

SUBSTITUTED CYCLIC COMPOUNDS AND METHODS OF TREATING PHENYLKETONURIA AND OTHER AMINO ACIDURIAS

TECHNICAL FIELD

5 The present disclosure relates generally compounds that may be used for the treatment of patients with phenylketonuria (PKU) and other amino acidurias, as well as methods of using the same.

BACKGROUND

10 Phenylalanine hydroxylase (PAH) is an enzyme that converts phenylalanine (Phe) consumed in food into tyrosine (Tyr) primarily in the liver. Loss of PAH function leads to toxic accumulation of Phe in the body, which is manifest by lower levels of Tyr and tryptophan and high levels of Phe (and Phe-derived metabolites such as phenolketones and phenolpyruvate) in the blood and brain. (van Spronsen et.al., *Phenylketonuria. Nat Rev Dis*
15 *Primers* 7, 35 (2021)). In the brain, such high levels of Phe can lead to reduced levels of dopamine and serotonin, reduced levels of neutral amino acids, white matter disruption, reduced glucose metabolism, and even amyloid-like fibril formation.

 PKU is caused by an autosomal-recessive inborn defect in PAH that results in loss of function and accumulation of Phe in the brain. Untreated PKU patients develop severe
20 intellectual disability, epilepsy and behavioral, psychiatric and/or movement problems.

 PKU occurs in about 1 in every 15,000 births in North America and Europe and there are about 50,000 patients currently living with PKU in the United States and Europe. Current treatment for PKU involves the use of a Phe-restricted diet, meaning that patients much watch the amount of Phe that is found in their foods. However, compliance with
25 unpalatable restricted diets is challenging for many adult and adolescent patients. Thus, patients who struggle to comply with a Phe-restricted diet need a new treatment option. Some doctors have begun treating PKU by administering PALYNZIQ®, a recombinant phenylalanine ammonia lyase (PAL) enzyme, to patients. However, some patients are

allergic to this product, which can cause such patients anaphylaxis that may be life-threatening. As such, new treatments are needed.

SLC6A19 (sometimes called B⁰AT1) is an amino acid transporter that is expressed only in the kidney and small intestine. SLC6A19 mediates greater than 95% of the free
5 neutral amino acid absorption from the diet, including Phe. Thus, inhibition (and even selective inhibition) of SLC6A19 causes the amount of neutral amino acids (including Phe) obtained from food to be drastically reduced. In this manner, elevated amounts of Phe and other neutral amino acids would be excreted and eliminated from the body. Such inhibition, especially if a small molecule, could be easy for patients to take, and would treat PKU and
10 other rare genetic disorders of amino acid and nitrogen metabolism. Moreover, human genetic SLC6A19 deficiency (Hartnup Disorder, frequency about 1:3,000) is typically benign and rare symptoms of such disease are treatable with niacin supplementation.

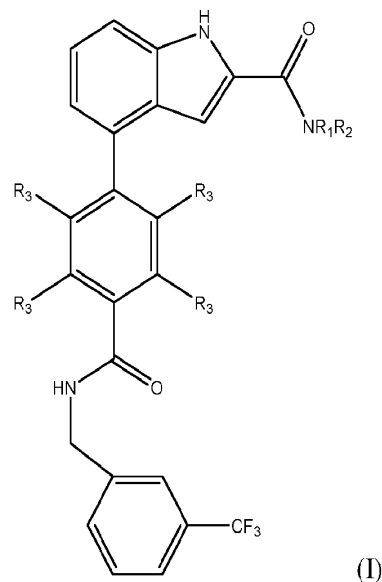
It has been shown that genetically inhibiting SLC6A19 in PKU mouse models
15 reduces plasma and brain Phe levels, normalizes neurotransmitter levels, improves neuronal morphology defects and rescues behavioural symptoms. Belanger, Adam M. et al., Inhibiting neutral amino acid transport for the treatment of phenylketonuria, *JCI Insight*. 2018; 3(14): e121762. Thus, inhibitors of SLC6A19 are an interesting target for treatment of PKU. See WO 2022/192370; Desai, Jigar, et. al., Discovery of novel, potent
20 and orally efficacious inhibitor of neutral amino acid transporter B0AT1 (SLC6A19), *Bioorg. Med. Chem. Lett.* 53 (2021) 128421; Yadav, Aditya, et. al. (2020) Novel Chemical Scaffolds to Inhibit the Neutral Amino Acid Transporter B0AT1 (SLC6A19), a Potential Target to Treat Metabolic Diseases, *Front. Pharmacol.* 11:140.

Thus, the present embodiments provide compounds that can be used to inhibit
25 SLC6A19, and thereby treat PKU and other aminoacidurias.

SUMMARY

The present disclosure relates generally compounds that inhibit SLC6A19 and can be used for the treatment of patients with phenylketonuria ("PKU") and other amino acidurias, as well as compositions containing the same and methods of using the same.

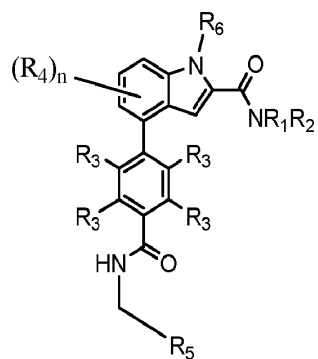
In one aspect, compounds of Formula (I), or a pharmaceutically acceptable salt thereof, are featured:



(I)

in which R₁, R₂, and R₃ can be as defined anywhere herein.

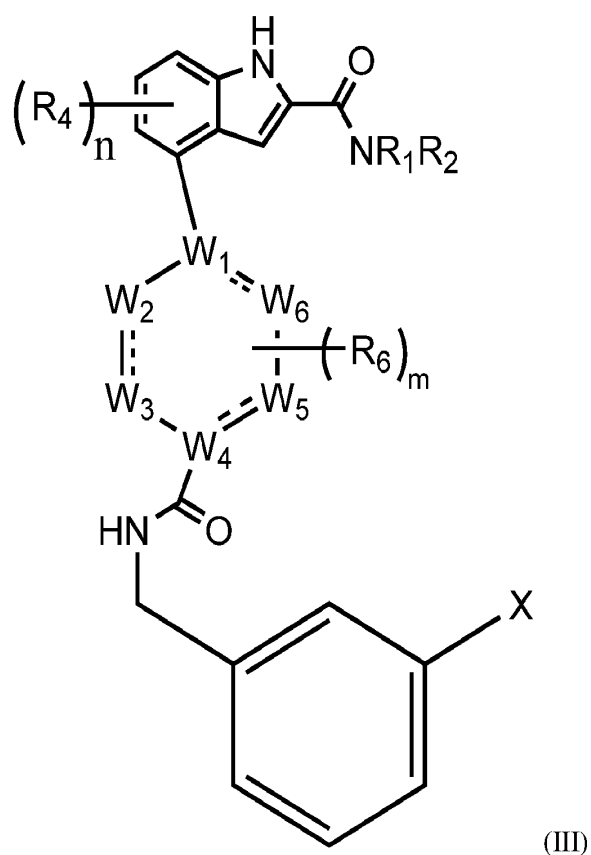
5 In another aspect, compounds of Formula (II), or a pharmaceutically acceptable salt thereof, are featured:



(II)

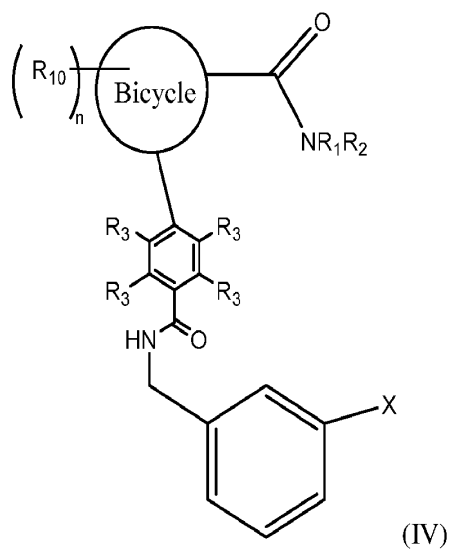
in which R₁, R₂, R₃, R₄, n, R₅, and R₆ can be as defined anywhere herein.

10 In a further aspect, compounds of Formula (III), or a pharmaceutically acceptable salt thereof, are featured:



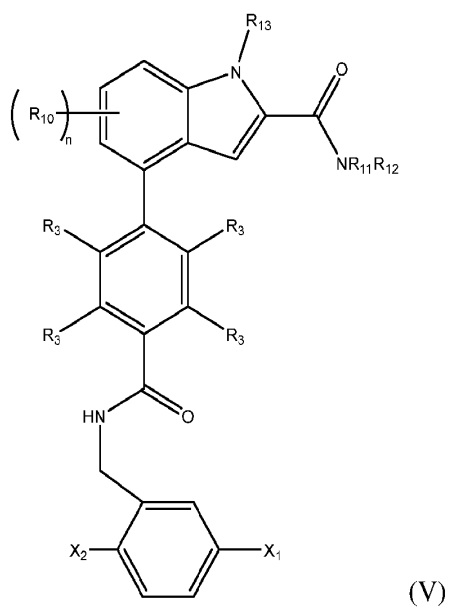
in which R_1 , R_2 , R_4 , R_6 , n , m , W_1 , W_2 , W_3 , W_4 , W_5 , W_6 , and X can be as defined anywhere herein.

In one aspect, compounds of Formula (IV), or a pharmaceutically acceptable salt thereof, are featured:



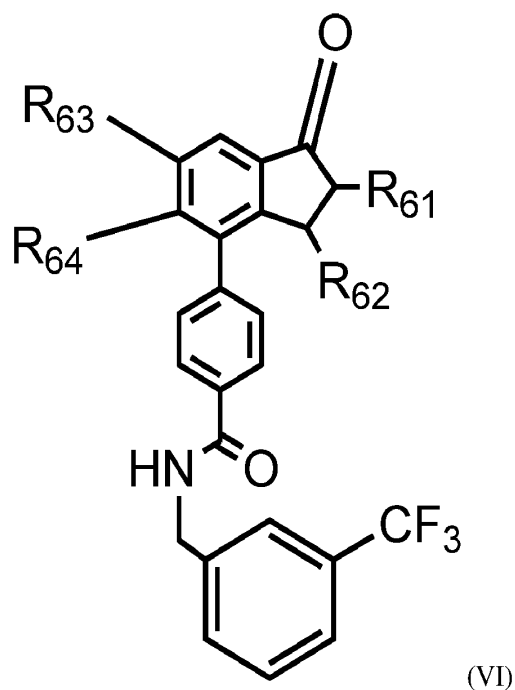
in which R_1 , R_2 , R_3 , R_{10} , n , bicycle, and X can be as defined anywhere herein.

In another aspect, compounds of Formula (V), or a pharmaceutically acceptable salt thereof, are featured:



in which R_3 , R_{10} , R_{11} , R_{12} , R_{13} , X_1 , X_2 , and n can be as defined anywhere herein.

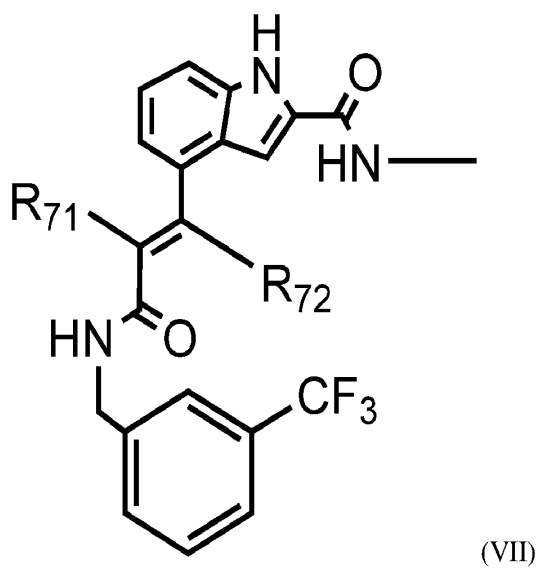
In another aspect, compounds of Formula (VI), or a pharmaceutically acceptable salt thereof, are featured:



(VI)

in which each of R_{61} , R_{62} , R_{63} , and R_{64} can be as defined anywhere herein, or a pharmaceutically acceptable salt thereof.

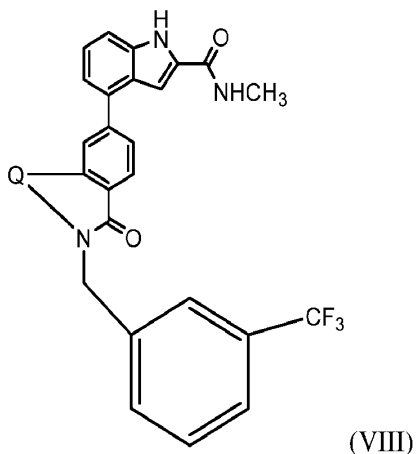
In another aspect, compounds of Formula (VII), or a pharmaceutically acceptable salt thereof, are featured:



(VII)

in which each of R_{71} and R_{72} can be as defined anywhere herein, or a pharmaceutically acceptable salt thereof.

In another aspect, compounds of Formula (VIII), or a pharmaceutically acceptable salt thereof, are featured:

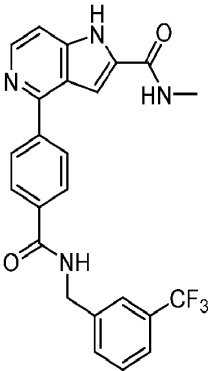
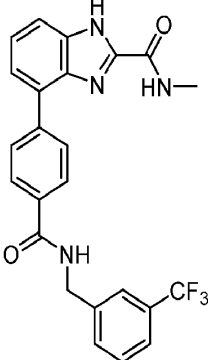
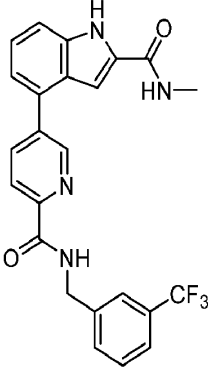


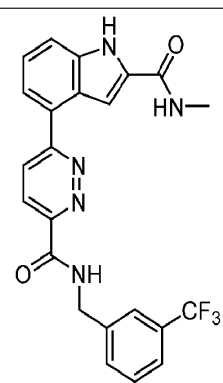
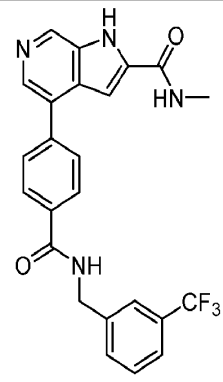
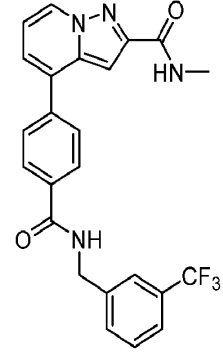
in which Q is $(CH_2)_n$ where in a ring and n is 1, 2, or 3 thereby forming a 5, 6 or 7 membered ring, or a pharmaceutically acceptable salt thereof.

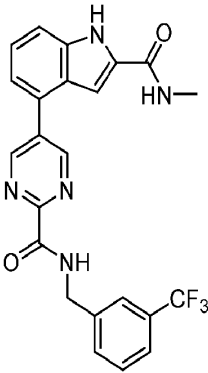
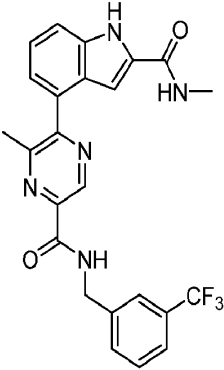
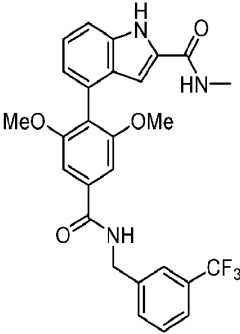
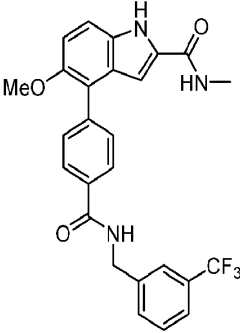
In a further aspect, compounds such as those delineated in Table 1 or a pharmaceutically acceptable salt thereof are featured.

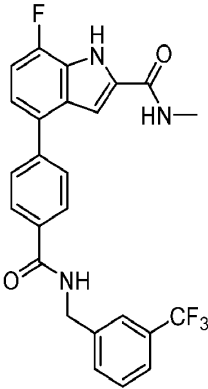
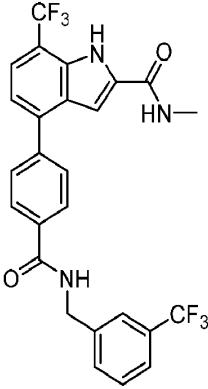
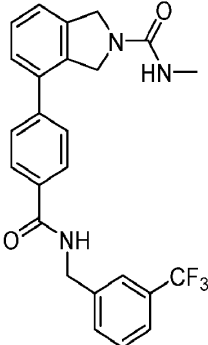
Table 1

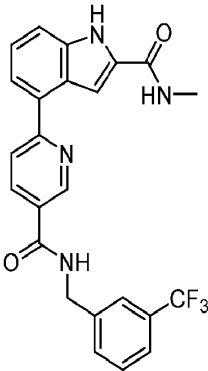
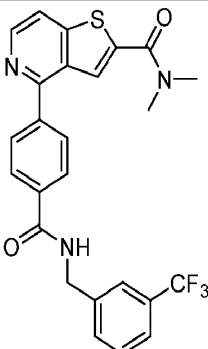
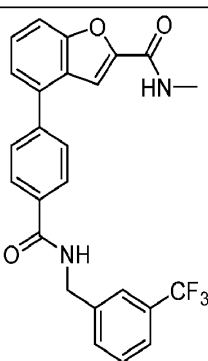
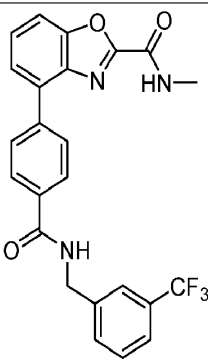
Example	Product
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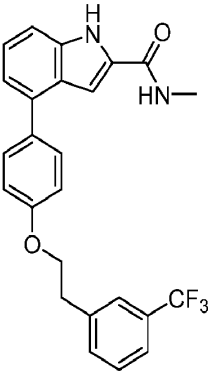
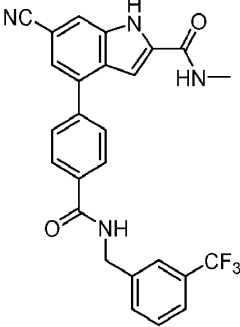
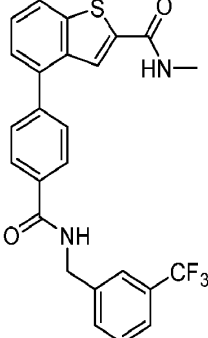
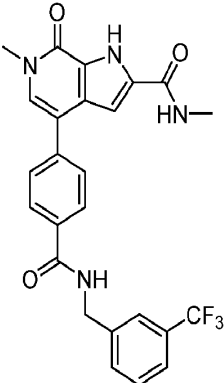
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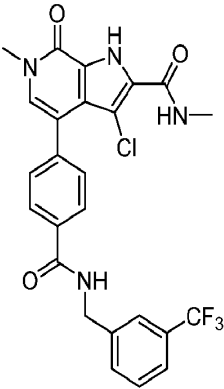
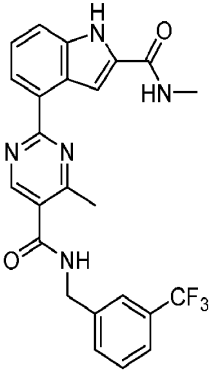
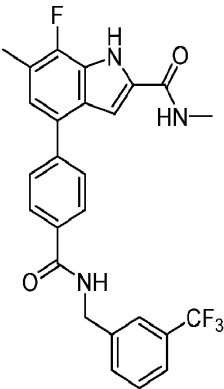
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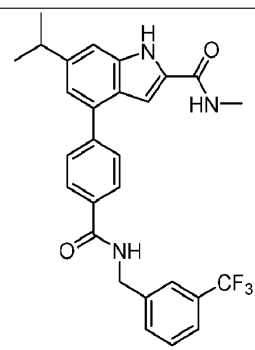
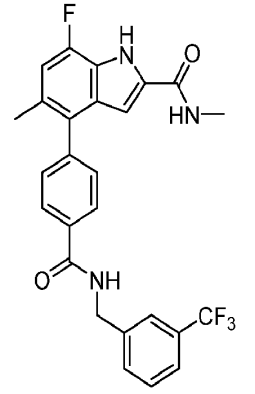
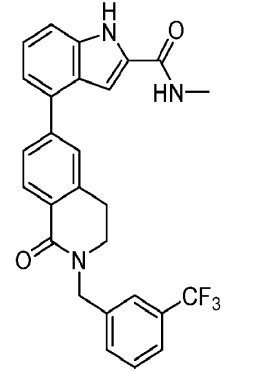
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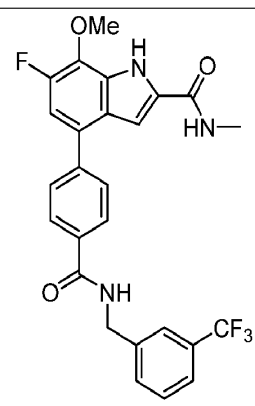
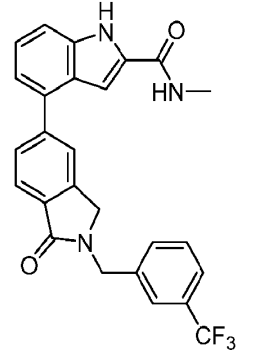
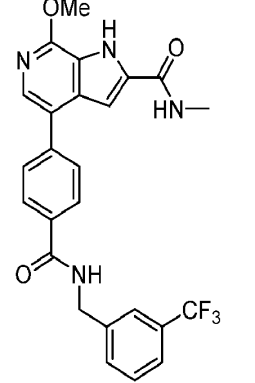
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13	 <chem>CN(C(=O)c1c[nH]c2cc(C(F)(F)F)ccc2c1)c3ccc(cc3)C(=O)NCCc4ccc(C(F)(F)F)cc4</chem>
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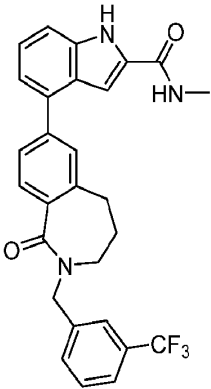
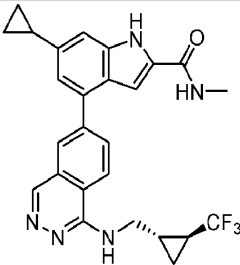
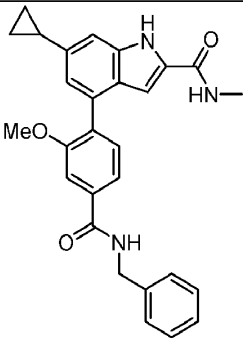
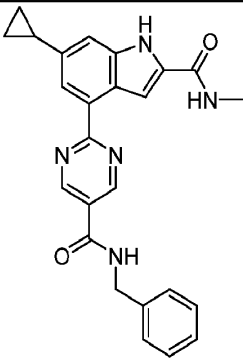
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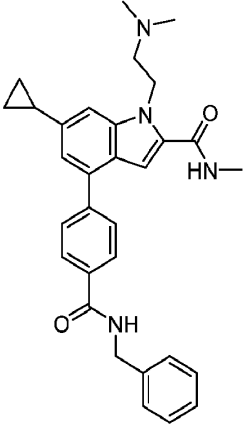
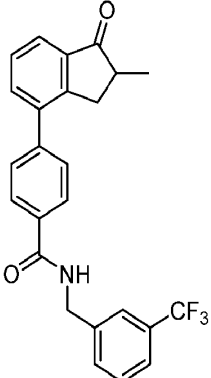
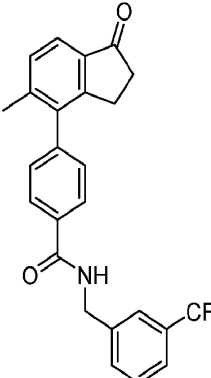
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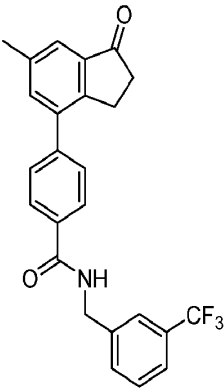
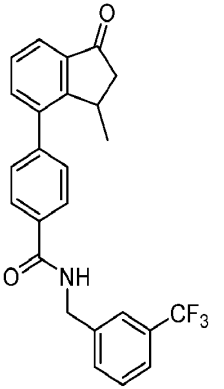
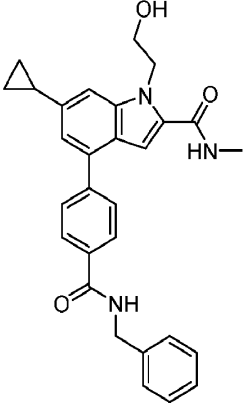
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24	 <chem>CN1C(=O)c2c(C3=CC=C(C=C3)NC(=O)Cc4ccc(C(F)(F)F)cc4)c(C5=CC=CC=C5N1C5=CC=CC=C5)C2=O</chem>
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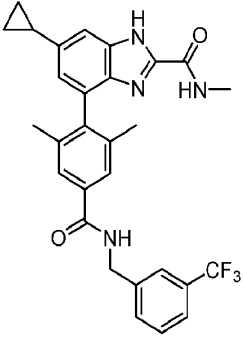
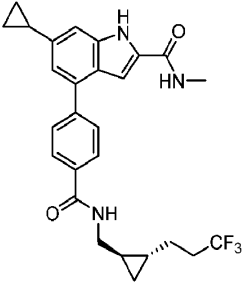
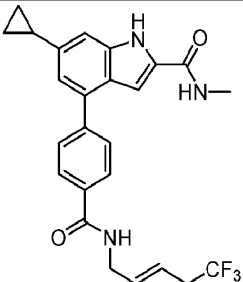
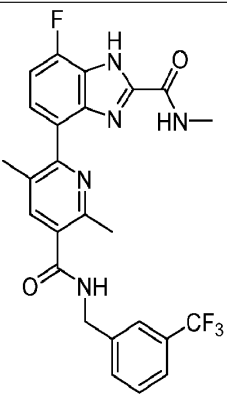
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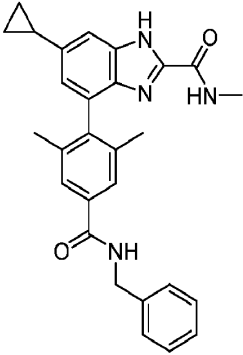
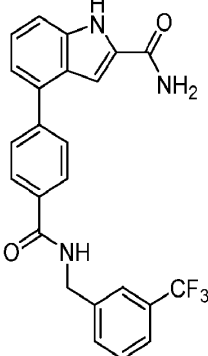
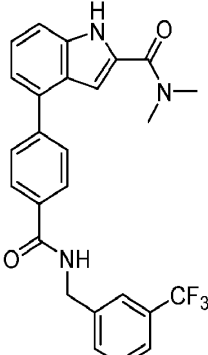
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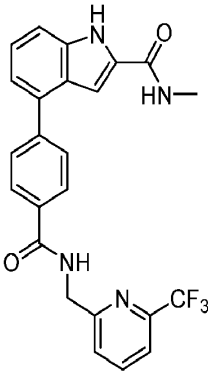
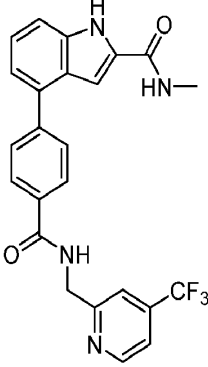
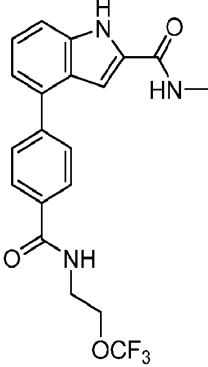
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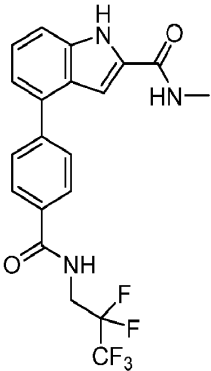
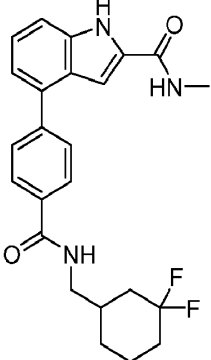
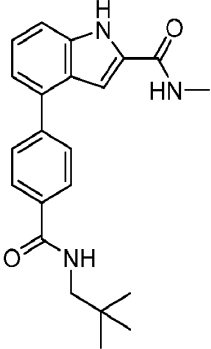
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37	 <chem>CC1Cc2ccccc2C(=O)O1c3ccc(cc3)C(=O)NCc4ccc(cc4)C(F)(F)F</chem>
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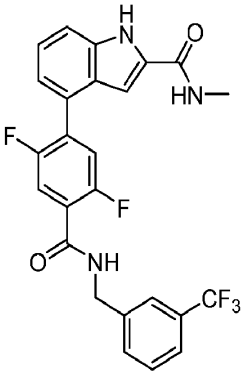
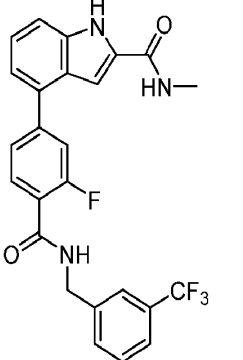
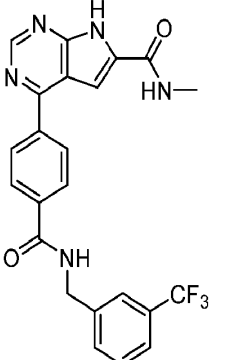
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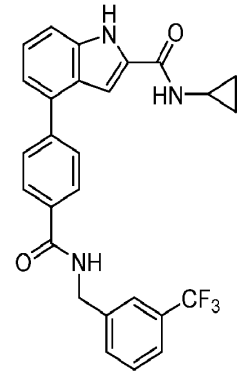
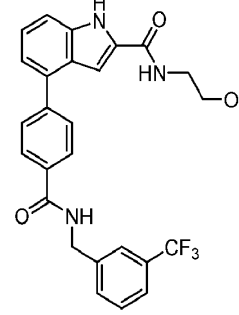
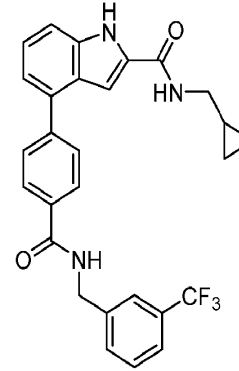
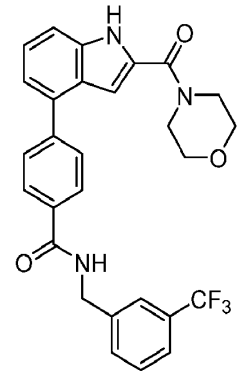
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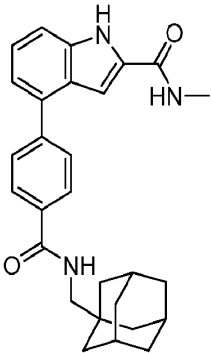
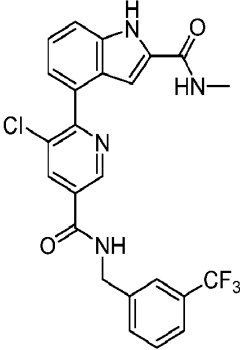
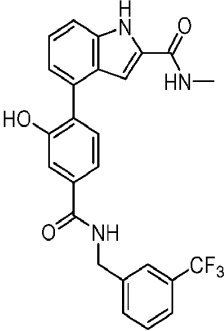
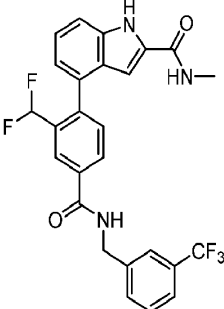
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47	 <chem>NC(=O)c1nc2ccccc2n1c3ccccc3C(=O)NCc4ccc(C(F)(F)F)cc4</chem>
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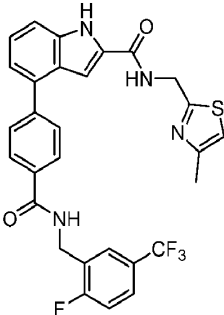
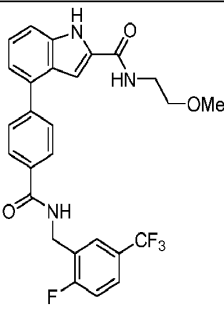
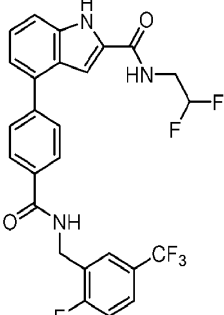
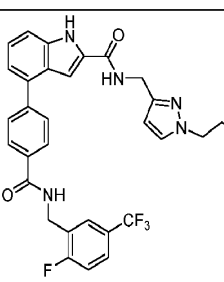
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52	 <chem>CN(C)C(=O)c1c[nH]c2cc(ccc12)C3=CC=C(C=C3)C(=O)NCC(F)(F)C(F)(F)F</chem>
53	 <chem>CN(C)C(=O)c1c[nH]c2cc(ccc12)C3=CC=C(C=C3)C(=O)NCC4CCCCC4(F)F</chem>
54	 <chem>CN(C)C(=O)c1c[nH]c2cc(ccc12)C3=CC=C(C=C3)C(=O)NCC(C)(C)C(C)(C)C</chem>

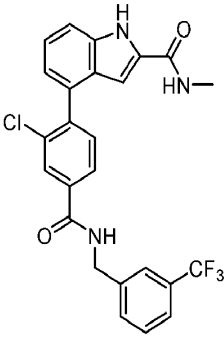
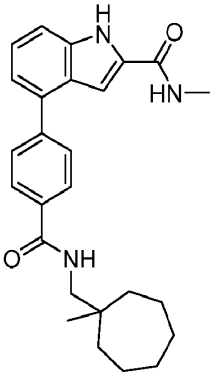
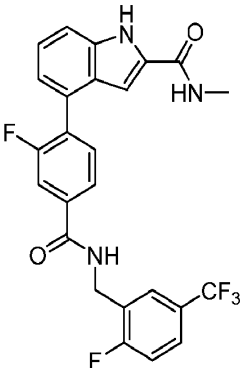
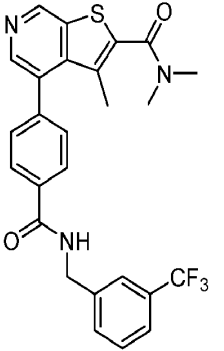
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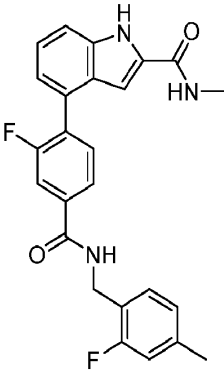
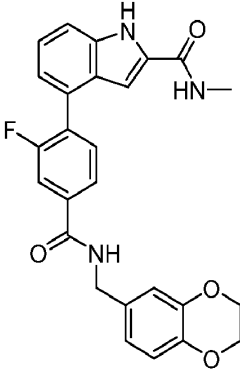
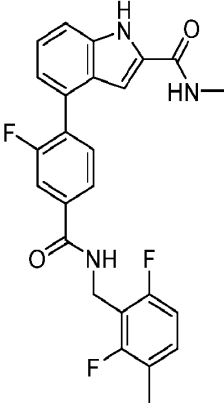
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59	 <chem>OCCNC(=O)c2c(c3ccccc3n2)C(=O)Nc4ccc(cc4)C(=O)NCC5=CC=CC=C5C(F)(F)F</chem>
60	 <chem>C1CC1CCNC(=O)c2c(c3ccccc3n2)C(=O)Nc4ccc(cc4)C(=O)NCC5=CC=CC=C5C(F)(F)F</chem>
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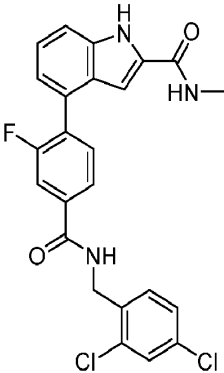
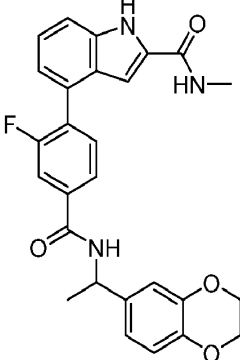
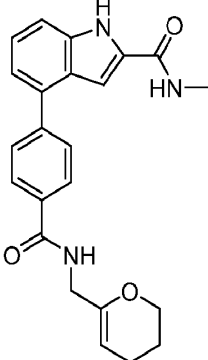
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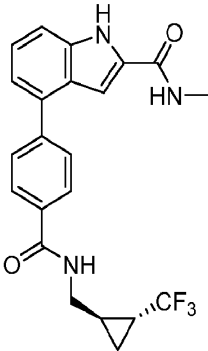
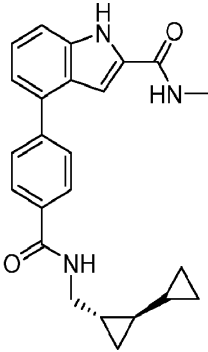
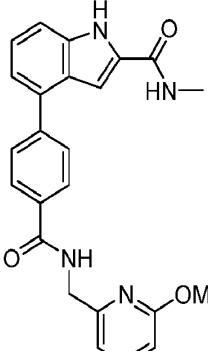
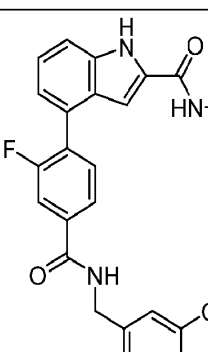
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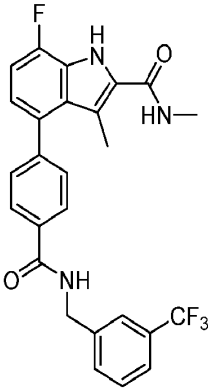
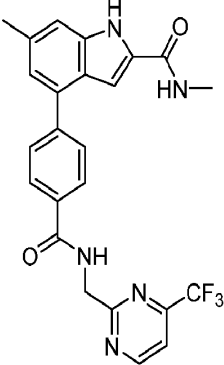
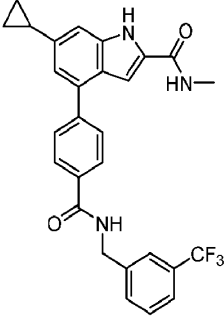
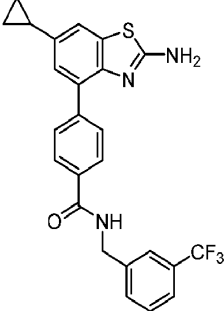
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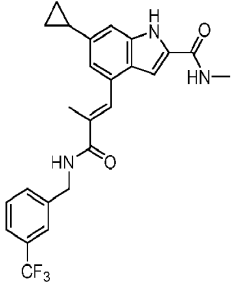
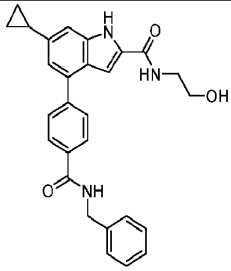
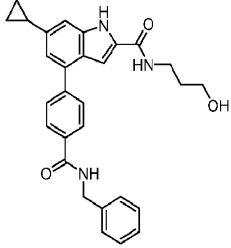
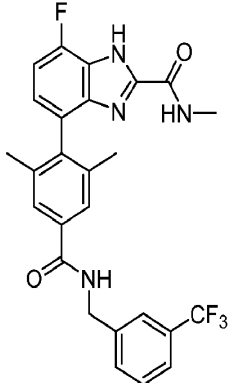
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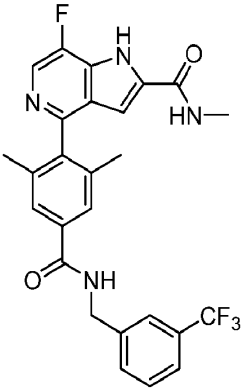
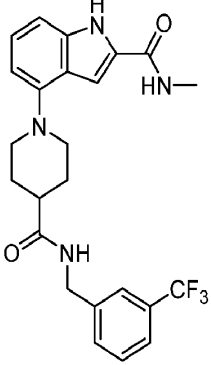
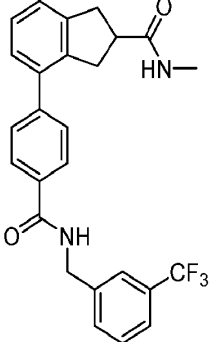
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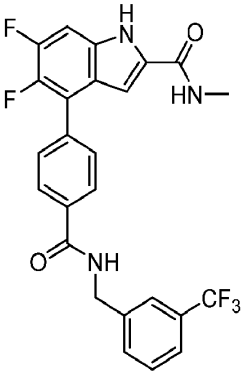
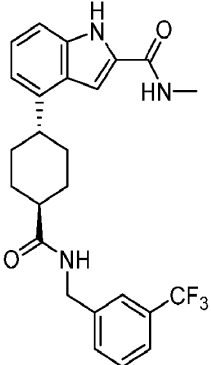
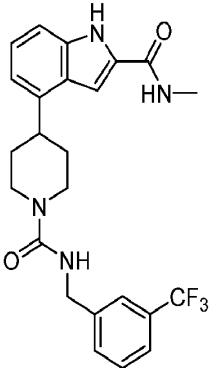
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82	 <chem>CN(C)C(=O)Nc1ccc(cc1)-c2ccc(cc2)-c3cc4c(cc3)occc4</chem>
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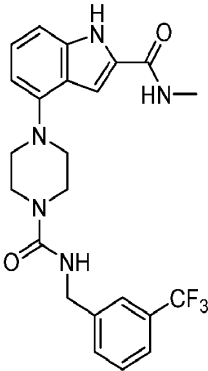
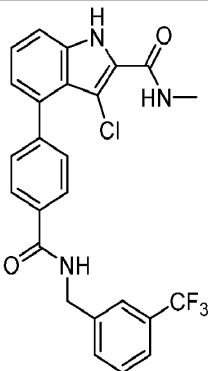
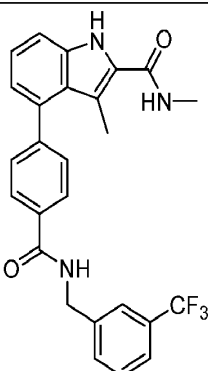
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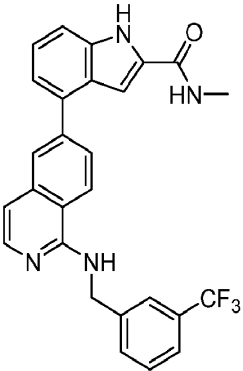
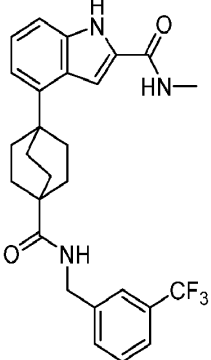
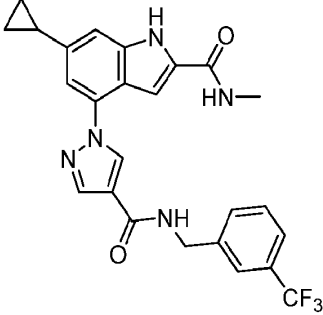
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96	 <chem>CN(C)C(=O)c1cc(C)c(C)c(c1)C2=CN=C3C(=N2)C(=C3)F</chem>
97	 <chem>CN(C)C(=O)c1ccc2c(c1)c(c[nH]2)C3CCN(CC3)C(=O)NCCc4ccc(C(F)(F)F)cc4</chem>
98	 <chem>CN(C)C(=O)c1ccc2c(c1)c(c[nH]2)C3=CC=CC=C3C(=C4C=CC(=C4)C(=O)NCCc5ccc(C(F)(F)F)cc5</chem>

99	 <chem>CN(C)C(=O)c1c[nH]c2cc(F)c(F)cc2c1-c1ccc(cc1)C(=O)NCc2ccc(C(F)(F)F)cc2</chem>
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101	 <chem>CN(C)C(=O)c1c[nH]c2ccccc2c1-c1ccncc1C(=O)NCc2ccc(C(F)(F)F)cc2</chem>

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or a pharmaceutically acceptable salt thereof.

In one aspect, pharmaceutical compositions are featured that include a compound described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same) and one or more pharmaceutically acceptable excipients.

In one aspect, this disclosure features methods of modulating (e.g., inhibiting) SLC6A19 in a subject, which include administering to the subject an effective amount of

a compound described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, said inhibiting can be *in vitro*. In some embodiments, said inhibiting can be *in vivo*.

5 In one aspect, methods of treating a condition, disease or disorder ameliorated by modulating (e.g., inhibiting) SLC6A19 are featured, e.g., treating a condition, disease or disorder in which altered (e.g., increased or excessive) SLC6A19 expression or activity contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). The methods include administering to a subject in need of such treatment an effective amount of a compound described herein
10 (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In another aspect, methods of treating an amino aciduria are featured that include administering to a subject in need of such treatment an effective amount of a compound described herein (e.g., a compound described generically or specifically herein or a
15 pharmaceutically acceptable salt thereof or compositions containing the same).

In a further aspect, methods of treating phenylketonuria, hyperphenylalaninemia, tyrosinemia, nonketotic hyperglycinemia, isovaleric acidemia, methylmalonic acidemia, propionic acidemia, maple syrup urine disease, DNAJC12 deficiency, urea cycle disorders, or hyperammonemia are featured that include administering to a subject in need of such
20 treatment an effective amount of a compound described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In an aspect, methods of treating a disease or disorder associated with a genetic defect in phenylalanine hydroxylase are featured that include administering to a subject in
25 need of such treatment an effective amount of a compound described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In an aspect, methods of treating PKU are featured that include administering to a subject in need of such treatment an effective amount of a compound described herein (e.g.,

a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In an aspect, methods of treating hyperphenylalaninemia are featured that include administering to a subject in need of such treatment an effective amount of a compound
5 described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In certain of the foregoing embodiments, the compound reduces systemic phenylalanine levels in the subject.

In an aspect, methods of treating tyrosinemia (Type I, II, or III) are featured that
10 include administering to a subject in need of such treatment an effective amount of a compound described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same). In certain of the foregoing embodiments, the compound reduces systemic tyrosine levels in the subject.

In an aspect, methods of treating nonketotic hyperglycinemia are featured that
15 include administering to a subject in need of such treatment an effective amount of a compound described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same). In certain of the foregoing embodiments, the compound reduces systemic glycine levels in
20 the subject.

In an aspect, methods of treating isovaleric acidemia, methylmalonic acidemia, propionic acidemia, maple syrup urine disease, DNAJC12 deficiency, urea cycle disorders, or hyperammonemia are featured that include administering to a subject in need of such
25 treatment an effective amount of a compound described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, as described herein for use in the treatment of a condition, disease or disorder associated with increased (e.g., excessive) SLC6A19 expression.

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, described herein for use in the treatment of any one or more of the foregoing indications (e.g., PKU).

5 In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for the treatment of a condition, disease or disorder associated with increased (e.g., excessive) SLC6A19 expression.

10 In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for the treatment of any one or more of the foregoing indications (e.g., PKU).

In another aspect, this disclosure features methods for modulating SLC6A19 in a mammalian cell, the methods include contacting the mammalian cell with an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

In some embodiments, the contacting occurs *in vivo*.

15 In some embodiments, the contacting occurs *in vitro*.

The chemical entity can be administered in combination with one or more additional therapeutic agents and/or regimens. For examples, methods can further include administering one or more (e.g., two, three, four, five, six, or more) additional agents.

20 The chemical entity can be administered in combination with one or more additional therapeutic agents and/or regimens that are useful for treating other SLC6A19-associated conditions (e.g., PKU).

The methods can further include identifying the subject.

Other embodiments include those described in the Detailed Description and/or in the claims.

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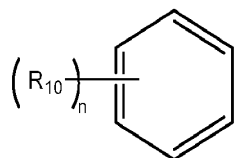
Additional Definitions

To facilitate understanding of the disclosure set forth herein, a number of additional terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein
30 are those well-known and commonly employed in the art. Unless defined otherwise, all

technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entirety.

As used herein, the term “SLC6A19” is meant to include, without limitation, nucleic acids, polynucleotides, oligonucleotides, sense and antisense polynucleotide strands, complementary sequences, peptides, polypeptides, proteins, antibodies, homologous and/or orthologous SLC6A19 molecules, isoforms, precursors, mutants, variants, derivatives, splice variants, alleles, different species, and active fragments thereof.

As used herein, notation such as:



and the like is intended to mean that a hydrogen atom on the ring (here, phenyl) can be replaced with any one or more of the indicated number (“n”) of substituent R^{10} . For example, if n is 0, 1, or 2, then 0, 1, or 2 hydrogen atoms on the rings can be replaced with 0, 1, or 2 R^{10} .

The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of a chemical entity being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate “effective” amount in any individual case is determined using any suitable technique, such as a dose escalation study.

The term “excipient” or “pharmaceutically acceptable excipient” means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In one embodiment, each

component is “pharmaceutically acceptable” in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed.*; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients, 6th ed.*; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.*; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.*; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

The term “pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The pharmacologically acceptable salts not specifically limited as far as it can be used in medicaments. Examples of a salt that the compounds described herein form with a base include the following: salts thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine, and ethanolamine; salts thereof with basic amino acids such as lysine and ornithine; and ammonium salt. The salts may be acid addition salts, which are specifically exemplified by acid addition salts with the following: mineral acids

such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid; organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, and ethanesulfonic acid; acidic amino acids such as aspartic acid and glutamic acid.

The term “pharmaceutical composition” refers to a mixture of a compound described herein with other chemical components (referred to collectively herein as “excipients”), such as carriers, stabilizers, diluents, dispersing agents, suspending agents, and/or thickening agents. The pharmaceutical composition facilitates the administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: rectal, oral, intravenous, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

The term “subject” refers to an animal, including, but not limited to, a primate (*e.g.*, human), monkey, cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms “subject” and “patient” are used interchangeably herein in reference, for example, to a mammalian subject, such as a human.

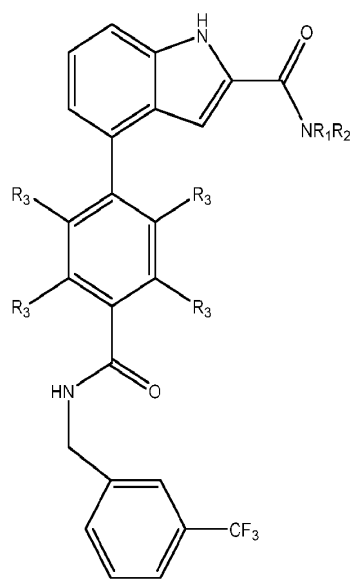
The terms “treat,” “treating,” and “treatment,” in the context of treating a disease or disorder, are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or to slowing the progression, spread or worsening of a disease, disorder or condition or of one or more symptoms thereof.

DETAILED DESCRIPTION

The present disclosure relates generally compounds that inhibit SLC6A19 and can be used for the treatment of patients with phenylketonuria (“PKU”) and other amino acidurias, as well as compositions containing the same and methods of using the same.

Formula (I) Compounds

In one aspect, the disclosure features compounds having Formula I:



wherein R_1 and R_2 are independently selected from H or CH_3 ;

wherein each R_3 is independently selected from H, OH, CH_3 , O- CH_3 , CHF_2 , F, or Cl, wherein at least two R_3 are H; or a pharmaceutically acceptable salt thereof.

5 In some embodiments, R_1 is CH_3 and R_2 is H.

In some embodiments, at least one R_3 is F.

In some embodiments, at least one R_3 is Cl.

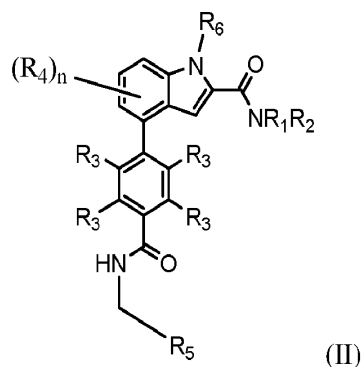
In some embodiments, at least one R_3 is CH_3 .

In some embodiments, R_1 and R_2 are both H.

10 In some embodiments, R_1 and R_2 are both CH_3 .

Formula (II) Compounds

In one aspect, the disclosure features compounds having Formula II:



wherein R_1 and R_2 are independently selected from H or CH_3 ;

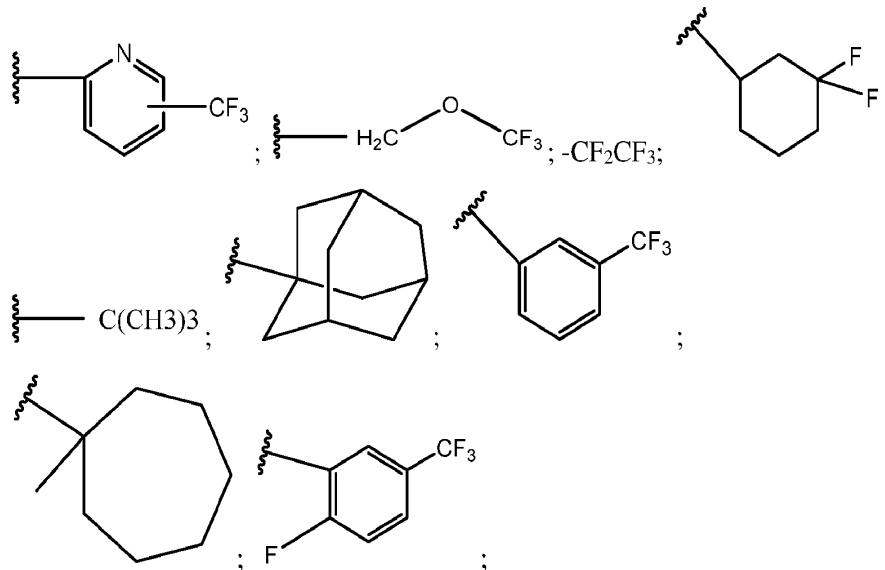
wherein each R_3 is independently selected from H, CH_2F_2 , OH, CH_3 , O- CH_3 , F, or Cl, wherein at least two R_3 are H;

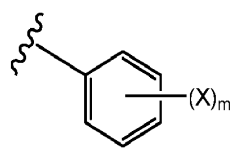
wherein n is 0, 1, 2, or 3;

wherein each occurrence of R_4 is independently selected from CH_3 , CF_3 , O- CH_3 , F, Cl, -CN, iso-propyl, or cyclopropyl;

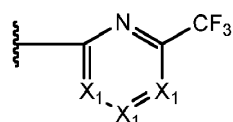
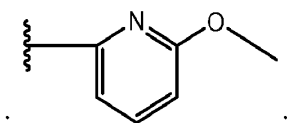
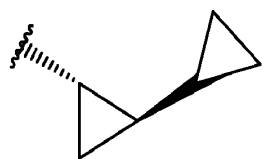
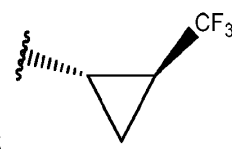
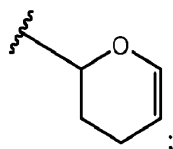
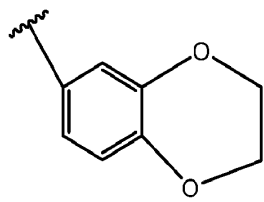
wherein R_6 is H, $-\text{CH}_2\text{CH}_2\text{OH}$, or $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$;

R_5 is:





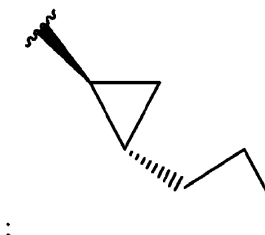
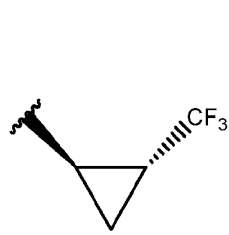
, wherein m is 0, 1, 2, 3, or 4, and X is CH₃, OCH₃, F, or Cl;



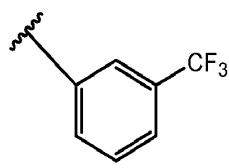
, wherein each X₁ is, independently, N or CH; provided that

5

one X₁ is N;



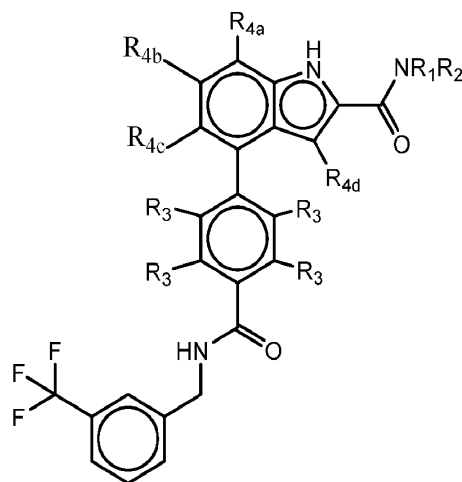
provided that n cannot be 0 when R₅ is:



10

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has the formula (II-A):



(II-A)

wherein each occurrence of R_{4a}, R_{4b}, R_{4c}, and R_{4d} is independently selected from H, CH₃, CF₃, O-CH₃, F, Cl, -CN, *iso*-propyl, or cyclopropyl; provided that at least one of R_{4a}, R_{4b}, R_{4c}, and R_{4d} is other than H; or a pharmaceutically acceptable salt thereof.

In some embodiments, one of R_{4a}, R_{4b}, R_{4c}, and R_{4d} is Cl; and the others are H, or a pharmaceutically acceptable salt thereof. For example, R_{4d} can be Cl.

In some embodiments, one of R_{4a}, R_{4b}, R_{4c}, and R_{4d} is CH₃; and the others are H, or a pharmaceutically acceptable salt thereof. For example, R_{4d} can be CH₃.

In some embodiments, one of R_{4a}, R_{4b}, R_{4c}, and R_{4d} is OCH₃; and the others are H, or a pharmaceutically acceptable salt thereof. For example, R_{4c} can be OCH₃.

In some embodiments, one of R_{4a}, R_{4b}, R_{4c}, and R_{4d} is F; and the others are H, or a pharmaceutically acceptable salt thereof. For example, R_{4a} can be F.

In some embodiments, one of R_{4a}, R_{4b}, R_{4c}, and R_{4d} is CF₃; and the others are H, or a pharmaceutically acceptable salt thereof. For example, R_{4a} can be CF₃.

In some embodiments, one of R_{4a}, R_{4b}, R_{4c}, and R_{4d} is CN; and the others are H, or a pharmaceutically acceptable salt thereof. For example, R_{4b} can be CN.

In some embodiments, one of R_{4a}, R_{4b}, R_{4c}, and R_{4d} is cyclopropyl; and the others are H, or a pharmaceutically acceptable salt thereof. For example, R_{4b} can be cyclopropyl.

In some embodiments, one of R_{4a}, R_{4b}, R_{4c}, and R_{4d} is *iso*-propyl; and the others are H, or a pharmaceutically acceptable salt thereof. For example, R_{4b} can be *iso*-propyl.

In some embodiments, two of R_{4a} , R_{4b} , R_{4c} , and R_{4d} are independently Cl, F or CH_3 ; and the others are H, or a pharmaceutically acceptable salt thereof.

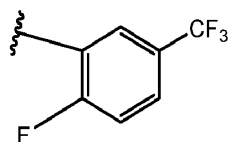
For example, R_{4b} and R_{4c} can be F.

As another example, one of R_{4a} and R_{4b} can be F, and the other of R_{4a} and R_{4b} can be CH_3 .

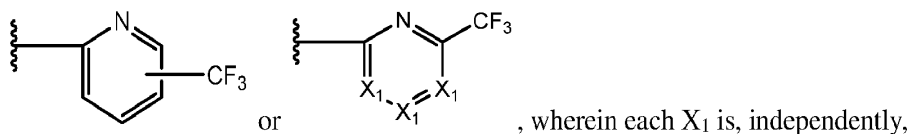
As another example, one of R_{4a} and R_{4b} can be F, and the other of R_{4b} and R_{4c} can be CH_3 .

As another example, one of R_{4a} and R_{4b} can be F, and the other of R_{4a} and R_{4d} can be CH_3 .

In some embodiments, R_5 is:

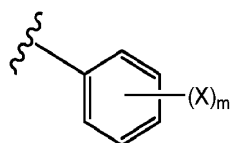


In some embodiments, R_5 is:



N or CH ; provided that one X_1 is N.

In some embodiments, R_5 is:



, wherein m is 0, 1, 2, 3, or 4, and X is CH_3 , OCH_3 , F, or Cl, or a pharmaceutically acceptable salt thereof.

