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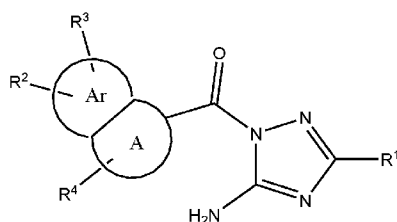
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(54) Title: AMINOTRIAZOLE IMMUNOMODULATORS FOR TREATING AUTOIMMUNE DISEASES



(1)

(57) Abstract: 1-Acyl-3-(heteroaryl)-1H-1,2,4-triazol-5-amines of formula (I) are disclosed. These compounds inhibit Coagulation Factor XIIa in the presence of thrombin and other coagulation factors. They are useful to treat autoimmune diseases.

AMINOTRIAZOLE IMMUNOMODULATORS FOR TREATING AUTOIMMUNE DISEASES

Cross-reference to Related Applications

[001] This application claims priority from US provisional application 62/277,149, filed January 11, 2016, which is incorporated herein by reference in its entirety.

Government Rights Statement

[002] This invention was made with Government support under grant DK085154 awarded by the National Science Foundation/National Institute of Diabetes and Digestive and Kidney Diseases. The Government has certain rights in the invention.

Field of the Invention

[003] The invention relates to 1-acyl-3-(heteroaryl)-1H-1,2,4-triazol-5-amines that selectively inhibit Coagulation Factor XIIa in the presence of thrombin and other coagulation factors. These compounds are useful to treat autoimmune diseases.

Background of the Invention

[004] Chemotaxis is directional movement in response to a specific chemical gradient. This cellular ability is necessary for immune homeostasis and the response to inflammation, among other critical biologic processes. Several chemokines have been identified along with their receptors, providing a molecular mechanism to orchestrate movement of distinct cell types in response to diverse stimuli. For example, chemokine receptor 7 (CCR7) and its ligands, CCL19 and CCL21, comprise a signaling axis required for chemotaxis of T-cells into and within lymphoid organs. CCR7-mediated chemotaxis is important in developing adaptive immunity, as well as maintaining tolerance and memory.

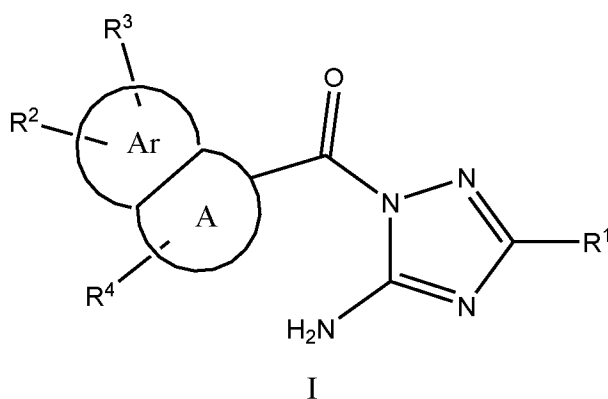
[005] Chemokines are broadly grouped as homeostatic or inflammatory. For the latter, acutely increasing production may be sufficient to control a chemotactic response. For

homeostatic chemokines, such as CCL19/21, signal modulation occurs by altering receptor density or effective ligand concentration. This is achieved either directly (e.g. increased receptor expression) or indirectly (e.g. atypical chemokine receptor scavenging of ligands). Indeed, for CCR7, exposure to serum promotes cell migration, and there is an enhanced chemotactic response of T-cells to CCL19/21 in the presence of serum, although the basis for this acceleration has not been previously described in the literature.

Summary of the Invention

[006] It has now been found that a fragment from high molecular weight kininogen (HK) is a potent cofactor that accelerates CCL19-mediated chemotaxis. This HK fragment is necessary and sufficient for accelerated chemotaxis towards CCL19, and for serum or plasma, the activity is dependent on coagulation factor XIIa. High molecular weight kininogen (HK) is well-known for a role in inflammation, particularly as the parent molecule of the nonapeptide bradykinin. Mechanistically, serum-accelerated chemotaxis is dependent on active coagulation factor XII (FXIIa), which is known to promote cleavage of HK. It has now been discovered that pre-treatment of native murine lymphocytes with this HK-derived fragment peptide enhances *in vivo* homing of T-cells to lymph nodes. A circulating cofactor that is activated at sites of inflammation and injury to enhance lymphocyte chemotaxis represents a new and powerful mechanism coupling inflammation to adaptive immunity. In particular, small molecule therapeutic agents that can modulate FXIIa function – and thereby production of the HK fragment - without significantly affecting thrombin activation offer a means of safely regulating immune cell chemotaxis through humoral cofactors.

[007] In one aspect, the invention relates to method for treating inflammation in a patient comprising administering to the patient a therapeutically effective amount of a compound of formula I



wherein

Ar/A is a fused bicycle in which Ar is an aromatic 5 or 6-membered ring and A is a non-aromatic 5, 6 or 7-membered ring and the point of attachment to the acyl triazole is on the non-aromatic ring;

R¹ is phenyl or an aromatic monocyclic heterocycle, said phenyl or heterocycle optionally substituted with one or more of: halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)fluoroalkyl, (C₁-C₄)fluoroalkoxy and di(C₁-C₄)alkylamino;

R² and R³ are attached to Ar/A at a carbon and are chosen independently from hydrogen, halogen, hydroxy, amino, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylamino, di(C₁-C₄)alkylamino, (C₁-C₄)acylamino, (C₁-C₄)fluoroalkyl and (C₁-C₄)fluoroalkoxy;

R⁴ is hydrogen or, when Ar/A contains a nitrogen, R⁴ is attached to nitrogen and is chosen from hydrogen, (C₁-C₁₀)hydrocarbyl, and benzyl substituted with one to three substituents chosen from halogen, hydroxy, amino, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylamino, di(C₁-C₄)alkylamino, (C₁-C₄)acylamino, (C₁-C₄)fluoroalkyl and (C₁-C₄)fluoroalkoxy; with the proviso that if R² or R³ is other than hydrogen, no non-hydrogen substituent may be attached to the same carbon as the acyl triazole group.

[008] In another aspect, the invention relates to a method for treating an immunological disorder comprising administering a compound of formula I.

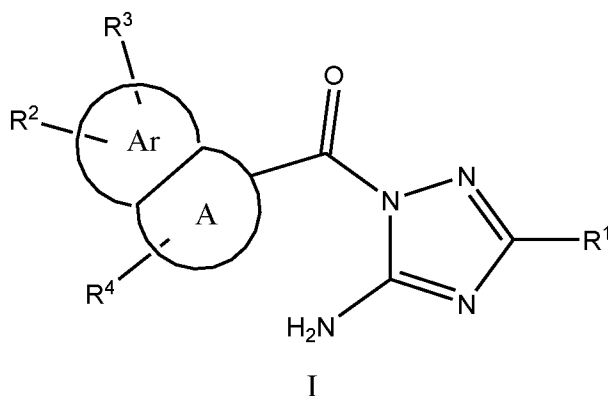
[009] In another aspect, the invention relates to a method for treating vasodilatation comprising administering a compound of formula I.

[010] In another aspect, the invention relates to compounds of formula I.

[011] In another aspect, the invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound of formula I.

Detailed Description of the Invention

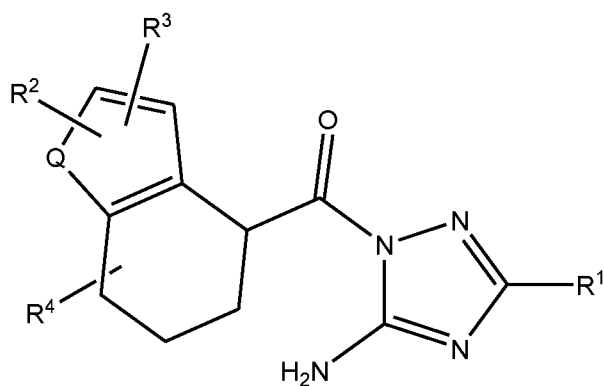
[012] In one aspect, the invention relates to compounds of formula I:



In these compounds, Ar/A is a fused bicycle in which Ar is an aromatic 5 or 6-membered ring and A is a non-aromatic 5, 6 or 7-membered ring and the point of attachment to the acyl triazole is on the non-aromatic ring. In some embodiments, A is a 5, 6 or 7-membered nitrogenous heterocycle, preferably an N-alkylated heterocycle. In other words, the acyltriazole is attached to A at a carbon and one of R², R³ and R⁴ is (C₁-C₄)alkyl and is attached to the nitrogen of A. In some embodiments, A is a 5, 6 or 7-membered oxygen heterocycle; in some A is a 5, 6 or 7-membered sulfur heterocycle; in some, A is a 5, 6 or 7-membered carbocycle, and in particular, a 6-membered carbocycle. In some embodiments, Ar may be chosen from benzene, pyridine, pyrrole, thiophene and furan.

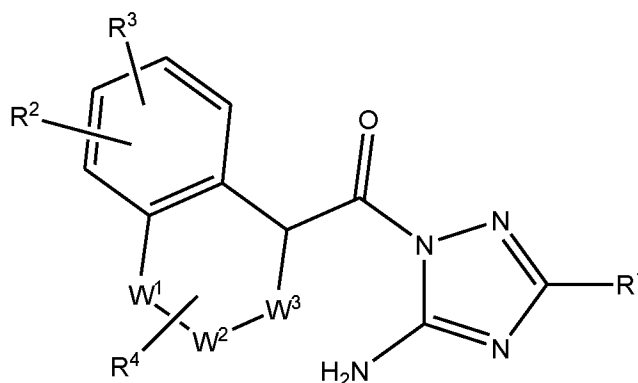
[013] Exemplary embodiments of the Ar/A fused bicycle include:

(a) compounds of the formula



wherein Q is O, S or NR⁴;

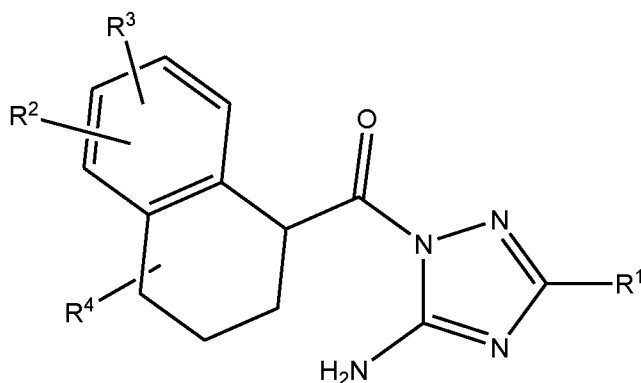
(b) compounds of the formula



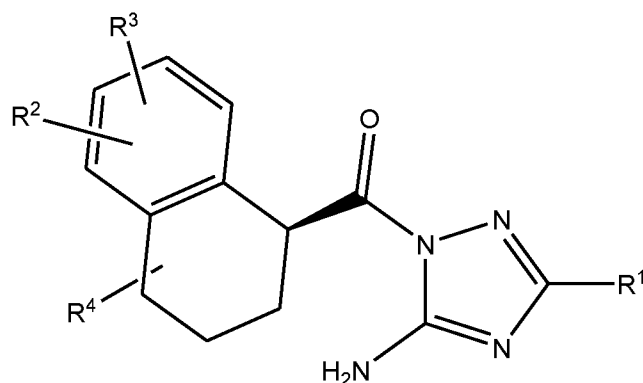
wherein one of W¹, W² and W³ is chosen from O, S and NR⁵ and the other two of W¹, W² and W³ are saturated carbons to which any of R², R³ and R⁴ may be attached; and

R⁵ is hydrogen or (C₁-C₁₀)hydrocarbon, particularly compounds wherein one of W¹ and W³ is chosen from -O- and -N(CH₃)-; and

(c) compounds of the formula



and in particular, compounds wherein the chiral center adjacent the carbonyl has (S) absolute configuration. These compounds may be represented by the formula



[014] In the compounds of formula I, R¹ may be an aromatic monocyclic heterocycle, optionally substituted with one or more of: halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)fluoroalkyl and (C₁-C₄)fluoroalkoxy. Exemplary aromatic heterocyclic rings (that may

carry substituents) include furanyl, thiophenyl, pyrrolyl, pyrimidinyl, pyridazinyl, pyrazinyl, and, preferably, pyridinyl. R^1 may also be optionally substituted phenyl. Preferred species in which R^1 is optionally substituted phenyl are those in which A is a six-membered carbocycle or heterocycle, and particularly those in which the triazolylcarbonyl is attached at a carbon of A, and the carbon bearing the triazolylcarbonyl is of the (S) configuration.

[015] In the compounds of formula I, R^2 and R^3 are chosen independently from hydrogen, halogen, hydroxy, amino, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylamino, di(C₁-C₄)alkylamino, (C₁-C₄)acylamino, (C₁-C₄)fluoroalkyl and (C₁-C₄)fluoroalkoxy. Preferably, R^2 , and R^3 are chosen independently from hydrogen, halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, di(C₁-C₄)alkylamino, (C₁-C₄)acylamino, (C₁-C₄)fluoroalkyl and (C₁-C₄)fluoroalkoxy. In some embodiments, at least two of R^2 , R^3 and R^4 are hydrogen. When Ar/A contains a nitrogen, for example when Ar/A is a tetrahydroindole (see example 8), R^4 is attached to nitrogen, and R^4 is hydrogen, (C₁-C₁₀)hydrocarbyl, or substituted benzyl. Preferred benzyl substituents are halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, di(C₁-C₄)alkylamino, (C₁-C₄)acylamino, (C₁-C₄)fluoroalkyl and (C₁-C₄)fluoroalkoxy.

[016] In all of the foregoing formulae, the depiction of attachment of substituents is drawn for convenience. It is intended that the substituents R^2 , R^3 and R^4 may be attached to the Ar/A bicycle at any chemically reasonable position, provided that, if one of R^2 , R^3 and R^4 is other than hydrogen, it cannot be attached to the same carbon as the acyl triazole group. It is not intended that R^2 and R^3 must be attached to the Ar ring and R^4 must be a substituent on the A ring - unless expressly so stated. Of course, as would be understood by persons of skill, instances in which R^2 , R^3 or R^4 is oxo would require that the substituent be on the A ring.

[017] Throughout this specification the terms and substituents retain their definitions.

[018] C₁ to C₂₀ hydrocarbon includes alkyl, cycloalkyl, polycycloalkyl, alkenyl, alkynyl, aryl and combinations thereof. Examples include benzyl, phenethyl, cyclohexylmethyl, adamantyl, camphoryl and naphthylethyl. Hydrocarbyl refers to any substituent comprised of hydrogen and carbon as the only elemental constituents. Aliphatic hydrocarbons are hydrocarbons that are not aromatic; they may be saturated or unsaturated, cyclic, linear or branched. Examples of aliphatic hydrocarbons include isopropyl, 2-butenyl, 2-butylnyl,

cyclopentyl, norbornyl, etc. Aromatic hydrocarbons include benzene (phenyl), naphthalene (naphthyl), anthracene, etc.

[019] Unless otherwise specified, alkyl (or alkylene) is intended to include linear or branched saturated hydrocarbon structures and combinations thereof. Alkyl refers to alkyl groups from 1 to 20 carbon atoms, preferably 1 to 10 carbon atoms, more preferably 1 to 6 carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl, t-butyl and the like.

[020] Cycloalkyl is a subset of hydrocarbon and includes cyclic hydrocarbon groups of from 3 to 8 carbon atoms. Examples of cycloalkyl groups include cy-propyl, cy-butyl, cy-pentyl, norbornyl and the like.

[021] Unless otherwise specified, the term “carbocycle” is intended to include ring systems in which the ring atoms are all carbon but of any oxidation state. Thus (C₃-C₁₀) carbocycle refers to both non-aromatic and aromatic systems, including such systems as cyclopropane, benzene and cyclohexene; (C₈-C₁₂) carbopolycycle refers to such systems as norbornane, decalin, indane and naphthalene. Carbocycle, if not otherwise limited, refers to monocycles, bicycles and polycycles.

[022] Heterocycle means an aliphatic or aromatic carbocycle residue in which from one to four carbons is replaced by a heteroatom selected from the group consisting of N, O, and S. The nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. Unless otherwise specified, a heterocycle may be non-aromatic (heteroaliphatic) or aromatic (heteroaryl). Examples of heterocycles include pyrrolidine, pyrazole, pyrrole, indole, quinoline, isoquinoline, tetrahydroisoquinoline, benzofuran, benzodioxan, benzodioxole (commonly referred to as methylenedioxyphenyl, when occurring as a substituent), tetrazole, morpholine, thiazole, pyridine, pyridazine, pyrimidine, thiophene, furan, oxazole, oxazoline, isoxazole, dioxane, tetrahydrofuran and the like. Examples of heterocyclyl residues include piperazinyl, piperidinyl, pyrazolidinyl, imidazolyl, imidazolynyl, imidazolidinyl, pyrazinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, tetrahydrofuryl, tetrahydropyranyl, thienyl (also historically called thiophenyl), benzothienyl, thiamorpholinyl, oxadiazolyl, triazolyl and tetrahydroquinolinyl.

[023] Hydrocarbyloxy refers to groups of from 1 to 20 carbon atoms, preferably 1 to 10 carbon atoms, more preferably 1 to 6 carbon atoms attached to the parent structure through an oxygen. Alkoxy is a subset of hydrocarbyloxy and includes groups of a straight or branched configuration. Examples include methoxy, ethoxy, propoxy, isopropoxy and the like. Lower-alkoxy refers to groups containing one to four carbons. The term "halogen" means fluorine, chlorine, bromine or iodine atoms.

[024] Unless otherwise specified, acyl refers to formyl and to groups of 1, 2, 3, 4, 5, 6, 7 and 8 carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. Examples include acetyl, benzoyl, propionyl, isobutyryl and the like. Lower-acyl refers to groups containing one to four carbons. The double bonded oxygen, when referred to as a substituent itself is called "oxo".

