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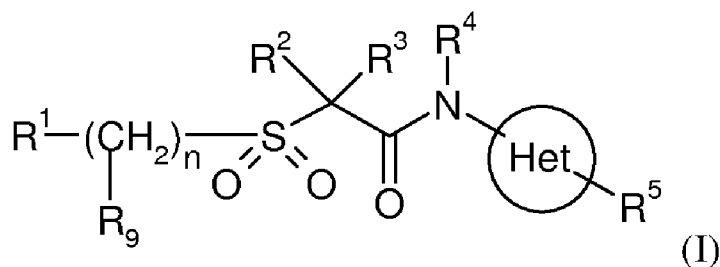
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(54) Title: COMPOUNDS WHICH SELECTIVELY MODULATE THE CB2 RECEPTOR



(57) **Abstract:** Compounds of formula I are disclosed. Compounds according to the invention bind to and are agonists, antagonists or inverse agonists of the CB2 receptor, and are useful for treating inflammation. Those compounds which are agonists are additionally useful for treating pain.

5

Compounds Which Selectively Modulate The CB2 Receptor

APPLICATION DATA

This application claims benefit to US provisional application serial no. 61/100,077 filed
10 September 25, 2008.

BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

The present invention relates to novel compounds which modulate the CB2 receptor and their
15 use as medicaments.

2. BACKGROUND INFORMATION

WO2008014199, WO2008039645 discuss the CB2 receptor, and the therapeutic uses of the
20 CB2 receptor agonist compounds disclosed therein. It is believed that the highly selective
activation of the CB2 receptor with an agonist may offer avenues of harnessing the beneficial
effects while avoiding the adverse effects seen with dual CB1/CB2 cannabinoid receptor
agonists (see e.g. Expert Opinion on Investigational Drugs (2005), 14(6), 695-703). It is
desirable therefore to provide agonists of CB2 with minimized CB1 activity.

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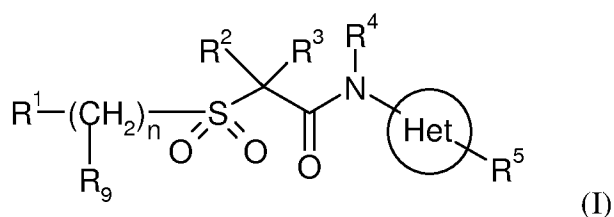
WO2008014199, WO2008039645 and WO 2009061652 disclose sulfone derivatives having
CB2 agonist activity. The compounds of the present invention differ structurally from the
above disclosed compounds, for example the present R⁵ in the formula (I) disclosed
hereinbelow. Additionally, the compounds of the present invention have lower CB1 activity
30 than the compounds disclosed in the cited art.

5 BRIEF SUMMARY OF THE INVENTION

The present invention provides novel compounds which bind to and modulate the CB2 receptor and have lower CB1 receptor activity. The invention also provides methods and pharmaceutical compositions for treating inflammation by way of the administration of therapeutic amounts of the compounds of the invention. Lastly, the invention provides a method and pharmaceutical compositions for treating pain by way of the administration of therapeutic amounts of the compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION

15 In the broadest generic embodiment 1, the invention provides compounds of the formula



wherein:

20

Het is a 5-membered heteroaryl ring optionally substituted by C₁₋₅ alkyl;

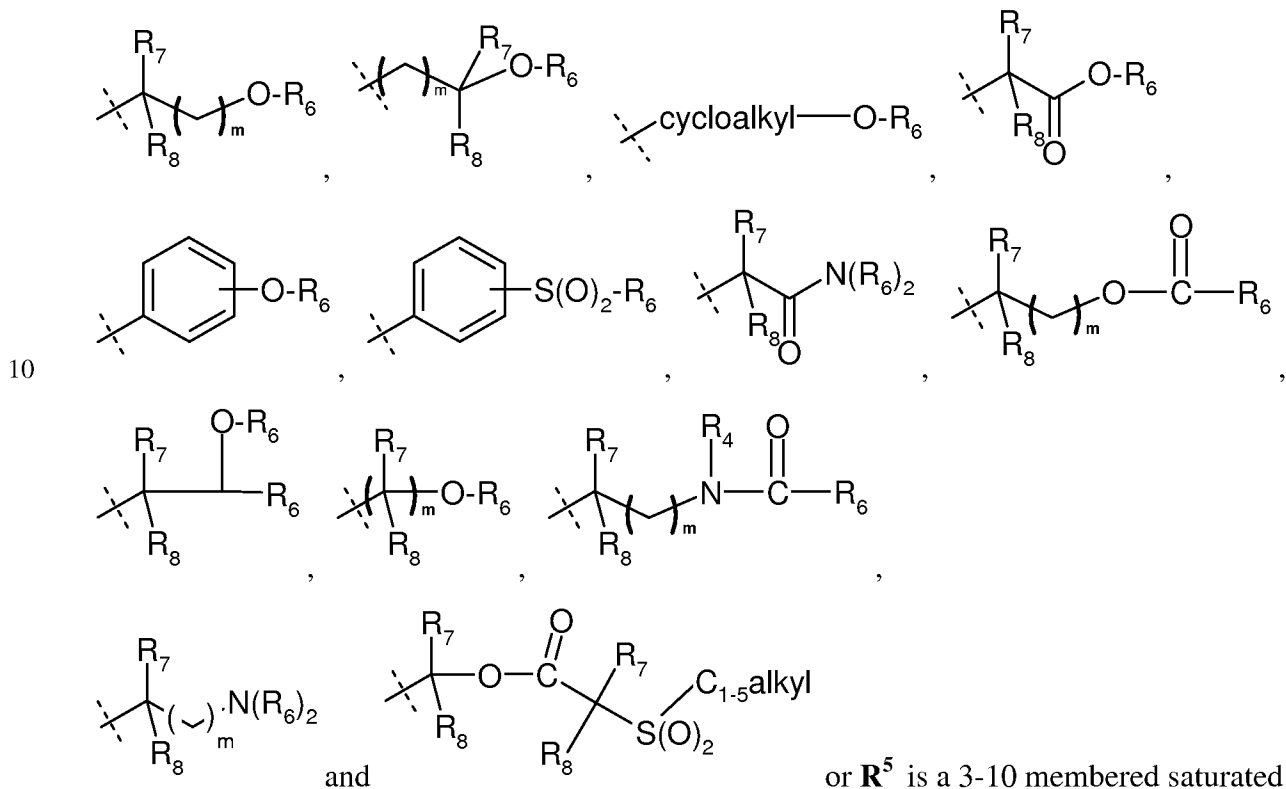
R¹ is C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl, 3-10 membered saturated heterocyclic ring, 5-10 membered mono or bicyclic heteroaryl ring or phenyl each optionally independently substituted with 1-3 substituents chosen from C₁₋₈ alkyl, C₁₋₄ alkoxy, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkylC₁₋₅ alkyl, C₁₋₄ alkylsulfonyl, C₁₋₄ acyl, oxo, cyano, phenyl, hydroxyl and halogen;

R² and **R³** are C₁₋₄ alkyl or hydrogen with the proviso that both R² and R³ cannot be hydrogen; or R² and R³ together with the carbon atom to which they are attached form a 3- to 6-membered cycloalkyl or heterocyclic ring;

5

R^4 is hydrogen or methyl;

R^5 is chosen from



heterocyclic ring optionally substituted with 1-3 C_{1-4} alkyl;

m is 0, 1, 2 or 3;

15

each R^6 is independently hydrogen, C_{1-6} alkyl, 3-10 membered saturated heterocyclic ring, aryl, benzyl or $-(CH_2)_{1-3}-O-(CH_2)_{0-1}-X$ wherein X is aryl or CH_3 each heterocyclic, benzyl or aryl ring is optionally substituted by one or more C_{1-4} alkyl, C_{1-4} alkoxy or halogen; wherein R^7 and R^8 are each independently hydrogen or C_{1-4} alkyl with the proviso that both R^7 and R^8 cannot be hydrogen, and wherein R^7 and R^8 optionally can cyclize to form a C_{3-7} cycloalkyl ring;

20

5 **R₉** is C₁₋₄ alkyl which replaces a methylene hydrogen on -(CH₂)_n- or is absent;

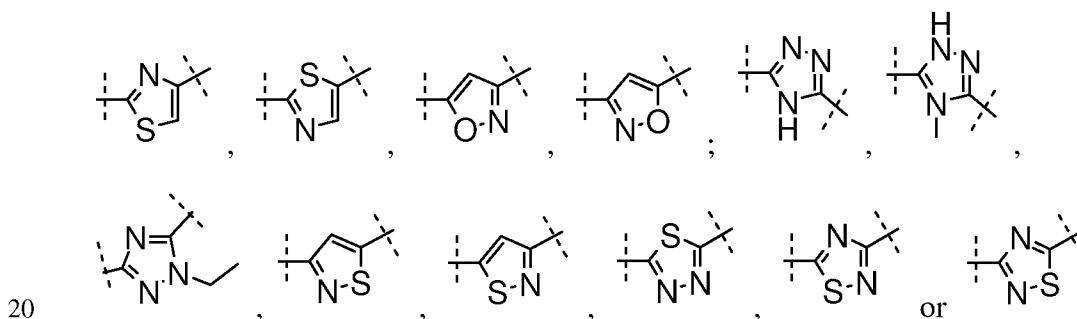
n is 0, 1 or 2;

wherein any carbon atom on the formula (I) or any R substituent listed above is optionally
10 partially or fully halogenated where possible;

or a pharmaceutically acceptable salt thereof.

15 In another embodiment 2, the invention provides compounds of the formula (I) according to any of the preceding embodiments described above, and wherein

Het is



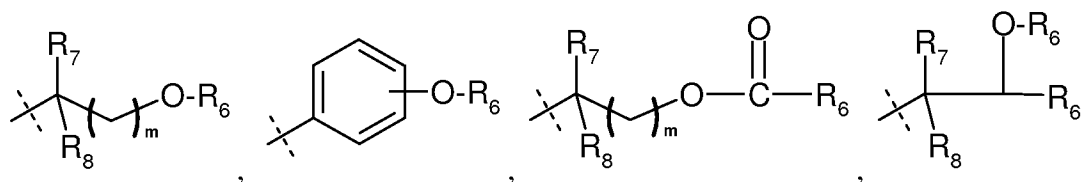
R¹ is C₁₋₆ alkyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, piperidiny; benzoxazolyl, benzothiazolyl, benzimidazolyl, dioxalanyl, dioxanyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, pyrrolyl, imidazolyl, thienyl, thiomorpholinyl, 1,1-Dioxo-1λ⁶-thiomorpholinyl, morpholinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolidinyl, piperazinyl, purinyl, quinolinyl, Dihydro-2H-quinolinyl, isoquinolinyl, quinazolinyl, indazolyl, indolyl, benzofuranyl, benzopyranyl or benzodioxolyl each optionally substituted

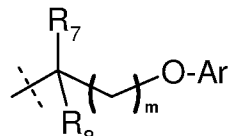
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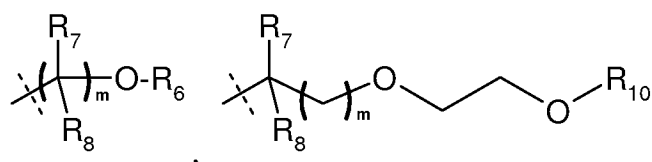
- 5 by 1-2 substituents chosen from halogen, C₁₋₆ alkyl, hydroxyl, C₁₋₄ alkoxy, C₁₋₄ alkylsulfonyl, C₃₋₁₀ cycloalkyl, C₁₋₅ alkyl or oxo;

- R**² and **R**³ are independently methyl, ethyl, n-propyl, isopropyl, or hydrogen with the proviso that both **R**² and **R**³ cannot be hydrogen; or **R**² and **R**³ together with the carbon to
10 which they are attached form a cyclopropyl, cyclobutyl, or cyclopentyl ring;

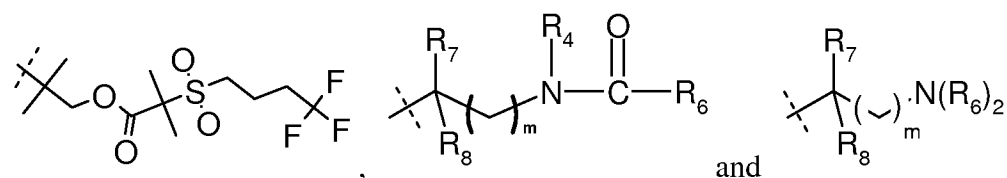
R⁵ is chosen from



- 15 **R**⁵ is chosen from  wherein Ar tetrahydropyranyl or tetrahydrofuranyl each optionally substituted by C₁₋₃ alkyl,



wherein **R**₁₀ is hydrogen or methyl,



or **R**⁵ is tetrahydropyranyl or tetrahydrofuranyl each optionally substituted by C₁₋₃ alkyl;

20

R⁶ is hydrogen, benzyl, phenyl or C₁₋₄ alkyl, each benzyl or phenyl ring is optionally substituted by one or more C₁₋₄ alkyl, C₁₋₄ alkoxy or halogen;

- 5 **R**⁷ and **R**⁸ are each C₁₋₃ alkyl or C₃₋₆ cycloalkyl wherein **R**⁷ and **R**⁸ optionally can cyclize to form a C₃₋₆ cycloalkyl ring.

In another embodiment 3, the invention provides compounds of the formula (I) according to any of the preceding embodiments described above, and wherein

10

R¹ is C₁₋₅ alkyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, dioxalanyl, dioxanyl, azetidiny, piperidiny, benzimidazolyl, pyrrolyl, pyridiny, pyrimidiny, pyridaziny, pyraziny, pyrrolidiny or piperaziny, each optionally substituted by 1-2 substituents chosen from halogen, C₁₋₆ alkyl, C₁₋₄ alkylsulfonyl, C₃₋₁₀ cycloalkyl, C₁₋₅ alkyl, hydroxyl, C₁₋₄ alkoxy and oxo;

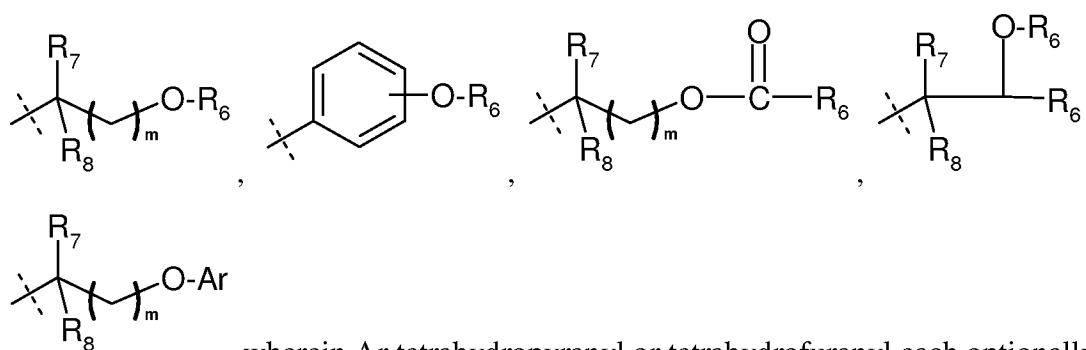
15

R² and **R**³ are independently methyl, ethyl, n-propyl, isopropyl or hydrogen with the proviso that both **R**² and **R**³ cannot be hydrogen; or **R**² and **R**³ together with the carbon to which they are attached form a cyclopropyl, cyclobutyl or cyclopentyl ring;

20

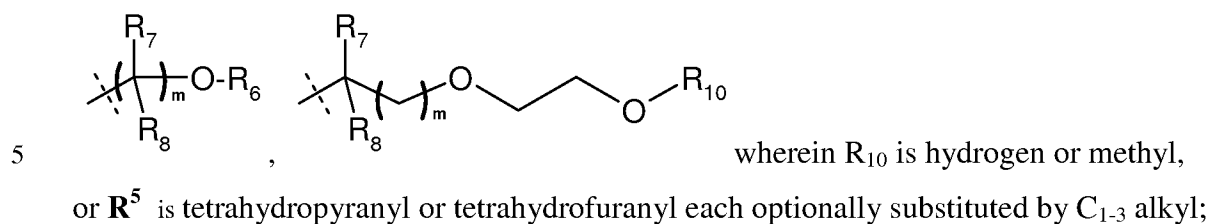
n is 0 or 1;

R⁵ is chosen from



25

wherein Ar tetrahydropyranyl or tetrahydrofuranyl each optionally substituted by C₁₋₃ alkyl,



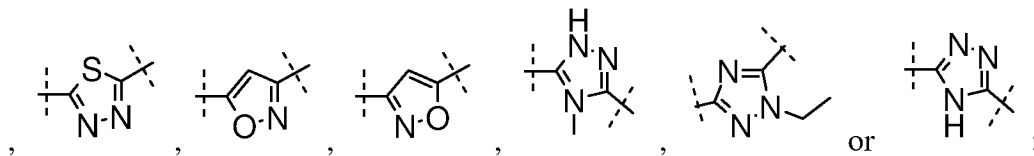
R^6 is hydrogen, benzyl, phenyl or C_{1-4} alkyl, each benzyl or phenyl ring is optionally substituted by one or more C_{1-4} alkyl, C_{1-4} alkoxy or halogen;

10

R^7 and R^8 are each C_{1-3} alkyl or C_{3-6} cycloalkyl wherein R^7 and R^8 optionally can cyclize to form a C_{3-6} cycloalkyl ring.

15 In another embodiment 4, the invention provides compounds of the formula (I) according to any of the preceding embodiments described above, and wherein

Het is



20 R^1 is phenyl or benzimidazolyl each optionally substituted by 1-2 substituents chosen from halogen, C_{1-6} alkyl, C_{1-4} alkylsulfonyl, C_{3-6} cycloalkyl, C_{1-3} alkyl, or oxo;

or R^1 is C_{1-5} alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl, tetrahydrofuranyl, azetidiny, pyrrolidinyl or piperidinyl each optionally substituted by a substituent chosen from by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylsulfonyl or oxo;

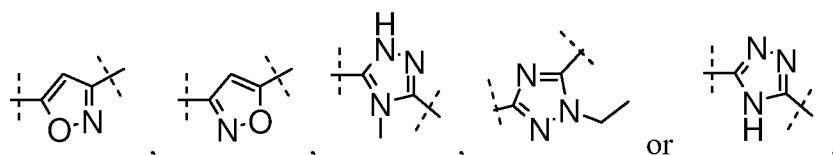
25 R^2 and R^3 are independently methyl, or R^2 and R^3 together with the carbon to which they are attached form a cyclopropyl or cyclobutyl ring

R^7 and R^8 are each C_{1-2} alkyl wherein R^7 and R^8 optionally can cyclize to form a C_{3-6} cycloalkyl ring.

5

In another embodiment 5, the invention provides compounds of the formula (I) according to any of the preceding embodiments described above, and wherein

10 **Het** is

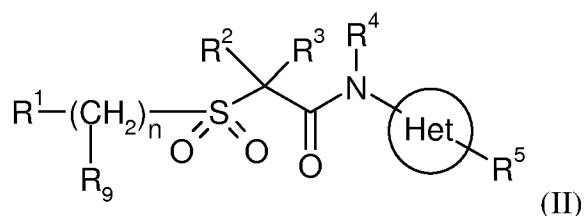


In another embodiment 6, the invention provides compounds of the formula (I) according to any of the preceding embodiments described above, and wherein

R¹ is phenyl or benzimidazolyl each optionally substituted by 1-2 substituents chosen from halogen, C₁₋₆ alkyl or C₃₋₅ cycloalkyl; C₁₋₃ alkyl;

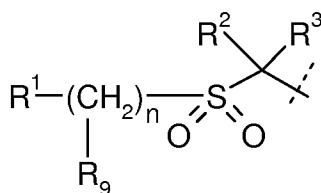
20 or **R¹** is C₁₋₅ alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl, tetrahydrofuranyl or piperidinyll each optionally substituted by a substituent chosen from by halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy or C₁₋₄ alkylsulfonyl.

25 In another embodiment there is provided a compound of the formula (II)

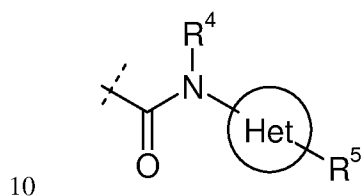


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wherein



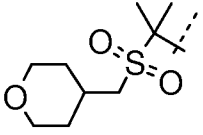
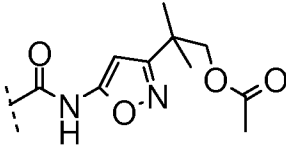
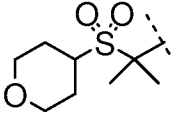
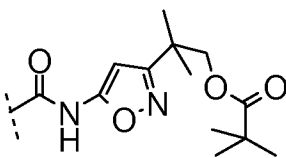
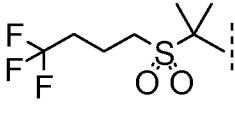
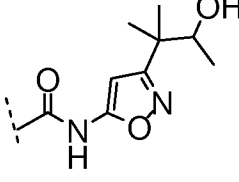
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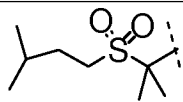
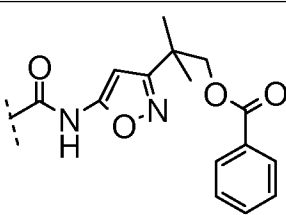
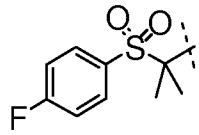
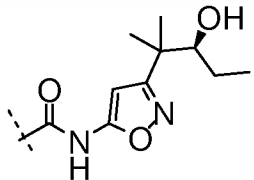
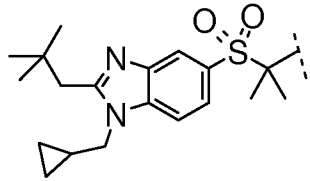
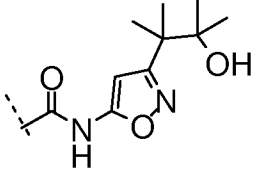
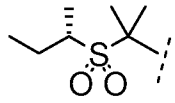
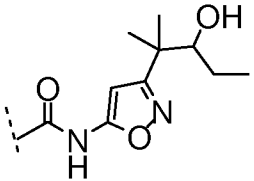
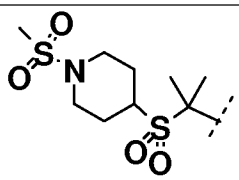
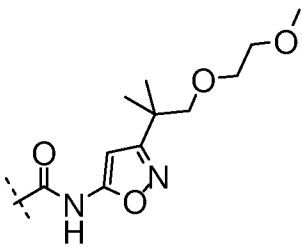
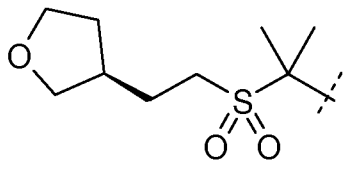
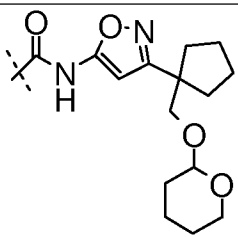


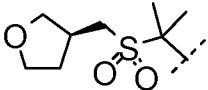
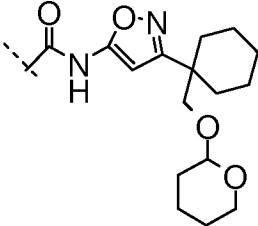
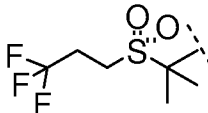
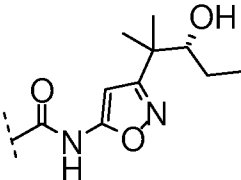
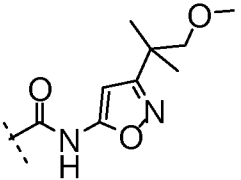
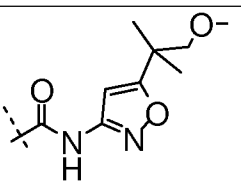
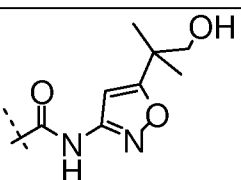
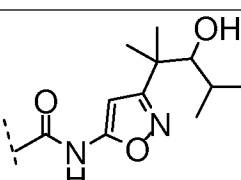
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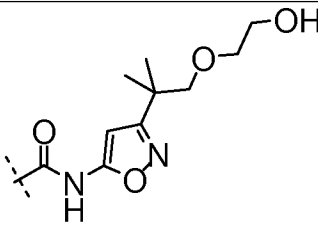
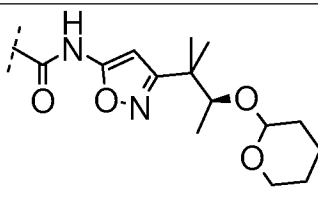
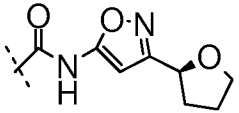
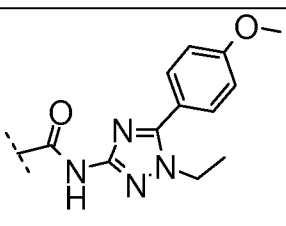
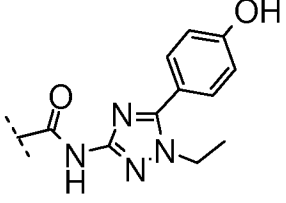
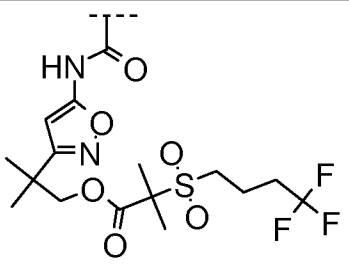
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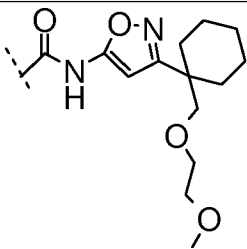
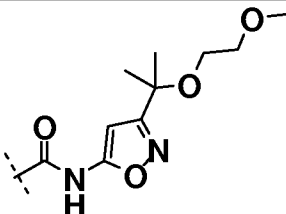
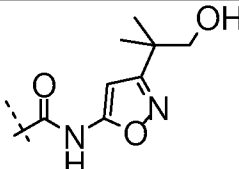
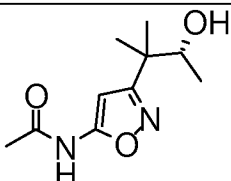
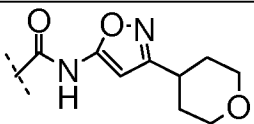
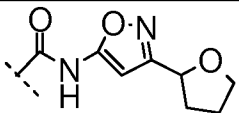
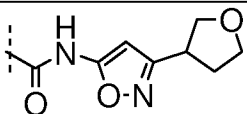
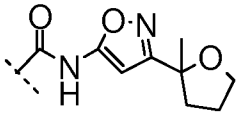
Table I

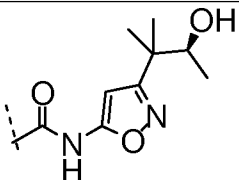
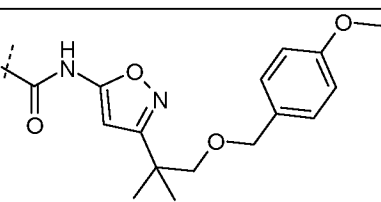
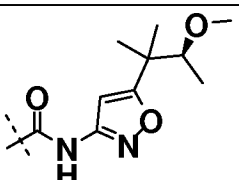
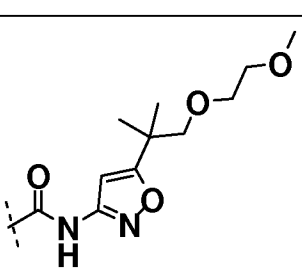
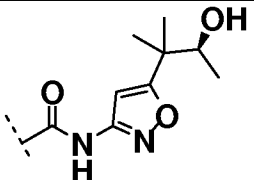
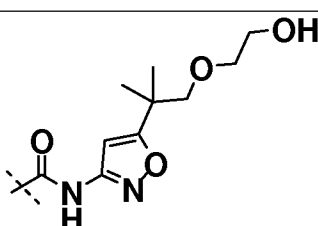
A1		B1	
A2		B2	
A3		B3	

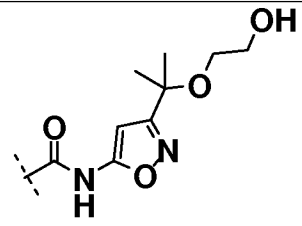
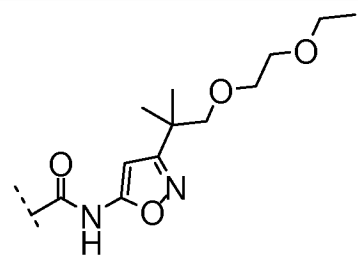
A4		B4	
A5		B5	
A6		B6	
A7		B7	
A8		B8	
A9		B9	

A10		B10	
A11		B11	
		B12	
		B13	
		B14	
		B15	

		B16	
		B17	
		B18	
		B19	
		B20	
		B21	

		B22	
		B23	
		B24	
		B25	
		B26	
		B27	
		B28	
		B29	

		B30	
		B30	
		B31	
		B32	
		B33	
		B34	

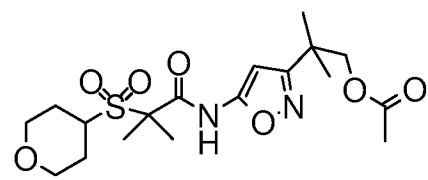
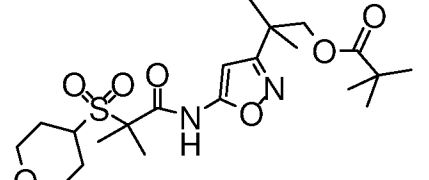
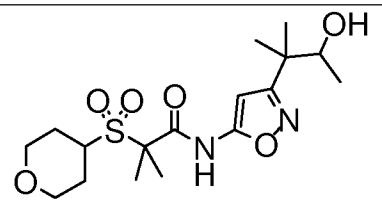
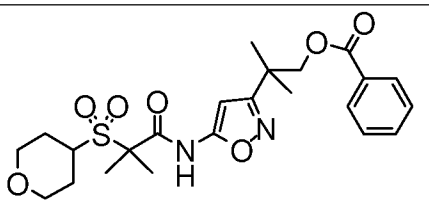
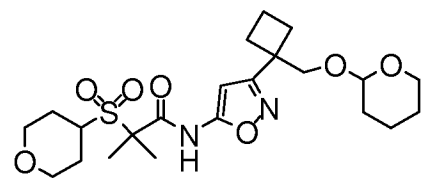
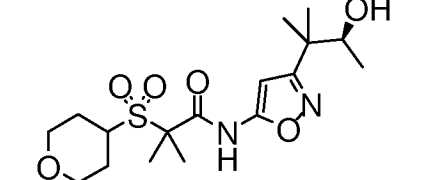
		B35	
		B36	

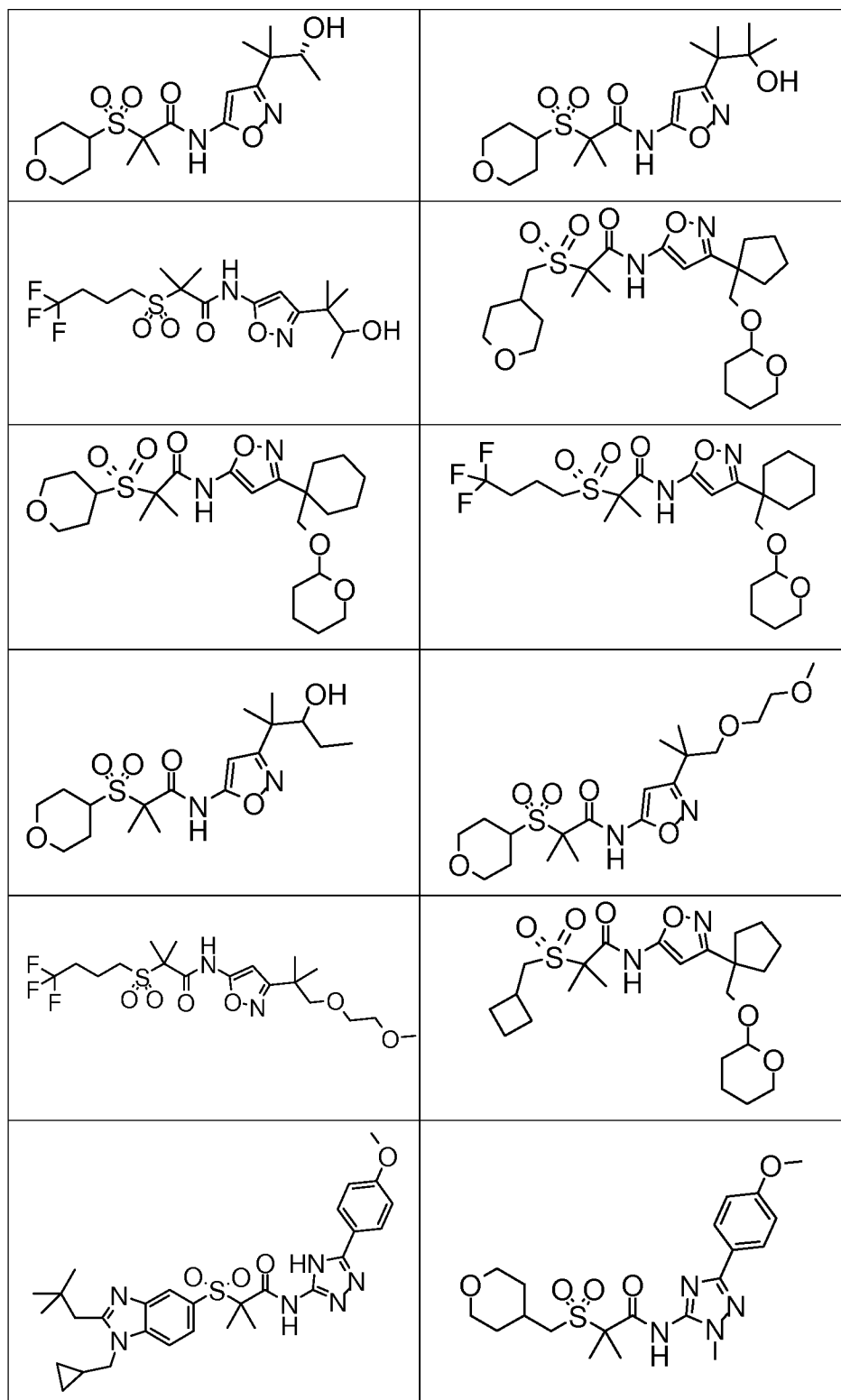
5 or a pharmaceutically acceptable salt thereof.

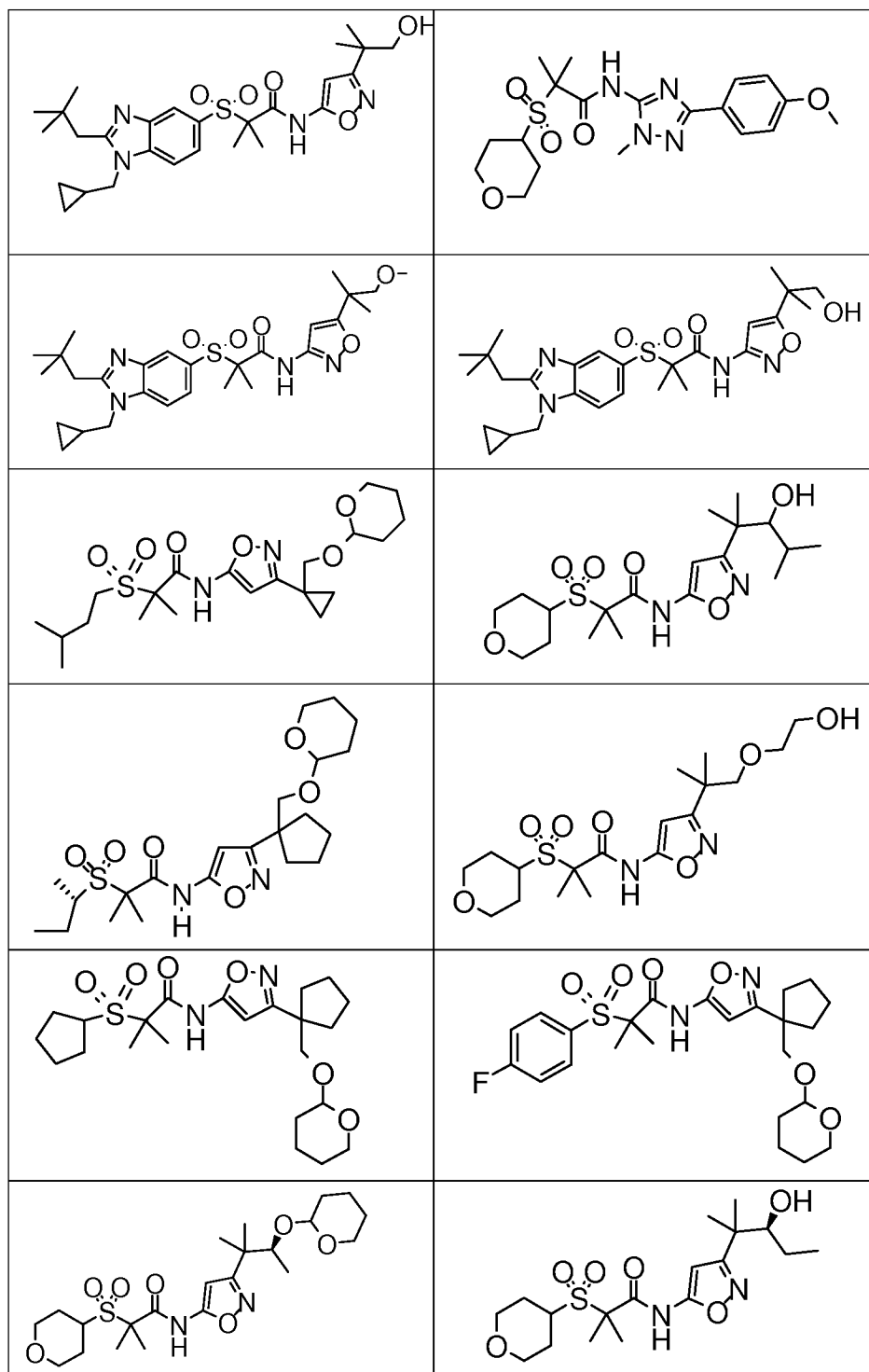
In another embodiment, the invention provides made compounds in Table II which can be made in view of the general schemes, examples and methods known in the art.

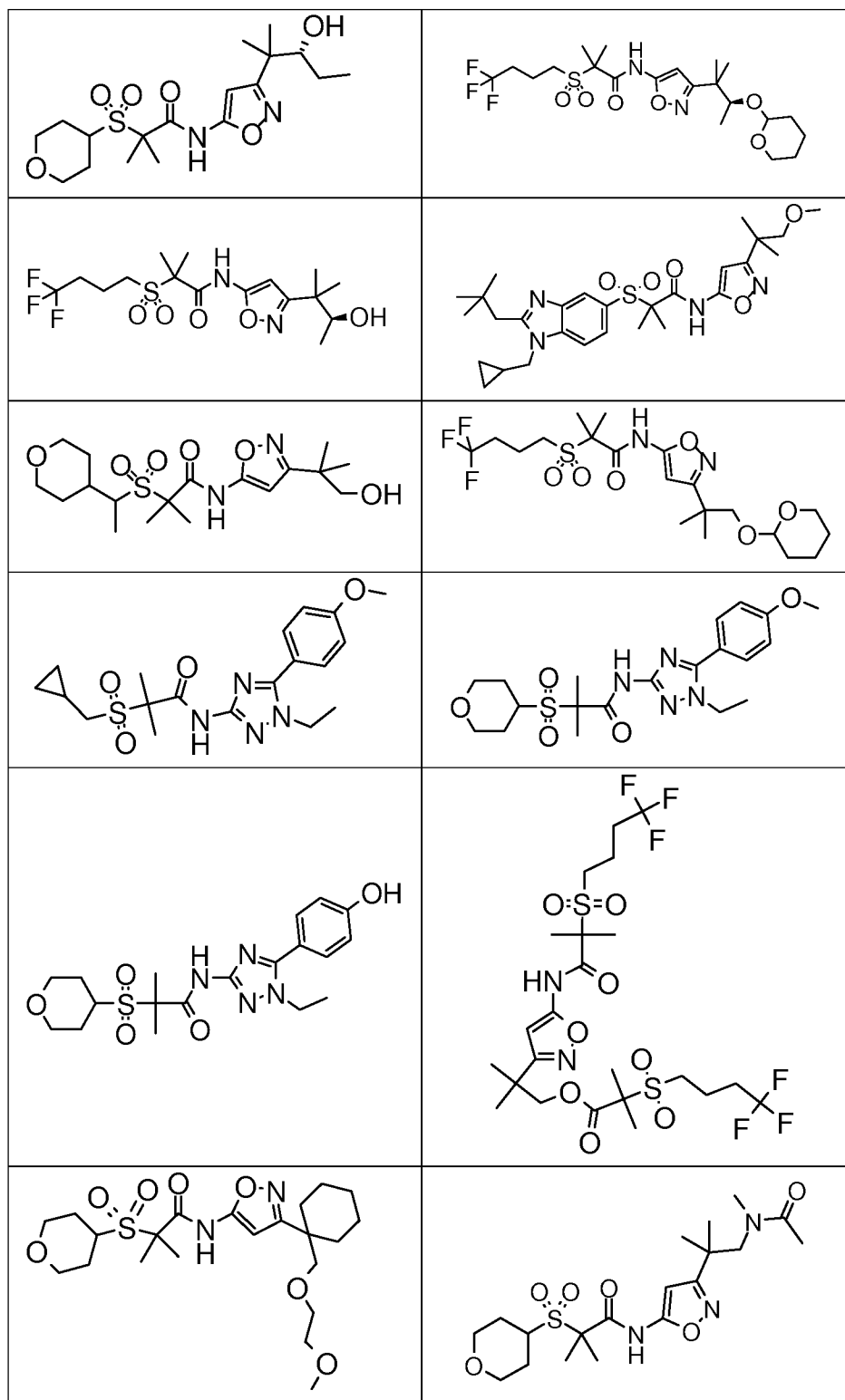
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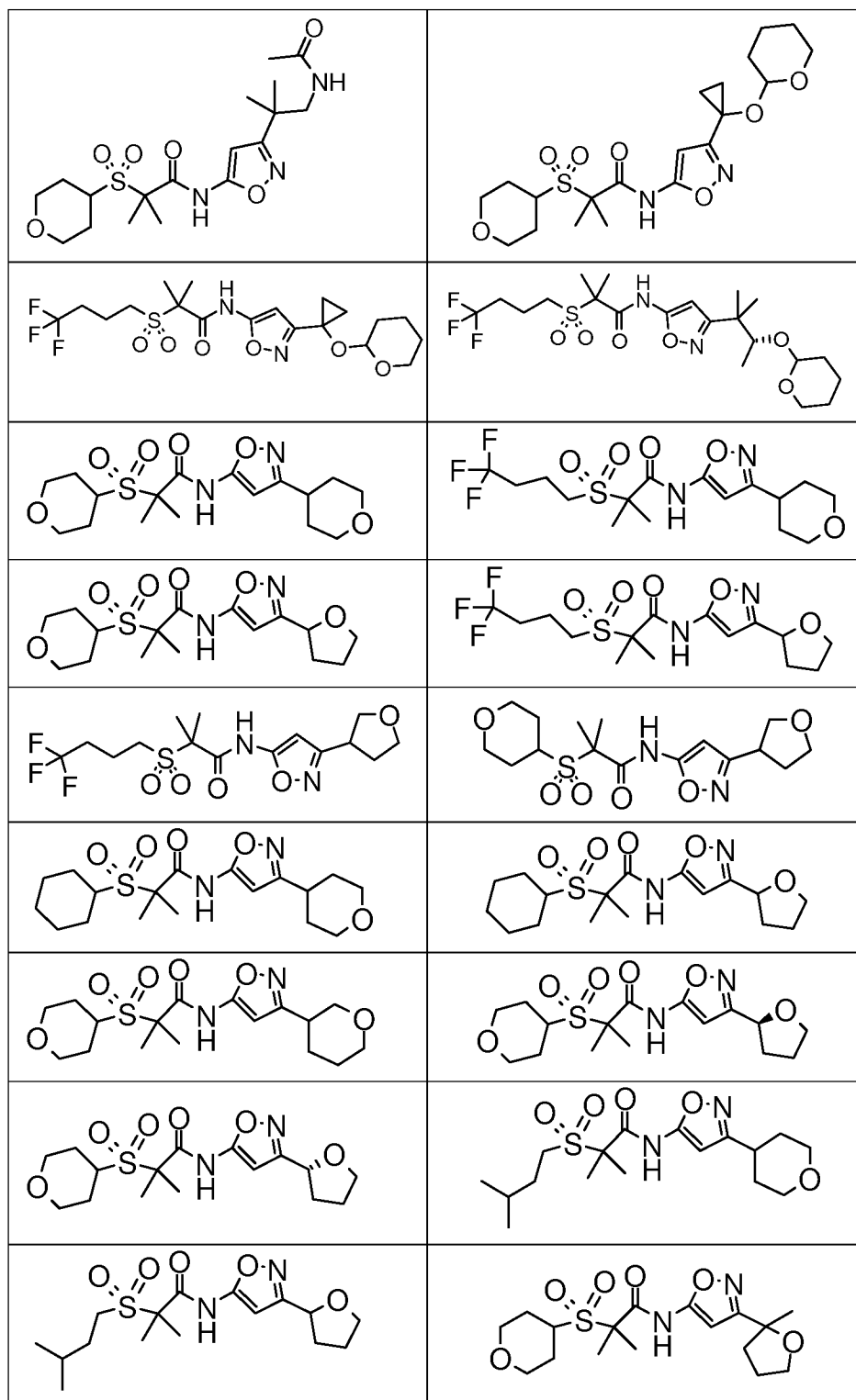
Table II

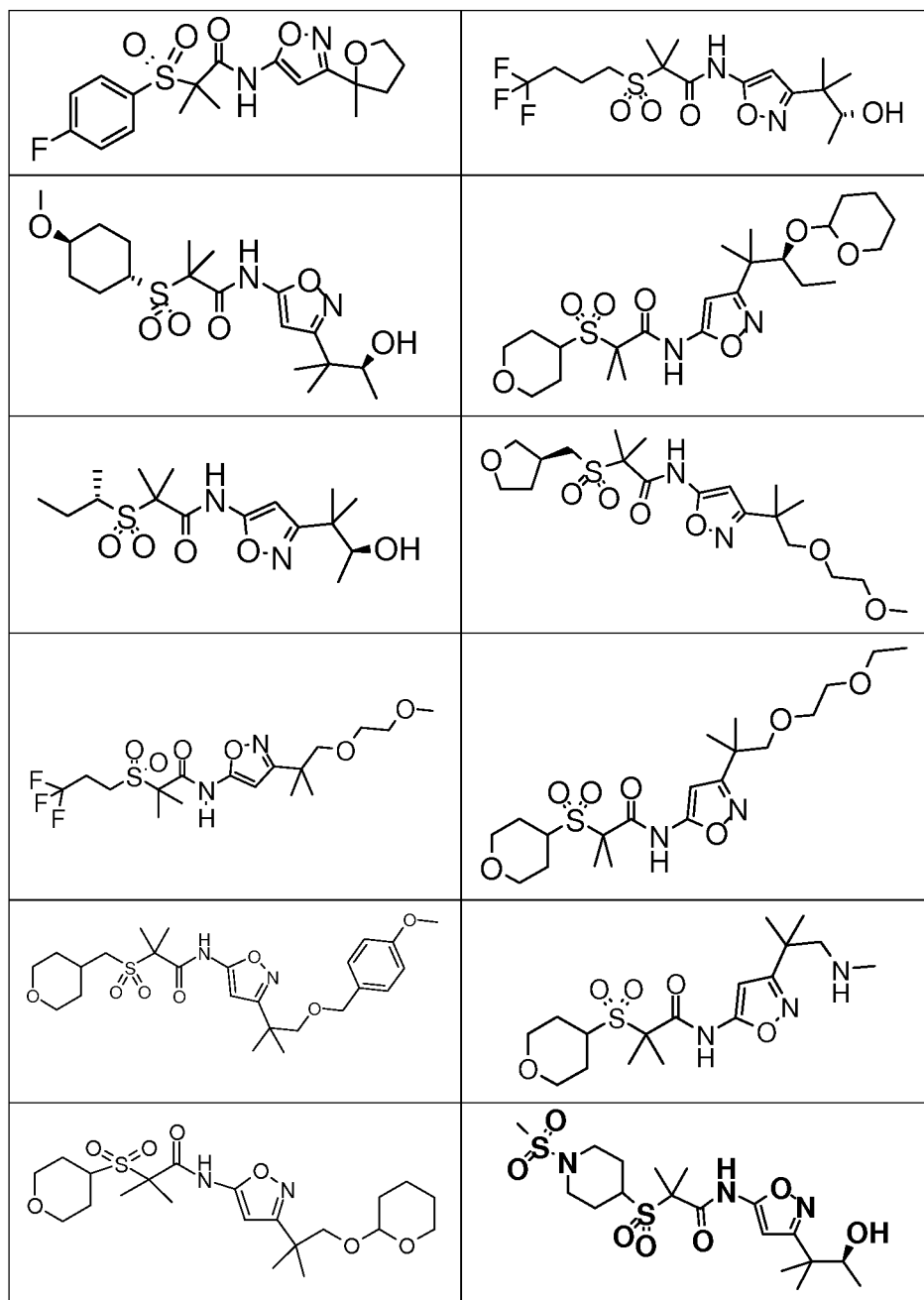
	
	
	

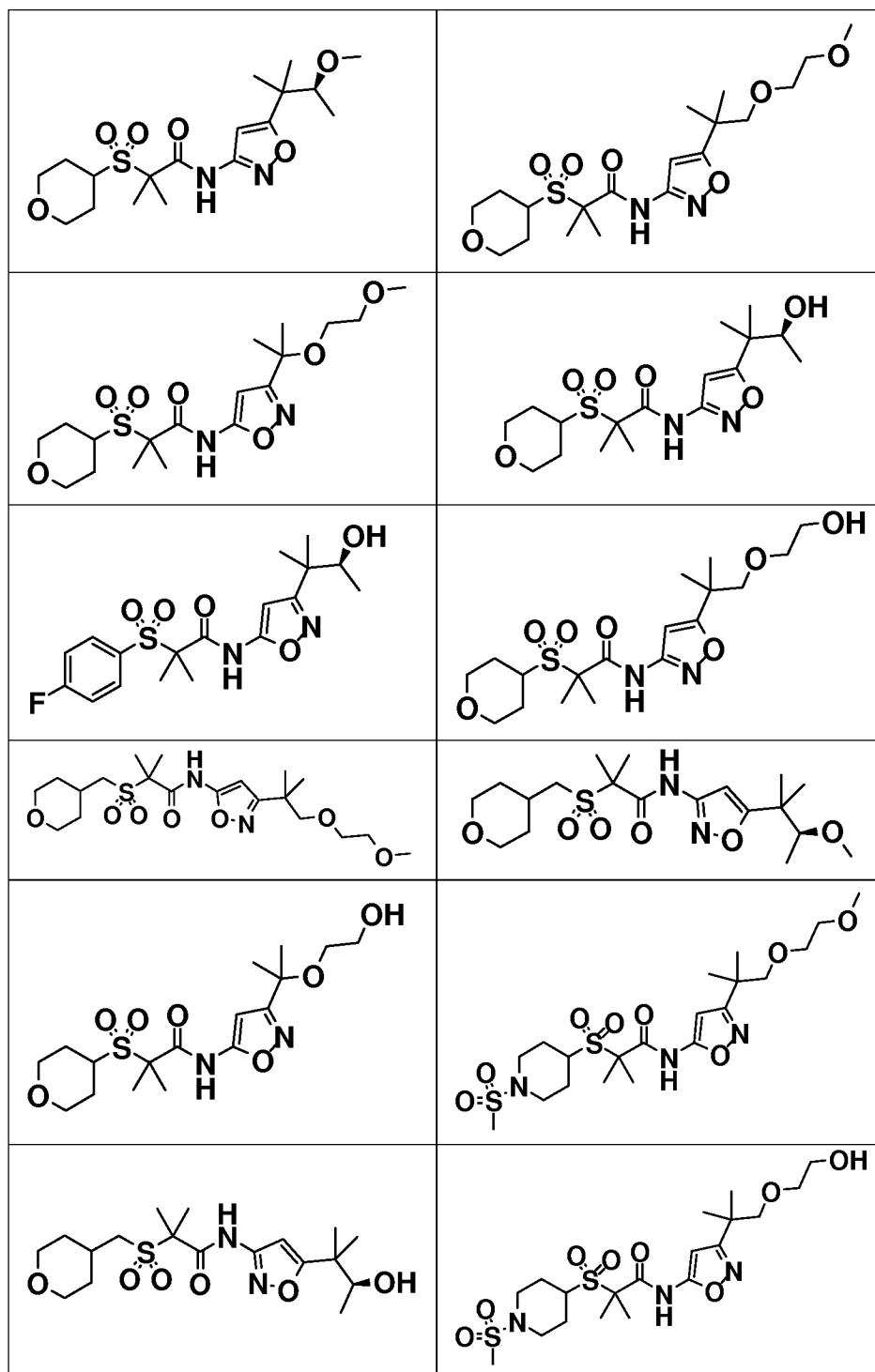


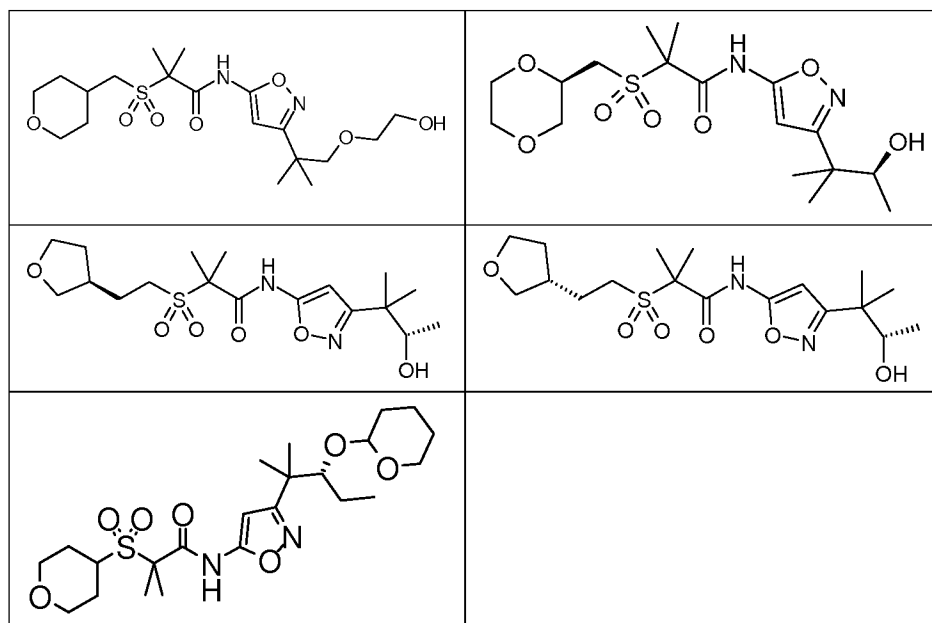












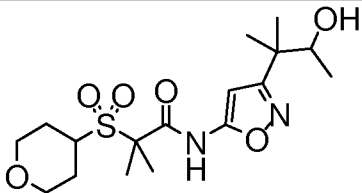
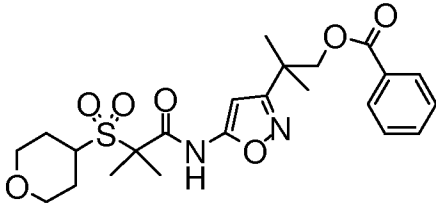
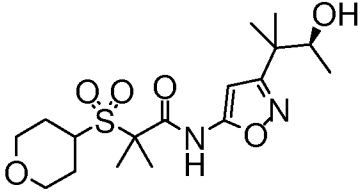
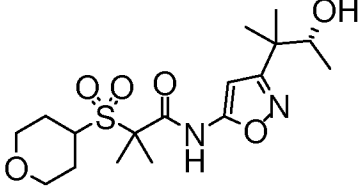
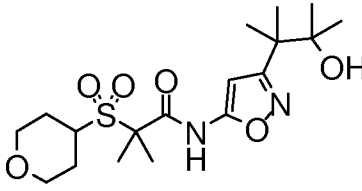
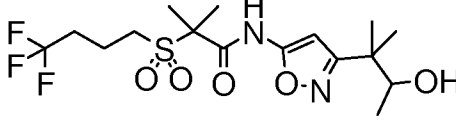
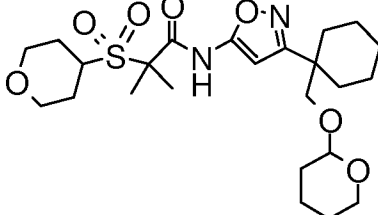
5 or a pharmaceutically acceptable salt thereof.

