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(54) **Title:** NOVEL RHO KINASE INHIBITORS AND METHODS OF USE

(57) **Abstract:** The subject invention concerns materials and methods for treating diseases and disorders associated with expression of Rho associated kinases (ROCKs). Examples of diseases and disorders contemplated within the scope of the invention include, but are not limited to, oncological disorders, cardiovascular diseases, CNS disorders, and inflammatory disorders. In one embodiment, a method of the invention comprises administering a therapeutically effective amount of one or more compounds of the present invention, or a composition comprising the compounds, to a person or animal in need of treatment. The subject invention also concerns compounds that inhibit ROCKs, and compositions that comprise the inhibitor compounds of the invention. Compounds contemplated within the scope of the invention include, but are not limited to, those compounds shown in Table (5).



DESCRIPTION

NOVEL RHO KINASE INHIBITORS AND METHODS OF USE

5

GOVERNMENT SUPPORT

This invention was made with government support under grant number CA067771 awarded by the National Institutes of Health. The government has certain rights in the invention.

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CROSS-REFERENCE TO RELATED APPLICATION

The present application claims the benefit of U.S. Provisional Application Serial No. 61/469,482, filed March 30, 2011, which is hereby incorporated by reference herein in its entirety, including any figures, tables, nucleic acid sequences, amino acid sequences, or drawings.

15

BACKGROUND OF THE INVENTION

20

Rho associated protein kinases (ROCKs) are Ser/Thr protein kinases, activated by small GTPases of the Rho family that act as molecular switches to mediate cell signaling. The Rho/ROCK signaling pathway (Lu *et al.* 2009) is known to participate in the regulation of numerous cellular functions such as actin cytoskeleton organization, contraction, cell adhesion, motility, and morphology, proliferation, cytokinesis, gene expression, and angiogenesis.

25

30

Rho kinases are important drug targets involved in several therapeutic areas including cardiovascular diseases (Shimokawa *et al.* (2007); Xing *et al.* (2006); Liao *et al.* (2007); Shimokawa *et al.* (2005); Dong *et al.* (2009); Hu *et al.* (2005)), CNS disorders (Kubo *et al.* (2008); Kubo *et al.* (2007)), inflammation (LoGrasso *et al.* (2009)), and cancer (Suwa *et al.* (1998); Kamai *et al.* (2004); Schmitz *et al.* (2000); Imamura *et al.* (2000); Somlyo *et al.* (2000); Uchida *et al.* (2000); Itoh *et al.* (1999); Uehata *et al.* (1997); Ishizaki *et al.* (2000); Narumiya *et al.* (2000); Nakajima *et al.* (2003a); Nakajima *et al.* (2003b); Ying *et al.* (2006); Somlyo *et al.* (2003); Hampson *et al.* (2009); Igishi *et al.* (2003); Liu *et al.* (2009); Ogata *et al.* (2009); Zohrabian *et al.* (2009); Micuda *et al.*

(2010)). Rho kinases and the effects of ROCK inhibitors upon several hallmarks of cancer, including invasion (Imamura *et al.* (2000); Somlyo *et al.* (2000)), metastasis (Itoh *et al.* (1999); Belgiovine *et al.* (2010)), proliferation and angiogenesis (Uchida *et al.* (2000); Nakabayashi *et al.* (2011); Yin *et al.* (2007)) have been reported.

5 Co-overexpression of Rho and ROCK proteins in cancer cells has been reported in ovarian cancer, pancreatic, testicular, and bladder cancer (Suwa *et al.* (1998); Kamai *et al.* (2004)). The Rho/ROCK pathway plays an important role in the development and progression of cancer by modulating the changes (required for malignant transformation and for the process of metastasis) in the migratory, invasive and adhesive properties of
10 tumor cells, and changes in the regulation cellular processes depending on the proper assembly/disassembly of actin-cytoskeleton (Schmitz *et al.* (2000)). The involvement of the Rho/ROCK signalling pathway in tumor cell invasion, angiogenesis, and metastasis has been well documented. In light of these findings inhibition of ROCKs has been proposed as a promising strategy in the prevention of cell invasion, a central event in the
15 process of metastasis (Itoh *et al.* (1999); Uehata *et al.* (1997); Ishizaki *et al.* (2000); Narumiya *et al.* (2000)).

The potential of ROCK inhibitors as anticancer drugs was demonstrated by the identification of ATP competitive inhibitors, **Y27632**, and **Wf536** (Figure 1) (Itoh *et al.* (1999); Nakajima *et al.* (2003a); Nakajima *et al.* (2003b); Somlyo *et al.* (2003)),
20 displaying high inhibitory potency for ROCKs. Specifically, **Y27632** was reported to reduce metastasis in animal model systems (Itoh *et al.* (1999)), while **Wf-536** has shown efficacy in preventing tumor metastasis *in vivo models* by inhibiting tumor-induced angiogenesis as well as tumor motility (Nakajima *et al.* (2003a); Nakajima *et al.* (2003b); Somlyo *et al.* (2003)). Han and coworkers have also investigated the ability of **Fasudil**,
25 currently the only ROCK inhibitor clinically approved (in Japan for the treatment of cerebral vasospasm) to inhibit tumor progression in human and rat tumor models (Ying *et al.* (2006)).

BRIEF SUMMARY OF THE INVENTION

30 The subject invention concerns materials and methods for treating diseases and disorders associated with expression of Rho associated kinases (ROCKs). Examples of diseases and disorders contemplated within the scope of the invention include, but are not

limited to, oncological disorders, cardiovascular diseases, CNS disorders, and inflammatory disorders. In one embodiment, a method of the invention comprises administering a therapeutically effective amount of one or more compounds of the present invention, or a composition comprising the compounds, to a person or animal in need of treatment.

The subject invention also concerns compounds that inhibit ROCKs, and compositions that comprise the inhibitor compounds of the invention. Compounds contemplated within the scope of the invention include, but are not limited to, those compounds shown in Table 5.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the ROCK inhibitors Wf536, Y27632, and Fasudil.

Figure 2 shows the structure of the compound NSC 135784 (1aa).

Figure 3 shows the structure of the compound H-1152P.

Figure 4 shows the structure of the compound CID5056270.

Figure 5 shows activity of ROCK inhibitors of the invention.

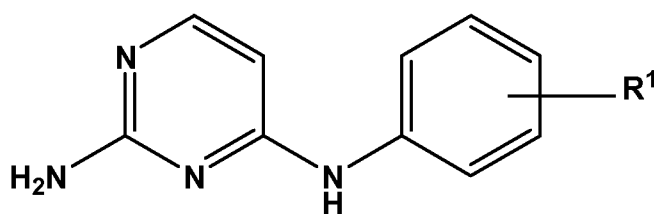
Figures 6a-6c: Molecular mode of action of compound 18. (Figure 6a) Surface presentation of the ROCK1 dimer in complex with **RPM1510** determined by X-ray crystallography at 3.25 Å resolution. Exploded view detailing the binding interactions of **RPM1510** (yellow) within the ATP site; the hinge and DFG regions are indicated in orange and cyan, respectively. Displayed in blue is the 2Fo-Fc electron density, contoured at 1σ around the inhibitor. (Figure 6b) Schematic presentation of the binding interactions between **RPM1510** and the ATP site. (Figure 6c) The mFo-Fc electron density map (red) contoured at 3σ around the inhibitor after **RPM1510** was omitted during refinement. Potential hydrogen bonding and van der Waal interactions are shown as black and green dotted lines, respectively.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention concerns materials and methods for treating diseases and disorders associated with expression of Rho associated kinases (ROCKs). Examples of diseases and disorders contemplated within the scope of the invention include, but are not limited to, oncological disorders, cardiovascular diseases, CNS disorders, and

inflammatory disorders. In one embodiment, a method of the invention comprises administering a therapeutically effective amount of one or more compounds of the present invention, or a composition comprising the compounds, to a person or animal in need of treatment.

The subject invention also concerns compounds that inhibit ROCKs, and compositions that comprise the inhibitor compounds of the invention. Compounds contemplated within the scope of the invention include, but are not limited to, those compounds shown in Table 5. In one embodiment, a compound of the invention has the structure shown in formula I:



formula I

R^1 is H, OH, S-alkyl, $\text{SO}_2\text{NR}^2\text{R}^3$, NO_2 , CONH_2 , SO_2 -alkyl, NHC(O) -alkyl, CO_2H , alkyl, cycloalkyl, alkoxy, cycloalkoxyl, heterocycloalkyl, alkoxycarbonyl, heteroaryl, aryl aryloxy or a halogen;

R^2 is H, CO, alkoxy, alkyl, aryl, heteroalkyl, heteroaryl, heterocycloalkyl, alkylcarbonyl, arylcarbonyl, or alkoxycarbonyl;

R^3 is H, CO, alkoxy, alkyl, aryl, heteroalkyl, heteroaryl, heterocycloalkyl, alkylcarbonyl, arylcarbonyl, or alkoxycarbonyl;

any of which of R^1 , R^2 , and R^3 can be optionally substituted with one or more of halogen, alkyl, alkoxy, or aryl optionally substituted with alkoxy;

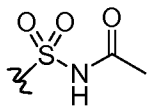
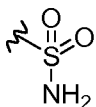
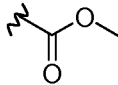
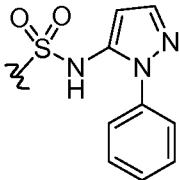
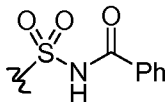
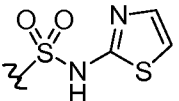
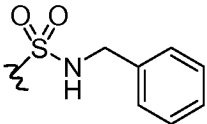
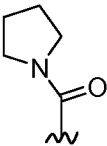
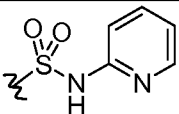
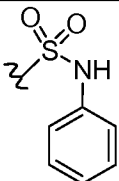
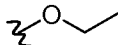
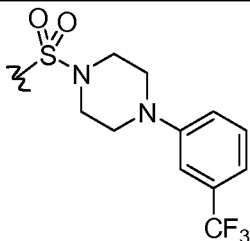
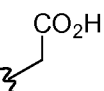
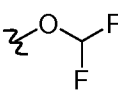
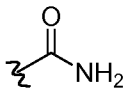
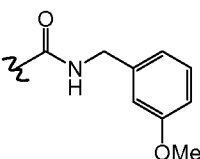
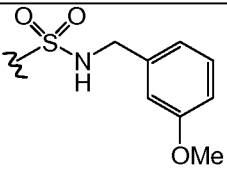
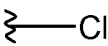
or a pharmaceutically acceptable salt or hydrate thereof.

Compounds of formula I can comprise one or more R substituents.

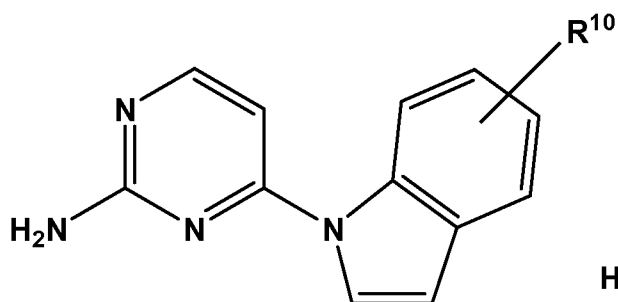
In one embodiment, a compound of the invention has the structure of formula I wherein:

Table 1.

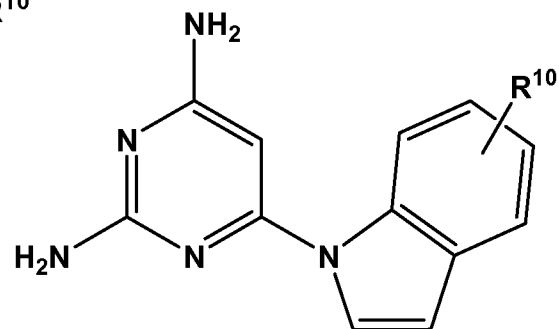
(ξ = point of attachment; Me = methyl group)

R^1 can be:	R^1 can be:	R^1 can be:	R^1 can be:
$\xi\text{SO}_2\text{NH}_2$			
			
			
		ξOMe	
			
			
			

6



formula IIa

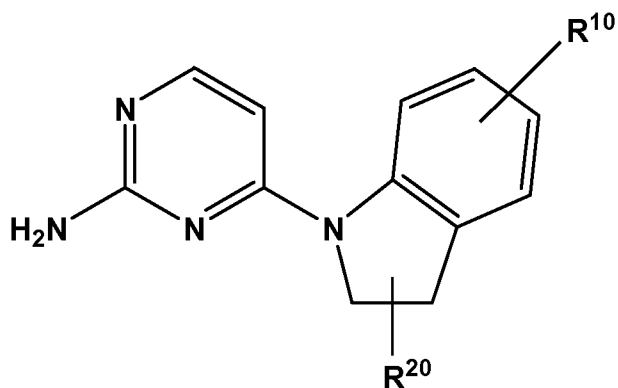


formula IIb

5 wherein

R^{10} is H, NO_2 , halogen, $-\text{CH}_3$, $-\text{SO}_2$ -alkyl, $-\text{OCH}_3$, alkoxy, $-\text{C}(\text{O})\text{NH}$ -alkyl, $-\text{C}(\text{O})\text{NH}$ -aryl, $-\text{NHC}(\text{O})$ -alkyl, $-\text{NHC}(\text{O})$ -aryl, or aryloxy, any of which can be substituted with one or more of aryl or alkoxy, any of which can be optionally substituted with halogen, $-\text{OH}$, alkoxy, or aryl optionally substituted with alkoxy;

10 or a pharmaceutically acceptable salt or hydrate thereof.



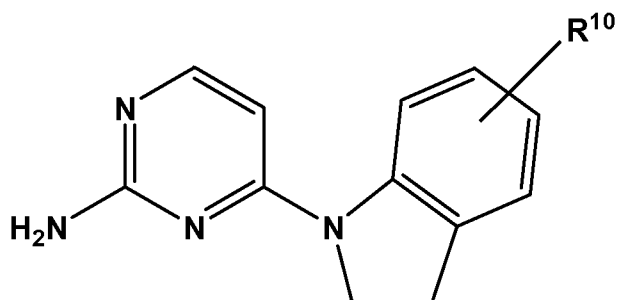
formula III

wherein

15 R^{10} is H, NO_2 , halogen, $-\text{CH}_3$, $-\text{SO}_2$ -alkyl, $-\text{OCH}_3$, alkoxy, $-\text{C}(\text{O})\text{NH}$ -alkyl, $-\text{C}(\text{O})\text{NH}$ -aryl, $-\text{NHC}(\text{O})$ -alkyl, $-\text{NHC}(\text{O})$ -aryl, or aryloxy, any of which can be substituted with one or more of aryl or alkoxy, any of which can be optionally substituted with halogen, $-\text{OH}$, alkoxy, or aryl optionally substituted with alkoxy;

R^{20} is $-\text{CH}_3$, $-\text{CO}_2\text{H}$, heteroalkyl, aryl, or alkyl;

20 or a pharmaceutically acceptable salt or hydrate thereof.



formula IV

wherein

- 5 R^{10} is H, NO_2 , halogen, $-CH_3$, $-SO_2$ -alkyl, $-OCH_3$, alkoxy, $-C(O)NH$ -alkyl, $-C(O)NH$ -aryl, $-NHC(O)$ -alkyl, $-NHC(O)$ -aryl, or aryloxy, any of which can be substituted with one or more of aryl or alkoxy, any of which can be optionally substituted with halogen, $-OH$, alkoxy, or aryl optionally substituted with alkoxy;
or a pharmaceutically acceptable salt or hydrate thereof.

- 10 Compounds of Formula IIa, IIb, III, and IV can comprise one or more R^{10} and/or R^{20} .

In one embodiment, a compound of the invention has the structure shown in formula IIa, formula IIb, formula III, or formula IV wherein:

- 15 Table 2.

(ξ = point of attachment; Me = methyl group; Et = ethyl group)

R^{10} can be:	R^{10} can be:	R^{10} can be:
ξOMe		

R ¹⁰ can be:	R ¹⁰ can be:	R ¹⁰ can be:

As used herein, alkyl means straight or branched chain, saturated or mono- or polyunsaturated hydrocarbon groups having from 1 to 20 carbon atoms and C_{1-x} alkyl

means straight or branched chain alkyl groups containing from one up to X carbon atoms. For example, C₁₋₆ alkyl means straight or branched chain alkyl groups containing from one up to 6 carbon atoms. Alkoxy means an alkyl-O- group in which the alkyl group is as previously described. Cycloalkyl includes a nonaromatic monocyclic or multicyclic ring system, including fused and spiro rings, of from about three to about 10 carbon atoms. A cyclic alkyl may optionally be partially unsaturated. Cycloalkoxy means a cycloalkyl-O- group in which cycloalkyl is as defined herein. Aryl means an aromatic monocyclic or multicyclic carbocyclic ring system, including fused and spiro rings, containing from about six to about 14 carbon atoms. Aryloxy means an aryl-O- group in which the aryl group is as described herein. Alkylcarbonyl means a RC(O)- group where R is an alkyl group as previously described. Alkoxycarbonyl means an ROC(O)- group where R is an alkyl group as previously described. Cycloalkylcarbonyl means an RC(O)- group where R is a cycloalkyl group as previously described. Cycloalkoxycarbonyl means an ROC(O)- group where R is a cycloalkyl group as previously described.

Heteroalkyl means a straight or branched-chain having from one to 20 carbon atoms and one or more heteroatoms selected from nitrogen, oxygen, or sulphur, wherein the nitrogen and sulphur atoms may optionally be oxidized, *i.e.*, in the form of an N-oxide or an S-oxide. Heterocycloalkyl means a monocyclic or multicyclic ring system (which may be saturated or partially unsaturated), including fused and spiro rings, of about five to about 10 elements wherein one or more of the elements in the ring system is an element other than carbon and is selected from nitrogen, oxygen, silicon, or sulphur atoms. Heteroaryl means a five to about a 14-membered aromatic monocyclic or multicyclic hydrocarbon ring system, including fused and spiro rings, in which one or more of the elements in the ring system is an element other than carbon and is selected from nitrogen, oxygen, silicon, or sulphur and wherein an N atom may be in the form of an N-oxide. Arylcarbonyl means an aryl-CO- group in which the aryl group is as described herein. Heteroarylcarbonyl means a heteroaryl-CO- group in which the heteroaryl group is as described herein and heterocycloalkylcarbonyl means a heterocycloalkyl-CO- group in which the heterocycloalkyl group is as described herein. Aryloxycarbonyl means an ROC(O)- group where R is an aryl group as previously described. Heteroaryloxycarbonyl means an ROC(O)- group where R is a heteroaryl group as previously described. Heteroaryloxy means a heteroaryl-O- group in which the

heteroaryl group is as previously described. Heterocycloalkoxy means a heterocycloalkyl-O- group in which the heterocycloalkyl group is as previously described. Heterocycloalkoxycarbonyl means an ROC(O)- group where R is a heterocycloalkyl group as previously described.

5 Examples of saturated alkyl groups include, but are not limited to, methyl, ethyl, N-propyl, isopropyl, N-butyl, tert-butyl, isobutyl, sec-butyl, N-pentyl, N-hexyl, N-heptyl, and N-octyl. An unsaturated alkyl group is one having one or more double or triple bonds. Unsaturated alkyl groups include, for example, ethenyl, propenyl, butenyl, hexenyl, vinyl, 2-propynyl, 2-isopentenyl, 2-butadienyl, ethynyl, 1-propynyl, 3-propynyl, 10 and 3-butenyl. Cycloalkyl groups include, for example, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, and cycloheptyl. Heterocycloalkyl groups include, for example, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 3-morpholinyl, 4-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and 1,4-diazabicyclooctane. Aryl groups include, for example, 15 phenyl, indenyl, biphenyl, 1-naphthyl, 2-naphthyl, anthracenyl, and phenanthracenyl. Heteroaryl groups include, for example, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridyl, indolyl, quinolinyl, isoquinolinyl, benzoquinolinyl, carbazolyl, and diazaphenanthrenyl.

20 As used herein, halogen means the elements fluorine (F), chlorine (Cl), Bromine (Br), and iodine (I).

25 Compounds of the subject invention also include physiologically-acceptable salts and hydrates of the subject compounds. Physiologically-acceptable salts include salts of the compounds of the invention which are prepared with acids or bases, depending on the particular substituents found on the subject complexes described herein. Examples of physiologically-acceptable base addition salts include sodium, potassium, calcium, ammonium, or magnesium salt. Examples of physiologically-acceptable acid addition salts include hydrochloric, hydrobromic, nitric, phosphoric, carbonic, sulphuric, and organic acids like acetic, propionic, benzoic, succinic, fumaric, mandelic, oxalic, citric, tartaric, maleic, and the like. Physiologically-acceptable salts of compounds of the 30 invention can be prepared using conventional techniques.

 It will be appreciated by those skilled in the art that certain of the compounds of the invention may contain one or more asymmetrically substituted carbon atoms which

can give rise to stereoisomers. It is understood that the invention extends to all such stereoisomers, including enantiomers, and diastereoisomers and mixtures, including racemic mixtures thereof.

The subject invention also concerns methods for treating a person or animal
5 having a disorder or condition associated with aberrant or excessive ROCK activity or expression in a cell. In one embodiment, the disorder or condition is an oncological disorder or condition. In another embodiment, the disorder or condition is a cardiovascular-related disorder or condition. Examples of cardiovascular disorders and conditions that can be treated using the compounds and/or compositions of the invention
10 include, but are not limited to, cerebral and coronary vasospasm, angina, hypertension, pulmonary hypertension, arteriosclerosis, ischemia/reperfusion injury, restenosis, stroke, and heart failure. In a further embodiment, the disorder or condition is a central nervous system (CNS) disorder or condition. Examples of CNS disorders and conditions that can be treated using the compounds and/or compositions of the invention include, but are not
15 limited to, spinal cord injury, stroke, and Alzheimer's disease (AD). In one embodiment, a person or animal in need of treatment is administered an effective amount of one or more inhibitor compounds or compositions of this invention. In a specific embodiment, the compound is the compound designated herein as 30b. In another embodiment, the compound is the compound designated herein as 30h. In a specific embodiment, the 30h
20 compound is the (R) stereoisomer. In one embodiment, compounds and compositions of the invention can be used in the methods of treatment in combination with other ROCK inhibitors, including, but not limited to, Y27632, Wf536, Fasudil, H-1152P, and/or CID5056270.

The subject invention also concerns methods of inhibiting migratory or invasive
25 capacity of a cell, or inhibiting metastatic potential of a cell. In one embodiment, a cell is contacted with an effective amount of one or more inhibitor compounds or compositions of this invention. In a specific embodiment, the compound is the compound designated herein as 30b. In another embodiment, the compound is the compound designated herein as 30h. In a specific embodiment, the 30h compound is the (R) stereoisomer. Cells can
30 be any animal cell, such as a mammalian cell. Cells can be any mammalian cell, such as a human cell, canine cell, feline cell, or equine cell. In one embodiment the cell is a tumor cell, a cancer cell or a transformed cell. In one embodiment, compounds and

compositions of the invention can be used in combination with other ROCK inhibitors, including, but not limited to, Y27632, Wf536, Fasudil, H-1152P, and/or CID5056270.

The subject invention also concerns methods for inhibiting ROCK activity in a cell. In one embodiment, a cell is contacted with an effective amount of one or more inhibitor compounds or compositions of this invention. In a specific embodiment, the compound is the compound designated herein as 30b. In another embodiment, the compound is the compound designated herein as 30h. In a specific embodiment, the 30h compound is the (R) stereoisomer. Cells can be any animal cell, such as a mammalian cell. Cells can be any mammalian cell, such as a human cell, canine cell, feline cell, or equine cell. In one embodiment the cell is a tumor cell, a cancer cell or a transformed cell. In one embodiment, compounds and compositions of the invention can be used in combination with other ROCK inhibitors, including, but not limited to, Y27632, Wf536, Fasudil, H-1152P, and/or CID5056270.

The subject invention also concerns a packaged dosage formulation comprising in one or more containers at least one inhibitor compound or composition of the invention. In one embodiment, a packaged dosage formulation comprises a compound designated herein as 30b. In another embodiment, the compound is the compound designated herein as 30h. In a specific embodiment, the 30h compound is the (R) stereoisomer. A packaged dosage formulation can optionally comprise in one or more containers a pharmaceutically acceptable carrier or diluent. A packaged dosage formulation can also optionally comprise, in addition to an inhibitor compound or composition of the invention, other ROCK inhibitors, including, but not limited to, Y27632, Wf536, Fasudil, H-1152P, and/or CID5056270.

In vivo application of the subject compounds, and compositions containing them, can be accomplished by any suitable method and technique presently or prospectively known to those skilled in the art. The subject compounds can be formulated in a physiologically- or pharmaceutically-acceptable form and administered by any suitable route known in the art including, for example, oral, nasal, rectal, and parenteral routes of administration. As used herein, the term parenteral includes subcutaneous, intradermal, intravenous, intramuscular, intraperitoneal, and intrasternal administration, such as by injection. Administration of the subject compounds of the invention can be a single

administration, or at continuous or distinct intervals as can be readily determined by a person skilled in the art.

The compounds of the subject invention, and compositions comprising them, can also be administered utilizing liposome technology, slow release capsules, implantable pumps, and biodegradable containers. These delivery methods can, advantageously, provide a uniform dosage over an extended period of time. The compounds of the invention can also be administered in their salt derivative forms or crystalline forms.

Compounds of the subject invention can be formulated according to known methods for preparing physiologically acceptable compositions. Formulations are described in detail in a number of sources which are well known and readily available to those skilled in the art. For example, *Remington's Pharmaceutical Science* by E.W. Martin describes formulations which can be used in connection with the subject invention. In general, the compositions of the subject invention will be formulated such that an effective amount of the compound is combined with a suitable carrier in order to facilitate effective administration of the composition. The compositions used in the present methods can also be in a variety of forms. These include, for example, solid, semi-solid, and liquid dosage forms, such as tablets, pills, powders, liquid solutions or suspension, suppositories, injectable and infusible solutions, and sprays. The preferred form depends on the intended mode of administration and therapeutic application. The compositions also preferably include conventional physiologically-acceptable carriers and diluents which are known to those skilled in the art. Examples of carriers or diluents for use with the subject compounds include ethanol, dimethyl sulfoxide, glycerol, alumina, starch, saline, and equivalent carriers and diluents. To provide for the administration of such dosages for the desired therapeutic treatment, compositions of the invention will advantageously comprise between about 0.1% and 99%, and especially, 1 and 15% by weight of the total of one or more of the subject compounds based on the weight of the total composition including carrier or diluent.

Compounds of the invention, and compositions comprising them, can be delivered to a cell either through direct contact with the cell or via a carrier means. Carrier means for delivering compounds and compositions to cells are known in the art and include, for example, encapsulating the composition in a liposome moiety. Another means for delivery of compounds and compositions of the invention to a cell comprises attaching

the compounds to a protein or nucleic acid that is targeted for delivery to the target cell. U.S. Patent No. 6,960,648 and Published U.S. Patent Application Nos. 20030032594 and 20020120100 disclose amino acid sequences that can be coupled to another composition and that allows the composition to be translocated across biological membranes. Published U.S. Patent Application No. 20020035243 also describes compositions for transporting biological moieties across cell membranes for intracellular delivery. Compounds can also be incorporated into polymers, examples of which include poly (D-L lactide-co-glycolide) polymer for intracranial tumors; poly[bis(p-carboxyphenoxy) propane:sebacic acid] in a 20:80 molar ratio (as used in GLIADEL); chondroitin; chitin; and chitosan.

The subject invention also concerns methods for treating oncological disorders in a patient. In one embodiment, an effective amount of one or more compounds or compositions of the present invention is administered to a patient having an oncological disorder and who is in need of treatment thereof. Methods of the invention can optionally include identifying a patient who is or may be in need of treatment of an oncological disorder. The patient can be a human or other mammal, such as a primate (monkey, chimpanzee, ape, *etc.*), dog, cat, cow, pig, or horse, or other animals having an oncological disorder. Means for administering and formulating compounds for administration to a patient are known in the art, examples of which are described herein. Oncological disorders within the scope of the invention include, but are not limited to, cancer and/or tumors of the anus, bile duct, bladder, bone, bone marrow, bowel (including colon and rectum), breast, eye, gall bladder, kidney, mouth, larynx, esophagus, stomach, testis, cervix, head, neck, ovary, lung, mesothelioma, neuroendocrine, penis, skin, spinal cord, thyroid, vagina, vulva, uterus, liver, muscle, pancreas, prostate, blood cells (including lymphocytes and other immune system cells), and brain. Specific cancers contemplated for treatment with the present invention include carcinomas, Kaposi's sarcoma, melanoma, mesothelioma, soft tissue sarcoma, pancreatic cancer, lung cancer, leukemia (acute lymphoblastic, acute myeloid, chronic lymphocytic, chronic myeloid, and other), and lymphoma (Hodgkin's and non-Hodgkin's), and multiple myeloma.

Examples of cancers that can be treated according to the present invention are listed in Table 3.

Table 3. Examples of Cancer Types

Acute Lymphoblastic Leukemia, Adult	Hairy Cell Leukemia
Acute Lymphoblastic Leukemia, Childhood	Head and Neck Cancer
Acute Myeloid Leukemia, Adult	Hepatocellular (Liver) Cancer, Adult (Primary)
Acute Myeloid Leukemia, Childhood	Hepatocellular (Liver) Cancer, Childhood (Primary)
Adrenocortical Carcinoma	Hodgkin's Lymphoma, Adult
Adrenocortical Carcinoma, Childhood	Hodgkin's Lymphoma, Childhood
AIDS-Related Cancers	Hodgkin's Lymphoma During Pregnancy
AIDS-Related Lymphoma	Hypopharyngeal Cancer
Anal Cancer	Hypothalamic and Visual Pathway Glioma, Childhood
Astrocytoma, Childhood Cerebellar	
Astrocytoma, Childhood Cerebral	
Basal Cell Carcinoma	Intraocular Melanoma
Bile Duct Cancer, Extrahepatic	Islet Cell Carcinoma (Endocrine Pancreas)
Bladder Cancer	
Bladder Cancer, Childhood	Kaposi's Sarcoma
Bone Cancer, Osteosarcoma/Malignant	Kidney (Renal Cell) Cancer
Fibrous Histiocytoma	Kidney Cancer, Childhood
Brain Stem Glioma, Childhood	
Brain Tumor, Adult	Laryngeal Cancer
Brain Tumor, Brain Stem Glioma, Childhood	Laryngeal Cancer, Childhood
Brain Tumor, Cerebellar Astrocytoma, Childhood	Leukemia, Acute Lymphoblastic, Adult
Brain Tumor, Cerebral	Leukemia, Acute Lymphoblastic, Childhood
Astrocytoma/Malignant Glioma, Childhood	Leukemia, Acute Myeloid, Adult
Brain Tumor, Ependymoma, Childhood	Leukemia, Acute Myeloid, Childhood
Brain Tumor, Medulloblastoma, Childhood	Leukemia, Chronic Lymphocytic
Brain Tumor, Supratentorial Primitive Neuroectodermal Tumors, Childhood	Leukemia, Chronic Myelogenous
Brain Tumor, Visual Pathway and Hypothalamic Glioma, Childhood	Leukemia, Hairy Cell
Brain Tumor, Childhood	Lip and Oral Cavity Cancer
Breast Cancer	Liver Cancer, Adult (Primary)
Breast Cancer, Childhood	Liver Cancer, Childhood (Primary)
Breast Cancer, Male	Lung Cancer, Non-Small Cell
Bronchial Adenomas/Carcinoids, Childhood	Lung Cancer, Small Cell
Burkitt's Lymphoma	Lymphoma, AIDS-Related
	Lymphoma, Burkitt's
	Lymphoma, Cutaneous T-Cell, see Mycosis Fungoides and Sézary Syndrome
	Lymphoma, Hodgkin's, Adult
	Lymphoma, Hodgkin's, Childhood
	Lymphoma, Hodgkin's During Pregnancy
	Lymphoma, Non-Hodgkin's, Adult
	Lymphoma, Non-Hodgkin's, Childhood
	Lymphoma, Non-Hodgkin's During Pregnancy
Carcinoid Tumor, Childhood	
Carcinoid Tumor, Gastrointestinal	
Carcinoma of Unknown Primary	

Central Nervous System Lymphoma, Primary Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma/Malignant Glioma, Childhood Cervical Cancer Childhood Cancers Chronic Lymphocytic Leukemia Chronic Myelogenous Leukemia Chronic Myeloproliferative Disorders Colon Cancer Colorectal Cancer, Childhood Cutaneous T-Cell Lymphoma, see Mycosis Fungoides and Sézary Syndrome Endometrial Cancer Ependymoma, Childhood Esophageal Cancer Esophageal Cancer, Childhood Ewing's Family of Tumors Extracranial Germ Cell Tumor, Childhood Extragonadal Germ Cell Tumor Extrahepatic Bile Duct Cancer Eye Cancer, Intraocular Melanoma Eye Cancer, Retinoblastoma Gallbladder Cancer Gastric (Stomach) Cancer Gastric (Stomach) Cancer, Childhood Gastrointestinal Carcinoid Tumor Germ Cell Tumor, Extracranial, Childhood Germ Cell Tumor, Extragonadal Germ Cell Tumor, Ovarian Gestational Trophoblastic Tumor Glioma, Adult Glioma, Childhood Brain Stem Glioma, Childhood Cerebral Astrocytoma Glioma, Childhood Visual Pathway and Hypothalamic Skin Cancer (Melanoma) Skin Carcinoma, Merkel Cell Small Cell Lung Cancer Small Intestine Cancer	Lymphoma, Primary Central Nervous System Macroglobulinemia, Waldenström's Malignant Fibrous Histiocytoma of Bone/Osteosarcoma Medulloblastoma, Childhood Melanoma Melanoma, Intraocular (Eye) Merkel Cell Carcinoma Mesothelioma, Adult Malignant Mesothelioma, Childhood Metastatic Squamous Neck Cancer with Occult Primary Multiple Endocrine Neoplasia Syndrome, Childhood Multiple Myeloma/Plasma Cell Neoplasm Mycosis Fungoides Myelodysplastic Syndromes Myelodysplastic/Myeloproliferative Diseases Myelogenous Leukemia, Chronic Myeloid Leukemia, Adult Acute Myeloid Leukemia, Childhood Acute Myeloma, Multiple Myeloproliferative Disorders, Chronic Nasal Cavity and Paranasal Sinus Cancer Nasopharyngeal Cancer Nasopharyngeal Cancer, Childhood Neuroblastoma Non-Hodgkin's Lymphoma, Adult Non-Hodgkin's Lymphoma, Childhood Non-Hodgkin's Lymphoma During Pregnancy Non-Small Cell Lung Cancer Oral Cancer, Childhood Oral Cavity Cancer, Lip and Oropharyngeal Cancer Osteosarcoma/Malignant Fibrous Histiocytoma of Bone Ovarian Cancer, Childhood Ovarian Epithelial Cancer Ovarian Germ Cell Tumor Ovarian Low Malignant Potential Tumor Pancreatic Cancer Pancreatic Cancer, Childhood Pancreatic Cancer, Islet Cell Paranasal Sinus and Nasal Cavity Cancer
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Soft Tissue Sarcoma, Adult Soft Tissue Sarcoma, Childhood Squamous Cell Carcinoma, see Skin Cancer (non-Melanoma) Squamous Neck Cancer with Occult Primary, Metastatic Stomach (Gastric) Cancer Stomach (Gastric) Cancer, Childhood Supratentorial Primitive Neuroectodermal Tumors, Childhood T-Cell Lymphoma, Cutaneous, see Mycosis Fungoides and Sézary Syndrome Testicular Cancer Thymoma, Childhood Thymoma and Thymic Carcinoma Thyroid Cancer Thyroid Cancer, Childhood Transitional Cell Cancer of the Renal Pelvis and Ureter Trophoblastic Tumor, Gestational Unknown Primary Site, Carcinoma of, Adult Unknown Primary Site, Cancer of, Childhood Unusual Cancers of Childhood Ureter and Renal Pelvis, Transitional Cell Cancer Urethral Cancer Uterine Cancer, Endometrial Uterine Sarcoma Vaginal Cancer Visual Pathway and Hypothalamic Glioma, Childhood Vulvar Cancer Waldenström's Macroglobulinemia Wilms' Tumor	Parathyroid Cancer Penile Cancer Pheochromocytoma Pineoblastoma and Supratentorial Primitive Neuroectodermal Tumors, Childhood Pituitary Tumor Plasma Cell Neoplasm/Multiple Myeloma Pleuropulmonary Blastoma Pregnancy and Breast Cancer Pregnancy and Hodgkin's Lymphoma Pregnancy and Non-Hodgkin's Lymphoma Primary Central Nervous System Lymphoma Prostate Cancer Rectal Cancer Renal Cell (Kidney) Cancer Renal Cell (Kidney) Cancer, Childhood Renal Pelvis and Ureter, Transitional Cell Cancer Retinoblastoma Rhabdomyosarcoma, Childhood Salivary Gland Cancer Salivary Gland Cancer, Childhood Sarcoma, Ewing's Family of Tumors Sarcoma, Kaposi's Sarcoma, Soft Tissue, Adult Sarcoma, Soft Tissue, Childhood Sarcoma, Uterine Sezary Syndrome Skin Cancer (non-Melanoma) Skin Cancer, Childhood
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For the treatment of oncological disorders, the compounds of this invention can be administered to a patient in need of treatment in combination with other antitumor or anticancer substances and/or with radiation and/or photodynamic therapy and/or with

surgical treatment to remove a tumor. These other substances or treatments may be given at the same as or at different times from the compounds of this invention. For example, the compounds of the present invention can be used in combination with mitotic inhibitors such as taxol or vinblastine, alkylating agents such as cyclophosphamide or ifosfamide, antimetabolites such as 5-fluorouracil or hydroxyurea, DNA intercalators such as adriamycin or bleomycin, topoisomerase inhibitors such as etoposide or camptothecin, antiangiogenic agents such as angiostatin, antiestrogens such as tamoxifen, and/or other anti-cancer drugs or antibodies, such as, for example, GLEEVEC (Novartis Pharmaceuticals Corporation) and HERCEPTIN (Genentech, Inc.), respectively. In one embodiment, compounds and compositions of the invention can be used in combination with other ROCK inhibitors, including, but not limited to, Y27632, Wf536, Fasudil, H-1152P, and CID5056270.

Many tumors and cancers have viral genome present in the tumor or cancer cells. For example, Epstein-Barr Virus (EBV) is associated with a number of mammalian malignancies. The compounds of the subject invention can also be used alone or in combination with anticancer or antiviral agents, such as ganciclovir, azidothymidine (AZT), lamivudine (3TC), *etc.*, to treat patients infected with a virus that can cause cellular transformation and/or to treat patients having a tumor or cancer that is associated with the presence of viral genome in the cells. The compounds of the subject invention can also be used in combination with viral based treatments of oncologic disease. For example, compounds of the invention can be used with mutant herpes simplex virus in the treatment of non-small cell lung cancer (Toyoizumi *et al.*, 1999).

The methods of the present invention can be used with humans and other animals. The other animals contemplated within the scope of the invention include domesticated, agricultural, or zoo- or circus-maintained animals. Domesticated animals include, for example, dogs, cats, rabbits, ferrets, guinea pigs, hamsters, pigs, monkeys or other primates, and gerbils. Agricultural animals include, for example, horses, mules, donkeys, burros, cattle, cows, pigs, sheep, and alligators. Zoo- or circus-maintained animals include, for example, lions, tigers, bears, camels, giraffes, hippopotamuses, and rhinoceroses.

While inhibitor compounds or agents of the invention can be administered as isolated compounds or agents, these compounds can also be administered as part of a

pharmaceutical composition. The subject invention thus further provides compositions comprising one or more compounds or agents in association with at least one pharmaceutically acceptable carrier. The pharmaceutical composition can be adapted for various routes of administration, such as enteral, parenteral, intravenous, intramuscular, 5 topical, subcutaneous, and so forth. Administration can be continuous or at distinct intervals, as can be determined by a person of ordinary skill in the art.

The inhibitor compounds or agents of the invention can be formulated according to known methods for preparing pharmaceutically useful compositions. Formulations are described in a number of sources which are well known and readily available to those 10 skilled in the art. For example, *Remington's Pharmaceutical Science* (Martin 1995) describes formulations which can be used in connection with the subject invention. Formulations suitable for administration include, for example, aqueous sterile injection solutions, which may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and 15 nonaqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the condition of the sterile liquid carrier, for example, water for injections, prior to use. Extemporaneous injection solutions and suspensions may be 20 prepared from sterile powder, granules, tablets, *etc.* It should be understood that in addition to the ingredients particularly mentioned above, the compositions of the subject invention can include other agents conventional in the art having regard to the type of formulation in question.

The compounds and agents of the present invention include all hydrates and salts 25 that can be prepared by those of skill in the art. Under conditions where the compounds and agents of the present invention are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids that form a physiological acceptable anion, for example, tosylate, methanesulfonate, 30 acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, alpha-ketoglutarate, and alpha-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts of a compound or agent may be obtained using standard procedures well known in the art, for example, by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

Therapeutic application of compounds and/or agents and compositions containing them can be accomplished by any suitable therapeutic method and technique presently or prospectively known to those skilled in the art. Further, compounds and agents of the invention have use as starting materials or intermediates for the preparation of other useful compounds and compositions.

Compounds and agents of the invention, and compositions thereof, may be locally administered at one or more anatomical sites, such as sites of unwanted cell growth (such as a tumor site or benign skin growth, *e.g.*, injected or topically applied to the tumor or skin growth) or sites of fungal infection, optionally in combination with a pharmaceutically acceptable carrier such as an inert diluent. Compounds and agents of the invention, and compositions thereof, may be systemically administered, such as intravenously or orally, optionally in combination with a pharmaceutically acceptable carrier such as an inert diluent, or an assimilable edible carrier for oral delivery. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, aerosol sprays, and the like.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For

instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac, or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

Compounds and agents and compositions of the invention, including pharmaceutically acceptable salts or analogs thereof, can be administered intravenously, intramuscularly, or intraperitoneally by infusion or injection. Solutions of the active agent or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations can contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. The ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. Optionally, the prevention of the action of microorganisms can be brought about by various other antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the inclusion of agents that delay absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating a compound and/or agent of the invention in the required amount in the appropriate solvent with various other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, compounds and agents of the invention may be applied in as a liquid or solid. However, it will generally be desirable to administer them topically to the skin as compositions, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid. Compounds and agents and compositions of the subject invention can be applied topically to a subject's skin to reduce the size (and may include complete removal) of malignant or benign growths, or to treat an infection site. Compounds and agents of the invention can be applied directly to the growth or infection site. Preferably, the compounds and agents are applied to the growth or infection site in a formulation such as an ointment, cream, lotion, solution, tincture, or the like. Drug delivery systems for delivery of pharmacological substances to dermal lesions can also be used, such as that described in U.S. Patent No. 5,167,649.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers, for example.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user. Examples of useful dermatological compositions which can be used to deliver a compound to the skin are disclosed in U.S.

Patent No. 4,608,392; U.S. Patent No. 4,992,478; U.S. Patent No. 4,559,157; and U.S. Patent No. 4,820,508.

Useful dosages of the compounds and agents and pharmaceutical compositions of the present invention can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Patent No. 4,938,949.

The present invention also concerns pharmaceutical compositions comprising a compound and/or agent of the invention in combination with a pharmaceutically acceptable carrier. Pharmaceutical compositions adapted for oral, topical or parenteral administration, comprising an amount of a compound constitute a preferred embodiment of the invention. The dose administered to a patient, particularly a human, in the context of the present invention should be sufficient to achieve a therapeutic response in the patient over a reasonable time frame, without lethal toxicity, and preferably causing no more than an acceptable level of side effects or morbidity. One skilled in the art will recognize that dosage will depend upon a variety of factors including the condition (health) of the subject, the body weight of the subject, kind of concurrent treatment, if any, frequency of treatment, therapeutic ratio, as well as the severity and stage of the pathological condition.

For the treatment of oncological disorders, compounds and agents and compositions contemplated by the present invention can be administered to a patient in need of treatment prior to, subsequent to, or in combination with other antitumor or anticancer agents or substances (*e.g.*, chemotherapeutic agents, immunotherapeutic agents, radiotherapeutic agents, cytotoxic agents, *etc.*) and/or with radiation therapy and/or with surgical treatment to remove a tumor. For example, compounds and agents and compositions of the present invention can be used in methods of treating cancer wherein the patient is to be treated or is or has been treated with mitotic inhibitors such as taxol or vinblastine, alkylating agents such as cyclophosphamide or ifosfamide, antimetabolites such as 5-fluorouracil or hydroxyurea, DNA intercalators such as adriamycin or bleomycin, topoisomerase inhibitors such as etoposide or camptothecin, antiangiogenic agents such as angiostatin, antiestrogens such as tamoxifen, and/or other anti-cancer drugs or antibodies, such as, for example, GLEEVEC (Novartis

Pharmaceuticals Corporation) and HERCEPTIN (Genentech, Inc.), respectively. These other substances or radiation treatments may be given at the same as or at different times from the compounds of this invention. Examples of other chemotherapeutic agents contemplated within the scope of the invention include, but are not limited to, altretamine, bleomycin, bortezomib (VELCADE), busulphan, calcium folinate, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, crisantaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, fludarabine, fluorouracil, gefitinib (IRESSA), gemcitabine, hydroxyurea, idarubicin, ifosfamide, imatinib (GLEEVEC), irinotecan, liposomal doxorubicin, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitoxantrone, oxaliplatin, paclitaxel, pentostatin, procarbazine, raltitrexed, streptozocin, tegafur-uracil, temozolomide, thiotepa, tioguanine/thioguanine, topotecan, treosulfan, vinblastine, vincristine, vindesine, vinorelbine. In an exemplified embodiment, the chemotherapeutic agent is melphalan. Examples of immunotherapeutic agents contemplated within the scope of the invention include, but are not limited to, alemtuzumab, cetuximab (ERBITUX), gemtuzumab, iodine 131 tositumomab, rituximab, trastuzumab (HERCEPTIN). Cytotoxic agents include, for example, radioactive isotopes (*e.g.*, I^{131} , I^{125} , Y^{90} , P^{32} , *etc.*), and toxins of bacterial, fungal, plant, or animal origin (*e.g.*, ricin, botulinum toxin, anthrax toxin, aflatoxin, jellyfish venoms (*e.g.*, box jellyfish), *etc.*)

The subject invention also concerns methods for treating an oncological disorder comprising administering an effective amount of a compound and/or agent of the invention prior to, subsequent to, and/or in combination with administration of a chemotherapeutic agent, an immunotherapeutic agent, a radiotherapeutic agent, or radiotherapy.

Examples of some chemotherapeutic agents that can be used according to the present invention are listed in Table 4.

Table 4. Examples of Chemotherapeutic Agents

- 13-cis-Retinoic Acid	- Mylocel
-2-Amino-6-Mercaptopurine	- Letrozole
- 2-CdA	- Neosar
- 2-Chlorodeoxyadenosine	- Neulasta
	- Neumega

- 5-fluorouracil	- Neupogen
- 5-FU	- Nilandron
- 6 - TG	- Nilutamide
- 6 - Thioguanine	- Nitrogen Mustard
- 6-Mercaptopurine	- Novaldex
- 6-MP	- Novantrone
- Accutane	- Octreotide
- Actinomycin-D	- Octreotide acetate
- Adriamycin	- Oncospar
- Adrucil	- Oncovin
- Agrylin	- Ontak
- Ala-Cort	- Onxal
- Aldesleukin	- Oprevelkin
- Alemtuzumab	- Orapred
- Alitretinoin	- Orasone
- Alkaban-AQ	- Oxaliplatin
- Alkeran	- Paclitaxel
- All-transretinoic acid	- Pamidronate
- Alpha interferon	- Panretin
- Altretamine	- Paraplatin
- Amethopterin	- Pediapred
- Amifostine	- PEG Interferon
- Aminoglutethimide	- Pegaspargase
- Anagrelide	- Pegfilgrastim
- Anandron	- PEG-INTRON
- Anastrozole	- PEG-L-asparaginase
- Arabinosylcytosine	- Phenylalanine Mustard
- Ara-C	- Platinol
- Aranesp	- Platinol-AQ
- Aredia	- Prednisolone
- Arimidex	- Prednisone
- Aromasin	- Prelone
- Arsenic trioxide	- Procarbazine
- Asparaginase	- PROCRIT
- ATRA	- Proleukin
- Avastin	- Prolifeprospan 20 with Carmustine implant
- BCG	- Purinethol
- BCNU	- Raloxifene
- Bevacizumab	- Rheumatrex
- Bexarotene	- Rituxan
- Bicalutamide	- Rituximab
- BiCNU	- Roveron-A (interferon alfa-2a)
- Blenoxane	- Rubex
- Bleomycin	- Rubidomycin hydrochloride
- Bortezomib	- Sandostatin

- Busulfan	- Sandostatin LAR
- Busulfex	- Sargramostim
- C225	- Solu-Cortef
- Calcium Leucovorin	- Solu-Medrol
- Campath	- STI-571
- Camptosar	- Streptozocin
- Camptothecin-11	- Tamoxifen
- Capecitabine	- Targretin
- Carac	- Taxol
- Carboplatin	- Taxotere
- Carmustine	- Temodar
- Carmustine wafer	- Temozolomide
- Casodex	- Teniposide
- CCNU	- TESPAs
- CDDP	- Thalidomide
- CeeNU	- Thalomid
- Cerubidine	- TheraCys
- cetuximab	- Thioguanine
- Chlorambucil	- Thioguanine Tabloid
- Cisplatin	- Thiophosphoamide
- Citrovorum Factor	- Thioplex
- Cladribine	- Thiotepa
- Cortisone	- TICE
- Cosmegen	- Toposar
- CPT-11	- Topotecan
- Cyclophosphamide	- Toremifene
- Cytadren	- Trastuzumab
- Cytarabine	- Tretinoin
- Cytarabine liposomal	- Trexall
- Cytosar-U	- Trisenox
- Cytosan	- TSPA
- Dacarbazine	- VCR
- Dactinomycin	- Velban
- Darbepoetin alfa	- Velcade
- Daunomycin	- VePesid
- Daunorubicin	- Vesanoid
- Daunorubicin hydrochloride	- Viadur
- Daunorubicin liposomal	- Vinblastine
- DaunoXome	- Vinblastine Sulfate
- Decadron	- Vincasar Pfs
- Delta-Cortef	- Vincristine
- Deltasone	- Vinorelbine
- Denileukin diftitox	- Vinorelbine tartrate
- DepoCyt	- VLB
	- VP-16

- Dexamethasone	- Vumon
- Dexamethasone acetate	- Xeloda
- dexamethasone sodium phosphate	- Zanosar
- Dexasone	- Zevalin
- Dexrazoxane	- Zinecard
- DHAD	- Zoladex
- DIC	- Zoledronic acid
- Diodex	- Zometa
- Docetaxel	- Gliadel wafer
- Doxil	- Glivec
- Doxorubicin	- GM-CSF
- Doxorubicin liposomal	- Goserelin
- Droxia	- granulocyte - colony stimulating factor
- DTIC	- Granulocyte macrophage colony stimulating factor
- DTIC-Dome	- Halotestin
- Duralone	- Herceptin
- Efudex	- Hexadrol
- Eligard	- Hexalen
- Ellence	- Hexamethylmelamine
- Eloxatin	- HMM
- Elspar	- Hycamtin
- Emcyt	- Hydrea
- Epirubicin	- Hydrocort Acetate
- Epoetin alfa	- Hydrocortisone
- Erbitux	- Hydrocortisone sodium phosphate
- Erwinia L-asparaginase	- Hydrocortisone sodium succinate
- Estramustine	- Hydrocortone phosphate
- Ethyol	- Hydroxyurea
- Etopophos	- Ibritumomab
- Etoposide	- Ibritumomab Tiuxetan
- Etoposide phosphate	- Idamycin
- Eulexin	- Idarubicin
- Evista	- Ifex
- Exemestane	- IFN-alpha
- Fareston	- Ifosfamide
- Faslodex	- IL - 2
- Femara	- IL-11
- Filgrastim	- Imatinib mesylate
- Floxuridine	- Imidazole Carboxamide
- Fludara	- Interferon alfa
- Fludarabine	- Interferon Alfa-2b (PEG conjugate)
- Fluoroplex	- Interleukin - 2
- Fluorouracil	- Interleukin-11
- Fluorouracil (cream)	- Intron A (interferon alfa-2b)

- Fluoxymesterone	- Leucovorin
- Flutamide	- Leukeran
- Folinic Acid	- Leukine
- FUDR	- Leuprolide
- Fulvestrant	- Leurocristine
- G-CSF	- Leustatin
- Gefitinib	- Liposomal Ara-C
- Gemcitabine	- Liquid Pred
- Gemtuzumab ozogamicin	- Lomustine
- Gemzar	- L-PAM
- Gleevec	- L-Sarcolysin
- Lupron	- Meticorten
- Lupron Depot	- Mitomycin
- Matulane	- Mitomycin-C
- Maxidex	- Mitoxantrone
- Mechlorethamine	- M-Prednisol
-Mechlorethamine Hydrochlorine	- MTC
- Medralone	- MTX
- Medrol	- Mustargen
- Megace	- Mustine
- Megestrol	- Mutamycin
- Megestrol Acetate	- Myleran
- Melphalan	- Iressa
- Mercaptopurine	- Irinotecan
- Mesna	- Isotretinoin
- Mesnex	- Kidrolase
- Methotrexate	- Lanacort
- Methotrexate Sodium	- L-asparaginase
- Methylprednisolone	- LCR

The subject invention also concerns methods for inhibiting a ROCK protein in a cell by contacting the cell with an effective amount of a compound, agent, or composition of the invention. In one embodiment, the cell is a human or mammalian cell, and can be a cancer or tumor cell or other cell that exhibits abnormal proliferation, survival, migration or differentiation. In one embodiment, the cell constitutively expresses or expresses elevated or abnormal levels of a ROCK protein. In a specific embodiment, the compound is the compound designated herein as 30b. In another embodiment, the compound is the compound designated herein as 30h. In a specific embodiment, the 30h compound is the (R) stereoisomer.