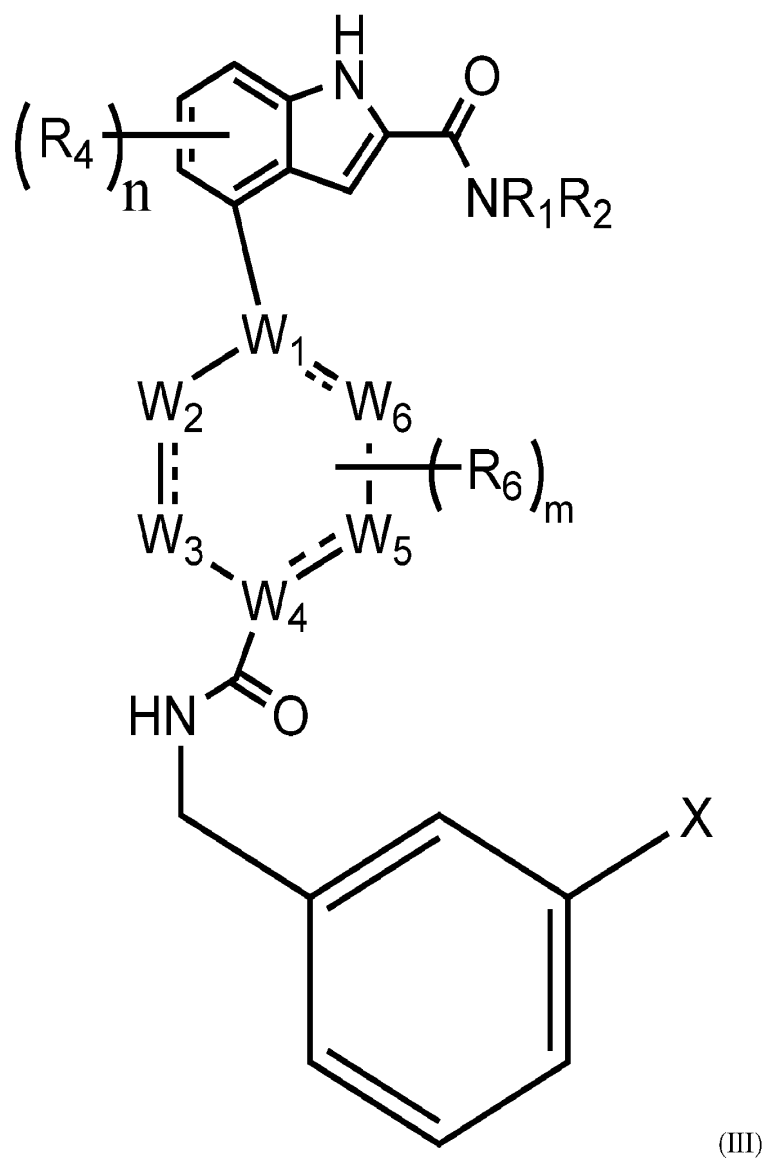
In some embodiments, R_1 is CH_3 and R_2 is H.

In some embodiments, R_3 is H.

In some embodiments, R_6 is H.

Formula (III) Compounds

In one aspect, the disclosure features compounds having Formula III:



wherein:

each of W_1 and W_4 is independently selected from N, C, or CH;

5 each of W_2 , W_3 , W_5 , and W_6 is independently selected from N, NH, CH, or CH_2 ;

n is 0, 1, 2, or 3;

each occurrence of R_4 is, independently, cyclopropyl, Cl, F, CH_3 , or OCH_3 ;

m is 0, 1, 2, or 3;

each occurrence of R_6 is, independently, F, Cl, or CH_3 ;
wherein R_1 and R_2 are independently selected from H or CH_3 ;
the dotted lines indicate the presence of a single or double bond; and
X is H or CF_3 , or a pharmaceutically acceptable salt thereof.

5

In some embodiments, W_3 is N, W_1 and W_4 are C; and each of W_2 , W_5 , and W_6 is CH.

In some embodiments, W_2 and W_3 are N, W_1 and W_4 are C; and each of W_5 and W_6 is CH.

10

In some embodiments, wherein each of W_3 and W_5 are N, W_1 and W_4 are C; and each of W_2 and W_6 , is CH.

In some embodiments, each of W_1 and W_4 is CH; and each of W_2 , W_3 , W_5 , and W_6 is CH_2 .

15

In some embodiments, W_1 is CH, and W_4 is N; and each of W_2 , W_3 , W_5 , and W_6 is CH_2 .

In some embodiments, W_3 and W_6 are N, W_1 and W_4 are C; W_2 is CR_6 , and W_5 is CH. In certain embodiments, R_6 is CH_3 .

In some embodiments, W_2 is N, W_1 and W_4 are C; and each of W_3 and W_5 is CH, and W_6 is CR_6 . In certain embodiments, R_6 is Cl.

20

In some embodiments, W_2 is N, W_1 and W_4 are C; and each of W_3 , W_5 , and W_6 is CH.

In some embodiments, W_2 and W_6 are N, W_1 and W_4 are C; W_3 is CR_6 , and W_5 is CH. In certain embodiments, R_6 is CH_3 .

25

In some embodiments, W_2 and W_6 are N, W_1 and W_4 are C; W_3 is CH, and W_5 is CH.

In some embodiments, W_2 is N, W_1 and W_4 are C; each of W_3 and W_6 is CR_6 , and W_5 is CH. In certain embodiments, R_6 is CH_3 .

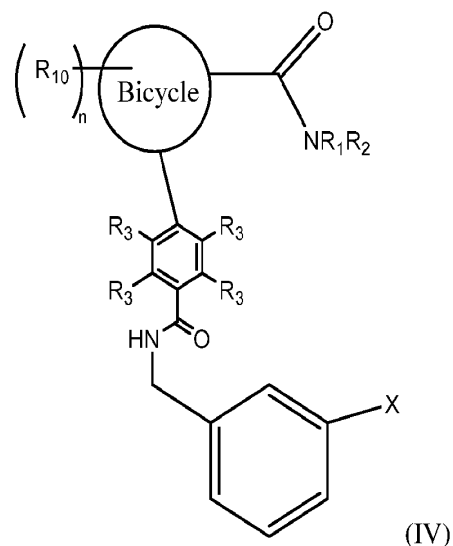
In some embodiments, R_1 is CH_3 and R_2 is H.

In some embodiments, n is 1, and R_4 is F or cyclopropyl.

30

Formula (IV) Compounds

In one aspect, the disclosure features compounds having Formula IV:



wherein R_1 and R_2 are independently selected from H or CH_3 ;

5 wherein each R_3 is independently selected from H, OH, CH_3 , O- CH_3 , CHF_2 , F, or Cl, wherein at least two R_3 are H;

wherein n is 0, 1, or 2;

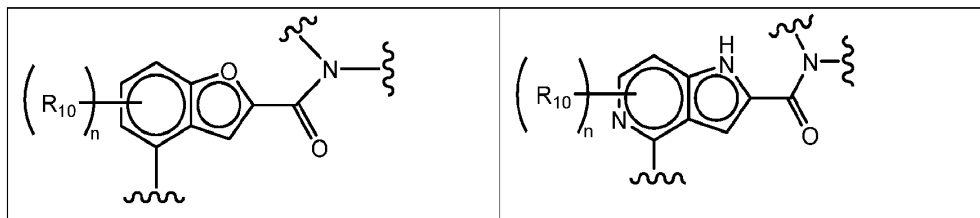
wherein each occurrence of R_{10} is, independently, methyl, F, OH, H, OCH₃, CH₃, or cyclopropyl;

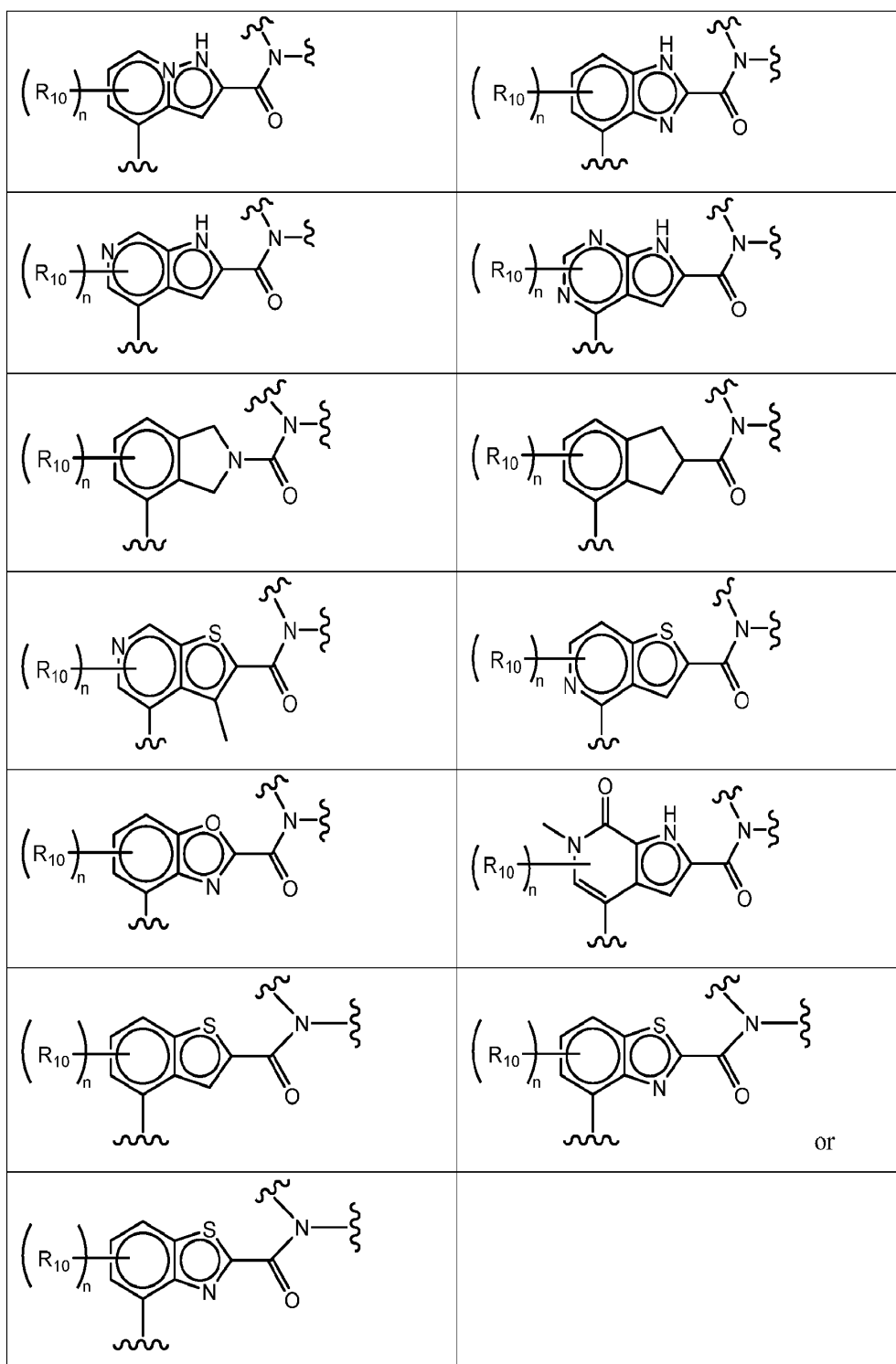
10 wherein X is H or CF₃; and

wherein the bicycle is a bicyclic ring that includes 8-10 constituent ring atoms, wherein 1-4 of the atoms are heteroatoms independently selected from N, O, or S, and wherein each of the two rings is independently a saturated, unsaturated, or aromatic ring; or a pharmaceutically acceptable salt thereof.

15

In some embodiments, the bicycle is selected from:





or a pharmaceutically acceptable salt thereof.

In some embodiments, R_1 is CH_3 and R_2 is H.

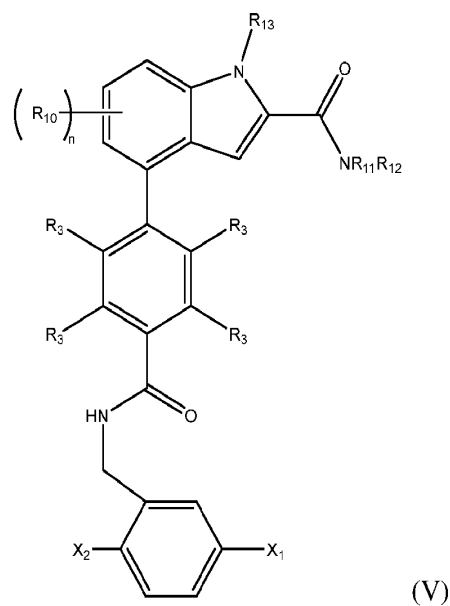
In some embodiments, each occurrence of R_3 is H.

In some embodiments, X is CF_3 .

5

Formula (V) Compounds

In one aspect, the disclosure features compounds having Formula V:



R_{11} is $-(CH_2)_m-A$

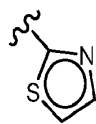
10

m is 0, 1, 2, or 3;

R_{12} is H;

R_{13} is H, $-CH_2CH_2OH$, or $-CH_2CH_2N(CH_3)_2$;

A is cyclopropyl, $-OH$, $-OCH_3$;



, $-CHF_2$; phenyl, 4-chlorophenyl;

15



, or 4-pyridyl;

n is 0, 1, 2, or 3;

each occurrence of R_{10} is, independently, cyclopropyl, Cl, F, CH_3 , or OCH_3 ;

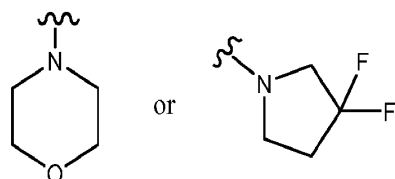
each R_3 is independently selected from H, OH, CH_3 , O- CH_3 , CHF_2 , F, or Cl,

wherein at least two R_3 are H; and

X_1 is H or CF_3 ;

5 X_2 is H or F;

or R_{11} and R_{12} together with the nitrogen atom to which each is attached forms:



or a pharmaceutically acceptable salt thereof.

10 In some embodiments, R_{11} is $-(CH_2)_m-A$, and R_{12} is H.

In some embodiments, m is 1 or 2.

In some embodiments, n is 1.

In some embodiments, R_3 is H.

In some embodiments, X_1 is CF_3 , and X_2 is H.

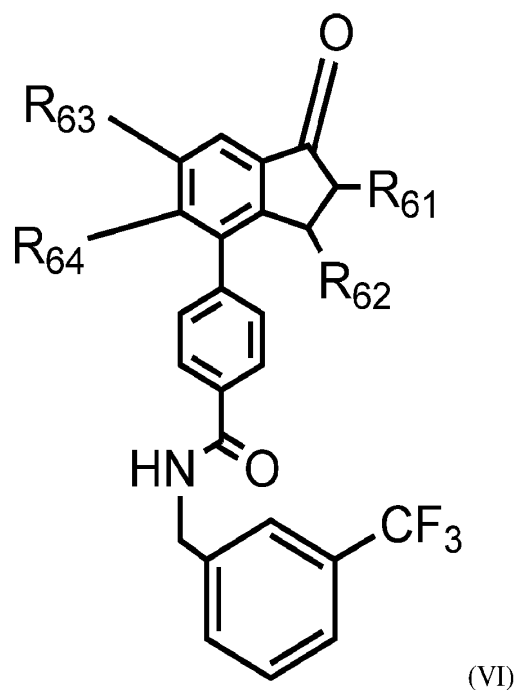
15 In some embodiments, X_1 is CF_3 , and X_2 is F.

In some embodiments, X_1 is H, and X_2 is H.

In some embodiments, R_{13} is H.

Formula (VI) Compounds

20 In one aspect, the disclosure features compounds having Formula VI:



wherein each of R_{61} , R_{62} , R_{63} , and R_{64} is independently selected from H and CH_3 , or a pharmaceutically acceptable salt thereof.

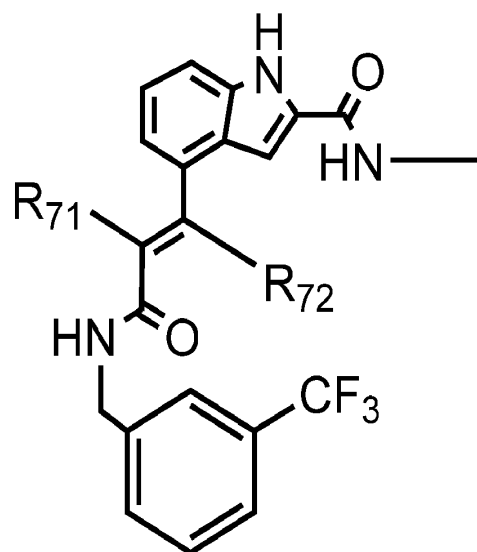
5 In some embodiments, one of R_{61} , R_{62} , R_{63} , and R_{64} is CH_3 , and the other three are H, or a pharmaceutically acceptable salt thereof.

 In some embodiments, one of R_{61} and R_{62} is CH_3 , and the other is H, or a pharmaceutically acceptable salt thereof.

 In some embodiments, one of R_{63} and R_{64} is CH_3 , and the other is H, or a
10 pharmaceutically acceptable salt thereof.

Formula (VII) Compounds

In one aspect, the disclosure features compounds having Formula VII:



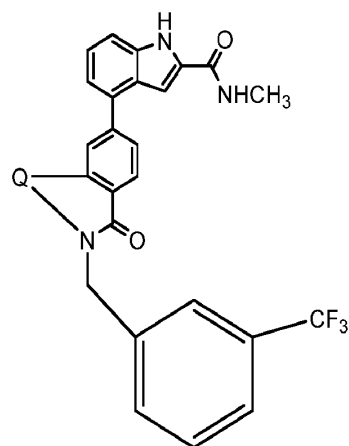
(VII)

each of R_{71} and R_{72} is independently selected from H and CH_3 , or a pharmaceutically acceptable salt thereof.

In some embodiments, one of R_{71} and R_{72} is CH_3 , and the other is H, or a pharmaceutically acceptable salt thereof.

Formula (VIII) Compounds

In one aspect, the disclosure features compounds having Formula **VIII**:



(VIII)

in which Q is $(CH_2)_n$ where n is 1, 2, or 3 thereby forming a 5, 6 or 7 membered ring, or a pharmaceutically acceptable salt thereof.

Pharmaceutical Compositions and Administration*General*

In some embodiments, a compound (e.g., a compound that inhibits (e.g., antagonizes) SLC6A19, or a pharmaceutically acceptable salt, and/or hydrate, and/or
5 cocrystal, and/or drug combination thereof) is administered as a pharmaceutical composition that includes the chemical entity and one or more pharmaceutically acceptable excipients, and optionally one or more additional therapeutic agents as described herein.

In some embodiments, the chemical entities can be administered in combination with one or more conventional pharmaceutical excipients. Pharmaceutically acceptable
10 excipients include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d- α -tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, poloxamers or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, tris, glycine, sorbic acid,
15 potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium-chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block
20 polymers, and wool fat. Cyclodextrins such as α -, β , and γ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl- β -cyclodextrins, or other solubilized derivatives can also be used to enhance delivery of compounds described herein. Dosage forms or compositions containing a chemical entity as described herein in the range of 0.005% to 100% with the
25 balance made up from non-toxic excipient may be prepared. The contemplated compositions may contain 0.001%-100% of a chemical entity provided herein, in one embodiment 0.1-95%, in another embodiment 75-85%, in a further embodiment 20-80%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*,
30 22nd Edition (Pharmaceutical Press, London, UK. 2012).

Routes of Administration and Composition Components

In some embodiments, the chemical entities described herein or a pharmaceutical composition thereof can be administered to subject in need thereof by any accepted route of administration. Acceptable routes of administration include, but are not limited to, buccal, cutaneous, endocervical, endosinusal, endotracheal, enteral, epidural, interstitial, intra-abdominal, intra-arterial, intrabronchial, intrabursal, intracerebral, intracisternal, intracoronary, intradermal, intraductal, intraduodenal, intradural, intraepidermal, intraesophageal, intragastric, intragingival, intraileal, intralymphatic, intramedullary, intrameningeal, intramuscular, intraovarian, intraperitoneal, intraprostatic, intrapulmonary, intrasinal, intraspinal, intrasynovial, intratesticular, intrathecal, intratubular, intratumoral, intrauterine, intravascular, intravenous, nasal, nasogastric, oral, parenteral, percutaneous, peridural, rectal, respiratory (inhalation), subcutaneous, sublingual, submucosal, topical, transdermal, transmucosal, transtracheal, ureteral, urethral and vaginal.

Compositions can be formulated for parenteral administration, e.g., formulated for injection via the intravenous, intramuscular, sub-cutaneous, or even intraperitoneal routes. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for use to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified. The preparation of such formulations will be known to those of skill in the art in light of the present disclosure.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that it may be easily injected. It also should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

The carrier also can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance
5 of the required particle size in the case of dispersion, and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various 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 or sodium chloride. Prolonged absorption of the injectable compositions
10 can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions
15 are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired
20 ingredient from a previously sterile-filtered solution thereof.

Pharmacologically acceptable excipients usable in the rectal composition as a gel, cream, enema, or rectal suppository, include, without limitation, any one or more of cocoa butter glycerides, synthetic polymers such as polyvinylpyrrolidone, PEG (like PEG ointments), glycerine, glycerinated gelatin, hydrogenated vegetable oils, poloxamers,
25 mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol Vaseline, anhydrous lanolin, shark liver oil, sodium saccharinate, menthol, sweet almond oil, sorbitol, sodium benzoate, anoxid SBN, vanilla essential oil, aerosol, parabens in phenoxyethanol, sodium methyl p-oxybenzoate, sodium propyl p-oxybenzoate, diethylamine, carbomers, carbopol, methyloxybenzoate, macrogol
30 cetostearyl ether, cocoyl caprylocaprate, isopropyl alcohol, propylene glycol, liquid

paraffin, xanthan gum, carboxy-metabisulfite, sodium edetate, sodium benzoate, potassium metabisulfite, grapefruit seed extract, methyl sulfonyl methane (MSM), lactic acid, glycine, vitamins, such as vitamin A and E and potassium acetate.

5 Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the chemical entity is mixed with one or more pharmaceutically acceptable excipients, such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) 10 disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, 15 solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

20 In one embodiment, the compositions will take the form of a unit dosage form such as a pill or tablet and thus the composition may contain, along with a chemical entity provided herein, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives or the like. In another solid 25 dosage form, a powder, marume, solution or suspension (*e.g.*, in propylene carbonate, vegetable oils, PEG's, poloxamer 124 or triglycerides) is encapsulated in a capsule (gelatin or cellulose base capsule). Unit dosage forms in which one or more chemical entities provided herein or additional active agents are physically separated are also contemplated; *e.g.*, capsules with granules (or tablets in a capsule) of each drug; two-layer tablets; two-

compartment gel caps, etc. Enteric coated or delayed release oral dosage forms are also contemplated.

Other physiologically acceptable compounds include wetting agents, emulsifying agents, dispersing agents or preservatives that are particularly useful for preventing the growth or action of microorganisms. Various preservatives are well known and include, for example, phenol and ascorbic acid.

In certain embodiments the excipients are sterile and generally free of undesirable matter. These compositions can be sterilized by conventional, well-known sterilization techniques. For various oral dosage form excipients such as tablets and capsules sterility is not required. The USP/NF standard is usually sufficient.

Topical compositions can include ointments and creams. Ointments are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. Creams containing the selected active agent are typically viscous liquid or semisolid emulsions, often either oil-in-water or water-in-oil. Cream bases are typically water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also sometimes called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and non-sensitizing.

Dosages

The dosages may be varied depending on the requirement of the patient, the severity of the condition being treating and the particular compound being employed. Determination of the proper dosage for a particular situation can be determined by one skilled in the medical arts. The total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery.

In some embodiments, the compounds described herein are administered at a dosage of from about 0.001 mg/Kg to about 500 mg/Kg (e.g., from about 0.01 mg/Kg to

about 100 mg/Kg; from about 0.01 mg/Kg to about 10 mg/Kg; from about 0.01 mg/Kg to about 1 mg/Kg; from from about 0.01 mg/Kg to about 0.1 mg/Kg; from about 0. 1 mg/Kg to about 100 mg/Kg; from about 0. 1 mg/Kg to about 10 mg/Kg).

5 *Regimens*

The foregoing dosages can be administered on a daily basis (e.g., as a single dose or as two or more divided doses) or non-daily basis (e.g., every other day, every two days, every three days, once weekly, twice weeks, once every two weeks, once a month).

10 In some embodiments, the period of administration of a compound described herein is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In an embodiment, a therapeutic compound is administered to an individual for a period of time followed by a separate period of time. In another embodiment, a therapeutic compound is administered for a first period and a second period following the first period, with administration stopped during the second period, followed by a third period where administration of the therapeutic compound is started and then a fourth period following the third period where administration is stopped. In an aspect of this embodiment, the period of administration of a therapeutic compound followed by a period where administration is stopped is repeated for a determined or undetermined period of time. In a further embodiment, a period of administration is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In a further embodiment, a period of during which administration is

stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more.

5

Methods of Treatment

In some embodiments, methods for treating a subject having condition, disease or disorder in which increased (e.g., excessive) SLC6A19 activity contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g.,
10 immune disorders, cancer) are provided.

One aspect of the invention provides compounds, compositions, and methods useful for treating or preventing a disease or disorder associated with abnormal levels of amino acids by modulation of SLC6A19 transport.

Another aspect of the invention relates to methods of modulating SLC6A19
15 transport in a subject in need thereof comprising administering to the subject an effective amount of a compound described herein.

This disclosure features methods of treating a disease or disorder associated with a genetic defect in phenylalanine hydroxylase in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I).

20 This disclosure features methods of treating phenylketonuria in a subject in need thereof comprising administering to the subject an effective amount of a compound described herein.

This disclosure features methods of treating hyperphenylalaninemia in a subject in need thereof comprising administering to the subject an effective amount of a compound
25 described herein.

In some embodiments, the compound reduces systemic phenylalanine levels in the subject.

This disclosure features methods of treating tyrosinemia (Type I, II, or III) in a subject in need thereof comprising administering to the subject an effective amount of a
30 compound described herein.

In some embodiments, the compound reduces systemic glycine levels in the subject. In some embodiments, the invention relates to methods of treating or preventing isovaleric acidemia, methylmalonic acidemia, propionic acidemia, maple syrup urine disease, DNAJC12 deficiency, urea cycle disorders, or hyperammonemia in a subject in need thereof comprising administering to the subject an effective amount of a compound described herein.

In some embodiments of any one of the disclosed methods, the compound modulates SLC6A19 in the subject.

In some embodiments of any one of the disclosed methods, the compound inhibits SLC6A19 in the subject.

In some embodiments of any one of the disclosed methods, the compound modulates SLC6A19 transport in the subject.

In some embodiments of any one of the disclosed methods, the compound inhibits SLC6A19 transport in the subject.

In some embodiments, the compound reduces systemic levels of an amino acid in the subject.

In some embodiments of any one of the disclosed methods, wherein the subject is a mammal. In some embodiments of any one of the disclosed methods, the mammal is a human.

Combination therapy

This disclosure contemplates both monotherapy regimens as well as combination therapy regimens. This may involve administering one or more of the compounds to a patient and then administering another agent to the patient.

In some embodiments, the methods described herein can further include administering one or more additional therapies (e.g., one or more additional therapeutic agents and/or one or more therapeutic regimens) in combination with administration of the compounds described herein.

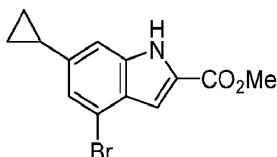
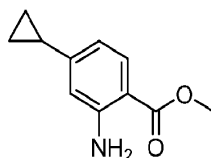
Compound Preparation

As can be appreciated by the skilled artisan, methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and RGM. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof. The starting materials used in preparing the compounds of the invention are known, made by known methods, or are commercially available. The skilled artisan will also recognize that conditions and reagents described herein that can be interchanged with alternative art-recognized equivalents. For example, in many reactions, triethylamine can be interchanged with other bases, such as non-nucleophilic bases (e.g. diisopropylamine, 1,8-diazabicycloundec-7-ene, 2,6-di-tert-butylpyridine, or tetrabutylphosphazene).

The skilled artisan will recognize a variety of analytical methods that can be used to characterize the compounds described herein, including, for example, ¹H NMR, heteronuclear NMR, mass spectrometry, liquid chromatography, and infrared spectroscopy. The foregoing list is a subset of characterization methods available to a skilled artisan and is not intended to be limiting.

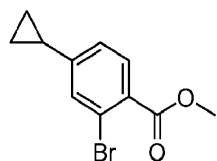
To further illustrate the foregoing, the following non-limiting, exemplary synthetic schemes are included. Variations of these examples within the scope of the claims are within the purview of one skilled in the art and are considered to fall within the scope of the invention as described, and claimed herein. The reader will recognize that the skilled artisan, provided with the present disclosure, and skill in the art is able to prepare and use the invention without exhaustive examples.

Preparation of Intermediates

General Procedure 1 : Synthesis of Indole-2-carboxylate intermediates**Intermediate 1: Preparation of methyl 4-bromo-6-cyclopropyl-1H-indole-2-carboxylate***Step 1: Preparation of methyl 2-amino-4-cyclopropylbenzoate*

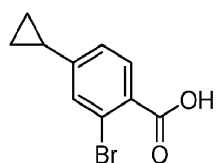
To a 1 L round-bottomed flask equipped with a magnetic stir bar, reflux condenser, and N₂ inlet was added methyl 2-amino-4-bromo-benzoate (25.00 g, 109 mmol), cyclopropylboronic acid (11.75 g, 137 mmol), palladium(II) acetate (733 mg, 3.26 mmol), tricyclohexylphosphine (1.85 g, 6.60 mmol), potassium phosphate tribasic (60.50 g, 285 mmol), toluene (300 mL), and water (50 mL). The mixture was degassed under vacuum/backfilled with N₂ (x 3). The brown mixture was then heated to reflux. After 2 h, LC/MS analysis revealed that the reaction was complete. The mixture was allowed to cool to room temperature and was filtered through Celite. The filter cake was washed with ethyl acetate (200 mL). The filtrate was washed with brine (150 mL), dried over magnesium sulfate, filtered, and concentrated to provide a brown oil. Chromatographic purification (CombiFlash, 330 g SiO₂ column, 0-20% ethyl acetate/heptane elute, combined fractions 25-30, rack 1 and 1-11, rack 2) afforded methyl 2-amino-4-cyclopropyl-benzoate (18.59 g, 97.2mmol, 90% Yield) as a light yellow solid; (M+1) = 192.

Step 2: Preparation of methyl 2-bromo-4-cyclopropylbenzoate



To a 1 L recovery flask equipped with a magnetic stir bar and addition funnel was added methyl 2-amino-4-cyclopropyl-benzoate (18.64 g, 97.5 mmol), 1,4-Dioxane (100 mL), and 48% hydrobromic acid solution (50 mL). The mixture was cooled to 0 °C while a solution of sodium nitrite (8.00 g, 116 mmol) in water (30 mL) was added via the addition funnel over 5 min. The resulting reddish mixture was allowed to stir at 0 °C. After 30 min, a mixture of copper(I) bromide (34.59 g, 241.1 mmol) in 48% hydrobromic acid solution (50 mL) was added to the mixture over 15 min via the addition funnel. The ice bath was removed, and the mixture was allowed to warm to room temperature. After 1 h, LC/MS analysis revealed that the reaction was complete. The mixture was diluted with water (300 mL) and was extracted with ethyl acetate (2 x 100 mL). The combined organic phases were washed with 3N ammonium hydroxide solution (200 mL) and brine (200 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated to provide a brown oil. Chromatographic purification (CombiFlash, 330 g SiO₂ column, 5-15% ethyl acetate/heptane elute, combined fractions 17-30, rack 1) afforded methyl 2-bromo-4-cyclopropyl-benzoate (15.85 g, 62.13 mmol, 64% Yield) as a yellow oil; (M+1) = 255.

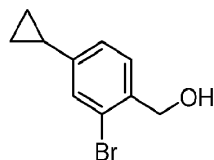
Step 3: Preparation of 2-bromo-4-cyclopropylbenzoic acid



To a 500 mL recovery flask equipped with a magnetic stir bar, reflux condenser, and N₂ inlet was added methyl 2-bromo-4-cyclopropyl-benzoate (17.36 g, 68.1 mmol), tetrahydrofuran (100 mL), and Water (50 mL). The solution was treated with lithium hydroxide monohydrate (8.50 g, 203 mmol), and the resulting mixture was heated to reflux.

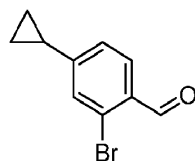
After 2 h, LC/MS analysis revealed that the reaction was complete. The mixture was allowed to cool to room temperature and was diluted with water (250 mL). The mixture was extracted with diethyl ether (150 mL, discarded). The phases were separated, and the aqueous phase was acidified with concentrated hydrochloric acid solution (~ 15 mL). The mixture was then extracted with diethyl ether (2 x 150 mL). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated to provide 2-bromo-4-cyclopropyl-benzoic acid (16.00 g, 66.37 mmol, 98% Yield) as a light yellow solid; (M-1) = 239.

Step 4: Preparation of (2-bromo-4-cyclopropylphenyl)methanol



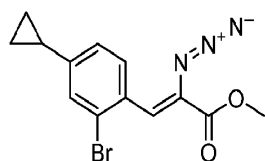
To a 1 L round-bottomed flask equipped with a magnetic stir bar, reflux condenser, and N₂ inlet was added 2-bromo-4-cyclopropyl-benzoic acid (16.00 g, 66.37 mmol) and tetrahydrofuran (100 mL). The solution was treated with borane dimethyl sulfide complex (9.6 mL, 100 mmol) via syringe over 3 min (gas evolution noted). The mixture was heated to reflux. After 30 min, LC/MS analysis revealed that the reaction was complete. The mixture was allowed to cool to room temperature. Methanol (15 mL) was slowly added to the reaction mixture (vigorous gas evolution!), and the resulting solution was allowed to stir. After 15 min, the mixture was concentrated to provide a milky white oil. Chromatographic purification (CombiFlash, 220 g SiO₂ column, 15-30% ethyl acetate/heptane elute, combined fractions 1-12, rack 1) afforded (2-bromo-4-cyclopropylphenyl)methanol (B, 13.69 g, 60.28 mmol, 91% Yield) as a white solid; (M+1) = 227.

Step 5: Preparation of 2-bromo-4-cyclopropylbenzaldehyde



To a 1L round-bottomed flask equipped with a magnetic stir bar, reflux condenser, and N₂ inlet was added (2-bromo-4-cyclopropyl-phenyl)methanol (26.10 g, 115 mmol), manganese(IV) oxide (85.00 g, 978 mmol), and chloroform (300 mL). The mixture was warmed to 70 °C and stirred. After 1 h, LC/MS analysis revealed that the reaction was complete. The mixture was allowed to cool to room temperature and was filtered through Celite. The filter cake was washed with chloroform (3 x 150 mL). The filtrate was concentrated to provide 2-bromo-4-cyclopropyl-benzaldehyde (25.30 g, 112 mmol, 98% Yield) as a light yellow oil.

Step 6: Preparation of methyl (Z)-2-azido-3-(2-bromo-4-cyclopropylphenyl)acrylate



To a 1L three-necked round-bottomed flask equipped with a magnetic stir bar, addition funnel, and N₂ inlet was added methanol (300 mL). Metallic sodium (5.12 g, 223 mmol) was added to the vessel, and the resulting mixture was allowed to stir as the solids dissolved. The resulting solution was cooled to -40 °C, and 2-bromo-4-cyclopropyl-benzaldehyde (12.50 g, 55.5 mmol) was added. The resulting mixture was allowed to stir at -40 °C for 15 min, and then methyl 2-azidoacetate (21.2 mL, 218 mmol) was added dropwise to the reaction mixture over 15 min. After the addition was complete, the yellow reaction mixture was allowed to slowly warm to room temperature. After 22 h, LC/MS analysis of the brown suspension revealed that the reaction was complete. The mixture was diluted with 1.0N hydrochloric acid solution (350 mL), and the resulting mixture was cooled to 0 °C and stirred. After 15 min, the mixture was filtered, and the filter cake was

washed with water (150 mL). The moist solids were dissolved in ethyl acetate (250 mL), and the resulting brown solution was dried over magnesium sulfate, filtered, and concentrated to provide methyl (Z)-2-azido-3-(2-bromo-4-cyclopropyl-phenyl)prop-2-enoate (13.28 g, 41.22 mmol, 74% Yield) as a brown oil.

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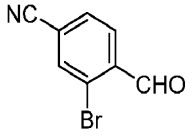
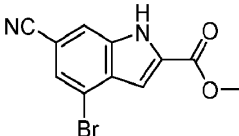
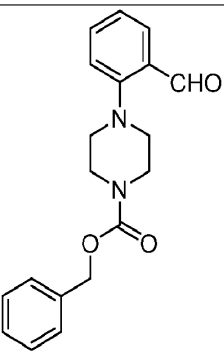
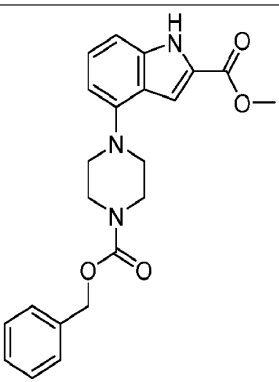
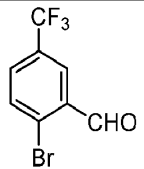
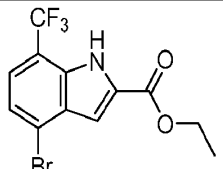
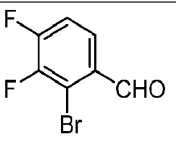
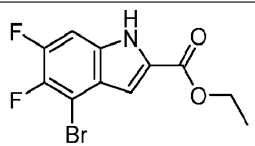
Step 7: Preparation of methyl 4-bromo-6-cyclopropyl-1H-indole-2-carboxylate

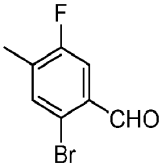
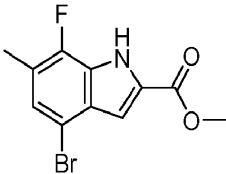
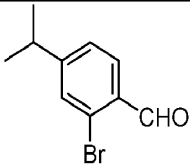
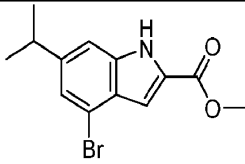
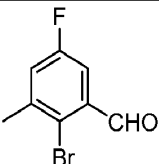
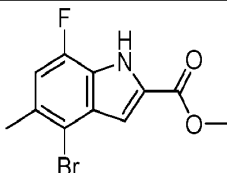
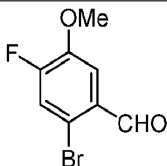
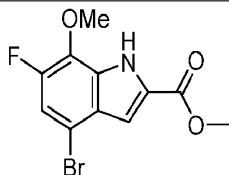
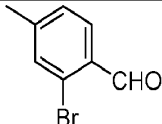
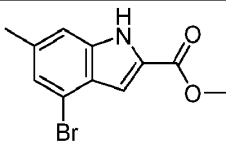
To a 1 L round-bottomed flask equipped with a magnetic stir bar, reflux condenser, and N₂ inlet was added methyl (Z)-2-azido-3-(2-bromo-4-cyclopropyl-phenyl)prop-2-enoate (14.08 g, 43.7 mmol) and p-xylene (300 mL). The mixture was heated to reflux. After 1.5 h, LC/MS analysis revealed that the reaction was complete. The mixture was allowed to cool to room temperature and was concentrated to provide an orange solid. The crude solid was suspended in heptane (150 mL) and ethyl acetate (15 mL). The mixture was heated to reflux. After 20 min, most of the solids had dissolved to provide a red-brown solution. The mixture was allowed to cool to room temperature and was then placed in the refrigerator overnight, resulting in the formation of a precipitate. The liquid phase of the mixture was decanted, and the remaining solid was subjected to chromatographic purification (CombiFlash, 220 g SiO₂ gold column, 10-40% ethyl acetate/heptane elute, combined fractions 10-30, rack 1) to afford a yellow solid. The solid was suspended in heptane (125 mL) and heated to reflux. The mixture was allowed to cool to room temperature and was further cooled in the refrigerator for 45 min. The cold suspension was filtered, and the filter cake was washed with a small amount of heptane (20 mL) and dried to provide methyl 4-bromo-6-cyclopropyl-1H-indole-2-carboxylate (9.09 g, 30.9 mmol, 71% Yield) as an off-white solid; (M+1) = 294

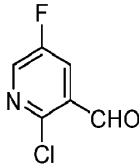
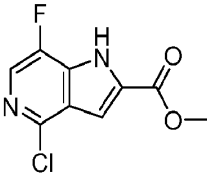
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The following indole-2-carboxylates were prepared from the corresponding aldehydes as described in **Steps 6-7 of General Procedure 1**:

Intermediate	Aldehyde	Indole-2-carboxylate	MS
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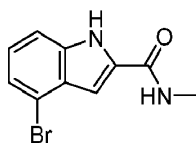
2	 Commercially Available CAS 89891-69-0		(M+1) = 277
3	 See WO2003094918		(M+1) = 394
4 (note: ethyl azidoacetate used in place of methyl azidoacetate)	 Commercially Available CAS 102684-91-3		(M+1) = 336
5 (note: ethyl azidoacetate used in place of methyl azidoacetate)	 Commercially Available CAS 1578156-21-4		(M-1) = 302

6	 Commercially Available CAS 916792-21-7		(M-1) = 284
7	 Commercially Available CAS 861897-63-4		(M-1) = 294
8	 Commercially Available CAS 1799977-88-0		(M-1) = 284
9	 Commercially Available CAS 865186-62-5		(M-1) = 300
10	 Commercially Available CAS 824-54-4		(M-1) = 266

11	 Commercially Available CAS 851484-95-2		(M-1) = 227
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5 **General Procedure 2: Preparation of heterocyclic carboxamides
via amination of esters**

**Intermediate 12: Preparation of 4-bromo-N-methyl-1H-indole-2-
carboxamide**

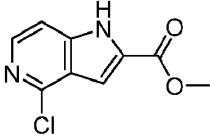
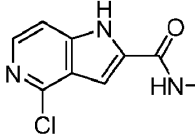
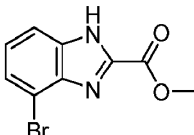
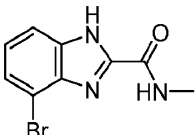
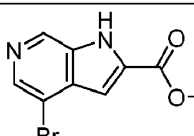
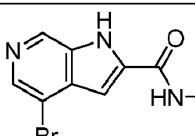
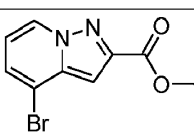
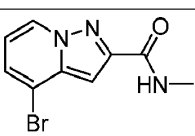
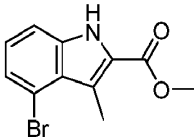
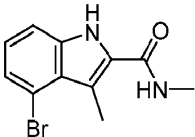
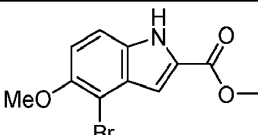
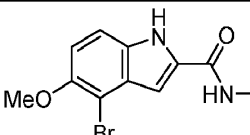
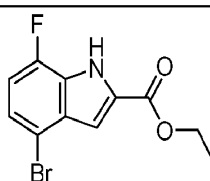
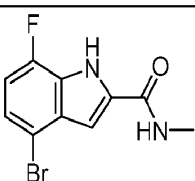
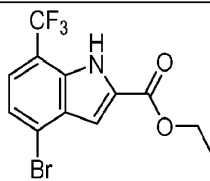
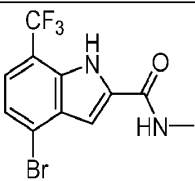


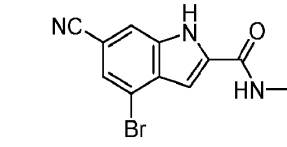
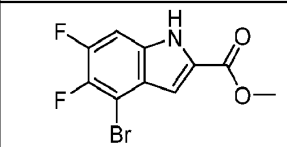
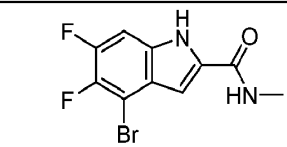
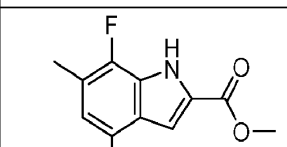
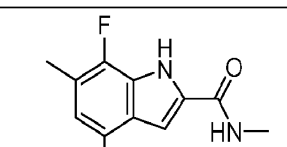
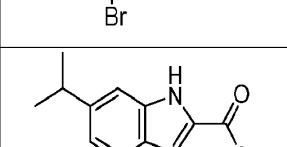
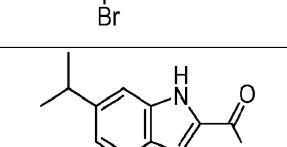
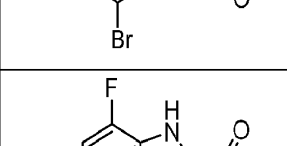
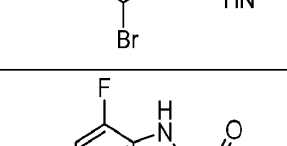
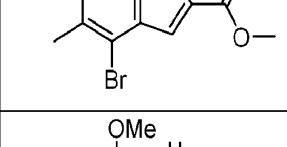
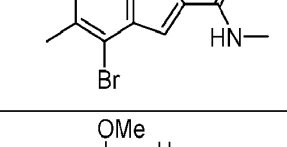
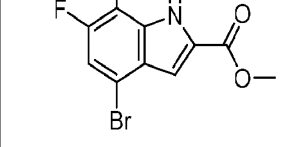
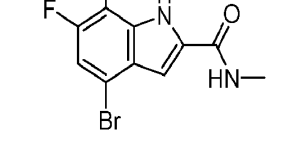
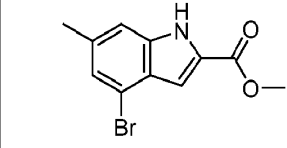
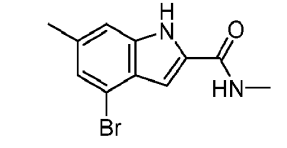
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To a 20 mL microwave reaction vial equipped with a magnetic stir bar was added methyl 4-bromo-1H-indole-2-carboxylate (11.06 g, 42.66 mmol, **CAS 167479-13-2**) and 33% methylamine solution in ethanol (15 mL, 120.49 mmol). The vessel was sealed and the contents were heated to 130 °C in the microwave reactor. After 1 h, LC/MS analysis revealed that the reaction was nearly complete. The mixture was allowed to cool to room temperature, resulting in the formation of a precipitate. The mixture was diluted with water (75 mL) and filtered. The filter cake was washed with water (50 mL) and dried to provide 4-bromo-N-methyl-1H-indole-2-carboxamide (10.25 g, 40.50 mmol, 95 % yield) as a white solid; (M+1) = 253.

20

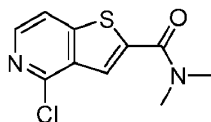
The following carboxamides were prepared from the corresponding esters as described in **General Procedure 2**:

Intermediate	Ester	Carboxamide	MS
13			(M+ 1) = 210
14			(M+ 1) = 254
15			(M- 1) = 252
16			(M+ 1) = 254
17			(M- 1) = 265
18			(M+ 1) = 283
19			(M+ 1) = 271
20			(M+ 1) = 321

21			(M+ 1) = 278
22			(M+ 1) = 289
23			(M- 1) = 283
24			(M- 1) = 293
25			(M- 1) = 283
26			(M+ 1) = 301
27			(M- 1) = 265
28			(M+ 1) = 295

General Procedure 3: Preparation of heterocyclic carboxamides via HATU-mediated amidation

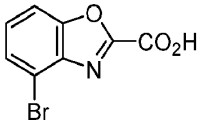
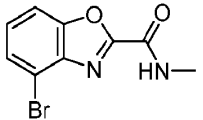
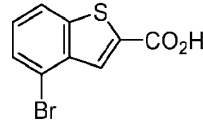
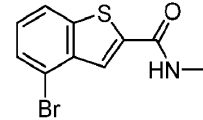
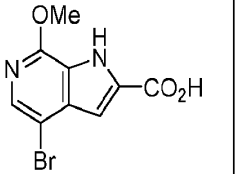
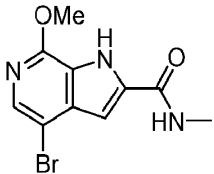
Intermediate 29: Preparation of 4-chloro-N,N-dimethylthieno[3,2-c]pyridine-2-carboxamide



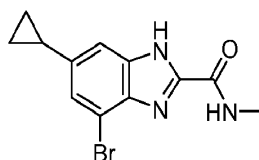
A mixture of 4-chlorothieno[3,2-c]pyridine-2-carboxylic acid (300 mg, 1.3 mmol, CAS 1360891-68-4), dimethylamine (2.7 mL, 5.3 mmol) (2 M in THF), and HATU (686.9 mg, 1.7 mmol) in DMF (5 mL) was stirred at 2 h. More HATU (140 mg) was added to drive the reaction to completion. LC/MS indicated all starting material was consumed. The reaction mixture was partitioned between 1 M NaOH and EtOAc. The two layers were separated, and the aqueous layer was extracted with EtOAc (2X). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The crude material was purified on silica gel with EtOAc (100%) as eluant to provide 4-chloro-N,N-dimethylthieno[3,2-c]pyridine-2-carboxamide (319 mg, 1.3 mmol, 99% yield) as a white solid; (M+1) = 241.

The following carboxamides were prepared from the corresponding acids as described in **General Procedure 3**:

Intermediate	Acid	Amine	Carboxamide	MS
30	 Commercially Available CAS 1369143-28-1	MeNH ₂		(M+1) = 254

31	 Commercially Available CAS 944907-35-1	MeNH ₂		(M + 1) = 255
32	 Commercially Available CAS 5194-37-6	MeN H ₂		(M + 1) = 270
33	 Commercially Available CAS 2383841-35-6	MeNH ₂		(M + 1) = 283

Intermediate 34: Preparation of 4-bromo-6-cyclopropyl-N-methyl-1H-benzo[d]imidazole-2-carboxamide

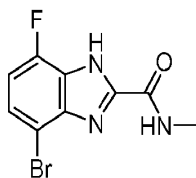


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A solution of 4-bromo-6-cyclopropyl-2-(trichloromethyl)-1H-benzimidazole (1.20 g, 3.39 mmol, see **WO2011097491**) in acetonitrile (20 mL) was treated with methylamine hydrochloride (0.45 g, 6.67 mmol), followed by the dropwise addition of 4M potassium carbonate solution (2.30 g, 16.9 mmol). The mixture was stirred at room temperature overnight, and then it was quenched by addition of brine and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel (MeOH/DCM: 0-5%) to provide 4-bromo-6-cyclopropyl-N-methyl-1H-benzo[d]imidazole-2-carboxamide as yellow solid (0.70 g, 70% Yield); (M+1) = 294.

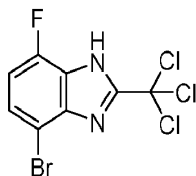
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Intermediate 35: Preparation of 4-bromo-7-fluoro-N-methyl-1H-benzo[d]imidazole-2-carboxamide



5

Step 1: Preparation of 4-bromo-7-fluoro-2-(trichloromethyl)-1H-benzo[d]imidazole



10

2,2,2-Trichloro-acetimidic acid benzyl ester (0.95 mL, 5.12 mmol) was added to a solution of 3-bromo-6-fluoro-benzene-1,2-diamine (1.0 g, 4.88 mmol, **CAS 1805502-21-9**) in acetic acid (30 mL), and the resulting solution was stirred at room temperature. After 1 h, water (20 mL) was added to the mixture and the suspension was filtered. The filter cake was washed with water and dried under vacuum to afford 4-bromo-7-fluoro-2-(trichloromethyl)-1H-benzo[d]imidazole which was used directly for the next step without further purification.

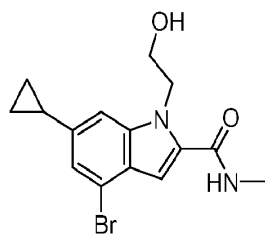
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Step 2: Preparation of 4-bromo-7-fluoro-N-methyl-1H-benzo[d]imidazole-2-carboxamide

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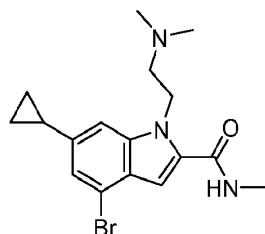
The title compound was prepared according to the procedure described for the preparation of **Intermediate 34**; (M+1) = 272.

Intermediate 36: Preparation of 4-bromo-6-cyclopropyl-1-(2-hydroxyethyl)-N-methyl-1H-indole-2-carboxamide



To a solution of 4-bromo-6-cyclopropyl-N-methyl-1H-indole-2-carboxamide (60 mg, 0.21 mmol, **Intermediate 28**), potassium hydroxide (34 mg, 0.61 mmol) and potassium iodide (7 mg, 0.04 mmol) in acetone (3 mL) was added (2-bromoethoxy)(tert-butyl)dimethylsilane (49 mg, 0.21 mmol). The mixture was allowed to stir at room temperature. After 16 h, LC/MS showed 20% of desilated product formed. Water (10 mL) was added and the mixture was extracted with ethyl acetate (15 mL×3). The combined organic layers were washed with water (10 mL×2) and brine, dried over anhydrous sodium sulfate and concentrated in vacuum. The residue was purified by silica gel column chromatography (eluted with PE:EA=1:1) to give 4-bromo-6-cyclopropyl-1-(2-hydroxyethyl)-N-methyl- indole-2-carboxamide (10 mg, 15% yield); (M+1) = 337.

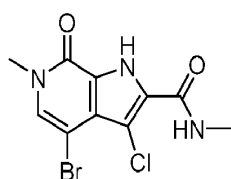
Intermediate 37: Preparation of 4-bromo-6-cyclopropyl-1-(2-(dimethylamino)ethyl)-N-methyl-1H-indole-2-carboxamide



To a 0 °C solution of 4-bromo-6-cyclopropyl-N-methyl-1H-indole-2-carboxamide (50 mg, 0.17 mmol, **Intermediate 28**) in tetrahydrofuran (3 mL) was added sodium hydride (6 mg, 0.26 mmol). The mixture was allowed to warm to at room temperature and stir. After 1 h, the mixture was treated with 2-bromo-N,N-dimethylethan-1-amine hydrobromide (44 mg, 0.19 mmol) and was allowed to stir at room temperature. After 1

h, the reaction was quenched by the addition of water and ethyl acetate, and the resulting mixture was filtered. The aqueous layer was washed two times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (PE:EA=4:1) to give ethyl 2-[benzyloxycarbonyl-[(4-bromophenyl)methyl]amino]acetate (25 mg, 0.07 mmol, 40% yield); (M+1) = 364.

Intermediate 38: Preparation of 4-bromo-3-chloro-N,6-dimethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

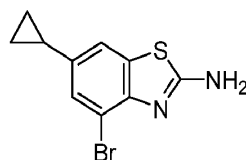


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To a 5 mL microwave reaction vial was added 4-bromo-N,6-dimethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (54 mg, 191 μ mol, see WO2017177955) and DMF (2 mL). The mixture was treated with N-chlorosuccinimide (27 mg, 200 μ mol). The mixture was allowed to stir at room temperature for 45 minutes, then was heated to 60°C for overnight. The heterogeneous reaction mixture was filtered, and the filter cake was dried to provide 4-bromo-3-chloro-N,6-dimethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (45 mg, 142 μ mol, 75% yield) as a white solid; (M+1) = 318.

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Intermediate 39: Preparation of 4-bromo-6-cyclopropylbenzo[d]thiazol-2-amine



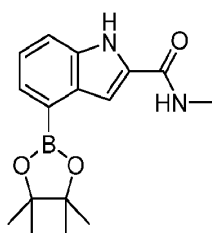
To a solution of 4-cyclopropylaniline (2.00 g, 15.0 mmol, CAS 3158-71-2) in acetic acid (40 mL) was added bromine (4.80 g, 30.0 mmol), and the resulting mixture was allowed to stir at the room temperature After 5 min, potassium thiocyanate (10.2 g,

25

105 mmol) was added. The mixture was allowed to stir at room temperature. After 2 h, the mixture was diluted with ethyl acetate and water. The aqueous layer was washed two times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography to give 4-bromo-6-cyclopropyl-1,3-benzothiazol-2-amine (180 mg, 0.67 mmol, 4% Yield); (M+)

5 = 269.

Intermediate 40: Preparation of N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-2-carboxamide



10

To a 500 mL round-bottomed flask equipped with a magnetic stir bar, reflux condenser, and N₂ inlet was added 4-bromo-N-methyl-1H-indole-2-carboxamide (6.49 g, 25.64 mmol, **Intermediate 12**), pinacolborane (5.75 mL, 38.46 mmol), bis(acetonitrile)palladium(II) chloride (134 mg, 513 μmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (859.35 mg, 2.05 mmol), triethylamine (10.78 mL, 76.93 mmol), and 1,4-dioxane (80 mL). The mixture was degassed under vacuum/backfilled with N₂ (x 3). The mixture was then heated to reflux. After 1 h, LC/MS analysis of the mixture

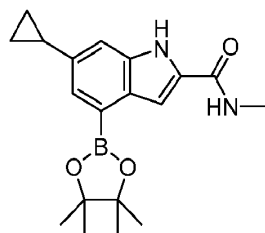
15 revealed the presence of several new products, including the desired boronate ester (major) and the de-halogenated starting material (minor)). The mixture was allowed to cool to room temperature and was diluted with water (300 mL). The resulting precipitate was isolated by filtration, and the filter cake was washed with water (50 mL). The moist solids were dissolved in ethyl acetate (150 mL), and the solution dried over magnesium sulfate,

20 filtered, and concentrated to provide N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-

25

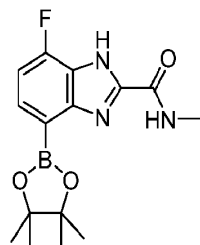
2-yl)-1H-indole-2-carboxamide (5.72 g, 19.06 mmol, 74 % yield) as a yellow solid; (M+1) = 301.

Intermediate 41: Preparation of 6-cyclopropyl-N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-2-carboxamide



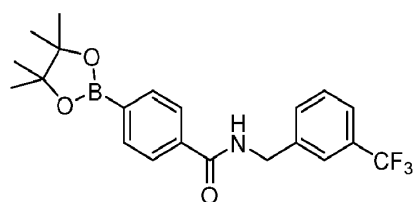
To a 20 mL microwave reaction vial equipped with a magnetic stir bar was added 4-bromo-6-cyclopropyl-N-methyl-1H-indole-2-carboxamide (1.05 g, 3.58 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.36 g, 5.36 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.15 g, 0.18 mmol), potassium acetate (1.41 g, 14.4 mmol), and 1,4-dioxane (12 mL). The vessel was sealed, and the contents were degassed under vacuum/backfilled with N₂ (x 3). The mixture was heated to 125 °C in a heating block. After 2.5 h, LC/MS analysis revealed that the reaction was complete. The mixture was allowed to cool to room temperature and was diluted with water (100 mL), resulting in the formation of a precipitate. The mixture was filtered, and the filter cake was washed with water (30 mL). The moist solids were dissolved in ethyl acetate (75 mL). The mixture was washed with brine (50 mL), and the resulting emulsion was filtered through Celite. The filter cake was washed with ethyl acetate (25 mL). The phases of the filtrate were separated, and the organic phase was dried over magnesium sulfate, filtered, and concentrated to provide 6-cyclopropyl-N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-2-carboxamide (794 mg, 2.33mmol, 65% Yield) as a brown solid; (M+1) = 341.

Intermediate 42: Preparation of 7-fluoro-N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole-2-carboxamide



5 The title compound was prepared from 4-bromo-7-fluoro-N-methyl-1H-benzo[d]imidazole-2-carboxamide (**Intermediate 35**) as described for the preparation of **Intermediate 41**; (M+1) = 320.

10 **Intermediate 43: Preparation of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(3-(trifluoromethyl)benzyl)benzamide**

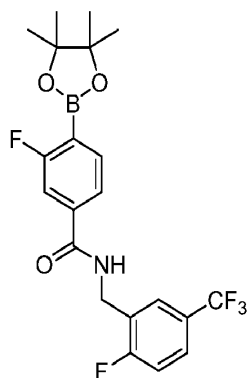


To a 500 mL round-bottomed flask equipped with a magnetic stir bar and N₂ inlet was added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (9.3 g, 37 mmol, 15 **CAS 180516-87-4**), HATU (15.00 g, 39.45 mmol), dichloromethane (200 mL), and N,N-diisopropylethylamine (8.5 mL, 49 mmol). The resulting suspension was allowed to stir at room temperature for 5 min, and then and 3-(trifluoromethyl)benzylamine (7.22 g, 41.2 mmol) was added. The mixture was allowed to continue to stir at room temperature. After 30 min, LC/MS analysis revealed that the reaction was complete. The mixture was diluted 20 with dichloromethane (50 mL) and was washed with 1.0N hydrochloric acid solution (200 mL), 1.0N sodium hydroxide solution (200 mL), and brine (150 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated. The crude product was suspended in heptane (300 mL) and was stirred vigorously. After 30 min, a solid had

formed. The suspension was filtered, and the filter cake was washed with heptane (50 mL) and dried to provide 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-[[3-(trifluoromethyl)phenyl]methyl]benzamide (10.15 g, 25.05 mmol, 67% Yield) as a white solid; (M+1) = 406.