[025] As used herein, the term "optionally substituted" may be used interchangeably with "unsubstituted or substituted". The term "substituted" refers to the replacement of one or more hydrogen atoms in a specified group with a specified radical. For example, substituted alkyl, aryl, cycloalkyl, heterocyclyl etc. refer to alkyl, aryl, cycloalkyl, or heterocyclyl wherein one or more H atoms in each residue are replaced with halogen, haloalkyl, alkyl, acyl, alkoxyalkyl, hydroxy lower alkyl, carbonyl, phenyl, heteroaryl, benzenesulfonyl, hydroxy, lower alkoxy, haloalkoxy, oxaalkyl, carboxy, alkoxycarbonyl [-C(=O)O-alkyl], alkoxycarbonylamino [HNC(=O)O-alkyl], aminocarbonyl (also known as carboxamido) [-C(=O)NH₂], alkylaminocarbonyl [-C(=O)NH-alkyl], cyano, acetoxo, nitro, amino, alkylamino, dialkylamino, (alkyl)(aryl)aminoalkyl, alkylaminoalkyl (including cycloalkylaminoalkyl), dialkylaminoalkyl, dialkylaminoalkoxy, heterocyclylalkoxy, mercapto, alkylthio, sulfoxide, sulfone, sulfonylamino, alkylsulfinyl, alkylsulfonyl, acylaminoalkyl, acylaminoalkoxy, acylamino, amidino, aryl, benzyl, heterocyclyl, heterocyclylalkyl, phenoxy, benzyloxy, heteroaryloxy, hydroxyimino, alkoxyimino, oxaalkyl, aminosulfonyl, trityl, amidino, guanidino, ureido, benzyloxyphenyl, and benzyloxy. "Oxo" is also included among the substituents referred to in "optionally substituted"; it will be appreciated by persons of skill in the art that, because oxo is a divalent radical, there are circumstances in which it will not be appropriate as a substituent (e.g. on phenyl). In one embodiment, 1, 2, or 3 hydrogen atoms are replaced with a specified radical. In the case of alkyl and cycloalkyl, more than three hydrogen atoms can be replaced by fluorine; indeed, all

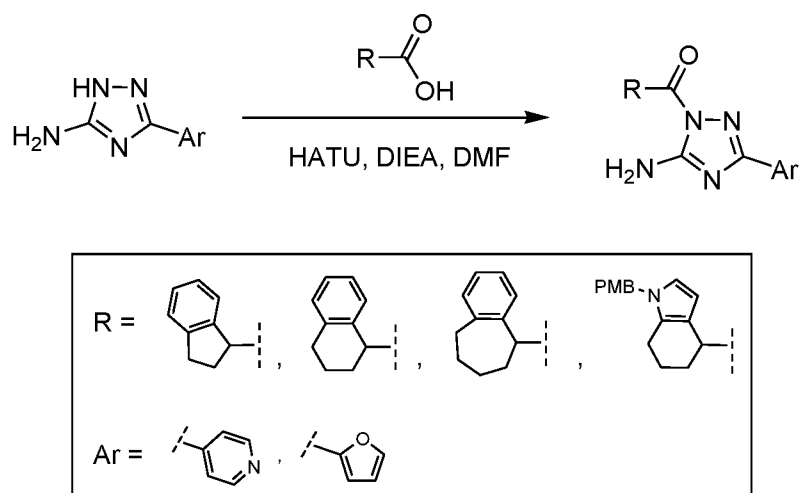
available hydrogen atoms could be replaced by fluorine. In particular embodiments, substituents are halogen, halo(C₁-C₄)hydrocarbyl, halo(C₁-C₄)hydrocarbyloxy, cyano, thiocyanato, (C₁-C₄)hydrocarbylsulfinyl, (C₁-C₄)hydrocarbyl-sulfonyl, aminosulfonyl, nitro, acetyl, and acetamido. Preferred substituents are halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)fluoroalkyl, (C₁-C₄)fluoroalkoxy, hydroxy, amino, (C₁-C₄)alkylamino, di(C₁-C₄)alkylamino, (C₁-C₄)acylamino, (C₁-C₄)fluoroalkyl and (C₁-C₄)fluoroalkoxy.

[026] Substituents Rⁿ are generally defined when introduced and retain that definition throughout the specification and in all independent claims.

[027] Preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. Suitable groups for that purpose are discussed in standard textbooks in the field of chemistry, such as *Protective Groups in Organic Synthesis* by T.W.Greene and P.G.M.Wuts [John Wiley & Sons, New York, 1999], in *Protecting Group Chemistry*, 1st Ed., Oxford University Press, 2000; and in *March's Advanced Organic chemistry: Reactions, Mechanisms, and Structure*, 5th Ed., Wiley-Interscience Publication, 2001.

[028] In general, compounds of formula I can be prepared as shown in Scheme 1. The appropriately substituted starting materials and intermediates used in the preparation of compounds of the invention are either commercially available or readily prepared by methods known in the literature to those skilled in the art. A generally useful synthesis of acyltriazolamines may also be found in PCT WO2014/145986, particularly pages 85-101.

[029] Scheme 1:



[030] The compounds described herein will, in almost all instances, contain an asymmetric center and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms which may be defined in terms of absolute stereochemistry as (*R*)- or (*S*)-. The present invention is meant to include all such possible isomers as racemates, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using homo-chiral synthons or homo-chiral reagents, or optically resolved using conventional techniques. All tautomeric forms are intended to be included.

[031] The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are taken from Maehr *J. Chem. Ed.* 62, 114-120 (1985): solid and broken wedges are used to denote the absolute configuration of a chiral element; wavy lines indicate disavowal of any stereochemical implication which the bond it represents could generate; solid and broken bold lines are geometric descriptors indicating the relative configuration shown but denoting racemic character; and wedge outlines and dotted or broken lines denote enantiomerically pure compounds of indeterminate absolute configuration. For nomenclature in the text corresponding to wedge outlines and dotted or broken lines, we define R* and S* as indicating single enantiomers of unknown absolute configuration. Thus, for example, in Examples 10 and 11 below, syntheses of (S*)-(5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1,2,3,4-tetrahydroquinolin-4-yl)methanone and (R*)-(5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1,2,3,4-tetrahydroquinolin-4-yl)methanone are described. The (S*) is intended to indicate that the product is a single enantiomer possessing the characteristics described (e.g. NMR, HPLC retention time, etc.), which is believed on the basis of circumstantial evidence to be of the chirality shown, but the absolute configuration has not been confirmed.

[032] As used herein, and as would be understood by the person of skill in the art, the recitation of “a compound” - unless expressly further limited - is intended to include salts of that compound. In a particular embodiment, the term “compound of formula” refers to the compound or a pharmaceutically acceptable salt thereof.

[033] The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases. When the compounds of the present invention are basic, salts may be prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Suitable pharmaceutically acceptable acid addition salts for the compounds of the present invention include acetic, adipic, alginic, ascorbic, aspartic, benzenesulfonic (besylate), benzoic, boric, butyric, camphoric, camphorsulfonic, carbonic, citric, ethanedithiolsulfonic, ethanesulfonic, ethylenediaminetetraacetic, formic, fumaric, glucoheptonic, gluconic, glutamic, hydrobromic, hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, laurylsulfonic, maleic, malic, mandelic, methanesulfonic, mucic, naphthylenesulfonic, nitric, oleic, pamoic, pantothenic, phosphoric, pivalic, polygalacturonic, salicylic, stearic, succinic, sulfuric, tannic, tartaric acid, teoclastic, p-toluenesulfonic, and the like. When the compounds contain an acidic side chain, suitable pharmaceutically acceptable base addition salts for the compounds of the present invention include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, arginine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium cations and carboxylate, sulfonate and phosphonate anions attached to alkyl having from 1 to 20 carbon atoms.

[034] Also provided herein is a pharmaceutical composition comprising a compound disclosed above, or a pharmaceutically acceptable salt form thereof, and a pharmaceutically acceptable carrier or diluent.

[035] While it may be possible for the compounds of formula I to be administered as the raw chemical, it is preferable to present them as a pharmaceutical composition. According to a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically carriers thereof and optionally one or more other therapeutic

ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[036] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration. The most suitable route may depend upon the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of formula I or a pharmaceutically acceptable salt thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[037] Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[038] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein.

[039] Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Formulations for parenteral administration also include aqueous and non-aqueous sterile suspensions, which

may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of a sterile liquid carrier, for example saline, phosphate-buffered saline (PBS) or the like, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

General Methods

[040] All solvents used were commercially available and were used without further purification. Reactions were typically run using anhydrous solvents under an inert atmosphere of nitrogen.

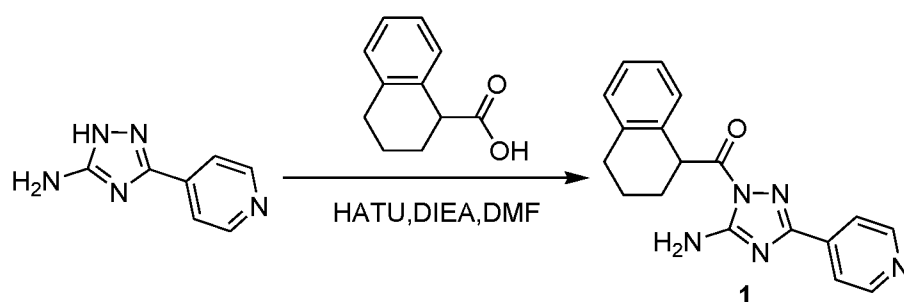
[041] ^1H spectra were recorded at 300 or 400 MHz for proton on a Bruker Mercury Plus 400 NMR Spectrometer equipped with a Bruker 400 BBO probe. All deuterated solvents contained typically 0.03% to 0.05% v/v tetramethylsilane, which was used as the reference signal (set at δ 0.00 for both ^1H and ^{13}C).

[042] LCMS analyses were performed on a SHIMADZU LCMS consisting of an UFLC 20-AD and LCMS 2020 MS detector. The column used was a Shim-pack XR-ODS, 2.2 μm , 3.0 $\times$ 50 mm. A linear gradient was applied, starting at 95 % A (A: 0.05% TFA in water) and ending at 100% B (B: 0.05% TFA in MeCN) over 2.2 min with a total run time of 3.6 min. The column temperature was at 40 $^{\circ}\text{C}$ with the flow rate of 1.0 mL/min. The Diode Array Detector was scanned from 190-400 nm. The mass spectrometer was equipped with an electrospray ion source (ESI) operated in a positive or negative mode. The mass spectrometer was scanned between m/z 90-900 with a scan time from 0.5 to 0.7 s.

[043] HPLC analyses were performed on a SHIMADZU UFLC with two LC20 AD pump and a SPD-M20A Photodiode Array Detector. The column used was an XBridge C₁₈, 3.5 μm , 4.60 $\times$ 100 mm. A linear gradient was applied, starting at 90 % A (A: 0.05% TFA in water) and ending at 95% B (B: 0.05% TFA in MeCN) over 10 min with a total run time of 15 min. The column temperature was at 40 $^{\circ}\text{C}$ with the flow rate of 1.5 mL/min. The Diode Array Detector was scanned from 200-400 nm.

[044] Thin layer chromatography (TLC) was performed on Alugram[®] (Silica gel 60 F₂₅₄) from Manchem-Nagel and UV was typically used to visualize the spots. Additional visualization methods were also employed in some cases. In these cases the TLC plate was developed with iodine (generated by adding approximately 1 g of I₂ to 10 g silica gel and thoroughly mixing), ninhydrin (available commercially from Aldrich), or Magic Stain (generated by thoroughly mixing 25 g (NH₄)₆Mo₇O₂₄·4H₂O, 5 g (NH₄)₂Ce(IV)(NO₃)₆ in 450 mL water and 50 mL concentrated H₂SO₄) to visualize the compound. Flash chromatography was performed using 40-63 μm (230-400 mesh) silica gel from Silicycle following analogous techniques to those disclosed in Still, W.C.; Kahn, M.; and Mitra, M. *Journal of Organic Chemistry*, **1978**, *43*, 2923. Typical solvents used for flash chromatography or thin layer chromatography were mixtures of chloroform/methanol, dichloromethane/methanol, ethyl acetate/methanol and hexanes/ethyl acetate.

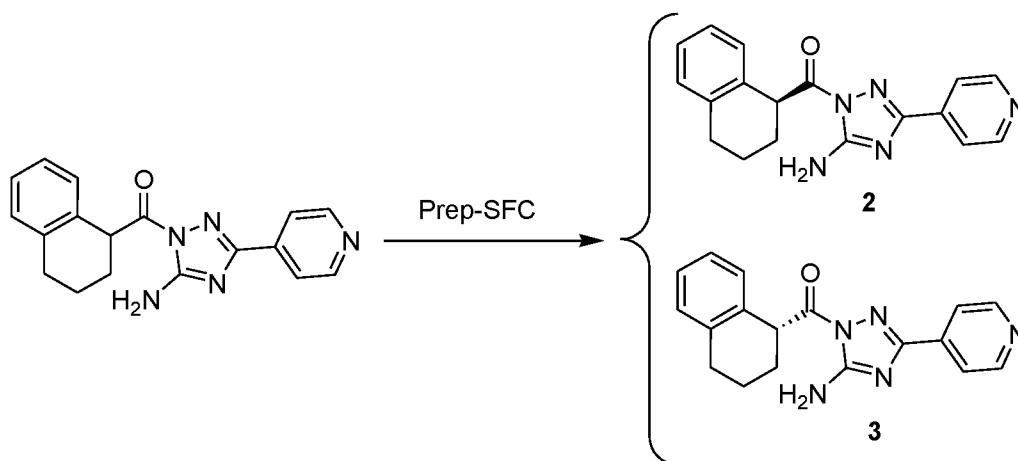
[045] Example 1: 3-(Pyridin-4-yl)-1-[(1, 2, 3, 4-tetrahydronaphthalen-1-yl) carbonyl]-1H-1, 2, 4-triazol-5-amine.



Into a 50-mL round-bottom flask, were placed 1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (39 mg, 0.22 mmol, 0.90 eq.) in N,N-dimethylformamide (3 mL), HATU (113.6 mg, 2.99 mmol, 1.20 eq.) and DIEA (96.1 mg, 0.74 mmol, 3.00 eq.). The mixture was stirred for 30 min at room temperature (20 °C). Then 3-(pyridin-4-yl)-1H-1, 2, 4-triazol-5-amine (40 mg, 0.25 mmol, 1.00 eq.) was added. The resulting solution was stirred overnight at 25 °C. The reaction mixture was diluted with DCM (80 mL), washed with H₂O (50mL x3) and brine (50mL x3) and dried with Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Analyse HPLC-SHIMADZU): Column, XBridge Shield RP18 OBD Column, 5μm, 19mm x150mm; mobile phase, Waters (0.1%FA) and ACN (20.0% ACN up to 70.0% in 7 min); Detector, 254 & 220nm. The collected fraction was lyophilized to give 14.5 mg

(18%) of 3-(pyridin-4-yl)-1-[(1, 2, 3, 4-tetrahydronaphthalen-1-yl) carbonyl]-1H-1, 2, 4-triazol-5-amine as a white solid. MS (ES, m/z) $[M+H]^+$: 320; $^1\text{HNMR}$ (DMSO, 400MHz, ppm): δ 8.72 (s, 2H); 7.93-7.91 (m, 2H); 7.83 (s, 2H); 7.20-7.15 (m, 2H); 7.12-7.07 (m, 2H); 5.06-5.03 (m, 1H); 2.85-2.74 (m, 2H); 2.24-2.08 (m, 2H); 1.94-1.87 (m, 1H); 1.81-1.76 (m, 1H).

[046] Examples 2 & 3: (S)-(5-Amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1,2,3,4-tetrahydronaphthalen-1-yl)methanone and (R)-(5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1,2,3,4-tetrahydronaphthalen-1-yl)methanone.



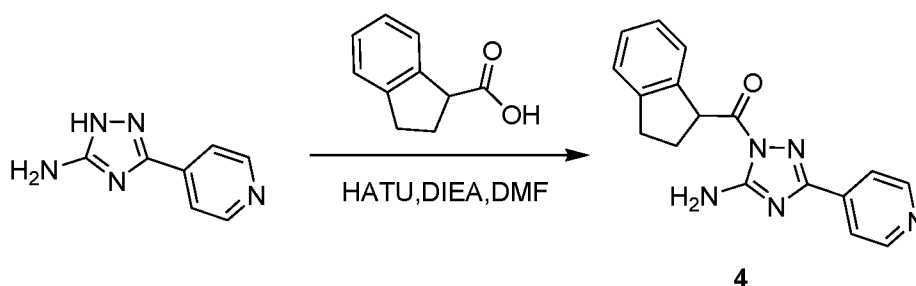
[047] A racemic mixture of 3-(Pyridin-4-yl)-1-[(1,2,3,4-tetrahydronaphthalen-1-yl)carbonyl]-1H-1,2,4-triazol-5-amine (100 mg) was separated by Prep-SFC with the following conditions (Analyse HPLC-SHIMADZU): Column, Chiralpak AD-H, 2 x 25cm Column; Mobile Phase A: CO_2 :70, Mobile Phase B: IPA:ACN=1:1 (30); Flow rate: 40 mL/min; 220 nm to give two enantiomers.

[048] Enantiomer A: (R)-(5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1,2,3,4-tetrahydronaphthalen-1-yl)methanone (assumed) (Example 3), R_t =3.93 min; Yield: 45.1 mg (45%) as an off-white solid. MS (ES, m/z) $[M+H]^+$: 320; $^1\text{HNMR}$ (DMSO- d_6 , 300MHz, ppm): δ 8.73 (d, J =5.7Hz, 2H); 7.92 (d, J =5.7Hz, 2H); 7.82 (s, 2H); 7.22-7.16 (m, 2H); 7.12-7.01 (m, 2H); 5.08-5.04 (m, 1H); 2.90-2.73 (m, 2H); 2.27-2.07 (m, 2H); 2.00-1.90 (m, 2H).

[049] Enantiomer B: (S)-(5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1,2,3,4-tetrahydronaphthalen-1-yl)methanone (assumed) (Example 2), R_t =4.77 min; Yield: 42.3 mg (42%) as an off-white solid. MS (ES, m/z) $[M+H]^+$: 320; $^1\text{HNMR}$ (DMSO- d_6 , 300MHz,

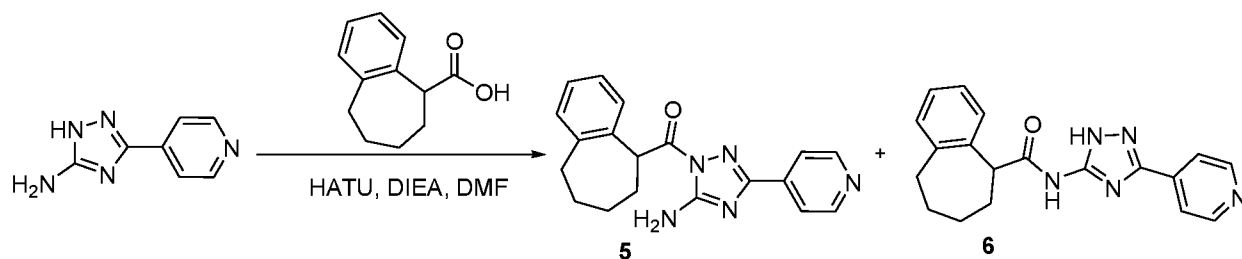
ppm): δ 8.73 (d, $J=6.6\text{Hz}$, 2H); 7.92 (d, $J=6.0\text{Hz}$, 2H); 7.82 (s, 2H); 7.21-7.16 (m, 2H); 7.12 (d, $J=1.8\text{Hz}$, 2H); 5.08-5.04 (m, 1H); 2.87-2.75 (m, 2H); 2.24-2.12 (m, 2H); 1.94-1.76 (m, 2H).

[050] Example 4: (5-Amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(2,3-dihydro-1H-inden-1-yl)methanone.



Into a 50-mL round-bottom flask, was placed 2, 3-dihydro-1H-indene-1-carboxylic acid (48.2 mg, 0.30 mmol, 1.20 eq.), N, N-dimethylformamide (3 mL), HATU (113 mg, 0.30 mmol, 1.20 eq.), DIEA (96.1 mg, 0.74 mmol, 3.00 eq.). The mixture was stirred for 30 min at room temperature. Then 3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine (40 mg, 0.25 mmol, 1.00 eq.) was added. The resulting solution was stirred overnight at 25°C. The reaction mixture was diluted with DCM (80 mL), washed with H₂O (50 mL x3) and brine (50 mL x3) and dried with Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (2#-Analyse HPLC-SHIMADZU(HPLC-10)): Column, XBridge Shield RP18 OBD Column, 5 μ m, 19mm x150mm; mobile phase, Waters(10 mmol/L NH₄HCO₃) and ACN (30.0% ACN up to 60.0% in 7 min); Detector, 254nm The collected fraction was lyophilized to give 14.5 mg (19%) of 1-[(2,3-dihydro-1H-inden-1-yl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine as a white solid. MS (ES, m/z) [$M+H$]⁺: 306; ¹HNMR (DMSO-d₆, 400MHz, *ppm*): δ 8.74-8.72 (m, 2H); 7.94-7.92 (m, 2H); 7.80-7.76 (m, 2H); 7.32 (d, $J=8.4\text{Hz}$, 2H); 7.25-7.21 (m, 1H); 7.17-7.13 (m, 1H); 5.23-5.20 (m, 1H); 3.14-3.06 (m, 1H); 3.02-2.96 (m, 1H); 2.51-2.37 (m, 2H).

