The compounds are inhibitors of microsomal prostaglandin E synthase-1.

The invention provides compounds of formula wherein R1, R2, R3, A and m are as defined in the specification and optical isomers, racemates and tautomers thereof, and pharmaceutically acceptable salts thereof; together with processes for their preparation, pharmaceutical compositions containing them and their use in therapy. The compounds are inhibitors of microsomal prostaglandin E synthase-1.
BIS-(SULFONYLAMINO) DERIVATIVES IN THERAPY 065

Field of the Invention
The present invention relates to bis-(sulfonylamino) derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

Background of the Invention
Modulation of prostaglandin metabolism is at the center of current anti-inflammatory therapies. NSAIDs and COX-2 inhibitors block the activity of cyclooxygenases and their ability to convert arachidonic acid into prostaglandin H2 (PGH2). PGH2 can be subsequently metabolized by terminal prostaglandin synthases to the corresponding biologically active PGs, namely, PGI2, thromboxane (Tx) A2, PGD2, PGF2α, and PGE2. A combination of pharmacological, genetic and neutralizing antibody approaches demonstrates the importance of PGE2 in inflammation. The conversion of PGH2 to PGE2 by prostaglandin E synthases (PGES) may therefore represent a pivotal step in the propagation of inflammatory stimuli.

Microsomal prostaglandin E synthase-1 (mPGES-1) is an inducible PGES after exposure to pro-inflammatory stimuli. mPGES-1 is induced in the periphery and in the CNS by inflammation and represents therefore a target for acute and chronic inflammatory disorders.

PGE2 is a major prostanoid driving inflammatory processes. The Prostanoid is produced from arachidonic acid liberated by Phospholipases (PLAs). Arachidonic acid is transformed by the action of Prostaglandin H Synthase (PGH Synthase, cyclooxygenase) into PGH2 which is a substrate for mPGES-1, that is the terminal enzyme transforming PGH2 to the pro-inflammatory PGE2.

NSAIDs reduce PGE2 by inhibiting cyclooxygenase, but at the same time reducing other prostanoids, giving side effects such as ulcerations in the GI tract. mPGES-1 inhibition gives a similar effect on PGE2 production without affecting the formation of other prostanoids, and hence a more favourable profile.
By blocking the formation of PGE2 in animal models of inflammatory pain a reduced inflammation, pain and fever response has been demonstrated, Kojima et. al, *The Journal of Immunology* 2008, 180, 8361-6, Xu et. al., *The Journal of Pharmacology and Experimental Therapeutics* 2008, 326, 754-63.

In abdominal aortic aneurism, inflammation leads to connective tissue degradation and smooth muscle apoptosis ultimately leading to aortic dilation and rupture. In animals lacking mPGES-1 a slower disease progression and disease severity has been demonstrated Wang et.al. *Circulation*, 2008, 117, 1302-1309.

Several lines of evidence indicate that PGE2 is involved in malignant growth. PGE2 facilitates tumour progression by stimulation of cellular proliferation and angiogenesis and by modulation of immunosupression. In support of a role for PGE2 in carcinogenesis genetic deletion of mPGES-1 in mice supress the intestinal tumourogenesis Nakanishi et.al. *Cancer Research* 2008, 68(9), 3251-9. In man, mPGES-1 is also upregulated in cancers such as colorectal cancer Schroder *Journal of Lipid Research* 2006, 47, 1071-80.

Myositis is chronic muscle disorder characterized by muscle weakness and fatigue. Proinflammatory cytokines and prostanoids have been implicated in the development of myositis. In skeletal muscle tissue from patients suffering from myositis an increase in cyclooxygenases and mPGES-1 has been demonstrated, implicating mPGES-1 as a target for treating this condition. Korotkova *Annals of the Rheumatic Diseases* 2008, 67, 1596-1602.

In atherosclerosis inflammation of the vasculature leads to atheroma formation that eventually may progress into infarction. In patients with carotid atherosclerosis an increase in mPGES-1 in plaue regions have been found Gomez-Hernandez *Atherosclerosis* 2006,187, 139-49. In an animal model of atherosclerosis, mice lacking the mPGES-1 receptor was found to show a retarded atherogenesis and a concomitant reduction in macrophage-derived foam cells together with an increase in vascular smooth muscle cells. Wang *Proceedings of National Academy of Sciences* 2006, 103(39), 14507-12.
The present invention is directed to novel compounds that are selective inhibitors of the microsomal prostaglandin E synthase-1 enzyme and would therefore be useful for the treatment of pain and inflammation in a variety of diseases or conditions.

Disclosure of the Invention

In one aspect we disclose a compound of formula (I) or a pharmaceutically acceptable salt thereof

\[
\begin{align*}
&\text{A is selected from mono- and bicyclic aryl, mono- and bicyclic heteroaryl, cycloalkenyl} \\
&\text{and mono- and bicyclic heterocyclyl;} \\
&R^1 \text{ is independently selected from halogen, nitro, SF}_2, \text{CHO, C}_{0-6} \text{alkylCN, OC}_{1-6} \text{alkylCN,} \\
&\text{C}_{0-6} \text{alkylOR}^5, \text{OC}_{2-6} \text{alkylOR}^5, \text{C}_{0-6} \text{alkylNR}^5 \text{R}^6, \text{OC}_{2-6} \text{alkylNR}^5 \text{R}^6, \\
&\text{OC}_{2-6} \text{alkylOR}^5, \text{OC}_{2-6} \text{alkylOR}^5, \text{C}_{0-6} \text{alkylCO}_2 \text{R}^5, \text{OC}_{1-6} \text{alkylCO}_2 \text{R}^5, \text{C}_{0-6} \text{alkylCON(R}^5 \text{)}, \\
&\text{OC}_{2-6} \text{alkylCON(R}^5 \text{)}, \text{OC}_{2-6} \text{alkylCON(R}^5 \text{)}, \text{OC}_{2-6} \text{alkylCOR}^5, \text{OC}_{2-6} \text{alkylCOR}^5, \\
&\text{OC}_{2-6} \text{alkylCOR}^5, \text{OC}_{2-6} \text{alkylCOR}^5, \text{OC}_{2-6} \text{alkylCOR}^5, \text{OC}_{2-6} \text{alkylCOR}^5, \\
&\text{and OC}_{2-6} \text{alkylCOR}^5, \text{OC}_{2-6} \text{alkylCOR}^5, \text{OC}_{2-6} \text{alkylCOR}^5, \text{OC}_{2-6} \text{alkylCOR}^5, \\
&\text{and OC}_{2-6} \text{alkylCOR}^5.
\end{align*}
\]
heteroaryl groups may be optionally fused with a 4, 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclyl group to form a bicyclic ring system where the bicyclic ring system is optionally substituted with one or more B;

\[ R^2 \text{ is } -L^1 -G^1 -G^2 - \]

\[ R^3 \text{ is hydrogen; } \]

\[ G^1 \text{ is selected from } C_3 \text{-iocycloalkyl, } C_4 \text{-i}_{2} \text{cycloalkenyl, } C_{7-12} \text{cycloalkynyl, aryl, heteroaryl, heterocyclyl, wherein said } C_3 \text{-iocycloalkyl, } C_4 \text{-i}_{2} \text{cycloalkenyl, } C_{7-12} \text{cycloalkynyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one or more } R^{10}; \]

\[ G^2 \text{ is selected from hydrogen, } C_5 \text{scycloalkyl, } C_4 \text{-i}_{2} \text{cycloalkenyl, } C_7 \text{-i}_{2} \text{cycloalkynyl, aryl, heteroaryl, heterocyclyl, wherein said } C_{3-8} \text{cycloalkyl, } C_4 \text{-i}_{2} \text{cycloalkenyl, } C_7 \text{-i}_{2} \text{cycloalkynyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one or more } R^{10}; \]

At each occurrence, \( R^5 \) is independently selected from hydrogen, \( C_{1-6} \text{alkyl, } C_{2-6} \text{alkenyl, } C_{2-6} \text{alkynyl, } C_{0-6} \text{alkylC}_{3-8} \text{cycloalkyl, } C_{0-6} \text{alkylC}_{2-6} \text{alkenyl, } C_{0-6} \text{alkylC}_{2-6} \text{alkynyl, } C_{0-6} \text{alkylC}_{0-6} \text{alkylheteroaryl and } C_{0-6} \text{alkylheterocyclyl, wherein said } C_{1-6} \text{alkyl, } C_{2-6} \text{alkenyl, } C_{2-6} \text{alkynyl, } C_{0-6} \text{alkylC}_{3} \text{gycloalkyl, } C_{0-6} \text{alkylC}_{3} \text{alkylaryl, } C_{0-6} \text{alkylheteroaryl or } C_{0-6} \text{alkylheterocyclyl is optionally substituted with one or more } B; \]

At each occurrence, \( R^6 \) is selected from hydrogen, \( C_{1-6} \text{alkyl, } C_{2-6} \text{alkenyl, } C_{2-6} \text{alkynyl, } C_{0-6} \text{alkylC}_{8} \text{cycloalkyl, } C_{0-6} \text{alkylC}_{2-6} \text{alkenyl, } C_{0-6} \text{alkylheteroaryl and } C_{0-6} \text{alkylheterocyclyl, wherein said } C_{1-6} \text{alkyl, } C_{2-6} \text{alkenyl, } C_{2-6} \text{alkynyl, } C_{0-6} \text{alkylC}_{3} \text{gycloalkyl, } C_{0-6} \text{alkylC}_{3} \text{alkylaryl, } C_{0-6} \text{alkylheteroaryl or } C_{0-6} \text{alkylheterocyclyl is optionally substituted with one or more } B; \text{ or } \]

\( R^5 \text{ and } R^6 \text{ may together with the linking atom or atoms to which they are bonded form a } 4 \text{ to } 6 \text{ membered heterocyclic ring containing one or more heteroatoms selected from } N, O \text{ or } S \text{ that is optionally substituted with } B; \text{ whenever two } R^5 \text{ groups occur in the structure}
then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, that is optionally substituted with one or more B;