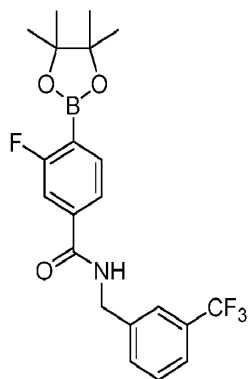
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Intermediate 44: Preparation of 3-fluoro-N-(2-fluoro-5-(trifluoromethyl)benzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



10 The title compound was prepared as from 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (CAS 867256-77-7) and (2-fluoro-5-(trifluoromethyl)phenyl)methanamine as described for the preparation of **Intermediate 43**; (M+1) = 442.

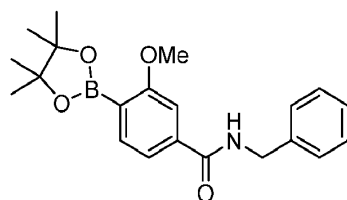
15 **Intermediate 45: Preparation of 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(3-(trifluoromethyl)benzyl)benzamide**



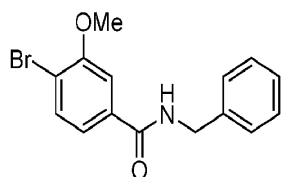
The title compound was prepared as from 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid and 3-(trifluoromethyl)benzylamine as described for the preparation of **Intermediate 43**; (M+1) = 424.

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Intermediate 46: Preparation of N-benzyl-3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



10 *Step 1: Preparation of N-benzyl-4-bromo-3-methoxybenzamide*

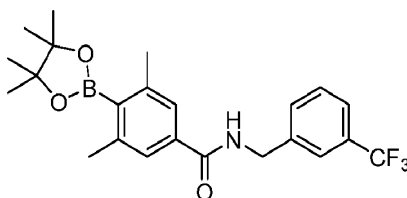


A mixture of 4-bromo-3-methoxy-benzoic acid (462 mg, 2.00 mmol, **CAS 56256-14-5**) and HATU (1.14 g, 3.00 mmol) in N,N-Dimethylformamide (5 mL) was allowed to stir at room temperature. After 15 min, benzylamine (225 mg, 2.10 mmol) and N,N-diisopropylethylamine (775 mg, 6.00 mmol) were added. The mixture was allowed to stir at room temperature. After 2 h, the mixture was diluted with ethyl acetate (60 mL) and water (15 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (40 mL x 2). The combined organic phases were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with flash chromatography (0-30% ethyl acetate/petroleum ether) to provide N-benzyl-4-bromo-3-methoxy-benzamide (550 mg, 86% yield); (M+1) = 320.

Step 2: Preparation of N-benzyl-3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

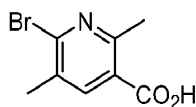
The title compound was prepared from N-benzyl-4-bromo-3-methoxybenzamide as described for the preparation of **Intermediate 41**.

Intermediate 47: Preparation of 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(3-(trifluoromethyl)benzyl)benzamide



The title compound was prepared from 4-bromo-3,5-dimethylbenzoic acid (CAS 7697-32-7) and (3-(trifluoromethyl)benzyl)amine as described in Steps 1-2 for the preparation of **Intermediate 45**; (M+1) = 434.

Intermediate 48: Preparation of 6-bromo-2,5-dimethylnicotinic acid

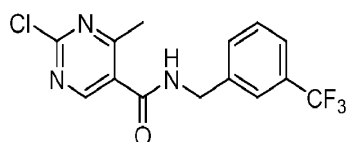


To a 100 mL recovery flask equipped with a magnetic stir bar and N₂ inlet was added silver nitrate (988 mg, 5.80 mmol) and water (10 mL). The solution was cooled to 0 °C while sodium hydroxide (597 mg, 14.93 mmol) in water (10 mL) was added in one portion. To the resulting brown suspension was added 6-bromo-2,5-dimethylnicotinaldehyde (744 mg, 3.48 mmol, see **WO2022266162**), and the mixture was allowed to stir at 0 °C. After 45 min, LC/MS analysis revealed that the reaction was complete. The mixture was filtered, and the filter cake was washed with water (15 mL). The pH of the filtrate was adjusted to ~ 3 by the addition of 1N hydrochloric acid solution (~ 8 mL), resulting in the formation of a precipitate. The mixture was filtered, and the filter cake was washed with water (15 mL). The moist solids were dissolved in ethyl acetate (20

mL), and the resulting solution was dried over magnesium sulfate, filtered, and concentrated to provide 6-bromo-2,5-dimethylnicotinic acid (693 mg, 3.01 mmol, 87% yield) as a white solid; (M+1) = 230.

5 **General Procedure 4: Preparation of halogenated coupling partners**

Intermediate 49: Preparation of 2-chloro-4-methyl-N-(3-(trifluoromethyl)benzyl)pyrimidine-5-carboxamide



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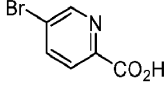
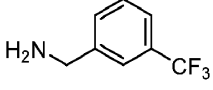
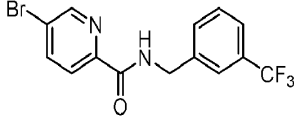
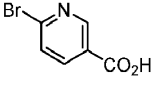
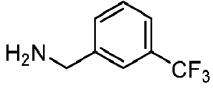
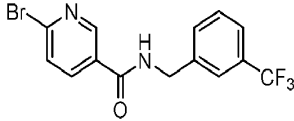
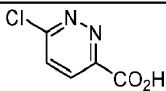
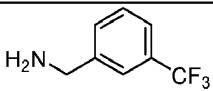
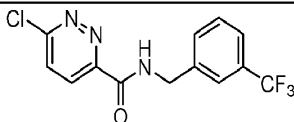
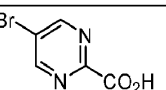
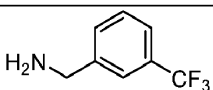
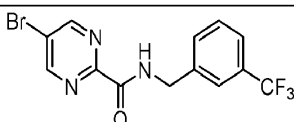
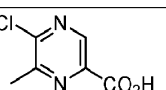
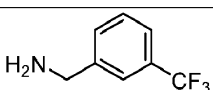
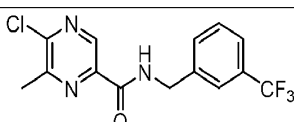
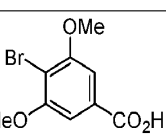
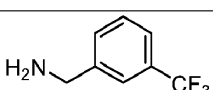
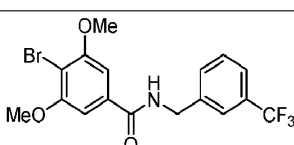
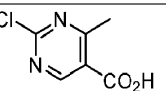
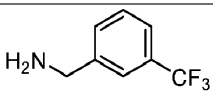
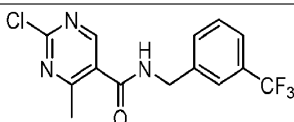
To a 200 mL recovery flask equipped with a magnetic stir bar and N₂ inlet was added 2-chloro-4-methylpyrimidine-5-carboxylic acid (517 mg, 3.00 mmol, **CAS 188781-10-4**), HATU (1.49 g, 3.89 mmol), N,N-dimethylformamide (20 mL), and N,N-diisopropylethylamine (1.58 mL, 8.99 mmol). The mixture was allowed to stir at room temperature for 5 min, and then 3-(trifluoromethyl)benzylamine (607 mg, 3.30 mmol) was added. The resulting yellow mixture was allowed to stir at room temperature. After 1 h, LC/MS analysis revealed that some of the desired material had formed. The mixture was diluted with water (50 mL) and extracted with diethyl ether (2 x 40 mL). The combined organic phases were washed with 1N hydrochloric acid solution (75 mL), dried over magnesium sulfate, filtered, and concentrated to provide a brown oil. Chromatographic purification (CombiFlash, 80 g SiO₂ gold column, 10-60% 3:1 ethyl acetate:ethanol/heptane elute, combined fractions 24-27, rack 1) afforded 2-chloro-4-methyl-N-(3-(trifluoromethyl)benzyl)pyrimidine-5-carboxamide (347 mg, 1.05 mmol, 35% yield) as a white solid; (M+1) = 330.

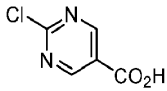
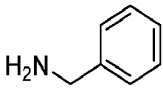
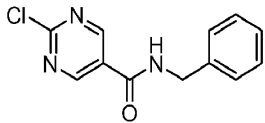
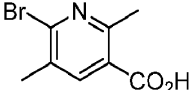
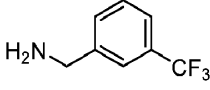
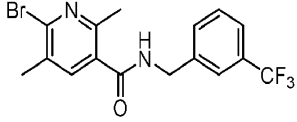
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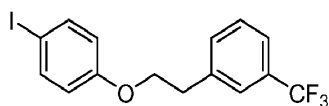
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The following carboxamides were prepared from the corresponding acids as described in **General Procedure 4**:

Intermediate	Acid	Amine	Carboxamide	Mass
50	 Commercially Available CAS 30766-11-1			(M+1) = 359
51	 Commercially Available CAS 6311-35-9			(M+1) = 359
52	 Commercially Available CAS 5096-73-1			(M+1) = 316
53	 Commercially Available CAS 37131-87-6			(M+1) = 360
54	 Commercially Available CAS 188781-36-4			(M+1) = 330
55	 Commercially Available CAS 56518-42-4			(M+1) = 418
56	 Commercially Available CAS 188781-10-4			(M-1) = 328

57	 Commercially Available CAS 374068-01-6			(M+1) = 248
58	 Intermediate 48			(M+1) = 387

Example 59: Preparation of 1-(2-(4-iodophenoxy)ethyl)-3-(trifluoromethyl)benzene

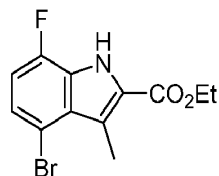


5

To a 100 mL recovery flask equipped with a magnetic stir bar and N₂ inlet was added 4-iodophenol (555 mg, 2.50 mmol), 3-(trifluoromethyl)phenethyl alcohol (418 μ l, 2.75 mmol), polymer-bound triphenylphosphine (1.15 g, 4.40 mmol), and tetrahydrofuran (25 mL). The mixture was treated with bis(2-methoxyethyl)diazene-1,2-dicarboxylate (819 mg, 3.50 mmol), resulting in a mild exotherm after ~ 3 min. The mixture was allowed to stir at room temperature. After 1.75 h, LC/MS analysis revealed that the reaction was complete. The mixture was filtered to remove the resin-bound material, and the filter cake was washed with ethyl acetate (40 mL). The filtrate was washed with 1N hydrochloric acid solution (30 mL), 1N sodium hydroxide solution (30 mL), and brine (30 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated to provide a yellow oil. Chromatographic purification (CombiFlash, 40 g SiO₂ gold column, 0-25% ethyl acetate/heptane elute, combined fractions 14-16, rack 1) afforded 1-(2-(4-iodophenoxy)ethyl)-3-(trifluoromethyl)benzene (488 mg, 1.24 mmol, 50 % yield) as a white solid; (no M+1/M-1 peak observed).

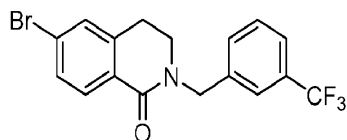
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Intermediate 60: Preparation of ethyl 4-bromo-7-fluoro-3-methyl-1H-indole-2-carboxylate



5 To a 500 mL round-bottomed flask equipped with a magnetic stir bar, reflux condenser, and N₂ inlet was added (5-bromo-2-fluorophenyl)hydrazine hydrochloride (4.16 g, 16.88 mmol, **CAS 214916-08-2**), ethanol (50 mL), and concentrated hydrochloric acid solution (50 mL). The solution was treated with 2-ketobutyric acid (1.81 g, 17.20 mmol), and the resulting mixture was heated to reflux. As the mixture warmed, a thick
10 yellow precipitate formed in the mixture. The solids gradually dissolved as heating continued to provide a dark brown mixture. After 2 h, LC/MS analysis revealed that the reaction was complete. This mixture was allowed to cool to room temperature and was diluted with water (300 mL) and ethyl acetate (100 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (100 mL). The combined organic
15 phases were washed with saturated sodium bicarbonate solution (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered, and concentrated to provide a brown solid. Chromatographic purification (CombiFlash, 220 g SiO₂ column, 10-50% ethyl acetate/heptane elute, combined fractions 3-11, rack 1) afforded ethyl 4-bromo-7-fluoro-3-methyl-1H-indole-2-carboxylate (2.02 g, 6.73 mmol, 39.9 % yield) as a light orange
20 solid; (M-1) = 298.

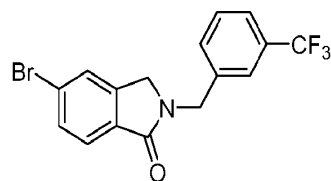
Intermediate 61: Preparation of 6-bromo-2-(3-(trifluoromethyl)benzyl)-3,4-dihydroisoquinolin-1(2H)-one



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To a stirred and cooled (0 °C) solution of 6-bromo-3,4-dihydroisoquinolin-1(2H)-one (1.50 g, 6.64 mmol, **CAS 147497-32-3**) in DMF (25 mL) was added a 60% dispersion of sodium hydride in mineral oil (0.350 g, 8.75 mmol, **CAS 402-23-3**). The frothy mixture was maintained at 0 °C for 30 minutes and then treated with 3-(trifluoromethyl)benzyl bromide (1.32 mL, 2.07 g, 8.64 mmol). Following the addition, the cooling bath was removed. One hour later the reaction was analyzed by LCMS and found to be complete. The mixture was concentrated and the residue was partitioned between ethyl acetate (~75 mL) and water (~100 mL). The organic layer was combined with a back extract of the aqueous layer (ethyl acetate, 1 x ~50 mL), dried over sodium sulfate and concentrated onto ~8 g of silica. The impregnated media was subjected to automated flash chromatography (Combiflash Rf instrument; 10 to 30% ethyl acetate in heptane; 120 g silica column) to afford purified product as a waxy, pale amber solid (2.53 g, 99% Yield); (M+1) = 384.

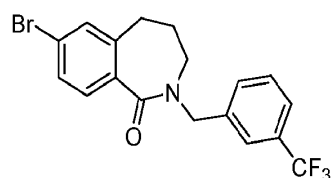
Intermediate 62: Preparation of 5-bromo-2-(3-(trifluoromethyl)benzyl)isoindolin-1-one



To a stirred solution of 5-bromoisindolin-1-one (2.00 g, 9.43 mmol, **CAS 552330-86-6**) in DMF (35 mL) was added a 60% dispersion of sodium hydride in mineral oil (0.490 g, 12.3 mmol, 1.30 eq). After gas evolution ceased, the reaction was cooled in an ice bath and treated with 3-(trifluoromethyl)benzyl bromide (1.87 mL, 2.93 g, 12.2 mmol). The cooling bath was removed and mixture was left to stir overnight at room temperature. After this time, the reaction was concentrated and the residue was partitioned between water (~125 mL) and ethyl acetate (~100 mL). The organic layer was washed a second time with water (1 x ~125 mL), dried over sodium sulfate and concentrated onto ~12 g of silica. The impregnated media was subjected to automated flash chromatography (Combiflash Rf

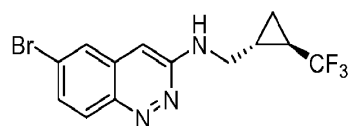
instrument; 20 to 30% ethyl acetate in heptane; 220 g silica column) to afford purified product as a light yellow solid (1.30 g, 37% Yield); (M+1) = 370.

5 **Intermediate 63: Preparation of 7-bromo-2-(3-(trifluoromethyl)benzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one**



To a stirred solution of 7-bromo-2,3,4,5-tetrahydro-1H-benzo[c]azepin-1-one (0.250 g, 1.04 mmol, CAS 1547064-78-7) in DMF (8 mL) was added a 60% dispersion of sodium hydride in mineral oil (54.1 mg, 1.35 mmol, 1.30 eq). After gas evolution ceased, the reaction was cooled in an ice bath and treated with 3-(trifluoromethyl)benzyl bromide (200 μ L, 0.313 g, 1.31 mmol, 1.26 eq). The cooling bath was removed and the reaction was allowed to warm to room temperature. After two hours, the mixture was diluted with water (~40 mL). The resulting suspension was sonicated until homogenous (10-15 minutes) and then suction filtered. The filter cake was rinsed with water (3 x ~10 mL) and heptane (2 x ~10 mL) before air drying on the frit under house vacuum. Crude product, which was deemed sufficiently pure to use without chromatography, was afforded as a tan solid (0.376 g, 91% Yield). (M+1) = 398.

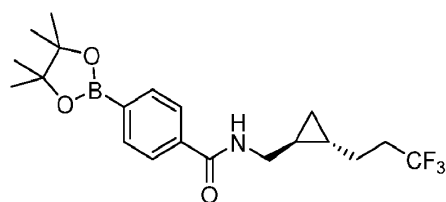
20 **Intermediate 64: Preparation of 6-bromo-N-((rac-(trans)-2-(trifluoromethyl)cyclopropyl)methyl)cinnolin-3-amine**



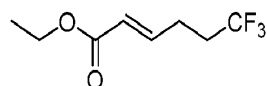
To a 20 mL microwave reaction vial equipped with a magnetic stir bar was added 6-bromo-3-chlorocinnoline (500 mg, 2.05 mmol, CAS 2665665-30-3), [rac-(trans)-2-(trifluoromethyl)cyclopropyl]methanamine hydrochloride (583 mg, 3.32 mmol, CAS

2137837-57-9), potassium carbonate (1.70 g, 12.3 mmol), and NMP (10 mL). The vessel was sealed, and the contents were heated to 115 °C in a heating block. After 16 h, LC/MS analysis revealed that the reaction was complete. The mixture was allowed to cool to room temperature and was diluted with water (60 mL). The mixture was extracted with ethyl acetate (50 mL). The organic phase was separated and was washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated to provide a brown oil. Chromatographic purification (CombiFlash, 40 g SiO₂ gold column, 20-60% 3:1 ethyl acetate; ethanol/heptane elute, combined fractions 13-15, rack 1) afforded 6-bromo-N-[[rac-(1R,2R)-2-(trifluoromethyl)cyclopropyl]methyl]cinnolin-3-amine (403 mg, 1.16 mmol, 57% Yield) as a brown foamy solid; (M+1) = 346.

Intermediate 65: Preparation of rac-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(((trans)-2-(3,3,3-trifluoropropyl)cyclopropyl)methyl)benzamide

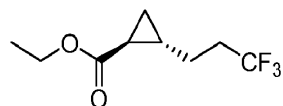


Step 1: Preparation of ethyl (E)-6,6,6-trifluorohex-2-enoate



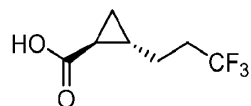
To a solution of 4,4,4-trifluorobutanal (3.8 mL, 36.5 mmol) in dichloromethane (50 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (19.1 g, 54.7 mmol), and the mixture was stirred at room temperature. After 3 h, the mixture was diluted with ethyl acetate (100 mL) and water (30 mL). The aqueous layer was washed with ethyl acetate (3×30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (eluted with PE/EA=20/1) to give ethyl (E)-6,6,6-trifluorohex-2-enoate (3.70 g, 52% Yield); (M+1) = 197.

Step 2: Preparation of *rac-trans*-ethyl-2-(3,3,3-trifluoropropyl)cyclopropane-1-carboxylate



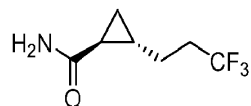
To a 0 °C mixture of 1-methyl-3-nitro-1-nitroso-guanidine (750 mg, 5.10 mmol) in diethyl ether (10 mL) was added a cold solution of potassium hydroxide (286 mg, 5.10 mmol) in water (2 mL). After stirring for 2 min, a portion of yellow ethereal solution of the resulting diazomethane was added to a solution of ethyl (E)-6,6,6-trifluorohex-2-enoate (1.00 g, 5.10 mmol) in ether (20 mL) at 0 °C. Palladium acetate (172 mg, 0.765 mmol) was added followed by an additional diazomethane solution. This process was continued until all the palladium acetate and diazomethane solution was added. The mixture was stirred at 0 °C for 4 h and acetic acid (5 drops) was added. Then removal of solvent in vacuo gave *rac-trans*-ethyl-2-(3,3,3-trifluoropropyl)cyclopropane-1-carboxylate (852 mg, 80% yield); (M+1) = 211.

Step 3: Preparation of *rac-trans*-2-(3,3,3-trifluoropropyl)cyclopropane-1-carboxylic acid



To a solution of *rac-trans*-ethyl-2-(3,3,3-trifluoropropyl)cyclopropane-1-carboxylate (852 mg, 4.05 mmol) in THF (10 mL) was added 1 N aqueous LiOH (971 mg, 40.5 mmol). The mixture was stirred overnight at room temperature. The mixture was adjusted to pH=3~4 using aq HCl, extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to provide *rac-trans*-2-(3,3,3-trifluoropropyl)cyclopropane-1-carboxylic acid (733 mg, Yield: 99% Yield); (M+1) = 183.

Step 4: Preparation of *rac-trans*-2-(3,3,3-trifluoropropyl)cyclopropanecarboxamide



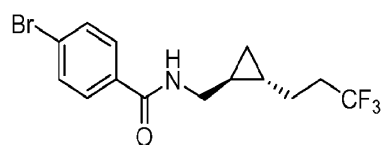
To a solution of rac-trans-2-(3,3,3-trifluoropropyl)cyclopropanecarboxylic acid (1.60 g, 8.78 mmol) in dichloromethane (20 mL) was added ammonium chloride (940 mg, 17.6 mmol), HATU (5.01 g, 13.2 mmol) and triethylamine (3.6 mL, 26.3 mmol). The mixture was stirred at room temperature. After 3 h, the reaction mixture was diluted with ethyl acetate and water, and the mixture was filtered. The aqueous layer was washed with ethyl acetate (3×30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to give rac-trans-2-(3,3,3-trifluoropropyl)cyclopropanecarboxamide (1.50 g, 94% yield); (M+1) = 182.

Step 5: Preparation of rac-trans-(2-(3,3,3-trifluoropropyl)cyclopropyl)methanamine



To a 0 °C solution of rac-trans-2-(3,3,3-trifluoropropyl)cyclopropanecarboxamide (1.50 g, 8.28 mmol) in tetrahydrofuran (30 mL) was added lithium aluminum hydride (3.14 g, 82.8 mmol). The mixture was allowed to warm to room temperature and stir. After 24 h, the reaction mixture was cooled to 0 °C and was quenched by the addition of water. The mixture was filtered, and the filter cake was washed with ethyl acetate (30 mL). The aqueous layer was washed with ethyl acetate (3×30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to give rac-trans-(2-(3,3,3-trifluoropropyl)cyclopropyl)methanamine (300 mg, 22% yield); (M+1) = 168.

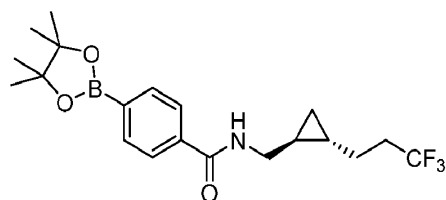
Step 6: Preparation of rac-trans-4-bromo-N-[[2-(3,3,3-trifluoropropyl)cyclopropyl]methyl]benzamide



To a solution of rac-trans-(2-(3,3,3-trifluoropropyl)cyclopropyl)methanamine (300 mg, 1.79 mmol) in dichloromethane (5 mL) was added 4-bromobenzoic acid (541 mg, 2.69 mmol), HATU (1.02 g, 2.69 mmol) and triethylamine (545 mg, 5.38 mmol). The mixture was stirred at room temperature. After 6 h, the reaction mixture was diluted with ethyl

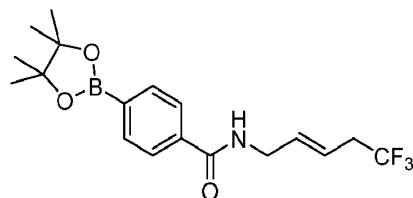
acetate and water. The aqueous layer was washed with ethyl acetate (3×30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography to give rac-trans-4-bromo-N-[[2-(3,3,3-trifluoropropyl)cyclopropyl]methyl]benzamide (200 mg, 32% yield); (M+1) = 350.

Step 7: Preparation of rac-trans-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-[[2-(3,3,3-trifluoropropyl)cyclopropyl]methyl]benzamide

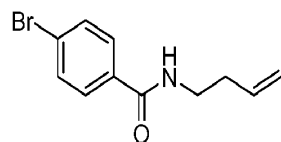


The title compound was prepared as described from rac-trans-4-bromo-N-[[2-(3,3,3-trifluoropropyl)cyclopropyl]methyl]benzamide as described for the preparation of **Intermediate 41**; (M+1) = 398.

Intermediate 66: Preparation of (E)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(5,5,5-trifluoropent-2-en-1-yl)benzamide



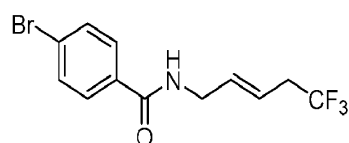
Step 1: Preparation of 4-bromo-N-(but-3-en-1-yl)benzamide



A mixture of 4-bromobenzoic acid (1.0 g) in thionyl chloride (20 mL) was heated to reflux and stirred. After 16 h, the mixture was concentrated, and the residue was dissolved in DCM (10 mL). This solution was added dropwise to a 0 °C mixture of but-3-

en-1-amine hydrochloride (0.64 g, 5.97 mmol) and N,N-diisopropylethylamine (2.6 mL, 14.9 mmol) in DCM (20 mL). The mixture was allowed to warm to room temperature and stir. After 16 h, the mixture was concentrated, and the residue was purified by flash silica gel column (PE/EtOAc 1:1) to afford 4-bromo-N-but-3-enyl-benzamide as a white solid (1.00 g, 79% Yield); (M+1) = 253.

Step 2: Preparation of (E)-4-bromo-N-(5,5,5-trifluoropent-2-en-1-yl)benzamide

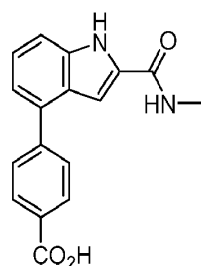


A mixture of 4-bromo-N-but-3-enyl-benzamide (0.60 g, 2.36 mmol), trimethyl(trifluoromethyl)silane (4.03 g, 28.3 mmol), potassium carbonate (3.92 g, 28.3 mmol), (diacetoxyiodo)benzene (4.56 g, 14.2 mmol) and copper(I) thiophene-2-carboxylate (0.45 g, 2.36 mmol) in NMP (30 mL) was heated to 80 °C under N₂. After 3 days, the mixture was diluted with DCM/MeOH (20:1), filtered through celite, and the filter cake was washed with MeOH (2x 100 mL). The filtrate was concentrated and then purified by C18 gel column (MeOH in H₂O.NH₄HCO₃ 0% to 80%) to afford a crude yellow oil. Then the oil was purified by flash silica gel column (PE/ EtOAc 10:1 to 5:1) to afford 4-bromo-N-[(E)-5,5,5-trifluoropent-2-enyl]benzamide as a yellow solid (0.32 g, 16% Yield); (M+1) = 322.

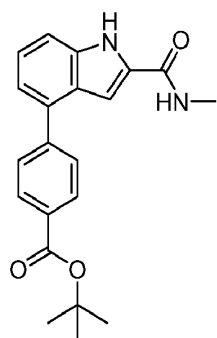
Step 3: Preparation of (E)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(5,5,5-trifluoropent-2-en-1-yl)benzamide

The title compound was prepared from afford 4-bromo-N-[(E)-5,5,5-trifluoropent-2-enyl]benzamide as described for the preparation of **Intermediate 41**; (M+1) = 370.

Intermediate 67: Preparation of 4-(2-(methylcarbamoyl)-1H-indol-4-yl)benzoic acid



Step 1: Preparation of tert-butyl 4-(2-(methylcarbamoyl)-1H-indol-4-yl)benzoate



5

To a 500 mL round-bottomed flask equipped with a magnetic stir bar, reflux condenser, and N₂ inlet was added 4-bromo-N-methyl-1H-indole-2-carboxamide (6.83 g, 27.0 mmol, **Intermediate 12**), (4-tert-butoxycarbonylphenyl)boronic acid (7.10 g, 32.0 mmol), (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride dichloromethane complex (1.05 g, 1.29 mmol), sodium carbonate (7.15 g, 67.5 mmol), 1,4-dioxane (100 mL), and water (30 mL). The mixture was degassed under vacuum/backfilled with N₂ (x 3), and then heated to 100 °C in an oil bath. After 45 min, LC/MS analysis revealed that the reaction was complete. The mixture was allowed to cool to room temperature and was diluted with water (30 mL). The mixture was extracted with ethyl acetate (30 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated to provide a brown oil. The crude oil was suspended in diethyl ether (250 mL) and briefly sonicated, resulting in the formation of a precipitate. The mixture was filtered, and the filter cake was dried to provide a brown solid. Chromatographic purification (CombiFlash, 330 g SiO₂ gold column, 10-55% 3:1 ethyl acetate:ethanol/heptane elute, combined fractions 12-27,

20

rack 2) provided a yellow solid. The solid was suspended in diethyl ether (250 mL) and briefly sonicated. The mixture was filtered, and the filter cake was dried to provide tert-butyl 4-[2-(methylcarbamoyl)-1H-indol-4-yl]benzoate 7.75 g, 22.1 mmol, 82% yield) as a light yellow solid; (M+1) = 351.

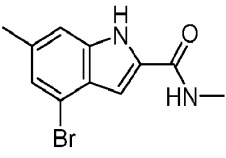
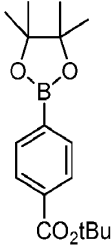
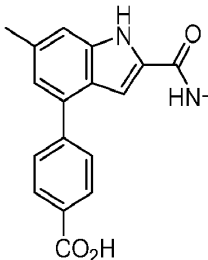
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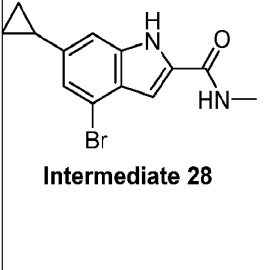
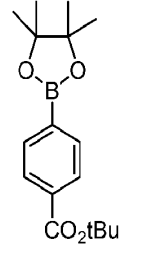
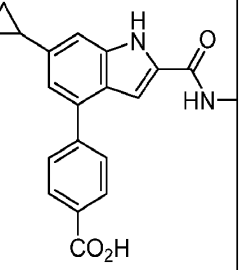
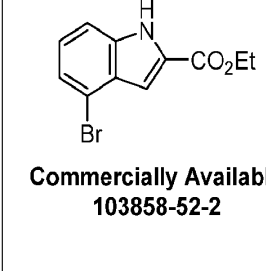
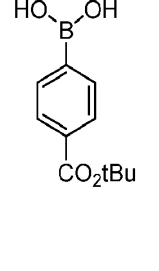
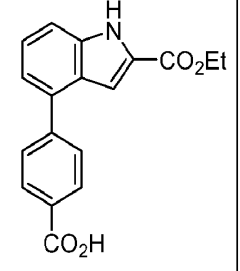
Step 2: Preparation of 4-(2-(methylcarbamoyl)-1H-indol-4-yl)benzoic acid

To a 100 mL recovery flask equipped with a magnetic stir bar, reflux condenser, and N₂ inlet was added tert-butyl 4-(2-(methylcarbamoyl)-1H-indol-4-yl)benzoate (3.80 g, 10.84 mmol) and dichloromethane (50 mL). The mixture was treated with trifluoroacetic acid (30 mL), and the resulting solution was allowed to stir at room temperature. After 30 min, LC/MS analysis revealed that the reaction was complete. The mixture was concentrated, and the residue was suspended in diethyl ether (30 mL). The mixture was filtered, and the filter cake was washed with diethyl ether (30 mL) and dried to provide 4-(2-(methylcarbamoyl)-1H-indol-4-yl)benzoic acid (3.05 g, 10.36 mmol, 96% yield) as a tan solid; (M+1) = 295.

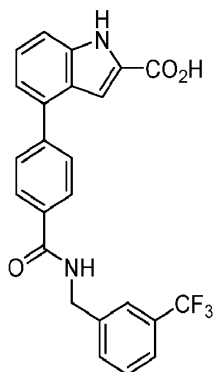
15

The following carboxylic acids were prepared using the procedure described for the synthesis of **Intermediate 67**:

Inter mediate	Bromide	Boron ate Ester	Carboxylic Acid	M S
68	 Intermediate 27	 CO₂tBu	 CO₂H	(M+1) = 309

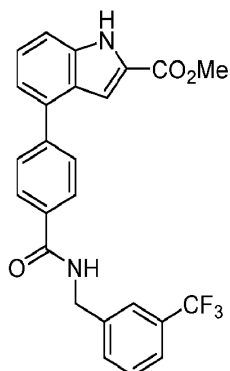
69	 Intermediate 28	 CO₂tBu	 CO₂H	(M+1) = 335
70	 Commercially Available 103858-52-2	 CO₂tBu	 CO₂H	(M-1) = 308

Intermediate 71: Preparation of 4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxylic acid



5

Step 1: Preparation methyl 4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxylate

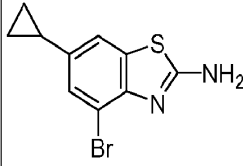
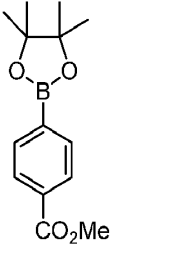
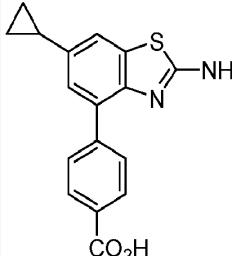
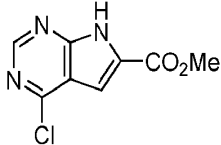
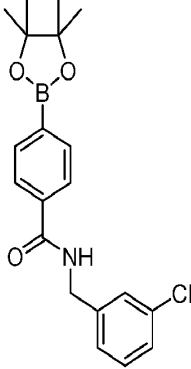
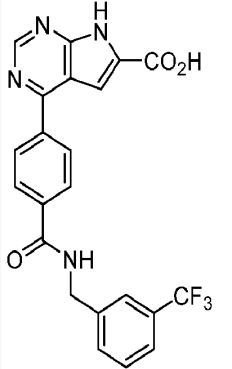
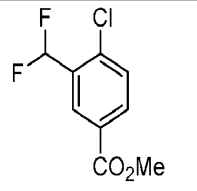
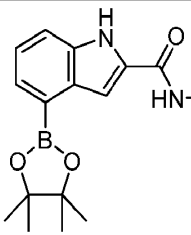
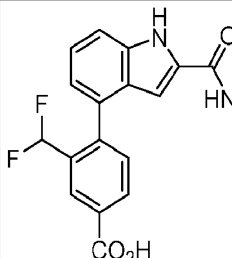


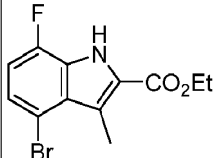
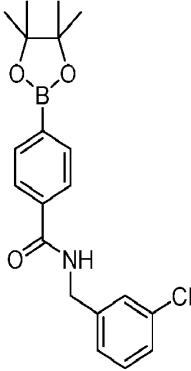
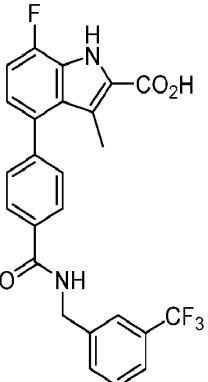
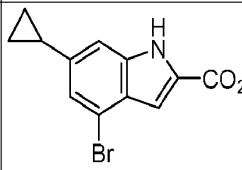
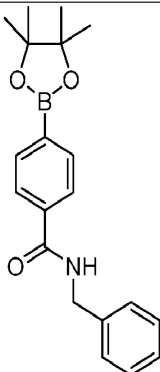
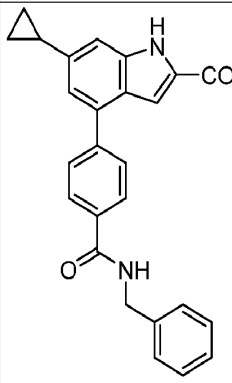
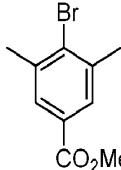
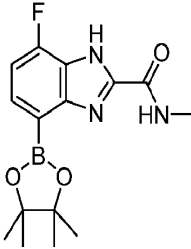
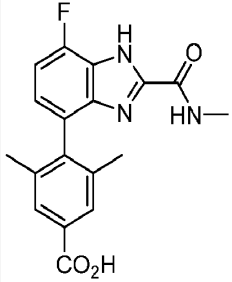
The title compound was prepared from methyl 4-bromo-1H-indole-2-carboxylate and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(3-(trifluoromethyl)benzyl)benzamide (**Intermediate 43**) as described in Step 1 of the preparation of **Intermediate 67**; (M+1) = 453.

Step 2: Preparation of 4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxylic acid

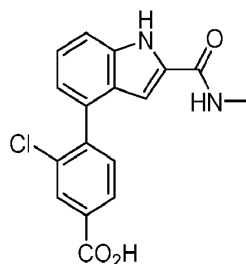
To a 250 mL recovery flask equipped with a magnetic stir bar, reflux condenser, and N₂ inlet was added methyl 4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxylate (1.40 g, 3.09 mmol) and methanol (60 mL). The suspension was treated with 1.0N sodium hydroxide solution (40 mL, 40.00 mmol), and the mixture was heated to reflux. After 30 min, LC/MS analysis revealed that the reaction was complete. The mixture was allowed to cool to room temperature and was diluted with 1N hydrochloric acid solution (60 mL), resulting in the formation of a precipitate. The mixture was filtered, and the filter cake was washed with water (30 mL). The moist solids were dissolved in ethyl acetate (50 mL). The solution was dried over magnesium sulfate, filtered, and concentrated to provide 4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxylic acid (1.30 g, 3.09 mmol, 94% yield) as a tan solid; (M-1) = 437.

The following carboxylic acids were prepared using this procedure:

Inter mediate	Halide	Boronate Ester	Carboxylic Acid	M S
72	 Intermediate 39	 Intermediate 42	 Intermediate 41	(M+1) = 311
73	 Commercially Available 944709-69-7	 Intermediate 43	 Intermediate 44	(M+1) = 441
74	 See WO2020182990	 Intermediate 46	 Intermediate 47	(M+1) = 345

75	 Intermediate 60	 Intermediate 43	 (M+1)) = 471
76	 Intermediate 1		 (M+1)) = 411
77	 Commercially Available CAS 432022-88-3	 Intermediate 42	 (M+1)) = 342

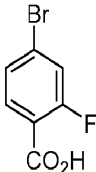
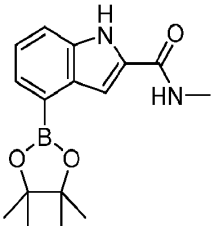
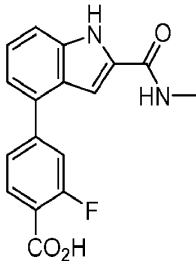
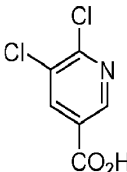
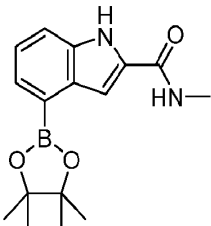
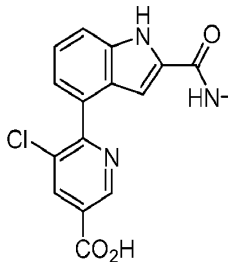
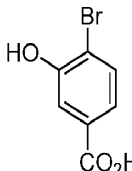
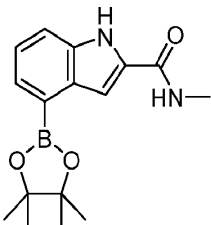
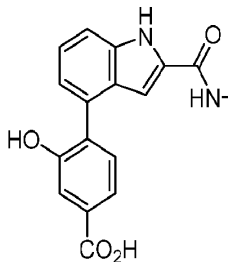
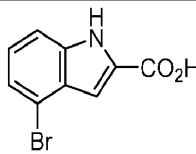
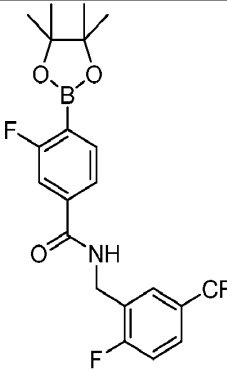
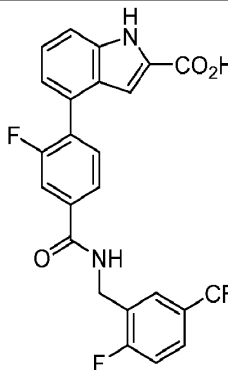
Intermediate 78: Preparation of 3-chloro-4-(2-(methylcarbamoyl)-1H-indol-4-yl)benzoic acid

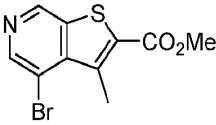
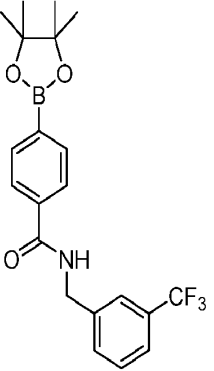
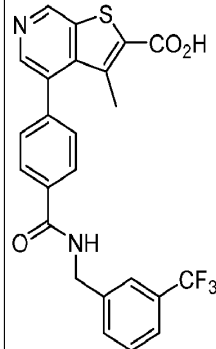
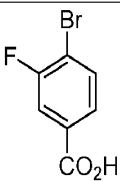
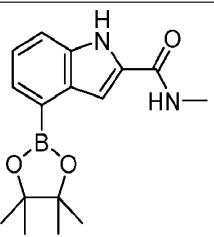
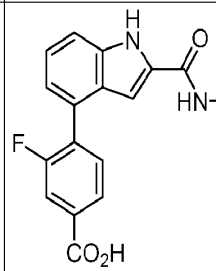
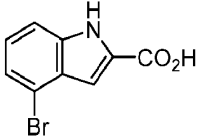
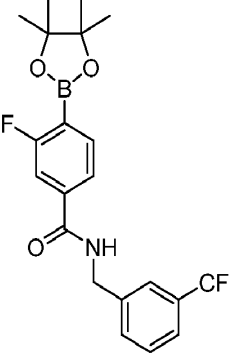
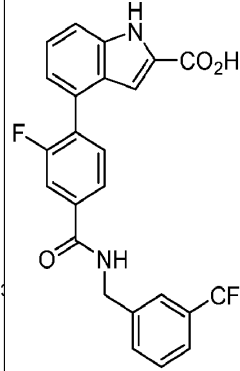


A mixture of N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-2-carboxamide (1.00 g, 3.30 mmol, **Intermediate 40**), 4-bromo-3-chlorobenzoic acid (817 mg, 3.30 mmol, **CAS 25118-59-6**), palladium(II) acetate (37 mg, 167 μ mol), tricyclohexylphosphine (95 mg, 333 μ mol), and potassium phosphate tribasic (2.20 g, 10.00 mmol) in 1,4-dioxane (8.0 mL) and water (4.0 mL) was microwaved at 125 $^{\circ}$ C for 1 h. LC/MS indicated that all starting material was consumed. The reaction mixture was filtered through Celite, and the filtered cake was washed with EtOAc and water. The filtrate was partitioned between water and EtOAc. The two layers were separated, and the aqueous layer was acidified to pH 2 with 1 M HCl. The solid formed was collected by suction filtration and dried to yield 3-chloro-4-(2-(methylcarbamoyl)-1H-indol-4-yl)benzoic acid (1.12 g, 3.41 mmol, >100 % yield) as a gray solid; (M+1) = 329.

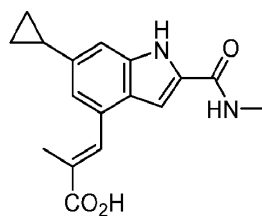
The following carboxylic acids were prepared using the procedure described for the synthesis of **Intermediate 78**:

Intermediate	Halide	Boronate Ester	Carboxylic Acid	M S
79	 Commercially Available CAS 28314-82-1	 Intermediate 40	 	(M+1) = 331

80	 Commercially Available CAS 112704-79-7	 Intermediate 40	 (M+1) = 313
81	 Commercially Available CAS 41667-95-2	 Intermediate 40	 (M+1) = 330
82	 Commercially Available CAS 14348-38-0	 Intermediate 40	 (M+1) = 311
83	 Commercially Available 16732-64-2	 Intermediate 44	 (M+1) = 475

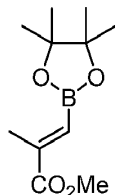
84	 Commercially Available CAS 870244-28-3	 Intermediate 43		(M+1) = 471
85	 Commercially Available CAS 153556-42-4	 Intermediate 40		(M+1) = 313
86	 Commercially Available CAS 16732-64-2	 Intermediate 45		(M+1) = 457

Intermediate 87: Preparation of (E)-3-(6-cyclopropyl-2-(methylcarbamoyl)-1H-indol-4-yl)-2-methylacrylic acid



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Step 1: Preparation of methyl (E)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate



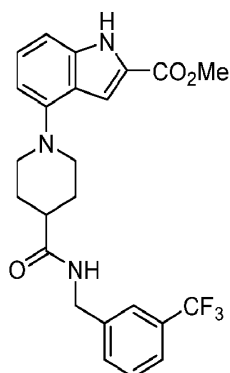
5 A mixture of methyl (E)-3-bromo-2-methyl-prop-2-enoate (0.179 g, 1.00 mmol),
4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane
(381 mg, 1.50 mmol), potassium acetate (245 mg, 2.50 mmol) and (1,1'-
bis(diphenylphosphino)ferrocene)palladium(II) dichloride dichloromethane complex (82
mg, 0.10 mmol) in dry DMSO (10 mL) was stirred at 80 °C under N₂. After 4 h, the mixture
10 was allowed to cool to room temperature and was poured into water (50 mL). The mixture
was extracted with EtOAc (3x 50 mL). The combined organic phases were dried over
sodium sulfate, concentrated, and purified by flash silica gel column (PE/EtOAc 95:5) to
afford methyl (E)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enoate
as a crude oil (0.188 g, 32% yield); (M+1) = 227.

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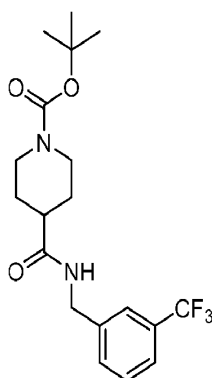
Step 2: Preparation of (E)-3-(6-cyclopropyl-2-(methylcarbamoyl)-1H-indol-4-yl)-2-methylacrylic acid

The title compound was prepared from 4-bromo-6-cyclopropyl-N-methyl-1H-indole-2-carboxamide (**Intermediate 28**) and methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enoate as described in **Steps 1-2** for the preparation of
20 **Intermediate 71**; (M+1) = 299.

Intermediate 88: Preparation of methyl 4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)piperidin-1-yl)-1H-indole-2-carboxylate



Step 1: Preparation of tert-butyl 4-((3-(trifluoromethyl)benzyl)carbamoyl)piperidine-1-carboxylate



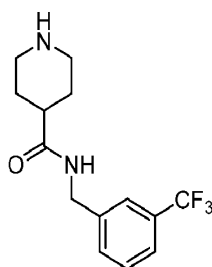
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To a 250 mL recovery flask equipped with a magnetic stir bar and N₂ inlet was added 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (1.02 g, 4.36 mmol), 3-(trifluoromethyl)benzylamine (670 μ l, 4.58 mmol), HATU (2.14 g, 5.45 mmol), and N,N-dimethylformamide (15 mL). The solution was treated with N,N-diisopropylethylamine (1.53 mL, 8.72 mmol) and allowed to stir at room temperature. After 75 min, LC/MS analysis revealed that the reaction was complete. The yellow solution was diluted with water (50 mL) and diethyl ether (50 mL). The phases were separated, and the aqueous phase was extracted with diethyl ether (2 x 50 mL). The combined organic phases were washed with 2N hydrochloric acid solution (25 mL), 2M sodium carbonate solution (25 mL), and brine (25 mL). The organic phase was dried over magnesium sulfate, filtered,

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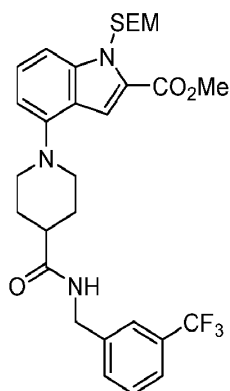
and concentrated to provide 1.57 g of a colorless oil. Chromatographic purification (CombiFlash, 80 g SiO₂ gold column, 25-75% ethyl acetate/heptane elute, combined fractions 13-23, rack 2) afforded tert-butyl 4-((3-(trifluoromethyl)benzyl)carbamoyl)piperidine-1-carboxylate (977 mg, 2.53 mmol, 58 %
5 yield) as a white solid; (M+1) = 387.

Step 2: Preparation of N-(3-(trifluoromethyl)benzyl)piperidine-4-carboxamide



To a 100 mL recovery flask equipped with a magnetic stir bar and N₂ inlet was added tert-butyl 4-((3-(trifluoromethyl)benzyl)carbamoyl)piperidine-1-carboxylate (3.01 g, 7.79 mmol) and dichloromethane (20 mL). The solution was treated with trifluoroacetic acid (10 mL, 129.80 mmol) and was allowed to stir at room temperature. After 30 min, LC/MS analysis revealed that the reaction was complete. The mixture was concentrated,
15 and the residue was dissolved in dichloromethane (50 mL). The solution was washed with 5N ammonium hydroxide solution (50 mL), dried over magnesium sulfate, filtered, and concentrated to provide N-(3-(trifluoromethyl)benzyl)piperidine-4-carboxamide (2.01 g, 7.02 mmol, 90 % yield) as a waxy off-white solid; (M+1) = 287.

20 *Step 3: Preparation of methyl 4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)piperidin-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-2-carboxylate*

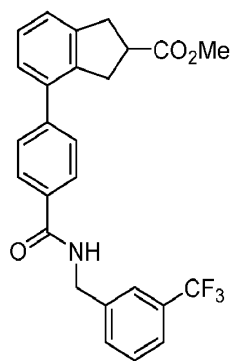


To a 20 mL microwave reaction vial equipped with a magnetic stir bar was added methyl 4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-2-carboxylate (691 mg, 1.80 mmol, see WO2017152076), N-(3-(trifluoromethyl)benzyl)piperidine-4-carboxamide (634 mg, 2.21 mmol), methanesulfonato(2-dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (168 mg, 191 μ mol), dicyclohexylphosphino -2',6'- di-i-propoxy-1,1'-biphenyl (94 mg, 198 μ mol), cesium carbonate (1.17 g, 3.60 mmol), and tert-butanol (6 mL). The vessel was sealed, and the contents were heated to 85 °C in an oil bath. After 19 h, the reaction mixture was allowed to cool to room temperature. After 65 h, LC/MS analysis revealed that the reaction was complete. The yellow suspension was diluted with water (75 mL) and extracted with ethyl acetate (75 mL). The organic phase was washed with 2N hydrochloric acid solution (30 mL) and brine (30 mL), dried over magnesium sulfate, filtered, and concentrated to provide 1.24 g of a yellow oil. Chromatographic purification (CombiFlash, 40 g SiO₂ gold column, 0-90% ethyl acetate/heptane elute, combined fractions 45-50, rack 1) afforded methyl 4-((3-(trifluoromethyl)benzyl)carbamoyl)piperidin-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-2-carboxylate (138 mg, 234.00 μ mol, 13.0 % yield) as a yellow solid; (M+1) = 590.

Step 4: Preparation of methyl 4-((3-(trifluoromethyl)benzyl)carbamoyl)piperidin-1-yl)-1H-indole-2-carboxylate

To a 50 mL recovery flask equipped with a magnetic stir bar and N₂ inlet was added methyl 4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)piperidin-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-2-carboxylate (138 mg, 234 μ mol) and dichloromethane (5 mL). The solution was treated with trifluoroacetic acid (3 mL, 38.94 mmol) and was allowed to stir at room temperature. After 1 h 45 min, LC/MS analysis of the red-brown solution revealed that the starting material had been consumed. The mixture was concentrated, and the residue was dissolved in dichloromethane (25 mL). The solution was washed with 5N ammonium hydroxide, dried over magnesium sulfate, filtered, and concentrated to provide 148 mgs of a tan solid. ¹HNMR analysis revealed that the isolated material was not the desired product, but rather the N-hydroxymethyl indole. The crude solid was dissolved in methanol (5 mL) and was treated with potassium carbonate (~ 100 mgs). The mixture was allowed to stir at room temperature. After 20 min, LC/MS analysis revealed that the reaction was complete. The mixture was concentrated, and the residue was partitioned between dichloromethane (15 mL) and water (15 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (3 x 15 mL). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated to provide methyl 4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)piperidin-1-yl)-1H-indole-2-carboxylate (89 mg, 193.70 μ mol, 82.8 % yield) as a tan solid; (M+1) = 460.

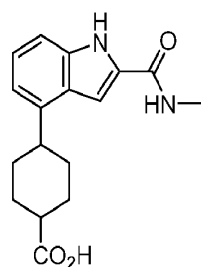
Intermediate 89: Preparation of methyl 4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-2,3-dihydro-1H-indene-2-carboxylate



The title compound was prepared from methyl 4-bromo-2,3-dihydro-1H-indene-2-carboxylate (see **US20080255239**) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(3-(trifluoromethyl)benzyl)benzamide (**Intermediate 43**) as described in Step 1 for the preparation of **Intermediate 67**; (M+1) = 454.

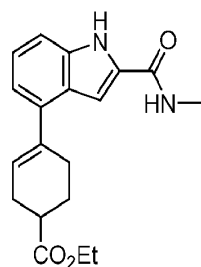
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Intermediate 90: Preparation of 4-(2-(methylcarbamoyl)-1H-indol-4-yl)cyclohexane-1-carboxylic acid



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Step 1: Preparation of ethyl 4-(2-(methylcarbamoyl)-1H-indol-4-yl)cyclohex-3-ene-1-carboxylate



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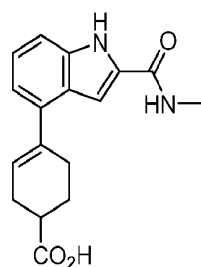
A mixture of 4-bromo-N-methyl-1H-indole-2-carboxamide (500 mg, 2.00 mmol), ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (1.20 g, 4.00 mmol), palladium(II) acetate (22 mg, 99 μ mol), tricyclohexylphosphine (57 mg, 198 μ mol), and potassium phosphate tribasic (1.28 g, 5.93 mmol) in 1,4-dioxane (8.0 mL) and water (4.0 mL) was microwaved at 125 °C for 30 min. LC/MS indicated that all starting material was consumed. Both product and acid were observed from LC/MS. The reaction mixture was filtered through Celite, and the filtered cake was washed with EtOAc. The filtrate was partitioned between water and EtOAc. The organic layer was washed brine,

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dried over MgSO₄, filtrate, and concentrated in vacuo. The crude material was purified on silica gel (liquid loaded) with heptane/EtOAc (80/20 to 0/100) to give ethyl 4-(2-(Methylcarbamoyl)-1H-indol-4-yl)cyclohex-3-ene-1-carboxylate (520 mg, 1.59 mmol, 80.6 % yield) as an amber sticky solid; (M+1) = 327.

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Step 2: Preparation of 4-(2-(methylcarbamoyl)-1H-indol-4-yl)cyclohex-3-ene-1-carboxylic acid



10 A suspension of ethyl 4-(2-(methylcarbamoyl)-1H-indol-4-yl)cyclohex-3-ene-1-carboxylate (520 mg, 1.60 mmol) in 1N sodium hydroxide solution (5.00 mL, 5.00 mmol), THF (5 mL), and methanol (5 mL) was heated at 40 °C for 6 h. LC/MS indicated that all the starting material was consumed, and the reaction became homogeneous. The reaction mixture was concentrated in vacuo to remove organic solvents. Water was added, and the solution was adjusted to pH 2 with 1 M HCl. The cloudy solution was extracted with EtOAc (2X). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give 4-(2-(methylcarbamoyl)-1H-indol-4-yl)cyclohex-3-ene-1-carboxylic acid (380 mg, 1.30 mmol, 80% yield) as a beige powder; (M+1) = 299.

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Step 3: Preparation of 4-(2-(methylcarbamoyl)-1H-indol-4-yl)cyclohexane-1-carboxylic acid

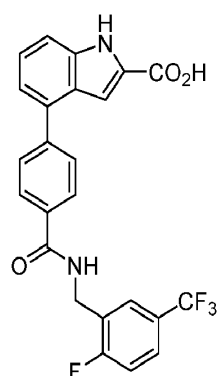
A mixture of 4-(2-(methylcarbamoyl)-1H-indol-4-yl)cyclohex-3-ene-1-carboxylic acid (90 mg, 302 μmol) and 10% palladium on carbon (30 mg, 282 μmol) in ethyl acetate (10 mL) and ethanol (10 mL) was hydrogenated at rt for 1 h. LC/MS indicated all starting

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material was consumed. The reaction mixture was filtered through Celite, and the filtered cake was washed with EtOAc. The filtrate was concentrated in vacuo to give 4-(2-(methylcarbamoyl)-1H-indol-4-yl)cyclohexane-1-carboxylic acid (78 mg, 260 μ mol, 86% yield) as a beige powder; (M+1) = 301

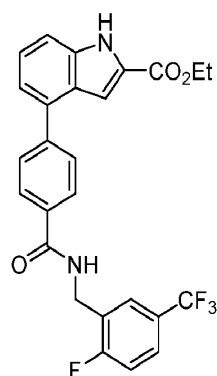
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Intermediate 91: Preparation of 4-(4-((2-fluoro-5-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxylic acid



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Step 1: Preparation of ethyl 4-(4-((2-fluoro-5-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxylate



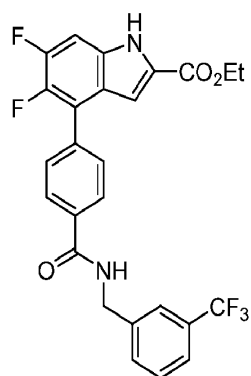
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The title compound was prepared from 4-(2-(ethoxycarbonyl)-1H-indol-4-yl)benzoic acid (**Intermediate 70**) and (2-fluoro-5-(trifluoromethyl)phenyl)methanamine as described in Step 1 for the synthesis of **Intermediate 88**; (M+1) = 485.

Step 2: Preparation of 4-(4-((2-fluoro-5-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxylic acid

The title compound was prepared from ethyl 4-(4-((2-fluoro-5-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxylate as described in Step 2 for the synthesis of **Intermediate 90**; (M+1) = 457.

Intermediate 92: Preparation of ethyl 5,6-difluoro-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxylate

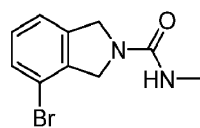


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The title compound was prepared from ethyl 4-bromo-5,6-difluoro-1H-indole-2-carboxylate (**Intermediate 5**) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(3-(trifluoromethyl)benzyl)benzamide (**Intermediate 43**) as described in Step 1 for the synthesis of **Intermediate 67**; (M+1) = 503.

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Intermediate 93: Preparation of 4-bromo-N-methylisoindoline-2-carboxamide

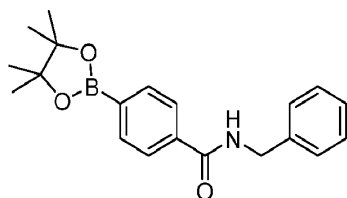


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To a 50 mL recovery flask equipped with a magnetic stir bar and N₂ inlet was added 4-bromoisindoline hydrochloride (255 mg, 1.03 mmol, CAS 923590-95-8), N,N-diisopropylethylamine (500 µL, 2.84 mmol), and ACETONITRILE (5 mL). The mixture

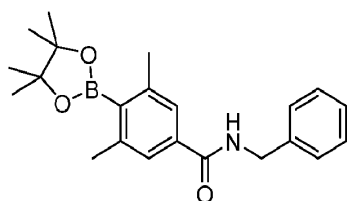
was treated with methyl isocyanate (70 mg, 1.23 mmol). After 5 min, a precipitate began to form. After 20 min, LC/MS analysis revealed that the reaction was complete. The mixture was diluted with water (30 mL), and the resulting suspension was filtered. The filter cake was washed with water (15 mL), and the moist solids were dissolved in ethyl acetate (30 mL). The solution was dried over magnesium sulfate, filtered, and concentrated to provide 4-bromo-N-methylisindoline-2-carboxamide (213 mg, 835 μ mol, 81 % yield) as a gray solid; (M+1) = 255.

