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ACETYLENIC ARYL SULFONAMIDE AND PHOSPHINIC ACID AMIDE HYDROXAMIC ACID TACE INHIBITORS

FIELD OF INVENTION

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This invention relates to acetylenic aryl sulfonamide hydroxamic acids which act as inhibitors of TNF- α converting enzyme (TACE). The compounds of the present invention are useful in disease conditions mediated by TNF- α , such as rheumatoid arthritis, osteoarthritis, sepsis, AIDS, ulcerative colitis, multiple sclerosis, Crohn's disease and degenerative cartilage loss.

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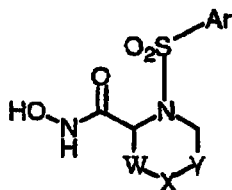
BACKGROUND OF THE INVENTION

TNF- α converting enzyme (TACE) catalyzes the formation of TNF- α from membrane bound TNF- α precursor protein. TNF- α is a pro-inflammatory cytokine that is believed to have a role in rheumatoid arthritis [Shire, M. G.; Muller, G. W. *Exp. Opin. Ther. Patents* 1998, 8(5), 531; Grossman, J. M.; Brahn, E. J. *Women's Health* 1997, 6(6), 627; Isomaki, P.; Punnonen, J. *Ann. Med.* 1997, 29, 499; Camussi, G.; Lupia, E. *Drugs*, 1998, 55(5), 613.] septic shock [Mathison, et. al. *J. Clin. Invest.* 1988, 81, 1925; Miethke, et. al. *J. Exp. Med.* 1992, 175, 91.], graft rejection [Piguet, P. F.; Grau, G. E.; et. al. *J. Exp. Med.* 1987, 166, 1280.], cachexia [Beutler, B.; Cerami, A. *Ann. Rev. Biochem.* 1988, 57, 505.], anorexia, inflammation [Ksontini, R.; MacKay, S. L. D.; Moldawer, L. L. *Arch. Surg.* 1998, 133, 558.], congestive heart failure [Packer, M. *Circulation*, 1995, 92(6), 1379; Ferrari, R.; Bachetti, T.; et. al. *Circulation*, 1995, 92(6), 1479.], post-ischaemic reperfusion injury, inflammatory disease of the central nervous system, inflammatory bowel disease, insulin resistance [Hotamisligil, G. S.; Shargill, N. S.; Spiegelman, B. M.; et. al. *Science*, 1993, 259, 87.] and HIV infection [Peterson, P. K.; Gekker, G.; et. al. *J. Clin. Invest.* 1992, 89, 574; Pallares-Trujillo, J.; Lopez-Soriano, F. J. *Argiles, J. M. Med. Res. Reviews*, 1995, 15(6), 533.], in addition to its well-documented antitumor properties [Old, L. *Science*, 1985, 230, 630.]. For example, research with anti-TNF- α antibodies and transgenic animals has demonstrated that blocking the formation of TNF- α inhibits the progression of arthritis [Rankin, E.C.; Choy, E.H.; Kassimos, D.; Kingsley, G.H.; Sopwith, A.M.; Isenberg, D.A.; Panayi, G.S. *Br. J. Rheumatol.* 1995, 34, 334; *Pharmaprojects*, 1996, Therapeutic Updates 17 (Oct.), au197-M2Z.]. This observation has recently been extended to humans as well as described in "TNF- α in Human Diseases", *Current Pharmaceutical Design*, 1996, 2, 662.

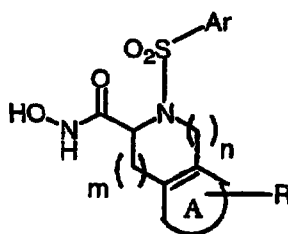
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Publications disclosing β -sulfonamide-hydroxamate inhibitors of MMPs and/or TACE in which the carbon alpha to the hydroxamic acid has been joined in a ring to the sulfonamide nitrogen, as shown below, include U. S. patent 5,753,653, WIPO international publications WO9633172, WO9720824, WO9827069, 5 WO9808815, WO9808822, WO9808823, WO9808825, WO9834918, WO9808827, Levin, *et. al. Bioorg. & Med. Chem. Letters* 1998, 8, 2657 and Pikul, *et. al. J. Med. Chem.* 1998, 41, 3568.

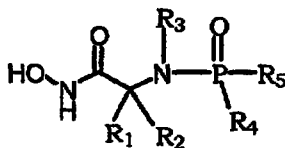


10 The patent applications DE19,542,189-A1, WO9718194, and EP803505 disclose additional examples of cyclic sulfonamides as MMP and/or TACE inhibitors. In this case the sulfonamide-containing ring is fused to a aromatic or heteroaromatic ring.



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Analogous to the sulfonamides are the phosphinic acid amide hydroxamic acid MMP/TACE inhibitors, exemplified by the structure below, which have been disclosed in WIPO international publication WO9808853.



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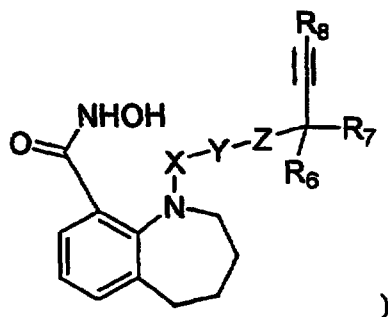
Sulfonamide MMP/TACE inhibitors in which a thiol is the zinc chelating group, as shown below, have been disclosed in WIPO international application 9803166.

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R_5 is hydrogen or alkyl of 1-6 carbon atoms;

or R_5 -N-A-, can form a benzazepine, benzoxazepine, benzothiazepine, benzodiazepine, benzazocine, benzodiazocine, benzoxazocine or benzothiazocane ring which may be optionally fused to another benzene ring, (for example a compound of formula B where R_5 -N-A- forms a benzazepine ring has the following formula:



R_6 and R_7 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, -CCH₃;

and R_8 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, naphthyl, 5 to 10 membered heteroaryl having from 1 to 3 heteroatoms selected from N, NR_x, O or S, or 5 to 9 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, NR_x, O or S;

R_9 is hydrogen, phenyl, naphthyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms;

and R_{10} is phenyl, naphthyl, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, 5 to 10 membered heteroaryl having from 1 to 3 heteroatoms selected from N, NR_x, O or S, or 5 to 9 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, NR_x, O or S; or a pharmaceutically acceptable salt thereof.

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the carbon of group A para to the $-NR^5-$ group has a substituent other than hydrogen;

Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively;

5 X is SO_2 ;
and Z is oxygen.

More preferred compounds of this invention include compounds of structure B in which A is a phenyl wherein:

10 both of the carbons of A adjacent to the $-NR^5-$ group has a substituent other than hydrogen; and

the carbon of group A para to the $-NR^5-$ group has a substituent other than hydrogen;

Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively;

15 X is SO_2 ;
Z is oxygen;
and R_6 and R_7 are hydrogen.

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both of the carbons of A adjacent to the $-NR^5-$ group has a substituent other than hydrogen;

25 the carbon of group A para to the $-NR^5-$ group has a substituent other than hydrogen;

Y is a phenyl ring substituted at the 1- and 4-positions by X and Z, respectively;

30 X is SO_2 ;
Z is oxygen;
 R_6 and R_7 are hydrogen;
and R_8 is $-CH_2OH$ or methyl.

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2-[Benzyl-(4-but-2-ynyloxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-benzamide;

5 5-Bromo-N-hydroxy-3-methyl-2-{methyl-[4-(4-pyrrolidin-1-yl-but-2-ynyloxy)-benzenesulfonyl]-amino}-benzamide;

5-Bromo-2-[[4-(4-diethylamino-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino]-N-hydroxy-3-methyl-benzamide;

10 5-Bromo-2-[(4-but-2-ynyloxy-benzenesulfonyl)-(4-methyl-piperazin-1-ylmethyl)-amino]-N-hydroxy-3-methyl-benzamide;

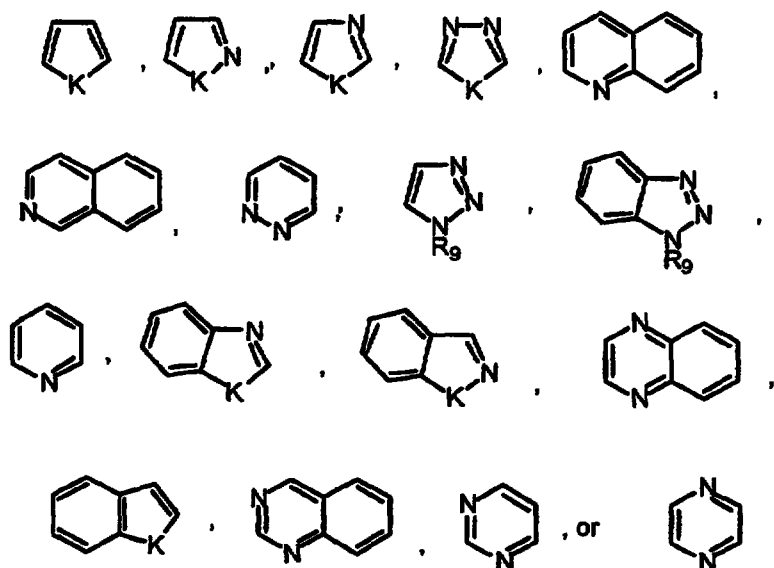
15 5-Bromo-N-hydroxy-3-methyl-2-(methyl-{4-[4-(tetrahydro-pyran-2-yloxy)-but-2-ynyloxy]-benzenesulfonyl}-amino)-benzamide;

5-Bromo-N-hydroxy-2-[[4-(4-hydroxy-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino]-3-methyl-benzamide;

20 4-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-5-(4-methyl-piperazin-1-ylmethyl)-biphenyl-3-carboxylic acid hydroxyamide dihydrochloride salt;

and pharmaceutical salts thereof.

