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(54) Title: BENZENESULFONAMIDE INHIBITOR OF CCR2 CHEMOKINE RECEPTOR

(57) Abstract: Disclosed are compounds of formula (I): or a pharmaceutically acceptable salt thereof, or a solvate thereof, or a combination thereof, as well as compositions of methods of use of the compound, wherein R¹, R², R³, and m are described herein.



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BENZENESULFONAMIDE INHIBITOR OF CCR2 CHEMOKINE RECEPTORBackground of the Invention

5 The present invention relates to novel compounds, pharmaceutical compositions containing them and their use in therapy, as modulators of chemokine receptors, particularly as CCR2 antagonists, as well as to processes for their preparation, and intermediates used in these processes.

10 Chemokines are chemotactic cytokines, of molecular weight 6-15 kDa, that are released by a wide variety of cells to attract and activate, among other cell types, macrophages, T and B lymphocytes, eosinophils, basophils and neutrophils (reviewed in: Luster, *New Eng. J. Med.* **1998**, 338, 436-445 and Rollins, *Blood* **1997**, 90, 909-928). There are two major classes of chemokines, CXC and CC, depending on whether the first two
15 cysteines in the amino acid sequence are separated by a single amino acid (CXC) or are adjacent (CC). The CXC chemokines, such as interleukin-8 (IL-8), neutrophil-activating protein-2 (NAP-2) and melanoma growth stimulatory activity protein (MGSA) are chemotactic primarily for neutrophils and T lymphocytes, whereas the CC chemokines, such as RANTES, MIP-1 α , MIP- β , the monocyte chemotactic proteins (MCP-1, MCP-2,
20 MCP-3, MCP-4, and MCP-5) and the eotaxins (-1 and -2) are chemotactic for, among other cell types, macrophages, T lymphocytes, eosinophils, dendritic cells, and basophils. There also exist the chemokines lymphotactin-1, lymphotactin-2 (both C chemokines), and fractalkine (a CX₃C chemokine) that do not fall into either of the major chemokine subfamilies.

25 The chemokines bind to specific cell-surface receptors belonging to the family of G-protein-coupled seven-transmembrane-domain proteins (reviewed in: Horuk, *Trends Pharm. Sci.* **1994**, 15, 159-165) which are termed "chemokine receptors." On binding their cognate ligands, chemokine receptors transduce an intracellular signal through the
30 associated trimeric G proteins, resulting in, among other responses, a rapid increase in intracellular calcium concentration, changes in cell shape, increased expression of cellular adhesion molecules, degranulation, and promotion of cell migration. There are at least ten human chemokine receptors that bind or respond to CC chemokines with following characteristic patterns (reviewed in Zlotnik and Oshie *Immunity* **2000**, 12, 121):
35 CCR-1 (or "CKR-1" or "CC-CKR-1") [MIP-1 α , MCP-3, MCP-4, RANTES] (Ben-Barruch,

et al., *cell* **1993**, 72, 415-425, and Luster, *New Eng. J. Med.* **1998**, 338, 436-445; CCR2A and CCR2B (or "CKR-2A"/"CKR-2B" or "CC-CKR-2A"/"CC-CKR-2B") [MCP-1, MCP-2, MCP-3, MCP-4, MCP-5] (Charo, et al., *Proc. Natl. Acad. Sci. USA* **1994**, 91, 2752-2756; Luster, *New Eng. J. Med.* **1998**, 338, 436-445); CCR-3 (or "CKR-3" or "CC-CKR-3") [eotaxin-1, eotaxin-2, RANTES, MCP-3, MCP-4] (Combadiere, et al., *J. Biol. Chem.* **1995**, 270, 16491-16494, and Luster, *New Eng. J. Med.* **1998**, 338, 436-445); CCR-4 (or "CKR-4" or "CC-CKR-4") [TARC, MDC] (Power, et al., *J. Biol. Chem.* **1995**, 270, 19495-19500, and Luster, *New Eng. J. Med.* **1998**, 338, 436-445); CCR-5 (or "CKR-5" or "CC-CKR-5") [MIP-1 α , RANTES, MIP-1 β] (Sanson, et al., *Biochemistry* **1996**, 35, 3362-3367); CCR-6 (or "CKR-6" [LARC] (Baba, et al., *J. Biol. Chem.* **1997**, 272, 14893-14898); CCR-7 (or "CKR-7" or "CC-CKR-7") [ELC] (Yoshie et al., *J. Leukoc. Biol.* **1997**, 62, 634-644); CCR-8 (or "CKR-8" or "CC-CKR-8") [1-309] (Napolitano et al., *J. Immunol.*, 1996, 157, 2759-2763); CCR-10 (or "CKR-10" or "CC-CKR-10") [MCP-1, MCP-3] (Bonini, et al., *DNA and Cell Biol.* **1997**, 16, 1249-1256); and CCR-11 [MCP-1, MCP-2, and MCP-4] (Schweickert, et al., *J. bio1. Chem.* **2000**, 275, 90550).

In addition to the mammalian chemokine receptors, mammalian cytomegaloviruses, herpes viruses and poxviruses have been shown to express, in infected cells, proteins with the binding properties of chemokine receptors (reviewed in: Wells and Schwartz, *Curr. Opin. Biotech.* **1997**, 8, 741-748). Human CC chemokines, such as RANTES and MCF-3, can cause rapid mobilization of calcium via these virally encoded receptors. Receptor expression may be permissive for infection by allowing for the subversion of normal immune system surveillance and response to infection. Additionally, human chemokine receptors, such as CXCR4, CCR2, CCR3, CCR5 and CCR8, can act as co-receptors for the infection of mammalian cells by microbes as with, for example, the human immunodeficiency viruses (HIV).

The chemokines and their cognate receptors have been implicated as being important mediators of inflammatory, infectious, and immunoregulatory disorders and diseases, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis (reviewed in: F. H. Carter, *Current Opinion in Chemical Biology* **2002**, 6, 510; Trivedi, et al, *Ann. Reports Med. Chem.* **2000**, 35, 191; Saunders and Tarby, *Drug Disc. Today* **1999**, 4, 80; Fremack and Schall, *Nature Medicine* **1996**, 2, 1174). For example, the chemokine monocyte chemoattractant-1 (MCP-1) and its receptor CC Chemokine Receptor 2 (CCR2) play a pivotal role in attracting leukocytes to sites of inflammation and in subsequently activating these cells.

When the chemokine MCP-1 binds to CCR2, it induces a rapid increase in intracellular calcium concentration, increased expression of cellular adhesion molecules, cellular degranulation, and the promotion of leukocyte migration. Demonstration of the importance of the MCP-1/CCR2 interaction has been provided by experiments with genetically modified mice. MCP-1 ^{-/-} mice had normal numbers of leukocytes and macrophages, but were unable to recruit monocytes into sites of inflammation after several different types of immune challenge (Bao Lu, et al., *J. Exp. Med.* **1998**, 187, 601). Likewise, CCR2 ^{-/-} mice were unable to recruit monocytes or produce interferon- γ when challenged with various exogenous agents; moreover, the leukocytes of CCR2 null mice did not migrate in response to MCP-1 (Landin Boring, et al., *J. Clin. Invest.* **1997**, 100, 2552), thereby demonstrating the specificity of the MCP-1/CCR2 interaction. Two other groups have independently reported equivalent results with different strains of CCR2 ^{-/-} mice (William A. Kuziel, et al., *Proc. Natl. Acad. Sci. USA* **1997**, 94, 12053, and Takao Kurihara, et al., *J. Exp. Med.* **1997**, 186, 1757). The viability and generally normal health of the MCP-1 ^{-/-} and CCR2 ^{-/-} animals is noteworthy, in that disruption of the MCP-1/CCR2 interaction does not induce physiological crisis. Taken together, these data lead one to the conclusion that molecules that block the actions of MCP-1 would be useful in treating a number of inflammatory and autoimmune disorders. This hypothesis has now been validated in a number of different animal disease models, as described below.

It is known that MCP-1 is upregulated in patients with rheumatoid arthritis (Alisa Koch, et al., *J. Clin. Invest.* **1992**, 90, 772 - 779). Moreover, several studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating rheumatoid arthritis. A DNA vaccine encoding MCP-1 was shown recently to ameliorate chronic polyadjuvant-induced arthritis in rats (Sawsan Youssef, et al., *J. Clin. Invest.* **2000**, 106, 361). Likewise, inflammatory disease symptoms could be controlled via direct administration of antibodies for MCP-1 to rats with collagen-induced arthritis (Hiroomi Ogata, et al., *J. Pathol.* **1997**, 182, 106), or streptococcal cell wall-induced arthritis (Ralph C. Schimmer, et al., *J. Immunol.* **1998**, 160, 1466). Perhaps most significantly, a peptide antagonist of MCP-1, MCP-1(9-76)₁ was shown both to prevent disease onset and to reduce disease symptoms (depending on the time of administration) in the MRL-1pr mouse model of arthritis (Jiang-Hong Gong, et al., *J. Exp. Med.* **1997**, 186, 131).

It is known that MCP-1 is upregulated in atherosclerotic lesions, and it has been shown that circulating levels of MCP-1 are reduced through treatment with therapeutic agents, plays a role in disease progression (Abdolreza Rezaie-Majd, et al, *Arterioscler. Thromb. Vasc. Biol.* **2002**, *22*, 1194 - 1199). Four key studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating atherosclerosis. For example, when MCP-1 $-/-$ mice are mated with LDL receptor-deficient mice, an 83% reduction in aortic lipid deposition was observed (Long Gu, et al., *Mol. Cell* **1998**, *2*, 275). Similarly, when MCP-1 was genetically ablated from mice which already overexpressed human apolipoprotein B, the resulting mice were protected from atherosclerotic lesion formation relative to the MCP-1 $+/+$ apoB control mice (Jennifa Gosling, et al., *J. Clin. Invest.* 1999, *103*, 773). Likewise, when CCR2 $-/-$ mice are crossed with apolipoprotein E $-/-$ mice, a significant decrease in the incidence of atherosclerotic lesions was observed (Landin Boring, et al, *Nature* **1998**, *394*, 894). Finally, when apolipoprotein E $-/-$ mice are administered a gene encoding a peptide antagonist of CCR2, then lesion size is decreased and plaque stability is increased (W Ni, et al. *Circulation* **2001**, *103*, 2096 -2101).

It is known that MCP-1 is upregulated in human multiple sclerosis, and it has been shown that effective therapy with interferon b-1b reduces MCP-1 expression in peripheral blood mononuclear cells, suggesting that MCP-1 plays a role in disease progression (Carla Iarlori, et al., *J. Neuroimmunol.* **2002**, *123*, 170 - 179). Other studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating multiple sclerosis; all of these studies have been demonstrated in experimental autoimmune encephalomyelitis (EAE), the conventional animal model for multiple sclerosis. Administration of antibodies for MCP-1 to animals with EAE significantly diminished disease relapse (K. J. Kennedy, et al., *J. Neuroimmunol.* **1998**, *92*, 98). Furthermore, two recent reports have now shown that CCR2 $-/-$ mice are resistant to EAB (Brian T. Fife, et al., *J. Exp. Med.* **2000**, *192*, 899; Leonid Izikson, et al., *J. Exp. Med.* **2000**, *192*, 1075).

It is known that MCP-1 is upregulated in patients who develop bronchiolitis obliterans syndrome after lung transplantation (Martine Reynaud-Gaubert, et al., *J. of Heart and Lung Transplant.*, **2002**, *21*, 721 - 730; John Belperio, et al., *J. Clin. Invest.* **2001**, *108*, 547 - 556). In a murine model of bronchiolitis obliterans syndrome, administration of an antibody to MCP-1 led to attenuation of airway obliteration; likewise, CCR2 $-/-$ mice were resistant to airway obliteration in this same model (John Belperio, et al., *J. Clin. Invest.*

2001, 108, 547 - 556). These data suggest that antagonism of MCP-1/CCR2 may be beneficial in treating rejection of organs following transplantation.

5 Other studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating asthma. Sequestration of MCP-1 with a neutralizing antibody in ovalbumin-challenged mice resulted in marked decrease in bronchial hyperresponsiveness and inflammation (Jose-Angel Gonzalo, et al., *J. Exp. Med.* **1998**, 188, 157). It proved possible to reduce allergic airway inflammation in *Schistosoma mansoni* egg-challenged mice through the administration of antibodies for MCP-1
10 (Nicholas W. Lukacs, et al., *J. Immunol.* 1997, 158, 4398). Consistent with this, MCP-1 -/- mice displayed a reduced response to challenge with *Schistosoma mansoni* egg (Bao Lu, et al., *J. Exp. Med.* **1998**, 187, 601).

15 Other studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating kidney disease. Administration of antibodies for MCP-1 in a murine model of glomerulonephritis resulted in a marked decrease in glomerular crescent formation and deposition of type I collagen (Clare M. Lloyd, et al., *J. Exp. Med.* **1997**, 185, 1371). In addition, MCP-1 -/- mice with induced nephrotoxic serum nephritis showed significantly less tubular damage than their MCP-1 +/- counterparts (Gregory H. Tesch, et al. *J. Cur. Invest.* **1999**, 103, 73).
20

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating systemic lupus erythematosus. Crossing of MCP-1 -/- mice with MRL-FAS1pr mice (the latter of which have a fatal autoimmune disease that is
25 analogous to human systemic lupus erythematosus) results in mice that have less disease and longer survival than the wildtype MRL-FAS1pr mice (Gregory H. Tesch, et al., *J. Exp. Med.* **1999**, 190, 1813). One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating colitis. CCR2 -/- mice were protected from the effects of dextran sodium sulfate-induced colitis (Pietro
30 G. Andres, et al., *J. Immunol.* **2000**, 164, 6303).

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating alveolitis. When rats with IgA immune complex lung injury were treated intravenously with antibodies raised against rat MCP-1 (JE), the symptoms
35 of alveolitis were partially alleviated (Michael L. Jones, et al., *J. Immunol.* **1992**, 149, 2147).

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating cancer. When immunodeficient mice bearing human breast carcinoma cells were treated with an anti-MCP-1 antibody, inhibition of lung micrometastases and increases in survival were observed (Rosalba Salcedo, et al, Blood 2000, 96, 34 - 40).

One study has demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating restinosis. Mice deficient in CCR2 showed reductions in the intimal area and in the intima/media ratio (relative to wildtype littermates) after injury of the femoral artery (Merce Roque, et al. *Arterioscler. Thromb. Vasc. Biol.* 2002, 22, 554 - 559).

Other studies have provided evidence that MCP-1 is overexpressed in various disease states not mentioned above. These reports provide correlative evidence that MCP-1 antagonists could be useful therapeutics for such diseases. Two reports described the overexpression of MCP-1 in the intestinal epithelial cells and bowel mucosa of patients with inflammatory bowel disease (H. C. Reinecker, et al., *Gastroenterology* 1995, 108, 40, and Michael C. Grimm, et al., *J. Leukoc. Biol.* 1996, 59, 804). Two reports describe the overexpression of MCP-1 rats with induced brain trauma (J. S. King, et al., *J. Neuroimmunol.* 1994, 56, 127, and Joan W. Berman, et al., *J. lininunol.* 1996, 156, 3017). Another study has demonstrated the overexpression of MCP-1 in rodent cardiac allografts, suggesting a role for MCP-1 in the pathogenesis of transplant arteriosclerosis (Mary E. Russell, et al. *Proc. Natl. Acad. Sci. USA* 1993, 90, 6086). The overexpression of MCP-1 has been noted in the lung endothelial cells of patients with idiopathic pulmonary fibrosis (Harry N. Antoniades, et al., *Proc. Natl. Acad. Sci. USA* 1992, 89, 5371). Similarly, the overexpression of MCP-1 has been noted in the skin from patients with psoriasis (M. Deleuran, et al., *J. Derinatol. Sci.* 1996, 13, 228, and R. Gillitzer, et al., *J. Invest. Dermatol.* 1993, 101, 127). Finally, a recent report has shown that MCP-1 is overexpressed in the brains and cerebrospinal fluid of patients with HIV-associated dementia (Alfredo Garzino-Demo, WO 99/46991).

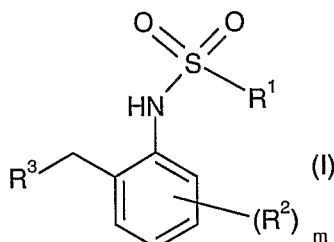
It should also be noted that CCR2 has been implicated as a co-receptor for some strains of HIV (B. J. Doranz, et al., *Cell* 1996, 85, 1149). It has also been determined that the use of CCR2 as an HIV co-receptor can be correlated with disease progression (Ruth I. Connor, et al., *J. Exp. Med.* 1997, 185, 621). This finding is consistent with the recent

finding that the presence of a CCR2 mutant, CCR2-641, is positively correlated with delayed onset of HIV in the human population (Michael W. Smith, et al., Science **1997**, 277,959). Although MCP-1 has not been implicated in these processes, it may be that MCP-1 antagonists that act via binding to CCR2 may have beneficial therapeutic effects in delaying the disease progression to AIDS in HIV-infected patients.

There is a need in the art to discover compounds that antagonize MCP-1 by binding to the CCR2 receptor, more particularly the CCR2b receptor.

10 Summary of the Invention

In a first aspect, the present invention is a compound as represented in formula (I):



or a salt thereof, or a solvate thereof, or a combination thereof; wherein

R¹ represents an aryl, a thienyl, a benzothienyl, an imidazolyl, a pyridyl, an isoquinoliny, a piperonyl, a benzoxathiadiazolyl, or a benzoxadiazolyl group optionally substituted with one to three R⁴ groups, wherein each R⁴ group is independently selected from the group consisting of C₁₋₆-alkyl, C₁₋₆-haloalkyl, C₁₋₆-alkoxy, C₁₋₆-haloalkoxy, halo, -NH₂, -OH, -CN, -NO₂, CF₃, phenyl, phenoxy, phenyl-C(O)-, isoxazolyl, and -C(O)NR⁷R⁸, wherein R⁷ and R⁸ each independently represent hydrogen or C₁₋₄ alkyl, or R⁷ and R⁸ together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated heterocyclic group optionally containing an additional heteroatom selected from nitrogen, oxygen and sulphur;

m is 1, 2, or 3;

each R² is independently selected from the group consisting of halo, -CN, OCF₃, and -CF₃;

5 R³ is a heteroaryl or a heterocycloalkyl group optionally substituted by up to three substituents independently selected from the group consisting of halo, hydroxy, hydroxy-C₁₋₆-alkyl-, C₁₋₄alkoxy-C₁₋₆alkyl-, C₁₋₄alkoxy-, C₁₋₄thioalkoxy, amino, R¹⁰R¹¹N-C₁₋₄alkyl-, heterocycloalkyl, heteroaryl, halogenated heteroaryl, phenyl, benzyl, halophenyl, C₁₋₄-alkylphenyl, methoxyphenyl, trifluoromethylphenyl, cyanophenyl, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, -CN, C₁₋₄alkylthio-, -CF₃, -CO₂H, -CONR⁷R⁸, -NC(O)R¹²N and -CO-C₁₋₄ alkyl, 10 wherein R¹⁰ and R¹¹ each independently represent hydrogen or C₁₋₆ alkyl and R¹² is C₁₋₆ alkyl or C₁₋₆ haloalkyl;

15 In a second aspect, the present invention is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, or a solvate thereof, or a combination thereof and a pharmaceutically acceptable carrier, diluent, or excipient or combination thereof.

20 In a third aspect, the present invention is a method for treating a disease or condition mediated by CCR2 comprising administering to a patient in need thereof a pharmaceutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate thereof or a combination thereof.

25 Compounds within the scope of the present invention have potential in the treatment of conditions wherein modulation, especially antagonism/inhibition, of the CCR2 receptor is thought to be beneficial.

30 For example, the compounds may be effective in the treatment of diseases such as atherosclerosis, asthma, seasonal and perennial allergic rhinitis, sinusitis, conjunctivitis, food allergy, scombroid poisoning, pulmonary fibrosis, restenosis, including vascular restenosis, myocarditis, ulcerative colitis, psoriasis, urticaria, pruritis, eczema, atopic dermatitis, inflammatory bowel disease, chronic obstructive pulmonary disease, thrombotic disease, otitis media, rheumatoid arthritis, nephritis (nephropathy), liver cirrhosis, multiple sclerosis and systemic sclerosis, lupus, erythematosus, hepatitis, pancreatitis, sarcoidosis, organ transplantation, Crohn's disease, endometriosis, cardiac 35 disease, congestive heart failure, viral meningitis, cerebral infarction, neuropathy,

Kawasaki disease, Alzheimer's disease, stroke, acute nerve injury, HIV infection, AIDS, autoimmune diseases, cancer, and sepsis.

Detailed Description of the Invention

5

It should be noted that CCR2 is also the receptor for the chemokines MCP-2, MCP-3, MCP-4, and MCP-5 (Luster, New Eng. J. Med. 1998, 338, 436-445). Since the new compounds of formula (I) described herein antagonize MCP-1 by binding to the CCR2 receptor, it may be that these compounds of formula (I) are also effective antagonists of the actions of MCP-2, MCP-3, MCP-4, and MCP-5 that are mediated by CCR2.

10

For the avoidance of doubt, the term "independently" means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

15

As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C₁₋₆ alkyl means a straight or branched alkyl containing at 1 to 6 carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isobutyl, isopropyl, t-butyl and 1,1-dimethylpropyl.

20

As used herein, the term "alkoxy" refers to a straight or branched alkoxy group containing the specified number of carbon atoms. For example, C₁₋₆ alkoxy means a straight or branched alkoxy group containing 1 to 6 carbon atoms. Examples of "alkoxy" include, but are not limited to methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy or hexyloxy.

25

As used herein, the term "alkylthio" refers to a straight or branched alkylthio group containing the specified number of carbon atoms. For example, C₁₋₆ alkylthio means a straight or branched alkylthio group containing 1 to 6 carbon atoms. Examples of "alkylthio" as used herein include, but are not limited to methylthio, ethylthio, propylthio, prop-2-thio, butylthio, but-2-thio, 2-methylprop-1-thio, 2-methylprop-2-thio.

30

As used herein the term C₃₋₆ cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups.

35

The term halogen or halo refers to fluoro, chloro, bromo and iodo.

Examples of heterocycloalkyl groups include, but are not limited to pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholino, thiomorpholino, piperazinyl, oxopiperidinyl, oxophenyltriazaspirodecyl, oxopyrazolidinyl, oxopyrazolyl, oxooxazolidinyl, oxoimidazolidinyl, dioxazaspirodecyl groups.

Heteroaryl groups include, but are not limited to, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzothienyl, indolyl, isoindolyl, benzoxazolyl, benzthiazolyl, indazolyl, indolaziny, benzimidazolyl, benzotriazolyl, purinyl, coumarinyl, isocoumarinyl, chromonyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, phthalazinyl, quinoxalinyl, pteridinyl, 1,8-naphthyridinyl, oxo- or dioxo- benzoxazolyl, -benzotriazolyl, -pyridinyl, -pyrazolyl, -benzopiperidinyl and -benzopiperazinyl.

Suitable examples of C₆₋₁₀ aryl ring systems include: phenyl and naphthyl.

It will be understood that ring systems covered by the definitions in this specification are those which are stable enough to be effective for the intended purpose. This stability is with reference to the preparation and storage of the compound containing said ring system and not with reference to *in vivo* metabolism.

As used herein, the term "pharmaceutically acceptable" means suitable for pharmaceutical use.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol, and acetic acid.

The compounds of formula (I) as defined above contain a basic grouping and may also contain an acidic grouping and therefore may form salts with physiologically acceptable acids or bases.

Physiologically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compounds. Such salts must clearly have a physiologically acceptable anion or cation. Suitably physiologically acceptable salts of the compounds of the present invention include acid addition salts
5 formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, phosphoric, metaphosphoric, nitric and sulfuric acids, and with organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, formic, propionic, glycolic, gluconic, maleic, succinic, camphorsulfuric, isothionic, mucic, gentisic, isonicotinic, saccharic, glucuronic, furoic, glutamic, ascorbic, anthranilic, salicylic, phenylacetic, mandelic,
10 embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, stearic, sulfinilic, alginic, galacturonic and arylsulfonic, for example benzenesulfonic and p-toluenesulfonic, acids; base addition salts formed with alkali metals and alkaline earth metals and organic bases such as N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), lysine and procaine; and internally
15 formed salts. Salts having a non-physiologically acceptable anion or cation are within the scope of the invention as useful intermediates for the preparation of physiologically acceptable salts and/or for use in non-therapeutic, for example, *in vitro*, situations.

Certain of the compounds of the invention may form acid addition salts with one or more
20 equivalents of the acid. Certain of the compounds of the invention may form acid addition salts with less than one equivalent of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or
25 more chiral centres are inverted. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.
30

When a specific enantiomer of a compound of general formula (I) is required, this may
35 be obtained, for example, by resolution of a corresponding enantiomeric mixture of a

compound of formula (I) using conventional methods. Thus the required enantiomer may be obtained from the racemic compound of formula (I) by use of chiral HPLC procedure.

According to a further aspect, the invention provides a method for treating a disease or condition mediated by CCR2 comprising administering to a patient in need thereof a pharmaceutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof, or a solvate thereof or a combination thereof.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention further provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, or a solvate thereof, or a combination thereof and a pharmaceutically acceptable carrier, diluent, or excipient or a combination thereof. The carrier, diluent and/or excipient must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the patient.

The compounds of the invention may be administered in conventional dosage forms prepared by combining a compound of the invention with standard pharmaceutical carriers, diluents or excipients according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, buccal, topical, inhalation or insufflation, implant, rectal or parenteral administration to mammals including humans.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate, glycine or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycolate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; solubilizers such as surfactants for example polysorbates or other agents such as cyclodextrins; and preservatives, for example, methyl or propyl p-hydroxybenzoates or ascorbic acid; and, if desired, conventional flavouring or colouring agents. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

25

The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For parenteral administration, fluid unit dosage forms are prepared utilising the compound and a sterile vehicle, water being preferred. The compound, depending on

the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

5 Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilised powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in
10 substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

15 It will further be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated, the route of administration and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician. In general however doses employed for adult
20 human treatment will typically be in the range of 1 to 1000mg per day, dependent upon the route of administration.

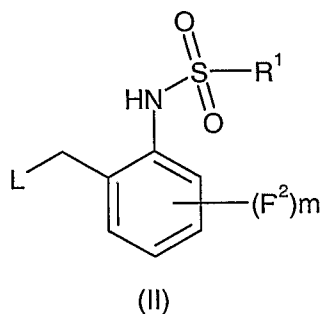
The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses
25 per day. Where the compositions comprise dosage units, each unit will typically contain from 1-1000 mg of the active ingredient.

Compounds of the invention may be prepared, in known manner, in a variety of ways. In the following reaction schemes and hereafter, unless otherwise stated R^1 to R^3 etc. are
30 as defined above. These processes form further aspects of the invention.

Those skilled in the art will appreciate that in the preparation of the compounds of the invention or a solvate thereof it may be necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions. Suitable
35 protecting groups for use according to the present invention are well known to those skilled in the art and may be used in a conventional manner. See, for example,

“Protective groups in organic synthesis” by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or “Protecting Groups” by P.J. Kocienski (Georg Thieme Verlag 1994). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g. benzyloxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g. 9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), isopropyloxycarbonyl, cyclohexyloxycarbonyl) and alkyl type protecting groups (e.g. benzyl, trityl, chlorotriyl). Examples of suitable oxygen protecting groups may include for example alkyl silyl groups, such as trimethylsilyl or *tert*-butyldimethylsilyl; alkyl ethers such as tetrahydropyranyl or *tert*-butyl; or esters such as acetate.

The compounds of formula (I), wherein the R^3 group is attached to the methylene linker via a nitrogen atom, may in general be prepared by the reaction of a compound of formula (II):



wherein L is a leaving group, and R^1 , R^2 and m are as defined above, with a compound of formula (III)



wherein R^3 is as defined above;

and thereafter optionally

(i) removing any protecting group(s); and/or

(ii) forming a salt; and/or

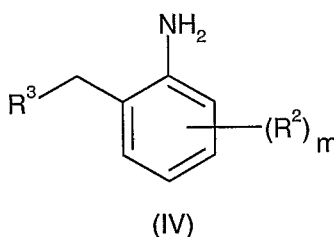
(iii) converting a compound of formula (I) or a salt thereof to another compound of formula (I) or a salt thereof.

Suitable leaving groups L include chloro or bromo. Alternatively L may represents a sulfonyloxy group such C₁₋₄ alkylsulfonyloxy (for example methanesulfonyloxy), C₁₋₄ alkylsulfonyloxy or haloC₁₋₄ alkylsulfonyloxy (for example trifluoromethanesulfonyloxy); or arylsulfonyloxy for example *para*-toluenesulfonyloxy.

5

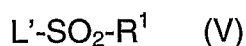
Typically, where L represents chloro, such a reaction may be carried out by dissolving the compound of formula (III) in a suitable solvent, for example 1,4-dioxane, in the presence of an appropriate crown ether, for example 18-crown-6-ether, and then reacting it with a deprotonating agent such as potassium *tert*-butoxide, and then reacting
 10 the resulting solution with the compound of formula (II). The reaction with the compound of formula (II) may generally be carried out at a temperature of between 50°C and 80°C for period of between 12 and 24 hours.

Alternatively, the compounds of formula (I) may be prepared by the reaction of a
 15 compound of formula (IV):



wherein R² and R³ are as defined above, with a compound of formula (V)

20



wherein L' is a suitable leaving group, and R¹ is as defined above;

25

and thereafter optionally,

(i) removing any protecting group(s); and/or

(ii) forming a salt; and/or

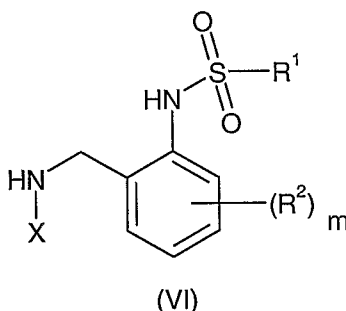
(iii) converting a compound of formula (I) or a salt thereof to another compound of formula (I) or a salt thereof.

30

Suitable leaving groups L' include chloro, bromo or pentafluorophenoxy.

Typically, where L' represents chloro, such a reaction may be carried out by dissolving the compound of formula (IV) in a suitable solvent, for example pyridine optionally mixed with a second solvent, such as chloroform or tetrahydrofuran, and reacting it with the compound of formula (V) also in a suitable solvent, for example pyridine. The addition of a catalytic quantity of dimethylaminopyridine may also be used. The reaction would generally be carried out at elevated temperature in the region of 80-250°C, for example at about 200°C, for a period of 30 minutes to 1 hour or at 80°C for a period of 5-24 hours.

- 10 To prepare a compound of formula (I) wherein R³ represents a ring system carrying one or more oxo substituents, and wherein the group R³ is joined to the methylene linker by a nitrogen atom, this ring system may be formed *de novo* by methods well-known to the person skilled in the art.
- 15 Thus in a representative process a compound of formula (II), as defined above, may be reacted with an appropriate reagent to prepare a compound of formula (VI):



- 20 wherein m, R¹ and R² are as defined above, and X is a group capable of being converted by reaction with appropriate reagents into the group R³ or a protected derivative thereof;

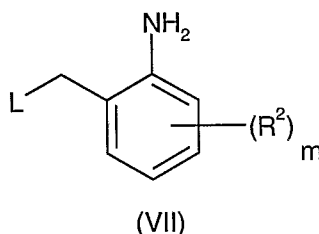
and thereafter, as necessary,

- (i) removing any protecting group(s); and/or
- 25 (ii) forming a salt; and/or
- (iii) converting a compound of formula (I) or a salt thereof to another compound of formula (I) or a salt thereof.