The subject invention also concerns methods for treating a person or animal having a disorder associated with constitutive, abnormal, or elevated expression of a ROCK protein in a cell, wherein a therapeutically effective amount of a compound, agent, or composition of the invention is administered to the person or animal. The disorder can be one characterized, for example, by abnormal cell proliferation, cell survival, cell migration, and/or cell differentiation. In a specific embodiment, the compound is the compound designated herein as 30b. In another embodiment, the compound is the compound designated herein as 30h. In a specific embodiment, the 30h compound is the (R) stereoisomer.

Depending upon the disorder or disease condition to be treated, a suitable dose(s) may be that amount that will reduce proliferation or growth of the target cell(s). In the context of cancer, a suitable dose(s) is that which will result in a concentration of the active agent in cancer tissue, such as a malignant tumor, which is known to achieve the desired response. The preferred dosage is the amount which results in maximum inhibition of cancer cell growth, without unmanageable side effects. Administration of a compound and/or agent can be continuous or at distinct intervals, as can be determined by a person of ordinary skill in the art.

To provide for the administration of such dosages for the desired therapeutic treatment, in some embodiments, pharmaceutical compositions of the invention can comprise between about 0.1% and 45%, and especially, 1 and 15%, by weight of the total of one or more of the compounds based on the weight of the total composition including carrier or diluents. Illustratively, dosage levels of the administered active ingredients can be: intravenous, 0.01 to about 20 mg/kg; intraperitoneal, 0.01 to about 100 mg/kg; subcutaneous, 0.01 to about 100 mg/kg; intramuscular, 0.01 to about 100 mg/kg; orally 0.01 to about 200 mg/kg, and preferably about 1 to 100 mg/kg; intranasal instillation, 0.01 to about 20 mg/kg; and aerosol, 0.01 to about 20 mg/kg of animal (body) weight.

The subject invention also concerns kits comprising a composition comprising an inhibitor compound and/or agent of the invention in one or more containers. Kits of the invention can optionally include pharmaceutically acceptable carriers and/or diluents. In one embodiment, a kit of the invention includes one or more other components, adjuncts, or adjuvants as described herein. In another embodiment, a kit includes one or more anti-cancer agents, such as those agents described herein. In one embodiment, a kit of the

invention includes instructions or packaging materials that describe how to administer a compound or composition of the kit. Containers of the kit can be of any suitable material, e.g., glass, plastic, metal, *etc.*, and of any suitable size, shape, or configuration. In one embodiment, a compound and/or agent of the invention is provided in the kit as a solid, such as a tablet, pill, or powder form. In another embodiment, a compound and/or agent of the invention is provided in the kit as a liquid or solution. In one embodiment, the kit comprises an ampoule or syringe containing a compound and/or agent of the invention in liquid or solution form. A kit of the invention can also optionally comprise, in addition to an inhibitor compound or composition of the invention, other ROCK inhibitors, including, but not limited to, Y27632, Wf536, Fasudil, H-1152P, and/or CID5056270.

Mammalian species which benefit from the disclosed methods include, but are not limited to, primates, such as apes, chimpanzees, orangutans, humans, monkeys; domesticated animals (e.g., pets) such as dogs, cats, guinea pigs, hamsters, Vietnamese pot-bellied pigs, rabbits, and ferrets; domesticated farm animals such as cows, buffalo, bison, horses, donkey, swine, sheep, and goats; exotic animals typically found in zoos, such as bear, lions, tigers, panthers, elephants, hippopotamus, rhinoceros, giraffes, antelopes, sloth, gazelles, zebras, wildebeests, prairie dogs, koala bears, kangaroo, opossums, raccoons, pandas, hyena, seals, sea lions, elephant seals, otters, porpoises, dolphins, and whales. Other species that may benefit from the disclosed methods include fish, amphibians, avians, and reptiles. As used herein, the terms “patient” and “subject” are used interchangeably and are intended to include such human and non-human species. Likewise, *in vitro* methods of the present invention can be carried out on cells of such human and non-human species.

The inventors have established a program to develop potent and selective ROCK1 inhibitors to provide *in vitro* and *in vivo* tools to probe the pharmacological inhibition of ROCK1 and to further establish its role in cancer and metastasis. The inventors undertook a screen of the NCI Diversity set using a Z-lyte FRET assay (Kang *et al.* (2009); Wu *et al.* (2010)) to measure kinase inhibition. NSC-135784 (de Suto-Nagy *et al.* (1941)) was identified as a weak inhibitor (IC₅₀ 92 μ M). Active in only 1 screen from 127 assessed in the Molecular Libraries Screening Centers Network (MLSCN) (Huryn *et al.* (2007); Huryn (2009)), NSC-135784 appeared to be a good hit for library development and was synthesized to confirm the identity of the NCI sample and the

ROCK inhibition [**1aa** (*in house* NSC-135784): ROCK1: IC₅₀ = 38 μ M; ROCK2: IC₅₀ = 25 μ M]. NSC-135784 was chosen as a starting point for the development of novel ROCK inhibitors.

5

MATERIALS AND METHODS

Chemistry

The inventors prepared the hit **1aa** following the synthetic routes depicted in Scheme 1 (EtOH, microwave heating, 120 °C, 10 min). To establish a preliminary structure activity relationship the library of 4-anilino-2-aminopyrimidines **1** was rapidly synthesized *via* microwave-assisted reaction of anilines **2** with 4-chloropyrimidin-2-amine (**3**) (Scheme 1). The use of microwave-assisted heating was successfully applied to the synthesis of analogs **6-8** that possess different A-rings (Scheme 2). The nitrogen atom linking the two rings of NSC-135784 was replaced by an oxygen atom as shown in Scheme 3. This library of 4-(2-aminopyrimidyl) phenyl ethers **10** was prepared by reacting with 4-chloropyrimidin-2-amine (**3**) with commercially available phenols **9** (microwave heating, 165 °C, 10 min).

The hit optimization process initially directed us towards the generation of a small library of indoline **13** and indoles **15** (Scheme 4, conditions b, c, d or e). The indoline building blocks **12** were either commercially available or prepared *in-house* *via* reduction of the corresponding commercially available indoles **11** (Scheme 4, conditions a). To further explore the structure activity relationships, additional analogs **16-18** were synthesized according to the route illustrated in Scheme 5.

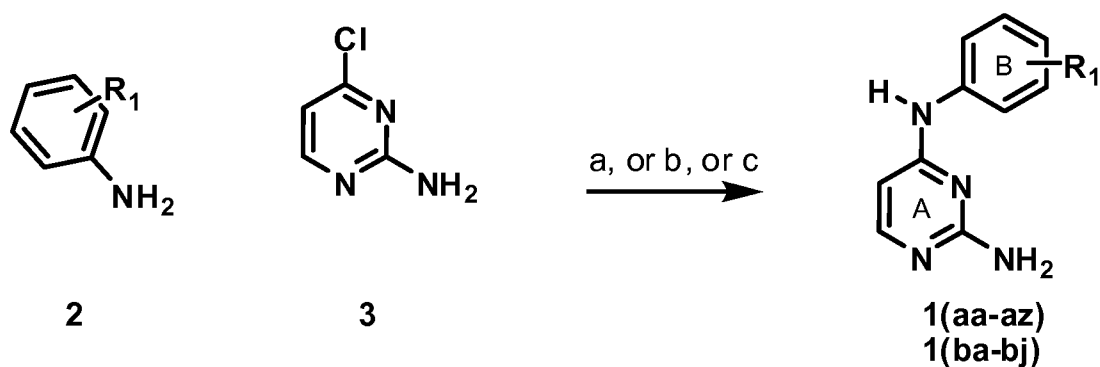
The series of indoles **21** was prepared as illustrated in Scheme 6. The synthesis involves the alkylation of available phenols with benzyl halides **19** to afford the indole building blocks **20**, which were subsequently reacted with 4-chloropyrimidin-2-amine (**3**) to afford the desired library **21**. The synthesis of amide building blocks **23** was achieved *via* coupling of various commercially indole carboxylic acids with inexpensive and readily available amines **22** (benzylamines, anilines, and phenethylamines) using EDC as coupling reagent in presence of catalytic amount of DMAP (Scheme 6). These conditions were also successfully applied to the preparation of reverse-amide building blocks **26** and the alpha-substituted benzylamides **29** from **25** and **28** respectively. Alternatively, EDC/HOBt coupling reagents were utilized for the synthesis of the alpha-substituted

benzylamides **29** (Scheme 6, condition c). Finally, microwave heating provided an efficient and convenient method for the rapid generation of the desired libraries **24**, **27** and **30** (Scheme 6) using the same conditions described for library **21** (DMF, Cs₂CO₃, 150 °C, microwave, 30 min). As seen in our preliminary SAR (compounds **6**, **7**, **8**), one aspect of the SAR focused on the effect of the modifications of the 2-amino-pyrimidyl position on selected compounds of interest. The synthesis of N-phenylpyrimidine **33** was successfully carried out via microwave-assisted heating under acidic conditions (aq. 0.1 M HCl) (Scheme 7). The pyrrolo containing pyrimidine **35** was prepared as under the conditions described in Scheme 8. Treatment of **30b** with acetic anhydride afforded the N-acyl derivative **36** (Scheme 9). Finally, reaction of **29a** and **37** afforded the target compound **38**.

The synthesis of analogs **46** and **47** is illustrated in Scheme 11 and 12. The synthesis of amide and sulfonamide building blocks **41** and **44** was achieved *via* coupling of commercially available *para*-nitrobenzoyl chloride and *para*-nitrosulfonyl chloride with 3-methoxybenzylamine **40** (Scheme 11). Tin chloride was utilized for the reduction of **41** and **44** to the corresponding aniline **42** and **45**. Finally, microwave heating provided an efficient and convenient method for the rapid generation of **46** and **47** (Scheme 12) (EtOH, 150 °C, microwave, 20 min).

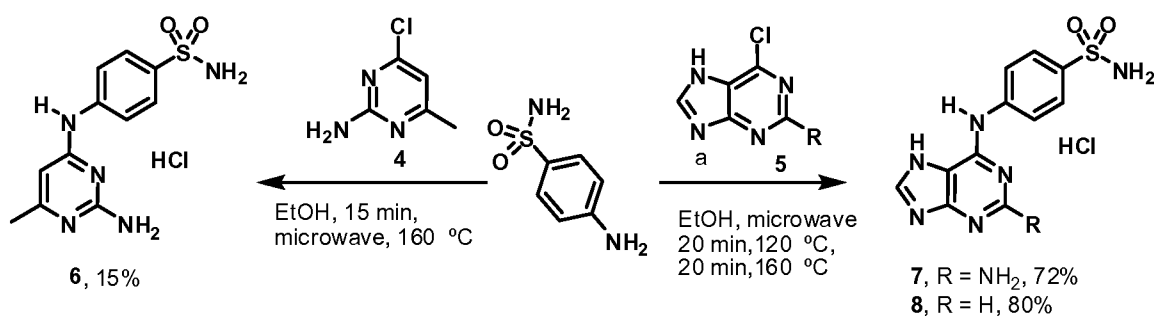
The structures of all final compounds were confirmed by their spectroscopy data. In addition, HPLC methods were also developed to assess the purity (generally > 96%) of the most potent compounds.

Scheme 1

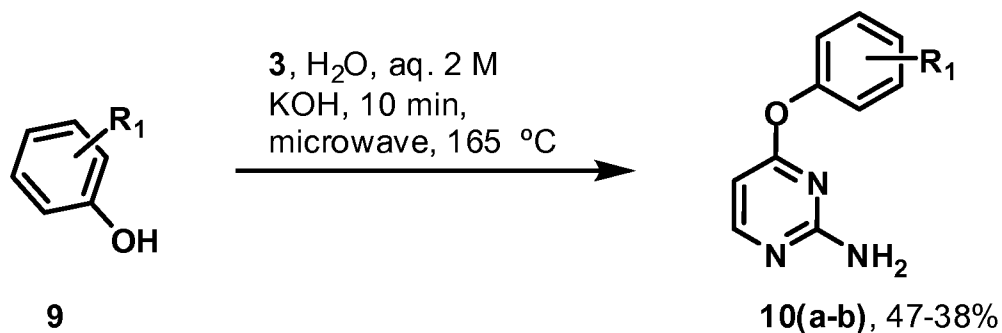


Conditions: a) EtOH, 10-20 min, microwave, 120 °C; EtOH, 15-20 min, microwave, 150 °C. Product **1** was isolated as the HCl salt from methods a and c, and as the freebase from method b.

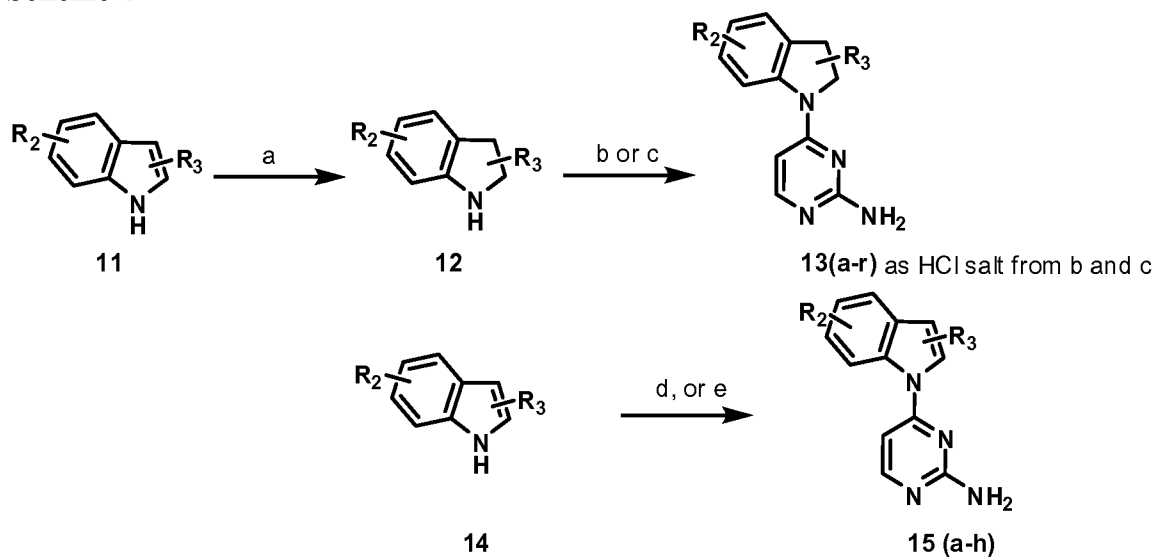
Scheme 2



Scheme 3

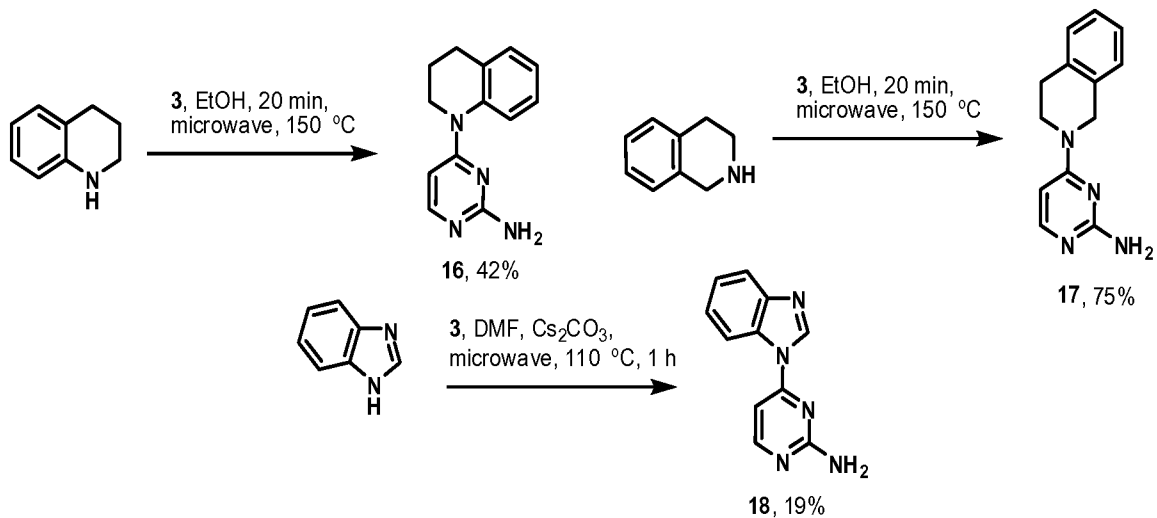


Scheme 4

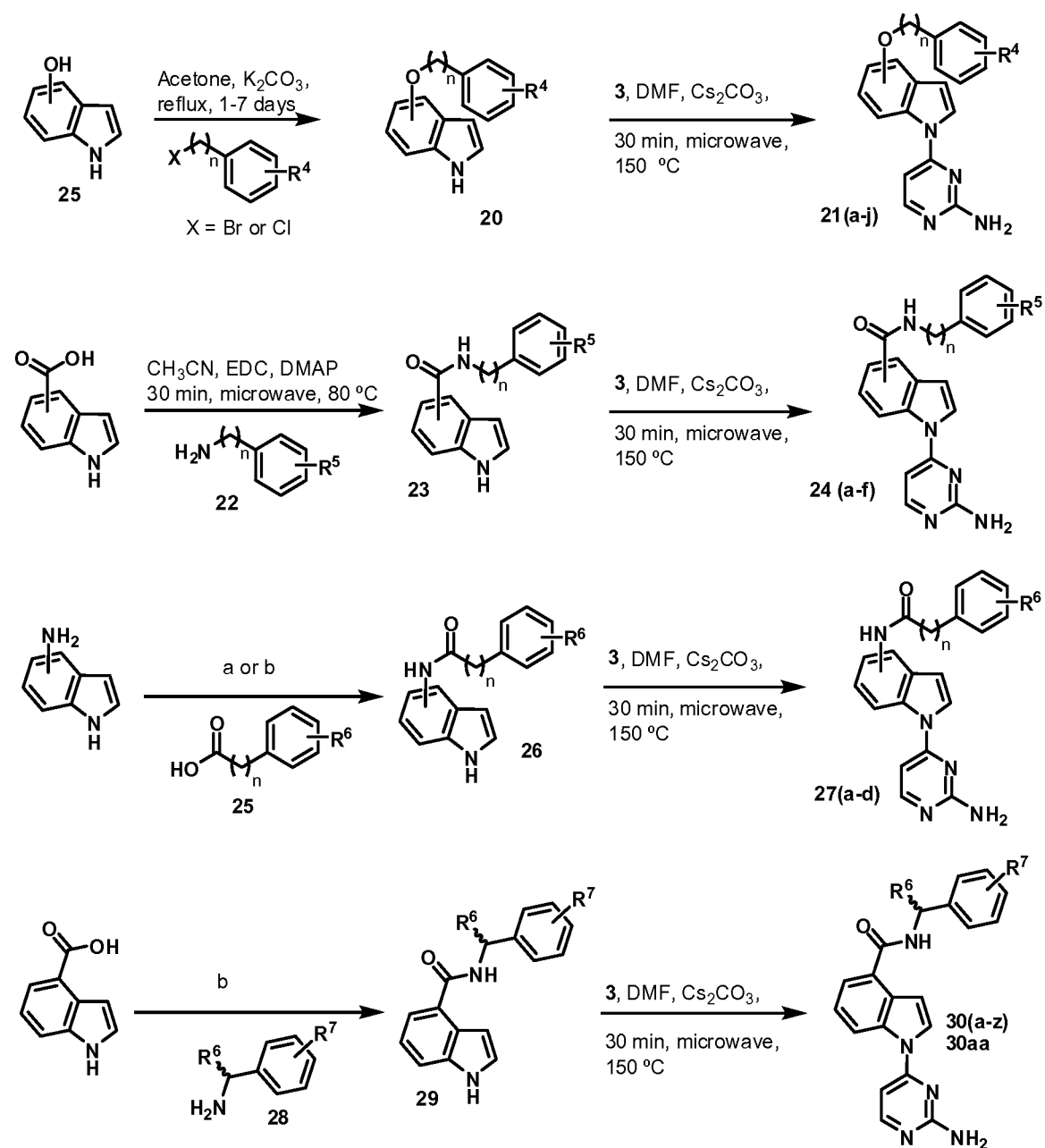


Conditions: a) AcOH NaCNBH₃, rt, 3 h; b) 3, EtOH, 20-30 min, microwave, 120 °C; c) 3, EtOH, 15 min, microwave, 150 °C; d) 3, DMF, Cs₂CO₃, microwave, 110 °C, 1 h; e) 3, NMP, Cs₂CO₃, microwave, 150 °C, 30 min.

Scheme 5



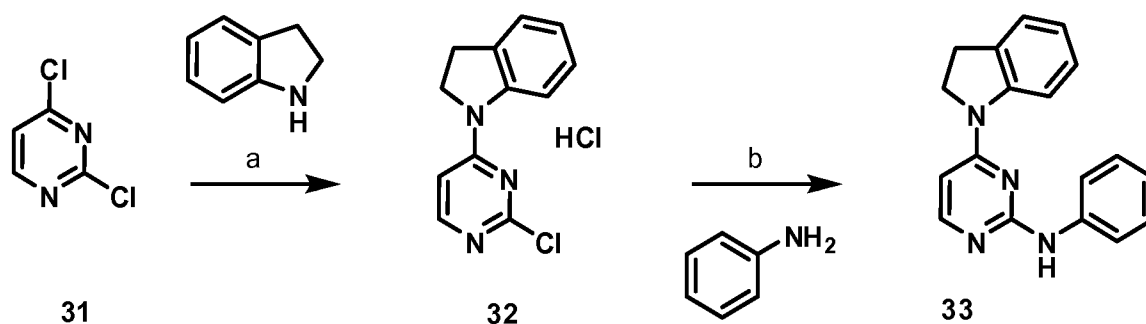
Scheme 6.



Conditions: a) CH₃CN, EDC, DMAP, 15-30 min, microwave, 60 °C; b) CH₃CN, EDC, DMAP, 15-60 min, microwave, 80 °C

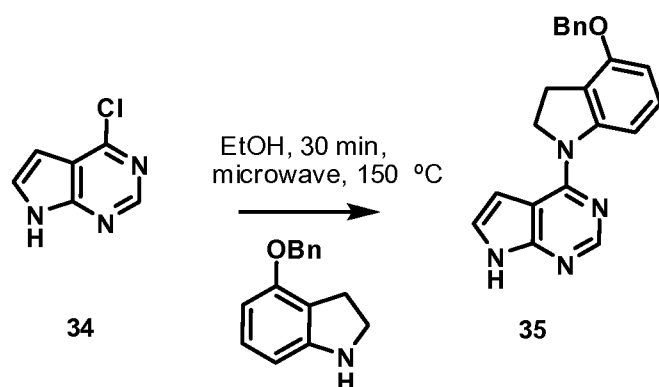
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Scheme 7.



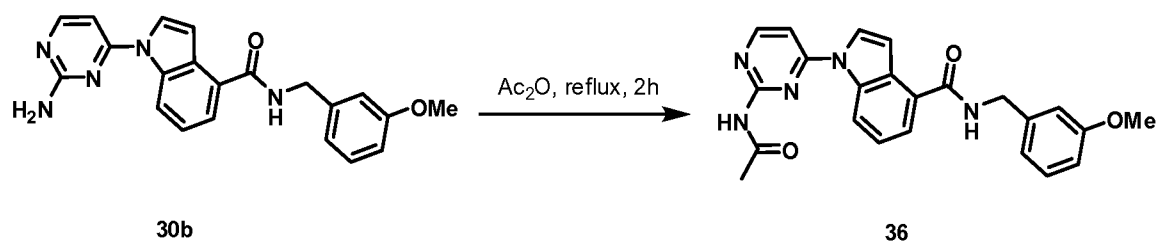
Conditions: a) Aq. 0.1M HCl, 30 min, microwave, 100 °C; b) Aq. 0.1M HCl, 15 min, microwave, 160 °C

Scheme 8.



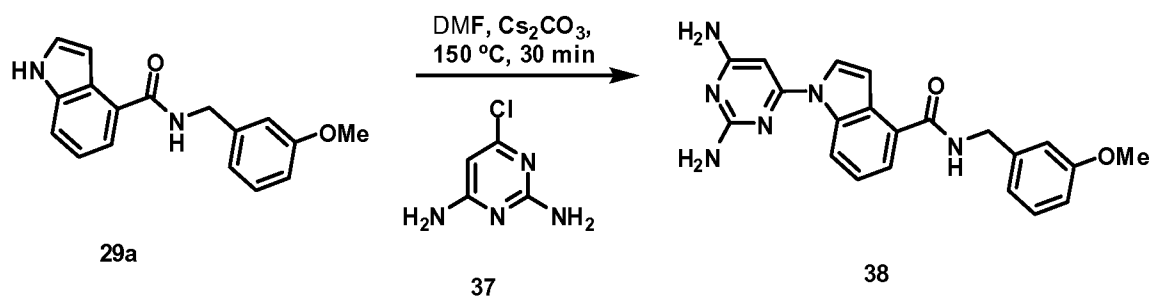
Conditions: a) EtOH 30 min, microwave, 100 °C; b) Aq. 0.1M HCl, 15 min, microwave, 160 °C.

Scheme 9.



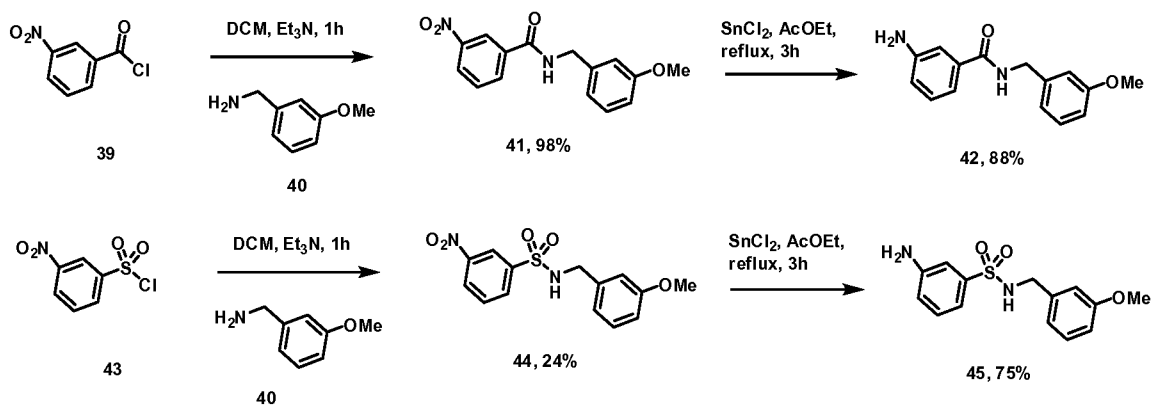
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Scheme 10



5

Scheme 11



Scheme 12

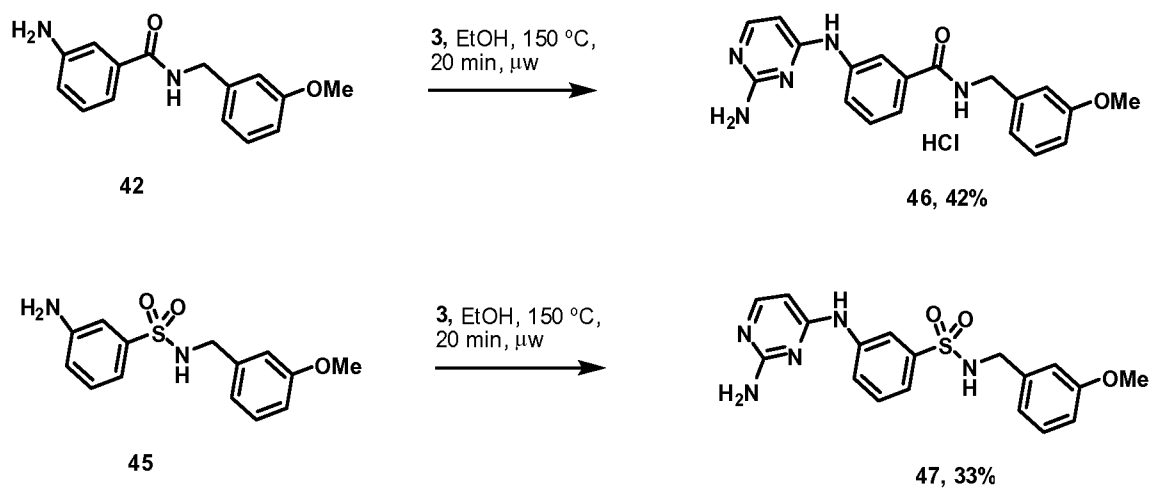
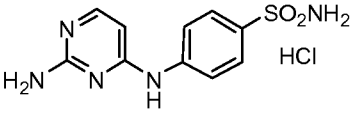
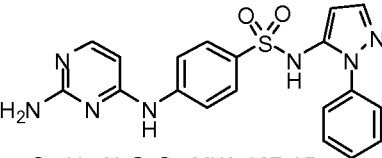
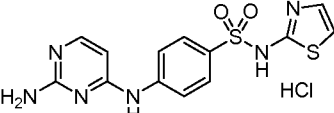
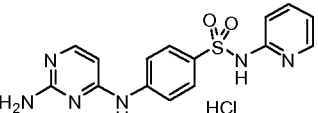
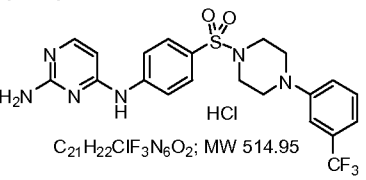
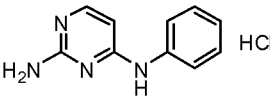
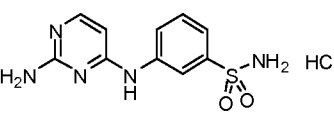
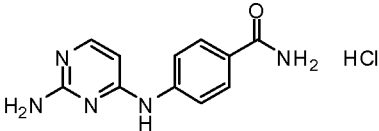
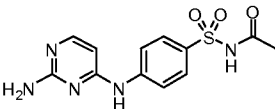
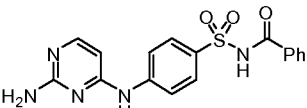
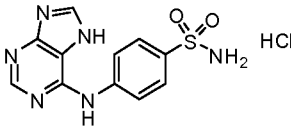
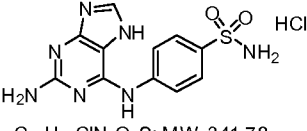
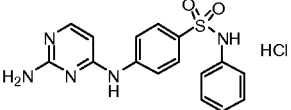
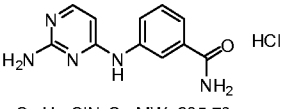
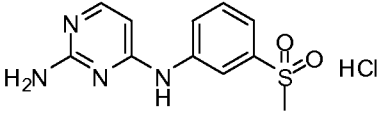
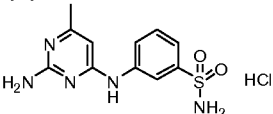
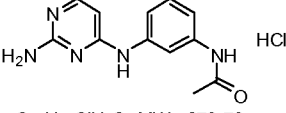
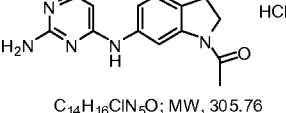
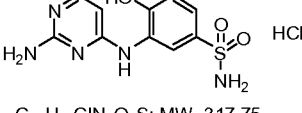
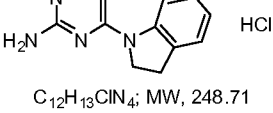
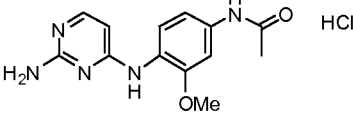
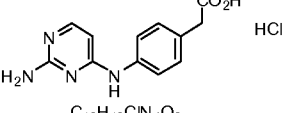
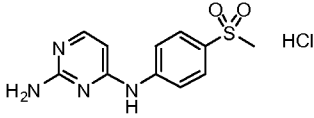
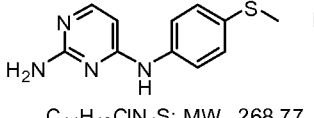
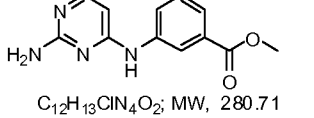
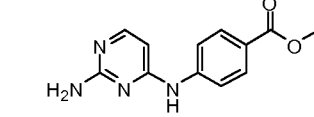
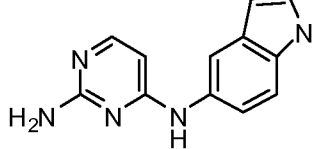
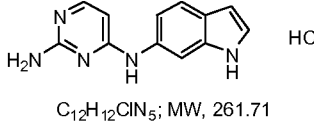
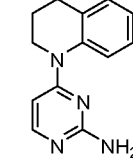


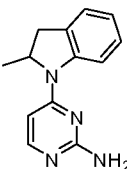
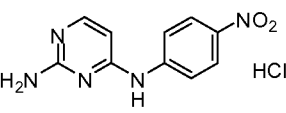
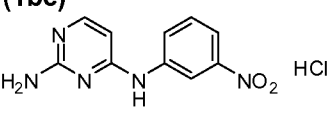
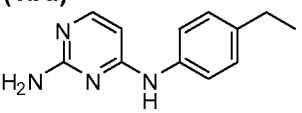
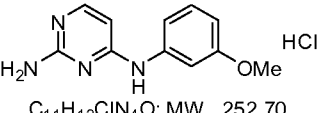
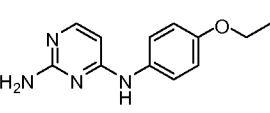
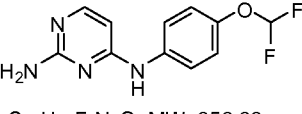
Table 5: Examples of compounds, structures and ROCK1&2 IC₅₀ (μM)

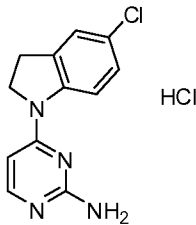
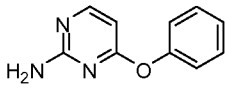
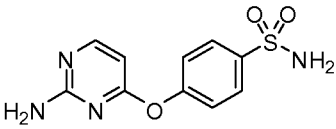
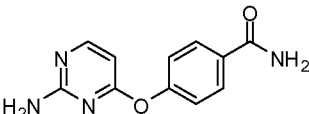
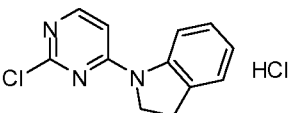
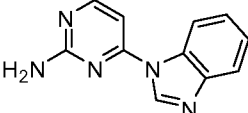
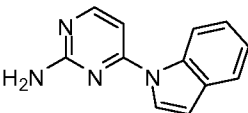
Compound ID, Structure, formula and MW	ROCK1 % inhibition @ 50 μM otherwise specified	ROCK1 IC ₅₀ (μM)	ROCK2 IC ₅₀ (μM)
(1aa) (in house NSC135784)  <chem>Nc1nc(NC2=CC=C(S(=O)(=O)N)C=C2)ncn1</chem> HCl C ₁₀ H ₁₂ ClN ₅ O ₂ S; MW, 301.75	60 ± 3	38.5 ± 3.4	25.5 ± 5.8
(1ab)  <chem>Nc1nc(NC2=CC=C(S(=O)(=O)N3C=CC4=CC=CC=C4N3)C=C2)ncn1</chem> C ₁₉ H ₁₇ N ₇ O ₂ S; MW, 407.45	1.8 ± 0.8	nd	nd
(1ac)  <chem>Nc1nc(NC2=CC=C(S(=O)(=O)N3C=CC=C(S3)C=C2)C=C2)ncn1</chem> HCl C ₁₃ H ₁₃ ClN ₆ O ₂ S ₂ ; MW, 384.86	21 ± 10	nd	nd
(1ad)  <chem>Nc1nc(NC2=CC=C(S(=O)(=O)N3C=CC=CC=N3)C=C2)ncn1</chem> HCl C ₁₅ H ₁₅ ClN ₆ O ₂ S; MW, 378.84	2.8 ± 2.3	nd	nd
(1ae)  <chem>Nc1nc(NC2=CC=C(S(=O)(=O)N3CCN(C3Cc4ccc(C(F)(F)F)cc4)C=C2)C=C2)ncn1</chem> HCl C ₂₁ H ₂₂ ClF ₃ N ₆ O ₂ ; MW 514.95	-0.3 ± 0.7	nd	nd
(1af)  <chem>Nc1nc(NC2=CC=CC=C2)ncn1</chem> HCl C ₁₀ H ₁₁ ClN ₄ ; MW, 222.67	47 ± 6	55.3 ± 13.4	>50
(1ag)  <chem>Nc1nc(NC2=CC=C(S(=O)(=O)N)C=C2)ncn1</chem> HCl C ₁₀ H ₁₂ ClN ₅ O ₂ S; MW, 301.75	90 ± 2	6.1 ± 0.6	6.1 ± 1.1

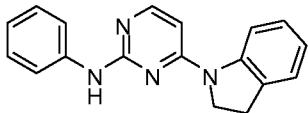
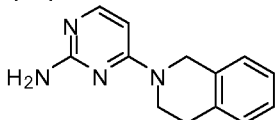
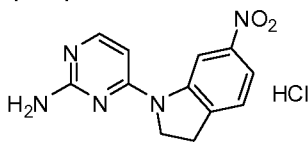
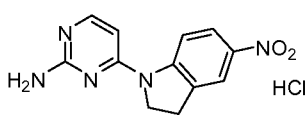
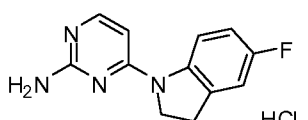
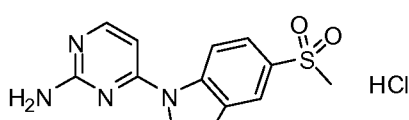
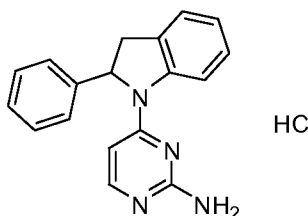
(1ah)  $C_{11}H_{12}ClN_5O$; MW, 265.70	82 ± 2	13.3 ± 1.7	11.5 ± 1.2
(1ai)  $C_{12}H_{13}N_5O_3S$; MW, 307.33	9 ± 1.5	nd	nd
(1aj)  $C_{17}H_{15}N_5O_3S$; MW, 369.40	2.1 ± 1.9	nd	nd
(1ak)  $C_{17}H_{16}ClN_5O_2S$; MW, 391.88	30 ± 1	nd	nd
(8)  $C_{11}H_{11}ClN_6O_2S$; MW, 326.76	54 ± 4	42.7 ± 0.9	nd
(7)  $C_{11}H_{12}ClN_7O_2S$; MW, 341.78	9 ± 2	nd	nd
(1al)  $C_{16}H_{16}ClN_5O_2S$; MW, 377.85	46 ± 4	>100	nd
(1am)  $C_{11}H_{12}ClN_5O$; MW, 265.70	54 ± 4	38.9 ± 0.9	33.3 ± 2.8

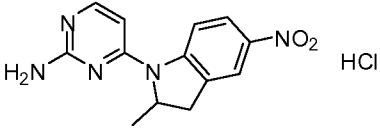
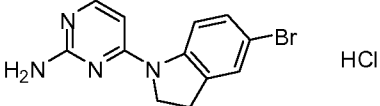
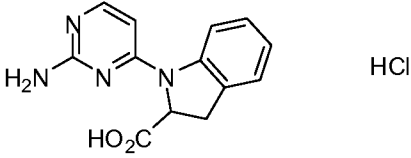
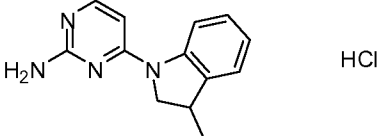
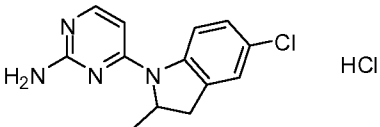
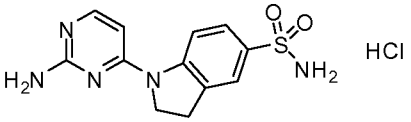
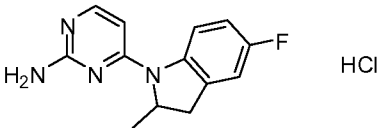
(1an)  $C_{11}H_{13}ClN_4O_2S$; MW, 300.76	90 ± 1	6.7 ± 1.3	7.3 ± 2.0
(6)  $C_{11}H_{14}ClN_5O_2S$; MW, 315.78	0.8 ± 1.2	nd	nd
(1ao)  $C_{12}H_{14}ClN_5O$; MW, 279.73	42 ± 6	nd	nd
(1ap)  $C_{14}H_{16}ClN_5O$; MW, 305.76	10 ± 12	nd	nd
(1aq)  $C_{10}H_{12}ClN_5O_3S$; MW, 317.75	36 ± 5	nd	nd
(13a)  $C_{12}H_{13}ClN_4$; MW, 248.71	85 ± 4	6.6 ± 0.5	3.4 ± 0.3
(1ar)  $C_{13}H_{16}ClN_5O_2$; MW, 309.75	2 ± 1	nd	nd
(1as)  $C_{12}H_{13}ClN_4O_2$ MW, 280.71	2 ± 1	nd	nd

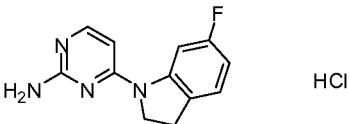
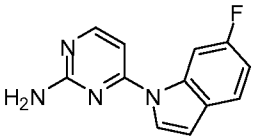
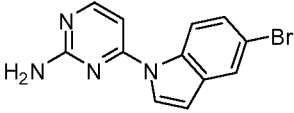
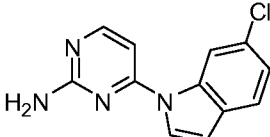
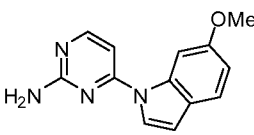
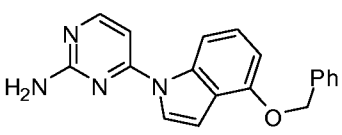
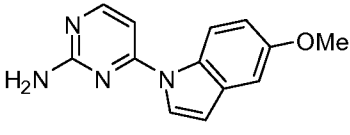
(1at)  $C_{11}H_{13}ClN_4O_2S$; MW, 300.76	38 ± 1	nd	nd
(1au)  $C_{11}H_{13}ClN_4S$; MW, 268.77	76 ± 2	21.0 ± 8.8	17.1 ± 2.8
(1av)  $C_{12}H_{13}ClN_4O_2$; MW, 280.71	63 ± 5	37.0 ± 8.8	39.6 ± 6.2
(1aw)  Chemical Formula: $C_{12}H_{13}ClN_4O_2$; MW, 280.71	77 ± 3	20.5 ± 8.0	13.9 ± 1.7
(1az)  $C_{12}H_{12}ClN_5$; MW, 261.71	37 ± 1	nd	nd
(1ba)  $C_{12}H_{12}ClN_5$; MW, 261.71	23 ± 1	nd	nd
(16)  $C_{13}H_{14}N_4$; MW, 226.28	69 ± 1	19.8 ± 4.3	35.3 ± 5.1

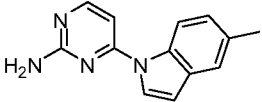
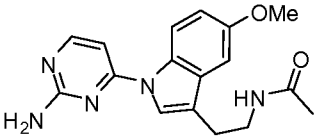
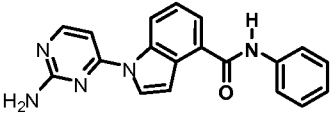
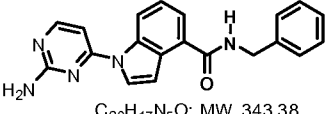
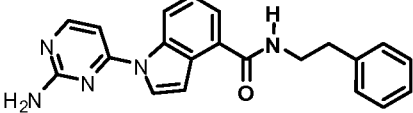
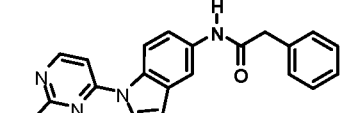
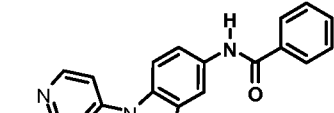
(13b)  <chem>Cc1c[nH]c2ccccc12c3nc(N)ncn3</chem> $C_{13}H_{14}N_4$; MW, 226.28	97 ± 1	1.7 ± 0.2	1.9 ± 0.4
(1bb)  <chem>Nc1nc(Nc2ccc([N+](=O)[O-])cc2)ncn1</chem> HCl $C_{10}H_{10}ClN_5O_2$; MW, 267.67	89 ± 2	3.9 ± 0.3	3.7 ± 0.8
(1bc)  <chem>Nc1nc(Nc2cccc([N+](=O)[O-])c2)ncn1</chem> HCl $C_{10}H_{10}ClN_5O_2$; MW, 267.67	91 ± 2	4.86 ± 0.6	7.82 ± 2.3
(1bd)  <chem>Nc1nc(Nc2ccc(CC)cc2)ncn1</chem> $C_{12}H_{14}N_4$; MW, 214.27	36 ± 6	nd	nd
(1be)  <chem>Nc1nc(Nc2ccc(OC)cc2)ncn1</chem> HCl $C_{11}H_{13}ClN_4O$; MW, 252.70	63 ± 5	30.2 ± 2.5	42.5 ± 6.7
(1bf)  <chem>Nc1nc(Nc2ccc(OCC)cc2)ncn1</chem> $C_{12}H_{14}N_4O$; MW, 230.27	31 ± 4	nd	nd
(1bg)  <chem>Nc1nc(Nc2ccc(OC(F)F)cc2)ncn1</chem> $C_{11}H_{10}F_2N_4O$; MW, 252.22	64 ± 7	30.0 ± 3.2	23.4 ± 5.5

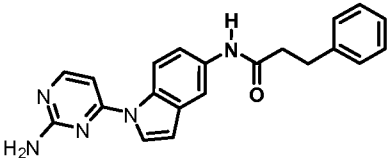
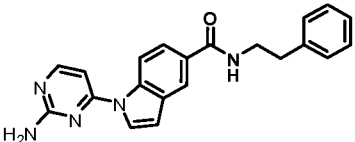
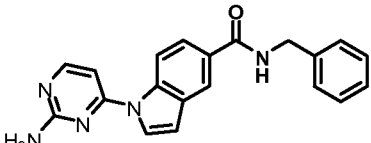
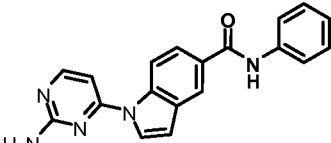
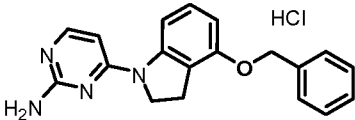
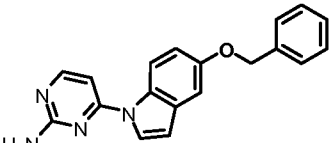
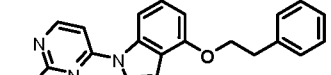
(13c)  <chem>C12H12Cl2N4</chem>; MW, 283.16	73 ± 3	1.5 ± 0.2	1.2 ± 0.2
(10a)  <chem>C10H9N3O</chem>; MW, 187.20	-0.5 ± 1	nd	nd
(10b)  <chem>C10H10N4O3S</chem>; MW, 266.28	-0.3 ± 1	nd	nd
(10c)  <chem>C11H10N4O2</chem>; MW, 230.22	2 ± 1	nd	nd
(32)  <chem>C12H11Cl2N3</chem>; MW, 268.14	-3 ± 1	nd	nd
(18)  <chem>C11H9N5</chem>; MW, 211.22	50 ± 1	38.7 ± 1.6	37.4 ± 4.0
(15a)  <chem>C12H10N4</chem>; MW, 210.23	88 ± 4	4.8 ± 0.3	4.0 ± 0.3

