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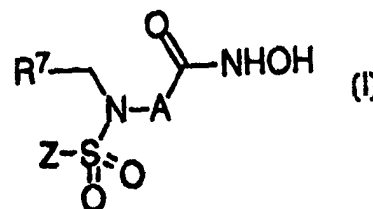
(51) International Patent Classification ⁶ : C07C 311/00	A2	(11) International Publication Number: WO 98/16503 (43) International Publication Date: 23 April 1998 (23.04.98)
(21) International Application Number: PCT/US97/18280 (22) International Filing Date: 8 October 1997 (08.10.97) (30) Priority Data: 08/732,631 16 October 1996 (16.10.96) US (71) Applicant: AMERICAN CYANAMID COMPANY [US/US]; Five Giralda Farms, Madison, NJ 07940-0974 (US). (72) Inventors: LEVIN, Jeremy, Ian; 190 Treetop Circle, Nanuet, NY 10954 (US). DU, Mila, T.; 17 Heather Hill Lane, Suffern, NY 10901 (US). VENKATESAN, Aranapakam, Mudumbai; 97-07 63rd Road #9K, Rego Park, NY 11374 (US). NELSON, Frances, Christy; 694 Terrace Heights, Wyckoff, NJ 07481 (US). ZASK, Arie; Apartment 9D, 200 Central Park S., New York, NY 10019 (US). GU, Yansong; 82 North Magnolia Avenue, Pearl River, NY 10965 (US). (74) Agents: ALICE, Ronald, W.; American Home Products Cor- poration, One Campus Drive, Parsippany, NJ 07054 (US) et al.		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.

(54) Title: THE PREPARATION AND USE OF ORTHO-SULFONAMIDO ARYL HYDROXAMIC ACIDS AS MATRIX METALLO-PROTEINASE AND TACE INHIBITORS

(57) Abstract

The present invention relates to the discovery of novel, low molecular weight, non-peptide inhibitors of matrix metallo-proteinases (e.g. gelatinases, stromelysins and collagenases) and TNF- α converting enzyme (TACE, tumor necrosis factor- α converting enzyme) which are useful for the treatment of diseases in which these enzymes are implicated such as arthritis, tumor growth

and metastasis, angiogenesis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease, HIV infection, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization. The TACE and MMP inhibiting ortho-sulfonamido aryl hydroxamic acids of the present invention are represented by formula (I) where the hydroxamic acid moiety and the sulfonamido moiety are bonded to adjacent carbons on group A where: A is phenyl or naphthyl, optionally substituted by R¹, R², R³ and R⁴; Z is aryl, heteroaryl, or heteroaryl fused to a phenyl, where aryl is phenyl or naphthyl optionally substituted by R¹, R², R³ and R⁴; heteroaryl is a 5-6 membered heteroaromatic ring having from 1 to 3 heteroatoms independently selected from N, O and S, and optionally substituted by R¹, R², R³ and R⁴; and when heteroaryl is fused to phenyl, either or both of the rings can be optionally substituted by R¹, R², R³ and R⁴; and R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are described in the specification, and the pharmaceutically acceptable salts thereof and the optical isomers and diastereomers thereof.



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THE PREPARATION AND USE OF ORTHO-SULFONAMIDO ARYL HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASE AND TACE INHIBITORS

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Background of the Invention

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The present invention relates to the discovery of novel, low molecular weight, non-peptide inhibitors of matrix metalloproteinases (e.g. gelatinases, stromelysins and collagenases) and TNF- α converting enzyme (TACE, tumor necrosis factor- α converting enzyme) which are useful for the treatment of diseases in which these enzymes are implicated such as arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system and HIV infection.

Matrix metalloproteinases (MMPs) are a group of enzymes that have been implicated in the pathological destruction of connective tissue and basement membranes [Woessner, J.F., Jr. *FASEB J.* **1991**, *5*, 2145; Birkedal-Hansen, H.; Moore, W.G.I.; Bodden, M.K.; Windsor, L.J.; Birkedal-Hansen, B.; DeCarlo, A.; Engler, J.A. *Crit. Rev. Oral Biol. Med.* **1993**, *4*, 197; Cawston, T.E. *Pharmacol. Ther.* **1996**, *70*, 163; Powell, W.C.; Matrisian, L.M. *Cur. Top. Microbiol. and Immunol.* **1996**, *213*, 1]. These zinc containing endopeptidases consist of several subsets of enzymes including collagenases, stromelysins and gelatinases. Of these classes, the gelatinases have been shown to be the MMPs most intimately involved with the growth and spread of tumors, while the collagenases have been associated with the pathogenesis of osteoarthritis [Howell, D.S.; Pelletier, J.-P. In *Arthritis and Allied Conditions*; McCarthy, D.J.; Koopman, W.J., Eds.; Lea and Febiger: Philadelphia, **1993**; *12th Edition* Vol. 2, pp. 1723; Dean, D.D. *Sem. Arthritis Rheum.* **1991**, *20*, 2; Crawford, H.C; Matrisian, L.M. *Invasion Metast.* **1994-95**, *14*, 234; Ray, J.M.; Stetler-Stevenson, W.G. *Exp. Opin. Invest. Drugs*, **1996**, *5*, 323].

It is known that the level of expression of gelatinase is elevated in malignancies, and that gelatinase can degrade the basement membrane which may lead to tumor metastasis [Powell, W.C.; Matrisian, L.M. *Cur. Top. Microbiol. and Immunol.* **1996**, *213*, 1; Crawford, H.C; Matrisian, L.M. *Invasion Metast.* **1994-95**, *14*, 234; Ray, J.M.; Stetler-Stevenson, W.G. *Exp. Opin. Invest. Drugs*, **1996**, *5*, 323; Himelstein, B.P.; Canete-Soler, R.; Bernhard, E.J.; Dilks, D.W.; Muschel, R.J. *Invasion Metast.* **1994-95**, *14*, 246; Nuovo, G.J.; MacConnell, P.B.; Simsir, A.; Valea, F.; French, D.L. *Cancer Res.*

1995, 55, 267-275; Walther, M.M.; Levy, A.; Hurley, K.; Venzon, D.; Linehen, W.M.; Stetler-Stevenson, W. *J. Urol.* **1995**, 153 (Suppl. 4), 403A; Tokuraku, M; Sato, H.; Murakami, S.; Okada, Y.; Watanabe, Y.; Seiki, M. *Int. J. Cancer*, **1995**, 64, 355; Himmelstein, B.; Hua, J.; Bernhard, E.; Muschel, R.J. *Proc. Am. Assoc. Cancer Res. Ann. Meet.* **1996**, 37, 632; Ueda, Y.; Imai, K.; Tsuchiya, H.; Fujimoto, N.; Nakanishi, I.; Katsuda, S.; Seiki, M.; Okada, Y. *Am. J. Pathol.* **1996**, 148, 611; Gress, T.M.; Mueller-Pillasch, F.; Lerch, M.M.; Friess, H.; Buechler, M.; Adler, G. *Int. J. Cancer*, **1995**, 62, 407; Kawashima, A.; Nakanishi, I.; Tsuchiya, H.; Roessner, A.; Obata, K.; Okada, Y. *Virchows Arch.*, **1994**, 424, 547-552.]. Angiogenesis, required for the growth of solid tumors, has also recently been shown to have a gelatinase component to its pathology [Crawford, H.C; Matrisian, L.M. *Invasion Metast.* **1994-95**, 14, 234; Ray, J.M.; Stetler-Stevenson, W.G. *Exp. Opin. Invest. Drugs*, **1996**, 5, 323.]. Furthermore, there is evidence to suggest that gelatinase is involved in plaque rupture associated with atherosclerosis [Dollery, C.M.; McEwan, J.R.; Henney, A.M. *Circ. Res.* **1995**, 77, 863; Zempo, N.; Koyama, N.; Kenagy, R.D.; Lea, H.J.; Clowes, A.W. *Arterioscler. Thromb. Vasc. Biol.* **1996**, 16, 28; Lee, R.T.; Schoen, F.J.; Loree, H.M.; Lark, M.W., Libby, P. *Arterioscler. Thromb. Vasc. Biol.* **1996**, 16, 1070.]. Other conditions mediated by MMPs are restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, periodontal disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization and corneal graft rejection.

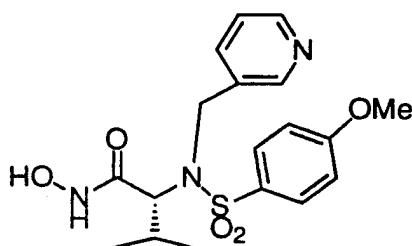
The hypothesis that MMPs are important mediators of the tissue destruction that occurs in arthritis has long been considered, since it was first recognized that these enzymes are capable of degrading collagens and proteoglycans which are the major structural components of cartilage [Sapolsky, A.I.; Keiser, H.; Howell, D.S.; Woessner, J.F., Jr.; *J. Clin. Invest.* **1976**, 58, 1030; Pelletier, J.-P.; Martel-Pelletier, J.; Howell, D.S.; Ghandur-Mnaymneh, L.; Enis, J.E.; Woessner, J.F., Jr., *Arthritis Rheum.* **1983**, 26, 63.], and continues to develop as new MMPs are identified. For example, collagenase-3 (MMP-13) was cloned from breast cancer cells in 1994, and the first report that it could be involved in arthritis appeared in 1995 [Freiji, J.M.; Diez-Itza, I.; Balbin, M.; Sanchez, L.M.; Blasco, R.; Tolivia, J.; Lopez-Otin, C. *J. Biol. Chem.* **1994**, 269, 16766; Flannery, C.R.; Sandy, J.D. **102-17**, 41st Ann. Meet. Orth. Res. Soc. Orlando, FL. February 13-16, 1995.].

Evidence is accumulating that implicates MMP-13 in the pathogenesis of arthritis. A major structural component of articular cartilage, type II collagen, is the preferred substrate for MMP-13 and this enzyme is significantly more efficient at cleaving type II collagen than the other collagenases [Knauper, V.; Lopez-Otin, C.; Smith, B.; Knight, G.; Murphy, G. *J. Biol. Chem.*, **1996**, *271*, 1544-1550; Mitchell, P.G.; Magna, H.A.; Reeves, L.M.; Lopresti-Morrow, L.L.; Yocum, S.A.; Rosner, P.J.; Geoghegan, K.F.; Hambor, J.E. *J. Clin. Invest.* **1996**, *97*, 761.]. MMP-13 is produced by chondrocytes, and elevated levels of MMP-13 has been found in human osteoarthritic tissues [Reboul, P.; Pelletier, J-P.; Hambor, J.; Magna, H.; Tardif, G.; Cloutier, J-M.; Martel-Pelletier, J. *Arthritis Rheum.* **1995**, *38* (Suppl. 9), S268; Shlopov, B.V.; Mainardi, C.L.; Hasty, K.A. *Arthritis Rheum.* **1995**, *38* (Suppl. 9), S313; Reboul, P.; Pelletier, J-P.; Tardif, G.; Cloutier, J-M.; Martel-Pelletier, J. *J. Clin. Invest.* **1996**, *97*, 2011]. Potent inhibitors of MMPs were described over 10 years ago, but the poor bioavailability of these early peptidic, substrate mimetic MMP inhibitors precluded their evaluation in animal models of arthritis. More bioavailable, non-peptidic MMP inhibitors may be preferred for the treatment of diseases mediated by MMPs.

TNF- α converting enzyme catalyzes the formation of TNF- α from membrane bound TNF- α precursor protein. TNF- α is a pro-inflammatory cytokine that is now thought to have a role in rheumatoid arthritis, septic shock, graft rejection, insulin resistance and HIV infection in addition to its well documented antitumor properties. 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. Other conditions mediated by TNF- α are congestive heart failure, cachexia, anorexia, inflammation, fever, inflammatory disease of the central nervous system, and inflammatory bowel disease.

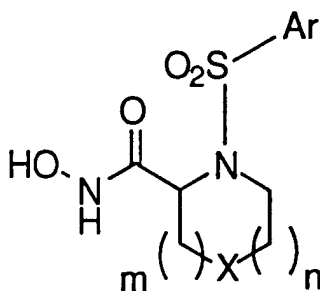
It is expected that small molecule inhibitors of gelatinase and TACE therefore have the potential for treating a variety of disease states. While a variety of MMP and TACE inhibitors have been identified and disclosed in the literature, the vast majority of these molecules are peptidic or peptide-like compounds that may have bioavailability and pharmacokinetic problems that would limit their clinical effectiveness. Low molecular weight, potent, long-acting, orally bioavailable inhibitors of gelatinases, collagenases and/or TACE are therefore highly desirable for the potential chronic treatment of the above mentioned disease states. Several non-peptidic, sulfur-containing hydroxamic acids have recently been disclosed and are listed below.

U. S. patents 5,455,258, 5,506,242 and 5,552,419, as well as European patent application EP606,046A1 and WIPO international publications WO96/00214 and WO97/22587 disclose non-peptide matrix metalloproteinase inhibitors of which the compound CGS27023A is representative. The discovery of this type of MMP inhibitor is further detailed by MacPherson, *et. al.* in *J. Med. Chem.*, (1997), 40, 2525. Additional publications disclosing sulfonamide based MMP inhibitors which are variants of the sulfonamide-hydroxamate shown below, or the analogous sulfonamide-carboxylates, are European patent application EP-757984-A1 and WIPO international publications WO95/35275, WO95/35276, WO96/27583, WO97/19068 and WO97/27174.

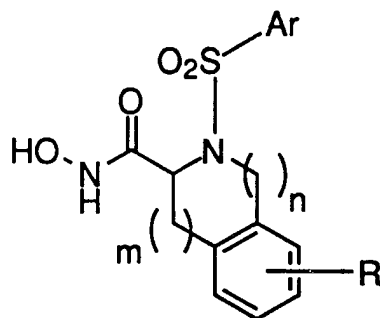


CGS 27023A

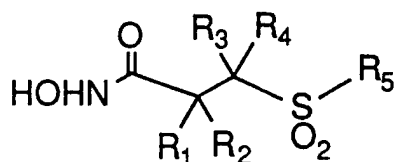
Publications disclosing β -sulfonamide-hydroxamate MMP inhibitor analogs of CGS 27023A in which the carbon alpha to the hydroxamic acid has been joined in a ring to the sulfonamide nitrogen, as shown below, include WIPO international publications WO96/33172 and WO97/20824.



The German patent application DE19,542,189-A1 discloses additional examples of cyclic sulfonamides as MMP inhibitors. In this case the sulfonamide-containing ring is fused to a phenyl ring to form an isoquinoline.



5 Analogs of the sulfonamide-hydroxamate MMP inhibitors in which the sulfonamide nitrogen has been replaced by a carbon atom, as shown in the general structure below, are European patent application EP-780386-A1 and WIPO international publication WO97/24117.

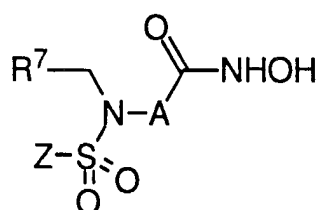


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Summary of the Invention

The TACE and MMP inhibiting ortho-sulfonamido aryl hydroxamic acids of the present invention are represented by the formula

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where the hydroxamic acid moiety and the sulfonamido moiety are bonded to adjacent carbons of group A where:

20

A is phenyl or naphthyl, optionally substituted by R¹, R², R³ and R⁴;

Z is aryl, heteroaryl, or heteroaryl fused to a phenyl,

where aryl is phenyl or naphthyl optionally substituted by R¹, R², R³ and R⁴;

25

heteroaryl is a 5-6 membered heteroaromatic ring having from 1 to 3 heteroatoms independently selected from N, O, and S, and optionally substituted by R¹, R², R³ and R⁴;

and when heteroaryl is fused to phenyl, either or both of the rings can be optionally substituted by R^1 , R^2 , R^3 and R^4 ;

R^1 , R^2 , R^3 and R^4 are independently -H, -COR⁵, -F, -Br, -Cl, -I,
 5 -C(O)NR⁵OR⁶, -CN, -OR⁵, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁵ where
 x is 0-2, -OPO(OR⁵)OR⁶, -PO(OR⁶)R⁵, -OC(O)NR⁵R⁶, -COOR⁵,
 -CONR⁵R⁶, -SO₃H, -NR⁵R⁶, -NR⁵COR⁶, -NR⁵COOR⁶,
 -SO₂NR⁵R⁶, -NO₂, -N(R⁵)SO₂R⁶, -NR⁵CONR⁵R⁶,
 10 -NR⁵C(=NR⁶)NR⁵R⁶, 3-6 membered cycloheteroalkyl having one
 to three heteroatoms independently selected from N, O, and S and
 optionally having 1 or 2 double bonds and optionally substituted by
 one to three groups each selected independently from R⁵; -aryl or
 heteroaryl as defined above, biphenyl optionally substituted by
 one to four groups each selected independently from R⁴, -SO₂NHCOR⁵ or -
 15 CONHSO₂R⁵ where R⁵ is not H, -tetrazol-5-yl, -SO₂NHCN, -
 SO₂NHCONR⁵R⁶ or straight chain or branched -C₁-C₆ alkyl, -C₂-C₆-
 alkenyl, or -C₂-C₆-alkynyl, or -C₃-C₆-cycloalkyl optionally having 1 or 2
 double bonds each optionally substituted with -COR⁵, -CN, -C₂-C₆
 alkenyl, -C₂-C₆ alkynyl, -OR⁵, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁵
 20 where x is 0-2, -OC(O)NR⁵R⁶, -COOR⁵, -CONR⁵R⁶, -SO₃H, -
 NR⁵R⁶, -NR⁵COR⁶, -NR⁵COOR⁶, -SO₂NR⁵R⁶, -NO₂, -
 N(R⁵)SO₂R⁶, -NR⁵CONR⁵R⁶, -C₃-C₆cycloalkyl as defined above,
 3-6 membered cycloheteroalkyl as defined above, aryl or heteroaryl
 as defined above, biphenyl, -SO₂NHCOR⁵ or -CONHSO₂R⁵ where
 25 R⁵ is not hydrogen; -PO(OR⁵)OR⁶, -PO(OR⁶)R⁵, -tetrazol-5-yl,
 C(O)NR⁵OR⁶, -NR⁵C(=NR⁶)NR⁵R⁶, -SO₂NHCONR⁵R⁶ or -
 SO₂NHCN;

with the proviso that when R^1 and R^2 are on adjacent carbons of A, R^1 and R^2
 together with the carbons to which they are attached can form a 5 to 7
 30 membered saturated or unsaturated heterocyclic ring or a 5-6 membered
 heteroaryl ring, each having 1 to 3 heteroatoms independently selected from
 O, S, or N, and each optionally substituted by one to four groups each
 selected independently from R⁴; or a 5 to 7 membered saturated or
 unsaturated carbocyclic ring optionally substituted by one to four groups
 35 each selected independently from R⁴;

R^5 and R^6 are independently H, aryl and heteroaryl as defined above,

-C₃-C₆-cycloalkyl as defined above, -C₃-C₆-cycloheteroalkyl as defined above, -C₁-C₄-perfluoroalkyl, or straight chain or branched -C₁-C₆ alkyl, -C₂-C₆-alkenyl, or -C₂-C₆-alkynyl each optionally substituted with -OH, -COR⁸, -CN, -C(O)NR⁸OR⁹, -C₂-C₆-alkenyl, -C₂-C₆-alkynyl, -OR⁸, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁸ where x is 0-2, -OPO(OR⁸)OR⁹, -PO(OR⁸)R⁹, -OC(O)NR⁸R⁹, -COOR⁸, -CONR⁸R⁹, -SO₃H, -NR⁸R⁹, -NCOR⁸R⁹, -NR⁸COOR⁹, -SO₂NR⁸R⁹, -NO₂, -N(R⁸)SO₂R⁹, -NR⁸CONR⁸R⁹, -C₃-C₆ cycloalkyl as defined above, 3-6 membered cycloheteroalkyl as defined above, aryl or heteroaryl as defined above, -SO₂NHCOR⁸ or -CONHSO₂R⁸ where R⁸ is not hydrogen, -tetrazol-5-yl, -NR⁸C(=NR⁹)NR⁸R⁹, -SO₂NHCONR⁸R⁹, or -SO₂NHCN;

R^7 is hydrogen, straight chain or branched -C₁-C₆-alkyl, -C₂-C₆-alkenyl, or -C₂-C₆-alkynyl each optionally substituted with -OH, -COR⁵, -CN, -C₂-C₆-alkenyl, -C₂-C₆-alkynyl, -OR⁵, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁵ where x is 0-2, -OPO(OR⁵)OR⁶, -PO(OR⁵)R⁶, -OC(O)NR⁵R⁶, -COOR⁵, -CONR⁵R⁶, -SO₃H, -NR⁵R⁶, -NR⁵COR⁶, -NR⁵COOR⁶, -SO₂NR⁵R⁶, -NO₂, -N(R⁵)SO₂R⁶, -NR⁵CONR⁵R⁶, -C₃-C₆ cycloalkyl as defined above, -C₃-C₆-cycloheteroalkyl as defined above, -aryl or heteroaryl as defined above, -SO₂NHCOR⁵ or -CONHSO₂R⁵ where R⁵ is not hydrogen, -tetrazol-5-yl, -NR⁵C(=NR⁶)NR⁵R⁶, -C(O)N R⁵OR⁶, -SO₂NHCONR⁵R⁶ or -SO₂NHCN;

or R^7 is phenyl or naphthyl, optionally substituted by R¹, R², R³ and R⁴ or a 5 to 6 membered heteroaryl group having 1 to 3 heteroatoms selected independently from N, O, and S and optionally substituted by R¹, R², R³ and R⁴;

or R^7 is C₃-C₆ cycloalkyl or 3-6 membered cycloheteroalkyl as defined above;

or R^7 CH₂-N-A-, where A is as defined above, can form a non-aromatic 1,2-benzofused 7-10 membered heterocyclic ring optionally containing an additional heteroatom selected from O, S and N wherein said heterocyclic ring may be optionally fused to another benzene ring;

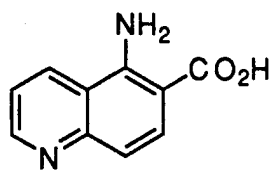
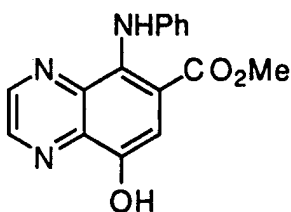
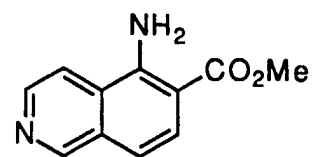
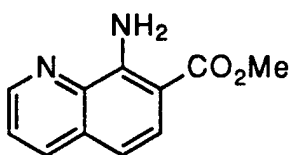
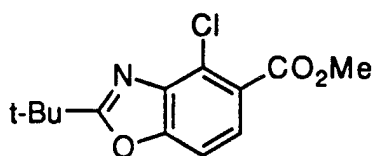
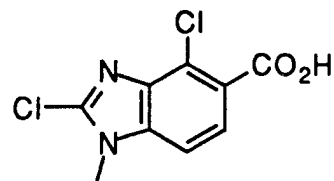
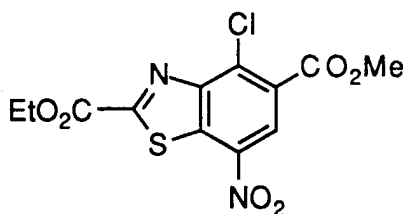
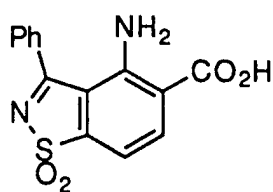
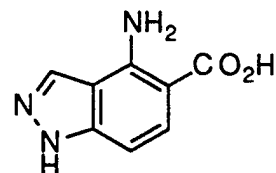
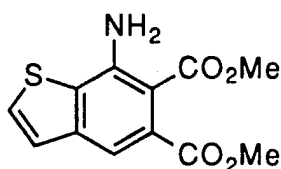
R⁸ and R⁹ are independently H, aryl or heteroaryl as defined above, -C₃-C₇-cycloalkyl or 3 to 6 membered cycloheteroalkyl as defined above, -C₁-C₄-perfluoroalkyl, straight chain or branched -C₁-C₆-alkyl, -C₂-C₆-alkenyl, or -C₂-C₆-alkynyl, each optionally substituted with hydroxy, alkoxy, aryloxy, 5 -C₁-C₄-perfluoroalkyl, amino, mono- and di-C₁-C₆-alkylamino, carboxylic acid, carboalkoxy and carboaryloxy, nitro, cyano, carboxamido primary, mono- and di-C₁-C₆-alkylcarbonyl;

and the pharmaceutically acceptable salts thereof and the optical isomers and diastereomers thereof.

10 Preferred compounds are those wherein both of the carbons of A adjacent to the carbon bearing the sulfonamido group have a substituent other than hydrogen. Also preferred are compounds where Z is 4-alkoxyphenyl, 4-aryloxyphenyl or heteroaryloxyphenyl.

In the above definitions, the term "heteroaryl" includes, but is not limited to 15 pyrrole, furan, thiophene, pyridine, pyrimidine, pyridazine, pyrazine, triazole, pyrazole, imidazole, isothiazole, thiazole, isoxazole and oxazole. The term "5 to 7 membered saturated or unsaturated heterocyclic ring" includes, but is not limited to oxazolidine, thiazolidine, imidazolidine, tetrahydrofuran, tetrahydrothiophene, tetramethylene sulfone, dihydropyran, tetrahydropyran, piperidine, pyrrolidine, dioxane, morpholine, azepine and 20 diazepine. The term "heteroaryl fused to a phenyl" includes, but is not limited to, benzoxazole, benzoisoxazole, indole, isoindole, benzothiophene, benzofuran, quinoline, quinazoline, quinoxaline, benzotriazole, benzimidazole, benzthiazole, benzopyrazole and isoquinoline.

The following compounds (**1-10**) which may be used in preparing invention 25 compounds are known and references are given hereinbelow.

**1****2****3****4****5****6****7****8****9****10**

Compound 1:

a) Meyer, Michael D.; Altenbach, Robert J.; Basha, Fatima Z.; Carroll, William A.; Drizin, Irene; Elmore, Steven W.; Kerwin, Jr James F.; Lebold, Suzanne A.; Lee, Edmund L.; Sippy, Kevin B.; Tietje, Karin R.; Wendt, Michael D. Tricyclic substituted hexahydrobenz[e]isoindole alpha-1 adrenergic antagonists. US 5597823. CAN 126:199575.

b) Meyer, Michael D.; Altenbach, Robert J.; Basha, Fatima Z.; Carroll, William A.; Drizin, Irene; Kerwin, James F., Jr.; Lebold, Suzanne A.; Lee, Edmund L.; Elmore, Steven W.; et al. Preparation of tricyclic substituted benz[e]isoindoles as alpha-1 adrenergic antagonists. PCT Int. Appl WO 9622992 A1 CAN 125:221858.

Compound 2:

Troll, Theodor; Schmid, Klaus. Preparation and reactions of a 2H-pyrrolo[3,4-b]pyridine and a 2H-pyrrolo[3,4-b]pyrazine. J. Heterocycl. Chem. (1986), 23(6), 1641-4.

Compound 3:

- 5 Meyer, Michael D.; Altenbach, Robert J.; Basha, Fatima Z.; Carroll, William A.; Drizin, Irene; Elmore, Steven W.; Kerwin, Jr James F.; Lebold, Suzanne A.; Lee, Edmund L.; Sippy, Kevin B.; Tietje, Karin R.; Wendt, Michael D. Tricyclic substituted hexahydrobenz[e]isoindole alpha-1 adrenergic antagonists. US 5597823. CAN 126:199575.

10 Compound 4:

- a) Meyer, Michael D.; Altenbach, Robert J.; Basha, Fatima Z.; Carroll, William A.; Drizin, Irene; Elmore, Steven W.; Kerwin, Jr James F.; Lebold, Suzanne A.; Lee, Edmund L.; Sippy, Kevin B.; Tietje, Karin R.; Wendt, Michael D. Tricyclic substituted hexahydrobenz[e]isoindole alpha-1 adrenergic antagonists. US 5597823. CAN 15 126:199575.

- b) Meyer, Michael D.; Altenbach, Robert J.; Basha, Fatima Z.; Carroll, William A.; Drizin, Irene; Kerwin, James F., Jr.; Lebold, Suzanne A.; Lee, Edmund L.; Elmore, Steven W.; et al. Preparation of tricyclic substituted benz[e]isoindoles as α_1 adrenergic antagonists. PCT Int. Appl. WO 9622992 A1 CAN 125:221858 .

20 Compound 5:

Geach, Neil; Hawkins, David William; Pearson, Christopher John; Smith, Philip Henry Gaunt; White, Nicolas. Preparation of isoxazoles as herbicides. Eur. Pat. Appl. EP 636622 A1 CAN 122:290845 .

Compound 6:

- 25 Kotovskaya, S. K.; Mokrushina, G. A.; Suetina, T. A.; Chupakhin, O. N.; Zinchenko, E. Ya.; Lesovaya, Z. I.; Mezentsev, A. S.; Chernyshov, A. I.; Samoilova, L. N. Benzimidazolyl derivatives of penicillin and cephalosporin: synthesis and antimicrobial activity. Khim.-Farm. Zh. (1989), 23(8), 952-6.

Compound 7:

- 30 Wagner, Klaus. Bactericidal and fungicidal 4-chlorobenzothiazoles. Ger. Offen. DE 2136924 CAN 78:111293 .

Compound 8:

Eggensperger, Heinz; Diehl, Karl H.; Kloss, Wilfried. 2-Hydroxy-4-alkoxybenzophenones. Ger. DE 1768599 711223. CAN 76:85557 .

Compound 9:

Lichtenthaler, Frieder W.; Moser, Alfred. Nucleosides. 44. Benzo-separated pyrazolopyrimidines: expeditious syntheses of [3,4-g]- and [3,4-h]-linked pyrazoloquinazolinones. Tetrahedron Lett. (1981), 22(44), 4397-400.

5 Compound 10:

Terpstra, Jan W.; Van Leusen, Albert M. A new synthesis of benzo[b]thiophenes and benzo[c]thiophenes by annulation of disubstituted thiophenes. J. Org. Chem. (1986), 51(2), 230-8.

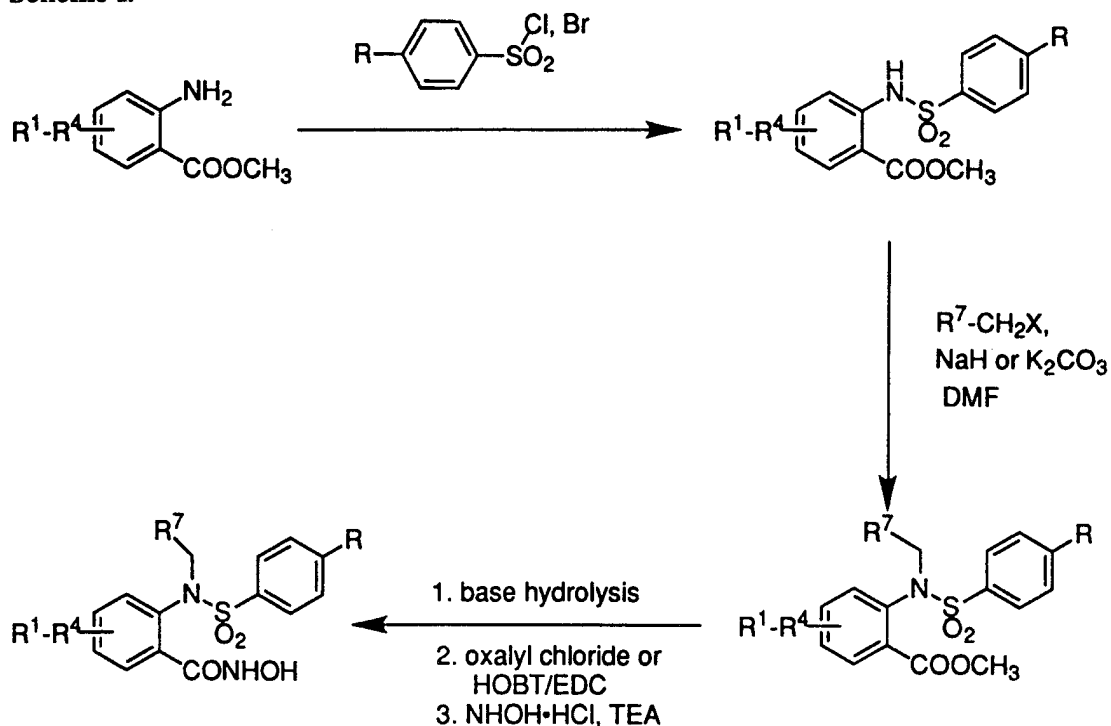
10 The compounds of this invention are shown to inhibit the enzymes MMP-1, MMP-9, MMP-13 and TNF- α converting enzyme (TACE) and inhibit cartilage weight loss and collagen content loss in-vivo are therefore useful in the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease and HIV infection.

15

Detailed Description of the Invention

The invention compounds are prepared using conventional techniques known to those skilled in the art of organic synthesis. The following scheme (Scheme I) illustrates the general reaction sequence employed. For purposes of illustration only, wherein the
20 group A shown is a phenyl, methyl anthranilate is reacted with p-methoxybenzenesulfonyl chloride to provide the requisite N-aryl sulfonamido-ester which is then alkylated to provide the N,N-disubstituted sulfonamide and subsequently converted into the corresponding hydroxamic acid in two further steps.

Scheme I.

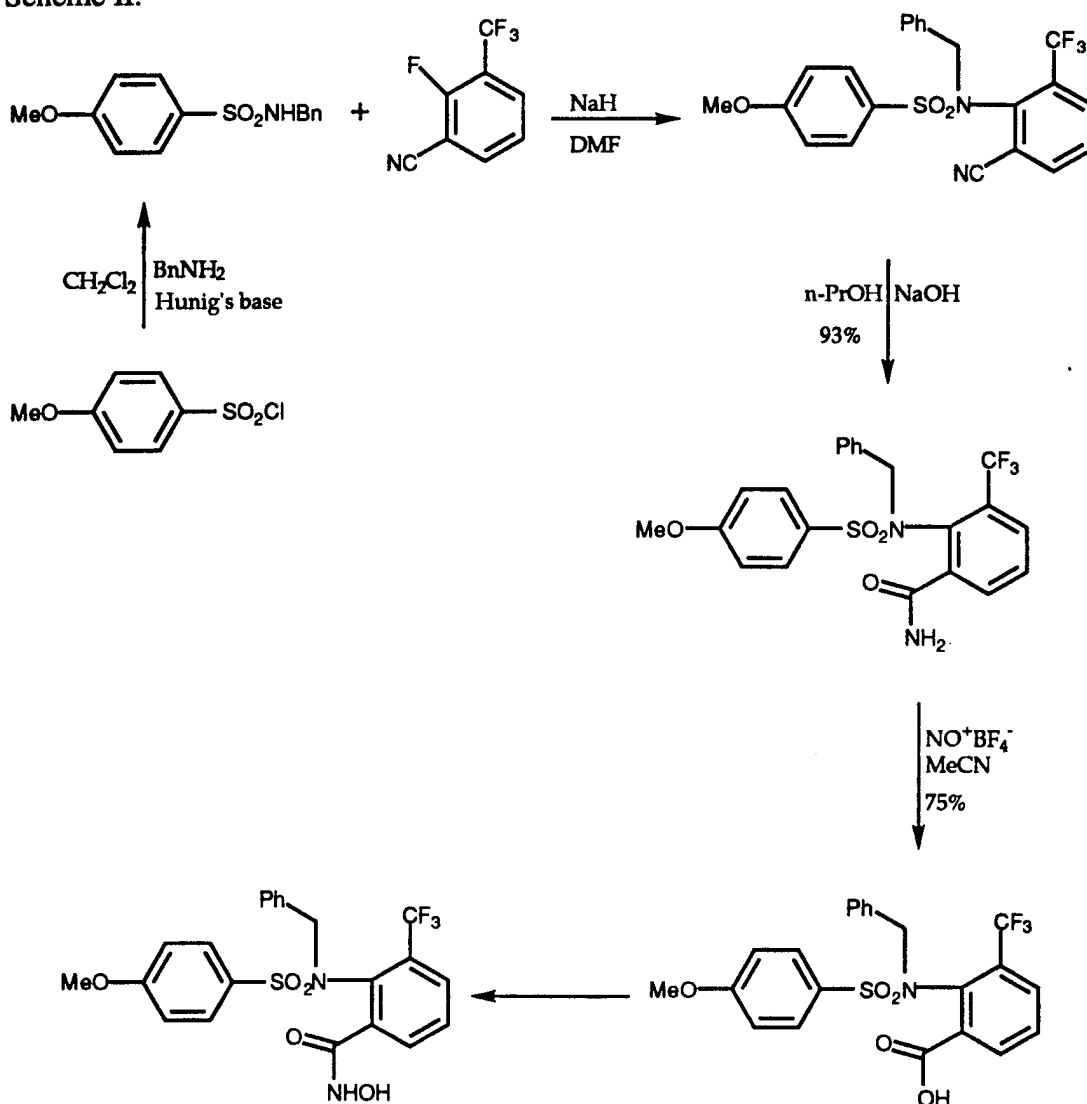


Basic salts of the hydroxamic acids can be formed with pharmaceutically acceptable alkali-forming metal cations such as lithium, sodium, potassium, calcium and aluminum. Acid addition salts can be formed when a substituent contains a basic amino group using a pharmaceutically acceptable inorganic or organic acid such as hydrochloric, hydrobromic, phosphoric, sulfuric, acetic, benzoic, succinic, lactic, malic, maleic, fumaric or methanesulfonic acids.

Where the requisite anthranilic acid is not available, certain invention compounds are prepared by various procedures as shown in the following schemes. In some of the schemes, certain conversions are not detailed but are understood to incorporate reactions denoted in a previous scheme. In certain reaction sequences a substituent R is not further identified by a number, but the identification of the substituent can readily be ascertained by those skilled in the art by referring to the definitions of the various substituents in the generic formula above.

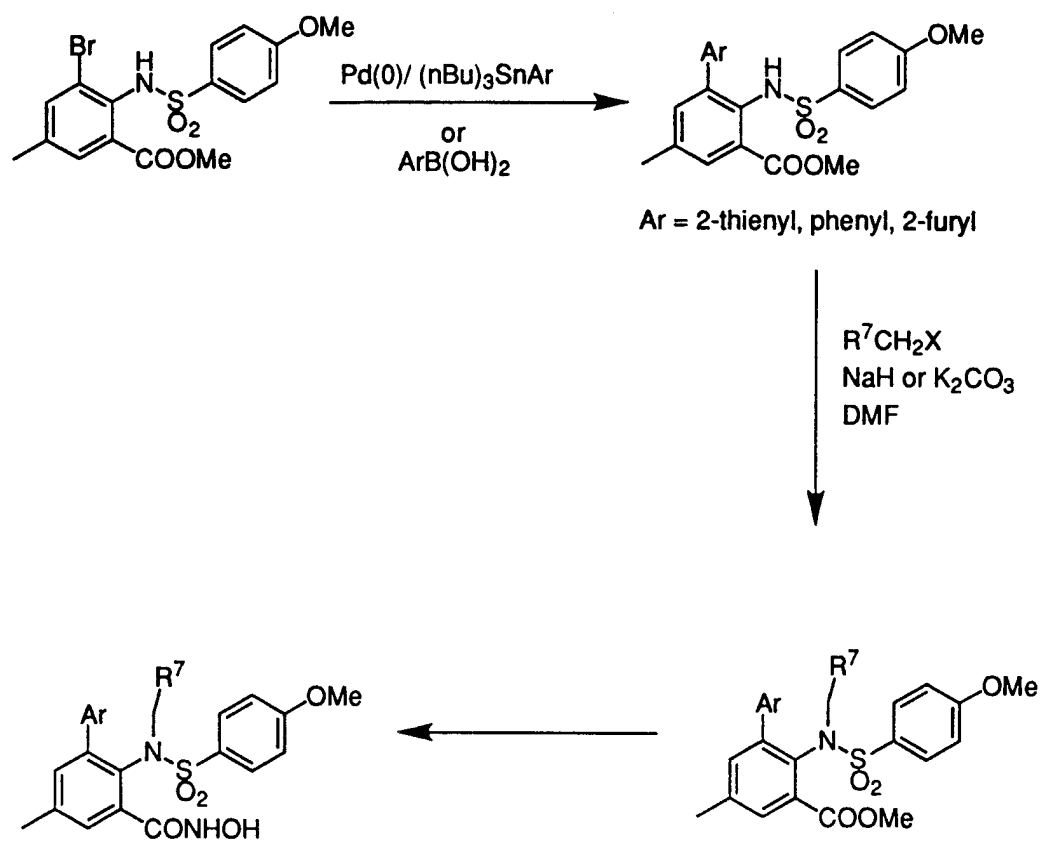
Scheme II below shows the synthetic route used to prepare the 3-trifluoromethyl compound of Example 125 via displacement of an ortho-fluorobenzonitrile.

Scheme II.