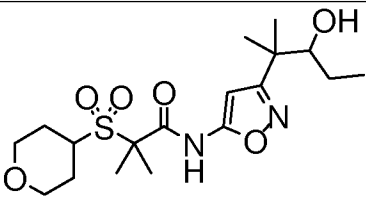
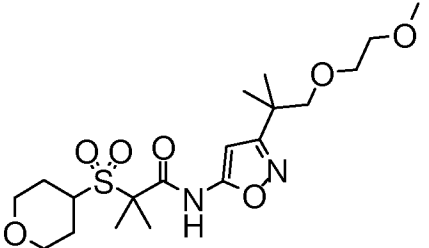
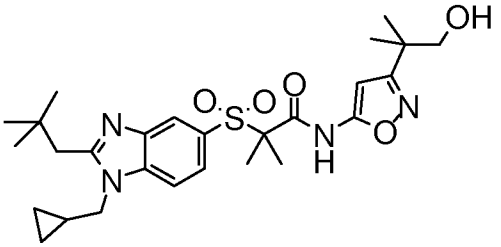
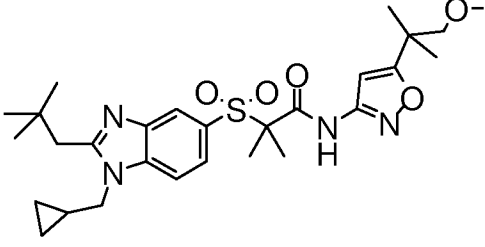
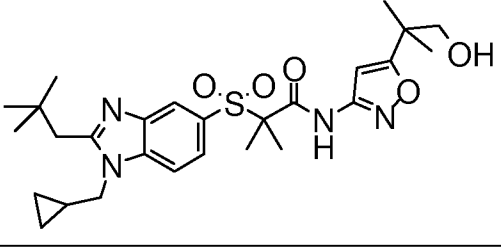
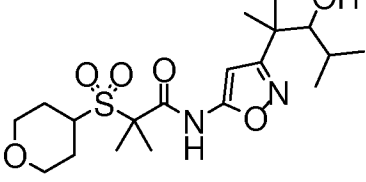
Of the above compounds, the following are preferred CB2 agonists:

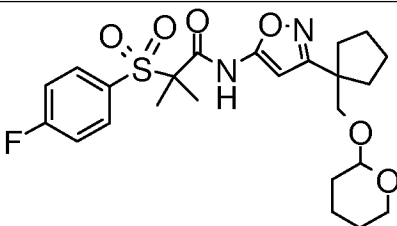
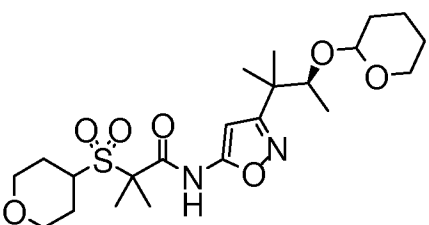
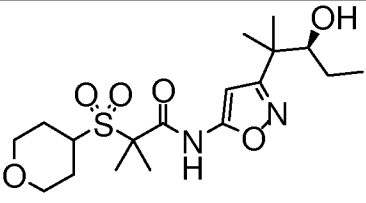
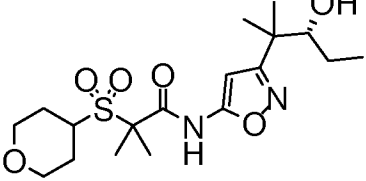
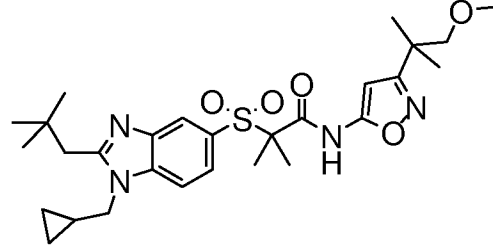
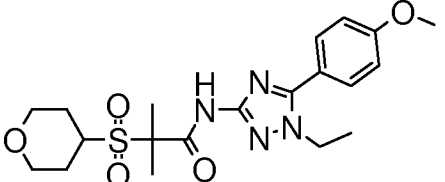
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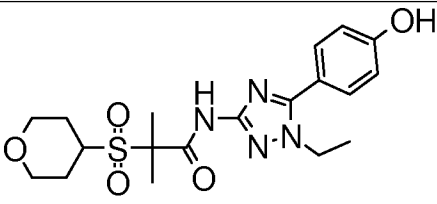
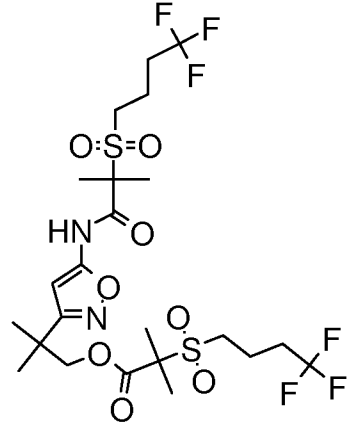
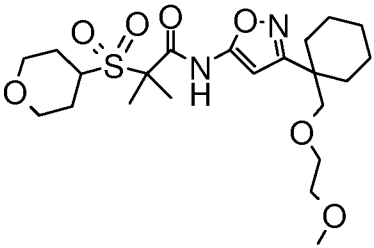
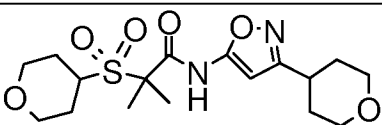
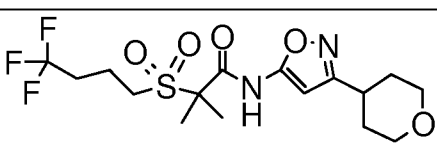
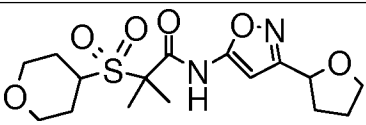
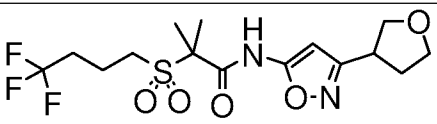
Table III

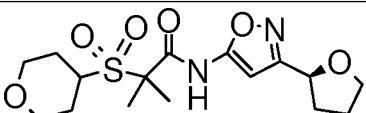
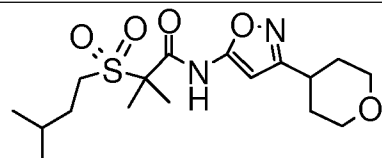
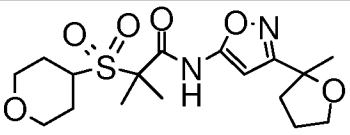
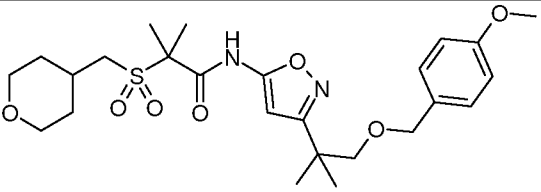
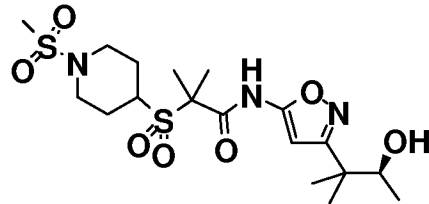
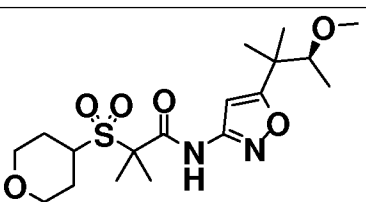
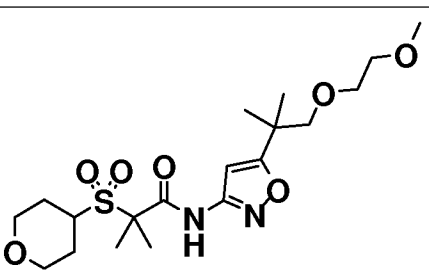
Compound	CB2 EC ₅₀ (nM)	CB1 EC ₅₀ (nM)
	4.2	>50000
	50	>50000

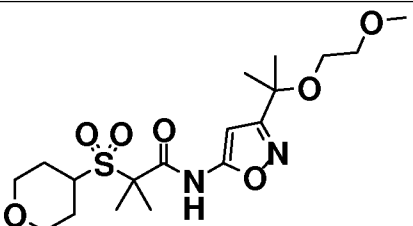
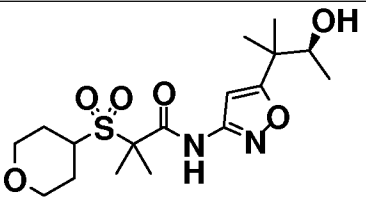
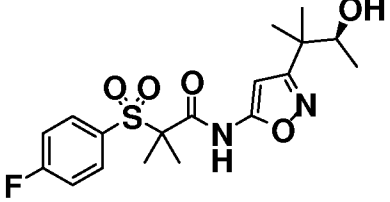
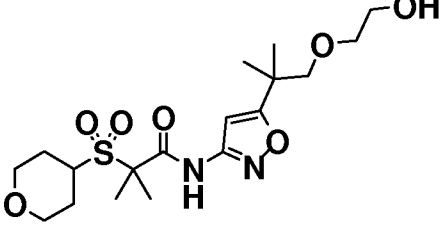
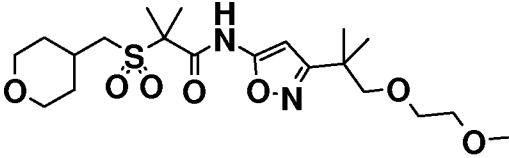
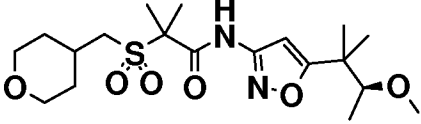
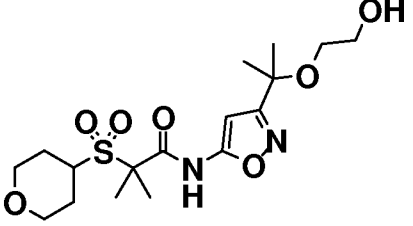
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	11	>50000
	14	>50000
	20	>50000
	116	>50000
	31	>20000
	22	>50000

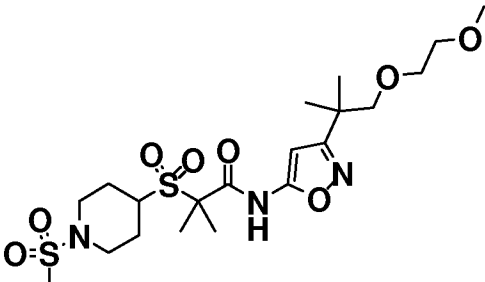
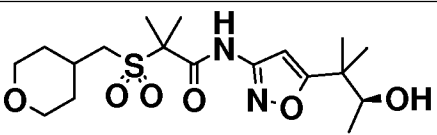
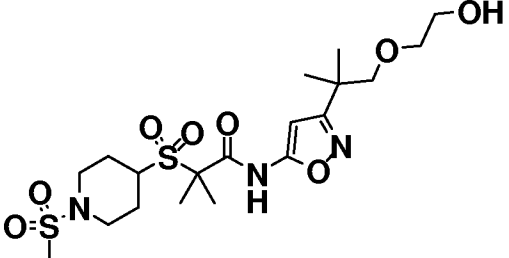
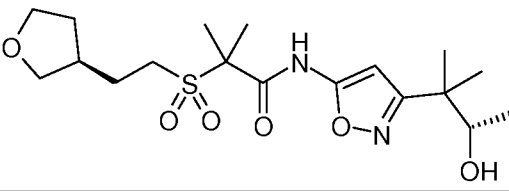
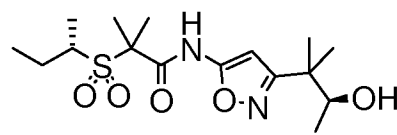
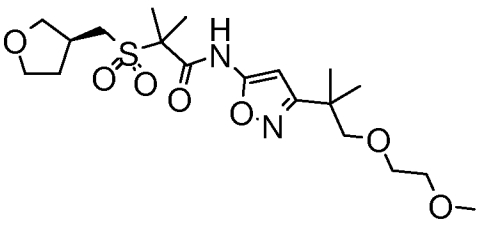
	29	>50000
	2.1	>50000
	8.0	>20000
	20	>20000
	21	>20000
	150	>50000

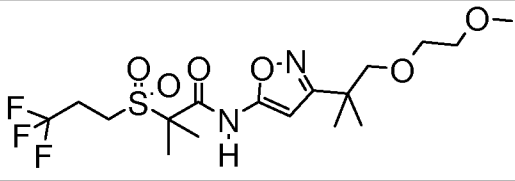
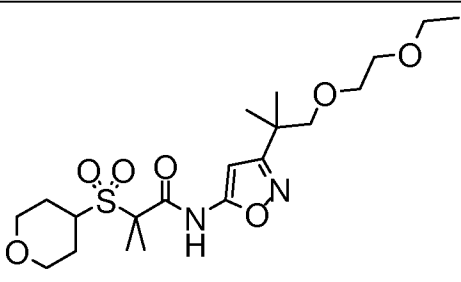
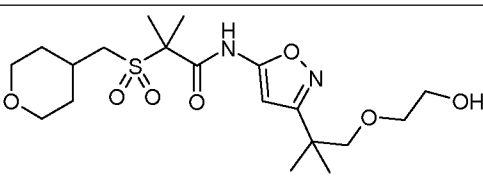
	5.3	>50000
	2.8	>50000
	47	>50000
	70	>50000
	2.5	>20000
	77	>500000

	10	>20000
	402	>50000
	59	>50000
	348	>50000
	368	>50000
	101	>50000
	172	>50000

	138	>50000
	97	>20000
	13	>50000
	167	>20000
	107	>50000
	10.8	>50000
	15	>50000

	96	>50000
	25	>50000
	42	>50000
	2.4	>50000
	15	>50000
	30	>50000
	28	>50000

	11	>50000
	121	>50000
	10	>50000
	15	21,034
	250	>50000
	98	>50000

	27	>50000
	1.5	>50000
	13	>50000

5

In all the compounds disclosed hereinabove in this application, in the event the nomenclature is in conflict with the structure, it shall be understood that the compound is defined by the structure.

10

The invention also relates to pharmaceutical preparations, containing as active substance one or more compounds of formula (I), or the pharmaceutically acceptable derivatives thereof, optionally combined with conventional excipients and/or carriers.

15

Compounds of the invention also include their isotopically-labelled forms. An isotopically-labelled form of an active agent of a combination of the present invention is identical to said active agent but for the fact that one or more atoms of said active agent have been replaced by an atom or atoms having an atomic mass or mass number different from the atomic mass or mass number of said atom which is usually found in nature. Examples of isotopes which are readily available commercially and which can be incorporated into an active agent of a combination of the present invention in accordance with well established procedures, include

20

5 isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, *e.g.*, ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. An active agent of a combination of the present invention, a prodrug thereof, or a pharmaceutically acceptable salt of either which contains one or more of the above-mentioned isotopes and/or other isotopes of other atoms is contemplated to be within the scope of the present invention.

10 The invention includes the use of any compounds of described above containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Isomers shall be defined as being enantiomers and diastereomers. All such isomeric forms of these compounds are expressly
15 included in the present invention. Each stereogenic carbon may be in the R or S configuration, or a combination of configurations.

Some of the compounds of formula (I) can exist in more than one tautomeric form. The invention includes methods using all such tautomers.

20 All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. For example, "C₁₋₄alkoxy" is a C₁₋₄alkyl with a terminal oxygen, such as methoxy, ethoxy, propoxy, butoxy. All alkyl, alkenyl and alkynyl groups shall be understood as being branched or unbranched where structurally possible and
25 unless otherwise specified. Other more specific definitions are as follows:

Carbocycles include hydrocarbon rings containing from three to twelve carbon atoms. These carbocycles may be either aromatic either aromatic or non-aromatic ring systems. The non-aromatic ring systems may be mono- or polyunsaturated. Preferred carbocycles include but
30 are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptanyl, cycloheptenyl, phenyl, indanyl, indenyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, naphthyl, decahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl. Certain terms for cycloalkyl such as cyclobutanyl and cyclobutyl shall

5 be used interchangeably.

The term "heterocycle" refers to a stable nonaromatic 4-8 membered (but preferably, 5 or 6 membered) monocyclic or nonaromatic 8-11 membered bicyclic heterocycle radical which may be either saturated or unsaturated. Each heterocycle consists of carbon atoms and one or
10 more, preferably from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure.

The term "heteroaryl" shall be understood to mean an aromatic 5-8 membered monocyclic or
15 8-11 membered bicyclic ring containing 1-4 heteroatoms such as N,O and S.

Unless otherwise stated, heterocycles and heteroaryl include but are not limited to, for example benzoxazolyl, benzothiazolyl, benzimidazolyl, tetrahydropyranyl, dioxanyl, dioxalanyl, tetrahydrofuranyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, pyrrolyl, imidazolyl,
20 thienyl, thiadiazolyl, triazolyl, thiomorpholinyl, 1,1-Dioxo-1 λ ⁶-thiomorpholinyl, morpholinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolidinyl, piperidinyl, piperazinyl, purinyl, quinolinyl, Dihydro-2H-quinolinyl, isoquinolinyl, quinazolinyl, indazolyl, thieno[2,3-d]pyrimidinyl, indolyl, isoindolyl, benzofuranyl, benzopyranyl and benzodioxolyl.

25 The term "heteroatom" as used herein shall be understood to mean atoms other than carbon such as O, N, S and P.

In all alkyl groups or carbon chains one or more carbon atoms can be optionally replaced by
30 heteroatoms: O, S or N, it shall be understood that if N is not substituted then it is NH, it shall also be understood that the heteroatoms may replace either terminal carbon atoms or internal carbon atoms within a branched or unbranched carbon chain. Such groups can be substituted

- 5 as herein above described by groups such as oxo to result in definitions such as but not limited to: alkoxycarbonyl, acyl, amido and thioxo.

The term “aryl” as used herein shall be understood to mean aromatic carbocycle or heteroaryl as defined herein. Each aryl or heteroaryl unless otherwise specified includes its partially or
10 fully hydrogenated derivative. For example, quinolinyl may include decahydroquinolinyl and tetrahydroquinolinyl, naphthyl may include its hydrogenated derivatives such as tetrahydronaphthyl. Other partially or fully hydrogenated derivatives of the aryl and heteroaryl compounds described herein will be apparent to one of ordinary skill in the art.

- 15 As used herein, “nitrogen” and “sulfur” include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen. . For example, for an -S-C₁₋₆ alkyl radical, unless otherwise specified, this shall be understood to include -S(O)-C₁₋₆ alkyl and -S(O)₂-C₁₋₆ alkyl.

The term “halogen” as used in the present specification shall be understood to mean bromine,
20 chlorine, fluorine or iodine, preferably fluorine. The definitions “partially or fully halogenated”; partially or fully fluorinated; “substituted by one or more halogen atoms”, includes for example, mono, di or tri halo derivatives on one or more carbon atoms. For alkyl, a nonlimiting example would be -CH₂CHF₂, -CF₃ etc.

- 25 The compounds of the invention are only those which are contemplated to be ‘chemically stable’ as will be appreciated by those skilled in the art. For example, a compound which would have a ‘dangling valency’, or a ‘carbanion’ are not compounds contemplated by the inventive methods disclosed herein.

- 30 The invention includes pharmaceutically acceptable derivatives of compounds of formula (I). A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable salt or ester, or any other compound which, upon administration to a patient, is capable of providing

5 (directly or indirectly) a compound useful for the invention, or a pharmacologically active metabolite or pharmacologically active residue thereof. A pharmacologically active metabolite shall be understood to mean any compound of the invention capable of being metabolized enzymatically or chemically. This includes, for example, hydroxylated or oxidized derivative compounds of the formula (I).

10

Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic, 15 malonic, naphthalene-2-sulfuric and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium and N-(C₁-C₄ alkyl)₄⁺ salts.

20

In addition, within the scope of the invention is use of prodrugs of compounds of the formula (I). Prodrugs include those compounds that, upon simple chemical transformation, are modified to produce compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction. Specifically, when a prodrug is administered to a patient, 25 the prodrug may be transformed into a compound disclosed hereinabove, thereby imparting the desired pharmacological effect.

The compounds of formula I may be made using the general synthetic methods described below, which also constitute part of the invention.

30

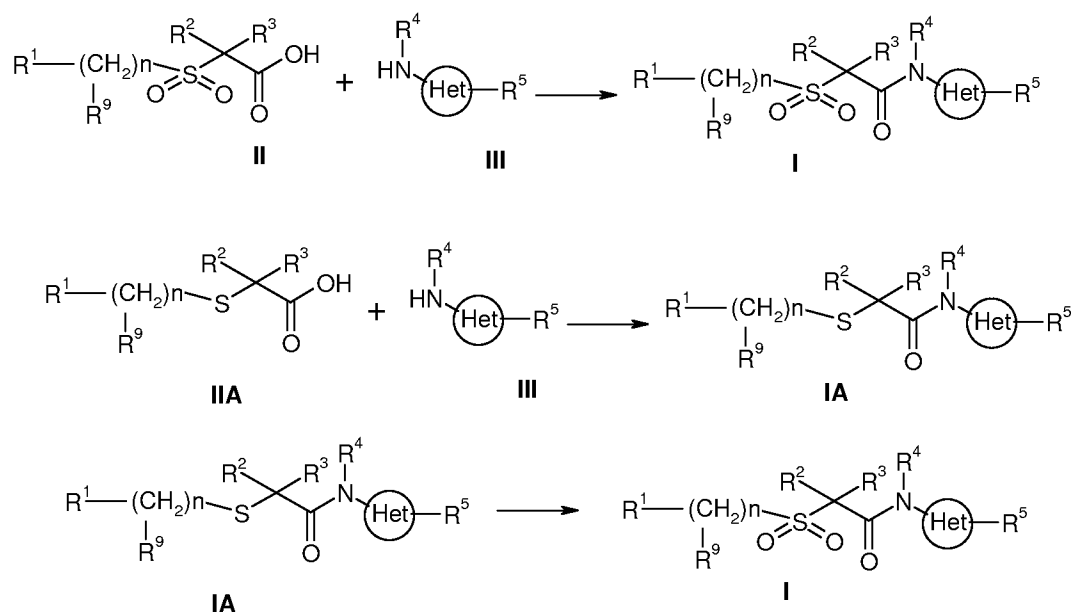
GENERAL SYNTHETIC METHODS

- 5 The invention also provides processes for making compounds of Formula (I). In all methods, unless specified otherwise, R^1 , R^2 , R^3 , R^4 , R^5 , n and Het in the formulas below shall have the meaning of R^1 , R^2 , R^3 , R^4 , R^5 , n and Het in Formula (I) of the invention described herein above.
- 10 Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Typically, reaction progress may be monitored by thin layer chromatography (TLC), if desired, and intermediates and products
- 15 may be purified by chromatography on silica gel and/or by recrystallization.

The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds without undue experimentation. Starting materials and intermediates used, in the methods

20 below, are either commercially available or easily prepared from commercially available materials by those skilled in the art. Synthetic methods disclosed in WO2008098025, WO2008014199, WO2008039645, and WO2009061652 may also be used in preparing compounds of the invention.

- 25 Compounds of Formula (I) may be synthesized by the method illustrated in Scheme 1



Scheme 1

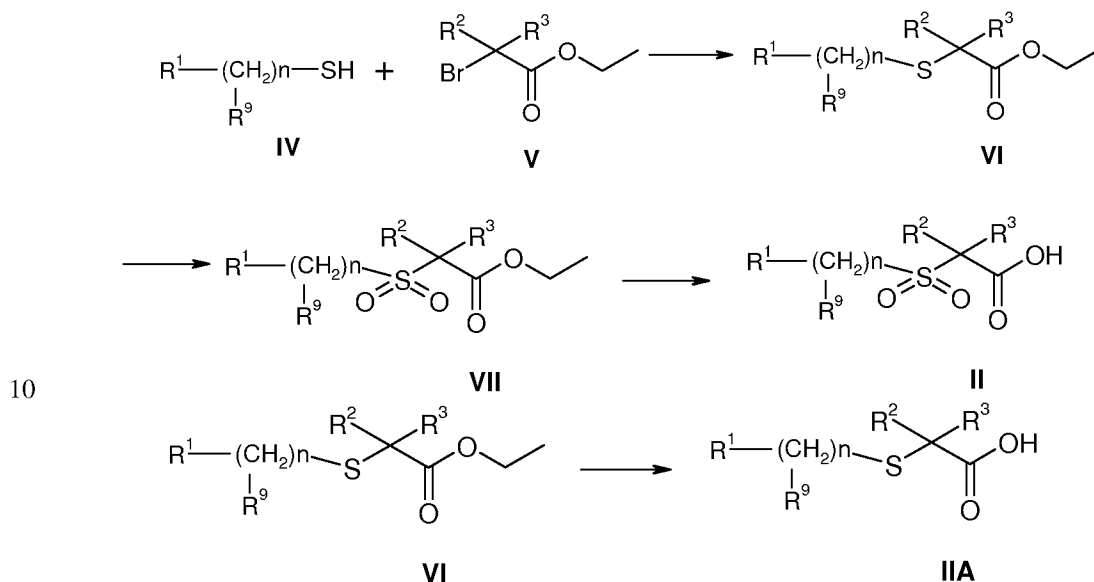
As shown in scheme 1, reacting the acid of formula II or IIA with a reagent such as thionyl chloride or oxalyl chloride, provides the acid chloride which is then reacted with an amine of formula III, in a suitable solvent, in the presence of a suitable base, to provide a compound of formula (I) or IA. Alternatively, the acid of formula II or IIA may also be coupled with an amine of formula III under standard coupling conditions, to provide a compound of formula (I) or IA. Standard peptide coupling reactions known in the art (see for example M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag) may be employed in these syntheses. An example of suitable coupling conditions is treatment of a solution of the carboxylic acid in a suitable solvent such as DMF with EDC, HOBt, and a base such as diisopropylethylamine, followed by the desired amine.

Oxidation of the compound of formula IA, under standard reaction conditions, using standard reagents, provides a compound of formula (I).

Further modification of the initial product of formula (I) by methods known in the art and illustrated in the Examples below, may be used to prepare additional compounds of this invention.

5

Intermediate acid II or IIA may be made by the method outlined in Scheme 2

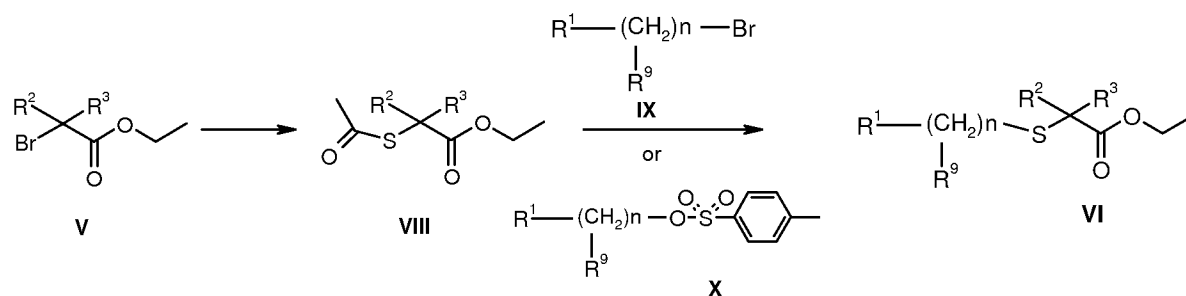


Scheme 2

- 15 As illustrated above, reaction of a thiol of formula IV with a bromo ethyl ester of formula V, in a suitable solvent, in the presence of a suitable base, provides a thioether of formula VI. Reacting the thioether of formula VI with a suitable oxidizing agent provides the corresponding sulfone of formula VII. Hydrolysis of the ester group of sulfone of formula VII, in a suitable solvent, in the presence of a suitable base such as lithium hydroxide, provides the
- 20 corresponding acid of formula II. Alternatively, hydrolysis of the ester group of the thioether of formula VI, under suitable conditions, provides an acid of formula IIA.

Intermediate acid II or IIA may also be made by the method outlined in Scheme 3

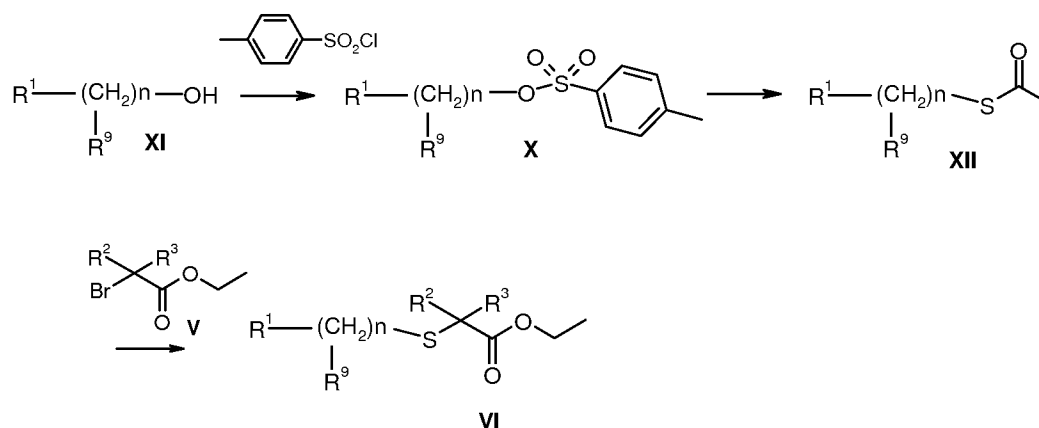
25



Scheme 3

Reaction of the starting bromoester of formula V with a reagent such as potassium thioacetate, in a suitable solvent, provides a thioacetic acid ester of formula VIII. Reaction of the thioacetic acid ester of formula VIII with a bromide of formula IX, in a suitable solvent, in the presence of a suitable base, provides the corresponding sulfanyl acid ethyl ester of formula VI. Alternatively, reaction of the thioacetic acid ester of formula VIII with a tosylate of formula X, in a suitable solvent, in the presence of a suitable base, provides the sulfanyl acid ethyl ester of formula VI. The sulfanyl acid ethyl ester of formula VI may be converted to intermediate acid of formula II or IIA by the sequence of steps shown in scheme 2.

Intermediate acid II or IIA may be made by the method outlined in Scheme 4



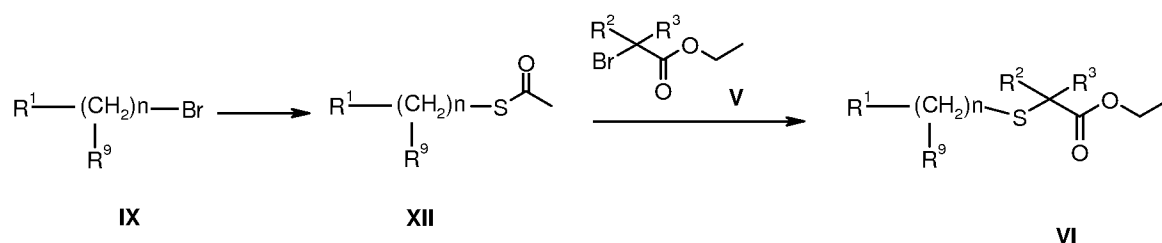
Scheme 4

As illustrated in scheme 4, reaction of an alcohol of formula XI with p-toluenesulfonyl chloride, in a suitable solvent, in the presence of a suitable base, provides a tosylate of formula

5 X. Reaction of the compound of formula X with potassium thioacetate, in a suitable solvent, provides a compound of formula XII. Reaction of the intermediate of formula XII with the bromoester of formula V, in a suitable solvent, in the presence of a suitable base, provides the intermediate of formula VI which may be converted to the desired intermediate acid of formula II or IIA by the reaction sequence shown in scheme 2.

10

Intermediate acid II or IIA may be prepared by the method outlined in Scheme 5



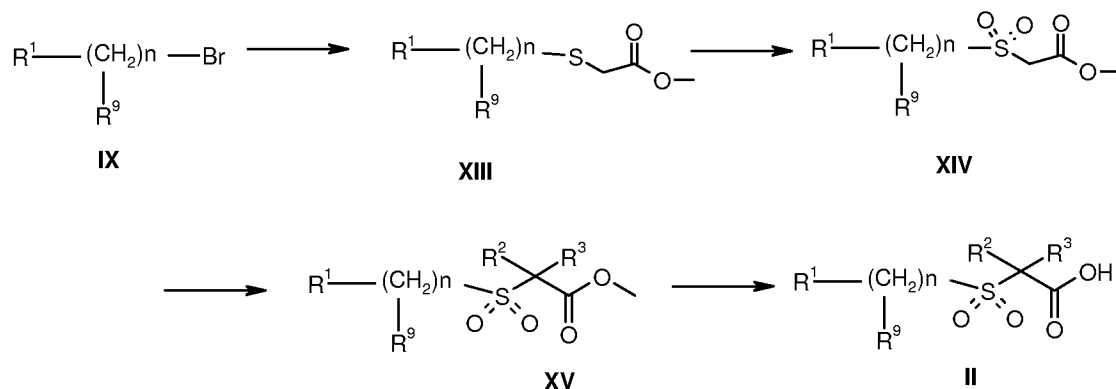
Scheme 5

15

As illustrated in scheme 5, reaction of a bromo compound of formula IX with a reagent such as potassium thioacetate, in a suitable solvent, provides an acetylsulfanyl compound of formula XII. Reaction of the compound of formula XII with a bromo ethyl ester of formula V, in a suitable solvent, in the presence of a suitable base, provides a thioether of formula VI. The thioether of formula VI may be converted to the corresponding acid of formula II or IIA by the reaction sequence shown in scheme 2.

20

Intermediate acid of formula II may also be synthesized as shown in Scheme 6.

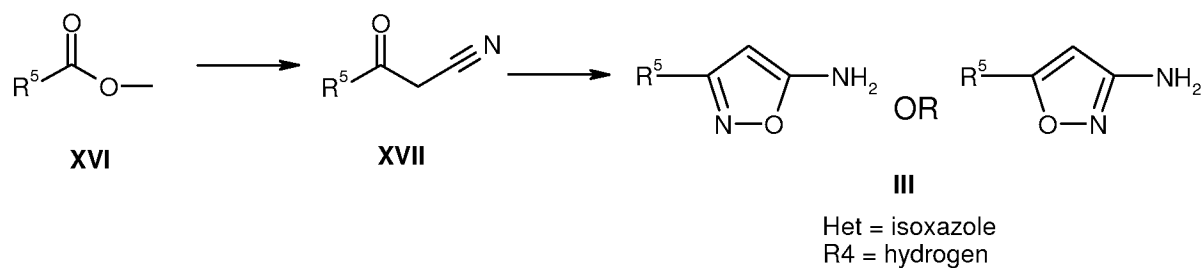


5

Scheme 6

As outlined in scheme 6, reaction of a bromo compound of formula IX with methyl
 10 mercaptoacetate, in a suitable solvent, in the presence of a suitable base and catalyst, provides
 a thioacetate of formula XIII. Oxidation of the thio compound of formula XIII with a suitable
 reagent such as m-chloroperbenzoic acid, provides the corresponding sulfone of formula XIV.
 Alkylation of the sulfone of formula XIV with an alkylating agent, in a suitable solvent, in the
 presence of a suitable base, provides a compound of formula XV. Hydrolysis of compound of
 15 formula XV, under standard conditions, provides an acid of formula II.

Intermediate amine III may be made by the method outlined in Scheme 7



20

Scheme 7

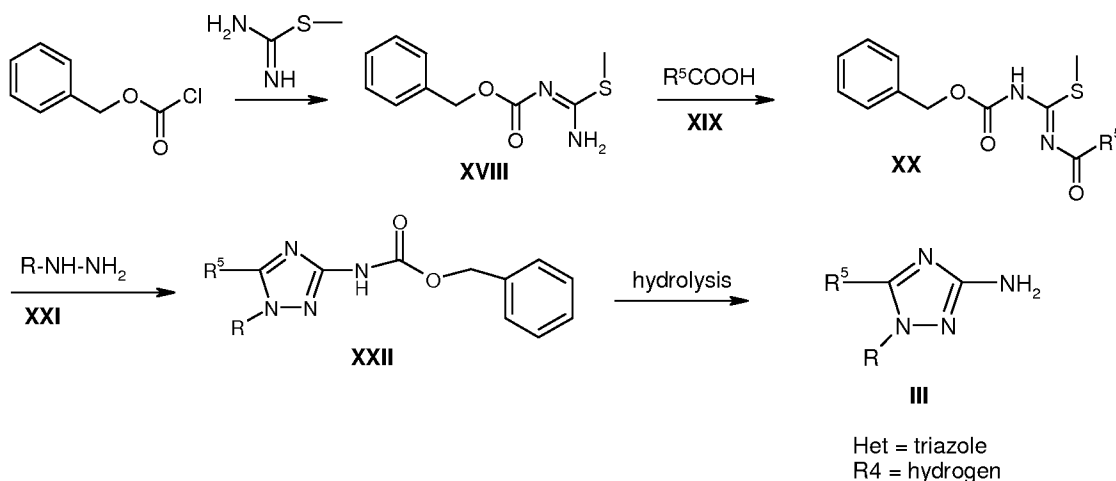
As outlined in scheme 7, reaction of an ester of formula XVI with acetonitrile, in the presence
 of a suitable base, provides the nitrile of formula XVII. Reaction of the nitrile of formula XVII

- 5 with hydroxylamine, in a suitable solvent, in the presence of a suitable base, provides the amine of formula III, wherein Het = isoxazolyl and $R^4 = H$.

Alternatively, adjusting the pH in step 2, provides the 3-amino isoxazole isomer.

Intermediate amine III may be prepared by the method shown in Scheme 8.

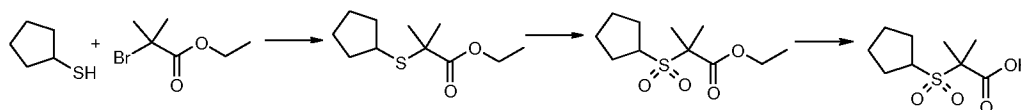
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- As shown in scheme 8, reaction of benzyl chloroformate with 2-methyl-isothiourea provides a
 15 benzyloxycarbonyl isothiourea of formula XVIII. Reaction of the compound of formula XVIII
 with an acid of formula XIX, under standard coupling conditions, provides an intermediate of
 formula XX. Reaction of the intermediate of formula XX with a suitable alkyl hydrazine of
 formula XXI, wherein $R = C_1-C_3$ alkyl, provides a triazole of formula XXII. Hydrolysis of this
 triazole, under suitable conditions, provides an amine of formula III, wherein Het = triazolyl
 20 and $R^4 = H$.

SYNTHETIC EXAMPLES

- The manner in which the compounds of the invention can be made will be further understood by
 25 way of the following Examples.

5 **Acid Method A:****Synthesis of 2-Cyclopentanesulfonyl-2-methyl-propionic acid****Step 1: Synthesis of 2-Cyclopentylsulfanyl-2-methyl-propionic acid ethyl ester**

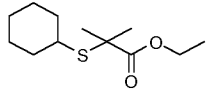
10 Prepared as described by adaptation of the following reference: Brown *et al. J. Med. Chem.* **1999**, 42, 3785-3788.

To a solution of 5 g (48.7 mmol) of cyclopentyl thiol in ethanol (50 mL) are added 2.7 g (48.75 mmol) of KOH pellets, followed by 9.5 g (48.7 mmol) of ethyl α -bromoisobutyrate. The reaction is heated to reflux for 2 h and then cooled to room temperature. The solid (KBr) is separated by
 15 filtration and rinsed with ethanol (20 mL). The filtrate is concentrated under reduced pressure and the residue dissolved in DCM (50 mL). The organic layer is washed with saturated aqueous NaHCO₃ solution (50 mL). The aqueous washes are back-extracted with DCM (10 mL). The combined organics are washed with brine, dried over Na₂SO₄. Filtration and concentration under reduced pressure affords 8.1 g of 2-cyclopentylsulfanyl-2-methyl-propionic acid ethyl ester. Yield:
 20 77%, ES-MS: m/z 217 [M+H]

According to this procedure the following thioethers are synthesized:

Table IV

Structure	¹ H-NMR	Yield [%]	m/z [M+H]
	(250 MHz, CHLOROFORM- <i>d</i>) δ ppm 1.29 (3 H, t, $J=7.14$ Hz), 1.36 - 1.77 (12 H, m), 1.95 - 2.13 (2 H, m), 3.08 - 3.26 (1 H, m), 4.18 (2 H, q, $J=7.14$ Hz)	77	217
	(400 MHz, CHLOROFORM- <i>d</i>) δ ppm 1.22 (3 H, t, $J=7.09$ Hz), 1.47 (6 H, s), 4.11 (2 H, q, $J=7.25$ Hz), 7.01 (2 H, t, $J=8.68$ Hz), 7.39 - 7.50 (2 H, m)	66	243

	(250 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.16 - 1.42 (9 H, m), 1.49 (6 H, s), 1.58 - 1.78 (2 H, m), 1.81 - 1.91 (2 H, m), 2.67 - 2.91 (1 H, m), 4.15 (2 H, q, J=7.14 Hz)	84	231
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Step 2: Synthesis of 2-Cyclopentanesulfonyl-2-methyl-propionic acid ethyl ester

Prepared as described by adaptation of the following reference:

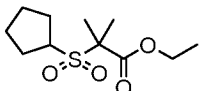
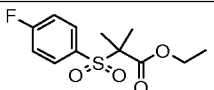
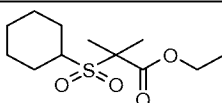
Aranapakam, V. *et al. J. Med. Chem.*, **2004**, 47, 6255-6269.

To a solution of 6 g (27.7 mmol) of 2-cyclopentylsulfanyl-2-methyl-propionic acid ethyl ester in dioxane/water (4/1, 100 mL) are added in one portion 51.2 g (83 mmol) of potassium monopersulfate triple salt (OXONE®). The white suspension is stirred at room temperature for 3 h. The white solid is separated by filtration and washed with dioxane (10 mL). The filtrate is concentrated under reduced pressure to remove the organic solvent. The resulting aqueous solution is extracted with DCM (3 x 40 mL). The combined organic extracts are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated under reduced pressure to afford 5.4 g of 2-cyclopentanesulfonyl-2-methyl-propionic acid ethyl ester. Yield: 78%, ES-MS: m/z 249 [M+H]

15

According to this procedure the following sulfones are synthesized:

Table V

Structure	¹ H-NMR	Yield [%]	m/z [M+H]
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.32 (3 H, t, J=7.21 Hz), 1.55 - 1.70 (8 H, m), 1.71 - 1.86 (2 H, m), 1.96 - 2.20 (4 H, m), 3.83 - 3.96 (1 H, m), 4.25 (2 H, q, J=7.09 Hz)	78	249
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.15 (3 H, t, J=7.09 Hz), 1.55 (6 H, s), 4.08 (2 H, q, J=7.17 Hz), 7.13 - 7.22 (2 H, m), 7.78 - 7.86 (2 H, m)	98	275
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.08 - 1.38 (6 H, m), 1.48 - 1.72 (9 H, m), 1.83 - 1.95 (2 H, m), 2.11 (2 H, d, J=13.94 Hz), 3.45 - 3.58 (1 H, m), 4.24 (2 H, q, J=7.17 Hz)	50	263

20

Step 3: Synthesis of 2-Cyclopentanesulfonyl-2-methyl-propionic acid

5 Prepared as described by adaptation of the following reference:

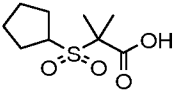
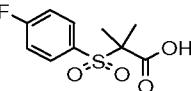
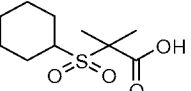
Troeger, Uhde., *J. Prakt. Chem.* **1899**, 59, 320- 349.

To a solution of 5.4 g (21.7 mmol) of 2-cyclopentanesulfonyl-2-methyl-propionic acid ethyl ester in THF/water (4/1, 60 mL) are added 2.3 g (56.6 mmol) of lithium hydroxide monohydrate. The reaction is stirred at room temperature for 18 h. The reaction is further diluted with water (20 mL) and then washed with DCM (2 x 15 mL). The basic aqueous layer is cooled in an ice bath and then acidified with 2M aqueous HCl solution to pH 2. The acidic aqueous layer is extracted with 2-propanol/chloroform (1/4, 100 mL). The combined organic extracts are washed with brine, dried over Na₂SO₄ and filtered. Concentration of the filtrate under reduced pressure affords 4.34 g of 2-cyclopentanesulfonyl-2-methyl-propionic acid. Yield: 92%, ES-MS: m/z 221 [M+H]

15

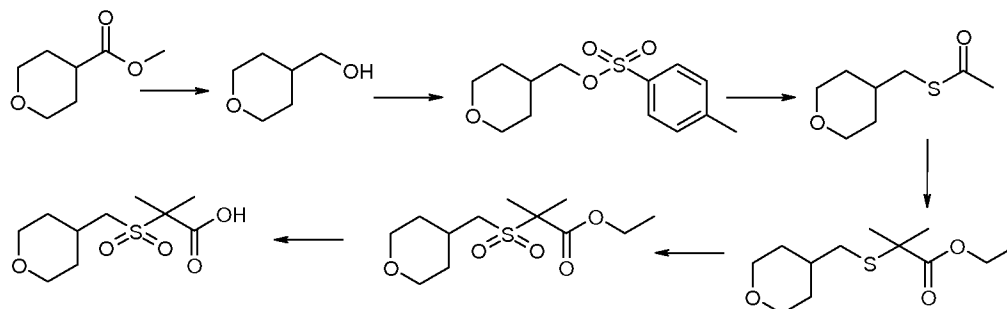
According to this procedure the following acids are synthesized:

Table VI

Structure	¹ H-NMR	Yield [%]	m/z [M+H]
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.54 - 1.72 (8 H, m), 1.72 - 1.88 (2 H, m), 1.98 - 2.22 (4 H, m), 3.87 - 4.00 (1 H, m), 9.26 (1 H, br. s.)	92	221
	(500 MHz, <i>MeOD</i>) δ ppm 1.57 (6 H, s), 7.35 (2 H, t, J=8.85 Hz), 7.94 (2 H, dd, J=9.00, 5.04 Hz)	70	247, 264 [M+H ₂ O]
	(250 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.11 - 1.49 (3 H, m), 1.53 - 1.79 (9 H, m), 1.85 - 2.00 (2 H, m), 2.06 - 2.22 (2 H, m), 3.37 - 3.56 (1 H, m)	64	258 [M+Na]

Acid Method B:

5 **Synthesis of 2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid**



Step 1: Synthesis of (Tetrahydro-pyran-4-yl)-methanol

To a solution of 250 mL of LiAlH_4 (2.3M solution in THF, 0.575 mol) in THF (200 mL) is added dropwise a solution of 130 mL (0.974 mol) of tetrahydro-pyran-4-carboxylic acid methyl ester in THF (900 mL) under nitrogen atmosphere (CAUTION: highly exothermic reaction!). The temperature is kept at 40-45 °C with an ice-bath. Upon complete addition, the reaction is stirred at room temperature for 1.5 h. The reaction is cooled in an ice-bath and quenched with addition of water (22 mL), 15% aqueous NaOH solution (21 mL) and water (66 mL). The resulting precipitate is removed by filtration through Celite® and is rinsed with THF (300 mL). The filtrate is concentrated under reduced pressure to afford 102.5 g of (tetrahydro-pyran-4-yl)-methanol as a clear oil. Yield: 91%; $^1\text{H-NMR}$ (400 MHz, *CHLOROFORM-d*) δ ppm 1.20 - 1.39 (2 H, m), 1.56 - 1.83 (3 H, m), 2.03 (1 H, br. s.), 3.29 - 3.52 (4 H, m), 3.89 - 4.05 (2 H, m)

Step 2: Synthesis of toluene-4-sulfonic acid tetrahydro-pyran-4-ylmethyl ester

Prepared as described by adaptation of the following literature reference:

Radziszewski, J.G. *et al. J. Am. Chem. Soc.* **1993**, 115, 8401.

To a solution of 97 g (810 mmol) of (tetrahydro-pyran-4-yl)-methanol in 2-methyltetrahydrofuran (190 mL) are added 165 mL of 50% aqueous NaOH solution. To this stirred suspension is added dropwise with cooling a solution of p-toluene-sulfonylchloride (283 g, 1.46 mol) in 2-methyltetrahydrofuran (280 mL). The reaction is stirred at 30-35 °C for 18 h. The suspension is poured into a mixture of ice-water (280 mL) and aqueous HCl solution (37%, 203 mL). After addition of methylcyclohexane (1.4 L) and further ice-water (0.2 L), the reaction mixture is stirred for 2 h in an ice-bath. The resulting crystalline precipitate is isolated by filtration and washed with

5 methylcyclohexane (0.5 L) and water (0.5 L). Drying under reduced pressure at 40 °C gave 216 g of toluene-4-sulfonic acid tetrahydro-pyran-4-ylmethyl ester as white crystalline solid. Yield: 99%, ES-MS: m/z 271 [M+H]; ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 1.19 - 1.35 (2 H, m), 1.54 - 1.63 (2 H, m), 1.85 - 2.02 (1 H, m), 2.45 (3 H, s), 3.28 - 3.39 (2 H, m), 3.86 (2H, d, J=6.60 Hz), 3.93 (2 H, dd, J=11.37, 4.52 Hz), 7.35 (2 H, d, J=9.29 Hz), 7.78 (2 H, d, J=8.31 Hz)

10

Step 3: Synthesis of Thioacetic acid S-(tetrahydro-pyran-4-ylmethyl) ester

Prepared as described by adaptation of the following literature reference:

Watson, R.J. *et al. Tetrahedron Lett.* **2002**, 43, 683-685.

To a solution of 224 g (0.83 mol) of toluene-4-sulfonic acid tetrahydro-pyran-4-ylmethyl ester in
15 methyl isobutylketone (1.6 L) are added 189 g (1.66 mol) of potassium thioacetate. The beige suspension is stirred at 70 °C for 4.5 h. The reaction mixture is cooled to room temperature and water (1.8 L) is added. The organic layer is washed with 10% aqueous K₂CO₃ solution (1.8 L) and water (1 L). The organic layer is filtered through celite® (20 g), activated charcoal (20 g) and Na₂SO₄ (20 g) and the filtrate is concentrated under reduced pressure. The residual oil is
20 azeotroped with methylcyclohexane (200 mL) and n-heptanes (250 mL) to afford 138 g of thioacetic acid S-(tetrahydro-pyran-4-ylmethyl) ester as a yellow-orange oil (CAUTION: Stench!). Yield: 96%; ES-MS: m/z 175 [M+H]; ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 1.23 - 1.40 (2 H, m), 1.59 - 1.78 (3 H, m), 2.33 (3 H, d, J=4.16 Hz), 2.82 (2 H, dd, J=6.24, 3.79 Hz), 3.27-3.39 (2 H, m), 3.88 - 4.02 (2 H, m)

25

Step 4: Synthesis of 2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid ethyl ester

A solution of 90 g (516 mmol) of thioacetic acid S-(tetrahydro-pyran-4-ylmethyl) ester in toluene (500 mL) under nitrogen atmosphere is cooled in an ice-bath. A solution of sodium ethoxide in
30 ethanol (21%, 231 mL) is added and the reaction is stirred for 50 min. Then 76 mL (516 mmol) of ethyl α-bromoisobutyrate are added and the reaction stirred for 1 h. To the reaction mixture are added glacial acetic acid (8.9 mL) and water (500 mL). The organic layer is separated and washed with water (500 mL). A 3-neck round bottom flask is charged with water (500 mL), oxone® (477 g, 775 mmol) and tetrabutylammonium-hydrogensulfate (5 g, 15 mmol) and the organic layer is

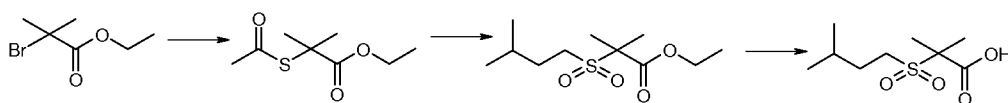
- 5 added. The biphasic reaction mixture is stirred for 2 d at room temperature. The solids are removed by filtration and the layers of the filtrate are separated. The organic layer is washed with water (2 x 500 mL). The solvent is removed under reduced pressure and further azeotroped with toluene to give 125 g of 2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid ethyl ester. Yield: 87%; ES-MS: m/z 279 [M+H];
- 10 ^1H NMR (250 MHz, *CHLOROFORM-d*) δ ppm 1.32 (3 H, t, $J=7.16$ Hz), 1.39 - 1.59 (2 H, m), 1.64 (6 H, s), 1.81 - 1.97 (2 H, m), 2.29 - 2.53 (1 H, m), 3.15 (2 H, d, $J=6.55$ Hz), 3.45 (2 H, dd, $J=1.83, 0.30$ Hz), 3.88 - 4.03 (2 H, m), 4.26 (2 H, d, $J=7.16$ Hz)

Step 5: Synthesis of 2-Methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid

- 15 Prepared as described by adaptation of Method A, step 3.
- To a solution of 123 g (0.44 mol) of 2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid ethyl ester in THF (450 mL) are added 663 mL of 2M aqueous sodium hydroxide solution (1.33 mol). The reaction is stirred at room temperature for 1 h. To the reaction mixture is added TBME (1.25 L) and the layers are separated. The aqueous layer is cooled in an ice bath and then
- 20 acidified with 37% aqueous HCl solution (123 mL). The resulting precipitate is isolated by filtration, washed with water (200 mL) and dried under reduced pressure at 50 °C to afford 101 g of 2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionic acid as white crystalline solids. Yield: 91%; ES-MS: m/z 251 [M+H]; ^1H NMR (400 MHz, *DMSO-d6*) δ ppm 1.31 - 1.45 (2 H, m), 1.49 (6 H, s), 1.70 - 1.79 (2 H, m), 2.13 - 2.28 (1 H, m), 3.24 (2 H, d, $J=6.60$ Hz), 3.28 - 3.38
- 25 (2 H, m), 3.76 - 3.85 (2 H, m), 13.65 (1 H, br. s.)

Acid Method C:

Synthesis of 2-Methyl-2-(3-methyl-butane-1-sulfonyl)-propionic acid



30

Step 1: Synthesis of 2-Acetylsulfonyl-2-methyl-propionic acid ethyl ester

- 5 To a solution of ethyl α -bromoisobutyrate (62 g, 0.32 mol) in DMF (500 mL) at room temperature is added potassium thioacetate (72 g, 0.63 mol). The reaction is stirred for 16 h and then concentrated under reduced pressure. The residue is diluted with a 2M aqueous HCl solution (500 mL) and extracted with ethyl acetate (3 x 500 mL). The organic fractions are combined, washed with brine (300 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure.
- 10 Purification by chromatography on silica eluting with heptanes/DCM provides 44 g of 2-acetylsulfanyl-2-methyl-propionic acid ethyl ester. Yield: 73%; m/z 191 $[\text{M}+\text{H}]$; ^1H NMR (250 MHz, *CHLOROFORM-d*) δ ppm 1.18 - 1.30 (3 H, m), 1.57 (6 H, s), 2.27 (3 H, s), 4.19 (2 H, q, $J=7.16$ Hz)

15 **Step 2: Synthesis of 2-Methyl-2-(3-methyl-butane-1-sulfonyl)-propionic acid ethyl ester**

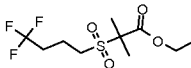
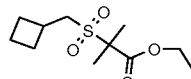
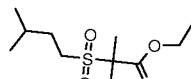
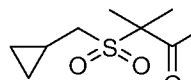
- To a solution of 5 g (26.5 mmol) of 2-acetylsulfanyl-2-methyl-propionic acid ethyl ester in ethanol (30 mL) are added 5.7 g (105 mmol) of sodium methoxide, followed by 4 g (26.5 mmol) of 1-bromo-3-methylbutane. The reaction is heated to 120 °C for 0.5 h in the microwave. The solvent is removed under reduced pressure. The residue is dissolved in DCM (50 mL) and washed with
- 20 saturated aqueous NaHCO_3 solution (2 x 20 mL). The aqueous layer is back-extracted with DCM (2 x 50 mL). The combined organic extracts are dried over Na_2SO_4 , filtered and the filtrate is concentrated under reduced pressure.