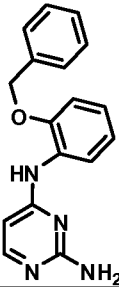
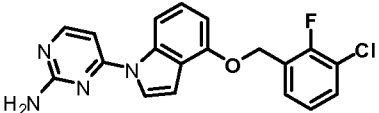
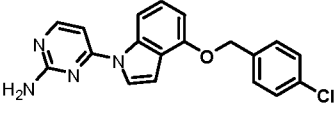
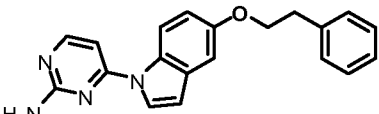
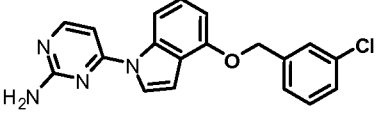
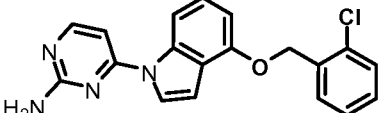
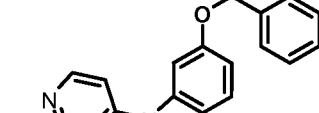
(33)  $C_{18}H_{16}N_4$; MW, 288.35	-1 ± 2	nd	nd
(17)  $C_{13}H_{14}N_4$; MW, 226.28	6 ± 1	nd	nd
(13d)  $C_{12}H_{12}ClN_5O_2$; MW, 293.71	51 ± 1	2.2 ± 0.3	1.8 ± 0.3
(13e)  $C_{12}H_{12}ClN_5O_2$; MW, 293.71	24 ± 2	nd	nd
(13f)  $C_{12}H_{12}ClFN_4$; MW, 266.70	89 ± 7	1.2 ± 0.2	0.7 ± 0.1
(13g)  $C_{13}H_{15}ClN_4O_2S$; MW, 326.80	49 ± 4	41.0 ± 2.3	37.9 ± 2.0
(13h)  $C_{18}H_{17}ClN_4$; MW, 324.81	18 ± 1	nd	nd

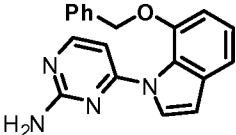
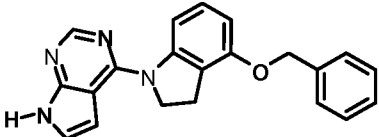
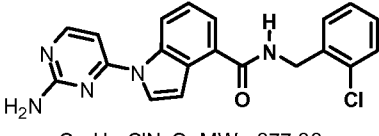
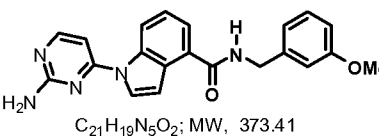
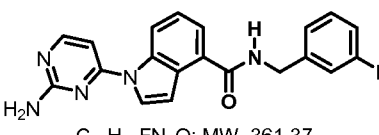
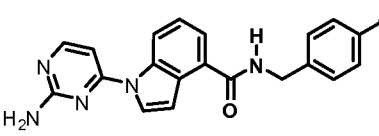
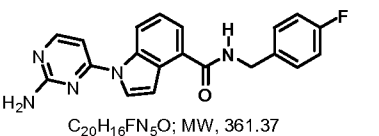
(13i)  <chem>C13H14ClN5O2</chem>; MW, 307.74	98 ± 2	0.5 ± 0.1	0.4 ± 0.1
(13j)  <chem>C12H12BrClN4</chem>; MW, 327.61	83 ± 5	1.7 ± 0.3	1.2 ± 0.1
(13k)  <chem>C13H13ClN4O2</chem>; MW, 292.72	6 ± 0.4	nd	nd
(13l)  <chem>C13H15ClN4</chem>; MW, 262.74	93 ± 2	4.8 ± 0.5	2.6 ± 0.1
(13m)  <chem>C13H14Cl2N4</chem>; MW, 297.18	87 ± 10	1.2 ± 0.1	0.5 ± 0.03
(13n)  <chem>C12H14ClN5O2S</chem>; MW, 327.79	73 ± 4	25.8 ± 2.6	10.3 ± 0.9
(13o)  <chem>C13H14ClFN4</chem>; MW, 280.73	97 ± 4	0.4 ± 0.1	0.2 ± 0.01

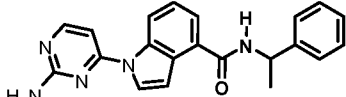
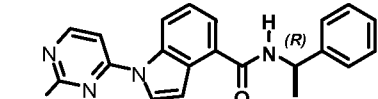
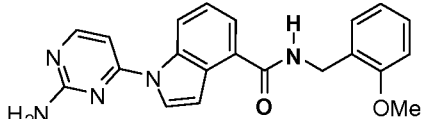
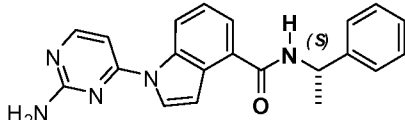
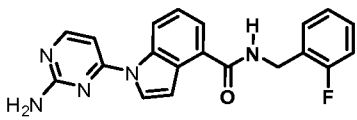
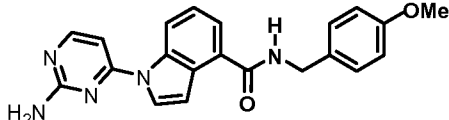
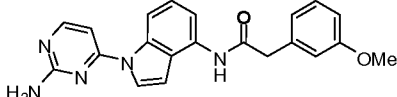
(13p)  <chem>Nc1nc2c(ncn2C3C=CC(=C3)F)C4=CC=CC=C4.Cl</chem> $C_{12}H_{12}ClFN_4$; MW, 266.70	89 ± 4	3.7 ± 0.4	1.34 ± 0.09
(15b)  <chem>Nc1nc2c(ncn2C3C=CC(=C3)F)C4=CC=CC=C4</chem> $C_{12}H_9FN_4$; MW, 228.23	86 ± 5	4.9 ± 0.5	1.7 ± 0.1
(15c)  <chem>Nc1nc2c(ncn2C3C=CC(=C3)Br)C4=CC=CC=C4</chem> $C_{12}H_9BrN_4$; MW, 289.13	89 ± 1	2.1 ± 0.3	1.7 ± 0.3
(15d)  <chem>Nc1nc2c(ncn2C3C=CC(=C3)Cl)C4=CC=CC=C4</chem> $C_{12}H_9ClN_4$; MW, 244.68	88 ± 0.3	1.2 ± 0.2	1.0 ± 0.3
(15e)  <chem>Nc1nc2c(ncn2C3C=CC(=C3)OC)C4=CC=CC=C4</chem> $C_{13}H_{12}N_4O$; MW, 240.26	88 ± 2	4.9 ± 0.5	4.9 ± 1.0
(21a)  <chem>Nc1nc2c(ncn2C3C=CC(=C3)OCC4=CC=CC=C4)C5=CC=CC=C5</chem> $C_{19}H_{16}N_4O$; MW, 316.36	80 ± 3	0.8 ± 0.5	0.4 ± 0.1
(15f)  <chem>Nc1nc2c(ncn2C3C=CC(=C3)OC)C4=CC=CC=C4</chem> $C_{13}H_{12}N_4O$; MW, 240.26	96 ± 3	0.4 ± 0.1	0.25 ± 0.13

(15g)  <chem>C13H12N4</chem>; MW, 224.26	82 ± 5	8.3 ± 0.9	7.1 ± 2.1
(15h)  <chem>C17H19N5O2</chem>; MW, 325.37	89 ± 1	4.9 ± 0.8	5.3 ± 1.2
(24a)  <chem>C19H15N5O</chem>; MW, 329.36	9 ± 1	nd	nd
(24b)  <chem>C20H17N5O</chem>; MW, 343.38	92 ± 1	1.0 ± 0.5	0.2 ± 0.1
(24c)  <chem>C21H19N5O</chem>; MW, 357.41	91 ± 1	2.0 ± 0.5	0.5 ± 0.1
(27a)  <chem>C20H17N5O</chem>; MW, 343.38	53 ± 1	20.8 ± 6.3	5.8 ± 1.4
(27b)  <chem>C19H15N5O</chem>; MW, 329.36	8 ± 3	nd	nd

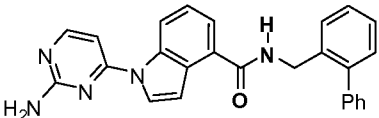
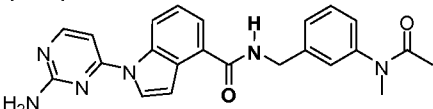
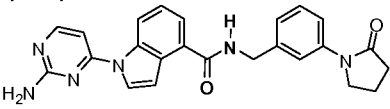
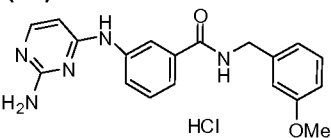
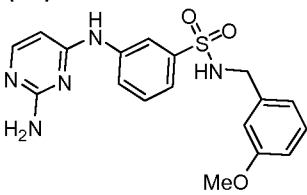
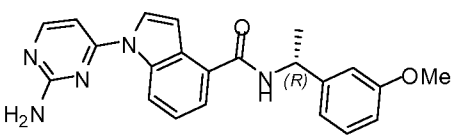
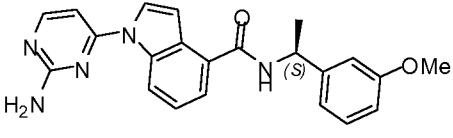
(27c)  $C_{21}H_{19}N_5O$; MW, 357.41	60 ± 2	54.1 ± 1.1	8.4 ± 2.0
(24d)  $C_{21}H_{19}N_5O$; MW, 357.41	96 ± 1	2.8 ± 0.3	0.7 ± 0.3
(24e)  $C_{20}H_{17}N_5O$; MW, 343.38	96 ± 1	2.4 ± 1.6	0.3 ± 0.1
(24f)  $C_{19}H_{15}N_5O$; MW, 329.36	17 ± 2	nd	nd
(13q)  $C_{19}H_{19}ClN_4O$; MW, 354.83	90 ± 1	0.48 ± 0.099	0.25 ± 0.07
(21b)  $C_{19}H_{16}N_4O$; MW, 316.36	76 ± 2	39.0 ± 6.9	16.3 ± 5.5
(21c)  $C_{20}H_{18}N_4O$; MW, 330.38	63 ± 5	53.6 ± 4.1	17.0 ± 1.7

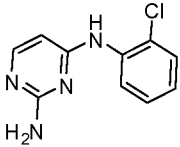
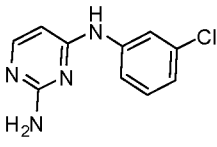
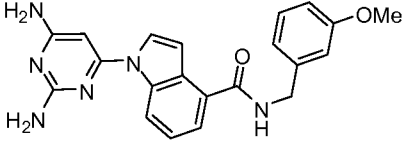
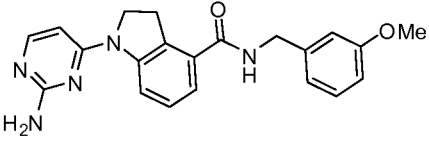
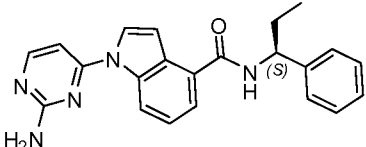
(1ah)  HCl	22 ± 4	nd	nd
(21d)  C₁₉H₁₄ClFN₄O; MW, 368.79	10 ± 2	nd	nd
(21e)  C₁₉H₁₅ClN₄O; MW, 350.80	71 ± 2	1.90 ± 0.42	0.46 ± 0.08
(21f)  C₂₀H₁₈N₄O; MW, 330.38	21 ± 14	nd	nd
(21g)  C₁₉H₁₅ClN₄O; MW, 350.80	44 ± 9	34.6 ± 8.2	32.7 ± 8.1
(21h)  C₁₉H₁₅ClN₄O; MW, 350.80	62 ± 6	29.1 ± 8.2	19.0 ± 5.9
(21i)  C₁₉H₁₆N₄O; MW, 316.36	-5 ± 2	nd	nd

(21j)  $C_{19}H_{16}N_4O$; MW, 316.36	-5 ± 0.5	nd	nd
(35)  $C_{21}H_{18}N_4O$; MW, 342.39	33 ± 4	nd	nd
(30a)  $C_{20}H_{16}ClN_5O$; MW, 377.83	39.22 ± 4.19	nd	nd
(30b)  $C_{21}H_{19}N_5O_2$; MW, 373.41	93 ± 7	0.15 ± 0.02	0.04 ± 0.03
(30c)  $C_{20}H_{16}ClN_5O$; MW, 377.83	86 ± 4	6.8 ± 3.0	0.72 ± 0.13
(30d)  $C_{20}H_{16}FN_5O$; MW, 361.37	72 ± 10	2.7 ± 1.78	0.26 ± 0.09
(30e)  $C_{20}H_{16}ClN_5O$ MW = 377.8269	31 ± 10	nd	nd
(30f)  $C_{20}H_{16}FN_5O$; MW, 361.37	70 ± 3	10.5 ± 1.0	1.10 ± 0.49

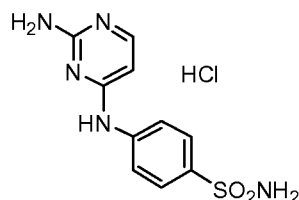
(30g)  $C_{21}H_{19}N_5O$; MW, 357.41	85 ± 6	1.7 ± 0.5	0.21 ± 0.15
(30h)  $C_{21}H_{19}N_5O$; MW, 357.41	105 ± 1	0.12 ± 0.02	0.06 ± 0.02
(30i)  $C_{21}H_{19}N_5O_2$; MW, 373.41	69 ± 3	6.0 ± 2.0	1.80 ± 0.68
(30j)  $C_{21}H_{19}N_5O$; MW, 357.41	102.2 ± 0.2	3.43 ± 0.44	1.20 ± 0.32
(30k)  $C_{20}H_{16}FN_5O$ MW 361.1339	88.71±5.96	5.67±0.32	0.92±0.48
(30l)  $C_{21}H_{19}N_5O_2$ MW 373.1539	19.44±13.73	nd	nd
(27d)  $C_{21}H_{19}N_5O_2$; MW, 373.41	ROCK1 % inhibition @ 100 μM 62 ± 12	13.03 ± 6.81	nd

(30m) <chem>Cc1ccc(NC(=O)c2c3c(c1)nc4c3nc(N)cn4)cc1S(=O)(=O)C</chem> $C_{21}H_{20}N_6O_3S$; MW, 436.49	ROCK1 % inhibition @ 100 μM 100 $\pm$ 8	3.26 $\pm$ 0.57	nd
(30n) <chem>CC(=O)Nc1ccc(NC(=O)c2c3c(c1)nc4c3nc(N)cn4)cc1</chem> $C_{22}H_{20}N_6O_2$; MW, 400.43	ROCK1 % inhibition @ 100 μM 117 $\pm$ 3	1.39 $\pm$ 0.26	nd
(30o) <chem>CCC[C@H](c1ccccc1)Nc2ccc(NC(=O)c3c4c(c2)nc5c4nc(N)cn5)cc3</chem> $C_{22}H_{21}N_5O$; MW, 371.44	ROCK1 % inhibition @ 100 μM 122 $\pm$ 1	1.77 $\pm$ 0.24	nd
(30p) <chem>COC[C@H](c1ccccc1)Nc2ccc(NC(=O)c3c4c(c2)nc5c4nc(N)cn5)cc3</chem> $C_{22}H_{21}N_5O_2$; MW, 387.43	ROCK1 % inhibition @ 100 μM 91 $\pm$ 9	15.43 $\pm$ 6.04	nd
(30q) <chem>COc1ccc(CNc2c3c(c1)nc4c3nc(N)cn4)cc2</chem> $C_{22}H_{21}N_5O_2$; MW, 387.43	ROCK1 % inhibition @ 100 μM 89 $\pm$ 6	15.25 $\pm$ 3.74	nd
(36) <chem>CC(=O)Nc1ccc(NC(=O)c2c3c(c1)nc4c3nc(N)cn4)cc2</chem> $C_{23}H_{21}N_5O_3$; MW, 415.44	ROCK1 % inhibition @ 100 μM 80 $\pm$ 0.5	15.42 $\pm$ 4.02	nd
(30r) <chem>COCCOCc1ccc(NC(=O)c2c3c(c1)nc4c3nc(N)cn4)cc2</chem> $C_{23}H_{23}N_5O_3$; MW, 417.46	ROCK1 % inhibition @ 100 μM 86 $\pm$ 10	9.31 $\pm$ 8.68	nd
(3s) <chem>CCOCc1ccc(NC(=O)c2c3c(c1)nc4c3nc(N)cn4)cc2</chem> $C_{22}H_{21}N_5O_2$; MW, 387.43	ROCK1 % inhibition @ 100 μM 61 $\pm$ 1.2	3.37 $\pm$ 0.53	nd

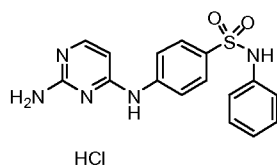
(30t)  <chem>C26H21N5O</chem>; MW, 419.48	ROCK1 % inhibition @ 100 μM 7 ± 1.1	nd	nd
(30u)  <chem>C23H22N6O2</chem>; MW, 414.46	ROCK1 % inhibition @ 100 μM 47 ± 1	40.33 ± 11.03	nd
(30v)  <chem>C24H22N6O2</chem>; MW, 426.47	ROCK1 % inhibition @ 100 μM 99 ± 7	8.31 ± 7.39	nd
(46)  <chem>C19H20ClN5O2</chem> M W: 385.8474	ROCK1 % inhibition @ 100 μM 97 ± 6	7.30 ± 1.29	nd
(47)  <chem>C18H19N5O3S</chem> MW: 385.4402	ROCK1 % inhibition @ 100 μM 70 ± 4	33.38 ± 8.52	nd
(30w)  <chem>C22H21N5O2</chem> MW 387.4344	ROCK1 % inhibition @ 100 μM 92 ± 1.3	0.213 ± 0.025	nd
(30z)  <chem>C22H21N5O2</chem> MW 387.4344	ROCK1 % inhibition @ 100 μM 97 ± 1	1.38 ± 0.63	nd

(1bi)  <chem>C10H9ClN4</chem> MW: 220.6583	ROCK1 % inhibition @ 100 μM 39 ± 1.5	nd	nd
(1bj)  <chem>C10H9ClN4</chem> MW: 220.6583	ROCK1 % inhibition @ 100 μM 89 ± 9	5.71 ± 1.44	nd
(38)  Molecular Weight: 388.4225	1.26 ± 0.79	nd	nd
(13r)  Molecular Weight: 375.4237	92.75 ± 3.64	1.62 ± 0.86	0.25 ± 0.02
(30aa)  <chem>C22H21N5O</chem> MW 371.4350	ROCK1 % inhibition @ 100 μM 88 ± 1.4	9.76 ± 0.86"	nd

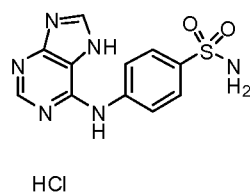
Experimental part



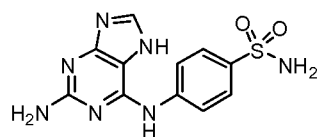
4-(2-Aminopyrimidin-4-ylamino)benzenesulfonamide hydrochloride 1aa. A mixture of 2-amino-4-chloropyrimidine (0.078 g, 0.602 mmol), 4-aminobenzenesulfonamide (0.103 g, 0.602 mmol) in anhydrous ethanol (0.6 ml) was stirred in a Biotage microwave reactor for 10 min at 120 °C. After cooling to room temperature, the solid precipitate was filtered and dried under vacuum to afford **1aa** (0.137 g, 0.516 mmol, 86%) as an off-white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.97 (d, *J* = 9.0 Hz, 2H), 7.90 (d, *J* = 8.9 Hz, 2H), 7.79 (d, *J* = 7.2 Hz, 1H), 6.36 (d, *J* = 7.2 Hz, 1H). HRMS (ESI+ve) calculated for C₁₀H₁₂N₄O₂S (M+H-Cl)⁺ 266.0706, found 266.0703.



4-(2-Aminopyrimidin-4-ylamino)-N-phenylbenzenesulfonamide hydrochloride (1al). This was prepared from 2-amino-4-chloropyrimidine (0.072 g, 0.556 mmol), and 4-amino-N-phenylbenzenesulfonamide (0.138 g, 0.556 mmol) in a similar manner as described for **1aa**. After cooling to room temperature, the solid precipitate was filtered and dried under vacuum to afford **1al** (0.071 g, 0.207 mmol, 37%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.45 (s, 1H), 11.08 (s, 1H), 10.28 (s, 1H), 7.97 (d, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 7.1 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.21 (t, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 7.00 (t, *J* = 7.9 Hz, 1H), 6.41 (d, *J* = 7.1 Hz, 1H). HRMS (ESI+ve) calculated for C₁₆H₁₇N₅O₂S (M+H-Cl)⁺ 342.1019, found 342.1039.

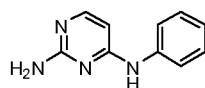


4-(7H-Purin-6-ylamino)benzenesulfonamide hydrochloride (8). A mixture of 6-chloro-7H-purine (0.286 g, 1.66 mmol), and 4-aminobenzenesulfonamide (0.257 g, 1.66 mmol) was stirred in a Biotage microwave reactor for 20 min at 120 °C and 10 min at 160 °C. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, ether, further triturated with methanol, filtered and dried under vacuum. Pure **8** (0.434 g, 1.33 mmol, 80%) was obtained as a green solid. ¹H NMR (400 MHz, CD₃OD) δ 8.71 (s, 1H), 8.59 (s, 1H), 7.99 (s, 4H). HRMS (ESI+ve) calculated for C₁₁H₁₁N₆O₂S (M+H-Cl)⁺ 291.0658, found 291.0659.



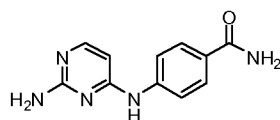
HCl

4-(2-amino-7H-purin-6-ylamino)benzenesulfonamide hydrochloride (7). A mixture of 6-chloro-7H-purin-2-amine (0.143 g, 0.8444 mmol), and 4-aminobenzenesulfonamide (0.145 g, 0.843 mmol) was stirred in a Biotage microwave reactor for 20 min at 120 °C and 20 min at 160 °C. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, ether, further and dried under vacuum. Pure **7** (0.186 g, 0.609 mmol, 72%) was obtained as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.30 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 8.08 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.31 (s, 2H), 6.73 (s, 2H). HRMS (ESI+ve) calculated for C₁₁H₁₂N₇O₂S (M+H-Cl)⁺ 306.0767, found 306.0779.



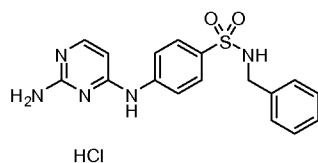
HCl

N⁴-phenylpyrimidine-2,4-diamine hydrochloride (1af). This was prepared from 2-amino-4-chloropyrimidine (0.084 g, 0.648 mmol), aniline (0.060 g, 0.648 mmol) in a similar manner as described for **1aa**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was solid triturated with ethyl acetate, filtered and dried under vacuum to afford **1af** (0.136 g, 0.610 mmol, 94%) as an off-white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.71-7.69 (m, 3H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.30 (d, *J* = 7.3 Hz, 1H). HRMS (ESI+ve) calculated for C₁₀H₁₁N₄ (M+H-Cl)⁺ 187.0978, found 187.0979.



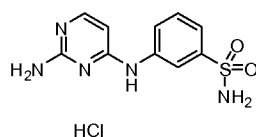
HCl

4-(2-aminopyrimidin-4-ylamino)benzamide hydrochloride (1ah). This was prepared from 2-amino-4-chloropyrimidine (0.096 g, 0.741 mmol), 4-aminobenzamide (0.100 g, 0.741 mmol) in a similar manner as described for **1aa**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was solid triturated with ethyl acetate, filtered and dried under vacuum to afford **1ah** (0.161 g, 0.606 mmol, 82%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.30 (s, 1H), 10.90 (s, 1H), 7.95-7.85 (m, 6H), 7.33 (s, 1H), 6.39 (d, *J* = 6.6 Hz, 1H). HRMS (ESI+ve) calculated for C₁₁H₁₂N₅O (M+H-Cl)⁺ 230.1036, found 230.1041.

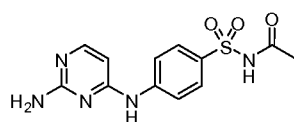


4-(2-aminopyrimidin-4-ylamino)-N-benzylbenzenesulfonamide hydrochloride (1ak).

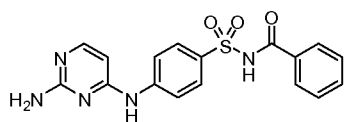
This was prepared from 2-amino-4-chloropyrimidine (0.076 g, 0.586 mmol), and 4-amino-*N*-benzylbenzenesulfonamide (0.153 g, 0.586 mmol) in a similar manner as described for **1aa**. After cooling to room temperature, the solvent was removed under reduced pressure and the remaining solid was triturated with DCM, filtered and dried under vacuum. Pure **1ak** (0.203 g, 0.518 mmol, 88%) was obtained as an off-white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.83-7.89 (m, 3H), 7.25-7.17 (m, 5H), 6.37 (dd, *J* = 7.3, 1.2 Hz, 1H), 4.07 (s, 2H). HRMS (ESI+ve) calculated for C₁₇H₁₈N₅O₂S (M+H-Cl)⁺ 356.1175, found 356.1188.



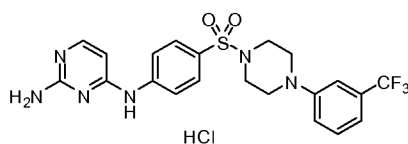
3-(2-aminopyrimidin-4-ylamino)benzenesulfonamide hydrochloride (1ag). This was prepared from 2-amino-4-chloropyrimidine (0.077 g, 0.594 mmol), and 3-aminobenzenesulfonamide (0.102 g, 0.594 mmol) in a similar manner as described for **1aa**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol and dried under vacuum. Pure **1ag** (0.159 g, 0.527 mmol, 89%) was obtained as an off-white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.41 (s, 1H), 7.88 (d, *J* = 6.2 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 6.35 (d, *J* = 7.3 Hz, 1H). HRMS (ESI+ve) calculated for C₁₀H₁₂N₅O₂S (M+H-Cl)⁺ 266.0706, found 266.0718.



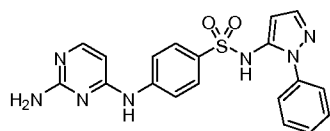
N-(4-(2-aminopyrimidin-4-ylamino)phenylsulfonyl)acetamide (1ai). This was prepared from 2-amino-4-chloropyrimidine (0.076 g, 0.586 mmol), and *N*-(4-aminophenylsulfonyl)acetamide (0.125 g, 0.586 mmol) in a similar manner as described for **1aa**. After cooling to room temperature, DIPEA (0.2 ml) was added and the solvent was removed under reduced pressure. The remaining solid was triturated with water, filtered, washed with acetonitrile, and dried under vacuum. Pure **1ai** (0.137 g, 0.445 mmol, 76%) was obtained as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 7.93 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 9.2 Hz, 2H), 7.82 (d, *J* = 7.5 Hz, 1H), 6.16 (d, *J* = 6.2 Hz, 1H), 1.93 (s, 3H). HRMS (ESI+ve) calculated for C₁₂H₁₄N₅O₃S (M+H)⁺ 308.0811, found 308.0818.



***N*-(4-(2-aminopyrimidin-4-ylamino)phenyl)sulfonylbenzamide (1aj).** This was prepared from 2-amino-4-chloropyrimidine (0.082 g, 0.632 mmol), and *N*-(4-aminophenylsulfonyl)benzamide (0.174 g, 0.632 mmol) in a similar manner as described for **1aa**. After cooling to room temperature, DIPEA (0.5 ml) was added and the solvent was removed under reduced pressure. The remaining solid was triturated with water, filtered, washed with acetonitrile, and dried under vacuum. Pure **1aj** (0.145 g, 0.392 mmol, 62%) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.07 (s, 1H), 7.85-7.81 (m, 7H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.14 (s, 2H), 6.16 (d, *J* = 6.4 Hz, 1H). HRMS (ESI+ve) calculated for C₁₇H₁₆N₅O₃S (M+H)⁺ 370.0968, found 370.0979.

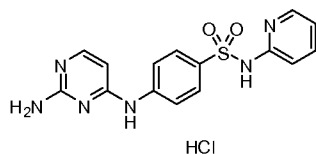


***N*-(4-(4-(3-(trifluoromethyl)phenyl)piperazin-1-ylsulfonyl)phenyl)pyrimidine-2,4-diamine hydrochloride (1ae).** A mixture of 2-amino-4-chloropyrimidine (0.031g, 0.241 mmol), 4-(4-(3-(trifluoromethyl)phenyl)piperazin-1-ylsulfonyl)aniline (0.093 g, 0.241 mmol) in anhydrous ethanol (0.4 ml) was stirred in a Biotage microwave reactor for 20 min at 150 °C. After cooling to room temperature, the solid precipitate was filtered, washed with Et₂O, and dried under vacuum to afford **1ae** (0.050 g, 0.104 mmol, 43%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.06 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 7.0 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.39 (t, *J* = 8.1 Hz, 1H), 7.18-7.13 (m, 2H), 7.08 (d, *J* = 7.3 Hz, 1H), 6.41 (d, *J* = 7.1 Hz, 1H), 3.00 (s, 4H). HRMS (ESI+ve) calculated for C₂₁H₂₂N₆F₃O₂S (M+H-Cl)⁺ 479.1471, found 479.1474.

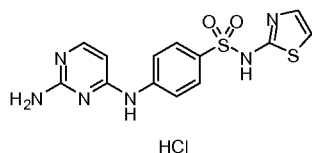


4-(2-aminopyrimidin-4-ylamino)-N-(1-phenyl-1H-pyrazol-5-yl)benzenesulfonamide (1ab). This was prepared from 2-amino-4-chloropyrimidine (0.093g, 0.717mmol), and 44-amino-N-(1-phenyl-1H-pyrazol-5-yl)benzenesulfonamide (0.255 g, 0.717 mmol) in a similar manner as described for **1ae**. After cooling to room temperature, the solvent was removed under reduced pressure. The crude material was redissolved in MeOH, followed by the addition of DIPEA (0.3 ml). The solvent was removed under reduced pressure. The obtained solid was slurried with water, filtered, washed with acetone, ether, dried under vacuum, dried under vacuum. Pure **1ab** was obtained as a white solid (0.093g, 0.228 mmol, 31%). ¹H NMR (400 MHz, CD₃OD) δ 7.91 (d, *J* = 8.6 Hz, 2H), 7.83 – 7.79 (m, 1H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.57 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.40 (dd, *J* = 8.0, 3.1 Hz,

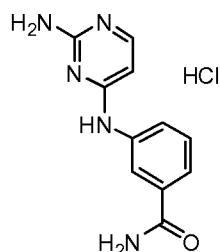
3H), 7.29 – 7.22 (m, 2H), 6.43 – 6.34 (m, 1H), 6.13 (dd, $J = 1.9, 0.6$ Hz, 1H). HRMS (ESI+ve) calculated for $C_{19}H_{18}N_7O_2S$ (M+H)⁺ 408.1237, found 408.1246.



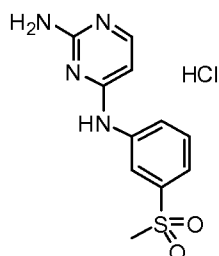
4-(2-aminopyrimidin-4-ylamino)-N-(pyridin-2-yl)benzenesulfonamide hydrochloride (1ad). This was obtained as a white solid (0.052g, 0.155 mmol, 20%) from 2-amino-4-chloropyrimidine (0.095g, 0.733mmol), and 4-amino-N-(pyridin-2-yl)benzenesulfonamide (0.183 g, 0.733 mmol) in a similar manner as described for **1ae**. ¹H NMR (400 MHz, CD₃OD) δ 7.97-7.93 (m, 5H), 7.77 (d, $J = 7.2$ Hz, 1H), 7.71-7.69 (m, 1H), 7.24 (d, $J = 8.7$ Hz, 1H), 6.90-6.87 (m, 1H), 6.35 (d, $J = 7.3$ Hz, 1H), HRMS (ESI+ve) calculated for $C_{15}H_{15}N_6O_2S$ (M+H-Cl)⁺ 343.0971, found 343.0974.



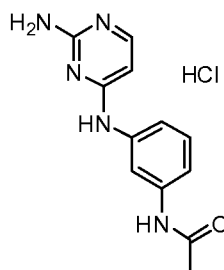
4-(2-aminopyrimidin-4-ylamino)-N-(thiazol-2-yl)benzenesulfonamide hydrochloride (1ac). This was obtained as a white solid (0.208g, 0.540 mmol, 67%) from 2-amino-4-chloropyrimidine (0.105g, 0.810 mmol), and 4-amino-N-(thiazol-2-yl)benzenesulfonamide (0.206 g, 0.810 mmol) in a similar manner as described for **1ae**. ¹H NMR (400 MHz, CD₃OD) δ 7.94-7.87 (m, 4H), 7.78 (d, $J = 7.2$ Hz, 1H), 7.10 (d, $J = 4.7$ Hz, 1H), 6.73 (d, $J = 4.7$ Hz, 1H), 6.35 (d, $J = 7.3$ Hz, 1H). HRMS (ESI+ve) calculated for $C_{13}H_{13}N_6O_2S_2$ (M+H-Cl)⁺ 349.0535, found 349.0542.



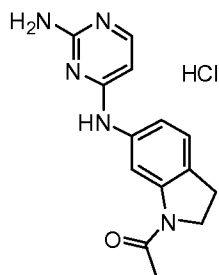
3-(2-aminopyrimidin-4-ylamino)benzamide hydrochloride (1am). A mixture of 2-amino-4-chloropyrimidine (0.099g, 0.764 mmol), 3-aminobenzamide (0.104 g, 0.764 mmol) in anhydrous ethanol (0.8 ml) was stirred in a Biotage microwave reactor for 15 min at 120 °C. After cooling to room temperature, the solid precipitate was filtered, washed with MeOH, and dried under vacuum to afford **1am** (0.137 g, 0.515 mmol, 67%) as an off-white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.44 (s, 1H), 7.76-7.74 (m, 2H), 7.68 (d, $J = 7.9$ Hz, 1H), 7.48 (t, $J = 7.9$ Hz, 1H), 6.32 (d, $J = 7.2$ Hz, 1H). HRMS (ESI+ve) calculated for $C_{11}H_{12}N_5O$ (M+H-Cl)⁺ 230.1036, found 230.1037.



N-(3-(methylsulfonyl)phenyl)pyrimidine-2,4-diamine hydrochloride (1an). This was obtained as an off-white solid (0.162 g, 0.482 mmol, 54%) from 2-amino-4-chloropyrimidine (0.166g, 0.895 mmol), 3-(methylsulfonyl)aniline (0.185 g, 0.895 mmol) in a similar manner as described for **1am**. After cooling to room temperature, the solid precipitate was filtered, washed with MeOH, and dried under vacuum to afford **1an**. ¹H NMR (400 MHz, CD₃OD) δ 8.42 (s, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.80-7.76 (m, 2H), 6.36 (d, *J* = 7.2 Hz, 1H), 3.18 (s, 3H). HRMS (ESI+ve) calculated for C₁₁H₁₂N₄O₂S (M+H-Cl)⁺ 265.0753, found 265.0757.

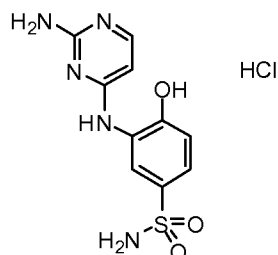


N-(3-(2-aminopyrimidin-4-ylamino)phenyl)acetamide hydrochloride (1ao). This was obtained as a white solid (0.216g, 0.771 mmol, 92%) from 2-amino-4-chloropyrimidine (0.106g, 0.837 mmol), and N-(3-aminophenyl)acetamide (0.150 g, 1.00 mmol) in a similar manner as described for **1ae**. After cooling to room temperature, the solid precipitate was filtered, washed with MeOH, and dried under vacuum to afford **1ao**. ¹H NMR (400 MHz, CD₃OD) δ 8.10 (s, 1H), 7.70 (d, *J* = 7.3 Hz, 1H), 7.48 (s, 1H), 7.32 (t, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 6.30 (d, *J* = 7.3 Hz, 1H), 2.14 (s, 3H). HRMS (ESI+ve) calculated for C₁₂H₁₄N₅O (M+H-Cl)⁺ 244.1192, found 244.1198.

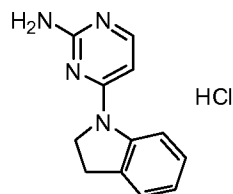


1-(6-(2-aminopyrimidin-4-ylamino)indolin-1-yl)ethanone hydrochloride (1ap). This was obtained as a white solid (0.130g, 0.430 mmol, 57%) from 2-amino-4-chloropyrimidine (0.097g, 0.748 mmol), and 1-(6-aminoindolin-1-yl)ethanone (0.131g,

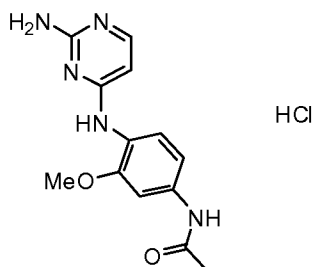
0.748 mmol) in a similar manner as described for **1am**. After cooling to room temperature, the solid precipitate was filtered, washed with MeOH, and dried under vacuum to afford **1ap**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.19 (s, 1H), 10.57 (s, 1H), 8.03 (s, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 6.27 (d, *J* = 6.7 Hz, 1H), 4.10 (t, *J* = 8.5 Hz, 2H), 3.11 (t, *J* = 8.4 Hz, 2H), 2.15 (s, 3H). HRMS (ESI+ve) calculated for C₁₄H₁₅N₅O (M+H-Cl)⁺ 270.1349, found 270.1357.



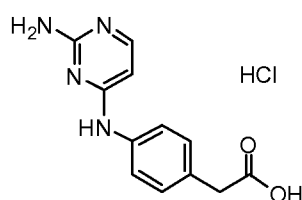
3-(2-aminopyrimidin-4-ylamino)-4-hydroxybenzenesulfonamide hydrochloride (1aq). This was obtained as a white solid (0.150g, 0.472 mmol, 72%) from 2-amino-4-chloropyrimidine (0.085g, 0.656 mmol), and 3-amino-4-hydroxybenzenesulfonamide (0.123 g, 656 mmol) in a similar manner as described for **1am**. After cooling to room temperature, the solid precipitate was filtered, washed with MeOH, and dried under vacuum to afford **1aq**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.16 (s, 1H), 10.57 (s, 1H), 8.03 (s, 1H), 7.90 (bs, 2H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 1H), 6.27 (d, *J* = 7.1 Hz, 1H), 4.10 (t, *J* = 8.6 Hz, 1H), 3.11 (t, *J* = 8.5 Hz, 1H), 2.15 (s, 1H). HRMS (ESI+ve) calculated for C₁₀H₁₂N₅O₃S (M+H-Cl)⁺ 282.0655, found 282.0658.



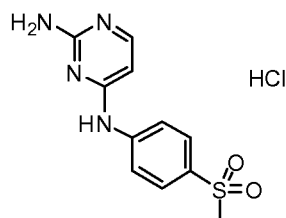
4-(indolin-1-yl)pyrimidin-2-amine hydrochloride (13a). A mixture of 2-amino-4-chloropyrimidine (0.097g g, 0.748 mmol), and indoline (0.098 g, 0.823 mmol) was stirred in a Biotage microwave reactor for 15 min at 120 °C and 10 min at 160 °C. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, ether, further triturated with methanol, filtered and dried under vacuum (0.106g). The methanolic solution was concentrated to dryness. The obtained solid was slurried with methanol, filtered and dried under vacuum (0.043 g). The two batches were combined to provide pure **13a** (0.149 g, 0.587 mmol, 78%) as a pale yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.66 (m, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.46 (s, 1H), 4.21 (t, *J* = 8.3 Hz, 3H). HRMS (ESI+ve) calculated for C₁₂H₁₂N₄ (M+H-Cl)⁺ 213.1134, found 213.1139.



N-(4-(2-aminopyrimidin-4-ylamino)-3-methoxyphenyl)acetamide hydrochloride (1ar). This was obtained from 2-amino-4-chloropyrimidine (0.087g, 0.671 mmol), and N-(4-amino-3-methoxyphenyl)acetamide (0.121 g, 0.671 mmol) in a similar manner as described for **1am**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, ether, further triturated with methanol, filtered and dried under vacuum (0.082g). The methanolic solution was concentrated to dryness. The obtained solid was slurried with methanol, filtered and dried under vacuum (0.019 g). The two batches were combined to provide pure **1ar** (0.101 g, 0.326 mmol, 49%) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.18 (s, 1H), 7.69 (d, *J* = 7.3 Hz, 1H), 7.30 (dd, *J* = 2.5, 9.0 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 6.37 (s, 1H), 3.87 (s, 3H), 2.11 (s, 4H). HRMS (ESI+ve) calculated for C₁₃H₁₆N₅O₂ (M+H-Cl)⁺ 274.1298, found 274.1301.

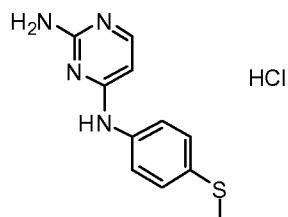


2-(4-(2-aminopyrimidin-4-ylamino)phenyl)acetic acid hydrochloride (1as). This was obtained from 2-amino-4-chloropyrimidine (0.092g, 0.710 mmol), and 2-(4-aminophenyl)acetic acid (0.107 g, 0.710 mmol) in a similar manner as described for **1am**. After cooling to room temperature, the solvent was removed under reduced pressure. The obtained the solid was filtered, slurried with acetone, filtered and dried under vacuum to provide pure **1as** (0.149g, 0.530g, 75%) -as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 7.69 (d, *J* = 7.3 Hz, 2H), 7.65 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.28 (d, *J* = 7.3 Hz, 1H), 3.60 (s, 2H).

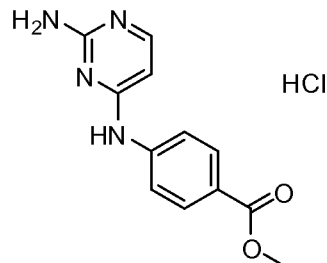


N-(4-(methylsulfonyl)phenyl)pyrimidine-2,4-diamine hydrochloride (1at). This was obtained from 2-amino-4-chloropyrimidine (0.104g, 0.802 mmol), and 4-

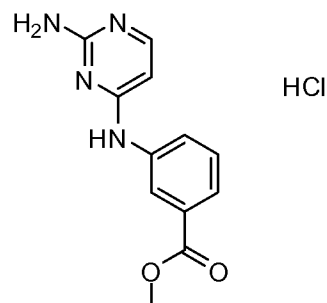
(methylsulfonyl)aniline (0.143 g, 827 μmol) in a similar manner as described for **1am**. After cooling to room temperature, the solid precipitate was filtered, slurried with MeOH, filtered, and dried under vacuum. Pure **1at** (0.165 g, 0.534 μmol , 67%) as a yellow solid. ^1H NMR (400 MHz, CD_3OD) δ 8.08 (d, $J = 8.7$ Hz, 2H), 7.96 (d, $J = 8.8$ Hz, 2H), 7.82 (d, $J = 7.2$ Hz, 1H), 6.39 (d, $J = 7.2$ Hz, 1H), 3.12 (s, 3H). MS ($\text{M}+\text{H}$) $^+$ 265.07.



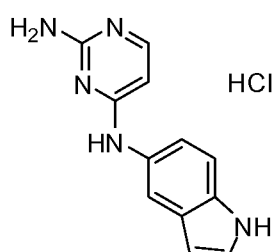
N-(4-(methylthio)phenyl)pyrimidine-2,4-diamine hydrochloride (1au). This was obtained from 2-amino-4-chloropyrimidine (0.099g, 0.764 μmol), and 4-(methylthio)aniline (0.106 g, 764 μmol) in a similar manner as described for **1am**. After cooling to room temperature, the solid precipitate was filtered, washed with DCM, and dried under vacuum. Pure **1au** (0.085 g, 0.316 μmol , 41%) as a yellow solid. ^1H NMR (400 MHz, CD_3OD) δ 7.69 (d, $J = 7.3$ Hz, 2H), 7.66 (s, 1H), 7.29 (d, $J = 8.7$ Hz, 2H), 6.28 (d, $J = 7.3$ Hz, 1H), 2.48 (s, 3H). HRMS (ESI+ve) calculated for $\text{C}_{11}\text{H}_{13}\text{N}_4\text{S}$ ($\text{M}+\text{H}-\text{Cl}$) $^+$ 232.0855, found 232.0864.



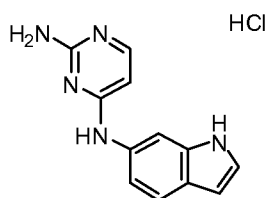
Methyl 4-(2-aminopyrimidin-4-ylamino)benzoate hydrochloride (1aw). A mixture of 2-amino-4-chloropyrimidine (0.140g, 1.08 μmol), and methyl-4-aminobenzoic acid (0.163g, 1.08 μmol) was stirred in a Biotage microwave reactor for 15 min at 150 $^\circ\text{C}$. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, DCM, dried under vacuum. Pure **1aw** (0.189 g, 0.908 μmol , 84%) as a pale yellow solid. ^1H NMR (400 MHz, CD_3OD) δ 8.03 (d, $J = 8.6$ Hz, 2H), 7.93 (d, $J = 8.6$ Hz, 2H), 7.78 (d, $J = 7.2$ Hz, 1H), 6.37 (d, $J = 7.2$ Hz, 1H), 3.90 (s, 3H). HRMS (ESI+ve) calculated for $\text{C}_{12}\text{H}_{13}\text{N}_4\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 245.1033, found 245.1043.



Methyl 3-(2-aminopyrimidin-4-ylamino)benzoate hydrochloride (1av). A mixture of 2-amino-4-chloropyrimidine (0.097 g, 0.748 mmol), and methyl-3-aminobenzoic acid (0.113 g, 0.748 mmol) was stirred in a Biotage microwave reactor for 15 min at 120 °C. After cooling to room temperature, the solvent was removed under reduced pressure and the obtained solid was slurried with DCM, filtered, dried under vacuum to provide pure **1av** (0.136 g, 0.485 mmol, 65%) as a pale yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.34 (s, 1H), 8.10 (s, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 6.32 (d, *J* = 7.2 Hz, 1H), 3.93 (s, 3H). HRMS (ESI+ve) calculated for C₁₂H₁₃N₄O₂ (M+H)⁺ 245.1033, found 245.1042.

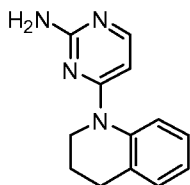


N-(1H-indol-5-yl)pyrimidine-2,4-diamine hydrochloride (1az). This was obtained as a white solid from 2-amino-4-chloropyrimidine (0.115g, 0.887 mmol), and 1H-indol-5-amine (0.117 g, 887 mmol) in a similar manner as described for **1am**. After cooling to room temperature, the solid precipitate was filtered, washed with DCM, and dried under vacuum. Pure **1az** (0.161 g, 0.612 mmol, 69%) was obtained as a brown solid. ¹H NMR (400 MHz, CD₃OD) δ 7.85 (s, 1H), 7.64 (d, 1H, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 2.9 Hz, 1H), 7.14 (s, 1H), 6.45 (d, *J* = 2.8 Hz, 1H), 6.27 (d, *J* = 6.8 Hz, 1H). HRMS (ESI+ve) calculated for C₁₂H₁₂N₅ (M+H-Cl)⁺ 226.1087, found 226.1092.

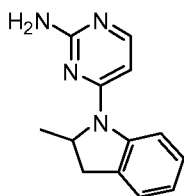


*N*⁴-(1H-indol-6-yl)pyrimidine-2,4-diamine hydrochloride

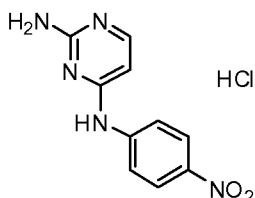
N-(1H-indol-6-yl)pyrimidine-2,4-diamine hydrochloride (1ba). This was obtained from 2-amino-4-chloropyrimidine (0.131g, 1.01 mmol), and 1H-indol-6-amine (0.133 g, 1.01 mmol) in a similar manner as described for **1am**. After cooling to room temperature, the solvent was removed under reduced pressure. The remaining solid was slurried with ether, DCM, filtered and dried under vacuum. Pure **1ba** (0.136 g, 0.519 mmol, 51%) as a brown solid. ¹H NMR (400 MHz, CD₃OD) δ 7.96 (s, 1H), 7.62 (d, *J* = 7.3 Hz, 1H), 7.39 (s, 1H), 7.28 (s, 2H), 6.46 (s, d, *J* = 2.3 Hz, 1H), 6.25 (s, 1H). HRMS (ESI+ve) calculated for C₁₂H₁₂N₅ (M+H-Cl)⁺ 226.1087, found 226.1095.



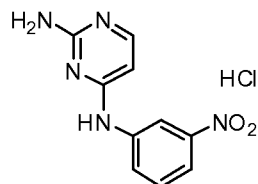
N 4-(3,4-dihydroquinolin-1(2H)-yl)pyrimidin-2-amine (16). This was obtained from 2-amino-4-chloropyrimidine (0.120g, 0.926 mmol), and 1,2,3,4-tetrahydroquinoline (0.185 g, 1.389mmol), in a similar manner as described for **1aw**. After cooling to room temperature, Et₃N (1ml) was added. The solvent was removed under reduced pressure. The remaining solid was slurried with water, filtered, washed with ether, dried under vacuum. Pure **16** (0.089g, 0.392mmol, 42%) was obtained as an off-white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.73 (d, *J* = 6.2 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.35 (d, *J* = 6.2 Hz, 1H), 3.91 (t, *J* = 6.3 Hz, 2H), 2.74 (t, *J* = 6.5 Hz, 2H), 1.94 (p, 2H, *J* = 6.5 Hz, 2H). HRMS (ESI+ve) calculated for C₁₃H₁₅N₄ (M+H)⁺ 227.1291, found 227.1294.