$L^1$ and $L^2$ independently represent a bond or a 1-7 membered non-cyclic linking group containing 0-2 heteroatoms selected from O, N, and S, said linking group optionally containing CO, S(O)$_n$, C=O or an acetylenic group, and optionally being substituted with one or more $R^8$;

$R^8$ is selected from halogen, nitro, CHO, CN, OH, OCl$_i$-alkyl, O(Ci$_i$-alkyl)O(Ci$_i$-alkyl), C$_i$-alkyl, C$_i$-alkenyl, C$_i$-alkynyl N(C$_i$-alkyl)(C$_i$-alkyl), NH$_2$, NH(C$_i$-alkyl), S(O)$_n$(C$_i$-alkyl), SO$_2$N(C$_i$-alkyl)(C$_i$-alkyl), SO$_2$NH$_2$, SO$_2$NH(C$_i$-alkyl), CF$_3$, CHF$_2$, CFH$_2$, C(O)(C$_i$-alkyl), C(O)N(C$_i$-alkyl)(C$_i$-alkyl), C(O)NH(C$_i$-alkyl), C(O)NH$_2$, N(C$_i$-alkyl)(CO)N(C$_i$-alkyl)(C$_i$-alkyl), N(C$_i$-alkyl)(CO)NH(C$_i$-alkyl), NH(CO)NH$_2$, N(C$_i$-alkyl)(CO)NH$_2$;

Whenever two $R^8$ groups are connected to the same atom of the linking group $L^1$, they may optionally together form a 3 to 6 membered non-aromatic, carbocyclic or heterocyclic (containing one or more heteroatoms selected from N, O or S) ring, that is optionally substituted with one or more $R^9$;

$R^9$ is selected from halogen, nitro, CHO, CN, OH, OCl$_i$-alkyl, O(Ci$_i$-alkyl)O(Ci$_i$-alkyl), C$_i$-alkyl, C$_i$-alkenyl, C$_i$-alkynyl N(C$_i$-alkyl)(C$_i$-alkyl), NH$_2$, NH(C$_i$-alkyl), S(O)$_n$(C$_i$-alkyl), SO$_2$N(C$_i$-alkyl)(C$_i$-alkyl), SO$_2$NH$_2$, SO$_2$NH(C$_i$-alkyl), CF$_3$, CHF$_2$, CFH$_2$, C(O)(C$_i$-alkyl), C(O)N(C$_i$-alkyl)(C$_i$-alkyl), C(O)NH(C$_i$-alkyl), C(O)NH$_2$, N(C$_i$-alkyl)(CO)N(C$_i$-alkyl)(C$_i$-alkyl), N(C$_i$-alkyl)(CO)NH(C$_i$-alkyl), NH(CO)NH$_2$, N(C$_i$-alkyl)(CO)NH$_2$;

B is selected from halogen, nitro, SF$_3$, OSF$_3$, CN, OR$_i$, OC$_i$-alkylNR$_{15}$R$_{16}$, NR$_{15}$R$_{16}$, CONR$_{15}$R$_{16}$, NR$_{15}$CO)R$_{16}$, O(CO)Ci$_i$-alkyl, (CO)OCi$_i$-alkyl, COR$_{15}$, (SO)NR$_{15}$R$_{16}$, NR$_{15}$SO$_2$R$_{15}$, SO$_2$R$_{15}$, SOR$_{15}$, (CO)Ci$_i$-alkylNR$_{15}$R$_{16}$, (SO)Ci$_i$-alkylNR$_{15}$R$_{16}$, OSO$_2$R$_{15}$,
C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, Co-6 alkylC_{3-8} cycloalkyl, C_{0-6} alkylary, Co-6 alkylheteroaryl and Co-6 alkylheterocyclyl;

R^{15} is selected from hydrogen, C_{i-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, Co-6 alkylC_{3-8} cycloalkyl, Co-6 alkylary, C_{0-6} alkylheteroaryl and Co-6 alkylheterocyclyl;

R^{16} is selected from hydrogen, C_{i-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, Co-6 alkylOR^{5}, Co-6 alkylC_{3-8} cycloalkyl, Co-6 alkylary, Co-6 alkylheteroaryl and Co-6 alkylheterocyclyl; or

R^{15} and R^{16} may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S; whenever two R^{15} groups occur in the structure then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S;

D is selected from halogen, nitro, SF_{5}, OSF_{5}, CN, OR^{13}, OC_{2-6} alkylNR^{13}R^{14}, NR^{13}R^{14}, CONR^{13}R^{14}, NR^{13}(CO)R^{14}, O(CO)C_{i-6} alkyl, (CO)OCl_{i-6} alkyl, COR^{13}, (SO_{2})NR^{13}R^{14}, NR^{13}SO_{2}R^{14}, SO_{2}R^{13}, SOR^{13}, (CO)d_{6} alkylNR^{13}R^{14}, (SO_{2})Cl_{i-6} alkylNR^{13}R^{14}, OSO_{2}R^{13}, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{0-6} alkylC_{3-8} cycloalkyl, and Co-6 alkylheterocyclyl;

R^{10} is independently selected from halogen, nitro, SF_{5}, OSF_{5}, CN, OR^{11}, C=CR^{11}, OC_{2-6} alkylNR^{13}R^{12}, NR^{11}R^{12}, CONR^{11}R^{12}, NR^{13}(CO)R^{12}, OC_{i-6} alkyl, (CO)OCl_{i-6} alkyl, COR^{11}, (SO_{2})NR^{13}R^{12}, NR^{11}SO_{2}R^{11}, SO_{2}R^{11}, SOR^{11}, (CO)C_{6} alkylNR^{11}R^{12}, (SO_{2})Cl_{i-6} alkylNR^{13}R^{12}, OSO_{2}R^{11}, C_{i-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{0-6} alkylC_{3-8} cycloalkyl, Co-6 alkylary, Co-6 alkylheteroaryl, Co-6 alkylheterocyclyl and OC_{2-6} alkylheterocyclyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, Co-6 alkylC_{3-8} cycloalkyl, Co-6 alkylary, Co-6 alkylheteroaryl, Co-6 alkylheterocyclyl or OC_{2-6} alkylheterocyclyl is optionally substituted with one or more E, and wherein any of the individual aryl or heteroaryl groups may be optionally fused with a 4, 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclyl group to form a bicyclic ring system where the bicyclic ring system is optionally substituted with one or more E;
At each occurrence, \( R^{11} \) is independently selected from hydrogen, \( C_{1-6} \) alkyl, \( C_{2-6} \) alkenyl, \( C_{2-6} \) alkynyl, \( \text{Co}-\text{6} \) alkylC\(_3\)\(_8\)cycloalkyl, \( \text{CO}_\text{6} \) alkylaryl, \( \text{Co}_\text{6} \) alkylheteroaryl and \( \text{Co}_\text{6} \) alkylheterocyclyl, wherein any of the individual \( \text{CI}_\text{6} \) alkyl, \( \text{C}_\text{2-6} \) alkenyl, \( \text{C}_\text{2-6} \) alkynyl, \( \text{Co}_\text{6} \) alkylC\(_3\)\(_8\)cycloalkyl, \( \text{Co}_\text{6} \) alkylaryl, \( \text{Co}_\text{6} \) alkylheteroaryl and \( \text{Co}_\text{6} \) alkylheterocyclyl groups may be optionally substituted with one or more \( E \);

\( R^{12} \) is selected from hydrogen, \( \text{Cl}_\text{6} \) alkyl, \( \text{C}_\text{2-6} \) alkenyl, \( \text{C}_\text{2-6} \) alkynyl, \( \text{Co}_\text{6} \) alkylC\(_3\)\(_8\)cycloalkyl, \( \text{Co}_\text{6} \) alkylaryl, \( \text{Co}_\text{6} \) alkylheteroaryl and \( \text{Co}_\text{6} \) alkylheterocyclyl, wherein any of the individual \( \text{Cl}_\text{6} \) alkyl, \( \text{C}_\text{2-6} \) alkenyl, \( \text{C}_\text{2-6} \) alkynyl, \( \text{Co}_\text{6} \) alkylC\(_3\)\(_8\)cycloalkyl, \( \text{Co}_\text{6} \) alkylaryl, \( \text{Co}_\text{6} \) alkylheteroaryl and \( \text{Co}_\text{6} \) alkylheterocyclyl groups may be optionally substituted with one or more \( E \); or

\( R^{11} \) and \( R^{12} \) may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S that is optionally substituted with B; whenever two \( R^{11} \) groups occur in the structure then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, where the ring system is optionally substituted with one or more \( E \);

\( R^{13} \) is independently selected from hydrogen, \( \text{C}_{1-6} \) alkyl, \( \text{C}_{2-6} \) alkenyl, \( \text{C}_{2-6} \) alkynyl, \( \text{Co}_\text{6} \) alkylC\(_3\)\(_8\)cycloalkyl, \( \text{Co}_\text{6} \) alkylaryl, \( \text{Co}_\text{6} \) alkylheteroaryl and \( \text{Co}_\text{6} \) alkylheterocyclyl;

\( R^{14} \) is selected from hydrogen, \( \text{Cl}_\text{6} \) alkyl, \( \text{C}_{2-6} \) alkenyl, \( \text{C}_{2-6} \) alkynyl, \( \text{Co}_\text{6} \) alkylOR\(^5\), \( \text{Co}_\text{6} \) alkylC\(_3\)\(_8\)cycloalkyl, \( \text{Co}_\text{6} \) alkylaryl, \( \text{Co}_\text{6} \) alkylheteroaryl and \( \text{Co}_\text{6} \) alkylheterocyclyl; or

\( R^{13} \) and \( R^{14} \) may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S; whenever two \( R^{11} \) groups occur in the structure then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S;
E is selected from halogen, nitro, SF5, OSF5, CN, OR5, OC6alkylNR6, NR5R6, CONR5R6, NR5(CO)R6, O(CO)C6alkyl, (CO)OC6alkyl, COR5, (SO2)NR5R6, NR5SO2R5, SO2R5, SOR5, (CO)C6alkylNR6, (SO2)C6alkylNR6, SO2R5, C6alkyl, C2-6alkenyl, Co6alkynyl, Co6alkylC3-8cycloalkyl, Co6alkylaryl, Co6alkylheteroaryl and Co6alkylheterocyclyl;

m = 0,1,2,3,4;
n = 0,1,2;

provided that compounds
1,2-Benzenedisulfonamide, NI-[(4,6-dimethyl-2-pyrimidinyl)amino]carbonyl];
1,2-Benzenedisulfonamide, NI-[(4,6-dimethoxy-1,3,5-triazin-2-yl)amino]carbonyl];
1,2-Benzenedisulfonamide, NI-[(4-methoxy-6-methyl-2-pyrimidinyl)amino]carbonyl];
1,2-Benzenedisulfonamide, NI-[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl] are excluded.