Intermediate 94: Preparation of N-benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

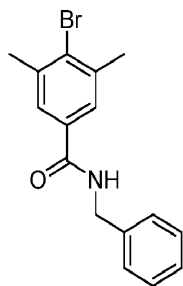


The title compound was prepared from 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid and benzylamine as described for the preparation of **Intermediate 43**; (M+1) = 338.

Intermediate 95: Preparation of N-benzyl-3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide



Step 1: Preparation of N-benzyl-4-bromo-3,5-dimethylbenzamide



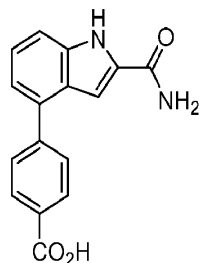
To a solution of 4-bromo-3,5-dimethylbenzoic acid (90 mg, 0.39 mmol) in
 5 dichloromethane (5 mL) was added benzylamine (46 mg, 0.43 mmol), HATU (224 mg,
 0.59 mmol) and triethylamine (0.137 mL, 0.98 mmol). The resulting mixture was stirred
 overnight at room temperature. The mixture was then diluted with water, and the organic
 layer was separated. The aqueous layer was extracted with dichloromethane, and the
 combined organic phases were washed with brine, dried and concentrated to provide N-
 10 benzyl-4-bromo-3,5-dimethylbenzamide as colorless oil (120 mg, 0.37 mmol, 96% yield).
 LCMS: 318.0, 320.0 (M+1).

*Step 2: Preparation of N-benzyl-3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-
 dioxaborolan-2-yl)benzamide*

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The title compound was prepared from N-benzyl-4-bromo-3,5-dimethylbenzamide
 and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-
 dioxaborolane as described for the preparation of **Intermediate 41**; (M+1) = 366.

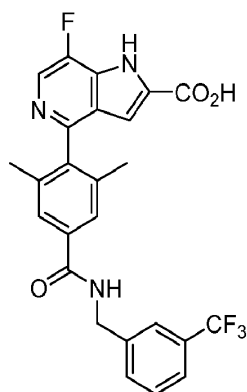
Intermediate 96: Preparation of 4-(2-carbamoyl-1H-indol-4-yl)benzoic acid



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The title compound was prepared from 4-bromo-1H-indole-2-carboxamide (CAS 955978-73-1) and methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate as described for the preparation of **Intermediate 71**; (M+1) = 281.

5 **Intermediate 97: Preparation of 4-(2,6-dimethyl-4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-7-fluoro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid**

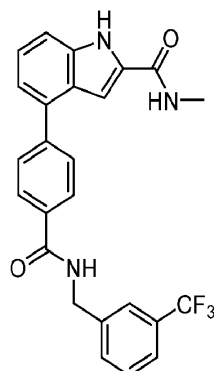


10 The title compound was prepared from methyl 4-chloro-7-fluoro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (**Intermediate 11**) and 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(3-(trifluoromethyl)benzyl)benzamide (**Intermediate 47**) as described for the preparation of **Intermediate 71**; (M+1) = 486.

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Preparation of Examples

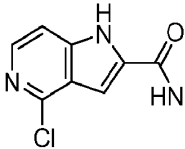
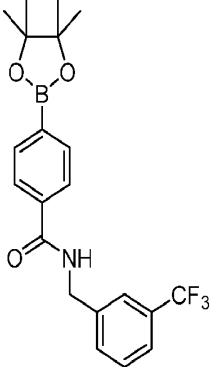
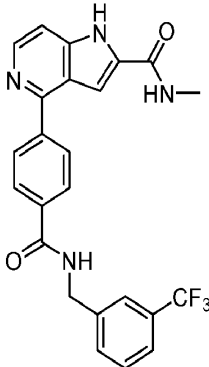
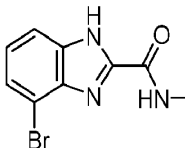
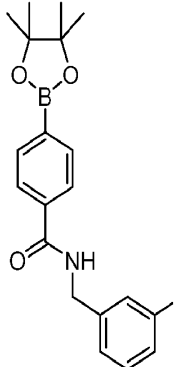
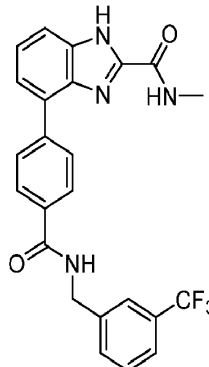
20 **Example 1: Preparation of N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxamide**

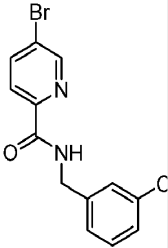
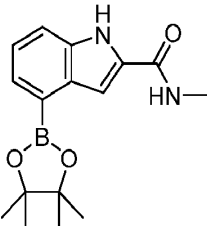
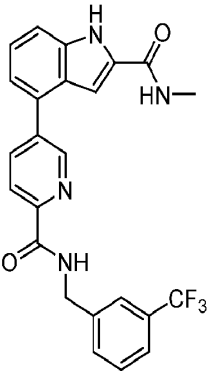
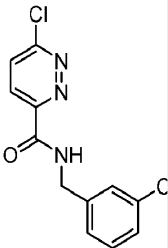
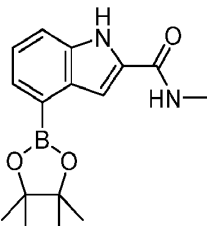
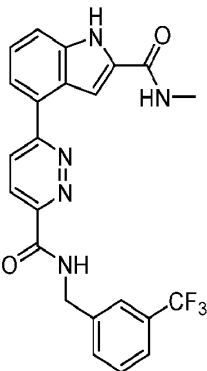


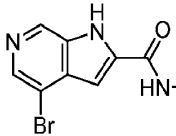
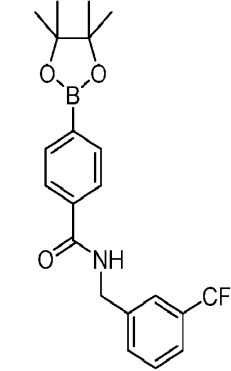
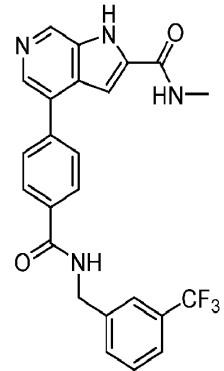
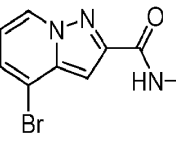
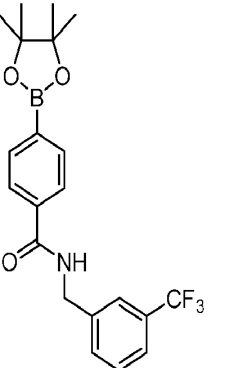
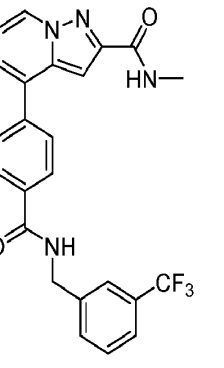
To a 500 mL round-bottomed flask equipped with a magnetic stir bar, reflux condenser, and N₂ inlet was added 4-bromo-N-methyl-1H-indole-2-carboxamide (3.77 g, 14.9 mmol, Intermediate 12), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-[[3-(trifluoromethyl)phenyl]methyl]benzamide (7.50 g, 19.0 mmol, Intermediate 43), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (1.00 g, 1.22 mmol), sodium carbonate (4.75 g, 44.8 mmol), 1,4-dioxane (75 mL), and water (20 mL). The mixture was degassed under vacuum/backfilled with N₂ (x 3). The mixture was then heated to 100 °C in an oil bath. After 1 h, LC/MS analysis revealed that the reaction was complete. The mixture was allowed to cool to room temperature and was diluted with water (50 mL). The mixture was extracted with ethyl acetate (50 mL). The resulting biphasic mixture was filtered through Celite, and the filter cake was washed with ethyl acetate (40 mL). The organic phase was separated and dried over magnesium sulfate, filtered, and concentrated to provide a brown oil. Chromatographic purification (CombiFlash, 330 g SiO₂ gold column, 25-70% 3:1 ethyl acetate:ethanol/heptane elute, combined fractions 24-30, rack 1 and 1-5, rack 2) afforded N-methyl-4-[4-[[3-(trifluoromethyl)phenyl]methyl]benzoyl]phenyl]-1H-indole-2-carboxamide (4.74 g, 10.5 mmol, 71% yield) as a white solid; ¹H NMR (400 MHz, DMSO-d₆) δ 11.81 (s, 1H), 9.26 (t, J = 5.9 Hz, 1H), 8.50 (q, J = 4.5 Hz, 1H), 8.13 – 8.03 (m, 2H), 7.86 – 7.75 (m, 2H), 7.75 – 7.55 (m, 4H), 7.54 – 7.45 (m, 1H), 7.36 – 7.26 (m, 2H), 7.20 (dd, J = 7.3, 1.0 Hz, 1H), 4.63 (d, J = 5.9 Hz, 2H), 2.81 (d, J = 4.5 Hz, 3H) ppm; (M+1) = 452.

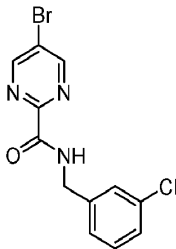
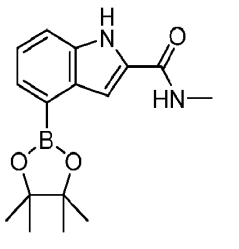
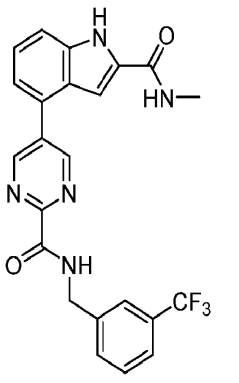
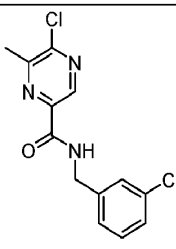
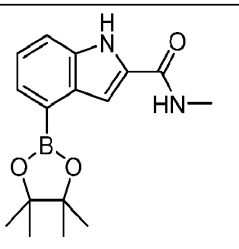
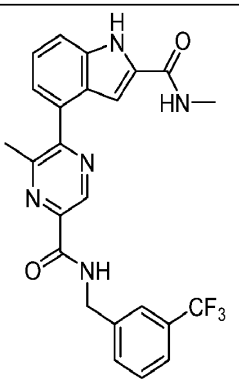
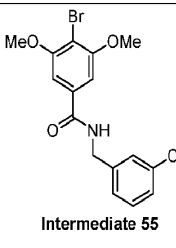
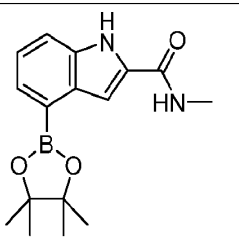
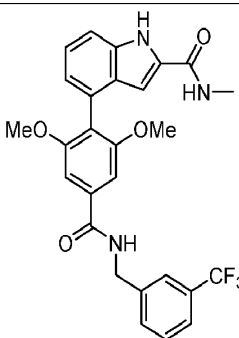
The following compounds were prepared as described for the synthesis of **Example**

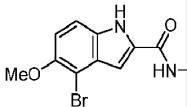
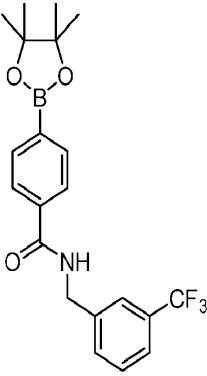
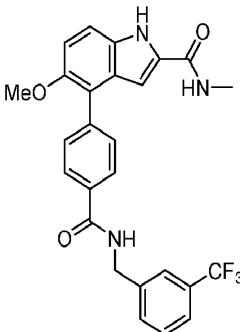
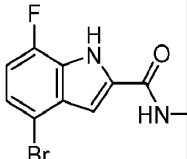
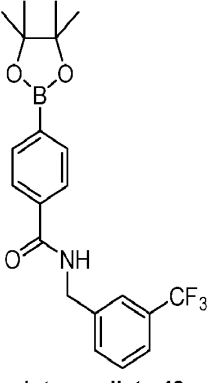
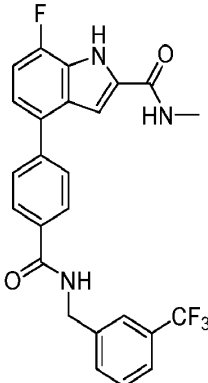
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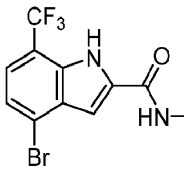
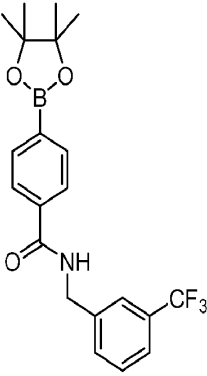
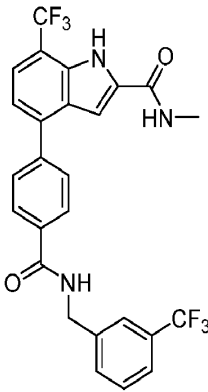
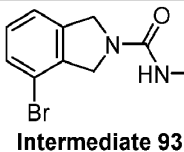
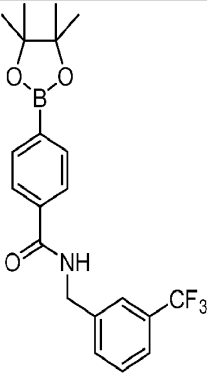
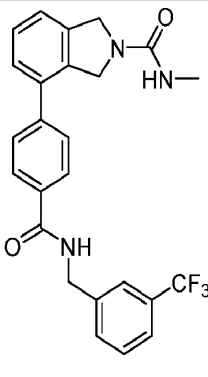
Example	Halide	Boronate Ester	Product	¹ H NMR/MS
2	 Intermediate 13	 Intermediate 43		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.20 (s, 1H), 9.28 (t, J = 5.9 Hz, 1H), 8.65 (q, J = 4.6 Hz, 1H), 8.36 (d, J = 5.7 Hz, 1H), 8.16 – 8.06 (m, 4H), 7.75 – 7.58 (m, 4H), 7.56 – 7.54 (m, 1H), 7.42 – 7.40 (dd, m, 1H), 4.63 (d, J = 5.9 Hz, 2H), 2.84 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 453.
3	 Intermediate 14	 Intermediate 4		¹ H NMR (400 MHz, CD ₃ OD) δ 8.17 – 8.11 (m, 2H), 8.03 – 7.97 (m, 2H), 7.72 – 7.63 (m, 2H), 7.62 – 7.49 (m, 4H), 7.46 – 7.40 (m, 1H), 4.69 (s, 2H), 2.98 (s, 3H) ppm; (M+1) = 453.

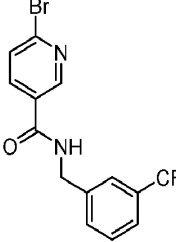
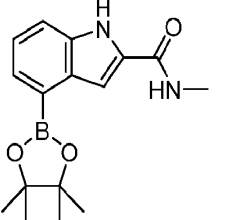
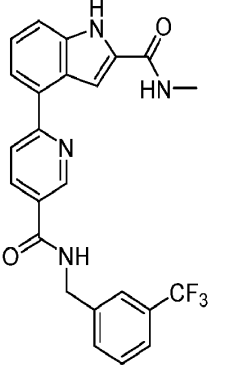
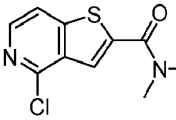
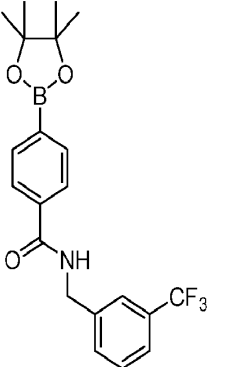
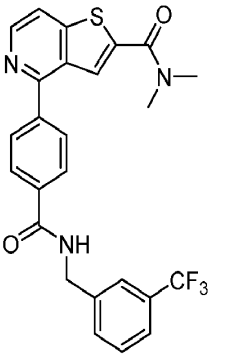
4	 Intermediate 50	 Intermediate 40	 ¹H NMR (400 MHz, DMSO-d₆) δ 11.88 (s, 1H), 9.58 (t, J = 6.4 Hz, 1H), 8.96 (dd, J = 2.2, 0.9 Hz, 1H), 8.50 (q, J = 4.6 Hz, 1H), 8.29 (dd, J = 8.1, 2.2 Hz, 1H), 8.21 (dd, J = 8.1, 0.9 Hz, 1H), 7.74 – 7.72 (m, 1H), 7.71 – 7.51 (m, 4H), 7.39 – 7.31 (m, 2H), 7.30 – 7.26 (m, 1H), 4.64 (d, J = 6.4 Hz, 2H), 2.81 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 453.
5	 Intermediate 52	 Intermediate 40	 ¹H NMR (400 MHz, DMSO-d₆) δ 11.91 (s, 1H), 9.97 (t, J = 6.3 Hz, 1H), 8.55 (q, J = 4.6 Hz, 1H), 8.39 (d, J = 8.8 Hz, 1H), 8.30 (d, J = 8.8 Hz, 1H), 7.78 – 7.75 (m, 1H), 7.74 – 7.57 (m, 6H), 7.42 – 7.37 (m, 1H), 4.68 (d, J = 6.3 Hz, 2H), 2.81 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 454.

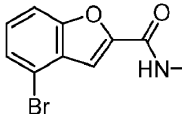
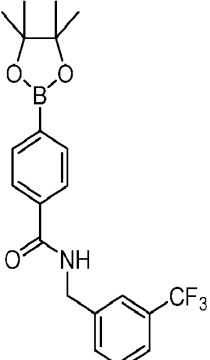
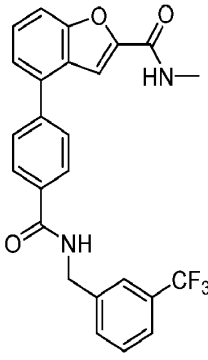
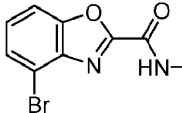
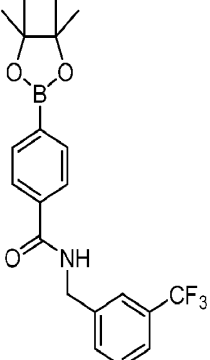
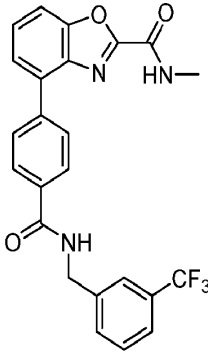
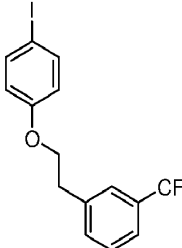
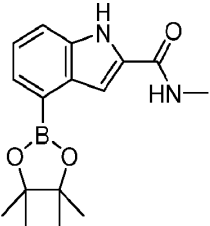
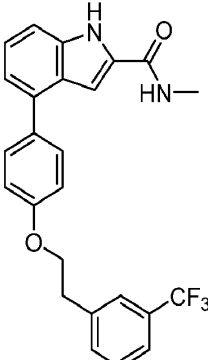
6	 Intermediate 15	 Intermediate 43	 ¹H NMR (400 MHz, DMSO-d₆) δ 12.31 (s, 1H), 9.26 (t, J = 5.9 Hz, 1H), 8.81 (d, J = 0.9 Hz, 1H), 8.71 (q, J = 4.6 Hz, 1H), 8.31 (s, 1H), 8.18 – 8.02 (m, 2H), 7.94 – 7.81 (m, 2H), 7.78 – 7.52 (m, 4H), 7.38 (dd, J = 2.2, 0.9 Hz, 1H), 4.62 (d, J = 5.9 Hz, 2H), 2.83 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 453.
7	 Intermediate 16	 Intermediate 43	 ¹H NMR (400 MHz, DMSO-d₆) δ 9.26 (t, J = 5.9 Hz, 1H), 8.73 (dt, J = 7.0, 1.0 Hz, 1H), 8.45 (q, J = 4.7 Hz, 1H), 8.15 – 8.02 (m, 2H), 7.92 – 7.80 (m, 2H), 7.77 – 7.54 (m, 4H), 7.46 (dd, J = 7.1, 0.9 Hz, 1H), 7.16 (t, J = 7.0 Hz, 1H), 7.07 (d, J = 1.0 Hz, 1H), 4.61 (d, J = 5.9 Hz, 2H), 2.80 (d, J = 4.7 Hz, 3H) ppm; (M+1) = 453.

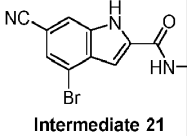
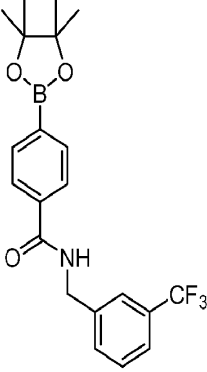
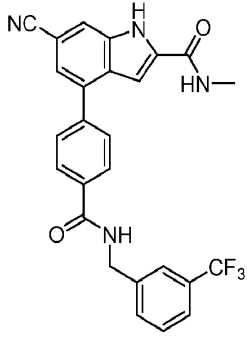
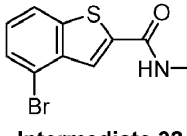
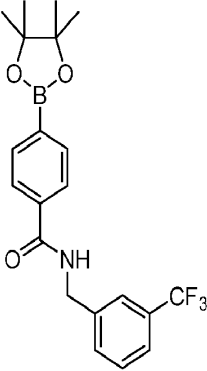
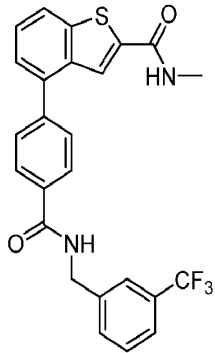
8	 Intermediate 53	 Intermediate 40		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.95 (s, 1H), 9.68 (t, J = 6.3 Hz, 1H), 9.28 (s, 2H), 8.51 (q, J = 4.6 Hz, 1H), 7.79 – 7.54 (m, 5H), 7.43 – 7.31 (m, 3H), 4.63 (d, J = 6.3 Hz, 2H), 2.81 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 454.
9	 Intermediate 54	 Intermediate 40		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.85 (s, 1H), 9.60 (t, J = 6.4 Hz, 1H), 9.16 (s, 1H), 8.40 (q, J = 4.6 Hz, 1H), 7.77 – 7.53 (m, 5H), 7.37 – 7.31 (m, 1H), 7.28 – 7.24 (m, 1H), 6.96 – 6.92 (m, 1H), 4.65 (d, J = 6.4 Hz, 2H), 2.77 (d, J = 4.6 Hz, 3H), 2.56 (s, 3H) ppm; (M+1) = 468.
10	 Intermediate 55	 Intermediate 40		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.49 (s, 1H), 9.25 (t, J = 5.9 Hz, 1H), 8.27 (t, J = 4.6 Hz, 1H), 7.71 (s, 1H), 7.69 – 7.59 (m, 3H), 7.36 (dt, J = 8.2, 0.9 Hz, 1H), 7.34 (s, 2H), 7.17 (dd, J = 8.2, 7.1 Hz,

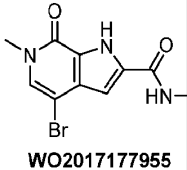
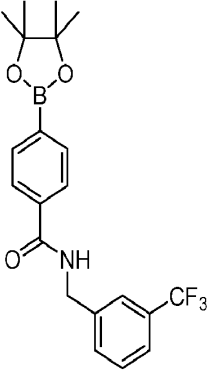
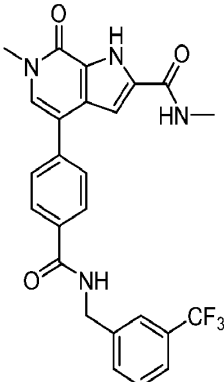
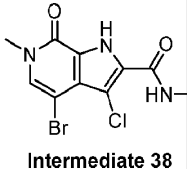
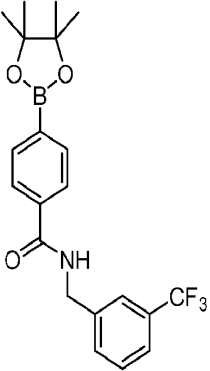
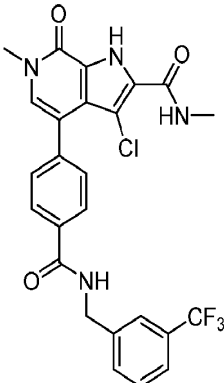
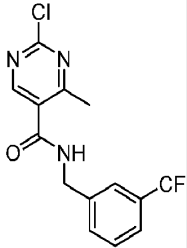
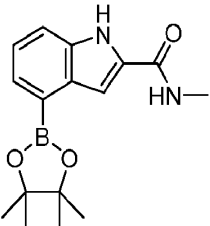
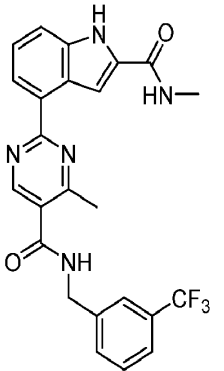
				1H), 6.83 (dd, J = 7.2, 1.0 Hz, 1H), 6.64 (dd, J = 2.2, 1.0 Hz, 1H), 4.64 (d, J = 5.9 Hz, 2H), 3.67 (s, 6H), 2.73 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 512.
11	 Intermediate 18	 Intermediate 43		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.55 (s, 1H), 9.21 (t, J = 6.0 Hz, 1H), 8.36 (q, J = 4.6 Hz, 1H), 8.06 - 7.96 (m, 2H), 7.70 (s, 1H), 7.69 - 7.55 (m, 5H), 7.42 (dd, J = 8.8, 0.8 Hz, 1H), 7.14 (d, J = 9.0 Hz, 1H), 6.90 (dd, J = 2.3, 0.9 Hz, 1H), 4.61 (d, J = 6.0 Hz, 2H), 3.72 (s, 3H), 2.75 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 482.
12	 Intermediate 19	 Intermediate 43		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.25 (s, 1H), 9.23 (t, J = 6.0 Hz, 1H), 8.50 (d, J = 4.7 Hz, 1H), 8.09 - 8.02 (m, 2H), 7.78 - 7.73 (m, 2H), 7.71 - 7.57 (m, 4H), 7.34 (t, J = 2.5 Hz, 1H), 7.18 - 7.09 (m, 2H), 4.61 (d, J =

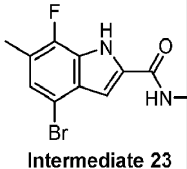
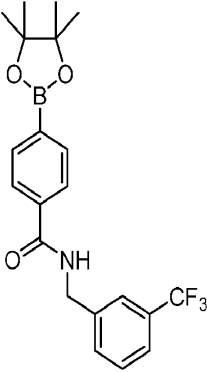
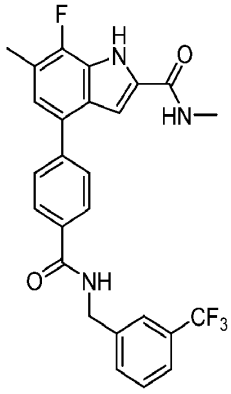
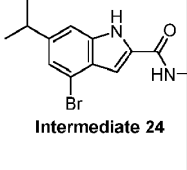
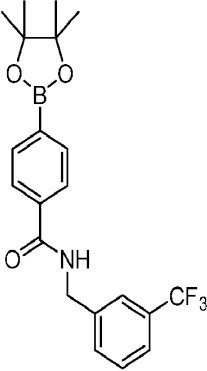
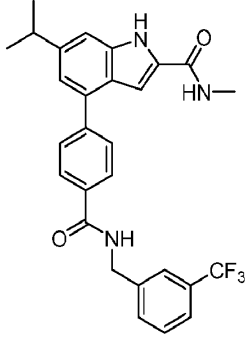
				6.0 Hz, 2H), 2.81 (d, J = 4.7 Hz, 3H) ppm; (M+1) = 470.
13	 Intermediate 20	 Intermediate 43		¹ H NMR (400 MHz, Chloroform-d) δ 9.49 (s, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.66 - 7.62 (m, 2H), 7.59 (t, J = 7.0 Hz, 2H), 7.51 (t, J = 7.6 Hz, 1H), 7.28 (s, 1H), 6.95 (d, J = 2.1 Hz, 1H), 6.54 (s, 1H), 6.17 (s, 1H), 4.77 (d, J = 5.8 Hz, 2H), 3.05 (d, J = 4.8 Hz, 3H) ppm; (M+1) = 520.
14	 Intermediate 93	 Intermediate 43		¹ H NMR (400 MHz, DMSO-d ₆) δ 9.23 (t, J = 5.9 Hz, 1H), 8.05 - 7.92 (m, 2H), 7.72 - 7.56 (m, 6H), 7.47 - 7.32 (m, 3H), 6.30 (q, J = 4.4 Hz, 1H), 4.68 - 4.62 (m, 4H), 4.60 (d, J = 5.9 Hz, 2H), 2.61 (d, J = 4.4 Hz, 3H) ppm; (M+1) = 454.

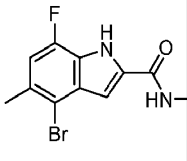
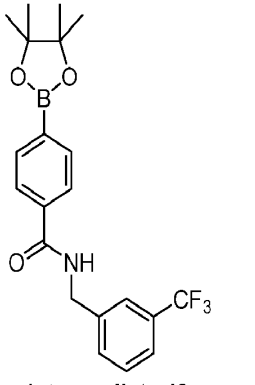
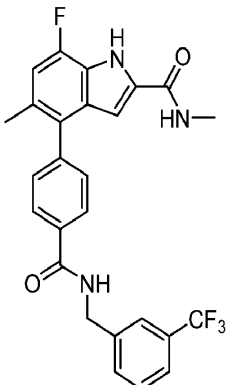
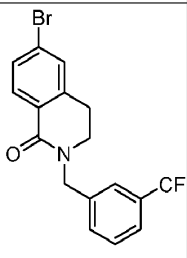
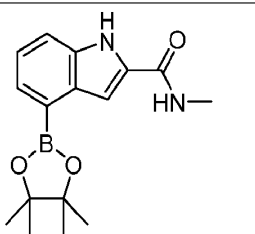
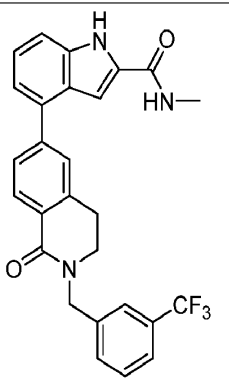
15	 Intermediate 51	 Intermediate 40		¹H NMR (400 MHz, DMSO-d₆) δ 11.81 (s, 1H), 9.39 (t, J = 5.9 Hz, 1H), 9.23 (dd, J = 2.3, 0.9 Hz, 1H), 8.61 – 8.47 (m, 1H), 8.37 (dd, J = 8.3, 2.3 Hz, 1H), 8.06 (dd, J = 8.3, 0.9 Hz, 1H), 7.78 – 7.52 (m, 7H), 7.32 (dd, J = 8.2, 7.4 Hz, 1H), 4.64 (d, J = 5.9 Hz, 2H), 2.82 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 453.
16	 Intermediate 29	 Intermediate 43		¹H NMR (400 MHz, DMSO-d₆) δ 9.29 (t, J = 5.9 Hz, 1H), 8.62 (d, J = 5.5 Hz, 1H), 8.14 (dd, J = 5.5, 0.8 Hz, 1H), 8.10 – 8.03 (m, 2H), 8.03 – 7.94 (m, 2H), 7.87 (d, J = 0.8 Hz, 1H), 7.76 – 7.53 (m, 4H), 4.61 (d, J = 5.9 Hz, 2H), 3.20 (s, 3H), 3.05 (s, 3H) ppm; (M+1) = 484.

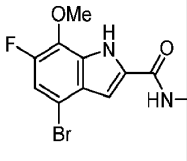
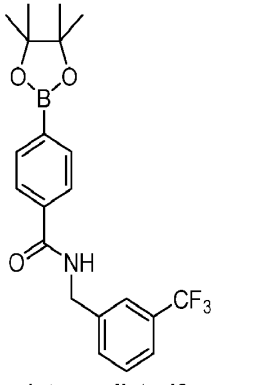
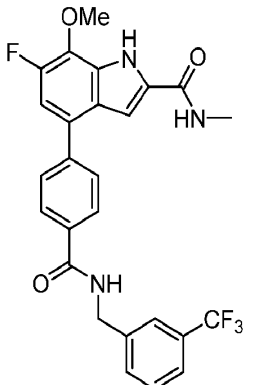
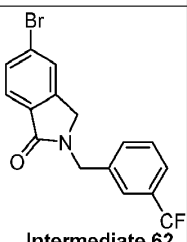
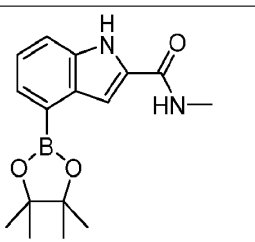
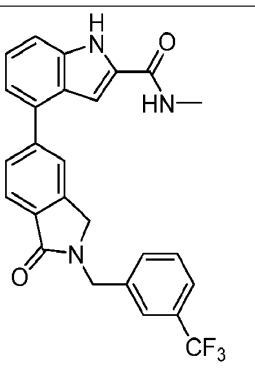
17	 Intermediate 30	 Intermediate 43	 ¹H NMR (400 MHz, DMSO-d₆) δ 9.26 (t, J = 5.9 Hz, 1H), 8.71 (q, J = 4.7 Hz, 1H), 8.17 - 7.98 (m, 2H), 7.87 - 7.75 (m, 2H), 7.75 - 7.55 (m, 7H), 7.52 (dd, J = 7.5, 1.0 Hz, 1H), 4.61 (d, J = 5.9 Hz, 2H), 2.81 (d, J = 4.7 Hz, 3H) ppm; (M+1) = 453.
18	 Intermediate 31	 Intermediate 43	 ¹H NMR (400 MHz, DMSO-d₆) δ 9.25 (t, J = 5.9 Hz, 1H), 9.13 (q, J = 4.8 Hz, 1H), 8.29 - 8.13 (m, 2H), 8.11 - 8.02 (m, 2H), 7.88 (dd, J = 8.3, 1.0 Hz, 1H), 7.81 (dd, J = 7.8, 1.0 Hz, 1H), 7.75 - 7.48 (m, 5H), 4.62 (d, J = 5.9 Hz, 2H), 2.86 (d, J = 4.8 Hz, 3H) ppm; (M+1) = 454.
19	 Intermediate 59	 Intermediate 40	 ¹H NMR (400 MHz, DMSO-d₆) δ 11.67 (s, 1H), 8.44 (q, J = 4.5 Hz, 1H), 7.75 (s, 1H), 7.69 (d, J = 7.3 Hz, 1H), 7.65 - 7.53 (m, 4H), 7.39 (d, J = 8.2 Hz, 1H), 7.28 - 7.18 (m, 2H), 7.14 - 7.01 (m, 3H), 4.32 (t, J =

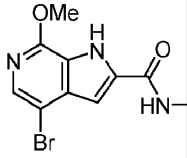
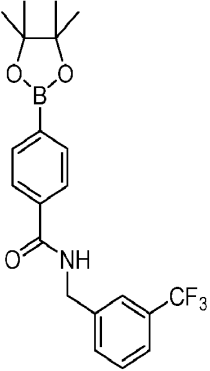
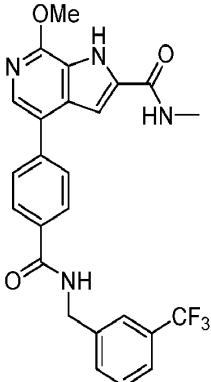
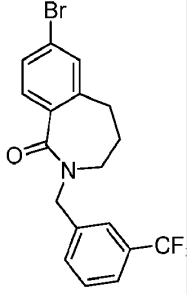
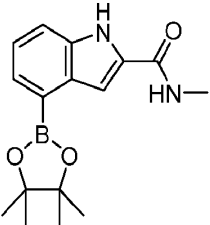
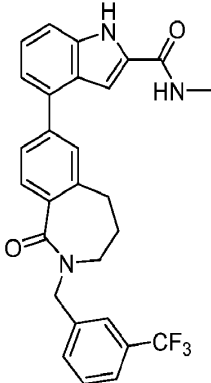
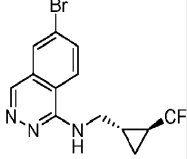
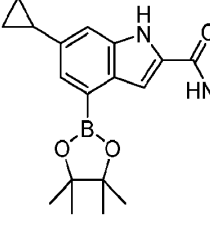
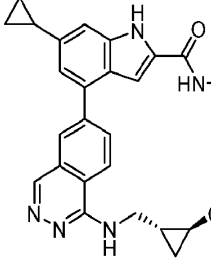
				6.6 Hz, 2H), 3.20 (t, J = 6.6 Hz, 2H), 2.79 (d, J = 4.5 Hz, 3H) ppm; (M+1) = 439.
20	 Intermediate 21	 Intermediate 43		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.38 (s, 1H), 9.28 (t, J = 5.9 Hz, 1H), 8.69 (q, J = 4.7 Hz, 1H), 8.13 - 8.06 (m, 2H), 7.93 - 7.87 (m, 2H), 7.86 - 7.81 (m, 2H), 7.68 - 7.58 (m, 3H), 7.53 (d, J = 1.3 Hz, 1H), 7.41 (s, 1H), 4.62 (d, J = 5.9 Hz, 2H), 2.82 (d, J = 4.7 Hz, 3H) ppm; (M+1)=477.
21	 Intermediate 32	 Intermediate 43		¹ H NMR (400 MHz, DMSO-d ₆) δ 9.28 (t, J = 6.0 Hz, 1H), 8.75 (q, J = 4.8 Hz, 1H), 8.11 - 8.05 (m, 4H), 7.73 - 7.54 (m, 7H), 7.46 (dd, J = 7.3, 1.1 Hz, 1H), 4.62 (d, J = 6.0 Hz, 2H), 2.77 (d, J = 4.8 Hz, 3H) ppm; (M+1) = 469.

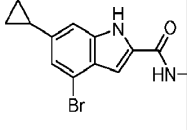
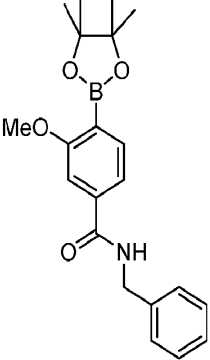
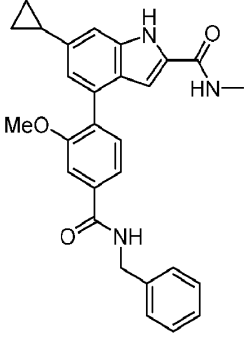
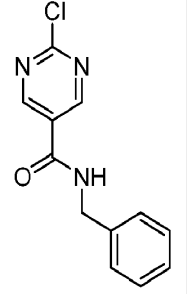
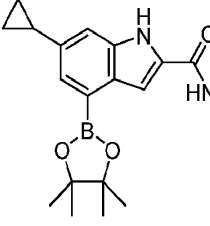
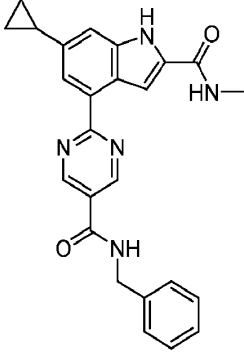
22	 WO2017177955	 Intermediate 43		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.38 (s, 1H), 9.20 (t, J = 5.9 Hz, 1H), 8.40 (q, J = 4.7 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.75 - 7.53 (m, 7H), 7.09 (s, 1H), 4.60 (d, J = 5.9 Hz, 2H), 3.60 (s, 3H), 2.79 (d, J = 4.7 Hz, 3H) ppm; (M+1) = 483.
23	 Intermediate 38	 Intermediate 43		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.77 (s, 1H), 9.20 (t, J = 5.9 Hz, 1H), 8.18 (q, J = 4.6 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.71 - 7.56 (m, 4H), 7.52 (d, J = 8.3 Hz, 2H), 7.26 (s, 1H), 4.58 (d, J = 5.9 Hz, 2H), 3.56 (s, 3H), 2.77 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 515.
24	 Intermediate 49	 Intermediate 40		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.79 (s, 1H), 9.26 (t, J = 6.0 Hz, 1H), 8.88 (s, 1H), 8.58 (q, J = 4.5 Hz, 1H), 8.21 (d, J = 7.5 Hz, 1H), 8.06 - 8.02 (m, 1H), 7.80 - 7.53 (m, 5H), 7.30 (t, J = 7.8 Hz, 1H), 4.59 (d, J = 6.0 Hz, 2H), 2.82 (d,

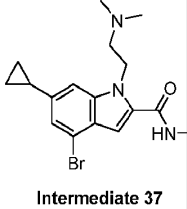
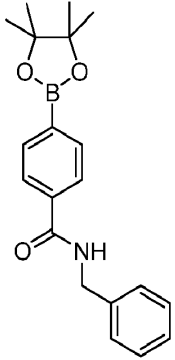
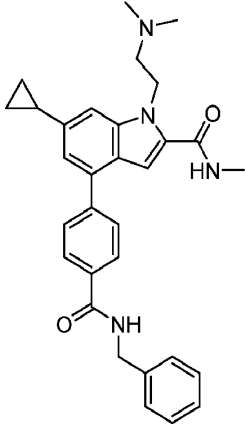
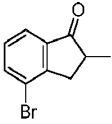
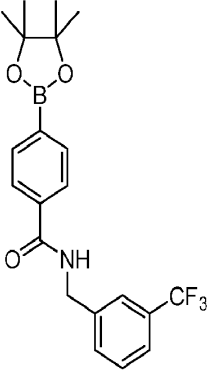
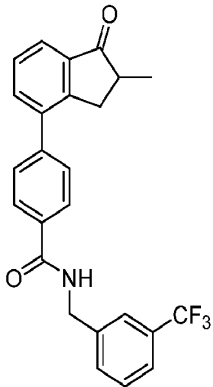
				J = 4.5 Hz, 3H), 2.70 (s, 3H) ppm; (M+1) = 468.
25	 Intermediate 23	 Intermediate 43		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.05 (s, 1H), 9.22 (t, J = 6.0 Hz, 1H), 8.44 (q, J = 4.6 Hz, 1H), 8.10 - 8.01 (m, 2H), 7.78 - 7.72 (m, 2H), 7.72 - 7.55 (m, 4H), 7.30 - 7.26 (m, 1H), 7.08 (d, J = 6.1 Hz, 1H), 4.61 (d, J = 6.0 Hz, 2H), 2.80 (d, J = 4.6 Hz, 3H), 2.39 (d, J = 2.1 Hz, 3H) ppm; (M+1) = 484.
26	 Intermediate 24	 Intermediate 43		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.63 (s, 1H), 9.23 (t, J = 6.0 Hz, 1H), 8.40 (q, J = 4.6 Hz, 1H), 8.10 - 8.01 (m, 2H), 7.85 - 7.75 (m, 2H), 7.73 - 7.56 (m, 4H), 7.32 - 7.28 (m, 1H), 7.26 - 7.22 (m, 1H), 7.12 - 7.08 (m, 1H), 4.62 (d, J = 6.0 Hz, 2H), 3.04 (sept, J = 6.9 Hz, 1H), 2.79 (d, J = 4.6 Hz, 3H), 1.29 (d, J = 6.9 Hz, 6H) ppm; (M+1) = 494.

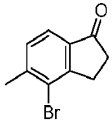
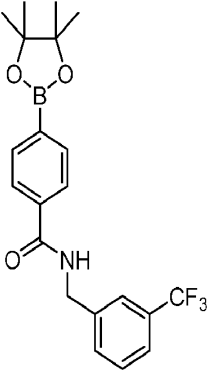
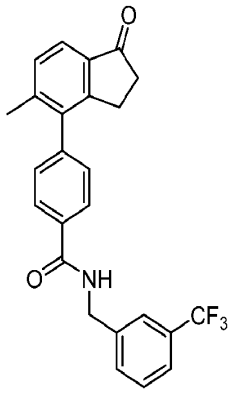
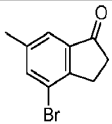
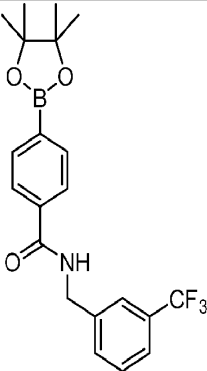
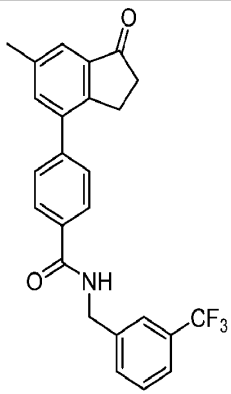
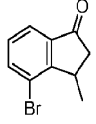
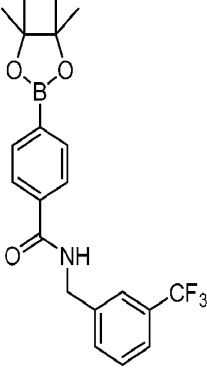
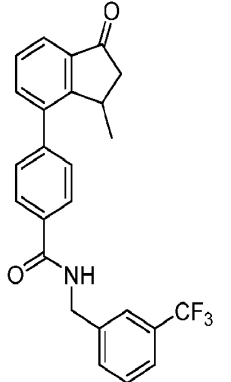
27	 Intermediate 25	 Intermediate 43	 ¹H NMR (400 MHz, DMSO-d₆) δ 10.69 (s, 1H), 9.25 (t, J = 6.0 Hz, 1H), 8.42 (q, J = 4.6 Hz, 1H), 8.10 - 7.99 (m, 2H), 7.75 - 7.56 (m, 4H), 7.51 - 7.38 (m, 2H), 7.12 (d, J = 2.0 Hz, 1H), 6.86 (d, J = 11.3 Hz, 1H), 4.62 (d, J = 6.0 Hz, 2H), 2.76 (d, J = 4.6 Hz, 3H), 2.17 (s, 3H) ppm; (M+1) = 484.
28	 Intermediate 61	 Intermediate 40	 ¹H NMR (400 MHz, DMSO-d₆) δ 11.80 (s, 1H), 8.47 (q, J = 4.5 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.76 - 7.55 (m, 6H), 7.48 (d, J = 8.2 Hz, 1H), 7.35 - 7.24 (m, 2H), 7.18 (d, J = 7.2 Hz, 1H), 4.85 (s, 2H), 3.67 - 3.56 (m, 2H), 3.16 - 3.04 (m, 2H), 2.81 (d, J = 4.5 Hz, 3H) ppm; (M+1) = 478.

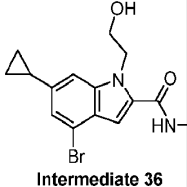
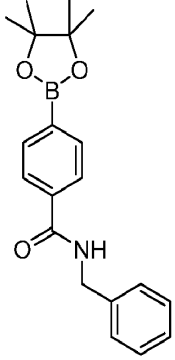
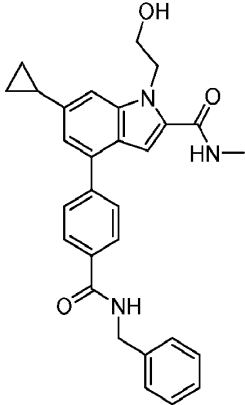
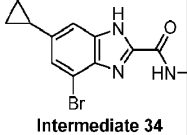
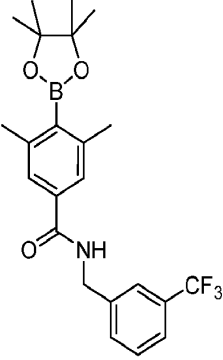
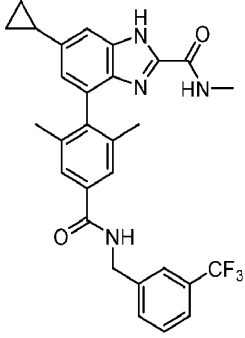
29	 Intermediate 26	 Intermediate 43	 ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 11.83 (s, 1H), 9.18 (t, <i>J</i> = 5.9 Hz, 1H), 8.36 (q, <i>J</i> = 4.6 Hz, 1H), 8.00 - 7.95 (m, 2H), 7.72 - 7.67 (m, 2H), 7.63 (s, 1H), 7.61 - 7.50 (m, 3H), 7.20 (d, <i>J</i> = 2.1 Hz, 1H), 7.09 (d, <i>J</i> = 12.8 Hz, 1H), 4.54 (d, <i>J</i> = 5.9 Hz, 2H), 3.93 (d, <i>J</i> = 1.2 Hz, 3H), 2.73 (d, <i>J</i> = 4.6 Hz, 3H) ppm; (M+1) = 500.
30	 Intermediate 62	 Intermediate 40	 ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 11.91 (s, 1H), 8.51 (q, <i>J</i> = 4.5 Hz, 1H), 7.92 - 7.76 (m, 3H), 7.76 - 7.55 (m, 4H), 7.48 (d, <i>J</i> = 8.1 Hz, 1H), 7.34 - 7.21 (m, 2H), 7.18 (dd, <i>J</i> = 7.3, 1.0 Hz, 1H), 4.89 (s, 2H), 4.51 (s, 2H), 2.80 (d, <i>J</i> = 4.5 Hz, 3H) ppm; (M+1) = 464.

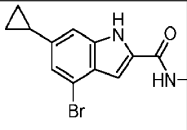
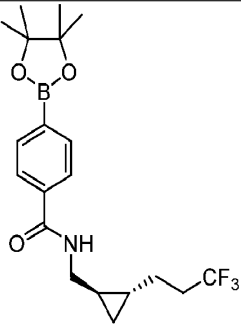
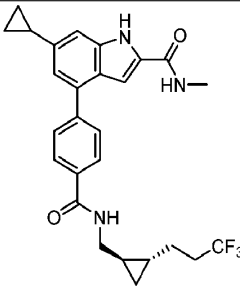
31	 Intermediate 33	 Intermediate 43	 ¹H NMR (400 MHz, DMSO-d₆) δ 12.25 (s, 1H), 9.22 (t, J = 5.9 Hz, 1H), 8.53 (d, J = 5.7 Hz, 1H), 8.05 (d, J = 8.0 Hz, 2H), 7.87 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.74 - 7.49 (m, 4H), 7.27 (d, J = 2.1 Hz, 1H), 4.61 (d, J = 5.9 Hz, 2H), 4.06 (s, 3H), 2.81 (d, J = 4.5 Hz, 3H); (M+1) = 483.
32	 Intermediate 63	 Intermediate 40	 ¹H NMR (400 MHz, DMSO-d₆) δ 11.78 (s, 1H), 8.48 (q, J = 4.6 Hz, 1H), 7.80 - 7.60 (m, 6H), 7.54 (d, J = 1.8 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.33 - 7.24 (m, 2H), 7.17 (dd, J = 7.2, 1.0 Hz, 1H), 4.85 (s, 2H), 3.32 - 3.23 (m, 2H), 2.86 - 2.74 (m, 5H), 1.89 (p, J = 6.6 Hz, 2H) ppm; (M+1) = 492.
33	 Intermediate 64	 Intermediate 41	 ¹H NMR (400 MHz, DMSO-d₆) δ 11.67 (d, J = 2.1 Hz, 1H), 9.02 (s, 1H), 8.44 - 8.36 (m, 2H), 8.21 - 8.16 (m, 2H), 7.73 (t, J = 5.8 Hz, 1H), 7.31 - 7.27 (m, 1H), 7.23 - 7.21 (m, 1H).

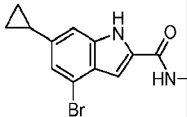
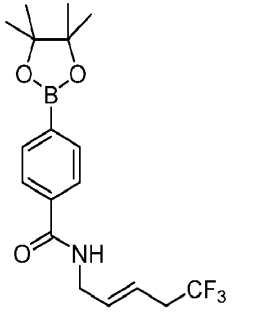
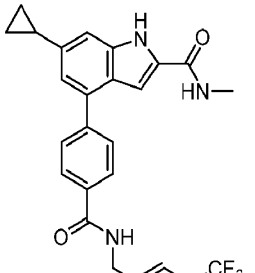
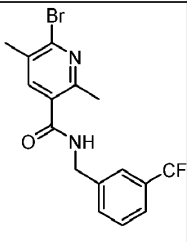
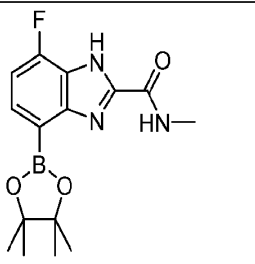
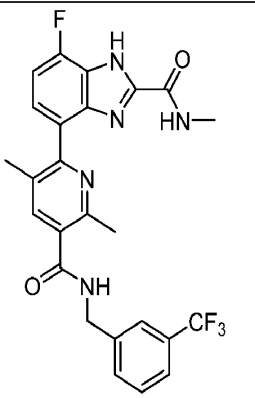
				(m, 1H), 7.03 (d, J = 1.5 Hz, 1H), 3.68 - 3.53 (m, 2H), 2.79 (d, J = 4.5 Hz, 3H), 2.15 - 2.05 (m, 1H), 1.99 - 1.87 (m, 1H), 1.83 - 1.71 (m, 1H), 1.05 - 0.92 (m, 4H), 0.81 - 0.70 (m, 2H) ppm; (M+1) = 480.
34	 Intermediate 28	 Intermediate 46		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.42 (s, 1H), 9.14 (t, J = 5.7 Hz, 1H), 8.28 (q, J = 4.4 Hz, 1H), 7.68 - 7.62 (m, 2H), 7.41 - 7.35 (m, 5H), 7.29 - 7.25 (m, 1H), 7.11 (s, 1H), 6.81 (s, 1H), 6.80 - 6.76 (m, 1H), 4.55 (d, J = 5.7 Hz, 2H), 3.78 (s, 3H), 2.75 (d, J = 4.4 Hz, 3H), 2.08 - 2.01 (m, 1H), 0.99 - 0.94 (m, 2H), 0.70 - 0.66 (m, 2H) ppm; (M+1) = 454.
35	 Intermediate 57	 Intermediate 41		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.68 (s, 1H), 9.44 (t, J = 5.6 Hz, 1H), 9.34 (s, 2H), 8.58 (q, J = 4.4 Hz, 1H), 8.05 - 7.98 (m, 2H), 7.40 - 7.27 (m, 6H), 4.57 (d, J = 5.6 Hz, 2H), 2.82 (d, J =

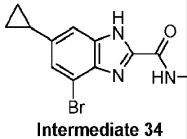
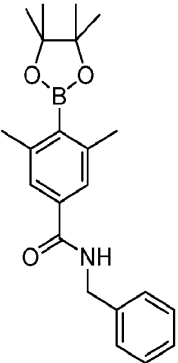
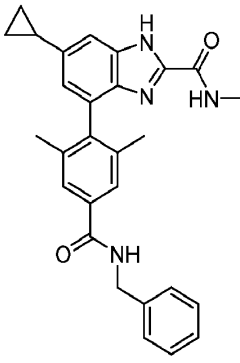
				4.8 Hz, 3H), 2.17 – 2.12 (m, 1H), 1.05 – 1.00 (m, 2H), 0.74 – 0.70 (m, 2H) ppm; (M+1) = 426.
36	 Intermediate 37	 Intermediate 94		¹ HNMR (400 MHz, DMSO-d ₆) δ 9.17 (t, J = 6.0 Hz, 1H), 8.46 (dd, J = 8.0, 4.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 4.0 Hz, 4H), 7.28–7.23 (m 2H), 7.16 (s, 1H), 6.94 (s, 1H), 4.73 – 4.62 (m, 2H), 4.53 (d, J = 4.0 Hz, 2H), 2.75 (d, J = 4.0 Hz, 3H), 2.54 (s, 2H), 2.23 (s, 6H), 2.15 – 2.06 (m, 1H), 1.03 – 0.98 (m, 2H), 0.85 – 0.81 (m, 2H) ppm; (M+1) = 495.
37	 Commercially available 174702-59-1	 Intermediate 43		¹ HNMR (500 MHz, DMSO-d ₆) δ 9.25 (t, J = 6.0 Hz, 1H), 8.03 (d, J = 4.0 Hz, 2H), 7.75 (dd, J = 8.0, 1.2 Hz, 1H), 7.72 – 7.68 (m, 4H), 7.67 – 7.55 (m, 4H), 4.60 (d, J = 4.0 Hz, 2H), 3.40 (dd, J = 16.0, 8.0 Hz, 1H), 2.86 (dd, J = 12.0, 4.0 Hz, 1H), 2.75 – 2.50

				(m, 1H), 1.20 (d, J = 4.0 Hz, 3H) ppm; (M+1) = 424.
38	 Commercially available 66790-62-3	 Intermediate 43		¹ HNMR (500 MHz, DMSO-d ₆) δ 9.25 (t, J = 6.0 Hz, 1H), 8.03 (d, J = 4.0 Hz, 2H), 7.71 - 7.58 (m, 5H), 7.43 (t, J = 8.0 Hz, 3H), 4.60 (d, J = 4.0 Hz, 2H), 2.79 - 2.73 (m, 2H), 2.60 - 2.54 (m, 2H), 2.19 (s, 3H) ppm; (M+1) = 424.
39	 Commercially available 876-91-5	 Intermediate 43		¹ HNMR (400 MHz, DMSO-d ₆) δ 9.27 - 9.25 (m, 1H), 8.03 - 8.01 (m, 2H), 7.70 - 7.58 (m, 7H), 7.51 (s, 1H), 4.60 (d, J = 4.4 Hz, 2H), 3.13 - 3.11 (m, 2H), 2.66 - 2.63 (m, 2H), 2.50 (s, 3H) ppm; (M+1) = 424.
40	 Commercially available 102539-53-7	 Intermediate 43		¹ H NMR (500 MHz, DMSO-d ₆) δ 9.26 (t, J = 5.8 Hz, 1H), 8.04-8.02 (m, 2H), 7.72 - 7.54 (m, 9H), 4.60 (d, J = 5.8 Hz, 2H), 4.01 - 3.91 (m, 1H), 3.02 - 2.97 (m, 1H), 2.25

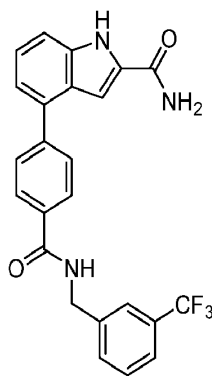
				– 2.22 (m, 1H), 0.80 (d, J = 7.0 Hz, 3H) ppm; (M+1) = 424.
41	 Intermediate 36	 Intermediate 94		¹ HNMR (500 MHz, DMSO-d ₆) δ 9.13 (t, J = 6.0 Hz, 1H), 8.43 (q, J = 4.6 Hz, 1H), 8.04 – 8.02 (m, 2H), 7.77 – 7.75 (m, 2H), 7.35 – 7.24 (m, 6H), 7.16 (s, 1H), 6.94 (s, 1H), 4.86 (br s, 1H), 4.60 (t, J = 6.0 Hz, 2H), 4.53 (d, J = 6.0 Hz, 2H), 3.69 – 3.67 (m, 2H), 2.75 (d, J = 4.6 Hz, 3H), 2.13 – 2.07 (m, 1H), 1.03 – 0.95 (m, 2H), 0.84 – 0.77 (m, 2H) ppm; (M+1) = 468.
42	 Intermediate 34	 Intermediate 47		¹ H NMR (500 M Hz, DMSO-d ₆) δ 13.12 (s, 1H), 9.11 (t, J = 6.0 Hz, 1H), 8.52 (q, J = 4.5 Hz, 1H), 7.60 – 7.69 (m, 6H), 7.19 (d, J = 1.2 Hz, 1H), 6.71 (d, J = 1.2 Hz, 1H), 4.59 (d, J = 6.0 Hz,

				2H), 2.73 (d, J = 4.5 Hz, 3H), 2.07 - 2.10 (m, 1H), 1.97 (s, 6H), 0.97 - 1.01 (m, 2H), 0.69 - 0.72 (m, 2H) ppm; (M+1) = 521.
43	 Intermediate 28	 Intermediate 65		¹ HNMR (500 MHz, DMSO-d ₆) δ 11.52 (s, 1H), 8.59 (t, J = 6.0 Hz, 1H), 8.24 (q, J = 4.6 Hz, 1H), 7.99 - 7.95 (m, 2H), 7.74 - 7.70 (m, 2H), 7.21 - 7.19 (m, 1H), 7.15 (s, 1H), 6.85 (s, 1H), 3.25 - 3.10 (m, 2H), 2.75 (d, J = 4.6 Hz, 3H), 2.40 - 2.30 (m, 2H), 2.10 - 2.02 (m, 1H), 1.50 - 1.40 (m, 2H), 0.99 - 0.95 (m, 2H), 0.92 - 0.88 (m, 1H), 0.75 - 0.69 (m, 3H), 0.50 - 0.46 (m, 1H), 0.39 - 0.35 (m, 1H) ppm; (M+1) = 484.