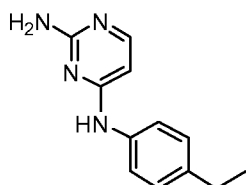
4-(2-methylindolin-1-yl)pyrimidin-2-amine (13b). This was obtained from 2-amino-4-chloropyrimidine (0.091g, 0.702 mmol) and 2-methylindoline (0.093g, 0.702 mmol), in a similar manner as described for **1aw**. After cooling to room temperature, Et₃N (1ml) was added. The solvent was removed under reduced pressure. The remaining solid was slurried with water, filtered, washed with ether, dried under vacuum. Pure **13b** (0.090g, 0.396mmol, 56%) was obtained as an off-white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.31 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 6.2 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 6.97 – 6.91 (m, 1H), 6.24 (d, *J* = 6.2 Hz, 1H), 4.69-4.61 (m, 1H), 3.40 (dd, *J* = 15.8, 9.1 Hz, 1H), 2.69 (d, *J* = 15.8 Hz, 1H), 1.26 (d, *J* = 6.3 Hz, 3H). HRMS (ESI+ve) calculated for C₁₃H₁₅N₄ (M+H)⁺ 227.1291, found 227.1292



N-(4-nitrophenyl)pyrimidine-2,4-diamine hydrochloride (1bb). This was obtained from 2-amino-4-chloropyrimidine (0.109g, 0.841 mmol) p-nitroaniline (0.116g, 0.841 mmol), in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, and dried under vacuum (0.116g). The methanolic solution was concentrated to dryness. The obtained solid was slurried with methanol, filtered and dried under vacuum (0.029g). The two batches were combined to provide pure **1bb** (0.145 g, 0.541 mmol, 64%) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.27 (d, *J* = 9.2 Hz, 2H), 8.07 (d, *J* = 8.9 Hz, 2H), 7.84 (d, *J* = 7.2 Hz, 1H), 6.41 (d, *J* = 7.2 Hz, 1H). HRMS (ESI+ve) calculated for C₁₀H₁₀N₅O₂ (M+H-Cl)⁺ 232.0829, found 232.0836

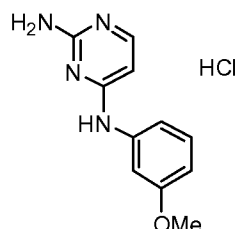


N-(3-nitrophenyl)pyrimidine-2,4-diamine hydrochloride (1bc). This was obtained from 2-amino-4-chloropyrimidine (0.133g, 1.02 mmol) m-nitroaniline (0.141g, 1.02 mmol), in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, and dried under vacuum. Pure **1bc** (0.213 g, 0.795 mmol, 76%) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.63 (s, 1H), 8.19 (d, *J* = 9.8 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 5.8 Hz, 1H), 7.64 (t, *J* = 8.2 Hz, 1H), 6.37 (d, *J* = 7.2 Hz, 1H). HRMS (ESI+ve) calculated for C₁₀H₁₀N₅O₂ (M+H-Cl)⁺ 232.0829, found 232.0838



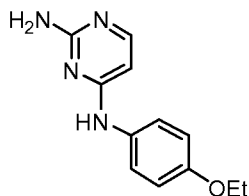
*N*⁴-(4-ethylphenyl)pyrimidine-2,4-diamine

N-(4-ethylphenyl)pyrimidine-2,4-diamine (1bd). This was obtained from 2-amino-4-chloropyrimidine (0.091g, 0.702 mmol), and p-ethylaniline (0.085 g, 0.702mmol) in a similar manner as described for **1aw**. After cooling to room temperature, Et₃N (1ml) was added. The solvent was removed under reduced pressure. The remaining solid was slurried with water, filtered, washed with ether, dried under vacuum. Pure **1bd** (0.064g, 0.299mmol, 43%) was obtained as an off-white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.72 (d, *J* = 6.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 6.02 (d, *J* = 6.0 Hz, 1H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H). HRMS (ESI+ve) calculated for C₁₂H₁₅N₄ (M+H-Cl)⁺ 215.1291, found 215.1308

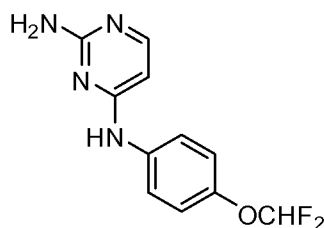


N-(3-methoxyphenyl)pyrimidine-2,4-diamine hydrochloride (1be). This was obtained from 2-amino-4-chloropyrimidine (0.090g, 0.694 mmol), and 3-methoxyaniline (0.085 g, 0.694 mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, ether, further triturated with methanol, filtered and dried under vacuum (0.015g). The methanolic solution was concentrated to dryness. The obtained solid was slurried with methanol, filtered and dried under vacuum (0.033 g). The methanolic solution was concentrated to dryness. The obtained solid was slurried with DCM, filtered and dried under vacuum (0.077 g). The three batches were combined to provide pure **1be** (0.125 g, 0.494 mmol, 71%) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 7.70 (d, *J* = 7.3 Hz, 1H), 7.35-

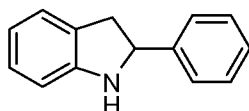
7.24 (m, 3H), 6.78 (d, $J = 7.2$ Hz, 1H), 6.29 (d, $J = 7.3$ Hz, 1H), 3.81 (s, 3H). HRMS (ESI+ve) calculated for $C_{11}H_{13}N_4O$ ($M+H-Cl$)⁺ 217.1083, found 217.1098.



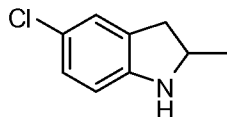
N-(4-ethoxyphenyl)pyrimidine-2,4-diamine (1bf). This was obtained from 2-amino-4-chloropyrimidine (0.118g, 0.910 mmol), and p-ethoxyaniline (0.124 g, 0.910 mmol) in a similar manner as described for **1aw**. After cooling to room temperature, Et₃N (1ml) was added. The solvent was removed under reduced pressure. The remaining solid was slurried with water, filtered, washed with ether, dried under vacuum. Pure **1bf** (0.137g, 0.593mmol, 65%) was obtained as an off-white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.70 (d, $J = 6.1$ Hz, 1H), 7.40 (d, $J = 8.9$ Hz, 2H), 6.87 (d, $J = 8.9$ Hz, 2H), 5.96 (d, $J = 4.5$ Hz, 1H), 4.01 (q, $J = 7.0$ Hz, 2H), 1.37 (t, $J = 7.0$ Hz, 3H). HRMS (ESI+ve) calculated for $C_{12}H_{15}N_4O$ ($M+H$)⁺ 231.1240, found 231.1253



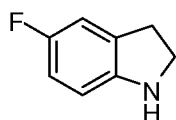
N-(4-(difluoromethoxy)phenyl)pyrimidine-2,4-diamine (1bg). This was obtained from 2-amino-4-chloropyrimidine (0.098g, 0.756 mmol), and 4-(difluoromethoxy)aniline (0.120 g, 0.756 mmol) in a similar manner as described for **1aw**. After cooling to room temperature, Et₃N (1ml) was added. The solvent was removed under reduced pressure. The remaining solid was slurried with water, filtered, washed with ether/hexane solution (1/1), dried under vacuum. Pure **1bg** (0.155g, 0.613mmol, 81%) was obtained as a brown solid. ¹H NMR (400 MHz, CD₃OD) δ 7.75 (d, $J = 6.0$ Hz, 1H), 7.66 (d, $J = 9.0$ Hz, 2H), 7.08 (d, $J = 9.0$ Hz, 2H), 6.73 (t, $J = 74.5$ Hz, 1H), 6.03 (d, $J = 6.0$ Hz, 1H). HRMS (ESI+ve) calculated for $C_{11}H_{11}F_2N_4O$ ($M+H$)⁺ 253.0895, found 253.0904.



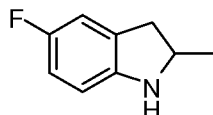
2-phenylindoline (12a) NaBH₃CN (2.11 g, 33.62 mmol) was added to a suspension of 2-phenylindole (1.083 g, 5.60 mmol) in acetic acid (glacial, 24 mL) at 0 °C under Argon. The reaction mixture was then stirred at room temperature for 3h. An aq. sat. solution of NaHCO₃ was then added slowly to pH 8-9. The mixture was then extracted with AcOEt, the organic phase separated, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **12a** (0.174 g, 0.892 mmol, 16%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.44–7.30 (m, 5H), 7.10–7.4 (m, 2H), 6.74 (td, $J = 7.5, 0.9$ Hz, 1H), 6.68 (d, $J = 7.7$ Hz, 1H), 4.96 (t, $J = 9.0$ Hz, 1H), 3.45 (dd, $J = 15.7, 9.1$ Hz, 1H), 2.99 (dd, $J = 15.6, 9.0$ Hz, 1H).



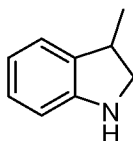
5 **5-chloro-2-methylindoline (12b)** This was obtained from 5-chloro-2-methylindole (0.372 g, 2.25 mmol), in a similar manner as described for **12a**. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **12b** (0.256 g, 1.532 mmol, 68%) as a brown oil. ¹H NMR (400 MHz, CDCl₃) δ 7.06–6.98 (m, 1H), 6.96–6.92 (m, 1H), 6.49 (d, *J* = 8.2 Hz, 1H), 4.08–3.92 (m, 1H), 3.12 (dd, *J* = 15.7, 8.5 Hz, 1H), 2.61 (dd, *J* = 15.7, 7.6 Hz, 1H), 1.27 (d, *J* = 6.3 Hz, 3H).



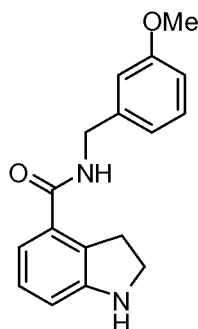
15 **5-fluoroindoline (12c)** This was obtained from 5-fluoroindole (0.316 g, 2.33 mmol), in a similar manner as described for **12a**. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **12c** (0.041 g, 0.299 mmol, 13%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.00–6.96 (m, 1H), 6.37–6.30 (m, 2H), 3.59 (t, *J* = 8.4 Hz, 2H), 2.97 (t, *J* = 8.4 Hz, 2H).



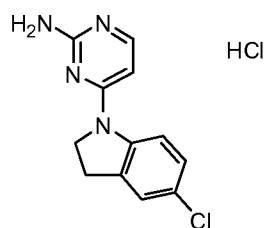
20 **5-fluoro-2-methylindoline (12d)** This was obtained from 5-fluoro-2-methylindole (0.426 g, 2.85 mmol), in a similar manner as described for **12a**. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **12d** (0.144 g, 0.953 mmol, 33%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 6.80–6.77 (m, 1H), 6.71–6.67 (m, 1H), 6.49 (dd, *J* = 8.4, 4.4 Hz, 1H), 4.07–3.84 (m, 1H), 3.12 (dd, *J* = 15.7, 8.4 Hz, 1H), 2.62 (dd, *J* = 15.7, 7.9 Hz, 1H), 1.28 (d, *J* = 6.2 Hz, 3H).



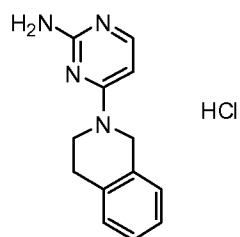
30 **3-methylindoline (12e)** This was obtained from 3-methylindole (0.414 g, 3.15 mmol), in a similar manner as described for **12a**. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **12e** (0.123 g, 0.924 mmol, 29%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.09–7.08 (m, 1H), 7.04–7.01 (m, 1H), 6.74 (t, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 3.70 (t, *J* = 8.6 Hz, 1H), 3.41–3.18 (m, 1H), 3.11 (t, *J* = 8.6 Hz, 1H), 1.33 (d, *J* = 6.7 Hz, 3H).



N-(3-methoxybenzyl)indoline-4-carboxamide (12f) This was obtained from **29a** (0.186 g, 0.663 mmol), in a similar manner as described for **12a**. The crude material (0.163 g, 0.578 mmol, 87%) was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.24 (t, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.90-6.85 (m, 3H), 6.81 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 6.47 (s, 1H), 4.54 (d, *J* = 5.7 Hz, 2H), 3.77 (s, 3H), 3.51 (t, *J* = 8.4 Hz, 2H), 3.25 (t, *J* = 8.4 Hz, 2H).

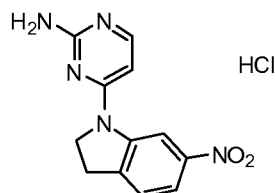


N-(5-chloroindolin-1-yl)pyrimidin-2-amine hydrochloride (13c). This was obtained from 2-amino-4-chloropyrimidine (0.100g, 0.771 mmol), and 5-chloroindoline (0.118 g, 0.771 mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with DCM and dried under vacuum. Pure **13c** (0.166g, 0.586mmol, 76%) was obtained as an off-white solid ¹H NMR (400 MHz, CD₃OD) δ 8.63 (s, 1H), 7.85 (d, *J* = 7.4 Hz, 1H), 7.31 (s, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 6.43 (t, *J* = 4.0 Hz, 1H), 4.23 (t, *J* = 8.2 Hz, 2H). HRMS (ESI+ve) calculated for C₁₂H₁₂N₄Cl (M+H)⁺ 247.0745, found 247.0753.

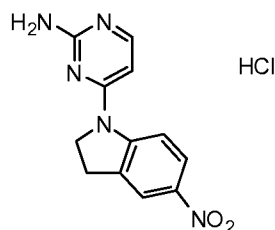


4-(3,4-dihydroisoquinolin-2(1H)-yl)pyrimidin-2-amine hydrochloride (17). This was obtained from 2-amino-4-chloropyrimidine (0.116g, 0.895 mmol), and 1,2,3,4-tetrahydroisoquinoline (0.262 g, 1.97 mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, dried under vacuum. Pure **17** (0.154 g, 0.679 mmol, 76%) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.75 (d, *J* = 6.4 Hz, 1H), 7.18-7.16 (m, 4H), 6.16 (d, *J* = 6.4

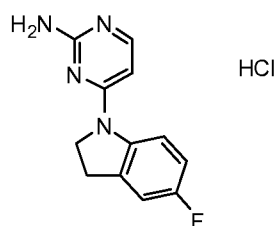
Hz, 1H), 4.72 (s, 2H), 3.83 (t, $J = 5.9$ Hz, 2H), 2.91 (t, $J = 5.9$ Hz, 2H). HRMS (ESI+ve) calculated for $C_{13}H_{15}N_4$ ($M+H-Cl$)⁺ 227.1291, found 227.1293.



4-(6-nitroindolin-1-yl)pyrimidin-2-amine hydrochloride (13d). This was obtained from 2-amino-4-chloropyrimidine (0.106g, 0.818 mmol), and 6-nitroindoline (0.134 g, 0.818 mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, dried under vacuum. Pure **13d** (0.200 g, 0.680 mmol, 83%) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 9.32 (s, 1H), 8.04 (dd, $J = 1.9, 8.4$ Hz, 1H), 7.94 (d, $J = 7.4$ Hz, 1H), 7.52 (d, 1H, $J = 8.2$ Hz, 1H), 6.52 (d, $J = 6.9$ Hz, 1H), 4.34 (t, $J = 8.5$ Hz, 2H), 3.42 (t, $J = 8.1$ Hz, 2H). HRMS (ESI+ve) calculated for $C_{12}H_{12}N_5O_2$ ($M+H-Cl$)⁺ 258.0985, found 258.0988.

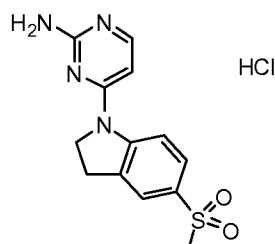


4-(5-nitroindolin-1-yl)pyrimidin-2-amine hydrochloride (13e). This was obtained from 2-amino-4-chloropyrimidine (0.103g, 0.795 mmol), and 5-nitroindoline (0.130 g, 0.795mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, dried under vacuum. Pure **13e** (0.174 g, 0.592 mmol, 75%) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.84 (d, $J = 7.6$ Hz, 1H), 8.24-8.17 (m, 2H), 7.97 (d, $J = 7.4$ Hz, 1H), 6.56 (d, 1H, $J = 7.5$ Hz, 1H), 4.35 (t, $J = 8.5$ Hz, 2H), 3.41 (t, $J = 8.5$ Hz, 2H).). HRMS (ESI+ve) calculated for $C_{12}H_{12}N_5O_2$ ($M+H-Cl$)⁺ 258.0985, found 258.0990.

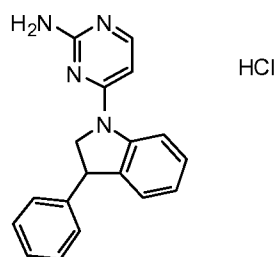


4-(5-fluoroindolin-1-yl)pyrimidin-2-amine hydrochloride (13f). This was obtained from 2-amino-4-chloropyrimidine (0.143g, 1.10 mmol), and 5-fluoroindoline (0.151g, 1.10mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, dried under vacuum. Pure **13f** (0.220g, 0.592 mmol, 75%) as an off white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.66 (s, 1H), 7.83 (d, $J = 7.5$ Hz, 1H), 7.08 (d, $J = 6.9$ Hz, 1H), 7.00-6.95 (m, 1H), 6.44 (d, $J = 6.3$

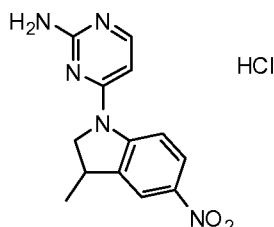
Hz, 1H), 4.25 (t, $J = 8.4$ Hz, 2H). HRMS (ESI+ve) calculated for $C_{12}H_{12}FN_5$ ($M+H-Cl$)⁺ 231.1040, found 231.1045.



4-(5-(methylsulfonyl)indolin-1-yl)pyrimidin-2-amine hydrochloride (13g). This was obtained from 2-amino-4-chloropyrimidine (0.110g, 0.849 mmol), and 5-(methylsulfonyl)indoline (0.167g, 0.849mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, dried under vacuum. Pure **13g** (0.214g, 0.654 mmol, 77%) as an off white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.87 (s, 1H), 7.95 (dd, $J = 0.8, 7.4$ Hz, 1H), 7.87 (s, 1H), 7.85-7.83 (m, 1H), 6.54 (d, $J = 7.4$ Hz, 1H), 4.32 (t, $J = 8.5$ Hz, 2H), 3.40 (t, $J = 8.6$ Hz, 2H), 3.12 (s, 3H). HRMS (ESI+ve) calculated for $C_{13}H_{14}N_4O_2S$ ($M+H-Cl$)⁺ 291.0910, found 291.0915.

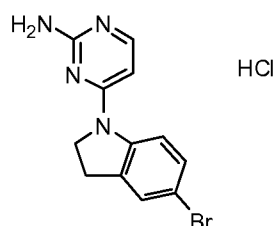


4-(3-phenylindolin-1-yl)pyrimidin-2-amine hydrochloride (13h). This was obtained from 2-amino-4-chloropyrimidine (0.077g, 0.594mmol), and **12a** (0.116g, 0.594mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, and dried under vacuum (0.036g). The methanolic solution was concentrated to dryness. The obtained solid was slurried with acetone, filtered and dried under vacuum (0.107g). The two batches were combined to provide pure **13h** (0.143 g, 0.440 mmol, 74%) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.75 (s, 1H), 7.67 (d, $J = 7.6$ Hz, 1H), 7.37-7.24 (m, 5H), 7.19 (t, $J = 7.4$ Hz, 3H), 6.22 (s, 1H), 5.78 (d, $J = 10.0$ Hz, 1H), 3.91 (dd, $J = 9.8, 16.5$ Hz, 1H), 3.04 (d, $J = 16.3$ Hz, 2H). HRMS (ESI+ve) calculated for $C_{18}H_{17}N_4$ ($M+H-Cl$)⁺ 289.1447, found 289.1447.

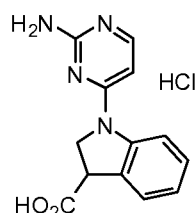


4-(3-methyl-5-nitroindolin-1-yl)pyrimidin-2-amine hydrochloride (13i). This was obtained from 2-amino-4-chloropyrimidine (0.115g, 0.887mmol), and 3-methyl-5-nitroindoline (0.158g, 0.887mmol) in a similar manner as described for **1aw**. After

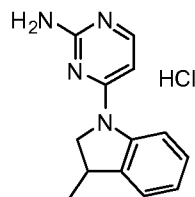
cooling to room temperature, the solid precipitate was filtered, washed with methanol, and dried under vacuum. Pure **13i** (0.094 g, 0.304 mmol, 34%) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 9.21 (s, 1H), 8.06 (dd, *J* = 2.1, 8.2 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 1H), 4.99-4.94 (m, 1H), 3.60 (dd, *J* = 9.0, 17.0 Hz, 1H), 2.97 (d, *J* = 17.0 Hz, 2H), 1.36 (d, *J* = 6.5 Hz, 3H). HRMS (ESI+ve) calculated for C₁₃H₁₄N₅O₂ (M+H-Cl)⁺ 272.1142, found 272.1141.



4-(5-bromoindolin-1-yl)pyrimidin-2-amine hydrochloride (13j). This was obtained from 2-amino-4-chloropyrimidine (0.081g, 0.625mmol), and 5-bromoindoline (0.123g, 0.625mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, and dried under vacuum. Pure **13j** (0.149 g, 0.455 mmol, 73%) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.59 (s, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.47 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 6.45 (d, *J* = 5.7 Hz, 1H), 4.23 (t, *J* = 8.5 Hz, 2H). HRMS (ESI+ve) calculated for C₁₂H₁₂BrN₄ (M+H-Cl)⁺ 291.0239, found 291.0240.

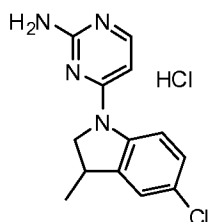


1-(2-aminopyrimidin-4-yl)indoline-3-carboxylic acid hydrochloride (13k). This was obtained from 2-amino-4-chloropyrimidine (0.070g, 0.540mmol), and indoline-3-carboxylic acid (0.088g, 0.540mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, and dried under vacuum. Pure **13k** (0.079 g, 0.269 mmol, 50%) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.70 (s, 1H), 7.85 (s, 1H), 7.32-7.28 (m, 3H), 7.16 (t, *J* = 7.3 Hz, 1H), 6.32 (s, 1H), 5.32 (s, 1H), 3.75-3.68 (m, 1H). HRMS (ESI+ve) calculated for C₁₃H₁₃O₂N₄ (M+H-Cl)⁺ 257.1033, found 257.1034.

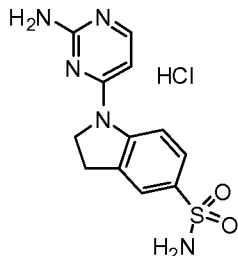


4-(3-methylindolin-1-yl)pyrimidin-2-amine hydrochloride (13l). This was obtained from 2-amino-4-chloropyrimidine (0.070g, 0.540mmol), and **12e** (0.072g, 0.540mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, and dried under vacuum (0.058g). The methanolic solution was concentrated to dryness. The obtained solid was slurried with acetone, filtered and dried under vacuum (0.050g). The two batches were combined to

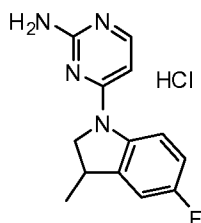
provide pure **13l** (0.108 g, 0.411 mmol, 76%) as a yellow solid. ^1H NMR (400 MHz, CD_3OD) δ 8.62 (s, 1H), 7.83 (d, $J = 7.5$ Hz, 1H), 7.33 (d, $J = 7.4$ Hz, 1H), 7.28 (t, $J = 7.2$ Hz, 1H), 7.17 (t, $J = 7.3$ Hz, 1H), 6.47 (d, $J = 6.1$ Hz, 1H), 4.40 (t, 1H, $J = 9.9$ Hz, 1H), 3.75 (dd, $J = 6.3, 10.9$ Hz, 1H), 3.61 (m, 1H), 1.40 (d, $J = 6.9$ Hz, 3H). HRMS (ESI+ve) calculated for $\text{C}_{13}\text{H}_{15}\text{N}_4$ ($\text{M}+\text{H}-\text{Cl}$) $^+$ 227.1291, found 227.1290



4-(5-chloro-3-methylindolin-1-yl)pyrimidin-2-amine hydrochloride (13m). This was obtained from 2-amino-4-chloropyrimidine (0.055g, 0.431mmol), and **12b** (0.072g, 0.341mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solvent was removed under reduced pressure. The obtained solid was slurried DCM, filtered and dried under vacuum. Pure **13m** (0.082g, 0.276mmol, 64%) was obtained as an off white solid. ^1H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 7.85 (d, $J = 7.5$ Hz, 1H), 7.35 (s, 1H), 7.26 (dd, $J = 8.5, 1.5$ Hz, 1H), 6.58 (d, $J = 7.4$ Hz, 1H), 3.50 (dd, $J = 8.9, 16.3$ Hz, 1H), 2.84 (d, $J = 16.3$ Hz, 1H), 1.32 (d, $J = 6.4$ Hz, 3H). HRMS (ESI+ve) calculated for $\text{C}_{13}\text{H}_{14}\text{ClN}_4$ ($\text{M}+\text{H}-\text{Cl}$) $^+$ 261.0901, found 261.0904

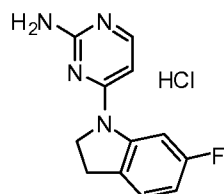


1-(2-aminopyrimidin-4-yl)indoline-5-sulfonamide hydrochloride (13n). This was obtained from 2-amino-4-chloropyrimidine (0.076g, 0.586mmol), and indoline-5-sulfonamide (0.116g, 0.586mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, and dried under vacuum. Pure **13n** (0.170 g, 0.518mmol, 88%) was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.72 (d, $J = 8.6$ Hz, 1H), 8.06 (d, $J = 7.2$ Hz, 1H), 7.70 (s, 1H), 7.64 (d, $J = 10.0$ Hz, 1H), 7.33 (s, 2H), 6.53 (s, 1H), 6.46 (d, $J = 7.2$ Hz, 1H), 4.21 (t, $J = 8.4$ Hz, 2H), 3.27 (t, $J = 8.3$ Hz, 2H). HRMS (ESI+ve) calculated for $\text{C}_{12}\text{H}_{14}\text{ClN}_5\text{O}_2\text{S}$ ($\text{M}+\text{H}-\text{Cl}$) $^+$ 292.0862, found 292.0863.

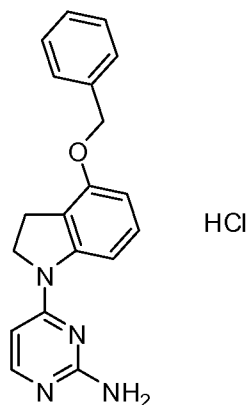


4-(5-fluoro-3-methylindolin-1-yl)pyrimidin-2-amine hydrochloride (13o). This was obtained from 2-amino-4-chloropyrimidine (0.042g, 0.324mmol), and **12d** (0.049g,

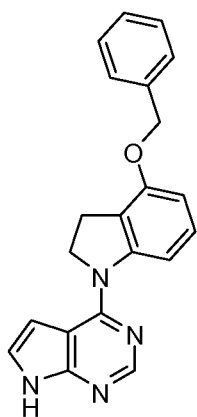
0.324mmol) in a similar manner as described for **1aw**. After cooling to room temperature, Et₃N was added. The solvent was removed under reduced pressure. The remaining solid was slurried with water, filtered, washed with ether, dried under vacuum. Pure **13o** (0.043g, 0.171mmol, 53%) was obtained as an off white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.39 (dd, *J* = 4.9, 8.8 Hz, 1H), 7.87 (d, *J* = 6.1 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.89 (td, *J* = 9.1, 2.7 Hz, 1H), 6.19 (d, *J* = 6.2 Hz, 1H), 4.69-4.62 (m, 1H), 3.42 (dd, *J* = 9.4, 16.5 Hz, 1H), 2.71 (d, *J* = 16.4 Hz, 1H), 1.26 (d, *J* = 6.3 Hz, 3H),. HRMS (ESI+ve) calculated for C₁₃H₁₄FN₄ (M+H-Cl)⁺ 245.1197, found 245.1211



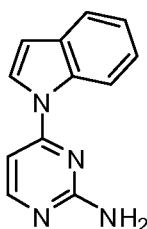
4-(6-fluoroindolin-1-yl)pyrimidin-2-amine hydrochloride (13p). This was obtained from 2-amino-4-chloropyrimidine (0.026g, 0.204mmol), and **12c** (0.028g, 0.204mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, and dried under vacuum. Pure **13p** (0.032 g, 0.120mmol, 59%) was obtained as an off white solid ¹H NMR (400 MHz, CD₃OD) δ 8.44 (d, *J* = 10.8 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.26-7.22 (m, 1H), 6.83-6.79 (m, 1H), 6.37 (dd, *J* = 7.1, 1.1 Hz, 1H), 4.22 (t, 2H, *J* = 8.3 Hz, 2H), 3.24 (t, *J* = 9.2 Hz, 2H), HRMS (ESI+ve) calculated for C₁₂H₁₂FN₄ (M+H-Cl)⁺ 231.1040, found 231.1038



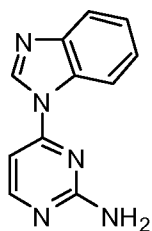
4-(4-(benzyloxy)indolin-1-yl)pyrimidin-2-amine hydrochloride (13q) This was obtained from 2-amino-4-chloropyrimidine (0.090g, 0.694mmol), and **4-(benzyloxy)indoline** (0.156g, 0.694mmol) in a similar manner as described for **1aw**. After cooling to room temperature, the solid precipitate was filtered, washed with methanol, and dried under vacuum. Pure **13q** (0.119 g, 0.336mmol, 48%) was obtained as as an off white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.30 (s, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.45-7.43 (m, 2H), 7.39-7.35 (m, 2H), 7.33-7.28 (m, 1H), 7.22 (t, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.39 (s, 1H), 5.15 (s, 2H), 4.21 (t, *J* = 8.2 Hz, 2H), 3.22 (t, *J* = 8.1 Hz, 2H). HPLC: Purity 99.53%, MeOH 60%, (0.1% TFA in H₂O) 40%, 20 min, Flow 1ml/min, R_t 10.067 min. HRMS (ESI-ve) calculated for C₁₉H₁₉N₄O (M+H)⁺ 319.1553, found 319.1563



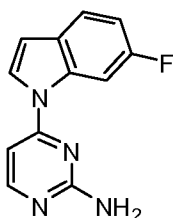
4-(4-(benzyloxy)indolin-1-yl)-7H-pyrrolo[2,3-d]pyrimidine (35) A mixture of (benzyloxy)indoline (0.060g, 0.266 mmol), 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (0.039 g, 0.253 mmol) in anhydrous ethanol (0.6 ml) was stirred in a Biotage microwave reactor for 30 min at 150 °C. After cooling to room temperature, Et₃N was added. The solvent was removed under reduced pressure. The remaining solid was slurried with water, filtered, washed with methanol, dried under vacuum. Pure **35** (0.046g, 0.134mmol, 53%) was obtained as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.86 (s, 1H), 8.29 (s, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 7.0 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.33-7.25 (m, 2H), 7.12 (t, *J* = 8.3 Hz, 1H), 6.69-6.67 (m, 2H), 5.16 (s, 2H), 4.53 (t, *J* = 9.5 Hz, 2H), 3.17 (t, *J* = 9.4 Hz, 2H). HRMS (ESI-ve) calculated for C₂₁H₁₉N₄O (M+H)⁺ 343.1553, found 343.1562



4-(1H-indol-1-yl)pyrimidin-2-amine (15a). A mixture of 2-amino-4-chloropyrimidine (0.206g, 1.590mmol), indole (0.372g, 3.180mmol) and Cs₂CO₃ (1.550g, 4.77 mmol) in anhydrous DMF (1.6 ml) was stirred in a Biotage microwave reactor for 1h at 110 °C. After cooling to room temperature, the reaction mixture diluted with water (5ml) and extracted with ethyl acetate (2 x 10ml). The combined organic extracts were dried over Na₂SO₄ and the solvent removed under reduced pressure. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **15a** (0.125 g, 0.593 mmol, 37%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.78 (d, 1H, *J* = 8.28 Hz), 8.23 (d, *J* = 5.64 Hz, 1H), 8.03 (d, *J* = 3.64 Hz, 1H), 7.59 (d, *J* = 7.76 Hz, 1H), 7.27-7.22 (m, 1H), 7.17 (t, *J* = 7.36 Hz, 1H), 6.93 (d, *J* = 5.92 Hz, 1H), (bs, 2H), 6.74 (d, *J* = 3.60 Hz, 1H); HRMS (ESI-ve) calculated for C₁₂H₁₁N₄ (M+H)⁺ 211.0978, found 211.0979.

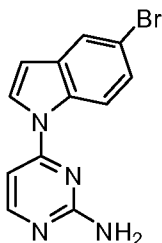


4-(1H-benzo[d]imidazol-1-yl)pyrimidin-2-amine (18). A mixture of 2-amino-4-chloropyrimidine (0.120g, 0.926mmol), imidazole (0.109g, 0.926mmol) and Cs_2CO_3 (0.603g, 1.852 mmol) in anhydrous DMF (0.9 ml) was stirred in a Biotage microwave reactor for 1h at 110 °C. After cooling to room temperature, water was added to the reaction mixture. The solid precipitate was filtered and dried under vacuum. The obtained solid was slurried with methanol, filtered, further slurried with ethyl acetate, filtered and dried under vacuum. Pure **18** (0.038 g, 0.178 mmol, 19%) was obtained as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.02 (s, 1H), 8.62 (d, $J = 7.0$ Hz, 1H), 8.34 (d, $J = 5.5$ Hz, 1H), 7.73 (d, $J = 8.5$ Hz, 1H), 7.38-7.30 (m, 2H), 7.12 (d, $J = 5.6$ Hz, 1H), 7.06 (s, 2H); HRMS (ESI-ve) calculated for $\text{C}_{11}\text{H}_{10}\text{N}_5$ ($\text{M}+\text{H}$) $^+$ 212.0930, found 212.0929.



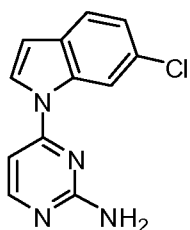
4-(6-fluoro-1H-indol-1-yl)pyrimidin-2-amine (15b)

A mixture of 2-amino-4-chloropyrimidine (0.062g, 0.478mmol), 6-fluoroindole (0.083g, 0.621mmol) and Cs_2CO_3 (0.467g, 1.43 mmol) in anhydrous NMP (0.5 ml) was stirred in a Biotage microwave reactor for 30min at 180 °C. After cooling to room temperature, the reaction mixture diluted with water (5ml) and extracted with ethyl acetate (2 x 10ml). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. Chromatography on silica gel using the FlashMaster 3 purification station ($\text{AcOEt}/\text{Hexane}$) afforded **15b** as a brown solid which was triturated with methanol, filtered, dried *in vacuo*. Pure **15b** was obtained (0.013 g, 0.057 mmol, 25%) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.66 (dd, $J = 2.5, 11.4$ Hz, 1H), 8.24 (d, $J = 5.6$ Hz, 1H), 8.06 (d, $J = 3.7$ Hz, 1H), 7.60 (dd, $J = 5.8, 8.6$ Hz, 1H), 7.05 (td, $J = 2.0, 8.8$ Hz, 1H), 6.95 (s, 2H) 6.93 (d, $J = 5.7$ Hz, 1H), 6.76 (d, $J = 3.7$ Hz, 1H); HPLC: Purity 97.73%, MeOH 40%, (0.1% TFA in H_2O) 60%, 20 min, Flow 1ml/min, R_t 11.533 min, HRMS (ESI-ve) calculated for $\text{C}_{12}\text{H}_{10}\text{N}_4$ ($\text{M}+\text{H}$) $^+$ 229.0884, found 229.0895

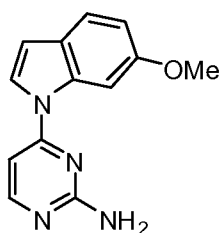


4-(5-bromo-1H-indol-1-yl)pyrimidin-2-amine (15c). A mixture of 2-amino-4-chloropyrimidine (0.091g, 0.702mmol), 5-bromoindole (0.083g, 0.621mmol) and Cs_2CO_3

(0.686g) in anhydrous NMP (0.8 ml) was stirred in a Biotage microwave reactor for 30min at 150 °C. After cooling to room temperature, the reaction mixture diluted with water and extracted with DCM. The organic extract was dried over Na₂SO₄ and the solvent removed under reduced pressure. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **15c** as an off white solid which was triturated with water, filtered, dried *in vacuo*. Pure **15c** was obtained (0.100 g, 0.345 mmol, 49%) as an off-white solid.¹H NMR (400 MHz, DMSO-*d*₆) δ 8.77 (d, *J* = 8.9 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 8.11 (d, *J* = 3.7 Hz, 1H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.35 (dd, *J* = 8.9, 2.1 Hz, 1H), 6.94-6.92 (m, 3H), 6.75 (d, *J* = 3.6 Hz, 1H). HPLC: Purity 99.02%, CH₃CN 30%, (0.1% TFA in H₂O) 70%, 20 min, Flow 1ml/min, R_t 11.533 min, Purity 98.18%, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min, R_t 16.240 min, HRMS (ESI-ve) calculated for C₁₂H₁₀BrN₄ (M+H)⁺ 289.0083, found 289.0077

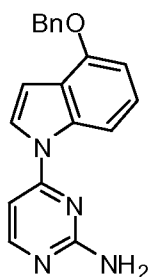


4-(6-chloro-1H-indol-1-yl)pyrimidin-2-amine (15d). This was obtained from 2-amino-4-chloropyrimidine (0.088g, 0.689mmol), and 6-chloroindole (0.154g, 1.01mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture diluted with water and extracted with DCM. The organic extract was dried over Na₂SO₄ and the solvent removed under reduced pressure. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **15d** as an orange oil. Water was added to the obtained oil and the solid precipitate was filtered, washed with water and dried *in vacuo*. Pure **15d** was obtained (0.089 g, 0.363 mmol, 49%) as an off-white solid.¹H NMR (400 MHz, DMSO-*d*₆) δ 8.84 (d, 1H, *J* = 1.92 Hz), 8.25 (d, *J* = 5.64 Hz, 1H), 8.08 (d, *J* = 3.68 Hz, 1H), 7.61 (d, *J* = 8.36 Hz, 1H), 7.21 (dd, *J* = 8.38, 1.98 Hz, 1H), 6.98 (bs, 2H, disappeared on D₂O shake), 6.93 (d, *J* = 5.68 Hz, 1H), 6.78 (dd, *J* = 3.68, 0.8 Hz, 1H). HPLC : Purity 99.02 %, CH₃CN 30%, (0.1% TFA in H₂O) 70%, 20 min, Flow 1ml/min, R_t 8.360 min, Purity 99.44 %, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min, R_t 10.933 min; HRMS (ESI-ve) calculated for C₁₂H₁₀ClN₄ (M+H)⁺ 245.0588, found 245.0589

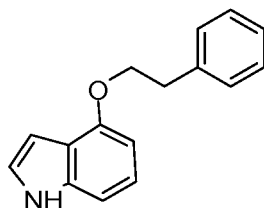


4-(6-methoxy-1H-indol-1-yl)pyrimidin-2-amine (15e). This was obtained from 2-amino-4-chloropyrimidine (0.089g, 0.686mmol), and 6-methoxyindole (0.151g, 1.02mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture diluted with water and extracted with DCM. The organic extract was

dried over Na_2SO_4 and the solvent removed under reduced pressure. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded pure **15e** (0.081g, 0.336 mmol, 49%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.32 (d, 1H, $J = 2.24$ Hz), 8.22 (d, $J = 5.64$ Hz, 1H), 7.87 (d, $J = 3.68$ Hz, 1H), 7.46 (d, $J = 8.52$ Hz, 1H), 6.89 (d, $J = 5.72$ Hz, 1H), 6.87 (bs, 2H), 6.82 (dd, $J = 8.58, 2.38$ Hz, 1H), 6.65 (d, $J = 3.12$ Hz, 1H), 3.83 (m, 3H). HPLC: Purity 99.02 %, CH_3CN 30%, (0.1% TFA in H_2O) 70%, 20 min, Flow 1ml/min: R_t 5.613 min; Purity 99.51 %, MeOH 50%, (0.1% TFA in H_2O) 50%, 20 min, Flow 1ml/min, R_t 6.600 min. HRMS (ESI-ve) calculated for $\text{C}_{13}\text{H}_{13}\text{ON}_4$ ($\text{M}+\text{H}$) $^+$ 241.1083, found 241.1083

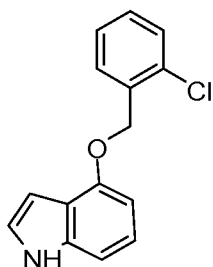


4-(4-(benzyloxy)-1H-indol-1-yl)pyrimidin-2-amine (21a). This was obtained from 2-amino-4-chloropyrimidine (0.087g, 0.671mmol), and 4-benzyloxyindole (0.224g, 1.00 mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture diluted with water and extracted with DCM. The organic extract was dried over Na_2SO_4 and the solvent removed under reduced pressure. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **21a** as an off white solid. Water was added to the obtained solid and the solid precipitate was filtered, washed with water and dried *in vacuo*. Pure **21a** was obtained (0.107 g, 0.337 mmol, 50%) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.35 (d, $J = 8.4$ Hz, 1H), 8.23 (d, $J = 5.6$ Hz, 1H), 7.94 (d, $J = 3.7$ Hz, 1H), 7.50 (d, $J = 7.1$ Hz, 2H), 7.39 (t, $J = 7.4$, Hz, 2H), 7.32 (t, $J = 7.3$ Hz, 1H), 7.16 (t, $J = 8.2$ Hz, 1H), 6.92 (d, $J = 5.7$ Hz, 1H), 6.87 (s, 2H), 6.81 (d, $J = 7.9$ Hz, 1H), 6.78 (d, $J = 3.4$ Hz, 1H), 5.24 (s, 2H). HPLC: Purity 99.46 %, CH_3CN 50%, (0.1% TFA in H_2O) 50%, 20 min, Flow 1ml/min: R_t 3.413 min, Purity 98.48 %, MeOH 60%, (0.1% TFA in H_2O) 40%, 20 min, Flow 1ml/min, R_t 12.600 min, HRMS (ESI-ve) calculated for $\text{C}_{19}\text{H}_{17}\text{ON}_4$ ($\text{M}+\text{H}$) $^+$ 317.1396, found 317.1399.

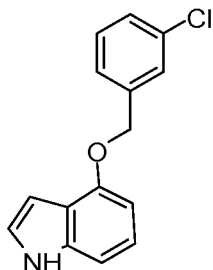


4-phenethoxy-1H-indole (20a) A mixture of 4-hydroxyindole (**1**) (0.400 g, 3.00 mmol), (2-bromoethyl)benzene (0.557 g, 3.00 mmol) and K_2CO_3 (1.243 g, 9.0 mmol) in acetone (3mL) was refluxed under argon for 4 days. After cooling to room temperature, the solid precipitate was filtered and washed with acetone. The filtrates were combined and the solvent was removed under reduced pressure to afford **20a** as a black oil (0.714 g, 3.00 mmol, quantitative). The crude material was used in the next step without purification. ^1H NMR (400 MHz, CDCl_3) δ 8.08 (s, 1H), 7.30 – 7.21 (m, 5H), 7.06 – 7.03 (m, 1H), 7.01

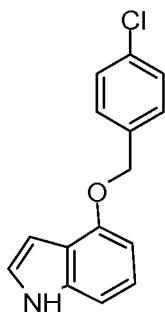
(d, $J = 7.8$ Hz, 1H), 6.95 (d, $J = 8.1$ Hz, 1H), 6.59 (t, $J = 1.6$ Hz, 1H), 6.45 (d, $J = 7.6$ Hz, 1H), 4.26 (t, $J = 7.1$ Hz, 2H), 3.13 (t, $J = 7.1$ Hz, 2H).



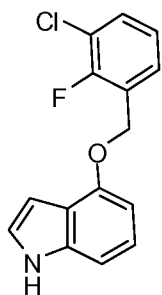
4-(2-chlorobenzoyloxy)-1H-indole (20b) A mixture of 4-hydroxyindole (0.133 g, 2.00 mmol), 3-chlorobenzylchloride (0.381 g, 2.4 mmol), and K_2CO_3 (0.829 g, 6.0 mmol) in acetone (15mL) was refluxed under argon for 9 days in presence of tetrabutylammonium bromide (0.038 g, 0.118 mmol). After cooling to room temperature, the solid precipitate was filtered and washed with acetone. The organic solutions were combined and the solvent removed under reduced pressure. Chromatography on silica gel, performed using a FlashMaster 3 purification station (AcOEt/Hexane), afforded **20b** (0.080 g, 0.311 mmol, 16%) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (bs, 1H), 7.61 (dd, $J = 1.4, 7.2$ Hz, 1H), 7.33 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.24-7.16 (m, 2H), 7.07-6.96 (m, 3H), 6.68 (m, 1H), 6.51 (d, $J = 7.5$ Hz, 1H).



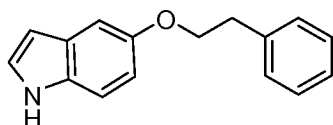
4-(3-chlorobenzoyloxy)-1H-indole (20c) This was prepared from 4-hydroxyindole (0.133 g, 2.0 mmol) and 3-chlorobenzylbromide (0.205 g, 2.4mmol) in the same manner as described for **20a**. Reaction time: 22hrs. Chromatography on silica gel performed twice using a FlashMaster 3 purification station (AcOEt/Hexane), afforded **20c** (0.267 g, 1.04 mmol, 52%) as a brown oil, Analysis of ^1H NMR revealed that a mixture of the desired product and an unknown impurity was isolated. The mixture was used as obtained in the next step. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.52 (s, 1H), 7.4 –7.28 (m, 3H), 7.16–7.05 (m, 3H), 6.78–6.71 (m, 1H), 6.56 (dd, $J = 7.3, 1.0$ Hz, 1H), 5.21 (s, 2H).



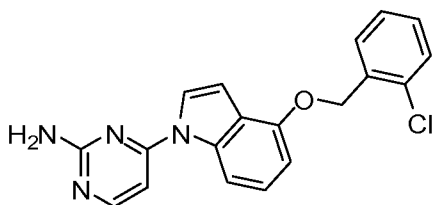
4-(4-chlorobenzoyloxy)-1H-indole (20d) This was prepared from 4-hydroxyindole (0.266 g, 2.0 mmol) and 4-chlorobenzylbromide (0.493 g, 2.4 mmol) in a similar manner as described for preparation of **20a**. Reaction time: 96 hours. Chromatography on silica gel, performed using the Flash Master purification station (AcOEt/Hexane), afforded an off white solid **20d** (0.372 g, 1.44 mmol, 72%). Analysis of ^1H NMR revealed that a mixture of the desired product and an unknown impurity was isolated. The mixture was used as obtained in the next step. ^1H NMR (400 MHz, CDCl_3) δ 8.13 (s, 1H), 7.37 (d, $J = 8.3$ Hz, 2H), 7.30-7.25 (m, 3H), 7.07 (t, $J = 3.0$ Hz, 1H), 7.03-6.94 (m, 1H), 6.63 (t, $J = 2.7$ Hz, 1H), 6.48 (d, $J = 7.4$ Hz, 1H), 5.13 (s, 2H).



4-(3-chloro-2-fluorobenzoyloxy)-1H-indole (20e) This was prepared from 4-hydroxyindole (0.100 g, 0.751 mmol) and 2-fluorobenzylbromide (0.201 g, 0.901 mmol) in a similar manner as described for preparation of **20a**. Reaction time: 34 hrs. Chromatography on silica gel, performed using the Flash Master purification station (AcOEt/Hexane), afforded an off-white solid, **20e** (0.372 g, 1.44 mmol, 72%) as an off white solid. Analysis of ^1H NMR revealed that a mixture of the desired product and an unknown impurity was isolated. The mixture was used as obtained in the next step. ^1H NMR (400 MHz, CDCl_3) δ 8.32 (s, 1H), 7.53 (t, $J = 7.0$ Hz, 1H), 7.41-7.34 (m, 1H), 7.14-7.01 (m, 4H), 6.72 (t, $J = 2.7$ Hz, 1H), 6.60 (d, $J = 7.6$ Hz, 1H), 5.32 (s, 2H).

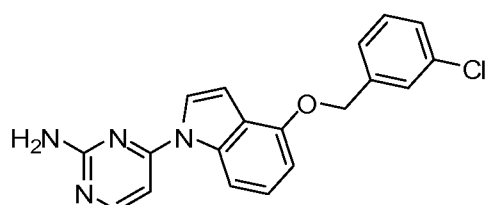


5-phenethoxy-1H-indole (20f) This was prepared from (2-bromoethyl)benzene (0.557 g, 3.00 mmol) and 5-hydroxyindole (0.400 g, 3.00 mmol) in a similar manner as described for preparation of **20a**. Reaction time: 24 hrs. Chromatography on silica gel, performed using the Flash Master purification station (AcOEt/Hexane), afforded **20f** (0.090 g, .378 mmol, 13%) as a brown oil. ^1H NMR (400 MHz, CDCl_3) δ 8.04 (bs, 1H), 7.35-7.32 (m, 2H), 7.26 (m, 3H), 7.18 (t, $J = 2.8$ Hz, 1H), 7.11 (d, $J = 2.3$ Hz, 1H), 6.87 (dd, $J = 2.4, 8.8$ Hz, 1H), 6.46 (m, 1H), 4.23 (t, $J = 7.2$ Hz, 2H), 3.13 (t, $J = 7.2$ Hz, 2H).

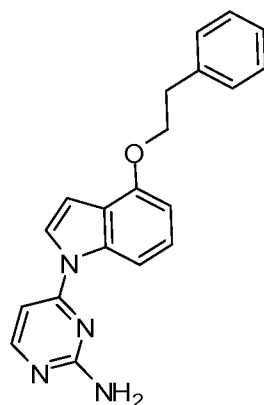


4-(4-(2-chlorobenzoyloxy)-1H-indol-1-yl)pyrimidin-2-amine (21h) A mixture of **20b** (0.068 g, .264 mmol) and 2-amino-4-chloropyrimidine (0.041 g, 0.317 mmol) in

anhydrous 1-Methyl-2-pyrrolidinone (0.42mL) and cesium carbonate (0.328 g, 1.00 mmol), was heated in the microwave at 150°C for 30minutes. After cooling to room temperature, the solvent was removed under reduced pressure. Chromatography on silica gel, performed using the Flash Master 3 purification station (AcOEt/Hexane) , afforded a yellow oil. Water was added and the solid precipitate was filtered, washed with water and dried under vacuum. Pure **21h** was obtained as an off white solid (0.017 g, 0.0486 mmol, 18%). ¹H NMR (400 MHz, CDCl₃) δ 8.27 (bs, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.58-7.56 (m, 2H), 7.35 (dd, *J* = 1.7, 7.2 Hz, 1H), 7.25-7.14 (m, 3H), 6.86 (d, *J* = 3.6 Hz, 1H), 6.74 (d, *J* = 4.9 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 5.27 (s, 2H), 5.21 (bs, 2H); HPLC purity 99.87% {*t_R* = 5.047 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):70/30)}; HRMS (ESI +ve) *m/z* calculated for C₁₉H₁₆N₄OCl (M + H)⁺ 351.1007, found 351.1000.

