MULTISUBSTITUTED AROMATIC COMPOUNDS AS INHIBITORS OF THROMBIN

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/319,175, filed March 30, 2010, the entire contents of which is hereby incorporated by reference herein and for all purposes.

BACKGROUND OF THE INVENTION

[0002] The present disclosure relates to compounds, e.g., multisubstituted aromatic compounds, which exhibit biological activity, e.g., inhibitory action, against thrombin (activated blood-coagulation factor II; EC 3.4.21.5).

[0003] In mammalian systems, blood vessel injuries result in bleeding events, which are dealt with by the blood coagulation cascade. The cascade includes the Extrinsic and Intrinsic pathways, involving the activation of at least 13 interconnected factors and a variety of co-factors and other regulatory proteins. Upon vascular injury, plasma factor VII interacts with exposed Tissue Factor (TF), and the resultant TF-fVIIa complex initiates a complex series of events. Factor fXa is produced directly 'downstream' from the TF-fVIIa complex, and amplified manifold via the Intrinsic Pathway. FXa then serves as the catalyst for formation of thrombin (fIIa), which in turn is the direct precursor to fibrinolysis. The outcome is a fibrinolytic clot, which stops the bleeding. Fibrinolysis of the polymeric clot into fibrin monomers leads to dissolution and a return of the system to the pre-clot state. The cascade is a complex balance of factors and co-factors and is tightly regulated.

[0004] In disease states, undesired up- or down-regulation of any factor leads to conditions such as bleeding or thrombosis. Historically, anticoagulants have been used in patients at risk of suffering from thrombotic complications, such as angina, stroke and heart attack. Warfarin has enjoyed dominance as a first-in-line anticoagulant therapeutic. Developed in the 1940s, it is a Vitamin K antagonist and inhibits factors II, VII, IX and X, amongst others. It is administered orally, but its ease of use is tempered by other effects: it has a very long half life (>2 days) and has serious drug-drug interactions. Importantly, since Vitamin K is a ubiquitous cofactor within the coagulation cascade, antagonism results in the simultaneous inhibition of many clotting factors and thus can lead to significant bleeding complications.

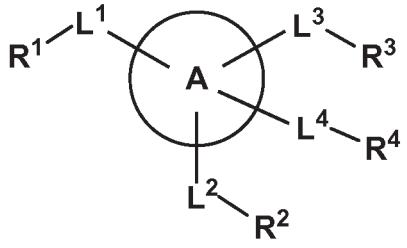
[0005] Much attention has been focused on heparin, the naturally-occurring polysaccharide that activates AT III, the endogenous inhibitor of many of the factors in the coagulation cascade. The need for parenteral administration for the heparin-derived therapeutics, and the inconvenient requirements for close supervision for the orally available warfarin, has resulted in a drive to discover and develop orally available drugs with wide therapeutic windows for safety and efficacy.

[0006] Indeed, the position of thrombin in the coagulation cascade has made it a popular target for drug discovery. Without wishing to be bound by any theory, it is believed that the ultimate development of direct thrombin inhibitors (DTIs) is usefully based upon the classical D-Phe-Pro-Arg motif, a sequence that mimics fibrinogen, which is a natural substrate of thrombin. Without further wishing to be bound by any theory, it is believed that the use of DTIs is very well precedented, such as with the hirudin-based anticoagulants, and thus there is strong interest in the discovery and development of novel DTIs.

[0007] A thorough discussion of thrombin and its roles in the coagulation process can be found in a variety of references, including the following which are incorporated herein by reference in their entireties and for all purposes: Wieland, H. A., et al., 2003, *Curr Opin Investig Drugs*, **4**:264-71; Gross, P. L. & Weitz, J. I., 2008, *Arterioscler Thromb Vasc Biol*, **28**:380-6; Hirsh, J., et al., 2005, *Blood*, **105**:453-63; Prezelj, A., et al., 2007, *Curr Pharm Des*, **13**:287-312.

BRIEF SUMMARY OF THE INVENTION

[0008] In a first aspect, there is provided a compound with structure of Formula (Ia)



(Ia)

or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof. Ring A is substituted or unsubstituted pyrazolyl, or substituted or unsubstituted triazolyl. L^1, L^2 and L^3 are independently a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, -SO_2-, -O-, -$NHSO_2$-, or -NR^5-. L^4 is absent, a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, -SO_2-, -O-, -$NHSO_2$-, or -NR^5-. R^1, R^2 and R^3 are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,

substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^4 is absent, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, provided that when L^4 is absent, then R^4 is absent. R^5 is independently hydrogen, or substituted or unsubstituted alkyl. It has been discovered that compounds described herein are useful for the inhibition of thrombin.

[0009] In another aspect, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient. The compound is a compound of any of Formulae (Ia), (Ib), (IIa), (IIb), (IIIa), (IIIb), (IV) or (V) as disclosed herein, or a compound as set forth in any of Tables A, B or C herein, or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof.

[0010] In yet another aspect, there is provided a method for treating a disease or disorder in a subject. The method includes administering a compound of any of Formulae (Ia), (Ib), (IIa), (IIb), (IIIa), (IIIb), (IV) or (V) as disclosed herein, compound as set forth in any of Tables A, B or C herein, pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, or pharmaceutical composition thereof, to a subject in need thereof in an amount effective to treat the disease or disorder.

[0011] In still another aspect, there is provided a method for preventing a disease or disorder in a subject. The method includes administering a compound of any of Formulae (Ia), (Ib), (IIa), (IIb), (IIIa), (IIIb), (IV) or (V) as disclosed herein, compound as set forth in any of Tables A, B or C herein, pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, or pharmaceutical composition thereof, to a subject in need thereof in an amount effective to prevent the disease or disorder.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Not applicable.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0013] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0014] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0015] As used herein, the term "attached" signifies a stable covalent bond, certain preferred points of attachment being apparent to those of ordinary skill in the art.

[0016] The terms "halogen" or "halo" include fluorine, chlorine, bromine, and iodine. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0017] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched chain, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. Accordingly, the term "alkyl" can refer to C_1-C_{16} straight chain saturated, C_1-C_{16} branched saturated, C_3-C_8 cyclic saturated and C_1-C_{16} straight chain or branched saturated aliphatic hydrocarbon groups substituted with C_3-C_8 cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, this definition shall include but is not limited to methyl (Me), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, isopropyl (i-Pr), isobutyl (i-Bu), tert-butyl (t-Bu), sec-butyl (s-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopropylmethyl, and the like.

[0018] The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the compounds

disclosed herein. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0019] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, consisting of at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P, S, and Si may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$.

[0020] Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0021] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl

include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

[0022] The term "alkenyl" includes C_2-C_{16} straight chain unsaturated, C_2-C_{11} branched unsaturated, C_5-C_8 unsaturated cyclic, and C_2-C_{16} straight chain or branched unsaturated aliphatic hydrocarbon groups substituted with C_3-C_8 cyclic saturated and unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Double bonds may occur in any stable point along the chain and the carbon-carbon double bonds may have either the *cis* or *trans* configuration. For example, this definition shall include but is not limited to ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, 1,5-octadienyl, 1,4,7-nonatrienyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, ethylcyclohexenyl, butenylcyclopentyl, l-pentenyl-3-cyclohexenyl, and the like. Similarly, "heteroalkenyl" refers to heteroalkyl having one or more double bonds.

[0023] The term "alkynyl" refers in the customary sense to alkyl additionally having one or more triple bonds. The term "cycloalkenyl" refers to cycloalkyl additionally having one or more double bonds. The term "heterocycloalkenyl" refers to heterocycloalkyl additionally having one or more double bonds.

[0024] The term "acyl" means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0025] Each of the above terms (e.g., "alkyl," "heteroalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided herein.

[0026] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN, and -NO_2 in a number ranging from zero to (2m'+1),

where m' is the total number of carbon atoms in such radical. R', R", R'", and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound disclosed herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

[0027] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR', -halogen, -SiR'R"R'", -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", $-NR"C(O)_2R'$, -NR-C(NR'R"R'")=NR"", -NR-C(NR'R")=NR'", $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, -CN, $-NO_2$, -R', $-N_3$, $-CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R'", and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound disclosed herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'", and R"" groups when more than one of these groups is present.

[0028] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-

forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

[0029] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently -NR-, -O-, -CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, -$S(O)_2$-, -$S(O)_2$NR'-, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CRR')_s$-X'- $(C"R"')_d$-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R", and R"' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0030] As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0031] The term "alkyloxy" (e.g. methoxy, ethoxy, propyloxy, allyloxy, cyclohexyloxy) represents an alkyl group as defined above having the indicated number of carbon atoms attached through an oxygen bridge (-O-).

[0032] The term "alkylthio" (e.g. methylthio, ethylthio, propylthio, cyclohexylthio and the like) represents an alkyl group as defined above having the indicated number of carbon atoms attached through a sulfur bridge (-S-).

[0033] The term "alkylamino" represents one or two alkyl groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The two alkyl groups maybe taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 8 carbon atoms with or without one C_1-C_{16}alkyl, arylC_0-C_{16}alkyl, or C_0-C_{16}alkylaryl substituent.

[0034] The term "alkylaminoalkyl" represents an alkylamino group attached through an alkyl group as defined above having the indicated number of carbon atoms.

[0035] The term "alkyloxy(alkyl)amino" (e.g. methoxy(methyl)amine, ethoxy(propyl)amine) represents an alkyloxy group as defined above attached through an amino group, the amino group itself having an alkyl substituent.

[0036] The term "alkylcarbonyl" (e.g. cyclooctylcarbonyl, pentylcarbonyl, 3-hexylcarbonyl) represents an alkyl group as defined above having the indicated number of carbon atoms attached through a carbonyl group.

[0037] The term "alkylcarboxy" (e.g. heptylcarboxy, cyclopropylcarboxy, 3-pentenylcarboxy) represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through an oxygen.

[0038] The term "alkylcarboxyalkyl" represents an alkylcarboxy group attached through an alkyl group as defined above having the indicated number of carbon atoms.

[0039] The term "alkylcarbonylamino" (e.g. hexylcarbonylamino, cyclopentylcarbonylaminomethyl, methylcarbonylaminophenyl) represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group.

[0040] The nitrogen group may itself be substituted with an alkyl or aryl group.

[0041] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term “heteroaryl” refers to aryl groups (or rings) that contain from one to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term “heteroaryl” includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl,

4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An “arylene” and a “heteroarylene,” alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. Accordingly, the term "aryl" can represent an unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic, biaryl and heterocyclic aromatic groups covalently attached at any ring position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art (e. g. 3-indolyl, 4-imidazolyl). The aryl substituents are independently selected from the group consisting of halo, nitro, cyano, trihalomethyl, C_{1-16}alkyl, arylC_{1-16}alkyl, C_{0-16}alkyloxyC_{0-16}alkyl, arylC_{0-16}alkyloxyC_{0-16}alkyl, C_{0-16}alkylthioC_{0-16}alkyl, arylC_{0-16}alkylthioC_{0-16}alkyl, C_{0-16}alkylaminoC_{0-16}alkyl, arylC_{0-16}alkylaminoC_{0-16}alkyl, di(arylC_{1-16}alkyl)aminoC_{0-16}alkyl, C_{1-16}alkylcarbonylC_{0-16}alkyl, arylC_{1-16}alkylcarbonylC_{0-16}alkyl, C_{1-16}alkylcarboxyC_{0-16}alkyl, arylC_{1-16}alkylcarboxyC_{0-16}alkyl, C_{1-16}alkylcarbonylaminoC_{0-16}alkyl, arylC_{1-16}alkylcarbonylaminoC_{0-16}alkyl,-C_{0-16}alkylCOOR$_4$, -C_{0-16}alkylCONR$_5$R$_6$ wherein R$_4$, R$_5$ and R$_6$ are independently selected from hydrogen, C_1-C_{11}alkyl, arylC_0-C_{11}alkyl, or R$_5$ and R$_6$ are taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 8 carbon atoms with or without one C_{1-16}alkyl, arylC_0-C_{16}alkyl, or C_0-Cl_{16}alkylaryl substituent. Aryl includes but is not limited to pyrazolyl and triazolyl.

[0042] For brevity, the term “aryl” when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the terms “arylalkyl,” “aralkyl” and the like are meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl, and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like), or a sulfur atom. Accordingly, the terms "arylalkyl" and the like (e.g. (4-hydroxyphenyl)ethyl, (2-aminonaphthyl)hexyl, pyridylcyclopentyl) represents an aryl group as defined above attached through an alkyl group as defined above having the indicated number of carbon atoms.

[0043] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[0044] The term "alkylsulfonyl," as used herein, means a moiety having the formula $-S(O_2)-R'$, where R' is an alkyl group as defined above. R' may have a specified number of carbons (e.g., "C_1-C_4 alkylsulfonyl").

[0045] The term "carbonyloxy" represents a carbonyl group attached through an oxygen bridge.

[0046] In the above definitions, the terms "alkyl" and "alkenyl" may be used interchangeably in so far as a stable chemical entity is formed, as would be apparent to those skilled in the art.

[0047] The term "linker" refers to attachment groups interposed between substituents, e.g., R^1, R^2, R^3 or R^4 described herein, e.g., Formula (Ia) and generically referred to as R^n, and the group which is substituted, e.g., "ring A" group of e.g., Formula (Ia). In some embodiments, the linker includes amido ($-CONH-R^n$ or $-NHCO-R^n$), thioamido ($-CSNH-R^n$ or $-NHCS-R^n$), carboxyl ($-CO_2-R^n$ or $-OCOR^n$), carbonyl ($-CO-R^n$), urea ($-NHCONH-R^n$), thiourea ($-NHCSNH-R^n$), sulfonamido ($-NHSO_2-R^n$ or $-SO_2NH-R^n$), ether ($-O-R^n$), sulfonyl ($-SO_2-R^n$), sulfoxyl ($-SO-R^n$), carbamoyl ($-NHCO_2-R^n$ or $-OCONH-R^n$), or amino ($-NHR^n$) linking moieties.

[0048] A "substituent group," as used herein, means a group selected from the following moieties:

(A) -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, oxo, halogen, -COOH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

(i) oxo, -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, halogen, -COOH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

(a) oxo, -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, halogen, -COOH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, substituted with at least one substituent selected from: oxo, -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, halogen, -COOH, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

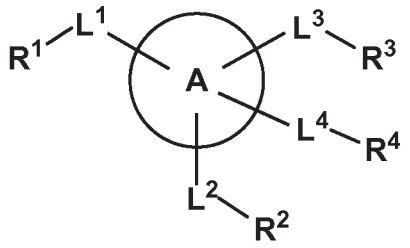
[0049] A "size-limited substituent" or " size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_4-C_8 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 4 to 8 membered heterocycloalkyl.

[0050] A "lower substituent" or " lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_5-C_7 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 5 to 7 membered heterocycloalkyl.

[0051] The term "about" used in the context of a numeric value indicates a range of +/- 10% of the numeric value, unless expressly indicated otherwise.

II. Compounds

[0052] In one aspect, there is provided a compound with structure of Formula (Ia):



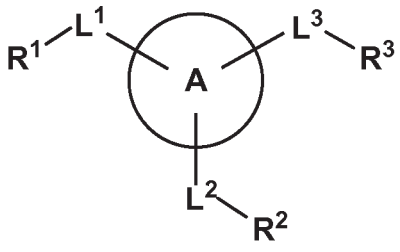
(Ia)

or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof. Ring A is substituted or unsubstituted pyrazolyl, or substituted or unsubstituted triazolyl. L^1, L^2 and L^3 are independently a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, $-SO_2$-, -O-, $-NHSO_2$-, or $-NR^5$-. L^4 is absent, a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, $-SO_2$-, -O-,

-$NHSO_2$-, or -NR^5-. R^1, R^2 and R^3 are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^4 is absent, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, provided that when L^4 is absent, then R^4 is absent. R^5 is independently hydrogen, or substituted or unsubstituted alkyl.

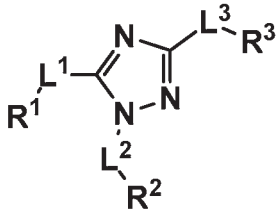
[0053] In some embodiments, the compound is a pharmaceutically acceptable salt, ester, solvate, or prodrug of a compound of Formula (Ia). In some embodiments, the compound is not an ester, not a solvate, and not a prodrug.

[0054] In some embodiments, L^4 and R^4 are absent, providing a compound with structure of Formula (Ib) following.

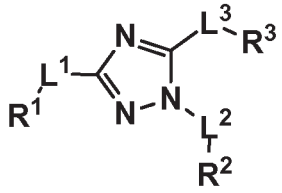


(Ib)

[0055] In some embodiments, there is provided a compound according to Formula (Ib) with structures of either of Formulae (IIa) or (IIb) following.



(IIa)



(IIb).

[0056] In some embodiments, the compound has the structure of Formula (IIa), wherein L^3 is a bond, and R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, the pendant heteroaryl R^3 is substituted or unsubstituted pyridyl, thienyl, or furyl. In some embodiments, the R^3 is unsubstituted pyridyl, thienyl, or furyl. In some embodiments, R^3 is unsubstituted aryl, preferably phenyl. In some embodiments, R^3 is substituted aryl, preferably halogen-substituted phenyl.

[0057] In some embodiments, a compound is provided with structure of Formula (IIa), wherein L^3 is a bond, substituted or unsubstituted alkylene, and R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heterocycloalkyl.

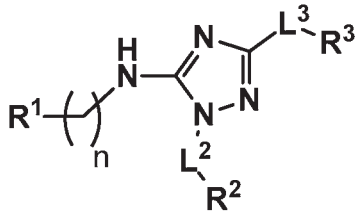
[0058] In some embodiments, the compound has the structure of Formula (IIa), wherein L^3 is -C(O)O-, and R^3 is substituted or unsubstituted alkyl, preferably unsubstituted alkyl, more preferably unsubstituted lower alkyl.

[0059] In some embodiments, the compound has the structure of Formula (IIa), wherein L^3 is -C(O)NR^5-, R^5 is hydrogen or alkyl, and R^3 is substituted or unsubstituted alkyl, or substituted or unsubstituted aryl.

[0060] Further to any embodiment above, in some embodiments L^1 is -S-, -NR^5-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, and R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In some embodiments, L^1 is -NC(O)-. In some embodiments, R^3 is substituted or unsubstituted aryl. In some embodiments, R^3 is unsubstituted aryl. In some embodiments, L^2 is a bond.. In some embodiments, L^2 is a bond and R^2 is hydrogen.

[0061] Further to any embodiment above, in some embodiments L^2 is substituted or unsubstituted alkylene or -C(O)-, and R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0062] In some embodiments, the compound of Formula (IIa) has the structure of Formula (IIc) following, wherein L^1 is -NH-$(CH_2)_n$-, n is 0 to 6, preferably 1, and R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

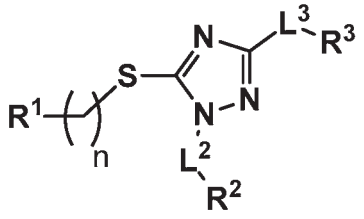


(IIc)

[0063] In some embodiments of the compound of Formula (IIc), L^1 is -$NHCH_2$- or -$NH(CH_2)_2$-, and R^1 is substituted or unsubstituted aryl. In some embodiments, R^1 is unsubstituted aryl. In some embodiments, R^1 is aryl, preferably phenyl, substituted with halogen, -CN or alkyloxy, preferably methoxy. In some embodiments, R^1 is unsubstituted

alkyl, preferably lower alkyl, more preferably methyl or ethyl. In some embodiments, n is 0, and R^1 is hydrogen.

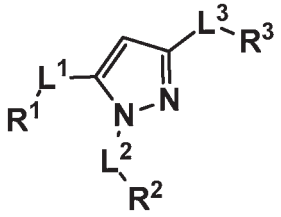
[0064] In some embodiments, the compound of Formula (IIa) has the structure of Formula (IId) following, wherein L^1 is a bond, and R^1 is unsubstituted alkyl, or substituted or unsubstituted aryl. In some embodiments, R^1 is unsubstituted alkyl, preferably lower alkyl. In some embodiments, R^1 is substituted aryl, preferably halogen-substituted phenyl.



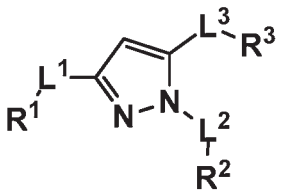
(IId)

[0065] In some embodiments, there is provided a compound with structure of Formula (IIb). In some embodiments, L^2 is a bond, or substituted or unsubstituted alkylene. In some embodiments, L^2 is a bond, and R^2 is alkyl, preferably lower alkyl. In some embodiments, L^2 is a substituted alkylene. In some embodiments, L^2 is an unsubstituted alkylene, preferably methylene or ethylene. In some embodiments, L^2 is an unsubstituted alkylene, and R2 is unsubstituted aryl, preferably phenyl. In some embodiments, R^2 is substituted or unsubstituted alkyl, or substituted or unsubstituted aryl.

[0066] In some embodiments, there is provided a compound according to Formula (Ib) with structure of either of Formulae (IIIa) or (IIIb) following.



(IIIa)



(IIIb)

[0067] In some embodiments, the compound has the structure of Formula (IIIa). In some embodiments, L^3 is a bond, or substituted or unsubstituted alkylene, and R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heterocycloalkyl. In some embodiments, R^3 is substituted or unsubstituted phenyl, or substituted or unsubstituted pyridyl. In some embodiments, R^3 is unsubstituted phenyl. In some embodiments, R^3 is unsubstituted pyridyl.

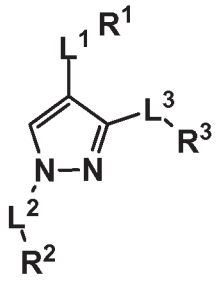
[0068] In some embodiments, the compound has the structure of Formula (IIIa) wherein L^3 is -C(O)O-, and R^3 is substituted or unsubstituted alkyl.

[0069] In some embodiments, the compound has the structure of Formula (IIIa) wherein L^3 is -C(O)NR^6, R^6 is hydrogen or alkyl, and R^3 is substituted or unsubstituted alkyl, or substituted or unsubstituted aryl.

[0070] Further to any embodiment above wherein the compound has the structure of Formula (IIIa), in some embodiments, L^1 is -S-, -NR^4-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, and R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl. In some embodiments, L^2 is a bond. In some embodiments, R^2 is hydrogen. In some embodiments, L^2 is substituted or unsubstituted alkylene or -C(O)-, and R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

[0071] In some embodiments, the compound has the structure of Formula (IIIb). In some embodiments, L^2 is a bond or substituted or unsubstituted alkylene. In some embodiments, L^2 is a bond. In some embodiments, L^2 is unsubstituted alkylene. In some embodiments, L^2 is substituted alkylene. In some embodiments, R^2 is substituted or unsubstituted alkyl, or substituted or unsubstituted aryl. Further to any particular L^2, in some embodiments R^2 is substituted or unsubstituted alkyl, or substituted or unsubstituted aryl. In some embodiments, R^2 is unsubstituted alkyl. In some embodiments, R^2 is unsubstituted aryl. In some embodiments, R^2 is substituted alkyl. In some embodiments, R^2 is substituted aryl.

[0072] In some embodiments, there is provided a compound according to Formula (Ib) with structure of Formulae (IV) following.

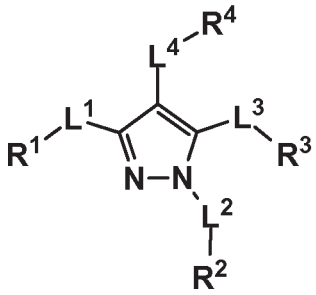


(IV)

[0073] In some embodiments, there is provided a compound according with Formula (IV) wherein L^3 is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, and R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, L^3 is a bond, -NH-, -$NHCH_2$- or -$NH(CH_2)_2$-.

[0074] Further to any embodiment of a compound with structure of Formula (IV), in some embodiments, L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -C(O)-, -C(O)-NR^6-. In some embodiments, R^1 is hydrogen, -COOH, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; substituted or unsubstituted heterocycloalkyl. In some embodiments, R^6 is hydrogen, or substituted or unsubstituted alkyl.

[0075] In some embodiments, there is provided a compound according to Formula (Ia) with structure of Formulae (V) following.



(V)

[0076] In some embodiments, there is provided a compound according with Formula (V) wherein L^4 is a bond; and R^4 is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. In some embodiments, R^4 is unsubstituted alkyl.

[0077] Exemplary compounds, e.g., multisubstituted aromatic compounds, in accordance with the present disclosure are provided herein. In Table A following, compound (Cmpd) number, chemical name (i.e., International Union of Pure and Applied Chemistry [IUPAC] name), molecular weight (MW_{calc} calculated mass and MW_{meas} measured mass) and biological activity (i.e., inhibition activity in a thrombin assay) are disclosed.

[0078] Regarding experimental molecular weights obtained by mass spectrometric analysis as described herein including Table A, unless indicated otherwise it is understood that the measured chemical species can be the protonated compound, e.g., $[M + H]^+$, whereby the measured mass is 1 atomic unit greater than the calculated mass of the compound, as well known in the art.

[0079] For Table A following, the disclosed compounds were assayed for inhibition of the protease activity of thrombin as described herein. In Table A, the level of inhibition in the thrombin assay is indicated as follows: a: $IC_{50} \leq 0.1$ μM; b: 0.1 μM < IC_{50} < 1 μM; c: $IC_{50} \geq$ 1 μM. Accordingly, in some embodiments, there is provided a compound as expressly set forth in Table A following.

Table A.

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
4	N-[(4-fluorophenyl)methyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	269	270	c
5	N-benzyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	251	252	c
6	N-[(4-fluorophenyl)methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	269	270	c
7	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	325	326	a
9	1-(5-[(2-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	325	326	b
10	4-([1-propanoyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile	332	333	c
11	N-benzyl-1-[(furan-2-yl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	345	346	a
12	1-[5-(benzylamino)-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl]-3-phenylpropan-1-one	383	384	a
13	N-[(4-fluorophenyl)methyl]-3-(pyridin-2-yl)-1-[(thiophen-2-yl)carbonyl]-1H-1,2,4-triazol-5-amine	379	380	a
14	1-benzoyl-N-[(4-fluorophenyl)methyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	373	374	a
15	N-[(4-fluorophenyl)methyl]-3-(pyridin-4-yl)-1-[(thiophen-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine	379	380	a
16	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)-2,2-dimethylpropan-1-one	365	366	a
17	N-[(4-fluorophenyl)methyl]-1-[(morpholin-4-yl)carbonyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	382	383	c
18	N-(2-fluorophenyl)-5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxamide	406	407	c
19	5-[(4-fluorophenyl)methyl]amino-N-methyl-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxamide	326	327	c
20	methyl 5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxylate	327	328	b
21	2-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-1-phenylethan-1-one	387	388	c
22	1-5-[(2-phenylethyl)amino]-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-ylpropan-1-one	321	322	c
23	1-(5-[2-(morpholin-4-yl)ethyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	330	331	c
24	1-[5-(dimethylamino)-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl]propan-1-one	245	246	c
26	N-[(4-fluorophenyl)methyl]-3-(furan-2-yl)-1-[(2-methoxyphenyl)carbonyl]-1H-1,2,4-triazol-5-amine	392	393	a
27	N-[(4-fluorophenyl)methyl]-1-[(2-methoxyphenyl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-	408	409	b

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
	triazol-5-amine			
28	3-(5-[(4-fluorophenyl)methyl]sulfanyl-1-[(2-methoxyphenyl)carbonyl]-1H-1,2,4-triazol-3-yl)pyridine	420	421	a
29	1-[(2-methoxyphenyl)carbonyl]-5-(methylsulfanyl)-3-(thiophen-2-yl)-1H-1,2,4-triazole	331	332	a
30	methyl 5-(benzylamino)-1-[(4-chlorophenyl)carbonyl]-1H-1,2,4-triazole-3-carboxylate	371	371,373	a
32	methyl 5-amino-1-[(2-chlorophenyl)carbonyl]-1H-1,2,4-triazole-3-carboxylate	281	281,283	a
33	N-benzyl-1-[(2-methoxyphenyl)carbonyl]-3-(pyrimidin-4-yl)-1H-1,2,4-triazol-5-amine	386	387	a
34	N-benzyl-1-[(2-methoxyphenyl)carbonyl]-3-(pyrimidin-5-yl)-1H-1,2,4-triazol-5-amine	386	387	a
35	N-benzyl-1-[(2-methoxyphenyl)carbonyl]-3-(pyrimidin-2-yl)-1H-1,2,4-triazol-5-amine	386	387	a
36	1-(5-[(4-fluorophenyl)methyl]amino-3-phenyl-1H-pyrazol-1-yl)-2,2-dimethylpropan-1-one	351	352	c
37	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-pyrazol-1-yl)-2,2-dimethylpropan-1-one	352	353	c
38	1-(5-[(4-fluorophenyl)methyl]amino-4-methyl-3-phenyl-1H-pyrazol-1-yl)-2,2-dimethylpropan-1-one	365	366	c
39	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-2-yl)-1H-pyrazol-1-yl)-2,2-dimethylpropan-1-one	352	353	a
40	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-2-yl)-1H-pyrazol-1-yl)propan-1-one	324	325	b
41	1-[(2-chlorophenyl)carbonyl]-N-[(4-fluorophenyl)methyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	407	407,409	b
42	1-(2-chlorophenyl)-3-(pyridin-2-yl)-1H-pyrazol-5-amine	271	271,273	c
43	N-[1-(2-chlorophenyl)-3-(pyridin-2-yl)-1H-pyrazol-5-yl]-4-fluorobenzamide	393	393,395	c
44	1-(2-chlorophenyl)-N,N-bis[(4-fluorophenyl)methyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	487	487,489	c
45	1-(2-chlorophenyl)-N-[(4-fluorophenyl)methyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	379	379,381	c
46	ethyl 3-[(4-fluorophenyl)methyl]amino-1-(pyridin-2-yl)-1H-pyrazole-4-carboxylate	340	341	c
47	3-[(4-fluorophenyl)methyl]amino-1-(pyridin-2-yl)-1H-pyrazole-4-carboxylic acid	312	313	c
48	3-[(4-fluorophenyl)methyl]amino-N-methoxy-N-methyl-1-(pyridin-2-yl)-1H-pyrazole-4-carboxamide	355	356	c
49	3-[(4-fluorophenyl)methyl]amino-N,N-dimethyl-1-(pyridin-2-yl)-1H-pyrazole-4-carboxamide	339	340	c

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
50	1-(3-[(4-fluorophenyl)methyl]amino-1-(pyridin-2-yl)-1H-pyrazol-4-yl)propan-1-one	324	325	c
51	ethyl 1-[2-(4-fluorophenyl)ethyl]-3-(pyridin-2-yl)-1H-pyrazole-5-carboxylate	339	340	c
52	1-[2-(4-fluorophenyl)ethyl]-3-(pyridin-2-yl)-1H-pyrazole-5-carboxylic acid	311	312	c
53	1-[2-(4-fluorophenyl)ethyl]-N-methoxy-N-methyl-3-(pyridin-2-yl)-1H-pyrazole-5-carboxamide	354	355	c
54	2-1-[2-(4-fluorophenyl)ethyl]-5-[(piperidin-1-yl)carbonyl]-1H-pyrazol-3-ylpyridine	378	379	c
55	1-1-[2-(4-fluorophenyl)ethyl]-3-(pyridin-2-yl)-1H-pyrazol-5-ylpropan-1-ol	325	326	c
56	1-1-[2-(4-fluorophenyl)ethyl]-3-(pyridin-2-yl)-1H-pyrazol-5-ylpropan-1-one	323	324	c
57	ethyl 1-[2-(4-fluorophenyl)ethyl]-5-(pyridin-2-yl)-1H-pyrazole-3-carboxylate	339	340	c
58	1-[2-(4-fluorophenyl)ethyl]-5-(pyridin-2-yl)-1H-pyrazole-3-carboxylic acid	311	312	c
59	2-1-[2-(4-fluorophenyl)ethyl]-3-[(piperidin-1-yl)carbonyl]-1H-pyrazol-5-ylpyridine	378	379	c
60	1-(3-[(4-fluorophenyl)methyl]amino-1-(pyridin-2-yl)-1H-pyrazol-4-yl)ethan-1-one	310	311	c
61	1-(3-[(4-fluorophenyl)methyl]amino-1-phenyl-1H-pyrazol-4-yl)ethan-1-one	309	310	c
62	1-(3-[(4-fluorophenyl)methyl]amino-1-phenyl-1H-pyrazol-4-yl)propan-1-one	323	324	c
63	1-(5-[(4-fluorophenyl)methyl]amino-3-(furan-2-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	314	315	a
64	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)-2,2-dimethylpropan-1-one	353	354	a
65	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)-2-methylpropan-1-one	339	340	a
66	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)-2-phenylethan-1-one	387	388	a
67	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)-3-methylbutan-1-one	353	354	a
68	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)-3-phenylpropan-1-one	401	402	a
69	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)butan-1-one	339	340	a
70	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	325	326	a
71	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-2,2-dimethylpropan-1-one	353	354	a
72	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-	367	368	c

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
	1H-1,2,4-triazol-1-yl)-3,3-dimethylbutan-2-one			
73	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)propan-2-one	325	326	c
74	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-pyrazol-1-yl)propan-1-one	324	325	c
75	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)-2,2-dimethylpropan-1-one	353	354	a
76	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)-2-methylpropan-1-one	339	340	a
77	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)-2-phenylethan-1-one	387	388	a
78	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)-3-methylbutan-1-one	353	354	a
79	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)-3-phenylpropan-1-one	401	402	a
80	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)butan-1-one	339	340	a
81	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	325	326	a
82	1-(5-[(4-fluorophenyl)methyl]amino-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl)-2,2-dimethylpropan-1-one	358	359	a
83	1-(5-[(4-fluorophenyl)methyl]amino-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	330	331	b
84	1-(5-[(4-fluorophenyl)methyl]amino-3-phenyl-1H-pyrazol-1-yl)propan-1-one	323	324	c
85	1-(5-[(4-fluorophenyl)methyl]amino-4-methyl-3-phenyl-1H-pyrazol-1-yl)propan-1-one	337	338	c
86	1-(5-[(4-fluorophenyl)methyl]sulfanyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	342	343	a
87	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)-2,2-dimethylpropan-1-one	365	366	a
88	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)-2-methylpropan-1-one	351	352	a
89	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)-2-phenylethan-1-one	399	400	a
90	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)-3-methylbutan-1-one	365	366	a
91	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)-3-phenylpropan-1-one	413	414	b
92	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)butan-1-one	351	352	a
93	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	337	338	a
94	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-2,2-dimethylpropan-1-one	365	366	a

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
95	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)-2-methylpropan-1-one	351	352	a
96	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)-2-phenylethan-1-one	399	400	a
97	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)-3-methylbutan-1-one	365	366	a
98	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)-3-phenylpropan-1-one	413	414	c
99	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)butan-1-one	351	352	a
100	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	337	338	b
101	1-[(2,2-difluoro-2H-1,3-benzodioxol-4-yl)carbonyl]-N-[(4-fluorophenyl)methyl]-3-phenyl-1H-1,2,4-triazol-5-amine	452	453	c
102	1-[(2,3-dihydro-1,4-benzodioxin-5-yl)carbonyl]-N-[(4-fluorophenyl)methyl]-3-phenyl-1H-1,2,4-triazol-5-amine	430	431	a
103	1-[(2-amino-4-methoxyphenyl)carbonyl]-N-benzyl-3-(2-fluorophenyl)-1H-pyrazol-5-amine	416	417	c
104	1-[(2-amino-4-methoxyphenyl)carbonyl]-N-benzyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	400	401	a
105	1-[(2-amino-4-methoxyphenyl)carbonyl]-N-benzyl-3-(pyridin-2-yl)-1H-pyrazol-5-amine	399	400	b
106	1-[(2-amino-4-methylphenyl)carbonyl]-N-benzyl-3-(2-fluorophenyl)-1H-pyrazol-5-amine	400	401	c
107	1-[(2-amino-4-methylphenyl)carbonyl]-N-benzyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	384	385	a
108	1-[(2-amino-4-methylphenyl)carbonyl]-N-benzyl-3-(pyridin-2-yl)-1H-pyrazol-5-amine	383	384	b
109	1-[(2-aminophenyl)carbonyl]-N-benzyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	370	371	a
110	1-[(2-chlorophenyl)carbonyl]-5-(methylsulfanyl)-3-(thiophen-2-yl)-1H-1,2,4-triazole	336	336,338	a
111	1-[(2-chlorophenyl)carbonyl]-N-[(4-fluorophenyl)methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	408	408,410	a
112	1-[(2-chlorophenyl)carbonyl]-N-[(4-fluorophenyl) methyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	408	408,410	a
113	1-[(2-chlorophenyl)carbonyl]-N-[(4-fluorophenyl) methyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine	413	413,415	a
114	1-[(2-chlorophenyl)carbonyl]-N-[(4-fluorophenyl)methyl]-3-phenyl-1H-pyrazol-5-amine	406	406,408	c
115	1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-N-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-amine	391	392	a

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
116	1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-N-(thiophen-2-ylmethyl)-1H-pyrazol-5-amine	390	391	b
117	1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-N-(thiophen-3-ylmethyl)-1H-1,2,4-triazol-5-amine	391	392	a
118	1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-N-(thiophen-3-ylmethyl)-1H-pyrazol-5-amine	390	391	b
119	1-[(2-methoxyphenyl)carbonyl]-N-(naphthalen-1-ylmethyl)-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	435	436	c
120	1-[(2-methoxyphenyl)carbonyl]-N-(naphthalen-2-ylmethyl)-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	435	436	c
121	1-[(4-chlorophenyl)carbonyl]-N-[(4-fluorophenyl) methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	408	408,410	a
122	1-[(4-chlorophenyl)carbonyl]-N-[(4-fluorophenyl) methyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	408	408,410	b
123	1-[(furan-2-yl)carbonyl]-N-[(4-methoxyphenyl) methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	375	376	b
124	1-[(furan-2-yl)carbonyl]-N-[(4-methoxyphenyl) methyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	375	376	b
125	1-[(furan-3-yl)carbonyl]-N-[(4-methoxyphenyl) methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	375	376	b
126	1-[(furan-3-yl)carbonyl]-N-[(4-methoxyphenyl) methyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	375	376	b
127	1-[(furan-3-yl)carbonyl]-N-[(4-methoxyphenyl) methyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	375	376	c
128	1-[2-(4-fluorophenyl)ethyl]-N,N-dimethyl-3-(pyridin-2-yl)-1H-pyrazole-5-carboxamide	338	339	c
129	1-[2-(4-fluorophenyl)ethyl]-N,N-dimethyl-5-(pyridin-2-yl)-1H-pyrazole-3-carboxamide	338	339	c
130	1-[2-(4-fluorophenyl)ethyl]-N-methyl-N-phenyl-3-(pyridin-2-yl)-1H-pyrazole-5-carboxamide	400	401	c
131	1-[2-(4-fluorophenyl)ethyl]-N-methyl-N-phenyl-5-(pyridin-2-yl)-1H-pyrazole-3-carboxamide	400	401	c
132	1-[5-(benzylamino)-3-(2-fluorophenyl)-1H-1,2,4-triazol-1-yl]propan-1-one	324	325	a
133	1-[5-(benzylamino)-3-(2-fluorophenyl)-1H-pyrazol-1-yl]-2,2-dimethylpropan-1-one	351	352	b
134	1-[5-(benzylamino)-3-(2-fluorophenyl)-1H-pyrazol-1-yl]-3-methylbutan-1-one	351	352	c
135	1-[5-(benzylamino)-3-(3-fluorophenyl)-1H-1,2,4-triazol-1-yl]propan-1-one	324	325	b
136	1-[5-(benzylamino)-3-(furan-2-yl)-1H-1,2,4-triazol-1-yl]-2,2-dimethylpropan-1-one	324	325	a
137	1-[5-(benzylamino)-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl]-2,2-dimethylpropan-1-one	335	336	a
138	1-[5-(benzylamino)-3-(pyridin-2-yl)-1H-1,2,4-triazol-	321	322	a

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
	1-yl]-2-methylpropan-1-one			
139	1-[5-(benzylamino)-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl]-2-phenylethan-1-one	369	370	a
140	1-[5-(benzylamino)-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl]-3-methylbutan-1-one	335	336	a
141	1-[5-(benzylamino)-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl]butan-1-one	321	322	a
142	1-[5-(benzylamino)-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl]propan-1-one	307	308	a
143	1-[5-(benzylamino)-3-(pyridin-2-yl)-1H-pyrazol-1-yl]-2,2-dimethylpropan-1-one	334	335	a
144	1-[5-(benzylamino)-3-(pyridin-2-yl)-1H-pyrazol-1-yl]-3-methylbutan-1-one	334	335	b
145	1-[5-(benzylamino)-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl]-2,2-dimethylpropan-1-one	335	336	a
146	1-[5-(benzylamino)-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl]-2-methylpropan-1-one	321	322	a
147	1-[5-(benzylamino)-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl]-2-phenylethan-1-one	369	370	a
148	1-[5-(benzylamino)-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl]-3-methylbutan-1-one	335	336	a
149	1-[5-(benzylamino)-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl]-3-phenylpropan-1-one	383	384	b
150	1-[5-(benzylamino)-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl]butan-1-one	321	322	a
151	1-[5-(benzylamino)-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl]propan-1-one	307	308	a
152	1-[5-(benzylamino)-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl]-2,2-dimethylpropan-1-one	340	341	a
153	1-[5-(methylsulfanyl)-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl]propan-1-one	248	249	c
154	1-[5-(methylsulfanyl)-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl]propan-1-one	253	254	c
155	1-[5-amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl]propan-1-one	217	218	c
156	1-benzoyl-N-[(4-fluorophenyl)methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	373	374	a
157	1-benzoyl-N-[(4-methoxyphenyl)methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	385	386	b
158	1-benzoyl-N-[(4-methoxyphenyl)methyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	385	386	c
159	1-benzoyl-N-benzyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	355	356	a
160	1-benzoyl-N-benzyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	355	356	a