[051] Examples 5 & 6: (5-Amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)methanone and N-[3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl]-6,7,8,9-tetrahydro-5H-benzo[7]annulene-5-carboxamide.

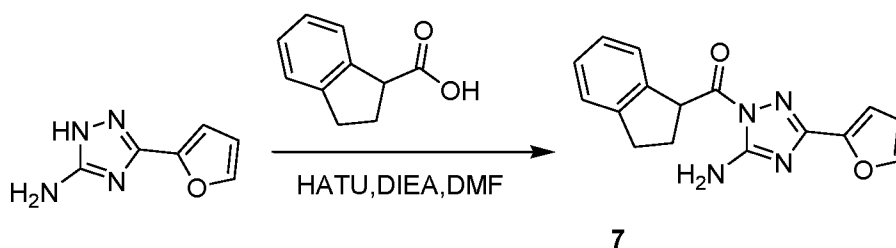


Into a 50-mL round-bottom flask, was placed 6, 7, 8, 9-tetrahydro-5H-benzo[7]annulene-5-carboxylic acid (42.5 mg, 0.22 mmol, 0.90 eq.), N,N-dimethylformamide (3 mL), HATU (113 mg, 0.30 mmol, 1.20 eq.), DIEA (96.1 mg, 0.74 mmol, 3.00 eq.). The mixture was stirred for 30 min at room temperature. Then 3-(pyridin-4-yl)-1H-1, 2, 4-triazol-5-amine (40 mg, 0.25 mmol, 1.00 eq.) was added. The resulting solution was stirred overnight at 25°C. The reaction mixture was diluted with EA (80 mL), washed with brine (120 mL x 3) and concentrated under reduced pressure. The residue was purified by Pre-TLC with ethyl acetate/petroleum ether (1:1). The crude product was further purified by Prep-HPLC with the following conditions (2#-Analyse HPLC-SHIMADZU(HPLC-10)): Column, XBridge Shield RP18 OBD Column, 5um, 19mm x150 mm; mobile phase, Waters(0.1%FA) and ACN (30.0% ACN up to 60.0% in 7 min); Detector, UV 254nm to give two fractions. The collected fraction was lyophilized.

[052] Fraction A: 9.0 mg (11%) of 3-(pyridin-4-yl)-1-([6, 7, 8, 9-tetrahydro-5H-benzo[7]annulen-5-yl]carbonyl)-1H-1,2,4-triazol-5-amine (**5**) as a white solid. MS (ES, m/z) $[M+H]^+$: 334; ^1H NMR (DMSO- d_6 , 400MHz, ppm): δ 8.67-8.60 (m, 2H); 7.89(s, 2H); 7.79-7.77 (m, 2H); 7.22-7.20 (m, 1H); 7.16-7.07 (m, 2H); 6.93 (d, $J=7.2\text{Hz}$, 1H); 5.09-5.06 (m, 1H); 3.00-2.88 (m, 2H); 2.16-2.07 (m, 1H); 1.99 (s, 1H); 1.83-1.77 (m, 3H); 1.50-1.45 (m, 1H).

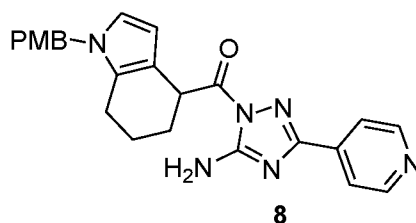
[053] Fraction B: 2.3 mg (3%) of N-[3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl]-6,7,8,9-tetrahydro-5H-benzo[7]annulene-5-carboxamide (**6**) as a white solid. MS (ES, m/z) $[M+H]^+$: 334; ^1H NMR (DMSO- d_6 , 400MHz, ppm): δ 13.93(s,1H), 11.81 (s, 1H), 8.67(d, $J=6.0\text{Hz}$, 2H), 7.86-7.84 (m, 2H), 7.20-7.10 (m, 3H), 7.03-7.00 (m, 1H), 4.14 (d, $J=8.0\text{ Hz}$, 1H), 2.96-2.91 (m, 1H), 2.84-2.78 (m, 1H), 2.05-1.95 (m, 1H), 1.90-1.84 (m, 4H), 1.45-1.35 (m, 1H).

[054] Example 7: (5-Amino-3-(furan-2-yl)-1H-1, 2, 4-triazol-1-yl)(2, 3-dihydro-1H-inden-1-yl)methanone.

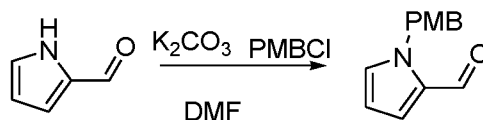


Into a 50-mL round-bottom flask, was placed 2,3-dihydro-1H-indene-1-carboxylic acid (38.9 mg, 0.24 mmol, 0.90 equiv), N,N-dimethylformamide (3 mL), HATU (121.6 mg, 0.32 mmol, 1.20 eq.), DIEA (103.2 mg, 0.80 mmol, 3.00 eq.). The mixture was stirred for 30 min at room temperature. Then 3-(furan-2-yl)-1H-1,2,4-triazol-5-amine (40 mg, 0.27 mmol, 1.00 equiv) was added. The resulting solution was stirred overnight at 25°C. The reaction mixture was diluted with EA (80 mL), washed with brine (3x120 mL) and dried with Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, XBridge C18 OBD Prep Column, 100A 5 um, 19mm x250 mm; mobile phase, Waters(0.1%FA) and ACN (hold 45.0% ACN in 9 min); Detector, 254nm. The collected fraction was lyophilized to give 9.2 mg (12%) of 1-[(2,3-dihydro-1H-inden-1-yl)carbonyl]-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine (**7**) as a white solid. MS (ES, *m/z*) [M+H]⁺: 295; ¹HNMR (DMSO-d₆, 400MHz, *ppm*): δ 7.87-7.87 (m, 1H); 7.14 (s, 2H); 7.32-7.29 (m, 2H); 7.24-7.21 (m, 1H); 7.17-7.13 (m, 1H); 7.01-7.00 (m, 1H); 6.68-6.66 (m, 1H); 5.16-5.12 (m, 1H); 3.08-3.04 (m, 1H); 3.01-2.95 (m, 1H); 2.48-2.38 (m, 2H).

[055] Example 8: (5-Amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1-(4-methoxybenzyl)-4,5,6,7-tetrahydro-1H-indol-4-yl)methanone.

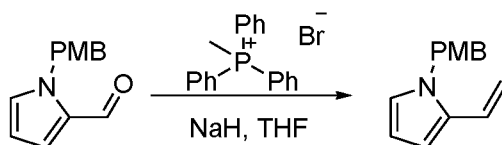


[056] Step 1. 1-(4-Methoxybenzyl)-1H-pyrrole-2-carbaldehyde.



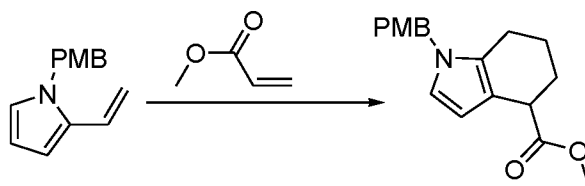
Into a 250 ml round-bottom flask, were placed a solution of 1H-pyrrole-2-carbaldehyde(10 g, 0.105 mol, 1.0 eq.) in N,N-dimethylformamide (100 mL), K₂CO₃(58.1 g, 0.42 mol, 4.0 eq.), and PMB-Cl(17.2 ml, 1.2eq.). After stirring overnight at 25 °C, the reaction mixture was diluted with ethyl acetate (400 mL), washed with brine (600 mL x 3), dried with Na₂SO₄ and. Filtered. The filtration was concentrated under vacuum to afford 20.5 g (90.7%) of 1-(4-methoxybenzyl)-1H-pyrrole-2-carbaldehyde as yellow oil. MS (ES, *m/z*) [M+H]⁺ : 216.

[057] Step 2. 1-(4-Methoxybenzyl)-2-vinyl-1H-pyrrole.



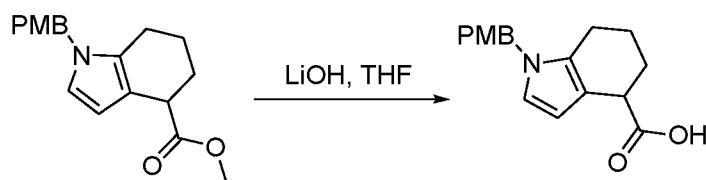
Into a 250-mL three necks round-bottom flask, was placed a slurry of NaH (1.12 g, 28 mmol, 60% oil dispersion, 1.2 eq.) in dry THF below 10 °C under nitrogen atmosphere, methyltriphenylphosphonium bromide (8.28 g, 23.3 mmol, 1.0 eq) was added. The resulting mixture was heated with stirring at 70 °C for 1 h. Upon cooled below 35 °C, a solution of 1-(4-methoxybenzyl)-1H-pyrrole-2-carbaldehyde(5.0 g, 23.2 mmol, 1.0 eq) in dry THF was added dropwise into the mixture with stirring, then heated to 70 °C and stirred for 3 h. The reaction mixture was filtered through neutral alumina with PE. The clear yellow filtrate was concentrated under vacuum to give a light yellow semi-solid residue which is taken up in PE and filtered through a cake of diatomaceous earth on neutral alumina. The resulting filtrate was concentrated under vacuum to afford 2.8 g (56.6%) of 1-(4-methoxybenzyl)-2-vinyl-1H-pyrrole as light yellow oil. MS (ES, *m/z*) [M+H]⁺ : 213.

[058] Step 3. Methyl 1-(4-methoxybenzyl)-4,5,6,7-tetrahydro-1H-indole-4-carboxylate.



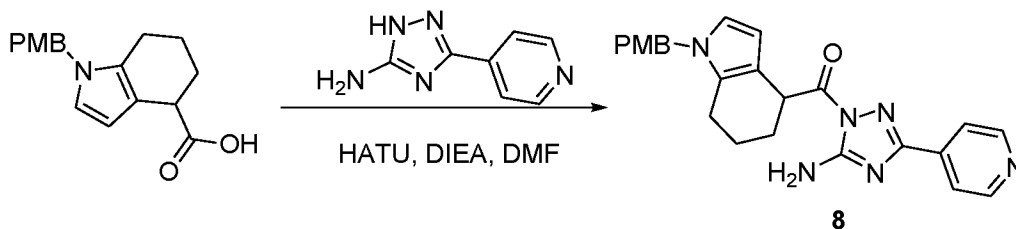
Into a 100-ml round-bottom flask, were placed 1-(4-methoxybenzyl)-2-vinyl-1H-pyrrole (1.0 g) and methyl acrylate(10 ml). The mixture was stirred overnight at 85 °C. The reaction mixture was concentrated under vacuum to afford 0.92 g (crude) of methyl 1-(4-methoxybenzyl)-4,5,6,7-tetrahydro-1H-indole-4-carboxylate as light yellow oil. MS (ES, *m/z*) [M+H]⁺ : 300.

[059] Step 4. 1-(4-Methoxybenzyl)-4,5,6,7-tetrahydro-1H-indole-4-carboxylic acid.



Into a 100- ml round-bottom flask, were placed methyl 1-(4-methoxybenzyl)-4,5,6,7-tetrahydro-1H-indole-4-carboxylate (0.92 g, 1.0 eq. 50% purity), LiOH (0.7 g, 19.0 eq.), MeOH (32 ml), THF (8 ml) and water (10 mL). The mixture was stirred overnight. The organic phase was concentrated under vacuum. The residue was diluting with water (20 mL) and extracted by EA (15 mL x 3). The aqueous phases were combined, adjusted PH to 4 with aq. HCl (1 mol/L) and extracted by EA (50 mL x3). The combined organic phase was concentrated under vacuum. The residue was purified by Prep-TLC with ethyl acetate/petroleum ether (1:1). The collected fraction was concentrated to afford 340 mg (85% purity) of 1-(4-methoxybenzyl)-4,5,6,7-tetrahydro-1H-indole-4-carboxylic acid as a yellow solid. MS (ES, m/z) $[M+H]^+$: 286.

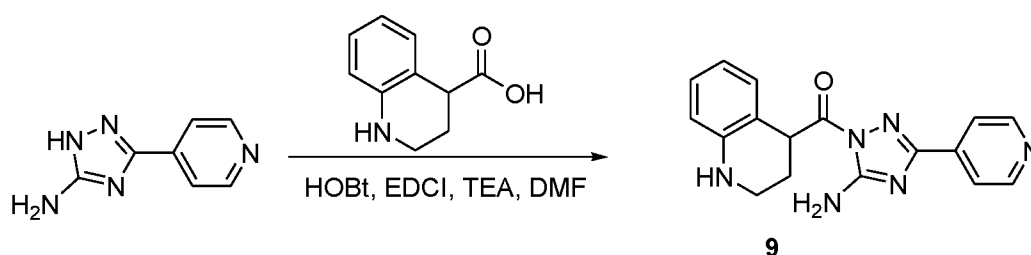
[060] Step 5. (5-Amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1-(4-methoxybenzyl)-4,5,6,7-tetrahydro-1H-indol-4-yl)methanone.



Into a 50-mL round-bottom flask, were placed 1-(4-methoxybenzyl)-4,5,6,7-tetrahydro-1H-indole-4-carboxylic acid (75 mg, 85% purity, 0.22 mmol, 0.90 eq.) in N,N-dimethylformamide (3 mL), HATU (113.6 mg, 2.99 mmol, 1.20 eq.) and DIEA (96.1 mg, 0.74 mmol, 3.00 eq). The mixture was stirred for 30 min at room temperature (20 °C). Then 3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine (40 mg, 0.25 mmol, 1.00 eq) was added. The resulting mixture was stirred overnight at 25 °C. The reaction mixture was diluted with DCM (80 mL), washed with H₂O (50 mL x 3) and brine (50 mL x 3) and dried with Na₂SO₄. After filtration, the filtrate was concentrated under vacuum. The residue was purified by TLC with ethyl acetate/petroleum ether (1:1). The crude product was further purified by Prep-HPLC with the following conditions (Analyse HPLC-SHIMADZU): Column, XBridge Shield RP18 OBD Column, 5μm, 19mm x 150mm; mobile phase, Waters (0.1%FA) and ACN (35.0% ACN

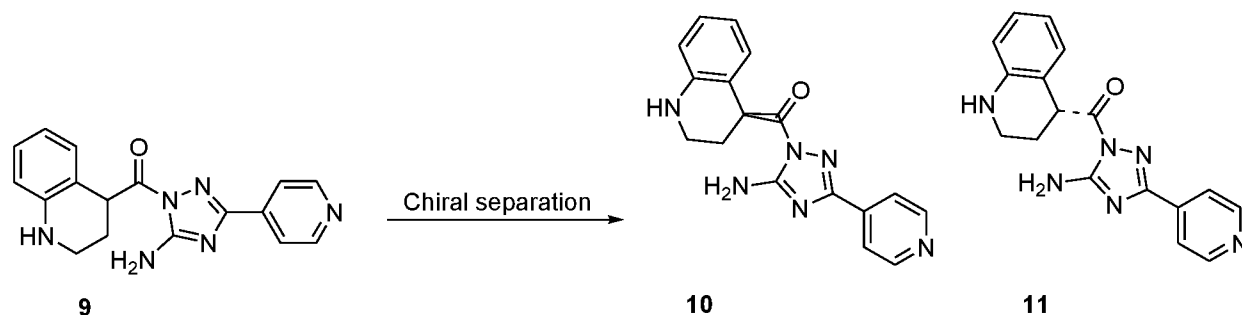
up to 60.0% in 7 min); Detector, 254 & 220nm. The collected fraction was lyophilized to give 18.4 mg (17%) of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1-(4-methoxybenzyl)-4,5,6,7-tetrahydro-1H-indol-4-yl)methanone (**8**) as a yellow solid. MS (ES, m/z) $[M+H]^+$: 429; ^1H NMR (DMSO- d_6 , 300MHz, ppm): δ 8.74 (d, $J=6.3\text{Hz}$, 2H); 7.96-7.94 (m, 2H); 7.77 (s, 2H); 7.06(d, $J=8.7\text{Hz}$, 2H); 6.91-6.87(m, 2H); 6.65(d, $J=3.0\text{Hz}$, 1H); 5.75(d, $J=2.7\text{Hz}$, 1H); 4.93(s, 2H); 4.76-4.72(m, 1H); 3.73(s, 3H); 2.49-2.37(m, 2H); 2.07-1.95(m, 3H); 1.85-1.69(m, 1H).

[061] Example 9. Synthesis of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1,2,3,4-tetrahydroquinolin-4-yl)methanone



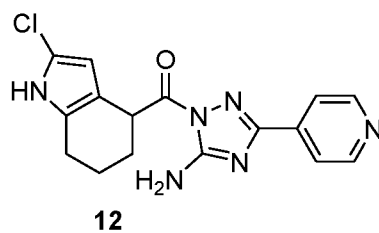
Into a 50-mL round-bottom flask, was placed 1,2,3,4-tetrahydroquinoline-4-carboxylic acid (50 mg, 0.28 mmol, 1.00 equiv), HOBT (57 mg, 0.42 mmol, 1.50 equiv), EDCI (81 mg, 0.42 mmol, 1.50 equiv), TEA (86 mg, 0.85 mmol, 3.00 equiv), N,N-dimethylformamide (3 mL). The resulting solution was stirred for 30 min at room temperature (19 °C). This was followed by the addition of 3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine (45 mg, 0.28 mmol, 1.00 equiv). The resulting solution was allowed to react, with stirring for overnight at room temperature (19 °C). The reaction was then quenched by the addition of water (40 mL). The resulting solution was extracted with ethyl acetate (50 mL x 3) and concentrated under vacuum. The residue was purified by preparative TLC (EA:PE = 1:1) to give 15.7 mg (17%) of 3-(pyridin-4-yl)-1-[(1,2,3,4-tetrahydroquinolin-4-yl)carbonyl]-1H-1,2,4-triazol-5-amine as a light yellow solid. MS (ES, m/z) $[M+1]$: 321; ^1H NMR (DMSO- d_6 , 300MHz, ppm): δ 8.72(d, $J=8.0$, 2H); 7.91(d, $J=8.0$, 2H); 7.81(s, 2H); 6.96-6.91(m, 2H); 6.55-6.52(m, 1H); 6.43-6.38(m, 1H); 5.93(s, 1H); 4.99-4.96(m, 1H); 3.29-3.24(m, 2H); 2.23-2.08(m, 2H).

[062] Examples 10 and 11. Chiral Separation of (S*)-(5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1,2,3,4-tetrahydroquinolin-4-yl)methanone (**10**) and (R*)-(5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1,2,3,4-tetrahydroquinolin-4-yl)methanone (**11**)

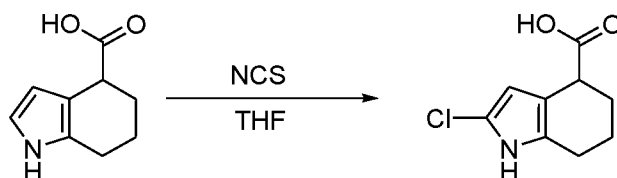


3-(pyridin-4-yl)-1-[(1,2,3,4-tetrahydroquinolin-4-yl)carbonyl]-1H-1,2,4-triazol-5-amine (170 mg, 0.53 mmol, 1.00 equiv) was purified by Chiral-Prep-HPLC with the following conditions (Hex): Column: CHIRALPAK IE, 2.0cm I.D*25cm L(5um); Mobile Phase A: Hex--HPLC, Mobile Phase B: IPA-HPLC; Flow rate: 20 mL/min; Gradient: 30 B to 30 B in 21 min; 254/220 nm. The first eluting isomer ($R_t=5.389$ min) 51.9 mg (31%) of (R^*)-(5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1,2,3,4-tetrahydroquinolin-4-yl)methanone **11** as a light yellow solid. MS (ES, m/z) [$M+1$]: 321; HNMR (DMSO- d_6 , 400MHz, ppm): δ 8.72(d, $J=6.0$, 2H); 7.91(d, $J=6.0$, 2H); 7.78(s, 2H); 6.95-6.91(m, 2H); 6.51-6.53(m, 1H); 6.43-6.38(m, 1H); 5.92(s, 1H); 4.99-4.97(m, 1H); 3.26-3.20(m, 2H); 2.24-2.17(m, 1H); 2.14-2.06(m, 1H). The second eluting isomer ($R_t=6.397$ min) was collected and lyophilized to give 53.1 mg (31%) of (S^*)-(5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1,2,3,4-tetrahydroquinolin-4-yl)methanone **10** as a light yellow solid. MS (ES, m/z) [$M+1$]: 321; HNMR (DMSO- d_6 , 400MHz, ppm): δ 8.72(d, $J=6.0$, 2H); 7.91(d, $J=6.0$, 2H); 7.78(s, 2H); 6.95-6.91(m, 2H); 6.55-6.53(m, 1H); 6.43-6.39(m, 1H); 5.91(s, 1H); 4.99-4.97(m, 1H); 3.27-3.16(m, 2H); 2.23-2.17(m, 1H); 2.12-2.05(m, 1H).