25 Heteroaryl, as used herein is a 5-10 membered mono- or bicyclic aromatic ring having from 1-3 heteroatoms selected from N, NR₉, S and O. Heteroaryl is preferably



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Alkyl, alkenyl, alkynyl, and perfluoroalkyl include both straight chain as well as branched moieties. Alkyl, alkenyl, alkynyl, and cycloalkyl groups may be unsubstituted (carbons bonded to hydrogen, or other carbons in the chain or ring) or may be mono- or poly-substituted.

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Halogen means bromine, chlorine, fluorine, and iodine.

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Suitable substituents of aryl, heteroaryl, alkyl, alkenyl, alkynyl, cycloalkyl and include, but are not limited to halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, $-OR_2$, $-CN$, $-COR_2$, perfluoroalkyl of 1-4 carbon atoms, $-O$ -perfluoroalkyl of 1-4 carbon atoms, $-CONR_2R_3$, $-S(O)_nR_2$, $-OPO(OR_2)OR_3$, $-PO(OR_2)R_3$, $-OC(O)NR_2R_3$, $-C(O)NR_2OR_3$, $-COOR_2$, $-SO_3H$, $-NR_2R_3$, $-N[(CH_2)_2]_2NR_2$, $-NR_2COR_3$, $-NR_2COOR_3$, $-SO_2NR_2R_3$, $-NO_2$, $-N(R_2)SO_2R_3$, $-NR_2CONR_2R_3$, $-NR_2C(=NR_2)NR_2R_3$, $-NR_2C(=NR_2)N(SO_2R_2)R_3$, $NR_2C(=NR_2)N(C=O)R_2R_3$, $NR_2C(=NR_2)N(SO_2R_2)R_3$, $NR_2C(=NR_2)N(COR_2)R_3$, $-SO_2NHCOR_3$, $-CONHSO_2R_3$, tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_2R_3$, phenyl, naphthyl, heteroaryl or heterocycloalkyl;

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wherein $-NR_2R_3$ may form a pyrrolidine, piperidine, morpholine, thiomorpholine, oxazolidine, thiazolidine, pyrazolidine, piperazine, or azetidine ring;

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R_2 and R_3 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, naphthyl, heteroaryl or heterocycloalkyl;

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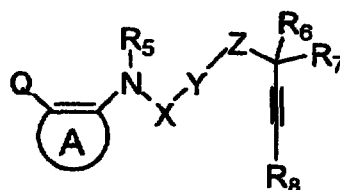
R_4 is alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms; perfluoroalkyl of 1-4 carbon atoms, phenyl, naphthyl, heteroaryl or heterocycloalkyl; and n is 0 to 2.

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healing, periodontal disease, graft rejection, insulin resistance, bone disease and HIV infection. In particular, the compounds of the invention provide enhanced levels of inhibition of the activity of TACE in vitro and in cellular assay and/or enhanced selectivity over MMP-1 and are thus particularly useful in the treatment of diseases mediated by TNF.

This invention also provides a process for preparing compounds of formula B as defined above which comprises one of the following:

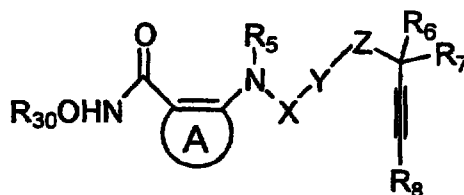
a) reacting a compound of formula V:



(V)

wherein R_5 , R_6 , R_7 , R_8 , A, X, Y and Z are as defined above and Q is COOH or a reactive derivative thereof, with hydroxylamine to give a corresponding compound of formula B; or

b) deprotecting a compound of formula VI:



(VI)

wherein R_5 , R_6 , R_7 , R_8 , A, X, Y and Z are as defined above, and R_{30} is a protecting group such as t-butyl, benzyl or trialkylsilyl, to give a compound of formula B;

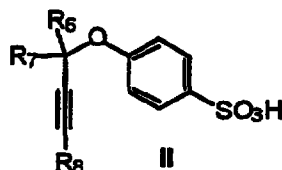
c) resolving a mixture (e.g. racemate) of optically active isomers of a compound of formula B to isolate one enantiomer or diastereomer substantially free of the other enantiomer or diastereomers;

or

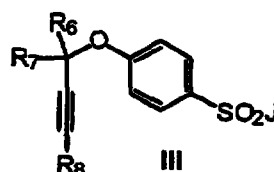
d) acidifying a basic compound of formula B with a pharmaceutically acceptable acid to give a pharmaceutically acceptable salt.

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into a compound of formula II



- 2) reacting a compound of formula II above, or a salt or solvate thereof, with a chlorinating agent such as thionyl chloride, chlorosulfonic acid, oxalyl chloride, phosphorus pentachloride, or other halogenating agents such as fluorosulfonic acid or thionyl bromide to a compound of formula III:



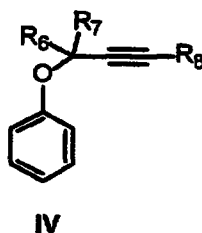
- 10 wherein J is fluorine, bromine, chlorine.

The resultant sulfonyl chloride, fluoride or bromide, may be further converted into triazolide, imidazolide or benzothiazolide derivatives, where J is 1,2,4-triazolyl, benzotriazolyl or imidazol-yl, by reacting the compound with 1,2,4-triazole, imidazole or benzotriazole, respectively. R₆, R₇ and R₈ are as defined above.

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The invention is still further directed to a process for making compounds of structure B involving one or more reactions as follows:

- 1) alkylating phenol, or a salt or solvate thereof, into a compound of formula IV:



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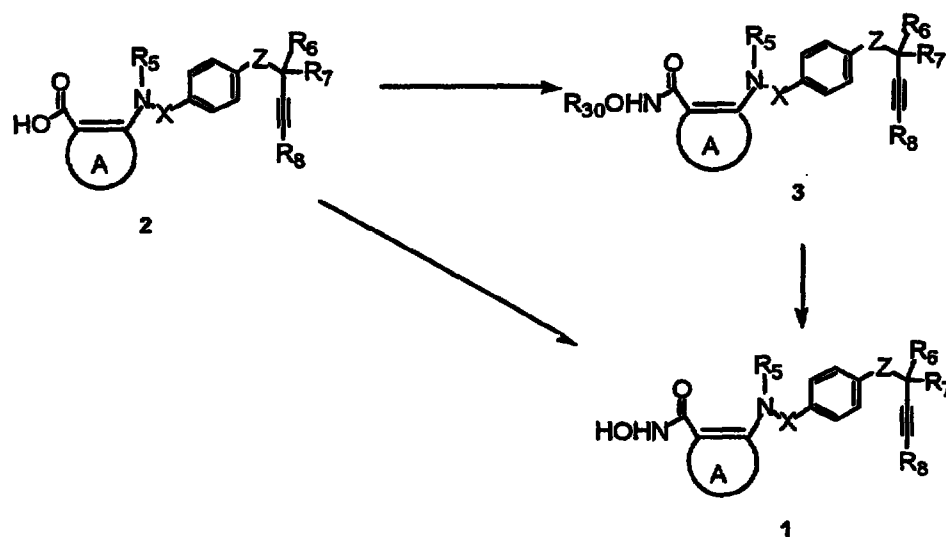
- 2) reacting a compound of formula IV above, or a salt or solvate thereof with chlorosulfonic acid to prepare a compound of formula II above.

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reaction with hydroxylamine to give 1, or with a protected hydroxylamine derivative to give 3. Compounds 3, wherein R_{30} is a t-butyl, benzyl, trialkylsilyl or other suitable masking group may then be deprotected by known methods to provide the hydroxamic acid 1.

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Scheme 1:

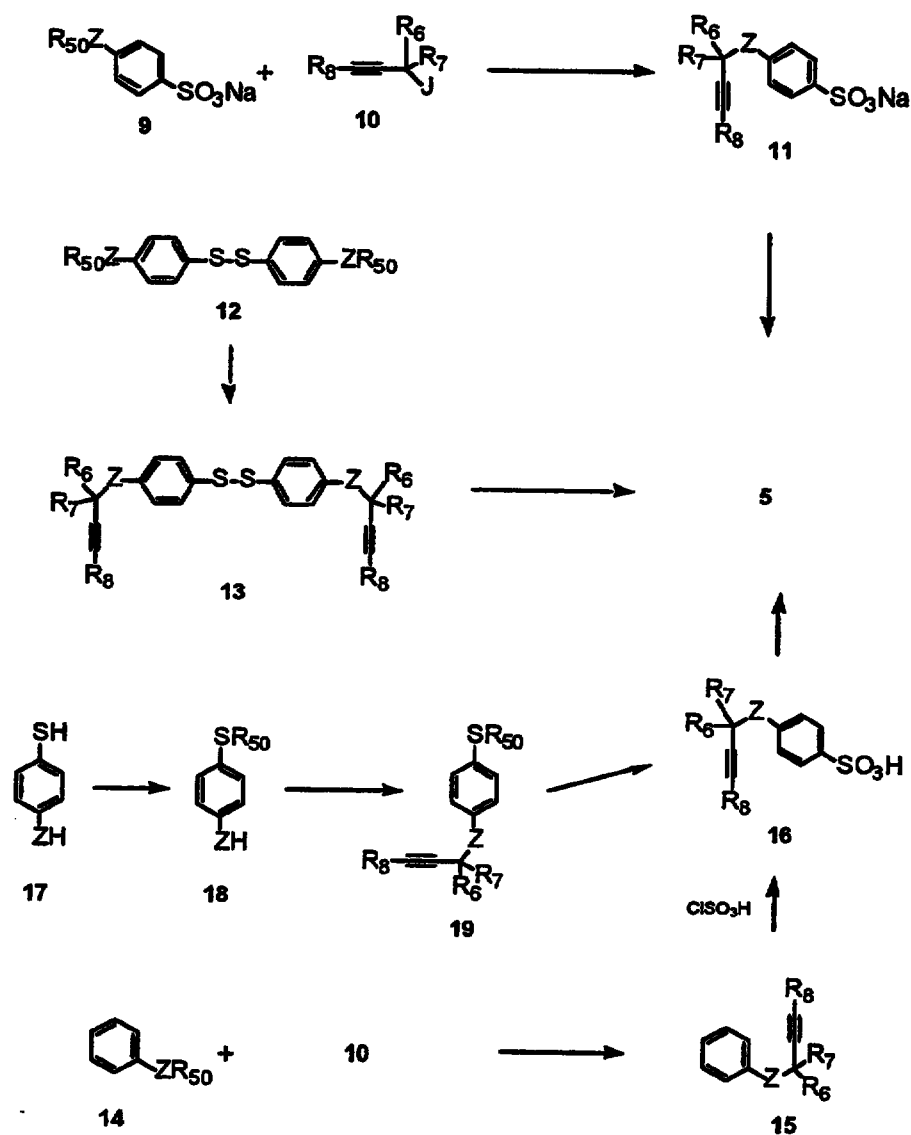


Carboxylic acids 2 may be prepared as shown in Scheme 2. Amino acid derivative 4, in which R_{40} is hydrogen or a suitable carboxylic acid protecting group, may be sulfonlated or phosphorylated by reacting with compounds 5, in which J is a suitable leaving group including, but not limited to chlorine. The N-H compound 6 may then be alkylated with R_3J and a base such as potassium carbonate or sodium hydride in a polar aprotic solvent such as acetone, N,N-dimethylformamide (DMF), or tetrahydrofuran (THF) to provide sulfonamide 7. Compound 7 is also available through direct reaction of 5 with an N-substituted amino acid derivative, 8. Conversion of 7 into the carboxylic acid is performed by acid, basic hydrolysis, or other method consistent with the choice of protecting group R_{40} and the presence of a carbon-carbon triple bond.

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where Z is O, N or S, and deprotection of the sulfur followed by oxidation to the sulfonic acid 16.

Scheme 3:

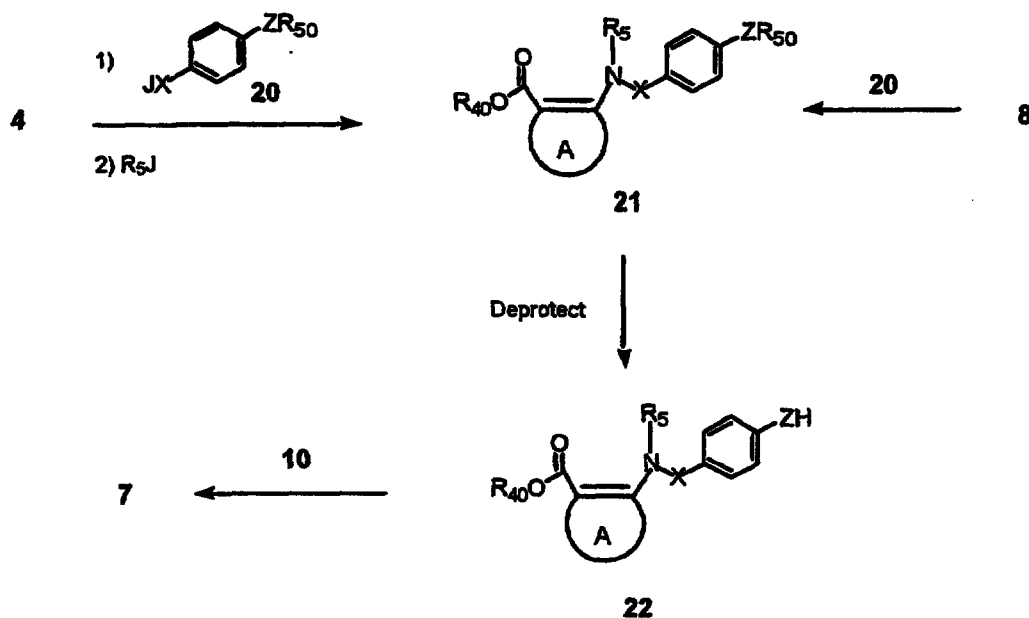


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The phosphorus containing analogs of 8 may be prepared using similar methodology, as shown in Scheme 4.

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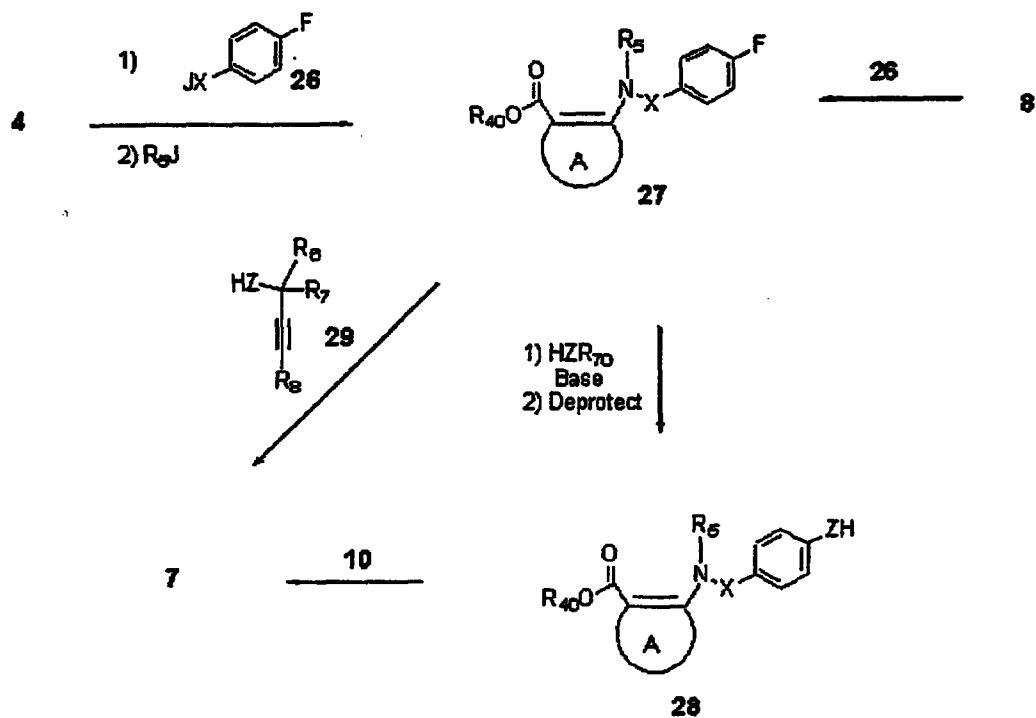
Scheme 5:



The propargylic amine analogs of **7** can be synthesized as shown in Scheme 6 starting from the amino acid derivatives **4** and/or **8**. Sulfonylation or phosphorylation with para-nitro aryl compound **23**, for example 4-nitrobenzenesulfonyl chloride, followed by alkylation with R_5J (for **4**) using a base such as potassium carbonate or sodium hydride in DMF provides **24**. Reduction of the nitro moiety with hydrogen and palladium on carbon, tin chloride or other known method to give aniline **25** and subsequent alkylation with **10** then provides **7**. Aniline **25** may be derivatized with a suitable nitrogen protecting group, such as t-butoxycarbonyl, to give **26** prior to alkylation with **10** subsequent deprotection after the alkylation step.