As used herein, "alkyl", used alone or as a suffix or prefix, denotes both branched and straight chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "Co-6 alkyl" denotes either a direct bond (Co) or an alkyl group having 1, 2, 3, 4, 5 or 6 carbon atoms. Thus a group such as Co-6 alkylCN may represent simply a CN group (C0) or a C6alkylCN group such as -CH2CN or -CH2CH2CN.

Thus a group such as C0-6alkylheteroaryl may represent simply a heteroaryl group (C0) or a C6alkylheteroaryl group such as -CH2-heteroaryl or -CH2CH2-heteroaryl.

In this way combinations may be formed of any of the herein defined groups, e.g. Co6alkyl that is covalent bonded to another herein defined group e.g. aryl is forming Co6alkylaryl.

Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, penty1, and hexyl. For the avoidance of doubt, where two or more alkyl moieties are present in a substituent, the alkyl moieties may be the same or different.
As used herein, "alkenyl" used alone or as a suffix or prefix denotes an alkyl group as defined above that contains one or more carbon-carbon double bonds. For example, "C\textsubscript{2-3}alkenyl" denotes alkenyl having 2, 3, 4, 5 or 6 carbon atoms. Examples of alkenyl include, but are not limited to, vinyl, allyl, 1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylbut-2-enyl, 3-methylbut-1-enyl, 1-pentenyl, 3-pentenyl and 4-hexenyl.

As used herein, "alkynyl" used alone or as a suffix or prefix denotes an alkyl group as defined above that contains one or more carbon-carbon triple bonds. For example, "C\textsubscript{2-6}alkynyl" denotes alkynyl having 2, 3, 4, 5 or 6 carbon atoms. Examples of alkynyl include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 3-butynyl, -pentynyl, hexynyl and 1-methylpent-2-ynyl.

As used herein, the term "aryl" refers to an aromatic ring structure made up of from 5 to 14 carbon atoms. Ring structures containing 5, 6, 7 and 8 carbon atoms would be single-ring (monocyclic) aromatic groups, for example, phenyl. Ring structures containing 8, 9, 10, 11, 12, 13, or 14 would be polycyclic, for example naphthyl. The aromatic ring can be substituted at one or more ring positions with such substituents as described above. The term "aryl" also includes - unless stated to the contrary - polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, for example, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls. The terms ortho, meta and para apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

As used herein, the term "cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms. These may include fused or bridged polycyclic systems. Preferred cycloalkyls have from 3 to 10 carbon atoms in their ring structure, and more preferably have 3, 4, 5, and 6 carbons in the ring structure. For example, "C\textsubscript{3-6}cycloalkyl" denotes such groups as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.
As used herein, "cycloalkenyl" refers to ring-containing hydrocarbyl groups having at least one carbon-carbon double bond in the ring, and having from 4 to 12 carbons atoms.

As used herein, "cycloalkynyl" refers to ring-containing hydrocarbyl groups having at least one carbon-carbon triple bond in the ring, and having from 7 to 12 carbons atoms.

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo.

As used herein, the term "heterocycl" or "heterocyclic" or "heterocycle" refers to a saturated, unsaturated or partially saturated, monocyclic, bicyclic or tricyclic ring (unless otherwise stated) containing 3 to 20 atoms of which 1, 2, 3, 4 or 5 ring atoms are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group is optionally replaced by a -C(O)-; and where unless stated to the contrary a ring nitrogen or sulphur atom is optionally oxidised to form the N-oxide or S-oxide(s) or a ring nitrogen is optionally quaternised; wherein a ring -NH is optionally substituted by acetyl, formyl, methyl or mesyl; and a ring is optionally substituted by one or more halo. It is understood that when the total number of S and O atoms in the heterocycl is exceeds 1, then these heteroatoms are not adjacent to one another. If the said heterocycl group is bi- or tricyclic then at least one of the rings may optionally be a heteroaromatic or aromatic ring provided that at least one of the rings is non-heteroaromatic. If the said heterocycl group is monocyclic then it must not be aromatic. Examples of heterocyclls include, but are not limited to, azetidinyl, pyrazolidinyl, piperidyl, piperidin-2,6-dionyl, piperidin-2-onyl, perhydroazepinyl (hexamethylene iminyl), piperezinyl, morpholinyl, thiomorpholinyl, S-oxothiomorpholinyl, S,S-dioxothiomorpholinyl, 1,3-dioxolanlyl, 1,4-dioxanyl, pyrrolidinyl, imidazolidinyl, imidazol-2-onyl, pyrrolidin-2-onyl, tetrahydrofuranyl, tetrahydrothienyl, S,S-dioxotetrahydrothienyl (tetramethylenesulfonyl), dithiolanyl, thiazolidinyl, oxazolidinyl, tetrahydropyranlyl and pyrazolinyl moiities. In one embodiment, a 5- to 8-membered heterocycl moiety is morpholinyl, tetrahydrofuranyl or S,S-dioxotetrahydrothienyl.
As used herein, "heteroaryl" or "heteroaromatic" refers to an aromatic heterocycle having at least one heteroatom ring member such as sulfur, oxygen, or nitrogen provided that no single ring contains more than three nitrogen atoms. Heteroaryl groups include - unless otherwise stated - monocyclic and polycyclic (e.g., having 2, 3 or 4 fused rings) systems. Examples of heteroaryl groups include without limitation, pyridyl (i.e., pyridinyl), pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl (i.e. furanyl), quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrryl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, thiazolyl, benzothienyl, purinyl, carbazolyl, fluorenonyl, benzimidazolyl, indoliny, and the like. In some embodiments, the heteroaryl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 4 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl or heteroaromatic group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms provided that no single ring contains more than three nitrogen atoms. In some embodiments, the heteroaryl or heteroaromatic group has 1 heteroatom. In one embodiment, a 5- or 6- membered heteroaryl moiety is pyrrolyl, thienyl, furanyl, pyridyl, pyrimidinyl, oxazolyl, thiazolyl or pyrazolyl moiety. For the avoidance of doubt, although the above definitions of heteroaryl and heterocyclyl groups refer to an "N" moiety which can be present in the ring, as will be evident to a skilled chemist the N atom will carry a hydrogen atom (or will carry a substituent as defined above) if it is attached to each of the adjacent ring atoms via a single bond.

As used herein, "L₁ and L₂" independently refer to a bond or a 1-7 membered non-aromatic linking group containing 0-2 heteroatoms selected from O, N, and S, said linking group optionally containing CO, S(O)ₙ, C=C or an acetylenic group, and optionally being substituted with one or more R₈. Examples include but are not limited to -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -CH₂-, -C(=O)-, -CH₂CH₂-, -CH=CH-, -C≡C-, -OCH₂-, -CH₂O-, -SCH₂-, -CH₂S-, -S(O)CH₂-, -CH₂S(O)-, -S(O)₂CH₂-, -CH₂S(O)₂-, -S(O)₂CH₂-, -CH₂S(O)₂-, -S(O)₂CH₂-, -CH₂S(O)₂-, -NHCH₂-, -CH₂NH-, -C(O)CH₂-, -CH₂C(O)-, -C(O)O-, -OCH₂CH₂-, -CH₂OCH₂-, -CH₂CH₂O-, -CH=CHCH₂-, CH₂=CH-, -CH₂S(O)₂CH₂-, -CH₂C=CH₂-, -C≡CCH₂-, -NHCHMeCH₂-, -(CH₂)₃-, -(CH₂)₄-, -(CH₂)₅-, -CH₂CH=CHCH₂-, -O(CH₂)₃O- and -CH₂NHC(O)-.
As used herein, a C_{1-6}alkoxy moiety is a said C_{1-6}alkyl moiety attached to an oxygen atom. Examples include methoxy and ethoxy.

Examples of bicyclic ring systems in which the two rings are fused together include naphthyl, indanyl, quinolyl, tetrahydroquinolyl, benzofuranyl, indolyl, isoindolyl, indoliny1, benzofuranyl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzmorpholinyl, isoquinolyl, chromanyl, indenyl, quinazolyl, quinoxalyl, isocromanyl, tetrahydronaphthyl, pyrido-oxazolyl, pyridothiazolyl, dihydrobenzofuranyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxinyl and 3,4-dihydro-isochromenyl. In one embodiment, a bicyclic fused ring system is a naphthyl, indanyl, indolyl, benzofuranyl, benzothienyl, benzthiazolyl, benzmorpholinyl, pyrido-oxazolyl, pyridothiazolyl or dihydrobenzofuranyl moiety.

Examples of tricyclic ring systems in which the three rings are fused together include xanthenyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, dibenzofuranyl, dibenzothienyl, S,S-dioxodibenzothienyl, fluorenyl, phenanthrenyl and anthracenyl. In one embodiment, a tricyclic fused ring system is a dibenzofuranyl or S,S-dioxodibenzothienyl moiety.