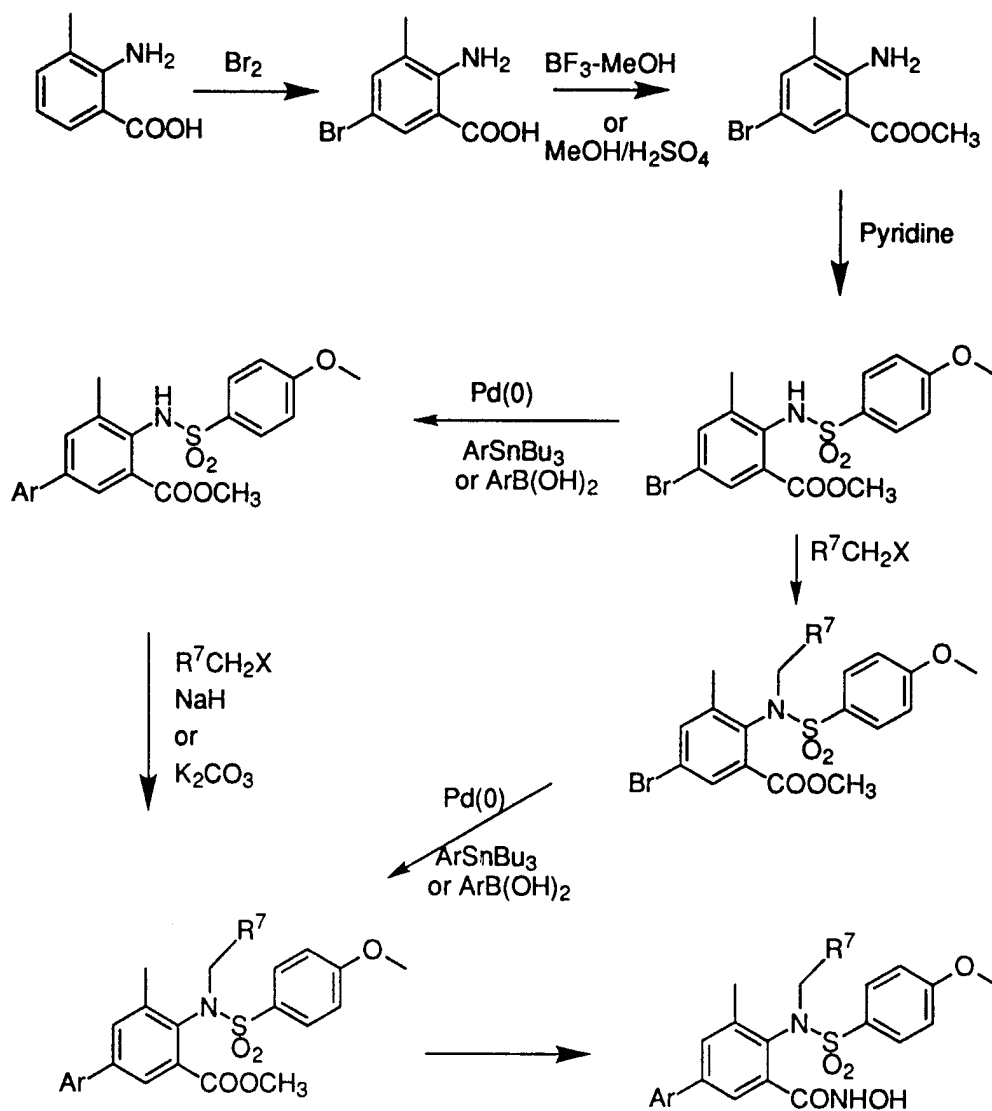


Synthesis of 3- and 5-aryl and heteroaryl analogs was accomplished following the
 5 procedures shown in Schemes III and IV. In both schemes the aryl/heteroaryl group may
 be appended through the use of Stille or Suzuki palladium catalyzed coupling reactions. As
 shown in Scheme IV, the palladium catalyzed Stille or Suzuki couplings at the 5-position of
 the anthranilic acid ring can be done before or after the alkylation of the sulfonamide
 nitrogen.

Scheme III.

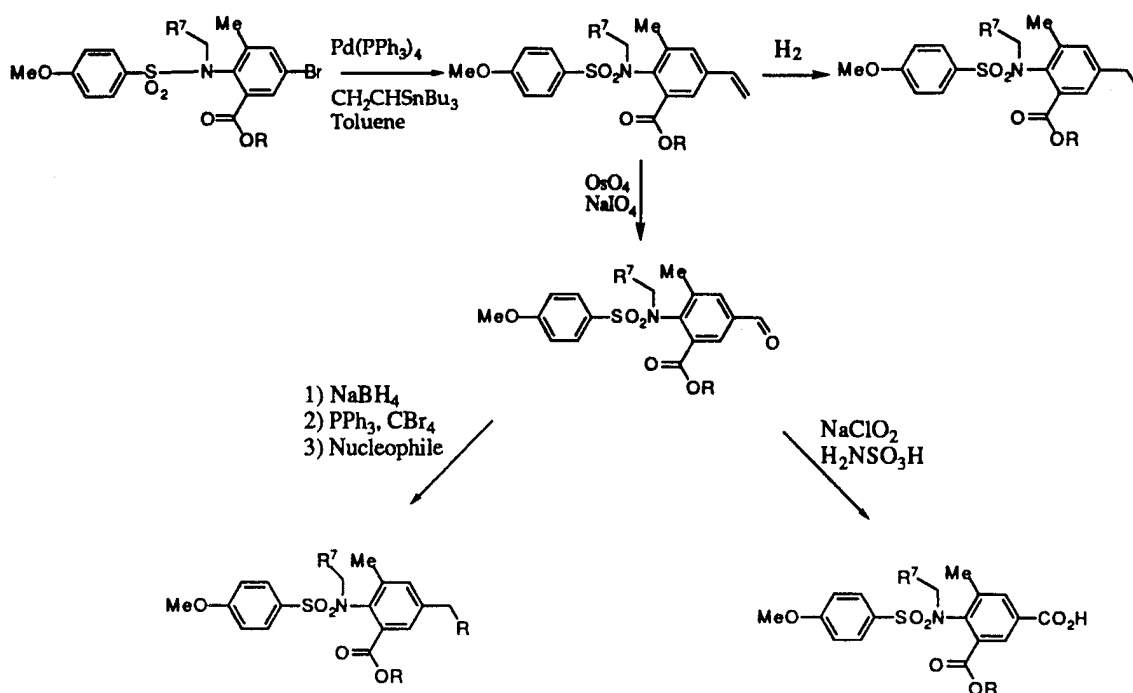


Scheme IV.



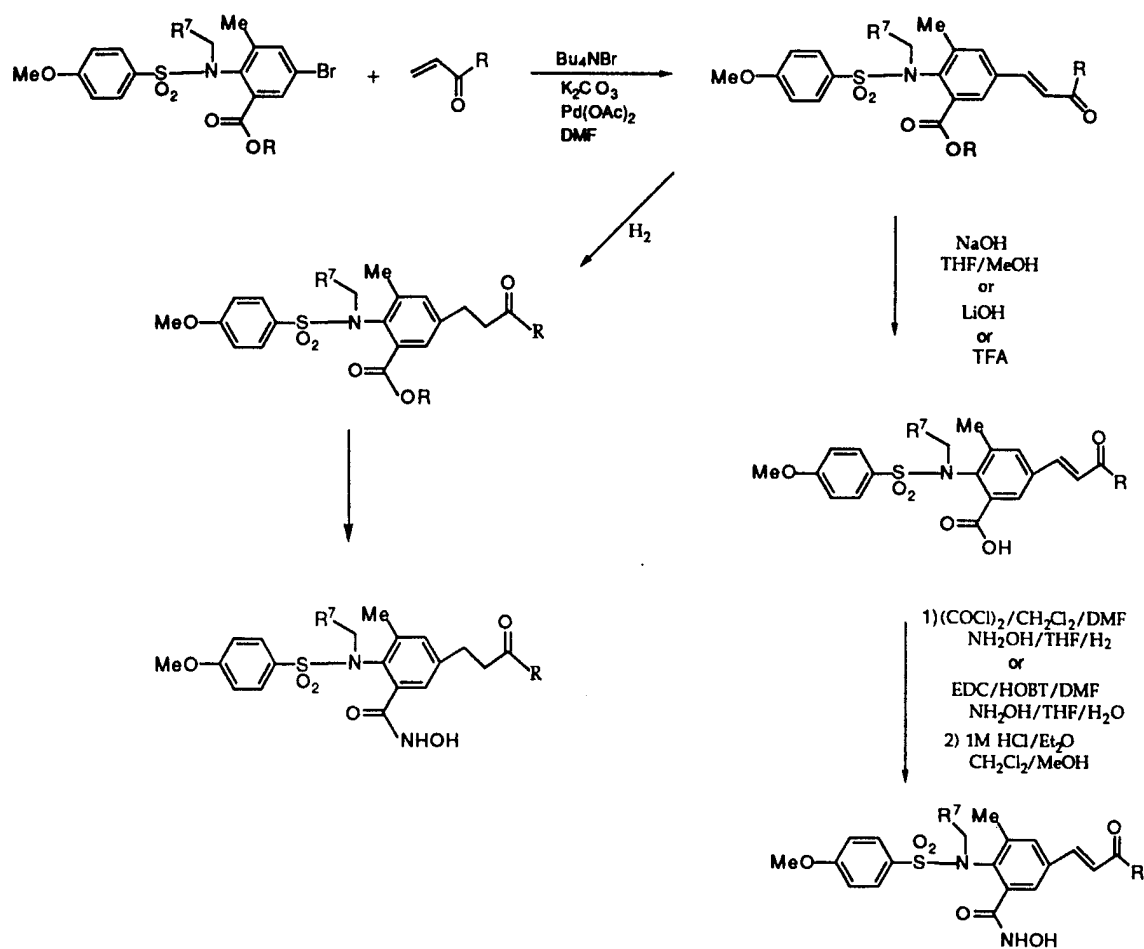
- 5 As shown in Scheme V, a Stille coupling of the 5-bromoaryl derivative, prepared as in Scheme IV, with a vinyl stannane provides access to the 5-substituted anthranilic acids bearing a wide variety of functionality including, but not limited to alkenes, alkanes, hydroxamic acids, alcohols, halogens and amines. All of the ester derivatives shown in the Scheme may then be converted into the requisite hydroxamic acids.

Scheme V.



- 5 The 5-position of the anthranilic acid ring can also be functionalized through the use of palladium catalyzed Heck reactions, as shown in Scheme VI. Thus, reaction of the 5-bromo aryl derivative, prepared as in Scheme IV, with an acrylamide, acrylic acid or acrylic ester provides the 5-cinnamate derivatives, which may then be manipulated and converted into the aryl-hydroxamic acids by known procedures. These cinnamates may also be
- 10 hydrogenated to give the phenethyl derivatives prior to conversion into the aryl-hydroxamic acids. A variety of substituents are tolerated on the anthranilic acid ring for these transformations and the scheme is presented solely for illustrative purposes.

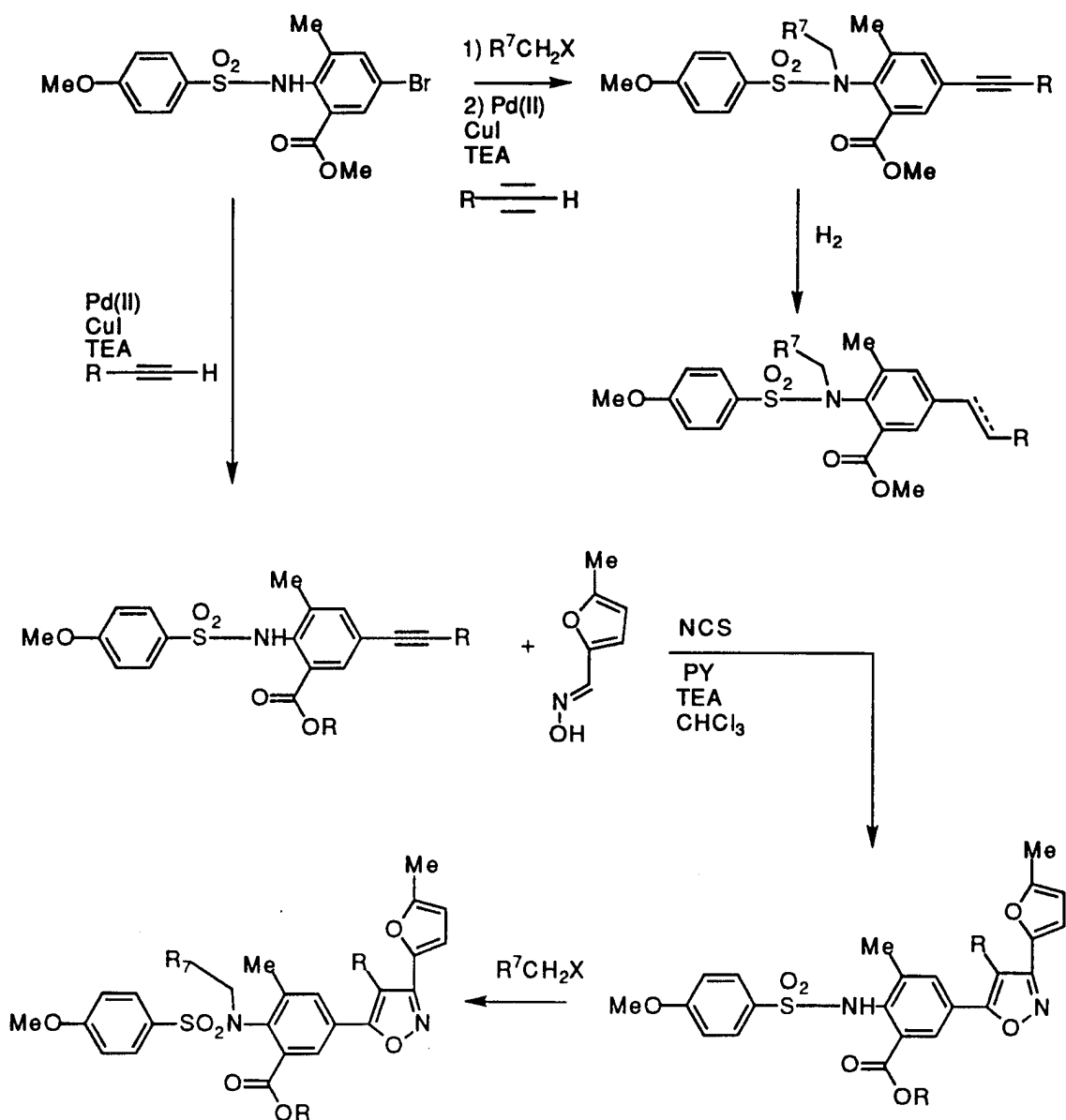
Scheme VI.



5

An additional route to anthranilic acid derivatives substituted at the 5-position, via palladium catalyzed couplings of the aryl halide with alkynes, is shown in Scheme VII. Again, conversion of the aryl esters into the hydroxamates is not shown.

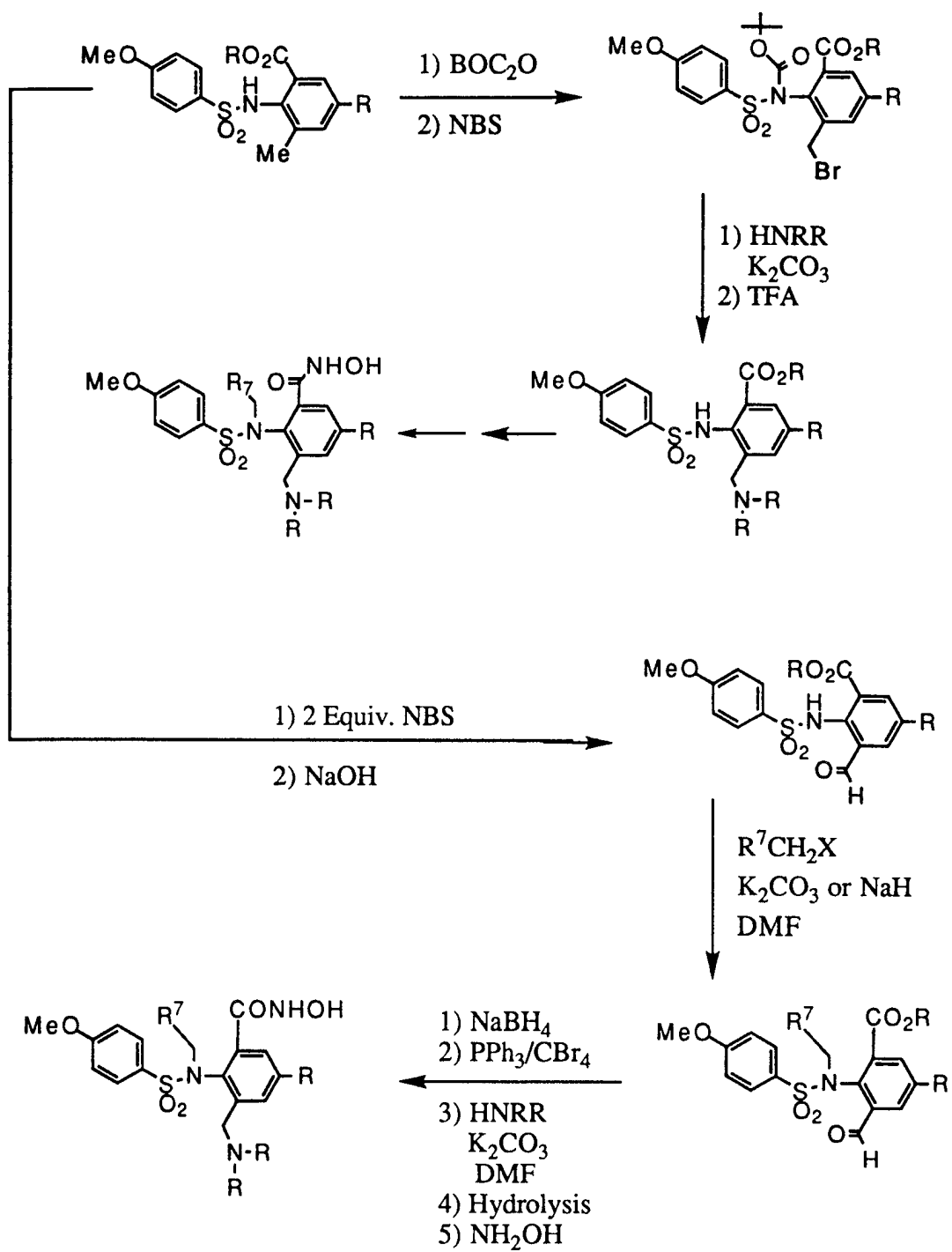
Scheme VII.



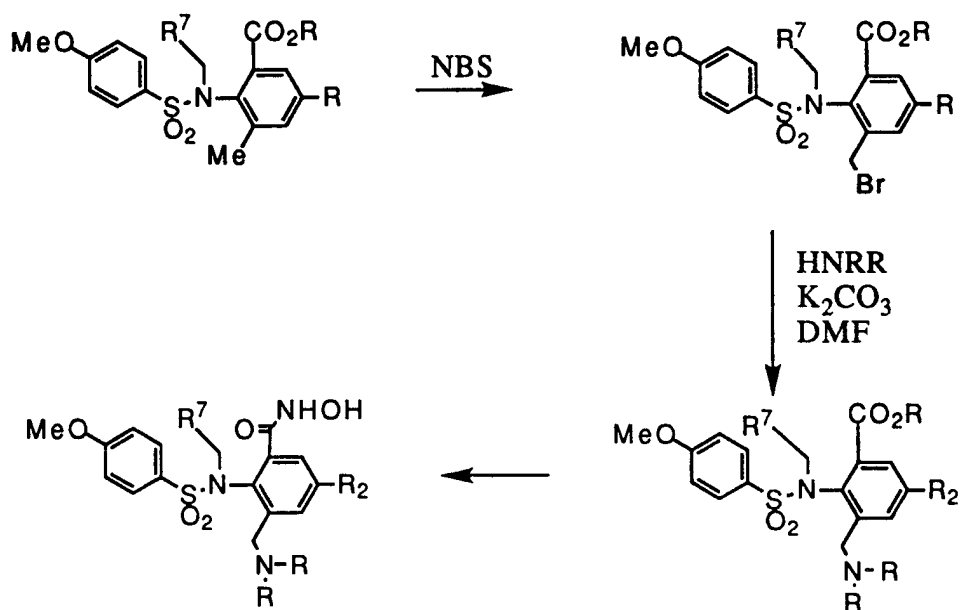
5 Schemes VIII and IX illustrate routes to anthranilic acid derivatives bearing amine-containing functionality at the 3-position of the anthranilic acid ring. The intermediate benzylic bromides can also be displaced with malonate anion or other carbon-based nucleophiles. The 5-substituent of the anthranilate may be manipulated before or after the amino group is added to the molecule.

10

Scheme VIII.



Scheme IX.

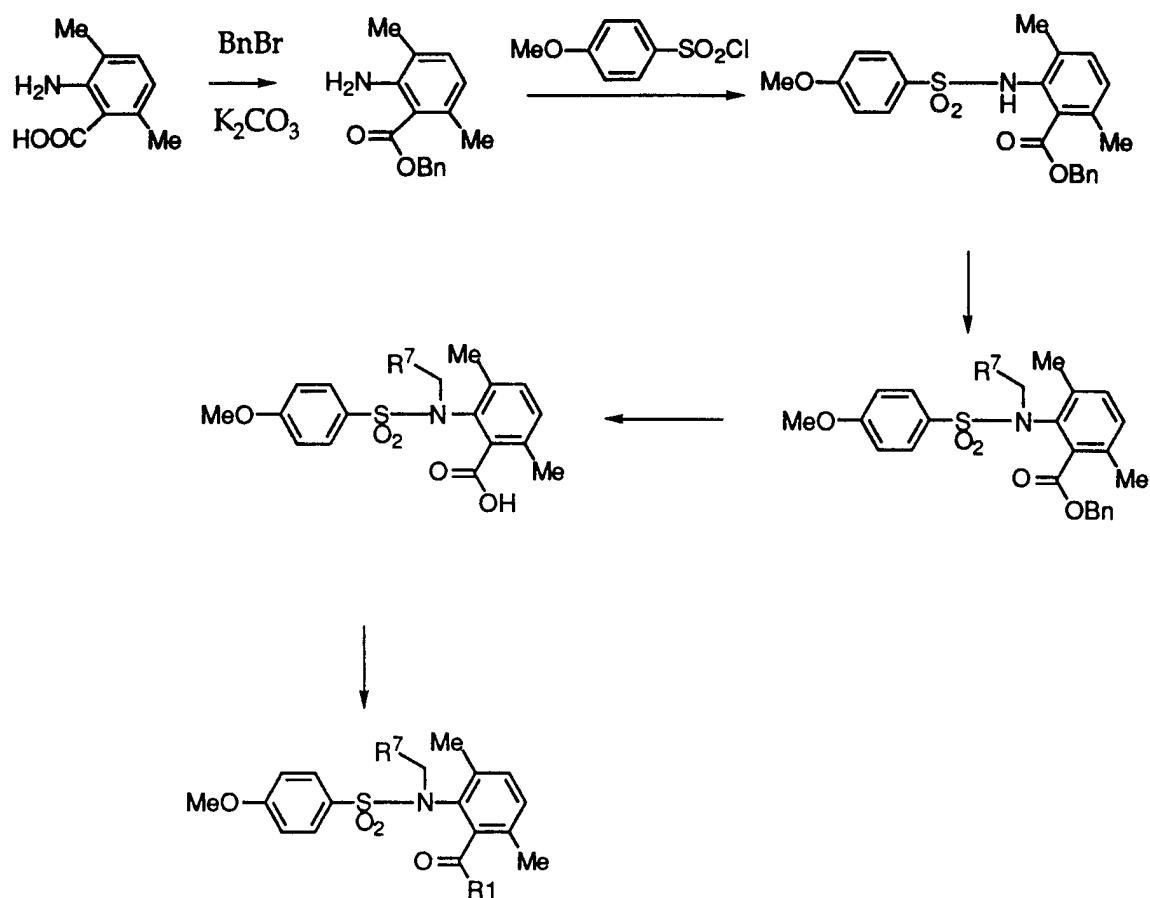


5

Scheme X shows the route used for the synthesis of 3,6-disubstituted anthranilic acid derivatives. Thus, the ester is converted into the hydroxamic acid by reduction to the alcohol followed by stepwise oxidation to the aldehyde and then the carboxylic acid. The carboxylic acid is then transformed into the hydroxamic acid by the usual procedures.

10

Scheme X.

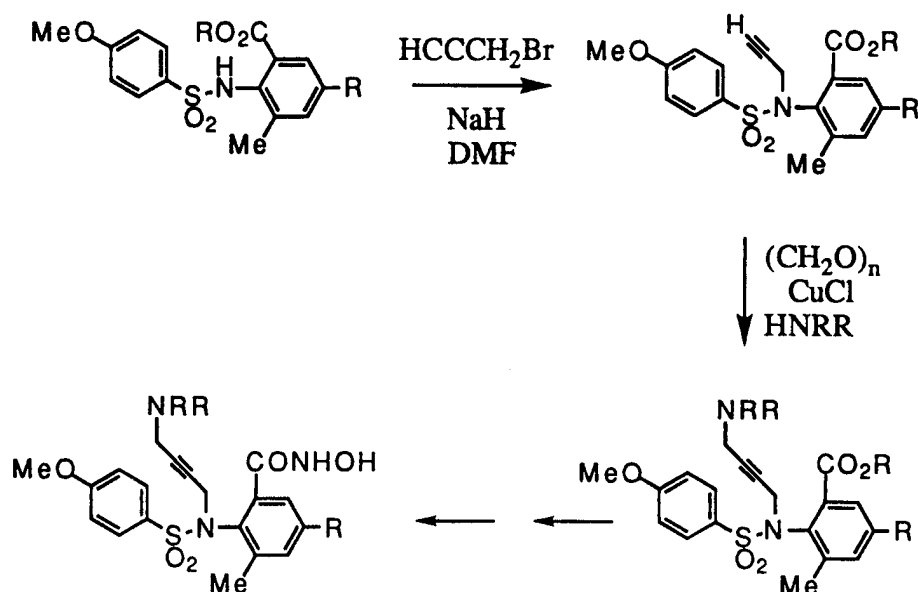


5

Schemes XI and XII illustrate two methods for incorporating amino groups into the substituent attached to the sulfonamide nitrogen of the compounds of the invention. Thus, in Scheme XI the NH-sulfonamide is alkylated with propargyl bromide to provide the propargyl sulfonamide. This alkyne is reacted with paraformaldehyde in the presence of a primary or secondary amine and cuprous chloride to give the propargyl amine which is converted, as before, to the desired hydroxamic acid.

10

Scheme XI.

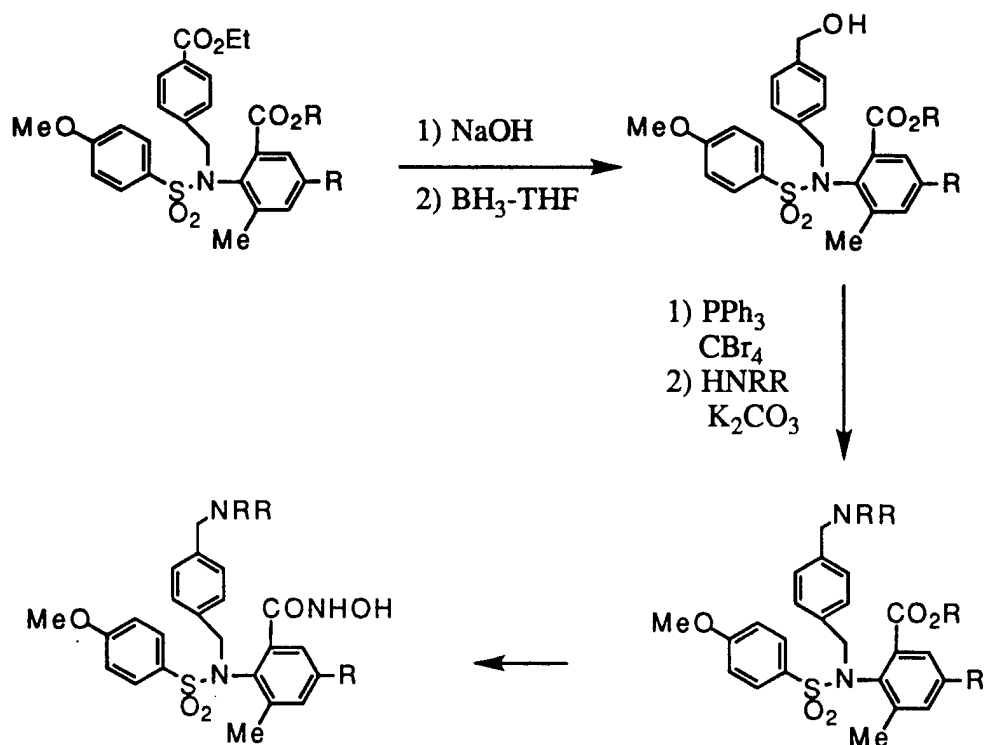


5

In Scheme XII, selective hydrolysis of the ester of the p-carboethoxybenzyl sulfonamide group provides a mono-carboxylic acid. This acid may be converted into an amide (not shown), followed by conversion of the anthranilate into the corresponding hydroxamate, or reduced to the corresponding alcohol with diborane. The alcohol may be converted into the analogous amine via the benzylic bromide, followed by conversion of the anthranilate into the corresponding hydroxamate.

10

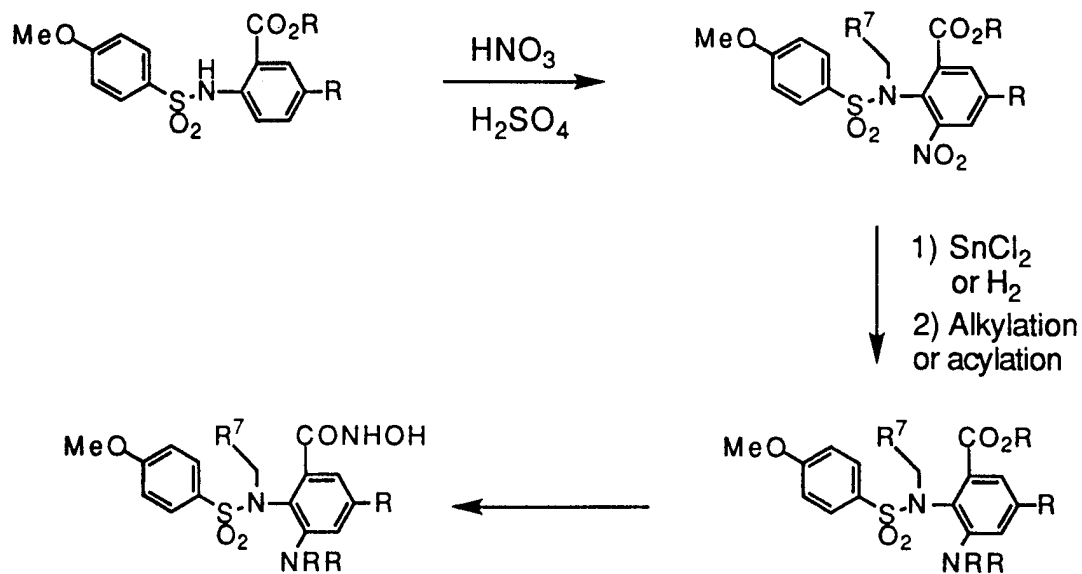
Scheme XII.



5

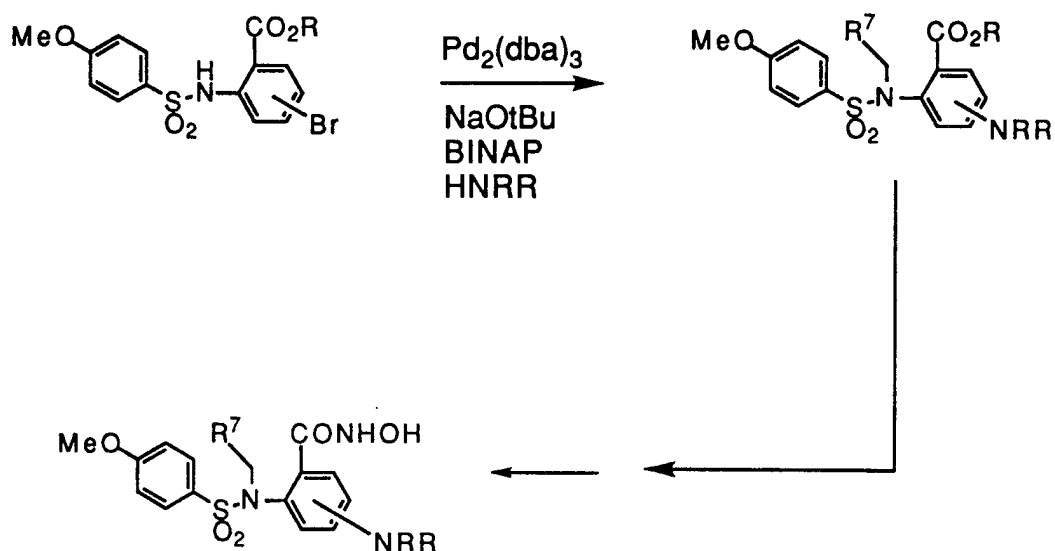
Amine substituents on the anthranilic acid are also available via the 3-nitro anthranilate derivative, as shown in Scheme XIII. The $\text{R}^7\text{CH}_2\text{-}$ group is added after the nitration reaction.

10 Scheme XIII.



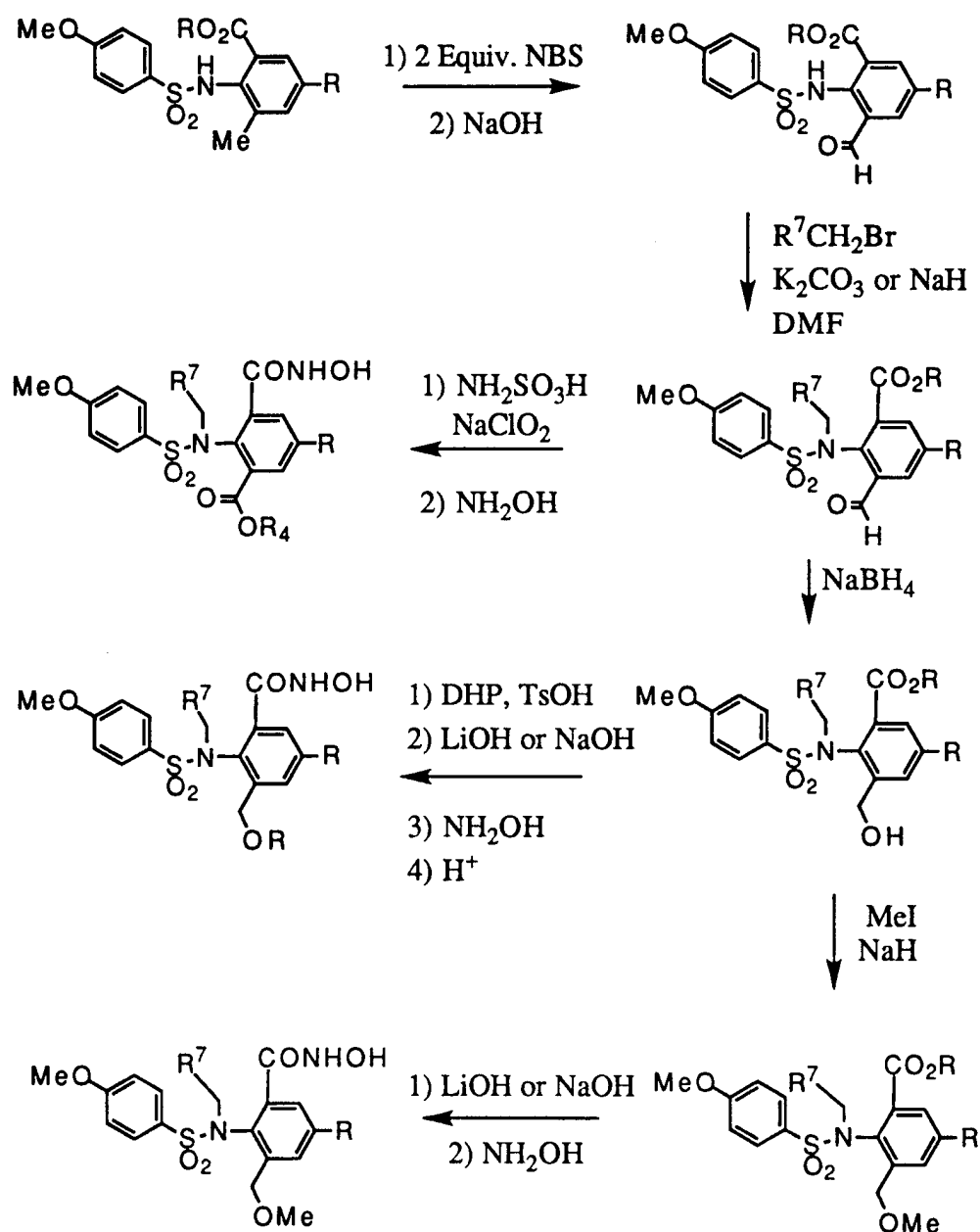
Palladium catalyzed couplings of the aryl bromides with the desired amines, as shown in Scheme XIV, can also be used to incorporate amino groups into the anthranilate ring. When R⁷ in Scheme XIV is a bromoaryl group, this methodology may also be used to generate the analogous aminoaryl derivative.

Scheme XIV.



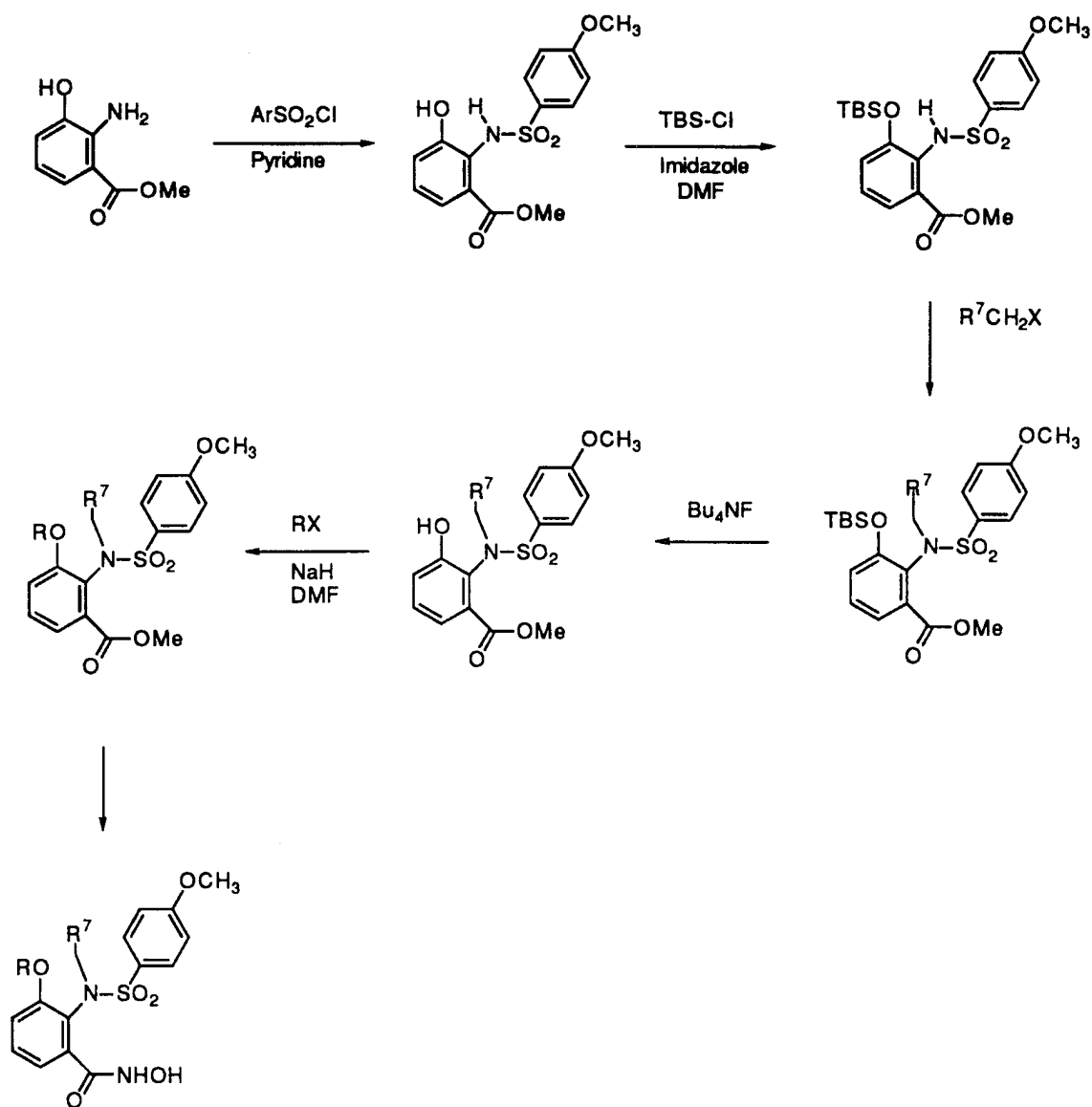
The manipulation of the 3-carboxaldehyde substituent, prepared as shown in Scheme VIII, to append alcohols, ethers and esters at the 3-position of the anthranilic acids is shown in Scheme XV. The carboxylic acid product of the sodium chlorite/sulfamic acid oxidation shown in this scheme may also be used to synthesize carboxamides. The methods illustrated here are applicable to substituents at any position of the anthranilate.

Scheme XV.