- The residue is dissolved in a mixture of dioxane/water (4/1, 60 mL) and 29 g (47.2 mmol) of oxone® are added. The reaction mixture is stirred at room temperature for 18 h. The solid is
- 25 removed by filtration and the filtrate is concentrated under reduced pressure. The residue is dissolved in DCM (50 mL) and is washed with saturated aqueous NaHCO_3 solution (20 mL), the aqueous layer is back-extracted with DCM (3 x 50 mL). The combined organic layer is dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford 3.78 g of 2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionic acid ethyl ester as pale yellow oil. Yield 57%; ES-MS: m/z
- 30 251 $[\text{M}+\text{H}]$;

According to this procedure the following esters are synthesized:

Table VII

Structure	^1H -NMR	Yield [%]	m/z
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			[M+H]
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.32 (3 H, t, $J=7.17$ Hz), 1.66 (6 H, s), 2.20 (2 H, quin, $J=7.59$ Hz), 2.28 - 2.41 (2 H, m), 3.34 (2 H, t, $J=7.48$ Hz), 4.27 (2 H, q, $J=7.17$ Hz)	81	291
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.32 (3 H, t, $J=7.17$ Hz), 1.63 (6 H, s), 1.82 - 2.07 (4 H, m), 2.18 - 2.33 (2 H, m), 2.92 - 3.07 (1 H, m), 3.32 (2 H, d, $J=7.32$ Hz), 4.26 (2 H, q, $J=7.07$ Hz)	43	249
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.96 (6 H, d, $J=6.41$ Hz), 1.32 (3 H, t, $J=7.17$ Hz), 1.66 (6 H, s), 1.69 - 1.84 (3 H, m), 3.17 - 3.26 (2 H, m), 4.27 (2 H, q, $J=7.07$ Hz)	57	251
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.42 (2 H, d, $J=4.57$ Hz), 0.73 (2 H, d, $J=7.09$ Hz), 1.13 - 1.36 (4 H, m), 1.62 (6 H, d, $J=2.21$ Hz), 3.17 (2 H, d, $J=7.25$ Hz), 4.19 - 4.29 (2 H, m)	62	235, 257 [M+Na]

5

Step 3: Synthesis of 2-Methyl-2-(3-methyl-butane-1-sulfonyl)-propionic acid

Prepared as described by adaptation of Method A, step 3.

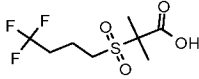
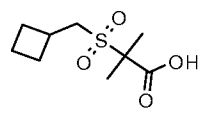
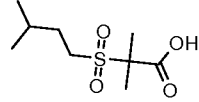
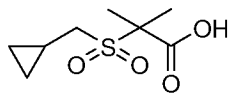
To a solution of 3.78 g (15.09 mmol) of 2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionic acid ethyl ester in THF/water (4/1, 50 mL) are added 1.58 g (37.74 mmol) of lithium hydroxide monohydrate. The reaction is stirred at room temperature for 18 h. The reaction mixture is concentrated under reduced pressure and the residue is dissolved in DCM (20 mL) and extracted with water (50 mL). The aqueous layer is cooled in an ice bath and then acidified with 6M aqueous HCl solution to pH 1. The resulting precipitate is isolated by filtration, and dried under reduced pressure at 50 °C to afford 3.35 g of 2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionic acid as white crystalline solids. Yield: 100%; ES-MS: m/z 221 [M-H].

15

According to this procedure the following acids are synthesized:

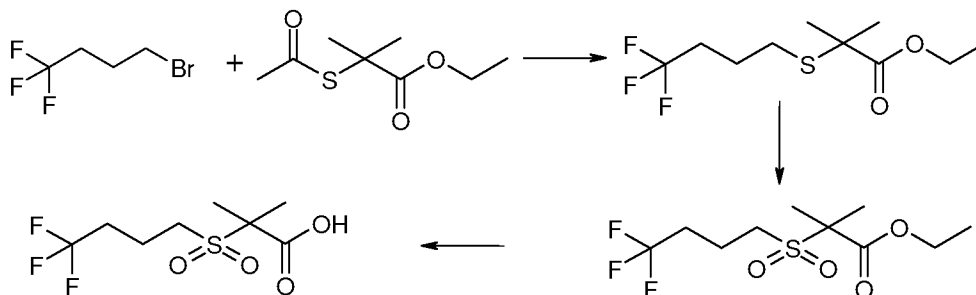
Table VIII

Structure	^1H NMR	Yield [%]	m/z [M-H]
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	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.71 (6 H, s), 2.18 - 2.28 (2 H, m), 2.30 - 2.42 (2 H, m), 3.38 (2 H, t, $J=7.48$ Hz), 6.96 (1 H, br. s.)	76	261
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.69 (6 H, s), 1.83 - 2.11 (4 H, m), 2.18 - 2.38 (2 H, m), 2.94 - 3.12 (1 H, m), 3.35 (2 H, d, $J=7.32$ Hz)	90	219
	(500 MHz, <i>DMSO-d6</i>) δ ppm 0.90 (6 H, d, $J=6.56$ Hz), 1.47 - 1.54 (6 H, m), 1.55 - 1.77 (3 H, m), 3.24 - 3.30 (3 H, m)	89	221
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.42 - 0.52 (2 H, m), 0.75 - 0.82 (2 H, m), 1.19 - 1.31 (1 H, m), 1.70 (6 H, s), 3.21 (2 H, d, $J=7.17$ Hz)	87	205

5

Synthesis of 2-Methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionic acid



Step 1: Synthesis of 2-Methyl-2-(4,4,4-trifluorobutylsulfonyl)-propionic acid ethyl ester

- 10 To a solution of 149 g (0.785 mol) of 2-acetylsulfanyl-2-methyl-propionic acid ethyl ester (prepared as described in Method C, step 1) in ethanol (1.2 L, degassed under nitrogen for 1 h) are added 169.7 g (0.105 mol) of sodium methoxide, followed by a solution of 150 g (0.785 mol) of 4-bromo-1,1,1-trifluoro-butane. The reaction is heated to 85 °C for 3 d. The solvent is removed under reduced pressure. The residue is dissolved in DCM (1 L) and washed with saturated aqueous
- 15 NaHCO_3 solution (2 x 1 L). The organic layer is dried over Na_2SO_4 , filtered and the filtrate is concentrated under reduced pressure to afford 171 g of 2-methyl-2-(4,4,4-trifluoro-butylsulfonyl)-propionic acid ethyl ester as a brown oil. Yield: 84%; ES-MS: m/z 259 $[\text{M}+\text{H}]$; ^1H NMR (500

5 MHz, *CHLOROFORM-d*) δ ppm 1.29 (3 H, t, $J=7.17$ Hz), 1.51 (6 H, s), 1.76 - 1.86 (2 H, m), 2.12 - 2.27 (2 H, m), 2.69 (2 H, t, $J=7.17$ Hz), 4.18 (2 H, q, $J=7.17$ Hz)

Step 2: Synthesis of 2-Methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionic acid ethyl ester

To a solution of 220 g (0.852 mol) of 2-methyl-2-(4,4,4-trifluoro-butylsulfanyl)-propionic acid
10 ethyl ester in dioxane/ water (1/1, 4 L) are added 1047 g (1.703 mol) of OXONE® in portions
over 0.5 h at room temperature. The reaction mixture is stirred at room temperature for 18 h. The
solid is removed by filtration and rinsed with dioxane (0.5 L). The filtrate is concentrated under
reduced pressure to remove the organic solvent. The aqueous residue is extracted with DCM (2 x 1
L). The combined organic extracts are washed with saturated aqueous NaHCO₃ solution (2 L),
15 dried over Na₂SO₄ and filtered. The filtrate is concentrated under reduced pressure to afford 226 g
of 2-methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionic acid ethyl ester as dark yellow oil.
Yield 92%; ES-MS: m/z 291 [M+H]; ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 1.32 (3 H, t,
 $J=7.17$ Hz), 1.66 (6 H, s), 2.20 (2 H, quin, $J=7.59$ Hz), 2.28 - 2.41 (2 H, m), 3.34 (2 H, t, $J=7.48$
Hz), 4.27 (2 H, q, $J=7.17$ Hz)

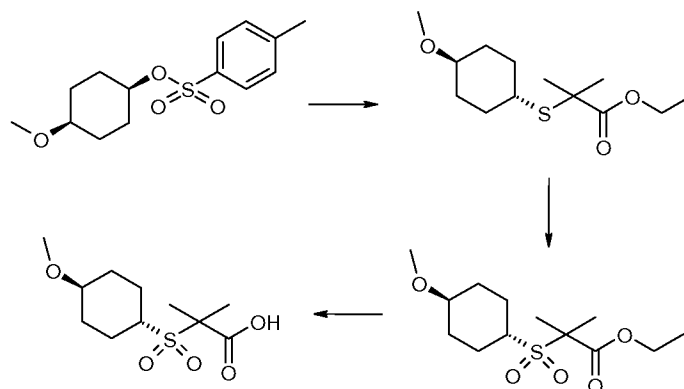
20

Step 3: Synthesis of 2-Methyl-2-(3-methyl-butane-1-sulfonyl)-propionic acid

To a solution of 170 g (0.59 mol) of 2-methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionic acid
ethyl ester in THF (3.4 L) are added 225.4 g (1.76 mol) of potassium trimethylsilanolate in
portions over 0.5 h. The reaction is stirred at room temperature for 18 h. The reaction mixture is
25 acidified with 2M aqueous HCl solution (2 L) to pH 2 and extracted with DCM (2 x 2 L). The
combined organic extracts are dried (Na₂SO₄) and filtered. The filtrate is concentrated under
reduced pressure to afford 143 g of 2-methyl-2-(3-methyl-butane-1-sulfonyl)-propionic acid as
yellow solids. Yield: 93%; ES-MS: m/z 261 [M-H]. ¹H-NMR (500 MHz, *CHLOROFORM-d*) δ
ppm 1.71 (6 H, s), 2.18 - 2.28 (2 H, m), 2.30 - 2.42 (2 H, m), 3.38 (2 H, t, $J=7.48$ Hz), 6.96 (1 H,
30 br. s.)

Acid Method D:

Synthesis of 2-(4-Methoxy-cyclohexanesulfonyl)-2-methyl-propionic acid



Step 1: Synthesis of 2-(4-Methoxy-cyclohexylsulfanyl)-2-methyl-propionic acid ethyl ester

Performed according to Step 2 for Method C employing 2.0 eq of NaOMe, 1.5 eq of 2-acetylsulfanyl-2-methyl-propionic acid ethyl ester 0.3M in EtOH and the crude product is purified by silica gel column chromatography, yield: 21%;

Step 2: Synthesis of 2-(4-Methoxy-cyclohexanesulfonyl)-2-methyl-propionic acid ethyl ester

Performed according to Step 2 for Method C employing 2.0 eq of Oxone in dioxane/ water 1/2.

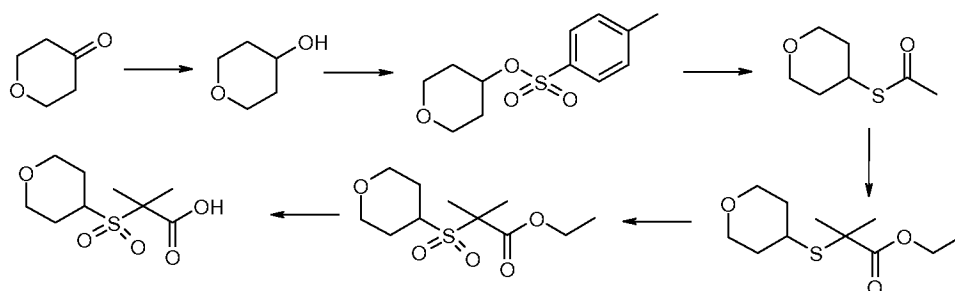
Step 3: Synthesis of 2-(4-Methoxy-cyclohexanesulfonyl)-2-methyl-propionic acid

Potassium trimethylsilanolate (3.1 g, 24.65 mmol) is added to a solution of 2-(4-methoxy-cyclohexanesulfonyl)-2-methyl-propionic acid ethyl ester (3.6 g, 12.3 mmol) in 100 mL of THF. After stirring the reaction mixture at room temperature for 4 h, the solvent is removed under reduced pressure, saturated aqueous NaHCO₃ solution is added and the mixtures is extracted with ethyl acetate. The two phases are separated and the aqueous layer is acidified with 2N aqueous HCl solution and extracted with ethyl acetate; the combined organic extracts are washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford 2.6 g of 2-(4-methoxy-cyclohexanesulfonyl)-2-methyl-propionic acid. Yield: 73%, over two steps. ¹H-NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.21 - 1.37 (2 H, m), 1.64 - 1.81 (8 H, m), 2.19 - 2.32 (4 H, m), 3.18 - 3.28 (1 H, m), 3.40 (3 H, s), 3.45 (1 H, tt, *J*=11.96, 3.53 Hz); ES-MS: *m/z* 263 [M-H]

Acid Method E:

Synthesis of 2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionic acid

5



Step 1: Synthesis of Tetrahydropyran-4-ol

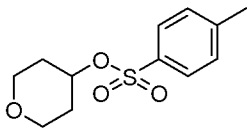
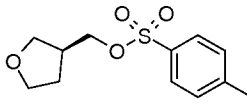
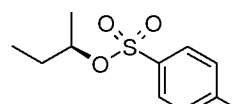
To a solution of 75 g (0.75 mol) of tetrahydropyran-4-one in THF (150 mL) is added a suspension of 28.4 g (0.75 mol) LiAlH₄ in THF (600 mL) under nitrogen atmosphere maintaining the temperature below 30 °C with the aid of an ice-bath. Then the reaction is allowed to warm to room temperature and stirred for 5 h. The reaction is quenched by addition of saturated aqueous NH₄Cl solution until effervescence ceased. The resulting precipitate is removed by filtration through Celite® and washed with THF (150 mL). The filtrate is concentrated under reduced pressure to afford 71.1 g of tetrahydropyran-4-ol as a pale yellow oil. Yield: 92%, ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.54 (2 H, m, *J*=13.37, 9.55, 9.55, 4.22 Hz), 1.81 - 1.92 (2 H, m), 2.11 (1 H, br. s.), 3.38 - 3.47 (2 H, m), 3.83 (1 H, tt, *J*=9.10, 4.38 Hz), 3.94 (2 H, dt, *J*=11.88, 4.15 Hz)

Step 2: Synthesis of Toluene-4-sulfonic acid tetrahydropyran-4-yl ester

To a solution of 133 g (1.31 mol) of tetrahydropyran-4-ol in pyridine (1.5 L) are added 373 g (1.95 mol) of p-toluenesulfonylchloride portionwise at 10 °C. After complete addition the reaction is allowed to warm to room temperature and stirred for 18 h. The reaction is poured onto a stirred mixture of aqueous HCl/ice. The resulting precipitate is isolated by filtration and dissolved in DCM (1 L). The organic layer is washed with 1M aqueous HCl solution (1 L), followed by saturated aqueous NaHCO₃ solution (1 L) and is then dried over Na₂SO₄. Filtration and concentration of the filtrate under reduced pressure gives 300 g of toluene-4-sulfonic acid tetrahydropyran-4-yl ester as an orange oil. Yield: 90%, ES-MS: *m/z*: 257 [M+H], 279 [M+Na]

According to this procedure the following esters are synthesized:

Table IX

Structure	¹ H NMR	Yield [%]	m/z [M+H]
	(250 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.66 - 1.96 (4 H, m), 2.45 (3 H, s), 3.47 (2 H, ddd, <i>J</i> =11.76, 8.19, 3.50 Hz), 3.79 - 3.95 (2 H, m), 4.69 (1 H, tt, <i>J</i> =8.13, 4.13 Hz), 7.35 (2 H, d, <i>J</i> =8.07 Hz), 7.76 - 7.87 (2 H, m)	90	257
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.51 - 1.60 (1 H, m), 1.96 - 2.06 (1 H, m), 2.46 (3 H, s), 2.60 (1 H, dt, <i>J</i> =13.58, 6.79 Hz), 3.50 (1 H, dd, <i>J</i> =9.16, 5.04 Hz), 3.69 (1 H, q, <i>J</i> =7.68 Hz), 3.73 - 3.83 (2 H, m), 3.89 - 3.95 (1 H, m), 3.97 - 4.02 (1 H, m), 7.36 (2 H, d, <i>J</i> =8.09 Hz), 7.79 (2 H, d, <i>J</i> =8.24 Hz) [#]	95	257
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.83 (3 H, t, <i>J</i> =7.48 Hz), 1.26 (3 H, d, <i>J</i> =6.26 Hz), 1.47 - 1.70 (2 H, m), 2.45 (3 H, s), 4.57 (1 H, sxt, <i>J</i> =6.23 Hz), 7.34 (2 H, d, <i>J</i> =8.39 Hz), 7.81 (2 H, d, <i>J</i> =8.24 Hz);	62	[α] ₅₇₈ ²⁵ *

5 * [α]₅₇₈²⁵ -12.36 (3, CCl₄) (lit. [α]₅₇₈²⁵ -10.9 (2-4, CCl₄), Allen *et al. J. Org. Chem.*, **2003**, 48, 4527-4530)

[#]3-tetrahydrofuran carboxylic acid is resolved according to WO2007/068739 (Glaxo Group Ltd.) to afford (3*S*)-tetrahydro-3-furanylmethanol and (3*R*)-tetrahydro-3-furanylmethanol, which are used as the corresponding starting materials.

10

Step 3: Synthesis of Thioacetic acid S-(tetrahydro-pyran-4-yl) ester

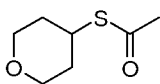
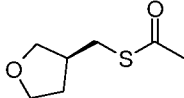
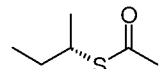
To a solution of 300 g (1.175 mol) of toluene-4-sulfonic acid tetrahydropyran-4-yl ester in DMF (3 L) are added 268 g (2.35 mol) potassium thioacetate, followed by a catalytic amount of NaI (0.12 g, 10 mol%) at room temperature. After complete addition, the reaction is heated to 50 °C
 15 for 20 h. The reaction mixture is partitioned between TBME (3 L) and water (3 L), the aqueous layer is extracted with TBME (2 L), then saturated with NaCl and extracted again with TBME (2 x 2 L). The combined organic extracts are dried over Na₂SO₄, filtered and the solvent is removed under reduced pressure to afford 153 g of thioacetic acid S-(tetrahydro-pyran-4-yl) ester. Yield: 81%; ES-MS: m/z 161 [M+H].

20

According to this procedure the following esters are synthesized:

Table X

Structure	¹ H-NMR	Yield [%]	m/z [M+H]
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	(250 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.47 - 1.98 (4 H, m), 2.30 (3 H, s), 3.41 - 3.74 (3 H, m), 3.88 (2 H, dt, $J=11.76, 3.86$ Hz)	86	161
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.57 - 1.69 (1 H, m), 2.07 - 2.15 (1 H, m), 2.36 (3 H, s), 2.47 (1 H, dt, $J=14.00, 6.96$ Hz), 2.92 - 3.04 (2 H, m), 3.48 (1 H, dd, $J=8.70, 6.10$ Hz), 3.77 (1 H, q, $J=7.73$ Hz), 3.84 - 3.93 (2 H, m)	81	161
	(500 MHz, <i>CHLOROFORM-d</i> + residual Et_2O) δ ppm 0.96 (3 H, t, $J=7.40$ Hz), 1.29 (3 H, d, $J=7.02$ Hz), 1.60 (2 H, quin, $J=7.25$ Hz), 2.31 (3 H, s), 3.46 - 3.55 (1 H, m under Et_2O peak)	76	N/A

5

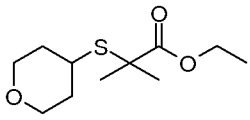
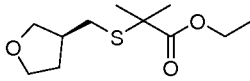
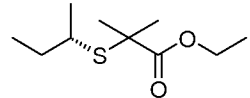
Step 4: Synthesis of 2-Methyl-2-(tetrahydro-pyran-4-ylsulfanyl)-propionic acid ethyl ester

A solution of 153 g (0.96 mol) of thioacetic acid S-(tetrahydro-pyran-4-yl) ester in ethanol (3.5 L) is degassed with nitrogen over 0.5 h and 125 g (2.23 mol) of KOH are added. Then a solution of 250 mL (1.68 mol) of ethyl α -bromoisobutyrate in EtOH (1 L) are added over 0.5 h, during which the temperature increased to 40 °C. The reaction is stirred for 18 h at room temperature under a nitrogen atmosphere. The reaction mixture is filtered, the solid is washed with ethanol (0.5 L) and the filtrate is concentrated under reduced pressure. The crude material is dryloaded onto silica and purified by dry-flash column chromatography (silica, eluent: n-heptanes, 2-10% ethyl acetate) to afford 158 g of 2-methyl-2-(tetrahydro-pyran-4-ylsulfanyl)-propionic acid ethyl ester as an orange-brown oil. Yield: 71%; ES-MS: m/z 233 [M+H]

According to this procedure the following esters are synthesized with the following modifications to be noted: for 1-(tetrahydro-pyran-4-ylsulfanyl)-cyclobutanecarboxylic acid ethyl ester: ethyl-1-bromocyclobutane carboxylate is used instead of ethyl α -bromoisobutyrate and the product is taken to the next step without further purification.

Table XI

Structure	^1H NMR	Yield [%]	m/z [M+H]
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	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.28 (3 H, t, $J=7.17$ Hz), 1.52 (6 H, s), 1.56 - 1.67 (2 H, m), 1.85 (2 H, dt, $J=13.35, 1.64$ Hz), 3.04 (1 H, tt, $J=10.60, 4.20$ Hz), 3.40 - 3.49 (2 H, m), 3.88 (2 H, dt, $J=11.75, 3.81$ Hz), 4.14 - 4.20 (2 H, m)	76	233
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.25 - 1.35 (3 H, m), 1.51 (6 H, s), 1.59 - 1.68 (1 H, m), 2.03 - 2.13 (1 H, m), 2.37 (1 H, dt, $J=14.27, 7.06$ Hz), 2.60 - 2.73 (2 H, m), 3.47 (1 H, dd, $J=8.70, 6.26$ Hz), 3.70 - 3.79 (1 H, m), 3.82 - 3.91 (2 H, m), 4.18 (2 H, q, $J=7.12$ Hz)	47	233
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.95 (3 H, t, $J=7.40$ Hz), 1.22 - 1.35 (7 H, m), 1.47 - 1.59 (7 H, m), 2.86 (1 H, sxt, $J=6.77$ Hz), 4.17 (2 H, q, $J=7.12$ Hz)	100	205

5

Step 5: Synthesis of 2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionic acid ethyl ester

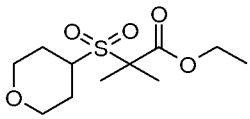
To a solution of 158 g (0.68 mol) of 2-methyl-2-(tetrahydro-pyran-4-ylsulfanyl)-propionic acid ethyl ester in dioxane/water (4/1, 1.6 L) are added 835 g (1.35 mol) of oxone® in portions over 50 min. The reaction mixture is stirred at room temperature for 18 h. The solid is removed by

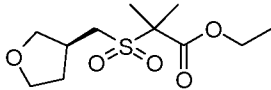
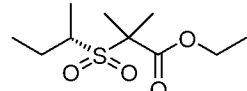
10 filtration and washed with dioxane (1 L). The combined filtrates are concentrated under reduced pressure. The residue is dissolved in ethyl acetate (1.5 L) and washed with water (1 L). The organic layer is dried over Na₂SO₄, filtered and the solvent is removed under reduced pressure to afford 166 g of 2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionic acid ethyl ester as a yellow oil. Yield: 92%, ES-MS: m/z 265 [M+H], 287 [M+Na].

15

According to this procedure the following esters are synthesized:

Table XII

Structure	¹ H-NMR	Yield [%]	m/z [M+H]
	(250 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.30 (3 H, t, $J=7.08$ Hz), 1.65 (6 H, s), 1.89 - 2.10 (4 H, m), 3.34 - 3.51 (2 H, m), 3.72 - 3.90 (1 H, m), 4.06 (2 H, dt, $J=11.69, 3.60$ Hz), 4.24 (2 H, q, $J=7.16$ Hz)	90	265, 287 [M+Na]

	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.34 (3 H, t, $J=7.10$ Hz), 1.67 (6 H, s), 1.74 - 1.83 (1 H, m), 2.30 (1 H, m, $J=12.57, 7.68, 7.68, 4.88$ Hz), 2.91 (1 H, dt, $J=14.23, 7.15$ Hz), 3.35 (2 H, d, $J=7.17$ Hz), 3.60 (1 H, dd, $J=8.85, 6.71$ Hz), 3.79 (1 H, q, $J=8.14$ Hz), 3.91 (1 H, td, $J=8.32, 4.88$ Hz), 4.05 (1 H, dd, $J=8.70, 7.32$ Hz), 4.28 (2 H, q, $J=7.17$ Hz)	83	265, 287 [M+Na]
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.05 (3 H, t, $J=7.48$ Hz), 1.34 (3 H, t, $J=7.10$ Hz), 1.40 (3 H, d, $J=6.87$ Hz), 1.62 - 1.70 (7 H, m), 2.06 (1 H, ddd, $J=13.96, 7.55, 3.81$ Hz), 3.54 - 3.63 (1 H, m), 4.27 (2 H, q, $J=7.17$ Hz)	80	237, 259 [M+Na]

5

Step 6: Synthesis of 2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionic acid

To a solution of 166 g (0.63 mol) of 2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionic acid ethyl ester in THF/water (4/1, 1.66 L) are added 50.5 g (1.26 mol) of NaOH pellets in portions over 20 min. The reaction is stirred at room temperature for 2.5 d. The organic solvent is removed under reduced pressure and the aqueous residue is diluted with water (2 L) and washed with DCM (2 L). The aqueous layer is acidified to pH 1-2 with concentrated HCl and then extracted with DCM (3 x 2 L). The acidic aqueous is further saturated with NaCl and extracted again with DCM (6 x 2 L). The combined organic extracts are concentrated under reduced pressure to give 123 g of 2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionic acid as a white solid. Yield: 83%, ES-MS: m/z 235 [M-H]

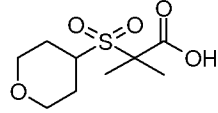
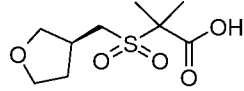
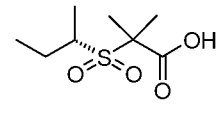
15

According to this procedure the following acids are synthesized with the following modification to be noted: for 1-(tetrahydro-pyran-4-sulfonyl)-cyclobutanecarboxylic acid: and 2-(butane-2-sulfonyl)-2-methyl-propionic acid, lithium hydroxide monohydrate is used instead of NaOH pellets.

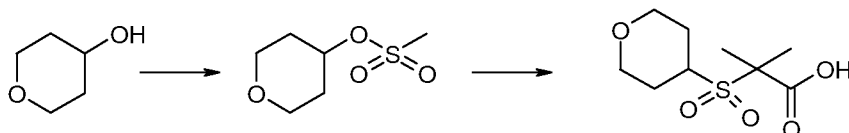
20

Table XIII

Structure	^1H NMR	Yield [%]	m/z [M-H]
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	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.71 (6 H, s), 1.94 - 2.12 (4 H, m), 3.47 (2 H, td, $J=11.41, 2.98$ Hz), 3.73 - 3.86 (1 H, m), 4.07 - 4.15 (2 H, m), 6.82 (1 H, br. s.)	69	235
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.66 - 1.71 (6 H, m), 1.79 - 1.89 (1 H, m), 2.32 (1 H, m, $J=12.61, 7.73, 7.73, 4.88$ Hz), 2.92 - 3.02 (1 H, m), 3.32 - 3.38 (1 H, m), 3.38 - 3.45 (1 H, m), 3.72 (1 H, dd, $J=9.08, 5.87$ Hz), 3.81 (1 H, q, $J=8.09$ Hz), 3.97 (1 H, td, $J=8.32, 4.88$ Hz), 4.03 (1 H, dd, $J=8.93, 7.10$ Hz)	100	237 [M+H], 259 [M+Na]
	(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.06 (3 H, t, $J=7.48$ Hz), 1.42 (3 H, d, $J=7.02$ Hz), 1.59 - 1.75 (7 H, m), 1.98 - 2.15 (1 H, m), 3.43 - 3.58 (1 H, m), 6.09 (1 H, br. s.)	40	207

5

Alternative Acid Method E:**Synthesis of 2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionic acid****Step 1: Synthesis of Methanesulfonic acid tetrahydropyran-4-yl ester**

10

10 kg tetrahydropyran-4-ol are dissolved in a mixture of 50 L toluene and 10.4 kg triethylamine. 11.55 kg methanesulfonyl chloride in 100 ml toluene are added while maintaining the internal temperature below 20°C by cooling, and the addition funnel is rinsed with 50 ml toluene. The stirring is continued for one hour. The precipitate is filtered and the filter cake is washed twice with 20 L toluene each. The filtrate is concentrated by vacuum evaporation (60 L were distilled off), seeding crystals and 50 L methylcyclohexane are added. The suspension is cooled to 2°C. After 1 h the product is isolated by filtration, washed with 30 L methylcyclohexane and dried at 30°C. 16.6 kg of the product are obtained as a white solid. Yield: 94%; ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 1.62-1.73 (2H, m), 1.92-2.00 (2H, m), 3.19 (3H, s), 3.42-3.49 (2H, m), 3.77-3.83 (2H, m), 4.80-4.88 (1H, m).

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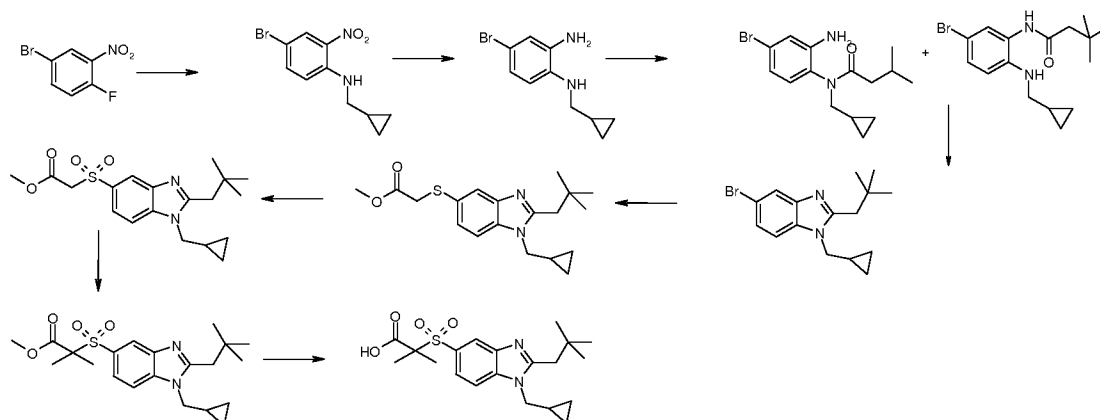
Step 2: Synthesis of 2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionic acid

30 g tetrahydro-2H-pyran-4-yl methansulfonate are dissolved in 270 ml degassed ethanol. 19.96 g potassium thioacetate are added and the reaction mixture is stirred at 77°C for 12-18 h. Upon cooling to 20°C, the precipitate is filtered and rinsed twice with 90 ml degassed ethanol. 6.66 g sodium hydroxide solution (50 %) are added to the filtrate, and the addition funnel is rinsed with 15 ml water. The reaction mixture is stirred at 25°C for 1 h. 32.47 g 2-bromo-2-methyl-propionic acid ethyl ester ethyl are added to the mixture, and the addition funnel is rinsed with 30 ml ethanol. The stirring is continued for 1 h at 25°C. Afterwards, 450 ml solvent are removed by vacuum evaporation. 240 ml toluene are added and 120 ml solvent are distilled off. 90 ml water are added and the phases are separated. To the organic layer subsequently 90 ml water, 2.75 g sodium tungstate dihydrate and 2.83 g tetrabutylammonium hydrogen sulfate are added. The reaction mixture is heated to 85°C and 80.88 g hydrogen peroxide solution (35%) are added over a period of 1 h. The addition funnel is rinsed with 30 ml water. The stirring is continued for 1 h at 85°C. The reaction mixture is filtered and the phases are separated. The organic phase is subsequently washed with 12.66 g sodium metabisulfite dissolved in 114 ml water and again with 126 ml water. 19.98 g sodium hydroxide solution (50 %) are added to the organic layer and the addition funnel is rinsed with 45 ml water. The reaction mixture is warmed to 50°C for 1 h. The phases are separated. The water phase is cooled to 5°C and acidified with 27.07 g HCl (37%). The stirring at 5°C is continued for 1 h. The precipitate is filtered, rinsed with 37.5 ml water and dried at 50°C. 14.03 g of the product are obtained as a white solid. Yield: 35%. ES-MS: m/z 237 [M+H]; ¹H NMR (400 MHz, *DMSO-d6*) δ ppm 1.53 (6H, s), 1.62-1.75 (2H, m), 1.85-1.92 (2H, m), 3.39 (2H, dt, ³J_{H,H} = 2.1 Hz, ³J_{H,H} = 11.7 Hz), 3.88-3.98 (3H, m), 13.63 (1H, s).

30

Acid Method F:

5 **Synthesis of 2-[1-Cyclopropylmethyl-2-(2,2-dimethyl-propyl)-1H-benzoimidazole-5-sulfonyl]-2-methyl-propionic acid**



10 The synthesis of 2-[1-cyclopropylmethyl-2-(2,2-dimethyl-propyl)-1H-benzoimidazole-5-sulfonyl]-2-methyl-propionic acid is described in WO2007/102059 (Pfizer Inc.).

Step 1 Synthesis of 4-Bromo-N-(cyclopropylmethyl)-2-nitroaniline

A mixture of 4-bromo-1-fluoro-2-nitrobenzene (9.25 g, 42 mmol), cyclopropanemethylamine (4.49 g, 63.1 mmol) and N,N-diisopropylethylamine (13.5 g, 105 mmol) in ethanol (100 mL) is stirred at 96 °C for 15 h. After cooling to room temperature, the mixture is concentrated under reduced pressure. The residue is purified by column chromatography (silica, eluent: ethyl acetate) to give 11.96 g of 4-bromo-N-(cyclopropylmethyl)-2-nitroaniline. Yield 100%, ES-MS: 271/273 [M+H].

Step 2: Synthesis of 4-Bromo-N¹-(cyclopropylmethyl)benzene-1,2-diamine

A mixture of 4-bromo-N-(cyclopropylmethyl)-2-nitroaniline (11.96, 44 mol), iron (12.3 g, 220 mmol) and ammonium chloride (236 mg, 4.4 mmol) in ethanol (120 mL) and water (40 mL) is stirred at 100 °C for 3 h. After cooling to room temperature, the mixture is filtered and the filtrate is concentrated under reduced pressure. The residue is dissolved in ethyl acetate (100 mL) and water (50 mL). The organic layer is separated, washed with brine (20 mL), dried over MgSO₄,

5 filtered and the filtrate is concentrated under reduced pressure to afford 9.6 g of 4-bromo-N¹-(cyclopropylmethyl)benzene-1,2-diamine as an oil. Yield: 90%, ES-MS: 241/243 [M+H].

Step 3: Synthesis of N-{5-bromo-2-[(cyclopropylmethyl)amino]phenyl}-3-3-dimethylbutanamide

10 To a solution of 4-bromo-N¹-(cyclopropylmethyl)benzene-1,2-diamine (9.6 g, 35 mmol) and N,N-diisopropylethylamine (4.6 g, 35 mmol) in DCM (77 mL) is added tert-butylacetyl chloride (4.7 g, 35 mmol) at 0 °C. The mixture is allowed to warm to room temperature and stirred for 3 d. The mixture is diluted with ethyl acetate (200 mL) and washed with saturated aqueous NaHCO₃ solution (100 mL x 2) and brine. The organic layer is dried over Na₂SO₄, filtered and concentrated
15 under reduced pressure. The residue is triturated with ethyl acetate, filtered and the solid rinsed with ethyl acetate to afford the title compound. The ethyl acetate washes are concentrated and the residue treated as above to afford additional crops, which are combined to yield 8.85 g of N-{5-bromo-2-[(cyclopropylmethyl)amino]phenyl}-3-3-dimethylbutanamide. Yield 74%, ES-MS: 339/341 [M+H]

20

Step 4: Synthesis of 5-Bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazole

A mixture of N-{5-bromo-2-[(cyclopropylmethyl)amino]phenyl}-3-3-dimethylbutanamide (8.85 g, 26 mmol) and p-toluenesulfonic acid monohydrate (4.97 g, 26 mmol) in toluene (177 mL) is
25 stirred at 130 °C temperature for 20 h with Dean Stark apparatus. The reaction is cooled to room temperature and further to 0 °C. The mixture is concentrated by $\frac{3}{4}$, diluted with ethyl acetate (150 mL) and washed with saturated aqueous NaHCO₃ solution (100 mL). The aqueous layer is extracted with ethyl acetate (100 mL) and the combined organic extracts are washed with brine (100 mL), dried over Na₂SO₄, filtered and the filtrate is concentrated under reduced pressure. The
30 residue is purified by column chromatography (silica, eluent: heptanes, 0-60% ethyl acetate) to afford a purple oil, which is taken up in heptanes, filtered and concentrated under reduced pressure to give 5.82 g of 5-bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazole as purple oil. Yield 69%, ES-MS: 321/323 [M+H]

5 **Step 5: Synthesis of Methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethyl-propyl)-1H-benzoimidazol-5-yl]thio}acetate**

To a solution of 5-bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazole (2.95 g, 9.2 mmol) in 1,4-dioxane (18 mL) is added N,N-diisopropylethylamine (2.38 g, 18.4 mmol), methyl mercapto acetate (0.98g, 9.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.21 g, 0.23 mmol) and 4,5bis(diphenylphosphino)-9,9-dimethylxanthene (0.27 g, 0.46 mmol). The mixture is stirred at 115 °C under nitrogen for 20 h. More tris(dibenzylideneacetone)dipalladium(0) (0.06 g, 0.07 mmol) and the reaction is heated for further 24 h. More tris(dibenzylideneacetone)dipalladium(0) (0.06 g, 0.07 mmol) and the reaction is heated for further 24 h. More tris(dibenzylideneacetone)dipalladium(0) (0.06 g, 0.07 mmol) and the reaction is heated for further 24 h. After cooling to room temperature, the mixture is filtered through Celite ® and the filter cake is washed with ethyl acetate. The filtrate is concentrated to dryness and the residue is purified by column chromatography (silica, eluent: cyclohexane, 0-50% ethyl acetate) to isolate 1.04 g of starting material, 5-bromo-1-(cyclopropylmethyl)-2-(2,2-dimethylpropyl)-1H-benzimidazole, and 1.91 g of methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethyl-propyl)-1H-benzoimidazol-5-yl]thio}acetate. Yield: 60% (93% based on recovered starting material); ES-MS: 347 [M+H].

Step 6: Synthesis of Methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethyl-propyl)-1H-benzoimidazol-5-yl]sulfonyl}acetate

25 To a solution of methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethyl-propyl)-1H-benzoimidazol-5-yl]thio}acetate (2.2 g, 6.3 mmol) in DCM (50 mL) is added m-chloroperbenzoic acid (3.31 g, 19.1 mmol) portionwise at 0 °C. The mixture is allowed to warm to room temperature and stirred for 3 h. The mixture is quenched with aqueous sodium sulfite solution (75 mL) and extracted with DCM (50 mL x 2). The combined organic extracts are dried, filtered and the filtrate is concentrated under reduced pressure. The residue is purified by column chromatography (silica, eluent: cyclohexane, 30-50% ethyl acetate) to afford 2.01 g of methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethyl-propyl)-1H-benzoimidazol-5-yl]sulfonyl}acetate. Yield: 84%, ES-MS: 379 [M+H].

5 **Step 7: Synthesis of Methyl 2-[[1-(cyclopropylmethyl)-2-(2,2-dimethyl-propyl)-1H-benzoimidazol-5-yl]sulfonyl]-2-methylpropanoate**

To a solution of methyl {[1-(cyclopropylmethyl)-2-(2,2-dimethyl-propyl)-1H-benzoimidazol-5-yl]sulfonyl}acetate (2 g, 5.28 mmol) in DMF (23 mL) under nitrogen is added NaH (60% dispersion in mineral oil, 0.47 g, 11.62 mmol) and methyl iodide (1.65 g, 11.62 mmol) at 0 °C.

10 The mixture is stirred at room temperature for 6 h. The mixture is quenched with saturated aqueous NH₄Cl solution (200 mL) and extracted with ethyl acetate (60 mL x 4). The combined organic extracts are washed with brine (20 mL), dried over Na₂SO₄, filtered and the filtrate is concentrated under reduced pressure. The residue is purified by column chromatography (silica, eluent: cyclohexane, 30% ethyl acetate) to afford 1.67g of methyl 2-[[1-(cyclopropylmethyl)-2-

15 (2,2-dimethyl-propyl)-1H-benzoimidazol-5-yl]sulfonyl]-2-methylpropanoate. Yield: 76%, ES-MS: 407 [M+H]

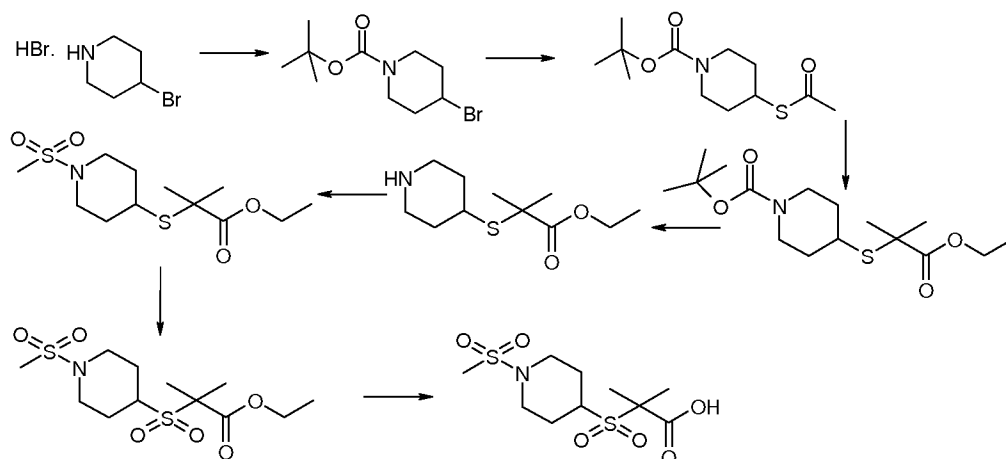
Step 8: Synthesis of 2-[[1-(Cyclopropylmethyl)-2-(2,2-dimethyl-propyl)-1H-benzoimidazol-5-yl]sulfonyl]-2-methylpropanoic acid

20 To a solution of methyl 2-[[1-(cyclopropylmethyl)-2-(2,2-dimethyl-propyl)-1H-benzoimidazol-5-yl]sulfonyl]-2-methylpropanoate (1.65 g, 4.06 mmol) in methanol (7.5 mL) and THF (7.5 mL) is added 2N aqueous NaOH solution at room temperature. The reaction is stirred for 3 h, then acidified with 2N aqueous HCl solution to pH 4 and concentrated under reduced pressure. The residue is partitioned between water (75 mL) and DCM (75 mL). The acidic aqueous layer is

25 extracted with DCM (50 mL x 2) and the combined organic extracts are dried over Na₂SO₄, filtered and the filtrate is concentrated under reduced pressure to afford 1.31 g of 2-[[1-(cyclopropylmethyl)-2-(2,2-dimethyl-propyl)-1H-benzoimidazol-5-yl]sulfonyl]-2-methylpropanoic acid. Yield: 82%, ES-MS: 393 [M+H]

30 **Acid Method G:**

Synthesis of 2-(1-Methanesulfonyl-piperidine-4-sulfonyl)-2-methyl-propionic acid



5

Step 1: Synthesis of 4-Bromo-piperidine-1-carboxylic acid tert-butyl ester

To a suspension of 5 g (0.02 mol) of 4-bromopiperidine hydrobromide salt in DCM (35 mL) are added 7.09 mL (0.04 mol) of N,N-diisopropylethyl amine dropwise at 0 °C. The reaction mixture is stirred for 30 min, then a solution of 6.67 g (0.31 mol) of di-tert-butyl dicarbonate in DCM (35 mL) is added dropwise to the reaction mixture. The reaction mixture is stirred for 18 h at room temperature, then washed with 1M aqueous HCl solution (2 x 30 mL) and brine (30 mL). The organic layer is dried over Na₂SO₄, filtered and the filtrate is concentrated under reduced pressure to afford 6.9 g of 4-bromo-piperidine-1-carboxylic acid tert-butyl ester as a yellow oil. Yield quantitative; ¹H NMR (250 MHz, *CHLOROFORM-d*) δ ppm 1.46 (9 H, s), 1.79 - 2.00 (2 H, m), 2.00 - 2.16 (2 H, m), 3.31 (2 H, ddd, *J*=13.67, 7.73, 3.73 Hz), 3.68 (2 H, ddd, *J*=13.55, 6.85, 3.65 Hz), 4.34 (1 H, tt, *J*=7.69, 3.81 Hz)

15

Step 2: Synthesis of 4-Acetylsulfanyl-piperidine-1-carboxylic acid tert-butyl ester

To a solution of 6.9 g (0.02 mol) of 4-bromo-piperidine-1-carboxylic acid tert-butyl ester in DMF (18 mL) are added 5.25 g (0.012 mmol) potassium thioacetate, followed by a catalytic amount of NaI (0.35 g, 10 mol%) at room temperature. After complete addition, the reaction is heated to 50 °C for 20 h. The reaction mixture is partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer is dried over Na₂SO₄, filtered and the solvent is removed under reduced pressure to afford 5.41 g of 4-acetylsulfanyl-piperidine-1-carboxylic acid tert-butyl ester as a brown oil. Yield: 81%; ES-MS: *m/z* 245 [*M*+*H*-CH₃], 160 [*M*+*H*-C₅H₉O₂]; ¹H NMR (250 MHz,

25

5 *CHLOROFORM-d*) δ ppm 1.37 - 1.64 (11 H, m), 1.78 - 1.99 (2 H, m), 2.25 - 2.35 (3 H, m), 3.06 (2 H, ddd, $J=13.63, 10.43, 3.05$ Hz), 3.61 (1 H, tt, $J=10.28, 4.04$ Hz), 3.76 - 3.96 (2 H, m)

Step 3: Synthesis of 4-(1-Ethoxycarbonyl-1-methyl-ethylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester

10 A solution of 5.41 g (0.02 mmol) of 4-acetylsulfanyl-piperidine-1-carboxylic acid tert-butyl ester in ethanol (50 mL) is degassed with nitrogen over 0.5 h and 2.34 g (0.04 mol) of KOH are added, followed by 8.14 g (0.04 mol) of ethyl α -bromoisobutyrate. The reaction is stirred for 18 h at room temperature under a nitrogen atmosphere. The reaction mixture is concentrated under reduced pressure. The residue is partitioned between DCM (100 mL) and water (100 mL). The organic layer is washed with water (50 mL), brine (250 mL), dried over Na_2SO_4 and filtered. The filtrate is concentrated under reduced pressure and purified by column chromatography (silica, eluent heptanes, 50% ethyl acetate) to afford 6.05 g of 4-(1-ethoxycarbonyl-1-methyl-ethylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester as a brown oil. Yield: 87%; ES-MS: m/z 354 $[\text{M}+\text{Na}]$, 232 $[[\text{M}+\text{H}-\text{C}_5\text{H}_9\text{O}_2]]$; ^1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 1.25 - 1.35 (3 H, m), 1.46 (9 H, s), 1.48 - 1.53 (2 H, m), 1.55 (6 H, s), 1.88 (2 H, dd, $J=13.31, 3.47$ Hz), 2.94 - 3.04 (3 H, m), 3.81 - 3.92 (2 H, m), 4.19 (2 H, q, $J=7.10$ Hz)

20

Step 4: Synthesis of 2-Methyl-2-(piperidin-4-ylsulfanyl)-propionic acid ethyl ester

Deprotection of 6.05 g (18.3 mmol) of 4-(1-ethoxycarbonyl-1-methyl-ethylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester is achieved by treatment with 4M aqueous HCl solution (9.13 mL) in dioxane (40 mL) at room temperature for 18 h. The reaction mixture is concentrated to afford 4.47 g of 2-methyl-2-(piperidin-4-ylsulfanyl)-propionic acid ethyl ester as its hydrochloride salt as a brown oil. Yield: 92%; ES-MS: m/z 232 $[\text{M}+\text{H}]$

25

^1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 1.21 (3 H, t, $J=7.13$ Hz), 1.45 (6 H, s), 1.80 - 1.90 (2 H, m), 2.17 (2 H, ddd, $J=10.78, 7.31, 3.66$ Hz), 2.96 - 3.05 (2 H, m), 3.07 - 3.15 (1 H, m), 3.18 - 3.30 (2 H, m), 4.09 (2 H, q, $J=7.12$ Hz), 9.44 (1 H, br. s.), 9.54 (1 H, br. s.)

30

5 **Step 5: Synthesis of 2-(1-Methanesulfonyl-piperidin-4-ylsulfanyl)-2-methyl-propionic acid ethyl ester**

To a solution of 4.47 g (16.74 mmol) of 2-methyl-2-(piperidin-4-ylsulfanyl)-propionic acid ethyl ester hydrochloride salt in anhydrous THF (30 mL) are added 13.45 mL (77.36 mmol) of N,N-diisopropylethylamine, followed by 2.98 mL (38.58 mmol) of methanesulfonyl chloride. The
10 reaction mixture is heated for 2 d to 60 °C. The mixture is concentrated under reduced pressure and the residue is partitioned between saturated aqueous NaHCO₃ solution (75 mL) and ethyl acetate (75 mL). The basic aqueous layer is extracted with ethyl acetate (2 x 50 mL). The combined organic layer is separated and washed with brine (50 mL), dried over MgSO₄ and filtered. The filtrate is concentrated under reduced pressure and the residue is purified by column
15 chromatography (silica, eluent: heptanes, 30% ethyl acetate) to give 2.17 g of 2-(1-methanesulfonyl-piperidin-4-ylsulfanyl)-2-methyl-propionic acid ethyl ester as a brown solid. Yield: 42%, ES-MS: m/z 310 [M+H]; ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.22 (3 H, t, *J*=7.11 Hz), 1.47 (6 H, s), 1.59 - 1.69 (2 H, m), 1.92 - 2.00 (2 H, m), 2.70 (3 H, s), 2.90 - 2.99 (3 H, m), 3.39 - 3.47 (2 H, m), 4.10 (2 H, q, *J*=7.12 Hz)

20

Step 6: Synthesis of 2-(1-Methanesulfonyl-piperidine-4-sulfonyl)-2-methyl-propionic acid ethyl ester

To a stirred solution of 2.17 g (7.02 mmol) of 2-(1-methanesulfonyl-piperidin-4-ylsulfanyl)-2-methyl-propionic acid ethyl ester in acetic acid (20 mL) are added 2.39 mL (35.1 mmol) of 50%
25 aqueous hydrogen peroxide solution. The reaction is stirred at 80 °C for 1.5 h. After cooling the reaction mixture is concentrated under reduced pressure to afford 2.91 g of 2-(1-methanesulfonyl-piperidine-4-sulfonyl)-2-methyl-propionic acid ethyl ester as a white solid, which is used in the next step without further purification. Yield: quantitative; ES-MS: m/z 342 [M+H]; ¹H NMR (250 MHz, CHLOROFORM-*d*) δ ppm 1.36 (3 H, t, *J*=7.14 Hz), 1.70 (6 H, s), 2.06 - 2.27 (4 H, m), 2.83
30 (3 H, s), 2.93 - 3.06 (2 H, m), 3.75 - 3.89 (3 H, m), 4.29 (2 H, q, *J*=7.13 Hz)

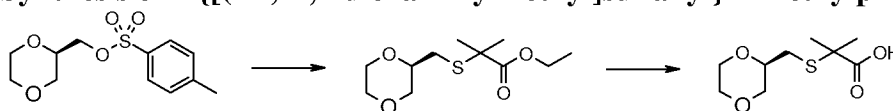
Step 7: Synthesis of 2-(1-Methanesulfonyl-piperidine-4-sulfonyl)-2-methyl-propionic acid

To a suspension of 2.91 g (8.53 mmol) of 2-(1-methanesulfonyl-piperidine-4-sulfonyl)-2-methyl-propionic acid ethyl ester in THF/water (1/1, 60 mL) are added 2.56 g (34.13 mmol) of lithium

5 hydroxide monohydrate. The reaction is stirred at room temperature for 3 d and then concentrated under reduced pressure. The residue is partitioned between brine (20 mL) and DCM (20 mL). The aqueous layer is further acidified with 2M aqueous HCl solution to pH 1 and extracted with DCM. The combined organic extracts are concentrated under reduced pressure to afford 1.68 g of 2-(1-methanesulfonyl-piperidine-4-sulfonyl)-2-methyl-propionic acid. Yield 63%, ES-MS: 314 [M+H];
 10 ¹H NMR (500 MHz, *MeOD*) δ ppm 1.66 (6 H, s), 1.86 - 1.97 (2 H, m), 2.24 (2 H, dd, *J*=13.64, 2.54 Hz), 2.87 (3 H, s), 2.92 (2 H, td, *J*=12.00, 2.59 Hz), 3.81 (2 H, dt, *J*=12.45, 3.13 Hz), 3.94 (1 H, tt, *J*=11.41, 3.79 Hz)

Acid Method H :

Synthesis of 2-[(2R)-1,4-dioxan-2-ylmethyl]sulfanyl}-2-methylpropanoic acid



Step 1: Synthesis of ethyl 2-[(2R)-1,4-dioxan-2-ylmethyl]sulfanyl}-2-methylpropanoate

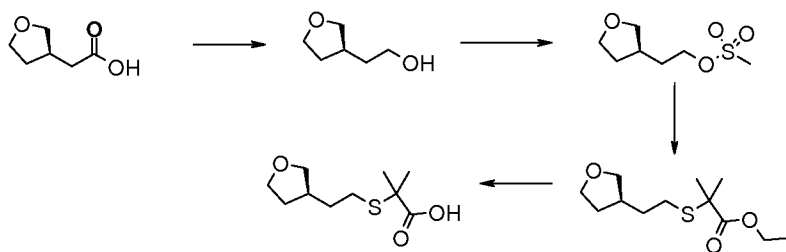
To a solution of 0.27 g (1.42 mmol) of 2-acetylsulfanyl-2-methyl-propionic acid ethyl ester in ethanol (4 mL, degassed) are added 0.31 g (5.7 mmol) of sodium methoxide, followed by 0.39
 20 g (1.42 mmol) of (2R)-1,4-dioxan-2-ylmethyl 4-methylbenzene-1-sulfonate (prepared according to WO2008/119663, F. Hoffmann-La Roche AG) under nitrogen atmosphere. The reaction is heated in a microwave to 130 °C for 0.5 h. The solvent is removed under reduced pressure. The residue is dissolved in DCM (10 mL) and washed with saturated aqueous NaHCO₃ solution (10 mL). The aqueous layer is extracted with DCM (10 mL). The combined
 25 organic extracts are dried over Na₂SO₄, filtered and the filtrate is concentrated under reduced pressure. The residue is purified by column chromatography (silica, eluent: heptanes, 20% ethyl acetate) to afford 0.17 g of ethyl 2-[(2R)-1,4-dioxan-2-ylmethyl]sulfanyl}-2-methylpropanoate (UV purity: 77%). Yield: 61%, *m/z* 271 [M+Na]; ¹H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 1.29 (3 H, t, *J*=7.17 Hz), 1.49 - 1.54 (6 H, m), 2.59 - 2.66 (1 H, m),
 30 2.70 - 2.77 (1 H, m), 3.28 - 3.36 (1 H, m), 3.55 - 3.63 (1 H, m), 3.64 - 3.76 (3 H, m), 3.77 - 3.85 (2 H, m), 4.18 (2 H, q, *J*=7.17 Hz)

Step 2: Synthesis of 2-[[[(2R)-1,4-dioxan-2-ylmethyl]sulfanyl]-2-methylpropanoic acid

To a solution of 169 mg (0.68 mmol) of ethyl 2-[[[(2R)-1,4-dioxan-2-ylmethyl]sulfanyl]-2-methylpropanoate in THF/water (1/1, 10 mL) are added 102 mg (1.36 mmol) of lithium hydroxide monohydrate. The reaction is stirred at room temperature for 18 d h. Then additional THF/water (1/1, 10 mL) is added and the reaction is for further 48 h.. The reaction mixture is concentrated under reduced pressure. The aqueous residue is washed with diether ether (10 mL), then acidified with 6M aqueous HCl solution and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts are dried (MgSO₄), filtered and the filtrate is concentrated under reduced pressure to afford 147 mg of 2-[[[(2R)-1,4-dioxan-2-ylmethyl]sulfanyl]-2-methylpropanoic acid. Yield: 86%; ES-MS: m/z 243 [M+Na]; ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.55 (6 H, s), 2.65 - 2.72 (1 H, m), 2.73 - 2.81 (1 H, m), 3.32 - 3.41 (1 H, m), 3.57 - 3.64 (1 H, m), 3.68 - 3.77 (3 H, m), 3.77 - 3.86 (2 H, m)

Acid Method I:

Synthesis of Synthesis of 2-Methyl-2-((2-[(3R)-oxolan-3-yl]ethyl)sulfanyl)propanoic acid



Step 1: Synthesis of 2-[(3S)-oxolan-3-yl]ethan-1-ol

To a solution of 1.20 g (9.22 mmol) of 2-[(3R)-oxolan-3-yl]acetic acid (prepared as described in Ghosh, A. K. *et al. J. Med. Chem.* **1993**, 36, 2300-2310) in anhydrous THF (10 ml) is added 0.93 ml of borane (14.75 mmol) slowly. The reaction is stirred at room temperature for 4 h, then 3M aqueous NaOH solution (8 mL) is added and the mixture is stirred for 1 h. The pH is then adjusted to 11 with 6M aqueous HCl solution and the aqueous mixture is saturated with potassium carbonate. The basic aqueous solution is extracted with diethyl ether (2 x 30 mL). The combined organic extracts are dried (MgSO₄), filtered and the filtrate is concentrated under reduced pressure to give 0.92 g of 2-[(3S)-oxolan-3-yl]ethan-1-ol. Yield: 86%, ¹H NMR

5 (500 MHz, *CHLOROFORM-d*) δ ppm 1.49 - 1.59 (1 H, m), 1.61 - 1.70 (1 H, m), 2.01 - 2.12 (1 H, m), 2.20 - 2.37 (2 H, m), 3.37 (1 H, t, $J=7.78$ Hz), 3.60 - 3.70 (2 H, m), 3.74 (1 H, q, $J=7.88$ Hz), 3.85 (1 H, td, $J=8.32, 4.58$ Hz), 3.91 (1 H, t, $J=7.78$ Hz).