For example, a suitable scheme to generate *de novo* a pyridazinone ring system would suitably involve reacting a compound of formula (II) wherein L represents chloro with *tert*-

butyl carbazate in a suitable solvent, for example DMF. Typically such a reaction would be carried out at ambient temperature for between 3 and 8 hours. The resulting product may then be dissolved in a suitable solvent containing 50% trifluoroacetic acid, for example dichloromethane, and stirred for a suitable time, typically 2 to 3 hours, at ambient temperature. Subsequent to the removal of the solvent the residue may be reacted with ethyl levulinate and glacial acetic acid, typically at elevated temperature in the region of 100°C for between 30 and 60 minutes. The final product will represent a compound of formula (I) wherein R³ represents a 3-methyl-6-oxo-5,6-dihydro-1(4H)-pyridazinyl group.

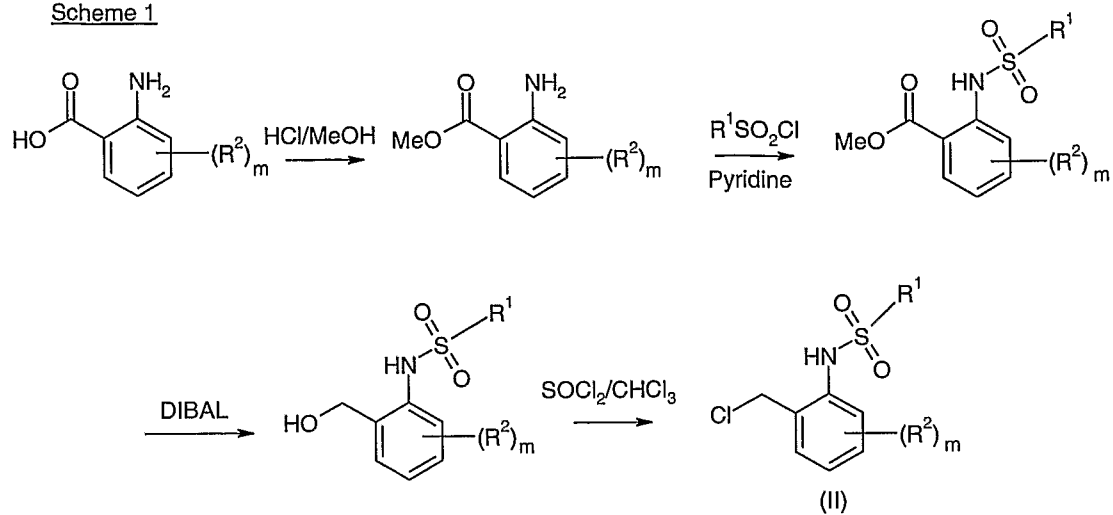
The compound of formula (IV), wherein the group R³ is joined to the methylene linker by a nitrogen atom, may be prepared by reacting a compound of formula (VII):



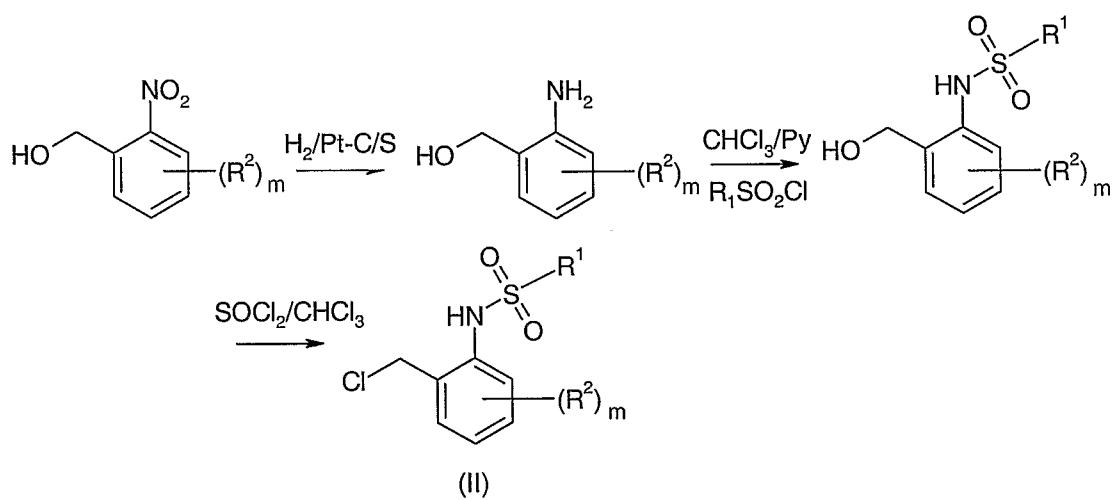
wherein L, R² and m are as defined above, with a compound of formula (III) as defined above. Such a reaction will be analogous to the reaction of a compound of formula (II) with a compound of formula (III) described above.

Compounds of formula (II) may in general be prepared by a process analogous to that set out in Schemes 1 or 2 below:

Scheme 1

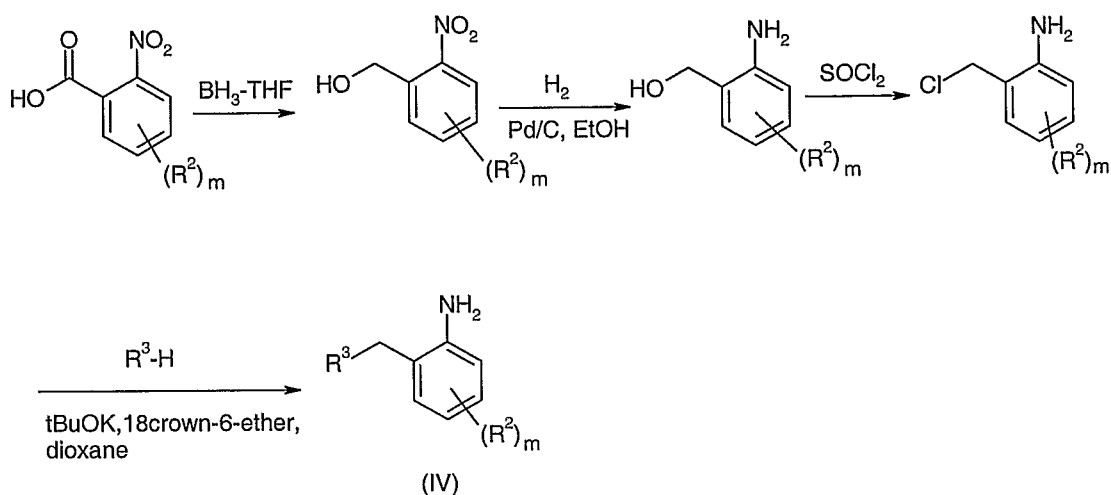


Scheme 2

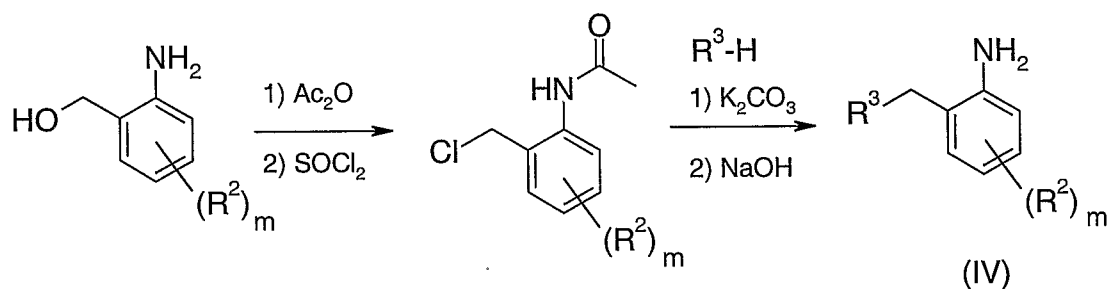


- 5 The compounds of formula (IV) may be prepared by a process analogous to that set out in Schemes 3 or 4 below:

Scheme 3



Scheme 4

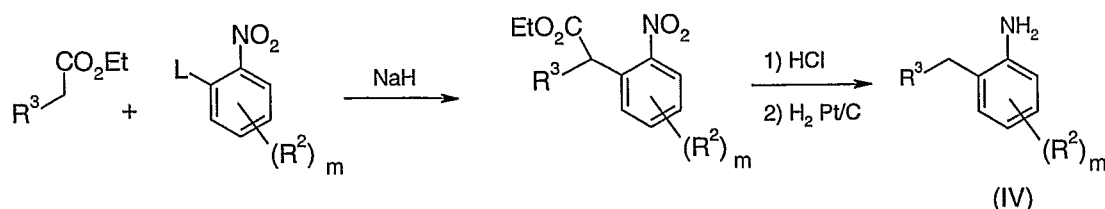


5

Compounds of formula (IV) wherein the R^3 group is joined to the methylene linker by a carbon atom may in general be prepared by a process analogous to that set out in Scheme 5 below. The ethyl ester starting materials may be prepared according to literature methods *J.Med.Chem.*, 1990, 2982. and *J.Am.Chem.Soc.*, 1958, 3908.

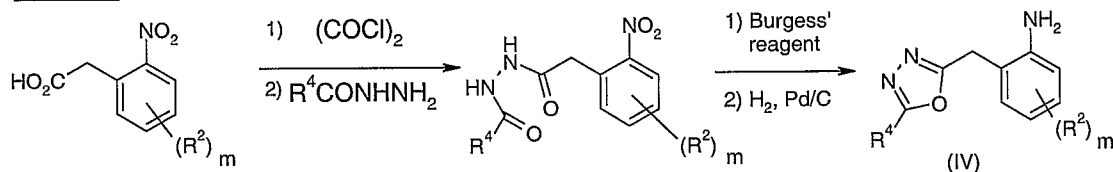
- 10 Treatment with an appropriate base, for example sodium hydride or sodium bis(trimethylsilyl) amide, and reaction with a nitro arene bearing a suitable leaving group L, such as chloro, gives intermediates of the type shown. Hydrolysis of the ester under hydrolytic conditions, for example aqueous hydrochloric acid in ethanol, concurrent decarboxylation and reduction of the nitro group using, for example, hydrogenation with
- 15 platinum or palladium catalysis in a suitable solvent, for example ethanol, give compounds of the formula (IV).

Scheme 5



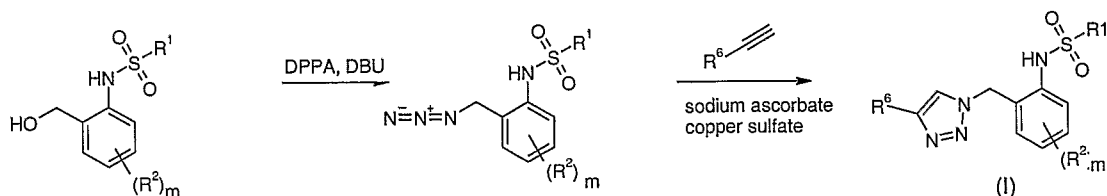
Alternatively, such compounds may be prepared by *de novo* generation of a hetero-aryl ring, for example by the general process outlined in Scheme 6. Generation of a di-acyl hydrazine of the type shown may be achieved by, for example, activation of a carboxylic acid to the acid chloride with oxalyl chloride in the presence of a catalytic quantity of dimethylformamide or dimethylacetamide and subsequent reaction with the appropriate acyl hydrazine. Dehydration of the diacylhydrazine intermediate may be achieved with an appropriate reagent such as Burgess' reagent. Reduction of the nitro-arene to the corresponding aniline (IV) may be achieved by hydrogenation with platinum or palladium catalysis in a suitable solvent, for example ethanol.

Scheme 6



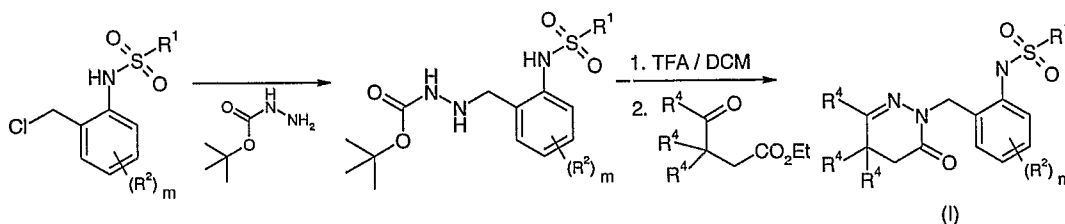
Substituted triazoly examples may be constructed as outlined by the general method provided in Scheme 7. Preparation of the intermediate azides may be achieved by treatment of relevant alcohol with an azidating reagent such as diphenylphosphoryl azide in the presence of an appropriate base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene. The triazole products may be prepared by reaction of appropriately substituted acetylenes catalysed by, for example, copper sulfate in the presence of sodium ascorbate.

Scheme 7



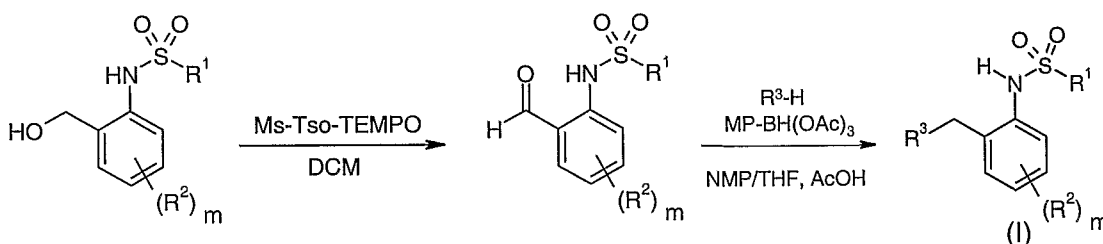
The compounds of formula (I), wherein the R^3 group is a dihydropyridazinone or a dihydropyrazolone may be prepared from a compound of formula (II) by a process analogous to that set out in Scheme 8. Direct displacement of the chloride with *t*-butyl carbazate followed by removal of the protecting group provides the hydrazine which can

Scheme 8



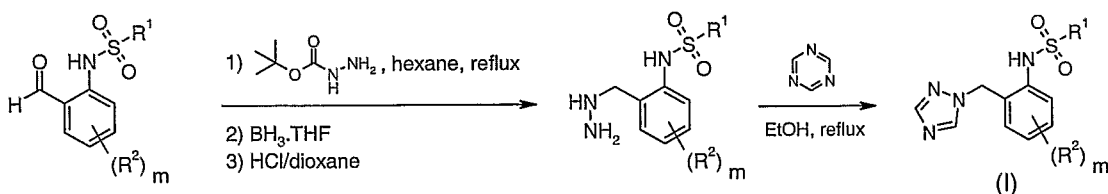
An alternative method of preparing the compounds of formula (I) wherein the R^3 group is attached to the methylene linker via a nitrogen atom is outlined in Scheme 9. Reductive amination of the aldehyde provides the amine of formula (I).

Scheme 9



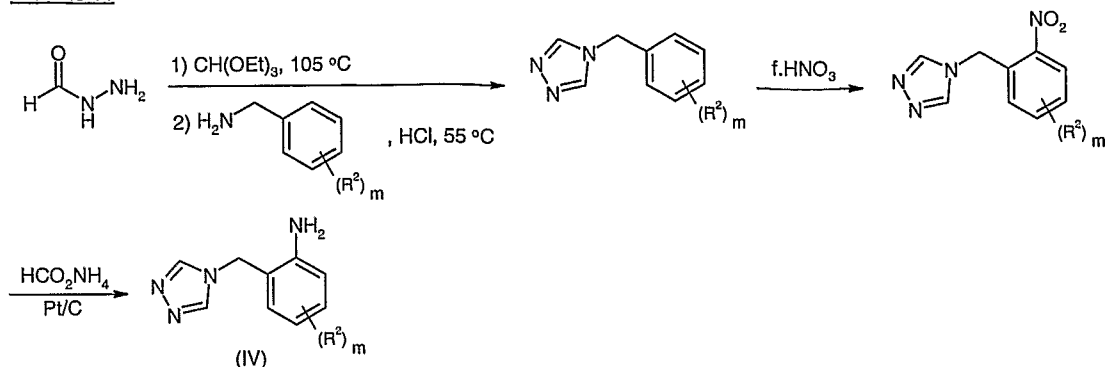
1,2,4-Triazole examples may be constructed as by the general procedure illustrated in Scheme 10. Treatment with *t*-butyl carbazate, followed by a borane reduction and removal of the protecting group provides the hydrazine. Addition of 1,3,5-triazine yields the triazole.

Scheme 10

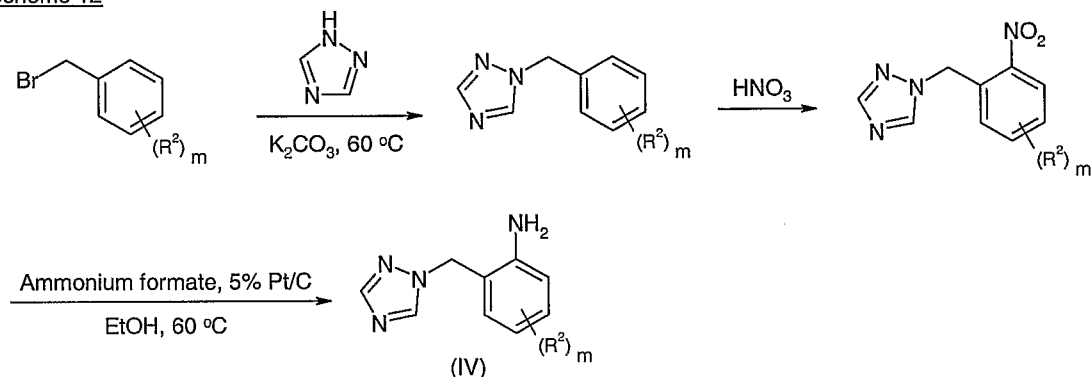


Alternatively, 1,2,4-triazoles of formula (IV) may be constructed by the general methods shown in Scheme 11 and Scheme 12.

Scheme 11

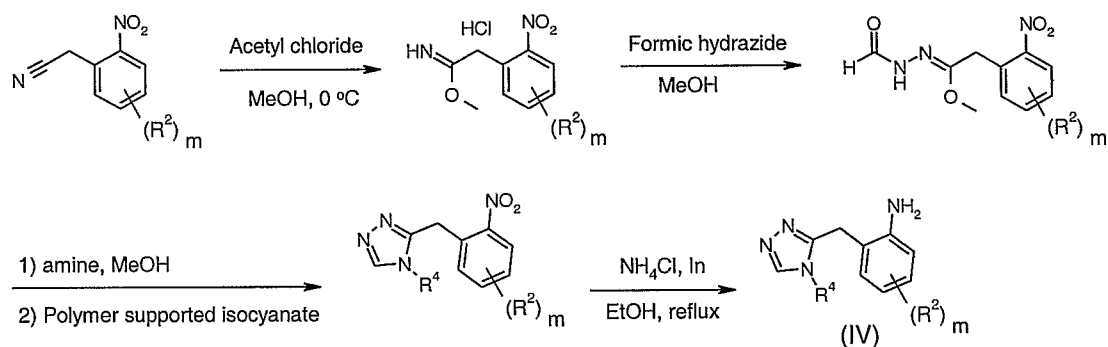


Scheme 12



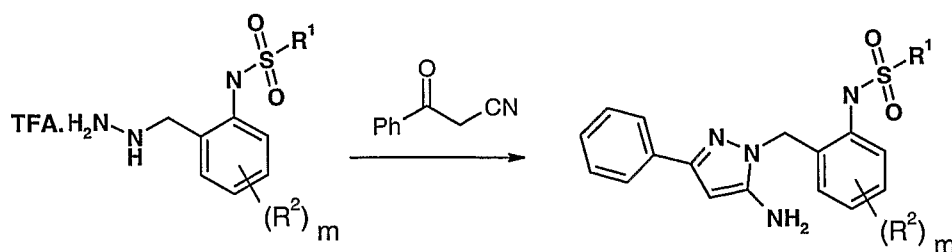
Carbon linked 1,2,4-triazoles of formula (IV) may be prepared by the method in Scheme 13. Treatment of the nitrile with acetyl chloride provides the imine which is converted to the formyl hydrazone. Addition of an amine allows for ring closure to the triazole. Polymer supported isocyanate is added to capture any excess amine. Reduction of the nitrobenzene then provides the aniline.

Scheme 13



Imidazoles of formula (I) may be constructed from the hydrazines in formed in Scheme 10 by the general procedure outlined in Scheme 14. Treatment of the hydrazine with a 3-substituted 3-oxopropanenitrile affords the imidazole.

Scheme 14



Interconversion reactions between compounds of formula (I) may be performed using methods well known in the art. Included are conversions of the substituent(s) within the group R^3 and/or conversions within groups R^2 and R^1 for example:

- 5 (i) converting an acid to an acid amide;
- (ii) converting an acid to an acid ester;
- (iii) converting an acid amide to a cyano.
- (iv) converting an aniline to a cyano
- 10 (v) converting an aniline to a chloro.

Abbreviations

HPLC – high-performance liquid chromatography

DCM – dichloromethane

DMF – dimethylformamide

15 DMSO – dimethylsulfoxide

IMS – industrial methylated spirit

HCl – hydrochloric acid

EDTA: Ethylene Diamine Tetra-acetic Acid

HBSS: Hanks Balanced Salt Solution

20 PMSF: Phenyl Methyl Sulfonyl Fluoride

DMEM: Dulbecco Minimal Essential Medium

GDP: Guanosine DiPhosphate

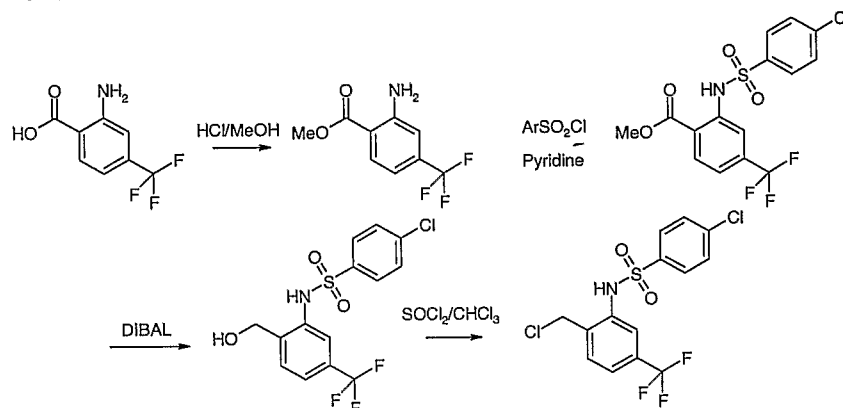
Mass spectra were obtained using either a Waters ZQ mass spectrometer or Micromass
 25 Platform 2 mass spectrometer and use electro-spray ionisation to observe either MH^+ or M^- . Proton Nuclear Magnetic Resonance (^1H -NMR) spectra were recorded at 400 MHz unless otherwise stated, chemical shifts are reported in ppm downfield from Me_4Si , used as internal standard, and are assigned as singlets (s), doublets (d), doublets of doublets (dd), triplets (t), doublet of triplets (dt), quartets (q) multiplets (m) or are

otherwise described in full. The prefix "br" refers to a broad peak; for example, a broad single may appear as br.s (or br s)..

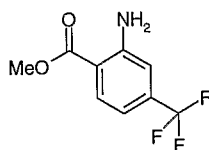
The following non-limiting examples illustrate the present invention.

5 Example Compounds and Intermediates

Intermediate 1: 4-chloro-N-[2-(chloromethyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide

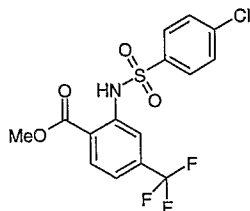


10 (a) Methyl-2-amino-4-(trifluoromethyl)benzoate



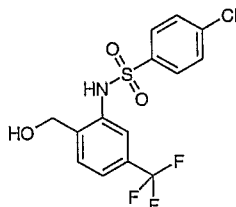
2-amino-4-(trifluoromethyl)benzoic acid (2.51 g, 12.24 mmol) was dissolved in methanol (100 mL) and concentrated hydrochloric acid was added (20 mL). The resulting solution was heated to reflux for 12 hours and then the volatiles removed under reduced pressure. The residue was partitioned between diethyl ether (2x100 mL) and sodium hydroxide solution (50 mL). This provided the desired compound methyl-2-amino-4-(trifluoromethyl)benzoate as a colourless oil (1.86 g). HPLC R_t = 3.15 minutes; m/z $[M+H]^+ = 220$. ^1H NMR (CD_3OD) δ 7.88 (d, 1H), 7.00 (s, 1H), 6.72 (d, 1H), 3.85 (s, 3H).

20 (b) Methyl-2-[(4-chlorophenyl)sulfonyl]amino-4-(trifluoromethyl)benzoate



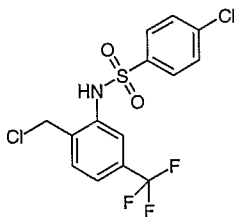
2-Amino-4-(trifluoromethyl)benzoate (1.86 g, 8.5 mmol) was dissolved in pyridine (12 mL) and 4-chlorobenzenesulfonyl chloride (1.79 g, 8.5 mmol) was added. The resulting solution was heated to 80 °C in a microwave reactor for 10 minutes and then concentrated to dryness. The crude product was purified by column chromatography on silica gel. The column was eluted with 0% to 30% ethyl acetate in cyclohexane to afford methyl 2-[[4-(4-chlorophenyl)sulfonyl]amino]-4-(trifluoromethyl)benzoate as a colourless oil (905 mg). HPLC Rt = 3.63 minutes; m/z [M+H]⁺ = 394. ¹H NMR (CD₃OD) δ 8.10 (d, 1H), 7.91 (s, 1H), 7.77 (d, 2H), 7.53 (d, 2H), 7.44 (d, 1H), 3.90 (s, 3H).

10 (c) 4-Chloro-N-[2-(hydroxymethyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide



Methyl 2-[[4-(4-chlorophenyl)sulfonyl]amino]-4-(trifluoromethyl)benzoate (460 mg, 1.17 mmol) was dissolved in tetrahydrofuran (50 mL) and cooled to 0 °C. Diisobutylaluminum hydride (1.5 M in toluene, 1.95 mL, 2.93 mmol) was added dropwise and then the reaction stirred at room temperature for 12 hours. A further portion of diisobutylaluminum hydride was added (1.17 mL, 1.76 mmol) and the solution allowed to stir for an additional 5 hours. The reaction was quenched with water and concentrated to dryness. The residue was partitioned between dichloromethane (2 x 100 mL) and 5% citric acid (50 mL), the organic phases combined, dried over magnesium sulfate and evaporated to dryness. This provided the title compound (341mg) which was used without further purification. HPLC Rt = 3.31 minutes; m/z [M-H]⁺ = 366. ¹H NMR (CD₃OD) δ 7.66 (d, 2H), 7.51 (m, 4H), 7.30 (s, 1H), 4.55 (s, 2H).

25 (d) 4-Chloro-N-[2-(chloromethyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide

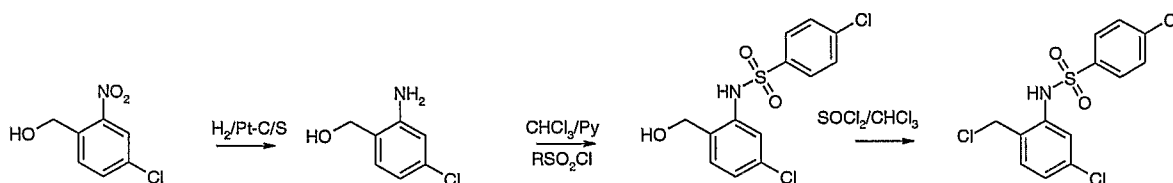


4-Chloro-N-[2-(hydroxymethyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide (341 mg, 0.93 mmol) dissolved in chloroform (25 mL) was added dropwise to a solution of thionyl chloride (332 mg, 2.79 mmol) in chloroform (25 mL). The resulting solution was stirred

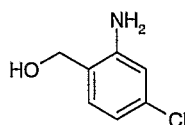
overnight at 40 °C and then poured into ice water. The organic phase was collected and dried over magnesium sulfate. This provided the title compound as a colourless oil (373 mg) which was used without further purification. HPLC Rt = 3.62 minutes; m/z [M+H]⁺ = 384. ¹H NMR (CDCl₃) δ 7.68 (d, 1H), 7.65 (d, 2H), 7.53 (m, 4H), 4.72 (s, 2H).

5

Intermediate 2: 4-Chloro-N-[5-chloro-2-(chloromethyl)phenyl]benzenesulfonamide

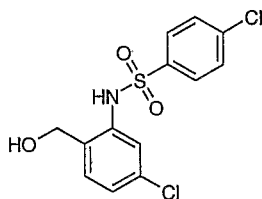


10 **(a) (2-Amino-4-chlorophenyl)methanol**



(4-chloro-2-nitrophenyl)methanol (40.0 g, 0.21 mol) was dissolved in ethanol (700 mL) and hydrogenated under hydrogen gas (20 psi) in the presence of 5% platinum on sulfided carbon (Pt-C/S) (5.00g). After 2 hours the catalyst was removed by filtration through Celite[®] and the solvent removed under reduced pressure. This provided the desired compound (2-amino-4-chlorophenyl)methanol (32.9 g) which was used without further purification. HPLC Rt = 1.70 minutes. ¹H NMR (CDCl₃) δ 6.96 (d, 1H), 6.67 (m, 2H), 4.64 (s, 2H), 4.27 (bs, 2H), 1.56 (bs, 1H).

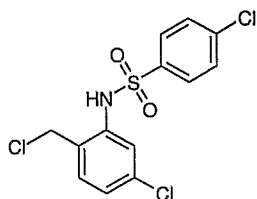
20 **(b) 4-Chloro-N-[5-chloro-2-(hydroxymethyl)phenyl]benzenesulfonamide**



A solution of (2-amino-4-chlorophenyl)methanol (5.00 g, 31.85 mmol) and pyridine (3.1 mL) in anhydrous chloroform (150 mL) was treated dropwise with a solution of 4-chlorobenzenesulfonyl chloride (7.26 g, 34.58 mmol) in chloroform (30 mL) over 20 minutes at room temperature. The reaction mixture was stirred for 5 hours and evaporated to dryness. The resulting residue was taken up in ethyl acetate (200 mL) and aqueous ammonium chloride (100 mL). After stirring for 30 minutes the organic phase was separated and further washed with dilute ammonium chloride (2 x 50 mL), dried

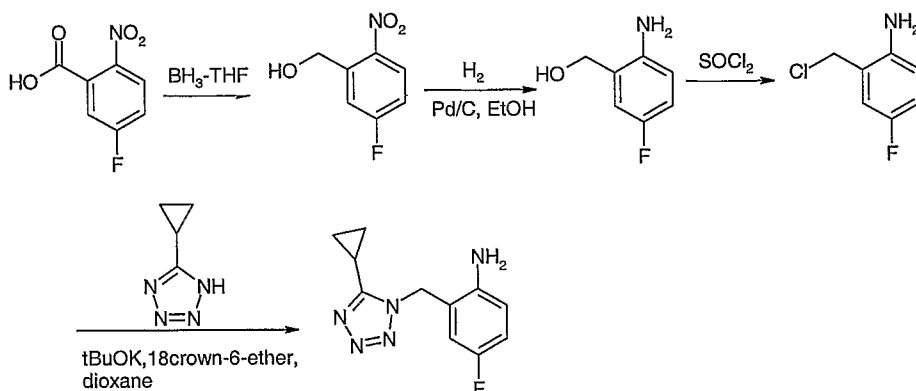
over sodium sulfate, filtered and evaporated to give an oil. This was triturated in hot hexane (100mL) and then stirred at ambient temperature for 2 hours. The solid was collected and washed with hexane to give the title compound (10.0 g). HPLC Rt = 3.04 minutes. ^1H NMR (CDCl_3) δ 7.75 (d, 2H), 7.53 (s, 1H), 7.45 (d, 2H), 7.09 (dd, 1H), 7.01 (d, 1H), 4.40 (s, 2H).