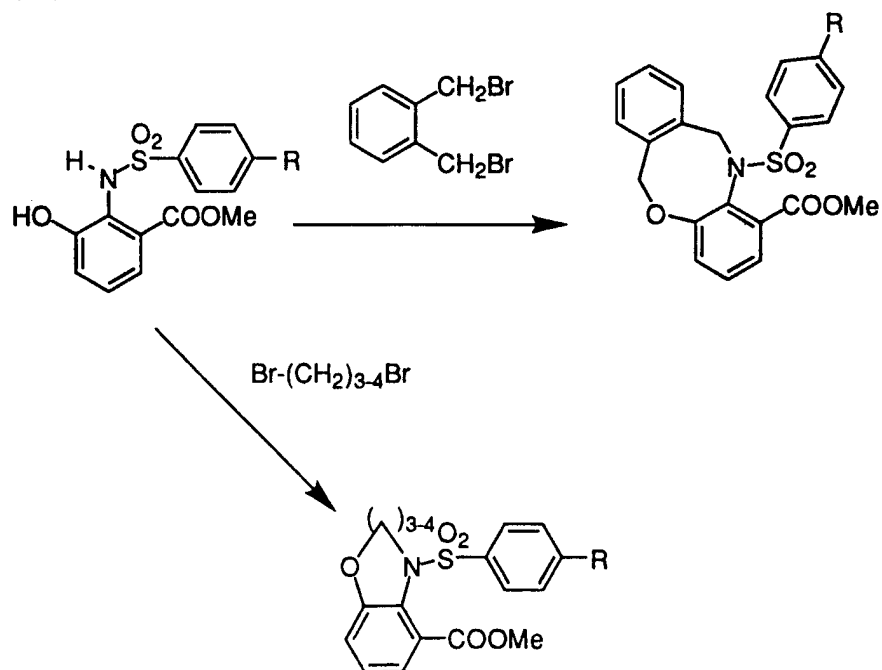
- 5 Scheme XVI shows the route used to prepare 3-alkoxy and substituted alkoxy compounds (Examples 34, 54-60, 101, 174)

Scheme XVI.



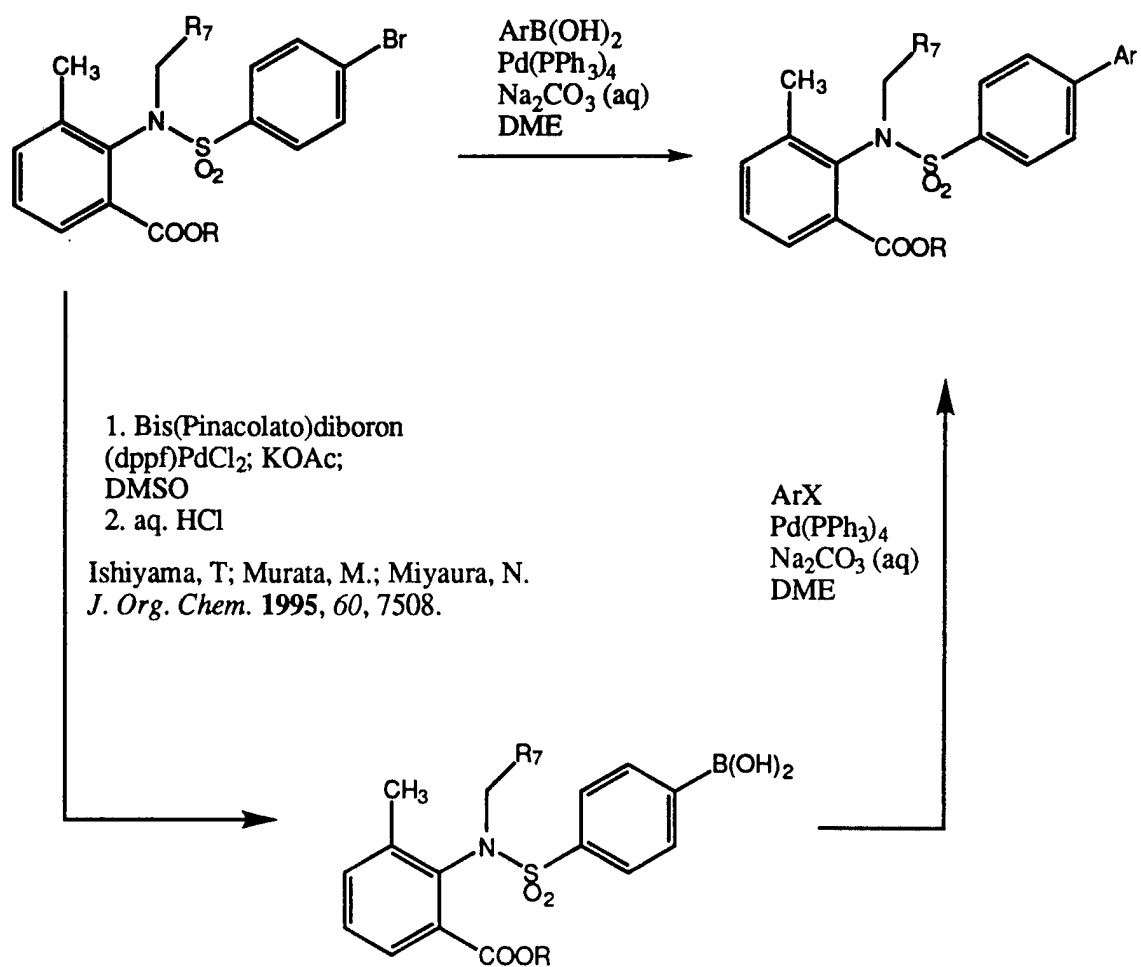
5 Scheme XVII shows the route used to prepare benzoic acid ester intermediates of the invention compounds where $\text{R}^7\text{-N-A}$ forms a non-aromatic heterocyclic ring.

Scheme XVII.



Methods for synthesizing variations of substituents on the sulfonyl aryl group are shown in Schemes XVIII through XXI. As shown in Scheme XVIII, biaryl sulfonyl groups are synthesized by Suzuki couplings on a bromo-substituted benzene sulfonamide. The starting bromo-substituted benzene sulfonamide is synthesized from the commercially available bromobenzenesulfonyl chloride and the anthranilate ester.

Scheme XVIII.

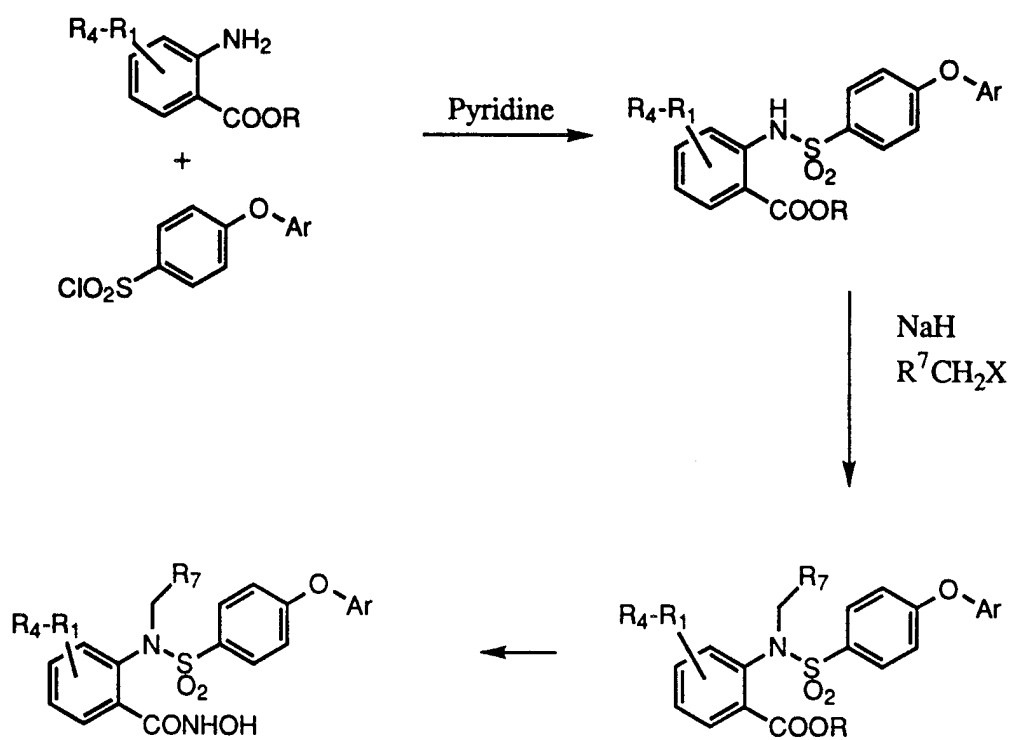


5

Methods for synthesizing sulfonyl aryl ethers are shown in Schemes XIX through XXI. In Scheme XIX biaryl ethers, or aryl heteroaryl ethers, are synthesized starting from the known sulfonyl chlorides (see for example: Zook SE; Dagnino, R; Deason, ME, Bender, SL; Melnick, MJ WO 97/20824).

10

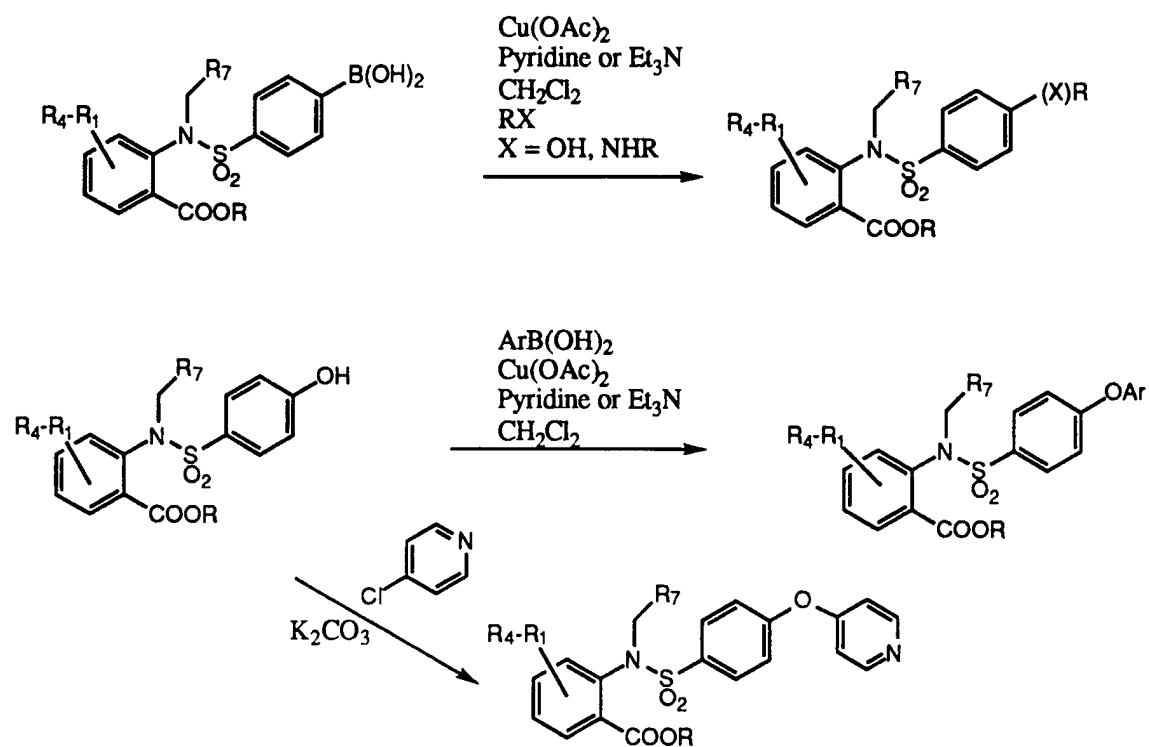
Scheme XIX.



5

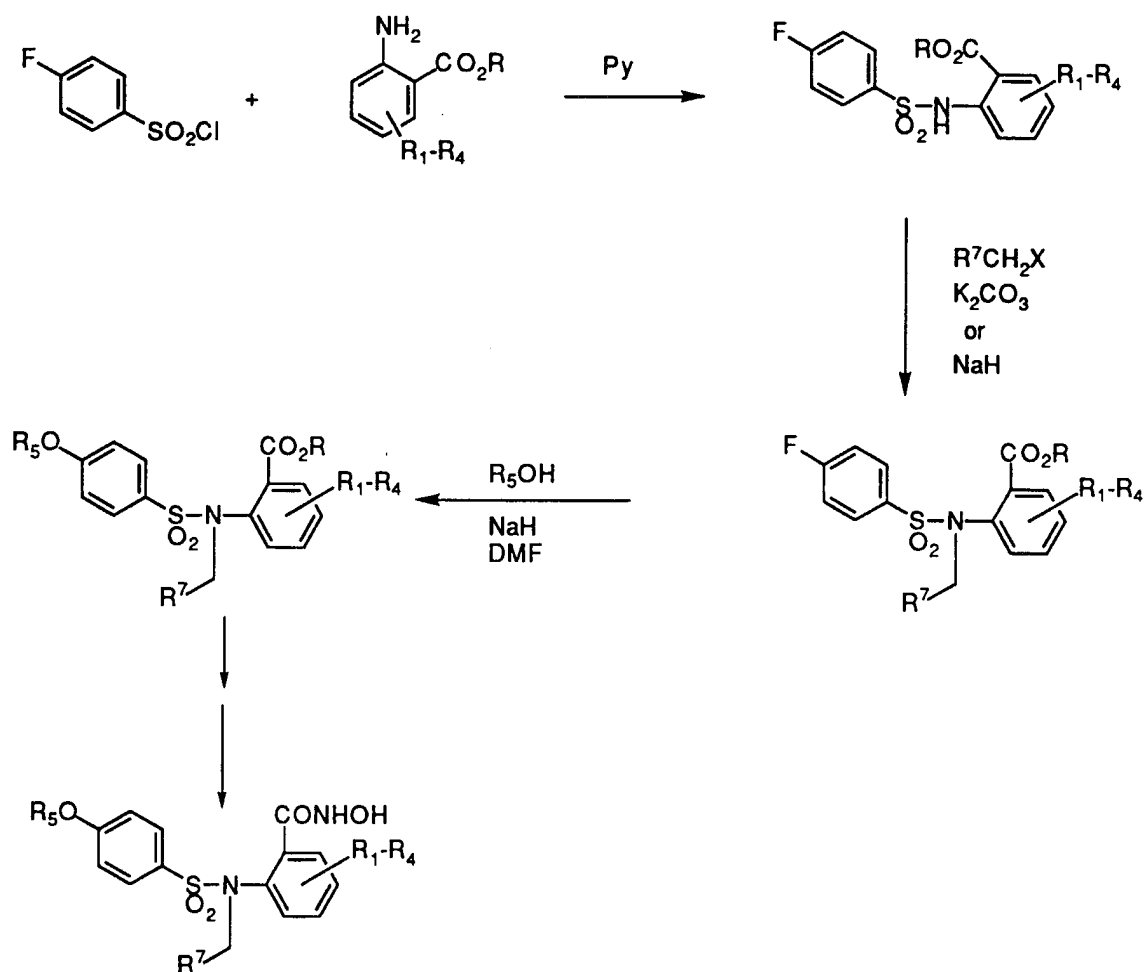
Alternatively, the biaryl ethers may be prepared from the corresponding boronic acids or via the sulfonyl phenols as shown in Scheme XX.

Scheme XX.



- 5 Aryl ethers may also be prepared via displacement of the fluorine from a para-fluorobenzene sulfonamide, as shown in Scheme XXI. Aryl or alkyl ethers may be prepared in this manner.

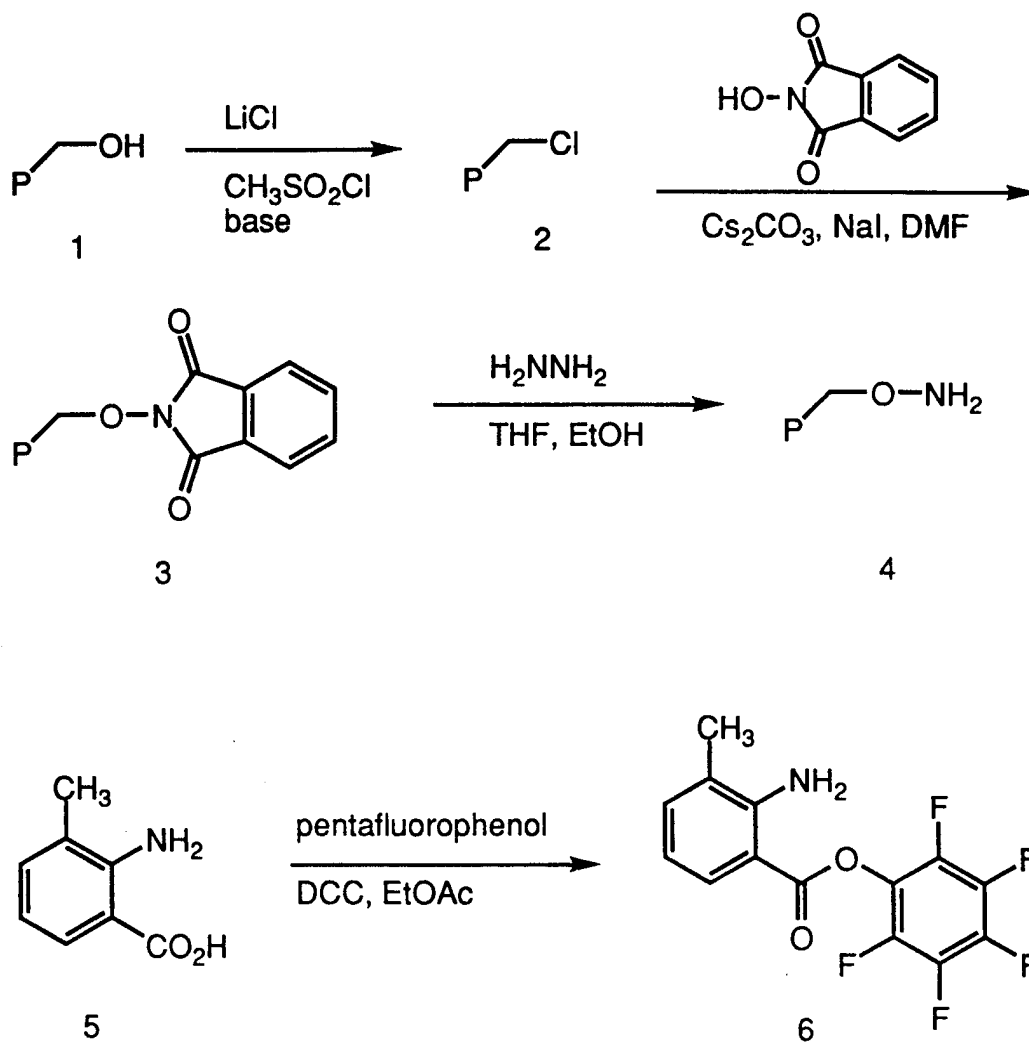
Scheme XXI.



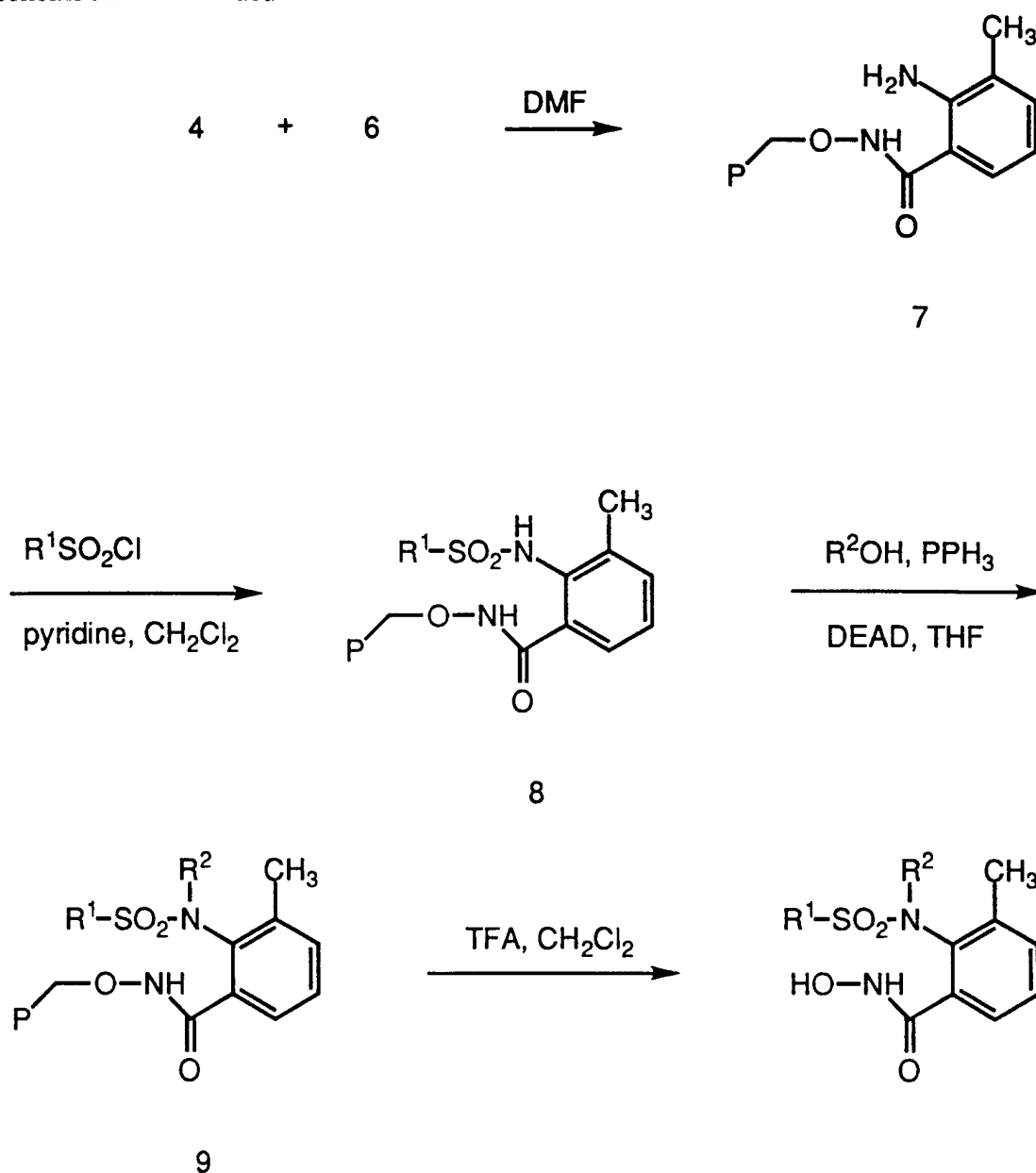
- 5 The procedure for the solid-phase synthesis of the compounds of the invention is illustrated in Scheme XXII. Thus, reaction of the resin-linked hydroxylamine, 4, with the pentafluorophenyl ester, 6, gives the resin-linked hydroxamic acid, 7. Sulfonylation of this compound followed by Mitsunobu type alkylation of the sulfonamide then gives compound 9 which is next cleaved from the resin by treatment with trifluoroacetic acid.

10

Scheme XXII.



Scheme XXII continued



The following specific examples are included for illustrative purposes and are not to be construed as limiting to this disclosure in any way. Other procedures useful for the preparation of the compounds of this invention will be apparent to those skilled in the art of synthetic organic chemistry.

Example 1

2-(4-Methoxy-benzenesulfonylamino)-benzoic acid methyl ester

To a solution of 2.00g (0.013mol) of methyl anthranilate dissolved in 20mL of chloroform was added 3.2mL (0.039mol) of pyridine followed by 2.733g (0.013mol) of p-methoxybenzenesulfonyl chloride. The reaction mixture was stirred at room temperature for 5h and then washed with 3N HCl and water. The organics were then dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting white solid was washed with ether and dried in vacuo to provide 3.7g (87%) of the desired sulfonamide. CI Mass Spec: 322 (M+H).

Example 2

3-Chloro-2-(4-methoxybenzenesulfonylamino)-benzoic acid methyl ester

In the same manner as described in Example 1, 4.07g (0.022mol) of methyl-3-chloro-anthranilate provided 0.932g (12%) of the desired sulfonamide as a white solid.

Example 3

2-(4-Methoxy-benzenesulfonylamino)-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 1, 6.24g (0.038mol) of methyl-3-methyl-anthranilate provided 6.21g (49%) of the desired sulfonamide as a white solid.

Electrospray Mass Spec 336.2 (M+H).

Example 4

2-(4-Methoxy-benzenesulfonylamino)-4-methyl-benzoic acid

To a room temperature solution of 2-amino-4-methyl benzoic acid (1.93g, 12.8mmol) in 20 ml of dioxane:H₂O (1:1) containing triethylamine (2.68ml, 19.2mmol), was added 4-methoxybenzenesulfonyl chloride (2.91g, 14.1mmol). The mixture was stirred at rt for 18 hr. The resulting mixture was diluted with methylene chloride, washed with 1N HCl, H₂O, brine, dried and concentrated. The crude liquid was triturated with 16 ml of EtOAc: hexane (1:3) to afford 2.358g of the desired product as a white solid (57%).

Electrospray Mass Spec 322 (M+H).

Example 5

2-(4-Methoxy-benzenesulfonylamino)-6-methyl-benzoic acid

In the same manner as described in Example 4, 1.93g of 2-amino-6-methylbenzoic acid (12.8mmol) gave 2.24g (55%) of the desired sulfonamide product as a white solid after silica gel chromatography (2% MeOH-0.1% AcOH in CH₂Cl₂). Electrospray Mass Spec: 322 (M+H).

Example 6

2-(4-Methoxy-benzenesulfonylamino)-3-methyl-benzoic acid

5 In the same manner as described in Example 4, 1.93g of 2-amino-3-methylbenzoic acid (12.8 mmol) gave 2.07g (50%) of the desired sulfonamide as a white solid after trituration with EtOAc: hexane (1:4). EI Spec: 321 (M⁺).

Example 7

2-(4-Methoxy-benzenesulfonylamino)-5-methyl-benzoic acid

10 In the same manner as described in Example 4, 1.93g of 2-amino-5-methylbenzoic acid (12.8 mmol) gave 2.498g (61%) of the desired sulfonamide as a white solid after trituration with CH₂Cl₂: hexane (1:2). Electrospray Mass Spec: 320 (M-H).

15 Example 8

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-benzoic acid benzyl and methyl esters

To a solution of 1.00g (3.12mmol) of the product of Example 1 in 45mL of DMF was added 0.37mL (3.12mmol) of benzyl bromide and 3.23g (0.023mol) of potassium carbonate. The reaction was heated to reflux for 24h and an additional 1.11mL of benzyl bromide was added and the reaction mixture was heated to reflux for another 48h, then cooled to room temperature and diluted with 400mL of water. The resulting mixture was extracted with ether and the combined organic layers were then washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/Hex (1:10) to provide 0.60g (40%) of the benzyl ester (CI Mass Spec: 488 (M+H)), which gave white crystals on trituration with ether, and 0.57g (44%) of the methyl ester (CI Mass Spec: 412 (M+H)).

Example 9

30 **2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-chloro-benzoic acid methyl ester**

To a solution of 0.90g (2.532mmol) of the product of Example 2 in 10mL of DMF was added 0.127g (3.165mmol) of 60% sodium hydride. The resulting mixture was stirred for 30min at room temperature and then 0.38mL (3.165mmol) of benzyl bromide was added. This reaction mixture was stirred overnight at room temperature, poured into water and then extracted with ether. The combined organics were washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo to provide a white solid which was

recrystallized from EtOAc/Hexanes to provide 0.44g (39%) of the desired product as white crystals. CI Mass Spec: 446 (M+H).

Example 10

**5 5-Bromo-2-(4-methoxy-benzenesulfonylamino)-3-methyl-benzoic acid
methyl ester**

To a solution of 1.00g (2.985mmol) of the product of Example 3 in 100mL of CHCl_3 was added 0.531g (2.985mmol) of N-bromosuccinimide and 0.025g of AIBN. The resulting mixture was heated to reflux for 18h and then an additional 0.411g of NBS and 0.013g of AIBN were added to the reaction. After refluxing the reaction for another 5h the reaction mixture was cooled to room temperature, washed with sodium sulfite solution and water, dried over MgSO_4 , filtered and concentrated in vacuo. The residue was triturated with ether-hexanes to provide 0.62g (50%) of the desired product as a white solid. EI Mass Spec 413 (M^+).

Example 11

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-bromo-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 9, 0.463g (1.118mmol) of the product of Example 10 provided 0.514g (91%) of the desired product as a colorless oil after chromatography on silica gel eluting with EtOAc/Hexanes (1:10). CI Mass Spec: 504 (M+H).

Example 12

25 **2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-4-methyl-benzoic acid
benzyl ester**

To a solution of 1.82g (5.66 mmol) of the product of Example 4 in 20 ml DMF, was added NaH (60% suspension in oil, 498mg, (12.5 mmol). The resulting mixture was stirred for 15 minutes and benzyl bromide (4.84g, 0.028 mol) was then added. The mixture was heated to 80-84° with stirring for 18 hr under N₂. The reaction was then cooled to room temperature, diluted with ether, washed with H₂O and brine, dried over MgSO₄ and concentrated in vacuo. The residue was triturated with EtOAc to afford 2.2g (77%) of the desired product as a white solid. Electrospray Mass Spec: 502 (M+H).

Example 13

**2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-6-methyl-benzoic acid
benzyl ester**

In the same manner as described in Example 12, 1.45g (4.5 mmol) of the product
5 of Example 5 gave 1.18g (52%) of the desired product as a white solid after silica gel
chromatography eluting with EtOAc:hexane (1:9). Electrospray Mass Spec: 502 (M+H).

Example 14

**2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-methyl-benzoic acid
benzyl ester**

In the same manner as described in Example 12, 1.6g (5.00mmol) of the product of
Example 6 gave 1.269g (50%) of the desired product as a white solid after silica gel
chromatography eluting with EtOAc:Hexane (1:9). CI Mass Spec: 502 (M+H).

15 Example 15

**2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-methyl-benzoic acid
benzyl ester**

In the same manner as described in Example 12, 1.821g (5.66mmol) of the product
of Example 7 gave 2.13g (75%) of the desired product as a white solid after silica gel
20 chromatography eluting with EtOAc:Hexane (1:5). Electrospray Mass Spec: 502 (M+H).

Example 16

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-benzoic acid

To a mixture of 0.60g (0.123mmol) of benzyl ester and 0.57g (0.139mmol) of
25 methyl ester of Example 8 dissolved in 30mL of methanol and 30mL of THF was added
30mL of 1N NaOH solution. The reaction mixture was stirred at room temperature for 48h
and the organics were removed in vacuo. The resulting mixture was acidified with 10%
HCl and extracted with EtOAc. The combined organics were washed with water and brine,
dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue was triturated
30 with hexanes and filtered to provide 0.87g (84%) of the desired carboxylic acid as a white
solid. CI Mass Spec: 398 (M+H).

Example 17

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-chloro-benzoic acid

In the same manner as described in Example 16, 0.404g (0.907mmol) of the
35 product of Example 9 provided 0.327g (84%) of the desired carboxylic acid as a white
solid. Electrospray Mass Spec 432 (M+H).

Example 18

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-bromo-3-methyl-benzoic acid

5 To a solution of 0.444g (0.881mmol) of the product of Example 11 in 20 mL of MeOH/THF (1:1) was added 9.3 mL 1N NaOH and the mixture heated at reflux for 18 h. The mixture was cooled to room temperature and the organic removed *in vacuo*. The remaining solution was acidified with 10% HCl and extracted with EtOAc. The extract was washed with water and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The
10 residue provided 0.364g (84%) of the desired carboxylic acid as a white solid after trituration with ether. CI Mass Spec: 490 (M+H).

Example 19

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-4-methyl-benzoic acid

15 To a solution of the product of Example 12 in 30mL of methanol was added 7.5mL (0.038mol) of 5N sodium hydroxide solution and the resulting mixture was heated to reflux for 66h. The reaction was then cooled to room temperature and the organics were removed *in vacuo*. The resulting mixture was acidified with 10% HCl and extracted with EtOAc. The
20 combined organics were washed with water and brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting residue was triturated with ether and filtered to provide 0.984g (79%) of the desired carboxylic acid as a white solid. Electrospray Mass Spec: 427 (M+H).

Example 20

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-6-methyl-benzoic acid

25 In the same manner as described in Example 19, 1.043g (2.08mmol) of the product of Example 13 provided 0.547g (64%) of the desired carboxylic acid as a white solid after recrystallization from EtOAc/Hexanes. Electrospray Mass Spec: 412 (M+H).

Example 21

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-methyl-benzoic acid

In the same manner as described in Example 19, 0.935g (1.864mmol) of the product of Example 14 provided 0.551g (72%) of the desired carboxylic acid as a white
35 solid after trituration with hexanes. Electrospray Mass Spec: 412 (M+H).

Example 22

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-methyl-benzoic acid

In the same manner as described in Example 19, 1.931g (3.85mmol) of the product of Example 15 provided 1.19g (70%) of the desired carboxylic acid as a white solid after trituration with CH₂Cl₂/hexanes (2:1). Electrospray Mass Spec: 412 (M+H).

Example 23

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-benzamide

To a solution of 0.50g (1.26mmol) of the product of Example 16 in 12.5mL of dichloromethane was added 0.095mL of DMF followed by 0.22mL of oxalyl chloride and the resulting reaction mixture was stirred at room temperature for 1h.

In a separate flask, 1.05mL (7.55mmol) of triethylamine was added to a 0 °C mixture of 0.35g (5.04mmol) of hydroxylamine hydrochloride in 5.5mL of THF and 1.4mL of water. After this mixture had stirred for 15min at 0 °C, the acid chloride solution was added to it in one portion and the resulting solution was allowed to warm to room temperature with stirring overnight. The reaction mixture was then acidified to pH3 with 10% HCl and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was trituated with ether to provide 0.43g (83%) of the desired hydroxamic acid as a white solid. CI Mass Spec: 413 (M+H).

Example 24

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-chloro-N-hydroxy-benzamide

In the same manner as described in Example 23, 0.280g (0.649mmol) of the product of Example 12 gave 0.161g (56%) of the desired hydroxamic acid as a white solid. Electrospray Mass Spec: 446 (M+H).

Example 25

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-bromo-N-hydroxy- 3-methyl-benzamide

In the same manner as described in Example 23, 0.303g (0.618mmol) of the product of Example 18 gave 0.164g (53%) of the desired hydroxamic acid as a white solid. Electrospray Mass Spec: 505 (M+H).

Example 26

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-4-methyl-benzamide

In the same manner as described in Example 23, 1.20g (2.91mmol) of the product of Example 19 gave 0.984g (79%) of the desired hydroxamic acid as a white solid after trituration with ether. Electrospray Mass Spec: 427 (M+H).

Example 27

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-6-methyl-benzamide

In the same manner as described in Example 23, 0.537g (1.30mmol) of the product of Example 20 gave 0.443g (80%) of the desired hydroxamic acid as a white solid after trituration with CH₂Cl₂/Hexanes (1:4). Electrospray Mass Spec: 427 (M+H).

Example 28

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methyl-benzamide

In the same manner as described in Example 23, 0.398g (0.967mmol) of the product of Example 21 gave 0.348g (84%) of the desired hydroxamic acid as a white solid after trituration with CH₂Cl₂/Hexanes (1:4). Electrospray Mass Spec: 427 (M+H).

Example 29

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-5-methyl-benzamide

: In the same manner as described in Example 23, 1.00g (2.43mmol) of the product of Example 22 gave 0.761g (73%) of the desired hydroxamic acid as a white solid after trituration with CH₂Cl₂/Hexanes (1:4). Electrospray Mass Spec: 427 (M+H).

Example 30

2-Amino-3-hydroxy-benzoic acid methyl ester

To a solution of 1.0g (6.53mmol) of 3-hydroxyanthranilic acid in 15mL of methanol was added 5.0mL of BF₃-methanol complex and the resulting solution was heated to reflux for 24h. After cooling to room temperature the reaction mixture was poured into saturated sodium carbonate solution and then extracted with ether. The combined organics were washed with water and brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide 0.90g (83%) of the desired product as a brown solid. Electrospray Mass Spec: 167.8 (M+H)+

Example 31

3-Hydroxy-2-(4-methoxy-benzenesulfonylamino)-benzoic acid methyl ester

To a solution of 0.748g (4.48mmol) of the product of Example 30 in 10.0mL of pyridine was added 0.928g (4.48mmol) of p-methoxybenzenesulfonyl chloride. The reaction mixture was stirred for 24h at room temperature and then diluted with chloroform and washed with 5% HCl solution and water. The organic layer was then dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with ether-hexanes and the resulting solid was filtered and dried to provide 0.86g (57%) of the desired product as a tan solid. Electrospray Mass Spec: 338.2 (M+H)+

Example 32

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-benzyloxy-benzoic acid methyl ester

In the same manner as described in Example 9, 0.50g (1.17mmol) of the product of Example 31 provided 0.60g (100%) of the desired product as a colorless oil. Electrospray Mass Spec: 518.2 (M+H)+

Example 33

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-benzyloxy-benzoic acid

In the same manner as described in Example 18, 0.25g (0.484mmol) of the product of Example 32 provided 0.22g (91%) of the desired product as a white solid. Electrospray Mass Spec: 504.2 (M+H)+

Example 34

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-benzyloxy-N-hydroxy-benzamide

In the same manner as described in Example 23, 0.19g (0.382mmol) of the product of Example 33 provided 0.16 (81%) of the desired product as a white solid. Electrospray Mass Spec: 519.2 (M+H)+

Example 35

3-(tert-Butyl-dimethyl-silanyloxy)-2-(4-methoxy-benzenesulfonylamino)-benzoic acid methyl ester

To a solution of 0.139g (0.412mmol) of the product of Example 31 in 2.0mL of DMF was added 0.70g (1.03mmol) of imidazole and 0.075g (0.495mmol) of t-butyldimethylsilyl chloride. The reaction mixture was then stirred at room temperature for 3h and then diluted

with 75mL of ether. The resulting mixture was washed with water and brine, dried over MgSO₄, filtered and concentrated *in vacuo* to provide 0.179g (96%) of the desired product as a white solid. Electrospray Mass Spec: 452.2 (M+H)+

5

Example 36

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-(tert-butyl-dimethyl-silanyloxy)-benzoic acid methyl ester

In the same manner as described in Example 9, 0.114g (0.253mmol) of the product of Example 35 provided 0.088 (64%) of the desired product as a colorless oil. Electrospray
10 Mass Spec: 542.3 (M+H)+

Example 37

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-hydroxy-benzoic acid methyl ester

15 To a solution of 4.42g (8.17mmol) of the product of Example 36 in 50mL of THF was added 16.3mL (16.3mmol) of a 1M solution of Bu₄NF/THF. The reaction mixture was stirred at room temperature for 0.5h and then diluted with ether and washed with 5% HCl solution, water and brine. The resulting solution was dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was triturated with ether to provide 2.81g (81%) of the
20 desired product as a white solid. Electrospray Mass Spec: 428.3 (M+H)+

Example 38

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-tert-butoxycarbonylmethoxy-benzoic acid methyl ester

25 To a solution of 0.40g (0.94mmol) of the product of Example 37 in 10mL of DMF was added 0.047g (1.171mmol) of a 60% suspension of sodium hydride in mineral oil. The resulting mixture was stirred at room temperature for 0.5h and then 0.277mL (1.873mmol) of t-butylbromoacetate was added in one portion. The reaction mixture was stirred for an additional 18h and then diluted with ether, washed with water and brine, dried
30 over MgSO₄, filtered and concentrated *in vacuo*. The residue was triturated with ether-hexanes to provide 0.423g (83%) of the desired product as a white solid. Electrospray Mass Spec: 524.3 (M+H)+

Example 39

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-(2,2,2-trifluoro-ethoxy)-benzoic acid methyl ester

In the same manner as described in Example 38, 0.40g (0.937mmol) of the product
5 of Example 37 and 0.185mL (1.873mmol) of 2-iodo-1,1,1-trifluoroethane provided
0.231g (48%) of the desired product as a colorless oil. Electrospray Mass Spec: 510.3
(M+H)+

Example 40

10 **2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-(2-methoxy-ethoxymethoxy)-benzoic acid methyl ester**

In the same manner as described in Example 38, 0.40g (0.937mmol) of the product
of Example 37 and 0.134mL (1.171mmol) of MEM-Cl provided 0.454g (94%) of the
desired product as a colorless oil. Electrospray Mass Spec: 516.2 (M+H)+

15

Example 41

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-(4-methoxycarbonyl-benzyloxy)-benzoic acid methyl ester

In the same manner as described in Example 38, 0.275g (0.644mmol) of the
20 product of Example 37 and 0.295g (1.288mmol) of methyl 4-(bromomethyl)benzoate
provided 0.322g (87%) of the desired product as a white solid. Electrospray Mass Spec:
576.2 (M+H)+

Example 42

25 **2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-(3-ethoxycarbonyl-propoxy)-benzoic acid methyl ester**

In the same manner as described in Example 38, 0.50g (1.171 mmol) of the product
of Example 37 and 0.419mL (2.927 mmol) of ethyl 4-bromobutyrate provided 0.530g
(84%) of the desired product as a colorless oil. Electrospray Mass Spec: 542.3 (M+H)+

30

Example 43

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-(4-methoxycarbonyl-butoxy)-benzoic acid methyl ester

In the same manner as described in Example 38, 0.50g (1.171 mmol) of the product
35 of Example 37 and 0.419mL (2.927mmol) of methyl 5-bromovalerate provided 0.477g
(75%) of the desired product as a white solid. Electrospray Mass Spec: 542.3 (M+H)+

Example 44

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-isopropoxy-benzoic acid methyl ester

To a solution of 0.20g (0.468mmol) of the product of Example 37 dissolved in 5.0mL of DMF was added 0.26mL (2.81mmol) of 2-bromopropane and 1.16g (8.43mmol) of potassium carbonate. The reaction mixture was then heated to 80 degrees for 18h, cooled to room temperature, diluted with ether and washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc-Hexanes (1:3) to provide 0.198g (90%) of the desired product as a colorless oil. Electrospray Mass Spec: 470.3 (M+H)+

Example 45

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-(pyridin-3-ylmethoxy)-benzoic acid methyl ester

To a solution of 0.40g (1.187 mmol) of the product of Example 31 dissolved in 5.0mL of DMF was added 0.409g (2.492mmol) of 3-picolyl chloride hydrochloride and 1.03g (7.477mmol) of potassium carbonate. The reaction mixture was then stirred at room temperature for 18h, diluted with water and extracted with ether. The organics were then extracted with 6N HCl solution and the aqueous acid layer was then basified with 6N NaOH solution and then extracted with ether. The resulting ether layer was dried over sodium sulfate, filtered and concentrated in vacuo to provide 0.34g (55%) of the desired product as a brown oil. Electrospray Mass Spec: 520.2 (M+H)+

Example 46

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-carboxymethoxy-benzoic acid

In the same manner as described in Example 18, 0.314g (0.580 mmol) of the product of Example 38 provided 0.262g (96%) of the desired product as a white solid. Electrospray Mass Spec: 472.1 (M+H)+

Example 47

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-(2,2,2-trifluoroethoxy)-benzoic acid

In the same manner as described in Example 18, 0.20 (0.393 mmol) of the product of Example 39 provided 0.168g (87%) of the desired product as a white solid. Electrospray
5 Mass Spec: 496.1 (M+H)+

Example 48

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-(2-methoxy-ethoxymethoxy)-benzoic acid

10

In the same manner as described in Example 18, 0.363g (0.705 mmol) of the product of Example 40 provided 0.336 (95%) of the desired product as a white foam. Electrospray Mass Spec: 502.2 (M+H)+

15

Example 49

benzyloxy)-benzoic acid

In the same manner as described in Example 18, 0.283g (0.492 mmol) of the product of Example 41 provided 0.245g (91%) of the desired product as a white solid. Electrospray Mass Spec: 548.1 (M+H)+

20

Example 50

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-(3-carboxy-propoxy)-benzoic acid

25

In the same manner as described in Example 18, 0.363g (0.671 mmol) of the product of Example 42 provided 0.260g (78%) of the desired product as a white solid. Electrospray Mass Spec: 498.1 (M-H)-

30

Example 51

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-(4-carboxy-butoxy)-benzoic acid

In the same manner as described in Example 18, 0.323g (0.597 mmol) of the product of Example 43 provided 0.243 (79%) of the desired product as a white solid. Electrospray Mass Spec: 512.1 (M-H)-

Example 52

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-isopropoxy-benzoic acid

In the same manner as described in Example 18, 0.348g (0.742 mmol) of the product of Example 44 provided 0.284g (84%) of the desired product as a white solid.