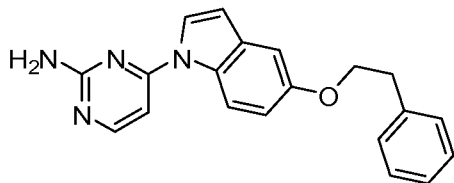


4-(4-(3-chlorobenzoyloxy)-1H-indol-1-yl)pyrimidin-2-amine (21g). This was prepared from **20c** (0.100 g, 0.382 mmol) and 2-amino-4-chloropyrimidine (0.060 g, 0.458 mmol) in a similar manner as described for **12h**. Chromatography on silica gel, performed using the Flash Master 3 purification station (AcOEt/Hexane) , afforded a yellow oil. Water was added and the solid precipitate was filtered, washed with water, dried under vacuum, triturated with a solution of hexane/ethyl acetate (8/2), filtered and dried under vacuum. Pure **21g** was obtained as an off white solid (0.020 g, 0.056 mmol, 15%). ¹H NMR (400 MHz, CDCl₃) δ 8.31 (d, *J* = 5.9 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 3.6 Hz, 1H), 7.51 (s, 1H), 7.34 (m, 3H), 7.22 (m, 1H), 6.90 (d, *J* = 3.6 Hz, 1H), 6.80 (d, *J* = 5.7 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 5.21 (s, 2H), 5.11 (s, 2H); HPLC purity 99.40% {*t_R* = 5.047 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):70/30)}; HRMS (ESI +ve) *m/z* calculated for C₁₉H₁₆N₄OCl (M + H)⁺ 351.1007, found 351.0997.

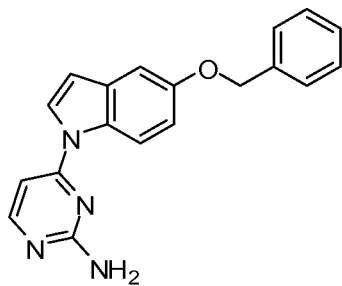


4-(4-phenethoxy-1H-indol-1-yl)pyrimidin-2-amine (21c). This was prepared from **20a** (0.211 g, 0.890 mmol) and 2-amino-4-chloropyrimidine (0.115 g, 0.890 mmol) in a similar manner as described for **12h**. Chromatography on silica gel, performed using the Flash Master 3 purification station, afforded a yellow oil. Water was added and the solid

precipitate was filtered, washed with water, dried under vacuum. Pure **21c** was obtained as an off white solid (0.071 g, 0.212 mmol, 24%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.32 (d, *J* = 8.4 Hz, 1H), 8.23 (d, *J* = 5.7 Hz, 1H), 7.91 (d, *J* = 3.7 Hz, 1H), 7.37 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.23-7.18 (m, 1H), 7.15 (t, *J* = 8.2 Hz, 1H), 6.91 (s, 0H), 6.86 (s, 2H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 3.6 Hz, 1H), 4.29 (t, *J* = 6.7 Hz, 2H), 3.10 (t, *J* = 6.6 Hz, 2H). HPLC purity 99.14% {*t*_R = 5.780 min, Flow 1ml/min, [(MeOH)/(0.1% TFA in H₂O):60/40]}; HRMS (ESI +ve) *m/z* calculated for C₂₀H₁₉N₄O (M + H)⁺ 331.1553, found 331.1551.

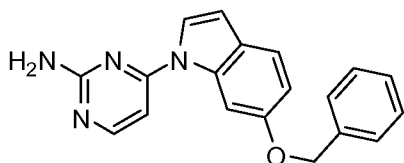


4-(5-phenethoxy-1H-indol-1-yl)pyrimidin-2-amine (21f) This was prepared from **20f** (0.100 g, 0.420 mmol) and 2-amino-4-chloropyrimidine (0.065 g, 0.504 mmol) in a similar manner as described for **12h**. Chromatography on silica gel, performed using the Flash Master 3 purification station, afforded a yellow oil. Water was added and the solid precipitate was filtered, washed with water, dried under vacuum. Pure **21f** was obtained as an off white solid (0.038 g, 0.115 mmol, 27%). ¹H NMR (400 MHz, CDCl₃) δ 8.37 (d, *J* = 9.1 Hz, 1H), 8.27 (d, *J* = 5.8 Hz, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 7.35-7.31 (m, 3H), 7.27-7.23 (m, 2H), 7.08 (d, *J* = 2.5 Hz, 1H), 6.94 (dd, *J* = 2.5, 9.1 Hz, 1H), 6.73 (d, *J* = 5.7 Hz, 1H), 6.62 (d, *J* = 3.6 Hz, 1H), 5.09 (s, 2H), 4.24 (t, *J* = 7.2 Hz, 2H), 3.14 (t, *J* = 7.2 Hz, 2H); HPLC purity 99.05% {*t*_R = 16.960 min, Flow 1ml/min, [(MeOH)/(0.1% TFA in H₂O):60/40]}; HRMS (ESI +ve) *m/z* calculated for C₂₀H₁₉N₄O (M + H)⁺ 331.1553, found 331.1545.

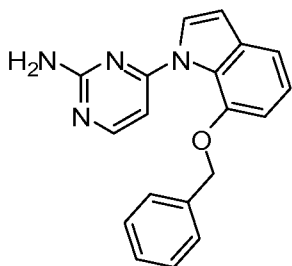


4-(5-(benzyloxy)-1H-indol-1-yl)pyrimidin-2-amine (21b) A mixture of 5-benzyloxyindole (0.207 g, 0.926 mmol), 2-amino-4-chloropyrimidine (0.080 g, 0.617 mmol), and cesium carbonate (0.600 g, 0.59 mmol) in NMP (0.65 mL) was stirred, at 150°C for 30 minutes in a microwave. After cooling to room temperature, water was added and the reaction mixture was extracted with DCM. The organic extract was dried over Na₂SO₄, the solvent removed under reduced pressure. Chromatography on silica gel, performed using the Flash Master 3 purification station (AcOEt/Hexane), afforded a yellow oil. Water was added and the solid precipitate was filtered, washed with water, dried under vacuum. Pure **21b** was obtained as an off white solid (0.058 g, 0.183 mmol, 30%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.71 (d, *J* = 9.1 Hz, 1H), 8.20 (d, *J* = 5.7, 1H), 8.01 (d, *J* = 3.6 Hz, 1H), 7.47 (d, *J* = 7.0, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 6.92-6.88 (m, 2H), 6.84 (bs, 2H), 6.67 (d, *J* = 3.6 Hz, 1H), 5.13 (s, 2H); HPLC purity 97.28 % {*t*_R = 10.960 min, Flow 1ml/min, [(MeOH)/(0.1% TFA

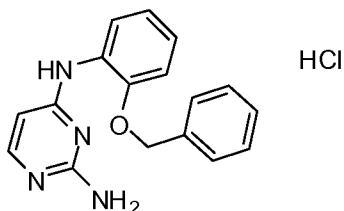
in H₂O):60/40]}; HRMS (ESI +ve) *m/z* calculated for C₁₈H₁₇N₄O (M + H)⁺ 317.1396, found 317.1396.



4-(6-(benzyloxy)-1H-indol-1-yl)pyrimidin-2-amine (21i) This was prepared from 6-(benzyloxy)-1H-indole (0.145 g, 0.643 mmol) and 2-amino-4-chloropyrimidine (0.100 g, 0.772 mmol) in a similar manner as described for **12h**.—Chromatography on silica gel, performed using the Flash Master 3 purification station (AcOEt/Hexane), afforded a yellow oil. Water was added and the solid precipitate was filtered, washed with water, dried under vacuum. Pure **21i** was obtained as a pink solid (0.069 g, 0.219 mmol, 34. ¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, *J* = 5.8 Hz, 1H), 8.06 (d, *J* = 2.2 Hz, 1H), 7.47 (d, *J* = 3.6 Hz, 1H), 7.43-/7.41 (m, 1H), 7.36-7.32 (m, 2H), 7.29-7.26 (d, *J* = 7.3 Hz, 1H), 6.91 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.61 (d, *J* = 5.8 Hz, 1H), 6.57 (d, *J* = 3.5 Hz, 1H), 5.12 (s, 2H), 4.99 (s, 1H).); HPLC purity 99.87 % {*t_R* = 3.733 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):70/30)]}; HRMS (ESI +ve) *m/z* calculated for C₁₉H₁₇N₄O (M + H)⁺ 317.1396, found 317.1387.

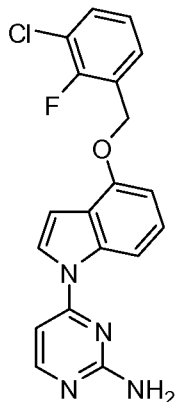


4-(6-(benzyloxy)-1H-indol-1-yl)pyrimidin-2-amine (21j) This was prepared from 7-(benzyloxy)-1H-indole (0.145 g, 0.643 mmol) and 2-amino-4-chloropyrimidine (0.100 g, 0.772 mmol) in a similar manner as described for **12h**.—Chromatography on silica gel, performed using the Flash Master 3 purification station (AcOEt/Hexane), afforded a yellow oil. Water was added and the solid precipitate was filtered, washed with water, dried under vacuum. Pure **21j** was obtained as a pink solid (0.016 g, 0.051 mmol, 7%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.04 (d, *J* = 5.4 Hz, 1H), 7.63 (d, *J* = 3.5 Hz, 1H), 7.35–7.28 (m, 5H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.72 (s, 2H), 6.67 (d, *J* = 3.3 Hz, 1H), 6.58 (d, *J* = 5.4 Hz, 1H), 5.15 (s, 2H). HPLC purity 98.79 % {*t_R* = 3.360 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):70/30)]}; HRMS (ESI +ve) *m/z* calculated for C₁₉H₁₇N₄O (M + H)⁺ 317.1396, found 317.1406.

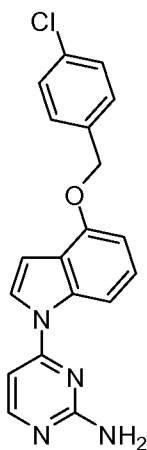


N4-(2-(benzyloxy)phenyl)pyrimidine-2,4-diamine (1ah) A mixture of 2-(benzyloxy)aniline (0.154 g, 0.772 mmol) and 2-amino-4-chloropyrimidine (0.100g, 0.77

2mmol) in anhydrous ethanol (0.700 mL) was stirred, at 150°C for 20 minutes in a microwave. After cooling to room temperature, the solvent was removed under reduced pressure. Ethyl acetate was added and the mixture was stirred under reflux for 2h. The solid precipitated was filtered, dried under vacuum. Pure **1ah** was obtained as an off white solid (0.135 g, 0.462 mmol, 60%). ¹H NMR (400 MHz, CD₃OD) δ 7.79 (s, 1H), 7.66 (s, 1H), 7.4-7.13 (m, 6H), 7.00 (s, 1H), 6.40 (s, 1H), 5.17 (s, 2H); purity 97.96 % {*t_R* = 7.327 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):50/50)}; HRMS (ESI +ve) *m/z* calculated for C₁₇H₁₇N₄O (M + H-Cl)⁺ 293.1396, found 293.1392.

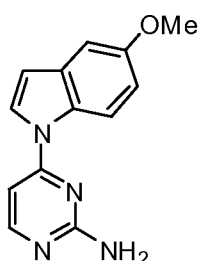


4-(4-(3-chloro-2-fluorobenzoyloxy)-1H-indol-1-yl)pyrimidin-2-amine (21d). This was obtained from 2-amino-4-chloropyrimidine (0.062g, 0.478mmol), and **20e** (0.088g, 0.319 mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture diluted with water and extracted with DCM. The organic extract was dried over Na₂SO₄ and the solvent removed under reduced pressure. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **21d** as an off white solid. The obtained solid was slurried with ether, filtered, and dried *in vacuo*. Pure **21d** was obtained (0.025g, 0.067 mmol, 21%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.39 (d, *J* = 8.5 Hz, 1H), 8.24 (d, *J* = 5.6 Hz, 1H), 7.95 (d, *J* = 3.7 Hz, 1H), 7.62-7.56 (m, 2H), 7.27 (t, *J* = 8.4 Hz, 1H), 7.19 (t, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 5.7 Hz, 1H), 6.87-6.85 (m, 3H), 6.77 (d, *J* = 3.6 Hz, 1H), 5.33 (s, 2H). HPLC: Purity 99.72%, MeOH 70%, (0.1% TFA in H₂O) 30%, 20 min, Flow 1ml/min, *R_t* 7.233 min. HRMS (ESI-ve) calculated for C₁₉H₁₅N₅OCIF (M+H)⁺ 369.0912, found 369.0912

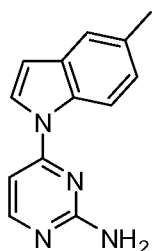


4-(4-(4-chlorobenzoyloxy)-1H-indol-1-yl)pyrimidin-2-amine (21e) This was obtained from 2-amino-4-chloropyrimidine (0.109g, 0.843mmol), and **20d** (0.144g, 0.562 mmol)

in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture diluted with water and extracted with DCM. The organic extract was dried over Na_2SO_4 and the solvent removed under reduced pressure. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **21e** as an off white solid. Water was added to the obtained solid and the solid precipitate was filtered, washed with water, slurried with a solution CH_3CN /Ether, filtered, and dried *in vacuo*. Pure **21e** was obtained (0.035g, 0.099 mmol, 18%) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.36 (d, $J = 8.5$ Hz, 1H), 8.24 (d, $J = 5.7$ Hz, 1H), 7.95 (d, $J = 3.7$ Hz, 1H), 7.53 (d, $J = 8.5$ Hz, 2H), 7.45 (d, $J = 8.5$ Hz, 2H), 7.17 (t, $J = 8.2$ Hz, 1H), 6.92 (d, $J = 5.7$ Hz, 1H), 6.87 (s, 2H), 6.80-6.78 (m, 2H), 5.24 (s, 2H). HPLC: Purity 99.77 %, MeOH 70%, (0.1% TFA in H_2O) 30%, 20 min, Flow 1ml/min, R_t 6.827 min. HRMS (ESI-ve) calculated for $\text{C}_{19}\text{H}_{16}\text{N}_5\text{OCl}$ ($\text{M}+\text{H}$) $^+$ 351.1007, found 351.1009

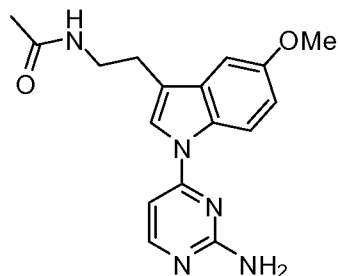


4-(5-methoxy-1H-indol-1-yl)pyrimidin-2-amine (15f). This was obtained from 2-amino-4-chloropyrimidine (0.103g, 0.795mmol), and 5-methoxyindole (0.175g, 1.19 mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture diluted with water and extracted with DCM. The organic extract was dried over Na_2SO_4 and the solvent removed under reduced pressure. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **15f** as an off white solid. Water was added to the obtained solid and the solid precipitate was filtered, washed with water and dried *in vacuo*. Pure **15f** was obtained (0.084 g, 0.348 mmol, 44%) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.70 (d, $J = 9.1$ Hz, 1H), 8.20 (d, $J = 5.7$ Hz, 1H), 8.01 (d, $J = 3.6$ Hz, 1H), 7.11 (d, $J = 2.5$ Hz, 1H), 6.89 (d, $J = 5.7$ Hz, 1H), 6.85-6.82 (m, 2H), 6.67 (d, $J = 3.5$ Hz, 1H), 3.77 (s, 3H); HPLC: Purity 98.73 %, CH_3CN 30%, (0.1% TFA in H_2O) 70%, 20 min, Flow 1ml/min: R_t 4.760 min; Purity 99.68 %, MeOH 40%, (0.1% TFA in H_2O) 60%, 20 min, Flow 1ml/min, R_t 14.147 min, HRMS (ESI-ve) calculated for $\text{C}_{13}\text{H}_{13}\text{ON}_4$ ($\text{M}+\text{H}$) $^+$ 241.1083, found 241.1086.



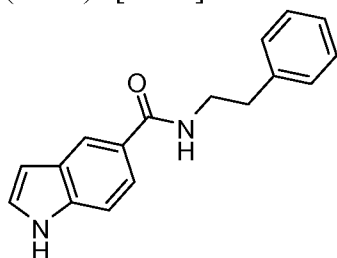
4-(5-methyl-1H-indol-1-yl)pyrimidin-2-amine (15g). This was obtained from 2-amino-4-chloropyrimidine (0.096g, 0.741mmol), and 5-methylindole (0.194g, 1.482 mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture diluted with water and extracted with DCM. The organic extract was dried over Na_2SO_4 and the solvent removed under reduced pressure. Chromatography on silica gel

using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **15g** as an off white solid. Water was added to the obtained solid and the solid precipitate was filtered, washed with water and dried *in vacuo*. Pure **15g** was obtained (0.056 g, 0.249 mmol, 37%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.65 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 5.7 Hz, 1H), 7.99 (d, *J* = 3.7 Hz, 1H), 7.37 (s, 1H), 7.07 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.90 (d, *J* = 5.7 Hz, 1H), 6.84 (s, 2H), 6.66 (d, *J* = 3.6 Hz, 1H), 2.38 (s, 3H). HPLC: Purity 99.52%, CH₃CN 30%, (0.1% TFA in H₂O) 70%, 20 min, Flow 1ml/min, R_t 7.873 min. HRMS (ESI-ve) calculated for C₁₃H₁₃N₄ (M+H)⁺ 225.1134, found 225.1134



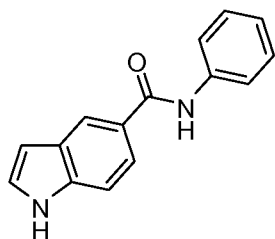
N-(2-(1-(2-aminopyrimidin-4-yl)-5-methoxy-1H-indol-3-yl)ethyl)acetamide (15h).

This was obtained from 2-amino-4-chloropyrimidine (0.043g, 0.333mmol), and melatonin (0.155g, 0.667 mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture diluted with water and extracted with DCM. The organic extract was dried over Na₂SO₄ and the solvent removed under reduced pressure. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/MeOH) afforded **15h** as an off white solid. Water was added to the obtained solid and the solid precipitate was filtered, washed with water and dried *in vacuo*. Pure **15h** was obtained (0.028 g, 0.086 mmol, 13%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.70 (d, *J* = 9.0 Hz, 1H), 8.17 (d, *J* = 5.7 Hz, 1H), 8.02 (t, *J* = 4.6 Hz, 1H), 7.83 (s, 1H), 7.10 (d, *J* = 2.5 Hz, 1H), 6.85-6.83 (m, 2H), 6.78 (s, 2H), 3.79 (s, 3H), 2.79 (t, *J* = 7.1 Hz, 2H), 1.79 (s, 3H). HPLC: Purity 91.11%, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min, R_t 4.153 min. HRMS (ESI-ve) calculated for C₁₇H₂₀N₅O₂ (M+H)⁺ [M+H]⁺ 326.1611, found 326.1620

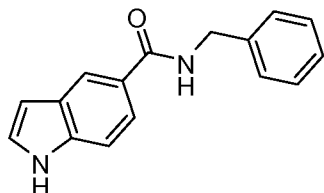


N-phenethyl-1H-indole-5-carboxamide (23a) A mixture of indole-5-carboxylic acid (0.173 g, 1.073 mmol) and 2-phenylethanamine (0.143g, 1.180mmol), EDC-HCl (0.226g, 1.178 mmol), cat. 4-dimethylaminopyridine in DCM (1.1 mL) was heated in the Biotage Microwave for 15min at 60°C. The solution was washed with aq. 1N HCl, extracted with DCM. The organic phase was separated, washed with aq. NaHCO₃ (sat. solution), separated, dried over Na₂SO₄, filtered, and the solvent removed under reduced pressure to provide **23a** (0.160g, 0.606mmol, 56%) as an off white solid. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H), 8.02 (d, *J* = 1.6 Hz, 1H), 7.58 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H),

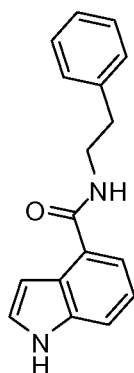
7.36–7.30 (m, 2H), 7.28–7.24 (m, 4H), 6.62 – 6.58 (m, 1H), 6.21 (s, 1H), 3.76 (q, $J = 6.8$ Hz, 2H), 2.96 (t, $J = 6.9$ Hz, 2H).



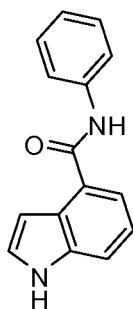
N-phenyl-1H-indole-5-carboxamide (23b) This was obtained as an off white solid (0.145g, 0.614mmol, 55%) from indole-5-carboxylic acid (0.182 g, 1.129 mmol) and aniline (0.115g, 1.242mmol) in a similar manner as described for **23a**. The crude material was used as obtained in the next step. ^1H NMR (400 MHz, CDCl_3) δ 8.49 (s, 1H), 8.21 (s, 1H), 7.91 (s, 1H), 7.75 (dd, $J = 8.5, 1.6$ Hz, 1H), 7.68 (d, $J = 8.0$ Hz, 2H), 7.47 (d, $J = 8.6$ Hz, 1H), 7.38 (t, $J = 7.9$ Hz, 2H), 7.32–7.30 (m, 1H), 7.15 (t, $J = 7.4$ Hz, 1H), 6.67–6.66 (m, 1H).



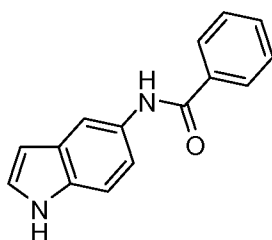
N-benzyl-1H-indole-5-carboxamide (23c) This was obtained as an off white solid (0.179g, 0.716mmol, 73%) from indole-5-carboxylic acid (0.158 g, 0.980 mmol) and benzylamine (0.115g, 1.078mmol) in a similar manner as described for **23a**. The crude material was used as obtained in the next step. ^1H NMR (400 MHz, CDCl_3) δ 9.32 (s, 1H), 8.13 (s, 1H), 7.63 (dd, $J = 8.5, 1.6$ Hz, 1H), 7.36–7.25 (m, 6H), 7.21 – 7.14 (t, $J = 2.7$ Hz, 1H), 6.72 (t, $J = 5.6$ Hz, 1H), 6.54–6.53 (m, 1H), 4.66 (d, $J = 5.7$ Hz, 2H).



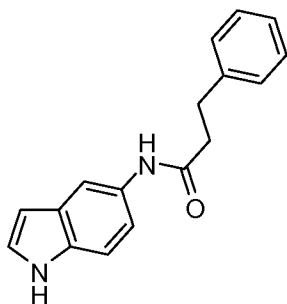
N-phenethyl-1H-indole-4-carboxamide (23d) This was obtained as an off white solid (0.206g, 0.780mmol, 67%) from indole-4-carboxylic acid (0.189 g, 1.172 mmol) and 2-phenylethanamine (0.56g, 1.290mmol) in a similar manner as described for **23a**. The crude material was used as obtained in the next step. ^1H NMR (400 MHz, CDCl_3) δ 9.22 (s, 1H), 7.45 (s, $J = 6.4$ Hz, 2H), 7.34–7.31 (m, 2H), 7.27–7.25 (m, 3H), 7.21 (t, $J = 2.7$ Hz, 1H), 7.15 (t, $J = 7.8$ Hz, 1H), 6.69 (s, 1H), 6.36–6.34 (m, 1H), 3.81 (q, $J = 6.8$ Hz, 2H), 2.99 (t, $J = 6.9$ Hz, 2H).



N-phenyl-1H-indole-4-carboxamide (23e) This was obtained as an off white solid (0.265g, 1.12mmol, 77%) from indole-4-carboxylic acid (0.235 g, 1.450 mmol) and aniline (0.149g, 1.603mmol) in a similar manner as described for **23a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 9.16 (s, 1H), 8.10 (s, 1H), 7.70 (d, *J* = 9.5 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.27–7.26 (m, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.18– 7.13 (m, 1H), 6.95–6.94 (m, 1H).

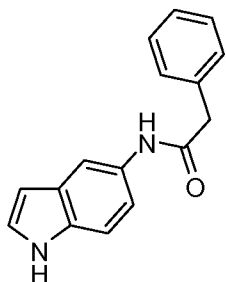


N-(1H-indol-5-yl)benzamide (26a) This was obtained from 5-aminoindole (0.235 g, 1.450 mmol) and benzoic acid (0.149g, 1.603mmol) in a similar manner as described for **21a**. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/hexane) afforded pure **26a** (0.137g, 0.580 mmol, 40%). ¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 7.98 (s, 1H), 7.91 (d, *J* = 7.0 Hz, 2H), 7.86 (s, 1H), 7.57–7.48 (m, 3H), 7.39–7.37 (m, 2H), 7.24 (t, *J* = 3.0 Hz, 1H), 6.55 (t, *J* = 2.5 Hz, 1H)

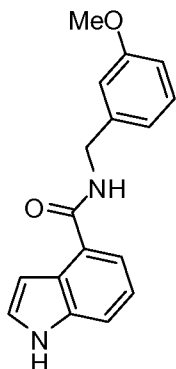


N-(1H-indol-5-yl)-3-phenylpropanamide (26b) This was obtained as an off white solid (0.343g, 0.972mmol, 74%) from 5-aminoindole (0.174 g, 1.316 mmol) and 3-phenylpropanoic acid (0.237g, 1.579 mmol) in a similar manner as described for **21a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 8.47

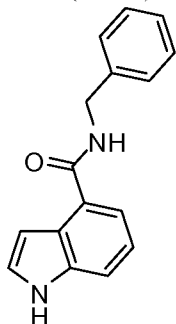
(s, 1H), 7.64 (d, $J = 1.7$ Hz, 1H), 7.30 (s, 1H), 7.23-7.11 (m, 6H), 7.07 – 7.04 (d, $J = 2.8$ Hz, 1H), 7.03 (dd, $J = 8.7, 1.9$ Hz, 1H), 6.38 (s, 1H), 2.98 (t, $J = 7.7$ Hz, 2H), 2.57 (t, $J = 7.7$ Hz, 2H).



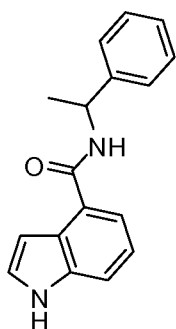
N-(1H-indol-5-yl)-2-phenylacetamide (26c). This was obtained as an off white solid (0.629g, 2.50mmol, 92%) from 5-aminoindole (0.357g, 2.70 mmol) and 2-phenylacetic acid (0.478 g, 3.51mmol) in a similar manner as described for **21a**. The crude material was used as obtained in the next step. ^1H NMR (400 MHz, CDCl_3) δ 8.22 (s, 1H), 7.74 (d, $J = 1.8$ Hz, 1H), 7.46-7.31 (m, 4H), 7.28-7.26 (m, 2H), 7.18 (d, $J = 2.6$ Hz, 1H), 7.12 (d, $J = 2.0$ Hz, 1H), 7.10 (d, $J = 2.0$ Hz, 1H), 6.48-6.46 (m, 1H), 3.77 (s, 2H).



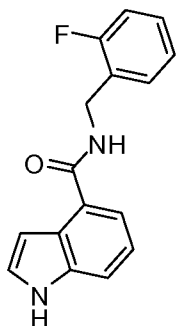
N-(3-methoxybenzyl)-1H-indole-4-carboxamide (29a) A mixture of indole-5-carboxylic acid (0.258g, 1.60 mmol) and 3-methoxybenzylamine (0.263 g, 1.92 mmol), EDC-HCl (0.432g g, 2.26 mmol), cat. 4-dimethylaminopyridine (0.007 g) in CH_3CN (1.1 mL) was heated in the Biotage Microwave for 30 min at 80°C . The solution was washed with aq. 1N HCl, extracted with DCM. The organic phase was separated, washed with aq. NaHCO_3 (sat. solution), separated, dried over Na_2SO_4 , filtered, and the solvent removed under reduced pressure to provide **29a** (0.311g, 1.11 mmol, 69%) as an off white solid. The crude material was used as obtained in the next step. ^1H NMR (400 MHz, CDCl_3) δ 8.48 (s, 1H), 7.53-7.50 (m, 2H), 7.34 – 7.27 (m, 2H), 7.24 – 7.19 (d, $J = 7.8$ Hz, 1H), 6.99 (d, $J = 7.7$ Hz, 1H), 6.95-6.93 (m, 2H), 6.84 (dd, $J = 8.1, 2.7$ Hz, 1H), 6.51 (s, 1H), 4.71 (d, $J = 5.8$ Hz, 2H), 3.80 (s, 3H).



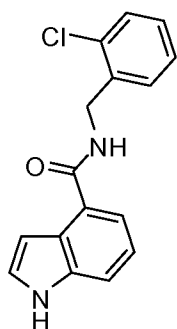
N-benzyl-1H-indole-4-carboxamide (23f) This was obtained as an off white solid (0.229g, 0.916mmol, 66%) from indole-4-carboxylic acid (0.225 g, 1.396 mmol) and benzylamine (0.165g, 1.535mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 8.86 (s, 1H), 7.51 (d, *J* = 4.3 Hz, 1H), 7.49 (d, *J* = 5.1 Hz, 1H), 7.40-7.33 (m, 4H), 7.31-7.25 (m, 2H), 7.17 (t, *J* = 8 Hz, 1H), 6.89 (s, 1H), 6.60 (s, 1H), 4.73 (d, *J* = 5.6 Hz, 2H).



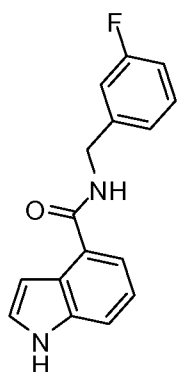
N-(1-phenylethyl)-1H-indole-4-carboxamide (29b) This was obtained as an off white solid (0.218g, 0.825mmol, 52%) from indole-4-carboxylic acid (0.256g, 1.588mmol) and 1-phenylethanamine (0.230g, 1.98mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 8.67 (s, 1H), 7.45-7.35 (m, 4H), 7.27 (t, *J* = 7.5 Hz, 2H), 7.20-7.14 (m, 2H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.81 (s, 1H), 6.42 (d, *J* = 7.9 Hz, 1H), 5.37 (quin, *J* = 7.0 Hz, 1H), 1.57 (d, *J* = 6.8 Hz, 3H).



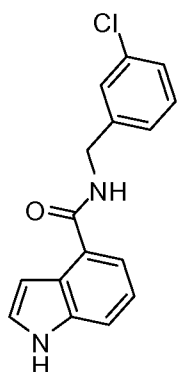
N-(2-fluorobenzyl)-1H-indole-4-carboxamide (29c) This was obtained as an off white solid (0.354g, 1.32mmol, 66%) from indole-4-carboxylic acid (0.322g, 1.99mmol) and 2-fluorobenzylamine (0.300g, 2.39mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 8.52 (s, 1H), 7.53-7.39 (m, 3H), 7.32 - 7.21 (m, 3H), 7.14-7.05 (m, 2H), 6.93 (s, 1H), 6.62 (s, 1H), 4.78 (d, *J* = 5.9 Hz, 2H).



5 **N-(2-chlorobenzyl)-1H-indole-4-carboxamide (29d)** This was obtained as an off white solid (0.373g, 1.31mmol, 71%) from indole-4-carboxylic acid (0.296g, 1.83mmol) and 2-chlorobenzylamine (0.312g, 2.20mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 8.53 (s, 1H), 7.58–7.49 (m, 3H), 7.42–7.38 (m, 1H), 7.32 (t, *J* = 3.0 Hz, 1H), 7.26–7.19 (m, 3H), 6.95 (m, 1H), 6.72 (s, 1H), 4.81 (d, *J* = 6.0 Hz, 2H).

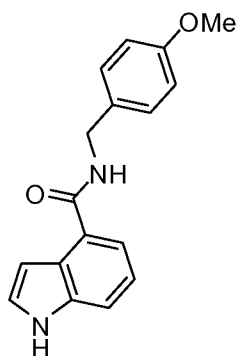


10 **N-(3-fluorobenzyl)-1H-indole-4-carboxamide (29e)** This was obtained as an off white solid (0.221g, 0.824mmol, 52%) from indole-4-carboxylic acid (0.257g, 1.59mmol) and 3-fluorobenzylamine (0.238g, 1.90mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 8.53 (s, 1H), 7.54–7.51 (m, 2H), 7.29–7.32 (m, 2H), 7.25–7.17 (m, 2H), 7.12 (d, *J* = 7.9 Hz, 1H),
15), 7.05–6.93 (m, 2H), 6.59 (s, 1H), 4.72 (d, *J* = 6.0 Hz, 2H).

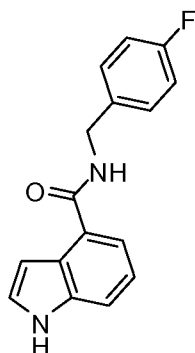


20 **N-(3-chlorobenzyl)-1H-indole-4-carboxamide (29f)** This was obtained as an off white solid (0.244g, 0.859mmol, 55%) from indole-4-carboxylic acid (0.252g, 1.56mmol) and 3-chlorobenzylamine (0.264g, 1.87mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 8.58

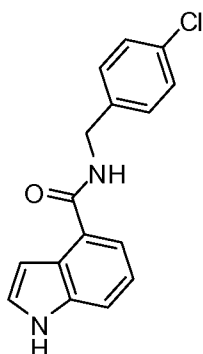
(s, 1H), 7.56–7.50 (m, 2H), 7.39 (d, $J = 1.9$ Hz, 1H), 7.32 (t, $J = 2.9$ Hz, 1H), 7.30 – 7.17 (m, 4H), 6.93 (t, $J = 2.6$ Hz, 1H), 6.58 (s, 1H), 4.71 (d, $J = 6.0$ Hz, 2H).



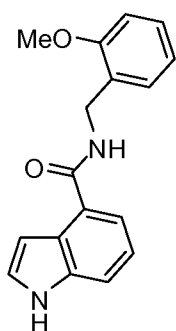
- 5 **N-(4-methoxybenzyl)-1H-indole-4-carboxamide (29g)** This was obtained as an off white solid (0.304g, 1.085mmol, 66%) from indole-4-carboxylic acid (0.266g, 1.65mmol) and 4-methoxybenzylamine (0.270g, 1.96mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ^1H NMR (400 MHz, CDCl_3) δ 9.06 (s, 1H), 7.50 (d, $J = 7.3$ Hz, 1H), 7.47 (d, $J = 8.2$ Hz, 1H), 7.31 (d, $J = 8.7$ Hz, 2H),
10 7.26 – 7.21 (m, 1H), 7.16 (t, $J = 7.8$ Hz, 1H), 6.92 – 6.85 (m, 3H), 6.54 (t, $J = 5.8$ Hz, 1H), 4.65 (d, $J = 5.6$ Hz, 2H), 3.79 (s, 3H).



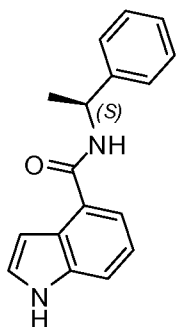
- 15 **N-(4-fluorobenzyl)-1H-indole-4-carboxamide (29h)** This was obtained as an off white solid (0.240g, 0.895mmol, 56%) from indole-4-carboxylic acid (0.257g, 1.59mmol) and 4-fluorobenzylamine (0.234g, 1.86mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ^1H NMR (400 MHz, CDCl_3) δ 8.62 (s, 1H), 7.52 (d, $J = 7.5$ Hz, 2H), 7.38-7.35 (m, 2H), 7.31 (t, $J = 2.9$ Hz, 1H), 7.21 (t, $J = 7.8$ Hz, 1H), 7.07 – 7.00 (m, 2H), 6.91-6.90 (m, 1H), 6.54 (s, 1H), 4.69 (d, $J = 5.8$ Hz, 2H).
20



N-(4-chlorobenzyl)-1H-indole-4-carboxamide (29i) This was obtained as an off white solid (0.289g, 1.017mmol, 56%) from indole-4-carboxylic acid (0.290g, 1.79mmol) and 4-chlorobenzylamine (0.287g, 2.05mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H), 7.56-7.52. (m, 2H), 7.36-7.32 (m, 5H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.92 (s, 1H), 6.54 (s, 1H), 4.68 (d, *J* = 5.6 Hz, 2H).

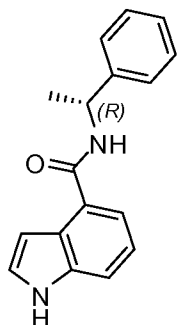


N-(2-methoxybenzyl)-1H-indole-4-carboxamide (20j) This was obtained as an off white solid (0.360g, 1.44mmol, 91%) from indole-4-carboxylic acid (0.251g, 1.55mmol) and 2-methoxybenzylamine (0.262g, 1.96mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 8.90 (s, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.22-7.18 (m, 2H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.92 – 6.66 (m, 4H), 4.65 (d, *J* = 5.8 Hz, 2H), 3.79 (s, 3H).

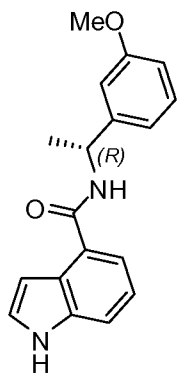


(S)-N-(1-phenylethyl)-1H-indole-4-carboxamide (29k) This was obtained as an off white solid (0.269g, 1.01mmol, 72%) from indole-4-carboxylic acid (0.230g, 1.42mmol) and (S)-1-phenylethylamine (0.190g, 1.57mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz,

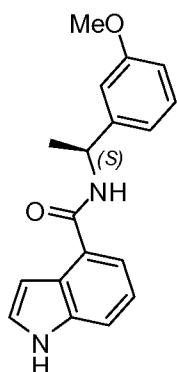
CDCl₃) δ 8.87 (s, 1H), 7.52 (d, J = 7.3 Hz, 1H), 7.47-7.42 (m, 3H), 7.36 (t, J = 7.5 Hz, 2H), 7.29-7.21 (m, 2H), 7.18 (t, J = 7.8 Hz, 1H), 6.88 (s, 1H), 6.53 (d, J = 7.4 Hz, 1H), 5.44 (quin, J = 7.0 Hz, 1H), 1.65 (d, J = 6.9 Hz, 3H).



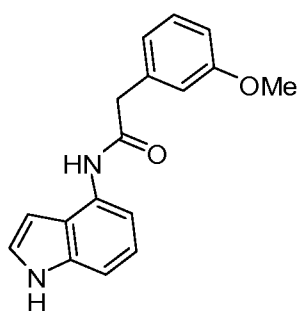
(R)-N-(1-phenylethyl)-1H-indole-4-carboxamide (29l) This was obtained as an off white solid (0.284g, 1.07mmol, 80%) from indole-4-carboxylic acid (0.217g, 1.34mmol) and (R)-1-phenylethanamine (0.190g, 1.57mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 9.03 (s, 1H), 7.51 (d, J = 7.4 Hz, 1H), 7.47-7.42 (m, 3H), 7.36 (t, J = 7.5 Hz, 2H), 7.29-7.21 (m, 2H), 7.18 (t, J = 7.8 Hz, 1H), 6.86 (s, 1H), 6.55 (d, J = 7.9 Hz, 1H), 5.45 (quin, J = 7.1 Hz, 1H), 1.65 (d, J = 6.9 Hz, 3H).



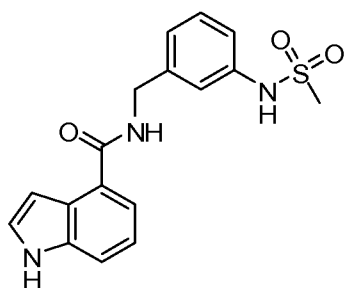
(R)-N-(1-(3-methoxyphenyl)ethyl)-1H-indole-4-carboxamide (29m) This was obtained as an off white solid (0.294g, 1.05 mmol, 28%) from indole-4-carboxylic acid (0.608 g, 3.77 mmol) and (R)-1-(3-methoxyphenyl)ethanamine (0.613 g, 4.06 mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 8.66 (s, 1H), 7.50 (t, J = 8.1 Hz, 2H), 7.31 – 7.24 (m, 2H), 7.19 (t, J = 7.7 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.98 (t, J = 2.1 Hz, 1H), 6.90-6.88 (m, 1H), 6.82 (dd, J = 8.2, 2.6 Hz, 1H), 6.47 (d, J = 7.5 Hz, 1H), 5.41 (quin, J = 7.0 Hz, 1H), 3.80 (s, 3H), 1.64 (d, J = 6.8 Hz, 3H).



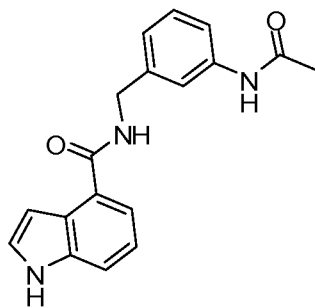
(S)-N-(1-(3-methoxyphenyl)ethyl)-1H-indole-4-carboxamide (29n) This was obtained as an off white solid (0.538g, 1.83 mmol, 66%) from indole-4-carboxylic acid (0.451 g, 2.79 mmol) and (S)-1-(3-methoxyphenyl)ethanamine (0.511 g, 3.38 mmol) in a similar manner as described for **29a**. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CDCl₃) δ 8.61 (s, 1H), 7.50-7.48 (m, 2H), 7.33 – 7.28 (m, 2H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.97 (t, *J* = 2.08 Hz, 1H), 6.90-6.89 (m, 1H), 6.82 (dd, *J* = 7.9, 2.7 Hz, 1H), 6.47 (d, *J* = 7.4 Hz, 1H), 5.41 (quin, *J* = 7.0 Hz, 1H), 3.80 (s, 3H), 1.64 (d, *J* = 6.8 Hz, 3H).



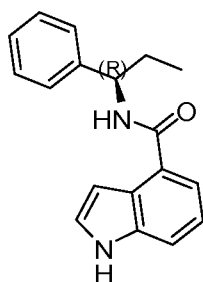
N-(1H-indol-4-yl)-2-(3-methoxyphenyl)acetamide (26d) A mixture of 4-Aminoindole (0.150 g, 1.135 mmol), 3-methoxyphenyl acetic acid (260 g, 1.564 mmol), EDC hydrochloride (0.440 g, 2.26 mmol), 4-dimethylaminopyridine (0.050 g, 0.410 mmol) in acetonitrile (4mL) was heated in the Biotage Microwave for 30min at 80°C. The solution was then washed with 10mL of 1N HCl, extracted with ethyl acetate, and then washed with 10mL of a saturated NaHCO₃ solution. The organic phase was dried over Na₂SO₄ and filtered. The solution was concentrated under reduced pressure to afford **26d** as a dark brown solid (0.312 g, 1.114 mmol, 99%). The crude material was used in the next step without purification. ¹H NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 7.79 (t, *J* = 4.4 Hz, 1H), 7.47 – 7.29 (m, 1H), 7.17 (d, *J* = 4.5 Hz, 2H), 7.11 (t, *J* = 2.9 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.94-6.92 (m, 1H), 5.99 (t, *J* = 2.2 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 2H).



N-(3-(methylsulfonylamino)benzyl)-1H-indole-4-carboxamide (29o) This was obtained as a green solid (0.056 g, 0.148 mmol, 59%) from N-(3-(aminomethyl)phenyl)methanesulfonamide (0.059 g, 0.249 mmol) and indole-4-carboxylic acid (0.036 g, 0.224 mmol) in a similar manner as described for preparation of **29a**. Reaction time: 1hr. The crude material; was used in the net step without further purification. ¹H NMR (400 MHz, CD₃OD) δ 7.55 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.37 – 7.28 (m, 3H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 2H), 6.84 (d, *J* = 3.1 Hz, 1H), 4.62 (s, 2H), 2.94 (s, 3H).

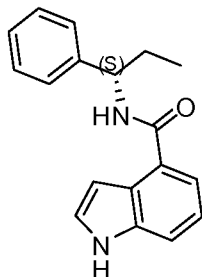


N-(3-(acetamidobenzyl)-1H-indole-4-carboxamide (29p). This was obtained as a brown oil (0.050 g, 0.163 mmol, 33%). from N-(3-(aminomethyl)phenyl)acetamide (0.110 g, 0.550 mmol) and indole-4-carboxylic acid (0.080 g, 0.495 mmol) in a similar manner as described for preparation of **29a**. Reaction time: 1hr. The crude material was used in the next step without purification. ¹H NMR (400 MHz, CD₃OD) δ 7.58-7.53 (m, 2H), 7.48-7.44 (m, 2H), 7.35 (d, *J* = 3.2 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.20 – 7.13 (m, 2H), 6.85 (dd, *J* = 3.1, 0.8 Hz, 1H), 4.62 (s, 2H), 2.10 (s, 3H).



(R)-N-(1-phenylpropyl)-1H-indole-4-carboxamide (29q) This was obtained as an off-white solid (0.072 g, 0.259 mmol, 38%) from (R)-1-phenylpropan-1-amine (0.110 g, 0.818 mmol, 0.080 mL) and indole-4-carboxylic acid (0.110 g, 0.682 mmol) in a similar manner as described for preparation of **29a**. Reaction time: 1hr. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CD₃OD) δ 7.53 (d, *J* = 8.2 Hz, 1H), 7.44-7.89 (m, 3H), 7.37 – 7.31 (m, 3H), 7.26-7.27 (m, 1H), 7.16 (t, *J* = 7.8 Hz, 1H),

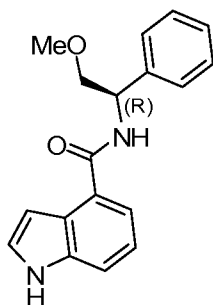
6.75 – 6.72 (m, 1H), 5.04 (t, $J = 7.6$ Hz, 1H), 1.94 (d, $J = 15.9$ Hz, 2H), 1.02 (t, $J = 7.4$ Hz, 3H).



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(S)-N-(1-phenylpropyl)-1H-indole-4-carboxamide (29r) This was obtained as an off-white solid (0.370 g, 1.329 mmol, 39%) from (S)-1-phenylpropan-1-amine (0.605 g, 4.478 mmol) and indole-4-carboxylic acid (0.603 g, 3.731 mmol) in a similar manner as described for preparation of **29a**. The crude material was used as obtained in the next step. ^1H NMR (400 MHz, CD_3OD) δ 7.53 (d, $J = 8.2$ Hz, 1H), 7.48-7.40 (m, 3H), 7.36 – 7.31 (m, 3H), 7.26 – 7.21 (m, 1H), 7.16 (t, $J = 7.8$ Hz, 1H), 6.73 (dd, $J = 3.1, 0.9$ Hz, 1H), 5.07-5.01 (m, 1H), 2.04 – 1.83 (m, 2H), 1.01 (t, $J = 7.4$ Hz, 3H).

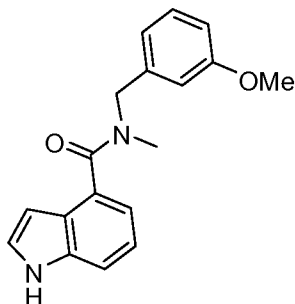
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(R)-N-(2-methoxy-1-phenylethyl)-1H-indole-4-carboxamide (29s) This was obtained a brown oil (0.035 g, 0.119 mmol, 30%) from (R)-2-methoxy-1-phenylethanamine (0.060 g, 0.397 mmol) and indole-4-carboxylic acid (0.64 g, 0.397 mmol) in a similar manner as described for preparation of **29a**. Reaction time: 1hr. The crude material was used as obtained in the next step. ^1H NMR (400 MHz, CD_3OD) δ 7.55 (d, $J = 8.2$ Hz, 1H), 7.45 (d, $J = 7.4$ Hz, 3H), 7.38 – 7.30 (m, 3H), 7.27 (t, $J = 7.8$ Hz, 1H), 7.18 (t, $J = 7.8$ Hz, 1H), 6.80 (d, $J = 3.1$ Hz, 1H), 5.46–5.28 (m, 1H), 3.90 – 3.65 (m, 2H), 3.42 (s, 3H).

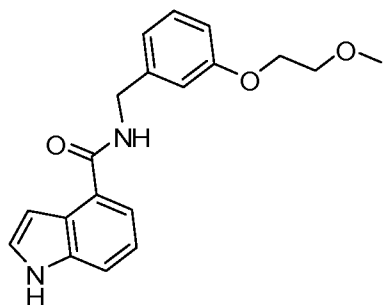
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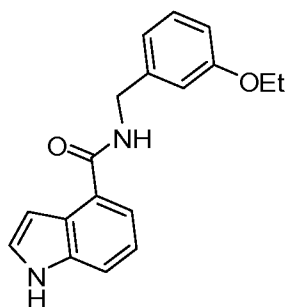
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N-(3-methoxybenzyl)-N-methyl-1H-indole-4-carboxamide (29t) This was obtained as a brown oil (0.062 g, 0.211 mmol, 34%) from 1-(3-methoxyphenyl)-N-methylmethanamine (0.114 g, 0.745 mmol, 0.11mL) and indole-4-carboxylic acid (0.100

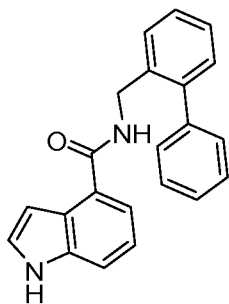
g, 0.621 mmol) in a similar manner as described for preparation of **29a**. Reaction time: 1hr. The crude material was used as obtained in the next step. MS (M+H)⁺ 295.14.



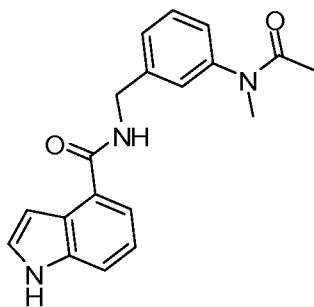
N-(3-(2-methoxyethoxy)benzyl)-1H-indole-4-carboxamide (29u) This was obtained as a green oil (.128 g, 0.395 mmol, 34%) from (3-(2-methoxyethoxy)phenyl)methanamine (0.256 g, 1.414 mmol, 0.15 mL) and indole-4-carboxylic acid (0.190 g, 1.178 mmol) in a similar manner as described for preparation of **29a**. Reaction time: 1hr. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, CD₃OD) δ 7.55 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.43 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.35 (d, *J* = 3.2 Hz, 1H), 7.25 (t, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 7.00-6.98 (m, 2H), 6.85-6.82 (m, 2H), 4.61 (s, 2H), 4.12 – 4.07 (m, 2H), 3.75 – 3.65 (m, 2H), 3.40 (s, 3H).



