382.41.
(234)		> 97 % [b]	Yellow solid. **Rf** (DCM/MeOH, 94/6) : 0.22. **^{1}H NMR (400 MHz, DMSO-d_6) δ :** 0.87 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.38 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.42 – 1.64 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.33 – 3.41 (m, 1H, H_{iPr}), 3.56 – 3.70 (m, 1H, H_{iPent}), 3.99 (s, 2H, $CH_{2\text{-}CO}$), 7.00 (d, J = 8.0 Hz, 1H, NH_{iPent}), 7.32 – 7.40 (m, 2H, 2xH_{Ar}), 7.59 (s, 1H, H_{Ar}), 8.48 – 8.56 (m, 2H, 2xH_{Ar}), 11.04 (s, 1H, $NH_{\text{-}CO}$). **^{13}C NMR (101 MHz, DMSO-d_6) δ :** 10.4 (2x$CH_{3\text{-}CH2}$), 19.4 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 25.9 (2x$CH_{2\text{-}CH3}$), 41.9 ($CH_{2\text{-}CO}$), 53.3 (CH_{iPent}), 99.7 (CH_{Ar}), 124.7 (2xCH_{Ar}), 131.7 (C_q), 138.5 (C_q), 144.3 (C_q), 149.6 (2xCH_{Ar}), 153.2 (C_q), 155.2 (C_q), 170.7 (C_q). **MS (ESI+) : m/z calcd for $C_{20}H_{27}N_7O$:** 382.24 [M+H]+, **found :** 382.42.

[a]Acidic conditions, [b]Alkaline conditions

PATHOLOGIES

Examples of diseases mediated A_3AR include, but are not limited to, ulcerative colitis, atopic dermatitis, glaucoma, asthma, liver fibrosis, kidney diseases in particular kidney fibrosis, nephropathy, acute kidney injury (AKI), chronic kidney disease (CKD) more particularly induced by ischemia and/or reperfusion injury, toxic nephropathy or myoglobinuria, diabetic kidney disease, kidney diseases induced by nephrotoxicity caused by therapeutic drugs, atherosclerosis, hypercholestemia, partial or a complete hearing loss induced by noise, acoustic trauma or ototoxic agents or conditions, and cancers developing under hypoxic conditions, in particular glioblastoma.

The compounds of formula (I) or any of its pharmaceutically acceptable salts, may in particular be useful in the treatment and/or in the prevention of hearing loss, in

particular induced by ototoxic agents, as well as in the treatment and/or in the prevention of kidney diseases, in particular induced by nephrotoxicity.

The compounds of formula (I) or any of its pharmaceutically acceptable salts may in particular be useful in the treatment and/or in the prevention of partial or a complete hearing loss, in particular induced by noise, acoustic trauma or ototoxic agents or conditions, more particularly induced by ototoxic agents or conditions.

The compounds of formula (I) or any of its pharmaceutically acceptable salts may in particular be useful in the treatment and/or in the prevention of partial or a complete hearing loss induced by ototoxic agents or conditions as described hereinafter.

As ototoxic agents, i.e. causing hear loss, the following may be cited:

- solvents, such as polyethylene glycol, propylene glycol or benzalkonium chloride;
- antibiotics, in particular topical and/or systemic antibiotics, more particularly aminoglycosides, macrolides or phenicol antibiotics, such as gentamycin, neomycin, tobramycin, kanamycin, nystatin, polymyxin B, amphotericin B, bacitracin or chloramphenicol;
- anticancer drugs, in particular platinum-based anticancer drugs, such as cisplatin or carboplatin,
- antiseptics, in particular acetic acid, alcohols such as ethanol, chlorhexidine, cresylate, gentian violet or povidone iodine;
- nonsteroidal anti-inflammatory drugs (NSAIDs), in particular salicylates, cyclodextrins, indomethacin, ibuprofen, phenylbutazone or paracetamol;
- topical combinations, in particular polymyxin/neomycin/hydrocortisone or ticarcilline/clavulanate;
- drugs for COVID-19, in particular lopinavir or ritonavir;
- antimalarial drugs, in particular quinine or chloroquine;
- cardiovascular drugs, in particular loop diuretics; or
- erectile dysfunction drugs, in particular phosphodiesterase type 5 (PDE-5) inhibitors.

The compounds of formula (I) or any of its pharmaceutically acceptable salts may in particular be useful in the treatment and/or in the prevention of hearing loss being a

partial or a complete hearing loss, in particular being induced by noise, acoustic trauma or ototoxic agents or conditions, more particularly platin-based anticancer drugs such as cisplatin or carboplatin, antibiotics, even more particularly macrolides or aminoglycosides such as gentamycin or neomycin, drugs for COVID-19 such as lopinavir or ritonavir, antimalarial drugs such as quinine or chloroquine, cardiovascular drugs such as loop diuretics, non-steroidal anti-inflammatory drugs such as salicylate or cyclodextrins, erectile dysfunction drugs such as phosphodiesterase type 5 inhibitors.

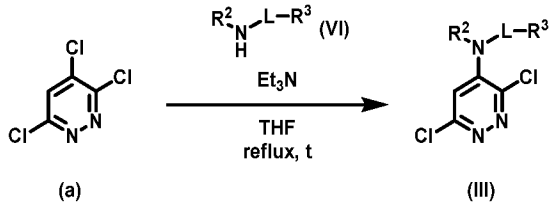
The compounds of formula (I) or any of its pharmaceutically acceptable salts may in particular be useful in the treatment and/or in the prevention of kidney diseases, in particular selected from nephropathy, acute kidney injury (AKI), chronic kidney disease (CKD) more particularly induced by ischemia and/or reperfusion injury, toxic nephropathy or myoglobinuria, and diabetic kidney disease, or kidney diseases induced by nephrotoxicity caused by therapeutic drugs.

The compounds of formula (I) or any of its pharmaceutically acceptable salts may in particular be useful in the treatment and/or in the prevention of kidney diseases induced by nephrotoxicity caused by therapeutic drugs as described hereinafter.

As therapeutic drugs causing nephrotoxicity, the following may be cited: acyclovir, ambisome, amikacin, aminoglycosides, antibiotics, amphotericin B, captopril, carboplatin, cefotaxime, ceftazidime, cefuroxime, cephalosporins, cidofovir, ciprofloxacin, cisplatin, colistimethate, cyclosporine, dapsone, enalaprilat, enalapril, Foscarnet, gadopentetate dimeglumine, gadoxetate, ganciclovir gentamicin, ibuprofen, ifosfamide, iodixanol, iohexol, iopamidol, ioversol, ketorolac, lisinopril, lithium, mesalamine, methotrexate, nafcillin disodium, penicillins, piperacillin/tazobactam, piperacillin, rifampin, sirolimus, sulfasalazine, tacrolimus, ticarcillin/clavulanic acid, tobramycin, topiramate, valacyclovir, valganciclovir, vancomycin or zonisamide.

The following examples illustrate in detail the preparation of some compounds according to the invention. The structures of the products obtained have been confirmed by NMR analyses and mass spectroscopy. The following examples further illustrate some biological activities of some compounds according to the invention.

Example 1: Synthesis of 3,6-dichloro-pyridazin-4-amine derivatives, as illustrated in step 1 of scheme 1



(a) (III)

Example 1.1: Synthesis of *N*-benzyl-3,6-dichloro-pyridazin-4-amine (1.1)

To a solution of 3,4,6-trichloropyridazine **(a)** (10.000 g, 52.88 mmol, 1.0 eq.) in THF (100.0 mL), triethylamine (8.93 mL, 63.46 mmol, 1.2 eq.) then benzylamine (6.48 mL, 58.17 mmol, 1.1 eq.) was added and the mixture was refluxed on 3 h. After cooling, the solid was filtered off, washed with THF then the filtrate was concentrated under vacuum. The resulting solid was triturated in Et_2O, filtered off, washed with a little amount of Et_2O and dried under vacuum to give **(1.1)** (13.000 g, 97 %) as a beige solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.52 (d, *J* = 6.3 Hz, 2H, CH_2), 6.82 (s, 1H, H_{Ar}), 7.26 (td, *J* = 5.9, 2.8 Hz, 1H, H_{Ar}), 7.34 (d, *J* = 5.4 Hz, 4H, 4xH_{Ar}), 7.97 (t, *J* = 6.3 Hz, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 44.7 (CH_2), 105.5 (CH_{Ar}), 127.0 (2xCH_{Ar}), 127.2 (CH_{Ar}), 128.6 (2xCH_{Ar}), 137.0 (C_q), 143.8 (C_q), 144.4 (C_q), 154.5 (C_q).

MS (ESI+) : m/z calcd for $C_{11}H_9Cl_2N_3$: 254.0 [M+H]+, **found :** 254.0.

Example 1.2: Synthesis of 3,6-dichloro-*N*-(2-pyridylmethyl)pyridazin-4-amine (1.2)

To a solution of 3,4,6-trichloropyridazine **(a)** (20.000 g, 105.77 mmol, 1.0 eq.) in THF (210.0 mL), triethylamine (19.36 mL, 137.50 mmol, 1.3 eq.) then corresponding amine (12.67 mL, 121.63 mmol, 1.15 eq.) was added and the mixture was refluxed on 4 h. After cooling, the solid was filtered off and washed with THF. The solid was washed with water then, in another vacuum flask, triturated in MeOH, washed with Et_2O and dried under vacuum to give first part of **(1.2)** (12.500 g). THF and MeOH/Et_2O filtrates were combined and concentrated under vacuum. The resulting solid was triturated in MeOH, filtered off, washed with Et_2O and dried under vacuum to give a second part of **(1.2)** (10.100 g). The filtrate was concentrated and the resulting solid triturated in a little amount of MeOH, filtered off, washed with Et_2O and dried under vacuum to give a third part of **(1.2)** (1.000 g). Total of **(1.2)**: 23.600 g, 87 % as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.60 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 6.90 (s, 1H, H_{Ar}), 7.31 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H, H_{Ar}), 7.35 (dt, *J* = 7.8, 1.1 Hz, 1H, H_{Ar}), 7.79 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.87 (t, *J* = 6.0 Hz, 1H, NH_{Bn}), 8.54 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 46.6 ($CH_{2\ Bn}$), 105.9 (CH_{Ar}), 121.6 (CH_{Ar}), 122.7 (CH_{Ar}), 137.1 (CH_{Ar}), 143.8 (C_q), 144.7 (C_q), 149.2 (CH_{Ar}), 154.6 (C_q), 156.3 (C_q).

MS (ESI+) : m/z calcd for $C_{10}H_8Cl_2N_4$: 255.0 [M+H]+, **found :** 255.1.

Example 1.3: Synthesis of 3,6-dichloro-*N*-(3-pyridylmethyl)pyridazin-4-amine (1.3)

To a solution of 3,4,6-trichloropyridazine **(a)** (3.100 g, 16.39 mmol, 1.0 eq.) in THF (33.0 mL), triethylamine (3.00 mL, 21.31 mmol, 1.3 eq.) then corresponding amine (2.04 mL, 19.67 mmol, 1.2 eq.) was added and the mixture was refluxed on 2 h. After cooling, the solid was filtered off and washed with THF. The filtrate was concentrated and the resulting solid was washed with water, then triturated with a little amount of MeOH and dried under vacuum to give **(1.3)** (2.320 g, 55 %) as a pale orange solid.

Rf (DCM/MeOH, 94/6) : 0.55

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.56 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 6.96 (s, 1H, H_{Ar}), 7.37 (dd, *J* = 7.8, 4.7 Hz, 1H, H_{Ar}), 7.73 (dt, *J* = 7.8, 2.0 Hz, 1H, H_{Ar}), 7.96 (t, *J* = 6.3 Hz, 1H, NH_{Bn}), 8.48 (dd, *J* = 4.8, 1.7 Hz, 1H, H_{Ar}), 8.59 (d, *J* = 2.3 Hz, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 42.4 ($CH_{2\ Bn}$), 105.5 (CH_{Ar}), 123.6 (CH_{Ar}), 132.7 (C_q), 134.9 (CH_{Ar}), 143.9 (C_q), 144.3 (C_q), 148.5 (CH_{Ar}), 148.8 (CH_{Ar}), 154.7 (C_q).

MS (ESI+) : m/z calcd for $C_{10}H_8Cl_2N_4$: 255.0 [M+H]+, **found :** 255.1.

Example 1.4: Synthesis of 3,6-dichloro-*N*-(4-pyridylmethyl)pyridazin-4-amine (1.4)

To a solution of 3,4,6-trichloropyridazine **(a)** (11.500 g, 60.82 mmol, 1.0 eq.) in THF (120.0 mL), triethylamine (11.13 mL, 79.06 mmol, 1.3 eq.) then corresponding amine (7.640 g, 69.94 mmol, 1.15 eq.) was added and the mixture was refluxed on 2 h. After cooling, the solid was filtered off and washed with THF. The filtrate was concentrated and the resulting solid was washed with water, then triturated with a little amount of MeOH and dried under vacuum to give **(1.4)** (2.320 g, 55 %) as a pale orange solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.57 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 6.84 (s, 1H, HAr), 7.27 – 7.36 (m, 2H, 2xHAr), 7.98 (t, *J* = 6.4 Hz, 1H, NH_{Bn}), 8.45 – 8.58 (m, 2H, 2xHAr).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 43.7 ($CH_{2\ Bn}$), 105.6 (CH_{Ar}), 122.0 ($2xCH_{Ar}$), 143.9 (C_q), 144.5 (C_q), 146.3 (C_q), 149.8 ($2xCH_{Ar}$), 154.7 (C_q).

MS (ESI+) : m/z calcd for $C_{10}H_8Cl_2N_4$: 255.0 [M+H]+, **found :** 255.1.

Example 1.5: Synthesis of 4-[[(3,6-dichloropyridazin-4-yl)amino]methyl]phenol (1.5)

In a sealed vial 2 - 5 mL with a stir bar was charged 3,4,6-trichloropyridazine **(a)** (1.500 g, 7.93 mmol, 1.0 eq.), DCM (19.0 mL), triethylamine (1.68 mL, 11.90 mmol, 1.5 eq.) and corresponding amine (1.172 g, 9.52 mmol, 1.2 eq.). The vial was sealed and put in heating bloc 15 h at 50 °C. After cooling, the mixture was concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (98/2 to 96/4) as eluent to give **(1.5)** (0.515 g, 24 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.38 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 6.68 – 6.76 (m, 2H, 2xHAr), 6.80 (s, 1H, H_{Ar}), 7.08 – 7.21 (m, 2H, $2xH_{Ar}$), 7.87 (t, *J* = 6.2 Hz, 1H, NH_{Bn}), 9.36 (s, 1H, OH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 44.3 ($CH_{2\ Bn}$), 105.4 (CH_{Ar}), 115.3 ($2xCH_{Ar}$), 126.9 (C_q), 128.3 ($2xCH_{Ar}$), 143.8 (C_q), 144.3 (C_q), 154.5 (C_q), 156.6 (C_q).

MS (ESI+) : m/z calcd for $C_{11}H_9Cl_2N_3O$: 270.0 [M+H]+, **found :** 270.1.

Example 1.6: Synthesis of 3-[[(3,6-dichloropyridazin-4-yl)amino]methyl]phenol (1.6)

In a sealed vial 2 - 5 mL with a stir bar was charged 3,4,6-trichloropyridazine **(a)** (1.500 g, 7.93 mmol, 1.0 eq.), DCM (19.0 mL), triethylamine (1.68 mL, 11.90 mmol, 1.5 eq.) and corresponding amine (1.172 g, 9.52 mmol, 1.2 eq.). The vial was sealed and put in heating bloc 15 h at 50 °C. After cooling, the mixture was concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (98/2 to 96/4) as eluent to give **(1.6)** (0.670 g, 31 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.43 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 6.64 (dd, *J* = 8.0, 2.4 Hz, 1H, H_{Ar}), 6.69 (t, *J* = 2.0 Hz, 1H, H_{Ar}), 6.74 (d, *J* = 7.6 Hz, 1H, H_{Ar}), 6.77 (s, 1H, H_{Ar}), 7.13 (t, *J* = 7.8 Hz, 1H, H_{Ar}), 7.94 (t, *J* = 6.3 Hz, 1H, NH_{Bn}), 9.39 (s, 1H, OH).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 44.6 ($CH_{2\ Bn}$), 105.5 (CH_{Ar}), 113.4 (CH_{Ar}), 114.2 (CH_{Ar}), 117.4 (CH_{Ar}), 129.6 (CH_{Ar}), 138.4 (C_q), 143.7 (C_q), 144.4 (C_q), 154.5 (C_q), 157.6 (C_q).

MS (ESI+) : m/z calcd for $C_{11}H_9Cl_2N_3O$: 270.0 [M+H]+, **found :** 270.1.

Example 1.7: Synthesis of 2-[[(3,6-dichloropyridazin-4-yl)amino]methyl]phenol (1.7)

To a solution of 3,4,6-trichloropyridazine **(a)** (3.700 g, 20.2 mmol, 1.0 eq.) in THF (50 mL), triethylamine (3.41 mL, 24.2 mmol, 1.2 eq.) then corresponding benzylamine (3.700 g, 24.2 mmol, 1.2 eq.) was added and the mixture was refluxed 3 h. After cooling, the mixture was filtered, washed with THF then the filtrate was concentrated, the crude residue was triturated in DCM/MeOH (94/4) to give a first part of **(1.7)** (1.450 g) after filtration. The filtrate was concentrated and the residue triturated in DCM/MeOH (98/2) to give a second part of **(1.7)** (0.950 g) after filtration. The filtrate was concentrated and purified by flash chromatography (96/4) to give a third part of **(1.7)** (0.900 g). Total of **(1.7)**: 3.400g, 62 %, as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 4.39 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 6.76 (td, J = 7.4, 1.2 Hz, 1H, H_{Ar}), 6.81 (s, 1H, H_{Ar}), 6.85 (dd, J = 8.0, 1.2 Hz, 1H, H_{Ar}), 7.06 – 7.14 (m, 2H, 2xH_{Ar}), 7.75 (t, J = 6.2 Hz, 1H, NH_{Bn}), 9.84 (s, 1H, OH).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 40.1 ($CH_{2\ Bn}$), 105.3 (CH_{Ar}), 115.1 (CH_{Ar}), 119.2 (CH_{Ar}), 122.4 (C_q), 128.2 (CH_{Ar}), 128.4 (CH_{Ar}), 143.7 (C_q), 144.4 (C_q), 154.6 (C_q), 154.9 (C_q).

MS (ESI+) : m/z calcd for $C_{11}H_9Cl_2N_3O$: 270.0 [M+H]+, **found :** 270.1.

Example 1.8: Synthesis of 3,6-dichloro-*N*-[(2-methoxyphenyl)methyl]pyridazin-4-amine (1.8)

To a solution of 3,4,6-trichloropyridazine **(a)** (2.600 g, 13.75 mmol, 1.0 eq.) in DCM (70.0 mL), triethylamine (3.87 mL, 27.50 mmol, 2.0 eq.) and corresponding amine (2.887 g, 20.63 mmol, 1.5 eq.) was added and the mixture was refluxed 19 h. After cooling, HCl 1M (50.0 mL) was added then the mixture was vigorously stirred 5 min and layers were separated. Aqueous layer was extracted twice with DCM (2x20.0 mL) then organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash

chromatography with DCM/MeOH (100/0 to 98/2) as eluent to give **(1.8)** (3.200 g, 82 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 3.85 (s, 3H, OCH_3), 4.44 (s, 2H, $CH_{2\ Bn}$), 6.75 (s, 1H, H_{Ar}), 6.87 – 6.95 (m, 1H, H_{Ar}), 7.00 – 7.06 (m, 1H, H_{Ar}), 7.13 (dd, *J* = 7.5, 1.8 Hz, 1H, H_{Ar}), 7.27 (td, *J* = 7.8, 1.8 Hz, 1H, H_{Ar}), 7.73 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 40.2 ($CH_{2\ Bn}$), 55.4 (CH_3), 105.4 (CH_{Ar}), 110.9 (CH_{Ar}), 120.5 (CH_{Ar}), 124.1 (C_q), 127.5 (CH_{Ar}), 128.7 (CH_{Ar}), 143.7 (C_q), 144.5 (C_q), 154.6 (C_q), 156.8 (C_q).

MS (ESI+) : m/z calcd for $C_{12}H_{11}Cl_2N_3O$: 284.0 [M+H]+, **found :** 284.1.

Example 1.9: Synthesis of 3,6-dichloro-*N*-(*1H*-indol-3-ylmethyl)pyridazin-4-amine (1.9)

In a 10 - 20 mL vial was introduced a stir bar, 3,4,6-trichloropyridazine **(a)** (1.750 g, 9.25 mmol, 1.0 eq.), DCM (18 mL), 1H-indol-2-ylmethanamine hydrochloride (2.135 g, 11.11 mmol, 1.2 eq.) and triethylamine (2.87 mL, 20.36 mmol, 2.2 eq.). The vial was sealed and put in heating bloc 17 h at 50 °C. After cooling, the mixture was concentrated then triturated in HCl 0.5M (60 mL, pH < 5) and EtOAc was added (30 mL). Heterogenous mixture was vigorously stirred then the precipitate was filtered off, washed with water (up to pH 7) then EtOAc and dried under vacuum to give the first part of **(1.9)** (1.465 g) as a white solid. Aqueous layer was extracted EtOAc (30mL) and organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5) as eluent to give the second part of **(1.9)** (0.430 g) as a white solid. Total of **(1.9)** : 1.895 g, 70 %.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.63 (d, *J* = 5.9 Hz, 2H, $CH_{2\ Bn}$), 7.01 (d, *J* = 7.4 Hz, 2H, 2xH_{Ar}), 7.08 (t, *J* = 7.5 Hz, 1H, H_{Ar}), 7.35 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.44 (d, *J* = 2.4 Hz, 1H, H_{Ar}), 7.73 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.85 (t, *J* = 5.9 Hz, 1H, NH_{Bn}), 10.97 (s, 1H, NH_{Indole}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 37.7 ($CH_{2\ Bn}$), 105.4 (CH_{Ar}), 109.1 (C_q), 111.6 (CH_{Ar}), 118.7 (CH_{Ar}), 118.8 (CH_{Ar}), 121.3 (CH_{Ar}), 124.7 (CH_{Ar}), 126.2 (C_q), 136.5 (C_q), 143.8 (C_q), 144.2 (C_q), 154.3 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{10}Cl_2N_4$: 293.0 [M+H]+, **found :** 293.1.

Example 1.10: Synthesis of 3,6-dichloro-*N*-(*1H*-indol-2-ylmethyl)pyridazin-4-amine (1.10)

In a 10 - 20 mL vial was introduced a stir bar, 3,4,6-trichloropyridazine **(a)** (1.750 g, 9.25 mmol, 1.0 eq.), DCM (18 mL), 1H-indol-2-ylmethanamine hydrochloride (2.135 g, 11.11 mmol, 1.2 eq.) and triethylamine (2.87 mL, 20.36 mmol, 2.2 eq.). The vial was sealed and put in heating bloc 17 h at 50 °C. After cooling, the mixture was concentrated then triturated in HCl 0.5M (60 mL, pH < 5) and EtOAc was added (30 mL). Heterogenous mixture was vigorously stirred then the precipitate was filtered off, washed with water (up to pH 7) then EtOAc and dried under vacuum to give the first part of **(1.10)** (2.040 g) as a white solid. Aqueous layer was extracted EtOAc (30mL) and organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5) as eluent to give the second part of **(1.10)** (0.300 g) as a white solid. Total of **(1.10)**: 2.340 g, 86 %.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.66 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 6.33 (d, *J* = 2.0 Hz, 1H, H_{Ar}), 6.95 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 6.98 (s, 1H, H_{Ar}), 7.04 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 7.33 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 7.45 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 7.79 (t, *J* = 6.1 Hz, 1H, NH_{Bn}), 10.96 (s, 1H, H_{Indole}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 39.3 ($CH_{2\ Bn}$), 99.7 (CH_{Ar}), 105.7 (CH_{Ar}), 111.2 (CH_{Ar}), 119.0 (CH_{Ar}), 119.7 (CH_{Ar}), 120.9 (CH_{Ar}), 127.8 (C_q), 134.6 (C_q), 136.2 (C_q), 143.9 (C_q), 144.5 (C_q), 154.6 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{10}Cl_2N_4$: 293.0 [M+H]+, **found :** 293.1.

Example 1.11: Synthesis of *N*-[(4-aminophenyl)methyl]-3,6-dichloro-pyridazin-4-amine (1.11)

To a solution of 3,4,6-trichloropyridazine **(a)** (22.953 g, 125.14 mmol, 1.3 eq.) in THF (200.0 mL), triethylamine (20.33 mL, 144.69 mmol, 1.5 eq.) and 4-(aminomethyl)aniline (12.000 g, 96.26 mmol, 1.0 eq.) was added then the mixture was refluxed 18 *N*-[(4-aminophenyl)methyl]-6-chloro-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine h. After cooling, the mixture was filtered off, the solid was washed with THF then the filtrate was concentrated. The residue was triturated in DCM and the solid was filtered off, washed with DCM and dried under vacuum to give **(1.11)** (23.950 g, 92 %) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.30 (d, *J* = 6.1 Hz, 2H, CH_2), 5.09 (s, 2H, NH_2), 6.41 – 6.69 (m, 2H, 2xH_{Ar}), 6.77 (s, 1H, H_{Ar}), 6.89 – 7.12 (m, 2H, 2xH_{Ar}), 7.80 (t, *J* = 6.1 Hz, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 44.6 (CH_2), 105.4 (CH_{Ar}), 113.9 (2xCH_{Ar}), 123.4 (C_q), 128.0 (2xCH_{Ar}), 143.7 (C_q), 144.3 (C_q), 147.8 (C_q), 154.4 (C_q).

MS (ESI+) : m/z calcd for $C_{11}H_{10}Cl_2N_4$: 269.0 [M+H]+, **found :** 269.1.

Example 1.12: Synthesis of *N*-[(2-aminophenyl)methyl]-3,6-dichloro-pyridazin-4-amine (1.12)

To a solution of 3,4,6-trichloropyridazine **(a)** (5.000 g, 27.3 mmol, 1.0 eq.) in THF (52 mL), triethylamine (4.22 mL, 30.0 mmol, 1.1 eq.) then 2-(aminomethyl)aniline (3.228 g, 25.9 mmol, 0.95 eq.) was added and the mixture was refluxed 3.5 h. After cooling, the mixture was filtered off, the solid was washed with THF then the filtrate was concentrated and directly purified by flash chromatography with DCM/MeOH (98/2 to 96/4) as eluent to give **(1.12)** (5.280 g, 76 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.30 (d, *J* = 6.0 Hz, 2H, $CH_{2\ Bn}$), 5.15 (s, 2H, NH_2), 6.52 (td, *J* = 7.4, 1.3 Hz, 1H, H_{Ar}), 6.65 (dd, *J* = 8.0, 1.3 Hz, 1H, H_{Ar}), 6.74 (s, 1H, H_{Ar}), 6.97 (td, *J* = 7.6, 1.6 Hz, 1H, H_{Ar}), 7.02 (dd, *J* = 7.5, 1.6 Hz, 1H, H_{Ar}), 7.74 (t, *J* = 6.0 Hz, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 42.0 ($CH_{2\ Bn}$), 105.6 (CH_{Ar}), 115.2 (CH_{Ar}), 116.1 (CH_{Ar}), 118.8 (C_q), 127.9 (CH_{Ar}), 128.1 (CH_{Ar}), 143.8 (C_q), 144.4 (C_q), 146.3 (C_q), 154.5 (C_q).

MS (ESI+) : m/z calcd for $C_{11}H_{10}Cl_2N_4$: 269.0 [M+H]+, **found :** 269.1.

Example 1.13: Synthesis of *N*-[(4-bromophenyl)methyl]-3,6-dichloro-pyridazin-4-amine (1.13)

To a solution of 3,4,6-trichloropyridazine **(a)** (4.000 g, 24.81 mmol, 1.0 eq.) in THF (87.0 mL), triethylamine (3.68 mL, 26.17 mmol, 1.2 eq.) and corresponding amine (3.03 mL, 23.99 mmol, 1.1 eq.) was added and the mixture was refluxed 3.5 h. After cooling, the solid was filtered off, washed with THF then the filtrate was concentrated. The residue was taken up in DCM (100.0 mL), washed with HCl 1M (40.0 mL) then organic layer was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with

DCM/MeOH (100/0 to 98/2) as eluent to give **(1.13)** (6.500 g, 90 %) as a pale yellow solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.49 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 6.84 (s, 1H, H_{Ar}), 7.25 – 7.35 (m, 2H, 2xH_{Ar}), 7.50 – 7.58 (m, 2H, 2xH_{Ar}), 7.97 (t, *J* = 6.4 Hz, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 44.0 ($CH_{2\ Bn}$), 105.5 (CH_{Ar}), 120.3 (C_q), 129.3 (2xCH_{Ar}), 131.4 (2xCH_{Ar}), 136.6 (C_q), 143.8 (C_q), 144.3 (C_q), 154.6 (C_q).

MS (ESI+) : m/z calcd for $C_{11}H_8BrCl_2N_3$: 331.9 [M+H]+, **found :** 331.9.

Example 1.14: Synthesis of 3,6-dichloro-*N*-[[4-(2-pyridyl)phenyl]methyl]pyridazin-4-amine (1.14)

To a solution of 3,4,6-trichloropyridazine **(a)** (0.500 g, 2.73 mmol, 1.0 eq.) in THF (13.5 mL), triethylamine (1.15 mL, 8.18 mmol, 3.0 eq.) then [4-(2-pyridyl)phenyl]methanamine (0.603 g, 3.27 mmol, 1.2 eq.) was added and the mixture was refluxed 3 h. After cooling, the mixture was filtered off, the solid was washed with THF then the filtrate was concentrated and directly purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(1.14)** (0.360 g, 40 %) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.59 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 6.86 (s, 1H, H_{Ar}), 7.33 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H, H_{Ar}), 7.45 (d, *J* = 8.1 Hz, 2H, 2xH_{Ar}), 7.86 (td, *J* = 7.7, 1.9 Hz, 1H, H_{Ar}), 7.93 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 8.02 (t, *J* = 6.0 Hz, 1H, NH_{Bn}), 8.04 – 8.10 (m, 2H, 2xH_{Ar}), 8.62 – 8.67 (m, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 44.5 ($CH_{2\ Bn}$), 105.6 (CH_{Ar}), 120.1 (CH_{Ar}), 122.6 (CH_{Ar}), 126.7 (2xCH_{Ar}), 127.4 (2xCH_{Ar}), 137.2 (CH_{Ar}), 137.7 (C_q), 138.0 (C_q), 143.9 (C_q), 144.4 (C_q), 149.5 (CH_{Ar}), 154.6 (C_q), 155.7 (C_q).

MS (ESI+) : m/z calcd for $C_{16}H_{12}Cl_2N_4$: 331.1 [M+H]+, **found :** 331.1.

Example 1.15: Synthesis of 2-(3,6-dichloropyridazin-4-yl)-3,4-dihydro-*1H*-isoquinoline (1.15)

To a solution of 3,4,6-trichloropyridazine **(a)** (5.000 g, 27.3 mmol, 1.0 eq.) in THF (54.0 mL), triethylamine (4.41 mL, 31.3 mmol, 1.1 eq.) then 2-(aminomethyl)aniline (3.228 g, 25.9 mmol, 0.95 eq.) was added and the mixture was refluxed 3.5 h. After cooling, the mixture was filtered off, the solid was washed with THF then the filtrate was concentrated

and directly purified by flash chromatography with DCM/EtOAc (100/0 to 92/8) as eluent to give **(1.15)** (6.800 g, 89 %) as a white crystalline solid.

Rf (DCM, 100%) : 0.42.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 2.99 (t, *J* = 5.8 Hz, 2H, $CH_{2\text{-}CH2\text{-}N}$), 3.69 (t, *J* = 5.8 Hz, 2H, $_{N\text{-}}CH_{2\text{-}CH2}$), 4.50 (s, 2H, $CH_{2\text{-}N}$), 7.13 – 7.29 (m, 4H, 4xH_{Ar}), 7.42 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 28.2 ($CH_{2\text{-}CH2\text{-}N}$), 47.5 ($_{N\text{-}}CH_{2\text{-}CH2}$), 50.4 ($CH_{2\text{-}N}$), 115.4 ($CH_{Ar}$), 126.1 ($CH_{Ar}$), 126.4 ($CH_{Ar}$), 126.7 ($CH_{Ar}$), 128.7 ($CH_{Ar}$), 132.8 ($C_q$), 133.9 ($C_q$), 147.9 ($C_q$), 148.9 ($C_q$), 154.9 ($C_q$).

MS (ESI+) : m/z calcd for $C_{13}H_{11}Cl_2N_3$: 280.0 [M+H]+, **found :** 280.1.

Example 1.16: Synthesis of 3,6-dichloro-N-(2-phenylethyl)pyridazin-4-amine (1.16)

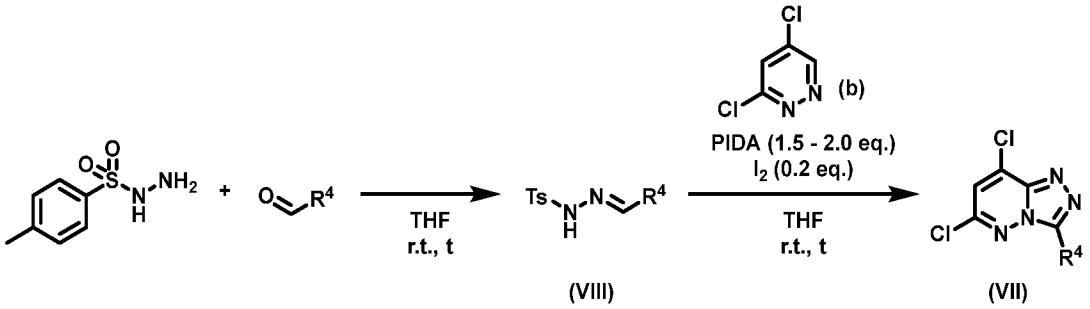
To a solution of 3,4,6-trichloropyridazine **(a)** (4.000 g, 21.8 mmol, 1.0 eq.) in THF (42 mL), Et_3N (6.45 mL, 45.8.0 mmol, 2.1 eq.) then corresponding amine hydrochloride (3.438 g, 21.8 mmol, 1.0 eq.) was added and the mixture was refluxed 3 h. After cooling, the mixture was filtered off, the solid was washed with THF then the filtrate was concentrated. The residue was triturated in HCl 1M (25.0 mL) then the resulting solid was filtered, washed with water up to neutral pH and taken up in EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated to give **(1.16)** (5.515 g, 88 %) as a beige solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 2.86 (t, *J* = 7.4 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.43 – 3.56 (m, 2H, $CH_{2\text{-}NH}$), 6.95 (s, 1H, H_{Ar}), 7.20 (ddd, *J* = 8.6, 5.6, 2.4 Hz, 1H, H_{Ar}), 7.27 (q, *J* = 4.2 Hz, 5H, NH & 5xH_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 33.8 ($CH_{2\text{-}CH2\text{-}NH}$), 43.1 ($CH_{2\text{-}NH}$), 105.2 ($CH_{Ar}$), 126.3 ($CH_{Ar}$), 128.3 (2x$CH_{Ar}$), 128.9 (2x$CH_{Ar}$), 138.8 ($C_q$), 143.5 ($C_q$), 144.3 ($C_q$), 154.7 ($C_q$).

MS (ESI+) : m/z calcd for $C_{12}H_{11}Cl_2N_3$: 268.0 [M+H]+, **found :** 268.1.

Example 2: Synthesis of 6,8-dichloro-[1,2,4]triazolo[4,3-*b*]pyridazine derivatives, as illustrated in step 1 of scheme 2



Example 2.1: Synthesis of 6,8-dichloro-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine (2.1)

A solution of 4-methylbenzenesulfonohydrazide (3.895 g, 20.91 mmol, 1.0 eq.) in THF (21.0 mL), corresponding aldehyde (1.97 mL, 21.33 mmol, 1.02 eq.) was added and the mixture was stirred 5 min at 50°C. The solvent was completely removed by evaporation then the crude residue was solubilised in THF (63.0 mL), 3,5-dichloropyridazine **(b)** (3.915 g, 24.97 mmol, 1.2 eq.) was added then successively I_2 (1.056 g, 4.16 mmol, 0.2 eq.) and portion wise PIDA (10.257g, 31.21 mmol, 1.5 eq.). The reaction was slightly exothermic and it was stirred 22 h at room temperature. Saturated $Na_2S_2O_3$ (30.0 mL) and water (15.0 mL) was added and vigorously stirred during 5 min. Layers were separated, aqueous layer was extracted twice with EtOAc (2x 20.0 mL) then organics layers were combined, washed with brine, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with EtOAc/Cyclohexane as eluent to give **(2.1)** (2.100 g, 44 %) as a pale yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.41 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.50 (hept, J = 6.9 Hz, 1H, H_{iPr}), 7.93 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 19.7 (2x$CH_{3\ iPr}$), 24.6 (CH_{iPr}), 121.2 (CH_{Ar}), 133.2 (C_q), 142.1 (C_q), 147.5 (C_q), 154.8 (C_q).

MS (ESI+) : m/z calcd for $C_8H_8Cl_2N_4$: 231.0 [M+H]+, **found :** 230.9.

Example 2.2: Synthesis of 6,8-dichloro-3-sec-butyl-[1,2,4]triazolo[4,3-*b*]pyridazine (2.2)

To a solution of 4-methylbenzenesulfonohydrazide (1.900 g, 9.90 mmol, 1.0 eq.) in THF (25.0 mL), 2-methylbutanal (1.12 mL, 9.90 mmol, 1.0 eq.) was added then the mixture was

stirred 25 min at room temperature. After completion, 3,5-dichloropyridazine **(b)** (1.552 g, 9.90 mmol, 1.0 eq.) was added then, in one portion, PIDA (6.505 g, 19.79 mmol, 2.0 eq.) and I_2 (0.502 g, 1.98 mmol, 0.2 eq.). The mixture was stirred 17 h at room temperature then saturated $Na_2S_2O_3$ (10.0 mL) and saturated $NaHCO_3$ (10.0 mL) was added, the mixture was stirred vigorously 5 min. Layers were separated and aqueous layer was extracted twice with EtOAc (2 x 10.0 mL), organics layers were combined, dried over $MgSO_4$, filtered and purified by flash chromatography with EtOAc/Cyclohexane (30/70) as eluent to give **(2.2)** (0.670 g, 28 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.86 (t, *J* = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.38 (d, *J* = 7.0 Hz, 3H, $CH_{3\text{-}CH}$), 1.69 – 2.00 (m, 2H, $CH_{2\text{-}CH3}$), 3.33 – 3.41 (m, 1H, $H_{C\text{-}CH3}$), 7.93 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 11.4 ($CH_{3\text{-}CH2}$), 17.4 ($CH_{3\text{-}CH}$), 26.7 ($CH_{2\text{-}CH3}$), 31.1 ($CH_{\text{-}CH3}$), 121.3 (CH_{Ar}), 133.3 (C_q), 142.1 (C_q), 147.6 (C_q), 154.0 (C_q).

MS (ESI+) : m/z calcd for $C_9H_{10}Cl_2N_4$: 245.0 [M+H]+, **found :** 245.1.

Example 2.3: Synthesis of 6,8-dichloro-3-(1-ethylpropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine (2.3)

To a solution of 4-methylbenzenesulfonohydrazide (1.600 g, 8.59 mmol, 1.0 eq.) in THF (20.0 mL), 2-ethylbutanal (1.14 mL, 8.59 mmol, 1.0 eq.) was added then the mixture was stirred 25 min at room temperature. After completion, 3,5-dichloropyridazine **(b)** (1.307 g, 8.59 mmol, 1.0 eq.) was added then PIDA (5.478 g, 16.67 mmol, 2.0 eq.) and I_2 (0.423 g, 1.67 mmol, 0.2 eq.) in one portion. The mixture was stirred 17 h at room temperature then saturated $Na_2S_2O_3$ (10.0 mL) and saturated $NaHCO_3$ (10.0 mL) was added, the mixture was stirred vigorously 5 min. Layers were separated and aqueous layer was extracted twice with EtOAc (2 x 10.0 mL), organics layers were combined, dried over $MgSO_4$, filtered and purified by flash chromatography with EtOAc/Cyclohexane (30/70) as eluent to give **(2.3)** (0.570 g, 26 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.80 (t, *J* = 7.4 Hz, 6H, $2xCH_{3\text{-}CH2}$), 1.75 – 1.97 (m, 4H, $2xCH_{2\text{-}CH3}$), 3.23 (tt, *J* = 8.3, 5.7 Hz, 1H, H_{iPent}), 7.94 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 11.4 ($2xCH_{3\text{-}CH2}$), 24.8 ($2xCH_{2\text{-}CH3}$), 38.3 (CH_{iPent}), 121.3 (CH_{Ar}), 133.3 (C_q), 142.1 (C_q), 147.7 (C_q),

MS (ESI+) : m/z calcd for $C_{10}H_{12}Cl_2N_4$: 259.1 [M+H]+, **found :** 259.1.

Example 2.4: Synthesis of 6,8-dichloro-3-isobutyl-[1,2,4]triazolo[4,3-*b*]pyridazine (2.4)

To a solution of 4-methylbenzenesulfonohydrazide (1.000 g, 5.37 mmol, 1.0 eq.) in THF (20.0 mL), 3-methylbutanal (0.58 mL, 5.37 mmol, 1.0 eq.) was added then the mixture was stirred 20 min at room temperature. After completion, 3,5-dichloropyridazine **(b)** (0.927 g, 5.91 mmol, 1.1 eq.) was added then, in one portion, PIDA (3.530 g, 10.74 mmol, 2.0 eq.) and I_2 (0.273 g, 1.07 mmol, 0.2 eq.). The mixture was stirred 2 h at room temperature then saturated $Na_2S_2O_3$ (20.0 mL) and H_2O (10.0 mL) was added, the mixture was stirred vigorously 5 min. Layers were separated and aqueous layer was extracted twice with EtOAc (2 x 20.0 mL), organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with EtOAc/Cyclohexane (85/15 to 50/50) as eluent to give **(2.4)** (0.452 g, 34 %) as a beige solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.96 (d, J = 6.7 Hz, 6H, 2x$CH_{3\ iPr}$), 2.23 (dp, J = 13.6, 6.8 Hz, 1H, H_{iPr}), 2.97 (d, J = 7.1 Hz, 2H, $CH_{2\text{-}CH}$), 7.93 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 22.2 (2x$CH_{3\ iPr}$), 26.3 ($CH_{\text{-}CH2}$), 32.2 ($CH_{2\text{-}CH}$), 121.2 (CH_{Ar}), 133.2 (C_q), 141.9 (C_q), 147.7 (C_q), 150.1 (C_q).

MS (ESI+) : m/z calcd for $C_9H_{12}Cl_2N_4$: 245.0 [M+H]+, **found :** 245.1.

Example 2.5: Synthesis of 6,8-dichloro-3-cyclopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine (2.5)

To a solution of 3,5-dichloropyridazine **(b)** (2.000 g, 12.7 mmol, 1.0 eq.) and *N*-(cyclopropylmethyleneamino)-4-methyl-benzenesulfonamide (4.559 g, 19.1 mmol, 1.5 eq.) in THF (95.0 mL), PIDA (6.288 g, 19.1mmol, 1.5 eq.) and I_2 (0.647 g, 2.5 mmol, 0.2 eq.) was added in one portion and the mixture was stirred 2 h at room temperature. After completion, a mixture of saturated $Na_2S_2O_3$ (20.0 mL) and water (10.0 mL) was added, the biphasique mixture was vigorously stirred 5 min then layers were separated. Aqueous layer was extracted twice with EtOAc (2 x 15.0 mL) and organics layers were combined, dried over $MgSO_4$, filtered and purified by flash chromatography with EtOAc/Cyclohexane (75/25 then 70/30) as eluent to give **(2.5)** (0.400 g, 14 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.07 – 1.27 (m, 4H, 2x$CH_{2\ cPr}$), 2.40 (tt, J = 8.3, 5.0 Hz, 1H, H_{cPr}), 7.91 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.9 (CH_{cPr}), 7.5 ($2xCH_{2\ cPr}$), 121.1 (CH_{Ar}), 133.1 (C_q), 142.1 (C_q), 147.7 (C_q), 152.3 (C_q).

MS (ESI+) : m/z calcd for $C_8H_6Cl_2N_4$: 229.0 [M+H]+, **found :** 228.9.

Example 2.6: Synthesis of 6,8-dichloro-3-cyclopentyl-[1,2,4]triazolo[4,3-*b*]pyridazine (2.6)

To a solution of 4-methylbenzenesulfonohydrazide (1.800 g, 9.38 mmol, 1.0 eq.) in THF (140.0 mL), cyclopentanecarbaldehyde (0.995 g, 9.84 mmol, 1.05 eq.) was added then the mixture was stirred 20 min at room temperature. After completion, 3,5-dichloropyridazine **(b)** (1.470 g, 9.38 mmol, 1.0 eq.) was added then, in one portion, PIDA (4.622 g, 14.06 mmol, 1.5 eq.) and I_2 (0.476 g, 1.88 mmol, 0.2 eq.). The mixture was stirred 1.3 h at room temperature then partially concentrated, the residue was diluted in EtOAc (50.0 mL). Organic layer was washed with a mixture of saturated $Na_2S_2O_3$ (40.0 mL) and water (80.0 mL). Aqueous layer was extracted twice with EtOAc (2 x 30.0 mL) and organics layers were combined, dried over $MgSO_4$, filtered and purified by flash chromatography with EtOAc/Cyclohexane (15/85 to 50/50) as eluent to give **(2.6)** (0.260 g, 11 %) as a white flakes.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.63 – 1.86 (m, 4H, $2xCH_{2\ cPent}$), 1.90 – 2.03 (m, 2H, $CH_{2\ cPent}$), 2.11 (dq, *J* = 12.3, 7.0, 6.0 Hz, 2H, $CH_{2\ cPent}$), 3.61 (p, *J* = 7.9 Hz, 1H, H_{cPent}), 7.92 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 25.1 ($2xCH_{2\ cPent}$), 30.1 ($2xCH_{2\ cPent}$), 34.3 (CH_{cPent}), 121.2 (CH_{Ar}), 133.2 (C_q), 142.2 (C_q), 147.5 (C_q), 154.0 (C_q).

MS (ESI+) : m/z calcd for $C_{10}H_{10}Cl_2N_4$: 257.0 [M+H]+, **found :** 257.1.

Example 2.7: Synthesis of 6,8-dichloro-3-sec-butyl-[1,2,4]triazolo[4,3-*b*]pyridazine (2.7)

To a solution of 4-methylbenzenesulfonohydrazide (1.102 g, 5.74 mmol, 1.2 eq.) in THF (15.0 mL), butanal (0.52 mL, 5.74 mmol, 1.2 eq.) was added then the mixture was stirred 10 min at room temperature. After completion, 3,5-dichloropyridazine **(b)** (0.750 g, 4.78 mmol, 1.0 eq.) was added then, in one portion, PIDA (6.505 g, 19.79 mmol, 2.0 eq.) and I_2 (0.502 g, 1.98 mmol, 0.2 eq.). The mixture was stirred 17 h at room temperature then

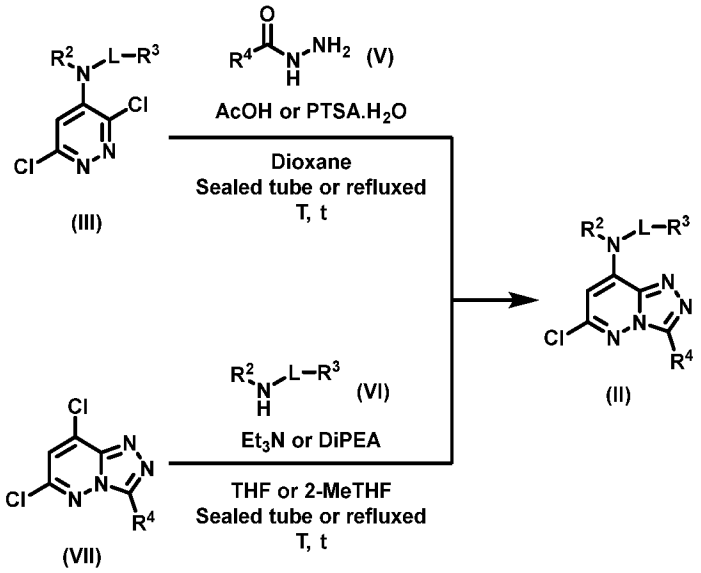
saturated $Na_2S_2O_3$ (10.0 mL) and saturated $NaHCO_3$ (10.0 mL) was added, the mixture was stirred vigorously 5 min. Layers were separated and aqueous layer was extracted twice with EtOAc (2 x 10.0 mL), organics layers were combined, dried over $MgSO_4$, filtered and purified by flash chromatography with EtOAc/Cyclohexane (30/70) as eluent to give **(2.7)** (0.957g with impurities (RMN purity 70%), calculated = 0.670 g, 28 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.86 (t, *J* = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.38 (d, *J* = 7.0 Hz, 3H, $CH_{3\text{-}CH}$), 1.69 – 2.00 (m, 2H, $CH_{2\text{-}CH3}$), 3.33 – 3.41 (m, 1H, $H_{C\text{-}CH3}$), 7.93 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 11.4 ($CH_{3\text{-}CH2}$), 17.4 ($CH_{3\text{-}CH}$), 26.7 ($CH_{2\text{-}CH3}$), 31.1 ($CH_{\text{-}CH3}$), 121.3 (CH_{Ar}), 133.3 (C_q), 142.1 (C_q), 147.6 (C_q), 154.0 (C_q).

MS (ESI+) : m/z calcd for $C_9H_{10}Cl_2N_4$: 245.0 [M+H]+, **found :** 245.1.

<u>Example 3</u>: Synthesis of 6-chloro-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine derivatives, as illustrated in step 2 of scheme 1 or in step 2 of scheme 2



Example 3.1: Synthesis of *N*-benzyl-6-chloro-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-8-amine (3.1)

In a sealed tube 10 – 20 mL with a stir bar was charged, **(1.1)** (0.250 g, 0.98 mmol, 1.0 eq.), dioxane (3.5 mL), isobutyric acid hydrazide (0.121 g, 1.18 mmol, 1.2 eq.) and AcOH (0.05 mL, 0.79 mmol, 0.8 eq.). The vial was sealed and then put on heating block, 4 h at 100 °C. The reaction mixture was cooled and $NaHCO_3$ sat. (8.0 mL) was added then

diluted with water (8.0 mL). The precipitate was filtered off, washed with water up to neutral pH then triturated in Et_2O and dried under vacuum to give the title compound **(3.1)** (0.220 g, 74 %) as a white solid.

Rf (DCM/EtOAc, 75/25) : 0.30.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.38 (d, *J* = 6.9 Hz, 6H, 2xCH_3), 3.43 (hept, *J* = 7.1 Hz, 1H, H_{Alk}), 4.60 (d, *J* = 4.2 Hz, 2H, CH_2), 6.14 (s, 1H, H_{Ar}), 7.22 – 7.31 (m, 1H, H_{Ar}), 7.32 – 7.44 (m, 4H, 4xH_{Ar}), 9.13 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 20.3 (CH_3), 24.9 (CH_{Alk}), 45.6 (CH_2), 92.0 (CH_{Ar}), 127.6 (CH_{Ar}), 127.7 (CH_{Ar}), 129.0 (CH_{Ar}), 137.9 (C_q), 139.9 (C_q), 142.8 (C_q), 149.9 (C_q), 154.4 (C_q).

MS (ESI+) : m/z calcd for $C_{15}H_{16}ClN_5$: 302.12 [M+H]+, **found :** 302.33.

Example 3.2: Synthesis of *N*-benzyl-6-chloro-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.2)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(1.1)** (0.850 g, 3.34 mmol, 1.0 eq.), dioxane (17.0 mL), formic hydrazide (0.221 g, 3.68 mmol, 1.1 eq.) and PTSA.H_2O (0.318 g, 1.67 mmol, 0.5 eq.). The mixture was refluxed for 36 h and after cooling, MeOH (2mL) then DCM (2mL) was added. The mixture was concentrated and purified by flash chromatography with DCM/EtOAc (8/2) as eluent to give the title compound **(3.2)** (0.250 g, 29 %) as a white solid.

Rf (DCM/EtOAc, 75/25) : 0.21.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.60 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 6.17 (s, 1H, H_{Ar}), 7.26 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 7.35 (t, *J* = 7.4 Hz, 2H, 2xH_{Ar}), 7.40 (d, *J* = 7.6 Hz, 2H, 2xH_{Ar}), 9.17 (s, 1H, NH), 9.41 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 45.2 (CH_2), 92.1 (CH_{Ar}), 127.2 (2xCH_{Ar}), 127.2 (CH_{Ar}), 128.5 (2xCH_{Ar}), 137.4 (C_q), 139.1 (C_q), 139.6 (CH_{Ar}), 142.1 (C_q), 150.0 (C_q).

MS (ESI+) : m/z calcd for $C_{12}H_{10}ClN_5$: 260.07 [M+H]+, **found :** 260.1.

Example 3.3: Synthesis of *N*-benzyl-6-chloro-3-cyclopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.3)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(1.1)** (0.300 g, 1.18 mmol, 1.0 eq.), dioxane (3.9 mL), cyclopropanecarboxylic acid hydrazide (0.130 g, 1.30 mmol, 1.1 eq.)

and PTSA.H_2O (0.023 g, 0.12 mmol, 0.1 eq.). The vial was sealed and then put on heating block, 20 h at 100 °C. The reaction mixture was cooled and MeOH (2mL) then DCM (2mL) was added. The mixture was concentrated and purified by flash chromatography with DCM/EtOAc (7/3) as eluent to give the title compound **(3.3)** (0.184 g, 52 %) as a white solid.

Rf (DCM/EtOAc, 7/3) : 0.44

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.06 – 1.15 (m, 4H, 2x$CH_{2\ Alk}$), 2.31 (ddd, *J* = 13.3, 8.0, 5.4 Hz, 1H, H_{Alk}), 4.58 (d, *J* = 6.5 Hz, 2H, CH_2), 6.12 (s, 1H, H_{Ar}), 7.26 (t, *J* = 7.1 Hz, 1H, H_{Ar}), 7.32 – 7.41 (m, 4H, 4xH_{Ar}), 9.08 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.8 (CH_{Alk}), 7.1 (2x$CH_{2\ Alk}$), 45.1 (CH_2), 91.5 (CH), 127.2 (2xCH_{Ar}), 127.2 (CH_{Ar}), 128.5 (2xCH_{Ar}), 137.4 (C_q), 139.4 (C_q), 142.3 (C_q), 149.6 (C_q), 151.4 (C_q).

MS (ESI+) : m/z calcd for $C_{15}H_{14}ClN_5$: 300.1 [M+H]+, **found :** 300.1.

Example 3.4: Synthesis of *N*-benzyl-6-chloro-3-cyclopentyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.4)

To a solution of **(2.6)** (0.200 g, 0.75 mmol, 1.0 eq.) in THF (15.0 mL), corresponding amine (0.17 mL, 1.51 mmol, 2.0 eq.) and Et_3N (0.21 mL, 1.51 mmol, 2.0 eq.) was added then the mixture was refluxed in 3 h. After cooling, the mixture was concentrated and the residue was triturated in water, solid was filtered off, washed wih water, then Et_2O and dried under vacuum to give **(3.4)** (0.220 g, 89 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.61 – 1.84 (m, 4H, 2x$CH_{2\ cPent}$), 1.92 (dq, *J* = 12.0, 7.4 Hz, 2H, $CH_{2\ cPent}$), 2.02 – 2.18 (m, 2H, $CH_{2\ cPent}$), 3.52 (p, *J* = 8.0 Hz, 1H, H_{cPent}), 4.58 (s, 2H, $CH_{2\ Bn}$), 6.13 (s, 1H, H_{Ar}), 7.26 (t, *J* = 7.1 Hz, 1H, H_{Ar}), 7.34 (t, *J* = 7.5 Hz, 2H, 2xH_{Ar}), 7.39 (d, *J* = 7.5 Hz, 2H, 2xH_{Ar}), 9.09 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 25.0 (2x$CH_{2\ cPent}$), 30.2 (2x$CH_{2\ cPent}$), 34.3 (CH_{cPent}), 45.1 ($CH_{2\ Bn}$), 91.5 (CH_{Ar}), 127.2 (2xCH_{Ar}), 127.2 (CH_{Ar}), 128.5 (2xCH_{Ar}), 137.4 (C_q), 139.5 (C_q), 142.28 (C_q), 149.4 (C_q), 153.1 (C_q).

MS (ESI+) : m/z calcd for $C_{17}H_{18}ClN_5$: 328.1 [M+H]+, **found :** 328.2.

Example 3.5: Synthesis of *N*-benzyl-6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.5)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(1.1)** (0.300 g, 1.18 mmol, 1.0 eq.), dioxane (3.9 mL), trifluoroacetic acid hydrazide (0.166 g, 1.30 mmol, 1.1 eq.) and PTSA.H_2O (0.023 g, 0.12 mmol, 0.1 eq.). The vial was sealed and then put on heating block, 20 h at 100 °C. The reaction mixture was cooled and MeOH (2mL) then DCM (2mL) was added. The mixture was concentrated and purified by flash chromatography with DCM/EtOAc (9/1) as eluent to give the title compound **(3.5)** (0.070 g, 18 %) as a white solid.