5 Electrospray Mass Spec: 456.3 (M+H)+

Example 53

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-(pyridin-3-ylmethoxy)-benzoic acid

10 To a solution of 0.311g (0.599mmol) of the product of Example 45 in 6.0mL of THF-MeOH (1:1) was added 0.050g (1.197mmol) of lithium hydroxide monohydrate. The reaction mix was heated to reflux for 24h and then concentrated in vacuo. The residue was washed with THF and filtered. The filtrate was concentrated in vacuo to provide 0.277g (91%) of the lithium salt of the title compound as a brown foam. Electrospray Mass Spec:

15 506.2 (M+H)+

Example 54

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-hydroxycarbamoylmethoxy-benzamide

20 In the same manner as described in Example 23, 0.110g (0.234 mmol) of the product of Example 46 provided 0.085g (75%) of the desired product as a white solid. Electrospray Mass Spec: 502.2 (M+H)+

Example 55

25 **2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-(2,2,2-trifluoroethoxy)-benzamide**

In the same manner as described in Example 23, 0.131 (0.265 mmol) of the product of Example 47 provided 0.092g (68%) of the desired product as a white solid. Electrospray Mass Spec: 511.1 (M+H)+

30

Example 56

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-(2-methoxyethoxymethoxy)-benzamide

35 In the same manner as described in Example 23, 0.296 (0.591 mmol) of the product of Example 48 provided 0.228g (75%) of the desired product as a brown glass. Electrospray Mass Spec: 517.2 (M+H)+

Example 57

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-[4-(hydroxyaminocarbonyl)-benzyloxy]-N-hydroxy-benzamide

In the same manner as described in Example 23, 0.207g (0.378 mmol) of the product of Example 49 provided 0.20g (92%) of the desired product as a white solid.
Electrospray Mass Spec: 576.0 (M-H)-

Example 58

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-(3-hydroxycarbamoyl-propoxy)-benzamide

In the same manner as described in Example 23, 0.224g (0.449 mmol) of the product of Example 50 provided 0.195g (82%) of the desired product as a white solid.
Electrospray Mass Spec: 530.1 (M+H)+

Example 59

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-(4-hydroxycarbamoyl-butoxy)-benzamide

In the same manner as described in Example 23, 0.20g (0.390 mmol) of the product of Example 51 provided 0.208g (98%) of the desired product as a tan solid. Electrospray Mass Spec: 544.1 (M+H)+

Example 60

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-isopropoxy-benzamide

In the same manner as described in Example 23, 0.245g (0.540 mmol) of the product of Example 52 provided 0.222g (88%) of the desired product as a white solid.
Electrospray Mass Spec: 471.2 (M+H)+

Example 61

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide

To a solution of 0.65mL (1.29mmol) of a 2M solution of oxalyl chloride in CH₂Cl₂ at 0 °C was added 0.10mL (1.29mmol) of DMF and the mixture was stirred at 0 °C for 15min, then let warm to room temperature and stirred for an additional 1h. A solution of 0.220g (0.43 mmol) of the product of Example 53, in 1mL of DMF, was then added to the reaction mixture and the reaction was stirred for 1h at room temperature.

In a separate flask, 1.35mL (9.675mmol) of triethylamine was added to a 0 °C mixture of 0.448g (6.45 mmol) of hydroxylamine hydrochloride in 6.8mL of THF and 1.8mL of water. After this mixture had stirred for 15min at 0 °C, the acid chloride solution was added to it in one portion and the resulting solution was allowed to warm to room temperature with stirring overnight. The reaction mixture next was diluted with CH₂Cl₂ and washed with water and saturated sodium bicarbonate solution. The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was triturated with ether to provide 0.124g (55%) of the desired hydroxamic acid as a white solid. Electrospray Mass Spec: 521.2 (M+H)+.

10

Example 62

2-(4-Methoxy-benzenesulfonylamino)-3,5-dimethyl-benzoic acid methyl ester

In the same manner as described in Example 31, 7.00g (0.039mol) of methyl 3,5-dimethylantranilate provided 11.5g (84%) of the desired product as a white solid. Electrospray Mass Spec: 350.3 (M+H)+.

15

Example 63

2-(4-Fluoro-benzenesulfonylamino)-3,5-dimethyl-benzoic acid methyl ester

In the same manner as described in Example 31, 2.00g (0.011mol) of methyl 2,5-dimethylantranilic acid and 2.17g (0.011mol) of 4-fluorobenzenesulfonyl chloride provided 3.09g (82%) of the desired product as a white solid. Electrospray Mass Spec: 338.3 (M+H)+.

20

Example 64

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid methyl ester

25

In the same manner as described in Example 9, 1.00g (0.2.865 mmol) of the product of Example 62 provided 1.065g (85%) of the desired product as a white solid. Electrospray Mass Spec: 440.3 (M+H)+.

30

Example 65

2-[Benzyl-(4-fluoro-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid methyl ester

In the same manner as described in Example 9, 1.00g (0.2.865 mmol) of the product of Example 63 provided 1.084g (85%) of the desired product as a white solid. Electrospray Mass Spec: 428.3 (M+H)+.

35

Example 66

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid

In the same manner as described in Example 18, 0.94g (2.141 mmol) of the product of Example 64 provided 0.827g (91%) of the desired product as a white solid. Electrospray Mass Spec: 426.3 (M+H)+.

Example 67

2-[Benzyl-(4-fluoro-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid

In the same manner as described in Example 9, 0.963g (2.255 mmol) of the product of Example 65 provided 0.486g (52%) of the desired product as a white solid. Electrospray Mass Spec: 414.3 (M+H)+.

Example 68

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

In the same manner as described in Example 23, 0.683g (1.607 mmol) of the product of Example 66 provided 0.436g (62%) of the desired product as a white solid. Electrospray Mass Spec: 441.3 (M+H)+.

Example 69

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

In the same manner as described in Example 23, 0.423g (1.024 mmol) of the product of Example 67 provided 0.364g (83%) of the desired product as a white solid. Electrospray Mass Spec: 429.3 (M+H)+.

Example 70

2-[Benzyl-(4-butoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid butyl ester

To a solution of the product of Example 65 in 10mL of DMF was added 0.429mL (4.684mmol) of n-butanol and 0.187g (4.684mmol) of 60% sodium hydride. The reaction mixture was stirred for 18h at room temperature and the quenched with 5% HCl solution. The resulting mixture was extracted with ether and the combined organics were washed with water, dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica eluting with EtOAc-Hexanes (1:10) to provide 0.134g (24%) of the desired product as a red oil. Electrospray Mass Spec: 524.4 (M+H)+.

Example 71

2-[Benzyl-(4-butoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid

In the same manner as described in Example 18, 0.134g (0.256mmol) of the product of Example 70 provided 0.115g (97%) of the desired product as a white solid.
Electrospray Mass Spec: 468.3 (M+H)+.

Example 72

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

In the same manner as described in Example 23, 0.139g (0.298 mmol) of the product of Example 71 provided 0.105g (73%) of the desired product as a yellow foam.
Electrospray Mass Spec: 483.3 (M+H)+.

Example 73

2-[Benzyl-(4-benzyloxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid

To a solution of 0.50g (1.171mmol) of the product of Example 65 in 10mL of DMF was added 0.485mL (4.684mmol) of benzyl alcohol and 0.187g (4.684mmol) of 60% sodium hydride. The reaction mixture was stirred for 18h at room temperature and the quenched with 5% HCl solution. The resulting mixture was extracted with ether and the combined organics were washed with water, dried over MgSO₄, filtered and concentrated in vacuo. The residue was dissolved 10mL of MeOH-THF (1:1) and 4.7mL of 1N sodium hydroxide solution was added. The resulting mixture was heated to reflux for 18h and then cooled to room temperature, acidified with 5% HCl and extracted with EtOAc. The combined organics were washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. Trituration of the residue with ether provided 0.432g (74%) of the desired product as a white solid. Electrospray Mass Spec: 502.3 (M+H)+.

Example 74

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

In the same manner as described in Example 23, 0.366 (0.731 mmol) of the product of Example 73 provided 0.347g (92%) of the desired product as a white solid. Electrospray Mass Spec: 517.2 (M+H)+.

Example 75

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-hex-1-ynyl-3-methyl-benzoic acid methyl ester

To a solution of 0.324g (0.643mmol) of the product of Example 11 in 2.0 mL of DMF and 2.0mL of triethylamine was added 0.088mL (0.771mmol) of 1-hexyne, 9mg (0.013mmol) of bis(triphenylphosphine)palladium(II)dichloride and 1.2mg of copper(I)iodide. The reaction mixture was then heated to 65 degrees for 5h and an additional 0.22mL of 1-hexyne was added to the reaction. The reaction was then heated to reflux for 6h and then cooled to room temperature and diluted with ether. The organics were washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica eluting with EtOAc-Hex (1:10) to provide 0.198g (61%) of the desired product as a yellow oil. Electrospray Mass Spec: 506.3 (M+H)+.

Example 76

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-hex-1-ynyl-3-methyl-benzoic acid

In the same manner as described in Example 18, 0.165g (0.327 mmol) of the product of Example 75 provided 0.123g (77%) of the desired product as a tan solid. Electrospray Mass Spec: 492.2 (M+H)+.

Example 77

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-hex-1-ynyl-N-hydroxy-3-methyl-benzamide

In the same manner as described in Example 23, 0.115g (0.234 mmol) of the product of Example 76 provided 0.097g (82%) of the desired product as a tan foam. Electrospray Mass Spec: 507.3 (M+H)+.

Example 78

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-ethynyl-3-methyl-benzoic acid methyl ester

To a solution of 0.277g (0.550mmol) of the product of Example 11 in 2.0 mL of DMF and 2.0mL of triethylamine was added 0.39mL (0.2.748 mmol) of trimethylsilyl acetylene, 19mg (0.027mmol) of bis(triphenylphosphine)palladium(II)dichloride and 2.6mg of copper(I)iodide. The reaction mixture was then heated to 65 degrees for 2h and then cooled to room temperature and diluted with ether. The organics were washed with 5%HCl solution, water and brine, dried over MgSO₄, filtered and concentrated in vacuo.

The residue was dissolved in 5mL of THF, 1mL of 1M tetrabutylammonium fluoride-THF solution was added and the reaction was stirred at room temperature for 1h, then diluted with ether, washed with 5% HCl solution, water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica eluting with EtOAc-Hex (1:10) to provide 0.197g (80%) of the desired product as a white foam. Electrospray Mass Spec: 450.3 (M+H)+.

Example 79

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-ethynyl-3-methyl-benzoic acid

In the same manner as described in Example 18, 0.177g (0.394 mmol) of the product of Example 78 provided 0.161g (94%) of the desired product as a tan solid. Electrospray Mass Spec: 436.2 (M+H)+.

Example 80

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-ethynyl-N-hydroxy- 3-methyl-benzamide

In the same manner as described in Example 23, 0.136g (0.313 mmol) of the product of Example 79 provided 0.116g (82%) of the desired product as a tan foam. Electrospray Mass Spec: 451.3 (M+H)+.

Example 81

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester

To a solution of 1.00g (2.985 mmol) of the product of Example 3 in 7.5mL of DMF was added 0.514g (3.134 mmol) of 3-picolyl chloride hydrochloride and 1.30g (9.50 mmol) of potassium carbonate. The reaction was stirred for 18h at room temperature and then an additional 0.051g of 3-picolyl chloride hydrochloride and 0.130g of potassium carbonate was added and the reaction was stirred for 18h at room temperature. The reaction was then diluted with water and extracted with ether. The combined organic layers were extracted with 6N HCl solution and the aqueous acid layer was then basified with 6N NaOH solution and then extracted with ether. The resulting ether layer was dried over sodium sulfate, filtered and concentrated in vacuo. Trituration of the residue with ether provided 1.058g (83%) of the desired product as a white solid. Electrospray Mass Spec: 427.3 (M+H)+.

Example 82

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid

To a solution of 0.924g (2.169 mmol) of the product of Example 81 in 10mL of THF-water (1:1) was added 0.091g of lithium hydroxide monohydrate. The reaction mixture was heated to reflux for 48h then cooled to room temperature and washed with ether. The aqueous layer was then concentrated in vacuo to provide 0.894g (100%) of the lithium salt of the title compound as a white solid. Electrospray Mass Spec: 413.2 (M+H)+

Example 83

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]- 3-methyl-benzamide

To a solution of 1.98 mL (3.966 mmol) of a 2M solution of oxalyl chloride in CH₂Cl₂ at 0 °C was added 0.307mL (3.966 mmol) of DMF and the mixture was stirred at 0 °C for 15min, then let warm to room temperature and stirred for an additional 1h. A solution of 0.829g (1.983 mmol) of the product of Example 82, in 1mL of DMF, was then added to the reaction mixture and the reaction was stirred for 1h at room temperature.

In a separate flask, 4.14mL (0.030 mol) of triethylamine was added to a 0 °C mixture of 1.378g (0.020 mol) of hydroxylamine hydrochloride in 19.5mL of THF and 5.6mL of water. After this mixture had stirred for 15min at 0 °C, the acid chloride solution was added to it in one portion and the resulting solution was allowed to warm to room temperature with stirring overnight. The reaction mixture next was diluted with CH₂Cl₂ and washed with water and saturated sodium bicarbonate solution. The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was triturated with EtOAc-ether to provide 0.414g (51%) of the title compound as a white solid.

To a room temperature solution of 0.403g (0.976mmol) of the hydroxamic acid in 10mL of CH₂Cl₂-MeOH (30:1) was added 0.27mL of a 4M HCl-ether solution. The reaction mixture was stirred for 0.5h and the resulting precipitate was collected by filtration and dried in vacuo to provide 0.439g (100%) of the hydrochloride salt of the title compound as a white solid. Electrospray Mass Spec: 428.2 (M+H)+.

Example 84

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-benzoic acid

To a solution of 0.958g (2.985 mmol) of the product of Example 1 in 7.5mL of DMF was added 0.514g (3.134 mmol) of 3-picolyl chloride hydrochloride and 1.30g (9.50 mmol) of potassium carbonate. The reaction was stirred for 18h at room temperature and then an additional 0.051g of 3-picolyl chloride hydrochloride and 0.130g of potassium

carbonate was added and the reaction was stirred for 18h at room temperature. The reaction was then diluted with water and extracted with ether. The combined organic layers were extracted with 6N HCl solution and the aqueous acid layer was then basified with 6N NaOH solution and then extracted with ether. The resulting ether layer was dried over sodium sulfate, filtered and concentrated in vacuo. Trituration of the residue with ether provided 0.843g (69%) of the sodium salt of the title compound as a pink solid.

To a solution of 0.830g (2.015 mmol) of the above product in 10mL of THF-water (1:1) was added 0.093g of lithium hydroxide monohydrate. The reaction mixture was heated to reflux for 48h then cooled to room temperature. The reaction mixture was then concentrated in vacuo to provide 0.813g (100%) of the lithium salt of the title compound as a white solid. Electrospray Mass Spec: 399.2 (M+H)+

Example 85

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-benzamide

In the same manner as described in Example 83, 0.618g (1.530 mmol) of the product of Example 84 provided 0.450g (62%) of the hydrochloride salt of the title compound as a tan solid. Electrospray Mass Spec: 414.2 (M+H)+

Example 85

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3,5-dimethyl-benzoic acid methyl ester

: In the same manner as described in Example 81, 1.00g (2.865 mmol) of the product of Example 62 provided 0.932g (74%) of the desired product as a tan solid. Electrospray Mass Spec: 441.3 (M+H)+

Example 87

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3,5-dimethyl-benzoic acid

In the same manner as described in Example 82, 0.810g (1.841 mmol) of the product of Example 86 provided 0.753g (96%) of the desired product as a tan foam. Electrospray Mass Spec: 427.3 (M+H)+

Example 88

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3,5-dimethyl-benzamide

In the same manner as described in Example 83, 0.645g (1.514 mmol) of the product of Example 87 provided 0.377g (62%) of the hydrochloride salt of the title compound as a white solid. Electrospray Mass Spec: 442.3 (M+H)+

Example 89

5-Bromo-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 81, 1.00g (2.415 mmol) of the product of Example 10 provided 0.961g (79%) of the desired product as a tan solid. Electrospray Mass Spec: 505.2 (M+H)+

Example 90

5-Bromo-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid

In the same manner as described in Example 82, 0.861g (1.708 mmol) of the product of Example 89 provided 0.837 (100%) of the lithium salt of the title compound as a tan solid. Electrospray Mass Spec: 491.1 (M+H)+

Example 91

5-Bromo-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide

In the same manner as described in Example 83, 0.767g (1.546 mmol) of the product of Example 90 provided 0.407g (56%) of the hydrochloride salt of the title compound as a white solid. Electrospray Mass Spec: 506.2 (M+H)+

Example 92

3-(4-Methoxy-benzenesulfonylamino)-naphthalene-2-carboxylic acid

In the same manner as described in Example 4, 2.5 g (13.4 mmol) of 3-amino-2-naphthoic acid gave 2.49g (52%) of the desired sulfonamide as a tan solid after trituration with EtOAc/hexane. Electrospray Mass Spec: 358 (M+H)+

Example 93

3-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-naphthalene- 2-carboxylic acid

In the same manner as described in Example 12, 1.2 g (3.36 mmol) of the product of Example 92 gave a brown oil which was dissolved in dioxane (20 mL) and treated with aqueous 2N sodium hydroxide. The resulting solution was heated at 80 °C for 3 days. Addition of 1N aqueous hydrochloric acid, extraction with EtOAc, drying with MgSO₄ and concentration in vacuo, followed by silica gel chromatography (hexane/EtOAc/HOAc) gave the desired carboxylic acid as a white solid (0.81 g, 54%). Electrospray Mass Spec: 448 (M+H)+

Example 94

3-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-naphthalene- 2-carboxylic acid hydroxyamide

In the same manner as described in Example 23, 200 mg (0.45mmol) of the product of Example 94 gave 0.155g (75%) of the desired hydroxamic acid as a white powder. Electrospray Mass Spec: 463 (M+H)+

Example 95

3-Methoxy-2-(4-methoxy-benzenesulfonylamino)-benzoic acid

In the same manner as described in Example 4, 2.14g (12.8 mmol) of 2-amino-3-methoxybenzoic acid gave 2.08g (48%) of the desired sulfonamide as a beige solid after trituration with CH₂Cl₂:hexane(1:2). CI Mass Spec 338.0(M+H).

Example 96

4-Chloro-2-(4-methoxy-benzenesulfonylamino)-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 1, 0.5g (2.5 mmol) of methyl 3-methyl-4-chloro anthranilate provided 0.56g (61%) of the desired sulfonamide as a white solid after trituration with ether. Electrospray Mass Spec 370.2(M+H).

Example 97

**2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-methoxy-benzoic acid
benzyl ester**

: In the same manner as described in Example 12, 1.73g (5.14 mmol) of the product of
5 Example 95 gave 2.01g (75%) of the desired product as a white solid after silica gel
chromatography eluting with CH₂Cl₂. CI Mass Spec 518.1 (M+H).

Example 98

**2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-4-chloro-3-methyl- benzoic
10 acid methyl ester**

In the same manner as described in Example 9, 0.5g (1.35 mmol) of the product of
Example 96 provided 0.566g (80%) of the desired product as a white solid after trituration
with hexane. Electrospray Mass Spec 460.2(M+H).

Example 99

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-methoxy-benzoic acid

In the same manner as described in Example 19, 1.86g (3.6 mmol) of the product
of Example 97 provided 1.39g (90%) of the desired carboxylic acid as a white solid after
trituration with CH₂Cl₂:hexane (1:4). CI Mass Spec 428.1 (M+H).

Example 100

**2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-4-chloro-3-methyl- benzoic
20 acid**

In the same manner as described in Example 19, except a mixture of MeOH and
25 THF was used instead of MeOH, 0.506g (1.1mmol) of the product of Example 98
provided 0.454g (93%) of the desired carboxylic acid as a white solid after trituration with
ether. Electrospray Mass Spec 446.1(M+H).

Example 101

**2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methoxy-
30 benzamide**

In the same manner as described in Example 23, 1.25g (2.91 mmol) of the product
of Example 99 gave 1.11g (86%) of the desired hydroxamic acid as a white solid. CI Mass
Spec 443.1 (M+H).

Example 102

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-4-chloro-N-hydroxy- 3-methyl-benzamide

In the same manner as described in Example 23, 0.4g (0.9 mmol) of the product of Example 100 provided 0.273g (66%) of the desired hydroxamic acid as a white solid after silica gel chromatography eluting with EtOAc:hexane:acetic acid(1.0:1.5:0.5). Electrospray Mass Spec 461.2(M+H).

Example 103

2-[(4-Methoxy-benzenesulfonyl)-(3-methoxy-benzyl)-amino]-3,5-dimethyl-benzoic acid methyl ester

To a solution of 0.699g (2.0 mmol) of the product of Example 62 in 5mL of DMF was added 0.096g (2.4mmol) of 60% sodium hydride. The resulting mixture was stirred for 30 min at room temperature and then 0.376g (2.4mmol) of m-methoxybenzyl chloride and 0.089g (0.24mmol) of tetrabutylammonium iodide were added. The reaction mixture was stirred for 18 hr at room temperature, poured into water and then extracted with ether. The combined organics were washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude solid was triturated with hexane to provide 0.768g (82%) of the desired product as white solid. Electrospray Mass Spec 470.3 (M+H).

Example 104

2-[(4-Methoxy-benzenesulfonyl)-(2,3,4,5,6-pentafluoro-benzyl)-amino]-3,5-dimethyl-benzoic acid methyl ester

In the same manner as described in Example 9, 0.699g (2.0mmol) of the product of Example 62 and 0.626g (2.4 mmol) of pentafluorobenzyl bromide provided 1.04g (98%) of the desired product as a white solid after trituration with hexane and preparative TLC eluting with CH₂Cl₂. Electrospray Mass Spec 530.1 (M+H).

Example 105

2-[(4-Methoxy-benzenesulfonyl)-propyl-amino]-3,5-dimethyl-benzoic acid methyl ester

In the same manner as described in Example 9, 0.699g (2.0 mmol) of the product of Example 62 and 0.295g (2.4 mmol) of 1-bromopropane provided 0.691g (88%) of the desired product as a yellow gum after preparative TLC eluting with 1:3 EtOAc:hexane. Electrospray Mass Spec 392.2(M+H).

Example 106

2-[(2-Bromo-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid methyl ester

In the same manner as described in Example 9, 0.699g (2.0mmol) of the product of Example 62 and 0.6g (2.4mmol) of 2-bromobenzyl bromide provided 0.761g (73%) of the desired product as a white solid after trituration with ether. Electrospray Mass Spec 518.1(M+H).

Example 107

2-[(3-Bromo-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid methyl ester

In the same manner as described in Example 9, 0.699g (2.0mmol) of the product of Example 62 and 0.6g (2.4 mmol) of m-bromobenzyl bromide provided 0.954g (92%) of the desired product as a white solid after trituration with ether. Electrospray Mass Spec 518.1 (M+H).

Example 108

2-[(4-Bromo-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid methyl ester

In the same manner as described in Example 9, 0.699g (2.0mmol) of the product of Example 62 and 0.6g (2.4mmol) of p-bromobenzyl bromide provided 0.896g (86%) of the desired product as a white solid after trituration with hexane/ether. Electrospray Mass Spec 518.1 (M+H)

Example 109

2-[(4-Methoxy-benzenesulfonyl)-(3-methoxy-benzyl)-amino]-3,5-dimethyl-benzoic acid

To a solution of 0.610g (1.3mmol) of the product of Example 103 in 6.5mL methanol and 6.5mL of THF was added 6.5mL of 1N NaOH solution. The reaction mixture was refluxed for 18 hr and the organics were removed in vacuo. The resulting mixture was diluted with water, acidified with 3N HCl and extracted with EtOAc. The combined organics were washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue was triturated with ether and filtered to provide 0.417g(79%) of the desired carboxylic acid as a white solid. Electrospray Mass Spec 456.3(M+H).

Example 110

2-[(4-Methoxy-benzenesulfonyl)-(2,3,5,6-tetrafluoro-4-methoxy-benzyl)-amino]-3,5-dimethyl-benzoic acid

In the same manner as described in Example 1109, 0.737g (1.39mmol) of the product of Example 104 provided 0.49g (67%) of N-p-methoxy tetrafluorobenzyl derivative of the desired carboxylic acid after trituration with ether. Electrospray Mass Spec 528.1 (M+H).

Example 111

2-[(4-Methoxy-benzenesulfonyl)-propyl-amino]-3,5-dimethyl-benzoic acid

In the same manner as described in Example 109, 0.602g (1.54mmol) of the product of Example 105 provided 0.461g (79%) of the desired carboxylic acid as a white solid after trituration with ether/hexane. Electrospray Mass Spec 378.2(M+H).

Example 112

2-[(2-Bromo-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid

In the same manner as described in Example 109, 0.518g (1.0mmol) of the product of Example 106 provided 0.4g (79%) of the desired carboxylic acid as a white solid after trituration with ether. Electrospray Mass Spec 504.0 (M+H).

Example 113

2-[(3-Bromo-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid

In the same manner as described in Example 109, 0.894g (1.725mmol) of the product of Example 107 provided 0.61g (70%) of the desired carboxylic acid after trituration with ether. Electrospray Mass Spec 506.0 (M+H).

Example 114

2-[(4-Bromo-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid

In the same manner as described in Example 109, 0.836g (1.61mmol) of the product of Example 108 provided 0.584g (72%) of the desired carboxylic acid as a white solid after trituration with ether. Electrospray Mass Spec 504 (M+H).

Example 115

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-(3-methoxy-benzyl)-amino]-3,5-dimethyl-benzamide

In the same manner as described in Example 23, 0.364g (0.8mmol) of the product of Example 109 provided 0.245g (65%) of the desired hydroxamic acid as a white solid after trituration with ether. Electrospray Mass Spec 471.3(M+H).

Example 116

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-(2,3,5,6-tetrafluoro-4-methoxy-benzyl)-amino]-3,5-dimethyl-benzamide

In the same manner as described in Example 23, 0.369g (0.7mmol) of the product of Example 110 provided 0.253g (67%) of the desired hydroxamic acid as a white solid after trituration with ether. Electrospray Mass Spec 543.1(M+H).

Example 117

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-propyl-amino]-3,5-dimethyl-benzamide

In the same manner as described in Example 23, 0.377g (1.0mmol) of the product of Example 111 provided 0.294g (75%) of the desired hydroxamic acid as a white solid after trituration with ether. Electrospray Mass Spec 393.2(M+H).

Example 118

2-[(2-Bromo-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-benzamide

In the same manner as described in Example 23, 0.353g (0.7mmol) of the product of Example 112 provided 0.205g (56%) of the desired hydroxamic acid as a white solid after trituration with ether. Electrospray Mass Spec 519.1 (M+H).

Example 119

2-[(3-Bromo-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-benzamide

In the same manner as described in Example 23, 0.546g (1.08mmol) of the product of Example 113 provided 0.397g (71%) of the desired hydroxamic acid as a white solid after trituration with ether. Electrospray Mass Spec 517.0(M-H).

Example 120

2-[(4-Bromo-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-benzamide

In the same manner as described in Example 23, 0.521g (1.03mmol) of the product of Example 114 provided 0.333g (62%) of the desired hydroxamic acid as a white solid after trituration with ether. Electrospray Mass Spec 517.0(M-H).

Example 121

N-Benzyl-4-methoxy-benzenesulfonamide

To a solution of 5.358g (0.05 mole) of benzylamine and 7.755g (0.06 mole) of N,N-diisopropylethylamine in 80 mL of CH₂Cl₂ at room temperature was added slowly 11.365g (0.055 mole) of 4-methoxybenzenesulfonyl chloride. The resulting mixture was stirred for 18 hr at room temperature and diluted with water. The organic layer was separated, washed with NaHCO₃, water, brine, dried over MgSO₄, filtered and concentrated. The residue was boiled in CH₂Cl₂:Hexane (1:4), cooled and filtered to provide 11.79g (85%) of the desired product as a cream solid.

Example 122

N-Benzyl-N-(2-cyano-6-trifluoromethyl-phenyl)-4-methoxy-benzenesulfonamide

To a solution of 3.05g (11.0mmol) of the product of Example 121 in 15mL of DMF was added 0.484g (12.1mmol) of 60% sodium hydride. The resulting mixture was stirred for 30 min at room temperature and then 1.89g (10.0mmol) of 2-fluoro-3-(trifluoromethyl)benzonitrile in 2 mL of DMF was added. The reaction mixture was stirred at 90 °C for 18 hr, poured into water and extracted with ether. The combined organics were washed with water, brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude solid was triturated with ether to provide 3.33g (75%) of the desired product as a white solid. Electrospray Mass Spec 447.2(M+H).

Example 123

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-trifluoromethyl-benzamide

To a solution of 1.78g (4.0mmol) of the product of Example 122 in 30mL of n-propanol was added 8mL of 5N NaOH solution. The resulting mixture was refluxed for 66h and concentrated. The residue was stirred in water and filtered to provide 1.725g (93%) of the desired amide as a white solid. Electrospray Mass Spec 465.2(M+H).

Example 124

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-trifluoromethyl-benzoic acid

To a suspension of 0.192g (0.41 mmol) of the product of Example 123 in 2.5mL of dry CH₃CN was added 0.068g(0.58mmol) of nitrosonium tetrafluoroborate. The resulting mixture was stirred for 1 h and then added 0.040g(0.34mmol) of the same reagent and stirred for additional 1 h. The reaction was quenched with water and filtered to provide 0.141g (74%) of the desired carboxylic acid as a white solid. Electrospray Mass Spec 466.2(M+H).

Example 125

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy- 3-trifluoromethyl-benzamide

In the same manner as described in Example 23, 0.17g (0.365mmol) of the product of Example 124 provided 0.79g (45%) of the desired hydroxamic acid as a cream solid. Electrospray Mass Spec 481.1 (M+H).

Example 126

2-[(4-Methoxy-benzenesulfonyl)-methyl-amino]-3,5-dimethyl-benzoic acid methyl ester

In the same manner as described in Example 9, 0.30g (0.860 mmol) of the product of Example 62 and 0.08mL (1.289 mmol) of iodomethane provided 0.3g (96%) of the desired product as a white solid. Electrospray Mass Spec 364.3(M+H).

Example 127

2-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid methyl ester

In the same manner as described in Example 9, 0.30g (0.860 mmol) of the product of Example 62 and 0.103mL (1.289 mmol) of iodoethane provided 0.324g (100%) of the desired product as a white solid. Electrospray Mass Spec 378.2(M+H).

Example 128

2-[(4-Methoxy-benzenesulfonyl)-methyl-amino]-3,5-dimethyl-benzoic acid

In the same manner as described in Example 18, 0.267g (0.738 mmol) of the product of Example 126 provided 0.23g (89%) of the desired product as a white solid. Electrospray Mass Spec 350.1(M+H).

Example 129

2-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid

In the same manner as described in Example 18, 0.254g (0.674 mmol) of the product of Example 127 provided 0.207g (84%) of the desired product as a white solid.

5 Electro spray Mass Spec 364.2(M+H).

Example 130

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3,5-dimethyl-benzamide

10 In the same manner as described in Example 23, 0.194g (0.557 mmol) of the product of Example 128 provided 0.140g (69%) of the desired product as a white solid. Electro spray Mass Spec 365.3(M+H).

Example 131

15 **2-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-benzamide**

In the same manner as described in Example 23, 0.175g (0.482 mmol) of the product of Example 129 provided 0.142g (78%) of the desired product as a white solid. Electro spray Mass Spec 379.2(M+H).

20

Example 132

2-Amino-5-bromo-3-methyl-benzoic acid

To a mixture of 1.5g (10mmol) of 3-methyl-2-amino benzoic acid in 50mL of glacial acetic acid was added 1.6 g (10 mmol) of bromine and the resulting mixture was stirred at room temperature for 5 h. The reaction mixture was then poured into water and
25 the precipitated solid was filtered, washed with water and air dried to provide 2.2g (95%) of the desired product as a brown solid. m.p.245°C. Electro spray Mass Spec 232 (M+H).

Example 133

2-Amino-5-bromo-3-methyl-benzoic acid methyl ester

30 To 20mL of 50% BF₃: MeOH complex was added 2.3 g (10 mmol) of the product of Example 132 and the mixture was heated to reflux for 48h. The reaction mixture was then cooled to room temperature, concentrated in vacuo, diluted with ice water and neutralized with 1N NaOH solution. The resulting mixture was extracted with chloroform, and the combined organics were washed with water, dried over MgSO₄, filtered and
35 concentrated in vacuo to provide 2.3g (93%) of the desired product as a brown semi-solid. Electro spray Mass Spec 246 (M+H).

Example 134

5-Bromo-2-(4-methoxy-benzenesulfonylamino)-3-methyl-benzoic acid methyl ester

To a stirred solution of 24.5 g (100 mmol) of the product of Example 133 in 100mL of pyridine was added 21.0 g (100mmol) of p-methoxybenzenesulfonyl chloride and the resulting mixture was heated to 80 °C for 24 h. The reaction mixture was then quenched with ice cold water and acidified with concentrated HCl. The resulting mixture was extracted with chloroform, washed with water, dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with diethyl ether, filtered and dried to provide 35g (84%) of the desired product as a brown solid. Electrospray Mass Spec 416, (M+H).

Example 135

3-Bromo-2-(4-methoxy-benzenesulfonylamino)-5-methyl-benzoic acid methyl ester

To a solution of 2.4g (10mmol) of methyl 2-amino-3-bromo-5-methyl benzoate in 20mL of pyridine was added 2.1g (10mmol) of p-methoxybenzenesulfonyl chloride. The reaction mixture was then heated to 70 °C for 16h and then poured into ice water and acidified with concentrated hydrochloric acid to pH2. The resulting mixture was extracted with chloroform, washed with water, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The residue was triturated with ether, filtered and dried to provide 3.8g (92%) of the desired product as a brown solid. m.p. 113°C. Electrospray Mass Spec: 416 (M+H).

Example 136

3-Bromo-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-benzoic acid methyl ester

To a stirred solution of 2.0 g (4.8 mmol) of the product of Example 135 in 20mL of DMF was added 1.0g (10mmol) of K₂CO₃ and 1.1g (7.2mmol) of 3-picolyl chloride hydrochloride. The reaction mixture was stirred for 48h at room temperature and then diluted with water. The resulting mixture was extracted with chloroform and the combined organic layers were washed with water, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with ethyl acetate: hexane (1:1) to provide 2.90g (82%) of the desired product as a brown oil. Electrospray Mass Spec: 508 (M+H).

Example 137

3-Bromo-2-[(4-methoxy-benzenesulfonyl-pyridin-3-ylmethyl)-amino]-5-methyl-benzoic acid

In the same manner as described in Example 16, 1.01g (2 mmol) of the product of Example 136 provided 0.90g (91%) of the desired product as a white powder after neutralization of the reaction mixture with acetic acid and extraction with ethyl acetate. m.p.198°C. Electrospray Mass Spec: 494 (M+H).

Example 138

3-Bromo-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-benzamide

In the same manner as described in Example 23, 0.986g (2mmol) of the product of Example 137 provided 0.61g (60%) of the title product. The corresponding hydrochloride salt was prepared in quantitative yield by bubbling HCl gas through a methanolic solution of the free base, followed by concentrating the reaction mixture in vacuo to provide a yellow spongy solid. m.p.87°C. Electrospray Mass Spec: 509 (M+H).

Example 139

2-(4-Methoxy-benzenesulfonylamino)-3-methyl-5-thiophen-2-yl-benzoic acid methyl ester

To a solution of 3.0 g (7.2 mmol) of the product of Example 134 in 200mL of degassed toluene was added 3.54g (10 mmol) of 2-thienyl tributyltin and 0.50g of tetrakis(triphenylphosphine)palladium and the resulting mixture was refluxed for 16h. The reaction mixture was then filtered through celite and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel eluting with 30% ethylacetate:hexane to provide 2.5g (83%) of the desired product as a gray solid. m.p.91°C. Electrospray Mass Spec: 417 (M+H).

Example 140

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-thiophen-2-yl-benzoic acid methyl ester

In the same manner as described in Example 136, 0.832g (2.0mmol) of the product of Example 139 provided 0.920g of the desired product as a brown oil. Electrospray Mass Spec: 509 (M+H).

Example 141

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-thiophen-2-yl-benzoic acid

In the same manner as described in Example 18, 0.800g (1.5 mmol) of the product of Example 140 provided 0.70g (94%) of the desired product as a white solid. m.p.191°C. Electro spray Mass. Spec: 495 (M+H).

Example 142

2-(4-Methoxy-benzenesulfonylamino)-5-methyl-3-thiophen-2-yl-benzoic acid methyl ester

In the same manner as described in Example 39, 3.0g (7.2mmol) of the product of Example 135 provided 2.0g (66%) of the desired product as a gray solid after chromatography on silica gel eluting with 30% ethyl acetate:hexane. m.p.141°C. Electro spray Mass Spec: 418 (M+H).

Example 143

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-3-thiophen-2-yl-benzoic acid methyl ester

In the same manner as described in Example 136, 2.0 g (4.8 mmol) of the product of Example 142 provided 2.1g (87%) of the desired product as a brown oil after chromatography on silica gel eluting with 50% ethyl acetate:hexane. Electro spray Mass Spec: 509 (M+H).

Example 144

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-3-thiophen-2-yl-benzoic acid

In the same manner as described in Example 16 starting with 1.5 g (2.9 mmol) of the product of Example 143 provided 1.3g (86%) of the desired product as a white powder after neutralization of the reaction mixture with acetic acid and extraction with ethyl acetate. m.p.67 °C. Electro spray Mass Spec: 495 (M+H).

Example 145

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-3-thiophen-2-yl-benzamide

In the same manner as described in Example 23, 1.0 gm (2.02 mmol) of the product of Example 144 provided 0.70g (63%) of the desired product. The corresponding hydrochloride salt was prepared in quantitative yield by bubbling HCl gas through a

methanolic solution of the free base, followed by concentrating the reaction mixture in vacuo to provide a yellow spongy solid. m.p.94 °C. Electrospray Mass Spec: 547 (M+H).

Example 146

5 **2-[(4-Methoxy-benzenesulfonyl)-methyl-amino]-3,5-dimethyl-benzoic acid methyl ester**

In the same manner as described in Example 9, 0.30g (0.860mmol) of the product of Example 62 was alkylated with methyl iodide to give 0.30g (96%) of the desired product as a white solid. Electrospray Mass Spec: 364 (M+H).

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Example 147

2-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid methyl ester

15 In the same manner as described in Example 9, 0.30g (0.860mmol) of the product of Example 62 was alkylated with ethyl iodide to give 0.324g (100%) of the desired product as a white solid. Electrospray Mass Spec: 378 (M+H).

Example 148

2-[(4-Methoxy-benzenesulfonyl)-methyl-amino]-3,5-dimethyl-benzoic acid

20 In the same manner as described in Example 18, 0.267g (0.738mmol) of the product of Example 146 gave 0.23g (89%) of the desired product as a white solid. Electrospray Mass Spec: 350 (M+H).

Example 149

25 **2-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-3,5-dimethyl-benzoic acid**

In the same manner as described in Example 18, 0.254g (0.674mmol) of the product of Example 147 gave 0.207g (84%) of the desired product as a white solid. Electrospray Mass Spec: 364 (M+H).

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Example 150

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3,5-dimethyl-benzamide

35 In the same manner as described in Example 23, 0.194g (0.557mmol) of the product of Example 148 gave 0.140g (69%) of the desired product as a pink solid. Electrospray Mass Spec: 365 (M+H).

Example 151

2-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-benzamide

In the same manner as described in Example 23, 0.175g (0.482mmol) of the
5 product of Example 149 gave 0.142g (78%) of the desired product as a white solid.
Electrospray Mass Spec: 379 (M+H).