(c) 4-Chloro-N-[5-chloro-2-(chloromethyl)phenyl]benzenesulfonamide

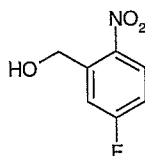


4-Chloro-N-[5-chloro-2-(hydroxymethyl)phenyl]benzenesulfonamide (4.00 g, 12.08 mmol) dissolved in chloroform (175 mL) was added dropwise to a solution of thionyl chloride (4.31 g, 36.24 mmol) in chloroform (175 mL). The resulting solution was stirred overnight at 40 °C and then poured into ice water. The organic phase was collected and dried over magnesium sulfate. This provided the title compound as a colourless oil (4.10 g) which was used without further purification. ^1H NMR (CDCl_3) δ 7.82 (d, 2H), 7.55 (d, 2H), 7.50 (d, 1H), 7.23 (dd, 1H), 7.03 (s, 1H), 4.38 (s, 2H).

Intermediate 3: 2-[(5-Cyclopropyl-1H-tetrazol-1-yl)methyl]-4-fluoroaniline

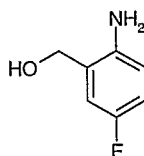


(a) (5-Fluoro-2-nitrophenyl)methanol



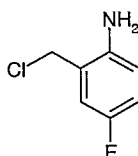
5-Fluoro-2-nitrobenzoic acid (5.00 g, 27.0 mmol) was dissolved in anhydrous tetrahydrofuran (15 mL). Borane-tetrahydrofuran complex (1M in tetrahydrofuran, 62.1 mL, 62.1 mmol) was then added slowly under nitrogen. The mixture was stirred at 60°C for 3 days and then quenched with water and evaporated to dryness. It was then loaded onto a 100 g flash silica chromatography column (pre-eluted with cyclohexane). The column was eluted with 20% ethylacetate/cyclohexane to afford (5-fluoro-2-nitrophenyl)methanol (2.54 g). HPLC Rt=2.10minutes; m/z [M+H]⁺=235. ¹HNMR (CDCl₃) δ 8.50 (m, 1H), 7.60 (m, 1H), 7.29 (m, 1H), 5.07 (d, 2H).

10 (b) (2-Amino-5-fluorophenyl)methanol



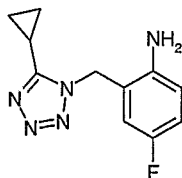
(5-Fluoro-2-nitrophenyl)methanol (2.54 g 14.85 mmol) was dissolved in ethanol (200 ml) and added to 10% palladium on carbon catalyst (500 mg). This mixture was stirred under hydrogen at atmospheric pressure at room temperature for 3 hours. The catalyst was then removed by filtration through Celite®. The ethanol was removed *in vacuo* to give (2-amino-5-fluorophenyl)methanol (2.06 g). HPLC Rt=1.24 minutes; m/z [M+H]⁺=142. ¹HNMR (CD₃OD) δ 8.33 (s, 1H), 8.00 (m, 1H), 6.72 (m, 1H), 3.93 (s, 2H).

(c) 2-(Chloromethyl)-4-fluoroaniline



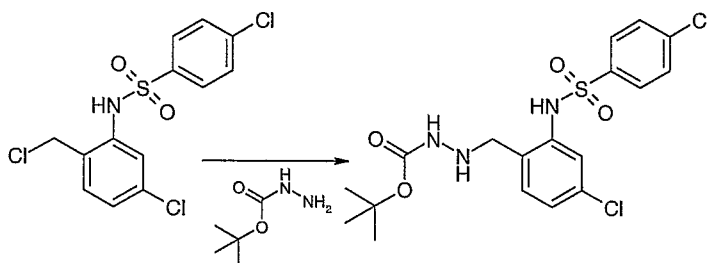
A solution of (2-amino-5-fluorophenyl)methanol (2.04 g, 14.46 mmol) in chloroform (50 ml) was added dropwise to a solution of thionyl chloride (5.74 g, 49 mmol) in dry chloroform (50 ml). The mixture was stirred at 40 °C under nitrogen for 2 hours, then the volatiles were removed *in vacuo* to give 2-(chloromethyl)-4-fluoroaniline (2.04 g, 12.8 mmol) which was used without further purification. HPLC Rt=1.75 minutes; m/z[M+H]⁺= 140. ¹HNMR (CDCl₃) δ 8.30 (d, 1H), 7.50 (d, 1H), 7.39 (dd, 1H), 4.90 (s, 2H).

(d) 2-[(5-Cyclopropyl-1H-tetrazol-1-yl)methyl]-4-fluoroaniline



A solution of 18-crown-6-ether (9.78 g, 37.0 mmol) dissolved in 1,4-dioxane (82 ml) was added to 5-cyclopropyl-4*H*-tetrazole (4.60 g, 41.5 mmol) under nitrogen. Potassium *tert*-butoxide solution (1M in tetrahydrofuran, 37 ml, 37 mmol) was then added, and the mixture stirred under nitrogen for 15 minutes. A solution of 2-(chloromethyl)-4-fluoroaniline (2.04 g, 14.5 mmol) was added and the reaction stirred at 60 °C. After 18 hours the reaction mixture was quenched with water and evaporated under reduced pressure. Ammonium chloride (20 mL) was added and the slurry extracted with ethyl acetate (2 x 100 mL). The organic phases were combined, dried over magnesium sulfate and evaporated under reduced pressure. The residue was loaded onto a 100 g flash silica chromatography column (pre-eluted with cyclohexane). The column was eluted with 50% ethyl acetate in cyclohexane to afford 2-[(5-cyclopropyl-1*H*-tetrazol-1-yl)methyl]-4-fluoroaniline (0.052 g). HPLC *R*_t=2.36 minutes; *m/z*[*M*+*H*]⁺=234. ¹H NMR (CD₃OD) δ 6.88(m, 1H), 6.79 (dd, 1H), 6.71 (dd, 1H), 5.58 (s, 2H), 2.14 (m, 1H), 1.17(m, 2H), 1.04 (m, 2H).

Intermediate 4: 1,1-dimethylethyl 2-[(4-chloro-2-[(4-chlorophenyl)sulfonyl]amino)phenyl)methyl]hydrazinecarboxylate

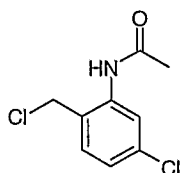


4-chloro-N-[5-chloro-2-(chloromethyl)phenyl]benzenesulfonamide (2.00 g, 5.20 mmol) and *tert*-butyl carbazate (1.38 g, 10.4 mmol) were dissolved in *N,N*-dimethylformamide (10 mL) at room temperature and stirred for 5 hours. The solvent was removed under reduced pressure and the residue loaded onto a silica column. The silica column was eluted with 0% to 50% ethyl acetate in cyclohexane to afford 1,1-dimethylethyl-2-[(4-chloro-2-[(4-chlorophenyl)sulfonyl]amino)phenyl)methyl]hydrazinecarboxylate as a white solid (931 mg). HPLC *R*_t = 3.68 minutes; *m/z* [*M*+*H*]⁺ = 446. ¹H NMR (CDCl₃) δ 9.46 (br

s, 1H), 7.76 (d, 2H), 7.62 (d, 1H), 7.42 (d, 2H), 7.01 (dd, 2H), 6.01 (br s, 1H), 4.00 (br d, 1H), 3.64 (d, 2H), 1.48 (s, 9H).

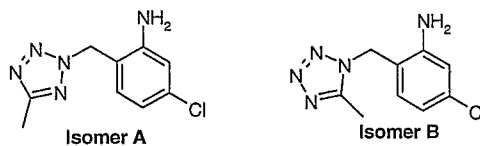
Intermediates 5 and 6: {5-chloro-2-[(5-methyl-2*H*-tetrazol-2-yl)methyl]phenyl}amine and {5-chloro-2-[(5-methyl-1*H*-tetrazol-1-yl)methyl]phenyl}amine (1:1 mixture)

(a) *N*-[5-chloro-2-(chloromethyl)phenyl]acetamide



A suspension of (2-amino-4-chlorophenyl)methanol (5.9 g) in ethyl acetate (100 mL) was heated until the former dissolved. Acetic anhydride (8 mL) was added and the mixture removed from the heat. The precipitate was filtered to give a white solid and the filtrate was concentrated and slurried with hexane and filtered to give further white solid. The two batches were combined to give 5.3 g of the alcohol intermediate. The first phase of the experiment was repeated on 3x the scale described above. 21 g of the combined products was dissolved in DCM (650mL) and added to a solution of thionyl chloride (23 mL) in DCM (225 mL) at room temperature under argon. The mixture was stirred for 30 minutes and concentrated to give a yellow/red solid. The solid was dissolved in DCM (500 mL), washed with saturated sodium bicarbonate (200 mL) and dried over magnesium sulfate. Removal of the solvent gave the 22 g of the title compound as a yellow/brown solid. ¹H NMR (CDCl₃) δ 8.01 (d, 1H), 7.52 (br. s, 1H), 7.23 (d, 1H), 7.12 (dd, 1H), 4.58 (s, 2H), 2.25 (s, 3H).

(b) {5-Chloro-2-[(5-methyl-2*H*-tetrazol-2-yl)methyl]phenyl}amine and {5-chloro-2-[(5-methyl-1*H*-tetrazol-1-yl)methyl]phenyl}amine (1:1 mixture)



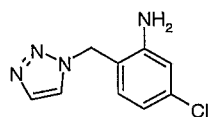
25

A mixture of *N*-[5-chloro-2-(chloromethyl)phenyl]acetamide (1.0 g), 5-methyl-1*H*-tetrazole (424 mg) and potassium carbonate (1.27 g) in DMF (10 mL) was heated to 70 °C under argon overnight. The DMF was removed *in vacuo* and water (10 mL) and ethyl acetate (70 mL) were added to the residue. The organic layer was separated and washed with water (2 x 10 mL) and brine (10 mL), dried over magnesium sulfate and reduced *in*

30

vacuo. The resulting solid was dissolved in IMS (2.5 mL) and water (30 mL) to which was added a 5M sodium hydroxide solution (1.5 mL). The mixture was then heated to reflux under argon overnight. The mixture was concentrated and the residue taken up in DCM (70 mL) and water (30 mL). The organic phase was separated, dried over magnesium sulfate and concentrated in *vacuo*. The residue was re-dissolved in IMS (2.5 mL) and water (30 mL) to which was added a 5M sodium hydroxide solution (1.5 mL) and the mixture heated to reflux under argon overnight. The mixture was concentrated and the residue taken up in DCM (70 mL) and water (30 mL). The organic phase was separated, dried over magnesium sulfate and concentrated to give a yellow oil containing a 1:1 mixture of tetrazole isomers which were used without further purification. ¹H NMR (d₆-DMSO; letter indicates isomer referred to) δ 6.97 (d, 1H, A), 6.79 (d, 1H, B), 6.72 (d, 1H, B), 6.70 (d, 1H, A), 6.53 (dd, 1H, B), 6.52 (dd, 1H, A), 5.68 (s, 2H, A), 5.52 (br. s, 2H, A), 5.50 (br. s, 2H, B), 5.40 (s, 2H, B), 2.45 (s, 3H, B), 2.40 (s, 3H, A).

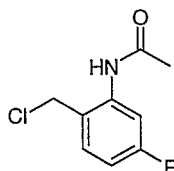
15 **Intermediate 7:** [5-Chloro-2-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]amine



Prepared by a similar procedure to that described for Intermediate 6 from *N*-[5-chloro-2-(chloromethyl)phenyl]acetamide and 1*H*-1,2,3-triazole. ¹H NMR (CDCl₃) δ 7.68 (d, 1H), 7.51 (d, 1H), 7.10 (d, 1H), 6.65-6.70 (m, 2H), 5.42 (s, 2H), 4.30 (br. s, 2H).

Intermediates 8 and 9: [5-Fluoro-2-(2*H*-tetrazol-2-ylmethyl)phenyl]amine and [5-Fluoro-2-(1*H*-tetrazol-1-ylmethyl)phenyl]amine (1:1 mixture)

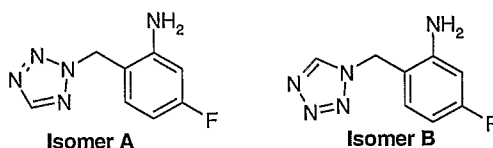
25 (a) *N*-[2-(chloromethyl)-5-fluorophenyl]acetamide



(2-Amino-4-fluorophenyl)-methanol (20 g) was dissolved in ethyl acetate (200 mL), heated to reflux, and treated with acetic anhydride (30 mL). The mixture was heated at reflux for 4 hours and cooled to room temperature overnight. The mixture was diluted with additional ethyl acetate (200 mL) and added to a saturated aqueous sodium bicarbonate solution (400 mL). The organic layer was separated and washed with further sodium bicarbonate solution (450 mL). The organic layer was dried over magnesium

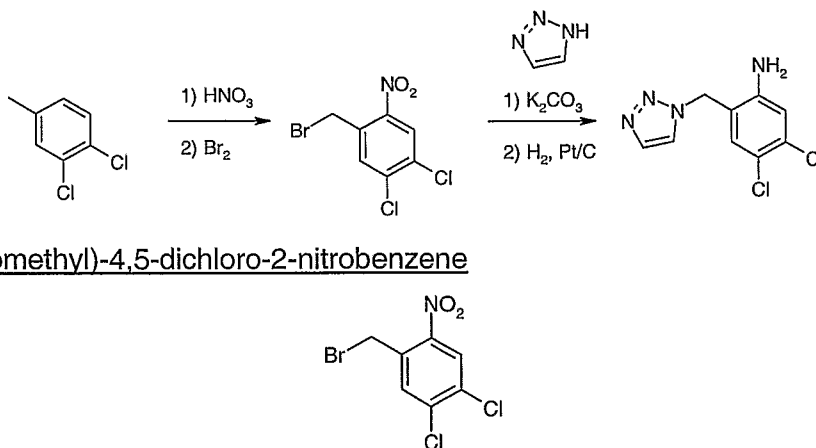
sulfate and reduced *in vacuo*. The residue was dissolved in methanol (120 mL), a solution of 0.5 M sodium hydroxide (250 mL) was added and the mixture was stirred at room temperature for 2 hours. The methanol was removed and the mixture extracted with DCM (2 x 250 mL), the combined organics dried over magnesium sulfate and concentrated. 7.1 g of the residue was dissolved in DCM (355 mL) and the mixture was added to a solution of thionyl chloride (8.5 mL) in DCM (120 mL) at room temperature under argon. The mixture was stirred at room temperature for 1 ½ hours then concentrated. The solid was dissolved in DCM (600 mL) and washed with saturated sodium bicarbonate (200 mL) and dried over magnesium sulfate. Removal of the solvent gave the 7.1 g of the title compound as a yellow/brown solid. ¹H NMR (CDCl₃) δ 7.82 (dd, 1H), 7.60 (br. s, 1H), 7.28 (dd, 1H), 6.83 (dt, 1H), 4.60 (s, 2H), 2.25 (s, 3H)

(b) [5-Fluoro-2-(2*H*-tetrazol-2-ylmethyl)phenyl]amine and [5-Fluoro-2-(1*H*-tetrazol-1-ylmethyl)phenyl]amine

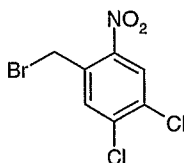


Prepared by a similar procedure to that described for Intermediate 6 from *N*-[2-(chloromethyl)-5-fluorophenyl]acetamide and 1*H*-tetrazole. ¹H NMR (d₃-MeOD) δ 9.04 (s, 1H, B), 8.67 (s, 1H, A), 6.32-6.50 (m, 3H, A+B), 5.76 (s, 2H, A), 5.55 (s, 2H, B).

Intermediate 10: [4,5-Dichloro-2-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]amine



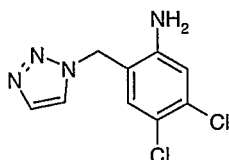
(a) 1-(Bromomethyl)-4,5-dichloro-2-nitrobenzene



Nitric acid was added slowly to a mixture of 1,2-dichloro-4-methylbenzene (10 g) in sulfuric acid at 0 °C, keeping the temperature below 10°C. The mixture was allowed to warm to room temperature, stirred for 10 minutes, poured over ice (250 g) and stirred for 10 further minutes. The solid was filtered, washed with water (50 mL) and dissolved in

DCM (150 mL). The resulting solution was washed with water (120 mL) and brine (100 mL), dried over magnesium sulfate and concentrated. To the resulting solid at 150 °C was added bromine (3.4 mL). The mixture stirred for 30 minutes, poured into hexane (50 mL) and stirred for a further 10 minutes. The solution was filtered and the filter-pad washed with hexanes. The filtrates were combined and washed with water (2 x 100 mL), dried over magnesium sulfate and concentrated to give the crude title compound (8.2 g).
¹H NMR (CDCl₃) δ 8.20 (s, 1H), 7.69 (s, 1H), 4.77 (s, 2H)

(b) [4,5-Dichloro-2-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]amine



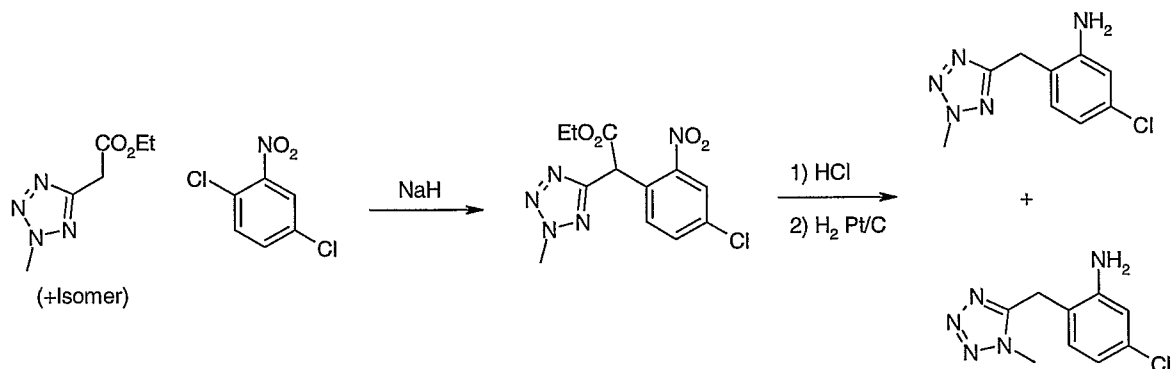
10

A mixture of 1-(bromomethyl)-4,5-dichloro-2-nitrobenzene (2.0 g), 1*H*-1,2,3-triazole (544 mg) and potassium carbonate (1.98 g) in DMF (20 mL) was heated to 70 °C under argon overnight. The mixture was diluted with water (200 mL) and extracted with diethyl ether (2 x 400 mL). The combined organics were washed with water (200 mL) and brine (100 mL), dried over magnesium sulfate and concentrated. The resulting brown oil was warmed in hexane and 650 mg of a light-brown solid collected by hot-filtration. The solid was dissolved in 2:1 ethyl acetate/IMS (9 mL) to which was added 1% platinum on carbon (650 mg) and the mixture warmed to 40 °C under a balloon of hydrogen. The mixture was left overnight and filtered through celite to give 527 mg of the title compound as a brown gum. ¹H NMR (d₆-DMSO) δ 8.11 (s, 1H), 7.71 (s, 1H), 7.08 (s, 1H), 6.85 (s, 1H), 5.68 (br. s, 2H), 5.44 (s, 2H).

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Intermediates 11 and 12: {5-chloro-2-[(2-methyl-2*H*-tetrazol-5-yl)methyl]phenyl}amine and {5-chloro-2-[(1-methyl-1*H*-tetrazol-5-yl)methyl]phenyl}amine



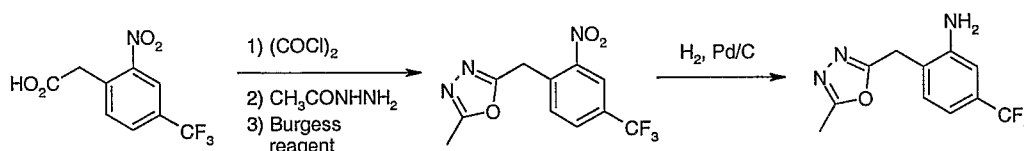
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Sodium hydride (461 mg) was washed with hexane (5 mL) and a solution of ethyl (2-methyl-2H-tetrazol-5-yl)acetate (see *Chem. Pharm. Bull.*, 1991, 1099. – contains other tetrazole isomer also, 1.5 g) in DMF was added. 2,5-Dichloronitrobenzene (1.38 g) was added, the mixture was stirred for 2 hours and neutralised with 2M HCl. The mixture was concentrated and partitioned between ethyl acetate (70 mL) and 2M HCl (50 mL). The layers were separated and the organic layer was washed with water (50 mL) and brine (50 mL). The resulting oil was dissolved in IMS (19 mL), concentrated HCl (6.25 mL) was added, and the mixture was heated to reflux for 18 hours. Upon cooling, the reaction mixture was poured on to ice (30 g) and extracted with DCM (2 x 50 mL). The combined organics were washed with brine (20 mL) and concentrated. The resulting yellow oil was dissolved in IMS (15 mL), 1% platinum on carbon (0.7 g) was added and the mixture stirred under a hydrogen balloon for 6 hours at 50 °C. The mixture was cooled, filtered through Celite® and reduced *in vacuo*. Separation of the isomers was achieved by silica column chromatography, eluting the products with 30% ethyl acetate/hexane in the order given below.

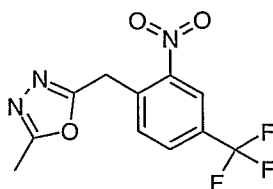
{5-Chloro-2-[(2-methyl-2H-tetrazol-5-yl)methyl]phenyl}amine; 229 mg. ¹H NMR (d₆-DMSO) δ 6.80 (m, 1H), 6.65 (m, 1H), 6.47 (m, 1H), 5.28 (br.s, 2H), 4.27 (s, 3H), 3.97 (s, 2H).

{5-Chloro-2-[(1-methyl-1H-tetrazol-5-yl)methyl]phenyl}amine; 409 mg. ¹H NMR (d₆-DMSO) δ 6.81 (d, 1H), 6.67 (d, 1H), 6.5 (dd, 1H), 5.34 (br.s, 2H), 4.05 (s, 2H), 3.93 (s, 3H).

Intermediate 13: [2-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]-5-(trifluoromethyl)phenyl]amine

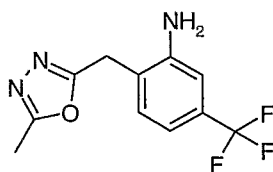


(a) 2-Methyl-5-[(2-nitro-4-(trifluoromethyl)phenyl)methyl]-1,3,4-oxadiazole



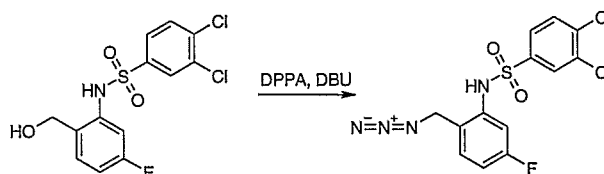
A solution of [2-nitro-4-(trifluoromethyl)phenyl]acetic acid (2 g) in dichloromethane (20 mL) was treated with oxalyl chloride (1 mL) and dimethyl acetamide (2 drops). The mixture was stirred for 1 hour and then overnight. The reaction was evaporated to give 2.1 g of a brownish oil. In the second step, a solution of 400 mg of this product was dissolved in 10 mL of DCM and treated portionwise with 270 mg of acetyl hydrazine. After 30 minutes 10 mL of saturated sodium bicarbonate was added. The mixture was filtered, the filtered solid washed with water and ether, and then dried to give 448 mg of a white solid. In a third step, 400 mg of this solid and 670 mg of Burgess' reagent ((methoxycarbonylsulfamoyl)triethylammonium hydroxide) in a microwave vial was treated with anhydrous THF, sealed and heated at 120 °C for 10 minutes. The mixture was cooled, evaporated and purified by flash column chromatography, eluting with cyclohexane and ethyl acetate to give the title compound as an off-white solid (230 mg). ¹H NMR (CDCl₃) δ 8.39 (s, 2H), 7.89 (d, 1H), 7.64 (d, 1H), 7.27 (s, 1H – partially obscured by chloroform) 4.61 (s, 3H).

(b) [2-[(5-Methyl-1,3,4-oxadiazol-2-yl)methyl]-5-(trifluoromethyl)phenyl]amine



230 mg of 2-methyl-5-[[2-nitro-4-(trifluoromethyl)phenyl]methyl]-1,3,4-oxadiazole in ethanol (10 mL) was added to 50 mg of wet palladium on carbon (10% wt, Degussa type) and the mixture stirred in a hydrogen atmosphere for four hours. The mixture was filtered and evaporated to give the title compound as a colourless gum (215 mg) ¹H NMR (CDCl₃) δ 7.26 (d, 1H – partially obscured by chloroform), 7.00 (d, 1H), 6.93 (s, 1H), 4.28 (br.s, 2H), 4.10 (s, 2H), 2.40 (s, 3H).

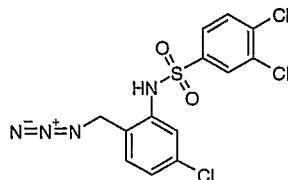
Intermediate 14: N-[2-(azidomethyl)-5-fluorophenyl]-3,4-dichlorobenzenesulfonamide



To a suspension of 3,4-dichloro-N-[5-fluoro-2-(hydroxymethyl)phenyl]benzenesulfonamide (906 mg, similarly prepared to 4-chloro-N-[5-chloro-2-(hydroxymethyl)phenyl]benzenesulfonamide) in toluene (13 mL) was added

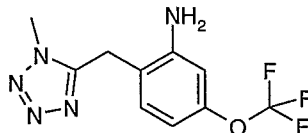
- 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.93 mL) and diphenylphosphoryl azide (DPPA, 0.78 mL). The mixture was stirred for 2 hours and water (20 mL), ethyl acetate (20 mL) and 2M HCl (3.2 mL) were added. The organic layer was washed with water, saturated sodium chloride, dried and reduced *in vacuo*. Column chromatography (ethyl acetate/cyclohexane) gave the title compound as a clear oil (460 mg). ¹H NMR (CDCl₃) δ 7.92 (d, 1H), 7.63 (dd, 1H), 7.57 (d, 1H), 7.16-7.27 (m, 3H), 6.89 (dt, 1H), 4.13 (s, 2H).

Intermediate 15: *N*-[2-(azidomethyl)-5-chlorophenyl]-3,4-dichlorobenzenesulfonamide



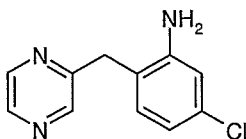
- Prepared by a similar procedure to that described for Intermediate 14 from 3,4-dichloro-*N*-[5-chloro-2-(hydroxymethyl)phenyl]benzenesulfonamide; ¹H NMR (CDCl₃) δ 7.91 (s, 1H), 7.61 (dd, 1H), 7.57 (d, 1H), 7.44 (d, 1H), 7.15-7.26 (m, 3H), 4.15 (2H).
- Intermediates 16 and 17 below were prepared employing methods analogous to those employed for Intermediates 12.

Intermediate 16: 2-[(1-methyl-1*H*-tetrazol-5-yl)methyl]-5-[(trifluoromethyl)oxy]aniline

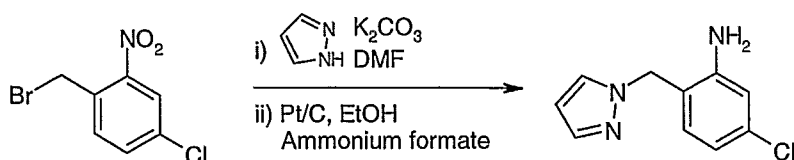


- Similarly prepared from 4-chloro-3-nitrophenyl trifluoromethyl ether (*J. Org. Chem.*, 1964, 5.). ¹H NMR (DMSO-*d*₆) δ 6.91 (d, 1H), 6.60 (s, 1), 6.41 (d, 1H), 5.45 (br.s, 2H), 4.10 (s, 2H), 3.98 (s, 3H).

Intermediate 17: 5-chloro-2-(2-pyrazinylmethyl)aniline

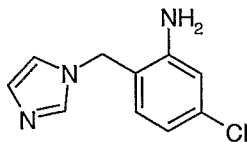


- Similarly prepared from methyl 2-pyrazinylacetate. ¹H NMR (CDCl₃) δ 8.54 (s, 1H), 8.43 (s, 2H), 7.06 (d, 1H), 6.66-6.71(m, 2H), 4.46 (br.s, 2H), 4.00 (s, 2H).

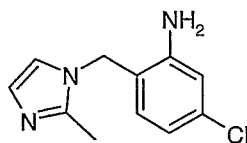
Intermediate 18: 5-chloro-2-(1*H*-pyrazol-1-ylmethyl)aniline

Potassium carbonate (3mmol) was added to a 0.5 M solution of pyrazole (3 mmol) in
 5 DMF, followed by a 1M solution of 1-(bromomethyl)-4-chloro-2-nitrobenzene (3 mmol,
 see *J.Med.Chem.*, 1975, 752) in DMF. Tetra-*n*-butylammonium iodide (20 mol %) was
 added, the mixture was stirred for 2.5 hours and reduced in volume by 50%. The
 resulting solution was diluted with ethyl acetate and water and the organic phase
 collected, dried (sodium sulfate) and reduced *in vacuo*. The resulting residue was
 10 purified by silica-gel column chromatography eluting with cyclohexane/DCM (0-50%
 DCM) to provide 83 mg of a clear oil. In a second synthetic step this compound was
 reduced to the aniline by transfer hydrogenation with ammonium formate (10 eq) in
 ethanol (0.25 M) in the presence of 5% platinum on carbon (1 mol %, 50% water,
 Degussa-type) at reflux for 18 hours. The mixture was filtered through celite onto a 5 g
 15 sulphonic acid ion-exchange column which was washed with ethanol (20 mL) and the
 product eluted in 2M ammonia in methanol. Reduction of the latter *in vacuo* gave 66 mg
 of the title compound as a brown oil.
 HPLC Rt = 2.9 minutes; m/z MH⁺ = 210/208.