Rf (DCM/EtOAc, 9/1) : 0.63

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.65 (d, *J* = 6.2 Hz, 2H, CH_2), 6.43 (s, 1H, H_{Ar}), 7.28 (dq, *J* = 7.2, 4.9, 3.3 Hz, 1H, H_{Ar}), 7.35 (dd, *J* = 8.3, 6.6 Hz, 2H, 2xH_{Ar}), 7.41 (d, *J* = 7.2 Hz, 2H, 2xH_{Ar}), 9.52 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 45.19 (CH_2), 93.80 (CH_{Ar}), 118.24 (q, *J* = 269.9 Hz, CF_3), 127.26 (2xCH_{Ar}), 127.32 (CH_{Ar}), 128.53 (2xCH_{Ar}), 136.98 (C_q), 138.45 (q, *J* = 41.0, 40.3 Hz, $C_{q\text{-}CF3}$), 141.85 (C_q), 142.29 (C_q), 151.64 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_9ClF_3N_5$: 328.1 [M+H]+, **found :** 328.1.

Example 3.6: Synthesis of *N*-benzyl-6-chloro-3-methyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.6)

To a solution of **(1.1)** (0.750 g, 2.95 mmol, 1.0 eq.) in dioxane (15.0 mL), acetohydrazide (0.228 g, 3.25 mmol, 1.1 eq.) and PTSA.H_2O (0.281 g, 1.48 mmol, 0.5 eq.) was added and refluxed during 24 h. The reaction mixture was cooled and MeOH (10.0 mL) was added. The mixture was concentrated with SiO_2 to make solid deposit and directly purified by flash chromatography with DCM/EtOAc/MeOH (60/40/0 to 60/30/10) as eluent to give the title compound **(3.6)** (0.350 g, 43 %) as a white solid.

Rf (DCM/EtOAc, 75/25) : 0.24

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 2.58 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 6.14 (s, 1H, H_{Ar}), 7.22 – 7.42 (m, 5H, 5xH_{Ar}), 9.09 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 9.4 (CH_3), 45.1 (CH_2), 91.4 (CH_{Ar}), 127.1 (2xCH_{Ar}), 127.2 (CH_{Ar}), 128.5 (2xCH_{Ar}), 137.4 (C_q), 139.2 (C_q), 142.3 (C_q), 146.8 (C_q), 149.6 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{12}ClN_5$: 274.1 [M+H]+, **found :** 274.1.

Example 3.7: Synthesis of *N*-benzyl-6-chloro-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.7)

To a solution of **(1.1)** (0.750 g, 2.95 mmol, 1.0 eq.) in dioxane (15.0 mL), benzohydrazide (0.442 g, 3.25 mmol, 1.1 eq.) and PTSA.H_2O (0.281 g, 1.48 mmol, 0.5 eq.) was added and refluxed during 22.5 h. The reaction mixture was cooled and MeOH (5.0 mL) was added. The mixture was concentrated with SiO_2 to make solid deposit and directly purified by flash chromatography with DCM/MeOH (94/6) as eluent to give the title compound **(3.7)** (0.425 g, 46 %) as a white solid.

Rf (DCM/MeOH, 94/6) : 0.46

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.64 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 6.27 (s, 1H, H_{Ar}), 7.27 (t, *J* = 7.2 Hz, 1H, H_{Ar}), 7.36 (t, *J* = 7.5 Hz, 2H, 2xH_{Ar}), 7.43 (d, *J* = 7.6 Hz, 2H, 2xH_{Ar}), 7.58 (dt, *J* = 13.3, 7.2 Hz, 3H, 3xH_{Ar}), 8.31 (d, *J* = 7.5 Hz, 2H, 2xH_{Ar}), 9.25 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{18}H_{14}ClN_5$: 336.1 [M+H]+, **found :** 336.1.

Example 3.8: Synthesis of 2-[[(6-chloro-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl)amino]methyl]phenol (3.8)

To a suspension of **(1.7)** (1.900 g, 7.03 mmol, 1.0 eq.) in dioxane (40.0 mL), isobutyric acid hydrazide (1.150 g, 11.25 mmol, 1.6 eq.) then AcOH (0.45 mL, 7.74 mmol, 1.1 eq.) was added. The mixture was refluxed 16 h and after cooling, MeOH (5.0 mL) was added then SiO_2 to make solid deposit directly. The mixture was concentrated and purified by flash chromatography with DCM/MeOH (97/3 to 93/7) as eluent to give **(3.8)** (1.000 g, 45 %) as a white solid.

Rf (DCM/MeOH, 92/8) : 0.15

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.38 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.42 (p, *J* = 6.9 Hz, 1H, CH_{iPr}), 4.37 – 4.61 (m, 2H, $CH_{2\ Bn}$), 6.12 (s, 1H, CH_{Ar}), 6.76 (t, *J* = 7.4 Hz, 1H, CH_{Ar}), 6.85 (d, *J* = 8.0 Hz, 1H, CH_{Ar}), 7.10 (t, *J* = 7.7 Hz, 1H, CH_{Ar}), 7.18 (d, *J* = 7.6 Hz, 1H, CH_{Ar}), 8.90 (s, 1H, NH_{Bn}), 9.82 (s, 1H, OH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 40.2 ($CH_{2\ Bn}$), 91.3 (CH_{Ar}), 115.1 (CH_{Ar}), 119.1 (CH_{Ar}), 122.9 (C_q), 128.4 (2xCH_{Ar}), 139.4 (C_q), 142.3 (C_q), 149.4 (C_q), 154.0 (C_q), 154.8 (C_q).

MS (ESI+) : m/z calcd for $C_{15}H_{16}ClN_5O$: 318.1 [M+H]+, **found :** 318.2.

Example 3.9: Synthesis of 3-[[(6-chloro-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl)amino]methyl]phenol (3.9)

In a sealed vial 10 - 20 mL with a stir bar was charged **(1.6)** (0.460 g, 1.70 mmol, 1.0 eq.) in dioxane (10.0 mL), isobutyric acid hydrazide (0.211 g, 2.04 mmol, 1.2 eq.) and PTSA.H_2O (0.197 g, 1.02 mmol, 0.6 eq.) was added. The vial was sealed and put on heating bloc 17 h at 100°C. After cooling, MeOH (3.0 mL) was added then the mixture was concentrated with SiO_2 to make solid deposit and directly purified by flash chromatography with DCM/MeOH (97/3 to 94/6) as eluent to give **(3.9)** (0.250 g, 46 %) as a white solid.

Rf (DCM/MeOH, 92/8) : 0.23

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.38 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.42 (p, J = 7.0 Hz, 1H, H_{iPr}), 4.50 (d, J = 6.2 Hz, 2H, $CH_{2\ Bn}$), 6.09 (s, 1H, H_{Ar}), 6.64 (dd, J = 8.0, 1.8 Hz, 1H, H_{Ar}), 6.75 (t, J = 2.0 Hz, 1H, H_{Ar}), 6.79 (d, J = 7.6 Hz, 1H, H_{Ar}), 7.12 (t, J = 7.8 Hz, 1H, H_{Ar}), 9.09 (s, 1H, NH_{Bn}), 9.37 (s, 1H, OH).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 19.9 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 45.0 ($CH_{2\ Bn}$), 91.5 (CH_{Ar}), 113.7 (CH_{Ar}), 114.2 (CH_{Ar}), 117.7 (CH_{Ar}), 129.5 (CH_{Ar}), 138.8 (Cq), 139.4 (Cq), 142.3 (Cq), 149.4 (Cq), 154.0 (Cq), 157.5 (Cq).

MS (ESI+) : m/z calcd for $C_{15}H_{16}ClN_5O$: 318.1 [M+H]+, **found :** 318.3.

Example 3.10: Synthesis of 4-[[(6-chloro-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl)amino]methyl]phenol (3.10)

In a sealed vial 10 - 20 mL with a stir bar was charged **(1.5)** (0.520 g, 1.93 mmol, 1.0 eq.) in dioxane (10.0 mL), isobutyric acid hydrazide (0.238 g, 2.31 mmol, 1.2 eq.) and PTSA.H_2O (0.223 g, 1.16 mmol, 0.6 eq.) was added. The vial was sealed and put on heating bloc 17 h at 100°C. After cooling, MeOH (3.0 mL) was added then the mixture was concentrated with SiO_2 to make solid deposit and directly purified by flash chromatography with DCM/MeOH (97/3 to 94/6) as eluent to give **(3.10)** (0.115 g, 19 %) as a white solid.

Rf (DCM/MeOH, 92/8) : 0.25.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.37 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.41 (hept, *J* = 7.0 Hz, 1H, H_{iPr}), 4.44 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 6.12 (s, 1H, H_{Ar}), 6.71 (d, *J* = 8.5 Hz, 2H, 2xH_{Ar}), 7.20 (d, *J* = 8.5 Hz, 2H, 2xH_{Ar}), 9.02 (s, 1H, NH_{Bn}), 9.34 (s, 1H, OH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 44.7 ($CH_{2\ Bn}$), 91.4 (CH_{Ar}), 115.2 (2xCH_{Ar}), 127.5 (C_q), 128.6 (2xCH_{Ar}), 139.5 (C_q), 142.2 (C_q), 149.4 (C_q), 153.9 (C_q), 156.6 (C_q).

MS (ESI+) : m/z calcd for $C_{15}H_{16}ClN_5O$: 318.1 [M+H]+, **found :** 318.3.

Example 3.11: Synthesis of 6-chloro-3-isopropyl-*N*-[(2-methoxyphenyl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.11)

To a suspension of **(1.8)** (3.000 g, 10.56 mmol, 1.0 eq.) in dioxane (40.0 mL), isobutyric acid hydrazide (1.307 g, 12.67 mmol, 1.2 eq.) then AcOH (0.67 mL, 11.61 mmol, 1.1 eq.) was added and the mixture was refluxed 16 h. After cooling, MeOH (10.0 mL) was added, stirred vigorously 5 min then SiO_2 to make solid deposit directly. The mixture was concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 97/3) as eluent to give **(3.11)** (1.490 g, 43 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.38 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.43 (hept, *J* = 7.1 Hz, 1H, H_{iPr}), 3.87 (s, 3H, OCH_3), 4.51 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 6.06 (s, 1H, H_{Ar}), 6.91 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 7.05 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.22 (d, *J* = 7.5 Hz, 1H, H_{Ar}), 7.28 (td, *J* = 7.9, 1.8 Hz, 1H, H_{Ar}), 8.90 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 40.2 ($CH_{2\ Bn}$), 55.4 (OCH_3), 91.3 (CH_{Ar}), 110.8 (CH_{Ar}), 120.4 (CH_{Ar}), 124.4 (C_q), 127.7 (CH_{Ar}), 128.6 (CH_{Ar}), 139.4 (C_q), 142.4 (C_q), 149.4 (C_q), 154.0 (C_q), 156.7 (C_q).

MS (ESI+) : m/z calcd for $C_{16}H_{18}ClN_5O$: 332.1 [M+H]+, **found :** 332.3.

Example 3.12: Synthesis of 6-chloro-3-isopropyl-*N*-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.12)

To a solution of **(2.1)** (0.150 g, 0.65 mmol, 1.0 eq.) in dry THF (5.0 mL), aniline (0.12 mL, 1.30 mmol, 2.0 eq.) then tBuOK 1M in THF (1.30 mL, 1.30 mmol, 2.0 eq.) was added and the mixture was stirred 1 h at room temperature. After completion, saturated NH_4Cl (5.0 mL) and water (1.5 mL) was added then biphasic mixture was vigorously stirred 5 min. Layers were separated, aqueous layer was extracted with EtOAc (2x5.0 mL) then organic

layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 98/2) as eluent to give **(3.12)** (0.175 g, 94 %) as a white solid.

Rf (DCM/MeOH, 96/4) : 0.40

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.41 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.48 (hept, *J* = 6.9 Hz, 1H, H_{iPr}), 6.35 (s, 1H, H_{Ar}), 7.27 (tt, *J* = 5.7, 2.4 Hz, 1H, H_{Ar}), 7.40 – 7.58 (m, 4H, 4xH_{Ar}), 10.46 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.5 (CH_{iPr}), 92.9 (CH_{Ar}), 123.6 (2xCH_{Ar}), 125.7 (CH_{Ar}), 129.5 (2xCH_{Ar}), 137.7 (C_q), 139.5 (C_q), 140.2 (C_q), 149.6 (C_q), 154.2 (C_q).

MS (ESI+) : m/z calcd for $C_{14}H_{14}ClN_5$: 288.1 [M+H]+, **found :** 288.1.

Example 3.13: Synthesis of 6-chloro-3-isopropyl-*N*-(2-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.13)

To a solution of **(2.1)** (0.100 g, 0.43 mmol, 1.0 eq.) in dry THF (5.0 mL), 2-aminopyridine (0.082, 0.87 mmol, 2.0 eq.) then tBuOK 1M in THF (0.87 mL, 0.87 mmol, 2.0 eq.) was added and the mixture was stirred 1 h at room temperature. After completion, saturated NH_4Cl (3.5 mL) and water (1.5 mL) was added then biphasic mixture was vigorously stirred 5 min. Layers were separated, aqueous layer was extracted with EtOAc (2x5.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2) as eluent to give **(3.13)** (0.120 g, 96 %) as a white solid.

Rf (DCM/MeOH, 96/4) : 0.27

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.42 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.50 (hept, *J* = 7.1, 6.5 Hz, 1H, H_{iPr}), 7.13 (ddd, *J* = 7.4, 5.0, 1.0 Hz, 1H, H_{Ar}), 7.61 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 7.82 (ddd, *J* = 9.0, 7.3, 2.0 Hz, 1H, H_{Ar}), 8.32 (s, 1H, H_{Ar}), 8.46 (d, *J* = 1.9 Hz, 1H, H_{Ar}), 10.90 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.5 (CH_{iPr}), 99.5 (CH_{Ar}), 114.7 (CH_{Ar}), 118.6 (CH_{Ar}), 136.6 (C_q), 138.3 (CH_{Ar}), 139.3 (C_q), 147.3 (CH_{Ar}), 149.7 (C_q), 153.9 (C_q), 154.3 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{13}ClN_6$: 289.1 [M+H]+, **found :** 289.2.

Example 3.14: Synthesis of 6-chloro-3-isopropyl-*N*-(3-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.14)

To a solution of **(2.1)** (0.100 g, 0.43 mmol, 1.0 eq.) in dry THF (5.0 mL), 3-aminopyridine (0.082, 0.87 mmol, 2.0 eq.) then tBuOK 1M in THF (0.87 mL, 0.87 mmol, 2.0 eq.) was added and the mixture was stirred 1 h at room temperature. After completion, saturated NH_4Cl (3.5 mL) and water (1.5 mL) was added then biphasic mixture was vigorously stirred 5 min. Layers were separated, aqueous layer was extracted with EtOAc (2x5.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 96/4) as eluent to give **(3.14)** (0.115 g, 92 %) as a white solid.

Rf (DCM/MeOH, 96/4) : 0.17

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.41 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.48 (hept, J = 6.9 Hz, 1H, H_{iPr}), 6.43 (s, 1H, H_{Ar}), 7.50 (dd, J = 8.2, 4.7 Hz, 1H, H_{Ar}), 7.91 (dt, J = 8.3, 1.9 Hz, 1H, H_{Ar}), 8.46 (dd, J = 4.8, 1.5 Hz, 1H, H_{Ar}), 8.69 (d, J = 2.6 Hz, 1H, H_{Ar}), 10.55 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 19.8 (2x$CH_{3\ iPr}$), 24.5 (CH_{iPr}), 93.8 (CH_{Ar}), 124.1 (CH_{Ar}), 130.8 (CH_{Ar}), 134.6 (C_q), 139.4 (C_q), 140.0 (C_q), 145.1 (CH_{Ar}), 146.4 (CH_{Ar}), 149.6 (C_q), 154.2 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{13}ClN_6$: 289.1 [M+H]+, **found :** 289.1.

Example 3.15: Synthesis of 6-chloro-3-isopropyl-*N*-(4-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.15)

To a solution of **(2.1)** (0.150 g, 0.65 mmol, 1.0 eq.) in dry THF (5.0 mL), 4-aminopyridine (0.123 g, 1.30 mmol, 2.0 eq.) then tBuOK 1M in THF (1.30 mL, 1.30 mmol, 2.0 eq.) was added and the mixture was stirred 1 h at room temperature. After completion, saturated NH_4Cl (5.0 mL) and water (1.5 mL) was added then biphasic mixture was vigorously stirred 5 min. Layers were separated, aqueous layer was extracted with EtOAc (2x5.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **(3.15)** (0.180 g, 96 %) as a white solid.

Rf (DCM/MeOH, 96/4) : 0.10

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.42 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.50 (hept, *J* = 6.9 Hz, 1H, H_{iPr}), 6.88 (s, 1H, H_{Ar}), 7.34 – 7.70 (m, 2H, 2xH_{Ar}), 8.39 – 8.68 (m, 2H, 2xH_{Ar}), 10.69 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.5 (CHi_{Pr}), 96.7 (CH_{Ar}), 115.5 (CH_{Ar}), 138.1 (C_q), 139.5 (C_q), 145.7 (C_q), 149.6 (C_q), 150.8 (CH_{Ar}), 154.3 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{13}ClN_6$: 289.1 [M+H]+, **found :** 289.1.

Example 3.16: Synthesis of 6-chloro-3-isopropyl-*N*-(4-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.16)

To a suspension of **(1.4)** (0.390 g, 1.53 mmol, 1.0 eq.) in dioxane (25.0 mL), isobutyric acid hydrazide (0.189 g, 1.89 mmol, 1.2 eq.) then APTS.H_2O (0.177 g, 0.92 mmol, 0.6 eq.) was added and the mixture was refluxed 20 h. After cooling, DCM (5.0 mL), MeOH (5.0 mL) and $NaHCO_3$ (0.100 g) was added and the mixture was stirred vigorously 5 min. SiO_2 was added to make solid deposit, the mixture was concentrated and purified by flash chromatography with DCM/MeOH (95/5 to 93/7) as eluent to give **(3.16)** (0.175 g, 38 %) as a beige solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.38 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.43 (p, *J* = 7.0 Hz, 1H, H_{iPr}), 4.64 (s, 2H, $CH_{2\ Bn}$), 6.15 (s, 1H, H_{Ar}), 7.31 – 7.43 (m, 2H, 2xH_{Ar}), 8.44 – 8.60 (m, 2H, 2xH_{Ar}), 9.12 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 44.1 ($CH_{2\ Bn}$), 91.7 (CH_{Ar}), 122.1 (2xCH_{Ar}), 139.4 (Cq), 142.4 (Cq), 146.5 (C_q), 149.5 (Cq), 149.7 (2xCH_{Ar}), 154.0 (Cq).

MS (ESI+) : m/z calcd for $C_{14}H_{15}ClN_6$: 303.1 [M+H]+, **found :** 303.2.

Example 3.17: Synthesis of 6-chloro-3-isopropyl-*N*-(3-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.17)

To a suspension of **(1.3)** (1.500 g, 5.88 mmol, 1.0 eq.) in dioxane (20.0 mL), isobutyric acid hydrazide (0.667 g, 6.47 mmol, 1.1 eq.) then AcOH (0.37 mL, 6.47 mmol, 1.1 eq.) was added and the mixture was refluxed 16 h. After cooling, MeOH (10.0 mL) and $NaHCO_3$ (1.000 g) was added, stirred vigorously 5 min then SiO_2 to make solid deposit directly. The mixture was concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give **(3.17)** (0.700 g, 39 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.37 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.42 (hept, *J* = 7.1 Hz, 1H, H_{iPr}), 4.63 (s, 2H, $CH_{2\ Bn}$), 6.26 (s, 1H, H_{Ar}), 7.37 (dd, *J* = 7.9, 4.8 Hz, 1H, H_{Ar}), 7.79 (dt, *J* = 7.9, 2.0 Hz, 1H, H_{Ar}), 8.48 (dd, *J* = 4.9, 1.6 Hz, 1H, H_{Ar}), 8.64 (d, *J* = 2.3 Hz, 1H, H_{Ar}), 9.10 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 42.8 ($CH_{2\ Bn}$), 91.6 (CH_{Ar}), 123.6 (CH_{Ar}), 133.1 (C_q), 135.1 (CH_{Ar}), 139.4 (C_q), 142.2 (C_q), 148.5 (CH_{Ar}), 148.9 (CH_{Ar}), 149.5 (C_q), 154.0 (C_q).

MS (ESI+) : m/z calcd for $C_{14}H_{15}ClN_6$: 303.1 [M+H]+, **found :** 303.3.

Example 3.18: Synthesis of 6-chloro-3-isopropyl-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.18)

To a solution of **(1.2)** (5.000 g, 19.60 mmol, 1.0 eq.) in dioxane (80.0 mL), isobutyric acid hydrazide (2.224 g, 21.560 mmol, 1.1 eq.) then AcOH (1.25 mL, 21.56 mmol, 1.1 eq.) was added and the mixture was refluxed 15 h. After cooling, the solvent was removed and the crude was triturated in water (150.0 ml). The resulting solid was filtered off, washed with water up to neutral pH, EtOH and Et_2O then dried under vacuum to give a first part of **(3.18)** (1.880 g). The aqueous layer was extracted twice with EtOAc (2x 50.0 mL) then organics layers were combined, washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtrered and concentrated to give second part of **(3.18)** (0.500 g). Quantity of **(3.18)**: 2.380 g, as a white solid.

Rf (DCM/MeOH, 94/6) : 0.30

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.38 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.43 (hept, *J* = 7.0 Hz, 1H, H_{iPr}), 4.46 – 4.78 (m, 2H, $CH_{2\ Bn}$), 6.15 (s, 1H, H_{Ar}), 7.30 (dd, *J* = 7.6, 4.8 Hz, 1H, H_{Ar}), 7.38 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.78 (td, *J* = 7.7, 1.9 Hz, 1H, H_{Ar}), 8.55 (d, *J* = 4.9 Hz, 1H, H_{Ar}), 8.98 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{14}H_{15}ClN_6$: 303.1 [M+H]+, **found :** 303.2.

Example 3.19: Synthesis of 6-chloro-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.19)

To a solution of **(1.2)** (4.000 g, 15.68 mmol, 1.0 eq.) in dioxane (52.0 mL), corresponding acid hydrazide (1.130 g, 18.82 mmol, 1.2 eq.) and APTS.H_2O (3.028 g, 15.68 mmol, 1.0

eq.) was added. The mixture was refluxed during 1 h then after cooling, MeOH (20.0 mL) and Na_2CO_3 (1.000 g) was added and stirred 5 min. SiO_2 was added to make solid deposit and after concentration it was directly purified by flash chromatography with DCM/MeOH (98/2 to 95/5) as eluent to give **(3.19)** (0.580 g, 14 %) as a light brown solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.69 (d, *J* = 5.9 Hz, 2H, $CH_{2\ Bn}$), 6.20 (s, 1H, H_{Ar}), 7.31 (dd, *J* = 7.5, 5.0 Hz, 1H, H_{Ar}), 7.39 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.78 (tt, *J* = 7.7, 1.6 Hz, 1H, H_{Ar}), 8.55 (d, *J* = 4.8 Hz, 1H, H_{Ar}), 9.02 (s, 1H, NH_{Bn}), 9.42 (d, *J* = 1.3 Hz, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 47.2 ($CH_{2\ Bn}$), 92.4 (CH_{Ar}), 121.5 (CH_{Ar}), 122.6 (CH_{Ar}), 137.1 (CH_{Ar}), 139.0 (C_q), 139.6 (CH_{Ar}), 142.2 (C_q), 149.1 (CH_{Ar}), 150.0 (C_q), 156.6 (C_q).

MS (ESI+) : m/z calcd for $C_{11}H_9ClN_6$: 261.1 [M+H]+, **found :** 261.2.

Example 3.20: Synthesis of 6-chloro-3-methyl-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.20)

To a solution of **(1.2)** (4.000 g, 15.68 mmol, 1.0 eq.) in dioxane (52.0 mL), corresponding acid hydrazide (1.467 g, 18.82 mmol, 1.2 eq.) and APTS.H_2O (3.028 g, 15.68 mmol, 1.0 eq.) was added. The mixture was refluxed during 1 h then after cooling, MeOH (10.0 mL) and NH_3 7N in MeOH (6.0 mL) was added and stirred 10 min. SiO_2 was added to make solid deposit and after concentration it was directly purified by flash chromatography with DCM/MeOH (98/2 to 95/5) as eluent to give **(3.20)** (1.150 g, 27 %) as a grey solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 2.59 (s, 3H, CH_3), 4.56 – 4.86 (m, 2H, $CH_{2\ Bn}$), 6.16 (s, 1H, H_{Ar}), 7.30 (dd, *J* = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.38 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.78 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 8.48 – 8.60 (m, 1H, H_{Ar}), 8.93 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 9.4 (CH_3), 47.2 ($CH_{2\ Bn}$), 91.7 (CH_{Ar}), 121.4 (CH_{Ar}), 122.6 (CH_{Ar}), 137.0 (CH_{Ar}), 139.2 (C_q), 142.4 (C_q), 146.8 (C_q), 149.1 (CH_{Ar}), 149.6 (C_q), 156.6 (C_q).

MS (ESI+) : m/z calcd for $C_{12}H_{11}ClN_6$: 275.1 [M+H]+, **found :** 275.2.

Example 3.21: Synthesis of 6-chloro-3-ethyl-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.21)

In a sealed tube 10 - 20 mL with a stir bar was charged **(1.2)** (2.000 g, 7.84 mmol, 1.0 eq.), dioxane sec (15.6 mL), corresponding hydrazide (0.768 g, 8.62 mmol, 1.1 eq.) and AcOH

(0.50 mL, 8.62 mmol, 1.1 eq.). The vial was sealed and then put on heating block, 23h h at 115°C. After cooling, the mixture was poured onto saturated $NaHCO_3$ (20.0 mL) then water (40.0 mL) was added. Aqueous mixture was extracted three times with EtOAc (3x30 mL) then organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (96/4 to 94/6) as eluent to give **(3.21)** (0.550 g, 24 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.34 (t, *J* = 7.5 Hz, 3H, $CH_{3\text{-}CH2}$), 3.00 (q, *J* = 7.6 Hz, 2H, $CH_{2\text{-}CH3}$), 4.68 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 6.16 (s, 1H, H_{Ar}), 7.30 (dd, *J* = 7.5, 4.8 Hz, 1H, H_{Ar}), 7.38 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.78 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 8.55 (d, *J* = 5.3 Hz, 1H, H_{Ar}), 8.96 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 10.8 ($CH_{3\text{-}CH2}$), 17.3 ($CH_{2\text{-}CH3}$), 47.2 ($CH_{2\ Bn}$), 91.8 (CH_{Ar}), 121.4 (CH_{Ar}), 122.6 (CH_{Ar}), 137.1 (CH_{Ar}), 139.3 (C_q), 142.5 (C_q), 149.1 (CH_{Ar}), 149.6 (C_q), 150.9 (C_q), 156.6 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{13}ClN_6$: 289.1 [M+H]+, **found :** 289.2.

Example 3.22: Synthesis of 6-chloro-3-propyl-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.22)

To a solution of **(2.7)** (~70 % purity, 0.800 g, 2.42 mmol, 1.0 eq.) in THF (11.0 mL), Et_3N (0.48 mL, 3.39 mmol, 1.4 eq.) and corresponding amine (0.367 g, 3.39 mmol, 1.4 eq.) was added and the mixture was refluxed during 1.5 h. After cooling, the solid was filtered off, washed with THF then the filtrate was concentrated and purified by flash chromatography with DCM/EtOAc (98/2 to 96/4) as eluent to give **(3.22)** (0.480 g, 65 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.96 (t, *J* = 7.4 Hz, 3H, CH_3), 1.80 (h, *J* = 7.4 Hz, 2H, CH_2), 2.97 (t, *J* = 7.5 Hz, 2H, CH_2), 4.58 – 4.81 (m, 2H, $CH_{2\ Bn}$), 6.16 (s, 1H, H_{Ar}), 7.31 (dd, *J* = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.38 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.78 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 8.55 (dd, *J* = 5.2, 1.8 Hz, 1H, H_{Ar}), 8.96 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 13.6 (CH_3), 19.4 (CH_2), 25.4 (CH_2), 47.2 ($CH_{2\ Bn}$), 91.8 (CH_{Ar}), 121.4 (CH_{Ar}), 122.6 (CH_{Ar}), 137.0 (CH_{Ar}), 139.2 (C_q), 142.5 (C_q), 149.1 (CH_{Ar}), 149.5 (C_q), 149.8 (C_q), 156.6 (C_q).

MS (ESI+) : m/z calcd for $C_{14}H_{15}ClN_6$: 303.1 [M+H]+, **found :** 303.3.

Example 3.23: Synthesis of 3-tert-butyl-6-chloro-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.23)

To a solution of **(1.2)** (2.000 g, 7.84 mmol, 1.0 eq.) in dry dioxane (31.0 mL), corresponding hydrazide (1.033 g, 8.62 mmol, 1.1 eq.) and AcOH (0.50 mL, 8.62 mmol, 1.1 eq.) was added then the mixture was refluxed 17 h. After cooling, the reaction mixture was poured onto saturated $NaHCO_3$ (100.0 mL) and EtOAc (60.0 mL). The biphasique mixture was vigorously stirred 10 min then layers were separated. Aqueous layer was extracted twice with EtOAc (2x 50.0 mL) then organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3 to 93/7) as eluent to give **(3.23)** (0.880 g, 35 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.50 (s, 9H, 3x$CH_{3\ tBu}$), 4.67 (d, J = 6.9 Hz, 2H, $CH_{2\ Bn}$), 6.15 (s, 1H, H_{Ar}), 7.30 (dd, J = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.38 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.78 (td, J = 7.7, 1.8 Hz, 1H, H_{Ar}), 8.49 – 8.63 (m, 1H, H_{Ar}), 8.96 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 27.0 (3x$CH_{3\ tBu}$), 32.4 ($C_{q\ tBu}$), 47.2 ($CH_{2\ Bn}$), 91.5 (CH_{Ar}), 121.4 (CH_{Ar}), 122.6 (CH_{Ar}), 137.1 (CH_{Ar}), 140.2 (CH_{Ar}), 142.5 (C_q), 148.7 (C_q), 149.1 (C_q), 155.2 (C_q), 156.7 (C_q).

MS (ESI+) : m/z calcd for $C_{15}H_{17}ClN_6$: 317.13 [M+H]+, **found :** 317.3.

Example 3.24: Synthesis of 6-chloro-3-cyclopropyl-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.24)

To a solution of **(1.2)** (4.000 g, 15.68 mmol, 1.0 eq.) in dioxane (52.0 mL), corresponding hydrazide (1.884 g, 18.82 mmol, 1.2 eq.) and AcOH (1.00 mL, 17.25 mmol, 1.1 eq.) was added. The mixture was refluxed 15h and after cooling, MeOH (20 mL) and DCM (20 mL) was added to solubilize reaction mixture. SiO_2 was added to make solid deposit and after concentration it was directly purified by flash chromatography with DCM/MeOH (98/2 to 95/5) as eluent to give **(3.24)** (1.620 g, 34 %) as a rose pale solid.

Rf (DCM/MeOH, 94/6) : 0.28

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.02 – 1.23 (m, 4H, 2x$CH_{2\ cPr}$), 2.32 (td, J = 8.2, 4.3 Hz, 1H, H_{cPr}), 4.67 (d, J = 6.0 Hz, 2H, $CH_{2\ Bn}$), 6.15 (s, 1H, H_{Ar}), 7.30 (dd, J = 7.4, 4.9 Hz, 1H, H_{Ar}), 7.37 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.78 (t, J = 7.7 Hz, 1H, H_{Ar}), 8.55 (d, J = 4.9 Hz, 1H, H_{Ar}), 8.94 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.8 (CH_{cPr}), 7.1 ($2xCH_{2\ cPr}$), 47.2 ($CH_{2\ Bn}$), 91.8 (CH_{Ar}), 121.4 (CH_{Ar}), 122.6 C(H_{Ar}), 137.0 (CH_{Ar}), 139.3 (C_q), 142.4 (C_q), 149.1 (CH_{Ar}), 149.6 (C_q), 151.4 (C_q), 156.6 (C_q).

MS (ESI+) : m/z calcd for $C_{14}H_{13}ClN_6$: 301.1 [M+H]+, **found :** 301.2.

Example 3.25: Synthesis of 6-chloro-3-cyclobutyl-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.25)

In a sealed tube 10 - 20 mL with a stir bar was charged **(1.2)** (1.900 g, 7.45 mmol, 1.0 eq.), dioxane sec (15.0 mL), corresponding hydrazide (0.984 g, 8.19 mmol, 1.1 eq.) and AcOH (0.47 mL, 8.19 mmol, 1.1 eq.). The vial was sealed and then put on heating block, 23h h at 115°C. After cooling, the mixture was poured onto saturated $NaHCO_3$ (20.0 mL) then water (40.0 mL) was added. Aqueous mixture was extracted three times with EtOAc (3x30 mL) then organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with EtOAc (100 %) as eluent to give **(3.25)** (0.550 g, 23 %) as a white solid.

Rf (EtOAc,100 %) : 0.14

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.91 – 2.03 (m, 1H, $H_{(CH2\ cBut)}$), 2.12 (dq, *J* = 10.8, 8.6 Hz, 1H, $H_{(CH2\ cBut)}$), 2.43 (ddd, *J* = 12.2, 6.2, 2.9 Hz, 4H, $2xCH_{2\ cBut}$), 3.95 (p, *J* = 8.4 Hz, 1H, H_{cBut}), 4.68 (s, 2H, $CH_{2\ Bn}$), 6.14 (s, 1H, H_{Ar}), 7.30 (dd, *J* = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.38 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.78 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 8.55 (d, *J* = 5.4 Hz, 1H, H_{Ar}), 8.97 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{15}H_{15}ClN_6$: 315.1 [M+H]+, **found :** 315.3.

Example 3.26: Synthesis of 6-chloro-3-cyclopentyl-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.26)

To a solution of **(1.2)** (4.000 g, 15.68 mmol, 1.0 eq.) in dioxane (52 mL), corresponding hydrazide (1.884 g, 18.82 mmol, 1.2 eq.) and AcOH (1.00 mL, 17.25 mmol, 0.1 eq.) was added. The mixture was refluxed 15h and after cooling, MeOH (20 mL) and DCM (20 mL) was added to solubilize reaction mixture. SiO_2 was added to make solid deposit and after concentration it was directly purified by flash chromatography with DCM/MeOH (94/6) as eluent to give **(3.26)** (1.620 g, 34 %) as a rose pale solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.64 – 1.85 (m, 4H, 2x$CH_{2\ cPent}$), 1.93 (dq, *J* = 11.9, 7.2 Hz, 2H, $CH_{2\ cPent}$), 2.10 (qd, *J* = 11.8, 9.6, 6.5 Hz, 2H, $CH_{2\ cPent}$), 3.53 (p, *J* = 8.0 Hz, 1H, CH_{cPent}), 4.60 – 4.76 (s, 2H, $CH_{2\ Bn}$), 6.15 (s, 1H, H_{Ar}), 7.30 (dd, *J* = 7.5, 4.8 Hz, 1H, H_{Ar}), 7.38 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.78 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 8.51 – 8.61 (m, 1H, H_{Ar}), 8.95 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{16}H_{17}ClN_6$: 329.1 [M+H]+, **found :** 329.3.

Example 3.27: Synthesis of 6-chloro-3-cyclohexyl-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.27)

In a sealed tube 10 - 20 mL with a stir bar was charged **(1.2)** (1.500 g, 5.88 mmol, 1.0 eq.), dioxane (17.8 mL), corresponding acid hydrazide (0.939 g, 6.47 mmol, 1.1 eq.) and AcOH (0.37 mL, 6.47 mmol, 1.1 eq.). The vial was sealed and then put on heating block, 21 h at 110 °C. The reaction mixture was cooled and MeOH (3.0 mL) was added. The mixture was concentrated with SiO_2 to make solid deposit and purified by flash chromatography with DCM/MeOH (97/3 to 93/7) as eluent to give **(3.27)** (0.800 g, 40 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.39 (dt, *J* = 36.4, 12.5 Hz, 3H, $H_{(CH2)\ cHex}$ & $CH_{2\ cHex}$), 1.67 (dt, *J* = 24.1, 12.5 Hz, 3H, $H_{(CH2)\ cHex}$ & $CH_{2\ cHex}$), 1.81 (d, *J* = 12.3 Hz, 2H, $CH_{2\ cHex}$), 2.01 (d, *J* = 12.6 Hz, 2H, $CH_{2\ cHex}$), 3.15 (t, *J* = 11.5 Hz, 1H, H_{cHex}), 4.68 (s, 2H, $CH_{2\ Bn}$), 6.14 (s, 1H, H_{Ar}), 7.30 (dd, *J* = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.38 (d, *J* = 7.7 Hz, 1H, H_{Ar}), 7.78 (td, *J* = 7.7, 3.7 Hz, 1H, H_{Ar}), 8.51 – 8.63 (m, 1H, H_{Ar}), 8.97 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 25.3 (2x$CH_{2\ cHex}$), 25.5 ($CH_{2\ cHex}$), 29.8 (2x$CH_{2\ cHex}$), 33.3 (CH_{cHex}), 47.2 ($CH_{2\ Bn}$), 91.8 (CH_{Ar}), 121.4 (CH_{Ar}), 122.6 (CH_{Ar}), 129.5 (C_q), 137.1 (CH_{Ar}), 139.2 (C_q), 142.5 (C_q), 149.1 (CH_{Ar}), 149.4 (C_q), 153.2 (C_q).

MS (ESI+) : m/z calcd for $C_{17}H_{19}ClN_6$: 343.1 [M+H]+, **found :** 343.3.

Example 3.28: Synthesis of 6-chloro-3-phenyl-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.28)

In a sealed tube 10 - 20 mL with a stir bar was charged **(1.2)** (1.500 g, 5.88 mmol, 1.0 eq.), dioxane (17.8 mL), corresponding acid hydrazide (0.899 g, 6.47 mmol, 1.1 eq.) and AcOH (0.37 mL, 6.47 mmol, 1.1 eq.). The vial was sealed and then put on heating block, 21 h at 110 °C. The reaction mixture was cooled and MeOH (3.0 mL) was added. The mixture was

concentrated with SiO_2 to make solid deposit and purified by flash chromatography with DCM/MeOH (97/3 to 93/7) as eluent to give **(3.28)** (0.750 g, 38 %) as a beige solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.73 (d, *J* = 5.9 Hz, 2H, $CH_{2\ Bn}$), 7.32 (dd, *J* = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.42 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.59 (dt, *J* = 13.6, 7.1 Hz, 3H, 3xH_{Ar}), 7.80 (t, *J* = 7.7 Hz, 1H, H_{Ar}), 8.32 (d, *J* = 7.6 Hz, 2H, H_{Ar}), 8.57 (d, *J* = 4.9 Hz, 1H, H_{Ar}), 9.11 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{17}H_{13}ClN_6$: 337.1 [M+H]+, **found :** 337.3.

Example 3.29: Synthesis of 6-chloro-*N*-(2-pyridylmethyl)-3-sec-butyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.29)

To a solution of **(2.2)** (0.565 g, 2.31 mmol, 1.0 eq.) in THF (23.0 mL), corresponding amine (0.44 mL, 3.00 mmol, 1.3 eq.) and DIPEA (0.61 mL, 3.46 mmol, 1.5 eq.) was added and the mixture was refluxed during 5 h. After cooling, the solvent was removed, the crude was triturated in H_2O (10.0 mL) and saturated $NaHCO_3$ (10.0 mL) and the resulting solid was filtered off, washed with water up to neutral pH then Et_2O and dried under vacuum to give **(3.29)** (0.600 g, 82 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.84 (t, *J* = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.35 (d, *J* = 7.0 Hz, 3H, $CH_{3\text{-}CH}$), 1.82 (ddq, *J* = 68.8, 13.8, 7.1 Hz, 2H, $CH_{2\text{-}CH3}$), 3.24 – 3.31 (m, 1H, $H_{C\text{-}CH3}$), 4.67 (d, *J* = 5.7 Hz, 2H, $CH_{2\ Bn}$), 6.15 (s, 1H, H_{Ar}), 7.31 (dd, *J* = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.39 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.78 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 8.55 (d, *J* = 4.9 Hz, 1H, H_{Ar}), 8.98 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 11.4 ($CH_{3\text{-}CH2}$), 17.6 ($CH_{3\text{-}CH}$), 26.8 ($CH_{2\text{-}CH3}$), 30.9 ($CH_{\text{-}CH3}$), 47.2 ($CH_{2\ Bn}$), 91.8 (CH_{Ar}), 121.5 (CH_{Ar}), 122.6 (CH_{Ar}), 137.1 (CH_{Ar}), 139.3 (C_q), 142.5 (C_q), 149.1 (CH_{Ar}), 149.4 (C_q), 153.2 (C_q), 156.6 (C_q).

MS (ESI+) : m/z calcd for $C_{15}H_{17}ClN_6$: 317.8 [M+H]+, **found :** 317.2.

Example 3.30: Synthesis of 6-chloro-3-(1-ethylpropyl)-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.30)

To a solution of **(2.3)** (0.510 g, 1.97 mmol, 1.0 eq.) in THF (20.0 mL), corresponding amine (0.38 mL, 2.56 mmol, 1.3 eq.) and DIPEA (0.52 mL, 2.95 mmol, 1.5 eq.) was added and the mixture was refluxed during 5 h. After cooling, the solvent was removed, the crude

was triturated in H_2O (10.0 mL) and saturated $NaHCO_3$ (10.0 mL) and the resulting solid was filtered off, washed with water up to neutral pH then Et_2O and dried under vacuum to give **(3.30)** (0.580 g, 89 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.77 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.83 (ddt, *J* = 37.0, 13.5, 6.9 Hz, 4H, 2x$CH_{2\text{-}CH3}$), 3.10 – 3.24 (m, 1H, H_{iPent}), 4.67 (d, *J* = 5.8 Hz, 2H, $CH_{2\ Bn}$), 6.15 (s, 1H, H_{Ar}), 7.31 (dd, *J* = 7.4, 4.9 Hz, 1H, H_{Ar}), 7.40 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.79 (td, *J* = 7.7, 1.7 Hz, 1H, H_{Ar}), 8.55 (d, *J* = 4.9 Hz, 1H, H_{Ar}), 8.98 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{16}H_{19}ClN_6$: 331.1 [M+H]+, **found :** 331.2.

Example 3.31: Synthesis of 6-chloro-3-isobutyl-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.31)

To a solution of **(2.4)** (0.290 g, 1.18 mmol, 1.0 eq.), THF (11.0 mL), corresponding amine (0.23 mL, 1.54 mmol, 1.3 eq.) and DIPEA (0.31 mL, 1.78 mmol, 1.5 eq.) was added then the mixture was refluxed 1 h. After cooling, Et_2O (30.0 mL), the precipitate was filtered off, washed with water, triturated in Et_2O then dried under vacuum to give **(3.31)** (0.285 g, 76 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.94 (d, *J* = 6.6 Hz, 6H, 2x$CH_{3\ iPr}$), 2.21 (hept, *J* = 6.8 Hz, 1H, H_{iPr}), 2.89 (d, *J* = 7.2 Hz, 2H, $CH_{2\text{-}CH}$), 4.68 (s, 2H, $CH_{2\ Bn}$), 6.16 (s, 1H, H_{Ar}), 7.31 (dd, *J* = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.39 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.79 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 8.55 (d, *J* = 4.7 Hz, 1H, H_{Ar}), 8.95 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{15}H_{17}ClN_6$: 317.8 [M+H]+, **found :** 317.2.

Example 3.32: Synthesis of 6-chloro-3-(2-pyridyl)-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.32)

In a sealed tube 10 - 20 mL with a stir bar was charged **(1.2)** (1.250 g, 4.90 mmol, 1.0 eq.), dioxane (10.0 mL), corresponding acid hydrazide (0.778 g, 5.39 mmol, 1.1 eq.) and PTSA.H_2O (0.946 g, 4.90 mmol, 1.0 eq.). The vial was sealed and then put on heating block, 19 h at 110 °C. After cooling, MeOH (5.0 mL) and NH_3 7M in MeOH (3.0 mL) was added then the mixture was concentrated with SiO_2 to make solid deposit and directly

purified by flash chromatography with DCM/MeOH (98/2 to 90/10) as eluent to give **(3.32)** (0.300 g, 18 %) as a yellow solid.

Rf (DCM/MeOH, 94/6) : 0.10

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.74 (s, 2H, $CH_{2\ Bn}$), 6.32 (s, 1H, H_{Ar}), 7.32 (dd, *J* = 7.5, 5.0 Hz, 1H, H_{Ar}), 7.43 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.53 – 7.65 (m, 1H, H_{Ar}), 7.80 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 8.05 (td, *J* = 7.8, 1.8 Hz, 1H, H_{Ar}), 8.23 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 8.57 (d, *J* = 4.9 Hz, 1H, H_{Ar}), 8.81 (d, *J* = 4.9 Hz, 1H, H_{Ar}), 9.13 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{16}H_{12}ClN_7$: 338.1 [M+H]+, **found :** 338.2.

Example 3.33: Synthesis of 6-chloro-3-(3-pyridyl)-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.33)

In a sealed tube 10 - 20 mL with a stir bar was charged **(1.2)** (1.250 g, 4.90 mmol, 1.0 eq.), dioxane (10.0 mL), corresponding hydrazide (0.754 g, 5.39 mmol, 1.1 eq.) and PTSA.H_2O (0.946 g, 4.90 mmol, 1.0 eq.). The vial was sealed and then put on heating block, 19h h at 110 °C. After cooling, NH_3 7N in MeOH (2.80 mL, 19.6 mmol, 4.0 eq.) was added and the mixture was concentrated with silica then directly purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give **(3.33)** (0.275 g, 17 %) as a white solid.

Rf (DCM/MeOH, 94/6) : 0.25

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.74 (s, 2H, $CH_{2\ Bn}$), 6.34 (s, 1H, H_{Ar}), 7.24 – 7.39 (m, 1H, H_{Ar}), 7.42 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.65 (dd, *J* = 8.1, 4.9 Hz, 1H, H_{Ar}), 7.75 – 7.90 (m, 1H, H_{Ar}), 8.57 (d, *J* = 4.8 Hz, 1H, H_{Ar}), 8.64 (dt, *J* = 8.1, 2.0 Hz, 1H, H_{Ar}), 8.74 (dd, *J* = 4.8, 1.7 Hz, 1H, H_{Ar}), 9.19 (s, 1H, NH_{Bn}), 9.44 (d, *J* = 2.2 Hz, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{16}H_{12}ClN_7$: 338.1 [M+H]+, **found :** 338.2.

Example 3.34: Synthesis of 6-chloro-3-(4-pyridyl)-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.34)

In a sealed tube 10 - 20 mL with a stir bar was charged **(1.2)** (1.250 g, 4.90 mmol, 1.0 eq.), dioxane (10.0 mL), corresponding hydrazide (0.778 g, 5.39 mmol, 1.1 eq.) and PTSA.H_2O (0.946 g, 4.90 mmol, 1.0 eq.). The vial was sealed and then put on heating block, 19h h at 110 °C. After cooling, NH_3 7N in MeOH (2.80 mL, 19.6 mmol, 4.0 eq.) was added and the

mixture was concentrated with silica then directly purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give **(3.34)** (0.310 g, 19 %) as a white solid.

Rf (DCM/MeOH, 94/6) : 0.29

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 4.74 (d, *J* = 6.1 Hz, 2H, $CH_{2\ Bn}$), 6.37 (s, 1H, H_{Ar}), 7.32 (dd, *J* = 7.3, 5.1 Hz, 1H, H_{Ar}), 7.42 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.80 (dd, *J* = 8.2, 6.5 Hz, 1H, H_{Ar}), 8.23 – 8.38 (m, 2H, 2xH_{Ar}), 8.56 (d, *J* = 4.9 Hz, 1H, H_{Ar}), 8.72 – 8.92 (m, 2H, 2xH_{Ar}), 9.21 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{16}H_{12}ClN_7$: 338.1 [M+H]+, **found :** 338.2.

Example 3.35: Synthesis of *N*-[(4-aminophenyl)methyl]-6-chloro-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.35)

To a solution of **(2.1)** (0.300 g, 1.30 mmol, 1.0 eq.) in THF (18.0 mL), 4-(aminomethyl)aniline dihydrochloride (0.512 g, 2.60 mmol, 2.0 eq.) and Et_3N (1.28 mL, 9.09 mmol, 7.0 eq.) were added then the mixture was refluxed 2 h. After cooling, the solid was filtered off, washed with THF then the filtrate was concentrated and directly purified by flash chromatography with DCM/MeOH (98/2 to 96/4) as eluent to give **(3.35)** (0.245 g, 60 %) as a pale yellow solid.

Rf (DCM/MeOH, 94/6) : 0.24

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.37 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.42 (h, *J* = 6.9 Hz, 1H, H_{iPr}), 4.37 (d, *J* = 6.3 Hz, 2H, $CH_{2\ Bn}$), 5.01 (s, 2H, NH_2), 6.10 (s, 1H, H_{Ar}), 6.51 (d, *J* = 8.4 Hz, 2H, 2xH_{Ar}), 7.05 (d, *J* = 8.3 Hz, 2H, 2xH_{Ar}), 8.95 (t, *J* = 6.2 Hz, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 45.0 ($CH_{2\ Bn}$), 91.3 (CH_{Ar}), 113.8 (2xCH_{Ar}), 124.0 (C_q), 128.2 (2xCH_{Ar}), 139.5 (C_q), 142.1 (C_q), 147.9 (C_q), 149.4 (C_q), 153.9 (C_q).

MS (ESI+) : m/z calcd for $C_{15}H_{17}ClN_6$: 317.1 [M+H]+, **found :** 317.2.

Example 3.36: Synthesis of *N*-[(3-aminophenyl)methyl]-6-chloro-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.36)

To a solution of **(2.1)** (0.300 g, 1.30 mmol, 1.0 eq.) in THF (18.0 mL), 3-(aminomethyl)aniline (0.320 g, 2.60 mmol, 2.0 eq.) and Et_3N (0.37 mL, 2.60 mmol, 2.0 eq.) were added then the mixture was refluxed 2 h. After cooling, the solid was filtered off,

washed with THF then the filtrate was concentrated and directly purified by flash chromatography with DCM/MeOH (98/2 to 96/4) as eluent to give **(3.36)** (0.280 g, 68 %) as a yellow solid.

Rf (DCM/MeOH, 96/4) : 0.27

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.38 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.42 (hept, *J* = 6.9 Hz, 1H, H_{iPr}), 4.43 (d, *J* = 6.4 Hz, 2H, $CH_{2\ Bn}$), 5.06 (s, 2H, NH_2), 6.02 (s, 1H, H_{Ar}), 6.40 – 6.56 (m, 3H, 3xH_{Ar}), 6.96 (t, *J* = 7.7 Hz, 1H, H_{Ar}), 9.03 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{15}H_{17}ClN_6$: 317.13 [M+H]+, **found :** 317.3.

Example 3.37: Synthesis of *N*-[(2-aminophenyl)methyl]-6-chloro-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.37)

To a solution of **(1.12)** (4.000 g, 14.86 mmol, 1.0 eq.) in dry dioxane (60.0 mL), isobutyric acid hydrazide (1.840 g, 17.84 mmol, 1.2 eq.) and AcOH (0.86 mL, 14.86 mmol, 1.0 eq.) was added then the mixture was refluxed 18 h. After cooling, the reaction mixture was concentrated, the residue was triturated in water, filtered off, washed with water up to neutral pH. The solid was taken up with DCM and MeOH, the filtrate was concentrated and purified by flash chromatography with DCM/MeOH (97/3 to 95/5) as eluent to give **(3.37)** (0.600 g, 13 %) as a pale yellow solid.

Rf (DCM/MeOH, 94/6) : 0.41

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.37 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.42 (p, *J* = 6.9 Hz, 1H, H_{iPr}), 4.39 (s, 2H, $CH_{2\ Bn}$), 5.17 (s, 2H, NH_2), 6.07 (s, 1H, H_{Ar}), 6.51 (t, *J* = 7.4 Hz, 1H, H_{Ar}), 6.65 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 6.97 (td, *J* = 7.6, 1.6 Hz, 1H, H_{Ar}), 7.09 (dd, *J* = 7.6, 1.6 Hz, 1H, H_{Ar}), 8.92 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 42.4 ($CH_{2\ Bn}$), 91.6 (CH_{Ar}), 115.1 (CH_{Ar}), 115.9 (CH_{Ar}), 119.3 (C_q), 128.1 (CH_{Ar}), 128.2 (CH_{Ar}), 139.5 (C_q), 142.3 (C_q), 146.3 (C_q), 149.4 (C_q), 154.0 (C_q).

MS (ESI+) : m/z calcd for $C_{15}H_{17}ClN_6$: 317.1 [M+H]+, **found :** 317.3.

Example 3.38: Synthesis of 2-(6-chloro-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl)-3,4-dihydro-*1H*-isoquinoline (3.38)

To a suspension of **(1.15)** (4.600 g, 16.42 mmol, 1.0 eq.) in dry dioxane (66 mL), isobutyric acid hydrazide (1.863 g, 18.06 mmol, 1.1 eq.) and AcOH (1.04 mL, 18.06 mmol, 1.1 eq.) was added then the mixture was refluxed 22 h. After cooling, MeOH (10.0 mL) was added, the mixture was concentrated with SiO_2 to make solid deposit and directly purified by flash chromatography with DCM/EtOAc (98/2 to 96/4) as eluent to give **(3.38)** (1.390 g, 26 %) as a white solid.

Rf (DCM/EtOAc, 98/2) : 0.23

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.38 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.02 (t, *J* = 5.9 Hz, 2H, $CH_{2\text{-}CH2\text{-}N}$), 3.44 (hept, *J* = 6.9 Hz, 1H, H_{iPr}), 4.42 (s, 2H, $_{N}$-$CH_{2\text{-}CH2}$), 5.18 (s, 2H, $CH_{2\text{-}N}$), 6.40 (s, 1H, H_{Ar}), 7.24 (td, *J* = 4.9, 4.5, 2.6 Hz, 4H, 4xH_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.7 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 28.0 ($CH_{2\text{-}CH2\text{-}N}$), 45.9 ($_{N}$-$CH_{2\text{-}CH2}$), 49.3 ($CH_{2\text{-}N}$), 94.0 ($CH_{Ar}$), 126.3 ($CH_{Ar}$), 126.3 ($CH_{Ar}$), 126.8 ($CH_{Ar}$), 128.3 ($CH_{Ar}$), 134.5 ($C_q$), 140.4 ($C_q$), 142.7 ($C_q$), 149.4 ($C_q$), 153.6 ($C_q$).

MS (EI-MS) : m/z calcd for $C_{17}H_{18}ClN_5$: 328.1 [M+H]+, **found :** 328.2.

Example 3.39: Synthesis of 6-chloro-8-isoindolin-2-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine (3.39)

To a solution of **(2.1)** (0.350 g, 1.52 mmol, 1.0 eq.) in THF (15.0 mL), corresponding amine hydrochloride (0.340 g, 2.12 mmol, 1.4 eq.) and Et_3N (0.64 mL, 4.54 mmol, 3.0 eq.) was added then the mixture was refluxed 1.5 h. After cooling, the precipitate was filtered, washed with THF then the filtrate was concentrated and purified by flash chromatography with DCM/MeOH (100/0 to 98/2) as eluent. The impur fraction was concentrated then the residu was triturated in Et_2O, filtered, washed with a little amount of Et_2O and dried under vacuum to give **(3.39)** (0.280 g, 59 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.40 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.46 (hept, *J* = 6.9 Hz, 1H, H_{iPr}), 4.87 (s, 2H, CH_2), 5.61 (s, 2H, CH_2), 6.10 (s, 1H, H_{Ar}), 7.37 (dd, *J* = 5.6, 3.2 Hz, 2H, 2xH_{Ar}), 7.44 (s, 1H, H_{Ar}), 7.50 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.7 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 54.9 (CH_2), 57.4 (CH_2), 93.4 (CH_{Ar}), 122.5 (CH_{Ar}), 122.8 (CH_{Ar}), 127.6 (2xCH_{Ar}), 134.8 (C_q), 136.7 (C_q), 140.2 (C_q), 141.5 (C_q), 149.3 (C_q), 153.6 (C_q).

MS (EI-MS) : m/z calcd for $C_{16}H_{16}ClN_5$: 314.1 [M+H]+, **found :** 314.3.