2-[(3R)-oxolan-3-yl]ethan-1-ol is synthesised from 2-[(3S)-oxolan-3-yl]acetic acid (prepared as described in Ghosh, A. K. *et al. J. Med. Chem.* **1993**, 36, 2300-2310) according to the
10 above procedure. Yield: 73%; ^1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 1.47 - 1.73 (3 H, m), 1.98 (1 H, br. s.), 2.02 - 2.12 (1 H, m), 2.31 (1 H, dt, $J=14.80, 7.40$ Hz), 3.37 (1 H, t, $J=7.78$ Hz), 3.59 - 3.79 (3 H, m), 3.85 (1 H, td, $J=8.32, 4.58$ Hz), 3.91 (1 H, t, $J=7.78$ Hz).

Step 2: Synthesis of 2-[(3R)-oxolan-3-yl]ethyl methanesulfonate

15 To a solution of 1.00 g (0.861 mmol) of 2-[(3S)-oxolan-3-yl]ethan-1-ol in anhydrous THF (1.5 mL) are added triethyl amine (0.13 mL, 0.947 mmol) and methanesulfonyl chloride (0.07 mL, 0.947 mmol) slowly at 0 °C. The reaction is stirred at room temperature for 2 h. The mixture is diluted with ethyl acetate (20 mL) and washed with saturated aqueous NaHCO_3 solution (2 x 5 mL) and 1M aqueous HCl solution (2 x 5 mL). The organic layer is dried (MgSO_4), filtered
20 and the filtrate is concentrated under reduced pressure to afford 167 mg of 2-[(3R)-oxolan-3-yl]ethyl methanesulfonate. Yield: 100%; ^1H NMR (250 MHz, *CHLOROFORM-d*) δ ppm 1.40 - 1.60 (1 H, m), 1.70 - 1.87 (1 H, m), 1.95 - 2.12 (1 H, m), 2.16 - 2.37 (1 H, m), 2.96 (3 H, s), 3.32 (1 H, dd, $J=8.22, 7.16$ Hz), 3.62 - 3.91 (3 H, m), 4.13 - 4.24 (2 H, m).

25 2-[(3S)-oxolan-3-yl]ethyl methanesulfonate is synthesised from 2-[(3R)-oxolan-3-yl]ethan-1-ol according to the above procedure. Yield: 100%; ^1H NMR (250 MHz, *CHLOROFORM-d*) δ ppm 1.48 - 1.62 (1 H, m), 1.78 - 1.93 (1 H, m), 2.01 - 2.20 (1 H, m), 2.24 - 2.43 (1 H, m), 3.02 (3 H, s), 3.40 (1 H, t, $J=7.69$ Hz), 3.73 - 3.99 (3 H, m), 4.26 (2 H, t, $J=6.47$ Hz)

30 Step 3: Synthesis of Ethyl 2-methyl-2-({2-[(3R)-oxolan-3-yl]ethyl}sulfanyl)propanoate

To a solution of 1.13 g (5.94 mmol) of 2-acetylsulfanyl-2-methyl-propionic acid ethyl ester in ethanol (20 mL, degassed) are added 1.28 g (23.7 mmol) of sodium methoxide, followed by

5 1.13 g (5.94 mmol) of 2-[(3R)-oxolan-3-yl]ethyl methanesulfonate under nitrogen atmosphere. The reaction is heated to 80 °C for 16 h. The solvent is removed under reduced pressure. The residue is dissolved in ethyl acetate (50 mL) and washed with saturated aqueous NaHCO₃ solution (2 x 15 mL) and 1M aqueous HCl solution (2 x 15 mL). The organic layer is dried over Na₂SO₄, filtered and the filtrate is concentrated under reduced pressure. The residue is
10 purified twice by column chromatography (silica, eluent: heptanes, ethyl acetate) to afford 0.43 g of ethyl 2-methyl-2-({2-[(3R)-oxolan-3-yl]ethyl}sulfanyl)propanoate (UV purity: 70%). Yield: 21%, m/z 247 [M+H]; ¹H NMR (250 MHz, CHLOROFORM-*d*) δ ppm 1.29 (3 H, t, *J*=7.08 Hz), 1.43 - 1.81 (9 H, m), 1.95 - 2.16 (1 H, m), 2.20 - 2.35 (1 H, m), 2.53 - 2.67 (2 H, m), 3.34 (1 H, dd, *J*=8.38, 7.16 Hz), 3.66 - 3.98 (3 H, m), 4.17 (2 H, q, *J*=7.06 Hz)

15

Ethyl 2-methyl-2-({2-[(3S)-oxolan-3-yl]ethyl}sulfanyl)propanoate is synthesised from 2-[(3S)-oxolan-3-yl]ethyl methanesulfonate according to the above procedure. This intermediate (67% purity) is taken on in the next step. Yield: 29%; m/z 247 [M+H]

20 **Step 4: Synthesis of 2-Methyl-2-({2-[(3R)-oxolan-3-yl]ethyl}sulfanyl)propanoic acid**

To a solution of 0.43 g (1.75 mmol) of ethyl 2-methyl-2-({2-[(3R)-oxolan-3-yl]ethyl}sulfanyl)propanoate in THF/water (4/1, 6.5 mL) are added 84 mg (3.49 mmol) of lithium hydroxide monohydrate. The reaction is stirred at room temperature for 18 h. Then methanol (0.5 mL) is added and the reaction is heated to 45 °C for 16h. Additional lithium
25 hydroxide monohydrate (83 mg, 3.49 mmol) is added and the reaction is heated to 55 °C for 3 h. The reaction mixture is partitioned between DCM (8 mL) and water (10 mL). The aqueous layer is cooled in an ice bath, acidified with 6M aqueous HCl solution to pH 1 and extracted with DCM (3 x 15 mL). The combined organic extracts are dried (MgSO₄), filtered and the filtrate is concentrated under reduced pressure to afford 351 mg of 2-methyl-2-({2-[(3R)-
30 oxolan-3-yl]ethyl}sulfanyl)propanoic acid. Yield: 92%; ES-MS: m/z 219 [M+H]; ¹H NMR (250 MHz, CHLOROFORM-*d*) δ ppm 1.43 - 1.76 (9 H, m), 1.96 - 2.16 (1 H, m), 2.31 (1 H, quin, *J*=7.31 Hz), 2.56 - 2.77 (2 H, m), 3.37 (1 H, dd, *J*=8.22, 7.16 Hz), 3.68 - 4.05 (3 H, m), 7.62 (1 H, br. s.)

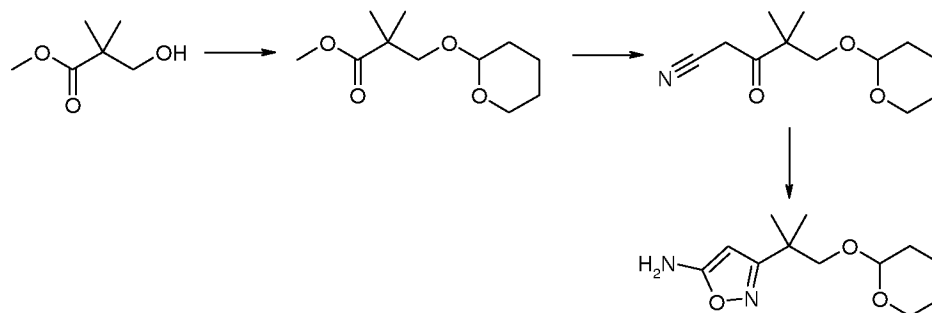
5

2-Methyl-2-({2-[(3S)-oxolan-3-yl]ethyl}sulfanyl)propanoic acid is synthesised from ethyl 2-methyl-2-({2-[(3S)-oxolan-3-yl]ethyl}sulfanyl)propanoate according to the above procedure. Yield: 85%; m/z 219 [M+H]; ¹H NMR (250 MHz, *CHLOROFORM-d*) δ ppm 1.43 - 1.73 (9 H, m), 1.98 - 2.15 (1 H, m), 2.31 (1 H, quin, *J*=7.35 Hz), 2.58 - 2.74 (2 H, m), 3.37 (1 H, dd, *J*=8.30, 7.23 Hz), 3.68 - 3.99 (3 H, m), 7.71 (1 H, br. s.)

10

Amine Method A:

Synthesis of 3-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-ylamine



15

Step 1: Synthesis of 2,2-Dimethyl-3-(tetrahydro-pyran-2-yloxy)-propionic acid methyl ester

To a solution of 66.3 mL (0.51 mol) of hydroxypivalic acid methyl ester in DCM (325 mL) are added 95.8 mL (1.04 mol) of 3,4-dihydro-2H-pyran. The reaction mixture is cooled to 0 °C and sulfuric acid on silica gel (2.04 g, 0.2 mL sulfuric acid/10 g silica gel) is added and the reaction mixture is stirred at room temperature for 25 minutes. After this time, the reaction mixture is filtered and concentrated under reduced pressure to yield 129 g of 2,2-dimethyl-3-(tetrahydro-pyran-2-yloxy)-propionic acid methyl ester as a yellow oil, which is used in the next step without further purification. Yield: quantitative; ¹H NMR (400 MHz, *DMSO-d6*) δ ppm 1.12 (6H, s), 1.13 (6H, s), 1.4-1.7 (6H, m), 3.3 (1H, m), 3.4 (1H, m), 3.6 (3H, s), 3.65 (1H, d), 3.7 (1H, m), 4.55 (1H, t).

25

Step 2: Synthesis of 4,4-Dimethyl-3-oxo-5-(tetrahydro-pyran-2-yloxy)-pentanenitrile

5 A solution of 129 g (0.60 mol) of 2,2-dimethyl-3-(tetrahydro-pyran-2-yloxy)-propionic acid methyl ester and 44 mL (0.84 mol) of acetonitrile in toluene (250 mL) is added dropwise to the refluxing suspension of 33 g (0.84 mol) of sodium hydride (60 % in mineral oil) in toluene (600 mL) over a period of 2 h. After the addition, the reaction mixture is stirred at reflux for 3 h. Additional 16.7 g (0.42 mol) of sodium hydride (60% dispersion in mineral oil) and 22 mL (0.42
10 mol) of acetonitrile are added to the reaction mixture and the refluxing is continued for another 1.5 h. After this time, the reaction mixture is cooled to room temperature and ice water (~ 0.8 L) is added. The layers are separated and the aqueous layer is neutralized to pH ~ 6-7 by adding 1M aqueous HCl solution. The aqueous layer is extracted with ethyl acetate (3 × 0.8 L). The organic layers are combined, washed with brine (1.5 L), dried over Na₂SO₄ and filtered. The filtrate is
15 concentrated under reduced pressure to yield 137 g of 4,4-dimethyl-3-oxo-5-(tetrahydro-pyran-2-yloxy)-pentanenitrile as a brown oil, which is used in the next step without further purification. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 1.09 (6H, s), 1.10 (6H, s), 1.4-1.7 (6H, m), 3.3 (1H, m), 3.35 (1H, d), 3.4 (1H, m), 3.6 (1H, d), 3.7 (1H, m), 4.2 (1H, s); 4.55 (1H, t)..

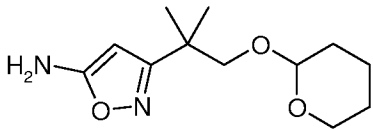
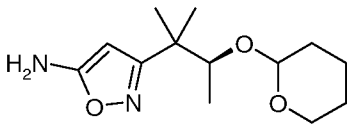
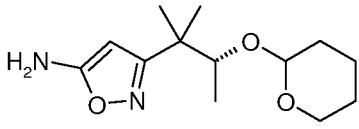
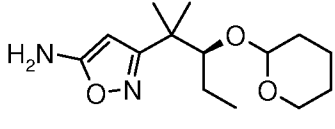
20 **Step 3: Synthesis of 3-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-ylamine**

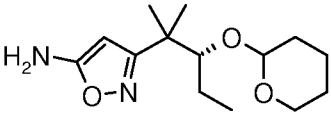
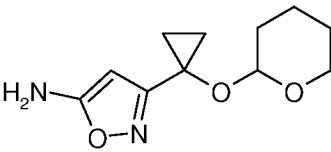
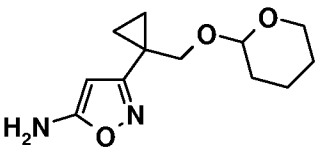
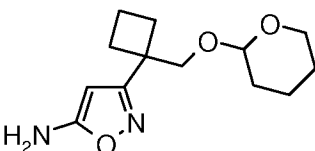
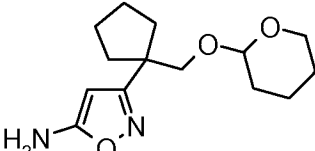
To a stirred solution of 134 g (0.60 mol) of 4,4-dimethyl-3-oxo-5-(tetrahydro-pyran-2-yloxy)-pentanenitrile and 51.3 g (1.28 mol) of sodium hydroxide in water (1.3 L) are added 48.9 g (0.30 mol) of hydroxylamine sulfate. The reaction mixture is stirred at reflux for 18 hours. After this
25 time, the reaction mixture is cooled to room temperature and extracted with ethyl acetate (3 × 0.8 L). The organic layers are combined and washed with brine (1 L), dried over Na₂SO₄ and filtered. The filtrate is concentrated under reduced pressure. The residual brown oil is triturated with hexanes (0.8 L) while stirring and the resulting precipitate is isolated by filtration and dried in a vacuum oven for 2 d to yield 85 g of 3-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-
30 isoxazol-5-ylamine as a yellow solid. Yield 60%; m/z 241 [M+H], 157 [M+H-84]; ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 1.18 (3H, s), 1.19 (3H, s), 1.45-1.75(6H, m), 3.26 (1H, d, J = 9.3Hz), 3.4 (1H, m), 3.59 (1H, d, J = 9.3 Hz), 3.68 (1H, m), 4.5 (1H, m), 4.88 (1H, s), 6.43 (2H, s).

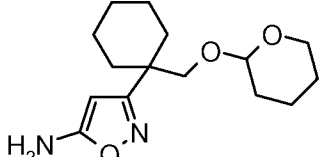
According to this procedure the following amines are synthesized:

5

Table XIV

Structure	¹ H-NMR	Yield [%]	m/z [M+H]
	(400 MHz, <i>DMSO-d</i> ₆) δ ppm 1.18 (3H, s), 1.19 (3H, s), 1.45-1.75(6H, m), 3.26 (1H, d, J = 9.3Hz), 3.4 (1H, m), 3.59 (1H, d, J = 9.3 Hz), 3.68 (1H, m), 4.5 (1H, m), 4.88 (1H, s), 6.43 (2H, s).	60	241
	Mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.99 (3H, d, isomer A), 1.15 (3H, d, isomer B), 1.23 (3H, s, isomer B), 1.26 (3H, s, isomer B), 1.30 (3H, s, isomer A), 1.32 (3H, s, isomer A), 1.43-1.61 (4H, isomer A+B), 1.61-1.86 (2H, isomer A+B), 3.42-3.50 (1H, m, isomer A+B), 3.48 (1H, s, isomer A+B), 3.61-3.95 (2H, m, isomer A+B), 4.53-4.57 (1H, m, isomer B), 4.70-4.74 (1H, m, isomer A), 5.09 (1H, s, isomer B), 5.12 (1H, s, isomer A).	56 ^{a, #}	255
	Mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.99 (3H, d, isomer A), 1.15 (3H, d, isomer B), 1.23 (3H, s, isomer B), 1.26 (3H, s, isomer B), 1.30 (3H, s, isomer A), 1.32 (3H, s, isomer A), 1.43-1.61 (4H, isomer A+B), 1.61-1.86 (2H, isomer A+B), 3.42-3.50 (1H, m, isomer A+B), 3.48 (1H, s, isomer A+B), 3.61-3.95 (2H, m, isomer A+B), 4.53-4.57 (1H, m, isomer B), 4.70-4.74 (1H, m, isomer A), 5.09 (1H, s, isomer B), 5.12 (1H, s, isomer A).	34 ^{a, #}	255
	Mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.88 (3H, t, isomer A), 0.95 (3H, t, isomer B), 1.22 (3H, s, isomer A), 1.25 (3H, s, isomer A), 1.30 (3H, s, isomer B), 1.32 (3H, s, isomer B), 1.19-1.40 (2H, m, isomer A+B), 1.42-1.62 (4H, m, isomer A+B), 1.68-1.88 (2H, m, isomer A+B),	16 ^{a, #}	269

	3.40-3.55 (2H, m, isomer A+B), 3.85-4.00 (1H, m, isomer A+B), 4.20-4.42 (2H, br, isomer A+B), 4.42-4.48 (1H, isomer A), 4.60-4.66 (1H, isomer B), 5.08 (1H, isomer A), 5.12 (1H, isomer B).		
	Mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.88 (3H, t, isomer A), 0.95 (3H, t, isomer B), 1.22 (3H, s, isomer A), 1.25 (3H, s, isomer A), 1.30 (3H, s, isomer B), 1.32 (3H, s, isomer B), 1.19-1.40 (2H, m, isomer A+B), 1.42-1.62 (4H, m, isomer A+B), 1.68-1.88 (2H, m, isomer A+B), 3.40-3.55 (2H, m, isomer A+B), 3.85-4.00 (1H, m, isomer A+B), 4.20-4.42 (2H, br, isomer A+B), 4.42-4.48 (1H, isomer A), 4.60-4.66 (1H, isomer B), 5.08 (1H, isomer A), 5.12 (1H, isomer B).	19 ^{a,#}	185 [M-83]
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.93-1.02 (1H, m), 1.13-1.25 (2H, m), 1.4-1.63 (4H, m), 1.65-1.90 (3H, m), 3.4-3.5 (1H, m), 3.8-3.9 (1H, m), 4.83-4.87 (1H, m), 5.15 (1H, s).	46 ^{b,#}	225
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.91 - 0.97 (m, 2H), 1.05 - 1.23 (m, 2H), 1.48 - 1.63 (m, 4H), 1.67 - 1.75 (m, 1H), 1.78 - 1.86 (m, 1H), 3.47 - 3.53 (m, 1H), 3.63 (d, 1H), 3.79 - 3.88 (m, 2H), 4.29 (bs, 2H), 4.67 (dd, 1H), 5.14 (s, 1H)	36 ^{a,#}	261 [M+Na]
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.45-1.62 (4H, m), 1.62-1.72 (1H, m), 1.72-1.90 (1H, m), 1.90-2.10 (2H, m), 2.10-2.35 (2H, m), 2.35-2.45 (2H, m), 3.44-3.60 (1H, m), 3.50 (1H, d), 3.75-3.90 (1H, m), 3.95 (1H, d), 4.50 (1H, t), 5.10 (1H, s)	20 ^b	253
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.40-1.90 (12H, m), 1.95-2.10 (2H, m), 3.40 (1H, d), 3.40-3.50 (1H, m), 3.70-3.80 (1H, m), 3.80 (1H, d), 4.55 (1H, t), 5.10 (1H, s)	32 ^b	265

	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.20-1.80 (14H, m), 1.90-2.10 (2H, m), 3.25 (1H, d), 3.40-3.50 (1H, m), 3.65- 3.75 (1H, m), 3.70 (1H, d), 4.50 (1H, t), 5.10 (1H, s)	16 ^b	281
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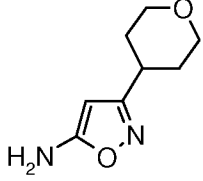
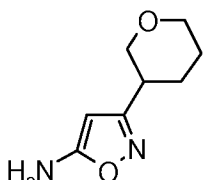
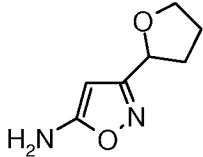
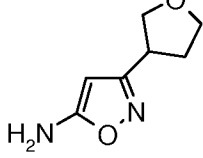
5 a) 2.0eq of NaH is used in one portion; 2.0eq of acetonitrile is used.

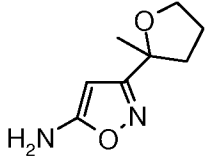
b) 1.4eq of NaH is used in one portion; 2.0eq of acetonitrile is used.

chromatographic column is performed after the third step

10 The following amines are synthesized following step 2 and 3 of Method A, starting from the corresponding methyl ester:

Table XV

Structure	¹ H-NMR	Yield over two steps [%]	m/z [M+H]
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.73 - 1.86 (m, 4H), 2.83 - 2.90 (m, 1H), 3.51 (td, 2H), 4.01 - 4.06 (m, 2H), 4.40 (bs, 2H), 5.02 (s, 1H).	12 (chromatographic column after first step)	169
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.65 - 1.76 (m, 3H), 2.09 - 2.12 (m, 1H), 2.89 - 2.95 (m, 1H), 3.47 - 3.52 (m, 2H), 3.92 - 3.95 (m, 1H), 4.04 - 4.08 (m, 1H), 4.40 (bs, 2H), 5.03 (s, 1H).	6 (chromatographic column after each steps)	169
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.97 - 2.13 (m, 3H), 2.23 - 2.32 (m, 1H), 3.86 - 3.92 (m, 1H), 3.95 - 4.00 (m, 1H), 4.40 (bs, 2H), 4.88 (dd, 1H), 5.14 (s, 1H).	38 (chromatographic column each steps)	155
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 2.02 - 2.11 (m, 1H), 2.27 - 2.36 (m, 1H), 3.38 - 3.45 (m, 1H), 3.79 (dd, 1H), 3.85 - 3.90 (m, 1H), 3.98 (td, 1H), 4.06 (dd, 1H), 5.04 (s, 1H).	15 (chromatographic column after first step)	177 [M+Na]

	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.53 (s, 3H), 1.85 - 2.02 (m, 3H), 2.42 - 2.48 (m, 1H), 3.81 - 3.86 (m, 1H), 3.93 - 3.98 (m, 1H), 4.43 (bs, 2H), 5.13 (s, 1H).	51 (precipitation after the second step)	169
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5

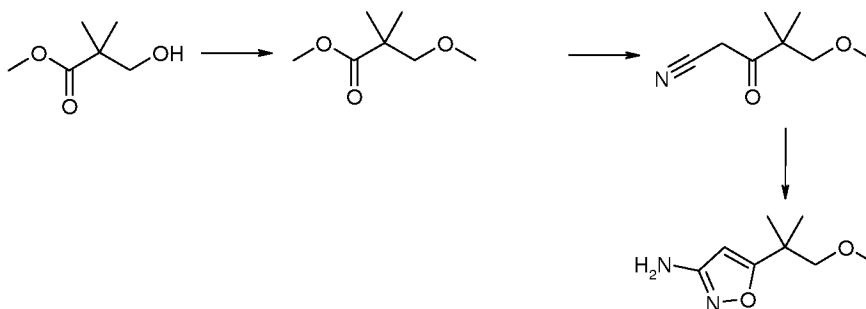
Alternate Amine Method A:

To a mixture of 11.5 kg 3-hydroxy-2,2-dimethyl-propionic acid methyl ester and 80.5 g conc. HCl in 34.5 L toluene are added 7.48 kg 3,4-dihydro-2H-pyran in 5.75 L toluene during 5 min at 70°C. The dropping funnel is rinsed with 5.75 L toluene. After 1 h 6.79 kg acetonitrile and 11.5 L toluene are added. 83.49 kg potassium tert-amylate (25% in toluene) are added during 30 min. The dropping funnel is rinsed with 11.5 L toluene. After 2 h the mixture is cooled to room temperature and 80.5 L water are added. The layers are separated and the organic layer is extracted with 23 L water. The combined aqueous layers are diluted with 17.25 L water and 7.71 kg hydroxylamine hydrochloride are added. The mixture is stirred for at 80°C for 2.5 h.

80.5 L solvent are distilled off by vacuum distillation and after cooling to 60°C 34.5 L methanol are added. Seeding crystals are added and after 1 h the mixture is cooled to 22°C within 1 h. After stirring for 13 h the suspension is cooled to 1°C. After 2 h the suspension is centrifuged and the filter cake is washed twice with 23 L methanol/water (1:1). After drying of the filter cake at 50°C 15.88 kg are obtained. Yield: 76%. ES-MS: m/z 241 [M+H]; ^1H NMR (400 MHz, *DMSO-d6*) δ ppm 1.18 (3H, s), 1.19 (3H, s), 1.36-1.53 (4H, m), 1.53-1.64 (1H, m), 1.64-1.76 (1H, m), 3.27 (1H, d, $^3J_{\text{H,H}} = 9.4$ Hz), 3.37-3.44 (1H, m), 3.59 (1H, d, $^3J_{\text{H,H}} = 9.2$ Hz), 3.64-3.73 (1H, m), 4.50-4.54 (1H, m), 4.88 (1H, s), 6.40 (2H, s).

Amine Method B:

25 **Synthesis of 5-(2-Methoxy-1,1-dimethyl-ethyl)-isoxazol-3-ylamine**



5

Step 1: Synthesis of 3-Methoxy-2,2-dimethyl-propionic acid methyl ester

3-Methoxy-2,2-dimethyl-propionic acid methyl ester is prepared according to the following reference:

Johnstone, R.A.W.; Rose, M.E.; *Tetrahedron*, **1979**, 35, 2169-2173.

To a solution of 3.52 g (63 mmol) of powdered potassium hydroxide in DMSO (150 mL) are added 2 mL (16 mmol) of hydroxypivalic acid methyl ester, followed by 3.9 mL (63 mmol) of methyl iodide. The reaction mixture is stirred for 0.5 h, then quenched with water (300 mL). The reaction mixture is extracted with DCM (3 x 300 mL). The combined organic extracts are washed with water (2 x 150 mL), brine (50 mL), dried over Na₂SO₄ and filtered. The filtrate is concentrated under reduced pressure to yield 1.76 g of 3-methoxy-2,2-dimethyl-propionic acid methyl ester as a pale yellow oil, which is used in the next step without further purification. Yield: 77%; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.1 (6H, s), 3.2 (3H, s), 3.3 (2H, s), 3.6 (3H, s).

20

Step 2: Synthesis of 5-Methoxy-4,4-dimethyl-3-oxo-pentanenitrile

A solution of 1.74 g (12 mmol) of 3-methoxy-2,2-dimethyl-propionic acid methyl ester and 0.9 mL (17 mmol) of acetonitrile in toluene (5 mL) is added dropwise to the refluxing suspension of 0.67 g (17 mmol) of sodium hydride (60 % in mineral oil) in toluene (5 mL). After the addition, the reaction mixture is stirred at reflux for 3 h. After this time, the reaction mixture is cooled to room temperature and neutralized to pH ~ 6-7 by adding 1M aqueous HCl solution. The aqueous layer is extracted with ethyl acetate (3 x 20 mL). The organic layers are combined, washed with

25

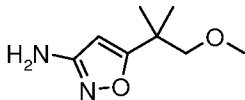
5 brine (1.5 L), dried over Na₂SO₄ and filtered. The filtrate is concentrated under reduced pressure to yield 1.69 g of 5-methoxy-4,4-dimethyl-3-oxo-pentanenitrile as a brown oil, which is used in the next step without further purification. Yield: 91%; ¹H NMR (400 MHz, DMSO-*d*6) δ ppm 1.1 (6H, s), 3.2 (3H, s), 3.3 (sH, s), 4.2 (2H, s).

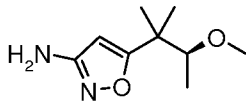
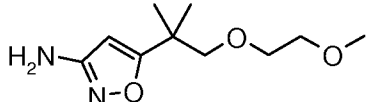
10 **Step 3: Synthesis of 5-(2-Methoxy-1,1-dimethyl-ethyl)-isoxazol-3-ylamine**

To a stirred solution of 1.68 g (10.8 mmol) of 5-methoxy-4,4-dimethyl-3-oxo-pentanenitrile and 0.49 g (11.9 mmol) of sodium hydroxide in water (13 mL) is added a solution of 0.98 g (5.9 mmol) of hydroxylamine sulfate in water (4 mL). The reaction mixture is heated to 100 °C for 1.5 h. After this time, the reaction mixture is cooled to room temperature and 0.8 mL (9.7 mmol) of 37% aqueous HCl solution is added. The reaction is heated to 100 °C for 0.5 h. After cooling, the pH of the reaction mixture is adjusted to pH~12 by addition of 1M aqueous NaOH solution and extracted with DCM (3 × 20 L). The organic layers are combined and washed with brine (20 mL), dried over Na₂SO₄ and filtered. The filtrate is concentrated under reduced pressure. The residual brown oil is purified by column chromatography (Biotage, eluent DCM, MeOH) to yield 0.94 g of 5-(2-methoxy-1,1-dimethyl-ethyl)-isoxazol-3-ylamine as a yellow oil. Yield 51%; m/z 171 [M+H]; ¹H NMR (400 MHz, DMSO-*d*6) δ ppm 1.17 (6H, 2), 3.22 (3H, s), 3.26 (2H, s), 5.40 (2H, m) 5.53 (1H, s).

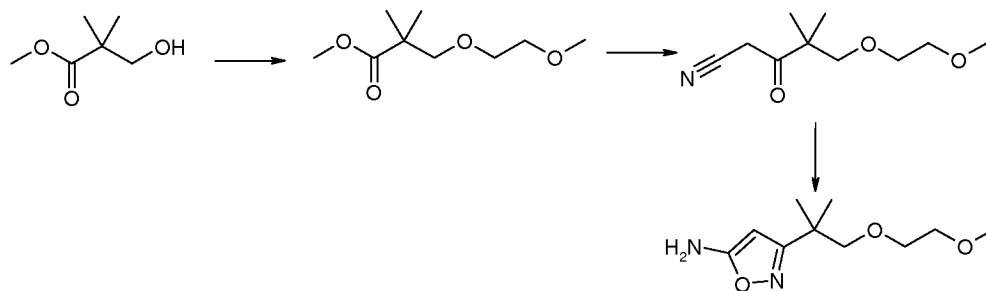
25 According to this procedure the following amines are synthesized:

Table XVI

Structure	¹ H-NMR	Yield [%]	m/z [M+H]
	(400 MHz, DMSO- <i>d</i> 6) δ ppm 1.17 (6H, 2), 3.22 (3H, s), 3.26 (2H, s), 5.40 (2H, m) 5.53 (1H, s).	36	171

	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.02 (3H, d), 1.22 (3H, s), 1.23 (3H, s), 3.30 (3H, s), 3.40 (1H, q), 3.50 (2H, brs), 5.62 (1H, s).	13	185
	(400MHz, <i>CHLOROFORM-d</i>): 1.29 (6H, s), 3.35 (3H, s), 3.50 (2H, s), 3.47-3.52 (2H, m), 3.52-3.58 (2H, m), 2.58-3.68 (2H, brs), 5.62 (1H, s).	15	215

5

Amine Method C:**Synthesis of 3-[2-(2-Methoxy-ethoxy)-1,1-dimethyl-ethyl]-isoxazol-5-ylamine**

10

Step 1: Synthesis of 3-(2-Methoxy-ethoxy)-2,2-dimethyl-propionic acid methyl ester

To a solution of methyl 3-hydroxy-2,2-dimethyl-propionate (2.72 mL, 21.28 mmol) in 3 mL of DMF is added 60% sodium hydride in mineral oil (1.70 g, 42.56 mmol) in one portion, followed by the addition of 2-bromoethyl methyl ether (4.0 mL, 42.56 mmol). The reaction mixture is stirred at room temperature for 3 hs. After this time, the reaction mixture is quenched with saturated aqueous NH_4Cl solution and the product is extracted with DCM twice. The organics are combined and washed with water 4 times then brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to yield the title compound. Yield: 76%; ^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 1.19 (6H, s), 3.36 (3H, s), 3.48 (2H, s), 3.48-3.52 (2H, m), 3.54-3.60 (2H, m), 3.67 (3H, s).

5 **Step 2: Synthesis of 5-(2-Methoxy-ethoxy)-4,4-dimethyl-3-oxo-pentanenitrile**

A solution of 3-(2-methoxy-ethoxy)-2,2-dimethyl-propionic acid methyl ester (3.08 g, 16.21 mmol) and acetonitrile (1.19 mL, 22.69 mmol) in toluene (6 mL) is added dropwise to the refluxing suspension of 60 % sodium hydride in mineral oil (907.6 mg, 22.69 mmol) in toluene
 10 (18 mL). After the addition, the reaction mixture is stirred at reflux for 3 h. After this time, the reaction mixture is cooled to room temperature and the aqueous layer is neutralized to pH ~ 7 by adding 1M aqueous HCl solution. The aqueous layer is extracted with ethyl acetate 3 times. The organic layers are combined, washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated under reduced pressure to yield the title compound. Yield: 94.2%. ¹H NMR (400
 15 MHz, *CHLOROFORM-d*) δ ppm 1.20 (6H, s), 3.38 (3H, s), 3.47 (2H, s), 3.50-3.55 (2H, m), 3.57-3.62 (2H, m), 3.80 (2H, s).

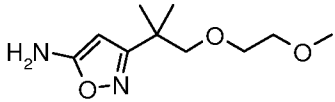
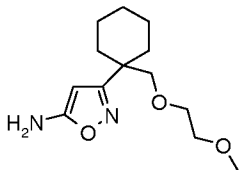
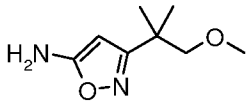
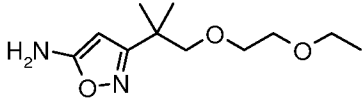
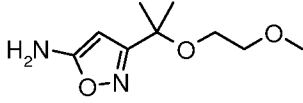
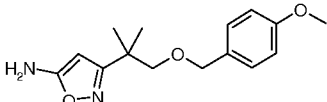
Step 3: Synthesis of 3-[2-(2-Methoxy-ethoxy)-1,1-dimethyl-ethyl]-isoxazol-5-ylamine

20 To a stirred solution of 5-(2-methoxy-ethoxy)-4,4-dimethyl-3-oxo-pentanenitrile (3.04 g, 15.27 mmol) and sodium hydroxide (1.31 g, 32.82 mmol) in water (34 mL) is added hydroxylamine sulfate (1.25 g, 7.63 mmol). The reaction mixture is stirred at reflux for 18 h. After this time, the reaction mixture is cooled to room temperature and extracted with ethyl acetate 3 times. The organic layers are combined and washed with brine, dried over Na₂SO₄, filtered and concentrated
 25 under reduced pressure. Purification by flash chromatography on silica gel using methanol/DCM provides the title compound. Yield: 35.8%. ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 1.30 (6H, s), 3.39 (3H, s), 3.50 (2H, s), 3.50-3.57 (2H, m), 3.57-3.62 (2H, m), 3.30-4.50 (2H, br), 5.16 (1H, s).

30 According to this procedure the following amines are synthesized:

Table XVII

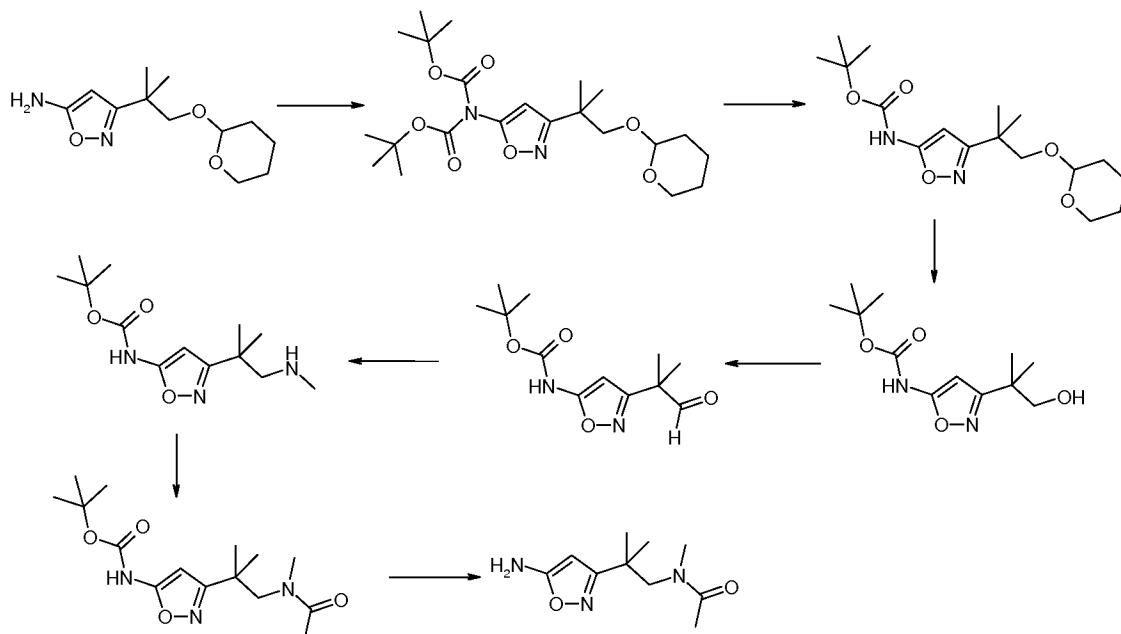
Structure	¹ H-NMR	Yield [%]	m/z [M+H]
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	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.30 (6H, s), 3.39 (3H, s), 3.50 (2H, s), 3.50-3.57 (2H, m), 3.57-3.62 (2H, m), 3.30-4.50 (2H, br), 5.16 (1H, s).	26	215
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.20-1.35 (1H, m), 1.35-1.60 (7H, m), 1.92-2.02 (2H, m), 3.33 (3H, s), 3.41 (2H, s), 3.45-3.53 (4H, m), 5.10 (1H, s).	19	255
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.25 (6H, s), 3.31 (3H, s), 3.45 (2H, s), 4.30 (2H, s), 5.05 (1H, s)	39 [#]	171
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.20 (3H, t), 1.29 (6H, s), 3.49 (2H, s), 3.51 (2H, q), 3.52-3.60 (4H, m), 5.12 (1H, s).	22	229
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 3.36 (3H, s), 3.41-3.45 (2H, m), 3.46-3.50 (2H, m), 5.19 (1H, s).	9	199 [M-H]
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.29 (6H, s), 3.44 (2H, s), 3.81 (3H, s), 4.35 (2H, br. s), 4.46 (2H, br. s), 5.06 (1H, s), 7.22-7.27 (2H, m), 6.86-6.89 (2H, m).	29	277

- 5 [#]4.1 equivalents of NaOH and 1.1 equivalent of hydroxylamine sulfate are used, the reaction is run for 2.5 hours at reflux.

10 **Amine Method D:**

Synthesis of *N*-[2-(5-Amino-isoxazol-3-yl)-2-methyl-propyl]-*N*-methyl-acetamide



5

Step 1: Synthesis of {3-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl}-di-carbamic acid di-*tert*-butyl ester

Di-*tert*-butyl dicarbonate (2.27 g, 10.40 mmol) is added to a solution of 3-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-ylamine (1.0 g, 4.16 mmol) in pyridine (4.0 mL) at room temperature, followed by the addition of 4-dimethylaminopyridine (4.0 mg, 0.033 mmol). The reaction mixture is stirred at room temperature for 4 h. After this time, the reaction mixture is quenched with 1 M aqueous HCl solution and then extracted with ethyl acetate twice. The organics are combined and washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound which is used crude in the next step. *m/z* 441 [M+H].

Step 2: Synthesis of {3-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl}-di-carbamic acid *tert*-butyl ester

{3-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl}-di-carbamic acid di-*tert*-butyl ester (1.83 g, 4.16 mmol) is dissolved in methanol (10.0 mL) and 40 % aqueous sodium hydroxide solution (416.1 mg, 4.16 mmol) is added and the reaction mixture is stirred at room

5 temperature for 1.5 h. After this time, the reaction mixture is concentrated under reduced pressure and then partitioned between ethyl acetate and water. The layers are separated and the organic layer is washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel using ethyl acetate/hexanes provides 1.15 g of the title compound. Yield: 81 %. m/z 341 [M+H].

10 **Step 3: Synthesis of [3-(2-Hydroxy-1,1-dimethyl-ethyl)-isoxazol-5-yl]-carbamic acid *tert*-butyl ester**

A solution of 933.0 mg (2.74 mmol) of {3-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl}-carbamic acid *tert*-butyl ester and 103.0 mg (0.41 mmol) of pyridinium p-
15 toluenesulfonate in ethanol (8.0 mL) is stirred at 65 °C for 1 h. After this time, the reaction mixture is concentrated under reduced pressure. Purification by flash chromatography on silica gel using ethyl acetate/heptane provides 602.0 mg of the title compound. Yield: 85.7 %. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.3 (6H, s), 1.55 (9H, s), 2.35 (1H, t, J = 8.0Hz), 3.7 (2H, d, J = 8.0Hz), 6.5 (1H, s), 7.3 (1H, s).

20 **Step 4: Synthesis of [3-(1,1-Dimethyl-2-oxo-ethyl)-isoxazol-5-yl]-carbamic acid *tert*-butyl ester**

Dess-Martin periodinane (1.39 g, 3.29 mmol) is added to a solution of [3-(2-hydroxy-1,1-dimethyl-ethyl)-isoxazol-5-yl]-carbamic acid *tert*-butyl ester (602.0 mg, 2.35 mmol) in DCM (20
25 mL). The reaction mixture is stirred at room temperature for 1 h. After this time, the reaction mixture is quenched with 50 mL (1:1) of saturated aqueous NaHCO₃ solution and saturated aqueous sodium thiosulfate solution and stirred at room temperature for 2 h then extracted with DCM twice. The organic extracts are combined and washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to provide 587.0 mg of the title compound. Yield: 98.3
30 %. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.45 (6H, s), 1.55 (9H, s), 6.05 (1H, s), 7.25 (1H, s), 9.65 (1H, s).

Step 5: Synthesis of [3-(1,1-Dimethyl-2-methylamino-ethyl)-isoxazol-5-yl]-carbamic acid *tert*-butyl ester

5 [3-(1,1-Dimethyl-2-oxo-ethyl)-isoxazol-5-yl]-carbamic acid tert-butyl ester (150.0 mg, 0.59 mmol) is dissolved in THF (1.0 mL) and 2M methylamine in THF (0.35 mL, 0.71 mmol) is added followed by the addition of MP-triacetoxyborohydride (546.0 mg, 2.70 mmol/g). The reaction mixture is placed on a shaker for 2 h. After this time, the reaction mixture is filtered and the filtrate is concentrated under reduced pressure to provide 163.0 mg of the title compound
10 which is used crude for the next step. m/z 270 [M+H].

Step 6: Synthesis of {3-[2-(Acetyl-methyl-amino)-1,1-dimethyl-ethyl]-isoxazol-5-yl}-carbamic acid *tert*-butyl ester

Pyridine (0.055 mL, 0.68 mmol) is added to a solution of [3-(1,1-dimethyl-2-methylamino-ethyl)-
15 isoxazol-5-yl]-carbamic acid tert-butyl ester (150.0 mg, 0.59 mmol) in THF (2.0 mL) followed by the addition of acetyl chloride (0.048 mL, 0.68 mmol). The reaction mixture is stirred at room temperature for 3 h. After this time, more pyridine (0.028 mL, 0.34 mmol) and more acetyl chloride (0.024 mL, 0.34 mmol) are added to the reaction mixture and stirred for another 1 h. After this time, the reaction mixture is quenched with saturated aqueous NaHCO₃ solution and extracted
20 with ethyl acetate twice. The organic extracts are combined and washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel using methanol/DCM provides 87.0 mg of the title compound. Yield: 47 %. m/z 312 [M+H].

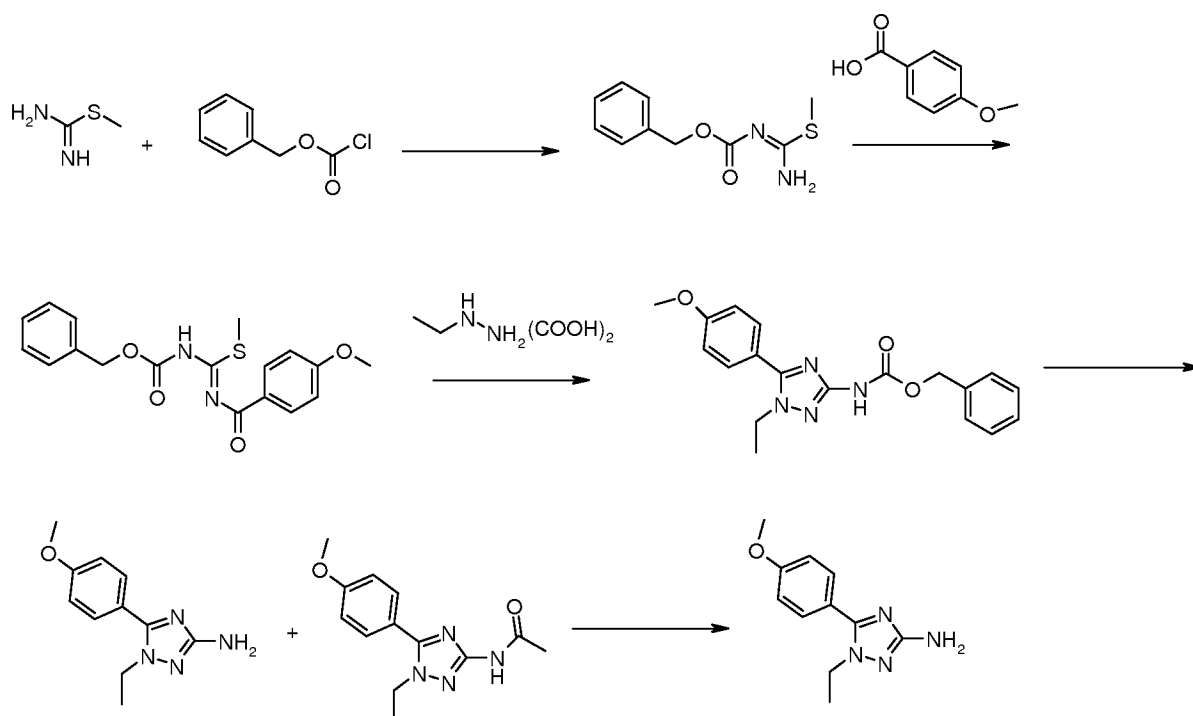
25 **Step 7: Synthesis of *N*-[2-(5-Amino-isoxazol-3-yl)-2-methyl-propyl]-*N*-methyl-acetamide**

Trifluoroacetic acid (0.108 mL, 1.4 mmol) is added to a solution of {3-[2-(acetyl-methyl-amino)-1,1-dimethyl-ethyl]-isoxazol-5-yl}-carbamic acid tert-butyl ester (87.0 mg, 0.28 mmol) in DCM (1 mL). The reaction mixture is stirred at room temperature for 1 h. More trifluoroacetic acid (0.20 mL, 2.59 mmol) is added to the reaction mixture and the reaction mixture is stirred for another
30 hour. After this time, the reaction mixture is diluted with DCM and quenched with saturated aqueous NaHCO₃ solution. The layers are separated and the aqueous layer is extracted with DCM twice. The organics are combined and washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to provide 28.0 mg of the title compound. Yield: 47 %. LC-MS Retention time: 0.94 mins. ESI + ion mode. Zorbax SB-C18 column (3.5µm, 4.6×30mm).

- 5 Gradient: 5% B to 80% B (0 min to 1.7 mins), 80% B to 95% B (1.7 mins to 2 mins), 95% B to 95% B (2 mins to 2.1 mins). Flow rate: 2.5 mL/min. A = (Water + 0.1% Formic Acid) B = (Acetonitrile + 0.1% Formic Acid). Diode Array Detector; m/z 212 [M+H].

10 **Amine Method E:**

Synthesis of 1-Ethyl-5-(4-methoxy-phenyl)-1H-1,2,4-triazol-3-ylamine



Step 1: Synthesis of 1-benzyl-2-methylisothiourea

- 15 Benzyl chloroformate (100.0 g, 588.0 mmol) and 2N aqueous NaOH solution (882.0 mmol) are added at 0°C to a solution of 2-methylisothiourea hemisulfate salt (196.0 g, 705.0 mmol) in DCM (1.0 L). After stirring the reaction mixture at 0 °C for 1 h, water is added and the two phases are separated. The organic layer is dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude product that is triturated with 30% EtOAc/Petroleum ether to afford 30 g of 1-benzyl-2-methylisothiourea as a white solid. Yield: 30%; m/z 225
- 20 [M+H].

5 **Step 2: Synthesis of 1-benzyloxycarbonyl-3-(4-methoxy-benzoyl)-2-methyl-isothiourea**

N,N-diisopropylethylamine (57.4 mL, 445.0 mmol), HOBt (54.0 g, 356.0 mmol) and EDC.HCl (68.0 g, 356.0 mmol) are added at room temperature to a solution of 1-benzyloxycarbonyl-2-methyl-isothiourea (40.0 g, 178.0 mmol) in DMF (0.4 L). After stirring the reaction mixture at room temperature for 14 h, water is added and the mixture is filtered. The filtrate is extracted with
10 DCM, the combined organic layers are washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford the crude product that is purified by silica gel column chromatography to afford 14 g of 1-benzyloxycarbonyl-3-(4-methoxy-benzoyl)-2-methyl-isothiourea as a white solid. Yield: 22%. ¹H-NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.51 (3H, 2s), 3.87 (3H, 2s), 5.24 (2H, 2s), 6.90 (1H, d, 8.8 Hz), 7.01 (1H, d, 8.8 Hz), 7.33-7.45 (5H, m), 7.93 (1H, d, 8.8 Hz), 8.23 (1H, d, 9.2 Hz)
15

Step 3: Synthesis of [1-Ethyl-5-(4-methoxy-phenyl)-1*H*-1,2,4-triazol-3-yl]-carbamic acid benzyl ester

N,N-diisopropylethylamine (9.9 g, 76.8 mmol) is added to a solution of 1-benzyloxycarbonyl-3-(4-methoxy-benzoyl)-2-methyl-isothiourea (11.0 g, 30.7 mmol) and ethyl hydrazine oxalate (11.6 g, 76.8 mmol) in DMF (110.0 mL) and the reaction mixture is heated at 50 °C for 12 h. Ice and ether are added to the reaction mixture and the two phases are separated. The organic phase is dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 10 g of [1-ethyl-5-(4-methoxy-phenyl)-1*H*-1,2,4-triazol-3-yl]-carbamic acid benzyl ester that is used in the next step
25 without further purification. m/z 353 [M+H].

Step 4: Synthesis of 1-Ethyl-5-(4-methoxy-phenyl)-1*H*-1,2,4-triazol-3-ylamine and *N*-[1-Ethyl-5-(4-methoxy-phenyl)-1*H*-1,2,4-triazol-3-yl]-acetamide

30 Hydrobromic acid in AcOH (40.0 mL) is added to [1-ethyl-5-(4-methoxy-phenyl)-1*H*-1,2,4-triazol-3-yl]-carbamic acid benzyl ester (10.0 g, 28.4 mmol) and the solution is stirred for 3 h at room temperature. The reaction mixture is concentrated and the residue is washed with ether to afford 7.0 g as a mixture of 1-ethyl-5-(4-methoxy-phenyl)-1*H*-1,2,4-triazol-3-ylamine and *N*-[1-

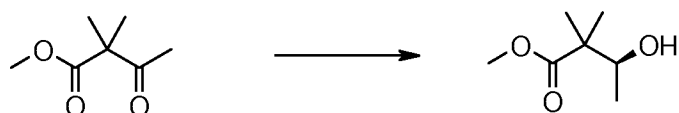
5 ethyl-5-(4-methoxy-phenyl)-1*H*-1,2,4-triazol-3-yl]-acetamide (87% / 13%) that is used in the next step without any further purification. *m/z* 219 [M+H]⁺; 261 [M+H]⁺.

Step 5: Synthesis of 1-ethyl-5-(4-methoxy-phenyl)-1*H*-1,2,4-triazol-3-ylamine

Sodium hydroxide (10.7 g, 269.2 mmol) is added to a mixture of 7 g of 1-ethyl-5-(4-methoxy-phenyl)-1*H*-1,2,4-triazol-3-ylamine and N-[1-ethyl-5-(4-methoxy-phenyl)-1*H*-1,2,4-triazol-3-yl]-acetamide in methanol (100.0 mL) and the solution is refluxed for 12 h. The solvent is removed under reduced pressure, water is added and the residue is extracted with DCM. The organic layer is dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude product that is purified by silica gel column chromatography to afford 1.7 g of 1-ethyl-5-(4-methoxy-phenyl)-1*H*-1,2,4-triazol-3-ylamine as an off-white solid. Yield: 25%, over three steps; *m/z* 219 [M+H]⁺; ¹H NMR (500 MHz, *MeOD*) δ ppm 1.40 (3 H, t, *J*=7.25 Hz), 3.87 (3 H, s), 4.04 (2 H, q, *J*=7.17 Hz), 7.04 - 7.11 (2 H, m), 7.49 - 7.57 (2 H, m).

Intermediate Synthesis.

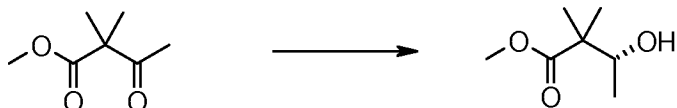
Synthesis of (S)-3-Hydroxy-2,2-dimethyl-butyric acid methyl ester



25 The reaction is carried out in a 100-mL autoclave. 2,2-Dimethyl-3-oxo-butyric acid methyl ester (4.0 g, 27.8 mmol) is dissolved in 35 mL of degassed methanol under Argon atmosphere. Dichloro[(S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium (II) (230.0 mg, 0.28 mmol) is added and the reaction mixture is purged with nitrogen twice and once with hydrogen. The autoclave is pressurized with hydrogen to 500 psi and stirred at 30 °C for 40 h. After this time, the reaction mixture is filtered through celite and concentrated under reduced pressure to provide 3.8 g of the title compound as a green oil with ee of 98 %. Yield: 95 %. ¹H NMR (400 MHz,

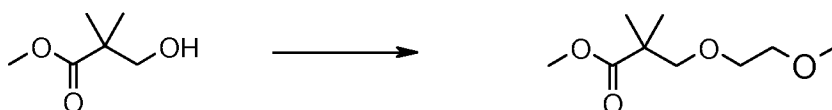
- 5 *CHLOROFORM-d*) δ ppm 1.15 (3H, d, $J = 6.4\text{Hz}$), 1.2 (6H, d, $J = 5.2\text{Hz}$), 2.6 (1H, br. s), 3.7 (3H, s), 3.9 (1H, q, $J = 6.4\text{Hz}$).