[063] Example 12. Synthesis of 1-[(2-chloro-4,5,6,7-tetrahydro-1H-indol-4-yl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine

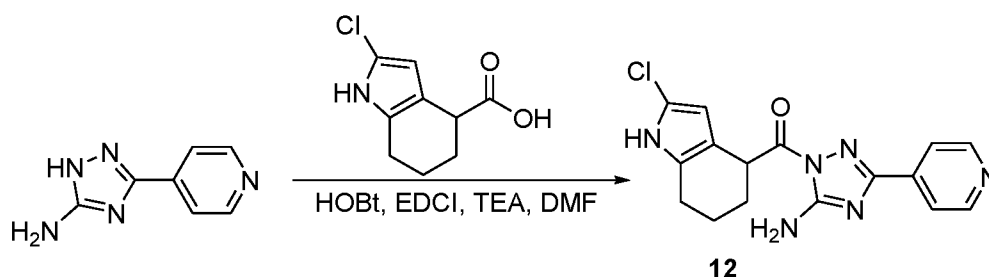


[064] Step1. 2-chloro-4,5,6,7-tetrahydro-1H-indole-4-carboxylic acid



Into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4,5,6,7-tetrahydro-1H-indole-4-carboxylic acid (500 mg, 3.03 mmol, 1.00 equiv) and tetrahydrofuran (8 mL). This was followed by the addition of a solution of 1-chloropyrrolidine-2,5-dione (365 mg, 2.73 mmol, 0.90 equiv) in tetrahydrofuran (4 mL) dropwise with stirring at -78 °C. The resulting solution was stirred for 2h at -78 °C. The reaction was then quenched by the addition of brine (30 mL). The resulting solution was extracted with ethyl acetate (30 mL x 3) and the organic layers combined. DMF (10 mL) was added and the mixture was concentrated under vacuum. The crude product was used to the next step directly without further purification.

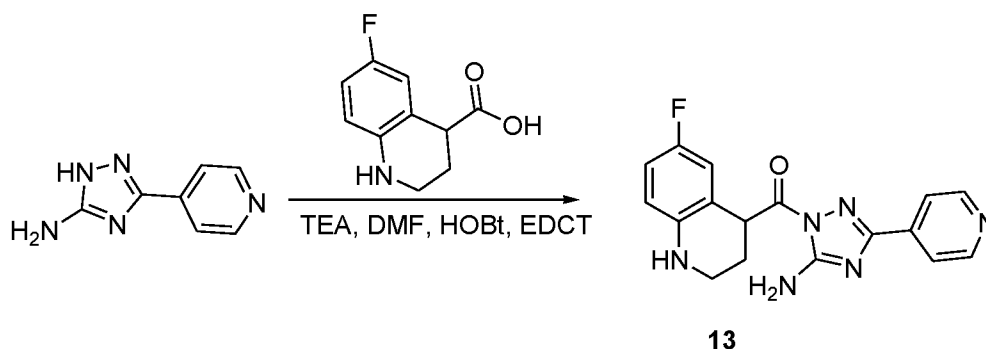
[065] Step 2. 1-[(2-chloro-4,5,6,7-tetrahydro-1H-indol-4-yl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine



Into a 25-mL round-bottom flask, was placed 2-chloro-4,5,6,7-tetrahydro-1H-indole-4-carboxylic acid (130 mg, crude) in DMF (20 mL), HOBT (132.3 mg, 0.98 mmol, 1.50 equiv), EDCI (188.1 mg, 0.98 mmol, 1.50 equiv), TEA (329.9 mg, 3.26 mmol, 5.00 equiv) and 3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine (126 mg, 0.78 mmol, 1.20 equiv). The resulting solution was stirred overnight at 25 °C. The resulting solution was diluted with EA (100 mL), washed with brine (60 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by preparative TLC (MeOH:DCM = 1:20). The crude product was repurified by Prep-HPLC with the following conditions Column: XSelect CSH Prep C18 OBD Column, 5um, 19*150mm; Mobile Phase A: Water (0.1%FA), Mobile Phase B: ACN; Flow rate: 20 mL/min; Gradient: 20% B to 50% B in 7 min; 254 nm; Rt: 6 min. The collected fraction was lyophilized to give 19.5 mg (9%) of 1-[(2-chloro-4,5,6,7-tetrahydro-1H-indol-4-yl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-

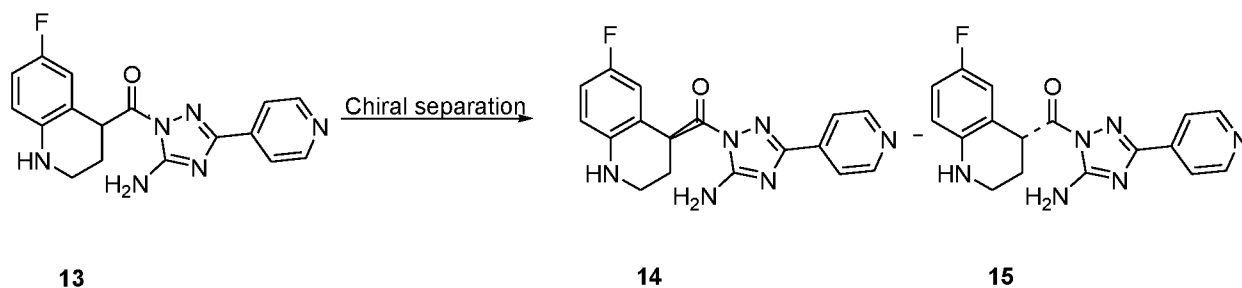
amine (**12**) as a yellow solid. MS (ES, m/z) $[M+H]^+$: 343, 345; HNMR (DMSO- d_6 , 400 MHz, ppm): 11.12 (s, 1H), 8.30 (d, $J=5.6$ Hz, 2H), 7.92 (d, $J=6.0$ Hz, 2H), 7.78 (s, 2H), 5.68 (s, 1H), 4.69-4.66 (m, 1H), 2.62 (m, 2H), 2.06-1.80 (m, 3H), 1.78-1.64 (m, 1H).

[066] Example 13. (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone



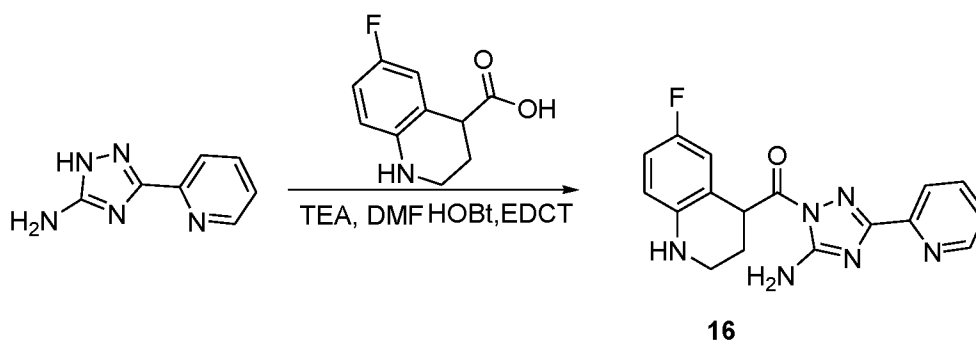
Into a 200-mL round-bottom flask, was placed 6-fluoro-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (2.0 g, 10.25 mmol, 1.00 equiv) in DMF (60 mL), HOBT (2.10 g, 15.54 mmol, 1.50 equiv), EDCI (2.94 g, 15.34 mmol, 1.50 equiv), TEA (3.11 g, 30.73 mmol, 3.00 equiv) and 3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine (1.66 g, 10.30 mmol, 1.00 equiv). The resulting mixture was stirred for 3 h at room temperature. The reaction was then quenched by the addition of 100 mL of water. The resulting solution was extracted with ethyl acetate (150mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by re-crystallization from DCM. The solids was washed with H₂O (100mL x 3) and dried to give 1.5 g (43%) of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**13**). MS (ES, m/z) $[M+H]^+$: 339; HNMR (DMSO- d_6 , 400 MHz, ppm) δ 8.74-8.72 (m, 2H), 7.93-7.91 (m, 2H), 7.81 (s, 2H), 6.90-6.79 (m, 2H), 6.55-6.52 (m, 1H), 5.86 (s, 1H), 4.94 (m, 1H), 3.20-3.19 (m, 2H), 2.23-2.09 (m, 2H).

[067] Examples 14 and 15. (S*)-(5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**14**) and (R*)-(5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**15**)



The racemic (5-amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone **13** (1.5 g, 4.4 mmol) was separated by Chiral-HPLC with the following condition : Column: Phenomenex Lux 5u Cellulose-3, 5*25cm,5um; Mobile Phase A:CO₂ :50, Mobile Phase B: IPA(HPLC):50; Flow rate: 180 mL/min; 220 nm. The first eluting isomer ($R_t=5.30$ min) was collected and concentrated to give 397.5 mg (53%) of (S*)-(5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**14**) as a yellow solid. MS (ES, m/z) [$M+H$]⁺: 339 ; HNMR (DMSO-*d*₆, 400 MHz, *ppm*): 8.74-8.72 (m, 2H), 7.93-7.91 (m, 2H), 7.81 (s, 2H), 6.89-6.79 (m, 2H), 6.55-6.52 (m, 1H), 5.87 (s, 1H), 4.94-4.92 (m, 1H), 3.20-3.19 (m, 2H), 2.24-2.13 (m, 1H), 2.12-2.08 (m, 1H). The second eluting isomer ($R_t=6.73$ min) was collected and concentrated to give 353.2 mg (47%) of (R*)-(5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**15**) as an off-white solid. MS (ES, m/z) [$M+H$]⁺: 339 ; HNMR (DMSO-*d*₆, 400 MHz, *ppm*): 8.74-8.72 (m, 2H), 7.93-7.91 (m, 2H), 7.81 (s, 2H), 6.89-6.79 (m, 2H), 6.55-6.52 (m, 1H), 5.87 (s, 1H), 4.94-4.92 (m, 1H), 3.24-3.19 (m, 2H), 2.24-2.13 (m, 1H), 2.12-2.08 (m, 1H).

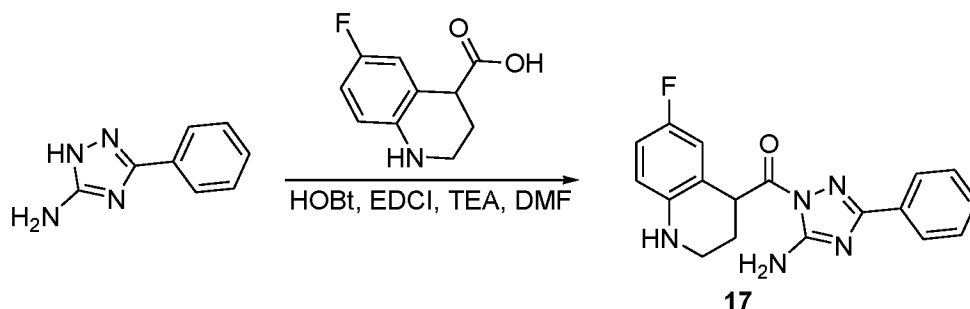
[068] Example 16. (5-amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone



Into a 100-mL round-bottom flask, was placed 6-fluoro-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (366 mg, 1.88 mmol, 1.00 equiv) in DMF (20 mL), 3-(pyridin-2-yl)-1H-

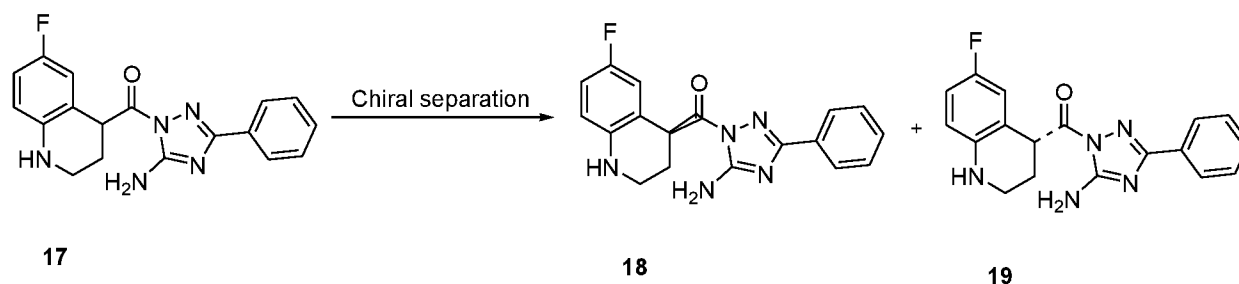
1,2,4-triazol-5-amine (300 mg, 1.86 mmol, 1.00 equiv), HOBT (381 mg, 2.82 mmol, 1.50 equiv), EDCI (534 mg, 2.79 mmol, 1.50 equiv) and TEA (939.6 g, 9.29 mol, 5.00 equiv). The resulting solution was stirred for 2.5 h at room temperature and then diluted with H₂O (100 mL). The resulting solution was extracted with ethyl acetate (100 mL x 3) and concentrated under vacuum. The residue was washed with CH₂Cl₂ (10 mL) and ethyl ether (10 mL). The solid was collected by filtration. This resulted in 144.3 mg (23%) of (5-amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**16**) as a yellow solid. MS (ES, m/z) [M+H]⁺: 339; HNMR (DMSO-*d*₆, 300MHz, ppm): δ 8.70 (d, J = 3.9 Hz, 1H), 8.06 (d, J=7.8, 1H), 7.97 (m, J = 8.0 Hz, 1H), 7.72 (s, 2H), 7.52-7.45 (m, 1H), 6.89-6.78 (m, 2H), 6.56-6.51 (m, 1H), 5.86 (s, 1H), 4.96-4.86 (m, 1H), 3.21-3.16 (m, 2H), 2.23-2.07 (m, 2H).

[069] Example 17. (5-amino-3-phenyl-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone



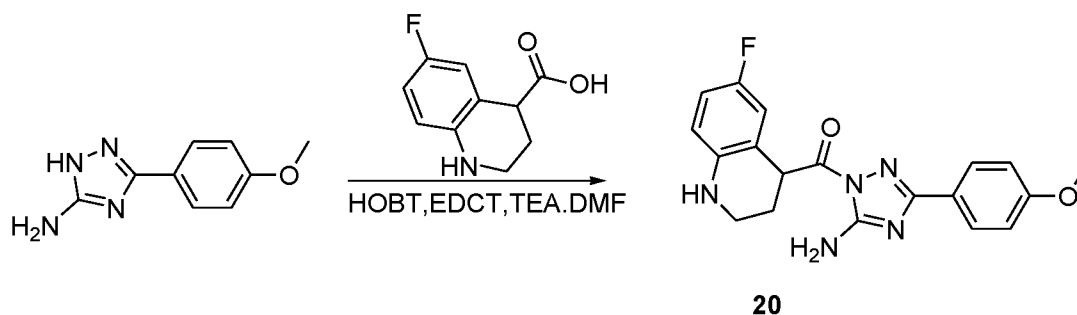
Into a 50-mL round-bottom flask, was placed 3-phenyl-1H-1,2,4-triazol-5-amine (246 mg, 1.54 mmol, 1.00 equiv) in DMF (15 mL), HOBT (311 mg, 2.30 mmol, 1.50 equiv), EDCI (440 mg, 2.30 mmol, 1.50 equiv) and triethylamine (466 mg, 4.61 mmol, 3.00 equiv). Then 6-fluoro-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (300 mg, 1.54 mmol, 1.00 equiv) was added in 2 mins later. The resulting mixture was stirred for 3 h at room temperature (25 °C). The reaction was then poured into 50 mL of water. The resulting solution was extracted with ethyl acetate (70 mL x 3), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied on a silica gel column and eluted with ethyl acetate/hexane (3/10). The collected fraction was concentrated to give 136.6 mg (26%) of (5-amino-3-phenyl-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**17**) as an off-white solid. MS (ES, m/z) [M+H]⁺: 338; HNMR (DMSO-*d*₆, 300MHz, ppm): δ 8.05-8.00 (m, 2H), 7.70 (s, 2H), 7.53-7.48(m,3H), 6.89-6.79 (m, 2H), 6.55-6.52 (m, 1H), 5.87 (s, 1H), 4.95 (m, 1H), 3.26-3.18 (m, 2H), 2.23-2.145 (m, 1H), 2.13-2.08 (m, 1H).

[070] Examples 18 and 19. (S*)-(5-amino-3-phenyl-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**18**) and (R*)-(5-amino-3-phenyl-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**19**)



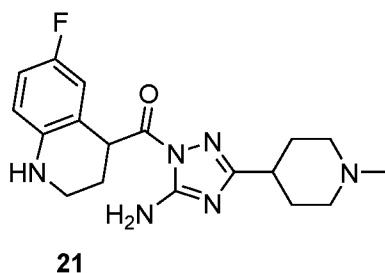
The racemic (5-amino-3-phenyl-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (PH-RU1-AT-871) (136.6 mg, 4.05x10⁻⁴ mol) was separated by Chiral-HPLC with the following condition: Column: Phenomenex Lux 5u Cellulose-4, AXIA Packed, 2.12*25cm, 5um; Mobile Phase A: Hex (HPLC), Mobile Phase B: IPA (HPLC); Flow rate: 20 mL/min; Gradient: 40 B to 40 B in 13 min; 254/220 nm; The first eluting isomer (R_t₁=5.60 min) was collected and concentrated to give 31.6 mg (46%) of (S*)-(5-amino-3-phenyl-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**18**) as a white solid. MS (ES, m/z) [M+H]⁺: 338; HNMR (DMSO-*d*₆, 400MHz, ppm): δ 8.04-8.01(m, 2H), 7.74-7.71(m, 2H), 7.52-7.48(m, 3H), 6.88-6.79(m, 2H), 6.55-6.51(m, 1H), 5.86(s, 1H), 4.98-4.92(m, 1H), 3.22-3.20(m, 2H), 2.22-2.19(m, 1H), 2.11-2.08(m, 1H). The second eluting isomer (R_t₂= 7.95 min) was collected and concentrated to give 45.2 mg (66%) of (R*)-(5-amino-3-phenyl-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**19**) as a white solid. MS (ES, m/z) [M+H]⁺: 338; HNMR (DMSO-*d*₆, 400MHz, ppm): δ 8.05-8.00(m, 2H), 7.75-7.71(m, 2H), 7.53-7.48(m, 3H), 6.89-6.79(m, 2H), 6.55-6.52(m, 1H), 5.89(s, 1H), 4.95-4.92(m, 1H), 3.26-3.18(m, 2H), 2.23-2.18(m, 1H), 2.15-2.08(m, 1H).