Example 3.40: Synthesis of 6-chloro-*N*-indan-1-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.40)

To a solution of **(2.1)** (0.250 g, 1.05 mmol, 1.0 eq.) in THF (13.0 mL), corresponding amine hydrochloride (0.273 g, 1.57 mmol, 1.5 eq.) and Et_3N (0.44 mL, 3.15 mmol, 3.0 eq.) was added then the mixture was refluxed 4 h. After cooling, the solvent was removed, the residue was triturated in water, filtered off, washed with water up to neutral pH and the solid was taken up in EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(3.40)** (0.300 g, 87 %) as a beige solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.39 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 2.19 (dt, J = 17.4, 8.0 Hz, 1H, $H_{(CH2)indane}$), 2.55 (s, 1H, $H_{(CH2)indane}$), 2.85 (dt, J = 16.2, 8.3 Hz, 1H, $H_{(CH2)indane}$), 3.03 (ddd, J = 15.9, 8.9, 3.1 Hz, 1H, $H_{(CH2)indane}$), 3.45 (hept, J = 7.7, 7.2 Hz, 1H, H_{iPr}), 5.41 (s, 1H, H_{indane}), 6.48 (s, 1H, H_{Ar}), 7.14 – 7.34 (m, 4H, 4xH_{Ar}), 8.75 (s, 1H, NH_{indane}).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 19.9 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 29.8 ($CH_{2\ indane}$), 31.6 ($CH_{2\ indane}$), 57.3 (CH_{indane}), 91.4 (CH_{Ar}), 123.8 (CH_{Ar}), 124.8 (CH_{Ar}), 126.4 (CH_{Ar}), 127.8 (CH_{Ar}), 139.4 (C_q), 142.3 (C_q), 142.7 (C_q), 143.1 (C_q), 149.8 (C_q), 154.0 (C_q).

MS (ESI+) : m/z calcd for $C_{17}H_{18}ClN_5$: 328.1 [M+H]+, **found :** 328.3.

Example 3.41: Synthesis of 6-chloro-*N*-(*1H*-indol-2-ylmethyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.41)

In a sealed tube 10 - 20 mL with a stir bar was charged **(1.10)** (1.100 g, 3.57 mmol, 1.0 eq.), dioxane (15.0 mL), isobutyric acid hydrazide (0.441 g, 4.28 mmol, 1.2 eq.) and AcOH (0.23 mL, 3.92 mmol, 1.1 eq.). The vial was sealed and then put on heating block, 17 h at 100 °C. After cooling, MeOH (10.0 mL) was added, stirred vigorously 5 min then the mixture was concentrated with SiO_2 to make solid deposit and directly purified by flash chromatography with DCM/MeOH (97/3 to 94/6) as eluent to give **(3.41)** (0.270 g, 22 %) as a beige solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.38 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.43 (hept, J = 7.1 Hz, 1H, H_{iPr}), 4.74 (s, 2H, $CH_{2\ Bn}$), 6.29 (s, 1H, H_{Ar}), 6.36 (d, J = 2.0 Hz, 1H, H_{Ar}), 6.94 (t, J = 7.4 Hz, 1H, H_{Ar}), 7.00 – 7.08 (m, 1H, H_{Ar}), 7.33 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.45 (d, J = 7.8 Hz, 1H, H_{Ar}), 8.89 (s, 1H, NH), 10.99 (s, 1H, NH_{indol}).

^{13}C NMR (101 MHz, DMSO-d_6) δ : N.D.

MS (ESI+) : m/z calcd for $C_{17}H_{17}ClN_6$: 341.1 [M+H]+, **found :** 341.3.

Example 3.42: Synthesis of *N*-[(4-bromophenyl)methyl]-6-chloro-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.42)

To a solution of **(1.13)** (4.100 g, 12.32 mmol, 1.0 eq.) in dioxane (50.0 mL), isobutyric acid hydrazide (1.524 g, 14.77 mmol, 1.2 eq.) and AcOH (0.78 mL, 13.54 mmol, 1.1 eq.) was added then the miture was refluxed 18 h. After cooling, the mixture was poured onto water (200.0 mL) then the precipitate was triturated, filtered off, washed with water up to neutral pH. The solid was triturated in EtOAc, filtered and dried under vacuum to give **(3.42)** (2.400 g, 51 %) as a pale yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.37 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.42 (hept, J = 7.0 Hz, 1H, H_{iPr}), 4.40 – 4.73 (m, 2H, $CH_{2\ Bn}$), 6.15 (s, 1H, H_{Ar}), 7.35 (d, J = 8.2 Hz, 2H, 2xH_{Ar}), 7.54 (d, J = 8.4 Hz, 2H, 2xH_{Ar}), 9.11 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-d_6) δ : N.D.

MS (ESI+) : m/z calcd for $C_{15}H_{15}BrClN_5$: 380.0 [M+H]+, **found :** 380.2.

Example 3.43: Synthesis of 6-chloro-3-isopropyl-*N*-(2-phenylethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.43)

To a solution of **(1.16)** (4.000 g, 14.92 mmol, 1.0 eq.) in dry dioxane (60 mL), isobutyric acid hydrazide (1.847 g, 17.90 mmol, 1.2 eq.) then AcOH (0.95 mL, 16.41 mmol, 1.1 eq.) was added and the mixture was refluxed 4 h. After cooling, the mixture was concentrated then the residue was suspended and triturated into water (120 mL). The solid was filtered off, washed with water up to neutral pH then taken up with EtOH, concentrated en dried under vacuum to give the title compound **(3.43)** (2.350 g, 50 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.37 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 2.94 (t, J = 7.3 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.42 (p, J = 6.9 Hz, 1H, H_{iPr}), 3.52 – 3.68 (m, 2H, $CH_{2\text{-}NH}$), 6.21 (s, 1H, H_{Ar}), 7.20 (tt, J = 5.6, 2.9 Hz, 1H, H_{Ar}), 7.25 – 7.38 (m, 4H, 4xH_{Ar}), 8.51 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 33.8 ($CH_{2\text{-}CH2\text{-}NH}$), 43.5 ($CH_{2\text{-}NH}$), 91.0 ($CH_{Ar}$), 126.2 ($CH_{Ar}$), 128.3 (2x$CH_{Ar}$), 128.9 (2x$CH_{Ar}$), 138.9 ($C_q$), 139.4 ($C_q$), 142.2 ($C_q$), 149.7 ($C_q$), 153.9 ($C_q$).

MS (ESI+) : m/z calcd for $C_{16}H_{18}ClN_5$: 316.1 [M+H]+, **found :** 316.2.

Example 3.44: Synthesis of 6-chloro-3-isopropyl-*N*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.44)

To a solution of **(2.1)** (0.300 g, 1.30 mmol, 1.0 eq.) in THF (3.9 mL), corresponding amine (0.190 g, 1.56 mmol, 1.2 eq.) and DIPEA (0.27 mL, 1.56 mmol, 1.2 eq.) was added and the mixture was stirred 16 h at room temperature. The precitpitate was filtered off, washed with THF then the filtrate was concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 95/5) as eluent to give **(3.44)** (0.270 g, 66 %) as a beige solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.37 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.09 (t, *J* = 7.1 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.42 (h, *J* = 7.0 Hz, 1H, H_{iPr}), 3.71 (d, *J* = 6.9 Hz, 2H, $CH_{2\text{-}NH}$), 6.18 (s, 1H, H_{Ar}), 7.23 (dd, *J* = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.34 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.70 (t, *J* = 7.7 Hz, 1H, H_{Ar}), 8.51 (d, *J* = 4.9 Hz, 1H, H_{Ar}), 8.56 (s, 1H, $NH_{\text{-}CH2}$).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 35.9 ($CH_{2\text{-}CH2\text{-}NH}$), 41.8 ($CH_{2\text{-}NH}$), 91.0 ($CH_{Ar}$), 121.7 ($CH_{Ar}$), 123.5 ($CH_{Ar}$), 136.5 ($CH_{Ar}$), 139.4 ($C_q$), 142.2 ($C_q$), 149.1 ($CH_{Ar}$), 149.6 ($C_q$), 153.9 ($C_q$), 158.6 ($C_q$).

MS (ESI+) : m/z calcd $C_{15}H_{17}ClN_6$: 317.13 [M+H]+, **found :** 317.2.

Example 3.45: Synthesis of 6-chloro-3-isopropyl-*N*-[2-(3-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.45)

To a solution of **(2.1)** (0.250 g, 1.08 mmol, 1.0 eq.), THF (10.0 mL), corresponding amine (0.181 g, 1.41 mmol, 1.3 eq.) and DIPEA (0.28 mL, 1.62 mmol, 1.5 eq.) was added then the mixture was refluxed 3 h. After cooling, Et_2O (30.0 mL) was added, the precipitate was filtered off, washed with water, triturated in Et_2O then dried under vacuum to give **(3.45)** (0.260 g, 76 %) as a white solid.

Rf (DCM/MeOH, 94/6) : 0.24

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.37 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 2.96 (t, *J* = 7.1 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.41 (hept, *J* = 7.0 Hz, 1H, H_{iPr}), 3.62 (d, *J* = 7.1 Hz, 2H, $CH_{2\text{-}NH}$), 6.26 (s, 1H, H_{Ar}), 7.31 (dd, *J* = 7.9, 4.8 Hz, 1H, H_{Ar}), 7.72 (d, *J* = 7.7 Hz, 1H, H_{Ar}), 8.41 (d, *J* = 4.8 Hz, 1H, H_{Ar}), 8.49 (d, *J* = 2.2 Hz, 1H, H_{Ar}), 8.55 (s, 1H, $NH_{\text{-}CH2}$).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 30.9 ($CH_{2\text{-}CH2\text{-}NH}$), 42.9 ($CH_{2\text{-}NH}$), 91.1 ($CH_{Ar}$), 123.3 ($CH_{Ar}$), 134.4 ($C_q$), 136.4 ($CH_{Ar}$), 139.4 ($C_q$), 142.2 ($C_q$), 147.5 ($CH_{Ar}$), 149.7 ($C_q$), 150.0 ($CH_{Ar}$), 153.9 ($C_q$).

MS (ESI+) : m/z calcd for $C_{15}H_{17}ClN_6$: 317.13 [M+H]+, **found :** 317.2.

Example 3.46: Synthesis of 6-chloro-3-isopropyl-*N*-[2-(4-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.46)

To a solution of **(2.1)** (0.250 g, 1.08 mmol, 1.0 eq.), THF (10.0 mL), corresponding amine (0.181 g, 1.41 mmol, 1.3 eq.) and DIPEA (0.28 mL, 1.62 mmol, 1.5 eq.) was added then the mixture was refluxed 3 h. After cooling, Et_2O (30.0 mL) was added, the precipitate was filtered off, washed with water, triturated in Et_2O then dried under vacuum to give **(3.46)** (0.285 g, 82 %) as a white solid.

Rf (DCM/MeOH, 94/6) : 0.27

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.37 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 2.97 (t, J = 7.1 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.42 (p, J = 7.0 Hz, 1H, H_{iPr}), 3.56 – 3.75 (m, 2H, $CH_{2\text{-}NH}$), 6.29 (s, 1H, H_{Ar}), 7.33 (d, J = 5.1 Hz, 2H, 2xH_{Ar}), 8.44 – 8.51 (m, 2H, 2xH_{Ar}), 8.54 (s, 1H, $NH_{\text{-}CH2}$).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 32.9 ($CH_{2\text{-}CH2\text{-}NH}$), 42.2 ($CH_{2\text{-}NH}$), 91.2 ($CH_{Ar}$), 124.4 (2x$CH_{Ar}$), 139.3 ($C_q$), 142.2 ($C_q$), 147.9 ($C_q$), 149.4 (2x$CH_{Ar}$), 149.7 ($C_q$), 153.9 ($C_q$).

MS (ESI+) : m/z calcd for $C_{15}H_{17}ClN_6$: 317.13 [M+H]+, **found :** 317.2.

Example 3.47: Synthesis of 6-chloro-3-cyclopropyl-*N*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.47)

To a solution of **(2.5)** (0.125 g, 0.51 mmol, 1.0 eq.) in THF (2.5 mL), corresponding amine (0.080 g, 0.62 mmol, 1.2 eq.) and Et_3N (0.15 mL, 1.04 mmol, 2.0 eq.) was added and the mixture was refluxed 1.5 h. After cooling, THF (10.0 mL) wad added, the precipitate was filtered off, washed with THF then the filtrate was concentrated. The residue was triturated in water, filtered off, washed with water then triturated in Et_2O, filtered, washed with Et_2O and dried under vacuum to give **(3.47)** (0.130 g, 80 %) as a beige solid.

Rf (DCM/MeOH, 96/4) : 0.14

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.03 – 1.18 (m, 4H, 2x$CH_{2\ cPr}$), 2.31 (tt, J = 8.2, 5.2 Hz, 1H, H_{cPr}), 3.09 (t, J = 7.1 Hz, 2H, CH_2), 3.64 – 3.81 (m, 2H, CH_2), 6.16 (s, 1H, H_{Ar}), 7.23 (dd, J = 7.6, 4.8 Hz, 1H, H_{Ar}), 7.33 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.70 (td, J = 7.7, 1.9 Hz, 1H, H_{Ar}), 8.46 – 8.61 (m, 2H, NH & H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.8 (CH_{cPr}), 7.2 ($2xCH_{2\ cPr}$), 35.9 (CH_2), 41.9 (CH_2), 91.0 (CH_{Ar}), 121.7 (CH_{Ar}), 123.5 (CH_{Ar}), 136.5 (CH_{Ar}), 139.3 (C_q), 142.2 (C_q), 149.1 (CH_{Ar}), 149.8 (C_q), 151.3 (C_q), 158.6 (C_q).

MS (ESI+) : m/z calcd for $C_{15}H_{15}ClN_6$: 315.1 [M+H]+, **found :** 315.1.

Example 3.48: Synthesis of 6-chloro-3-cyclopropyl-*N*-[2-(3-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.48)

To a solution of **(2.5)** (0.125 g, 0.51 mmol, 1.0 eq.) in THF (2.5 mL), corresponding amine (0.080 g, 0.62 mmol, 1.2 eq.) and Et_3N (0.15 mL, 1.04 mmol, 2.0 eq.) was added and the mixture was refluxed 1.5 h. After cooling, THF (10.0 mL) wad added, the precitpitate was filtered off, washed with THF then the filtrate was concentrated. The residue was triturated in water, filtered off, washed with water then triturated in Et_2O, filtered, washed with Et_2O and dried under vacuum to give **(3.48)** (0.127 g, 80 %) as a beige solid.

Rf (DCM/MeOH, 94/6) : 0.20

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.00 – 1.20 (m, 4H, $2xCH_{2\ cPr}$), 2.31 (tt, *J* = 8.1, 5.3 Hz, 1H, H_{cPr}), 2.96 (t, *J* = 7.1 Hz, 2H, CH_2), 3.49 – 3.76 (m, 2H, CH_2), 6.24 (s, 1H, H_{Ar}), 7.31 (dd, *J* = 7.8, 4.8 Hz, 1H, H_{Ar}), 7.71 (dt, *J* = 7.8, 2.0 Hz, 1H, H_{Ar}), 8.41 (dd, *J* = 4.8, 1.7 Hz, 1H, H_{Ar}), 8.49 (d, *J* = 2.3 Hz, 1H, H_{Ar}), 8.52 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.8 (CH), 7.1 ($2xCH_2$), 30.9 (CH_2), 42.9 (CH_2), 91.1 (CH_{Ar}), 123.3 (CH_{Ar}), 134.4 (C_q), 136.4 (CH_{Ar}), 139.3 (C_q), 142.2 (C_q), 147.5 (CH_{Ar}), 149.9 (C_q), 150.0 (CH_{Ar}), 151.3 (C_q).

MS (ESI+) : m/z calcd for $C_{15}H_{15}ClN_6$: 315.1 [M+H]+, **found :** 315.2.

Example 3.49: Synthesis of 6-chloro-3-cyclopropyl-*N*-[2-(4-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.49)

To a solution of **(2.5)** (0.125 g, 0.51 mmol, 1.0 eq.) in THF (2.5 mL), corresponding amine (0.080 g, 0.62 mmol, 1.2 eq.) and Et_3N (0.15 mL, 1.04 mmol, 2.0 eq.) was added and the mixture was refluxed 1.5 h. After cooling, THF (10.0 mL) wad added, the precitpitate was filtered off, washed with THF then the filtrate was concentrated. The residue was triturated in water, filtered off, washed with water then triturated in Et_2O, filtered, washed with Et_2O and dried under vacuum to give **(3.49)** (0.134 g, 82 %) as an orange solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.05 – 1.17 (m, 4H, 2x$CH_{2\ cPr}$), 2.31 (ddt, *J* = 10.9, 8.1, 5.2 Hz, 1H, H_{cPr}), 2.96 (t, *J* = 7.1 Hz, 2H, CH_2), 3.63 (d, *J* = 7.9 Hz, 2H, CH_2), 6.28 (s, 1H, H_{Ar}), 7.27 – 7.39 (m, 2H, 2xH_{Ar}), 8.42 – 8.48 (m, 2H, 2xH_{Ar}), 8.51 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.8 (CH_{cPr}), 7.2 (2x$CH_{2\ cPr}$), 32.9 (CH_2), 42.3 (CH_2), 91.2 (CH_{Ar}), 124.4 (CH_{Ar}), 139.3 (C_q), 142.2 (C_q), 147.9 (C_q), 149.4 (CH_{Ar}), 149.9 (C_q), 151.3 (C_q).

MS (ESI+) : m/z calcd for $C_{15}H_{15}ClN_6$: 315.1 [M+H]+, **found :** 315.2.

Example 3.50: Synthesis of 6-chloro-3-isopropyl-*N*-[3-(2-pyridyl)propyl]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.50)

To a solution of **(2.1)** (0.200 g, 0.87 mmol, 1.0 eq.) in THF (8.7 mL), corresponding amine (0.161 g, 1.13 mmol, 1.3 eq.) and Et_3N (0.24 mL, 1.73 mmol, 2.0 eq.) was added and the mixture was refluxed 3 h. After cooling, the solvent was removed, the residue was triturated in water (20.0 mL) and saturated $NaHCO_3$ (10.0 mL), the solid was filtered off, washed with water up to neutral pH then taken up in EtOAc. Organic filtrate was dried over $MgSO_4$, filtered and concentrated to give **(3.50)** (0.250 g, 87 %) as a pale yellow solid.

Rf (DCM/MeOH, 94/6) : 0.42

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.38 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 2.03 (p, *J* = 7.3 Hz, 2H, CH_2), 2.83 (t, *J* = 7.5 Hz, 2H, CH_2), 3.41 (td, *J* = 13.7, 6.8 Hz, 3H, H_{iPr} & CH_2), 6.20 (s, 1H, H_{Ar}), 7.20 (dd, *J* = 7.6, 4.9 Hz, 1H, H_{Ar}), 7.28 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.69 (td, *J* = 7.6, 1.9 Hz, 1H, H_{Ar}), 8.45 – 8.54 (m, 1H, H_{Ar}), 8.70 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 27.2 (CH_2), 34.5 (CH_2), 41.8 (CH_2), 90.8 (CH_{Ar}), 121.3 (CH_{Ar}), 122.9 (CH_{Ar}), 136.5 (CH_{Ar}), 139.5 (C_q), 142.4 (C_q), 148.9 (CH_{Ar}), 153.9 (C_q), 160.8 (C_q).

MS (ESI+) : m/z calcd for $C_{16}H_{19}ClN_6$: 331.1 [M+H]+, **found :** 331.2.

Example 3.51: Synthesis of 6-chloro-3-isopropyl-*N*-[3-(3-pyridyl)propyl]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.51)

To a solution of **(2.1)** (0.200 g, 0.87 mmol, 1.0 eq.) in THF (8.7 mL), corresponding amine dihydrochloride (0.248 g, 1.13 mmol, 1.3 eq.) and Et_3N (0.73 mL, 5.19 mmol, 6.0 eq.) was added and the mixture was refluxed 3 h. Water (0.43 mL) was added and the mixture was

refluxed 3 h to complete the reaction. After cooling, EtOAc (15.0 mL) was added, the mixture was dried over $MgSO_4$, filtered and concentrated. The residue was triturated in water (20.0 mL), the solid was filtered off, taken up in EtOAc then organic filtrate was dried over $MgSO_4$, filtered and concentrated to give **(3.51)** (0.240 g, 84 %) as a beige solid.

Rf (DCM/MeOH, 94/6) : 0.35

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.39 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.89 – 1.98 (m, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 2.66 – 2.75 (m, 2H, $CH_{2\text{-}CH2\text{-}CH2\text{-}NH}$), 3.36 (s, 2H, $CH_{2\text{-}NH}$), 3.43 (p, *J* = 6.9 Hz, 1H, H_{iPr}), 6.18 (s, 1H, H_{Ar}), 7.31 (dd, *J* = 7.8, 4.8 Hz, 1H, H_{Ar}), 7.68 (dt, *J* = 7.9, 2.0 Hz, 1H, H_{Ar}), 8.40 (dd, *J* = 4.8, 1.7 Hz, 1H, H_{Ar}), 8.47 (d, *J* = 2.3 Hz, 1H, H_{Ar}), 8.61 (s, 1H, $NH_{\text{-}CH2}$).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{16}H_{19}ClN_6$: 331.1 [M+H]+, **found :** 331.2.

Example 3.52: Synthesis of 6-chloro-3-isopropyl-*N*-[3-(4-pyridyl)propyl]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.52)

To a solution of **(2.1)** (0.200 g, 0.87 mmol, 1.0 eq.) in THF (8.7 mL), corresponding amine (0.161 g, 1.13 mmol, 1.3 eq.) and Et_3N (0.24 mL, 1.73 mmol, 2.0 eq.) was added and the mixture was refluxed 3 h. After cooling, the solvent was removed, the residue was triturated in water (20.0 mL) and saturated $NaHCO_3$ (10.0 mL), the solid was filtered off, washed with water up to neutral pH then taken up in EtOAc. Organic filtrate was dried over $MgSO_4$, filtered and concentrated to give **(3.52)** (0.260 g, 91 %) as an orange solid.

Rf (DCM/MeOH, 94/6) : 0.33

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.38 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.94 (p, *J* = 7.2 Hz, 2H, CH_2), 2.65 – 2.72 (m, 2H, CH_2), 3.33 – 3.38 (m, 2H, CH_2), 3.42 (p, *J* = 7.0 Hz, 1H, H_{iPr}), 6.18 (s, 1H, H_{Ar}), 7.19 – 7.37 (m, 2H, 2xH_{Ar}), 8.31 – 8.48 (m, 2H, 2xH_{Ar}), 8.60 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{16}H_{19}ClN_6$: 331.1 [M+H]+, **found :** 331.2.

Example 3.53: Synthesis of 6-chloro-3-cyclopropyl-*N*-[3-(2-pyridyl)propyl]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.53)

To a solution of **(2.5)** (0.170 g, 0.74 mmol, 1.0 eq.) in THF/H_2O (15.0/0.5 mL), corresponding amine dihydrochloride (0.229 g, 1.04 mmol, 1.3 eq.) and Et_3N (0.63 mL, 4.45 mmol, 6.0 eq.) was added and the mixture was refluxed 16 h. After cooling, THF (10.0 mL) was added, the precipitate was filtered off, washed with THF then the filtrate was concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 95/5) as eluent to give **(3.53)** (0.080 g, 33 %) as a beige solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.11 (tt, *J* = 8.0, 2.7 Hz, 4H, 2x$CH_{2\ cPr}$), 1.85 – 2.02 (m, 2H, CH_2), 2.32 (tt, *J* = 8.2, 5.2 Hz, 1H, H_{cPr}), 2.64 – 2.76 (m, 2H, CH_2), 3.32 – 3.42 (m, 2H, CH_2), 6.16 (s, 1H, H_{Ar}), 7.30 (dd, *J* = 7.8, 4.7 Hz, 1H, H_{Ar}), 7.66 (dt, *J* = 7.9, 2.0 Hz, 1H, H_{Ar}), 8.39 (dd, *J* = 4.8, 1.6 Hz, 1H, H_{Ar}), 8.46 (d, *J* = 2.3 Hz, 1H, H_{Ar}), 8.57 (t, *J* = 5.6 Hz, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.8 (CH_{cPr}), 7.1 (2x$CH_{2\ cPr}$), 29.1 (CH_2), 29.4 (CH_2), 41.7 (CH_2), 90.8 (CH_{Ar}), 123.4 (CH_{Ar}), 135.8 (CH_{Ar}), 136.9 (C_q), 139.4 (C_q), 142.3 (C_q), 147.2 (CH_{Ar}), 149.6 (CH_{Ar}), 149.8 (C_q), 151.3 (C_q).

MS (ESI+) : m/z calcd for $C_{16}H_{17}ClN_6$: 329.1 [M+H]+, **found :** 329.2.

Example 3.54: Synthesis of 6-chloro-3-isopropyl-*N*-(pyrimidin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.54)

To a solution of **(2.1)** (0.190 g, 0.82 mmol, 1.0 eq.) in THF (9.0 mL), corresponding amine hydrochloride (0.164 g, 1.07 mmol, 1.3 eq.) and DIPEA (0.36 mL, 2.06 mmol, 2.5 eq.) was added then the mixture was refluxed 3 h. After cooling, the solvent was removed, the residue was triturated in saturated $NaHCO_3$ (10.0 mL), the solid was filtered off, washed with water then EtOAc to give a first part of **(3.54)** (0.072 g). The biphasique filtrate was separated, aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organic layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give the second part of **(3.54)** (0.020 g). Total of **(3.54)**: 0.092 g, 37 % yield, as a white solid.

Rf (DCM/MeOH, 94/6) : 0.40

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.39 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.44 (p, *J* = 7.0 Hz, 1H, H_{iPr}), 4.80 (s, 2H, $CH_{2\ Bn}$), 6.22 (s, 1H, H_{Ar}), 7.45 (t, *J* = 4.9 Hz, 1H, NH_{Bn}), 8.74 – 8.89 (m, 3H, 3xH_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{13}H_{14}ClN_7$: 304.1 [M+H]+, **found :** 304.2.

Example 3.55: Synthesis of 6-chloro-3-isopropyl-*N*-(pyrazin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.55)

To a solution of **(2.1)** (0.290 g, 1.26 mmol, 1.0 eq.) in THF (10.0 mL), corresponding amine (0.187 g, 1.63 mmol, 1.3 eq.) and DIPEA (0.33 mL, 1.88 mmol, 1.5 eq.) was added then the mixture was refluxed 1 h. After cooling, the precipitate was filtered off and washed with THF. The solid was washed with water then Et_2O and dried under vacuum to give a first part of **(3.55)** (0.103 g). THF filtrate was concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 95/5) as eluent to give the second part of **(3.55)** (0.015 g). Total of **(3.55)**: 0.118 g, 31 % yield, as a white solid.

Rf (EtOAc/Cyclohexane, 7/3) : 0.37

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.38 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.43 (p, J = 7.0 Hz, 1H, H_{iPr}), 4.77 (s, 2H, $CH_{2\ Bn}$), 6.29 (s, 1H, H_{Ar}), 8.57 (d, J = 2.6 Hz, 1H, H_{Ar}), 8.60 – 8.63 (m, 1H, H_{Ar}), 8.69 (d, J = 1.5 Hz, 1H, H_{Ar}), 8.98 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-d_6) δ : N.D.

MS (ESI+) : m/z calcd for $C_{13}H_{14}ClN_7$: 304.1 [M+H]+, **found :** 304.2.

Example 3.56: Synthesis of 6-chloro-3-isopropyl-*N*-(pyrimidin-5-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.56)

To a solution of **(2.1)** (0.190 g, 0.82 mmol, 1.0 eq.) in THF (9.0 mL), corresponding amine hydrochloride (0.164 g, 1.07 mmol, 1.3 eq.) and DIPEA (0.36 mL, 2.06 mmol, 2.5 eq.) was added then the mixture was refluxed 3 h. After cooling, the solvent was removed, the residue was triturated in saturated $NaHCO_3$ (10.0 mL), the solid was filtered off, washed with water then EtOAc to give a first part of **(3.56)** (0.055 g). The biphasique filtrate was separated, aqueous layer was extracted twice with EtOAc (2x10.0 mL). Orgnics layers were combined, dired over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give the second part of **(3.56)** (0.055 g), total of **(3.56)**: 0.110 g, 44 % yield, as a white solid.

Rf (DCM/MeOH, 94/6) : 0.30

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.37 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.42 (hept, J = 6.6 Hz, 1H, H_{iPr}), 4.66 (s, 2H, $CH_{2\ Bn}$), 6.37 (s, 1H, H_{Ar}), 8.85 (s, 2H, 2xH_{Ar}), 9.05 (s, 1H, NH_{Bn}), 9.10 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-d_6) δ : N.D.

MS (ESI+) : m/z calcd for $C_{13}H_{14}ClN_7$: 304.1 [M+H]+, **found :** 304.2.

Example 3.57: Synthesis of 6-chloro-3-isopropyl-*N*-(pyridazin-3-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.57)

To a solution of **(2.1)** (0.300 g, 1.30 mmol, 1.0 eq.) in THF (9.0 mL), corresponding amine dihydrochloride (0.323 g, 1.69 mmol, 1.3 eq.) and DIPEA (0.75 mL, 4.28 mmol, 3.3 eq.) was added and the mixture was stirred 16 h at room temperature then refluxed 2 h to complete the reaction. After cooling, the solvent was removed, the crude was triturated in water and the resulting solid was filtered off, washed with water up to neutral pH, triturated in Et_2O, filtered and dried to give **(3.57)** (0.286 g, 73 %) as a white solid.

Rf (DCM/MeOH, 94/6) : 0.38

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.38 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.43 (p, J = 6.9 Hz, 1H, H_{iPr}), 4.89 (s, 2H, $CH_{2\ Bn}$), 6.27 (s, 1H, H_{Ar}), 7.69 (d, J = 3.3 Hz, 2H, 2xH_{Ar}), 9.08 (s, 1H, NH_{Bn}), 9.17 (t, J = 3.4 Hz, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 19.8 ($CH_{3\ iPr}$), 24.4 (CH_{iPr}), 45.7 ($CH_{2\ Bn}$), 92.0 (CH_{Ar}), 125.7 (CH_{Ar}), 127.5 (CH_{Ar}), 139.4 (C_q), 142.5 (C_q), 149.4 (C_q), 151.0 (CH_{Ar}), 154.0 (C_q), 159.3 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{14}ClN_7$: 304.1 [M+H]+, **found :** 304.1.

Example 3.58: Synthesis of 6-chloro-3-isopropyl-*N*-[[4-(2-pyridyl)phenyl]methyl]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.58)

A 10 - 20 mL vial with a stir bar was charged **(1.14)** (0.300 g, 0.91 mmol, 1.0 eq.), dioxane (4.9 mL), isobutyric acid hydrazide (0.112 g, 1.09 mmol, 1.2 eq.) and AcOH (0.06 mL, 1.00 mmol, 1.1 eq.). The vial was sealed and then put on heating block, 22 h at 110 °C. After cooling, reaction mixture was poured onto saturated $NaHCO_3$ (20.0 mL) and vigorously stirred 5 min. The resulting precipitate was filtered off, washed with water then solubilized in DCM (10.0 mL). Aqueous filtrate was extracted twice with EtOAc (2 x 10.0 mL) and combined with DCM solution, all was dried over $MgSO_4$, filtered, concentrated

and purified by flash chromatography with DCM/MeOH (98/2 to 95/5) as eluent to give the title compound **(3.58)** (0.140 g, 41 %) as a white solid.

Rf (DCM/MeOH, 94/6) : 0.47

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.38 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.42 (hept, *J* = 7.1 Hz, 1H, H_{iPr}), 4.65 (d, *J* = 3.9 Hz, 2H, $CH_{2\ Bn}$), 6.18 (s, 1H, H_{Ar}), 7.33 (dd, *J* = 7.4, 4.9 Hz, 1H, H_{Ar}), 7.51 (d, *J* = 8.1 Hz, 2H, 2xH_{Ar}), 7.86 (td, *J* = 7.7, 1.9 Hz, 1H, H_{Ar}), 7.93 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 8.06 (d, *J* = 8.1 Hz, 2H, 2xH_{Ar}), 8.65 (d, *J* = 3.8 Hz, 1H, H_{Ar}), 9.17 (s, 1H, NH_{Bn}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 44.9 ($CH_{2\ Bn}$), 91.6 (CH_{Ar}), 120.1 (CH_{Ar}), 122.5 (CH_{Ar}), 126.7 (2xCH_{Ar}), 127.5 (2xCH_{Ar}), 137.2 (CH_{Ar}), 137.7 (C_q), 138.3 (C_q), 139.4 (C_q), 142.3 (C_q), 149.4 (C_q), 149.5 (CH_{Ar}), 154.0 (C_q), 155.7 (C_q).

MS (ESI+) : m/z calcd for $C_{20}H_{19}ClN_6$: 379.1 [M+H]+, **found :** 379.3.

Example 3.59: Synthesis of 6-chloro-3-isopropyl-*N*-[[4-(4-pyridyl)phenyl]methyl]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.59)

To a solution of 4-(4-pyridyl)benzonitrile (0.224 g, 1.24 mmol, 1.15 eq.) in dry THF (12.0 mL), $LiAlH_4$ (0.066 g, 1.73 mmol, 1.6 eq.) was added portionwise then the mixture was stirred 45 min. After completion, saturated NH_4Cl (10.0 mL), water (5.0 mL) and EtOAc (10.0 mL) was added and the mixture was vigorously stirred 5 min. Layers were separated, aqueous layer was extracted with EtOAc (2x10.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residu was directly used in THF (18.0 mL) with **(2.1)** (0.250 g, 1.08 mmol, 1.0 eq.) and Et_3N (0.46 mL, 3.25 mmol, 3.0 eq.) and the mixture was refluxed 3 h. After cooling, the solid was filtered, washed with THF then the filtrate was concentrated and directly purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give **(3.59)** (0.110 g, 27 %) as a white solid.

Rf (DCM/MeOH, 94/6) : 0.25

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.38 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.42 (p, *J* = 6.9 Hz, 1H, H_{iPr}), 4.66 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 6.19 (s, 1H, H_{Ar}), 7.54 (d, *J* = 8.1 Hz, 2H, 2xH_{Ar}), 7.66 – 7.75 (m, 2H, 2xH_{Ar}), 7.76 – 7.87 (m, 2H, 2xH_{Ar}), 8.56 – 8.70 (m, 2H, 2xH_{Ar}), 9.18 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.4 (CH_{iPr}), 44.7 (CH_2), 91.6 (CH_{Ar}), 121.1 (2xCH_{Ar}), 127.0 (2xCH_{Ar}), 128.0 (2xCH_{Ar}), 136.0 (C_q), 138.8 (C_q), 139.4 (C_q), 142.3 (C_q), 146.6 (C_q), 149.4 (C_q), 150.2 (2xCH_{Ar}), 154.0 (C_q).

MS (ESI+) : m/z calcd for $C_{20}H_{19}ClN_6$: 379.1 [M+H]+, **found :** 379.2.

Example 3.60: Synthesis of 6-chloro-3-isopropyl-*N*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.60)

To a solution of **(2.1)** (0.100 g, 0.433 mmol, 1.0 eq.) in dry THF (3.33 mL), 3-aminopyridazine (0.084 g, 0.866 mmol, 2.0 eq.) then tBuOK 1.65M in THF (0.52 mL, 0.866 mmol, 2.0 eq.) were added and the mixture was stirred 0.8h at room temperature. After completion, saturated NH_4Cl (3.33 mL) and water (1 mL) were added then biphasic mixture was vigorously stirred 5 min. The precipitate formed was filtered off, washed with H_2O and Et_2O to give **(3.60)** (0.023 g, 18%) as a white solid. Layers of filtrate were separated, aqueous layer was extracted with EtOAc (2x10.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was triturated in Et_2O, filtered off, washed with Et_2O and dried under vacuum to give **(3.60)** as a beige solid (0.063 g, 51%). **(3.60)** was obtained with a yield of 69% (0.086 g).

Rf (DCM/MeOH, 96/4) : 0.28

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.43 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.53 (h, *J* = 6.9 Hz, 1H, H_{iPr}), 7.73 (dd, *J* = 9.0, 4.6 Hz, 1H, H_{Ar}), 7.89 (dd, *J* = 9.0, 1.4 Hz, 1H, H_{Ar}), 8.39 (s, 1H, H_{Ar}), 9.00 (dd, *J* = 4.6, 1.4 Hz, 1H, H_{Ar}), 11.13 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.83 (2x$CH_{3\ iPr}$), 24.50 (CH_{iPr}), 101.29 (CH_{Ar}), 119.50 (CH_{Ar}), 128.69 (CH_{Ar}), 136.05 (C_q), 139.24 (C_q), 147.89 (CH_{Ar}), 149.82 (C_q), 154.39 (C_q), 157.23 (C_q).

MS (ESI+) : m/z calcd for $C_{12}H_{12}ClN_7$: 290.1 [M+H]+, **found :** 290.2.

Example 3.61: Synthesis of 6-chloro-3-isopropyl-*N*-(pyridazin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.61)

To a solution of **(2.1)** (0.350 g, 1.515 mmol, 1.0 eq.) in dry THF (11.5 mL), 4-aminopyridazine (0.294 g, 3.029 mmol, 2.0 eq.) then tBuOK 1M in THF (1.84 mL, 3.029 mmol, 2.0 eq.) were added and the mixture was stirred 1.25h at room temperature. After completion, saturated NH_4Cl (11.5 mL) and water (5.23 mL) were added then biphasic

mixture was vigorously stirred 5 min. Layers of mixture were separated, aqueous layer was extracted with EtOAc (2x10.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(3.61)** (0.256 g, 58%) as a yellow solid.

Rf (DCM/MeOH, 94/6) : 0.28

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.42 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.50 (hept, *J* = 6.9 Hz, 1H, H_{iPr}), 7.06 (s, 1H, H_{Ar}), 7.77 (dd, *J* = 6.2, 2.9 Hz, 1H, H_{Ar}), 9.09 (d, *J* = 5.9 Hz, 1H, H_{Ar}), 9.38 (d, *J* = 2.7 Hz, 1H, H_{Ar}), 10.88 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.80 (2xCH_{3iPr}), 24.50 (CH_{iPr}), 98.77 (CH_{Ar}), 115.13 (CH_{Ar}), 137.58 (C_q), 138.40 (C_q), 139.48 (C_q), 145.30 (CH_{Ar}), 149.54 (C_q), 151.27 (CH_{Ar}), 154.37 (C_q).

MS (ESI+) : m/z calcd for $C_{12}H_{12}ClN_7$: 290.1 [M+H]+, **found :** 290.1.

Example 3.62: Synthesis of 6-chloro-3-isopropyl-*N*-(pyrimidin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.62)

To a solution of **(2.1)** (0.40 g, 1.731 mmol, 1.0 eq.) in dry THF (13.14 mL), 4-aminopyrimidine (0.281 g, 2.891 mmol, 2.0 eq.) then tBuOK 1.65M in THF (1.75 mL, 2.891 mmol, 2.0 eq.) were added and the mixture was stirred 1 h at room temperature. After completion, saturated NH_4Cl (13.14 mL) and water (5.97 mL) were added then biphasic mixture was vigorously stirred 5 min. Layers of mixture were separated, aqueous layer was extracted with EtOAc (2x10.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was triturated in DCM, filtered off, washed with MeOH and Et_2O and dried under vacuum to give **(3.62)** as a pale yellow/beige solid (0.171 g, 34%). The filtrate was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give the second part of **(3.62)** (0.150 g, 30%) as a beige solid. Total of **(3.62):** 0.321 g, 64%.

Rf (DCM/MeOH, 94/6) : 0.35

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.42 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.50 (hept, *J* = 7.0 Hz, 1H, H_{iPr}), 7.60 (dd, *J* = 5.8, 1.3 Hz, 1H, H_{Ar}), 8.37 (s, 1H, H_{Ar}), 8.62 (d, *J* = 5.8 Hz, 1H, H_{Ar}), 8.99 (d, *J* = 1.2 Hz, 1H, H_{Ar}), 11.28 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ : 19.81 (2xCH$_{3\ iPr}$), 24.48 (CH$_{iPr}$), 102.67 (CH$_{Ar}$), 110.88 (CH$_{Ar}$), 135.84 (C$_q$), 139.11 (C$_q$), 149.48 (C$_q$), 154.39 (C$_q$), 157.07 (CH$_{Ar}$), 157.72 (CH$_{Ar}$), 159.68 (C$_q$).

MS (ESI+) : m/z calcd for $C_{12}H_{10}ClN_7$: 290.1 [M+H]+, **found :** 290.1.

Example 3.63: Synthesis of 6-chloro-3-isopropyl-*N*-(pyrimidin-5-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.63)

To a solution of **(2.1)** (0.200 g, 0.866 mmol, 1.0 eq.) in dry THF (6.63 mL), 5-aminopyrimidine (0.166 g, 1.731 mmol, 2.0 eq.) then tBuOK 1.65M in THF (1.05 mL, 1.731 mmol, 2.0 eq.) were added and the mixture was stirred 1.5h at room temperature. After completion, saturated NH_4Cl (6.63 mL) and water (1.77 mL) were added then biphasic mixture was vigorously stirred 5 min. The precipitate formed was filtered off, washed with H_2O and Et_2O to give **(3.63)** (0.150 g, 60%) as a white solid. Layers of filtrate were separated, aqueous layer was extracted with EtOAc (2x10.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give the second part of (**3.63**) (0.048 g, 19%) as a white solid. Total of **(3.63)** was obtained with a yield of 79% (0.198 g).

Rf (DCM/MeOH, 94/6) : 0.25

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.42 (d, *J* = 7.0 Hz, 6H, 2xCH$_{3\ iPr}$), 3.49 (p, *J* = 6.9 Hz, 1H, H$_{iPr}$), 6.65 (s, 1H, H$_{Ar}$), 8.95 (s, 2H, 2xH$_{Ar}$), 9.06 (s, 1H, H$_{Ar}$), 10.57 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO) δ : 19.81 (2xCH$_{3\ iPr}$), 24.49 (CH$_{iPr}$), 95.16 (CH$_{Ar}$), 133.98 (C$_q$), 139.40 (C$_q$), 139.60 (C$_q$), 149.66 (C$_q$), 151.64(2xCH$_{Ar}$), 154.23 (C$_q$), 154.71 (CH$_{Ar}$).

MS (ESI+) : m/z calcd for $C_{12}H_{10}ClN_7$: 290.1 [M+H]+, **found :** 290.2.

Example 3.64: Synthesis of 6-chloro-3-isopropyl-*N*-(pyrimidin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.64)

To a solution of **(2.1)** (0.152 g, 0.664 mmol, 1.0 eq.) in dry THF (5.04 mL), 2-aminopyrimidine (0.126 g, 1.316 mmol, 2.0 eq.) then tBuOK 1.65M in THF (0.80 mL, 1.316 mmol, 2.0 eq.) were added and the mixture was stirred 2.25h at room temperature. After completion, saturated NH_4Cl (5.04 mL) and water (2.3 mL) were added then biphasic mixture was vigorously stirred 5 min. Layers were separated, aqueous layer was extracted

with EtOAc (2x10.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was triturated in Et_2O, filtered off, washed with Et_2O and dried under vacuum to give **(3.64)** (0.124 g, 65%) as a beige solid.

Rf (DCM/MeOH, 94/6) : 0.48

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.42 (d, *J* = 6.9, 2.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.45 – 3.56 (m, 1H, H_{iPr}), 7.26 (dt, *J* = 4.9, 3.1 Hz, 1H, H_{Ar}), 8.16 (s, 1H, H_{Ar}), 8.80 (dd, *J* = 4.9, 1.9 Hz, 2H, 2xH_{Ar}), 10.31 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.81 (2x$CH_{3\ iPr}$), 24.49 (CH_{iPr}), 101.32 (CH_{Ar}), 116.40 (CH_{Ar}), 136.11 (C_q), 139.01 (C_q), 149.61 (C_q), 154.38 (C_q), 158.56 (C_q), 158.64 (2xCH_{Ar}).

MS (ESI+) : m/z calcd for $C_{12}H_{12}ClN_7$: 290.1 [M+H]+, **found :** 290.2.

Example 3.65: Synthesis of 6-chloro-3-isopropyl-*N*-(pyrazin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.65)

To a solution of **(2.1)** (0.100 g, 0.433 mmol, 1.0 eq.) in dry THF (3.33 mL), 2-aminopyrazine (0.082 g, 0.866 mmol, 2.0 eq.) then tBuOK 1.65M in THF (0.52 mL, 0.866 mmol, 2.0 eq.) were added and the mixture was stirred 0.8h at room temperature. After completion, saturated NH_4Cl (3.33 mL) and water (1 mL) were added then biphasic mixture was vigorously stirred 5 min. Layers were separated, aqueous layer was extracted with EtOAc (2x10.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was triturated in Et_2O, filtered off, washed with Et_2O and dried under vacuum to give **(3.65)** (0.093 g, 74%) as a beige solid.

Rf (DCM/MeOH, 96/4) : 0.31

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.43 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.51 (hept, *J* = 6.8 Hz, 1H, H_{iPr}), 8.19 (s, 1H, H_{Ar}), 8.33 (d, *J* = 2.7 Hz, 1H, H_{Ar}), 8.47 (dd, *J* = 2.7, 1.4 Hz, 1H, H_{Ar}), 8.93 (d, *J* = 1.5 Hz, 1H, H_{Ar}), 11.32 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.83 (2x$CH_{3\ iPr}$), 24.48 (CH_{iPr}), 100.32 (CH_{Ar}), 136.30 (C_q), 137.69 (CH_{Ar}), 138.02 (CH_{Ar}), 139.21 (C_q), 141.16 (CH_{Ar}), 149.60 (C_q), 150.64 (C_q), 154.37 (C_q).

MS (ESI+) : m/z calcd for $C_{12}H_{12}ClN_7$: 290.1 [M+H]+, **found :** 290.2

Example 3.66: Synthesis of 6-chloro-3-isopropyl-*N*-(6-methoxypyridin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.66)

Under inert gas, to a solution of **(2.1)** (0.125 g, 0.54 mmol, 1.0 eq.) and corresponding aminopyridine derivative (0.102 g, 0.81 mmol, 1.5 eq.) in dry THF (7.5 mL), tBuOK 1M in THF (0.81 mL, 0.81 mmol, 1.5 eq.) was added dropwise. The mixture was stirred 3.5 h at room temperature then saturated NH_4Cl (3.0 mL), water (1.0 mL) and EtOAc (3.0 mL) were added. The mixture was vigorously stirred 5 min then layers were separated and aqueous layer was extracted twice with EtOAc (2x5.0 mL). Organic layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 98/2) as eluent to give **(3.66)** (0.128 g, 74 %) as a light orange solid.

Rf (DCM/MeOH, 98/2) : 0.30

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.42 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.50 (hept, J = 6.9 Hz, 1H, H_{iPr}), 3.95 (s, 3H, $CH_{3\text{-}O}$), 6.55 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.18 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.73 (t, J = 8.0 Hz, 1H, H_{Ar}), 8.26 (s, 1H, H_{Ar}), 10.91 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 19.8 (2x$CH_{3\ iPr}$), 24.5 (CH_{iPr}), 53.6 ($CH_{3\text{-}O}$), 99.7 (CH_{Ar}), 103.7 (CH_{Ar}), 106.3 (CH_{Ar}), 136.4 (C_q), 139.3 (C_q), 141.0 (CH_{Ar}), 149.6 (C_q), 152.0 (C_q), 154.3 (C_q), 162.4 (C_q).

Example 3.67: Synthesis of 6-chloro-3-isopropyl-*N*-(5-methoxypyridin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.67)

Under inert gas, to a solution of **(2.1)** (0.125 g, 0.54 mmol, 1.0 eq.) and corresponding aminopyridine derivative (0.102 g, 0.81 mmol, 1.5 eq.) in dry THF (7.5 mL), tBuOK 1M in THF (0.81 mL, 0.81 mmol, 1.5 eq.) was added dropwise. The mixture was stirred 3.5 h at room temperature then saturated NH_4Cl (3.0 mL), water (1.0 mL) and EtOAc (3.0 mL) were added. The mixture was vigorously stirred 5 min then layers were separated and aqueous layer was extracted twice with EtOAc (2x5.0 mL). Organic layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 98/2) as eluent to give **(3.67)** (0.112 g, 65 %) as an orange solid.

Rf (DCM/MeOH, 98/2) : 0.24

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.42 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.48 (hept, J = 6.9 Hz, 1H, H_{iPr}), 3.83 (s, 3H, $CH_{3\text{-}O}$), 7.50 (dd, J = 9.0, 3.0 Hz, 1H, H_{Ar}), 7.56 (d, J = 9.0 Hz, 1H, H_{Ar}), 8.15 (s, 1H, H_{Ar}), 8.18 (d, J = 3.0 Hz, 1H, H_{Ar}), 10.82 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.5 (CH_{iPr}), 55.9 ($CH_{3\text{-}O}$), 97.8 (CH_{Ar}), 115.6 (CH_{Ar}), 124.9 (CH_{Ar}), 132.7 (CH_{Ar}), 136.7 (C_q), 139.3 (C_q), 147.3 (C_q), 149.8 (C_q), 151.8 (C_q), 154.2 (C_q).

MS (ESI+) : m/z calcd for $C_{14}H_{15}ClN_6O$: 319.1 [M+H]+, **found :** 319.2.

Example 3.68: Synthesis of 6-chloro-3-isopropyl-*N*-(4-methoxypyridin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.68)

Under inert gas, to a solution of **(2.1)** (0.125 g, 0.54 mmol, 1.0 eq.) and corresponding aminopyridine derivative (0.102 g, 0.81 mmol, 1.5 eq.) in dry THF (7.5 mL), tBuOK 1M in THF (0.81 mL, 0.81 mmol, 1.5 eq.) was added dropwise. The mixture was stirred 3.5 h at room temperature then saturated NH_4Cl (3.0 mL), water (1.0 mL) and EtOAc (3.0 mL) were added. The mixture was vigorously stirred 5 min then layers were separated and aqueous layer was extracted twice with EtOAc (2x5.0 mL). Organic layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 98/2) as eluent to give **(3.68)** (0.125 g, 72 %) as a light orange solid.

Rf (DCM/MeOH, 98/2) : 0.25

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.42 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.49 (hept, *J* = 6.9 Hz, 1H, H_{iPr}), 3.83 (s, 3H, $CH_{3\text{-}O}$), 6.76 (dd, *J* = 5.9, 2.3 Hz, 1H, H_{Ar}), 7.25 (d, *J* = 2.3 Hz, 1H, H_{Ar}), 8.26 (d, *J* = 5.9 Hz, 1H, H_{Ar}), 8.32 (s, 1H, H_{Ar}), 10.74 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.5 (CH_{iPr}), 55.3 ($CH_{3\text{-}O}$), 99.1 (CH_{Ar}), 99.7 (CH_{Ar}), 106.6 (CH_{Ar}), 136.7 (C_q), 139.3 (C_q), 148.5 (CH_{Ar}), 149.7 (C_q), 154.3 (C_q), 155.6 (C_q), 166.5 (C_q).

Example 3.69: Synthesis of 6-chloro-3-isopropyl-*N*-(3-methoxypyridin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.69)

Under inert gas, to a solution of **(2.1)** (0.125 g, 0.54 mmol, 1.0 eq.) and corresponding aminopyridine derivative (0.102 g, 0.81 mmol, 1.5 eq.) in dry THF (7.5 mL), tBuOK 1M in THF (0.81 mL, 0.81 mmol, 1.5 eq.) was added dropwise. The mixture was stirred 3.5 h at room temperature then saturated NH_4Cl (3.0 mL), water (1.0 mL) and EtOAc (3.0 mL) were added. The mixture was vigorously stirred 5 min then layers were separated and aqueous layer was extracted twice with EtOAc (2x5.0 mL). Organic layers were combined,

dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 98/2) as eluent to give **(3.69)** (0.120 g, 70 %) as a white solid.

Rf (DCM/MeOH, 98/2) : 0.38

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.42 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.49 (hept, *J* = 7.0 Hz, 1H, H_{iPr}), 4.01 (s, 3H, $CH_{3\text{-}O}$), 7.10 – 7.29 (m, 1H, H_{Ar}), 7.55 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 8.04 (d, *J* = 4.9 Hz, 1H, H_{Ar}), 8.14 (s, 1H, H_{Ar}), 8.78 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.5 (CH_{iPr}), 56.4 ($CH_{3\text{-}O}$), 99.3 (CH_{Ar}), 118.1 (CH_{Ar}), 119.4 (CH_{Ar}), 135.2 (C_q), 138.3 (CH_{Ar}), 139.1 (C_q), 142.7 (C_q), 144.0 (C_q), 149.7 (C_q), 154.5 (C_q).

MS (ESI+) : m/z calcd for $C_{14}H_{15}ClN_6O$: 319.1 [M+H]+, **found :** 319.2.

Example 3.70: Synthesis of 6-chloro-3-isopropyl-*N*-(3-phenylpropyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.70)

To a solution of **(2.1)** (0.130 g, 0.56 mmol, 1.0 eq.) in THF (6.0 mL), corresponding amine (0.16 mL, 1.12 mmol, 2.0 eq.) and Et_3N (0.16 mL, 1.12 mmol, 2.0 eq.) were added and the mixture was refluxed 2 h. After cooling, the precipitate was filtered off, washed with THF then the filtrate was concentrated and the residu was purified by flash chromatography with DCM/MeOH (98/2) as eluent to give **(3.70)** (0.177 g, 95 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.39 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.84 – 2.02 (m, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 2.68 (dd, *J* = 8.8, 6.7 Hz, 2H, $CH_{2\text{-}Ph}$), 3.33 - 3.39 (m, 2H, $CH_{2\text{-}NH}$), 3.44 (h, *J* = 7.0 Hz, 1H, H_{iPr}), 6.13 (s, 1H, H_{Ar}), 7.14 – 7.23 (m, 1H, H_{Ar}), 7.21 – 7.33 (m, 4H, 4xH_{Ar}), 8.61 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 20.3 (2x$CH_{3\ iPr}$), 24.9 (CH_{iPr}), 29.9 ($CH_{2\text{-}CH2\text{-}NH}$), 32.9 ($CH_{2\text{-}Ph}$), 42.2 ($CH_{2\text{-}NH}$), 91.2 ($CH_{Ar}$), 126.3 ($CH_{Ar}$), 128.8 (2x$CH_{Ar}$), 128.8 ($CH_{Ar}$), 139.9 ($C_q$), 142.0 ($C_q$), 142.9 ($C_q$), 150.1 ($C_q$), 154.4 ($C_q$).

Example 3.71: Synthesis of 6-chloro-3-cyclopropyl-*N*-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.71)

Under inert gas, to a solution of **(2.5)** (0.150 g, 0.65 mmol, 1.0 eq.) in dry THF (5.0 mL), aniline (0.12 mL, 1.31 mmol, 2.0 eq.) was added then tBuOK 1M in THF (1.31 mL, 1.31 mmol, 2.0 eq.). The mixture was stirred 1 h at room temperature then saturated NH_4Cl (5.0 mL) and water (1.5 mL) were added and stirred vigorously 5 min. Layers were separated

and aqueous layer was extracted twice with EtOAc (2x5.0 mL). Orgnics layers were combined, dried over $MgSO_4$, filtered, concentrated and the residu was purified by flash chromatography with DCM/MeOH (99/1 to 98/2) as eluent to give **(3.71)** (0.175 g, 94 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.10 – 1.26 (m, 4H, 2x$CH_{2\ cPr}$), 2.37 (tt, *J* = 8.1, 5.3 Hz, 1H, H_{cPr}), 6.34 (s, 1H, H_{Ar}), 7.27 (ddd, *J* = 8.5, 5.9, 2.2 Hz, 1H, H_{Ar}), 7.38 – 7.55 (m, 4H, 4xH_{Ar}), 10.43 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.9 (CH_{cPr}), 7.2 (2x$CH_{2\ cPr}$), 92.9 (CH_{Ar}), 123.5 (2xCH_{Ar}), 125.7 (CH_{Ar}), 129.5 (2xCH_{Ar}), 137.7 (C_q), 139.5 (C_q), 140.2 (C_q), 149.8 (C_q), 151.6 (C_q).

MS (ESI+) : m/z calcd for $C_{14}H_{12}ClN_5$: 286.1 [M+H]+, **found :** 286.2.

Example 3.72: Synthesis of 6-chloro-3-cyclopropyl-*N*-(2-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.72)

Under inert gas, to a solution of **(2.5)** (0.150 g, 0.65 mmol, 1.0 eq.) in dry THF (5.0 mL), corresponding aminopyridine (0.125 g, 1.31 mmol, 2.0 eq.) was added then tBuOK 1M in THF (1.31 mL, 1.31 mmol, 2.0 eq.). The mixture was stirred 1 h at room temperature then saturated NH_4Cl (5.0 mL) and water (1.5 mL) were added and stirred vigorously 5 min. Layers were separated and aqueous layer was extracted twice with EtOAc (2x5.0 mL). Orgnics layers were combined, dried over $MgSO_4$, filtered, concentrated and the residu was purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **(3.72)** (0.085 g, 45 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.11 – 1.21 (m, 4H, 2x$CH_{2\ cPr}$), 2.39 (tt, *J* = 8.0, 5.4 Hz, 1H, CH_{cPr}), 7.13 (ddd, *J* = 7.3, 5.0, 1.0 Hz, 1H, H_{Ar}), 7.48 – 7.66 (m, 1H, H_{Ar}), 7.82 (ddd, *J* = 8.4, 7.3, 2.0 Hz, 1H, H_{Ar}), 8.31 (s, 1H, H_{Ar}), 8.45 (dd, *J* = 5.3, 1.9 Hz, 1H, H_{Ar}), 10.87 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.9 (CH_{cPr}), 7.2 (2x$CH_{2\ cPr}$), 99.5 (CH_{Ar}), 114.6 (CH_{Ar}), 118.6 (CH_{Ar}), 136.6 (C_q), 138.3 (CH_{Ar}), 139.2 (C_q), 147.3 (CH_{Ar}), 150.0 (C_q), 151.7 (C_q), 153.9 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{11}ClN_6$: 287.1 [M+H]+, **found :** 287.2.