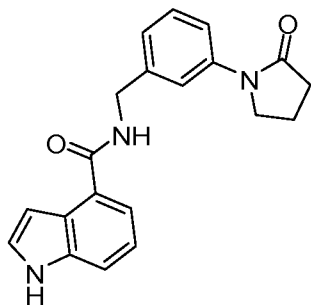
N-(3-ethoxybenzyl)-1H-indole-4-carboxamide (29v) This was obtained as a red oil (0.304 g, 1.033 mmol, 83%) from (3-ethoxyphenyl)methanamine (0.225 g, 1.490 mmol, 0.22 mL) and indole-4-carboxylic acid (0.200 g, 1.241 mmol) in a similar manner as described for preparation of **29a**. Reaction time: 1hr. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.26 (s, 1H), 8.72 (t, *J* = 5.8 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 2.9 Hz, 1H), 7.21 (t, *J* = 8.1 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.9 – 6.82 (m, 3H), 6.78-6.76 (m, 1H), 4.46 (d, *J* = 6.0 Hz, 2H), 3.98 (q, *J* = 6.9 Hz, 2H), 1.29 (t, *J* = 6.9 Hz, 3H).



N-(biphenyl-2-ylmethyl)-1H-indole-4-carboxamide (29w) This was obtained as a white solid (0.207 g, 0.634 mmol, 51%). from biphenyl-2-ylmethanamine (0.274 g, 1.495 mmol, 0.26 mL) and indole-4-carboxylic acid (0.200 g, 1.241 mmol) in a similar manner as described for preparation of **29a**. Reaction time: 1hr. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.25 (s, 1H), 8.64 (t, *J* = 5.8 Hz, 1H), 7.55–7.29 (m, 11H), 7.23 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.81 (s, 1H), 4.45 (d, *J* = 5.8 Hz, 2H).



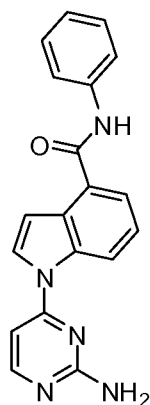
N-(3-(N-methylacetamido)benzyl)-1H-indole-4-carboxamide (29x) This was obtained as a brown oli (0.075 g, 0.210 mmol, 17%) from N-(3-(aminomethyl)phenyl)-N-methylacetamide (0.320 g, 1.495 mmol) and indole-4-carboxylic acid (0.200 g, 1.241 mmol) in a similar manner as described for preparation of **29a**. Reaction time: 1hr. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.27 (s, 1H), 8.78 (t, *J* = 6.0 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 6.8 Hz, 1H), 7.42 (t, *J* = 2.7 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.30-2.27 (m, 2H), 7.19 (d, *J* = 6.9 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.82 (s, 1H), 4.52 (d, *J* = 6.0 Hz, 2H), 3.13 (s, 3H), 1.76 (s, 3H).



N-(3-(2-oxopyrrolidin-1-yl)benzyl)-1H-indole-4-carboxamide (29y) This was obtained as a brown oil (0.086 g, 0.258 mmol, 35%) from 1-(3-(aminomethyl)phenyl)pyrrolidin-2-one (0.170 g, 0.894 mmol) and indole-4-carboxylic acid (0.120 g, 0.745 mmol) in a similar manner as described for preparation of **29a**. Reaction time: 1hr. The crude material was used as obtained in the next step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.27 (s,

1H), 8.78 (t, $J = 5.9$ Hz, 1H), 7.66 (s, 1H), 7.53 (t, $J = 8.5$ Hz, 2H), 7.47 (d, $J = 7.3$ Hz, 1H), 7.43 – 7.39 (m, 1H), 7.32 (t, $J = 7.8$ Hz, 1H), 7.15–7.11 (m, 2H), 6.85 (s, 1H), 4.50 (d, $J = 5.8$ Hz, 2H), 3.81 (t, $J = 7.0$ Hz, 2H), 2.13–1.96 (m, 2H).

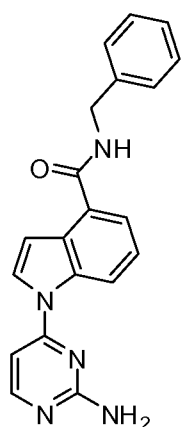
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1-(2-aminopyrimidin-4-yl)-N-phenyl-1H-indole-4-carboxamide (24a) This was obtained from 2-amino-4-chloropyrimidine (0.065g, 0.501mmol), and **23e** (0.155g, 0.667 mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture diluted with water. The solid precipitated was filtered. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/hexane) afforded pure **24a** (0.032g, 0.097mmol, 19%) as an off white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 10.33 (s, 1H), 9.03 (d, $J = 8.5$ Hz, 1H), 8.27 (d, $J = 5.6$ Hz, 1H), 8.18 (d, $J = 3.7$ Hz, 1H), 7.84 – 7.72 (m, 2H), 7.68 (d, $J = 7.1$ Hz, 1H), 7.41–7.32 (m, 3H), 7.10–7.05 (m, 2H), 6.97 (d, $J = 5.8$ Hz, 1H), 6.95 (s, 2H). HPLC: Purity 97.51%, MeOH 60%, (0.1% TFA in H_2O) 40%, 20 min, Flow 1ml/min, R_t 3.600 min. HRMS (ESI-ve) calculated for $\text{C}_{19}\text{H}_{16}\text{N}_5\text{O}$ ($\text{M}+\text{H}$) $^+$ 330.1349, found 330.1359

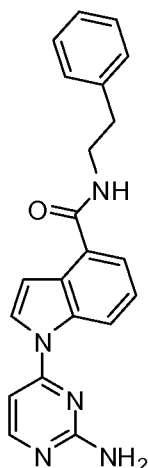
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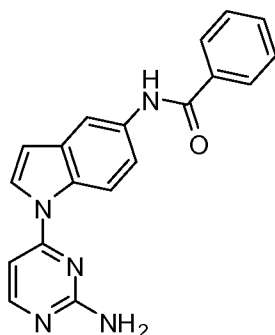
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1-(2-aminopyrimidin-4-yl)-N-benzyl-1H-indole-4-carboxamide (24b). This was obtained from 2-amino-4-chloropyrimidine (0.072g, 0.555mmol), and **23f** (0.203g, 0.812 mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with CH_3CN , filtered and dried under vacuum. Pure **24b** (0.081g, 0.235mmol, 42%) was obtained as an off white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.00–8.93 (m, 2H), 8.26

(d, $J = 5.6$ Hz, 1H), 8.12 (d, $J = 3.6$ Hz, 1H), 7.62 (d, $J = 7.5$ Hz, 1H), 7.36-7.30 (m, 5H), 7.25-7.21 (m, 1H), 7.15 (d, $J = 3.6$ Hz, 1H), 6.94 (d, $J = 5.8$ Hz, 1H), 6.92 (s, 2H), 4.51 (d, $J = 6.0$ Hz, 2H). MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min: R_t 7.113 min, Purity 97.99%. HRMS (ESI-ve) calculated for C₂₀H₁₈N₅O (M+H)⁺ 344.1505, found 344.1514



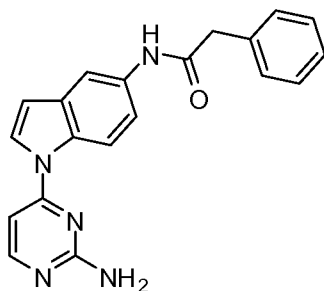
1-(2-aminopyrimidin-4-yl)-N-phenethyl-1H-indole-4-carboxamide (24c) This was obtained from 2-amino-4-chloropyrimidine (0.672g, 0.517mmol), and **23d** (0.187g, 0.708 mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with CH₃CN, filtered and dried under vacuum. Pure **24c** (0.144g, 0.402mmol, 72%) was obtained as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) 8.94 (d, $J = 8.4$ Hz, 1H), 8.47 (t, $J = 5.6$ Hz, 1H), 8.25 (d, $J = 5.7$ Hz, 1H), 8.11 (d, $J = 3.7$ Hz, 1H), 7.49 (d, $J = 7.3$ Hz, 1H), 7.31-7.25 (m, 5H), 7.21-7.18 (m, 1H), 7.06 (d, $J = 3.6$ Hz, 1H), 6.95 (d, $J = 5.8$ Hz, 1H), 6.91 (s, 2H), 3.52 (q, $J = 6.0$ Hz, 1H), 2.88 (t, $J = 7.4$ Hz, 2H). MeOH 60%, (0.1% TFA in H₂O) 40%, 20 min, Flow 1ml/min: R_t 4.087 min, Purity 92.23%. HRMS (ESI-ve) calculated for C₂₁H₂₀N₅O (M+H)⁺ 358.1662, found 358.1670



N-(1-(2-aminopyrimidin-4-yl)-1H-indol-5-yl)benzamide (27b) This was obtained from 2-amino-4-chloropyrimidine (0.046g, 0.355mmol), and **26a** (0.123g, 0.521 mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/hexane) afforded pure **27b** (0.060g, 0.182mmol, 51%) as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.25 (s, 1H), 8.78 (d, $J = 9.1$ Hz, 1H), 8.23 (d, $J = 5.7$ Hz, 1H), 8.15 (s, 1H), 8.06 (d, $J = 3.7$

Hz, 1H), 7.97-7.95 (m, 1H), 7.58-7.52 (m, 4H), 6.93 (d, $J = 5.8$ Hz, 1H), 6.88 (s, 2H), 6.76 (d, 1H, $J = 3.7$ Hz, 1H). HPLC: Purity 98.93%, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min, R_t 8.007 min, HRMS (ESI-ve) calculated for C₁₉H₁₆N₅O (M+H)⁺ 330.1349, found 330.1349

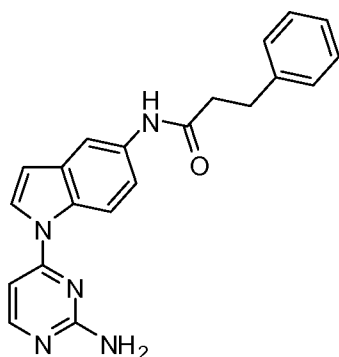
5



N-(1-(2-aminopyrimidin-4-yl)-1H-indol-5-yl)-2-phenylacetamide (27a).

This was obtained from 2-amino-4-chloropyrimidine (0.104g, 0.802mmol), and **26c** (0.301g, 1.20mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/hexane) afforded **27a** as an off white solid. CH₃CN was added to the obtained solid and the solid precipitate was filtered, washed with water and dried *in vacuo*. Pure **27a** was obtained (0.040 g, 0.116 mmol, 15%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.15 (s, 1H), 8.72 (d, $J = 8.9$ Hz, 1H), 8.21 (d, $J = 5.7$ Hz, 1H), 8.02 (d, $J = 3.6$ Hz, 1H), 7.98 (d, $J = 2.1$ Hz, 1H), 7.37-7.29 (m, 4H), 7.25-7.21 (m, 1H), 6.90 (d, $J = 5.8$ Hz, 1H), 6.85 (s, 2H), 6.71 (d, $J = 3.6$ Hz, 1H), 3.64 (s, 2H). HPLC: Purity 95.87%, MeOH 60%, (0.1% TFA in H₂O) 40%, 20 min, Flow 1ml/min, R_t 3.963 min, HRMS (ESI-ve) calculated for C₂₀H₁₈N₅O (M+H)⁺ 344.1505, found 344.1516

20

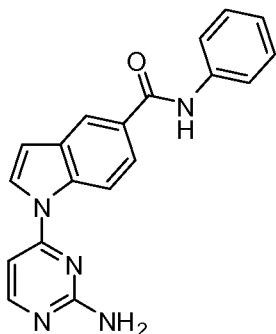


N-(1-(2-aminopyrimidin-4-yl)-1H-indol-5-yl)-3-phenylpropanamide (27c) This was obtained from 2-amino-4-chloropyrimidine (0.072g, 0.555mmol), and **26a** (0.219g, 0.829 mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/MeOH) afforded **27c** as an off white solid. Water was added to the obtained solid and the solid precipitate was filtered, washed with water and dried *in vacuo*. Pure **27c** was obtained (0.058 g, 0.162 mmol, 29%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.89 (s, 1H), 8.71 (d, $J = 4.5$ Hz, 1H), 8.21 (d, $J = 5.7$ Hz, 1H), 8.02 (d, $J = 3.7$ Hz, 1H), 7.99 (d, $J = 1.8$ Hz, 1H), 7.32-7.19 (m, 4H), 7.19-7.14 (m, 1H), 6.90 (d, $J = 5.8$ Hz,

25

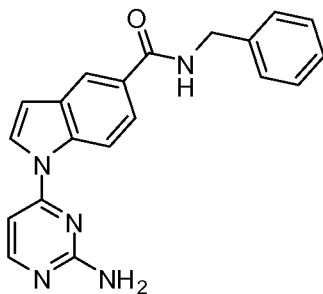
30

1H), 6.84 (s, 2H), 6.72 (d, $J = 3.5$ Hz, 1H), 2.92 (t, $J = 7.6$ Hz, 2H), 2.62 (t, $J = 7.8$ Hz, 2H),. HRMS (ESI-ve) calculated for $C_{21}H_{20}N_5O$ ($M+H$)⁺ 358.1662, found 358.1664.

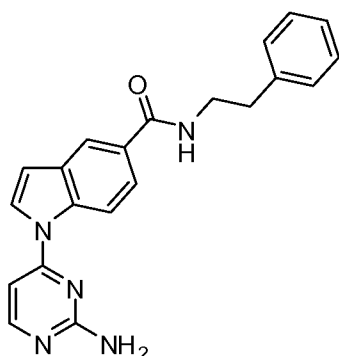


1-(2-aminopyrimidin-4-yl)-N-phenyl-1H-indole-5-carboxamide (24f)

This was obtained from 2-amino-4-chloropyrimidine (0.052g, 0.401mmol), and **23b** (0.114g, 0.483 mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/hexane) afforded pure **24f** (0.014 g, 0.042 mmol, 11%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.26 (s, 2H), 8.89 (d, $J = 8.8$ Hz, 1H), 8.29-7.27 (m, 2H), 8.18 (d, $J = 3.8$ Hz, 1H), 7.86 (dd, $J = 1.8, 8.7$ Hz, 1H), 7.80-7.78 (m, 1H), 7.36-7.32 (m, 2H), 7.09-7.05 (m, 1H), 6.99 (d, $J = 5.8$ Hz, 1H), 6.96 (s, 2H), 6.92 (d, $J = 3.5$ Hz, 1H). HPLC: Purity 96.46%, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min, R_t 9.440 min. HRMS (ESI-ve) calculated for $C_{19}H_{16}N_5O$ ($M+H$)⁺ 330.1349, found 330.1343

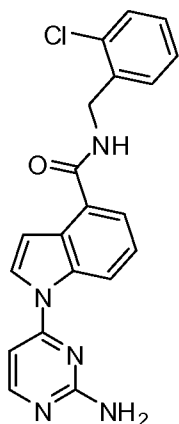


1-(2-aminopyrimidin-4-yl)-N-benzyl-1H-indole-5-carboxamide (24e) This was obtained from 2-amino-4-chloropyrimidine (0.042g, 0.416mmol), and **23c** (0.124g, 0.486 mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with CH₃CN, filtered and dried under vacuum. Pure **24e** (0.083g, 0.241mmol, 58%) was obtained as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.05 (t, $J = 6.0$ Hz, 1H), 8.82 (d, $J = 8.9$ Hz, 1H), 8.27 (d, $J = 5.7$ Hz, 1H), 8.20 (d, $J = 1.5$ Hz, 1H), 8.14 (d, $J = 3.7$ Hz, 1H), 7.81 (dd, $J = 1.8, 8.8$ Hz, 1H), 7.32-7.29 (m, 4H), 7.25-7.20 (m, 1H), 6.97 (d, $J = 5.8$ Hz, 1H), 6.94 (s, 2H), 6.86 (d, $J = 3.2$ Hz, 1H), 4.50 (d, $J = 6.0$ Hz, 1H). HRMS (ESI-ve) calculated for $C_{20}H_{18}N_5O$ ($M+H$)⁺ 344.1505, found 344.1515



1-(2-aminopyrimidin-4-yl)-N-phenethyl-1H-indole-5-carboxamide (24d)

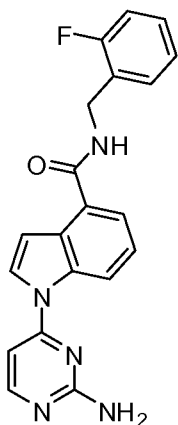
This was obtained from 2-amino-4-chloropyrimidine (0.051g, 0.393mmol), and **23a** (0.146g, 0.553 mmol) in a similar manner as described for **15c**. After cooling to room temperature, the reaction mixture diluted with water and extracted with AcOEt. The organic extract was dried over Na₂SO₄ and the solvent removed under reduced pressure. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/hexane) afforded **24d** as an off white solid. Water was added to the obtained solid and the solid precipitate was filtered, washed with water and dried *in vacuo*. Pure **24d** was obtained (0.025 g, 0.070 mmol, 19%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81 (d, *J* = 8.8 Hz, 1H), 8.56 (t, *J* = 5.9 Hz, 1H), 8.27 (d, *J* = 5.7 Hz, 1H), 8.13 (d, *J* = 3.7 Hz, 1H), 8.11 (d, *J* = 1.5 Hz, 1H), 7.74 (dd, *J* = 1.7, 8.9 Hz, 1H), 7.30-7.23 (m, 4H), 7.20-7.16 (m, 1H), 6.96 (d, *J* = 5.7 Hz, 1H), 6.94 (s, 2H), 6.85 (d, *J* = 3.7 Hz, 1H), 3.51-3.46 (m, 2H), 2.85 (t, *J* = 7.2 Hz, 2H). HPLC: Purity 85.18% MeOH 60%, (0.1% TFA in H₂O) 40%, 20 min, Flow 1ml/min, R_t 4.687 min, HRMS (ESI-ve) calculated for C₂₁H₂₀N₅O (M+H)⁺ 358.1662, found 358.1674.



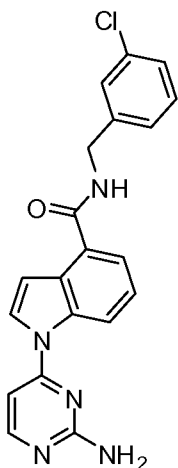
1-(2-aminopyrimidin-4-yl)-N-(2-chlorobenzyl)-1H-indole-4-carboxamide (30a)

A mixture of 2-amino-4-chloropyrimidine (0.037g, 0.285mmol), **29d** (0.121g, 0.424mmol) and Cs₂CO₃ (0.308g) in anhydrous DMF (0.4 ml) was stirred in a Biotage microwave reactor for 30 min at 150 °C. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with methanol, filtered, washed with methanol and dried under vacuum. Pure **30a** (0.072g, 0.190mmol, 69%) was obtained as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.02-8.98 (m, 2H), 8.26 (d, *J* = 5.7 Hz, 1H), 8.14 (d, *J* = 3.7 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.46 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.41 (dd, *J* = 1.6, 7.1 Hz, 1H), 7.36-7.26 (m, 3H), 7.16 (d, *J* = 3.8 Hz, 1H), 6.95 (d, *J* = 5.7 Hz, 1H), 6.94 (s, 2H), 4.57 (d, *J* = 5.7 Hz, 2H). HPLC: Purity 97.81

%, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min, R_t 12.807 min, Purity 97.91 %, CH₃CN 30%, (0.1% TFA in H₂O) 70%, 20 min, Flow 1ml/min, R_t 13.007 min, HRMS (ESI-ve) calculated for C₂₀H₁₇N₅OCl (M+H)⁺ 378.1116, found 378.1115.

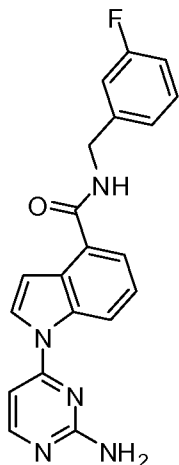


1-(2-aminopyrimidin-4-yl)-N-(2-fluorobenzyl)-1H-indole-4-carboxamide (30k) This was obtained from 2-amino-4-chloropyrimidine (0.057g, 0.439mmol), and **29c** (0.171g, 0.638 mmol) in a similar manner as described for **30a**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with methanol, filtered, washed with methanol and dried under vacuum. Pure **30k** (0.113g, 0.312mmol, 71%) was obtained as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98-8.95 (m, 2H), 8.26 (d, *J* = 5.7 Hz, 1H), 8.13 (d, *J* = 3.7 Hz, 1H), 7.63 (d, *J* = 6.7 Hz, 1H), 7.42-7.39 (m, 1H), 7.35-7.26 (m, 2H), 7.20-7.13 (m, 3H), 6.94 (d, *J* = 5.8 Hz, 1H), 6.92 (s, 2H), 4.54 (d, *J* = 6.0 Hz, 2H). HPLC: Purity 98.68%, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min: R_t 7.573 min, Purity 99.00%, CH₃CN 30%, (0.1% TFA in H₂O) 70%, 20 min, Flow 1ml/min, R_t 7.933 min, HRMS (ESI-ve) calculated for C₂₀H₁₇N₅OF (M+H)⁺ 362.1411, found 362.1407.

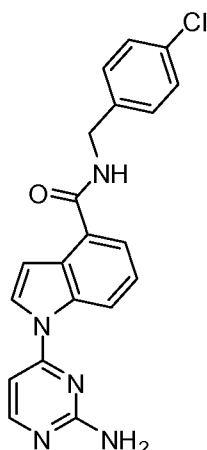


1-(2-aminopyrimidin-4-yl)-N-(3-chlorobenzyl)-1H-indole-4-carboxamide (30c) This was obtained from 2-amino-4-chloropyrimidine (0.036g, 0.277mmol), and **29f** (0.114g, 0.400 mmol) in a similar manner as described for **30a**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with methanol, filtered, washed with methanol and dried under vacuum. Pure **30c** (0.048g, 0.127mmol, 46%) was obtained as an off white solid. ¹H NMR (400

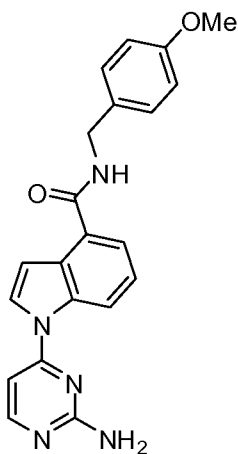
MHz, DMSO-*d*₆) δ 9.04 (t, *J* = 5.7 Hz, 1H), 8.99 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 5.7 Hz, 1H), 8.14 (d, *J* = 3.7 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.40-7.27 (m, 4H), 7.15 (d, *J* = 3.2 Hz, 1H), 6.95 (d, *J* = 5.7 Hz, 1H), 6.93 (s, 2H), 4.50 (d, *J* = 6.1 Hz, 2H). HPLC: Purity 98.68 %, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min, R_t 15.520 min, Purity 99.13%, CH₃CN 30%, (0.1% TFA in H₂O) 70%, 20 min, Flow 1ml/min, R_t 15.227 min, HRMS (ESI-ve) calculated for C₂₀H₁₇N₅OCl (M+H)⁺ 378.1116, found 378.1113.



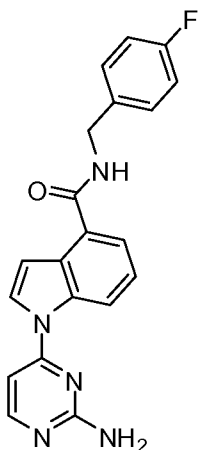
1-(2-aminopyrimidin-4-yl)-N-(3-fluorobenzyl)-1H-indole-4-carboxamide (30d) This was obtained from 2-amino-4-chloropyrimidine (0.039g, 0.301mmol), and **29e** (0.118g, 0.439 mmol) in a similar manner as described for **30a**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with methanol, filtered, washed with methanol and dried under vacuum. Pure **30d** (0.066g, 0.182mmol, 60%) was obtained as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.03 (t, *J* = 6.1 Hz, 1H), 8.98 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 5.7 Hz, 1H), 8.14 (d, *J* = 3.7 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.42-7.31 (m, 2H), 7.20-7.13 (m, 3H), 7.06 (td, *J* = 8.6, 2.7 Hz, 1H), 6.95 (d, *J* = 5.7 Hz, 1H), 6.92 (s, 2H), 4.52 (d, *J* = 6.0 Hz, 2H). HPLC: Purity 98.78 %, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min: R_t 8.333 min, Purity 99.24%, CH₃CN 30%, (0.1% TFA in H₂O) 70%, 20 min, Flow 1ml/min, R_t 8.620 min, HRMS (ESI-ve) calculated for C₂₀H₁₇N₅OF (M+H)⁺ 362.1411, found 362.1411.



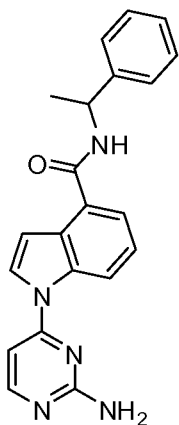
1-(2-aminopyrimidin-4-yl)-N-(4-chlorobenzyl)-1H-indole-4-carboxamide (30e) This was obtained from 2-amino-4-chloropyrimidine (0.035g, 0.270mmol), and **29i** (0.113g, 0.396 mmol) in a similar manner as described for **30a**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with methanol, filtered, washed with methanol and dried under vacuum. Pure **30e** (0.079g, 0.209mmol, 77%) was obtained as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.02 (t, *J* = 4.8 Hz, 1H), 8.98 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 5.7 Hz, 1H), 8.13 (d, *J* = 3.7 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.40 (d, *J* = 8.9 Hz, 2H), 7.37 (d, *J* = 9.1 Hz, 2H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 3.6 Hz, 1H), 6.95 (d, *J* = 5.8 Hz, 1H), 6.92 (s, 2H), 4.48 (d, *J* = 6.0 Hz, 2H). HPLC: Purity 99.73%, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min, R_t 16.340 min; Purity 99.91%, CH₃CN 30%, (0.1% TFA in H₂O) 70%, 20 min, Flow 1ml/min, R_t 15.560 min. HRMS (ESI-ve) calculated for C₂₀H₁₇N₅OCl (M+H)⁺ 378.1116, found 378.1116



1-(2-aminopyrimidin-4-yl)-N-(4-methoxybenzyl)-1H-indole-4-carboxamide (30l) This was obtained from 2-amino-4-chloropyrimidine (0.039g, 0.301mmol), and **29g** (0.118g, 0.449 mmol) in a similar manner as described for **30a**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with methanol, filtered, washed with CH₃CN and dried under vacuum. Pure **30l** (0.055g, 0.147mmol, 49%) was obtained as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.96 (d, *J* = 8.4 Hz, 1H), 8.91 (t, *J* = 6.1 Hz, 1H), 8.25 (d, *J* = 5.7 Hz, 1H), 8.12 (d, *J* = 3.7 Hz, 1H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 3.6 Hz, 1H), 6.94 (d, *J* = 5.8 Hz, 1H), 6.92 (s, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.43 (d, *J* = 6.0 Hz, 2H), 3.71 (s, 3H). HPLC: Purity 98.32 %, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min, R_t 6.807 min, Purity 97.77 %, CH₃CN 30%, (0.1% TFA in H₂O) 70%, 20 min, Flow 1ml/min: R_t 6.987 min, HRMS (ESI-ve) calculated for C₂₁H₂₀N₅O₂ (M+H)⁺ 374.1611, found 374.1601

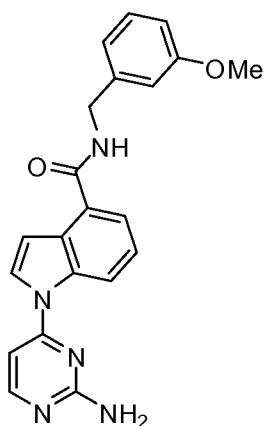


1-(2-aminopyrimidin-4-yl)-N-(4-fluorobenzyl)-1H-indole-4-carboxamide (30f) This was obtained from 2-amino-4-chloropyrimidine (0.035g, 0.270mmol), and **29h** (0.109g, 0.406 mmol) in a similar manner as described for **30a**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with methanol, filtered, washed with methanol and dried under vacuum. Pure **30f** (0.063g, 0.174mmol, 65%) was obtained as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10-8.96 (m, 2H), 8.26 (d, *J* = 5.7 Hz, 1H), 8.13 (d, *J* = 3.7 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.40-7.37 (m, 2H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.17-7.13 (m, 3H), 6.95 (d, *J* = 5.7 Hz, 1H), 6.92 (s, 2H), 4.48 (d, *J* = 6.0 Hz, 2H). HPLC: Purity 98.37 %, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min, R_t 8.407 min; Purity 99.08 %, CH₃CN 30%, (0.1% TFA in H₂O) 70%, 20 min, Flow 1ml/min, R_t 8.580 min, HRMS (ESI-ve) calculated for C₂₁H₁₇N₅O₂F (M+H)⁺ 362.1411, found 362.1412



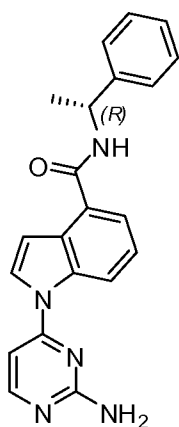
1-(2-aminopyrimidin-4-yl)-N-(1-phenylethyl)-1H-indole-4-carboxamide (30g) This was obtained from 2-amino-4-chloropyrimidine (0.040g, 0.308mmol), and **29b** (0.115g, 0.435 mmol) in a similar manner as described for **30a**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with methanol, filtered, washed with methanol and dried under vacuum. Pure **30g** (0.074g, 0.207mmol, 67%) was obtained as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.96 (d, *J* = 8.4 Hz, 1H), 8.81 (d, *J* = 8.2 Hz, 1H), 8.25 (d, *J* = 5.7 Hz, 1H), 8.11 (d, *J* = 3.7 Hz, 1H), 7.63 (d, *J* = 7.1 Hz, 1H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 3H), 7.21 (t, *J* = 6.7 Hz, 1H), 7.06 (d, *J* = 3.6 Hz, 1H), 6.94 (d, *J* = 5.7 Hz, 1H), 6.92 (s, 2H), 5.20 (quin, *J* = 6.7 Hz, 1H), 1.48 (d, *J* = 7.1 Hz, 3H). HPLC: Purity 99.95 %, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min, R_t 9.053 min, Purity

99.68 %, CH₃CN 30%, (0.1% TFA in H₂O) 70%, 20 min, Flow 1ml/min: R_t 9.867 min; HRMS (ESI-ve) calculated for C₂₁H₂₀N₅O (M+H)⁺ 358.1662, found 358.1687



1-(2-aminopyrimidin-4-yl)-N-(3-methoxybenzyl)-1H-indole-4-carboxamide (30b).

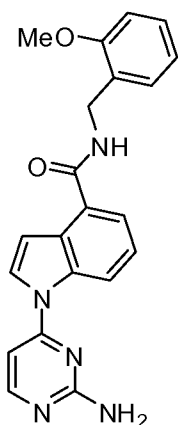
This was obtained from 2-amino-4-chloropyrimidine (0.079g, 0.609mmol), and **29a** (0.202g, 0.720 mmol) in a similar manner as described for **30a**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with methanol, filtered, washed with methanol and dried under vacuum. Pure **30b** (0.079g, 0.212mmol, 35%) was obtained as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98-8.95 (m, 2H), 8.26 (d, *J* = 5.7 Hz, 1H), 8.13 (d, *J* = 3.7 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.24 (t, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 3.6 Hz, 1H), 6.95-6.91 (m, 5H), 6.81-6.79 (m, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.72 (s, 3H). HPLC: Purity 98.10 %, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min: R_t 7.153 min; Purity 97.57 %, CH₃CN 30%, (0.1% TFA in H₂O) 70%, 20 min, Flow 1ml/min: R_t 7.687 min, HRMS (ESI-ve) calculated for C₂₁H₂₀N₅O₂ (M+H)⁺ 374.1601, found 374.1601



(R)-1-(2-aminopyrimidin-4-yl)-N-(1-phenylethyl)-1H-indole-4-carboxamide (30h).

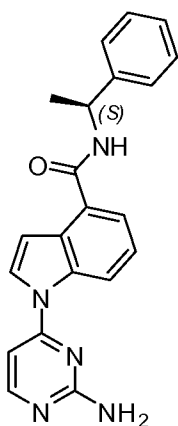
This was obtained from 2-amino-4-chloropyrimidine (0.051g, 0.393mmol), and **29l** (0.120g, 0.454 mmol) in a similar manner as described for **30a**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with methanol, filtered, washed with methanol and dried under vacuum. Pure **30h** (0.059g, 0.165mmol, 42%) was obtained as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.96 (d, *J* = 8.4 Hz, 1H), 8.82 (d, *J* = 8.2 Hz, 1H), 8.25 (d, *J* = 5.7 Hz,

1H), 8.11 (d, $J = 3.7$ Hz, 1H), 7.62 (d, $J = 7.4$ Hz, 1H), 7.42 (d, $J = 7.7$ Hz, 2H), 7.32 (t, $J = 7.8$ Hz, 3H), 7.23-7.19 (m, 1H), 7.06 (d, $J = 3.7$ Hz, 1H), 6.94 (d, $J = 5.8$ Hz, 1H), 6.92 (s, 2H), 5.19 (quin, $J = 7.3$ Hz, 1H), 1.48 (d, $J = 7.1$ Hz, 3H),. HRMS (ESI-ve) calculated for $C_{21}H_{20}N_5O$ ($M+H$)⁺ 358.1662, found 358.1654.



1-(2-aminopyrimidin-4-yl)-N-(2-methoxybenzyl)-1H-indole-4-carboxamide. (30i)

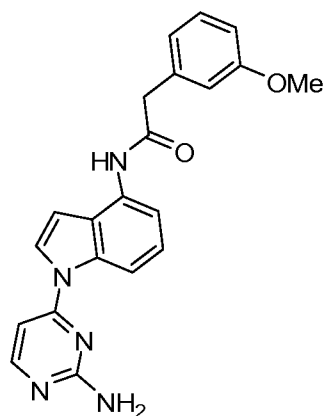
This was obtained from 2-amino-4-chloropyrimidine (0.050g, 0.385mmol), and **20j** (0.126g, 0.449 mmol) in a similar manner as described for **30a**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with methanol, filtered, washed with methanol and dried under vacuum. Pure **30i** (0.077g, 0.206mmol, 54%) was obtained as an off white solid ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (d, $J = 8.4$ Hz, 1H), 8.79 (t, $J = 6.0$ Hz, 1H), 8.26 (d, $J = 5.7$ Hz, 1H), 8.13 (d, $J = 3.7$ Hz, 1H), 7.66 (d, $J = 6.8$ Hz, 1H) 7.33 (t, $J = 7.7$ Hz, 1H), 7.25-7.21 (m, 2H), 7.15 (d, 1H, $J = 3.3$ Hz, 1H), 7.00-6.88 (m, 5H), 4.48 (d, $J = 5.9$ Hz, 2H), 3.83 (s, 3H). HRMS (ESI-ve) calculated for $C_{21}H_{20}N_5O_2$ ($M+H$)⁺ 374.1611, found 374.1603



(S)-1-(2-aminopyrimidin-4-yl)-N-(1-phenylethyl)-1H-indole-4-carboxamide (30j).

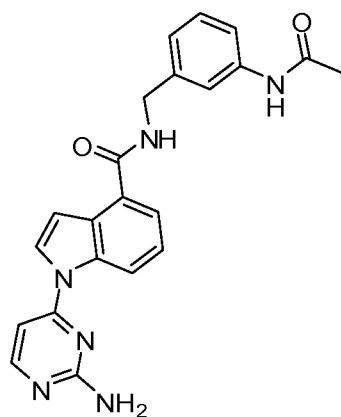
This was obtained from 2-amino-4-chloropyrimidine (0.048g, 0.370mmol), and **29k** (0.130g, 0.492 mmol) in a similar manner as described for **30a**. After cooling to room temperature, the reaction mixture was diluted with water. The solid precipitated was filtered, slurried with methanol, filtered, washed with methanol and dried under vacuum. Pure **30j** (0.080g, 0.224mmol, 60%) was obtained as an off white solid ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.97 (d, $J = 8.3$ Hz, 1H), 8.82 (d, $J = 8.0$ Hz, 1H), 8.26 (d, 1H, $J = 5.7$ Hz, 1H), 8.11 (d, $J = 3.7$ Hz, 1H), 7.63 (d, $J = 7.3$ Hz, 1H), 7.43 (d, $J = 7.3$ Hz, 2H), 7.33 (t, $J = 7.8$ Hz, 3H), 7.23-7.19 (m, 1H), 7.07 (d, $J = 3.6$ Hz, 1H), 6.94 (d, $J = 5.8$ Hz, 1H),

6.93 (s, 2H), 5.21 (quin, $J = 7.3$ Hz, 1H), 1.48 (d, $J = 7.1$ Hz, 3H),. HRMS (ESI-ve) calculated for $C_{21}H_{20}N_5O$ ($M+H$)⁺ 358.1662, found 358.1653.



N-(1-(2-aminopyrimidin-4-yl)-1H-indol-4-yl)-2-(3-methoxyphenyl)acetamide (27d).

A mixture of **26d** (0.32 g, 0.245 mmol) and 2-amino-4-chloropyrimidine (0.080 g, 0.215 mmol) in anhydrous DMF (0.50 mL) and Cs_2CO_3 (0.195 g, 0.602 mmol), was heated in the microwave at 150 °C for 30 minutes. After cooling to room temperature, water (3 mL) was added and the solution was filtered. The obtained solid was slurried with acetonitrile, filtered, dried under vacuum to afford pure **27d** as an orange solid (0.050 g, 0.134 mmol, 55%), which was dried under vacuum. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.91 (s, 1H), 8.52 (d, $J = 8.4$ Hz, 1H), 8.24 (d, $J = 5.7$ Hz, 1H), 8.02 (d, $J = 3.8$ Hz, 1H), 7.68 (d, $J = 7.8$ Hz, 1H), 7.24 (t, $J = 7.9$ Hz, 1H), 7.18 (t, $J = 8.1$ Hz, 1H), 7.00 – 6.85 (m, 6H), 6.82 (dd, $J = 8.6, 2.2$ Hz, 1H), 3.74 (s, 5H), 2.07 (s, 2H); HPLC purity 97.38% { $t_R = 7.787$ min, Flow 1ml/min, [(CH₃CN/(0.1% TFA in H₂O):30/70]}; HRMS (ESI +ve) m/z calculated for $C_{21}H_{19}N_5O_2$ ($M + H$)⁺ 374.1615, found 374.1605.

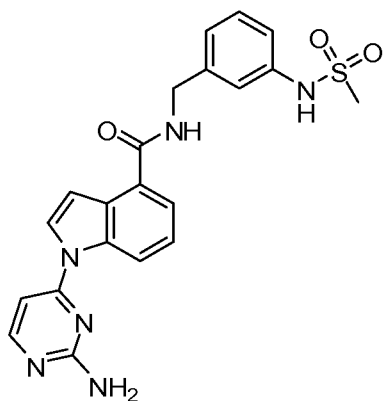


N-(3-acetamidobenzyl)-1-(2-aminopyrimidin-4-yl)-1H-indole-4-carboxamide (30n).

A mixture of **29p** (0.085 g, 0.235 mmol) and 2-amino-4-chloropyrimidine (0.037 g, 0.282 mmol) in anhydrous DMF (0.4 mL) and Cs_2CO_3 (0.245 g, 0.752 mmol), was heated in the microwave at 150°C for 45 minutes. After cooling to room temperature, MeOH (5mL) was added and the solution was filtered. The filtrate was concentrated under reduced pressure. The obtained solid was then washed with water and filtered. Slurry with acetonitrile afforded a brown solid **30n** (0.035 g, 0.087 mmol, 37%). ¹H NMR (400 MHz, CD₃OD) δ 8.90 (d, $J = 8.5$ Hz, 1H), 8.23 (d, $J = 5.8$ Hz, 1H), 7.96 (d, $J = 3.9$ Hz, 1H),

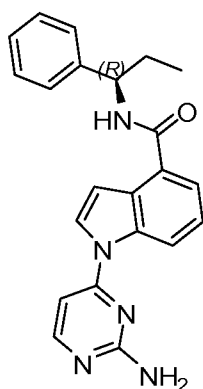
7.69–7.52 (m, 2H), 7.45 (d, $J = 8.1$ Hz, 1H), 7.36 (t, $J = 7.9$ Hz, 1H), 7.29 (t, $J = 7.8$ Hz, 1H), 7.15 (s, 1H), 6.90 (d, $J = 5.9$ Hz, 1H), 2.10 (s, 3H). HPLC purity 96.99% ($t_R = 5.883$ min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):50/50)]; HRMS (ESI +ve) m/z calculated for C₂₂H₂₁N₆O₂ (M + H)⁺ 401.1720, found 401.1722.

5



1-(2-aminopyrimidin-4-yl)-N-(3-(methylsulfonamido)benzyl)-1H-indole-4-carboxamide (30m). This was prepared from **29o** (0.035 g, 0.097 mmol) and 2-amino-4-chloropyrimidine (0.014 g, 0.111 mmol) in a similar manner as described for preparation of **30n**. After cooling to room temperature, water (10 mL) was added and the solid precipitate filtered and dried under vacuum. The obtained solid was slurried with MeOH, filtered, dried under vacuum to afford pure **30m** (0.014 g, 0.030 mmol, 32%) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.72 (s, 1H), 8.97 (d, $J = 6.9$ Hz, 2H), 8.26 (d, $J = 4.7$ Hz, 1H), 8.13 (d, $J = 3.6$ Hz, 1H), 7.63 (d, $J = 7.6$ Hz, 1H), 7.37 – 7.25 (m, 3H), 7.23 (s, 1H), 7.16 (d, $J = 2.7$ Hz, 1H), 7.09 (d, $J = 7.1$ Hz, 2H), 6.95 (d, $J = 5.8$ Hz, 1H), 6.90 (s, 2H), 4.48 (d, $J = 5.0$ Hz, 2H), 2.97 (s, 4H). HPLC purity 96.92% ($t_R = 4.200$ min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):40/60)]; HRMS (ESI +ve) m/z calculated for C₂₁H₂₁N₆O₃S (M + H)⁺ 437.1390, found 437.1391.

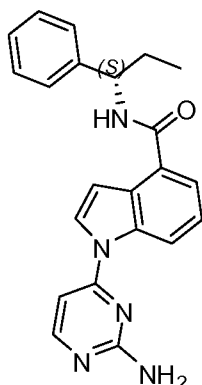
20



(R)-1-(2-aminopyrimidin-4-yl)-N-(1-phenylpropyl)-1H-indole-4-carboxamide (30o) This was prepared from **29q** (0.036 g, 0.129 mmol) and 2-amino-4-chloropyrimidine (0.020 g, 0.154 mmol) in a similar manner as described for preparation of **30n**. After the reaction, water (5 mL) was added and the mixture extracted with ethyl acetate. The organic phase was washed with NaHCO₃ (aq., sat.), separated, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Slurry with methanol afforded **30o** (0.012 g, 0.032 mmol, 25 %) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.90 (d, $J = 8.4$ Hz,

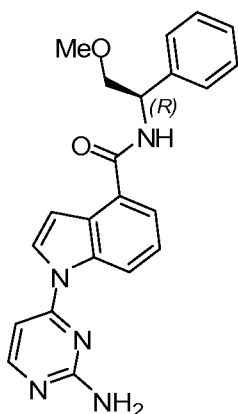
25

1H), 8.23 (d, $J = 5.7$ Hz, 1H), 7.95 (d, $J = 3.4$ Hz, 1H), 7.55 (d, $J = 7.5$ Hz, 1H), 7.43 (d, $J = 7.6$ Hz, 2H), 7.38-7.33 (m, 3H), 7.25 (t, $J = 8.0$ Hz, 1H), 7.02 (d, $J = 3.5$ Hz, 1H), 6.90 (d, $J = 5.9$ Hz, 1H), 5.05-5.01 (m, 1H), 1.98-1.89 (m, 1H), 1.02 (t, $J = 7.3$ Hz, 3H). HPLC purity 99.98% ($t_R = 17.167$ min, Flow 1ml/min, [(CH₃CN/(0.1% TFA in H₂O):30/70)]; HRMS (ESI +ve) m/z calculated for C₂₂H₂₂N₅O (M + H)⁺ 372.1818, found 372.1819.



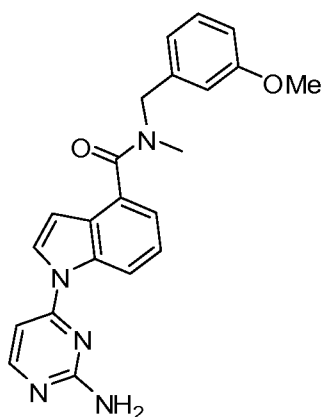
(S)-1-(2-aminopyrimidin-4-yl)-N-(1-phenylpropyl)-1H-indole-4-carboxamide (3aa)

This was prepared from **29r** (0.036 g, 0.129 mmol) and 2-amino-4-chloropyrimidine (0.020 g, 0.154 mmol) in a similar manner as described for preparation of **30n**. After the reaction, water (5 mL) was added and the mixture extracted with ethyl acetate. The organic phase was washed with NaHCO₃ (aq., sat.), separated, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Slurry with methanol afforded **30aa** (0.012 g, 0.032 mmol, 25 %) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.96 (d, $J = 8.5$ Hz, 1H), 8.76 (d, $J = 7.9$ Hz, 1H), 8.25 (d, $J = 4.1$ Hz, 1H), 8.10 (s, 1H), 7.61 (d, $J = 7.4$ Hz, 1H), 7.41 (d, $J = 6.8$ Hz, 2H), 7.32 (t, $J = 7.3$ Hz, 3H), 7.21 (t, $J = 7.3$ Hz, 1H), 7.03 (s, 1H), 6.92 (s, 3H), 5.1 –4.75 (m, 1H), 1.86-1.75 (m, 2H), 0.91 (t, $J = 6.4$ Hz, 3H). HPLC purity 97.30 % ($t_R = 8.967$ min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):60/40)]; HRMS (ESI +ve) m/z calculated for C₂₂H₂₂N₅O (M + H)⁺ 372.1818, found 372.1816.



(R)-1-(2-aminopyrimidin-4-yl)-N-(2-methoxy-1-phenylethyl)-1H-indole-4-

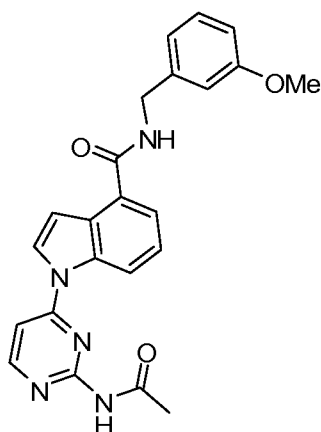
carboxamide (30p) This was prepared from **29s** (0.035 g, 0.119 mmol) and 2-amino-4-chloropyrimidine (0.020 g, 0.154 mmol) in a similar manner as described for preparation of **30n**. After the reaction, water (5 mL) was added and the mixture extracted with ethyl acetate. The organic phase was washed with NaHCO₃ (aq., sat.), separated, dried (Na₂SO₄), filtered and concentrated under reduced pressure. Slurry with acetonitrile afforded **30p** (0.012 g, 0.032 mmol, 25%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.98 (d, *J* = 8.1 Hz, 1H), 8.85 (d, *J* = 8.6 Hz, 1H), 8.26 (d, *J* = 5.4 Hz, 1H), 8.13 (d, *J* = 3.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.30–7.21 (m, 1H), 7.08 (d, *J* = 3.3 Hz, 1H), 6.95–6.93 (m, 3H), 5.32–5.27 (m, 1H), 3.70 (t, *J* = 8.8 Hz, 1H), 3.55 (dd, *J* = 10.1, 5.4 Hz, 2H). HPLC purity 96.86% {*t*_R = 15.600 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):40/60]}; HRMS (ESI +ve) *m/z* calculated for C₂₂H₂₁N₅O₂ (M + H)⁺ 388.1768, found 388.1766..

**1-(2-aminopyrimidin-4-yl)-N-(3-methoxybenzyl)-N-methyl-1H-indole-4-**

carboxamide (30q) A mixture of **29t** (0.062 g, 0.211 mmol), 2-amino-4-chloropyrimidine (0.033 g, 0.253 mmol), and Cs₂CO₃ (0.206 g, 0.633 mmol) in DMF (0.5 mL) was heated in the Biotage Microwave for 45 min at 150°C. The solvent was then removed under reduced pressure. Chromatography on silica gel, performed using a FlashMaster 3 purification station afforded **30q** (0.028 g, 0.074 mmol, 34%) as a tan solid. HRMS (ESI +ve) *m/z* calculated for C₂₂H₂₁N₅O₂ (M + H)⁺ 388.17680, found 388.17691

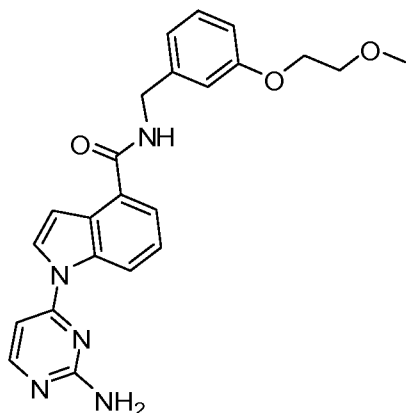
¹H NMR (400 MHz, DMSO-*d*₆, 25°C, two rotamers present) δ 8.88 (d, *J* = 8.0 Hz, 1H), 8.27 (d, *J* = 5.6 Hz, 1H), 8.16 (d, *J* = 3.6 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.23 (d, *J* = 7.1 Hz, 1H), 6.95 (d, *J* = 6.1 Hz, 3H), 6.89 (d, *J* = 6.4 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 14.7 Hz, 1H), 6.59 (d, *J* = 19.5 Hz, 2H), 4.72 (s, 2H), 4.41 (s, 1H), 3.77 (s, 2H), 3.68 (s, 1H), 2.95 (s, 1H), 2.74 (s, 1H), 1.90 (s, 2H).

¹H NMR (400 MHz, DMSO-*d*₆, 80°C) δ 8.75 (d, *J* = 7.7 Hz, 1H), 8.27 (d, *J* = 5.5 Hz, 1H), 8.06 (d, *J* = 3.7 Hz, 1H), 7.30 (q, *J* = 17.0, 8.7 Hz, 2H), 7.21 (d, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 5.7 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 2H), 6.66 – 6.57 (m, 3H), 3.75 (s, 3H), 2.86 (s, 2H), 1.90 (s, 3H).