[071] Example 20. (5-amino-3-(4-methoxyphenyl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone

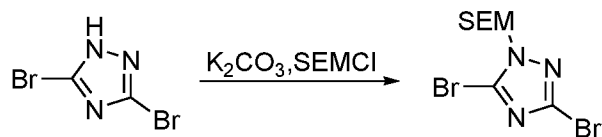


Into a 100-mL round-bottom flask, was placed 3-(4-methoxyphenyl)-1H-1,2,4-triazol-5-amine (300 mg, 1.58 mmol, 1.00 equiv) in DMF (30 mL), 6-fluoro-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (308 mg, 1.58 mmol, 1.00 equiv), HOBT (320 mg, 2.37 mmol, 1.50 equiv), EDCI (455 mg, 2.37 mmol, 1.50 equiv) and TEA (798 mg, 7.90 mmol, 5.00 equiv). The resulting mixture was stirred for 3 h at room temperature and then diluted with water with water (180 mL). The resulting solution was extracted with ethyl acetate (60 mL x 3), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by Pre-TLC (EA: PE = 1:1). The collected fraction was concentrated and the residue was washed with DCM (20 mL). The solid was filtered and dried to give 146.7 mg (25%) of (5-amino-3-(4-methoxyphenyl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**20**) as a yellow solid. MS (ES, m/z) $[M+H]^+$: 368; ¹H NMR (DMSO- d_6 , 300 MHz, ppm): δ 7.95 (d, $J=9.0$ Hz, 2H), 7.67 (s, 2H), 7.05 (d, $J=9.0$ Hz, 2H), 6.88-6.78 (m, 2H), 6.55-6.50 (m, 1H), 5.85 (s, 1H), 4.94-4.90 (m, 1H), 3.82 (s, 3H), 3.28-3.21 (m, 2H), 2.23-2.01 (m, 2H).

[072] Example 21. (5-amino-3-(1-methylpiperidin-4-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone

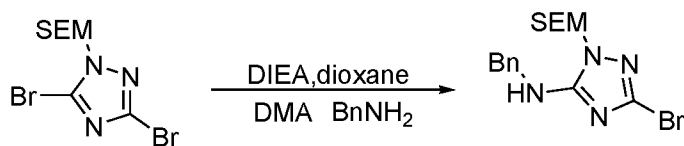


[073] Step 1. 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole



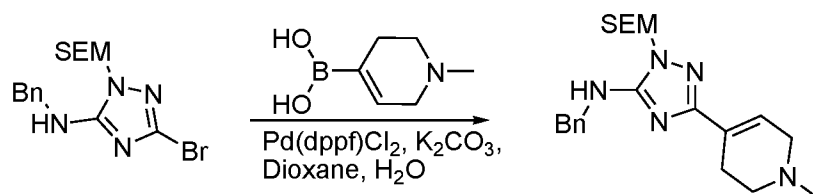
Into a 250-mL round-bottom flask, was placed 3,5-dibromo-1H-1,2,4-triazole (5 g, 22.04 mmol, 1.00 equiv) in N,N-dimethylformamide (25 mL) and potassium carbonate (9 g, 65.12 mmol, 3.00 equiv). This was followed by the addition of SEMCl (4.43 g, 26.53 mmol, 1.20 equiv) dropwise with stirring at 0 °C. The resulting mixture was stirred overnight at 25 °C. The resulting solution was diluted with 100 mL of EA, washed with 5 x 100 mL of saturated brine and concentrated. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1/10). This resulted in 7.26 g (92%) of 3,5-dibromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole as yellow oil. MS (ES, m/z) [M+H]⁺: 356, 358, 360.

[074] Step 2. N-benzyl-5-bromo-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,4-triazol-3-amine



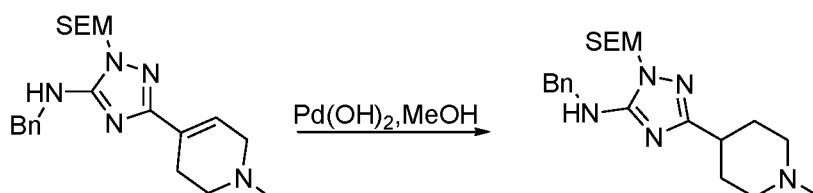
Into a 20-mL sealed tube, was placed 3,5-dibromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-1,2,4-triazole (1.5 g, 4.20 mmol, 1.00 equiv), BnNH₂ (1.8 g, 16.82 mmol, 4.00 equiv), DIEA (1.09 g, 8.43 mmol, 2.00 equiv), DMA (4 mL) and dioxane (8 mL). The resulting solution was stirred overnight at 120 °C. The mixture was cooled to room temperature and diluted with 100 mL of ethyl acetate. The resulting mixture was washed with 3 x 100 mL of water and 3x100 ml saturated brine. The ethyl acetate was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (85/15). The collected fraction was concentrated to give 1.2 g (75%) of N-benzyl-3-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-1,2,4-triazol-5-amine as yellow oil. MS (ES, m/z) [M+H]⁺: 383, 385

[075] Step 3. N-benzyl-5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,4-triazol-3-amine



Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed N-benzyl-3-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-1,2,4-triazol-5-amine (1.36 g, 3.55 mmol, 1.00 equiv) in dioxane (20 mL), Pd(dppf)Cl₂·CH₂Cl₂ (873 mg, 1.07 mmol, 0.30 equiv), potassium carbonate (1.47 g, 10.64 mmol, 3.00 equiv), water (5 mL) and 1-methyl-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (1.19 g, 5.33 mmol, 1.50 equiv). The resulting solution was stirred overnight at 100 °C. The mixture was cooled to room temperature (30 °C). The resulting solution was diluted with 60 mL of H₂O, extracted with 3 x 80 mL of dichloromethane, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with dichloromethane/methanol (10/1). The collected fraction was concentrated to give 1.4 g (99%) of N-benzyl-5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,4-triazol-3-amine as brown oil. MS (ES, m/z) [M+H]⁺: 400.

[076] Step 4. N-benzyl-5-(1-methylpiperidin-4-yl)-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,4-triazol-3-amine



Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of H₂, was placed N-benzyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-1,2,4-triazol-5-amine (1.4 g, 3.50 mmol, 1.00 equiv) in methanol (20 mL), Pd(OH)₂ (1.4 g, 9.97 mmol, 2.85 equiv) and AcOH (2 mL). The resulting solution was stirred for 3 h at 25 °C. The solids were filtered out. The filtrate was concentrated under vacuum. This resulted in 1.4 g (99%) of N-benzyl-5-(1-methylpiperidin-4-yl)-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,4-triazol-3-amine as yellow oil. MS (ES, m/z) [M+H]⁺: 402.

[077] Step 5. N-benzyl-5-(1-methylpiperidin-4-yl)-2H-1,2,4-triazol-3-amine



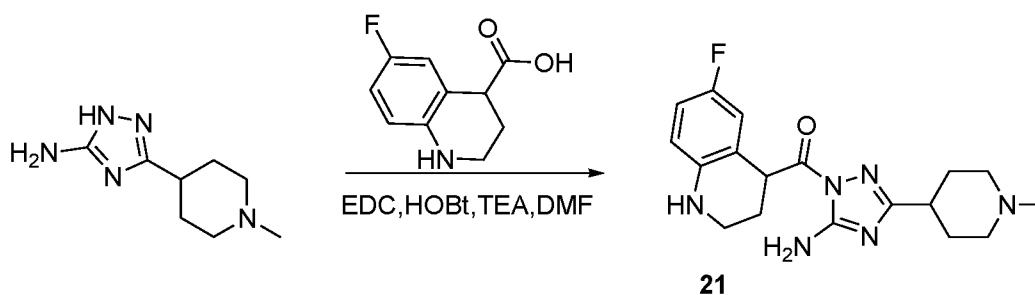
Into a 250-mL round-bottom flask, was placed N-benzyl-3-(1-methylpiperidin-4-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-1,2,4-triazol-5-amine (1.4 g, 3.49 mmol, 1.00 equiv), dichloromethane (10 mL). This was followed by the addition of trifluoroacetic acid (5 mL) dropwise with stirring at 0 °C. The resulting solution was stirred for 4 h at 20 °C. The resulting mixture was concentrated under vacuum to give 1.4 g (crude) of N-benzyl-5-(1-methylpiperidin-4-yl)-2H-1,2,4-triazol-3-amine as yellow oil which can be used to the next step without any purification. MS (ES, m/z) [M+H]⁺: 272.

[078] Step 6. 5-(1-methylpiperidin-4-yl)-2H-1,2,4-triazol-3-amine



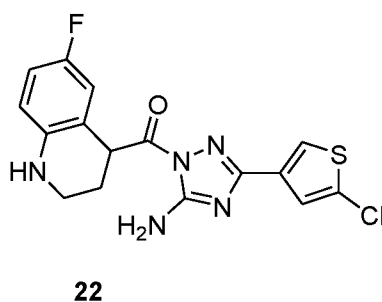
Into a 250-mL round-bottom flask, was placed N-benzyl-3-(1-methylpiperidin-4-yl)-1H-1,2,4-triazol-5-amine (1.4 g, 5.16 mmol, 1.00 equiv) and dichloromethane (10 mL). This was followed by the addition of TfOH (8 mL) dropwise with stirring at 0 °C. The resulting solution was stirred for 3 h at 25 °C. The resulting mixture was concentrated under vacuum. The crude product was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, waters (NH₄HCO₃ 10mmol/L) and ACN (0-10%) within 25 min; Detector, UV 210/220 nm. The collected fraction was concentrated under vacuum to give 450 mg (48%) of 5-(1-methylpiperidin-4-yl)-2H-1,2,4-triazol-3-amine as a white solid. MS (ES, m/z) [M+H]⁺: 182.

[079] Step 7. (5-amino-3-(1-methylpiperidin-4-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone

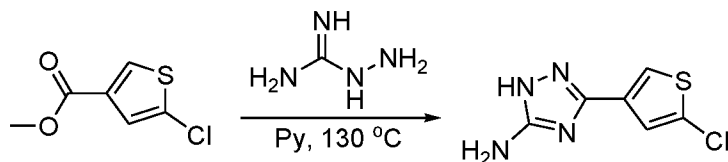


Into a 20-mL round-bottom flask, was placed 6-fluoro-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (284 mg, 1.45 mmol, 1.20 equiv) in DMF (8 mL), 3-(1-methylpiperidin-4-yl)-1H-1,2,4-triazol-5-amine (220 mg, 1.21 mmol, 1.00 equiv), HOBT (246 mg, 1.82 mmol, 1.50 equiv), EDCI (349 mg, 1.82 mmol, 1.50 equiv) and TEA (368 mg, 3.64 mmol, 3.00 equiv). The resulting solution was stirred for 3 h at 25 °C. The reaction mixture was diluted with DCM (80 mL), washed with H₂O (50 mL x 3) and brine (50 mL x 3), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, water (10mmol/L NH₄HCO₃) and ACN (5.0% ACN up to 75.0% in 45 min); Detector, UV 254/220 nm. The collected fraction was extracted with 5 x 180 mL of dichloromethane and the organic layers combined. The organic layer was concentrated under vacuum to give 115 mg (26%) of (5-amino-3-(1-methylpiperidin-4-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**21**) as a white solid. MS (ES, m/z) [M+H]⁺: 359; HNMR (DMSO-d₆, 400MHz, ppm): δ 7.50 (s, 2H), 6.82-6.77 (m, 2H), 6.53-6.49 (m, 1H), 5.81 (s, 1H), 4.79-4.76 (m, 1H), 3.32-3.14 (m, 2H), 2.81-2.67 (m, 2H), 2.50-2.47 (m, 1H), 2.18 (s, 3H), 2.15-1.99 (m, 4H), 1.95-1.82 (m, 2H), 1.80-1.65 (m, 2H).

[080] Example 22. (5-amino-3-(5-chlorothiophen-3-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone

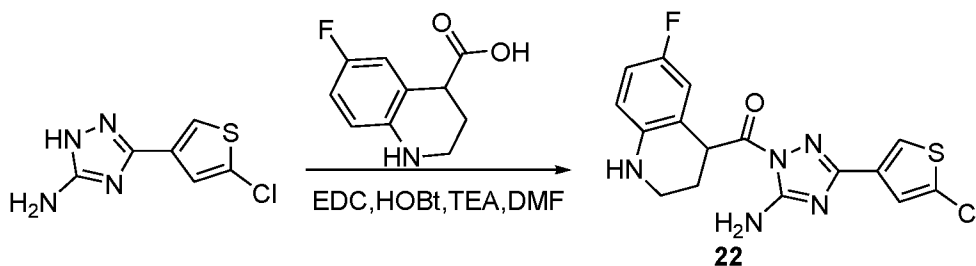


[081] Step 1. 5-(5-chlorothiophen-3-yl)-2H-1,2,4-triazol-3-amine



Into a 100-mL round-bottom flask, was placed methyl 5-chlorothiophene-3-carboxylate (500 mg, 2.83 mmol, 1.00 equiv), pyridine (20 mL), aminoguanidine bicarbonate (966 mg, 7.10 mmol, 2.50 equiv). The resulting solution was stirred overnight at 130 °C. The mixture was cooled at 30 °C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with dichloromethane/methanol (20/1). The collected fraction was concentrated to give 150 mg (26%) of 3-(5-chlorothiophen-3-yl)-1H-1,2,4-triazol-5-amine as a yellow solid. MS (ES, m/z) $[M+H]^+$: 201

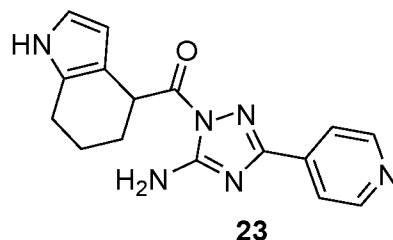
[082] Step 2. (5-amino-3-(5-chlorothiophen-3-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)methanone



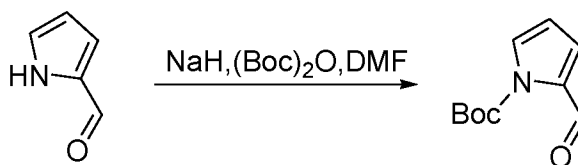
Into a 50-mL round-bottom flask, was placed 6-fluoro-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (150 mg, 0.77 mmol, 1.00 equiv) in DMF (5 mL), 3-(5-chlorothiophen-3-yl)-1H-1,2,4-triazol-5-amine (176 mg, 0.88 mmol, 1.20 equiv), HOBT (153 mg, 1.13 mmol, 1.50 equiv), EDCI (217 mg, 1.13 mmol, 1.50 equiv) and TEA (379 mg, 3.75 mmol, 5.00 equiv). The resulting solution was stirred for 4 h at 25 °C. The resulting solution was diluted with 80 mL of ethyl acetate, washed with H₂O (50 mL x 5) and brine (50 mL x 5), dried with Na₂SO₄, filtered and concentrated under reduced pressure. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1/1). The collected fraction was concentrated to give 70 mg (24%) of 3-(5-chlorothiophen-3-yl)-1-[(6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)carbonyl]-1H-1,2,4-triazol-5-amine (**22**) as a yellow solid.

MS (ES, m/z) $[M+H]^+$: 378, 380; (DMSO- d_6 , 300MHz, ppm): δ 8.02 (s, 1H), 7.92 (s, 2H), 7.67 (s, 1H), 6.93-6.76 (m, 2H), 6.53-6.48 (m, 1H), 5.81 (s, 1H), 4.88-4.84 (m, 1H), 3.31-3.18 (m, 2H), 2.25-1.97 (m, 2H).

[083] Example 23. Synthesis of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(4,5,6,7-tetrahydro-1H-indol-4-yl)methanone

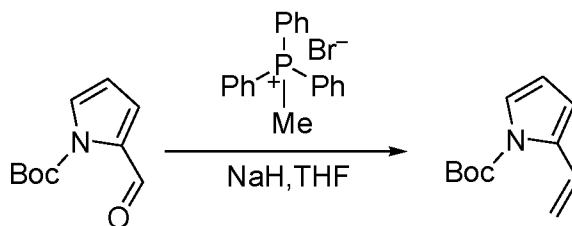


[084] Step 1. Tert-butyl 2-formyl-1H-pyrrole-1-carboxylate.



Into a 100-mL 3-necked round-bottom flask, was placed 1H-pyrrole-2-carbaldehyde (2.5 g, 26.29 mmol, 1.00 equiv), N,N-dimethylformamide (50 mL). This was followed by the addition of sodium hydride (1.58 g, 39.50 mmol, 1.50 equiv, 60% in oil) at 5 °C. After 10 min, a solution of (Boc)₂O (6.3 g, 28.87 mmol, 1.10 equiv) in N,N-dimethylformamide (10 mL) was added with dropwise. The resulting solution was stirred overnight at 20 °C. The reaction mixture was then poured into water/ice (150 mL). The resulting solution was extracted with ethyl acetate (100 mL x 3) and the organic layers combined. The resulting mixture was washed with brine (200 mL x 3), dried over anhydrous sodium sulfate and concentrated to give in 4.0 g (78%) of tert-butyl 2-formyl-1H-pyrrole-1-carboxylate as a yellow solid. MS: (ES, *m/z*) [M+H]⁺:196.

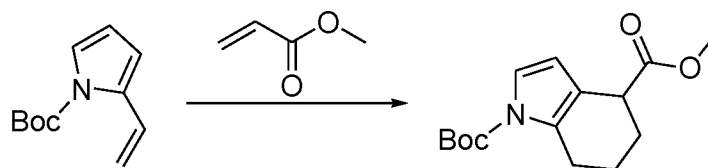
[085] Step 2. Tert-butyl 2-vinyl-1H-pyrrole-1-carboxylate.



Into a 100-mL 3-necked round-bottom flask, was placed sodium hydride (740 mg, 18.50 mmol, 1.20 equiv, 60% in oil) in dry THF (20 mL), methyltriphenyl bromide phosphonium (5.5 g, 15.45 mmol, 1.0 equiv). The resulting mixture was heated to 70 °C for 1 h. To the above was added a solution of tert-butyl 2-formyl-1H-pyrrole-1-carboxylate (3.0 g, 15.37 mmol, 1.0 equiv) in dry THF (10 mL) at 35 °C. The resulting mixture was heated to 70 °C for 3 h. The reaction mixture was filtered, and the clear yellow filtrate was concentrated under

vacuum to give a light yellow semi-solid residue which is taken up in petroleum ether and filtered through a cake of diatomaceous earth on neutral alumina. This resulted in 2.5 g (84%) of tert-butyl 2-ethenyl-1H-pyrrole-1-carboxylate as reddish crude oil. MS: (ES, m/z) $[M+H]^+$:194.

[086] Step 3. 1-tert-butyl 4-methyl 4,5,6,7-tetrahydroindole-1,4-dicarboxylate.



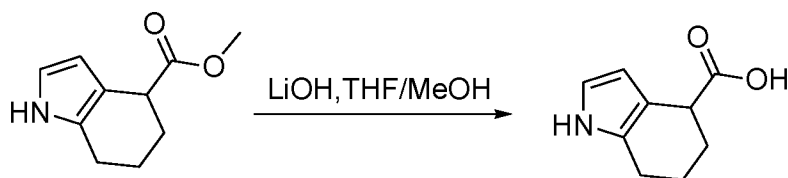
Into a 100-mL round-bottom flask, was placed tert-butyl 2-ethenyl-1H-pyrrole-1-carboxylate (8.41 g, 43.52 mmol, 1.00 equiv), methyl prop-2-enoate (7.49 g, 87.00 mmol, 2.00 equiv). The resulting solution was stirred for 3.0 h at 80 °C. The reaction mixture was cooled to 25 °C and then concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (0-4%). The collected fraction was concentrated to give 0.902 g (7.4%) of 1-tert-butyl 4-methyl 4,5,6,7-tetrahydro-1H-indole-1,4-dicarboxylate as light yellow oil. MS: (ES, m/z) $[M+H]^+$:280.