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
161	1-benzyl-N-[(4-fluorophenyl)methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	359	360	c
162	1-benzyl-N-[(4-fluorophenyl)methyl]-5-(pyridin-2-yl)-1H-1,2,4-triazol-3-amine	359	360	c
163	1-1-[2-(4-fluorophenyl)ethyl]-3-(pyridin-2-yl)-1H-pyrazol-5-ylethan-1-ol	311	312	c
164	1-1-[2-(4-fluorophenyl)ethyl]-3-(pyridin-2-yl)-1H-pyrazol-5-ylethan-1-one	309	310	c
165	1-5-[(furan-2-ylmethyl)amino]-3-(pyridin-2-yl)-1H-pyrazol-1-yl-2,2-dimethylpropan-1-one	324	325	b
166	1-5-[(furan-3-ylmethyl)amino]-3-(pyridin-2-yl)-1H-pyrazol-1-yl-2,2-dimethylpropan-1-one	324	325	b
167	2,2-dimethyl-1-[3-(pyridin-2-yl)-5-[(thiophen-2-ylmethyl)amino]-1H-pyrazol-1-yl]propan-1-one	340	341	a
168	2,2-dimethyl-1-[3-(pyridin-2-yl)-5-[(thiophen-3-ylmethyl)amino]-1H-pyrazol-1-yl]propan-1-one	340	341	b
169	2,2-dimethyl-N-3-[(morpholin-4-yl)carbonyl]-1H-1,2,4-triazol-5-ylpropanamide	281	282	c
170	2-chloro-N-3-[(morpholin-4-yl)carbonyl]-1H-1,2,4-triazol-5-ylbenzamide	336	336,338	c
171	2-chloro-N-3-[(pyrrolidin-1-yl)carbonyl]-1H-1,2,4-triazol-5-ylbenzamide	320	320,322	c
172	2-chlorophenyl 5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxylate	424	424,426	c
173	2-fluorophenyl 5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxylate	407	408	c
174	2-methoxyphenyl 5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxylate	419	420	c
175	2-1-[2-(4-fluorophenyl)ethyl]-5-[(2-methoxyphenyl)carbonyl]-1H-pyrazol-3-ylpyridine	401	402	c
176	2-[5-(benzylamino)-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile	380	381	b
177	2-[5-(benzylamino)-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl]carbonylphenyl acetate	413	414	a
178	3-(pyridin-3-yl)-N-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-amine	257	258	c
179	3-([1-propanoyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile	332	333	c
180	3-1-[(2-chlorophenyl)carbonyl]-5-(methylsulfanyl)-1H-1,2,4-triazol-3-ylpyridine	331	331,333	a
181	3-1-[(2-chlorophenyl)carbonyl]-5-[(4-fluorophenyl)methyl]sulfanyl-1H-1,2,4-triazol-3-ylpyridine	425	425,427	b
182	3-1-[(2-methoxyphenyl)carbonyl]-5-(methylsulfanyl)-1H-1,2,4-triazol-3-ylpyridine	326	327	a

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
183	3-[(4-fluorophenyl)methyl]amino-N-phenyl-1-(pyridin-2-yl)-1H-pyrazole-4-carboxamide	387	388	c
184	4-chloro-N-3-[(morpholin-4-yl)carbonyl]-1H-1,2,4-triazol-5-ylbenzamide	336	336,338	c
185	4-methyl-N-3-[(morpholin-4-yl)carbonyl]-1H-1,2,4-triazol-5-ylbenzamide	315	316	c
186	5-C-(2-chlorobenzene)-3-N,3-N-dimethyl-1H-1,2,4-triazole-3,5-dicarboxamide	294	294,296	c
187	5-C-(2-chlorobenzene)-3-N-methyl-1H-1,2,4-triazole-3,5-dicarboxamide	280	280,282	c
188	5-[(4-fluorophenyl)methyl]amino-N,N-dimethyl-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxamide	340	341	c
189	5-[(4-fluorophenyl)methyl]amino-N-(2-methoxyphenyl)-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxamide	418	419	c
190	5-[(4-fluorophenyl)methyl]amino-N-(propan-2-yl)-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxamide	354	355	c
191	5-[(4-fluorophenyl)methyl]amino-N-phenyl-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxamide	388	389	c
192	ethyl 5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxylate	341	342	b
193	methyl 5-[(2-fluorobenzene)amido]-1H-1,2,4-triazole-3-carboxylate	264	265	c
194	methyl 5-[(2-methoxybenzene)amido]-1H-1,2,4-triazole-3-carboxylate	276	277	c
195	methyl 5-[(3-chlorobenzene)amido]-1H-1,2,4-triazole-3-carboxylate	281	281,283	c
196	methyl 5-[(4-methylbenzene)amido]-1H-1,2,4-triazole-3-carboxylate	260	261	c
197	methyl 5-amino-1-[(4-chlorophenyl)carbonyl]-1H-1,2,4-triazole-3-carboxylate	281	281,283	a
198	N-(1-benzothiophen-2-ylmethyl)-1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	442	442	c
199	N-(1-benzothiophen-3-ylmethyl)-1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	442	442	c
200	N-(2-chlorophenyl)-5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxamide	423	423,425	c
201	N-(furan-2-ylmethyl)-1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	374	375	b
202	N-(furan-3-ylmethyl)-1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	374	375	b
203	N-[(4-fluorophenyl)methyl]-1-(2-phenylethyl)-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	373	374	c

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
204	N-[(4-fluorophenyl)methyl]-1-(2-phenylethyl)-5-(pyridin-2-yl)-1H-1,2,4-triazol-3-amine	373	374	c
205	N-[(4-fluorophenyl)methyl]-1-[(2-methoxy-4-methylphenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine	416	417	b
206	N-[(4-fluorophenyl)methyl]-1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	403	404	a
207	N-[(4-fluorophenyl)methyl]-1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	403	404	a
208	N-[(4-fluorophenyl)methyl]-1-[(2-methoxyphenyl) carbonyl]-3-phenyl-1H-pyrazol-5-amine	401	402	c
209	N-[(4-fluorophenyl)methyl]-1-[(2-methylphenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine	386	387	b
210	N-[(4-fluorophenyl)methyl]-1-[(furan-2-yl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	363	364	a
211	N-[(4-fluorophenyl)methyl]-1-[(furan-2-yl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	363	364	a
212	N-[(4-fluorophenyl)methyl]-1-[(furan-3-yl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	363	364	a
213	N-[(4-fluorophenyl)methyl]-1-[(furan-3-yl)carbonyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	363	364	a
214	N-[(4-fluorophenyl)methyl]-1-[(furan-3-yl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	363	364	a
215	N-[(4-fluorophenyl)methyl]-1-[(piperidin-1-yl)carbonyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	380	381	c
216	N-[(4-fluorophenyl)methyl]-1-propyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	311	312	c
217	N-[(4-fluorophenyl)methyl]-1-propyl-5-(pyridin-2-yl)-1H-1,2,4-triazol-3-amine	311	312	c
218	N-[(4-fluorophenyl)methyl]-2,2-dimethyl-N-(4-methyl-3-phenyl-1H-pyrazol-5-yl)propanamide	365	366	c
219	N-[(4-fluorophenyl)methyl]-3-(pyridin-2-yl)-1-[(thiophen-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine	379	380	a
220	N-[(4-fluorophenyl)methyl]-3-(pyridin-3-yl)-1-[(thiophen-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine	379	380	a
221	N-[(4-fluorophenyl)methyl]-3-(pyridin-4-yl)-1-[(thiophen-2-yl)carbonyl]-1H-1,2,4-triazol-5-amine	379	380	b
222	N-[(4-fluorophenyl)methyl]-3-phenyl-1-[(thiophen-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine	378	379	a
223	N-[(4-fluorophenyl)methyl]-4-[(2-methoxyphenyl)carbonyl]-1-(pyridin-2-yl)-1H-pyrazol-3-amine	402	403	c

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
224	N-[(4-fluorophenyl)methyl]-4-[(2-methoxyphenyl) carbonyl]-1-phenyl-1H-pyrazol-3-amine	401	402	c
225	N-[(4-fluorophenyl)methyl]-4-[(piperidin-1-yl)carbonyl]-1-(pyridin-2-yl)-1H-pyrazol-3-amine	379	380	c
226	N-[(4-methoxyphenyl)methyl]-3-(pyridin-2-yl)-1-[(thiophen-2-yl)carbonyl]-1H-1,2,4-triazol-5-amine	391	392	c
227	N-[(4-methoxyphenyl)methyl]-3-(pyridin-2-yl)-1-[(thiophen-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine	391	392	b
228	N-[(4-methoxyphenyl)methyl]-3-(pyridin-3-yl)-1-[(thiophen-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine	391	392	c
229	N-[(4-methoxyphenyl)methyl]-3-(pyridin-4-yl)-1-[(thiophen-2-yl)carbonyl]-1H-1,2,4-triazol-5-amine	391	392	c
230	N-[(4-methoxyphenyl)methyl]-3-(pyridin-4-yl)-1-[(thiophen-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine	391	392	b
231	N-benzyl-1-[(2,2-difluoro-2H-1,3-benzodioxol-4-yl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	435	436	c
232	N-benzyl-1-[(2,3-dihydro-1,4-benzodioxin-5-yl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	413	414	a
233	N-benzyl-1-[(2,3-dimethoxyphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	415	416	a
234	N-benzyl-1-[(2,4-dimethoxyphenyl)carbonyl]-3-(2-fluorophenyl)-1H-pyrazol-5-amine	431	432	c
235	N-benzyl-1-[(2,4-dimethoxyphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	415	416	a
236	N-benzyl-1-[(2,4-dimethoxyphenyl)carbonyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	414	415	b
237	N-benzyl-1-[(2,4-dimethylphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	383	384	b
238	N-benzyl-1-[(2,6-dichlorophenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	424	424,426, 428	c
239	N-benzyl-1-[(2,6-difluorophenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	391	392	b
240	N-benzyl-1-[(2-bromophenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	434	434,436	a
241	N-benzyl-1-[(2-bromophenyl)carbonyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	433	433,435	b
242	N-benzyl-1-[(2-chlorophenyl)carbonyl]-3-(2-fluorophenyl)-1H-pyrazol-5-amine	406	406,408	b
243	N-benzyl-1-[(2-chlorophenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	390	390,392	a
244	N-benzyl-1-[(2-chlorophenyl)carbonyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	389	389,391	b
245	N-benzyl-1-[(2-chlorophenyl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	390	390,392	a
246	N-benzyl-1-[(2-ethylphenyl)carbonyl]-3-(pyridin-2-yl)-	383	384	b

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
	1H-1,2,4-triazol-5-amine			
247	N-benzyl-1-[(2-ethylphenyl)carbonyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	382	383	c
248	N-benzyl-1-[(2-fluoro-4-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	403	404	a
249	N-benzyl-1-[(2-fluoro-4-methylphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	387	388	a
250	N-benzyl-1-[(2-fluorophenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	373	374	a
251	N-benzyl-1-[(2-fluorophenyl)carbonyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	372	373	a
252	N-benzyl-1-[(2-fluorophenyl)carbonyl]-N-methyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	387	388	b
253	N-benzyl-1-[(2-methoxy-4-methylphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	399	400	a
254	N-benzyl-1-[(2-methoxyphenyl)carbonyl]-3-(pyridazin-3-yl)-1H-1,2,4-triazol-5-amine	386	387	a
255	N-benzyl-1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	385	386	a
256	N-benzyl-1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	384	385	b
257	N-benzyl-1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	385	386	a
258	N-benzyl-1-[(2-methoxyphenyl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine	390	391	a
259	N-benzyl-1-[(2-methylphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	369	370	a
260	N-benzyl-1-[(2-methylphenyl)carbonyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	368	369	c
261	N-benzyl-1-[(3-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	385	386	a
262	N-benzyl-1-[(4-chlorophenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	390	390,392	a
263	N-benzyl-1-[(4-chlorophenyl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	390	390,392	a
264	N-benzyl-1-[(4-methoxy-2-methylphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	399	400	a
265	N-benzyl-1-[(4-methoxyphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	385	386	a
266	N-benzyl-1-[(furan-2-yl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	345	346	a
267	N-benzyl-1-[(furan-3-yl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	345	346	a
268	N-benzyl-1-[(furan-3-yl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	345	346	a

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
269	N-benzyl-1-[(naphthalen-1-yl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	405	406	a
270	N-benzyl-1-[(naphthalen-1-yl)carbonyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	404	405	c
271	N-benzyl-1-[(naphthalen-2-yl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	405	406	b
272	N-benzyl-1-[(naphthalen-2-yl)carbonyl]-3-(pyridin-2-yl)-1H-pyrazol-5-amine	404	405	c
273	N-benzyl-1-[2-(dimethylamino)phenyl]carbonyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	398	399	c
274	N-benzyl-1-[2-(methylamino)phenyl]carbonyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	384	385	N/A
275	N-benzyl-1-[2-(propan-2-yl)phenyl]carbonyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	397	398	c
276	N-benzyl-1-[2-(propan-2-yl)phenyl]carbonyl-3-(pyridin-2-yl)-1H-pyrazol-5-amine	396	397	c
277	N-benzyl-3-(2-fluorophenyl)-1-[(2-fluorophenyl)carbonyl]-1H-pyrazol-5-amine	389	390	b
278	N-benzyl-3-(2-fluorophenyl)-1-[(2-methoxyphenyl)carbonyl]-1H-pyrazol-5-amine	401	402	c
279	N-benzyl-3-(2-fluorophenyl)-1-[(thiophen-3-yl)carbonyl]-1H-pyrazol-5-amine	377	378	c
280	N-benzyl-3-(furan-2-yl)-1-[(2-methoxyphenyl)carbonyl]-1H-1,2,4-triazol-5-amine	374	375	a
281	N-benzyl-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine	240	241	c
282	N-benzyl-3-(pyridin-2-yl)-1-[(thiophen-2-yl)carbonyl]-1H-1,2,4-triazol-5-amine	361	362	a
283	N-benzyl-3-(pyridin-2-yl)-1-[(thiophen-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine	361	362	a
284	N-benzyl-3-(pyridin-2-yl)-1-[(thiophen-3-yl)carbonyl]-1H-pyrazol-5-amine	360	361	a
285	N-benzyl-3-(pyridin-2-yl)-1-[2-(trifluoromethoxy) phenyl]carbonyl-1H-1,2,4-triazol-5-amine	439	440	a
286	N-benzyl-3-(pyridin-2-yl)-1-[2-(trifluoromethyl) phenyl]carbonyl-1H-1,2,4-triazol-5-amine	423	424	c
287	N-benzyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	251	252	c
288	N-benzyl-3-(pyridin-4-yl)-1-[(thiophen-2-yl)carbonyl]-1H-1,2,4-triazol-5-amine	361	362	a
289	N-benzyl-3-(pyridin-4-yl)-1-[(thiophen-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine	361	362	a
290	N-benzyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	251	252	c
291	N-benzyl-3-(thiophen-2-yl)-1-[(thiophen-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine	366	367	b
292	N-benzyl-N-[3-(2-fluorophenyl)-1H-pyrazol-5-yl]-2-	401	402	c

Cmpd No.	IUPAC name	MW_{calc}	MW_{meas}	Thrombin Activity
	methoxybenzamide			
293	N-ethyl-1-[2-(4-fluorophenyl)ethyl]-N-methyl-3-(pyridin-2-yl)-1H-pyrazole-5-carboxamide	352	353	c
294	N-ethyl-1-[2-(4-fluorophenyl)ethyl]-N-methyl-5-(pyridin-2-yl)-1H-pyrazole-3-carboxamide	352	353	c
295	N-ethyl-3-[(4-fluorophenyl)methyl]amino-1-(pyridin-2-yl)-1H-pyrazole-4-carboxamide	339	340	c
296	N-ethyl-5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxamide	340	341	c
297	N-ethyl-5-[(4-fluorophenyl)methyl]amino-N-methyl-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxamide	354	355	c
298	phenyl 5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxylate	389	390	a
299	propan-2-yl 5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxylate	355	356	c
300	tert-butyl 5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazole-1-carboxylate	369	370	c
301	tert-butyl N-(2-[5-(benzylamino)-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl]carbonylphenyl)carbamate	471	471	c
302	tert-butyl N-(4-acetyl-1-phenyl-1H-pyrazol-3-yl)-N-[(4-fluorophenyl)methyl]carbamate	409	410	c
303	tert-butyl N-[(4-fluorophenyl)methyl]-N-4-[(2-methoxyphenyl)carbonyl]-1-phenyl-1H-pyrazol-3-ylcarbamate	502	502	c
304	1-[2-(4-fluorophenyl)ethyl]-3-(pyridin-2-yl)-1H-pyrazol-5-yl(2-methoxyphenyl)methanol	403	404	c

[0080] In some embodiments, there is provided a compound as expressly set forth in Table B following.

Table B.

Cmpd No	IUPAC name
413	1-[3-(4-chlorophenyl)-5-[(4-fluorophenyl)methyl]amino-1H-1,2,4-triazol-1-yl]-2-methoxyethan-1-one
414	1-[5-(benzylamino)-3-(furan-2-yl)-1H-1,2,4-triazol-1-yl]-3-methylbutan-1-one
415	1-[5-(benzylamino)-3-(furan-2-yl)-1H-1,2,4-triazol-1-yl]ethan-1-one
416	1-[5-(benzylamino)-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl]ethan-1-one
417	1-[5-(benzylamino)-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl]ethan-1-one
418	1-[5-(benzylamino)-3-(pyridin-3-yl)-1H-pyrazol-1-yl]-2-methylpropan-1-one
419	1-[5-(benzylamino)-3-(pyridin-3-yl)-1H-pyrazol-1-yl]-2-phenylethan-1-one
420	1-[5-(benzylamino)-3-(pyridin-3-yl)-1H-pyrazol-1-yl]-3-methylbutan-1-one

Cmpd No	IUPAC name
421	1-[5-(benzylamino)-3-(pyridin-3-yl)-1H-pyrazol-1-yl]-3-phenylpropan-1-one
422	1-[5-(benzylamino)-3-(pyridin-3-yl)-1H-pyrazol-1-yl]butan-1-one
423	1-[5-(benzylamino)-3-(pyridin-3-yl)-1H-pyrazol-1-yl]ethan-1-one
424	1-[5-(benzylamino)-3-(pyridin-3-yl)-1H-pyrazol-1-yl]propan-1-one
425	1-[5-(benzylamino)-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl]ethan-1-one
426	1-[5-(benzylamino)-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl]-2-methylpropan-1-one
427	1-[5-(benzylamino)-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl]-2-phenylethan-1-one
428	1-[5-(benzylamino)-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl]-3-methylbutan-1-one
429	1-[5-(benzylamino)-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl]-3-phenylpropan-1-one
430	1-[5-(benzylamino)-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl]butan-1-one
431	1-[5-(benzylamino)-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl]ethan-1-one
432	1-[5-(benzylamino)-3-phenyl-1H-1,2,4-triazol-1-yl]-2-methylpropan-1-one
433	1-[5-(benzylamino)-3-phenyl-1H-1,2,4-triazol-1-yl]-3-methylbutan-1-one
434	1-[5-(benzylamino)-3-phenyl-1H-1,2,4-triazol-1-yl]butan-1-one
435	1-[5-(benzylamino)-3-phenyl-1H-1,2,4-triazol-1-yl]ethan-1-one
436	1-[5-(benzylamino)-3-phenyl-1H-pyrazol-1-yl]-2-methylpropan-1-one
437	1-[5-(benzylamino)-3-phenyl-1H-pyrazol-1-yl]-2-phenylethan-1-one
438	1-[5-(benzylamino)-3-phenyl-1H-pyrazol-1-yl]-3-methylbutan-1-one
439	1-[5-(benzylamino)-3-phenyl-1H-pyrazol-1-yl]-3-phenylpropan-1-one
440	1-[5-(benzylamino)-3-phenyl-1H-pyrazol-1-yl]butan-1-one
441	1-[5-(benzylamino)-3-phenyl-1H-pyrazol-1-yl]ethan-1-one
442	1-[5-(benzylamino)-3-phenyl-1H-pyrazol-1-yl]propan-1-one
443	1-benzoyl-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine
444	1-benzoyl-3-(furan-2-yl)-N-(pyridin-2-ylmethyl)-1H-1,2,4-triazol-5-amine
445	1-benzoyl-3-(furan-2-yl)-N-(pyridin-2-ylmethyl)-1H-1,2,4-triazol-5-amine
446	1-benzoyl-3-(furan-2-yl)-N-(pyridin-3-ylmethyl)-1H-1,2,4-triazol-5-amine
447	1-benzoyl-3-(furan-2-yl)-N-(pyridin-3-ylmethyl)-1H-1,2,4-triazol-5-amine
448	1-benzoyl-3-(furan-2-yl)-N-(pyridin-4-ylmethyl)-1H-1,2,4-triazol-5-amine
449	1-benzoyl-3-(furan-2-yl)-N-(pyridin-4-ylmethyl)-1H-1,2,4-triazol-5-amine
450	1-benzoyl-3-(furan-2-yl)-N-[(2-methylphenyl)methyl]-1H-1,2,4-triazol-5-amine
451	1-benzoyl-3-(furan-2-yl)-N-[(3-methoxyphenyl)methyl]-1H-1,2,4-triazol-5-amine
452	1-benzoyl-3-(furan-2-yl)-N-[(3-methylphenyl)methyl]-1H-1,2,4-triazol-5-amine
453	1-benzoyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
454	1-benzoyl-3-(pyridin-2-yl)-N-(pyridin-2-ylmethyl)-1H-1,2,4-triazol-5-amine
455	1-benzoyl-3-(pyridin-2-yl)-N-(pyridin-3-ylmethyl)-1H-1,2,4-triazol-5-amine
456	1-benzoyl-3-(pyridin-2-yl)-N-(pyridin-4-ylmethyl)-1H-1,2,4-triazol-5-amine
457	1-benzoyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine
458	1-benzoyl-3-(pyridin-3-yl)-1H-pyrazol-5-amine

Cmpd No	IUPAC name
459	1-benzoyl-3-(pyridin-3-yl)-N-(pyridin-3-ylmethyl)-1H-1,2,4-triazol-5-amine
460	1-benzoyl-3-(pyridin-3-yl)-N-(pyridin-3-ylmethyl)-1H-pyrazol-5-amine
461	1-benzoyl-3-(pyridin-3-yl)-N-(pyridin-3-ylmethyl)-1H-pyrazol-5-amine
462	1-benzoyl-3-(pyridin-3-yl)-N-(pyridin-4-ylmethyl)-1H-1,2,4-triazol-5-amine
463	1-benzoyl-3-(pyridin-3-yl)-N-(pyridin-4-ylmethyl)-1H-pyrazol-5-amine
464	1-benzoyl-3-(pyridin-3-yl)-N-(pyridin-4-ylmethyl)-1H-pyrazol-5-amine
465	1-benzoyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
466	1-benzoyl-3-(pyridin-4-yl)-N-(pyridin-4-ylmethyl)-1H-1,2,4-triazol-5-amine
467	1-benzoyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
468	1-benzoyl-3-phenyl-1H-1,2,4-triazol-5-amine
469	1-benzoyl-3-phenyl-1H-pyrazol-5-amine
470	1-benzoyl-3-phenyl-N-(pyridin-2-ylmethyl)-1H-pyrazol-5-amine
471	1-benzoyl-3-phenyl-N-(pyridin-2-ylmethyl)-1H-pyrazol-5-amine
472	1-benzoyl-3-phenyl-N-(pyridin-3-ylmethyl)-1H-1,2,4-triazol-5-amine
473	1-benzoyl-3-phenyl-N-(pyridin-3-ylmethyl)-1H-1,2,4-triazol-5-amine
474	1-benzoyl-3-phenyl-N-(pyridin-3-ylmethyl)-1H-pyrazol-5-amine
475	1-benzoyl-3-phenyl-N-(pyridin-3-ylmethyl)-1H-pyrazol-5-amine
476	1-benzoyl-3-phenyl-N-(pyridin-4-ylmethyl)-1H-pyrazol-5-amine
477	1-benzoyl-3-phenyl-N-(pyridin-4-ylmethyl)-1H-pyrazol-5-amine
478	1-benzoyl-N-(pyridin-2-ylmethyl)-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine
479	1-benzoyl-N-(pyridin-2-ylmethyl)-3-(pyridin-3-yl)-1H-pyrazol-5-amine
480	1-benzoyl-N-(pyridin-2-ylmethyl)-3-(pyridin-3-yl)-1H-pyrazol-5-amine
481	1-benzoyl-N-(pyridin-2-ylmethyl)-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
482	1-benzoyl-N-(pyridin-2-ylmethyl)-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
483	1-benzoyl-N-(pyridin-2-ylmethyl)-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
484	1-benzoyl-N-(pyridin-3-ylmethyl)-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
485	1-benzoyl-N-(pyridin-3-ylmethyl)-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
486	1-benzoyl-N-(pyridin-3-ylmethyl)-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
487	1-benzoyl-N-(pyridin-4-ylmethyl)-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
488	1-benzoyl-N-(pyridin-4-ylmethyl)-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
489	1-benzoyl-N-[(2-chlorophenyl)methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
490	1-benzoyl-N-[(2-chlorophenyl)methyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine
491	1-benzoyl-N-[(2-chlorophenyl)methyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
492	1-benzoyl-N-[(2-chlorophenyl)methyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
493	1-benzoyl-N-[(2-chlorophenyl)methyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
494	1-benzoyl-N-[(2-chlorophenyl)methyl]-3-phenyl-1H-1,2,4-triazol-5-amine
495	1-benzoyl-N-[(2-chlorophenyl)methyl]-3-phenyl-1H-pyrazol-5-amine
496	1-benzoyl-N-[(2-fluorophenyl)methyl]-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine

Cmpd No	IUPAC name
497	1-benzoyl-N-[(2-fluorophenyl)methyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
498	1-benzoyl-N-[(2-fluorophenyl)methyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
499	1-benzoyl-N-[(2-fluorophenyl)methyl]-3-phenyl-1H-1,2,4-triazol-5-amine
500	1-benzoyl-N-[(2-fluorophenyl)methyl]-3-phenyl-1H-pyrazol-5-amine
501	1-benzoyl-N-[(2-methoxyphenyl)methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
502	1-benzoyl-N-[(2-methoxyphenyl)methyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
503	1-benzoyl-N-[(2-methoxyphenyl)methyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
504	1-benzoyl-N-[(2-methoxyphenyl)methyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
505	1-benzoyl-N-[(2-methoxyphenyl)methyl]-3-phenyl-1H-1,2,4-triazol-5-amine
506	1-benzoyl-N-[(2-methoxyphenyl)methyl]-3-phenyl-1H-pyrazol-5-amine
507	1-benzoyl-N-[(2-methylphenyl)methyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine
508	1-benzoyl-N-[(2-methylphenyl)methyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
509	1-benzoyl-N-[(2-methylphenyl)methyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
510	1-benzoyl-N-[(2-methylphenyl)methyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
511	1-benzoyl-N-[(2-methylphenyl)methyl]-3-phenyl-1H-1,2,4-triazol-5-amine
512	1-benzoyl-N-[(2-methylphenyl)methyl]-3-phenyl-1H-pyrazol-5-amine
513	1-benzoyl-N-[(3-chlorophenyl)methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
514	1-benzoyl-N-[(3-chlorophenyl)methyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
515	1-benzoyl-N-[(3-chlorophenyl)methyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
516	1-benzoyl-N-[(3-chlorophenyl)methyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
517	1-benzoyl-N-[(3-chlorophenyl)methyl]-3-phenyl-1H-1,2,4-triazol-5-amine
518	1-benzoyl-N-[(3-chlorophenyl)methyl]-3-phenyl-1H-pyrazol-5-amine
519	1-benzoyl-N-[(3-fluorophenyl)methyl]-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine
520	1-benzoyl-N-[(3-fluorophenyl)methyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
521	1-benzoyl-N-[(3-fluorophenyl)methyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
522	1-benzoyl-N-[(3-fluorophenyl)methyl]-3-phenyl-1H-1,2,4-triazol-5-amine
523	1-benzoyl-N-[(3-fluorophenyl)methyl]-3-phenyl-1H-pyrazol-5-amine
524	1-benzoyl-N-[(3-methoxyphenyl)methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
525	1-benzoyl-N-[(3-methoxyphenyl)methyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine
526	1-benzoyl-N-[(3-methoxyphenyl)methyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
527	1-benzoyl-N-[(3-methoxyphenyl)methyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
528	1-benzoyl-N-[(3-methoxyphenyl)methyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
529	1-benzoyl-N-[(3-methoxyphenyl)methyl]-3-phenyl-1H-1,2,4-triazol-5-amine
530	1-benzoyl-N-[(3-methoxyphenyl)methyl]-3-phenyl-1H-pyrazol-5-amine
531	1-benzoyl-N-[(3-methylphenyl)methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
532	1-benzoyl-N-[(3-methylphenyl)methyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine
533	1-benzoyl-N-[(3-methylphenyl)methyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
534	1-benzoyl-N-[(3-methylphenyl)methyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine

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535	1-benzoyl-N-[(3-methylphenyl)methyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
536	1-benzoyl-N-[(3-methylphenyl)methyl]-3-phenyl-1H-1,2,4-triazol-5-amine
537	1-benzoyl-N-[(3-methylphenyl)methyl]-3-phenyl-1H-pyrazol-5-amine
538	1-benzoyl-N-[(4-chlorophenyl)methyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
539	1-benzoyl-N-[(4-chlorophenyl)methyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
540	1-benzoyl-N-[(4-chlorophenyl)methyl]-3-phenyl-1H-1,2,4-triazol-5-amine
541	1-benzoyl-N-[(4-chlorophenyl)methyl]-3-phenyl-1H-pyrazol-5-amine
542	1-benzoyl-N-[(4-fluorophenyl)methyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
543	1-benzoyl-N-[(4-fluorophenyl)methyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
544	1-benzoyl-N-[(4-fluorophenyl)methyl]-3-phenyl-1H-pyrazol-5-amine
545	1-benzoyl-N-[(4-methoxyphenyl)methyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
546	1-benzoyl-N-[(4-methoxyphenyl)methyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
547	1-benzoyl-N-[(4-methoxyphenyl)methyl]-3-phenyl-1H-pyrazol-5-amine
548	1-benzoyl-N-[(4-methylphenyl)methyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
549	1-benzoyl-N-[(4-methylphenyl)methyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
550	1-benzoyl-N-[(4-methylphenyl)methyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
551	1-benzoyl-N-[(4-methylphenyl)methyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
552	1-benzoyl-N-[(4-methylphenyl)methyl]-3-phenyl-1H-1,2,4-triazol-5-amine
553	1-benzoyl-N-[(4-methylphenyl)methyl]-3-phenyl-1H-pyrazol-5-amine
554	1-benzoyl-N-benzyl-3-(2-fluorophenyl)-1H-1,2,4-triazol-5-amine
555	1-benzoyl-N-benzyl-3-(2-methylphenyl)-1H-1,2,4-triazol-5-amine
556	1-benzoyl-N-benzyl-3-(3-fluorophenyl)-1H-1,2,4-triazol-5-amine
557	1-benzoyl-N-benzyl-3-(3-methylphenyl)-1H-1,2,4-triazol-5-amine
558	1-benzoyl-N-benzyl-3-(4-fluorophenyl)-1H-1,2,4-triazol-5-amine
559	1-benzoyl-N-benzyl-3-(4-methylphenyl)-1H-1,2,4-triazol-5-amine
560	1-benzoyl-N-benzyl-3-(pyridin-3-yl)-1H-pyrazol-5-amine
561	1-benzoyl-N-benzyl-3-(pyridin-3-yl)-1H-pyrazol-5-amine
562	1-benzoyl-N-benzyl-3-(pyridin-3-yl)-1H-pyrazol-5-amine
563	1-benzoyl-N-benzyl-3-(pyridin-3-yl)-1H-pyrazol-5-amine
564	1-benzoyl-N-benzyl-3-(pyridin-3-yl)-1H-pyrazol-5-amine
565	1-benzoyl-N-benzyl-3-(pyridin-3-yl)-1H-pyrazol-5-amine
566	1-benzoyl-N-benzyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
567	1-benzoyl-N-benzyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
568	1-benzoyl-N-benzyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
569	1-benzoyl-N-benzyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
570	1-benzoyl-N-benzyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
571	1-benzoyl-N-benzyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
572	1-benzoyl-N-benzyl-3-phenyl-1H-pyrazol-5-amine

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573	1-benzoyl-N-benzyl-3-phenyl-1H-pyrazol-5-amine
574	1-benzoyl-N-benzyl-3-phenyl-1H-pyrazol-5-amine
575	1-benzoyl-N-benzyl-3-phenyl-1H-pyrazol-5-amine
576	1-benzoyl-N-benzyl-3-phenyl-1H-pyrazol-5-amine
577	1-benzoyl-N-benzyl-3-phenyl-1H-pyrazol-5-amine
578	1-benzoyl-N-[2-(dimethylamino)phenyl]methyl-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine
579	1-benzoyl-N-[2-(dimethylamino)phenyl]methyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
580	1-benzoyl-N-[2-(dimethylamino)phenyl]methyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine
581	1-benzoyl-N-[2-(dimethylamino)phenyl]methyl-3-(pyridin-3-yl)-1H-pyrazol-5-amine
582	1-benzoyl-N-[2-(dimethylamino)phenyl]methyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
583	1-benzoyl-N-[2-(dimethylamino)phenyl]methyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
584	1-benzoyl-N-[2-(dimethylamino)phenyl]methyl-3-phenyl-1H-1,2,4-triazol-5-amine
585	1-benzoyl-N-[2-(dimethylamino)phenyl]methyl-3-phenyl-1H-pyrazol-5-amine
586	1-benzoyl-N-[3-(dimethylamino)phenyl]methyl-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine
587	1-benzoyl-N-[3-(dimethylamino)phenyl]methyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
588	1-benzoyl-N-[3-(dimethylamino)phenyl]methyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine
589	1-benzoyl-N-[3-(dimethylamino)phenyl]methyl-3-(pyridin-3-yl)-1H-pyrazol-5-amine
590	1-benzoyl-N-[3-(dimethylamino)phenyl]methyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
591	1-benzoyl-N-[3-(dimethylamino)phenyl]methyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
592	1-benzoyl-N-[3-(dimethylamino)phenyl]methyl-3-phenyl-1H-1,2,4-triazol-5-amine
593	1-benzoyl-N-[3-(dimethylamino)phenyl]methyl-3-phenyl-1H-pyrazol-5-amine
594	1-benzoyl-N-[4-(dimethylamino)phenyl]methyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
595	1-benzoyl-N-[4-(dimethylamino)phenyl]methyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine
596	1-benzoyl-N-[4-(dimethylamino)phenyl]methyl-3-(pyridin-3-yl)-1H-pyrazol-5-amine
597	1-benzoyl-N-[4-(dimethylamino)phenyl]methyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
598	1-benzoyl-N-[4-(dimethylamino)phenyl]methyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
599	1-benzoyl-N-[4-(dimethylamino)phenyl]methyl-3-phenyl-1H-pyrazol-5-amine
600	2-([1-benzoyl-3-(furan-2-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
601	2-([1-benzoyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
602	2-([1-benzoyl-3-(pyridin-3-yl)-1H-pyrazol-5-yl]aminomethyl)benzonitrile
603	2-([1-benzoyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
604	2-([1-benzoyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
605	2-[(1-benzoyl-3-phenyl-1H-1,2,4-triazol-5-yl)amino]methylbenzonitrile
606	2-[(1-benzoyl-3-phenyl-1H-pyrazol-5-yl)amino]methylbenzonitrile
607	2-[5-(benzylamino)-3-(furan-2-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
608	2-[5-(benzylamino)-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
609	2-[5-(benzylamino)-3-(pyridin-3-yl)-1H-pyrazol-1-yl]carbonylbenzonitrile
610	2-[5-(benzylamino)-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile

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611	2-[5-(benzylamino)-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
612	2-[5-(benzylamino)-3-phenyl-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
613	2-[5-(benzylamino)-3-phenyl-1H-pyrazol-1-yl]carbonylbenzonitrile
614	3-([1-benzoyl-3-(furan-2-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
615	3-([1-benzoyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
616	3-([1-benzoyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
617	3-([1-benzoyl-3-(pyridin-3-yl)-1H-pyrazol-5-yl]aminomethyl)benzonitrile
618	3-([1-benzoyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
619	3-([1-benzoyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
620	3-[(1-benzoyl-3-phenyl-1H-1,2,4-triazol-5-yl)amino]methylbenzonitrile
621	3-[(1-benzoyl-3-phenyl-1H-pyrazol-5-yl)amino]methylbenzonitrile
622	3-[5-(benzylamino)-3-(furan-2-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
623	3-[5-(benzylamino)-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
624	3-[5-(benzylamino)-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
625	3-[5-(benzylamino)-3-(pyridin-3-yl)-1H-pyrazol-1-yl]carbonylbenzonitrile
626	3-[5-(benzylamino)-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
627	3-[5-(benzylamino)-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
628	3-[5-(benzylamino)-3-phenyl-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
629	3-[5-(benzylamino)-3-phenyl-1H-pyrazol-1-yl]carbonylbenzonitrile
630	4-([1-benzoyl-3-(furan-2-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
631	4-([1-benzoyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
632	4-([1-benzoyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
633	4-([1-benzoyl-3-(pyridin-3-yl)-1H-pyrazol-5-yl]aminomethyl)benzonitrile
634	4-([1-benzoyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
635	4-([1-benzoyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-yl]aminomethyl)benzonitrile
636	4-[(1-benzoyl-3-phenyl-1H-1,2,4-triazol-5-yl)amino]methylbenzonitrile
637	4-[(1-benzoyl-3-phenyl-1H-pyrazol-5-yl)amino]methylbenzonitrile
638	4-[5-(benzylamino)-3-(furan-2-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
639	4-[5-(benzylamino)-3-(pyridin-2-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
640	4-[5-(benzylamino)-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
641	4-[5-(benzylamino)-3-(pyridin-3-yl)-1H-pyrazol-1-yl]carbonylbenzonitrile
642	4-[5-(benzylamino)-3-(pyridin-4-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
643	4-[5-(benzylamino)-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
644	4-[5-(benzylamino)-3-phenyl-1H-1,2,4-triazol-1-yl]carbonylbenzonitrile
645	4-[5-(benzylamino)-3-phenyl-1H-pyrazol-1-yl]carbonylbenzonitrile
646	ethyl 5-[(E)-(pyridin-3-ylmethylidene)amino]-1H-1,2,4-triazole-3-carboxylate
647	N-(2,4-dichlorophenyl)-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-1,2,4-triazole-3-carboxamide
648	N-benzyl-1-[(2-chlorophenyl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine

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649	N-benzyl-1-[(2-chlorophenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine
650	N-benzyl-1-[(2-chlorophenyl)carbonyl]-3-phenyl-1H-pyrazol-5-amine
651	N-benzyl-1-[(2-fluorophenyl)carbonyl]-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine
652	N-benzyl-1-[(2-fluorophenyl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
653	N-benzyl-1-[(2-fluorophenyl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
654	N-benzyl-1-[(2-fluorophenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine
655	N-benzyl-1-[(2-fluorophenyl)carbonyl]-3-phenyl-1H-pyrazol-5-amine
656	N-benzyl-1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
657	N-benzyl-1-[(2-methoxyphenyl)carbonyl]-3-phenyl-1H-pyrazol-5-amine
658	N-benzyl-1-[(2-methylphenyl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
659	N-benzyl-1-[(2-methylphenyl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
660	N-benzyl-1-[(2-methylphenyl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
661	N-benzyl-1-[(2-methylphenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine
662	N-benzyl-1-[(2-methylphenyl)carbonyl]-3-phenyl-1H-pyrazol-5-amine
663	N-benzyl-1-[(3-chlorophenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
664	N-benzyl-1-[(3-chlorophenyl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
665	N-benzyl-1-[(3-chlorophenyl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
666	N-benzyl-1-[(3-chlorophenyl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
667	N-benzyl-1-[(3-chlorophenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine
668	N-benzyl-1-[(3-chlorophenyl)carbonyl]-3-phenyl-1H-pyrazol-5-amine
669	N-benzyl-1-[(3-fluorophenyl)carbonyl]-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine
670	N-benzyl-1-[(3-fluorophenyl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
671	N-benzyl-1-[(3-fluorophenyl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
672	N-benzyl-1-[(3-fluorophenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine
673	N-benzyl-1-[(3-fluorophenyl)carbonyl]-3-phenyl-1H-pyrazol-5-amine
674	N-benzyl-1-[(3-methoxyphenyl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
675	N-benzyl-1-[(3-methoxyphenyl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
676	N-benzyl-1-[(3-methoxyphenyl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
677	N-benzyl-1-[(3-methoxyphenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine
678	N-benzyl-1-[(3-methoxyphenyl)carbonyl]-3-phenyl-1H-pyrazol-5-amine
679	N-benzyl-1-[(3-methylphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
680	N-benzyl-1-[(3-methylphenyl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
681	N-benzyl-1-[(3-methylphenyl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
682	N-benzyl-1-[(3-methylphenyl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
683	N-benzyl-1-[(3-methylphenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine
684	N-benzyl-1-[(3-methylphenyl)carbonyl]-3-phenyl-1H-pyrazol-5-amine
685	N-benzyl-1-[(4-chlorophenyl)carbonyl]-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine
686	N-benzyl-1-[(4-chlorophenyl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine

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687	N-benzyl-1-[(4-chlorophenyl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
688	N-benzyl-1-[(4-chlorophenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine
689	N-benzyl-1-[(4-chlorophenyl)carbonyl]-3-phenyl-1H-pyrazol-5-amine
690	N-benzyl-1-[(4-fluorophenyl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
691	N-benzyl-1-[(4-fluorophenyl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
692	N-benzyl-1-[(4-fluorophenyl)carbonyl]-3-phenyl-1H-pyrazol-5-amine
693	N-benzyl-1-[(4-methoxyphenyl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
694	N-benzyl-1-[(4-methoxyphenyl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
695	N-benzyl-1-[(4-methoxyphenyl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
696	N-benzyl-1-[(4-methoxyphenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine
697	N-benzyl-1-[(4-methoxyphenyl)carbonyl]-3-phenyl-1H-pyrazol-5-amine
698	N-benzyl-1-[(4-methylphenyl)carbonyl]-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
699	N-benzyl-1-[(4-methylphenyl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
700	N-benzyl-1-[(4-methylphenyl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
701	N-benzyl-1-[(4-methylphenyl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
702	N-benzyl-1-[(4-methylphenyl)carbonyl]-3-phenyl-1H-pyrazol-5-amine
703	N-benzyl-1-[(furan-2-yl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
704	N-benzyl-1-[(furan-2-yl)carbonyl]-3-phenyl-1H-pyrazol-5-amine
705	N-benzyl-1-[(pyridin-2-yl)carbonyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine
706	N-benzyl-1-[(pyridin-2-yl)carbonyl]-3-(pyridin-3-yl)-1H-pyrazol-5-amine
707	N-benzyl-1-[(pyridin-2-yl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
708	N-benzyl-1-[(pyridin-2-yl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
709	N-benzyl-1-[(pyridin-3-yl)carbonyl]-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
710	N-benzyl-1-[(pyridin-3-yl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
711	N-benzyl-1-[(pyridin-4-yl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
712	N-benzyl-1-[2-(dimethylamino)phenyl]carbonyl-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine
713	N-benzyl-1-[2-(dimethylamino)phenyl]carbonyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine
714	N-benzyl-1-[2-(dimethylamino)phenyl]carbonyl-3-(pyridin-3-yl)-1H-pyrazol-5-amine
715	N-benzyl-1-[2-(dimethylamino)phenyl]carbonyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
716	N-benzyl-1-[2-(dimethylamino)phenyl]carbonyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
717	N-benzyl-1-[2-(dimethylamino)phenyl]carbonyl-3-phenyl-1H-1,2,4-triazol-5-amine
718	N-benzyl-1-[2-(dimethylamino)phenyl]carbonyl-3-phenyl-1H-pyrazol-5-amine
719	N-benzyl-1-[3-(dimethylamino)phenyl]carbonyl-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine
720	N-benzyl-1-[3-(dimethylamino)phenyl]carbonyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
721	N-benzyl-1-[3-(dimethylamino)phenyl]carbonyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine
722	N-benzyl-1-[3-(dimethylamino)phenyl]carbonyl-3-(pyridin-3-yl)-1H-pyrazol-5-amine
723	N-benzyl-1-[3-(dimethylamino)phenyl]carbonyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
724	N-benzyl-1-[3-(dimethylamino)phenyl]carbonyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine

Cmpd No	IUPAC name
725	N-benzyl-1-[3-(dimethylamino)phenyl]carbonyl-3-phenyl-1H-1,2,4-triazol-5-amine
726	N-benzyl-1-[3-(dimethylamino)phenyl]carbonyl-3-phenyl-1H-pyrazol-5-amine
727	N-benzyl-1-[4-(dimethylamino)phenyl]carbonyl-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine
728	N-benzyl-1-[4-(dimethylamino)phenyl]carbonyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine
729	N-benzyl-1-[4-(dimethylamino)phenyl]carbonyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine
730	N-benzyl-1-[4-(dimethylamino)phenyl]carbonyl-3-(pyridin-3-yl)-1H-pyrazol-5-amine
731	N-benzyl-1-[4-(dimethylamino)phenyl]carbonyl-3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine
732	N-benzyl-1-[4-(dimethylamino)phenyl]carbonyl-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine
733	N-benzyl-1-[4-(dimethylamino)phenyl]carbonyl-3-phenyl-1H-1,2,4-triazol-5-amine
734	N-benzyl-1-[4-(dimethylamino)phenyl]carbonyl-3-phenyl-1H-pyrazol-5-amine
735	N-benzyl-3-(furan-2-yl)-1-[(3-methoxyphenyl)carbonyl]-1H-1,2,4-triazol-5-amine
736	N-benzyl-3-(furan-2-yl)-1-[(4-methoxyphenyl)carbonyl]-1H-1,2,4-triazol-5-amine
737	N-benzyl-3-(furan-2-yl)-1-[(pyridin-2-yl)carbonyl]-1H-1,2,4-triazol-5-amine
738	N-benzyl-3-(furan-2-yl)-1-[(pyridin-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine
739	N-benzyl-3-(furan-2-yl)-1-[(pyridin-4-yl)carbonyl]-1H-1,2,4-triazol-5-amine
740	N-benzyl-3-(pyridin-2-yl)-1-[(pyridin-2-yl)carbonyl]-1H-1,2,4-triazol-5-amine
741	N-benzyl-3-(pyridin-2-yl)-1-[(pyridin-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine
742	N-benzyl-3-(pyridin-2-yl)-1-[(pyridin-4-yl)carbonyl]-1H-1,2,4-triazol-5-amine
743	N-benzyl-3-(pyridin-3-yl)-1-[(pyridin-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine
744	N-benzyl-3-(pyridin-3-yl)-1-[(pyridin-3-yl)carbonyl]-1H-pyrazol-5-amine
745	N-benzyl-3-(pyridin-3-yl)-1-[(pyridin-4-yl)carbonyl]-1H-1,2,4-triazol-5-amine
746	N-benzyl-3-(pyridin-3-yl)-1-[(pyridin-4-yl)carbonyl]-1H-pyrazol-5-amine
747	N-benzyl-3-(pyridin-3-yl)-1-[(thiophen-2-yl)carbonyl]-1H-pyrazol-5-amine
748	N-benzyl-3-(pyridin-4-yl)-1-[(pyridin-4-yl)carbonyl]-1H-1,2,4-triazol-5-amine
749	N-benzyl-3-phenyl-1-[(pyridin-2-yl)carbonyl]-1H-1,2,4-triazol-5-amine
750	N-benzyl-3-phenyl-1-[(pyridin-2-yl)carbonyl]-1H-pyrazol-5-amine
751	N-benzyl-3-phenyl-1-[(pyridin-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine
752	N-benzyl-3-phenyl-1-[(pyridin-3-yl)carbonyl]-1H-pyrazol-5-amine
753	N-benzyl-3-phenyl-1-[(pyridin-4-yl)carbonyl]-1H-1,2,4-triazol-5-amine
754	N-benzyl-3-phenyl-1-[(pyridin-4-yl)carbonyl]-1H-pyrazol-5-amine
755	N-benzyl-3-phenyl-1-[(thiophen-2-yl)carbonyl]-1H-pyrazol-5-amine

[0081] Compounds disclosed herein also include racemic mixtures, stereoisomers and mixtures of the compounds, including isotopically-labeled and radio-labeled compounds. See e.g., Goding, 1986, MONOCLONAL ANTIBODIES PRINCIPLES AND PRACTICE; Academic Press, p. 104. Such isomers can be isolated by standard resolution techniques, including e.g.,

fractional crystallization, chiral chromatography, and the like. See e.g., Eliel, E. L. & Wilen S. H., 1993, STEREOCHEMISTRY IN ORGANIC COMPOUNDS ; John Wiley & Sons, New York.