Example 3.73: Synthesis of 6-chloro-3-cyclopropyl-*N*-(3-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.73)

Under inert gas, to a solution of **(2.5)** (0.150 g, 0.65 mmol, 1.0 eq.) in dry THF (5.0 mL), corresponding aminopyridine (0.125 g, 1.31 mmol, 2.0 eq.) was added then tBuOK 1M in THF (1.31 mL, 1.31 mmol, 2.0 eq.). The mixture was stirred 1 h at room temperature then saturated NH_4Cl (5.0 mL) and water (1.5 mL) were added and stirred vigorously 5 min. Layers were separated and aqueous layer was extracted twice with EtOAc (2x5.0 mL). Organic layers were combined, dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **(3.73)** (0.080 g, 43 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.15 (tt, J = 7.7, 2.6 Hz, 4H, 2x$CH_{2\ cPr}$), 2.38 (tt, J = 8.1, 5.3 Hz, 1H, H_{cPr}), 6.42 (s, 1H, H_{Ar}), 7.50 (dd, J = 8.2, 4.7 Hz, 1H, H_{Ar}), 7.91 (ddd, J = 8.3, 2.7, 1.5 Hz, 1H, H_{Ar}), 8.46 (dd, J = 4.8, 1.5 Hz, 1H, H_{Ar}), 8.69 (d, J = 2.6 Hz, 1H, H_{Ar}), 10.51 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-d_6) δ : N.D.

MS (ESI+) : m/z calcd for $C_{13}H_{11}ClN_6$: 287.1 [M+H]+, **found :** 287.2.

Example 3.74: Synthesis of 6-chloro-3-cyclopropyl-*N*-(4-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.74)

Under inert gas, to a solution of **(2.5)** (0.150 g, 0.65 mmol, 1.0 eq.) in dry THF (5.0 mL), corresponding aminopyridine (0.125 g, 1.31 mmol, 2.0 eq.) was added then tBuOK 1M in THF (1.31 mL, 1.31 mmol, 2.0 eq.). The mixture was stirred 1 h at room temperature then saturated NH_4Cl (5.0 mL) and water (1.5 mL) were added and stirred vigorously 5 min. Layers were separated and aqueous layer was extracted twice with EtOAc (2x5.0 mL). Orgnics layers were combined, dried over $MgSO_4$, filtered, concentrated and the residu was purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **(3.74)** (0.090 g, 48 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.16 (tt, J = 8.0, 2.8 Hz, 4H, 2x$CH_{2\ cPr}$), 2.38 (ddd, J = 10.5, 8.3, 5.2 Hz, 1H, H_{cPr}), 6.87 (s, 1H, H_{Ar}), 7.42 – 7.58 (m, 2H, 2xH_{Ar}), 8.54 (d, J = 5.4 Hz, 2H, 2xH_{Ar}), 10.66 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 4.9 (CH_{cPr}), 7.3 (2x$CH_{2\ cPr}$), 96.8 (CH_{Ar}), 115.5 (CH_{Ar}), 138.0 (C_q), 139.4 (C_q), 145.7 (C_q), 149.8 (C_q), 150.7 (CH_{Ar}), 151.8 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{11}ClN_6$: 287.1 [M+H]+, **found :** 287.2.

Example 3.75: Synthesis of 6-chloro-3-cyclopropyl-*N*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.75)

To a solution of **(2.5)** (0.250 g, 1.091 mmol, 1.0 eq.) in dry THF (8.38 mL), 3-aminopyridazine (0.212 g, 2.183 mmol, 2.0 eq.) then tBuOK 1M in THF (1.32 mL, 2.183 mmol, 2.0 eq.) were added and the mixture was stirred 2h at room temperature. After completion, saturated NH_4Cl (8.38 mL) and water (2.53 mL) were added then biphasic mixture was vigorously stirred 5 min. The precipitate formed was filtered off, washed with H_2O and Et_2O to give **(3.75)** (0.286 g, 91%) as a beige solid.

Rf (DCM/MeOH, 96/4) : 0.38

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.12 – 1.22 (m, 4H, 2x$CH_{2\ cPr}$), 2.40 (td, J = 8.1, 4.0 Hz, 1H, H_{cPr}), 7.72 (dd, J = 9.0, 4.6 Hz, 1H, H_{Ar}), 7.87 (d, 1H, H_{Ar}), 8.37 (s, 1H, H_{Ar}), 9.00 (d, J = 4.6 Hz, 1H, H_{Ar}), 11.10 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 4.87 (CH_{cPr}),7.28 (2x$CH_{2\ cPr}$), 101.25 (CH_{Ar}), 119.51 (CH_{Ar}), 128.67 (CH_{Ar}), 136.07 (C_q), 139.23 (C_q), 147.86 (CH_{Ar}), 150.02 (C_q), 151.82 (C_q), 157.27 (C_q).

MS (ESI+) : m/z calcd for $C_{12}H_{10}ClN_7$: 288.1 [M+H]+, **found :** 288.1.

Example 3.76: Synthesis of 6-chloro-3-cyclopropyl-*N*-(pyridazin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.76)

To a solution of **(2.5)** (0.087 g, 0.380 mmol, 1.0 eq.) in dry THF (2.94 mL), 4-aminopyridazine (0.074 g, 0.760 mmol, 2.0 eq.) then tBuOK 1M in THF (0.76 mL, 0.760 mmol, 2.0 eq.) were added and the mixture was stirred 1.2h at room temperature. After completion, saturated NH_4Cl (2.94 mL) and water (0.871 mL) were added then biphasic mixture was vigorously stirred 5 min. Layers were separated, aqueous layer was extracted with EtOAc (2x10 mL) then organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was triturated in Et_2O, filtered off, washed with Et_2O and dried under vacuum. The residue was then triturated in DCM, filtered off, washed with DCM and dried under vacuum to give (**3.76**) (0.094 g, 86%) as a white solid.

Rf (DCM/MeOH, 96/4) : 0.35

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.10 – 1.23 (m, 4H, 2x$CH_{2\ cPr}$), 2.35 – 2.44 (m, 1H, H_{cPr}), 7.05 (s, 1H, H_{Ar}), 7.76 (dd, *J* = 6.2, 2.9 Hz, 1H, H_{Ar}), 9.08 (d, *J* = 5.9 Hz, 1H, H_{Ar}), 9.37 (s, 1H, H_{Ar}), 10.87 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.85 (CH_{cPr}), 7.30 (2x$CH_{2\ cPr}$), 98.78 (CH_{Ar}), 115.07 (CH_{Ar}), 137.63 (C_q), 138.57 (C_q), 139.43 (C_q), 145.29 (CH_{Ar}), 149.72 (C_q), 151.17 (CH_{Ar}), 151.82 (C_q).

MS (ESI+) : m/z calcd for $C_{12}H_{10}ClN_7$: 288.1 [M+H]+, **found :** 288.2.

Example 3.77: Synthesis of 6-chloro-3-cyclopropyl-*N*-pyrimidin-4-yl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.77)

To a solution of **(2.5)** (0.500 g, 2.183 mmol, 1.0 eq.) in dry THF (16.77 mL), 4-aminopyrimidine (0.416 g, 4.366 mmol, 2.0 eq.) then tBuOK 1.65M in THF (2.65 mL, 4.366 mmol, 2.0 eq.) were added and the mixture was stirred 1.3h at room temperature. After completion, saturated NH_4Cl (16.77 mL) and water (5.06 mL) were added then biphasic mixture was vigorously stirred 5 min. The precipitate formed was filtered off, washed with H_2O, Et_2O and pentane and dried under vacuum to give **(3.77)** (0.463 g, 74%) as a yellow solid.

Rf (DCM/MeOH, 96/4) : 0.31

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.11 – 1.23 (m, 4H, 2x$CH_{2\ cPr}$), 2.35 – 2.44 (m, 1H, CH_{cPr}), 7.58 (d, *J* = 5.8 Hz, 1H, H_{Ar}), 8.36 (s, 1H, H_{Ar}), 8.62 (d, *J* = 5.8 Hz, 1H, H_{Ar}), 9.00 (s, 1H, H_{Ar}), 11.25 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.84 (CH_{cPr}), 7.30 (2x$CH_{2\ cPr}$), 102.66 (CH_{Ar}), 110.86 (CH_{Ar}), 135.79 (C_q), 139.05 (C_q), 149.69 (C_q), 151.85 (C_q), 157.08 (CH_{Ar}), 157.73 (CH_{Ar}), 159.67 (C_q).

MS (ESI+) : m/z calcd for $C_{12}H_{10}ClN_7$: 288.1 [M+H]+, **found :** 288.2.

Example 3.78: Synthesis of 6-chloro-3-cyclopropyl-*N*-(pyrimidin-5-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.78)

To a solution of **(2.5)** (0.135 g, 0.589 mmol, 1.0 eq.) in dry THF (4.53 mL), 5-aminopyrimidine (0.113 g, 1.179 mmol, 2.0 eq.) then tBuOK 1M in THF (1.18 mL, 1.179 mmol, 2.0 eq.) were added and the mixture was stirred 1h at room temperature. After completion, saturated NH_4Cl (4.53 mL) and water (1.35 mL) were added then biphasic

mixture was vigorously stirred 5 min. Layers were separated, aqueous layer was extracted with EtOAc (2x10.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was triturated in Et_2O, filtered off, washed with Et_2O, solubilised in DCM and concentrated under vacuum to give **(3.78)** (0.153 g, 90%) as a beige solid.

Rf (DCM/MeOH, 92/8) : 0.54

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.09 – 1.20 (m, 4H, 2x$CH_{2\ cPr}$), 2.34 – 2.42 (m, 1H, H_{cPr}), 6.63 (s, 1H, H_{Ar}), 8.94 (d, *J* = 1.4 Hz, 2H, 2xH_{Ar}), 9.05 (d, *J* = 1.4 Hz, 1H, H_{Ar}), 10.54 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.86 (CH_{cPr}), 7.26 (2x$CH_{2\ cPr}$), 95.16 (CH_{Ar}), 133.99 (C_q), 139.34 (C_q), 139.54 (C_q), 149.85 (C_q), 151.58 (2xCH_{Ar}), 151.68 (C_q), 154.67 (CH_{Ar}).

MS (ESI+) : m/z calcd for $C_{12}H_{10}ClN_7$: 288.1 [M+H]+, **found :** 288.2.

Example 3.79: Synthesis of 6-chloro-3-cyclopropyl-*N*-(pyrimidin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.79)

To a solution of **(2.5)** (0.100 g, 0.437 mmol, 1.0 eq.) in dry THF (3.36 mL), 2-aminopyrimidine (0.084 g, 0.873 mmol, 2.0 eq.) then tBuOK 1M in THF (0.87 mL, 0.873 mmol, 2.0 eq.) were added and the mixture was stirred 1.4h at room temperature. After completion, saturated NH_4Cl (3.36 mL) and water (1.0 mL) were added then biphasic mixture was vigorously stirred 5 min. Layers were separated, aqueous layer was extracted with EtOAc (2x5.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was triturated in Et_2O, filtered off, washed with Et_2O and dried under vacuum to give **(3.79)** (0.100 g, 80%) as a white solid.

Rf (DCM/MeOH, 96/4) : 0.57

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.12 – 1.22 (m, 4H, 2x$CH_{2\ cPr}$), 2.39 (td, *J* = 8.2, 4.1 Hz, 1H, H_{cPr}), 7.26 (t, *J* = 4.8 Hz, 1H, H_{Ar}), 8.15 (s, 1H, H_{Ar}), 8.79 (d, *J* = 4.8 Hz, 2H, 2xH_{Ar}), 10.28 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.84 (CH_{cPr}), 7.28 (2x$CH_{2\ cPr}$), 99.52 (C_q), 101.30 (CH_{Ar}), 116.39 (CH_{Ar}), 136.08 (C_q), 138.96 (C_q), 149.82 (C_q), 151.82 (C_q), 158.64 (2xCH_{Ar}).

MS (ESI+) : m/z calcd for $C_{12}H_{10}ClN_7$: 288.1 [M+H]+, **found :** 288.2.

Example 3.80: Synthesis of 6-chloro-3-cyclopropyl-*N*-(pyrazin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.80)

To a solution of **(2.5)** (0.080 g, 0.349 mmol, 1.0 eq.) in dry THF (2.68 mL), 2-aminopyrazine (0.066 g, 0.699 mmol, 2.0 eq.) then tBuOK 1M in THF (0.70 mL, 0.699 mmol, 2.0 eq.) were added and the mixture was stirred 1.2h at room temperature. After completion, saturated NH_4Cl (2.68 mL) and water (0.81 mL) were added then biphasic mixture was vigorously stirred 5 min. The precipitate formed was filtered off, washed with H_2O and Et_2O to give **(3.80)** (0.072 g, 72%) as a white solid. Layers of filtrate were separated, aqueous layer was extracted with EtOAc (2x5.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was triturated in Et_2O, filtered off, washed with Et_2O and dried under vacuum to give the second part of **(3.80)** (0.012 g, 12%) as a white solid. Total of **(3.80)** : 0.084 g, 84%.

Rf (DCM/MeOH, 96/4) : 0.11

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.12 – 1.21 (m, 4H, 2x$CH_{2\ cPr}$), 2.39 (tt, *J* = 8.0, 5.3 Hz, 1H, H_{cPr}), 8.18 (s, 1H, H_{Ar}), 8.32 (d, *J* = 2.8 Hz, 1H, H_{Ar}), 8.44 – 8.50 (m, 1H, H_{Ar}), 8.91 (s, 1H, H_{Ar}), 11.29 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.84 (CH_{cPr}), 7.28 (2x$CH_{2\ cPr}$), 100.30 (CH_{Ar}), 136.25 (C_q), 137.68 (CH_{Ar}), 138.02 (CH_{Ar}), 139.14 (C_q), 141.16 (CH_{Ar}), 149.80 (C_q), 150.63 (C_q), 151.81 (C_q).

MS (ESI+) : m/z calcd for $C_{12}H_{10}ClN_7$: 288.1 [M+H]+, **found :** 288.1.

Example 3.81: Synthesis of 6-chloro-3-cyclopropyl-*N*-(6-methoxypyridin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.81)

Under inert gas, to a solution of **(2.5)** (0.125 g, 0.55 mmol, 1.0 eq.) in dry THF (7.5 mL), 6-methoxypyridin-2-amine (0.103 g, 0.82 mmol, 1.5 eq.) was added then tBuOK 1M in THF (0.82 mL, 0.82 mmol, 1.5 eq.). The mixture was stirred 3 h at room temperature then saturated NH_4Cl (6.0 mL) and water (1.5 mL) were added and stirred vigorously 5 min. Layers were separated and aqueous layer was extracted twice with EtOAc (2x5.0 mL). Orgnics layers were combined, dried over $MgSO_4$, filtered, concentrated and the residu was purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **(3.81)** (0.115 g, 67 %) as a white solid.

Rf (DCM/MeOH, 98/2) : 0.28

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.12 – 1.20 (m, 4H, 2x$CH_{2\ cPr}$), 2.38 (tt, *J* = 8.0, 5.4 Hz, 1H, H_{cPr}), 3.95 (s, 3H, OCH_3), 6.54 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 7.16 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.72 (t, *J* = 7.9 Hz, 1H, H_{Ar}), 8.25 (s, 1H, H_{Ar}), 10.87 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.9 (C_q), 7.3 (2x$CH_{2\ cPr}$), 53.6 (OCH_3), 99.6 (CH_{Ar}), 103.7 (CH_{Ar}), 106.3 (CH_{Ar}), 136.4 (C_q), 139.2 (C_q), 140.9 (CH_{Ar}), 149.8 (C_q), 151.7 (C_q), 152.0 (C_q), 162.4 (C_q).

MS (ESI+) : m/z calcd for $C_{14}H_{13}ClN_6O$: 317.1 [M+H]+, **found :** 317.3.

Example 3.82: Synthesis of 6-chloro-3-cyclopropyl-*N*-(2-methoxypyridin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.82)

Under inert gas, to a solution of **(2.5)** (0.125 g, 0.55 mmol, 1.0 eq.) in dry THF (7.5 mL), 2-methoxypyridin-3-amine (0.103 g, 0.82 mmol, 1.5 eq.) was added then tBuOK 1M in THF (0.82 mL, 0.82 mmol, 1.5 eq.). The mixture was stirred 3 h at room temperature then saturated NH_4Cl (6.0 mL) and water (1.5 mL) were added and stirred vigorously 5 min. Layers were separated and aqueous layer was extracted twice with EtOAc (2x5.0 mL). Orgnics layers were combined, dried over $MgSO_4$, filtered, concentrated and the residu was purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **(3.82)** (0.113 g, 65 %) as a white solid.

Rf (DCM/MeOH, 98/2) : 0.28

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.08 – 1.21 (m, 4H, 2x$CH_{2\ cPr}$), 2.36 (tt, *J* = 7.6, 5.1 Hz, 1H, H_{cPr}), 3.90 (s, 3H, OCH_3), 5.85 (s, 1H, H_{Ar}), 7.11 (dd, *J* = 7.5, 4.9 Hz, 1H, H_{Ar}), 7.78 (dd, *J* = 7.6, 1.7 Hz, 1H, H_{Ar}), 8.18 (dd, *J* = 4.9, 1.8 Hz, 1H, H_{Ar}), 9.99 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.9 (CH_{cPr}), 7.2 (2x$CH_{2\ cPr}$), 53.5 (OCH_3), 94.2 (CH_{Ar}), 117.5 (CH_{Ar}), 120.7 (C_q), 135.7 (CH_{Ar}), 139.3 (C_q), 140.5 (C_q), 145.0 (CH_{Ar}), 149.5 (C_q), 151.5 (C_q), 157.9 (C_q).

MS (ESI+) : m/z calcd for $C_{14}H_{13}ClN_6O$: 317.1 [M+H]+, **found :** 317.3.

Example 3.83: Synthesis of 6-chloro-3-cyclopropyl-*N*-(2-methoxypyrimidin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.83)

Under inert gas, to a solution of 2-methoxypyrimidin-4-amine (0.112 g, 0.85 mmol, 1.3 eq.) in dry THF (6.5 mL), KHMDS 0.5M in toluene (1.83 mL, 0.92 mmol, 1.4 eq.) was added. The mixture was stirred 10 min at room temperature then **(2.5)** (0.150 g, 0.65

mmol, 1.0 eq.) was added and the mixture was stirred 2.5 h at room temperature. After completion, NH_4Cl (0.5 mL) and water (0.5 mL) were added and stirred vigorously 5 min then the mixture was concentrated with SiO_2 to make solid deposit and purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(3.83)** (0.097 g, 47 %) as a white solid.

Rf (DCM/MeOH, 96/4) : 0.22

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.11 – 1.23 (m, 4H, 2x$CH_{2\ cPr}$), 2.39 (tt, *J* = 8.1, 5.3 Hz, 1H, H_{cPr}), 3.95 (s, 3H, $CH_{3\text{-}O}$), 7.20 (d, *J* = 5.6 Hz, 1H, H_{Ar}), 8.30 (s, 1H, H_{Ar}), 8.39 (d, *J* = 5.6 Hz, 1H, H_{Ar}), 11.21 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.8 (CH_{cPr}), 7.3 (2xCH_{cPr}), 54.5 ($CH_{3\text{-}O}$), 103.0 (CH_{Ar}), 104.4 (CH_{Ar}), 135.7 (C_q), 139.0 (C_q), 149.6 (C_q), 151.8 (C_q), 158.9 (CH_{Ar}), 161.7 (C_q), 164.4 (C_q).

Example 3.84: Synthesis of 6-chloro-3-cyclopropyl-*N*-(6-methoxypyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.84)

Under inert gas, to a solution of 6-methoxypyridazin-3-amine (0.112 g, 0.85 mmol, 1.3 eq.) in dry THF (6.5 mL), KHMDS 0.5M in toluene (1.83 mL, 0.92 mmol, 1.4 eq.) was added. The mixture was stirred 10 min at room temperature then **(2.5)** (0.150 g, 0.65 mmol, 1.0 eq.) was added and the mixture was stirred 2.5 h at room temperature. After completion, NH_4Cl (0.5 mL) and water (0.5 mL) were added and stirred vigorously 5 min then the mixture was concentrated with SiO_2 to make solid deposit and purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(3.84)** (0.110 g, 53 %) as a white solid.

Rf (DCM/MeOH, 96/4) : 0.34

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.17 (dd, *J* = 7.8, 5.4 Hz, 4H, 2x$CH_{2\ cPr}$), 2.39 (tt, *J* = 8.0, 5.3 Hz, 1H, H_{cPr}), 4.02 (s, 3H, $CH_{3\text{-}O}$), 7.32 (d, *J* = 9.4 Hz, 1H, H_{Ar}), 7.85 (d, *J* = 9.5 Hz, 1H, H_{Ar}), 8.26 (s, 1H, H_{Ar}), 10.98 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.9 (CH_{cPr}), 7.3 (2xCH_{cPr}), 54.4 ($CH_{3\text{-}O}$), 100.3 (CH_{Ar}), 120.1 (CH_{Ar}), 124.0 (CH_{Ar}), 136.0 (C_q), 139.1 (C_q), 150.1 (C_q), 151.8 (C_q), 153.7 (C_q), 161.6 (C_q).

Example 3.85: Synthesis of 6-chloro-3-cyclopropyl-*N*-(pyridazin-3-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.85)

To a solution of **(2.5)** (0.100 g, 0.44 mmol, 1.0 eq.) in THF/H_2O (6.0/0.1 mL), corresponding amine dihydrochloride (0.103 g, 0.57 mmol, 1.3 eq.) and DIPEA (0.33 mL, 1.88 mmol, 4.3 eq.) were added and the mixture was refluxed 2 h. After cooling, the precipitate was filtered off and washed with THF. In another vacuum flask, washed the solid with water then washed again with THF in the first flask. The solid was dried under vacuum to give the first part of **(3.85)** (0.063 g). Organics filtrates were combined, dried ver $MgSO_4$, concentrated and the residu was purified by flash chromatography with DCM/MeOH (98/2) as eluent to give the second part of **(3.85)** (0.018 g). Total of **(3.85)**: 0.081 g, 61 %, as a white solid.

Rf (DCM/MeOH, 96/4) : 0.18

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.06 – 1.16 (m, 4H, 2x$CH_{2\ cPr}$), 2.32 (tt, *J* = 8.1, 5.3 Hz, 1H, H_{cPr}), 4.89 (s, 2H, $CH_{2\ Bn}$), 6.26 (s, 1H, H_{Ar}), 7.63 – 7.75 (m, 2H, 2xH_{Ar}), 9.04 (s, 1H, NH_{Bn}), 9.17 (dd, *J* = 4.0, 2.6 Hz, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.8 (CH_{cPr}), 7.1 (2x$CH_{2\ cPr}$), 45.7 ($CH_{2\ Bn}$), 92.0 (CH_{Ar}), 125.7 (CH_{Ar}), 127.5 (CH_{Ar}), 139.3 (C_q), 142.5 (C_q), 149.7 (C_q), 151.0 (CH_{Ar}), 151.4 (C_q), 159.3 (C_q).

Example 3.86: Synthesis of 6-chloro-3-cyclopropyl-*N*-phenethyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.86)

To a solution of **(2.5)** (0.100 g, 0.44 mmol, 1.0 eq.) in THF/H_2O (6.0/0.1 mL), corresponding amine hydrochloride (0.089 g, 0.57 mmol, 1.3 eq.) and DIPEA (0.23 mL, 1.31 mmol, 3.0 eq.) were added and the mixture was refluxed 1.5 h. After cooling, the solvent was removed then the residu was triturated in water, the solid was filtered off, washed with water then Et_2O and dried under vacuum to give **(3.86)** (0.115 g, 84 %) as a white solid.

Rf (DCM/MeOH, 96/4) : 0.66

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.10 (ddt, *J* = 8.7, 7.5, 2.6 Hz, 4H, 2x$CH_{2\ cPr}$), 2.31 (tt, *J* = 8.1, 5.3 Hz, 1H, H_{cPr}), 2.94 (dd, *J* = 8.0, 6.6 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.58 (d, *J* = 7.2 Hz, 2H, $CH_{2\text{-}NH}$), 6.19 (s, 1H, H_{Ar}), 7.12 – 7.35 (m, 5H, 5xH_{Ar}), 8.48 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 4.8 (CH_{cPr}), 7.2 ($2xCH_{2\ cPr}$), 33.8 ($CH_{2\text{-}CH2\text{-}NH}$), 43.5 ($CH_{2\text{-}NH}$), 91.0 ($CH_{Ar}$), 126.2 ($CH_{Ar}$), 128.3 ($2xCH_{Ar}$), 128.9 ($CH_{Ar}$), 138.9 ($C_q$), 139.3 ($C_q$), 142.2 ($C_q$), 149.9 ($C_q$), 151.3 ($C_q$).

MS (ESI+) : m/z calcd for $C_{16}H_{16}ClN_5$: 314.1 [M+H]+, **found :** 314.2.

Example 3.87: Synthesis of 6-chloro-3-isopropyl-*N*-(6-methoxypyridin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.87)

Reaction was carried out on **(2.1)** (0.180 g, 0.78 mmol, 1 eq), aminopyridine derivative (0.145 g, 1.17 mmol, 1.5 eq), and *t*BuOK 1M in THF (1.17 mL, 1.17 mmol, 1.5 eq) in dry THF (10.8 mL) and stirred in a round flask at r.t for 4h. After completion, saturated NH_4Cl , water and EtOAc were added. The reaction mixture was extracted twice with AcOEt, filtered over $MgSO_4$, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 98/2) has eluent to give **(3.87)** (0.175 g, 71%) as a light orange solid.

^{1}H NMR (400 MHz, DMSO) δ : 10.04 (s, 1H), 8.18 (dd, J = 4.9, 1.8 Hz, 1H), 7.78 (dd, J = 7.6, 1.8 Hz, 1H), 7.12 (dd, J = 7.6, 4.9 Hz, 1H), 5.84 (s, 1H), 3.91 (s, 3H), 3.48 (hept, J = 6.9 Hz, 1H), 1.41 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, DMSO) δ : 158.0, 154.1, 149.3, 145.1, 140.5, 139.3, 135.7, 120.6, 117.5, 94.2, 53.5, 24.5, 19.8.

Example 3.88: Synthesis of 6-chloro-3-isopropyl-*N*-(6-methoxypyridin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.88)

Reaction was carried out on **(2.1)** (0.180 g, 0.78 mmol, 1 eq), aminopyridine derivative (0.145 g, 1.17 mmol, 1.5 eq), and *t*BuOK 1M in THF (1.17 mL, 1.17 mmol, 1.5 eq) in dry THF (10.8 mL) and stirred in a round flask at r.t for 4h. After completion, saturated NH_4Cl , water and EtOAc were added. The reaction mixture was extracted twice with AcOEt, filtered over $MgSO_4$, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 98/2) has eluent to give **(3.88)** (0.106 g, 43%) as a light orange solid.

^{1}H NMR (400 MHz, DMSO) δ : 10.32 (s, 1H), 8.24 (d, J = 2.7 Hz, 1H), 7.80 (dd, J = 8.8, 2.7 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.15 (s, 1H), 3.88 (s, 3H), 3.47 (hept, J = 6.9 Hz, 1H), 1.41 (d, J = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, DMSO) δ : 161.6, 154.2, 149.6, 143.0, 141.2, 139.4, 136.1, 128.3, 111.1, 92.9, 53.5, 24.9, 19.8.

Example 3.89: Synthesis of 6-chloro-3-isopropyl-*N*-(5-methoxypyridin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.89)

Reaction was carried out on **(2.1)** (0.180 g, 0.78 mmol, 1 eq), aminopyridine derivative (0.145 g, 1.17 mmol, 1.5 eq), and *t*BuOK 1M in THF (1.17 mL, 1.17 mmol, 1.5 eq) in dry THF (10.8 mL) and stirred in a round flask at r.t for 4h. After completion, saturated NH_4Cl , water and EtOAc were added. The reaction mixture was extracted twice with AcOEt, filtered over $MgSO_4$, concentrated and purified by flash chromatography with DCM/AcOEt (8/2 to 35/65) has eluent to give **(3.89)** (0.162 g, 65%) as a light orange solid.

^{1}H NMR (400 MHz, DMSO) δ : 10.50 (s, 1H), 8.31 (d, *J* = 2.0 Hz, 1H), 8.20 (d, *J* = 2.6 Hz, 1H), 7.49 (s, 1H), 6.49 (s, 1H), 3.86 (s, 3H), 3.49 (hept, *J* = 6.9 Hz, 1H), 1.41 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, DMSO) δ : 155.7, 154.2, 149.7, 140.0, 139.5, 136.9, 135.3, 134.2, 115.7, 94.3, 55.8, 24.5, 19.8.

Example 3.90: Synthesis of 6-chloro-3-isopropyl-*N*-(4-methoxypyridin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.90)

Reaction was carried out on **(2.1)** (0.400 g, 1.73 mmol, 1 eq), aminopyridine derivative (0.322 g, 2.60 mmol, 1.5 eq), and *t*BuOK 1M in THF (2.6 mL, 2.60 mmol, 1.5 eq) in dry THF (20.0 mL) and stirred in a round flask at r.t for 4h. After completion, saturated NH_4Cl , water and EtOAc were added. The reaction mixture was extracted twice with AcOEt, filtered over $MgSO_4$, concentrated and purified by flash chromatography with DCM/AcOEt (8/2 to 35/65) has eluent to give **(3.90)** (0.261 g, 47%) as a brown solid.

^{1}H NMR (400 MHz, DMSO) δ : 10.15 (s, 1H), 8.48 (d, *J* = 5.7 Hz, 1H), 8.40 (s, 1H), 7.26 (d, *J* = 5.7 Hz, 1H), 5.74 (s, 1H), 3.89 (s, 3H), 3.53 – 3.41 (m, 1H), 1.41 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, DMSO) δ : 160.6, 154.6, 150.7, 149.8, 148.8, 141.7, 139.8, 123.0, 108.8, 94.5, 56.4, 23.0, 20.3.

Example 3.91: Synthesis of 6-chloro-3-isopropyl-N-(3-phenylpropyl)-[1,2,4]triazolo[4,3-b]pyridazin-8-amine (3.91)

To a solution of **(2.1)** (0.130 g, 0.56 mmol, 1.0 eq.) in THF (6.0 mL), corresponding amine (0.152 g, 1.12 mmol, 2.0 eq.) and Et_3N (0.16 mL, 1.12 mmol, 2.0 eq.) was added and the mixture was refluxed 2 h. After cooling, the precitpitate was filtered off, washed with THF then the filtrate was concentrated and the residu was purified by flash chromatography with DCM/MeOH (98/2) as eluent to give **(3.91)** (0.177 g, 95 %) as a white solid.

Rf (DCM/MeOH, 94/6) : 0.20

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.00 – 1.20 (m, 4H, 2x$CH_{2\ cPr}$), 2.31 (tt, *J* = 8.1, 5.3 Hz, 1H, H_{cPr}), 2.96 (t, *J* = 7.1 Hz, 2H, CH_2), 3.49 – 3.76 (m, 2H, CH_2), 6.24 (s, 1H, H_{Ar}), 7.31 (dd, *J* = 7.8, 4.8 Hz, 1H, H_{Ar}), 7.71 (dt, *J* = 7.8, 2.0 Hz, 1H, H_{Ar}), 8.41 (dd, *J* = 4.8, 1.7 Hz, 1H, H_{Ar}), 8.49 (d, *J* = 2.3 Hz, 1H, H_{Ar}), 8.52 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.8 (CH), 7.1 (2xCH_2), 30.9 (CH_2), 42.9 (CH_2), 91.1 (CH_{Ar}), 123.3 (CH_{Ar}), 134.4 (C_q), 136.4 (CH_{Ar}), 139.3 (C_q), 142.2 (C_q), 147.5 (CH_{Ar}), 149.9 (C_q), 150.0 (CH_{Ar}), 151.3 (C_q).

Example 3.92: Synthesis of 6-chloro-3-isopropyl-*N*-(2-methoxypyrimidin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.92)

To a solution of **(2.1)** (0.125 g, 0.54 mmol, 1.0 eq.) in dry THF (5.4 mL), 2-methoxypyrimidin-4-amine (0.107 g, 0.81 mmol, 1.5 eq.) then tBuOK 1M in THF (1.00 mL, 0.81 mmol, 1.5 eq.) was added and the mixture was stirred 4 h at room temperature. After completion, water (0.5 mL) was added and SiO_2 to make solid deposit. The solvent was removed and the crude was purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **(3.92)** (0.113 g, 65 %) as a white solid.

Rf (DCM/MeOH, 95/5) : 0.32.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.42 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.51 (hept, *J* = 6.9 Hz, 1H, H_{iPr}), 3.96 (s, 3H, $CH_{3\text{-}O}$), 7.24 (d, *J* = 5.6 Hz, 1H, H_{Ar}), 8.34 (s, 1H, H_{Ar}), 8.42 (d, *J* = 5.6 Hz, 1H, H_{Ar}), 11.30 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.5 (CH_{iPr}), 54.5 ($CH_{3\text{-}O}$), 103.1 (CH_{Ar}), 104.4 (CH_{Ar}), 135.7 (C_q), 139.1 (C_q), 149.4 (C_q), 154.4 (C_q), 158.9 (CH_{Ar}), 161.7 (C_q), 164.4 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{14}ClN_7O$: 320.1 [M+H]+, **found :** 320.3.

Example 3.93: Synthesis of 6-chloro-3-isopropyl-*N*-(5-methoxypyrimidin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.93)

To a solution of **(2.1)** (0.125 g, 0.54 mmol, 1.0 eq.) in dry THF (5.4 mL), 5-methoxypyrimidin-4-amine (0.107 g, 0.81 mmol, 1.5 eq.) then tBuOK 1M in THF (1.00 mL, 0.81 mmol, 1.5 eq.) was added and the mixture was stirred 4 h at room temperature. After completion, water (0.5 mL) was added and SiO_2 to make solid deposit. The solvent was removed and the crude was purified by flash chromatography with DCM/MeOH (99/1 to 98/2) as eluent to give **(3.93)** (0.130 g, 75 %) as a white solid.

Rf (DCM/MeOH, 95/5) : 0.39.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.42 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.52 (p, *J* = 7.0 Hz, 1H, H_{iPr}), 4.10 (s, 3H, $CH_{3\text{-}O}$), 8.22 (s, 1H, H_3), 8.51 (s, 1H, H_3), 8.68 (s, 1H, H_3), 8.84 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_{13}H_{14}ClN_7O$: 320.1 [M+H]+, **found :** 320.3.

Example 3.94: Synthesis of 6-chloro-3-isopropyl-*N*-(6-methoxypyrimidin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.94)

To a solution of **(2.1)** (0.125 g, 0.54 mmol, 1.0 eq.) in dry THF (5.4 mL), 6-methoxypyrimidin-4-amine (0.107 g, 0.81 mmol, 1.5 eq.) then tBuOK 1M in THF (1.00 mL, 0.81 mmol, 1.5 eq.) was added and the mixture was stirred 4 h at room temperature. After completion, water (0.5 mL) was added and SiO_2 to make solid deposit. The solvent was removed and the crude was purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **(3.94)** (0.105 g, 61 %) as a white solid.

Rf (DCM/MeOH, 95/5) : 0.59.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.42 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 3.50 (hept, *J* = 6.9 Hz, 1H, H_{iPr}), 3.92 (s, 3H, $CH_{3\text{-}O}$), 6.98 (d, *J* = 1.0 Hz, 1H, H_{Ar}), 8.30 (s, 1H, H_{Ar}), 8.70 (d, *J* = 0.9 Hz, 1H, H_{Ar}), 11.09 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.8 (2x$CH_{3\ iPr}$), 24.5 (CH_{iPr}), 53.9 ($CH_{3\text{-}O}$), 93.8 (CH_{Ar}), 102.0 (CH_{Ar}), 136.1 (C_q), 139.1 (C_q), 149.5 (C_q), 154.4 (C_q), 157.7 (CH_{Ar}), 161.0 (C_q), 169.8 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{14}ClN_7O$: 320.1 [M+H]+, **found :** 320.3.

Example 3.95: Synthesis of 6-chloro-3-isopropyl-*N*-(6-methoxypyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (3.95)

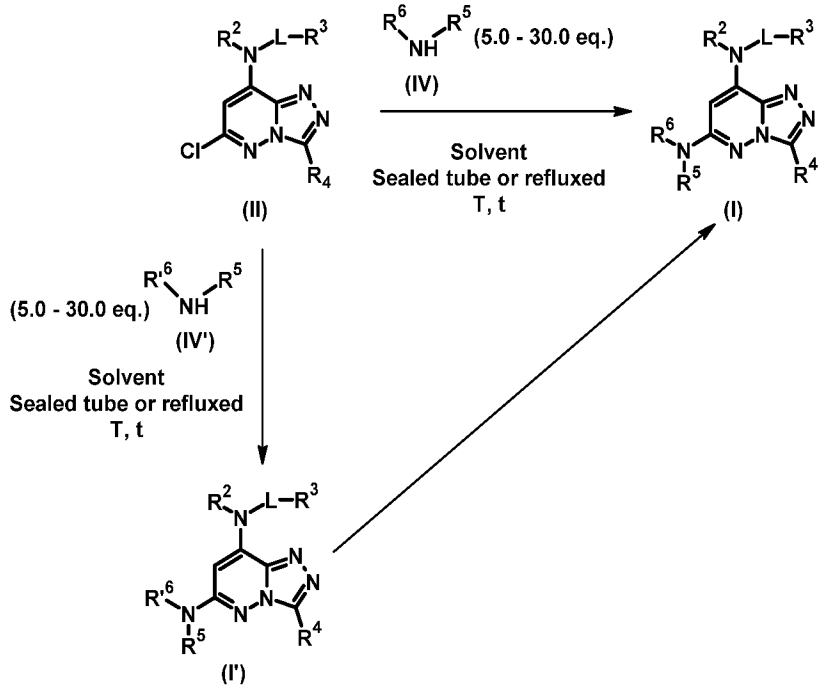
To a solution of **(2.1)** (0.200 g, 0.87 mmol, 1.0 eq.) in dry THF (8.7 mL), KHMDS 0.5M in toluene (2.42 mL, 1.21 mmol, 1.4 eq.) was added and the mixture was stirred 10 min at room temperature. 6-methoxypyridazin-3-amine (0.160 g, 1.21 mmol, 1.4 eq.) was added and the mixture was stirred 5 h at room temperature. After completion, saturated NH_4Cl (0.5 mL) and water (0.5 mL) were added then the solvent was removed and the crude was purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(3.95)** (0.075 g, 27 %) as a green solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.43 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.50 (hept, J = 7.0 Hz, 1H, H_{iPr}), 4.02 (s, 3H, $CH_{3\text{-}O}$), 7.32 (d, J = 9.4 Hz, 1H, H_{Ar}), 7.86 (d, J = 9.4 Hz, 1H, H_{Ar}), 8.27 (s, 1H, H_{Ar}), 11.03 (s, 1H, NH).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 19.8 (2x$CH_{3\ iPr}$), 24.5 (CH_{iPr}), 54.4 ($CH_{3\text{-}O}$), 100.3 (CH_{Ar}), 120.1 (CH_{Ar}), 124.1 (CH_{Ar}), 136.1 (C_q), 139.2 (C_q), 149.9 (C_q), 153.7 (C_q), 154.3 (C_q), 161.7 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{14}ClN_7O$: 320.1 [M+H]+, **found :** 320.2.

<u>Example 4:</u> Synthesis of [1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine derivatives, as illustrated in scheme 1 or in step 3 of scheme 2



Example 4.1: Synthesis of (2*R*)-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (1)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.1)** (0.100 g, 0.33 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.42 mL, 5.30 mmol, 16.0 eq.). The vial was sealed and then put on heating block, 20 h at 180 °C. After cooling, the mixture was poured in EtOAc (10 mL) then organic layer was washed twice with water and brine. The organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (94/6) as eluent to give **(1)** (0.070 g, 61 %) as a pale yellow solid.

Example 4.2: Synthesis of (2*S*)-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (2)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.1)** (0.200 g, 0.66 mmol, 1.0 eq.), NMP (2.0 mL) and corresponding amine (0.32 mL, 3.98 mmol, 6.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was poured in water (10 mL), the resulting precipitate was filtered off then washed with water. A new precipitate was formed in the filtrate and it was filtered off then washed with water. The residue was taken up in EtOAc/MeOH (7/3), the organic filtrate was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5 then 94/6) as eluent to give **(2)** (0.094 g, 40 %) as a white solid.

Example 4.3: Synthesis of 2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propane-1,3-diol (3)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.1)** (0.200 g, 0.66 mmol, 1.0 eq.), NMP (2.0 mL) and serinol (0.362 g, 3.98 mmol, 6.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was poured in water (10 mL), the precipitate was filtered off, washed with water. A new precipitate was formed in filtrate, it was filtered off and washed with water. The residue was taken up in EtOAc/MeOH (7/3), the organic filtrate was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5 then 94/6) as eluent to give **(3)** (0.092 g, 39 %) as a white solid.

Example 4.4: Synthesis of (2*R*,3*R*)-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]245yridazine-6-yl]amino]butane-1,3-diol (4)

In a sealed tube 2 – 5 mL with a stir bar was charged **(3.1)** (0.175 g, 0.58 mmol, 1.0 eq.), NMP (1.75 mL) and D-threoninol (0.754 g, 6.96 mmol, 12.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was poured in a funnel with water (30 mL), aqueous layer was extracted twice with EtOAc (2x20 mL) and combined organics layers were washed with HCl 0.1M (20 mL) then brine and dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5 then 94/6) as eluent to give **(4)** (0.137 g, 64 %) as a white solid.

Example 4.5: (2*R*,3*R*)-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol (5)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.1)** (0.175 g, 0.58 mmol, 1.0 eq.), NMP (1.75 mL) and D-threoninol (0.754 g, 6.96 mmol, 12.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was poured in a funnel with water (30 mL), aqueous layer was extracted twice with EtOAc (2x20 mL) and combined organics layers were washed with HCl 0.1M (20 mL) then brine and dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5 then 94/6) as eluent to give **(5)** (0.137 g, 64 %) as a white solid.

Example 4.6: Synthesis of *N*-benzyl-3-isopropyl-6-morpholino-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (6)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.1)** (0.200 g, 0.66 mmol, 1.0 eq.), NMP (1.5 mL) and morpholine (0.82 mL, 9.28 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was poured in a funnel with water (30 mL), aqueous layer was extracted twice with EtOAc (2x25 mL) and combined organics layers were washed with brine, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3 then 96/4) as eluent to give **(6)** (0.116 g, 50 %) as a white solid.

Example 4.7: Synthesis of (2*S*)-3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propane-1,2-diol (7)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.1)** (0.175 g, 0.58 mmol, 1.0 eq.), NMP (1.25 mL) and (*S*)-(-)-3-amino-1,2-propanediol (0.755 g, 8.12 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was poured in a funnel with $NaHCO_3$ sat. (15 mL), aqueous layer was extracted twice with EtOAc (2x15 mL) and combined organics layers were washed with brine, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5) as eluent to give **(7)** (0.087 g, 42 %) as a white solid.

Example 4.8: Synthesis of *N*6-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-*N*8-benzyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (8)

In a vial 2 - 5 mL with a stir bar was charged **(3.1)** (0.250 g, 0.83 mmol, 1.0 eq.), NMP (1.25 mL) and 2-[2-(2-aminoethoxy)ethoxy]ethanamine (0.97 mL, 6.63 mmol, 8.0 eq.). The vial was closed and put under microwave irradiation 4h at 180 °C. After cooling, the mixture was diluted in EtOAc (20 mL), organic layer was washed with water (40 mL). Aqueous Layer was extracted with EtOAc (20 mL) and organics layer were combined, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3 then 86/14) as eluent to give **(8)** (0.125 g, 36 %) as a white crystalline solid.

Example 4.9: Synthesis of 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propan-1-ol (9)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.1)** (0.200 g, 0.66 mmol, 1.0 eq.), NMP (0.3 mL) and corresponding amine (0.72 mL, 9.28 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 17 h at 180 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) and organic layer was washed with a mixture brine/water (2/1, 3x20.0 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (96/4) as eluent to give **(9)** (0.072 g, 32 %) as a white solid.

Example 4.10: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(3-methoxypropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (10)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.1)** (0.500 g, 1.66 mmol, 1.0 eq.), NMP (1.3 mL) and 3-methoxypropylamine (2.40 mL, 23.20 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 4 h at 180 °C. After cooling, the mixture was diluted in EtOAc (40 mL) and organic layer was washed three times with a mixture brine/water (2/1, 3x50 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3) as eluent to give **(10)** (0.460 g, 78 %) as a white solid.

Example 4.11: Synthesis of 2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]ethanol (11)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.1)** (0.200 g, 0.66 mmol, 1.0 eq.), NMP (0.6 mL) and ethanolamine (0.57 mL, 9.28 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 16 h at 180 °C. After cooling, the mixture was diluted in EtOAc (20 mL) and organic layer was washed three times with a mixture brine/water (2/1, 3x20 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (96/4) as eluent to give **(11)** (0.082 g, 38 %) as a white solid.

Example 4.12: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(2-methoxyethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (12)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.1)** (0.200 g, 0.66 mmol, 1.0 eq.), NMP (0.6 mL) and 2-methoxyethanamine (0.81 mL, 9.28 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 16 h at 180 °C. After cooling, the mixture was diluted in EtOAc (20 mL) and organic layer was washed three times with a mixture brine/water (2/1, 3x20 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5) as eluent to give **(12)** (0.152 g, 67 %) as a white crystalline solid.

Example 4.13: Synthesis of 3-isopropyl-*N6*,*N8*-bis(2-methoxyethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (112)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.1)** (0.200 g, 0.66 mmol, 1.0 eq.), NMP (0.6 mL) and 2-methoxyethanamine (0.81 mL, 9.28 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 16 h at 180 °C. After cooling, the mixture was diluted in EtOAc (20 mL) and organic layer was washed three times with a mixture brine/water (2/1, 3x20 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5) as eluent to give the secondary compound **(112)** (0.052 g, 25 %) as a beige solid.

Example 4.14: Synthesis of 4-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (13)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.1)** (0.400 g, 1.33 mmol, 1.0 eq.), NMP (1.2 mL) and corresponding amine (1.76 mL, 18.56 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 16 h at 180 °C. After cooling, the mixture was diluted in EtOAc (40.0 mL) and organic layer was washed with a mixture brine/water (2/1, 3x50 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (96/4) as eluent to give **(13)** (0.220 g, 47 %) as a white solid.

Example 4.15: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(4-methoxybutyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (14)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.1)** (0.100 g, 0.33 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.249 g, 2.65 mmol, 8.0 eq.) then the vial was sealed and put on heating block 17 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) and organic layer was washed three times with a mixture brine/water (3/1, 3x10 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(14)** (0.096 g, 79 %) as a white crystalline solid.

Example 4.16: Synthesis of 5-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]pentan-1-ol (15)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.1)** (0.400 g, 1.33 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (2.24 mL, 18.56 mmol, 14.0 eq.). The vial was

sealed and then put on heating block, 16 h at 180 °C. After cooling, the mixture was diluted in EtOAc (40.0 mL) and organic layer was washed with a mixture brine/HCl 0.05M (2/1, 3x40 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5) as eluent to give **(15)** (0.250 g, 51 %) as a white solid.

Example 4.17: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(5-methoxypentyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (16)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.1)** (0.100 g, 0.33 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.327 g, 2.65 mmol, 8.0 eq.) then the vial was sealed and put on heating block 17 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) and organic layer was washed three times with a mixture brine/water (3/1, 3x10 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(16)** (0.100 g, 79 %) as a light yellow solid.

Example 4.18: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(3-methylsulfanylpropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (17)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.1)** (0.250 g, 1.30 mmol, 1.0 eq.), NMP (0.75 mL) and 3-methylsulfanylpropan-1-amine (1.46 mL, 13.02 mmol, 10.0 eq.). The vial was sealed and then put on heating block, 2 h at 180 °C. After cooling, the mixture was diluted in EtOAc (30 mL) and organic layer was washed three times with a mixture brine/water (2/1, 3x30 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (96/4) as eluent to give **(17)** (0.270 g, 88 %) as a beige solid.

Example 4.19: Synthesis of *N8*-benzyl-*N6*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (18)

In a 2 - 5 mL vial with a stir bar was charged, **(3.1)** (0.250 g, 0.83 mmol, 1.0 eq.), NMP (0.8 mL) and pentan-3-amine (0.88 mL, 7.46 mmol, 9.0 eq.). The vial was sealed and then put on heating block, 24 h at 180 °C. After cooling, the mixture was diluted in EtOAc (20 mL) and organic layer was washed three times with a mixture brine/water (2/1, 3x20 mL).

Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3) as eluent. Fractions containing NMP traces were concentrated, diluted in EtOAc (20 mL), washed three times with water (3x25 mL) and organic layer was dried over Na_2SO_4, filtered, concentrated to give **(18)** (0.096 g, 33 %) as a white crystalline solid.

Example 4.20: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-[(3*R*)-tetrahydrofuran-3-yl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (19)

In a 2 - 5 mL vial with a stir bar was charged, **(3.1)** (0.200 g, 0.66 mmol, 1.0 eq.), NMP (0.6 mL) and corresponding amine (0.84 mL, 9.28 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 24 h at 180 °C. After cooling, the mixture was diluted in EtOAc (30.0 mL) and organic layer was washed with a mixture brine/water (2/1, 3x20 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (96/4) as eluent to give **(19)** (0.149 g, 64 %) as a white solid.

Example 4.21: Synthesis of *N8*-benzyl-3-cyclopentyl-*N6*-[(3*R*)-tetrahydrofuran-3-yl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (20)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.4)** (0.160 g, 0.49 mmol, 1.0 eq.), NMP (0.8 mL) and corresponding amine (0.358 g, 3.91 mmol, 8.0 eq.). The vial was sealed and then put on heating block 23 h at 170 °C. After cooling, water (7.0 mL) is added and stirred 5 min, the resulting dough ball was filtered, washed with water then solubilise with DCM. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give **(20)** (0.071 g, 38 %) as a white solid.

Example 4.22: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-[(3*R*)-tetrahydropyran-3-yl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (21)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.1)** (0.420 g, 1.24 mmol, 1.0 eq.), dioxane (1.2 mL) then benzylamine (0.83 mL, 7.42 mmol, 6.0 eq.). The vial was sealed and then put on heating block, 4h at 110 °C. After cooling, the mixture was diluted in DCM (20 mL) and the resulting organic layer was washed with HCl 0.5 M (20 mL).

Aqueous layer was extracted twice with DCM (2x10 mL) and organic layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3 to 95/5) as eluent to give **(21)** (0.175 g, 39 %) as a white solid.

Example 4.23: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-[(3*S*)-tetrahydropyran-3-yl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (22)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.1)** (0.250 g, 0.83 mmol, 1.0 eq.) and NMP (3.5 mL) then (*3S*)-tetrahydropyran-3-amine hydrochloride (1.080 g, 7.46 mmol, 9.0 eq.) and K_2CO_3 (0.555 g, 3.98 mmol, 4.8 eq.). The vial was sealed and then put on heating block, 15 h at 180 °C. After cooling, the mixture was poured onto water (50 mL), stirring 5min vigorously and the resulting precipitate was filtered off, washed with water (up to neutral pH) then EtOAc and the organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3 to 95/5) as eluent to give **(22)** (0.040 g, 13 %) as a white crystalline solid.

Example 4.24: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-tetrahydropyran-4-yl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (23)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.1)** (0.250 g, 0.83 mmol, 1.0 eq.) and corresponding amine (1.29 mL, 12.43 mmol, 15.0 eq.) then the vial was sealed and then put on heating block, 5.5 h at 180 °C. After cooling, the mixture was diluted in EtOAc (3.0 mL), water (3.0 mL) was added and the biphasique mixture was stirred 5 min. Layers were separated, aqueous layer was extracted twice with EtOAc (2x3.0 mL), organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (94/6) as eluent to give **(23)** (0.085 g, 28 %) as a beige solid.

Example 4.25: Synthesis of *N*-[3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propyl]acetamide (24)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.1)** (0.100 g, 0.33 mmol, 1.0 eq.), NMP (0.2 mL) then corresponding amine (0.405 g, 3.31 mmol, 10.0 eq.). The vial was sealed and then put on heating block, 15 h at 180 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) then organic layer was washed with brine/water (2/1, 3x20.0

mL), dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (96/4) as eluent to give **(24)** (0.118g, 94 %) as a white solid.

Example 4.26: Synthesis of 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propanoic acid (4.26)

In a sealed tube 10 - 20 mL with a stir bar was charged, **(3.1)** (0.800 g, 2.65 mmol, 1.0 eq.) and DMSO (6.5 mL) then β-alanine (1.431 g, 15.91 mmol, 6.0 eq.) and K_3PO_4 (3.376 g, 15.91 mmol, 6.0 eq.). The vial was sealed and then put on heating block, 4 h at 180 °C. After cooling, the mixture was poured into HCl 1M (150 mL) in ice bath, and water (40 mL). After 20 min, the precipitate was filtered, washed with water (to pH 7) then the solid was taken off with EtOH and acetone, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 92/8 then 92/8) as eluent to give **(4.26)** (0.505 g, 54 %) as a beige solid.

Rf (DCM/MeOH, 92/8) : 0.30

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 2.51 (m, 2H, $CH_{2\text{-}CO}$), 3.34 (d, *J* = 9.7 Hz, 3H, H_{iPr} & $CH_{2\text{-}NH}$), 4.42 (d, *J* = 6.2 Hz, 2H, $CH_{2\ Bn}$), 5.39 (s, 1H, H_{Ar}), 6.64 (t, *J* = 5.4 Hz, 1H, NH), 7.17 – 7.43 (m, 5H, 5xH_{Ar}), 7.93 (t, *J* = 6.4 Hz, 1H, NH_{Bn}), 12.16 (s, 1H, COOH).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.6 (2x$CH_{3\ iPr}$), 24.7 (CH_{iPr}), 33.3 ($CH_{2\text{-}CO}$), 36.9 ($CH_{2\text{-}NH}$), 45.2 ($CH_{2\ Bn}$), 84.1 (CH_{Ar}), 126.8 (2xCH_{Ar}), 126.9 (CH_{Ar}), 128.4 (2xCH_{Ar}), 138.3 (C_q), 139.7 (C_q), 139.9 (C_q), 152.9 (C_q), 155.7 (C_q), 173.2 (C_q).

MS (ESI+) : m/z calcd for $C_{18}H_{22}N_6O_2$: 355.19 [M+H]+, **found :** 355.27.

Example 4.27: Synthesis of 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propanamide (25)

To a solution of **(4.26)** (0.110 g, 0.31 mmol, 1.0 eq.) in THF (3.1 mL) was added HOBt.H_2O (0.062 g, 0.40 mmol, 1.3 eq.), EDCi (0.058 g, 0.37 mmol, 1.2 eq.) and ammonia 0.5M in THF (0.81 mL, 0.40 mmol, 1.3 eq.). The mixture was stirred 4 h at room temperature and after completion the mixture was directly concentrated and purified on solid deposit by flash chromatography with DCM/MeOH (94/6) as eluent to give **(25)** (0.090 g, 82 %) as a white solid.

Example 4.28: Synthesis of 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]-*N*-methyl-propanamide (26)

To a solution of **(4.26)** (0.120 g, 0.34 mmol, 1.0 eq.) in THF (3 mL) was added HOBt.H_2O (0.069 g, 0.44 mmol, 1.3 eq.), methylamine 2M in THF (0.24 mL, 0.47 mmol, 1.4 eq.) and EDCi (0.065 g, 0.41 mmol, 1.2 eq.). The mixture was stirred 3 h at room temperature and after completion the mixture was directly concentrated and purified on solid deposit by flash chromatography with DCM/MeOH (95/5) as eluent to give **(26)** (0.121 g, 97 %) as a white solid.

Example 4.29: Synthesis of 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]-*N*,*N*-dimethyl-propanamide (27)

To a solution of **(4.26)** (0.120 g, 0.34 mmol, 1.0 eq.) in THF (3 mL) was added HOBt.H_2O (0.069 g, 0.44 mmol, 1.3 eq.), dimethylamine 2M in THF (0.24 mL, 0.47 mmol, 1.4 eq.) and EDCi (0.065 g, 0.41 mmol, 1.2 eq.). The mixture was stirred 3 h at room temperature and after completion the mixture was directly concentrated and purified on solid deposit by flash chromatography with DCM/MeOH (95/5) as eluent to give **(27)** (0.124 g, 96 %) as a white solid.

Example 4.30: Synthesis of methyl 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propanoate (28)

A solution of **(4.26)** (0.110 g, 2.65 mmol, 1.0 eq.) in MeOH (10 mL) with two drops of H_2SO_4 was refluxed 30 min. After cooling, Na_2CO_3 (0.075 g) was added and stirred 5 min at room temperature. The mixture was directly concentrated and purified by flash chromatography with DCM/MeOH (95/5) as eluent to give **(28)** (0.100 g, 87 %) as a white solid.

Example 4.31: Synthesis of ethyl 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propanoate (29)

A solution of **(4.26)** (0.110 g, 2.65 mmol, 1.0 eq.) in EtOH (10 mL) with two drops of H_2SO_4 was refluxed 30 min. After cooling, Na_2CO_3 (0.075 g) was added and stirred 5 min at room temperature. The mixture was directly concentrated and purified by flash

chromatography with DCM/MeOH (94/6) as eluent to give **(29)** (0.082 g, 69 %) as a white solid.