In one embodiment, A is selected from phenyl or pyridyl; said phenyl or pyridyl being optionally fused to a phenyl, a 5- or 6-membered heteroaryl, Cs-heterocyclyl or Cs-heterocyclyl ring. Examples of fused ring systems for A include naphthyl, indanyl, quinolyl, tetrahydroquinolyl, benzofuranyl, indolyl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, indenyl, tetrahydronaphthyl, pyrido-oxazolyl, pyridothiazolyl, dihydrobenzofuranyl, 1,3-benzodioxolyl and 2,3-dihydro-1,4-benzodioxinyl.

In another embodiment, A is phenyl or pyridyl.

In another embodiment, A is phenyl. In another embodiment, A is pyridyl.

In one embodiment, R^1 is independently selected from halogen, nitro, SF_5, CHO, CN, NR^5R^6, CO_2R^5, CON(R^5)_2, NR^5(CO)R^6, 0(CO)NR^5R^6, NR^5(CO)OR^6, NR^5(CO)NR^5R^6, 0(CO)OR^5, 0(CO)R^5, COR^5, NR^5(CO)(CO)R^5, NR^5(CO)(CO)NR^5R^6, SR^5, (SO_2)NR^5R^6,
(SO)NR⁵R⁶, OSO₂R⁵, NR⁵(SO₂)NR⁵R⁶, NR⁵(SO)R⁶, SO₂R⁵, SOR⁵, C₆₉₆alkyl, C₆₉₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, Cs-scycloalkyl, Co₆alkylaryl, Co₆alkylheteroaryl and heterocyclyl, wherein said C₆₉₆alkyl, C₆₉₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, Cs-scycloalkyl, Co₆alkylaryl, Co₆alkylheteroaryl or heterocyclyl is optionally substituted with one or more B, and wherein any of the individual aryl or heteroaryl groups may be optionally fused with a 4, 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclyl group to form a bicyclic ring system where the bicyclic ring system is optionally substituted with one or more B;

In one embodiment, R¹ is independently selected from halogen, nitro, SF₅, OH, CHO,

C₁₋₄alkyl or C₁₋₄alkoxy; said C₁₋₄alkyl or C₁₋₄alkoxy being optionally substituted by OH or by one or more F atoms.

In another embodiment, R¹ is independently selected from halogen, C₁₋₄alkyl or C₁₋₄alkoxy; said C₁₋₄alkyl or C₁₋₄alkoxy being optionally substituted by OH or by one or more F atoms.

In one embodiment, m represents an integer Oor 1 or 2. In one embodiment, m represents an integer Oor 1. In another embodiment, m represents an integer o.

In one embodiment, R³ is independently selected from hydrogen, CN, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl and C₁₋₆alkylNR⁵R⁶, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one or more D.

In one embodiment, each R³ is independently selected from hydrogen, CN and C₁₋₄alkyl.

In another embodiment, each R³ represents hydrogen.

In one embodiment, each R⁵ and R⁶ is independently selected from hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, Cs-scycloalkyl, aryl, C₁₋₆alkylaryl, heteroaryl, C₁₋₆alkylheteroaryl and heterocyclyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, Cs-scycloalkyl, aryl, C₁₋₆alkylaryl, heteroaryl, C₁₋₆alkylheteroaryl and heterocyclyl are optionally substituted with one B.

In one embodiment, each R⁵ and R⁶ is independently selected from hydrogen and C₁₋₆alkyl wherein said Chalky! is optionally substituted with one B.
In one embodiment, each $R^{11}$ and $R^{12}$ group is independently selected from hydrogen, C$_{1-6}$alkyl, C$_{2-6}$alkenyl, Co$_{6}$alkylC$_{3-8}$cycloalkyl, Co$_{6}$alkylaryl, Co$_{6}$alkylheteroaryl, wherein any of the individual C$_{1-6}$alkyl, C$_{2-6}$alkenyl, Co$_{6}$alkylC$_{3-8}$cycloalkyl, Co$_{6}$alkylaryl, Co$_{6}$alkylheteroaryl groups may be optionally substituted with one or more E;

In one embodiment, $R^{11}$ and $R^{12}$ are independently selected from hydrogen and C$_{1,6}$alkyl wherein said C$_{1,6}$alkyl is optionally substituted with one or more E.

In one embodiment E is halogen or OR$_5$;

In one embodiment, $L^1$ represents a direct bond, -CH$_2^-$, -CH$_2$CH$_2^-$ or -CH=CH-. In another embodiment, $L^1$ represents -CH$_2^-$. In another embodiment, $L^1$ represents a direct bond.

In one embodiment, $L^2$ represents -C≡C-, -OCH$_2^-$ or -CH$_2^-$. In another embodiment, $L^2$ represents a direct bond, -O-, -OCH$_2^-$, -CH$_2^-$. In another embodiment, $L^2$ represents a direct bond.

In another embodiment, $L^2$ represents -CH$_2^-$. In another embodiment, $L^2$ represents a direct bond. In another embodiment, $L^2$ represents -C≡C-.

In one embodiment, $G^1$ represents phenyl or 5- or 6-membered heteroaryl; optionally fused to one further ring independently selected from phenyl and 5- or 6-membered heteroaryl.

In another embodiment, $G^1$ represents phenyl; optionally fused to one further ring independently selected from phenyl and 5- or 6-membered heteroaryl.

In another embodiment, $G^1$ represents phenyl, 5- or 6-membered heteroaryl or C$_3$-iocycloalkyl optionally fused to one further ring selected from phenyl and 5- or 6-membered heteroaryl wherein said phenyl, 5- or 6-membered heteroaryl or C$_3$-iocycloalkyl optionally fused to one further ring selected from phenyl and 5- or 6-membered heteroaryl is optionally substituted with one or more R$_{10}$. 
In another embodiment, G\textsuperscript{1} represents phenyl, 5- or 6-membered heteroaryl or C\textsubscript{3}-8cycloalkyl optionally fused to one further ring selected from phenyl and 5- or 6-membered heteroaryl wherein said phenyl, 5- or 6-membered heteroaryl or C\textsubscript{3}-8cycloalkyl optionally fused to one further ring selected from phenyl and 5- or 6-membered heteroaryl is optionally substituted with one or more R\textsuperscript{10}.

In another embodiment, G\textsuperscript{1} represents phenyl.

In one embodiment, G\textsuperscript{2} represents H, phenyl or 5- or 6-membered heteroaryl; said phenyl or 5- or 6-membered heteroaryl being optionally fused to one further ring independently selected from phenyl, a 5- or 6-membered heteroaryl, Cs-Carbocyclyl or Cs-heterocyclyl ring.

In one embodiment, G\textsuperscript{2} represents H, phenyl, Cs-scycloalkyl or 5- or 6-membered heteroaryl; said phenyl or 5- or 6-membered heteroaryl being optionally fused to one further ring independently selected from phenyl, a 5- or 6-membered heteroaryl ring wherein said phenyl or 5- or 6-membered heteroaryl being optionally fused to one further ring independently selected from phenyl, a 5- or 6-membered heteroaryl ring is optionally substituted with one or more R\textsuperscript{10}.

In one embodiment, R\textsuperscript{10} is independently selected from halogen, nitro, SF\textsubscript{5}, OSF\textsubscript{5}, CN, OR\textsuperscript{11}, C≡CR\textsuperscript{11}, OC\textsuperscript{11}alkylNR\textsuperscript{11}R\textsuperscript{12}, NR\textsuperscript{11}R\textsuperscript{12}, CONR\textsuperscript{11}R\textsuperscript{12}, NR\textsuperscript{5}(CO)R\textsuperscript{12}, O(CO)Ci\textsuperscript{6}alkyl, (CO)OCi\textsuperscript{6}alkyl, COR\textsuperscript{11}, (SO\textsubscript{2})NR\textsuperscript{11}R\textsuperscript{12}, NR\textsuperscript{11}SO\textsubscript{2}R\textsuperscript{11}, SO\textsubscript{2}R\textsuperscript{11}, SOR\textsuperscript{11}, (CO)C\textsubscript{1}.6alkylNR\textsuperscript{5}R\textsuperscript{12}, (SO\textsubscript{2})Ci\textsuperscript{6}alkylNR\textsuperscript{5}R\textsuperscript{12}, OSO\textsubscript{2}R\textsuperscript{11}, C\textsubscript{6}alkyl, C\textsubscript{2,6}alkenyl, C\textsubscript{2,6}alkynyl, C\textsubscript{3,8}cycloalkyl, aryl, heteroaryl, heterocyclyl and OC\textsuperscript{11}alkylheterocyclyl, wherein said Ci\textsubscript{6}alkyl, C\textsubscript{2,6}alkenyl, C\textsubscript{2,6}alkynyl, C\textsubscript{3,8}cycloalkyl, aryl, heteroaryl, heterocyclyl or OC\textsubscript{2}alkylheterocyclyl is optionally substituted with one or more E, and wherein any of the individual aryl or heteroaryl groups may be optionally fused with a 4, 5, 6 or 7 membered cycloalkyl, cycloalkeny1 or heterocyclyl group to form a bicyclic ring system where the bicyclic ring system is optionally substituted with one or more E. For the
avoidance of doubt, when a molecule of formula (I) contains more than one $R^{10}$ group, each $R^{10}$ group is chosen independently.

In one embodiment $R^{10}$ is independently selected from halogen, CN, C^aUcy, OR^11, C≡CR^11, (CO)OCi^6alkyl, C^3,8cycloalkyl or heteroaryl said d$^{-}$alkyl, OR^11, (CO)OCi^6alkyl, C^a$cycloalkyl$, Co-alkylaryl or Co-alkylheteroaryl being optionally substituted by OH or by one or more F atoms.

In one embodiment, each $R^{10}$ group is independently selected from halogen, CN, NO2, C^1-alkyl and C^1-alkoxy; said C^1-alkyl or C^1-alkoxy being optionally substituted by OH or by one or more F atoms.

In one embodiment, each $R^{10}$ group is independently selected from halogen, CN, Ci^6alkyl, Ci^alkoxy, C≡CR^11, (CO)OCi^6alkyl, C^3,8cycloalkyl or heteroaryl, said Ci^alkyl, (CO)OCi^6alkyl, C^3,8cycloalkyl, heteroaryl or C^1-alkoxy being optionally substituted by OH or by one or more F atoms.