[0082] In some embodiments, compounds disclosed herein have asymmetric centers and may occur as racemates, racemic mixtures, and as individual enantiomers or diastereoisomers, with all isomeric forms as well as mixtures thereof being contemplated for use in the compounds and methods described herein. The compounds contemplated for use in the compounds and methods described herein do not include those that are known in the art to be too unstable to synthesize and/or isolate.

[0083] The compounds disclosed herein may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds disclosed herein, whether radioactive or not, are encompassed within the contemplated scope.

[0084] In some embodiments, metabolites of the compounds disclosed herein are useful for the methods disclosed herein.

[0085] In some embodiments, compounds contemplated herein are provided in the form of a prodrug. The term "prodrug" refers to a compound that can be converted into a compound (e.g., a biologically active compound) described herein *in vivo*. Prodrugs can be useful for a variety of reason known in the art, including e.g., ease of administration due e.g., to enhanced bioavailable in oral administration, and the like. The prodrug may also have improved solubility in pharmaceutical compositions over the biologically active compounds. An example, without limitation, of a prodrug is a compound which is administered as an ester (i.e., the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in DESIGN OF PRODRUGS, (ed. H. Bundgaard, Elsevier, 1985), which is hereby incorporated herein by reference for the limited purpose describing procedures and preparation of suitable prodrug derivatives.

[0086] Accordingly, in some embodiments, compounds contemplated herein are provided in the form of a prodrug ester. The term "prodrug ester" refers to derivatives of the compounds disclosed herein formed by the addition of any of a variety of ester-forming groups, e.g., groups known in the art, that are hydrolyzed under physiological conditions.

Examples of prodrug ester groups include pivaloyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art, including a (5-R-2-oxo-1,3-dioxolen-4-yl)methyl group. Other examples of prodrug ester groups can be found in, for example, T. Higuchi and V. Stella, in "Pro-drugs as Novel Delivery Systems", Vol. 14, A.C.S. Symposium Series, American Chemical Society (1975); and BIOREVERSIBLE CARRIERS IN DRUG DESIGN: THEORY AND APPLICATION, edited by E. B. Roche, Pergamon Press: New York, 14-21 (1987) (providing examples of esters useful as prodrugs for compounds containing carboxyl groups). Each of the above-mentioned references is herein incorporated by reference for the limited purpose of disclosing ester-forming groups that can form prodrug esters.

[0087] In some embodiments, prodrugs can be slowly converted to the compounds described herein useful for the methods described herein when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0088] Certain compounds disclosed herein can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of contemplated compounds. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the compounds and methods contemplated herein and are intended to be within the scope disclosed herein.

III. Biological Activities

[0089] In some embodiments, compounds described herein exhibit inhibitory activity against thrombin with activities ≥ 1 μM, e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 μM, or even greater. In some embodiments, the compounds exhibit inhibitory activity against thrombin with activities between 0.1 μM and 1 μM, e.g., about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 or 1.0 μM. In some embodiments, compounds described herein exhibit inhibitory activity against thrombin with activities ≤ 0.1 μM, e.g., about 1, 2, 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, or 100 nM. Ranges of values using a combination of any of the values recited herein as upper and/or lower limits are also contemplated, for example, but not limited to, 1-10 nM, 10-100 nM, 0.1−1 μM, 1−10 μM, 10-100 μM, 100-200 μM, 200-500 μM, or even 500-1000 μM. In some embodiments, the inhibitory activity is in the range of about 1-10 nM, 10-100 nM, 0.1−1 μM, 1−10 μM, 10-100 μM, 100-200 μM, 200-500 μM, or

even 500-1000 μM. It is understood that for purposes of quantification, the terms "activity," "inhibitory activity," "biological activity," "thrombin activity" and the like in the context of an inhibitory compound disclosed herein can be quantified in a variety of ways known in the art. Unless indicated otherwise, as used herein such terms refer to IC_{50} in the customary sense (i.e., concentration to achieve half-maximal inhibition).

[0090] Inhibitory activity against thrombin in turn inhibits the blood coagulation process. Accordingly, compounds disclosed herein are indicated in the treatment or management of thrombotic disorders. In some embodiments, a dose or a therapeutically effective dose of a compound disclosed herein will be that which is sufficient to achieve a plasma concentration of the compound or its active metabolite(s) within a range set forth herein, e.g., about 1-10 nM, 10-100 nM, 0.1–1 μM, 1–10 μM, 10-100 μM, 100-200 μM, 200-500 μM, or even 500-1000 μM, preferably about 1-10 nM, 10-100 nM, or 0.1–1 μM. Without wishing to be bound by any theory, it is believe that such compounds are indicated in the treatment or management of thrombotic disorders.

IV. Methods of Treating and Preventing Disease

[0091] **Thrombosis.** Thrombotic diseases are the primary indications for thrombin inhibition, because of thrombin's location in the coagulation cascade and, in turn, the importance of the coagulation cascade in the progression of blood clotting processes. However, without wishing to be bound by any theory, it is believed the coagulation cascade in general, and thrombin in particular, is important in a variety other disease states.

[0092] It has been discovered that compounds described herein, e.g., multisubstituted aromatic compounds, exhibit inhibitory action against thrombin (activated blood-coagulation factor II; EC 3.4.21.5). This, in turn inhibits the blood coagulation process.

[0093] This inhibitory action is useful in the treatment of a variety of thrombotic disorders, such as, but not limited to, acute vascular diseases such as acute coronary syndromes; venous-, arterial- and cardiogenic thromboembolisms; the prevention of other states such as disseminated intravascular coagulation, or other conditions that involve the presence or the potential formation of a blood clot thrombus. Other indications for methods described herein include the following.

[0094] **Cancer.** It has long been recognized that cancer progression is accompanied by venous thrombosis, but it has not been understood how each disease is related. From several clinical trials studying the treatment of VTE, metaanalyses have shown that low molecular

weight heparins (LMWHs) improve overall survival in subgroups of cancer patients. *See* e.g., Zacharski, L. R. & Lee, A. Y., 2008, *Expert Opin Investig Drugs*, **17**:1029-1037; Falanga, A. & Piccioli, A., 2005, *Current Opinion in Pulmonary Medicine*, **11**:403-407; Smorenburg, S. M., et al., 1999, *Thromb Haemost*, **82**:1600-1604; Hettiarachchi, R. J., et al., 1999, *Thromb Haemost*, **82**:947-952. This finding was substantiated in later clinical trials that measured specifically the survival of cancer patients. See e.g., Lee, A. Y.et al., 2005, *J Clin Oncol*, 23:2123-2129; Klerk, C. P.et al., *J Clin Oncol* 2005, **23**:2130-2135; Kakkar, A. K., et al., 2004, *J Clin Oncol*, **22**:1944-1948; Altinbas, M., et al., 2004, *J Thromb Haemost*, **2**:1266-1271.

[0095] More recently, researchers have focused on the specific anticancer effect of DTIs. For example, it was shown that heparin significantly prolonged the survival of patients with limited small cell lung cancer. See e.g., Akl, E. A., et al., 2008, *J Exp Clin Cancer Res*, **27**:4. Other investigators found that systemic use of argatroban reduced tumor mass and prolonged survival time in rat glioma models leading to the conclusion that argatroban should be considered as a novel therapeutic for glioma, a notoriously difficult to treat cancer type. See e.g., Hua, Y., et al., 2005, *Acta Neurochir*, Suppl 2005, **95**:403-406; Hua, Y., et al., 2005, *J Thromb Haemost,* **3**:1917-1923. Very recently, it was demonstrated that dabigatran etexilate, a DTI recently FDA-approved (see e.g., Hughes, B., 2010, *Nat Rev Drug Discov*, **9**,:903-906) for DVT indications, inhibited both the invasion and metastasis of malignant breast tumors. See e.g., DeFeo, K.et al., 2010, *Thrombosis Research*, **125** (Supplement 2): S188-S188; Defeo, K., et al., 2010, *Cancer Biol Ther*, **10**:1001-1008. Thus, dabigatran etexilate treatment led to a 50% reduction in tumor volume at 4 weeks with no weight loss in treated mice. Dabigatran etexilate also reduced tumor cells in the blood and liver micrometastases by 50-60%. These investigators concluded that dabigatran etexilate may be beneficial in not only preventing thrombotic events in cancer patients, but also as adjunct therapy to treat malignant tumors.

[0096] Further, hirudin and the LMWH nadroparin dramatically reduced the number of lung metastases when administered prior to cancer cell inoculation. *See* e.g., Hu, L., et al., 2004, *Blood*, **104**:2746-51.

[0097] The de novo thrombin inhibitor d-Arg-Oic-Pro-d-Ala-Phe(p-Me) has been found to block thrombin-stimulated invasion of prostate cancer cell line PC-3 in a concentration dependent manner. See e.g., Nieman, M. T., et al., 2008, *J Thromb Haemost*, **6**:837-845. A reduced rate of tumor growth was observed in mice dosed with the pentapeptide through their drinking water. The mice also showed reduced fold rate in tumor size and reduced overall

tumor weight compared to untreated mice. Microscopic examination of treated tumors showed reduced number of large blood vessels thus concluding that the pentapeptide interfered with tumor angiogenesis. Nieman, M. T., et al., *Thromb Haemost*, **104**:1044-8.

[0098] In view of these and related studies, it is suggested that anticoagulants affect tumor metastasis; that is, angiogenesis, cancer cell adhesion, migration and invasion processes. *See* e.g., Van Noorden, C. J., et al., 2010, *Thromb Res*, **125 Suppl 2**:S77-79.

[0099] **Fibrosis.** Several studies have shown the utility of anticoagulant therapy in fibrotic disorders. For example, in a rat model of CCl_4-induced chronic liver injury, the DTI SSR182289 decreased liver fibrogenesis significantly after 7 weeks of administration (ref 24). Similar observations were made in other studies using the LMWHs nadroparin (ref 25), tinzaparin (ref 25), enoxaparin (ref 26), and dalteparin sodium (ref 27). See e.g., Duplantier, J. G., et al., 2004, *Gut*, **53**:1682-1687; Abdel-Salam, O. M., et al., 2005, *Pharmacol Res*, **51**:59-67; Assy, N., et al., 2007, *Dig Dis Sci*, **52**:1187-1193; Abe, W., et al., 2007, *J Hepatol*, **46**:286-294.

[0100] In another example, the DTI melagatran greatly reduced ischemia reperfusion injury in a kidney transplant model in the large white pig. This led to a drastically improved kidney graft survival at 3 months. See e.g., Favreau, F., et al., 2010, *Am J Transplant*, **10**:30-39.

[0101] Recent studies have shown that in a bleomycin-induced mouse model of pulmonary fibrosis, dabigatran etexilate treatment reduced important profibrotic events in lung fibroblasts, including the production of collagen and connective tissue growth factor. *See* e.g., Silver, R. M., et al., 2010, *Am. J. Respir. Crit. Care Med.*, **181**:A6780; Bogatkevich, G. S., et al., 2009, *Arthritis Rheum*, **60**:3455-3464.

[0102] The above experimental evidence points to a close relationship between thrombin and fibrosis (ref 31) and suggests novel therapeutic opportunities for fibrosis using thrombin inhibitors (refs 32-34). See e.g., Calvaruso, V., et al., 2008, *Gut*, **57**:1722-1727; Chambers, R. C., 2008, *Br J Pharmacol*, **153** Suppl 1:S367-378; Chambers, R. C. & Laurent, G. J., 2002, *Biochem Soc Trans*, **30**:194-200; Howell, D. C., et al., 2001, *Am J Pathol*, **159**:1383-1395.

[0103] **Alzheimer's Disease.** Very recent experiments confirm higher thrombin levels in brain endothelial cells of patients with Alzheimer's disease. While 'normal' thrombin levels are connected to regulatory CNS functions, thrombin accumulation in the brain is toxic. It has also been found that the neural thrombin inhibitor Protease Nexin 1 (PN-1) is significantly reduced in the Alzheimer's disease brain, despite the fact that PN-1 mRNA

levels are unchanged. These observations have led some investigators to suggest that reduction of CNS-resident thrombin will prove useful in Alzheimer's Disease (AD) treatment. See e.g., Vaughan, P. J., et al., 1994, *Brain Res*, **668**:160-170; Yin, X., et al., 2010, *Am J Pathol*, **176**:1600-1606; Akiyama, H., et al., 1992, *Neurosci Lett*, **146**:152-154.

[0104] **Multiple Sclerosis.** Investigators found that hirudin treatment in an animal model of Multiple Sclerosis (MS) showed a dramatic improvement in disease severity (ref 38). See e.g., Han, M. H., et al., 2008, *Nature*, **451**:1076-1081. Similar results were obtained following treatment with heparin (ref 39) (a DTI) and dermatan sulfate (ref 40) another coagulation inhibitor. See e.g., Chelmicka-Szorc, E. & Arnason, B. G., 1972, *Arch Neurol*, **27**:153-158; Inaba, Y., et al., 1999, *Cell Immunol*, **198**:96-102. Other evidence shows that naturally occurring antithrombin III has anti-inflammatory effects in diseases such as endotoxemia and other sepsis-related conditions. See e.g., Wiedermann, C. J. & Romisch, J., 2002, *Acta Med Austriaca*, **29**:89-92. Naturally occurring thrombin inhibitors are presumably synthesized *in situ* and have protective roles in CNS inflammation. Therefore, therapeutic thrombin inhibition has been proposed as a potential MS treatment. *See* e.g., Luo, W., et al., 2009, In: THROMBIN, Maragoudakis, M. E.; Tsopanoglou, N. E., Eds. Springer New York: 2009; pp 133-159.

[0105] **Pain.** In a rat pain model with partial lesion of the sciatic nerve, intrathecal hirudin prevented the development of neuropathic pain and curbed pain responses for 7 days. The investigators found that following injury, neuropathic pain was mediated by thrombin generation, which in turn activated PAR-1 receptor in the spinal cord. Hirudin inhibited thrombin generation and ultimately led to pain relief (refs 43, 44). See e.g., Garcia, P. S., et al., 2010, *Thromb Haemost*, **103**:1145-1151; Narita, M., et al., 2005, *J Neurosci*, **25**:10000-10009. Researchers hypothesize that thrombin and the PARs are involved not just as part of the coagulation cascade, but in inflammation, nociception and neurodevelopment. Development of a DTI to intersect an unexploited pharmacology will lead to pain therapeutics distinct from opioids and NSAIDs, whose shortcomings are well documented. See e.g., Garcia 2010, *Id.*

[0106] Accordingly, in a further aspect, there is provided a method for treating a disease or disorder in a subject in need thereof. The method includes administering a compound of any of Formulae (Ia), (Ib), (IIa), (IIb), (IIIa), (IIIb), (IV) or (V) as disclosed herein, a compound as set forth in any of Tables A, B or C, pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, or pharmaceutical composition thereof, to a subject in need thereof in an amount effective to treat the disease or disorder. The terms "therapeutically effective

amount," "amount effective to treat," "amount effective to prevent" and the like refer to that amount of drug or pharmaceutical agent (e.g., compound or pharmaceutical composition disclosed herein) that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

[0107] Compounds useful for methods disclosed herein include the compounds set forth for Formulae (Ia), (Ib), (IIa), (IIb), (IIIa), (IIIb), (IV) and (V), and for the compounds set forth in Tables A and B above. Additionally, compounds useful for methods disclosed herein include the compounds set forth in Table C following. For Table C, the compounds were assayed for inhibition of the protease activity of thrombin as described for Table A.

Table C.

Cmpd No	IUPAC name	Thrombin Activity
1	3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	c
2	3-(pyridin-2-yl)-1H-1,2,4-triazol-5-amine	c
3	3-(pyridin-4-yl)-1H-1,2,4-triazol-5-amine	c
8	1-(5-[(3-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	b
25	3-(furan-2-yl)-1H-1,2,4-triazol-5-amine	c
31	methyl 5-[(2-chlorobenzene)amido]-1H-1,2,4-triazole-3-carboxylate	c
305	1-(5-[(2-methoxyphenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-2-methylpropan-1-one	c
306	1-(5-[(4-chlorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-2-methylpropan-1-one	a
307	1-(5-[(4-chlorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)ethan-1-one	a
308	1-(5-[(4-chlorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	a
309	1-(5-[(4-fluorophenyl)methyl]amino-3-(furan-2-yl)-1H-1,2,4-triazol-1-yl)-2,2-dimethylpropan-1-one	a
310	1-(5-[(4-fluorophenyl)methyl]amino-3-(furan-2-yl)-1H-1,2,4-triazol-1-yl)-2-methylpropan-1-one	a
311	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-2-methoxyethan-1-one	c
312	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-2-methylpropan-1-one	a
313	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-2-phenylethan-1-one	a
314	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-3-methylbutan-1-one	a
315	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-3-	a

Cmpd No	IUPAC name	Thrombin Activity
	phenylpropan-1-one	
316	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)butan-1-one	a
317	1-(5-[(4-fluorophenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)ethan-1-one	a
318	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-2-methylpropan-1-one	a
319	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-2-phenylethan-1-one	a
320	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-3-methylbutan-1-one	a
321	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)-3-phenylpropan-1-one	b
322	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)butan-1-one	a
323	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)ethan-1-one	b
324	1-(5-[(4-methoxyphenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	b
325	1-(5-[(4-methylphenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)ethan-1-one	a
326	1-(benzenesulfonyl)-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	c
327	1-(benzenesulfonyl)-3-(pyridin-3-yl)-N-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-amine	c
328	1-(benzenesulfonyl)-3-[(morpholin-4-yl)carbonyl]-1H-1,2,4-triazol-5-amine	c
329	1-(ethanesulfonyl)-3-[(morpholin-4-yl)carbonyl]-1H-1,2,4-triazol-5-amine	c
330	1-[(2-chlorophenyl)carbonyl]-3-(furan-2-yl)-5-(methylsulfanyl)-1H-1,2,4-triazole	a
331	1-[(2-chlorophenyl)carbonyl]-N-[(4-fluorophenyl)methyl]-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine	a
332	1-[(2-chlorophenyl)carbonyl]-N-[(4-fluorophenyl)methyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	a
333	1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	b
334	1-[(2-methoxyphenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine	c
335	1-[(2-methoxyphenyl)carbonyl]-3-phenyl-N-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-amine	a
336	1-[(4-chlorobenzene)sulfonyl]-3-(pyridin-3-yl)-N-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-amine	c
337	1-[(4-chlorobenzene)sulfonyl]-3-[(morpholin-4-yl)carbonyl]-1H-1,2,4-triazol-5-amine	c
338	1-[(4-chlorophenyl)carbonyl]-N-[(4-fluorophenyl)methyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	a
339	1-[(4-methylphenyl)carbonyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	b

Cmpd No	IUPAC name	Thrombin Activity
340	1-[(furan-2-yl)carbonyl]-N-[(4-methoxyphenyl)methyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	b
341	1-[3-(furan-2-yl)-5-(methylsulfanyl)-1H-1,2,4-triazol-1-yl]propan-1-one	c
342	1-[3-(pyridin-3-yl)-5-[(thiophen-2-ylmethyl)amino]-1H-1,2,4-triazol-1-yl]butan-1-one	a
343	1-[3-(pyridin-3-yl)-5-[(thiophen-2-ylmethyl)amino]-1H-1,2,4-triazol-1-yl]ethan-1-one	a
344	1-[3-(pyridin-3-yl)-5-[(thiophen-2-ylmethyl)amino]-1H-1,2,4-triazol-1-yl]propan-1-one	a
345	1-[5-(benzylamino)-3-(4-fluorophenyl)-1H-1,2,4-triazol-1-yl]propan-1-one	c
346	1-[5-(benzylamino)-3-(furan-2-yl)-1H-1,2,4-triazol-1-yl]-2-phenylethan-1-one	a
347	1-[5-(benzylamino)-3-(furan-2-yl)-1H-1,2,4-triazol-1-yl]-3-phenylpropan-1-one	a
348	1-[5-(benzylamino)-3-(furan-2-yl)-1H-1,2,4-triazol-1-yl]propan-1-one	a
349	1-[5-(benzylamino)-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl]-2-methylpropan-1-one	a
350	1-[5-(benzylamino)-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl]-3-methylbutan-1-one	a
351	1-[5-(benzylamino)-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl]propan-1-one	a
352	1-[5-(benzylamino)-3-(thiophen-2-yl)-1H-1,2,4-triazol-1-yl]propan-1-one	a
353	1-[5-(benzylamino)-3-phenyl-1H-1,2,4-triazol-1-yl]-2-phenylethan-1-one	a
354	1-[5-(benzylamino)-3-phenyl-1H-1,2,4-triazol-1-yl]-3-phenylpropan-1-one	c
355	1-[5-(benzylamino)-3-phenyl-1H-1,2,4-triazol-1-yl]propan-1-one	b
356	1-benzoyl-N-[(4-fluorophenyl)methyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	a
357	1-benzoyl-N-[(4-methoxyphenyl)methyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	b
358	1-benzoyl-N-benzyl-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine	a
359	1-benzoyl-N-benzyl-3-phenyl-1H-1,2,4-triazol-5-amine	a
360	1-methanesulfonyl-3-[(morpholin-4-yl)carbonyl]-1H-1,2,4-triazol-5-amine	c
361	1-5-[(furan-2-ylmethyl)amino]-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl-2-methylpropan-1-one	a
362	1-5-[(furan-2-ylmethyl)amino]-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-ylbutan-1-one	a
363	1-5-[(furan-2-ylmethyl)amino]-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-ylethan-1-one	a
364	1-5-[(furan-2-ylmethyl)amino]-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-ylpropan-1-one	b
365	2-fluoro-N-[5-(furan-2-yl)-1H-1,2,4-triazol-3-yl]benzamide	c
366	2-methyl-1-(5-[(4-methylphenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)propan-1-one	a
367	3-(furan-2-yl)-1-[(2-methoxyphenyl)carbonyl]-5-(methylsulfanyl)-1H-1,2,4-	a

Cmpd No	IUPAC name	Thrombin Activity
	triazole	
368	3-(furan-2-yl)-1-[(pyridin-3-yl)carbonyl]-N-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-amine	a
369	3-(furan-2-yl)-1-methanesulfonyl-N-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-amine	c
370	3-(furan-2-yl)-N-[(2-methoxyphenyl)methyl]-1-[(4-methylphenyl)carbonyl]-1H-1,2,4-triazol-5-amine	b
371	3-(furan-2-yl)-N-[(4-methoxyphenyl)methyl]-1-[(4-methylphenyl)carbonyl]-1H-1,2,4-triazol-5-amine	b
372	3-(pyridin-3-yl)-1-[(pyridin-3-yl)carbonyl]-N-(thiophen-2-ylmethyl)-1H-1,2,4-triazol-5-amine	b
373	3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine	c
374	3-methyl-1-(5-[(4-methylphenyl)methyl]amino-3-(pyridin-3-yl)-1H-1,2,4-triazol-1-yl)butan-1-one	a
375	3-methyl-1-[3-(pyridin-3-yl)-5-[(thiophen-2-ylmethyl)amino]-1H-1,2,4-triazol-1-yl]butan-1-one	a
376	ethyl 5-amino-3-(4-chlorophenyl)-1H-pyrazole-1-carboxylate	c
377	methyl 3-[(2,4-dichlorobenzene)amido]-1H-1,2,4-triazole-5-carboxylate	c
378	methyl 5-(2,2-dimethylpropanamido)-1H-1,2,4-triazole-3-carboxylate	c
379	methyl 5-(2-methylfuran-3-amido)-1H-1,2,4-triazole-3-carboxylate	c
380	methyl 5-[(2-methylbenzene)amido]-1H-1,2,4-triazole-3-carboxylate	c
381	methyl 5-[(3,4,5,6-tetrahydro-2H-azepin-7-yl)amino]-1H-1,2,4-triazole-3-carboxylate	c
382	methyl 5-[(3-methylbenzene)amido]-1H-1,2,4-triazole-3-carboxylate	c
383	methyl 5-[(4-bromobenzene)amido]-1H-1,2,4-triazole-3-carboxylate	c
384	methyl 5-[(4-chlorobenzene)amido]-1H-1,2,4-triazole-3-carboxylate	c
385	methyl 5-[(4-fluorobenzene)amido]-4H-1,2,4-triazole-3-carboxylate	b
386	methyl 5-[(4-tert-butylbenzene)amido]-1H-1,2,4-triazole-3-carboxylate	b
387	methyl 5-[(pyridin-3-ylmethylidene)amino]-1H-1,2,4-triazole-3-carboxylate	c
388	methyl 5-[3-(4-methylphenyl)propanamido]-1H-1,2,4-triazole-3-carboxylate	c
389	methyl 5-amino-1H-1,2,4-triazole-3-carboxylate	c
390	N-(2,4-dichlorophenyl)-5-(1H-1,2,4-triazol-1-ylmethyl)-4H-1,2,4-triazole-3-carboxamide	c
391	N-(2-chlorophenyl)-3-(4H-1,2,4-triazol-4-yl)-1H-1,2,4-triazole-5-carboxamide	c
392	N-(4-bromophenyl)-3-(4H-1,2,4-triazol-4-yl)-1H-1,2,4-triazole-5-carboxamide	c
393	N-(4-ethoxyphenyl)-3-(4H-1,2,4-triazol-4-yl)-1H-1,2,4-triazole-5-carboxamide	c
394	N-(furan-2-ylmethyl)-1-[(2-methoxyphenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine	a
395	N-(furan-2-ylmethyl)-1-methanesulfonyl-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	c
396	N-(furan-2-ylmethyl)-3-(pyridin-3-yl)-1-[(pyridin-3-yl)carbonyl]-1H-1,2,4-	c

Cmpd No	IUPAC name	Thrombin Activity
	triazol-5-amine	
397	N-[(2-chlorophenyl)methyl]-3-(furan-2-yl)-1-[(pyridin-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine	b
398	N-[(2-methoxyphenyl)methyl]-3-(pyridin-3-yl)-1-[(pyridin-3-yl)carbonyl]-1H-1,2,4-triazol-5-amine	c
399	N-[(4-fluorophenyl)methyl]-1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	a
400	N-[(4-fluorophenyl)methyl]-1-[(2-methoxyphenyl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine	a
401	N-[(4-fluorophenyl)methyl]-1-[(4-methylphenyl)carbonyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	a
402	N-[(4-fluorophenyl)methyl]-1-[(furan-2-yl)carbonyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	a
403	N-[(4-fluorophenyl)methyl]-3-(pyridin-3-yl)-1-[(thiophen-2-yl)carbonyl]-1H-1,2,4-triazol-5-amine	a
404	N-[(4-methoxyphenyl)methyl]-1-[(4-methylphenyl)carbonyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	b
405	N-[(4-methoxyphenyl)methyl]-3-(pyridin-3-yl)-1-[(thiophen-2-yl)carbonyl]-1H-1,2,4-triazol-5-amine	c
406	N-[5-(benzylamino)-1H-1,2,4-triazol-3-yl]acetamide	c
407	N-[5-(furan-2-yl)-1H-1,2,4-triazol-3-yl]benzamide	c
408	N-benzyl-1-[(2-chlorophenyl)carbonyl]-3-(furan-2-yl)-1H-1,2,4-triazol-5-amine	a
409	N-benzyl-1-[(2-chlorophenyl)carbonyl]-3-(thiophen-2-yl)-1H-1,2,4-triazol-5-amine	a
410	N-benzyl-1-[(2-methoxyphenyl)carbonyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	A
411	N-benzyl-1-[(4-methylphenyl)carbonyl]-3-(pyridin-3-yl)-1H-1,2,4-triazol-5-amine	A
412	N-benzyl-3-(thiophen-2-yl)-1-[(thiophen-2-yl)carbonyl]-1H-1,2,4-triazol-5-amine	C

[0108] In some embodiments, the disease or disorder is a thrombotic disease or disorder. In some embodiments, the thrombotic disease or disorder is acute coronary syndrome, venous thromboembolism, arterial thromboembolism or cardiogenic thromboembolism. In some embodiments, the thrombotic disease or disorder is acute coronary syndrome. In some embodiments, the thrombotic disease or disorder is venous thromboembolism. In some embodiments, the thrombotic disease or disorder is arterial thromboembolism. In some embodiments, the thrombotic disease or disorder is cardiogenic thromboembolism.

[0109] In some embodiments, the disease or disorder is fibrosis, Alzheimer's Disease, multiple sclerosis, pain, or cancer. In some embodiments, the disease or disorder is Alzheimer's Disease. In some embodiments, the disease or disorder is multiple sclerosis.

[0110] In some embodiments, the disease or disorder is fibrosis. In some embodiments contemplating fibrosis, the method is directed to treating chronic liver injury. In some embodiments, the disease or disorder is ischemia reperfusion injury. In some embodiments, the disease or disorder is pulmonary fibrosis.

[0111] In some embodiments, the disease or disorder is pain. In some embodiments, the pain is neuropathic pain.

[0112] In some embodiments, the disease or disorder is cancer. In some embodiments, the cancer is limited small cell lung cancer. In some embodiments, the cancer is a glioma. In some embodiments, the cancer is malignant breast cancer. In some embodiments, the cancer is a micrometastasis. In some embodiments, the micrometastasis is of the blood or liver. In some embodiments, the cancer is a lung metastasis. In some embodiments, the cancer is prostatic cancer.

[0113] In another aspect, there is provided a method for preventing a disease or disorder in a subject. The method includes administering a compound of any of Formulae (Ia), (Ib), (IIa), (IIb), (IIIa), (IIIb), (IV) or (V) as disclosed herein, compound as set forth in any of Tables A, B or C herein, pharmaceutically acceptable salt, ester, solvate, or prodrug thereof, or pharmaceutical composition thereof, to a subject in need thereof in an amount effective to prevent the disease or disorder.

[0114] In some embodiments, the disease or disorder is a thrombotic disorder. In some embodiments, the thrombotic disorder is acute coronary syndrome, venous thromboembolism, arterial thromboembolism or cardiogenic thromboembolism. In some embodiments, the thrombotic disease or disorder is disseminated intravascular coagulation. In some embodiments, the thrombotic disorder involves the presence or the potential formation of a blood clot thrombus.

[0115] Yet further to this aspect, in some embodiments, the disease or disorder is fibrosis, Alzheimer's Disease, multiple sclerosis, pain, or cancer. In some embodiments, the disease or disorder is fibrosis. In some embodiments, the disease or disorder is Alzheimer's Disease. In some embodiments, the disease or disorder is multiple sclerosis. In some embodiments, the disease or disorder is pain. In some embodiments, the disease or disorder is cancer.

V. Assays

[0116] Compounds described herein can be assayed, by a variety of methods known in the art and described herein, for inhibition of biological activity, e.g., protease activity, of a variety of proteins, e.g., thrombin. For example, the protease activity of such proteins, e.g., thrombin, can be monitored using a chromophoric substrate, e.g., a p-nitroanilide peptide substrate, which upon hydrolysis releases p-nitroanilide, which in turn gives rise to a color change which can be determined spectrophotometrically. *See* e.g., Lottenberg, R, et al, 1983, *Biochemica et Biophysica Acta*, **752**:539-557. Accordingly, the change in color can be monitored with a spectrophotometer at e.g., 405 nm to provide a signal which is directly proportional to the proteolytic activity of the enzyme.

[0117] The thrombin activity reported herein (e.g., Table A) was obtained as follows. Human thrombin was obtained from Haematologic Technologies Inc. The chromogenic substrate S-2238 was obtained from DiaPharma. Thrombin was assayed in buffer containing 0.05 M Tris (pH 7.4), 0.015 M NaCl and 0.01% PEG-8000. The final concentration of enzyme used was 3 nM thrombin. The final concentration of substrate used was 125 μM S-2238 for thrombin. All assays were performed in 96-well microtiter plates at room temperature (RT). The enzyme and inhibitor were pre-incubated for 10 minutes then substrate was added and read at 405 nm in a SpectraMax Plus Spectrophotometer (Molecular Devices). Inhibitor IC_{50} values were determined by adding test compound as ten point, three-fold serial dilutions in buffer solution, as known in the art. The plate was read at 10 minutes after substrate addition. The IC_{50} was calculated by plotting the percent (%) inhibition against compound concentration and fitting the data to a constrained four parameter sigmoidal curve, as known in the art.

VI. Pharmaceutical Compositions

[0118] In another aspect, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient. The compound is a compound of any of Formulae (Ia), (Ib), (IIa), (IIb), (IIIa), (IIIb), (IV) or (V) as disclosed herein, a compound as set forth in any of Tables A, B or C herein, or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof. In some embodiments, the compound is set forth in Table A herein. In some embodiments, the compound is set forth in Table B herein. In some embodiments, the compound is set forth in Table C herein.

[0119] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the

particular substituents found on the compounds described herein. When compounds disclosed herein contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds disclosed herein contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds disclosed herein contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0120] Compounds disclosed herein may exist as salts, such as with pharmaceutically acceptable acids. Accordingly, the compounds contemplated herein includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

[0121] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0122] Pharmaceutically acceptable salts of the compounds above, where a basic or acidic group is present in the structure, are also included within the scope of compounds contemplated herein. When an acidic substituent is present, such as $-NHSO_3H$, -COOH and

-$P(O)(OH)_2$, there can be formed the ammonium, sodium, potassium, calcium salt, and the like, for use as the dosage form. Basic groups, such as amino or basic heteroaryl radicals, or pyridyl and acidic salts, such as hydrochloride, hydrobromide, acetate, maleate, palmoate, methanesulfonate, p-toluenesulfonate, and the like, can be used as the dosage form.

[0123] Also, in the embodiments in which R-COOH is present, pharmaceutically acceptable esters can be employed, e. g. , methyl, ethyl, tert-butyl, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

A. Formulations

[0124] The compounds disclosed herein can be prepared and administered in a wide variety of oral, parenteral, and topical dosage forms. Thus, the compounds can be administered by injection (e.g. intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally). Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds disclosed herein can be administered transdermally. It is also envisioned that multiple routes of administration (e.g., intramuscular, oral, transdermal) can be used to administer the compounds disclosed herein. In some embodiments, the compounds disclosed herein may be administered orally as tablets, aqueous or oily suspensions, lozenges, troches, powders, granules, emulsions, capsules, syrups or elixirs. The composition for oral use may contain one or more agents selected from the group of sweetening agents, flavoring agents, coloring agents and preserving agents in order to produce pharmaceutically elegant and palatable preparations. Accordingly, there are also provided pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient and one or more compounds disclosed herein.

[0125] In some embodiments, tablets contain the acting ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be, for example, (1) inert diluents, such as calcium carbonate, lactose, calcium phosphate, carboxymethylcellulose, or sodium phosphate; (2) granulating and disintegrating agents, such as corn starch or alginic acid; (3) binding agents, such as starch, gelatin or acacia; and (4) lubricating agents, such as magnesium stearate, stearic acid or talc. These tablets may be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl

distearate may be employed. Coating may also be performed using techniques described in the U. S. Pat. Nos.

[0126] For preparing pharmaceutical compositions from the compounds disclosed herein, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substance that may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0127] A compound disclosed herein, in the form of a free compound or a pharmaceutically-acceptable pro-drug, metabolite, analogue, derivative, solvate or salt, can be administered, for in vivo application, parenterally by injection or by gradual perfusion over time. Administration may be intravenously, intraperitoneally, intramuscularly, subcutaneously, intracavity, or transdermally. For in vitro studies the compounds may be added or dissolved in an appropriate biologically acceptable buffer and added to a cell or tissue.

[0128] In powders, the carrier is a finely divided solid in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0129] The powders and tablets preferably contain from 5% to 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0130] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0131] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0132] When parenteral application is needed or desired, particularly suitable admixtures for the compounds disclosed herein are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. In particular, carriers for parenteral administration include aqueous solutions of dextrose, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-block polymers, and the like. Ampoules are convenient unit dosages. The compounds disclosed herein can also be incorporated into liposomes or administered via transdermal pumps or patches. Pharmaceutical admixtures suitable for use in the pharmaceuticals compositions and methods disclosed herein include those described, for example, in PHARMACEUTICAL SCIENCES (17th Ed., Mack Pub. Co., Easton, PA) and WO 96/05309, the teachings of both of which are hereby incorporated by reference.

[0133] In some embodiments, preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, growth factors and inert gases and the like.

[0134] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0135] Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the

active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0136] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0137] The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 10000 mg, more typically 1.0 mg to 1000 mg, most typically 10 mg to 500 mg, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

[0138] Some compounds may have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: Polysorbate 20, 60, and 80; Pluronic F-68, F-84, and P-103; cyclodextrin; and polyoxyl 35 castor oil. Such co-solvents are typically employed at a level between about 0.01 % and about 2% by weight.

[0139] Viscosity greater than that of simple aqueous solutions may be desirable to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation, and/or otherwise to improve the formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, chondroitin sulfate and salts thereof, hyaluronic acid and salts thereof, and combinations of the foregoing. Such agents are typically employed at a level between about 0.01% and about 2% by weight.

[0140] The compositions disclosed herein may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides, and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes.

[0141] By the present, there are provided methods for ameliorating wound healing and for mediating tissue repair (including but not limited to treatment of peripheral and coronary vascular disease). According to these methods, a subject having a wound or in need of tissue repair, is treated at the site of the wound or damaged tissue or treated systemically, with a compound disclosed herein in the form of a free compound or a pharmaceutically-acceptable prodrug, metabolite, analogue, derivative, solvate or salt.

[0142] Generally, the terms "treating", "treatment" and the like are used herein to mean affecting a subject, tissue or cell to obtain a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or disorder or sign or symptom thereof, and/or may be therapeutic in terms of a partial or complete cure for a disorder and/or adverse effect attributable to it. "Treating" as used herein covers any treatment of, or prevention of a disease or disorder in a vertebrate, a mammal, particularly a human, and includes: (a) preventing the disease or disorder from occurring in a subject that may be predisposed to the disease or disorder, but has not yet been diagnosed as having it; (b) inhibiting the disease or disorder, i. e. , arresting its development; or (c) relieving or ameliorating the disease or disorder, i. e. , cause regression of the disease or disorder.

[0143] There are provided various pharmaceutical compositions useful for ameliorating diseases and disorders, including thrombosis. In some embodiments, the disease or disorder is a thrombotic disorder. In some embodiments, the disease or disorder is acute coronary syndrome, venous thromboembolism, arterial thromboembolism or cardiogenic thromboembolism. In some embodiments, the disease or disorder is fibrosis. In some embodiments, the disease or disorder is Alzheimer's Disease. In some embodiments, the disease or disorder is multiple sclerosis. In some embodiments, the disease or disorder is pain. In some embodiments, the disease or disorder is cancer. The pharmaceutical compositions according to one embodiment are prepared by formulating a compound disclosed herein in the form of a free compound or a pharmaceutically-acceptable pro-drug, metabolite, analogue, derivative, solvate or salt, either alone or together with other pharmaceutical agents, suitable for administration to a subject using carriers, excipients and additives or auxiliaries. Frequently used carriers or auxiliaries include magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatin, starch, vitamins, cellulose and its derivatives, animal and vegetable oils, polyethylene glycols and solvents, such as sterile water, alcohols, glycerol and polyhydric alcohols. Intravenous vehicles include fluid and nutrient replenishers.