Example 4.32: Synthesis of (*2R*)-2-[[8-(benzylamino)-3-cyclopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (30)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.3)** (0.135 g, 0.45 mmol, 1.0 eq.), NMP (1.0 mL) and (*R*)-(-)-2-amino-1-butanol (0.57 mL, 7.21 mmol, 16.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was poured in EtOAc (20 mL) then organic layer was washed three times with brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (96/4) as eluent to give **(30)** (0.112 g, 71 %) as a beige solid.

Example 4.33: Synthesis of *N8*-benzyl-3-cyclopropyl-*N6*-(3-methoxypropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (31)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.3)** (0.250 g, 0.83 mmol, 1.0 eq.), NMP (0.8 mL) and 3-methoxypropylamine (1.21 mL, 11.68 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was diluted in EtOAc (30 mL) and organic layer was washed three times with a mixture brine/water (2/1, 3x20 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3) as eluent to give **(31)** (0.145 g, 49 %) as a white solid.

Example 4.34: Synthesis of 3-cyclopropyl-*N6*,*N8*-bis(3-methoxypropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (110)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.3)** (0.250 g, 0.83 mmol, 1.0 eq.), NMP (0.8 mL) and 3-methoxypropylamine (1.21 mL, 11.68 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was diluted in EtOAc (30 mL) and organic layer was washed three times with a mixture brine/water (2/1, 3x20 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3) as eluent to give the compound **(110)** (0.120 g, 43 %) as a white solid.

Example 4.35: Synthesis of *N8*-benzyl-*N6*-(3-methoxypropyl)-3-methyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (32)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.6)** (0.125 g, 0.46 mmol, 1.0 eq.), NMP (0.4 mL) and 3-methoxypropylamine (0.65 mL, 6.39 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 16 h at 180 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL), organic layer was washed with brine (3x10.0 mL), dired over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5) as eluent to give **(32)** (0.086 g, 58 %) as a white solid.

Example 4.36: Synthesis of (*2R*)-2-[[8-(benzylamino)-3-methyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (33)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.6)** (0.125 g, 0.46 mmol, 1.0 eq.), NMP (0.4 mL) and (*R*)-(-)-2-amino-1-butanol (0.51 mL, 5.48 mmol, 12.0 eq.). The vial was sealed and then put on heating block, 16 h at 180 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL), organic layer was washed with brine (3x10.0 mL), dired over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5) as eluent to give **(33)** (0.086 g, 58 %) as a white solid.

Example 4.37: Synthesis of *N8*-benzyl-*N6*-(3-methoxypropyl)-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (34)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.7)** (0.125 g, 0.38 mmol, 1.0 eq.), NMP (0.35 mL) and 3-methoxypropylamine (0.55 mL, 5.34 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was diluted in EtOAc (25.0 mL), organic layer was washed with brine/water (2/1, 3x20.0 mL), dired over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5) as eluent to give **(34)** (0.086 g, 58 %) as a white solid.

Example 4.38: Synthesis of *N6,N8*-bis(3-methoxypropyl)-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (109)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.7)** (0.125 g, 0.38 mmol, 1.0 eq.), NMP (0.35 mL) and 3-methoxypropylamine (0.55 mL, 5.34 mmol, 14.0 eq.). The vial was

sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was diluted in EtOAc (25.0 mL), organic layer was washed with brine/water (2/1, 3x20.0 mL), dired over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5) as eluent to give the secondary compound **(109)** (0.055 g, 39 %) as a white solid.

Example 4.39: Synthesis of (*2R*)-2-[[8-(benzylamino)-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (35)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.7)** (0.150 g, 0.46 mmol, 1.0 eq.), NMP (1.0 mL) and (*R*)-(-)-2-amino-1-butanol (0.59 mL, 6.41 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was diluted in EtOAc (25.0 mL), organic layer was washed with brine/water (2/1, 3x20.0 mL), dired over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (95/5) as eluent to give **(35)** (0.115 g, 65 %) as a white solid.

Example 4.40: Synthesis of *N8*-benzyl-*N6*-(3-methoxypropyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (36)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.5)** (0.125 g, 0.38 mmol, 1.0 eq.), NMP (0.4 mL) and 3-methoxypropylamine (0.55 mL, 5.34 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) and organic layer was washed three times with a mixture brine/water (2/1, 3x20 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1) as eluent to give **(36)** (0.110 g, 76 %) as a white solid.

Example 4.41: Synthesis of *N6*,*N8*-bis(3-methoxypropyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (111)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.5)** (0.125 g, 0.38 mmol, 1.0 eq.), NMP (0.4 mL) and 3-methoxypropylamine (0.55 mL, 5.34 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) and organic layer was washed three times with a mixture brine/water (2/1, 3x20 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated

and purified by flash chromatography with DCM/MeOH (99/1) as eluent to give the secondary compound **(111)** (0.010 g, 7 %) as a white solid.

Example 4.42: Synthesis of (*2R*)-2-[[8-(benzylamino)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (37)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.5)** (0.110 g, 0.34 mmol, 1.0 eq.), NMP (0.3 mL) and (*R*)-(-)-2-amino-1-butanol (0.44 mL, 4.70 mmol, 14.0 eq.). The vial was sealed and then put on heating block, 18 h at 180 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) and organic layer was washed three times with a mixture brine/water (2/1, 3x20 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3) as eluent to give **(37)** (0.070 g, 55 %) as a white solid.

Example 4.43: Synthesis of (2*R*)-2-[[8-(benzylamino)-3-isopropyl-7-methyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (115)

Under inert gas, in a solution of **(1)** (0.880 g, 2.48 mmol, 1.0 eq.) and dry THF (48.0 mL), NaH 60% (0.119 g, 2.98 mmol, 1.2 eq.) was added portionwise then the mixture was stirred 10 min at room temperature. The solution was cooled at 0 °C and MeI (0.17 mL, 2.73 mmol, 1.1 eq.) was added dropwise then stirred 2 h at room temperature. To complete the reaction, MeI (0.03 mL, 0.50 mmol, 0.2 eq.) was added and the mixture was stirred 1 h. After completion, MeOH (9.0 mL) was added slowly and the mixture was directly concentrated with SiO_2 to make solid deposit and purified by flash chromatography with DCM/MeOH (98/2 to 96/4) as eluent to give the secondary compound **(115)** (0.092 g, 10 %) as a beige solid.

Example 4.44: Synthesis of 2-[[[6-[[(*1R*)-1-(hydroxymethyl)propyl]amino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol (38)

In a sealed tube 2 - 5 mL with a stir bar was charged with **(3.8)** (0.150 g, 0.47 mmol, 1.0 eq.) and (*R*)-(-)-2-amino-1-butanol (0.91 mL, 9.44 mmol, 20.0 eq.) then the vial was sealed and put on heating block, 15 h at 160 °C. After cooling, the mixture was diluted in EtOAc (25.0 mL) and organic layer was washed twice with water/brine mixture (1/3, 2x30.0 mL) then dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with

DCM/MeOH (96/4 to 92/8) as eluent to give the title compound **(38)** (0.010 g, 6 %) as a beige solid.

Example 4.45: Synthesis of 2-[[[3-isopropyl-6-(3-methoxypropylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol (39)

In a sealed tube 2 - 5 mL with a stir bar was charged with **(3.8)** (0.150 g, 0.47 mmol, 1.0 eq.) and 3-methoxypropylamine (1.07 mL, 9.44 mmol, 20.0 eq.) then the vial was sealed and put on heating block, 19 h at 150 °C. After cooling, the mixture was diluted in EtOAc (25.0 mL) and organic layer was washed twice with water/brine mixture (1/3, 2x30.0 mL) then dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (93/7 to 92/8) as eluent to give the title compound **(39)** (0.070 g, 40 %) as a white solid.

Example 4.46: Synthesis of 2-[[[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol (40)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.8)** (0.140 g, 0.44 mmol, 1.0 eq.), NMP (1.0 mL) and 3-aminopentane (0.52 mL, 4.41 mmol, 10.0 eq.). The vial was sealed and then put on heating block, 16 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) and organic layer was washed three times with a mixture brine/water (2/1, 3x20 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 95/5) as eluent to give **(40)** (0.021 g, 13 %) as a white crystalline solid.

Example 4.47: Synthesis of 3-[[[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol (41)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.9)** (0.450 g, 1.42 mmol, 1.0 eq.), NMP (3.3 mL) and 3-aminopentane (3.33 mL, 28.32 mmol, 20.0 eq.). The vial was sealed and then put on heating block, 16 h at 170 °C. After cooling, the mixture was poured onto saturated $NaHCO_3$ (20.0 mL) then water (30.0 mL) was added and the mixture was stirred 5 min. The resulting solid was filtered off, washed wih water up to neutral pH then the solid was taken up in DCM, organic filtrate was dried over $MgSO_4$, filtered, concentrated

and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give **(41)** (0.080 g, 15 %) as a white solid.

Example 4.48: Synthesis of 4-[[[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol (42)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.10)** (0.085 g, 0.27 mmol, 1.0 eq.), NMP (1.0 mL) and 3-aminopentane (0.31 mL, 2.68 mmol, 10.0 eq.). The vial was sealed and then put on heating block, 16 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) and organic layer was washed three times with a mixture brine/water (2/1, 3x10.0 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 95/5) as eluent to give **(42)** (0.015 g, 15 %) as a white crystalline solid.

Example 4.49: Synthesis of 2-[[[3-isopropyl-6-[[(3*R*)-tetrahydropyran-3-yl]amino]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol (43)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.8)** (0.200 g, 0.63 mmol, 1.0 eq.), corresponding amine hydrochloride (0.912 g, 6.29 mmol, 10.0 eq.) and DIPEA (1.54 mL, 8.81 mmol, 14.0 eq.) then the vial was sealed and put on heating block 24 h at 150 °C. After cooling, water (5.0 mL) was added, the precipitate was triturated then the mixture was poured in water (15.0 mL), stirred 5 min and the precipitate was filtered off, washed with water up to neutral pH and taken up in EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (96/4 to 94/6) as eluent to give **(43)** (0.018 g, 7 %) as a white solid.

Example 4.50: Synthesis of 2-[[[3-isopropyl-6-(tetrahydropyran-4-ylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol (44)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.8)** (0.250 g, 0.79 mmol, 1.0 eq.) and corresponding amine (0.98 mL, 9.44 mmol, 12.0 eq.) then the vial was sealed and put on heating block 15 h at 160 °C. After cooling, EtOAc (4.0 mL) and water (4.0 mL) was added, stirred 5 min then layers were separated. Aqueous layer was extracted twice with EtOAc (2x3.0 mL) then organics layers were combined, dried over $MgSO_4$, filtered,

concentrated and purified by flash chromatography with DCM/MeOH (96/4 to 93/7) as eluent to give **(44)** (0.030 g, 10 %) as a white solid.

Example 4.51: Synthesis of (2*S*)-2-[[8-[(4-bromophenyl)methylamino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (101)

In a sealed tube 10 - 20 mL with a stir bar was charged **(3.42)** (1.800 g, 4.73 mmol, 1.0 eq.), NMP (5.0 mL) and (2*S*)-2-aminobutan-1-ol (8.12 mL, 85.11 mmol, 18.0 eq.) then the vial was sealed and put on heating block 24 h at 180 °C. After cooling, the reaction mixture was poured onto water (100.0 mL), vigorously stirred 5 min and the aqueous mixture was extracted with EtOAc (3x30.0 mL). Organic layers were combined, washed with brine (20.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give **(101)** (1.290 g, 63 %) as a beige solid.

Example 4.52: Synthesis of *N8*-[(4-bromophenyl)methyl]-3-isopropyl-*N6*-methyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (116)

In a sealed tube 10 - 20 mL with a stir bar was charged **(3.42)** (1.800 g, 4.73 mmol, 1.0 eq.), NMP (5.0 mL) and (2*S*)-2-aminobutan-1-ol (8.12 mL, 85.11 mmol, 18.0 eq.) then the vial was sealed and put on heating block 24 h at 180 °C. After cooling, the reaction mixture was poured onto water (100.0 mL), vigorously stirred 5 min and the aqueous mixture was extracted with EtOAc (3x30.0 mL). Organic layers were combined, washed with brine (20.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give the secondary compound **(116)** (0.300 g, 17 %) as a white solid.

Example 4.53: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (45)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.12)** (0.090 g, 0.31 mmol, 1.0 eq.), cineol (0.7 mL) and 3-aminopentane (0.55 mL, 4.69 mmol, 15.0 eq.). The vial was sealed and put on heating block 40 h at 170 °C. After cooling, the mixture was concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (99/1 to 97/3) as eluent to give **(45)** (0.010 g, 9 %) as a white solid.

Example 4.54: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(2-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (46)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.13)** (0.090 g, 0.31 mmol, 1.0 eq.), cineol (0.7 mL) and 3-aminopentane (0.55 mL, 4.68 mmol, 15.0 eq.). The vial was sealed and put on heating block 40 h at 170 °C. After cooling, the mixture was concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (99/1 to 97/3) as eluent to give **(46)** (0.021 g, 20 %) as a beige solid.

Example 4.55: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(3-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (47)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.14)** (0.090 g, 0.31 mmol, 1.0 eq.), cineol (0.7 mL) and 3-aminopentane (0.55 mL, 4.68 mmol, 15.0 eq.). The vial was sealed and put on heating block 40 h at 170 °C. After cooling, the mixture was concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **(47)** (0.025 g, 24 %) as a beige solid.

Example 4.56: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(4-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (48)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.15)** (0.090 g, 0.31 mmol, 1.0 eq.), cineol (0.7 mL) and 3-aminopentane (0.55 mL, 4.68 mmol, 15.0 eq.). The vial was sealed and put on heating block 40 h at 170 °C. After cooling, the mixture was concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(48)** (0.060 g, 57 %) as a white solid.

Example 4.57: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(4-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (49)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.16)** (0.100 g, 0.33 mmol, 1.0 eq.), NMP (0.17 mL) and 3-aminopentane (0.58 mL, 4.95 mmol, 15.0 eq.) then the vial was sealed and put on heating block 15 h at 160 °C. To complete the reaction, NMP (0.34 mL) was added the the vial was sealed and put on heating block 23 h at 180 °C. After cooling, the mixture was diluted in EtOAc (10.0 mL) and organic layer was washed three times

with a mixture brine/water (2/1, 3x10.0 mL). Organic layer was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(49)** (0.054 g, 46 %) as a white solid.

Example 4.58: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(3-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (50)

In a sealed tube 10 - 20 mL with a stir bar was charged **(3.17)** (0.580 g, 1.92 mmol, 1.0 eq.), NMP (4.1 mL) and 3-aminopentane (4.06 mL, 34.48 mmol, 18.0 eq.) then the vial was sealed and put on heating block 20 h at 180 °C. After cooling, the mixture was poured onto saturated $NaHCO_3$ (20.0 mL), rinse the vial and adjust with water up to 80.0 mL then the mixture was stirred 10 min. The resulting precipitate was filtered off, washed with water up to neutral pH, change the flask and washed the solid with EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give **(50)** (0.160 g, 24 %) as a light pink solid.

Example 4.59: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (51)

In a sealed tube 10 - 20 mL with a stir bar was charged **(3.18)** (0.750 g, 2.48 mmol, 1.0 eq.), NMP (5.0 mL) and 3-aminopentane (4.96 mL, 42.11 mmol, 17.0 eq.) then the vial was sealed and put on heating block 69 h at 180 °C. After cooling, the mixture was poured onto saturated $NaHCO_3$ (20.0 mL), rinse the vial and adjust with water up to 80.0 mL then the mixture was stirred 10 min. The resulting precipitate was filtered off, washed with water up to neutral pH, change the flask and washed the solid with DCM. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give **(51)** (0.420 g, 48 %) as a white solid.

Example 4.60: Synthesis of *N6*-tert-butyl-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (52)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.18)** (0.250 g, 0.83 mmol, 1.0 eq.), NMP (2.0 mL) and corresponding amine (0.45 mL, 4.13 mmol, 5.0 eq.). The vial was sealed and then put on heating block, 65 h at 170 °C. After cooling, the reaction mixture was poured onto brine/water (1/1, 30 mL) and stirred vigorously 5 min. The resulting

precipitate was filtered, washed with water, taken up in DCM and organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 93/7) as eluent to give **(52)** (0.020 g, 7 %) as a white solid.

Example 4.61: Synthesis of 3-isopropyl-*N8*-(2-pyridylmethyl)-*N6*-spiro[3.3]heptan-2-yl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (53)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.18)** (0.200 g, 0.66 mmol, 1.0 eq.), NMP (1.0 mL), corresponding amine hydrochloride (0.399 g, 2.64 mmol, 4.0 eq.) and DIPEA (0.69 mL, 3.96 mmol, 6.0 eq.). The vial was sealed and then put on heating block 23 h at 170 °C. After cooling, the mixture was diluted in water (10.0 mL), the resulting precipitate was triturated in water, filtered off and washed with a little amount of water. The solid was triturated with EtOAc, filtered and organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give **(53)** (0.035 g, 14 %) as a grey solid.

Example 4.62: Synthesis of *N6*-(3,3-difluorocyclobutyl)-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (54)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.18)** (0.200 g, 0.66 mmol, 1.0 eq.), NMP (1.0 mL), corresponding amine hydrochloride (0.399 g, 2.64 mmol, 4.0 eq.) and DIPEA (0.69 mL, 3.96 mmol, 6.0 eq.). The vial was sealed and then put on heating block 23 h at 170 °C. After cooling, the mixture was diluted in water (10.0 mL), the resulting precipitate was triturated in water, filtered off and washed with a little amount of water. The solid was triturated with EtOAc, filtered and organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give **(54)** (0.035 g, 14 %) as a beige solid.

Example 4.63: Synthesis of *N6*-(4,4-difluorocyclohexyl)-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (55)

In a sealed tube 2 - 5 mL with a stir bar was charged, **(3.18)** (0.200 g, 0.66 mmol, 1.0 eq.), NMP (1.0 mL), corresponding amine hydrochloride (0.399 g, 2.64 mmol, 4.0 eq.) and DIPEA (0.69 mL, 3.96 mmol, 6.0 eq.). The vial was sealed and then put on heating block 23 h at 170 °C. After cooling, the mixture was diluted in water (10.0 mL), the resulting

precipitate was triturated in water, filtered off and washed with a little amount of water. The solid was triturated with EtOAc, filtered and organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give **(55)** (0.010 g, 14 %) as a white solid.

Example 4.64: Synthesis of *N6*-benzyl-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (56)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.18)** (0.150 g, 0.50 mmol, 1.0 eq.), NMP (1.0 mL) and benzylamine (0.33 mL, 2.97 mmol, 6.0 eq.). The vial was sealed and then put on heating block 17 h at 180 °C. After cooling, the mixture was diluted in brine (30.0 mL) and water (10.0 mL) then aqueous layer was extracted twice with EtOAc (2x20.0 mL). Organics layers were combined, washed with brine, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 84/6) as eluent to give **(56)** (0.070 g, 38 %) as a white solid.

Example 4.65: Synthesis of *N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (57)

In a sealed tube 10 - 20 mL with a stir bar was charged **(3.19)** (0.500 g, 1.92 mmol, 1.0 eq.), NMP (4.5 mL) and corresponding amine (4.51 mL, 38.36 mmol, 20.0 eq.). The vial was sealed and then put on heating block 18 h at 180 °C. After cooling, the mixture was poured onto saturated $NaHCO_3$ (50.0 mL), rinse the vial and adjust with water up to 100.0 mL then the mixture was stirred 10 min. The resulting precipitate was filtered off, washed with water up to neutral pH, change the flask and washed the solid with EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give **(57)** (0.180 g, 30 %) as a white solid.

Example 4.66: Synthesis of *N6*-(1-ethylpropyl)-3-methyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (58)

In a sealed tube 10 - 20 mL with a stir bar was charged **(3.20)** (0.550 g, 2.00 mmol, 1.0 eq.), NMP (4.7 mL) and corresponding amine (4.71 mL, 40.04 mmol, 20.0 eq.). The vial was sealed and then put on heating block 18 h at 180 °C. After cooling, the mixture was poured onto saturated $NaHCO_3$ (50.0 mL), rinse the vial and adjust with water up to 100.0

mL then the mixture was stirred 10 min. The resulting precipitate was filtered off, washed with water up to neutral pH, change the flask and washed the solid with EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give **(58)** (0.100 g, 15 %) as a white solid.

Example 4.67: Synthesis of 3-ethyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (59)

In a sealed tube 10 - 20 mL with a stir bar was charged **(3.21)** (0.350 g, 1.21 mmol, 1.0 eq.), NMP (2.85 mL) and corresponding amine (2.85 mL, 24.24 mmol, 20.0 eq.). The vial was sealed and then put on heating block 21 h at 180 °C. After cooling, the mixture was poured onto saturated $NaHCO_3$ (20.0 mL), rinse the vial and adjust with water up to 40.0 mL then the mixture was stirred 10 min. Aqueous mixture was extracted three times with EtOAc (3x15.0 mL) then organics layers were combined, washed with brine (15.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give **(59)** (0.074 g, 18 %) as a white solid.

Example 4.68: Synthesis of *N6*-(1-ethylpropyl)-3-propyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (60)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.22)** (0.200 g, 0.66 mmol, 1.0 eq.), NMP (0.7 mL) and corresponding amine (0.78 mL, 6.61 mmol, 10.0 eq.) then the vial was sealed and put on heating block 22 h at 180 °C. After cooling, the mixture was diluted in brine (30.0 mL) and water (30.0 mL) and the mixture was stirred 10 min. The resulting precipitate was filtered off, washed with water up to neutral pH then taken up in EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 95/5) as eluent to give **(60)** (0.065 g, 28 %) as a beige solid.

Example 4.69: Synthesis of 3-tert-butyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (61)

In a sealed tube 10 - 20 mL with a stir bar was charged **(3.23)** (0.500g, 1.58 mmol, 1.0 eq.), NMP (3.7mL) and corresponding amine (3.72 mL, 31.57 mmol, 20.0 eq.). The vial was sealed and then put on heating block 21 h at 180 °C. After cooling, the mixture was poured

onto saturated $NaHCO_3$ (20.0 mL), rinse the vial and adjust with water up to 40.0 mL then the mixture was stirred 10 min. Aqueous mixture was extracted three times with EtOAc (3x15.0 mL) then organics layers were combined, washed with brine (15.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give **(61)** (0.105 g, 18 %) as a white solid.

Example 4.70: Synthesis of 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (62)

In a sealed tube 10 - 20 mL with a stir bar was charged **(3.24)** (1.000 g, 3.32 mmol, 1.0 eq.), NMP (5.9 mL) and corresponding amine (5.87 mL, 49.88 mmol, 15.0 eq.). The vial was sealed and then put on heating block 18 h at 180 °C. After cooling, the mixture was poured onto saturated $NaHCO_3$ (50.0 mL), rinse the vial and adjust with water up to 100.0 mL then the mixture was stirred 10 min. The resulting precipitate was filtered off, washed with water up to neutral pH, change the flask and washed the solid with EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give **(62)** (0.160 g, 14 %) as a grey solid.

Example 4.71: Synthesis of 3-cyclobutyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (63)

In a sealed tube 10 - 20 mL with a stir bar was charged **(3.25)** (0.320 g, 1.02 mmol, 1.0 eq.), NMP (2.4 mL) and corresponding amine (2.39 mL, 20.33 mmol, 20.0 eq.). The vial was sealed and then put on heating block 21 h at 180 °C. After cooling, the mixture was poured onto saturated $NaHCO_3$ (20.0 mL), rinse the vial and adjust with water up to 60.0 mL then the mixture was stirred 10 min. Aqueous mixture was extracted three times with EtOAc (3x15.0 mL) then organics layers were combined, washed with brine (15.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give **(63)** (0.093 g, 25 %) as a white solid.

Example 4.72: Synthesis of 3-cyclopentyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (64)

In a sealed tube 10 - 20 mL with a stir bar was charged **(3.26)** (0.500 g, 1.52 mmol, 1.0 eq.), NMP (3.6 mL) and corresponding amine (3.58 mL, 30.41 mmol, 20.0 eq.). The vial

was sealed and then put on heating block 21 h at 180 °C. After cooling, the mixture was poured onto saturated $NaHCO_3$ (20.0 mL), rinse the vial and adjust with water up to 60.0 mL then the mixture was stirred 10 min. The resulting precipitate was filtered off, washed with water up to neutral pH then the solid was taken up in DCM. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give **(64)** (0.124 g, 21 %) as a white solid.

Example 4.73: Synthesis of 3-cyclohexyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (65)

In a sealed tube 10 - 20 mL with a stir bar was charged **(3.27)** (0.600 g, 1.75 mmol, 1.0 eq.), NMP (3.9 mL), corresponding amine (3.91 mL, 33.25 mmol, 19.0 eq.). The vial was sealed and then put on heating block, 16 h at 180 °C. After cooling, the mixture was poured onto saturated $NaHCO_3$ (20.0 mL), rinse the vial and adjust with water up to 80.0 mL then the mixture was stirred 10 min. The resulting precipitate was filtered off, washed with water up to neutral pH, the vacuum flask was changed then the solid was triturated and washed with EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 97/7) as eluent to give **(65)** (0.110 g, 16 %) as a white solid.

Example 4.74: Synthesis of *N6*-(1-ethylpropyl)-3-phenyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (66)

In a sealed tube 10 - 20 mL with a stir bar was charged **(3.28)** (0.550 g, 1.63 mmol, 1.0 eq.), NMP (4.0 mL), corresponding amine (4.04 mL, 34.30 mmol, 21.0 eq.). The vial was sealed and then put on heating block, 20 h at 180 °C. After cooling, the mixture was poured onto saturated $NaHCO_3$ (20.0 mL), rinse the vial and adjust with water up to 80.0 mL then the mixture was stirred 10 min. The resulting precipitate was filtered off, washed with water up to neutral pH, the vacuum flask was changed then the solid was triturated and washed with a mixture of DCM/MeOH (98/2). Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give **(66)** (0.265 g, 42 %) as a white solid.

Example 4.75: Synthesis of *N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-3-sec-butyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (67)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.29)** (0.100 g, 0.39 mmol, 1.0 eq.), mono ethylene glycol (1.0 mL) and 3-aminopentane (0.98 mL g, 8.29 mmol, 15.0 eq.) then the vial was sealed and put on heating block 16 h at 180 °C. After cooling, the reaction mixture was poured onto saturated $NaHCO_3$ (10.0 mL), the resulting precipitate was triturated, filtered, washed with water up to neutral pH and taken up in EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to **(67)** (0.047 g, 23 %) as a white solid.

Example 4.76: Synthesis of *N6*,3-bis(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (68)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.30)** (0.200 g, 0.61 mmol, 1.0 eq.), mono ethylene glycol (1.0 mL) and 3-aminopentane (1.07 mL, 9.07 mmol, 15.0 eq.) then the vial was sealed and put on heating block 19 h at 180 °C. After cooling, the reaction mixture was poured onto cold water (30.0 mL), stirred 5 min then the resulting precipitate was filtered off, washed with cold water up to neutral pH and taken up in DCM. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to **(68)** (0.085 g, 37 %) as a white solid.

Example 4.77: Synthesis of *N6*-(1-ethylpropyl)-3-isobutyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (69)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.31)** (0.250 g, 0.79 mmol, 1.0 eq.), NMP (1.9 mL) and 3-aminopentane (1.86 mL g, 15.78 mmol, 20.0 eq.) then the vial was sealed and put on heating block 15 h at 180 °C. After cooling, the reaction mixture was poured onto saturated $NaHCO_3$ (30.0 mL) then aqueous mixture was extracted with EtOAc (3x20.0 mL). Organics layers were combined, washed with brine (40.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to **(69)** (0.065 g, 22 %) as a white solid.

Example 4.78: Synthesis of *N6*-(1-ethylpropyl)-3-(2-pyridyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (70)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.32)** (0.200 g, 0.59 mmol, 1.0 eq.), mono ethylene glycol (1.0 mL) and 3-aminopentane (1.05 mL, 8.88 mmol, 15.0 eq.) then the vial was sealed and put on heating block 19 h at 180 °C. After cooling, the reaction mixture was poured onto cold water (30.0 mL) then aqueous mixture was extracted with 2-MeTHF (3x15.0 mL). Orgnics layers were combined, washed with brine (20.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3 to 90/10) as eluent to **(70)** (0.070 g, 30 %) as a white solid.

Example 4.79: Synthesis of *N6*-(1-ethylpropyl)-3-(3-pyridyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (71)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.33)** (0.200 g, 0.59 mmol, 1.0 eq.), mono ethylene glycol (1.0 mL) and 3-aminopentane (1.05 mL, 8.88 mmol, 15.0 eq.) then the vial was sealed and put on heating block 19 h at 180 °C. After cooling, the reaction mixture was poured onto cold water (30.0 mL), stirred 5 min then the resulting precipitate was filtered off, washed with cold water up to neutral pH and taken up in DCM. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3 to 93/7) as eluent to **(71)** (0.086 g, 37 %) as a grey solid.

Example 4.80: Synthesis of *N6*-(1-ethylpropyl)-3-(4-pyridyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (72)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.34)** (0.200 g, 0.59 mmol, 1.0 eq.), mono ethylene glycol (1.0 mL) and 3-aminopentane (1.05 mL, 8.88 mmol, 15.0 eq.) then the vial was sealed and put on heating block 19 h at 180 °C. After cooling, the reaction mixture was poured onto cold water (30.0 mL), stirred 5 min then the resulting precipitate was filtered off, washed with cold water up to neutral pH and taken up in DCM. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3 to 93/7) as eluent to **(72)** (0.160 g, 70 %) as a beige solid.

Example 4.81: Synthesis of (*2R*)-2-[[8-[(4-aminophenyl)methylamino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (74)

In a sealed tube 10-20 mL with a stir bar was charged **(3.35)** (0.400 g, 1.26 mmol, 1.0 eq.), NMP (3.0 mL) and corresponding amine (3.04 mL, 31.57 mmol, 25.0 eq.). The vial was

sealed and then put on heating block 17.5 h at 180 °C. After cooling, the mixture was poured onto water (100.0 mL), aqueous layer was extracted with EtOAc (3 x 30.0 mL) then organic layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3 to 90/10) as eluent to give **(74)** (0.100 g, 21 %) as a white solid.

Example 4.82: Synthesis of *N8*-[(4-aminophenyl)methyl]-*N6*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (75)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.35)** (0.100 g, 0.32 mmol, 1.0 eq.), NMP (0.3 mL) and corresponding amine (0.55 mL, 4.74 mmol, 15.0 eq.) then the vial was sealed and put on heating block 22 h at 180 °C. After cooling, the mixture was diluted in DCM (5.0 mL), Si_2O was added to make solid deposit then purfied by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(75)** (0.020 g, 17 %) as a white solid.

Example 4.83: Synthesis of *N8*-[(3-aminophenyl)methyl]-*N6*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (76)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.36)** (0.190 g, 0.60 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.71 mL, 6.00 mmol, 10.0 eq.) then the vial was sealed and put on heating block 22 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) and organic layer was washed three times with a mixture brine/water (3/1, 3x10 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(76)** (0.020 g, 9 %) as a light brown solid.

Example 4.84: Synthesis of *N8*-[(2-aminophenyl)methyl]-*N6*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (77)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.37)** (0.200 g, 0.63 mmol, 1.0 eq.), NMP (1.4 mL) and corresponding amine (0.74 mL, 6.31 mmol, 10.0 eq.) then the vial was sealed and put on heating block 19 h at 170 °C. After cooling, the mixture was diluted in EtOAc (25.0 mL) and organic layer was washed three times with a mixture brine/water (3/1, 3 x 20.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash

chromatography with DCM/MeOH (97/3 to 92/8) as eluent to give **(77)** (0.021 g, 14 %) as a light brown solid.

Example 4.85: Synthesis of *N6*-(1-ethylpropyl)-*N8*-(*1H*-indol-2-ylmethyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (78)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.41)** (0.150 g, 0.42 mmol, 1.0 eq.) and pentan-3-amine (1.48 mL, 12.54 mmol, 30.0 eq.). The vial was sealed and then put on heating block 21 h at 160 °C. After cooling, the mixture was poured into cold water (10 mL), the precipitate was filtered off, washed with water, dried under vacuum. The solid was taken up in EtOAc, the organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3) as eluent to give **(78)** (0.015 g, 9 %) as a beige solid.

Example 4.86: Synthesis of *N*-(1-ethylpropyl)-8-isoindolin-2-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-amine (79)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.39)** (0.150 g, 0.48 mmol, 1.0 eq.), NMP (1.5 mL) and corresponding amine (0.45 mL, 3.82 mmol, 8.0 eq.) then the vial was sealed and put on heating block 65 h at 170 °C. After cooling, the mixture was diluted in EtOAc then organic layer was washed three times with a mixture of brine/water (3/1, 3x10.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give the title compound **(79)** (0.065 g, 37 %) as a beige solid.

Example 4.87: Synthesis of 8-(3,4-dihydro-*1H*-isoquinolin-2-yl)-*N*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-amine (80)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.38)** (0.150 g, 0.46 mmol, 1.0 eq.), NMP (1.0 mL), corresponding amine (0.54 mL, 4.58 mmol, 10.0 eq.). The vial was sealed and then put on heating block 17 h at 170 °C. The reaction mixture was diluted in EtOAc (20.0 mL) then the organic layer was washed with a mixture of brine/saturated $NaHCO_3$ (3/1, 3 x 10.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **(80)** (0.033 g, 33 %) as light brown oil.

Example 4.88: Synthesis of *N6*-(1-ethylpropyl)-*N8*-indan-1-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (81)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.40)** (0.200 g, 0.61 mmol, 1.0 eq.), NMP (1.0 mL), corresponding amine (0.72 mL, 6.10 mmol, 10.0 eq.). The vial was sealed and then put on heating block, 16 h at 170 °C. The reaction mixture was poured onto cold water (30.0 mL), the mixture was stirred 5 min then the precipitate was filtered off, washed with water and taken up in EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 92/8) as eluent to give **(81)** (0.025 g, 11 %) as a beige solid.

Example 4.89: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(2-phenylethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (82)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.43)** (0.240 g, 0.76 mmol, 1.0 eq.) in ethylene glycol (0.9 mL), corresponding amine (0.89 mL, 7.60 mmol, 10.0 eq.) was added then the tube was sealed and put on heating block 21 h at 180 °C. After cooling, the mixture was solublized in a mixture of DCM/MeOH (9/1) then concentrated with silica and directly purified by flash chromatography with DCM/MeOH (99/1 to 94/6) to give **(82)** (0.060 g, 22 %) as a white amorphous solid.

Example 4.90: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (83)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.44)** (0.250 g, 0.79 mmol, 1.0 eq.), ethylene glycol (1.5 mL) and 3-aminopentane (1.39 mL, 11.84 mmol, 15.0 eq.). The vial was sealed and put on heating bloc 18 h at 170 °C. After cooling, the mixture was poured onto cold water (30.0 mL), stirred 5 min then the precipitate was filtered off and washed with cold water. On an other flask, the solid was washed with EtOAc, organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give **(83)** (0.045 g, 16 %) as a white solid.

Example 4.91: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[2-(3-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (84)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.45)** (0.235 g, 0.74 mmol, 1.0 eq.), ethylene glycol (1.5 mL) and 3-aminopentane (1.31 mL, 11.13 mmol, 15.0 eq.). The vial was sealed and put on heating bloc 16 h at 170 °C. After cooling, the mixture was poured onto cold water (15.0 mL), stirred 5 min then the precipitate was filtered off, washed with cold water and taken up in DCM. Aqueous filtrate was extracted with DCM (10.0 mL) then organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give **(84)** (0.063 g, 23 %) as a white solid.

Example 4.92: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[2-(4-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (85)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.46)** (0.255 g, 0.81 mmol, 1.0 eq.), ethylene glycol (1.5 mL) and 3-aminopentane (1.42 mL, 12.07 mmol, 15.0 eq.). The vial was sealed and put on heating bloc 16 h at 170 °C. After cooling, the mixture was poured onto cold water (15.0 mL), stirred 5 min then the precipitate was filtered off, washed with cold water and taken up in DCM. Aqueous filtrate was extracted with DCM (10.0 mL) then organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give **(85)** (0.048 g, 16 %) as a white solid.

Example 4.93: Synthesis of 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (86)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.47)** (0.110 g, 0.35 mmol, 1.0 eq.), NMP (1.0 mL) and 3-aminopentane (0.41 mL, 3.50 mmol, 10.0 eq.) was added then the vial was sealed and put on heating bloc 17 h at 180 °C. After cooling, the mixture was poured onto cold water (20.0 mL) and brine (30.0 mL) then the resulting precipitate was filtered off, washed with water and taken up in EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography wth DCM/MeOH (98/2 to 93/7) as eluent to give **(86)** (0.020 g, 16 %) as a white solid.

Example 4.94: Synthesis of 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-[2-(3-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (87)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.48)** (0.110 g, 0.35 mmol, 1.0 eq.), NMP (1.0 mL) and 3-aminopentane (0.41 mL, 3.50 mmol, 10.0 eq.) was added then the vial was sealed and put on heating bloc 17 h at 180 °C. After cooling, the mixture was poured onto cold water (20.0 mL) and brine (30.0 mL) then the resulting precipitate was filtered off, washed with water and taken up in EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography wth DCM/MeOH (97/3 to 92/8) as eluent to give **(87)** (0.030 g, 23 %) as a beige solid.

Example 4.95: Synthesis of 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-[2-(4-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (88)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.49)** (0.110 g, 0.35 mmol, 1.0 eq.), NMP (1.0 mL) and 3-aminopentane (0.41 mL, 3.50 mmol, 10.0 eq.) was added then the vial was sealed and put on heating bloc 17 h at 180 °C. After cooling, the mixture was poured onto cold water (20.0 mL) and brine (30.0 mL) then the resulting precipitate was filtered off, washed with water and taken up in EtOAc. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography wth DCM/MeOH (97/3 to 92/8) as eluent to give **(88)** (0.039 g, 31 %) as a white solid.

Example 4.96: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[3-(2-pyridyl)propyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (89)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.50)** (0.100 g, 0.30 mmol, 1.0 eq.), NMP (0.9 mL) and 3-aminopentane (0.36 mL, 3.02 mmol, 10.0 eq.) was added then the vial was sealed and put on heating bloc 64 h at 170 °C. After cooling, the mixture was poured onto cold water (30.0 mL) then aqueous layer was extracted with EtOAc (3x 15.0 mL). Oganic layers were combined, washed with brine (10.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography wth DCM/MeOH (98/2 to 92/8) as eluent to give **(89)** (0.040 g, 35 %) as a beige solid.

Example 4.97: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[3-(3-pyridyl)propyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (90)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.51)** (0.180 g, 0.54 mmol, 1.0 eq.), NMP (0.5 mL) and 3-aminopentane (0.64 mL, 5.44 mmol, 10.0 eq.) was added then the

vial was sealed and put on heating bloc 17 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL), organic layer was washed with a mixture brine/water (3/1, 3x10.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography wth DCM/MeOH (98/2 to 92/8) as eluent to give **(90)** (0.018 g, 9 %) as a white solid.

Example 4.98: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[3-(4-pyridyl)propyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (91)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.52)** (0.200 g, 0.61 mmol, 1.0 eq.), NMP (0.6 mL) and 3-aminopentane (0.71 mL, 6.05 mmol, 10.0 eq.) was added then the vial was sealed and put on heating bloc 17 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL), organic layer was washed with a mixture brine/water (3/1, 3x10.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography wth DCM/MeOH (98/2 to 92/8) as eluent to give **(91)** (0.030 g, 13 %) as a beige solid.

Example 4.99: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(pyrimidin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (92)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.54)** (0.070 g, 0.23 mmol, 1.0 eq.), ethylene glycol (0.5 mL) and 3-aminopentane (0.41 mL, 3.46 mmol, 15.0 eq.) was added then the vial was sealed and put on heating bloc 17 h at 180 °C. After cooling, the mixture was diluted in DCM, concentrated then the crude was triturated in saturated $NaHCO_3$ (10.0 mL). The solid was filtered off, washed with water up to neutral pH, taken up in EtOAc then organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography wth DCM/MeOH (98/2 to 93/7) as eluent to give **(92)** (0.022 g, 27 %) as a white solid.

Example 4.100: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(pyrimidin-5-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (93)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.56)** (0.080 g, 0.26 mmol, 1.0 eq.), ethylene glycol (0.5 mL) and 3-aminopentane (0.46 mL, 3.95 mmol, 15.0 eq.) was added then the vial was sealed and put on heating bloc 17 h at 180 °C. After cooling, the mixture

was diluted in DCM, concentrated then the crude was triturated in saturated $NaHCO_3$ (10.0 mL). The solid was filtered off, washed with water up to neutral pH, taken up in EtOAc then organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography wth DCM/MeOH (98/2 to 93/7) as eluent to give **(93)** (0.010 g, 11 %) as a white solid.

Example 4.101: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(pyrazin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (94)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.55)** (0.080 g, 0.26 mmol, 1.0 eq.), ethylene glycol (0.8 mL) and 3-aminopentane (0.62 mL, 5.27 mmol, 20.0 eq.) was added then the vial was sealed and put on heating bloc 18 h at 180 °C. After cooling, saturated $NaHCO_3$ (5.0 mL) was added and the mixture was vigorously stirred 5 min, the precipitate was filtered off, washed with water up to neutral pH and taken up in DCM. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography wth DCM/MeOH (98/2 to 94/6) as eluent to give **(94)** (0.032 g, 34 %) as a white solid.

Example 4.102: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(pyridazin-3-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (95)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.57)** (0.270 g, 0.89 mmol, 1.0 eq.), ethylene glycol (2.0 mL) and 3-aminopentane (1.57 mL, 13.33 mmol, 15.0 eq.) was added then the vial was sealed and put on heating bloc 18 h at 170 °C. After cooling, the mixture was poured onto cold water (20.0 mL) and brine (30.0 mL) then the resulting precipitate was filtered off, washed with water and taken up in DCM. Organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography wth DCM/MeOH (98/2 to 93/7) as eluent to give **(95)** (0.045 g, 14 %) as a white solid.

Example 4.103: Synthesis of *N8*-benzyl-*N6*-cyclobutyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (117)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. cyclobutylamine at 180 °C for 6h. Purification by TLC Prep (DCM/MeOH gradient) gives **(117)** with 6 % yield as a beige solid.

Example 4.104: Synthesis of *N8*-benzyl-*N6*-cyclopentyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (118)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. of cyclopentylamine at 180 °C for 6h15. Purification by flash chromatography (DCM/MeOH gradient) gives **(118)** with 40 % yield as a beige solid.

Example 4.105: Synthesis of *N8*-benzyl-*N6*-cyclohexyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (119)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. of cyclohexylamine at 180 °C for 45h. Purification by flash chromatography (DCM/MeOH gradient) gives **(119)** with 45 % yield as a beige solid.

Example 4.106: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(4-methoxycyclohexyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (120)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. of 4-methoxycyclohexanamine at 200 °C for 16h. Purification by flash chromatography (DCM/MeOH gradient) gives **(120)** with 37 % yield as a beige solid.

Example 4.107: Synthesis of *N8*-benzyl-*N6*-cycloheptyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (121)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. of cycloheptylamine at 200 °C for 45h. Purification by flash chromatography (DCM/MeOH gradient) gives **(121)** with 22 % yield as a white solid.

Example 4.108: Synthesis of *N8*-benzyl-*N6*-(cyclopropylmethyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (122)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. aminomethylcyclopropane at 180 °C for 16h. Purification by TLC Prep (DCM/MeOH gradient) gives **(122)** with 22 % yield as a beige solid.

Example 4.109: Synthesis of *N8*-benzyl-*N6*-(cyclopropylmethyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (123)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. of 1-cyclobutylmethylamine at 180 °C for 40h. Purification by flash chromatography (DCM/MeOH gradient) gives **(123)** with 40 % yield as a beige solid.

Example 4.110: Synthesis of *N8*-benzyl-*N6*-(cyclohexylmethyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (124)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. of cyclohexanemethylamine at 180°C for 6h15. Purification by TLC Prep (DCM/MeOH gradient) gives **(124)** with 46 % yield as a white solid.

Example 4.111: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(tetrahydropyran-4-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (125)

Reaction carried out in NMP (0.2M) on a 166 µmol scale of **(3.1)**, with 5.0 eq. of aminomethyltetrahydropyran at 180°C for 16h. Purification by TLC Prep (DCM/MeOH gradient) gives **(125)** with 50 % yield as a white solid.

Example 4.112: Synthesis of *N8*-benzyl-*N6*-(2-ethylbutyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (126)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. of 2-ethyl-1-butylamine at 180 °C for 45h. Purification by flash chromatography (DCM/MeOH gradient) gives **(126)** with 25 % yield as a beige solid.

Example 4.113: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(2-phenylethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (127)

Reaction carried out in NMP (0.2M) on a 166 µmol scale of **(3.1)**, with 5.0 eq. of phenylethylamine at 180 °C for 20h. Purification by TLC Prep (DCM/MeOH gradient) gives **(127)** with 32 % yield as a white solid.

Example 4.114: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(2-phenoxyethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (128)

Reaction carried out in NMP (0.2M) on a 166 µmol scale of **(3.1)**, with 5.0 eq. of 2-phenoxyethylamine at 180 °C for 36h. Purification by TLC Prep (DCM/MeOH gradient) gives **(128)** with 14 % yield as a white solid.

Example 4.115: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-[(1-methylimidazol-2-yl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (129)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. of (1-methyl-1H-imidazol-2-yl)methylamine at 180 °C for 16h. Purification by flash chromatography (DCM/MeOH gradient) gives **(129)** with 30 % yield as a white solid.

Example 4.116: Synthesis of *N6*,*N8*-dibenzyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (130)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. of 4-benzylamine at 180 °C for 16h. Purification by flash chromatography (DCM/MeOH gradient) gives **(130)** with 49 % yield as a white solid.

Example 4.117: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (131)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. of 2-(aminomethyl)pyridine at 180 °C for 16h. Purification by flash chromatography (DCM/MeOH gradient) gives **(131)** with 25 % yield as a brown solid.

Example 4.118: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(3-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (132)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. of 3-(aminomethyl)pyridine at 180 °C for 23h. Purification by flash chromatography (DCM/MeOH gradient) gives **(132)** with 33 % yield as a white solid.

Example 4.119: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(4-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (133)

Reaction carried out in NMP (0.2M) on a 232 µmol scale of **(3.1)**, with 5.0 eq. of 4-(aminomethyl)pyridine at 180 °C for 23h. Purification by flash chromatography (DCM/MeOH gradient) gives **(133)** with 10 % yield as a white solid.

Example 4.120: Synthesis of racemic trans-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]cyclohexanol (134)

Reaction carried out in NMP (0.25M) on a 248 µmol scale of **(3.1)**, with 5.0 eq. of (1S*,2S*)-2-aminocyclohexan-1-ol at 180 °C for 27h. Purification by flash chromatography (DCM/MeOH gradient) gives **(134)** with 58 % yield as a brown solid.

Example 4.121: Synthesis of racemic trans-4-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]cyclohexanol (135)

Reaction carried out in NMP (0.25M) on a 248 µmol scale of **(3.1)**, with 5.0 eq. of *trans*-4-aminocyclohexan-1-ol at 180 °C for 27h. Purification by flash chromatography (DCM/MeOH gradient) gives **(135)** with 59 % yield as a light brown solid.

Example 4.122: Synthesis of racemic trans-4-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]cyclohexanol (136)

Reaction carried out in NMP (0.25M) on a 248 µmol scale of **(3.1)**, with 5.0 eq. of (1-methylcyclohexyl)methanamine at 180 °C for 24h. Purification by flash chromatography and PTLC (DCM/MeOH gradient) gives **(136)** with 58 % yield as a beige solid.

Example 4.123: Synthesis of *N6*-(1-adamantyl)-*N8*-benzyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (137)

Reaction carried out in NMP (0.2M) on a 215 µmol scale of **(3.1)**, with 5.0 eq. of 1-adamantylamine at 180 °C for 7 days. Purification by flash chromatography (DCM/MeOH gradient) gives **(137)** with 10 % yield as a brown solid.

Example 4.124: Synthesis of *N8*-benzyl-*N6*-indan-2-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (138)

Reaction carried out in NMP (0.25M) on a 248 µmol scale of **(3.1)**, with 5.0 eq. of 2-aminoindane at 180 °C for 96h. Purification by flash chromatography and PTLC (DCM/MeOH gradient) gives **(138)** with 12 % yield as a light brown solid.

Example 4.125: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-[(5-methylpyrazin-2-yl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (139)

Reaction carried out in NMP (0.25M) on a 248 µmol scale of **(3.1)**, with 5.0 eq. of (5-methylpyrazin-2-yl)methan-amine at 180 °C for 40h. Purification by flash chromatography (DCM/MeOH gradient) and trituration in MTBE give **(139)** with 27 % yield as a beige solid.

Example 4.126: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-[(1-methylpyrazol-4-yl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (140)

Reaction carried out in NMP (0.2M) on a 215 µmol scale of **(3.1)**, with 5.0 eq. of (1-methyl-1H-pyrazol-4-yl)methanamine at 180 °C for 16h. Purification by flash chromatography (DCM/MeOH gradient) gives **(140)** with 53 % yield as a pale yellow solid.

Example 4.127: Synthesis of *N8*-benzyl-*N6*-[(3,5-dimethylphenyl)methyl]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (141)

Reaction carried out in NMP (0.2M) on a 215 µmol scale of **(3.1)**, with 5.0 eq. of 3,5-dimethylbenzylamine at 180 °C for 16h. Purification by flash chromatography (DCM/MeOH gradient) gives **(141)** with 15 % yield as a white solid.

Example 4.128: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(tetrahydrofuran-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (142)

Reaction carried out in NMP (0.2M) on a 215 µmol scale of **(3.1)**, with 5.0 eq. of tetrahydrofurfurylamine at 180 °C for 22h. Purification by flash chromatography (DCM/MeOH gradient) gives **(142)** with 24 % yield as a colorless oil.

Example 4.129: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(2-methylsulfanylethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (143)

Reaction carried out in NMP (0.2M) on a 215 µmol scale of **(3.1)**, with 5.0 eq. of 2-(methylthio)-ethylamine at 180 °C for 16h. Purification by flash chromatography (DCM/MeOH gradient) gives **(143)** with 36 % yield as a colourless oil.

Example 4.130: Synthesis of *N8*-benzyl-3-isopropyl-*N6*-(1-methylimidazol-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (144)

Reaction carried out in NMP (0.2M) on a 215 µmol scale of **(3.1)**, with 5.0 eq. of 1-Methyl-1H-imidazol-2-amine at 180 °C for 16h. Purification by flash chromatography (DCM/MeOH gradient) gives **(144)** with 11 % yield as a white oil.

Example 4.131: Synthesis of *N8*-benzyl-*N6*-[(4,6-dimethylpyrimidin-2-yl)methyl]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (145)

Reaction carried out in NMP (0.2M) on a 215 µmol scale of **(3.1)**, with 5.0 eq. of (4,6-dimethylpyrimidin-2-yl)methanamine, hydrochloride and 3.0 eq. of K_2CO_3 at 180 °C for 16h. Purification by flash chromatography (DCM/MeOH gradient) gives **(145)** with 13 % yield as an off-white solid.

Example 4.132: Synthesis of *N8*-benzyl-*N6*-indan-1-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (146)

Reaction carried out in NMP (0.2M) on a 215 µmol scale of **(3.1)**, with 5.0 eq. of 1-amino-indane at 180 °C for 16h. Purification by flash chromatography (DCM/MeOH gradient) gives **(146)** with 20 % yield as a colourless oil.

Example 4.133: Synthesis of (2*S*)-2-[[3-isopropyl-8-[[4-(2-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (105)

In a sealed tube 10 – 20 mL with a stir bar was charged **(3.58)** (0.120 g, 0.32 mmol, 1.0 eq.), NMP (0.5 mL) and (2*S*)-2-aminobutan-1-ol (0.54 mL, 5.70 mmol, 18.0 eq.) then the vial was sealed and put on heating block 16 h at 170 °C. After cooling, water (4.0 mL) and saturated $NaHCO_3$ (4.0 mL) was added then the mixture was vigorously stirred 5 min. The precipitate was filtered off, washed with water up to neutral pH, washed with EtOAc and DCM to give a first part of **(105)** (0.039 g). Organic filtrate was dried over $MgSO_4$,

filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give the second part of **(105)** (0.035 g). Total of **(105)**: 0.074 g, 54 %, as a white solid.

Example 4.134: Synthesis of (2*R*,3*R*)-2-[[8-[(4-bromophenyl)methylamino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol (106)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.42)** (0.250 g, 0.66 mmol, 1.0 eq.), NMP (0.7 mL) and (2*R*,3*R*)-2-aminobutane-1,3-diol (0.712 g, 6.57 mmol, 10.0 eq.) then the vial was sealed and put on heating block 24 h at 180 °C. After cooling, the mixture was poured onto water (30.0 mL) and extracted with EtOAc (3x20.0 mL). Organic layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 95/5) as eluent. Fractions contains the desired impur compound was concentrated, the residu was triturated in DCM and the solid was filtered off, washed with DCM and dried under vacuum to give **(106)** (0.135 g, 46 %) as a white solid.

Example 4.135: Synthesis of (2*R*,3*R*)-2-[[3-isopropyl-8-[[4-(2-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol (107)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.58)** (0.200 g, 0.53 mmol, 1.0 eq.), NMP (0.5 mL) and (2*R*,3*R*)-2-aminobutane-1,3-diol (0.286 g, 2.64 mmol, 5.0 eq.) then the vial was sealed and put on heating block 17 h at 180 °C. After cooling, the reaction mixture was diluted in EtOAc (20.0 mL), the resulting solid was filtered, washed with EtOAc. Organic filtrate was washed with brine (2x20.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 93/7) as eluent to give **(107)** (0.100 g, 42 %) as a beige solid.

Example 4.136: Synthesis of (2*R*,3*R*)-2-[[3-isopropyl-8-[[4-(4-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol (108)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.58)** (0.200 g, 0.53 mmol, 1.0 eq.), NMP (0.5 mL) and (2*R*,3*R*)-2-aminobutane-1,3-diol (0.286 g, 2.64 mmol, 5.0 eq.) then the vial was sealed and put on heating block 17 h at 180 °C. After cooling, the reaction mixture was diluted in DCM (10.0 mL) with SiO_2 to make solid deposit and directly purified by flash chromatography with DCM/MeOH (97/3 to 90/10) as eluent to give **(108)** (0.015 g, 14 %) as a white solid.

Example 4.137: Synthesis of (2*S*)-2-[[3-isopropyl-8-[(4-phenylphenyl)methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (102)

In a sealed tube 10 - 20 mL with a stir bar was charged **(101)** (0.200 g, 0.46 mmol, 1.0 eq.), phenylboronic acid (0.116 g, 0.92 mmol, 2.0 eq.), K_2CO_3 (0.191 g, 1.39 mmol, 3.0 eq.) and a mixture of dioxane/water (9/1, 5.0 mL). The mixure was degassed 5 min with inert gas then $Pd(PPh_3)_4$ (0.053 g, 0.05 mmol, 0.1 eq.) was added, the vial was sealed and put on heating bloc 2.5 h at 110 °C. After cooling, the mixture was directly concentrated with SiO_2 to make solid deposit and purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give **(102)** (0.160 g, 81 %) as a white solid.

Example 4.138: Synthesis of (2*S*)-2-[[3-isopropyl-8-[[4-(4-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (103)

In a sealed tube 10 - 20 mL with a stir bar was charged **(101)** (0.200 g, 0.46 mmol, 1.0 eq.), 4-pyridylboronic acid (0.119 g, 0.92 mmol, 2.0 eq.), K_2CO_3 (0.191 g, 1.39 mmol, 3.0 eq.) and a mixture of dioxane/water (9/1, 5.0 mL). The mixure was degassed 5 min with inert gas then $Pd(PPh_3)_4$ (0.053 g, 0.05 mmol, 0.1 eq.) was added, the vial was sealed and put on heating bloc 2.5 h at 110 °C. After cooling, the mixture was directly concentrated with SiO_2 to make solid deposit and purified by flash chromatography with DCM/MeOH (97/3 to 92/8) as eluent to give **(103)** (0.190 g, 95 %) as a yellow solid.

Example 4.139: Synthesis of (2*S*)-2-[[3-isopropyl-8-[[4-(3-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (104)

In a sealed tube 10 - 20 mL with a stir bar was charged **(101)** (0.200 g, 0.46 mmol, 1.0 eq.), 3-pyridylboronic acid (0.119 g, 0.92 mmol, 2.0 eq.), K_2CO_3 (0.191 g, 1.39 mmol, 3.0 eq.) and a mixture of dioxane/water (9/1, 5.0 mL). The mixure was degassed 5 min with inert gas then $Pd(PPh_3)_4$ (0.053 g, 0.05 mmol, 0.1 eq.) was added, the vial was sealed and put on heating bloc 2.5 h at 110 °C. After cooling, the mixture was directly concentrated with SiO_2 to make solid deposit and purified by flash chromatography with DCM/MeOH (97/3 to 92/8) as eluent to give **(104)** (0.180 g, 90 %) as a yellow solid.