20 Intermediates 19 to 26 were prepared employing methods analogous to those employed
 for Intermediates 18.

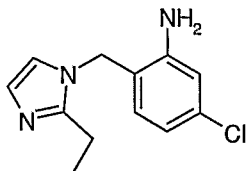
Intermediate 19: 5-chloro-2-(1*H*-imidazol-1-ylmethyl)aniline

25 Similarly prepared. HPLC Rt = 1.8 minutes; m/z MH⁺ = 210/208.

Intermediate 20: 5-chloro-2-[(2-methyl-1*H*-imidazol-1-yl)methyl]aniline

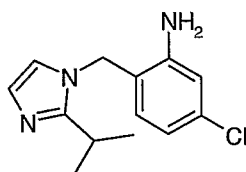
Similarly prepared. HPLC Rt = 1.9 minutes; m/z MH⁺ = 224/222.

Intermediate 21: 5-chloro-2-[(2-ethyl-1H-imidazol-1-yl)methyl]aniline



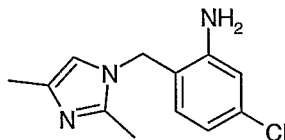
- 5 Similarly prepared; required heating at 80°C during the first step. HPLC Rt = 2.0 minutes; m/z MH⁺ = 238/236.

Intermediate 22: 5-chloro-2-{[2-(1-methylethyl)-1H-imidazol-1-yl]methyl}aniline



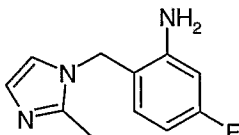
- 10 Similarly prepared; required heating at 80 °C during the first step. HPLC Rt = 2.3 minutes; m/z MH⁺ = 251/250.

Intermediate 23: 5-chloro-2-[(2,4-dimethyl-1H-imidazol-1-yl)methyl]aniline



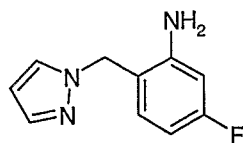
- 15 Similarly prepared; required heating at 80 °C during the first step. HPLC Rt = 2.2 minutes; m/z MH⁺ = 238/226.

Intermediate 24: 5-fluoro-2-[(2-methyl-1H-imidazol-1-yl)methyl]aniline



- 20 Similarly prepared from 1-(bromomethyl)-4-fluoro-2-nitrobenzene (*J.Het.Chem.*, 1982, 401). HPLC Rt = 2.1 minutes.

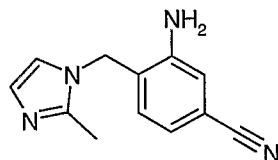
Intermediate 25: 5-fluoro-2-(1H-pyrazol-1-yl)methyl]aniline



Similarly prepared from 1-(bromomethyl)-4-fluoro-2-nitrobenzene (*J.Het.Chem.*, 1982, 401); during the first step the reaction was heated in a microwave at 100°C for 1 minute (50W). HPLC Rt = 2.7 minutes.

5

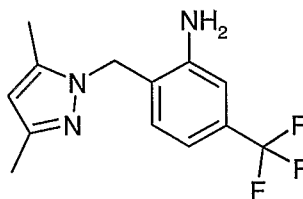
Intermediate 26: 3-amino-4-[(2-methyl-1*H*-imidazol-1-yl)methyl]benzonitrile



Similarly prepared from 4-(bromomethyl)-3-nitrobenzonitrile (*Chem. Ber.*, 1894, 2165). HPLC Rt = 1.03 minutes; m/z MH⁺ = 213.

10

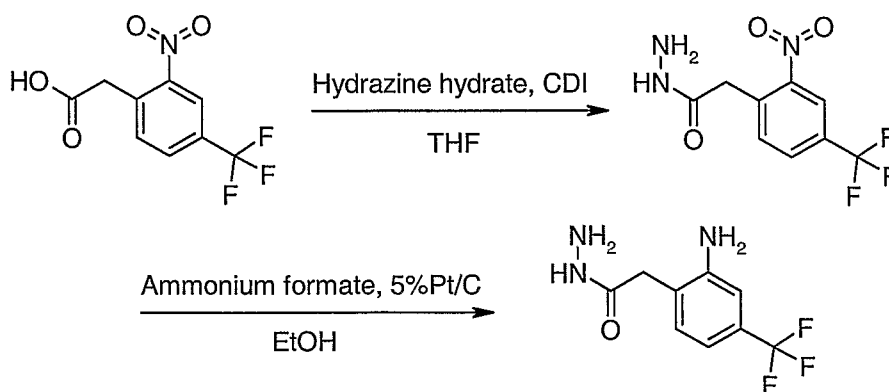
Intermediate 27: [2-[(3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]amine



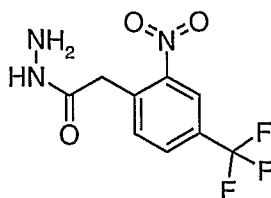
Prepared by a similar procedure to that described for Intermediate 3 (steps b-d) from [2-nitro-4-(trifluoromethyl)phenyl]methanol (in step b) and 3,5-dimethyl-1*H*-pyrazole (in step d). HPLC Rt = 3.23 minutes; m/z MH⁺ = 270.

15

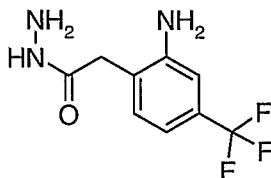
Intermediate 28: 2-[2-amino-4-(trifluoromethyl)phenyl]acetohydrazide



20

a) 2-[2-nitro-4-(trifluoromethyl)phenyl]acetohydrazide

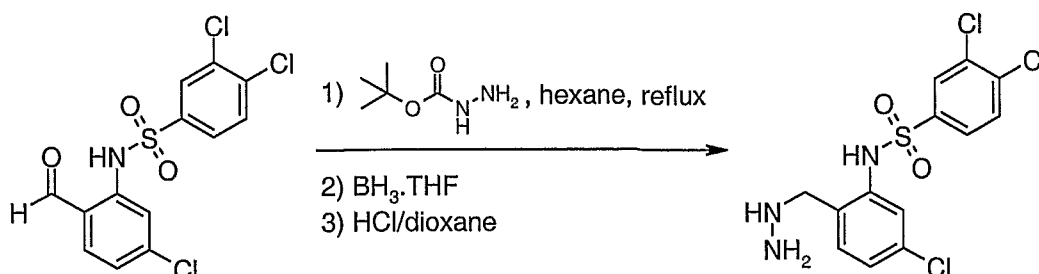
N,N'-Carbonyldiimidazole (1.42 g, 8.76 mmol) was added to a solution of [2-nitro-4-(trifluoromethyl)phenyl]acetic acid (2.0 g, 7.96 mmol) in THF (50 mL). After stirring at
 5 room temperature for 15 minutes, hydrazine hydrate was added and the reaction was stirred for an additional 20 minutes. The reaction was extracted with EtOAc (3x) and the organic layer was washed with NaHCO₃ (3x), dried over MgSO₄, and concentrated to give the titled product (1.4 g, 67%) as a light yellow solid. m/z MH⁺ = 264.

10 b) 2-[2-Amino-4-(trifluoromethyl)phenyl]acetohydrazide

To 5% Pt/C catalyst (0.1 g) in a flask was added 2-[2-nitro-4-(trifluoromethyl)phenyl]acetohydrazide (0.2 g, 0.7 mmol) as a solution in ethanol (10 mL).
 15 The flask was then flushed with nitrogen and ammonium formate (0.22 g, 3.5 mmol) was added to the stirred solution. The reaction was heated at reflux under nitrogen overnight. On cooling to room temperature the catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The residue was partitioned between water and EtOAc, the aqueous extract was further extracted with EtOAc. The combined organic extracts were
 20 washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to afford the titled compound.

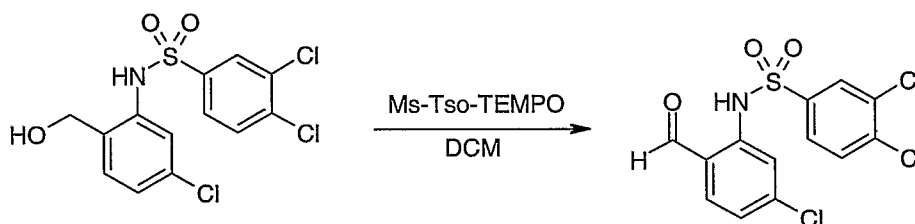
Intermediate 29: 3,4-Dichloro-N-[5-chloro-2-(hydrazinomethyl)phenyl]benzenesulfonamide

25



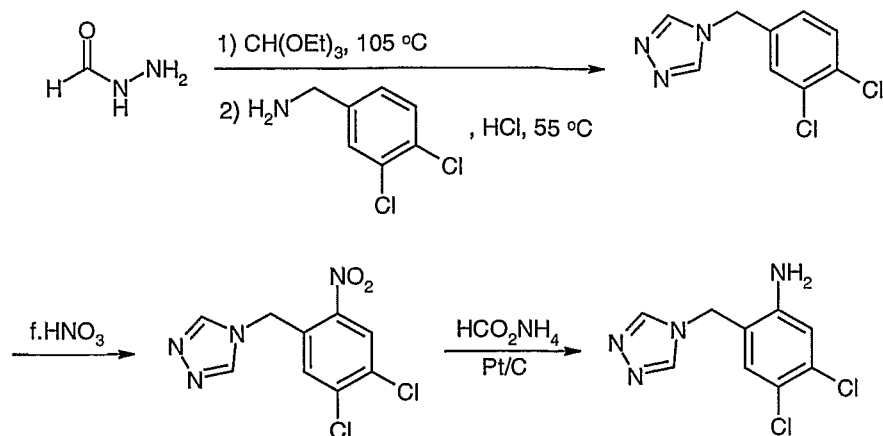
tert-Butyl carbazate (0.08 g, 0.63 mmol) was added to a solution of 3,4-dichloro-*N*-(5-chloro-2-formylphenyl)benzenesulfonamide (0.19 g, 0.52 mmol) in hexane (8 mL) and the reaction mixture was heated under reflux for 1 hour. A solution of 1M $\text{BF}_3 \cdot \text{THF}$ (2 mL) was added and the reaction was stirred at room temperature for 14 minutes. The reaction was then treated with HCl (1N in dioxane, 2 mL) for 18 hours and concentrated. The residue was taken up in THF and filtered. The filtrate was concentrated to afford the titled product (0.15 g, 76%)

Intermediate 30: 3,4-Dichloro-*N*-(5-chloro-2-formylphenyl)benzenesulfonamide

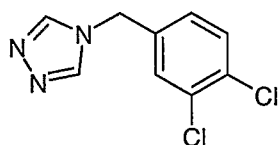


Activated Ms-Tso-TEMPO resin (21 g, 10.91 mmol) was added to a solution of 3,4-dichloro-*N*-[5-chloro-2-(hydroxymethyl)phenyl]benzenesulfonamide (2.0 g, 5.45 mmol) in DCM (100 mL) and a slow stream of air was bubbled through the reaction for 10 minutes. The resulting mixture was shaken for 24 hours. The resin was filtered off and washed with DCM (3 x 50 mL). The filtrate was evaporated to give the desired intermediate as an off-white solid (1.98 g, 100%). HPLC R_t = 3.37 minutes m/z $[\text{MH}]^+ = 364$ ^1H NMR (MeOD) δ 9.90 (s, 1H), 7.99 (s, 1H), 7.81 (d, 1H), 7.73 (m, 2H), 7.54 (d, 1H), 7.33 (dd, 1H).

Intermediate 31: [4,5-Dichloro-2-(4*H*-1,2,4-triazol-4-ylmethyl)phenyl]amine

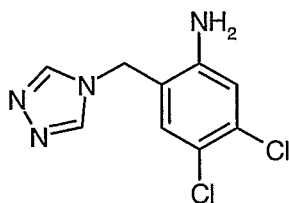


a) 4-[(3,4-Dichlorophenyl)methyl]-4H-1,2,4-triazole



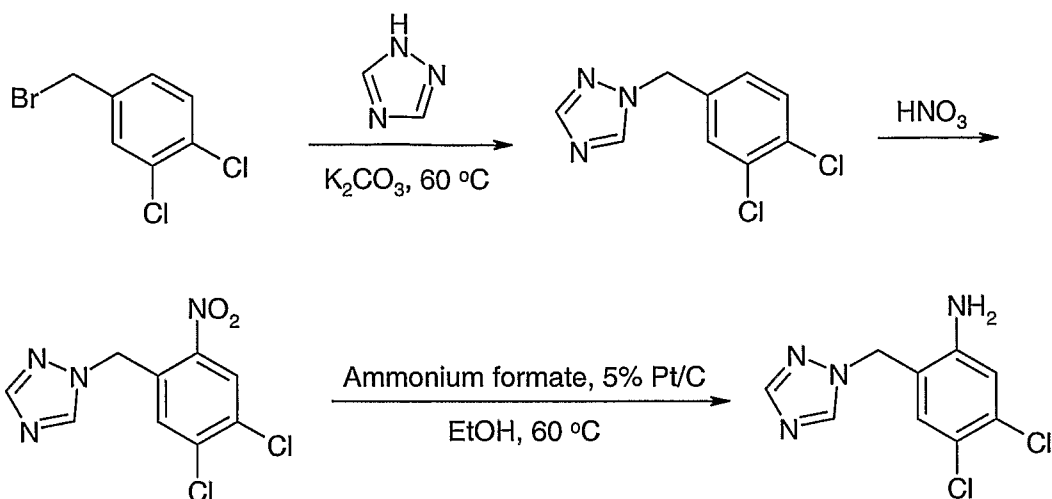
- 5 A mixture of formylhydrazine (5 g) and triethylorthoformate (10.2 mL) was stirred at 105 °C for 2 hours. The reaction solution was cooled to 50 °C and a suspension of 1-(3,4-dichlorophenyl)methanamine (9.7 g) in 0.1N aqueous HCl (160 mL) was added dropwise over 5 minutes. The resultant mixture was heated at 55 °C for 72 hours. The mixture was cooled and extracted with DCM (3 x 75 mL), the combined organic extracts were washed
- 10 with water and brine, dried over Na₂SO₄, and concentrated. The crude oil isolated was purified by silica gel chromatography eluting from 10-100% ethyl acetate in cyclohexane to afford the title compound (2.83 g). HPLC Rt= 2.48 minutes, m/z [MH]⁺= 228

b) [4,5-Dichloro-2-(4H-1,2,4-triazol-4-ylmethyl)phenyl]amine

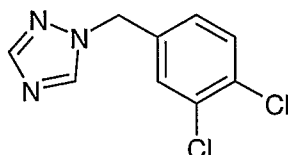


- 15 4,5-dichloro-2-(4H-1,2,4-triazol-4-ylmethyl)aniline was prepared in a similar manner to intermediate 10 from 4-[(3,4-dichlorophenyl)methyl]-4H-1,2,4-triazole to afford the title compound. HPLC Rt = 2.30 minutes, m/z [MH]⁺= 243.

- 20 Intermediate 32: 4,5-dichloro-2-(1H-1,2,4-triazol-1-ylmethyl)aniline

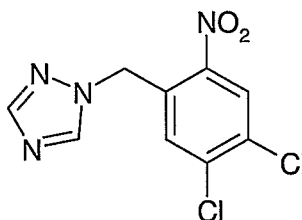


a) 1-[(3,4-Dichlorophenyl)methyl]-1H-1,2,4-triazole



To a solution of 4-(bromomethyl)-1,2-dichlorobenzene (5 g) in DMF (50 mL) was added 1,2,4 triazole (1.58 g) and potassium carbonate (5.75 g). The mixture was heated to $60\text{ }^\circ\text{C}$ for 1 hour, cooled, and concentrated *in vacuo*. The resulting residue was partitioned between DCM (150ml) and water (50ml). The organic layer was washed with water and brine, dried over Na_2SO_4 , and concentrated to afford the title compound (4.8 g). HPLC R_t = 2.73 minutes, m/z $[MH]^+$ = 228. Product contains approx 15% of 1,3,4 N linked triazole isomer.

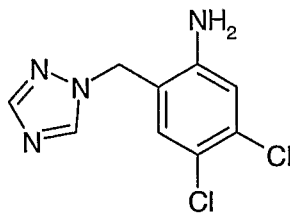
b) 1-[(4,5-Dichloro-2-nitrophenyl)methyl]-1H-1,2,4-triazole



- 15 To a suspension of 1-[(3,4-dichlorophenyl)methyl]-1H-1,2,4-triazole (1 g) in concentrated sulphuric acid (10 mL) at room temperature was added fuming nitric acid (210 μL) in 1 portion. The mixture was stirred for 30 minutes and then poured into ice. The acidic aqueous was adjusted to pH 12 using 2N sodium hydroxide solution and then extracted with DCM (4 x 20 mL). The organic extracts were washed with water and brine, dried

over Na₂SO₄, and concentrated to afford the title compound (0.36 g). HPLC Rt = 2.73 minutes, m/z [MH]⁺=273. Product still contains approx 15% of triazole regioisomer.

c) 4,5-Dichloro-2-(1*H*-1,2,4-triazol-1-ylmethyl)aniline

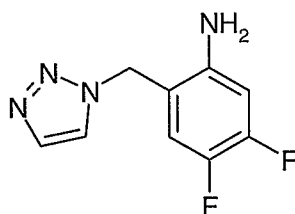


5

To a solution of 1-[(4,5-dichloro-2-nitrophenyl)methyl]-1*H*-1,2,4-triazole (0.36 g) in ethanol (10 mL) was added ammonium formate (1.7 g) and 5% platinum on carbon (0.2 g). The mixture was heated to 60°C for 3 hours, filtered through Celite, concentrated in vacuo and resubmitted back using the condition described previously for an additional 16

10 hours. The mixture was filtered through Celite, concentrated and the residue was partitioned between water and DCM (15 mL each). The organic layer was concentrated *in vacuo* to afford the title compound (245mg). HPLC Rt = 2.71 minutes, m/z [MH]⁺=243. The product contains less than 10% of triazole regioisomer.

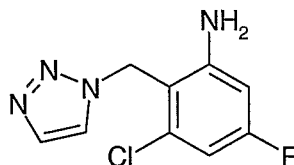
15 **Intermediate 33:** 4,5-difluoro-2-(1*H*-1,2,3-triazol-1-ylmethyl)aniline



Prepared by a similar procedure to that described for Intermediate 32 from 4-(bromomethyl)-1,2-difluorobenzene and 1*H*-1,2,3-triazole. HPLC Rt = 2.32 minutes, m/z

20 [MH]⁺ = 211.

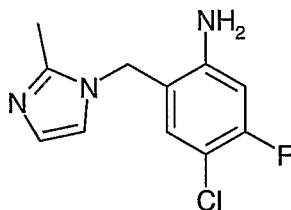
Intermediate 34: 3-chloro-5-fluoro-2-(1*H*-1,2,3-triazol-1-ylmethyl)aniline



25

Prepared by a similar procedure to that described for Intermediate 32 from 1-(bromomethyl)-2-chloro-4-fluorobenzene and 1*H*-1,2,3-triazole. HPLC Rt = 2.70 minutes, m/z [MH]⁺ = 227

5 **Intermediate 35: 4-chloro-5-fluoro-2-[(2-methyl-1*H*-imidazol-1-yl)methyl]aniline**



10 Prepared by a similar procedure to that described for Intermediate 32 from 4-(bromomethyl)-2-chloro-1-fluorobenzene and 2-methyl-1*H*-imidazole.

Intermediates 36 and 37: 4,5-dichloro-2-[(1-methyl-1*H*-tetrazol-5-yl)methyl]aniline and 4,5-dichloro-2-[(2-methyl-2*H*-tetrazol-5-yl)methyl]aniline



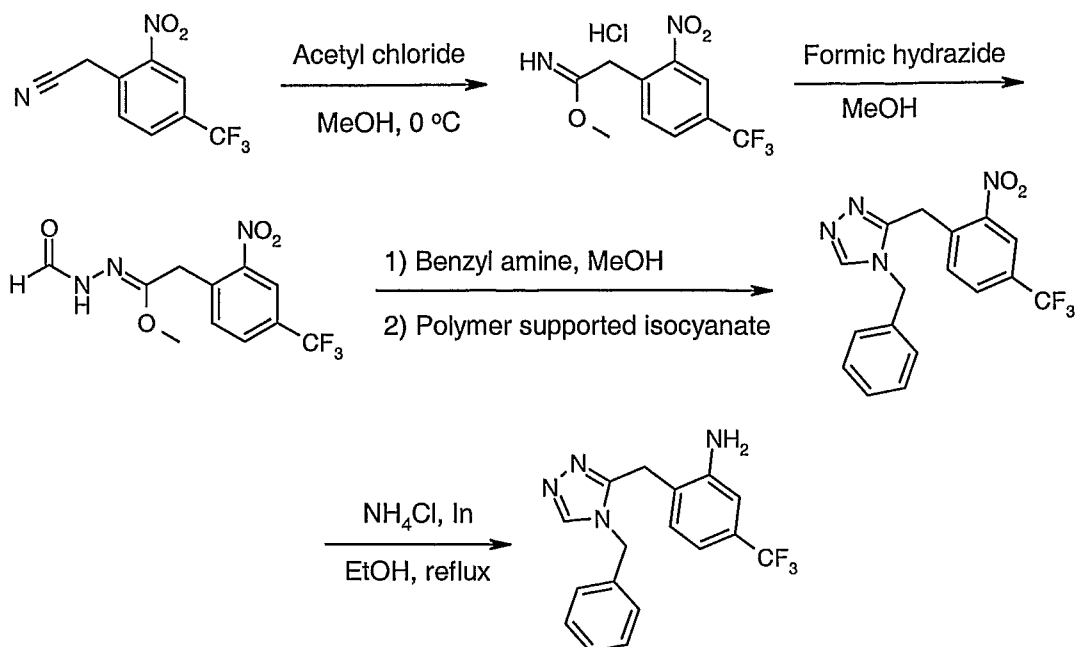
15

These intermediates were prepared by a similar procedure to that described for Intermediates 11 and 12 from 1,2-dichloro-4-fluoro-5-nitrobenzene. Separation of the regio isomers was performed after the hydrolysis and decarboxylation step.

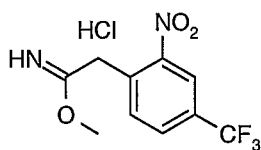
20 4,5-dichloro-2-[(1-methyl-1*H*-tetrazol-5-yl)methyl]aniline. HPLC Rt = 2.81 minutes, m/z [MH]⁺ = 258

4,5-dichloro-2-[(2-methyl-2*H*-tetrazol-5-yl)methyl]aniline. HPLC Rt = 2.99, m/z [MH]⁺ = 258

25 **Intermediate 38: [2-{[4-(Phenylmethyl)-4*H*-1,2,4-triazol-3-yl]methyl}-5-(trifluoromethyl)phenyl]amine**



a) Methyl 2-[[2-nitro-4-(trifluoromethyl)phenyl]ethanimidoate hydrochloride

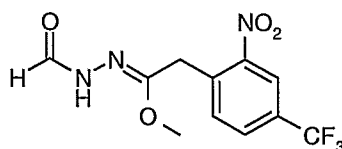


5

To a sealable tube containing methanol (10 mL) at 0 °C was added acetyl chloride (12 mL) dropwise. [2-Nitro-4-(trifluoromethyl)phenyl]acetonitrile was then added. The tube was sealed and allowed to stand at 0 °C overnight. The resulting precipitate was filtered, washed with ether, and dried to provide the title product (5.3 g). HPLC Rt = 2.8 minutes

10

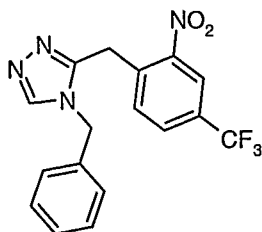
b) Methyl (1Z)-N-formyl-2-[[2-nitro-4-(trifluoromethyl)phenyl]ethanehydrazonoate



15

To a solution of methyl 2-[[2-nitro-4-(trifluoromethyl)phenyl]ethanimidoate hydrochloride (0.153 g) in methanol (2 mL) was added formic hydrazide (0.031 g). After 2 hours, the solution was diluted with saturated sodium bicarbonate and ether. The layers were separated, and the ether layer was washed with brine. After drying over Na_2SO_4 , the solution was filtered and concentrated to provide the title product (0.11 g). HPLC Rt = 2.4 minutes; m/z $[\text{MH}]^+ = 306$

c) 3-{[2-Nitro-4-(trifluoromethyl)phenyl]methyl}-4-(phenylmethyl)-4*H*-1,2,4-triazole



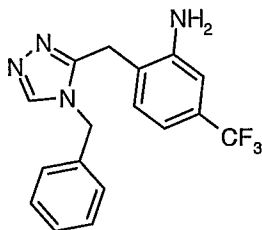
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To a solution of methyl (1*Z*)-*N*-formyl-2-[2-nitro-4-(trifluoromethyl)phenyl]ethanehydrazonoate (0.1 g) in methanol (1.6 mL) was added benzylamine (0.36 mL). The reaction mixture was stirred for three days whereupon polymer supported isocyanate was added (3 g). Stirring was continued for 12 hours at room temperature. The mixture was filtered and the filtrate was concentrated. Purification by flash column chromatography (10% MeOH in CH₂Cl₂) provided the title product (0.028 g). HPLC Rt = 2.6 minutes; m/z [MH]⁺ = 363

10

d) [2-{[4-(Phenylmethyl)-4*H*-1,2,4-triazol-3-yl]methyl}-5-(trifluoromethyl)phenyl]amine

15

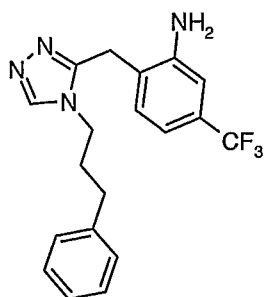


To a solution of 3-{[2-nitro-4-(trifluoromethyl)phenyl]methyl}-4-(phenylmethyl)-4*H*-1,2,4-triazole (0.028 g) in ethanol (3 mL) was added saturated ammonium chloride (1 mL) and indium powder (0.062 g). The reaction mixture was heated to reflux for 12 hours. After cooling to room temperature, the heterogeneous mixture was filtered. The aqueous mixture was then extracted with diethyl ether. The ether layer was concentrated and taken up in methanol (5 mL). Filtration through an acidic SPE column (H₂SO₄) followed by elution with 5% NH₃/MeOH and concentration provided the title product (0.017 g). HPLC Rt = 2.5 minutes; m/z [MH]⁺ = 333

20

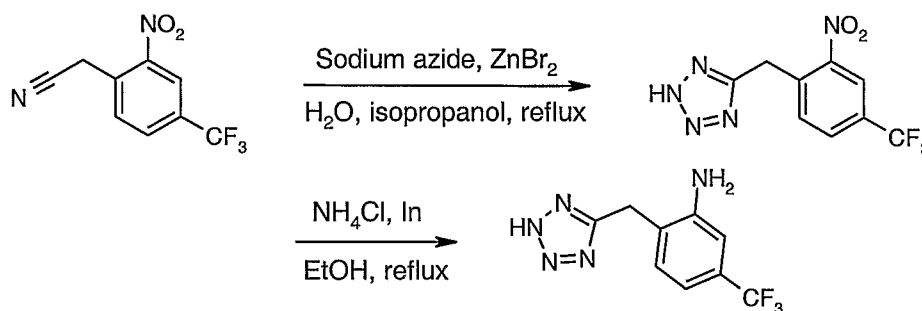
25

Intermediate 39: [2-{[4-(3-phenylpropyl)-4*H*-1,2,4-triazol-3-yl]methyl}-5-(trifluoromethyl)phenyl]amine



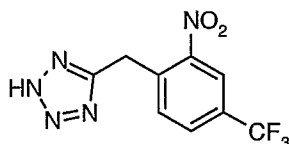
Prepared by a similar procedure to that described for Intermediate 38 except substituting
 5 3-phenylpropylamine for benzyl amine in step c. HPLC Rt = 2.5 minutes; m/z [MH]⁺ = 361.

Intermediate 40: [2-(1H-tetrazol-5-ylmethyl)-5-(trifluoromethyl)phenyl]amine



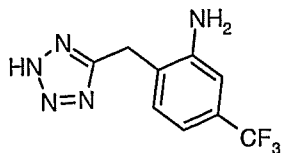
10

a) 5-[[2-Nitro-4-(trifluoromethyl)phenyl]methyl]-1H-tetrazole



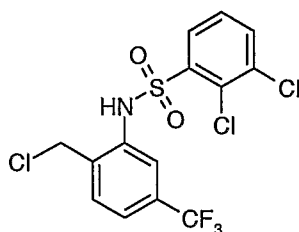
A solution containing [2-nitro-4-(trifluoromethyl)phenyl]acetonitrile (0.206 g), sodium
 15 azide (0.064 g), zinc bromide (0.203 g), water (1.8 mL), and isopropanol (0.18 mL) was
 brought to reflux for 48 hours. After cooling to room temperature, the mixture was diluted
 with ether (3 mL), and the layers were separated. The aqueous layer was diluted with
 2N HCl and reextracted with ethyl acetate. The ethyl acetate layer was dried over
 Na₂SO₄, filtered, and concentrated to provide the title product (0.17 g). HPLC Rt = 2.4
 20 minutes; m/z [MH]⁺ = 274

b) [2-(1H-tetrazol-5-ylmethyl)-5-(trifluoromethyl)phenyl]amine



Prepared by a similar procedure to that described for Intermediate 38 step d except substituting 5-[[2-nitro-4-(trifluoromethyl)phenyl]methyl]-1H-tetrazole for 3-[[2-nitro-4-(trifluoromethyl)phenyl]methyl]-4-(phenylmethyl)-4H-1,2,4-triazole. HPLC Rt = 2.3 minutes; m/z [MH]⁺ = 244.

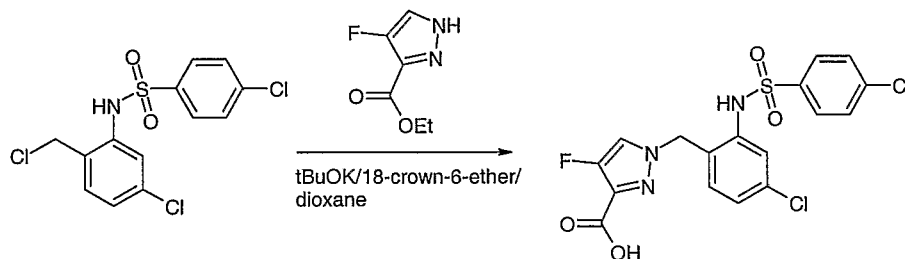
Intermediate 41: 2,3-dichloro-N-[2-(chloromethyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide



Prepared by a similar procedure to that described for Intermediate 1 except substituting 2,3-dichlorobenzenesulfonyl chloride for 4-chlorobenzenesulfonyl chloride in step b. HPLC Rt = 3.65 minutes; m/z [M+H]⁺ = no M+1. ¹H NMR (CDCl₃) δ 8.03 (d, 1H), 7.75 (d, 1H), 7.45 (m, 2H), 7.35 (m 2H), 4.6 (s, 2H).