1-(2-acetamidopyrimidin-4-yl)-N-(3-methoxybenzyl)-1H-indole-4-carboxamide (36)

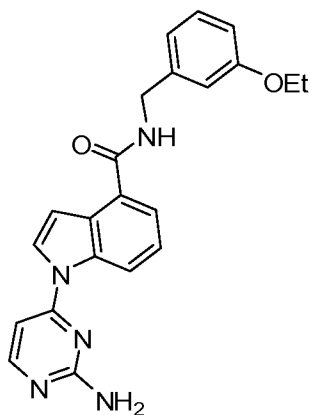
A mixture of acetic anhydride (1.75 mL) and **30b** (0.100 g, 0.270 mmol) was refluxed under Argon for 2 hours. The mixture was then cooled to room temperature. The solid precipitate was filtered and washed with ethyl ether, dried under vacuum to afford **36** (0.044 g, 0.106 mmol, 39 %) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 10.83 (s, 1H), 9.56 (d, *J* = 7.6 Hz, 1H), 9.01 (t, *J* = 5.5 Hz, 1H), 8.63 (d, *J* = 5.7 Hz, 1H), 8.28 (d, *J* = 4.3 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 6.1 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.28 – 7.20 (m, 2H), 6.98 – 6.89 (m, 2H), 6.82 (d, *J* = 9.3 Hz, 1H), 4.49 (d, *J* = 5.3 Hz, 1H), 3.74 (s, 2H), 2.21 (s, 2H). HPLC purity 97.88% {*t_R* = 15.300 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):40/60)}; HRMS (ESI +ve) *m/z* calculated for C₂₃H₂₂N₅O₃ (M + H)⁺ 416.1717, found 416.1712.



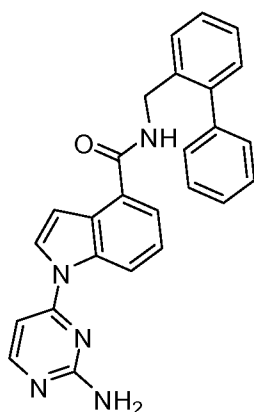
1-(2-aminopyrimidin-4-yl)-N-(3-(2-methoxyethoxy)benzyl)-1H-indole-4-carboxamide (30r)

This was prepared from **29u** (0.128 g, 0.395 mmol) and 2-amino-4-chloropyrimidine (0.061 g, 0.474 mmol) in a similar manner as described for preparation of **27d**. After cooling to room temperature, the solvent was removed under reduced pressure. Water (5 mL) added and the solid precipitated was filtered and dried under vacuum. The obtained solid was slurried with acetonitrile, filtered, slurried with and methanol, filtered dried under vacuum to **30r** (0.082 g, 0.197 mmol, 50%) as an off-white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.98-8.92 (m, 2H), 8.26 (d, *J* = 5.7 Hz, 1H), 8.12 (d, *J* = 3.7 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.23 (t, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 3.7 Hz, 1H), 6.97–6.87 (m, 5H), 6.81 (dd, *J* = 7.8, 2.0 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 4.08–4.03 (m, 2H), 3.65–3.60 (m, 2H), 3.27 (s, 3H). HPLC

purity 99.15% { t_R = 9.253 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):50/50)]; HRMS (ESI +ve) m/z calculated for C₂₃H₂₄N₅O₃ (M + H)⁺ 418.1873, found 418.1874.

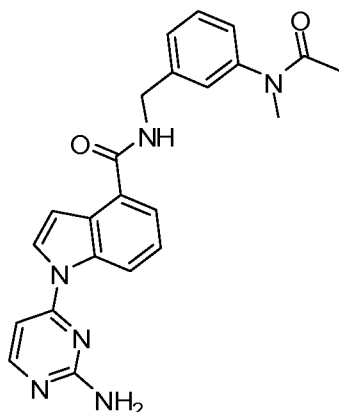


1-(2-aminopyrimidin-4-yl)-N-(3-ethoxybenzyl)-1H-indole-4-carboxamide (30s) This was prepared from **29v** (0.283 g, 0.963 mmol) and 2-amino-4-chloropyrimidine (0.150 g, 1.155 mmol) in a similar manner as described for preparation of **27d**. After cooling to room temperature, water (5 mL) added and the solid precipitated was filtered and dried under vacuum. The obtained solid was slurried with methanol, filtered dried under vacuum to a white solid **30s** (0.212 g, 0.548 mmol, 57% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.96-8.91 (m, 2H), 8.25 (d, J = 5.6 Hz, 1H), 8.11 (d, J = 3.6 Hz, 1H), 7.61 (d, J = 7.3 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 6.96-6.85 (m, 3H), 6.78 (d, J = 8.9 Hz, 1H), 4.46 (d, J = 5.9 Hz, 3H), 3.98 (q, J = 7.0 Hz, 2H), 1.29 (t, J = 6.9 Hz, 2H). HPLC purity 96.39% { t_R = 3.583 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):40/60)]; HRMS (ESI +ve) m/z calculated for C₂₂H₂₂N₅O₂ (M + H)⁺ 388.1768, found 388.1771.

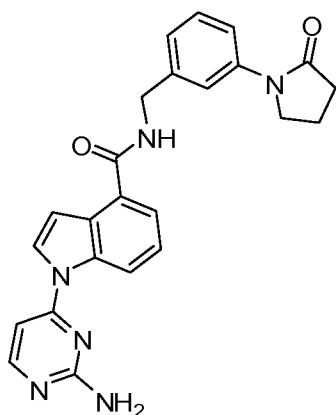


1-(2-aminopyrimidin-4-yl)-N-(biphenyl-2-ylmethyl)-1H-indole-4-carboxamide (30t) This was prepared from **29w** (0.207 g, 0.634 mmol) and 2-amino-4-chloropyrimidine (0.099 g, 0.764 mmol) in a similar manner as described for preparation of **27d**. Reaction time: 55 min. After cooling to room temperature, water (10 mL) added and the solid precipitated was filtered and dried under vacuum. The obtained solid was slurried with methanol to afford **30t** (0.160 g, 0.381 mmol, 60%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.96 (d, J = 8.3 Hz, 1H), 8.85 (t, J = 5.6 Hz, 1H), 8.26 (d, J = 5.6 Hz, 1H), 8.11 (d, J = 3.6 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.52-7.28 (m, 10H), 7.23 (d, J = 7.3 Hz, 1H), 7.12 (d, J = 3.5 Hz, 1H), 6.94 (d, J = 5.7 Hz, 1H), 6.90 (s, 2H), 4.46 (d, J = 5.6

Hz, 2H). HPLC purity 96.23% { t_R = 8.950 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):40/60)}; HRMS (ESI +ve) m/z calculated for C₂₆H₂₂N₅O (M + H)⁺ 420.1818, found 420.1824.

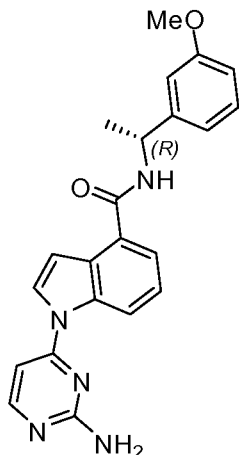


1-(2-aminopyrimidin-4-yl)-N-(3-(N-methylacetamido)benzyl)-1H-indole-4-carboxamide (30u) This was prepared from **29x** (0.075 g, 0.210 mmol) and 2-amino-4-chloropyrimidine (0.0333 g, 0.252 mmol) in a similar manner as described for preparation of **27d**. After cooling to room temperature, the solvents was removed under reduced pressure and the obtained solid was slurried with 10 mL of water (10 mL), filtered and dried under vacuum. The obtained solid was slurried with acetonitrile, filtered, dried under vacuum to afford **30u** (0.015 g, 0.036 mmol, 17%) as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.99-8.95 (m, 2H), 8.25 (d, J = 5.6 Hz, 1H), 8.12 (d, J = 3.7 Hz, 1H), 7.62 (d, J = 7.1 Hz, 1H), 7.41-7.27 (m, 4H), 7.19 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 3.6 Hz, 1H), 6.94 (d, J = 5.7 Hz, 1H), 6.90 (s, 2H), 4.53 (d, J = 6.0 Hz, 2H), 3.11 (s, 3H), 1.75 (s, 3H). HPLC purity 98.11% { t_R = 8.033 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):40/60)}; HRMS (ESI +ve) m/z calculated for C₂₃H₂₁N₆O₂ (M + H)⁺ 415.1877, found 415.1872.

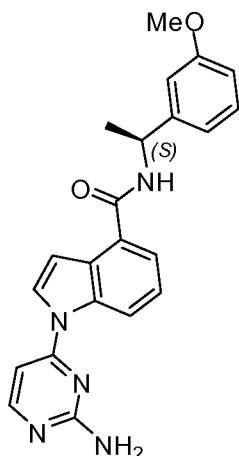


1-(2-aminopyrimidin-4-yl)-N-(3-(2-oxopyrrolidin-1-yl)benzyl)-1H-indole-4-carboxamide (30v) This was prepared from **29y** (0.086 g, 0.258 mmol) and 2-amino-4-chloropyrimidine (0.040 g, 0.310 mmol) in a similar manner as described for preparation of **27d**. After cooling to room temperature, water (10 mL) added and the solid precipitated was filtered and dried under vacuum. The obtained solid was slurried with ethyl acetate afforded an off white solid **30v** (0.054 g, 0.127 mmol, 49%). ¹H NMR (400

MHz, DMSO-*d*₆) δ 8.98-8.94 (m, 2H), 8.25 (d, *J* = 5.6 Hz, 1H), 8.12 (d, *J* = 3.7 Hz, 1H), 7.68 (s, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.32 (td, *J* = 8.0, 3.1 Hz, 2H), 7.16 (d, *J* = 3.4 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 6.94 (d, *J* = 5.7 Hz, 1H), 6.89 (s, 2H), 4.50 (d, *J* = 5.9 Hz, 2H), 3.80 (t, *J* = 7.0 Hz, 2H), 2.03 (quin, *J* = 7.6 Hz, 2H). HPLC purity 98.11% {*t*_R = 9.317 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):40/60)}; HRMS (ESI +ve) *m/z* calculated for C₂₄H₂₃N₆O₂ (M + H)⁺ 427.1877, found 427.1887.

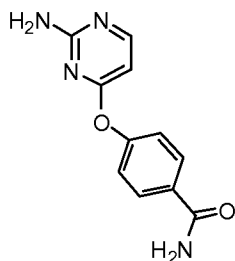


(R)-1-(2-aminopyrimidin-4-yl)-N-(1-(3-methoxyphenyl)ethyl)-1H-indole-4-carboxamide (30w) This was prepared from **29m** (0.131 g, 0.445 mmol) and 2-amino-4-chloropyrimidine (0.051 g, 0.393 mmol) in a similar manner as described for preparation of **30a**. After cooling to room temperature, the reaction mixture diluted with water (10ml) and extracted with ethyl acetate (2 x 10ml). The combined organic extracts were dried over Na₂SO₄ and the solvent removed under reduced pressure to provide an off white solid. The obtained solid was slurried with methanol (3 ml), filtered, washed with methanol and dried under vacuum to afford pure **30w** as a white solid (0.063 g, 0.162 mmol, 41%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.95 (d, *J* = 8.4 Hz, 1H), 8.77 (d, *J* = 8.2 Hz, 1H), 8.25 (d, *J* = 5.7 Hz, 1H), 8.10 (d, *J* = 3.7 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 8.1 Hz, 1H), 7.06 (d, *J* = 3.6 Hz, 1H), 7.02 – 6.98 (m, 2H), 6.93 (d, *J* = 5.7 Hz, 1H), 6.90 (s, 1H), 6.79 (m, 1H), 5.16 (quin, *J* = 7.5 Hz, 1H), 3.71 (s, 3H), 1.46 (d, *J* = 7.0 Hz, 2H). HPLC purity 98.33% {*t*_R = 6.750 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):50/50)}; HRMS (ESI +ve) *m/z* calculated for C₂₂H₂₂N₅O₂ (M + H)⁺ 388.1768, found 388.1769.

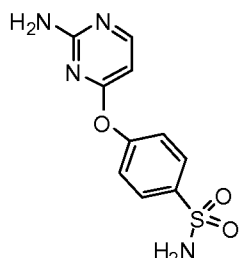


(S)-1-(2-aminopyrimidin-4-yl)-N-(1-(3-methoxyphenyl)ethyl)-1H-indole-4-

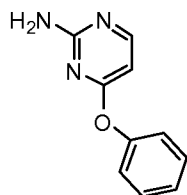
carboxamide (30z) This was prepared from **29n** (0.151 g, 0.513 mmol) and 2-amino-4-chloropyrimidine (0.058 g, 0.447 mmol) in a similar manner as described for preparation of **30a**. After cooling to room temperature, the reaction mixture diluted with water (10ml) and extracted with ethyl acetate (2 x 10ml). The combined organic extracts were dried over Na₂SO₄ and the solvent removed under reduced pressure to provide an off white solid. The obtained solid was slurried with methanol (3 ml), filtered, washed with methanol and dried under vacuum to afford pure **30z** as a white solid (0.087 g, 0.224 mmol, 50%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.96 (d, *J* = 8.5 Hz, 1H), 8.79 (d, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 8.11 (d, *J* = 3.8 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.25-7.21 (m, 1H), 7.06 (d, *J* = 3.8 Hz, 1H), 7.01 – 6.97 (m, 2H), 6.94 (d, *J* = 5.7 Hz, 1H), 6.92 (s, 2H), 6.82–6.76 (m, 1H), 5.34 – 5.08 (m, 1H), 3.72 (s, 3H), 1.46 (d, *J* = 7.0 Hz, 3H). HPLC purity 97.92% {*t*_R = 6.700 min, Flow 1ml/min, [(MeOH/(0.1% TFA in H₂O):50/50]}; HRMS (ESI +ve) *m/z* calculated for C₂₂H₂₂N₅O₂ (M + H)⁺ 388.1768, found 388.1765.



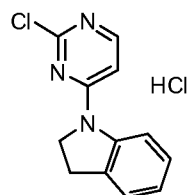
4-(2-aminopyrimidin-4-yloxy)benzamide (10c). A mixture of 2-amino-4-chloropyrimidine (0.092g, 0.715mmol), 4-hydroxybenzamide (0.108g, 0.787 mmol) in water (2.5 ml) was stirred in a Biotage microwave reactor for 10 min at 165 °C in presence of aq. KOH (2M, 0.392 ml). After cooling to room temperature, the precipitate was filtered, washed with cold water, and dried under vacuum. Pure **10c** (0.062 g, 0.269 mmol, 38%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.11 (d, *J* = 5.5 Hz, 1H), 7.97 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.36 (s, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.64 (s, 2H), 6.15 (d, *J* = 5.5 Hz, 1H). HRMS (ESI+ve) calculated for C₁₁H₁₁N₄O₂ (M+H)⁺ 231.0876, found 231.0877.



4-(2-aminopyrimidin-4-yloxy)benzenesulfonamide (10b). This was obtained from 2-amino-4-chloropyrimidine (0.069g, 0.535mmol), 4-hydroxybenzenesulfonamide (0.102g, 0.588 mmol), in a similar manner as described for **10c**. After cooling to room temperature, the solid precipitate was filtered, washed with water, further slurried with a solution methanol/water (50/50), filtered and dried under vacuum (0.018g). The methanolic solution was concentrated to dryness. The obtained solid was slurried with water filtered and dried under vacuum (0.025 g). The two batches were combined to provide pure **10b** (0.043g, 0.141mmol, 30%) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.11 (d, *J* = 6.3 Hz, 1H), 7.95 (d, *J* = 8.9 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 2H), 6.26 (d, *J* = 5.1 Hz, 1H), HRMS (ESI+ve) calculated for C₁₁H₁₁N₄O₂S (M+H)⁺ 267.0546, found 267.0550

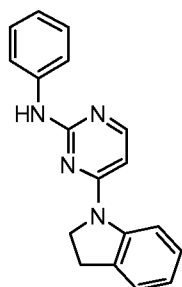


4-phenoxy pyrimidin-2-amine (10a). This was obtained from 2-amino-4-chloropyrimidine (0.161g, 1.71mmol), phenol (0.201g, 1.55 mmol), in a similar manner as described for **10c**. After cooling to room temperature, the precipitate was filtered, washed with cold water, further slurried with a solution methanol/ether (50/50), filtered and dried under vacuum. Pure **10a** (0.136 g, 0.724 mmol, 47%) as an a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.08 (d, 1H, *J* = 5.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.60 (s, 2H), 6.06 (d, *J* = 5.6 Hz, 1H). HRMS (ESI+ve) calculated for C₁₀H₁₀N₃O (M+H)⁺ 188.0818, found 188.0839

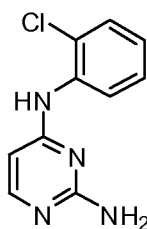


1-(2-chloropyrimidin-4-yl)indoline hydrochloride (32). A mixture of 2,4-dichloropyrimidine (0.165g, 1.10mmol), indoline (0.131g, 1.10mmol) in aq. HCl (0.1M, 3ml) was stirred in a Biotage microwave reactor for 30min at 100 °C. After cooling to room temperature, the precipitate was filtered, washed with water, ether, and dried under vacuum. The obtained solid was slurried with methanol, filtered and dried under vacuum (0.029g). The methanolic solution was concentrated to dryness. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **32** (0.055 g). The two batches were combined to afford pure **32** (0.085g, 0.313mmol, 28%) as an off

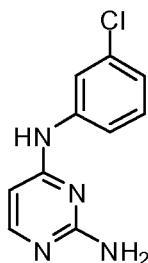
white solid ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.29 (d, J = 6.7 Hz, 1H), 8.26 (d, J = 7.3 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.23 (t, J = 8.1 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 6.0 Hz, 1H), 4.05 (t, J = 8.5 Hz, 2H), 3.21 (t, J = 8.5 Hz, 2H), HRMS (ESI+ve) calculated for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{Cl}$ ($\text{M}+\text{H}$) $^+$ 232.0636, found 232.0645



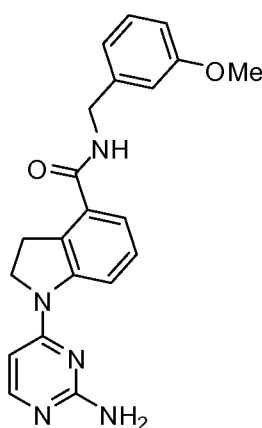
4-(indolin-1-yl)-N-phenylpyrimidin-2-amine (33). A mixture of **32** (0.044g, 0.164mmol), aniline (0.015g, 0.164mmol) in aq. HCl (0.1M, 0.7ml) was stirred in a Biotage microwave reactor for 15min at 160 °C. After cooling to room temperature, DIPEA (1.5ml) was added. The solvent was removed under reduced pressure. The obtained solid was slurried with water, filtered, dried under vacuum, washed with a solution hexane/DCM (11/2), dried under vacuum. Pure **33** (0.027g, 0.093mmol, 57%) was obtained as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.22 (s, 1H), 8.44 (d, J = 8.9 Hz, 1H), 8.14 (d, J = 5.9 Hz, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.26 (t, J = 7.8 Hz, 2H), 7.21 (d, J = 6.8 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.94-6.89 (m, 2H), 6.27 (d, J = 5.9 Hz, 1H), 4.01 (t, J = 8.6 Hz, 2H), 3.18 (t, J = 8. Hz, 2H), HRMS (ESI+ve) calculated for $\text{C}_{18}\text{H}_{17}\text{N}_4$ ($\text{M}+\text{H}$) $^+$ 289.1447, found 289.1449.



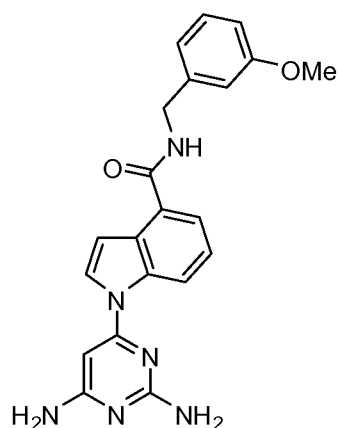
N4-(2-chlorophenyl)pyrimidine-2,4-diamine (1bi). A mixture of 2-amino-4-chloropyrimidine (0.460g, 3.55 mmol), 2-chloroaniline (0.544g, 4.26 mmol) EtOH (3.5 ml) was stirred in a Biotage microwave reactor for 20 min at 150 °C. After cooling to room temperature, the solvent was removed under reduced pressure and the crude material was diluted with MeOH (10 mL), followed by the addition of Et_3N (1.5 ml). The solvent was then removed under reduced pressure. Water (10 mL) was added and the solid precipitated was filtered, washed with water (10 mL), dried under vacuum to provide **1bi** (0.640 g, 2.89 mmol, 82%) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.51 (s, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 5.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.10 (t, J = 7.7 Hz, 1H), 6.12 (s, 2H), 6.03 (d, J = 5.7 Hz, 1H).; HPLC: Purity 98.37 %, MeOH 40%, (0.1% TFA in H_2O) 60%, 20 min, Flow 1ml/min: R_t 4.467 min. HRMS (ESI+ve) calculated for $\text{C}_{10}\text{H}_{10}\text{N}_4$ ($\text{M}+\text{H}$) $^+$ 221.0588, found 221.0587.



N4-(3-chlorophenyl)pyrimidine-2,4-diamine (1bj). This was obtained from 2-amino-4-chloropyrimidine (0.495g, 3.82 mmol), 3-chloroaniline (0.625g, 3.82 mmol), in a similar manner as described for **1bi**. After cooling to room temperature, the solvent was removed under reduced pressure and the obtained solid was triturated with AcOEt (15 mL), filtered, washed with AcOEt (5 mL x 2), dried, suspended in a saturated solution of aq. sat. NaHCO₃ (15 mL). The mixture was sonicated at room temperature, filtered, washed with aq. sat. NaHCO₃ (15 mL), water (10 mL), dried under vacuum to provide **1bj** (0.692 g, 3.13 mmol, 82%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.28 (s, 1H), 7.90 (t, *J* = 2.0 Hz, 1H), 7.82 (d, *J* = 5.7 Hz, 1H), 7.61 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.25 (t, *J* = 8.1 Hz, 1H), 6.95 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.30 (s, 2H), 5.98 (d, *J* = 5.6 Hz, 1H). HPLC: Purity 98.84 %, MeOH 50%, (0.1% TFA in H₂O) 50%, 20 min, Flow 1ml/min: R_t 4.347 min. HRMS (ESI-ve) calculated for C₁₀H₁₀N₄ (M+H)⁺ 221.0588, found 221.0587.

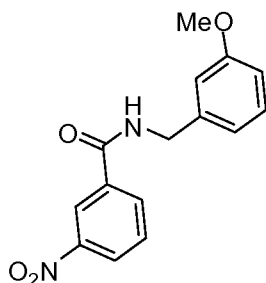


1-(2-aminopyrimidin-4-yl)-N-(3-methoxybenzyl)indoline-4-carboxamide (13r) A mixture of 2-amino-4-chloropyrimidine (0.033 g, 0.254 mmol), **12f** (0.115 g, 0.403 mmol) in EtOH (0.7 ml) was stirred in a Biotage microwave reactor for 30 min at 120 °C. After cooling to room temperature, the solvent was removed under reduced pressure. Acetone was added and the solid precipitated was filtered, washed with acetone (3 ml x 2), hexane (3 ml x 2), dried under vacuum. The obtained solid was then suspended in an aq. sat. solution of NaHCO₃ (3 ml). The solid precipitate was filtered, washed with water (3ml x 2), acetone (1.5 ml x 2), hexane (5 ml x 2), dried under vacuum to provide **13r** (0.054 g, 0.143 mmol, 56%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.83 (t, *J* = 6.0 Hz, 1H), 8.68 (quin, *J* = 3.9 Hz, 1H), 7.95 (d, *J* = 5.8 Hz, 1H), 7.25-7.20 (m, 3H), 6.89-6.87 (m, 2H), 6.80-6.78 (m, 1H), 6.37 (s, 2H), 6.00 (d, *J* = 5.9 Hz, 1H), 4.41 (d, *J* = 6.0 Hz, 2H), 3.94 (t, *J* = 8.7 Hz, 2H), 3.72 (s, 2H), 3.36 (t, *J* = 8.7 Hz, 2H). HRMS (ESI-ve) calculated for C₂₁H₂₂N₅O₂ (M+H)⁺ 376.1768, found 376.1765.

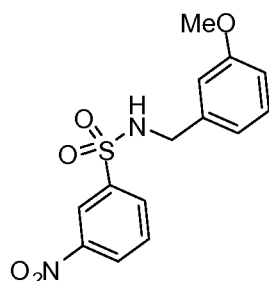


1-(2,6-diaminopyrimidin-4-yl)-N-(3-methoxybenzyl)-1H-indole-4-carboxamide (38)

This was prepared from **29a** (0.171 g, 0.610 mmol) and 6-chloropyrimidine-2,4-diamine (0.070 g, 0.484 mmol) in a similar manner as described for preparation of **30a**. After cooling to room temperature, the solvent was removed under reduced pressure. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **38** as an off white solid. The obtained solid was slurried with ether, filtered, and dried *in vacuo*. Pure **38** was obtained (0.008g, 0.020 mmol, 4 %) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.92 (t, *J* = 6.1 Hz, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 3.5 Hz, 1H), 7.56 (d, *J* = 7.1 Hz, 1H), 7.29-7.21 (m, 2H), 7.07 (d, *J* = 3.6 Hz, 1H), 6.92 – 6.91 (m, 2H), 6.83 – 6.78 (m, 1H), 6.45 (s, 2H), 6.24 (s, 2H), 5.92 (s, 1H), 4.47 (d, *J* = 6.1 Hz, 2H), 3.72 (s, 2H).

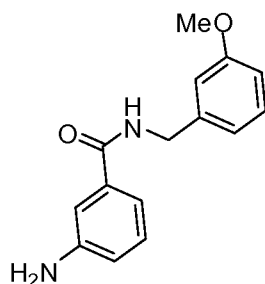


3-Nitro-N-(3-methoxybenzyl)benzamide (41). A solution of 3-nitrobenzoyl chloride (2.27 g, 12.238 mmol) and 3-methoxybenzylamine (2.015 g, 14.686 mmol) in anhydrous DCM (12 mL) was stirred at room temperature for 1 h in presence of Et₃N (1.9 mL). DCM (10 mL) was then added followed by aq. HCl (1M, 15 mL). The mixture was filtered. The filtrate was recovered, the organic phase separated, washed with aq. sat NaHCO₃, water, dried (Na₂SO₄), filtered and the solvent removed under reduced pressure to provide a white solid (3.443 g, 12.026 mmol, 98%). The crude material was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.40 (s, 1H), 8.71 (d, *J* = 1.6 Hz, 1H), 8.37 (d, *J* = 8.1 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 7.78 (t, *J* = 8.9 Hz, 1H), 7.23 (t, *J* = 7.0 Hz, 1H), 6.88 – 6.76 (m, 3H), 4.47 (d, *J* = 5.7 Hz, 2H), 3.72 (s, 3H).

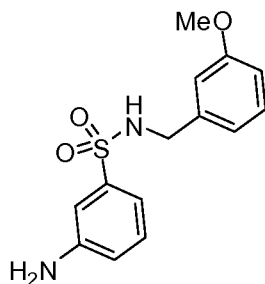


N-(3-methoxybenzyl)-3-nitrobenzenesulfonamide

This was obtained from 3-nitrosulfonyl chloride (2.207 g, 9.958 mmol) and 3-methoxybenzylamine (1.639 g, 11.950 mmol) in a similar manner as described for preparation of **41**. Chromatography on silica gel using the FlashMaster 3 purification station (AcOEt/Hexane) afforded **44** (0.770 g, 2.39 mmol, 24%) as a yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 8.52 (t, *J* = 6.3 Hz, 1H), 8.38 – 8.30 (m, 2H), 8.10 (d, *J* = 7.7 Hz, 1H), 7.78 (t, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 6.75 – 6.52 (m, 3H), 4.05 (d, *J* = 6.3 Hz, 2H), 3.62 (s, 3H). HRMS (ESI +ve) *m/z* calculated for C₁₄H₁₄N₂O₅SNa (M + Na)⁺ 345.0515, found 345.0522.



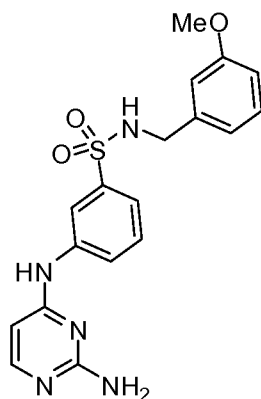
3-amino-N-(3-methoxybenzyl)benzamide 42. A solution of **41** (0.300 g, 1.048 mmol) in AcOEt (4 mL) was refluxed for 3 h in presence of SnCl₂·H₂O (1.182 g, 5.240 mmol). After cooling to room temperature, AcOEt and aq. sat NaHCO₃ were added. The mixture was filtered. The filtrate was collected, the organic phase separated, dried (Na₂SO₄) and the solvent removed under reduced pressure to provide a brown oil (0.233 g, 0.917 mmol, 88%). The crude material was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.73 (t, *J* = 5.9 Hz, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.07 – 7.00 (m, 2H), 6.95 (d, *J* = 7.7 Hz, 1H), 6.83–6.82 (m, 2H), 6.77–6.75 (m, 1H), 6.65 (dd, *J* = 8.2, 1.6 Hz, 1H), 5.18 (s, 2H), 4.36 (d, *J* = 6.0 Hz, 2H), 3.69 (s, 3H).



3-amino-N-(3-methoxybenzyl)benzenesulfonamide (45). This was obtained as a yellow oil (0.204 g, 0.698 mmol, 75%) from **44** (0.300 g, 0.931 mmol) in a similar manner as described for preparation of **42**. The crude material was used in the next step without

further purification. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.86 (t, $J = 6.2$ Hz, 1H), 7.15-7.10 (m, 2H), 6.96 (s, 1H), 6.85 (d, $J = 7.6$ Hz, 1H), 6.80 – 6.62 (m, 4H), 5.49 (s, 2H), 3.85 (d, $J = 6.1$ Hz, 1H), 3.64 (s, 3H).

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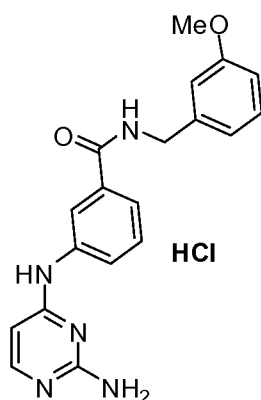


3-(2-aminopyrimidin-4-ylamino)-N-(3-methoxybenzyl)benzenesulfonamide (47) This was prepared from **45** (0.204 g, 0.698 mmol) and 2-amino-4-chloropyrimidine (0.091 g, 0.698 mmol) in a similar manner as described for preparation of **1ae**. After cooling to room temperature the solid precipitate was filtered, washed with methanol, and dried under vacuum. The obtained solid was dissolved in ethyl acetate the mixture was then washed with an aq. sat. solution of NaHCO_3 . The organic phase was separated, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. The obtained solid was slurried with methanol, filtered, dried under vacuum to provide pure **47** as a white solid (0.026 g, 0.063 mmol, 10%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.41 (s, 1H), 8.13 (s, 2H), 8.02 (d, $J = 7.8$ Hz, 1H), 7.83 (d, $J = 5.3$ Hz, 1H), 7.42 (t, $J = 7.8$ Hz, 1H), 7.31 (d, $J = 7.2$ Hz, 1H), 7.15 (t, $J = 7.6$ Hz, 1H), 6.81-6.73 (m, 3H), 6.25 (s, 2H), 6.00 (d, $J = 5.3$ Hz, 1H), 3.95 (d, $J = 5.6$ Hz, 3H), 3.65 (s, 3H). HPLC purity 98.01% ($t_R = 12.000$ min, Flow 1ml/min, [(MeOH/(0.1% TFA in H_2O):50/60)]; HRMS (ESI +ve) m/z calculated for $\text{C}_{18}\text{H}_{20}\text{N}_5\text{O}_3\text{S}$ ($\text{M} + \text{H}$) $^+$ 386.1281, found 386.1280.

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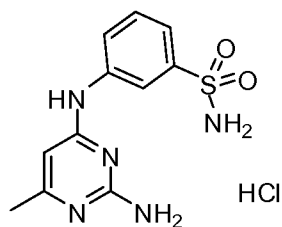


3-(2-aminopyrimidin-4-ylamino)-N-(3-methoxybenzyl)benzamide hydrochloride (46) This was prepared from **42** (0.233 g, 0.917 mmol) and 2-amino-4-chloropyrimidine (0.120 g, 0.917 mmol) in a similar manner as described for preparation of **1ae**. After cooling to room temperature, ethyl acetate was added and the solid precipitated was filtered, washed with water and dried under vacuum. Pure **46** was obtained as a white

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solid (0.134 g, 0.386 mmol, 42%). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 12.29 (s, 1H), 10.82 (s, 1H), 9.06 (t, $J = 5.2$ Hz, 1H), 8.07 (s, 2H), 7.98 (s, 1H), 7.84 (d, $J = 7.2$ Hz, 1H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.47 (t, $J = 7.9$ Hz, 2H), 7.22 (t, $J = 8.0$ Hz, 1H), 6.87-6.86 (m, 2H), 6.79 (d, $J = 8.7$ Hz, 1H), 6.34 (d, $J = 7.0$ Hz, 1H), 4.43 (d, $J = 5.9$ Hz, 2H), 3.70 (s, 3H). HPLC purity 99.32% ($t_R = 5.317$ min, Flow 1ml/min, [(MeOH)/(0.1% TFA in H_2O):50/50]); HRMS (ESI +ve) m/z calculated for $\text{C}_{19}\text{H}_{19}\text{N}_5\text{O}_3$ ($\text{M} + \text{H}$) $^+$ 350.16.11, found 350.1608

(6)



3-(2-amino-6-methylpyrimidin-4-ylamino)benzenesulfonamide hydrochloride (6). A mixture of 2-amino-6-methyl-4-chloropyrimidine (0.095 g, 0.660 mmol), and 4-aminobenzenesulfonamide (0.113 g, 0.660 mmol) in anhydrous ethanol (0.7 ml) was stirred in a Biotage microwave reactor for 15 min at 160 °C. After cooling to room temperature, the solid precipitate was filtered, slurried with methanol and dried under vacuum to afford **6** (0.033 g, 0.105 mmol, 16%) as an off-white solid. ^1H NMR (400 MHz, CD_3OD) δ 8.39 (s, 1H), 7.84 (s, 1H), 7.70 (d, $J = 8.2$ Hz, 1H), 7.55 (t, $J = 7.9$ Hz, 1H), 6.16 (s, 1H), 2.34 (s, 3H). HRMS (ESI+ve) calculated for $\text{C}_{11}\text{H}_{15}\text{N}_5\text{O}_2\text{S}$ ($\text{M} + \text{H} - \text{Cl}$) $^+$ 280.0862, found 280.0867.

All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims. In addition, any elements or limitations of any invention or embodiment thereof disclosed herein can be combined with any and/or all other elements or limitations (individually or in any combination) or any other invention or embodiment thereof disclosed herein, and all such combinations are contemplated with the scope of the invention without limitation thereto.

Example - Crystal structure of human Rock1 with RPM1510

To experimentally determine the mode of action of the aminopyrimidineindole containing ROCK1 inhibitor series, we co-crystallized **RPM1510** (also shown as compound 30b herein) with the kinase domain of human ROCK1 (residues 6-415). The ROCK1-**RPM1510** complex crystallized in space group C222₁ with two dimers per asymmetric unit. The structure was refined to 3.25 Å resolution with current R_{cryst} and R_{free} values of 22.5 % and 29.1 %, respectively (**Table 3**). The inhibitor binds to the ATP site of ROCK1 through hydrogen bonding interactions between the aminopyrimidine moiety and the main chain of residue Met156 of the hinge region (**Figure 6**). In addition, the amide functionality adjacent to the indole ring establishes a single hydrogen bond with Asp216 of the DFG motif. The *m*-methoxy-phenyl ring is sandwiched between the P-loop (Arg84–Gly88) of the upper N-terminal lobe and the side chain of the catalytic residue Lys105. RPM1510 is further stabilized through a series of van der Waals (hydrophobic) interactions with Gly88, Val90, Ala103, Lys105, Leu107, Met128, Met153, Leu205, Ala215, and Asp216.

Table 3. Summary of data collection and structure refinement

Structure	ROCK1-RPM1510
Data Collection	
Wavelength (Å)	1.54
Space group	C222 ₁
Unit cell dimensions (Å)	a=147.39
	b=153.27
	c=205.24
Resolution range	20-3.25 (3.3-3.25)
Unique reflections	36456 (1629)
Completeness (%)	98.7 (99.3)
I/σI	21.3 (3.9)
R _{merge} ^a (%)	7.8 (42.3)
Structure refinement	
Protein atoms	12888 (2 dimers)
Average B-factor (Å ²)	95
Ligand atoms	56
Average B-factor (Å ²)	98
Solvent molecules	14
Average B-factor (Å ²)	39
r.m.s.d. ^b bonds (Å)	0.011
r.m.s.d. angles (°)	1.4
R _{cryst} ^c (%)	22.5
R _{free} ^d (%)	29.1
R _{free} reflection set size	1094 (3.0 %)
Coordinate error (Å)	0.47

^a R_{merge} = quality of amplitudes (F) in the scaled data set (Diederichs & Karplus (1997), Nature Struct. Biol. 4, 269-275).

^b r.m.s.d. = root mean square deviation from ideal values.

^c R_{cryst} = 100 x Σ | F_{obs} - F_{model} | / F_{obs} where F_{obs} and F_{model} are observed and calculated structure factor amplitudes, respectively.

^d R_{free} is R_{cryst} calculated for randomly chosen unique reflections, which were excluded from the refinement.

MATERIALS AND METHODS

Reagents and compounds. Reagents and compounds were purchased from Sigma–Aldrich (St. Louis, MO) and Hampton Research unless otherwise indicated. The concentration of crystallization grade proteins was determined by A280 molar absorbance using a nanodrop ND-1000 spectrophotometer (Nanodrop Technologies).

Cloning and expression. The gene for human ROCK1 (comprising residues 6-415) was custom-synthesized, cloned into the pFB-Dual-PBL bacmid to provide an N-terminal His-Puritin-tag, and over-expressed in SF9 insect cells after 72 h infection (BlueSky, Worcester, MA).

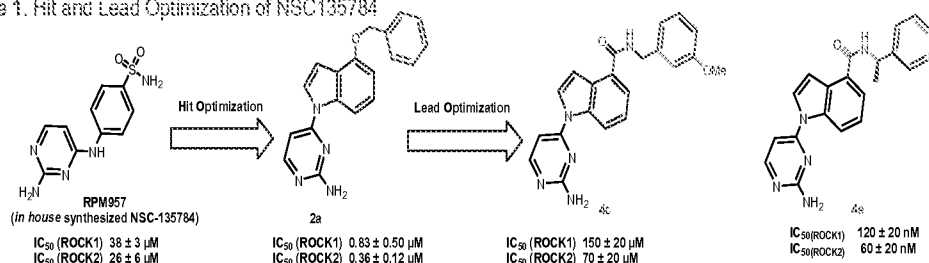
Enzyme purification. Harvested cells were resuspended in 100 mM Na/K phosphate buffer (pH 7.4) containing 300 mM NaCl, 10 mM MgCl₂, 10 mM imidazole, and 0.01 % Triton X-100 at 4 °C for 1 h. After sonication and centrifugation (1 h at 29000 x g), the supernatant was purified by Ni²⁺ affinity column chromatography (GE LifeSciences, Piscataway, NJ). Following incubation of peak fractions with TEV protease (20:1) at 4°C, the cleaved His-Puritin-tag was separated using a Superdex 75 26/60 column (GE LifeSciences), and eluted with 50 mM HEPES buffer (pH 7.4) containing 150 mM NaCl, 10 mM MgCl₂, and 1 mM DTT. Purified ROCK1 was exchanged into 50 mM HEPES buffer (pH 7.4) containing 1 mM DTT and concentrated to 20 mg mL⁻¹ prior to crystallization.

Protein crystallography. Crystallization was performed at 18 °C using the sitting drop vapor-diffusion method. Crystals of the ROCK1-RPM1510 complex were grown from 0.1 M HEPES (pH 7.4), 5% tacsimate (pH 7.0), and 10% PEG 5000 MME, in the presence of 1 mM inhibitor. Crystals were harvested in cryo-protectant mixture (reservoir solution including 25% (v/v) ethylene glycol and 1mM inhibitor) and a complete data set was recorded at -180 °C using CuK α radiation generated by a Rigaku Micro-Max 007-HF rotating anode (MSC, The Woodlands, TX) using a CCD Saturn 944+ in the Moffitt Structural Biology Core facility. Data were reduced with XDS (Kabsch, 1993), the structure was solved by molecular replacement using the MolRep program from CCP4 (Acta Crystallogr D Biol Crystallogr, 1994) with pdb 3TWJ as a starting model. PHENIX (Adams *et al.*, 2010) was employed for refinement, and model building was performed using Coot (Emsley *et al.*, 2004). Figures were prepared using PyMol (Schrödinger, LLC).

Introduction

Rho associated protein kinase (ROCK) is a Ser/Thr kinase, activated by small GTPases of the Rho family,¹ which phosphorylates signaling proteins involved with tumor cell invasion,^{2,3} angiogenesis,⁴ and migration.⁵ Although small molecule inhibition of Rho kinase is an established approach for the treatment of cardiovascular disease and CNS disorders, ROCK has only recently received attention for its role in cancer. ROCK activity affects the morphology, adhesion and invasion of cells, which are three important steps in the process of tumor growth and metastasis.⁶ Overexpression of Rho and ROCK has been reported in a number of cancers including bladder, ovarian, pancreatic, and testicular, implicating the possible benefits of ROCK inhibition.^{7,8} Our group focused on identification and optimization of ROCK1 inhibitors. Using *in vitro* assays, crystallography and molecular modeling we have developed a number of small molecules that inhibit ROCK1 activity at nanomolar concentrations.

Figure 1. Hit and Lead Optimization of NSC135784



Hit Optimization

We describe the identification of potent ROCK inhibitors from the NCI Diversity set.

- From initial screening, **NSC135784** (Figure 1) was found to inhibit ROCK1 enzymatic activity, IC₅₀ 92 ± 6 μM (FRET-based Z'-Lyte assay).^{9,10} *In house* synthesized analogs of **NSC135784** [**RPM957**] led to the identification of compound **2a** (ROCK1 IC₅₀ 0.83 ± 0.50 μM, ROCK2 IC₅₀ 0.36 ± 0.12 μM) as a promising scaffold for further development.

Lead Optimization

- In effort to optimize the potency and selectivity of **2a**, we identified a number of amide analogs, including **4c** and **4e** (Figure 1) as potent inhibitors of ROCK1 and ROCK2.
- SAR studies from the hit optimization process, crystallography and molecular modeling assisted in the development of the pyrimidine-indole analogs.

Library synthesis

- Libraries of compounds have been designed to aid the hit-to-lead process and probe structure activity relationships.
- Scheme 1 illustrates the synthetic routes followed for the synthesis of our molecular library.
- All compounds were first assessed for *in vitro* ROCK1 inhibition, using a Z'-Lyte kinase assay.^{9,10} Only selected compounds were then screened for activity against the ROCK2 isoform.
- 4c** and ROCK1 were co-crystallized (Figure 4) to aid in the development of more potent ROCK inhibitors.

Scheme 1. Synthesis of Library 1

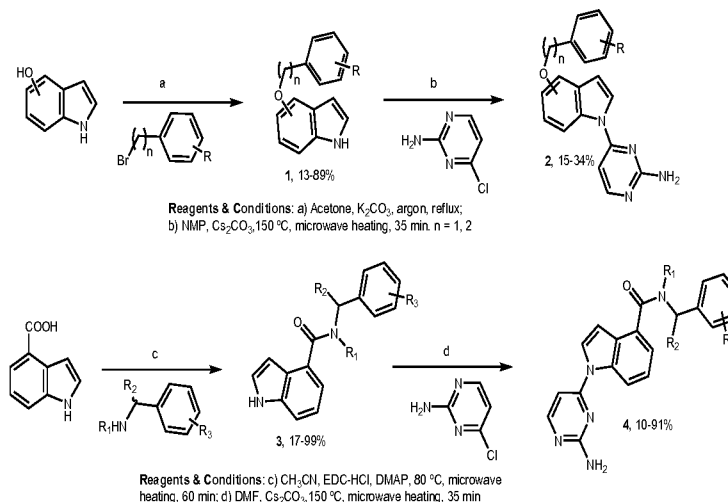
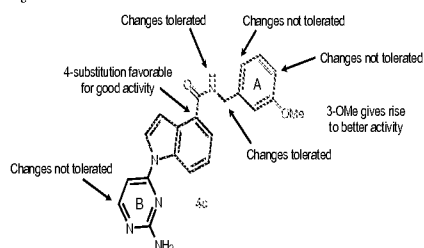


Figure 3. In vitro SAR around scaffold of 4c



Results and Discussion

- Hit to Lead Optimization of **NSC135784** and **2a** aided in the development of analogs containing the amide-linker, similar to **4c** and **4s**.
- Analogs of **2a**, **4c**, and **4s** were synthesized and evaluated for their inhibition of ROCK1 and ROCK2 enzymatic activity.
- Compound **4c** and **4s** displayed ROCK1 IC₅₀ values of 150 nM and 120 nM, respectively (Table 2).
- The ability ROCK1 and ROCK2 to discriminate between an enantiomeric pair of small molecules has been established (Table 2).
- Through initial hit and lead optimization we determined:
 - The indole scaffold acts as a spacer
 - Substitution on the indole's C4 position is optimal for ROCK inhibition
 - Meta substitution of the **A** ring is optimal for ROCK inhibition
 - (R) stereoisomer, **4s**, is preferred over the (S) stereoisomer, **4c**, in the amide linker

Crystallography

- X-Ray crystallography has provided new information regarding ROCK1 and **4c** binding.
 - Ring **A** is buried in a hydrophobic pocket created by the Glycine Rich Loop
 - Pyrimidine moiety **B** acts as the hinge binder
 - 3-OMe may be interacting with ROCK1 via hydrogen bonding
- Guided by the crystallography data, a new set of pyrimidine-indole analogs were created, **4h-s**, and will be tested.

Summary and Conclusions

- In search of novel ROCK1 selective inhibitors, **2a** was chosen as a starting point for the synthesis of a focused library of pyridines. Structure activity relationship studies led to the identification of potent in vitro inhibitors of ROCK1 and ROCK2, showing nanomolar potency, as exemplified by compound **4c** and **4s**. Crystallography has provided new information regarding molecular binding and orientation. These tools will be used to further develop potent ROCK inhibitors and elucidate the role of Rho kinase in cancer.

Acknowledgements

All the members of the Drug Discovery Department for help and cooperation, and the H. Lee Moffitt Cancer Center and Research Institute and NIH (U19CA67771-14) for funding, are gratefully acknowledged.

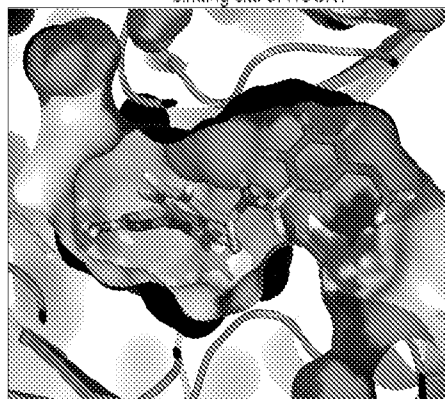
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Table 2. In vitro SAR of **4c** and analogs

Name	Entry	R ¹	R ²	R ³	ROCK1 IC ₅₀ (μM) ^a	ROCK2 IC ₅₀ (μM) ^a
RPM1418	4a	H	H	H	1.03±0.47	0.23±0.08
RPM1532	4b	H	H	<i>o</i> -OMe	5.99±1.98	1.80±0.68
RPM1510	4c	H	H	<i>m</i> -OMe	0.15±0.02	0.07±0.02
RPM1503	4d	H	H	<i>p</i> -OMe	-	-
RPM1533	4s	H	(R)-Me	H	0.12±0.02	0.06±0.02
RPM1536	4t	H	(S)-Me	H	3.43±0.44	1.20±0.32
BA1-081B	4h	H	H	<i>m</i> -NH ₂ SO ₂ CH ₃	To be tested	To be tested
BA1-085A	4i	H	(R)-Me	<i>m</i> -OMe	To be tested	To be tested
BA1-085B	4j	H	H	<i>m</i> -NHCOCH ₃	To be tested	To be tested
BA1-085D	4k	H	(R)-Et	H	To be tested	To be tested
BA1-085E	4l	H	(R)-CH ₂ OMe	H	To be tested	To be tested
BA1-090	4m	Me	H	<i>m</i> -OMe	To be tested	To be tested
BA1-093	4n	H	H	<i>m</i> -OH	To be tested	To be tested
BA1-109	4o	H	H	<i>m</i> -OCH ₂ CH ₂ OCH ₃	To be tested	To be tested
BA1-110	4p	H	H	<i>m</i> -OEt	To be tested	To be tested
BA1-114	4q	H	H	<i>o</i> -Ph	To be tested	To be tested
BA1-116A	4r	H	H	<i>m</i> -NCH ₃ COCH ₃	To be tested	To be tested
BA1-116B	4s	H	H	<i>m</i> -pyrrolidin-2-one	To be tested	To be tested

Key: a) (FRET)-based Z'-Lyte assay. Y27632: positive control, 90% inhibition @ 2.5 μM

Figure 2. X-Ray Crystal structure of **4c** bound to the ATP binding site of ROCK1

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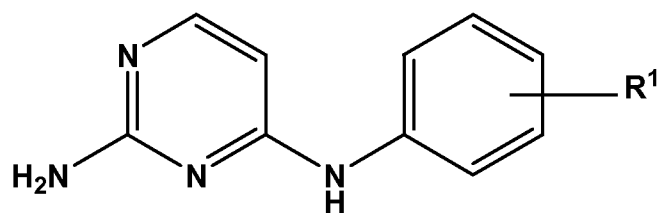
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CLAIMS

We claim:

1. A compound having the chemical structure shown in formula I:



formula I

wherein

R^1 is H, OH, S-alkyl, $SO_2NR^2R^3$, NO_2 , $CONH_2$, SO_2 -alkyl, $NHC(O)$ -alkyl, CO_2H , alkyl, cycloalkyl, alkoxy, cycloalkoxy, heterocycloalkyl, alkoxycarbonyl, heteroaryl, or aryl;

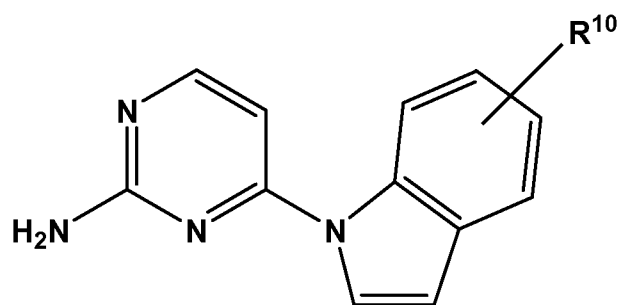
R^2 is H, CO, alkoxy, alkyl, aryl, heteroalkyl, heteroaryl, heterocycloalkyl, alkylcarbonyl, arylcarbonyl, or alkoxycarbonyl;

R^3 is H, CO, alkoxy, alkyl, aryl, heteroalkyl, heteroaryl, heterocycloalkyl, alkylcarbonyl, arylcarbonyl, or alkoxycarbonyl;

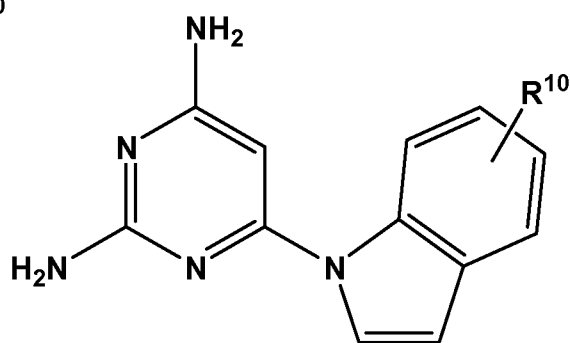
any of which of R^1 , R^2 , and R^3 can be optionally substituted with one or more of halogen, alkyl, alkoxy or aryl optionally substituted with alkoxy;

or a pharmaceutically acceptable salt or hydrate thereof; and said compound can comprise one or more R^1 .