Synthesis of (R)-3-Hydroxy-2,2-dimethyl-butyric acid methyl ester



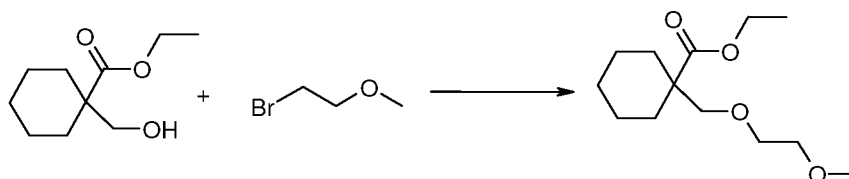
- 10 The reaction is carried out in a 100-mL autoclave. 2,2-Dimethyl-3-oxo-butyric acid methyl ester (4.0 g, 27.8 mmol) is dissolved in 35 mL of degassed methanol under Argon atmosphere. Dichloro[(R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium (II) (230.0 mg, 0.28 mmol) is added and the reaction mixture is purged with nitrogen twice and once with hydrogen. The autoclave is pressurized with hydrogen to 500 psi and stirred at 30 °C for 40 h. After this time,
15 the reaction mixture is filtered through celite and concentrated under reduced pressure to provide 3.8 g of the title compound as a green oil with ee of 96 %. Yield: 95 %. ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 1.15 (3H, d, $J = 6.4\text{Hz}$), 1.2 (6H, d, $J = 5.2\text{Hz}$), 2.6 (1H, br. s), 3.7 (3H, s), 3.9 (1H, q, $J = 6.4\text{Hz}$).

20 **Synthesis of 3-(2-Methoxy-ethoxy)-2,2-dimethyl-propionic acid methyl ester**



- 60 % Sodium hydride in mineral oil (1.70 g, 42.56 mmol) is added to a solution of 3-hydroxy-2,2-dimethyl-propionic acid methyl ester (2.71 mL, 21.28 mmol) in 40 mL of DMF, followed by the
25 addition of 2-bromoethyl methyl ether (4.0 mL, 42.56 mmol) and the reaction mixture is stirred at room temperature for 3 h. After this time, the reaction mixture is quenched with saturated aqueous NH_4Cl solution and then extracted with DCM twice. The organic extracts are combined and concentrated under reduced pressure to yield the title compound. Yield: 76%. ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 1.2 (6H, s), 3.4 (3H, s), 3.5 (2H, s), 3.45-3.55 (2H, m), 3.55-3.65 (2H, m), 3.7 (3H, s).
30

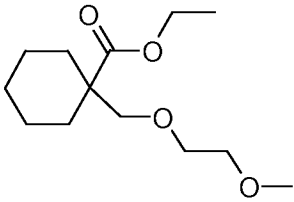
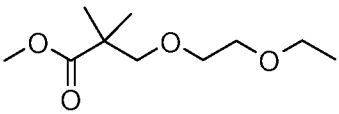
5

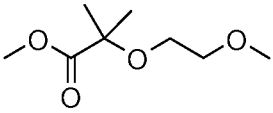
Intermediate Method A**Synthesis of 1-(2-Methoxy-ethoxymethyl)-cyclohexanecarboxylic acid ethyl ester**

1-Hydroxymethyl-cyclohexanecarboxylic acid ethyl ester (2.0 g, 10.9 mmol) is added to a solution of 60 % sodium hydride (0.86 g, 21.7 mmol) in 5.0 mL of DMF at 0°C and the reaction mixture is stirred for 30 minutes; 2-bromoethyl methyl ether (3.0g, 21.7 mmol) is added over a period of 10 minutes and then the reaction mixture is stirred at room temperature for 14 h. Ice water and 20% ethyl acetate in petroleum ether are added. The two phases are separated and the organic layer is washed with water and brine and dried over Na₂SO₄. After filtration the solvent is removed under reduced pressure to provide 2.0 g of the title compound as a yellow liquid that is used in the next step without further purification. m/z 245 [M+H].

The following intermediates are synthesized according to Intermediate Method A:

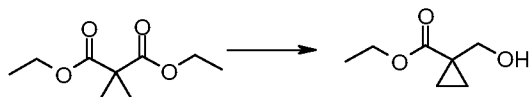
Table XVIII

Structure	Yield [%]	m/z
	77	245 [M+H]
	65	227 [M+Na]

	34	177 [M+H]
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5

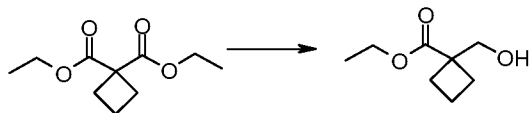
Synthesis of 1-Hydroxymethyl-cyclopropanecarboxylic acid ethyl ester



A solution of lithium aluminum-tri-tert-butoxyhydride 1.0M in THF (28.5mL, 28.5mmol) is added to a solution of diethyl 1,1-cyclopropanedicarboxylate (2.0 mL, 11.4 mmol) in anhydrous THF (85.0 mL). After stirring the reaction mixture for 4 h, 10 mL of lithium aluminum-tri-tert-butoxyhydride 1.0M solution in THF is added and the solution is stirred for 18 h. The reaction mixture is diluted with DCM, washed with 1N aqueous HCl solution, saturated aqueous NaHCO₃ solution and brine. After drying the organic phase over anhydrous Na₂SO₄, removal of the solvent under reduced pressure affords 1.60 g of 1-hydroxymethyl-cyclopropanecarboxylic acid ethyl ester that is used in the next step without further purification. Yield: 85%. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.88 (2H, q, J = 4.1 Hz), 1.21-1.33 (5H, m), 2.59 (1H, t, J = 6.9 Hz), 3.63 (2H, d, J = 7.2 Hz), 4.17 (2H, q, J = 7.1 Hz).

20 Intermediate Method B:

Synthesis of 1-hydroxymethyl-cyclobutanecarboxylic acid ethyl ester

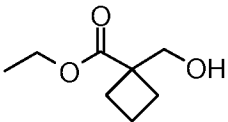
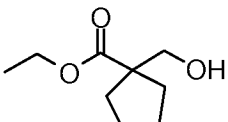
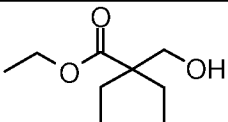


A solution of lithium aluminum-tri-tert-butoxyhydride 1.0M in THF (100.0 mL, 100.0 mmol) is added at -78°C to a solution of diethyl 1,1-cyclobutanedicarboxylate (10.0 g, 50.0 mmol) in anhydrous THF (50.0 mL). After stirring the reaction mixture at room temperature for 14 h, 10% aqueous KHSO₄ solution is added and the reaction mixture diluted with ethyl acetate. After separating the two phases, the organic phase is washed with water and brine and dried over

- 5 anhydrous Na_2SO_4 . Filtration and removal of the solvent under reduced pressure affords 5.0 g of 1-hydroxymethyl-cyclobutanecarboxylic acid ethyl ester that is used in the next step without further purification. Yield: 63%; m/z 159 $[\text{M}+\text{H}]$.

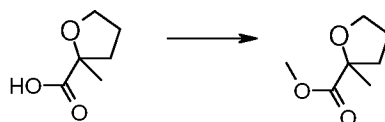
The following intermediates are synthesized according to Intermediate Method B:

10 **Table XIX**

Structure	Yield [%]	m/z [$\text{M}+\text{H}$]
	63	159
	50	173
	50	187

Intermediate Method C:

Synthesis of methyl 2-methyltetrahydro-2-furancarboxylate

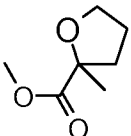
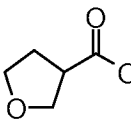


- 15 Thionyl chloride (0.15 mL, 2.1 mmol) is added dropwise at 0 °C to a solution of 2-methyltetrahydro-2-furancarboxylic acid (250 mg, 1.9mmol) in methanol (2.0 mL). After bringing the reaction mixture to room temperature, it is heated under reflux for 1 h. The solvent is removed under reduced pressure, the crude is dissolved in DCM and filtered through a pad of silica. Removal of the solvent under reduced pressure affords 276.0 mg of methyl 2-methyltetrahydro-2-furancarboxylate that is used in the next step without further purification. Yield: 93%. ^1H NMR
- 20

- 5 (400 MHz, *CHLOROFORM-d*) δ ppm 1.49 (3H, s), 1.78-1.85 (1H, m), 1.91-1.99 (2H, m), 2.30-2.37 (1H, m), 3.75 (3H, s), 3.92-4.02 (2H, m).

The following intermediates are synthesized according to Intermediate Method C:

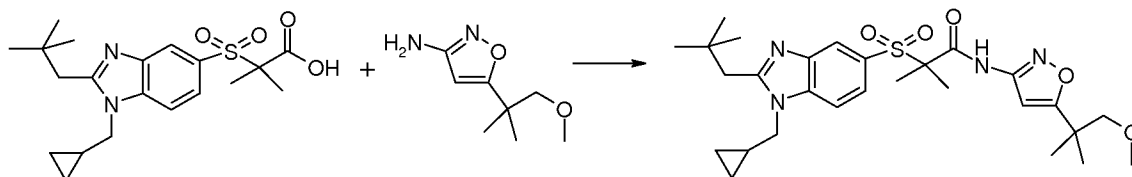
Table XX

Structure	¹ H-NMR	Yield [%]	m/z [M+H]
	(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.49 (3H, s), 1.78-1.85 (1H, m), 1.91-1.99 (2H, m), 2.30-2.37 (1H, m), 3.75 (3H, s), 3.92-4.02 (2H, m).	93	
	(400 MHz, <i>CHLOROFORM-d</i>) 2.10 – 2.24 (m, 2H), 3.07 – 3.14 (m, 1H), 3.7 (s, 3H), 3.79 – 4.01 (m, 4H)	quantitative	131

10

Amide Method A:

Synthesis of 2-[1-Cyclopropylmethyl-2-(2,2-dimethyl-propyl)-1H-benzoimidazole-5-sulfonyl]-N-[5-(2-methoxy-1,1-dimethyl-ethyl)-isoxazol-3-yl]-2-methyl-propionamide (Example 21) .



15

Activation of 300 mg (0.76 mmol) of 2-[1-cyclopropylmethyl-2-(2,2-dimethyl-propyl)-1H-benzoimidazole-5-sulfonyl]-2-methyl-propionic acid as the corresponding acid chloride is achieved by treatment with thionyl chloride (1.5 mL) at 75 °C for 2 h. The reaction is cooled to room temperature and excess thionyl chloride is removed under reduced pressure.

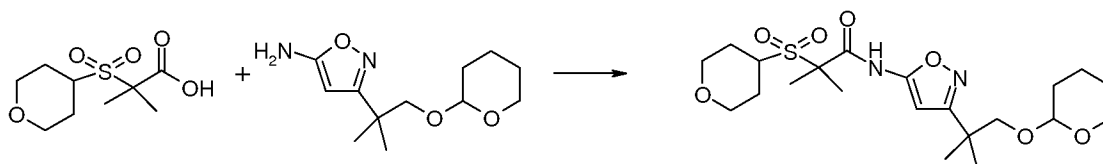
- 20 The crude acid chloride is dissolved in anhydrous THF (5 mL) and heated to 50 °C. Then N,N-diisopropylethylamine (0.16 mL, 0.92 mmol) is added, followed by N,5-(2-methoxy-1,1-dimethyl-

ethyl)-isoxazol-3-ylamine (156 mg, 0.92 mmol). The reaction is stirred at 75 °C for 18 h. The reaction mixture is concentrated under reduced pressure. The residue is partitioned between DCM (10 mL) and saturated aqueous NaHCO₃ solution (10 mL). The organic layer is washed with 10% aqueous citric acid solution, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product is purified by column chromatography (silica, eluent: DCM, 0-20% ethyl acetate) to yield 368 mg of 2-[1-cyclopropylmethyl-2-(2,2-dimethyl-propyl)-1H-benzimidazole-5-sulfonyl]-N-[5-(2-methoxy-1,1-dimethyl-ethyl)-isoxazol-3-yl]-2-methyl-propionamide. Yield: 88%; ES-MS: m/z 545 [M+H]

Compounds in Table XXII, amide method A are made according to this procedure, with the following modifications to be noted: for Example 19 removal of the tetrahydropyran protecting group is also achieved under these conditions and the crude product is purified by column chromatography (silica, eluent: DCM, 0-50% ethyl acetate), followed by trituration with TBME.

Amide Method B:

Synthesis of N-{3-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl}-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (Example 71).



Activation of 103 g (0.44 mol) of 2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionic acid as the corresponding acid chloride is achieved by treatment with thionyl chloride (63 mL, 0.88 mol) and DMF (cat., 10 mol%) in toluene (0.72 L) at 100 °C for 2 h. The reaction is cooled to room temperature and toluene (0.3 L) is removed by distillation, whilst adding fresh toluene (0.3 L). This process is repeated once.

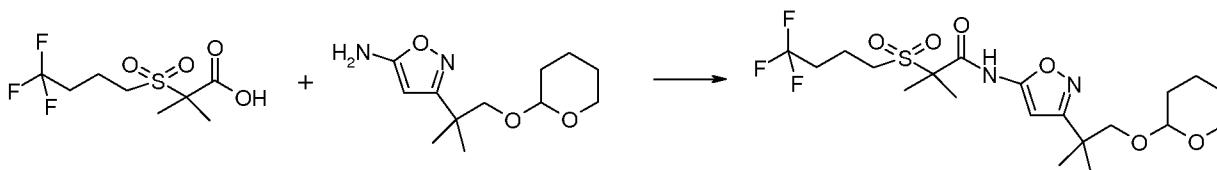
This acid chloride solution is added dropwise over 0.5 h to a stirred suspension of 70 g (0.29 mol) of 3-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-ylamine and 101 mL (0.58 mol) of N,N-diisopropylethylamine in toluene (0.28 L) at 35 °C. After complete addition the reaction is heated to 60 °C for 17 h. The reaction is cooled to room temperature and the solvent is

5 removed under reduced pressure. The residue is dissolved in ethyl acetate (2.8 L) and washed with water (2 x 2.8 L), brine (2.8 L). The organic layer is concentrated under reduced pressure and the residue purified twice by dry-flash column chromatography (silica, eluent heptanes, 10-40% ethyl acetate) to yield 103 g of N-{3-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl}-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide. Yield: 80%; ES-MS: m/z 481 [M+Na],
10 375 [M+H-C₅H₈O]

Alternate synthesis of N-{3-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl}-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

3791 g 2-Methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionic acid are suspended in 28.5 L
15 toluene. 5 L of solvent are distilled off to remove traces of water. After addition of 5 L toluene and 20 mL dimethylformamide, 1398 mL thionyl chloride are added at 55°C. The mixture is heated to reflux for 3.5 h. Then 35 L of solvent are distilled off while adding 35 L toluene at the same time. After cooling the solution to 45°C, 3854 g 3-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-ylamine dissolved in 16 L toluene and 3295 mL N,N-diisopropylethylamine at 70°C, are added during 30 min. The dropping funnel are rinsed twice
20 with 2 L toluene. The suspension is stirred for 16 h at 30°C. The mixture is added to 20 L water (rewashed with 1 L toluene). After phase separation, the organic layer is washed again with 20 L water. The organic layer is transferred back into the reaction vessel (rewashed twice with 1 L toluene) and 31.5 L solvent are distilled off. To the residue is added 40 L
25 methylcyclohexane keeping the solution at 54°C. The mixture is cooled to 23°C and seeding crystals are added. The suspension is stirred for 2.5 h while cooling to 1°C. The suspension is filtered and the filter cake is washed with 5 L of a 4:1 mixture of methylcyclohexane and toluene. After drying of the filter cake 6866g product were obtained. ES-MS: m/z 459 [M+H];
30 ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.26 (3H, s), 1.27 (3H, s), 1.68 (6H, s), 1.35-1.72 (8H, m), 1.78-1.85 (2H, m), 3.32-3.42 (4H, m), 3.60-3.69 (3H, m), 3.84-3.91 (2H, m), 4.52-4.55 (1H, m), 6.35 (1H, s), 11.29 (1H, s).

5 **Synthesis of N-{3-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl}-2-methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionamide (Example 36).**



Activation of 72 g (0.27 mol) of 2-Methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionic acid as the corresponding acid chloride is achieved by treatment with thionyl chloride (50 mL, 0.55 mol) and DMF (cat., 10 mol%) in toluene (0.7 L) at 100 °C for 6 h. The reaction is cooled to room temperature and toluene (0.2 L) is removed by distillation, whilst adding fresh toluene (0.2 L). This process is repeated twice.

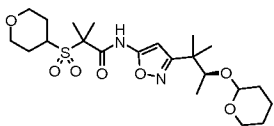
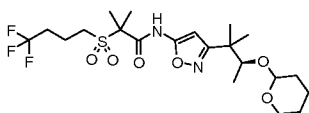
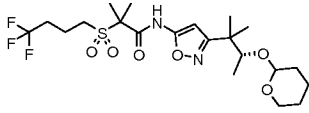
This acid chloride solution is added dropwise over 0.5 h to a stirred suspension of 56 g (0.23 mol) of 3-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-ylamine and 92 mL (0.55 mol) of N,N-diisopropylethylamine in toluene (0.3 L) at 35 °C. After complete addition the reaction is heated to 60 °C for 17 h. The reaction is cooled to room temperature and the solvent is removed under reduced pressure. The residue is dissolved in ethyl acetate (1 L) and washed with saturated aqueous NaHCO₃ solution (0.7 L), brine (0.7 L) dried (Na₂SO₄) and filtered. The filtrate is concentrated under reduced pressure and the residue purified twice by dry-flash column chromatography (silica, eluent heptanes, 30% ethyl acetate) to yield 85 g of N-{3-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl}-2-methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionamide. Yield: 64%; ES-MS: m/z 483 [M-H]; ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.36 (6 H, d, *J*=13.12 Hz), 1.45 - 1.73 (5 H, m), 1.74 - 1.87 (7 H, m), 2.15 - 2.25 (2 H, m), 2.27 - 2.40 (2H, m), 3.11 (2 H, t, *J*=7.55 Hz), 3.38 (1 H, d, *J*=9.31 Hz), 3.46 - 3.53 (1 H, m), 3.75 - 3.84 (2 H, m), 4.59 (1 H, t, *J*=3.43 Hz), 6.37 (1 H, s), 9.24 (1 H, s)

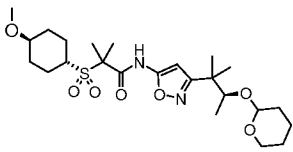
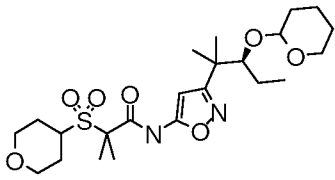
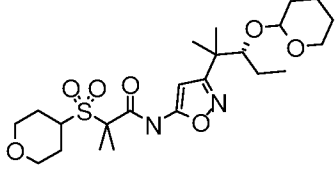
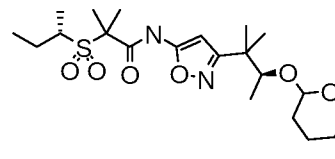
Compounds in Table XXII, amide method B, are made according to this procedure with the following modifications to be noted: for example 72, zinc-dust (0.1 eq.) is added to the reaction mixture. For Example 82, the reaction is performed in THF. Example 56 and 57 are obtained through chiral chromatography of Example 49 on Chiralpak AD-H preparative column 2 x 25 cm on Agilent 1100 HPLC systems; mobile Phase: 60% (1:1:1 mixture of ethanol:methanol:isopropanol):40% heptane; flow: 8ml/min; detector: UV @ 250nm

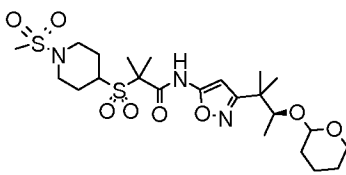
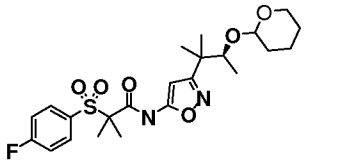
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According to this method the following amides are made:

Table XXI

Structure	¹ H-NMR	Yield [%]	m/z
	Approximately 1:1 mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.99 (3H, d, isomer A), 1.15 (3H, d, isomer B), 1.28 (3H, s, isomer A), 1.30 (3H, s, isomer A), 1.35 (3H, s, isomer B), 1.36 (3H, s, isomer B), 1.42-1.70 (5H, m, isomer A+B), 1.73 (6H, s, isomer A), 1.74 (6H, s, isomer B), 1.75-2.03 (5H, m, isomer A+B), 3.30-3.50 (4H, m, isomer A+B), 3.66-3.94 (2H, m, isomer A+B), 3.99-4.10 (2H, m, isomer A+B), 4.48-4.55 (1H, m, isomer A), 4.68-4.75 (1H, m, isomer B), 6.29 (1H, s, isomer A), 6.32 (1H, s, isomer B), 9.53 (1H, s, isomer A), 9.54 (1H, s, isomer B).	87	473 [M+H]
	Approximately 1:1 mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.99 (3H, d, isomer A), 1.15 (3H, d, isomer B), 1.29 (3H, s, isomer B), 1.30 (3H, s, isomer B), 1.35 (6H, s, isomer A), 1.45-1.88 (6H, m, isomer A+B), 1.75 (6H, s, isomer A+B), 2.10-2.23 (2H, m, isomer A+B), 2.23-2.40 (2H, m, isomer A+B), 3.10 (2H, t, isomer A+B), 3.28-3.50 (1H, m, isomer A+B), 3.65-3.95 (2H, m, isomer A+B), 4.52-4.57 (1H, m, isomer B), 4.70-4.75 (1H, m, isomer A), 6.33 (1H, s, isomer B), 6.38 (1H, s, isomer A), 9.19 (1H, s, isomer A), 9.20 (1H, s, isomer B).	85	499 [M+H]
	Approximately 1:1 mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.99 (3H, d, isomer A), 1.15 (3H, d, isomer B), 1.29 (3H, s, isomer B), 1.31 (3H, s, isomer B), 1.35 (6H, s, isomer A), 1.45-1.88 (6H, m, isomer A+B), 1.75 (6H, s, isomer A+B), 2.10-2.23 (2H, m, isomer A+B), 2.23-2.40 (2H, m, isomer A+B), 3.10 (2H, t, isomer	75	499 [M+H]

	A+B), 3.28-3.50 (1H, m, isomer A+B), 3.65-3.95 (2H, m, isomer A+B), 4.52-4.57 (1H, m, isomer B), 4.70-4.75 (1H, m, isomer A), 6.33 (1H, s, isomer B), 6.38 (1H, s, isomer A), 9.19 (1H, s, isomer A), 9.20 (1H, s, isomer B).		
	^a LC-MS Retention Time: 1.48 mins.	Quantitative (not purified)	501 [M+H]
	Approximately 1:1.66 mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.84 (3H, t, isomer A), 0.93 (3H, t, isomer B), 1.28 (3H, s, isomer B), 1.30 (3H, s, isomer B), 1.33 (3H, s, isomer A), 1.36 (3H, s, isomer A), 1.43-1.61 (7H, m, isomer A+B), 1.73 (6H, s, isomer A+B), 1.77-2.01 (5H, m, isomer A+B), 3.30-3.60 (5H, m, isomer A+B), 3.79-3.97 (1H, m, isomer A+B), 3.97-4.07 (2H, m, isomer A+B), 4.39-4.45 (1H, m, isomer B), 4.58-4.64 (1H, m, isomer A), 6.28 (1H, s, isomer B), 6.32 (1H, s, isomer A), 9.51 (1H, s, isomer A), 9.54 (1H, s, isomer B).	57	487 [M+H]
	Approximately 1:1.25 mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.84 (3H, t, isomer A), 0.93 (3H, t, isomer B), 1.28 (3H, s, isomer B), 1.29 (3H, s, isomer B), 1.33 (3H, s, isomer A), 1.36 (3H, s, isomer A), 1.43-1.61 (7H, m, isomer A+B), 1.73 (6H, s, isomer A+B), 1.77-2.01 (5H, m, isomer A+B), 3.30-3.60 (5H, m, isomer A+B), 3.79-3.97 (1H, m, isomer A+B), 3.97-4.07 (2H, m, isomer A+B), 4.39-4.45 (1H, m, isomer B), 4.58-4.64 (1H, m, isomer A), 6.28 (1H, s, isomer B), 6.32 (1H, s, isomer A), 9.51 (1H, s, isomer A), 9.54 (1H, s, isomer B).	59	487 [M+H]
	^a LC-MS Retention Time: 1.55 mins.	81	445 [M+H]

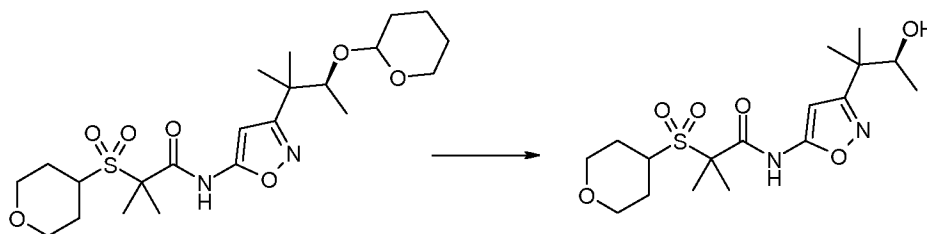
	Approximately 1:1 mixture of two diastereomers: (500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.02 (2 H, d, $J=6.10$ Hz), 1.18 (2 H, d, $J=6.41$ Hz), 1.23 - 1.35 (8 H, m), 1.38 (6 H, d, $J=2.90$ Hz), 1.42 - 1.89 (26 H, m + water), 1.95 - 2.18 (8 H, m), 2.77 - 2.88 (10 H, m), 3.27 - 3.39 (2 H, m), 3.48 (2 H, dd, $J=10.53, 4.88$ Hz), 3.75 - 3.97 (6 H, m), 4.54 - 4.58 (1 H, m), 4.75 (1 H, s), 6.32 (1 H, s), 6.35 (1 H, s), 9.34 (1H, s), 9.47 (1 H, s)	44	572 [M+Na]
	^a LC-MS Retention Time: 1.57 mins.	80	483 [M+H]

5 **a)** ESI + ion mode, Agilent Eclipse plus C18 column (1.8 μ m, 3.0 $\times$ 50mm). Gradient: 12% B to 30 % B (0 min to 0.25 mins), 30% B to 40% B (0.25 mins to 0.30 mins), 40% B to 95% B (0.30 mins to 1.19 mins), 95% B to 100% B (1.19 mins to 1.75 mins). Flow rate: 1.5 mL/min. A = (Water + 0.1% Formic Acid), B = (Acetonitrile + 0.1% Formic Acid). Diode Array Detector.

10

Amide Method B1: Deprotection with PPTS

Synthesis of N-[3-((S)-2-Hydroxy-1,1-dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (Example 6).



15

A solution of *N*-{3-[(*S*)-1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-propyl]-isoxazol-5-yl}-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (1.14 g, 2.41 mmol) and pyridinium *p*-toluenesulfonate (120.63 mg, 0.48 mmol) in ethanol (11 mL) is stirred at 65 °C for 3 h. After this time, the reaction mixture is concentrated under reduced pressure and partitioned between ethyl acetate and water. The layers are separated and the aqueous layer is extracted with ethyl acetate

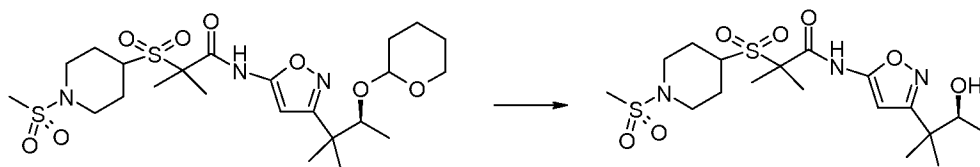
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once. The organic extracts are combined and washed with brine, dried over Na₂SO₄, filtered and concentrated. The resulting solid is triturated in ethanol and filtered to yield the title compound. Yield 76.4%; (400 MHz, *CHLOROFORM-d*) δ ppm 1.15 (3H, d), 1.28 (6H, s), 1.72 (6H, s), 1.80-1.90 (2H, m), 1.90-2.02 (2H, m), 2.26 (1H, d), 3.32-3.43 (2H, m), 3.40-3.50 (1H, m), 3.85-3.93 (1H, m), 4.00-4.10 (2H, m), 6.29 (1H, s), 9.62 (1H, s). ES-MS: *m/z* 389 [M+H].

Compounds in Table XXII, amide method B1, are made according to this procedure.

Amide Method B2: Deprotection with MP-TsOH

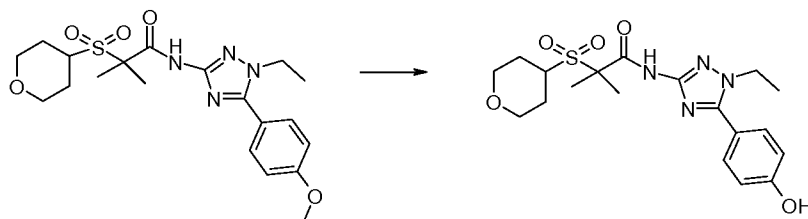
Synthesis of N-{3-[(3S)-3-hydroxy-2-methylbutan-2-yl]-1,2-oxazol-5-yl}-2-(1-methanesulfonylpiperidine-4-sulfonyl)-2-methylpropanamide (Example 72)



A solution of 192 mg (0.35 mmol) of 2-(1-methanesulfonylpiperidine-4-sulfonyl)-2-methyl-N-{3-[(3S)-2-methyl-3-(oxan-2-yloxy)butan-2-yl]-1,2-oxazol-5-yl}propanamide in DCM/methanol (1/1, 4 mL) is treated with 241 mg (1.40 mmol) of MP-TsOH resin (loading 3.3 mmol/g) at room temperature for 18 h. The resin is removed by filtration and washed alternating with DCM and methanol. The combined filtrates are concentrated under reduced pressure and the resulting residue is purified by column chromatography (silica, eluent: heptanes, 50-100% ethyl acetate) to yield 163 mg of N-{3-[(3S)-3-hydroxy-2-methylbutan-2-yl]-1,2-oxazol-5-yl}-2-(1-methanesulfonylpiperidine-4-sulfonyl)-2-methylpropanamide. Yield 78%; ES-MS: *m/z* 466 [M+H]

Amide Method C:

**Synthesis of N-[1-Ethyl-5-(4-hydroxy-phenyl)-1H-[1,2,4]triazol-3-yl]-2-methyl-2-(tetrahydro-
pyran-4-sulfonyl)-propionamide (Example 39)**



Prepared as described by adaptation of the following reference:

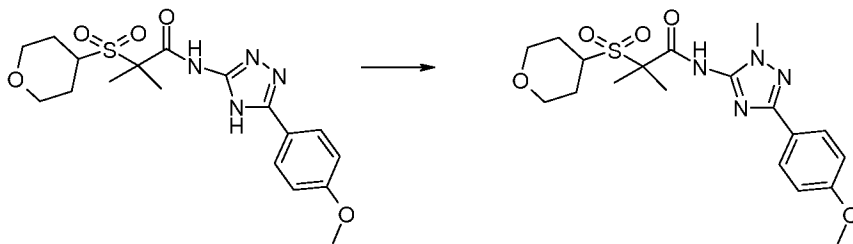
Van Muijlwijk-Koezen *et al.* *J. Med. Chem.* **2001**, *44*, (749-762).

To a solution of 446 mg (1.02 mmol) of N-[1-ethyl-5-(4-methoxy-phenyl)-1H-[1,2,4]triazol-3-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide in ethanethiol (5 mL) are added 801 mg (3.01 mmol) of aluminium tribromide. The reaction is stirred at room temperature for 3 h. The reaction is quenched by addition of 6M aqueous HCl solution (2 mL). The resulting precipitate is isolated by filtration, washed with methanol and retreated with 801 mg (3.01 mmol) of aluminium tribromide in ethanethiol (5 mL) at room temperature for further 3 h. The reaction is quenched by addition of 6M aqueous HCl solution (2 mL). The aqueous layer is extracted with ethyl acetate (3 x 20 mL). The combined organic extracts are dried over Na₂SO₄, filtered and the filtrate is concentrated under reduced pressure. The residue is purified by mass-directed preparative HPLC (neutral method) to afford 110 mg of N-[1-ethyl-5-(4-hydroxy-phenyl)-1H-[1,2,4]triazol-3-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide. Yield: 26%, ES-MS: m/z 423 [M+H].

Compounds in Table XXII, amide method C, are made according to this procedure with the following modifications to be noted: for Example 26, 76, 78, 81, 83, 85 and 86 AlCl_3 is used instead of AlBr_3 ; for Example 22 the compound is purified by column chromatography (silica, eluent: DCM, 0-50% EtOAc).

Amide Method D:

30 **Synthesis of N-[5-(4-Methoxy-phenyl)-2-methyl-2H-[1,2,4]triazol-3-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (Example 20).**



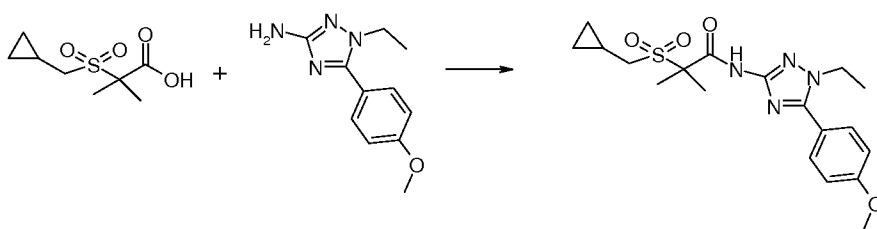
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To a solution of 238 mg (0.58 mmol) of N-[5-(4-methoxy-phenyl)-4H-[1,2,4]triazol-3-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (prepared according to Amide Method A) in anhydrous THF (2 mL) at room temperature are added 94 mg (2.32 mmol) of sodium hydride (60% dispersion in mineral oil). The reaction mixture is stirred for 1 h and then 145 μ L (2.32 mmol) of methyl iodide are added. The reaction is stirred at room temperature for 1 h. The reaction mixture is quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts are dried over Na_2SO_4 , filtered and the filtrate is concentrated under reduced pressure. The residue is triturated with methanol and the resulting precipitate is purified by mass-directed preparative HPLC (neutral method) to afford 90 mg of N-[5-(4-methoxy-phenyl)-2-methyl-2H-[1,2,4]triazol-3-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide. Yield: 97%, ES-MS: m/z 423 $[\text{M}+\text{H}]$.

Compounds in Table XXII, amide method D, are made according to this procedure

20 **Amide Method E:**

Synthesis of 2-Cyclopropylmethanesulfonyl-N-[1-ethyl-5-(4-methoxy-phenyl)-1H-[1,2,4]triazol-3-yl]-2-methyl-propionamide (Example 37)



25 Activation of 0.43 g (2.09 mmol) of 2-cyclopropylmethanesulfonyl-2-methyl-propionic acid as the corresponding acid chloride is achieved by treatment with thionyl chloride (3 mL) at 50 $^{\circ}\text{C}$ for 3 h.

5 The reaction is cooled to room temperature and excess thionyl chloride is removed under reduced pressure. The crude acid chloride is dissolved in THF (5 mL) and N,N-diisopropylethylamine (0.39 mL, 2.25 mmol) solution is added followed by 0.30 g (1.38 mmol) of 1-ethyl-5-(4-methoxy-phenyl)-1H-[1,2,4]triazol-3-ylamine. After complete addition the reaction is heated to 70 °C for 18 h. The reaction is cooled to room temperature and the reaction mixture is diluted with DCM (20 mL) and washed with saturated aqueous NaHCO₃ solution (20 mL). The combined organic layers are dried over Na₂SO₄, filtered and the filtrate is concentrated under reduced pressure. The residue is slurried in DCM/ether (1/1, 10 mL) to yield 0.52 g of 2-cyclopropylmethanesulfonyl-N-[1-ethyl-5-(4-methoxy-phenyl)-1H-[1,2,4]triazol-3-yl]-2-methyl-propionamide. Yield: 92%; ES-MS: m/z 407 [M+H].

15

Compounds in Table XXII, amide method E are made according to this procedure, with the following modifications to be noted: for Example 17 the crude product is purified by column chromatography (silica, eluent: DCM, 0-30% ethyl acetate)

20 Amide Method F:

Synthesis of Acetic acid 2-methyl-2-{5-[2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionylamino]-isoxazol-3-yl}-propyl ester (Example 1).



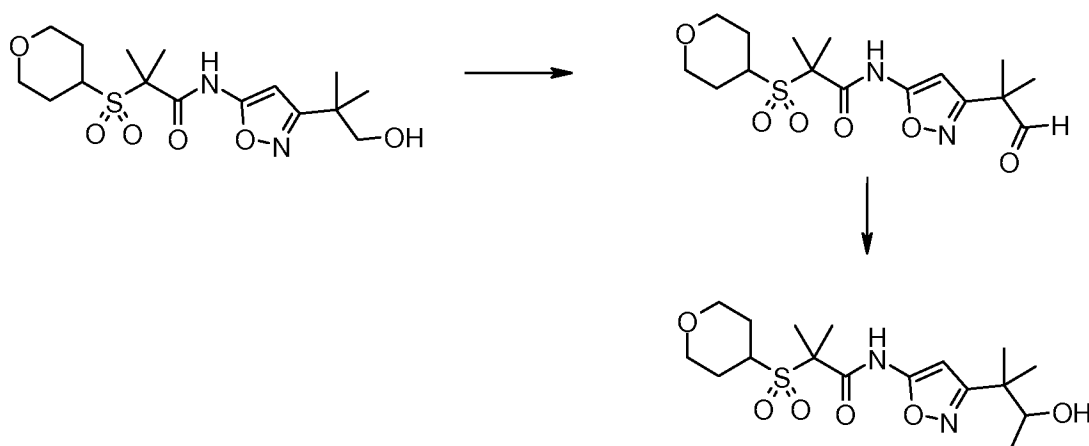
Acetic anhydride (24 uL, 0.26 mmol) and a catalytic amount of DMAP are added in sequence to a solution of N-[3-(2-hydroxy-1,1-dimethyl-ethyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (80.0 mg, 0.21 mmol) and pyridine (21 uL, 0.26 mmol) in anhydrous DCM (2.1 mL). The solution is stirred at room temperature until complete consumption of starting material. After removal of the solvent under reduced pressure, the crude is purified by silica gel column chromatography to afford 71 mg of acetic acid 2-methyl-2-{5-[2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionylamino]-isoxazol-3-yl}-propyl ester. Yield: 80%; m/z 417 [M+H].

30

- 5 Compounds in Table XXII, amide method F, are made according to this procedure with the following modifications to be noted: for Example 2, 2.3eq of pyridine and 1.5eq of pivaloyl chloride are added

Amide Method G:

- 10 **Synthesis of *N*-[3-(2-Hydroxy-1,1-dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (Example 3)**



- 15 **Step 1: Synthesis of *N*-[3-(1,1-Dimethyl-2-oxo-ethyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide**

- Dess-Martin periodinane (950 g, 2.24 mmol) is added to a solution of *N*-[3-(2-hydroxy-1,1-dimethyl-ethyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (600 mg, 1.60 mmol) (see Amide Method B1 or B2) in DCM (10 mL). The reaction mixture is stirred at room temperature for 40 minutes. After this time, the reaction mixture is quenched with 50 mL (1:1) saturated aqueous NaHCO₃ solution and saturated aqueous sodium thiosulfate solution and stirred at room temperature for 3 h then extracted with DCM 3 times. The organic extracts are combined and washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to provide the title compound. Yield: quantitative. ¹H NMR (400 MHz, DMSO-*d*) δ ppm 1.4 (6H, s), 1.65 (2H, m), 1.7 (6H, s), 1.8 (2H, m), 3.4 (2H, m), 3.9 (3H, m), 6.4 (1H, s), 9.6 (1H, s), 11.5 (1H, s).
- 20
25

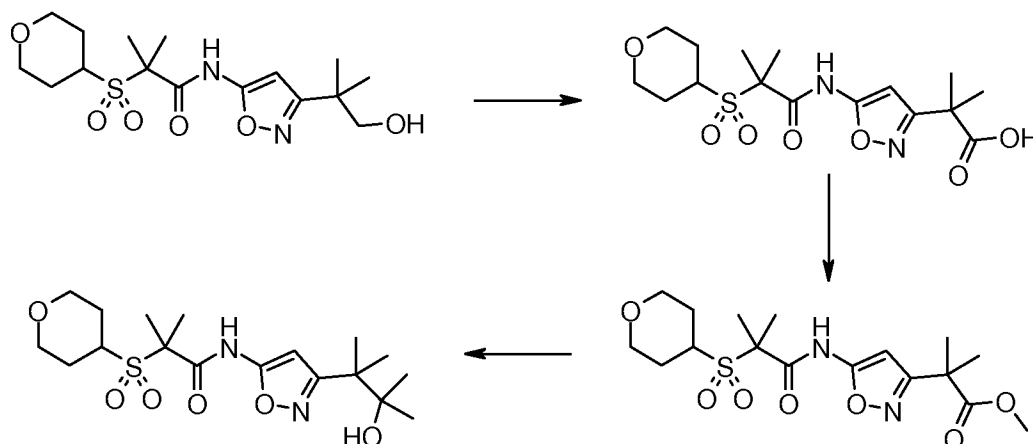
5 **Step 2: Synthesis of *N*-[3-(2-Hydroxy-1,1-dimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide**

To a cooled (- 20 °C) solution of *N*-[3-(1,1-Dimethyl-2-oxo-ethyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (792 mg, 2.13 mmol) in DCM (16 mL) is added dropwise 1.4 M methylmagnesium bromide toluene/THF solution (75: 25) over 10 minutes. DCM
10 (7 mL) is added after 1/3 of the addition of 1.4 M methylmagnesium bromide toluene/THF solution. After the addition, the reaction mixture is stirred in a cold bath and slowly warmed up to 3 °C after 30 minutes. After this time, the reaction mixture is quenched with saturated aqueous NH₄Cl solution and extracted with ethyl acetate twice. The organics are combined and washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The solids are
15 dissolved in DCM (30 mL) and PS-TsNHNH₂ (200 mg, 0.55 mmol) is added and the mixture is placed on a shaker for 1 h. After this time, the reaction mixture is filtered and the filtrate is concentrated under reduced pressure. Purification by preparative HPLC affords the title compound. Yield: 80 %; m/z 389 [M+H].

20 Compounds in Table XXII, amide method G, are made according to this procedure. Example 7 has been obtained through chiral chromatography of Example 3 on Chiralcel OD-H preparative column 2 x 25 cm on Agilent 1100 HPLC systems; mobile Phase: 85% heptane:15% isopropanol (with 0.5% diethyl amine); flow: 0.85 ml/min; diode array detector.

25 **Amide Method H:**

Synthesis of *N*-[3-(2-Hydroxy-1,1,2-trimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (Example 8)



5

Step 1: Synthesis of 2-Methyl-2-{5-[2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionylamino]-isoxazol-3-yl}-propionic acid

Jones reagent (1.28 mL, 10.24 mmol) is added dropwise to a solution of *N*-[3-(2-Hydroxy-1,1-dimethyl-ethyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (560 mg, 1.50 mmol) in a mixture of acetone (4 mL) and dichloromethane (4 mL) at 0 °C. The reaction mixture is stirred at 0 °C for 3 minutes then room temperature for 2.5 h. After this time, the reaction mixture is diluted with acetone and filtered through celite and the celite is washed with acetone. The filtrate is concentrated under reduced pressure. The residue is dispersed in water and filtered to yield the title compound. Yield: 64 %; *m/z* 389 [M+H].

15

Step 2: Synthesis of 2-Methyl-2-{5-[2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionylamino]-isoxazol-3-yl}-propionic acid methyl ester

2-Methyl-2-{5-[2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionylamino]-isoxazol-3-yl}-propionic acid (208 mg, 0.54 mmol) is dispersed in acetonitrile (5 mL). 1,8-diazabicyclo[5,4,0]undec-7-ene (0.096 mL, 0.64 mmol) is added and followed by the addition of methyl iodide (0.073 mL, 1.18 mmol). The reaction mixture is stirred at room temperature for 3.5 h. After this time, the reaction mixture is quenched with saturated aqueous NH₄Cl solution and extracted with ethyl acetate twice. The organic extracts are combined and washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to provide the title compound. Purification by flash chromatography on silica gel using methanol/DCM provides the title compound. Yield: 79 %; *m/z* 403 [M+H].

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Step 3: Synthesis of *N*-[3-(2-Hydroxy-1,1,2-trimethyl-propyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide.

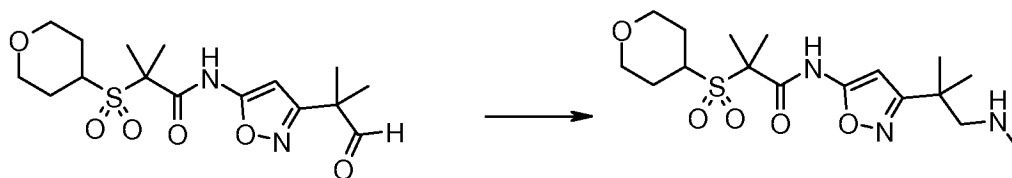
To a cooled (-10 °C) solution of 2-methyl-2-{5-[2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionylamino]-isoxazol-3-yl}-propionic acid methyl ester (139 mg, 0.35 mmol) in THF (3 mL) under nitrogen atmosphere is added dropwise methylmagnesium chloride (3M solution in THF, 0.52 mL, 1.56 mmol) over 3 minutes. After the addition, the reaction mixture is stirred at room temperature for 4 h. After this time, more methylmagnesium chloride (3M solution in THF, 0.52 mL, 1.56 mmol) is added to the reaction mixture and the stirring is continued for 1 h. After this time, the reaction mixture is quenched with saturated aqueous NH₄Cl solution and extracted with ethyl acetate twice. The organics are combined and washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel using methanol/DCM provides the title compound. Yield: 53 %; m/z 403 [M+H].

Compounds in Table XXII, amide method H, are made according to this procedure.

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Amide Method I:

Synthesis of *N*-[3-(1,1-Dimethyl-2-methylamino-ethyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (Example 70)



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To a solution of *N*-[3-(1,1-Dimethyl-2-oxo-ethyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (50 mg, 0.13 mmol) (see Amide Method G) in THF (0.5 mL) is added methylamine (2M solution in THF, 0.25 mL, 0.5 mmol) and 2.44 mmol/g of MP-cyanoborohydride (137 mg, 0.34 mmol). The reaction mixture is placed on a shaker for 2 h. After this time, more methylamine (2 M solution in THF, 0.13 mL, 0.26 mmol) and 2.44 mmol/g of MP-cyanoborohydride (137 mg, 0.34 mmol) are added to the reaction mixture and the stirring is

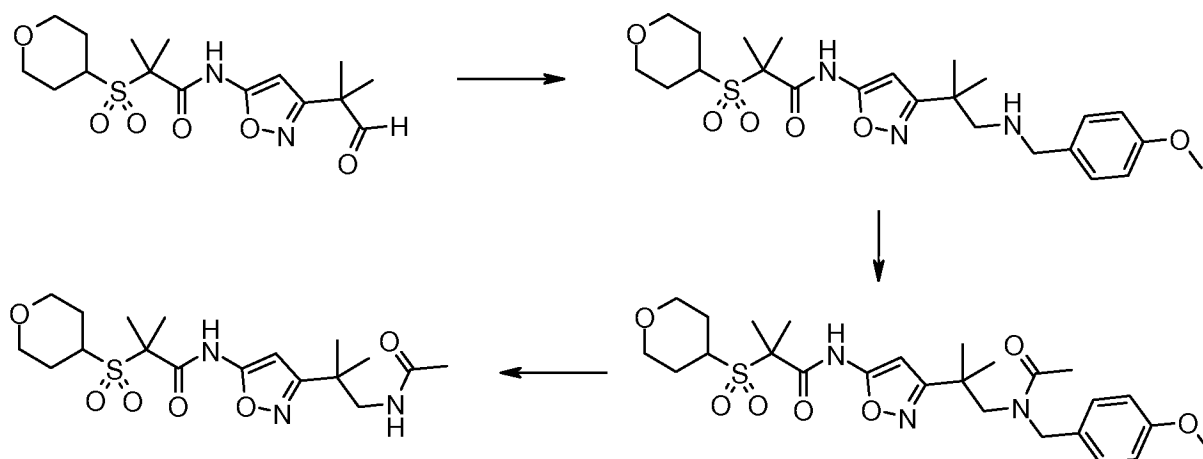
30

continued for 18 hs. After this time, the reaction mixture is filtered and the filtrate is concentrated under reduced pressure. Purification by preparative HPLC provides the title compound. Yield: 21 %; m/z 388 [M+H].

Compounds in Table XXII, amide method I, are made according to this procedure.

Amide Method J:

Synthesis of *N*-[3-(2-Acetylamino-1,1-dimethyl-ethyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (Example 43)



Step 1: Synthesis of *N*-[3-[2-(4-Methoxy-benzylamino)-1,1-dimethyl-ethyl]-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

To a solution of *N*-[3-(1,1-dimethyl-2-oxo-ethyl)-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (130 mg, 0.35 mmol) in THF (2 mL) is added 4-methoxybenzylamine (0.055 mL, 0.42 mmol) and 2.7 mmol/g of MP-triacetoxyborohydride (323 mg, 0.87 mmol). The reaction mixture is placed on a shaker for 18 h. After this time, the reaction mixture is filtered and the filtrate is concentrated under reduced pressure. Purification by flash chromatography on silica gel using methanol/DCM provides the title compound. Yield: 83 %; LC-MS retention time: 1.23 mins. ESI + ion mode. Zorbax SB-C18 column (3.5 μ m, 4.6 $\times$ 30mm). Gradient: 5% B to 80% B (0 min to 1.7 mins), 80% B to 95% B (1.7 mins to 2 mins), 95% B to 95% B (2 mins to 2.1 mins).

- 5 Flow rate: 2.5 mL/min. A = (Water + 0.1% Formic Acid) B = (Acetonitrile + 0.1% Formic Acid). Diode Array Detector; m/z 494 [M+H].

Step 2: Synthesis of *N*-(3-{2-[Acetyl-(4-methoxy-benzyl)-amino]-1,1-dimethyl-ethyl}-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

- 10 To a solution of *N*-(3-[2-(4-methoxy-benzylamino)-1,1-dimethyl-ethyl]-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (143 mg, 0.29 mmol) in THF (1.5 mL) are added pyridine (0.035 mL, 0.44 mmol) and acetyl chloride (0.031 mL, 0.44 mmol). The reaction mixture is stirred at room temperature for 3.5 h. After this time, more pyridine (0.018 mL, 0.22 mmol) and acetyl chloride (0.016 mL, 0.22 mmol) are added to the reaction mixture and the stirring is
- 15 continued for 1 h. After this time, the reaction mixture is quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate twice. The organic extracts are combined and washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel using methanol/DCM provides the title compound. Yield: 75 %; LC-MS retention time: 1.62 mins. ESI + ion mode. Zorbax SB-C18
- 20 column (3.5µm, 4.6×30mm). Gradient: 5% B to 80% B (0 min to 1.7 mins), 80% B to 95% B (1.7 mins to 2 mins), 95% B to 95% B (2 mins to 2.1 mins). Flow rate: 2.5 mL/min. A = (Water + 0.1% Formic Acid), B = (Acetonitrile + 0.1% Formic Acid). Diode Array Detector; m/z 536 [M+H].

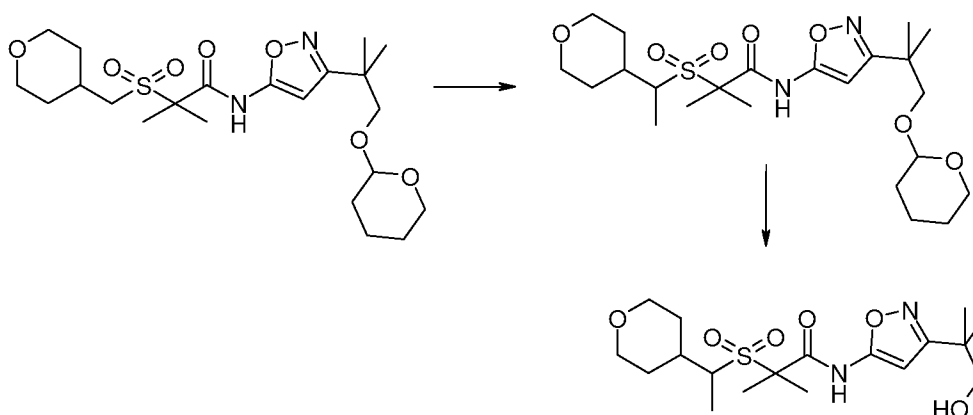
Step 3: Synthesis of *N*-(3-(2-Acetylamino-1,1-dimethyl-ethyl)-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide

- 25 To a solution of *N*-(3-{2-[acetyl-(4-methoxy-benzyl)-amino]-1,1-dimethyl-ethyl}-isoxazol-5-yl)-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (116 mg, 0.22 mmol) in the mixture of acetonitrile (2 mL) and water (0.7 mL) is added ceric ammonium nitrate (476 mg, 0.87 mmol). The reaction mixture is stirred at room temperature for 40 minutes. After this time, the reaction
- 30 mixture is quenched with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate 3 times. The organics are combined and washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by preparative HPLC provides the title compound. Yield: 4 %; m/z 416 [M+H].

5 Compounds in Table XXII, amide method J, are made according to this procedure.

10 **Amide Method K:**

Synthesis of N-[3-(2-Hydroxy-1,1-dimethyl-ethyl)-isoxazol-5-yl]-2-methyl-2-[1-(tetrahydro-pyran-4-yl)-ethanesulfonyl]-propionamide (Example 35).



15 **Step 1: Synthesis of N-{3-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl}-2-methyl-2-[1-(tetrahydro-pyran-4-yl)-ethanesulfonyl]-propionamide**

A solution of 0.4 g (0.85 mmol) of N-{3-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl}-2-methyl-2-(tetrahydro-pyran-4-ylmethanesulfonyl)-propionamide (synthesized according to method B, step 1) in anhydrous THF (5 mL) under nitrogen is cooled to -78 °C. A 2.5 M solution of n-butyl lithium in hexanes (1 mL) is added dropwise. The reaction mixture is stirred at -78 °C for 1 h, followed by addition of 0.11 mL (1.69 mmol) of methyl iodide. The reaction is allowed to warm to room temperature and stirred for 18 h. The mixture is quenched by addition of water (5 mL) and the organic solvent is removed under reduced pressure. The aqueous residue is extracted with DCM (2 x 10 mL). The combined organic extracts are washed with brine (10 mL), dried (Na₂SO₄) and filtered. The filtrate is concentrated under reduced pressure and the residue is purified by mass-triggered preparative LC (neutral method) to afford 0.1 g of N-{3-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl}-2-methyl-2-[1-(tetrahydro-pyran-4-yl)-ethanesulfonyl]-propionamide. Yield:24%, ES-MS: 403 [M+H].