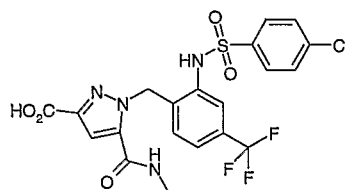
EXAMPLE COMPOUNDS

Example 1: 3-[(4-Chloro-2-[(4-chlorophenyl)sulfonyl]amino)phenyl]methyl]-4-fluoro-1H-pyrazole-3-carboxylic acid



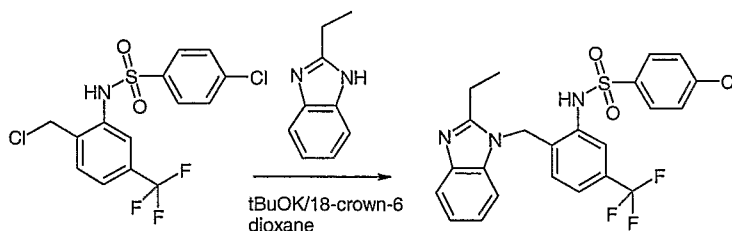
To ethyl 4-fluoro-1H-pyrazole-3-carboxylate (0.034 g, 0.26 mmol) a solution of 18-crown-6-ether (144 mg, 0.55 mmol) dissolved in 1,4-dioxane (2 mL) was added under nitrogen. Potassium *tert*-butoxide solution (1M in tetrahydrofuran, 0.2 mL, 0.2 mmol) was then added and the mixture stirred under nitrogen for 15 minutes. A solution of 4-chloro-*N*-[5-chloro-2-(chloromethyl)phenyl]benzenesulfonamide (0.05 g, 0.13 mmol) in 1,4-dioxane (2 mL) was added and the reaction stirred at 60 °C. After 18 hours the reaction mixture was quenched with water and evaporated *in vacuo*. Ammonium chloride (10 mL) was added and the slurry extracted with ethyl acetate (2 x 50 mL). The organic phases were combined, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by mass directed autoprep to give the desired product isomer 3-[(4-chloro-2-[[4-(chlorophenyl)sulfonyl]amino]phenyl)methyl]-4-fluoro-1H-pyrazole-3-carboxylic acid (9.6 mg). HPLC Rt=3.58minutes; m/z [M+H]⁺=494. ¹H NMR (CD₃OD) δ 7.68 (m, 3H), 7.57 (d, 2H), 7.55 (s, 1H), 7.27 (d, 1H), 7.00 (s, 1H), 5.47 (s, 2H).

Example 2: 1-[[2-[[4-(chlorophenyl)sulfonyl]amino]-4-(trifluoromethyl)phenyl]methyl]-5-[(methylamino)carbonyl]-1H-pyrazole-3-carboxylic acid



Example 2 was prepared similarly to Example 1 using the appropriate starting materials. HPLC Rt = 3.6 minutes; m/z M⁺ = 517.

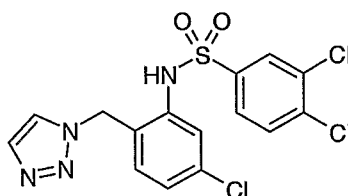
Example 3: 4-Chloro-*N*-[2-[(2-ethyl-1H-benzimidazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide



2-Ethyl-1H-benzimidazole (0.03 g, 0.26 mmol) was added under nitrogen to a solution of 18-crown-6-ether (0.07 g, 0.27 mmol) dissolved in 1,4-dioxane (2 mL). Potassium *tert*-butoxide solution (1M in tetrahydrofuran, 0.2 mL, 0.2 mmol) was then added, and the mixture stirred under nitrogen for 15 minutes. A solution of 4-chloro-*N*-[2-(chloromethyl)-

5-(trifluoromethyl)phenyl]benzenesulfonamide (0.05 g, 0.13 mmol) in 1,4-dioxane (2 mL) was added and the reaction was stirred at 60 °C. After 18 hours the reaction mixture was quenched with water and evaporated under reduced pressure. Aqueous saturated ammonium chloride (10 mL) was added and the slurry extracted with ethyl acetate (2 x 50 mL). The organic phases were combined, dried over magnesium sulfate and then concentrated *in vacuo*. The mixture was purified by mass directed autoprep to give the desired product isomer (18 mg). HPLC Rt=3.99 minutes; m/z[M+H]=493. ¹H NMR (CDCl₃) δ 7.70 (d, 2H), 7.64 (d, 1H), 7.55 (d, 2H), 7.33 (d, 1H), 7.23 (t, 1H), 7.17 (t, 1H), 7.05 (d, 1H), 7.01(s, 1H), 6.54 (d, 1H), 5.56 (s, 2H), 2.77 (q, 2H), 1.29 (t, 3H).

Example 4: 3,4-dichloro-N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]benzenesulfonamide

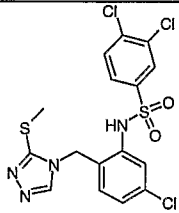
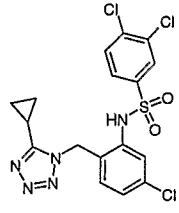
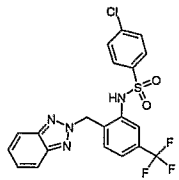
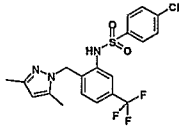
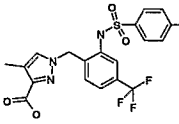


To a solution of intermediate 7 (1.03 g) in pyridine (12 mL) was added 4-(dimethylamino)-pyridine (6 mg) and 3,4-dichlorobenzenesulfonyl chloride (0.84 mL). These reagents were heated to 90 °C for 4 hours cooled and allowed to stand for 68 hours. The mixture was reduced *in vacuo* and purified by silica-gel column chromatography eluting with 0-100% ethyl acetate in cyclohexane. The resulting solid was triturated with DCM to provide the product upon drying *in vacuo*. HPLC Rt = 3.5 minutes; m/z MH+ = 419. ¹H NMR (MeOD) δ 7.94 (s, 1H), 7.79 (d, 1H), 7.73 (dd, 1H), 7.56 (dd, 1H), 7.24 (dd, 1H), 7.04 (d, 1H), 6.71 (d, 1H), 5.74 (s, 2H).

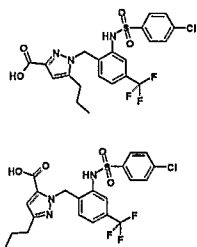
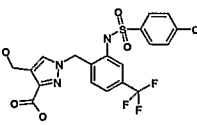
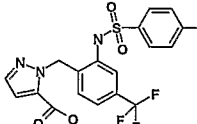
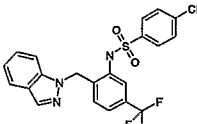
The following compounds of formula (I) set out in Table 1 were prepared by a similar procedure to that described for Example 3 and 4 using the appropriate starting materials.

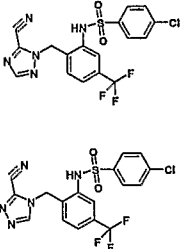
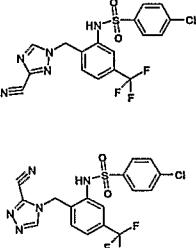
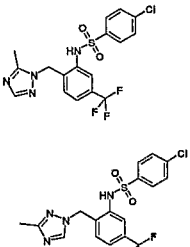
Table 1

Ex	Structure	Parent Mwt	Rt/ min	+ve	-ve	Name
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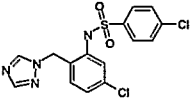
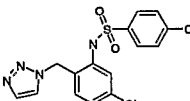
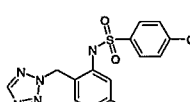
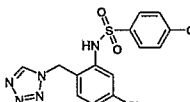
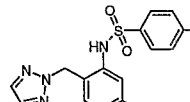
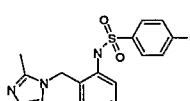
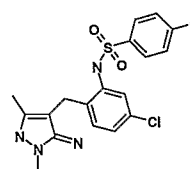
Ex	Structure	Parent Mwt	Rt/min	+ve	-ve	Name
5		464	3.3	465	463	3,4-dichloro- <i>N</i> -(5-chloro-2-([3-(methylthio)-4 <i>H</i> -1,2,4-triazol-4-yl)methyl]phenyl)benzenesulfonamide
6		459	3.5	460	456	3,4-dichloro- <i>N</i> -{5-chloro-2-[(5-cyclopropyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl}benzenesulfonamide
7		467	3.7	467	465	<i>N</i> -[2-(2 <i>H</i> -1,2,3-benzotriazol-2-ylmethyl)-5-(trifluoromethyl)phenyl]-4-chlorobenzenesulfonamide
8		444	3.7	444	442	4-chloro- <i>N</i> -[2-[(3,5-dimethyl-1 <i>H</i> -pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
9		474	3.4	474	472	1-{[2-[(4-chlorophenyl)sulfonyl]amino]-4-(trifluoromethyl)phenyl]methyl}-4-methyl-1 <i>H</i> -pyrazole-3-carboxylic acid

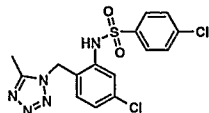
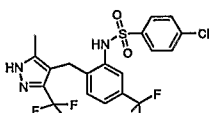
Ex	Structure	Parent Mwt	Rt/ min	+ve	-ve	Name
10		474	3.4 4.0	474	472	1-([2-([(4-chlorophenyl)sulfonyl]amino)-4-(trifluoromethyl)phenyl]methyl)-4-methyl-1H-pyrazole-3-carboxylic acid and 1-([2-([(4-chlorophenyl)sulfonyl]amino)-4-(trifluoromethyl)phenyl]methyl)-4-methyl-1H-pyrazole-5-carboxylic acid (1:1)
11		460	3.4	461	458	1-([2-([(4-chlorophenyl)sulfonyl]amino)-4-(trifluoromethyl)phenyl]methyl)-1H-pyrazole-4-carboxylic acid
12		516	3.8	516	514	3-butyl-1-([2-([(4-chlorophenyl)sulfonyl]amino)-4-(trifluoromethyl)phenyl]methyl)-1H-pyrazole-5-carboxylic acid
13		502	3.8	502	500	1-([2-([(4-chlorophenyl)sulfonyl]amino)-4-(trifluoromethyl)phenyl]methyl)-3-propyl-1H-pyrazole-5-carboxylic acid

Ex	Structure	Parent Mwt	Rt/min	+ve	-ve	Name
14		502	3.7 3.8	502	500	1-([2-((4-chlorophenyl)sulfonyl)amino]-4-(trifluoromethyl)phenyl)methyl]-3-propyl-1H-pyrazole-5-carboxylic acid and 1-([2-((4-chlorophenyl)sulfonyl)amino]-4-(trifluoromethyl)phenyl)methyl]-5-propyl-1H-pyrazole-3-carboxylic acid (1:1)
15		490	3.4	491	488	1-([2-((4-chlorophenyl)sulfonyl)amino]-4-(trifluoromethyl)phenyl)methyl]-4-(hydroxymethyl)-1H-pyrazole-3-carboxylic acid
16		460	3.6	461	459	1-([2-((4-chlorophenyl)sulfonyl)amino]-4-(trifluoromethyl)phenyl)methyl]-1H-pyrazole-5-carboxylic acid
17		466	3.9	466	464	4-chloro-N-[2-(1H-indazol-1-ylmethyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide

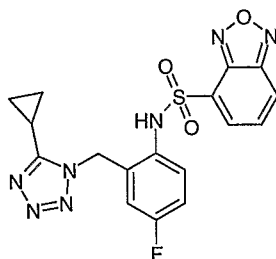
Ex	Structure	Parent Mwt	Rt/min	+ve	-ve	Name
18		442	3.4 3.6	442	440	4-chloro- <i>N</i> -[2-[(3-cyano-4 <i>H</i> -1,2,4-triazol-4-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide and 4-chloro- <i>N</i> -[2-[(5-cyano-1 <i>H</i> -1,2,4-triazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide (1:1)
19		442	3.5 3.6	442	440	4-chloro- <i>N</i> -[2-[(3-cyano-4 <i>H</i> -1,2,4-triazol-4-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide and 4-chloro- <i>N</i> -[2-[(3-cyano-1 <i>H</i> -1,2,4-triazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide (1:1)
20		431	3.3 3.2	431	429	4-chloro- <i>N</i> -[2-[(3-methyl-1 <i>H</i> -1,2,4-triazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide and 4-chloro- <i>N</i> -[2-[(5-methyl-1 <i>H</i> -1,2,4-triazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide (1:1)

Ex	Structure	Parent Mwt	Rt/ min	+ve	-ve	Name
21		498	3.9 4.0	500	498	4-chloro- <i>N</i> -[2-([5-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-1-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide and 4-chloro- <i>N</i> -[2-([3-methyl-5-(trifluoromethyl)-1 <i>H</i> -pyrazol-1-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide (1:1)
22		408	3.2	408	406	4-chloro- <i>N</i> -[2-[(5-cyclopropyl-1 <i>H</i> -tetrazol-1-yl)methyl]-3-fluorophenyl]benzenesulfonamide
23		424	4.3	425	423	4-chloro- <i>N</i> -[5-chloro-2-[(5-cyclopropyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl]benzenesulfonamide
24		408	3.2	408	406	4-chloro- <i>N</i> -[2-[(5-cyclopropyl-1 <i>H</i> -tetrazol-1-yl)methyl]-4-fluorophenyl]benzenesulfonamide
25		398	3.3	399	397	4-chloro- <i>N</i> -[5-chloro-2-[(5-methyl-2 <i>H</i> -tetrazol-2-yl)methyl]phenyl]benzenesulfonamide
26		383	2.9	384	382	4-chloro- <i>N</i> -[5-chloro-2-(4 <i>H</i> -1,2,4-triazol-4-ylmethyl)phenyl]benzenesulfonamide

Ex	Structure	Parent Mwt	Rt/min	+ve	-ve	Name
27		383	3.1	384	382	4-chloro- <i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,4-triazol-1-ylmethyl)phenyl]benzenesulfonamide
28		383	3.2	384	382	4-chloro- <i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]benzenesulfonamide
29		384	3.3	385	383	4-chloro- <i>N</i> -[5-chloro-2-(2 <i>H</i> -tetrazol-2-ylmethyl)phenyl]benzenesulfonamide
30		384	3.3	385	383	4-chloro- <i>N</i> -[5-chloro-2-(1 <i>H</i> -tetrazol-1-ylmethyl)phenyl]benzenesulfonamide
31		383	3.4	384	382	4-chloro- <i>N</i> -[5-chloro-2-(2 <i>H</i> -1,2,3-triazol-2-ylmethyl)phenyl]benzenesulfonamide
32		397.3	3.15	398	396	4-chloro- <i>N</i> -{5-chloro-2-[(3-methyl-4 <i>H</i> -1,2,4-triazol-4-yl)methyl]phenyl}benzenesulfonamide
33		425.3	3.11	426	424	4-chloro- <i>N</i> -{5-chloro-2-[(3-imino-2,5-dimethyl-2,3-dihydro-1 <i>H</i> -pyrazol-4-yl)methyl]phenyl}benzenesulfonamide

Ex	Structure	Parent Mwt	Rt/min	+ve	-ve	Name
34		398	3.2	398	396	4-chloro- <i>N</i> -{5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl}benzenesulfonamide
35		497	3.7	498	496	4-chloro- <i>N</i> -[2-{[5-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-yl]methyl}-5-(trifluoromethyl)phenyl]benzenesulfonamide

Example 36: *N*-{2-[(5-cyclopropyl-1*H*-tetrazole-1-yl)methyl]-4-fluorophenyl}-2,11,3-benzoxadiazole-4-sulfonamide

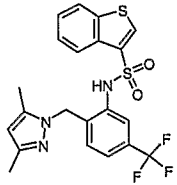
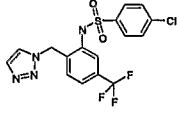
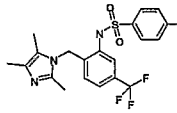
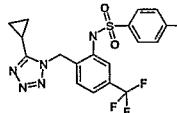
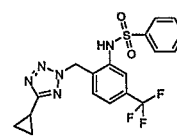
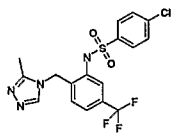


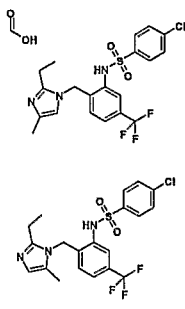
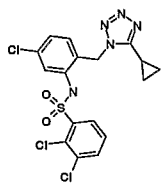
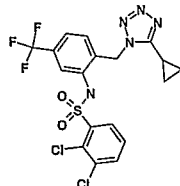
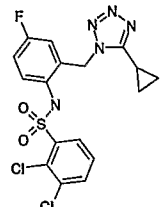
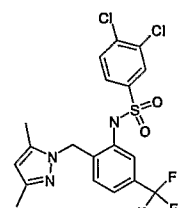
- 5 To a solution of 2-[(5-cyclopropyl-1*H*-tetrazole-1-yl)methyl]-4-fluoroaniline (40 mg, 0.18 mmol) in pyridine (1 ml), was added a solution of 2,1,3-benzoxadiazole-4-sulfonyl chloride (0.075 g, 0.34 mmol) in pyridine (1 ml) and *N,N*-dimethyl-4-pyridinamine (5 mg) and the mixture was heated to 200 °C for 30 minutes in a microwave reactor. The pyridine was removed *in vacuo* and the mixture was dissolved in
- 10 dimethylsulfoxide/methanol 1:1 (1 mL). The resulting solution was purified by mass directed autoprep to give *N*-{2-[(5-cyclopropyl-1*H*-tetrazole-1-yl)methyl]-4-fluorophenyl}-2,11,3-benzoxadiazole-4-sulfonamide (0.061 g). HPLC Rt=2.92 minutes; *m/z* [M+H]⁺=416. ¹H NMR (CD₃OD) δ 8.23 (d, 1H), 7.92 (d, 1H), 7.61 (t, 1H), 6.93 (m, 1H), 6.83 (m, 1H), 6.61 (m, 1H), 5.93 (s, 2H), 2.10 (m, 1H), 1.20 (m, 2H), 1.07 (m, 2H).

15

The following compounds of formula (I) set out in Table 2 were prepared by a similar procedure to that described for Example 36 using the appropriate starting materials.

Table 2

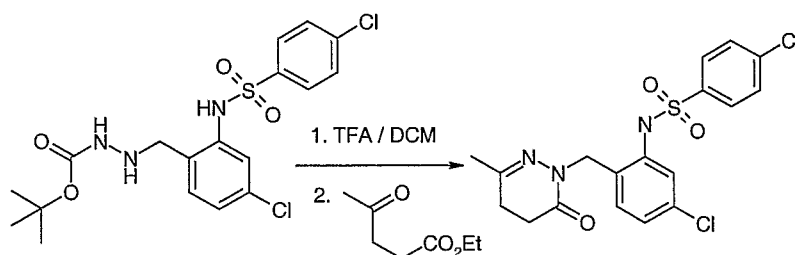
Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
37		466	3.1	466	464	<i>N</i> -[2-[(3,5-dimethyl-1 <i>H</i> -pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]-1-benzothiophene-3-sulfonamide
38		419	3.2	415	418	4-chloro- <i>N</i> -[2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
39		458	2.7	461	458	4-chloro- <i>N</i> -{5-(trifluoromethyl)-2-[(2,4,5-trimethyl-1 <i>H</i> -imidazol-1-yl)methyl]phenyl}benzenesulfonamide
40		458	4.4	456	458	4-chloro- <i>N</i> -[2-[(5-cyclopropyl-1 <i>H</i> -tetrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
41		458	3.7	458	456	4-chloro- <i>N</i> -[2-[(5-cyclopropyl-2 <i>H</i> -tetrazol-2-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
42		431	3.1	431	429	4-chloro- <i>N</i> -[2-[(3-methyl-4 <i>H</i> -1,2,4-triazol-4-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
43		458	2.7 2.8	458	456	Formic acid salt of 4-chloro-N-[2-[(2-ethyl-4-methyl-1H-imidazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide and formic acid salt of 4-chloro-N-[2-[(2-ethyl-5-methyl-1H-imidazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
44		459	3.5	460	458	2,3-dichloro-N-{5-chloro-2-[(5-cyclopropyl-1H-tetrazol-1-yl)methyl]phenyl}benzenesulfonamide
45		492	4.4	493	491	2,3-dichloro-N-[2-[(5-cyclopropyl-1H-tetrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
46		442	3.2	443	441	2,3-dichloro-N-[2-[(5-cyclopropyl-1H-tetrazol-1-yl)methyl]-4-fluorophenyl]benzenesulfonamide
47		478	3.2	479	477	3,4-dichloro-N-[2-[(3,5-dimethyl-1H-pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
48		450	3.1	451	449	5-chloro- <i>N</i> -[2-[(3,5-dimethyl-1 <i>H</i> -pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]-2-thiophenesulfonamide
49		418	3.2	419	415	3,4-dichloro- <i>N</i> -[5-chloro-2-(2 <i>H</i> -1,2,3-triazol-2-ylmethyl)phenyl]benzenesulfonamide
50		418	3.5	419	416	3,4-dichloro- <i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,4-triazol-1-ylmethyl)phenyl]benzenesulfonamide
51		417.7	3.39	419	416	3,4-dichloro- <i>N</i> -[5-chloro-2-(4 <i>H</i> -1,2,4-triazol-4-ylmethyl)phenyl]benzenesulfonamide
52		432	3.3	433	431	3,4-dichloro- <i>N</i> -[5-chloro-2-[(3-methyl-4 <i>H</i> -1,2,4-triazol-4-yl)methyl]phenyl]benzenesulfonamide
53		419	3.5	420	418	3,4-dichloro- <i>N</i> -[5-chloro-2-(1 <i>H</i> -tetrazol-1-ylmethyl)phenyl]benzenesulfonamide

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
54		462	3.3	462	460	4-chloro-N-[2-[(3,5-dimethyl-1H-pyrazol-1-yl)methyl]-3-fluoro-5-(trifluoromethyl)phenyl]benzenesulfonamide
55		476	4.5	476	474	4-chloro-N-[2-[(5-cyclopropyl-1H-tetrazol-1-yl)methyl]-3-fluoro-5-(trifluoromethyl)phenyl]benzenesulfonamide
56		476	3.7	476	474	4-chloro-N-[2-[(5-cyclopropyl-2H-tetrazol-2-yl)methyl]-3-fluoro-5-(trifluoromethyl)phenyl]benzenesulfonamide

Example 57: 4-Chloro-N-{5-chloro-2-[(3-methyl-6-oxo-5,6-dihydro-1(4H)-pyridazinyl)methyl]phenyl}benzenesulfonamide



5

1,1-Dimethylethyl 2-[(4-chloro-2-[[4-chlorophenyl]sulfonyl]amino)phenyl]methyl-

hydrazinecarboxylate (25 mg, 0.06 mmol) in 50 % trifluoroacetic acid / dichloromethane

(2 mL) was stirred at room temperature for 2 hours. The solvent was evaporated under

reduced pressure and then ethyl levulinate (9 mg, 0.06 mmol) and glacial acetic acid (1

10

mL) added. The mixture was heated at 100 °C for 30 mins in a microwave reactor. The

solvent was removed under reduced pressure and the residue dissolved in dimethyl

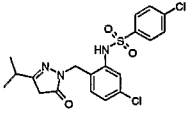
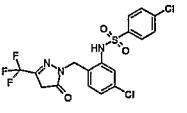
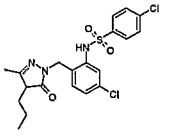
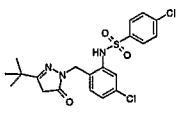
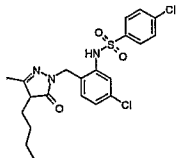
sulphoxide (0.5 mL) and then purified by mass directed autoprep to give 4-chloro-N-{5-

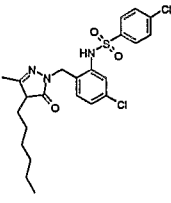
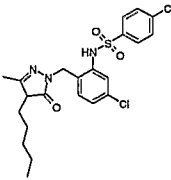
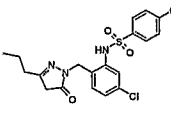
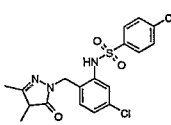
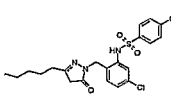
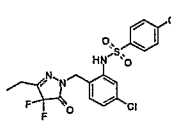
chloro-2-[(3-methyl-6-oxo-5,6-dihydro-1(4H)-

pyridaziny]methyl]phenyl}benzenesulfonamide as a colourless gum (10.3 mg). HPLC Rt = 3.43 minutes; m/z [M+H]⁺ = 426 / 428. ¹H NMR (CD₃OD) δ 7.72 (d, 2H), 7.54 (d, 2H), 7.32 (d, 1H), 7.24(d, 1H), 7.12 (dd, 1H), 4.47 (s, 2H), 2.47 (m, 4H), 2.04 (s, 3H).

- 5 The following compounds of formula (I) set out in Table 3 were prepared by a similar procedure to that described for Example 57 using the appropriate starting materials.

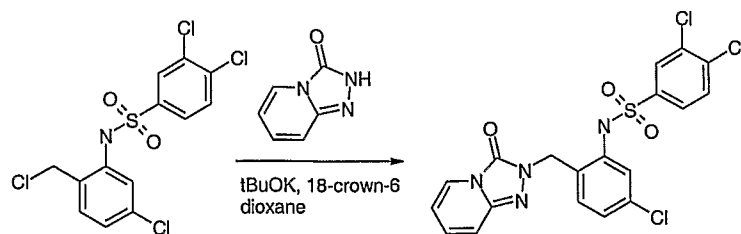
Table 3

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
58		440	3.5	440	438	4-chloro-N-(5-chloro-2-([3-(1-methylethyl)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]methyl)phenyl)benzenesulfonamide
59		466	4.0	466	464	4-chloro-N-(5-chloro-2-([5-oxo-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-1-yl]methyl)phenyl)benzenesulfonamide
60		454	3.5	454	452	4-chloro-N-(5-chloro-2-([3-(1,1-dimethylethyl)-5-oxo-4-propyl-4,5-dihydro-1H-pyrazol-1-yl]methyl)phenyl)benzenesulfonamide
61		454	3.7	454	452	4-chloro-N-(5-chloro-2-([3-(1,1-dimethylethyl)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]methyl)phenyl)benzenesulfonamide
62		468	3.7	468	466	N-{2-[(4-butyl-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)methyl]-5-chlorophenyl}-4-chlorobenzenesulfonamide

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
63		497	4.0	496	494	4-chloro-N-{5-chloro-2-[(4-hexyl-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)methyl]phenyl}benzenesulfonamide
64		482	3.9	482	480	4-chloro-N-{5-chloro-2-[(3-methyl-5-oxo-4-pentyl-4,5-dihydro-1H-pyrazol-1-yl)methyl]phenyl}benzenesulfonamide
65		440	3.5	440	438	4-chloro-N-{5-chloro-2-[(5-oxo-3-propyl-4,5-dihydro-1H-pyrazol-1-yl)methyl]phenyl}benzenesulfonamide
66		426	3.4	426	424	4-chloro-N-{5-chloro-2-[(3,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)methyl]phenyl}benzenesulfonamide
67		468	3.8	468	466	4-chloro-N-{5-chloro-2-[(5-oxo-3-pentyl-4,5-dihydro-1H-pyrazol-1-yl)methyl]phenyl}benzenesulfonamide
68		462	3.8	462	460	4-chloro-N-{5-chloro-2-[(3-ethyl-4,4-difluoro-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)methyl]phenyl}benzenesulfonamide

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
69		440	3.6	440	438	4-chloro-N-{5-chloro-2-[(4-ethyl-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)methyl]phenyl}benzenesulfonamide
70		468	3.7	468	466	4-chloro-N-{5-chloro-2-[(4,4-diethyl-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)methyl]phenyl}benzenesulfonamide
71		454	3.6	454	452	4-chloro-N-{5-chloro-2-[(4-ethyl-3,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)methyl]phenyl}benzenesulfonamide
72		440	3.5	440	438	4-chloro-N-{5-chloro-2-[(3,4,4-trimethyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)methyl]phenyl}benzenesulfonamide
73		426	3.4	426	424	4-chloro-N-{5-chloro-2-[(3-ethyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)methyl]phenyl}benzenesulfonamide

Example 74: 3,4-Dichloro-N-{5-chloro-2-[(3-oxo[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)methyl]phenyl}benzenesulfonamide

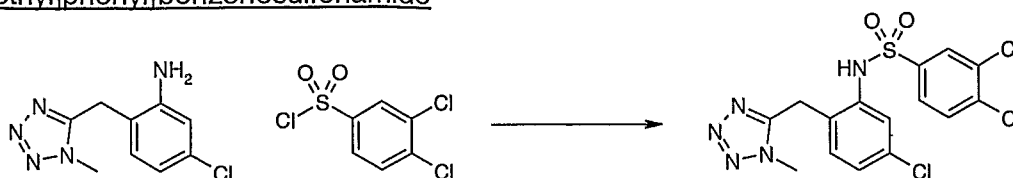


To the commercially available [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (27 mg, 0.20 mmol) and 18-crown-6 ether (55 mg, 0.21 mmol) in anhydrous 1,4-dioxane (1 mL) was added a 1M solution of potassium *tert*-butoxide in tetrahydrofuran (210 μ L, 0.21 mmol). The mixture was stirred at room temperature for 15 minutes and then 1 mL of a solution of 3,4-dichloro-N-[5-chloro-2-(chloromethyl)phenyl]benzenesulfonamide (655 mg, 1.7 mmol) in anhydrous 1,4-dioxane (17 mL) was added. The mixture was heated at 60 °C for 15 hours and then left to cool to room temperature. The solvent was removed under reduced pressure and the residue dissolved in dimethyl sulphoxide (0.5 mL) and then purified by mass directed autoprep to give 3,4-dichloro-N-{5-chloro-2-[(3-oxo[1,2,4]triazolo[4,3-a]pyridin-2(3H)-yl)methyl]phenyl}benzenesulfonamide as a white solid (6.6mg). HPLC Rt = 3.23 minutes; m/z [M+H]⁺ = 483. ¹H NMR (d₆-DMSO) δ 7.85 (m, 3H), 7.63 (d, 1H), 7.28 (d, 1H), 7.24 (t, 1H), 7.17 (d, 1H), 7.09 (d, 1H), 6.99 (s, 1H), 6.63 (t, 1H), 5.00 (s, 2H).

The following compounds of formula (I) set out in Table 4 were prepared by a similar procedure to that described for Example 74 using the appropriate starting materials.