44	 Intermediate 28	 Intermediate 66	 ¹HNMR (400 MHz, DMSO-d₆) δ 11.52 (s, 1H), 8.80 (t, J = 5.6 Hz, 1H), 8.40 (q, J = 4.5 Hz, 1H), 8.03 – 7.96 (m, 2H), 7.76 – 7.74 (m, 2H), 7.22 – 7.17 (m, 2H), 6.91 – 6.93 (m, 1H), 5.95 – 5.88 (m, 1H), 5.58 – 5.50 (m, 1H), 3.97 – 3.95 (m, 2H), 3.13 – 3.06 (m, 2H), 2.78 (d, J = 4.5 Hz, 3H), 2.10 – 2.04 (m, 1H), 1.00 – 0.95 (m, 2H), 0.75 – 0.70 (m, 2H) ppm; (M+1) = 456.
45	 Intermediate 58	 Intermediate 42	 ¹H NMR (400 MHz, DMSO-d₆) δ 9.27 – 9.25 (m, 1H), 9.01 – 8.97 (m, 1H), 8.04 – 8.00 (m, 1H), 7.75 – 7.63 (m, 4H), 7.33 – 7.24 (m, 2H), 4.61 (d, J = 5.8 Hz, 2H), 2.81 (d, J = 4.6 Hz, 3H), 2.59 (s, 3H), 2.18 (s, 3H) ppm; (M+1) = 500.

46	 Intermediate 34	 Intermediate 95	 ¹HNMR (400MHz, DMSO-d₆) δ 13.12 (s, 1H), 8.99 (t, J = 4.8 Hz, 1H), 8.51 (q, J = 4.6 Hz, 1H), 7.66 (s, 2H), 7.32 - 7.36 (m, 4H), 7.25 - 7.27 (m, 1H), 7.18 (d, J = 1.2 Hz, 1H), 6.71 (s, 1H), 4.51 (d, J = 4.8 Hz, 2H), 2.73 (d, J = 4.6 Hz, 3H), 2.10 - 2.07 (m, 1H), 1.96 (s, 6H), 1.01 - 0.98 (m, 2H), 0.72 - 0.69 (m, 2H) ppm; (M+1) = 453.
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Example 47: Preparation of 4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxamide



5

To a 50 mL recovery flask equipped with a magnetic stir bar and N₂ inlet was added 4-(2-carbamoyl-1H-indol-4-yl)benzoic acid (98 mg, 350 μmol, **Intermediate 96**), 3-(trifluoromethyl)benzylamine (54 μl, 367 μmol), HATU (171 mg, 437 μmol), and N,N-dimethylformamide (5 mL). The solution was treated with N,N-diisopropylethylamine

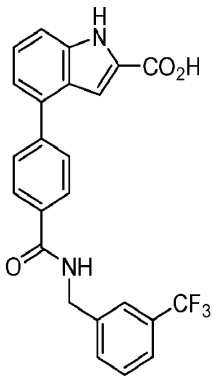
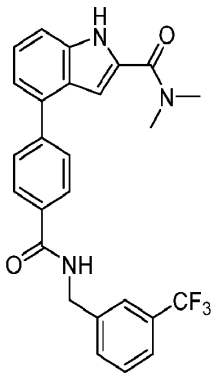
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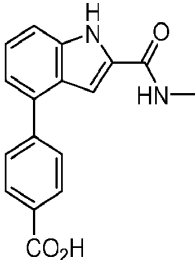
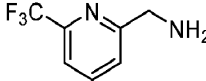
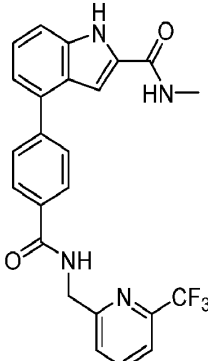
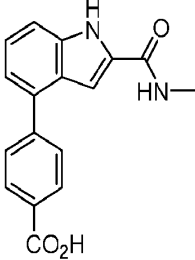
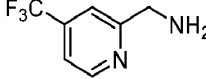
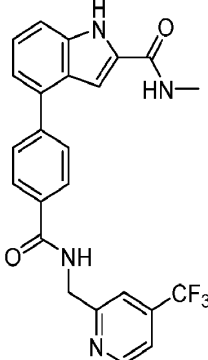
(122 μ l, 699 μ mol) and allowed to stir at room temperature. After 30 min, LC/MS analysis revealed that the reaction was complete. The yellow solution was diluted with water (25 mL), and the resulting precipitate was isolated by filtration. The filter cake was washed with water (25 mL), and the moist solids were dissolved in ethyl acetate (50 mL). The solution was washed with 2N hydrochloric acid solution (25 mL), 2M sodium carbonate solution (25 mL), and brine (25 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated to provide 154 mgs of a yellow oil. Chromatographic purification (CombiFlash, 12 g SiO₂ gold column, 50% ethyl acetate/heptane to 100% ethyl acetate elute, combined fractions 3-8, rack 1) afforded 4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxamide (99 mg, 226 μ mol, 65 % yield) as a foamy white solid; ¹H NMR (400 MHz, DMSO-d₆) δ 11.74 (s, 1H), 9.23 (t, J = 5.9 Hz, 1H), 8.10 – 8.01 (m, 2H), 7.97 (br s, 1H), 7.84 – 7.75 (m, 2H), 7.74 – 7.54 (m, 4H), 7.49 – 7.45 (m, 1H), 7.41 – 7.24 (m, 3H), 7.12 – 7.16 (m, 1H), 4.62 (d, J = 5.9 Hz, 2H) ppm; (M+1) = 438.

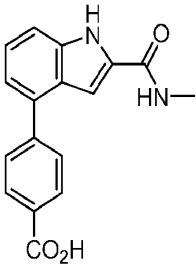
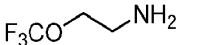
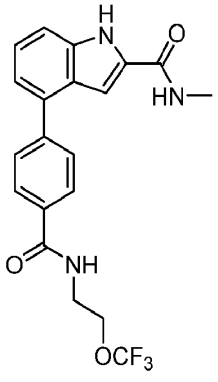
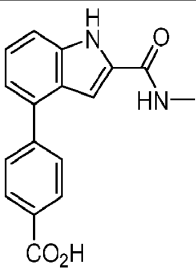
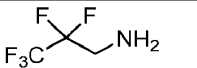
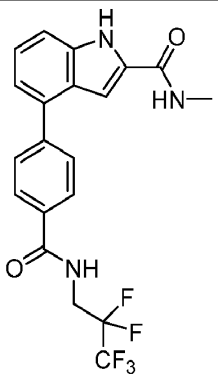
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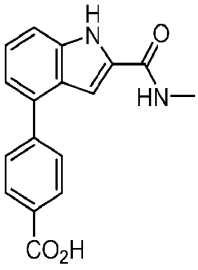
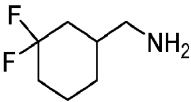
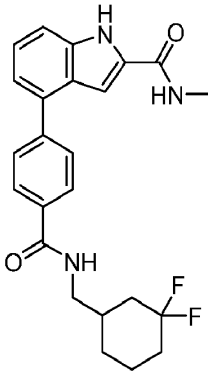
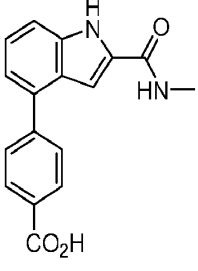
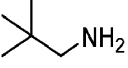
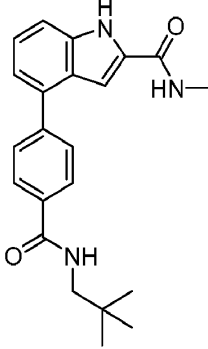
The following compounds were prepared as described for the synthesis of **Example**

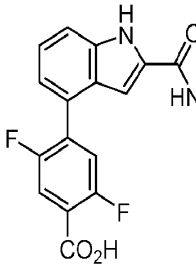
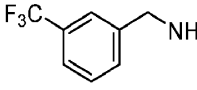
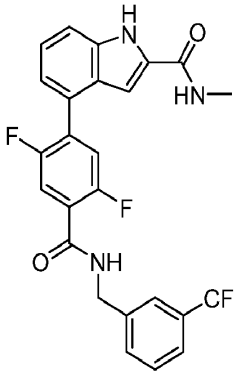
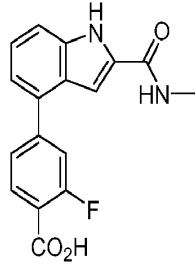
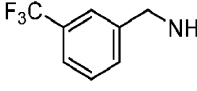
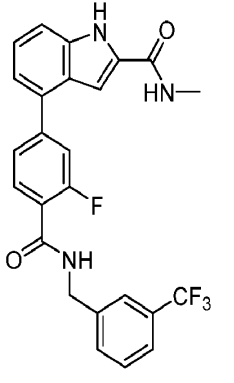
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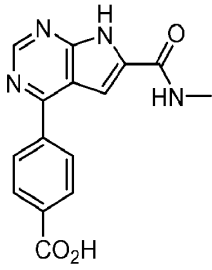
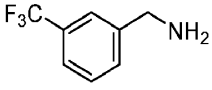
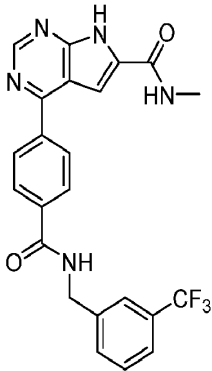
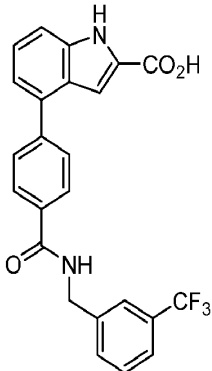
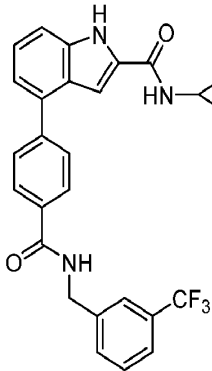
Example	Acid	Amine	Product	¹ H NMR/MS
48	 Intermediate 71			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.78 (s, 1H), 9.22 (t, J = 5.9 Hz, 1H), 8.13 – 7.99 (m, 2H), 7.87 – 7.75 (m, 2H), 7.75 – 7.57 (m, 4H), 7.50 (dd, J = 8.2, 1.0 Hz, 1H), 7.32 (dd, J = 8.2, 7.2 Hz, 1H), 7.20 (dd, J = 7.2, 1.0 Hz, 1H), 6.94-6.92 (m, 1H), 4.61 (d, J = 5.9 Hz, 2H), 3.32

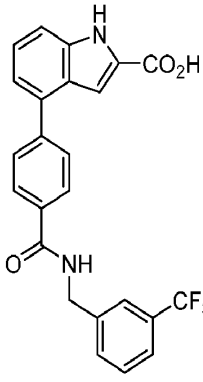
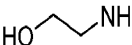
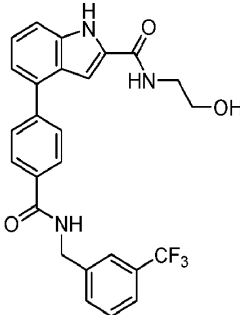
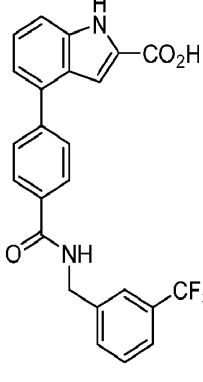
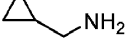
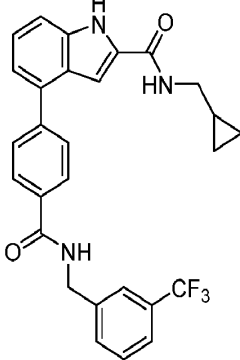
				(br s, 6H) ppm; (M+1) = 466.
49	 Intermediate 67			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.79 (s, 1H), 9.34 (t, <i>J</i> = 5.9 Hz, 1H), 8.49 (q, <i>J</i> = 4.5 Hz, 1H), 8.14 – 8.05 (m, 3H), 7.86 – 7.73 (m, 3H), 7.70 – 7.66 (m, 1H), 7.55 – 7.45 (m, 1H), 7.37 – 7.25 (m, 2H), 7.22 – 7.18 (m, 1H), 4.70 (d, <i>J</i> = 5.9 Hz, 2H), 2.81 (d, <i>J</i> = 4.5 Hz, 3H) ppm; (M+1) = 453.
50	 Intermediate 67			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.79 (s, 1H), 9.29 (t, <i>J</i> = 5.8 Hz, 1H), 8.84 (d, <i>J</i> = 5.1 Hz, 1H), 8.48 (q, <i>J</i> = 4.6 Hz, 1H), 8.15 – 8.02 (m, 2H), 7.85 – 7.77 (m, 2H), 7.72 – 7.66 (m, 2H), 7.51 – 7.45 (m, 1H), 7.38 – 7.25 (m, 2H), 7.23 – 7.17 (m, 1H), 4.74 (d, <i>J</i> = 5.8 Hz, 2H), 2.81 (d, <i>J</i> = 4.6 Hz, 3H) ppm; (M+1) = 453.

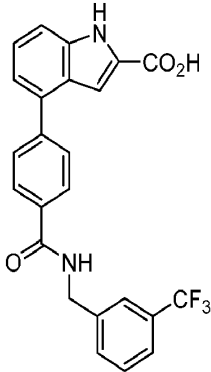
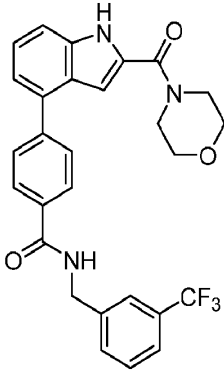
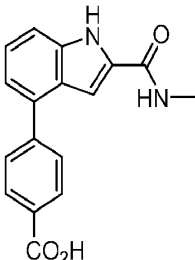
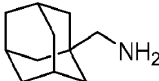
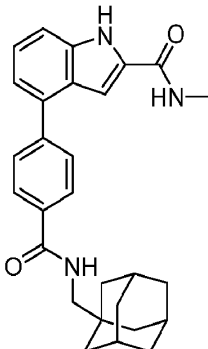
51	 Intermediate 67			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.59 (s, 1H), 8.81 (t, J = 5.6 Hz, 1H), 8.47 (q, J = 4.6 Hz, 1H), 8.17 – 7.93 (m, 2H), 7.92 – 7.70 (m, 2H), 7.48 (d, J = 8.2 Hz, 1H), 7.40 – 7.25 (m, 2H), 7.25 – 7.05 (m, 1H), 4.30 – 4.20 (m, 2H), 3.68 – 3.60 (m, 2H), 2.80 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 406.
52	 Intermediate 67			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.79 (s, 1H), 9.14 (t, J = 6.3 Hz, 1H), 8.47 (q, J = 4.6 Hz, 1H), 8.12 – 7.95 (m, 2H), 7.88 – 7.74 (m, 2H), 7.48 (dt, J = 8.2, 1.0 Hz, 1H), 7.38 – 7.25 (m, 2H), 7.19 (dd, J = 7.3, 1.0 Hz, 1H), 4.19 (td, J = 15.5, 6.1 Hz, 2H), 2.80 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 426.

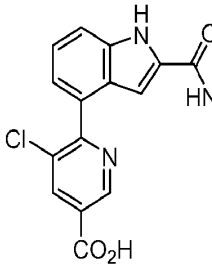
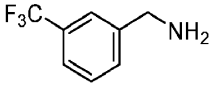
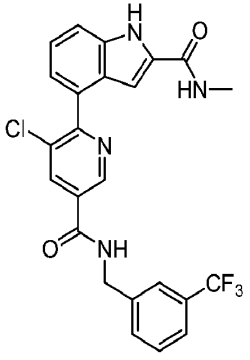
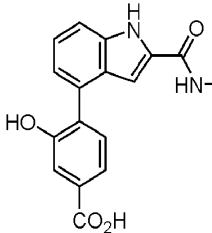
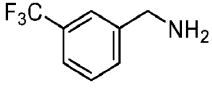
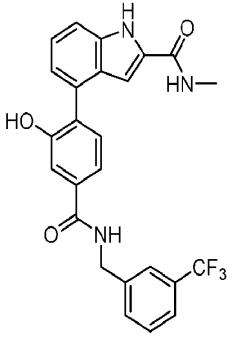
53	 Intermediate 67			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.77 (s, 1H), 8.59 (t, J = 5.9 Hz, 1H), 8.46 (q, J = 4.6 Hz, 1H), 8.14 – 7.92 (m, 2H), 7.85 – 7.69 (m, 2H), 7.47 (dt, J = 8.2, 1.0 Hz, 1H), 7.37 – 7.25 (m, 2H), 7.17 (dd, J = 7.2, 1.0 Hz, 1H), 3.28 – 3.20 (m, 2H), 2.80 (d, J = 4.6 Hz, 3H), 2.23 – 1.34 (m, 8H), 1.14 – 0.96 (m, 1H) ppm; (M+1) = 426.
54	 Intermediate 67			¹ H NMR (600 MHz, DMSO-d ₆) δ ppm 11.78 (s, 1H), 8.46 – 8.50 (m, 1H), 8.42 (t, J = 6.6 Hz, 1H), 8.01 – 8.04 (m, 2H), 7.75 – 7.78 (m, 2H), 7.47 (d, J = 8.5 Hz, 1 H), 7.27 – 7.31 (m, 2H), 7.18 (dd, J = 7.4, 0.9 Hz, 1H), 3.15 (d, J = 6.6 Hz, 2H), 2.79 (d, J=4.7 Hz, 3H), 0.92 (s, 9H) ppm; (M+1) = 362.

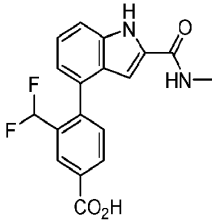
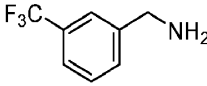
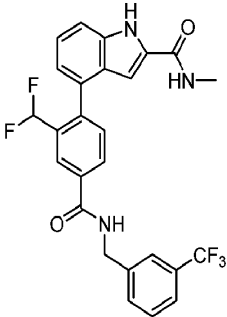
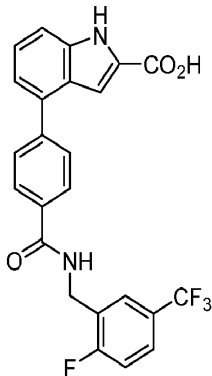
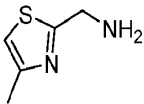
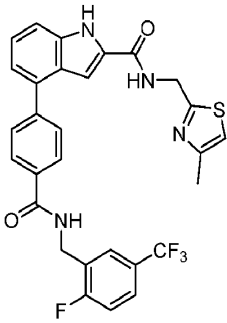
55	 Intermediate 79			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.82 (d, J = 2.2 Hz, 1H), 9.14 (td, J = 6.1, 2.0 Hz, 1H), 8.46 (d, J = 4.9 Hz, 1H), 7.85 – 7.44 (m, 7H), 7.30 (dd, J = 8.3, 7.2 Hz, 1H), 7.15 (dt, J = 7.2, 1.2 Hz, 1H), 7.05 (q, J = 1.9 Hz, 1H), 4.61 (d, J = 5.9 Hz, 2H), 2.79 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 488.
56	 Intermediate 80			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.85 (s, 1H), 9.18 – 8.95 (m, 1H), 8.52 (q, J = 4.7 Hz, 1H), 7.80 (t, J = 7.9 Hz, 1H), 7.77 – 7.57 (m, 6H), 7.50 (dt, J = 8.2, 1.0 Hz, 1H), 7.37 – 7.26 (m, 2H), 7.22 (dd, J = 7.3, 1.0 Hz, 1H), 4.61 (d, J = 6.0 Hz, 2H), 2.81 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 470.

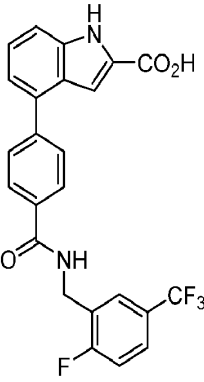
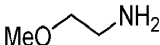
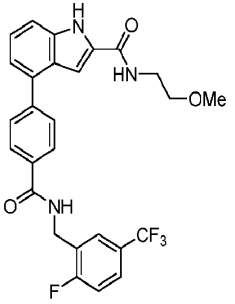
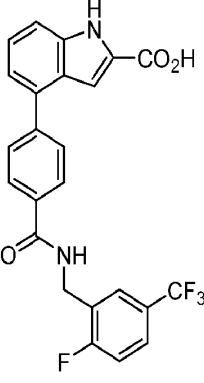
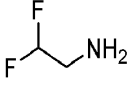
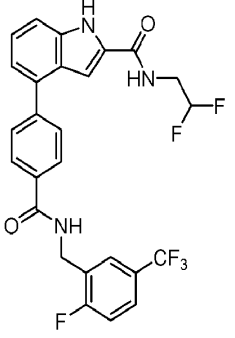
57	 Intermediate 73			¹ H NMR (400 MHz, DMSO-d ₆) δ 12.82 (s, 1H), 9.35 (t, J = 5.9 Hz, 1H), 8.95 (s, 1H), 8.71 (q, J = 4.6 Hz, 1H), 8.33 - 8.25 (m, 2H), 8.17 - 8.10 (m, 2H), 7.74 - 7.56 (m, 5H), 4.63 (d, J = 5.9 Hz, 2H), 2.86 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 454.
58	 Intermediate 71			¹ H NMR (600 MHz, DMSO-d ₆) δ ppm 11.79 (s, 1H), 9.26 (t, J = 6.1 Hz, 1H), 8.49 (d, J = 4.4 Hz, 1H), 8.07 - 8.11 (m, 2H), 7.82 - 7.78 (m, 2H), 7.73 - 7.61 (m, 4H), 7.50 (d, J = 8.5 Hz, 1H), 7.34 - 7.29 (m, 2H), 7.19 (dd, J = 7.4, 1.0 Hz, 1H), 4.64 (d, J = 6.1 Hz, 2H), 2.89 - 2.85 (m, 1H), 0.72 - 0.66 (m, 2H), 0.58 - 0.55 (m, 2H) ppm; (M+1) = 478.

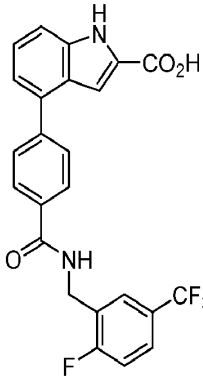
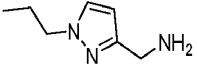
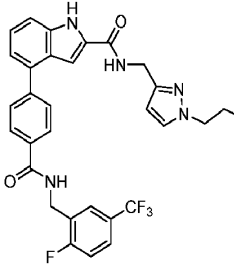
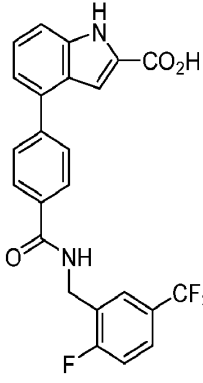
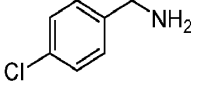
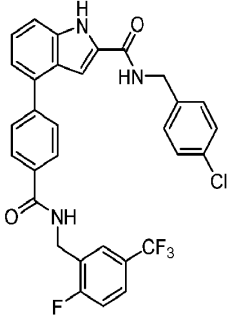
59	 Intermediate 71			¹ H NMR (600 MHz, DMSO-d ₆) δ 11.80 (s, 1H), 9.27 (t, J = 6.1 Hz, 1H), 8.54 (t, J = 5.9 Hz, 1H), 8.13 – 8.09 (m, 2H), 7.85 – 7.81 (m, 2H), 7.62 – 7.74 (m, 4H), 7.51 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 2.3 Hz, 1H), 7.32 (dd, J = 8.4, 7.4 Hz, 1H), 7.20 – 7.23 (m, 1H), 4.65 (d, J = 6.1 Hz, 2H), 3.66 (br s, 1H), 3.53 (t, J = 6.4 Hz, 2H), 3.35 (q, J = 6.3 Hz, 2H) ppm; (M+1) = 482.
60	 Intermediate 71			¹ H NMR (600 MHz, DMSO-d ₆) δ ppm 11.78 (s, 1H), 9.24 (t, J=6.1 Hz, 1H), 8.60 (t, J=5.9 Hz, 1H), 8.09 – 8.07 (m, 2H), 7.82 – 7.79 (m, 2H), 7.72 – 7.59 (m, 4H), 7.48 (d, J = 8.4 Hz, 1H), 7.36 (dd, J = 2.3, 1.0 Hz, 1H), 7.29 (dd, J = 8.4, 7.4 Hz, 1H), 7.18 (dd, J = 7.4, 1.0 Hz, 1H), 4.62 (d, J = 6.1 Hz, 2H), 3.17 (t, J = 6.4 Hz, 2H), 1.07 – 1.00 (m, 1H), 0.47 – 0.43 (m, 2H), 0.26 – 0.22 (m, 2H).

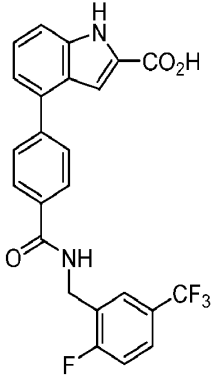
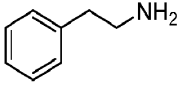
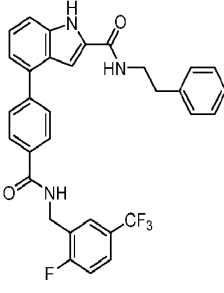
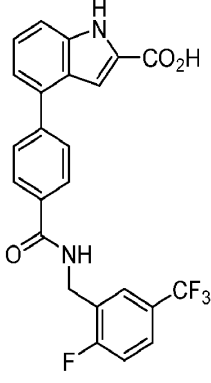
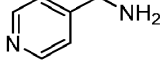
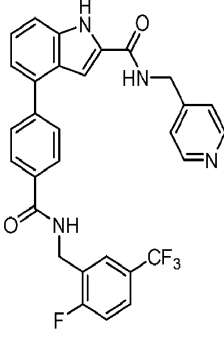
				(m, 2 H) ppm; (M+1) = 492.
61	 Intermediate 71			¹ H NMR (600 MHz, DMSO-d ₆) δ 11.84 (d, J = 2.3 Hz, 1H), 9.22 (t, J = 6.1 Hz, 1H), 8.06 – 8.03 (m, 2H), 7.81 – 7.78 (m, 2H), 7.71 – 7.58 (m, 4H), 7.48 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 8.4, 7.4 Hz, 1H), 7.20 (dd, J = 7.4, 1.0 Hz, 1H), 6.86 (dd, J = 2.3, 1.0 Hz, 1H), 4.61 (d, J = 6.1 Hz, 2H), 3.74 (br s, 4H), 3.66 – 3.59 (m, 4H) ppm; (M+1) = 508.
62	 Intermediate 67			¹ H NMR (400 MHz, Methanol-d ₄) δ 8.00 - 7.92 (m, 2H), 7.84 - 7.75 (m, 2H), 7.48 (dt, J = 8.2, 1.0 Hz, 1H), 7.32 (dd, J = 8.3, 7.2 Hz, 1H), 7.28 - 7.16 (m, 2H), 4.10 (q, J = 7.1 Hz, 1H), 3.14 (d, J = 6.4 Hz, 2H), 2.92 (s, 3H), 2.00 (d, J = 5.5 Hz, 5H), 1.83 - 1.66 (m, 6H), 1.66 - 1.56 (m, 6H) ppm; (M-1) = 440.

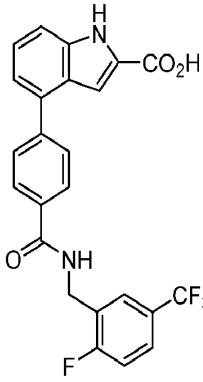
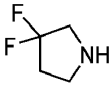
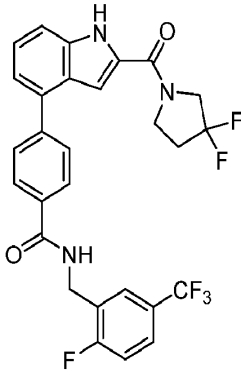
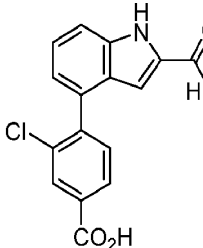
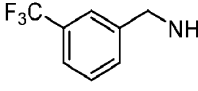
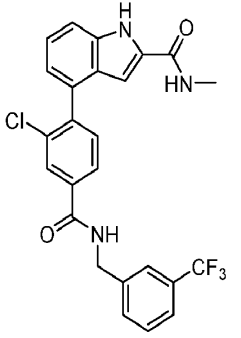
63	 Intermediate 81			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.78 (s, 1H), 9.50 (t, J = 5.8 Hz, 1H), 9.13 (d, J = 1.9 Hz, 1H), 8.53 (d, J = 1.9 Hz, 1H), 8.40 (q, J = 4.6 Hz, 1H), 7.81 – 7.59 (m, 4H), 7.55 (dt, J = 8.1, 1.0 Hz, 1H), 7.31 (dd, J = 8.1, 7.2 Hz, 1H), 7.24 (dd, J = 7.2, 1.0 Hz, 1H), 6.92 (dd, J = 2.2, 0.9 Hz, 1H), 4.65 (d, J = 5.8 Hz, 2H), 2.77 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 487.
64	 Intermediate 82			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.59 (s, 1H), 9.64 (s, 1H), 9.12 (t, J = 5.9 Hz, 1H), 8.37 (q, J = 4.6 Hz, 1H), 7.77 – 7.55 (m, 4H), 7.52 (d, J = 1.7 Hz, 1H), 7.50 – 7.32 (m, 3H), 7.22 (dd, J = 8.2, 7.2 Hz, 1H), 7.07 (dd, J = 7.2, 1.0 Hz, 1H), 6.95 (dd, J = 2.3, 1.0 Hz, 1H), 4.58 (d, J = 5.9 Hz, 2H), 2.76 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 468.

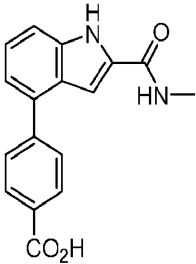
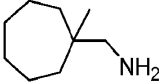
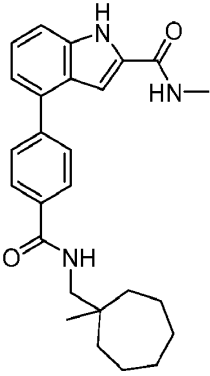
65	 Intermediate 74		 ¹H NMR (400 MHz, Methanol-<i>d</i>₄) δ 8.39 - 8.34 (m, 1H), 8.11 (ddd, <i>J</i> = 8.1, 2.0, 1.0 Hz, 1H), 7.74 - 7.49 (m, 8H), 7.33 (dd, <i>J</i> = 8.4, 7.1 Hz, 1H), 7.00 (dd, <i>J</i> = 7.2, 0.9 Hz, 1H), 6.78 (d, <i>J</i> = 0.9 Hz, 1H), 6.53 (m, 1H), 4.70 (s, 2H), 2.87 (s, 3H), 2.01 (s, 1H) ppm; (<i>M</i>+1) = 502.
66	 Intermediate 91		 ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ 11.93 (s, 1H), 9.40 (t, <i>J</i> = 6.2 Hz, 1H), 9.23 (t, <i>J</i> = 5.9 Hz, 1H), 8.11 - 8.07 (m, 2H), 7.85 - 7.76 (m, 4H), 7.53 - 7.46 (m, 3H), 7.35 (t, <i>J</i> = 7.9 Hz, 1H), 7.23 (d, <i>J</i> = 7.4 Hz, 1H), 7.18 (s, 1H), 4.74 (d, <i>J</i> = 6.2 Hz, 2H), 4.65 (br d, <i>J</i> = 5.8 Hz, 2H), 2.32 (s, 3H) ppm; (<i>M</i>+1) = 567.

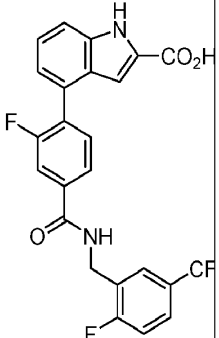
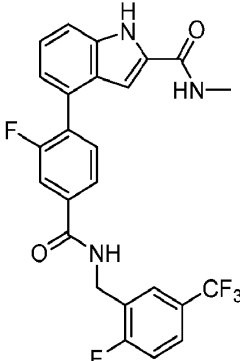
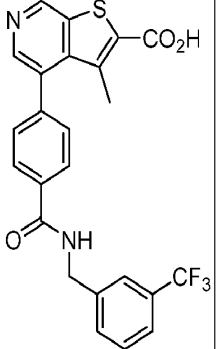
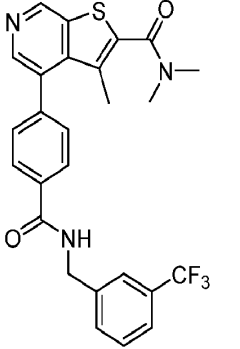
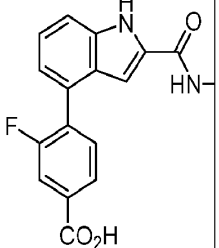
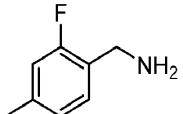
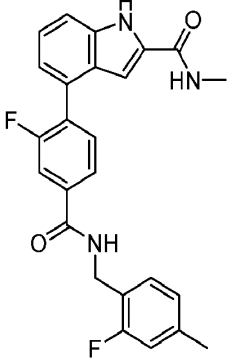
67	 Intermediate 91			¹ H NMR (600 MHz, DMSO-d ₆) δ 11.79 (s, 1 H), 9.21 (t, J = 5.9 Hz, 1H), 8.58 (t, J = 5.5 Hz, 1H), 8.08 – 8.05 (m, 2H), 7.81 – 7.74 (m, 4H), 7.51 – 7.47 (m, 2H), 7.40 – 7.36 (m, 1H), 7.30 (dd, J = 8.5, 7.4 Hz, 1H), 7.21 – 7.18 (m, 1H), 4.64 (d, J = 5.9 Hz, 2H), 3.52 – 3.36 (m, 4H), 3.26 (s, 3H) ppm; (M+1) = 514.
68	 Intermediate 91			¹ H NMR (600 MHz, DMSO-d ₆) δ 11.88 (s, 1 H), 9.21 (t, J = 6.0 Hz, 1H), 8.88 (t, J = 6.2 Hz, 1H), 8.09 – 8.06 (m, 2H), 7.82 – 7.75 (m, 4H), 7.51 – 7.44 (m, 3H), 7.33 (dd, J = 8.5, 7.4 Hz, 1H), 7.21 (dd, J = 7.4, 1.0 Hz, 1H), 6.14 (tt, J = 57.0, 4.1 Hz, 1H), 4.64 (d, J = 5.9 Hz, 2H), 3.74 – 3.66 (m, 2H) ppm; (M+1) = 520.

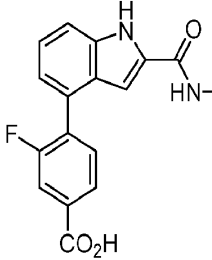
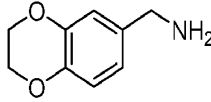
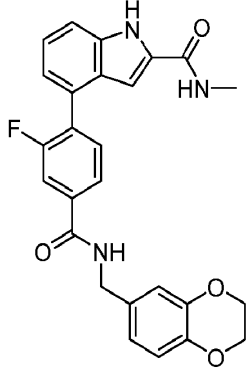
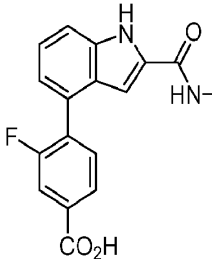
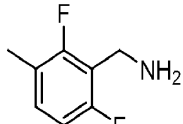
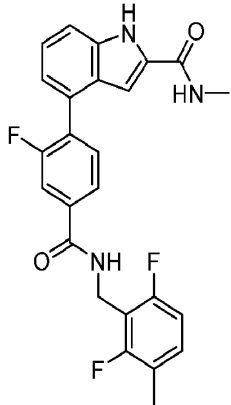
69	 Intermediate 91			¹ H NMR (600 MHz, DMSO-d ₆) δ 11.82 (d, J = 2.3 Hz, 1H), 9.22 (t, J = 5.9 Hz, 1H), 8.95 (t, J = 6.1 Hz, 1H), 8.09 – 8.05 (m, 2H), 7.83 – 7.76 (m, 4H), 7.64 (d, J = 2.3 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.45 (d, J = 2.3 Hz, 1H), 7.32 (dd, J = 8.5, 7.4 Hz, 1H), 7.21 (dd, J = 7.4, 1.0 Hz, 1H), 6.15 (d, J = 2.3 Hz, 1H), 4.64 (d, J = 5.8 Hz, 2H), 4.45 (d, J = 6.0 Hz, 2H), 4.01 (t, J = 7.2 Hz, 2H), 1.74 (sept, J = 7.4 Hz, 2H), 0.81 (t, J = 7.6 Hz, 3H) ppm; (M+1) = 578.
70	 Intermediate 91			¹ H NMR (600 MHz, DMSO-d ₆) δ ppm 11.84 (d, J = 2.2 Hz, 1H), 9.19 (t, J = 5.9 Hz, 1H), 9.08 (t, J = 6.2 Hz, 1H), 8.08 – 8.04 (m, 2H), 7.81 – 7.73 (m, 4H), 7.51 – 7.46 (m, 2H), 7.41 – 7.29 (m, 6H), 7.19 (dd, J = 7.4, 1.0 Hz, 1H), 4.62 (d, J = 5.9 Hz, 2H), 4.48 (d, J = 6.2

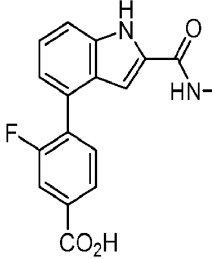
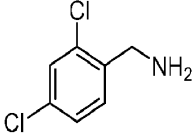
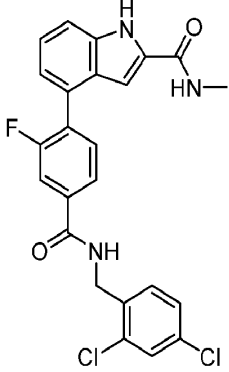
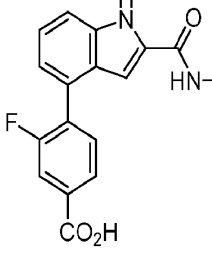
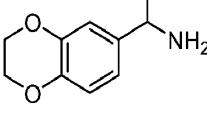
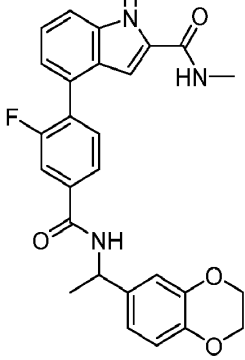
				Hz, 2H) ppm; (M+1) = 580.
71	 Intermediate 91			¹ H NMR (600 MHz, DMSO-d ₆) δ 11.78 (d, J = 2.3 Hz, 1H), 9.25 – 9.19 (m, 1H), 8.62 (t, J = 5.8 Hz, 1H), 8.10 – 8.03 (m, 2H), 7.82 – 7.75 (m, 4H), 7.54 – 7.47 (m, 2H), 7.34 – 7.24 (m, 5H), 7.22 – 7.18 (m, 2H), 4.66 – 4.61 (m, 2H), 3.57 – 3.47 (m, 3H), 2.88 – 2.82 (m, 2H) ppm; (M+1) = 560.
72	 Intermediate 91			¹ H NMR (600 MHz, DMSO-d ₆) δ 11.93 (br s, 1H), 9.34 (br t, J = 6.0 Hz, 1H), 9.25 (br t, J = 5.8 Hz, 1H), 8.79 (br d, J = 5.8 Hz, 2H), 8.12 (br d, J = 8.1 Hz, 2H), 7.86 (br d, J = 8.1 Hz, 2H), 7.83 – 7.77 (m, 4H), 7.57 – 7.48 (m, 3H), 7.37 (t, J = 7.9 Hz, 1H), 7.26 (d, J = 7.4 Hz, 1H), 4.74 (br d, J = 6.1 Hz, 2H), 4.67 (br d, J = 5.8 Hz, 2H) ppm; (M+1) = 547.

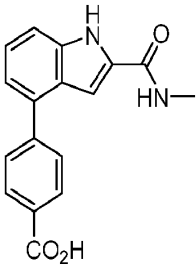
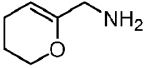
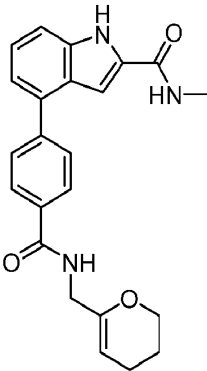
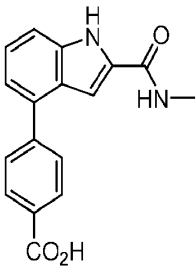
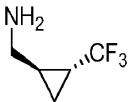
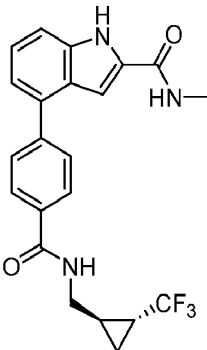
73	 Intermediate 91			¹ H NMR (600 MHz, DMSO-d ₆) δ 11.92 (br s, 1H), 9.24 (br t, J = 5.9 Hz, 1H), 9.25 (br t, J = 5.8 Hz, 1H), 8.10 (br d, J = 8.1 Hz, 2H), 7.88 (br d, J = 8.0 Hz, 2H), 7.83 (br d, J = 6.7 Hz, 1H), 7.80 (br s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.52 (br t, J = 9.4 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.25 (d, J = 7.4 Hz, 1H), 4.66 (br d, J = 5.8 Hz, 2H), 4.36 – 3.82 (m, 4H), 2.60 – 2.39 (m, 2H) ppm; (M+1) = 547.
74	 Intermediate 91			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.78 (s, 1H), 9.50 (t, J = 5.8 Hz, 1H), 9.13 (d, J = 1.9 Hz, 1H), 8.53 (d, J = 1.9 Hz, 1H),

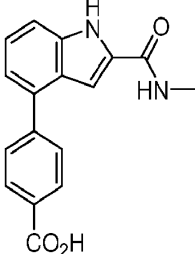
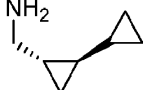
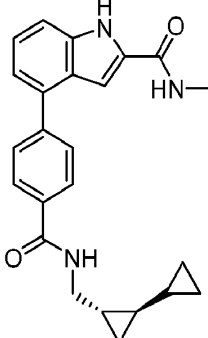
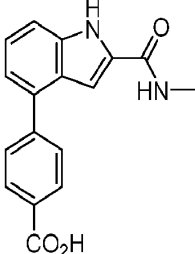
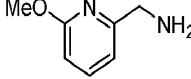
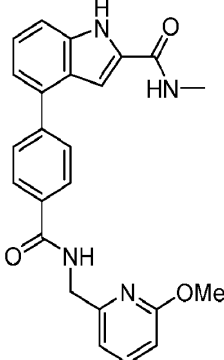
				8.40 (q, J = 4.6 Hz, 1H), 7.81 – 7.59 (m, 5H), 7.55 (dt, J = 8.1, 1.0 Hz, 1H), 7.31 (dd, J = 8.2, 7.2 Hz, 1H), 7.24 (dd, J = 7.2, 1.1 Hz, 1H), 6.92 (dd, J = 2.2, 0.9 Hz, 1H), 4.65 (d, J = 5.8 Hz, 2H), 2.77 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 486.
75	 Intermediate 67			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.80 – 11.75 (m, 1H), 8.47 (q, J = 4.7 Hz, 1H), 8.37 (t, J = 6.4 Hz, 1H), 8.04 – 7.93 (m, 2H), 7.79 – 7.72 (m, 2H), 7.47 (dt, J = 8.2, 1.0 Hz, 1H), 7.33 – 7.24 (m, 2H), 7.17 (dd, J = 7.2, 1.0 Hz, 1H), 3.16 (d, J = 6.4 Hz, 2H), 2.89 (s, 1H), 2.80 (d, J = 4.7 Hz, 3H), 2.75 – 2.67 (m, 2H), 1.54 (dd, J = 13.8, 8.8 Hz, 2H), 1.49 (s, 5H), 1.29 (dd, J = 14.0, 7.5 Hz, 2H).

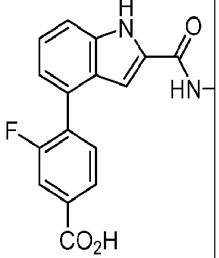
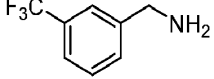
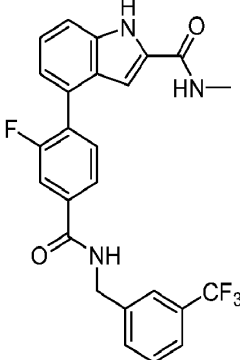
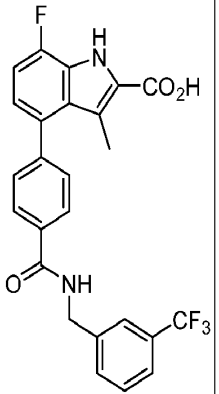
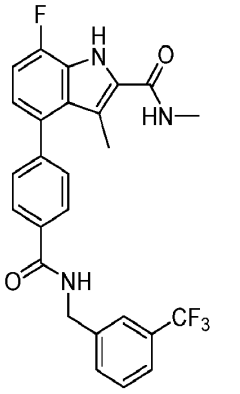
				0.88 (s, 3H) ppm; (M+1) = 418.
76	 Intermediate 83	$\text{NH}_2 \cdot \text{HCl}$		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.97 (s, 1H), 9.29 (t, J = 5.7 Hz, 1H), 8.44 (q, J = 4.7 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.83 – 7.69 (m, 3H), 7.58 – 7.44 (m, 2H), 7.31 (t, J = 7.9 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 7.02 (s, 1H), 4.65 (d, J = 5.7 Hz, 2H), 2.78 (d, J = 4.7 Hz, 3H) ppm; (M+1) = 488.
77	 Intermediate 84	$\text{H}-\text{N}-\text{CH}_3$		¹ H NMR (400 MHz, DMSO-d ₆) δ 9.31 (s, 1H), 9.27 (t, J = 5.9 Hz, 1H), 8.31 (s, 1H), 8.08 – 7.96 (m, 2H), 7.78 – 7.48 (m, 6H), 4.61 (d, J = 5.9 Hz, 2H), 3.02 (s, 3H), 2.91 (s, 3H), 1.74 (s, 3H) ppm; (M+1) = 498.
78	 Intermediate 85			¹ H NMR (600 MHz, DMSO-d ₆) δ 11.78 (s, 1H), 9.15 (t, J = 5.9 Hz, 1H), 8.43 (q, J = 4.5 Hz, 1H), 7.91 – 7.87 (m, 2H), 7.68 (t, J = 8.0 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.12 (d, J = 7.4 Hz, 1H), 7.03 –

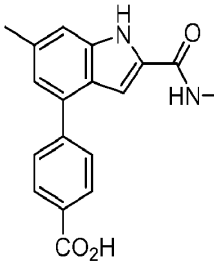
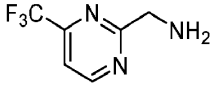
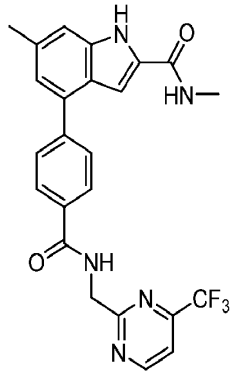
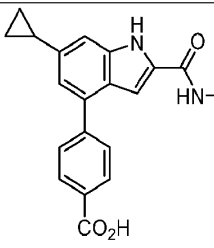
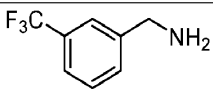
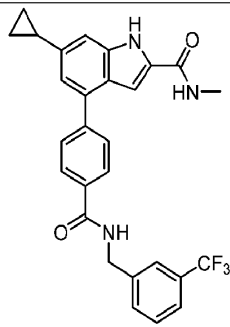
				6.98 (m, 3H), 4.51 (d, $J = 5.8$ Hz, 2H), 2.77 (d, $J = 4.7$ Hz, 3H), 2.31 – 2.28 (m, 3H) ppm; (M+1) = 434.
79	 Intermediate 85			¹ H NMR (600 MHz, DMSO-d ₆) δ ppm 11.78 (s, 1H), 9.15 (t, $J = 6.0$ Hz, 1H), 8.45 (q, $J = 4.7$ Hz, 1H), 7.93 – 7.88 (m, 2H), 7.69 (t, $J = 8.0$ Hz, 1H), 7.53 (d, $J = 8.5$ Hz, 1H), 7.31 (t, $J = 7.9$ Hz, 1H), 7.14 (d, $J = 7.3$ Hz, 1H), 7.03 (s, 1H), 6.91 – 6.80 (m, 3H), 4.42 (d, $J = 6.0$ Hz, 2H), 4.25 – 4.21 (m, 4H), 2.78 (d, $J = 4.7$ Hz, 3H) ppm; (M+1) = 460.
80	 Intermediate 85			¹ H NMR (600 MHz, DMSO-d ₆) δ ppm 11.78 (s, 1H), 9.04 (t, $J = 5.2$ Hz, 1H), 8.46 – 8.41 (m, 1H), 7.89 – 7.88 (m, 1H), 7.87 (dd, $J = 6.4, 1.7$ Hz, 1H), 7.67 (t, $J = 8.0$ Hz, 1H), 7.55 – 7.47 (m, 1H), 7.34 – 7.25 (m, 2H), 7.12 (d, $J = 7.4$ Hz, 1H), 7.03 – 6.98 (m, 2H), 4.57 (d, $J = 5.2$ Hz, 2H), 2.76 (d, J

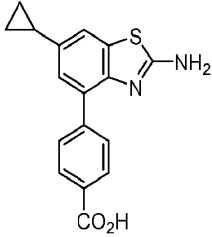
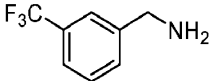
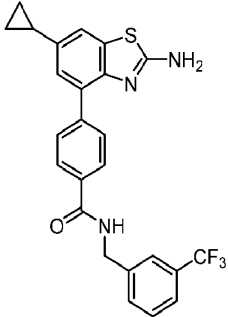
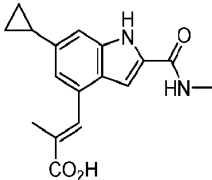
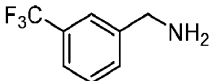
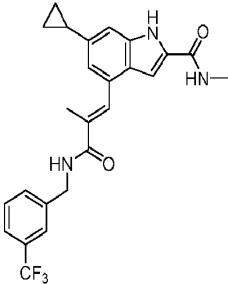
				= 4.7 Hz, 3H), 2.21 (s, 3H) ppm; (M+1) = 452.
81	 Intermediate 85			¹ H NMR (600 MHz, DMSO-d ₆) δ ppm 11.79 (s, 1H), 9.26 (t, J = 5.8 Hz, 1H), 8.46 (q, J = 4.7 Hz, 1H), 7.96 – 7.90 (m, 2H), 7.72 (t, J = 8.0 Hz, 1H), 7.67 (d, J = 2.2 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.31 (dd, J = 8.5, 7.4 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 7.03 (s, 1H), 4.59 (d, J = 5.8 Hz, 2H), 2.79 (d, J = 4.7 Hz, 3H) ppm; (M+1) = 470.
82	 Intermediate 85			¹ H NMR (600 MHz, DMSO-d ₆) δ 11.77 (s, 1H), 8.87 (d, J = 8.3 Hz, 1H), 8.42 (q, J = 4.7 Hz, 1H), 7.91 – 7.87 (m, 2H), 7.67 (t, J = 7.9 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.30 (dd, J = 8.5, 7.4 Hz, 1H), 7.12 (d, J = 7.4 Hz, 1H), 7.01 (s, 1H), 6.91 (d, J = 2.1 Hz, 1H), 6.87 – 6.84 (m, 1H), 6.82 – 6.79 (m, 1H), 5.10 (pent, J = 7.5

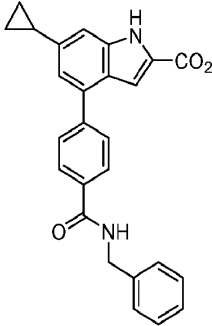
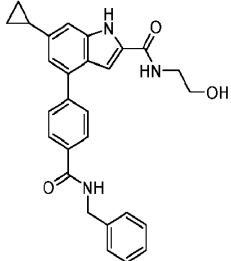
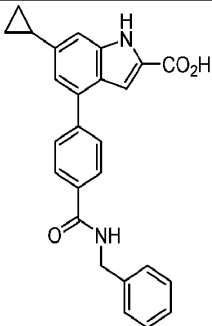
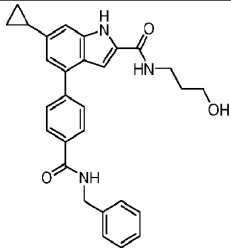
				Hz, 1H), 4.24 – 4.19 (m, 4H), 2.77 (d, J = 4.7 Hz, 3H), 1.45 (d, J = 7.2 Hz, 3H) ppm; (M+1) = 474.
83	 Intermediate 67			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.77 (s, 1H), 8.71 (t, J = 5.9 Hz, 1H), 8.47 (q, J = 4.6 Hz, 1H), 8.07 – 7.98 (m, 2H), 7.80 – 7.71 (m, 2H), 7.47 (dt, J = 8.2, 1.0 Hz, 1H), 7.34 – 7.23 (m, 2H), 7.18 (dd, J = 7.2, 1.0 Hz, 1H), 4.65 (t, J = 3.8 Hz, 1H), 4.01 – 3.90 (m, 2H), 3.87 – 3.79 (m, 2H), 2.80 (d, J = 4.6 Hz, 3H), 1.99 – 1.96 (m, 2H), 1.78 – 1.74 (m, 2H) ppm; (M+1) = 390.
84	 Intermediate 67			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.79 (s, 1H), 8.73 (t, J = 5.9 Hz, 1H), 8.48 (q, J = 4.6 Hz, 1H), 8.05 – 7.96 (m, 2H), 7.83 – 7.73 (m, 2H), 7.52 – 7.44 (m, 1H), 7.34 – 7.24 (m, 2H), 7.18 (dd, J = 7.2, 1.0 Hz, 1H), 3.41 – 3.25 (m, 2H), 2.80 (d, J = 4.6 Hz, 3H), 1.90 – 1.80 (m,

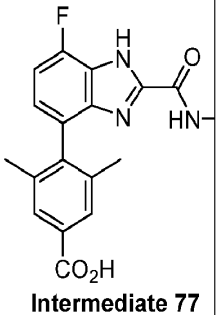
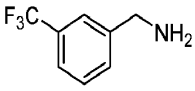
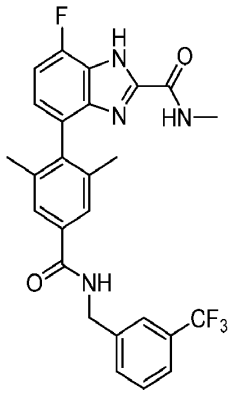
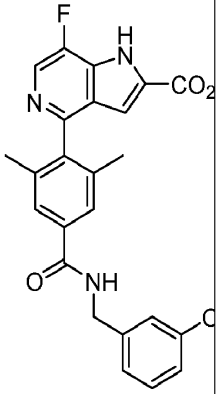
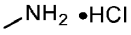
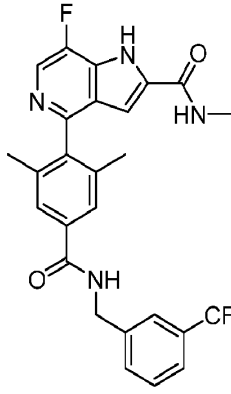
				1H), 1.58 - 1.47 (m, 1H), 1.01 - 0.83 (m, 2H) ppm; (M+1) = 416.
85	 Intermediate 67			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.78 (s, 1H), 8.61 (t, J = 5.8 Hz, 1H), 8.48 (d, J = 4.7 Hz, 1H), 8.05 - 7.92 (m, 2H), 7.82 - 7.69 (m, 2H), 7.49 - 7.44 (m, 1H), 7.35 - 7.24 (m, 2H), 7.18 (dd, J = 7.2, 1.0 Hz, 1H), 3.25 - 3.08 (m, 2H), 2.80 (d, J = 4.7 Hz, 3H), 0.86 - 0.77 (m, 3H), 0.40 - 0.29 (m, 3H), 0.28 - 0.22 (m, 1H), 0.04 - 0.02 (m, 2H) ppm; (M+1) = 388.
86	 Intermediate 67			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.79 (s, 1H), 9.16 (t, J = 6.0 Hz, 1H), 8.49 (q, J = 4.7 Hz, 1H), 8.13 - 8.03 (m, 2H), 7.85 - 7.74 (m, 2H), 7.71 - 7.64 (m, 1H), 7.50 - 7.45 (m, 1H), 7.35 - 7.26 (m, 2H), 7.19 (dd, J = 7.2, 1.0 Hz, 1H), 6.91 (dd, J = 7.3, 0.8 Hz, 1H), 6.75 - 6.64 (m, 1H), 4.54 (d, J =

				6.0 Hz, 2H), 3.86 (s, 3H), 2.80 (d, J = 4.7 Hz, 3H) ppm; (M+1) = 415.
87	 Intermediate 85			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.78 (bs, 1H), 9.32 (t, J = 5.9 Hz, 1H), 8.43 (q, J = 4.6 Hz, 1H), 7.99 - 7.79 (m, 2H), 7.77 - 7.55 (m, 5H), 7.55 - 7.43 (m, 1H), 7.29 (dd, J = 8.3, 7.2 Hz, 1H), 7.13 (dt, J = 7.2, 1.1 Hz, 1H), 7.02 (d, J = 2.5 Hz, 1H), 4.62 (d, J = 5.9 Hz, 2H), 2.78 (d, J = 4.6 Hz, 3H) ppm (M+1) = 470.
88	 Intermediate 75	—NH ₂		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.70 (s, 1H), 9.21 (t, J = 6.0 Hz, 1H), 8.08 (q, J = 4.6 Hz, 1H), 8.01 - 7.90 (m, 2H), 7.75 - 7.55 (m, 4H), 7.52 - 7.42 (m, 2H), 7.12 - 7.06 (m, 1H), 6.86 - 6.80 (m, 1H), 4.60 (d, J = 6.0 Hz, 2H), 2.80 (d, J = 4.6 Hz, 3H), 2.00 (s, 3H) ppm; (M+1) = 484.

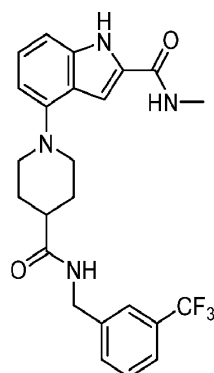
89	 Intermediate 68			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.64 (s, 1H), 9.30 (t, J = 5.8 Hz, 1H), 9.18 (d, J = 5.1 Hz, 1H), 8.42 (q, J = 4.6 Hz, 1H), 8.09 - 8.04 (m, 2H), 7.95 (d, J = 5.1 Hz, 1H), 7.81 - 7.74 (m, 2H), 7.29 - 7.21 (m, 2H), 7.06 - 7.04 (m, 1H), 4.80 (d, J = 5.8 Hz, 2H), 2.79 (d, J = 4.6 Hz, 3H), 2.46 (s, 3H) ppm; (M+1) = 468.
90	 Intermediate 69			¹ H NMR (400 MHz, DMSO-d ₆) δ 11.60 (d, J = 2.1 Hz, 1H), 9.24 (t, J = 5.9 Hz, 1H), 8.41 (q, J = 4.6 Hz, 1H), 8.11 - 8.00 (m, 2H), 7.82 - 7.73 (m, 2H), 7.73 - 7.55 (m, 4H), 7.23 (dd, J = 2.2, 0.9 Hz, 1H), 7.20 - 7.14 (m, 1H), 6.91 (d, J = 1.5 Hz, 1H), 4.62 (d, J = 5.9 Hz, 2H), 2.78 (d, J = 4.6 Hz, 3H), 2.07 (tt, J = 8.4, 5.1 Hz, 1H), 1.04 - 0.91 (m, 2H), 0.79 - 0.67 (m, 2H) ppm; (M+1) = 492.

91	 Intermediate 72			¹ HNMR (400 MHz, DMSO-d ₆) δ 9.17 (t, J = 9.6, 1H), 7.96 – 7.94(m, 2H), 7.87 – 7.85 (m, 2H), 7.68 – 7.57 (m, 6H), 7.42 (d, J, = 1.2 Hz, 1H), 7.11 (d, J = 1.6Hz, 1H), 4.60 (d, J = 4.8 Hz, 2H), 2.03 – 1.97 (m, 1H), 0.95 – 0.92 (m, 2H), 0.72 – 0.71 (m, 2H) ppm; (M+1) = 468.
92	 Intermediate 87			¹ HNMR (400 MHz, DMSO-d ₆) δ 11.52 (s, 1H), 8.76 (t, J = 6.0 Hz, 1H), 8.42 (q, J = 4.6 Hz, 1H), 7.69 – 7.60 (m, 5H), 7.10 – 7.07 (m, 2H), 6.78 (s, 1H), 4.50 (d, J = 6.0 Hz, 2H), 2.78 (d, J = 4.6 Hz, 3H), 2.05 – 2.00 (m, 4H), 0.97 – 0.95 (m, 2H), 0.67 – 0.64 (m, 2H) ppm; (M+1) = 456.