In another embodiment, each $R^{10}$ group is optionally substituted by one or more substituents independently selected from halogen, C^1-alkyl and C^1-alkoxy; said C^1-alkyl being optionally substituted by OH or by one or more F atoms.

In one embodiment B is selected from halogen, nitro, SF5, OSF5, CN, OR^15, OC^2, alkylNR^15R^16, NR^15R^16, CONR^15R^16, NR^15(CO)R^16, 0(CO)C^i^alkyl, (CO)OCi^alkyl, COR^15, (SO^2)NR^15R^16, NR^15SO^2R^15, SO^2R^15, SOR^15, (CO)d^alkynlNR^15R^15, (SO^2)C^1, alkylNR^15R^16, OSO^2R^15, Ci^alkyl, C^alkenyl, C^alkynyl, C^alkylC^3,8cycloalkyl, Co-alkylaryl, Co-alkylheteroaryl and Co-alkylheterocyclyl;

In one embodiment B is OR^15;

In one embodiment $R^15$ is selected from hydrogen, Ci^alkyl, C^alkenyl, C^alkynyl, Co-

alkylC^3,8cycloalkyl, Co-alkylaryl, Co-alkylheteroaryl and Co-alkylheterocyclyl;
In one embodiment R$^{16}$ is selected from hydrogen, C$_1$-$6$alkyl, C$_2$-$6$alkenyl, C$_2$-$6$alkynyl, Co-$6$alkylOR$^5$, Co-$6$alkylC$_3$-$8$cycloalkyl, Co-$6$alkylaryl, Co-$6$alkylheteroaryl and Co-$6$alkylheterocyclyl;

In one embodiment R$^{15}$ and R$^{16}$ may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S; whenever two R$^{15}$ groups occur in the structure then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S;

In one embodiment, A is phenyl or pyridyl; R$^1$ is independently selected from halogen, C$_1$-$4$alkyl or C$_1$-$4$alkoxy; said C$_1$-$4$alkyl or C$_1$-$4$alkoxy being optionally substituted by OH or by one or more F atoms; m represents an integer 0 or 1; each R$^3$ represents hydrogen; L$^1$ represents a direct bond; L$^2$ represents a direct bond; G$^1$ represents phenyl; optionally fused to one further ring independently selected from phenyl and 5- or 6-membered heteroaryl; G$^2$ represents H, phenyl or 5- or 6-membered heteroaryl; optionally fused to one further ring independently selected from phenyl, a 5- or 6-membered heteroaryl, C$_5$-$6$carbocycl or C$_5$-$6$heterocycl ring; and G$^1$ and G$^2$ are independently optionally substituted by one or more substituents independently selected from halogen, C$_1$-$6$alkyl and C$_1$-$6$alkoxy; said C$_1$-$6$alkyl being optionally substituted by OH or by one or more F atoms.

In one embodiment, A is phenyl; m represents an integer 0; each R$^3$ represents hydrogen; L$^1$ represents a direct bond; L$^2$ represents a direct bond; G$^1$ represents phenyl; optionally fused to one further ring independently selected from phenyl and 5- or 6-membered heteroaryl; G$^2$ represents H, phenyl or 5- or 6-membered heteroaryl; optionally fused to one further ring independently selected from phenyl, a 5- or 6-membered heteroaryl, C$_5$-$6$carbocycl or C$_5$-$6$heterocycl ring; and G$^1$ and G$^2$ are independently optionally
substituted by one or more substituents independently selected from halogen, C_{1-6}alkyl and C_{1-6}alkoxy; said C_{1-6}alkyl being optionally substituted by OH or by one or more F atoms.

In one embodiment, A is phenyl; m represents an integer 0; each R^3 represents hydrogen; L^1 represents a direct bond; L^2 represents -C≡C-; G^1 represents phenyl; optionally fused to one further ring independently selected from phenyl and 5- or 6-membered heteroaryl; G^2 represents H; and any phenyl or heteroaryl moieties in G^1 is optionally substituted by one or more substituents independently selected from halogen, C_{1-6}alkyl and C_{1-6}alkoxy; said C_{1-6}alkyl being optionally substituted by OH or by one or more F atoms.

In one embodiment A represents aryl or heteroaryl, then -G^1·L^2·G^2 does not represent aryl or heteroaryl substituted in the ortho position (with respect to L^1) with a 3-6 membered linking group attached to a further aryl or heteroaryl ring; or when R^1 represents aryl or heteroaryl and m = 1, then A does not represent aryl or heteroaryl substituted in the ortho position (with respect to the -SO2NHCO- group) with a 3-6 membered linking group attached to an aryl or heteroaryl ring;

In one embodiment R^1 is independently selected from halogen, nitro, SF_5, CHO, CO, alkylCN, OCi_6alkylCN, C_{0-6}alkylOR^5, OC_{2-6}alkylOR^5, C_{0-6}alkylNR^5R^6, OC_{2-6}, alkylNR^5R^6, OC_{2-6}alkylOC_{2-6}alkylNR^5R^6, C_{0-6}alkylCO_{2-6}R^5, OC_{2-6}alkylCO_{2-6}R^5, C_{0-6}alkylCON(R^5)_2, OC_{2-6}alkylCON(R^5)_2, OC_{2-6}alkylNR^5(CO)R^6, C_{0-6}alkylNR^5(CO)R^6, OC_{2-6}alkylCOR^5, NR^5(CO)(CO)R^5, NR^5(CO)(CO)NR^5R^6, C_{0-6}alkylCOR^5, NR^5(CO)(CO)NR^5R^6, C_{0-6}alkylSR^5, C_{0-6}alkyl(SO_2)_NR^5R^6, OC_{2-6}alkyl(SO_2)NR^5R^6, OC_{2-6}alkyl(SO_2)NR^5R^6, C_{0-6}alkyl(SO)NR^5R^6, OC_{2-6}alkyl(SO)NR^5R^6, C_{0-6}alkyl(OS0)_{2-6}R^5, C_{0-6}alkylNR^5(SO_2)NR^5R^6, C_{0-6}alkylNR^5(SO_2)NR^5R^6, OC_{2-6}alkylNR^5(SO)R^6, OC_{2-6}alkylSO_{2-6}R^5, C_{0-6}alkylS0_{2-6}R^5, C_{0-6}alkylSOR^5, C_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, OC_{2-6}alkylC_5cycloalkyl, OC_{2-6}alkylaryl, C_{0-6}alkylheteroaryl and C_{0-6}alkylheterocyclyl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_3cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl or C_{0-6}alkylheterocyclyl is optionally substituted with one or more B, and wherein any of the individual aryl or heteroaryl groups
may be optionally fused with a 4, 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclyl group to form a bicyclic ring system where the bicyclic ring system is optionally substituted with one or more B;

Examples of compounds of the invention include:

5-Benzofuran-2-yl-N-(2-sulfamoylphenyl)sulfonyl-pyridine-2-carboxamide
5-(2,3-Dichlorophenyl)-N-(2-sulfamoylphenyl)sulfonyl-pyridine-2-carboxamide
4-Benzofuran-2-yl-N-(2-sulfamoylphenyl)sulfonyl-benzamide
4-Benzothiophen-2-yl-N-(2-sulfamoylphenyl)sulfonyl-benzamide
4-Benzothiazol-2-yl-N-(2-sulfamoylphenyl)sulfonyl-benzamide
4-(7-Oxa-3,9-diazabicyclo[4.3.0]nona-2,4,8,10-tetraen-8-yl)-N-(2-sulfamoylphenyl)sulfonyl-benzamide
4-(7-Oxa-5,9-diazabicyclo[4.3.0]nona-2,4,8,10-tetraen-8-yl)-N-(2-sulfamoylphenyl)sulfonyl-benzamide
4-Benzooxazol-2-yl-N-(2-sulfamoylphenyl)sulfonyl-benzamide
2-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-benzofuran-6-carboxamide
4-Bromo-N-(2-sulfamoylphenyl)sulfonyl-benzamide
4-Bromo-2-chloro-N-(2-sulfamoylphenyl)sulfonyl-benzamide
4-Bromo-3-methyl-N-(2-sulfamoylphenyl)sulfonyl-benzamide
4-Bromo-3-fluoro-N-(2-sulfamoylphenyl)sulfonyl-benzamide
4-Bromo-2-fluoro-N-(2-sulfamoylphenyl)sulfonyl-benzamide
4-Bromo-2-methyl-N-(2-sulfamoylphenyl)sulfonyl-benzamide
2-(1-Adamantyl)-N-(2-sulfamoylphenyl)sulfonyl-acetamide
N-(2-Sulfamoylphenyl)sulfonylnorbornane-2-carboxamide
1-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-cyclohexane-1-carboxamide
3-(Difluoromethoxy)-N-(2-sulfamoylphenyl)sulfonyl-benzamide
3-Bromo-4-fluoro-N-(2-sulfamoylphenyl)sulfonyl-benzamide
N-(2-Sulfamoylphenyl)sulfonyl-3-(2,2,3,3-tetrafluoropropanoxymethyl)benzamide
4-Methyl-N-(2-sulfamoylphenyl)sulfonyl-2-[3-(trifluoromethyl)phenyl]l,3-thiazole-5-carboxamide
4-Chloro-2-fluoro-N-(2-sulfamoylphenyl)sulfonyl-benzamide
2-Benzyl-4-chloro-N-(2-sulfamoylphenyl)sulfonyl-benzamide
2-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-benzofuran-5-carboxamide
4-Methyl-N-(2-sulfamoylphenyl)sulfonyl-2-[4-(trifluoromethyl)phenyl]l,3-thiazole-5-
carboxamide
2-(2,3-Dihydrobenzofuran-5-yl)-4-methyl-N-(2-sulfamoylphenyl)sulfonyl-l,3-thiazole-5-
carboxamide
2-(4-Chlorophenyl)-4-methyl-N-(2-sulfamoylphenyl)sulfonyl-l, 3-thiazole-5-carboxamide
4-Methyl-2-phenyl-N-(2-sulfamoylphenyl)sulfonyl-l,3-thiazole-5-carboxamide
4-Phenylmethoxy-N-(2-sulfamoylphenyl)sulfonyl-benzamide
4-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-benzamide
N-(2-Sulfamoylphenyl)sulfonyl-4-tert-butyl-benzamide
1-Methyl-N-(2-sulfamoylphenyl)sulfonyl-indole-2-carboxamide
5-Pyridin-2-yl-N-(2-sulfamoylphenyl)sulfonyl-thiophene-2-carboxamide
5-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-thiophene-2-carboxamide
5-(3,4-Dichlorophenyl)-N-(2-sulfamoylphenyl)sulfonylfuran-2-carboxamide
N-(2-Sulfamoylphenyl)sulfonyl-5-[3-(trifluoromethyl)phenyl]furan-2-carboxamide
1-(3,5-Dichlorophenyl)-5-propyl-N-(2-sulfamoylphenyl)sulfonyl-pyrazole-4-carboxamide
3,6-Dichloro-N-(2-sulfamoylphenyl)sulfonyl-benzothiophene-2-carboxamide
N-(2-Sulfamoylphenyl)sulfonylbenzothiophene-3-carboxamide
Ethyl 4-[5-[2-Sulfamoylphenyl]sulfonylcarbamoyl]-2-furylbenzoate
2-(3-Chlorophenyl)-4-methyl-N-(2-sulfamoylphenyl)sulfonyl-l,3-thiazole-5-carboxamide
4-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenyl)sulfonyl)benzamide
4-(3-Hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenyl)sulfonyl)benzamide
4-(Benzofuran-2-yl)-2-methyl-N-(2-sulfamoylphenyl)sulfonyl)benzamide;
4-(Benzofuran-2-yl)-2-methyl-N-(2-sulfamoylphenyl)sulfonyl)benzamide;
4-(Benzofuran-2-yl)-3,5-dimethoxy-N-(2-sulfamoylphenyl)sulfonyl)benzamide;
4-(Benzofuran-2-yl)-2-methoxy-N-(2-sulfamoylphenyl)sulfonyl)benzamide;
4-(Benzofuran-2-yl)-2-hydroxy-N-(2-sulfamoylphenyl)sulfonyl)benzamide;
4-(Benzofuran-2-yl)-3-methoxy-N-(2-sulfamoylphenyl)sulfonyl)benzamide;
4-(Benzofuran-2-yl)-3-hydroxy-N-(2-sulfamoylphenyl)sulfonyl)benzamide;
4-(Benzofuran-2-yl)-2,6-dimethyl-N-(2-sulfamoylphenyl)sulfonyl)benzamide;
4-(3-Methoxyprop-1-ynyl)-N-(2-sulfamoylphenyl)sulfonyl)benzamide;
4-(3-Methylbut-3-en-1-ynyl)-N-(2-sulfamoylphenyl)sulfonyl)benzamide;
6-(Phenylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
4-(3-Ethyl-3-hydroxyprop-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3-Hydroxy-3-methylpent-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-((1-Hydroxy cyclopentyl) ethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
3-(3-Hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
3-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)-1-naphthamide;
4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)-1-naphthamide;
2-(Benzofuran-2-yl)-4-methyl-N-(2-sulfamoylphenylsulfonyl)thiazole-5-carboxamide;
3'-(3-Hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzofuranyl-2-carboxamide;
4-(Cyclopentylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
3-(Cyclopentylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopentylethynyl)-2-methyl-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3,3-Dimethylbut-1-ynyl)-3-methoxy-2-methyl-N-(2-sulfamoylphenylsulfonyl)-benzamide;
4-(Benzofuran-2-yl)-3-methoxy-2-methyl-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Pyridin-3-yethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Pyridin-2-yethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Phenylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3,3-Dimethylbut-1-ynyl)-3-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
2-(3-Methoxyphenyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(4-Methoxyphenyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-tert-Butyl-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(1-Hydroxycyclopentyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-Cyclopentyl-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
3-Cyano-4-(3,3-dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-3-cyano-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-Chloro-2-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-Bromo-2-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-2-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3,3-Dimethylbut-1-ynyl)-2-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopentylethynyl)-2-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopentylethynyl)-2-fluoro-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-2-fluoro-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
5-(Cyclohexylethynyl)-N-(2-sulfamoylphenylsulfonyl)picolinamide;
5-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)picolinamide;
4-(3,3-Dimethylbut-1-ynyl)-2-fluoro-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-2-chloro-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopentylethynyl)-2-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
6-(Cyclopentylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Pyridin-2-ylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Pyridin-3-ylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
2-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)pyrimidine-5-carboxamide;
N-(2-Sulfamoylphenylsulfonyl)-4-((3,3,3-trifluoropropoxy)methyl)benzamide;
4-(Cyclopentylethynyl)-3-(hydroxymethyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
6-(3-Methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
3-(Hydroxymethyl)-4-(phenylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclohexylethynyl)-3-(hydroxymethyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
2-((4-Chlorophenylethynyl)-N-(2-sulfamoylphenylsulfonyl)pyrimidine-5-carboxamide;
4-(Benzofuran-2-yl)-3-(hydroxymethyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)cyclohexancarboxamide;
(RS,4S)-4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)cyclohexancarboxamide;
(IR,4R)-4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)cyclohexancarboxamide;
4-(Benzofuran-2-yl)-1-methyl-N-(2-sulfamoylphenylsulfonyl)cyclohexancarboxamide;
(SR,4R)-4-(Benzofuran-2-yl)-1-methyl-N-(2-sulfamoylphenylsulfonyl)cyclohexancarboxamide;
4-(3,3-Dimethylbut-1-ynyl)-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopropylethynyl)-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3-Methoxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3-Methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
3-Methoxy-4-(3-methoxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
3-Hydroxy-4-(3-methoxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
6-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
4-(3,3-Dimethylbut-1-ynyl)-3-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-3-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)benzamide;
2-(2-Methoxyphenyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(l-tert-Butoxyethyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(Pyridin-2-yl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(Pyridin-3-yl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(2-Hydroxypropan-2-yl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(2-Methoxypropan-2-yl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-Cyclopropyl-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
4-(Benzofuran-2-yl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3,3-Dimethylbut-1-ynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3-Hydroxy-3-methylbut-1-ynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopentylethynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclohexylethynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopropylethynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-((1-Hydroxy cycloheptyl)ethynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
6-(3,3-Dimethylbut-1-ynyl)-5-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Benzofuran-2-yl)-5-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Cyclopentylethynyl)-5-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Cyclopentylethynyl)-5-methoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Cyclohexylethynyl)-5-methoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
5-Methoxy-N-(2-sulfamoylphenylsulfonyl)-6-((4-(trifluoromethyl)phenyl)-ethynyl)nicotinamide;
N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride;
1-(2-Methoxyethyl)-2-phenyl-N-(2-sulfamoylphenylsulfonyl)-1H-indole-5-carboxamide;
6-(Cyclopropylethynyl)-5-isopropoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Cyclopentylethynyl)-5-isopropoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Cyclohexylethynyl)-5-isopropoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
4-(Benzofuran-2-yl)-3-(3-methoxy-3-methylbutoxy)-N-(2-sulfamoylphenylsulfonyl)-benzamide;
4-(Cyclopentylethynyl)-3-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
6-(Benzofuran-2-yl)-5-chloro-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
5-Chloro-6-(cyclopentylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
5-Chloro-6-(3,3-dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)-2-(trifluoromethyl)benzamide;
4-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)-2-(trifluoromethyl)-benzamide;
4-(Benzofuran-2-yl)-2,6-difluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopentylethynyl)-2,6-difluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-3-(3-hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenyl-sulfonyl)benzamide;
4-(Benzofuran-2-yl)-3-bromo-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzyloxy)-3-(3-hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)-benzamide;
4-(Benzyloxy)-3-iodo-N-(2-sulfamoylphenylsulfonyl)benzamide;
2-Benzyl-N-(2-sulfamoylphenylsulfonyl)-1H-indole-5-carboxamide;
7-(Cyclopropylethynyl)-2,2-difluoro-N-(2-sulfamoylphenylsulfonyl)-benzo[d][1,3]dioxole-4-carboxamide;
4-(Cyclopentylethynyl)-N-(2-sulfamoylphenylsulfonyl)-3-(3,3,3-trifluoropropoxy)-benzamide;
4-(Benzofuran-2-yl)-N-(4-(hydroxymethyl)-2-sulfamoylphenylsulfonyl)benzamide;
Benzene-1,2-disulfonic acid 1-amide 2[(quinoline-3-carbonyl)-amide]
and pharmaceutically acceptable salts of any one thereof.
The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined above which comprises,

(a) reacting a compound of formula (II)

wherein \( R_1, R_3, A \) and \( m \) are as defined in formula (I),

with a compound of formula (III)

wherein \( L_1, L_2, G_1 \) and \( G_2 \) are as defined in formula (I) and \( X \) represents a leaving group such as OH or halogen; or

(b) when \( L_2 \) represents a direct bond and \( G_1 \) and \( G_2 \) are both aromatic moieties, reacting a compound of formula (IV)

wherein \( \text{Hal} \) represents a halogen atom and \( R_1, R_3, A, m \) and \( L_1 \) are as defined in formula (I),
with a nucleophile \( G^2 - M \) wherein \( M \) represents an organo-tin or organo boronic acid group;
and optionally after (a) or (b) carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

In process (a), the reaction may conveniently be carried out in an organic solvent such as acetonitrile, dichloromethane, N,N-dimethylformamide or N-methylpyrrolidinone at a temperature, for example, in the range from 0 °C to the boiling point of the solvent. If necessary or desired, a base and/or a coupling reagent such as 4-(dimethylamino)pyridine (DMAP), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), HATU (O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), 0-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium (HBTU), HOAT (1-Hydroxy-7-azabenzotriazole), HOBT (1-Hydroxybenzotriazole hydrate), triethylamine or DIEA (N,N-Diisopropylethylamine), and any combinations of the above, may be added. In one embodiment, the solvent is N,N-dimethylformamide and 4-(dimethylamino)pyridine (DMAP) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) are used as reagents.