Table 4

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
75		436	3.4	435	433	3,4-dichloro-N-{5-chloro-2-[(2-oxo-1,3-oxazolidin-3-yl)methyl]phenyl}benzenesulfonamide
76		484	3.9	483	481	3,4-dichloro-N-{5-chloro-2-[(2-oxo-1,3-benzoxazol-3(2H)-yl)methyl]phenyl}benzenesulfonamide
77		448	3.6	447	445	3,4-dichloro-N-{5-chloro-2-[(2-oxo-1-piperidinyl)methyl]phenyl}benzenesulfonamide

Example 78: 3,4-Dichloro-*N*-[5-chloro-2-[(1-methyl-1*H*-tetrazol-5-yl)methyl]phenyl]benzenesulfonamide

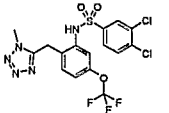
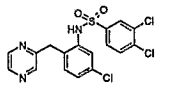
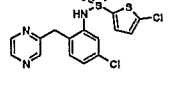
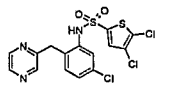
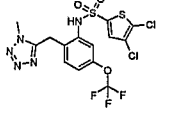
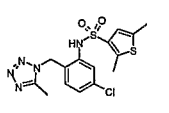
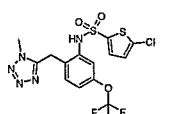
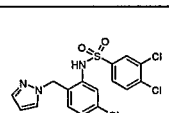
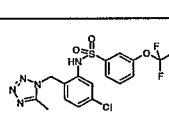
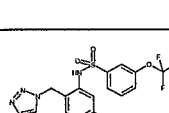
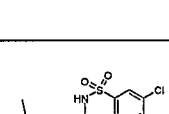
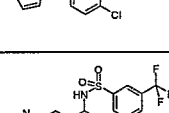
- 5 A mixture of {5-chloro-2-[(1-methyl-1*H*-tetrazol-5-yl)methyl]phenyl}amine (163 mg), 3,4-dichlorobenzenesulfonyl chloride (197 mg) and 4-(dimethylamino)-pyridine (10 mg) in pyridine (3 mL) was stirred overnight at 80 °C under an atmosphere of argon. The mixture was cooled and concentrated. The resulting residue was partitioned between ethyl acetate (20 mL) and 2M HCl (3 mL), the organic layer was washed with brine (3
- 10 mL) and concentrated. The resulting residue was purified by column chromatography (10-30% ethyl acetate in hexane) and the product slurried in methanol, cooled and filtered to give the title compound, 130 mg. HPLC Rt = 3.4 minutes; *m/z* [*M*]⁺ = 432. ¹H NMR (d₆-DMSO) δ 10.2 (s, 1H), 7.88 (d, 1H), 7.81 (d, 1H), 7.59 (dd, 1H), 7.32 (br.d, 1H), 7.25 (d, 1H), 6.91 (d, 1H), 7.21 (s, 2H), 3.95 (s, 3H).
- 15 The following compounds of formula (I) set out in Table 5 were prepared by a similar procedure to that described for Example 78 using the appropriate starting materials.

Table 5

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
79		431	3.2	432	-	4-chloro- <i>N</i> -[2-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
80		465	3.4	466	-	3,4-dichloro- <i>N</i> -[2-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
81		433	3.6	434	432	3,4-dichloro- <i>N</i> -[5-chloro-2-[(5-methyl-2 <i>H</i> -tetrazol-2-yl)methyl]phenyl]benzenesulfonamide
82		419	3.6	420	-	3,4-dichloro- <i>N</i> -[5-chloro-2-(2 <i>H</i> -tetrazol-2-ylmethyl)phenyl]benzenesulfonamide
83		402	3.4	-	402	3,4-dichloro- <i>N</i> -[5-fluoro-2-(1 <i>H</i> -tetrazol-1-ylmethyl)phenyl]benzenesulfonamide

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
84		402	3.4	-	402	3,4-dichloro- <i>N</i> -[5-fluoro-2-(2 <i>H</i> -tetrazol-2-ylmethyl)phenyl]benzenesulfonamide
85		401	3.3	-	399	3,4-dichloro- <i>N</i> -[5-fluoro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]benzenesulfonamide
86		415	3.3	416	414	3,4-dichloro- <i>N</i> -{5-fluoro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl}benzenesulfonamide
87		415	3.5	416	414	3,4-dichloro- <i>N</i> -{5-fluoro-2-[(5-methyl-2 <i>H</i> -tetrazol-2-yl)methyl]phenyl}benzenesulfonamide
88		401	3.3	401	399	3,4-dichloro- <i>N</i> -[5-fluoro-2-(1 <i>H</i> -1,2,4-triazol-1-ylmethyl)phenyl]benzenesulfonamide
89		388	3.2	389	387	5-chloro- <i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-2-thiophenesulfonamide
90		424	3.5	425	423	4,5-dichloro- <i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-2-thiophenesulfonamide
91		439	3.5	440	438	4,5-dichloro- <i>N</i> -{5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl}-2-thiophenesulfonamide
92		403	3.3	404	402	5-chloro- <i>N</i> -{5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl}-2-thiophenesulfonamide
93		381	3.0	381	380	<i>N</i> -{5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl}-3-fluorobenzenesulfonamide
94		397	3.2	398	396	3-chloro- <i>N</i> -{5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl}benzenesulfonamide
95		366	3.0	367	365	<i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-3-fluorobenzenesulfonamide
96		383	3.2	383	381	3-chloro- <i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]benzenesulfonamide

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
97		452	3.7	-	451	3,4-dichloro- <i>N</i> -[4,5-dichloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]benzenesulfonamide
98		424	3.5	-	422	5-chloro- <i>N</i> -[4,5-dichloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-2-thiophenesulfonamide
99		458	4.0	-	457	4,5-dichloro- <i>N</i> -[4,5-dichloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-2-thiophenesulfonamide
100		433	3.5	-	432	3,4-dichloro- <i>N</i> -[5-chloro-2-[(2-methyl-2 <i>H</i> -tetrazol-5-yl)methyl]phenyl]benzenesulfonamide
101		408	3.1	409	407	<i>N</i> -[5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl]-3-nitrobenzenesulfonamide
102		303	3.0	304	302	<i>N</i> -[5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl]benzenesulfonamide
103		432	3.3	433	431	2,3-dichloro- <i>N</i> -[5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl]benzenesulfonamide
104		411	3.3	412	410	3-chloro- <i>N</i> -[5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl]-4-fluorobenzenesulfonamide
105		440	3.6	441	439	4,5-dichloro- <i>N</i> -[5-chloro-2-[(2-methyl-2 <i>H</i> -tetrazol-5-yl)methyl]phenyl]-2-thiophenesulfonamide
106		403	3.3	404	402	5-chloro- <i>N</i> -[5-chloro-2-[(2-methyl-2 <i>H</i> -tetrazol-5-yl)methyl]phenyl]-2-thiophenesulfonamide
107		403	3.4	404	-	5-chloro- <i>N</i> -[5-chloro-2-[(1-methyl-1 <i>H</i> -tetrazol-5-yl)methyl]phenyl]-2-thiophenesulfonamide
108		439	3.4	440	-	4,5-dichloro- <i>N</i> -[5-chloro-2-[(1-methyl-1 <i>H</i> -tetrazol-5-yl)methyl]phenyl]-2-thiophenesulfonamide
109		439	3.5	440	438	2,5-dichloro- <i>N</i> -[5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl]-3-thiophenesulfonamide

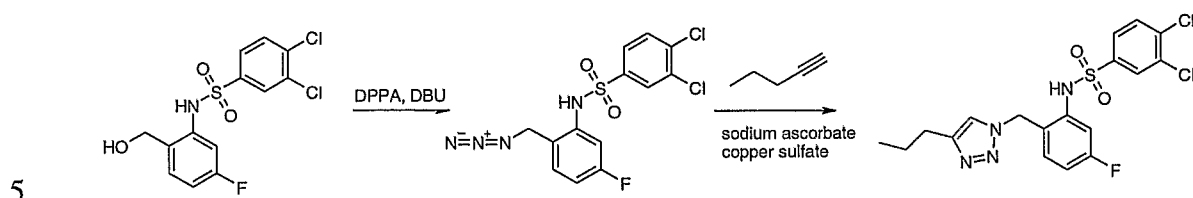
Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
110		481	3.5	482	480	3,4-dichloro- <i>N</i> -{2-[(1-methyl-1 <i>H</i> -tetrazol-5-yl)methyl]-5-[(trifluoromethyl)oxy]phenyl}benzenesulfonamide
111		429	3.6	430	428	3,4-dichloro- <i>N</i> -[5-chloro-2-(2-pyrazinylmethyl)phenyl]benzenesulfonamide
112		400	3.4	400	398	5-chloro- <i>N</i> -[5-chloro-2-(2-pyrazinylmethyl)phenyl]-2-thiophenesulfonamide
113		435	3.6	436	434	4,5-dichloro- <i>N</i> -[5-chloro-2-(2-pyrazinylmethyl)-phenyl]-2-thiophene-sulfonamide
114		488	3.6	488	486	4,5-dichloro- <i>N</i> -{2-[(1-methyl-1 <i>H</i> -tetrazol-5-yl)methyl]-5-[(trifluoromethyl)oxy]phenyl}-2-thiophenesulfonamide
115		398	3.3	398	396	<i>N</i> -{5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl}-2,5-dimethyl-3-thiophenesulfonamide
116		454	3.3	454	452	5-chloro- <i>N</i> -{2-[(1-methyl-1 <i>H</i> -tetrazol-5-yl)methyl]-5-[(trifluoromethyl)oxy]phenyl}-2-thiophenesulfonamide
117		417	3.7	418	416	3,4-dichloro- <i>N</i> -[5-chloro-2-(1 <i>H</i> -pyrazol-1-ylmethyl)phenyl]benzenesulfonamide
118		448	3.3	448	446	<i>N</i> -[5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl]-3-[(trifluoromethyl)oxy]benzenesulfonamide
119		433	3.3	433	431	<i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-3-[(trifluoromethyl)oxy]benzenesulfonamide
120		431	2.8	432	430	3,4-dichloro- <i>N</i> -{5-chloro-2-[(2-methyl-1 <i>H</i> -imidazol-1-yl)methyl]phenyl}benzenesulfonamide
121		432	3.2	432	430	<i>N</i> -[5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl]-3-(trifluoromethyl)benzenesulfonamide

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
122		417	3.2	417	415	<i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide
123		405	3.2	405	403	<i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-1-benzothiophene-3-sulfonamide
124		420	3.2	420	418	<i>N</i> -{5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl}-1-benzothiophene-3-sulfonamide
125		406	3.1	406	404	<i>N</i> -{5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl}-2,1,3-benzoxadiazole-4-sulfonamide
126		391	2.9	391	389	<i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-2,1,3-benzoxadiazole-4-sulfonamide
127		425	3.2	425	423	7-chloro- <i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-2,1,3-benzoxadiazole-4-sulfonamide
128		440	3.2	440	438	7-chloro- <i>N</i> -[5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl]-2,1,3-benzoxadiazole-4-sulfonamide
129		414	2.8	414	412	3,4-dichloro- <i>N</i> -[5-fluoro-2-[(2-methyl-1 <i>H</i> -imidazol-1-yl)methyl]phenyl]benzenesulfonamide
130		421	2.6	421	419	3,4-dichloro- <i>N</i> -[5-cyano-2-[(2-methyl-1 <i>H</i> -imidazol-1-yl)methyl]phenyl]benzenesulfonamide
131		406	3.7	406	404	4,5-dichloro- <i>N</i> -[5-fluoro-2-(1 <i>H</i> -pyrazol-1-ylmethyl)phenyl]-2-thiophenesulfonamide
132		459	3.0	460	458	3,4-dichloro- <i>N</i> -(5-chloro-2-[(2-(1-methylethyl)-1 <i>H</i> -imidazol-1-yl)methyl]phenyl)benzenesulfonamide

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
133		437	2.8	438	436	4,5-dichloro- <i>N</i> -{5-chloro-2-[(2-methyl-1 <i>H</i> -imidazol-1-yl)methyl]phenyl}-2-thiophenesulfonamide
134		423	3.8	424	422	4,5-dichloro- <i>N</i> -[5-chloro-2-(1 <i>H</i> -pyrazol-1-ylmethyl)phenyl]-2-thiophenesulfonamide
135		417	2.7	418	416	3,4-dichloro- <i>N</i> -[5-chloro-2-(1 <i>H</i> -imidazol-1-ylmethyl)phenyl]benzenesulfonamide
136		445	2.8	446	444	3,4-dichloro- <i>N</i> -[5-chloro-2-[(2-ethyl-1 <i>H</i> -imidazol-1-yl)methyl]phenyl]benzenesulfonamide
137		410	2.8	410	408	4-chloro- <i>N</i> -[5-chloro-2-[(2-ethyl-1 <i>H</i> -imidazol-1-yl)methyl]phenyl]benzenesulfonamide
138		424	2.7	424	422	4-chloro- <i>N</i> -(5-chloro-2-[(2-(1-methylethyl)-1 <i>H</i> -imidazol-1-yl)methyl]phenyl)benzenesulfonamide
139		376	3.2	377	376	<i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-3,4-dimethylbenzenesulfonamide
140		445	2.8	446	444	3,4-dichloro- <i>N</i> -[5-chloro-2-[(2,4-dimethyl-1 <i>H</i> -imidazol-1-yl)methyl]phenyl]benzenesulfonamide
141		425	3.2	425	423	<i>N</i> -[4,5-dichloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-2,1,3-benzoxadiazole-4-sulfonamide
142		460	3.6	461	459	7-chloro- <i>N</i> -[4,5-dichloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-2,1,3-benzoxadiazole-4-sulfonamide
143		418	3.4	419	417	4-chloro- <i>N</i> -[4,5-dichloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]benzenesulfonamide

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
144		412	3.3	412	410	3-chloro-N-{5-chloro-2-[(5-methyl-1H-tetrazol-1-yl)methyl]phenyl}-4-methylbenzenesulfonamide

Example 145: 3,4-dichloro-N-{5-fluoro-2-[(4-propyl-1H-1,2,3-triazol-1-yl)methyl]phenyl}benzenesulfonamide



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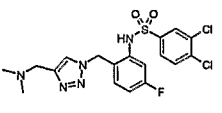
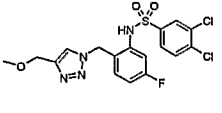
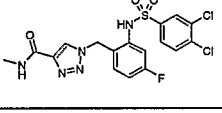
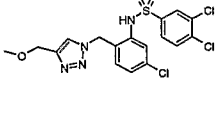
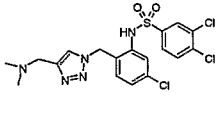
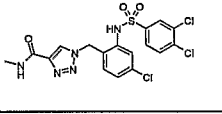
N-[2-(azidomethyl)-5-fluorophenyl]-3,4-dichlorobenzenesulfonamide (450 mg) was dissolved in 2-methyl propanol (5 mL). To one-fifth of this solution was added a 0.025M aqueous solution of sodium ascorbate (1 mL) and a 0.1 M aqueous solution of copper sulfate (0.024 mL). 1-Pentyne (0.24 mL) was added and the mixture stirred for 72 hours at room temperature. DCM (5 mL) and water (1 mL) was added and the mixture vigorously stirred for 5 minutes. The aqueous layer was removed using a hydrophobic frit and washed with DCM (2 x 1 mL) and the combined DCM layers concentrated. The title compound was retained on an isolate SCX ion-exchange column and eluted in 2M ammonia in methanol to give 40 mg upon removal of solvent. HPLC *Rt* = 3.7 minutes; *m/z* [MH]⁺ = 443 ¹H NMR (CDCl₃) δ 7.97 (d, 1H), 7.70 (dd, 1H), 7.57 (d, 1H), 7.27 (d, 1H), 7.25 (dd, 1H), 7.14 (dd, 1H), 6.89 (dt, 1H), 5.19 (s, 2H), 2.66 (t, 2H), 1.67 (sextet, 2H), 0.96 (t, 3H).

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The following compounds of formula (I) set out in Table 6 were prepared by a similar procedure to that described for Example 145 using the appropriate starting materials. In some cases the product was isolated *via* additional silica chromatography or mass-directed autopreparative HPLC.

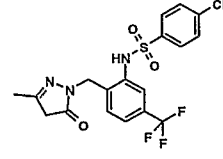
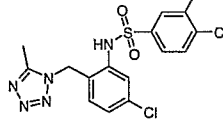
Table 6

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
146		459	3.7	460	-	3,4-dichloro-N-{5-chloro-2-[(4-propyl-1H-1,2,3-triazol-1-yl)methyl]phenyl}benzenesulfon

						amide
147		458	3.7	458	-	3,4-dichloro- <i>N</i> -[2-({4-[(dimethylamino)methyl]-1 <i>H</i> -1,2,3-triazol-1-yl}methyl)-5-fluorophenyl]benzenesulfonamide
148		445	3.4	445	-	3,4-dichloro- <i>N</i> -[5-fluoro-2-({4-[(methyloxy)methyl]-1 <i>H</i> -1,2,3-triazol-1-yl}methyl)phenyl]benzenesulfonamide
149		458	3.3	458	-	1-[(2-({(3,4-dichlorophenyl)sulfonyl}amino)-4-fluorophenyl)methyl]- <i>N</i> -methyl-1 <i>H</i> -1,2,3-triazole-4-carboxamide
150		462	3.5	463	-	3,4-dichloro- <i>N</i> -[5-chloro-2-({4-[(methyloxy)methyl]-1 <i>H</i> -1,2,3-triazol-1-yl}methyl)phenyl]benzenesulfonamide
151		475	2.8	476	-	3,4-dichloro- <i>N</i> -[5-chloro-2-({4-[(dimethylamino)methyl]-1 <i>H</i> -1,2,3-triazol-1-yl}methyl)phenyl]benzenesulfonamide
152		474	3.4	475	-	1-[(4-chloro-2-({(3,4-dichlorophenyl)sulfonyl}amino)phenyl)methyl]- <i>N</i> -methyl-1 <i>H</i> -1,2,3-triazole-4-carboxamide

The following compounds of formula (I) set out in Table 7 were prepared by a similar procedure to that described for Example 3 using the appropriate starting materials.

5 Table 7

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
153		446	3.4	446	444	4-chloro- <i>N</i> -[2-[(3-methyl-5-oxo-4,5-dihydro-1 <i>H</i> -pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
154		433	3.4	434	432	3,4-dichloro- <i>N</i> -[5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl]benzenesulfonamide

155		432	3.1	432	430	<i>N</i> -[5-chloro-2-[(5-cyclopropyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl]-2,1,3-benzoxadiazole-4-sulfonamide
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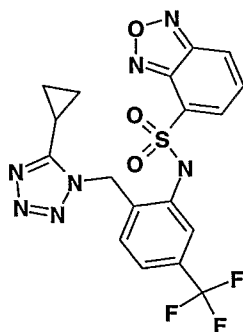
The following compounds of formula (I) set out in Table 8 were prepared by a similar procedure to that described for Example 74 using the appropriate starting materials.

Table 8

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
156		463	3.6	464	462	3,4-dichloro- <i>N</i> -[5-chloro-2-[(3-methyl-2,5-dioxo-1-imidazolidinyl)methyl]phenyl]benzenesulfonamide
157		449	3.7	450	448	3,4-dichloro- <i>N</i> -[5-chloro-2-[(3-methyl-2-oxo-1-imidazolidinyl)methyl]phenyl]benzenesulfonamide
158		458	3.8	459	457	3,4-dichloro- <i>N</i> -[5-chloro-2-[(5-methyl-2-oxo-1(2 <i>H</i>)-pyridinyl)methyl]phenyl]benzenesulfonamide

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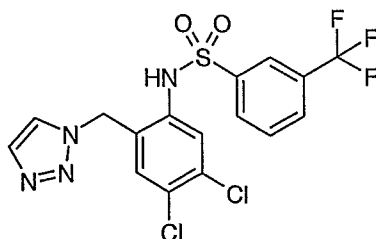
Example 159: *N*-[2-[(5-cyclopropyl-1*H*-tetrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]-2,1,3-benzoxadiazole-4-sulfonamide



Example 159 was prepared by a similar procedure to that described for Example 36 using the appropriate starting materials. HPLC Rt = 3.2 minutes; m/z $[MH]^+ = 466$

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Example 160: *N*-[4,5-dichloro-2-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide



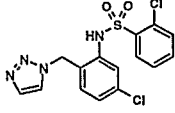
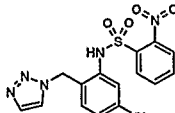
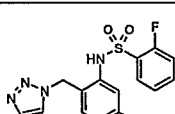
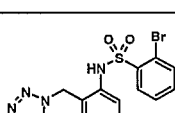
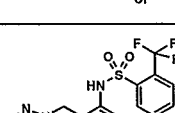
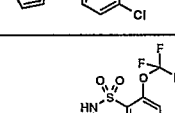
To a solution of intermediate 10 (100 mg) in pyridine was added 4-(dimethylamino)-pyridine (2.5 mg) and 3-(trifluoromethyl)-benzenesulfonyl chloride (79 μ L). The mixture was stirred at 20 °C overnight and passed through a 5 g amino-propyl ion-exchange column. The sulfonamide was eluted in 2 M ammonia in methanol and the solvent removed. The residue was partitioned between DCM and water and the organic layer separated and the solvent removed to provide 53 mg of the title compound as a cream solid. HPLC R_t = 3.4 minutes; m/z MH^+ = 451. ^1H NMR ($CDCl_3$) δ 8.12 (s, 1H), 8.05 (d, 1H), 7.88 (d, 1H), 7.75-7.62 (m, 3H), 7.33 (s, 1H), 7.18 (s, 1H), 5.35 (s, 1H).

The following compound of formula (I) set out in Table 9 was prepared by a similar procedure to that described for Example 160 using the appropriate starting materials.

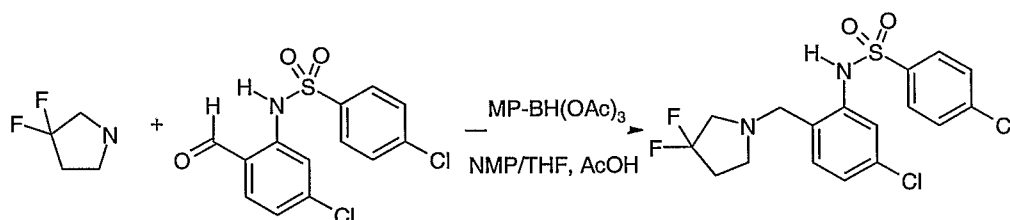
Table 9

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
161		393	3.03	394	392	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3-nitrobenzenesulfonamide
162		424	3.40	425	423	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3-biphenylsulfonamide
163		378	3.01	379	377	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3-(methoxy)benzenesulfonamide
164		440	3.39	441	439	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3-(phenyloxy)benzenesulfonamide
165		427	3.21	429	427	3-bromo-N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]benzenesulfonamide

166		348	2.95	349	347	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]benzenesulfonamide
167		373	2.91	374	372	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3-cyanobenzenesulfonamide
168		362	3.08	363	361	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3-methylbenzenesulfonamide
169		427	3.22	429	427	4-bromo-N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]benzenesulfonamide
170		416	3.26	417	415	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-4-(trifluoromethyl)benzenesulfonamide
171		393	3.06	394	392	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-4-nitrobenzenesulfonamide
172		378	2.99	379	377	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-4-(methoxy)benzenesulfonamide
173		362	3.09	363	361	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-4-methylbenzenesulfonamide
174		373	2.94	374	372	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-4-cyanobenzenesulfonamide
175		366	3.03	367	365	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-4-fluorobenzenesulfonamide
176		432	3.30	433	431	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-4-[(trifluoromethyl)oxy]benzenesulfonamide
177		452	3.23	453	451	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3-(phenylcarbonyl)benzenesulfonamide

178		382	3.04	383	381	2-chloro-N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]benzenesulfonamide
179		393	2.99	394	392	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-2-nitrobenzenesulfonamide
180		366	2.94	367	365	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-2-fluorobenzenesulfonamide
181		427	3.09	429	427	2-bromo-N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]benzenesulfonamide
182		416	3.11	417	415	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-2-(trifluoromethyl)benzenesulfonamide
183		432	3.18	433	431	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-2-[(trifluoromethyl)oxy]benzenesulfonamide

Example 184: 4-chloro-N-[5-chloro-2-[(3,3-difluoro-1-pyrrolidinyl)methyl]phenyl]benzenesulfonamide



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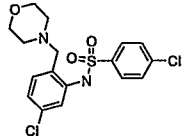
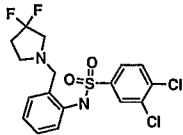
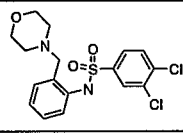
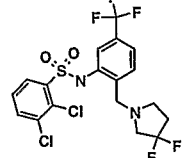
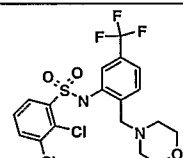
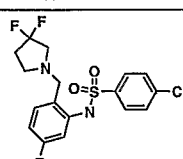
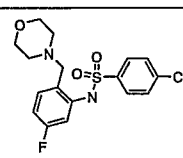
A 0.5 M solution of the aldehyde in 2:1 THF:NMP (200 μ l, 0.1 mmol) was added to the Reaction Vessel (RV). Then a 0.5 M solution of the amine in 2:1 THF:NMP (240 μ l, 0.12 mmol) was added to the RV. A 0.65M solution of acetic acid in THF (200 μ l, 0.13 mmol) was added to the RV. MP-tricetoxyborohydride (140 mg, loading 1.8 mmol/g) was added to the RV. The mixture was then vortexed for 24 hrs at room temperature. A further quantity of MP-triacetoxyborohydride (140 mg) was added. The mixture was then vortexed for 24 hrs at room temperature. Scavenger resins were added (70 mg MP-TsNHNH₂; 70 mg MP-Benzaldehyde for primary amines or 70 mg PS-Isocyanate for secondary amines). A 1:1 mixture of DCM:THF (1 ml) was added to the RV and

10

vortexed for 2 days. The resin was removed by filtration using a filter probe and washed with a further 4 washes of DMF (500 ul). The combined washes were evaporated to dryness and appropriate compounds were treated with 90% aq. trifluoroacetic acid to remove BOC protecting groups. The resulting material was analysed by LCMS and
 5 purified by Mass Directed Auto Prep if its purity was <80%. HPLC Rt = 3.6 minutes; m/z MH⁺ = 421.

The following compounds of formula (I) set out in Table 10 were prepared similarly to example 184 described above using the appropriate aldehyde and amine starting materials.

10 Table 10

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
185		400	2.76	401		4-chloro- <i>N</i> -[5-chloro-2-(4-morpholinylmethyl)phenyl]benzenesulfonamide
186		420	3.46	421		3,4-dichloro- <i>N</i> -{2-[(3,3-difluoro-1-pyrrolidinyl)methyl]phenyl}benzenesulfonamide
187		400	2.53	401		3,4-dichloro- <i>N</i> -[2-(4-morpholinylmethyl)phenyl]benzenesulfonamide
188		488	3.68	489		2,3-dichloro- <i>N</i> -[2-[(3,3-difluoro-1-pyrrolidinyl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
189		468	3.31	469		2,3-dichloro- <i>N</i> -[2-(4-morpholinylmethyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
190		404	3.43	405		4-chloro- <i>N</i> -{2-[(3,3-difluoro-1-pyrrolidinyl)methyl]-5-fluorophenyl}benzenesulfonamide
191		384	2.57	385		4-chloro- <i>N</i> -[5-fluoro-2-(4-morpholinylmethyl)phenyl]benzenesulfonamide

192		438	3.59	439	3,4-dichloro- <i>N</i> -[2-[(3,3-difluoro-1-pyrrolidinyl)methyl]-5-fluorophenyl]benzenesulfonamide
193		418	2.79	419	3,4-dichloro- <i>N</i> -[5-fluoro-2-(4-morpholinylmethyl)phenyl]benzenesulfonamide
194		438	3.63	439	3,4-dichloro- <i>N</i> -[2-[(3,3-difluoro-1-pyrrolidinyl)methyl]-3-fluorophenyl]benzenesulfonamide
195		418	2.82	419	3,4-dichloro- <i>N</i> -[3-fluoro-2-(4-morpholinylmethyl)phenyl]benzenesulfonamide
196		384	2.65	385	4-chloro- <i>N</i> -[3-fluoro-2-(4-morpholinylmethyl)phenyl]benzenesulfonamide
197		454	3.75	455	3,4-dichloro- <i>N</i> -[5-chloro-2-[(3,3-difluoro-1-pyrrolidinyl)methyl]phenyl]benzenesulfonamide
198		434	2.97	435	3,4-dichloro- <i>N</i> -[5-chloro-2-(4-morpholinylmethyl)phenyl]benzenesulfonamide
199		384	2.51	385	4-chloro- <i>N</i> -[5-chloro-2-(1-pyrrolidinylmethyl)phenyl]benzenesulfonamide
200		416	2.88	417	4-chloro- <i>N</i> -[5-chloro-2-(4-thiomorpholinylmethyl)phenyl]benzenesulfonamide
201		437	3.42	438	4-chloro- <i>N</i> -[5-chloro-2-(1,5,6,7-tetrahydro-4H-[1,2,3]triazolo[4,5-b]pyridin-4-ylmethyl)phenyl]benzenesulfonamide
202		416	2.98	417	2-chloro- <i>N</i> -[5-chloro-2-(4-thiomorpholinylmethyl)phenyl]benzenesulfonamide
203		437	3.3	438	2-chloro- <i>N</i> -[5-chloro-2-(1,5,6,7-tetrahydro-4H-[1,2,3]triazolo[4,5-b]pyridin-4-ylmethyl)phenyl]benzenesulfonamide

204		437	3.4	438		3,4-dichloro- <i>N</i> -[2-(1,5,6,7-tetrahydro-4 <i>H</i> -[1,2,3]triazolo[4,5- <i>b</i>]pyridin-4-ylmethyl)phenyl]benzenesulfonamide
205		484	3.41	485		2,3-dichloro- <i>N</i> -[2-(4-thiomorpholinylmethyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
206		505	3.43	506		2,3-dichloro- <i>N</i> -[2-(1,5,6,7-tetrahydro-4 <i>H</i> -[1,2,3]triazolo[4,5- <i>b</i>]pyridin-4-ylmethyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
207		416	2.68	417		4-chloro- <i>N</i> -[2-(1,3-dihydro-2 <i>H</i> -isoindol-2-ylmethyl)-5-fluorophenyl]benzenesulfonamide
208		400	2.67	401		4-chloro- <i>N</i> -[5-fluoro-2-(4-thiomorpholinylmethyl)phenyl]benzenesulfonamide
209		421	3.28	422		4-chloro- <i>N</i> -[5-fluoro-2-(1,5,6,7-tetrahydro-4 <i>H</i> -[1,2,3]triazolo[4,5- <i>b</i>]pyridin-4-ylmethyl)phenyl]benzenesulfonamide
210		450	2.85	451		3,4-dichloro- <i>N</i> -[2-(1,3-dihydro-2 <i>H</i> -isoindol-2-ylmethyl)-5-fluorophenyl]benzenesulfonamide
211		434	2.87	435		3,4-dichloro- <i>N</i> -[5-fluoro-2-(4-thiomorpholinylmethyl)phenyl]benzenesulfonamide
212		455	3.42	456		3,4-dichloro- <i>N</i> -[5-fluoro-2-(1,5,6,7-tetrahydro-4 <i>H</i> -[1,2,3]triazolo[4,5- <i>b</i>]pyridin-4-ylmethyl)phenyl]benzenesulfonamide
213		434	2.57	435		3,4-dichloro- <i>N</i> -[5-fluoro-2-[(4-fluoro-1-piperidinyl)methyl]phenyl]benzenesulfonamide
214		452	3.16	453		3,4-dichloro- <i>N</i> -[2-[(4,4-difluoro-1-piperidinyl)methyl]-5-fluorophenyl]benzenesulfonamide

215		430	2.69	431	3,4-dichloro- <i>N</i> -{5-fluoro-2-[(4-methyl-1-piperidiny)methyl]phenyl}benzenesulfonamide
216		396	2.4	397	<i>N</i> -[5-fluoro-2-(4-thiomorpholinylmethyl)phenyl]-4-(methoxy)benzenesulfonamide
217		434	2.85	435	3,4-dichloro- <i>N</i> -[3-fluoro-2-(4-thiomorpholinylmethyl)phenyl]benzenesulfonamide
218		455	3.53	456	3,4-dichloro- <i>N</i> -[3-fluoro-2-(1,5,6,7-tetrahydro-4 <i>H</i> -[1,2,3]triazolo[4,5- <i>b</i>]pyridin-4-ylmethyl)phenyl]benzenesulfonamide
219		400	2.71	401	2-chloro- <i>N</i> -[3-fluoro-2-(4-thiomorpholinylmethyl)phenyl]benzenesulfonamide
220		404	3.56	405	4-chloro- <i>N</i> -{2-[(3,3-difluoro-1-pyrrolidinyl)methyl]-3-fluorophenyl}benzenesulfonamide
221		400	2.63	401	4-chloro- <i>N</i> -[3-fluoro-2-(4-thiomorpholinylmethyl)phenyl]benzenesulfonamide
222		418	2.56	419	3,4-dichloro- <i>N</i> -[5-chloro-2-(1-pyrrolidinylmethyl)phenyl]benzenesulfonamide
223		490	2.77	491	3,4-dichloro- <i>N</i> -[5-chloro-2-(1,4-dioxo-8-azaspiro[4.5]dec-8-ylmethyl)phenyl]benzenesulfonamide
224		450	3.08	451	3,4-dichloro- <i>N</i> -[5-chloro-2-(4-thiomorpholinylmethyl)phenyl]benzenesulfonamide
225		432	2.57	433	3,4-dichloro- <i>N</i> -[5-chloro-2-(1-piperidinylmethyl)phenyl]benzenesulfonamide
226		471	3.55	472	3,4-dichloro- <i>N</i> -[5-chloro-2-(1,5,6,7-tetrahydro-4 <i>H</i> -[1,2,3]triazolo[4,5- <i>b</i>]pyridin-4-ylmethyl)phenyl]benzenesulfonamide

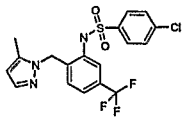
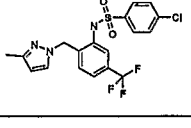
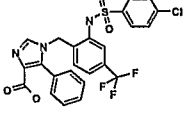
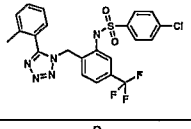
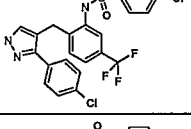
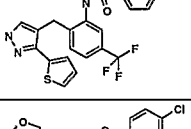
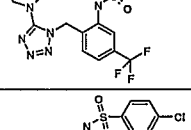
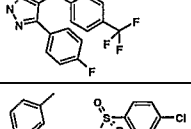
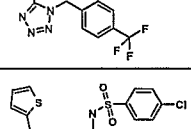
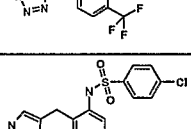
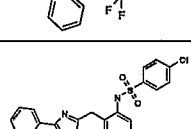
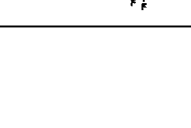
227		475	2.45	476		1-[(4-chloro-2-[(3,4-dichlorophenyl)sulfonyl]amino)phenyl]methyl]-3-piperidinecarboxamide
228		562	2.51	449		3,4-dichloro- <i>N</i> -{5-chloro-2-[(3-hydroxy-1-piperidinyl)methyl]phenyl}benzenesulfonamide trifluoroacetate (salt)
229		450	2.74	451		3,4-dichloro- <i>N</i> -{5-chloro-2-[(4-fluoro-1-piperidinyl)methyl]phenyl}benzenesulfonamide
230		468	3.39	469		3,4-dichloro- <i>N</i> -{5-chloro-2-[(4,4-difluoro-1-piperidinyl)methyl]phenyl}benzenesulfonamide
231		500	3.2	501		3,4-dichloro- <i>N</i> -(5-chloro-2-[(4-(trifluoromethyl)-1-piperidinyl)methyl]phenyl)benzenesulfonamide
232		446	2.66	447		3,4-dichloro- <i>N</i> -{5-chloro-2-[(2,5-dimethyl-1-pyrrolidinyl)methyl]phenyl}benzenesulfonamide

The following compound of formula (I) set out in Table 11 was prepared by a similar procedure to that described for Example 3 using the appropriate starting materials.

