Abstract: The invention is directed to compounds of formula (I): that modulate, e.g., inhibit, aggrecanase proteolytic activity, which is implicated in joint diseases including osteoarthritis, joint injury, reactive arthritis, acute pyrophosphate arthritis, psoriatic arthritis, and rheumatoid arthritis. The current invention also relates to processes for making the compounds of the invention and to pharmaceutical compositions containing these compounds. The present invention further provides methods of treating diseases associated with aggrecanase activity, e.g., osteoarthritis and other joint diseases, using the compounds of the invention.
2,4-DIAMINO-1,3,5-TRIAZINE AND 4,6-DIAMINO-PYRIMIDINE DERIVATIVES
AND THEIR USE AS AGGRECANASE INHIBITORS

FIELD OF THE INVENTION

[0001] The invention is directed to compounds that inhibit aggrecanase proteolytic activity which is implicated in joint diseases including osteoarthritis, joint injury, reactive arthritis, acute pyrophosphate arthritis, psoriatic arthritis, rheumatoid arthritis, and other diseases and pathological conditions. The invention is also directed to processes for making the invention compounds, to pharmaceutical compositions, and to methods of treatment osteoarthritis and other joint diseases using the invention compounds.

BACKGROUND OF THE INVENTION

[0002] Osteoarthritis is characterized by progressive enzymatic destruction of type II collagen and aggrecan, which are the two major components of cartilage matrix.
[0003] Type II collagen is essential for cartilage tensile strength and its degradation causes progression of osteoarthritis.
[0004] Aggrecan is composed of a core protein of approximately 2400 amino acids. The molecule consists of several structural and functional domains (Fallowery et al., Matrix Biology 16, 1998, 507-511). Three domains are defined on the N-terminal side: (1) the Gl, (2) the interglobular, and (3) the G2 domain. The aggrecan C-terminal side comprises two glycosaminoglycan rich domains. The G1 domain is separated from a second globular domain, G2, by about 150 amino acids, known as the interglobular domain. From the G2 domain to the C-terminus there is a long extended region consisting of two glycosaminoglycan-rich domains. The first is rich in keratan sulfate, whereas that which follows is rich in chondroitin sulfate. The G1 domain of aggrecan binds to long hyaluronic acid polymers, thereby forming multi molecular aggregates that effectively immobilize aggrecan within the collagen fibrillar meshwork. The glycosaminoglycan domains provide osmotic pressure, which enables cartilage to resist compression.
[0005] The loss of aggrecan contributes to the progression of osteoarthritis. In osteoarthritis and rheumatoid arthritis, aggrecan is one of the first cartilage matrix components to undergo measurable loss (Mankin et al., J. Bone Joint Surg. 52A, 424-434 (1970)). In human arthritis in particular, aggrecan degradation is associated with
amino acid cleavage within the interglobular domain, at either the Asn^{341}-Phe^{342} or the Glu^{373}-Ala^{374} site. In vitro studies have demonstrated that the aggrecan Asn^{341}-Phe^{342} bond can be cleaved by several collagenases including collagenase-1 and collagenase-3 (Fonsang et al., FEBS Lett. 380: 17-20, 1996a); however, digestion of aggrecan with a number of these purified proteases has not resulted in cleavage at the Glu^{373}-Ala^{374} site (Fonsang et al., J. Biol. Chem. 267, 19470-19074, (1992); Flannery et al J. Biol. Chem. 267, 1008-1014 (1992)).

[0006] Current osteoarthritis therapies (e.g., non-steroidal anti-inflammatory or "NSAIDs") have limited symptomatic benefit and have only modest, if any, effects on slowing cartilage destruction in osteoarthritic joints. NSAIDs, such as, acetaminophen, act by inhibiting the synthesis of cytokines, such as, prostaglandins that cause pain and swelling. While inhibitors of cartilage degrading enzymes will block cartilage collagen and aggrecan degradation (thereby blocking or slowing the progression of osteoarthritis), NSAIDs do not directly prevent cartilage destruction. Inhibition of aggrecanase should have a more direct and specific effect on cartilage breakdown than cytokine inhibition in the treatment of osteoarthritis, joint injury, reactive arthritis, acute pyrophosphate arthritis, psoriatic arthritis, and rheumatoid arthritis.

SUMMARY OF THE INVENTION

[0007] These and other needs are met by the present invention which in one aspect is directed to a compound of formula I

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, wherein:

Y is H, halo, ORi, SRi, (d-C \(_3\))alkyl, (C\(_3\)-C\(_6\))cycloalkyl, aryl, aralkyl, (C\(_3\)-C\(_6\))heterocycloalkyl, heteroaryl, heteroaralkyl, or NRi,Rj;

Ri is hydrogen, (C\(_i\)-C\(_j\))alkyl, aryl, aralkyl, (C\(_i\)-C\(_j\))cycloalkyl, (C\(_3\)-C\(_6\))cycloalkyl(C\(_i\)-C\(_j\))alkyl, (C\(_3\)-C\(_6\))heterocycloalkyl, (C\(_3\)-C\(_6\))heterocycloalkyl(C\(_i\)-C\(_j\))alkyl, heteroaryl, heteroaralkyl, (C\(_i\)-C\(_j\))carboxyalkyl, arylalkyl(C\(_i\)-C\(_j\))alkyl, -alkylene-NR'R'', wherein R' and R'' are each independently hydrogen, (C\(_i\)-C\(_j\))alkyl, or taken together with the nitrogen to which they are attached, form a 3,
4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R"", wherein R"" is hydrogen or (Ci-C₆)alkyl; R₁ is optionally substituted with 1, 2 or 3 (d-C₆)alkyl, (Ci-C₆)alkoxy or (Ci-C₆)haloalkyl or 1, 2 or 3 groups independently selected from Rₐ;
R₂ is hydrogen, (Ci-C₆)alkyl, aryl, aralkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₆-C₆)alkyl, (C₃-C₆)cycloalkyl, heterocycloalkyl, heteroaryl, heteroaralkyl, (Ci-C₆)carboxyalkyl, aryloxy(Ci-C₆)alkyl, -alkylene-NR'R", wherein R' and R" are each independently hydrogen, (Ci-C₆)alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R"", wherein R"" is hydrogen or (Ci-C₆)alkyl; R₂ is optionally substituted with 1, 2 or 3 (d-C₆)alkyl, (Ci-C₆)alkoxy or (Ci-C₆)haloalkyl or 1, 2 or 3 groups independently selected from Rₐ;
R₃ is hydrogen or (Ci-C₆)alkyl;
m is 0, 1, or 2;
X is absent, -CONR₄⁺, Or-SO₂⁻, -SO₂NR₄⁺, or -COO⁻;
R₆ is hydrogen or (Ci-C₆)alkyl;
R₇ is hydrogen, (Ci-C₆)alkyl, (C₃-C₆)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups independently selected from Rₐ or in which Rₙ is hydrogen or (Ci-C₆)alkyl; R₁₂ is hydrogen, (Ci-C₆)alkyl, -CO(d-C₆)alkyl, -CO(Ci-C₆)cycloalkyl, -CO(Ci-C₆)heterocycloalkyl, -CO(Ci-C₆)aryl, -CO(Ci-C₆)heteroaryl, cycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups independently selected from Rₐ; or Rₙ and R₁₂ can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3 heteroatoms and optionally substituted with Rₐ;
R₆ is hydrogen or (Ci-C₆)alkyl;
R₁ and R₈ are each independently hydrogen, halogen, (Ci-C₆)alkyl or (Ci-
Ce)alkoxy, either of which may be optionally substituted on carbon with 1, 2, or
3 groups independently selected from R₉;
R₉ is hydrogen, halo or (Ci-C₆)alkyl;
R₁₀ is hydrogen or (Ci-Ce)alkyl; or
R₉ and R₁₀ together with the atoms to which they are attached, form a 4-8
membered ring, optionally substituted on carbon with 1, 2, or 3 groups selected
from halo,
(Ci-C₆)alkyl, and -O-(d-C₆)alkyl, -S-(d-C₆)alkyl, any of which may be
optionally substituted on carbon with 1, 2, or 3 halo, or taken together with the
attached carbon form C=O;
(A) is aryl, aryloxy, heteroaryl, cycloalkyl, or heterocycloalkyl;
at least two of three of Z₁, Z₂, and Z₃ are N and the other is C-R₄, wherein R₄ is
hydrogen, halogen, (Ci-Ce)alkyl, or (Ci-C₆)alkoxy;
R₄ is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino,
(Ci-C₆)alkyl-NH, ((Ci-C₆)alkyl)₂-N, aryl, heteroaryl, (C₃-C₇)cycloalkyl, (C₁-
C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (Ci-Ce)alkoxy, (C₂-C₆)alkenyloxy, (C₁-
C₆)alkynylthio, (Ci-Ce)alkylsulfanyl, (Ci-Ce)alkylsulfonyl, amino, (Ci-Ce)alkylamino, di-[[(Ci-C₆)alkyl]amino, formyl, -C(=O)(Ci-C₆)alkyl,
-C(=N)(Ci-C₆)alkyl, carboxy, CO₂-(d-C₆)alkyl, CONH₂, -C(=N)NH₂, -
C(=N)NH(Ci-C₆)alkyl, -CN=N(N(Ci-C₆)alkyl)₂, CONH(Ci-C₆)alkyl, C(O(N((d-
C₆)alkyl)_2, -OC(O)(C₁-C₆)alkyl, -OC(O)NH(C₁-C₆)alkyl, -
OC(O)NH((Ci-C₆)alkyl)₂, -NHCO(O)(Ci-C₆)alkyl, -N(Ci-C_e)alkyl-C(O)(Ci-
C₆)alkyl, -NH-C(O)NH₂, -N(d-C₆)alkyl-C(O)NH₂, N(Ci-C₆)alkyl-C(O)NH(d-
C₆)alkyl, N(Ci-C_e)alkyl-C(O)NH(Ci-C₆)alkyl)₂, -NH-C(O)NH(d-C₆)alkyl)₂, N-
(Ci-C₆)alkylsulfamoyl, N,N-di-[(d-C₆)alkyl]sulfamoyl, (C₁-
C₆)alkylsulfanilamino, or N-(Ci-C₆)alkyl-(Ci-C₆)alkylsulfanilamino, any of
which may be optionally substituted on carbon with R₅, and
R₅ is halogen, trifluoromethyl, trifluoromethoxy, (Ci-C₆)alkyl, amino, cyano,
nitro, or hydroxyl.
In one embodiment, the invention is directed to a compound of formula II

or a pharmaceutically acceptable salt thereof, wherein:

\( R_1 \) is hydrogen, (C\(_1\)-C\(_6\))alkyl, aryl, aralkyl, (C\(_3\)-C\(_6\))cycloalkyl, (C\(_3\)-C\(_6\))cycloalkyl(C\(_1\)-C\(_6\))alkyl, (C\(_3\)-C\(_6\))heterocycloalkyl, (C\(_3\)-C\(_6\))heterocycloalkyl(Ci-Ce)alkyl, heteroaryl, heteroaralkyl, (Ci-Ce)carboxyalkyl, aryloxy(Ci-Ce)alkyl, -alkylene-NR'R'', wherein R' and R'' are each independently hydrogen, (Ci-Ce)alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R'''', wherein R'''' is hydrogen or (Ci-Ce)alkyl; \( R_1 \) is optionally substituted with 1, 2 or 3 (C\(_1\)-C\(_6\))alkyl, (C\(_1\)-C\(_6\))aryloxy or (C\(_1\)-C\(_6\))haloalkyl or 1, 2 or 3 groups independently selected from \( R_a \);

\( R_2 \) is hydrogen, (Ci-C\(_6\))alkyl, aryl, aralkyl, (C\(_3\)-C\(_6\))cycloalkyl, (C\(_3\)-C\(_6\))cycloalkyl(C\(_1\)-C\(_6\))alkyl, (C\(_3\)-C\(_6\))heterocycloalkyl, (C\(_3\)-C\(_6\))heterocycloalkyl(Ci-Ce)alkyl, heteroaryl, heteroaralkyl, (Ci-Ce)carboxyalkyl, aryloxy(Ci-Ce)alkyl, -alkylene-NR'R'', wherein R' and R'' are each independently hydrogen, (Ci-Ce)alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R'''', wherein R'''' is hydrogen or (Ci-Ce)alkyl; \( R_2 \) is optionally substituted with 1, 2 or 3 (d-C\(_6\))alkyl, (Ci-C\(_6\))aryloxy or (Ci-C\(_6\))haloalkyl or 1, 2 or 3 groups independently selected from \( R_a \);

or \( R_i \) and \( R_2 \) can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3 heteroatoms and optionally substituted with \( R_a \);

\( R_3 \) is hydrogen or (Ci-C\(_6\))alkyl;

\( m \) is 0, 1, or 2;

\( X \) is absent, -CONR\(_4\)'', -SOR\(_2\)', -SO\(_2\)NR\(_4\)'', or -COO-'';

\( R_4 \) is hydrogen or (Ci-C\(_6\))alkyl;
R₂ is hydrogen, (Ci-C₆)alkyl, (C₃-C₆)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups

\[
\begin{array}{c}
\text{R}_{12}^a \\
\text{R}_{12}^b \\
\text{R}_{12}^c \\
\text{R}_{12}^d \\
\end{array}
\]

independently selected from Rₐ or R₈ in which Rₙ is hydrogen or (Ci-C₆) alkyl; R₁₂ is hydrogen, (Ci-C₆) alkyl, -CO(Ci-C₆)alkyl, -CO(Ci-C₆)cycloalkyl, -CO(Ci-C₆)heterocycloalkyl, -CO(Ci-C₆) aryl, -CO(Ci-C₆)heteroaryl, cycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups independently selected from Ra; or Rₙ and R₁₂ can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3 heteroatoms and optionally substituted with Rₐ;

R₆ is hydrogen or (Ci-C₆)alkyl;
R₇ and R₈ are each independently hydrogen, halogen, (Ci-C₆)alkyl or (Ci-C₆)alkoxy, either of which may be optionally substituted on carbon with 1, 2, or 3 groups independently selected from Rₐ;
R₉ is hydrogen, halo or (Ci-C₆)alkyl;
R io is hydrogen or (Ci-C₆)alkyl; or
R₉ and R io together with the atoms to which they are attached, form a 4-8 membered ring, optionally substituted on carbon with 1, 2, or 3 groups selected from halo,
(Ci-C₆)alkyl, and -O-(Ci-C₆)alkyl, -S-(Ci-C₆)alkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 halo, or taken together with the attached carbon form C=O;

[A] is aryl, arylxxy, heteroaryl, cycloalkyl, or heterocycloalkyl;
at least two of three of Zi, Z₄, and Z₅ are N and the other is C-Rₒ, wherein Rₒ is hydrogen, halogen, (Ci-C₆)alkyl, or (Ci-C₆)alkoxy;
Rₐ is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, (Ci-C₆)alkyl-NH, ((Ci-C₆)alkyl)₂-N, aryl, heteroaryl, (C₃-C₆)cycloalkyl, (C₆-C₆)alkyl, (C₂-C₆)alkeny1, (C₂-C₆)alkynyl, (Ci-C₆)alkoxy, (Ci-C₆)alkenyloxy, (Ci-C₆)alkynlyloxy, (Ci-C₆)alkylthio, (Ci-C₆)alkylsulfinyl, (Ci-C₆)alkylsulfonyl, amino, (Ci-C₆)alkylamino, di-[(Ci-C₆)alkyl]amino, formyl, -C(=O)(Ci-C₆)alkyl, -C(=N)(Ci-C₆)alkyl, carboxy, CO₂(Ci-C₆)alkyl, CONH₂, -C(=N)NH₂, -C(=N)NH(Ci-C₆)alkyl, -C(=N)N(Ci-C₆)alkyl, CONH(Ci-C₆)alkyl, C0N((d-
C₆alkyl)₂, -OC(O)(Ci-C₆)alkyl, -OC(O)NH₂, -OC(O)NH(Ci-C₆)alkyl, -OC(O)NH(Ci-C₆)alkyl, -NH-C(O)alkyl-C(O) Ci-C₆alkyl, -N-d(C₆alkyl)-alkyl-C(O) NH₂, N(Ci-C₆)alkyl-C(O)NH(Ci-C₆)alkyl, N(Ci-C₆)alkyl-C(O)NH(Ci-C₆)alkyl, -NH-C(O)NH(Ci-C₆)alkyl)₂, N-(Ci-C₆)alkylsulfonyl, N.N-di[(Ci-C₆)alkyl]sulfamoyl, (C₁-C₆)alkylsulfonylamino, or N-Ci-C₆alkyl-(Ci-C₆)alkylsulfonylamino, any of which may be optionally substituted on carbon with R₃ and R₄ is halogen, trifluoromethyl, trifluoromethoxy, (Ci-C₆)alkyl, amino, cyano, nitro, or hydroxyl.

[0009] In one embodiment, the invention is directed to a compound of formula III:

III:

or a pharmaceutically acceptable salt thereof, wherein:

Y is H, halo, OR₁, SR₁, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, aryl, aralkyl, (C₃-C₆)cycloalkyl, heterocycloalkyl, heteroaryl, heteroaralkyl, or NR₁R₂;
R₁ is hydrogen, (C₁-C₆)alkyl, aryl, aralkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)cycloalkyl(C₁-C₆)cycloalkyl, heterocycloalkyl(C₁-C₆)cycloalkyl, heterocycloalkyl, heteroaryl, heteroaralkyl, (C₃-C₆)carboxyalkyl, ary10Xyl(C₁-C₆)alkyl, -alkylene-NR₁R₂, wherein R₁' and R₂' are each independently hydrogen, (C₃-C₆)cycloalkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R₂'', wherein R₂'' is hydrogen or (C₁-C₆)alkyl; R₁ is optionally substituted with 1, 2 or 3 (C₁-C₆)alkyl, (C₃-C₆)alkoxy or (C₃-C₆)alkoxyalkyl or 1, 2 or 3 groups independently selected from R₃;
R₂ is hydrogen, (C₁-C₆)alkyl, aryl, aralkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl(C₁-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)cycloalkyl(C₁-C₆)cycloalkyl, heterocycloalkyl(C₁-C₆)cycloalkyl, heterocycloalkyl(C₁-C₆)carboxyalkyl, ary10Xyl(C₁-C₆)alkyl, -alkylene-NR₁R₂, wherein R₁' and R₂' are each independently hydrogen, (C₃-C₆)cycloalkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R₂'', wherein R₂'' is hydrogen or (C₁-C₆)alkyl; R₂ is optionally substituted with 1, 2 or 3 (C₁-C₆)alkyl, (C₃-C₆)alkoxy or (C₃-C₆)alkoxyalkyl or 1, 2 or 3 groups independently selected from R₃;
alkyl, or taken together with the nitrogen to which they are attached, form a 3,
4, 5, or 6-membered saturated or partially unsaturated ring optionally containing
0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2,
or N-R”, wherein R” is hydrogen or (Ci-Cg)alkyl; R2 is optionally substituted
with 1, 2 or 3 (d-Cg)alkyl, (Ci-Cg)alkoxy or (Ci-Cg)haloalkyl or 1, 2 or 3 groups
independently selected from R'a;

or R1 and R2 can be taken together to form a 5-7 membered heterocycle having 1,
2 or 3 heteroatoms and optionally substituted with R’a;

R3 is hydrogen or (Ci-Cg)alkyl;
m is o, 1, or 2;

R4 is hydrogen or (Ci-Cg)alkyl;
R6 is hydrogen or (Ci-Cg)alkyl;

R7 and R8 are each independently hydrogen, halogen, (Ci-Cg)alkyl or (Ci-
Ce)alkoxy, either of which may be optionally substituted on carbon with 1, 2, or
3 groups independently selected from R'a;

R9 is hydrogen, halo or (Ci-Cg)alkyl;
Rio is hydrogen or (Ci-Cg)alkyl; or

R9 and R10 together with the atoms to which they are attached, form a 4-8
membered ring, optionally substituted on carbon with 1, 2, or 3 groups selected
from halo,

(Cr Cg)alkyl, and -O-(Cr Cg)alkyl, -S-(Cr Cg)alkyl, any of which may be
optionally substituted on carbon with 1, 2, or 3 halo, or taken together with the
attached carbon form C=O;

A

is aryl, aryloxy, heteroaryl, cycloalkyl, or heterocycloalkyl;

B

is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Rn is hydrogen or (Ci-Cg) alkyl; R12 is hydrogen, (Ci-Cg) alkyl, -CO(Ci-
Cg)alkyl, -CO(C1-Cg)cycloalkyl, -CO(Ci-Cg)heterocycloalkyl, -CO(Ci-Cg) aryl, -
CO(Ci-Cg)heteroaryl, cycloalkyl, aryl, or heteroaryl, any of which may be
optionally substituted with 1, 2, or 3 groups independently selected from Ra; or

Rn and R12 can be taken together to form a 5-7 membered heterocycle having 1,
2 or 3 heteroatoms and optionally substituted with R'a;
at least two of three of Zi, Z₂, and Z₃ are N and the other is C-Rₜ, wherein Rₜ is hydrogen, halogen, (Cᵢ-Cₖ)alkyl, or (Cᵢ-Cₖ)alkoxy;
Rₖ is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, (Cᵢ-Cₖ)alkyl-NH, ((Cᵢ-Cₖ)alkyl)₂-N, aryl, heteroaryl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (Cᵢ-C₆)alkoxy, (Cᵢ-C₆)alkynlyoxy, (Cᵢ-C₆)alkylthio, (Cᵢ-C₆)alkylsulfanyl, amino, (Cᵢ-C₆)alkylaminio, di-[(Cᵢ-C₆)alkyl]amino, formyl, -C(=O)(Cᵢ-C₆)alkyl, -C(=N)N(Cᵢ-C₆)alkyl, carboxy, CO₂(Cᵢ-C₆)alkyl, CONH₂, -C(=N)NH₂, -C(=N)NH(Cᵢ-C₆)alkyl, -C(=N)N(Cᵢ-C₆)alkyl, -CONH(Cᵢ-C₆)alkyl, CONH(Cᵢ-C₆)alkyl, CON((d-C₆)alkyl)₂, -OC(O)(Cᵢ-C₆)alkyl, -OC(O)NH₂, -OC(O)NH(Cᵢ-C₆)alkyl, -OC(O)N((Cᵢ-C₆)alkyl)₂, -OC(O)N(Cᵢ-C₆)alkyl, -OC(O)NH((Cᵢ-C₆)alkyl)₂, -NHC(O)(Cᵢ-C₆)alkyl, -N(N(Cᵢ-C₆)alkyl-C(O)(Cᵢ-C₆)alkyl, -NH-C(O)NH₂, -N(N-C₆)alkyl-C(O)NH₂, N(Cᵢ-C₆)alkyl-C(O)NH(d-C₆)alkyl, N(Cᵢ-C₆)alkyl-C(O)NH(Cᵢ-C₆)alkyl, -NH-C(O)NH(Cᵢ-C₆)alkyl, -N-(Cᵢ-C₆)alkylsulfamoyl, N,N-di-[(Cᵢ-C₆)alkyl]sulfamoyl, (Cᵢ-C₆)alkylsulfonamilo, or N-(Cᵢ-C₆)alkyl-(Cᵢ-C₆)alkylsulfonilamino, any of which may be optionally substituted on carbon with Rₛ, and
Rₜ is halogen, trifluoromethyl, trifluoromethoxy, (Cᵢ-C₆)alkyl, amino, cyano, nitro, or hydroxy.