[087] Step 4. Methyl 4,5,6,7-tetrahydro-1H-indole-4-carboxylate.



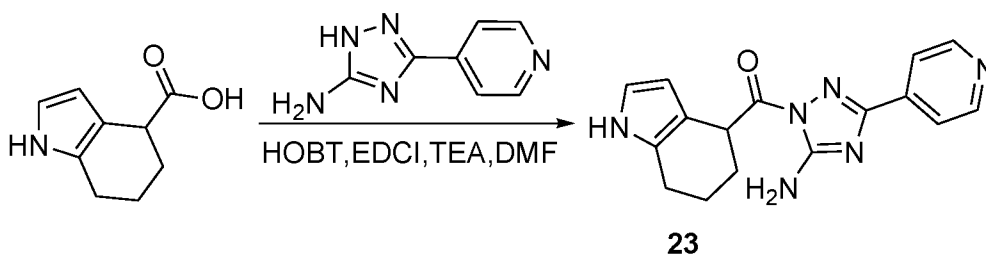
Into a 50-mL round-bottom flask, was placed a solution of 1-tert-butyl 4-methyl 4,5,6,7-tetrahydro-1H-indole-1,4-dicarboxylate (600 mg, 2.15 mmol, 1.00 equiv) in dichloromethane (15 mL) and CF_3COOH (3 mL). The resulting solution was stirred for 1.5 h at 25 °C. The reaction was then poured into 50 mL of sat. $NaHCO_3$. The resulting solution was extracted with dichloromethane (50 mL x 3) and the organic layers combined. The resulting mixture was washed with brine (200 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with MeOH/ CH_2Cl_2 (0-5%). The collected fraction was concentrated to give 100 mg (26%) of methyl 4,5,6,7-tetrahydro-1H-indole-4-carboxylate as light yellow oil. MS: (ES, m/z) $[M+H]^+$:180.

[088] Step 5. 4,5,6,7-tetrahydro-1H-indole-4-carboxylic acid.



Into a 50-mL round-bottom flask, was placed methyl 4,5,6,7-tetrahydro-1H-indole-4-carboxylate (180 mg, 1.00 mmol, 1.00 equiv), THF/MeOH (4/1) (10 mL). To this was added a solution of LiOH (104.8 L, 4.00 equiv) in water (5 mL). The resulting solution was stirred overnight at 20 °C. The resulting mixture was concentrated under vacuum to remove the THF. The resulting solution was extracted with ethyl acetate (30 mL x 2) and the aqueous layers combined. The pH value of the solution was adjusted to 6 with HCl (1 mol/L). The resulting solution was extracted with ethyl acetate (30 mL x 3). The organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 80 mg (48%) of 4,5,6,7-tetrahydro-1H-indole-4-carboxylic acid as light yellow solid which was used to the next step without any purification. MS: (ES, m/z) $[M+H]^+$: 166.

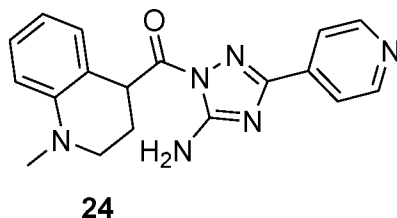
[089] Step 6. (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(4,5,6,7-tetrahydro-1H-indol-4-yl)methanone.



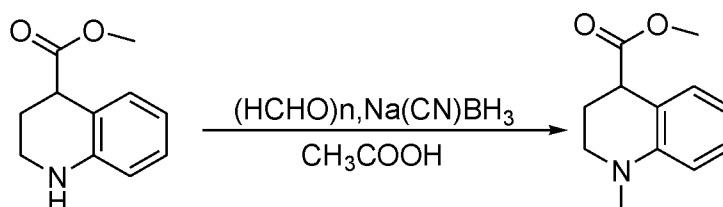
Into a 50-mL round-bottom flask, was placed 4,5,6,7-tetrahydro-1H-indole-4-carboxylic acid (40 mg, 0.24 mmol, 0.90 equiv) in N,N-dimethylformamide (3 mL), 3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine (43.4 mg, 0.27 mmol, 1.00 equiv), HOBT (53.2 mg, 0.39 mmol, 1.50 equiv), EDCI (77.6 mg, 0.40 mmol, 1.50 equiv) and TEA (136.1 mg, 1.34 mmol, 5.00 equiv). The resulting solution was stirred overnight at 25 °C. The resulting solution was diluted with EA (100 mL). The resulting mixture was washed with brine (120 mL x 2), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (HPLC-SHIMADZU): Column, XBridge Shield RP18 OBD Column, 5 μ m, 19*150mm; mobile phase, water (0.1% FA) and CAN (40% ACN up to 70% in 8 min); Detector, UV 254 nm. The collected fraction was lyophilized to give 14.9 mg (18%) of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(4,5,6,7-tetrahydro-1H-

indol-4-yl)methanone (**23**) as an off-white solid. MS: (ES, m/z) $[M+H]^+$:309; HNMR (DMSO, 400MHz, ppm): δ 10.46(s, 1H); 8.72-8.70(m, 2H), 7.90-7.89(m, 2H), 7.73(s, 2H), 6.49-6.48(m, 1H), 5.71-5.70(m, 1H), 4.76-4.73(m, 1H), 2.56-2.54(m, 2H), 2.06-1.99(m, 3H), 1.80-1.75(m, 1H).

[090] Example 24. Synthesis of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)methanone

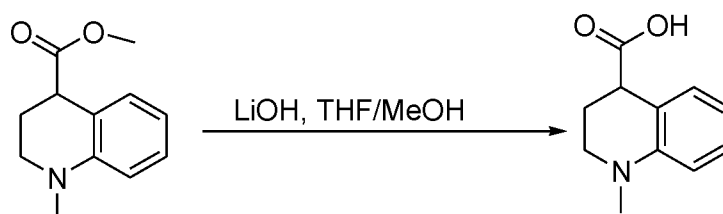


[091] Step 1. Methyl 1-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate.



Into a 50-mL round-bottom flask, was placed methyl 1,2,3,4-tetrahydroquinoline-4-carboxylate (200 mg, 1.05 mmol, 1.00 equiv), (HCHO) $_n$ (471.2 mg, 15.71 mmol, 15.00 equiv), acetic acid (10 mL). The mixture was stirred for 5 min, then Na(CN)BH₃ (329.8 mg, 5.23 mmol, 5.00 equiv) was added. The resulting solution was stirred overnight at room temperature (20 °C). The solids were filtered out. The filtrate was concentrated under vacuum. The residue was purified by preparative TLC with ethyl acetate/petroleum ether (1:1). This resulted in 140 mg (65%) of methyl 1-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate as yellow oil. MS: (ES, m/z) $[M+H]^+$:206

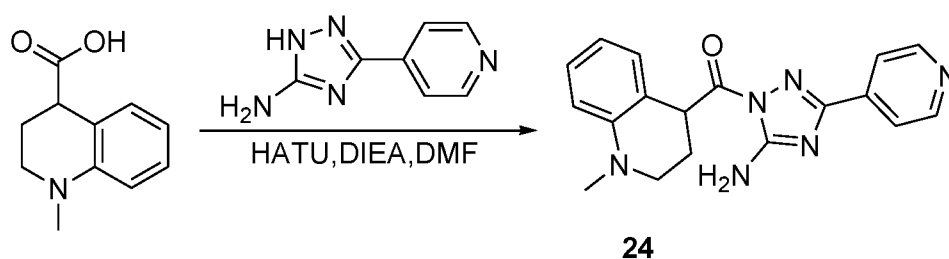
[092] Step 2. 1-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acid.



Into a 100-mL round-bottom flask, was placed methyl 1-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (140 mg, 0.68 mmol, 1.00 equiv), MeOH/THF(4/1) (20 mL), a solution of

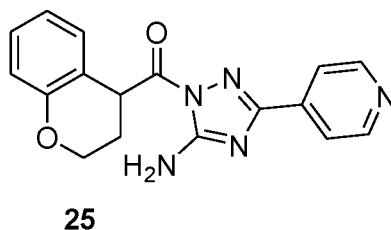
LiOH (131.1 mg, 5.47 mmol, 8.00 equiv) in H₂O (10 mL). The resulting solution was stirred overnight at room temperature (20 °C). The resulting mixture was concentrated under vacuum. The residue was extracted with ethyl acetate (30 mL) and the aqueous layers combined. HCl (1 mol/L) was employed to adjust the pH to 4. The resulting solution was extracted with ethyl acetate (40 mL x 3). The organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum to give 110 mg (84%) of 1-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acid as a reddish solid which was used to the next step without any purification. MS: (ES, *m/z*) [M+H]⁺: 192

[093] Step 3. (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)methanone.

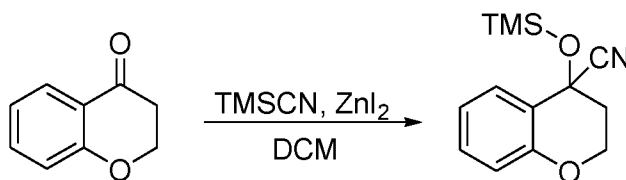


Into a 50-mL round-bottom flask, was placed 1-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acid (42.7 mg, 0.22 mmol, 0.90 equiv) in N,N-dimethylformamide (3 mL), HATU (141.6 mg, 0.37 mmol, 1.50 equiv) and DIEA (160.2 mg, 1.24 mmol, 5.00 equiv). The mixture was stirred for 30 min at room temperature. Then 3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine (40 mg, 0.25 mmol, 1.00 equiv) was added. The resulting solution was stirred overnight at room temperature (20 °C). The resulting solution was diluted with ethyl acetate (80 mL). The resulting mixture was washed with brine (120 mL x 2), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:1). The crude product was repurified by Prep-HPLC with the following conditions (HPLC-SHIMADZU): Column, Select CSH F-phenyl OBD Column, 19 x 250 mm, 5 μm; mobile phase, water (0.1%FA) and ACN (5.0% ACN up to 55.0% in 7 min); Detector, UV 254&220 nm. The collected fraction was lyophilized to give 9.9 mg (12%) (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)methanone (**24**) as an off-white solid. MS (ES, *m/z*) [M+H]⁺: 335; HNMR (DMSO, 400MHz, *ppm*): δ 8.72(d, J=5.6Hz, 2H), 7.91(d, J=6.0Hz, 2H), 7.81-7.76(m, 2H), 7.11-7.07(m, 1H), 6.99(d, J=7.6Hz, 1H), 6.68(d, J=8.4Hz, 1H), 6.55-6.51(m, 1H), 5.02-4.99(m, 1H), 3.35-3.29(m, 1H), 3.26-3.20(m, 1H), 2.88(s, 3H), 2.30-2.20(m, 2H).

[094] Example 25. Synthesis of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(chroman-4-yl)methanone

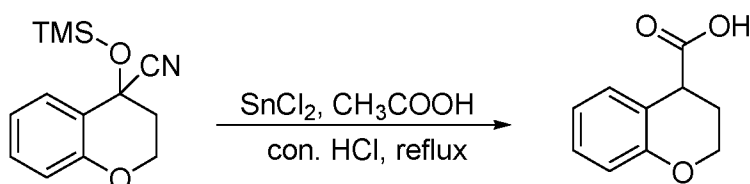


[095] Step 1. 4-(trimethylsilyloxy)chroman-4-carbonitrile



Into a 250-mL round-bottom flask, was placed 3,4-dihydro-2H-1-benzopyran-4-one (2 g, 13.50 mmol, 1.00 equiv), ZnI_2 (8.6 g, 26.94 mmol, 2.00 equiv), dichloromethane (40 mL). This was followed by the addition of TMSCN (2 g, 20.20 mmol, 1.50 equiv) dropwise with stirring at 0 °C. The resulting solution was stirred overnight at room temperature. The resulting mixture was washed with sat. NaHCO_3 (50 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. This resulted in 1.5 g (45%) of 4-(trimethylsilyloxy)chroman-4-carbonitrile as a yellow solid.

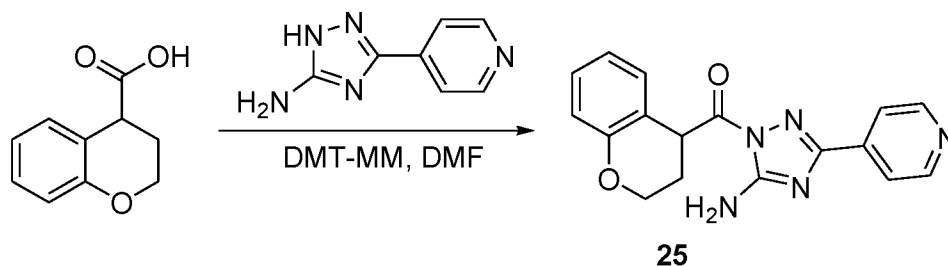
[096] Step 2. Chroman-4-carboxylic acid



Into a 100-mL round-bottom flask, was placed 4-[(trimethylsilyl)oxy]-3,4-dihydro-2H-1-benzopyran-4-carbonitrile (1.5 g, 6.06 mmol, 1.00 equiv), $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (5.5 g, 24.37 mmol, 4.00 equiv), AcOH (10 mL), con. HCl (10 mL). The resulting solution was stirred for 3 days at 115 °C. The resulting solution was cooled to 18 °C and diluted with water (50 mL). The resulting solution was extracted with ethyl acetate (100 mL x 2). The organic layers combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether

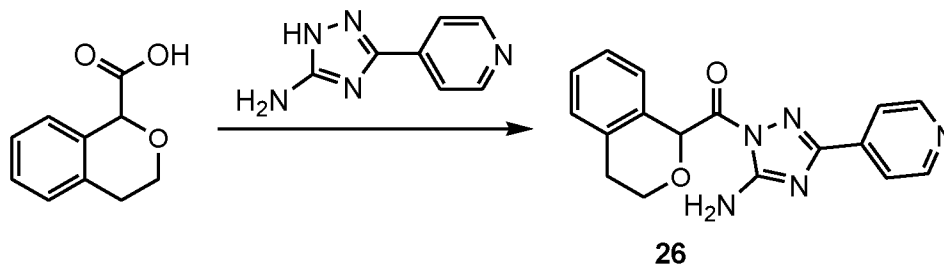
(1/2). The collected fraction was concentrated to give 400 mg (37%) of chroman-4-carboxylic acid as a yellow solid. MS (ES, m/z) $[M+H]^+$: 179.

[097] Step 3. (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(chroman-4-yl)methanone



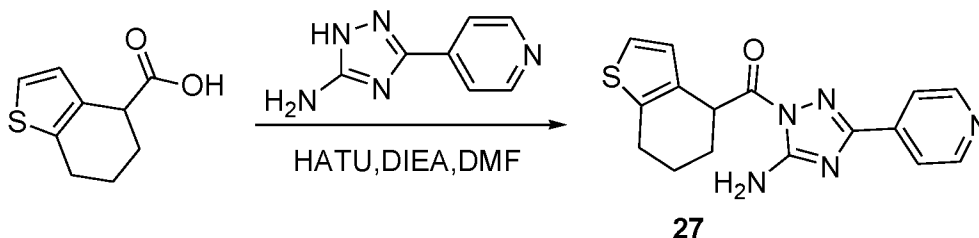
Into a 50 mL of round bottom flask, was placed dihydro-2H-1-benzopyran-4-carboxylic acid (133 mg, 0.72 mmol, 3.00 equiv), N,N-dimethylformamide (5 mL), DMTMM (206 mg, 0.74 mmol, 3.00 equiv). The mixture was stirred for 30 min at room temperature. Then 3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine (40 mg, 0.25 mmol, 1.00 equiv) was added. The resulting solution was stirred overnight at 35 °C. The reaction was then quenched by the addition of water (30 mL). The resulting solution was extracted with ethyl acetate (30 mL x 3) and the organic layers combined. The resulting mixture was washed with brine (50 mL x 3). The mixture was dried over anhydrous sodium sulfate. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was washed with 10 mL of PE/EA (30:1) to give 5.4 mg (7%) of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(chroman-4-yl)methanone (**25**) as a light yellow solid. MS (ES, m/z) $[M+H]^+$: 322; HNMR (DMSO- d_6 , 400MHz, ppm): δ 8.73(d, $J=4.4$, 2H), 7.92(d, $J=5.6$, 2H), 7.88-7.84(m, 2H), 7.20-7.15(m, 2H), 6.86-6.82(m, 2H), 5.08-5.05(m, 1H), 4.26-4.19(m, 2H), 2.41-2.30(m, 2H).

[098] Example 26. Synthesis of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(isochroman-1-yl)methanone



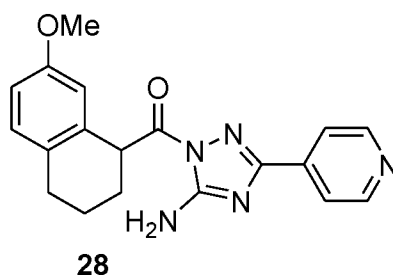
5-Amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(isochroman-1-yl)methanone may be prepared in analogous fashion to Example 25, substituting 3,4-dihydro-1H-isochromene-1-carboxylic acid for dihydro-2H-1-benzopyran-4-carboxylic acid.

[0099] Example 27. Synthesis of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(4,5,6,7-tetrahydrobenzo [b]thiophen-4-yl) methanone

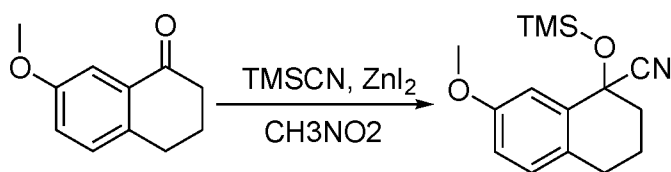


Into a 50-mL round-bottom flask, was placed 4,5,6,7-tetrahydro-1-benzothiophene-4-carboxylic acid (50.8 mg, 0.28 mmol, 0.90 equiv), HATU (177 mg, 0.47 mmol, 1.50 equiv), N,N-dimethylformamide (3 mL), DIEA (120.2 mg, 0.93 mmol, 3.00 equiv). The mixture was stirred for 30 min at 25 °C. Then 3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine (50 mg, 0.31 mmol, 1.00 equiv) was added. The resulting solution was stirred overnight at 25 °C and diluted with EA (80 mL). The resulting mixture was washed with brine (120 mL x 2), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU (HPLC-10)): Column, XBridge Shield RP18 OBD Column, 5um, 19 x150 mm; mobile phase, water (0.1%FA) and ACN (20.0% ACN up to 50.0% in 7 min); Detector, UV 254/220nm. The collected fraction was lyophilized to give 27.9 mg (28%) of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(4,5,6,7-tetrahydrobenzo[b]thiophen-4-yl)methanone (**27**) as a light yellow solid. MS (ES, *m/z*) [*M*+*H*]⁺: 326; HNMR (DMSO, 400MHz, *ppm*): δ 8.72(d, *J*=6.0Hz, 2H), 7.91-7.90(m, 2H), 7.81(s, 2H), 7.26(d, *J*=5.2Hz, 1H), 6.83(d, *J*=5.2Hz, 1H), 4.90-4.87(m, 1H), 2.85-2.80(m, 2H), 2.23-2.16(m, 1H), 2.08-1.98(m, 2H), 1.90-1.81(m, 1H).