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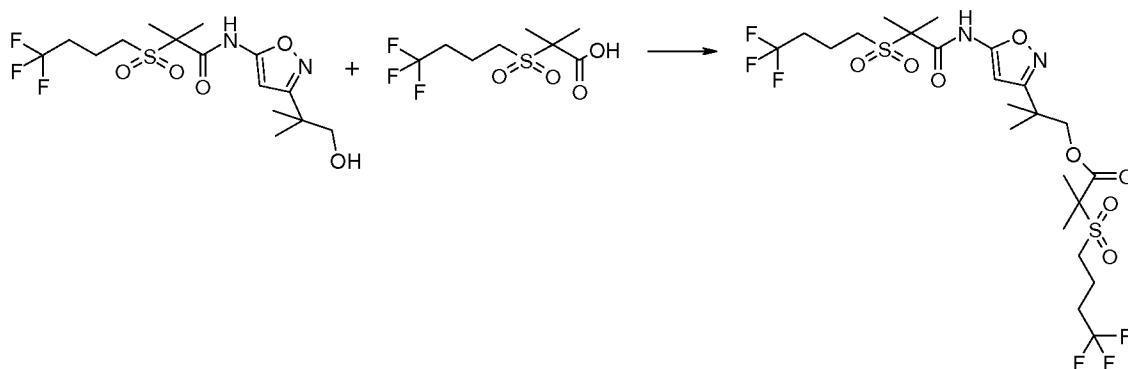
Step 2: Synthesis of N-[3-(2-Hydroxy-1,1-dimethyl-ethyl)-isoxazol-5-yl]-2-methyl-2-[1-(tetrahydro-pyran-4-yl)-ethanesulfonyl]-propionamide

A solution of 100 mg (0.24 mmol) of N-{3-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl}-2-methyl-2-[1-(tetrahydro-pyran-4-yl)-ethanesulfonyl]-propionamide in DCM/ethanol (1/1, 10 mL) is treated with 145 mg (0.48 mmol) of MP-TsOH resin (loading 3.3 mmol/g) at room temperature for 18 h. The resin is removed by filtration and washed with DCM (10 mL) and methanol (10 mL). The combined filtrates are concentrated under reduced pressure and the resulting residue is slurried in heptanes/ethyl acetate (7/3) to yield 74 mg of N-[3-(2-hydroxy-1,1-dimethyl-ethyl)-isoxazol-5-yl]-2-methyl-2-[1-(tetrahydro-pyran-4-yl)-ethanesulfonyl]-propionamide. Yield 87%; ES-MS: m/z 403 [M+H].

Compounds in Table XXII, amide method K, are made according to this procedure.

Amide Method L:

Synthesis of 2-Methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionic acid 2-methyl-2-{5-[2-methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionylamino]-isoxazol-3-yl}-propyl ester (Example 40).

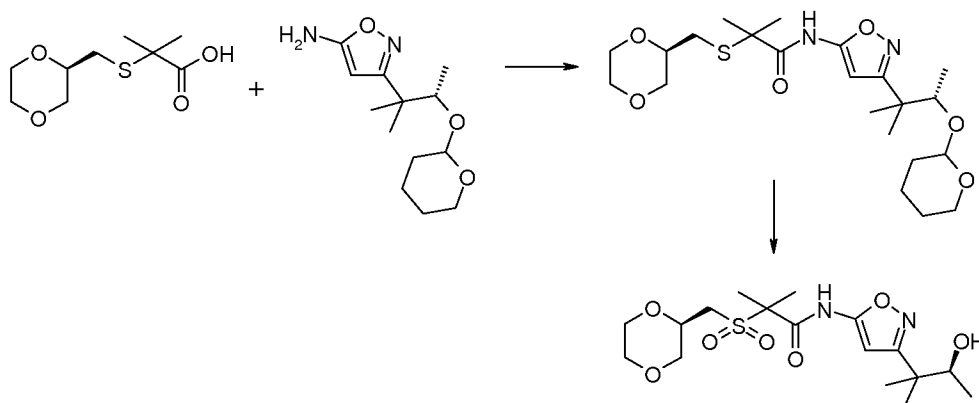


Activation of 0.14 g (0.53 mmol) of 2-methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionic acid as the corresponding acid chloride is achieved by treatment with thionyl chloride (0.08 mL, 1.07 mmol) and DMF (1 drop) in toluene (2 mL) at 80 °C for 4 h. The reaction is cooled to room temperature and toluene (1 mL) is removed by distillation, whilst adding fresh toluene (1 mL). This process is repeated once.

- 5 This acid chloride solution is added dropwise to a stirred suspension of 0.21 g (0.53 mmol) of N-[3-(2-hydroxy-1,1-dimethyl-ethyl)-isoxazol-5-yl]-2-methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionamide (synthesized according to method B) and 0.18 mL (1.07 mmol) of N,N-diisopropylethylamine in toluene (1 mL) at 35 °C. After complete addition the reaction is heated to 80 °C for 17 h. The biphasic reaction mixture is concentrated under reduced pressure and the
- 10 residue is dissolved in anhydrous THF (2 mL). Additional 100 mg of 2-methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionic acid are activated as its acid chloride as described above. This acidchloride solution and N,N-diisopropylethylamine (0.18 mL) are added to the reaction mixture and heated to 90 °C for 18 h. The reaction is cooled to room temperature and the solvent is removed under reduced pressure. The residue is dissolved in ethyl acetate and washed with brine.
- 15 The organic layer is concentrated under reduced pressure and the residue purified by mass-triggered preparative LC (MeCN/water, 0.1% TFA) to yield 0.09 g of 2-methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionic acid 2-methyl-2-{5-[2-methyl-2-(4,4,4-trifluoro-butane-1-sulfonyl)-propionylamino]-isoxazol-3-yl}-propyl ester. Yield: 25%; ES-MS: m/z 645 [M+H].
- 20 Compounds in Table XXII, amide method L, are made according to this procedure.

Amide Method M:

Synthesis of 2-[[2-(2R)-1,4-dioxan-2-ylmethane]sulfonyl]-N-{3-[(3S)-3-hydroxy-2-methylbutan-2-yl]-1,2-oxazol-5-yl}-2-methylpropanamide (Example 87)



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5 **Step 1: Synthesis of 2-([(2R)-1,4-dioxan-2-ylmethyl]sulfanyl)-2-methyl-N-{3-[(3S)-2-methyl-3-(oxan-2-yloxy)butan-2-yl]-1,2-oxazol-5-yl}propanamide**

Activation of 145 mg (0.58 mmol) of 2-([(2R)-1,4-dioxan-2-ylmethyl]sulfanyl)-2-methylpropanoic acid as its acid chloride is achieved by treatment with oxalyl chloride (0.1 mL, 1.16 mmol) and DMF (1 drop) in DCM (15 mL) at room temperature for 16 h. The
10 solvent is removed under reduced pressure and the crude acid chloride is dissolved in anhydrous THF (5 mL) and added to a solution of 147 mg (0.58 mmol) of 3-[(3S)-2-methyl-3-(oxan-2-yloxy)butan-2-yl]-1,2-oxazol-5-amine and N,N-diisopropylethylamine (0.30 mL, 1.73 mmol) in THF (10 mL). The reaction is heated to 60 °C for 18 h. After cooling to room temperature, the reaction mixture is concentrated under reduced pressure. The residue is
15 diluted with DCM (20 mL) and washed with saturated aqueous NaHCO₃ solution (10 mL). The organic layer is dried (MgSO₄), filtered and the filtrate is concentrated under reduced pressure. The residue is purified by column chromatography (silica, eluent: heptanes, 0-30% ethyl acetate) to afford 226 mg of 2-([(2R)-1,4-dioxan-2-ylmethyl]sulfanyl)-2-methyl-N-{3-[(3S)-2-methyl-3-(oxan-2-yloxy)butan-2-yl]-1,2-oxazol-5-yl}propanamide of 63% purity.
20 This intermediate is taken on in the next step without further purification. Yield: 54%, ES-MS: m/z 479 [M+Na]

25 **Step 2: Synthesis of 2-([(2R)-1,4-dioxan-2-ylmethane]sulfonyl)-N-{3-[(3S)-3-hydroxy-2-methylbutan-2-yl]-1,2-oxazol-5-yl}-2-methylpropanamide**

To a stirred solution of 227 mg (0.31 mmol) of 2-([(2R)-1,4-dioxan-2-ylmethyl]sulfanyl)-2-methyl-N-{3-[(3S)-2-methyl-3-(oxan-2-yloxy)butan-2-yl]-1,2-oxazol-5-yl}propanamide (67% purity) in 1,4 dioxane/water (1/1, 10 mL) are added 385 mg (0.63 mmol) of OXON
(potassium monopersulfate triple salt). The reaction mixture is stirred at room temperature for
30 18 h. (Note: under this reaction conditions, the O-protecting group is cleaved). The solid is removed by filtration and the filtrate is concentrated under reduced pressure. The residue is dissolved in ethyl acetate (25 mL) and washed with saturated aqueous NaHCO₃ solution (2 x 2

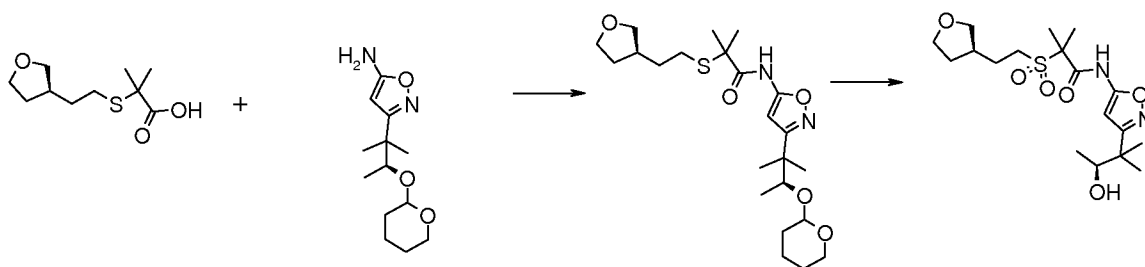
5 mL). The organic layer is dried over MgSO_4 , filtered and the filtrate is concentrated under reduced pressure. The residue is purified by column chromatography (silica, eluent: heptanes, 0-50% ethyl acetate) followed by recrystallisation from heptanes/ethyl acetate to afford 95 mg of 2-{[(2R)-1,4-dioxan-2-ylmethane]sulfonyl}-N-{3-[(3S)-3-hydroxy-2-methylbutan-2-yl]-1,2-oxazol-5-yl}-2-methylpropanamide. Yield: 75%, ES-MS: m/z 405 $[\text{M}+\text{H}]$

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Compounds in Table XXII, amide method M, are made according to this procedure.

Amide Method N:

15 **Synthesis of N-{3-[(3S)-3-hydroxy-2-methylbutan-2-yl]-1,2-oxazol-5-yl}-2-methyl-2-[(2-[(3R)-oxolan-3-yl]ethane)sulfonyl]propanamide (Example 89)**



Step 1: Synthesis of 2-Methyl-N-{3-[(3S)-2-methyl-3-(oxan-2-yloxy)butan-2-yl]-1,2-oxazol-5-yl}-2-[(2-[(3R)-oxolan-3-yl]ethyl)sulfonyl]propanamide

20 Activation of 0.35 g (1.61 mmol) of 2-methyl-2-[(2-[(3R)-oxolan-3-yl]ethyl)sulfonyl]propanoic acid as the corresponding acid chloride is achieved by treatment with oxalyl chloride (0.28 mL, 3.22 mmol) and DMF (cat., 0.01 mL) in DCM (15 mL) at room temperature for 3 h. The reaction mixture is concentrated under reduced pressure. The residue is dissolved in THF (5 mL) and concentrated under reduced pressure. This process is repeated. Then the crude acid chloride is dissolved in anhydrous THF (10 mL) and 0.32 mL (1.81 mmol) of N,N-diisopropylethylamine are added followed by 0.17 g (0.66 mmol) of 3-[(3S)-2-methyl-3-(oxan-2-yloxy)butan-2-yl]-1,2-oxazol-5-amine. After complete addition the reaction is heated to 60 °C for 17 h. The reaction is cooled to room temperature and the solvent is removed under reduced pressure. The residue is dissolved in ethyl acetate (20 mL) and washed

5 with saturated aqueous NaHCO₃ solution (2 x 5 mL) and 1M aqueous HCl solution (2 x 5 mL). The organic layer is dried (Na₂SO₄) and filtered. The filtrate is concentrated under reduced pressure and the residue purified by column chromatography (silica, eluent heptanes, 30% ethyl acetate) to yield 133 mg of 2-methyl-N-{3-[(3S)-2-methyl-3-(oxan-2-yloxy)butan-2-yl]-1,2-oxazol-5-yl}-2-({2-[(3R)-oxolan-3-yl]ethyl}sulfanyl)propanamide. Yield: 55%; ES-
 10 MS: m/z 453 [M-H]; ¹H NMR (250 MHz, CHLOROFORM-*d*) δ ppm approx 1:1 mixture of diastereoisomers: 1.00 (4 H, d, *J*=6.24 Hz), 1.14 - 1.20 (4 H, m), 1.22 - 1.39 (11 H, m), 1.41 - 1.91 (27 H, m), 1.94 - 2.13 (2 H, m), 2.20 - 2.36 (2 H, m), 2.48 - 2.67 (4 H, m), 3.26 - 3.38 (2 H, m), 3.41 - 3.55 (2 H, m), 3.63 - 3.98 (12 H, m), 4.53 - 4.59 (1 H, m), 4.74 (1 H, t, *J*=3.12 Hz), 6.31 (1 H, s), 6.35 (1 H, s), 9.50 (2 H, s)

15

2-Methyl-N-{3-[(3S)-2-methyl-3-(oxan-2-yloxy)butan-2-yl]-1,2-oxazol-5-yl}-2-({2-[(3S)-oxolan-3-yl]ethyl}sulfanyl)propanamide is synthesised from 2-methyl-2-({2-[(3S)-oxolan-3-yl]ethyl}sulfanyl)propanoic acid according to the above procedure. Yield: 78%; m/z 453 [M-H]; ¹H NMR (250 MHz, CHLOROFORM-*d*) δ ppm approx. 1:1 mixture of diastereoisomers
 20 0.99 (4 H, d, *J*=6.24 Hz), 1.16 (4 H, d, *J*=6.40 Hz), 1.21 - 1.39 (11 H, m), 1.41 - 1.89 (27 H, m), 1.92 - 2.14 (2 H, m), 2.16 - 2.36 (2 H, m), 2.46 - 2.67 (4 H, m), 3.27 - 3.38 (2 H, m), 3.41 - 3.53 (2 H, m), 3.64 - 3.99 (12 H, m), 4.51 - 4.58 (1 H, m), 4.73 (1 H, t, *J*=3.12 Hz), 6.31 (1 H, s), 6.34 (1 H, s), 9.52 (2 H, s)

25 **Step 2: Synthesis of N-{3-[(3S)-3-Hydroxy-2-methylbutan-2-yl]-1,2-oxazol-5-yl}-2-methyl-2-({2-[(3R)-oxolan-3-yl]ethane}sulfonyl)propanamide**

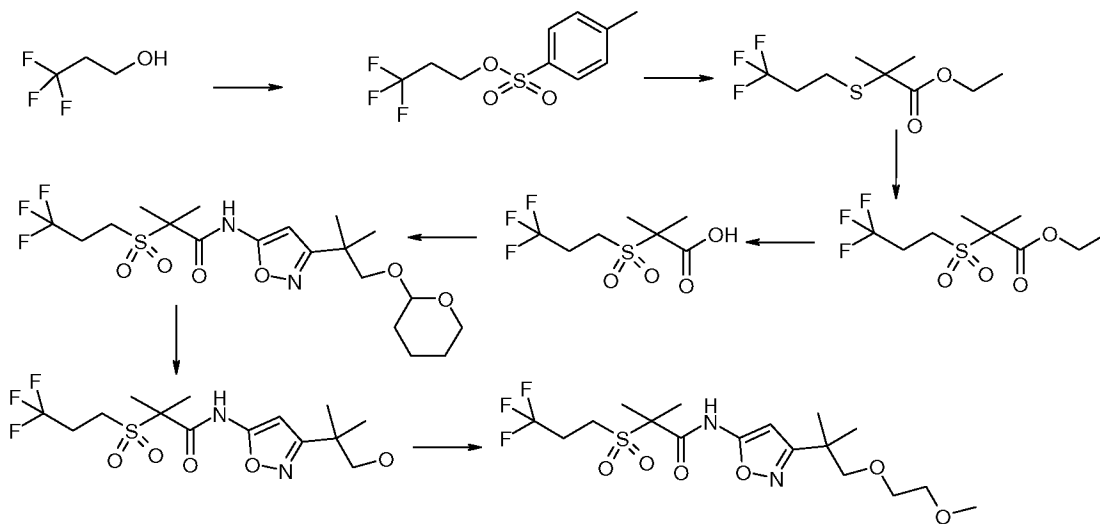
To a solution of 133 mg (0.29 mmol) of 2-methyl-N-{3-[(3S)-2-methyl-3-(oxan-2-yloxy)butan-2-yl]-1,2-oxazol-5-yl}-2-({2-[(3R)-oxolan-3-yl]ethyl}sulfanyl)propanamide in
 30 1,4-dioxane/water (1/4, 5 mL) are added 0.36g (0.585 mmol) of OXONE (potassium monopersulfate triple salt). The reaction mixture is stirred at room temperature for 3 h (Note: under this acidic reaction condition, the O-protecting group is also cleaved). The reaction

- 5 mixture is diluted with ethyl acetate (20 mL) and washed with saturated aqueous NaHCO_3 solution (2 x 2 mL). The organic layer is dried (Na_2SO_4), filtered and the filtrate is concentrated under reduced pressure. The residue is purified by column chromatography (silica, eluent, heptanes, ethyl acetate) to afford 65 mg of **N-{3-[(3S)-3-hydroxy-2-methylbutan-2-yl]-1,2-oxazol-5-yl}-2-methyl-2-({2-[(3R)-oxolan-3-yl]ethane)sulfonyl}propanamide**. Yield:55%; m/z 403 [M+H];

Compound in Table XXII, Method N are made according to this procedure

Amide Method O:

- 15 Synthesis of N-[3-[2-(2-Methoxy-ethoxy)-1,1-dimethyl-ethyl]-isoxazol-5-yl]-2-methyl-2-(3,3,3-trifluoro-propane-1-sulfonyl)-propionamide (Example 68)



Step 1: Synthesis of toluene-4-sulfonic acid 3,3,3-trifluoro-propyl ester:

- 20 To a solution of 3,3,3-trifluoro-propan-1-ol (1.1 g, 10.0 mmol) in DCM (10mL) are added p-toluenesulfonyl chloride (2.3 g, 12.0 mmol), N,N-dimethylaminopyridine (0.1 g, 1.0 mmol) and triethyl amine (2.8 mL, 20.0 mmol). The reaction is stirred at room temperature for 3 d, then poured into water and extracted with DCM. The combined organic extracts are washed with 1N aqueous HCl solution, saturated aqueous NaHCO_3 solution, brine and dried over Na_2SO_4 , filtered

5 and concentrated to afford 2.34 g of title compound. ^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 2.47 (3H, s), 2.47-2.6 (2H, m), 4.22 (2H, t, $J=6.4\text{Hz}$), 7.36 (2H, d, $J=8.08\text{Hz}$), 7.8 (2H, d, $J=7.8\text{Hz}$)

Step 2: Synthesis of 2-methyl-2-(3,3,3-trifluoro-propylsulfanyl)-propionic acid ethyl ester:

10 A solution of 2-acetylsulfanyl-2-methyl-propionic acid ethyl ester (1.7 g, 8.72 mmol), toluene-4-sulfonic acid 3,3,3-trifluoro-propyl ester (2.3 g, 8.72 mmol) and sodium methoxide (1.9 g, 34.9 mmol) in ethanol (13 mL) are heated to 130°C in a sealed tube for 4 h. The reaction is cooled to room temperature and concentrated under reduced pressure. The residue is diluted with DCM and washed with saturated aqueous NaHCO_3 solution and brine. The organic layer is dried (Na_2SO_4),
15 filtered and the filtrate concentrated under reduced pressure to afford 1.76 g of title compound as a brown solid. ^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 1.28 (3H, t, $J=7\text{ Hz}$), 1.51 (3H, s), 2.26-2.42 (2H, m), 2.76-2.85 (2H, m), 4.18 (2H, q, $J=6.96\text{Hz}$)

Step 3: Synthesis of 2-methyl-2-(3,3,3-trifluoro-propane-1-sulfonyl)-propionic acid ethyl ester:

20 To crude 2-methyl-2-(3,3,3-trifluoro-propylsulfanyl)-propionic acid ethyl ester (1.8 g, 7.2 mmol) in dioxane/water (1/1, 14mL) is added OXONE (potassium monopersulfate triple salt, 6.7 g, 10.9 mmol). The reaction is stirred for 18 h at room temperature. The reaction mixture is filtered and the solid is washed with dioxanes. The filtrate is concentrated under reduced pressure to remove
25 the organic solvent and extracted with DCM. The combined organic extracts are washed with saturated aqueous NaHCO_3 solution, dried (Na_2SO_4), filtered and concentrated to afford 1.28g of title compound. ^1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 1.301 (3H, t, $J=7.2\text{ Hz}$), 1.66 (3H, s), 2.58-2.77 (2H, m), 3.42-3.52 (2H, m), 4.26 (2H, q, $J=6.8\text{Hz}$)

30 **Step 4: Synthesis of 2-methyl-2-(3,3,3-trifluoro-propane-1-sulfonyl)-propionic acid:**

2-Methyl-2-(3,3,3-trifluoro-propane-1-sulfonyl)-propionic acid ethyl ester (1.3 g, 4.63 mmol) is dissolved in THF/water (14mL, 4:1 ratio) and LiOH (0.2 g, 9.27 mmol, 2eq.) is added. The mixture is stirred for 18 h at room temperature, then concentrated under reduced pressure to

5 remove the organic solvent. The aqueous residue is further diluted with water, washed with DCM and then acidified to pH ~ 2 and extracted with DCM. The combined acidic organic extracts are concentrated to afford 0.97g of title compound. ¹H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 1.72 (3H, s), 2.64-2.81 (2H, m), 3.46-3.6 (2H, m)

10 **Step 5: Synthesis of N-[3-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl]-2-methyl-2-(3,3,3-trifluoro-propane-1-sulfonyl)-propionamide**

To a solution of 2-methyl-2-(3,3,3-trifluoro-propane-1-sulfonyl)-propionic acid (3.75 mmol) in 17.0 mL toluene is added thionyl chloride (7.49 mmol, 2eq) and a catalytic amount of DMF. The mixture is heated at reflux for 1h in a sealed tube. The mixture is
15 cooled and concentrated to a volume of ~5.0 mL. Additional 5.0 mL of toluene are added and the mixture is concentrated to ~4.0 mL.

The above acid chloride solution (0.94 mmol) is added dropwise over 0.5 h to a stirred suspension of 3-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-ylamine (0.226 g, 0.940 mmol) and N,N-diisopropylethylamine (0.327 mL, 1.88 mmol) in toluene (2mL) at
20 room temperature. After complete addition the reaction is heated at 60 °C for 1 h. The reaction is cooled to room temperature and the solvent is removed under reduced pressure. The residue is dissolved in ethyl acetate (5 mL) and washed with aqueous saturated sodium bicarbonate solution (2 x 5 mL) and 1N HCl (2 x 5 mL). The organic layer is concentrated under reduced pressure and used crude in subsequent reaction. m/z 471 [M+H].

25

Step 6: Synthesis of N-[3-(2-Hydroxy-1,1-dimethyl-ethyl)-isoxazol-5-yl]-2-methyl-2-(3,3,3-trifluoro-propane-1-sulfonyl)-propionamide

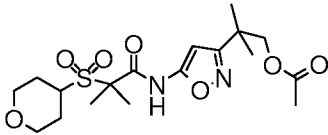
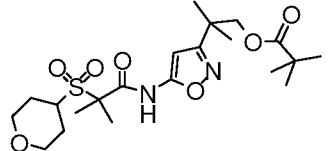
A solution of N-[3-[1,1-Dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-yl]-2-methyl-2-(tetrahydro-pyran-4-sulfonyl)-propionamide (441.0 mg, 0.940 mmol) and
30 pyridinium p-toluenesulfonate (24 mg, 0.094 mmol) in ethanol (15.0 mL) is stirred at 75 °C for 40 minutes. After this time, the reaction mixture is concentrated and purified by reverse phase HPLC to provide the title compound. Yield: 53 %; m/z 387 [M+H].

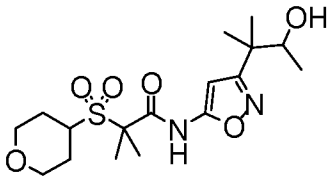
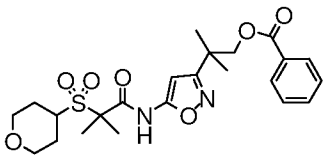
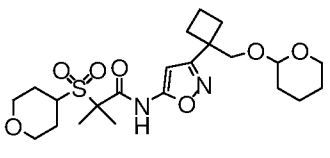
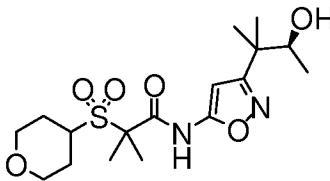
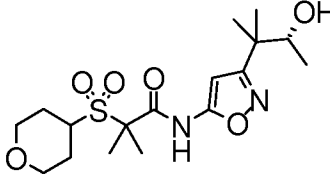
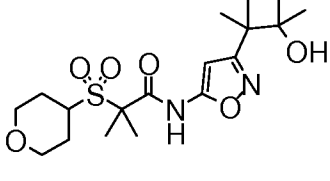
5 **Step7: Synthesis of *N*-[3-[2-(2-Methoxy-ethoxy)-1,1-dimethyl-ethyl]-isoxazol-5-yl]-2-methyl-2-(3,3,3-trifluoro-propane-1-sulfonyl)-propionamide**

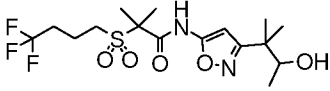
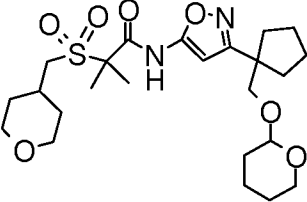
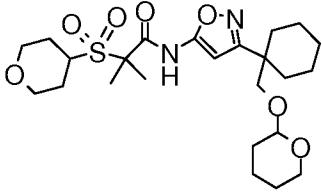
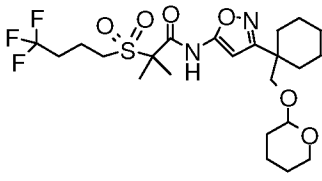
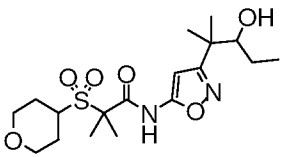
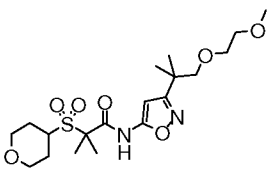
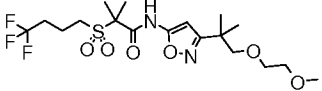
To a solution of NaH (60% in mineral oil; 11.0 mg; 0.284 mmol) in anhydrous THF (2.0 mL) is added *N*-[3-(2-Hydroxy-1,1-dimethyl-ethyl)-isoxazol-5-yl]-2-methyl-2-(3,3,3-trifluoro-propane-1-sulfonyl)-propionamide (50.0 mg; 0.129 mmol). The reaction is stirred at room
 10 temperature for 15 minutes and then 1-bromo-2-methoxy-ethane (0.037 mL, 0.387 mmol) is added. The reaction is stirred at 50°C for 6h and monitored by LC MS. Additional NaH (60% in mineral oil; 0.011 g; 0.284 mmol) and 1-bromo-2-methoxy-ethane (0.037 mL; 0.387mmol) is added and the reaction is stirred overnight at room temperature. The crude mixture is diluted with water and extracted with ethyl acetate. The combined organics are dried over
 15 sodium sulfate, filtered and concentrated under reduced pressure. The title compound is obtained after purification by prep HPLC to afford 8mg. Yield 14%. ESI m/z 445[M+H].

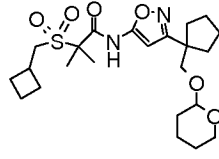
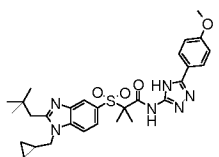
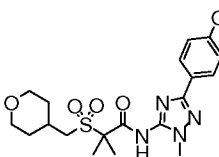
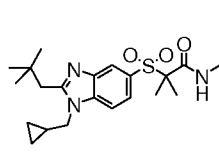
Compounds in Table XXII, amide method O, are made according to this procedure.

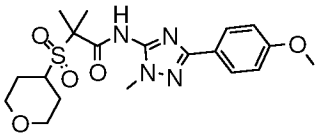
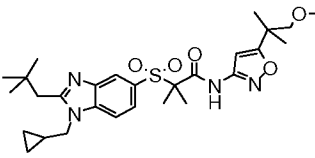
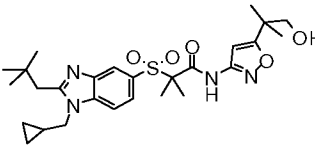
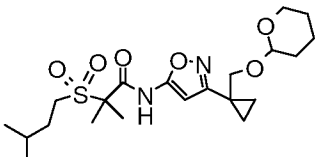
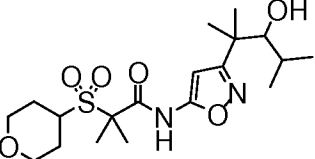
20 **Table XXII: Examples**

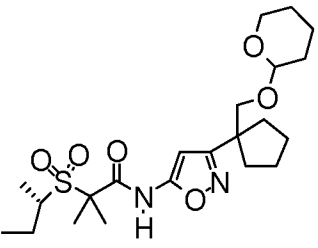
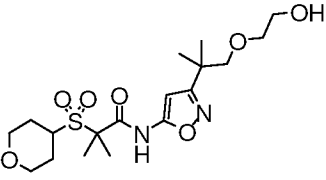
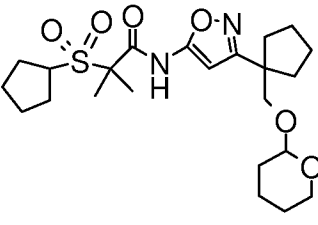
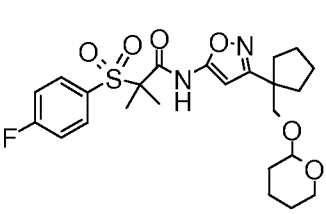
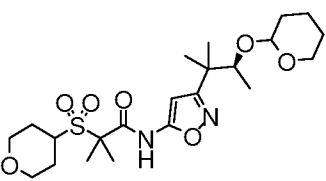
#	Structure	¹ H-NMR	m/z [M+H]	Acid Method	Amine Method	Amide Method
1		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.36 (s, 6H), 1.75 (s, 6H), 1.84 – 1.88 (m, 2H), 1.98 (qd, 2H), 2.09 (s, 3H), 3.38 (td, 2H), 3.42 – 3.49 (m, 1H), 4.04 – 4.09 (m, 2H), 4.14 (s, 2H), 6.28 (s, 1H), 9.62 (s, 1H).	417	not applicable	not applicable	F
2		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.17 (s, 9H), 1.37 (s, 6H), 1.74 (s, 6H), 1.82 – 1.87 (m, 2H), 1.96 (qd, 2H), 3.37 (td, 2H), 3.42 – 3.49 (m, 1H), 4.03 – 4.07 (m, 2H), 4.10 (s, 2H), 6.29 (s, 1H), 9.60 (s, 1H).	459	not applicable	not applicable	F

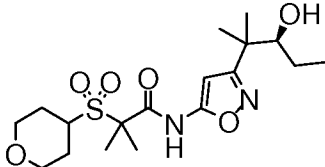
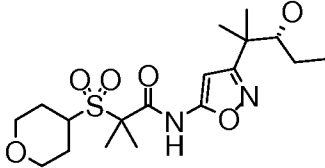
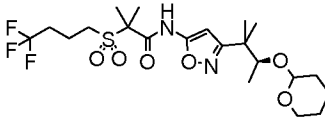
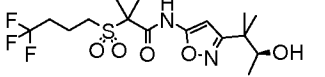
3		(400 MHz, <i>DMSO-d</i>) δ ppm 0.92 (3H, d), 1.18 (6H, d), 1.58-1.72 (2H, m), 1.67 (6H, s), 1.78-1.86 (2H, m), 3.33-3.43 (2H, m), 3.62-3.70 (1H, m), 3.84-3.96 (3H, m), 4.71 (1H, d), 6.29 (1H, s), 11.29 (1H, s).	389	not applicable	not applicable	G
4		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.54 (s, 6H), 1.74 (s, 6H), 1.81 – 1.85 (m, 2H), 1.93 (qd, 2H), 3.34 (td, 2H), 3.40 – 3.48 (m, 1H), 3.99 – 4.02 (m, 2H), 4.36 (s, 2H), 6.36 (s, 1H), 7.41 – 7.45 (m, 2H), 7.54 – 7.58 (m, 1H), 7.99 – 8.02 (m, 2H), 9.62 (s, 1H).	479	not applicable	not applicable	F
5		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.43 - 1.56 (m, 4H), 1.56 - 1.81 (m, 10H), 1.85 - 2.00 (m, 4H), 2.13 - 2.23 (m, 2H), 2.32 - 2.40 (m, 2H), 3.31 (td, 2H), 3.36 - 3.46 (m, 2H), 3.50 (d, 1H), 3.71 - 3.77 (m, 1H), 3.94 (d, 1H), 3.97 - 4.00 (m, 2H), 4.56 (t, 1H), 6.22 (s, 1H), 9.52 (s, 1H).	469 (M-H)	E	A	B
6		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.15 (3H, d), 1.28 (6H, s), 1.72 (6H, s), 1.80-1.90 (2H, m), 1.90-2.02 (2H, m), 2.26 (1H, d), 3.32-3.43 (2H, m), 3.40-3.50 (1H, m), 3.85-3.93 (1H, m), 4.00-4.10 (2H, m), 6.29 (1H, s), 9.62 (1H, s).	389	E	A	B ₁
7		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.15 (3H, d), 1.28 (6H, s), 1.72 (6H, s), 1.80-1.90 (2H, m), 1.90-2.02 (2H, m), 2.26 (1H, d), 3.32-3.43 (2H, m), 3.40-3.50 (1H, m), 3.85-3.93 (1H, m), 4.00-4.10 (2H, m), 6.29 (1H, s), 9.62 (1H, s).	389	not applicable	not applicable	G
8		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.20 (6H, s), 1.36 (6H, s), 1.75 (6H, s), 1.82-1.90 (2H, m), 1.91-2.04 (2H, m), 2.49 (1H, s), 3.33-3.43 (2H, m), 3.42-3.51 (1H, m), 4.02-4.10 (2H, m), 6.32 (1H, s), 9.62 (1H, s).	403	not applicable	not applicable	H

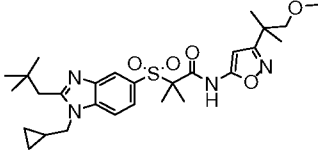
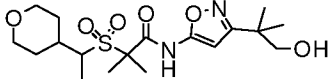
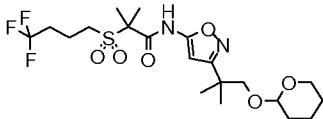
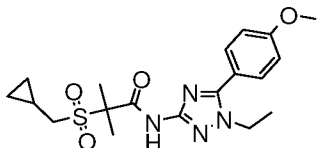
9		(400 MHz, <i>MeOD</i>) δ ppm 0.97 (3H, d), 1.20 (6H, d), 1.65 (6H, s), 1.90-2.01 (2H, m), 2.20-2.35 (2H, m), 3.25 (2H, t), 3.72 (1H, t), 6.30 (1H, s).	415	not applicable	not applicable	G
10		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.41-1.93 (m, 22H), 2.02-2.11 (m, 2H), 2.34-2.43 (m, 1H), 2.90 (d, 2H), 3.38-3.49 (m, 4H), 3.73-3.79 (m, 1H), 3.82 (d, 1H), 3.92 - 3.95 (m, 2H), 4.56 (bt, 1H), 6.33 (s, 1H), 9.33 (s, 1H)	497 (M-H)	B	A	B
11		^a (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.41 - 1.67 (m, 14H), 1.76 (s, 6H), 1.86 - 1.90 (m, 2H), 1.94 - 2.14 (m, 4H), 3.31 (d, 1H), 3.36 - 3.52 (m, 4H), 3.66 - 3.71 (m, 1H), 3.75 (d, 1H), 4.04 - 4.08 (m, 2H), 4.51 (bt, 1H), 6.31 (s, 1H), 9.56 (s, 1H)	497 (M-H)	E	A	B
12		^a (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.42 - 1.63 (m, 14H), 1.76 (s, 6H), 2.04 - 2.24 (m, 4H), 2.25 - 2.34 (m, 2H), 3.11 (t, 2H), 3.30 (d, 1H), 3.44 - 3.47 (m, 1H), 3.64 - 3.76 (m, 2H), 4.50 (bd, 1H), 6.33 (s, 1H), 9.21 (s, 1H)	523 (M-H)	C	A	B
13		(400 MHz, <i>DMSO-d</i>) δ ppm 0.80 (3H, t), 0.90-1.05 (1H, m), 1.10 (6H, d), 1.10-1.30 (1H, m), 1.50-1.70 (2H, m), 1.60 (6H, s), 1.80-1.90 (2H, m), 3.20-3.50 (4H, m), 3.75-3.90 (3H, m), 6.20 (1H, s), 11.25 (1H, s).	403	not applicable	not applicable	G
14		(400 MHz, <i>DMSO-d</i>) δ ppm 1.22 (6H, s), 1.60-1.75 (2H, m), 1.70 (6H, s), 1.75-1.85 (2H, m), 3.22 (3H, s), 3.31 (1H, s), 3.36-3.44 (3H, m), 3.45 (2H, s), 3.47-3.52 (2H, m), 3.85-3.95 (3H, m), 6.32 (1H, s), 11.35 (1H, s).	433	E	C	B
15		(400 MHz, <i>DMSO-d</i>) δ ppm 1.23 (6H, s), 1.67 (6H, s), 1.85-1.95 (2H, m), 2.39-2.55 (2H, m), 3.23 (3H, s),	459	C	C	B

		3.30-3.40 (4H, m), 3.40-3.43 (2H, m), 3.45 (2H, s), 3.47-3.52 (2H, m), 6.32 (1H, s), 11.40 (1H, s).				
16		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.48 - 2.10 (m, 24H), 2.20 - 2.26 (m, 2H), 2.90 - 3.00 (m, 1H), 3.10 (d, 2H), 3.41 (d, 1H), 3.44 - 3.50 (m, 1H), 3.73 - 3.79 (m, 1H), 3.82 (d, 1H), 4.57 (bt, 1H), 6.34 (s, 1H), 9.42 (s, 1H)	467 (M-H)	C	A	B
17		(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.31 - 0.43 (2 H, m), 0.57 - 0.72 (2 H, m), 1.10 (9 H, s), 1.13 - 1.22 (1 H, m), 1.72 (6 H, s), 2.84 (2 H, s), 3.87 (3 H, s), 4.09 (2 H, d, $J=6.71$ Hz), 6.98 (2 H, d, $J=8.85$ Hz), 7.44 (1 H, d, $J=8.85$ Hz), 7.67 (1 H, d, $J=10.07$ Hz), 8.02 (2 H, d, $J=8.85$ Hz), 8.29 (1 H, d, $J=1.22$ Hz), 10.09 (1 H, br. s.), 11.60 (1 H, br. s.)	564	F	commercial	E
18		(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.38 - 1.55 (2 H, m), 1.75 (6 H, s), 1.86 (2 H, dd, $J=12.82, 1.83$ Hz), 2.35 - 2.50 (1 H, m), 3.03 (2 H, d, $J=6.41$ Hz), 3.42 (2 H, td, $J=11.90, 1.83$ Hz), 3.88 (3 H, s), 3.90 - 4.02 (5 H, m), 6.98 - 7.07 (2 H, m), 7.52 - 7.67 (2 H, m), 8.93 (1 H, s)	437	not applicable	not applicable	D
19		(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.36 - 0.46 (2 H, m), 0.62 - 0.73 (2 H, m), 1.10 (9 H, s), 1.15 - 1.24 (1 H, m), 1.31 (6 H, s), 1.69 (6 H, s), 2.71 (1 H, br. s.), 2.85 (2 H, s), 3.68 (2 H, s), 4.11 (2 H, d, $J=6.71$ Hz), 6.27 (1 H, s), 7.48 (1 H, d, $J=8.54$ Hz), 7.69 (1 H, dd, $J=8.54, 1.83$ Hz), 8.19 (1 H, d, $J=1.22$ Hz), 9.84 (1 H, s)	531	F	A	A

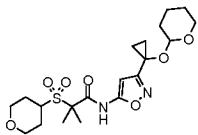
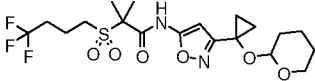
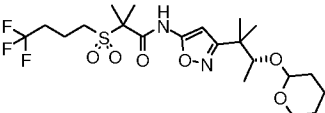
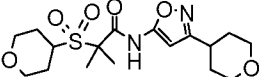
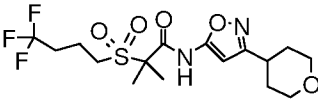
20		(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.74 (6 H, s), 1.90 - 2.07 (4 H, m), 3.36 (2 H, td, $J=11.67, 2.59$ Hz), 3.47 - 3.61 (1 H, m), 3.85 (3 H, s), 3.93 (3 H, s), 4.02 (2 H, dd, $J=10.83, 3.20$ Hz), 7.00 (2 H, d, $J=8.54$ Hz), 7.58 (2 H, d, $J=8.54$ Hz), 9.18 (1 H, s)	423	not applicable	not applicable	D
21		(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.35 - 0.44 (2 H, m), 0.62 - 0.71 (2 H, m), 1.11 (9 H, s), 1.14 - 1.25 (1 H, m), 1.34 (6 H, s), 1.69 (6 H, s), 2.85 (2 H, s), 3.34 (3 H, s), 3.45 (2 H, s), 4.11 (2 H, d, $J=6.41$ Hz), 6.62 (1 H, s), 7.46 (1 H, d, $J=8.54$ Hz), 7.70 (1 H, dd, $J=8.54, 1.53$ Hz), 8.28 (1 H, s), 9.53 (1 H, s)	545	F	B	A
22		(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.36 - 0.44 (2 H, m), 0.61 - 0.71 (2 H, m), 1.09 (9 H, s), 1.14 - 1.24 (1 H, m), 1.35 (6 H, s), 1.70 (6 H, s), 2.42 (1 H, br. s.), 2.85 (2 H, s), 3.68 (2 H, s), 4.10 (2 H, d, $J=6.71$ Hz), 6.64 (1 H, s), 7.47 (1 H, d, $J=8.54$ Hz), 7.72 (1 H, dd, $J=8.54, 1.83$ Hz), 8.17 (1 H, d, $J=1.53$ Hz), 9.49 (1 H, s)	531	not applicable	not applicable	C
23		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.93 (d, 6H), 1.02 - 1.05 (m, 2H), 1.13 - 1.15 (m, 2H), 1.58 - 1.66 (m, 2H), 1.68 - 1.76 (m, 13H), 2.97 - 3.01 (m, 2H), 3.48 - 3.54 (m, 1H), 3.73 - 3.89 (m, 3H), 4.70 (bt, 1H), 6.32 (s, 1H), 9.41 (s, 1H)	441	C	A	B
24		(400 MHz, <i>MeOD</i>) δ ppm 0.77 (3H, d), 0.85 (3H, d), 1.32 (6H, d), 1.74 (6H, s), 1.78-1.85 (2H, m), 1.85-1.95 (2H, m), 3.40-3.50 (3H, m), 3.80-3.90 (1H, m), 3.95-4.02 (2H, m), 6.41 (1H, s).	417	not applicable	not applicable	G

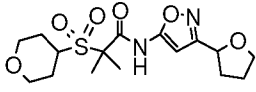
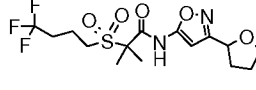
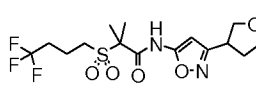
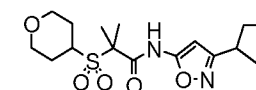
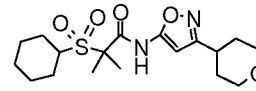
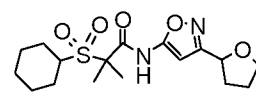
25		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.03 (t, 3H), 1.33 (d, 3H), 1.48 - 1.53 (m, 2H), 1.59 - 1.66 (m, 4H), 1.71 - 1.74 (m, 10H), 1.78 - 2.10 (m, 6H), 3.21 - 3.24 (m, 1H), 3.42 (d, 1H), 3.46 - 3.51 (m, 1H), 3.73 - 3.79 (m, 1H), 3.84 (d, 1H), 4.58 (bs, 1H), 6.33 (s, 1H), 9.71 (s, 1H)	455	E	A	B
26		(400 MHz, <i>MeOD</i>) δ ppm 1.32 (6H, s), 1.75 (6H, s), 1.80-1.90 (2H, m), 1.85-1.98 (2H, m), 3.45 (2H, t), 3.45-3.55 (2H, m), 3.55 (2H, s), 3.60-3.68 (2H, m), 3.80-2.90 (1H, m), 3.95-4.03 (2H, m), 6.40 (1H, s).	419	not applicable	not applicable	C
27		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.45 - 1.93 (m, 22H), 1.96 - 2.08 (m, 6H), 3.40 (d, 1H), 3.44 - 3.49 (m, 1H), 3.49 - 3.58 (m, 1H), 3.72 - 3.77 (m, 1H), 3.82 (d, 1H), 4.56 (bt, 1H), 6.32 (s, 1H), 9.50 (s, 1H)	467 (M-H)	A	A	B
28		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.47 - 1.53 (m, 2H), 1.57 - 1.60 (m, 2H), 1.63 - 1.95 (m, 14H), 2.03 - 2.12 (m, 2H), 3.42 (d, 1H), 3.47 - 3.51 (m, 1H), 3.74 - 3.80 (m, 1H), 3.83 (d, 1H), 4.58 (bt, 1H), 6.28 (s, 1H), 7.22 - 7.27 (m, 2H), 7.83 - 7.87 (m, 2H), 9.53 (s, 1H)	493 (M-H)	A	A	B
29		Approximately 1:1 mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.99 (3H, d, isomer A), 1.15 (3H, d, isomer B), 1.28 (3H, s, isomer A), 1.30 (3H, s, isomer A), 1.35 (3H, s, isomer B), 1.36 (3H, s, isomer B), 1.42-1.70 (5H, m, isomer A+B), 1.73 (6H, s, isomer A), 1.74 (6H, s, isomer B), 1.75-2.03 (5H, m, isomer A+B), 3.30-3.50 (4H, m, isomer A+B), 3.66-3.94 (2H, m, isomer A+B), 3.99-4.10 (2H, m, isomer A+B), 4.48-4.55 (1H, m, isomer A), 4.68-4.75 (1H, m, isomer B), 6.29 (1H, s,	473	E	A	B

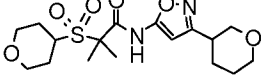
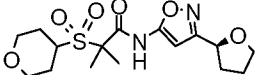
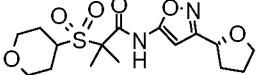
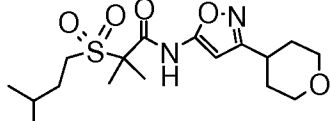
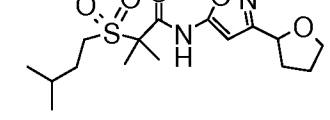
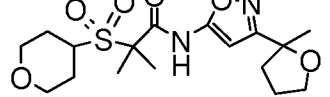
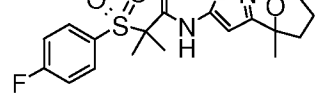
		isomer A), 6.32 (1H, s, isomer B), 9.53 (1H, s, isomer A), 9.54 (1H, s, isomer B).				
30		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.00 (3H, t), 1.20-1.32 (1H, m), 1.30 (6H, d), 1.51-1.62 (1H, m), 1.74 (6H, s), 1.82-1.90 (2H, m), 1.90-2.02 (2H, m), 3.33-3.43 (2H, m), 3.41-3.50 (1H, m), 3.50-3.57 (1H, m), 4.02-4.10 (2H, m), 6.30 (1H, s), 9.62 (1H, s).	403	E	A	B 1
31		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.00 (3H, t), 1.20-1.32 (1H, m), 1.30 (6H, d), 1.51-1.62 (1H, m), 1.74 (6H, s), 1.82-1.90 (2H, m), 1.90-2.02 (2H, m), 3.33-3.43 (2H, m), 3.41-3.50 (1H, m), 3.50-3.57 (1H, m), 4.02-4.10 (2H, m), 6.30 (1H, s), 9.62 (1H, s).	403	E	A	B 1
32		Approximately 1:1 mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.99 (3H, d, isomer A), 1.15 (3H, d, isomer B), 1.29 (3H, s, isomer B), 1.30 (3H, s, isomer B), 1.35 (6H, s, isomer A), 1.45-1.88 (6H, m, isomer A+B), 1.75 (6H, s, isomer A+B), 2.10-2.23 (2H, m, isomer A+B), 2.23-2.40 (2H, m, isomer A+B), 3.10 (2H, t, isomer A+B), 3.28-3.50 (1H, m, isomer A+B), 3.65-3.95 (2H, m, isomer A+B), 4.52-4.57 (1H, m, isomer B), 4.70-4.75 (1H, m, isomer A), 6.33 (1H, s, isomer B), 6.38 (1H, s, isomer A), 9.19 (1H, s, isomer A), 9.20 (1H, s, isomer B).	499	C	A	B
33		(400 MHz, <i>DMSO-d</i>) δ ppm 0.92 (3H, d), 1.18 (6H, d), 1.67 (6H, s), 1.83-1.93 (2H, m), 2.40-2.52 (2H,	415	C	A	B 1

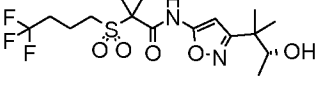
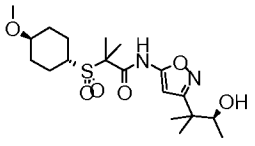
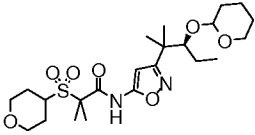
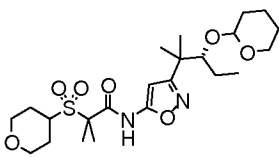
		m), 3.37 (2H, t), 3.60-3.70 (1H, m), 4.71 (1H, d), 6.30 (1H, s), 11.35 (1H, s).				
34		(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.35 - 0.45 (2 H, m), 0.61 - 0.70 (2 H, m), 1.11 (9 H, s), 1.15 - 1.24 (1 H, m), 1.34 (6 H, s), 1.69 (6 H, s), 2.85 (2 H, s), 3.35 (3 H, s), 3.43 (2 H, s), 4.11 (2 H, d, J=6.64 Hz), 6.28 (1 H, s), 7.47 (1 H, d, J=8.54 Hz), 7.68 (1 H, dd, J=8.58, 1.64 Hz), 8.27 (1 H, d, J=1.30 Hz), 9.84 (1 H, s)	545	F	C	A
35		(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.30 (3 H, d, J=7.32 Hz), 1.31 (6 H, d, J=2.75 Hz), 1.40 - 1.46 (1 H, m), 1.50 - 1.58 (1 H, m), 1.62 - 1.66 (1 H, m), 1.73 (6 H, d, J=12.82 Hz), 1.76 - 1.81 (1 H, m), 2.29 (1 H, br. s.), 2.42 - 2.50 (1 H, m), 3.18 - 3.25 (1 H, m), 3.33 (1 H, td, J=11.83, 1.98 Hz), 3.44 (1 H, td, J=11.75, 2.14 Hz), 3.69 (2 H, br. s.), 3.93 - 4.03 (2 H, m), 6.32 (1 H, s), 9.68 (1 H, s)	403	not applicable	not applicable	K
36		(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.36 (6 H, d, J=13.12 Hz), 1.45 - 1.73 (5 H, m), 1.74 - 1.87 (7 H, m), 2.15 - 2.25 (2 H, m), 2.27 - 2.40 (2H, m), 3.11 (2 H, t, J=7.55 Hz), 3.38 (1 H, d, J=9.31 Hz), 3.46 - 3.53 (1 H, m), 3.75 - 3.84 (2 H, m), 4.59 (1 H, t, J=3.43 Hz), 6.37 (1 H, s), 9.24 (1 H, s)	485	C	A	B
37		(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.25 - 0.39 (2 H, m), 0.51 - 0.72 (2 H, m), 1.02 - 1.14 (1 H, m), 1.39 (3 H, t, J=7.25 Hz), 1.67 (6 H, s), 3.02 (2 H, d, J=7.32 Hz), 3.77 (3 H, s), 4.13 (2 H, q, J=7.22 Hz), 6.92 (2 H, d, J=8.70 Hz), 7.45 (2 H, d, J=8.85 Hz), 9.12 (1 H, s)	407	C	E	E

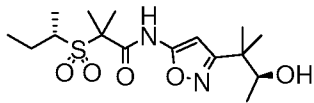
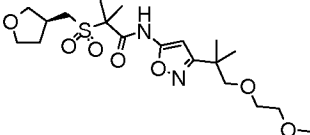
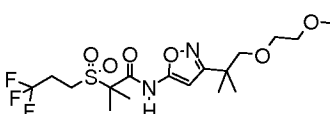
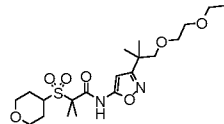
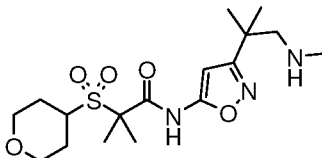
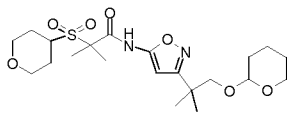
38		(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.44 (3 H, t, $J=7.25$ Hz), 1.71 (6 H, s), 1.86 - 2.05 (4 H, m), 3.26 - 3.37 (2 H, m), 3.44 - 3.59 (1 H, m), 3.81 (3 H, s), 3.92 - 4.03 (2 H, m), 4.17 (2 H, q, $J=7.22$ Hz), 6.96 (2 H, d, $J=8.70$ Hz), 7.50 (2 H, d, $J=8.85$ Hz), 9.15 (1 H, s)	437	E	E	E
39		(500 MHz, <i>MeOD</i>) δ ppm 1.45 (3 H, t, $J=7.17$ Hz), 1.76 (6 H, s), 1.82 - 1.96 (2 H, m), 1.95 - 2.06 (2 H, m), 3.47 (2 H, td, $J=11.79, 2.21$ Hz), 3.80 - 3.96 (1 H, m), 3.95 - 4.06 (2 H, m), 4.23 (2 H, q, $J=7.17$ Hz), 6.91 - 6.99 (2 H, m), 7.49 - 7.53 (2 H, m)	423	not applicable	not applicable	C
40		(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.40 (6 H, s), 1.63 (6 H, s), 1.76 (6 H, s), 2.09 - 2.24 (4 H, m), 2.26 - 2.40 (4 H, m), 3.11 (2 H, t, $J=7.55$ Hz), 3.26 (2 H, t, $J=7.51$ Hz), 4.29 (2 H, s), 6.35 (1 H, s), 9.30 (1 H, s)	645	C	not applicable	L
41		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.31 - 1.48 (m, 3H), 1.52 - 1.65 (m, 6H), 1.76 (s, 6H), 1.85 - 1.90 (m, 2H), 1.98 (td, 2H), 2.03 - 2.09 (m, 2H), 3.35 (s, 3H), 3.39 (td, 2H), 3.43 - 3.49 (m, 5H), 3.51 - 3.53 (m, 2H), 4.04 - 4.09 (m, 2H), 6.30 (s, 1H), 9.59 (s, 1H).	473	E	C	B
42		Two rotomers in the ratio of 1: 2.45, (400 MHz, <i>MeOD</i>) δ ppm 1.33 (4.26H, s), 1.40 (1.74H, s), 1.76 (6H, s), 1.78-1.95 (4H, m), 1.95 (0.87H, s), 2.07 (2.13H, s), 2.78 (0.87H, s), 2.88 (2.13H, s), 3.41-3.51 (2H, m), 3.63 (2H, s), 3.79-3.91 (1H, m), 3.95-4.03 (2H, m), 5.50 (1H, s), 6.45 (1H, s).	430	E	D	B
43		(400 MHz, <i>MeOD</i>) δ ppm 1.20 (6H, s), 1.55 (6H, s), 1.70-1.80 (2H, m), 1.75-1.85 (2H, m), 1.80 (3H, s), 3.30-3.40 (2H, m), 3.70-3.80 (1H, m), 3.85-3.95 (2H, m), 6.30 (1H, s).	416	not applicable	not applicable	J