[00010] In one embodiment, the invention is directed to a compound of formula IV:

![IV][1]

or a pharmaceutically acceptable salt thereof, wherein:

Y is H, halo, ORᵣ, SRᵣ, (d-C₆)alkyl, (C₃-C₆)cycloalkyl, aryl, aralkyl, (C₃-C₆)heterocycloalkyl, heteroaryl, heteroaralkyl, or NRᵣRᵣ₂;
Rᵣ is hydrogen, (Cᵢ-C₆)alkyl, aryl, aralkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(Cᵢ-C₆)alkyl, (C₅-C₆)heterocycloalkyl, (C₅-C₆)heterocycloalkyl(Cᵢ-C₆)alkyl, heteroaryl, heteroaralkyl, (Cᵢ-dicarboxyalkyl, aryloxy(Cᵢ-C₆)alkyl, alkylene-NRᵣRᵣ², wherein Rᵣ' and Rᵣ'' are each independently hydrogen, (Cᵢ-C₆)alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing
0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2,
or N-R””, wherein R”” is hydrogen or (Ci-Cφ)alkyl; R11 is optionally substituted
with 1, 2 or 3 (d-C 2)alkyl, (Ci-Cφ)alkoxy or (Ci-Cφ)haloalkyl or 1, 2 or 3 groups
independently selected from Rα:
R2 is hydrogen, (Ci-Cφ)alkyl, aryl, aralkyl, (C3-C6)cycloalkyl, (C3-
C6)cycloalkyl(Ci-Cφ)alkyl, (C3-C6)heterocycloalkyl, (C3-C6)heterocycloalkyl(Ci-
Ce)alkyl, heteroaryl, heteroaralkyl, (CrC φ)carboxyalkyl, aryloxycarbonylalkyl,
alkylene-NR”’R”, wherein R’ and R” are each independently hydrogen, (C1-
Ce)alkyl, or taken together with the nitrogen to which they are attached, form a 3,
4, 5, or 6-membered saturated or partially unsaturated ring optionally containing
0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2,
or N-R””, wherein R”” is hydrogen or (Q-Cejalkyl; R2 is optionally substituted
with 1, 2 or 3 (C1-Cφ)alkyl, (C1-Cφ)alkoxy or (Q-Cejialoalkyl or 1, 2 or 3 groups
independently selected from Rα:
or R1 and R2 can be taken together to form a 5-7 membered heterocycle having 1,
2 or 3 heteroatoms and optionally substituted with Rα:
R3 is hydrogen or (C1-Ce)alkyl;
m is 0, 1, or 2;
X is absent, -CONR ₄⁻, Or-SO ₂⁻, -SO ₂NRR⁻, or -COO⁻;
R4 is hydrogen or (C1-C6)alkyl;
R5 is hydrogen, (C1-C6)alkyl, (C3-C6)cycloalkyl, heterocycloalkyl, aryl, or
heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups
independently selected from Rα or
in which R11 is hydrogen or (C1-
C6) alkyl; R12 is hydrogen, (C1-C6) alkyl, -CO(C1-C6)alkyl, -CO(C1-
C6)cycloalkyl, -C0td-Cφeterocycloalkyl, -CO(C1-C6) aryl, -CO(C1-
C6)heteroaryl, cycloalkyl, aryl, or heteroaryl, any of which may be optionally
substituted with 1, 2, or 3 groups independently selected from Rα; or R11 and R12
can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3
heteroatoms and optionally substituted with Rα:
R6 is hydrogen or (Ci-Cφ)alkyl; n is 0, 1, 2 or 3;
R\textsubscript{7} and R\textsubscript{8} are each independently hydrogen, halogen, (Ci-C\textsubscript{6})alkyl or (Ci- Ce)alkoxy, either of which may be optionally substituted on carbon with 1, 2, or 3 groups independently selected from R\textsubscript{a};

\(A\) is aryl, aryloxy, heteroaryl, cycloalkyl, or heterocycloalkyl;

at least two of three of Z\textsubscript{1}, Z\textsubscript{2}, and Z\textsubscript{3} are N and the other is C-R\textsubscript{b}, wherein R\textsubscript{b} is hydrogen, halogen, (Ci-C\textsubscript{6})alkyl, or (CrC\textsubscript{6})alkoxy;

R\textsubscript{a} is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, (Ci-C\textsubscript{6})alkyl-NH, (((Ci-C\textsubscript{6})alkyl))\textsubscript{2}-N, aryl, heteroaryl, (C\textsubscript{3}-C\textsubscript{7})cycloalkyl, (C\textsubscript{1}- C\textsubscript{6})alkyl, (C\textsubscript{2}-C\textsubscript{6})alkenyl, (C\textsubscript{2}-C\textsubscript{6})alkynyl, (Ci-C\textsubscript{6})alkoxy, (C\textsubscript{1}- C\textsubscript{6})alkynyloxy, (Ci-C\textsubscript{6})alkylthio, (Ci-C\textsubscript{6})alkylsulfanyl, amino, (Ci-C\textsubscript{6})alkylamino, di-[(Ci-C\textsubscript{6})alkyl]amino, formyl, -C(=O)(Ci-C\textsubscript{6})alkyl, -C(=N)(Ci-C\textsubscript{6})alkyl, carboxy, CO\textsubscript{2}(Ci-C\textsubscript{6})alkyl, CONH\textsubscript{2}, -C(=N)NH\textsubscript{2}, -C=N(NH(Ci-C\textsubscript{6})alkyl)\textsubscript{2}, CONH(Ci-C\textsubscript{6})alkyl, CO\textsubscript{2}((Ci-C\textsubscript{6})alkyl), -OC(O)(Ci-C\textsubscript{6})alkyl, -OC(O)NH\textsubscript{2}, -OC(O)NH((Ci-C\textsubscript{6})alkyl)\textsubscript{2}, NHC((d- C\textsubscript{1}-C\textsubscript{6})alkyl)\textsubscript{2}, -NH-C(O)(Ci-C\textsubscript{6})alkyl, -N(Ci-C\textsubscript{6})alkyl-C(O)(Ci- C\textsubscript{6})alkyl, -NMe-C(O)(Ci-C\textsubscript{6})alkyl, -NMe-C(O)NH\textsubscript{2}, -NMe-C(O)NH((Ci-C\textsubscript{6})alkyl)\textsubscript{2}, NMe-NMe-[(Ci-C\textsubscript{6})alkyl]sulfamoyl, (C\textsubscript{1}- C\textsubscript{6})alkylsulfonylamino, or N-(Ci-C\textsubscript{6})alkyl-(Ci-C\textsubscript{6})alkylsulfonylamino, any of which may be optionally substituted on carbon with R\textsubscript{c}.

R\textsubscript{c} is halogen, trifluoromethyl, trifluoromethoxy, (Ci-Ce)alkyl, amino, cyano, nitro, or hydroxyl.

[00011] In another embodiment, the invention is directed to a compound of any of formulae I-IV, wherein the compound is selected from:
or a pharmaceutically acceptable salt thereof.
In another aspect, the invention is directed to a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound disclosed herein, e.g., a compound of formulae I-IV, or a pharmaceutically acceptable salt thereof.

[00013] In another aspect, the invention is directed to a method for treating or preventing an inflammatory disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein, e.g., a compound of formulae I-IV, or a pharmaceutically acceptable salt thereof.

[00014] In another aspect, the invention is directed to a method of treating a condition or disease mediated by aggrecanase, e.g., osteoarthritis, in a mammalian subject. The method comprises administering to the subject a therapeutically effective amount of a compound disclosed herein, e.g., a compound of formulae I-IV, or a pharmaceutically acceptable salt thereof.

[00015] In another aspect, the invention is directed to a method of treating a subject suffering from osteoarthritis, joint injury, reactive arthritis, acute pyrophosphate arthritis, psoriatic arthritis, or rheumatoid arthritis, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, e.g., a compound of formulae I-IV, or a pharmaceutically acceptable salt thereof.

[00016] In another aspect, the invention is directed to a process for making a compound disclosed herein, e.g., a compound of formulae I-IV, comprising the steps outlined in Schemes 1-8 infra.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[00017] In order to more clearly and concisely describe the subject matter of the claims, the following definitions are intended to provide guidance as to the meaning of specific terms used herein.

[00018] It is to be noted that the singular forms "a," "an," and "the" as used herein include "at least one" and "one or more" unless stated otherwise. Thus, for example, reference to "a pharmacologically acceptable carrier" includes mixtures of two or more carriers as well as a single carrier, and the like.

[00019] "Halogen" means fluoro, chloro, iodo, and bromo.
"Alkyl" includes both straight and branched chain alkyl groups. (Ci-Ce)alkyl means an alkyl group having 6 carbon atoms. Examples of alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl, t-hexyl.

The term "alkylene" used alone or as suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serves to links two structures together.

"Cycloalkyl" means a partially or fully saturated ring ring system. "(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl" means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

"Heterocycloalkyl" means a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or partially unsaturated and may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween.

"(Ci-C<sub>6</sub>)AlkOXY", "(C<sub>2</sub>-C<sub>6</sub>)alkenylolxy", and "(C<sub>2</sub>-C<sub>6</sub>)alkenyloxy" refer to alkyl, alkenyl, and alkylnyl groups as defined above that are attached to O. Examples include methoxy, ethoxy, vinyloxy, allyloxy, ethynyloxy, and 2-propynyloxy.

"(Ci-C<sub>6</sub>)Alkylthio" means an alkyl group attached to S. Examples include methylthio, ethylthio and propylthio.

"(Ci-C<sub>6</sub>)Alkylsulfanyl" means an alkyl group attached to SO. Examples include methylsulphinyl and ethylsulphinyl.

"(Ci-C<sub>6</sub>)Alkylsulfonyl" means an alkyl group attached to SO<sub>2</sub>. Examples include methylsulfonfonyl and ethylsulfonfonyl.

"Amino" means NH<sub>2</sub>.

"(Ci-C<sub>6</sub>)Alkylamino" means (C<sub>t</sub>-C<sub>6</sub>)alkyl-NH. Examples include methylamino, ethylamino, propylamino, isopropylamino and butylamino.

"(Ci-C<sub>6</sub>)alkyl(2) amino" means ((Ci-C<sub>6</sub>)alkyl)<sub>2</sub>-N. Examples include dimethylamino, diethylamino, N-ethyl- N-methylamino and diisopropylamino.

"Formyl" means C(=O)-H.

"(C<sub>2</sub>-C<sub>6</sub>)alkanoyl" means C(=O)-(d-C<sub>6</sub>)alkyl. Examples include acetyl and propionyl.
"Carboxy" means CO\textsubscript{2}H.

"(Ci-C\textsubscript{6})Alkoxycarbonyl" means CO\textsubscript{2}-(d-C\textsubscript{6})alkyl. Examples include methoxycarbonyl, ethoxycarbonyl, propoxy- carbonyl and tert-butoxycarbonyl.

"(Ci-C\textsubscript{6})Alkanoyloxy" means O-C(=O)-(Ci-C\textsubscript{6})alkyl. Examples include acetoxy and propionyloxy.

"Carbamoyl" means C(=O)NH\textsubscript{2}.

"N-(Ci-C\textsubscript{6})alkyl-carbamoyl" means C(=O)NH(Ci-C\textsubscript{6})alkyl. Examples include N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl.

"N-((Ci-C\textsubscript{6})alkyl)\textsubscript{2}-carbamoyl" means C(=O)N((Ci-C\textsubscript{6})alkyl)\textsubscript{2}. Examples include N,N- dimethylcarbamoyl, and N,N-diethylcarbamoyl.

"(C\textsubscript{2}-C\textsubscript{6})Alkanoylamino" means N-C(=O)-(C\textsubscript{r}C\textsubscript{6})alkyl. Examples include acetamido and propionamido.

"N-(Ci-C\textsubscript{6})alkyl-(C\textsubscript{2}-C\textsubscript{6})Alkanoylamino" means N(d-C\textsubscript{6})alkyl-C(=O)-(Ci-C\textsubscript{6})alkyl. Examples include N-methylacetamido and N-methylpropionamido.

"Carbamimidoyl" means C(=O)NH\textsubscript{2}.

"Ureido" means -NH-C(O)NH\textsubscript{2}.

"Sulfamoyl" means SO\textsubscript{2}NH\textsubscript{2}.

"N-(Ci-C\textsubscript{6})alkylsulfamoyl" means SO\textsubscript{2}NH(Ci-C\textsubscript{6})alkyl. Examples include N-methylsulfamoyl and N-ethyl-sulphamoyl.

"N,N-di-(Ci-C\textsubscript{6})alkylsulfamoyl" means SO\textsubscript{2}N((Ci-C\textsubscript{6})alkyl)\textsubscript{2}. Examples include N,N, dimethylsulfamoyl.

"(Ci-C\textsubscript{6})alkylsulfonylamino" means -NH-SO\textsubscript{2}-(C\textsubscript{r}C\textsubscript{6})alkyl.

"Arylsulfonylamino" means -NH-SO\textsubscript{2}-aryl.

"Aryl" means an optionally substituted monocyclic or bicyclic ring system containing at least one aromatic ring. Examples and suitable values of the term "aryl" are phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indyl and indenyl.

"Heteroaryl" means an optionally substituted monocyclic or bicyclic ring system containing at least one aromatic ring and at least one heteroatom selected independently from N, O or S. Examples of "heteroaryl" include thiophene, thi-enyl, pyridyl, thiazolyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxadiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolonyl, oxazolonyl, thiazolonyl, tetrazolyl and thiadiazolyl, benzoimidazolyl, benzooxazolyl, tetrahydrotriazolopyridyl.
tetrahydrotriazolopyrimidinyl, benzofuryl, indolyl, isoindolyl, pyridonyl, pyridazinyl, pyrimidinyl, imidazopyridyl, oxazolopyridyl, thiazolopyridyl, pyridyl, imidazopyridazinyl, oxazolopyridazinyl, thiazolopyridazinyl and purinyl.

[00050] "Aralkyl", "heteroaralkyl", and "cycloalkylalkyl" refer to a substituent that is attached via the alkyl group to an aryl, heteroaryl or cycloalkyl group.

[00051] Unless otherwise stated, a "5- or 6-membered ring" refers to aromatic and heteroaromatic rings, as well as carbocyclic and heterocyclic rings, which may be partially or fully saturated. Examples of such rings include, but are not limited to furyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrol, thiazolyl, thienyl, imidazolyl, imidazolidinyl, imidazolinyl, triazolyl, morpholiny, piperazinyl, piperidyl, piperidonyl, pyrazolyl, pyrazoliny, pyrrolidiny, pyrroliny, tetrahydropyran, thiomorpholinyl, phenyl, cyclohexyl, cyclopentyl and cyclohexenyl.

[00052] As used herein, the phrase "pharmaceutically acceptable salts" means derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, trifluoroacetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

[00053] The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or
acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

[00054] The compounds described herein may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like, can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

[00055] The term "substituted", as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the normal valency of the designated atom is not exceeded, and that the substitution results in a stable compound. When the substituted group is C=O, then 2 hydrogens on the carbon atom in question have been replaced.

[00056] When any variable such as n, x, R', or R_a occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R_a (that is, when n= 0, 1, or 2) then that group may optionally be substituted with up to two R_a groups and R_a at each occurrence is selected independently from the definition of R_a. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[00057] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then that substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then that substituent may be bonded via any atom of that substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.
"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective to modulate, e.g., inhibit, aggreganase activity in a subject. A therapeutically effective amount of a compound of the invention, as defined herein, may vary according to factors such as the disease state, age, and weight of the subject, and the ability of the compound to elicit a desired response in the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. An effective amount is also one in which any toxic or detrimental effects (e.g., side effects) of the compound are outweighed by the therapeutically beneficial effects.

A therapeutically effective amount of a compound of the invention (i.e., an effective dosage) may range from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 30 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including, but not limited to, the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present, if any. Moreover, treatment of a subject with a therapeutically effective amount of a compound of the invention can include a single treatment or, preferably, can include a series of treatments. In one example, a subject is treated with a compound of the invention in the range of about 0.1 and 20 mg/kg body weight, one time per week for about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of a compound used for treatment may increase or decrease over the course of a particular treatment.

Compounds of the Invention

In some aspects, the present invention is directed to compounds of formula I:

![Chemical Structure](image)
or a pharmaceutically acceptable salt thereof, wherein:

Y is H, halo, ORi, SRi, (d-C₈)alkyl, (C₅-C₆)cycloalkyl, aryl, aralkyl, (C₃-
C₆)heterocycloalkyl, heteroaryl, heteroaralkyl, or NR₁R₂;

R₁ is hydrogen, (C₁-C₆)alkyl, aryl, aralkyl, (C₃-C₆)cycloalkyl, (C₃-
C₆)cycloalkyl(C₁-C₆)alkyl, (C₃-C₆)heterocycloalkyl, (C₃-C₆)heterocycloalkyl(Ci-
Ce)alkyl, heteroaryl, heteroaralkyl, (C₁-C₆)carboxyalkyl, aryloxy(C₁-C₆)alkyl, -
alkylene-NR'R", wherein R' and R" are each independently hydrogen, (Ci-
Ce)alkyl, or taken together with the nitrogen to which they are attached, form a 3,
4, 5, or 6-membered saturated or partially unsaturated ring optionally containing
0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2,
or N-R'”, wherein R’’ is hydrogen or (C₁-C₆)alkyl; R₁ is optionally substituted
with 1, 2 or 3 (d-C₈)alkyl, (C₁-C₆)alkoxy or (C₁-C₆)haloalkyl or 1, 2 or 3 groups
independently selected from Rₐ₁;

R₂ is hydrogen, (C₁-C₆)alkyl, aryl, aralkyl, (C₃-C₆)cycloalkyl, (C₃-
C₆)cycloalkyl(C₁-C₆)alkyl, (C₃-C₆)heterocycloalkyl, (C₃-C₆)heterocycloalkyl(Ci-
Ce)alkyl, heteroaryl, heteroaralkyl, (C₁-C₆)carboxyalkyl, aryloxy(C₁-C₆)alkyl, -
alkylene-NR'R", wherein R' and R" are each independently hydrogen, (Ci-
Ce)alkyl, or taken together with the nitrogen to which they are attached, form a 3,
4, 5, or 6-membered saturated or partially unsaturated ring optionally containing
0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2,
or N-R’”, wherein R’’ is hydrogen or (C₁-C₆)alkyl; R₂ is optionally substituted
with 1, 2 or 3 (Cᵣ C₆)alkyl, (Cᵣ C₆)alkoxy or (Cᵣ C₆)haloalkyl or 1, 2 or 3 groups
independently selected from Rₐ₁;

or R₁ and R₂ can be taken together to form a 5-7 membered heterocycle with 1, 2
or 3 heteroatoms and optionally substituted with Rₐ₁;

R₃ is hydrogen or (C₁-C₆)alkyl;

m is 0, 1, or 2;

X is absent, -CONR₄⁺, -SO₂⁻, -SO₂NR₄⁺, or -COO⁻;

R₄ is hydrogen or (C₁-C₆)alkyl;

R₅ is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, heterocycloalkyl, aryl, or
heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups
independently selected from Rₐ or Rₐ in which Rₐ₁ is hydrogen or (C₁-C₆) alkyl; R₁₂ is hydrogen, (C₁-C₆) alkyl, -CO(C₁-C₆)alkyl, -CO(C₁-C₆)cycloalkyl, -CO(C₁-C₆)heterocycloalkyl, -CO(C₁-C₆)aryl, -CO(C₁-C₆)heteroaryl, cycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups independently selected from Rₐ; or Rₐ₁ and R₁₂ can be taken together to form a 5-7 membered heterocycle having 1, 2, or 3 heteroatoms and optionally substituted with Rₐ; R₆ is hydrogen or (C₁-C₆) alkyl; R₇ and R₈ are each independently hydrogen, halogen, (C₁-C₆)alkyl or (C₁-C₆)alkoxy, either of which may be optionally substituted on carbon with 1, 2, or 3 groups independently selected from Rₐ; R₉ is hydrogen, halo or (C₁-C₆)alkyl; R₁₀ is hydrogen or (Q-C₅)alkyl; or R₉ and R₁₀ together with the atoms to which they are attached, form a 4-8 membered ring, optionally substituted on carbon with 1, 2, or 3 groups selected from halo, (C₁-C₆)alkyl, and -O-(C₁-C₆)alkyl, -S-(C₁-C₆)alkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 halo, or taken together with the attached carbon form C=O;

A is aryl, aryloxy, heteroaryl, cycloalkyl, or heterocycloalkyl;
at least two of three of Z₁, Z₂, and Z₃ are N and the other is C-R₉b, wherein R₉b is hydrogen, halogen, (Q-C₅)alkyl, or (Q-C₅)alkoxy;
R₉ is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, (C₁-C₆)alkyl-NH, ((C₁-C₆)alkyl)₂-N, aryl, heteroaryl, (C₅-C₇)cycloalkyl, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (d-QOalkoxy, (C₂-C₆)alkenyloxy, (C₁-C₆)alkynloxy, (C₁-C₆)alkythio, (Q-C₅)alkylsulfinyl, (Q-QOalkylsulfonyl, amino, (CrC₅)alkylamino, di-IXCrC₅Oalkylamino, formyl, -(C=O)(C₁-C₆)alkyl, -C(=N)(d-C₆)alkyl, carboxy, CO₂(C₁-C₆)alkyl, CONH₂, -(Q=NNH)₂, -C(=N)NH(C₁-C₆)alkyl, -C(=N)N(C₁-C₆)alkyl)², CONH(C₁-C₆)alkyl, CON((C₁-C₆)alkyl)², -OC(O)(C₁-C₆)alkyl, -OC(O)NH₂, -OC(O)NH(C₁-C₆)alkyl, -OC(O)NH((C₁-C₆)alkyl)², -NHC(O)(d-C₆)alkyl, -N(C₁-C₆)alkyl-C(O)(C₁-C₆)alkyl,
C₆alkyl, -NH-C(O)NH₂, -N(C₆)alkyl-C(O)NH₂, N(C₆)alkyl-C(O)NH(d-C₆)alkyl, N(C₆)alkyl-C(O)NH(C₆)alkyl, -(NH-C(O)NH(C₆)alkyl)₂, N-(C₆)alkylsulfonyl, N,N-di-[(C₆)alkyl]sulfamoyl, (C₆)alkylsulfonylaminio, or N-(C₆)alkyl-(C₆)alkylsulfonylamino, any of which may be optionally substituted on carbon with R_c, and R_c is halogen, trifluoromethyl, trifluoromethoxy, (C₆)alkyl, amino, cyano, nitro, or hydroxyl.

In some embodiments, Y is selected from the group consisting of H, halo, ORi, (C₆)alkyl, and NRiR₂. In some embodiments, Y is H. In some embodiments, Y is Cl. In some embodiments, Y is OH. In some embodiments, Y is OMe. In some embodiments, Y is -NRiR₂, e.g., a compound of formula II.

In some embodiments, Ri is selected from the group consisting of hydrogen and (C₆)alkyl. In some embodiments, R₃ is hydrogen. In some embodiments, R₃ is methyl. In some embodiments, R₃ is ethyl.

In some embodiments, R₄ is hydrogen. In some embodiments, R₄ is methyl. In some embodiments, R₄ is ethyl. In some embodiments, R₄ is propyl.

In some embodiments, R₅ is methyl. In some embodiments, R₅ is ethyl. In some embodiments, R₅ is phenyl. In some embodiments, R₅ is substituted with 1 group selected from R_a or R_b. In some embodiments, -X-R₅ is -SO₂CH₃. In some embodiments, -X-R₅ is -COOH. In some embodiments, -X-R₅ is -C(CH₃)₃.

In some embodiments, Rn is hydrogen. In some embodiments, Rn is methyl. In some embodiments, R₁₂ is hydrogen. In some embodiments, R₁₂ is methyl. In some embodiments, R₁₂ is heteroaryl optionally substituted with 1 group selected from R_a. In some embodiments, R₁₂ is thiazole optionally substituted with 1 group selected from R_a. In some embodiments, R₁₂ is COCH₃.

In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2.
In some embodiments, $R_6$ is methyl. In some embodiments, $R_6$ is fluoro. In some embodiments, $R_6$ is chloro. In some embodiments, $R_6$ is hydrogen.

In some embodiments, $R_7$ is hydrogen. In some embodiments, $R_7$ is methoxy. In some embodiments, $R_7$ is methyl. In some embodiments, $R_7$ is halogen. In some embodiments, $R_7$ is chloro.

In some embodiments, $R_8$ is hydrogen. In some embodiments, $R_8$ is methoxy. In some embodiments, $R_8$ is methyl. In some embodiments, $R_8$ is halogen. In some embodiments, $R_8$ is chloro.

In some embodiments, $R_9$ is hydrogen. In some embodiments, $R_9$ is methyl. In some embodiments, $R_{10}$ is hydrogen. In some embodiments, $R_{10}$ is methyl. In some embodiments, $R_9$ and $R_{10}$ are taken together to form a 5-6 membered ring.

In some embodiments, $A$ is phenyl. In some embodiments, $A$ is pyridyl. In some embodiments, $A$ is cyclohexyl.

In some embodiments, $Z_1$ is $N$. In some embodiments, $Z_2$ is $N$. In some embodiments, $Z_3$ is $N$. In some embodiments, each of $Z_1$, $Z_2$ and $Z_3$ are independently $N$.

In some embodiments, $X$ is $\text{-SO}_2\text{-}$. In some embodiments, $X$ is $\text{-CONR}_4\text{-}$. In some embodiments, $X$ is $\text{-COO\text{-}}$. In some embodiments, $X$ is $\text{-SO}_2\text{NR}_4\text{-}$.