[0100] Example 28. Synthesis of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanone

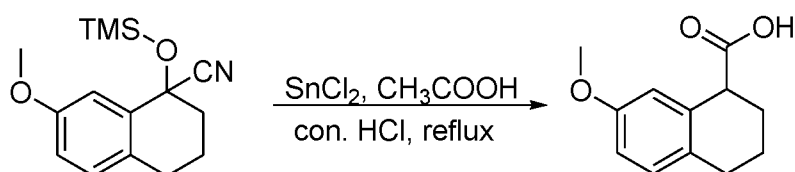


[0101] Step 1. 7-methoxy-1-(trimethylsilyloxy)-1,2,3,4-tetrahydronaphthalene-1-carbonitrile



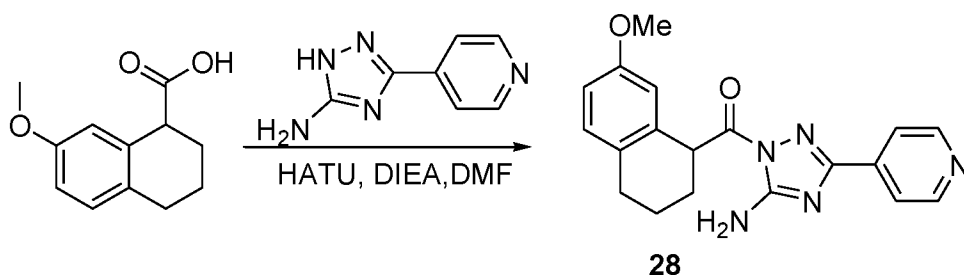
Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 7-methoxy-1,2,3,4-tetrahydronaphthalen-1-one (1 g, 5.67 mmol, 1.00 equiv), CH₃NO₂ (4 mL) and ZnI₂ (400 mg, 1.25 mmol, 0.22 equiv). This was followed by the addition of TMSCN (1.8 g, 3.20 equiv) at 0 °C. The resulting solution was stirred for 4 days at room temperature. The resulting solution was diluted with water (40 mL), extracted with dichloromethane (250 mL) and the organic layers combined. The resulting mixture was washed with brine (100 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. This resulted in 1.69 g (crude) of 7-methoxy-1-(trimethylsilyloxy)-1,2,3,4-tetrahydronaphthalene-1-carbonitrile as brown oil which can be used to the next step with any purification.

[0102] Step 2. 7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid



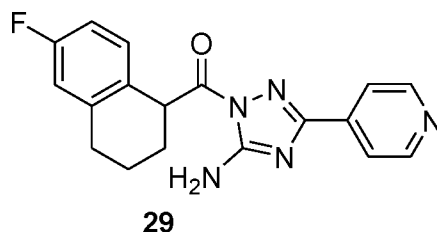
Into a 100-mL round-bottom flask, was placed [(7-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)oxy]trimethylsilane (1.67 g, 6.32 mmol, 1.00 equiv), SnCl₂·2H₂O (10 g, 44.32 mmol, 7.30 equiv), AcOH (10 mL), HCl (36.5%, 10 mL). The resulting solution was stirred for 3 days at 110 °C. The reaction mixture was cooled to room temperature. The resulting solution was diluted with 10 mL of water, extracted with dichloromethane (100 mL x 2) and the organic layers combined. The resulting mixture was washed with brine (100 mL x 2), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1/5). The collected fraction was concentrated to give 60 mg (5%) of 7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid as brown oil. MS (ES, *m/z*): 207[M+H]⁺

[0103] Step 3. (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanone

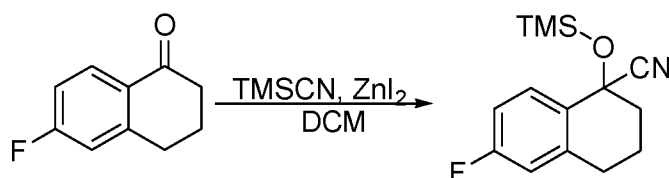


Into a 50-mL round-bottom flask, was placed 7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (40 mg, 0.19 mmol, 0.90 equiv), N,N-dimethylformamide (3 mL), HATU (125 mg, 0.33 mmol, 1.50 equiv) and DIEA (85 mg, 0.66 mmol, 3.00 equiv). The mixture was stirred for 30 min at room temperature (19 °C). Then 3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine (35 mg, 0.22 mmol, 1.00 equiv) was added. The resulting solution was stirred overnight at room temperature (19 °C). The resulting solution was diluted with 30 mL of EA, washed with H₂O (50 mL x 3) and brine (50 mL x 3), dried with Na₂SO₄ filtered and concentrated under reduced pressure. The crude product was purified by Prep-TLC with ethyl acetate/petroleum ether (1/1). The crude product was repurified by Prep-HPLC with the following conditions (2#-AnalyseHPLC- SHIMADZU (HPLC-10)): Column, XBridge Shield RP18 OBD Column, 5um, 19x150mm; mobile phase, water (0.1%FA) and ACN (20.0% ACN up to 40.0% in 10 min); Detector, UV 254/220nm. The collected fraction was lyophilized to give 3.4 mg (4%) of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanone (**28**) as off-white solid. MS (ES, *m/z*) [M+H]⁺: 350; HNMR (400MHz, DMSO-d₆, *ppm*): δ 8.73(d, *J*=6.0Hz, 2H), 7.93-7.91 (m, 2H), 7.80 (s, 2H), 7.07 (d, *J*=8.4Hz, 1H), 6.80-6.77 (m, 1H), 6.73 (d, *J*=2.4Hz, 1H), 5.01-4.98 (m, 1H), 3.64 (s, 3H), 2.77-2.65 (m, 2H), 2.19-2.08 (m, 2H), 1.87-1.83 (m, 2H).

[0104] Example 29. Synthesis of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl)methanone

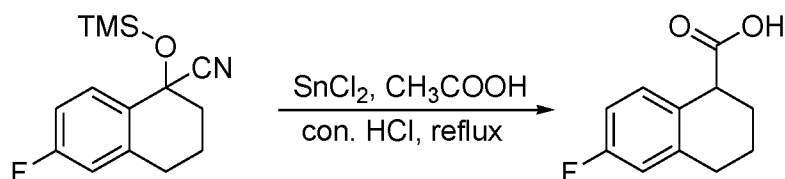


[0105] Step 1. 6-fluoro-1-(trimethylsilyloxy)-1,2,3,4-tetrahydronaphthalene-1-carbonitrile



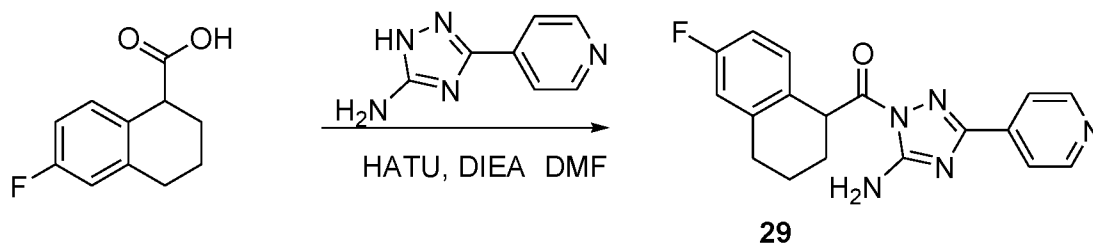
Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 6-fluoro-1,2,3,4-tetrahydronaphthalen-1-one (500 mg, 3.05 mmol, 1.00 equiv), dichloromethane (18 mL). This was followed by the addition of TMSCN (905 mg, 9.14 mmol, 3.00 equiv) and ZnI₂ (195 mg, 0.61 mmol, 0.20 equiv) at 0 °C. The resulting solution was stirred overnight at room temperature. The resulting solution was diluted with water (40 mL), extracted with dichloromethane (100 mL x 2), washed with brine (100 mL x 2) and concentrated under vacuum to give 4.7 g (crude) of 6-fluoro-1-(trimethylsilyloxy)-1,2,3,4-tetrahydronaphthalene-1-carbonitrile as a black solid.

[0106] Step 2. 6-fluoro-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid



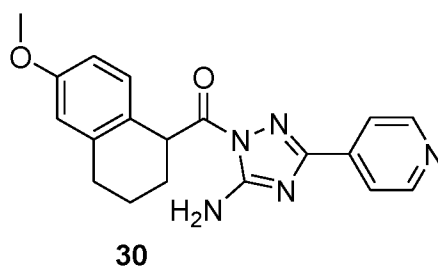
Into a 100-mL round-bottom flask, was placed 6-fluoro-1-[(trimethylsilyl)oxy]-1,2,3,4-tetrahydronaphthalene-1-carbonitrile (481 mg, 1.83 mmol, 1.00 equiv), AcOH (5 mL), HCl (conc.) (5 mL) and SnCl₂·2H₂O (1.65 g, 7.31 mmol, 4.00 equiv). The resulting solution was stirred overnight at 110 °C. The reaction mixture was cooled to room temperature and diluted with water (40 mL). The resulting solution was extracted with dichloromethane (100 mL x 2), dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 160 mg (45%) of 6-fluoro-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid as a brown solid. MS (ES, *m/z*) 195[M+H]⁺

[0107] Step 3. (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl)methanone

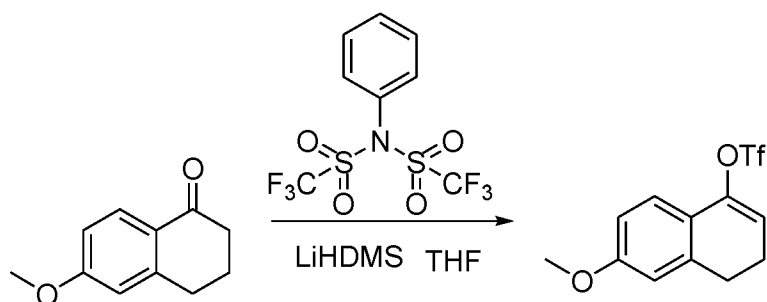


Into a 50-mL round-bottom flask, was placed 6-fluoro-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (60 mg, 0.31 mmol, 0.90 equiv), N,N-dimethylformamide (3 mL), HATU (194 mg, 0.51 mmol, 1.50 equiv) and DIEA (132 mg, 1.02 mmol, 3.00 equiv). The mixture was stirred for 30 min at room temperature (19 °C). Then 3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine (55 mg, 0.34 mmol, 1.00 equiv) was added. The resulting solution was stirred overnight at room temperature (19 °C). The resulting solution was diluted with EA (30 mL), washed with H₂O (50mL x 3) and brine (50mL x 3), dried with Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by Prep-TLC with ethyl acetate/petroleum ether (1/1). The crude product was repurified by Prep-HPLC with the following conditions (2#-AnalyseHPLC- SHIMADZU (HPLC-10)): Column, XBridge Shield RP18 OBD Column, 5 um, 19 x 150 mm; mobile phase, water (0.1%FA) and ACN (18.0% ACN up to 40.0% in 12 min); Detector, UV 254/220nm. The collected fraction was lyophilized to give 10.4 mg (9%) of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(6-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl)methanone (**29**) as a white solid. MS (ES, *m/z*): 338 [M+H]⁺; HNMR (400MHz, DMSO-d₆, *ppm*): δ 8.76 (s, 2H), 7.99 (d, *J*=6.0Hz, 2H), 7.22 (s, 2H), 7.20-7.18 (m, 1H), 7.03-6.92 (m, 2H), 5.02-4.99 (m, 1H), 2.86-2.76 (m, 2H), 2.33-2.10 (m, 2H), 1.86-1.75 (m, 2H).

[0108] Example 30. Synthesis of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanone

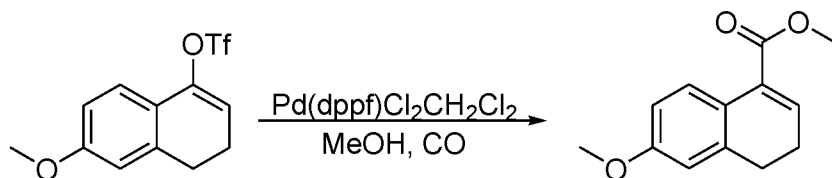


[0109] Step 1. 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate



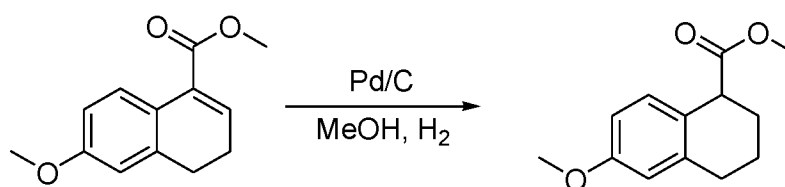
Into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 6-methoxy-1,2,3,4-tetrahydronaphthalen-1-one (500 mg, 2.84 mmol, 1.00 equiv) in tetrahydrofuran (14 mL). This was followed by the addition of LiHMDS (1M in tetrahydrofuran) (4.3 mL) at -78 °C. The mixture was stirred for 1h at -78 °C. To this was added phenyl [(trifluoromethane) sulfonyloxy] amino trifluoromethanesulfonate (1.52 g, 3.90 mmol, 1.90 equiv). The resulting solution was stirred overnight at room temperature (20 °C). The resulting solution was diluted with 40 mL of EA, washed with brine (100 mL x 2) and of sat. NH₄Cl (100 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was applied onto a silica gel column with EA:PE (0-10%). The collected fraction was concentrated to give 330 mg (38%) of 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate as a yellow solid. MS (ES, *m/z*): 309 [M+H]⁺

[0110] Step 2. Methyl 6-methoxy-3,4-dihydronaphthalene-1-carboxylate



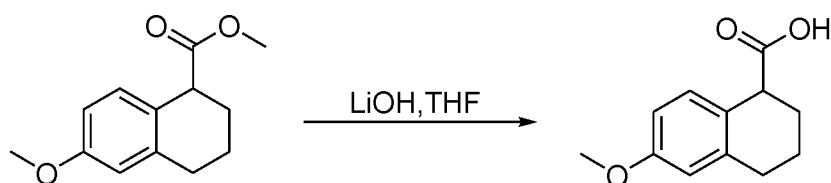
Into a 30-mL pressure tank reactor (60 atm) purged and maintained with an inert atmosphere of CO, was placed 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (300 mg, 0.97 mmol, 1.00 equiv), Pd(dppf)Cl₂·CH₂Cl₂ (400 mg, 0.49 mmol, 0.50 equiv), TEA (492 mg, 4.86 mmol, 5.00 equiv), MeOH (8 mL). The resulting solution was stirred overnight at 120 °C. The resulting solution was cooled to 25 °C. The solids were filtered out. The filtrate was concentrated under vacuum. The crude product was purified by Prep-TLC with ethyl acetate/petroleum ether (1/12). This resulted in 170 mg (80%) of methyl 6-methoxy-3,4-dihydronaphthalene-1-carboxylate as yellow oil. MS (ES, *m/z*): 219 [M+H]⁺

[0111] Step 3. Methyl 6-hydroxy-1,2,3,4-tetrahydronaphthalene-1-carboxylate



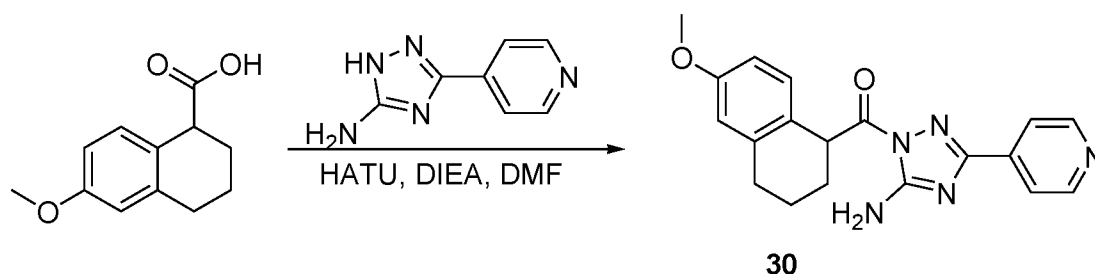
Into a 100-mL round-bottom flask, was placed methyl 6-methoxy-3,4-dihydronaphthalene-1-carboxylate (170 mg, 0.78 mmol, 1.00 equiv), Pd/C (10%) (170 mg), MeOH (10 mL). To the above hydrogen was introduced in. The resulting solution was stirred overnight at room temperature (20 °C). The solids were filtered out. The filtrate was concentrated under vacuum. This resulted in 164 mg (crude) of methyl 6-methoxy-3,4-dihydronaphthalene-1-carboxylate as yellow oil, which was used to the next step without any purification. MS (ES, m/z): 221 $[M+H]^+$

[0112] Step 4. 6-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid



Into a 100-mL round-bottom flask, was placed methyl 6-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylate (160 mg, 0.73 mmol, 1.00 equiv), methanol (10 mL), tetrahydrofuran (2.5 mL), LiOH (87.3 mg, 3.65 mmol, 5.00 equiv), water (2.5 mL). The resulting solution was stirred overnight at room temperature (19 °C). The resulting solution was diluted with H₂O (30 mL). The resulting mixture was washed with DCM (100 mL x 2). The pH value of the aqueous layers was adjusted to 5-6 with hydrochloric acid (1 mol/L). The resulting solution was extracted with dichloromethane (100 mL x 2), dried over anhydrous sodium sulfate and concentrated under vacuum to give 140 mg (93%) of 6-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid as a brown solid. MS (ES, m/z): 207 $[M+H]^+$

[0113] Step 5. (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanone



Into a 50-mL round-bottom flask, was placed 6-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (45 mg, 0.22 mmol, 0.90 equiv), N,N-dimethylformamide (3 mL), HATU (143 mg, 0.38 mmol, 1.50 equiv), DIEA (97 mg, 0.75 mmol, 3.00 equiv). The above mixture was stirred for 30 min at 19 °C. To the above was added 3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine (40 mg, 0.25 mmol, 1.00 equiv). The resulting solution was stirred overnight at room temperature (19 °C). The resulting solution was diluted with EA (30 mL), washed with H₂O (50 mL x 3) and brine (50mL x 3), dried with Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (2#-AnalyseHPLC-SHIMADZU(HPLC-10)): Column, XBridge C18 OBD Prep Column, 100A, 5 um, 19 mm x 250 mm; mobile phase, waters(0.1%FA) and ACN (25.0% ACN up to 50.0% in 8 min); Detector, UV 254nm. This collected fraction was lyophilized to give 5 mg (6%) of (5-amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanone (**30**) as a pink solid. MS (ES, *m/z*): 350 [M+H]⁺; HNMR (300MHz, DMSO-d₆, *ppm*): δ 8.73-8.71 (m, 2H), 7.92-7.90 (m, 4H), 7.03 (d, *J*=8.1Hz, 1H), 6.71 (d, *J*=2.7Hz, 2H), 4.97 (s, 1H), 3.72 (s, 3H), 2.81-2.73 (m, 2H), 2.14-1.76 (m, 4H).

[0114] Example 31. As a negative control, N-benzyl-1-[(naphthalen-1-yl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine was synthesized according to the procedures described in PCT WO 2011/126903, where it is example 269.

[0115] The compounds of the invention were tested in the following screens:

[0116] Factor XIIa (FXIIa) inhibitory activity:

In a 96-well clear bottom plate, 80μl of assay buffer was added to each well. Assay buffer consists of 0.5x Hank's Balanced Salt Solution (Invitrogen), buffered with 25mM HEPES pH 7.4 (Invitrogen) and 0.5x Tris-buffered saline with Tween-20 0.05% (Santa Cruz Biotechnology). Test compounds were first dissolved in DMSO (Sigma) and then 4μl were

added to test wells containing assay buffer. Serial dilutions using an automated multi-channel pipette were used to generate a concentration range of approximately 1-100 μ M. Human FXIIa (Enzyme Research Labs) was diluted in assay buffer to a final concentration of 12.5nM. 80 μ l of this enzyme solution was added to the assay wells. The enzyme/compound mixtures were incubated for 10 minutes at room temperature. Chromogenic substrate (Pefachrome XIIa; Enzyme Research Labs) was added to assay wells at a final concentration of 400 μ M. The assay plate was spun for 1 minute at 1500g and then read at 37°C in a SpectraMax M2 plate reader (λ = 405nm). Activity was quantified as the rate of change in absorbance, which corresponds to the rate of substrate cleavage. IC₅₀ values were determined as the concentration of inhibitor that produced 50% of the rate of change of control wells without any inhibitor. For compounds with activity <1 μ M, the assay was repeated with a lower concentration range, typically from 10-1000nM, and the final Human FXIIa concentration was 2nM.