[0144] Preservatives include antimicrobial, anti-oxidants, chelating agents and inert gases. Other pharmaceutically acceptable carriers include aqueous solutions, non-toxic excipients, including salts, preservatives, buffers and the like, as described, for instance, in Remington's Pharmaceutical Sciences, 15th ed. Easton: Mack Publishing Co. , 1405-1412, 1461-1487 (1975) and The National Formulary XIV., 14th ed. Washington: American Pharmaceutical Association (1975), the contents of which are hereby incorporated by reference. The pH and exact concentration of the various components of the pharmaceutical composition are adjusted according to routine skills in the art. *See* e.g., Goodman and Gilman (eds.), 1990, THE PHARMACOLOGICAL BASIS FOR THERAPEUTICS (7th ed.).

[0145] The pharmaceutical compositions are preferably prepared and administered in dose units. Solid dose units are tablets, capsules and suppositories. For treatment of a subject, depending on activity of the compound, manner of administration, nature and severity of the disease or disorder, age and body weight of the subject, different daily doses can be used.

[0146] Under certain circumstances, however, higher or lower daily doses may be appropriate. The administration of the daily dose can be carried out both by single administration in the form of an individual dose unit or else several smaller dose units and also by multiple administrations of subdivided doses at specific intervals.

[0147] The pharmaceutical compositions contemplated herein may be administered locally or systemically in a therapeutically effective dose. Amounts effective for this use will, of course, depend on the severity of the disease or disorder and the weight and general state of the subject. Typically, dosages used in vitro may provide useful guidance in the amounts useful for in situ administration of the pharmaceutical composition, and animal models may be used to determine effective dosages for treatment of particular disorders.

[0148] Various considerations are described, e. g. , in Langer, 1990, *Science*, **249**: 1527; Goodman and Gilman's (eds.), 1990, *Id.*, each of which is herein incorporated by reference and for all purposes. Dosages for parenteral administration of active pharmaceutical agents can be converted into corresponding dosages for oral administration by multiplying parenteral dosages by appropriate conversion factors. As to general applications, the parenteral dosage in mg/m2 times 1.8 = the corresponding oral dosage in milligrams ("mg"). As to oncology applications, the parenteral dosage in mg/m2 times 1.6 = the corresponding oral dosage in mg. An average adult weighs about 70 kg. *See* e.g., Miller-Keane, 1992, ENCYCLOPEDIA & DICTIONARY OF MEDICINE, NURSING & ALLIED HEALTH, 5th Ed., (W. B. Saunders Co.), pp. 1708 and 1651.

[0149] The method by which the compound disclosed herein may be administered for oral use would be, for example, in a hard gelatin capsule wherein the active ingredient is mixed with an inert solid diluent, or soft gelatin capsule, wherein the active ingredient is mixed with a co-solvent mixture, such as PEG 400 containing Tween-20. A compound disclosed herein may also be administered in the form of a sterile injectable aqueous or oleaginous solution or suspension. The compound can generally be administered intravenously or as an oral dose of 0.1 ug to 20 mg/kg given, for example, every 3 - 12 hours.

[0150] Formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

[0151] Aqueous suspensions normally contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspension. Such excipients may be (1) suspending agent such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; (2) dispersing or wetting agents which may be (a) naturally occurring phosphatide such as lecithin; (b) a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate ; (c) a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethylenoxycetanol; (d) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and hexitol such as polyoxyethylene sorbitol monooleate, or (e) a condensation product of ethylene oxide with a partial ester derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

[0152] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to known methods using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0153] A compound disclosed herein may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[0154] The compounds disclosed herein as used in the methods disclosed herein may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

[0155] For topical use, creams, ointments, jellies, solutions or suspensions, etc. , containing the compounds disclosed herein, are employed.

[0156] In addition, some of the compounds disclosed herein may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the methods contemplated herein.

B. Effective Dosages

[0157] Pharmaceutical compositions provided herein include compositions wherein the active ingredient is contained in a therapeutically effective amount, i.e., in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, *inter alia,* on the condition being treated. For example, when administered in methods to treat thrombosis, such compositions will contain an amount of active ingredient effective to achieve the desired result (e.g. decreasing the extent of the thrombosis).

[0158] The dosage and frequency (single or multiple doses) of compound administered can vary depending upon a variety of factors, including route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; nature and extent of symptoms of the disease being treated (e.g., the disease responsive to inhibition of thrombin); presence of other diseases or other health-related problems; kind of concurrent treatment; and complications from any disease or treatment regimen. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds disclosed herein.

[0159] For any compound described herein, the therapeutically effective amount can be initially determined from a variety of techniques known in the art, e.g., biochemical characterization of inhibition of thrombin, cell culture assays, and the like. Target

concentrations will be those concentrations of active compound(s) that are capable of decreasing thrombin enzymatic activity as measured, for example, using the methods described.

[0160] Therapeutically effective amounts for use in humans may be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring thrombin inhibition and adjusting the dosage upwards or downwards, as described above.

[0161] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the methods disclosed herein, should be sufficient to affect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side effects. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. In some embodiments of a method disclosed herein, the dosage range is 0.001% to 10% w/v. In some embodiments, the dosage range is 0.1% to 5% w/v.

[0162] Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0163] Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is entirely effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration, and the toxicity profile of the selected agent.

[0164] Accordingly, in some embodiments, dosage levels of the compounds disclosed herein as used in the present methods are of the order of e.g., about 0.1 mg to about 1 mg, about 1 mg to about 10 mg, about 0.5 mg to about 20 mg per kilogram body weight, an average adult weighing 70 kilograms, with a preferred dosage range between about 0.1 mg to about 20 mg per kilogram body weight per day (from about 0.7 mg to about 1.4 gm per

patient per day). The amount of the compound disclosed herein that may be combined with the carrier materials to produce a single dosage will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain about 5 ug to 1 g of a compound disclosed herein with an appropriate and convenient amount of carrier material that may vary from about 5 to 95 percent of the total composition. Dosage unit forms will generally contain between from about 0.1 mg to 500 mg of a compound disclosed herein.

[0165] It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

C. Toxicity

[0166] The ratio between toxicity and therapeutic effect for a particular compound is its therapeutic index and can be expressed as the ratio between LD_{50} (the amount of compound lethal in 50% of the population) and ED_{50} (the amount of compound effective in 50% of the population). Compounds that exhibit high therapeutic indices are preferred. Therapeutic index data obtained from in vitro assays, cell culture assays and/or animal studies can be used in formulating a range of dosages for use in humans. The dosage of such compounds preferably lies within a range of plasma concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. See, *e.g.* Fingl *et al., In:* THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Ch.1, p.l, 1975. The exact formulation, route of administration, and dosage can be chosen by the individual practitioner in view of the patient's condition and the particular method in which the compound is used. For in vitro formulations, the exact formulation and dosage can be chosen by the individual practitioner in view of the patient's condition and the particular method in which the compound is used.

VII. Examples

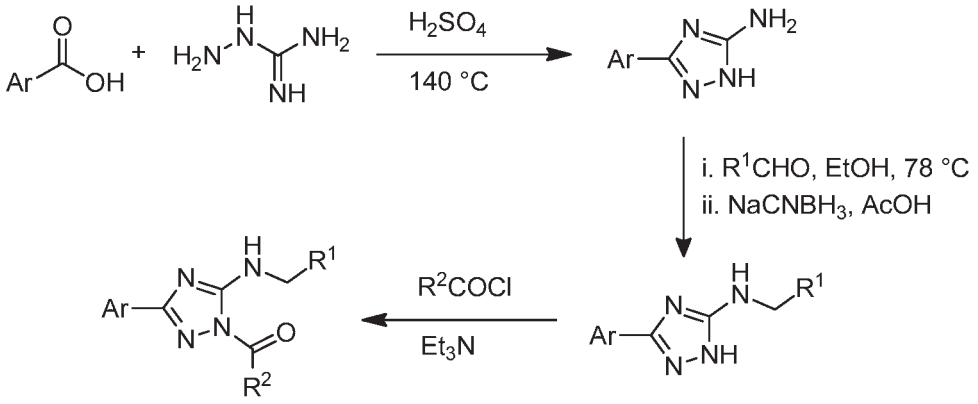
[0167] The examples below are meant to illustrate certain embodiments of the invention and not to limit the scope of the invention. Abbreviations used herein have their conventional meaning in the art, unless indicated otherwise. Specific abbreviations include the following: Å = Ångström; Ac_2O = acetic anhydride; AcOH = acetic acid; aq = aqueous; Bt = benzotriazole; BOC = *N*-*tert*-butoxycarbonyl; br = broad; *t*-BuOH = *tert*-butanol; °C = degree

Celsius; d = doublet; DABCO = 1,4-diazabicyclo[2.2.2]octane; DCE = 1,2-dichloroethane; DCM = dichloromethane; dd = doublet of doublets; DIEA = diethylisopropylamine; DMAP = 4-dimethylaminopyridine; DMF = *N*,*N*-dimethylformamide; DMSO = dimethylsulfoxide; δ = chemical shift (given in ppm, unless otherwise indicated); EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; eq = equivalent; Et_2O = diethyl ether; Et_3N = triethylamine; EtOAc = ethyl acetate; EtOH = ethanol; g = gram; h (or hr) = hour; HOBt = hydroxybenzotriazole; HPLC = high performance liquid chromatography; Hz = Hertz; IC_{50} = inhibitory concentration at 50% inhibition; *J* = coupling constant (given in Hz, unless otherwise indicated); LC = liquid chromatography; LHMDS = lithium hexamethyldisilazide; m = multiplet; M = molar; $[M+H]^+$ = parent mass spectrum peak plus H^+; MS = mass spectrum; ms = molecular sieves; MP = melting point; Me_2NH = dimethylamine; MeOH = methanol; mg = milligram; mL = milliliter; mM = millimolar; mmol = millimole; min = minute; μL = microliter; μM = micromolar; ng = nanogram; nM = nanomolar; NMR = nuclear magnetic resonance; ppm = parts per million; q = quartet; R_f = retention factor; RT = room temperature; s = singlet; t = triplet; TFA = trifluoroacetic acid; THF = tetrahydrofuran; TLC = thin layer chromatography.

Example 1 - Preparation of Cmpd 1

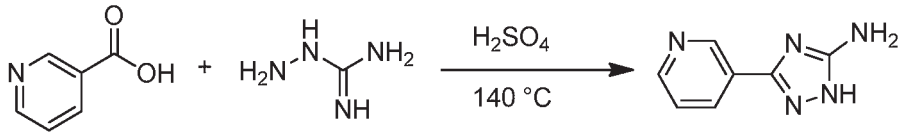
[0168] General Scheme I. A synthetic scheme useful for synthesis of compounds described herein is disclosed in General Scheme I following, wherein the term "Ar" in General Scheme I refers to substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and the terms "R^1" and "R^2" are as defined above.

General Scheme I



[0169] The synthesis of Cmpd 1 followed General Procedure 1 following.

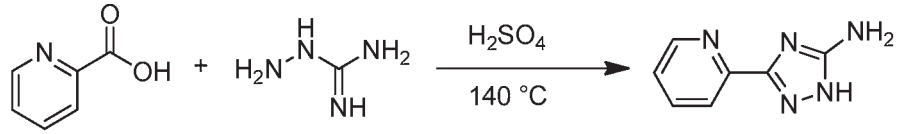
General Procedure 1



Cmpd 1

[0170] A solution of nicotinic acid (9.9 g, 80.9 mmol) in water (30 mL) was added slowly portion-wise to a previously stirred mixture of aminoguanidine sulfate (10 g, 73.5 mmol) in concentrated H_2SO_4 (8.8 mL, 162 mmol), and the reaction mixture was stirred at 140 °C for 72 h. The reaction mixture was diluted with water (50 mL) and neutralized with saturated aqueous K_2CO_3 (30 mL), and the resultant solid was filtered. The residue was washed with water (2 × 30 mL), Et_2O (2 × 30 mL) and dried under vacuum to afford Cmpd 1 (4.6 g, 39%) as an off-white solid. ^{1}H NMR: (DMSO-d_6) δ 12.23 (s, 1H), 9.05 (s, 1H), 8.54 (d, J = 2.8 Hz, 1H), 8.17 (d, J = 7.4 Hz, 1H), 7.42-7.52 (m, 1H), 6.19 (s, 2H); MS: 162 $[M + H]^+$; MP: 234-236 °C; TLC: 20% MeOH/NH_3 in $CHCl_3$: R_f: 0.40.

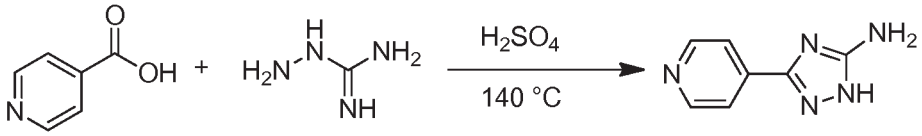
Example 2 - Preparation of Cmpd 2



Cmpd 2

[0171] General Procedure 1 was followed to obtain Cmpd 2 (8.5 g, 46%). ^{1}H NMR: (DMSO-d_6) δ 8.60 (d, J = 4.4 Hz, 1H), 7.86-7.91 (m, 2H), 7.37 (br s, 1H), 5.79 (br s, 2H); MS: 162 $[M + H]^+$; MP: 218-220 °C; TLC: 20% MeOH/NH_3 in $CHCl_3$: R_f: 0.40.

Example 3 - Preparation of Cmpd 3



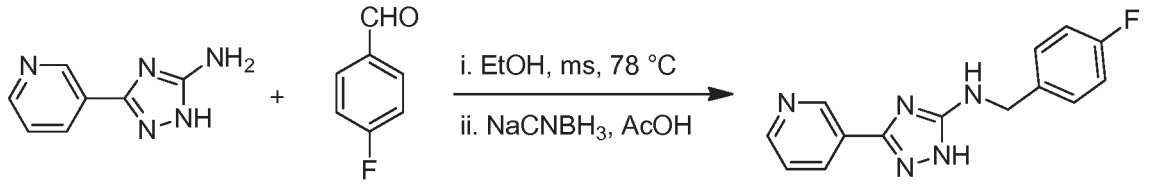
Cmpd 3

[0172] General Procedure 1 was followed to obtain Cmpd 3 (12 g, 67%). ^{1}H NMR: (DMSO-d_6) δ 12.35 (br s, 1H), 8.59 (d, J = 5.5 Hz, 2H), 7.76-7.78 (m, 2H), 6.23 (s, 2H); MS: 162 $[M + H]^+$; TLC: 20% MeOH/NH_3 in $CHCl_3$: R_f: 0.40.

Example 4 - Preparation of Cmpd 4

[0173] The synthesis of Cmpd 4 followed the procedure of General Procedure 2 following.

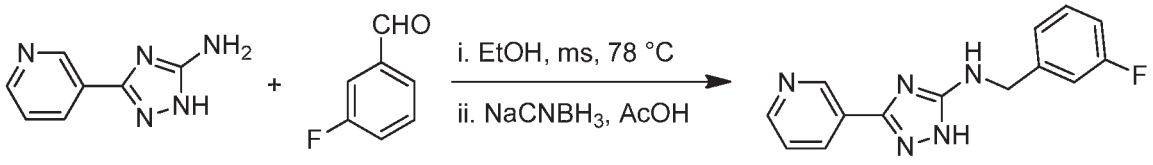
General Procedure 2



Cmpd 1 **Cmpd 4**

[0174] 4-Fluorobenzaldehyde (3.1 g, 24.8 mmol, 2 eq) and molecular sieves (4Å powder) were added to a solution of **Cmpd 1** (2 g, 12.4 mmol) in EtOH (20 mL) at RT and refluxed for 8 h. Then was added a catalytic quantity of AcOH, $NaCNBH_3$ (1.6 g, 24.8 mmol, 2 eq) at 0 °C and with stirring for 15 h at RT. The solvent was distilled off, and the residue was dissolved in EtOAc (200 mL) and filtered through a Celite® pad to remove inorganic materials. The filtrate was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resultant compound was purified by column chromatography over silica gel (100-200 mesh) by using a solvent gradient of 0-10% MeOH-$CHCl_3$ as the eluent to afford **Cmpd 4** (1.7 g, 51%). ^1H NMR: (DMSO-d_6) δ 12.50 (s, 1H), 9.06 (d, J = 1.4 Hz, 1H), 8.53-8.55 (m, 1H), 8.17-8.20 (m, 1H), 7.33-7.45 (m, 4H), 7.12-7.19 (m, 2H), 4.40 (d, J = 6.4 Hz, 2H); MS: 270 $[M + H]^+$; MP: 185-186 °C; TLC: 10% MeOH in $CHCl_3$: R_f: 0.25.

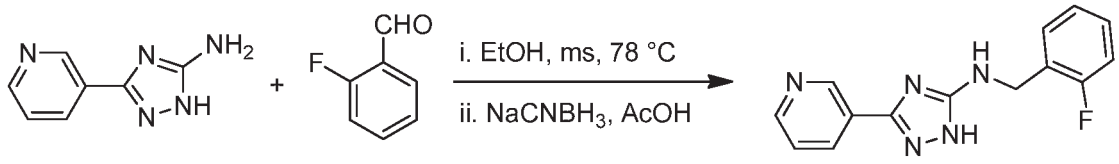
Example 5 - Preparation of Intermediate 1



Cmpd 1 **Intermediate 1**

[0175] General Procedure 2 was followed to obtain Intermediate 1 (80 mg). ^1H NMR: (DMSO-d_6) δ 12.53 (s, 1H), 9.05 (d, J = 1.3 Hz, 1H), 8.50-8.54 (m, 1H), 8.18-8.20 (m, 1H), 7.01-7.62 (m, 6H), 4.44 (d, J = 6.2 Hz, 2H); TLC: 10% MeOH in $CHCl_3$: R_f: 0.25.

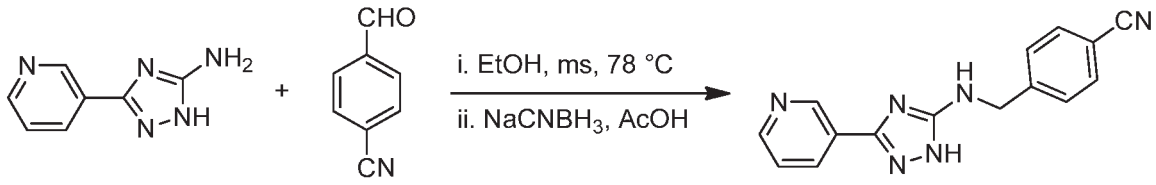
Example 6 - Preparation of Intermediate 2



Cmpd 1 **Intermediate 2**

[0176] General Procedure 2 was followed to obtain Intermediate 2 (75 mg). ^{1}H NMR: (DMSO-d_6) δ 12.51 (s, 1H), 9.06 (d, J = 1.8 Hz, 1H), 8.54-8.55 (m, 1H), 8.17-8.20 (m, 1H), 7.15-7.45 (m, 6H), 4.49 (d, J = 6.2 Hz, 2H); TLC: 10% MeOH in $CHCl_3$: R_f: 0.25.

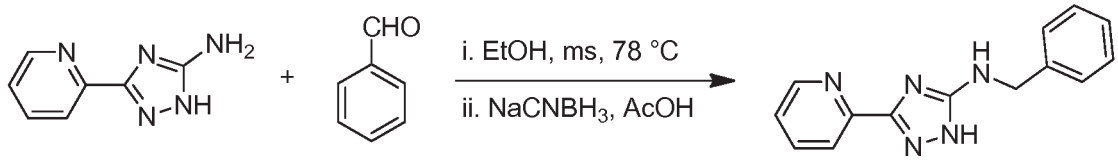
Example 7 - Preparation of Intermediate 3



Cmpd 1 **Intermediate 3**

[0177] General Procedure 2 was followed to obtain Intermediate 3 (180 mg). ^{1}H NMR: (DMSO-d_6) δ 12.57 (s, 1H), 9.05 (s, 1H), 8.54-8.55 (m, 1H), 8.16-8.18 (m, 1H), 7.41-7.95 (m, 6H), 4.52 (d, J = 6.6 Hz, 2H); TLC: 10% MeOH in $CHCl_3$: R_f: 0.25.

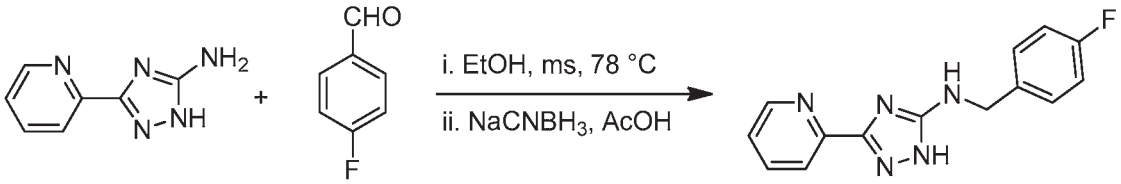
Example 8 - Preparation of Cmpd 5



Cmpd 2 **Cmpd 5**

[0178] General Procedure 2 was followed to obtain Cmpd 5 (2.8 g, 60%). MS: 252 $[M + H]^+$; MP: 226-228 °C; TLC: 10% MeOH in $CHCl_3$: R_f: 0.30.

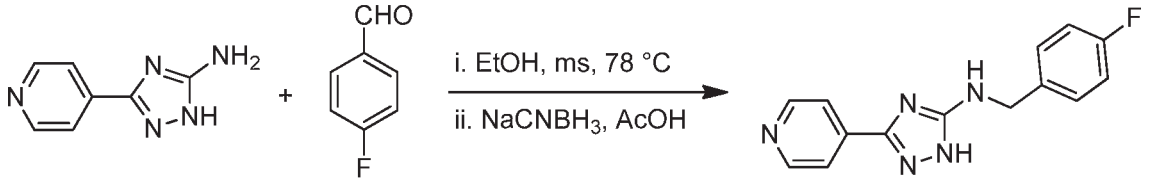
Example 9 - Preparation of Cmpd 6



Cmpd 2 **Cmpd 6**

[0179] General Procedure 2 was followed to obtain Cmpd 6 (1.6 g, 48%). ^{1}H NMR: (DMSO-d_6) δ 13.15 (br s, 1H), 8.60 (d, J = 4.0 Hz, 1H), 7.86-7.93 (m, 2H), 7.30-7.42 (m, 3H), 7.02-7.15 (m, 2H), 6.84 (br s, 1H), 4.37 (d, J = 6.2 Hz, 2H); MS: 270 $[M + H]^+$; MP: 219-220 °C; TLC: 10% MeOH in $CHCl_3$: R_f: 0.25.

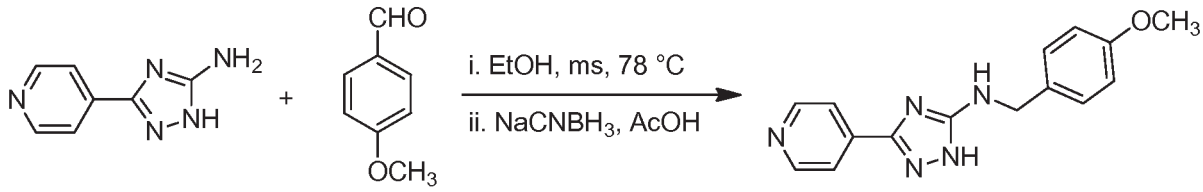
Example 10 - Preparation of Intermediate 4



Cmpd 3 **Intermediate 4**

[0180] General Procedure 2 was followed to obtain Intermediate 4 (1.4 g, 42%). MS: 270 $[M + H]^+$; **TLC:** 10% MeOH in $CHCl_3$: R_f: 0.25.

Example 11 - Preparation of Intermediate 5



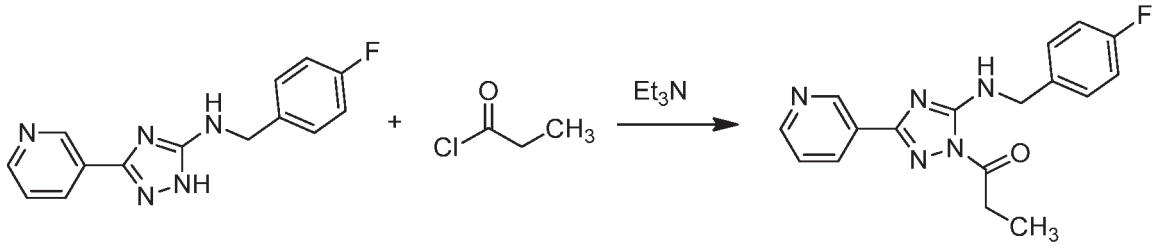
Cmpd 3 **Intermediate 5**

[0181] General Procedure 2 was followed to obtain Intermediate 5 (1.3 g, 38%). MS: 282 $[M + H]^+$; TLC: 10% MeOH in $CHCl_3$: R_f: 0.30.

Example 12 - Preparation of Cmpd 7

[0182] The synthesis of Cmpd 7 followed General Procedure 3 following.

General Procedure 3

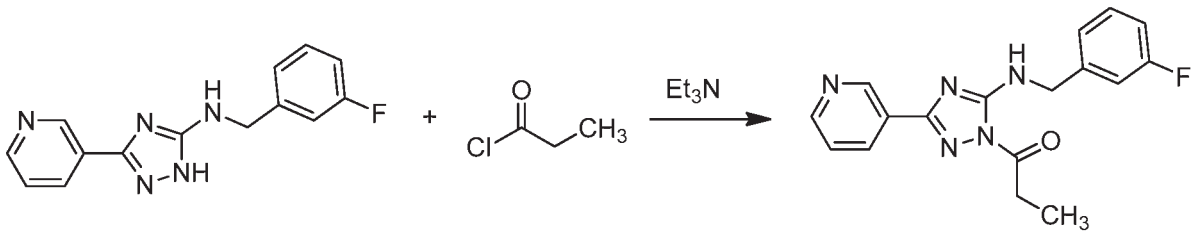


Cmpd 4 **Cmpd 7**

[0183] Propionyl chloride (39 µL, 0.44 mmol, 1.2 eq) was added to a solution of Cmpd 4 (100 mg, 0.37 mmol) in triethylamine (3 mL) at RT and stirred for 5 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (20 mL). The organic layer washed with water (2 × 5 mL), saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Cmpd 7 (40 mg, 33%). ^1H NMR: (DMSO-d_6) δ 9.14 (d, J = 1.8 Hz, 1H), 8.66-8.67 (m, 1H), 8.28-8.34 (m, 2H), 7.47-7.53 (m, 3H), 7.13-7.17 (m,

2H), 4.63 (d, J = 6.2 Hz, 2H), 3.05 (q, J = 7.5 Hz, 2H), 1.16 (t, J = 7.5 Hz, 3H); MS: 326 [M + H]$^+$; TLC: 50% EtOAc in hexane: R_f: 0.60.

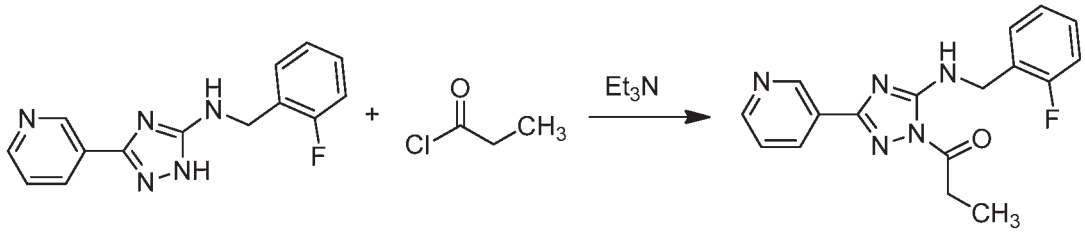
Example 13 - Preparation of Cmpd 8



Intermediate 1 **Cmpd 8**

[0184] General Procedure 3 was followed to obtain Cmpd 8 (50 mg, 51%). ^{1}H NMR: (DMSO-d_6) δ 9.13 (d, J = 1.8 Hz, 1H), 8.65-8.67 (m, 1H), 8.42 (t, J = 6.4 Hz, 1H), 8.27-8.29 (m, 1H), 7.50-7.53 (m, 1H), 7.24-7.41 (m, 3H), 7.06-7.10 (m, 1H), 4.67 (d, J = 6.6 Hz, 2H), 3.06 (q, J = 7.3 Hz, 2H), 1.16 (t, J = 7.3 Hz, 3H); MS: 326 [M + H]$^+$; MP: 140-142 °C; TLC: 50% EtOAc in hexane: R_f: 0.60.

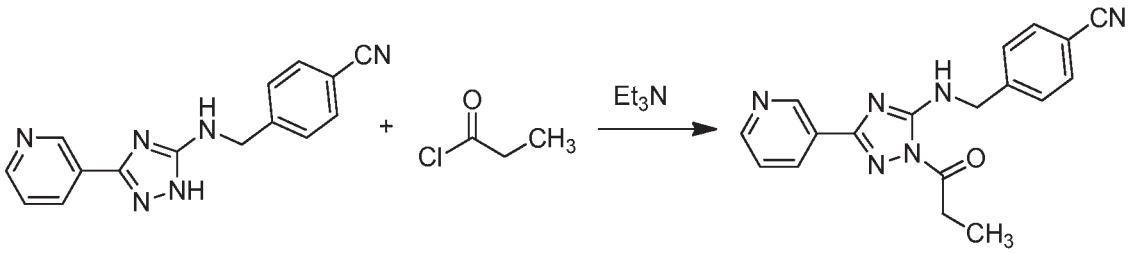
Example 14 - Preparation of Cmpd 9



Intermediate 2 **Cmpd 9**

[0185] General Procedure 3 was followed to obtain Cmpd 9 (35 mg, 38%). ^{1}H NMR: (DMSO-d_6) δ 9.12 (d, J = 1.3 Hz, 1H), 8.65-8.67 (m, 1H), 8.26-8.32 (m, 2H), 7.45-7.52 (m, 2H), 7.15-7.33 (m, 3H), 4.73 (d, J = 6.2 Hz, 2H), 3.07 (q, J = 7.5 Hz, 2H), 1.16 (t, J = 7.3 Hz, 3H); MS: 326 [M + H]$^+$; MP: 142-144 °C; TLC: 50% EtOAc in hexane: R_f: 0.60.

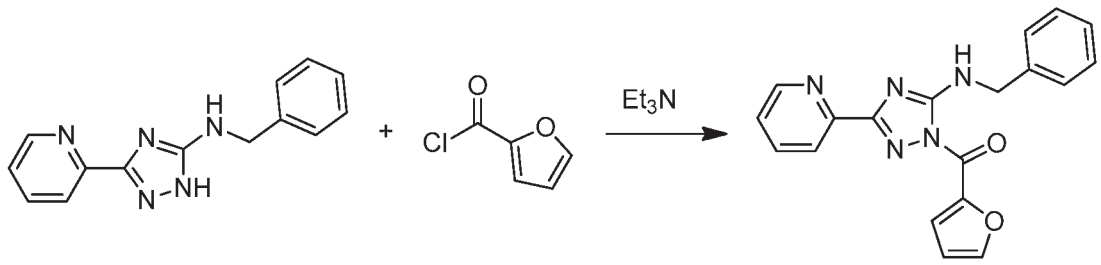
Example 15 - Preparation of Cmpd 10



Intermediate 3 **Cmpd 10**

[0186] General Procedure 3 was followed to obtain Cmpd 10 (25 mg, 20%). ^{1}H NMR: (DMSO-d_6) δ 9.11 (s, 1H), 8.50-8.67 (m, 2H), 8.26 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.8 Hz, 2H), 7.49-7.62 (m, 3H), 4.73 (d, J = 6.3 Hz, 2H), 3.06 (q, J = 7.1 Hz, 2H), 1.16 (t, J = 7.3 Hz, 3H); MS: 333 $[M + H]^+$; MP: 143-145 °C; TLC: 50% EtOAc in hexane: R_f: 0.65.

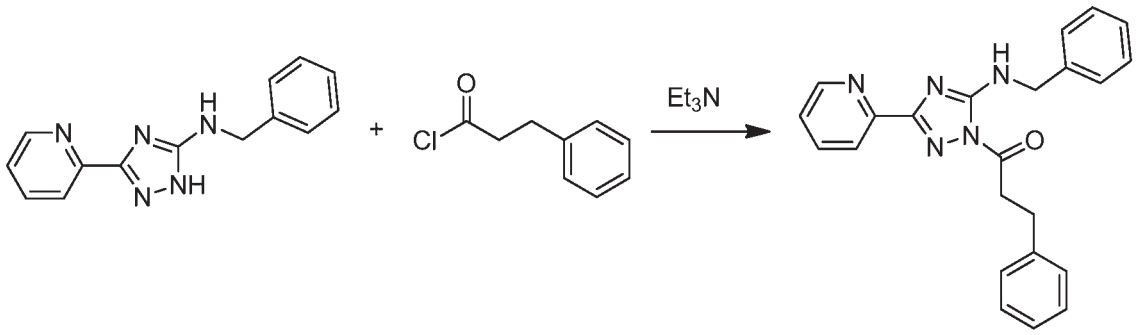
Example 16 - Preparation of Cmpd 11



Cmpd 5 **Cmpd 11**

[0187] General Procedure 3 was followed to obtain Cmpd 11 (48 mg, 35%). ^{1}H NMR: (DMSO-d_6) δ 8.71 (d, J = 4.0 Hz, 1H), 8.46 (br s, 1H), 8.13-8.23 (m, 3H), 7.92-7.96 (m, 1H), 7.24-7.52 (m, 6H), 6.88-6.89 (m, 1H), 4.74 (d, J = 6.2 Hz, 2H); MS: 346 $[M + H]^+$; MP: 143-145 °C; TLC: 50% EtOAc in hexane: R_f: 0.60.

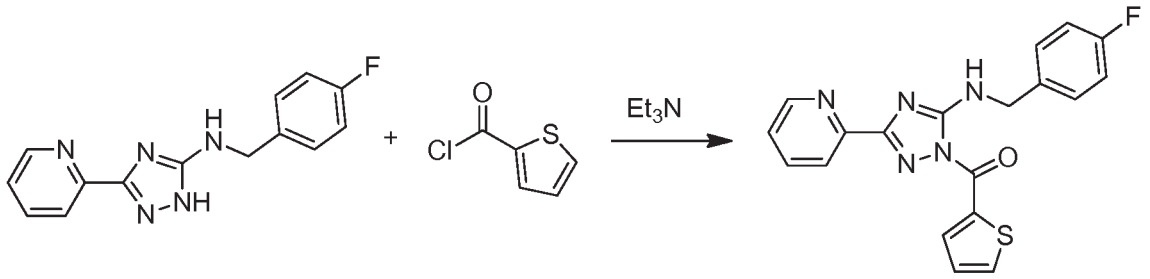
Example 17 - Preparation of Cmpd 12



Cmpd 5 **Cmpd 12**

[0188] General Procedure 3 was followed to obtain Cmpd 12 (25 mg, 16%). ^{1}H NMR: (DMSO-d_6) δ 8.65 (d, J = 4.0 Hz, 1H), 8.26 (br s, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.90 (t, J = 7.7 Hz, 1H), 7.19-7.48 (m, 11H), 4.67 (d, J = 6.0 Hz, 2H), 3.30-3.41 (m, 2H), 2.99-3.03 (m, 2H); MS: 384 $[M + H]^+$; MP: 118-120 °C; TLC: 50% EtOAc in hexane: R_f: 0.40.

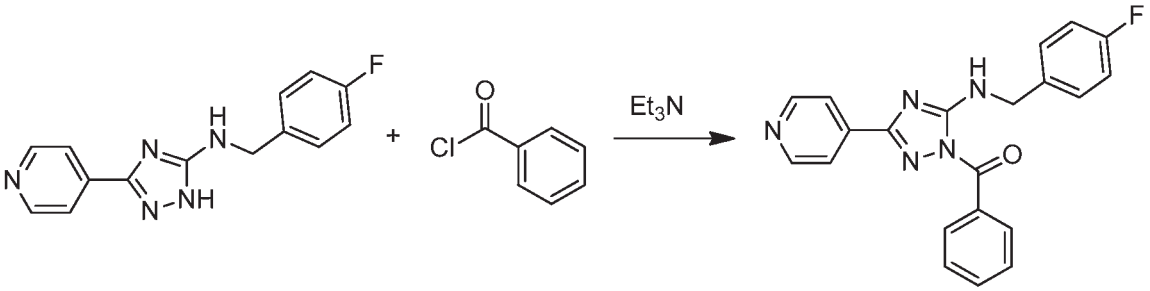
Example 18 - Preparation of Cmpd 13



Cmpd 6 **Cmpd 13**

[0189] General Procedure 3 was followed to obtain Cmpd 13 (40 mg, 28%). ^{1}H NMR: (DMSO-d_6) δ 8.72 (d, J = 4.6 Hz, 1H), 8.47-8.54 (m, 2H), 8.12-8.23 (m, 2H), 7.94-7.98 (m, 1H), 7.48-7.52 (m, 3H), 7.34-7.36 (m, 1H), 7.16 (t, J = 9.0 Hz, 2H), 4.71 (d, J = 6.1 Hz, 2H); MS: 380 $[M + H]^+$; MP: 159-160 °C; TLC: 50% EtOAc in hexane: R_f: 0.60.

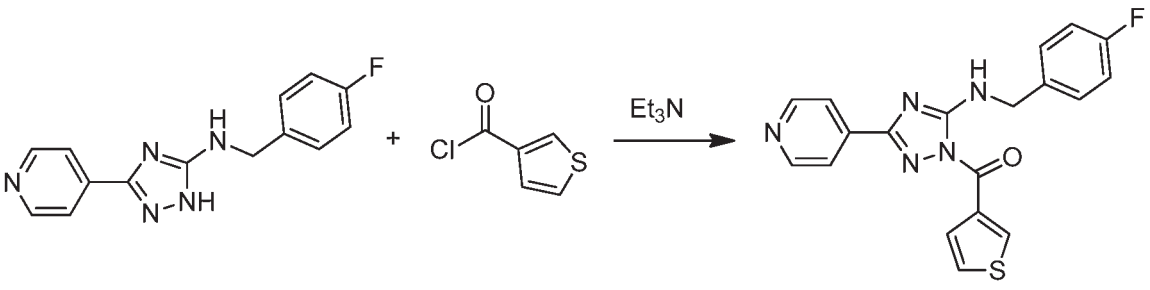
Example 19 - Preparation of Cmpd 14



Intermediate 4 **Cmpd 14**

[0190] General Procedure 3 was followed to obtain Cmpd 14 (48 mg, 46%). ^{1}H NMR: (DMSO-d_6) δ 8.68-8.70 (m, 3H), 8.14-8.16 (m, 2H), 7.85-7.87 (m, 2H), 7.53-7.73 (m, 5H), 7.18 (t, J = 8.9 Hz, 2H), 4.70 (d, J = 6.2 Hz, 2H); MS: 374 $[M + H]^+$; MP: 174-178 °C; TLC: 50% EtOAc in hexane: R_f: 0.50.

Example 20 - Preparation of Cmpd 15

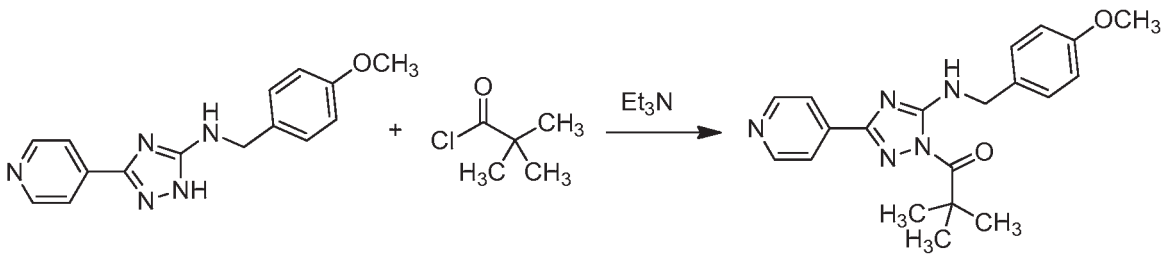


Intermediate 4 **Cmpd 15**

[0191] General Procedure 3 was followed to obtain Cmpd 15 (20 mg, 14%). ^{1}H NMR: (DMSO-d_6) δ 9.19 (d, J = 1.3 Hz, 1H), 8.63-8.73 (m, 3H), 8.00 (d, J = 5.7 Hz, 2H), 7.72-7.88

(m, 2H), 7.50-7.54 (m, 2H), 7.17 (t, J = 8.8 Hz, 2H), 4.70 (d, J = 6.2 Hz, 2H); MS: 380 [M + H]$^+$; MP: 187-188 °C; TLC: 50% EtOAc in hexane: R_f: 0.60.

Example 21 - Preparation of Cmpd 16



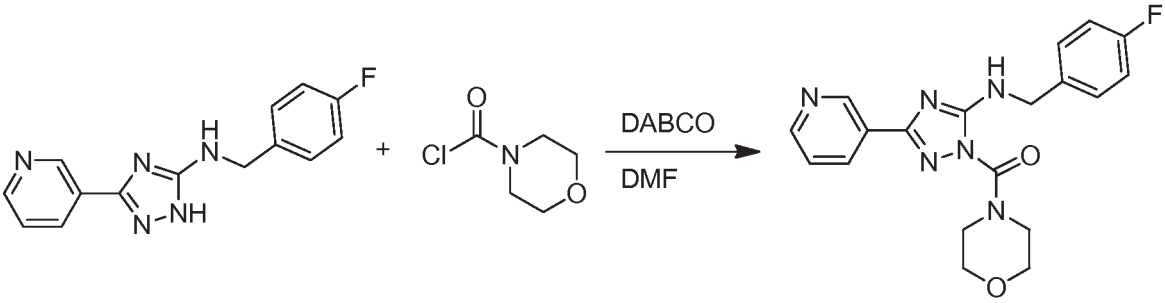
Intermediate 5 **Cmpd 16**

[0192] General Procedure 3 was followed to obtain Cmpd 16 (35 mg, 36%). ^{1}H NMR: (DMSO-d_6) δ 8.71 (d, J = 6.2 Hz, 2H), 8.38 (t, J = 6.2 Hz, 1H), 7.90 (d, J = 5.7 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.58 (d, J = 6.2 Hz, 2H), 3.72 (s, 3H), 1.46 (s, 9H); MS: 366 [M + H]$^+$; MP: 143-146 °C; TLC: 50% EtOAc in hexane: R_f: 0.60.

Example 22 - Preparation of Cmpd 17

[0193] The synthesis of Cmpd 17 followed General Procedure 4 following.

General Procedure 4



Cmpd 4 **Cmpd 17**

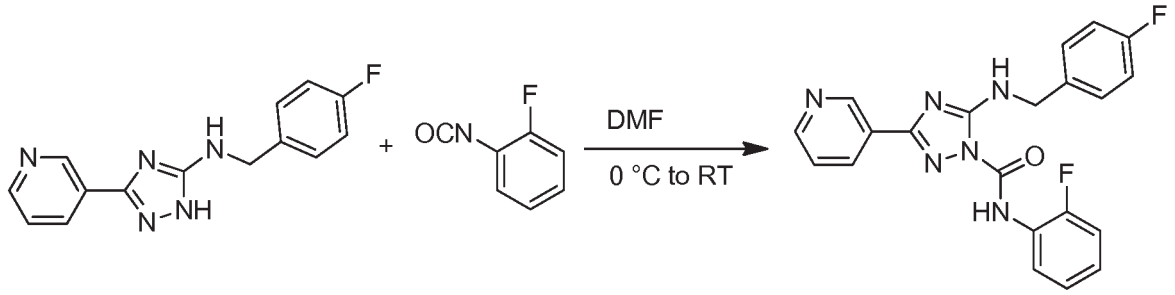
[0194] A solution of Cmpd 4 (100 mg, 0.37 mmol) in dry DMF (2 mL) was added to a solution of morpholinecarbonyl chloride (86 µL, 0.74 mmol, 2 eq), DABCO (124 mg, 1.11 mmol, 3 eq) in DMF (3 mL) at RT and stirred for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (30 mL). The organic layer washed with water (2 × 5 mL), saturated aqueous $NaHCO_3$ (2 × 5 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to get a crude residue. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-50% EtOAc-hexane as the eluent to afford Cmpd 17 (33 mg, 23%). ^{1}H NMR: (DMSO-d_6) δ 9.11 (s, 1H), 8.64 (d, J = 4.8 Hz, 1H), 8.25 (d, J = 7.9 Hz, 1H), 7.90 (s, 1H), 7.46-7.52 (m, 3H),

7.16 (t, J = 8.8, 2H), 4.59 (d, J = 6.2 Hz, 2H), 3.70-3.99 (m, 8H); MS: 383 $[M + H]^+$; TLC: 50% EtOAc in hexane: R_f: 0.40.