93	 Intermediate 76	HOCH ₂ CH ₂ NH ₂		¹ HNMR (400 MHz, DMSO-d ₆) δ 11.60 (s, 1H), 9.13 (t, J = 9.2 Hz, 1H), 8.44 (t, J = 9.2 Hz, 1H), 8.06 – 8.04 (m, 2H), 7.78 – 7.76 (m, 2H), 7.37 – 7.33 (m, 4H), 7.28 – 7.25 (m, 2H), 7.16 (s, 1H), 6.90 (s, 1H), 4.74 (t, J = 8.8 Hz, 1H), 4.54 (d, J = 4.4 Hz, 2H), 3.52 – 3.49 (m, 2H), 3.34 – 3.31 (m, 2H), 2.09 – 2.06 (m, 1H), 0.99 – 0.97 (m, 2H), 0.76– 0.72 (m, 2H) ppm; (M+1) = 454.
94	 Intermediate 76	HOCH ₂ CH ₂ CH ₂ NH ₂		¹ HNMR (400 MHz, DMSO-d ₆) δ 11.6 (s, 1H), 9.13 (t, J = 4.8 Hz, 1H), 8.43 – 8.41 (m, 1H), 8.06 – 8.04 (m, 2H), 7.77 – 7.75 (m, 2H), 7.37 – 7.33 (m, 4H), 7.25 (s, 2H), 7.16 (s, 1H), 6.90 (s, 1H), 4.54 (d, J = 4.8 Hz, 2H), 4.46 (t, J = 8.4 Hz, 1H), 3.48 – 3.44 (m, 2H), 3.34 – 3.31 (m, 2H), 2.08 – 2.05 (m, 1H), 1.70 – 1.64 (m, 2H), 0.99 – 0.96 (m, 2H), 0.75 –

				0.71 (m, 2H) ppm; (M+1) = 468.
95	 Intermediate 77			¹ H NMR (500 MHz, DMSO-d ₆) δ 9.16 (s, 1H), 7.71 – 7.58 (m, 7H), 7.19 (s, 1H), 7.01 (s, 1H), 4.59 (d, J = 5.9 Hz, 2H), 2.79 (d, J = 4.6 Hz, 3H), 1.94 (s, 6H) ppm; (M+1) = 499.
96	 Intermediate 97			¹ H NMR (500 MHz, DMSO-d ₆) δ 12.93 – 12.76 (m, 1H), 9.18 (s, 1H), 8.53 (s, 1H), 8.33 (s, 1H), 7.73 (s, 2H), 7.70 (s, 1H), 7.67 – 7.59 (m, 3H), 6.82 (s, 1H), 4.60 (d, J = 5.9 Hz, 2H), 2.75 (d, J = 4.5 Hz, 3H), 1.94 (s, 6H) ppm; (M+1) = 499.

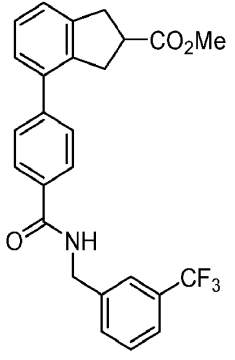
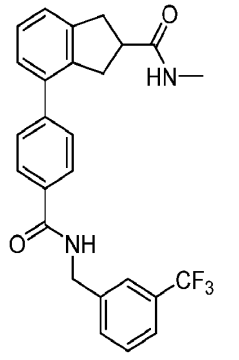
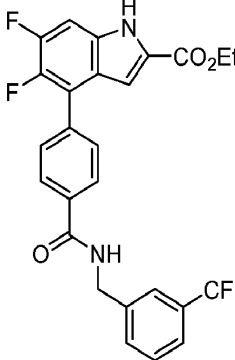
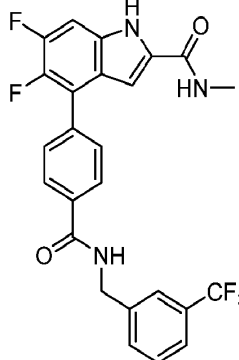
Example 97: Preparation of N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)piperidin-1-yl)-1H-indole-2-carboxamide



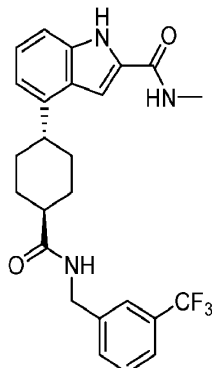
To a 5 mL microwave reaction vial equipped with a magnetic stir bar was added methyl 4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)piperidin-1-yl)-1H-indole-2-carboxylate (89 mg, 194 μ mol, **Intermediate 88**) and 33% methylamine solution in ethanol (4 mL, 32.13 mmol). The vessel was sealed, and the contents were heated to 100 °C in the microwave reactor. After 30 min, LC/MS analysis revealed that the reaction was not complete. The mixture was subjected to another cycle of heating in the microwave reactor (125 °C). After 30 min, LC/MS analysis revealed that the reaction was nearly complete. The brown mixture was concentrated to provide a brown oil. Chromatographic purification (CombiFlash, 12 g SiO₂ gold column, 1-5% methanol/dichloromethane elute, combined fractions 27-31, rack 1) afforded N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)piperidin-1-yl)-1H-indole-2-carboxamide (26 mg, 57 μ mol, 29 % yield) as a tan solid; ¹H NMR (400 MHz, DMSO-d₆) δ 11.45 (s, 1H), 8.51 (t, J = 5.9 Hz, 1H), 8.40 (q, J = 4.6 Hz, 1H), 7.65 – 7.56 (m, 4H), 7.16 (d, J = 2.3 Hz, 1H), 7.08 – 6.99 (m, 2H), 6.46 (dd, J = 5.9, 2.3 Hz, 1H), 4.40 (d, J = 5.9 Hz, 2H), 3.70 – 3.60 (m, 2H), 2.81 (d, J = 4.6 Hz, 3H), 2.76 – 2.64 (m, 2H), 2.48 – 2.37 (m, 1H), 2.00 – 1.85 (m, 4H) ppm; (M+1) = 459.

The following compounds were prepared as described for the synthesis of **Example 97**:

Example	Ester	Amine	Product	¹ HNMR/MS
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98	 Intermediate 89	-NH ₂		¹ H NMR (400 MHz, CDCl ₃) δ 7.84 (d, J = 7.9 Hz, 2H), 7.70 – 7.46 (m, 6H), 7.24 – 7.18 (m, 3H), 6.70 (br s, 1H), 5.61 (br s, 1H), 4.73 (d, J = 5.9 Hz, 2H), 3.40 – 3.32 (m, 2H), 3.20 – 3.04 (m, 3H), 2.82 (d, J = 4.8 Hz, 3H) ppm; (M+1) = 453.
99	 Intermediate 92	-NH ₂		¹ H NMR (400 MHz, DMSO-d ₆) δ 11.92 (s, 1H), 9.27 (t, J = 6.0 Hz, 1H), 8.45 (q, J = 4.6 Hz, 1H), 8.16 – 8.02 (m, 2H), 7.81 – 7.54 (m, 6H), 7.41 – 7.35 (m, 1H), 7.12 – 7.08 (m, 1H), 4.62 (d, J = 6.0 Hz, 2H), 2.77 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 488.

Example 100: Preparation of N-methyl-4-((1r,4r)-4-((3-(trifluoromethyl)benzyl)carbamoyl)cyclohexyl)-1H-indole-2-carboxamide



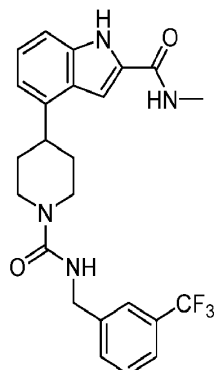
5 A mixture of 4-(2-(methylcarbamoyl)-1H-indol-4-yl)cyclohexane-1-carboxylic acid (78 mg, 260 μ mol, **Intermediate 90**), 3-(trifluoromethyl)benzylamine (46 μ L, 312 μ mol), HATU (153 mg, 390 μ mol), and N,N-diisopropylethylamine (136 μ L, 779 μ mol) in N,N-dimethylformamide (5.0 mL) was stirred at rt for 3 h. LC/MS indicated that all starting material was consumed. The reaction mixture was partitioned between water and

10 Et₂O. The two layers were separated, and the aqueous layer was extracted with Et₂O once. The combined organic layers were washed with water, 1 M HCl, saturated NaHCO₃, and brine, dried over MgSO₄, filtered, and concentrated. The crude material was purified on silica gel (liquid loaded) with CH₂Cl₂/EtOAc (80/20 to 0/100) as eluant to give N-methyl-4-((3-(trifluoromethyl)benzyl)carbamoyl)cyclohexyl)-1H-indole-2-carboxamide (69

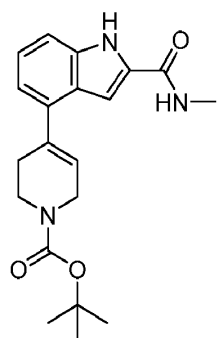
15 mg, 150.82 μ mol, 58.1 % yield) as a white powder (mixture of cis and trans isomers). The mixture was separated by HPLC to give N-methyl-4-((1r,4r)-4-((3-(trifluoromethyl)benzyl)carbamoyl)cyclohexyl)-1H-indole-2-carboxamide (21 mg, 70 μ mol, 28 % yield); ¹H NMR (400 MHz, DMSO-d₆) δ 11.51 (s, 1H), 8.58 – 8.31 (m, 2H), 7.62 – 7.52 (m, 4H), 7.35 – 7.19 (m, 2H), 7.10 (t, J = 7.7 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 4.39 (d, J = 6.0 Hz, 2H), 2.93 – 2.85 (m, 1H), 2.82 (d, J = 4.6 Hz, 3H), 2.40 – 2.32 (m, 1H),

20 2.01 – 1.93 (m, 4H), 1.69 – 1.61 (m, 4H) ppm; (M+1) = 458.

Example 101: Preparation of N-methyl-4-(1-((3-(trifluoromethyl)benzyl)carbamoyl)piperidin-4-yl)-1H-indole-2-carboxamide



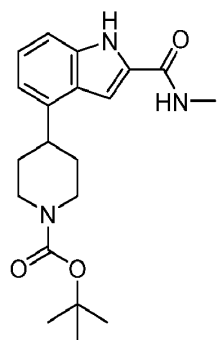
5 *Step 1: Preparation of tert-butyl 4-(2-(methylcarbamoyl)-1H-indol-4-yl)-3,6-dihydropyridine-1(2H)-carboxylate*



10 To a 20 mL microwave reaction vial equipped with a magnetic stir bar was added 4-bromo-1H-indole-2-carboxamide (915 mg, 3.83 mmol), N-boc-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (1.37 g, 4.21 mmol), palladium(II) acetate (43 mg, 191 μ mol), tricyclohexylphosphine (110 mg, 383 μ mol), potassium phosphate tribasic (2.49 g, 11.48 mmol), 1,4-dioxane (10 mL), and water (5 mL). The vessel was
15 sealed, and the contents were heated to 125 °C in the microwave reactor. After 30 min, LC/MS analysis revealed that the reaction was mostly complete. The mixture was diluted with ethyl acetate (50 mL) and water (30 mL). The phases were separated, and the organic

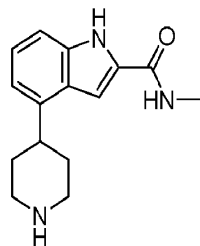
phase was washed with 2N hydrochloric acid solution (25 mL) and saturated potassium carbonate solution (25 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated to provide 1.66 g of a yellow solid. Chromatographic purification (CombiFlash, 40 g SiO₂ gold column, 50-80% ethyl acetate/heptane elute, combined
5 fractions 6-15, rack 1) afforded tert-butyl 4-(2-carbamoyl-1H-indol-4-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.22 g, 3.57 mmol, 93.4 % yield) as a white solid; (M-1) = 354.

Step 2: Preparation of tert-butyl 4-(2-(methylcarbamoyl)-1H-indol-4-yl)piperidine-1-carboxylate
10



To a 200 mL recovery flask equipped with a magnetic stir bar and 3-way stopcock
15 was added tert-butyl 4-(2-(methylcarbamoyl)-1H-indol-4-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.19 g, 3.35 mmol), 10% palladium on carbon (1.12 g, 1.05 mmol), and tetrahydrofuran (40 mL). The mixture was degassed under vacuum/backfilled with N₂ (x 3). After a final evacuation, the atmosphere was replaced with hydrogen (via balloon), and the mixture was allowed to stir at room temperature. After 45 min, LC/MS analysis
20 revealed that the reaction was complete. The atmosphere was replaced with N₂, and the mixture was filtered through Celite with the aid of ethyl acetate (100 mL). The filtrate was concentrated to provide tert-butyl 4-(2-(methylcarbamoyl)-1H-indol-4-yl)piperidine-1-carboxylate (1.13 g, 3.16 mmol, 94 % yield) as an off-white solid; (M-1) = 356.

Step 3: Preparation of *N*-methyl-4-(piperidin-4-yl)-1*H*-indole-2-carboxamide



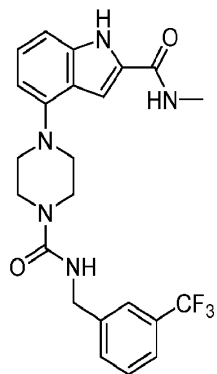
To a 20 mL microwave reaction vial equipped with a magnetic stir bar was added
 5 tert-butyl 4-(2-(methylcarbamoyl)-1*H*-indol-4-yl)piperidine-1-carboxylate (1.13 g, 3.16 mmol) and dichloromethane (20 mL). The suspension was treated with trifluoroacetic acid (10 mL, 130 mmol), resulting in formation of a homogeneous red solution. After 30 min, LC/MS analysis revealed that the reaction was complete. The mixture was concentrated, and the residue was dissolved in water (30 mL). The yellow solution was treated with
 10 concentrated ammonium hydroxide solution (10 mL), resulting in the formation of a precipitate. The mixture was filtered, and the solids were washed with water (25 mL) and dried to provide *N*-methyl-4-(piperidin-4-yl)-1*H*-indole-2-carboxamide (800 mg, 3.11 mmol, 98 % yield) as an off-white solid; (*M*+1) = 258.

15 Step 4: Preparation of *N*-methyl-4-((1*r*,4*r*)-4-((3-(trifluoromethyl)benzyl)carbamoyl)cyclohexyl)-1*H*-indole-2-carboxamide

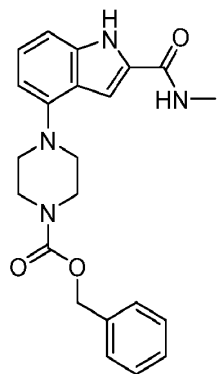
To a 50 mL recovery flask equipped with a magnetic stir bar and N₂ inlet was added
 20 *N*-methyl-4-(piperidin-4-yl)-1*H*-indole-2-carboxamide (150 mg, 582.89 μmol) and acetonitrile (5 mL). The suspension was treated with 1-(isocyanatomethyl)-3-(trifluoromethyl)benzene (130 mg, 612 μmol). The mixture was warmed with a heat gun until a homogeneous solution was obtained (~ 1 min), and the resulting solution was allowed to stir. After 45 min, a white precipitate had formed, and LC/MS analysis revealed that the reaction was complete. The mixture was filtered. The filter cake was washed with
 25 acetonitrile (10 mL) and dried to provide a white solid. Chromatographic purification (CombiFlash, 12 g SiO₂ gold column, 0-20% methanol/dichloromethane elute, combined

fractions 1-5, rack 1) afforded N-methyl-4-(1-((3-(trifluoromethyl)benzyl)carbamoyl)piperidin-4-yl)-1H-indole-2-carboxamide (120 mg, 262 μ mol, 45 % yield) as a white solid; ^1H NMR (400 MHz, DMSO- d_6) δ 11.53 (s, 1H), 8.44 (q, J = 4.6 Hz, 1H), 7.68 – 7.51 (m, 4H), 7.32 – 7.20 (m, 3H), 7.10 (dd, J = 8.2, 7.1 Hz, 1H), 6.84 (d, J = 7.1 Hz, 1H), 4.35 (d, J = 5.7 Hz, 2H), 4.24 – 4.16 (m, 2H), 3.12 – 3.02 (m, 1H), 2.94 – 2.82 (m, 2H), 2.81 (d, J = 4.6 Hz, 3H), 1.92 – 1.82 (m, 2H), 1.73 – 1.59 (m, 2H) ppm; (M+1) = 459.

Example 102: Preparation of N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)piperazin-1-yl)-1H-indole-2-carboxamide

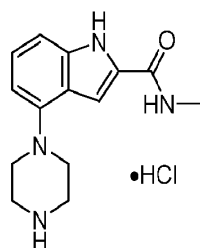


Step 1: Preparation of benzyl 4-(2-(methylcarbamoyl)-1H-indol-4-yl)piperazine-1-carboxylate



A 20 mL microwave reaction vessel equipped with a stir bar was loaded with methyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-1H-indole-2-carboxylate (0.910 g, 2.31 mmol, **Intermediate 3**), ethanol (6 mL) and a 33 weight% solution of methylamine in ethanol (6.0 mL, 48 mmol). The vessel was sealed with a septum and stirred overnight at 50 °C. After this time, LCMS analysis showed that the reaction was incomplete. An additional portion of methylamine solution (2.0 mL, 16 mmol) was added and the reaction was continued at 50 °C for a second night. The mixture was concentrated to yield crude product as a foamy amber solid (0.969 g, 107%) which was used in the next reaction with purification; (M+1) = 393.

Step 2: Preparation of N-methyl-4-(piperazin-1-yl)-1H-indole-2-carboxamide hydrochloride



To a stirred solution of benzyl 4-(2-(methylcarbamoyl)-1H-indol-4-yl)piperazine-1-carboxylate (0.735 g, 1.87 mmol) in a mixture of methanol (15 mL) and 1.0 N hydrochloric acid (2.0 mL, 1.07 eq) was added 10% palladium on carbon (0.150 g). The suspension was cycled between vacuum and a nitrogen atmosphere three times. The vessel was evacuated a final time and then backfilled with hydrogen. After stirring for one hour, the reaction was evacuated and then opened to air. LCMS analysis showed that the reaction was nearly complete. Additional portions of 1.0 N hydrochloric acid (2.0 mL, 1.07 eq) and catalyst (0.050 g) were added and the reaction was restarted as before. After 45 minutes under hydrogen, the reaction was opened to air and the suspension was suction filtered through a short column of Celite. The reaction flask and filtering agent were rinsed with methanol and the combined filtrate was concentrated to afford N-methyl-4-(piperazin-1-

yl)-1H-indole-2-carboxamide hydrochloride as a pale amber solid (0.531 g, 96% yield); (M+1) = 259.

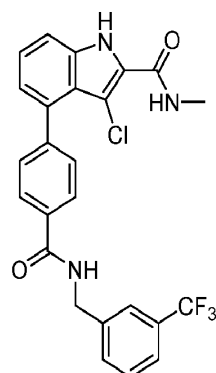
Step 3: Preparation of N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)piperazin-1-yl)-1H-indole-2-carboxamide

5

To a stirred and cooled (0 °C) solution of 1,1'-carbonyldiimidazole (0.076 g, 0.469 mmol) in dichloromethane (8 mL) was added a solution of 3-(trifluoromethyl)benzylamine (0.082 g, 0.47 mmol) in dichloromethane (2 mL). After 15 mins at 0 °C, N-methyl-4-(piperazin-1-yl)-1H-indole-2-carboxamide hydrochloride (0.115 g, 0.39 mmol) was added, followed by N,N-diisopropylethylamine (82 µl, 0.468 mmol) and N-hydroxysuccinimide (0.054 g, 0.47 mmol). The reaction vessel was sealed and heated at 60 °C for one hour in a microwave reactor. After cooling to room temperature, the mixture was partitioned between chloroform (20 mL) and dilute aqueous sodium carbonate solution (30 mL). The organic layer was combined with an additional extract (chloroform, 1 x 20 mL), dried over sodium sulfate and concentrated onto ~4 g of silica. The impregnated media was subjected to automated flash chromatography (Combiflash Rf instrument; 10 to 45% 3:1 ethyl acetate/ethanol solution in heptane; 80 g Gold silica column) to afford partially purified product as a foamy, tan solid. This material was further purified by automated, reverse phase flash chromatography (InterChim PuriFlash XS420 system; 30 to 100% acetonitrile in water with 0.1% formic acid; 55 g InterChim C18 column; sample loaded as a solution in DMSO) to provide N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)piperazin-1-yl)-1H-indole-2-carboxamide as a white solid (0.081 g, 45%); ¹H NMR (400 MHz, CD₃OD) δ 7.66 – 7.46 (m, 4H), 7.21 – 7.09 (m, 3H), 6.61 (dd, J = 6.2, 2.2 Hz, 1H), 4.46 (s, 2H), 3.76 – 3.63 (m, 4H), 3.28 – 3.19 (m, 4H), 2.93 (s, 3H) ppm; (M+1) = 460.

25

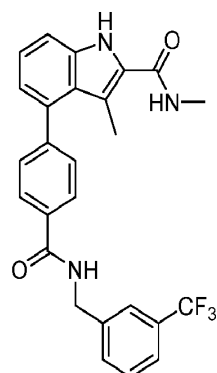
Example 103: Preparation of 3-chloro-N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxamide



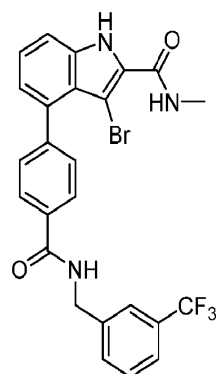
5 To a 20 ml vial was added a stir bar, N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxamide (54 mg, 120 μ mol, **Example 1**), N-chlorosuccinimide (16 mg, 120 μ mol) and N,N-dimethylformamide (2 mL). The mixture was sonicated briefly, and then allowed to stir at room temperature. After 20 min, the mixture was heated to 55 $^{\circ}$ C. The reaction was held at this temperature for 3 h, and then it was heated to 140 $^{\circ}$ C. After 20 min at this temperature, the mixture was allowed to cool to room temperature and was diluted with water (30 mL). The mixture was extracted with dichloromethane (3 x 20 mL), and the combined organic phases were dried over sodium sulfate, filtered, and concentrated to provide a brown oil. The crude material was purified via silica gel chromatography (0-40% 3:1 ethyl acetate:ethanol/heptane elute) to provide 3-chloro-N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxamide (0.032 g, 64 μ mol, 53% yield) as a white solid; 1 H NMR (400 MHz, DMSO- d_6) δ 12.16 (s, 1H), 9.24 (t, J = 5.9 Hz, 1H), 8.01 – 7.93 (m, 2H), 7.91 (q, J = 4.6 Hz, 1H), 7.74 - 7.51 (m, 7H), 7.34 (dd, J = 8.3, 7.2 Hz, 1H), 7.01 (dd, J = 7.2, 1.0 Hz, 1H), 4.61 (d, J = 5.9 Hz, 2H), 2.86 (d, J = 4.6 Hz, 3H) ppm; (M+1) = 486.

20

Example 104: Preparation of N,3-dimethyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxamide



Step 1: Preparation of 3-bromo-N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxamide



5

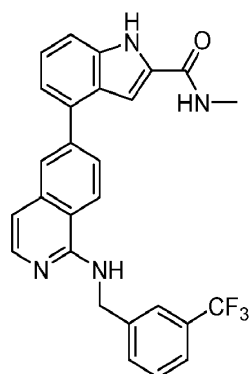
To a 20 mL vial was added a stir bar, N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxamide (210 mg, 465 μ mol, **Example 1**), N-bromosuccinimide (96 mg, 535 μ mol) and N,N-dimethylformamide (2 mL). The mixture was sonicated briefly, and then allowed to stir at room temperature overnight. The brown mixture was diluted with water (20 mL) and sonicated, resulting in the formation of a precipitate. The mixture was filtered, and the filter cake was washed with water (20 mL) and dried to provide 3-bromo-N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1H-indole-2-carboxamide (240 mg, 452 μ mol, 96 % yield) as a white solid; (M+1) = 530.

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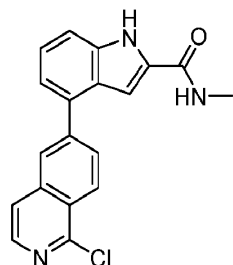
Step 2: Preparation of *N*,3-dimethyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1*H*-indole-2-carboxamide

To a 5 mL microwave reaction vial equipped with a magnetic stir bar was added
5 3-bromo-*N*-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1*H*-indole-2-
carboxamide (240 mg, 452 μ mol), potassium phosphate tribasic (288 mg, 1.36 mmol),
XPhos Pd G4 (22 mg, 26 μ mol) and a 4:1 mixture of 1,4-Dioxane/water (2.5mL). The
mixture was degassed under vacuum/backfilled with N₂ (X 2), and then trimethylboroxine
(160.10 μ l, 1.13 mmol) was added. The resulting dark mixture was heated to 140 °C,
10 After 25 min, the organic layer of the reaction mixture was loaded to Celite directly and
the aqueous phase of the reaction mixture was extracted with dichloromethane (5 mL).
This solution was also loaded to Celite. The celite pad was dried, and the crude material
was purified via silica gel chromatography (0-40% 3:1 ethyl acetate:ethanol/heptane elute)
to provide *N*,3-dimethyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)phenyl)-1*H*-indole-
15 2-carboxamide (15 mg, 25 μ mol, 6% yield) as an off-white solid; ¹H NMR (400 MHz,
Methanol-d₄) δ 7.97 – 7.90 (m, 2H), 7.71 – 7.69 (m, 1H), 7.68 – 7.64 (m, 1H), 7.61 – 7.54
(m, 2H), 7.53 – 7.48 (m, 2H), 7.42 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.25 (dd, *J* = 8.3, 7.1 Hz, 1H),
6.89 (dd, *J* = 7.1, 1.0 Hz, 1H), 4.68 (s, 2H), 2.93 (s, 3H), 2.04 (s, 3H) ppm; (M+1) = 466.

20 **Example 105: Preparation of *N*-methyl-4-(1-((3-(trifluoromethyl)benzyl)amino)isoquinolin-6-yl)-1*H*-indole-2-carboxamide**



Step 1: Preparation of 4-(1-chloroisoquinolin-6-yl)-N-methyl-1H-indole-2-carboxamide



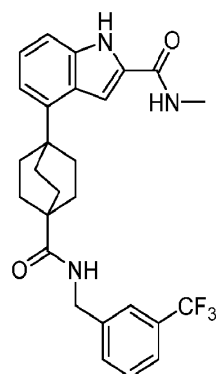
5 A 20 mL microwave reaction vial charged with 6-bromo-1-chloroisoquinoline (50 mg, 206 μ mol, **CAS 205055-63-6**), N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-2-carboxamide (68 mg, 227 μ mol, **Intermediate 40**), potassium carbonate (86 mg, 618 μ mol), 1,4-dioxane (3 mL) and water (0.5 mL) was degassed with nitrogen. To the reaction mixture was added 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (12 mg, 14 μ mol). The reaction was heated at 100 °C. LCMS showed desired product as the major component. The reaction was allowed to cool to room temperature and diluted with EtOAc and 1M HCl. The biphasic mixture was filtered, and the filtrate separated. The organic layer was washed with 1M HCl. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was taken up in MeOH the resulting precipitate was isolated via vacuum filtration. The solid was air dried to provide 4-(1-chloroisoquinolin-6-yl)-N-methyl-1H-indole-2-carboxamide (20 mg, 60 μ mol, 29 % yield); (M+1) = 336.

Step 2: Preparation of N-methyl-4-(1-((3-(trifluoromethyl)benzyl)amino)isoquinolin-6-yl)-1H-indole-2-carboxamide

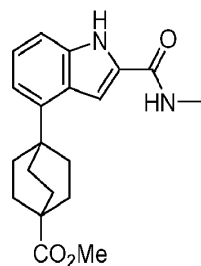
A 5 mL microwave reaction vial charged with 4-(1-chloroisoquinolin-6-yl)-N-methyl-1H-indole-2-carboxamide (20 mg, 60 μ mol), (3-(trifluoromethyl)phenyl)methanamine (13 μ l, 89 μ mol), cesium carbonate (39 mg, 119 μ mol) and N,N-dimethylformamide (1 mL) was degassed with nitrogen. To the reaction

was added Xantphos Pd G3 (3 mg, 3.0 μ mol). The reaction was stirred at 100°C overnight. The reaction was diluted with EtOAc and 1M HCl. The phases were separated, and the organic layer washed with 1M HCl and brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was taken up in 2 mL of methanol and injected onto a C18 RP HPLC. Elution from 15% to 80% acetonitrile:water (0.1% formic acid conditioner) afforded N-methyl-4-(1-((3-(trifluoromethyl)benzyl)amino)isoquinolin-6-yl)-1H-indole-2-carboxamide as an off-white solid (8 mg, 16 μ mol, 27 % yield); ^1H NMR (400 MHz, methanol- d_4) δ 8.32 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 1.8 Hz, 1H), 7.88 (dd, J = 8.6, 1.8 Hz, 1H), 7.79 (d, J = 6.0 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.57 – 7.48 (m, 3H), 7.36 (dd, J = 8.2, 7.2 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.07 (dd, J = 6.1, 0.8 Hz, 1H), 4.90 (s, 2H), 2.91 (s, 3H) ppm; (M+1) = 475.

Example 106: Preparation of N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)bicyclo[2.2.2]octan-1-yl)-1H-indole-2-carboxamide

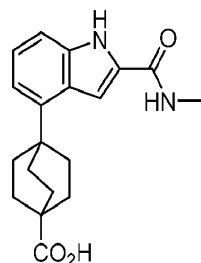


Step 1: Preparation of methyl 4-(2-(methylcarbamoyl)-1H-indol-4-yl)bicyclo[2.2.2]octane-1-carboxylate



To a reaction vial #1 was added 4-bromo-N-methyl-1H-indole-2-carboxamide (500 mg, 1.98 mmol, **Intermediate 12**), methyl 4-bromobicyclo[2.2.2]octane-1-carboxylate (725 mg, 2.79 mmol, CAS 23062-51-3), $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbpy})\text{PF}_6$ (25 mg, 0.022 mmol, CAS 870987-63-6), 2,6-lutidine (0.43 mL, 3.7 mmol), tris(trimethylsilyl)silane (0.66 mL, 2.1 mmol), and DME (10 mL). To another reaction vial #2 was added 4,4'-di-tert-butyl-2,2'-dipyridyl (52 mg, 0.19 mmol), nickel(II) chloride ethylene glycol dimethyl ether complex (45 mg, 0.20 mmol), and DME (5 mL). The resulting mixture in the vial #2 was stirred at room temperature for 15 min to get a light green solution. Then, this solution was added to vial #1. The resulting mixture in vial #1 was bubbled with nitrogen for 15 min. The reaction mixture was sealed and irradiated in a Photo reactor (EvoluChem PhotoRedOx Box device from HepatoChem, Blue light source - Kessil 35W) for 45 hours. The reaction mixture was diluted with water and EtOAc. The resulting mixture was vigorously stirred for 10 min. The organic layer was separated, dried over MgSO_4 , filtered, and concentrated under reduced pressure to give the crude material again that was purified by reverse phase preparative HPLC (30% MeCN in water to 65% MeCN in water, gradient, Teledyne Isco ACCQPrep HP125 with a Sunfire C18 30 x 150 dimensions column, 5 μm). The fractions containing the desired product were combined and concentrated under reduced pressure until MeCN was evaporated. To the residual aqueous layer were added EtOAc and solid sodium carbonate until the aqueous became basic. The resulting mixture was stirred for 10 min. The organic layer was separated, washed with saturated aqueous NaHCO_3 (2x), dried over MgSO_4 , filtered, and concentrated under reduced pressure to afford methyl 4-[2-(methylcarbamoyl)-1H-indol-4-yl]bicyclo[2.2.2]octane-1-carboxylate (66 mg, 0.18 mmol, 9 % yield) as a yellow solid; $(\text{M}+1) = 341$.

Step 2: Preparation of 4-(2-(methylcarbamoyl)-1H-indol-4-yl)bicyclo[2.2.2]octane-1-carboxylic acid



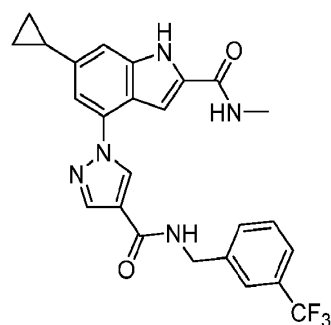
5 To a suspension of methyl 4-[2-(methylcarbamoyl)-1H-indol-4-yl]bicyclo[2.2.2]octane-1-carboxylate (109 mg, 0.32 mmol) in THF-MeOH (1 mL/3 mL) at room temperature was added dropwise 2 M aqueous solution of lithium hydroxide (0.32 mL, 0.64 mmol). The reaction mixture was stirred at room temperature for an hour. Then, the reaction mixture was heated at 45 °C for 23 hours. A significant amount of the starting material still remained. The reaction mixture was heated at 55 °C for additional 28 hours. The reaction mixture was cooled to room temperature and acidified to pH 2 to 3 with 2 M aqueous solution of hydrochloric acid (0.32 mL, 0.64 mmol). The resulting mixture was diluted with water and then extracted with EtOAc (2x). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to afford 4-[2-(methylcarbamoyl)-1H-indol-4-yl]bicyclo[2.2.2]octane-1-carboxylic acid (104 mg, 0.32 mmol, 99 % Yield) as a yellow solid; (M+1) = 327.

Step 3: Preparation of N-methyl-4-(4-((3-(trifluoromethyl)benzyl)carbamoyl)bicyclo[2.2.2]octan-1-yl)-1H-indole-2-carboxamide

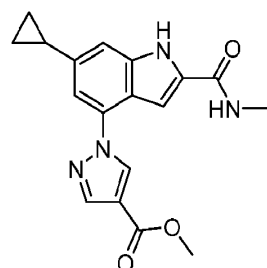
20 To a mixture solution of 4-[2-(methylcarbamoyl)-1H-indol-4-yl]bicyclo[2.2.2]octane-1-carboxylic acid (40 mg, 0.12 mmol) and HOBt (25 mg, 0.18 mmol) in DMF (3 mL) at room temperature was added EDCI (36 mg, 0.19 mmol). The resulting mixture was stirred at room temperature for an hour. Then, 3-(trifluoromethyl)benzylamine (0.020 mL, 0.14 mmol) and TEA (0.050 mL, 0.36 mmol)

were added consecutively. The resulting mixture was stirred at room temperature for 22 hours. The acid starting material still remained. To this mixture was added N,N-diisopropylethylamine (0.050 mL, 0.29 mmol) followed by HATU (61 mg, 0.16 mmol). The resulting mixture was stirred at room temperature for additional one hour. The reaction mixture was concentrated under reduced pressure to give the crude material that was diluted with EtOAc. The organic layer was washed with saturated aqueous NaHCO₃ (2x), dried over MgSO₄, filtered, and concentrated under reduced pressure to give the crude material that was purified by reverse phase preparative HPLC (35% MeCN in water to 70% MeCN in water, gradient, Teledyne Iseo ACCQPrep HP125 with a Sunfire C18 30 x 150 dimensions column, 5 μ m). The fractions containing the desired product were combined and concentrated under reduced pressure until MeCN was evaporated. To the residual aqueous layer were added EtOAc and solid sodium carbonate until the aqueous became basic. The resulting mixture was stirred for 10 min. The organic layer was separated, washed with saturated aqueous NaHCO₃ (2x), dried over MgSO₄, filtered, and concentrated under reduced pressure to afford N-methyl-4-[4-[[3-(trifluoromethyl)phenyl][methylcarbamoyl]-1-bicyclo[2.2.2]octanyl]-1H-indole-2-carboxamide (50 mg, 0.10 mmol, 84% Yield) as a yellow solid; ¹HNMR (400 MHz, DMSO-d₆) δ 11.53 (s, 1H), 8.47 – 8.36 (m, 1H), 8.18 (t, J = 6.0 Hz, 1H), 7.64 – 7.50 (m, 4H), 7.44 (dd, J = 2.2, 0.9 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 7.06 (dd, J = 8.2, 7.3 Hz, 1H), 6.82 (dd, J = 7.3, 1.0 Hz, 1H), 4.37 (d, J = 6.0 Hz, 2H), 2.83 (d, J = 4.6 Hz, 3H), 2.07 – 1.97 (m, 6H), 1.95 – 1.85 (m, 6H) ppm; (M+1) = 484.

Example 107: Preparation of 4-(4-(benzylcarbamoyl)-1H-pyrazol-1-yl)-6-cyclopropyl-N-methyl-1H-indole-2-carboxamide



Step 1: Preparation of methyl 1-(6-cyclopropyl-2-(methylcarbamoyl)-1H-indol-4-yl)-1H-pyrazole-4-carboxylate

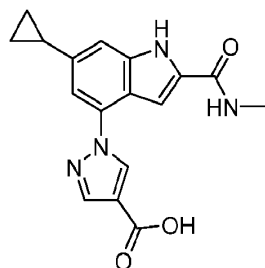


5

A mixture of 4-bromo-6-cyclopropyl-N-methyl-1H-indole-2-carboxamide (0.100 g, 0.341 mmol), methyl 1H-pyrazole-4-carboxylate (0.065 g, 0.512 mmol), 1,2-dimethylethylenediamine (0.006 g, 0.068 mmol), potassium carbonate (0.099 g, 0.716 mmol) and copper(I) iodide (0.003 g, 0.017 mmol) in 1,4-dioxane (1 mL) was stirred at 110 °C in a sealed tube under N₂ for 48 h. The mixture was concentrated and purified by flash silica gel column (DCM/MeOH 50:1 to 20:1) to afford methyl 1-[6-cyclopropyl-2-(methylcarbamoyl)-1H-indol-4-yl]pyrazole-4-carboxylate as a brown oil (0.07 g, 0.160 mmol, 47% yield); (M+1) = 339.

15

Step 2: Preparation of 1-(6-cyclopropyl-2-(methylcarbamoyl)-1H-indol-4-yl)-1H-pyrazole-4-carboxylic acid



A mixture of methyl 1-[6-cyclopropyl-2-(methylcarbamoyl)-1H-indol-4-yl]pyrazole-4-carboxylate (0.070 g, 0.160 mmol, **Intermediate 28**) and lithium hydroxide monohydrate (0.087 g, 2.07 mmol) in tetrahydrofuran (3 mL) and water (3 mL) was stirred at room temperature. After 16 h, the mixture was concentrated to provide a yellow oil; (M+1) = 325.

Step 3: Preparation 4-[4-(benzylcarbamoyl)-1H-pyrazol-1-yl]-6-cyclopropyl-N-methyl-1H-indole-2-carboxamide

A mixture of 1-[6-cyclopropyl-2-(methylcarbamoyl)-1H-indol-4-yl]pyrazole-4-carboxylic acid (0.067 g, 0.207 mmol), benzylamine (0.044 g, 0.417 mmol), HATU, (0.118 g, 0.310 mmol) and N,N-diisopropylethylamine (0.067 g, 0.517 mmol) in tetrahydrofuran (2 mL) was stirred at room temperature. After 16 h, the mixture was purified by flash silica gel column (DCM/MeOH 20:1) to afford a crude oil. The oil was purified by flash C18 gel column (MeOH in H₂O.NH₄HCO₃ 0% to 80%) to afford 4-[4-(benzylcarbamoyl)pyrazol-1-yl]-6-cyclopropyl-N-methyl-1H-indole-2-carboxamide as a white solid (0.025 g, 0.060 mmol, 29% yield); ¹HNMR (400 MHz, DMSO-d₆) δ 11.76 (s, 1H), 8.88 (s, 1H), 8.80 (t, J = 6.0 Hz, 1H), 8.56 (q, J = 4.4 Hz, 1H), 8.24 (s, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.40–7.35 (m, 4H), 7.28–7.25 (m, 1H), 7.19 (s, 1H), 7.07 (d, J = 1.2 Hz, 1H), 4.49 (d, J = 6.0 Hz, 2H), 2.79 (d, J = 4.4 Hz, 3H), 2.09–2.06 (m, 1H), 1.01–0.97 (m, 2H), 0.77–0.74 (m, 2H) ppm; (M+1) = 414.

Determination of *in vitro* activity versus human and mouse SLC6A19

Cell Culture: All cell culture materials were purchased from ThermoFisher Scientific (Waltham, MA, USA) unless otherwise specified. MDCK cells (NBL-2; ATCC, Manassas, VA, USA) stably expressing human SLC6A19 + TMEM27 were generated in-house and cultured in DMEM with 10% fetal bovine serum supplemented with 5 µg/mL Blastidicin and Puromycin. Similar stable cell lines were created in the MDCK background that expressed the mouse versions of the transporter, mSLC6a19 and its cofactor, mTMEM27. All experiments described here were conducted using cells that had undergone less than 5 passages.

Test Compound Collection: The test compounds were obtained as 10 mM DMSO stock solutions in source plates. Appropriate amounts of the stock solutions were plated onto the 384-well assay plates for testing in the Uptake assays using the ECHO 555 Liquid Handler (Labcyte Inc, San Jose, California, USA). Assay buffer was added to dissolve the compounds and achieve a final test concentration of 10 µM for each compound and a DMSO concentration of 0.1% v/v.

Stable Isotope Uptake Assay: MDCK cells stably expressing hSLC6A19 + hTMEM27 were plated in a poly-d-lysine coated, black clear bottom, 384 well microplate (Corning Life Sciences, Corning, NY, USA) at a density of 2,200 cells/well in culture medium and allowed to incubate for 48 hours in a humidified 37°C, 95%/5% air/CO₂ incubator. Following the incubation period, the culture medium was aspirated and cells washed twice with HBSS. Cells were incubated at 37 °C for 20 minutes with 20 µM (2X) of test compounds in assay buffer (137 mM NaCl, 5 mM KCl, 1 mM CaCl₂, 1 mM MgCl₂, 10 mM HEPES, 10 mM Glucose, pH 7.2) following which 2 mM ¹³C₆, ¹⁵N-L-Isoleucine (Sigma Aldrich, St. Louis, MO, USA) in assay buffer was added and incubated for 20 minutes more. One column (16 wells) of each plate was dedicated for positive control for inhibition (preincubated with a saturating concentration of an internally identified specific SLC6a19 reference inhibitor before adding 2 mM substrate ¹³C₆, ¹⁵N-L-Isoleucine; 0%

transporter activity or 100% Inhibition) and 2 columns (32 wells) dedicated for negative controls ($^{13}\text{C}6$, ^{15}N -L-Isoleucine at 2 mM for uptake assay without reference inhibitor)(100% transporter activity or 0% Inhibition). One column (16 wells) was dedicated to carry a reference inhibitor in a dose response fashion (8 concentrations in duplicate). The solution was then aspirated and cells washed six times in cold assay buffer and most liquid aspirated. Plates were air dried and subjected to a freeze thaw cycle to lyse cells. 30 μL /well of extraction buffer (10% methanol, 1% formic acid, 250 nM L-Leucine-1- ^{13}C and Cell Dissociation Buffer) was added and plates shaken for 5 minutes and incubated at 37 $^{\circ}\text{C}$ for 15-20 minutes following which an additional 60 μL of extraction buffer was added per well. 80 μL of cell extract was clarified by centrifuging through an AcroPrep 384-well, 30K cutoff filtration plate (Pall Corporation, Port Washington, NY, USA). The clarified cell extracts were analyzed using a ThermoFisher LX-4 chromatograph coupled to an ABSciex API-4000 triple quad mass spectrometer (Sciex, Framingham, MA, USA). Waters Acquity UPLC BEH 2.1 x 30 mm C18 chromatography columns (Waters Corporation, Milford, MA, USA) were used and mobile phases A and B were water with 0.1% formic acid and acetonitrile with 0.1% formic acid, respectively. The columns were held at room temperature and the sample injection size was 5 μL . The chromatography was run at a flow rate of 0.5 mL/min with the initial condition being 95% mobile phase A. The 95% mobile phase A condition was held for 12 seconds after injection followed by a 6 second gradient to 50% mobile phase A, and held for 10 seconds before returning to the initial conditions. The ABSciex API-4000 mass spectrometer was operated in positive mode monitoring the $133 \rightarrow 86$ m/z transition for L-Leucine-1- ^{13}C and $139 \rightarrow 92$ m/z for $^{13}\text{C}6$, ^{15}N -L-Isoleucine using a collision energy of 16 eV. The peak areas of $^{13}\text{C}6$, ^{15}N -L-Isoleucine were normalized to L-Leucine-1- ^{13}C which served as an internal standard. The Z' of each plate was determined by using the average and standard deviation obtained from the negative and positive control wells using the standard formula: $Z' = 1 - [3(\text{SDNeg} + \text{SDPos})/(\text{MeanPos} - \text{MeanNeg})]$. Only plates with a $Z' > 0.4$ were accepted. The dose response curve and IC_{50} of the reference compound obtained from each plate was tracked and evaluated for reproducibility of assay performance across plates. Compounds were evaluated for activity against the mouse transporter using the same protocol described

above but substituting the mSLC6a19+mTMEM27 expressing MDCK cell lines and a final concentration of $^{13}\text{C}_6$, ^{15}N -L-Isoleucine of 4 mM.

- 5 **Data Analysis Software:** Dose response data was plotted using a four parameter, variable slope equation without constraints on the curve top and bottom provided in the curve fitting program Prism (GraphPad Software, La Jolla, CA). The equation was of the form: $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogIC}_{50} - X) * \text{HillSlope}))}$. Screening data was visualized using SpotFire (Tibco Software, Inc., Palo Alto, CA, USA).

Example	hSLC6A19 IC ₅₀ (μM)	mSLC6A19 IC ₅₀ (μM)
1	0.007	0.005
2	0.065	0.024
3	0.050	0.023
4	0.088	0.011
5	0.110	0.046
6	0.132	0.108
7	1.54	0.340
8	0.686	0.451
9	0.021	0.023
10	0.163	0.124
11	0.005	0.003
12	0.004	0.002
13	0.136	0.163
14	0.527	0.477
15	0.011	0.009
16	0.085	0.024
17	0.893	0.424
18	0.291	0.216

19	3.25	3.82
20	0.042	0.020
21	0.089	0.082
22	0.070	0.100
23	0.009	0.011
24	0.358	1.02
25	0.005	0.003
26	0.005	0.002
27	1.15	1.29
28	0.140	0.100
29	0.159	0.234
30	0.591	0.233
31	0.008	0.004
32	0.365	0.407
33	0.445	0.451
34	0.022	0.017
35	0.308	0.440
36	5.85	4.04
37	0.504	0.106
38	1.04	0.323
39	0.670	0.445
40	1.10	0.423
41	4.85	2.14
42	0.012	0.017
43	0.615	0.134
44	0.144	0.094
45	0.115	0.138
46	0.080	0.157
47	0.109	0.030

48	0.313	0.153
49	0.169	0.121
50	0.025	0.017
51	0.857	1.14
52	0.897	0.723
53	0.983	1.45
54	2.09	0.479
55	0.017	0.009
56	0.009	0.006
57	0.351	0.202
58	0.117	0.099
59	0.153	0.156
60	0.458	0.415
61	1.09	0.690
62	0.129	0.048
63	0.022	0.037
64	0.009	0.008
65	0.026	0.022
66	0.047	0.032
67	0.131	0.060
68	0.140	0.081
69	0.159	0.085
70	0.730	0.580
71	1.19	0.541
72	1.25	0.932
73	1.36	0.606
74	0.003	0.003
75	2.11	0.453
76	0.004	0.002

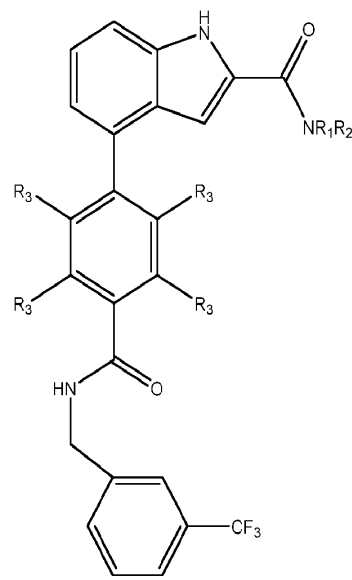
77	0.136	0.066
78	0.025	0.033
79	0.084	0.059
80	0.201	0.206
81	0.936	0.776
82	2.82	1.57
83	0.514	0.548
84	0.402	0.450
85	0.539	0.532
86	2.93	3.01
87	0.008	0.004
88	0.009	0.014
89	0.219	0.285
90	0.007	0.006
91	0.131	0.061
92	1.02	0.581
93	0.215	0.192
94	1.94	1.47
95	0.143	0.207
96	0.073	0.180
97	0.197	1.22
98	0.216	0.052
99	0.022	0.021
100	0.023	0.038
101	0.629	0.588
102	0.509	0.800
103	0.004	0.003
104	0.008	0.009
105	1.27	2.84

106	0.024	0.060
107	2.30	3.65

Other embodiments are within the scope of the following claims.

NUMBERED EMBODIMENTS

1. A compound of the formula:



wherein R_1 and R_2 are independently selected from H or CH_3 ;

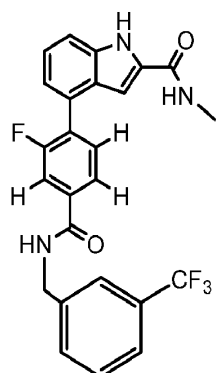
wherein each R_3 is independently selected from H, OH, CH_3 , O- CH_3 , CHF_2 , F, or Cl, wherein at least two R_3 are H;

or a pharmaceutically acceptable salt thereof.

2. The compound of embodiment 1 wherein R_1 is CH_3 and R_2 is H, or pharmaceutically acceptable salt thereof.

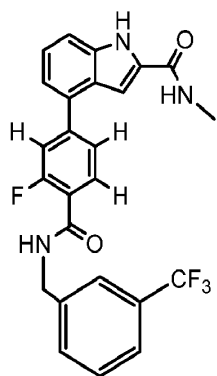
3. The compound of any of embodiments 1-2, wherein at least one R_3 is F, or pharmaceutically acceptable salt thereof.

4. The compound of any of the preceding embodiments, wherein the compound has the formula:



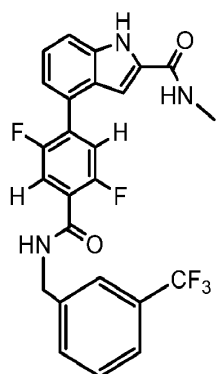
or a pharmaceutically acceptable salt thereof.

5. The compound of embodiment 3, wherein the compound has the formula:



5 or a pharmaceutically acceptable salt thereof.

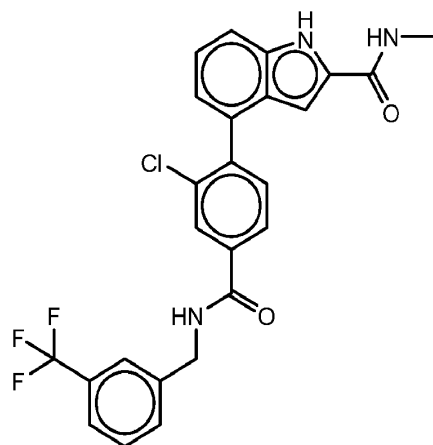
6. The compound of embodiment 3, wherein the compound has the formula:



or a pharmaceutically acceptable salt thereof.

7. The compound of embodiment 2, wherein at least one R₃ is Cl, or a
10 pharmaceutically acceptable salt thereof.

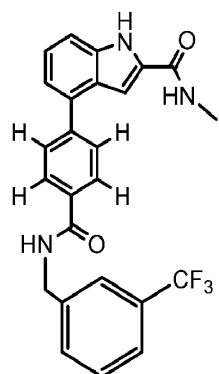
8. The compound of embodiment 7, wherein the compound has the formula:



or a pharmaceutically acceptable salt thereof.

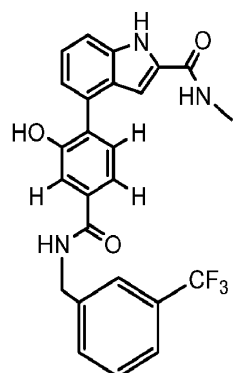
- 5 9. The compound of embodiment 2, wherein at least one R₃ is CH₃, or a pharmaceutically acceptable salt thereof.

10. The compound of embodiment 2, wherein the compound has the formula:



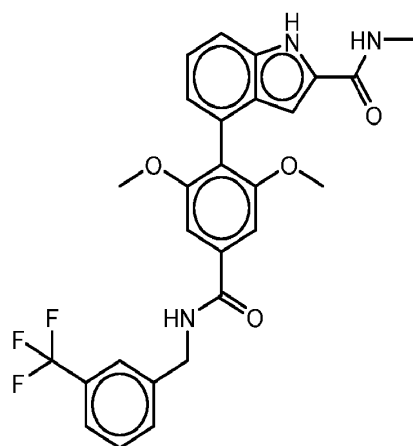
- 10 or a pharmaceutically acceptable salt thereof.

11. The compound of embodiment 2 wherein the compound has the formula:



or a pharmaceutically acceptable salt thereof.

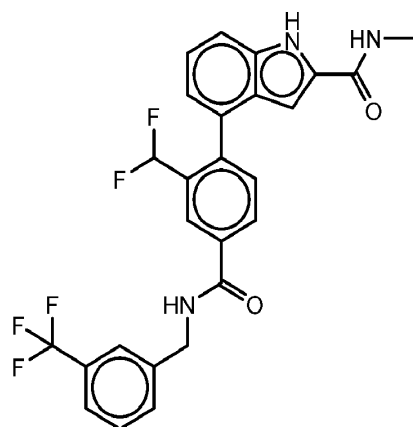
12. The compound of embodiment 2 wherein the compound has the formula:



5

or a pharmaceutically acceptable salt thereof.

13. The compound of embodiment 2 wherein the compound has the formula:

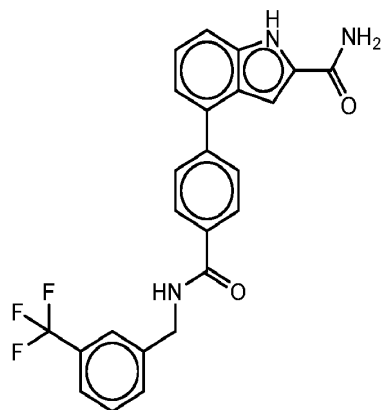


(Compound 36)

or a pharmaceutically acceptable salt thereof.

14. The compound of embodiment 1 wherein R_1 and R_2 are both H, or
 5 pharmaceutically acceptable salt thereof.

15. The compound of embodiment 2 wherein the compound has the formula:



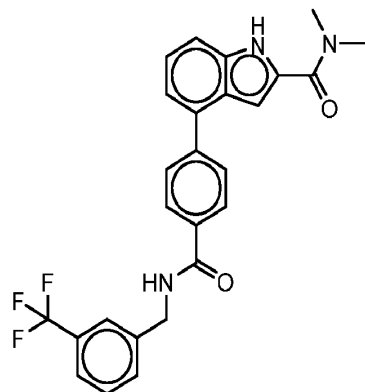
(Compound 1)

or a pharmaceutically acceptable salt thereof.

10

16. The compound of embodiment 1 wherein R_1 and R_2 are both CH_3 , or
 pharmaceutically acceptable salt thereof.

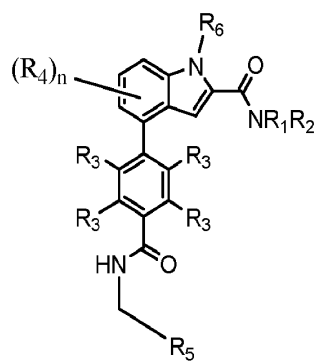
17. The compound of embodiment 2 wherein the compound has the formula:



(Compound 2)

or a pharmaceutically acceptable salt thereof.

5 18. A compound of the formula:



(II)

wherein R_1 and R_2 are independently selected from H or CH_3 ;

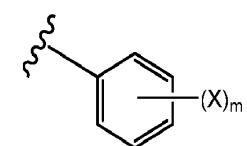
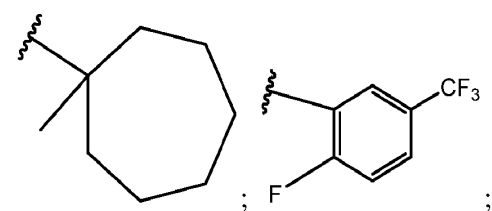
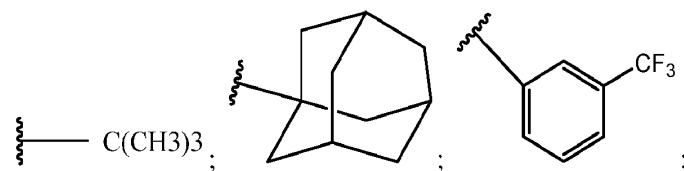
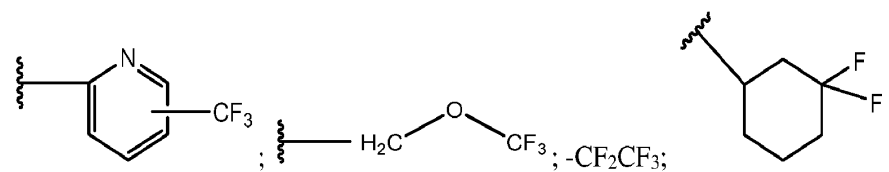
wherein each R_3 is independently selected from H, OH, CH_3 , O- CH_3 , CH_2F_2 , F, or Cl, wherein at least two R_3 are H;

wherein n is 0, 1, 2, or 3;

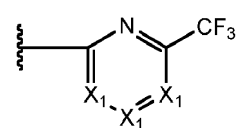
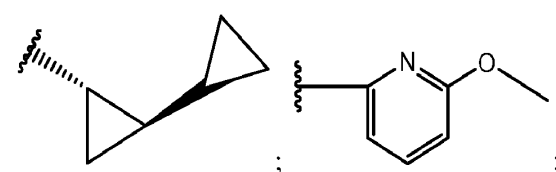
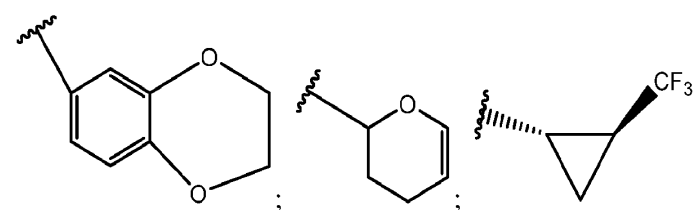
wherein each occurrence of R_4 is independently selected from CH_3 , CF_3 , O- CH_3 , F, Cl, -CN, iso-propyl, or cyclopropyl;

wherein R_6 is H, $-CH_2CH_2OH$, or $-CH_2CH_2N(CH_3)_2$;

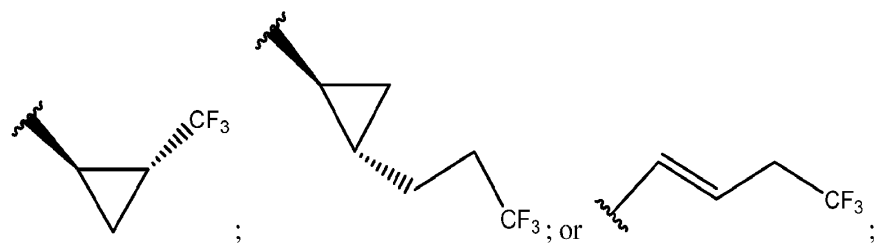
R₅ is:



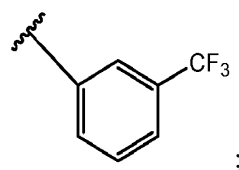
5, wherein m is 0, 1, 2, 3, or 4, and X is CH₃, OCH₃, F, or Cl;



, wherein each X₁ is, independently, N or CH; provided that one X₁ is N;

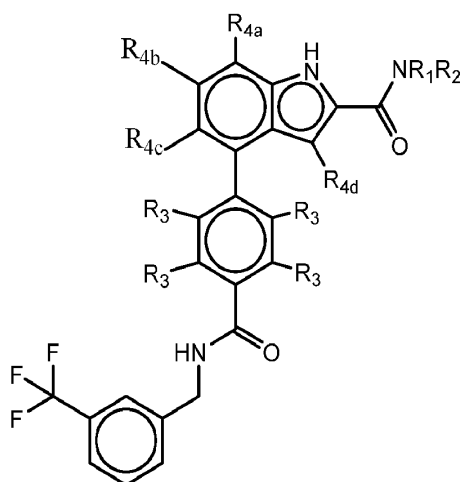


provided that n cannot be 0 when R_5 is:



5 or a pharmaceutically acceptable salt thereof.