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Scheme 7:



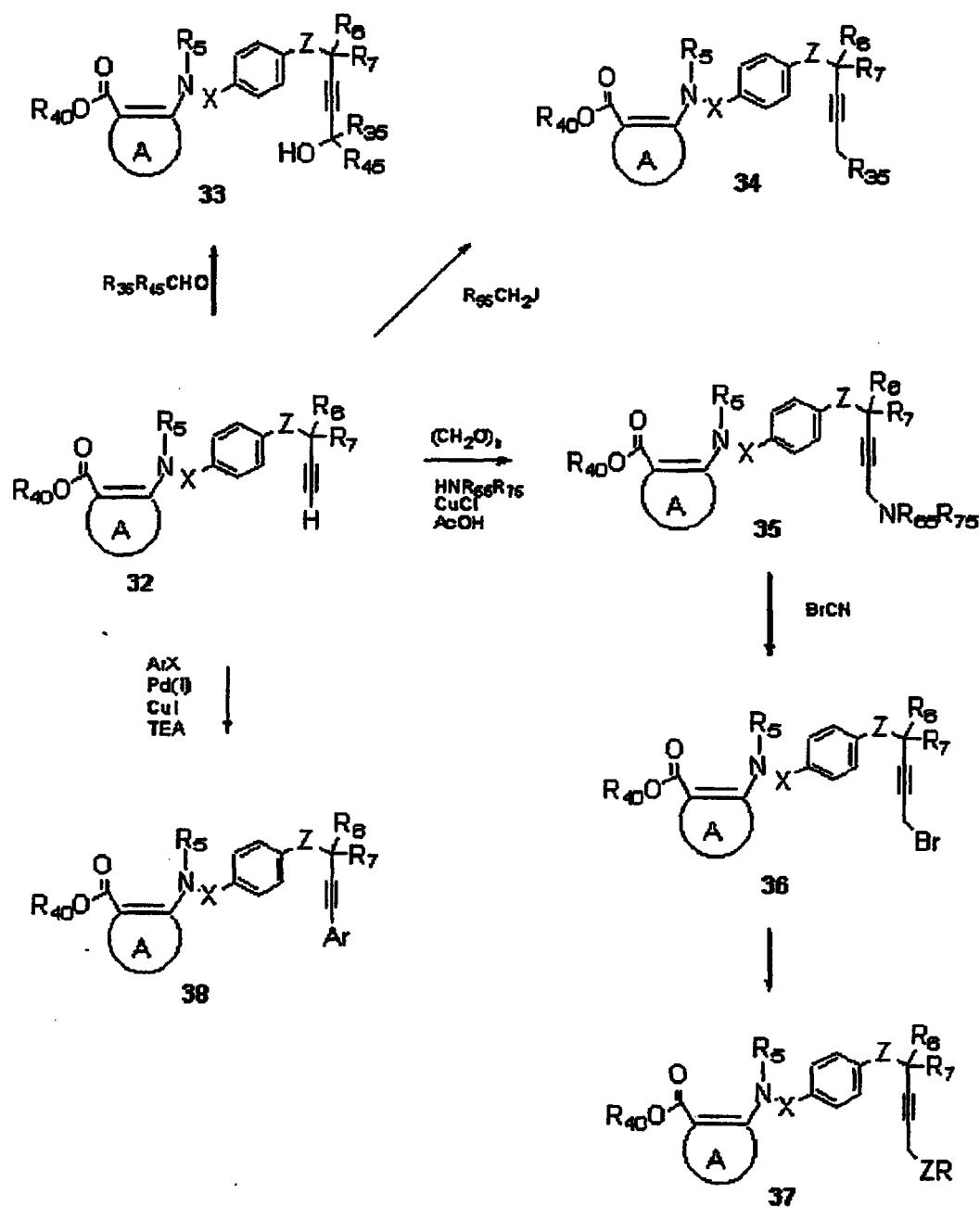
Compound 7, wherein Z is a methylene group, is available via 30, as shown in Scheme 8. Benzylic bromination of 30 with N-bromosuccinimide in a chlorinated hydrocarbon solvent provides bromide 31. This is followed by displacement of the bromide with the appropriate propynyl cuprate to provide sulfonamide 8.

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heteroaryl acetylenes 38. It is recognized by those skilled in the art of organic synthesis that the successful use of these methods is dependent upon the compatibility of substituents on other parts of the molecule. Protecting groups and/or changes in the order of steps described herein may be required.

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Scheme 9:



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Example 3**5-Bromo-2-[(4-hydroxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid**

To a solution of 17.0 mL (0.227 mol) of 2-butyne-1-ol in 375 mL of DMF at room temperature was added 9.08g (0.227 mol) of 60% sodium hydride. The
5 resulting mixture was stirred for 0.5h and then a solution of 17.8g (0.045 mol) of the product of **Example 2** dissolved in 50 mL of DMF was added to the reaction. The reaction mixture was then heated to reflux for 24h, cooled to room temperature and then acidified to pH 2 with 10% HCl solution. After stirring for 1h the resulting mixture was diluted with water and extracted with ethyl acetate. The combined
10 organics were then dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate/hexanes (1:3) to provide 12.5g (69%) of the desired phenol-carboxylic acid product as a white solid. Electrospray Mass Spec: 401.8 (M+H)⁺

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Example 4**5-Bromo-2-[(4-hydroxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid methyl ester**

To a solution of 15.2g (0.038 mol) of the product of **Example 3** in 125 mL of DMF was added 9.58g (0.114 mol) of sodium bicarbonate followed by 4.7 mL (0.076
20 mol) of iodomethane. The resulting mixture was stirred at room temperature for 5h and then diluted with ether and water. The organics were separated and washed with water, dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate/hexanes (1:3) to provide 12.27g (78%) of the desired phenol-ester product as a pale yellow solid. Electrospray
25 Mass Spec: 413.7 (M+H)⁺

Example 5**5-Bromo-3-methyl-2-[methyl-(4-prop-2-ynyloxy-benzenesulfonyl)-amino]-benzoic acid methyl ester**

30 To a solution of 0.317g (1.208 mmol) of triphenylphosphine dissolved in 5 mL of benzene and 2 mL of THF was added 0.070 mL (1.208 mmol) of propargyl

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Example 8**5-Bromo-2-[(4-hept-2-ynyloxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid**

According to the procedure of **Example 6** 0.250g (0.604 mmol) of the
5 product of **Example 4** was reacted with 0.077 mL (0.604 mmol) of 2-heptyn-1-ol to
give 0.246g of the ether-ester, followed by basic hydrolysis to give 0.214g (90%) of
the carboxylic acid as a white solid. Electrospray Mass Spec 494.0 (M+H)⁺

Example 9

10 **5-Bromo-2-[(4-hex-2-ynyloxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic
acid methyl ester**

According to the procedure of **Example 5** 0.250g (0.604 mmol) of the
product of **Example 4** was reacted with 0.059g (0.604 mmol) of 2-hexyn-1-ol to give
0.206g (69%) of the alkynyloxy ether. Electrospray Mass Spec 494.0 (M+H)⁺

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Example 10**5-Bromo-2-[(4-hex-2-ynyloxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic
acid**

To a solution of 0.206g (0.417 mmol) of the product of **Example 9** dissolved
20 in 4.0 mL of THF/methanol (1:1) and 0.5mL of 5.0N sodium hydroxide solution was
added. The reaction was stirred overnight at room temperature and then acidified with
10% HCl solution. The mixture was extracted with dichloromethane and the
combined organics were dried over MgSO₄, filtered and concentrated in vacuo to
provide a white solid which was washed with ether/hexanes (1:1) and dried in vacuo
25 to give 0.163g (82%) of the desired carboxylic acid product as a white solid.
Electrospray Mass Spec: 477.9 (M-H)⁻

Example 15**5-Bromo-3-methyl-2-(methyl-{4-[4-(tetrahydro-pyran-2-yloxy)-but-2-ynyloxy]-benzenesulfonyl}-amino)-benzoic acid methyl ester**

5 According to the procedure of **Example 5** 0.500g (1.208 mmol) of the product of **Example 4** was reacted with 0.226g (1.328 mmol) of 4-tetrahydropyran-2-butyn-1,4-diol to give 0.60g (88%) of the alkynyloxy ether as a colorless oil. Electrospray Mass Spec 567.9 (M+H)⁺

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Example 16**5-Bromo-2-[[4-(tert-butyl-dimethyl-silanyloxy)-benzenesulfonyl]-methyl-amino]-3-methyl-benzoic acid methyl ester**

 To a solution of 1.25g (3.019 mmol) of the product of **Example 4** in 5.0 mL of DMF was added 0.514g (7.548 mmol) of imidazole followed by 0.546g (3.623
15 mmol) of t-butyldimethylsilyl chloride. The resulting mixture was stirred at room temperature for 15h and then diluted with ether and water. The organics were washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate/hexanes (1:10) to provide 1.34g (84%) of the silyl ether as a white solid. Electrospray Mass Spec 527.8 (M+H)⁺

20

Example 17**2-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-5-iodo-3-methyl-benzoic acid methyl ester**

 To a solution of 0.340g (0.644 mmol) of the product of **Example 16** in 30 mL of dioxane was added 1.30 mL (2.576 mmol) of bis(tributyltin) followed by 0.059g
25 (0.051 mmol) of tetrakis(triphenylphosphine)palladium(0). The resulting mixture was heated to reflux overnight and then concentrated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate/hexanes (1:20) to provide 0.34g (72%) of the desired aryl stannane.

30

 The stannane was then dissolved in 50 mL of chloroform and 10 mL of a 0.1M solution of iodine in chloroform was added dropwise. After 15 minutes at room

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over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate/hexanes (1:3) to provide 0.090g (87%) of the phenol-ester. Electrospray Mass Spec 425.9 (M+H)⁺

5

Example 20**2-[Benzyl-(4-but-2-ynyloxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid methyl ester**

According to the procedure of **Example 5** 0.250g (0.588 mmol) of the product of **Example 19** was reacted with 0.44 mL (0.588 mmol) of 2-butyne-1-ol to give 0.203g (72%) of the alkynyloxy ether as a white solid. Electrospray Mass Spec 477.9 (M+H)⁺

10

Example 21**5-Bromo-2-[(4-hydroxy-benzenesulfonyl)-(4-methyl-piperazin-1-ylmethyl)-amino]-3-methyl-benzoic acid methyl ester**

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To a solution of 1.0g (1.894 mmol) of the product of **Example 16** in 60 mL of carbon tetrachloride was added 0.405g of N-bromosuccinimide. The resulting mixture was heated to reflux for 2h while being irradiated by a sun lamp. The reaction was then cooled to room temperature, washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo.