Example 4.140: Synthesis of *N6*-(2-ethylbutyl)-3-isopropyl-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (147)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.60)** (0.080 g, 0.28 mmol, 1.0 eq.), NMP (1.0 mL) and 2-ethylbutan-1-amine (0.30 mL, 2.21 mmol, 8.0 eq.). The vial was sealed and put on heating block 21 h at 170 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x5.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent. Impur solid product was triturated in HCl 0.5M, filtered off and washed with water up to neutral pH then dried under vacuum to give the title compound **(147)** (0.030 g, 31 %) as a beige solid.

Example 4.141: Synthesis of 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (148)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.60)** (0.084 g, 4.349 mmol, 1.0 eq.), cineol (0.67 mL) and 3-aminopentane (0.53 mL, 4.349 mmol, 15.0 eq.). The vial was sealed and put on heating block 24h at 170 °C. After cooling, the mixture was diluted in THF and concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(148)** (0.044 g, 45%) as a white solid.

Example 4.142: Synthesis of 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (149)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.61)** (0.250 g, 0.863 mmol, 1.0 eq.), cineol (1.99 mL) and 3-aminopentane (1.57 mL, 12.943 mmol, 15.0 eq.). The vial was

sealed and put on heating block 73h at 140 °C. After cooling, the mixture was diluted in THF and concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give a moiety with (**13**) with an impurity. This moiety was triturated in MeOH, filtered off, washed with MeOH and dried under vacuum to give **(149)** (0.015 g, 5%) as a pale pink solid.

Example 4.143: Synthesis of 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (150)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.62)** (0.250 g, 0.863 mmol, 1.0 eq.), cineol (2 mL) and 3-aminopentane (1.57 mL, 12.943 mmol, 15.0 eq.). The vial was sealed and put on heating block 96h at 140°C. After cooling, the mixture was diluted in THF and concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(150)** (0.060 g, 20%) as a yellow solid.

Example 4.144: Synthesis of 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-5-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (151)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.63)** (0.197 g, 0.680 mmol, 1.0 eq.), cineol (1.56 mL) and 3-aminopentane (1.24 mL, 10.199 mmol, 15.0 eq.). The vial was sealed and put on heating block 92.3h at 130 °C. After cooling, the mixture was diluted in THF and concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with EtOAc/MeOH (100/0 to 97/3) as eluent to give a moiety with **(151)** and an impurity. This one was concentrated and the residue was triturated with saturated $NaHCO_3$, filtered off, washed with $NaHCO_3$ and H_2O, solubilized with DCM and concentrated. The residue was purified by flash chromatography with DCM/MeOH (95/5) as eluent to give **(151)** (0.019 g, 8 %) as a white solid.

Example 4.145: Synthesis of 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (152)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.64)** (0.120 g, 0.414 mmol, 1.0 eq.), cineol (0.95 mL) and 3-aminopentane (0.75 mL, 6.213 mmol, 15.0 eq.). The vial was sealed and put on heating block 21h at 170 °C. After cooling, the mixture was diluted in

THF and the precipitate in the mixture was filtered. The filtrate was concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give a pure moiety. This one was concentrated and the residue was tritured in Et_2O, filtered off, washed with Et_2O and pentane and dried under vacuum to give **(152)** (0.012 g, 9 %) as a beige solid.

Example 4.146: Synthesis of 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrazin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (153)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.65)** (0.086 g, 0.297 mmol, 1.0 eq.), cineol (0.68 mL) and 3-aminopentane (0.54 mL, 4.452 mmol, 15.0 eq.). The vial was sealed and put on heating block 21h at 170 °C. After cooling, the mixture was diluted in THF and concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(153)** (0.023 g, 23 %) as a white solid.

Example 4.147: Synthesis of 3-isopropyl-*N8*-(6-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (154)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.66)** (0.090 g, 0.28 mmol, 1.0 eq.), NMP (1.0 mL) and 3-aminopentane (0.33 mL, 2.82 mmol, 10.0 eq.). The vial was sealed and then put on heating block 17 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x5.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give the title compound **(154)** (0.049 g, 47 %) as a white solid.

Example 4.148: Synthesis of 3-isopropyl-*N8*-(5-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (155)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.67)** (0.090 g, 0.28 mmol, 1.0 eq.), NMP (1.0 mL) and 3-aminopentane (0.33 mL, 2.82 mmol, 10.0 eq.). The vial was sealed and then put on heating block 17 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x5.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash

chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give the title compound **(155)** (0.047 g, 45 %) as a white solid.

Example 4.149: Synthesis of 3-isopropyl-*N8*-(4-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (156)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.68)** (0.090 g, 0.28 mmol, 1.0 eq.), NMP (1.0 mL) and 3-aminopentane (0.33 mL, 2.82 mmol, 10.0 eq.). The vial was sealed and then put on heating block 17 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x5.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give the title compound **(156)** (0.047 g, 45 %) as a white solid.

Example 4.150: Synthesis of 3-isopropyl-*N8*-(3-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (157)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.69)** (0.090 g, 0.28 mmol, 1.0 eq.), NMP (1.0 mL) and 3-aminopentane (0.33 mL, 2.82 mmol, 10.0 eq.). The vial was sealed and then put on heating block 17 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x5.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give the title compound **(157)** (0.039 g, 37 %) as a white solid.

Example 4.151: Synthesis of 3-isopropyl-*N*8-(2-methoxypyridin-3-yl)-*N*6-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (158)

In a sealed tube with a stir bar was charged **(3.87)** (80 mg, 250.97 µmol, 1.0 eq.), NMP (1.0 mL) and aminopentane (0.32 mL, 2.52 mmol, 10.0 eq.). The vial was sealed and then put on heating block 17 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x5.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(158)** (0.016 g, 17 %) as a pale grey solid.

Example 4.152: Synthesis of 3-isopropyl-*N*8-(6-methoxypyridin-3-yl)-*N*6-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (159)

In a sealed tube with a stir bar was charged **(3.88)** (80 mg, 250.97 µmol, 1.0 eq.), NMP (1.0 mL) and aminopentane (319 µL, 2.52 mmol, 10.0 eq.). The vial was sealed and then put on heating block 17 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x5.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(159)** (0.044 g, 47 %) as a brown viscous oil.

Example 4.153: Synthesis of 3-isopropyl-*N*8-(5-methoxypyridin-3-yl)-*N*6-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (160)

In a sealed tube with a stir bar was charged **(3.89)** (80 mg, 250.97 µmol, 1.0 eq.), NMP (1.0 mL) and aminopentane (319 µL, 2.52 mmol, 10.0 eq.). The vial was sealed and then put on heating block 17 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x5.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(160)** (0.045 g, 48 %) as a pale beige solid.

Example 4.154: Synthesis of 3-isopropyl-*N*8-(4-methoxypyridin-3-yl)-*N*6-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (161)

In a sealed tube with a stir bar was charged **(3.90)** (80 mg, 250.97 µmol, 1.0 eq.), NMP (1.0 mL) and aminopentane (319 µL, 2.52 mmol, 10.0 eq.). The vial was sealed and then put on heating block 17 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x5.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (98/2) as eluent to give **(161)** (0.006 g, 6 %) as a brown solid.

Example 4.155: Synthesis of (2*R*)-2-[[3-isopropyl-8-(2-pyridylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (163)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.13)** (0.070 g, 0.24 mmol, 1.0 eq.), NMP (1.0 mL) and (*R*)-2-aminobutan-1-ol (0.23 mL, 2.42 mmol, 10.0 eq.). The vial was sealed and put on heating block 64 h at 170 °C. After cooling, the mixture was diluted in AcOEt (25.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x10.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was triturated in DCM, filtered off, washed with DCM and dried under vacuum to give **(163)** (0.052 g, 63 %) as a white solid.

Example 4.156: Synthesis of *N6*-(2-ethylbutyl)-3-isopropyl-*N8*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (164)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.44)** (0.060 g, 0.19 mmol, 1.0 eq.), NMP (1.0 mL), corresponding amine hydrochloride (0.165 g, 1.14 mmol, 6.0 eq.) and DIPEA (0.23 mL, 1.33 mmol, 7.0 eq.). The vial was sealed and put on heating block 19 h at 180 °C. After cooling, the mixture was diluted in AcOEt (25.0 mL) then organic layer was washed two times with sat. NaCl + H_2O (2/1, 2x15.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 92/8) as eluent to give **(164)** (0.018 g, 25 %) as a light brown solid.

Example 4.157: Synthesis of *N6*-cyclopentyl-3-isopropyl-*N8*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (165)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.44)** (0.060 g, 0.19 mmol, 1.0 eq.), NMP (0.8 mL) and corresponding amine (0.08 mL, 0.79 mmol, 5.0 eq.). The vial was sealed and put on heating block 19 h at 180 °C. After cooling, the mixture was diluted in AcOEt (25.0 mL) then organic layer was washed two times with sat. NaCl + H_2O (2/1, 2x15.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 92/8) as eluent to give **(165)** (0.036 g, 62 %) as a light brown solid.

Example 4.158: Synthesis of *N6*-(2-ethylbutyl)-3-isopropyl-*N8*-[2-(3-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (166)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.45)** (0.060 g, 0.19 mmol, 1.0 eq.), NMP (1.0 mL), corresponding amine hydrochloride (0.165 g, 1.14 mmol, 6.0 eq.) and DIPEA (0.23 mL, 1.33 mmol, 7.0 eq.). The vial was sealed and put on heating block 19 h at 180 °C. After cooling, the mixture was diluted in AcOEt (25.0 mL) then organic layer was washed two times with sat. NaCl + H_2O (2/1, 2x15.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 92/8) as eluent to give **(166)** (0.029 g, 40 %) as a light brown solid.

Example 4.159: Synthesis of *N6*,*N8*-bis(2-ethylbutyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (167)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.45)** (0.060 g, 0.19 mmol, 1.0 eq.), NMP (1.0 mL), corresponding amine hydrochloride (0.165 g, 1.14 mmol, 6.0 eq.) and DIPEA (0.23 mL, 1.33 mmol, 7.0 eq.). The vial was sealed and put on heating block 19 h at 180 °C. After cooling, the mixture was diluted in AcOEt (25.0 mL) then organic layer was washed two times with sat. NaCl + H_2O (2/1, 2x15.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 92/8) as eluent to give the secondary product **(167)** (0.006 g, 9 %) as a light brown solid.

Example 4.160: Synthesis of (*2R*)-2-[[3-isopropyl-8-(2-pyridylmethylamino)imidazo[1,2-*b*]pyridazin-6-yl]amino]butan-1-ol (169)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.18)** (0.150 g, 0.47 mmol, 1.0 eq.), NMP (1.0 mL) and (*R*)-2-aminobutan-1-ol (0.45 mL, 4.71 mmol, 10.0 eq.). The vial was sealed and put on heating block 17 h at 170 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (98/2 to 92/8) to give **(169)** (0.077 g, 46 %) as a white solid.

Example 4.161: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(3-phenylpropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (170)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.91)** (0.100 g, 0.30 mmol, 1.0 eq.), cineol (1.0 mL) and 3-aminopentane (0.54 mL, 4.55 mmol, 15.0 eq.). The vial was sealed and put on heating block 93 h at 190 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then concentrated with SiO_2 to make solid deposit and purified by flash chromatography with DCM/MeOH (98/2 to 96/4) to give **(170)** (0.010 g, 7 %) as a brown oil.

Example 4.162: Synthesis of 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (171)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.71)** (0.100 g, 0.35 mmol, 1.0 eq.), cineol (1.0 mL) and 3-aminopentane (0.41 mL, 3.50 mmol, 10.0 eq.). The vial was sealed and put on heating block 70 h at 170 °C. After cooling, the mixture was diluted in THF (20.0 mL) then concentrated with SiO_2 to make solid deposit and purified by flash chromatography with DCM/MeOH (99/1 to 96/4) to give **(171)** (0.015 g, 13 %) as a white solid.

Example 4.163: Synthesis of 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (172)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.72)** (0.070 g, 0.24 mmol, 1.0 eq.), cineol (1.0 mL) and 3-aminopentane (0.43 mL, 36.62 mmol, 15.0 eq.). The vial was sealed and put on heating block 18 h at 170 °C. After cooling, the mixture was diluted in THF (20.0 mL) then concentrated with SiO_2 to make solid deposit and purified by flash chromatography with DCM/MeOH (99/1 to 95/5) to give **(172)** (0.020 g, 24 %) as a white solid.

Example 4.164: Synthesis of 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-(3-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (173)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.73)** (0.070 g, 0.24 mmol, 1.0 eq.), cineol (1.0 mL) and 3-aminopentane (0.43 mL, 36.62 mmol, 15.0 eq.). The vial was sealed and put on heating block 18 h at 170 °C. After cooling, the mixture was diluted in THF (20.0 mL) then concentrated with SiO_2 to make solid deposit and purified by flash

chromatography with DCM/MeOH (99/1 to 95/5) to give **(173)** (0.020 g, 24 %) as a white solid.

Example 4.165: Synthesis of 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-(4-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (174)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.74)** (0.070 g, 0.24 mmol, 1.0 eq.), cineol (1.0 mL) and 3-aminopentane (0.43 mL, 36.62 mmol, 15.0 eq.). The vial was sealed and put on heating block 18 h at 170 °C. After cooling, the mixture was diluted in THF (20.0 mL) then concentrated with SiO_2 to make solid deposit and purified by flash chromatography with DCM/MeOH (99/1 to 95/5) to give **(174)** (0.015 g, 18 %) as a white solid.

Example 4.166: Synthesis of 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (175)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.75)** (0.075 g, 0.261 mmol, 1.0 eq.), cineol (0.6 mL) and 3-aminopentane (0.47 mL, 3.91 mmol, 15.0 eq.). The vial was sealed and put on heating block 24h at 170 °C. After cooling, the mixture was diluted in THF and the precipitate in the mixture was filtered. The filtrate was concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(175)** (0.014 g, 16 %) as a white solid.

Example 4.167: Synthesis of 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (176)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.76)** (0.140 g, 0.487 mmol, 1.0 eq.), cineol (1.1 mL) and 3-aminopentane (0.89 mL, 7.299 mmol, 15.0 eq.). The vial was sealed and put on heating block 25.3h at 150 °C. After cooling, the mixture was diluted in THF and the precipitate in the mixture was filtered. The precipitate was solubilised with DCM and MeOH and concentrated. The residue was purified by flash chromatography with DCM/MeOH (95/5 then 94/6) as eluent to give **(176)** (0.003 g, 2%) as a white solid.

Example 4.168: Synthesis of 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (177)

In four sealed tubes 2 - 5 mL with a stir bar was charged **(3.77)** (4x0.150 g, 2.085 mmol, 1.0 eq.), cineol (4x1.2 mL) and 3-aminopentane (4x0.95 mL, 31.281 mmol, 15.0 eq.). The vials were sealed and put on heating block 95h at 150 °C. After cooling, the mixture was diluted in THF and concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(177)** (0.060 g, 9 %) as a beige solid.

Example 4.169: Synthesis of 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-pyrimidin-5-yl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (178)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.78)** (0.132 g, 0.459 mmol, 1.0 eq.), cineol (1.06 mL) and 3-aminopentane (0.84 mL, 6.882 mmol, 15.0 eq.). The vial was sealed and put on heating block 23h at 150 °C. After cooling, the mixture was diluted in THF and concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with EtOAc/MeOH (100/0 to 98/2) as eluent to give a moiety with **(178)** and an impurity. This moiety was purified by flash chromatography with DCM/MeOH (96/4 to 90/10) as eluent to give **(178)** (0.004 g, 3%) as an orange solid.

Example 4.170: Synthesis of 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (179)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.79)** (0.090 g, 0.313 mmol, 1.0 eq.), cineol (0.72 mL) and 3-aminopentane (0.57 mL, 4.692 mmol, 15.0 eq.). The vial was sealed and put on heating block 21h at 170 °C. After cooling, the mixture was diluted in THF and the precipitate in the mixture was filtered. The filtrate was concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(179)** (0.015 g, 14 %) as a white solid.

Example 4.171: Synthesis of 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrazin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (180)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.80)** (0.075 g, 0.261 mmol, 1.0 eq.), cineol (0.6 mL) and 3-aminopentane (0.47 mL, 3.91 mmol, 15.0 eq.). The vial was sealed and put on heating block 21h at 170 °C. After cooling, the mixture was diluted in THF and the precipitate in the mixture was filtered. The filtrate was concentrated with SiO_2 to make

solid deposit then directly purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(180)** (0.009 g, 10 %) as a white solid.

Example 4.172: Synthesis of (*R*)-2-((3-cyclopropyl-8-(pyridazin-3-ylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino)butan-1-ol (181)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.75)** (0.100 g, 0.348 mmol, 1.0 eq.), cineol (0.785 mL) and (*R*)-(−)-2-amino-1-butanol (0.50 mL, 3.91 mmol, 15.0 eq.). The vial was sealed and put on heating block 25h at 170 °C. After cooling, the mixture was diluted in THF and the precipitate in the mixture was filtered, washed with H_2O and Et_2O to give **(181)** (0.011, 9%) as a white solid.

Example 4.173: Synthesis of (*S*)-2-((3-cyclopropyl-8-(pyridazin-3-ylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino)butan-1-ol (182)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.75)** (0.100 g, 0.348 mmol, 1.0 eq.), cineol (0.785 mL) and (*S*)-(+)-2-amino-1-butanol (0.50 mL, 5.214 mmol, 15.0 eq.). The vial was sealed and put on heating block 23h at 170 °C. After cooling, the mixture was diluted in THF and concentrated with SiO_2 to make solid deposit then directly purified by flash chromatography with DCM/MeOH (98/2 to 91/9) as eluent to give a moiety with **(182)** and an impurity which was concentrated. The residue was solubilised with DCM and the white solid in the mixture was filtrated, washed with H_2O and Et_2O to give **(182)** (0.019 g, 16 %) as a white solid.

Example 4.174: Synthesis of 3-cyclopropyl-*N8*-(6-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (183)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.81)** (0.090 g, 0.28 mmol, 1.0 eq.), NMP (1.0 mL) and 3-aminopentane (0.33 mL, 2.84 mmol, 10.0 eq.). The vial was sealed and put on heating block 20 h at 160 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(183)** (0.045 g, 43 %) as a white solid.

Example 4.175: Synthesis of 3-cyclopropyl-*N8*-(2-methoxypyridin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (184)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.82)** (0.090 g, 0.28 mmol, 1.0 eq.), NMP (1.0 mL) and 3-aminopentane (0.33 mL, 2.84 mmol, 10.0 eq.). The vial was sealed and put on heating block 20 h at 160 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(184)** (0.015 g, 14 %) as a yellow crystalline solid.

Example 4.176: Synthesis of (2*R*)-2-[[3-cyclopropyl-8-[2-(2-pyridyl)ethylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol (185)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.47)** (0.090 g, 0.29 mmol, 1.0 eq.), NMP (1.0 mL) and (*R*)-(−)-2-amino-1-butanol (0.28 mL, 2.86 mmol, 10.0 eq.). The vial was sealed and put on heating block 19 h at 170 °C. After cooling, the mixture was diluted in AcOEt (25.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x10.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 93/7) as eluent to give **(185)** (0.035 g, 33 %) as a light yellow solid.

Example 4.177: Synthesis of *N6*-benzyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (186)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.100 g, 0.33 mmol, 1.0 eq.), NMP (1.0 mL) and benzylamine (0.22 mL, 2.00 mmol, 6.0 eq.). The vial was sealed and put on heating block 20 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed two times with sat. NaCl + H_2O (3/1, 2x10.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(186)** (0.035 g, 33 %) as a light yellow solid.

Example 4.178: Synthesis of 3-cyclopropyl-*N6*-(4-methoxybenzyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (187)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.100 g, 0.33 mmol, 1.0 eq.), NMP (1.0 mL) and 4-methoxybenzylamine (0.32 mL, 2.00 mmol, 6.0 eq.). The vial was sealed and put on heating block 17 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed two times with sat. NaCl + H_2O (3/1, 3x10.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(187)** (0.080 g, 60 %) as a white solid.

Example 4.179: Synthesis of 3-cyclopropyl-*N6*-(4-methoxybenzyl)-*N6*-methyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (188)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.100 g, 0.33 mmol, 1.0 eq.), NMP (1.0 mL) and 1-(4-methoxyphenyl)-N-methylmethanamine (0.308 g, 2.00 mmol, 6.0 eq.). The vial was sealed and put on heating block 17 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed two times with sat. NaCl + H_2O (3/1, 3x10.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(188)** (0.100 g, 72 %) as a white solid.

Example 4.180: Synthesis of 3-cyclopropyl-*N6*-ethyl-*N6*-(4-methoxybenzyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (4.180)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.100 g, 0.33 mmol, 1.0 eq.), NMP (1.0 mL) and N-(4-methoxybenzyl)ethanamine (0.340 g, 2.00 mmol, 6.0 eq.). The vial was sealed and put on heating block 17 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed two times with sat. NaCl + H_2O (3/1, 3x10.0 mL), dried over $MgSO_4$, filtered,

concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(4.180)** (0.030 g, 21 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.98 (d, *J* = 6.9 Hz, 3H, $CH_{3\text{-}CH2}$), 1.07 (ddt, *J* = 26.3, 6.0, 2.9 Hz, 4H, $2xCH_{2\ cPr}$), 2.23 – 2.31 (m, 1H, H_{cPr}), 3.39 (q, *J* = 6.9 Hz, 2H, $CH_{2\text{-}CH3}$), 3.71 (s, 3H, OCH_3), 4.50 (s, 2H, $CH_{2\ PMB}$), 4.57 (d, *J* = 6.0 Hz, 2H, $CH_{2\ Bn}$), 5.62 (s, 1H, H_{Ar}), 6.77 – 6.86 (m, 2H, $2xH_{Ar}$), 7.10 – 7.18 (m, 2H, $2xH_{Ar}$), 7.22 – 7.28 (m, 1H, H_{Ar}), 7.30 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.72 (td, *J* = 7.7, 1.8 Hz, 1H, H_{Ar}), 7.99 (t, *J* = 6.1 Hz, 1H, NH), 8.47 (d, *J* = 4.8 Hz, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 5.3 (CH_{cPr}), 6.4 ($2xCH_{2\ cPr}$), 12.4 ($CH_{3\text{-}CH2}$), 42.9 ($CH_{2\text{-}CH3}$), 47.3 ($CH_{2\ Bn}$), 50.3 ($CH_{2\ PMB}$), 55.0 (OCH_3), 82.4 (CH_{Ar}), 113.7 ($2xCH_{Ar}$), 121.3 (CH_{Ar}), 122.3 (CH_{Ar}), 128.5 ($2xCH_{Ar}$), 130.6 (C_q), 136.9 (CH_{Ar}), 138.9 (C_q), 140.5 (C_q), 148.9 (CH_{Ar}), 149.9 (C_q), 155.6 (C_q), 157.6 (C_q), 158.2 (C_q).

MS (ESI+) : m/z calcd for $C_{24}H_{27}N_7O$: 430.23 [M+H]+, **found :** 430.42.

Example 4.181: Synthesis of 3-cyclopropyl-*N6*-methyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (219)

A solution of **(188)** (0.090 g, 0.22 mmol, 1.0 eq.) in DCM/TFA (9.0/3.0 mL) was stirred 1 h at room temperature. After completion, solvent was removed, the residu was taken up in DCM, washed with sat. Na_2CO_3 (10.0 mL) then aqueous layer was extracted twice wih DCM (2x5.0 mL). Organics layers were combined, dired over $MgSO_4$, filtered, concentrated and the residu was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(219)** (0.058 g, 91 %) as a white solid.

Example 4.182: Synthesis of 3-cyclopropyl-*N6*-ethyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (189)

A solution of **(4.180)** (0.020 g, 0.05 mmol, 1.0 eq.) in DCM/TFA (5.0/1.5 mL) was stirred 1 h at room temperature. After completion, solvent was removed, the residu was taken up in DCM, washed with sat. Na_2CO_3 (10.0 mL) then aqueous layer was extracted twice wih DCM (2x5.0 mL). Organics layers were combined, dired over $MgSO_4$, filtered, concentrated and the residu was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(189)** (0.011 g, 76 %) as a white solid.

Example 4.183: Synthesis of 3-cyclopropyl-*N6*-propyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (190)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.130 g, 0.43 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.36 mL, 4.32 mmol, 10.0 eq.). The vial was sealed and put on heating block 22 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed two times with sat. NaCl + H_2O (3/1, 2x10.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(190)** (0.035 g, 33 %) as a light yellow solid.

Example 4.184: Synthesis of *N6*-butyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (191)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.130 g, 0.43 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.43 mL, 4.32 mmol, 10.0 eq.). The vial was sealed and put on heating block 22 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed two times with sat. NaCl + H_2O (3/1, 2x10.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(191)** (0.055 g, 38 %) as a white solid.

Example 4.185: Synthesis of 3-cyclopropyl-*N6*-isopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (192)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.130 g, 0.43 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.37 mL, 4.32 mmol, 10.0 eq.). The vial was sealed and put on heating block 48 h at 160 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed two times with sat. NaCl + H_2O (3/1, 2x10.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(192)** (0.075 g, 54 %) as a white solid.

Example 4.186: Synthesis of *N6*-(sec-butyl)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (193)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.130 g, 0.43 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.46 mL, 3.66 mmol, 10.0 eq.). The vial was sealed and then put on heating block, 24 h at 180 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) and organic layer was washed three times with a mixture brine/water (3/1, 3x8 mL). Organic layer was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(193)** (0.060 g, 41 %) as a white solid.

Example 4.187: Synthesis of 3-cyclopropyl-*N6*-isobutyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (194)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.268 g, 3.66 mmol, 10.0 eq.). The vial was sealed and put on heating block 20 h 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(194)** (0.055 g, 45 %) as a white solid.

Example 4.188: Synthesis of *N6*-(tert-butyl)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (195)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.39 mL, 3.66 mmol, 10.0 eq.). The vial was sealed and put on heating block 65 h at 160 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(195)** (0.006 g, 5 %) as light brown solid.

Example 4.189: Synthesis of 3-cyclopropyl-*N6*-(2-ethylbutyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (196)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL), corresponding amine hydrochloride (0.268 g, 1.83 mmol, 5.0 eq.) and DIPEA (0.38 mL, 2.19 mmol, 6.0 eq.). The vial was sealed and put on heating block 20 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(196)** (0.036 g, 27 %) as a white solid.

Example 4.190: Synthesis of *N6*,3-dicyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (197)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.130 g, 0.43 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.30 mL, 4.32 mmol, 10.0 eq.). The vial was sealed and put on heating block 48 h at 160 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(197)** (0.020 g, 14 %) as a white solid.

Example 4.191: Synthesis of *N6*-cyclobutyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (198)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.130 g, 0.43 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.37 mL, 4.32 mmol, 10.0 eq.). The vial was sealed and put on heating block 20 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and

the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(198)** (0.045 g, 32 %) as a white solid.

Example 4.192: Synthesis of *N6*-cyclopentyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (199)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.36 mL, 3.66 mmol, 10.0 eq.). The vial was sealed and put on heating block 18 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **199** (0.057 g, 45 %) as a white solid.

Example 4.193: Synthesis of *N6*-cyclohexyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (200)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.42 mL, 3.66 mmol, 10.0 eq.). The vial was sealed and put on heating block 18 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(200)** (0.075 g, 56 %) as a white solid.

Example 4.194: Synthesis of *N6*-cycloheptyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (201)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.47 mL, 3.66 mmol, 10.0 eq.). The vial was sealed and put on heating block 18 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(201)** (0.049 g, 35 %) as a white solid.

Example 4.195: Synthesis of *N6*-((3s,5s,7s)-adamantan-1-yl)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (202)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.570 g, 3.66 mmol, 10.0 eq.). The vial was sealed and then put on heating block, 16 h at 170 °C. After cooling, the mixture was diluted in EtOAc (20.0 mL) and organic layer was washed three times with a mixture brine/water (3/1, 3x8 mL). Organic layer was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(202)** (0.012 g, 8 %) as a white solid.

Example 4.196: Synthesis of 3-cyclopropyl-*N6*-(cyclopropylmethyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (203)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.100 g, 0.33 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.29 mL, 3.32 mmol, 10.0 eq.). The vial was sealed and put on heating block 20 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(203)** (0.020 g, 14 %) as a white solid.

Example 4.197: Synthesis of *N6*-(cyclobutylmethyl)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (204)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.321 g, 3.32 mmol, 10.0 eq.). The vial was sealed and put on heating block 18 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(204)** (0.030 g, 23 %) as a white solid.

Example 4.198: Synthesis of 3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(spiro[3.3]heptan-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (205)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL), corresponding amine hydrochloride (0.284 g, 1.83 mmol, 5.0 eq.) and DIPEA (0.38 mL, 2.19 mmol, 6.0 eq.). The vial was sealed and put on heating block 65 h at 160 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(205)** (0.013 g, 9 %) as a white solid.

Example 4.199: Synthesis of 3-cyclopropyl-*N6*-((1-methylcyclobutyl)methyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (206)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.130 g, 0.43 mmol, 1.0 eq.), NMP (1.0 mL), corresponding amine hydrochloride (0.359 g, 2.59 mmol, 6.0 eq.) and DIPEA (0.53 mL, 3.03 mmol, 7.0 eq.). The vial was sealed and put on heating block 24 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(206)** (0.035 g, 22 %) as a white solid.

Example 4.200: Synthesis of 3-cyclopropyl-*N*-(pyridin-2-ylmethyl)-6-(pyrrolidin-1-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (220)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.080 g, 0.27 mmol, 1.0 eq.), NMP (0.8 mL) and corresponding amine (0.23 mL, 2.66 mmol, 10.0 eq.). The vial was sealed and then put on heating block, 3 h at 180 °C. After cooling, the mixture was poured on sat. $NaHCO_3$ (5.0 mL) and water (15.0 mL) and stirred 5 min. The precipitate was filtered off, washed with water then MeOH and Et_2O. The solid was dried under vacuum to give **(220)** (0.070 g, 78 %) as a white solid.

Example 4.201: Synthesis of 3-cyclopropyl-6-(1-piperidyl)-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (207)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.130 g, 0.33 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.0.33 mL, 3.33 mmol, 10.0 eq.). The vial was sealed and then put on heating block, 3 h at 180 °C. The reaction mixture was cooled and water (6.0 mL) was added. The precipitate was filtered, washed with water up to neutral pH then the solid was taken up in DCM. Organic filtrate was dried over MgSO4, filtered and concentrated to give **(207)** (0.090 g, 77 %) as a light grey solid.

Example 4.202: Synthesis of 3-cyclopropyl-*N6*-(furan-2-ylmethyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (208)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.299 g, 2.93 mmol, 8.0 eq.). The vial was sealed and put on heating block 21 h at 170 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed with water (20.0 mL). Aqueous layer was extracted twice with EtOAc (2x10.0 mL). Organics layers were combined, washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(208)** (0.045 g, 34 %) as a white solid.

Example 4.203: Synthesis of 3-cyclopropyl-*N6*-(furan-3-ylmethyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (209)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.299 g, 2.93 mmol, 8.0 eq.). The vial was sealed and put on heating block 21 h at 170 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(209)** (0.042 g, 32 %) as a white solid.

Example 4.204: Synthesis of 3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(thiophen-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (210)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.349 g, 2.93 mmol, 8.0 eq.). The vial was sealed and put on heating block 21 h at 170 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(210)** (0.050 g, 36 %) as a white solid.

Example 4.205: Synthesis of (*R*)-2-((3-cyclopropyl-8-((pyridin-2-ylmethyl)amino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino)butan-1-ol (211)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.35 mL, 3.66 mmol, 10.0 eq.). The vial was sealed and put on heating block 18 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(211)** (0.035 g, 27 %) as a light yellow solid.

Example 4.206: Synthesis of (*S*)-2-((3-cyclopropyl-8-((pyridin-2-ylmethyl)amino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino)butan-1-ol (212)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.35 mL, 3.66 mmol, 10.0 eq.). The vial was sealed and put on heating block 18 h at 180 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(212)** (0.055 g, 43 %) as a white solid.

Example 4.207: Synthesis of (*R*)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(tetrahydrofuran -3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (213)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.31 mL, 3.66 mmol, 10.0 eq.). The vial was sealed and put on heating block 16 h at 170 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(213)** (0.055 g, 43 %) as a white solid.

Example 4.208: Synthesis of (*R*)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(tetrahydro-*2H*-pyran-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (214)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL), corresponding amine hydrochloride (0.403 g, 2.93 mmol, 8.0 eq.) and DIPEA (0.58 mL, 3.29 mmol, 9.0 eq.). The vial was sealed and put on heating block 16 h at 170 °C. After cooling, the mixture was poured onto cold water (25.0 mL), stirred 10 min then the precipitate was filtered off, washed with cold water and taken up in DCM/MeOH (99/1). Organic filtrate was dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(214)** (0.008 g, 6 %) as a white solid.

Example 4.209: Synthesis of 3-cyclopropyl-*N8*-(6-methoxypyridazin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (215)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.84)** (0.080 g, 0.25 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.30 mL, 2.52 mmol, 10.0 eq.). The vial was sealed and put on heating block 18 h at 170 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(215)** (0.026 g, 28 %) as a beige solid.

Example 4.210: Synthesis of 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-3-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (216)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.85)** (0.065 g, 0.21 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.25 mL, 2.15 mmol, 10.0 eq.). The vial was sealed and put on heating block 15 h at 170 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(216)** (0.013 g, 17 %) as a light brown solid.

Example 4.211: Synthesis of 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-phenethyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (217)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.86)** (0.100 g, 0.32 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.38 mL, 3.19 mmol, 10.0 eq.). The vial was sealed and put on heating block 15 h at 170 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 97/3) as eluent to give **(217)** (0.013 g, 17 %) as a white cloudy oil.

Example 4.212: Synthesis of 3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(thiophen-3-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (218)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.24)** (0.110 g, 0.37 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.349 g, 2.93 mmol, 8.0 eq.). The vial was sealed and put on heating block 21 h at 170 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x8.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(218)** (0.055 g, 40 %) as a white solid.

Example 4.213: Synthesis of 3-isopropyl-*N8*-(2-methoxypyrimidin-4-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (221)

In a sealed vial 2-5 mL with a stir bar was charged **(3.92)** (0.080 g, 0.25 mmol, 1.0 eq.), dioxane (2.0 mL) and corresponding amine (0.23 mL, 2.00 mmol, 8.0 eq.). The vial was

sealed and then put on heating block 41 h at 150 °C. After cooling, the solvant was removed and the residue was purified directly by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(221)** (0.009 g, 10 %) as a white solid.

Example 4.214: Synthesis of 3-isopropyl-*N8*-(5-methoxypyrimidin-4-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (222)

In a sealed vial 2-5 mL with a stir bar was charged **(3.93)** (0.080 g, 0.25 mmol, 1.0 eq.), dioxane (2.0 mL) and corresponding amine (0.23 mL, 2.00 mmol, 8.0 eq.). The vial was sealed and then put on heating block 41 h at 150 °C. After cooling, the solvant was removed and the residue was purified directly by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(222)** (0.006 g, 6 %) as a white solid.

Example 4.215: Synthesis of 3-isopropyl-*N8*-(6-methoxypyrimidin-4-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (223)

In a sealed vial 2-5 mL with a stir bar was charged **(3.94)** (0.080 g, 0.25 mmol, 1.0 eq.), dioxane (2.0 mL) and corresponding amine (0.23 mL, 2.00 mmol, 8.0 eq.). The vial was sealed and then put on heating block 41 h at 150 °C. After cooling, the solvant was removed and the residue was purified directly by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(223)** (0.005 g, 5 %) as a light brown solid.

Example 4.216: Synthesis of 3-isopropyl-*N8*-(6-methoxypyridazin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (224)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.95)** (0.080 g, 0.25 mmol, 1.0 eq.), dioxane (2.0 mL) and 3-aminopentane (0.23 mL, 2.00 mmol, 8.0 eq.). The vial was sealed and then put on heating block, 41 h at 150 °C. After cooling, the mixture was concentrated and the residu was directly purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(224)** (0.006 g, 6 %) as a light yellow solid.

Example 4.217: Synthesis of 3-cyclopropyl-*N6*-(2-ethylbutyl)-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (225)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.75)** (0.080 g, 0.28 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.27 mL, 1.95 mmol, 7.0 eq.). The vial was

sealed and put on heating block 21 h at 170 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x6.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(225)** (0.062 g, 63 %) as a beige solid.

Example 4.218: Synthesis of 3-cyclopropyl-*N6*-(2-ethylbutyl)-*N8*-(6-methoxypyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (226)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.84)** (0.080 g, 0.28 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.27 mL, 1.95 mmol, 7.0 eq.). The vial was sealed and put on heating block 18 h at 150 °C. After cooling, the mixture was diluted in AcOEt (20.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x6.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(226)** (0.061 g, 34 %) as a white solid.

Example 4.219: Synthesis of *N6*-(2-ethylbutyl)-3-isopropyl-*N8*-(6-methoxypyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (229)

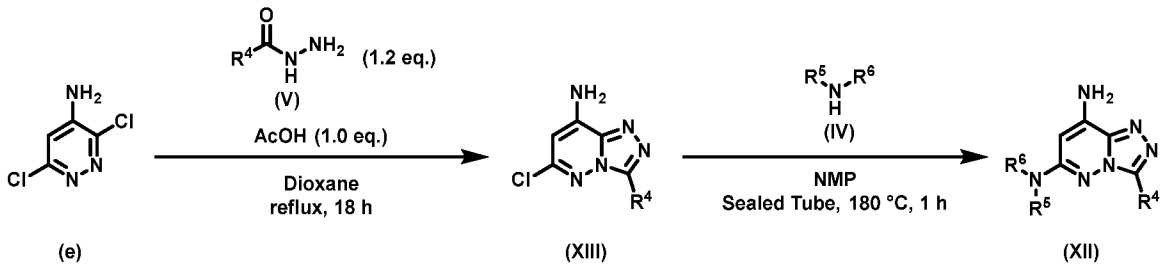
In a sealed tube 2 - 5 mL with a stir bar was charged **(3.95)** (0.080 g, 0.25 mmol, 1.0 eq.), NMP (1.0 mL) and corresponding amine (0.21 mL, 1.50 mmol, 6.0 eq.). The vial was sealed and put on heating block 22 h at 160 °C. After cooling, the mixture was diluted in AcOEt (15.0 mL) then organic layer was washed three times with sat. NaCl + H_2O (3/1, 3x6.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(229)** (0.020 g, 21 %) as a white solid.

Example 4.210: Synthesis of *N6*-(3-ethylpentyl)-3-isopropyl-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (230)

In a sealed tube 2 - 5 mL with a stir bar was charged **(3.60)** (0.040 g, 0.14 mmol, 1.0 eq.), dioxane (2.0 mL) and corresponding amine (0.100 mg, 83 mmol, 6.0 eq.). The vial was sealed and put on heating block 39 h at 160 °C. After cooling, the mixture was

concentrated and the residue was directly purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(230)** (0.023 g, 45 %) as a white solid.

Example 5: 8-amino-[1,2,4]triazolo[4,3-*b*]pyridazine-6-amine derivatives as illustrated in steps 1 and 2 of scheme 4



Example 5.1: Synthesis of 6-chloro-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (5.1)

To a solution of 3,6-dichloropyridazin-4-amine (3.600 g, 20.85 mmol, 1.0 eq.) in dioxane (84.0 mL), isobutyric acid hydrazide (2.582 g, 25.03 mmol, 1.2 eq.) and AcOH (1.20 mL, 20.85 mmol, 1.0 eq.) was added and refluxed during 18 h. The reaction mixture was concentrated and the resulting crude was triturated in water (100 mL), the solid was filtered off, washed with water until pH = 7 then Et_2O and dried under vacuum to give **(5.1)** (2.100 g, 48 %) as a white solid.

Rf (DCM/MeOH, 92/8) : 0.33

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.38 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 3.42 (hept, J = 7.0 Hz, 1H, H_{iPr}), 6.11 (s, 1H, H_{Ar}), 7.89 (s, 2H, NH_2).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 19.8 (2x$CH_{3\ iPr}$), 24.5 (CH_{iPr}), 93.7 (CH_{Ar}), 139.6 (C_q), 143.9 (C_q), 149.2 (C_q), 153.9 (C_q).

MS (ESI+) : m/z calcd for $C_8H_{10}ClN_5$: 212.1 [M+H]+, **found :** 212.1.

Example 5.2: Synthesis of 6-chloro-3-cyclopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine (5.2)

To a solution of 3,6-dichloropyridazin-4-amine (3.800 g, 22.01 mmol, 1.0 eq.) in dioxane (110.0 mL), cyclopropanecarbohydrazide (2.784 g, 26.42 mmol, 1.2 eq.) and AcOH (1.27 mL, 22.01 mmol, 1.0 eq.) was added and refluxed during 24 h. The reaction mixture was

concentrated and the resulting crude was triturated in water (150 mL), the solid was filtered off, washed with water until pH = 7 then the solid was taken up in MeOH and concentrated to remove water. The residue was purified by flash chromatography with DCM/MeOH (97/3 to 96/4) as eluent to give **(5.2)** with cyclopropanoic acid impurity. The resulting solid was triturated saturated $NaHCO_3$ to remove a maximum of acid, washed with water then Et_2O and dried under vacuum to give pure **(5.2)** (2.398 g, 52 %) as a white solid.

Rf (DCM/MeOH, 96/4) : 0.27

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.04 – 1.18 (m, 4H, 2x$CH_{2\ cPr}$), 2.31 (tt, *J* = 8.1, 5.3 Hz, 1H, H_{cPr}), 6.10 (s, 1H, H_{Ar}), 7.86 (s, 2H, NH_2).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 4.9 (CH_{cPr}), 7.2 (2x$CH_{2\ cPr}$), 93.7 (CH_{Ar}), 139.5 (C_q), 143.9 (C_q), 149.4 (C_q), 151.3 (C_q).

Example 5.3: Synthesis of (*2R*)-2-[(8-amino-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino]butan-1-ol (5.3) (illustrative intermediate compound (5.3), not reused in the following examples for preparing compounds of formula (I))

In a sealed tube 2 - 5 mL with a stir bar was charged **(5.1)** (0.100 g, 0.47 mmol, 1.0 eq.) and (*R*)-(-)-2-amino-1-butanol (1.34 mL, 14.17 mmol, 30.0 eq.). The vial was sealed and then put on heating block 22 h at 150 °C. After cooling, the mixture was diluted in EtOAc (15 mL) and organic layer was washed with water (2 x 30 mL). Aqueous layers were extracted twice with EtOAc (2 x 15 mL) then organic layers were combined, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (96/4 to 92/8) as eluent to give **(5.3)** (0.027 g, 22 %) as a pale yellow solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.88 (t, *J* = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.35 (d, *J* = 6.7 Hz, 6H, 2x$CH_{3\ iPr}$), 1.54 (ddt, *J* = 85.7, 14.1, 7.2 Hz, 2H, $CH_{2\text{-}CH3}$), 3.25 – 3.33 (m, 1H, H_{iPr}), 3.44 (dh, *J* = 22.0, 5.4 Hz, 2H, $CH_{2\text{-}OH}$), 3.66 (dq, *J* = 12.4, 6.7, 6.0 Hz, 1H, H_{Alk}), 4.58 (t, *J* = 5.4 Hz, 1H, OH), 5.64 (s, 1H, H_{Ar}), 6.29 (d, *J* = 7.8 Hz, 1H, NH), 6.61 (s, 2H, NH_2).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 10.6 ($CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.6 ($CH_{2\text{-}CH3}$), 24.8 (CH_{iPr}), 53.8 (CH_{Alk}), 62.2 ($CH_{2\text{-}OH}$), 86.6 (CH_{Ar}), 140.0 (C_q), 140.8 (C_q), 152.6 (C_q), 156.1 (C_q).

MS (ESI+) : m/z calcd for $C_{12}H_{20}N_6O$: 265.18 [M+H]+, **found :** 265.24.

Example 5.4: Synthesis of (2*R*)-2-[[6-[[(1*R*)-1-(hydroxymethyl)propyl]amino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]butan-1-ol (113)

In a sealed tube 2 - 5 mL with a stir bar was charged **(5.1)** (0.150 g, 0.71 mmol, 1.0 eq.), NMP (1.0 mL) and (*R*)-(-)-2-amino-1-butanol (1.03 mL, 10.63 mmol, 15.0 eq.). The vial was sealed and then put on heating block 22 h at 170 °C. After cooling, the mixture was diluted in EtOAc (15.0 mL), organic layer was washed with a mixture of brine/water (3/1, 3x20.0 mL), dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (96/4 to 92/8) as eluent to give the secondary compound **(113)** (0.018 g, 8 %) as a white solid.

Example 5.5: Synthesis of 3-isopropyl-*N6*-(3-methoxypropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (5.5) (illustrative intermediate compound (5.5), not reused in the following examples for preparing compounds of formula (I))

In a sealed tube 2 - 5 mL with a stir bar was charged **(5.1)** (0.150 g, 0.71 mmol, 1.0 eq.), NMP (1.0 mL) and 3-methoxypropylamine (0.98 mL, 10.63 mmol, 15.0 eq.). The vial was sealed and then put on heating block 5 h at 170 °C. After cooling, the mixture was diluted in EtOAc (15 mL) and organic layer was washed three times with a mixture brine/water (3/1, 3x20 mL). Organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography with DCM/MeOH (96/4 to 92/8) as eluent to give **(5.5)** (0.087 g, 46 %) as a white solid.

Rf (DCM/MeOH, 92/8) : 0.18

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.78 (p, *J* = 6.6 Hz, 2H, $CH_{2\text{-}CH2\text{-}NH}$), 3.19 (dd, *J* = 6.9, 5.4 Hz, 2H, $CH_{2\text{-}NH}$), 3.23 (s, 3H, OCH_3), 3.32 (p, *J* = 6.9 Hz, 1H, H_{iPr}), 3.39 (t, *J* = 6.3 Hz, 2H, $CH_{2\text{-}OCH3}$), 5.58 (s, 1H, H_{Ar}), 6.57 (t, *J* = 5.4 Hz, 1H, NH), 6.65 (s, 2H, NH_2).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.6 (2x$CH_{3\ iPr}$), 24.7 (CH_{iPr}), 28.6($CH_{2\text{-}CH2\text{-}NH}$), 37.9 ($CH_{2\text{-}NH}$), 57.8 ($OCH_3$), 69.8 ($CH_{2\text{-}OCH3}$), 86.2 ($CH_{Ar}$), 140.0 ($C_q$), 140.9 ($C_q$), 152.7 ($C_q$), 156.1 ($C_q$).

MS (ESI+) : m/z calcd for $C_{12}H_{20}N_6O$: 265.18 [M+H]+, **found :** 265.19.

Example 5.6: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (5.6)

In a microwave tube 2 - 5 mL with a stir bar was charged **(5.1)** (1.200 g, 4.72 mmol, 1.0 eq.), NMP (9.0 mL) and pentan-3-amine (9.9 mL, 85.0 mmol, 15.0 eq.). The vial was closed and then put on microwave cavity 3 h at 220 °C. After cooling, the mixture was concentrated, the oil residue was diluted in EtOAc (100 mL) then organic layer was washed four times with 50 mL of brine/water (3/1), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3 to 92/8) as eluent to give **(5.6)** (0.364 g, 24 %) as a beige solid.

Rf (DCM/MeOH, 98/2) : 0.34

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.86 (t, *J* = 7.3 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.35 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.39 – 1.62 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.27 – 3.35 (m, 1H, H_{iPr}), 3.59 (h, *J* = 6.9 Hz, 1H, H_{iPent}), 5.62 (s, 1H, H_{Ar}), 6.30 (d, *J* = 8.0 Hz, 1H, NH_{iPent}), 6.60 (s, 2H, NH_2).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 10.4 (2x$CH_{3\text{-}CH2}$), 19.5 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 26.3 (2x$CH_{2\text{-}CH3}$), 52.9 (CH_{iPent}), 86.5 (CH_{Ar}), 140.0 (C_q), 140.7 (C_q), 152.5 (C_q), 156.1 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{22}N_6$: 263.20 [M+H]+, **found** : 263.26.

Example 5.7: Synthesis of *N6*,*N8*-bis(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (114)

In a sealed tube 2 - 5 mL with a stir bar was charged **(5.1)** (0.200 g, 0.95 mmol, 1.0 eq.), NMP (2.20 mL) and 3-aminopentane (1.10 mL, 9.45 mmol, 10.0 eq.). The vial was sealed and then put on microwave 1 h at 240 °C After cooling, the reaction mixture was diluted in EtOAc (30 mL) and the resulting organic layer was washed three times with a mixture of brine/water (3/1, 3x20 mL) then dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3 to 94/6) as eluent to give the secondary compound **(114)** (0.095 g, 30 %) as a white crystalline solid.

Example 5.8: Synthesis of 3-cyclopropyl-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (5.8)

In a sealed tube 10 - 20 mL with a stir bar was charged **(5.2)** (1.200 g, 5.72 mmol, 1.0 eq.), NMP (5.7 mL) and 3-aminopentane (3.33 mL, 28.62 mmol, 5.0 eq.) then the vial was sealed and put on heating bloc : 200 °C, 17 h. After cooling, the mixture was poured onto

cold water (100.0 mL) and stirred 5 min. The resulting precipitate was filtered off and washed with water. The solid was taken up in THF to make solid deposit with Si_2O and purified by flash chromatography with DCM/MeOH (98/2 to 91/9) as eluent to give **(5.8)** (0.225 g, 15 %) as a yellow solid.

Rf (DCM/MeOH, 94/6) : 0.30

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.87 (t, *J* = 7.3 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 0.97 – 1.17 (m, 4H, 2x$CH_{2\ cPr}$), 1.36 – 1.63 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.23 (tt, *J* = 8.8, 5.1 Hz, 1H, H_{cPr}), 3.59 (h, *J* = 6.5 Hz, 1H, H_{iPent}), 5.61 (s, 1H, H_{Ar}), 6.30 (d, *J* = 8.1 Hz, 1H, NH_{iPent}), 6.58 (s, 2H, NH_2).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 5.4 (CH_{cPr}), 6.3 (2x$CH_{2\ cPr}$), 10.4 (2x$CH_{3\text{-}CH2}$), 26.3 (2x$CH_{2\text{-}CH3}$), 52.8 (CH_{iPent}), 86.5 (CH_{Ar}), 139.9 (C_q), 140.7 (C_q), 149.7 (C_q), 156.4 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{20}N_6$: 261.18 [M+H]+, **found :** 261.28.

Example 5.9: Synthesis of *N6*-(2-ethylbutyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (5.9)

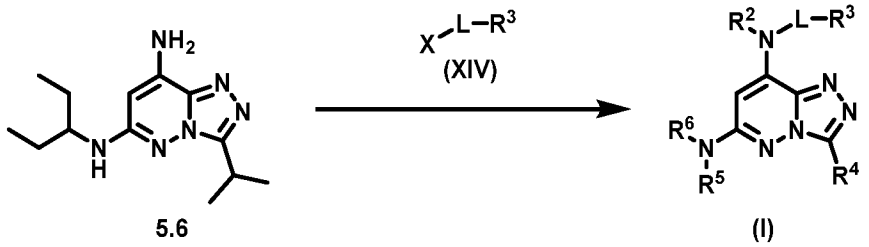
In a sealed tube 2 - 5 mL with a stir bar was charged **(5.1)** (0.400 g, 1.80 mmol, 1.0 eq.), NMP (1.8 mL) and corresponding amine (1.23 mL, 8.98 mmol, 5.0 eq.). The vial was sealed and put on heating block 21 h at 160 °C. After cooling, the mixture was diluted in AcOEt (30.0 mL) then organic layer was washed three times with sat. NH_4Cl + H_2O (3/1, 3x5.0 mL), dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(5.9)** (0.209 g, 46 %) as a white solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.88 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.25 – 1.34 (m, 4H, 2x$CH_{2\text{-}CH3}$), 1.36 (d, *J* = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.52 (p, *J* = 6.2 Hz, 1H, $H_{C\text{-}CH2\text{-}NH}$), 3.10 (t, *J* = 6.0 Hz, 2H, $CH_{2\text{-}NH}$), 3.25 - 3.32 (m, 1H, H_{iPr}), 5.61 (s, 1H, H_{Ar}), 6.55 (t, *J* = 5.7 Hz, 1H, $NH_{\text{-}CH2}$), 6.61 (s, 2H, NH_2).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 10.9 (2x$CH_{3\text{-}CH2}$), 19.6 (2x$CH_{3\ iPr}$), 23.5 (2x$CH_{2\text{-}CH3}$), 24.7 (CH_{iPr}), 39.8 ($CH_{\text{-}CH2\text{-}NH}$), 43.4 ($CH_{2\text{-}NH}$), 86.3 ($CH_{Ar}$), 140.0 ($C_q$), 140.8 ($C_q$), 152.6 ($C_q$), 156.3 ($C_q$).

MS (ESI+) : m/z calcd for $C_{14}H_{24}N_6$: 277.21 [M+H]+, **found** : 277.30.

Example 6: [1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine derivatives, as illustrated in step 3 of scheme 4



5.6 (I)

Example 6.1: Synthesis of *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]benzamide (96)

To a solution of **(5.6)** (0.075 g, 0.29 mmol, 1.0 eq.) in dry ACN (1 mL), DMAP (0.035 g, 0.29 mmol, 1.0 eq.), DIPEA (0.07 mL, 0.40 mmol, 1.4 eq.) then corresponding acyle chloride (0.04 mL, 0.34 mmol, 1.2 eq.) was added and the mixture was refluxed on 2 h. After cooling, the mixture was concentrated, taken up in a minimum amount of DCM/MeOH (98/2) and purified directly by flash chromatography with DCM/MeOH (98/2) as eluent to give **(96)** (0.073 g, 70 %) as a white solid.

Example 6.1: Synthesis of *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]pyridine-2-carboxamide (97)

To a suspension of **(5.6)** (0.090 g, 0.34 mmol, 1.0 eq.) in dry THF (6.0 mL), NaH 60% suspended in mineral oil (0.033 g, 0.82 mmol, 2.4 eq.) was added and the mixture was stirred 10 min at room temperature. Pyridine-2-carbonyl chloride hydrochloride (0.076 g, 0.41 mmol, 1.2 eq.) was added and the mixture was stirred 1.2 h at room temperature. After completion, saturated NH_4Cl (2.0 mL), water (2.0 mL) and EtOAc (6.0 mL) was added and the reaction mixture was vigorously stirred 5 min. Aqueous layer was extracted twice with EtOAC (2 x 10 mL) then organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 97/3) as eluent to give **(97)** (0.019 g, 15 %) as a white solid.

Example 6.3: Synthesis of *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]-2-phenyl-acetamide (98)

Under inert gas, to a solution of **(5.6)** (0.085 g, 0.32 mmol, 1.0 eq.) in dry THF (3.2 mL), was added NaH 60% suspended in mineral oil (0.026 g, 0.65 mmol, 2.0 eq.). The mixture was stirred 5 min at room temperature then corresponding acetyl chloride (0.05 mL, 0.39 mmol, 1.2 eq.) was added and stirred 1.6 h at room temperature. After completion, a mixture of 2 mL of saturated NH_4Cl and 0.5 mL of water was added then EtOAc (3.0 mL). The mixture was vigorously stirred during 5 min then layers were separated. Aqueous layer was extracted twice with EtOAc (2 x 2.0 mL), organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 97/3) as eluent to give **(98)** (0.050 g, 41 %) as a pale yellow solid.

Example 6.4: Synthesis of 2-(3-pyridyl)acetyl chloride hydrochloride (6.4)

To a solution of 2-(pyridin-3-yl)acetic acid hydrochloride (0.500 g, 2.74 mmol, 1.0 eq.) in dry DCM (27.0 mL), DMF (0.01 mL, 0.14 mmol, 0.05 eq.) then oxalyle chloride (0.30 mL, 3.56 mmol, 1.3 eq.) were added and the mixture was stirred 19 h at room temperature. After completion, THF was added (50.0 mL) then the resulting precipitate was filtered off, washed with THF and dried under vacuum to give the title compound **(6.4)** (0.445 g, 85 %) as a black solid. The compound would be used without other purification.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 4.02 (d, J = 16.7 Hz, 2H, $CH_{2\text{-}CO}$), 8.03 – 8.16 (m, 1H, H_{Ar}), 8.63 (d, J = 8.1 Hz, 1H, H_{Ar}), 8.80 (t, J = 5.7 Hz, 1H, H_{Ar}), 8.88 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-d_6) δ : N.D.

Example 6.5: Synthesis of *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]-2-(3-pyridyl)acetamide (168)

Under inert gaz, to a solution of **(5.6)** (0.100 g, 0.39 mmol, 1.0 eq.) in dry THF (11.5 mL), NaH 60% in mineral oil (0.061 g, 1.52 mmol, 4.0 eq.) was added and the mixture was stirred 15 min at room temperature. The compound **(6.4)** (0.110 g, 0.57 mmol, 1.5 eq.) was added and the mixture was stirred 3 h at room temperature. After completion, sat. NH_4Cl (10.0 mL), H_2O (5.0 mL) and EtOAc (10.0 mL) was added and the mixture was vigorously stirred 5 min. Layers were separated and aqueous layer was extracted twice with EtOAc (2x10.0 mL), organivs layers were combined, dried over $MgSO_4$, filtered, concentrated and the residu was purified by flash chromatography with EtOAc/MeOH (100/0 to 95/5) as eluent to give **(168)** (0.052 g, 36 %) as a white solid.