In some embodiments, $R_a$ is fluoro. In some embodiments, $R_a$ is chloro. In some embodiments, $R_a$ is methyl. In some embodiments, $R_a$ is ethyl. In some embodiments, $R_a$ is trifluoromethyl. In some embodiments, $R_a$ is methoxy. In some embodiments, $R_a$ is ethoxy. In some embodiments, $R_a$ is trifluoromethoxy. In some embodiments, $R_a$ is cyano. In some embodiments, $R_a$ is nitro. In some embodiments, $R_a$ is hydroxyl. In some embodiments, $R_a$ is amino. In some embodiments, $R_a$ is $\text{-NHCH}_3\text{-}$. In some embodiments, $R_a$ is $\text{-N(CH}_3)_2\text{\text{-}}$. In some embodiments, $R_a$ is phenyl. In some embodiments, $R_a$ is pyridyl. In some embodiments, $R_a$ is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, $R_a$ is vinyl, propenyl, or butenyl. In some embodiments, $R_a$ is acetylenyl, propynyl or butynyl. In some embodiments, $R_a$ is...
methylthio. In some embodiments, $R_a$ is methylsulfinyl. In some embodiments, $R_a$ is methylsulfonyl. In some embodiments, $R_a$ is formyl. In some embodiments, $R_a$ is -C(=O)CH$_3$. In some embodiments, $R_a$ is -C(=N)CH$_3$. In some embodiments, $R_a$ is carboxy. In some embodiments, $R_a$ is CO$_2$CH$_3$. In some embodiments, $R_a$ is CONH$_2$. In some embodiments, $R_a$ is -C(=N)NH$_2$. In some embodiments, $R_a$ is -C(=N)NH(CH$_3$)$_2$. In some embodiments, $R_a$ is CONH(CH$_3$)$_2$. In some embodiments, $R_a$ is CON(CH$_3$)$_2$. In some embodiments, $R_a$ is OC(O)(CH$_3$). In some embodiments, $R_a$ is -OC(O)NH$_2$. In some embodiments, $R_a$ is -OC(O)NH(CH$_3$)$_2$. In some embodiments, $R_c$ is chloro. In some embodiments, $R_c$ is fluoro. In some embodiments, $R_c$ is methyl. In some embodiments, $R_c$ is trifluoromethyl. In some embodiments, $R_c$ is trifluoromethoxy. In some embodiments, $R_c$ is cyano. In some embodiments, $R_c$ is nitro. In some embodiments, $R_c$ is hydroxyl.

[00076] In one embodiment, the compounds of the invention are compounds of formula IA

![Chemical structure of formula IA](image)

or pharmaceutically acceptable salts thereof.

[00077] In one embodiment, the compounds of the invention are compounds of formula IA-i

![Chemical structure of formula IA-i](image)

or pharmaceutically acceptable salts thereof.
In another embodiment, the compounds of the invention are compounds of formula IB or pharmaceutically acceptable salts thereof.

In another embodiment, compounds of the invention are compounds of formula IC or pharmaceutically acceptable salts thereof.

In yet another embodiment, compounds of the invention are compounds of formula ID or pharmaceutically acceptable salts thereof.

In a further embodiment, compounds of the invention are compounds of formula IE or pharmaceutically acceptable salts thereof.
In another embodiment, compounds of the invention are compounds of formula IF or pharmaceutically acceptable salts thereof.

In yet another embodiment, compounds of the invention are compounds of formula IG or pharmaceutically acceptable salts thereof.

In another embodiment, compounds of the invention are compounds of formula IH or pharmaceutically acceptable salts thereof.

In a further embodiment, compounds of the invention are compounds of formula IJ or pharmaceutically acceptable salts thereof.
In a further embodiment, compounds of the invention are compounds of formula IJ-i or pharmaceutically acceptable salts thereof.

In another embodiment, compounds of the invention are compounds of formula IK or pharmaceutically acceptable salts thereof.

In another embodiment, compounds of the invention are compounds of formula IK-i or pharmaceutically acceptable salts thereof.

In another embodiment, compounds of the invention are compounds of formula IK-ii or pharmaceutically acceptable salts thereof.
In another embodiment, compounds of the invention are compounds of formula IK-iii or pharmaceutically acceptable salts thereof.

In yet another embodiment, compounds of the invention are compounds of formula IL or pharmaceutically acceptable salts thereof.

In yet another embodiment, compounds of the invention are compounds of formula IL-i or pharmaceutically acceptable salts thereof.

In another embodiment, compounds of the invention are compounds of formula IM.
or pharmaceutically acceptable salts thereof.

[00094] In another embodiment, compounds of the invention are compounds of formula IM-i

![Chemical Structure IM-i](image)

or pharmaceutically acceptable salts thereof.

[00095] In one embodiment, the compounds of the invention are compounds of formula IN

![Chemical Structure IN](image)

or pharmaceutically acceptable salts thereof.

[00096] In another embodiment, the compounds of the invention are compounds of formula IO

![Chemical Structure IO](image)

or pharmaceutically acceptable salts thereof.

[00097] In another embodiment, compounds of the invention are compounds of formula IP

![Chemical Structure IP](image)

pharmaceutically acceptable salts thereof.
In one embodiment, the compounds of the invention are compounds of formula IQ or pharmaceutically acceptable salts thereof. In some embodiments R₅ is hydrogen. In some embodiments, R₅ is methyl.

In another embodiment, the compounds of the invention are compounds of formula IR or pharmaceutically acceptable salts thereof. In some embodiments R₅ is hydrogen. In some embodiments, R₅ is methyl.

The substituents and embodiments disclosed for the compounds of formulae IA-IR are the same as those disclosed herein for compounds of formula I.

In one embodiment, the invention is directed to a compound of formula II or a pharmaceutically acceptable salt thereof, wherein:

R₁ is hydrogen, (Ci-C₆)alkyl, aryl, aralkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(Ci-C₆)alkyl, (C₃-C₆)heterocycloalkyl, (C₃-C₆)heterocycloalkyl(Ci-Ce)alkyl, heteroaryl, heteroaralkyl, (Ci-C₆)carboxyalkyl, aryloxy(Ci-C₆)alkyl, -alkylene-NR'R”, wherein R’ and R” are each independently hydrogen, (Ci-Ce)alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2,
or N-R''', wherein R''' is hydrogen or (C\textsubscript{i}-C\textsubscript{6})alkyl; R\textsubscript{i} is optionally substituted with 1, 2 or 3 (d-C\textsubscript{6})alkyl, (C\textsubscript{i}-C\textsubscript{6})alkoxy or (C\textsubscript{i}-C\textsubscript{6})haloalkyl or 1, 2 or 3 groups independently selected from R\textsubscript{a};

R\textsubscript{2} is hydrogen, (C\textsubscript{i}-C\textsubscript{6})alkyl, aryl, aralkyl, (C\textsubscript{3}-C\textsubscript{6})cycloalkyl, (C\textsubscript{3}-C\textsubscript{6})cycloalkyl(C\textsubscript{i}-C\textsubscript{6})alkyl, (C\textsubscript{3}-C\textsubscript{6})heterocycloalkyl, (C\textsubscript{3}-C\textsubscript{6})heterocycloalkyl(C\textsubscript{i}-C\textsubscript{6})alkyl, heteroaryl, heteroaralkyl, (C\textsubscript{i}-C\textsubscript{6})carboxyalkyl, aryloxy(C\textsubscript{i}-C\textsubscript{6})alkyl, -alkylene-NR'R''', wherein R' and R''' are each independently hydrogen, (C\textsubscript{i}-C\textsubscript{6})alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R''', wherein R''' is hydrogen or (C\textsubscript{i}-C\textsubscript{6})alkyl; R\textsubscript{2} is optionally substituted with 1, 2 or 3 (d-C\textsubscript{6})alkyl, (C\textsubscript{i}-C\textsubscript{6})alkoxy or (C\textsubscript{i}-C\textsubscript{6})haloalkyl or 1, 2 or 3 groups independently selected from R\textsubscript{a};

or R\textsubscript{i} and R\textsubscript{2} can be taken together to form a 5-7 membered heterocycle with having 1, 2 or 3 heteroatoms and optionally substituted with R\textsubscript{a};

R\textsubscript{3} is hydrogen or (C\textsubscript{i}-C\textsubscript{6})alkyl;

m is 0, 1, or 2;

X is absent, -CONR\textsubscript{4}, -SO\textsubscript{2}, -SO\textsubscript{2}NR\textsubscript{4}, or -COO-;

R\textsubscript{4} is hydrogen or (C\textsubscript{i}-C\textsubscript{6})alkyl;

R\textsubscript{5} is hydrogen, (C\textsubscript{i}-C\textsubscript{6})alkyl, (C\textsubscript{3}-C\textsubscript{6})cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups

\[
\begin{array}{c}
\text{O} \\
\text{R}_{12}^\alpha - \overset{\text{O}}{\text{S}} - \overset{\text{1/2}}{\text{N}} - \text{R} \text{11} \\
\end{array}
\]

in which R\textsubscript{11} is hydrogen or (C\textsubscript{i}-C\textsubscript{6})alkyl; R\textsubscript{12} is hydrogen, (C\textsubscript{1}-C\textsubscript{6})alkyl, -CO(C\textsubscript{1}-C\textsubscript{6})alkyl, -CO(C\textsubscript{i}-C\textsubscript{6})cycloalkyl, -CO(C\textsubscript{i}-C\textsubscript{6})heteroaryl, cycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups independently selected from R\textsubscript{a}; or R\textsubscript{11} and R\textsubscript{12} can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3 heteroatoms and optionally substituted with R\textsubscript{a};

R\textsubscript{6} is hydrogen or (C\textsubscript{i}-C\textsubscript{6})alkyl;
R₁ and R₈ are each independently hydrogen, halogen, (Ci-C₆)alkyl or (Ci-
Ce)alkoxy, either of which may be optionally substituted on carbon with 1, 2, or
3 groups independently selected from R₂;
R₉ is hydrogen, halo or (Ci-C₆)alkyl;
R₁₀ is hydrogen or (Ci-Ce)alkyl; or
R₉ and R₁₀ together with the atoms to which they are attached, form a 4-8
membered ring, optionally substituted on carbon with 1, 2, or 3 groups selected
from halo,
(Ci-C₆)alkyl, and -O-(d-C ₆)alkyl, -S-(d-C ₆)alkyl, any of which may be
optionally substituted on carbon with 1, 2, or 3 halo, or taken together with the
attached carbon form C=O;
A is aryl, aryloxyl, heteroaryl, cycloalkyl, or heterocycloalkyl;
at least two of three of Z₁, Z₂, and Z₃ are N and the other is C-R₁₀, wherein R₁₀ is
hydrogen, halogen, (Ci-Ce)alkyl, or (Ci-Ce)alkoxy;
R₄ is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino,
(Ci-Ce)alkyl-NH, ((Ci-Ce)alkyl)₂-N, aryl, heteroaryl, (C₃-C₇)cycloalkyl, (C₁-
C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (Ci-Ce)alkoxy, (C₂-C₆)alkenylxly, (C₁-
C₆)alkynlyoxy, (Ci-Ce)alkylthio, (Ci-Ce)alkylsulfanyl, (Ci-Ce)alkylsulfonyl,
amino, (Ci-C₆)alkylamino, di-[(Ci-C₆)alkyl]amino, formyl, -C=O(Ci-Ce)alkyl,
-C(=N)(Ci-Ce)alkyl, carboxy, CO₂(d-C ₆)alkyl, CONH₂, -C(=N)NH₂, -
C(=N)NH(Ci-C₆)alkyl, -C(=N)NH(Ci-C₆)alkyl, CONH(Ci-C₆)alkyl, C(N((d-
C₆)alkyl)₂, -OC(O)(C₁-C₆)alkyl, -OC(O)NH(C₁-C₆)alkyl, -
OC(O)(NH((C₁-C₆)alkyl)₂, -NH-C(O)NH₂, -N(Ci-C₆)alkyl-C(O)(C₁-
C₆)alkyl, -NH-C(O)NH₂, -N((d-C₆)alkyl-C(O)NH₂, N(Ci-C₆)alkyl-C(O)NH(d-
C₆)alkyl, N(Ci-C₆)alkyl-C(O)NH(Ci-C₆)alkyl)₂, -NH-C(O)NH(d-C ₆)alkyl)₂, N-
(Ci-C₆)alkylsulfamoyl, N,N-di-[(d-C ₆)alkyl]sulfamoyl, (C₁-
C₆)alkylsulfonylamino, or N-(Ci-C₆)alkyl-(Ci-C₆)alkylsulfonylamino, any of
which may be optionally substituted on carbon with R₂, and
R₅ is halogen, trifluoromethyl, trifluoromethoxy, (Ci-C₆)alkyl, amino, cyano,
nitro, or hydroxyl.

[000102] In some embodiments, Rᵢ is selected from the group consisting of
hydrogen and (Ci-C₆)alkyl. In some embodiments, Rᵢ is hydrogen. In some
embodiments, Rᵢ is methyl. In some embodiments, Rᵢ is ethyl.
In some embodiments, \( R_2 \) is methyl. In some embodiments, \( R_2 \) is isopropyl. In some embodiments, \( R_2 \) is cyclohexyl. In some embodiments, \( R_2 \) is benzyl.

\[
\text{Me} \quad \text{N} \quad \text{N} \\
\text{Me} \quad \text{N} \quad \text{N} \\
\text{Me} \quad \text{N} \quad \text{N}
\]

In some embodiments, \( R_2 \) is phenyl. In some embodiments, \( R_2 \) is wherein "—" indicates the point of attachment. In some embodiments, \( R_2 \) is

\[
\text{Me} \quad \text{N} \quad \text{N} \\
\text{Me} \quad \text{N} \quad \text{N} \\
\text{Me} \quad \text{N} \quad \text{N}
\]

In some embodiments, \( R_2 \) is wherein "—" indicates the point of attachment. In some embodiments, \( R_2 \) is

\[
\text{Me} \quad \text{N} \quad \text{N} \\
\text{Me} \quad \text{N} \quad \text{N} \\
\text{Me} \quad \text{N} \quad \text{N}
\]

\[ \text{R}_2 \text{ is} \]

In some embodiments, \( R_3 \) is hydrogen. In some embodiments, \( R_3 \) is methyl. In some embodiments, \( R_3 \) is ethyl.

\[ \text{R}_3 \text{ is} \]

In some embodiments, \( R_3 \) is hydrogen. In some embodiments, \( R_3 \) is methyl.

\[ \text{R}_3 \text{ is} \]

In some embodiments, \( R_3 \) is hydrogen. In some embodiments, \( R_3 \) is methyl.

\[ \text{R}_3 \text{ is} \]

In some embodiments, \( R_3 \) is hydrogen. In some embodiments, \( R_3 \) is methyl.

\[ \text{R}_3 \text{ is} \]

In some embodiments, \( R_3 \) is hydrogen. In some embodiments, \( R_3 \) is methyl.

\[ \text{R}_3 \text{ is} \]

In some embodiments, \( R_3 \) is hydrogen. In some embodiments, \( R_3 \) is methyl.

\[ \text{R}_3 \text{ is} \]

In some embodiments, \( R_3 \) is hydrogen. In some embodiments, \( R_3 \) is methyl.

\[ \text{R}_3 \text{ is} \]

In some embodiments, \( R_3 \) is hydrogen. In some embodiments, \( R_3 \) is methyl. Optionally substituted with 1 group selected from \( R_a \) or 

\[
\text{O} \\
\text{O=SO}_2 \\
\text{N} \\
\text{R}_{12} \\
\text{N} \\
\text{R}_{11}
\]

In some embodiments, \( -X-R_5 \) is \( \text{SO}_2\text{CH}_3 \). In some embodiments, \( -X-R_5 \) is \( \text{COOH} \). In some embodiments, \( -X-R_5 \) is \( \text{C(CH}_3)_3 \).

\[ \text{R}_5 \text{ is} \]

In some embodiments, \( R_n \) is hydrogen. In some embodiments, \( R_n \) is methyl. In some embodiments, \( R_{12} \) is hydrogen. In some embodiments, \( R_{12} \) is methyl.
In some embodiments, R₁₂ is heteroaryl optionally substituted with 1 group selected from Rₐ. In some embodiments, R₁₂ is thiaizazole optionally substituted with 1 group selected from Rₐ.

In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2.

In some embodiments, R₆ is methyl. In some embodiments, R₆ is fluoro. In some embodiments, R₆ is chloro. In some embodiments, R₆ is hydrogen.

In some embodiments, R₇ is hydrogen. In some embodiments, R₇ is methoxy. In some embodiments, R₇ is methyl. In some embodiments, R₇ is halogen. In some embodiments, R₇ is chloro.

In some embodiments, R₈ is hydrogen. In some embodiments, R₈ is methoxy. In some embodiments, R₈ is methyl. In some embodiments, R₈ is halogen. In some embodiments, R₈ is chloro.

In some embodiments, R₉ is hydrogen. In some embodiments, R₉ is methyl. In some embodiments, R₁₀ is hydrogen. In some embodiments, R₁₀ is methyl. In some embodiments, R₉ and R₁₀ are taken together to form a 5-6 membered ring.

In some embodiments, A is phenyl. In some embodiments, A is pyridyl. In some embodiments, A is cyclohexyl.

In some embodiments, Z₁ is N. In some embodiments, Z₂ is N. In some embodiments, Z₃ is N. In some embodiments, each of Z₁, Z₂ and Z₃ are independently N.

In some embodiments, X is -SO₂-. In some embodiments, X is -CONR₄-. In some embodiments, X is -COO-. In some embodiments, X is -SO₂NR₄⁻.

In some embodiments, Rₐ is fluoro. In some embodiments, Rₐ is chloro. In some embodiments, Rₐ is methyl. In some embodiments, Rₐ is ethyl. In some embodiments, Rₐ is trfluoromethyl. In some embodiments, Rₐ is methoxy. In some embodiments, Rₐ is ethoxy. In some embodiments, Rₐ is trifluoromethoxy. In some

-42-
embodiments, Rₐ is cyano. In some embodiments, Rₐ is nitro. In some embodiments, Rₐ is hydroxyl. In some embodiments, Rₐ is amino. In some embodiments, Rₐ is -NHCH₃. In some embodiments, Rₐ is -N(CH₃)₂. In some embodiments, Rₐ is phenyl. In some embodiments, Rₐ is pyridyl. In some embodiments, Rₐ is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, Rₐ is vinyl, propenyl, or butenyl. In some embodiments, Rₐ is acetylenyl, propynyl or butynyl. In some embodiments, Rₐ is methylthio. In some embodiments, Rₐ is methylsulfinyl. In some embodiments, Rₐ is methylsulfonyl. In some embodiments, Rₐ is formyl. In some embodiments, Rₐ is -CC=O)CH₃. In some embodiments, Rₐ is -C(=N)CH₃. In some embodiments, Rₐ is carboxy. In some embodiments, Rₐ is CO₂CH₃. In some embodiments, Rₐ is CONH₂. In some embodiments, Rₐ is -C(=N)NH₂. In some embodiments, Rₐ is -C(=N)NH(CH₃). In some embodiments, Rₐ is -C(=N)N(CH₃)₂. In some embodiments, Rₐ is CONH(CH₃). In some embodiments, Rₐ is CON(CH₃)₂. In some embodiments, Rₐ is OC(O)(CH₃). In some embodiments, Rₐ is -OC(O)NH₂. In some embodiments, Rₐ is -OC(O)NH(CH₃). In some embodiments, Rₐ is chloro. In some embodiments, Rₐ is fluoro. In some embodiments, Rₐ is methyl. In some embodiments, Rₐ is trifluoromethyl. In some embodiments, Rₐ is trifluoromethoxy. In some embodiments, Rₐ is cyano. In some embodiments, Rₐ is nitro. In some embodiments, Rₐ is hydroxyl.

In one embodiment, compounds of the invention are compounds of formula HA

![Chemical Structure]

or pharmaceutically acceptable salts thereof.

In another embodiment, compounds of the invention are compounds of formula HB
or pharmaceutically acceptable salts thereof.

[000120] In yet another embodiment, compounds of the invention are compounds of formula H C

or pharmaceutically acceptable salts thereof.

[000121] In a further embodiment, compounds of the invention are compounds of formula H D

or pharmaceutically acceptable salts thereof.

[000122] In another embodiment, compounds of the invention are compounds of formula H E
or pharmaceutically acceptable salts thereof.

[000123] In another embodiment, compounds of the invention are compounds of formula HF

![Formula HF]

or pharmaceutically acceptable salts thereof.

[000124] In yet another embodiment, compounds of the invention are compounds of formula HG

![Formula HG]

or pharmaceutically acceptable salts thereof.

[000125] In another embodiment, compounds of the invention are compounds of formula IIH

![Formula IIH]

or pharmaceutically acceptable salts thereof.

[000126] In another embodiment, compounds of the invention are compounds of formula IU
or pharmaceutically acceptable salts thereof.

[000127] In yet another embodiment, compounds of the invention are compounds of formula HK

or pharmaceutically acceptable salts thereof.

[000128] In another embodiment, compounds of the invention are compounds of formula HL

or pharmaceutically acceptable salts thereof.

[000129] In a further embodiment, compounds of the invention are compounds of formula IIM

or pharmaceutically acceptable salts thereof.
In another embodiment, compounds of the invention are compounds of formula UN or pharmaceutically acceptable salts thereof.

The substituents and embodiments disclosed for the compounds of formulae IIA-IIN are the same as those disclosed herein for compounds of formula II.

In one embodiment, the invention is directed to a compound of formula III:

Y is H, halo, ORi, SRi, (d=Ci-C6)alkyl, (C3-C6)cycloalkyl, aryl, aralkyl, (C3-C6)heterocycloalkyl, heteroaryl, heteroaralkyl, or NR1,R2;
Ri is hydrogen, (Ci-C6)alkyl, aralkyl, (C3-C6)cycloalkyl, (C3-C6)cycloalkyl(Ci-C6)alkyl, (C3-C6)cycloalkyl(Ci-C6)cycloalkyl(Ci-C6)alkyl, heteroaryl, heteroaralkyl, (Ci-C6)carboxyalkyl, aryloxy(Ci-C6)alkyl, alkylene-NR'R", wherein R' and R" are each independently hydrogen, (Ci-C6)alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R"", wherein R"" is hydrogen or (Ci-C6)alkyl; Ri is optionally substituted with 1, 2 or 3 (d=Ci-C6)alkyl, (Ci-C6)alkoxy or (Ci-C6)haloalkyl or 1, 2 or 3 groups independently selected from R1i;
R2 is hydrogen, (Ci-C6)alkyl, aralkyl, (C3-C6)cycloalkyl, (C3-C6)cycloalkyl(Ci-C6)alkyl, (C3-C6)heterocycloalkyl, (C3-C6)heterocycloalkyl(Ci-C6)alkyl, or pharmaceutically acceptable salts thereof.
Ce)alkyl, heteroaryl, heteroaralkyl, (Ci-C₆)carboxyalkyl, aryloxy(Ci-C₆)alkyl, alkylene-NR'R", wherein R' and R" are each independently hydrogen, (Ci-Ce)alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R"", wherein R"" is hydrogen or (Ci-C₆)alkyl; R₂ is optionally substituted with 1, 2 or 3 (Ci-C₆)alkyl, (Ci-C₆)alkoxy or (Ci-C₆)haloalkyl or 1, 2 or 3 groups independently selected from Rₐ;
or R₁ and R₂ can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3 heteroatoms and optionally substituted with Rₐ;
R₃ is hydrogen or (Ci-C₆)alkyl;
m is 0, 1, or 2;
R₄ is hydrogen or (Ci-C₆)alkyl;
R₅ is hydrogen or (Ci-C₆)alkyl;
R₇ and R₈ are each independently hydrogen, halogen, (Ci-C₆)alkyl or (Ci-Ce)alkoxy, either of which may be optionally substituted on carbon with 1, 2, or 3 groups independently selected from Rₐ;
R₉ is hydrogen, halo or (Ci-C₆)alkyl;
R₁₀ is hydrogen or (Ci-C₆)alkyl; or
R₉ and R₁₀ together with the atoms to which they are attached, form a 4-8 membered ring, optionally substituted on carbon with 1, 2, or 3 groups selected from halo,
(Ci-C₆)alkyl, and -O-(d-C₆)alkyl, -S-(d-C₆)alkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 halo, or taken together with the attached carbon form C=O;

A is aryl, aryloxy, heteroaryl, cycloalkyl, or heterocycloalkyl;

B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

Rn is hydrogen or (Ci-C₆) alkyl; R₁₂ is hydrogen, (Ci-C₆) alkyl, -CO(Ci-C₆)alkyl, -CO(Ci-C₆)cycloalkyl, -CO(Ci-C₆)heterocycloalkyl, -CO(Ci-C₆) aryl, -CO(Ci-C₆)heteroaryl, cycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups independently selected from Ra; or
RN and R\textsubscript{12} can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3 heteroatoms and optionally substituted with R\textsubscript{q};
at least two of three of Z\textsubscript{1}, Z\textsubscript{2}, and Z\textsubscript{3} are N and the other is C-R\textsubscript{b}, wherein R\textsubscript{b} is hydrogen, halogen, (Ci-C\textsubscript{6})alkyl, or (Ci-C\textsubscript{6})alkoxy;
R\textsubscript{a} is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, (Ci-C\textsubscript{6})alkyl-NH, ((Ci-C\textsubscript{6})alkyl)\textsubscript{2}-N, aryl, heteroaryl, (C\textsubscript{3}-C\textsubscript{7})cycloalkyl, (C\textsubscript{1}-
C\textsubscript{6})alkyl, (C\textsubscript{2}-C\textsubscript{6})alkenyl, (C\textsubscript{2}-C\textsubscript{6})alkynyl, (C\textsubscript{1}-C\textsubscript{6})alkoxy, (C\textsubscript{1}-
C\textsubscript{6})alkenyl, (C\textsubscript{1}-C\textsubscript{6})alkynyl, (C\textsubscript{1}-
C\textsubscript{6})alkylthio, (C\textsubscript{1}-C\textsubscript{6})alkylsulfanyl, (C\textsubscript{1}-C\textsubscript{6})alkylsulfanyl, amino, (Ci-C\textsubscript{6})alkylamino, di-[(Ci-C\textsubscript{6})alkyl]amino, formyl, -C(=O)(Ci-C\textsubscript{6})alkyl, -C(=N)(Ci-C\textsubscript{6})alkyl, carboxy, CO\textsubscript{2}(Ci-C\textsubscript{6})alkyl, CONH\textsubscript{2}, -C(=N)NH\textsubscript{2}, -
C(=N)NH(Ci-C\textsubscript{6})alkyl, -C(=N)N(Ci-C\textsubscript{6})alkyl\textsubscript{2}, CONHCi-C\textsubscript{6})alkyl, CON(d-
C\textsubscript{6})alkyl\textsubscript{2}, -OC(O)(Ci-C\textsubscript{6})alkyl, -OC(O)NH\textsubscript{2}, -OC(O)NH(Ci-C\textsubscript{6})alkyl, -
OC(O)NH((Ci-C\textsubscript{6})alkyl)\textsubscript{2}, -NHC(O)(Ci-C\textsubscript{6})alkyl, -N(Ci-C\textsubscript{6})alkyl-C(O)(Ci-
C\textsubscript{6})alkyl, -NH-C(O)NH\textsubscript{2}, -N(N(Ci-C\textsubscript{6})alkyl-C(O)NH\textsubscript{2}, N(Ci-C\textsubscript{6})alkyl-C(O)NH(d-
C\textsubscript{6})alkyl, N(N(Ci-C\textsubscript{6})alkyl-C(O)NH(Ci-C\textsubscript{6})alkyl)\textsubscript{2}, -NH-C(O)NH(Ci-C\textsubscript{6})alkyl, N-
(Ci-C\textsubscript{6})alkylsulfamoyl, N,N-di-[(Ci-C\textsubscript{6})alkyl]sulfamoyl, (C\textsubscript{1}-
C\textsubscript{6})alkylsulfamyl, or N-(Ci-C\textsubscript{6})alkyl-(Ci-C\textsubscript{6})alkylsulfamylaminol, any of
which may be optionally substituted on carbon with R\textsubscript{c} and
R\textsubscript{c} is halogen, trifluoromethyl, trifluoromethoxy, (Ci-C\textsubscript{6})alkyl, amino, cyano, 
nitro, or hydroxyl.