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The residue was dissolved in 5.0 mL of DMF and 0.784g (5.682 mmol) of potassium carbonate was added followed by 0.21 mL (1.894 mmol) of 1-methylpiperazine. The resulting mixture was stirred for 48h at room temperature and then diluted with water and ethyl acetate. The organics were washed with water and then extracted with 10% HCl solution. The acid layer was neutralized with 1.0N NaOH solution and extracted with dichloromethane. The combined dichloromethane extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to provide 0.501g (52%) of the piperazine-phenol as a white solid. Electrospray Mass Spec 511.9 (M+H)⁺

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Example 24**5-Bromo-2-([4-(4-diethylamino-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino)-3-methyl-benzoic acid methyl ester**

According to the procedure of **Example 23** 1.00g (2.212 mmol) of the
5 product of **Example 5** provides 0.749g (63%) of the diethylamino-alkyne as a yellow
oil after chromatography on silica gel eluting with ethyl acetate. Electrospray Mass
Spec 536.9 (M+H)⁺

Example 25

10 **5-Bromo-2-([4-(4-bromo-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino)-3-
methyl-benzoic acid methyl ester**

To a 0° solution of 0.707g (1.317 mmol) of the product of **Example 24**
dissolved in 10 mL of ether was added 0.53 mL of a 3.0M solution of cyanogen
bromide in dichloromethane. The reaction was warmed to room temperature and
15 stirred overnight. The reaction mixture was then filtered and the filtrate was diluted
with ether, washed with 5% HCl solution and brine. The organics were dried over
Na₂SO₄, filtered and concentrated in vacuo to provide 0.628g (88%) of the
propargylic bromide as a light brown oil.

20

Example 26

**5-Bromo-2-([4-(4-methoxy-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino)-3-
methy-l-benzoic acid**

To a solution of 0.117g (0.215 mmol) of the product of **Example 25** in 1.0
mL of THF and 3.0 mL of methanol was added 0.5 mL of a 5.0N solution of sodium
25 hydroxide followed by 3.6mg of tetrabutylammonium hydrogen sulfate. The resulting
reaction mixture was stirred at room temperature for 15h and then acidified with 10%
HCl solution and extracted with dichloromethane. The combined organics were dried
over MgSO₄, filtered and concentrated in vacuo to provide 0.083g (81%) of the bis-
propargylic ether carboxylic acid as a white solid. Electrospray Mass Spec 481.8
30 (M+H)⁺

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0.061 mL (0.792 mmol) of DMF and the mixture was stirred at 0° for 15 minutes. A solution of 0.164g of the carboxylic acid, dissolved in 1 mL of DMF, was then added and the reaction was warmed to room temperature. The resulting mixture is stirred for 1h at room temperature and then poured into a 0° mixture of 0.8 mL of water, 4.0 mL of THF and 0.25 mL of a 50% aqueous solution of hydroxylamine. The reaction is allowed to warm to room temperature overnight and the organics are then concentrated in vacuo. The residue is diluted with ethyl acetate, washed with water and saturated sodium bicarbonate, dried over Na₂SO₄, filtered and concentrated in vacuo to provide 0.153g (91%) of the carbamate-hydroxamic acid as a white foam.

Electrospray Mass Spec 637.9 (M+H)⁺

Example 29

5-Bromo-3-methyl-2-{methyl-[4-(4-methylamino-but-2-ynyloxy)-benzenesulfonyl]-amino}-benzoic acid methyl ester

According to the procedure of Example 27 0.325g (0.596 mmol) of the product of Example 25 reacted with methylamine to provide 0.132g (45%) of the propargylic methylamine as a brown oil. Electrospray Mass Spec 495.0 (M+H)⁺

Example 30

(4-{4-[(4-Bromo-2-hydroxycarbamoyl-6-methyl-phenyl)-methyl-sulfamoyl]-phenoxy}-but-2-ynyl)-methyl-carbamic acid tert-butyl ester

According to the procedure of Example 28 0.110g (0.222 mmol) of the product of Example 29 was converted into 0.090g of the carbamate-hydroxamic acid. Electrospray Mass Spec 598.0 (M+H)⁺

Example 31

5-Bromo-2-{[4-(4-cyclobutylamino-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino}-N-hydroxy-3-methyl-benzamide

To a solution of 0.100g (0.157 mmol) of the product of Example 28 in 2.0 mL of dichloromethane was added 1.0 mL of trifluoroacetic acid. The resulting solution was stirred at room temperature for 1h and then concentrated in vacuo. The

Example 34**5-Bromo-2-((4-[4-(2-dimethylamino-ethylamino)-but-2-ynloxy]-benzenesulfonyl)-methyl-amino)-N-hydroxy-3-methyl-benzamide**

5 According to the procedure of Example 27 0.300g (0.550 mmol) of the product of Example 25 reacted with 0.302 mL (2.75 mmol) of N,N-dimethylethylenediamine to provide 0.114g (38%) of the propargylic diamine-ester.

According to the procedure of Example 28 0.192g (0.348 mmol) of the diamine-ester was converted to the t-butyl carbamate, followed by hydrolysis of the ester and conversion of the carboxylic acid into 0.073g of the carbamate-hydroxamic acid.

According to the procedure of Example 31 0.057g of the carbamate-hydroxamic acid was converted into 0.040g of the desired bis-hydrochloride salt of the diamino-hydroxamic acid, obtained as a brown solid. Electrospray Mass Spec

15 553.0 (M+H)⁺

Example 35**5-Bromo-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid methyl ester**

20 To a solution of 5.00g (0.012 mol) of 5-bromo-2-(4-methoxy-benzenesulfonylamino)-3-methyl-benzoic acid methyl ester (U. S. Patent 5,776,961) in 40 mL of DMF was added 0.604g (0.015 mol) of 60% sodium hydride. The resulting mixture was stirred at room temperature for 0.5h and then 1.2 mL (0.018 mol) of iodomethane was added. The reaction was then stirred for 15h and then

25 diluted with ether. The organics were washed with water, dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with ether and the resulting white solid was collected by filtration and dried in vacuo to provide 4.45g (86%) of the N-methyl sulfonamide. Electrospray Mass Spec 429.8 (M+H)⁺

Example 38**5-Bromo-2-[(4-butoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid**

To a solution of 0.204g (0.434 mmol) of the product of **Example 37** in 6.0 mL of THF/methanol (1:1) was added 2.2mL of 1.0N sodium hydroxide solution.

- 5 The reaction was heated to reflux overnight, cooled to room temperature and acidified with 5% HCl solution. The mixture was extracted with ethyl acetate, washed with brine and the combined organics were then dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with ether/hexanes (1:1) and the solid was collected and dried in vacuo to provide 0.206g (104%) of the desired
- 10 carboxylic acid product as a white solid. Electrospray Mass Spec: 455.8 (M+H)⁺

Example 39**5-Bromo-2-[(4-butoxy-benzenesulfonyl)-methyl-amino]-N-hydroxy-3-methyl-benzamide**

- 15 To a 0° solution of 0.54 mL (1.072 mmol) of a 2.0M solution of oxalyl chloride in dichloromethane, diluted with 4.7 mL of dichloromethane, is added 0.083 mL (1.072 mmol) of DMF and the reaction is stirred for 15 minutes at 0° C. A solution of 0.163g (0.357 mmol) of the carboxylic acid product of **Example 38**, dissolved in 1 mL of DMF, was added to the reaction and the resulting mixture is
- 20 stirred for 1h at room temperature and then poured into a 0° mixture of 1.0 mL of water, 5.4 mL of THF and 0.34 mL of a 50% aqueous solution of hydroxylamine. The reaction is allowed to warm to room temperature overnight and the organics are then concentrated in vacuo. The residue is diluted with ethyl acetate, washed with 5% HCl solution, water and saturated sodium bicarbonate, dried over Na₂SO₄, filtered
- 25 and concentrated in vacuo to provide 0.157g (93%) of the hydroxamic acid as a white foam. Electrospray Mass Spec 506.8 (M+H)⁺

Example 40**4-Amino-5-methyl-biphenyl-3-carboxylic acid methyl ester**

- 30 To a solution of 5.0g (0.021 mol) of 2-amino-5-bromo-3-methyl-benzoic acid methyl ester and 2.8g (0.023 mol) of phenyl boronic acid in 150 mL of

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reaction mixture was quenched by the addition of water and the aqueous layer was extracted three times with dichloromethane. The organics were combined, washed with water and brine, dried over MgSO_4 , and concentrated in vacuo to provide 0.9 g (68%) of 5-methyl-4-[4-(1-methylpyridinium-4-oxy-benzenesulfonyl)-methyl-amino]-biphenyl-3-carboxylic acid methyl ester iodide as a yellow solid. Electrospray Mass Spec: 503.1 (M+H)⁺

To a solution of 0.4 g (0.79 mmol) of the pyridinium salt in $\text{THF}:\text{MeOH}:\text{H}_2\text{O}$ (2:1:1, 3 mL total) was added 0.037g (0.88 mmol) of lithium hydroxide and the reaction was heated to reflux overnight. The reaction was neutralized with 6M HCl solution and extracted three times with ethyl acetate. The organics were combined, washed with brine, dried over MgSO_4 , and concentrated in vacuo to provide 282 mg (86%) of 4-[(4-hydroxy-benzenesulfonyl)-methyl-amino]-5-methyl-biphenyl-3-carboxylic acid methyl ester. Electrospray Mass Spec: 412.0 (M+H)⁺

15

Example 43

4-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide

According to the procedure of Example 5 242 mg (0.58 mmol) of the product of Example 42 and 0.049 ml (0.65 mmol) of 2-butyne-1-ol provides 0.239g (98%) of 4-[(4-but-2-ynyloxy-benzenesulfonyl)-methyl-amino]-5-methyl-biphenyl-3-carboxylic acid methyl ester. Electrospray Mass Spec: 464.2 (M+H)⁺.