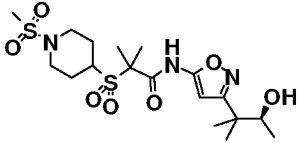
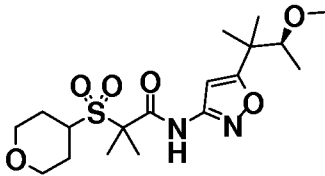
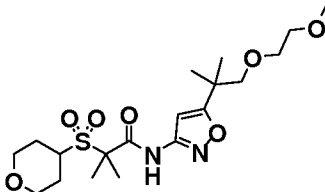
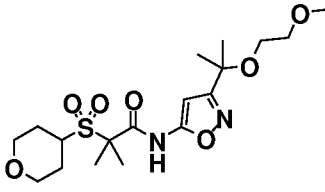
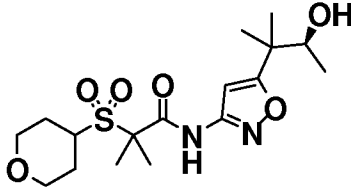
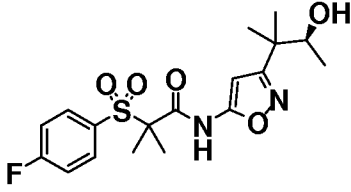
44		(400 MHz, <i>DMSO-d6</i>) δ ppm 0.98-1.13 (2H, m), 1.20-1.30 (1H, m), 1.35-1.55 (6H, m), 1.57-1.68 (3H, m), 1.68 (6H, d), 1.75-1.84 (2H, m), 3.30-3.42 (3H, m), 3.69-3.76 (1H, m), 3.83-3.95 (3H, m), 4.78-4.83 (1H, m), 6.30 (1H, s), 11.42 (1H, s)	443	E	A	B
45		(400 MHz, <i>MeOD</i>) δ ppm 1.10-1.35 (4H, m), 1.40-1.60 (4H, m), 1.60-1.70 (2H, m), 1.75 (6H, s), 2.13-2.23 (2H, m), 2.23-2.40 (2H, m), 3.08 (2H, t), 3.40-3.50 (1H, m), 3.80-3.90 (1H, m), 4.83-4.90 (1H, m), 6.35 (1H, s), 9.25 (1H, s)	469	C	A	B
46		Approximately 1:1 mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.99 (3H, d, isomer A), 1.15 (3H, d, isomer B), 1.29 (3H, s, isomer B), 1.31 (3H, s, isomer B), 1.35 (6H, s, isomer A), 1.45-1.88 (6H, m, isomer A+B), 1.75 (6H, s, isomer A+B), 2.10-2.23 (2H, m, isomer A+B), 2.23-2.40 (2H, m, isomer A+B), 3.10 (2H, t, isomer A+B), 3.28-3.50 (1H, m, isomer A+B), 3.65-3.95 (2H, m, isomer A+B), 4.52-4.57 (1H, m, isomer B), 4.70-4.75 (1H, m, isomer A), 6.33 (1H, s, isomer B), 6.38 (1H, s, isomer A), 9.19 (1H, s, isomer A), 9.20 (1H, s, isomer B).	499	C	A	B
47		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.75 (s, 6H), 1.80 – 2.02 (m, 6H), 2.93 – 3.00 (m, 1H), 3.35 – 3.55 (m, 7H), 4.02 – 4.08 (m, 4H), 6.23 (s, 1H), 9.60 (s, 1H).	387	E	A	B
48		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.75 (s, 6H), 1.80 – 1.92 (m, 4H), 2.15 – 2.22 (m, 2H), 2.26 – 2.38 (m, 2H), 2.93 – 3.01 (m, 1H), 3.10 (t, 2H), 3.52 (td, 2H), 4.02 – 4.06 (m, 2H), 6.28 (s, 1H), 9.30 (s, 1H).	413	C	A	B

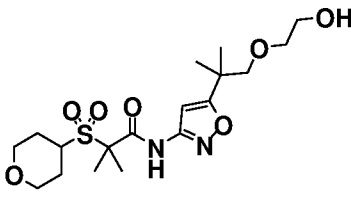
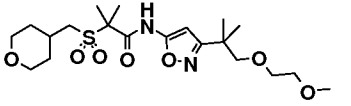
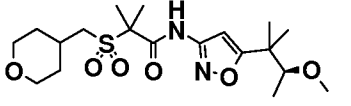
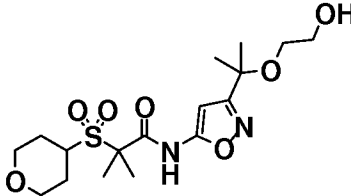
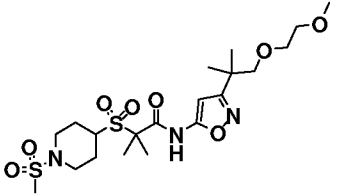
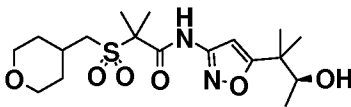
49		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.74 (s, 6H), 1.79 – 1.89 (m, 2H), 1.91 – 2.13 (m, 5H), 2.28 – 2.34 (m, 1H), 2.28 – 2.34 (m, 1H), 3.75 (tt, 2H), 3.41 – 3.47 (m, 1H), 3.89 – 3.94 (m, 1H), 3.97 – 4.08 (m, 3H), 4.96 – 5.00 (m, 1H), 6.35 (s, 1H), 9.64 (s, 1H).	373	E	A	B
50		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.76 (s, 6H), 1.97 – 2.12 (m, 3H), 2.14 – 2.22 (m, 2H), 2.26 – 2.38 (m, 3H), 3.09 (t, 2H), 3.89 – 4.02 (m, 2H), 4.96 – 5.00 (m, 1H), 6.38 (s, 1H), 9.28 (s, 1H).	399	C	A	B
51		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.75 (s, 6H), 2.04 – 2.22 (m, 3H), 2.26 – 2.40 (m, 3H), 3.10 (m, 2H), 3.48 – 3.55 (m, 1H), 3.80 – 3.84 (m, 1H), 3.87 – 3.93 (m, 1H), 3.98 – 4.03 (m, 1H), 4.08 (dd, 1H), 6.30 (s, 1H), 9.29 (s, 1H).	399	C	A	B
52		^a (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.75 (s, 6H), 1.83 – 1.87 (m, 2H), 1.92 – 1.99 (m, 1H), 2.01 – 2.15 (m, 1H), 2.31 – 2.40 (m, 1H), 3.34 – 3.55 (m, 4H), 3.81 – 3.85 (dd, 1H), 3.87 – 3.95 (m, 1H), 3.98 – 4.11 (m, 5H), 6.25 (s, 1H), 9.64 (s, 1H).	373	E	A	B
53		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.18 – 1.40 (m, 4H), 1.53 – 1.63 (m, 2H), 1.73 (s, 6H), 1.81 – 1.92 (m, 6H), 2.01 – 2.05 (m, 2H), 2.93 – 3.01 (m, 1H), 3.21 (tt, 1H), 3.53 (td, 2H), 4.03 – 4.07 (m, 2H), 6.24 (s, 1H), 9.87 (s, 1H).	385	A	A	B
54		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.21 – 1.31 (m, 4H), 1.56 – 1.61 (m, 1H), 1.69 – 1.75 (m, 7H), 1.89 – 1.92 (m, 2H), 1.99 – 2.14 (m, 5H), 2.29 – 2.37 (m, 1H), 3.21 (tt, 1H), 3.91 – 4.04 (m, 2H), 4.98 – 5.01 (m, 1H), 6.36 (s, 1H), 9.88 (s, 1H).	371	A	A	B

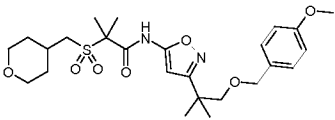
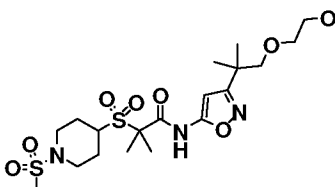
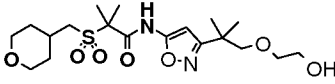
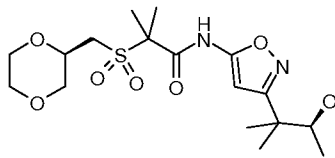
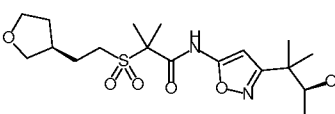
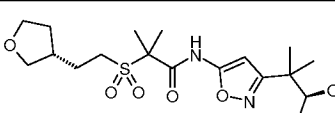
55		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.71 – 1.74 (m, 9H), 1.80 – 1.87 (m, 2H), 1.96 (qd, 2H), 2.10 – 2.14 (m, 1H), 2.97 – 3.04 (m, 1H), 3.37 (td, 2H), 3.41 – 3.55 (m, 3H), 3.90 – 3.95 (m, 1H), 4.03 – 4.09 (m, 3H), 6.24 (s, 1H), 9.64 (s, 1H).	387	E	A	B
56		^b LC-MS Retention Time: 6.28 mins.	373	not applicable	not applicable	B
57		^b LC-MS Retention Time: 6.30 mins	373	not applicable	not applicable	B
58		^a (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.93 (d, 6H), 1.66 – 1.91 (m, 13H), 2.94 – 3.01 (m, 3H), 3.52 (td, 2H), 4.02 – 4.06 (m, 2H), 6.27 (s, 1H), 9.47 (s, 1H).	373	C	A	B
59		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.89 (d, 6H), 1.62 – 1.74 (m, 9H), 1.95 – 2.09 (m, 3H), 2.24 – 2.32 (m, 1H), 2.95 – 2.99 (m, 2H), 3.86 – 3.91 (m, 1H), 3.93 – 3.99 (m, 1H), 4.93 – 4.97 (m, 1H), 6.34 (s, 1H), 9.48 (s, 1H).	359	C	A	B
60		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.58 (s, 3H), 1.74 (s, 6H), 1.83 – 2.03 (m, 7H), 2.44 – 2.51 (m, 1H), 3.35 – 3.49 (m, 3H), 3.84 – 3.89 (m, 1H), 3.97 – 4.08 (m, 3H), 6.36 (s, 1H), 9.62 (s, 1H).	387	E	A	B
61		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.55 (s, 3H), 1.62 (s, 3H), 1.63 (s, 3H), 1.87 – 2.03 (m, 3H), 2.39 – 2.46 (m, 1H), 3.80 – 3.86 (m, 1H), 3.93 – 3.98 (m, 1H), 6.28 (s, 1H), 7.20 – 7.24 (m, 2H), 7.79 – 7.82 (m, 2H), 9.54 (s, 1H).	397	A	A	B

62		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.15 (3H, d), 1.29 (6H, s), 1.75 (6H, s), 2.13-2.22 (2H, m), 2.25-2.40 (2H, m), 3.10 (2H, t), 3.89 (1H, q), 6.32 (1H, s), 9.28 (1H, s).	415	C	A	B 1
63		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.16-1.18 (3H, m), 1.2-1.29 (2H, m), 1.31 (6H, s), 1.63-1.73 (2H, m), 1.74 (6H, s), 2.04 (2H, bs), 2.09-2.1 (2H, m), 2.19-2.24 (2H, m), 3.09-3.22 (2H, m), 3.34 (3H, s), 3.89-3.94 (1H, m), 6.32 (1H, s), 9.81 (1H, s).	417	D	A	B 1
64		Approximately 1:1.66 mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.84 (3H, t, isomer A), 0.93 (3H, t, isomer B), 1.28 (3H, s, isomer B), 1.30 (3H, s, isomer B), 1.33 (3H, s, isomer A), 1.36 (3H, s, isomer A), 1.43-1.61 (7H, m, isomer A+B), 1.73 (6H, s, isomer A+B), 1.77-2.01 (5H, m, isomer A+B), 3.30-3.60 (5H, m, isomer A+B), 3.79-3.97 (1H, m, isomer A+B), 3.97-4.07 (2H, m, isomer A+B), 4.39-4.45 (1H, m, isomer B), 4.58-4.64 (1H, m, isomer A), 6.28 (1H, s, isomer B), 6.32 (1H, s, isomer A), 9.51 (1H, s, isomer A), 9.54 (1H, s, isomer B).	487	E	A	B
65		Approximately 1:1.25 mixture of two diastereomers, (400 MHz, <i>CHLOROFORM-d</i>) δ ppm 0.84 (3H, t, isomer A), 0.93 (3H, t, isomer B), 1.28 (3H, s, isomer B), 1.29 (3H, s, isomer B), 1.33 (3H, s, isomer A), 1.36 (3H, s, isomer A), 1.43-1.61 (7H, m, isomer A+B), 1.73 (6H, s, isomer A+B), 1.77-2.01 (5H, m, isomer A+B), 3.30-3.60 (5H, m, isomer A+B), 3.79-3.97 (1H, m, isomer A+B), 3.97-4.07 (2H, m, isomer A+B), 4.39-4.45 (1H, m, isomer B), 4.58-4.64 (1H, m, isomer	487	E	A	B

		A), 6.28 (1H, s, isomer B), 6.32 (1H, s, isomer A), 9.51 (1H, s, isomer A), 9.54 (1H, s, isomer B).				
66		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.30 (3H, t), 1.16 (3H, d), 1.30 (6H, s), 1.33 (3H, d), 1.55-1.70 (2H, m), 1.73 (6H, d), 1.95-2.07 (1H, m), 3.15-3.30 (1H, m), 3.90 (1H, q), 6.30 (1H, s), 9.80 (1H, s).	361	E	A	B 1
67		(400 MHz, <i>MeOD</i>) δ ppm 1.35 (6H, s), 1.78 (6H, s), 1.75-1.85 (1H, m), 2.20-2.30 (1H, m), 2.77-2.89 (1H, m), 3.32-3.48 (3H, m), 3.36 (3H, s), 3.52-3.57 (4H, m), 3.57-3.63 (2H, m), 3.73-3.81 (1H, m), 3.84-3.92 (1H, m), 3.97-4.04 (1H, m), 6.48 (1H, s).	433	E	C	B
68		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.35 (6H, s), 1.6 (4H, s), 1.79 (6H, s), 2.65-2.75 (2H, m), 3.25-3.3 (2H, m), 3.38 (3H, s), 3.53 (2H, s), 3.54-3.55 (2H, m), 3.59-3.63 (2H, m), 6.39 (1H, s), 9.11 (1H, s).	445	not applicable	not applicable	O
69		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.18 (3H, t), 1.32 (6H, s), 1.73 (6H, s), 1.82-1.89 (2H, m), 1.90-2.00 (2H, m), 3.33-3.41 (2H, m), 3.41-3.62 (9H, m), 4.01-4.09 (2H, m), 6.30 (1H, s), 9.57 (1H, s).	447	E	C	B
70		(400 MHz, <i>MeOD</i>) δ ppm 1.40 (6H, s), 1.75 (6H, s), 1.70-1.95 (4H, m), 2.72 (3H, s), 3.29 (2H, s, overlapped with solvent residual peak), 3.40-3.49 (2H, m), 3.80-3.90 (1H, m), 3.93-4.02 (2H, m), 6.48 (1H, s).	388	not applicable	not applicable	I
71		(500 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.35 (3 H, s), 1.37 (3 H, s), 1.45 - 1.63 (4 H, m), 1.64 - 1.72 (1 H, m), 1.75 (6 H, s), 1.77 - 1.90 (3 H, m), 1.92 - 2.03 (2 H, m), 3.34 - 3.53 (5 H, m), 3.74 - 3.82 (2 H, m), 4.06 (2 H, dd, $J=11.60, 3.51$ Hz), 4.58 (1 H, t, $J=3.36$ Hz), 6.33 (1 H,	481 [M+ Na], 375 [M+ H- C ₅ H ₈ O]	E	A	B

		s), 9.58 (1 H, s)				
72		(500 MHz, <i>MeOD</i>) δ ppm 1.07 (3 H, d, $J=6.41$ Hz), 1.28 (6 H, d, $J=8.16$ Hz), 1.75 (6 H, s), 1.80 - 1.91 (2 H, m), 2.15 (2 H, d, $J=12.59$ Hz), 2.84 (3 H, s), 2.84 - 2.91 (2 H, m), 3.73 - 3.86 (4 H, m), 6.37 (1 H, s)	466	G	A	B 2
73		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.05 (3H, d), 1.30 (6H, d), 1.72 (6H, s), 1.85-1.90 (2H, m), 1.90-2.05 (2H, m), 3.29 (3H, s), 3.33-3.42 (2H, m), 3.40-3.51 (2H, m), 4.00-4.08 (2H, m), 6.60 (1H, s), 9.28 (1H, s).	403	E	B	B
74		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.32 (6H, s), 1.71 (6H, s), 1.83-1.90 (2H, m), 1.90-2.02 (2H, m), 3.35 (3H, s), 3.35-3.46 (3H, m), 3.46-3.50 (2H, m), 3.53 (2H, s), 3.53-3.57 (2H, m), 4.00-4.08 (2H, m), 6.51 (1H, s), 9.28 (1H, s).	433	E	B	B
75		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.54 (6H, s), 1.73 (6H, s), 1.81-1.88 (2H, m), 1.90-1.99 (2H, m), 3.34 (3H, s), 3.36-3.49 (7H, m), 4.01-4.08 (2H, m), 6.38 (1H, s), 9.60 (1H, s).	419	E	C	B
76		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.12 (3H, d), 1.32 (6H, d), 1.72 (6H, s), 1.84-1.91 (2H, m), 1.92-2.04 (2H, m), 3.32-3.41 (2H, m), 3.41-3.50 (2H, m), 3.91 (1H, q), 4.00-4.08 (2H, m), 6.62 (1H, s), 9.30 (1H, s).	389	not applicable	not applicable	C
77		(400 MHz, <i>DMSO-d</i>) δ ppm 0.92 (3H, d), 1.18 (6H, d), 1.59 (6H, s), 3.60-3.70 (1H, m), 4.80 (1H, d), 6.20 (1H, s), 7.49 (2H, t), 7.78-7.85 (2H, m), 11.30 (1H, s).	399	A	A	B 1

78		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.35 (6H, s), 1.73 (6H, s), 1.84-1.92 (2H, m), 1.92-2.01 (2H, m), 3.32-3.41 (2H, m), 3.41-3.51 (1H, m), 3.51-3.55 (2H, m), 3.55 (2H, s), 3.64-3.69 (2H, m), 4.00-4.08 (2H, m), 6.61 (1H, s), 9.30 (1H, s).	419	not applicable	not applicable	C
79		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.33 (6H, s), 1.41-1.53 (2H, m), 1.72 (6H, s), 1.80-1.90 (2H, m), 2.33-2.48 (1H, m), 2.90 (2H, d), 3.36 (3H, s), 3.37-3.46 (2H, m), 3.47-3.55 (2H, m), 3.52 (2H, s), 3.56-3.62 (2H, m), 3.90-4.00 (2H, m), 6.35 (1H, s), 9.33 (1H, s).	447	B	C	B
80		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.55 (3H, d), 1.30 (6H, d), 1.40-1.52 (2H, m), 1.71 (6H, s), 1.80-1.90 (2H, m), 2.33-2.47 (1H, m), 2.93 (2H, d), 3.30 (3H, s), 3.37-3.50 (3H, m), 3.90-3.98 (2H, m), 6.65 (1H, s), 9.05 (1H, s).	417	B	B	B
81		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.57 (6H, s), 1.73 (6H, s), 1.80-1.89 (2H, m), 1.89-2.02 (2H, m), 3.30-3.50 (5H, m), 3.62-3.72 (2H, m), 3.98-4.12 (2H, m), 6.31 (1H, s), 9.65 (1H, s).	405	not applicable	not applicable	C
82		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.33 (6H, s), 1.74 (6H, s), 1.93-2.15 (4H, m), 2.74-2.85 (2H, m), 2.80 (3H, s), 3.26-3.40 (1H, m), 3.36 (3H, s), 3.47-3.55 (2H, m), 3.52 (2H, s), 3.56-3.62 (2H, m), 3.80-3.89 (2H, m), 6.31 (1H, s), 9.42 (1H, s).	510	G	C	B
83		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.11-1.15 (3H, d), 1.30-1.36 (6H, d), 1.40-1.53 (2H, m), 1.72 (6H, s), 1.81-1.88 (2H, m), 2.31-2.47 (1H, m), 2.93 (2H, d), 3.38-3.46 (2H, m), 3.89-3.97 (2H, m), 6.70 (1H, s), 9.10 (1H, s).	403	not applicable	not applicable	C

84		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.35 (6H, s), 1.45-1.55 (2H, m), 1.8 (6H, s), 1.85-1.92 (2H, m), 2.35-2.50 (1H, m), 2.95 (2H, d), 3.40-3.50 (2H, m), 3.50 (2H, s), 3.85 (3H, s), 3.95-4.02 (2H, m), 4.5 (2H, s), 6.35 (1H, s), 6.9 (2H, d), 7.25 (2H, d), 9.4 (1H, s)	509	B	C	B
85		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.33 (6H, s), 1.74 (6H, s), 1.92-2.13 (4H, m), 2.75-2.85 (2H, m), 2.79 (3H, s), 3.25-3.37 (1H, m), 3.53 (2H, s), 3.52-3.57 (2H, m), 3.65-3.70 (2H, m), 3.80-3.89 (2H, m), 6.30 (1H, s), 9.48 (1H, s).	496	not applicable	not applicable	C
86		(400 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.32 (6H, s), 1.43-1.53 (2H, m), 1.71 (6H, s), 1.80-1.88 (2H, m), 2.30-2.47 (1H, m), 2.89 (2H, d), 3.36-3.45 (2H, m), 3.54 (2H, s), 3.52-3.58 (2H, m), 3.65-3.72 (2H, m), 3.89-3.99 (2H, m), 6.32 (1H, s), 9.35 (1H, s).	433	not applicable	not applicable	C
87		(250 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.15 (3 H, d, $J=6.40$ Hz), 1.29 (6 H, s), 1.75 (6 H, d, $J=2.59$ Hz), 2.97 (1 H, dd, $J=14.62$, 3.50 Hz), 3.27 - 3.42 (2 H, m), 3.44 - 3.70 (4 H, m), 3.80 (1 H, dd, $J=11.42$, 2.74 Hz), 3.91 (1 H, q, $J=6.40$ Hz), 4.11 - 4.29 (1 H, m), 6.34 (1 H, s), 9.66 (1 H, s)	405	H	A	M
88		(250 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.17 (3 H, d, $J=6.40$ Hz), 1.30 (6 H, s), 1.42 - 1.64 (1 H, m), 1.73 (6 H, s), 1.81 - 2.18 (4 H, m), 2.23 - 2.44 (1 H, m), 2.94 - 3.13 (2 H, m), 3.39 (1 H, dd, $J=8.53$, 6.40 Hz), 3.69 - 3.98 (4 H, m), 6.36 (1 H, s), 9.40 (1 H, s)	403	I	A	N
89		(250 MHz, <i>CHLOROFORM-d</i>) δ ppm 1.16 (3 H, d, $J=6.40$ Hz), 1.28 (6 H, s), 1.44 - 1.60 (1 H, m), 1.75 (6 H, s), 1.85 - 2.16 (4 H, m), 2.22 -	403	I	A	N

		2.40 (1 H, m), 2.96 - 3.11 (2 H, m), 3.38 (1 H, dd, $J=8.60, 6.47$ Hz), 3.67 - 3.97 (4 H, m), 6.35 (1 H, s), 9.42 (1 H, s)				
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5 ^a Impurities are present

^b ESI+/- ion mode, Zorbax Eclipse XDB-C8, 5 μ m 4.6 x 150mm Column; Gradient: 5% B to 5% B (0 min to 2 mins), 5% B to 90% B (2 mins to 7 mins), 90% B to 95% B (7 mins to 9 mins), 95% B to 5% B (9 mins to 9.3 mins), 5% B to 5% B (9.3 mins to 10.0 mins). Flow rate: 1.5 mL/min. A = (Water + 0.1% Formic Acid) B = (Acetonitrile + 0.1% Formic Acid). Diode Array Detector

10

Assessment of Biological Properties

15 The biological properties of the compounds of the formula I are assessed using the assays described below.

A. Human CB1 and CB2 Receptor Binding:

Experimental Method:

20 CB2 membranes are purchased and made from HEK293 EBNA cells stably transfected with human CB2 receptor cDNA (Perkin Elmer Life and Analytical Sciences). CB1 membranes are isolated from HEK cells stably co-transfected with human CB1 receptor and G α 16 cDNA's. The membrane preparation is bound to scintillation beads (Ysi-Poly-L-lysine SPA beads, GE Healthcare) for 4 h at room temperature in assay buffer containing 50mM Tris, pH 7.5, 2.5mM
25 EDTA, 5mM MgCl₂, 0.8% fatty acid free Bovine Serum Albumin. Unbound membrane is removed by washing in assay buffer. Membrane-bead mixture is added to 96-well assay plates in the amounts of 15ug membrane per well (CB2) or 2.5ug per well (CB1) and 1mg SPA bead per well. Compounds are added to the membrane-bead mixture in dose-response concentrations ranging from 1x 10⁻⁵ M to 1x10⁻¹⁰ M with 0.25% DMSO, final. The competition reaction is
30 initiated with the addition of ³H-CP55940 (Perkin Elmer Life and Analytical Sciences) at a final

5 concentration of 1.5nM (CB2) or 2.5nM (CB1). The reaction is incubated at room temperature for 18 h and read on TopCount NXT plate reader. Total and non-specific binding is determined in the absence and presence of 1.25uM Win 55212 (Sigma). IC50 values for each compound are calculated as the concentration of compound that inhibits the specific binding of the radioactively labeled ligand to the receptor by 50% using the XLFit 4.1 four parameter logistic
10 model. IC50 values are converted to inhibition constant (Ki) values using Cheng-Prusoff equation.

B. CB2R mediated modulation of cAMP synthesis:

Compounds of the invention are evaluated for their CB2 agonist or inverse agonistic activity
15 in accordance with the following experimental method. Compounds which are shown to bind to CB2 by the binding assay described above but which are not shown to exhibit CB2R-mediated modulation of cAMP synthesis by this assay are presumed to be CB2 antagonists.

Experimental Method:

20 CHO cells expressing human CB2R (Euroscreen) are plated at a density of 5000 cells per well in 384 well plates and incubated overnight at 37°C. After removing the media, the cells are treated with test compounds diluted in stimulation buffer containing 1mM IBMX, 0.25% BSA and 10uM Forskolin. The assay is incubated for 30 minutes at 37°C. Cells are lysed and the cAMP concentration is measured using DiscoverX –XS cAMP kit, following the
25 manufacturer's protocol. In this setting, agonists will decrease forskolin induced production of cAMP while inverse agonists will further increase forskolin induced production of cAMP. EC50 of agonists are calculated as follows. The maximal amount of cAMP produced by forskolin compared to the level of cAMP inhibited by 1uM CP55940 is defined as 100%. The EC50 value of each test compound is determined as the concentration at which 50% of the
30 forskolin-stimulated cAMP synthesis is inhibited. Data is analyzed using a four-parameter logistic model. (Model 205 of XLfit 4.0).

C. CB1R mediated modulation of cAMP synthesis:

5 Compounds of the invention are evaluated for their CB1 agonist or inverse agonistic activity in accordance with the following experimental method. Compounds which are shown to bind to CB1 by the binding assay described above but which are not shown to exhibit CB1-mediated modulation of cAMP synthesis by this assay are presumed to be CB1 antagonists.

10 Experimental Method:

CHO cells expressing human CB1R (Euroscreen) are plated at a density of 5000 cells per well in 384 well plates and incubated overnight at 37°C. After removing the media, the cells are treated with test compounds diluted in stimulation buffer containing 1mM IBMX, 0.25% BSA and 10uM Forskolin. The assay is incubated for 30 minutes at 37°C. Cells are lysed and the
15 cAMP concentration is measured using DiscoverX –XS cAMP kit, following the manufacturer's protocol. In this setting, agonists will decrease forskolin induced production of cAMP while inverse agonists will further increase forskolin induced production of cAMP. EC50 of agonists are calculated as follows. The maximal amount of cAMP produced by forskolin compared to the level of cAMP inhibited by 1uM CP55940 is defined as 100%. The
20 EC50 value of each test compound is determined as the concentration at which 50% of the forskolin-stimulated cAMP synthesis is inhibited. Data is analyzed using a four-parameter logistic model. (Model 205 of XLfit 4.0).

Compounds Having Agonist Activity

25

Through the use of the above described assays compounds are found to exhibit agonistic activity and thus to be particularly well suited for the treatment of pain as well as for the treatment of inflammation. Preferred compounds of the invention will have an activity range of CB2 (<500nM) and CB1 (>20000).

30

Therapeutic Use

- 5 As can be demonstrated by the assays described above, the compounds of the invention are useful in modulating the CB2 receptor function. By virtue of this fact, these compounds have therapeutic use in treating disease-states and conditions mediated by the CB2 receptor function or that would benefit from modulation of the CB2 receptor function.
- 10 As the compounds of the invention modulate the CB2 receptor function, they have very useful anti-inflammatory and immune-suppressive activity and they can be used in patients as drugs, particularly in the form of pharmaceutical compositions as set forth below, for the treatment of disease-states and conditions.
- 15 As noted before, those compounds which are CB2 agonists can also be employed for the treatment of pain.

The agonist, antagonist and inverse agonist compounds according to the invention can be used in patients as drugs for the treatment of the following disease-states or indications that are
20 accompanied by inflammatory processes:

- (i) Lung diseases: e.g. asthma, bronchitis, allergic rhinitis, emphysema, adult respiratory distress syndrome (ARDS), pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease (COPD), asthma including allergic asthma (atopic or
25 non-atopic) as well as exercise-induced bronchoconstriction, occupational asthma, viral- or bacterial exacerbation of asthma, other non-allergic asthmas and "wheezy-infant syndrome", pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis;
- (ii) Rheumatic diseases or autoimmune diseases or musculoskeletal diseases: all
30 forms of rheumatic diseases, especially rheumatoid arthritis, acute rheumatic fever, and polymyalgia rheumatica; reactive arthritis; rheumatic soft tissue diseases; inflammatory soft tissue diseases of other genesis; arthritic symptoms in degenerative

- 5 joint diseases (arthroses); tendinitis, bursitis, osteoarthritis, traumatic arthritis; collagenoses of any genesis, e.g., systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis, Sjögren syndrome, Still disease, Felty syndrome; and osteoporosis and other bone resorption diseases;
- 10 (iii) Allergic diseases: all forms of allergic reactions, e.g., angioneurotic edema, hay fever, insect bites, allergic reactions to drugs, blood derivatives, contrast agents, etc., anaphylactic shock (anaphylaxis), urticaria, angioneurotic edema, and contact dermatitis;
- (iv) Vascular diseases: panarteritis nodosa, polyarteritis nodosa, periarteritis nodosa, arteritis temporalis, Wegner granulomatosis, giant cell arthritis,
- 15 atherosclerosis, reperfusion injury and erythema nodosum;
- (v) Dermatological diseases: e.g. dermatitis, psoriasis; sunburn, burns, eczema;
- (vi) Renal diseases: e.g. nephrotic syndrome; and all types of nephritis, e.g., glomerulonephritis; pancreatitis;
- (vii) Hepatic diseases: e.g. acute liver cell disintegration; acute hepatitis of various
- 20 genesis, e.g., viral, toxic, drug-induced; and chronically aggressive and/or chronically intermittent hepatitis;
- (viii) Gastrointestinal diseases: e.g. inflammatory bowel diseases, irritable bowel syndrome, regional enteritis (Crohn's disease), colitis ulcerosa; gastritis; aphthous ulcer, celiac disease, regional ileitis, gastroesophageal reflux disease;
- 25 (ix) Neuroprotection: e.g. in the treatment of neurodegeneration following stroke; cardiac arrest; pulmonary bypass; traumatic brain injury; spinal cord injury or the like;
- (x) Eye diseases: allergic keratitis, uveitis, or iritis; conjunctivitis; blepharitis; neuritis nervi optici; choroiditis; glaucoma and sympathetic ophthalmia;
- (xi) Diseases of the ear, nose, and throat (ENT) area: e.g. tinnitus; allergic rhinitis
- 30 or hay fever; otitis externa; caused by contact eczema, infection, etc.; and otitis media;
- (xii) Neurological diseases: e.g. brain edema, particularly tumor-related brain edema; multiple sclerosis; acute encephalomyelitis; meningitis; acute spinal cord

- 5 injury; trauma; dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease; Parkinson's disease and Creutzfeldt-Jacob disease; Huntington's chorea, Pick's disease; motor neuron disease), vascular dementia (including multi-infarct dementia) as well as dementia associated with intracranial space occupying lesions; infections and related conditions (including HIV infection);
- 10 Guillain-Barre syndrome; myasthenia gravis, stroke; and various forms of seizures, e.g., nodding spasms;
- (xiii) Blood diseases: acquired hemolytic anemia; aplastic anemia, and idiopathic thrombocytopenia;
- (xiv) Tumor diseases: acute lymphatic leukemia; Hodgkin's disease, malignant
- 15 lymphoma; lymphogranulomatoses; lymphosarcoma; solid malignant tumors; extensive metastases,;
- (xv) Endocrine diseases: endocrine ophthalmopathy; endocrine orbitopathy; thyrotoxic crisis; Thyroiditis de Quervain; Hashimoto thyroiditis; Morbus Basedow; granulomatous thyroiditis; struma lymphomatosa; and Graves disease; type I diabetes
- 20 (insulin-dependent diabetes);
- (xvi) Organ and tissue transplantations and graft-versus-host diseases;
- (xvii) Severe states of shock, e.g., septic shock, anaphylactic shock, and systemic inflammatory response syndrome (SIRS);
- (xviii) Acute pain such as dental pain, perioperative, post-operative pain, traumatic
- 25 pain, muscle pain, pain in burned skin, sun burn, trigeminal neuralgia, sun burn; spasm of the gastrointestinal tract or uterus, colics;
- (xix) Visceral pain such as pain associated with chronic pelvic pain, pancreatitis, peptic ulcer, interstitial cystitis, renal colic, angina, dysmenorrhoea, menstruation, gynaecological pain, irritable bowel syndrome (IBS), non-ulcer dyspepsia, non-cardiac
- 30 chest pain, myocardial ischemia;
- (xx) Neuropathic pain such as low back pain, non-herpetic neuralgia, post herpetic neuralgia, diabetic neuropathy, nerve injury, acquired immune deficiency syndrome

- 5 (AIDS) related neuropathic pain, head trauma, painful traumatic mononeuropathy, toxin and chemotherapy induced pain, phantom limb pain, painful polyneuropathy, thalamic pain syndrome, post-stroke pain, central nervous system injury, post surgical pain, stump pain, repetitive motion pain, pain induced by post mastectomy syndrome, multiple sclerosis, root avulsions, postthoracotomy syndrome, neuropathic pain
- 10 associated hyperalgesia and allodynia.
- (xxi) Inflammatory/nociceptive pain induced by or associated with disorders such as osteoarthritis, rheumatoid arthritis, rheumatic disease, teno-synovitis, gout, vulvodynia, myofascial pain (muscular injury, fibromyalgia), tendonitis, osteoarthritis, juvenile arthritis, spondylitis, gouty arthritis, psoriatic arthritis, musculoskeletal pain,
- 15 fibromyalgia, sprains and strains, sympathetically maintained pain, myositis, pain associated with migraine, toothache, influenza and other viral infections such as the common cold, rheumatic fever, systemic lupus erythematosus;
- (xxii) Cancer pain induced by or associated with tumors such as lymphatic leukemia; Hodgkin's disease, malignant lymphoma; lymphogranulomatoses; lymphosarcoma;
- 20 solid malignant tumors; extensive metastases;
- (xxiii) Headache such as cluster headache, migraine with and without aura, tension type headache, headache with different origins, headache disorders including prophylactic and acute use;
- (xxiv) various other disease-states or conditions including, restenosis following
- 25 percutaneous transluminal coronary angioplasty, acute and chronic pain, atherosclerosis, reperfusion injury, congestive heart failure, myocardial infarction, thermal injury, multiple organ injury secondary to trauma, necrotizing enterocolitis and syndromes associated with hemodialysis, leukopheresis, and granulocyte transfusion, sarcoidosis, gingivitis, pyrexia. edema resulting from trauma associated
- 30 with burns, sprains or fracture, cerebral oedema and angioedema, Diabetes such as diabetic vasculopathy, diabetic neuropathy, diabetic retinopathy, post capillary

5 resistance or diabetic symptoms associated with insulinitis (e.g. hyperglycemia, diuresis, proteinuria and increased nitrite and kallikrein urinary excretion).

Other indications include: epilepsy, septic shock e.g. as antihypovolemic and/or antihypotensive agents, cancer, sepsis, osteoporosis, benign prostatic hyperplasia and
10 hyperactive bladder, pruritis, vitiligo, general gastrointestinal disorders, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, burns, tissue damage and postoperative fever, syndromes associated with Itching.

Besides being useful for human treatment, these compounds are also useful for veterinary
15 treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like.

For treatment of the above-described diseases and conditions, a therapeutically effective dose will generally be in the range from about 0.01 mg to about 100 mg/kg of body weight per
20 dosage of a compound of the invention; preferably, from about 0.1 mg to about 20 mg/kg of body weight per dosage. For Example, for administration to a 70 kg person, the dosage range would be from about 0.7 mg to about 7000 mg per dosage of a compound of the invention, preferably from about 7.0 mg to about 1400 mg per dosage. Some degree of routine dose optimization may be required to determine an optimal dosing level and pattern. The active
25 ingredient may be administered from 1 to 6 times a day.

General Administration and Pharmaceutical Compositions

When used as pharmaceuticals, the compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using
30 procedures well known in the pharmaceutical art and comprise at least one compound of the invention. The compounds of the invention may also be administered alone or in combination with adjuvants that enhance stability of the compounds of the invention, facilitate

5 administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increased inhibitory activity, provide adjunct therapy, and the like. The compounds according to the invention may be used on their own or in conjunction with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances. In general, the compounds of
10 this invention are administered in a therapeutically or pharmaceutically effective amount, but may be administered in lower amounts for diagnostic or other purposes.

Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted modes of
15 administration of pharmaceutical compositions. Thus, administration can be, for Example, orally, buccally (e.g., sublingually), nasally, parenterally, topically, transdermally, vaginally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for
20 simple administration of precise dosages. The pharmaceutical compositions will generally include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, vehicles, or combinations thereof. Such pharmaceutically acceptable excipients, carriers, or additives as well as methods of making pharmaceutical
25 compositions for various modes or administration are well-known to those of skill in the art. The state of the art is evidenced, e.g., by *Remington: The Science and Practice of Pharmacy*, 20th Edition, A. Gennaro (ed.), Lippincott Williams & Wilkins, 2000; *Handbook of Pharmaceutical Additives*, Michael & Irene Ash (eds.), Gower, 1995; *Handbook of Pharmaceutical Excipients*, A.H. Kibbe (ed.), American Pharmaceutical Ass'n, 2000; H.C.
30 Ansel and N.G. Popovich, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger, 1990; each of which is incorporated herein by reference in their entireties to better describe the state of the art.

5

As one of skill in the art would expect, the forms of the compounds of the invention utilized in a particular pharmaceutical formulation will be selected (e.g., salts) that possess suitable physical characteristics (e.g., water solubility) that is required for the formulation to be efficacious.

10

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

15

Pharmaceutical compositions suitable for parenteral administration comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection. Injectable pharmaceutical formulations are commonly based upon injectable sterile saline, phosphate-buffered saline, oleaginous suspensions, or other injectable carriers known in the art and are generally rendered sterile and isotonic with the blood. The injectable pharmaceutical formulations may therefore be provided as a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, including 1,3-butanediol, water, Ringer's solution, isotonic sodium chloride solution, fixed oils such as synthetic mono- or diglycerides, fatty acids such as oleic acid, and the like. Such injectable pharmaceutical formulations are formulated according to the known art using suitable dispersing or setting agents and suspending agents. Injectable compositions will generally contain from 0.1 to 5% w/w of a compound of the invention.

30

Solid dosage forms for oral administration of the compounds include capsules, tablets, pills, powders, and granules. For such oral administration, a pharmaceutically acceptable composition containing a compound(s) of the invention is formed by the incorporation of any

5 of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, pregelatinized starch, magnesium stearate, sodium saccharine, talcum, cellulose ether derivatives, glucose, gelatin, sucrose, citrate, propyl gallate, and the like. Such solid pharmaceutical formulations may include formulations, as are well-known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by
10 any number of mechanisms, which include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form.

15

Liquid dosage forms for oral administration of the compounds include emulsions, microemulsions, solutions, suspensions, syrups, and elixirs, optionally containing pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like. These compositions can also contain additional adjuvants such
20 as wetting, emulsifying, suspending, sweetening, flavoring, and perfuming agents.

Topical dosage forms of the compounds include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, eye ointments, eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives,
25 solvents to assist drug penetration and emollients in ointments and creams. Topical application may be once or more than once per day depending upon the usual medical considerations. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles. The formulations may also contain compatible conventional carriers, such as cream or ointment
30 bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation, more usually they will form up to about 80% of the formulation.

5

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Such patches suitably contain a compound of the invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%.

For administration by inhalation, the compounds of the invention are conveniently delivered in the form of an aerosol spray from a pump spray device not requiring a propellant gas or from a pressurized pack or a nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide, or other suitable gas. In any case, the aerosol spray dosage unit may be determined by providing a valve to deliver a metered amount so that the resulting metered dose inhaler (MDI) is used to administer the compounds of the invention in a reproducible and controlled way. Such inhaler, nebulizer, or atomizer devices are known in the prior art, for example, in PCT International Publication Nos. WO 97/12687 (particularly Figure 6 thereof, which is the basis for the commercial RESPIMAT® nebulizer); WO 94/07607; WO 97/12683; and WO 97/20590, to which reference is hereby made and each of which is incorporated herein by reference in their entireties.

Rectal administration can be effected utilizing unit dose suppositories in which the compound is admixed with low-melting water-soluble or insoluble solids such as fats, cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, or fatty acid esters of polyethylene glycols, or the like. The active

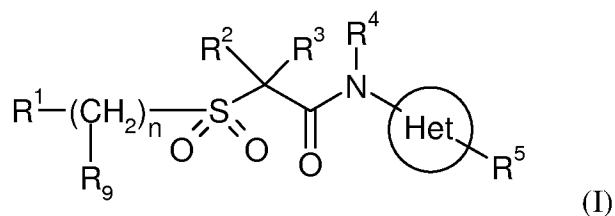
- 5 compound is usually a minor component, often from about 0.05 to 10% by weight, with the remainder being the base component.

In all of the above pharmaceutical compositions, the compounds of the invention are formulated with an acceptable carrier or excipient. The carriers or excipients used must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the patient. The carrier or excipient can be a solid or a liquid, or both, and is preferably formulated with the compound of the invention as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Such carriers or excipients include inert fillers or diluents, binders, lubricants, disintegrating agents, solution retardants, resorption accelerators, absorption agents, and coloring agents. Suitable binders include starch, gelatin, natural sugars such as glucose or β -lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

Pharmaceutically acceptable carriers and excipients encompass all the foregoing additives and the like.

5 CLAIMS

1. A compound of the formula (I)



10

wherein:

Het is a 5-membered heteroaryl ring optionally substituted by C₁₋₅ alkyl;

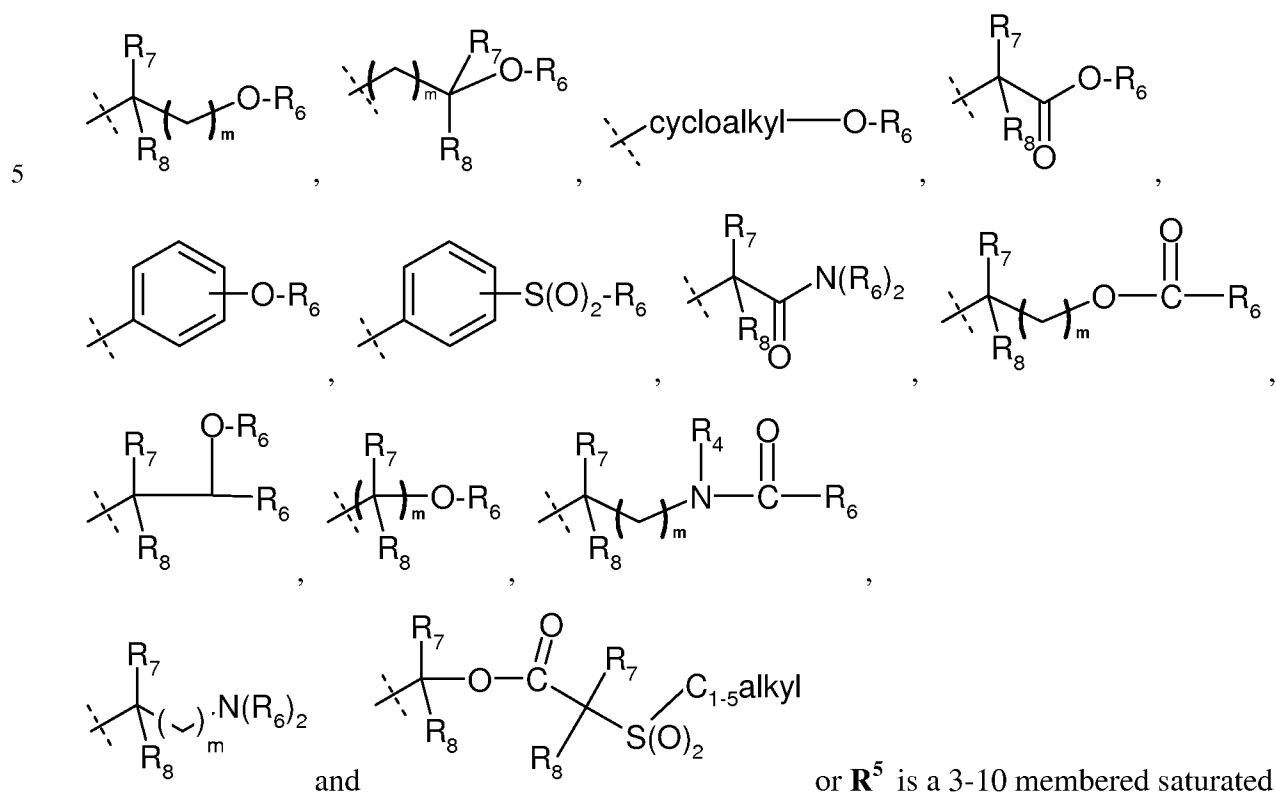
15 **R¹** is C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl, 3-10 membered saturated heterocyclic ring, 5-10 membered mono or bicyclic heteroaryl ring or phenyl each optionally independently substituted with 1-3 substituents chosen from C₁₋₈ alkyl, C₁₋₄ alkoxy, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkylC₁₋₅ alkyl, C₁₋₄ alkylsulfonyl, C₁₋₄ acyl, oxo, cyano, phenyl, hydroxyl and halogen;

20 **R²** and **R³** are C₁₋₄ alkyl or hydrogen with the proviso that both R² and R³ cannot be hydrogen; or R² and R³ together with the carbon atom to which they are attached form a 3- to 6-membered cycloalkyl or heterocyclic ring;

R⁴ is hydrogen or methyl;

25

R⁵ is chosen from



heterocyclic ring optionally substituted with 1-3 C₁₋₄ alkyl;

10 **m** is 0, 1, 2 or 3;

each **R**⁶ is independently hydrogen, C₁₋₆ alkyl, 3-10 membered saturated heterocyclic ring, aryl, benzyl or -(CH₂)₁₋₃-O-(CH₂)₀₋₁-X wherein X is aryl or CH₃ each heterocyclic, benzyl or aryl ring is optionally substituted by one or more C₁₋₄ alkyl, C₁₋₄ alkoxy or halogen;

15 wherein **R**⁷ and **R**⁸ are each independently hydrogen or C₁₋₄ alkyl with the proviso that both **R**⁷ and **R**⁸ cannot be hydrogen, and wherein **R**⁷ and **R**⁸ optionally can cyclize to form a C₃₋₇ cycloalkyl ring;

R₉ is C₁₋₄ alkyl which replaces a methylene hydrogen on -(CH₂)_n- or is absent;

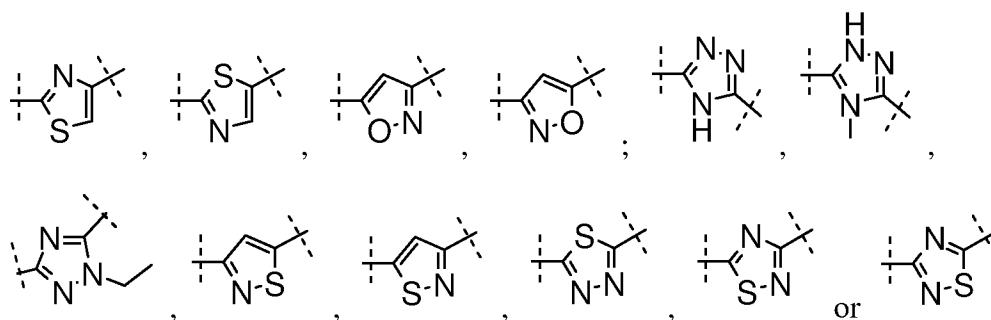
20

n is 0, 1 or 2;

- 5 wherein any carbon atom on the formula (I) or any R substituent listed above is optionally partially or fully halogenated where possible;
or a pharmaceutically acceptable salt thereof.

- 10 2. The compound according to claim 1, and wherein

Het is



15

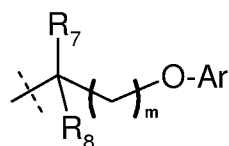
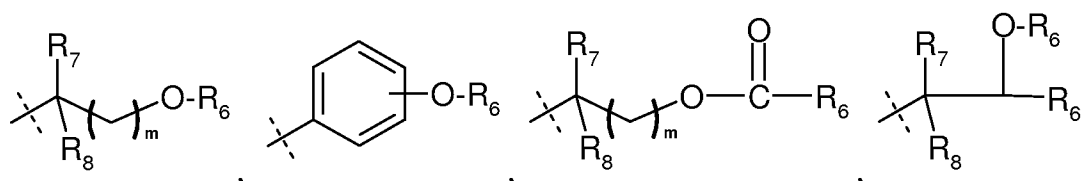
- R¹** is C₁₋₆ alkyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, piperidiny, benzoxazolyl, benzothiazolyl, benzimidazolyl, dioxalanyl, dioxanyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, pyrrolyl, imidazolyl, thienyl, thiomorpholinyl, 1,1-Dioxo-1λ⁶-thiomorpholinyl, morpholinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolidinyl, piperazinyl, purinyl, quinolinyl, Dihydro-2H-quinolinyl, isoquinolinyl, quinazolinyl, indazolyl, indolyl, benzofuranyl, benzopyranyl or benzodioxolyl each optionally substituted by 1-2 substituents chosen from halogen, C₁₋₆ alkyl, hydroxyl, C₁₋₄ alkoxy, C₁₋₄ alkylsulfonyl, C₃₋₁₀ cycloalkyl, C₁₋₅ alkyl or oxo;

25

R² and **R³** are independently methyl, ethyl, n-propyl, isopropyl, or hydrogen with the proviso that both R² and R³ cannot be hydrogen; or R² and R³ together with the carbon to which they are attached form a cyclopropyl, cyclobutyl or cyclopentyl ring;

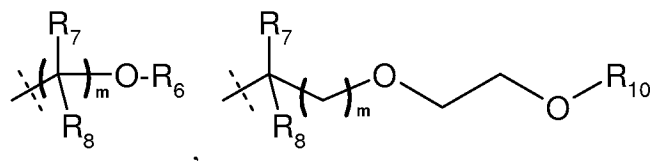
5

R^5 is chosen from

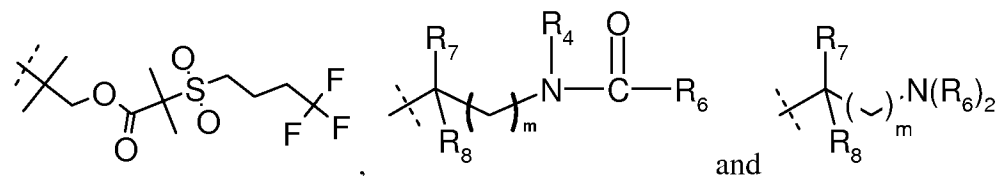


wherein Ar tetrahydropyranyl or tetrahydrofuranyl each optionally

10 substituted by C_{1-3} alkyl,



wherein R_{10} is hydrogen or methyl,



or R^5 is tetrahydropyranyl or tetrahydrofuranyl each optionally substituted by C_{1-3} alkyl;

15 R^6 is hydrogen, benzyl, phenyl or C_{1-4} alkyl, each benzyl or phenyl ring is optionally substituted by one or more C_{1-4} alkyl, C_{1-4} alkoxy or halogen;

R^7 and R^8 are each C_{1-3} alkyl or C_{3-6} cycloalkyl wherein R^7 and R^8 optionally can cyclize to form a C_{3-6} cycloalkyl ring.

20

3. The compound according to claim 2, and wherein

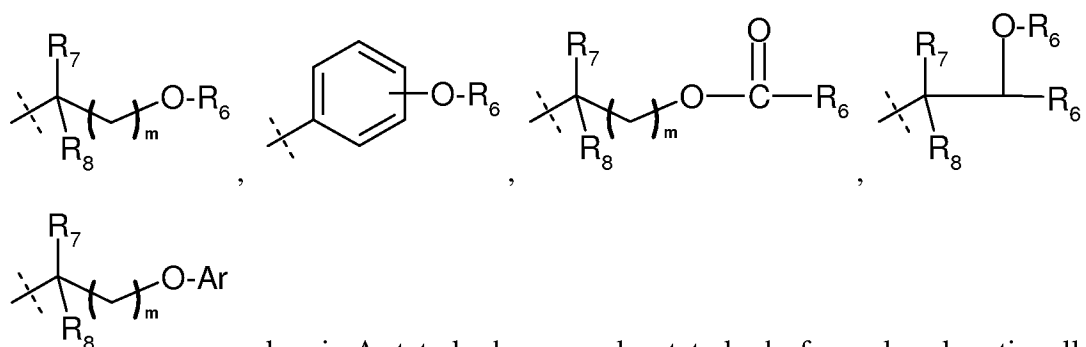
5 **R¹** is C₁₋₅ alkyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, dioxalanyl, dioxanyl, azetidiny, piperidiny, benzimidazolyl, pyrrolyl, pyridiny, pyrimidiny, pyridaziny, pyraziny, pyrrolidiny or piperaziny, each optionally substituted by 1-2 substituents chosen from halogen, C₁₋₆ alkyl, C₁₋₄ alkylsulfonyl, C₃₋₁₀ cycloalkylC₁₋₅ alkyl, hydroxyl, C₁₋₄ alkoxy and oxo;

10

R² and **R³** are independently methyl, ethyl, n-propyl, isopropyl or hydrogen with the proviso that both **R²** and **R³** cannot be hydrogen; or **R²** and **R³** together with the carbon to which they are attached form a cyclopropyl, cyclobutyl or cyclopentyl ring;

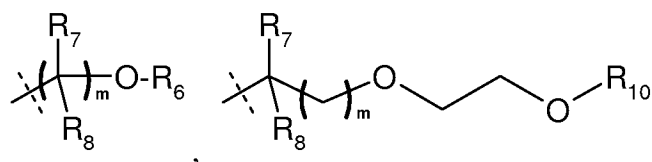
15 **n** is 0 or 1;

R⁵ is chosen from



wherein Ar tetrahydropyranyl or tetrahydrofuranyl each optionally

20 substituted by C₁₋₃ alkyl,



wherein R₁₀ is hydrogen or methyl,

or **R⁵** is tetrahydropyranyl or tetrahydrofuranyl each optionally substituted by C₁₋₃ alkyl;

R⁶ is hydrogen, benzyl, phenyl or C₁₋₄ alkyl, each benzyl or phenyl ring is optionally

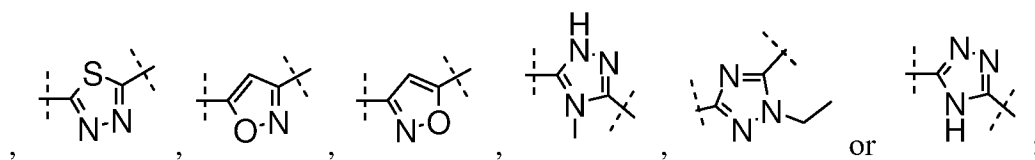
25 substituted by one or more C₁₋₄ alkyl, C₁₋₄ alkoxy or halogen;

5

R⁷ and **R**⁸ are each C₁₋₃ alkyl or C₃₋₆ cycloalkyl wherein **R**⁷ and **R**⁸ optionally can cyclize to form a C₃₋₆ cycloalkyl ring.