Example 152

**3,4,5-Trimethoxy-2-(4-methoxy-benzenesulfonylamino)-benzoic acid
10 methyl ester**

In the same manner as described in Example 31, 2.0g (8.289mmol) of methyl-
3,4,5-trimethylantranilate gave 1.945 (57%) of the desired product as a white solid.
Electrospray Mass Spec: 412 (M+H).

Example 153

**3,4,5-Trimethoxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-
15 amino]-benzoic acid methyl ester**

In the same manner as described in Example 45, 0.60g (1.46 mmol) of the product
of Example 152 gave 0.716g (98%) of the desired product as a brown oil. Electrospray
20 Mass Spec: 503 (M+H).

Example 154

**2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3,4,5-trimethoxy-benzoic
25 acid methyl ester**

In the same manner as described in Example 9, 0.60g (1.46 mmol) of the product
of Example 152 gave 0.669g (92%) of the desired product as a white solid. Electrospray
Mass Spec: 502 (M+H).

Example 155

**2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3,4,5-trimethoxy-benzoic
30 acid**

In the same manner as described in Example 18, 0.594g (1.186 mmol) of the
product of Example 154 gave 0.532g (92%) of the desired product as a white solid.
Electrospray Mass Spec: 488 (M+H).

35

Example 156

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy- 3,4,5-trimethoxy-benzamide

In the same manner as described in Example 23, 0.463g (0.951 mmol) of the product of Example 155 gave 0.353g (74%) of the desired product as a white solid. Electro spray Mass Spec: 503 (M+H).

Example 157

3,4,5-Trimethoxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-benzoic acid

In the same manner as described in Example 53, 0.640g (1.275 mmol) of the product of Example 153 gave 0.631g (100%) of the desired product as a tan foam. Electro spray Mass Spec: 489 (M+H).

Example 158

N-Hydroxy-3,4,5-trimethoxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-benzamide

In the same manner as described in Example 61, 0.549g (1.109 mmol) of the product of Example 157 gave 0.395g (71%) of the desired product as a brown foam. Electro spray Mass Spec: 504 (M+H).

Example 159

12-(4-Methoxy-benzenesulfonyl)-11,12-dihydro-6H-dibenz[b,f][1,4]oxazocine-1-carboxylic acid methyl ester

To a solution of 0.350g (1.039mmol) of the product of Example 31 in 35mL of DMF was added 0.104g (2.596mmol) of 60% sodium hydride and the solution was stirred at room temperature for 15 minutes. To the resulting mixture was then added 0.384g (1.454mmol) of a,a'-dibromo-o-xylene and the reaction mixture was then heated to 80 °C for 18h, cooled to room temperature, diluted with ether and washed with water. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue was chromatographed on silica gel eluting with EtOAc/Hexanes (1:3) to provide 0.358g (79%) of the desired product as a white solid. Electro spray Mass Spec: 440 (M+H).

Example 160

6-(4-Methoxy-benzenesulfonyl)-3,4,5,6-tetrahydro-2H-1,6-benzoxazocine-7-carboxylic acid methyl ester

In the same manner as described in Example 159, 0.400g (1.187 mmol) of the product of Example 31 and 0.198mL (1.662mmol) of 1,4-dibromobutane provided 0.139g (30%) of the desired product as a white solid. Electrospray Mass Spec: 392 (M+H).

Example 161

5-(4-Methoxy-benzenesulfonyl)-2,3,4,5-tetrahydro- [1,5]benzoxazepine-6-carboxylic acid methyl ester

In the same manner as described in Example 159, 0.300g (0.890 mmol) of the product of Example 31 and 0.127mL (1.246 mmol) of 1,3-dibromopropane provided 0.156g (46%) of the desired product as a colorless oil. Electrospray Mass Spec: 378 (M+H).

Example 162

5-(4-Methoxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1,5-benzoxazepine- 6-carboxylic acid

In the same manner as described in Example 18, 0.174g (0.462 mmol) of the product of Example 161 provided 0.133g (79%) of the desired product as a white solid. Electrospray Mass Spec: 364 (M+H).

Example 163

12-(4-Methoxy-benzenesulfonyl)-11,12-dihydro-6H-dibenz[b,f][1,4]oxazocine-1-carboxylic acid

In the same manner as described in Example 18, 0.306g (0.697 mmol) of the product of Example 159 provided 0.261g (88%) of the desired product as a white solid. Electrospray Mass Spec: 426 (M+H).

Example 164

6-(4-Methoxy-benzenesulfonyl)-3,4,5,6-tetrahydro-2H-1,6-benzoxazocine-7-carboxylic acid

In the same manner as described in Example 18, 0.125g (0.320 mmol) of the product of Example 160 provided 0.106g (88%) of the desired product as a white solid. Electrospray Mass Spec: 378 (M+H).

Example 165

5-(4-Methoxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1,5-benzoxazepine-6-carboxylic acid hydroxyamide

In the same manner as described in Example 23, 0.107g (0.295 mmol) of the product of Example 162 provided 0.100g (90%) of the desired product as a white solid. Electro spray Mass Spec: 379 (M+H).

Example 166

12-(4-Methoxy-benzenesulfonyl)-11,12-dihydro-6H-dibenz[b,f][1,4]oxazocine-1-carboxylic acid hydroxyamide

In the same manner as described in Example 23, 0.230 g (0.541 mmol) of the product of Example 163 provided 0.192g (81%) of the desired product as a white solid. Electro spray Mass Spec: 441 (M+H).

Example 167

6-(4-Methoxy-benzenesulfonyl)-3,4,5,6-tetrahydro- 2H-1,6-benzoxazocine-7-carboxylic acid hydroxyamide

In the same manner as described in Example 23, 0.081g (0.215 mmol) of the product of Example 164 provided 0.074g (88%) of the desired product as a white solid. Electro spray Mass Spec: 393 (M+H).

Example 168

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-nitro-benzoic acid methyl ester

To a solution of 29.5g (0.092mol) of the product of Example 1 suspended in 131mL of acetic anhydride at 0 °C was dropwise added a mixture of 17.5mL of acetic anhydride, 22.5 mL of 70% nitric acid and 15.75mL of acetic acid over 1 hour. The reaction was stirred at 0 °C for an additional 2h and then poured into ice water. The precipitate was filtered and washed with ether. The filtrate was transferred to a separatory funnel and the layers were separated. The aqueous layer was washed with chloroform and the combined organics were dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/Hexanes (1:10) to provide 1.03g of the nitro-sulfonamide as a yellow solid.

0.250g (0.683mmol) of the sulfonamide reacted with sodium hydride and benzyl bromide in the same manner as described in Example 9 to provide 0.215g (69%) of the desired product as a pale yellow solid. Electro spray Mass Spec: 457 (M+H).

Example 169

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-nitro-benzoic acid

In the same manner as described in Example 18, 0.199g (0.436 mmol) of the product of Example 168 provided 0.172g (89%) of the desired product as a pale yellow solid. Electrospray Mass Spec: 443 (M+H).

Example 170

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-nitro-benzamide

In the same manner as described in Example 23, 0.136g (0.308 mmol) of the product of Example 169 provided 0.106g (75%) of the desired product as a tan foam. Electrospray Mass Spec: 458 (M+H).

Example 171

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-[3-(tert-butyl-dimethyl-silanyloxy)-propoxy]-benzoic acid methyl ester

In the same manner as described in Example 38, 0.35g (0.820 mmol) of the product of Example 37 and 0.290g (1.147mmol) of 1-t-butyldimethylsilyloxy-3-bromopropane provided 0.355g (72%) of the desired product as a colorless oil. Electrospray Mass Spec: 600 (M+H).

Example 172

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-(3-hydroxy-propoxy)-benzoic acid

In the same manner as described in Example 18, 0.310g (0.518 mmol) of the product of Example 171 provided 0.188g (77%) of the desired product as a white foam. Electrospray Mass Spec: 470 (M-H).

Example 173

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-[3-(tert-butyl-dimethyl-silanyloxy)-propoxy]-benzoic acid

To a solution of 0.145g (0.308 mmol) of the product of Example 172 in 5.0mL of DMF was added 0.105g (1.539mmol) of imidazole and 0.111g (0.739mmol) of t-butyldimethylsilyl chloride. The reaction was stirred at room temperature for 18h and then 0.40mL of 1N sodium hydroxide solution was added and the resulting mixture was stirred for 1h. The reaction mixture was then diluted with water, acidified with 5% HCl solution and extracted with EtOAc. The combined organics were washed with water, dried over

was dissolved in chloroform and washed well with water. The organic layer was then dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue chromatographed on silica gel eluting with 30% Ethyl acetate/Hexane to give 1.8g (79%) of the desired product as a brown oil. Electrospray Mass Spec 527 (M+H).

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Example 178

2-[Benzyl-(4-methoxybenzenesulfonylamino)-3-cyano-5-methyl-benzoic acid

To a solution of 1.5g (2.8mmol) of the product of Example 177 in 100mL of THF:MeOH (1:1) was added 10mL of 10N NaOH. The reaction mixture was stirred at room temperature for 8h and then concentrated in vacuo. The residue was neutralized with concentrated HCl and the resulting separated solid was dissolved in chloroform and washed well with water. The organic layer was dried over MgSO₄, filtered and concentrated. The resulting solid was triturated with ether and filtered to provide 1.1 g (91%) of the desired product as a brown solid. Electrospray Mass Spec 437 (M+H).

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Example 179

2-[Benzyl-(4-methoxybenzenesulfonylamino)-N-hydroxy-3-cyano-5-methyl-benzamide

In the same manner as described in Example 23, 1.0g (2.3mmol) of the product of Example 178 provided 0.70g (67%) of the desired product as a white solid. m.p. 175 °C; Electrospray Mass Spec 452 (M+H).

20

Example 180

5-Cyano-2-(4-methoxybenzenesulfonylamino)-3-methyl-benzoic acid

To a solution of 4.0g (10 mmol) of the product of Example 10 in 60mL of pyridine was added 2.0g (22 mmol) of copper (I) cyanide and the resulting mixture was refluxed for 48h. The reaction mixture was then cooled to room temperature, poured over cold water, stirred for 16h and then carefully acidified with concentrated HCl solution. The resulting solid was filtered and washed with water, dissolved in chloroform, dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with ether, filtered and dried to provide 2.0g (58%) of the desired product as a white solid. m.p. 175 °C; Electrospray Mass Spec 347 (M+H).

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Example 181

2-[Benzyl-(4-methoxybenzenesulfonylamino)-5-cyano-3-methylbenzoic acid

In the same manner as described in Example 177, 4.5g (13 mmol) of the product of Example 180 and 5mL of benzylbromide provided 3.5g (51%) of the desired product as brown solid after trituration with ether. m.p. 123 °C; Electrospray Mass Spec 527 (M+H).

Example 182

2-[Benzyl-(4-methoxybenzenesulfonylamino)-5-cyano-3-methyl-benzoic acid

In the same manner as described in Example 178, 3.0g (5.7 mmol) of the product of Example 215 provided 2.2g (88%) of the desired product as a brown semi-solid. Electrospray Mass Spec 437 (M+H).

Example 183

3-Furan-2-yl-2-(4-methoxybenzenesulfonylamino)-5-methyl-benzoic acid methyl ester

To a solution of 4.1g (10 mmol) of the product of Example 135 in 300mL of degassed toluene was added 6.0g (16 mmol) of 2-(tributylstannyl)furan and 500 mg of tetrakis(triphenylphosphine)palladium(0) and the resulting mixture was heated to reflux for 24h. The reaction mixture was then cooled, filtered through celite and concentrated in vacuo. The resulting residue was triturated with ether to provide 3.5g (87%) of the desired product as a gray solid. m.p. 133 °C; Electrospray Mass Spec 402 (M+H).

Example 184

3-Furan-2-yl-2-[(4-methoxybenzenesulfonyl)-pyridin-3-ylmethylamino]-5-methyl-benzoic acid methyl ester

To solution of 3.0g (7.4 mmol) of the product of Example 183 in 25mL of DMF was added 1.64g (10 mmol) of 3-picolyl chloride hydrochloride and 4.0g of K₂CO₃ and the resulting mixture was stirred for 72 h at room temperature. The reaction mixture was then poured over water, extracted with chloroform and washed well with water. The organic layer was dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with 50% ethyl acetate/hexane to provide 2.5g (68%) of the desired product as a brown oil. Electrospray Mass Spec 493 (M+H).

Example 185

3-Furan-2-yl-2-[(4-methoxybenzenesulfonyl)-pyridin-3-ylmethylamino]-5-methyl-benzoic acid

In the same manner as described in Example 24 2.0g (4.0 mmol) of the product of Example 184 provided 1.5g (79%) of the desired product as a brown solid. m.p. 82 °C; Electro spray Mass Spec 479 (M+H).

Example 186

3-Furan-2-yl-N-hydroxy-2-[(4-methoxybenzenesulfonyl)-pyridin-3-ylmethylamino]-5-methyl-benzamide

In the same manner as described in Example 23, 1.0g (2.01 mmol) of the product of Example 185 provided 0.60g (58%) of the desired product as a white solid after chromatography on silica gel eluting with ethyl acetate/methanol (95:5) m.p. 160 °C; Electro spray Mass Spec 494 (M+H).

Example 187

2-[(4-Methoxybenzenesulfonyl)-methylamino]-3-methyl-benzoic acid methyl ester

To a solution of 1.0g (2.985 mmol) of the product of Example 3 in 10mL of DMF was added 0.149g (3.731 mmol) of 60% sodium hydride. The resulting mixture was stirred for 30 minutes at room temperature and then 0.28mL (4.478 mmol) of iodomethane was added. The reaction was then stirred for 18h, and next diluted with ether. The organics were washed with water, dried over MgSO₄, filtered and concentrated in vacuo to provide a white solid. The solid was washed with ether/hexanes (1:1) to give 0.788g (76%) of the desired product as a white solid. Electro spray Mass Spec: 350.1 (M+H).

Example 188

3-Bromomethyl-2-[(4-methoxybenzenesulfonyl)-methylamino]-benzoic acid methyl ester

To a solution of 0.723g (2.072 mmol) of the product of Example 187 in 70mL of carbon tetrachloride was added 0.406g (2.279 mmol) of N-bromosuccinimide and 0.14g of dibenzoyl peroxide. The resulting mixture was heated to reflux for 18h and then cooled to room temperature, washed with sodium bisulfite solution and water, dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with ether/hexanes (1:1) and then filtered to provide 0.504g (57%) of the desired product as a white solid. Electro spray Mass Spec: 428 (M+H).

Example 189

3-Diethylaminomethyl-2-[(4-methoxybenzenesulfonyl)-methylamino]benzoic acid methyl ester

To a solution of 0.25g (0.584 mmol) of the product of Example 188 in 2.0mL of DMF was added 0.242g (1.752 mmol) of potassium carbonate, 0.066mL (0.643 mmol) of diethylamine and 2mg of tetrabutylammonium iodide. The reaction mixture was then stirred at room temperature for 5h, diluted with water and extracted with ether. The organics were then extracted with 6N HCl solution and the aqueous acid layer was then basified with 6N NaOH solution and then extracted with ether. The resulting ether layer was dried over sodium sulfate, filtered and concentrated in vacuo to provide 0.19g (78%) of the desired product as a colorless oil. Electrospray Mass Spec: 421.3 (M+H)⁺

Example 190

3-Diethylaminomethyl-2-[(4-methoxybenzenesulfonyl)-methylamino]benzoic acid

To a solution of 0.158g (0.376 mmol) of the product of Example 189 in 4.0mL of THF/water/MeOH (1:1:0.5) was added 0.032g (0.752 mmol) of lithium hydroxide monohydrate and the resulting mixture was then heated to reflux for 18h, cooled to room temperature and concentrated in vacuo. The residue was washed with THF and filtered, and the filtrate was then concentrated and dried in vacuo to provide 0.132g (85%) of the lithium salt of the title compound as a white foam. Electrospray Mass Spec: 407.2 (M+H)⁺

Example 191

3-Diethylaminomethyl-N-hydroxy-2-[(4-methoxybenzenesulfonyl)-methylamino]benzamide

In the same manner as described in Example 61, 0.110g (0.267 mmol) of the product of Example 190 provided 0.125g (100%) of the hydrochloride salt of the title compound as a brown foam. Electrospray Mass Spec: 422.1 (M+H)⁺.

Example 192

2-[(4-methoxybenzenesulfonyl)-methylamino]-3-(4-methylpiperazin-1-ylmethyl)-benzoic acid methyl ester

In the same manner as described in Example 189, 0.500g (1.168 mmol) of the product of Example 188 and 0.143mL (1.285 mmol) of N-methylpiperazine provided 0.368g (70%) of the desired product as a tan solid. Electrospray Mass Spec: 448.0 (M+H)⁺

Example 193

2-[(4-methoxybenzenesulfonyl)-methylamino]-3-(4-methylpiperazin-1-ylmethyl)-benzoic acid

5 In the same manner as described in Example 190, 0.310g (0.693 mmol) of the product of Example 192 provided 0.305g (100%) of the lithium salt of the title compound as a white foam. Electrospray Mass Spec: 432.1 (M-H)⁻

Example 194

10 **N-Hydroxy-2-[(4-methoxybenzenesulfonyl)-methylamino]-3-(4-methylpiperazin-1-ylmethyl)-benzamide**

In the same manner as described in Example 61, 0.150g (0.334 mmol) of the product of Example 193 provided 0.174g (100%) of the hydrochloride salt of the title compound as a
15 brown solid. Electrospray Mass Spec: 448.9 (M+H)⁺.

Example 195

2-[Benzyl-(4-methoxybenzenesulfonyl)amino]-3-(1-ethoxycarbonyl-1-methylethoxy-benzoic acid methyl ester

20 To a solution of 0.250g (0.585mmol) of the product of Example 37, in 10mL of DMF was added 2.42g (17.56 mmol) of potassium carbonate and 0.86mL (5.854 mmol) of ethyl 2-bromoisobutyrate. The resulting mixture was heated to 80 °C. for 18h and then cooled to room temperature and diluted with ether. The organics were washed with water, dried over MgSO₄, filtered and concentrated in vacuo to provide 0.186g (59%) of the desired product
25 as a white solid. Electrospray Mass Spec: 442.2 (M+H)⁺.

Example 196

2-[Benzyl-(4-methoxybenzenesulfonyl)amino]-3-(1-ethoxycarbonyl-1-methylethoxy-benzoic acid

30 In the same manner as described in Example 9, 0.147g (0.272 mmol) of the product of Example 195 provided 0.107g (79%) of the desired product as a white solid. Electrospray Mass Spec: 500.2 (M+H)⁺

Example 197

2-[Benzyl-(4-methoxybenzenesulfonyl)amino]-3-(1-ethoxycarbonyl-N-hydroxy-1-methylethoxy-benzamide

In the same manner as described for Example 23, 0.085g (0.170 mmol) of the product of Example 196 provided 0.052g (58%) of the desired product as a white solid. Electrospray Mass Spec: 530.1 (M+H)⁺

Example 198

3-Bromo-2[-(4-methoxybenzenesulfonyl)amino]-benzoic acid methyl ester

To 0.096g (0.5 mmol) of 4-methoxyphenylsulphonamide in 3mL of DMF was added in one portion 0.020g (0.50 mmol) of 60% sodium hydride and the reaction was stirred at 25°C for 15 min. Then, 0.135g (0.58 mmol) of methyl 3-bromo-2-fluorobenzylate was added to the solution in one portion and the resulting mixture was heated at 90 °C (bath temperature) for 18h. The reaction was cooled to room temperature, acidified with 1N HCl and extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was chromatographed on silica eluting with 30%-50% ethyl acetate/hexane to provide 0.037g (19%) of the desired product. ¹HNMR(CDCl₃): 8 ppm (s, 1H, NH), 6.8-7.8 ppm (m, 7H, Ar), 3.9 ppm (s, 1H, OMe), 3.7 ppm (s, 1H, OMe).

Example 199

3-Bromo-2-[benzyl-(4-methoxybenzenesulfonyl)amino]-benzoic acid methyl ester

To a solution of 0.413g (1.03mmol) of the product of Example 198 in 10mL of DMF was added 0.062g (1.55mmol) of 60% sodium hydride. Stirring was continued for 15 min at 25°C and 0.125 mL (1.442 mmol) of benzyl bromide was then added and the mixture was stirred for 18 h at 55 °C. The reaction was cooled to room temperature and the reaction mixture was poured into 200 mL water and 50 mL 1N HCl. The aqueous layer was then extracted with dichloromethane (100 mL) and ethyl acetate (100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was chromatographed on silica eluting with 10%-20% ethyl acetate/hexane to provide 0.390g (77%) of the desired product. Electrospray Mass Spec 490.0 (M+H)

Example 200

3-Bromo-2-[benzyl-(4-methoxybenzenesulfonyl)amino]-benzoic acid

In the same manner as described in Example 16, 0.390g (0.80 mmol) of the product of Example 199 provided 0.180g (84%) of the desired carboxylic acid as a white solid.

5 ¹HNMR(CDCl₃): 9-10 ppm (br, 1H, COOH), 7-8 ppm (m, 12H, Ar), 4.5 ppm (m, 2H, -CH₂-), 3.9 ppm (s, 1H, OMe).

Example 201

3-Bromo-2-[benzyl-(4-methoxybenzenesulfonyl)amino]-N-hydroxy-benzamide

10

In the same manner as described in Example 23, 0.177g (0.372 mmol) of the product of Example 200 gave 0.155g (85%) of the desired hydroxamic acid as a white solid.

Electrospray Mass Spec: 491.0 (M+H).

15

Example 202

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

20 In the same manner as described in Example 9, 27.0g (65 mmol) of the product of Example 10 and 4.87ml (78 mmol) of methyl iodide provided 22.06g (86%) of the desired product as a white solid after trituration with ether. Electrospray Mass Spec 430 (M+H).

Example 203

5-(2-tert-Butoxycarbonyl-vinyl)-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid methyl ester

25

A mixture of 1.28g (3.0 mmol) of the product of Example 202, 1.31ml (9.0 mmol) of t-butylacrylate, 33.75mg (0.15 mmol) of palladium diacetate, 1.0g (3.15 mmol) of t-butyl ammonium bromide and 1.24g (9.0 mmol) of K₂CO₃ in 10 ml of DMF was stirred at 85°C for 6h. The reaction mixture was poured into water and extracted with ethyl acetate.

30 The combined organics were washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue was dissolved in 20ml of dichloromethane and stirred with 1.0g of celite and 1.0g of silica gel for 20 min, filtered and concentrated in vacuo. The resulting residue was chromatographed on silica gel eluting with EtOAc/Hexane (1:5) to provide 1.26g (88%) of the desired product as a white solid.

35 Electrospray Mass Spec 476(M+H).

Example 204

5-(2-Carboxy-vinyl)-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid methyl ester

To a solution of 237.8mg (0.5 mmol) of the product of Example 203 in 2ml dichloromethane, was added 1ml of trifluoroacetic acid and the reaction was stirred at room temperature for 2h. The resulting mixture was concentrated in vacuo to provide 200mg (95%) of the desired product as a white solid after trituration with hexane/ether (2:1). Electrospray Mass Spec 418(M-H).

Example 205

2-[(4-Methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-5-[2-(methyl-octyl-carbamoyl)-vinyl]-benzoic acid methyl ester

A mixture of 182.6mg (0.43 mmol) of the product of Example 204, 183mg of molecular sieves and 105.8mg (0.65 mmol) of 1,1'-dicyclohexylcarbodiimidazole in 4ml THF was stirred for 1h under nitrogen. A solution of N-methyloctylamine in 0.5ml THF was then added to the reaction and the mixture was stirred for 18 hr at room temperature. The resulting mixture was filtered and the filtrate was diluted with ethyl acetate, washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/Hexane (1:1) to provide 200mg (84%) of the desired product as a colorless oil. Electrospray Mass Spec 545(M+H).

Example 206

2-[(4-Methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-5-[2-(methyl-octyl-carbamoyl)-vinyl]-benzoic acid

In the same manner as described in Example 18, 188mg (0.35 mmol) of the product of Example 205 provided 170mg (93%) of the desired carboxylic acid as a white solid after trituration with Hexane/EtOAc (2:1). Electrospray Mass Spec 575(M+HCOOH-H).

Example 207

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-5-[2-(methyl-octyl-carbamoyl)-vinyl]-benzamide

In the same manner as described in Example 23, 154mg (0.29 mmol) of the product of Example 206 provided 45mg (28%) of the desired hydroxamic acid as an off white solid. Electrospray Mass Spec 546(M+H).

Example 208

5-(2-tert-Butoxycarbonyl-ethyl)-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid methyl ester

A mixture of 340mg (0.71 mmol) of the product of Example 203 and 35mg of 10% palladium on carbon in 15ml of ethanol was hydrogenated on a Parr shaker for 2 hr. The resulting mixture was filtered through Celite and Magnesol to provide 325mg (95%) of the desired product as a colorless gum. Electrospray Mass Spec 478(M+H).

Example 209

5-(2-Carboxy-ethyl)-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 204, 206mg (0.43 mmol) of the product of Example 208 provides 181mg (100%) the desired product as colorless gum. Electrospray Mass Spec 420(M-H).

Example 210

2-[(4-Methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-5-[2-(methyl-octyl-carbamoyl)-ethyl]-benzoic acid methyl ester

In the same manner as described in Example 205, 286mg (0.68 mmol) of the product of Example 209 provides 362mg (97%) of the desired product as a colorless gum. Electrospray Mass Spec 547(M+H).

Example 211

2-[(4-Methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-5-[2-(methyl-octyl-carbamoyl)-ethyl]-benzoic acid

In the same manner as described in Example 18, 340mg (0.62 mmol) of the product of Example 210 provided 304mg (92%) of the desired carboxylic acid as a pale yellow crystalline solid. Electrospray Mass Spec 533(M+H).

Example 212

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-5-[2-(methyl-octyl-carbamoyl)-ethyl]-benzamide

To a slurry of 300mg (0.56 mmol) of the product of Example 211 and 106mg (0.78 mmol) of 1-hydroxybenzotriazole in 5ml DMF was added 183mg (0.95 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and the reaction was stirred for 30 min at room temperature. Hydroxylamine hydrochloride (227mg, 3.26 mmol) and 0.68ml (4.89 mmol) of triethylamine and the reaction was stirred for 18 hr. The resulting

mixture was diluted with water and extracted with dichloromethane. The combined organics were washed with water and brine, dried over MgSO_4 , filtered and concentrated in vacuo. The residue was chromatographed on silica gel with 2% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ as the eluant to provide 190mg (62%) of the desired hydroxamic acid as an off white solid. Electrospray Mass Spec 548(M+H).

Example 213

5-(2-Dimethylcarbamoyl-vinyl)-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 203, 428.3mg (1.0 mmol) of the product of Example 202 and 0.309ml (3.0 mmol) of N,N-dimethylacrylamide provided 418mg (93%) of the desired product as a colorless gum. Electrospray Mass Spec 447(M+H).

Example 214

5-(2-Dimethylcarbamoyl-vinyl)-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid

In the same manner as described in Example 18, 418mg (0.94 mmol) of the product of Example 213 provided 303mg (75%) of the desired carboxylic acid as a white solid. Electrospray Mass Spec 477 (M+HCOOH-H).

Example 215

5-(2-Dimethylcarbamoyl-vinyl)-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzamide

In the same manner as described in Example 212, 303mg (0.70 mmol) of the product of Example 214 provided 268mg (85%) of the desired hydroxamic acid as a white solid. Electrospray Mass Spec 448(M+H).

Example 216

N-Ethyl-N-pyridin-4-ylmethyl-acrylamide

To a 0°C solution of 0.835ml (6.0 mmol) of 4-(ethylaminomethyl) pyridine and 1.05ml (7.5 mmol) of triethylamine in 10ml dichloromethane, was dropwise added 0.406ml (5.0 mmol) of acryloyl chloride. The reaction mixture was warmed to room temperature and stirred for 18 hr. The resulting mixture was washed with water and brine, dried over MgSO_4 , filtered and concentrated in vacuo. The residue was chromatographed on silica gel with 3% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ as the eluant to provide 651mg (68%) of the desired product as a yellow gum. Electrospray Mass Spec 191(M+H).

Example 217

5-[2-(Ethyl-pyridin-4-ylmethyl-carbamoyl)-vinyl]-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid methyl ester

5 In the same manner as described in Example 203, 342.6mg (0.80 mmol) of the product of Example 202 and 456.6mg (2.4 mmol) of the product of Example 216 provided 405mg (94%) of the desired product as a yellow gum. Electrospray Mass Spec 538(M+H).

Example 218

5-[2-(Ethyl-pyridin-4-ylmethyl-carbamoyl)-vinyl]-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid

10 To a solution of 405mg (0.75 mmol) of the product of Example 217 in 8ml of THF:MeOH:H₂O (2:1:1) was added 126.4mg (3.01 mmol) of lithium hydroxide monohydrate. The reaction mixture was heated to reflux for 18hr and then concentrated in vacuo. The residue was diluted with water, neutralized with 3N HCl and extracted with
15 dichloromethane. The combined organics were washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo to provide 222mg (56%) of the desired carboxylic acid as a beige solid. Electrospray Mass Spec 524(M+H).

Example 219

5-[2-(Ethyl-pyridin-4-ylmethyl-carbamoyl)-vinyl]-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzamide

20 In the same manner as described in Example 212, 214mg (0.408 mmol) of the product of Example 218 provided 156mg (71%) of the desired hydroxamic acid, which was then dissolved in 2 ml of CH₂Cl₂ and treated with 0.32ml (0.32 mmol) of 1M
25 HCl/Et₂O. The resulting mixture was stirred for 1 hr at room temperature and concentrated in vacuo to provide 150mg (64%) of the desired hydroxamic acid hydrochloride as a beige solid. Electrospray Mass Spec 539(M+H).

Example 220

5-(2-tert-Butoxycarbonyl-vinyl)-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester

30 In the same manner as described in Example 203, 1.08g (2.13 mmol) of the product of Example 89 provided 771mg(65%) of the desired product as a brown oil. Electrospray
35 Mass Spec 553(M+H).

Example 221

5-(2-Carboxy-vinyl)-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 204, 750mg (1.36 mmol) of the product of Example 220 provided 500mg (60%) of the desired product. Electrospray Mass Spec 541(M+HCOOH-H)

Example 222

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-[2-(methyl-octyl-carbamoyl)-vinyl]-benzoic acid methyl ester

In the manner as described in Example 205, 270mg (0.54 mmol) of the product of Example 221 provided 162mg (48%) of the desired product as a colorless gum. Electrospray Mass Spec 622(M+H).

Example 223

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-[2-(methyl-octyl-carbamoyl)-vinyl]-benzoic acid

In the same manner as described in Example 218, 386mg (0.62 mmol) of the product of Example 222 provided 274mg (73%) of the desired carboxylic acid as a white crystalline solid. Electrospray Mass Spec 652(M+HCOOH-H).

Example 224

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-[2-(methyl-octyl-carbamoyl)-vinyl]-benzamide

In the same manner as described in Example 219, 261mg (0.43 mmol) of the product of Example 223 provided 211mg(75%) of the desired product as a beige solid. Electrospray Mass Spec 623(M+H).

Example 225

5-(2-Dimethylcarbamoyl-vinyl)-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 203, 550.4mg (1.0 mmol) of the product of Example 89 and 297.4mg (3.0 mmol) of N,N-dimethylacrylamide provided 419mg (80%) of the desired product as a white solid. Electrospray Mass Spec 524(M+H).

Example 226

5-(2-Dimethylcarbamoyl-vinyl)-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid

In the same manner as described in Example 218, 404mg (0.77 mmol) of the product of Example 225 provided 250mg (64%) of the desired carboxylic acid as a pale yellow solid. Electrospray Mass Spec 508(M-H).

Example 227

5-(2-Dimethylcarbamoyl-vinyl)-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide

In the same manner as described in Example 219, 230mg (0.45 mmol) of the product of Example 226 provided 54mg (20%) of the desired product as a yellow solid. Electrospray Mass Spec 525(M+H).

Example 228

5-[2-(Ethyl-phenyl-carbamoyl)-vinyl]-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 203, 550.4mg (1.0 mmol) of the product of Example 89 and 425mg (2.43 mmol) of N-ethylacrylanilide provided 392mg (65%) of the desired product as a brown solid. Electrospray Mass Spec 600(M+H).

Example 229

5-[2-(Ethyl-phenyl-carbamoyl)-vinyl]-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid

In the same manner as described in Example 218, 582mg (0.97 mmol) of the product of Example 228 provided 404.7mg (71%) of the desired carboxylic acid as a mustard solid. Electrospray Mass Spec 584(M-H).

Example 230

5-[2-(Ethyl-phenyl-carbamoyl)-vinyl]-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide

In the same manner as described in Example 219, 402mg (0.69 mmol) of the product of Example 229 provided 190mg (43%) of the desired product as a beige solid. Electrospray Mass Spec 601(M+H).

Example 231

5-(2-Diallylcarbamoyl-vinyl)-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 203, 550.4mg (1.0 mmol) of the product of Example 89 and 453.6mg (3.0 mmol) of N,N-diallylacrylamide provided 309mg (53%) of the desired product as a yellow gum. Electrospray Mass Spec 576(M+H).

Example 232

5-(2-Diallylcarbamoyl-vinyl)-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid

In a same manner as described in Example 218, 276mg (0.48 mmol) of the product of Example 231 provided 149mg (55%) of the desired carboxylic acid as a beige solid. Electrospray Mass Spec 562(M+H).

Example 233

5-(2-Diallylcarbamoyl-vinyl)-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide

In the same manner as described in Example 219, 188mg (0.34 mmol) of the product of Example 232 provided 134mg (65%) of the desired product as a brown solid. Electrospray Mass Spec 577(M+H).

Example 234

5-Bromo-2-(dimethylamino-methyleneamino)-3-methyl-benzoic acid tert-butyl ester

A mixture of 5.0g (21.7 mmol) of the product of Example 132 and 20.8ml (86.9 mmol) of N,N-dimethylformamide di-t-butylacetal in 30ml of toluene was heated to reflux for 2 hr. The reaction mixture was cooled to room temperature, washed with water and brine, dried over MgSO₄ and concentrated in vacuo to provide 3.61g (49%) of the desired product as an yellow oil. Electrospray Mass Spec 341(M+H).

Example 235

2-Amino-5-bromo-3-methyl-benzoic acid tert-butyl ester

A mixture of 3.52g (10.3mmole) of the product of Example 234 and 6.12g (44.94 mmol) of zinc chloride in 50ml of absolute ethanol was heated to reflux for 18hr. The reaction mixture was concentrated in vacuo and the residue was diluted with CH₂Cl₂ and washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo to

provide 2.48g (84%) of the desired product as a pale brown liquid. Electrospray Mass Spec 286(M+H).

Example 236

5 **5-Bromo-2-(4-methoxy-benzenesulfonylamino)-3-methyl-benzoic acid tert-butyl ester**

In the same manner as described in Example 1, 2.48g (8.66 mmol) of the product of Example 235 provided 3.41g (86%) of the desired product as a pale yellow oil. Electrospray Mass Spec 402(M-t-bu-H).

10

Example 237

5-Bromo-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid tert-butyl ester

15 In the same manner as described in Example 81, 3.15g (6.9 mmol) of the product of Example 235 provided 2.6g (69%) of the desired product as a white solid. Electrospray Mass Spec 547(M+H).

Example 238

20 **2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-(3-morpholin-4-yl-3-oxo-propenyl)-benzoic acid tert-butyl ester**

In the same manner as described in Example 203, 547.5mg (1.0 mmol) of the product of Example 237 and 423mg (3.0 mmol) of N-acryloylmorpholine provided 542mg (89%) of the desired product as a pale yellow gum. Electrospray Mass Spec 608(M+H).

25

Example 239

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-(3-morpholin-4-yl-3-oxo-propenyl)-benzoic acid

30 In the same manner as described in Example 204, 492mg (0.809 mmol) of the product of Example 238 provided 464mg (86%) of the desired product as a pale yellow solid. Electrospray Mass Spec 552(M+H).

Example 240

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl) pyridin-3-ylmethyl-amino]-3-methyl-5-(3-morpholin-4-yl-3-oxo-propenyl)-benzamide

35 In the same manner as described in Example 219, 150mg (0.27 mmol) of the product of Example 239 provided 114mg (25%) of the desired product as a cream solid. Electrospray Mass Spec 567(M+H).

Example 241

2'-Formyl-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid methyl ester

To 5ml of degassed ethylene glycol dimethyl ether, was added 505.4mg (1.0 mmol) of the product of Example 89, 165mg (1.1 mmol) of 2-formylbenzene boronic acid, 58mg (0.05 mmol) of tetrakis(triphenylphosphine)palladium and 1ml (2.0 mmol) of 2M aqueous Na₂CO₃ and the mixture was heated to reflux under nitrogen for 18 hr. The reaction was cooled to room temperature, diluted with ethyl acetate, washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/Hexane (1:1) as eluant to provide 499mg (94%) of the desired product as a yellow solid. Electrospray Mass Spec 531 (M+H).

Example 242

2'-Formyl-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid

In the same manner as described in Example 218, 478mg(0.9 mmol) of the product of Example 241 provided 392mg (84%) of the desired carboxylic acid as a pale yellow solid. Electrospray Mass Spec 515 (M-H).

Example 243

2'-(Hydroxyimino-methyl)-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide

In the same manner as described in Example 219, 380mg(0.74 mmol) of the product of Example 242 provided 310mg (53%) of the desired product as a cream solid. Electrospray Mass Spec 547 (M+H).

Example 244

3'-Formyl-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid methyl ester

In the same manner as described in Example 241, 505.4mg (1.0 mmol) of the product of Example 89 and 165mg (1.1 mmol) of 3-formylbenzeneboronic acid provided 530mg (100%) of the desired product as a pale yellow crystal. Electrospray Mass Spec 531 (M+H).

Example 245

3'-Formyl-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid

In the same manner as described in Example 218, 500mg (0.96 mmol) of the product of Example 244 provided 214mg (43%) of the desired carboxylic acid as a white solid. Electrospray Mass Spec 515 (M-H).

Example 246

3'-(Hydroxyimino-methyl)-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide

In the same manner as described in Example 219, 196mg (0.38 mmol) of the product of example 245 provided 176mg (80%) of the desired product as a cream solid. Electrospray Mass Spec 547 (M+H).

Example 247

4'-Formyl-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid methyl ester

In the same manner as described in Example 241, 505.4mg (1.0 mmol) of the product from Example 89 and 165mg (1.1 mmol) of 4-formylbenzene boronic acid provided 519mg (98%) of the desired product as a pale yellow solid. Electrospray Mass Spec 531 (M+H).

Example 248

4'-Formyl-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid

In the same manner as described in Example 218, 486mg (0.92 mmol) of the product of Example 247 provided 362mg (76%) of the desired product as a white solid. Electrospray Mass Spec 515 (M-H).

Example 249

4'-(Hydroxyimino-methyl)-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide

In the same manner as described in Example 219, 320mg (0.62 mmol) of the product of Example 248 provided 166mg (49%) of the desired product as a cream solid. Electrospray Mass Spec 547 (M+H).

Example 250

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-2'-trifluoromethyl-biphenyl-3-carboxylic acid methyl ester

5 In the same manner as described in Example 241, 505.4mg (1.0 mmol) of the product of Example 89 and 244mg (1.1 mmol) of 2-trifluoromethylbenzene boronic acid provided 559mg (98%) of the desired product as a pale yellow gum. Electrospray Mass spec 571 (M+H).

Example 251

10 **4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-2'-trifluoromethyl-biphenyl-3-carboxylic acid**

In the same manner as described in Example 218, 541mg (0.95 mmol) of the product of Example 250 provided 475mg (90%) of the desired carboxylic acid as a white solid. Electrospray Mass Spec 557 (M+H).

15

Example 252

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-2'-trifluoromethyl-biphenyl-3-carboxylic acid hydroxyamide

20 In the same manner as described in Example 61, 447mg (0.803 mmol) of the product of Example 251 provided the desired product, which was dissolved in 3ml of dichloromethane and 3ml of methanol and treated with 0.76ml (0.76mmol) of 1M HCl/Et₂O. The reaction mixture was stirred for 1hr at room temperature and concentrated in vacuo to provide 373mg (76%) of the desired product. as a beige solid. Electrospray Mass Spec 572 (M+H).

25

Example 253

5-Furan-2-yl-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester

30 In the same manner as described in Example 241, 505.4mg (1.0 mmol) of the product of Example 89 and 123mg (1.1 mmol) of furan-2-boronic acid provided 432mg (88%) of the desired product as a pale yellow solid. Electrospray Mass Spec 493 (M+H).

Example 254

5-Furan-2-yl-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid

5 In the same manner as described in Example 218, 419mg (0.85 mmol) of the product of Example 253 provided 227mg (47%) of the desired carboxylic acid as a white solid after trituration with ether. Electrospray Mass Spec 477 (M-H).

Example 255

10 **5-Furan-2-yl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide**

In the same manner as described in Example 219, 220mg (0.46 mmol) of the product of Example 254 provided 185mg (76%) of the desired product as a cream solid. Electrospray Mass Spec 494 (M+H).

15 Example 256

5-(3-Formyl-thiophen-2-yl)-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester

20 In the same manner as described in Example 241, 505.4mg (1.0 mmol) of the product of Example 89 and 343.2mg (2.2 mmol) of 3-formylthiophene-2-boronic acid provided 379mg (71%) of the desired product as a pale yellow solid. Electrospray Mass Spec 537 (M+H).

Example 257

25 **5-(3-Formyl-thiophen-2-yl)-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid**

In the same manner as described in Example 218, 364mg (0.68 mmol) of the product of Example 256 provided 229mg (65%) of the desired carboxylic acid as a pale yellow solid. Electrospray Mass Spec 521 (M-H).