Example 23 - Preparation of Cmpd 18 [General Procedure 5]

[0195] The synthesis of Cmpd 18 followed General Procedure 5 following.

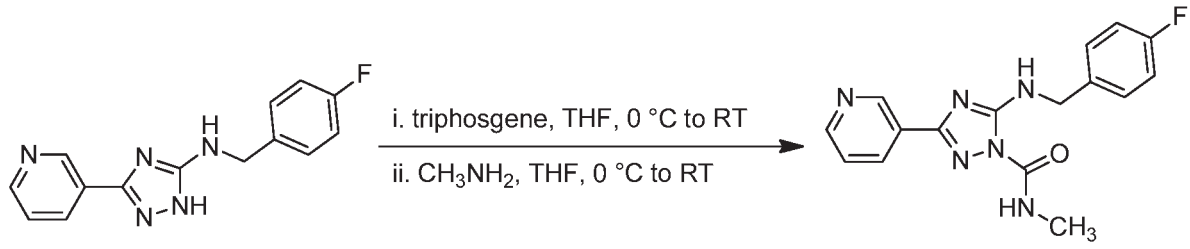
General Procedure 5



Cmpd 4 **Cmpd 18**

[0196] 2-Fluorophenyl isocyanate (29 μL, 0.26 mmol, 0.7 eq) was added to a solution of Cmpd 4 (100 mg, 0.37 mmol) in DMF (5 mL) at 0 °C and stirred at RT for 6 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (30 mL). The organic layer washed with water (2 x 5 mL), saturated aqueous $NaHCO_3$ (2 × 5 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo* to get crude a residue. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Cmpd 18 (60 mg, 39%). ^1H NMR: (DMSO-d_6) δ 9.94 (s, 1H), 9.23 (s, 1H), 8.68 (d, J = 4.4 Hz, 1H), 8.34-8.36 (m, 1H), 8.11-8.14 (m, 1H), 7.48-7.67 (m, 4H), 7.14-7.38 (m, 5H), 4.64 (d, J = 5.7 Hz, 2H); MS: 407 $[M + H]^+$; MP: 157-159 °C; TLC: 40% EtOAc in hexane: R_f: 0.50.

Example 24 - Preparation of Cmpd 19

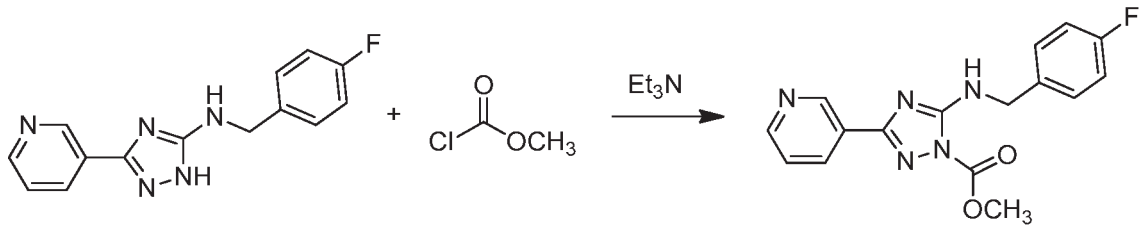


Cmpd 4 **Cmpd 19**

[0197] A solution of Cmpd 4 (200 mg, 0.74 mmol) in dry THF (5 mL) was added to a solution of triphosgene (100 mg, 0.37 mmol, 0.5 eq) in THF (3 mL) at 0 °C and stirred at RT for 1 h. The reaction re-cooled to 0 °C, added methylamine (2.47 mL, 3M solution in THF, 7.43 mmol, 10 eq), sealed the reaction vessel, and stirred at RT for 16 h. The reaction mixture

was diluted with water (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layer was washed with water (2 × 30 mL), saturated aqueous $NaHCO_3$ (20 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-50% EtOAc-hexane as eluent to afford Cmpd 19 (70 mg, 34%). ^{1}H NMR: (DMSO-d_6) δ 9.16 (d, J = 1.3 Hz, 1H), 8.64-8.66 (m, 1H), 8.24-8.29 (m, 2H), 8.01 (t, J = 6.2 Hz, 1H), 7.46-7.54 (m, 3H), 7.16 (t, J = 9.0 Hz, 2H), 4.61 (d, J = 6.2 Hz, 2H), 2.81 (d, J = 4.4 Hz, 3H); MS: 327 $[M + H]^+$; MP: 154-158 °C; TLC: 50% EtOAc in hexane: R_f: 0.50.

Example 25 - Preparation of Cmpd 20



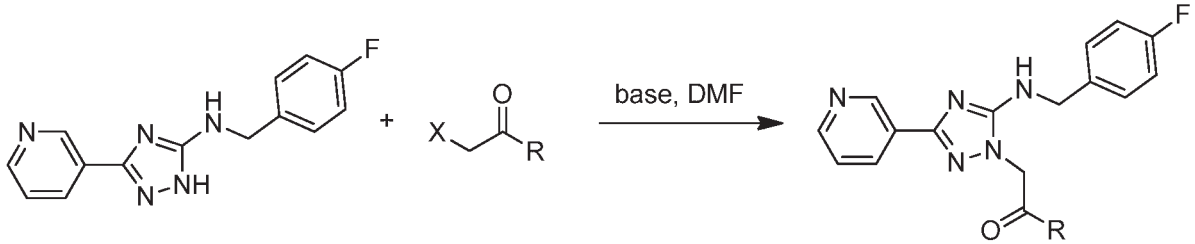
Cmpd 4 **Cmpd 20**

[0198] General Procedure 3 was followed to obtain Cmpd 20 (44 mg, 40%). ^{1}H NMR: (DMSO-d_6) δ 9.14 (d, J = 1.3 Hz, 1H), 8.65-8.67 (m, 1H), 8.26-8.29 (m, 1H), 8.13 (t, J = 6.2, 1H), 7.47-7.52 (m, 3H), 7.14-7.18 (m, 2H), 4.63 (d, J = 6.2 Hz, 2H), 3.99 (s, 3H); MS: 328 $[M + H]^+$; MP: 134-137 °C; TLC: 60% EtOAc in hexane: R_f: 0.50.

Example 26 - Preparation of Cmpd 21

[0199] **General Scheme II.** A synthetic scheme useful for synthesis of compounds described herein is disclosed in General Scheme II following, wherein the term "X" in General Scheme II refers to halogen, e.g., Cl, Br, "base" is a base known in the art, e.g., K_2CO_3, Et_3N, and the like, and "R" is a substituent as disclosed herein, e.g., substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

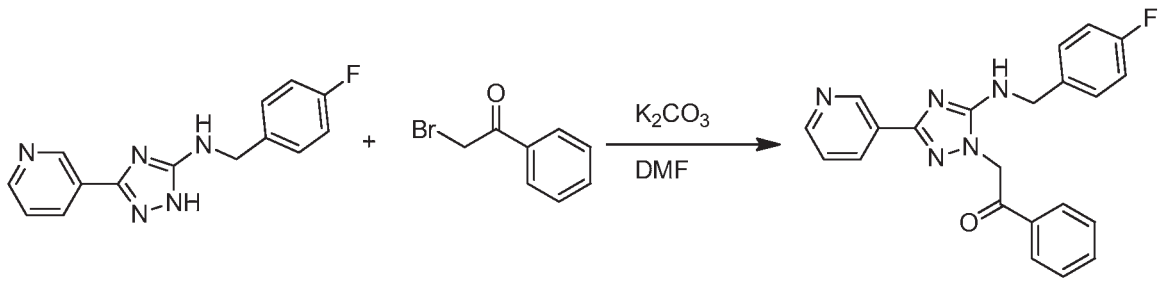
General Scheme II



X = Cl, Br base = K_2CO_3 or Et_3N

[0200] Synthesis of Cmpd 21 followed General Procedure 6 following.

General Procedure 6



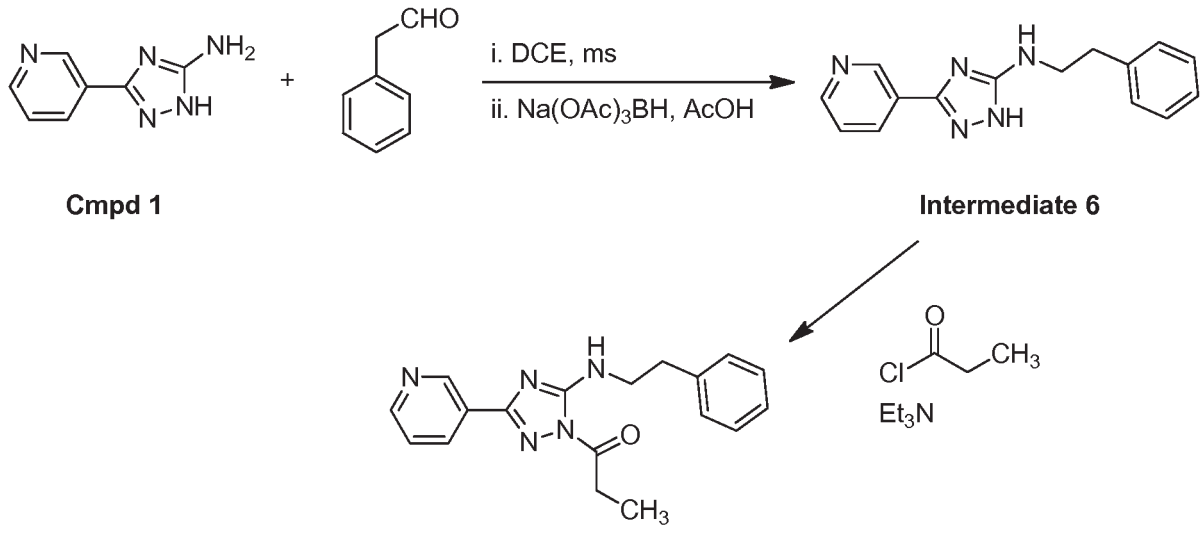
Cmpd 4 **Cmpd 21**

[0201] 2-Bromoacetophenone (44 mg, 0.22 mmol) was added to a solution of Cmpd 4 (100 mg, 0.37 mmol), K_2CO_3 (102 mg, 0.74 mmol) in DMF (4 mL) at RT and stirred for 5 h. The reaction mixture was diluted with water (10 mL), and extracted with EtOAc (30 mL). The organic layer washed with water (2 × 5 mL), saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-5% MeOH/$CHCl_3$ as the eluent to afford Cmpd 21 (25 mg, 17%). ^{1}H NMR: (DMSO-d_6) δ 9.06 (d, *J* = 1.3 Hz, 1H), 8.55-8.57 (m, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 8.06 (d, *J* = 7.0, 2H), 7.59-7.75 (m, 3H), 7.41-7.46 (m, 3H), 7.15-7.29 (m, 3H), 5.74 (s, 2H), 4.52 (d, *J* = 5.7, 2H); MS: 388 $[M + H]^+$; TLC: 10% MeOH in $CHCl_3$: R_f: 0.50.

Example 27 - Preparation of Cmpd 22

[0202] A useful scheme for the preparation of compounds of the type of Cmpd 22 is provided in Scheme 1 following.

Scheme 1

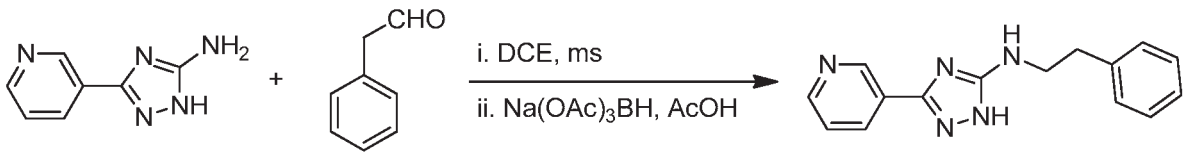


Cmpd 1 **Intermediate 6**

Cmpd 22

[0203] A detailed description of the preparation of Intermediate 6 and Cmpd 22 follows.

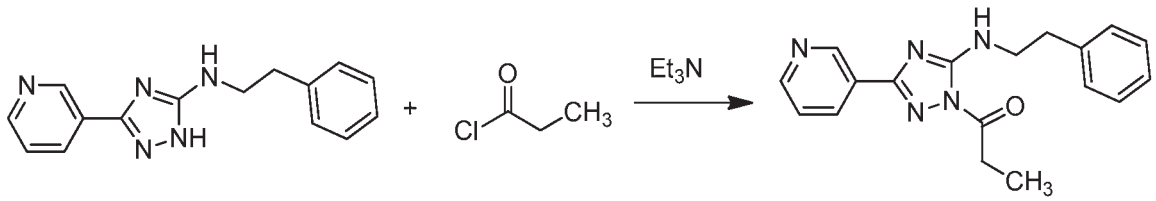
Preparation of Intermediate 6



Cmpd 1 **Intermediate 6**

[0204] Phenylacetaldehyde (0.29 mL, 2.48 mmol, 2 eq), molecular sieves (4Å powder), AcOH (0.1 mL, 2.48 mmol, 2 eq), and $Na(OAc)_3BH$ (655 mg, 7.71 mmol, 6.2 eq) at 0 °C were added to a solution of Cmpd 1 (200 mg, 1.24 mmol) in DCE (10 mL) and stirred at RT for 18 h. The solvent was distilled-off and the residue was diluted with EtOAc (150 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain crude Intermediate 6 (220 mg) which was used without additional purification. TLC: 10% MeOH in $CHCl_3$: R_f: 0.40.

Preparation of Cmpd 22



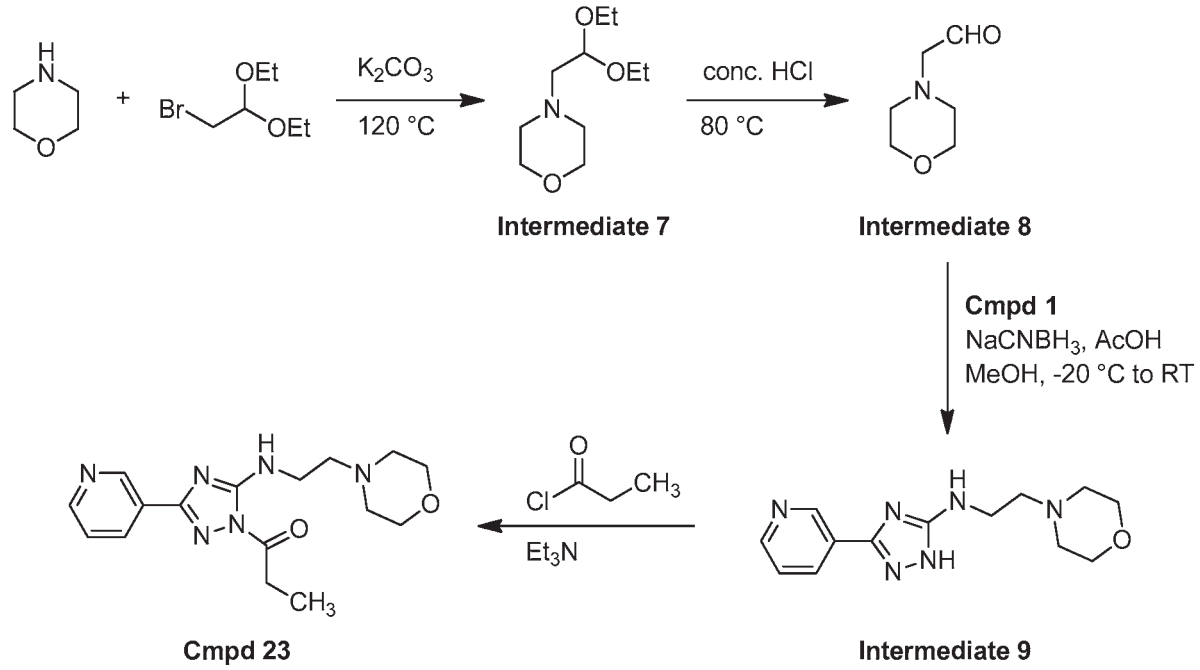
Intermediate 6 **Cmpd 22**

[0205] General Procedure 3 was followed to obtain Cmpd 22 (13 mg, 5%). ^1H NMR: (DMSO-d_6) δ 9.17 (s, 1H), 8.68 (d, J = 4.4 Hz, 1H), 8.33 (d, J = 7.9 Hz, 1H), 7.83 (t, J = 5.7 Hz, 1H), 7.52-7.55 (m, 1H), 7.21-7.34 (m, 5H), 3.70 (q, J = 6.6 Hz, 2H), 2.95-3.07 (m, 4H), 1.14 (t, J = 7.3 Hz, 3H); MS: 322 $[M + H]^+$; MP: 98-100 °C; TLC: 60% EtOAc in hexane: R_f: 0.60.

Example 28 - Preparation of Cmpd 23

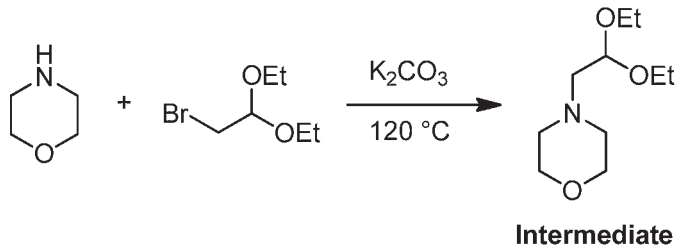
[0206] A useful scheme for the preparation of compounds of the type of Cmpd 23 is provided in Scheme 2 following.

Scheme 2



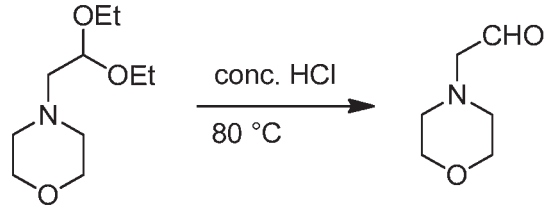
[0207] A detailed description of the preparation of Intermediates 7-9 and Cmpd 23 follows.

Preparation of Intermediate 7



[0208] A mixture of 2-bromoacetaldehyde diethyl acetal (4.5 g, 22.9 mmol), morpholine (2.0 g, 22.9 mmol) and K_2CO_3 (6.34 g, 45.9 mmol, 2 eq) was stirred at 120 °C for 16 h. The reaction mixture was cooled to RT, diluted with water (50 mL) and extracted with DCM (3 × 50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated to get crude a residue. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-50% EtOAc-hexane as the eluent to afford Intermediate 7 (2.6 g, 56%) as a pale yellow liquid. ^{1}H NMR: ($CDCl_3$) δ 4.64 (t, J = 5.3 Hz, 1H), 3.63-3.70 (m, 6H), 3.50-3.58 (m, 2H), 2.52-2.55 (m, 6H), 1.20 (t, J = 7.0 Hz, 6H); TLC: 60% EtOAc in hexane: R_f: 0.50.

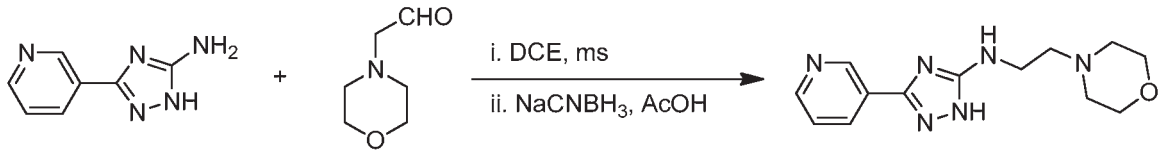
Preparation of Intermediate 8



Intermediate 7 **Intermediate 8**

[0209] A solution of Intermediate 7 (600 mg, 2.95 mmol) dissolved in concentrated aqueous HCl (4 mL) was stirred at 80 °C for 2 h. The reaction mixture was cooled to RT, made alkaline (pH ~10) with saturated aqueous $NaHCO_3$ (20 mL) and the resulting solution was extracted with DCM (3 × 50 mL). The combined organic layers were washed with water (50 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain crude Intermediate 8 (340 mg) as a colorless oil which was used without additional purification. TLC: 60% EtOAc in hexane: R_f: 0.30.

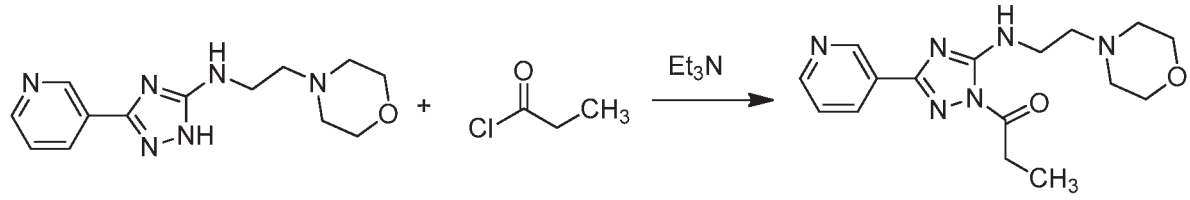
Preparation of Intermediate 9



Cmpd 1 **Intermediate 8** **Intermediate 9**

[0210] Intermediate 8 (320 mg, 2.48 mmol, 2 eq) and molecular sieves (4Å powder) were added to a solution of Cmpd 1 (200 mg, 1.24 mmol) in MeOH (10 mL) at -20 °C and the resulting solution was stirred at RT. After 16 h, added AcOH (1 mL) and $NaCNBH_3$ (156 mg, 2.48 mmol, 2 eq) at 0 °C and the reaction mixture was stirred for 3 h at RT. The solvent was evaporated and the residue was dissolved in EtOAc (75 mL) and filtered through a Celite pad to remove inorganic materials. The filtrate was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a solvent gradient of 0-80% EtOAc-hexane as the eluent to afford Intermediate 9 (210 mg). TLC: 10% MeOH in $CHCl_3$: R_f: 0.40.

Preparation of Cmpd 23



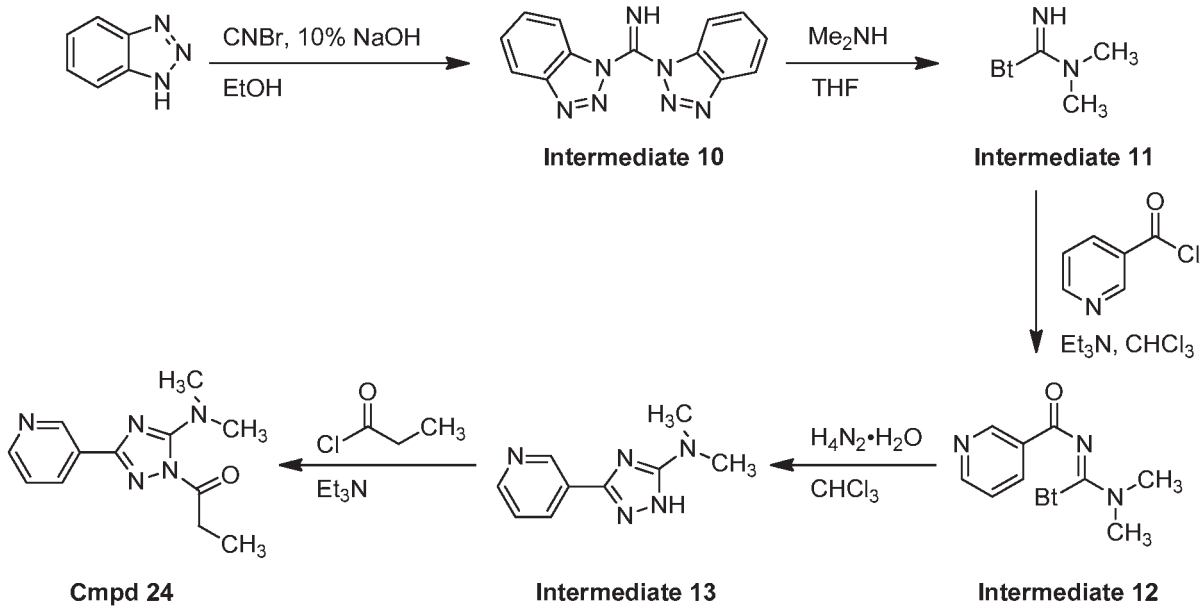
Intermediate 9 **Cmpd 23**

[0211] General Procedure 3 was followed to obtain Cmpd 23 (10 mg, 4%). ^{1}H NMR: (DMSO-d_6) δ 9.15 (s, 1H), 8.67 (d, J = 4.8 Hz, 1H), 8.30 (d, J = 7.9 Hz, 1H), 7.83 (br s, 1H), 7.51-7.54 (m, 1H), 3.58 (d, J = 4.4 Hz, 6H), 3.02-3.08 (m, 2H), 2.44-2.59 (m, 6H), 1.15 (t, J = 7.3 Hz, 3H); MS: 331 $[M + H]^+$; TLC: 50% EtOAc in hexane: R_f: 0.50.

Example 29 - Preparation of Cmpd 24

[0212] A useful scheme for the preparation of compounds of the type of Cmpd 24 is provided in Scheme 3 following.

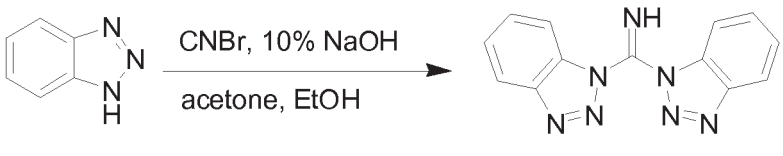
Scheme 3



Intermediate 10 **Intermediate 11** **Intermediate 12** **Intermediate 13** **Cmpd 24**

[0213] A detailed description of the preparation of Intermediates 10-13 and Cmpd 24 follows.

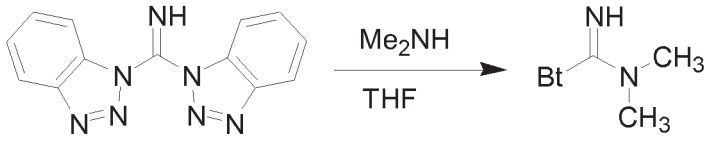
Preparation of Intermediate 10



Intermediate 10

[0214] A solution of cyanogen bromide (1.3 g, 12.6 mmol) in acetone (5 mL) was added portion-wise slowly to a mixture of benzotriazole (3 g, 25.2 mmol, 2 eq) in EtOH (50 mL) followed by 10% aqueous NaOH (6 mL, 12.6 mmol, 1 eq) at 0 °C. The reaction mixture was then stirred at RT for 30 min. Solid formation was observed. The solid was filtered and washed with cold EtOH. The resulting material was recrystallized from benzene to afford Intermediate 10 (2.2 g, 33%) as a white solid. ^{1}H NMR: (DMSO-d_6) δ 11.76 (s, 1H), 8.29-8.39 (m, 2H), 7.86-8.09 (m, 2H), 7.44-7.72 (m, 4H), MS: 264 $[M + H]^+$; TLC: 30% EtOAc in hexane: R_f: 0.50.

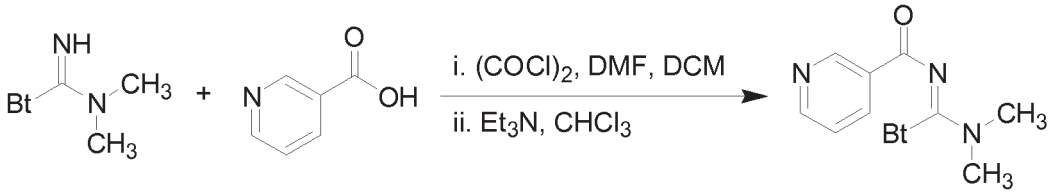
Preparation of Intermediate 11



Intermediate 10 **Intermediate 11**

[0215] Dimethylamine (1.59 mL, 7.60 mmol, 1 eq) was added to Intermediate 10 (2 g, 7.60 mmol) in THF (30 mL) at RT and the resulting mixture was allowed to stir for 24 h. The solvent was evaporated and the residue was dissolved in DCM (100 mL). The organic layer was washed with 10% Na_2CO_3 (3 × 5 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford Intermediate 11 (1.2 g, 71%) as a light yellow liquid which was used without additional purification. ^{1}H NMR: (DMSO-d_6) δ 8.17 (d, J = 8.4 Hz, 1H), 7.65-7.80 (m, 3H), 7.49-7.53 (m, 1H), 2.87 (s, 6H); MS: 190 $[M + H]^+$; TLC: 30% EtOAc in hexane: R_f: 0.30.

Preparation of Intermediate 12

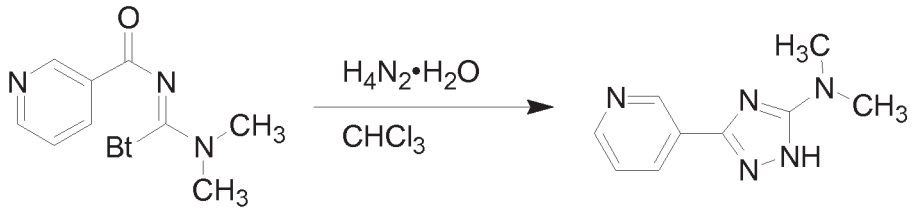


Intermediate 11 **Intermediate 12**

[0216] Oxalyl chloride (2 mL, 23.3 mmol, 1.4 eq) was added to a solution of nicotinic acid (2 g, 16.3 mmol) in DCM followed by catalytic amount of DMF (0.5 mL) at 0 °C and stirred for 5 h at RT. The solvent was then evaporated to afford nicotinic acid chloride as a yellow solid. Nicotinic acid chloride (1.1 g, 7.93 mmol, 1.5 eq) was then added to a solution of Intermediate 11 (1 g, 5.29 mmol) in $CHCl_3$ (30 mL) followed by Et_3N (0.7 mL, 5.29 mmol, 1 eq) at 0 °C. The reaction mixture was allowed to warm to RT for stir for 18 h. The mixture was then diluted with $CHCl_3$ (20 mL). The organic layer was washed with water (10 mL),

brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-50% EtOAc-hexane as the eluent to afford Intermediate 12 (900 mg, 60%) as a white solid. MS: 295 $[M + H]^+$; TLC: 50% EtOAc in DCM: R_f: 0.40.

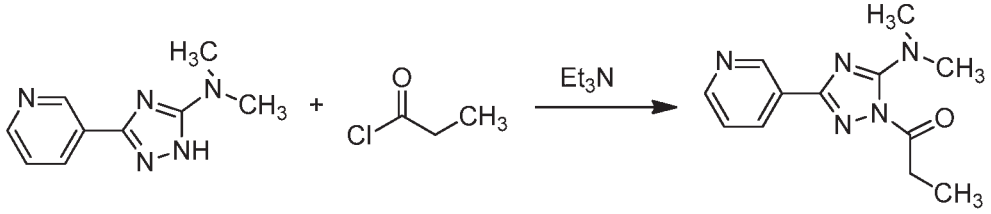
Preparation of Intermediate 13



Intermediate 12 **Intermediate 13**

[0217] Hydrazine hydrate (5 mL) was added solution of Intermediate 12 (900 mg, 25.2 mmol) in chloroform (20 mL) at RT and the resulting mixture was allowed to stir for 24 h. The mixture was diluted with excess $CHCl_3$ (20 mL). The organic layer was then washed with water (15 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was partially purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-50% EtOAc-hexane as the eluent to afford Intermediate 13 (150 mg) as a thick brown mass. MS: 190 $[M + H]^+$; TLC: 10% MeOH in $CHCl_3$: R_f: 0.30.

Preparation of Cmpd 24



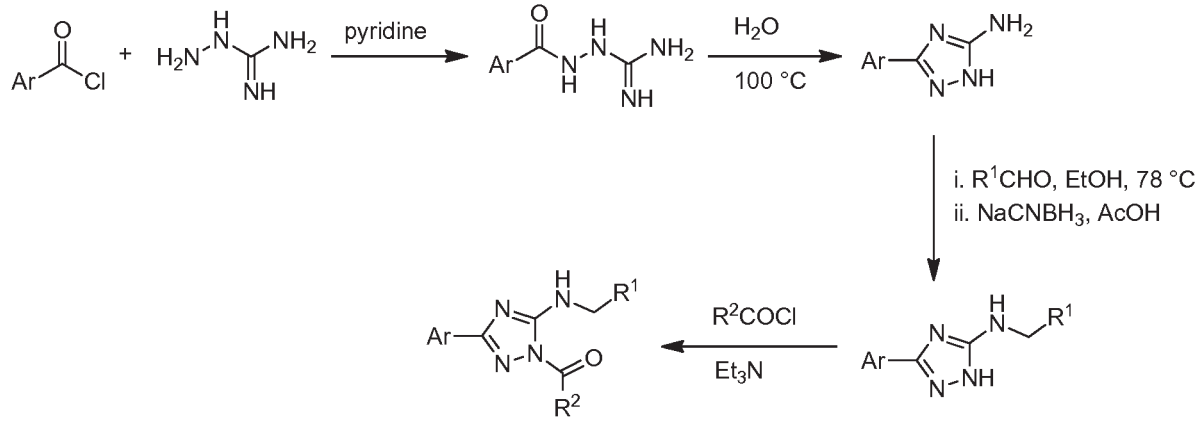
Intermediate 13 **Cmpd 24**

[0218] General Procedure 3 was followed to obtain Cmpd 24 (13 mg, 6%). ^1H NMR: (DMSO-d_6) δ 9.15 (s, 1H), 8.68 (d, J = 3.5 Hz, 1H), 8.31 (d, J = 7.9 Hz, 1H), 7.53 (dd, J = 7.9, 4.8 Hz, 1H), 3.04-3.14 (m, 8H), 1.15 (t, J = 7.3 Hz, 3H); MS: 246 $[M + H]^+$; TLC: 50% EtOAc in DCM: R_f: 0.50.

Example 30 - Triazolyl ring formation

[0219] A general chemical scheme which includes the formation of the triazolyl ring is provided in General Scheme III following, wherein "Ar," "R^1" and "R^2" are as defined in Example 1.

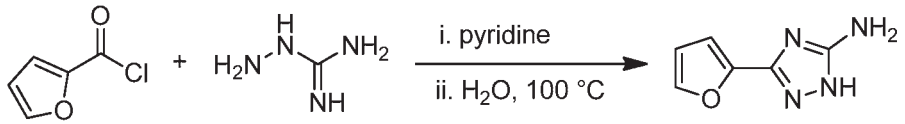
General Scheme III



Example 31 - Preparation of Cmpd 25

[0220] Synthesis of Cmpd 25 followed General Procedure 7 following.

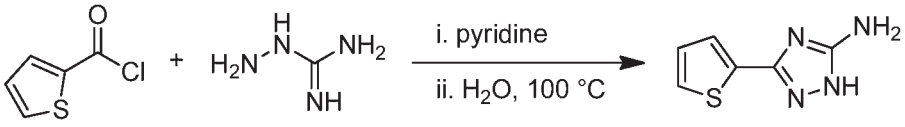
General Procedure 7



Cmpd 25

[0221] 2-Furoyl chloride (7.9 mL, 75.2 mmol) was added to a solution of aminoguanidine sulfate (10 g, 75.2 mmol, 1 eq) in pyridine (50 mL) at 0 °C. The reaction mixture was then allowed to stir at RT for 14 h before being neutralized with saturated aqueous $NaHCO_3$ (20 mL), extracted with *t*-BuOH (3 × 100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was then dissolved in water (150 mL) and stirred at 100 °C for 6 h. The reaction mixture was cooled to 0 °C and extracted with EtOAc (5 × 100 mL), dried over Na_2SO_4, filtered and concentrated to afford Cmpd 25 (3.5 g, 31%) as an off-white solid. ^1H NMR: (DMSO-d_6) δ 12.17 (br s, 1H), 7.69 (s, 1H), 6.69 (d, J = 2.5 Hz, 1H), 6.55 (dd, J = 2.9, 1.8 Hz, 1H), 6.05 (br s, 2H); MS: 151 $[M + H]^+$; MP: 202-204 °C; TLC: 20% MeOH/NH_3 in $CHCl_3$: R_f: 0.40.

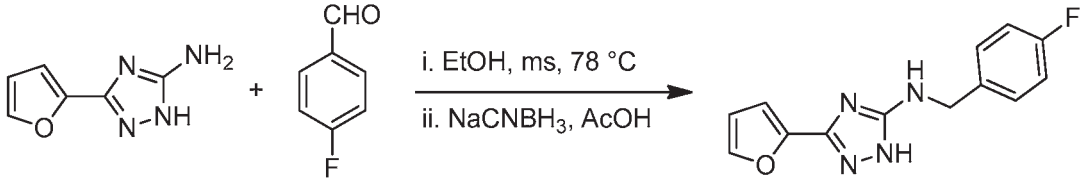
Example 32 - Preparation of Intermediate 14



Intermediate 14

[0222] General Procedure 7 was followed to obtain crude Intermediate 14 (2.2 g). ^1H NMR: (DMSO-d_6) δ 12.07 (br s, 1H), 7.39-7.46 (m, 2H), 7.07 (s, 1H), 6.09 (br s, 2H); MS: 167 $[M + H]^+$; MP: 206-208 °C; TLC: 20% MeOH/NH_3 in $CHCl_3$: R_f: 0.40.

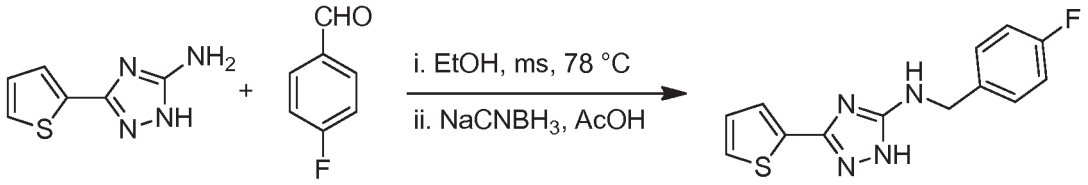
Example 33 - Preparation of Intermediate 15



Cmpd 25 **Intermediate 15**

[0223] General Procedure 2 was followed to obtain Intermediate 15 (350 mg, 25%). MS: 259 $[M + H]^+$; TLC: 10% MeOH in $CHCl_3$: R_f: 0.25.

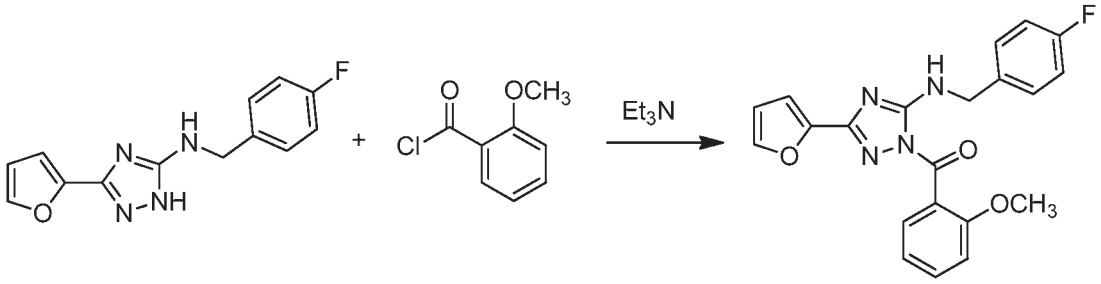
Example 34 - Preparation of Intermediate 16



Intermediate 14 **Intermediate 16**

[0224] General Procedure 2 was followed to obtain Intermediate 16 (500 mg, 38%). ^1H NMR: (DMSO-d_6) δ 12.27 (s, 1H), 7.38-7.47 (m, 4H), 7.07-22 (m, 4H), 4.37 (d, J = 6.2 Hz, 2H); MS: 275 $[M + H]^+$; TLC: 10% MeOH in $CHCl_3$: R_f: 0.25.

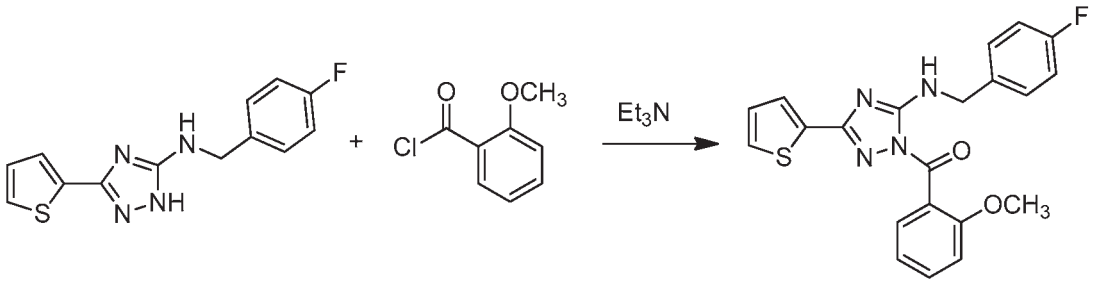
Example 35 - Preparation of Cmpd 26



Intermediate 15 **Cmpd 26**

[0225] General Procedure 3 was followed to obtain Cmpd 26 (20 mg, 17%). ^1H NMR: (DMSO-d_6) δ 8.51 (t, J = 6.2 Hz, 1H), 7.76 (s, 1H), 7.49-7.57 (m, 4H), 7.06-7.21 (m, 4H), 6.94 (d, J = 3.5 Hz, 1H), 6.59 (m, 1H), 4.64 (d, J = 6.2 Hz, 2H), 3.77 (s, 3H); MS: 393 $[M + H]^+$; MP: 150-152 °C; TLC: 50% EtOAc in hexane: R_f: 0.60.

Example 36 - Preparation of Cmpd 27



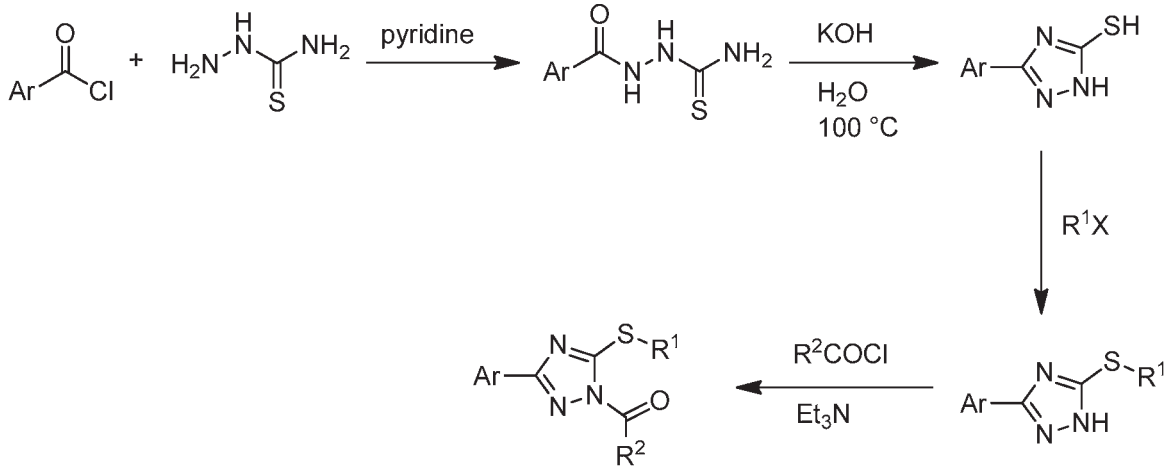
Intermediate 16 **Cmpd 27**

[0226] General Procedure 3 was followed to obtain Cmpd 27 (25 mg, 21%). ^{1}H NMR: (DMSO-d_6) δ 8.47 (t, J = 6.2 Hz, 1H), 7.50-7.63 (m, 6H), 7.06-7.22 (m, 5H), 4.65 (d, J = 6.2 Hz, 2H), 3.77 (s, 3H); MS: 409 $[M + H]^+$; MP: 151-152 °C; TLC: 50% EtOAc in hexane: R_f: 0.60.