According to the procedure of Example 38 0.239g (0.58 mmol) of the ester was hydrolyzed to provide 0.2 g (76%) of 4-[(4-but-2-ynyloxy-benzenesulfonyl)-methyl-amino]-5-methyl-biphenyl-3-carboxylic acid. Electrospray Mass Spec: 448.3.0 (M-H)⁻

According to the procedure of Example 39 0.20g (0.44 mmol) of the carboxylic acid was converted to the hydroxamic acid 4-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide providing 0.150g (73%) of pure product. Electrospray Mass Spec: 465.0 (M+H)⁺

30

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with 5% HCl solution. The mixture was extracted with ethyl acetate, washed with brine and the combined organics were then dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with ether/hexanes (1:1) and the solid was collected and dried in vacuo to provide 0.159g (62%) of the desired carboxylic acid product as a white solid. Electrospray Mass Spec: 543.8 (M+H)⁺

Example 47

5-Bromo-2-({4-[3-(4-methoxy-phenyl)-prop-2-ynyloxy]-benzenesulfonyl}-methyl-amino)-3-methyl-benzoic acid

To a solution of 0.217g (0.389 mmol) of the product of Example 14 in 6.0 mL of THF/methanol (1:1) was added 1.9mL of 1.0N sodium hydroxide solution. The reaction was heated to reflux overnight, cooled to room temperature and acidified with 5% HCl solution. The mixture was extracted with ethyl acetate, washed with brine and the combined organics were then dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with ether/hexanes (1:1) and the solid was collected and dried in vacuo to provide 0.191g (90%) of the desired carboxylic acid product as a white solid. Electrospray Mass Spec: 543.8 (M+H)⁺

Example 48

2-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-5-iodo-3-methyl-benzoic acid

To a solution of 0.102g (0.199 mmol) of the product of Example 17 in 6.0 mL of THF/methanol (1:1) was added 1.0mL of 1.0N sodium hydroxide solution. The reaction was heated to reflux overnight, cooled to room temperature and acidified with 5% HCl solution. The mixture was extracted with ethyl acetate, washed with brine and the combined organics were then dried over MgSO₄, filtered and concentrated in vacuo to provide 0.089g (90%) of the desired carboxylic acid product as a white solid. Electrospray Mass Spec: 499.8 (M+H)⁺

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Example 52**5-Bromo-3-methyl-2-[methyl-(4-prop-2-ynyloxy-benzenesulfonyl)-amino]-benzoic acid**

According to the procedure of **Example 38** 0.250g (0.553 mmol) of the product of **Example 5** provides 0.237g (98%) of the desired carboxylic acid as a white solid. Electrospray Mass Spec: 435.8 (M-H)⁺

Example 53**5-Bromo-N-hydroxy-3-methyl-2-[methyl-(4-prop-2-ynyloxy-benzenesulfonyl)-amino]-benzamide**

According to the procedure of **Example 39** 0.173g of the product of **Example 52** provides 0.176g (98%) of the hydroxamic acid as a white solid. Electrospray Mass Spec: 452.8 (M+H)⁺

Example 54**5-Benzofuran-2-yl-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester**

According to the procedure of **Example 39** 0.084g of the product of **Example 6** provides 0.087g (100%) of the hydroxamic acid as a white foam. Electrospray Mass Spec: 466.8 (M+H)⁺

Example 55**5-Bromo-N-hydroxy-3-methyl-2-[methyl-(4-pent-2-ynyloxy-benzenesulfonyl)-amino]-benzamide**

According to the procedure of **Example 39** 0.162g of the product of **Example 7** provides 0.135g (81%) of the hydroxamic acid as a tan foam. Electrospray Mass Spec: 480.8 (M+H)⁺

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Example 60

5-Bromo-N-hydroxy-2-((4-[3-(3-methoxy-phenyl)-prop-2-ynyloxy]-benzenesulfonyl)-methyl-amino)-3-methyl-benzamide

According to the procedure of Example 39 0.154g of the product of Example 45 provides 0.151g (96%) of the hydroxamic acid as a light orange solid. Electrospray Mass Spec: 558.8 (M+H)⁺

Example 61

5-Bromo-N-hydroxy-2-((4-[3-(2-methoxy-phenyl)-prop-2-ynyloxy]-benzenesulfonyl)-methyl-amino)-3-methyl-benzamide

According to the procedure of Example 39 0.135g of the product of Example 46 provides 0.132g (95%) of the hydroxamic acid as a white foam. Electrospray Mass Spec: 558.9 (M+H)⁺

15

Example 62

5-Bromo-N-hydroxy-2-((4-[3-(4-methoxy-phenyl)-prop-2-ynyloxy]-benzenesulfonyl)-methyl-amino)-3-methyl-benzamide

According to the procedure of Example 39 0.158g of the product of Example 47 provides 0.116g (72%) of the hydroxamic acid as a pale yellow foam. Electrospray Mass Spec: 558.9 (M+H)⁺

20

Example 63

2-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-N-hydroxy-5-iodo-3-methyl-benzamide

According to the procedure of Example 39 0.109g of the product of Example 48 provides 0.112g (100%) of the hydroxamic acid as a white foam. Electrospray Mass Spec: 514.8 (M+H)⁺

25

Example 66**5-Bromo-2-[[4-(4-diethylamino-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino]-N-hydroxy-3-methyl-benzamide**

To a 0° solution of 0.38 mL (0.757 mmol) of a 2.0M solution of oxalyl chloride in dichloromethane, diluted with 3.1 mL of dichloromethane, is added 0.059 mL (0.757 mmol) of DMF and the reaction is stirred for 15 minutes at 0°. A solution of 0.132g (0.252 mmol) of the carboxylic acid product of **Example 51**, dissolved in 1 mL of DMF, was added to the reaction and the resulting mixture is stirred for 1h at room temperature and then poured into a 0° mixture of 0.8 mL of water, 3.9 mL of THF and 0.24 mL of a 50% aqueous solution of hydroxylamine. The reaction is allowed to warm to room temperature overnight and the organics are then concentrated in vacuo. The residue is diluted with ethyl acetate, washed with water and saturated sodium bicarbonate, dried over Na₂SO₄, filtered and concentrated in vacuo to provide 0.126g (93%) of the hydroxamic acid as a tan foam.

To a solution of 0.093g (0.173 mmol) of the amino-hydroxamic acid dissolved in 3.0 mL of dichloromethane was added 0.35 mL (0.35 mmol) of a 1.0M solution of HCl in ether. The resulting mixture was stirred for 1h at room temperature and then diluted with ether. The precipitate was filtered, washed with ether and dried in vacuo to provide 0.091g (92%) of the hydrochloride salt of the amino-hydroxamic acid as a tan solid. Electrospray Mass Spec: 540.0 (M+H)⁺

Example 67**5-Bromo-2-[(4-but-2-ynyloxy-benzenesulfonyl)-(4-methyl-piperazin-1-ylmethyl)-amino]-N-hydroxy-3-methyl-benzamide**

According to the procedure of **Example 50** 0.128g (0.228 mmol) of the product of **Example 22** provided 0.117g (94%) of the carboxylic acid. Electrospray Mass Spec: 550.0 (M+H)⁺

To a 0° solution of 0.27 mL (0.547 mmol) of a 2.0M solution of oxalyl chloride in dichloromethane, diluted with 2.4 mL of dichloromethane, is added 0.042 mL (0.547 mmol) of DMF and the reaction is stirred for 15 minutes at 0°. A solution

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washed with water, 5% HCl solution and saturated sodium bicarbonate solution. The organics were dried over Na₂SO₄, filtered and concentrated in vacuo to provide 0.337g (80%) of the hydroxamic acid as a white foam. Electrospray Mass Spec: 568.8 (M+H)⁺

5

Example 70

5-Bromo-N-hydroxy-2-[[4-(4-hydroxy-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino]-3-methyl-benzamide

To a solution of 0.274g (0.483 mmol) of the product of **Example 69** in 4.0 mL of methanol was added 0.012g (0.048 mmol) of pyridinium *p*-toluenesulfonate and the resulting mixture was heated to reflux for 18h. The reaction was then concentrated in vacuo, diluted with ethyl acetate and washed with 5% HCl solution, water and saturated sodium bicarbonate solution. The organics were dried over Na₂SO₄, filtered and concentrated in vacuo to provide 0.159g (68%) of the hydroxamic acid as a white powder. Electrospray Mass Spec: 482.8 (M+H)⁺

15

Example 71

4-[(4-Hydroxy-benzenesulfonyl)-methyl-amino]-5-methyl-biphenyl-3-carboxylic acid methyl ester

To 28 mL of degassed ethylene glycol dimethyl ether was added 2.15g (5.19 mmol) of the product of **Example 4**, 0.696g (5.71 mmol) of phenylboronic acid, 0.300g (0.26 mmol) of tetrakis(triphenylphosphine)palladium(0), and 10.4 mL (20.8 mmol) of 2M Na₂CO₃, and the mixture was refluxed under nitrogen for 18h. The reaction was then cooled, diluted with ethyl acetate, washed with water and brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was triturated with 1:3 dichloromethane/hexanes to provide 1.89g (89%) of the desired biphenyl product as a pale orange solid. Electrospray Mass Spec 412.4 (M+H)⁺