30 Example 258

N-Hydroxy-5-[3-(hydroxyimino-methyl)-thiophen-2-yl]-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide

35 In the same manner as described in Example 219, 220mg (0.42 mmol) of the product of Example 257 provided 168mg (68%) of the desired product as a cream solid. Electrospray Mass Spec 553 (M+H).

Example 259

5-(5-Chloro-thiophen-2-yl)-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 241, 505mg (1.0 mmol) of the product of Example 89 and 357mg (2.2 mmol) of 5-chlorothiophene-2-boronic acid provided 332mg (61%) of the desired product as an yellow solid. Electrospray Mass Spec 543 (M+H)

Example 260

5-(5-Chloro-thiophen-2-yl)-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid

In the same manner as described in Example 218, 312mg (0.58 mmol) of the product of Example 259 provided 277mg (91%) of the desired carboxylic acid as a pale yellow solid. Electrospray Mass Spec 527 (M-H).

Example 261

5-(5-Chloro-thiophen-2-yl)-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide

In the same manner as described in Example 219, 277mg (0.524 mmol) of the product of Example 260 provided 135mg (44%) of the desired product as a pale yellow solid. Electrospray Mass Spec 544 (M+H).

Example 262

5-(5-Acetyl-thiophen-2-yl)-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 241, 505.4mg (1.0 mmol) of the product of Example 89 and 374mg (2.2 mmol) of 5-acetylthiophene-2-boronic acid provided 525mg (95%) of the desired product as a cream colored solid. Electrospray Mass Spec 551 (M+H).

Example 263

5-(5-Acetyl-thiophen-2-yl)-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid

In the same manner as described in Example 218, 500mg (0.9 mmol) of the product of Example 262 provided 390mg (81%) of the desired carboxylic acid as a pale yellow solid. Electrospray Mass Spec 535 (M-H).

Example 264

5-(5-Acetyl-thiophen-2-yl)-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide

In the same manner as described in Example 219, 400mg (0.75 mmol) of the product of Example 263 provided 226mg (52%) of the desired product as a white solid. Electro spray Mass Spec 552 (M+H).

Example 265

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-methyl-5-vinyl-benzoic acid methyl ester

In the same manner as described in Example 139, 728mg (1.44 mmol) of the product of Example 11 and 0.552ml (2.0 mmol) of vinyltributyltin provided 430mg (66%) of the desired product as a white solid. Electro spray Mass Spec 452 (M+H).

Example 266

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-methyl-5-vinyl-benzoic acid

In the same manner as described in Example 18, 160mg (0.35 mmol) of the product of Example 265 provided 133mg (85%) of the desired carboxylic acid as a white solid. Electro spray Mass Spec 436 (M-H).

Example 267

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methyl-5-vinyl-benzamide

In the same manner as described in Example 23, 120mg (0.27 mmol) of the product of Example 266 provided 63.4mg (51%) of the desired hydroxamic acid as a white solid. Electro spray Mass Spec 453 (M+H).

Example 268

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-formyl-3-methyl-benzoic acid methyl ester

To a solution of 2.21g (4.89mmole) of the product of Example 265 in 20ml of dioxane:H₂O (3:1) was added 0.3ml of a 2.5 weight % solution of osmium tetroxide in t-butanol and the reaction was stirred until the solution turned dark brown. Then 2.09g (9.78 mmol) of sodium periodate was added portionwise over a period of 20 min. The resulting mixture was stirred for 1.5hr, diluted with ether, washed with water and brine, dried over

MgSO₄, filtered and concentrated in vacuo to provide 1.73g (78%) of the desired product as a white solid after trituration with ether. Electrospray Mass Spec 454 (M+H).

Example 269

**5 4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-methyl-isophthalic acid
3-methyl ester**

To a solution of 317mg (0.7 mmol) of the product of Example 268 and 102mg (1.05 mmol) of sulfamic acid in 40ml of water:THF(3:1) was added 98mg (1.08 mmol) of sodium chlorite. The resulting mixture stirred for 2 hr, diluted with ether, washed with water and brine, dried over MgSO_4 , filtered and concentrated in vacuo to provide 325mg (99%) of the desired carboxylic acid as a white solid. Electrospray Mass Spec 468 (M-H).

Example 270

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-methyl-isophthalic acid
15 In the same manner as described in Example 18, 325mg (0.7 mmol) of the product of example 169 provided 224.3mg (70%) of the desired product as a white solid. Electrospray Mass Spec 454 (M-H).

Example 271

20 **4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N(1),N(3)-dihydroxy-5-methyl-isophthalamide**

In the same manner as described in Example 23, 210mg (0.46 mmol) of the product of Example 270 provided 160mg (72%) of the desired product as a cream solid. Electrospray Mass Spec 486 (M+H).

Example 272

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N(1),N(3)-dihydroxy-5-methyl-isophthalamide di-sodium salt

To a solution of 100mg (0.206 mmol) of the product of Example 271 in 2ml of methanol was added 0.412ml (.412 mmol) of 1N NaOH and the reaction was stirred at room temperature for 2 hr. The reaction mixture was concentrated in vacuo, and the residue was triturated with ether to provide 109mg (100%) of the desired product as a pale yellow solid. Electrospray Mass Spec 486 (M+H).

Example 273

2-(4-Methoxy-benzenesulfonylamino)-3-methyl-5-vinyl-benzoic acid methyl ester

In the same manner as described in Example 139, 700mg (1.69 mmol) of the product of Example 10 and 0.73ml (2.5 mmol) of vinyltributyltin provided 500mg (82%) of the desired product as a white solid. Electrospray Mass Spec 362 (M+H).

Example 274

5-Ethyl-2-(4-methoxy-benzenesulfonylamino)-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 208, 479mg (1.33 mmol) of the product of Example 273 provided 480mg (100%) of the desired product as a white solid. Electrospray Mass Spec 364 (M+H).

Example 275

5-Ethyl-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester

In the same manner as described in Example 81, 455mg (1.25 mmol) of the product of Example 274 provided 544mg (96%) of the desired product as a pale yellow oil. Electrospray Mass Spec 455 (M+H).

Example 276

5-Ethyl-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid

In the same manner as described in Example 218, 496mg (1.09 mmol) of the product of Example 275 provided 345mg (72%) of the desired carboxylic acid as a beige solid. Electrospray Mass Spec 441 (M+H).

Example 277

5-Ethyl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide

In the same manner as described in Example 23, 320mg (0.73 mmol) of the product of Example 276 provided 166mg (50%) of the desired hydroxamic acid. The hydroxamic acid was then dissolved in 4ml of dichloromethane and 0.1ml of methanol and 0.4ml (.4 mmol) of 1M HCl/ether was added. The reaction mixture was stirred for 1 hr and concentrated in vacuo. The residue was triturated with ether to provide 177mg (98%) of the desired product as a cream solid. Electrospray Mass Spec 456 (M+H).

Example 278

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-hydroxymethyl-3-methyl-benzoic acid methyl ester

5 To a mixture of 907mg (2.0 mmol) of the product of Example 268 in 50ml of MeOH:THF (4:1) was added sodium borohydride. The reaction was then stirred at room temperature for 30min and concentrated in vacuo. The residue was dissolved in dichloromethane, washed with 5% HCl and brine, dried over MgSO₄, filtered and concentrated in vacuo to provide 872mg (96%) of the desired product as a white crystalline
10 solid. Electrospray Mass Spec 456 (M+H).

Example 279

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-bromomethyl-3-methyl-benzoic acid methyl ester

15 To a 0°C solution of 1.08g (2.37 mmol) of the product of Example 278 and 983mg (2.96 mmol) of carbon tetrabromide in 24ml of dichloromethane was added 933mg (3.55 mmol) of triphenyl phosphine. The resulting mixture was stirred for 15 min and then concentrated in vacuo. The residue was chromatographed on silica gel using EtOAc:Hexane (1:6) as eluant to provide 1.1g (96%) of the desired product as a white crystalline solid.
20 Electrospray Mass Spec 520 (M+H).

Example 280

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-diethylaminomethyl-3-methyl-benzoic acid methyl ester

25 A solution of 518.4mg (1.0mmole) of the product of Example 279, 0.5ml (4.8 mmol) of diethylamine and 0.172ml (2.0 mmol) of pyridine in 10ml of dichloromethane was stirred at room temperature for 18hr. The resulting mixture washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel with 2% MeOH/CH₂Cl₂ as eluant to provide 425mg (83%).
30 Electrospray Mass Spec 511 (M+H).

Example 281

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-diethylaminomethyl-3-methyl-benzoic acid

35 In the same manner as described in Example 218, 400mg (.78 mmol) of the product of Example 280 provided 324mg (85%) of the desired carboxylic acid as a white solid. Electrospray Mass Spec 497 (M+H).

Example 282

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-diethylaminomethyl-N-hydroxy-3-methyl-benzamide

5 In the same manner as described in Example 219, 324mg (0.65 mmol) of the product of example 281 provided 162mg (45%) of the desired product as a beige solid. Electrospray Mass Spec 512 (M+H).

Example 283

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-pyridin-3-yl-benzoic acid methyl ester

10 In the same manner as described in Example 139, 505mg (1.0 mmol) of the product of Example 89 and 515mg (1.4 mmol) of 3-(tributylstannyl)pyridine provided 437mg (87%) of the desired product as a pale yellow solid. Electrospray Mass Spec 504 (M+H).

Example 284

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-pyridin-3-yl-benzoic acid

15 In the same manner as described in Example 218, 422mg (0.84 mmol) of the product of Example 283 provided 410mg (100%) of the desired carboxylic acid as a cream solid. Electrospray Mass Spec 490 (M+H).

Example 285

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-pyridin-3-yl-benzamide

20 In the same manner as described in Example 219, 420mg (0.85 mmol) of the product of Example 284 provided 160mg (33%) of the desired product as a pinkish solid. Electrospray Mass Spec 505(M+H).

Example 286

2-Amino-3,6-dimethyl-benzoic acid benzyl ester

30 A mixture of 940mg (5.73 mmol) of 2-amino-3,6-dimethylbenzoic acid, 0.750ml (6.3 mmol) of benzyl bromide, 1.04g (7.5mmole) of potassium carbonate and 40mg (0.27mmole) of sodium iodide in 20ml of acetone was heated to reflux for 20hr. The resulting mixture was then concentrated in vacuo and the residue was chromatographed with EtOAc/Hexane (1:50) as eluant to provide 697mg (48%) of the desired product as a yellow oil. Electrospray Mass Spec 256 (M+H).

Example 287

2-(4-Methoxy-benzenesulfonylamino)-3,6-dimethyl-benzoic acidbenzyl ester

5 In the same manner as described in Example 1, 971mg (3.8 mmol) of the product of Example 286 provided 1.415g (87%) of the desired product as a cream solid after trituration with Ether/Hexane(1:1). Electrospray Mass Spec 426 (M+H).

Example 288

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3,6-dimethyl-benzoic acid benzyl ester

10 In the same manner as described in Example 9, 321mg (0.754 mmol) of the product of Example 287 provided 356mg (92%) of the desired product as a white solid after trituration with hexane. Electrospray Mass Spec 516 (M+H).

Example 289

N-Benzyl-N-(2-hydroxymethyl-3,6-dimethyl-phenyl)-4-methoxy-benzenesulfonamide

15 To a slurry of 211mg (5.04 mmol) of lithium aluminum hydride in 6ml of dry THF under nitrogen, was added dropwise a solution of 649mg (1.26 mmol) of the product of Example 288 in 6ml of dry THF. The reaction mixture was stirred for 3 hr and then sodium sulfate pentahydrate was slowly added until sizzling stopped and thick solid formed. The solid was filtered and the filtrate was concentrated in vacuo to provide 454mg (87%) of the desired product as a white solid after trituration with hexane. Electrospray Mass Spec 412 (M+H).

Example 290

N-Benzyl-N-(2-formyl-3,6-dimethyl-phenyl)-4-methoxy-benzenesulfonamide

30 To a solution of 438.7mg of the product of Example 289 in 20ml of acetone was added 5.33ml (10.07 mmol) of Jones reagent and the reaction was stirred at room temperature for 18 hr. The resulting mixture was concentrated in vacuo and the residue was diluted with dichloromethane, washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with hexane to provide 35 396mg (91%) of the desired product as a white solid. Electrospray Mass Spec 410 (M+H).

Example 291

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3,6-dimethyl-benzoic acid

In the same manner as described in Example 269, 378mg (0.92 mmol) of the product of Example 290 provided 260mg (66%) of the desired carboxylic acid as a white solid. Electrospray Mass Spec 426 (M+H).

Example 292

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3,6-dimethyl-benzamide

In the same manner as described in Example 23, 255mg (0.6 mmol) of the product of Example 291 provided 206mg (78%) of the desired product as a white solid. Electrospray Mass Spec 441 (M+H).

Example 293

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3,6-dimethyl-benzoic acid benzyl ester

In the same manner as described in Example 81, 1.415g (3.33 mmol) of the product of example 287 provided 1.02mg (59%) of the desired product as a white solid after trituration with ether. Electrospray Mass Spec 517 (M+H).

Example 294

N-(2-Hydroxymethyl-3,6-dimethyl-phenyl)-4-methoxy-N-pyridin-3-ylmethyl-benzenesulfonamide

In the same manner as described in Example 289, 993mg (1.92 mmol) of the product of Example 293 provided 633mg (80%) of the desired product as a yellow oil. Electrospray Mass Spec 413 (M+H).

Example 295

N-(2-Formyl-3,6-dimethyl-phenyl)-4-methoxy-N-pyridin-3-ylmethyl-benzenesulfonamide

In the same manner as described in Example 290, 633mg (1.54 mmol) of the product of Example 294 provided 438mg (787%) of the desired product as a yellow solid. Electrospray Mass Spec 411 (M+H).

Example 296

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3,6-dimethyl-benzoic acid

In the same manner as described in Example 269, 438mg (1.07 mmol) of the product of Example 295 provided 345mg (76%) of the desired carboxylic acid as an off white solid. Electrospray Mass Spec 425 (M-H).

Example 297

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3,6-dimethyl-benzamide

In the same manner as described in Example 252, 130mg (0.31 mmol) of the product of Example 296 provided 100mg (74%) of the desired hydroxamic acid. A sample of 235mg (0.53 mmol) of this product provided 229mg (90%) of the desired hydroxamic acid hydrochloride as a cream colored solid after trituration with ether. Electrospray Mass Spec 442 (M+H).

Example 298

2-(4-Methoxy-benzenesulfonylamino)-3-methyl-5-[3-(5-methyl-furan-2-yl)-isoxazol-5-yl]-benzoic acid methyl ester

To a solution of 146.6mg (1.1 mmol) of N-chlorosuccinimide and 0.006ml of pyridine in 3.0ml of chloroform under nitrogen was added 348.2mg (1.09 mmol) of 5-methyl-furan-2-carboxaldehyde oxime at room temperature. The reaction mixture was stirred for 30 min and 392mg (1.09 mmol) of 5-ethynyl-2-(4-methoxybenzenesulfonylamino)-3-methyl-benzoic acid methyl ester was added in one portion followed by the dropwise addition of 0.16ml (1.15 mmol) of triethylamine over a period of 1 hr. The resulting mixture was stirred at room temperature for 18 hr, diluted with dichloromethane, washed with water and brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc/Hexane (1:9) as eluant to provide 313mg (60%) of the desired product. as a white solid. Electrospray Mass Spec 483 (M+H).

Example 299

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-[3-(5-methyl-furan-2-yl)-isoxazol-5-yl]-benzoic acid methyl ester

In the same manner as described in Example 81, 305mg (6.3 mmol) of the product of Example 298 provided 240mg (66%) of the desired product as a colorless gum. Electrospray Mass Spec 574 (M+H).

Example 300

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-[3-(5-methyl-furan-2-yl)-isoxazol-5-yl]-benzoic acid

5 In the same manner as described in Example 218, 234mg (0.408 mmol) of the product of Example 299 provided 149mg (65%) of the desired carboxylic acid as a pale yellow solid. Electrospray Mass Spec 560 (M+H).

Example 301

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-[3-(5-methyl-furan-2-yl)-isoxazol-5-yl]-benzamide

10 In the same manner as described in Example 219, 141mg (0.25 mmol) of the product of Example 300 provided 30mg (19%) of the desired product as a brownish solid. Electrospray Mass Spec 575 (M+H).

Example 302

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

20 The product of Example 65 (2.0g, 4.68 mmol) is reacted with ethyl alcohol according to the procedure of Example 73 to give 0.461g (21%) of the p-ethoxybenzene sulfonamide-ester.

The sulfonamide-ester (0.440g, 0.941 mmol) is hydrolyzed according to the procedure of Example 18 to give 0.318g (77%) of the carboxylic acid.

25 The carboxylic acid (0.290g, 0.650 mmol) is converted into its acid chloride followed by reaction with hydroxylamine according to the procedure of Example 23 to give 0.092g (31%) of the hydroxamate. Electrospray Mass Spec: 455.3 (M+H)+.

Example 303

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

30 The product of Example 65 (1.0g, 2.339 mmol) is reacted with n-propanol according to the procedure of Example 73 to give 0.456g (46%) of the para-n-propoxybenzene sulfonamide-ester.

35 The sulfonamide-ester (0.486g, 0.980 mmol) is hydrolyzed according to the procedure of Example 18 to give 0.217g (49%) of the carboxylic acid.

The carboxylic acid (0.190g, 0.419 mmol) is converted into its acid chloride followed by reaction with hydroxylamine according to the procedure of Example 23 to give 0.104g (53%) of the hydroxamate. Electrospray Mass Spec: 469.0 (M+H)+.

5

Example 304

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

The product of Example 65 (2.0g, 4.68 mmol) is reacted with isopropanol according to the procedure of Example 73 to give 0.706g (30%) of the para-n-propoxybenzene sulfonamide-ester.

The sulfonamide-ester (0.400g, 0.827 mmol) is hydrolyzed according to the procedure of Example 18 to give 0.180g (48%) of the carboxylic acid.

The carboxylic acid (0.113g, 0.331 mmol) is converted into its acid chloride followed by reaction with hydroxylamine according to the procedure of Example 23 to give 0.056g (36%) of the hydroxamate. Electrospray Mass Spec: 468.9 (M+H)+.

Example 305

5-Bromo-2-(4-fluoro-benzenesulfonylamino)-3-methyl-benzoic acid

By following the procedure of Example 134 the product of Example 133 and 4-fluorobenzenesulfonyl chloride provides 5-bromo-2-(4-fluoro-benzenesulfonylamino)-3-methyl-benzoic acid as a yellow solid in 36% yield. Electrospray Mass Spec: 386.0 (M-H)-

Example 306

2-[Benzyl-(4-fluoro-benzenesulfonyl)-amino]-5-bromo-3-methyl-benzoic acid benzyl ester

To a solution of 0.25g (0.687 mmol) of the product of Example 305 in 5.0mL of DMF was added 0.23mL (1.923 mmol) of benzyl bromide and 0.06g (1.511 mmol) of 60% sodium hydride. The reaction mixture was stirred for 18h at room temperature and then diluted with ether, washed with water, dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue was chromatographed on silica gel eluting with EtOAc/Hexanes (1:10) to provide 0.324g (82%) of the product as a colorless oil. Electrospray Mass Spec: 568.1 (M+H)+.

Example 307

2-[Benzyl-(4-benzyloxy-benzenesulfonyl)-amino]-5-bromo-3-methyl-benzoic acid

By following the procedure of Example 73, 0.284g (0.493 mmol) of the product of Example 306 gives 0.185g (66%) of the desired product as a white solid. Electrospray Mass Spec: 565.9 (M-H)-.

Example 308

2-[Benzyl-(4-benzyloxy-benzenesulfonyl)-amino]-5-bromo-N-hydroxy-3-methyl-benzamide

By following the procedure of Example 23, 0.168g (0.297 mmol) of the product of Example 307 gives 0.131g (76%) of the desired product as a white solid. Electrospray Mass Spec: 581.0 (M+H)+.

Example 309

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-morpholin-4-ylmethyl-benzamide

Following the procedure of Example 189, the product of Example 188 (0.50g, 1.168 mmol) and morpholine gives 0.325g (64%) of the benzylic amine-ester.

Following the procedure of Example 190, 0.291g (0.670 mmol) of the ester is then hydrolyzed to give 0.286g (100%) of the carboxylic acid.

Following the procedure of Example 23, 0.229g (0.536 mmol) of the carboxylic acid gives 0.186g of the hydroxamic acid as a white solid. The hydroxamate is dissolved in 4mL of dichloromethane and 0.2mL of methanol and 0.85mL of 1.0M HCl in ether is added. The reaction is stirred at room temperature for 1h, diluted with ether and the resulting solid is collected by filtration and dried in vacuo to give 0.139g of the hydroxamate-amine salt as a white solid. Electrospray Mass Spec: 435.9 (M+H)+.

Example 310

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-pyrrolidin-1-ylmethyl-benzamide

Following the procedure of Example 189, the product of Example 188 (0.50g, 1.168 mmol) and pyrrolidine gives 0.327g (69%) of the benzylic amine-ester.

Following the procedure of Example 190, 0.307g (0.734 mmol) of the ester is then hydrolyzed to give 0.302g (100%) of the carboxylic acid.

Following the procedure of Example 309, 0.251g (0.610 mmol) of the carboxylic acid gives 0.127g of the hydroxamic acid-amine salt as a white solid. Electrospray Mass Spec: 419.9 (M+H)+.

5

Example 311

N-Hydroxy-3-imidazol-1-ylmethyl-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-benzamide

Following the procedure of Example 189, the product of Example 188 (0.75g, 1.752 mmol) and imidazole gives 0.441g (61%) of the benzylic amine-ester.

10

Following the procedure of Example 190, 0.435g (1.048 mmol) of the ester is then hydrolyzed to give 0.308g (72%) of the carboxylic acid.

Following the procedure of Example 309, 0.261g (0.640 mmol) of the carboxylic acid gives 0.154g of the hydroxamic acid-amine salt as a white solid. Electrospray Mass Spec: 416.9 (M+H)+.

15

Example 312

5-Bromo-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-(4-methyl-piperazin-1-ylmethyl)-benzoic acid methyl ester

To a solution of 3.0g (7.01 mmol) of the product of Example 202 in 170mL of carbon tetrachloride was added 1.56g (8.76 mmol) of N-bromosuccinimide and the mixture was heated to reflux while irradiated by a sunlamp for 3h. The resulting mixture was cooled, washed with water, dried over MgSO₄, filtered and concentrated in vacuo.

To a solution of 0.477g (0.941 mmol) of the resulting benzylic bromide in 5.0mL of DMF was added 0.115mL (1.035 mmol) of N-methylpiperazine and 0.389g (2.822 mmol) of potassium carbonate. The reaction mixture was then stirred overnight at room temperature and then diluted with ether, washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting residue was chromatographed on silica gel eluting with chloroform/methanol (9:1) to provide 0.29g (59%) of the product as a brown oil. Electrospray Mass Spec: 526.1 (M+H)+.

30

Example 313

5-Bromo-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-(4-methyl-piperazin-1-ylmethyl)-benzamide

Following the procedure of Example 190, 0.25g (0.475 mmol) of the product of Example 312 gives 0.475g (100%) of the desired carboxylate salt as a white solid.

35

Following the procedure of Example 309 the carboxylate is converted into the corresponding hydroxamic acid-amine salt, isolated as a white solid. Electrospray Mass Spec: 527.1 (M+H)+.

Example 314

5-Bromo-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methylamino]-3-pyrrolidin-1-ylmethyl-benzamide

Following the procedure of Example 312, the product of Example 202 and pyrrolidine gives the benzylic amine-ester.

Following the procedure of Example 190 the ester is hydrolyzed to the corresponding carboxylate.

Following the procedure of Example 309 the carboxylate is converted into the corresponding hydroxamic acid-amine salt, isolated as a tan solid. Electrospray Mass Spec: 498.0 (M+H)+.

Example 315

2-[(4-Methoxy-benzenesulfonyl)-(tert-butoxycarbonyl)-amino]-3-methyl-benzoic acid methyl ester

To a solution of 2.5g (7.463 mmol) of the product of Example 3 in 10mL of DMF and 6.0mL of pyridine was added 1.95g (8.955 mmol) of di-t-butyl dicarbonate and 0.228g (1.866 mmol) of 4-dimethylaminopyridine. The resulting mixture was stirred overnight at room temperature and then diluted with ether, washed with 5%HCl solution, water and 1N sodium hydroxide solution. The organics were then dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with ether/hexanes (1:1) to give 3.2g (98%) of the product as a white solid. Electrospray Mass Spec: 436.0 (M+H)+.

Example 316

2-[(4-Methoxy-benzenesulfonyl)-(tert-butoxycarbonyl)-amino]-

3-(pyrrolidin-1-ylmethyl)-benzoic acid methyl ester

To a solution of 3.05 (7.011 mmol) of the product of Example 315 in 165mL of carbon tetrachloride was added 1.498g (8.414 mmol) of N-bromosuccinimide and the mixture was heated to reflux while irradiated by a sunlamp for 3h. The resulting mixture was cooled, washed with water, dried over MgSO₄, filtered and concentrated in vacuo.

To a solution of the resulting benzylic bromide in 30.0mL of DMF was added 0.644mL (7.71 mmol) of pyrrolidine and 2.90g of potassium carbonate. The reaction mixture was then stirred overnight at room temperature and then diluted with ether, washed

with water, dried over Na_2SO_4 , filtered and concentrated in vacuo. The resulting residue was chromatographed on silica gel eluting with chloroform/methanol (9:1) to provide 2.076g (59%) of the product as a white solid. Electrospray Mass Spec: 505.2 (M+H)+.

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Example 317

2-(4-Methoxy-benzenesulfonylamino)-3-pyrrolidin-1-ylmethyl-benzoic acid methyl ester

To a solution of the product of example 316 in 10mL of dichloromethane was added 10.0mL of trifluoroacetic acid. The resulting solution was stirred at room temperature for 1h and then concentrated in vacuo. The resulting residue was diluted with ether washed with saturated sodium bicarbonate solution, dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was then triturated with ether to provide 0.93g (57%) of the product as a pale yellow solid. Electrospray Mass Spec: 405.1 (M+H)+.

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Example 318

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-pyrrolidin-1-ylmethyl-benzoic acid methyl ester

By following the procedure of Example 45, 0.80g (1.98 mmol) of the product of Example 317 gives 0.804g (82%) of the product as a brown solid. Electrospray Mass Spec: 496.5 (M+H)+.

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Example 319

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-pyrrolidin-1-ylmethyl-benzoic acid

25

To a solution of 0.754g (1.523 mmol) of the product of Example 318 in 15mL of THF/Methanol (1:1) was added 7.6mL of 1.0N sodium hydroxide solution. The resulting mixture was heated to reflux for 15h and then concentrated in vacuo. The residue was diluted with water, neutralized with 5%HCl solution and extracted with dichloromethane. The organics were dried over Na_2SO_4 , filtered and concentrated in vacuo to provide 0.496g (67%) of the product as a tan solid. Electrospray Mass Spec: 482.5 (M+H)+.

30

Example 320

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-pyrrolidin-1-ylmethyl-benzamide

35

By following the procedure of Example 61 the product of Example 319 gives 0.174g of the hydroxamic acid as a tan solid. Electrospray Mass Spec: 497.5 (M+H)+.

Example 321

3-Formyl-2-(4-methoxy-benzenesulfonylamino)-benzoic acid methyl ester

5 To a solution of 1.0g (2.985 mmol) of the product of Example 3 in 100mL of carbon tetrachloride was added 0.20g of dibenzoyl peroxide and 1.168g (6.568 mmol) of N-bromosuccinimide. The resulting mixture was refluxed for 18h, cooled, washed with sodium bisulfite solution and water, dried over MgSO₄, filtered and concentrated in vacuo. The residue was diluted with 10mL of THF and 10mL of 1N sodium hydroxide solution
10 and the mixture was stirred at room temperature for 3h. The reaction mixture was then acidified with 5%HCl and extracted with ether. The organics were dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with ether to provide 0.477g (47%) of the product as a white solid. Electrospray Mass Spec: 350.1 (M+H)+.

Example 322

3-Formyl-2-[(4-methoxy-benzenesulfonyl)-octyl-amino]-benzoic acid methyl ester

To a solution of 1.0g (2.865 mmol) of the product of Example 321 in 7.5mL of DMF was added 0.143g (3.582 mmol) of 60% sodium hydride followed by 0.74mL (4.30
20 mmol) of n-octyl bromide. The reaction was stirred overnight at room temperature then diluted with ether, washed with water, dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue was chromatographed on silica gel eluting with EtOAc/hexanes (1:3) to provide 0.592g (49%) of the product as a white solid. Electrospray Mass Spec: 462.1 (M+H)+.

Example 323

3-Hydroxymethyl-2-[(4-methoxy-benzenesulfonyl)-octyl-amino]-benzoic acid methyl ester

To a solution of 0.547g (1.187 mmol) of the product of Example 322 in 10mL of methanol and 3mL of THF was added 0.045g (1.187 mmol) of sodium borohydride. The
30 reaction was stirred for 2h at room temperature and then concentrated in vacuo. The residue was diluted with ether and washed with 5%HCl and water, dried over MgSO₄, filtered and concentrated in vacuo to provide 0.549g (100%) as a colorless oil. Electrospray Mass Spec: 464.2 (M+H)+.

Example 324

2-[(4-Methoxy-benzenesulfonyl)-octyl-amino]-3-(4-methyl-piperazin-1-ylmethyl)-benzoic acid methyl ester

To a solution of 0.515g (1.112 mmol) of the product of Example 323 in dichloromethane was added 0.438g (1.668 mmol) of triphenylphosphine and 0.461g (1.390 mmol) of carbon tetrabromide. The mixture was stirred for 1h at room temperature and then concentrated in vacuo. The residue was filtered through a pad of silica gel eluting with EtOAc/hexanes (1:10) to provide the benzylic bromide.

To a solution of the bromide in 6.0mL of DMF was added 0.136mL (1.224 mmol) of N-methylpiperazine and 0.491g (3.559 mmol) of potassium carbonate. The resulting mixture was stirred at room temperature overnight, diluted with ether, washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo to provide 0.57g (94%) of the benzylic amine-ester as a white solid. Electrospray Mass Spec: 546.2 (M+H)+.

Example 325

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-octyl-amino]-3-(4-methyl-piperazin-1-ylmethyl)-benzamide

Following the procedure of Example 18, 0.507g (0.930 mmol) of the product of Example 324 is converted into the corresponding carboxylate.

Following the procedure of Example 61 the carboxylate gives 0.343g of the hydroxamic acid as a brown solid. Electrospray Mass Spec: 547.7 (M+H)+.

Example 326

3-Formyl-2-[(4-methoxy-benzenesulfonyl)-thiophen-3-ylmethyl-amino]-benzoic acid methyl ester

Following the procedure of Example 322, 1.0g (2.865 mmol) of the product of Example 321 is reacted with 3-bromomethyl thiophene to give 1.10g (86%) of the product as a white solid after chromatography on silica gel eluting with EtOAc/Hexanes (1:3). Electrospray Mass Spec: 446.1 (M+H)+.

Example 327

2-[(4-Methoxy-benzenesulfonyl)-thiophen-3-ylmethyl-amino]-3-(4-methyl-piperazin-1-ylmethyl)-benzoic acid

Following the procedure of Example 323, 1.06g (2.387 mmol) of the product of Example 326 is converted into the corresponding alcohol.

Following the procedure of Example 324 the alcohol is converted into the corresponding benzylic amine-ester.

Following the procedure of Example 319 then gives 0.52g of the carboxylic acid as a white solid. Electrospray Mass Spec: 516.2 (M+H)+.

Example 328

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-thiophen-3-ylmethyl-amino]-3-(4-methyl-piperazin-1-ylmethyl)-benzamide

To a solution of 0.475g (0.922 mmol) of the product of Example 327 in 8.0mL of DMF was added 0.149g (1.107 mmol) of HOBt and 0.235g (1.227 mmol) of EDC. The reaction was then stirred for 1h at room temperature and 0.28mL (4.612 mmol) of a 50% solution of hydroxylamine in water was added. The reaction was stirred overnight and then concentrated in vacuo. The residue was diluted with EtOAc, washed with water and sodium bicarbonate solution, dried over Na₂SO₄, filtered and concentrated in. The residue was dissolved in 5.0mL of dichloromethane and 1.8mL of a 1N solution of HCl in ether was added. After 1h the reaction was diluted with ether and the resulting solid was filtered and dried in vacuo to give 0.242g of the product as a white solid. Electrospray Mass Spec: 531.5 (M+H)+.

Example 329

N-Hydroxy-2-[[[(4-methoxyphenyl)sulfonyl](phenylmethyl)-amino]-3-[(4-methyl-1-piperazinyl)methyl]benzamide

Following the procedure of Example 322, 1.25g (3.582 mmol) of the product of Example 321 reacts with benzyl bromide to give the N-benzyl sulfonamide.

Following the procedures of Examples 327, and 328, the sulfonamide gives 0.204g of the hydroxamic acid as a white solid. Electrospray Mass Spec: 525.4 (M+H)+.

Example 330

2-(4-Methoxy-benzenesulfonylamino)-3-methyl-benzoic acid tert-butylester

To a solution of 15.0g (0.047 mol) of the product of Example 6 in 45mL of toluene was added 50mL of N,N-dimethylformamide di-t-butyl acetal and the mixture was then heated to reflux for 18h. The reaction was then cooled to room temperature and chromatographed on silica gel eluting with EtOAc/Hexanes (1:3) to give 8.94g (51%) of the product as a white solid. Electrospray Mass Spec: 378.1 (M+H)+.

Example 331

2-[(4-Methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid tert-butyl ester

Following the procedure of Example 187 2.5g (6.631 mmol) of the product of Example 330 gives 2.59g (100%) of the N-methyl sulfonamide as a white foam.
Electrospray Mass Spec: 392.4 (M+H)+.

Example 332

(2S)-1-{3-tert-Butoxycarbonyl-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-benzyl}-pyrrolidine-2-carboxylic acid methyl ester

Following the procedure of Example 316, using L-proline methyl ester hydrochloride instead of pyrrolidine, 2.30g (5.882 mmol) of the product of Example 331 gives 1.45g (48%) of the diester as a white solid. Electrospray Mass Spec: 519.5 (M+H)+.

Example 333

(2S)-1-{3-Carboxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-benzyl}-pyrrolidine-2-carboxylic acid methyl ester

To a solution of 1.39g (2.678 mmol) of the product of Example 332 in 5.0mL of dichloromethane was added 5.0mL of trifluoroacetic acid. The reaction was stirred at room temperature for 2h and then concentrated in vacuo. The residue was chromatographed on silica gel eluting with chloroform/methanol (9:1) to give 1.24g (100%) of the carboxylic acid as a white foam. Electrospray Mass Spec: 463.0 (M+H)+.

Example 334

(2S)-1-{3-Hydroxycarbamoyl-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-benzyl}-pyrrolidine-2-carboxylic acid methyl ester

Following the procedure of Example 61 1.305g (2.262 mmol) of the product of Example 333 gives 0.285g of the hydroxamic acid as a tan solid. Electrospray Mass Spec: 478.1 (M+H)+.

Example 335

3-Formyl-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-benzoic acid methyl ester

To a solution of 0.20g (0.573 mmol) of the product of Example 321 in 2.5mL of DMF was added 0.099g (0.602 mmol) of 3-picoyl chloride hydrochloride and 0.249g (1.805 mmol) of potassium carbonate. The reaction was stirred for 18h at room temperature and then the reaction was then diluted with water and extracted with ether. The combined

organics were washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was triturated with ether to give 0.158g (63%) of the product as tan crystals. Electrospray Mass Spec: 440.9 (M+H)+.

5

Example 336

3-Hydroxymethyl-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-benzoic acid methyl ester

To a solution of 0.10g (0.227 mmol) of the product of Example 335 in 5mL of methanol and 2.0mL of THF was added 8.6mg of sodium borohydride. The reaction was stirred for 1h at room temperature and then concentrated in vacuo. The residue was diluted with dichloromethane, washed with water, and the organics were then dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting tan solid was washed with ether and dried in vacuo to give 0.086g (86%) of the alcohol. Electrospray Mass Spec: 442.9 (M+H)+.

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Example 337

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-(tetrahydropyran-2-yloxymethyl)-benzoic acid methyl ester

To a solution of 0.500g of the product of Example 336 in 15mL of dichloromethane was added 0.21mL (2.262 mmol) of dihydropyran and 0.030g of toluenesulfonic acid monohydrate. The reaction was stirred at room temperature for 24h and then diluted with dichloromethane. The organics were washed with 1N sodium hydroxide solution and water, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc to give 0.436g (73%) of the THP-ether as a brown foam. Electrospray Mass Spec: 527.2 (M+H)+.

25

Example 338

2-[[[(4-Methoxyphenyl)sulfonyl](3-pyridinylmethyl)amino]-3-[[[(tetrahydro-2H-pyran-2-yl)oxy]methyl]benzoic acid

Following the procedure of Example 190 0.376g (0.715 mmol) of the product of Example 337 gives 0.370g (100%) of the carboxylate salt as a brown foam. Electrospray Mass Spec: 511.1 (M-H)-.

30

Example 339

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-(tetrahydro-pyran-2-yloxymethyl)-benzamide

To a solution of 0.851g (1.662 mmol) of the product of Example 338 in 10.0mL of DMF was added 0.269g (1.995 mmol) of HOBT (1-hydroxybenzotriazole) and 0.424g (2.211 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC). The reaction was then stirred for 1h at room temperature and 0.578g (8.311 mmol) of hydroxylamine hydrochloride and 1.73mL of triethylamine was added. The reaction was stirred overnight and then concentrated in vacuo. The residue was diluted with ether, washed with water and sodium bicarbonate solution, dried over Na₂SO₄, filtered and concentrated in vacuo to provide 0.635g (72%) of the hydroxamic acid as a tan foam. Electrospray Mass Spec: 528.1 (M+H)+.

Example 340

N-Hydroxy-3-hydroxymethyl-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-benzamide

To a solution of 0.352g (0.668 mmol) of the product of Example 339 in 6.5mL of dichloromethane and 1.3mL of methanol was added 1.3mL of a 1M solution of HCl in ether. The reaction was stirred at room temperature for 5h and the resulting precipitate was collected by filtration, washed with ether and dried in vacuo to give 0.320g (100%) of the alcohol as a white solid. Electrospray Mass Spec: 444.2 (M+H)+.

Example 341

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-(2-hydroxy-ethoxy)-benzoic acid methyl ester

To a solution of 2.53g (4.677 mmol) of the product of Example 38 in 20mL of dichloromethane was added 5.0mL of trifluoroacetic acid. The reaction was stirred at room temperature for 3h and then concentrated in vacuo. The residue was triturated with Ether/Hexanes (1:1) and the resulting white solid (2.063g) was collected by filtration and dried in vacuo.

The carboxylic acid was then dissolved in 40mL of dry THF cooled to 0° and 19.6mL of a 1M solution of Borane/THF was added. The reaction was allowed to warm to room temperature and stirred for 18h. The reaction was quenched with 10mL of acetic acid-water (1:1), diluted with water and extracted with ether. The organics were dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/Hexanes (1:1) to provide 1.845g of the alcohol as a white solid. Electrospray Mass Spec: 472.2 (M+H)+.

Example 342

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-(2-hydroxy-ethoxy)-benzoic acid

5 To a solution of the product of 1.459g (3.098 mmol) of Example 341 in 30mL of THF/Methanol (1:1) was added 15.5mL of 1N sodium hydroxide solution and the reaction mixture was then heated to reflux overnight. The reaction was then cooled to room temperature, acidified with 5% HCl solution and extracted with ether. The combined organics were dried over MgSO₄, filtered and concentrated in vacuo. The residue was
10 chromatographed on silica gel eluting with EtOAc/hexanes (2:1) to provide 1.22g of the carboxy-alcohol as a white solid. Electrospray Mass Spec: 456.1 (M-H)-.

Example 343

15 **2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-benzoic acid**

To a solution of 1.22g (2.67 mmol) of the product of Example 342 in 6.0ml of DMF was added 0.966g (6.407 mmol) of t-butyldimethylsilyl chloride and 0.908g (0.013 mol) of imidazole. The reaction was stirred for 5h at room temperature and then diluted
20 with water and 1N sodium hydroxide solution and stirred for an additional hour. The reaction was then acidified to pH5 and extracted with ether. The organics were dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/hexanes (1:3) to provide 1.34g (88%) of the carboxylic acid as a white solid. Electrospray Mass Spec: 570.0 (M+H)+.

25

Example 344

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-N-hydroxy-benzamide

Following the procedure of Example 328, 1.107g (1.939 mmol) of the product of
30 Example 343 gives 1.0g (88%) of the hydroxamic acid as a white foam. Electrospray Mass Spec: 587.6 (M+H)+.

Example 345

35 **2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-(2-hydroxy-ethoxy)-benzamide**

To a solution of 0.957g (1.633 mmol) of the product of Example 344 in 20mL of acetonitrile was added 1.5mL of 48% hydrofluoric acid. The reaction was stirred at room

Example 349

5-Bromo-N-hydroxy-3-[2-(hydroxycarbamoyl)-ethyl]-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-benzamide

5 Following the procedure of Example 23 0.304g (0.644 mmol) of the product of Example 348 gives 0.114g (35%) of the bis-hydroxamic acid as a white solid. Electrospray Mass Spec: 504.0 (M+H)+.

Example 350

N-Hydroxy-3-[2-(hydroxycarbamoyl)-ethyl]-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-benzamide

10 Following the procedures of Examples 346 to 349 the product of Example 188 gives the bis-hydroxamic acid as a white foam. Electrospray Mass Spec: 424.2 (M+H)+.