Example 37 - Preparation of Cmpd 28

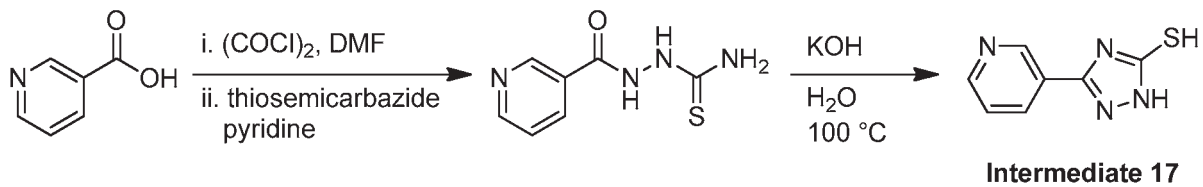
[0227] A general chemical scheme for the formation of compounds of the type of Cmpd 28 is provided in General Scheme IV following, wherein "Ar," "R^1" and "R^{2}" are as defined in Example 1.

General Scheme IV



[0228] A detailed description of the preparation of Intermediates 17, 18 and Cmpd 28 follows.

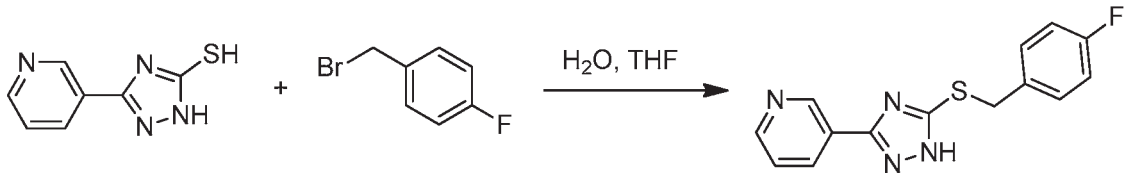
Preparation of Intermediate 17



Intermediate 17

[0229] Oxlayl chloride (5.4 mL, 61.0 mmol, 1.5 eq) and DMF (3 mL) was added sequentially to a solution of nicotinic acid (5 g, 40.7 mmol) in dry DCM (300 mL) at RT. The reaction mixture was allowed to stir at RT for 2 h. The solvent was removed and co-distilled with dry toluene (2 × 50 mL) and to afford 5 g of crude nicotinic acid chloride (5 g, 35.5 mmol). This material was added slowly portion-wise to a solution of thiosemicarbazide (5 g, 54.9 mmol, 1.5 eq) in pyridine (50 mL) at 0 °C over a period of 1 h and then allowed to stir at RT for 14 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ (30 mL) and extracted with *t*-BuOH (3 × 100 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dissolved in water (20 mL) along with 10% aqueous KOH (50 mL) and the resulting mixture was allowed to stir at 100 °C for 3 h. The reaction mixture was then cooled to 0 °C and neutralized with 10% aqueous AcOH (60 mL), extracted with EtOAc (2 × 150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude Intermediate 17 (1.2 g) as an off-white solid. MS: 179 $[M + H]^+$; TLC: 20% MeOH/NH_3 in $CHCl_3$: R_f: 0.30.

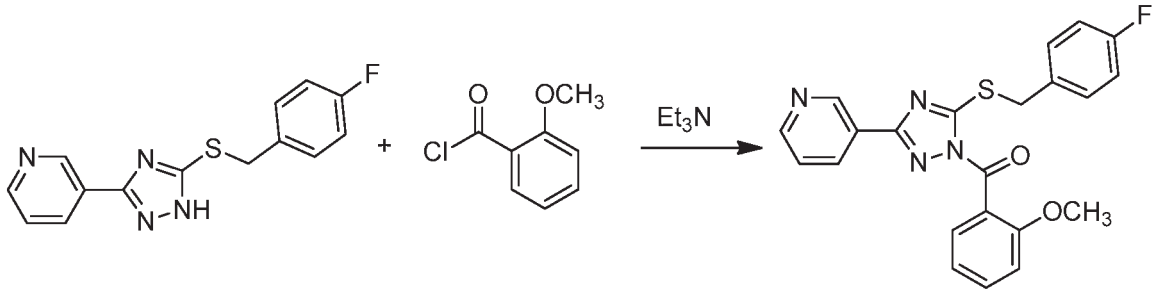
Preparation of Intermediate 18



Intermediate 17 **Intermediate 18**

[0230] 4-Flourobenzyl bromide (0.12 mL, 1.01 mmol, 0.6 eq) was added to a solution of Intermediate 17 (300 mg, 1.68 mmol) in water (5 mL) and THF (15 mL) at -10 °C and the reaction mixture was allowed to stir at -10 °C for 8 h. The solvent was removed and the residue was diluted with water (10 mL) and extracted with EtOAc (50 mL). The organic layer was washed with water (15 mL), saturated aqueous $NaHCO_3$ (10 mL), brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a solvent gradient mixture of 0-10% MeOH-$CHCl_3$ as the eluent to afford Intermediate 18 (110 mg, 23%) as an off-white solid. MS: 287 $[M + H]^+$; TLC: EtOAc: R_f: 0.40.

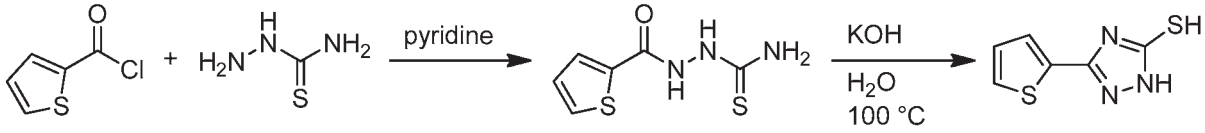
Preparation of Cmpd 28



Intermediate 18 **Cmpd 28**

[0231] General Procedure 3 was followed to obtain Cmpd 28 (20 mg, 30%). ^{1}H NMR: (DMSO-d_6) δ 9.13 (s, 1H), 8.71 (d, J = 4.0 Hz, 1H), 8.26 (d, J = 7.9 Hz, 1H), 7.53-7.67 (m, 5H), 7.09-7.25 (m, 4H), 4.64 (s, 2H), 3.75 (s, 3H); MS: 421 $[M + H]^+$; MP: 108-112 °C; TLC: 30% EtOAc in hexane: R_f: 0.40.

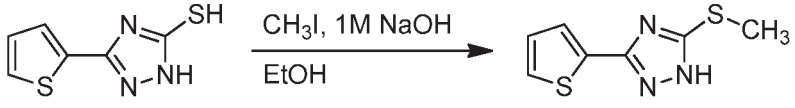
Example 38 - Preparation of Intermediate 19



Intermediate 19

[0232] 2-Thiophene carboxylic acid chloride (6.5 mL, 60.4 mmol) was added slowly portion-wise to a solution of thiosemicarbazide (5 g, 54.9 mmol, 1.1 eq) in pyridine (50 mL) at 0 °C over a period of 1 h and then allowed to stir at RT for 14 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ (50 mL) and extracted with *t*-BuOH (3 × 100 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was dissolved in water (30 mL) along with 10% aqueous KOH (60 mL) and the resulting mixture was allowed to stir at 100 °C for 3 h. The reaction mixture was then cooled to 0 °C and neutralized with 10% aqueous AcOH, extracted with EtOAc (2 × 150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude Intermediate 19 (1.2 g) as an off-white solid. MS: 184 $[M + H]^+$; TLC: 10% MeOH/NH_3 in $CHCl_3$: R_f: 0.60.

Example 39 - Preparation of Intermediate 20

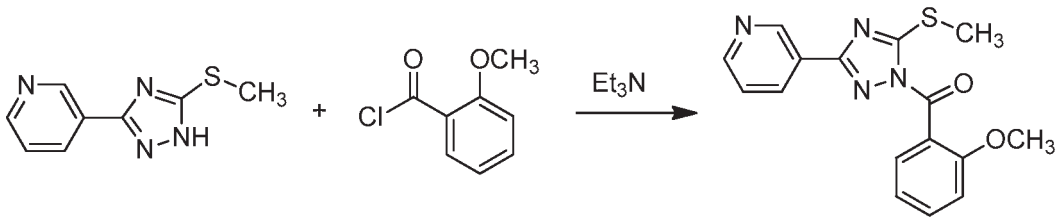


Intermediate 19 **Intermediate 20**

[0233] A solution of methyl iodide (65 µL, 1.04 mmol, 1.6 eq) in EtOH (2 mL) was added to a solution of Intermediate 19 (120 mg, 0.66 mmol) in 1M aqueous NaOH (3 mL) at RT

and the resulting mixture was allowed to stir for 3 h. The reaction mixture was then neutralized with 10% aqueous AcOH (5 mL) and extracted with EtOAc (30 mL). The organic layer was washed with water (10 mL), saturated aqueous $NaHCO_3$ (5 mL), brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a solvent gradient mixture of 0-10% MeOH-$CHCl_3$ as the eluent to afford Intermediate 20 (90 mg, 70%) as an off-white solid. ^1H NMR: (DMSO-d_6) δ 14.19 (br s, 1H), 7.62-7.67 (m, 2H), 7.16-7.18 (m, 1H), 2.60 (s, 3H); MS: 198 $[M + H]^+$; TLC: 50% EtOAc in hexane: R_f: 0.50.

Example 40 - Preparation of Cmpd 29



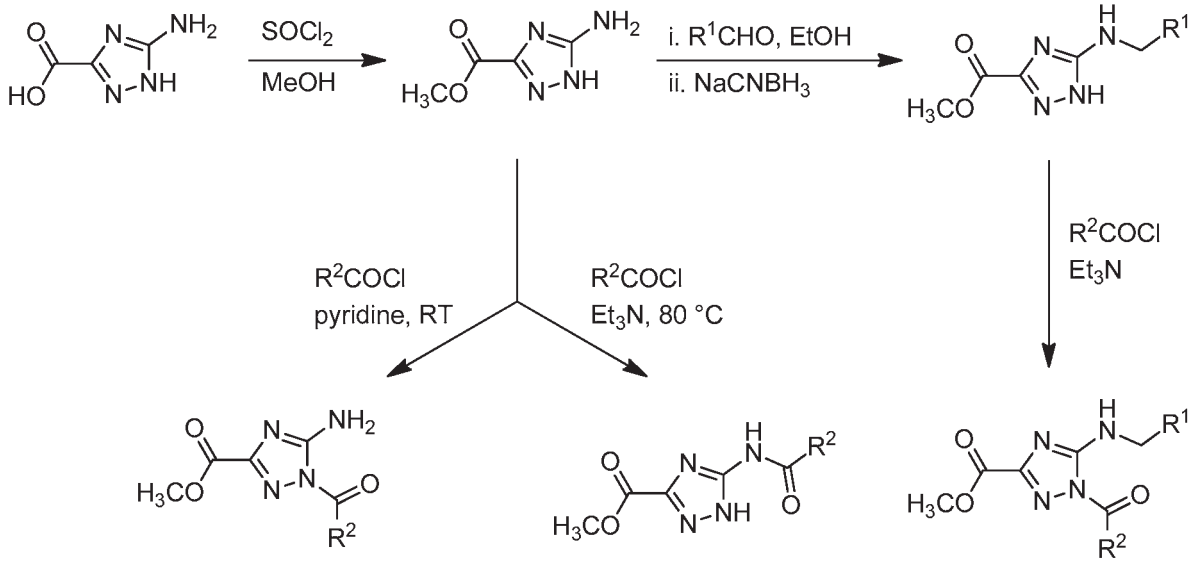
Intermediate 20 **Cmpd 29**

[0234] General Procedure 3 was followed to obtain Cmpd 29 (30 mg, 29%). ^1H NMR: (DMSO-d_6) δ 7.72 (d, J = 4.8 Hz, 1H), 7.56-7.65 (m, 3H), 7.25 (d, J = 8.8 Hz, 1H), 7.09-7.24 (m, 2H), 3.77 (s, 3H), 2.73 (s, 3H); MS: 332 $[M + H]^+$; MP: 165-167 °C; TLC: 30% EtOAc in hexane: R_f: 0.40.

Example 41 - Preparation of Cmpd 30

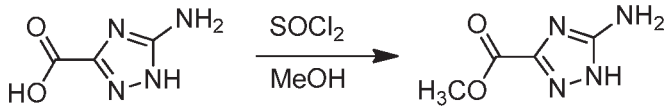
[0235] A general chemical scheme for the formation of compounds of the type of Cmpd 30 is provided in General Scheme V following, wherein "R^1" and "R^2" are as defined in Example 1.

General Scheme V



[0236] A detailed description of the preparation of Intermediates 21, 22 and Cmpd 30 follows.

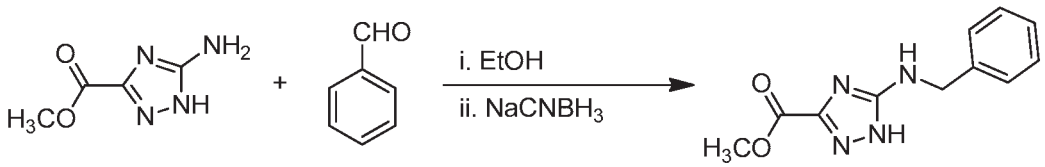
Preparation of Intermediate 21



Intermediate 21

[0237] Thionyl chloride (5.43 mL, 74.9 mmol, 3.2 eq) was added to a cold solution of 5-amino-[1,2,4]triazole-3-carboxylic acid (3 g, 23.4 mmol) in MeOH (21 mL) at RT and the resulting mixture was allowed to stir for 24 h. The solvent was then removed and the crude residue was recrystallized from a mixture of MeOH-Et_2O to afford Intermediate 21 (3.5 g, 98%) as an HCl salt. ^1H NMR: (DMSO-d_6) δ 12.62 (s, 1H), 6.23 (s, 2H), 3.76 (s, 3H); MS: 143 $[M + H]^+$; MP: 240-241 °C; TLC: 15% MeOH in $CHCl_3$: R_f: 0.50.

Preparation of Intermediate 22

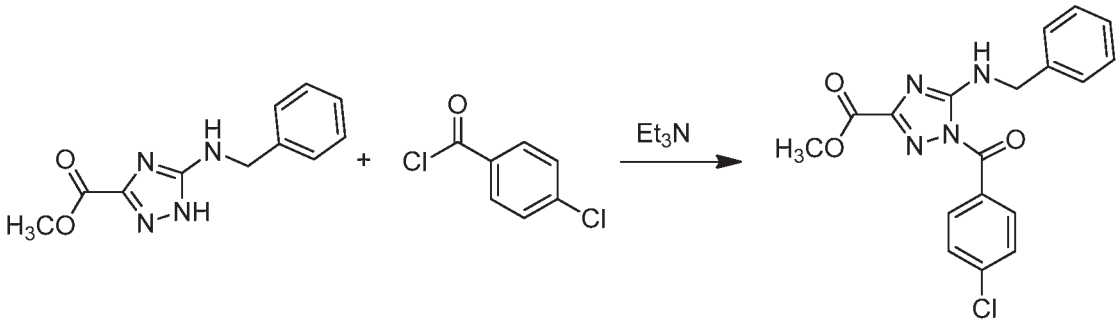


Intermediate 21 **Intermediate 22**

[0238] Benzaldehyde (0.7 mL, 6.74 mmol, 2 eq) was added to a solution of Intermediate 21 (600 mg, 3.37 mmol) in EtOH (10 mL) and the resulting solution was allowed to stir for 6 h at 75 °C. $NaCNBH_3$ (424 mg, 6.74 mmol, 2 eq) was then added and the mixture was allowed

to stir for 16 h at RT. The reaction mixture was then diluted with water (20 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography over silica (100-200mesh) using a gradient mixture of 10-40% of EtOAc-hexane as the eluent to afford Intermediate 22 (120 mg, 15%) as a yellow solid. ^{1}H NMR: (DMSO-d_6) δ 12.87 (s, 1H), 7.23-7.38 (m, 7H), 4.39 (d, J = 6.6 Hz, 2H), 3.76 (s, 3H), 3.08-3.10 (m, 1H); MS: 233 $[M + H]^+$; TLC: EtOAc: R_f: 0.70.

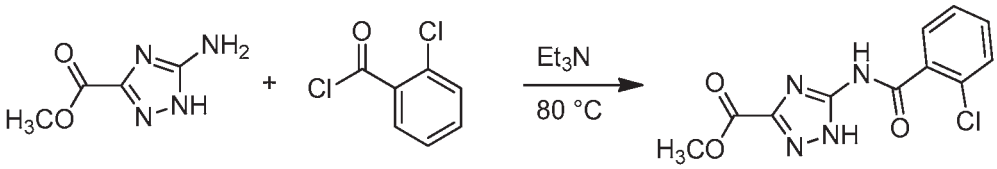
Preparation of Cmpd 30



Intermediate 22 **Cmpd 30**

[0239] General Procedure 3 was followed to obtain Cmpd 30 (25 mg, 47%). ^{1}H NMR: (DMSO-d_6) δ 8.56 (t, J = 6.4 Hz, 1H), 8.06 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.24-7.41 (m, 5H), 4.67 (d, J = 6.2 Hz, 2H), 3.82 (s, 3H); MS: 371 $[M + H]^+$; TLC: 20% EtOAc in hexane: R_f: 0.50.

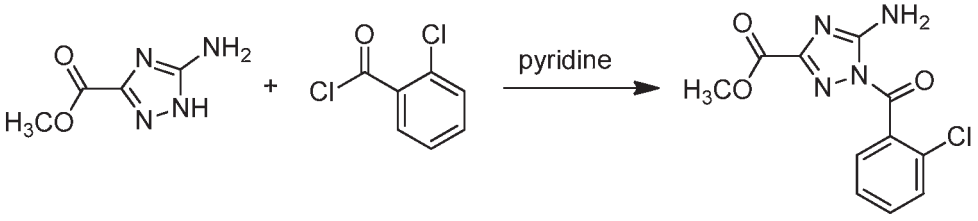
Example 42 - Preparation of Cmpd 31



Intermediate 21 **Cmpd 31**

[0240] 2-Chlorobenzoyl chloride (0.33 mL, 2.46 mmol, 1.1 eq) was added to a solution of Intermediate 21 (400 mg, 2.24 mmol) in Et_3N (6 mL) at 0 °C. The resulting mixture was heated to 80 °C and allowed to stir for 4 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with DCM (3 × 40mL). The combined organic layers were washed with water (40 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography over silica gel (100-200 mesh) using a gradient mixture of 0-6% MeOH-$CHCl_3$ as the eluent to afford Cmpd 31 (80 mg, 12%). ^{1}H NMR: (DMSO-d_6) δ 14.36 (s, 1H), 12.37 (s, 1H), 7.46-7.67 (m, 4H), 3.84 (s, 3H); MS: 281 $[M + H]^+$; MP: 100-101 °C; TLC: 10% MeOH in $CHCl_3$: R_f: 0.60.

Example 43 - Preparation of Cmpd 32



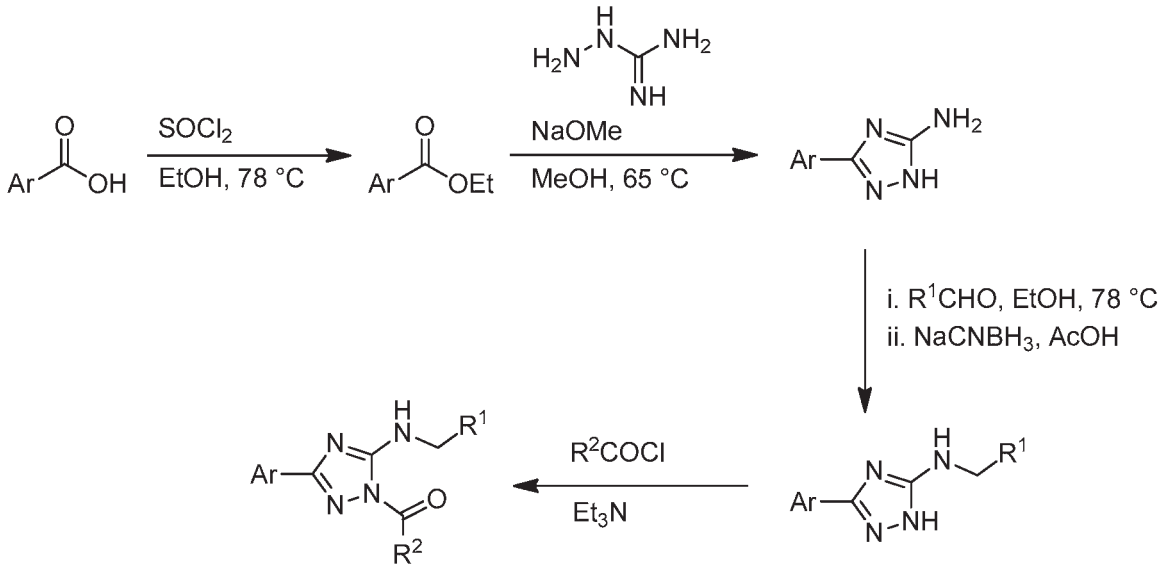
Intermediate 21 **Cmpd 32**

[0241] 2-Chlorobenzoyl chloride (0.24 mL, 1.80 mmol, 1.1 eq) was added to a solution of Intermediate 21 (300 mg, 1.68 mmol) in pyridine (6 mL) at 0 °C. The resulting solution was warmed to RT and allowed to stir for 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (3 × 40 mL). The combined organic layers were washed with water (40 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography over silica gel (100-200mesh) using a gradient mixture of 0-6% MeOH-$CHCl_3$ as the eluent to afford Cmpd 32 (99 mg, 21%). ^{1}H NMR: (DMSO-d_6) δ 8.00 (s, 2H), 7.73 (d, J = 7.5 Hz, 1H), 7.49-7.64 (m, 3H), 3.77 (s, 3H); MS: 281 $[M + H]^+$; TLC: 10% MeOH in $CHCl_3$: R_f: 0.60.

Example 44 - Preparation of Cmpd 33

[0242] **General Scheme VI.** A synthetic scheme useful for synthesis of compounds described herein including Cmpd 33 is disclosed in General Scheme VI following, wherein the terms "Ar," "R^1" and "R^2" are as defined in Example 1.

General Scheme VI

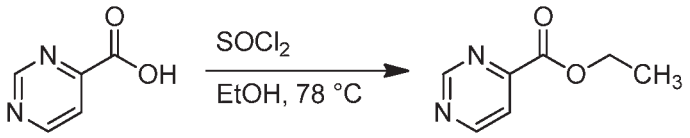


[0243] A description of the synthesis of Intermediates 23-28 and Cmpd 33 follows. Synthesis of Intermediate 23 followed General Procedure 8 following.

Preparation of Intermediate 23 [General Procedure 8]

[0244] General procedure 8 was followed in the preparation of Intermediate 23.

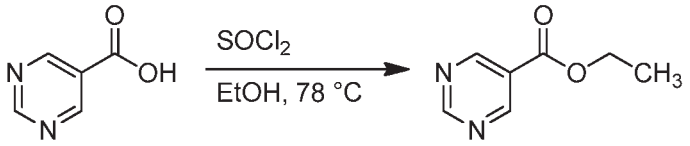
General Procedure 8



Intermediate 23

[0245] Thionyl chloride (3.55mL, 48.4 mmol, 3 eq) was added drop-wise to a solution of pyrimidine-4-carboxylic acid (2 g, 16.1 mmol) in EtOH (15 mL) and the resulting mixture was heated to reflux for 14 h. The mixture was then cooled to RT and made alkaline with saturated aqueous $NaHCO_3$ to pH 8. The basic solution was then extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford Intermediate 23 (1.7g, 77%). ^{1}H NMR: (DMSO-d_6) δ 9.40 (d, J = 1.0 Hz, 1H), 9.10 (d, J = 5.1 Hz, 1H), 8.05 (dd, J = 5.1, 1.3 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); MS: 153 $[M + H]^+$; TLC: 40% hexane in EtOAc: R_f: 0.40.

Preparation of Intermediate 24



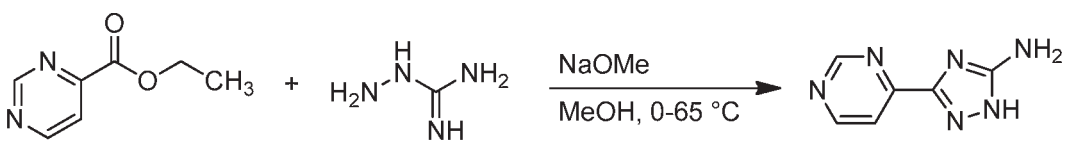
Intermediate 24

[0246] General Procedure 8 was followed to obtain crude Intermediate 24 (950 mg, 86%). ^{1}H NMR: (DMSO-d_6) δ 9.43 (s, 1H), 9.26 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); TLC: 40% EtOAc in hexane: R_f: 0.50.

Preparation of Intermediate 25 [General Procedure 9]

[0247] General Procedure 9 was followed in the preparation of Intermediate 25.

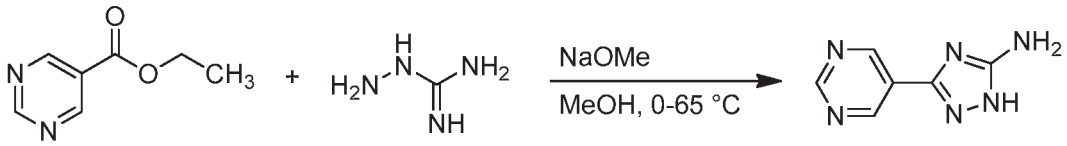
General Procedure 9



Intermediate 23 **Intermediate 25**

[0248] **Interm**ediate 23 (1.6 g, 10.5 mmol) was added drop-wise to a vigorously stirring mixture of aminoguanidine sulfate (10.3 g, 42.1 mmol, 4 eq) in freshly prepared NaOMe (using 968 mg, 42.1 mmol of Na in 28 mL of dry MeOH) at 0 °C. The resulting mixture was heated to reflux for 20 h. The mixture was then cooled to RT, carefully poured over ice cold water (20 mL) and concentrated *in vacuo*. The crude residue was purified over neutral alumina using 4-10% MeOH-$CHCl_3$ as the eluent to give Intermediate 25 (500mg, 26%). MS: 163 $[M + H]^+$; TLC: 20% MeOH in $CHCl_3$: R_f: 0.20.

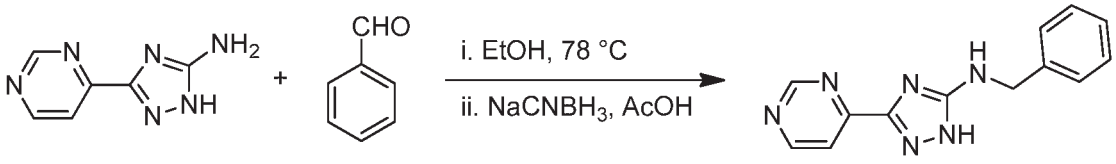
Preparation of Intermediate 26



Intermediate 24 **Intermediate 26**

[0249] General Procedure 9 was followed to obtain Intermediate 26 (500 mg, 45%). ^1H NMR: (DMSO-d_6) δ 12.44 (br s, 1H), 9.17-9.18 (m, 3H), 6.32 (s, 2H); **TLC:** 20% MeOH in $CHCl_3$: R_f: 0.20.

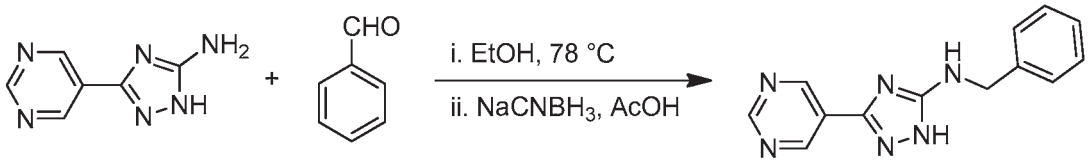
Preparation of Intermediate 27



Intermediate 25 **Intermediate 27**

[0250] General Procedure 2 was followed to obtain Intermediate 27 (210 mg, 34%). ^1H NMR: (DMSO-d_6) δ 12.80 (s, 1H), 9.18 (s, 1H), 8.83 (s, 1H), 7.92 (d, J = 4.4 Hz, 1H), 7.25-7.40 (m, 5H), 4.44 (d, J = 5.7 Hz, 2H); TLC: EtOAc: R_f: 0.30.

Preparation of Intermediate 28



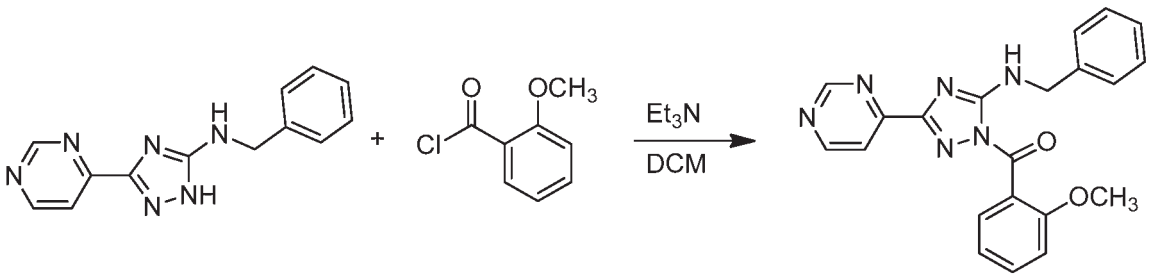
Intermediate 26 **Intermediate 28**

[0251] General Procedure 2 was followed to obtain Intermediate 28 (160 mg, 20%). MS: 253 $[M + H]^+$; TLC: EtOAc: R_f: 0.30.

Preparation of Cmpd 33 [General Procedure 10]

[0252] General Procedure 10 was followed in the preparation of Cmpd 33.

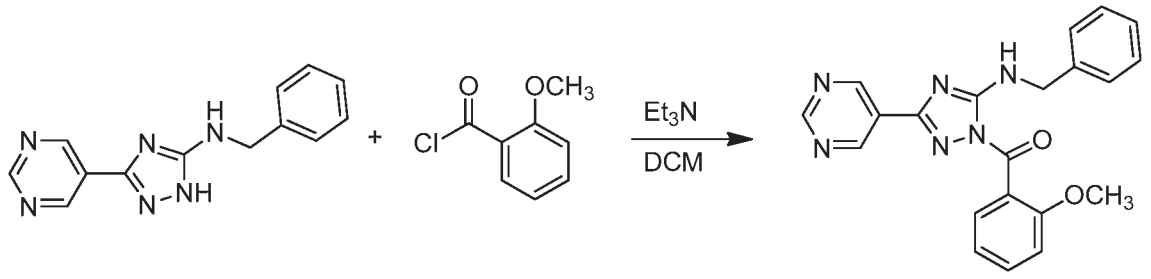
General Procedure 10



Intermediate 27 **Cmpd 33**

[0253] 2-Methoxybenzoyl chloride (72 μL, 0.54 mmol, 2 eq) was added to a solution of Intermediate 27 (70 mg, 0.27 mmol) in Et_3N (0.18 mL, 1.35 mmol) and DCM (3 mL) at 0 °C. The resulting mixture was allowed to stir at RT for 2 h. The reaction mixture was then diluted with water (5 mL) and extracted with DCM (3 × 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL), water (2 × 5 mL), brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) using a gradient mixture of 0-70% EtOAc-hexane as the eluent to afford Cmpd 33 (45 mg, 29%). ^{1}H NMR: (DMSO-d_6) δ 9.21 (s, 1H), 8.90 (d, J = 5.1 Hz, 1H), 8.59 (t, J = 6.0 Hz, 1H), 7.93 (d, J = 5.1 Hz, 1H), 7.08-7.60 (m, 10H), 4.72 (d, J = 5.7 Hz, 2H), 3.77 (s, 3H); MS: 387 $[M + H]^+$; MP: 192-195 °C; TLC: 40% hexane in EtOAc: R_f: 0.30.

Example 45 - Preparation of Cmpd 34



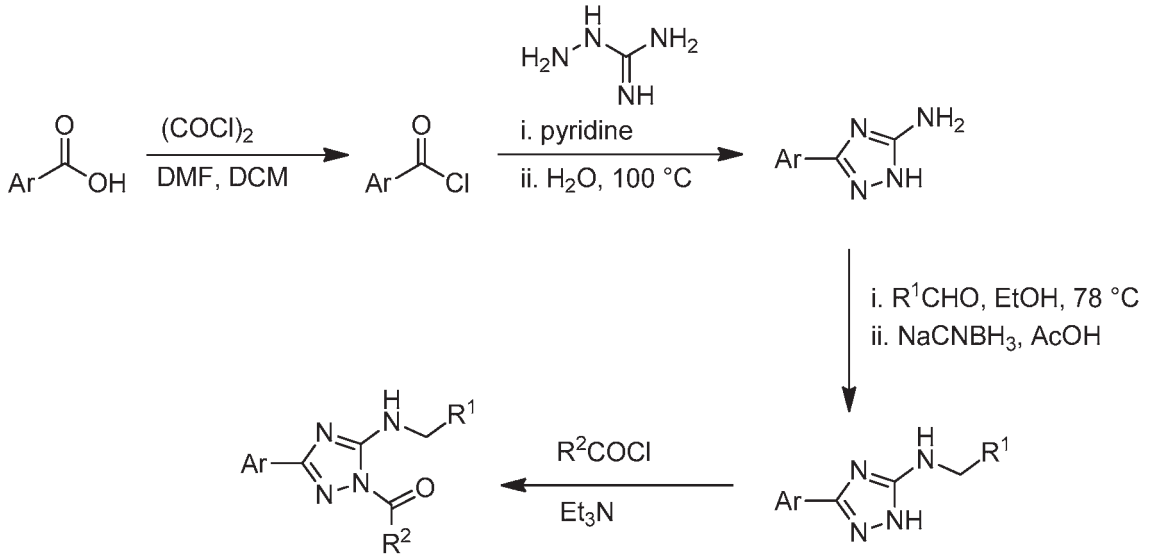
Intermediate 28 **Cmpd 34**

[0254] General Procedure 10 was followed by preparative HPLC purification to obtain Cmpd 34 (30 mg, 16%). ^{1}H NMR: (DMSO-d_6) δ 9.26 (s, 1H), 9.11 (s, 2H), 8.64 (t, J = 6.3 Hz, 1H), 7.07-7.60 (m, 9H), 4.71 (d, J = 6.3 Hz, 2H), 3.78 (s, 3H); MS: 387 $[M + H]^+$; MP: 154-157 °C; TLC: 40% EtOAc in hexane: R_f: 0.20.

Example 46 - Preparation of Cmpd 35

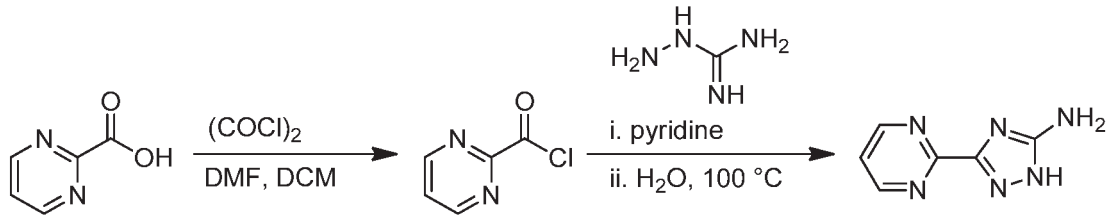
[0255] **General Scheme VII.** A synthetic scheme useful for synthesis of compounds described herein including Cmpd 35 is disclosed in General Scheme VII following, wherein the terms "Ar," "R^1" and "R^2" are as defined in Example 1.

General Scheme VII



[0256] A description of the synthesis of Intermediates 29, 30 and Cmpd 35 follows.

Preparation of Intermediate 29

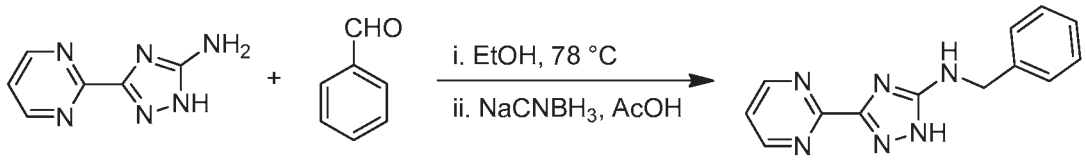


Intermediate 29

[0257] Oxalyl chloride (2.36 mL, 24.2 mmol, 1.5 eq) and a catalytic quantity of DMF were added to a solution of pyrimidine-2-carboxylic acid (2 g, 16.1 mmol) in dry DCM (30 mL) at 0 °C. The resulting mixture was allowed to warm to RT and stir for 3 h. The volatiles were removed *in vacuo* and the residue was thoroughly dried to afford pyrimidine-2-carboxylic acid chloride (2.1 g, 14.8 mmol) as a black solid. The crude material was added portion-wise to a solution of aminogaunidine sulfate (5.5 g, 22.2 mmol, 1.5 eq) in pyridine (20 mL) at 0 °C. The resulting mixture was allowed to warm to RT and stir for 14 h. The mixture was then neutralized with saturated aqueous $NaHCO_3$, extracted with *t*-BuOH (5 × 50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was dissolved in water (45 mL) and the resulting solution was heated to 100 °C for 24 h. The reaction mixture was then cooled to RT, extracted with *t*-BuOH (5 × 30 mL), dried over Na_2SO_4, filtered and

concentrated *in vacuo* to afford Intermediate 29 (650 mg, 25 %) as off-white solid. TLC: 30% MeOH in $CHCl_3$: R_f: 0.20.

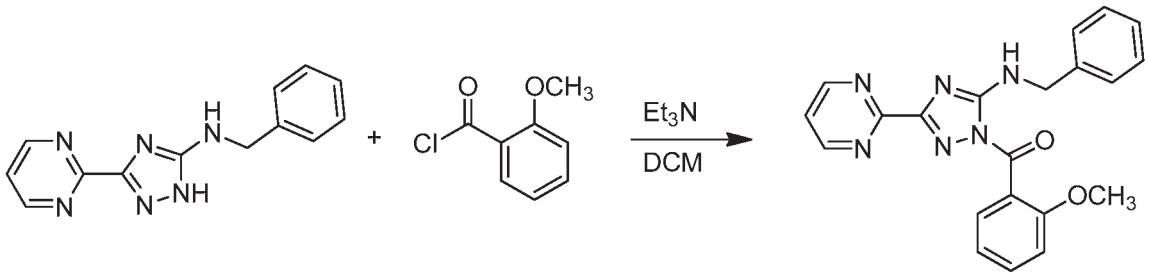
Preparation of Intermediate 30



Intermediate 29 **Intermediate 30**

[0258] General Procedure 2 was followed to obtain Intermediate 30 (120 mg, 17%). MS: 253 $[M + H]^+$; TLC: EtOAc: R_f: 0.30.

Preparation of Cmpd 35



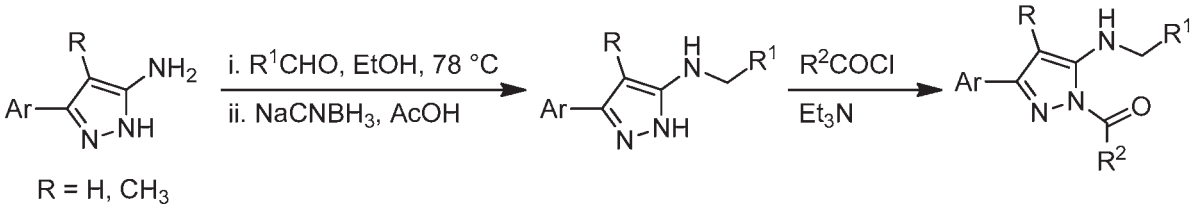
Intermediate 30 **Cmpd 35**

[0259] General Procedure 10 was followed to obtain Cmpd 35 (32 mg, 21%). ^1H NMR: (DMSO-d_6) δ 8.86 (d, J = 5.1 Hz, 2H), 8.44 (t, J = 6.0 Hz, 1H), 7.08-7.59 (m, 10H), 4.73 (d, J = 6.3 Hz, 2H), 3.77 (s, 3H); MS: 387 $[M + H]^+$; MP: 203-205 °C; TLC: 40% hexane in EtOAc: R_f: 0.40.

Example 47 - Preparation of Cmpd 36

[0260] **General Scheme VIII**. A synthetic scheme useful for synthesis of compounds described herein including Cmpd 36 is disclosed in General Scheme VII following, wherein the terms "Ar," "R^1" and "R^2" are as defined in Example 1.

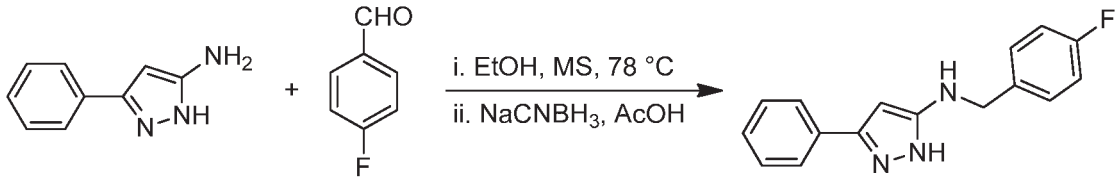
General Scheme VIII.



Preparation of Intermediate 31

[0261] General Procedure 11 was followed in the preparation of Intermediate 31.

General Procedure 11



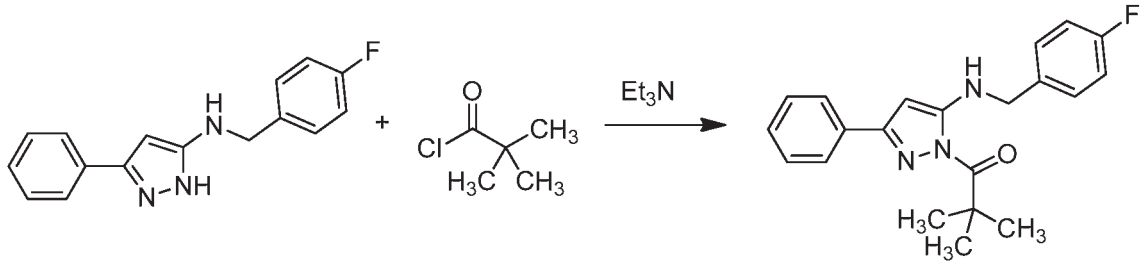
Intermediate 31

[0262] 4-Fluorobenzaldehyde (0.54 mL, 5.03 mmol, 2 eq) and molecular sieves (4Å powder) were added to a solution of 3-amino-5-phenylpyrazole (400 mg, 2.51 mmol) in EtOH (20 mL) at RT and the resulting mixture was heated to reflux. After 8 h, the reaction mixture was cooled to 0 °C and AcOH (0.4 mL) and $NaCNBH_3$ (316 mg, 5.03 mmol, 2 eq) were added. The mixture was then allowed to warm to RT and stir for 15 h. The solvent was evaporated and the residue was dissolved in EtOAc (100 mL) and filtered through a Celite pad to remove inorganic materials. The filtrate was then washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a solvent gradient of 0-50% EtOAc-petroleum ether as the eluent to afford Intermediate 31 (240 mg, 36%) as an off white solid. MS: 268 $[M + H]^+$; TLC: EtOAc: R_f: 0.60.