19. The compound of embodiment 18, wherein the compound has the formula:



10

wherein each occurrence of R_{4a} , R_{4b} , R_{4c} , and R_{4d} is independently selected from H, CH_3 , CF_3 , $O-CH_3$, F, Cl, $-CN$, iso-propyl, or cyclopropyl; provided that at least one of R_{4a} , R_{4b} , R_{4c} , and R_{4d} is other than H;

or a pharmaceutically acceptable salt thereof.

15

20. The compound of embodiment 19, wherein one of R_{4a} , R_{4b} , R_{4c} , and R_{4d} is Cl; and the others are H, or a pharmaceutically acceptable salt thereof.

21. The compound of embodiment 20, wherein R_{4d} is Cl, or a pharmaceutically acceptable salt thereof.

5 22. The compound of embodiment 19, wherein one of R_{4a} , R_{4b} , R_{4c} , and R_{4d} is CH_3 ; and the others are H, or a pharmaceutically acceptable salt thereof.

23. The compound of embodiment 22, wherein R_{4d} is CH_3 , or a pharmaceutically acceptable salt thereof.

24. The compound of embodiment 19, wherein one of R_{4a} , R_{4b} , R_{4c} , and R_{4d} is OCH_3 ; and the others are H, or a pharmaceutically acceptable salt thereof.

25. The compound of embodiment 24, wherein R_{4c} is OCH_3 , or a pharmaceutically acceptable salt thereof.

26. The compound of embodiment 19, wherein one of R_{4a} , R_{4b} , R_{4c} , and R_{4d} is F; and the others are H, or a pharmaceutically acceptable salt thereof.

15 27. The compound of embodiment 26, wherein R_{4a} is F, or a pharmaceutically acceptable salt thereof.

28. The compound of embodiment 19, wherein one of R_{4a} , R_{4b} , R_{4c} , and R_{4d} is CF_3 ; and the others are H, or a pharmaceutically acceptable salt thereof.

20 29. The compound of embodiment 28, wherein R_{4a} is CF_3 , or a pharmaceutically acceptable salt thereof.

30. The compound of embodiment 19, wherein one of R_{4a} , R_{4b} , R_{4c} , and R_{4d} is CN; and the others are H, or a pharmaceutically acceptable salt thereof.

31. The compound of embodiment 30, wherein R_{4b} is CN, or a pharmaceutically acceptable salt thereof.

25 32. The compound of embodiment 19, wherein one of R_{4a} , R_{4b} , R_{4c} , and R_{4d} is cyclopropyl; and the others are H, or a pharmaceutically acceptable salt thereof.

33. The compound of embodiment 32, wherein R_{4b} is cyclopropyl, or a pharmaceutically acceptable salt thereof.

30 34. The compound of embodiment 19, wherein one of R_{4a} , R_{4b} , R_{4c} , and R_{4d} is *iso*-propyl; and the others are H, or a pharmaceutically acceptable salt thereof.

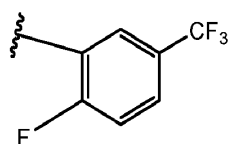
35. The compound of embodiment 34, wherein R_{4b} is *iso*-propyl, or a pharmaceutically acceptable salt thereof.

36. The compound of embodiment 19, wherein two of R_{4a} , R_{4b} , R_{4c} , and R_{4d} are independently Cl, F or CH_3 ; and the others are H, or a pharmaceutically acceptable salt thereof.

37. The compound of embodiment 36, wherein R_{4b} and R_{4c} are F, or a pharmaceutically acceptable salt thereof.

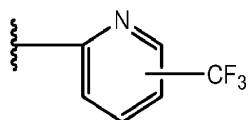
38. The compound of embodiment 36, wherein one of R_{4a} and R_{4b} is F, and the other of R_{4a} and R_{4b} is CH_3 ; or one of R_{4b} and R_{4c} is F, and the other of R_{4b} and R_{4c} is CH_3 ; or one of R_{4a} and R_{4d} is F, and the other of R_{4a} and R_{4d} is CH_3 , or a pharmaceutically acceptable salt thereof.

39. The compound of embodiment 18, wherein R_5 is:

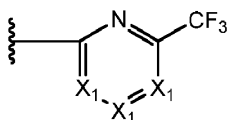


, or a pharmaceutically acceptable salt thereof.

40. The compound of embodiment 18, wherein R_5 is:



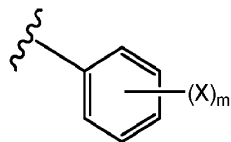
or



, wherein each X_1 is,

independently, N or CH ; provided that one X_1 is N, or a pharmaceutically acceptable salt thereof.

41. The compound of embodiment 18, wherein R_5 is:



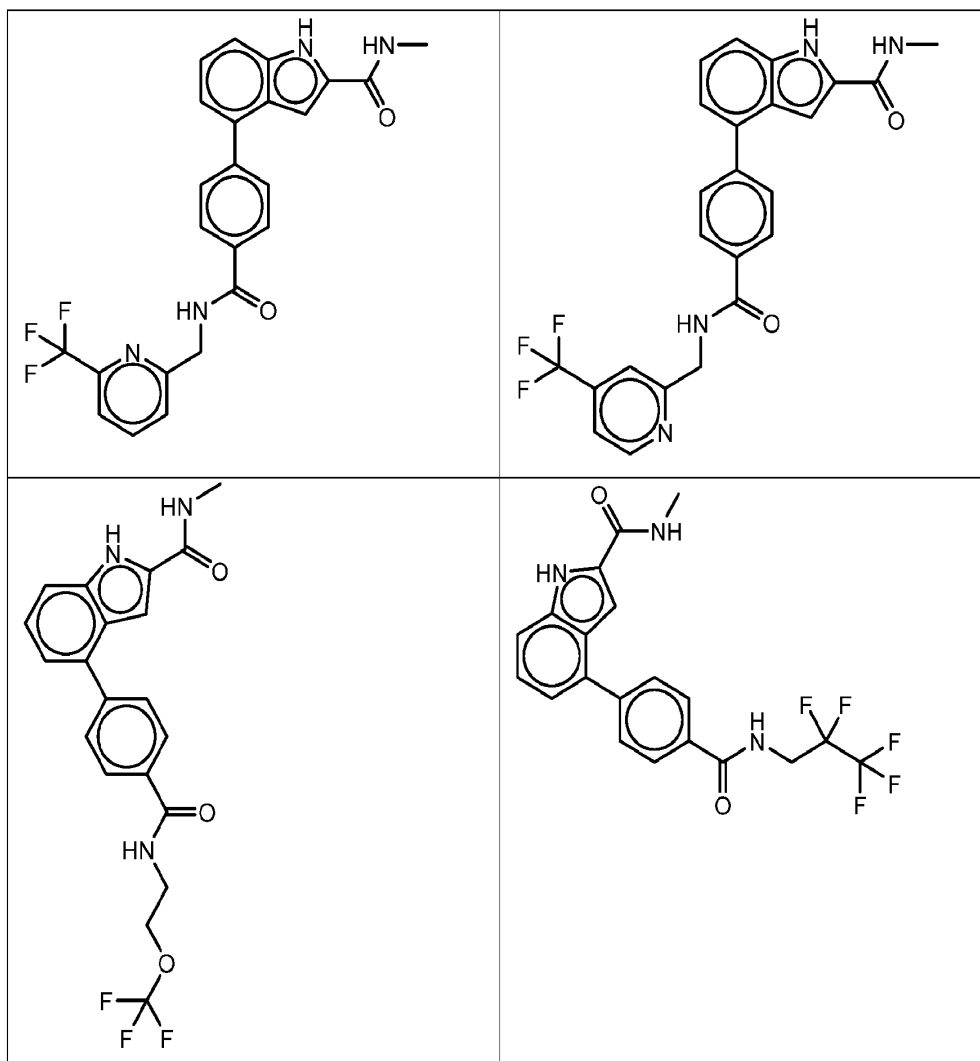
, wherein m is 0, 1, 2, 3, or 4, and X is CH_3 , OCH_3 , F, or Cl,

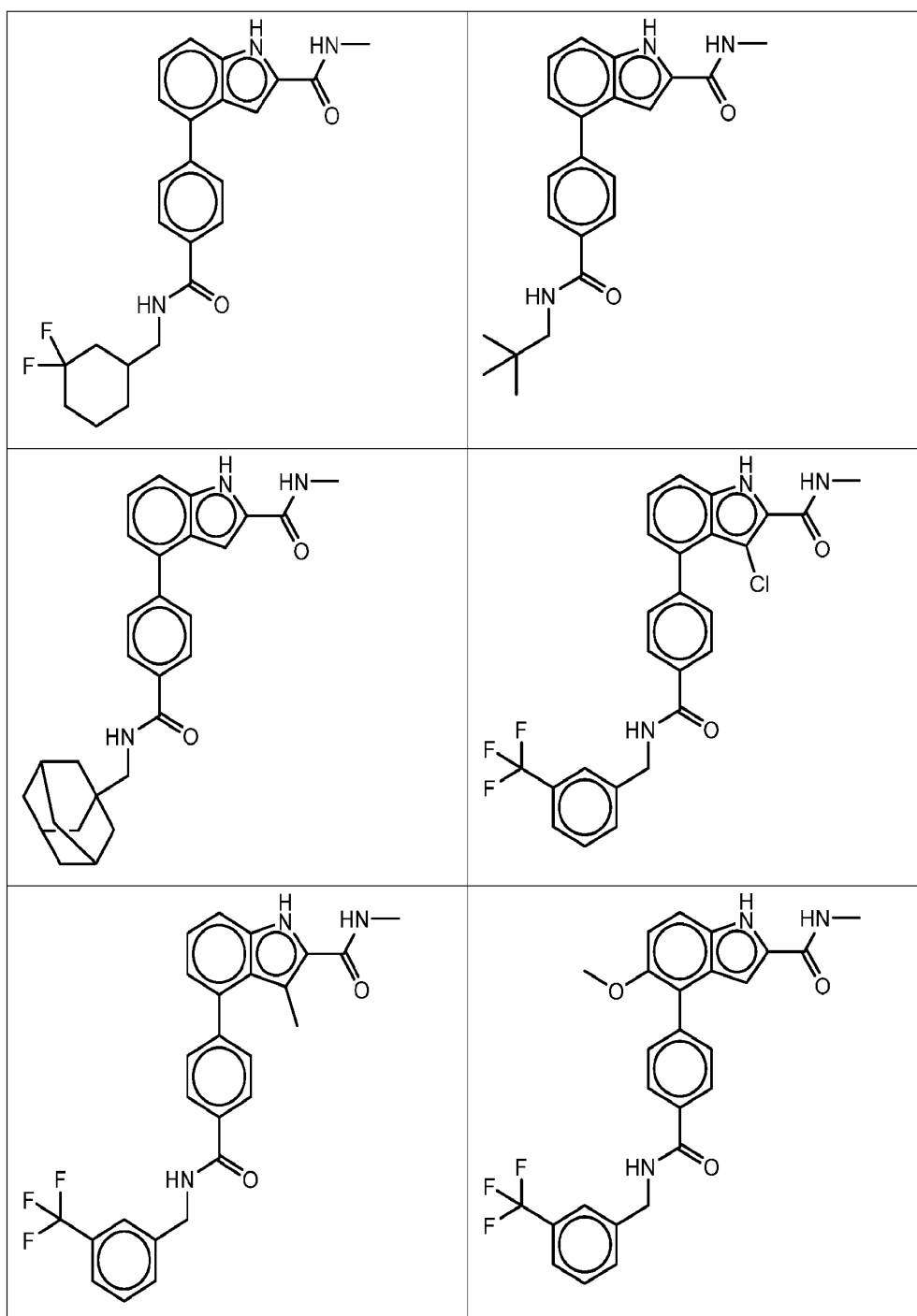
or a pharmaceutically acceptable salt thereof.

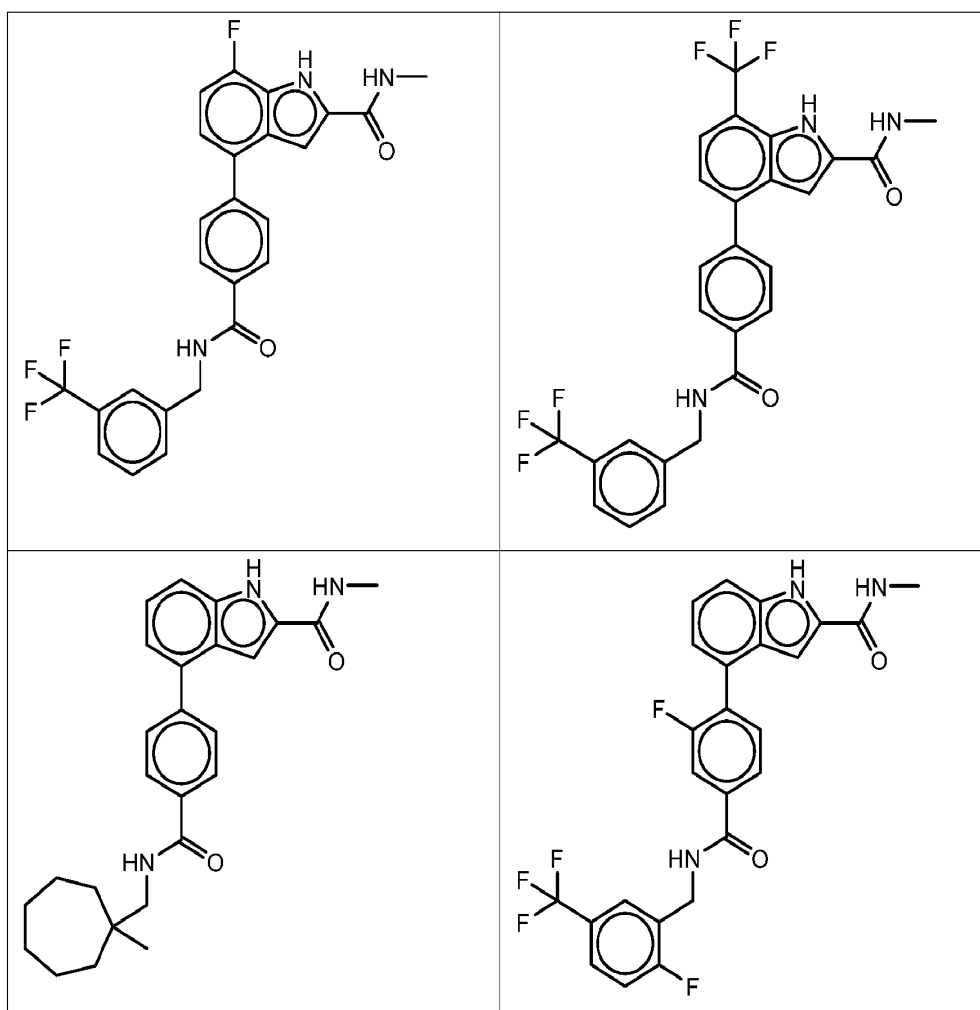
42. The compound of any one of embodiments 18-41, wherein R_1 is CH_3 and R_2 is H, or a pharmaceutically acceptable salt thereof.

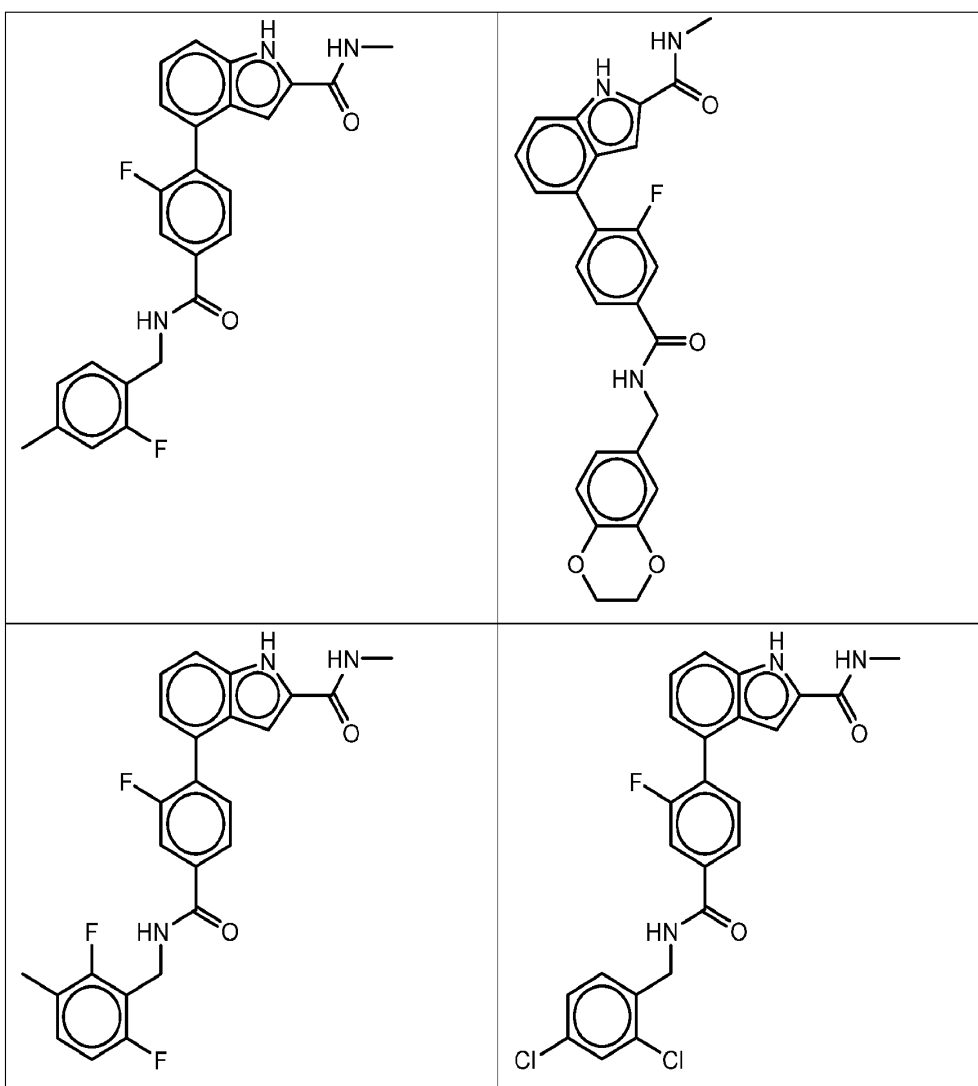
43. The compound of any one of embodiments 18-42, wherein each occurrence of R_3 is H, or a pharmaceutically acceptable salt thereof.

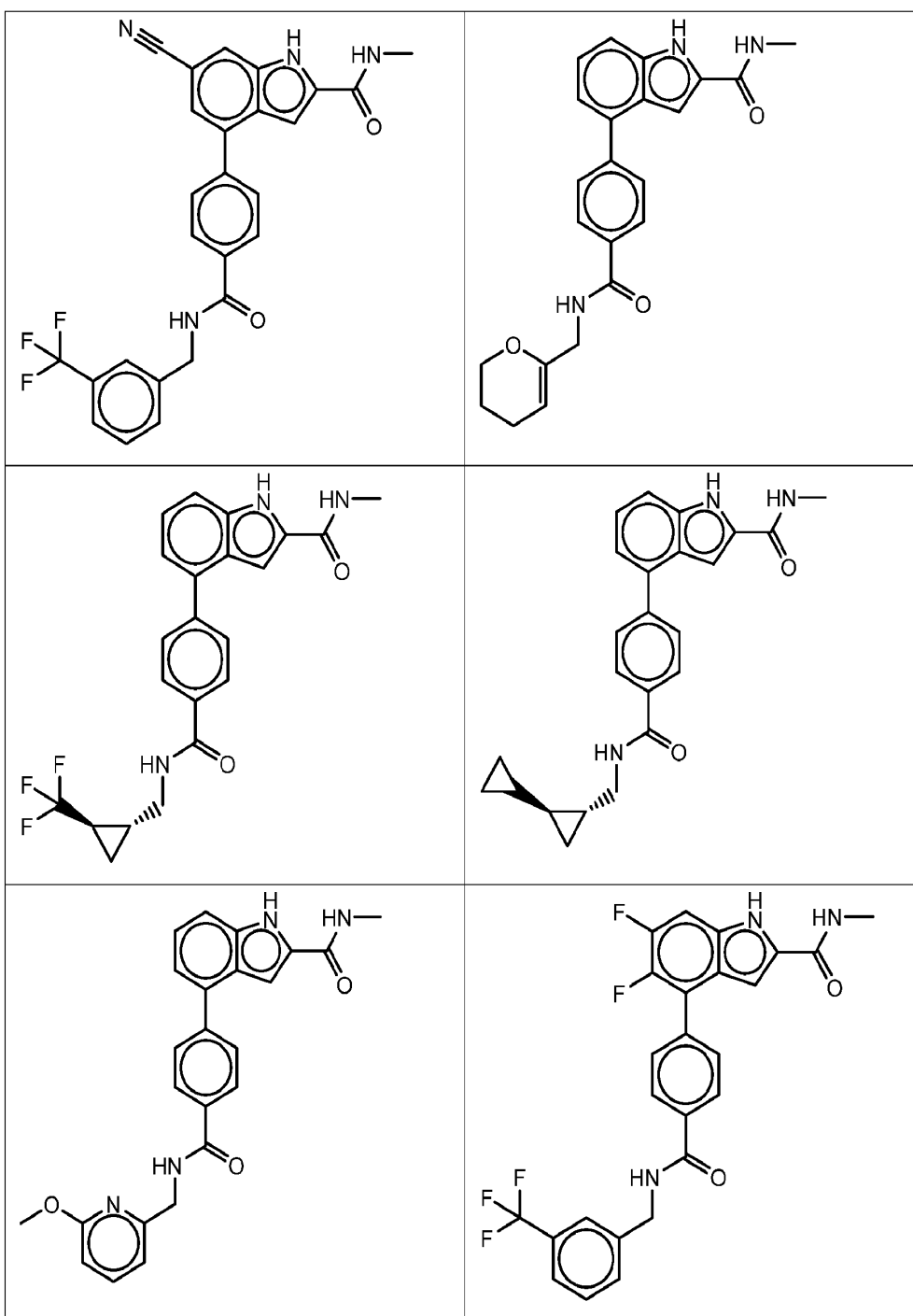
5 44. The compound of embodiment 18, wherein the compound is selected from:

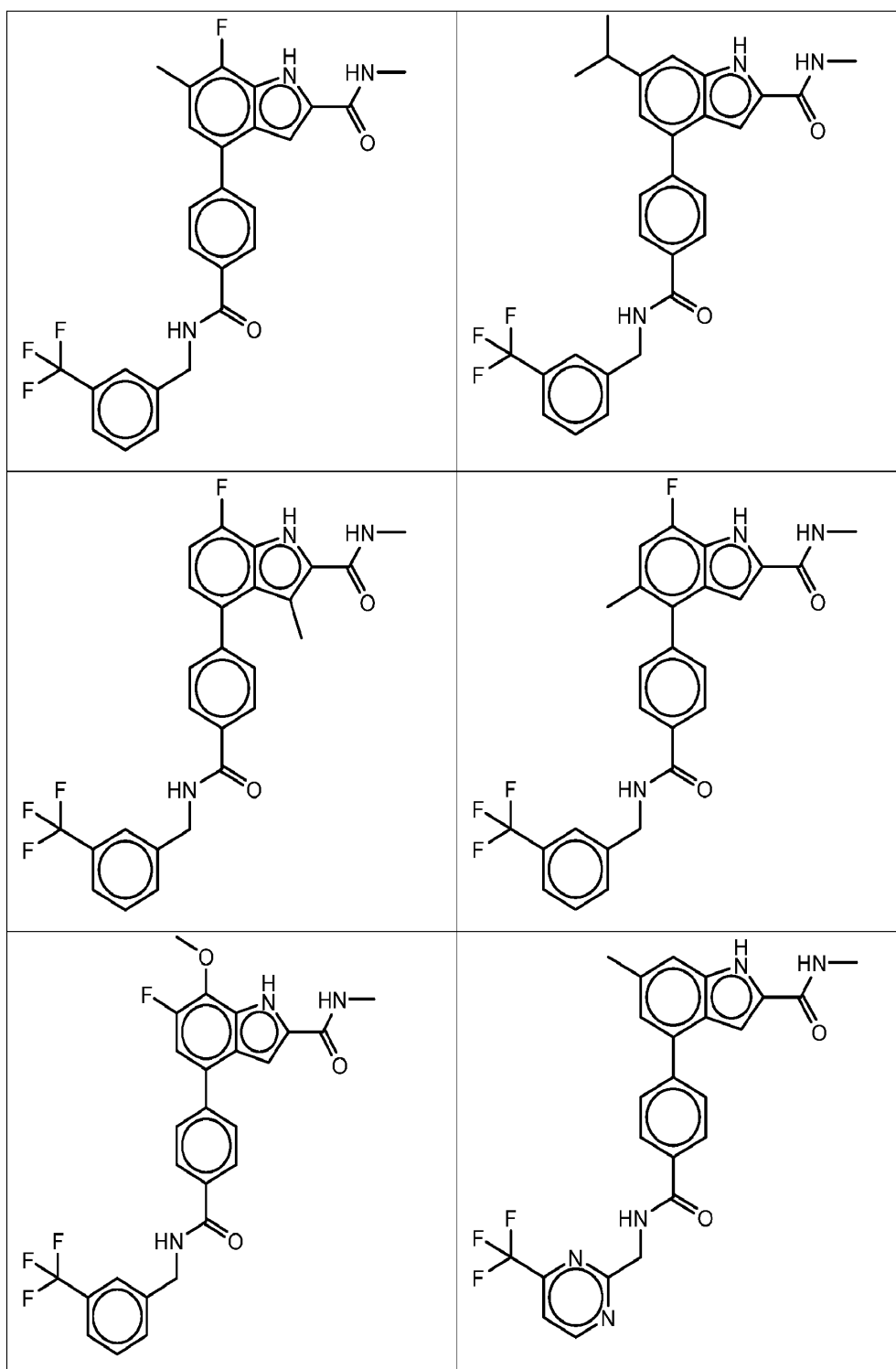


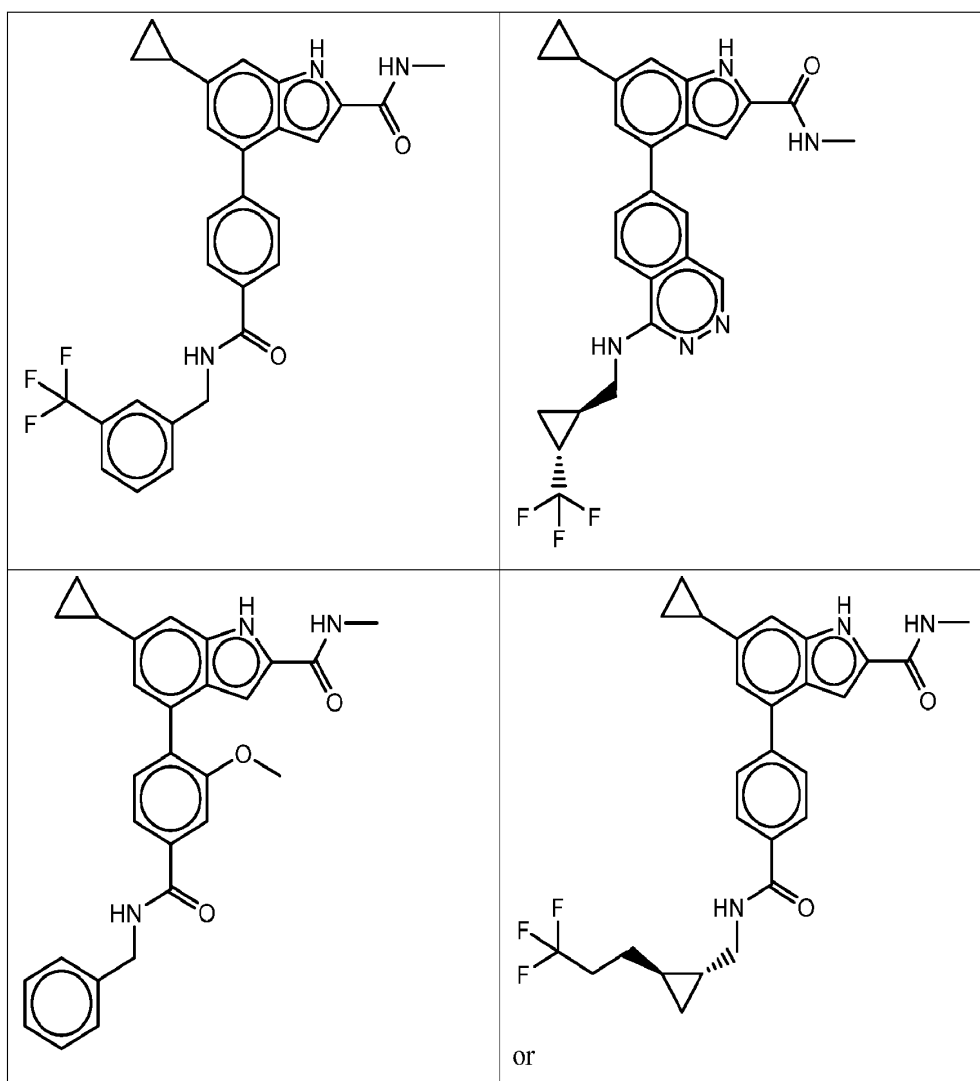


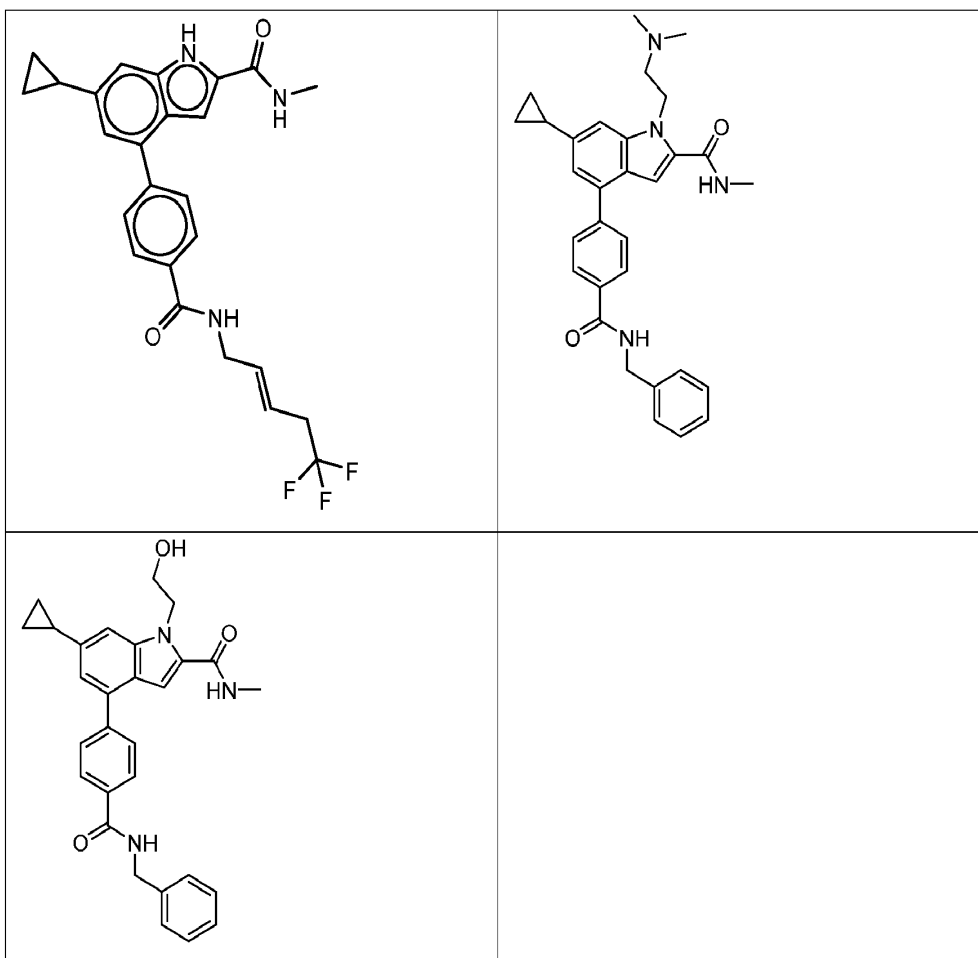






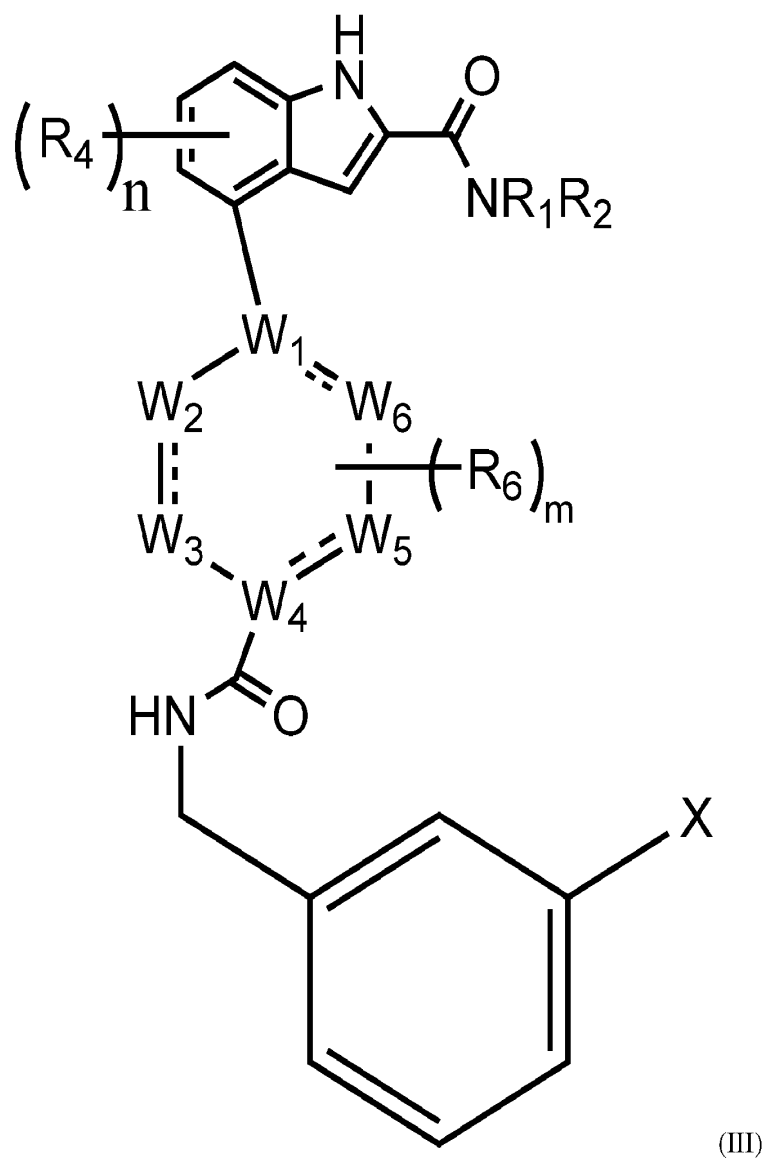






or a pharmaceutically acceptable salt thereof.

45. A compound of the formula:



each of W_1 and W_4 is independently selected from N, C, or CH;

each of $W_2, W_3, W_5,$ and W_6 is independently selected from N, NH, CH, or CH_2 ;

5 n is 0, 1, 2, or 3;

each occurrence of R_4 is, independently, cyclopropyl, Cl, F, CH_3 , isopropyl, CF_3 ,
-CN or OCH_3 ;

m is 0, 1, 2, or 3;

each occurrence of R_6 is, independently, F, Cl, or CH_3 ;
wherein R_1 and R_2 are independently selected from H or CH_3 ;
the dotted lines indicate the presence of a single or double bond; and
X is H or CF_3 , or a pharmaceutically acceptable salt thereof.

5

46. The compound of embodiment 45, wherein W_3 is N, W_1 and W_4 are C;
and each of W_2 , W_5 , and W_6 is CH, or a pharmaceutically acceptable salt thereof.

47. The compound of embodiment 45, wherein W_2 and W_3 are N, W_1 and W_4
are C; and each of W_5 and W_6 is CH, or a pharmaceutically acceptable salt thereof.

10 48. The compound of embodiment 45, wherein W_3 and W_5 are N, W_1 and W_4
are C; and each of W_2 and W_6 is CH, or a pharmaceutically acceptable salt thereof.

49. The compound of embodiment 45, wherein each of W_1 and W_4 is CH; and
each of W_2 , W_3 , W_5 , and W_6 is CH_2 , or a pharmaceutically acceptable salt thereof.

15 50. The compound of embodiment 45, wherein each of W_1 is CH, and W_4 is
N; and each of W_2 , W_3 , W_5 , and W_6 is CH_2 , or a pharmaceutically acceptable salt thereof.

51. The compound of embodiment 45, wherein W_3 and W_6 are N, W_1 and W_4
are C; W_2 is CR_6 , and W_5 is CH, or a pharmaceutically acceptable salt thereof.

52. The compound of embodiment 51, wherein R_6 is CH_3 , or a
pharmaceutically acceptable salt thereof.

20 53. The compound of embodiment 45, wherein W_2 is N, W_1 and W_4 are C;
and each of W_3 and W_5 is CH, and W_6 is CR_6 , or a pharmaceutically acceptable salt
thereof.

54. The compound of embodiment 53, wherein R_6 is Cl, or a pharmaceutically
acceptable salt thereof.

25 55. The compound of embodiment 45, wherein W_2 is N, W_1 and W_4 are C;
and each of W_3 , W_5 , and W_6 is CH, or a pharmaceutically acceptable salt thereof.

56. The compound of embodiment 45, wherein W_2 and W_6 are N, W_1 and W_4
are C; W_3 is CR_6 , and W_5 is CH, or a pharmaceutically acceptable salt thereof.

30 57. The compound of embodiment 56, wherein R_6 is CH_3 , or a
pharmaceutically acceptable salt thereof.

58. The compound of embodiment 45, wherein W_2 and W_6 are N, W_1 and W_4 are C; W_3 is CH, and W_5 is CH, or a pharmaceutically acceptable salt thereof.

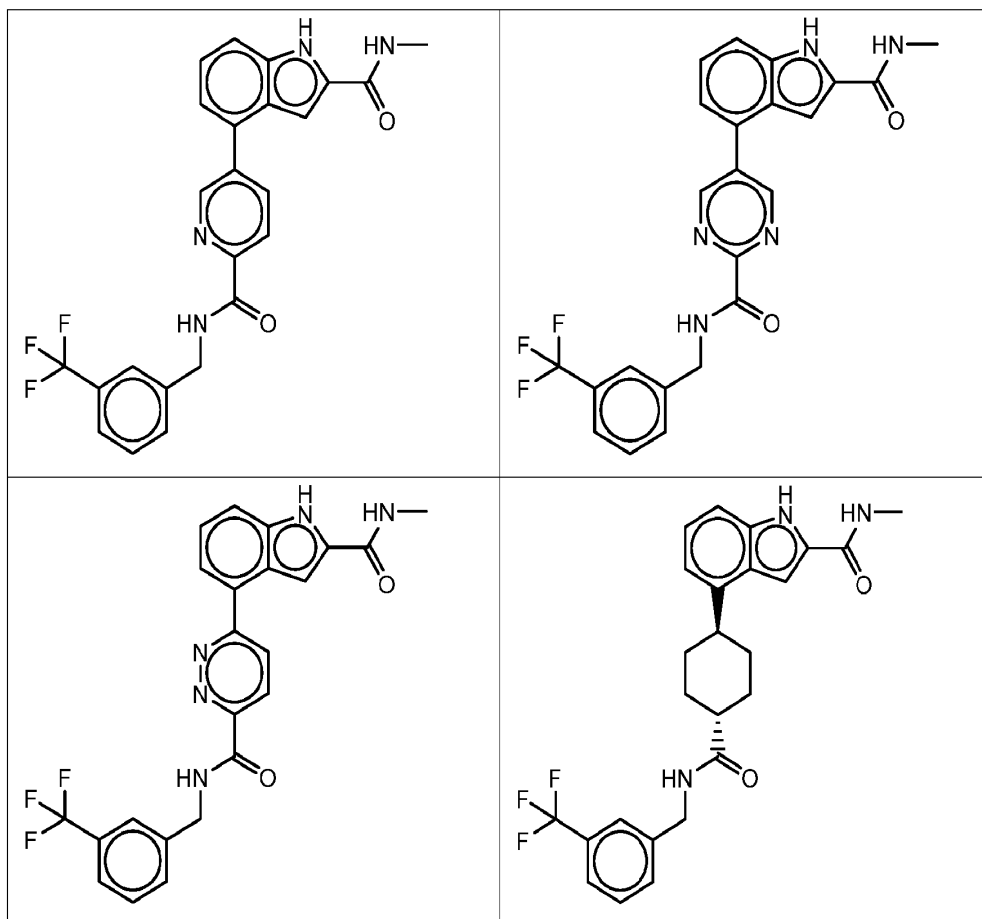
59. The compound of embodiment 45, wherein W_2 is N, W_1 and W_4 are C; each of W_3 and W_6 is CR_6 , and W_5 is CH, or a pharmaceutically acceptable salt thereof.

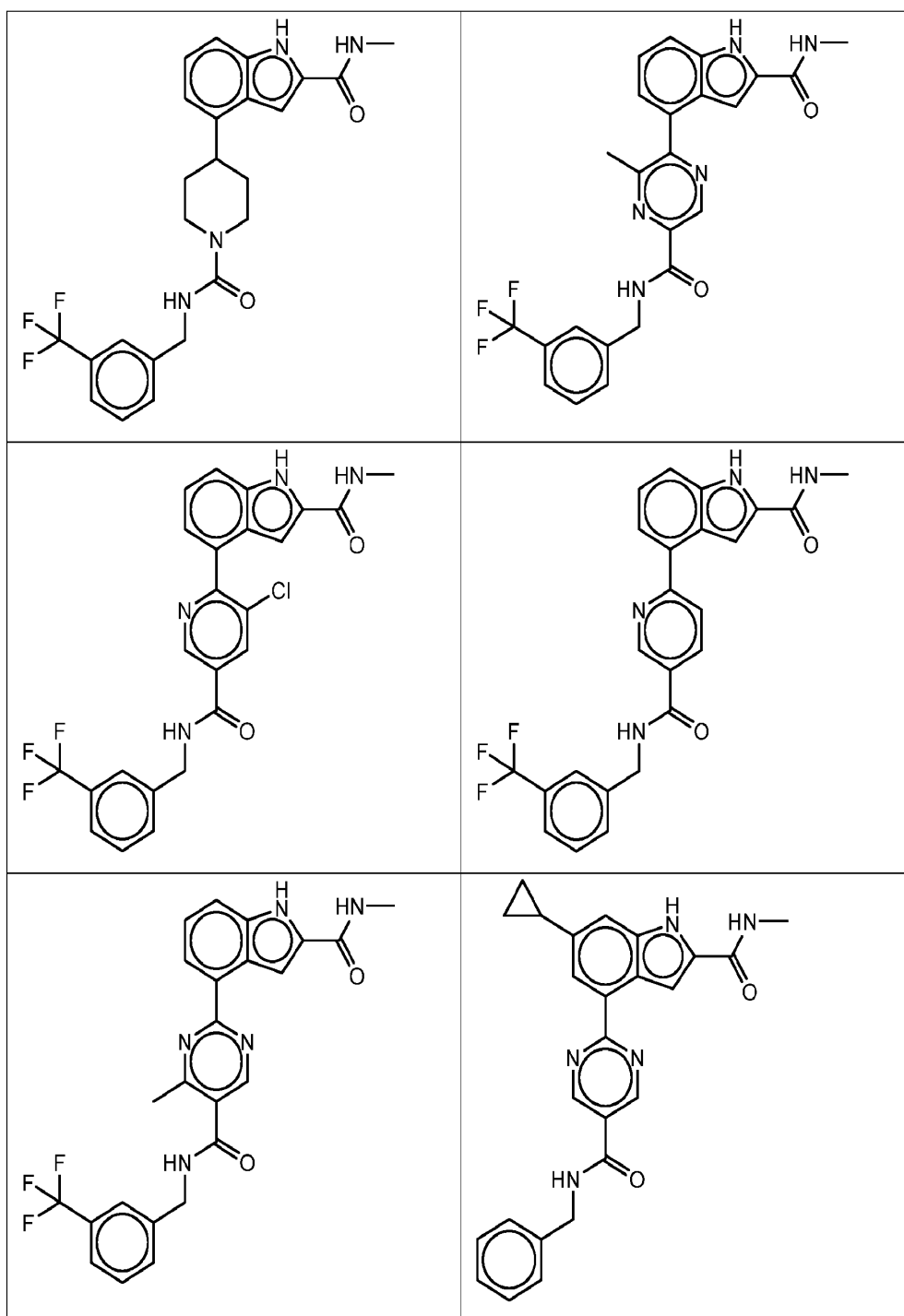
5 60. The compound of embodiment 59, wherein R_6 is CH_3 , or a pharmaceutically acceptable salt thereof.

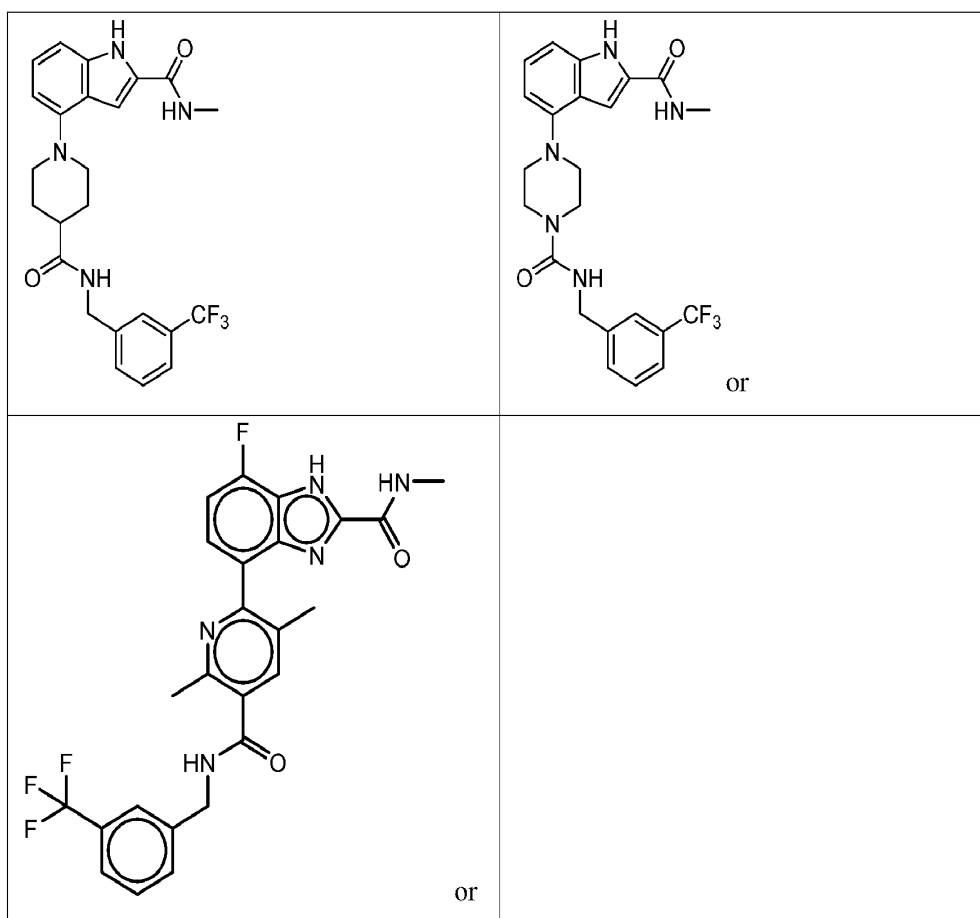
61. The compound of any one of embodiments 45-60, wherein R_1 is CH_3 and R_2 is H, or a pharmaceutically acceptable salt thereof.

10 62. The compound of any one of embodiments 45-61, wherein n is 1, and R_4 is F or cyclopropyl, or a pharmaceutically acceptable salt thereof.

63. The compound of embodiment 45, wherein the compound is selected from:

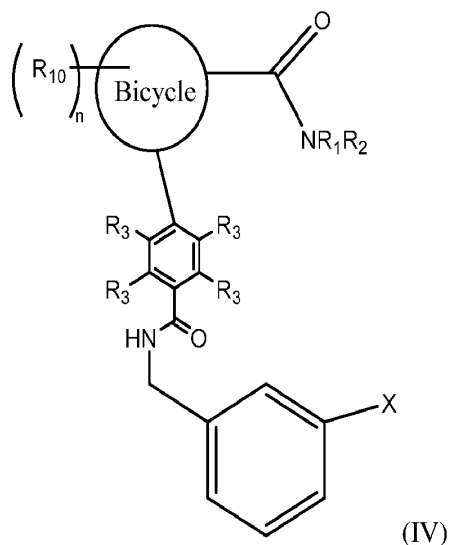






or a pharmaceutically acceptable salt thereof.

64. A compound of the formula:



wherein R₁ and R₂ are independently selected from H or CH₃;

wherein each R₃ is independently selected from H, OH, CH₃, O-CH₃, CHF₂, F, or

5 Cl, wherein at least two R₃ are H;

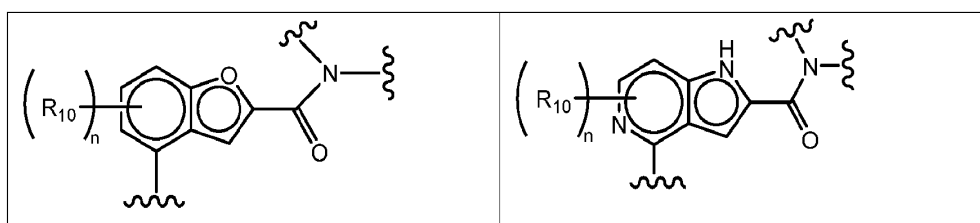
wherein n is 0, 1, or 2;

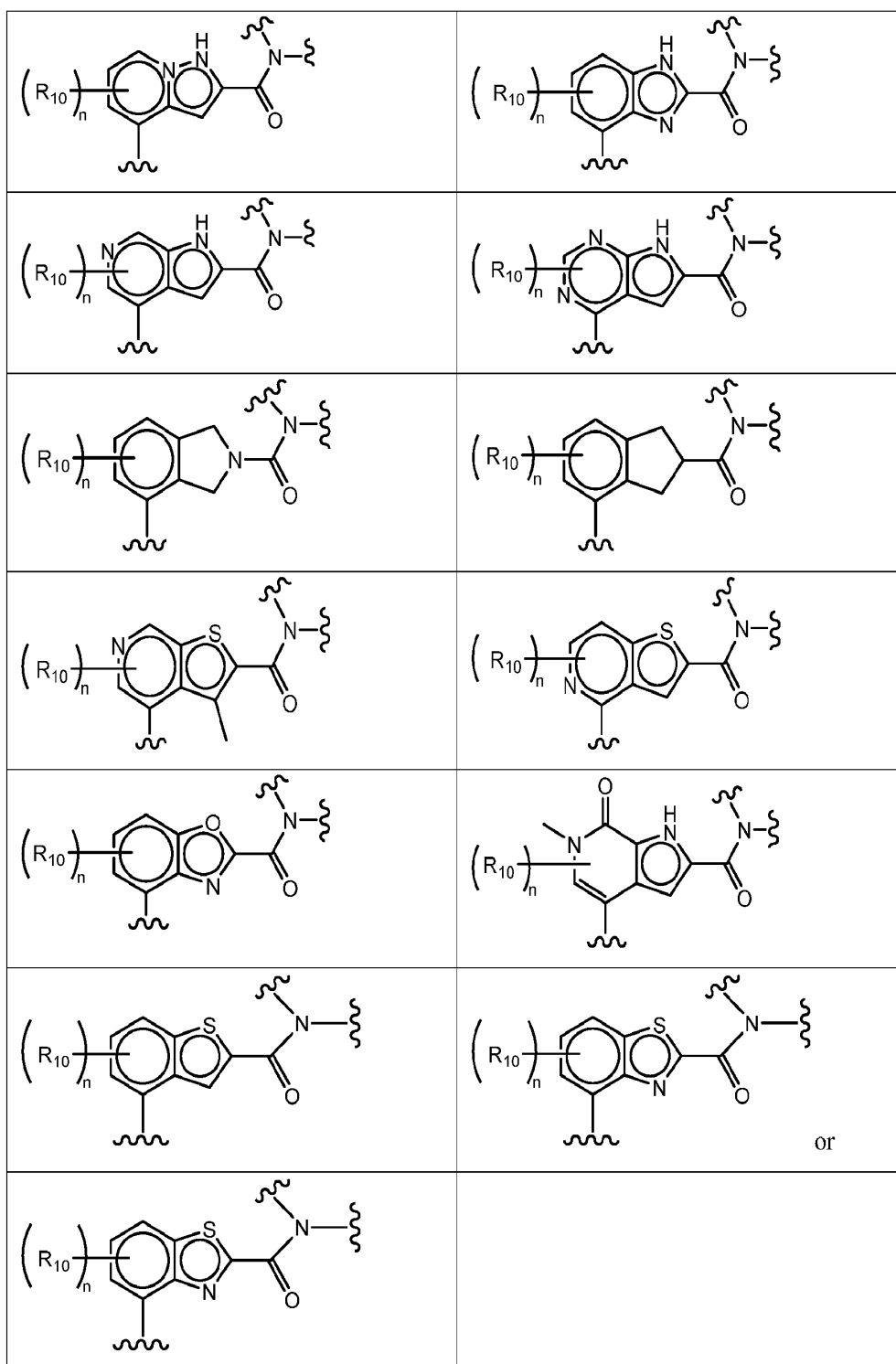
wherein each occurrence of R₁₀ is, independently, methyl, F, OH, H, OCH₃, CH₃,
or cyclopropyl;

wherein X is H or CF₃; and

10 wherein the bicycle is a bicyclic ring that includes 8-10 constituent ring atoms,
wherein 1-4 of the atoms are heteroatoms independently selected from N, O, or S, and
wherein each of the two rings is independently a saturated, unsaturated, or aromatic ring;
or a pharmaceutically acceptable salt thereof.

15 65 The compound of embodiment 64, wherein the bicycle is selected from:





or a pharmaceutically acceptable salt thereof.

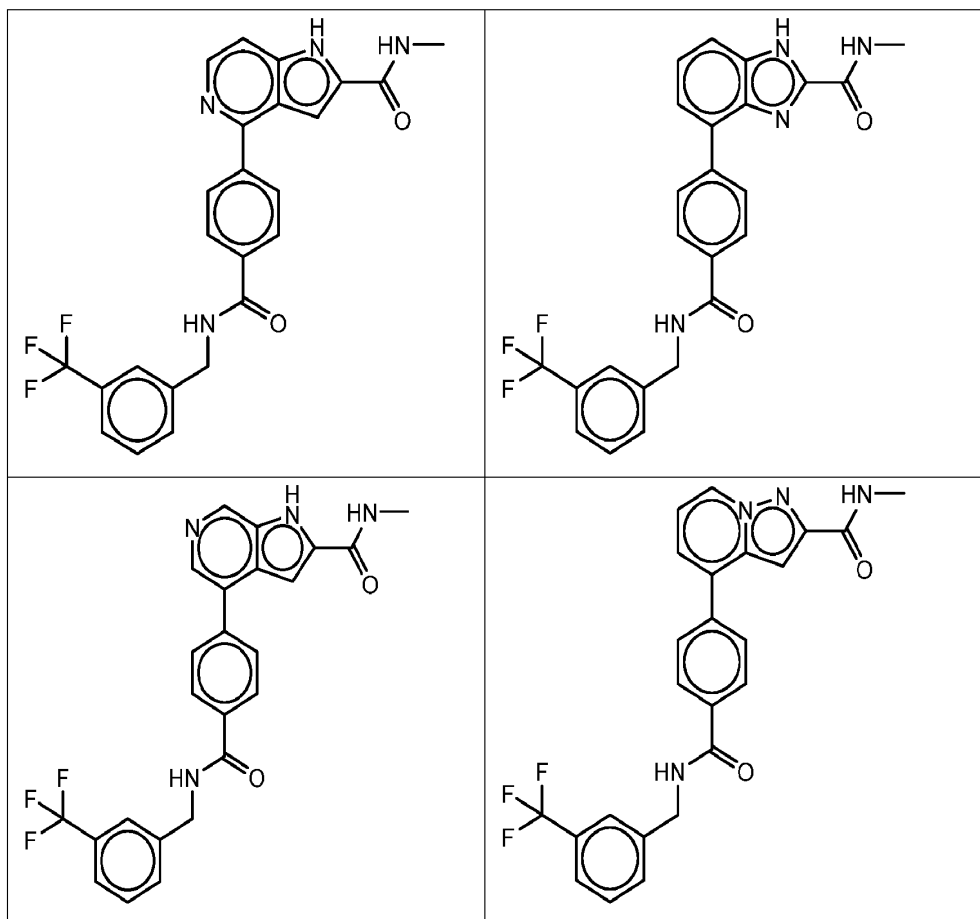
66. The compound of embodiments 64 or 65, wherein R_1 is CH_3 and R_2 is H, or a pharmaceutically acceptable salt thereof.

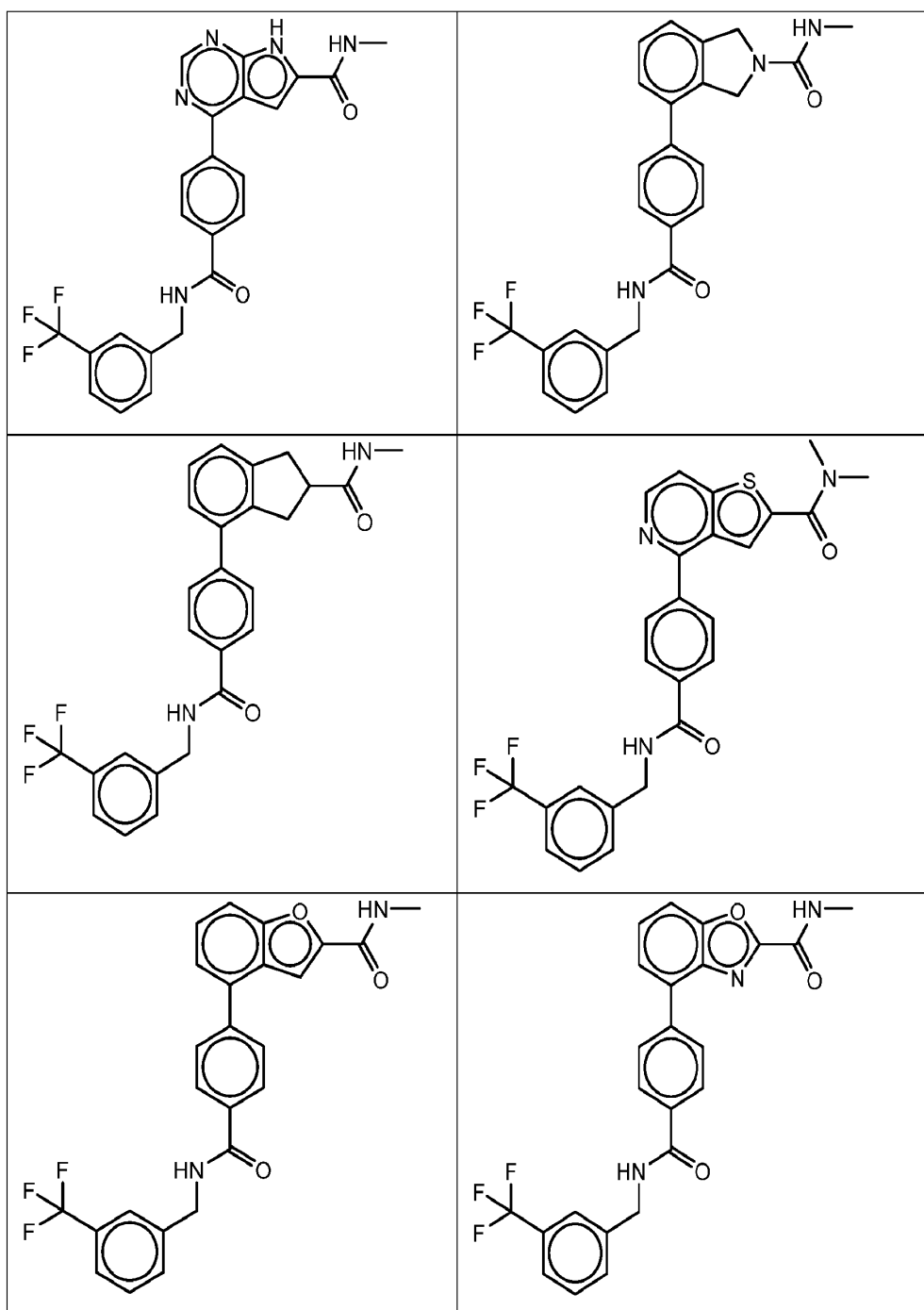
5 67. The compound of any one of embodiments 64-66, wherein each occurrence of R_3 is H, or a pharmaceutically acceptable salt thereof.