Example 351

5-Biphenyl-4-ylethynyl-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid methyl ester

15 To a solution of 1.0g (2.336 mmol) of the product of Example 202 in 7.5mL of DMF was added 0.50g (2.804 mmol) of ethynyl biphenyl, 0.033g (0.047 mmol) of bis triphenylphosphine palladium(II) dichloride 4.4mg of copper(I) iodide and 7.5mL of triethylamine. The reaction was heated to 80° for 5h and then diluted with ether. the organics were washed with water, 5% HCl solution and sodium bicarbonate solution, dried over MgSO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/hexanes (1:3) to provide 0.777g (63%) of the alkyne as a brown foam. Electrospray Mass Spec: 526.2 (M+H)+.

20

25

Example 352

5-Biphenyl-4-ylethynyl-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid

30 Following the procedure of Example 18, 0.400g (0.762 mmol) of the product of Example 351 gives 0.383g (98%) of the carboxylic acid as a brown foam. Electrospray Mass Spec: 510.1 (M-H)-.

Example 353

5-Biphenyl-4-ylethynyl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzamide

Following the procedure of Example 23, 0.132g (0.258 mmol) of the product of Example 352 gives 0.107g (79%) of the hydroxamic acid as a yellow solid. Electrospray Mass Spec: 527.1 (M+H)+.

Example 354

5-(2-Biphenyl-4-yl-ethyl)-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid

To a solution of 0.20g (0.391 mmol) of the product of Example 352 in 25mL of methanol and 10mL of ethyl acetate was added 0.050g of 10% palladium on carbon. The mixture was hydrogenated in a Parr apparatus at 30psi of hydrogen for 5h, then filtered through Celite. The Celite pad was washed with 100mL of methanol and 100mL of ethyl acetate and the filtrate was concentrated in vacuo. The residue was triturated with ether to give 0.173g (86%) of the carboxylic acid as a pale yellow solid. Electrospray Mass Spec: 514.2 (M-H)-.

Example 355

5-(2-Biphenyl-4-yl-ethyl)-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzamide

Following the procedure of Example 23, 0.138g (0.268 mmol) of the product of Example 354 gives 0.091g (64%) of the hydroxamic acid as a yellow solid. Electrospray Mass Spec: 531.1 (M+H)+.

Example 356

5-Dodec-1-ynyl-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid methyl ester

Following the procedure of Example 351, using 1-dodecyne instead of ethynyl biphenyl, 1.0g (2.336 mmol) of the product of Example 202 gives 0.874g (73%) of the alkyne as a brown oil. Electrospray Mass Spec: 514.4 (M+H)+.

Example 357

5-Dodec-1-ynyl-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid

Following the procedure of Example 18, 0.808g (1.575 mmol) of the product of
5 Example 356 gives 0.731g (93%) of the carboxylic acid as a pale yellow oil. . Electrospray
Mass Spec: 498.2 (M-H)-.

Example 358

5-Dodec-1-ynyl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzamide

Following the procedure of Example 23, 0.200g (0.401 mmol) of the
product of Example 357 gives 0.170g (83%) of the hydroxamic acid as a colorless oil.
Electrospray Mass Spec: 515.2 (M+H)+.

15 Example 359

5-Dodecyl-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzoic acid

Following the procedure of Example 354, 0.217g (0.435 mmol) of the product of
Example 357 gives 0.214g (98%) of the carboxylic acid as a pale white solid . Electrospray
20 Mass Spec: 502.3 (M-H)-.

Example 360

5-Dodecyl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzamide

Following the procedure of Example 23, 0.189g (0.376 mmol) of the
product of Example 359 gives 0.153g (79%) of the hydroxamic acid as a brown oil.
Electrospray Mass Spec: 519.2 (M+H)+.

Example 361

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methoxymethyl-benzoic acid methyl ester

To a solution of 0.200g (0.452 mmol) of the product of Example 336 in 5.0mL of
dry THF was added 0.022g (0.543 mmol) of 60% sodium hydride followed by 0.028mL
of iodomethane. The reaction was stirred at room temperature for 18h and then diluted with
ethyl acetate. The organics were washed with water and brine, dried over Na₂SO₄, filtered
35 and concentrated in vacuo. The residue was chromatographed on silica gel eluting with

EtOAc to provide 0.057g (28%) of the methyl ether as a yellow solid. Electrospray Mass Spec: 457.3 (M+H)+.

Example 362

5 **2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-**

Following the procedure of Example 53, 0.275g (0.603 mmol) of the product of Example 361 gives 0.267g (100%) of the carboxylate salt as a yellow foam. Electrospray Mass Spec: 443.1 (M+H)+.

10 Example 363

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methoxymethyl-benzamide

Following the procedure of Example 328, 0.260g (0.588 mmol) of the product of Example 362 gives 0.151g of the hydroxamic acid as a tan solid. Electrospray Mass Spec:
15 456.3 (M-H)-.

Example 364

3-Formyl-2-(4-methoxy-benzenesulfonylamino)-benzoic acid tert-butyl ester

20 Following the procedure of Example 321, 1.90g (5.04 mmol) of the product of Example 330 gives 1.19g (60%) of the aldehyde as a pale yellow solid. Electrospray Mass Spec: 392.2 (M+H)+.

Example 365

25 **3-Formyl-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethylamino]-benzoic acid tert-butyl ester**

Following the procedure of Example 335, 1.106g (2.829 mmol) of the product of Example 364 gives 1.282 (94%) of the N-picolyl sulfonamide as a brown oil. Electrospray Mass Spec: 483.4 (M+H)+.

30

Example 366

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-isophthalic acid mono-tert-butyl ester

35 To a solution of 0.417g (0.865 mmol) of the product of Example 365 in 40mL of water and 25mL of THF was added 0.126g (1.298 mmol) of sulfamic acid and 0.122g (1.341 mmol) of sodium chlorite. The reaction was stirred overnight at room temperature and then concentrated in vacuo. The residue was diluted with water and extracted with

chloroform. The organics were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was triturated with ether to give 0.080g (77%) of the carboxylic acid as a pale yellow solid. Electrospray Mass Spec: 499.4 (M+H)+.

5

Example 367

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-isophthalamic acid tert-butyl ester

Following the procedure of Example 328, 0.354g (0.711 mmol) of the product of Example 366 gives 0.063g (17%) of the hydroxamic acid as a brown foam. Electrospray
10 Mass Spec: 514.3 (M+H)+.

Example 368

2-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-isophthalic acid monomethyl ester

15 Following the procedure of Example 366, 0.10g (0.227 mmol) of the product of Example 335 gives 0.080g (77%) of the carboxylic acid as a white solid. Electrospray Mass Spec: 457.3 (M+H)+.

20

Example 369

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-isophthalamic acid methyl ester

Following the procedure of Example 23, 0.600g (1.316 mmol) of the product of Example 368 gives 0.48g (77%) of the hydroxamic acid. The hydroxamate was dissolved
25 in 10.0mL of dichloromethane and 0.5mL of methanol and 2.0mL of a 1N solution of HCl in ether was added. After 1h the resulting solid was filtered and dried in vacuo to give 0.358g of the product as a tan solid. Electrospray Mass Spec: 472.2 (M+H)+.

30

Example 370

3-Acetoxymethyl-5-bromo-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-benzoic acid methyl ester

To a solution of 1.00g (2.336 mmol) of the product of Example 202 in 50mL of carbon tetrachloride was added 0.457g (2.57 mmol) of N-bromosuccinimide the reaction was heated to reflux under a sunlamp for 1h, cooled and washed with water. The organics
35 were dried over MgSO₄, filtered and concentrated in vacuo. The residue was dissolved in 15mL of DMF and 0.958g (0.012 mmol) of sodium acetate was added. The reaction was heated to 80° for 4h, cooled to room temperature and diluted with ether. The organics were

washed with water, dried over MgSO_4 , filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/hexanes (1:3) to provide 0.408g (36%) of the acetate as a colorless oil. Electrospray Mass Spec: 487.8 (M+H)+.

5

Example 371

5-Bromo-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-isophthalic acid monomethyl ester

To a solution of 0.272g (0.826 mmol) of the product of Example 370 in 2.0mL of THF/MeOH (1:1) was added 0.87mL of 1N sodium hydroxide solution and the reaction was stirred for 3h at room temperature. The reaction was then extracted with ether. The combined organics were dried over MgSO_4 , filtered and concentrated in vacuo. The residue was triturated with ether to give 0.241g of the alcohol as a white solid.

The alcohol was then dissolved in 1.5mL of DMF and 0.366g (0.973 mmol) of pyridinium dichromate was added and the reaction was stirred overnight. The reaction mixture was then diluted with ether, washed with water, dried over MgSO_4 , filtered and concentrated in vacuo. The residue was dissolved in 17mL of THF and 28mL of water and 0.091g (1.005 mmol) of sodium chlorite and 0.094g (0.973 mmol) of sulfamic acid was added. The reaction was stirred overnight at room temperature, concentrated in vacuo, diluted with water and extracted with chloroform. The organics were dried over MgSO_4 , filtered and concentrated in vacuo. The residue was triturated with ether to give 0.282g of the carboxylic acid as a white solid. Electrospray Mass Spec: 456.0 (M-H)-.

Example 372

2-[(4-Methoxy-benzenesulfonyl)-methyl-amino]-isophthalic acid monomethyl ester

Following the procedure of Example 370, 0.50g (1.168 mmol) of the product of Example 188 gives 0.314g (66%) of the acetate. Following the procedure of Example 371 0.287g (0.705 mmol) of the acetate gives 0.152g of the carboxylic acid as a white solid. Electrospray Mass Spec: 377.9 (M-H)-.

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Example 373

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-isophthalamic acid methyl ester

Following the procedure of Example 23, 0.126g (0.332 mmol) of the product of Example 372 gives 0.116g (89%) of the hydroxamic acid as a white solid. Electrospray Mass Spec: 394.8 (M+H)+.

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Example 374

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-isophthalamic acid

To a solution of 0.235g (0.458 mmol) of the product of Example 367 dissolved in 5mL of dichloromethane was added 2mL of trifluoroacetic acid. The reaction was stirred at room temperature for 2h and then concentrated in vacuo. The residue was triturated with ether and the resulting solid was collected by filtration and dried in vacuo to give 0.178 (65%) of the hydroxamic acid as a tan solid. Electrospray Mass Spec: 456.4 (M-H)-.

Example 375

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-2-ylmethyl-amino]-3-methyl-benzamide

Following the procedure of Example 45, 0.750g (2.239 mmol) of the product of Example 3 was alkylated with 2-picolyl chloride hydrochloride to give 0.916g (96%) of the N-picolyl sulfonamide.

Following the procedure of Example 53 the ester was then hydrolyzed to provide the corresponding carboxylic acid.

Following the procedure of Example 369 the acid was converted into the hydroxamic acid to give 0.180g of the pyridinium salt as a brown foam. Electrospray Mass Spec: 428.1 (M+H)+.

Example 376

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-4-ylmethyl-amino]-3-methyl-benzamide

Following the procedure of Example 45, 0.750g (2.239 mmol) of the product of Example 3 was alkylated with 4-picolyl chloride hydrochloride to give 0.897g (94%) of the N-picolyl sulfonamide.

Following the procedure of Example 53 the ester was then hydrolyzed to provide the corresponding carboxylic acid.

Following the procedure of Example 369 the acid was converted into the hydroxamic acid to give 0.180g of the pyridinium salt as a brown foam. Electrospray Mass Spec: 428.2 (M+H)+.

Example 377

2-[(4-Diethylaminomethyl-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methyl-benzamide

Following the procedure of Example 9, 1.50g (4.478 mmol) of the product of Example 3 was alkylated with 4-carboethoxybenzyl bromide to give 2.00g (93%) of the benzylated sulfonamide as a tan solid. Electrospray Mass Spec: 484.2 (M+H)+.

This ester was dissolved in 9.0mL of MeOH/THF (1:1) and 4.3mL of 1.0N sodium hydroxide solution was added. The reaction was stirred for 3h at room temperature, acidified with 5% HCl solution and extracted with ethyl acetate. The combined organics were dried over MgSO₄, filtered and concentrated in vacuo to give the carboxylic acid as a white solid which was washed with ether and dried. Electrospray Mass Spec: 468.5 (M-H)-.

The acid was then reduced with borane-THF as in Example 341, to provide the alcohol as a white solid. Electrospray Mass Spec: 456.2 (M+H)+.

The alcohol was converted into the corresponding diethylamine, according to the procedure in Example 324, isolated as a white solid. Electrospray Mass Spec: 511.5 (M+H)+.

Hydrolysis of the benzoate ester according to the procedure of Example 319, followed by conversion to the hydroxamic acid and salt formation according to the procedure of Example 369 gives 0.105g of the hydroxamate as a white solid. Electrospray Mass Spec: 512.1 (M+H)+.

Example 378

2-[(4-Dimethylaminomethyl-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methyl-benzamide

Following the procedures of Example 377, 1.50g (4.478 mmol) of the product of Example 3 was converted into the dimethylamine-hydroxamate, isolated as a white foam. Electrospray Mass Spec: 483.9 (M+H)+.

Example 379

2-[(4-Methoxy-benzenesulfonyl)-prop-2-ynyl-amino]-3-methyl-benzoic acid methyl ester

Following the procedure of Example 9, 1.50g (4.478 mmol) of the product of Example 3 was alkylated with propargyl bromide to give 1.33g (79%) of the propargyl sulfonamide as a white solid. Electrospray Mass Spec: 374.3 (M+H)+.

Example 380

2-[(4-Diethylamino-but-2-ynyl)-(4-methoxy-benzenesulfonyl)-amino]-3-methyl-benzoic acid methyl ester

To a solution of 1.27g (3.61 mmol) of the product of Example 379 in 11mL of dioxane and 1.3mL of acetic acid was added 0.293g of paraformaldehyde, 0.75mL of diethylamine and 13mg of cuprous chloride. The reaction was stirred at room temperature for 15 minutes and then heated to reflux for 1.5h, after which the reaction color had changed from green to brown. The reaction was cooled and then extracted with 10% HCl solution. The acid wash was then basified with 1N sodium hydroxide solution and extracted with ether. The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo to give 1.56g (100%) of the propargylic amine as a brown oil. Electrospray Mass Spec: 459.5 (M+H)+.

Example 381

2-[(4-Diethylamino-but-2-ynyl)-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methyl-benzamide

Following the procedure of Example 319, 1.50g (3.275 mmol) of the product of Example 380 was hydrolyzed to give 0.86g (59%) of the carboxylic acid as a tan foam. Electrospray Mass Spec: 443.4 (M-H)-.

Following the procedure of Example 328, 0.649g (1.462 mmol) of the carboxylic acid gives 0.228g of the hydroxamic acid-amine salt as a tan solid. Electrospray Mass Spec: 460.1 (M+H)+.

Example 382

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-[4-(4-methyl-piperazin-1-yl)-benzyl]-amino]-3-methyl-benzamide

Following the procedure of Example 9, 1.50g (4.478 mmol) of the product of Example 3 was alkylated with 4-bromobenzyl bromide to give 2.16g (96%) of the benzylated sulfonamide as a pale yellow solid. Electrospray Mass Spec: 504.0 (M+H)+.

To a solution of 2.04g (4.048 mmol) of the aryl bromide in 60mL of toluene was added 0.99mL (8.91 mmol) of N-methylpiperazine, 0.856g (8.91 mmol) of sodium t-butoxide, 0.148g (0.162 mmol) of tris-(dibenzylideneacetone)dipalladium and 0.301g (0.486 mmol) of (R)-(+)-2,2'-bis(diphenylphosphino)-1'-binaphthyl (BINAP). The resulting mixture was heated to 80° for 3h then cooled to room temperature. The reaction was diluted with ether and filtered through Celite. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel eluting with ethyl acetate to give 1.3g of the aryl piperazine.

Following the procedure of Example 319 the aryl piperazine-ester was hydrolyzed to give 0.837g (66%) of the carboxylic acid as a brown foam. Electrospray Mass Spec: 508.6 (M-H)-.

Following the procedure of Example 328 the carboxylic acid was converted into
5 0.432g of the hydroxamic acid-amine salt, isolated as a pale yellow solid. Electrospray Mass Spec: 525.1 (M+H)+.

Example 383

10 4-[(2-Hydroxycarbamoyl-6-methyl-phenyl)-(4-methoxy-benzenesulfonyl)-amino]-butyric acid ethyl ester

Following the procedure of Example 45, 0.750g (1.989 mmol) of the product of Example 330 was reacted with ethyl bromobutyrate to give 0.96g (98%) of the alkylated sulfonamide as a colorless oil. Electrospray Mass Spec: 492.4 (M+H)+.

To a solution of 0.828g (1.686 mmol) of the t-butyl ester in 5mL of
15 dichloromethane was added 5.0mL of trifluoroacetic acid. The reaction was stirred at room temperature for 2h and then concentrated in vacuo. The residue was triturated with ether/hexanes (1:1) and the resulting white solid carboxylic acid (0.653g) was collected by filtration and dried in vacuo. Electrospray Mass Spec: 434.2 (M-H)-.

Following the procedure of Example 23, 0.603g (1.386 mmol) of the carboxylic
20 acid gives 0.234g (38%) of the hydroxamic acid as a white foam. Electrospray Mass Spec: 451.4 (M+H)+.

Example 384

25 5-[(2-Hydroxycarbamoyl-6-methyl-phenyl)-(4-methoxy-benzenesulfonyl)-amino]-pentanoic acid ethyl ester

Following the procedure of Example 45, 0.750g (1.989 mmol) of the product of Example 330 was reacted with ethyl bromovalerate to give 0.93g (93%) of the alkylated sulfonamide as a white solid. Electrospray Mass Spec: 506.4 (M+H)+.

To a solution of 0.813g (1.610 mmol) of the t-butyl ester in 5mL of
30 dichloromethane was added 5.0mL of trifluoroacetic acid. The reaction was stirred at room temperature for 2h and then concentrated in vacuo. The residue was triturated with ether/hexanes (1:1) and the resulting white solid carboxylic acid (0.693g) was collected by filtration and dried in vacuo. Electrospray Mass Spec: 448.1 (M-H)-.

Following the procedure of Example 23, 0.631g (1.405 mmol) of the carboxylic
35 acid gives 0.219g (34%) of the hydroxamic acid as a brown glass. Electrospray Mass Spec: 465.4 (M+H)+.

Example 385

[(2-Hydroxycarbamoyl-6-methyl-phenyl)-(4-methoxy-benzenesulfonyl)-amino]-acetic acid benzyl ester

Following the procedure of Example 9, 1.50g (3.979 mmol) of the product of Example 330 was reacted with benzyl 2-bromoacetate to give 2.03g (97%) of the alkylated sulfonamide as a colorless oil. Electrospray Mass Spec: 526.3 (M+H)+.

To a solution of 1.00g (1.905 mmol) of the t-butyl ester in 5mL of dichloromethane was added 5.0mL of trifluoroacetic acid. The reaction was stirred at room temperature for 1h and then concentrated in vacuo to give 0.893g (100%) of the carboxylic acid as a white foam. Electrospray Mass Spec: 468.2 (M-H)-.

Following the procedure of Example 23, 0.802g (1.71 mmol) of the carboxylic acid gives 0.675g (82%) of the hydroxamic acid as a white foam. Electrospray Mass Spec: 485.3 (M+H)+.

Example 386

N-Hydroxy-2-[[[(4-methoxyphenyl)sulfonyl][2-oxo-2-[(2-pyridinylmethyl)amino]ethyl]amino]-3-methylbenzamide

Following the procedure of Example 9, 4.0g (0.011 mol) of the product of Example 330 was reacted with benzyl 2-bromoacetate to give 5.57g (100%) of the alkylated sulfonamide as a colorless oil. Electrospray Mass Spec: 526.3 (M+H)+.

To a solution of 5.50g (0.010 mol) of the benzyl ester in 150mL of ethanol was added 3.30g (0.052 mol) of ammonium formate and 0.550g of 10% palladium on carbon. The reaction was stirred at room temperature for 18h and then filtered through celite. The filtrate was concentrated in vacuo, diluted with ethyl acetate, washed with water, dried over MgSO₄, filtered and concentrated. The residue was chromatographed on silica gel eluting with EtOAc/hexanes (1:1) to give the carboxylic acid as a white foam. Electrospray Mass Spec: 436.2 (M+H)+.

To a solution of 1.00g (2.299 mmol) of the carboxylic acid in 10mL of dichloromethane was added 0.36mL of DMF followed by 2.3mL of a 2M solution of oxalyl chloride in dichloromethane. The reaction was stirred at room temperature for 1h and then poured into a 0°C solution of 0.47mL (4.598 mmol) of 2-aminomethylpyridine and 0.96mL of triethylamine in 10mL of dichloromethane. The reaction was stirred overnight and then poured into water and extracted with ether. The organics were then washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate to give 1.094g (91%) of the amide as a white foam. Electrospray Mass Spec: 526.4 (M+H)+.

Next, HCl gas was bubbled through a solution of 0.985g (1.876 mmol) of the amide dissolved in 20mL of dichloromethane for 10 minutes. The reaction was stoppered and stirred for an additional 1h and then diluted with 50mL of ether and let sit overnight. The resulting white solid carboxylic acid was collected by filtration and dried in vacuo.

5 Electropray Mass Spec: 468.1 (M-H)-.

Following the procedure of Example 328, 0.850g (1.682 mmol) of the carboxylic acid gives 0.693g of the hydroxamic acid-amine salt as a tan solid. Electropray Mass Spec: 485.3 (M+H)+.

10 Example 387

N-Hydroxy-2-((4-methoxy-benzenesulfonyl)-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amino}-3-methyl-benzamide

Following the procedure of Example 9, 4.0g (0.011 mol) of the product of Example 330 was reacted with benzyl 2-bromoacetate to give 5.57g (100%) of the alkylated
15 sulfonamide as a colorless oil. Electropray Mass Spec: 526.3 (M+H)+.

To a solution of 5.50g (0.010 mol) of the benzyl ester in 150mL of ethanol was added 3.30g (0.052 mol) of ammonium formate and 0.550g of 10% palladium on carbon. The reaction was stirred at room temperature for 18h and then filtered through celite. The filtrate was concentrated in vacuo, diluted with ethyl acetate, washed with water, dried over
20 MgSO₄, filtered and concentrated. The residue was chromatographed on silica gel eluting with EtOAc/hexanes (1:1) to give the carboxylic acid as a white foam. Electropray Mass Spec: 436.2 (M+H)+.

To a solution of 1.00g (2.299 mmol) of the carboxylic acid in 10mL of dichloromethane was added 0.36mL of DMF followed by 2.3mL of a 2M solution of
25 oxalyl chloride in dichloromethane. The reaction was stirred at room temperature for 1h and then poured into a 0° solution of 1.3 mL (0.011 mmol) of N-methylpiperazine in 10mL of dichloromethane. The reaction was stirred overnight and then poured into water and extracted with ether. The organics were then washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting
30 with ethyl acetate to give 1.19g (100%) of the amide as a colorless oil. Electropray Mass Spec: 518.4 (M+H)+.

Next, HCl gas was bubbled through a solution of 1.10g (2.128 mmol) of the amide dissolved in 25mL of dichloromethane for 10 minutes. The reaction was stoppered and stirred for an additional 1h and then diluted with 50mL of ether and let sit overnight. The
35 resulting white solid carboxylic acid was collected by filtration and dried in vacuo. Electropray Mass Spec: 459.8 (M-H)-.

Following the procedure of Example 328, 0.927g (1.863 mmol) of the carboxylic acid gives 0.350g of the hydroxamic acid-amine salt as a white solid. Electrospray Mass Spec: 477.3 (M+H)+.

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Example 388

N-Hydroxy-2-[(2-hydroxy-ethyl)-(4-methoxy-benzenesulfonyl)-amino]-3-methyl-benzamide

Following the procedure of Example 9, 2.0g (5.97 mmol) of the product of Example 3 was reacted with t-butyl bromoacetate to give 2.38g (89%) of the alkylated sulfonamide as a colorless oil. Electrospray Mass Spec: 449.9 (M+H)+.

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To a solution of 2.20g (4.90 mmol) of the t-butyl ester in 10mL of dichloromethane was added 5.0mL of trifluoroacetic acid. The reaction was stirred at room temperature for 2h and then concentrated in vacuo. The residue was triturated with ether and the resulting white solid carboxylic acid (1.85g) was collected by filtration and dried in vacuo.

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Electrospray Mass Spec: 392.0 (M-H)-.

The acid (1.75g, 4.45 mmol) was then reduced with borane-THF as in Example 341, to provide 1.21g of the alcohol as a white solid. Electrospray Mass Spec: 379.9 (M+H)+.

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Following the procedure of Example 337, 0.812g (2.142 mmol) of the alcohol then gives 0.910g (92%) of the tetrahydropyranyl ether. This ether-ester is then hydrolyzed following the procedure of Example 19 to give 0.634g (72%) of the carboxylic acid as a brown glass. Electrospray Mass Spec: 372.2 (M+Na)+.

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Following the procedure of Example 328, 0.592g (1.318 mmol) of the ether-carboxylate then gives 0.105g of the hydroxy-hydroxamic acid as a tan solid. Electrospray Mass Spec: 381.1 (M+H)+.

Example 389

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-dimethylamino-N-hydroxy-3-methyl-benzamide

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To a solution of 0.831g (1.649 mmol) of the product of Example 11 in 25.0mL of toluene was added 0.639 (3.627 mmol) of tris(dimethylamino)borane, 0.349 (3.627 mmol) of sodium t-butoxide, 0.060g (0.066 mmol) of tris-(dibenzylideneacetone)-dipalladium and 0.123 (0.198 mmol) of BINAP. The resulting mixture was heated to 80° for 3h then cooled to room temperature. The reaction was diluted with ether and filtered through Celite. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel eluting with EtOAc/Hexanes (1:3) to give 0.342g (44%) of the N,N-dimethyl aniline-ester.

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Following the procedure of Example 53 0.356g (0.761 mmol) of the N,N-dimethyl aniline-ester is hydrolyzed to give 0.170g (50%) of the carboxylic acid as a white solid. Electrospray Mass Spec: 453.1 (M-H)-.

Following the procedure of Example 369, 0.225g (0.496 mmol) of the carboxylic acid gives 0.159g (69%) of the hydroxamic acid-aniline salt as a pale yellow foam. Electrospray Mass Spec: 469.9 (M+H)+.

Example 390

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-dimethylamino-N-hydroxy-benzamide

To a solution of 0.100g (0.219 mmol) of the product of Example 168 in 10mL of ethanol was added 0.247g (1.096 mmol) of SnCl₂ dihydrate and the reaction mixture was then heated to reflux for 3h. After cooling to room temperature the reaction was concentrated in vacuo and then diluted with ether. The organics were washed with 1N sodium hydroxide solution and water, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was triturated with ether to give 0.060g of the aniline as a white solid. Electrospray Mass Spec: 426.9 (M+H)+.

To a solution of 0.455g (1.068 mmol) of the aniline in 10mL of DMF was added 1.44g (0.011 mol) of potassium carbonate and 0.66mL of iodomethane and the reaction was heated to 80° for 18h. The reaction was then allowed to cool to room temperature and diluted with ether. The organics were washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/hexanes (1:3) to give 0.44g (91%) of the N,N-dimethyl aniline-ester as a pink oil. Electrospray Mass Spec: 454.9 (M+H)+.

Following the procedure of Example 53, 0.388g (0.855 mmol) of the N,N-dimethyl aniline-ester gives 0.314g (82%) of the N,N-dimethyl aniline-carboxylate as a white foam. Electrospray Mass Spec: 439.0 (M-H)-.

Following the procedure of Example 369, 0.251g (0.563 mmol) of the carboxylate gives 0.226g (88%) of the hydroxamic acid as a pink foam. Electrospray Mass Spec: 455.9 (M+H)+.

Example 391

4-(2-Piperidin-1-yl-ethoxy)-benzyl chloride

To a stirred solution of 4-hydroxy benzaldehyde (12.2 gm, 0.1 mol) and K₂CO₃ (25 gm, excess) in N,N-dimethylformamide (250 ml) was added 1-(2-chloroethyl)piperidine monohydrochloride (20.0 gm, 1.08 mol). The reaction mixture was heated to 80°C for 24 hrs and cooled to room temperature. The reaction mixture was quenched with ice cold

water and extracted with chloroform. The organics were washed with water, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. The residue was dissolved in methanol and sodium borohydride (10 gms, excess) was slowly added at 0°C . The reaction mixture was stirred at room temperature for 2h and then quenched with water. The alcohol was extracted with chloroform, the organics were washed well with water, dried over Na_2SO_4 , filtered and concentrated in vacuo.

The crude alcohol thus obtained was dissolved in THF (200 ml) and HCl gas was passed through for 30 minutes at 0°C . To the suspension of hydrochloride thus obtained, thionyl chloride (30 ml, excess) was slowly added. The reaction mixture was refluxed for thirty minutes and cooled to room temperature. The reaction mixture was then concentrated to dryness and triturated with anhydrous ether. The precipitated solid was filtered and dried under vacuum at room temperature to give 25g (86%) of the product as a white solid. m.p. $145 - 148^\circ\text{C}$. Electrospray Mass Spec: 256 (M+H).

Example 392

4-(2-N,N-Diethyl-ethoxy)-benzyl chloride

To a stirred solution of 4-hydroxy benzaldehyde (12.2 gm, 0.1 mol) and K_2CO_3 (25 gm, excess) in N,N-dimethylformamide (250 ml) was added 2-diethyl-aminoethyl chloride monohydrochloride (20.0 gm, 1.2 mol). The reaction mixture was heated at 80°C for 24 hrs and cooled to room temperature. The reaction mixture was quenched with ice cold water and extracted with chloroform. The organics were washed with water, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. The residue was dissolved in methanol and sodium borohydride (10 gms, excess) was slowly added at 0°C . The reaction mixture was stirred at room temperature for 2h and then quenched with water. The alcohol was extracted with chloroform, washed well with water, dried, filtered and concentrated in vacuo.

The crude alcohol thus obtained was dissolved in THF (200 ml) and HCl gas was passed through for 30 minutes at 0°C . To the suspension of hydrochloride thus obtained, thionyl chloride (30 ml, excess) was slowly added. The reaction mixture was refluxed for thirty minutes and cooled to room temperature. The reaction mixture was then concentrated to dryness and triturated with anhydrous ether. The precipitated solid was filtered and dried under vacuum at room temperature to give 18g (65%) of the product as a white solid, m.p. $76-79^\circ\text{C}$. Electrospray Mass Spec: 244 (M+H).

Example 393

N-Hydroxy-2-[[4-methoxyphenyl)sulfonyl][4-[2-(1-piperidinyl)ethoxy]phenyl)methyl]amino]-3-methylbenzamide

Following the procedure of Example 45, 1.00g (2.985 mmol) of the product of Example 3 reacts with 0.952g (3.284 mmol) of the product of Example 391 to give 0.965g (58%) of the piperidine-ester as a colorless oil. Electrospray Mass Spec: 553.5 (M+H)+.

Following the procedure of Example 319, 0.889g (1.611 mmol) of the ester gives 0.872g of the carboxylic acid as a white foam. Electrospray Mass Spec: 539.2 (M+H)+.

Following the procedure for Example 328, 0.814g (1.513 mmol) of the carboxylic acid gives 0.179g of the hydroxamate-amine salt as a white solid. Electrospray Mass Spec: 554.5 (M+H)+.

Example 394

2-[[4-(2-Diethylamino-ethoxy)-benzyl]-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methyl-benzamide

Following the procedure of Example 45, 1.00g (2.653 mmol) of the product of Example 30 reacts with 0.811g (2.918 mmol) of the product of Example 392 to give 0.575g (37%) of the piperidine-ester as a tan foam. Electrospray Mass Spec: 583.1 (M+H)+.

Following the procedure of Example 374, 0.539g (0.926 mmol) of the ester gives 0.369g of the carboxylic acid as a white solid. Electrospray Mass Spec: 525.2 (M-H)-.

Following the procedure for Example 369, 0.328g (0.513 mmol) of the carboxylic acid gives 0.194g of the hydroxamate-amine salt as a white solid. Electrospray Mass Spec: 542.3 (M+H)+.

Example 395

5-Bromo-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-amino]-3-methyl-benzamide

Following the procedures for Example 393, 1.00g (2.415 mmol) of the product of Example 202 gives 0.470g of the hydroxamate-amine salt as a pale yellow solid. Electrospray Mass Spec: 632.2 (M+H)+.

Example 396

N-Hydroxy-2-[[4-methoxyphenyl)sulfonyl][4-[[2-(1-piperidinyl)ethyl]amino]carbonyl]phenyl)methyl]amino]-3-methylbenzamide

Following the procedure of Example 9, 1.00g (2.653 mmol) of the product of Example 330 reacts with 0.851g (3.714 mmol) of para-carbomethoxy benzyl bromide to

give 1.30g (94%) of the benzylated sulfonamide-ester as a white foam. Electrospray Mass Spec: 526.4 (M+H)+.

To a solution of 0.1.249g (2.379 mmol) of the ester in 24.0mL of THF/MeOH (1:1) was added 12mL of 1N sodium hydroxide solution and the reaction was stirred for 3h at room temperature. The reaction was then acidified and extracted with ethyl acetate. The combined organics were dried over MgSO₄, filtered and concentrated in vacuo to give 0.1.08g (89%) of the carboxylic acid as a white foam. Electrospray Mass Spec: 512.3 (M+H)+.

To a solution of 1.01g (1.977 mmol) of the carboxylic acid in 10mL of dichloromethane was added 0.306mL of DMF followed by 2.0mL of a 2M solution of oxalyl chloride in dichloromethane. The reaction was stirred at room temperature for 1h and then poured into a 0°C solution of 0.56mL (3.95 mmol) of aminoethyl piperidine and 0.825mL of triethylamine in 7mL of dichloromethane. The reaction was stirred overnight and then poured into water and extracted with ether. The organics were then washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo to give 1.23g (100%) of the amide as a white foam. Electrospray Mass Spec: 622.6 (M+H)+.

Next, HCl gas was bubbled through a solution of 1.167g (1.879 mmol) of the amide dissolved in 20mL of dichloromethane for 10 minutes. The reaction was stoppered and stirred for an additional 1h and then diluted with 50mL of ether and let sit overnight. The resulting white solid carboxylic acid was collected by filtration and dried in vacuo. Electrospray Mass Spec: 566.6 (M+H)+.

Following the procedure of Example 328, 1.023g (1.704 mmol) of the carboxylic acid gives 0.177g of the hydroxamate-amine salt as a white solid. Electrospray Mass Spec: 581.0 (M+H)+.

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Example 397

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide hydrochloride salt

Following the procedure of Example 241 the product of Example 89 reacts with phenylboronic acid to give the corresponding biaryl-sulfonamide-ester. The ester is subsequently hydrolyzed to the carboxylic acid following the procedure of Example 319 and then converted into the hydroxamic acid hydrochloride salt following the method of Example 369. Electrospray Mass Spec: 504.5 (M+H)+

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Example 398

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-thiophen-3-yl-benzamide hydrochloride salt

Following the procedure of Example 241 the product of Example 89 reacts with thiophene-3-boronic acid to give the corresponding biaryl-sulfonamide-ester. The ester is subsequently hydrolyzed to the carboxylic acid following the procedure of Example 319 and then converted into the hydroxamic acid hydrochloride salt following the method of Example 369. Electrospray Mass Spec: 508.1 (M-H)-

Example 399

4''-Methoxy-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-[1,1';4',1'']terphenyl-3-carboxylic acid hydroxyamide hydrochloride salt

Following the procedure of Example 241 the product of Example 89 reacts with 4-(4'-methoxyphenyl)phenylboronic acid to give the corresponding biaryl-sulfonamide-ester. The ester is subsequently hydrolyzed to the carboxylic acid following the procedure of Example 319 and then converted into the hydroxamic acid hydrochloride salt following the method of Example 369. Electrospray Mass Spec: 609.9 (M+H)+

Example 400

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-3'-nitro-biphenyl-3-carboxylic acid hydroxyamide hydrochloride salt

Following the procedure of Example 241 the product of Example 89 reacts with 3-nitrobenzeneboronic acid to give the corresponding biaryl-sulfonamide-ester. The ester is subsequently hydrolyzed to the carboxylic acid following the procedure of Example 319 and then converted into the hydroxamic acid hydrochloride salt following the method of Example 369. Electrospray Mass Spec: 549.1 (M+H)+

Example 401

4'-Methoxy-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide hydrochloride salt

Following the procedure of Example 241 the product of Example 89 reacts with 4-methoxybenzeneboronic acid to give the corresponding biaryl-sulfonamide-ester. The ester is subsequently hydrolyzed to the carboxylic acid following the procedure of Example 319

and then converted into the hydroxamic acid hydrochloride salt following the method of Example 369. Electrospray Mass Spec: 534.1 (M+H)+

5

Example 402

5-Benzo[b]thiophen-2-yl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide hydrochloride salt

Following the procedure of Example 241 the product of Example 89 reacts with benzo[b]thiophene-2-boronic acid to give the corresponding biaryl-sulfonamide-ester. The ester is subsequently hydrolyzed to the carboxylic acid following the procedure of Example 319 and then converted into the hydroxamic acid hydrochloride salt following the method of Example 369. Electrospray Mass Spec: 560.1 (M+H)+

15

Example 403

5-Benzo[b]furan-2-yl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide hydrochloride salt

Following the procedure of Example 241 the product of Example 89 reacts with benzo[b]furan-2-boronic acid to give the corresponding biaryl-sulfonamide-ester. The ester is subsequently hydrolyzed to the carboxylic acid following the procedure of Example 319 and then converted into the hydroxamic acid hydrochloride salt following the method of Example 369. Electrospray Mass Spec: 544.3 (M+H)+

25

Example 404

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid hydroxyamide hydrochloride salt

Following the procedure of Example 241 the product of Example 89 reacts with 4-trifluoromethoxybenzeneboronic acid to give the corresponding biaryl-sulfonamide-ester. The ester is subsequently hydrolyzed to the carboxylic acid following the procedure of Example 319 and then converted into the hydroxamic acid hydrochloride salt following the method of Example 369. Electrospray Mass Spec: 588.1 (M+H)+

35

Example 405:

5-Benzo[1,3]dioxol-5-yl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide hydrochloride salt

Following the procedure of Example 241 the product of Example 89 reacts with
5 3,4-methylenedioxybenzeneboronic acid to give the corresponding biaryl-sulfonamide-ester. The ester is subsequently hydrolyzed to the carboxylic acid following the procedure of Example 319 and then converted into the hydroxamic acid hydrochloride salt following the method of Example 369. Electrospray Mass Spec: 548.1 (M+H)+

10

Example 406

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-3'-trifluoromethyl-biphenyl-3-carboxylic acid hydroxyamide hydrochloride salt

Following the procedure of Example 241 the product of Example 89 reacts with 3-
15 trifluoromethylbenzeneboronic acid to give the corresponding biaryl-sulfonamide-ester. The ester is subsequently hydrolyzed to the carboxylic acid following the procedure of Example 319 and then converted into the hydroxamic acid hydrochloride salt following the method of Example 369. Electrospray Mass Spec: 572.0 (M+H)+

20

Example 407

2-[(4-Chloro-benzyl)-(5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-N-hydroxy-3-methyl-benzamide

A mixture of Wang resin (Wang, S. J. Am. Chem. Soc. 1973, 95, 1328-1333)
25 (Advanced ChemTech 200-400 mesh, 1% crosslinked; loading: 0.92 mmol/g; 15.0 g, 0.011 mol), LiCl (1.4 g, 0.033 mol) and DMF (150 mL) was magnetically stirred for 40 min. Collidine (4.0 g, 0.033 mol) was added and the mixture was cooled (0-5 °C) with an ice bath. Methanesulfonyl chloride (3.8 g, 0.033 mol) was added over 5 min. After 10 min, the cooling bath was removed and stirring was continued for 68 h. The mixture was
30 filtered and the resin was washed with DMF (250 mL), 30% H₂O/DMF ((2 x 300 mL), DMF (2 x 250 mL), EtOH (3 x 250 mL), CH₂Cl₂ (3 x 300 mL), and hexane (2 x 250 mL). The resin was dried over P₂O₅ in vacuo to give 14.3 g; ¹³C NMR (CDCl₃) δ 46.22 (CH₂Cl); IR (KBr) cm⁻¹: 2900, 1600, 1520, 1485, 1450.

A mixture of chloro-Wang resin (1.13 mmol/g, 1 g), NaI (169 mg, 1.13 mmol),
35 Cs₂CO₃ (1.11 g, 3.39 mmol) and N-hydroxyphthalimide (922 mg, 5.65 mmol) in DMF was heated at 50°C for 16 h. After filtration, the resin was washed with DMF/H₂O (3:2, 4 X 25 mL), DMF/H₂O (9:1, 4 X 25 mL), DMF (2 X 25 mL), dichloromethane (3 X 25 mL)

and MeOH (2 X 20 mL). The resin was then dried under vacuum to give the product resin (1.1 g, 96%). N% theory 1.38%, found 1.09%.

Phthalimido hydroxylamine resin (10 g) was treated with a mixture of THF/EtOH/NH₂NH₂ (80 mL/80 mL/26 mL) for 18 h at room temperature. The mixture
5 was filtered and the resin was washed with MeOH (200 mL), DMF (200 mL), and the process was repeated. The resin was then washed with MeOH (200 mL) and dichloromethane (2 X 150 mL). Finally the resin was dried under vacuum.

A cold (-5°C, ice-salt bath) solution of 2-amino-3-methylbenzoic acid (1.51 g, 10 mmol) and pentafluorophenol (2 g, 11 mmol) in dry DMF (2 mL) was treated with a
10 solution of DCC (2.27 g, 11 mmol) in EtOAc (20 mL). The reaction mixture was stored at 0°C overnight. The precipitate was removed by filtration and washed with EtOAc (~10 mL). The washings were combined with the filtrate and washed with 5% aqueous NaHCO₃ (2 X 15 mL), H₂O (15 mL) and dried (Na₂SO₄). The solvent was removed to give the product (3.2 g, 100%) as a solid.