2. A compound having the chemical structure shown in formula II:



formula IIa



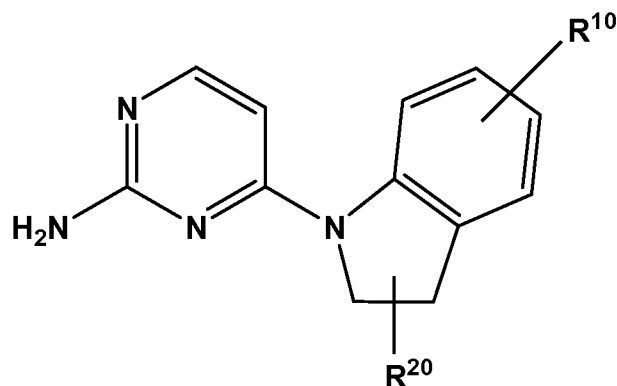
formula IIb

wherein

R^{10} is H, NO_2 , halogen, $-CH_3$, $-SO_2$ -alkyl, $-OCH_3$, alkoxy, $-C(O)NH$ -alkyl, $-C(O)NH$ -aryl, $-NHC(O)$ -alkyl, $-NHC(O)$ -aryl, or aryloxy, any of which can be substituted with one or more

of aryl or alkoxy, any of which can be optionally substituted with halogen, -OH, alkoxy, or aryl optionally substituted with alkoxy;
 or a pharmaceutically acceptable salt or hydrate thereof; and said compound can comprise one or more R^{10} .

3. A compound having the chemical structure shown in formula III:



formula III

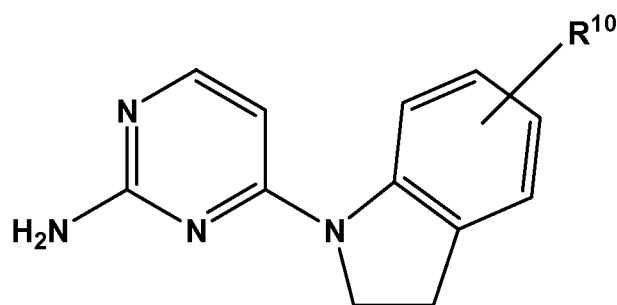
wherein

R^{10} is H, NO_2 , halogen, $-\text{CH}_3$, $-\text{SO}_2$ -alkyl, $-\text{OCH}_3$, alkoxy, $-\text{C}(\text{O})\text{NH}$ -alkyl, $-\text{C}(\text{O})\text{NH}$ -aryl, $-\text{NHC}(\text{O})$ -alkyl, $-\text{NHC}(\text{O})$ -aryl, or aryloxy, any of which can be substituted with one or more of aryl or alkoxy, any of which can be optionally substituted with halogen, -OH, alkoxy, or aryl optionally substituted with alkoxy;

R^{20} is $-\text{CH}_3$, $-\text{CO}_2\text{H}$, heteroalkyl, aryl, or alkyl;

or a pharmaceutically acceptable salt or hydrate thereof; and said compound can comprise one or more R^{10} and/or R^{20} .

4. A compound having the chemical structure shown in formula IV:



formula IV

wherein

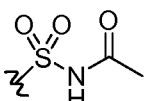
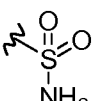
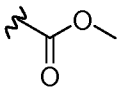
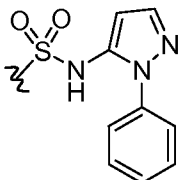
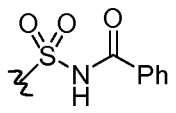
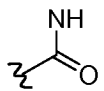
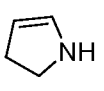
R^{10} is H, NO_2 , halogen, $-CH_3$, $-SO_2$ -alkyl, $-OCH_3$, alkoxy, $-C(O)NH$ -alkyl, $-C(O)NH$ -aryl, $-NHC(O)$ -alkyl, $-NHC(O)$ -aryl, or aryloxy, any of which can be substituted with one or more of aryl or alkoxy, any of which can be optionally substituted with halogen, $-OH$, alkoxy, or aryl optionally substituted with alkoxy;
 or a pharmaceutically acceptable salt or hydrate thereof;
 and said compound can comprise one or more R^{10} .

5. A composition comprising a compound of any of claims 1 to 4 or 8 to 10.

6. A method for treating a person or animal having a disorder or condition associated with aberrant or excessive ROCK activity or interaction in a cell or decreased apoptosis of a cell, or a disorder or condition associated with inhibition or downregulation of apoptosis of a cell, wherein the method comprises administering to the person or animal an effective amount of one or more compounds of any of claims 1 to 4 or 8 to 10, or a composition comprising said one or more compounds.

7. The method according to claim 6, wherein the disorder or condition is an oncological disorder or condition, or a cardiovascular-related disorder or condition, or a CNS disorder or condition.

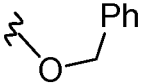
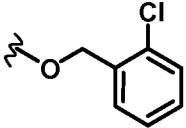
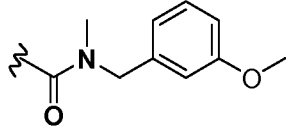
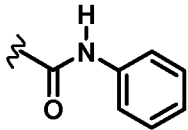
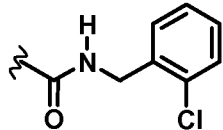
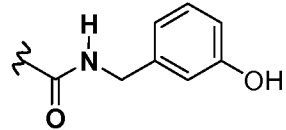
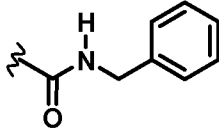
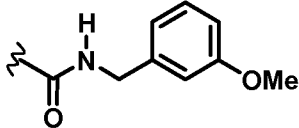
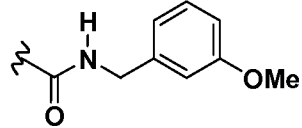
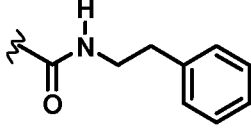
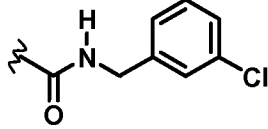
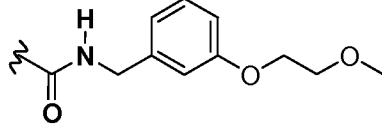
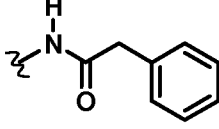
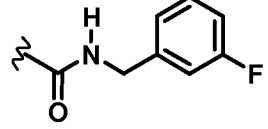
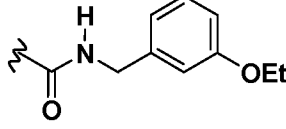
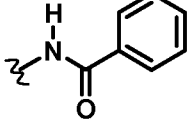
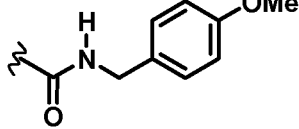
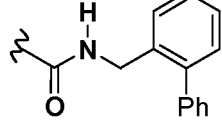
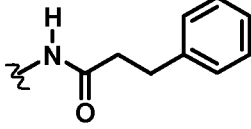
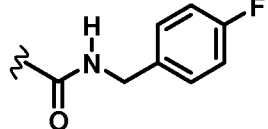
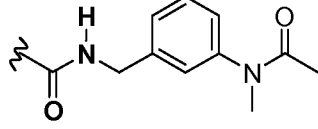
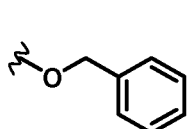
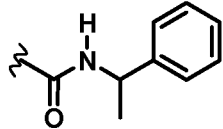
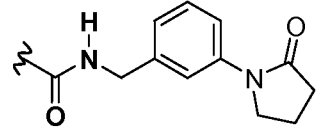
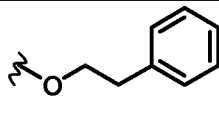
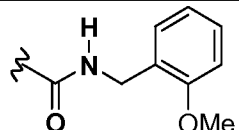
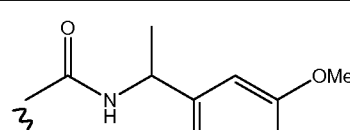
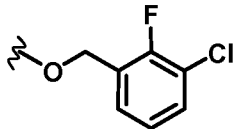
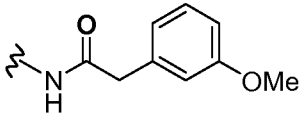
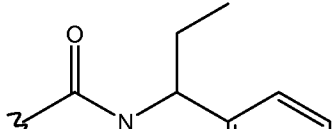
8. The compound according to claim 1, wherein R^1 is any of (ξ =point of attachment):

R^1 can be:	R^1 can be:	R^1 can be:	R^1 can be:
ξSO_2NH_2			
			

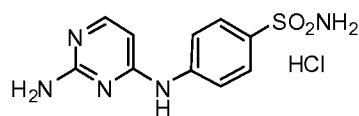
R ¹ can be:	R ¹ can be:	R ¹ can be:	R ¹ can be:
		ξOMe	

9. The compound according to any of claims 2-4, wherein R¹⁰ is any of (ξ =point of attachment):

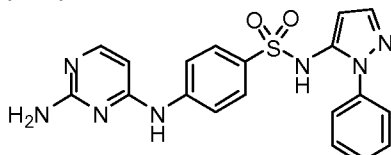
R ¹⁰ can be:	R ¹⁰ can be:	R ¹⁰ can be:
ξOMe		

R^{10} can be:	R^{10} can be:	R^{10} can be:
		
		
		
		
		
		
		
		
		
		

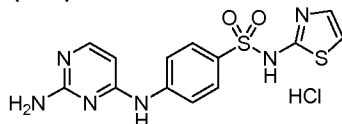
10. A compound having a chemical structure selected from:

(1aa) (in house NSC135784)

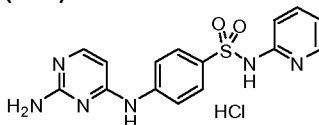
$C_{10}H_{12}ClN_5O_2S$; MW, 301.75

(1ab)

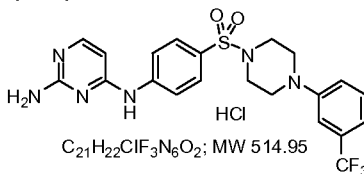
$C_{19}H_{17}N_7O_2S$; MW, 407.45

(1ac)

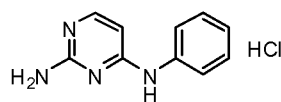
$C_{13}H_{13}ClN_6O_2S_2$; MW, 384.86

(1ad)

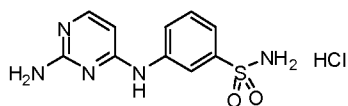
$C_{15}H_{15}ClN_6O_2S$; MW, 378.84

(1ae)

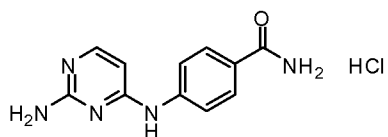
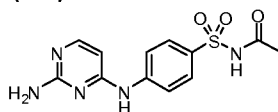
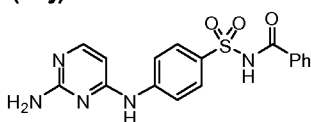
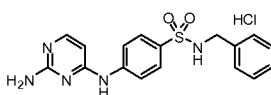
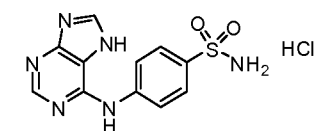
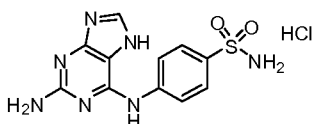
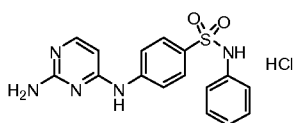
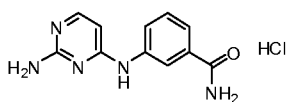
$C_{21}H_{22}ClF_3N_6O_2$; MW 514.95

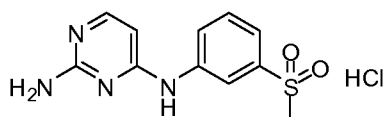
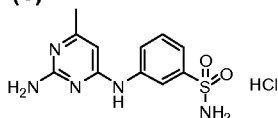
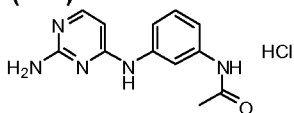
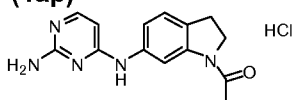
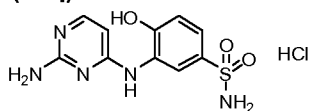
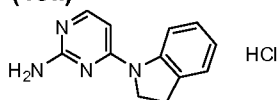
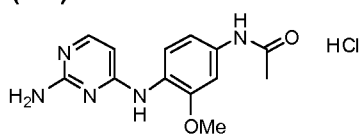
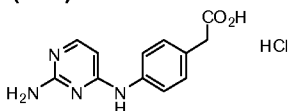
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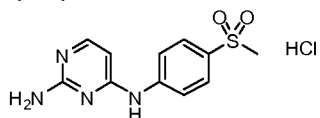
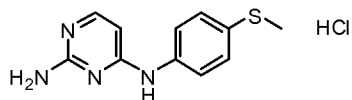
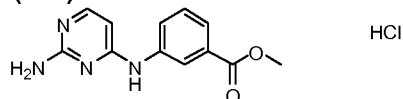
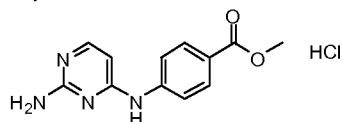
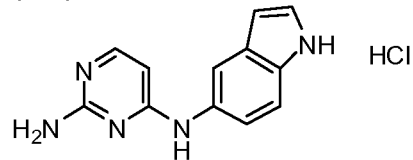
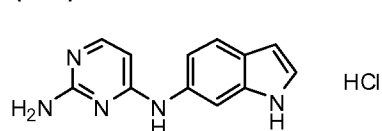
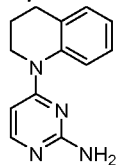
$C_{10}H_{11}ClN_4$; MW, 222.67

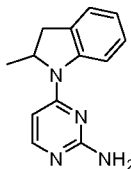
(1ag)

$C_{10}H_{12}ClN_5O_2S$; MW, 301.75

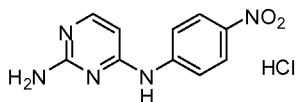
(1ah) $C_{11}H_{12}ClN_5O$; MW, 265.70**(1ai)** $C_{12}H_{13}N_5O_3S$; MW, 307.33**(1aj)** $C_{17}H_{15}N_5O_3S$; MW, 369.40**(1ak)** $C_{17}H_{18}ClN_5O_2S$; MW, 391.88**(8)** $C_{11}H_{11}ClN_6O_2S$; MW, 326.76**(7)** $C_{11}H_{12}ClN_7O_2S$; MW, 341.78**(1al)** $C_{16}H_{16}ClN_5O_2S$; MW, 377.85**(1am)** $C_{11}H_{12}ClN_5O$; MW, 265.70

(1an)C₁₁H₁₃ClN₄O₂S; MW, 300.76**(6)**C₁₁H₁₄ClN₅O₂S; MW, 315.78**(1ao)**C₁₂H₁₄ClN₅O; MW, 279.73**(1ap)**C₁₄H₁₆ClN₅O; MW, 305.76**(1aq)**C₁₀H₁₂ClN₅O₃S; MW, 317.75**(13a)**C₁₂H₁₃ClN₄; MW, 248.71**(1ar)**C₁₃H₁₆ClN₅O₂; MW, 309.75**(1as)**C₁₂H₁₃ClN₄O₂
MW, 280.71

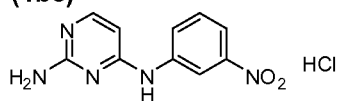
(1at)C₁₁H₁₃ClN₄O₂S; MW, 300.76**(1au)**C₁₁H₁₃ClN₄S; MW, 268.77**(1av)**C₁₂H₁₃ClN₄O₂; MW, 280.71**(1aw)**Chemical Formula: C₁₂H₁₃ClN₄O₂; MW, 280.71**(1az)**C₁₂H₁₂ClN₅; MW, 261.71**(1ba)**C₁₂H₁₂ClN₅; MW, 261.71**(16)**C₁₃H₁₄N₄; MW, 226.28

(13b)

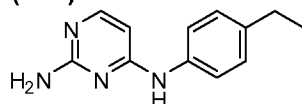
$C_{13}H_{14}N_4$; MW, 226.28

(1bb)

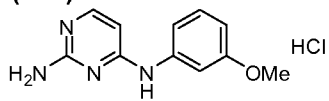
$C_{10}H_{10}ClN_5O_2$; MW, 267.67

(1bc)

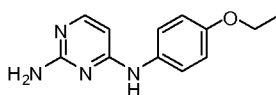
$C_{10}H_{10}ClN_5O_2$; MW, 267.67

(1bd)

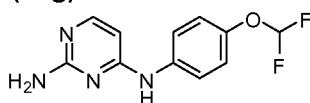
$C_{12}H_{14}N_4$; MW, 214.27

(1be)

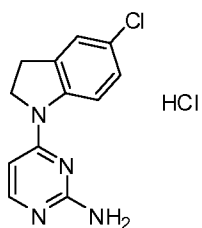
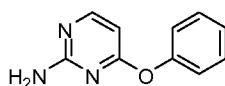
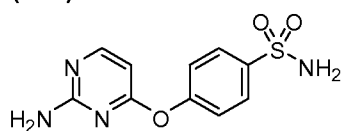
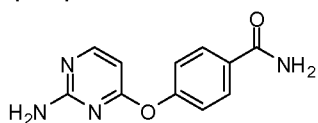
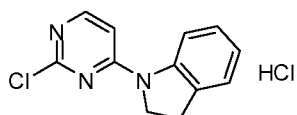
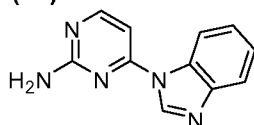
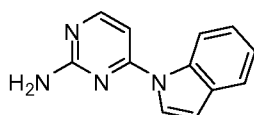
$C_{11}H_{13}ClN_4O$; MW, 252.70

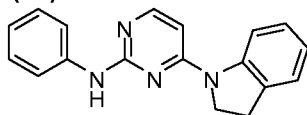
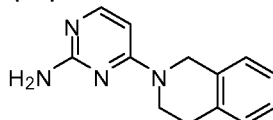
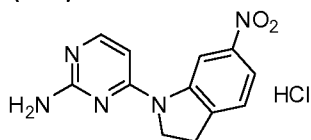
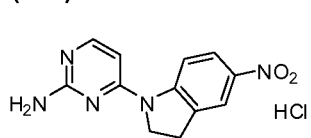
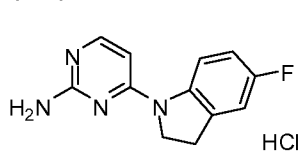
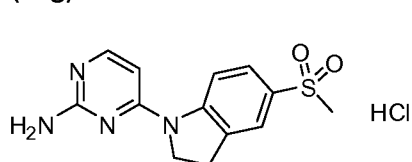
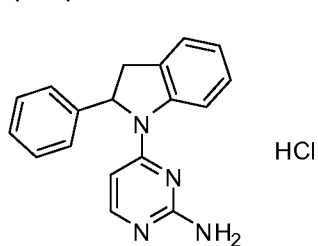
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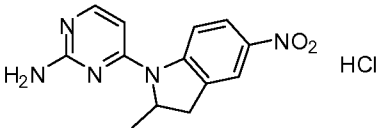
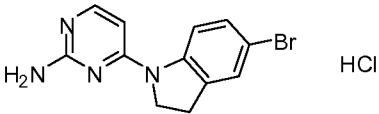
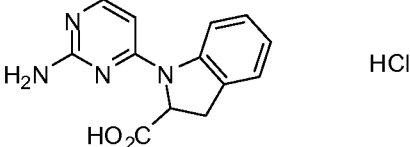
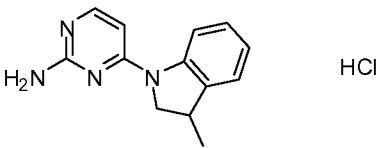
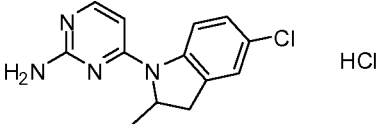
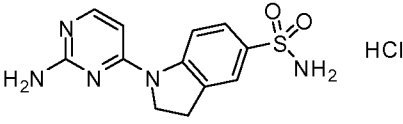
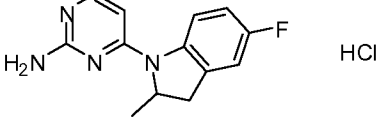
$C_{12}H_{14}N_4O$; MW, 230.27

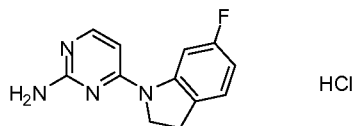
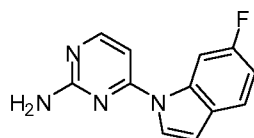
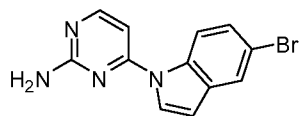
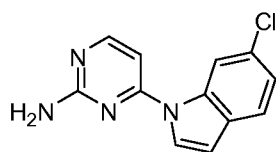
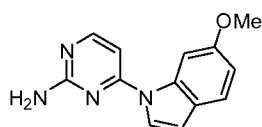
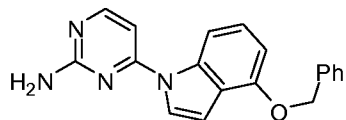
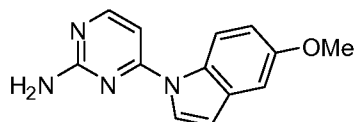
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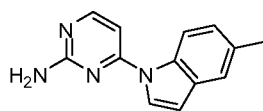
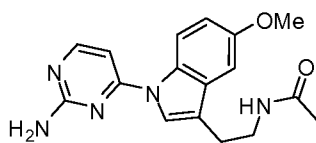
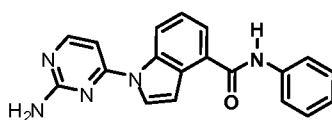
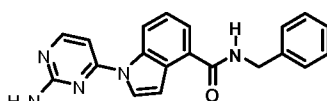
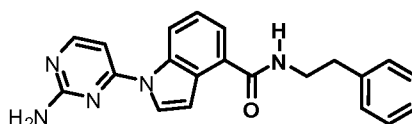
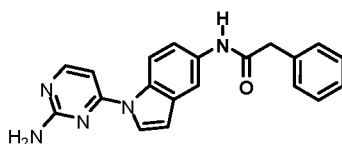
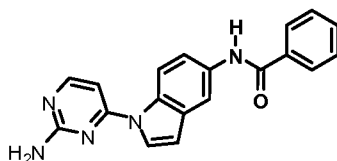
$C_{11}H_{10}F_2N_4O$; MW, 252.22

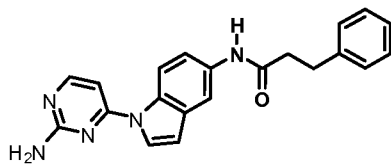
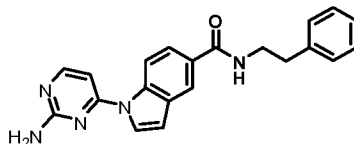
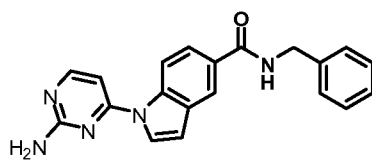
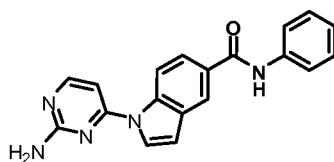
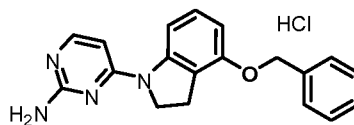
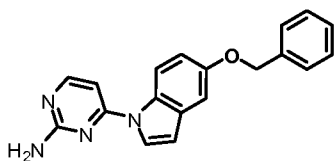
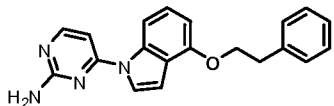
(13c) $\text{C}_{12}\text{H}_{12}\text{Cl}_2\text{N}_4$; MW, 283.16**(10a)** $\text{C}_{10}\text{H}_9\text{N}_3\text{O}$; MW, 187.20**(10b)** $\text{C}_{10}\text{H}_{10}\text{N}_4\text{O}_3\text{S}$; MW, 266.28**(10c)** $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_2$; MW, 230.22**(32)** $\text{C}_{12}\text{H}_{11}\text{Cl}_2\text{N}_3$; MW, 268.14**(18)** $\text{C}_{11}\text{H}_9\text{N}_5$; MW, 211.22**(15a)** $\text{C}_{12}\text{H}_{10}\text{N}_4$; MW, 210.23

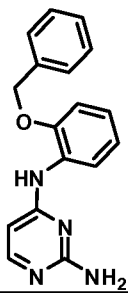
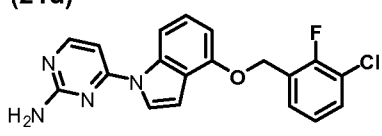
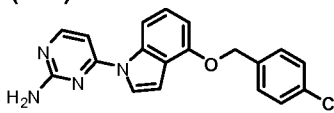
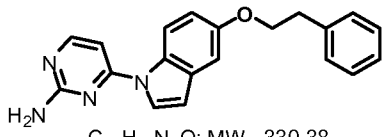
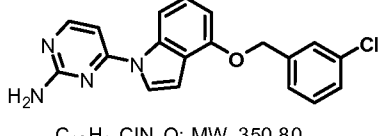
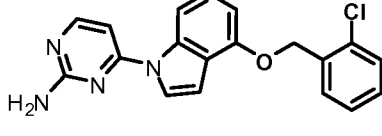
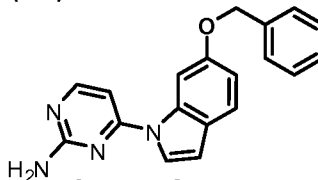
(33) $C_{18}H_{16}N_4$; MW, 288.35**(17)** $C_{13}H_{14}N_4$; MW, 226.28**(13d)** $C_{12}H_{12}ClN_5O_2$; MW, 293.71**(13e)** $C_{12}H_{12}ClN_5O_2$; MW, 293.71**(13f)** $C_{12}H_{12}ClFN_4$; MW, 266.70**(13g)** $C_{13}H_{15}ClN_4O_2S$; MW, 326.80**(13h)** $C_{18}H_{17}ClN_4$; MW, 324.81

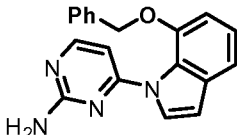
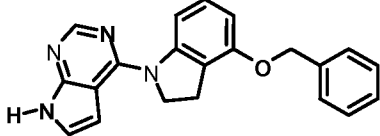
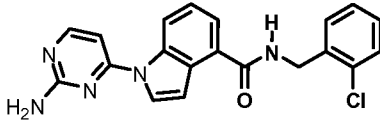
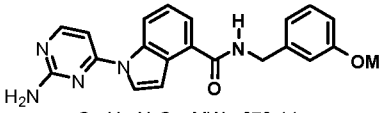
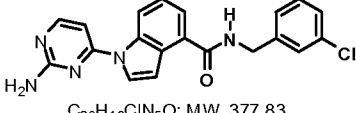
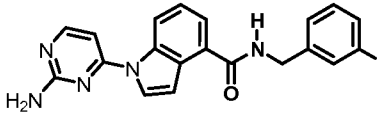
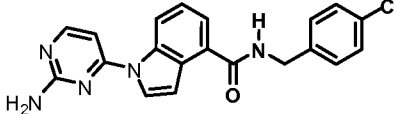
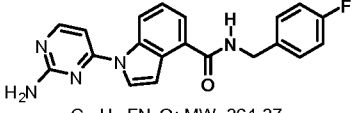
(13i)  $C_{13}H_{14}ClN_5O_2$; MW, 307.74
(13j)  $C_{12}H_{12}BrClN_4$; MW, 327.61
(13k)  $C_{13}H_{13}ClN_4O_2$; MW, 292.72
(13l)  $C_{13}H_{15}ClN_4$; MW, 262.74
(13m)  $C_{13}H_{14}Cl_2N_4$; MW, 297.18
(13n)  $C_{12}H_{14}ClN_5O_2S$; MW, 327.79
(13o)  $C_{13}H_{14}ClFN_4$; MW, 280.73

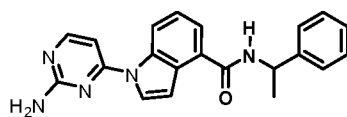
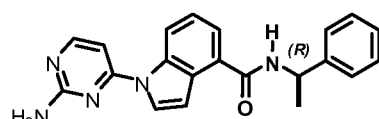
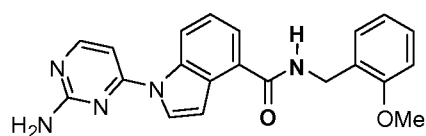
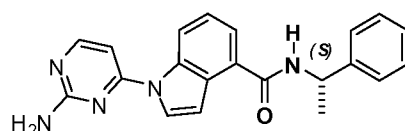
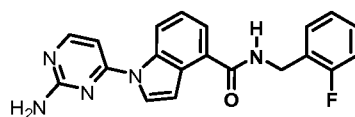
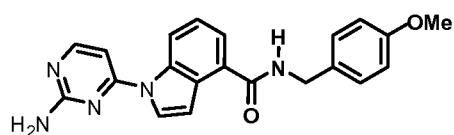
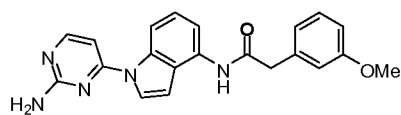
(13p) $C_{12}H_{12}ClFN_4$; MW, 266.70**(15b)** $C_{12}H_9FN_4$; MW, 228.23**(15c)** $C_{12}H_9BrN_4$; MW, 289.13**(15d)** $C_{12}H_9ClN_4$; MW, 244.68**(15e)** $C_{13}H_{12}N_4O$; MW, 240.26**(21a)** $C_{19}H_{16}N_4O$; MW, 316.36**(15f)** $C_{13}H_{12}N_4O$; MW, 240.26

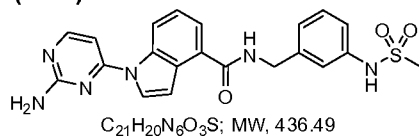
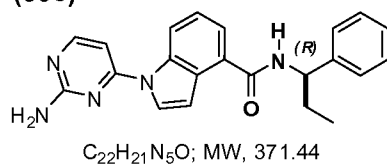
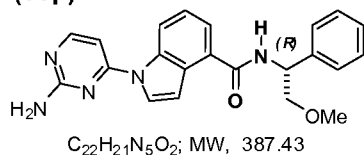
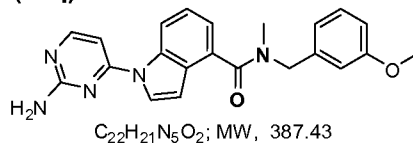
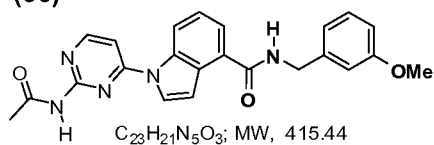
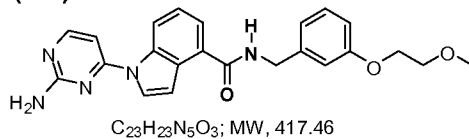
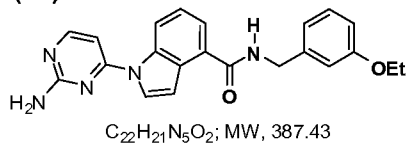
(15g) $C_{13}H_{12}N_4$; MW, 224.26**(15h)** $C_{17}H_{19}N_5O_2$; MW, 325.37**(24a)** $C_{19}H_{15}N_5O$; MW, 329.36**(24b)** $C_{20}H_{17}N_5O$; MW, 343.38**(24c)** $C_{21}H_{19}N_5O$; MW, 357.41**(27a)** $C_{20}H_{17}N_5O$; MW, 343.38**(27b)** $C_{19}H_{15}N_5O$; MW, 329.36

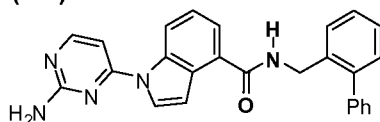
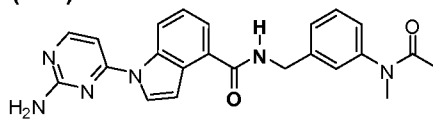
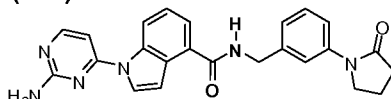
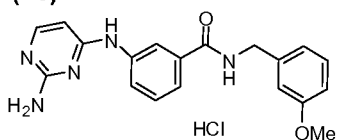
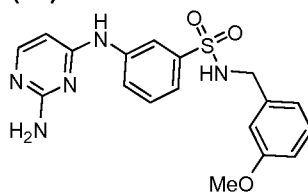
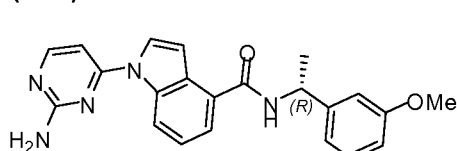
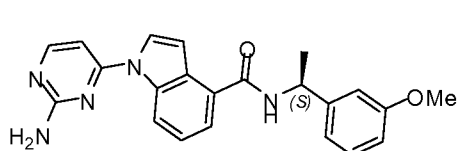
(27c) $C_{21}H_{19}N_5O$; MW, 357.41**(24d)** $C_{21}H_{19}N_5O$; MW, 357.41**(24e)** $C_{20}H_{17}N_5O$; MW, 343.38**(24f)** $C_{19}H_{15}N_5O$; MW, 329.36**(13q)** $C_{19}H_{19}ClN_4O$; MW, 354.83**(21b)** $C_{19}H_{16}N_4O$; MW, 316.36**(21c)** $C_{20}H_{18}N_4O$; MW, 330.38

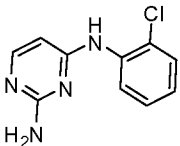
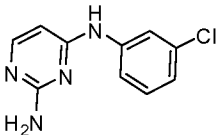
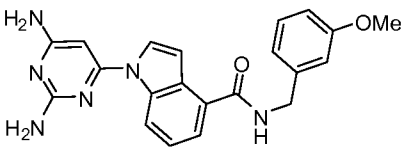
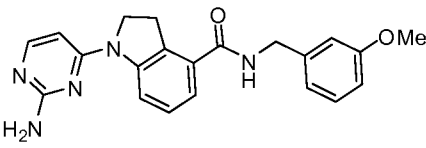
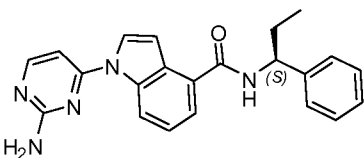
(1ah)  HCl
(21d)  $C_{19}H_{14}ClFN_4O$; MW, 368.79
(21e)  $C_{19}H_{15}ClN_4O$; MW, 350.80
(21f)  $C_{20}H_{18}N_4O$; MW, 330.38
(21g)  $C_{19}H_{15}ClN_4O$; MW, 350.80
(21h)  $C_{19}H_{15}ClN_4O$; MW, 350.80
(21i)  $C_{19}H_{16}N_4O$; MW, 316.36

(21j)  $C_{19}H_{16}N_4O$; MW, 316.36
(35)  $C_{21}H_{18}N_4O$; MW, 342.39
(30a)  $C_{20}H_{16}ClN_5O$; MW, 377.83
(30b)  $C_{21}H_{19}N_5O_2$; MW, 373.41
(30c)  $C_{20}H_{16}ClN_5O$; MW, 377.83
(30d)  $C_{20}H_{16}FN_5O$; MW, 361.37
(30e)  $C_{20}H_{16}ClN_5O$ MW = 377.8269
(30f)  $C_{20}H_{16}FN_5O$; MW, 361.37

(30g) $C_{21}H_{19}N_5O$; MW, 357.41**(30h)** $C_{21}H_{19}N_5O$; MW, 357.41**(30i)** $C_{21}H_{19}N_5O_2$; MW, 373.41**(30j)** $C_{21}H_{19}N_5O$; MW, 357.41**(30k)** $C_{20}H_{16}FN_5O$ MW 361.1339**(30l)** $C_{21}H_{19}N_5O_2$ MW 373.1539**(27d)** $C_{21}H_{19}N_5O_2$; MW, 373.41

(30m)**(30n)****(30o)****(30p)****(30q)****(36)****(30r)****(3s)**

(30t) $C_{26}H_{21}N_5O$; MW, 419.48**(30u)** $C_{23}H_{22}N_6O_2$; MW, 414.46**(30v)** $C_{24}H_{22}N_6O_2$; MW, 426.47**(46)** $C_{19}H_{20}ClN_5O_2$ M W: 385.8474**(47)** $C_{18}H_{19}N_5O_3S$ MW: 385.4402**(30w)** $C_{22}H_{21}N_5O_2$ MW 387.4344**(30z)** $C_{22}H_{21}N_5O_2$ MW 387.4344

(1bi)  $C_{10}H_9ClN_4$ MW: 220.6583
(1bj)  $C_{10}H_9ClN_4$ MW: 220.6583
(38)  Molecular Weight: 388.4225
(13r)  Molecular Weight: 375.4237
(30aa)  $C_{22}H_{21}N_5O$ MW 371.4350

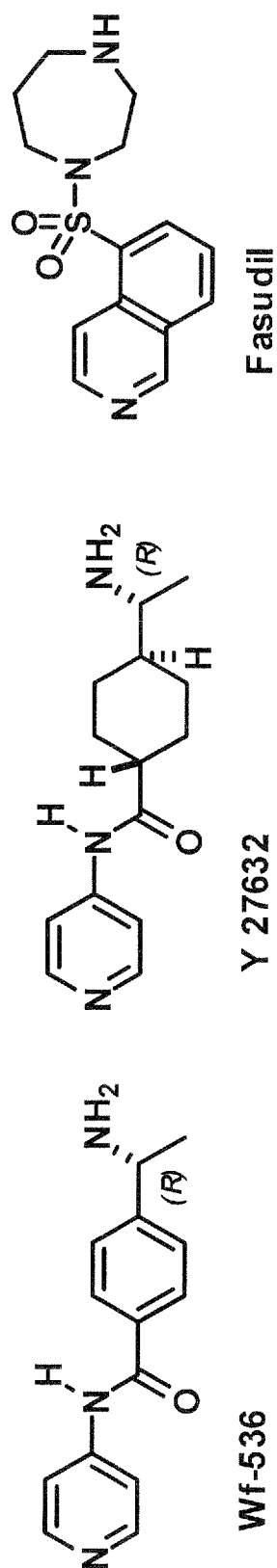
11. A method for inhibiting ROCK activity in a cell, comprising contacting the cell with an effective amount of one or more compounds of any of claims 1 to 4 or 8 to 10, or a composition comprising said one or more compounds.

12. The method according to claim 11, wherein said cell is a cancer or tumor cell.

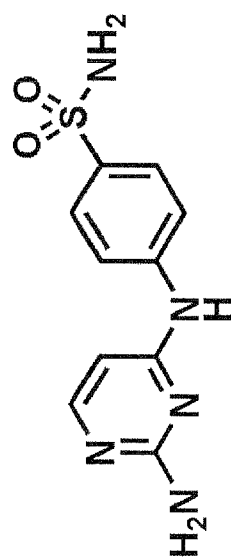
13. The method according to claims 6, 7, 11, or 12, wherein said compound is the compound designated as compound 30b or 30h.

14. The method according to claims 6, 7, 11, or 12, wherein said method further comprises use of a ROCK inhibitor selected from Y27632, Wf536, Fasudil, H-1152P, or CID5056270.

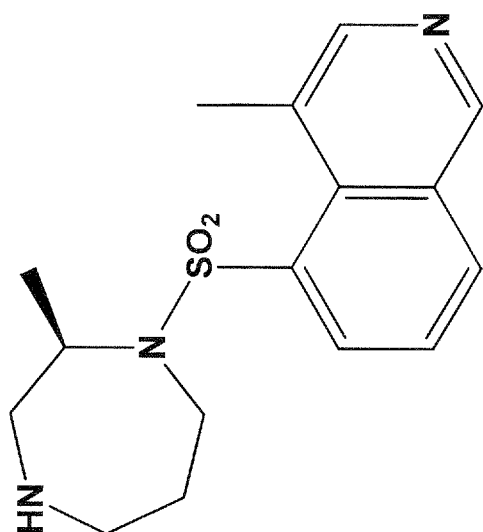
1/4

**FIG. 1**

NSC-135784
ROCK1 IC₅₀ = 92 ± 6 μM
1aa (in house **NSC-135784**)
ROCK1 IC₅₀ = 38 ± 3 μM
ROCK2 IC₅₀ = 25 ± 6 μM

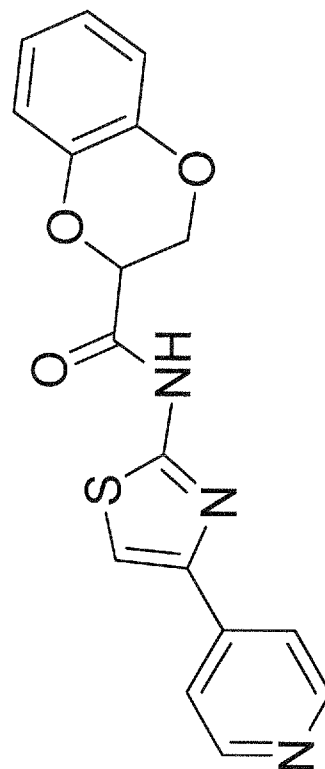
**FIG. 2**

2/4



H-1152P

FIG. 3



CID5056270

FIG. 4

Purpose: To validate ROCK inhibitor hits in whole cells- RPM957 series.

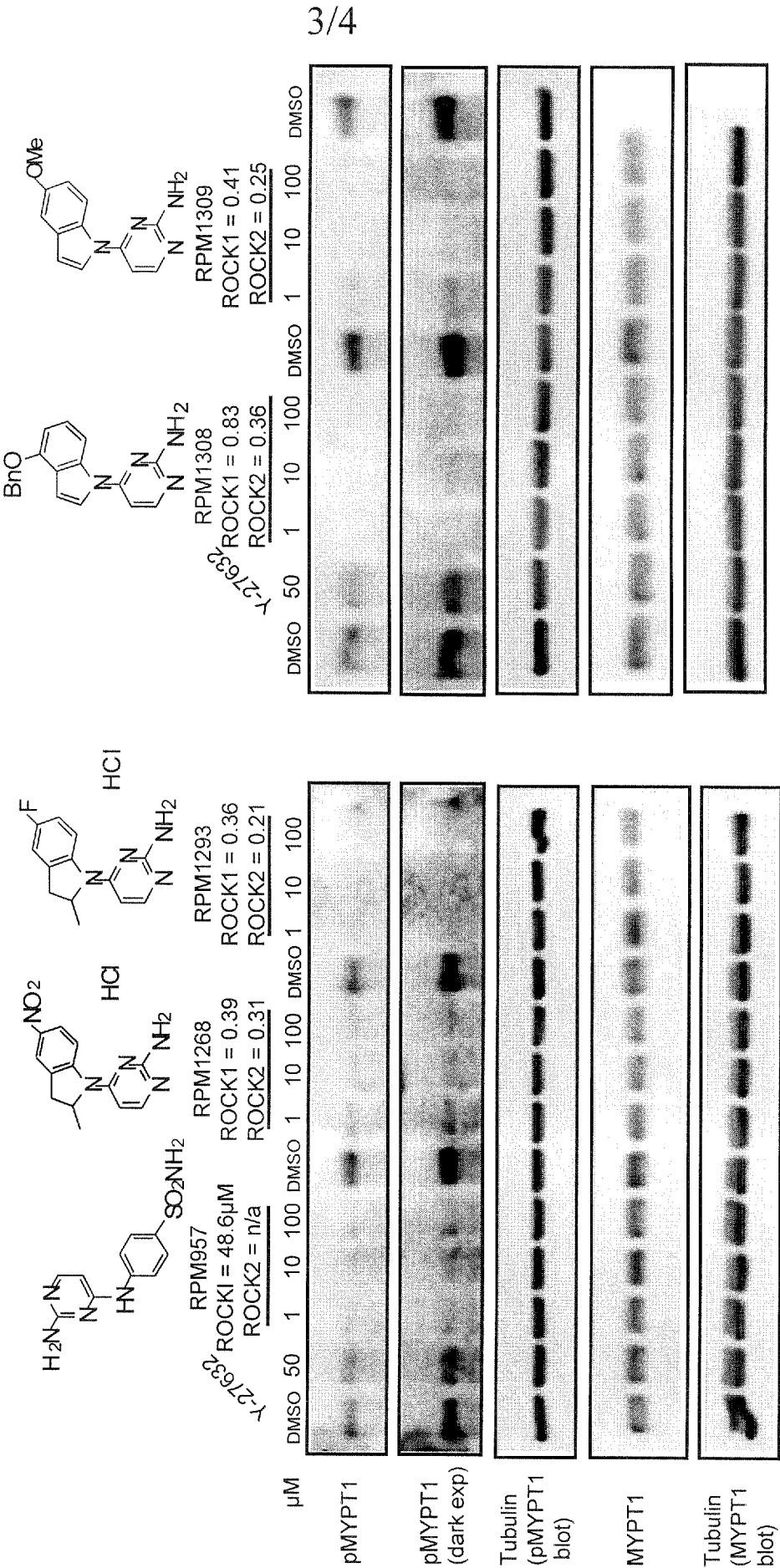


FIG. 5

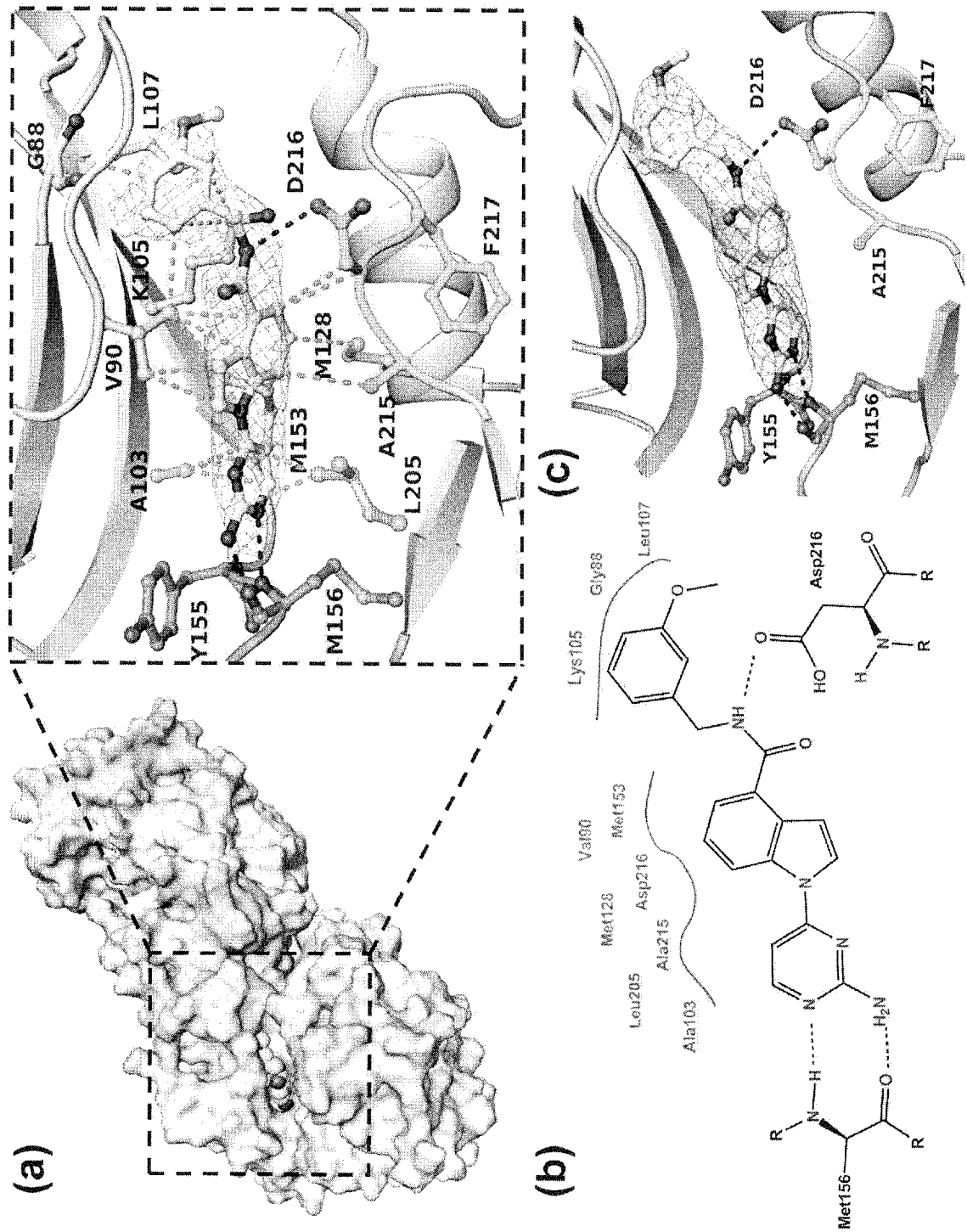


FIG. 6