Preparation of Cmpd 36

[0263] General Procedure 12 was followed in the preparation of Cmpd 36.

General Procedure 12

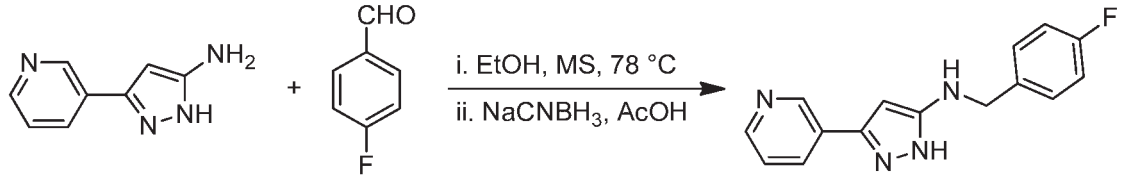


Intermediate 31 **Cmpd 36**

[0264] Pivaloyl chloride (32 μL, 0.26 mmol, 1.2 eq) was added to a solution of Intermediate 31 (60 mg, 0.22 mmol) in triethylamine (3 mL) at RT and stirred for 3 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (20 mL). The organic layer was washed with water (2 × 5 mL), saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude compound was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-10% EtOAc-hexane as the eluent to afford Cmpd 36 (23 mg, 29%). ^1H NMR:

(DMSO-d_6) δ 7.79-7.84 (m, 3H), 7.37-7.49 (m, 5H), 7.17 (t, J = 8.8 Hz, 2H), 5.89 (s, 1H), 4.38 (d, J = 6.2 Hz, 2H), 1.49 (s, 9H); MS: 352 $[M + H]^+$; TLC: 20% EtOAc in hexane: R_f: 0.60.

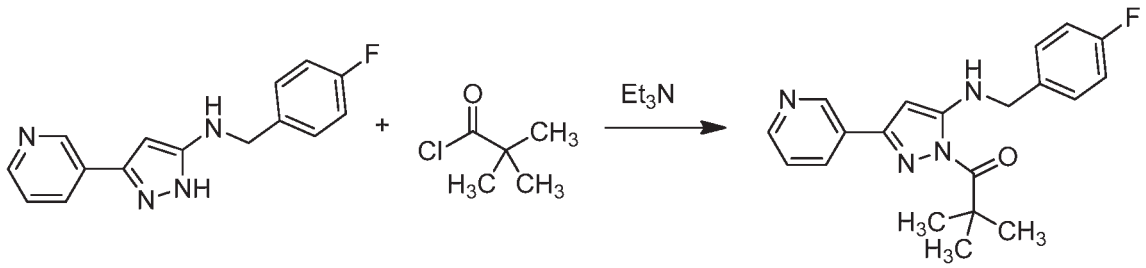
Example 48 - Preparation of Intermediate 32



Intermediate 32

[0265] General Procedure 11 was followed to afford Intermediate 32 (200 mg, 24%). MS: 269 $[M + H]^+$; TLC: EtOAc: R_f: 0.40.

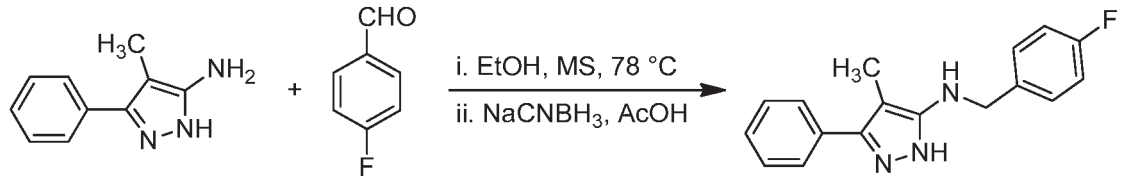
Example 49 - Preparation of Cmpd 37



Intermediate 32 **Cmpd 37**

[0266] General Procedure 12 was followed to afford Cmpd 37 (10 mg, 15%). ^{1}H NMR: (DMSO-d_6) δ 8.99 (d, J = 1.5 Hz, 1H), 8.58 (dd, J = 4.9, 1.3 Hz, 1H), 8.14-8.16 (m, 1H), 7.83 (t, J = 6.4 Hz, 1H), 7.45-7.48 (m, 3H), 7.16 (t, J = 8.7 Hz, 2H), 6.01 (s, 1H), 4.38 (d, J = 6.1 Hz, 2H), 1.49 (s, 9H); MS: 353 $[M + H]^+$; TLC: 30% EtOAc in hexane: R_f: 0.60.

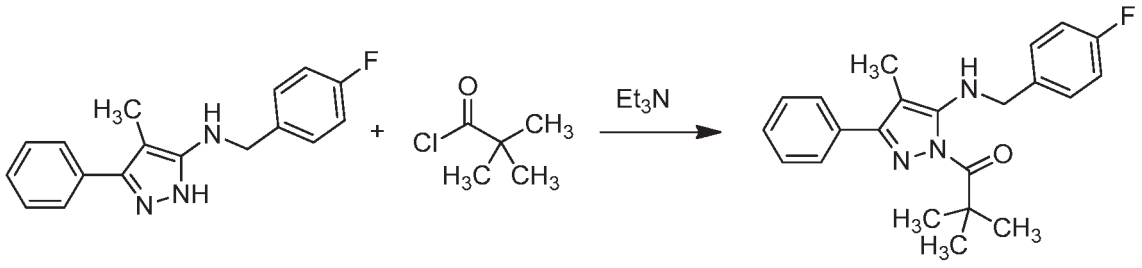
Example 50 - Preparation of Intermediate 33



Intermediate 33

[0267] General Procedure 11 was followed to afford Intermediate 33 (35 mg, 44%). MS: 282 $[M + H]^+$; TLC: 50% EtOAc in hexane: R_f: 0.50.

Example 51 - Preparation of Cmpd 38



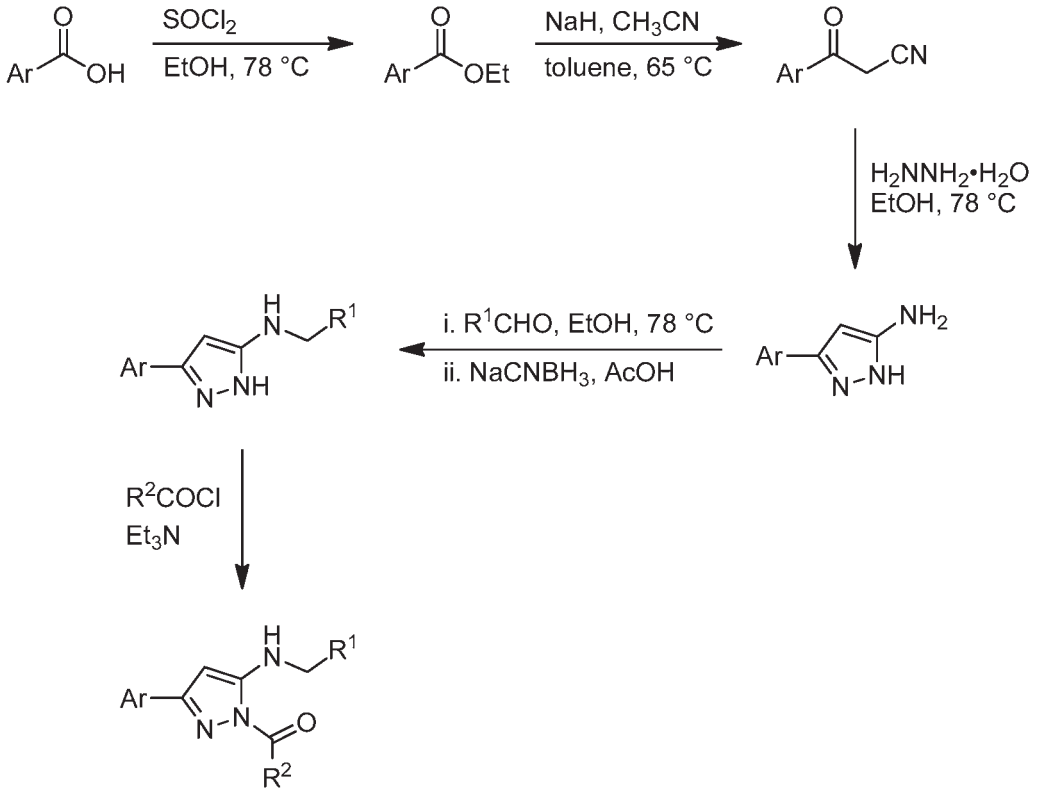
Intermediate 33 **Cmpd 38**

[0268] General Procedure 12 was followed to afford Cmpd 38 (6 mg, 7%). ^{1}H NMR: (DMSO-d_6) δ 7.56-7.59 (m, 2H), 7.34-7.49 (m, 6H), 7.18 (t, J = 9.0 Hz, 2H), 4.52 (d, J = 6.8 Hz, 2H), 2.04 (s, 3H), 1.43 (s, 9H); MS: 366 $[M + H]^+$; TLC: 20% EtOAc in hexane: R_f: 0.70.

Example 52 - Preparation of Cmpd 39

[0269] **General Scheme IX**. A synthetic scheme useful for synthesis of compounds described herein including Cmpd 39 is disclosed in General Scheme IX following, wherein the terms "Ar," "R^1" and "R^2" are as defined in Example 1.

General Scheme IX

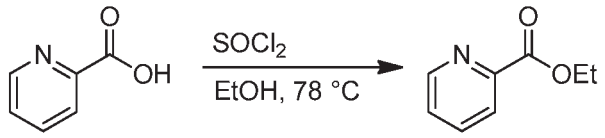


[0270] A description of the syntheses of Intermediates 34-37 and Cmpd 39 follows.

Preparation of Intermediate 34 [General Procedure 13]

[0271] General Procedure 13 was followed in the preparation of Intermediate 34.

General Procedure 13



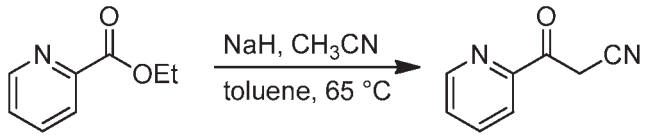
Intermediate 34

[0272] Thionyl chloride (5.4 mL, 73.2 mmol, 3 eq) was added to a solution of picolinic acid (3 g, 24.4 mmol) in EtOH (50 mL) at 0 °C. The resulting mixture was heated to reflux and allowed to stir for 2 h. The mixture was then cooled and the solvent was evaporated. The resulting residue was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using DCM as the eluent to afford Intermediate 34 (3 g, 81%) as a colorless liquid. MS: 152 $[M + H]^+$; TLC: 10% MeOH/NH_3 in $CHCl_3$: R_f: 0.70.

Preparation of Intermediate 35 [General Procedure 14]

[0273] General Procedure 14 was followed in the preparation of Intermediate 35.

General Procedure 14



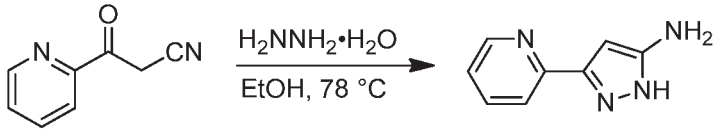
Intermediate 34 **Intermediate 35**

[0274] A solution of Intermediate 34 (3 g, 19.6 mmol) and CH_3CN (0.8 mL, 19.6 mmol, 1 eq) in dry toluene (10 mL) was slowly added to a mixture of NaH (784 mg, 19.6 mmol, 1 eq, 60% in mineral oil) in toluene (50 mL) at 65 °C. The resulting mixture was allowed to stir at 65 °C for 16 h. The reaction mixture was then cooled to RT and quenched with ice cold water (20 mL). The resulting solid was filtered to afford Intermediate 35 (1.5 g, 53%) as a brown solid. ^1H NMR: ($CDCl_3$) δ 8.70 (d, J = 4.8 Hz, 1H), 8.12 (d, J = 7.5 Hz, 1H), 7.90-7.94 (m, 1H), 7.56-7.60 (m, 1H), 4.41 (s, 2H); MS: 147 $[M + H]^+$; TLC: EtOAc: R_f: 0.40.

Preparation of Intermediate 36 [General Procedure 15]

[0275] General Procedure 15 was followed in the preparation of Intermediate 36.

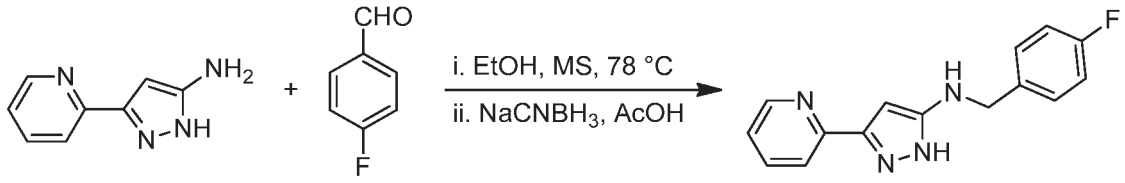
General Procedure 15



Intermediate 35 **Intermediate 36**

[0276] Hydrazine hydrate (0.34 mL, 6.8 mmol, 1 eq) was added to a solution of Intermediate 35 (1 g, 6.8 mmol) in EtOH (30 mL) at RT. The mixture was then heated to reflux and allowed to stir for 20 h. The solvent was then evaporated. The resulting crude material was triturated with Et_2O (2 × 20 mL) and dried under vacuum to afford Intermediate 36 (700 mg, 64%) as a brown liquid. ^{1}H NMR: (DMSO-d_6) δ 8.53 (d, J = 4.4 Hz, 1H), 7.78 (d, J = 4.4 Hz, 2H), 7.23-7.26 (m, 1H), 5.95 (s, 1H), 4.84 (br s, 2H); MS: 161 $[M + H]^+$; TLC: EtOAc: R_f: 0.20.

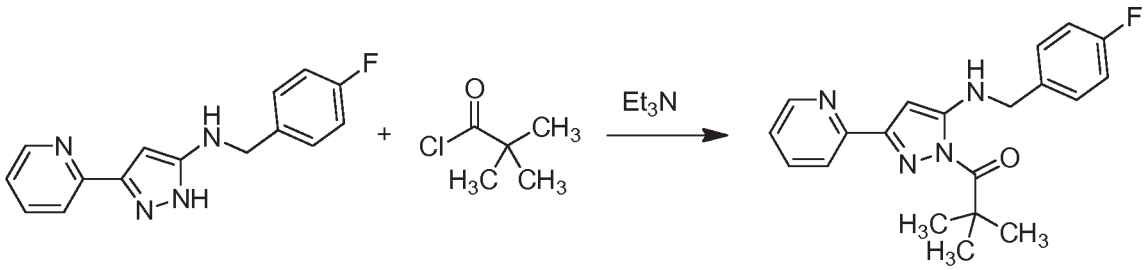
Preparation of Intermediate 37



Intermediate 36 **Intermediate 37**

[0277] General Procedure 11 was followed to afford Intermediate 37 (450 mg). MS: 269 $[M + H]^+$; TLC: EtOAc: R_f: 0.40.

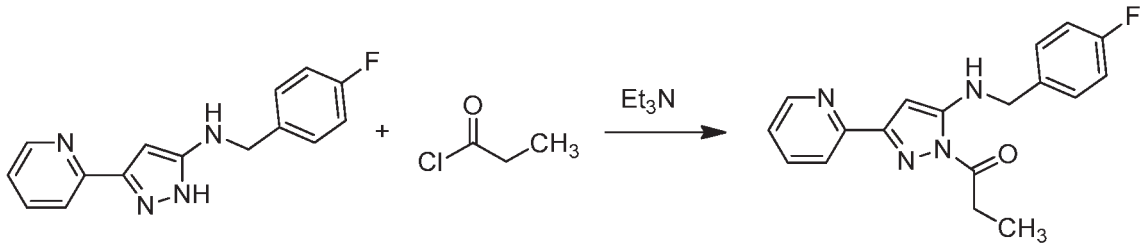
Preparation of Cmpd 39



Intermediate 37 **Cmpd 39**

[0278] General Procedure 12 was followed to afford Cmpd 39 (40 mg, 30%). ^{1}H NMR: (DMSO-d_6) δ 8.58 (d, J = 4.4 Hz, 1H), 7.86-7.98 (m, 3H), 7.38-7.46 (m, 3H), 7.18 (t, J = 8.8 Hz, 2H), 5.84 (s, 1H), 4.40 (d, J = 6.2 Hz, 2H), 1.50 (s, 9H); MS: 353 $[M + H]^+$; MP: 102-103 °C; TLC: 20% EtOAc in hexane: R_f: 0.60.

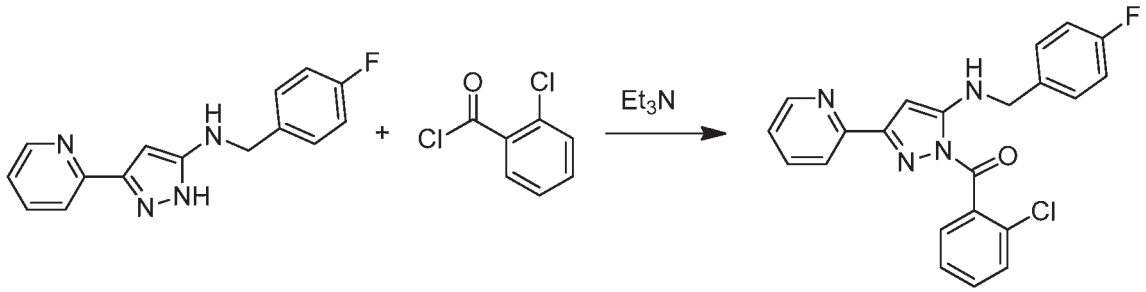
Example 53 - Preparation of Cmpd 40



Intermediate 37 **Cmpd 40**

[0279] General Procedure 12 was followed to afford Cmpd 40 (38 mg, 29%). ^{1}H NMR: (DMSO-d_6) δ 8.58 (d, J = 4.4 Hz, 1H), 7.97 (d, J = 7.9 Hz, 1H), 7.79-7.88 (m, 2H), 7.37-7.46 (m, 3H), 7.17 (t, J = 8.8 Hz, 2H), 5.87 (s, 1H), 4.42 (d, J = 6.2 Hz, 2H), 3.13 (q, J = 7.3 Hz, 2H), 1.17 (t, J = 7.3 Hz, 3H); MS: 325 $[M + H]^+$; MP: 106-108 °C; TLC: 20% EtOAc in hexane: R_f: 0.50.

Example 54 - Preparation of Cmpd 41



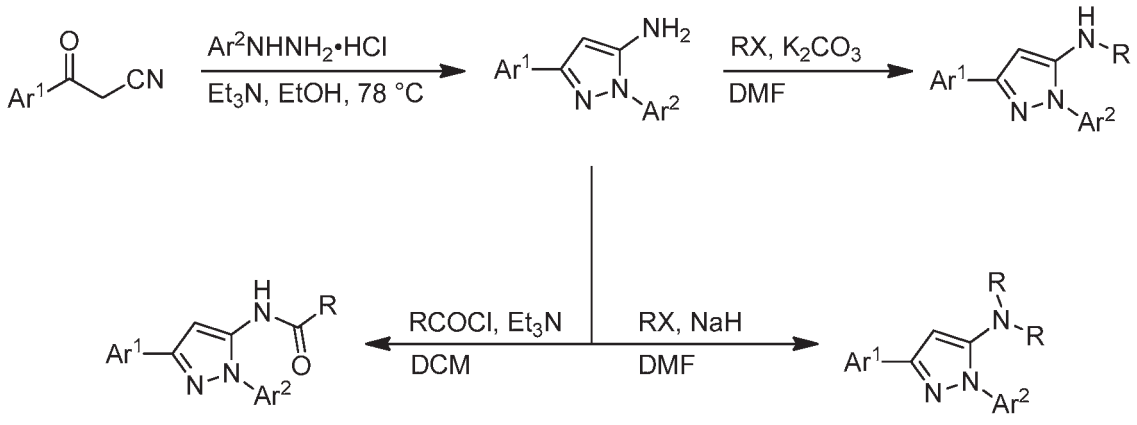
Intermediate 37 **Cmpd 41**

[0280] **General Procedure 12** was followed to afford **Cmpd 41** (30 mg, 20%). **^{1}H NMR:** (DMSO-d_6) δ 8.55 (d, J = 4.4 Hz, 1H), 7.97 (t, J = 5.9 Hz, 1H), 7.71-7.78 (m, 2H), 7.49-7.63 (m, 6H), 7.34-7.37 (m, 1H), 7.20 (t, J = 8.8 Hz, 2H), 5.94 (s, 1H), 4.49 (d, J = 6.2 Hz, 2H); **MS:** 407 $[M + H]^+$, 409 $[M + 2 + H]^+$; **MP:** 137-136 °C; **TLC:** 20% EtOAc in hexane: R_f: 0.30.

Example 55 - General Scheme X

[0281] A synthetic scheme useful for synthesis of compounds described herein is disclosed in General Scheme X following, wherein the term "R" is each occurrence is independently "R^1" and "R^2" as defined in Example 1, and "Ar^1" and "Ar^2" are defined as "Ar" in Example 1.

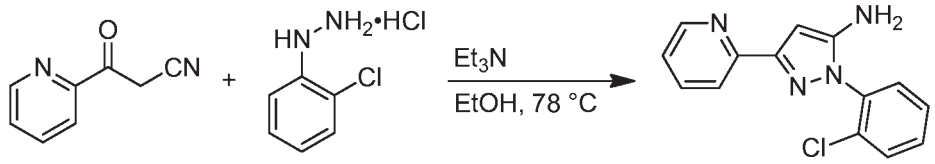
General Scheme X



Example 56 - Preparation of Cmpd 42 [General Procedure 16]

[0282] General Procedure 16 was followed in the preparation of Cmpd 42.

General Procedure 16



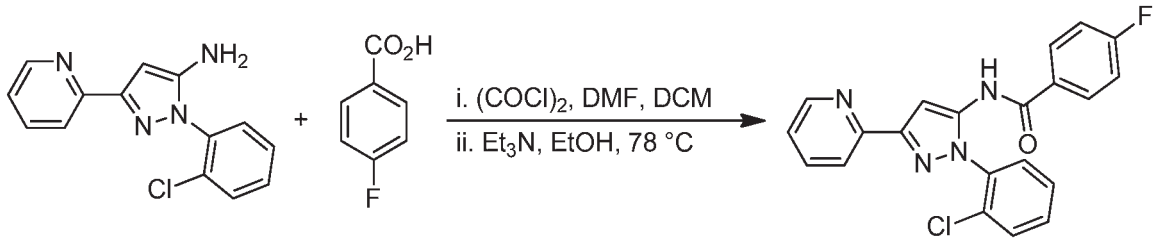
Intermediate 35 **Cmpd 42**

[0283] 2-Chlorophenylhydrazine hydrochloride (122 mg, 0.68 mmol, 1 eq) and Et_3N (95 μL, 0.68 mmol, 1 eq) was added to a solution of Intermediate 35 (100 mg, 0.68 mmol) in EtOH (3 mL). The resulting solution was heated to reflux and allowed to stir for 2 h. The solvent was then evaporated. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-70% EtOAc-hexane as the eluent to afford Cmpd 42 (70 mg, 37%). ^{1}H NMR: (DMSO-d_6) δ 8.56 (d, J = 4.4 Hz, 1H), 7.64-7.84 (m, 3H), 7.28-7.29 (m, 1H), 6.00 (s, 1H), 5.31 (s, 2H); MS: 271 $[M + H]^+$, 273 $[M + 2 + H]^+$; MP: 134-137 °C; TLC: EtOAc: R_f: 0.20.

Example 57 - Preparation of Cmpd 43 [General Procedure 17]

[0284] General Procedure 17 was followed in the preparation of Cmpd 43.

General Procedure 17



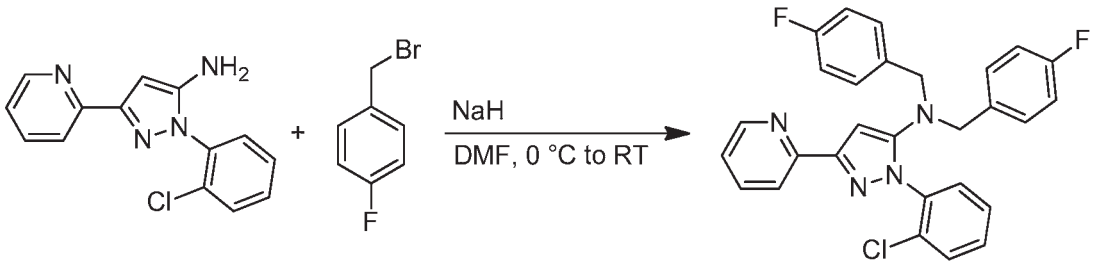
Cmpd 42 **Cmpd 43**

[0285] Oxalyl chloride (7.2 mL, 5.37 mmol, 1.5 eq) and DMF (0.5 mL) was added to a solution of 4-fluorobenzoic acid in DCM (20 mL) at 0 °C. The resulting mixture was allowed to warm to RT and stir for 1 h. The volatiles were evaporated and the mixture was co-distilled with toluene (30 mL). The resulting material was dried under vacuum to afford crude 4-fluorobenzoyl chloride (500 mg) as a colorless liquid, which was used without additional purification. 4-Fluorobenzoyl chloride (49 mg, 0.31 mmol, 1.2 eq) and Et_3N (0.36 mL, 2.59 mmol, 10 eq) were added to a solution of Cmpd 42 (70 mg, 0.26 mmol) in DCM (4 mL) at RT and the resulting mixture was allowed to stir for 3 h. The mixture was diluted with water (10 mL) and extracted into EtOAc (30 mL). The organic layer washed with water (2 × 5 mL), saturated aqueous $NaHCO_3$ (2 × 5 mL) brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-60% EtOAc-hexane as the eluent to afford Cmpd 43 (25 mg, 25%). ^{1}H NMR: (DMSO-d_6) δ 10.57 (s, 1H), 8.64 (d, J = 4.4 Hz, 1H), 7.97 (d, J = 7.9 Hz, 1H), 7.82-7.88 (m, 3H), 7.49-7.68 (m, 4H), 7.31-7.39 (m, 3H), 7.06 (s, 1H); MS: 393 $[M + H]^+$, 395 $[M + 2 + H]^+$; MP: 186-188 °C; TLC: EtOAc: R_f: 0.40.

Example 58 - Preparation of Cmpd 44 [General Procedure 18]

[0286] General Procedure 18 was followed in the preparation of Cmpd 44.

General Procedure 18



Cmpd 42 **Cmpd 44**

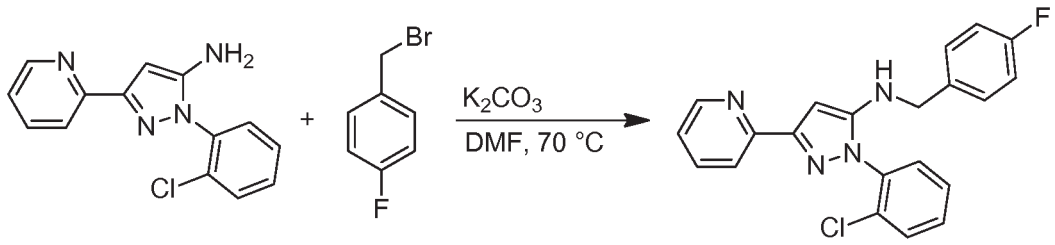
[0287] Sodium hydride (17.7 mg, 0.37 mmol, 1 eq, 60% in mineral oil) was added to a solution of Cmpd 42 (100 mg, 0.37 mmol) and 4-fluorobenzyl bromide (30 µL, 0.22 mmol, 0.6 eq) in DMF (4 mL) at 0°C. The resulting mixture was allowed to warm to RT and stir for 1 h. The mixture was diluted with water (10 mL) and extracted into EtOAc (30 mL). The organic layer washed with water (2 × 5 mL), saturated aqueous $NaHCO_3$ (2 × 5 mL) brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-20% EtOAc-hexane as the eluent to afford Cmpd 44 (25 mg, 13%). ^{1}H NMR: (DMSO-d_6) δ 8.57 (d, J = 4.4 Hz, 1H), 7.73-7.88 (m, 3H), 7.49-7.62 (m, 3H), 7.30-7.33 (m,

1H), 7.06-7.15 (m, 8H), 6.63 (s, 1H), 3.96 (s, 4H); MS: 487 $[M + H]^+$, 489 $[M + 2 + H]^+$; MP: 113-117 °C; TLC: EtOAc: Rf: 0.60.

Example 59 - Preparation of Cmpd 45 [General Procedure 19]

[0288] General Procedure 19 was followed in the preparation of Cmpd 45.

General Procedure 19



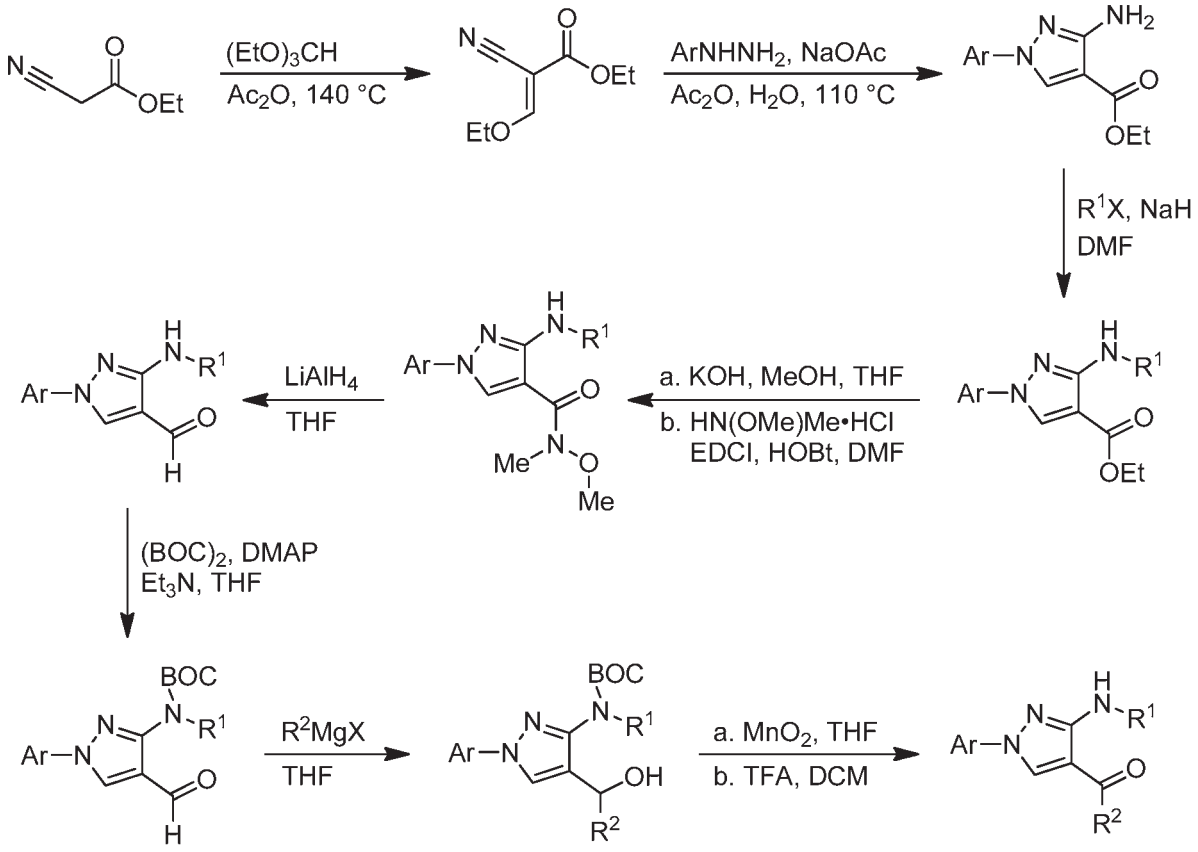
Cmpd 42 **Cmpd 45**

[0289] 4-Fluorobenzyl bromide (126 mg, 0.67 mmol, 0.6 eq) and K_2CO_3 (310 mg, 2.24 mmol, 2 eq) were added to a solution of Cmpd 42 (300 mg, 1.11 mmol) in DMF (8 mL) at RT. The resulting mixture was heated to 70 °C and allowed to stir for 8 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (30 mL). The organic layer was washed with water (2 × 5 mL), saturated aqueous $NaHCO_3$ (2 × 5 mL) brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was partially purified by preparative-TLC using 40% EtOAc-hexane and subsequently by preparative-HPLC to afford Cmpd 45 (16 mg, 4%) as an off-white solid. ^1H NMR: (DMSO-d_6) δ 8.51 (d, J = 4.4 Hz, 1H), 7.70-7.83 (m, 3H), 7.54-7.60 (m, 3H), 7.40-7.43 (m, 2H), 7.12-7.27 (m, 3H), 6.13 (t, J = 5.7 Hz, 1H), 5.87 (s, 1H), 4.24 (d, J = 5.7 Hz, 2H); MS: 379 $[M + H]^+$, 381 $[M + 2 + H]^+$; MP: 159-162 °C; TLC: EtOAc: R_f: 0.30.

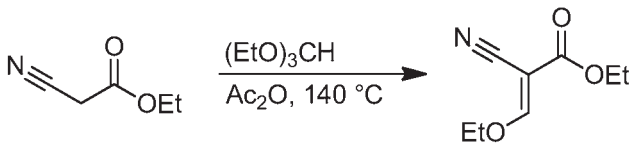
Example 60 - General Scheme XI

[0290] A synthetic scheme useful for synthesis of compounds described herein is disclosed in General Scheme XI following, wherein the terms "Ar," "R^1" and "R^2" are as defined in Example 1.

General Scheme XI



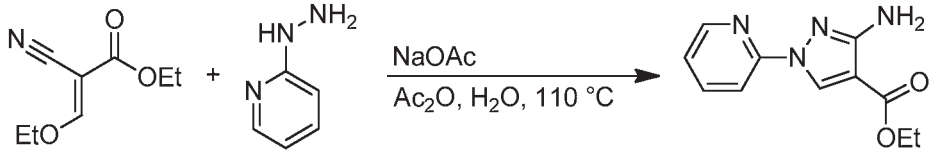
Example 61 - Preparation of Intermediate 38



Intermediate 38

[0291] A solution of ethyl cyanoacetate (20 g, 176.8 mmol) and triethyl orthoformate (29.4 mL, 176.8 mmol) in acetic anhydride (100 mL) was heated to 140 °C and allowed to stir for 5 h. The solvent was then evaporated to afford crude Intermediate 38 (23 g, 76%) as low melting solid. MS: 170 $[M + H]^+$; TLC: 30% EtOAc in hexane: R_f: 0.40.

Example 62 - Preparation of Intermediate 39

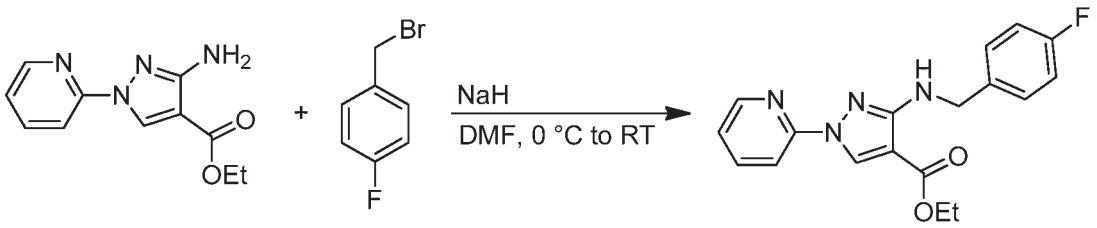


Intermediate 38 **Intermediate 39**

[0292] Sodium acetate (8.2 g, 100 mmol, 2 eq) was added to a solution of Intermediate 38 (8.45 g, 50.0 mmol) and 2-hydrazinopyridine (5 g, 45.5 mmol, 0.9 eq) in AcOH (100 mL) and water (20 mL). The resulting mixture was heated at 110 °C and allowed to stir for 16 h.

The mixture was then allowed to cool and ice-cold water was added. The precipitate was collected by filtration and washed with Et_2O and dried under vacuum to afford Intermediate 39 (4 g, 38%) as a pale yellow solid. ^{1}H NMR: (DMSO-d_6) δ 8.48-8.49 (m, 1H), 8.00-8.04 (m, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.79 (s, 1H), 7.65 (br s, 2H), 7.33-7.36 (m, 1H), 4.22 (q, J = 7.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H); MS: 233 $[M + H]^+$; TLC: 15% EtOAc in hexane: R_f: 0.50.

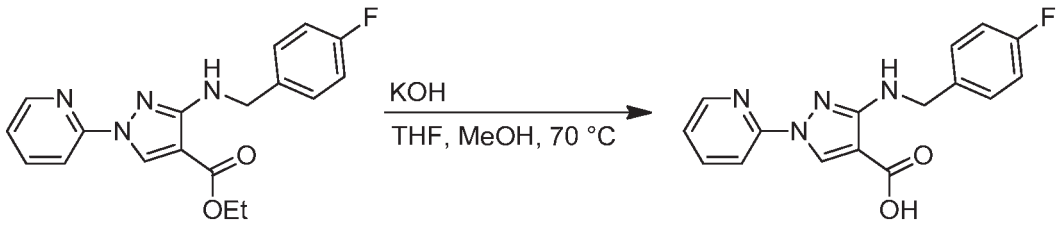
Example 63 - Preparation of Cmpd 46



Intermediate 39 **Cmpd 46**

[0293] Sodium hydride (603 mg, 15.1 mmol, 1 eq, 60% in mineral oil) was added to a solution of Intermediate 39 (3.5 g, 15.1 mmol) in DMF (300 mL) at 0 °C. After 30 minutes, a solution of 4-fluorobenzyl bromide (2.85 g, 15.1 mmol, 1 eq) in DMF (50 mL) was added and the resulting mixture was allowed to warm to RT. After 5 h, the reaction mixture was diluted with water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water (5 × 50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-5% EtOAc-hexane as the eluent to afford a partially pure product. The material was then recrystallized from Et_2O and pentane to afford Cmpd 46 (2.8 g, 55%) as a pale yellow solid. ^{1}H NMR: (DMSO-d_6) δ 9.50 (t, J = 6.6 Hz, 1H), 8.45-8.46 (m, 1H), 8.00-8.05 (m, 1H), 7.82-7.89 (m, 2H), 7.24-7.38 (m, 3H), 7.11 (t, J = 8.8 Hz, 2H), 4.88 (d, J = 6.6 Hz, 2H), 4.17 (q, J = 7.0 Hz, 2H), 1.24 (t, J = 7.0 Hz, 3H); MS: 341 $[M + H]^+$; MP: 99-100 °C; TLC: 15% EtOAc in hexane: R_f: 0.40.

Example 64 - Preparation of Cmpd 47



Cmpd 46 **Cmpd 47**

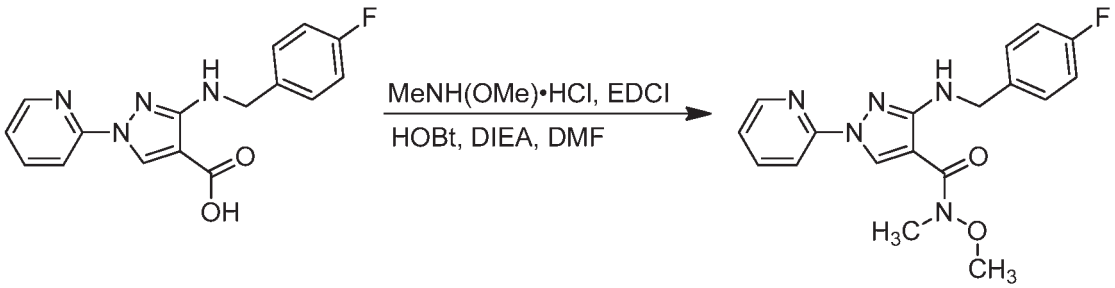
[0294] Potassium hydroxide (922 mg, 16.5 mmol) was added to a solution of Cmpd 46 (2.8 g, 8.23 mmol) in THF (10 mL) and MeOH (10 mL). The resulting mixture was heated to 70

°C and allowed to stir for 16 h. The reaction mixture was then neutralized with aqueous HCl (2*N*) and the resulting precipitate was collected by filtration, washed with water (50 mL) and dried thoroughly to afford Cmpd 47 (2.1 g, 84%) as an off-white solid. MS: 313 $[M + H]^+$; TLC: 50% EtOAc in hexane: R_f: 0.30.

Example 65 - Preparation of Cmpd 48 [General Procedure 20]

[0295] General Procedure 20 was followed in the preparation of Cmpd 48.

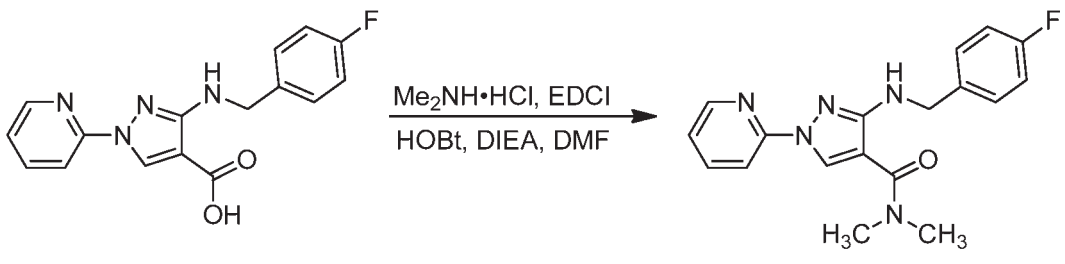
General Procedure 20



Cmpd 47 **Cmpd 48**

[0296] *N,O*-Dimethylhydroxylamine hydrochloride (979 mg, 10.1 mmol, 1.5 eq) was added to a mixture of EDCI (2.0 g, 10.1 mmol, 1.5 eq), HOBt (3.1 g, 21.2 mmol, 3.2 eq), DIEA (3.5 mL, 20.2 mmol, 3 eq) and Cmpd 47 (2.1 g, 6.73 mmol) in DMF (30 mL). The resulting mixture was allowed to stir at RT for 16 h. The mixture was then diluted with water (50 mL) and extracted with EtOAc (100 mL). The organic layer was washed with water (2 × 50mL), saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Cmpd 48 (1.5 g, 65%). ^1H NMR: (DMSO-d_6) δ 9.29 (t, J = 6.6 Hz, 1H), 8.49 (d, J = 4.9 Hz, 1H), 7.98-8.04 (m, 1H), 7.82-7.85 (m, 1H), 7.69 (s, 1H), 7.34-7.38 (m, 1H), 7.06-7.19 (m, 4H), 4.54 (d, J = 7.0 Hz, 2H), 3.28 (s, 3H), 3.14 (s, 3H); MS: 356 $[M + H]^+$; MP: 88-99 °C; TLC: 50% EtOAc in hexane: R_f: 0.30.