[000133] In some embodiments, Y is selected from the group consisting of H, halo,
OR\textsubscript{1}, (CrC\textsubscript{6})alkyl, and NR\textsubscript{1}R\textsubscript{2}. In some embodiments, Y is H. In some embodiments, Y is Cl. In some embodiments, Y is OH. In some embodiments, Y is OMe. In some
embodiments, Y is -NR\textsubscript{1}R\textsubscript{2}.

[000134] In some embodiments, R\textsubscript{1} is selected from the group consisting of
hydrogen and (Ci-C\textsubscript{6})alkyl. In some embodiments, R\textsubscript{1} is hydrogen. In some
embodiments, R\textsubscript{1} is methyl. In some embodiments, R\textsubscript{1} is ethyl.

[000135] In some embodiments, R\textsubscript{2} is methyl. In some embodiments, R\textsubscript{2} is
isopropyl. In some embodiments, R\textsubscript{2} is cyclohexyl. In some embodiments, R\textsubscript{2} is benzyl.

In some embodiments, R\textsubscript{2} is phenyl. In some embodiments, R\textsubscript{2} is
wherein "—" indicates the point of attachment. In some embodiments, $R_2$ is

![Chemical Structure](image)

wherein "—" indicates the point of attachment. In some embodiments, $R_2$

is

![Chemical Structure](image)

wherein "—" indicates the point of attachment. In some embodiments, $R_2$

is

![Chemical Structure](image)

wherein "—" indicates the point of attachment.

[000136] In some embodiments, $R_3$ is hydrogen. In some embodiments, $R_3$ is methyl. In some embodiments, $R_3$ is ethyl.

[000137] In some embodiments, $R_4$ is hydrogen. In some embodiments, $R_4$ is methyl. In some embodiments, $R_4$ is ethyl. In some embodiments, $R_4$ is propyl.

[000138] In some embodiments, $R_n$ is hydrogen. In some embodiments, $R_n$ is methyl. In some embodiments, $R_{i2}$ is hydrogen. In some embodiments, $R_{i2}$ is methyl. In some embodiments, $R_{i2}$ is heteroaryl optionally substituted with 1 group selected from $R_{a'}$. In some embodiments, $R_{i2}$ is thiazole optionally substituted with 1 group selected from $R_{a'}$. In some embodiments, $R_{i2}$ is -COCH$_3$.

[000139] In some embodiments, $m$ is 0. In some embodiments, $m$ is 1. In some embodiments, $m$ is 2.

[000140] In some embodiments, $R_6$ is methyl. In some embodiments, $R_6$ is fluoro. In some embodiments, $R_6$ is chloro. In some embodiments, $R_6$ is hydrogen.

[000141] In some embodiments, $R_7$ is hydrogen. In some embodiments, $R_7$ is methoxy. In some embodiments, $R_7$ is methyl. In some embodiments, $R_7$ is halogen. In some embodiments, $R_7$ is chloro.

[000142] In some embodiments, $R_8$ is hydrogen. In some embodiments, $R_8$ is methoxy. In some embodiments, $R_8$ is methyl. In some embodiments, $R_8$ is halogen. In some embodiments, $R_8$ is chloro.
In some embodiments, \( R_9 \) is hydrogen. In some embodiments, \( R_9 \) is methyl. In some embodiments, \( R_{10} \) is hydrogen. In some embodiments, \( R_{10} \) is methyl. In some embodiments, \( R_9 \) and \( R_{10} \) are taken together to form a 5-6 membered ring.

In some embodiments, \( A \) is phenyl. In some embodiments, \( A \) is pyridyl. In some embodiments, \( B \) is cyclohexyl. In some embodiments, \( B \) is phenyl. In some embodiments, \( B \) is pyridyl. In some embodiments, \( B \) is cyclohexyl.

In some embodiments, \( Z_1 \) is \( N \). In some embodiments, \( Z_2 \) is \( N \). In some embodiments, \( Z_3 \) is \( N \). In some embodiments, each \( \text{Of} Z_1, Z_2 \) and \( Z_3 \) are independently \( N \).

In some embodiments, \( X \) is \(-\text{SO}_2\) -. In some embodiments, \( X \) is \(-\text{CONR}_4\) -. In some embodiments, \( X \) is \(-\text{COO}\) -.

In some embodiments, \( R_a \) is fluoro. In some embodiments, \( R_a \) is chloro. In some embodiments, \( R_a \) is methyl. In some embodiments, \( R_a \) is ethyl. In some embodiments, \( R_a \) is trifluoromethyl. In some embodiments, \( R_a \) is methoxy. In some embodiments, \( R_a \) is ethoxy. In some embodiments, \( R_a \) is trifluoromethoxy. In some embodiments, \( R_a \) is cyano. In some embodiments, \( R_a \) is nitro. In some embodiments, \( R_a \) is hydroxyl. In some embodiments, \( R_a \) is amino. In some embodiments, \( R_a \) is \(-\text{NHCH}_3\) -. In some embodiments, \( R_a \) is \(-\text{N(CHs)}_2\) -. In some embodiments, \( R_a \) is phenyl. In some embodiments, \( R_a \) is pyridyl. In some embodiments, \( R_a \) is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, \( R_a \) is vinyl, propenyl, or butenyl. In some embodiments, \( R_a \) is acetylenyl, propynyl or butynyl. In some embodiments, \( R_a \) is methylthio. In some embodiments, \( R_a \) is methylsulfanyl. In some embodiments, \( R_a \) is formyl. In some embodiments, \( R_a \) is \(-\text{C(=O)}\text{CH}_3\) -. In some embodiments, \( R_a \) is \(-\text{C(=N)}\text{CH}_3\) -. In some embodiments, \( R_a \) is carboxy. In some embodiments, \( R_a \) is \(\text{CO}_2\text{CH}_3\) -. In some embodiments, \( R_a \) is \(\text{CONH}_2\) -. In some embodiments, \( R_a \) is \(-\text{C(=N)}\text{NH}(\text{CH}_3)\) -. In some embodiments, \( R_a \) is \(-\text{C(=N)}\text{NH}(\text{CH}_3)\) -.
In some embodiments, $R_a$ is -C(=N)N(CH$_3$)$_2$. In some embodiments, $R_a$ is CONH(CH$_3$)$_2$. In some embodiments, $R_a$ is OC(O)(CH$_3$)$_2$. In some embodiments, $R_a$ is -OC(O)NH$_2$. In some embodiments, $R_a$ is -OC(O)NH(CH$_3$)$_2$.

[000148] In some embodiments, $R_c$ is chloro. In some embodiments, $R_c$ is fluoro. In some embodiments, $R_c$ is methyl. In some embodiments, $R_c$ is trifluoromethyl. In some embodiments, $R_c$ is trifluoromethoxy. In some embodiments, $R_c$ is cyano. In some embodiments, $R_c$ is nitro. In some embodiments, $R_c$ is hydroxyl.

[000149] In one embodiment, compounds of the invention are compounds of formula IIIA

![III A](image)

or pharmaceutically acceptable salts thereof.

[000150] In one embodiment, compounds of the invention are compounds of formula IIIB

![III B](image)

or pharmaceutically acceptable salts thereof.

[000151] In another embodiment, compounds of the invention are compounds of formula IIIC

![III C](image)
or pharmaceutically acceptable salts thereof.

[000152] In another embodiment, compounds of the invention are compounds of formula HII

![Chemical Structure](image)

or pharmaceutically acceptable salts thereof.

[000153] In another embodiment, compounds of the invention are compounds of formula HIE

![Chemical Structure](image)

or pharmaceutically acceptable salts thereof.

[000154] In another embodiment, compounds of the invention are compounds of formula III

![Chemical Structure](image)

or pharmaceutically acceptable salts thereof.

[000155] In another embodiment, compounds of the invention are compounds of formula IIIG

![Chemical Structure](image)
or pharmaceutically acceptable salts thereof.

The substituents and embodiments disclosed for the compounds of formulae IIIA-IIIG are the same as those disclosed herein for compounds of formula III.

In one embodiment, the invention is directed to a compound of formula IV or a pharmaceutically acceptable salt thereof, wherein:

- Y is H, halo, ORi, SRi, (d-C₈)alkyl, (C₃-C₆)cycloalkyl, aryl, aralkyl, (C₃-C₆)heterocycloalkyl, heteroaryl, heteroaralkyl, or NR₁R₂;
- R₁ is hydrogen, (Ci-C₆)alkyl, aryl, aralkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)heterocycloalkyl(Ci-C₆)alkyl, heteroaryl, heteroaralkyl, (C₃-C₆)carboxyalkyl, aryloxy(Ci-C₆)alkyl, -alkylene-NR'R'', wherein R' and R'' are each independently hydrogen, (C₃-C₆)alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R''', wherein R''' is hydrogen or (Ci-Ce)alkyl; R₁ is optionally substituted with 1, 2 or 3 (d-C₈)alkyl, (Cᵢ-Cᵦ)alkoxy or (Ci-C₆)haloalkyl or 1, 2 or 3 groups independently selected from Rₙ;
- R₂ is hydrogen, (Ci-C₆)alkyl, aryl, aralkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)heterocycloalkyl(Ci-C₆)alkyl, (C₃-C₆)heterocycloalkyl(Ci-Ce)alkyl, heteroaryl, heteroaralkyl, (C₃-C₆)carboxyalkyl, aryloxy(Ci-C₆)alkyl, -alkylene-NR'R'', wherein R' and R'' are each independently hydrogen, (Ci-
alkyl, or taken together with the nitrogen to which they are attached, form a 3,
4, 5, or 6-membered saturated or partially unsaturated ring optionally containing
0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2,
or N-R””, wherein R”” is hydrogen or (Ci-Cg)alkyl; R2 is optionally substituted
with 1, 2 or 3 (d-C g)alkyl, (Ci-Cg)alkoxy or (Ci-Cg)haloalkyl or 1, 2 or 3 groups
independently selected from Ra;
or R1 and R2 can be taken together to form a 5-7 membered heterocycle having 1,
2 or 3 heteroatoms and optionally substituted with R3a;
R3 is hydrogen or (Ci-Cg)alkyl;
m is 0, 1, or 2;
X is absent, -CONR4, Or-SO2, SO2NR4, or -COO-;
R4 is hydrogen or (Ci-Cg)alkyl;
R5 is hydrogen, (Ci-Cg)alkyl, (C3-Cg)cycloalkyl, heterocycloalkyl, aryl, or
heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups
\[
\begin{align*}
R_{12}^- & \quad N \quad R_{11}^- \\
O & \quad S \quad -\frac{1}{2}
\end{align*}
\]
in which R11 is hydrogen or (C1-Cg) alkyl; R12 is hydrogen, (C1-Cg) alkyl, -CO(C1-Cg)alkyl, -CO(C1-Cg)
Cg)cycloalkyl, -CO(C1-Cg)heterocycloalkyl, -CO(C1-Cg) aryl, -CO(C1-
Cg)heteroaryl, cycloalkyl, aryl, or heteroaryl, any of which may be optionally
substituted with 1, 2, or 3 groups independently selected from Ra; or R11 and R12
can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3
heteroatoms and optionally substituted with Ra;
R6 is hydrogen or (Ci-Cg)alkyl; n is 0, 1, 2 or 3;
R7 and R8 are each independently hydrogen, halogen, (C1-Cg)alkyl or (C1-
Cg)alkoxy, either of which may be optionally substituted on carbon with 1, 2, or
3 groups independently selected from Ra;
A is aryl, aryloxy, heteroaryl, cycloalkyl, or heterocycloalkyl;
at least two of three of Z1, Z2, and Z3 are N and the other is C-Rb, wherein Rb is
hydrogen, halogen, (CrCg)alkyl, or (CrCg)alkoxy;
R4 is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino,
(C1-Cg)alkyl-NH, ((C1-Cg)alkyl)2-N, aryl, heteroaryl, (C3-Cg)cycloalkyl, (C1-
Cg)alkyl, (C2-Cg)alkenyl, (C2-Cg)alkynyl, (C1-Cg)alkoxy, (C2-Cg)alkenyloxy, (C1-
C₆)alkynyloxy, (C₆)alkylthio, (C₆)alkylsulfanyl, (C₆)alkylsulfonyl, amino, (C₆)alkylamino, di-[(C₆)alkyl]amino, formyl, -C(=O)(d-C₆)alkyl, -C(=N)(C₆)alkyl, carboxy, CO₂(C₆)alkyl, CONH₂, -Q=N)NH₂, -C(=N)NH(C₆)alkyl, -C(=N)N(C₆)alkyl₂, CONH(C₆)alkyl, -CONH(C₆)alkyl, -OC(O)(C₆)alkyl, -OC(O)NH₂, -OC(O)NH(C₆)alkyl, -OC(O)NH((C₆)alkyl)₂, -NHC(O)(C₆)alkyl, -N(C₆)alkyl-C(O)(C₆)alkyl, -NHC(O)(C₆)alkyl, -NH-C(O)NH₂, -N(C₁-C₆)alkyl-C(O)NH₂, N(C₁-C₆)alkyl-C(O)NH(C₁-C₆)alkyl, -NH-C(O)NH(C₁-C₆)alkyl₂, N-(C₆)alkylsulfamoyl, N,N-di-[(C₆)alkyl]sulfamoyl, (C₁-C₆)alkylsulfonylamino, or N-(C₆)alkyl-(C₆)alkylsulfonylamino, any of which may be optionally substituted on carbon with Rₗ and Rₗ is halogen, trifluoromethyl, trifluoromethoxy, (C₆)alkyl, amino, cyano, nitro, or hydroxyl.

[000158] In another embodiment, the invention is directed to a compound of any of formulae I-III, wherein the compound is selected from:
<table>
<thead>
<tr>
<th>Chemical Structure 1</th>
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<tbody>
<tr>
<td>Chemical Structure 2</td>
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<td>Chemical Structure 3</td>
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<td>Chemical Structure 9</td>
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<tr>
<td>Chemical Structure 10</td>
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</tbody>
</table>
or a pharmaceutically acceptable salt thereof.
Biological Activity


The ADAM TS4 (aggrecanase) fluorogenic assay was performed using the WAAG-3R fluorescent substrate (Anaspec, Catalog # 60431-1 Abz-TEGARGSV-IDap(Dnp)-KK). The assay buffer contains 50mM HEPES (pH 7.5) 100mM NaCl, 5mM CaCl₂, 0.1% CHAPS, 5% Glycerol. The total reaction volume is 40µl. The aggrecanase enzyme (full length 68kDa supplied by GSK) is used at a final concentration of 48nM. The inhibitor compounds are re-suspended in 100% DMSO and then diluted with 1x assay buffer to a 10x concentration (10% DMSO). The aggrecanase enzyme is incubated with various inhibitor compound concentrations, shaking, for 30 minutes at room temperature. The reaction is initiated by adding the diluted WAAG-3R substrate (final concentration 25µM). The fluorescence was monitored at an excitation of 340nM and an emission of 420nM. The reaction is run at 37°C and readings are taken every 30 seconds for 1 hour. Activity is measured as the % inhibition using the following equation: 100*(1-(slope of enzyme + inhibitor/ slope of enzyme alone). Activities for invention compounds were measured as IC₅₀ values, which is the concentration of inhibitor that blocks enzyme activity to 50%

The compounds described herein had IC₅₀ values of 100 µM or less. For example:
<table>
<thead>
<tr>
<th>Structure 1</th>
<th>Structure 2</th>
<th>Structure 3</th>
<th>Structure 4</th>
<th>Structure 5</th>
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<tr>
<th>Chemical Structure</th>
<th>Note</th>
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<td><img src="image1" alt="Chemical Structure 1" /></td>
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<tr>
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<tr>
<td>Structure 1</td>
<td>Structure 2</td>
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</tbody>
</table>

**
* = IC_{50} of 0.001 - 0.050 µM
** = IC_{50} of 0.051 - 0.200 µM
*** = IC_{50} of 0.201-0.500 µM
**** = IC_{50} of 0.501-1.000 µM
***** = IC_{50} of 1.001-5.000 µM
****** = IC_{50} of 5.001-100.000 µM
Pharmaceutical Formulations

[000163] The compounds of the present invention can be administered orally using any pharmaceutically acceptable dosage form known in the art for such administration. The active ingredient can be supplied in solid dosage forms such as dry powders, granules, tablets or capsules, or in liquid dosage forms, such as syrups or aqueous suspensions. The active ingredient can be administered alone, but is generally administered with a pharmaceutical carrier. A valuable treatise with respect to pharmaceutical dosage forms is Remington's Pharmaceutical Sciences, Mack Publishing.

[000164] The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-inflammatory and anti-arthritic agent.

[000165] The compounds of this invention can be administered by any means that produces contact of the active agent with the agent’s site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

[000166] The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.
By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. For a normal male adult human of approximately 70 kg of body weight, this translates into a dosage of 70 to 1400 mg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as carrier materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate,
magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can 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 phosphatidylicholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide -phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyeptilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyanetals, polydihydropyrrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition. The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.
In general, water, suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Methods of Making Invention Compounds and Examples

Scheme 1 summarizes the preparation of the compounds of the invention.

**Scheme 1**

Preparation of 4-(aminomethyl)-Λ^-ethyl-Λ^-ro^-tolylbenzamide

A solution of 4-(Boc-aminomethyl)benzoic acid (1.0 g, 3.98 mmol, 1 equivalent), N-ethyl m-toluidine (614 mg, 4.54 mmol, 1.14 equivalents) and DMAP (98 mg, 0.80 mmol, 0.2 equivalent) in dichloromethane (15 ml) was cooled with stirring in
an ice bath. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI, 955 mg, 4.98 mmol, 1.25 equivalents) was added, and the reaction mixture was stirred at room temperature overnight. The solution was diluted with dichloromethane (50 ml), which was further washed with saturated sodium bicarbonate (25 ml), water (25 ml), salt (25 ml) and dried over MgSO₄. The solvent was removed in vacuo to give tert-butyl A-(ethyl(m-tolyl)carbamoyl)benzylcarbamate. Without purification, the acylation product was treated with 50% TFA in dichloromethane (25 ml) at room temperature for 20 minutes. The reaction mixture was condensed to give the yellow oil which was further purified by RP-HPLC (Luna, 5µ C8(2), 100x21mm, 10-40% CH₂CN/H₂O, 0.1% TFA, 20 min) to give the desired product as the TFA salt (1.172g, 77% in 2 steps). MS: calcd for C₁₇H₂₀N₂O⁺+H⁺ 269.36, found 269.20.

**Preparation of 2-(4,6-dichloro-1,3,5-triazin-2-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline**

A mixture of cyanuric chloride (520 mg, 2.82 mmol, lequiv) in CH₂CN/H₂O (1/1, 20 ml) was cooled to 0°C. 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (647.2 mg, 2.82 mmol, 1 equiv) was added. The reaction mixture was adjusted to a pH of about 9-10 using 1N NaOH. The reaction was stirred at cold for about 20 min, during which a white solid was formed. The solid was collected by filtration to give the desired product with >95% purity (755.5 mg, 79% yield). MS: calcd for C₁₄H₁₄Cl₂N₄O₂+H⁺ 341.06, found 341.19.

**Preparation of 2-(4,6-dichloro-1,3,5-triazin-2-yl)-1,2,3,4-tetrahydroisoquinoline**
A mixture of cyanuric chloride (544 mg, 2.95 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 20 ml) was cooled to 0°C. 1,2,3,4-Tetrahydroisoquinoline hydrochloride (500.5 mg, 2.95 mmol, 1 equivalent) was added. The reaction mixture was adjusted to a pH of about 9-10 using IN NaOH. The reaction was stirred at cold for 20 min, during which a white solid was formed. The solid was collected by filtration to give the desired product with >95% purity (774.5 mg, 93.5% yield). MS: calcd for C$_{12}$H$_{10}$Cl$_2$N$_4$+H$^+$ 281.04, found 281.19.

**Preparation of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(l H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-7-ethyl-N-rø-tolylbenzamide**

To a mixture of 2-(4,6-dichloro-1,3,5-triazin-2-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.15 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, ~ 4 ml) was added 4-(aminomethyl)-N-ethyl-N-m-tolylbenzamide as the TFA salt (58 mg, 0.15 mmol, 1 equivalent). The pH of the reaction mixture was adjusted with IN NaOH to about 9-10, and the reaction was stirred at room temperature overnight. LC-MS showed the complete conversion to the desired product. Without workup, the product in the reaction solution will be used directly for the next step. The pure product can be obtained through the purification with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 40-95% CH$_3$CN/H$_2$O, 0.1% TFA, 20 min). MS: calcd for C$_{31}$H$_{33}$ClN$_6$O$_3$+H$^+$ 573.24, found 573.3.

**Preparation of 4-((4-chloro-6-(3,4-dihydroisoquinolin-2(l H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-7-ethyl-N-rø-tolylbenzamide**
To a mixture of 2-(4,6-dichloro-1,3,5-triazin-2-yl)-1,2,3,4-tetrahydroisoquinoline (30 mg, 0.107 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 2 ml) was added A-(aminomethyl)-N-ethyl-N-m-tolylbenzamide as the TFA salt (41 mg, 0.107 mmol, 1 equivalent). The pH of the reaction mixture was adjusted with IN NaOH to about 9-10, and the reaction was stirred at room temperature overnight. LC-MS showed complete conversion to the desired product. Without workup, the product in the reaction solution will be used directly for the next step. The pure product can be obtained through the purification with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 40-95% CH$_3$CN/H$_2$O, 0.1% TFA, 20 min). MS: calcd for C29H29C1N6O$^+$/H 513.22, found 513.30.