Example 6.6: Synthesis of ethyl *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]carbamate (99)

Under inert gas, to a solution of **(5.6)** (0.070 g, 0.25 mmol, 1.0 eq.) in dry THF (3.0 mL) was added NaH 60% suspended in mineral oil (0.012 g, 0.30 mmol, 1.2 eq.). The mixture was stirred 5 min at room temperature then corresponding chloroformate (0.034 g, 0.30 mmol, 1.1 eq.) was added and stirred 1.5 h at room temperature. After completion, 2 mL of saturated NH_4Cl and 0.5 mL of water were added then EtOAc (4.0 mL). The mixture was vigorously stirred during 5 min then layers were separated. Aqueous layer was extracted twice with EtOAc (2 x 2.0 mL), organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2 to 95/5) as eluent to give **99** (0.045 g, 53 %) as a white solid.

Example 6.7: Synthesis of phenyl *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]carbamate (100)

Under inert gas, to a solution of **(5.6)** (0.100 g, 0.38 mmol, 1.0 eq.) in dry THF (3.0 mL) was added NaH 60% suspended in mineral oil (0.023 g, 0.57 mmol, 1.5 eq.). The mixture was stirred 10 min at room temperature then corresponding chloroformate (0.069 g, 0.42 mmol, 1.1 eq.) was added and stirred 5.5 h at room temperature. After completion, 2.5 mL of saturated NH_4Cl and 1.0 mL of water were added then EtOAc (5.0 mL). The mixture was vigorously stirred during 5 min then layers were separated. Aqueous layer was extracted twice with EtOAc (2 x 5.0 mL), organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **(100)** (0.075 g, 51 %) as a white solid.

Example 6.8: Synthesis of 3-chloro-5-methoxypyridazine (6.8)

To a solution of 3,5-dichloropyridazine (1.000 g, 6.38 mmol, 1.0 eq.) in MeOH (33.0 mL), MeONa (0.399 g, 7.01 mmol, 1.1 eq.) was added and the mixture was stirred 18 h at room temperature. The mixture was concentrated then the residue was taken up in DCM, solid was filtered off, washed with DCM and the filtrate was concentrated and directly purified by flash chromatography with DCM/EtOAc (100/0 to 80/20) as eluent to give **(6.8)** (0.520 g, 56 %) as a light yellow solid.

Rf (DCM, 100%) : 0.22

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 3.94 (s, 3H, $CH_{3\text{-}O}$), 7.54 (d, *J* = 2.6 Hz, 1H, H_{Ar}), 9.00 (d, *J* = 2.6 Hz, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 56.6 ($CH_{3\text{-}O}$), 110.4 (CH_{Ar}), 144.0 (CH_{Ar}), 156.1 (C_q), 159.2 (C_q).

MS (ESI+) : m/z calcd for $C_5H_5ClN_2O$: 145.0 [M+H]+, **found :** 144.9

Example 6.9: Synthesis of 3-isopropyl-*N8*-(5-methoxypyridazin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (162)

Under inert gas, in a sealed tube 2 - 5 mL with a stir bar was charged **(5.6)** (0.050 g, 0.19 mmol, 1.0 eq.), 3-chloro-5-methoxypyridazine **(6.8)** (0.030 g, 0.21 mmol, 1.1 eq.), Cs_2CO_3 (0.094 g, 0.29 mmol, 1.5 eq.), $Pd(OAc)_2$ (0.003 g, 0.015 mmol, 0.08 eq.) and Xantphos (0.018 g, 0.030 mmol, 0.16 eq.). Dioxane (2.0 mL) degased 5min with argon was added then the tube was sealed and put on heating block 16 h at 110 °C. After cooling, the mixture was diluted with a little amount of DCM/MeOH (95/5) and SiO_2 was added to make solid deposit then directly purified by flash chromatography with DCM/MeOH (98/2 to 94/6) as eluent to give **(162)** (0.015 g, 34 %) as a light yellow solid.

Example 6.10: Synthesis of *N8*-(6-chloropyridazin-3-yl)-3-isopropyl-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (227)

Under inert gas, to a solution of **(5.6)** (0.075 g, 0.29 mmol, 1.0 eq.) in dry THF (3.0 mL), was added NaH 60% suspended in mineral oil (0.023 g, 0.57 mmol, 2.0 eq.). The mixture was stirred 5 min at room temperature then 3,6-dichloropyridazine (0.063 g, 0.40 mmol, 1.4 eq.) was added and the mixture was stirred 4.5 h at room temperature. After completion, saturated NH_4Cl solution (1.0 mL) and DCM (10.0 mL) were added and the mixture was vigorously stirred during 5 min. The precipitate was filtered off, washed with DCM then organic filtrate was dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(227)** (0.050 g, 47 %) as a white solid.

Example 6.11: Synthesis of 3-isopropyl-*N8*-(6-(methoxy-*d3*)pyridazin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (231)

In a sealed tube 10 - 20 mL with a stir bar was charged dry THF (6.0 mL), CD_3OD (0.12 mL, 2.84 mmol, 32.0 eq.) and NaH 60% suspended in mineral oil (0.106 g, 2.66 mmol, 30.0 eq.). The mixture was stirred 10 min at room temperature then **(227)** (0.035 g, 0.09 mmol, 1.0 eq.) was added. The tube was sealed and put on heating block 16 h at 150 °C. After cooling, saturated NH_4Cl solution (2.0 mL), H_2O (0.5 mL) and EtOAc (4.0 mL) were added and the mixture was vigorously stirred during 5 min. Layers were separated and aqueous layer was extracted twice with EtOAc (2x3.0 mL). Organic layers were combined, dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/EtOAc (30/70 to 10/90) as eluent to give **(231)** (0.025 g, 75 %) as a white solid.

Example 6.12: Synthesis of *N8*-(2-chloropyrimidin-4-yl)-3-isopropyl-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (228)

Under inert gas, to a solution of **(5.6)** (0.075 g, 0.29 mmol, 1.0 eq.) in dry THF (3.0 mL), was added NaH 60% suspended in mineral oil (0.023 g, 0.57 mmol, 2.0 eq.). The mixture was stirred 5 min at room temperature then 2,4-dichloropyrimidine (0.060 g, 0.40 mmol, 1.4 eq.) was added and the mixture was stirred 2 h at room temperature. TLC control show two products, saturated NH_4Cl solution (1.0 mL), H_2O (0.3 mL) and EtOAc (3.0 mL) were added and the mixture was vigorously stirred during 5 min. Layers were separated and aqueous layer was extracted twice with EtOAc (2x3.0 mL). Organic layers were combined, dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 95/5) as eluent to give **(228)** (0.046 g, 43 %) as a light yellow solid.

Example 6.13: Synthesis of *N8*-(6-chloropyridazin-3-yl)-*N6*-(2-ethylbutyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (232)

Under inert gas, to a solution of **(5.9)** (0.110 g, 0.40 mmol, 1.0 eq.) in dry THF (10.0 mL), was added NaH 60% suspended in mineral oil (0.040 g, 0.99 mmol, 2.5 eq.). The mixture was stirred 5 min at room temperature then 3,6-dichloropyridazine (0.087 g, 0.56 mmol, 1.4 eq.) was added and the mixture was stirred 4.5 h at room temperature. After completion, saturated NH_4Cl solution (6.0 mL), H_2O (2.0 mL) and EtOAc (10.0 mL) were added and the mixture was vigorously stirred during 5 min. Layers were separated and

aqueous layer was extracted with EtOAc (3x10.0 mL). Organic layers were combined, dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(232)** (0.020 g, 13 %) as a light yellow solid.

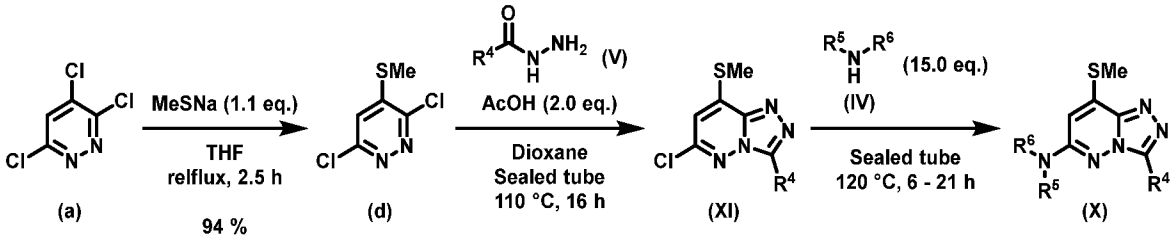
Example 6.14: Synthesis of *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]-2-(2-pyridyl)acetamide (233)

To a solution of **(5.6)** (0.100 g, 0.39 mmol, 1.0 eq.) and 2-(pyridin-2-yl)acetic acid hydrochloride (0.050 g, 0.27 mmol, 1.02 eq.) in DMF (2.0 mL), HATU (0.186 g, 0.48 mmol, 1.8 eq.) then DIPEA (0.13 mL, 0.72 mmol, 2.7 eq.) were added and the mixture was stirred 21 h at room temperature. The mixture was poured onto saturated $NaHCO_3$ (15.0 mL) then aqueous layer was extracted with EtOAc (3x10.0 mL). Organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with EtOAc/MeOH (100/0 to 95/5) as eluent to give impure compound **(233)**. Another purification was carried out with DCM/MeOH (97/3) to give **(233)** (0.016 g, 16 %) as a beige solid.

Example 6.15: Synthesis of *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]-2-(4-pyridyl)acetamide (234)

To a solution of **(5.6)** (0.070 g, 0.37 mmol, 1.0 eq.) and 2-(pyridin-4-yl)acetic acid hydrochloride (0.073 g, 0.40 mmol, 1.5 eq.) in DMF (2.5 mL), HATU (0.186 g, 0.48 mmol, 1.8 eq.) then DIPEA (0.16 mL, 0.93 mmol, 3.5 eq.) were added and the mixture was stirred 24 h at room temperature. The mixture was poured onto saturated $NaHCO_3$ (15.0 mL) then aqueous layer was extracted with EtOAc (3x10.0 mL). Organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash chromatography with DCM/MeOH (98/2 to 94/6) to give **(234)** (0.020 g, 20 %) as a yellow solid.

Example 7: 8-methylsulfanyl-[1,2,4]triazolo[4,3-*b*]pyridazine derivatives, as illustrated in steps 1 to 3 of scheme 3



Example 7.1: Synthesis of 3,6-dichloro-4-methylsulfanyl-pyridazine (d)

To a solution of 3,4,6-trichloropyridazine (4.000 g, 21.8 mmol, 1.0 eq.) in THF (43 mL), MeSNa (1.775 mL, 24.0 mmol, 1.1 eq.) was added and the mixture was refluxed 2.5 h. After cooling, $MgSO_4$ was added and the mixture was filtered, the solid was washed with THF then the filtrate was concentrated to give **(d)** (4.000 g, 94 %) as a white solid.

Rf (DCM, 100 %) : 0.46

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 2.63 (s, 3H, SCH_3), 7.76 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 13.6 (CH_3), 124.1 (CH_{Ar}), 147.5 (C_q), 152.1 (C_q), 154.8 (C_q).

MS (ESI+) : m/z calcd for $C_5H_4Cl_2N_2S$: 195.0 [M+H]+, **found :** 195.0.

Example 7.2: Synthesis of 6-chloro-8-methylsulfanyl-[1,2,4]triazolo[4,3-*b*]pyridazine (7.2)

In a 10 - 20 mL vial with a stir bar was charged **(d)** (1.250 g, 6.41 mmol, 1.0 eq.), dioxane (6.4 mL), formohydrazide (0.462 g, 7.69 mmol, 1.2 eq.) and AcOH (0.74 mL, 12.82 mmol, 2.0 eq.). The vial was sealed than put on heating bloc, 16 h at 110°C. After cooling, MeOH (5 mL) was added to solubilise the reaction mixture then it was concentrated with silica and directly purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **7.2** (0.210 g, 16 %) as a beige solid.

Rf (DCM, 100%) : 0.23.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 2.65 (s, 3H, $CH_{3\text{-}S}$), 8.09 (s, 1H, H_{Ar}), 9.57 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : N.D.

MS (ESI+) : m/z calcd for $C_6H_5N_4ClOS$: 201.0 [M+H]+, **found :** N.D.

Example 7.3: Synthesis of 6-chloro-3-isopropyl-8-methylsulfanyl-[1,2,4]triazolo[4,3-*b*]pyridazine (7.3)

In a 10 - 20 mL vial with a stir bar was charged **(d)** (1.250 g, 7.69 mmol, 1.0 eq.), dioxane (6.4 mL), corresponding hydrazide (0.952 g, 9.23 mmol, 1.2 eq.) and AcOH (0.89 mL, 15.38 mmol, 2.0 eq.). The vial was sealed than put on heating bloc, 16 h at 110°C. After cooling, MeOH (5 mL) and Na_2CO_3 (1.223 g, 11.53 mmol, 1.5 eq.) was added to solubilise and neutralise the reaction mixture then it was concentrated with silica and directly purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **7.3** (0.810 g, 43 %) as a beige solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.40 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 2.64 (s, 3H, SCH_3), 3.47 (hept, *J* = 7.0 Hz, 1H, H_{iPr}), 8.03 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 14.5 (SCH_3), 19.8 (2x$CH_{3\ iPr}$), 24.3 (CH_{iPr}), 117.2 (CH_{Ar}), 134.7 (C_q), 143.8 (C_q), 146.3 (C_q), 152.3 (C_q).

MS (ESI+) : m/z calcd for $C_9H_{11}ClN_4S$: 243.0 [M+H]+, **found :** 243.1.

Example 7.4: Synthesis of *N*-(1-ethylpropyl)-8-methylsulfanyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-amine (7.4)

In a 2 - 5 mL vial with a stir bar was charged **(7.2)** (0.150 g, 0.75 mmol, 1.0 eq.), 3-aminopentane (1.32 mL, 11.21 mmol, 15.0 eq.). The vial was sealed and then put on heating block, 6 h at 120 °C. After cooling, the mixture was diluted in THF (15.0 mL), the solid was filtered, washed with THF and the filtrate was concentrated. The residu was purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **7.4** (0.130 g, 69 %) as a white solid.

Rf (DCM/MeOH, 96/4) : 0.57

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.86 (t, *J* = 7.4 Hz, 6H (2x$CH_{3\text{-}CH2}$), 1.52 – 1.70 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.63 (s, 3H, SCH_3), 3.81 (h, *J* = 6.8 Hz, 1H, H_{iPent}), 5.95 (d, *J* = 8.4 Hz, 1H, NH_{iPent}), 7.76 (s, 1H, H_{Ar}), 9.05 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 10.5 (2x$CH_{3\text{-}CH2}$), 14.5 (SCH_3), 25.8 (2x$CH_{2\text{-}CH3}$), 54.2 (CH_{iPent}), 115.8 (CH_{Ar}), 129.3 (C_q), 137.4 (CH_{Ar}), 142.1 (C_q), 151.1 (C_q).

MS (ESI+) : m/z calcd for $C_{11}H_{17}N_5S$: 252.13 [M+H]+, **found :** 252.14.

Example 7.5: Synthesis of *N*-(1-ethylpropyl)-3-isopropyl-8-methylsulfanyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-amine (7.5)

A vial 2 - 5 mL with a stir bar was charged **(7.3)** (0.500 g, 2.06 mmol, 1.0 eq.), 3-aminopentane (3.64 mL, 30.90 mmol, 15.0 eq.). The vial was sealed and then put on heating block, 21 h at 120 °C. After cooling, the mixture was diluted in THF (15.0 mL), the solid was filtered, washed with THF and the filtrate was concentrated. The residu was purified by flash chromatography with DCM/MeOH (99/1 to 96/4) as eluent to give **(7.5)** (0.590 g, 98 %) as a white solid.

Rf (DCM/MeOH, 96/4) : 0.47

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.88 (t, *J* = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.38 (d, *J* = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.53 – 1.73 (m, 4H, 2x$CH_{2\text{-}CH3}$), 2.62 (s, 3H, SCH_3), 3.33 – 3.40 (m, 1H, H_{iPr}), 3.78 (dtd, *J* = 13.2, 7.7, 5.4 Hz, 1H, H_{iPent}), 5.96 (d, *J* = 8.1 Hz, 1H, NH_{Alk}), 7.71 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 10.7 (2x$CH_{3\text{-}CH2}$), 14.6 (SCH_3), 19.4 (2x$CH_{3\ iPr}$), 24.7 (CH_{iPr}), 25.9 (2x$CH_{2\text{-}CH3}$), 54.7 (CH_{iPent}), 116.7 (CH_{Ar}), 127.6 (C_q), 142.9 (C_q), 150.3 (C_q), 151.3 (C_q).

MS (ESI+) : m/z calcd for $C_{14}H_{23}N_5S$: 294.17 [M+H]+, **found :** 294.27.

Example 7.6: Synthesis of 3-isopropyl-8-methylsulfanyl-*N*-[(*3R*)-tetrahydropyran-3-yl]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-amine (7.6)

In a 10 - 20 mL vial with a stir bar was charged **(7.3)** (0.300 g, 0.93 mmol, 1.0 eq.), corresponding amine hydrochloride (0.772 g, 5.61 mmol, 4.5 eq.) and DIPEA (1.18 mL, 6.54 mmo, 5.5 eq.). The vial was sealed and then put on heating block, 18 h at 120 °C. After cooling, EtOAc (10.0 mL) and water (10.0 mL) was added and the mixture was vigorously stirred 5 min. Aqueous layer was extracted twice with EtOAc (2 x 10.0 mL) then organics layers were combined, washed with brine (20.0 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (100/0 to 97/3) as eluent to give **(7.6)** (0.240 g, 64 %) as a beige solid.

Rf (DCM/MeOH, 96.4) : 0.09

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 1.38 (dd, *J* = 7.0, 2.7 Hz, 6H, 2x$CH_{3\ iPr}$), 1.61 (dt, *J* = 9.3, 4.1 Hz, 1H, $_{CH2\text{-}H(CH2)\text{-}CH2}$), 1.69 (dt, *J* = 13.5, 4.1 Hz, 1H, $_{CH2\text{-}H(CH2)\text{-}CH2}$), 1.75 – 1.87 (m, 1H, $_{CH\text{-}H(CH2)\text{-}CH2}$), 1.95 (d, *J* = 6.8 Hz, 1H, $_{CH\text{-}H(CH2)\text{-}CH2}$), 2.62 (s, 3H, SCH_3), 3.37 (m,

3H, H_{iPr} & $_{O}$-$H_{(CH2)-CH\ THP}$ & $_{O}$-$H_{(CH2)-CH2}$), 3.73 (dt, *J* = 11.5, 4.1 Hz, 1H, $_{O}$-$H_{(CH2)-CH2}$), 3.92 (m, 2H, H_{THP} & $_{O}$-$H_{(CH2)-CH\ THP}$), 6.04 (d, *J* = 7.3 Hz, 1H, NH_{Alk}), 7.76 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 14.6 (SCH_3), 19.5 ($CH_{3\ iPr}$), 19.5 ($CH_{3\ iPr}$), 24.4 ($CH_{2\ THP}$), 24.7 (CH_{iPr}), 27.7 ($CH_{2\ THP}$), 47.7 (CH_{THP}), 67.2 ($CH_{2\ THP}$), 69.3 ($CH_{2\ THP}$), 117.1 (CH_{Ar}), 127.6 (C_q), 142.9 (C_q), 149.5 (C_q), 151.5 (C_q).

MS (ESI+) : m/z calcd for $C_{14}H_{21}N_5OS$: 308.15 [M+H]+, **found :** 308.24.

Example 7.7: Synthesis of (*2R*)-2-[(3-isopropyl-8-methylsulfanyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino]butan-1-ol (7.7)

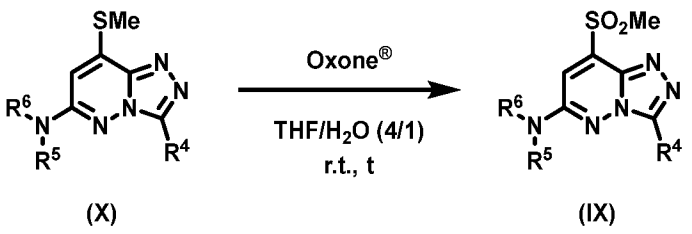
A solution of **(7.3)** (0.250 g, 1.02 mmol, 1.0 eq.) and (2*R*)-2-aminobutan-1-ol (0.98 mL, 10.20 mmol, 10.0 eq.) was heated 45 min at 120 °C. After cooling, the mixture was poured onto water (20 mL) then HCl 1M (20 mL) was added. Aqueous layer was extracted three times with DCM (3x15 mL), organics layers were combined, dried over $MgSO_4$, filtered, concentrated then purified by flash chromatography with DCM/MeOH (99/1 to 96/5) as eluent to give **(7.7)** (0.100 g, 83 %) as a pale pink solid.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.90 (t, *J* = 7.4 Hz, 3H, $CH_{3\text{-}CH2}$), 1.38 (dd, *J* = 7.0, 4.7 Hz, 6H, 2x$CH_{3\ iPr}$), 1.59 – 1.73 (m, 2H, $CH_{2\text{-}CH3}$), 2.62 (s, 3H, SCH_3), 3.37 (p, *J* = 7.0 Hz, 1H, H_{iPr}), 3.57 (dq, *J* = 12.9, 5.5 Hz, 2H, $CH_{2\text{-}OH}$), 3.83 (dtd, *J* = 11.7, 6.7, 4.9 Hz, 1H, $H_{C\text{-}NH}$), 4.84 (t, *J* = 5.4 Hz, 1H, OH), 5.84 (d, *J* = 7.6 Hz, 1H, NH), 7.76 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 10.6 ($CH_{3\text{-}CH2}$), 14.7 (SCH_3), 19.4 ($CH_{3\ iPr}$), 19.5 ($CH_{3\ iPr}$), 23.0 ($CH_{2\text{-}CH3}$), 24.7 (CH_{iPr}), 54.8 ($CH_{\text{-}NH}$), 61.4 ($CH_{2\text{-}OH}$), 117.3 (CH_{Ar}), 127.4 (C_q), 142.9 (C_q), 150.0 (C_q), 151.4 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{21}N_5OS$: 296.15 [M+H]+, **found :** 296.22.

<u>Example 8</u>: 8-methylsulfonyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-amine derivatives



(X) (IX)

Example 8.1: Synthesis of *N*-(1-ethylpropyl)-3-isopropyl-8-methylsulfonyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-amine (8.1)

To a solution of **(7.5)** (0.500 g, 1.70 mmol, 1.0 eq.) in THF/H_2O (4/1, 30 mL) was added Oxone (1.728 g, 5.62 mmol, 3.3 eq.). The reaction mixture was stirred 16 h at room temperature then brine (5 mL) was added. Aqueous layer was extracted twice with EtOAc (2 x 10 mL), orgnics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 97/3) as eluent to give **(8.1)** (0.500 g, 90 %) as a pale yellow solid.

Rf (DCM/MeOH, 94/6) : 0.62.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 0.92 (t, J = 7.4 Hz, 6H, 2x$CH_{3\text{-}CH2}$), 1.41 (d, J = 7.0 Hz, 6H, 2x$CH_{3\ iPr}$), 1.59 – 1.72 (m, 4H, 2x$CH_{2\text{-}CH3}$), 3.41 – 3.49 (m, 4H, H_{iPr} & $CH_{3\text{-}SO2}$), 3.82 (h, J = 6.3 Hz, 1H, H_{iPent}), 6.41 (d, J = 7.5 Hz, 1H, NH_{Alk}), 8.56 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-d_6) δ : 10.2 (2x$CH_{3\text{-}CH2}$), 19.3 (2x$CH_{3\ iPr}$), 24.8 (CH_{iPr}), 25.5 (2x$CH_{2\text{-}CH3}$), 42.8 ($CH_{3\text{-}SO2}$), 54.1 (CH_{iPent}), 124.7 (C_q), 129.0 (CH_{Ar}), 141.5 (C_q), 148.2 (C_q), 153.4 (C_q).

MS (ESI+) : m/z calcd for $C_{14}H_{23}N_5O_2S$: 326.16 [M+H]+, **found :** 326.25.

Example 8.2: Synthesis of 3-isopropyl-8-methylsulfonyl-*N*-[(*3R*)-tetrahydropyran-3-yl]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-amine (8.2)

To a solution of **(7.6)** (0.715 g, 2.33 mmol, 1.0 eq.) in THF (37 mL) was added Oxone (2.361 g, 7.68 mmol, 3.3 eq.) and water (9 mL). The mixture was stirred 18 h at room temperature then NaCl was added to give two phases. Aqueous layer was extracted twice with EtOAc (2x10 mL) and organic layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (97/3 to 95/5) as eluent to give **(8.2)** (0.520 g, 66 %) as a pale yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ : 1.41 (d, J = 6.9 Hz, 6H, 2x$CH_{3\ iPr}$), 1.51 – 1.78 (m, 2H, $_{CH2}$-$CH_{2\text{-}CH2}$), 1.82 – 2.00 (m, 2H, $_{CH}$-$CH_{2\text{-}CH2}$), 3.40 – 3.51 (m, 4H, SO_2CH_3 & H_{iPr}), 3.54 – 3.59 (m, 1H, $_{O}$-$H_{(CH2)\text{-}CH}$), 3.61 (t, J = 5.3 Hz, 2H, $_{O}$-$CH_{2\text{-}CH2}$), 3.86 (dd, J = 11.1, 3.0 Hz, 1H, $_{O}$-$H_{(CH2)\text{-}CH}$), 3.96 (tt, J = 6.5, 3.1 Hz, 1H, H_{THP}), 6.75 (d, J = 7.4 Hz, 1H, NH_{THP}), 8.59 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 19.4 (2x$CH_{3\ iPr}$), 23.0 ($CH_{2\ THP}$), 24.7 (CH_{iPr}), 26.7 ($CH_{2\ THP}$), 42.9 (SO_2CH_3), 46.9 (CH_{THP}), 67.3 ($CH_{2\ THP}$), 69.4 ($CH_{2\ THP}$), 124.6 (C_q), 129.3 (CH_{Ar}), 141.5 (C_q), 147.6 (C_q), 153.5 (C_q).

MS (ESI+) : m/z calcd for $C_{14}H_{21}N_5O_3S$: 340.14 [M+H]+, **found :** 340.19.

Example 8.3: Synthesis of (*2R*)-2-[(3-isopropyl-8-methylsulfonyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino]butan-1-ol (8.3)

To a solution of **(7.7)** (0.720 g, 2.44 mmol, 1.0 eq.) in THF/H_2O (4/1, 45.0 mL) was added Oxone (2.472 g, 8.04 mmol, 3.3 eq.). The mixture was stirred 19 h at room temperature then brine (10.0 mL) and EtOAc (20.0 mL) was added to give two phases. Aqueous layer was extracted twice with EtOAc (2x10 mL) and organic layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (99/1 to 94/6) as eluent to give **(8.3)** (0.310 g, 39 %) as a yellow solid.

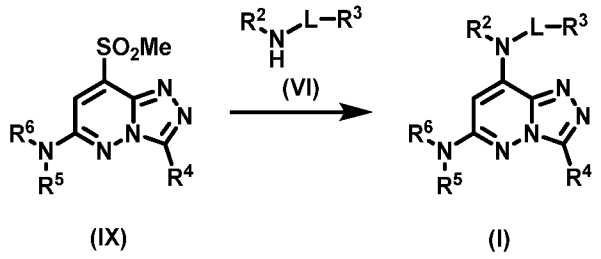
Rf (DCM/MeOH, 96/4) : 0.22

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ : 0.94 (t, *J* = 7.5 Hz, 3H, $CH_{3\text{-}CH2}$), 1.41 (dd, *J* = 7.0, 3.1 Hz, 6H, 2x$CH_{3\ iPr}$), 1.67 (pd, *J* = 7.1, 3.2 Hz, 2H, $CH_{2\text{-}CH3}$), 3.38 – 3.49 (m, 4H, H_{iPr} & $CH_{3\text{-}SO2}$), 3.54 – 3.67 (m, 2H, $CH_{2\text{-}OH}$), 3.85 (dtd, *J* = 11.1, 6.6, 4.4 Hz, 1H, H_{Alk}), 4.94 (t, *J* = 6.3 Hz, 1H, OH), 6.66 (d, *J* = 7.3 Hz, 1H, NH_{Alk}), 8.55 (s, 1H, H_{Ar}).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ : 10.4 ($CH_{3\text{-}CH2}$), 19.3 ($CH_{3\ iPr}$), 19.3 ($CH_{3\ iPr}$), 22.9 ($CH_{2\text{-}CH3}$), 24.7 (CH_{iPr}), 42.7 ($CH_{3\text{-}SO2}$), 54.4 (CH_{Alk}), 60.8 ($CH_{2\text{-}OH}$), 124.8 (C_q), 129.0 (CH_{Ar}), 141.5 (C_q), 148.2 (C_q), 153.4 (C_q).

MS (ESI+) : m/z calcd for $C_{13}H_{21}N_5O_3S$: 328.14 [M+H]+, **found :** 328.17.

<u>Example 9:</u> Synthesis of [1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine derivatives, as illustrated in step 5 of scheme 3



Example 9.1: Synthesis of *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[(2-methoxyphenyl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine (73)

A 2 - 5 mL vial with a stir bar was charged with **(8.1)** (0.100 g, 0.31 mmol, 1.0 eq.) and dioxane (0.3 mL) and corresponding amine (0.25 mL, 1.84 mmol, 6.0 eq.) then the vial was sealed and put on heating block 3 h at 110 °C. After cooling, the mixture was diluted in EtOAc (2.0 mL) then HCl 0.5M (3.8 mL) was added, stirred 5 min and layers were separated. Aqueous layer was extracted with EtOAc (2x3.0 mL) then organics layers were combined, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography with DCM/MeOH (98/2to 95/5) as eluent to give **(73)** (0.047 g, 40 %) as a white solid.

Example 10: Biological Activity

Example 10.1: ADORA3 inhibition potency

MATERIAL AND METHODS

Adenosine receptors antagonism assay (Eurofins)

The compounds of formula (I) were tested as potential antagonists on human recombinant A_3AR (expressed in HEK-293 cells) in an assay based on the use of an agonist radioligand, [^{125}I]-AB-MECA (0.15 nM) and 1 µM IB-MECA. Assays were carried out at r.t. for 120 min. Compounds were initially tested at three concentrations (0.01, 0.1, 1 µM). Active compounds were tested in duplicates in 8-point dose-response curves. IC_{50} values, which is the concentration causing a half-maximal inhibition of control specific binding, and Hill coefficients (nH) were determined by non-linear regression analysis of the competition curves generated with mean replicate values using Hill equation curve fitting. The inhibition constants (Ki) were calculated using the Cheng Prusoff equation. IB-MECA was used as a positive control (IC_{50}: 0.215 nM; Ki: 0.130 nM).

RESULTS

The A_3AR inhibition potency classification was done according to the following ranges of IC_{50} values:

Some compounds have an IC_{50} being inferior or equal to 1000 nM and superior or equal to 100 nM. These compounds correspond to the above-reported class **A**. Some

compounds have an IC_{50} inferior to 100 nM and superior or equal to 10 nM. These compounds correspond to the above-reported class **B**. Some compounds have an IC_{50} inferior to 10 nM and superior or equal to 1 nM. These compounds correspond to the above-reported class **C**. Some compounds have an IC_{50} inferior to 1 nM. These compounds correspond to the above-reported class **D**. Said letters **A** to **D** were used to quote the activity/efficacy of the compounds of the invention in the following **Table 3**.

Table 3: A_3AR inhibitory activities of the compounds of formula (I). IC_{50} values were calculated from dose-response curves. Compounds were further classified in terms of efficacy on A_3AR (increasing potency range: A to D).

Cpd N°	Potency Class A_3AR	Cpd N°	Potency Class A_3AR	Cpd N°	Potency Class A_3AR
1	**B**	**18**	**C**	**36**	**B**
2	**B**	**19**	**B**	**37**	**B**
3	**A**	**21**	**B**	**38**	**C**
4	**A**	**22**	**B**	**39**	**B**
5	**A**	**23**	**B**	**40**	**C**
6	**A**	**24**	**A**	**41**	**C**
8	**A**	**25**	**A**	**42**	**C**
9	**A**	**26**	**B**	**43**	**B**
10	**B**	**27**	**A**	**44**	**B**
11	**A**	**28**	**B**	**45**	**C**
12	**A**	**29**	**B**	**46**	**D**
13	**B**	**30**	**A**	**47**	**D**
14	**B**	**31**	**B**	**48**	**C**
15	**A**	**32**	**A**	**49**	**C**
16	**A**	**34**	**A**	**50**	**C**
17	**B**	**35**	**B**	**51**	**C**

Cpd N°	Potency Class A_3AR	Cpd N°	Potency Class A_3AR	Cpd N°	Potency Class A_3AR
52	C	78	B	104	B
53	C	79	A	105	B
54	B	80	C	106	A
55	B	81	B	107	B
56	C	82	C	108	A
57	A	83	D	109	A
58	B	84	C	110	B
59	C	85	C	111	B
60	B	86	D	112	A
61	B	87	D	113	A
62	C	88	C	114	C
63	C	89	B	115	A
64	B	90	C	116	A
65	A	91	C	117	B
66	B	92	B	118	C
67	C	93	C	119	B
68	C	94	C	120	A
69	B	95	C	121	B
70	A	96	B	122	B
71	B	97	B	123	B
72	B	98	D	124	B
73	C	99	C	125	A
74	B	100	C	126	C
75	C	101	B	127	B
76	C	102	B	128	A
77	B	103	B	129	A

Cpd N°	Potency Class A_3AR	Cpd N°	Potency Class A_3AR	Cpd N°	Potency Class A_3AR
130	C	157	B	184	B
131	B	158	D	185	B
132	B	159	D	186	C
133	A	160	C	187	C
134	B	162	D	188	A
136	B	163	B	189	B
137	A	164	D	190	B
138	B	165	C	191	C
139	A	166	C	192	C
140	B	167	C	193	C
141	A	168	D	194	B
142	A	169	B	195	C
143	B	170	C	196	C
144	A	171	D	197	B
145	A	172	D	198	C
146	B	173	D	199	C
147	D	174	D	200	C
148	D	175	D	201	C
149	C	176	C	202	C
150	D	177	D	203	B
151	D	178	D	204	C
152	B	179	B	205	C
153	D	180	D	206	C
154	D	181	D	207	A
155	D	182	D	208	C
156	C	183	D	209	C

Cpd N°	Potency Class A_3AR	Cpd N°	Potency Class A_3AR	Cpd N°	Potency Class A_3AR
210	**C**	**221**	**D**	**230**	**D**
211	**B**	**222**	**A**	**231**	**D**
212	**B**	**223**	**D**	**232**	**D**
213	**A**	**224**	**D**	**233**	**C**
214	**A**	**225**	**D**	**234**	**D**
215	**D**	**226**	**D**		
216	**C**	**227**	**D**		
217	**C**	**228**	**D**		
218	**C**	**229**	**D**		

CONCLUSION

Based on the previous results, it can be concluded that the compounds of formula (I) exert an inhibitory activity on A_3AR and thus are useful in the treatment of pathologies mediated by A_3AR. The most potent inhibitory activity on A_3AR is displayed by compounds (1), (2), (10), (13), (14), (17) to (19), (21) to (23), (26), (28), (29), (31), (35) to (56), (58) to (64), (66) to (69), (71) to (78), (80) to (105), (107), (110), (111), (114), (117) to (119), (121) to (124), (126), (127), (130) to (132), (134), (136), (138), (140), (143), (146) to (160), (162) to (187), (189) to (206), (208) to (212), (215) to (218), (221) and (223) to (234), in particular compounds (18), (38), (40) to (42), (45) to (53), (56), (59), (62), (63), (67), (68), (73), (75), (76), (80), (82) to (88), (90), (91), (93) to (95), (98) to (100), (114), (118), (126), (130), (147) to (151), (153) to (156), (158) to (160), (162), (164) to (168), (170) to (178), (180) to (183), (186), (187), (191) to (193), (195), (196), (198) to (202), (204) to (206), (208) to (210), (215) to (218), (221) and (223) to (234), and more particularly compounds (46), (47), (83), (86), (87), (98), (147), (148), (150), (151), (153) to (155), (158), (159), (162), (164), (168), (171) to (175), (177), (178), (180) to (183), (215), (221), (223) to (232) and (234).

Example 10.2: A_3R selectivity study on a panel of 168 GPCRs

MATERIAL AND METHODS

Compound (175) was tested at 1 μM as a potential agonist or antagonist of a panel of 168 GPCRs utilizing the PathHunter β-arrestin enzyme fragment complementation (EFC) technology (Eurofins – DiscoveRx – LeadHunter Discovery Services). In brief, when the GPCR is activated and β-Arrestin is recruited to the receptor, the two fragments of β-galactosidase complementation occurs, restoring β- galactosidase activity which is measured using chemiluminescent PathHunter® Detection Reagents. The tested compound can be evaluated as a potential agonist or, in the presnece of a specifi agonits of each GPCR, as a potential antagonist. Results are provided in reference to the assay performed in the absence of tested compound.

RESULTS

The results of an evaluation of the potential agonist or antagonist activity of compound (175) on 168 GPCRs are depicted in figure 2. As shown in figure 2, in the agonist mode (uneven numbers on X-axis), each GPCR was exposed to 0.1 μM of compound (175) only, while in the antagonist mode (even numbers on X-axis), each GPCR was exposed to its specific ligand and to 0.1 μM of compound (175). As demonstrated in figure 2, only A_3AR among 168 GPCRs was found to be fully inhibited by compound (175). All other GPCRs were not or marginally impacted by the presence of compound (175).

CONCLUSION

Based on the previous results, it can be concluded that compound (175) is only selective to A_3AR among 168 GPCRs.

Example 10.3: A_3R selectivity study among ARs and A_3R functional assay

MATERIAL AND METHODS

Adenosine receptors antagonism assay (Eurofins) for A_3R selectivity study

Compound (175) was tested as potential antagonist on human recombinant A_1AR (expressed in CHO cells) in an assay based on the use of an agonist radioligand, [^{3}H]-CCPA (1 nM) and 10 μM CPA. The assay was run at r.t. for 60 min in duplicates in 8-point dose-response curves.

Compound (175) was tested as potential antagonist on human recombinant $A_{2A}AR$ (expressed in HEK-293 cells) in an assay based on the use of an agonist radioligand, [^{3}H]-CGS (6 nM) and 10 μM NECA. The assay was run at r.t. for 120 min in duplicates in 8-point dose-response curves.

Compound (175) was tested as potential antagonist on human recombinant $A_{2B}AR$ (expressed in HEK-293 cells) in an assay based on the use of an agonist radioligand, [^{3}H]-CPX (5 nM) and 100 μM NECA. The assay was run at r.t. for 120 min in duplicates in 8-point dose-response curves.

IC_{50} values were calculated as described above in example 10.1 and the inhibition constants (Ki) were calculated using the Cheng Prusoff equation.

A_3AR functional assay

Human recombinant A_3AR expressed in CHO cells was used to evaluate compound (175) as a potential A_3AR agonist (no stimulus, 100 nM IB-MECA as positive control) or as a potential A_3AR antagonist (stimulation: 10 nM IB-MECA). Both assays were run for 20 min at 37°C, and cAMP levels measured by HTRF (homogeneous time resolved fluorescence) was used as an endpoint. The EC_{50} values (concentration producing a half-maximal response) and IC_{50} values (concentration causing a half-maximal inhibition of the control agonist response) were determined by non-linear regression analysis of the concentration-response curves generated with mean replicate values using Hill equation curve fitting.

RESULTS

The results of a study evaluating the selectivity of compound (175) towards various ARs are depicted in figure 3. Compound (175) was tested as a potential antagonist of all four adenosine receptors, A_1AR, $A_{2A}AR$, $A_{2B}AR$ and A_3AR. IC_{50} values (expressed in μM) were calculated from the dose-response curves. In figure 3, Ki values (expressed in μM) are shown in parentheses, in bold and italics. The A_3AR experiment was repeated three times independently.

The results of the A_3AR functional assay is depicted in figure 4. It clearly demonstrates that compound (175) is an inhibitor of A_3AR, at least up to 65% under these conditions.

CONCLUSION

As demonstrated in figure 3, compound (175) was found to be selective of A_3AR compared to other ARs notably A_1AR, $A_{2A}AR$ and $A_{2B}AR$.

As demonstrates in figure 4, compound (175) acts as a partial antagonist inhibitor of A_3A.

COMPLEMENTARY RESULTS

An antagonistic activity in a radioligand assay can be due to competition to the same site by either an agonist or an antagonist (inhibitor). Compound (175) was tested in a cellular functional assay using recombinant human A_3AR expressed in CHO cells in the absence of ligand (allowing the detection of an A_3AR agonist activity) or in the presence of an agonist (IB-MECA) (allowing the detection of an A_3AR antagonist activity). Assays were run for 20 min at 37°C and cAMP level measured by HTRF was used as an endpoint measure of the A_3AR activity. These experiments demonstrated that compound (175) behaves as an antagonist of A_3AR, displaying an IC_{50} belonging to class D as defined in example 10.1. In contrast no agonist effect was detected (concentrations of compound (175) tested: 1 nM to 3.3 µM) (data not shown).

As a conclusion, compounds of formula (I) according to the present invention act as antagonists of A_3AR.

Example 10.4: Otoprotective effects in *ex vivo* model of organs of Corti

MATERIAL AND METHODS

Biological reagents and organotypic culture

Organs of Corti were obtained from mice at the P0-P3 stage. Organs of Corti were cultured ex vivo for 24 h before addition of cisplatin (20 µM), gentamycin (100 µM) or neomycin (3 mM) with or without compound (175) (1 or 0.1 µM) added 2 hrs before the ototoxins. After 24 hrs incubation, outer and inner ciliated hair cells were stained with an antibody directed against myosine 7a.

RESULTS

As expected, in figure 5, the anticancer drug cisplatin (figure 5A), or the aminoglycosides antibiotics gentamycin (figure 5B) and neomycin (figure 5C) induced the death of hair cells in isolated organs of Corti cultured *ex vivo*. Co-incubation with compound (175) (0.1-1 µM) prevented cell death induced by these three ototoxic agents.

The levels of cell deaths between ototoxin- and ototoxin+ compound (175) were statistically different (data not shown).

CONCLUSION

Based on the previous results, it can be concluded that compound (175) displays potent otoprotective effects towards death hair cells of organs of Corti induced by ototoxic agents, in particlar platinum-based anticancer drugs such as cisplatin, or by antibiotics, in particular aminoglycosides such as gentamycin and neomycin.

Example 10.5: Anticancer activity of cisplatin

MATERIAL AND METHODS

The following cancer cell lines were used: A549 (human lung carcinoma), PANC-1 (human pancreatic cancer), and MDA-435 (human breast cancer). Cells were cultivated under classical conditions and exposed for 2 hours to different concentrations of compound (175) (0.3, 1, 3, 10 or 30 µM) or vehicle (DMSO), before addition of a dose range of cisplatin (1 to 100 µM). Cell survival was estimated by the MTS assay. IC_{50} values were calculated from the dose-response curves (figure 6) for each cancer cell lines A549, PANC-1 and MDA-435 respectively shown in figure 6-A, figure 6-B and figure 6-C.

RESULTS

Table 4: Effects of compound (175) on the antiproliferative activity of cisplatin. IC_{50} values were calculated from the dose response curves (figure 6) and are shown in µM.

	Cisplatine IC_{50} (µM)		
Compound (175) concentration (µM)	**Cancer cell line PANC-1**	**Cancer cell line A549**	**Cancer cell line MDA-435**
0.0	13.5	9.4	11.20
0.3	25.2	12.6	6.40
1.0	20.3	9.8	5.6
3.0	19.9	8.7	11.2
10.0	24.2	7.1	6.4
30.0	29.7	5.9	5.6

CONCLUSION

Based on the previous results, it can be concluded that compounds of formula (I), in particular compound (175), have modest effects on the sensitivity of three cancer cell lines to cisplatin. In PANC-1, a doubling of the cisplatin IC_{50} value was observed, while in A549 and MDA-435, cisplatin cytotoxicity was slightly increased. Moreover, compound (175) alone had no effect on these cancer cell lines (IC_{50} >100 µM).

Thus, compound (175) does not modify the susceptibility of various cancer cell lines to cisplatin.

Example 10.6: Antibiotic activity of aminoglycosides

MATERIAL AND METHODS

The following antibiotics were used: Gentamicin sulfate (Sigma G1264), Kanamycin sulfate (Gibco 11815-032), Neomycin sulfate (Gibco 21810-031), Streptomycin sulfate (Gibco 11860-038), and Tobramycin sulfate (Sigma T1783). Compound (175) and compound (147) were stored as 10 mM stock solutions in 100% DMSO.

The following *P. aeruginosa* strains were used for this experiment: PA-19660, PA-Xen5, PA-F1758, and PA-CH2678. PA-19660 was isolated from a septicaemia. PA-Xen5 derives from PA 19660, carrying a single stable copy of the *Photorhabdus luminescens* lux operon on the bacterial chromosome. PA-F1758 and PA-CH2678 were isolated from the respiratory tract of patients (Bactome collection). In addition, a *Staphylococcus aureus* Newman strain (originally isolated in 1952 from a human infection) was used.

(i) Bacterial growth

For each *P. aeruginosa* bacterial strain, a pre-culture was run by inoculating 5 mL of Mueller Hinton broth (MHB) with a single colony. For each antibiotic, a stock solution was prepared by diluting 5 mg of powder in 1 mL of physiological serum (Versylene®). A range of concentrations was prepared by 2-fold serial dilutions in water in 96 well-plates. 20 µL of each dilution were then transferred into 4-well plates (3 transparent + 1 black with transparent bottom). For each bacterial strain, an inoculum was prepared by diluting 25 µL of an overnight culture in 25 mL MHB. 180 µL of each inoculum were mixed with 20 µL of antibiotics in each well. The bioluminescent strain PA Xen5 was evaluated in the black wells plates to determine growth kinetics at 30°C during several hours (with measurements every 10 min), considering both OD (Optical density) absorbance (at 600

nm) and luminescence emission (at 450 nm), using the Mithras 2 (Berthold) incubator. PA-19660, PA-F1758, and PA-CH2678 were tested in transparent well-plates, with endpoint readings (absorbance at 600 nm) after 24 h incubation at 37°C under constant stirring at 180 rpm. At the end of the incubation, 5 µL from each well were deposited on an LB agar plate.

A PA-19660 bacterial pre-culture was prepared by inoculating 5 mL of MHB with a single colony. A range of compound (175) concentrations was prepared by 10-fold serial dilutions in water to test with bacteria in 96-well plates. The plate was incubated 30°C during 16 hours, with regular shaking and OD measurements at 600 nm were performed every 10 min.

(ii) Antibiograms

A PA-19660 bacterial pre-culture was prepared by inoculating 5 mL of MHB with a single colony of PA-19660. After an overnight incubation at 37°C under constant stirring (180 rpm), 5 µL of the pre-culture were diluted in 5 mL of MHB in two tubes. Then, 5 µL of either 100% DMSO or 10 mM compound (175) were added to reach a final concentration of 0.1% DMSO or 10 µM compound (175), respectively. After incubation at 37°C for 2 hours under constant stirring, two square plates (containing 4 mm thick MHB agar medium) were inoculated using the flooding method with each of the two inoculums. The excess of volume was discarded and plates were allowed to dry under the hood. An additional third plate was inoculated with an extemporaneous dilution of 5 µL of pre-culture in 5 mL of MHB (i.e. with bacteria without any pre-incubation). 16 blank disks (Oxoid blank antimicrobial susceptibility disks, ref CT0998B; 0.6 cm in diameter) were then carefully deposited on each agar plate. These disks were loaded with each of the five antibiotics stock solutions or water: Gentamicin (10 µg), Kanamycin (30 µg), Neomycin (30 µg), Streptomycin (10 µg), Tobramycin (10 µg). After a 20 hours incubation at 37°C, a picture of each plate was taken and the inhibition zones were measured.

RESULTS

(i) Bacterial growth

The antibiotics' Minimum Inhibitory Concentrations (MIC) and Minimum Bactericidal Concentrations (MBC) (Table 5), as well as the growth curves were

determined for each of the five antibiotics for the five *P. aeruginosa* strains (data not shown). Growth kinetics were determined for the PA-Xen5 strain.

The kinetic growth of all bacterial strains remained unchanged (same lag times, same profiles) in the presence of compound (175) up to 100 µM (data not shown). The absence of any effect was further confirmed with spots deposited on an agar plate (data not shown). Thus compound (175) does not have any detectable effect on the normal growth of *P. aeruginosa*.

The susceptibility of PA-19660 to Gentamicin (0.1 - 6.25 µg/mL), Kanamycin (6.25 - 400 µg/mL), Neomycin (0.39 - 25 µg/mL), Streptomycin (1.56 - 100 µg/mL), and Tobramycin (0.05 - 3.13 µg/mL) to the presence 10 µM compound (175) was next determined. Bacteria were pre-incubated with compound (175) for 2 hours at 37°C before addition of 7 escalating doses of each aminoglycoside (doses selected according to strain sensitivity to each antibiotic).

Table 5: Minimum Inhibitory Concentrations (MIC) and Minimum Bactericidal Concentrations (MBC) of several aminoglycosides following pre-incubation of *Pseudomonas aeruginosa* PA-19660 with either 0.1% DMSO or 10 µM compound (175). Average of triplicate determinations.

	MIC (µg/mL)		MBC (µg/mL)	
	DMSO	**Compound (175)**	**DMSO**	**Compound (175)**
Gentamicin	0.391	0.391	0.521	0.521
Kanamycin	12.5	20.8	16.67	33.33
Neomycin	1.563	1.563	1.563	1.563
Streptomycin	6.25	8.33	12.5	16.67
Tobramycin	0.195	0.195	0.195	0.326

The active doses (MIC and MBC) found for all tested antibiotics were very similar or identical whether bacteria were pre-incubated with 10 µM compound (175) or vehicle (DMSO), showing that compound (175) had no effect on the susceptibility of PA-19660 to aminoglycosides (Table 5).

(ii) Antibiograms

To confirm these results, experiments were repeated using standard antibiogram assays. PA-19660 was grown in plates in the presence of paper disks containing 10 µg

Gentamicin (G), 30 µg Kanamycin (K), 30 µg Neomycin (N), 10 µg Streptomycin (S), 10 µg Tobramycin (T) or water (W), without preincubation (A) or after a 2 hours incubation with 0.1% DMSO (vehicule) (B) or 10 µM of compound (175). After 20 hours incubation at 37 °C, the inhibition zones were measured (figures 7 and 8 left). Average of six independent determinations (vehicle, compound (175)) are shown in figure 8 left. No noticeable differences in the inhibition potency of the different aminoglycosides were observed between compound (175) and vehicle-treated *P. aeruginosa* PA-19660 bacteria.

Similar experiments on PA-19660 were run with compound (147) and average of three independent determinations (compound (147)) are shown in figure 8 left. Similar results were obtained, i.e. no impact of the compound (147) on the growth inhibition properties of aminoglycosides (figure 8 left).

Similar experiments were also run with compounds (175) and (147) by replacing *P. aeruginosa* (PA-19660 bacteria) by *Staphylococcus aureus* Newman (figure 8 right). Average of six independent determinations (vehicle, compound (175)) and three independent determinations (compound (147)) are shown in figure 8 right. Neither compound (175) nor compound (147) had any influence on the antibiotic properties of the five aminoglycosides (figure 8 right).

CONCLUSION

Based on the previous results, it can be concluded that compounds of formula (I), in particular compounds (175) and (147), do not modify the susceptibility of bacterial strains, in particular *Pseudomonas aeruginosa* and *Staphylococcus aureus*, to antibiotics, in particular aminoglycosides and more particularly Gentamicin, Kanamycin, Neomycin, Streptomycin and Tobramycin.

The present invention further relates to a pharmaceutical composition comprising at least one compound of formula (I) as defined above or any of its pharmaceutically acceptable salts, or at least any of compounds (1) to (234) as defined above or any of their pharmaceutically acceptable salts, and also at least one pharmaceutically acceptable excipient.

Pharmaceutical compositions of the invention can contain one or more compound(s) of the invention in any form described herein.

Still a further object of the present invention consists of the use of at least one compound of formula (I) as defined above, and compounds (1) to (234) as defined above, or one of their pharmaceutically acceptable salts according to the present invention for preparing a drug for preventing and/or treating diseases associated with A_3AR. According to a particular embodiment, the treatment is continuous or non-continuous.

A "continuous treatment" means a long-term treatment which can be implemented with various administration frequencies, such as once every day, every three days, once a week, or once every two weeks or once every month or by transdermal patch delivery.

According to one embodiment, the compound of formula (I), or any of its pharmaceutically acceptable salts, is administered at a dose varying from 0.1 to 1000 mg. in particular varying from 1 to 500 mg, or for example varying from 5 to 100 mg.

Another object of the invention relates to a therapeutic method for the treatment and/or for the prevention of diseases associated with A_3AR, and in particular for the treatment and/or for the prevention of ulcerative colitis, atopic dermatitis, glaucoma, asthma, liver fibrosis, kidney diseases in particular kidney fibrosis, nephropathy, acute kidney injury (AKI), chronic kidney disease (CKD) more particularly induced by ischemia and/or reperfusion injury, toxic nephropathy or myoglobinuria, diabetic kidney disease, kidney diseases induced by nephrotoxicity caused by therapeutic drugs, atherosclerosis, hypercholestemia, partial or a complete hearing loss induced by noise, acoustic trauma or ototoxic agents or conditions, and cancers developing under hypoxic conditions, in particular glioblastoma, consisting in administering to a patient in need thereof of a compound of formula (I) or any of its pharmaceutically acceptable salt or of at least any of compounds (1) to (234) as defined above, of any of their pharamecutically acceptable salt.

According to one embodiment, the invention relates to a therapeutic method for the treatment and/or for the prevention of hearing loss, in particular induced by ototoxic agents, as well as in the treatment and/or in the prevention of kidney diseases, in particular induced by nephrotoxicity, consisting in administering to a patient in need thereof of a compound of formula (I) or any of its pharmaceutically acceptable salt or of at least any of compounds (1) to (234) as defined above, of any of their pharamecutically acceptable salt.

According to one embodiment, the invention relates to a therapeutic method for the treatment and/or for the prevention of partial or a complete hearing loss, in particular

induced by noise, acoustic trauma or ototoxic agents or conditions, more particularly induced by ototoxic agents or conditions, consisting in administering to a patient in need thereof of a compound of formula (I) or any of its pharmaceutically acceptable salt or of at least any of compounds (1) to (234) as defined above, of any of their pharamecutically acceptable salt.

According to one embodiment, the invention relates to a therapeutic method for the treatment and/or for the prevention of partial or a complete hearing loss induced by ototoxic agents or conditions as described hereinafter, consisting in administering to a patient in need thereof of a compound of formula (I) or any of its pharmaceutically acceptable salt or of at least any of compounds (1) to (234) as defined above, of any of their pharamecutically acceptable salt.

As ototoxic agents, i.e. causing hear loss, the following may be cited:

- solvents, such as polyethylene glycol, propylene glycol or benzalkonium chloride;
- antibiotics, in particular topical and/or systemic antibiotics, more particularly aminoglycosides, macrolides or phenicol antibiotics, such as gentamycin, neomycin, tobramycin, kanamycin, nystatin, polymyxin B, amphotericin B, bacitracin or chloramphenicol;
- anticancer drugs, in particular platinum-based anticancer drugs, such as cisplatin or carboplatin,
- antiseptics, in particular acetic acid, alcohols such as ethanol, chlorhexidine, cresylate, gentian violet or povidone iodine;
- nonsteroidal anti-inflammatory drugs (NSAIDs), in particular salicylates, cyclodextrins, indomethacin, ibuprofen, phenylbutazone or paracetamol;
- topical combinations, in particular polymyxin/neomycin/hydrocortisone or ticarcilline/clavulanate;
- drugs for COVID-19, in particular lopinavir or ritonavir;
- antimalarial drugs, in particular quinine or chloroquine;
- cardiovascular drugs, in particular loop diuretics; or
- erectile dysfunction drugs, in particular phosphodiesterase type 5 (PDE-5) inhibitors.

According to one embodiment, the invention relates to a therapeutic method for the treatment and/or for the prevention of hearing loss being a partial or a complete hearing loss, in particular being induced by noise, acoustic trauma or ototoxic agents or conditions, more particularly platin-based anticancer drugs such as cisplatin or carboplatin, antibiotics, even more particularly macrolides or aminoglycosides such as gentamycin or neomycin, drugs for COVID-19 such as lopinavir or ritonavir, antimalarial drugs such as quinine or chloroquine, cardiovascular drugs such as loop diuretics, non-steroidal anti-inflammatory drugs such as salicylate or cyclodextrins, erectile dysfunction drugs such as phosphodiesterase type 5 inhibitors, consisting in administering to a patient in need thereof of a compound of formula (I) or any of its pharmaceutically acceptable salt or of at least any of compounds (1) to (234) as defined above, of any of their pharamecutically acceptable salt.