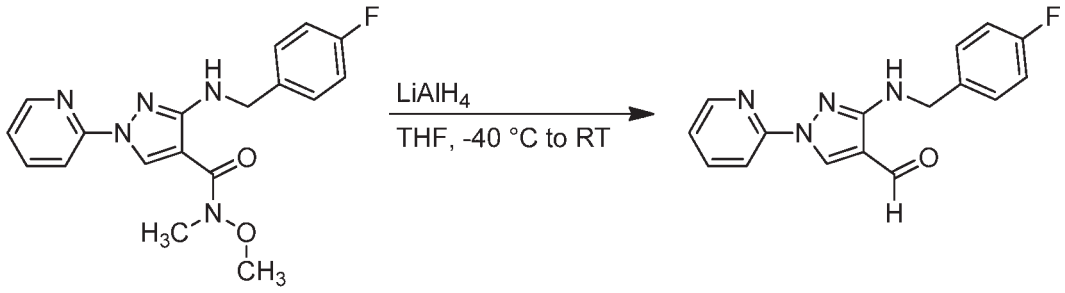
Example 66 - Preparation of Cmpd 49



Cmpd 47 **Cmpd 49**

[0297] General Procedure 20 was followed to afford Cmpd 49 (31 mg, 32%). ^{1}H NMR: (DMSO-d_6) δ 9.23 (t, J = 6.6 Hz, 1H), 8.48 (d, J = 3.5 Hz, 1H), 7.99-8.03 (m, 1H), 7.88-7.91 (m, 1H), 7.49 (s, 1H), 7.32-7.35 (m, 1H), 7.09-7.20 (m, 4H), 4.50 (d, J = 6.6 Hz, 2H), 2.57-2.89 (m, 6H); MS: 340 $[M + H]^+$; MP: 107-109 °C; TLC: 50% EtOAc in hexane: R_f: 0.30.

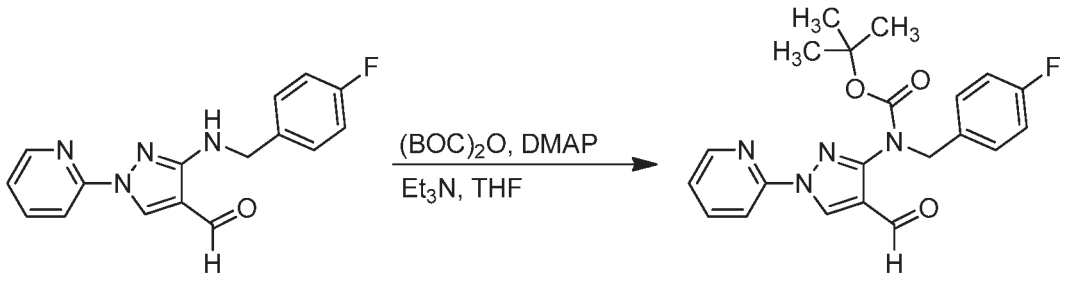
Example 67 - Preparation of Intermediate 40



Cmpd 48 **Intermediate 40**

[0298] Lithium aluminum hydride (642 mg, 16.9 mmol) was added to a solution of Cmpd 48 (1.5 g, 4.22 mmol) in THF (20 mL) at -40 °C. The resulting mixture was allowed to warm to 0 °C and stir for 5 h. The mixture was then quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (30 mL). The organic layer washed with water (2 × 50 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-10% EtOAc-hexane as the eluent to afford Intermediate 40 (1 g, 80%). ^{1}H NMR: (DMSO-d_6) δ 10.09 (s, 1H), 9.53 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H), 8.05 (t, J = 7.9 Hz, 1H), 7.99 (s, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.34-7.37 (m, 3H), 7.15-7.20 (m, 2H), 4.96 (d, J = 6.3 Hz, 2H); MS: 297 $[M + H]^+$; TLC: 20% EtOAc in hexane: R_f: 0.30.

Example 68 - Preparation of Intermediate 41

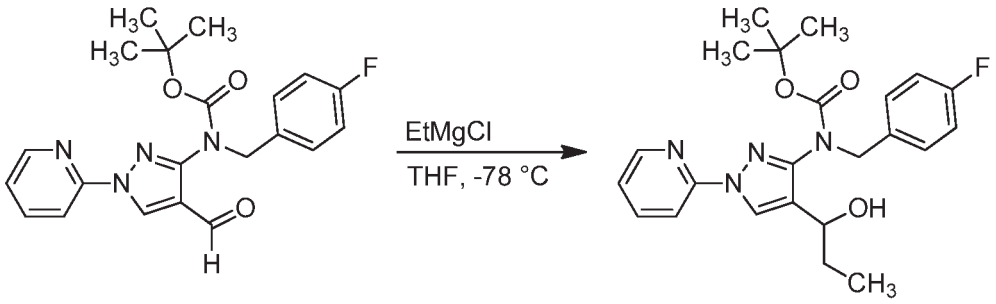


Intermediate 40 **Intermediate 41**

[0299] Triethylamine (4.6 mL, 33.7 mmol, 10 eq), DMAP (410 mg, 3.36 mmol, 1 eq) and $(BOC)_2O$ (5 mL, 20.5 mmol, 6.1 eq) was added to a solution of Intermediate 40 (1 g, 3.36 mmol) in THF (3 mL). The resulting mixture was allowed to stir at RT for 16 h. The mixture

was then diluted with water (75 mL) and extracted with EtOAc (150 mL). The organic layer was washed with water (2 × 75 mL), brine (75 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-15% EtOAc-hexane as the eluent to afford Intermediate 41 (1 g, 76%) as a pale yellow liquid. MS: 397 $[M + H]^+$; TLC: 30% EtOAc in hexane: R_f: 0.50.

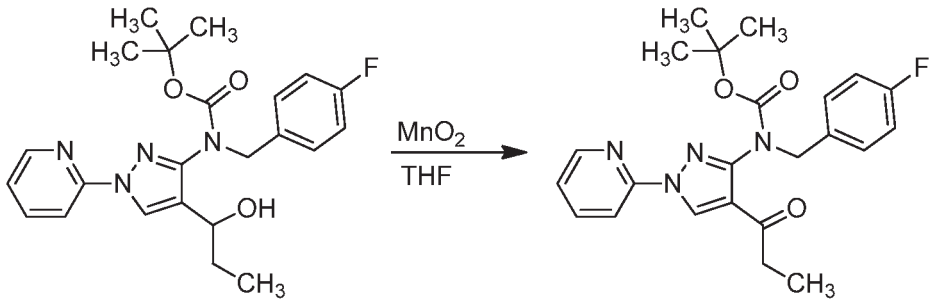
Example 69 - Preparation of Intermediate 42



Intermediate 41 **Intermediate 42**

[0300] Ethyl magnesium chloride (0.75 mL, 1.5 mmol, 3 eq, 2M in THF) was added to a solution of Intermediate 41 (200 mg, 0.50 mmol) in THF (10 mL) at -78 °C. The resulting mixture was warmed to 0 °C and allowed to stir for 4 h. The reaction was then quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (30 mL). The organic layer washed with water (10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Intermediate 42 (140 mg, 65%) as a yellow solid. MS: 427 $[M + H]^+$; TLC: 50% EtOAc in hexane: R_f: 0.50.

Example 70 - Preparation of Intermediate 43

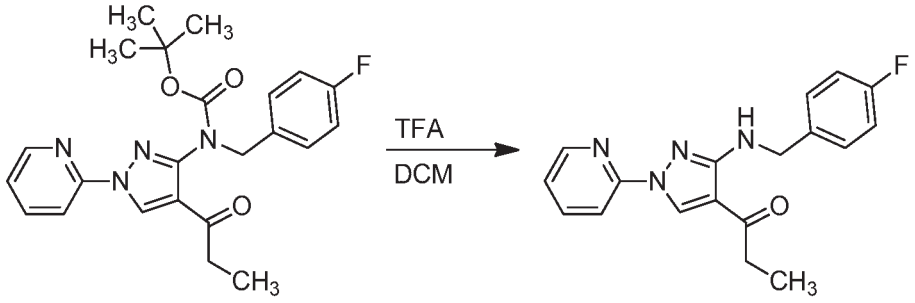


Intermediate 42 **Intermediate 43**

[0301] Manganese dioxide (245 mg, 2.81 mmol) was added to a solution of Intermediate 42 (120 mg, 0.28 mmol) in THF (10 mL) and the resulting mixture was allowed to stir at RT for 48 h. The mixture was then filtered through Celite and washed with EtOAc (20 mL). The

organic phase was washed with water (10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Intermediate 43 (90 mg, 75%). MS: 425 $[M + H]^+$; TLC: 40% EtOAc in hexane: R_f: 0.50.

Example 71 - Preparation of Cmpd 50



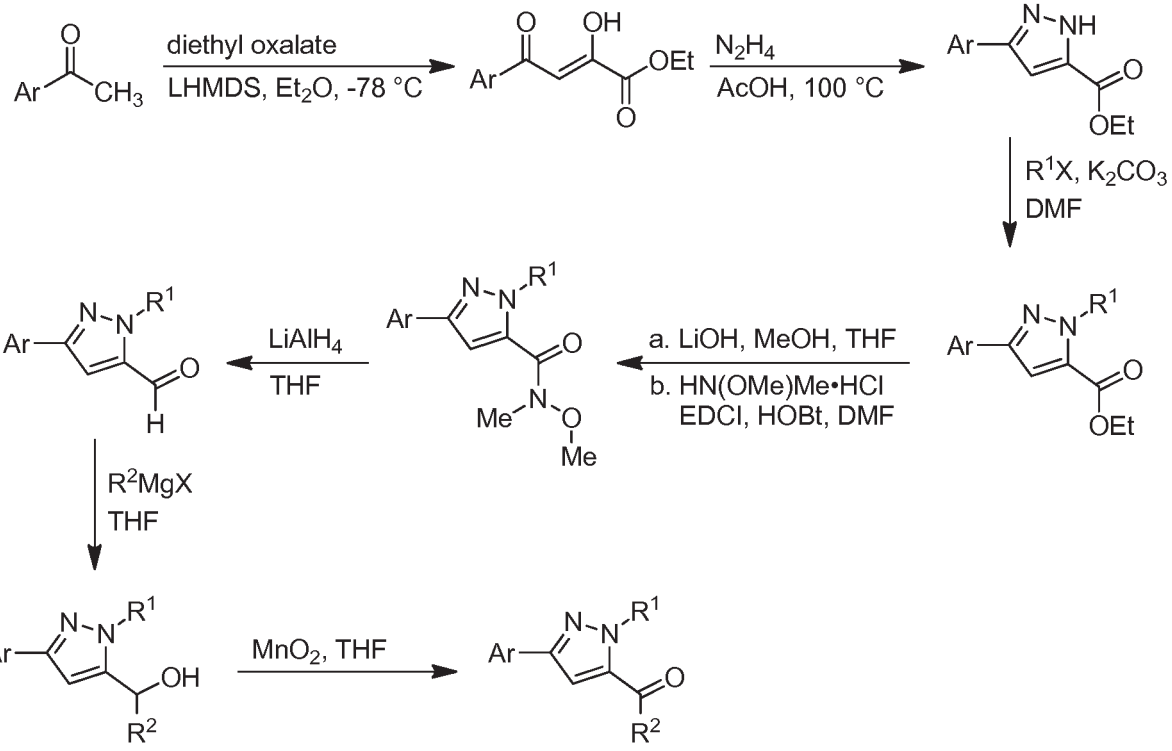
Intermediate 43 **Cmpd 50**

[0302] Trifluoroacetic acid (2 mL) was added to a solution of Intermediate 43 (90 mg, 0.21 mmol) in DCM (2 mL) at 0 °C. The resulting mixture was allowed to warm to RT and stir for 2 h. The reaction mixture was then neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc (30 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-20% EtOAc-hexane as the eluent to afford Cmpd 50 (50 mg, 73%). ^1H NMR: (DMSO-d_6) δ 9.40-9.43 (m, 1H), 8.46 (d, J = 3.2 Hz, 1H), 7.97-8.08 (m, 2H), 7.79 (d, J = 8.2 Hz, 1H), 7.35-7.38 (m, 1H), 7.03-7.14 (m, 4H), 4.72 (d, J = 6.7 Hz, 2H), 2.70 (q, J = 7.3 Hz, 2H), 1.00 (t, J = 7.5 Hz, 3H); MS: 325 $[M + H]^+$; MP: 108-110 °C; TLC: 50% EtOAc in hexane: R_f: 0.40.

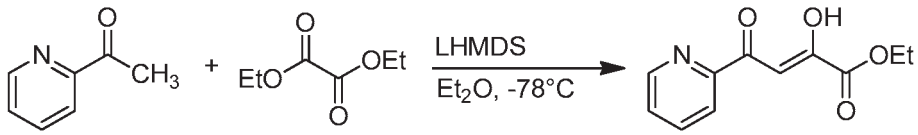
Example 72 - General Scheme XII

[0303] A synthetic scheme useful for synthesis of compounds described herein is disclosed in General Scheme XII following, wherein the terms "Ar," "R^1" and "R^2" are as defined in Example 1, and the term "X" refers to halogen, e.g., Cl, Br.

General Scheme XII



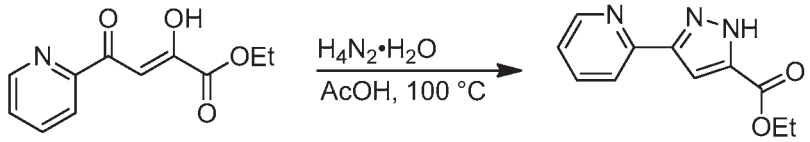
Example 73 - Preparation of Intermediate 44



Intermediate 44

[0304] Lithium hexamethyldisilazide (24.8 mL, 24.8 mmol, 1 eq, 1M in THF) was diluted with anhydrous Et_2O (100 mL) and cooled to -78 °C under an argon atmosphere. After 15 min, 2-acetylpyridine (3 g, 24.8 mmol) in Et_2O (20 mL) was added to the cold mixture. After 30 min at -78 °C, diethyl oxalate (3.61 g, 24.8 mmol, 1 eq) in Et_2O (25 mL) was added in a single portion and the resulting mixture was allowed to warm to RT and stir for 20 h. The resulting precipitate was collected by filtration and dried to afford Intermediate 44 (4 g, 74%) as the lithium salt. MS: 222 $[M + H]^+$; TLC: EtOAc: R_f: 0.10.

Example 74 - Preparation of Intermediate 45

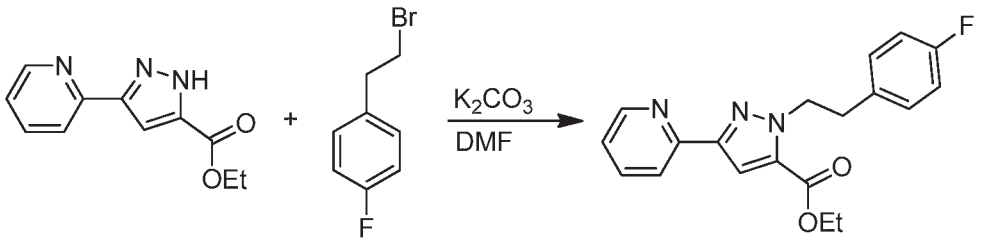


Intermediate 44 **Intermediate 45**

[0305] Hydrazine hydrate (602 mg, 13.3 mmol, 15 eq) was added to a solution of Intermediate 44 (200 mg, 0.90 mmol) in AcOH (5 mL). The resulting mixture was heated to

100 °C and allowed to stir for 12 h. The reaction mixture was then neutralized with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (40 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 ×10 mL), water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was washed with pentane (2 × 10 mL) and dried under vacuum to afford Intermediate 45 (120 mg, 66%) as a viscous liquid. MS: 218 $[M + H]^+$; TLC: EtOAc: R_f: 0.40.

Example 75 - Preparation of Cmpd 51



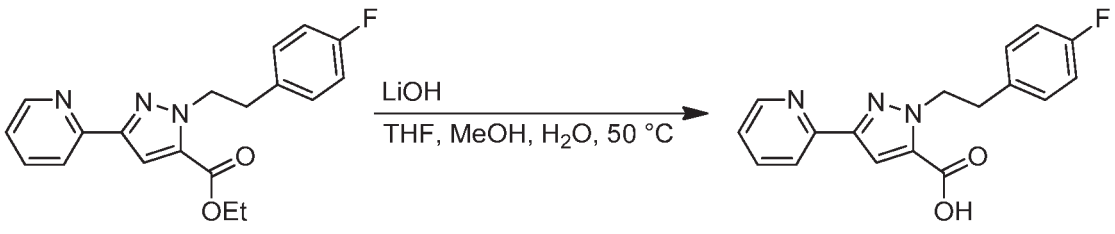
Intermediate 45 **Cmpd 51**

[0306] Anhydrous K_2CO_3 (1.27 g, 9.21 mmol, 2.5 eq) and 4-fluorophenethyl bromide (1 g, 4.61 mmol, 1.25 eq) was added to a solution of Intermediate 45 (744 mg, 3.68 mmol) in DMF (30 mL) and the resulting mixture was allowed to stir at RT for 8 h. The mixture was then diluted with water (30 mL) and extracted with EtOAc (100 mL). The organic layer was washed with water (2 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 15 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-10% EtOAc-hexane as the eluent to afford Cmpd 51 (700 mg, 58%). ^{1}H NMR: (DMSO-d_6) δ 8.61 (d, J = 4.3 Hz, 1H), 7.85-7.96 (m, 2H), 7.31-7.38 (m, 2H), 7.07-7.19 (m, 4H), 4.78 (t, J = 7.2 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 3.12 (t, J = 7.2 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H); MS: 340 $[M + H]^+$; MP: 94-95 °C; TLC: 30% EtOAc in hexane: R_f: 0.40.

Example 76 - Preparation of Cmpd 52 [General Procedure 21]

[0307] General Procedure 21 was followed in the preparation of Cmpd 52.

General Procedure 21



Cmpd 51 **Cmpd 52**

[0308] To a solution of Cmpd 51 (300 mg, 0.88 mmol) in THF (3 mL) was added $LiOH•H_2O$ (185 mg, 4.42 mmol, 5 eq) in water (3 mL) and MeOH (3 mL). The mixture was heated to 50 °C and allowed to stir for 3 h. The reaction mixture was then neutralized with aqueous HCl (2*N*) and the precipitate was collected by filtration, washed with water (20 mL) and dried thoroughly to afford Cmpd 52 (220 mg, 83%) as a pale pink solid. ^{1}H NMR: (DMSO-d_6) δ 8.74 (d, *J* = 4.5 Hz, 1H), 8.29-8.33 (m, 2H), 7.72 (br s, 2H), 7.08-7.19 (m, 4H), 4.84 (t, *J* = 6.7 Hz, 2H), 3.16 (t, *J* = 7.0 Hz, 2H); MS: 312 $[M + H]^+$; MP: 256-258 °C; TLC: EtOAc: R_f: 0.10.

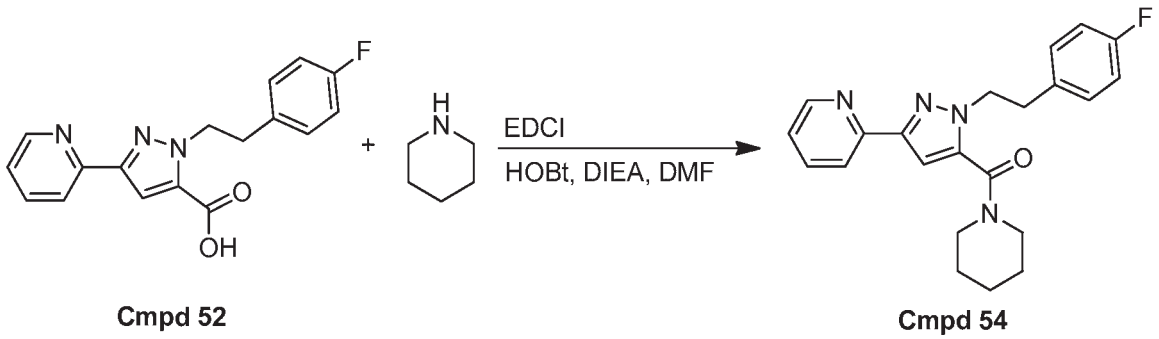
Example 77 - Preparation of Cmpd 53



Cmpd 52 **Cmpd 53**

[0309] General Procedure 20 was followed to afford Cmpd 53 (190 mg, 55%). ^{1}H NMR: (DMSO-d_6) δ 8.60 (d, *J* = 4.4 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.86-7.88 (m, 1H), 7.34-7.37 (m, 1H), 7.07-7.21 (m, 5H), 4.67 (t, *J* = 7.1 Hz, 2H), 3.57 (s, 3H), 3.25 (s, 3H), 3.12 (t, *J* = 7.1 Hz, 2H); MS: 355 $[M + H]^+$; MP: 110-111 °C; TLC: 50% EtOAc in hexane: R_f: 0.30.

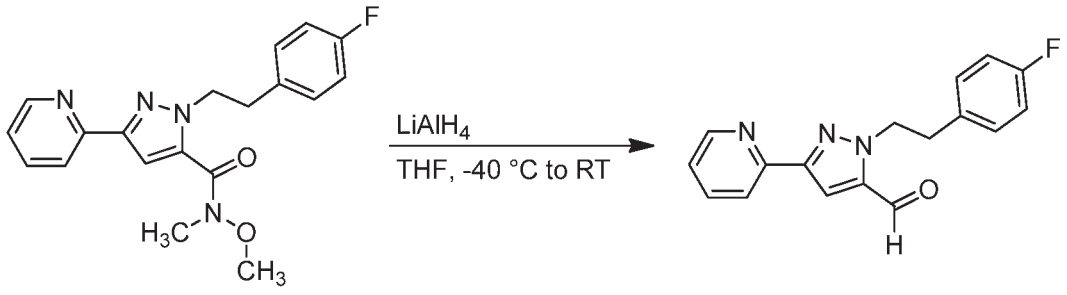
Example 78 - Preparation of Cmpd 54



Cmpd 52 **Cmpd 54**

[0310] General Procedure 20 was followed to afford Cmpd 54 (25 mg, 21%). ^{1}H NMR: (DMSO-d_6) δ 8.57 (d, *J* = 4.4 Hz, 1H), 7.82-7.94 (m, 2H), 7.31-7.34 (m, 1H), 7.04-7.14 (m, 4H), 6.84 (s, 1H), 4.56 (t, *J* = 7.0 Hz, 2H), 3.52 (br s, 2H), 3.25 (br s, 2H), 3.10 (t, *J* = 7.0 Hz, 2H), 1.41-1.58 (m, 6H); MS: 379 $[M + H]^+$; MP: 88-90 °C; TLC: EtOAc: R_f: 0.50.

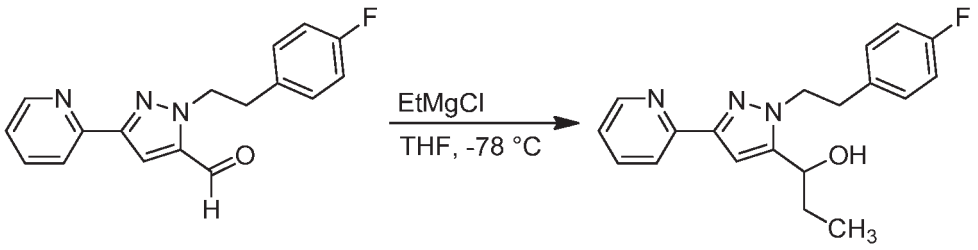
Example 79 - Preparation of Intermediate 46



Cmpd 53 **Intermediate 46**

[0311] Lithium aluminum hydride (11 mg, 0.28 mmol) was added to a solution of Cmpd 53 (100 mg, 0.28 mmol) in THF (4 mL) at -40 °C. The resulting mixture was allowed to slowly warm to 0 °C and stir for 2 h. The mixture was then quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (30 mL). The organic layer washed with water (10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was washed with pentane (2 × 5 mL) and dried under vacuum to afford Intermediate 46 (65 mg, 79%). ^{1}H NMR: (DMSO-d_6) δ 9.82 (s, 1H), 8.63 (d, J = 3.5 Hz, 1H), 7.86-7.97 (m, 2H), 7.54 (s, 1H), 7.36-7.39 (m, 1H), 7.07-7.19 (m, 4H), 4.75-4.78 (m, 2H), 3.11-3.14 (m, 2H); TLC: 30% EtOAc in hexane: R_f: 0.50.

Example 80 - Preparation of Cmpd 55

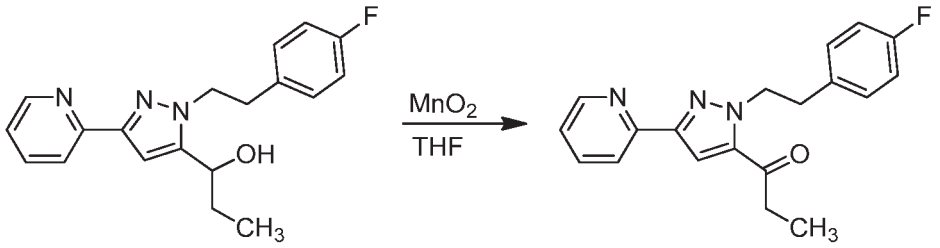


Intermediate 46 **Cmpd 55**

[0312] Ethyl magnesium chloride (0.33 mL, 0.66 mmol, 3 eq, 2M in THF) was added to a solution of Intermediate 46 (65 mg, 0.22 mmol) in THF (4 mL) at -78 °C. The resulting mixture was warmed to 0 °C and allowed to stir for 4 h. The reaction was then quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (30 mL). The organic layer washed with water (10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Cmpd 55 (60 mg, 84%) as an off-white solid. ^{1}H NMR: (DMSO-d_6) δ 8.55 (d, J = 3.8 Hz, 1H), 7.79-7.93 (m, 2H), 7.10-7.30 (m, 5H), 6.65 (s, 1H), 5.31 (d, J = 6.0 Hz, 1H), 4.25-4.39 (m, 3H), 3.14-3.16 (m, 2H), 1.58-1.69 (m, 2H), 0.81

(t, J = 7.3 Hz, 3H); MS: 326 $[M + H]^+$; MP: 91-96 °C; TLC: 50% EtOAc in hexane: R_f: 0.20.

Example 81 - Preparation of Cmpd 56



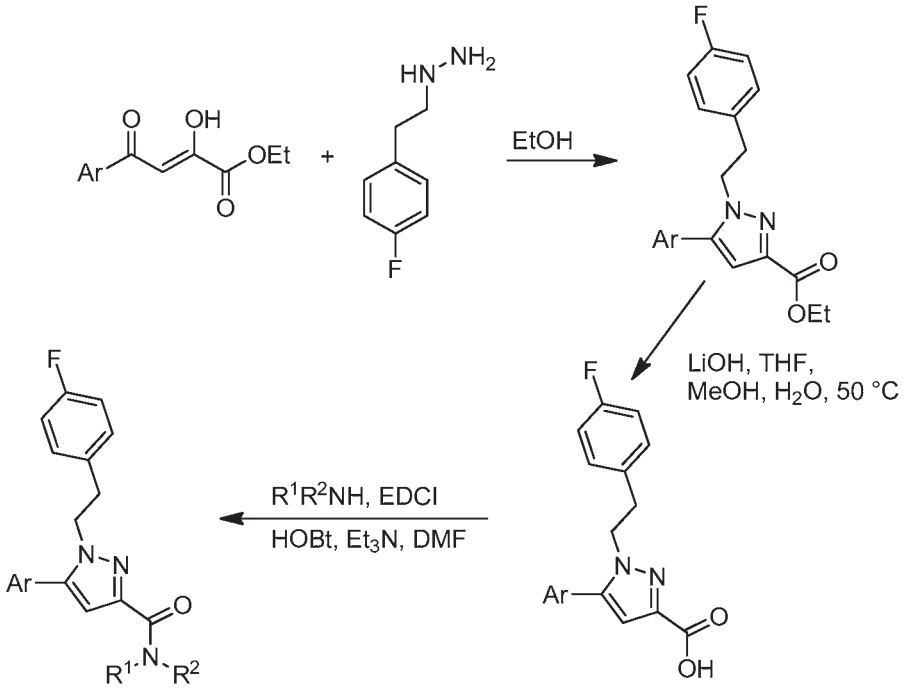
Cmpd 55 **Cmpd 56**

[0313] Manganese dioxide (83 mg, 0.96 mmol, 3 eq) was added to a solution of Cmpd 55 (100 mg, 0.32 mmol) in THF (4 mL) and the resulting mixture was allowed to stir at RT for 14 h. The mixture was then filtered through Celite and washed with EtOAc (20 mL). The organic phase was washed with water (10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a gradient mixture of 0-30% EtOAc-hexane as the eluent to afford Cmpd 56 (22 mg, 21%). ^1H NMR: (DMSO-d_6) δ 8.61 (d, J = 5.1 Hz, 1H), 7.85-7.95 (m, 2H), 7.60 (s, 1H), 7.35-7.38 (m, 1H), 7.08-7.21 (m, 4H), 4.74 (t, J = 7.6 Hz, 2H), 3.06 (t, J = 7.3 Hz, 2H), 2.94 (q, J = 7.2 Hz, 2H), 1.03 (t, J = 7.3 Hz, 3H); MS: 324 $[M + H]^+$; MP: 129-130 °C; TLC: 50% EtOAc in hexane: R_f: 0.50.

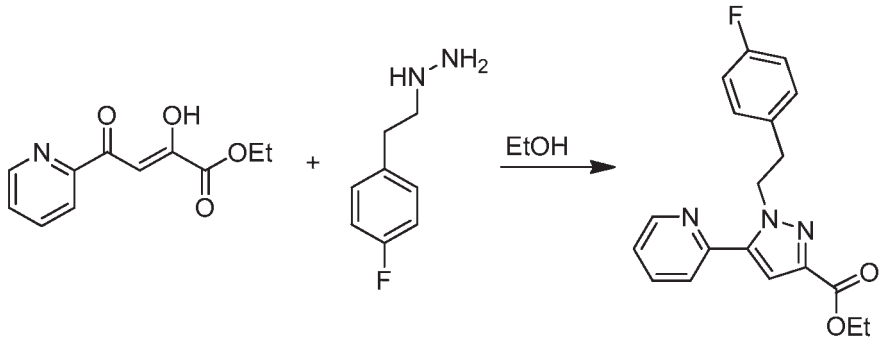
Example 82 - General Scheme XIII

[0314] A synthetic scheme useful for synthesis of compounds described herein is disclosed in General Scheme XII following, wherein the terms "Ar," "R^1" and "R^2" are as defined in Example 1.

General Scheme XIII



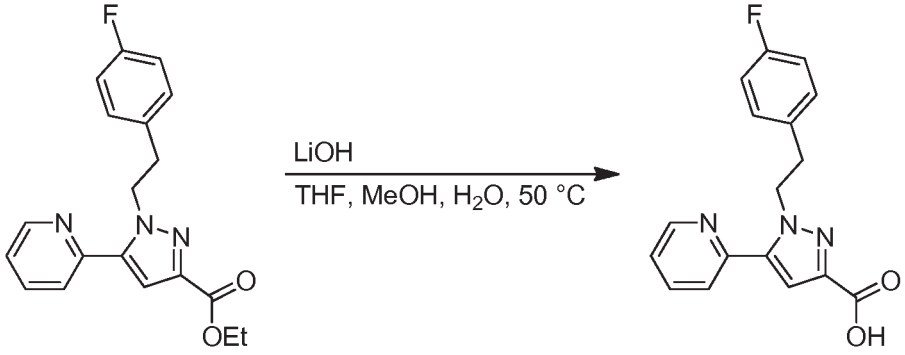
Example 83 - Preparation of Cmpd 57



Intermediate 44 **Cmpd 57**

[0315] [2-(4-Fluorophenyl)-ethyl]-hydrazine (348 mg, 2.26 mmol, 2 eq) was added to a solution of Intermediate 44 (500 mg, 2.26 mmol) in EtOH (30 mL) and the resulting mixture was allowed to stir for 12 h. The solvent was evaporated and the residue was dissolved in EtOAc (100 mL) and filtered through Celite to remove any residual inorganic material. The filtrate was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography over silica gel (100-200 mesh) by using a solvent gradient of 0-15% EtOAc-hexane as the eluent to afford Cmpd 57 (400 mg, 52%). ^{1}H NMR: (DMSO-d_6) δ 8.72-8.73 (m, 1H), 7.87-7.91 (m, 1H), 7.75-7.77 (m, 1H), 7.41-7.44 (m, 1H), 7.29 (s, 1H), 6.99-7.15 (m, 4H), 4.91 (t, J = 7.6 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 3.06 (t, J = 7.6 Hz, 2H), 1.3 (t, J = 7.0 Hz, 3H); MS: 340 $[M + H]^+$; MP: 91-92 °C; TLC: 30% EtOAc in hexane: R_f: 0.30.

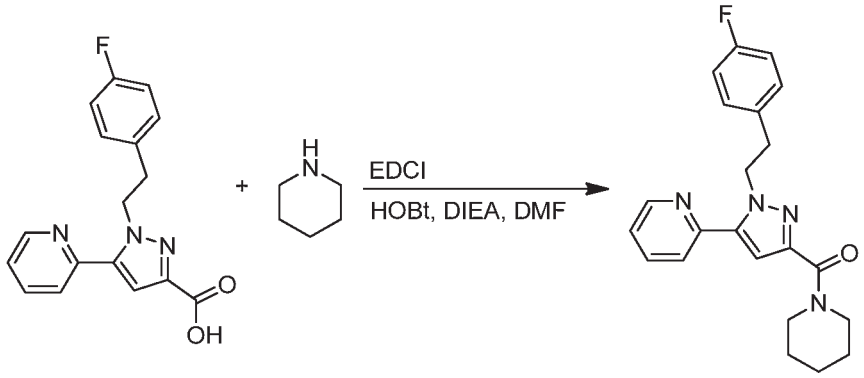
Example 84 - Preparation of Cmpd 58



Cmpd 57 **Cmpd 58**

[0316] General Procedure 21 was followed to afford Cmpd 58 (230 mg, 84%) as an off-white solid. ^{1}H NMR: (DMSO-d_6) δ 12.84 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 7.73-7.90 (m, 2H), 7.40-7.43 (m, 1H), 6.99-7.22 (m, 5H), 4.88 (t, J = 7.3 Hz, 2H), 3.06 (t, J = 7.6 Hz, 2H); MS: 312 $[M + H]^+$; MP: 132-134 °C; TLC: EtOAc: R_f: 0.10.

Example 85 - Preparation of Cmpd 59



Example 58 **Cmpd 59**

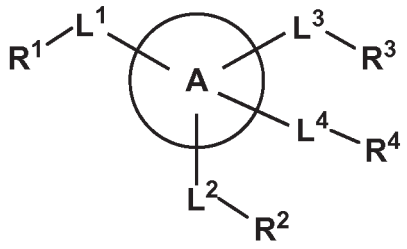
[0317] General Procedure 20 was followed to afford Cmpd 59 (25 mg, 21%). ^{1}H NMR: (DMSO-d_6) δ 8.69 (d, J = 4.4 Hz, 1H), 7.85-7.89 (m, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.38-7.41 (m, 1H), 6.95-7.06 (m, 5H), 4.86 (t, J = 7.0 Hz, 2H), 3.54-3.95 (m, 4H), 3.01 (t, J = 7.0 Hz, 2H), 1.42-1.60 (m, 6H); MS: 379 $[M + H]^+$; TLC: EtOAc: R_f: 0.50.

[0318] The contents of all references, patents, and published applications cited herein are hereby incorporated by reference in their entirety and for all purposes.

[0319] While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

WHAT IS CLAIMED IS:

1. A compound with structure of Formula (Ia):



(Ia)

or pharmaceutically acceptable salt, ester, solvate, or prodrug thereof;

wherein

ring A is substituted or unsubstituted pyrazolyl, or substituted or unsubstituted triazolyl;

L^1, L^2 and L^3 are independently a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, $-SO_2-$, -O-, $-NHSO_2-$, or $-NR^5-$;

L^4 is absent, a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -S-, -SO-, $-SO_2-$, -O-, $-NHSO_2-$, or $-NR^5-$;

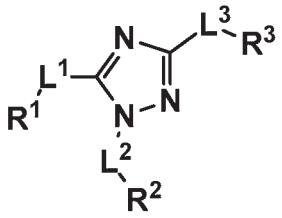
R^1, R^2 and R^3 are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

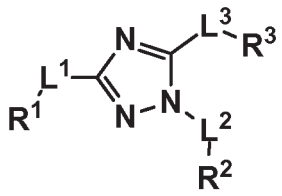
R^4 is absent, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, provided that when L^4 is absent, then R^4 is absent; and

R^5 is independently hydrogen, or substituted or unsubstituted alkyl.

2. The compound according to claim 1, wherein L^4 and R^4 are absent.

3. The compound according to claim 2, with structure of Formula (IIa) or Formula (IIb):


(IIa)


(IIb).

4. The compound according to claim 3, with structure of Formula (IIa), wherein L^3 is a bond, and R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

5. The compound according to claim 4, wherein said heteroaryl is pyridyl, thienyl, or furyl.

6. The compound according to claim 3, with structure of Formula (IIa), wherein L^3 is a bond, substituted or unsubstituted alkylene, and R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heterocycloalkyl.

7. The compound according to claim 3, with structure of Formula (IIa), wherein L^3 is -C(O)O-, and R^3 is substituted or unsubstituted alkyl.

8. The compound according to claim 3, with structure of Formula (IIa), wherein L^3 is -C(O)NR^5-, R^5 is hydrogen or alkyl, and R^3 is substituted or unsubstituted alkyl, or substituted or unsubstituted aryl.

9. The compound according to any of claims 3 to 8,

wherein

L^1 is -S-, -NR^4-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, and

R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

10. The compound according to claim 9, wherein L^1 is -NC(O)-.

11. The compound according to claim 10, wherein R^3 is substituted aryl.

12. The compound according to claim 9, wherein L^2 is a bond.

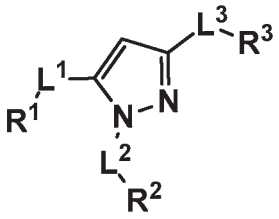
13. The compound according to claim 12, wherein R^2 is hydrogen.

14. The compound according to claim 9, wherein L^2 is substituted or unsubstituted alkylene or -C(O)-, and R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

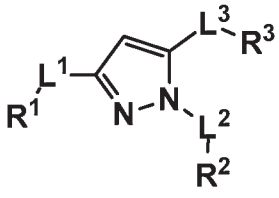
15. The compound according to claim 3, with structure of Formula (IIb), wherein L^2 is a bond or substituted or unsubstituted alkylene.

16. The compound according to claim 15, wherein R^2 is substituted or unsubstituted alkyl, or substituted or unsubstituted aryl.

17. The compound according to claim 2, with structure of Formula (IIIa) or Formula (IIIb):



(IIIa)



(IIIb).

18. The compound according to claim 17, with structure of Formula (IIIa), wherein L^3 is a bond, or substituted or unsubstituted alkylene, and R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heterocycloalkyl.

19. The compound according to claim 17, with structure of Formula (IIIa), wherein L^3 is -C(O)O-, and R^3 is substituted or unsubstituted alkyl.

20. The compound according to claim 17, with structure of Formula (IIIa), wherein L^3 is -C(O)NR^6, R^6 is hydrogen or alkyl, and R^3 is substituted or unsubstituted alkyl, or substituted or unsubstituted aryl.

21. The compound according to claim 18, wherein R^3 is phenyl or pyridyl.

22. The compound according to any of claims 17 to 21, wherein L^1 is -S-, -NR^4-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, and R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

23. The compound according to claim 22, wherein L^2 is a bond.

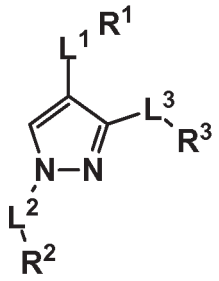
24. The compound according to claim 23, wherein R^2 is hydrogen.

25. The compound according to claim 22, wherein L^2 is substituted or unsubstituted alkylene or -C(O)-, and R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocycloalkyl.

26. The compound according to claim 17, with structure of Formula (IIIb), wherein L^2 is a bond or substituted or unsubstituted alkylene.

27. The compound according to claim 26, wherein R^2 is substituted or unsubstituted alkyl, or substituted or unsubstituted aryl.

28. The compound according to claim 2, with structure of Formula (IV):



(IV).

29. The compound according to claim 28, wherein L^3 is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, and R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

30. The compound according to claim 29, wherein L^3 is a bond, -NH-, $-NHCH_2-$ or $-NH(CH_2)_2-$.

31. The compound according to any of claims 28 to 30,

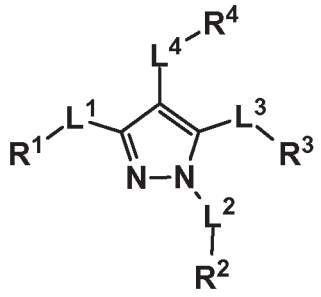
wherein

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, -C(O)-, $-C(O)-NR^6-$,

R^1 is hydrogen, -COOH, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; substituted or unsubstituted heterocycloalkyl; and

R^6 is hydrogen, or substituted or unsubstituted alkyl.

32. The compound according to claim 1, with structure of Formula (V):



(V).

33. The compound according to claim 32, wherein L^4 is a bond; and R^4 is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl.

34. The compound according to claim 33, wherein R^4 is unsubstituted alkyl.

35. The compound according to any of claims 1 to 34 as set forth in Table A.

36. The compound according to any of claims 1 to 34 as set forth in Table B.

37. A pharmaceutical composition comprising a compound according to any of claims 1 to 36, or a compound as set forth in Table C, and a pharmaceutically acceptable excipient.

38. A method for treating a disease or disorder in a subject, comprising administering a compound according to any of claims 1 to 36 or a pharmaceutical composition according to claim 37, to a subject in need thereof in an amount effective to treat said disease or disorder.

39. The method according to claim 38, wherein said disease or disorder is a thrombotic disorder.

40. The method according to claim 39, wherein said thrombotic disorder is acute coronary syndrome, venous thromboembolism, arterial thromboembolism or cardiogenic thromboembolism.

41. The method according to claim 38, wherein said disease or disorder is fibrosis.

42. The method according to claim 38, wherein said disease or disorder is Alzheimer's Disease.

43. The method according to claim 38, wherein said disease or disorder is multiple sclerosis.

44. The method according to claim 38, wherein said disease or disorder is pain.

45. The method according to claim 38, wherein said disease or disorder is cancer.

46. A method for preventing a disease or disorder in a subject, comprising administering a compound according to any of claims 1 to 36 or a pharmaceutical composition according to claim 37, to a subject in need thereof in an amount effective to prevent said disease or disorder.

47. The method according to claim 46, wherein said disease or disorder is a thrombotic disorder.

48. The method according to claim 47, wherein said thrombotic disorder is acute coronary syndrome, venous thromboembolism, arterial thromboembolism or cardiogenic thromboembolism.

49. The method according to claim 47, wherein said thrombotic disorder is disseminated intravascular coagulation.

50. The method according to claim 47, wherein said thrombotic disorder involves the presence or the potential formation of a blood clot thrombus.