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Example 74**4-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-5-(4-methyl-piperazin-1-yl methyl)-biphenyl-3-carboxylic acid methyl ester**

To a solution of 0.810g (1.59 mmol) of the product of **Example 73** and 0.594
5 mL (7.95 mmol) of 2-butyne-1-ol in 8 mL of THF, was added 2.08g (7.95 mmol) of
triphenylphosphine and then 1.25 mL (7.95 mmol) of diethyl azodicarboxylate. The
mixture was stirred at room temperature for 18h, diluted with ethyl acetate, washed
with water and brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was
chromatographed on silica gel with 2% methanol/dichloromethane to provide 0.830g
10 (93%) of the desired product as a beige solid. Electrospray Mass Spec 562.1 (M+H)⁺

Example 75**4-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-5-(4-methyl-piperazin-1-yl methyl)-biphenyl-3-carboxylic acid**

A mixture of 0.965g (1.72 mmol) of the product of **Example 74** and 8.6 mL
15 (8.59 mmol) of 1N NaOH in 8.6 mL of THF and 8.6 mL of methanol was heated to
reflux for 18h. The reaction mixture was cooled and neutralized with 3N HCl. The
organic solvents were removed and the resulting aqueous solution was extracted with
dichloromethane. The organic layer was separated, washed with water and brine,
20 dried over Na_2CO_3 , and concentrated in vacuo. The residue was triturated with ether to
provide 0.829g (89%) of the desired product as a cream solid. Electrospray Mass
Spec 548.1 (M+H)⁺

Example 76**4-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-5-(4-methyl-piperazin-1-yl methyl)-biphenyl-3-carboxylic acid hydroxyamide dihydro-chloride salt**

To a solution of 0.244 mL (0.487 mmol) of a 2M solution of oxalyl chloride
in dichloromethane at 0° C was added 0.038 mL (0.487 mmol) of DMF and the
mixture was stirred for 1h at room temperature. A solution of 0.089g (0.163 mmol)
30 of the product of **Example 75** in 0.5 mL dichloromethane was then added to the
reaction mixture and the resulting mixture was stirred for 1h at room temperature.

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Example 79**5-Bromo-N-hydroxy-3-methyl-2-{methyl-[4-(1-methyl-prop-2-ynyloxy)-benzenesulfonyl]-amino}-benzamide**

5 According to the procedure of Example 39, 0.068g (0.150 mmol) of the product of Example 34 provided 0.070g (100%) of the hydroxamic acid as a white foam. Electrospray Mass Spec 466.9 (M+H)⁺

Example 80**3-[3-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-prop-2-yn-1-ol**

10 To a solution of 2.0g (9.091 mmol) of 3-iodophenol in 10 mL of DMF was added 1.55g (0.023 mol) of imidazole and 1.64g (0.011 mol) of t-butyldimethylsilyl chloride and the resulting mixture was stirred at room temperature for 48h. The reaction was then diluted with ether and washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was used in the next step without
15 purification.

To a solution of 3.04g (9.091 mmol) of the silylated iodoaryl in 55 mL of diethylamine was added 0.53 mL of propargyl alcohol followed by 0.173g (0.909 mmol) of copper (I) iodide and 0.32g (0.456 mmol) of bis(triphenyl-phosphine)-palladium(II)dichloride. The resulting mixture was stirred for 4h at room temperature
20 and then concentrated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate/hexanes (1:10) to provide 0.73g (31%) of the aryl acetylene as a brown oil. EI Mass Spec 262 (M⁺)

Example 81

25 **5-Bromo-2-({4-[3-(3-hydroxy-phenyl)-prop-2-ynyloxy]-benzenesulfonyl}-methyl-amino)-3-methyl-benzoic acid**

According to the procedure of Example 5, 0.158g (0.604 mmol) of the product of Example 80 and 0.250g (0.604 mmol) of the product of Example 4 provided 0.315g of the propargylic ether.

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dried over Na_2SO_4 and concentrated in vacuo to give 0.031g (38%) of the phenol hydroxamic acid as a pale yellow solid. Electrospray Mass Spec 544.9 (M+H)⁺

Example 85

5 4-But-2-ynyloxy-benzenesulfonic acid sodium salt

To a solution of 52.35g (0.225 mol) of 4-hydroxybenzenesulfonate sodium salt in 1L of isopropanol and 225 mL of a 1.0N solution of sodium hydroxide was added 59.96g (0.45 mol) of 1-bromo-2-butyne. The resulting mixture was heated to 70° for 15h and then the isopropanol was removed by evaporation in vacuo. The
10 resulting white precipitate was collected by filtration, washed with isopropanol and ether and dried in vacuo to give 56.0g (100%) of the butynyl ether as a white solid.

Example 86

4-But-2-ynyloxy-benzenesulfonyl chloride

15 To a 0° solution of 43.8 mL (0.087 mol) of 2M oxalyl chloride/dichloromethane solution in 29 mL of dichloromethane was dropwise added 6.77 mL (0.087 mol) of DMF followed by 7.24g (0.029 mol) of the product of Example 85. The reaction mixture was stirred for 10 minutes at 0° then let warm to room temperature and stirred for 2 days. The reaction was then poured into ice and extracted with 150
20 mL of hexanes. The organics were washed with water and brine, dried over Na_2SO_4 , filtered and concentrated in vacuo to provide 6.23g (88%) of the sulfonyl chloride as a yellow solid; m.p. 63-65°C. EI Mass Spec: 243.9 MH⁺

Example 87

25 But-2-ynyloxy-benzene

According to the procedure of Example 5, 2.00g (0.021 mol) of phenol and 1.64g (0.023 mol) of 2-butyne-1-ol provided 2.18g (70%) of the butynyl ether as a clear liquid. EI Mass Spec: 146.0 MH⁺

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increase in color is monitored spectrophotometrically for 5 minutes at 405 nm on a plate reader and the increase in color over time is plotted as a linear line.

Alternatively, a fluorescent peptide substrate is used. In this test procedure, the peptide substrate contains a fluorescent group and a quenching group. Upon
5 cleavage of the substrate by an MMP, the fluorescence that is generated is quantitated on the fluorescence plate reader. The assay is run in HCBC assay buffer (50mM HEPES, pH 7.0, 5 mM Ca^{+2} , 0.02% Brij, 0.5% Cysteine), with human recombinant MMP-1, MMP-9, or MMP-13. The substrate is dissolved in methanol and stored frozen in 1 mM aliquots. For the assay, substrate and enzymes are diluted in HCBC
10 buffer to the desired concentrations. Compounds are added to the 96 well plate containing enzyme and the reaction is started by the addition of substrate. The reaction is read (excitation 340 nm, emission 444 nm) for 10 min. and the increase in fluorescence over time is plotted as a linear line.

For either the thiopeptide or fluorescent peptide test procedures, the slope of
15 the line is calculated and represents the reaction rate. The linearity of the reaction rate is confirmed ($r^2 > 0.85$). The mean ($x \pm \text{sem}$) of the control rate is calculated and compared for statistical significance ($p < 0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generated using multiple doses of drug and IC_{50} values with 95% CI are estimated using linear
20 regression.

Test Procedure for Measuring TACE Inhibition

Using 96-well black microtiter plates, each well receives a solution composed of 10 μL TACE (final concentration 1 $\mu\text{g/mL}$), 70 μL Tris buffer, pH 7.4 containing 10% glycerol (final concentration 10 mM), and 10 μL of test compound solution in
25 DMSO (final concentration 1 μM , DMSO concentration $< 1\%$) and incubated for 10 minutes at room temperature. The reaction is initiated by addition of a fluorescent peptidyl substrate (final concentration 100 μM) to each well and then shaking on a shaker for 5 sec.

The reaction is read (excitation 340 nm, emission 420 nm) for 10 min. and the
30 increase in fluorescence over time is plotted as a linear line. The slope of the line is calculated and represents the reaction rate.

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the beginning of the incubation period to give final concentrations of 100 mM, 30 mM, 10 mM, 3 mM, 1 mM, 300 nM, and 100 nM. Cell exposure to DMSO was limited to 0.1 % final concentration. Positive control wells were included in the experiment which had mitogen added but no drug. Vehicle control wells were included as well, which were identical to the positive control wells, except that DMSO was added to give a final concentration of 0.083%. Negative control wells were included in the experiment which had vehicle but no mitogen or drug added to the cells. Compounds can be evaluated for their effect on basal (non-stimulated) shedding of the receptors by replacing the LPS with 50 ml/well of THP-1 media. Plates are placed into an incubator set at 5% CO₂ and at 37°C. After 4 hours of incubation, 300 ml/well of tissue culture supernatant (TCS) is removed for use in an TNF- α ELISA. Following 24 hours of incubation, 700 ml/well of TCS is removed and used for analysis in TNF-R p75/80, TNF-R p55/60 and IL-8 ELISAs.

In addition, at the 24 hours timepoint, and the cells for each treatment group are collected by resuspension in 500 μ l/well of THP-1 media and transferred into a FACS tube. Two ml/tube of a 0.5 mg/ml stock of propidium iodide (PI) (Boehringer Mannheim cat. # 1348639) is added. The samples are run on a Becton Dickinson FaxCaliber FLOW cytometry machine and the amount of dye taken up by each cell is measured in the high red wavelength (FL3). Only cells with compromised membranes (dead or dying) can take up PI. The percent of live cells is calculated by the number of cells not stained with PI, divided by the total number of cells in the sample. The viability values calculated for the drug treated groups were compared to the viability value calculated for the vehicle treated mitogen stimulated group ("vehicle positive control") to determine the "percent change from control". This "percent change from control" value is an indicator of drug toxicity.