**Preparation of 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1)$H$-yl)-6-(methylamino)-1,3,5-triazin-2-ylamino)methyl)-N^-ethyl-N^-rø-tolylbenzamide**

The above solution for the preparation of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1)$H$-yl)-1,3,5-triazin-2-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide (-0.03 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, - 0.8 ml) was treated with methylamine (40% in water, 16 µl, 0.20 mmol, 7 equivalents) at 80°C for 2 hours. The reaction mixture was condensed down to give the crude product which was further purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 10-60% CH$_3$CN/H$_2$O, 0.1% TFA, 16 min). MS: calcd for C32H37N7O3$^+$/H 568.70, found 568.40.

**Preparation of 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1)$H$-yl)-6-(2-(4-methylpiperazin-1-yl)ethylamino)-1,3,5-triazin-2-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide**
The solution for the preparation of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (0.293 mmol, 1 equivalent) in CH₃CN/H₂O (1/1, 10 ml) was treated with 2-(4-methyl-piperazin-1-yl)-ethylamine (168 µl, 1.172 mmol, 4 equivalents) at 80°C for 7 hours. The reaction mixture was condensed down to give the crude product which was further purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 10-60% CH₃CN/H₂O, 0.1% TFA, 16 min) to give the desired product as a TFA salt (76.4 mg, 33% yield in 2 steps). MS: calcd for C₃₈H₄₉N₉O₃+H⁺ 680.88, found 680.5.

**Example of a preparation of 4-((4-(3,4-dihydroisoquinolin-2(1H)-yl)-6-(2-(4-methylpiperazin-1-yl)ethylamino)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide**

To the solution of 4-((4-chloro-6-(3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (8 mg, 0.0156 mmol, 1 equivalent) in CH₃CN/H₂O (1/1, 1 ml) was added 2-(4-methyl-piperazin-1-yl)ethylamine (20 mg, 0.142 mmol, 9 equivalents). The reaction was heated at 80°C overnight. The reaction solution was condensed down to give the residue which was acidified and purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 20-80%
CH$_3$CN/H$_2$O, 0.1% TFA, 20 min) to give the desired product as a TFA salt. MS: calcd for C$_{36}$H$_{45}$N$_9$O$^+$$\cdot$H$^+$ 620.38, found 620.44.

**Example of a preparation of** 4-((4-(benzylamino)-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1-$H$)-yl)-1,3,5-triazin-2-ylamino)methyl)-$\Lambda^7$-ethyl-$\Lambda^7$-rø-tolylbenzamide

To the reaction solution for the preparation of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1-$H$)-yl)-1,3,5-triazin-2-ylamino)methyl)-$N$-ethyl-$N$-$m$-tolylbenzamide ($-0.03$ mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, - 0.8 ml) was added benzylamine (22 $\mu$L, 0.2 mmol, 6.7 equivalents). The reaction mixture was heated at 80$^\circ$C for 2 hours. The solution was condensed down to give the crude product which was further purified with RP-HPLC (Luna, 5$\mu$ C8(2), 100x21mm, 30-75% CH$_3$CN/H$_2$O, 0.1% TFA, 16 min). MS: calcd for C$_{38}$H$_{41}$N$_7$O$_3$+H$^+$ 644.80, found 644.5.

**Example of a preparation of** 4-((4-(benzylamino)-6-(3,4-dihydroisoquinolin-2(1-$H$)-yl)-1,3,5-triazin-2-ylamino)methyl)-$\Lambda^7$-ethyl-$\Lambda^7$-rø-tolylbenzamide

To the reaction solution for the preparation of 4-((4-chloro-6-(3,4-dihydroisoquinolin-2(1-$H$)-yl)-1,3,5-triazin-2-ylamino)methyl)-$N$-ethyl-$N$-$m$-tolylbenzamide ($-0.03$ mmol, 1 equivalent) in NMP (1 ml) was added benzylamine
(16.5 µl, 0.15 mmol, 5 equivalents). The reaction mixture was heated at 80°C for 3-4 hours. The solvent was evaporated in vacuo and the residue was further purified with PR-HPLC to give the desired product (4.54 mg). MS: calcd for C36H37N7O+H+ 584.75, found 584.5.

**Example of a preparation of 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1 H)-yl)-6-(2-(furan-2-yl)ethylamino)-1,3,5-triazin-2-ylamino)methyl)- N^-ethyl-N^-m- tolylbenzamide**

![Structure](image)

To the reaction solution for the preparation of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1 H)-yl)-1,3,5-triazin-2-ylamino)methyl)- N^-ethyl-N^-m- tolylbenzamide (-0.03 mmol, 1 equivalent) in CH₃CN/H₂O (1/1, - 0.8 ml) was added 2-furan-2-yl-ethylamine (22 mg, 0.2 mmol, 6.7 equivalents). The reaction mixture was stirred at 80°C for 2 hours. The solvent was evaporated and the residue was acidified and purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 30-80% CH₃CN/H₂O, 0.1% TFA, 16 min) to give the desired product. MS: calcd for C37H41N7O₄+H+ 648.79, found 648.4.

**Example of a preparation of 4-((4-(cyclohexylamino)-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1 H)-yl)-1,3,5-triazin-2-ylamino)methyl)- N^-ethyl-N^-m- tolylbenzamide**

![Structure](image)

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To the reaction solution for the preparation of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (-0.03 mmol, 1 equivalent) in CH₃CN/H₂O (1/1, - 0.8 ml) was added cyclohexylamine (24 µl, 0.21 mmol, 7 equivalents). The reaction was heated at 80°C for 2 hours. The solvent was evaporated *in vacuo* to give the residue which was further purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 30-80% CH₃CN/H₂O, 0.1% TFA, 16 min). MS: calcd for C37H45N7O3+H⁺ 636.82, found 636.5.

**Example of a preparation of** 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-6-(2-(thiophen-2-yl)ethylamino)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide

![Chemical Structure]

To the reaction solution for the preparation of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (-0.03 mmol, 1 equivalent) in NMP (1 ml) was added 2-thiopheneethylamine (19.5 mg, 0.15 mmol, 5 equivalents). The reaction mixture was heated at 80°C for 3-4 hours. The solvent was evaporated *in vacuo* to give the residue which was further purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 30-80% CH₃CN/H₂O, 0.1% TFA, 18 min). MS: calcd for C37H41N7O3S+H⁺ 664.85, found 664.4.

**Example of a preparation of** 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-6-(isopropylamino)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide
To the reaction solution for the preparation of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolyllbenzamide (-0.03 mmol, 1 equivalent) in NMP (1 ml) was added isopropylamine (9 mg, 0.15 mmol, 5 equivalents). The reaction mixture was heated at 80°C for 3-4 hours. The solvent was evaporated *in vacuo* to give the residue which was further purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 36-75% CH3CN/H2O, 0.1% TFA, 18 min). MS: calcd for C34H41N7O3+H+ 596.76, found 596.5.

**Example of a preparation of** 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-6-(phenylamino)-1,3,5-triazin-2-ylamino)methyl)-N^-ethyl-N^-rø-tolyllbenzamide

To the reaction solution for the preparation of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolyllbenzamide (-0.03 mmol, 1 equivalent) in NMP (1 ml) was added aniline (14 mg, 0.15 mmol, 5 equivalents). The reaction mixture was heated at 80°C for 3-4 hours. The solvent was evaporated *in vacuo* to give the residue which was further purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 36-70% CH3CN/H2O, 0.1% TFA, 18 min). MS: calcd for C37H39N7O3+H+ 630.77, found 630.5.
Example of a preparation of 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-6-(2-(dimethylamino)ethylamino)-1,3,5-triazin-2-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide

To the reaction solution for the preparation of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide (-0.058 mmol, 1 equivalent) in NMP (~1 ml) was added N,N-dimethylethlenediamine (52.8 mg, 0.6 mmol, -10 equivalents). The reaction mixture was heated at 80°C for 5 hours. The solution was neutralized with IN HCl. The solvent was evaporated in vacuo and the crude was purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 20-95% CH₃CN/H₂O, 0.1% TFA, 20 min) to give the desired product as a TFA salt (2.1 mg). MS: calcd for C35H44N8O3+H+ 625.80, found 625.42.

Example of a preparation of 4-((4-(3,4-dihydroisoquinolin-2(1H)-yl)-6-(2-(dimethylamino)ethylamino)-1,3,5-triazin-2-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide

The solution of 4-((4-chloro-6-(3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide (8 mg, 0.0156 mmol, 1 eq) in CH₃CN/H₂O (1/1, 2 ml) was treated with N,N-dimethylthlenediamine in CH₃CN (0.2 M, 650 µl, 0.13 mmol, 8.3 equivalents) at 80°C overnight. The solvent was evaporated...
and the crude was purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 25-85% CH₃CN/H₂O, 0.1% TFA, 20 min) to give the desired product as a TFA salt (10 mg, -100%). MS: calcd for C33H40N8O+H⁺ 565.33, found 565.39.

Preparation of 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1)H)-yl)-6-hydroxy-1,3,5-triazin-2-ylamino)methyl)-α7-ethyl-α7-ð-tolylbenzamide

To the reaction solution for the preparation of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1)H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (-0.04 mmol, 1 equivalent) in CH₃CN/H₂O (1/1, 0.3 ml) was added 6N HCl (0.3 ml). The reaction mixture was heated at 80°C overnight. The solvent was evaporated in vacuo and the crude was purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 20-65% CH₃CN/H₂O, 0.1% TFA, 17 min) to give the desired product (10.1 mg, 45% yield). MS: calcd for C31H34N6O4+H⁺ 555.64, found 555.33.

Preparation of 4-((4-(3,4-dihydroisoquinolin-2(1)H)-yl)-6-hydroxy-1,3,5-triazin-2-ylamino)methyl)-α7-ethyl-α7-ð-tolylbenzamide

To the reaction solution of the preparation of 4-((4-chloro-6-(3,4-dihydroisoquinolin-2(1)H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (-20 mg, 0.04 mmol, 1 equivalent) in CH₃CN/H₂O (1/1, 0.7 ml) was added 6N HCl (0.3 ml). The reaction mixture was heated at 80°C overnight. The solvent was evaporated in vacuo and the crude was purified with RP-HPLC (Luna, 5µ C8(2),
100x21mm, 20-75% CH$_3$CN/H$_2$O, 0.1% TFA, 20 min) to give the desired compound (13.73 mg, -70% yield). MS: calcd for C$_{29}$H$_{30}$N$_6$O$_2$+H$^+$ 495.61, found 495.30.

**Preparation of 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1 H)-yl)-1,3,5-triazin-2-ylamino)methyl)-A7-ethyl-A7-rø-tolylbenzamide**

To the solution of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1 H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (~2 mg) in MeOH (1 ml) was added 10% Pd/C (2 mg). The reaction mixture was stirred under an H$_2$ balloon at room temperature for 2 hours. The reaction solution was filtered through celite and concentrated. The crude product was purified with RP-HPLC to give the desired compound (0.25 mg). MS: calcd for C$_{31}$H$_{34}$N$_6$O$_3$+H$^+$ 539.66, found 539.39.

**Preparation of 4-((4-(3,4-dihydroisoquinolin-2(1 H)-yl)-1,3,5-triazin-2-ylamino)methyl)-A7-ethyl-A7-rø-tolylbenzamide**

To the solution of 4-((4-chloro-6-(3,4-dihydroisoquinolin-2(1 H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (7 mg) in MeOH (0.8 ml) was added 10% Pd/C (2 mg). The reaction mixture was stirred under an H$_2$ balloon at room temperature for 1 hour. The reaction solution was filtered through celite and concentrated. The crude product was purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 30-85% CH$_3$CN/H$_2$O, 0.1% TFA, 17 min) to give the desired compound (4 mg, 61.5%). MS: calcd for C$_{29}$H$_{30}$N$_6$O+H$^+$ 479.59, found 479.35.
Preparation of 2-(4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-6-(4-(ethyl(ρ-tolyl)carbamoyl)benzylamino)-1,3,5-triazin-2-ylamino)acetic acid

To the reaction solution for the preparation of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (0.044 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 5 ml) was added H-Glycine-OMe hydrochloride (55.25 mg, 0.44 mmol, 10 equivalents). The pH of the reaction solution was adjusted to around 9-10 by adding IN NaOH. The reaction was heated at 80°C overnight. Neutralize the solution with HCl. The solvent was evaporated in vacuo and the crude was purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 20-85% CH$_3$CN/H$_2$O, 0.1% TFA, 20 min) to give the desired product (14.25 mg, 58% yield). MS: calcd for C$_{33}$H$_{37}$N$_7$O$_5$+H $^+ 612.29$, found 612.3.
Preparation of 4-(aminomethyl)-Λ^-ethyl-Λ^-methylbenzamide

To a solution of 4-(Boc-aminomethyl)benzoic acid (0.534 g, 2.125 mmol, 1 equivalent) in DMF (8 ml) was added HATU (807 mg, 2.125 mmol, 1 equivalent) in DMF (5 ml), followed by adding DIEA (740 µl, 4.25 mmol, 2 equivalents). After being stirred at room temperature for 5 min, N-ethylmethylamine (219 µl, 2.55 mmol, 1.25 equivalents) was added. The reaction mixture was stirred at room temperature for 2 hours. The solvent was evaporated and the residue was redissolved in EtOAc, which was further washed with sat. NaHCU₃, water, salt and dried over MgSO₄. The solvent was removed in vacuo to give the crude which was purified with silicon chromatography (eluant: 60-70% EtOAc/Hexane). The product was collected and condensed to give the residue which was redissolved in dichloromethane (20 ml). TFA (20 ml) was added and the solution was stirred at room temperature for 1 hour. The solvents were evaporated to
give the desired product which was lypholized to get rid of the extra TFA and would be used without further purification. MS: calcd for C11H16N2O+H+ 193.14, found 193.03.

**Preparation of** 4-((4-chloro-6-(3,4-dihydroisoquinolin-2(1\(H\))-yl)-1,3,5-triazin-2-ylamino)methyl)-N7-ethyl-N7-methylbenzamide

![Chemical Structure](image)

To a solution of 2-(4,6-dichloro-1,3,5-triazin-2-yl)-1,2,3,4-tetrahydroisoquinoline (54.7 mg, 0.195 mmol, 1 equivalent) in dichloromethane (2 ml) was added 4-(aminomethyl)-N-ethyl-N-methylbenzamide as the TFA salt (-80 mg, 0.261 mmol, 1.34 equivalents), followed by adding triethylamine (144 µl, 1 mmol, 5 equivalents). The reaction was stirred at room temperature for about 1 hour. The solvent was evaporated and the residue was washed with water to give the white solid which will be used directly for the next step. MS: calcd for C23H25C1N6O+H+ 437.19, found 437.3.

**Preparation of** 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1\(H\))-yl)-1,3,5-triazin-2-ylamino)methyl)-N7-ethyl-N7-methylbenzamide

![Chemical Structure](image)

To a solution of 2-(4,6-dichloro-1,3,5-triazin-2-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (46.59 mg, 0.1366 mmol, 1 equivalent) in dichloromethane (2 ml) was added 4-(aminomethyl)-N-ethyl-N-methylbenzamide as the TFA salt (-70 mg, 0.23 mmol, 1.34 equivalents), followed by adding triethylamine (144 µl, 1 mmol, 5 equivalents). The reaction was stirred at room temperature for about 1 hour. The solvent was evaporated and the crude was purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 30-75% CH3CN/H2O, 0.1% TFA, 20 min) to give the desired product (30 mg, 44% yield). MS: calcd for C25H29C1N6O3+H+ 497.21, found 497.3.
**Preparation of 4-((4-(3,4-dihydroisoquinolin-2(1)H)-yl)-1,3,5-triazin-2-ylamino)methyl)- N7-ethyl-N7-methylbenzamide**

To a solution of crude 4-((4-chloro-6-(3,4-dihydroisoquinolin-2(1)H)-yl)-l,3,5-triazin-2-ylamino)methyl)- N-ethyl-N-methylbenzamide (-25 mg, -0.05 mmol, 1 equivalent) in MeOH (1 ml) and dichloromethane (0.5 ml) was added 10% Pd/C (-70 mg). Under an H₂ balloon, the reaction mixture was stirred at room temperature for 2.5 hours. The solid was filtered and the solution was condensed to give the crude which was further purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 30-60% CH₃CN/H₂O, 0.1% TFA, 20 min) to give the desired product (3.1 mg). MS: calcd for C23H26N₆O+H⁺ 403.23, found 403.4.

**Preparation of 4-((4-(3,4-dihydroisoquinolin-2(1)H)-yl)-6-(2-(dimethylamino)ethylamino)-1,3,5-triazin-2-ylamino)methyl)- N-ethyl-N-methylbenzamide**

To a solution of crude 4-((4-chloro-6-(3,4-dihydroisoquinolin-2(1)H)-yl)-l,3,5-triazin-2-ylamino)methyl)- N-ethyl-N-methylbenzamide (-25 mg, -0.05 mmol, 1 equivalent) in NMP (1 ml) was added N,N-dimethylethylenediamine (200 µl, 1.8 mmol, 36 equivalents). The reaction mixture was heated at 80°C overnight. After being neutralized with 1N HCl, the reaction solution was directly put on RP-HPLC for purification to give the desired product as a TFA salt (6.7 mg, -22% yield in 2 steps). MS: calcd for C27H36N8O+H⁺ 489.31, found 489.34.
Preparation of 4-((4-(3,4-dihydroisoquinolin-2(1\(H\))-yl)-6-(ethyl(methyl)amino)-1,3,5-triazin-2-ylamino)methyl)-\(N\)-ethyl-\(N\)-methylbenzamide

To a solution of crude 4-((4-chloro-6-(3,4-dihydroisoquinolin-2(1\(H\))-yl)-1,3,5-triazin-2-ylamino)methyl)-\(N\)-ethyl-\(N\)-methylbenzamide (25 mg, 0.05 mmol, 1 equivalent) in NMP (1 ml) was added \(N\)-methylethanamine (200 \(\mu\)l, 2.3 mmol, 46 equivalents). The reaction mixture was heated at 80\(^\circ\)C for 2 hours. The solvent was evaporated in vacuo and the crude was purified with RP-HPLC to give the desired product (8.2 mg, -37% yield in 2 steps). MS: calcd for C26\(H\)33\(N\)7\(O\)+\(H\)\(^+\) 460.28, found 460.37.

Preparation of 4-((4-(3,4-dihydroisoquinolin-2(1\(H\))-yl)-6-(4-methylpiperazin-1-yl)-1,3,5-triazin-2-ylamino)methyl)-\(N\)-ethyl-\(N\)-methylbenzamide

To a solution of crude 4-((4-chloro-6-(3,4-dihydroisoquinolin-2(1\(H\))-yl)-1,3,5-triazin-2-ylamino)methyl)-\(N\)-ethyl-\(N\)-methylbenzamide (-0.065 mmol, 1 equivalent) in \(CH_3CN/H_2O\) (1/1, 1 ml) was added 1-methylpiperazine (65 mg, 0.65 mmol, 10 equivalents). The reaction mixture was heated at 80\(^\circ\)C overnight. The reaction solution was neutralized and directly purified with RP-HPLC (Luna, 5\(\mu\) C8(2), 100x21mm, 10-50% \(CH_3CN/H_2O\), 0.1% TFA, 19 min) to give the desired product as a TFA salt (20 mg, -40% yield in 2 steps). MS: calcd for C28\(H\)36\(N\)8\(O\)+\(H\)\(^+\) 501.31, found 501.27.
Preparation of 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1)H)-yl)-6-(4-methylpiperazin-1-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-methylbenzamide

To a solution of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1)H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-methylbenzamide (6 mg, 0.012 mmol, 1 equivalent) in CH₃CN/H₂O (1/1, 1 ml) was added 1-methylpiperazine (12 mg, 0.12 mmol, 10 equivalents). The reaction mixture was heated at 80°C overnight. The reaction solution was neutralized and directly purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 4-40% CH₃CN/H₂O, 0.1% TFA, 19 min) to give the desired product as a TFA salt (2.5 mg, 31% yield). MS: calcd for C30H40N8O3+H⁺ 561.33, found 561.27.

Preparation of 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1)H)-yl)-6-(2-(dimethylamino)ethylamino)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-methylbenzamide

To a solution of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1)H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-methylbenzamide (6 mg, 0.012 mmol, 1 equivalent) in CH₃CN/H₂O (1/1, 1 ml) was added N,N-dimethylethylenediamine (10.6 mg, 0.12 mmol, 10 equivalents). The reaction mixture was heated at 80°C overnight. The reaction solution was neutralized and directly purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 4-40% CH₃CN/H₂O, 0.1% TFA, 19 min) to give the desired product.
as a TFA salt (2 mg, 25% yield). MS: calcd for C29H40N8O3+H⁺ 549.33, found 549.23.

**Preparation of 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-6-(2-(4-methylpiperazin-1-yl)ethylamino)-1,3,5-triazin-2-ylamino)methyl)-N⁷-ethyl-N⁷-methylbenzamide**

To a solution of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N⁷-ethyl-N⁷-methylbenzamide (6 mg, 0.012 mmol, 1 equivalent) in CH₃CN/H₂O (1/1, 1 ml) was added 2-(4-methyl-piperazin-1-yl)ethylamine (17 mg, 0.12 mmol, 10 equivalents). The reaction mixture was heated at 80°C overnight. The reaction solution was neutralized and directly purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 4-40% CH₃CN/H₂O, 0.1% TFA, 19 min) to give the desired product as a TFA salt (3.5 mg, 35% yield). MS: calcd for C32H45N9O3+H⁺ 604.37, found 604.28.

**Preparation of 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N⁷-ethyl-.<V-methylbenzamide**

To a solution of 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N⁷-ethyl-.<V-methylbenzamide (12 mg, 0.024 mmol, 1 equivalent) in MeOH (1 ml) was added 10% Pd/C (~8 mg). Under an H₂ balloon, the reaction mixture was stirred at room temperature for 40 min. The solid was filtered and the solution was condensed to give the crude which was further purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 30-60% CH₃CN/H₂O, 0.1% TFA, 20 min) to give the
desired product (1.3 mg, 11.6% yield). MS: calcd for C25H30N6O3+H + 463.25, found 463.4.

Scheme 3

Preparation of 4-(((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-6-(2-(4-methylpiperazin-1-yl)ethylamino)-1,3,5-triazin-2-ylamino)methyl)benzoic acid
To the mixture of 2-(4,6-dichloro-1,3,5-triazin-2-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (100 mg, 0.293 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 8 ml) was added 4-(aminomethyl)benzoic acid methyl ester (59.1 mg, 0.293 mmol, 1 equivalent). The pH of the reaction solution was kept at about 9-10 by adding IN NaOH. The reaction was stirred at room temperature overnight. The solvent was removed in vacuo to give the crude product which would be used directly for the next step.

Methyl 4-((4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1$H$)-yl)-1,3,5-triazin-2-ylamino)methyl)benzoate (0.15 mmol, 1 equivalent) was dissolved in NMP (3 ml). 2-(4-methyl-piperazin-1-yl)-ethylamine (125.88 mg, 0.88 mmol, 6 equivalents) was added, and the reaction mixture was heated at 80°C for 5 hours. LC-MS showed the reaction has completed. 2/3 (0.1 mmol) of the reaction mixture was further treated with IN NaOH (0.4 ml, 0.4 mmol, 4 equivalents). The reaction mixture was stirred at room temperature overnight. The reaction solution was neutralized and condensed to give the crude which was purified with RP-HPLC (Luna, 5μ C8(2), 100x21mm, 15-95% CH$_3$CN/H$_2$O, 0.1% TFA, 20 min) to give the desired product as a TFA salt (26.2 mg, -33% in 3 steps). MS: calcd for C29H38N8O4+H $^+$ 563.68, found 563.4.

**Preparation of 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1$H$)-yl)-6-(2-(4-methylpiperazin-1-yl)ethylamino)-1,3,5-triazin-2-ylamino)methyl)-$N$-$m$-tolylbenzamide**

A solution of 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1$H$)-yl)-6-(2-(4-methylpiperazin-1-yl)ethylamino)-1,3,5-triazin-2-ylamino)methyl)benzoic acid (8 mg, 0.01 mmol, 1 equivalent), m-toluidine (1.76 μl, 0.0162 mmol, 1.6 equivalents) and DMAP (0.3 mg, 0.003 mmol, 0.3 equivalents) in dichloromethane (1 ml) was cooled with stirring in an ice bath. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI, 3.41 mg, 0.0178 mmol, 1.8 equivalents) was added, and the
reaction mixture was stirred at 0°C for 2 hours and at room temperature overnight. The solution was diluted with dichloromethane, which was further washed with saturated sodium bicarbonate, water, salt and dried over MgSO₄. The solvent was removed *in vacuo* to give the crude compound, which was further purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 10-95% CH₃CN/H₂O, 0.1% TFA, 15 min) to give the desired product as a TFA salt. MS: calcd for C36H45N₉O₃+H + 652.82, found 652.42.