In process (b), the reaction may conveniently be carried out by reaction with an appropriate aryl boronic acid or an aryl boronic ester. The reaction may be carried out using a suitable palladium catalyst such as \( \text{Pd(PPh}_3\text{)}_4 \), \( \text{Pd(dppf)}\text{Cl}_2 \), or \( \text{Pd(OAc)}_2 \) or \( \text{Pd(dba)}_3 \) together with a suitable ligand such as \( \text{P(tert-butyl)}_3 \), 2-(dicyclohexylphosphino)biphenyl, or 2-(2',6'-dimethoxybiphenyl)-dicyclohexylphosphine, or a nickel catalyst such as nickel on charcoal or Ni(dppe)Cl\(_2\) together with zinc and sodium triphenylphosphinetrimesulfonate. A suitable base such as an alkyl amine, e.g. triethylamine, or potassium carbonate, sodium carbonate, cesium carbonate, sodium hydroxide or cesium fluoride may be used in the reaction, which can be performed in the temperature range of +20 °C to +160 °C, using an oil bath or a microwave oven, in a suitable solvent or solvent mixture such as toluene, tetrahydrofuran, dimethoxyethane/water, \( \text{N,N-di} \text{methylformamide or dioxane}. \) The boronic acid or boronic ester may be formed in situ, by reaction of the corresponding aryl halide (e.g., the aryl bromide) with an alkyllithium reagent such as butyllithium to form an
intermediate aryl lithium species, which then is reacted with a suitable boron compound, e.g., trimethyl borate, tributyl borate or triisopropyl borate. Alternatively, the reaction may be carried out by reaction with an appropriate alkyne. The reaction may be carried out using a suitable palladium catalyst such as Pd(PPh₃)₄, PdCl₂(PPh₃)₂, [PdCl₂(CH₃CN)₂] or Pd(PPh₃)₂(OAc)₂. The reaction may be preformed in the presence of a suitable ligand such as Xphos. The reaction may be preformed in the presence of a suitable copper catalyst such as copper(I) iodide. A suitable base such as triethylamine, buthylamine, diisopropylamine or cesium carbonate may be used in the reaction, which can be performed in the temperature range of +20 °C to +160 °C, using an oil bath or a microwave oven, in a suitable solvent or a mixture of solvents such as N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, toluene, tetrahydrofuran, dimethoxyethane/water or dioxane.

Specific processes for the preparation of compounds of Formula (I) are disclosed within the Examples section of the present specification. Such processes form an aspect of the present invention.

The necessary starting materials are either commercially available, are known in the literature or may be prepared using known techniques. Specific processes for the preparation of certain key starting materials are disclosed within the Examples section of the present specification and such processes form an aspect of the present invention.

Certain intermediates are novel. Such novel intermediates form another aspect of the invention.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the addition and/or removal of one or more protecting groups.

As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases such as alkyl amines, aralkyl amines and heterocyclic amines.

Compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Enantiomerically pure forms are particularly desired.

The compounds of formula (I) and their pharmaceutically acceptable salts have activity as pharmaceuticals, in particular as selective inhibitors of the microsomal prostaglandin E synthase-1 enzyme, and may therefore be beneficial in the treatment or prophylaxis of pain and of inflammatory diseases and conditions. Furthermore, by selectively inhibiting the pro-inflammatory PGE2, it is believed that compounds of the invention would have a reduced potential for side effects associated with the inhibition of other prostaglandins by conventional non-steroidal anti-inflammatory drugs, such as gastrointestinal and renal toxicity.

More particularly, the compounds of formula (I) and their pharmaceutically acceptable salts may be used in the treatment of osteoarthritis, rheumatoid arthritis, acute or chronic pain, neuropathic pain, apnea, sudden infant death (SID), wound healing, cancer, benign or malignant neoplasias, stroke, atherosclerosis and Alzheimer's disease.

Even more particularly, the compounds of formula (I) and their pharmaceutically acceptable salts may be used in the treatment of osteoarthritis, rheumatoid arthritis, benign or malignant neoplasias or acute or chronic pain.

Thus, the present invention provides a compound of formula (I) or a pharmaceutically-acceptable salt thereof as hereinbefore defined for use in therapy.
In a further aspect, the present invention provides the use of a compound of formula (I) or
a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a
medicament for use in therapy.

One aspect of the invention provides compound of formula (I) or a pharmaceutically
acceptable salt thereof

wherein:

A is selected from mono- and bicyclic aryl, mono- and bicyclic heteroaryl, cycloalkenyl
and mono- and bicyclic heterocyclyl;

R¹ is independently selected from halogen, nitro, SF₅, CHO, Co₆alkylCN, OCi₆alkylCN,
C₆alkylOR, OC₂₋₆alkylOR, C₆₋₁₀alkylNR, OC₂₋₆alkylNR, OC₂₋₆alkylCON(R₂)₂,
OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylNR₅(CO)R₆, C₆₋₁₀alkylNR₅(CO)R₆, 0(CO)NR₅R₆,
NR₅(CO)OR₆, NR₅(CO)NR₅R₆, 0(CO)OR, 0(CO)R, C₆₋₁₀alkylCOR, OCi₆₋₁₀alkylCOR,
OC₆₋₁₀alkylCOR, C₆₋₁₀alkylCON(R₂)₂,
OCi₆₋₁₀alkylCON(R₅)₂, OC₂₋₆alkylNR₅(CO)R₆, C₆₋₁₀alkylNR₅(CO)R₆, 0(CO)NR₅R₆,
NR₅(CO)OR₆, NR₅(CO)NR₅R₆, 0(CO)OR, 0(CO)R, C₆₋₁₀alkylCOR, OCi₆₋₁₀alkylCOR,
OC₆₋₁₀alkylCOR, C₆₋₁₀alkylCON(R₂)₂,
OCi₆₋₁₀alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂,
OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂,
OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂,
OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂,
OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂,
OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂, OC₂₋₆alkylCON(R₅)₂,
R² is \( -L^1 - G^1 - L^2 - G^2 \);

R³ is independently selected from hydrogen, CN, C\(^\text{^a}H\text{cyl}\), C\(_2\text{^o-6}\)alkenyl, C\(_2\text{^o-6}\)alkynyl, C\(_\text{o-6}\)alkylCs-scycloalkyl, aryl, heteroaryl, C\(_\text{o-6}\)alkylheterocyclyl, and C\(_\text{o-6}\)alkylheterocyclyl is optionally substituted with one or more D;

G\(^1\) is selected from C\(_3\)-iocycloalkyl, C\(_4\)-i\(_2\)cycloalkenyl, C\(_7\)-i\(_2\)cycloalkynyl, aryl, heteroaryl, wherein said C\(_3\)-iocycloalkyl, C\(_4\)-i\(_2\)cycloalkenyl, C\(_7\)-i\(_2\)cycloalkynyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one or more R\(^1\);

G\(^2\) is selected from hydrogen, C\(_\text{s-scycloalkyl}\), C\(_4\)-i\(_2\)cycloalkenyl, Cy.^cycloalkynyl, aryl, heteroaryl, heterocyclyl, wherein said C\(_3\)-iocycloalkyl, C\(_4\)-i\(_2\)cycloalkenyl, C\(_7\)-i\(_2\)cycloalkynyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one or more R\(^1\);

At each occurrence, R⁵ is independently selected from hydrogen, C\(_1\)-alanyl, C\(_2\)-6alkenyl, C\(_2\)-6alkynyl, C\(_\text{o-6}\)alkylC\(_3\)-8cycloalkyl, C\(_\text{o-6}\)alkylaryl, C\(_\text{o-6}\)alkylheteroaryl and C\(_\text{o-6}\)alkylheterocyclyl, wherein said C\(_1\)-alanyl, C\(_2\)-6alkenyl, C\(_2\)-6alkynyl, C\(_\text{o-6}\)alkylC\(_3\)-8cycloalkyl, C\(_\text{o-6}\)alkylaryl, C\(_\text{o-6}\)alkylheteroaryl or C\(_\text{o-6}\)alkylheterocyclyl is optionally substituted with one or more B;

At each occurrence, R⁶ is selected from hydrogen, C\(_\text{i-6}\)alanyl, C\(_2\)-6alkenyl, C\(_2\)-6alkynyl, C\(_\text{o-6}\)alkyl0R⁵, C\(_\text{o-6}\)alkylC\(_3\)-8cycloalkyl, C\(_\text{o-6}\)alkylaryl, C\(_\text{o-6}\)alkylheteroaryl and C\(_\text{o-6}\)alkylheterocyclyl, wherein said C\(_1\)-alanyl, C\(_2\)-6alkenyl, C\(_2\)-6alkynyl, C\(_\text{o-6}\)alkylC\(_3\)-8cycloalkyl, C\(_\text{o-6}\)alkylaryl, C\(_\text{o-6}\)alkylheteroaryl or C\(_\text{o-6}\)alkylheterocyclyl is optionally substituted with one or more B; or