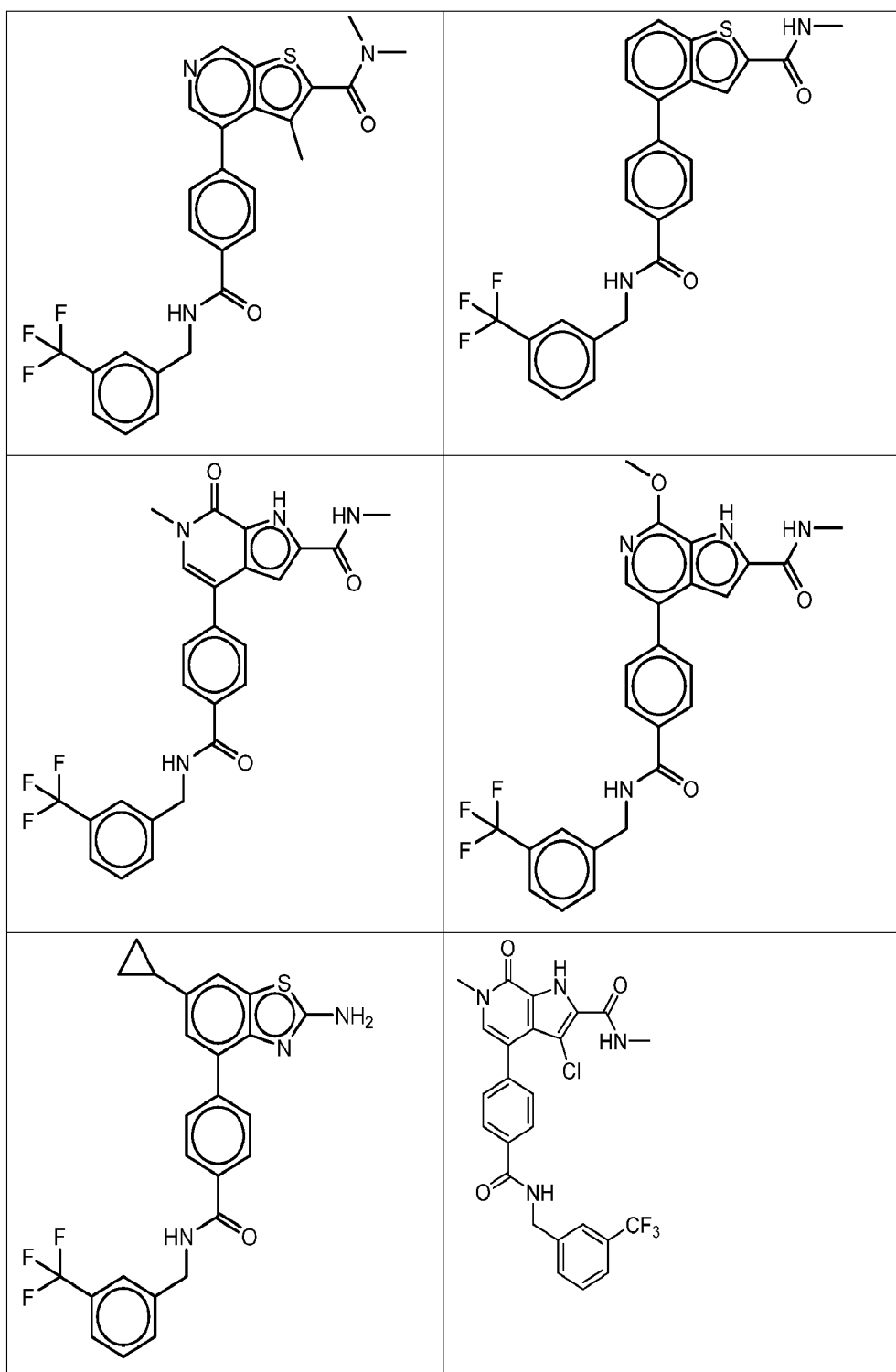
68. The compound of any one of embodiments 64-67, wherein X is CF_3 , or a pharmaceutically acceptable salt thereof.

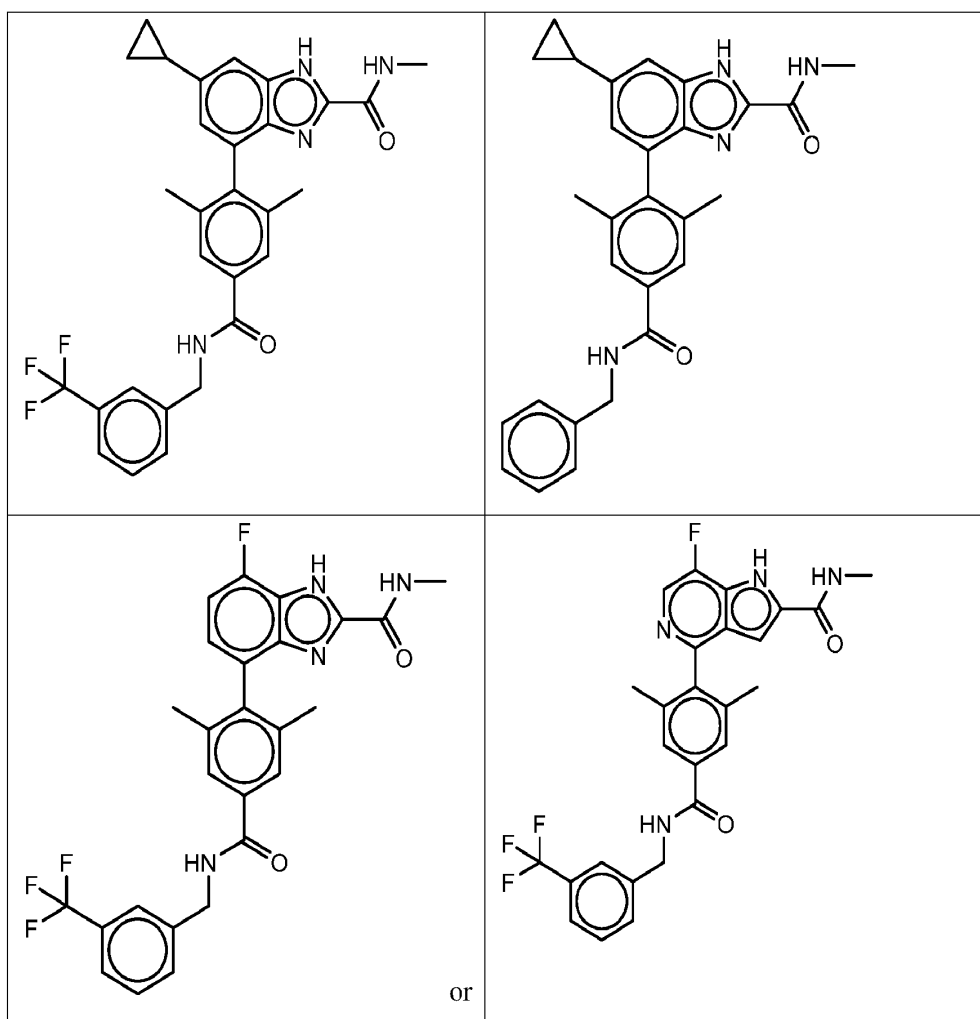
10

69. The compound of embodiment 64, wherein the compound is selected from:



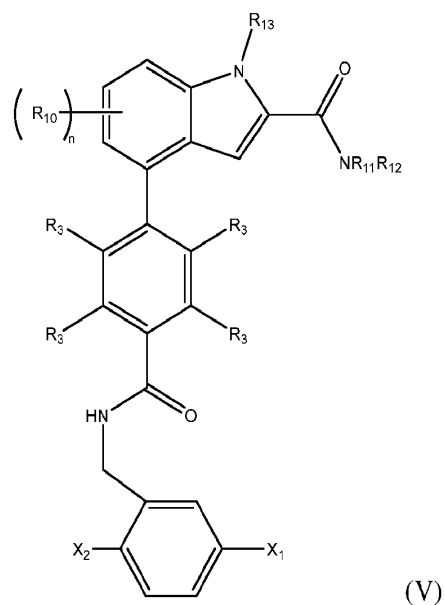






or a pharmaceutically acceptable salt thereof.

70. A compound having the formula:



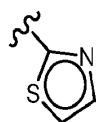
R_{11} is $-(CH_2)_m-A$

5 m is 0, 1, 2, or 3;

R_{12} is H;

R_{13} is H, $-CH_2CH_2OH$, or $-CH_2CH_2N(CH_3)_2$;

A is cyclopropyl, $-OH$, $-OCH_3$;



, $-CHF_2$; phenyl, 4-chlorophenyl;



10 , or 4-pyridyl;

n is 0, 1, 2, or 3;

each occurrence of R_{10} is, independently, cyclopropyl, Cl, F, CH_3 , or OCH_3 ;

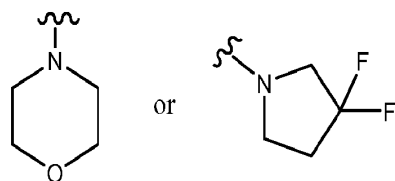
each R_3 is independently selected from H, OH, CH_3 , $O-CH_3$, CHF_2 , F, or Cl,

wherein at least two R_3 are H; and

15 X_1 is H or CF_3 ;

X_2 is H or F;

or R₁₁ and R₁₂ together with the nitrogen atom to which each is attached forms:



or a pharmaceutically acceptable salt thereof.

5 71. The compound of embodiment 70, wherein m is 1 or 2, or a pharmaceutically acceptable salt thereof.

72. The compound of embodiments 70 or 71, wherein n is 1, or a pharmaceutically acceptable salt thereof.

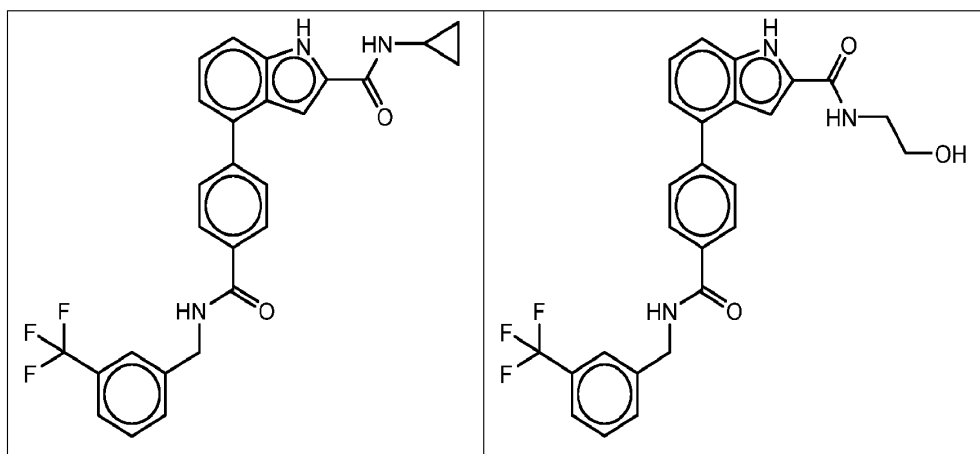
73. The compound of any one of embodiments 70-72, wherein each
10 occurrence of R₃ is H, or a pharmaceutically acceptable salt thereof.

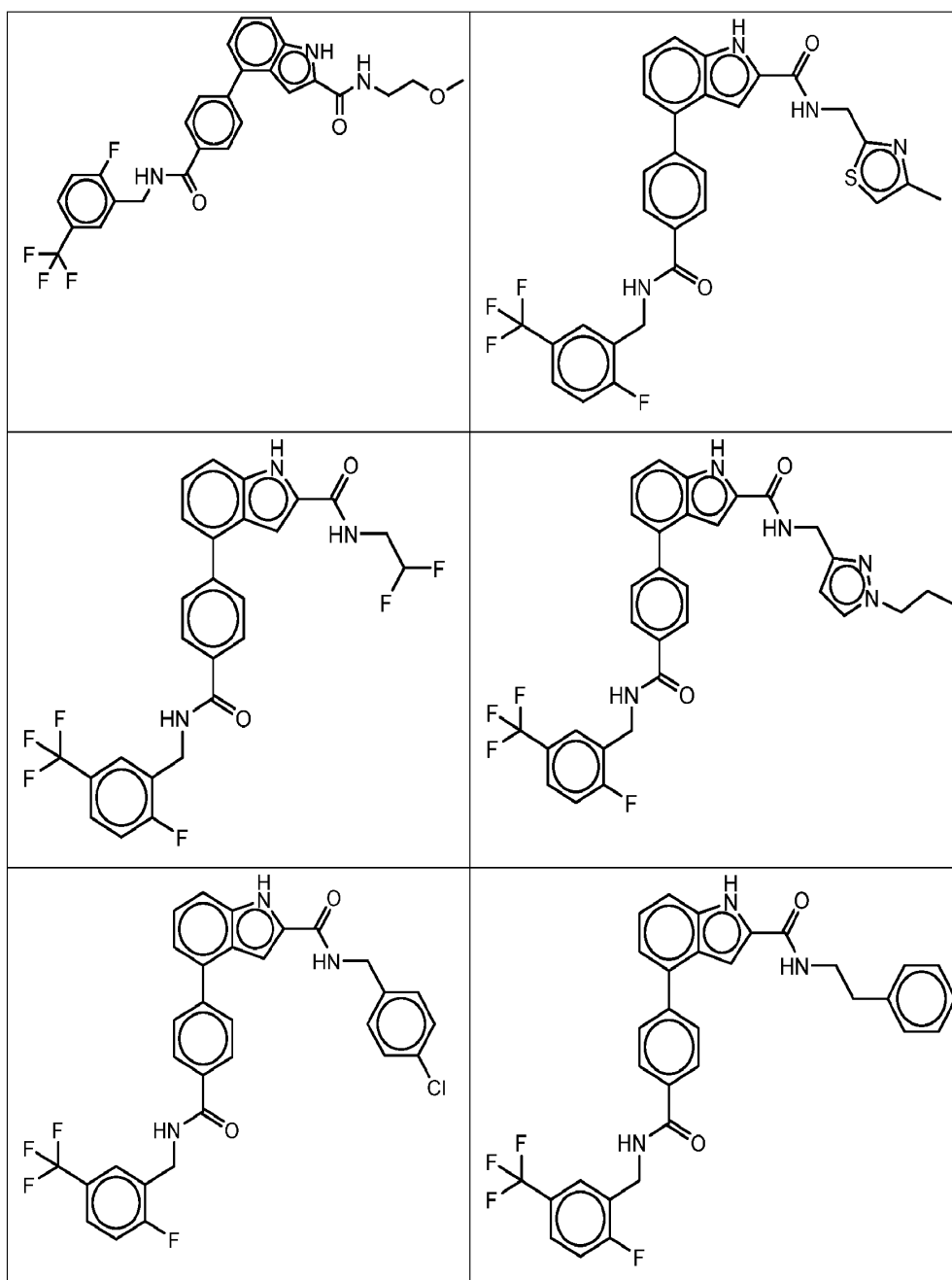
74. The compound of any one of embodiments 70-73, wherein X₁ is CF₃, and X₂ is H, or a pharmaceutically acceptable salt thereof.

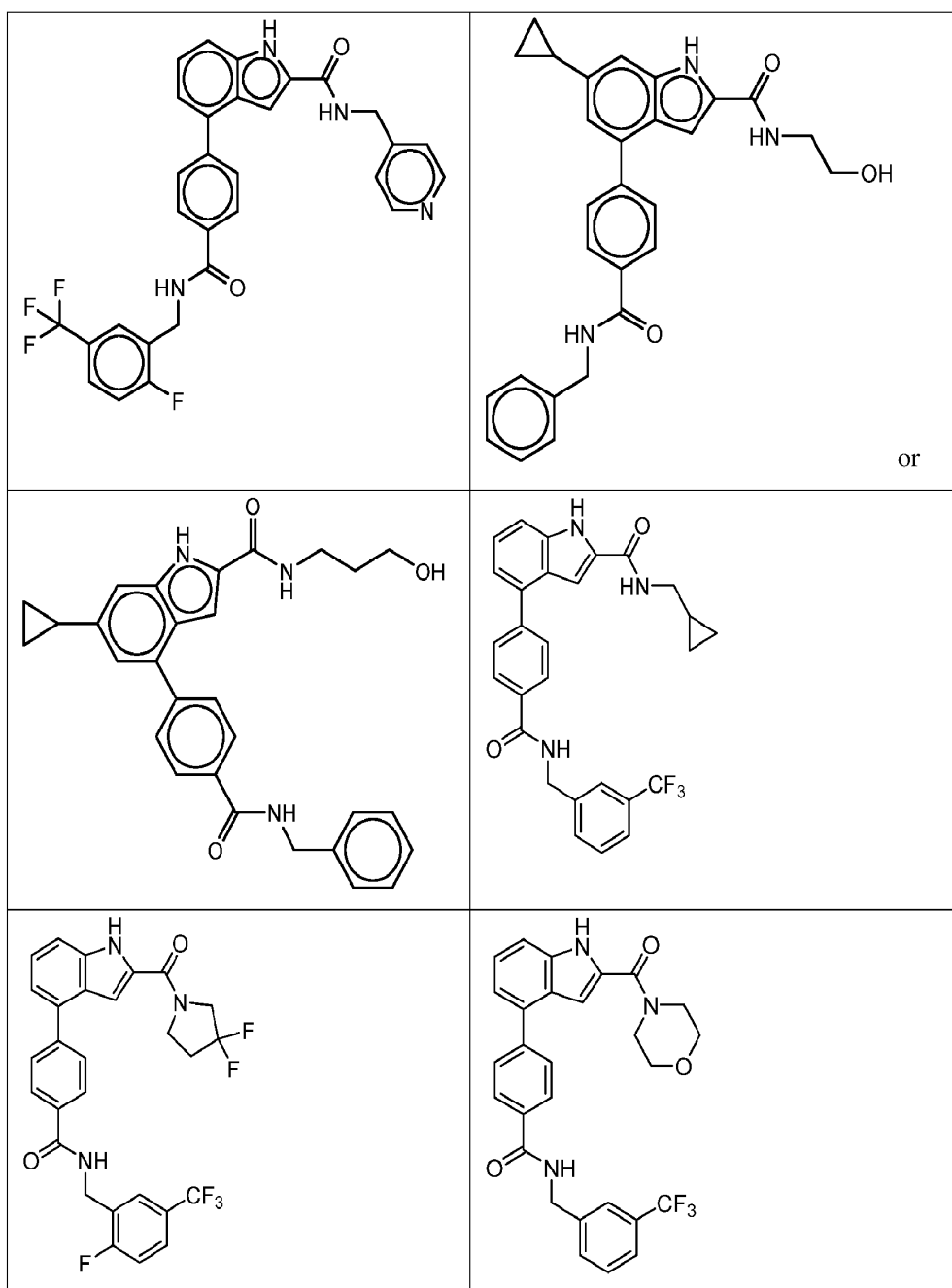
75. The compound of any one of embodiments 70-73, wherein X₁ is CF₃, and X₂ is F, or a pharmaceutically acceptable salt thereof.

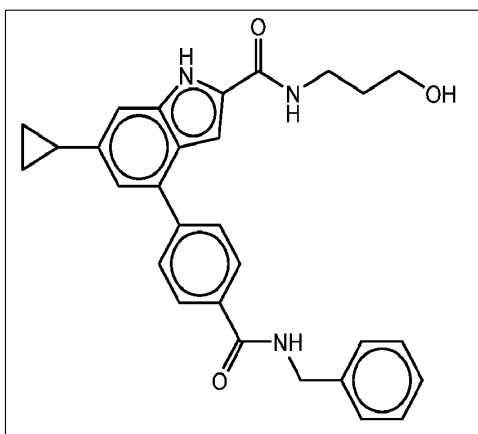
15 76. The compound of any one of embodiments 70-73, wherein X₁ is H, and X₂ is H, or a pharmaceutically acceptable salt thereof.

77. The compound of embodiment 70, wherein the compound is selected from:



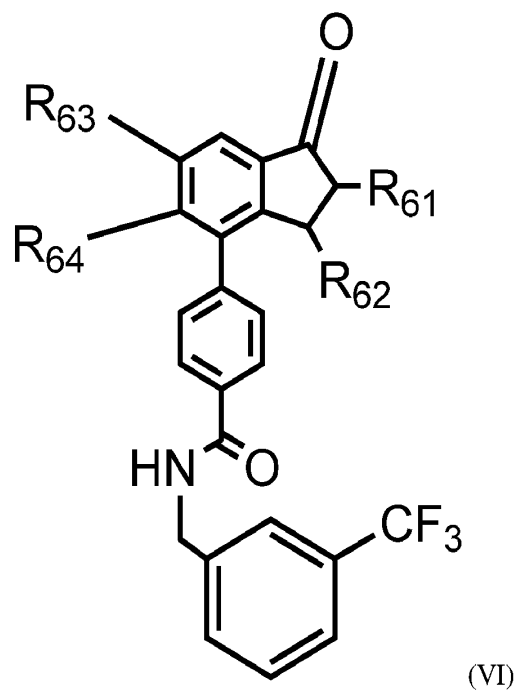






or a pharmaceutically acceptable salt thereof.

78. A compound having the formula:



(VI)

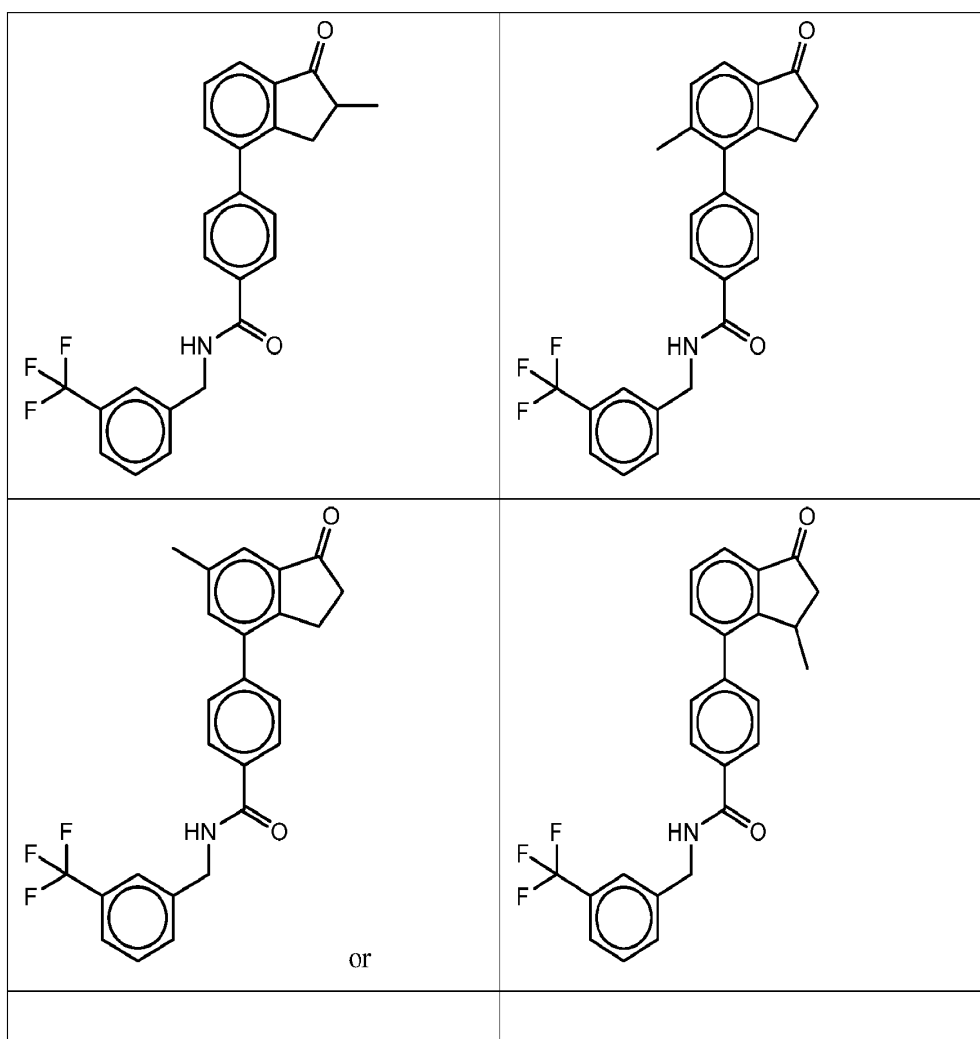
5 wherein each of R₆₁, R₆₂, R₆₃, and R₆₄ is independently selected from H and CH₃, or a pharmaceutically acceptable salt thereof.

79. The compound of embodiment 78, wherein one of R₆₁, R₆₂, R₆₃, and R₆₄ is CH₃, and the other three are H, or a pharmaceutically acceptable salt thereof.

80. The compound of embodiments 78 or 79, wherein one of R₆₁ and R₆₂ is CH₃, and the other is H, or a pharmaceutically acceptable salt thereof.

81. The compound of embodiments 78 or 79, wherein one of R₆₃ and R₆₄ is CH₃, and the other is H, or a pharmaceutically acceptable salt thereof.

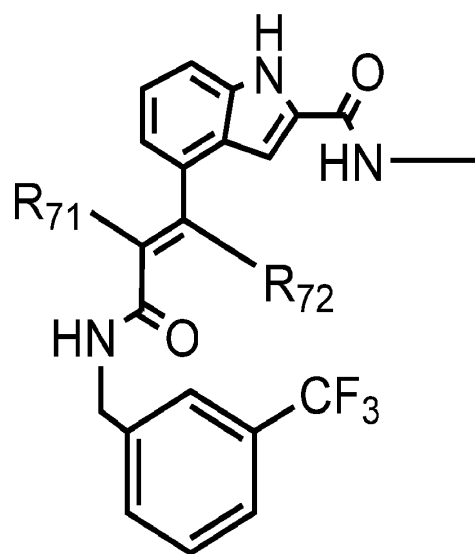
82. The compound of embodiment 78, wherein the compound is selected from:



or

or a pharmaceutically acceptable salt thereof.

83. A compound having the formula:



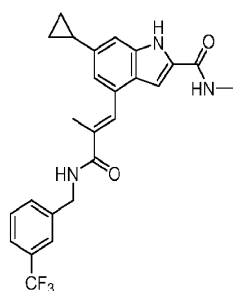
(VII)

each of R_{71} and R_{72} is independently selected from H and CH_3 , or a pharmaceutically acceptable salt thereof.

5

84. The compound of embodiment 83, wherein one of R_{71} and R_{72} is CH_3 , and the other is H, or a pharmaceutically acceptable salt thereof.

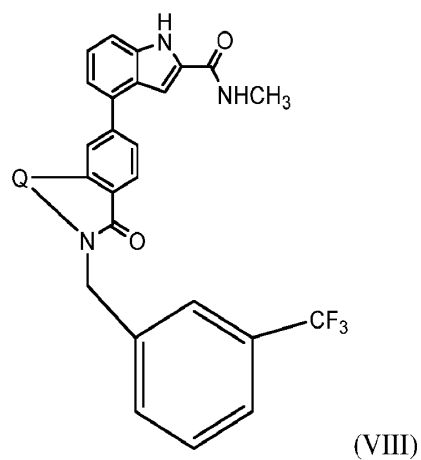
85. The compound of embodiment 83, wherein the compound is:



10

, or a pharmaceutically acceptable salt thereof.

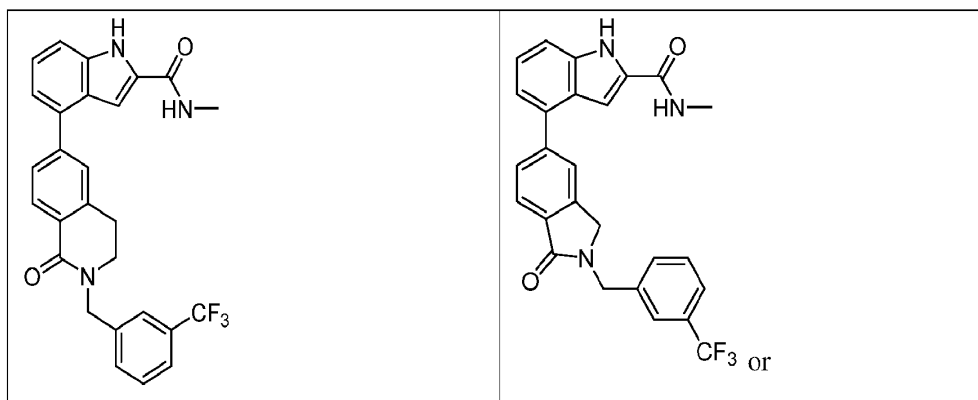
86. A compound having the formula:

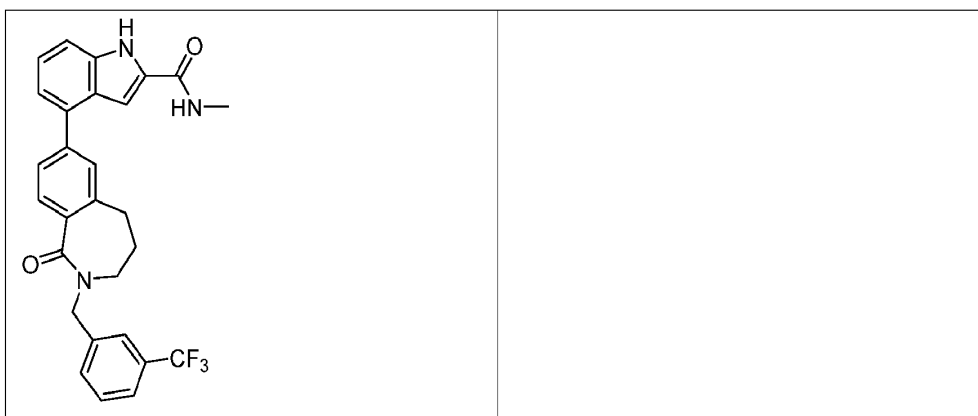


wherein Q is $(CH_2)_n$ where in a ring and n is 1, 2, or 3 thereby forming a 5, 6 or 7 membered ring, or a pharmaceutically acceptable salt thereof.

5

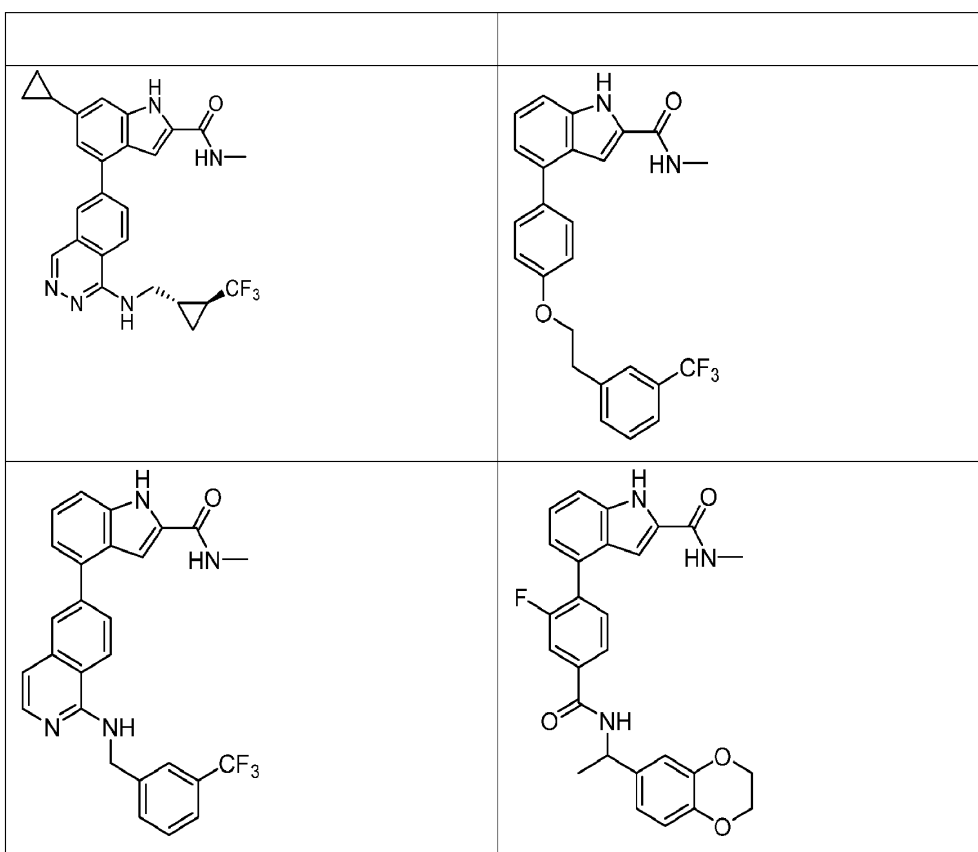
87. The compound of embodiment 86, wherein the compound is selected from:

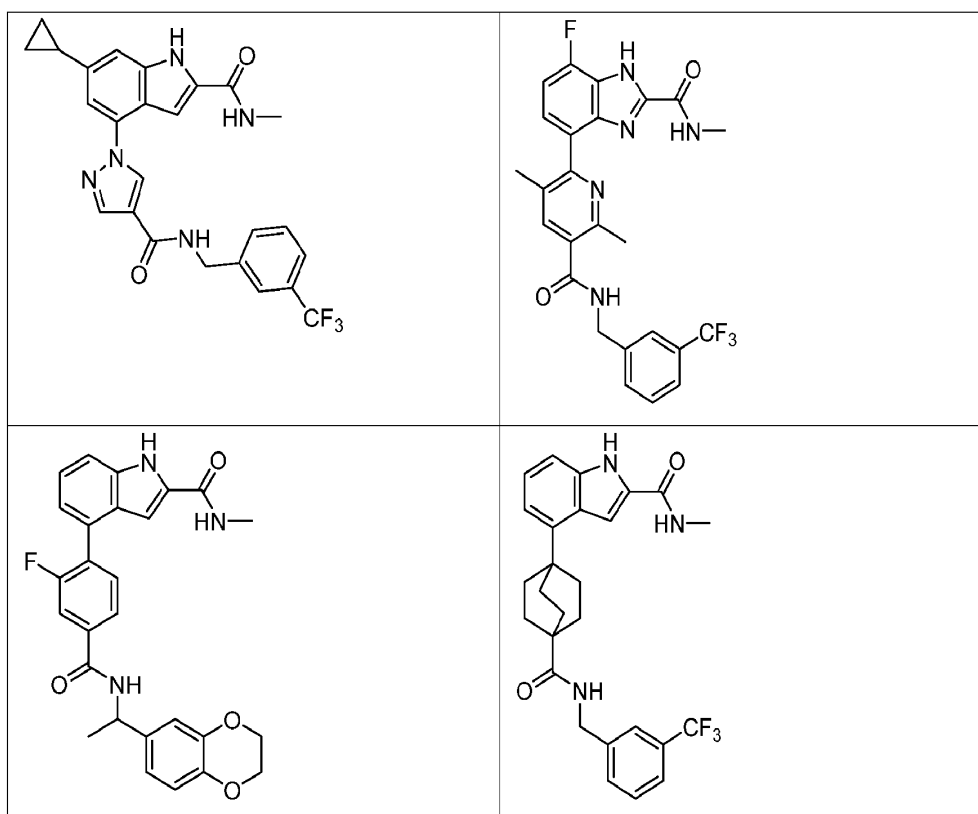




or a pharmaceutically acceptable salt thereof.

88. A compound selected from:





or a pharmaceutically acceptable salt thereof.

89. A pharmaceutical composition, comprising a compound of any one of
embodiments 1-88, or a pharmaceutically acceptable salt thereof; and a pharmaceutically
5 acceptable excipient.

90. A method of treating a disease or disorder associated with a genetic defect
in phenylalanine hydroxylase, comprising administering to a subject in need thereof an
effective amount of a compound of any one of embodiments 1-88, or a pharmaceutically
acceptable salt thereof; or a pharmaceutical composition as in embodiment 89.

10 91. A method of treating phenylketonuria, comprising administering to a
subject in need thereof an effective amount of a compound of any one of embodiments 1-
88, or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition as in
embodiments 89.

92. A method of treating hyperphenylalaninemia, comprising administering to a subject in need thereof an effective amount of a compound of any one of **embodiments 1-88**, or a **pharmaceutically acceptable salt thereof**; or a pharmaceutical composition as in **embodiment 89**.

5 93. The method of any one of **embodiments 91-92**, wherein the compound reduces systemic phenylalanine levels in the subject.

94. A method of treating or preventing tyrosinemia (Type I, II, or III), comprising administering to a subject in need thereof an effective amount of a compound of any one of **embodiments 1-88**, or a **pharmaceutically acceptable salt thereof**; or a
10 pharmaceutical composition as in **embodiment 89**.

95. The method of **embodiment 94**, wherein the compound reduces systemic tyrosine levels in the subject.

96. A method of treating or preventing nonketotic hyperglycinemia, comprising administering to a subject in need thereof an effective amount of a compound of any one
15 of **embodiments 1-88**, or a **pharmaceutically acceptable salt thereof**; or a pharmaceutical composition as in **embodiments 89**.

97. The method of **embodiments 96**, wherein the compound reduces systemic glycine levels in the subject.

98. A method of treating or preventing isovaleric acidemia, methylmalonic
20 acidemia, propionic acidemia, maple syrup urine disease, DNAJC12 deficiency, urea cycle disorders, or hyperammonemia, comprising administering to a subject in need thereof an effective amount of a compound of any one of **embodiments 1-88**, or a **pharmaceutically acceptable salt thereof**; or a pharmaceutical composition as in **embodiment 89**.

99. The method of any one of **embodiments 90-98**, wherein the compound inhibits
25 SLC6A19 in the subject.

100. A compound for use in the treatment of a disease or disorder associated with a genetic defect in phenylalanine hydroxylase, comprising administering to a subject in need thereof an effective amount of a compound of any one of **embodiments 1-88**, or a
30 **pharmaceutically acceptable salt thereof**; or a pharmaceutical composition as in **embodiment 89**.

101. A compound for use in the treatment of phenylketonuria, comprising administering to a subject in need thereof an effective amount of a compound of any one of embodiments 1-88, or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition as in embodiment 89.

5 102. A compound for use in the treatment of hyperphenylalaninemia, comprising administering to a subject in need thereof an effective amount of a compound of any one of embodiments 1-88, or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition as in embodiment 89.

10 103. A compound for use in the treatment of the diseases of embodiments 101 or 102, wherein the compound reduces systemic phenylalanine levels in the subject.

104. A compound for use in the treatment or prevention of tyrosinemia (Type I, II, or III), comprising administering to a subject in need thereof an effective amount of a compound of any one of embodiments 1-88, or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition as in embodiments 89.

15 102. A compound for use in the treatment or prevention of tyrosinemia as in embodiment 101, wherein the compound reduces systemic tyrosine levels in the subject.

20 103. A compound for use in the treatment or prevention of nonketotic hyperglycinemia, comprising administering to a subject in need thereof an effective amount of a compound of any one of embodiments 1-85, or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition as in embodiment 86.

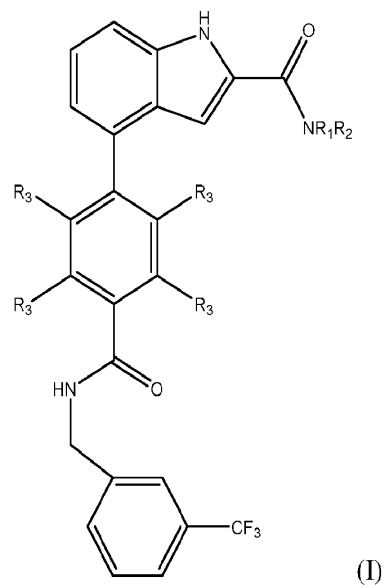
104. A compound for use in the treatment or prevention of nonketotic hyperglycinemia as in embodiment 103, wherein the compound reduces systemic glycine levels in the subject.

25 105. A compound for use in treating or preventing isovaleric acidemia, methylmalonic acidemia, propionic acidemia, maple syrup urine disease, DNAJC12 deficiency, urea cycle disorders, or hyperammonemia, comprising administering to a subject in need thereof an effective amount of a compound of any one of embodiments 1-85, or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition as in embodiment 86.

106. A compound for use in the treatment or prevention of the diseases of embodiments 97-105, wherein the compound inhibits SLC6A19 in the subject.

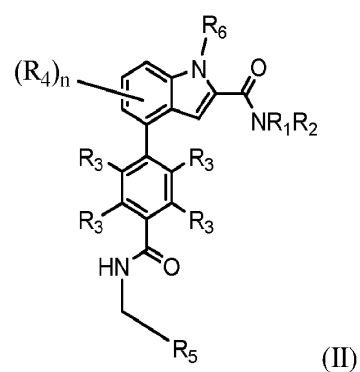
WHAT IS CLAIMED IS:

1. A compound of the formula:



- 5 wherein R_1 and R_2 are independently selected from H or CH_3 ;
 wherein each R_3 is independently selected from H, OH, CH_3 , O- CH_3 , CHF_2 , F, or Cl, wherein at least two R_3 are H;
 or a pharmaceutically acceptable salt thereof.

- 10 2. A compound of the formula:



wherein R_1 and R_2 are independently selected from H or CH_3 ;

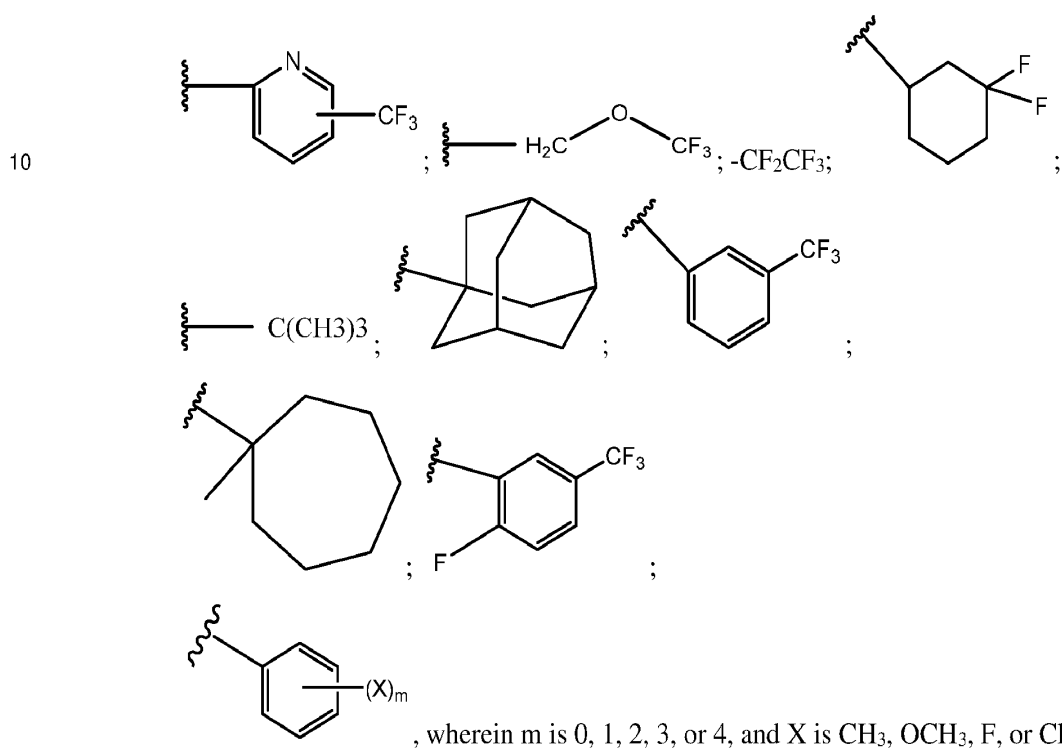
wherein each R_3 is independently selected from H, OH, CH_3 , O- CH_3 , CH_2F_2 , F, or Cl, wherein at least two R_3 are H;

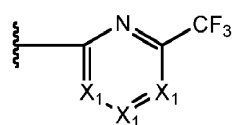
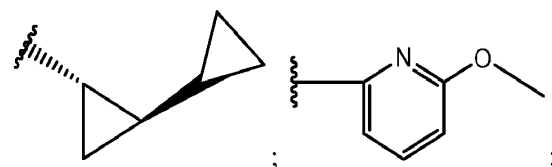
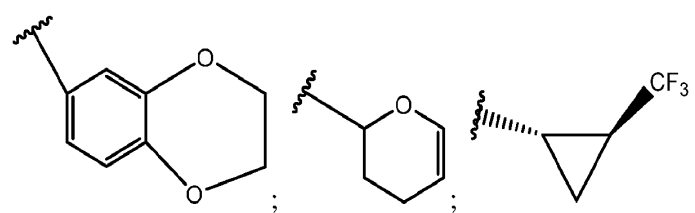
wherein n is 0, 1, 2, or 3;

5 wherein each occurrence of R_4 is independently selected from CH_3 , CF_3 , O- CH_3 , F, Cl, -CN, iso-propyl, or cyclopropyl;

wherein R_6 is H, $-CH_2CH_2OH$, or $-CH_2CH_2N(CH_3)_2$;

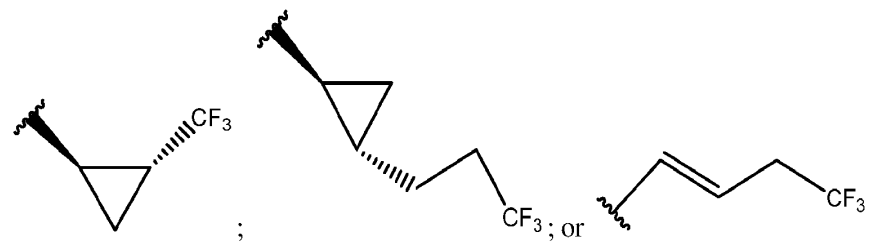
R_5 is:



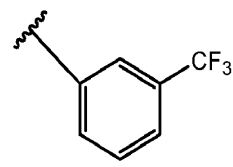


, wherein each X_1 is, independently, N or CH; provided that

one X_1 is N;

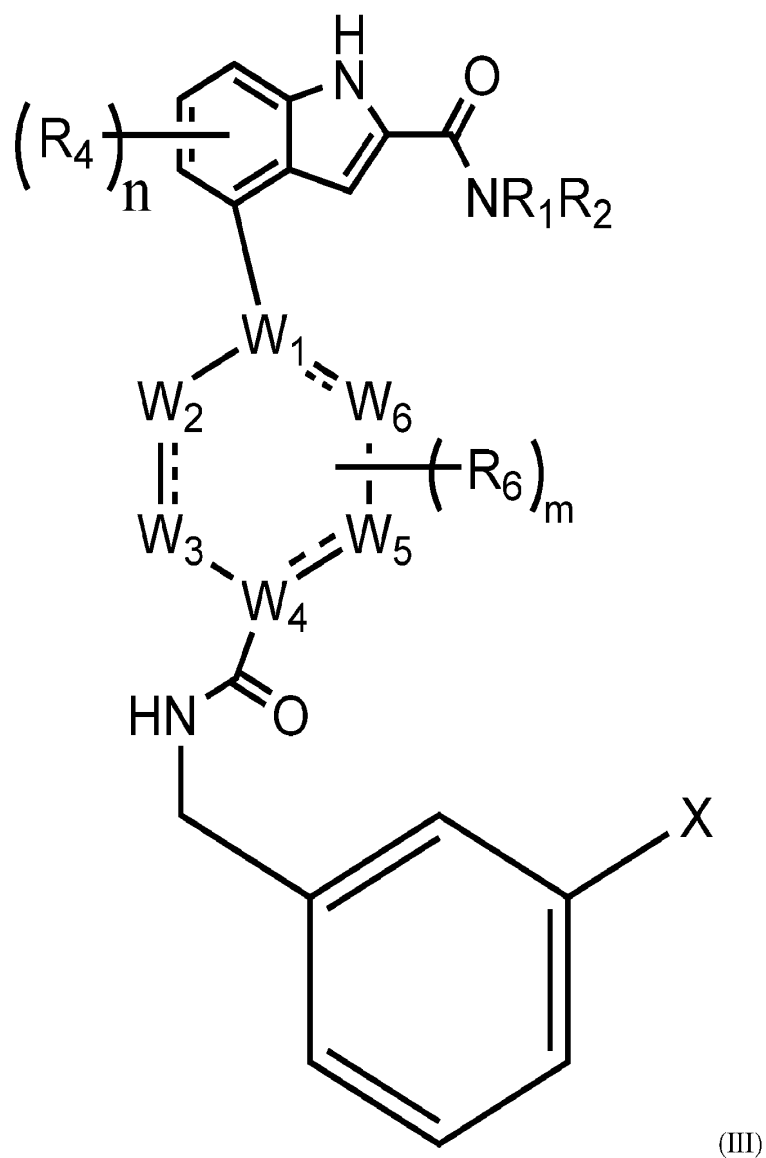


provided that n cannot be 0 when R_5 is:



or a pharmaceutically acceptable salt thereof.

3. A compound of the formula:



each of W_1 and W_4 is independently selected from N, C, or CH;

each of W_2, W_3, W_5 , and W_6 is independently selected from N, NH, CH, or CH_2 ;

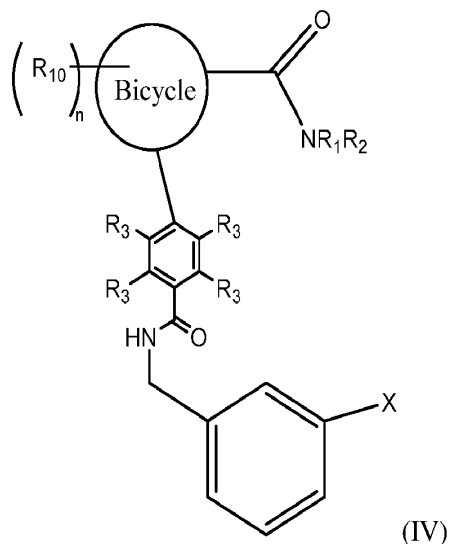
5 n is 0, 1, 2, or 3;

each occurrence of R_4 is, independently, cyclopropyl, Cl, F, CH_3 , isopropyl, CF_3 ,
-CN or OCH_3 ;

m is 0, 1, 2, or 3;

each occurrence of R_6 is, independently, F, Cl, or CH_3 ;
 wherein R_1 and R_2 are independently selected from H or CH_3 ;

4. A compound of the formula:



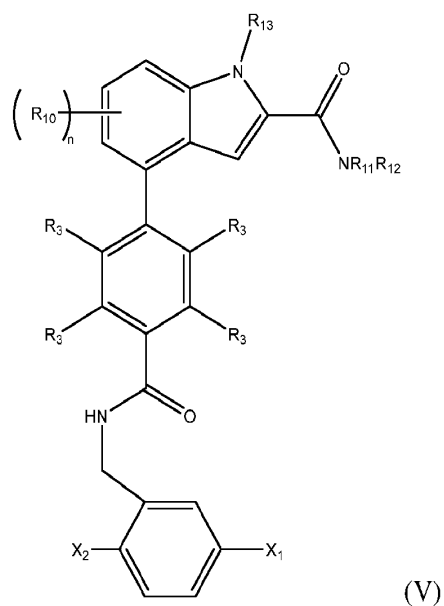
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wherein R_1 and R_2 are independently selected from H or CH_3 ;
 wherein each R_3 is independently selected from H, OH, CH_3 , O- CH_3 , CHF_2 , F, or Cl, wherein at least two R_3 are H;
 wherein n is 0, 1, or 2;
 wherein each occurrence of R_{10} is, independently, methyl, F, OH, H, OCH₃, CH_3 , or cyclopropyl;
 wherein X is H or CF_3 ; and
 wherein the bicycle is a bicyclic ring that includes 8-10 constituent ring atoms,
 wherein 1-4 of the atoms are heteroatoms independently selected from N, O, or S, and
 wherein each of the two rings is independently a saturated, unsaturated, or aromatic ring;
 or a pharmaceutically acceptable salt thereof.

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5. A compound having the formula:



R_{11} is $-(CH_2)_m-A$

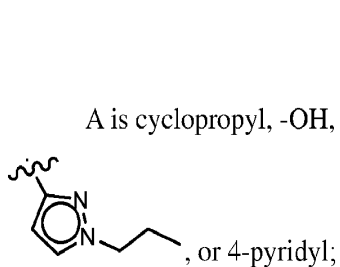
m is 0, 1, 2, or 3;

5

R_{12} is H;

R_{13} is H, $-CH_2CH_2OH$, or $-CH_2CH_2N(CH_3)_2$;

A is cyclopropyl, $-OH$, $-OCH_3$;



10

n is 0, 1, 2, or 3;

each occurrence of R_{10} is, independently, cyclopropyl, Cl, F, CH_3 , or OCH_3 ;

each R_3 is independently selected from H, OH, CH_3 , $O-CH_3$, CHF_2 , F, or Cl,

wherein at least two R_3 are H; and

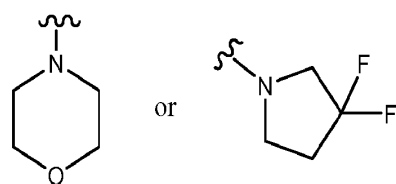
X_1 is H or CF_3 ;

15

X_2 is H or F;

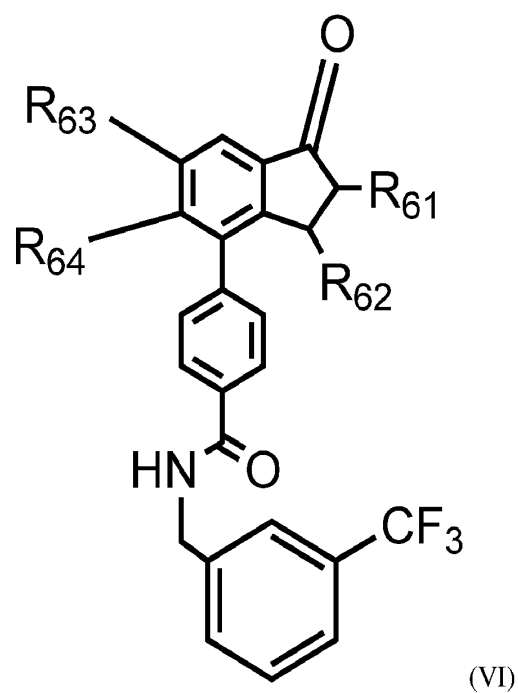
or R_{11} and R_{12} together with the nitrogen atom to which each is attached forms:

240



or a pharmaceutically acceptable salt thereof.

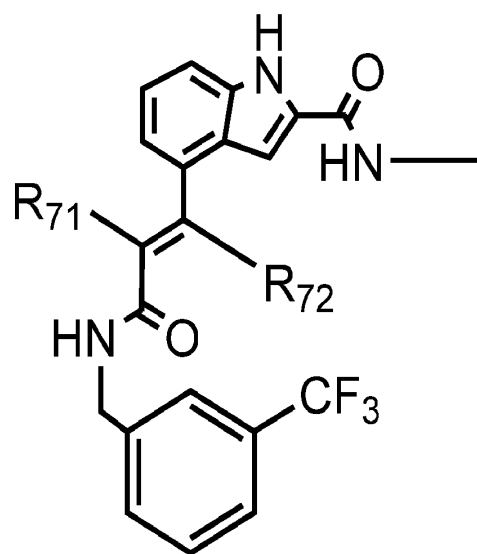
- 5 6. A compound having the formula:



(VI)

wherein each of R₆₁, R₆₂, R₆₃, and R₆₄ is independently selected from H and CH₃,
or a pharmaceutically acceptable salt thereof.

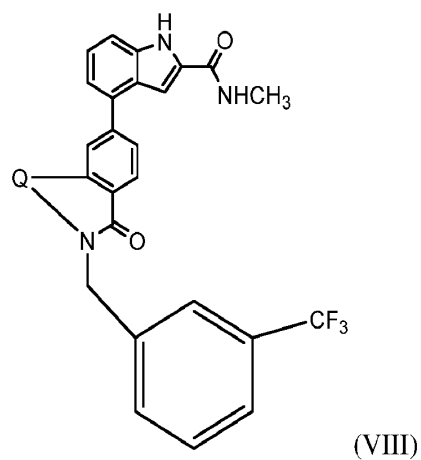
7. A compound having the formula:



(VII)

each of R₇₁ and R₇₂ is independently selected from H and CH₃, or a pharmaceutically acceptable salt thereof.

8. A compound having the formula:

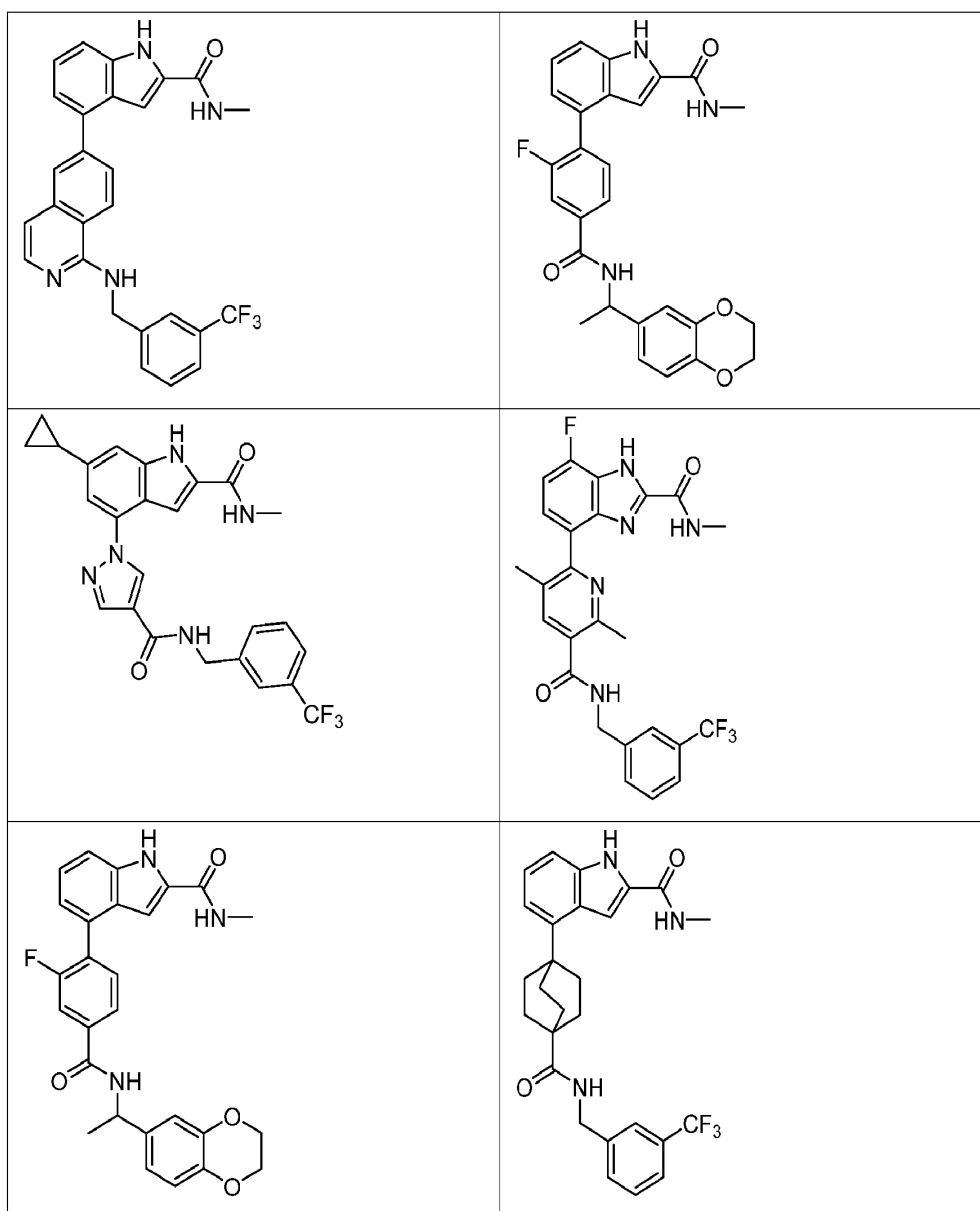


wherein Q is $(\text{CH}_2)_n$ where in a ring and n is 1, 2, or 3 thereby forming a 5, 6 or 7 membered ring, or a pharmaceutically acceptable salt thereof.

5

9. A compound selected from:

--	--



or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition, comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

11. A compound for use in the treatment of a disease or disorder associated with a genetic defect in phenylalanine hydroxylase, comprising administering to a subject in

need thereof an effective amount of a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition as claimed in claim 10.

5 12. A compound for use in the treatment of phenylketonuria, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition as claimed in claim 10.

10 13. A compound for use in the treatment of hyperphenylalaninemia, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-9 or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition as claimed in claim 10.

14. A compound for use in the treatment of the diseases recited in any of claims 11, 12, or 13 wherein the compound reduces systemic phenylalanine levels in the subject.

15 15. A compound for use in the treatment of the diseases recited in any of claims 11, 12, or 13, wherein the compound inhibits SLC6A19 in the subject.

20