**Preparation of 4-((4-(6,7-dimethoxy-3,4-dihyroisoquinolin-2(1H)-yl)-6-(2-(4-methylpiperazin-1-yl)ethylamino)-1,3,5-triazin-2-ylamino)methyl)-N-methylbenzamide**

Following the same procedure as preparation of 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-6-(2-(4-methylpiperazin-1-yl)ethylamino)-1,3,5-triazin-2-ylamino)methyl)-N-m-tolylbenzamide, 4-((4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-6-(2-(4-methylpiperazin-1-yl)ethylamino)-1,3,5-triazin-2-ylamino)methyl)benzoic acid (8 mg, 0.01 mmol, 1 equivalent) in dichloromethane (1 ml) was coupled with methylamine (2 M in THF, 8 µl, 0.016 mmol, 1.6 equivalents) under the activation of EDCI (3.41 mg, 0.0178 mmol, 1.8 equivalents) and DMAP (0.3 mg, 0.003 mmol, 0.3 equivalent). The crude was purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 10-95% CH₃CN/H₂O, 0.1% TFA, 15 min) to give the desired product as a TFA salt (1.23 mg, 15% yield). MS: calcd for C30H42N₉O₃+H + 576.71, found 576.38.
Preparation of 4-chloro-$\Lambda$-cyclohexyl-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1$H$)-yl)-1,3,5-triazin-2-amine

To the solution of 2-(4,6-dichloro-1,3,5-triazin-2-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (157 mg, 0.46 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 10 ml) was added cyclohexylamine (52.7 µl, 0.46 mmol, 1 equivalent). The pH of the reaction mixture was adjusted with IN NaOH to about 9-10, and the reaction was stirred at room temperature for 1 hour. Without workup, the reaction solution will be used directly for the next step.
Preparation of N-benzyl-4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-amine

To the solution of 2-(4,6-dichloro-1,3,5-triazin-2-yl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (43 mg, 0.126 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 2 ml) was added benzylamine (13.7 µl, 0.126 mmol, 1 equivalent). The pH of the reaction mixture was adjusted to about 9-10 with IN NaOH (126 µl, 1 equivalent), and the reaction was stirred at room temperature for 1 hour. Without workup, the reaction solution will be used directly for the next step.

Preparation of 6^-benzyl-6^-cyclohexyl-6(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazine-2,4-diamine

To the above reaction solution of N-benzyl-4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-amine (-0.126 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 2 ml) was added cyclohexylamine (29 µl, 0.252 mmol, 2 equivalents), followed by adding IN NaOH (126 µl, 0.126 mmol, 1 equivalent). The reaction mixture was heated at 80°C overnight. The solvent was evaporated and the residue was acidified and purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 25-75% CH$_3$CN/H$_2$O, 0.1% TFA, 17 min) to give the desired product. MS: cacld for C$_{27}$H$_{34}$N$_6$O$_2$+H$^+$ 475.28, found 475.4.
Preparation of N\textsuperscript{2}-benzyl-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1\ H)-yl)-N\textsuperscript{4}-(2-(4-methylpiperazin-1-yl)ethyl)-1,3,5-triazine-2,4-diamine

To the above reaction solution of N\textsuperscript{4}-benzyl-4-chloro-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1\ H)-yl)-1,3,5-triazin-2-amine (0.126 mmol, 1 equivalent) in CH\textsubscript{3}CN/H\textsubscript{2}O (1/1, 2 ml) was added 2-(4-methyl-piperazin-1-yl)-ethyamine (36 mg, 0.252 mmol, 2 equivalents), followed by adding IN NaOH (126 µl, 0.126 mmol, 1 equivalent). The reaction mixture was heated at 80\degree C overnight. The solvent was evaporated and the residue was acidified and purified with RP-HPLC (Luna, 5\mu C8(2), 100x21mm, 10-60\% CH\textsubscript{3}CN/H\textsubscript{2}O, 0.1\% TFA, 17 min) to give the desired product. MS: cacld for C28H38N8O2+H\textsuperscript{+} 519.32, found 519.4.

Preparation of 4-((4-(cyclohexylamino)-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1\ H)-yl)-1,3,5-triazin-2-ylamino)methyl)benzoic acid

To the above reaction solution of 4-chloro-N\textsuperscript{4}-cyclohexyl-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1\ H)-yl)-1,3,5-triazin-2-amine (0.46 mmol, 1 equivalent) in CH\textsubscript{3}CN/H\textsubscript{2}O (1/1, 2 ml) was added methyl 4-(aminomethyl)benzoate hydrochloride (371 mg, 1.84 mmol, 4 equivalents), followed by adding IN NaOH (∼ 2.76 ml, 2.76 mmol, 6 equivalents). The reaction mixture was heated at 80\degree C overnight. The reaction mixture was cooled down and further treated with ∼2M KOH (2 ml) at room temperature for 2 hours. The solvent was evaporated and the residue was acidified and purified with RP-HPLC (Luna, 5\mu C8(2), 100x21mm, 20-95\% CH\textsubscript{3}CN/H\textsubscript{2}O, 0.1\% TFA, 20 min) to give the desired product. MS: cacld for C28H34N6O4+H\textsuperscript{+} 519.63, found 519.37.
**Preparation of 4-((4-(cyclohexylamino)-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N7-methylbenzamide**

A solution of 4-((4-(cyclohexylamino)-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)benzoic acid (13.3 mg, 0.0257 mmol, 1 equivalent), methylamine (2.0M in THF, 66 µl, 5 equivalents) and DMAP (0.6 mg, 0.005 mmol, 0.2 equivalents) in dichloromethane (2 ml) was cooled with stirring in an ice bath. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI, 6.15 mg, 0.0321 mmol, 1.25 equivalents) was added, and the reaction mixture was stirred at room temperature overnight. The solution was diluted with dichloromethane, which was further washed with saturated sodium bicarbonate, water, salt and dried over MgSO₄. The solvent was removed *in vacuo* to give the crude compound, which was further purified with RP-HPLC (Luna, 5 µ C8(2), 100x21mm, 20-95 CH₃CN/H₂O, 0.1% TFA, 20 min) to give the desired product (1.42 mg, 10% yield). MS: calcd for C₂₉H₃₇N₇O₃+H + 532.67, found 532.37.

**Scheme 5**
Preparation of 4-((6-chloropyrimidin-4-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide

A solution of 4,6-dichloropyrimidine (50.7 mg, 0.34 mmol, 1 equivalent) in DMF (1.5 ml) was added 4-(aminomethyl)-N^-ethyl-N^-m-tolylbenzamide as a TFA salt (130 mg, 0.34 mmol, 1 equivalent), followed by adding triethylamine (94.8 µl, 0.68 mmol, 2 equivalents). The reaction was heated at 80°C for 2 hours. LC-MS showed the completion of the reaction. The reaction solution will be used directly for the next step.

MS: calcd for C21H21ClN4O+H+ 381.15, found 381.2.

Preparation of 4-((6-(3,4-dihydroisoquinolin-2(1\(H\)))-yl)pyrimidin-4-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide

1/3 of the above reaction solution to prepare 4-((6-chloropyrimidin-4-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide (~0.11 mmol, 1 equivalent) was added the solution of 1,2,3,4-tetrahydroisoquinoline hydrochloride (74.6 mg, 0.44 mmol, 4 equivalents) in DMF (0.5 ml), followed by adding triethylamine (76.7 µl, 0.55 mmol, 5 equivalents). The reaction was heated at 115°C over weekend. The solvent was evaporated and the crude was purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 25-70% CH\(_3\)CN/H\(_2\)O, 0.1% TFA, 17 min) to give the desired product (18.9 mg, -40% in 2 steps). MS: calcd for C30H31N5O+H+ 478.26, found 478.32.
Preparation of 4-((6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1\(H\))-yl)pyrimidin-4-ylamino)methyl)-\(N\)-ethyl-\(N\)-\(r\)-tolylbenzamide

1/3 of the above reaction solution to prepare 4-((6-chloropyrimidin-4-ylamino)methyl)-\(N\)-ethyl-\(N\)-\(m\)-tolylbenzamide (~0.11 mmol, 1 equivalent) was added the solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (101.1 mg, 0.44 mmol, 4 equivalents) in DMF (0.5 ml), followed by adding triethylamine (76.7 \(\mu\)l, 0.55 mmol, 5 equivalents). The reaction was heated at 115\(^\circ\)C over weekend. The solvent was evaporated and the crude was purified with RP-HPLC (Luna, 5\(\mu\) C8(2), 100x21mm, 25-65% CH\(_3\)CN/H\(_2\)O, 0.1% TFA, 17 min) to give the desired product (22.6 mg, \(-42\%\) in 2 steps). MS: calcd for C\(_{32}\)H\(_{35}\)N\(_5\)O\(_3\)+H\(^+\) 538.28, found 538.32.

Preparation of 4-((6-chloro-2-methylpyrimidin-4-ylamino)methyl)-\(N\)-ethyl-\(N\)-\(m\)-tolylbenzamide

A solution of 4,6-dichloro-2-methylpyrimidine (50.7 mg, 0.311 mmol, 1 equivalent) in DMF (1.5 ml) was added 4-(aminomethyl)-\(N\)-ethyl-\(N\)-\(m\)-tolylbenzamide as a TFA salt (118.8 mg, 0.311 mmol, 1 equivalent), followed by adding triethylamine (86.7 \(\mu\)l, 0.68 mmol, 2 equivalents). The reaction was heated at 80\(^\circ\)C for 2 hours. LC-MS showed the completion of the reaction. The reaction solution will be used directly for the next step. MS: calcd for C\(_{22}\)H\(_{23}\)ClN\(_4\)O+H\(^+\) 395.16, found 395.2.
Preparation of 4-((6-(3,4-dihydroisoquinolin-2(1H)-yl)-2-methylpyrimidin-4-ylamino)methyl)-N7-ethyl-N7-ø-tolylbenzamide

1/3 of the above reaction solution to prepare 4-((6-chloro-2-methylpyrimidin-4-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (-0.104 mmol, 1 equivalent) was added the solution of 1,2,3,4-tetrahydroisoquinoline hydrochloride (70.6 mg, 0.41 mmol, 4 equivalents) in DMF (1 ml), followed by adding triethylamine (72.5 µl, 0.52 mmol, 5 equivalents). The reaction was heated at 115°C over weekend. The solvent was evaporated and the crude was purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 25-65% CH3CN/H2O, 0.1% TFA, 17 min) to give the desired product (17.2 mg, -35% in 2 steps). MS: calcd for C31H33N5O+H + 492.28, found 492.32.

Preparation of 4-((6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-methylpyrimidin-4-ylamino)methyl)-N7-ethyl-N7-ø-tolylbenzamide

1/3 of the above reaction solution to prepare 4-((6-chloro-2-methylpyrimidin-4-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (-0.104 mmol, 1 equivalent) was added the solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (95.6 mg, 0.416 mmol, 4 equivalents) in DMF (0.5 ml), followed by adding triethylamine (72.5 µl, 0.52 mmol, 5 equivalents). The reaction was heated at 115°C over weekend. The solvent was evaporated and the crude was purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 25-65% CH3CN/H2O, 0.1% TFA, 17 min) to give the desired product (21 mg, -38% in 2 steps). MS: calcd for C33H37N5O3+H + 552.30, found 552.35.
Preparation of 4-((2-amino-6-chloropyrimidin-4-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide

A solution of 4,6-dichloropyrimidin-2-amine (50.0 mg, 0.305 mmol, 1 equivalent) in DMF (1.5 ml) was added 4-(aminomethyl)-N^-ethyl-N^-m-tolylbenzamide as a TFA salt (116.46 mg, 0.305 mmol, 1 equivalent), followed by adding triethylamine (85 µl, 0.61 mmol, 2 equivalents). The reaction was heated at 80°C for 2 hours. LC-MS showed the completion of the reaction. The reaction solution will be used directly for the next step. MS: calcd for C21H22C1N5O+H+ 396.16, found 396.2.

Preparation of 4-((2-amino-6-(3,4-dihydroisoquinolin-2(lH)-yl)pyrimidin-4-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide

1/2 of the above reaction solution to prepare 4-((2-amino-6-chloropyrimidin-4-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide (-0.15 mmol, 1 equivalent) was added the solution of 1,2,3,4-tetrahydroisoquinoline hydrochloride (101.8 mg, 0.6 mmol, 4 equivalents) in DMF (0.5 ml), followed by adding triethylamine (111.5 µl, 0.8 mmol, 6 equivalents). The reaction was heated at 115°C over weekend. The solvent was evaporated and the crude was purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 25-65% CH3CN/H2O, 0.1% TFA, 17 min) to give the desired product (8.7 mg, -12% in 2 steps). MS: calcd for C30H32N6O+H+ 493.27, found 493.33.
**Preparation of** 4-((2-amino-6-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)pyrimidin-4-ylamino)methyl)-N7-ethyl-N7-rø-tolylbenzamide

1/2 of the above reaction solution to prepare 4-((2-amino-6-chloropyrimidin-4-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (-0.15 mmol, 1 equivalent) was added the solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (137.8 mg, 0.6 mmol, 4 equivalents) in DMF (0.5 ml), followed by adding triethylamine (111.5 µl, 0.8 mmol, 6 equivalents). The reaction was heated at 115°C over weekend. The solvent was evaporated and the crude was purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 25-65% CH3CN/H2O, 0.1% TFA, 17 min) to give the desired product (13.5 mg, -16% in 2 steps). MS: calcd for C32H36N6O3+H + 553.29, found 553.33.

**Scheme 6**
Preparation of 4-((4-chloro-1,3,5-triazin-2-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide

![Chemical Structure](image)

At 0°C, the solution of 2,4-dichloro-1,3,5-triazine (95%, 20.4 mg, 0.13 mmol, 1 equivalent) and 4-(aminomethyl)-N^-ethyl-N^-m-tolylbenzamide as a TFA salt (52 mg, 0.136 mmol, 1 equivalent) in NMP (1.5 ml) was added diisopropylethylamine (59 µl, 0.34 mmol, 2.5 equivalents). The reaction was stirred at cold for 1-2 hours, followed by stirring at room temperature overnight. The reaction solution will be used directly for the next step. MS: calcd for C20H20ClN5O+H+ 382.14, found 382.2.

Preparation of N-ethyl-4-((4-(7-fluoro-3,4-dihydroisoquinolin-2(l H)-yl)-1,3,5-triazin-2-ylamino)methyl)-N^-rø-tolylbenzamide

![Chemical Structure](image)

1/5 of the above reaction solution to prepare 4-((4-chloro-1,3,5-triazin-2-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide (-0.025 mmol, 1 equivalent) was added the solution of 7-fluoro-1,2,3,4-tetrahydroisoquinoline (21 mg, 0.136 mmol, 5 equivalents) in NMP (0.5 ml). The reaction was heated at 80°C for 1 hour. The reaction solution was neutralized and directly purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 20-65% CH3CN/H2O, 0.1% TFA, 17 min) to give the desired product (5.5 mg, -46% in 2 steps). MS: calcd for C29H29FN6O+H+ 496.25, found 497.34.
Preparation of \(\Lambda^\text{-ethyl-4-((4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-1,3,5-triazin-2-ylamino)methyl)-\Lambda^\text{-rø-tolylbenzamide}\)

1/5 of the above reaction solution to prepare 4-((4-chloro-1,3,5-triazin-2-ylamino)methyl)-\(N\)-ethyl-\(N\)-m-tolylbenzamide (-0.025 mmol, 1 equivalent) was added the solution of 6-fluoro-1,2,3,4-tetrahydroisoquinoline (21 mg, 0.136 mmol, 5 equivalents) in NMP (0.5 ml). The reaction was heated at 80\(^\circ\)C for 1 hour. The reaction solution was neutralized and directly purified with RP-HPLC (Luna, 5\(\mu\)C8(2), 100x21mm, 20-65% \(\text{CH}_3\text{CN/H}_2\text{O}\), 0.1% TFA, 17 min) to give the desired product (4.7 mg, -39% in 2 steps). MS: calcd for C29H29FN6O\(^+\) 497.36.

Preparation of \(\Lambda^\text{-ethyl-4-((4-(isoindolin-2-yl)-1,3,5-triazin-2-ylamino)methyl)-\Lambda^\text{-ro-tolylbenzamide}\)

1/5 of the above reaction solution to prepare 4-((4-chloro-1,3,5-triazin-2-ylamino)methyl)-\(N\)-ethyl-\(N\)-m-tolylbenzamide (-0.025 mmol, 1 equivalent) was added the solution of isoindoline (15.4 \(\mu\)l, 0.136 mmol, 5 equivalents) in NMP (0.5 ml). The reaction was heated at 80\(^\circ\)C for 1 hour. The reaction solution was neutralized and directly purified with RP-HPLC (Luna, 5\(\mu\)C8(2), 100x21mm, 20-65% \(\text{CH}_3\text{CN/H}_2\text{O}\), 0.1% TFA, 17 min) to give the desired product (5.3 mg, -46% in 2 steps). MS: calcd for C28H28N6O\(^+\) 465.24, found 465.34.
Preparation of 4-((4-(3,4-dimethoxybenzylamino)-1,3,5-triazin-2-ylamino)methyl)-N^-ethyl-N^-m-tolylbenzamide

1/5 of the above reaction solution to prepare 4-((4-chloro-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (-0.025 mmol, 1 equivalent) was added the solution of (3,4-dimethoxyphenyl)methanamine (22.7 mg, 0.136 mmol, 5 equivalents) in NMP (0.5 ml). The reaction was heated at 80°C for 1 hour. The reaction solution was neutralized and directly purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 20-65% CH₃CN/H₂O, 0.1% TFA, 17 min) to give the desired product (5.3 mg, -46% in 2 steps). MS: calcd for C29H32N6O3+H⁺ 513.26, found 513.22.

Preparation of N^-ethyl-4-((4-(piperidin-1-yl)-1,3,5-triazin-2-ylamino)methyl) N^-m-tolylbenzamide

1/5 of the above reaction solution to prepare 4-((4-chloro-1,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (-0.025 mmol, 1 equivalent) was added the solution of piperidine (13.5 µl, 0.136 mmol, 5 equivalents) in NMP (0.5 ml). The reaction was heated at 80°C for 1 hour. The reaction solution was neutralized and directly purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 20-65% CH₃CN/H₂O, 0.1% TFA, 17 min) to give the desired product (6.7 mg, -62% in 2 steps). MS: calcd for C25H30N6O+H⁺ 431.26, found 431.33.
Preparation of (lr,4r)-4-(aminomethyl)-Λ^(4)-(Λ^(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl)cyclohexanecarboxamide
A solution of trans 4-(Boc-aminomethyl)cyclohexanecarboxylic acid (0.25 g, 0.971 mmol, 1 equivalent) in DMF (12 ml) was added HATU (369.2 mg, 0.971 mmol, 1 equivalent), followed by adding DIEA (338 ul, 1.94 mmol, 2 equivalents). 4-Amino-N-(5-methyl-1,3,4-thiadiazol-2-yl)benzenesulfonamide (262.5 mg, 0.971 mmol, 1 equivalent) was added to the reaction mixture. The reaction was stirred at room temperature for 1 hour. The solution was concentrated and the crude product was further purified with silica chromatography (Eluant: 85% EtOAc in Hexane) to give the desired acylation product (lr,4r)-4-(N-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenylcarbamoyl)cyclohexyl)methylcarbamate. MS: calcd for C22H37N5O5S2+Na+ 532.18, found 532.08.

The acylation product was treated with 20% TFA in dichloromethane at room temperature for 1 hour. The reaction mixture was condensed to give the desired product which will be used without further purification. MS: calcd for C17H23N5O3S2+H+ 410.12, found 410.10.

**Preparation of 4,6-dichloro \( \Lambda^7\)-(2,3-dimethylbenzyl)-1,3,5-triazin-2-amine**

![Chemical Structure](image)

A mixture of cyanuric chloride (20 mg, 0.11 mmol, equivalent) in CH\(_3\)CN/H\(_2\)O (1/1, 2 ml) was cooled to 0°C. 2,3-Dimethylbenzylamine (14.78 mg, 0.11 mmol, 1 equivalent) was added. The reaction mixture was adjusted to a pH of about 9-10 using 1N NaOH. Total about 1 equivalent of base was required. The reaction was completed in about 1 hour. Without work-up and purification, it was used for the next amine addition in the same reaction vessel. MS: calcd for C12H12Cl2N4+H+ 283.04, found 282.99.

**Preparation of 4,6-dichloro \( \Lambda^7\)-(3-chloro-2-methylbenzyl)-1,3,5-triazin-2-amine**

![Chemical Structure](image)

A mixture of cyanuric chloride (10 mg, 0.055 mmol, 1 equivalent) in CH\(_3\)CN/H\(_2\)O (1/1, 1 ml) was cooled to 0°C. (3-Chloro-2-methylphenyl)methanamine (8.5 mg, 0.055 mmol, 1 equivalent) was added. The reaction mixture was adjusted to a
pH of about 9-10 using IN NaOH. Total about 1 equivalent of base was required. LC-MS was used to monitor the reaction. Within about 1 hour, the reaction was completed. Without work-up and purification, it was used for the next amine addition in the same reaction vessel. MS: calcd for C11H9C13N4+H+ 302.99, found 303.07.

**Preparation of** $(lr,4r)$-4-((4-chloro-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)- $\Lambda^7$-(4-(<V-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl)cyclohexanecarboxamide

To the reaction solution of preparation of 4,6-dichloro-$N$-(2,3-dimethylbenzyl)-1,3,5-triazin-2-amine (0.11 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 2 ml) was added $(lr,4r)$-4-(aminomethyl)-$N$-(4-(<N-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl)cyclohexanecarboxamide as the TFA salt (44.7 mg, 0.085 mmol, 0.85 equivalent). IN NaOH was added to the reaction to adjust the pH to about 9-10. The reaction mixture was stirred at room temperature overnight. Without work-up, the desired product was used directly in the next step. MS: calcd for C29H34C11N9O3S2+H$^+$ 656.19, found 656.15.

**Preparation of** $(lr,4r)$-4-((4-chloro-6-(3-chloro-2-methylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)- $\Lambda^7$-(4-(<V-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl)cyclohexanecarboxamide

To the reaction solution of preparation of 4,6-dichloro-$N$-(3-chloro-2-methylbenzyl)-1,3,5-triazin-2-amine (0.055 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 1
mL) was added (lr,4r)-4-(aminomethyl)- N-(4-(N-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl)cyclohexanecarboxamide as the TFA salt (22.4 mg, 0.043 mmol, 0.8 equivalent). IN NaOH was added to the reaction to adjust the pH to about 9-10. The reaction mixture was stirred at room temperature overnight. Without work-up, the desired product was used directly in the next step. MS: calc'd for C28H31Cl2N9O3S2+H+ 676.14, found 676.12.

**Preparation of** (lr,4r)-4-((4-(benzylamino)-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)- N^-(4-(N^-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl)cyclohexanecarboxamide

To the reaction solution of preparation of (lr,4r)-4-((4-chloro-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)- N^-(4-(N^-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl)cyclohexanecarboxamide (0.055 mmol, 1 equivalent) in CH3CN/H2O (1/1, 1 ml) was added benzylamine (54.1 mg, 0.55 mmol, 10 equivalents). The reaction mixture was heated at 80°C overnight. The reaction mixture was neutralized and purified by RP-HPLC (Luna, 5µ C8(2), 100x21mm, 20-70% CH3CN/H2O, 0.1% TFA, 19 min) to give the desired product (5.25 mg, 13% in 3 steps). MS: calc'd for C36H42N10O3S2+H+ 727.29, found 727.35.

**Preparation of** (lr,4r)-4-((4-(2,3-dimethylbenzylamino)-6-(methylamino)-1,3,5-triazin-2-ylamino)methyl)- N^-(4-(N^-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl)cyclohexanecarboxamide

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To the reaction solution of preparation of (Ir,4r)-4-((4-chloro-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)-N-(4-(N-(5-methyl-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl)cyclohexanecarboxamide (0.055 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 1 ml) was added methylamine (40% in water, 43 µl, 0.55 mmol, 10 equivalents). The reaction mixture was heated at 80°C overnight. The reaction mixture was neutralized and directly purified by RP-HPLC (Luna, 5µ C8(2), 100x21mm, 20-70% CH$_3$CN/H$_2$O, 0.1% TFA, 19 min) to give the desired product (1.23 mg, yield 3.5% in 3 steps). MS: calcd for C$_{30}$H$_{38}$N$_{10}$O$_3$S$_2$+H $^+$ 651.26, found 651.29.