According to one embodiment, the invention relates to a therapeutic method for the treatment and/or for the prevention of kidney diseases, in particular selected from nephropathy, acute kidney injury (AKI), chronic kidney disease (CKD) more particularly induced by ischemia and/or reperfusion injury, toxic nephropathy or myoglobinuria, and diabetic kidney disease, or kidney diseases induced by nephrotoxicity caused by therapeutic drugs, consisting in administering to a patient in need thereof of a compound of formula (I) or any of its pharmaceutically acceptable salt or of at least any of compounds (1) to (234) as defined above, of any of their pharamecutically acceptable salt.

According to one embodiment, the invention relates to a therapeutic method for the treatment and/or for the prevention of kidney diseases induced by nephrotoxicity caused by therapeutic drugs as described hereinafter, consisting in administering to a patient in need thereof of a compound of formula (I) or any of its pharmaceutically acceptable salt or of at least any of compounds (1) to (234) as defined above, of any of their pharamecutically acceptable salt.

As therapeutic drugs causing nephrotoxicity, the following may be cited: acyclovir, ambisome, amikacin, aminoglycosides, antibiotics, amphotericin B, captopril, carboplatin, cefotaxime, ceftazidime, cefuroxime, cephalosporins, cidofovir, ciprofloxacin, cisplatin, colistimethate, cyclosporine, dapsone, enalaprilat, enalapril, Foscarnet, gadopentetate dimeglumine, gadoxetate, ganciclovir gentamicin, ibuprofen, ifosfamide, iodixanol, iohexol, iopamidol, ioversol, ketorolac, lisinopril, lithium, mesalamine,

methotrexate, nafcillin disodium, penicillins, piperacillin/tazobactam, piperacillin, rifampin, sirolimus, sulfasalazine, tacrolimus, ticarcillin/clavulanic acid, tobramycin, topiramate, valacyclovir, valganciclovir, vancomycin or zonisamide.

All combinations of doses, frequencies and treatment period are encompassed within the scope of the present invention.

Various sequences or cycles of administration respectively of the compound of formula (I) as defined herein above, a pharmaceutically acceptable salt thereof, prodrug thereof may be implemented within the framework of the present invention.

The compounds of formula (I) as defined above can be administered through any mode of administration such as, for example, intramuscular, intravenous. intranasal or oral route, transtympanic, intra-cochlear, transdermal patch, etc.

The inventive composition can further include one or more additives such as diluents, excipients, stabilizers and preservatives. Such additives are well known to those skilled in the art and are described notably in "*Ullmann's Encyclopedia of Industrial Chemistry, 6th Ed.*" (various editors, 1989-1998, Marcel Dekker) and in "*Pharmaceutical Dosage Forms and Drug Delivery Systems*" (ANSEL *et al,* 1994, WILLIAMS & WILKINS).

The aforementioned excipients are selected according to the dosage form and the desired mode of administration.

Compositions of this invention may be administered in any manner, including, but not limited to, orally, parenterally, sublingually, transdermally, vaginally, rectally, transmucosally, topically, intranasally via inhalation, via buccal or intranasal administration, or combinations thereof. Parenteral administration includes, but is not limited to, intravenous, intra-arterial, intra-peritoneal, subcutaneous, intramuscular, intra-thecal, and intra-articular. The compositions of this invention may also be administered in the form of an implant, which allows slow release of the compositions as well as a slow controlled i.v. infusion.

For example, a compound of formula (I) according to the present invention can be present in any pharmaceutical form which is suitable for enteral or parenteral administration, in association with appropriate excipients, for example in the form of plain

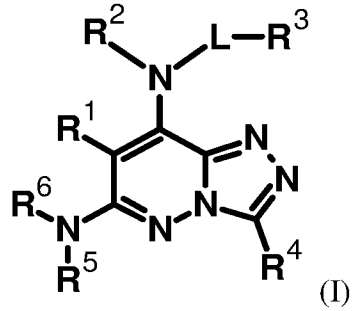
or coated tablets, hard gelatine, soft shell capsules and other capsules, suppositories, or drinkable, such as suspensions, syrups, or injectable solutions or suspensions.

In a particular embodiment, a compound of formula (I) according to the invention is administered orally.

Oral route of administration is in particular preferred in the prophylaxis or treatment aspect of the invention.

CLAIMS

1. A compound of formula (I) or any of its pharmaceutically acceptable salt



(I)

wherein

R¹ represents a hydrogen atom or a (C_1-C_6)alkyl group;

R² represents a hydrogen atom;

R³ represents

- a linear or branched (C_1-C_6)alkyl group, substituted by
  - one phenyl group, optionally substituted by at least one substituent selected from a -OR^7 group, a -NH_2 group, a halogen atom, a phenyl group and a (C_5-C_6)heteroaryl group,
  - one (C_6-C_{10})heteroaryl group, or
  - one -OR^7 group,
- a phenyl group or a phenyl group fused with a (C_4-C_6)cycloalkyl group; or
- a (C_5-C_6)heteroaryl group, optionally substituted by one to three substituents selected from a (C_1-C_4)alkyl group, a deuterated (C_1-C_4)alkyl group, a (C_1-C_4)alkoxy group, a deuterated (C_1-C_4)alkoxy group and a halogen atom, in particular a fluorine atom or a chlorine atom;

L represents a bond or a -CO- group;

or alternately **L** is a bond and **R²** and **R³** form together with the nitrogen atom bearing them a (C_5-C_6)heterocycloalkyl group containing at least a nitrogen atom fused with a phenyl group;

R⁴ represents a hydrogen atom, a linear or branched (C_1-C_6)alkyl group, a (C_3-C_6)cycloalkyl group, a (C_1-C_4)alkoxy group, a (C_5-C_6)heterocyclocalkyl group, a phenyl group, a (C_5-C_6)heteroaryl group or a -CF_3 group;

R⁵ represents a hydrogen atom or a (C_1-C_4)alkyl group;

R⁶ represents

- a linear or branched (C_1-C_8)alkyl group, optionally interrupted by one or two oxygen atoms and optionally substituted by
    - one phenyl group, optionally substituted by one or two substituents selected from a (C_1-C_4)alkyl group and a (C_1-C_4)alkoxy group,
    - one (C_3-C_8)cycloalkyl group, optionally substituted by one or two substituents selected from a halogen atom, a (C_1-C_4)alkyl group and a -OR^7 group,
    - one (C_5-C_6)heterocycloalkyl,
    - one (C_5-C_6)heteroaryl group, optionally substituted by one or two (C_1-C_6)alkyl group,
    - one or two -OR^7 groups,
    - one -SR^7 group,
    - one -C(O)NR^8R^9 group,
    - one -C(O)OR^{10} group, or
    - one -NHR^{11} group,
- a (C_3-C_7)cycloalkyl group, optionally substituted by one or two substituents selected from a halogen atom, a (C_1-C_4)alkyl group and a -OR^7 group,
- one bridged (C_6-C_{10})cycloalkyl group,
- one spiro(C_5-C_{11})bicyclic ring,
- a (C_5-C_6)heteroaryl group,
- a (C_5-C_6)heterocycloalkyl group, or
- a phenyl group fused with a (C_4-C_6)cycloalkyl group;

or **R^5** and **R^6** form together with the nitrogen atom bearing them a (C_5-C_6)heterocycloalkyl group;

R^7 represents a hydrogen atom, a (C_1-C_4)alkyl group or a deuterated (C_1-C_4)alkyl group;

R^8 and **R^9** independently represent a hydrogen atom or a (C_1-C_6)alkyl group;

R^{10} represents a (C_1-C_4)alkyl group; and

R^{11} represents a hydrogen atom or a -CO-(C_1-C_6)alkyl group;

provided that when NR^2LR^3 represents a benzylamino group, then R^4 does not represent a hydrogen atom.

2. The compound of formula (I) or any of its pharmaceutically acceptable salt as defined in claim 1, wherein **R**^{1} represents a hydrogen atom or a methyl group.

3. The compound of formula (I) or any of its pharmaceutically acceptable salt, as defined in claim 1 or 2, wherein

R^{2} represents a hydrogen atom;

R^{3} represents

- a linear or branched (C_1-C_6)alkyl group, substituted by
  - one phenyl group, optionally substituted by one substituent selected from a hydroxy group, a methoxy group, an amino group, a halogen atom, a phenyl group and a pyridyl group,
  - one pyridyl, one pyrazinyl, one pyrimidinyl or one pyridazinyl group, in particular one pyridyl, pyridazinyl or pyrimidinyl group, or one indolyl or isoindolyl group, in particular an indolyl group,
  - one hydroxy group,
  - one methoxy group, one deuterated methoxy group, or
  - a halogen atom, in particular a fluorine atom or a chlorine atom,
- a phenyl group or an indanyl group, or
- a pyridyl, a pyrazinyl, a pyrimidinyl or a pyridazinyl group, optionally substituted by one methoxy group or deuterated methoxy group, in particular a pyridyl group;

L represents a bond or a -CO- group;

or alternately **L** is a bond and **R**^{2} and **R**^{3} form together with the nitrogen atom bearing them an indolinyl, an isoindolinyl, a tetrahydroquinolinyl or a tetrahydroisoquinolinyl group, in particular an isoindolinyl or a tetrahydroisoquinolinyl group.

4. The compound of formula (I) or any of its pharmaceutically acceptable salt, as defined in any claim 1 to 3, wherein **R**^{4} represents a hydrogen atom, a linear or branched (C_1-C_5)alkyl group, a (C_3-C_6)cycloalkyl group, a phenyl group, a pyridyl group or a -CF_3 group.

5. The compound of formula (I) or any of its pharmaceutically acceptable salt, as defined in any claim 1 to 4, wherein

$\mathbf{R^5}$ represents a hydrogen atom or a (C_1-C_4) alkyl group, in particular a methyl group;

$\mathbf{R^6}$ represents

- a linear or branched (C_1-C_8)alkyl group, optionally interrupted by one or two oxygen atoms and optionally substituted by
  - one phenyl group, optionally substituted by one or two substituents selected from a methyl group and a methoxy group,
  - one (C_3-C_6)cycloalkyl group, optionally substituted by a methyl group,
  - one tetrahydropyranyl or one tetrahydrofuranyl group,
  - one pyrazolyl, imidazolyl, pyrimidinyl, pyrazinyl, pyridyl, furanyl or thienyl group, optionally substituted by one or two methyl group,
  - one or two hydroxy group or methoxy group,
  - one methylthio group,
  - one -$CONH_2$ group, one –$CONHCH_3$ group or one -$CON(CH_3)_2$ group,
  - one -$COOCH_3$ or one -$COOCH_2CH_3$ group, or
  - one -NH_2 group or one -$NCOCH_3$ group,
- a (C_3-C_7)cycloalkyl group, optionally substituted by one or two substituents selected from a halogen atom, a hydroxy group or a methoxy group,
- an adamantyl group,
- a spiro[3.3]heptanyl group,
- an imidazolyl group, optionally substituted by one or two methyl group,
- a morpholinyl group, a tetrahydropyranyl or a tetrahydrofuranyl group, or
- an indanyl group;

or $\mathbf{R^5}$ and $\mathbf{R^6}$ form together with the nitrogen atom bearing them a morpholinyl group or a piperidinyl group.

6. A compound, or any of its pharmaceutically acceptable salt, selected from

(1) (2*R*)-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(2) (2*S*)-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(3) 2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propane-1,3-diol,

(4) (2*R*,3*R*)-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol,

(5) (2*S*,3*S*)-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol,

(6) *N*-benzyl-3-isopropyl-6-morpholino-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine

(7) (2*S*)-3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propane-1,2-diol,

(8) *N*6-[2-[2-(2-aminoethoxy)ethoxy]ethyl]-*N8*-benzyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(9) 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propan-1-ol,

(10) *N8*-benzyl-3-isopropyl-*N6*-(3-methoxypropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(11) 2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]ethanol,

(12) *N8*-benzyl-3-isopropyl-*N6*-(2-methoxyethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(13) 4-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(14) *N8*-benzyl-3-isopropyl-*N6*-(4-methoxybutyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(15) 5-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]pentan-1-ol,

(16) *N8*-benzyl-3-isopropyl-*N6*-(5-methoxypentyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(17) *N8*-benzyl-3-isopropyl-*N6*-(3-methylsulfanylpropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(18) *N8*-benzyl-*N6*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(19) *N8*-benzyl-3-isopropyl-*N6*-[(3*R*)-tetrahydrofuran-3-yl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(20) *N8*-benzyl-3-cyclopentyl-*N6*-[(3*R*)-tetrahydrofuran-3-yl]-[1,2,4]triazolo[4,3-

b]pyridazine-6,8-diamine,

(21) *N8*-benzyl-3-isopropyl-*N6*-[(3*R*)-tetrahydropyran-3-yl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(22) *N8*-benzyl-3-isopropyl-*N6*-[(3*S*)-tetrahydropyran-3-yl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(23) *N8*-benzyl-3-isopropyl-*N6*-tetrahydropyran-4-yl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(24) *N*-[3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propyl]acetamide,

(25) 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propanamide,

(26) 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]-*N*-methyl-propanamide,

(27) 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]-*N*,*N*-dimethyl-propanamide,

(28) Methyl 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propanoate,

(29) ethyl 3-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]propanoate,

(30) (2*R*)-2-[[8-(benzylamino)-3-cyclopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(31) *N8*-benzyl-3-cyclopropyl-*N6*-(3-methoxypropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(32) *N8*-benzyl-*N6*-(3-methoxypropyl)-3-methyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(33) (2*R*)-2-[[8-(benzylamino)-3-methyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(34) *N8*-benzyl-*N6*-(3-methoxypropyl)-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(35) (2*R*)-2-[[8-(benzylamino)-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(36) *N8*-benzyl-*N6*-(3-methoxypropyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-

b]pyridazine-6,8-diamine,

(37) (*2R*)-2-[[8-(benzylamino)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(38) 2-[[[6-[[(*1R*)-1-(hydroxymethyl)propyl]amino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(39) 2-[[[3-isopropyl-6-(3-methoxypropylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(40) 2-[[[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(41) 3-[[[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(42) 4-[[[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(43) 2-[[[3-isopropyl-6-[[(3*R*)-tetrahydropyran-3-yl]amino]-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(44) 2-[[[3-isopropyl-6-(tetrahydropyran-4-ylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]methyl]phenol,

(45) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(46) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(2-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(47) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(3-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(48) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(4-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(49) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(4-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(50) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(3-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(51) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(52) *N6*-tert-butyl-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-

6,8-diamine,

(53) 3-isopropyl-*N8*-(2-pyridylmethyl)-*N6*-spiro[3.3]heptan-2-yl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(54) *N6*-(3,3-difluorocyclobutyl)-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(55) *N6*-(4,4-difluorocyclohexyl)-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(56) *N6*-benzyl-3-isopropyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(57) *N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(58) *N6*-(1-ethylpropyl)-3-methyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(59) 3-ethyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(60) *N6*-(1-ethylpropyl)-3-propyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(61) 3-tert-butyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(62) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(63) 3-cyclobutyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(64) 3-cyclopentyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(65) 3-cyclohexyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(66) *N6*-(1-ethylpropyl)-3-phenyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(67) *N6*-(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-3-sec-butyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(68) *N6*,3-bis(1-ethylpropyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-

6,8-diamine,

(69) *N6*-(1-ethylpropyl)-3-isobutyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(70) *N6*-(1-ethylpropyl)-3-(2-pyridyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(71) *N6*-(1-ethylpropyl)-3-(3-pyridyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(72) *N6*-(1-ethylpropyl)-3-(4-pyridyl)-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(73) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[(2-methoxyphenyl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(74) (*2R*)-2-[[8-[(4-aminophenyl)methylamino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(75) *N8*-[(4-aminophenyl)methyl]-*N6*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(76) *N8*-[(3-aminophenyl)methyl]-*N6*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(77) *N8*-[(2-aminophenyl)methyl]-*N6*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(78) *N6*-(1-ethylpropyl)-*N8*-(*1H*-indol-2-ylmethyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(79) *N*-(1-ethylpropyl)-8-isoindolin-2-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-amine,

(80) 8-(3,4-dihydro-*1H*-isoquinolin-2-yl)-*N*-(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-amine,

(81) *N6*-(1-ethylpropyl)-*N8*-indan-1-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(82) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(2-phenylethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(83) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(84) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[2-(3-pyridyl)ethyl]-[1,2,4]triazolo[4,3-

b]pyridazine-6,8-diamine,

(85) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[2-(4-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(86) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(87) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-[2-(3-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(88) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-[2-(4-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(89) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[3-(2-pyridyl)propyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(90) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[3-(3-pyridyl)propyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(91) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-[3-(4-pyridyl)propyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine

(92) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(pyrimidin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(93) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(pyrimidin-5-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(94) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(pyrazin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(95) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(pyridazin-3-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(96) *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]benzamide,

(97) *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]pyridine-2-carboxamide,

(98) *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]-2-phenyl-acetamide,

(99) ethyl *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]carbamate,

(100) phenyl *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-

yl]carbamate,

(101) (2*S*)-2-[[8-[(4-bromophenyl)methylamino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(102) (2*S*)-2-[[3-isopropyl-8-[(4-phenylphenyl)methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(103) (2*S*)-2-[[3-isopropyl-8-[[4-(4-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(104) (2*S*)-2-[[3-isopropyl-8-[[4-(3-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(105) (2*S*)-2-[[3-isopropyl-8-[[4-(2-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(106) (2*R*,3*R*)-2-[[8-[(4-bromophenyl)methylamino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol,

(107) (2*R*,3*R*)-2-[[3-isopropyl-8-[[4-(2-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol,

(108) (2*R*,3*R*)-2-[[3-isopropyl-8-[[4-(4-pyridyl)phenyl]methylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butane-1,3-diol,

(109) *N6,N8*-bis(3-methoxypropyl)-3-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(110) 3-cyclopropyl-*N6*,*N8*-bis(3-methoxypropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(111) *N6*,*N8*-bis(3-methoxypropyl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(112) 3-isopropyl-*N6*,*N8*-bis(2-methoxyethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(113) (2*R*)-2-[[6-[[(1*R*)-1-(hydroxymethyl)propyl]amino]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]amino]butan-1-ol,

(114) *N6*,*N8*-bis(1-ethylpropyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(115) (2*R*)-2-[[8-(benzylamino)-3-isopropyl-7-methyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(116) *N8*-[(4-bromophenyl)methyl]-3-isopropyl-*N6*-methyl-[1,2,4]triazolo[4,3-

b]pyridazine-6,8-diamine,

(117) *N8*-benzyl-*N6*-cyclobutyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(118) *N8*-benzyl-*N6*-cyclopentyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(119) *N8*-benzyl-*N6*-cyclohexyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(120) *N8*-benzyl-3-isopropyl-*N6*-(4-methoxycyclohexyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(121) *N8*-benzyl-*N6*-cycloheptyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(122) *N8*-benzyl-*N6*-(cyclopropylmethyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(123) *N8*-benzyl-*N6*-(cyclobutylmethyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(124) *N8*-benzyl-*N6*-(cyclohexylmethyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(125) *N8*-benzyl-3-isopropyl-*N6*-(tetrahydropyran-4-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(126) *N8*-benzyl-*N6*-(2-ethylbutyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(127) *N8*-benzyl-3-isopropyl-*N6*-(2-phenylethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(128) *N8*-benzyl-3-isopropyl-*N6*-(2-phenoxyethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(129) *N8*-benzyl-3-isopropyl-*N6*-[(1-methylimidazol-2-yl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(130) *N6*,*N8*-dibenzyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(131) *N8*-benzyl-3-isopropyl-*N6*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(132) *N8*-benzyl-3-isopropyl-*N6*-(3-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(133) *N8*-benzyl-3-isopropyl-*N6*-(4-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(134) racemic trans-2-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]cyclohexanol,

(135) racemic trans-4-[[8-(benzylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]cyclohexanol,

(136) *N8*-benzyl-3-isopropyl-*N6*-[(1-methylcyclohexyl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(137) *N6*-(1-adamantyl)-*N8*-benzyl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(138) *N8*-benzyl-*N6*-indan-2-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(139) *N8*-benzyl-3-isopropyl-*N6*-[(5-methylpyrazin-2-yl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(140) *N8*-benzyl-3-isopropyl-*N6*-[(1-methylpyrazol-4-yl)methyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(141) *N8*-benzyl-*N6*-[(3,5-dimethylphenyl)methyl]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(142) *N8*-benzyl-3-isopropyl-*N6*-(tetrahydrofuran-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(143) *N8*-benzyl-3-isopropyl-*N6*-(2-methylsulfanylethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(144) *N8*-benzyl-3-isopropyl-*N6*-(1-methylimidazol-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(145) *N8*-benzyl-*N6*-[(4,6-dimethylpyrimidin-2-yl)methyl]-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(146) *N8*-benzyl-*N6*-indan-1-yl-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(147) *N6*-(2-ethylbutyl)-3-isopropyl-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(148) 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(149) 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(150) 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(151) 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-5-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(152) 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(153) 3-isopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrazin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(154) 3-isopropyl-*N8*-(6-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(155) 3-isopropyl-*N8*-(5-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(156) 3-isopropyl-*N8*-(4-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(157) 3-isopropyl-*N8*-(3-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(158) 3-isopropyl-*N8*-(2-methoxypyridin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(159) 3-isopropyl-*N8*-(6-methoxypyridin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(160) isopropyl-*N8*-(5-methoxypyridin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(161) 3-isopropyl-*N*8-(4-methoxypyridin-3-yl)-*N*6-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(162) 3-isopropyl-*N8*-(5-methoxypyridazin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(163) (2*R*)-2-[[3-isopropyl-8-(2-pyridylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(164) *N6*-(2-ethylbutyl)-3-isopropyl-*N8*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(165) *N6*-cyclopentyl-3-isopropyl-*N8*-[2-(2-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(166) *N6*-(2-ethylbutyl)-3-isopropyl-*N8*-[2-(3-pyridyl)ethyl]-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(167) *N6*,*N8*-bis(2-ethylbutyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine

(168) *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]-2-(3-pyridyl)acetamide,

(169) (*2R*)-2-[[3-isopropyl-8-(2-pyridylmethylamino)imidazo[1,2-*b*]pyridazin-6-yl]amino]butan-1-ol,

(170) *N6*-(1-ethylpropyl)-3-isopropyl-*N8*-(3-phenylpropyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(171) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-phenyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(172) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-(2-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(173) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-(3-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(174) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-(4-pyridyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(175) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(176) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(177) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(178) 3-cyclopropyl-*N6*-(1-ethylpropyl)-*N8*-pyrimidin-5-yl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(179) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrimidin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(180) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyrazin-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(181) (*R*)-2-((3-cyclopropyl-8-(pyridazin-3-ylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-

yl)amino)butan-1-ol,

(182) (*S*)-2-((3-cyclopropyl-8-(pyridazin-3-ylamino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino)butan-1-ol,

(183) 3-cyclopropyl-*N8*-(6-methoxypyridin-2-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(184) 3-cyclopropyl-*N8*-(2-methoxypyridin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(185) (2*R*)-2-[[3-cyclopropyl-8-[2-(2-pyridyl)ethylamino]-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]amino]butan-1-ol,

(186) *N6*-benzyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(187) 3-cyclopropyl-*N6*-(4-methoxybenzyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(188) 3-cyclopropyl-*N6*-(4-methoxybenzyl)-*N6*-methyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(189) 3-cyclopropyl-*N6*-ethyl-*N8*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(190) 3-cyclopropyl-*N6*-propyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(191) *N6*-butyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(192) 3-cyclopropyl-*N6*-isopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(193) *N6*-(sec-butyl)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(194) 3-cyclopropyl-*N6*-isobutyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(195) *N6*-(tert-butyl)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(196) 3-cyclopropyl-*N6*-(2-ethylbutyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(197) *N6*,3-dicyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-

6,8-diamine,

(198) *N6*-cyclobutyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(199) *N6*-cyclopentyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(200) *N6*-cyclohexyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(201) *N6*-cycloheptyl-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(202) *N6*-((3s,5s,7s)-adamantan-1-yl)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(203) 3-cyclopropyl-*N6*-(cyclopropylmethyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(204) *N6*-(cyclobutylmethyl)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(205) 3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(spiro[3.3]heptan-2-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(206) 3-cyclopropyl-*N6*-((1-methylcyclobutyl)methyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(207) 3-cyclopropyl-6-(1-piperidyl)-*N*-(2-pyridylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine,

(208) 3-cyclopropyl-*N6*-(furan-2-ylmethyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(209) 3-cyclopropyl-*N6*-(furan-3-ylmethyl)-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(210) 3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(thiophen-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(211) (*R*)-2-((3-cyclopropyl-8-((pyridin-2-ylmethyl)amino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino)butan-1-ol,

(212) (*S*)-2-((3-cyclopropyl-8-((pyridin-2-ylmethyl)amino)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl)amino)butan-1-ol,

(213) (*R*)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(tetrahydrofuran -3-yl)-

[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(214) (*R*)-3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(tetrahydro-*2H*-pyran-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(215) 3-cyclopropyl-*N8*-(6-methoxypyridazin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(216) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-(pyridazin-3-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(217) 3-cyclopropyl-*N6*-(pentan-3-yl)-*N8*-phenethyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(218) 3-cyclopropyl-*N8*-(pyridin-2-ylmethyl)-*N6*-(thiophen-3-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(219) 3-cyclopropyl-*N6*-methyl-*N8*-(pyridin-2-ylmethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(220) 3-cyclopropyl-*N*-(pyridin-2-ylmethyl)-6-(pyrrolidin-1-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-8-amine,

(221) 3-isopropyl-*N8*-(2-methoxypyrimidin-4-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(222) 3-isopropyl-*N8*-(5-methoxypyrimidin-4-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(223) 3-isopropyl-*N8*-(6-methoxypyrimidin-4-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(224) 3-isopropyl-*N8*-(6-methoxypyridazin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(225) 3-cyclopropyl-*N6*-(2-ethylbutyl)-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(226) 3-cyclopropyl-*N6*-(2-ethylbutyl)-*N8*-(6-methoxypyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(227) *N8*-(6-chloropyridazin-3-yl)-3-isopropyl-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(228) *N8*-(2-chloropyrimidin-4-yl)-3-isopropyl-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(229) *N6*-(2-ethylbutyl)-3-isopropyl-*N8*-(6-methoxypyridazin-3-yl)-[1,2,4]triazolo[4,3-

b]pyridazine-6,8-diamine,

(230) *N6*-(3-ethylpentyl)-3-isopropyl-*N8*-(pyridazin-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(231) 3-isopropyl-*N8*-(6-(methoxy-*d3*)pyridazin-3-yl)-*N6*-(pentan-3-yl)-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

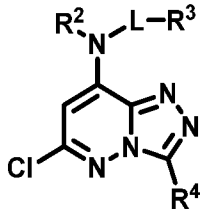
(232) *N8*-(6-chloropyridazin-3-yl)-*N6*-(2-ethylbutyl)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6,8-diamine,

(233) *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]-2-(2-pyridyl)acetamide,

(234) *N*-[6-(1-ethylpropylamino)-3-isopropyl-[1,2,4]triazolo[4,3-*b*]pyridazin-8-yl]-2-(4-pyridyl)acetamide,

in particular selected from compounds (1), (2), (10), (13), (14), (17) to (19), (21) to (23), (26), (28), (29), (31), (35) to (56), (58) to (64), (66) to (69), (71) to (78), (80) to (105), (107), (110), (111), (114), (117) to (119), (121) to (124), (126), (127), (130) to (132), (134), (136), (138), (140), (143), (146) to (160), (162) to (187), (189) to (206), (208) to (212), (215) to (218), (221) and (223) to (234) and their pharmaceutically acceptable salts, more particularly from compounds (18), (38), (40) to (42), (45) to (53), (56), (59), (62), (63), (67), (68), (73), (75), (76), (80), (82) to (88), (90), (91), (93) to (95), (98) to (100), (114), (118), (126), (130), (147) to (151), (153) to (156), (158) to (160), (162), (164) to (168), (170) to (178), (180) to (183), (186), (187), (191) to (193), (195), (196), (198) to (202), (204) to (206), (208) to (210), (215) to (218), (221) and (223) to (234) and their pharmaceutically acceptable salts, and even more particularly from compounds (46), (47), (83), (86), (87), (98), (147), (148), (150), (151), (153) to (155), (158), (159), (162), (164), (168), (171) to (175), (177), (178), (180) to (183), (215), (221), (223) to (232) and (234) and their pharmaceutically acceptable salts.

7. Synthesis process for manufacturing a compound of formula (I) as defined in anyone of claim 1 to 5 or any of its pharmaceutically acceptable salts, or at least any of compounds (1) to (234) as defined in claim 6 or any of their pharmaceutically acceptable salts, comprising at least a step of reacting a compound of formula (II)

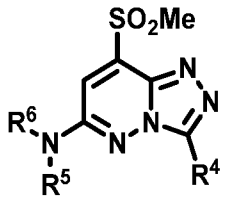

(II)

wherein L, R^2, R^3 and R^4 are as defined in anyone of claim 1, 3 or 4, with an amine of formula (IV)

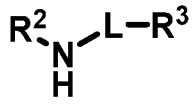
NHR^5R^6 (IV)

wherein R^5 and R^6 are as defined in claim 1 or 5, for example in a molar ratio ranging from 1 to 20 eq, with respect to the compound of formula (II), in an aprotic solvent or without solvent or else in a protic solvent.

8. Synthesis process for manufacturing a compound of formula (I) as defined in anyone of claim 1 to 5 or any of its pharmaceutically acceptable salts, or at least any of compounds (1) to (234) as defined in claim 6 or any of their pharmaceutically acceptable salts, comprising at least a step of reacting a compound of formula (IX)

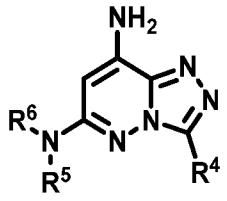

(IX)

wherein R^4, R^5 and R^6 are as defined in claim 1, 4 and 5, with a compound of formula (VI)

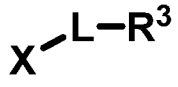

(VI)

wherein R^2 and R^3 are as defined in claim 1 or 3, in an aprotic solvent, for example in a molar ratio ranging from 1 to 10 eq, with respect to the compound of formula (IX).

9. Synthesis process for manufacturing a compound of formula (I) as defined in anyone of claim 1 to 5 or any of its pharmaceutically acceptable salts, or at least any of compounds (1) to (234) as defined in claim 6 or any of their pharmaceutically acceptable salts, comprising at least a step of reacting a compound of formula (XII)

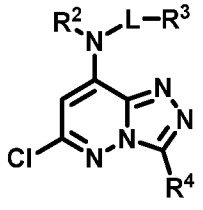
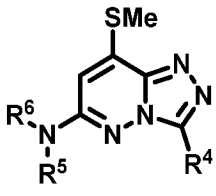
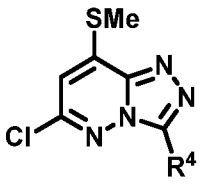
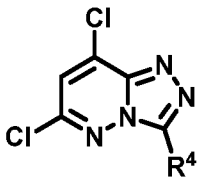

(XII)

wherein R^5 and R^6 are as defined in claim 1 or 5, with a compound of formula (XIV)


(XIV)

wherein L and R^3 are as defined in claim 1 or 3 and X represents a hydroxy group, a chlorine atom, a bromine atom, an (C_1-C_3)alkyl sulfonate group or a phenyl sulfonate group, in an aprotic solvent for example in a molar ratio ranging from 1 to 10 eq, with respect to the compound of formula (XII).

10. A compound of formula (II), (X), (XI) or (VII), in particular as an intermediate compound


(II),

(X),

(XI), or

(VII)

wherein L, R^2, R^3, R^4, R^5 and R^6 are as defined in claims 1, 3, 4 or 5, provided that R^4 is not a methyl group in formula (XI).

11. A compound of formula (I) as defined in anyone of claim 1 to 5 or any of its pharmaceutically acceptable salts, or at least any of compounds (1) to (234) as defined in claim 6 or any of their pharmaceutically acceptable salts, for use as a medicament.

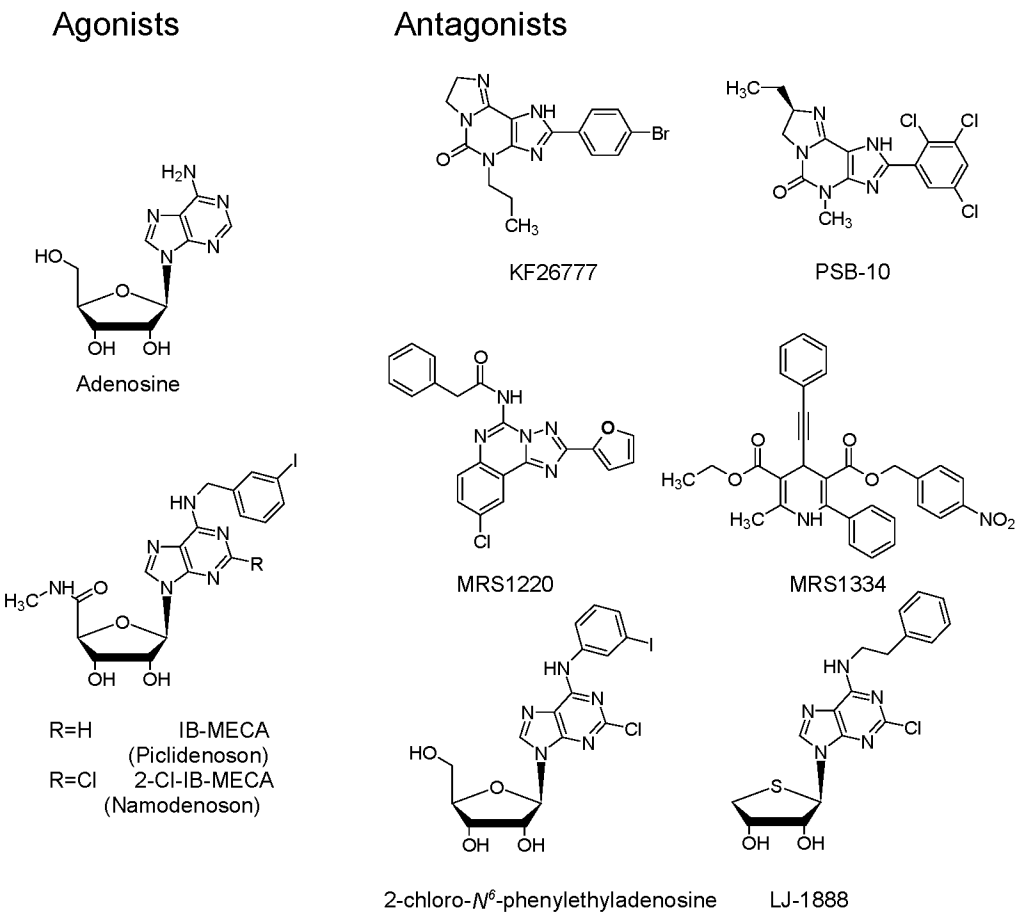
12. A compound of formula (I) as defined in anyone of claim 1 to 5 or any of its pharmaceutically acceptable salts, or at least any of compounds (1) to (234) as defined in claim 6 or any of their pharmaceutically acceptable salts, for use in the prevention and/or the treatment of ulcerative colitis, atopic dermatitis, glaucoma, asthma, liver fibrosis, kidney diseases, atherosclerosis, hypercholestemia, hearing loss and cancers developing under hypoxic conditions, in particular glioblastoma.

13. A compound for use as defined in claim 12, wherein the hearing loss is a partial or a complete hearing loss, in particular being induced by noise, acoustic trauma or ototoxic agents or conditions, more particularly platin-based anticancer drugs such as cisplatin or carboplatin, antibiotics, even more particularly macrolides or aminoglycosides such as gentamycin or neomycin, drugs for COVID-19 such as lopinavir or ritonavir, antimalarial drugs such as quinine or chloroquine, cardiovascular drugs such as loop diuretics, non-steroidal anti-inflammatory drugs such as salicylate or cyclodextrins, erectile dysfunction drugs such as phosphodiesterase type 5 inhibitors.

14. A compound for use as defined in claim 12, wherein the kidney disease is selected from kidney fibrosis, nephropathy, acute kidney injury, chronic kidney disease in particular induced by ischemia and/or reperfusion injury, toxic nephropathy or myoglobinuria, and diabetic kidney disease, or the kidney disease is induced by nephrotoxicity caused by therapeutic drugs, more particularly cytotoxic agents, such as platin-based anticancer drugs for example cisplatin or carboplatin.

15. A pharmaceutical composition comprising at least one compound of formula (I) as defined in anyone of claim 1 to 5 or any of its pharmaceutically acceptable salt, or at least any of compounds (1) to (234) as defined in claim 6 or any of their pharmaceutically acceptable salts.

FIG 1.


Agonists
Antagonists
Adenosine
KF26777
PSB-10
MRS1220
MRS1334
R=H IB-MECA (Piclidenoson)
R=Cl 2-Cl-IB-MECA (Namodenoson)
2-chloro-N6-phenylethyladenosine
LJ-1888

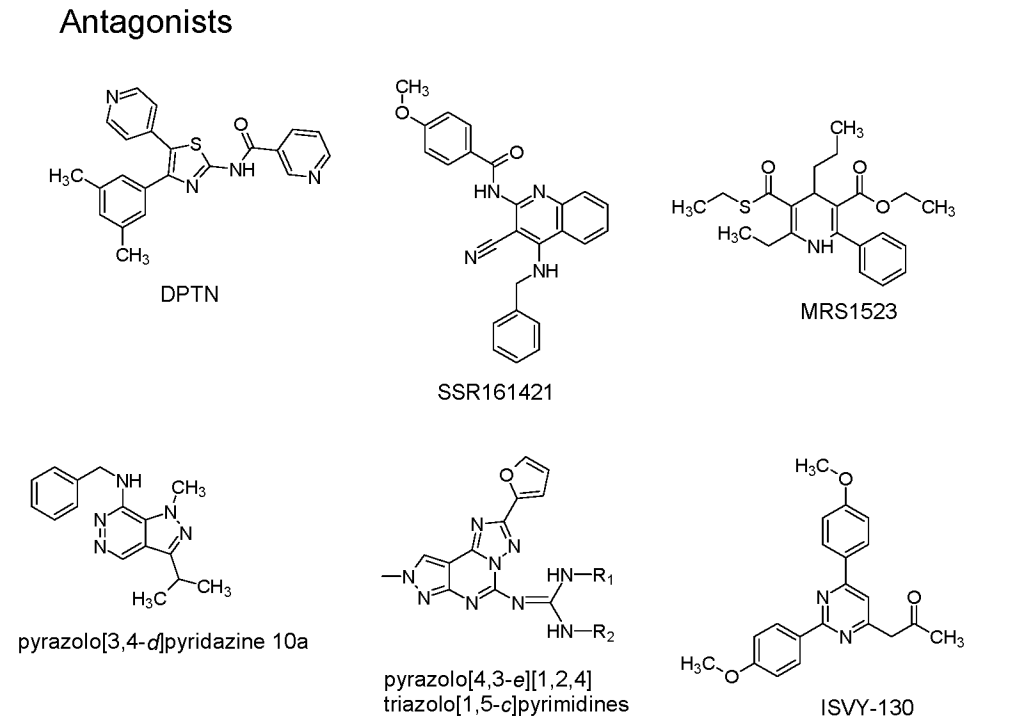

Antagonists
DPTN
SSR161421
MRS1523
pyrazolo[3,4-d]pyridazine 10a
pyrazolo[4,3-e][1,2,4] triazolo[1,5-c]pyrimidines
ISVY-130

FIG 2.

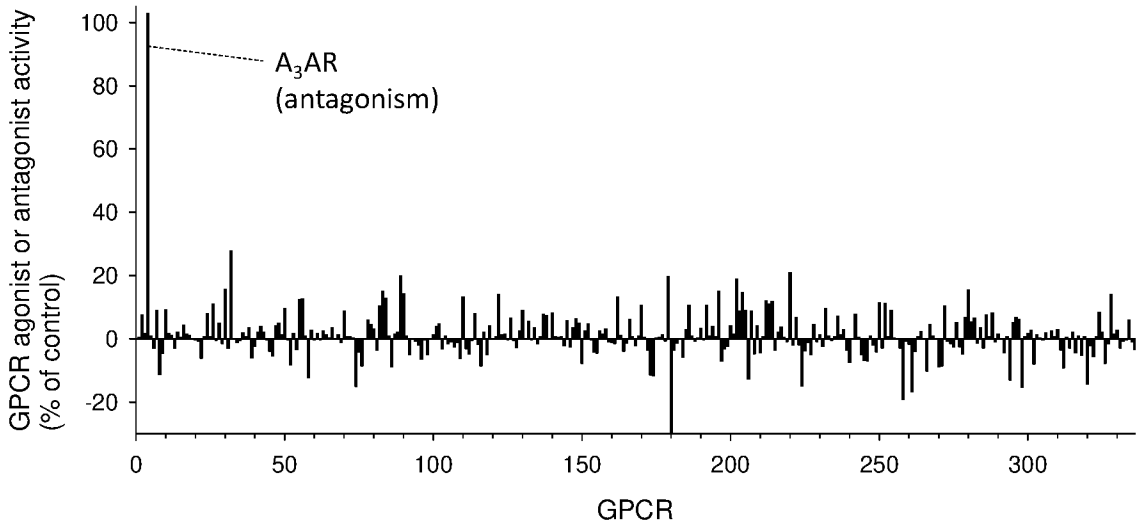
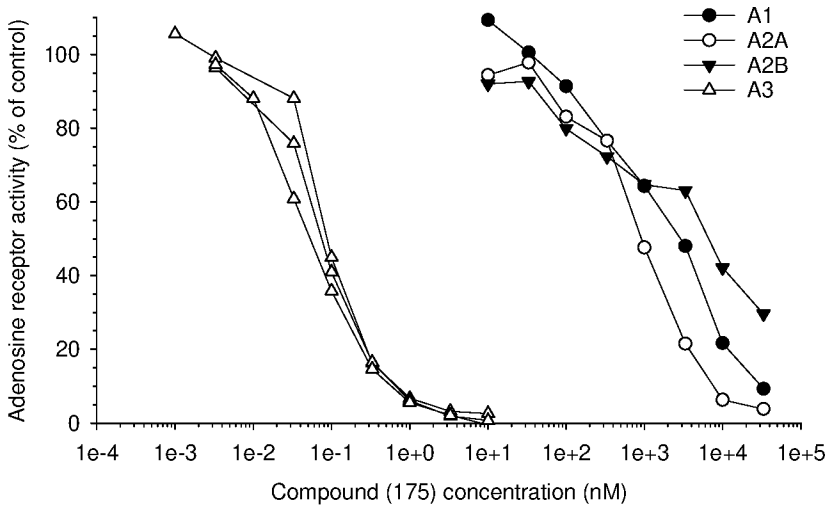


FIG. 3



Adenosine receptor	IC_{50} (*Ki*) (μM)
A_1AR	1.5 (***0.62***)
$A_{2A}AR$	1.0 (***0.82***)
$A_{2B}AR$	5.7 (***5.3***)
A_3AR	0.000066 (***0.000039***)

FIG. 4

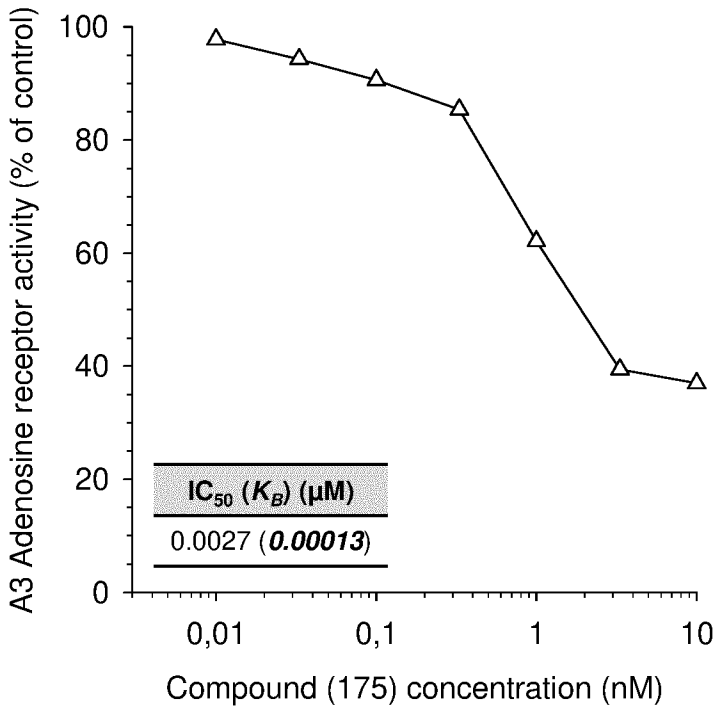

A3 Adenosine receptor activity (% of control)
100
80
60
40
20
0
0,01
0,1
1
10
Compound (175) concentration (nM)
IC50 (KB) (µM)
0.0027 (0.00013)

FIG. 5

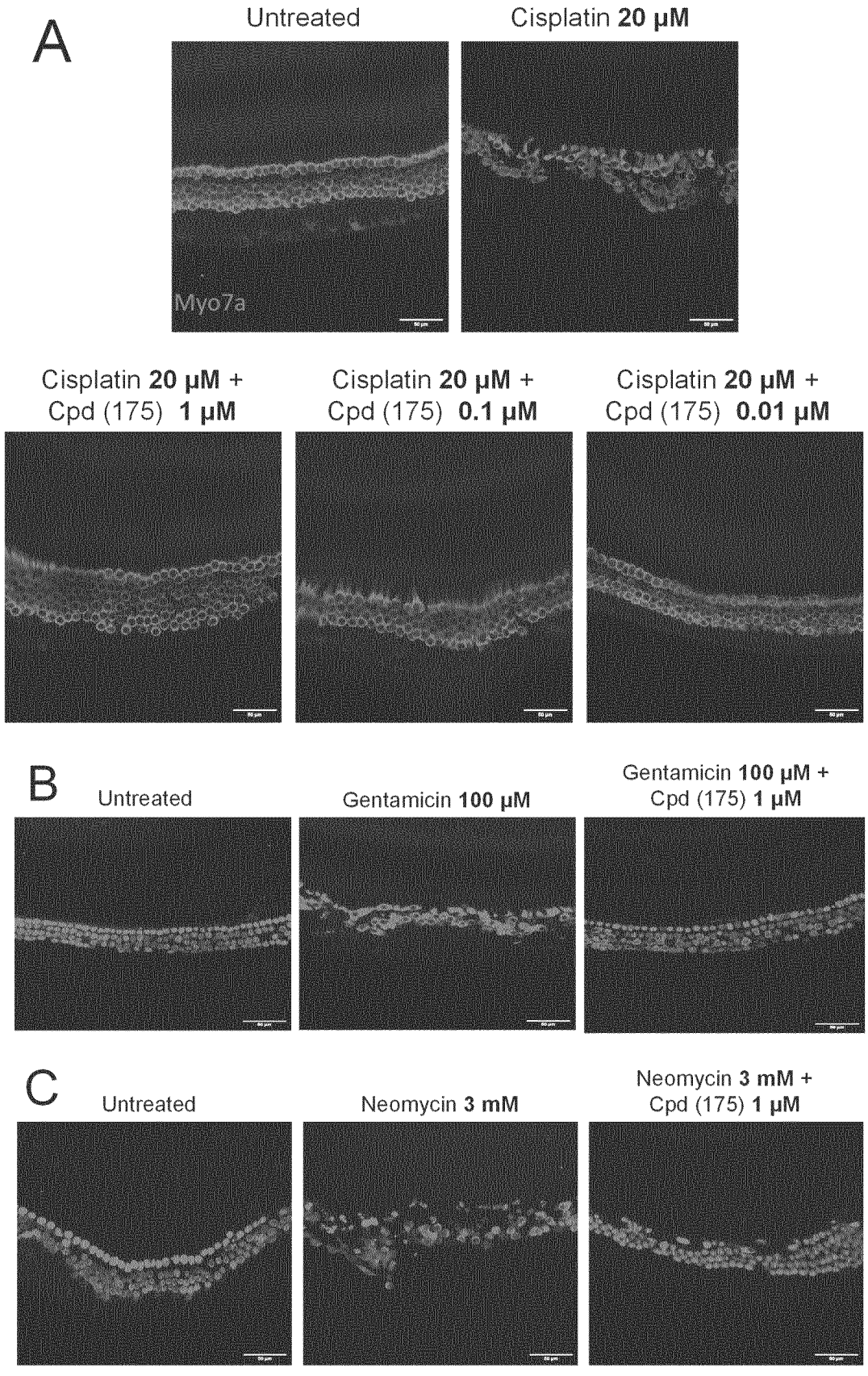

A
Untreated
Cisplatin 20 µM
Myo7a
Cisplatin 20 µM + Cpd (175) 1 µM
Cisplatin 20 µM + Cpd (175) 0.1 µM
Cisplatin 20 µM + Cpd (175) 0.01 µM
B
Untreated
Gentamicin 100 µM
Gentamicin 100 µM + Cpd (175) 1 µM
C
Untreated
Neomycin 3 mM
Neomycin 3 mM + Cpd (175) 1 µM

FIG. 6

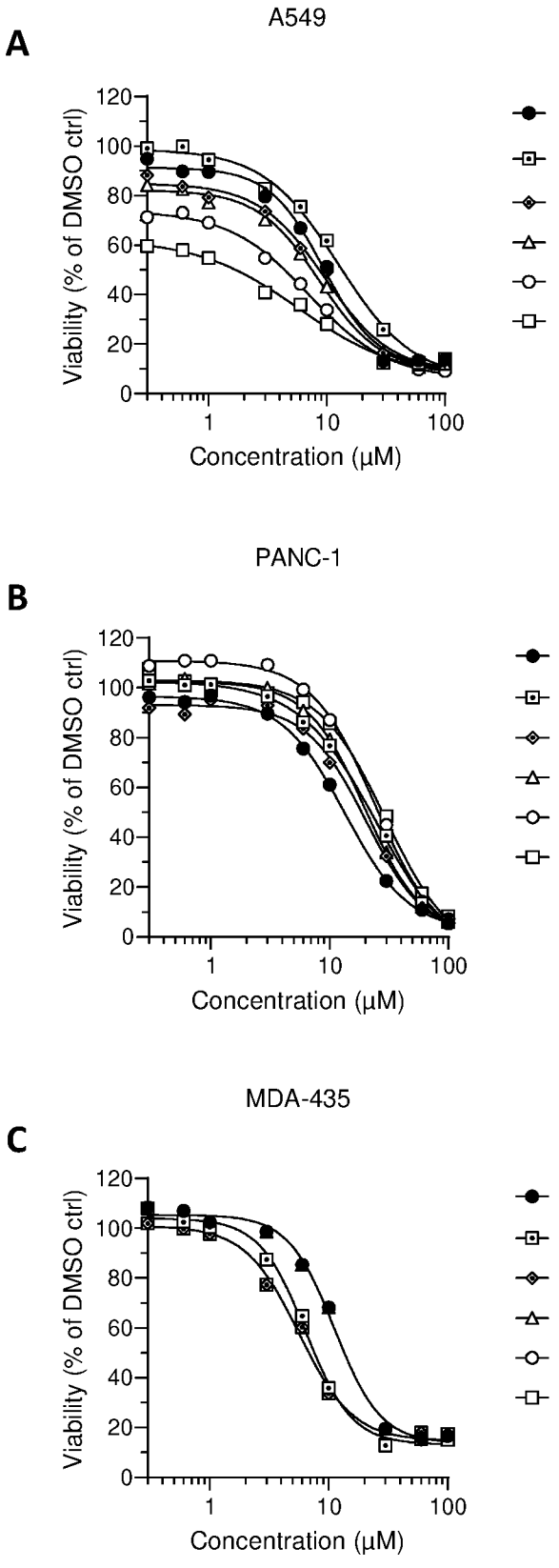

A
A549
Viability (% of DMSO ctrl)
120
100
80
60
40
20
0
1
10
100
Concentration (µM)
B
PANC-1
Viability (% of DMSO ctrl)
120
100
80
60
40
20
0
1
10
100
Concentration (µM)
C
MDA-435
Viability (% of DMSO ctrl)
120
100
80
60
40
20
0
1
10
100
Concentration (µM)

FIG. 7

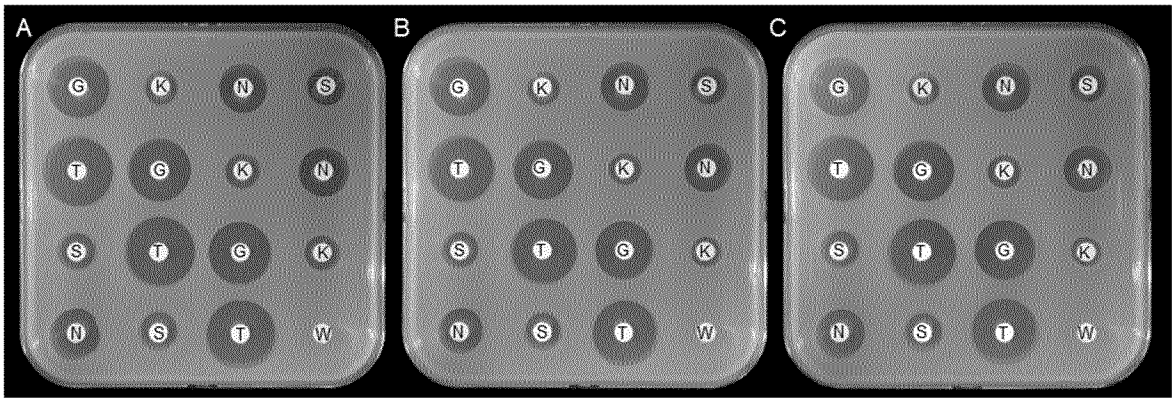
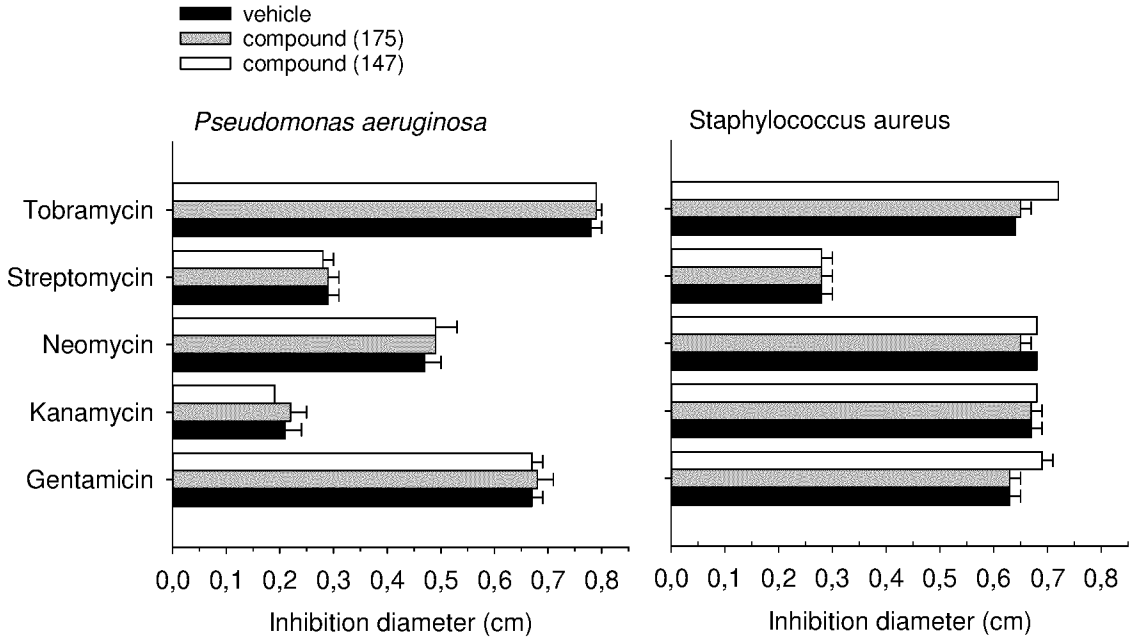

A
B
C
G K N S
T G K N
S T G K
N S T W

FIG. 8


vehicle
compound (175)
compound (147)
Pseudomonas aeruginosa
Staphylococcus aureus
Tobramycin
Streptomycin
Neomycin
Kanamycin
Gentamicin
0,0 0,1 0,2 0,3 0,4 0,5 0,6 0,7 0,8
Inhibition diameter (cm)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/066286

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/5025 A61P27/16 A61P35/00 A61P13/12 A61P1/04

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/135336 A1 (ENGELHARDT HARALD [AT] ET AL) 15 May 2014 (2014-05-15) description, page 17, compound I-5; description, page 12-13, scheme 1, intermediate G; description page 16, intermediate G-8; Claim 23 -----	1-5,7, 10-15
X	WO 2012/174487 A2 (CONSTELLATION PHARMACEUTICALS INC [US]; ALBRECHT BRIAN K [US] ET AL.) 20 December 2012 (2012-12-20) description, page 81, example 11, description, page 73, scheme 3, step 6; claims 31-33; claim 18 -----	1-5, 11-15
A	WO 2009/052310 A1 (CV THERAPEUTICS INC [US]; ZABLOCKI JEFF [US] ET AL.) 23 April 2009 (2009-04-23) Whole document, particularly claim 1 -----	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
7 August 2024	20/08/2024

Name and mailing address of the ISA/	Authorized officer
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1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/066286

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2012174487 A2	20-12-2012
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		JP 2011500716 A	06-01-2011
		US 2009099212 A1	16-04-2009
		WO 2009052310 A1	23-04-2009