Table 11

5

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
233		541	4.59	543	541	1-[[2-[[4-(chlorophenyl)sulfonyl]amino]-4-(trifluoromethyl)phenyl]methyl]-5-(2-thienyl)-1 <i>H</i> -pyrazole-3-carboxylic acid
234		536	4.73	537	535	1-[[2-[[4-(chlorophenyl)sulfonyl]amino]-4-(trifluoromethyl)phenyl]methyl]-5-(2-pyridinyl)-1 <i>H</i> -pyrazole-3-carboxylic acid

235		429	3.55	430	428	4-chloro- <i>N</i> -[2-[(5-methyl-1 <i>H</i> -pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
236		429	3.55	430	428	4-chloro- <i>N</i> -[2-[(3-methyl-1 <i>H</i> -pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
237		435	3.58	536	534	1-[[2-[(4-chlorophenyl)sulfonyl]amino]-4-(trifluoromethyl)phenyl]methyl]-5-phenyl-1 <i>H</i> -imidazole-4-carboxylic acid
238		507	3.7	508	506	4-chloro- <i>N</i> -[2-[[5-(2-methylphenyl)-1 <i>H</i> -tetrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
239		525	3.86	526	524	4-chloro- <i>N</i> -[2-[[3-(4-chlorophenyl)-1 <i>H</i> -pyrazol-4-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
240		497	3.67	498	496	4-chloro- <i>N</i> -[2-[[3-(2-thienyl)-1 <i>H</i> -pyrazol-4-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
241		502	3.38	504	502	4-chloro- <i>N</i> -[2-[[5-(4-morpholinyl)-1 <i>H</i> -tetrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
242		509	3.72	510	508	4-chloro- <i>N</i> -[2-[[3-(4-fluorophenyl)-1 <i>H</i> -pyrazol-4-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
243		507	3.72	509	506	4-chloro- <i>N</i> -[2-[[5-(3-methylphenyl)-1 <i>H</i> -tetrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
244		499	4.61	500	498	4-chloro- <i>N</i> -[2-[[5-(2-thienyl)-1 <i>H</i> -tetrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
245		491	2.96	492	490	4-chloro- <i>N</i> -[2-[[3-(phenyl)-1 <i>H</i> -pyrazol-4-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
246		492	2.98	493	491	4-chloro- <i>N</i> -[2-[[4-(3-pyridinyl)-1 <i>H</i> -imidazol-2-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide

247		531	3.87	533	531	4-chloro- <i>N</i> -[2-[[3-(5-chloro-2-thienyl)-1 <i>H</i> -pyrazol-4-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
248		507	3.74	508	506	4-chloro- <i>N</i> -[2-[[5-(4-methylphenyl)-1 <i>H</i> -tetrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
249		507	3.74	508	506	4-chloro- <i>N</i> -[2-[[5-(phenylmethyl)-1 <i>H</i> -tetrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
250		527	3.77	529	527	4-chloro- <i>N</i> -[2-[[5-(4-chlorophenyl)-1 <i>H</i> -tetrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
251		505	3.7	507	505	4-chloro- <i>N</i> -[2-[(3-methyl-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
252		500	3.36	502	500	4-chloro- <i>N</i> -[2-[(5-chloro-1 <i>H</i> -1,2,3-benzotriazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
253		500	3.36	502	500	4-chloro- <i>N</i> -[2-[(6-chloro-1 <i>H</i> -1,2,3-benzotriazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
254		556	2.96	511	509	formic acid - 4-chloro- <i>N</i> -[2-[[6-(dimethylamino)-9 <i>H</i> -purin-9-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide (1:1)
255		527	3.77	529	527	4-chloro- <i>N</i> -[2-[[5-(3-chlorophenyl)-1 <i>H</i> -tetrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
256		534	3.9	536	534	4-chloro- <i>N</i> -[2-[(5,6-dichloro-1 <i>H</i> -benzimidazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
257		507	3.96	508	506	4-chloro- <i>N</i> -[2-[[5-(2-methylphenyl)-2 <i>H</i> -tetrazol-2-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide

258		526	4.09	527	525	4-chloro- <i>N</i> -[2-[[5-(4-chlorophenyl)-1 <i>H</i> -pyrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
259		497	3.98	498	496	4-chloro- <i>N</i> -[2-[[5-(2-thienyl)-1 <i>H</i> -pyrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
260		502	3.52	504	502	4-chloro- <i>N</i> -[2-[[5-(4-morpholinyl)-2 <i>H</i> -tetrazol-2-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
261		509	3.95	511	508	4-chloro- <i>N</i> -[2-[[5-(4-fluorophenyl)-1 <i>H</i> -pyrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
262		507	3.95	509	507	4-chloro- <i>N</i> -[2-[[5-(3-methylphenyl)-2 <i>H</i> -tetrazol-2-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
263		499	3.82	501	498	4-chloro- <i>N</i> -[2-[[5-(2-thienyl)-2 <i>H</i> -tetrazol-2-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
264		491	3.95	493	491	4-chloro- <i>N</i> -[2-[[5-(phenyl)-1 <i>H</i> -pyrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
265		497	3.9	498	496	4-chloro- <i>N</i> -[2-[[3-methyl-5-(trifluoromethyl)-1 <i>H</i> -pyrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
266		538	3.6	493	491	formic acid - 4-chloro- <i>N</i> -[2-[[5-(3-pyridinyl)-1 <i>H</i> -imidazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide (1:1)
267		531	4.09	532	530	4-chloro- <i>N</i> -[2-[[5-(5-chloro-2-thienyl)-1 <i>H</i> -pyrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
268		531	4.09	532	530	4-chloro- <i>N</i> -[2-[[3-(5-chloro-2-thienyl)-1 <i>H</i> -pyrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
269		507	3.92	508	506	4-chloro- <i>N</i> -[2-[[5-(4-methylphenyl)-2 <i>H</i> -tetrazol-2-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide

270		528	4.06	529	527	4-chloro- <i>N</i> -[2-([5-(4-chlorophenyl)-2 <i>H</i> -tetrazol-2-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
271		506	3.04	507	505	4-chloro- <i>N</i> -[2-((2-methyl-4-phenyl-1 <i>H</i> -imidazol-1-yl)methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
272		501	3.54	502	500	4-chloro- <i>N</i> -[2-([5-chloro-2 <i>H</i> -1,2,3-benzotriazol-2-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
273		557	3.18	511	509	formic acid - 4-chloro- <i>N</i> -[2-([6-(dimethylamino)-7 <i>H</i> -purin-7-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide (1:1)
274		528	4.07	529	527	4-chloro- <i>N</i> -[2-([5-(3-chlorophenyl)-2 <i>H</i> -tetrazol-2-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
275		526	4.1	527	525	4-chloro- <i>N</i> -[2-([3-(4-chlorophenyl)-1 <i>H</i> -pyrazol-1-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
276		497	3.99	499	496	4-chloro- <i>N</i> -[2-([3-(2-thienyl)-1 <i>H</i> -pyrazol-1-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
277		509	3.95	510	508	4-chloro- <i>N</i> -[2-([3-(4-fluorophenyl)-1 <i>H</i> -pyrazol-1-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
278		538	3.6	493	491	formic acid - 4-chloro- <i>N</i> -[2-([4-(3-pyridinyl)-1 <i>H</i> -imidazol-1-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide (1:1)
279		538	3.6	493	491	formic acid - 4-chloro- <i>N</i> -[2-([5-(3-pyridinyl)-1 <i>H</i> -imidazol-1-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide (1:1)
280		532	4.09	533	530	4-chloro- <i>N</i> -[2-([3-(5-chloro-2-thienyl)-1 <i>H</i> -pyrazol-1-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide

281		474	3.63	475	473	4-chloro- <i>N</i> -(5-chloro-2-([5-(phenylmethyl)-2 <i>H</i> -tetrazol-2-yl]methyl)phenyl)benzenesulfonamide
282		474	3.69	475	473	4-chloro- <i>N</i> -(5-chloro-2-([5-(phenylmethyl)-1 <i>H</i> -tetrazol-1-yl]methyl)phenyl)benzenesulfonamide
283		478	3.43	479	477	4-chloro- <i>N</i> -(5-chloro-2-([5-(2-fluorophenyl)-1 <i>H</i> -tetrazol-1-yl]methyl)phenyl)benzenesulfonamide
284		496	3.95	497	495	4-chloro- <i>N</i> -(5-chloro-2-([5-(2,6-difluorophenyl)-1 <i>H</i> -tetrazol-1-yl]methyl)phenyl)benzenesulfonamide
285		474	3.05	475	473	4-chloro- <i>N</i> -(5-chloro-2-([5-(4-methylphenyl)-1 <i>H</i> -tetrazol-1-yl]methyl)phenyl)benzenesulfonamide
286		529	3.6	530	528	4-chloro- <i>N</i> -(5-chloro-2-([5-(2,3-dichlorophenyl)-1 <i>H</i> -tetrazol-1-yl]methyl)phenyl)benzenesulfonamide
287		516	3.8	517	515	4-chloro- <i>N</i> -[5-chloro-2-([5-[4-(1,1-dimethylethyl)phenyl]-1 <i>H</i> -tetrazol-1-yl]methyl)phenyl]benzenesulfonamide
288		478	3.74	479	477	4-chloro- <i>N</i> -(5-chloro-2-([5-(2-fluorophenyl)-2 <i>H</i> -tetrazol-2-yl]methyl)phenyl)benzenesulfonamide
289		496	3.61	497	495	4-chloro- <i>N</i> -(5-chloro-2-([5-(2,6-difluorophenyl)-2 <i>H</i> -tetrazol-2-yl]methyl)phenyl)benzenesulfonamide
290		529	3.9	530	528	4-chloro- <i>N</i> -(5-chloro-2-([5-(2,3-dichlorophenyl)-2 <i>H</i> -tetrazol-2-yl]methyl)phenyl)benzenesulfonamide

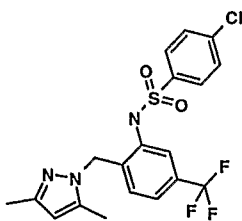
The following compound of formula (I) set out in Table 12 was prepared by a similar procedure to that described for Example 160 using the appropriate starting materials except that no N,N-dimethyl-4-pyridinamine was used and that the product was purified by mass directed autoprep instead of amino-propyl ion-exchange column.

5

Table 12

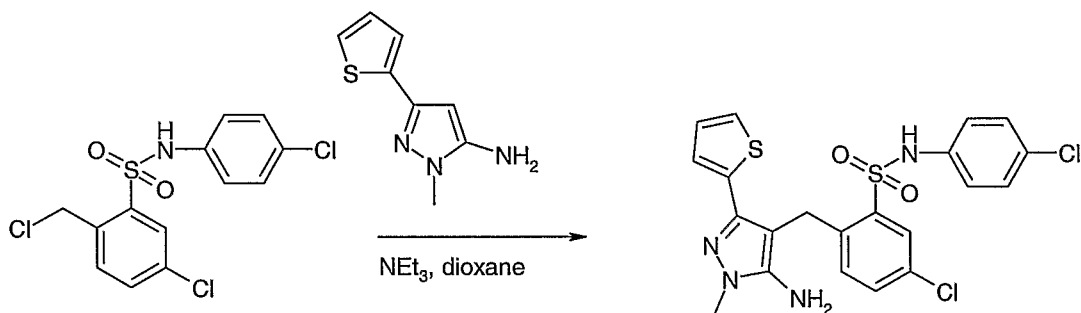
Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
291		494	3.15	495	493	3,5-dichloro- <i>N</i> -[2-[(3,5-dimethyl-1 <i>H</i> -pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]-2-hydroxybenzenesulfonamide
292		460	2.81	461	459	<i>N</i> -[2-[(3,5-dimethyl-1 <i>H</i> -pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]-5-isoquinolinesulfonamide
293		461	3.1	462	460	5-chloro- <i>N</i> -[2-[(3,5-dimethyl-1 <i>H</i> -pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]-1,3-dimethyl-1 <i>H</i> -pyrazole-4-sulfonamide
294		482	2.97	483	481	<i>N</i> -[2-[(3,5-dimethyl-1 <i>H</i> -pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]-5-(3-isoxazolyl)-2-thiophenesulfonamide
295		410	2.81	411	409	<i>N</i> -[2-[(3,5-dimethyl-1 <i>H</i> -pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]-2-pyridinesulfonamide
296		502	3.72	503	501	<i>N</i> -[2-[(3,5-dimethyl-1 <i>H</i> -pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]-6-(phenyloxy)-3-pyridinesulfonamide

Example 297: 4-chloro-*N*-[2-[(3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide



Example 297 was prepared by a similar procedure to that described for example 36 using the appropriate starting materials with the exception that no *N,N*-dimethyl-4-pyridinamine was used. HPLC *R*_t=3.65 minutes; *m/z* [M+H]⁺= 444.

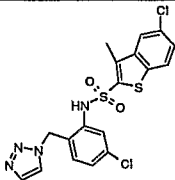
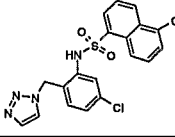
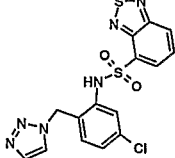
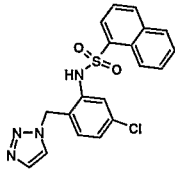
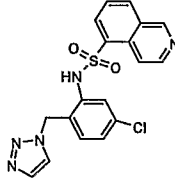
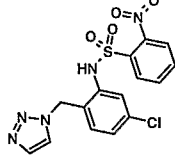
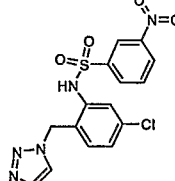
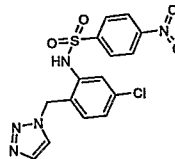
Example 298: *N*-(2-[[5-Amino-1-methyl-3-(2-thienyl)-1*H*-pyrazol-4-yl]methyl]-5-chlorophenyl)-4-chlorobenzenesulfonamide



To a solution of 5-chloro-2-(chloromethyl)-*N*-(4-chlorophenyl)benzenesulfonamide (0.05 g, 0.14 mmol) in a microwave tube was added a solution of 1-methyl-3-(2-thienyl)-1*H*-pyrazol-5-amine (0.051 g, 0.28 mmol) in dioxane (1.5 mL) and NEt₃ (0.029 g, 0.28 mmol). The reaction mixture was heated to 100 °C for 30 minutes in a microwave reactor. Dioxane was then removed and half of the crude mixture was dissolved in dimethylsulfoxide/methanol 1:1 (1 mL). The resulting solution was purified by mass directed autoprep to give *N*-(2-[[5-amino-1-methyl-3-(2-thienyl)-1*H*-pyrazol-4-yl]methyl]-5-chlorophenyl)-4-chlorobenzenesulfonamide (0.0092 g, 13%). HPLC *R*_t=3.41 minutes; *m/z* [M+H]⁺= 494.

The following compounds of formula (I) set out in Table 13 were prepared by a similar procedure to that described for Example 160 using the appropriate starting materials.

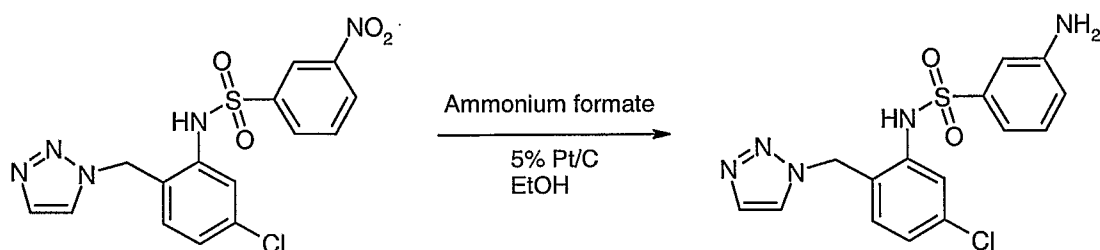
Table 13

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
299		452	3.6	453	451	5-chloro-N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3-methyl-1-benzothiophene-2-sulfonamide
300		432	3.5	433	431	5-chloro-N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-1-naphthalenesulfonamide
301		406	2.9	407	405	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-2,1,3-benzothiadiazole-4-sulfonamide
302		398	3.3	399	397	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-1-naphthalenesulfonamide
303		399	2.8	400	398	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-5-isoquinolinesulfonamide
304		393	3.0	394	392	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-2-nitrobenzenesulfonamide
305		393	3.1	394	392	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3-nitrobenzenesulfonamide
306		393	3.0	394	392	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-4-nitrobenzenesulfonamide

307		578	0.98	465		3,4-dichloro-N-[2-[(3-methyl-1H-1,2,4-triazol-5-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide trifluoroacetate
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Example 308 : 3-Amino-N-[5-chloro-2-(1H-1,2,3-triazol-1-yl)methyl]phenyl]benzenesulfonamide

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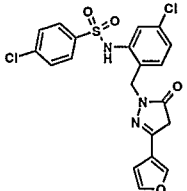
To 5% Pt/C catalyst (50 mg) (Degussa type F101 RAW) in a flask was added N-[5-chloro-2-(1H-1,2,3-triazol-1-yl)methyl]phenyl]-3-nitrobenzenesulfonamide (0.44 g) as a solution in ethanol (20 mL). The flask was then flushed with nitrogen and ammonium formate (0.705 g) was added with stirring. The reaction was heated at reflux under nitrogen overnight. On cooling to room temperature the catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The residue was partitioned between water (10 mL) and EtOAc (25 mL), and the aqueous phase was further extracted with EtOAc (25 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to afford the titled compound (0.38g). HPLC Rt=2.8 minutes m/z[M+H]=364, [M-H] 362

The following compounds of formula (I) set out in Table 14 were prepared by a similar procedure to that described for Example 57 using the appropriate starting materials.

Table 14

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
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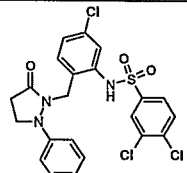
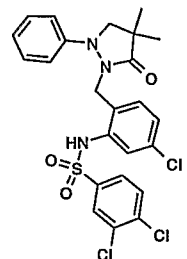
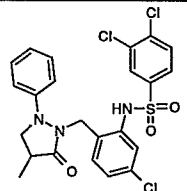
309		498	3.99	499	497	4-chloro-N-(5-chloro-2-([3-(4-cyanophenyl)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]methyl)phenyl)benzenesulfonamide
310		491	3.99	492	490	4-chloro-N-(5-chloro-2-([3-(2-fluorophenyl)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]methyl)phenyl)benzenesulfonamide
311		541	4.16	542	540	4-chloro-N-[5-chloro-2-([5-oxo-3-[3-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrazol-1-yl]methyl)phenyl]benzenesulfonamide
312		463	3.74	464	462	4-chloro-N-(5-chloro-2-([3-(2-furanyl)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]methyl)phenyl)benzenesulfonamide
313		473	3.97	474	472	4-chloro-N-{5-chloro-2-[(5-oxo-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methyl]phenyl}benzenesulfonamide
314		474	3.62	475	473	4-chloro-N-(5-chloro-2-([5-oxo-3-(3-pyridinyl)-4,5-dihydro-1H-pyrazol-1-yl]methyl)phenyl)benzenesulfonamide
315		503	3.95	504	502	4-chloro-N-[5-chloro-2-([3-[3-(methoxy)phenyl]-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]methyl)phenyl]benzenesulfonamide
316		501	3.72	502	500	4-chloro-N-(5-chloro-2-([3-methyl-5-oxo-4-(phenylmethyl)-4,5-dihydro-1H-pyrazol-1-yl]methyl)phenyl)benzenesulfonamide

317		463	3.7	464	462	4-chloro-N-(5-chloro-2-[(3-(3-furanyl)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)methyl]phenyl)benzenesulfonamide
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The following compounds of formula (I) set out in Table 15 were prepared by a similar procedure to that described for Example 74 using the appropriate starting materials.

Table 15

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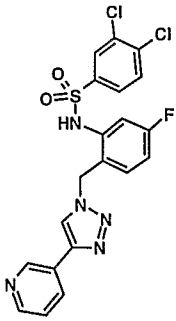
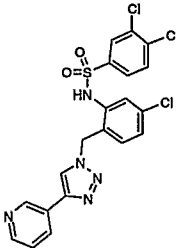
Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
318		509	3.85	510	508	3,4-dichloro-N-{5-chloro-2-[(5-oxo-2-phenyl-1-pyrazolidinyl)methyl]phenyl}benzenesulfonamide
319		537	4.04	538	536	3,4-dichloro-N-{5-chloro-2-[(4,4-dimethyl-5-oxo-2-phenyl-1-pyrazolidinyl)methyl]phenyl}benzenesulfonamide
320		523	3.97	524	522	3,4-dichloro-N-{5-chloro-2-[(4-methyl-5-oxo-2-phenyl-1-pyrazolidinyl)methyl]phenyl}benzenesulfonamide

The following compounds of formula (I) set out in Table 16 were prepared by a similar procedure to that described for Example 145 using the appropriate starting materials. As is appreciated by those skilled in the art, these analogous examples may involve routine variations in synthetic procedure.

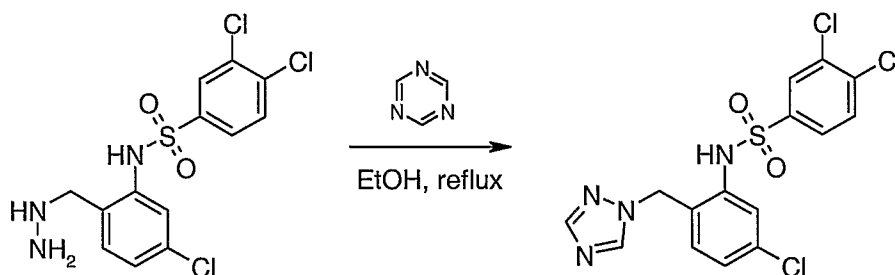
10

Table 16

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
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321		477	3.57	478	476	3,4-dichloro-N-(5-fluoro-2-([4-(3-pyridinyl)-1H-1,2,3-triazol-1-yl]methyl)phenyl)benzenesulfonamide
322		493	3.67	495	-	3,4-dichloro-N-(5-chloro-2-([4-(3-pyridinyl)-1H-1,2,3-triazol-1-yl]methyl)phenyl)benzenesulfonamide

Example 323: 3,4-Dichloro-N-[5-chloro-2-(1H-1,2,4-triazol-1-yl)methyl]phenyl]benzenesulfonamide trifluoroacetate



1,3,5-Triazine (0.096 g, 1.18 mmol) was added to a solution of 3,4-dichloro-N-[5-chloro-2-(hydrazinomethyl)phenyl]benzenesulfonamide (0.15 g, 0.39 mmol) in EtOH (10 mL) and the reaction was heated at reflux for 18 hours. After cooled down, the reaction was filtered and purified by preparative HPLC (Sunfire prep C18, 30 x 150 mm, 50 mL/min; CH₃CN/H₂O, 0.1% TFA; UV detection at 214 nm) to yield the titled product (0.054 g) as a white solid. HPLC Rt=1.04 minutes m/z[M+H]=419

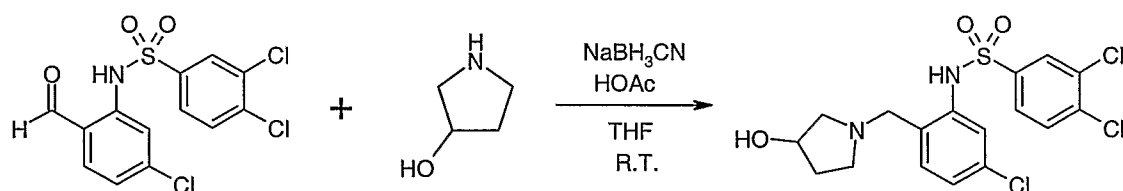
The following compounds of formula (I) set out in Table 17 were prepared by a similar procedure to that described for Example 78 using the appropriate starting materials. As is appreciated by those skilled in the art, these analogous examples may involve routine variations in synthetic procedure.

Table 17

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
324		396	2.56	397		4-chloro-N-{5-chloro-2-[(2-methyl-1H-imidazol-1-yl)methyl]phenyl}benzenesulfonamide
325		410	2.61	411		4-chloro-N-{5-chloro-2-[(2,4-dimethyl-1H-imidazol-1-yl)methyl]phenyl}benzenesulfonamide
326		423	2.86	424		N-{5-chloro-2-[(5-methyl-1H-tetrazol-1-yl)methyl]phenyl}-3,4-bis(methoxy)benzenesulfonamide

Example 327: 3,4-Dichloro-N-{5-chloro-2-[(3-hydroxy-1-pyrrolidinyl)methyl]phenyl}benzenesulfonamide

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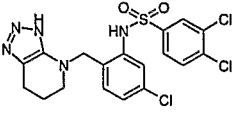
3-Pyrrolidinol (0.02 g, 0.23 mmol) was added to a solution of 3,4-dichloro-N-(5-chloro-2-formylphenyl)benzenesulfonamide (0.07 g, 0.19 mmol) in anhydrous THF (2 mL) at room temperature. After stirring for 10 minutes, sodium cyanoborohydride (0.24 g, 0.38 mmol) and acetic acid (0.1 mL) were added. The resulting reaction mixture was stirred at room temperature for additional 12 hours until the starting material was consumed completely.

Saturated K₂CO₃ aqueous solution (4 mL) was added to quench the reaction. After stirring for 5 min, the solution was extracted with ethyl acetate (2 X 3mL). The combined organic extracts were dried over Na₂SO₄ and concentrated. The residue was purified by Gilson HPLC (Phenomenex 75x30 mm column, 40 mL/min, A: 0.1% TFA in acetonitrile B: 0.1% TFA in water, A: 10 to 100% over 15 min, UV detection at 215 nm) to give the desired product. HPLC Rt = 2.24 minutes m/z [MH]⁺ = 437. ¹H NMR (MeOD) δ 7.79 (m, 2H), 7.68 (d, 1H), 7.59(dd, 1H), 7.48 (dd, 1H), 6.61 (d, 1H), 4.70(m, 2H), 4.59 (m, 1H), 3.64(m, 1H), 3.50(m, 2H), 2.33(m, 1H), 2.10(m, 2H).

- 10 The following compounds in Table 18 were prepared by a similar procedure to that described above for Example 327 using the appropriate starting materials. In some cases the product was isolated *via* additional silica chromatography or mass-directed autoperparative HPLC.