[0117] Counterscreens for selectivity:

Thrombin. In a 96-well white opaque plate, 80 μ l of assay buffer was added to each well. Test compounds were added, and serially diluted as above, to generate a concentration range of approximately 1-100 μ M. Human alpha-thrombin (Enzyme Research Labs) was diluted in assay buffer to a final concentration of 12.5nM. 80 μ l of this enzyme solution was added to the assay wells. The enzyme/compound mixtures were incubated for 10 minutes at room temperature. Fluorogenic substrate (Boc-Val-Pro-Arg-7-amido-4-methylcoumarin; Sigma) was added to assay wells at a final concentration of 20 μ M. The assay plate was spun for 1 minute at 1500g and then read at 37°C in a SpectraMax M2 plate reader (λ_{ex} = 380nm and λ_{em} = 460nm). Activity was quantified as the rate of change in fluorescence, which corresponds to the rate of substrate cleavage. IC₅₀ values were determined as the concentration of inhibitor that produced 50% of the rate of change of control wells without any inhibitor. For compounds with activity <1 μ M, the assay was repeated with a lower concentration range, typically from 10-1000nM.

[0118] *Factor IXa*. In a 96-well white opaque plate, 80 μ l of assay buffer was added to each well. Test compounds were added, and serially diluted as above, to generate a concentration range of approximately 1-100 μ M. Human FIXa-beta (Enzyme Research Labs) was diluted in assay buffer to a final concentration of 12.5nM. 80 μ l of this enzyme solution was added to

the assay wells. The enzyme/compound mixtures were incubated for 10 minutes at room temperature. Fluorogenic substrate (Peflafluor FIXa; Enzyme Research Labs) was added to assay wells at a final concentration of 100 μ M. The assay plate was spun for 1 minute at 1500g and then read at 37°C in a SpectraMax M2 plate reader ($\lambda_{\text{ex}} = 380\text{nm}$ and $\lambda_{\text{em}} = 460\text{nm}$). Activity was quantified as the rate of change in fluorescence, which corresponds to the rate of substrate cleavage. IC₅₀ values were determined as the concentration of inhibitor that produced 50% of the rate of change of control wells without any inhibitor.

[0119] *Factor Xa*. In a 96-well white opaque plate, 80 μ l of assay buffer was added to each well. Test compounds were added, and serially diluted as above, to generate a concentration range of approximately 1-100 μ M. Human FXa (Enzyme Research Labs) was diluted in assay buffer to a final concentration of 12.5nM. 80 μ l of this enzyme solution was added to the assay wells. The enzyme/compound mixtures were incubated for 10 minutes at room temperature. Fluorogenic substrate (Peflafluor FXa; Enzyme Research Labs) was added to assay wells at a final concentration of 80 μ M. The assay plate was spun for 1 minute at 1500g and then read at 37°C in a SpectraMax M2 plate reader ($\lambda_{\text{ex}} = 380\text{nm}$ and $\lambda_{\text{em}} = 460\text{nm}$). Activity was quantified as the rate of change in fluorescence, which corresponds to the rate of substrate cleavage. IC₅₀ values were determined as the concentration of inhibitor that produced 50% of the rate of change of control wells without any inhibitor.

[0120] *Factor XIa*. In a 96-well clear-bottom plate, 80 μ l of assay buffer was added to each well. Test compounds were added, and serially diluted as above, to generate a concentration range of approximately 1-100 μ M. Human FXIa (Enzyme Research Labs) was diluted in assay buffer to a final concentration of 12.5nM. 80 μ l of this enzyme solution was added to the assay wells. The enzyme/compound mixtures were incubated for 10 minutes at room temperature. Chromogenic substrate (Pefachrome FXIa 3371; Enzyme Research Labs) was added to assay wells at a final concentration of 100 μ M. The assay plate was spun for 1 minute at 1500g and then read at 37°C in a SpectraMax M2 plate reader ($\lambda = 405$). Activity was quantified as the rate of change in absorbance, which corresponds to the rate of substrate cleavage. IC₅₀ values were determined as the concentration of inhibitor that produced 50% of the rate of change of control wells without any inhibitor.

[0121] *Plasma Kallikrein*. In a 96-well white opaque plate, 80 μ l of assay buffer was added to each well. Test compounds were added, and serially diluted as above, to generate a concentration range of approximately 1-100 μ M. Human plasma kallikrein (Enzyme Research Labs) was diluted in assay buffer to a final concentration of 12.5nM. 80 μ l of this enzyme solution was added to the assay wells. The enzyme/compound mixtures were incubated for 10 minutes at room temperature. Fluorogenic substrate (Z-Phe-Arg 7-amido-4-methylcoumarin; Sigma) was added to assay wells at a final concentration of 50 μ M. The assay plate was spun for 1 minute at 1500g and then read at 37°C in a SpectraMax M2 plate reader (λ_{ex} = 380nm and λ_{em} = 460nm). Activity was quantified as the rate of change in fluorescence, which corresponds to the rate of substrate cleavage. IC₅₀ values were determined as the concentration of inhibitor that produced 50% of the rate of change of control wells without any inhibitor. Results of testing in the foregoing screens are shown in Table 1, wherein the IC₅₀s are given in μ M:

Table 1

Example #	IC ₅₀ FXIIa	IC ₅₀ thrombin	IC ₅₀ FIXa	IC ₅₀ FXa	IC ₅₀ FXIa	IC ₅₀ kallikrein
1	0.09	6				
2	0.055	50	20	>40	>50	>40
3	1.50	5	1.2	>40	3.5	>40
4	0.2	0.5				
5	5.0	50				
6	>25	>25				
7	0.6	0.2				
8	0.4	70				
9	0.03	0				
10	0.015	2.5				
11	0.6	0.35				
12	0.03	0				
13	0.01	0.4				
14	0.01	0.65				
15	0.55	0.4				
16	0.01	0.035				
17	0.13	1				
18	0.15	11				
19	20.0	NT				
20	0.13	70				
21	0.18	2				
22	0.3	0.6				
23	0.02	0.8				
24	0.03	1.2				
25	0.15	1.5				
26	5.5	7				
27	0.06	0.2				
28	0.35	1				
29	0.06	20				
30	0.05	9				

Example 31 was tested as described above and exhibited an IC₅₀ of 20 μ M versus Factor XIIa and an IC₅₀ of <0.5 μ M versus thrombin. Example 31 was highly selective for thrombin.

[0122] The compounds provided herein can be used for treating inflammation, for treating an immunological disorder, or for treating pathologies associated with vasodilatation. The method comprises administering to a patient a therapeutically effective amount of a compound of formula I.

[0123] For *in vivo* confirmation of efficacy, the experimental autoimmune encephalomyelitis (EAE) model may be used. This is a standard and well-validated animal model of multiple sclerosis. Briefly, female mice approximately 10 weeks old are immunized with a fragment of brain protein, such as myelin oligodendrocyte glycoprotein (MOG), residues 35-55 in an emulsion with Freund's Complete adjuvant. Two subcutaneous injections are performed, one on the upper back, and one on the lower back. Approximately 2 hours later, animals receive an intraperitoneal injection of pertussis toxin. Twenty-four hours later, animals receive a second dose of pertussis toxin. Disease onset occurs within approximately 10-14 days, and disease severity is scored using a standard EAE scoring guide:

EAE SCORE	CLINICAL SIGNS
0	Normal; no signs of disease
1	Limp tail
2	Paraparesis: limp tail and hind limb weakness; Waddling gait
3	Hind limb Paralysis Total loss of movement in hind limbs. Mouse moves itself with forelimbs.
4	Quadriplegia
5	Moribund, or complete hind limb paralysis with moderate to severe forelimb paresis

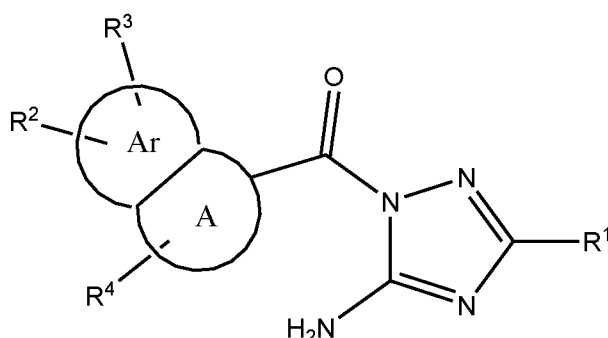
Test compounds are administered either with MOG inoculation (prophylactic model), or beginning at the earliest sign of disease (therapeutic model). Compound efficacy is assessed by determining the EAE severity score 4 weeks after inoculation, as well as by determining EAE onset and peak severity in relation to comparator and/or control groups. The compound of Example 2 was evaluated in this test with the following results:

Treatment	EAE incidence (%)	p value	Median day of onset (all mice)	p value	MMS +/- SD	p value	End score +/- SD	p value	End % body weight +/- SD	p value
Vehicle	91.7		16.0		2.75 +/- 1.25		1.33 +/- 1.27		91.4 +/- 11.2	
Example 2	25.0	0.0005	>28.0*	0.0013	0.79 +/- 1.44	0.0018	0.71 +/- 1.32	0.0103	105.2 +/- 8.7	0.0026

* Median day of onset cannot be calculated because 50% or less of mice developed disease

CLAIMS

1. A compound of formula



wherein

Ar/A is a fused bicycle in which Ar is an aromatic 5 or 6-membered ring and A is a non-aromatic 5, 6 or 7-membered ring and the point of attachment to the acyl triazole is on the non-aromatic ring;

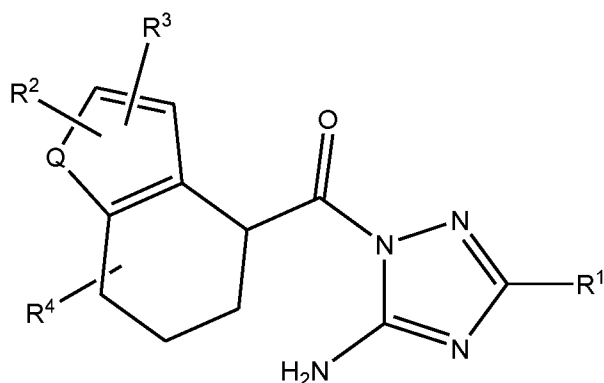
R¹ is phenyl or an aromatic monocyclic heterocycle, said phenyl or heterocycle optionally substituted with one or more of: halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)fluoroalkyl, (C₁-C₄)fluoroalkoxy and di(C₁-C₄)alkylamino;

R² and R³ are attached to Ar/A at a carbon and are chosen independently from hydrogen, halogen, hydroxy, amino, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylamino, di(C₁-C₄)alkylamino, (C₁-C₄)acylamino, (C₁-C₄)fluoroalkyl and (C₁-C₄)fluoroalkoxy;

R⁴ is hydrogen or, when Ar/A contains a nitrogen, R⁴ is attached to nitrogen and is chosen from hydrogen, (C₁-C₁₀)hydrocarbyl, and benzyl substituted with one to three substituents chosen from halogen, hydroxy, amino, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkylamino, di(C₁-C₄)alkylamino, (C₁-C₄)acylamino, (C₁-C₄)fluoroalkyl and (C₁-C₄)fluoroalkoxy; with the proviso that if R² or R³ is other than hydrogen, the non-hydrogen substituent may not be attached to the same carbon as the acyl triazole group.

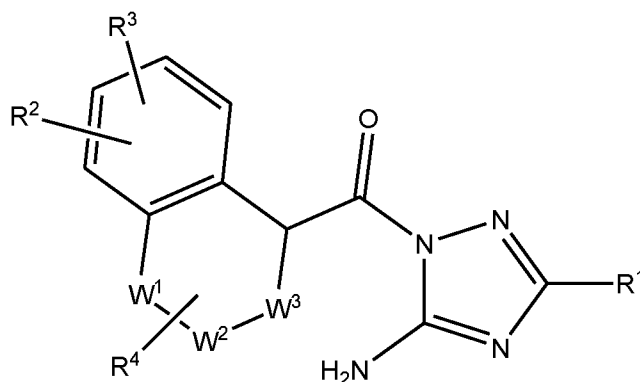
2. A compound according to claim 1 wherein A is a 5, 6 or 7-membered nitrogenous heterocycle.
3. A compound according to claim 2 wherein A is an N-alkyl nitrogenous heterocycle.
4. A compound according to claim 1 wherein A is a 5, 6 or 7-membered oxygen heterocycle.

5. A compound according to claim 1 wherein A is a 5, 6 or 7-membered sulfur heterocycle.
6. A compound according to claim 1 wherein A is a 5, 6 or 7-membered carbocycle.
7. A compound according to claim 6 wherein A is a 6-membered carbocycle.
8. A compound according to claim 1 wherein Ar is chosen from benzene, pyridine, pyrrole, thiophene and furan.
9. A compound according to claim 8 of the formula



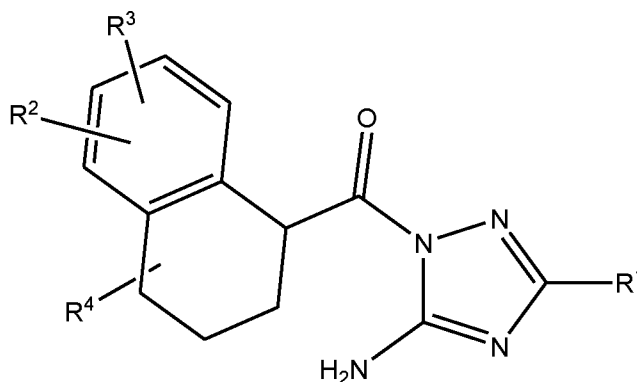
wherein Q is O, S or NR⁴.

10. A compound according to claim 8 of the formula

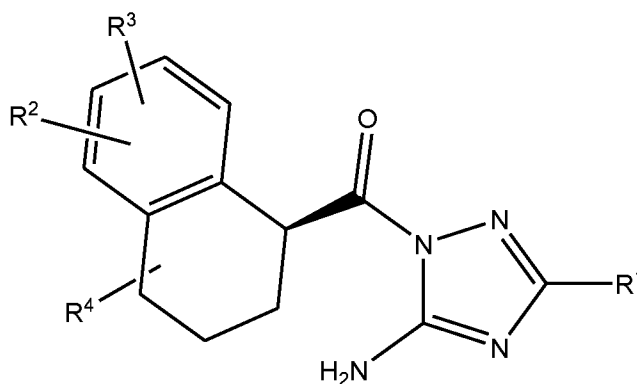


wherein one of W¹, W² and W³ is chosen from O, S and NR⁵ and the other two of W¹, W² and W³ are saturated carbons to which any of R², R³ and R⁴ may be attached; and R⁵ is hydrogen or (C₁-C₁₀)hydrocarbon.

11. A compound according to claim 10 wherein one of W^1 and W^3 is chosen from $-O-$ and $-N(CH_3)-$.
12. A compound according to claim 10 wherein W^2 and W^3 are $-CH_2-$ and W^1 is chosen from $-CH_2-$, $-NH-$, and $-N(CH_3)-$.
13. A compound according to claim 7 of the formula



14. A compound according to claim 13 wherein the chiral center adjacent carbonyl has (S) absolute configuration, said compound having the formula



15. A compound according to any of claims 1 to 14 wherein R^1 is chosen from optionally substituted furanyl, thiophenyl and pyrrolyl.
16. A compound according to any of claims 1 to 14 wherein R^1 is chosen from optionally substituted pyrimidinyl, pyridazinyl and pyrazinyl.

17. A compound according to any of claims 1 to 14 wherein R¹ is optionally substituted pyridinyl.
18. A compound according to claim 17 wherein R¹ is optionally substituted pyridin-4-yl.
19. A compound according to any of claims 1 to 14 wherein R¹ is optionally substituted phenyl.
20. A compound according to claim 19 wherein R¹ is phenyl optionally substituted with from one to three substituents chosen from fluoro, chloro, methoxy, trifluoromethyl, trifluoromethoxy or dimethylamino.
21. A compound according to any of claims 1 to 14 wherein R² and R³ are chosen independently from hydrogen, halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, di(C₁-C₄)alkylamino, (C₁-C₄)acylamino, (C₁-C₄)fluoroalkyl and (C₁-C₄)fluoroalkoxy.
22. A compound according to any of claims 1 to 14 wherein at least two of R², R³ and R⁴ are hydrogen.
23. A compound according to claim 21 wherein R³ and R⁴ are hydrogen and R² is fluoro.
24. A compound according to claim 23 wherein R² is a substituent on the Ar ring.
25. A method for inhibiting Factor XIIa in a mammal comprising administering to said mammal an inhibitory amount of a compound according to any of claims 1 to 14.
26. A method for selectively inhibiting Factor XIIa in the presence of thrombin and kallikrein said method comprising bringing an inhibitory amount of a compound according to any of claims 1 to 14 into contact with Factor XIIa.
27. An *in vivo* method according to claim 26.
28. An *in vitro* method according to claim 26.

29. A method for treating inflammation in a patient, said method comprising administering to said patient a therapeutically effective amount of a compound according to any of claims 1 to 14.
30. A method for treating an immunological disorder in a patient, said method comprising administering to said patient a therapeutically effective amount of a compound according to any of claims 1 to 14.
31. A method for treating vasodilatation in a patient said method comprising administering to said patient a therapeutically effective amount of a compound according to any of claims 1 to 14.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/12796

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 9/50, A61K 9/00, A61K 9/28, A61K 9/16 (2017.01) CPC - A61K 9/5047, A61K 9/1623, A61K 9/0056 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8) - A61K 9/50, A61K 9/00, A61K 9/28, A61K 9/16 (2017.01) CPC - A61K 9/5047, A61K 9/1623, A61K 9/0056 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatBase, Google Scholar, Reaxys, PubChem; search terms: triazol triazole triazolyl methanone amino acyl fused ring factor xia thrombin kallikrein vivo vitro immunological disorders vasodilatationin flammation inhibitors administer patient		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2013/0040950 A1 (Short et al.) 14 February 2013 (14.02.2013); Title, Abstract, p6, p8, p12, p13, p23, para[0041], para[0059], para[0068], para[0088], para[0101], para[0172], para[0176]	1-25, 29-31 ----- 26-28
Y	US 2008/0161373 A1 (Pinto et al.) 03 July 2008 (03.07.2008); Abstract, para[0506], para[0910], para[0933], para[0937]	26-28
A	Cirino et al. 'Thrombin Functions as an Inflammatory Mediator through Activation of Its Receptor', The Journal of Experimental Medicine, 01 March 1996 (01.03.1996). Vol.183, page821-827; p821	29, 31
A	Zoller et al. 'Autoimmune diseases and venous thromboembolism: a review of the literature', American Journal of Cardiovascular Disease, 15 August 2012 (15.08.2014), Vol.2, page171-183; p171, p183	30
A	US 2015/0152048 A1 (Imagawa et al.) 04 June 2015 (04.06.2015); entire document	1-31
A	US 2014/0274960 A1 (Orwat et al.) 18 September 2014 (18.09.2014); entire document	1-31
☐ Further documents are listed in the continuation of Box C. ☐		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 24 February 2017		Date of mailing of the international search report 07 APR 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774