**Preparation of (Ir,4r)-4-((4-(2-(dimethylamino)ethylamino)-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)-N^+-((N^+-5-methyl-1,3,4-thiadiazol^-yOsulfamoyOphenyOcyclohexanecarboxamide**

To the reaction solution of preparation of (Ir,4r)-4-((4-chloro-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)-N^+-((N^+-5-methyl-1,3,4-thiadiazol^-yOsulfamoyOphenyOcyclohexanecarboxamide (0.055 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 1 ml) was added N,N-dimethylethylenediamine (48 mg, 0.55 mmol, 10 equivalents). The reaction mixture was heated at 80°C overnight. The reaction mixture was neutralized with 1N HCl and purified by RP-HPLC (Luna, 5µ C8(2), 100x21mm, 20-65% CH$_3$CN/H$_2$O, 0.1% TFA, 19 min) to give desired product (5.6 mg, yield 12.4% in 3 steps). MS: calcd for C$_{33}$H$_{45}$N$_{11}$O$_3$S$_2$+H $^+$ 708.31, found 708.35.
**Preparation of** (lr,4r)-4-((4-((benzylamino)-6-(3-chloro-2-methylbenzylamino)-1,3,5-
triazin-2-ylamino)methyl)-Λ^-(4-(Λ^-(5-methyl-1,3,4-thiadiazol-2-
yl)sulfamoyl)phenyl)cyclohexanecarboxamide

To the reaction solution of preparation of (lr,4r)-4-((4-chloro-6-(3-chloro-2-
methylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)- N-(4-(N-(5-methyl-1,3,4-
 thiadiazol-2-yl)sulfamoyl)phenyl)cyclohexanecarboxamide (0.055 mmol, 1 equivalent)
in CH₃CN/H₂O (1/1, 1 ml) was added benzylamine (54.1 mg, 0.55 mmol, 10 equivalents). The reaction mixture was heated at 80°C overnight. The reaction mixture was neutralized and purified by RP-HPLC (Luna, 5µ C8(2), 100x21mm, 25-85% CH₃CN/H₂O, 0.1% TFA, 20 min) to give the desired product (1.05 mg, 2.6% in 3 steps).

MS: calcd for C₃₅H₃₉ClN₁₀O₃S₂+H + 747.23, found 747.31.
Preparation of (I.r,4r)-4-((4-chloro-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)cyclohexanecarboxylic acid

To the reaction solution of preparation of 4,6-dichloro-N-(2,3-dimethylbenzyl)-1,3,5-triazin-2-amine (2.5 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 20 mL) was added trans 4-aminomethyl cyclohexanecarboxylic acid (393 mg, 2.5 mmol, 1 equivalent). IN NaOH was added to the reaction to adjust the pH to about 9-10. The reaction mixture was stirred at room temperature overnight. Without work-up, the desired product was used directly in the next step. MS: calcd for C$_{20}$H$_{26}$ClN$_5$O$_2$+H$^+$ 404.18, found 404.13.
**Preparation of** (lr,4r)-4-((4-(benzylamino)-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)cyclohexanecarboxylic acid

To the reaction solution of preparation of (lr,4r)-4-((4-chloro-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)cyclohexanecarboxylic acid (2.5 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (-1/1, -40 ml) was added benzylamine (2.7 g, 25 mmol, 10 equivalents). The reaction mixture was heated at 80°C overnight. The solvent was evaporated and the residue was acidified and purified by RP-HPLC (Luna, 5µ C8(2), 100x21mm, 20-80% CH$_3$CN/H$_2$O, 0.1% TFA, 25 min) to give the desired product (847.8 mg, yield 71.5% in 3 steps). MS: calcd for C$_{27}$H$_{34}$N$_{6}$O$_2$+H $^{+}$ 475.27, found 475.38.

**Preparation of** (lr,4r)-4-((4-(benzylamino)-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)-Λ$^\text{--}$-(4-(Λ$^\text{--}$-thiazol-2-ylsulfamoyl)phenyl)cyclohexanecarboxamide

A solution of (lr,4r)-4-((4-(benzylamino)-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)cyclohexanecarboxylic acid (40 mg, 0.084 mmol, 1 equivalent), 4-amino-$N$-(thiazol-2-yl)benzenesulfonamide (24.5 mg, 0.096 mmol, 1.14 equivalents) and DMAP (2.1 mg, 0.017 mmol, 0.2 equivalent) in dichloromethane (1 ml)
was cooled with stirring in an ice bath. l-Ethyl-3-[3-
(dimethylamino)propyl]carbodiimide hydrochloride (EDCI, 20.2 mg, 0.105 mmol, 1.25 equivalents) was added. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature overnight. The solution was diluted with dichloromethane (1 ml), which was further washed with saturated sodium bicarbonate and water. The solvent was removed \textit{in vacuo} to give the crude which was further purified by RP-HPLC (Luna, 5µ C8(2), 100x21mm, 5-80% CH$_3$CN/H$_2$O, 0.1% TFA, 25 min) to give the desired product (45.6 mg, yield 76%). MS: calcd for C36H41N9O3S$_2$+H $^+$ 712.28, found 712.4.

\textbf{Preparation of (1r,4r)-4-((4-(benzylamino)-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)Λ-(4-sulfamoylphenyl)cyclohexanecarboxamide}

A solution of (1r,4r)-4-((4-(benzylamino)-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)cyclohexanecarboxylic acid (40 mg, 0.084 mmol, 1 equivalent), 4-aminobenzenesulfonylamine (16.5 mg, 0.096 mmol, 1.14 equivalents) and DMAP (2.1 mg, 0.017 mmol, 0.2 equivalent) in dichloromethane (1 ml) was cooled with stirring in an ice bath. l-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI, 20.2 mg, 0.105 mmol, 1.25 equivalents) was added. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature overnight. The solution was diluted with dichloromethane (1 ml), which was further washed with saturated sodium bicarbonate and water. The solvent was removed \textit{in vacuo} to give the crude which was further purified by RP-HPLC (Luna, 5µ C8(2), 100x21mm, 5-80% CH$_3$CN/H$_2$O, 0.1% TFA, 25 min) to give the desired product (12.4, yield 24%) MS: calcd for C33H40N8O3S+H $^+$ 629.29, found 629.4.
Preparation of (lr,4r)-Λ^-((4-(Λ^-acetylsulfamoyl)phenyl)-4-((4-(benzylamino)-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)cyclohexanecarboxamide

A solution of (lr,4r)-4-((4-(benzylamino)-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)cyclohexanecarboxylic acid (40 mg, 0.084 mmol, 1 equivalent), N-(4-aminophenylsulfonyl)acetamide (20.6 mg, 0.096 mmol, 1.14 equivalents) and DMAP (2.1 mg, 0.017 mmol, 0.2 equivalent) in dichloromethane (1 mL) was cooled with stirring in an ice bath. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI, 20.2 mg, 0.105 mmol, 1.25 equivalents) was added. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature overnight. The solution was diluted with dichloromethane (1 mL), which was further washed with saturated sodium bicarbonate and water. The solvent was removed in vacuo to give the crude which was further purified by RP-HPLC (Luna, 5µ C8(2), 100x21mm, 5-80% CH3CN/H2O, 0.1% TFA, 30 min) to give the desired product (14.2, yield 25%) MS: calcd for C35H42N8O4S+H+ 671.31, found 671.4.

Preparation of (lr,4r)-4-((4-(benzylamino)-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)-A7-ethyl-A7-rø-tolycyclohexanecarboxamide
A solution of (Ir,4r)-4-((4-(benzylamino)-6-(2,3-dimethylbenzylamino)-1,3,5-triazin-2-ylamino)methyl)cyclohexanecarboxylic acid (40 mg, 0.084 mmol, 1 equivalent), N-ethyl m-toluidine (13 mg, 0.096 mmol, 1.14 equivalents) and DMAP (2.1 mg, 0.017 mmol, 0.2 equivalent) in dichloromethane (1 ml) was cooled with stirring in an ice bath. L-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI, 20.2 mg, 0.105 mmol, 1.25 equivalents) was added. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature overnight. The solution was diluted with dichloromethane (1 ml), which was further washed with saturated sodium bicarbonate and water. The solvent was removed in vacuo to give the crude which was further purified by RP-HPLC (Luna, 5μ C8(2), 100x21mm, 5-80% CH₃CN/H₂O, 0.1% TFA, 25 min) to give the desired product (29.1 mg, yield 59%) MS: calcd for C₃₆H₄₅N₇O+H + 592.37, found 592.4.

Scheme 9
General procedure for the first amine addition

A mixture of cyanuric chloride (577.7 mg, 3.13 mmol, 1 equivalent) in
CH\textsubscript{3}CN/H\textsubscript{2}O (1/1, 40 ml) was cooled to 0°C. The first amine (1 equivalent) was added. The reaction mixture was adjusted to a pH of about 9-10 using IN NaOH. The reaction was continued stirring at cold until the completion of the reaction, monitored by LC-MS. Without workup, the solution will be used directly for the second amine addition.

Example of a preparation of 4,6-dichloro-N-(1-(3-methoxyphenyl)ethyl)-1,3,5-triazin-2-amine

Following the above general procedure, cyanuric chloride (577.7 mg, 3.13 mmol, 1 equivalent) in CH\textsubscript{3}CN/H\textsubscript{2}O (1/1, 40 ml) was allowed to undergo reaction with 1-(3-methoxyphenyl)ethanamine (437.7 mg, 3.13 mmol, 1 equivalent) at cold for 30 min to give the desired product. MS: calcd for C\textsubscript{12}H\textsubscript{12}C\textsubscript{12}N\textsubscript{4}O\textsuperscript{+}H\textsuperscript{+} 299.04, found 299.0.

Example of a preparation of 2,4-dichloro-6-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1,3,5-triazine

Following the above general procedure, cyanuric chloride (584.9 mg, 3.17 mmol, 1 equivalent) in CH\textsubscript{3}CN/H\textsubscript{2}O (1/1, 40 ml) was allowed to undergo reaction with 1-(5-(trifluoromethyl)pyridin-2-yl)piperazine (733.4 mg, 3.17 mmol, 1 equivalent) at cold for 1 hour to give the desired product.

General procedure for the second amine addition

To the above solution of first amine addition (~ 1 mmol, 1 equivalent) in CH\textsubscript{3}CN/H\textsubscript{2}O (1/1, -15 ml) was added second amine (1 equivalent). The solution was adjusted to a pH of about 9-10 using 1N NaOH (~ 1 equivalent). The reaction mixture
was stirred at room temperature for about 3-4 hours, monitored by LC-MS. Without workup, the solution will be used directly for the third amine addition.

**Example of a preparation of α^*-benzyl- 6-chloro- α^*-Cl-CS-methoxyphenyloethyl)-1,3,5-triazine-2,4-diamine**

Following the above general procedure, the solution of 4,6-dichloro-N-(1-(3-methoxyphenyl)ethyl)-1,3,5-triazin-2-amine (~1 mmol, 1 equivalent) in CH₃CN/H₂O (1/1, ~14 ml) was allowed to undergo reaction with benzylamine (113 µl, 1.04 mmol, 1 equivalent) at room temperature for 2 hours to give the desired product. MS: calcd for C₁₉H₂₀ClN₅O+H⁺ 370.14, found 370.2.

**Example of a preparation of α^*-benzyl-4-chloro-6-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1,3,5-triazin-2-amine**

Following the above general procedure, the solution of 2,4-dichloro-6-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1,3,5-triazine (~1 mmol, 1 equivalent) in CH₃CN/H₂O (1/1, ~13 ml) was allowed to undergo reaction with benzylamine (109 µl, 1 mmol, 1 equivalent) at room temperature for 3-4 hours to give the desired product.

**Example of a preparation of 4-chloro-N-(2-phenoxyethyl)-6-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1,3,5-triazin-2-amine**
Following the above general procedure, the solution of 2,4-dichloro-6-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1,3,5-triazine (~1 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, -13 ml) was allowed to undergo reaction with 2-phenoxyethanamine (137 mg, 1 mmol, 1 equivalent) at room temperature for 3-4 hours to give the desired product.

**General procedure for the third amine addition**

To the above solution of second amine addition (~ 0.2 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, ~2 ml) was added third amine (2.5 equivalents). IN NaOH (2.5 equivalents) was added if the amine was in HCl salt. The reaction mixture was heated at 80°C overnight. The solvent was removed *in caccuo* and the residue was purified with RP-HPLC using TFA buffer.

**Example of a preparation of $N^2$-benzyl-$N^4$-(1-(3-methoxyphenyl)ethyl)-$N^6$-(4-(methylsulfonyl)benzyl)-1,3,5-triazine-2,4,6-triamine**

Following the above general procedure, the solution of $N^2$-benzyl-$N^4$-(1-(3-methoxyphenyl)ethyl)-1,3,5-triazine-2,4-diamine (~0.14 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 2 ml) was allowed to undergo reaction with (4-(methylsulfonyl)phenyl)methanamine as HCl salt (78 mg, 0.35 mmol, 2.5 equivalents) at 80°C overnight to give the desired product. MS: calcd for C$_{27}$H$_{30}$N$_6$O$_3$S$^+$H$^+$ 519.22, found 519.3.
Example of a preparation of $\Lambda^2$-benzyl-$\Lambda^4$-($4$-$\text{tert}$-butylbenzyl)-$\Lambda^6$-(1-(3-methoxyphenyl)ethyl)-1,3,5-triazine-2,4,6-triamine

Following the above general procedure, the solution of $N^\Lambda$-benzyl-$\Lambda$-chloro-$N^4$-(1-(3-methoxyphenyl)ethyl)-1,3,5-triazine-2,4-diamine (-0.14 mmol, 1 equivalent) in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1/1, 2 ml) was allowed to undergo reaction with ($4$-$\text{tert}$-butylphenyl)methanamine (57 mg, 0.35 mmol, 2.5 equivalents) at 80°C overnight to give the desired product. MS: calcd for C30H36N6O+H+ 497.30, found 497.4.

Example of a preparation of $\Lambda^2$-benzyl-$\Lambda^4$-($4$-$\text{tert}$-butylbenzyl)-6-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1,3,5-triazine-2,4-diamine

Following the above general procedure, the solution of $N^\Lambda$-benzyl-4-chloro-6-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1,3,5-triazine-2-amine (-0.2 mmol, 1 equivalent) in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1/1, 2 ml) was allowed to undergo reaction with ($4$-$\text{tert}$-butylphenyl)methanamine (82 mg, 0.5 mmol, 2.5 equivalents) at 80°C overnight to give the desired product. MS: calcd for C31H35F3N8+H+ 577.30, found 577.4.

Example of a preparation of $\Lambda^2$-(4-(methylsulfonyl)benzyl)-$\Lambda^4$-(2-phenoxyethyl)-6-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1,3,5-triazine-2,4-diamine
Following the above general procedure, the solution of 4-chloro-N-(2-phenoxyethyl)-6-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)-1,3,5-triazin-2-amine (-0.2 mmol, 1 equivalent) in CH$_3$CN/H$_2$O (1/1, 2 ml) was allowed to undergo reaction with (4-(methylsulfonyl)phenyl)methanamine as HCl salt (112 mg, 0.5 mmol, 2.5 equivalents) at 80°C overnight to give the desired product. MS: calcd for C$_2$H$_3$F$_3$N$_8$O$_3$S+H + 629.23, found 629.4.

**Scheme 8**

Preparation of 4-((4-chloro-6-(3,4-dihydroquinolin-1(2$H$)-yl)-1,3,5-triazin-2-ylamino)methyl)-$\Lambda^7$-ethyl-$\Lambda^7$-$\sigma$-tolylbenzamide
At 0°C, the mixture of cyanuric chloride (50 mg, 0.375 mmol, 1 equivalent) in pH 9.4 borate buffer (0.5 M, 4 ml) was added 1,2,3,4-tetrahydroquinoline (69 mg, 0.375 mmol, 1 equivalent). The pH of the solution was adjusted to about 9-10 with IN NaOH. The reaction was stirred at 4°C overnight. 4-(Aminomethyl)-N-ethyl-N-m-tolylbenzamide as a TFA salt (143 mg, 0.375 mmol, 1 equivalent) was added, followed by adding IN NaOH (30 µl, 0.75 mmol, 2 equivalents). The reaction was heated at 50°C for 4-5 hrs. More 4-(Aminomethyl)-N-ethyl-N-m-tolylbenzamide was added to push the reaction to completion. The solvent was evaporated and the crude was purified with RP-HPLC (Luna, 5µ C8(2), 100x21mm, 50-98% CH3CN/H2O, 0.1% TFA, 20 min) to give the desired compound (36.8 mg, 19% in 2 steps). MS: calcd for C29H29C1N6O+H+ 513.22, found 513.30.

**Preparation of 4-((4-(3,4-dihydroquinolin-l(2 H)-yl)-6-(2-(4-methylpiperazin-l-yl)ethylamino)-l,3,5-triazin-2-ylamino)methyl)-N^-ethyl-N^-rø-tolylbenzamide**

To the solution of 4-((4-chloro-6-(3,4-dihydroquinolin-l(2 H)-yl)-l,3,5-triazin-2-ylamino)methyl)-N-ethyl-N-m-tolylbenzamide (20 mg, 0.039 mmol, 1 equivalent) in NMP (0.5 ml) was added 2-(4-methyl-piperazin-l-yl)-ethylamine (28 mg, 0.195 mmol, 5 equivalents). The reaction mixture was heated at 80°C for about 3 hours. The reaction solution was acidified and directly purified with RP-HPLC (Luna, 5µ C8(2),
100x21mm, 40-95% CH₃CN/H₂O, 0.1% TFA, 20 min) to give the desired product as TFA salt (18.9 mg, 57%). MS: calcd for C₃₆H₄₅N₉O⁺H+ 620.83, found 620.5.

EQUIVALENTS
[0010] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

INCORPORATION BY REFERENCE
[0011] The contents of all references, patents and published patent applications cited throughout this application are hereby incorporated by reference.
CLAIMS
What is claimed is:
1. A compound of formula I:

or a pharmaceutically acceptable salt thereof, wherein:

- $Y$ is H, halo, OR,t, SR,t, (d-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)cycloalkyl, aryl, aralkyl,
- (C<sub>3</sub>-C<sub>9</sub>)heterocycloalkyl, heteroaryl, heteroaralkyl, or NR,tR';
- R<sub>t</sub> is hydrogen, (C<sub>3</sub>-C<sub>9</sub>)alkyl, aryl, aralkyl, (C<sub>5</sub>-C<sub>9</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>9</sub>)heterocycloalkyl, (C<sub>3</sub>-C<sub>9</sub>)heterocycloalkyl(Ci-C<sub>9</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heterocycloalkyl(Ci-C<sub>9</sub>)alkyl, heteroaryl, heteroaralkyl, (Ci-
- Ce)carboxyalkyl, aryloxy(Ci-C<sub>9</sub>)alkyl,
- alkylene-NR'R'', wherein R' and R'' are each independently hydrogen, (Ci-C<sub>9</sub>)alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R''t, wherein R''t is hydrogen or (Ci-C<sub>9</sub>)alkyl; R<sub>t</sub> is optionally substituted with 1, 2 or 3 (d-C<sub>6</sub>)alkyl, (Ci-
- Ce)alkoxy or (Ci-C<sub>9</sub>)haloalkyl or 1, 2 or 3 groups independently selected from R<sub>t</sub>;,
- R<sub>2</sub> is hydrogen, (Ci-Ce)alkyl, aryl, aralkyl, (C<sub>5</sub>-C<sub>9</sub>)cycloalkyl, (C<sub>3</sub>-C<sub>9</sub>)cycloalkyl(Ci-C<sub>9</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heterocycloalkyl, (C<sub>3</sub>-C<sub>9</sub>)heterocycloalkyl(Ci-C<sub>9</sub>)alkyl, heteroaryl, heteroaralkyl, (Ci-
- Ce)carboxyalkyl, aryloxy(Ci-C<sub>9</sub>)alkyl,
- alkylene-NR'R'', wherein R' and R'' are each independently hydrogen, (Ci-Ce)alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R''t, wherein R''t is hydrogen or (Ci-Ce)alkyl; R<sub>2</sub> is optionally substituted with 1, 2 or 3 (Ci-Ce)alkyl, (Ci-
Ce)alkoxy or (Ci-C₆)haloalkyl or 1, 2 or 3 groups independently selected from Rₐ;
or R₁ and R₂ can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3 heteroatoms and optionally substituted with Rₐ;
R₃ is hydrogen or (Ci-C₆)alkyl;
m is 0, 1, or 2;
X is absent, -CONR₄₋, or -SO₂₋, -SO₂NR₄₋, or -COO⁻;
R₄ is hydrogen or (Ci-C₆)alkyl;
R₅ is hydrogen, (Ci-C₆)alkyl, (C₃-C₆)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups independently selected from Rₐ or in which Rₙ is hydrogen or (Ci-C₆) alkyl; R₁₂ is hydrogen, (Ci-C₆) alkyl, -CO(Ci-C₆)alkyl, -CO(Ci-C₆)cycloalkyl, -CO(C₁-C₆)heterocycloalkyl, -CO(Ci-C₆) aryl, -CO(Ci-Ce)heteroaryl, cycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups independently selected from Ra or Rn and R₁₂ can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3 heteroatoms and optionally substituted with Rₐ;
R₉ is hydrogen or (Ci-Ce)alkyl;
R₉ and R₈ are each independently hydrogen, halogen, (Ci-C₆)alkyl or (Ci-Ce)alkoxy, either of which may be optionally substituted on carbon with 1, 2, or 3 groups independently selected from Rₐ;
R₉ is hydrogen, halo or (Ci-C₆)alkyl;
Rio is hydrogen or (Ci-Ce)alkyl; or
R₉ and Rio together with the atoms to which they are attached, form a 4-8 membered ring, optionally substituted on carbon with 1, 2, or 3 groups selected from halo, (Ci-C₆)alkyl, and -O-(d-C₆)alkyl, -S-(d-C₆)alkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 halo, or taken together with the attached carbon form C=O;

A is aryl, aryloxy, heteroaryl, cycloalkyl, or heterocycloalkyl;
at least two of three of $Z_i$, $Z_2$, and $Z_3$ are $N$ and the other is $C-R_b$, wherein
$R_b$ is hydrogen, halogen, (Ci-C$_6$)alkyl, or (Ci-C$_6$)alkoxy;
$R_a$ is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy,
amino, (Ci-C$_6$)alkyl-NH, ((Ci-C$_6$)alkyl)$_2$-N, aryl, heteroaryl, (C$_3$-
C$_6$)cycloalkyl,
(Ci-C$_6$)alkyl, (C$_2$-C$_6$)alkenyl, (C$_2$-C$_6$)alkynyl, (Ci-C$_6$)alkoxy, (C$_2$-
C$_6$)alkenyl, (C$_2$)alkynyl, (C$_2$)alkyl, (C$_2$)alkylthio, (C$_2$)alkylsulfanyl,
(Ci-C$_6$)alkylsulfonyl, amino, (Ci-C$_6$)alkylamino, di-[(Ci-C$_6$)alkyl]amino,
formyl, -C(=O)(Ci-C$_6$)alkyl,
-C(=N)(Ci-C$_6$)alkyl, carboxy, CO$_2$(d-C$_6$)alkyl, CONH$_2$, -C(=N)NH$_2$,
-C(=N)NH[(Ci-C$_6$)alkyl], -C(=N)N[(Ci-C$_6$)alkyl]$_2$, CONH[(Ci-C$_6$)alkyl],
-CON[(Ci-C$_6$)alkyl]$_2$, -OC(O)(Ci-C$_6$)alkyl, -OC(O)NH$_2$, -OC(O)NH[(Q-
Ci-C$_6$)alkyl], -OC(O)NH[(Ci-C$_6$)alkyl]$_2$, -NHC(O)[(Ci-C$_6$)alkyl],
-N[C(O)NH[(Ci-C$_6$)alkyl]$_2$, -NH-C(O)NH$_2$, -N(Q-C$_6$)alkyl-
C(O)NH$_2$, N[(Ci-C$_6$)alkyl-C(O)NH(Ci-C$_6$)alkyl, N(Q-C$_6$)alkyl-
C(O)NH(Ci-C$_6$)alkyl]$_2$,
-NH-C(O)NH[(Ci-C$_6$)alkyl]$_2$, N-(Ci-C$_6$)alkylsulfamoyl,
N,N-di-[(Ci-C$_6$)alkylsulfamoyl, (Ci-C$_6$)alkylsulfonlamino, or N-(Q-
C$_6$)alkyl-(Ci-C$_6$)alkylsulfonlamino, any of which may be optionally
substituted on carbon with $R_c$ and
$R_c$ is halogen, trifluoromethyl, trifluoromethoxy, (Q-C$_6$)alkyl, amino,
cyano, nitro, or hydroxyl.