15 Table 18

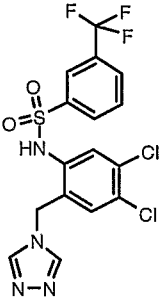
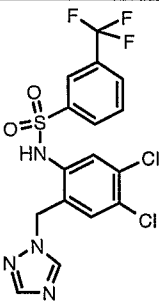
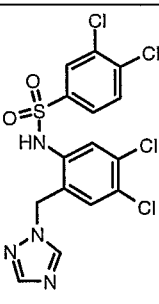
Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
328		450	2.41	451		3,4-dichloro- <i>N</i> -(5-chloro-2-[(2 <i>S</i>)-2-(hydroxymethyl)-1-pyrrolidinyl]methyl)phenyl)benzenesulfonamide
329		464	2.50	465		1-[(4-chloro-2-[(3,4-dichlorophenyl)sulfonyl]amino)phenyl)methyl]proline
330		580	1.90	581		3,4-dichloro- <i>N</i> -{5-chloro-2-[(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-8-yl)methyl]phenyl}benzenesulfonamide
331		456	2.41	456		3,4-dichloro- <i>N</i> -{5-chloro-2-[(3,3-difluoro-1-pyrrolidinyl)methyl]phenyl}benzenesulfonamide
332		531	2.51	532		<i>N</i> -[(3 <i>S</i>)-1-[(4-chloro-2-[(3,4-dichlorophenyl)sulfonyl]amino)phenyl)methyl]-3-pyrrolidinyl]-2,2,2-trifluoroacetamide
333		477	1.64	478		<i>N</i> -{1-[(4-chloro-2-[(3,4-dichlorophenyl)sulfonyl]amino)phenyl)methyl]-3-pyrrolidinyl}-2,2,2-trifluoroacetamide

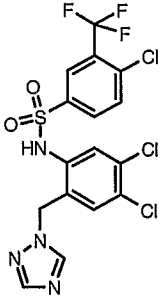
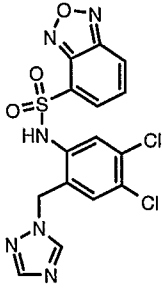
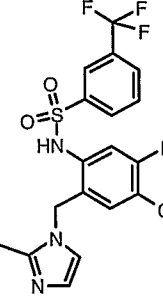
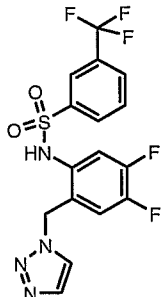
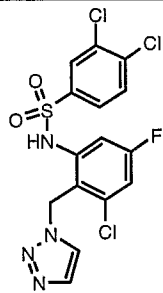
						pyrrolidinyl}acetamide
334		473	3.29	474		3,4-dichloro-N-[5-chloro-2-(1,5,6,7-tetrahydro-4H-[1,2,3]triazolo[4,5-b]pyridin-4-ylmethyl)phenyl]benzenesulfonamide

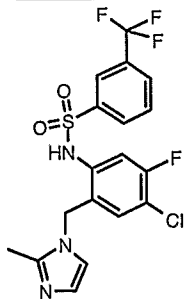
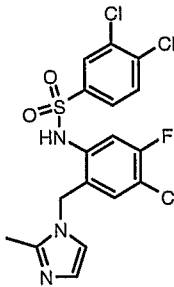
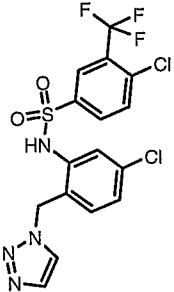
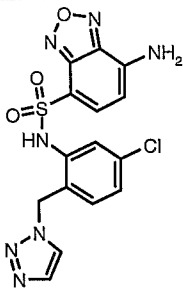
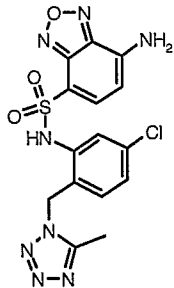
The following compounds in Table 19 were prepared by a similar procedure to that described for Example 78 using the appropriate starting materials.

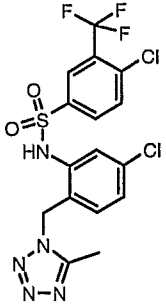
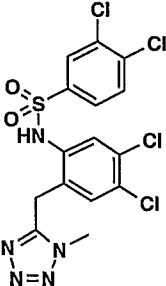
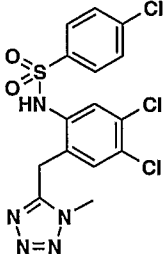
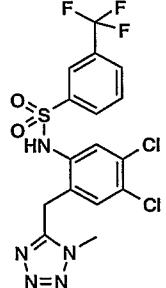
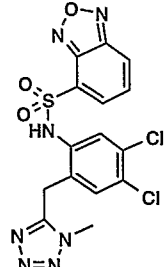
Table 19

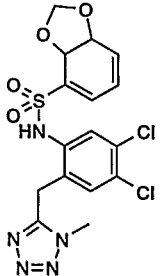
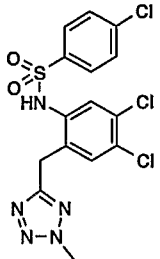
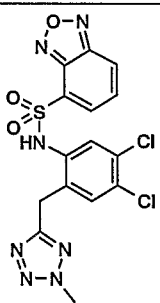
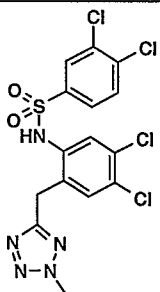
5

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
335		450	3.14	450		N-[4,5-dichloro-2-(4H-1,2,4-triazol-4-ylmethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide
336		450	3.37	451		N-[4,5-dichloro-2-(1H-1,2,4-triazol-1-ylmethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide
337		450	3.59	451		3,4-dichloro-N-[4,5-dichloro-2-(1H-1,2,4-triazol-1-ylmethyl)phenyl]benzenesulfonamide

338		484	3.60	485		4-chloro- <i>N</i> -[4,5-dichloro-2-(1 <i>H</i> -1,2,4-triazol-1-ylmethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide
339		424	3.17	425		<i>N</i> -[4,5-dichloro-2-(1 <i>H</i> -1,2,4-triazol-1-ylmethyl)phenyl]-2,1,3-benzoxadiazole-4-sulfonamide
340		447				<i>N</i> -{4-chloro-5-fluoro-2-[(2-methyl-1 <i>H</i> -imidazol-1-yl)methyl]phenyl}-3-(trifluoromethyl)benzenesulfonamide
341		418	3.22	419		<i>N</i> -[4,5-difluoro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide
342		434	3.19	435		<i>N</i> -[4,5-difluoro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide

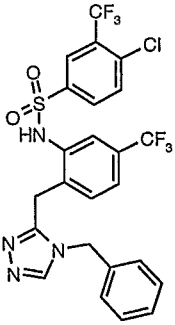
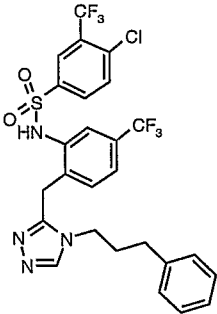
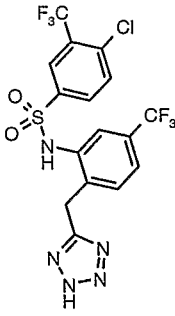
343		447	2.66	448		<i>N</i> -{4-chloro-5-fluoro-2-[(2-methyl-1 <i>H</i> -imidazol-1-yl)methyl]phenyl}-3-(trifluoromethyl)benzenesulfonamide
344		447	2.77	448		3,4-dichloro- <i>N</i> -{4-chloro-5-fluoro-2-[(2-methyl-1 <i>H</i> -imidazol-1-yl)methyl]phenyl}benzenesulfonamide
345		450	3.40	451		4-chloro- <i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide
346		405	2.85	406		7-amino- <i>N</i> -[5-chloro-2-(1 <i>H</i> -1,2,3-triazol-1-ylmethyl)phenyl]-2,1,3-benzoxadiazole-4-sulfonamide
347		420	2.79	421		7-amino- <i>N</i> -[5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl]-2,1,3-benzoxadiazole-4-sulfonamide

348		465	3.40	466		4-chloro- <i>N</i> -{5-chloro-2-[(5-methyl-1 <i>H</i> -tetrazol-1-yl)methyl]phenyl}-3-(trifluoromethyl)benzenesulfonamide
349		465	3.57	466		3,4-dichloro- <i>N</i> -{4,5-dichloro-2-[(1-methyl-1 <i>H</i> -tetrazol-5-yl)methyl]phenyl}benzenesulfonamide
350		431	3.39	433		4-chloro- <i>N</i> -{4,5-dichloro-2-[(1-methyl-1 <i>H</i> -tetrazol-5-yl)methyl]phenyl}benzenesulfonamide
351		465	3.43	466		<i>N</i> -{4,5-dichloro-2-[(1-methyl-1 <i>H</i> -tetrazol-5-yl)methyl]phenyl}-3-(trifluoromethyl)benzenesulfonamide
352		439	3.19	440		<i>N</i> -{4,5-dichloro-2-[(1-methyl-1 <i>H</i> -tetrazol-5-yl)methyl]phenyl}-2,1,3-benzoxadiazole-4-sulfonamide

353		443	3.25	444		<i>N</i> -{4,5-dichloro-2-[(1-methyl-1 <i>H</i> -tetrazol-5-yl)methyl]phenyl}-3a,7a-dihydro-1,3-benzodioxole-4-sulfonamide
354		431	3.38	432		4-chloro- <i>N</i> -{4,5-dichloro-2-[(2-methyl-2 <i>H</i> -tetrazol-5-yl)methyl]phenyl}benzenesulfonamide
355		439	3.30	440		<i>N</i> -{4,5-dichloro-2-[(2-methyl-2 <i>H</i> -tetrazol-5-yl)methyl]phenyl}-2,1,3-benzoxadiazole-4-sulfonamide
356		465	3.66	468		3,4-dichloro- <i>N</i> -{4,5-dichloro-2-[(2-methyl-2 <i>H</i> -tetrazol-5-yl)methyl]phenyl}benzenesulfonamide

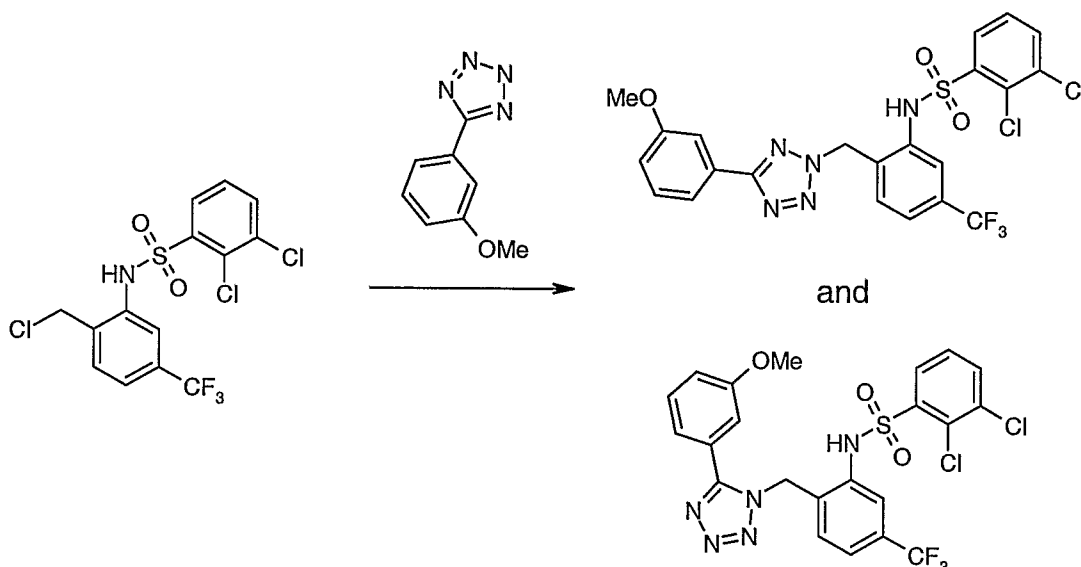
The following compounds in Table 20 were prepared by a similar procedure to that described for Example 78 using the appropriate starting materials.

Table 20

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
357		574	2.9	575		4-chloro- <i>N</i> -[2-{[4-(phenylmethyl)-4 <i>H</i> -1,2,4-triazol-3-yl]methyl}-5-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide
358		602	3.0	603		4-chloro- <i>N</i> -[2-{[4-(3-phenylpropyl)-4 <i>H</i> -1,2,4-triazol-3-yl]methyl}-5-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide
359		485	2.9	486		4-chloro- <i>N</i> -[2-(1 <i>H</i> -tetrazol-5-ylmethyl)-5-(trifluoromethyl)phenyl]-3-(trifluoromethyl)benzenesulfonamide

Example 360: 2,3-Dichloro-*N*-[2-({5-[3-(methyloxy)phenyl]-2*H*-tetrazol-2-yl)methyl}-5-(trifluoromethyl)phenyl]benzenesulfonamide and 2,3-dichloro-*N*-[2-({5-[3-(methyloxy)phenyl]-1*H*-tetrazol-1-yl)methyl}-5-(trifluoromethyl)phenyl]benzenesulfonamide

5



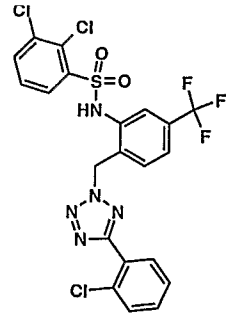
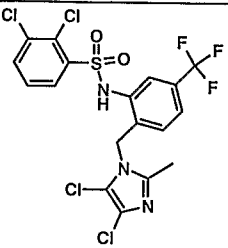
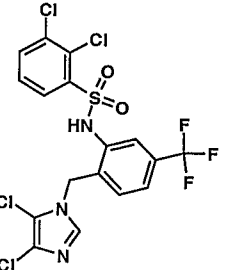
Acetonitrile (2.75 mL) was added to 5-[3-(methyloxy)phenyl]-1*H*-tetrazole (0.0145 g, 0.0825 mmol) and polymer supported BEMP (0.150 g, 0.33 mmol). A solution of trifluoromethyl 2,3-dichloro-*N*-[2-(chloromethyl)-5-()phenyl]benzenesulfonamide (0.0314 g, 0.075 mmol) in *N*-methyl pyrrolidinone (0.5 mL) was also added and the reaction was stirred at 120 °C in a Biotage microwave. After 30 minutes the reaction mixture was filtered and the resin was washed with methanol (2 x 20 mL). The resin was then washed with a mixture of ethanol:acetic acid (90:10) (2 x 20 mL) and the acidic fractions were evaporated *in vacuo*. The residue was purified by mass directed autoprep to give the desired product isomer 2,3-dichloro-*N*-[2-({5-[3-(methyloxy)phenyl]-2*H*-tetrazol-2-yl)methyl}-5-(trifluoromethyl)phenyl]benzenesulfonamide (5.5 mg) as determined by NMR (NOE). HPLC Rt=3.83 minutes; $m/z[M+H]^+=558/560$ (2Cl). ¹H NMR (CDCl₃) δ 8.1 (dd, 1H), 7.73 (m, 4H), 7.5 (m, 5H), 7.07 (dd, 1H), 5.92 (s, 2H), 3.92 (s, 3H) and product isomer 2,3-dichloro-*N*-[2-({5-[3-(methyloxy)phenyl]-1*H*-tetrazol-1-yl)methyl}-5-(trifluoromethyl)phenyl]benzenesulfonamide (5.5 mg) as determined by NMR (NOE). HPLC RT =3.6 minutes; $m/z[M+H]^+=558/560$ (2Cl). ¹H NMR (CDCl₃) δ 7.9 (dd, 1H), 7.76 (dd, 2H), 7.42 (m, 5H), 7.17 (m, 3H), 5.83 (s, 2H), 3.88 (s, 3H)

The following compounds in Table 24 were prepared by a similar procedure to that described for Example 360 using the appropriate starting materials.

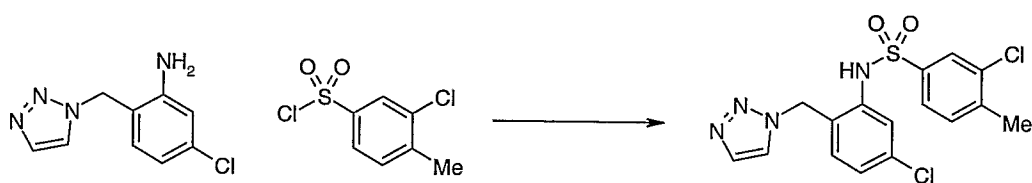
Table 21

Ex	Structure	Parent Mwt	Rt min	+ve	-ve	Name
361		545	3.58	546/ 548	544/ 546	2,3-dichloro-N-[2-([5-(2-fluorophenyl)-1H-tetrazol-1-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
362		557	3.82	558/ 560	556/ 558	2,3-dichloro-N-[2-([5-[4-(methoxy)phenyl]-1H-tetrazol-1-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
363		563	3.56	564/ 566	562/ 564	2,3-dichloro-N-[2-([5-(2,6-difluorophenyl)-1H-tetrazol-1-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
364		567	3.83	568/ 570	566/ 568	2,3-dichloro-N-[2-([5-(5-chloro-2-thienyl)-1H-tetrazol-1-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide
365		545	3.63	546/ 548	544/ 546	2,3-dichloro-N-[2-([5-(3-fluorophenyl)-1H-tetrazol-1-yl]methyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide

366		561	3.65	562/ 564	560/ 562	2,3-dichloro-N-[2-[[5-(2-chlorophenyl)-1H-tetrazol-1-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
363		545	3.78	546/ 548	544/ 546	2,3-dichloro-N-[2-[[5-(2-fluorophenyl)-2H-tetrazol-2-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
367		563	3.74	564/ 566	562/ 564	2,3-dichloro-N-[2-[[5-(2,6-difluorophenyl)-2H-tetrazol-2-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
368		567	4.01	567/ 569/ 571	565/ 567/ 569	2,3-dichloro-N-[2-[[5-(5-chloro-2-thienyl)-2H-tetrazol-2-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
369		545	3.88	546/ 548	544/ 546	2,3-dichloro-N-[2-[[5-(3-fluorophenyl)-2H-tetrazol-2-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide

370		561	3.89	562/ 564/ 566	560/ 562/ 564	2,3-dichloro-N-[2-[[5-(2-chlorophenyl)-2H-tetrazol-2-yl]methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
371		531	3.62	532/ 534/ 536	530/ 532/ 534	2,3-dichloro-N-[2-[(4,5-dichloro-2-methyl-1H-imidazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide
372		517	3.63	518/ 520/ 522	516/ 518/ 520	2,3-dichloro-N-[2-[(4,5-dichloro-2-methyl-1H-imidazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]benzenesulfonamide

Example 373: 3-chloro-N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-4-methylbenzenesulfonamide



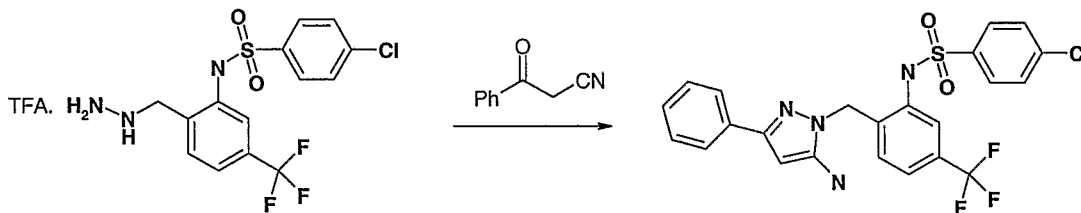
5-Chloro-2-(1H-1,2,3-triazol-1-ylmethyl)aniline (62.4 mg, 0.3 mmol, 1 equiv) was dissolved in chloroform (1.5 mL). Pyridine (0.049 mL, 0.6 mmol, 2 equiv) was added. A solution of 3-chloro-4-methylbenzenesulfonyl chloride (67.5 mg, 0.3 mmol, 1 equiv) in chloroform (1.5 mL) was added to the reaction mixture. The reaction was stirred at room temperature for 16 hours. The mixture was concentrated and redissolved in DMSO. Purification by reverse phase HPLC (35-70% CH₃CN/H₂O + 0.1% TFA, 50 mL/min over 10 min, 30 x 50 Sunfire Prep C18) afforded the title compound as a white powder (94.4 mg, 79% yield). LC-MS m/z [MH]⁺ = 397.

The following compounds of formula (I) set out in Table 22 were prepared by a similar procedure to that described for Example 373 using the appropriate starting materials.

5 Table 22

Ex	Structure	Parent Mwt	Rt min	+ve	Name
374		385	0.96	385/387	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3,4-difluorobenzenesulfonamide
375		467	1.10	467/469	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3-chloro-4-trifluoromethoxybenzenesulfonamide
376		397	0.93	397/399	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3-fluoro-4-(methoxy)benzenesulfonamide
377		397	0.94	397/399	N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-4-fluoro-3-(methoxy)benzenesulfonamide
378		401	1.00	401/403	4-chloro-N-[5-chloro-2-(1H-1,2,3-triazol-1-ylmethyl)phenyl]-3-fluorobenzenesulfonamide

Example 379: *N*-[2-[(5-amino-3-phenyl-1*H*-pyrazol-1-yl)methyl]-5-(trifluoromethyl)phenyl]-4-chlorobenzenesulfonamide

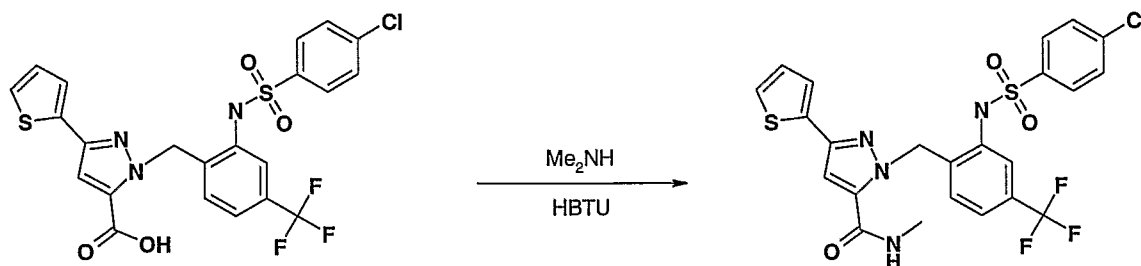


10

4-chloro-*N*-[2-(hydrazinomethyl)-5-(trifluoromethyl)phenyl]benzenesulfonamide (50 mg, 0.10 mmol) and 3-oxo-3-phenylpropanenitrile (16 mg, 0.11 mmol) were refluxed in toluene overnight. The solvent was then removed and the desired compound isolated by

mass directed autoprep. LC-MS Rt = 3.82 min; m/z[+ve]=507. ¹H NMR (CD₃OD) δ 7.75-7.70 (m, 4H), 7.50 (d, 2H), 7.45-7.25 (m, 6H), 5.85 (s, 1H), 5.10 (s, 2H).

Example 380: 1-[[2-[[[(4-chlorophenyl)sulfonyl]amino]-4-(trifluoromethyl)phenyl]methyl]-3-(2-thienyl)-1H-pyrazole-5-carboxamide



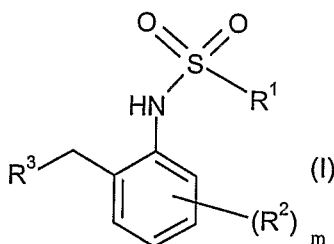
1-[[2-[[[(4-chlorophenyl)sulfonyl]amino]-4-(trifluoromethyl)phenyl]methyl]-3-(2-thienyl)-1H-pyrazole-5-carboxylic acid (45 mg, 0.098 mmol), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (44 mg, 0.116 mmol) and dimethylamine (0.1 mL, 2M in THF, 0.2 mmol) was stirred in acetonitrile (5 mL) overnight at room temperature. Additional HBTU (20 mg) and amine (0.15 mL) was added and stirring was continued for 10 hours at 60 °C. The solvent was removed in vacuo and the desired product isolated by mass directed autoprep. LC-MS Rt = 3.79 min; m/z[+ve]=555. ¹H NMR (CD₃OD) δ 7.65 (m, 2H), 7.47 (m, 2H), 7.41 (m, 4H), 7.29 (d, 1H), 7.07 (m, 1H), 6.99 (s, 1H), 5.63 (s, 2H), 3.61 (s, 3H).

Example 381: 3,4-dichloro-*N*-[5-fluoro-2-(1-pyrrolidinylmethyl)phenyl]benzenesulfonamide

The title compound was prepared according to the method described for Example 184 using appropriate starting materials. LC-MS Rt = min; m/z[+ve]=403.

Claims

1. A compound as represented in formula (I):



or a salt thereof, or a solvate thereof, or a combination thereof; wherein

R^1 represents an aryl, a thienyl, a benzothienyl, an imidazolyl, a pyridyl, an isoquinolinyl, a piperonyl, a benzoxathiadiazolyl, or a benzoxadiazolyl group optionally substituted with one to three R^4 groups, wherein each R^4 group is independently selected from the group consisting of C_{1-6} -alkyl, C_{1-6} -haloalkyl, C_{1-6} -alkoxy, C_{1-6} -haloalkoxy, halo, $-NH_2$, $-OH$, $-CN$, $-NO_2$, CF_3 , phenyl, phenoxy, phenyl- $C(O)-$, isoxazolyl, and $-C(O)NR^7R^8$, wherein R^7 and R^8 each independently represent hydrogen or C_{1-4} alkyl, or R^7 and R^8 together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated heterocyclic group optionally containing an additional heteroatom selected from nitrogen, oxygen and sulphur;

m is 1, 2, or 3;

each R^2 is independently selected from the group consisting of halo, $-CN$, $-OCF_3$, and $-CF_3$;

R^3 is a heteroaryl or a heterocycloalkyl group optionally substituted by up to three substituents independently selected from the group consisting of halo, hydroxy, hydroxy- C_{1-6} -alkyl-, C_{1-4} alkoxy- C_{1-6} alkyl-, C_{1-4} alkoxy-, C_{1-4} thioalkoxy, amino, $R^{10}R^{11}N-C_{1-4}$ alkyl-, heterocycloalkyl, heteroaryl, halogenated heteroaryl, phenyl, benzyl, halophenyl, C_{1-4} alkylphenyl, methoxyphenyl, trifluoromethylphenyl, cyanophenyl, C_{1-6} -alkyl, C_{3-6} -cycloalkyl, $-CN$, C_{1-4} alkylthio-, $-CF_3$, $-CO_2H$, $-CONR^7R^8$, $-NC(O)R^{12}N$ and $-CO-C_{1-4}$ alkyl, wherein R^{10} and R^{11} each independently represent hydrogen or C_{1-6} alkyl and R^{12} is C_{1-6} alkyl or C_{1-6} haloalkyl;

4. The compound of Claim 1 wherein R¹ is substituted with up to three substituents selected from the group consisting of -F, -Cl, -Br, -CF₃, -CH₃, -OCH₃, -OCF₃, -NO₂, phenyl, phenoxy, -NH₂, -OH, phenyl-C(O)-, isoxazolyl, and -CN;

5 R² is selected from the group consisting of F, Cl, -CF₃, -OCF₃ and -CN;

m is 1 or 2; and

R³ is a) triazolyl or benzotriazolyl optionally substituted with up to two substituents selected from the group consisting of methyl, propyl, benzyl, pyridyl, CH₃S-, -CN, dimethylaminomethyl, methoxymethyl, C(O)NHCH₃, and phenpropyl; b) tetrazolyl optionally substituted with a substituent selected from the group consisting of methyl, benzyl, tolyl, fluorophenyl, difluorophenyl, chlorophenyl, dichlorophenyl, thienyl, chlorothienyl, methoxyphenyl, cyclopropyl, and N-morpholino; c) imidazolyl or benzimidazolyl optionally substituted with up to 3 substituents selected from the group consisting of methyl, ethyl, isopropyl, phenyl, -COOH, -Cl, and pyridinyl; d) pyrazolyl optionally substituted with 1 to 3 substituents selected from the group consisting of methyl, propyl, butyl, hydroxymethyl, phenyl, -COOH, amino, thienyl, pyridinyl, -C(O)NHCH₃, chlorophenyl, fluorophenyl, chlorothienyl, trifluoromethyl, and fluoro; e) oxypyrazolidinyl or oxypyrazolyl optionally substituted with a substituent selected from the group consisting of methyl, cyanophenyl, fluorophenyl, trifluoromethylphenyl, furyl, phenyl, pyridinyl, methoxyphenyl, benzyl, isopropyl, trifluoromethyl, *n*-propyl, *t*-butyl, *n*-butyl, *n*-hexyl, *n*-pentyl, fluoro; f) dimethylaminopurinyl; g) indazolyl; h) methyl dihydropyridazinonyl; i) oxooxazolidinyl; j) oxobenzoxazolyl; k) oxopiperidinyl; l) methyloxadiazolyl; m) oxobenzotriazolyl; n) pyrazinyl; o) methyl dioxoimidazolidinyl; p) methyloxoimidazolidinyl; q) methyloxypyridinyl; r) pyrrolidinyl optionally substituted with up to 3 substituents selected from the group consisting of hydroxymethyl, methyl, -COOH, hydroxy, fluoro, -NHC(O)CF₃, and -NHC(O)CH₃; s) piperidinyl optionally substituted with up to 3 substituents selected from the group consisting of fluoro, methyl, trifluoromethyl, hydroxy, -C(O)NH₂; t) morpholino; u) thiomorpholino; v) tetrahydrotriazolylpyridinyl; w) isoindolyl; x) dioxazaspirodecyl; or y) oxophenyltriazaspirodecyl; or a pharmaceutically acceptable salt thereof, or a solvate thereof, or a combination thereof.

3. The compound of Claim 1 wherein R¹ is substituted with one or two substituents selected from the group consisting of -F, -Cl, -CF₃, -CH₃, -OCH₃, -OCF₃, and -CN;

R² is selected from the group consisting of F, Cl, -CF₃, -OCF₃, -CN; m is 1 or 2;

5 and the substituent or one of the substituents is *para* to the -CH₂R³ group; and

R³ is a) triazolyl optionally substituted with up to two substituents selected from the group consisting of methyl and propyl b) tetrazolyl optionally substituted with methyl. c) imidazolyl or benzimidazolyl optionally substituted with up to 3 substituents selected from
10 the group consisting of methyl, ethyl, isopropyl, and -COOH; d) pyrazolyl optionally substituted with up to 3 substituents selected from the group consisting of methyl, -COOH, and trifluoromethyl; e) oxopyrazolidinyl or oxodihydropyrazolidinyl optionally substituted with a substituent selected from the group consisting of methyl, trifluoromethyl, *n*-propyl, *t*-butyl, *n*-butyl, *n*-hexyl, or *n*-pentyl; f) pyrrolidinyl optionally
15 substituted with up to 3 substituents selected from the group consisting of hydroxymethyl, methyl, -COOH, hydroxy, and fluoro; g) piperidinyl optionally substituted with up to 3 substituents selected from the group consisting of fluoro and methyl; h) morpholino; i) thiomorpholino; j) tetrahydrotriazolylpyridinyl; or a pharmaceutically acceptable salt thereof, or a solvate thereof, or a combination thereof.

20 4. A method for treating or preventing a disease or condition mediated by CCR2 comprising administering to a patient in need thereof a pharmaceutically effective amount of the compound of Claim 1, or a pharmaceutically acceptable salt thereof, or a solvate thereof, of a combination thereof.

25 5. A pharmaceutical composition comprising a) a compound of formula (I) or a pharmaceutically acceptable salt thereof, or a solvate thereof, or a combination thereof and b) a pharmaceutically acceptable carrier, diluent, or excipient or combination thereof.