The quantity of soluble TNF- α , TNF-R p75/80 and TNF-R p55/60 and IL-8 in the TCS of the THP-1 cell cultures are obtained with commercially available ELISAs from R&D Systems, by extrapolation from a standard curve generated with kit standards. The number of cells that either take up or exclude PI are measured by the FLOW cytometry machine and visualized by histograms using commercially available Cytologic software for each treatment group including all controls.

Biological variability in the magnitude of the response of THP-1 cell cultures requires that experiments be compared on the basis of percent change from "vehicle positive control" for each drug concentration. Percent change in each soluble protein evaluated from the "vehicle positive control" was calculated for each compound concentration with the following formula:

-65-

Tsuchiya, S., Yamabe, M., Yamaguchi, Y., Kobayashi, Y., Konno, T., and Tada, K. Establishment and characterization of a human acute monocytic leukemia cell line (THP-1). *Int. J. Cancer.* 26:1711-176, 1980.

- 5 Results of the above in-vitro matrix metalloproteinase inhibition, TACE inhibition and THP standard pharmacological test procedures are given in Table I below.

10 Table I. Inhibition in MMP, TACE and THP assays:

Table 1						% Inhib. @ 3μM
IC ₅₀ (nM) or % Inhibition (μM)						
15	Example #	MMP-1	MMP-9	MMP-13	TACE	THP
	31	19%(10)	301	724	44	6
	32	26%(10)	643	255	58	15
	33	32%(10)	1205	908	29	14
20	34	39%(10)	790	383	127	22
	36	114	11	21	32	14
	39	2488	21	68	67	0
	43	4243	578	518	135	76
	53	113	15	52	11	55
25	54	1616	304	154	16	84
	55	1228	800	289	12	48
	56	53%(10)	389	701	34	16
	57	2364	232	358	47	11
	58	7803	387	233	11	46
30	59	3815	857	321	66	20
	60	1029	671	935	91	1
	61	52%(10)	1507	1199	193	0
	62	3602	901	588	104	15
	63	901	840	275	16	87
35	64	1187	830	312	105	48

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Applicable solid carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferable sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

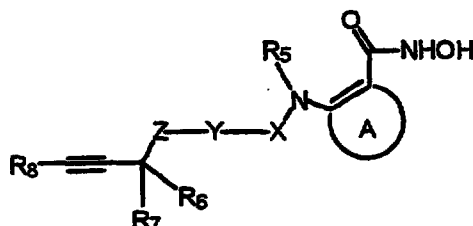
The compounds of this invention may be administered rectally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an

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CLAIMS

1. A compound having the formula:

5



where the C(=O)NHOH moiety and the -NR₅- moiety are bonded to adjacent carbons of group A;

- 10 wherein A is phenyl, naphthyl, or phenyl fused to a 5 to 7 membered saturated or unsaturated cycloalkyl ring, a 5 to 9 membered saturated or unsaturated heterocycloalkyl ring having 1 or 2 heteroatoms selected from N, NR₉, O or S, or a heteroaryl ring having 5-10 members and from 1-3 heteroatoms selected from N, NR₉, O or S;
- 15 X is SO₂ or -P(O)R₁₀;
- Y is phenyl, naphthyl or heteroaryl, with the proviso that X and Z may not be bonded to adjacent atoms of Y;
- Z is O, NH, CH₂ or S;
- R₅ is hydrogen or alkyl of 1-6 carbon atoms;
- 20 or R₅-N-A-, can form a benzazepine, benzoxazepine, benzothiazepine, benzodiazepine, benzazocine, benzodiazocine, benzoxazocine or benzothiazocane ring which may be optionally fused to another benzene ring;
- 25 R₆ and R₇ are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, -CCH₃;
- and R₈ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, naphthyl, 5 to 10 membered heteroaryl having from 1 to 3 heteroatoms selected from N, NR₉, O or S, or 5 to 9 membered heterocycloalkyl
- 30 having 1 or 2 heteroatoms selected from N, NR₉, O or S;

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10. A compound according to Claim 1 which is selected from the group consisting of:

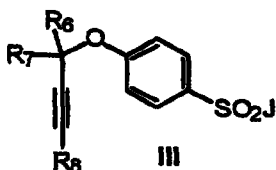
- 5 5-Bromo-2-[[4-(4-cyclobutylamino-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino]-N-hydroxy-3-methyl-benzamide;
- 5-Bromo-N-hydroxy-3-methyl-2-[methyl-[4-(4-methylamino-but-2-ynyloxy)-benzenesulfonyl]-amino]-benzamide;
- 10 5-Bromo-2-([4-[4-(3-dimethylamino-propylamino)-but-2-ynyloxy]-benzenesulfonyl]-methyl-amino)-N-hydroxy-3-methyl-benzamide;
- 5-Bromo-2-([4-[4-(2-dimethylamino-ethylamino)-but-2-ynyloxy]-benzenesulfonyl]-methyl-amino)-N-hydroxy-3-methyl-benzamide;
- 15 4-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide;
- 5-Bromo-N-hydroxy-3-methyl-2-[methyl-(4-prop-2-ynyloxy-benzenesulfonyl)-amino]-benzamide;
- 20 5-Bromo-N-hydroxy-3-methyl-2-[methyl-(4-pent-2-ynyloxy-benzenesulfonyl)-amino]-benzamide;
- 5-Bromo-2-[(4-hept-2-ynyloxy-benzenesulfonyl)-methyl-amino]-N-hydroxy-3-methyl-benzamide;
- 25 5-Bromo-2-[(4-hex-2-ynyloxy-benzenesulfonyl)-methyl-amino]-N-hydroxy-3-methyl-benzamide;
- 30 5-Bromo-N-hydroxy-2-[[4-(4-methoxy-but-2-ynyloxy)-benzenesulfonyl]-methyl-amino]-3-methyl-benzamide;
- 5-Bromo-N-hydroxy-3-methyl-2-[methyl-[4-(3-phenyl-prop-2-ynyloxy)-benzenesulfonyl]-amino]-benzamide;
- 35 5-Bromo-N-hydroxy-2-([4-[3-(3-methoxy-phenyl)-prop-2-ynyloxy]-benzenesulfonyl]-methyl-amino)-3-methyl-benzamide;
- 5-Bromo-N-hydroxy-2-([4-[3-(2-methoxy-phenyl)-prop-2-ynyloxy]-benzenesulfonyl]-methyl-amino)-3-methyl-benzamide;
- 40 5-Bromo-N-hydroxy-2-([4-[3-(4-methoxy-phenyl)-prop-2-ynyloxy]-benzenesulfonyl]-methyl-amino)-3-methyl-benzamide;
- 45 2-[(4-But-2-ynyloxy-benzenesulfonyl)-methyl-amino]-N-hydroxy-5-iodo-3-methyl-benzamide;

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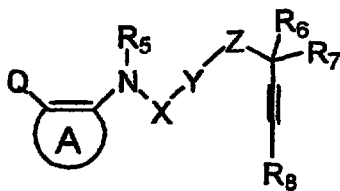
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wherein R_6 and R_7 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, -CCH;

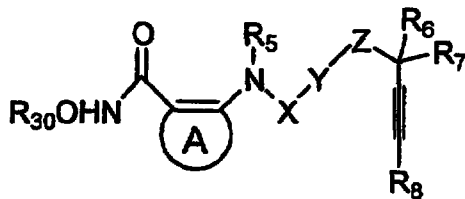
- 5 R_8 is of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, naphthyl, 5 to 10 membered heteroaryl having from 1 to 3 heteroatoms selected from N, NR_x , O or S, or 5 to 9 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, NR_x , O or S; and
- 10 J is fluorine, bromine, chlorine, 1,2,4-triazolyl, benzotriazolyl or imidazol-yl.

13. A process for preparing a compound of formula B as claimed in claim 1 which comprises:
- 15 a) reacting a compound of formula V:



(V)

- wherein R_6 , R_7 , R_8 , A, X, Y and Z are as defined in claim 1 and Q is COOH or a reactive derivative thereof, with hydroxylamine to give a corresponding compound of formula B; or
- 20 b) deprotecting a compound of formula VI:



(VI)

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benzothiazocane ring which may be optionally fused to another benzene ring;

R_6 and R_7 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, -CCH₃;

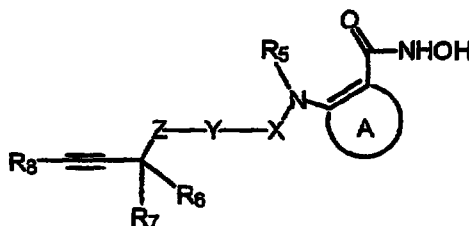
R_8 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, phenyl, naphthyl, 5 to 10 membered heteroaryl having from 1 to 3 heteroatoms selected from N, NR₉, O or S, or 5 to 9 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, NR₉, O or S;

R_9 is hydrogen, phenyl, naphthyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms; and

R_{10} is phenyl, naphthyl, alkyl of 1-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, 5 to 10 membered heteroaryl having from 1 to 3 heteroatoms selected from N, NR₉, O or S, or 5 to 9 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, NR₉, O or S; or a pharmaceutically acceptable salt thereof.

15. The method according to Claim 14 wherein the condition treated is rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection.

16. A pharmaceutical composition comprising a compound having the formula



where the C(=O)NHOH moiety and the -NR⁵- moiety are bonded to adjacent carbons of group A;

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