2. A compound of formula II:

![Chemical structure](attachment:chemical结构.png)

or a pharmaceutically acceptable salt thereof, wherein:
$R_i$ is hydrogen, (Q-C$_6$)alkyl, aryl, aralkyl, (C$_3$-C$_6$)cycloalkyl, (C$_3$-
C$_6$)cycloalkyl(Ci-C$_6$)alkyl, (C$_3$-C$_6$)heterocycloalkyl, (C$_3$-
C$_6$)heterocycloalkyl(Q-C$_6$)alkyl, heteroaryl, heteroaralkyl, (Q-
C$_6$)alkyl,
-C(=O)(Ci-C$_6$)alkyl,
-C(=N)(Ci-C$_6$)alkyl, carboxy, CO$_2$(d-C$_6$)alkyl, CONH$_2$, -C(=N)NH$_2$,
-C(=N)NH[(Ci-C$_6$)alkyl], -C(=N)N[(Ci-C$_6$)alkyl]$_2$, CONH[(Ci-C$_6$)alkyl],
-CON[(Ci-C$_6$)alkyl]$_2$, -OC(O)(Ci-C$_6$)alkyl, -OC(O)NH$_2$, -OC(O)NH[(Q-
Ci-C$_6$)alkyl], -OC(O)NH[(Ci-C$_6$)alkyl]$_2$, -NHC(O)[(Ci-C$_6$)alkyl],
-N[C(O)NH[(Ci-C$_6$)alkyl]$_2$, -NH-C(O)NH$_2$, -N(Q-C$_6$)alkyl-
C(O)NH$_2$, N[(Ci-C$_6$)alkyl-C(O)NH(Ci-C$_6$)alkyl, N(Q-C$_6$)alkyl-
C(O)NH(Ci-C$_6$)alkyl]$_2$,
-NH-C(O)NH[(Ci-C$_6$)alkyl]$_2$, N-(Ci-C$_6$)alkylsulfamoyl,
N,N-di-[(Ci-C$_6$)alkylsulfamoyl, (Ci-C$_6$)alkylsulfonlamino, or N-(Q-
C$_6$)alkyl-(Ci-C$_6$)alkylsulfonlamino, any of which may be optionally
substituted on carbon with $R_c$ and
$R_c$ is halogen, trifluoromethyl, trifluoromethoxy, (Q-C$_6$)alkyl, amino,
cyano, nitro, or hydroxyl.
C_6)carboxyalkyl, aryloxy(C_6)alkyl, -alkylene-NR'R", wherein R' and R" are each independently hydrogen, (Ci-Ce)alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R"", wherein R"" is hydrogen or (Ci-Ce)alkyl; R_1 is optionally substituted with 1, 2 or 3 (Ci-Ce)alkyl, (Ci-Ce)alkoxy or (Ci-Ce)haloalkyl or 1, 2 or 3 groups independently selected from R_a:

R_2 is hydrogen, (Ci-Ce)alkyl, aryl, aralkyl, (Ci-Ce)cycloalkyl, (Ci-Ce)cycloalkyl(Ci-Ce)alkyl, (Ci-Ce)cycloalkyl(Ci-Ce)alkyl, (Ci-Ce)cycloalkyl(Ci-Ce)alkyl, heteroaryl, heteroaralkyl, (Ci-Ce)carboxyalkyl, aryloxy(Ci-Ce)alkyl, -alkylene-NR'R", wherein R' and R" are each independently hydrogen, (Ci-Ce)alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R"", wherein R"" is hydrogen or (Ci-Ce)alkyl; R_2 is optionally substituted with 1, 2 or 3 (Ci-Ce)alkyl, (Ci-Ce)alkyl, (Ci-Ce)alkoxy or (Ci-Ce)haloalkyl or 1, 2 or 3 groups independently selected from R_a:

or R_1 and R_2 can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3 heteroatoms and optionally substituted with R_a:

R_1 is hydrogen or (Ci-Ce)alkyl;
m is 0, 1, or 2;
X is absent, -CONR_4-, or -SO_2-, -SO_2NR_4-, or -COO-;
R_4 is hydrogen or (Ci-Ce)alkyl;
R_4 is hydrogen, (Ci-Ce)alkyl, (Ci-Ce)cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups independently selected from R_a or

\[ \begin{array}{c}
\text{O} \\
\text{N} \\
\text{R_{12}^{-}} \\
\text{R_{11}^{+}}
\end{array} \] 

in which R_{11} is hydrogen or (Ci-Ce) alkyl; R_{12} is hydrogen, (Ci-Ce) alkyl, -CO(Ci-Ce)
alkyl, -CO(C₁₋C₆)cycloalkyl, -CO(C₁₋C₆)heterocycloalkyl, -CO(C₁₋C₆)aryl, -CO(C₁₋C₆)heteroaryl, cycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups independently selected from Rₐ; or Rₙ and Rₙ can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3 heteroatoms and optionally substituted with Rₐ:

R₆ is hydrogen or (Ci-C₆)alkyl;

R₇ and R₈ are each independently hydrogen, halogen, (Ci-C₆)alkyl or (Ci-C₆)alkoxy, either of which may be optionally substituted on carbon with 1, 2, or 3 groups independently selected from Rₐ;

R₉ is hydrogen, halo or (Ci-C₆)alkyl;

R₁₀ is hydrogen or (Ci-C₆)alkyl; or

R₉ and R₁₀ together with the atoms to which they are attached, form a 4-8 membered ring, optionally substituted on carbon with 1, 2, or 3 groups selected from halo, (C₁₋C₆)alkyl, and -O-(d-C)alkyl, -S-(d-C)alkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 halo, or taken together with the attached carbon form C=O;

A is aryl, aryloxy, heteroaryl, cycloalkyl, or heterocycloalkyl;

at least two of three of Zₗ, Z₂, and Z₃ are N and the other is C-Rₙ, wherein

Rₖ is hydrogen, halogen, (Ci-C₆)alkyl, or (Ci-C₆)alkoxy;

Rₐ is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, (C₁₋C₆)alkyl-NH, (C₁₋C₆)alkyl-NH, aryloxy, aryl, heteroaryl, (C₃₋C₆)cycloalkyl, (C₁₋C₆)alkyl, (C₂₋C₆)alkenyl, (C₂₋C₆)alkynyl, (C₁₋C₆)alkoxy, (C₂₋C₆)alkenylxoy, (C₁₋C₆)alkynlyoxy, (C₁₋C₆)alkylthio, (C₁₋C₆)alkylsulfonyl, amino, (C₁₋C₆)alkylamino, di-[-(Ci-C₆)alkylamino, formyl, -C(=O)(C₁-C₆)alkyl, -C(=N)(C₁-C₆)alkyl, carboxy, CO₂(C₁-C₆)alkyl, CONH₂, -C(=N)NH₂, -C(=N)NH(C₁-C₆)alkyl), -C(=N)N(C₁-C₆)alkyl), -CON((C₁-C₆)alkyl)₂, -OC(O)(d-C)alkyl, -OC(O)NH₂, -OC(O)NH(C₁-C₆)alkyl, -OC(O)NH(C₁-C₆)alkyl, -NHC(O)(C₁-C₆)alkyl, -NHC(O)(C₁-C₆)alkyl, -N(C₁-C₆)alkyl-C(O)(C₁-C₆)alkyl, -N(C₁-C₆)alkyl-C(O)NH₂, -N(C₁-C₆)alkyl-C(O)NH₂, N(C₁-C₆)alkyl-C(O)NH(C₁-C₆)alkyl, N(C₁-C₆)alkyl-C(O)NH(C₁-C₆)alkyl,
3. A compound of formula III:

or a pharmaceutically acceptable salt thereof, wherein:

Y is H, halo, ORi, SRi, (C3-C6)alkyl, (C3-C6)cycloalkyl, aryl, aralkyl, (C3-
C6)heterocycloalkyl, heteroaryl, heteroaralkyl, or NRiRj;

Ri is hydrogen, (C3-C6)alkyl, aryl, aralkyl, (C3-C6)cycloalkyl, (C3-
C6)cycloalkyl(Ci-C6)alkyl, (C3-C6)heterocycloalkyl, (C3-C6)heterocycloalkyl(Ci-
Ce)alkyl, heteroaryl, heteroaralkyl, (Ci-C6)carboxyalkyl, aryloxy(Ci-C6)alkyl, -
alkylene-NR'R", wherein R' and R" are each independently hydrogen, (Q-
Ce)alkyl, or taken together with the nitrogen to which they are attached, form a 3,
4, 5, or 6-membered saturated or partially unsaturated ring optionally containing
0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2,
or N-R"", wherein R"" is hydrogen or (Ci-C6)alkyl; Ri is optionally substituted
with 1, 2 or 3 (d-C6)alkyl, (Ci-C6)alkoxy or (Ci-C6)haloalkyl or 1, 2 or 3 groups
independently selected from Rg:

Rg is hydrogen, (C3-C6)alkyl, aryl, aralkyl, (C3-C6)cycloalkyl, (C3-
C6)cycloalkyl(Ci-C6)alkyl, (C3-C6)heterocycloalkyl, (C3-C6)heterocycloalkyl(Ci-
alkyl, heteroaryl, heteroaralkyl, (C6)carboxyalkyl, aryloxycarbonylalkyl, alkenylen-NR'R", wherein R' and R" are each independently hydrogen, (C6)alkyl, or taken together with the nitrogen to which they are attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from O, S(O)x, wherein x is 0, 1, or 2, or N-R"", wherein R"" is hydrogen or (C6)alkyl; R2 is optionally substituted with 1, 2 or 3 (C1-C6)alkyl, (C1-C6)alkoxy or (C1-C6)haloalkyl or 1, 2 or 3 groups independently selected from Rα; 
or R1 and R2 can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3 heteroatoms and optionally substituted with Rα;
R3 is hydrogen or (C6)alkyl;
m is 0, 1, or 2;
R4 is hydrogen or (C6)alkyl;
R5 is hydrogen or (C6)alkyl;
R6 and R7 are each independently hydrogen, halogen, (C6)alkyl or (C6)alkoxy, either of which may be optionally substituted on carbon with 1, 2, or 3 groups independently selected from Rα;
R8 is hydrogen, halo or (C6)alkyl;
Rio is hydrogen or (C6)alkyl; or
R9 and R10 together with the atoms to which they are attached, form a 4-8 membered ring, optionally substituted on carbon with 1, 2, or 3 groups selected from halo,
(C6)alkyl, and -O-(d-C6)alkyl, -S-(d-C6)alkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 halo, or taken together with the attached carbon form C=O;
A is aryl, aryloxy, heteroaryl, cycloalkyl, or heterocycloalkyl;
B is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;
Rn is hydrogen or (C6)alkyl; R12 is hydrogen, (C6)alkyl, -CO(C6)alkyl, -CO(C1-C6)cycloalkyl, -CO(C6)heterocycloalkyl, -CO(C6)aryl, -CO(C6)heteroaryl, cycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups independently selected from Ra; or
Rn and R12 can be taken together to form a 5-7 membered heterocycle having 1.
2, or 3 heteroatoms having 1, 2 or 3 heteroatoms and optionally substituted with 
R_a,
at least two of three of Z_1, Z_2, and Z_3 are N and the other is C-R_b, wherein R_b is 
hydrogen, halogen, (Ci-C_6)alkyl, or (Ci-C_6)alkoxy;
R_a is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, 
(Ci-C_6)alkyl-NH, ((Ci-C_6)alkyl)_2-N, aryl, heteroaryl, (C_3-C_7)cycloalkyl, (C_1-
C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, (C_1-C_6)
alkenyloxy, (C_1-C_6)alkynlyoxy, (C_1-C_6)alkylthio, (C_1-C_6)alkylsulfanyl, (C_1-C_6)
alkylsulfonyl, amino, (Ci-C_6)alkylamino, di-[(Ci-C_6)alkyl]amino, formyl, -C(=O)(Ci-C_6)alkyl,
-C(=N)(Ci-C_6)alkyl, carboxy, CO_2(Ci-C_6)alkyl, CONH_2, -C(=N)NH_2, -
C(=N)NH(Ci-C_6)alkyl, -C(=N)N(Ci-C_6)alkyl)_2, CONH(Ci-C_6)alkyl, CON((d-
C_6)alkyl)_2, -OC(O)(Ci-C_6)alkyl, -OC(O)NH_2, -OC(O)NH(Ci-C_6)alkyl, -
OC(O)NH((Ci-C_6)alkyl)_2, -NHCO(Ci-C_6)alkyl, -N(Ci-C_6)alkyl-C(O)(Ci-
C_6)alkyl, -NH(Ci-C_6)NH_2, -N(Ci-C_6)alkyl-C(O)NH_2, N(Ci-C_6)alkyl-C(O)NH(d-
C_6)alkyl, N(Ci-C_6)alkyl-C(O)NH(Ci-C_6)alkyl)_2, -NH-C(O)NH(Ci-C_6)alkyl)_2, N-
(Ci-C_6)alkylsulfamoyl, N,N-di-[(Ci-C_6)alkyl]sulfamoyl, (C_1-
C_6)alkylsulfonylamino, or N-(Ci-C_6)alkyl-(Ci-C_6)alkylsulfonylamino, any of 
which may be optionally substituted on carbon with R_c and 
R_c is halogen, trifluoromethyl, trifluoromethoxy, (Ci-C_6)alkyl, amino, cyano, 
nitro, or hydroxyl.

4. A compound of formula IV:

or a pharmaceutically acceptable salt thereof, wherein:

Y is H, halo, OR_i, SR_i, (d-C_6)alkyl, (C_3-C_6)cycloalkyl, aryl, aralkyl, 
(C_3-C_6)heterocycloalkyl, heteroaryl, heteroaralkyl, or NR_iR_j;
R_i is hydrogen, (Ci-C_6)alkyl, aryl, aralkyl, (C_3-C_6)cycloalkyl, (C_3-
C_6)cycloalkyl(Ci-C_6)alkyl, (C_3-C_6)heterocycloalkyl, (C_3-
C_6)heterocycloalkyl(Ci-C_6)alkyl, heteroaryl, heteroaralkyl, (C_1-
C_6)carboxyalkyl, aryloxy(Ci-C_6)alkyl,
-alkylene-NR'R", wherein R' and R" are each independently hydrogen, (Ci-C6)alkyl, or taken together with the nitrogen to which they are
attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from
O, S(O)x, wherein x is 0, 1, or 2, or N-R"", wherein R"" is hydrogen or
(Ci-Ce)alkyl; Ri is optionally substituted with 1, 2 or 3 (Ci-C6)alkyl, (Ci-
Ce)alkoxy or (Ci-C6)heteroalkyl or 1, 2 or 3 groups independently selected from R'a:
R2 is hydrogen, (Ci-Ce)alkyl, aralkyl, (C3-C6)cycloalkyl, (C3-
C6)cycloalkyl(Ci-C6)alkyl, (C3-C6)heterocycloalkyl, (C3-
C6)heterocycloalkyl(Ci-C6)alkyl, heteroaryl, heteroaralkyl, (Ci-
Ce)carboxyalkyl, ailoxy(Ci-C6)alkyl,
-alkylene-NR'R", wherein R' and R" are each independently hydrogen, (Ci-C6)alkyl, or taken together with the nitrogen to which they are
attached, form a 3, 4, 5, or 6-membered saturated or partially unsaturated ring optionally containing 0, 1, or 2 additional heteroatoms selected from
O, S(O)x, wherein x is 0, 1, or 2, or N-R"", wherein R"" is hydrogen or
(Ci-C6)alkyl; R2 is optionally substituted with 1, 2 or 3 (d-C6)alkyl, (Ci-
Ce)alkoxy or (Ci-C6)heteroalkyl or 1, 2 or 3 groups independently selected from R'a:
or Ri and R2 can be taken together to form a 5-7 membered heterocycle
having 1, 2 or 3 heteroatoms and optionally substituted with R'a;
R3 is hydrogen or (Ci-Ce)alkyl;
m is 0, 1, or 2;
X is absent, -CONR4-, or -SO2-, -SO2NR4-, or -COO-;
R4 is hydrogen or (Ci-C6)alkyl;
R5 is hydrogen, (Ci-Ce)alkyl, (C3-C6)cycloalkyl, heterocycloalkyl, aryl,
or heteroaryl, any of which may be optionally substituted with 1, 2, or 3

\[
\begin{array}{c}
\text{R}_{12}^N \\
\text{R}_{11}^O \\
\end{array}
\]

in which Rn is hydrogen or (Ci-C6) alkyl; R12 is hydrogen, (Ci-C6) alkyl, -CO(Ci-
Ce)alkyl, -CO(Ci-C6)cycloalkyl, -CO(C1-C6)heterocycloalkyl, -CO(C1-
Ce) aryl, -CO(Cr-Cr)heteroaryl, cycloalkyl, aryl, or heteroaryl, any of which may be optionally substituted with 1, 2, or 3 groups independently selected from Ra; or Rb; and Rb can be taken together to form a 5-7 membered heterocycle having 1, 2 or 3 heteroatoms and optionally substituted with Rb;

Re is hydrogen or (C1-Ce)alkyl; n is 0, 1, 2 or 3;

Rb and Rb are each independently hydrogen, halogen, (CrC6)alkyl or (C1-Ce)alkoxy, either of which may be optionally substituted on carbon with 1, 2, or 3 groups independently selected from Rb;

A is aryl, aryloxy, heteroaryl, cycloalkyl, or heterocycloalkyl;

at least two of three of Z1, Z2, and Z3 are N and the other is C-Rb, wherein Rb is hydrogen, halogen, (CrC6)alkyl, or (CrC6)alkoxy;

Rc is halogen, trifluoromethyl, trifluoromethoxy, cyano, nitro, hydroxy, amino, (C1-C6)alkyl-NH, ((C1-C6)alkyl)2-N, aryl, heteroaryl, (C5-C6)alkycycloalkyl, (C1-C6)alkyl, (C2-C6)alkenyl, (C1-C6)alkynyl, (C1-C6)alkoxy, (C2-C6)alkenlyloxy, (C1-C6)alkylthio, (C1-C6)alkylsulfinyl, (C1-C6)alkylsulfanyl, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, formyl, -C(=O)(C1-C6)alkyl, -C(=N)(C1-C6)alkyl, carboxy, CO2(C1-C6)alkyl, CONH2, -C(=NH)NH2, -Q=N)NH(C1-C6)alkyl, -Q=N)N(C1-C6)alkyl2, CONH(C1-C6)alkyl, C0N((C1-C6)alkyl)2, -OC(O)(C1-C6)alkyl, -OC(O)NH2, -OC(O)NH(C1-C6)alkyl, -OC(O)NH((C1-C6)alkyl)2, -NHC(O)(C1-C6)alkyl, -N(C1-C6)alkyl-C(O)(C1-C6)alkyl, -NH-C(O)NH2, -N(C1-C6)alkyl-C(O)NH2, N(C1-C6)alkyl-C(O)NH(C1-C6)alkyl, N(C1-C6)alkyl-C(O)NH(C1-C6)alkyl2, -NH-C(O)NH(C1-C6)alkyl2, N-(C1-C6)alkylsulfamoyl, N,N-di-[(C1-C6)alkyl]sulfamoyl, (C1-C6)alkylsulfonylamino, or N-(C1-C6)alkyl-(C1-C6)alkylsulfonylamino, any of which may be optionally substituted on carbon with Rc, and

Rc is halogen, trifluoromethyl, trifluoromethoxy, (C1-Ce)alkyl, amino, cyano, nitro, or hydroxy.
5. A compound selected from the group consisting of:
6. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of any of the preceding claims or a pharmaceutically acceptable salt thereof.

7. A method for treating or preventing an inflammatory disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of the preceding claims or a pharmaceutically acceptable salt thereof, thereby treating or preventing said inflammatory disorder.
8. A method of treating a condition or disease mediated by aggrecanase in a mammalian subject, comprising administering to the subject in need thereof a therapeutically effective amount of a compound of any of the preceding claims or a pharmaceutically acceptable salt thereof, thereby treating said condition or disease.

9. A method of treating a subject suffering from a disease selected from the group consisting of osteoarthritis, joint injury, reactive arthritis, acute pyrophosphate arthritis, psoriatic arthritis and rheumatoid arthritis, comprising administering to the subject a therapeutically effective amount of a compound of any of the preceding claims or a pharmaceutically acceptable salt thereof, thereby treating said subject.
## INTERNATIONAL SEARCH REPORT

### A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

### B. FIELDS SEARCHED

**Minimum documentation searched (classification system followed by classification symbols)**

C07D A61K A61P

**Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched**

**Electronic data base consulted during the international search (name of data base and, where practical, search terms used)**

- EPO-Internal, WPI Data, BEILSTEIN Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.

See patent family annex.

- Special categories of cited documents:
  - 'A' document defining the general state of the art which is not considered to be of particular relevance
  - 'E' earlier document but published on or after the international filing date
  - 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - 'O' document referring to an oral disclosure, use, exhibition or other means
  - 'P' document published prior to the international filing date but later than the priority date claimed
  - 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  - 'X' document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  - 'Y' document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
  - 'S' document member of the same patent family

Date of the actual completion of the international search: 20 August 2009

Date of mailing of the international search report: 31/08/2009

Name and mailing address of the ISA:
European Patent Office, P.B 5818 Patentlaan 2
NL - 2280 HV RIJSWIJK
Tel. (+31-70) 340-2040, Fax (+31-70) 340-3016

Authorized officer: Skulj, Primoz
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<td>LOWIK D W P ET AL: &quot;Synthesis of Macrocyclic, Triazine-Based Receptor Molecules&quot;</td>
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<td>EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, WILEY-VCH VERLAG, WEINHEIM, DE, 2001, pages 2825-2839, XP002274796</td>
<td></td>
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<tr>
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<td>ISSN: 1434-193X compounds 32-33</td>
<td></td>
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<td>IRIKURA TSUTOMU ET AL: &quot;New s-Triazine Derivatives as Depressants for Reticuloendothelial Hyperfunction Induced by Bacterial Endotoxin&quot;</td>
<td>1,6</td>
</tr>
<tr>
<td></td>
<td>ISSN: 0022-2623 table III; compounds 109,124,138</td>
<td></td>
</tr>
<tr>
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<td>SCHUERER, STEPHAN C. ET AL: &quot;Prospective Exploration of Synthetically Feasible, Medicinally Relevant Chemical Space&quot;</td>
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<tr>
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<td>JOURNAL OF CHEMICAL INFORMATION AND MODELING, 45(2), 239-248 CODEN: JCISD8; ISSN: 1549-9596, 2005, XP002475631</td>
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</tr>
<tr>
<td>X</td>
<td>US 2003/191307 A1 (BLUMENKOPF TODD A [US] ET AL) 9 October 2003 (2003-10-09) paragraphs [0103], [OH1]; claims 1,29; examples 17,18</td>
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<td>WO 2007/109045 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; BATT DAVID BRYANT [US]; B) 27 September 2007 (2007-09-27) paragraphs [0023] - [0031], [0073], [0137]; claims 1, 48</td>
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<td>WO 00/53595 A (ASTRAZENECA AB [SE]; BREAULT GLORIA ANNE [GB]; JAMES STEWART RUSSELL [ ] 14 September 2000 (2000-09-14) example 6</td>
<td>4, 6</td>
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<tr>
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<td>WO 2005/009980 A (NEUROGEN CORP [US]; BAKTHAVATCHALAM RAJAGOPAL [US]; DARROW JAMES W [US]; 3 February 2005 (2005-02-03) claims 1, 93</td>
<td>1, 2, 6, 7, 9</td>
</tr>
<tr>
<td>X</td>
<td>WO 2006/034473 A (REDDY US THERAPEUTICS INC [US]; KALLEDA SRINIVAS [IN]; PADAKANTI SRINI; 30 March 2006 (2006-03-30) page 161; example 26</td>
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<tr>
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<td>WO 03/031431 A (SQUIBB BRISTOL MYERS CO [US]; 17 April 2003 (2003-04-17) page 1, paragraph 1 claim 1</td>
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### INTERNATIONAL SEARCH REPORT

Information on patent family members

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<td></td>
<td>EP 1390354 Al</td>
<td>25-02-2004</td>
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<tr>
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<td>WO 02083653 Al</td>
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<td>EP 2001864 Al</td>
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<td>AU 754967 B2</td>
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<td>AU 2818700 A</td>
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