To a suspension of hydroxylamine on Wang resin (3.05 g, 1.13 mmol/g) in DMF
15 was added a solution of pentafluorophenyl 2-amino-3-methylbenzoate (4.37 g, 13.8 mmol) followed by 4-dimethylaminopyridine (2.1 g, 17.2 mmol). The resultant mixture was shaken at room temperature for 40 h. The resin was filtered and washed with DMF (4 X 100 mL), dichloromethane (3 X 80 mL), MeOH (2 X 80 mL), and dichloromethane (4 X
20 80 mL). Finally the resin was dried under vacuum to give product resin (3.51 g, 100%).

To a suspension of 2-amino-3-methylbenzoic acid hydroxyamide on Wang resin (3.51 g, 0.98 mmol/g) in dichloromethane (20 mL) was added pyridine (2.78 mL, 34.4 mmol). After 5 min, a solution of 5-(pyridin-2-yl)thiophen-2-yl-sulfonyl chloride (4.46 g, 17.2 mmol) in dichloromethane (15 mL) was added to the reaction mixture. The resultant
25 suspension was shaken at room temperature for 24 h. The resin was filtered and washed with DMF (4 X 40 mL), dichloromethane (3 X 40 mL), MeOH (2 X 40 mL) and dichloromethane (4 X 40 mL), and dried under vacuum to give 4.25 g (97%) of product resin.

To confirm the completion of the reaction, a sample of resin (100 mg) was
30 suspended in TFA/ dichloromethane (1:1, 2 mL) and allowed to sit for 1 h. The resin was filtered and washed with dichloromethane (2 X 1.5 mL). The combined filtrates were evaporated to dryness to give 24.7 mg of product, (5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-N-hydroxy-3-methyl-benzamide on Wang Resin. Mass Spec: expected 389.0504, found 389.9.

To a suspension of (5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-N-hydroxy-3-
35 methyl-benzamide on Wang resin (100 mg, 0.84 mmol/g) in a solution of 4-chlorobenzyl alcohol (0.485 mmol) in THF (1 mL) was added a solution of triphenylphosphine (0.485

mmol) and diethyl azodicarboxylate (0.485 mmol) in THF (1.24 mL). The resultant mixture was shaken for 4 h at room temperature. The resin was filtered, washed with THF (4 X 3 mL) and dichloromethane (4 X 3 mL), and dried under vacuum. The resin was suspended in trifluoroacetic acid/ dichloromethane (1:1, 2 mL) and allowed to sit for 1 h.
5 The resin was filtered and washed with dichloromethane (2 X 1.5 mL). The combined filtrates were evaporated to dryness, and the crude product was purified on a solid phase extraction cartridge (reverse phase) to give 16.7 mg of product, 2-[(4-chloro-benzyl)-(5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-N-hydroxy-3-methyl-benzamide. Mass Spec: expected 513.0584, found 513.8.

10

Example 408

2-[(3,4-Dimethyl-benzyl)-(5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-N-hydroxy-3-methyl-benzamide

15 To a suspension of (5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-N-hydroxy-3-methyl-benzamide on Wang resin, the product of Example 407 (100 mg, 0.84 mmol/g), in a solution of 3,4-dimethylbenzyl alcohol (0.485 mmol) in THF (1 mL) was added a solution of triphenylphosphine (0.485 mmol) and diethyl azodicarboxylate (0.485 mmol) in THF (1.24 mL). The resultant mixture was shaken for 4 h at room temperature. The resin
20 was filtered, washed with THF (4 X 3 mL) and dichloromethane (4 X 3 mL), and dried under vacuum. The resin was suspended in trifluoroacetic acid/ dichloromethane (1:1, 2 mL) and allowed to sit for 1 h. The resin was filtered and washed with DCM (2 X 1.5 mL). The combined filtrates were evaporated to dryness, and the crude product was purified on a solid phase extraction cartridge (reverse phase) to give 18.1 mg of product.
25 Mass Spec: expected 507.1286, found 507.9.

Example 409

2-[(4-Bromo-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzoic acid methyl ester

30 Following the procedure of Example 1, methyl-3-methyl anthranilate reacts with p-bromobenzenesulfonyl chloride to provide the aryl sulfonamide as a white powder. Electrospray Mass Spec: 475 (M+H)+.

Example 410

N-Hydroxy-3-methyl-2-[pyridin-3-ylmethyl-(4'-trifluoromethyl-biphenyl-4-sulfonyl)-amino]-benzamide

Following the procedure of Example 241, the product of Example 409 is converted
5 into the biaryl sulfonamide-ester. Hydrolysis of the ester according to the procedure of
Example 190 gives the corresponding carboxylic acid. The carboxylic acid is then
converted into the hydroxamic acid, isolated as an off-white powder, according to the
procedure of Example 68. Electrospray Mass Spec: 542.1 (M+H)+.

10 Example 411

2-[(2',4'-Dimethoxy-biphenyl-4-sulfonyl)-pyridin-3-ylmethyl-amino]-N-hydroxy-3-methyl-benzamide

Following the procedure of Example 241, the product of Example 409 is converted
into the biaryl sulfonamide-ester. Hydrolysis of the ester according to the procedure of
15 Example 190 gives the corresponding carboxylic acid. The carboxylic acid is then
converted into the hydroxamic acid, isolated as an off-white powder, according to the
procedure of Example 68. Electrospray Mass Spec: 534.0 (M+H)+.

Example 412

20 **N-Hydroxy-3-methyl-2-[pyridin-3-ylmethyl-(4-thiophen-2-yl-benzenesulfonyl)-amino]-benzamide**

Following the procedure of Example 241, the product of Example 409 is converted
into the biaryl sulfonamide-ester. Hydrolysis of the ester according to the procedure of
Example 190 gives the corresponding carboxylic acid. The carboxylic acid is then
25 converted into the hydroxamic acid, isolated as an off-white powder, according to the
procedure of Example 68. Electrospray Mass Spec: 480.3 (M+H)+.

Example 413

30 **2-[(4-Ethynyl-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-N-hydroxy-3-methyl-benzamide**

Following the procedure of Example 78 the product of Example 409 is converted
into the alkynyl-aryl sulfonamide-ester. Hydrolysis of the ester according to the procedure of
Example 190 gives the corresponding carboxylic acid. The carboxylic acid is then
converted into the hydroxamic acid, isolated as an off-white powder, according to the
35 procedure of Example 68. Electrospray Mass Spec: 422.3 (M+H)+.

Example 414

2-[(4-Benzo[b]thiophen-2-yl-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-N-hydroxy-3-methyl-benzamide

Following the procedure of Example 241, the product of Example 409 is converted
5 into the biaryl sulfonamide-ester. Hydrolysis of the ester according to the procedure of
Example 190 gives the corresponding carboxylic acid. The carboxylic acid is then
converted into the hydroxamic acid, isolated as an off-white powder, according to the
procedure of Example 68. Electrospray Mass Spec: 530.0 (M+H)+.

10

Example 415

2-[(4-Benzo[1,3]dioxol-5-yl-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-N-hydroxy-3-methyl-benzamide

Following the procedure of Example 241, the product of Example 409 is converted
into the biaryl sulfonamide-ester. Hydrolysis of the ester according to the procedure of
15 Example 190 gives the corresponding carboxylic acid. The carboxylic acid is then
converted into the hydroxamic acid, isolated as an off-white powder, according to the
procedure of Example 68. Electrospray Mass Spec: 518 (M+H)+.

Example 416

3-Methyl-2-[4-(pyridin-4-yloxy)-benzensulfonylamino]-N-hydroxy-benzoic acid methyl ester

Following the procedure of Example 1, the product of Example 3 reacts with 4-
[(pyrid-4-yl)oxy]benzenesulfonyl chloride hydrochloride to provide the NH-sulfonamide as
a white powder. Electrospray Mass Spec: 399 (M+H)+.

25

Example 417

3-Methyl-2-[4-(pyridin-4-yloxy)-benzensulfonylamino]-N-hydroxy-benzamide

Following the procedure of Example 9, the NH-sulfonamide product of Example
30 416 reacts with iodomethane to provide the N-methyl sulfonamide-ester.

Hydrolysis of the ester according to the procedure of Example 190 gives the
corresponding carboxylic acid. The carboxylic acid is then converted into the hydroxamic
acid, isolated as a white powder, according to the procedure of Example 68. Electrospray
Mass Spec: 414 (M+H)+.

Pharmacology

Procedures for Measuring MMP-1, MMP-9, and MMP-13 Inhibition

5 These assays are based on the cleavage of a thiopeptide substrates such as Ac-Pro-Leu-Gly(2-mercapto-4-methyl-pentanoyl)-Leu-Gly-OEt by the matrix metalloproteinases MMP-1, MMP-13 (collagenases) or MMP-9 (gelatinase), which results in the release of a substrate product that reacts colorimetrically with DTNB (5,5'-dithiobis(2-nitro-benzoic acid)). The enzyme activity is measured by the rate of the color increase. The thiopeptide
10 substrate is made up fresh as a 20 mM stock in 100% DMSO and the DTNB is dissolved in 100% DMSO as a 100 mM stock and stored in the dark at room temperature. Both the substrate and DTNB are diluted together to 1 mM with substrate buffer (50 mM HEPES pH 7.5, 5 mM CaCl₂) before use. The stock of enzyme is diluted with assay buffer (50 mM HEPES, pH 7.5, 5 mM CaCl₂, 0.02% Brij) to the desired final concentration. The assay
15 buffer, enzyme, vehicle or inhibitor, and DTNB/substrate are added in this order to a 96 well plate (total reaction volume of 200 μ l) and the 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 assay, the peptide
20 substrate contains a fluorescent group and a quenching group. Upon 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
25 assay, substrate and enzymes are diluted in HCBC 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 assays, the slope of the line is
30 calculated and represents the reaction rate. The linearity of the reaction rate is confirmed ($r^2 > 0.85$). The mean ($\bar{x} \pm \text{sem}$) 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 IC₅₀ values with 95% CI are estimated using linear regression.

35

In vivo MMP Inhibition

 A 2 cm piece of dialysis tubing (molecular weight cut-off 12-14,000, 10 mm flat width) containing matrix metalloproteinase enzyme (stromelysin, collagenase or gelatinase

in 0.5 mL of buffer) is implanted either ip or sc (in the back) of a rat (Sprague-Dawley, 150-200g) or mouse (CD-1, 25-50g) under anesthesia. Drugs are administered PO, IP, SC or IV through a canula in the jugular vein. Drugs are administered in a dose volume of 0.1 to 0.25 mL/animal. Contents of the dialysis tubing is collected and enzyme activity
5 assayed.

Enzyme reaction rates for each dialysis tube are calculated. Tubes from at least 3 different animals are used to calculate the mean $\pm$ sem. Statistical significance ($p < 0.05$) of vehicle-treated animals versus drug-treated animals is determined by analysis of variance. (*Agents and Actions* 21: 331, 1987).

10

Procedure for Measuring TACE Inhibition

Using 96-well black microtiter plates, each well receives a solution composed of 10 μ L TACE (Immunex, final concentration 1 μ g/mL), 70 μ L Tris buffer, pH 7.4 containing
15 10% glycerol (final concentration 10 mM), and 10 μ L of test compound solution in DMSO (final concentration 1 μ M, 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 μ M) 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
20 increase in fluorescence over time is plotted as a linear line. The slope of 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
25 generate using multiple doses of drug and IC_{50} values with 95% CI are estimated using linear regression.

Results of the above in-vitro and in-vivo matrix metalloproteinase inhibition and TACE inhibition pharmacological assays are given in Table I below.

Table I. Inhibition of MMP and TACE

	Example	MMP-1 ¹	MMP-9 ¹	MMP-13 ¹	in-vivo MMP ²	TACE ¹
	23	639	650	555		>1000
	24	398	31			1000
	25				32%(100), ip	>1000
5	26	884	346	982		>1000
	27	1573	440	717		>1000
	28	115	23	50		460
	29	553	353	728		1000
	34	281	28	69	31.6(100), ip	>1000
10	54	24	3	4		
	55	670	29	216		>1000
	56	>1000	57	138		>1000
	57	>500	12	33		1000
	58	244	5	36		682
15	59	242	8	34		>1000
	60	152	7	15		232
	61		34	33	46(20), po 59(50), po	289
	68	82	21	15		239
20	69	153	874	1370		>1000
	72	>1000	144	137		377
	74	>1000	554	959		429
	77		131			
	80	109	21	18		134
25	83		34	32		
	85		663			>1000
	88	132	15	11		50
	91		24	20	55(100), po	
	94	1000	276	209		>1000
30	101	267	23	138		422
	102	314	29			162
	115	>1000	11	20		173
	116	201	13	14		271
	117	114	10	10	28.3(100), ip	154
35	118	248	345	229		>1000

Table I. Continued

	Example	MMP-1 ¹	MMP-9 ¹	MMP-13 ¹	in-vivo MMP ²	TACE ¹
	119	223	27	14		252
	120	238	18	39		310
	125	>1000	27	134		300
5	130	213	4	13		76
	131	212	54	48		80
	138	258	77	57		215
	145	55	7	3		158
	150	213	4	13		76
10	151	212	54	48		80
	156	>1000	104	134		
	158	>1000	11	62		
	165		286	350		
	166		203	>300		
15	167		42	178		
	170	347	12	39		176
	174	323	16	71		50%
	175	90	7	4		57
	179	680	40	53		64%
20	186	37	13	1.4		61
	191	1239	10	67		210
	194	306		12		154
	197	711	5	6		32%
	201	104	11	27		1000
25	207	1117	2.0	2.5		375
	212	415	5.2	11		314
	214	423	6.4	19		232
	219	290	6.7	5.8		548
	224	957	11	14		715
30	227	193	3.1	4.1		446
	230	20	2.4	1.9		47%(1)
	233	32	2.3	1.8		450
	240	86	3.5	1.6		548
	243	528	6.6	3.1		66
35	246	106	6.0	3.6		56

Table I. Continued

	Example	MMP-1 ¹	MMP-9 ¹	MMP-13 ¹	in-vivo MMP ²	TACE ¹
	249	231	2.8	6.0		100
	252	652	15	10		346
	255	48	7.1	3.2		65
5	258	169	8.0	7.0		110
	261	247	1.3	2.8		54
	264	159	3.7	6.4		77
	267	59	3.0	13		136
	272	66	0.5	6.0		311
10	277	56	4.0	4.0		34
	282	1050	5.0	113		44%(1)
	285	312	6.0	9.8		61
	292	184	8.0	29		7%(1)
	297	297	9.0	14		58%(1)
15	301	211	6.9	8.7		1484
	302	291		24		173
	303	2782	64	104		218%(1)
	304	4100		305		25%(1)
	308	10%(1)	45%(1)	36%(1)		285
20	309	608	5	14		174
	310	4800	21	101		154
	311	781	10	43		157
	313	180	1.4	6.3		26
	314	954	8.4	13		27
25	320	2188	46	150		142
	325	15%(1)	49%(1)	60%(1)		1640
	325	20	2.4	1.9		47%(1)
	328	326	4.9	13		263
	329	319	6.1	23		173
30	339	216	5.2	5.7		564
	340	522	11	30		110
	344	1173	69	320		529
	345	1158	31	134		523
	349	396	8	9		32
35	350	450	5	21		373

Table I. Continued

	Example	MMP-1 ¹	MMP-9 ¹	MMP-13 ¹	in-vivo MMP ²	TACE ¹
	353	23%(1)	61	141		780
	355	701	28	20		288
	358	25%(10)	101	107		1054
5	360	14%(10)	525	1260		1405
	363	449	20	54		137
	367	597	12	13		2700
	369	207	6.4	3.8		38
	373	1280	26	59		539
10	374	56%(10)	36%(1)	17%(1)		29%(1)
	375	329	7.1	18		356
	376	391	8.4	18		645
	377	123	4.7	15		258
	378	213	2.9	11		243
15	381	470	11	19		218
	382	142	6.5	20		146
	383	34%(1)	87%(1)	48%(1)		45%(1)
	384	48%(1)	52%(1)	61%(1)		55%(1)
	385	25%(1)	65%(1)	66%(1)		56%(1)
20	386	21%(1)	16%(1)	11%(1)		46%(1)
	387	2715	96	307		38%(1)
	388	66%(10)	47%(1)	39%(1)		35%(1)
	389	63	2	39		633
	390	19%(1)	64	531		39%(1)
25	393	176	6.9	56		277
	394	96	2.3	8.8		215
	395	35	2.3	3.1		108
	396	184	6.3	35		363
	397	195	3.0	3.7		64
30	398	85	2.0	3.7		56
	399	2197	45	41		25%(1)
	400	295	6.0	4.9		231
	401	176	1.4	2.8		146
	402	543	2.6	8.5		639
35	404	1800	5.9	9.5		54%(1)

Table I. Continued

Example	MMP-1 ¹	MMP-9 ¹	MMP-13 ¹	in-vivo	
				MMP ²	TACE ¹
405	176	4.1	5.8		151
406	542	1.1	1.6		294
407	1690	199	35		
5 408	3450	731	148		
410	47%(10)	28%(1)	40%(.1)		2%(1)
411	32%(10)	39%(1)	44%(1)		9%(1)
412	69%(10)	44%(1)	42%(.1)		3%(1)
413	529	55	75		43%(1)
10 414	29%(10)	68%(1)	38		6%(1)
415	37%(10)	43%(1)	26		9%(1)
417	3245	6.8	3.7		

1. IC₅₀ nM or % inhibition at 1μM concentration

2. % inhibition vs. MMP-9(dose, mg/kg), ip = intraperitoneal, po = oral

15

Cartilage Degradation in the Rat

Twenty mg slices of cartilage are obtained from the knee of freshly slaughtered cattle. Discs of cellulose sponge, 6 mm in diameter, are cut and a 2 mm hole put in the center of the sponge. 100 μl of a sterile suspension containing 1 mg of heat-killed Mycobacterium tuberculosis is applied to the sponge. After air-drying overnight, the sponges are autoclaved and a cartilage slice is placed in the hole cut in the sponge disc. Under sterile conditions, the cartilage-sponge disc is placed subcutaneously in the back of an anesthetized rat (Lewis strain, 200 to 250 g). The incision is closed with staples and the rat allowed to recover from anesthesia. Approximately 5 days after sponge implantation, osmotic minipumps (Alza Corp., Palo Alto, CA), containing either investigational compound or vehicle were implanted intraperitoneally in the anesthetized rat under sterile conditions. After 19 days, the rats are euthanized by asphyxiation with CO₂ and the granulomas containing the implanted sponge excised from the surrounding tissue.

The weight of the piece of cartilage recovered from the sponge was recorded and the collagen content of the cartilage was determined. The mean of the cartilage weights and collagen content was determined for the vehicle and drug-treated groups. The inhibition of cartilage weight and collagen content loss produced by the compounds compared with vehicle-treated rats was determined. Statistical significance (p < 0.05) of vehicle-treated animals versus drug-treated animals was determined by analysis of variance.

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Results:

<u>Treatment</u>	Average Daily Dose (mg/kg)	% Inhibition of Cartilage Weight Loss	% Inhibition of Cartilage Collagen Loss
Example 83	50	44.6	51.2*
Example 313	50	45.5	28.0*

*=p<0.05 vs Vehicle-treated rats

- 5 **Reference:** Bishop J., Greenham AK., Lewis EJ. A novel in vivo model for the study of cartilage degradation. J. Pharmacol. Toxicol. Methods, 30:19-25, 1993.

10

Pharmaceutical Composition

Compounds of this invention may be administered neat or with a pharmaceutical carrier to a patient in need thereof. The pharmaceutical carrier may be solid or liquid.

- 15 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
- 20 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.

- 25 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,
- 30 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 aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semi-solid emulsions of either the oil in water or water in oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

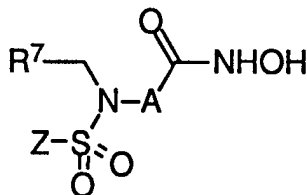
The dosage to be used in the treatment of a specific patient suffering from a disease or condition in which MMPs and TACE are involved must be subjectively determined by the attending physician. The variables involved include the severity of the dysfunction, and the size, age, and response pattern of the patient. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated and standard medical principles.

Preferably the pharmaceutical composition is in unit dosage form, e.g., as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for

example packed powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

What is claimed:

1. A compound having the formula



where the hydroxamic acid moiety and the sulfonamido moiety are bonded to adjacent carbons on the phenyl or naphthyl ring of group A where:

A is phenyl or naphthyl, optionally substituted by R^1 , R^2 , R^3 and R^4 ;

Z is aryl, heteroaryl, or heteroaryl fused to a phenyl,

where aryl is phenyl or naphthyl optionally substituted by R^1 , R^2 , R^3 and R^4 ;

heteroaryl is a 5-6 membered heteroaromatic ring having from 1 to 3

heteroatoms independently selected from N, O, and S, and

optionally substituted by R^1 , R^2 , R^3 and R^4 ;

and when heteroaryl is fused to phenyl, either or both of the rings can be

optionally substituted by R^1 , R^2 , R^3 and R^4 ;

R^1 , R^2 , R^3 and R^4 are independently -H, -COR⁵, -F, -Br, -Cl, -I,

-C(O)NR⁵OR⁶, -CN, -OR⁵, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁵ where

x is 0-2, -OPO(OR⁵)OR⁶, -PO(OR⁶)R⁵, -OC(O)NR⁵R⁶, -COOR⁵,

-CONR⁵R⁶, -SO₃H, -NR⁵R⁶, -NR⁵COR⁶, -NR⁵COOR⁶,

-SO₂NR⁵R⁶, -NO₂, -N(R⁵)SO₂R⁶, -NR⁵CONR⁵R⁶,

-NR⁵C(=NR⁶)NR⁵R⁶, 3-6 membered cycloheteroalkyl having one

to three heteroatoms independently selected from N, O, and S and

optionally having 1 or 2 double bonds and optionally substituted by

one to three groups each selected independently from R⁵; -aryl or

heteroaryl as defined above, biphenyl optionally substituted by

one to four groups each selected independently from R⁴, -SO₂NHCOR⁵ or -

CONHSO₂R⁵ where R⁵ is not H, -tetrazol-5-yl, -SO₂NHCN, -

SO₂NHCONR⁵R⁶ or straight chain or branched -C₁-C₆ alkyl, -C₂-C₆-

alkenyl, or -C₂-C₆-alkynyl, or -C₃-C₆-cycloalkyl optionally having 1 or 2

double bonds each optionally substituted with -COR⁵, -CN, -C₂-C₆

alkenyl, -C₂-C₆ alkynyl, -OR⁵, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁵

where x is 0-2, -OC(O)NR⁵R⁶, -COOR⁵, -CONR⁵R⁶, -SO₃H, -NR⁵R⁶, -NR⁵COR⁶, -NR⁵COOR⁶, -SO₂NR⁵R⁶, -NO₂, -N(R⁵)SO₂R⁶, -NR⁵CONR⁵R⁶, -C₃-C₆cycloalkyl as defined above, 3-6 membered cycloheteroalkyl as defined above, aryl or heteroaryl as defined above, biphenyl, -SO₂NHCOR⁵ or -CONHSO₂R⁵ where R⁵ is not hydrogen; -PO(OR⁵)OR⁶, -PO(OR⁶)R⁵, -tetrazol-5-yl, C(O)NR⁵OR⁶, -NR⁵C(=NR⁶)NR⁵R⁶, -SO₂NHCONR⁵R⁶ or -SO₂NHCN;

with the proviso that when R¹ and R² are on adjacent carbons of A, R¹ and R² together with the carbons to which they are attached can form a 5 to 7 membered saturated or unsaturated heterocyclic ring or a 5-6 membered heteroaryl ring, each having 1 to 3 heteroatoms independently selected from O, S, or N, and each optionally substituted by one to four groups each selected independently from R⁴; or a 5 to 7 membered saturated or unsaturated carbocyclic ring optionally substituted by one to four groups each selected independently from R⁴;

R⁵ and R⁶ are independently H, aryl and heteroaryl as defined above, -C₃-C₆-cycloalkyl as defined above, -C₃-C₆-cycloheteroalkyl as defined above, -C₁-C₄-perfluoroalkyl, or straight chain or branched -C₁-C₆ alkyl, -C₂-C₆-alkenyl, or -C₂-C₆-alkynyl each optionally substituted with -OH, -COR⁸, -CN, -C(O)NR⁸OR⁹, -C₂-C₆-alkenyl, -C₂-C₆-alkynyl, -OR⁸, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁸ where x is 0-2, -OPO(OR⁸)OR⁹, -PO(OR⁸)R⁹, -OC(O)NR⁸R⁹, -COOR⁸, -CONR⁸R⁹, -SO₃H, -NR⁸R⁹, -NCOR⁸R⁹, -NR⁸COOR⁹, -SO₂NR⁸R⁹, -NO₂, -N(R⁸)SO₂R⁹, -NR⁸CONR⁸R⁹, -C₃-C₆ cycloalkyl as defined above, 3-6 membered cycloheteroalkyl as defined above, aryl or heteroaryl as defined above, -SO₂NHCOR⁸ or -CONHSO₂R⁸ where R⁸ is not hydrogen, -tetrazol-5-yl, -NR⁸C(=NR⁹)NR⁸R⁹, -SO₂NHCONR⁸R⁹, or -SO₂NHCN;

R⁷ is hydrogen, straight chain or branched -C₁-C₆-alkyl, -C₂-C₆-alkenyl, or -C₂-C₆-alkynyl each optionally substituted with -OH, -COR⁵, -CN, -C₂-C₆-alkenyl, -C₂-C₆-alkynyl, -OR⁵, -C₁-C₄-perfluoroalkyl, -S(O)_xR⁵ where x is 0-2, -OPO(OR⁵)OR⁶, -PO(OR⁵)R⁶, -OC(O)NR⁵R⁶, -COOR⁵, -CONR⁵R⁶, -SO₃H, -NR⁵R⁶, -NR⁵COR⁶, -NR⁵COOR⁶, -SO₂NR⁵R⁶, -NO₂, -N(R⁵)SO₂R⁶, -NR⁵CONR⁵R⁶, -C₃-C₆

cycloalkyl as defined above, -C₃-C₆-cycloheteroalkyl as defined
 above, -aryl or heteroaryl as defined above, -SO₂NHCOR⁵ or -
 CONHSO₂R⁵ where R⁵ is not hydrogen, -tetrazol-5-yl, -
 NR⁵C(=NR⁶)NR⁵R⁶, -C(O)N R⁵OR⁶, -SO₂NHCONR⁵R⁶ or -
 SO₂NHCN;
 or R⁷ is phenyl or naphthyl, optionally substituted by R¹, R², R³ and R⁴ or
 a 5 to 6 membered heteroaryl group having 1 to 3 heteroatoms
 selected independently from N, O, and S and optionally substituted
 by R¹, R², R³ and R⁴;
 or R⁷ is C₃-C₆ cycloalkyl or 3-6 membered cycloheteroalkyl as defined
 above;
 or R⁷CH₂-N-A-, where A is as defined above, can form a non-aromatic 1,2-benzo-
 fused 7-10 membered heterocyclic ring optionally containing an additional
 heteroatom selected from O, S and N wherein said heterocyclic ring may be
 optionally fused to another benzene ring;
 R⁸ and R⁹ are independently H, aryl or heteroaryl as defined above, -C₃-C₇-
 cycloalkyl or 3 to 6 membered cycloheteroalkyl as defined above, -C₁-C₄-
 perfluoroalkyl, straight chain or branched -C₁-C₆-alkyl, -C₂-C₆-alkenyl, or
 -C₂-C₆-alkynyl, each optionally substituted with hydroxy, alkoxy, aryloxy,
 -C₁-C₄-perfluoroalkyl, amino, mono- and di-C₁-C₆-alkylamino, carboxylic
 acid, carboalkoxy and carboaryloxy, nitro, cyano, carboxamido primary,
 mono- and di-C₁-C₆-alkylcarbonyl;
 a pharmaceutically acceptable salt thereof where one may be formed;
 and an optical isomer or diastereomer thereof where optical isomers and
 diastereomers exist..

2. A compound according to claim 1 wherein both of the carbons of A adjacent to the carbon bearing the sulfonamido group have a substituent other than hydrogen.
3. A compound according to claim 2 wherein the Z group is para-alkoxyphenyl, para-aryloxyphenyl or para-heteroaryloxyphenyl.
4. A compound according to claim 3 which is selected from the group consisting of:
 2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-chloro-N-hydroxy-benzamide,

- 2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-bromo-N-hydroxy-3-methyl-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methyl-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-benzyloxy-N-hydroxy-
5 benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-hydroxycarbamoyl-methoxy-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-(2,2,2-trifluoroethoxy)-benzamide,
10 2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-(2-methoxyethoxymethoxy)-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-[4-(hydroxyaminocarbonyl)-benzyloxy]-N-hydroxy-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-(3-hydroxycarbamoyl-propoxy)-benzamide,
15 2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-(4-hydroxycarbamoyl-butoxy)-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-isopropoxy-benzamide,
20 N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-benzamide,
2-[Benzyl-(4-fluoro-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-benzamide,
25 2-[Benzyl-(4-butoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-benzamide,
2-[Benzyl-(4-benzyloxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-hex-1-ynyl-N-hydroxy-3-methyl-benzamide,
30 2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-ethynyl-N-hydroxy-3-methyl-benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide,
35 N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3,5-dimethyl-benzamide,

- 5-Bromo-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-
3-methyl-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methoxy-
benzamide,
5 2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-4-chloro-N-hydroxy-3-methyl-
benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-(3-methoxy-benzyl)-amino]-3,5-
dimethyl-benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-(2,3,5,6-tetrafluoro-4-methoxy-
10 benzyl)-amino]-3,5-dimethyl-benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-propyl-amino]-3,5-dimethyl-
benzamide,
2-[(2-Bromo-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-
dimethyl-benzamide,
15 2-[(3-Bromo-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-
dimethyl-benzamide,
2-[(4-Bromo-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-
dimethyl-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy- 3-trifluoromethyl-
20 benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3,5-dimethyl-
benzamide,
2-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-
benzamide,
25 3-Bromo-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-
5-methyl-benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-
3-thiophen-2-yl-benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3,5-dimethyl-
30 benzamide,
2-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-
benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy- 3,4,5-trimethoxy-
benzamide,
35 N-Hydroxy-3,4,5-trimethoxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-
amino]-benzamide,

- 5-(4-Methoxy-benzenesulfonyl)-2,3,4,5-tetrahydro-1,5-benzoxazepine-6-carboxylic acid hydroxyamide,
12-(4-Methoxy-benzenesulfonyl)-11,12-dihydro-6H-dibenz[b,f][1,4]oxazocine-1-carboxylic acid hydroxyamide,
5 6-(4-Methoxy-benzenesulfonyl)-3,4,5,6-tetrahydro-2H-1,6-benzoxazocine-7-carboxylic acid hydroxyamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-nitro-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-(3-hydroxy-propoxy)-benzamide,
10 N-Hydroxy-2-[(4-methoxybenzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-thiophen-2-yl benzamide,
2-[Benzyl-(4-methoxybenzenesulfonylamino)-N-hydroxy-3-cyano-5-methyl-benzamide,
3-Furan-2-yl-N-hydroxy-2-[(4-methoxybenzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-benzamide,
15 3-Diethylaminomethyl-N-hydroxy-2-[(4-methoxybenzenesulfonyl)-methylamino]-benzamide,
N-Hydroxy-2-[(4-methoxybenzenesulfonyl)-methylamino]-3-(4-methylpiperazin-1-ylmethyl)-benzamide,
20 2-[Benzyl-(4-methoxybenzenesulfonyl)amino]-3-(1-ethoxycarbonyl-N-hydroxy-1-methylethoxy)-benzamide,
3-Bromo-2-[benzyl-(4-methoxybenzenesulfonyl)amino]-N-hydroxy-benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-5-[2-(methyl-octyl- carbamoyl)-vinyl]-benzamide,
25 N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-5-[2-(methyl-octyl- carbamoyl)-ethyl]-benzamide,
5-(2-Dimethylcarbamoyl-vinyl)-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzamide,
5-[2-(Ethyl-pyridin-4-ylmethyl-carbamoyl)-vinyl]-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzamide,
30 N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-[2-(methyl-octyl-carbamoyl)-vinyl]-benzamide,
5-(2-Dimethylcarbamoyl-vinyl)-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide,
35 5-[2-(Ethyl-phenyl-carbamoyl)-vinyl]-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide,

- 5-(2-Diallylcarbamoyl-vinyl)-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl) pyridin-3-ylmethyl-amino]-3-methyl-5-(3-morpholin-4-yl-3-oxo-propenyl)-benzamide,
5 2'-(Hydroxyimino-methyl)-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide,
3'-(Hydroxyimino-methyl)-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide,
4'-(Hydroxyimino-methyl)-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide,
10 4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-2'-trifluoromethyl-biphenyl-3-carboxylic acid hydroxyamide,
5-Furan-2-yl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide,
15 N-Hydroxy-5-[3-(hydroxyimino-methyl)-thiophen-2-yl]-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide,
5-(5-Chloro-thiophen-2-yl)-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide,
5-(5-Acetyl-thiophen-2-yl)-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide,
20 2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methyl-5-vinyl-benzamide,
4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N(1),N(3)-dihydroxy-5-methyl-isophthalamide di-sodium salt,
25 5-Ethyl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-diethylaminomethyl-N-hydroxy-3-methyl-benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-pyridin-3-yl-benzamide,
30 2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3,6-dimethyl-benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3,6-dimethyl-benzamide,
35 N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-[3-(5-methyl-furan-2-yl)-isoxazol-5-yl]-benzamide,

- 2-[Benzyl-(4-ethoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-
benzamide,
2-[Benzyl-(4-propoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-
benzamide,
5 2-[Benzyl-(4-isopropoxy-benzenesulfonyl)-amino]-N-hydroxy-3,5-dimethyl-
benzamide,
2-[Benzyl-(4-benzyloxy-benzenesulfonyl)-amino]-5-bromo-N-hydroxy-3-methyl-
benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-morpholin-4-
10 ylmethyl-benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-pyrrolidin-1-
ylmethyl-benzamide,
N-Hydroxy-3-imidazol-1-ylmethyl-2-[(4-methoxy-benzenesulfonyl)-methyl-
amino]-benzamide,
15 5-Bromo-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-(4-
methyl-piperazin-1-ylmethyl)-benzamide,
5-Bromo-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methylamino]-3-pyrrolidin-
1-ylmethyl-benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl--amino]-3-
20 pyrrolidin-1-ylmethyl-benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-octyl-amino]-3-(4-methyl-piperazin-
1-ylmethyl)-benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-thiophen-3-ylmethyl-amino]-3-(4-
methyl-piperazin-1-ylmethyl)-benzamide,
25 N-Hydroxy-2-[[[(4-methoxyphenyl)sulfonyl](phenylmethyl)-amino]-3-[(4-methyl-
1-piperazinyl)methyl]benzamide,
N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-
(tetrahydro-pyran-2-yloxymethyl)-benzamide,
N-Hydroxy-3-hydroxymethyl-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-
30 ylmethyl-amino]-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-[2-(tert-butyl-dimethyl-
silanyloxy)-ethoxy]-N-hydroxy-benzamide,
2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-(2-hydroxy-
ethoxy)-benzamide,
35 5-Bromo-N-hydroxy-3-[2-(hydroxycarbamoyl)-ethyl]-2-[(4-methoxy-
benzenesulfonyl)-methyl-amino]-benzamide,

- N-Hydroxy-3-[2-(hydroxycarbamoyl)-ethyl]-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-benzamide,
- 5-Biphenyl-4-ylethynyl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzamide,
- 5 5-(2-Biphenyl-4-yl-ethyl)-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzamide,
- 5-Dodec-1-ynyl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzamide,
- 5-Dodecyl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-3-methyl-benzamide,
- 10 N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methoxymethyl-benzamide,
- N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-isophthalamic acid tert-butyl ester,
- 15 N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-isophthalamic acid methyl ester,
- N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-methyl-amino]-isophthalamic acid methyl ester,
- N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-isophthalamic acid,
- 20 N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-2-ylmethyl-amino]-3-methyl-benzamide,
- N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-4-ylmethyl-amino]-3-methyl-benzamide,
- 25 2-[(4-Diethylaminomethyl-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methyl-benzamide,
- 2-[(4-Dimethylaminomethyl-benzyl)-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methyl-benzamide,
- 2-[(4-Diethylamino-but-2-ynyl)-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methyl-benzamide,
- 30 N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-[4-(4-methyl-piperazin-1-yl)-benzyl]-amino]-3-methyl-benzamide,
- 4-[(2-Hydroxycarbamoyl-6-methyl-phenyl)-(4-methoxy-benzenesulfonyl)-amino]-butyric acid ethyl ester,
- 35 5-[(2-Hydroxycarbamoyl-6-methyl-phenyl)-(4-methoxy-benzenesulfonyl)-amino]-pentanoic acid ethyl ester,

- [(2-Hydroxycarbamoyl-6-methyl-phenyl)-(4-methoxy-benzenesulfonyl)-amino]-acetic acid benzyl ester,
- N-Hydroxy-2-[[4-methoxyphenyl)sulfonyl][2-oxo-2-[(2-pyridinylmethyl)amino]ethyl]amino]-3-methylbenzamide,
- 5 N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]- amino]-3-methyl-benzamide,
- N-Hydroxy-2-[(2-hydroxy-ethyl)-(4-methoxy-benzenesulfonyl)-amino]-3-methylbenzamide,
- 2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-5-dimethylamino-N-hydroxy-3-methyl-benzamide,
- 10 2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-3-dimethylamino-N-hydroxy-benzamide,
- N-Hydroxy-2-[[4-methoxyphenyl)sulfonyl][4-[2-(1-piperidinyl)ethoxy]phenyl)methyl]amino]-3-methylbenzamide,
- 15 2-[[4-(2-Diethylamino-ethoxy)-benzyl]-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-3-methyl-benzamide,
- 5-Bromo-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-amino]-3-methyl-benzamide,
- N-Hydroxy-2-[[4-methoxyphenyl)sulfonyl][4-[[2-(1-piperidinyl)ethyl]amino]carbonyl]phenyl)methyl]amino]-3-methylbenzamide,
- 20 4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide hydrochloride salt,
- N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-5-thiophen-3-yl-benzamide hydrochloride salt,
- 25 4"-Methoxy-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-[1,1';4',1'']terphenyl-3-carboxylic acid hydroxyamide hydrochloride salt,
- 4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-3'-nitro-biphenyl-3-carboxylic acid hydroxyamide hydrochloride salt,
- 30 4'-Methoxy-4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-biphenyl-3-carboxylic acid hydroxyamide hydrochloride salt,
- 5-Benzo[b]thiophen-2-yl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide hydrochloride salt,
- 35 5-Benzo[b]furaphen-2-yl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide hydrochloride salt,

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid hydroxyamide hydrochloride salt,

5 5-Benzo[1,3]dioxol-5-yl-N-hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-3-methyl-benzamide hydrochloride salt,

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-5-methyl-3'-trifluoromethyl-biphenyl-3-carboxylic acid hydroxyamide hydrochloride salt,

10 2-[(4-Chloro-benzyl)-(5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-N-hydroxy-3-methyl-benzamide,

2-[(3,4-Dimethyl-benzyl)-(5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-N-hydroxy-3-methyl-benzamide,

N-Hydroxy-3-methyl-2-[pyridin-3-ylmethyl-(4'-trifluoromethyl-biphenyl-4-sulfonyl)-amino]-benzamide,

15 2-[(2',4'-Dimethoxy-biphenyl-4-sulfonyl)-pyridin-3-ylmethyl-amino]-N-hydroxy-3-methyl-benzamide,

N-Hydroxy-3-methyl-2-[pyridin-3-ylmethyl-(4-thiophen-2-yl-benzenesulfonyl)-amino]-benzamide,

20 2-[(4-Ethynyl-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-N-hydroxy-3-methyl-benzamide,

2-[(4-Benzo[b]thiophen-2-yl-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-N-hydroxy-3-methyl-benzamide,

2-[(4-Benzo[1,3]dioxol-5-yl-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-N-hydroxy-3-methyl-benzamide and

25 3-Methyl-2-[4-(pyridin-4-yloxy)-benzensulfonylamino]-N-hydroxy-benzamide.

5. A compound according to claim 1 which is selected from the group consisting of:

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-benzamide,

30 2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-4-methyl-benzamide,

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-6-methyl-benzamide,

2-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-N-hydroxy-5-methyl-benzamide,

N-Hydroxy-2-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-benzamide, and

35 3-[Benzyl-(4-methoxybenzenesulfonyl)-amino]-naphthalene-2-carboxylic acid hydroxyamide.

6. A method of inhibiting pathological changes mediated by matrix metalloproteinases in mammals which comprises administration to a mammal in need thereof a therapeutically effective amount of a matrix metalloproteinase inhibiting compound according to claim 1.
- 5 7. A method according to claim 6 wherein the condition treated is atherosclerosis, atherosclerotic plaque formation, reduction of coronary thrombosis from atherosclerotic plaque rupture, restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound
10 healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, or periodontal disease.
- 15 8. A method according to claim 6 wherein the condition treated is age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization and corneal graft rejection.
- 20 9. A method of inhibiting pathological changes mediated by TNF- α converting enzyme (TACE) in mammals which comprises administration to a mammal in need thereof a therapeutically effective amount of a TACE inhibiting compound according to claim 1.
- 25 10. The method according to claim 9 wherein the condition treated is rheumatoid arthritis, graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease, or HIV infection.
- 30 11. A pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically effective amount of a matrix metalloproteinase or TACE inhibiting compound according to claim 1.