10 4. The compound according to claim 3, and wherein

Het is



15 **R**¹ is phenyl or benzimidazolyl each optionally substituted by 1-2 substituents chosen from halogen, C₁₋₆ alkyl, C₁₋₄ alkylsulfonyl, C₃₋₆ cycloalkylC₁₋₃ alkyl, or oxo;
or **R**¹ is C₁₋₅ alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl,
tetrahydrofuranyl, azetidiny, pyrrolidinyl or piperidinyl each optionally substituted by a
substituent chosen from by halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylsulfonyl or oxo;

20

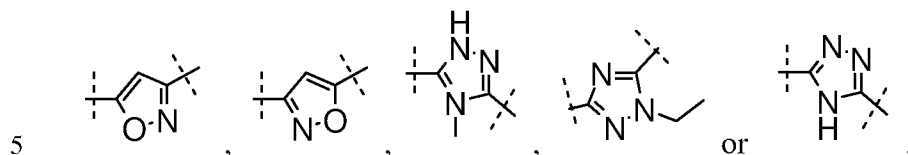
R² and **R**³ are independently methyl, or **R**² and **R**³ together with the carbon to which they are attached form a cyclopropyl or cyclobutyl ring;

R⁷ and **R**⁸ are each C₁₋₂ alkyl wherein **R**⁷ and **R**⁸ optionally can cyclize to form a C₃₋₆ cycloalkyl ring.

25

5. The compound according to claim 4, and wherein

Het is

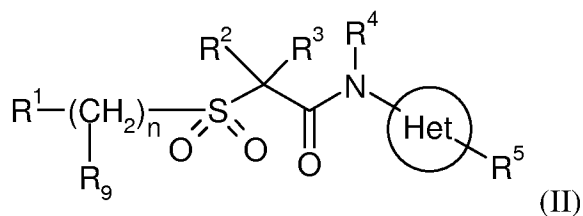


6. The compound according to claim 5, and wherein

- 10 **R¹** is phenyl or benzimidazolyl each optionally substituted by 1-2 substituents chosen from halogen, C₁₋₆ alkyl or C₃₋₅ cycloalkylC₁₋₃ alkyl;
 or **R¹** is C₁₋₅ alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl, tetrahydrofuranyl or piperidinyl each optionally substituted by a substituent chosen from by halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy or C₁₋₄ alkylsulfonyl.

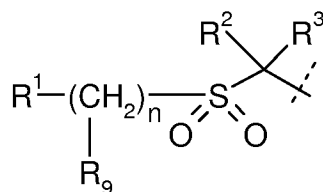
15

7. A compound of the formula (II)

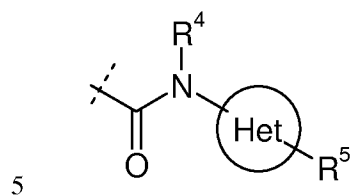


20

wherein



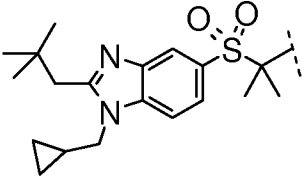
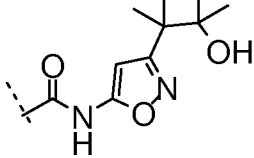
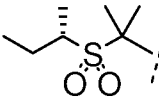
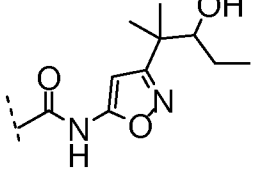
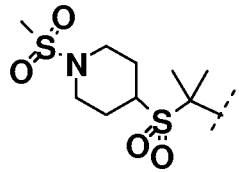
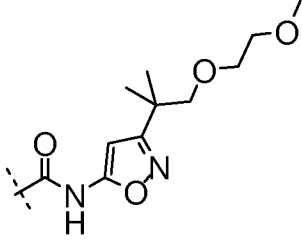
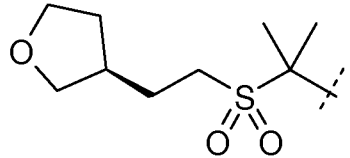
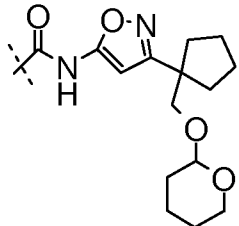
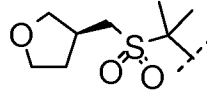
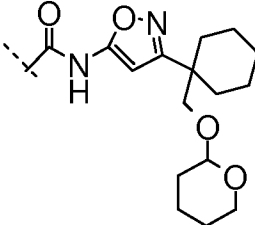
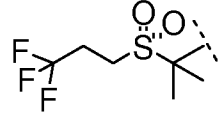
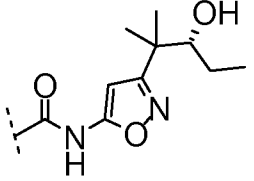
of the formula (I) is chosen from column A1 – A11 in Table I, and

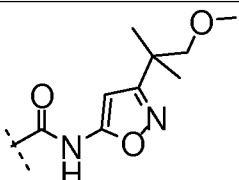
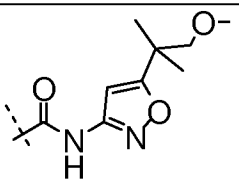
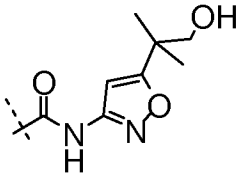
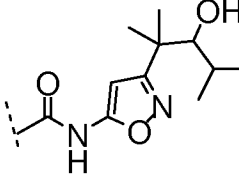
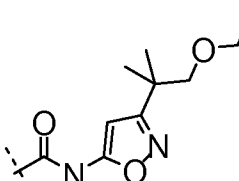
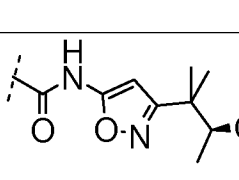
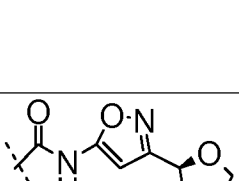


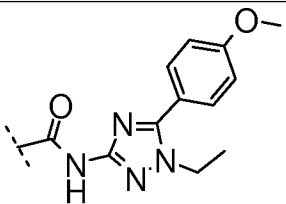
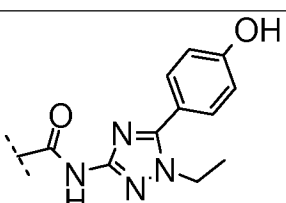
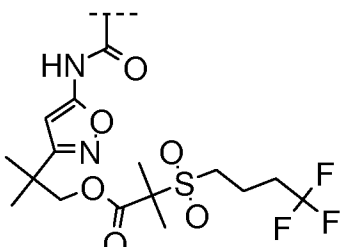
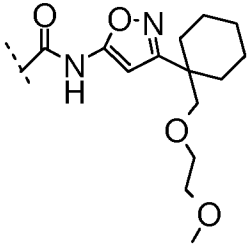
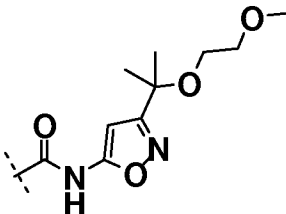
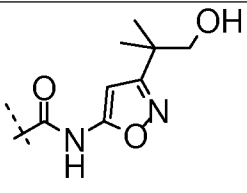
of the formula (I) is chosen from column B1 – B36 in Table I,

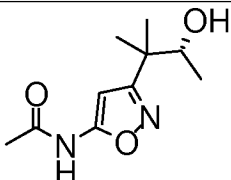
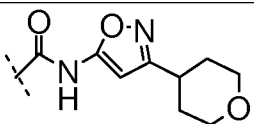
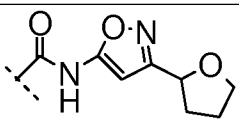
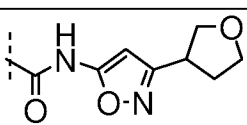
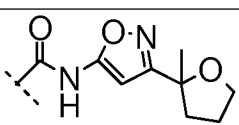
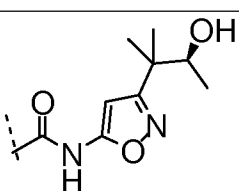
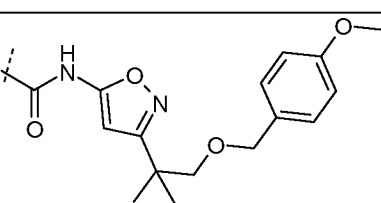
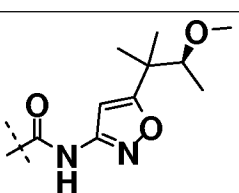
Table I

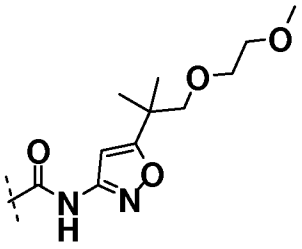
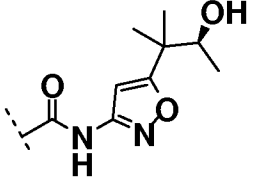
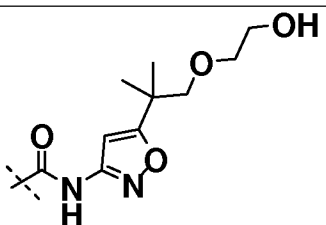
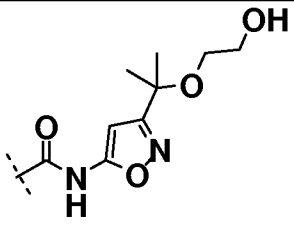
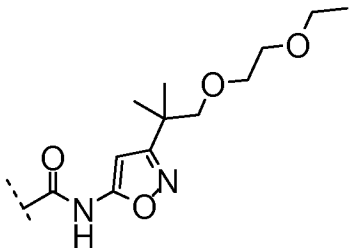
A1		B1	
A2		B2	
A3		B3	
A4		B4	
A5		B5	

A6		B6	
A7		B7	
A8		B8	
A9		B9	
A10		B10	
A11		B11	

		B12	
		B13	
		B14	
		B15	
		B16	
		B17	
		B18	

		B19	
		B20	
		B21	
		B22	
		B23	
		B24	

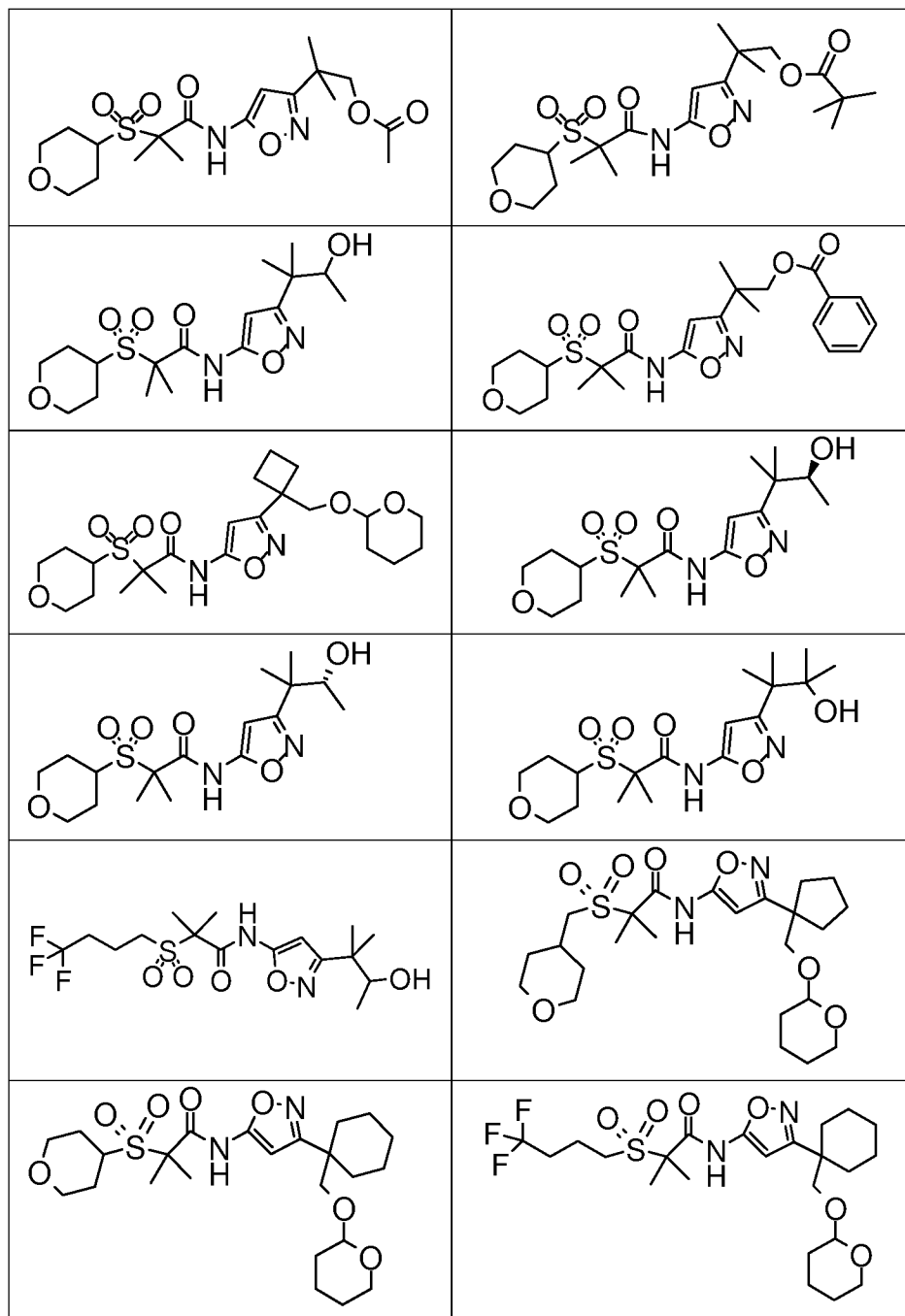
		B25	
		B26	
		B27	
		B28	
		B29	
		B30	
		B30	
		B31	

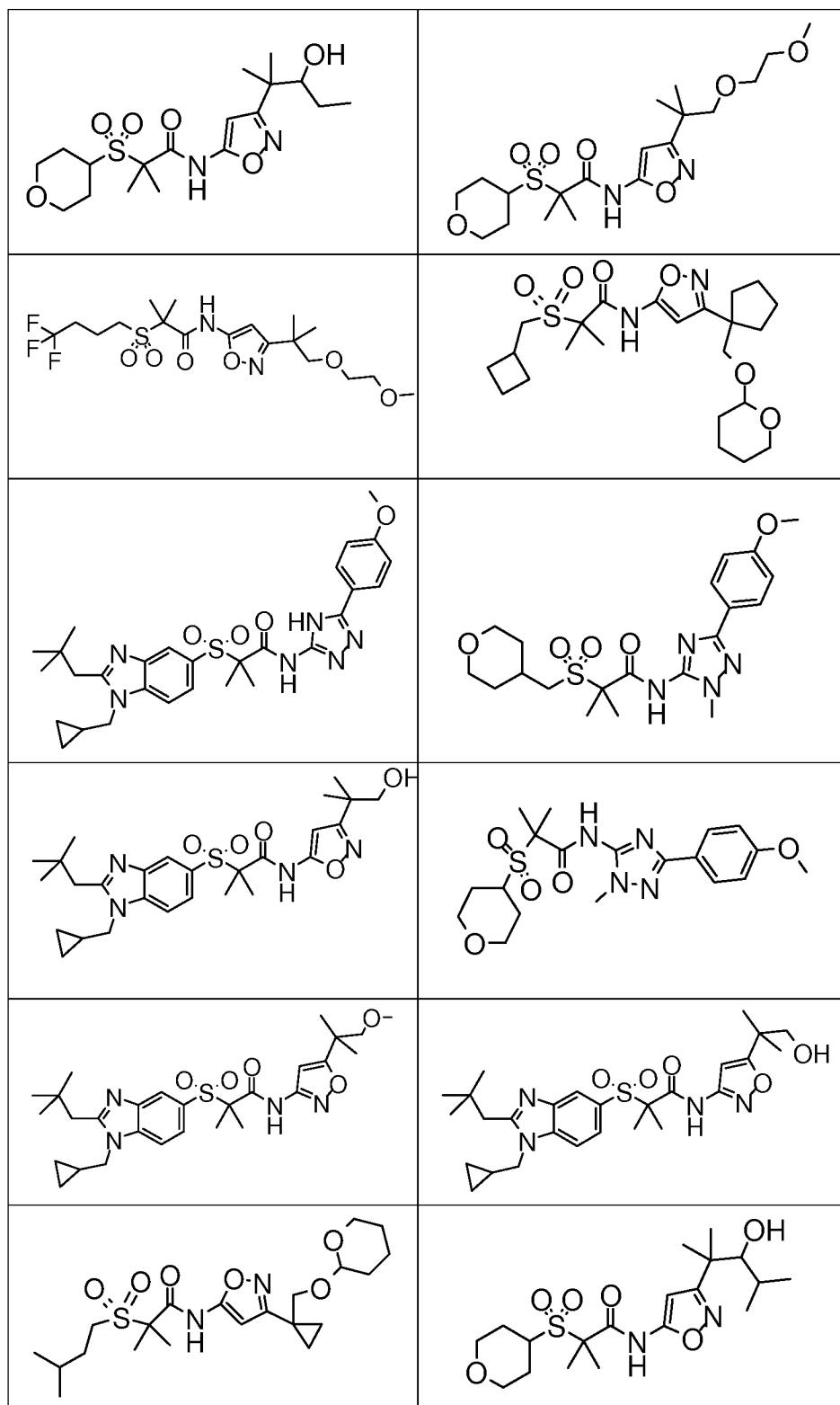
		B32	
		B33	
		B34	
		B35	
		B36	

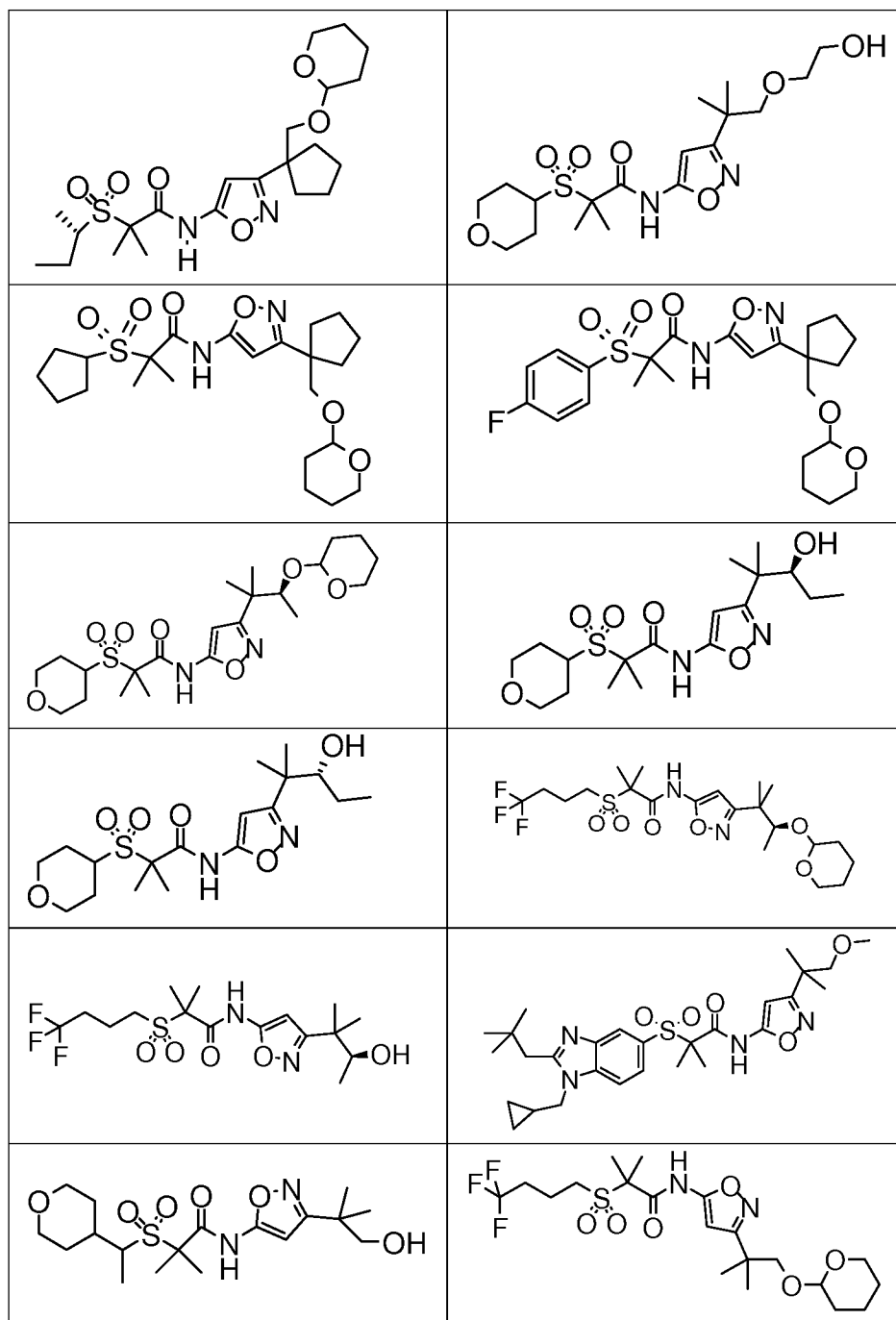
5 or a pharmaceutically acceptable salt thereof.

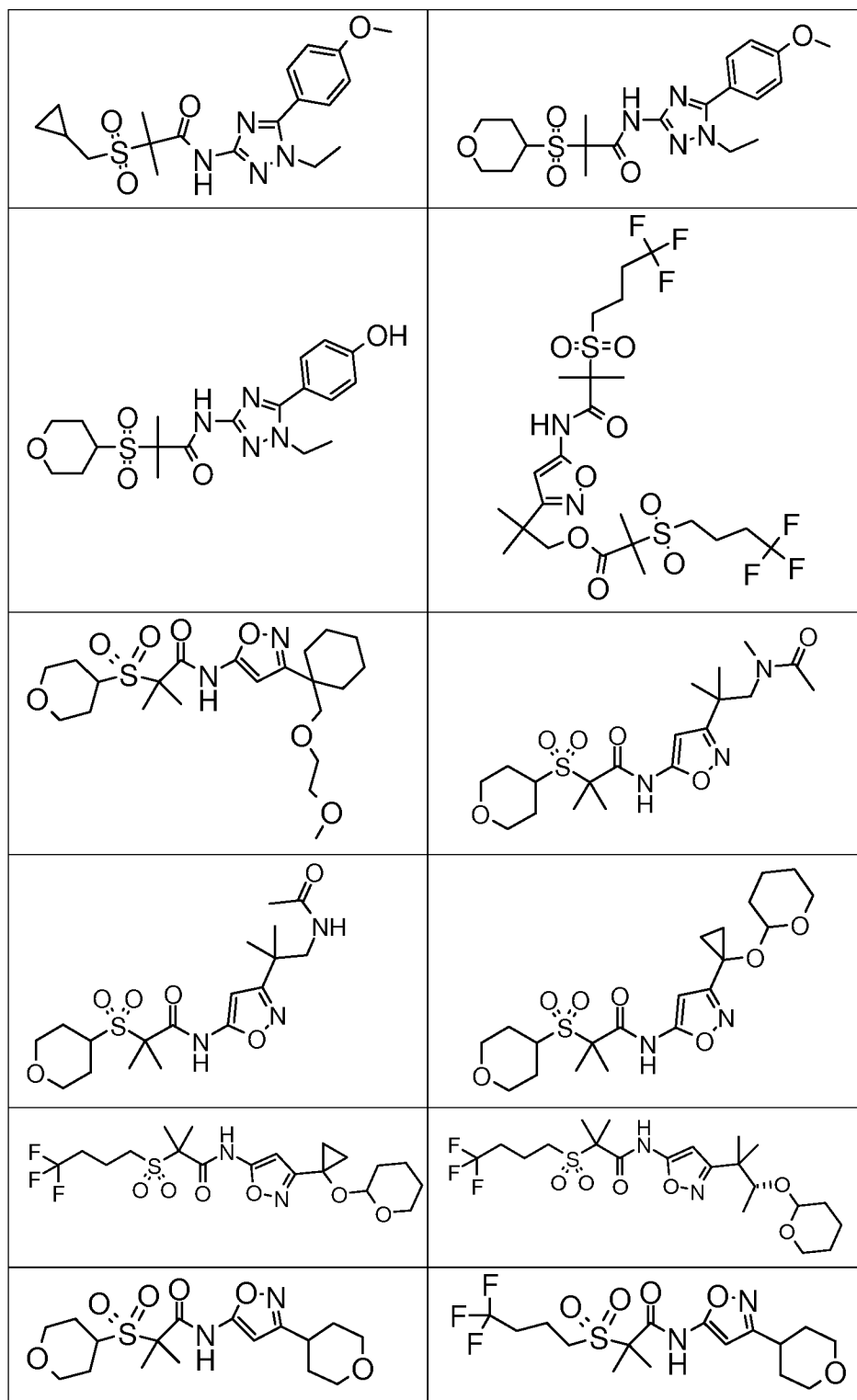
8. A compound chosen from

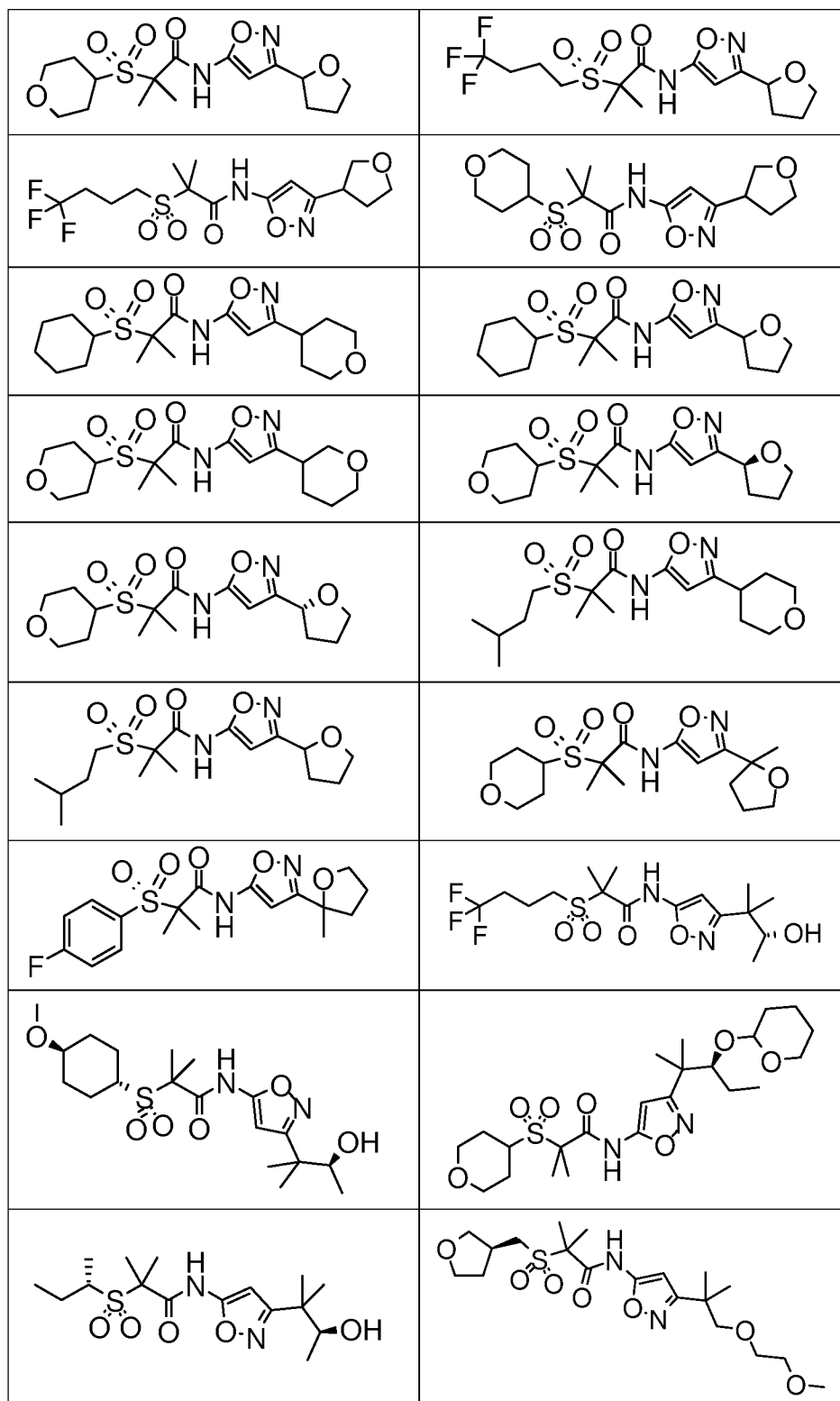
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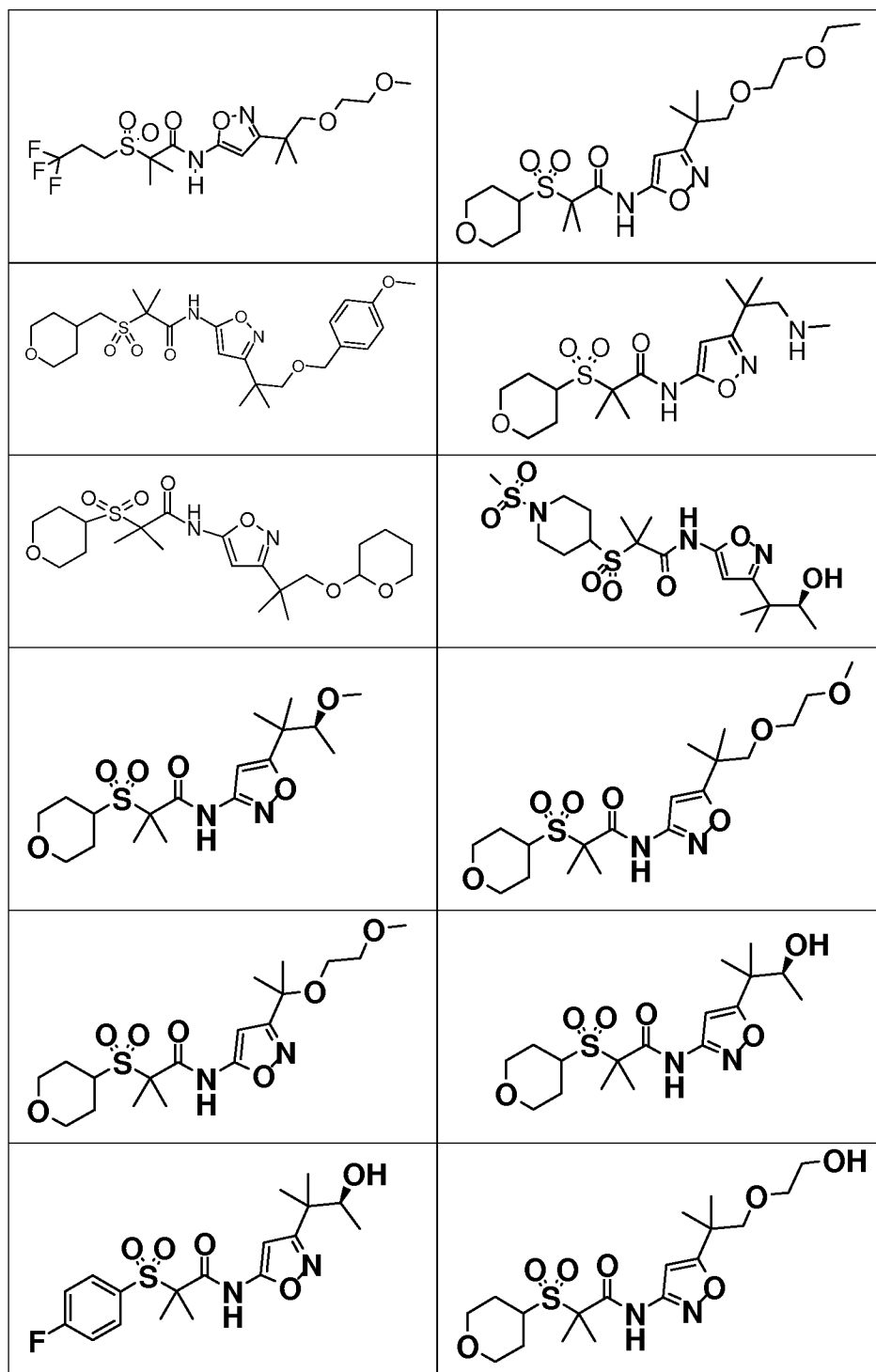


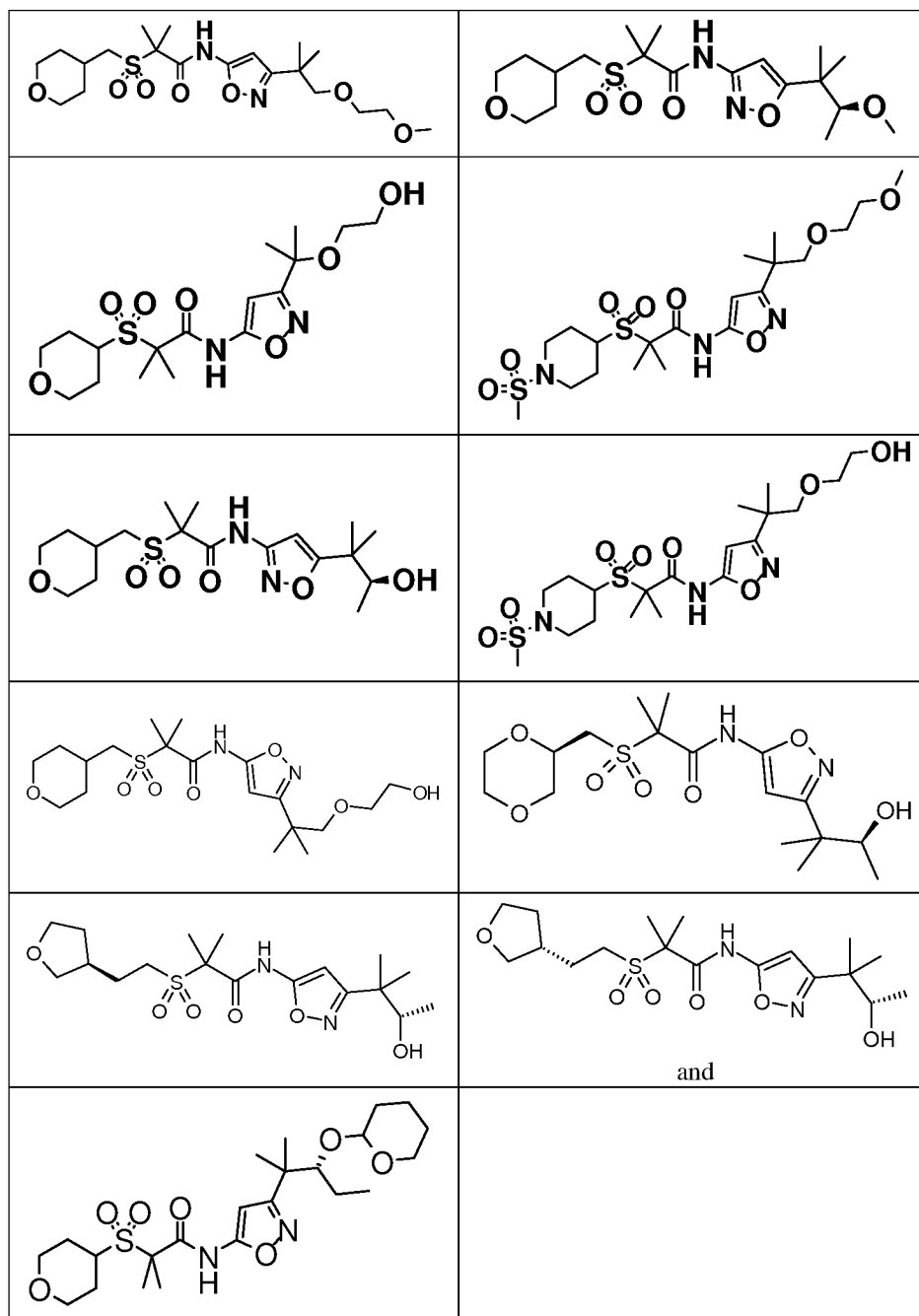






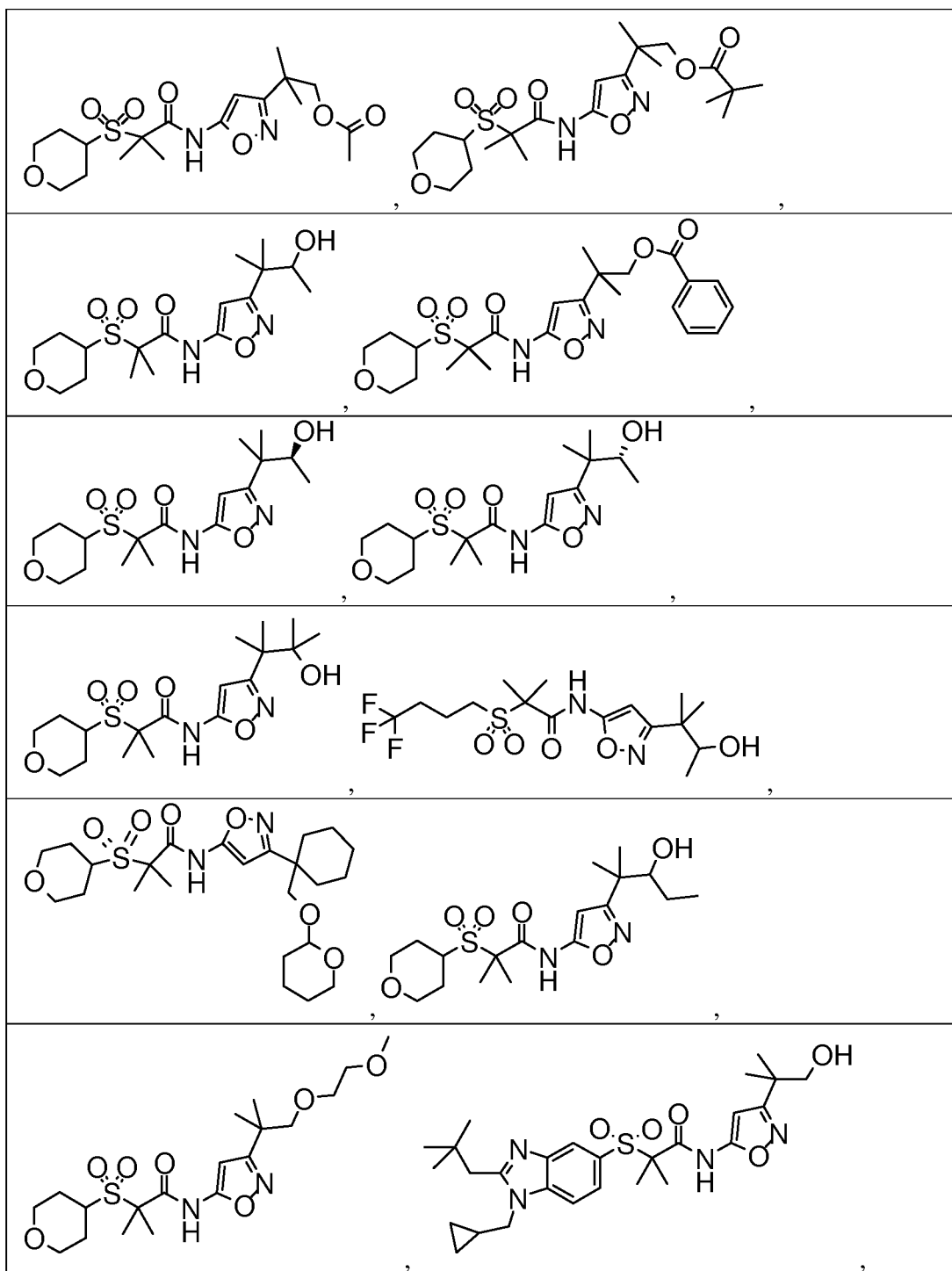


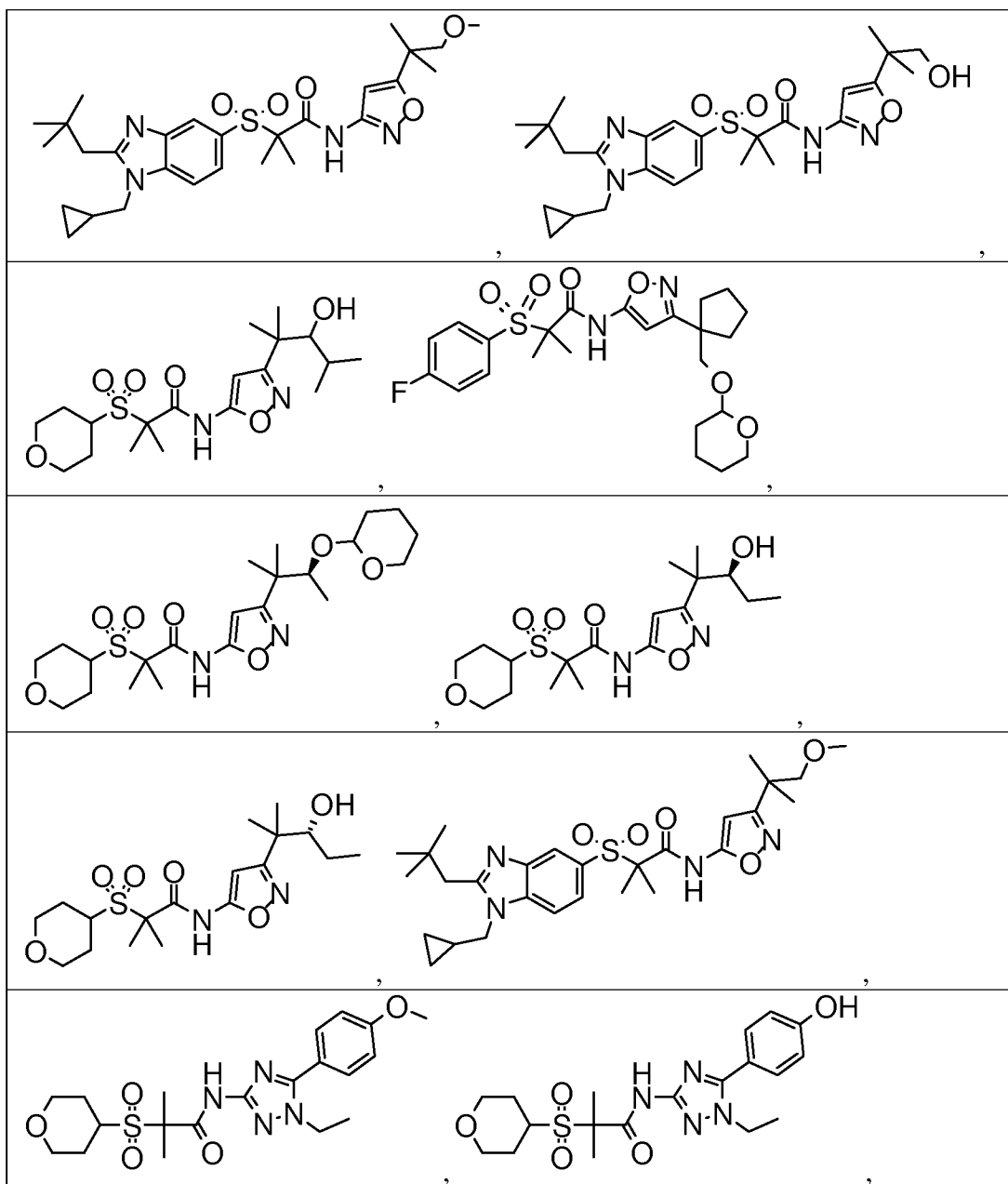


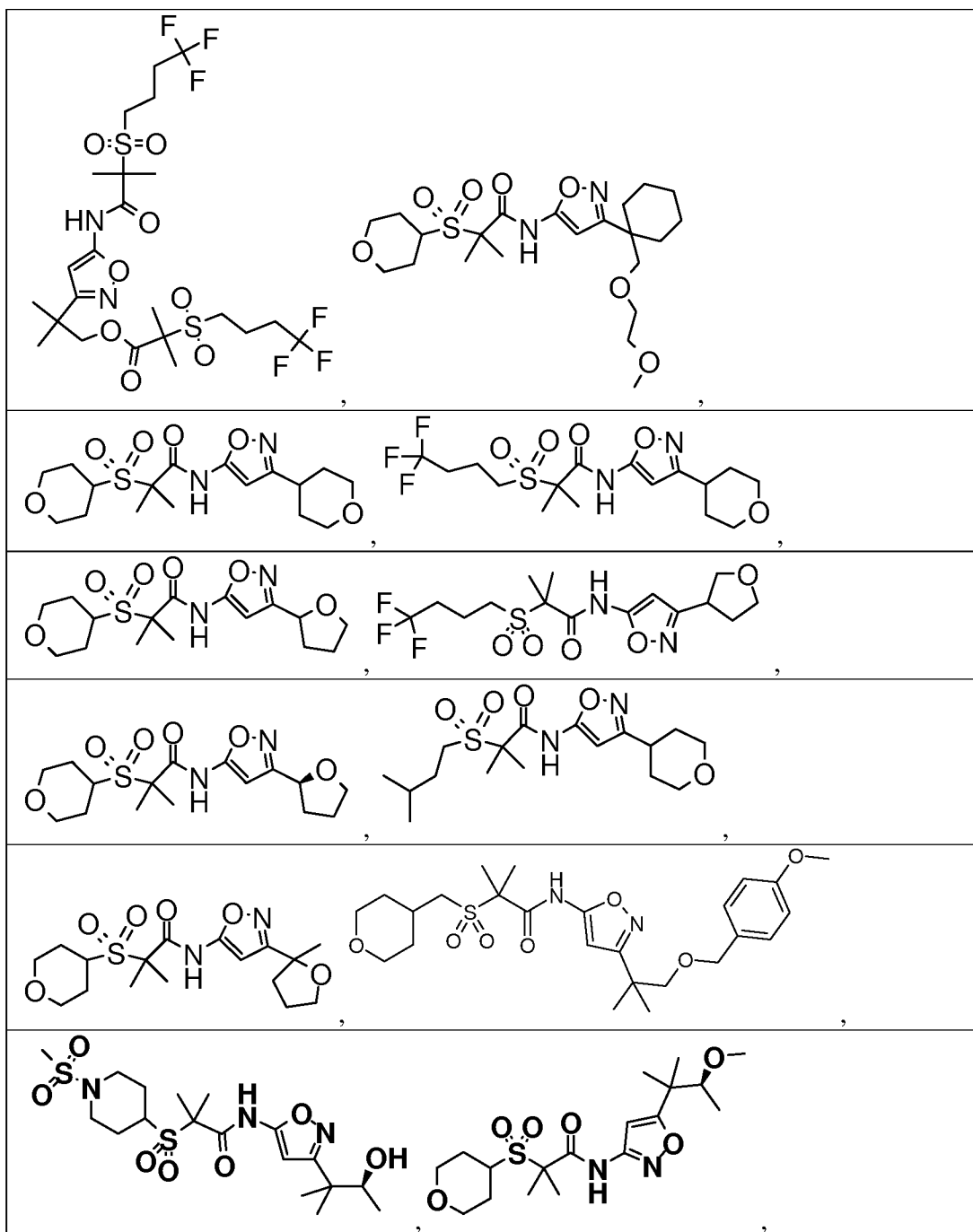


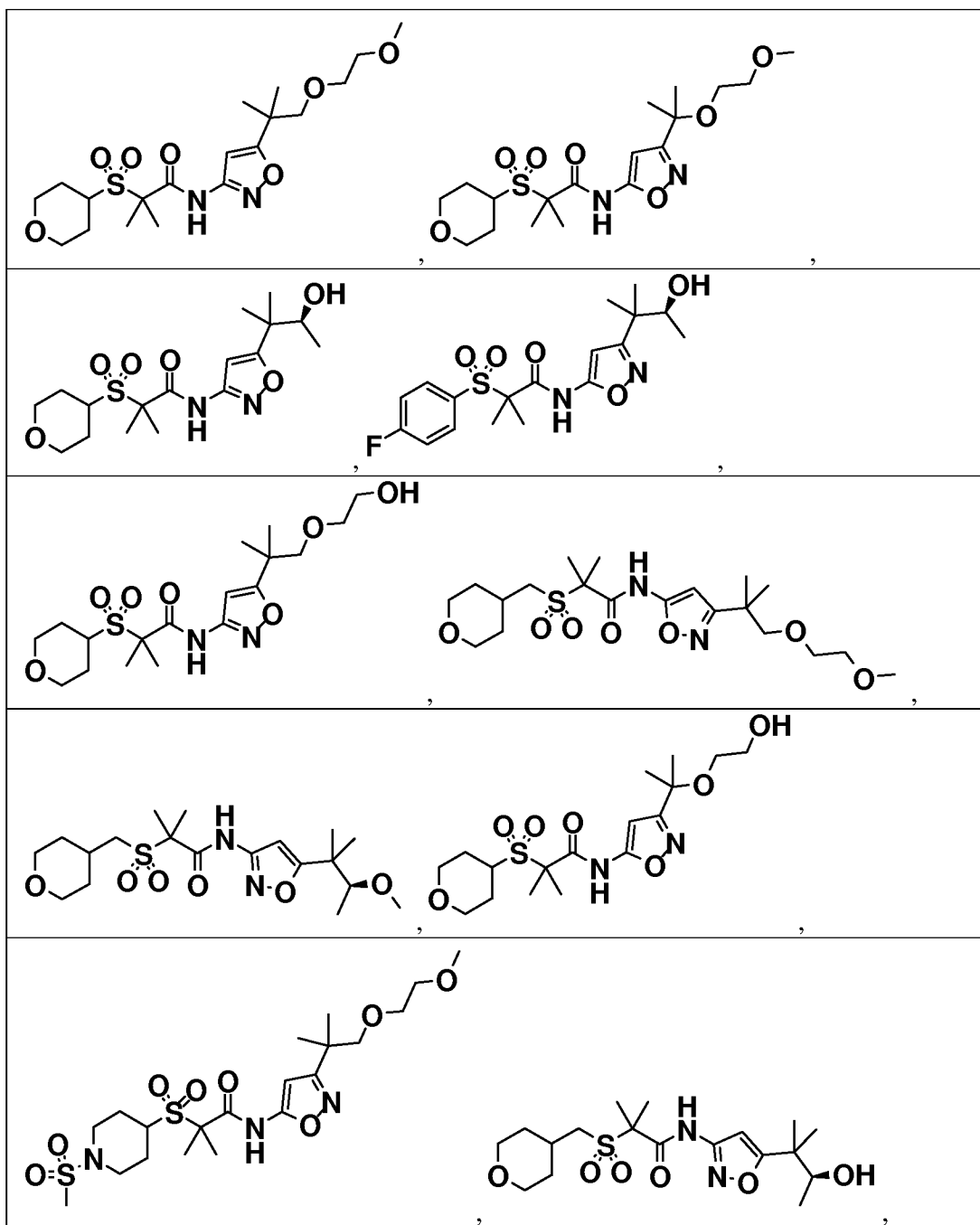
5 or a pharmaceutically acceptable salt thereof.

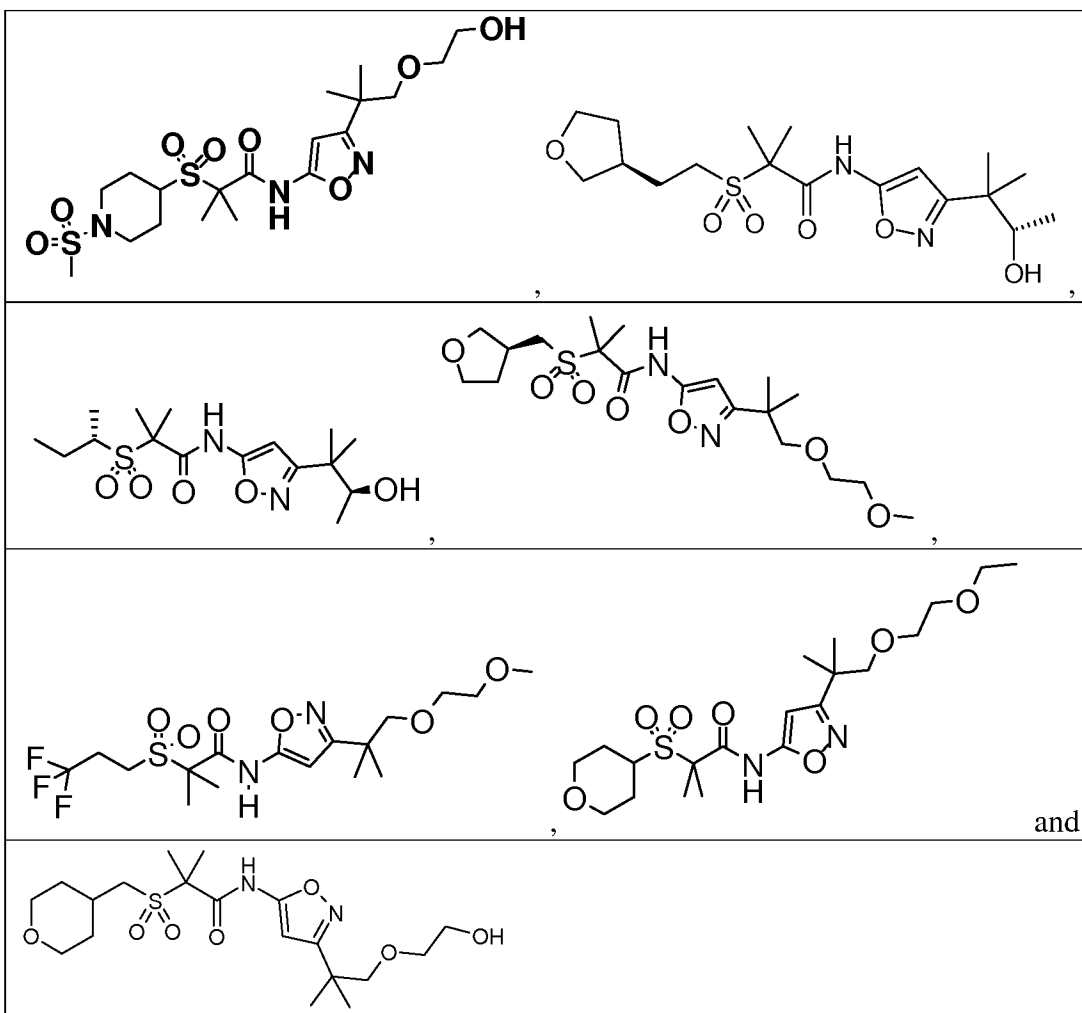
9. A compound chosen from











5

or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 – 9 and one or more pharmaceutically acceptable carriers and/or adjuvants.

10

11. A method of treating pain comprising administering a therapeutically effective amount of a compound according to any one of claims 1 - 10.

- 5 12. A method of treating a disease or condition chosen from a lung disease, a rheumatic disease, an autoimmune disease, a musculoskeletal disease, an allergic disease, an allergic reaction, a vascular disease, a dermatological disease, a renal disease, a hepatic disease, a gastrointestinal disease, neurodegeneration eye disease, diseases of the ear, nose, and throat, neurological disease blood disease, tumors, endocrine diseases, organ and tissue
- 10 transplantations and graft-versus-host diseases, severe states of shock, acute pain, visceral pain, spasm of the gastrointestinal tract or uterus, colics, neuropathic pain, inflammatory and nociceptive pain, cancer pain, headache, restenosis, atherosclerosis, reperfusion injury, congestive heart failure, myocardial infarction, thermal injury, multiple organ injury secondary to trauma, necrotizing enterocolitis and syndromes associated with hemodialysis,
- 15 leukopheresis, and granulocyte transfusion, sarcoidosis, gingivitis and pyrexia comprising administering a therapeutically effective amount of a compound according to any one of claims 1 - 10.

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