R⁵ and R⁶ may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S that is optionally substituted with B; whenever two R⁵ groups occur in the structure.
then they may optionally together form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, that is optionally substituted with one or more B;

\[ L^1 \text{ and } L^2 \text{ independently represent a bond or a 1-7 membered non-cyclic linking group containing 0-2 heteroatoms selected from O, N, and S, said linking group optionally containing CO, } S(O)_n \text{, } C=\text{C or an acetylenic group, and optionally being substituted with one or more } R^8; \]

\[ R^8 \text{ is selected from halogen, nitro, } \text{CHO, CN, OH, } \text{OCl}_{1-6} \text{alkyl, } \text{O(Ci}_{4-6} \text{alkyl})\text{O(Ci}_{1-6} \text{alkyl), } \text{C}_{1-6} \text{alkyl, } \text{C}_{2-6} \text{alkenyl, } \text{C}_{2-6} \text{alkynyl N(Ci}_{1-6} \text{alkyl})(\text{C}_{1-6} \text{alkyl), } \text{NH}_2, \text{NH(Ci}_{1-6} \text{alkyl), } \text{S(O)}_n(\text{Ci}_{1-6} \text{alkyl), } \text{SO}_2\text{N(\text{C}_{1-6} \text{alkyl})}, \text{SO}_2\text{NH}, \text{SO}_2\text{NH(Ci}_{1-6} \text{alkyl), } \text{CF}_3, \text{CHF}_2, \text{CFH}_2, \text{C(O)(Ci}_{4-6} \text{alkyl), } \text{C(O)N(Ci}_{6} \text{alkyl)(Ci}_{-6} \text{alkyl), } \text{C(O)NH(Ci}_{4-6} \text{alkyl), } \text{C(O)NH}_2, \text{N(Ci}_{1-6} \text{alkyl)(CO)NH(Ci}_{6} \text{alkyl), } \text{N(Ci}_{6} \text{alkyl)(CO)NH(Ci}_{-6} \text{alkyl), } \text{NH(CO)NH}_2, \text{N(Ci}_{6} \text{alkyl)(CO)NH}_2, \]

Whenever two \( R^8 \) groups are connected to the same atom of the linking group \( L^1 \), they may optionally together form a 3 to 6 membered non-aromatic, carbocyclic or heterocyclic (containing one or more heteroatoms selected from N, O or S) ring, that is optionally substituted with one or more \( R^9 \);

\[ R^9 \text{ is selected from halogen, nitro, } \text{CHO, CN, OH, } \text{OCl}_{1-6} \text{alkyl, } \text{O(Ci}_{4-6} \text{alkyl})\text{O(Ci}_{1-6} \text{alkyl), } \text{C}_{1-6} \text{alkyl, } \text{C}_{2-6} \text{alkenyl, } \text{C}_{2-6} \text{alkynyl N(Ci}_{1-6} \text{alkyl})(\text{C}_{1-6} \text{alkyl), } \text{NH}_2, \text{NH(Ci}_{1-6} \text{alkyl), } \text{S(O)}_n(\text{Ci}_{1-6} \text{alkyl), } \text{SO}_2\text{N(\text{C}_{1-6} \text{alkyl})}, \text{SO}_2\text{NH}, \text{SO}_2\text{NH(Ci}_{1-6} \text{alkyl), } \text{CF}_3, \text{CHF}_2, \text{CFH}_2, \text{C(O)(Ci}_{4-6} \text{alkyl), } \text{C(O)N(Ci}_{6} \text{alkyl)(Ci}_{-6} \text{alkyl), } \text{C(O)NH(Ci}_{4-6} \text{alkyl), } \text{C(O)NH}_2, \text{N(Ci}_{1-6} \text{alkyl)(CO)NH(Ci}_{6} \text{alkyl), } \text{N(Ci}_{6} \text{alkyl)(CO)NH(Ci}_{-6} \text{alkyl), } \text{NH(CO)NH}_2, \text{N(Ci}_{6} \text{alkyl)(CO)NH}_2, \]

\( B \) is selected from halogen, nitro, \( \text{SF}_3, \text{OSF}_5, \text{CN, OR}^5, \text{OC}_{2-6} \text{alkylNR}^5\text{R}^6, \text{NR}^5\text{R}^6, \text{CONR}^5\text{R}^6, \text{NR}^5(\text{CO})\text{R}^6, \text{O(CO)Ci}_{4-6} \text{alkyl, } \text{(CO)OCi}_{4-6} \text{alkyl, } \text{COR}^5, \text{(SO}_2\text{)NR}^5\text{R}^6, \text{NR}^5\text{SO}_2\text{R}^5, \text{SO}_2\text{R}^5, \text{SOR}^5, \text{(CO)Ci}_{4-6} \text{alkylNR}^5\text{R}^6, \text{(SO}_2\text{)Ci}_{6} \text{alkylNR}^5\text{R}^6, \text{OSO}_2\text{R}^5, \text{Ci}_{6} \text{alkyl, } \text{C}_{2-6} \text{alkenyl,} \]
C₂₋₆ alkynyl, C₀₋₆ alkyl, C₃₋₈ cycloalkyl, C₀₋₆ alkylnyl, C₀₋₆ alkylnyl and Co₋₆ alkylnylheterocyclyl;

D is selected from halogen, nitro, SF₅, OSF₅, CN, OR³⁻, OC₂₋₆ alkylnR¹⁴, NR¹⁴R¹⁴, CONR¹³⁻¹⁴, NR¹³(CO)R¹⁴, O(CO)C₁₋₆ alkylnyl, (CO)OOC₁₋₆ alkyln, COR¹³, (SO₂)NR¹³⁻¹⁴, NR¹³SO₂R¹⁴, SO₂R¹³, SOR¹³, (CO)₂₋₆ alkylnR¹³⁻¹⁴, (SO₂)C₁₋₆ alkylnR¹³⁻¹⁴, OSO₂R¹³, C₁₋₆ alkylnyl, C₂₋₆ alkenyl, C₂₋₆ alkylnyl, Co₋₆ alkylnC₃₋₈ cycloalkyl, and Co₋₆ alkylnheterocyclyl;

R¹₀ is independently selected from halogen, nitro, SF₅, OSF₅, CN, OR¹¹⁻, C=CR¹¹⁻, OC₂₋₆ alkylnR¹², NR¹¹⁻¹², CONR¹¹⁻¹², NR⁻¹(CO)R¹⁻², 0(CO)C₁₋₆ alkylnyl, (CO)OC₁₋₆ alkylnyl, COR¹¹⁻, (SO₂)NR¹¹⁻¹², NR¹¹⁻SO₂R¹¹⁻, SO₂R¹¹⁻, SOR¹¹⁻, (CO)²₋₆ alkylnR¹¹⁻¹², (SO₂)C₁₋₆ alkylnR¹¹⁻¹², OSO₂R¹¹⁻, C₁₋₆ alkylnyl, C₂₋₆ alkenyl, C₂₋₆ alkylnyl, Co₋₆ alkylnC₃₋₈ cycloalkyl, Co₋₆ alkylnary, Co₋₆ alkylnheteroaryl, Co₋₆ alkylnheterocyclyl and OC₂₋₆ alkylnheterocyclyl, wherein said C₁₋₆ alkylnyl, C₂₋₆ alkenyl, Co₋₆ alkylnC₃₋₈ cycloalkyl, Co₋₆ alkylnary, Co₋₆ alkylnheteroaryl, Co₋₆ alkylnheterocyclyl or OC₂₋₆ alkylnheterocyclyl is optionally substituted with one or more E, and wherein any of the individual aryl or heteroaryl groups may be optionally fused with a 4, 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclyl group to form a bicyclic ring system where the bicyclic ring system is optionally substituted with one or more E;

R¹¹ is independently selected from hydrogen, C₁₋₆ alkylnyl, C₂₋₆ alkenyl, C₂₋₆ alkylnyl, Co₋₆ alkylnC₃₋₈ cycloalkyl, Co₋₆ alkylnary, Co₋₆ alkylnheteroaryl, and Co₋₆ alkylnheterocyclyl, wherein any of the individual C₁₋₆ alkylnyl, C₂₋₆ alkenyl, C₂₋₆ alkylnyl, Co₋₆ alkylnC₃₋₈ cycloalkyl, Co₋₆ alkylnary, Co₋₆ alkylnheteroaryl and Co₋₆ alkylnheterocyclyl groups may be optionally substituted with one or more E;

R¹² is selected from hydrogen, C₁₋₆ alkylnyl, C₂₋₆ alkenyl, C₂₋₆ alkylnyl, Co₋₆ alkylnC₃₋₈ cycloalkyl, Co₋₆ alkylnary, Co₋₆ alkylnheteroaryl, and Co₋₆ alkylnheterocyclyl, wherein any of the individual C₁₋₆ alkylnyl, C₂₋₆ alkenyl, C₂₋₆ alkylnyl, Co₋₆ alkylnC₃₋₈ cycloalkyl, Co₋₆ alkylnary, Co₋₆ alkylnheteroaryl and Co₋₆ alkylnheterocyclyl groups may be optionally substituted with one or more E; or
R\textsuperscript{11} and R\textsuperscript{12} may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S that is optionally substituted with B; whenever two R\textsuperscript{11} groups occur in the structure then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, where the ring system is optionally substituted with one or more E;

R\textsuperscript{13} is independently selected from hydrogen, C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, Co\textsubscript{6} alkylC\textsubscript{3-8}cycloalkyl, Co\textsubscript{6} alkylaryl, Co\textsubscript{6} alkylheteroaryl and Co\textsubscript{6} alkylheterocyclyl;

R\textsuperscript{14} is selected from hydrogen, Ci\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, Co\textsubscript{6} alkylOR\textsubscript{5}, Co\textsubscript{6} alkylC\textsubscript{3-8}cycloalkyl, Co\textsubscript{6} alkylaryl, Co\textsubscript{6} alkylheteroaryl and Co\textsubscript{6} alkylheterocyclyl; or

R\textsuperscript{13} and R\textsuperscript{14} may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S; whenever two R\textsuperscript{13} groups occur in the structure then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S;

E is selected from halogen, nitro, SF\textsubscript{5}, OSF\textsubscript{5}, CN, OR\textsubscript{5}, OC\textsubscript{2-6} alkylNR\textsubscript{5}R\textsubscript{6}, NR\textsubscript{5}R\textsubscript{6}, CONR\textsubscript{5}R\textsubscript{6}, NR\textsubscript{5}(CO)R\textsubscript{6}, O(CO)C\textsubscript{i-6} alkyl, (CO)OC\textsubscript{i-6} alkyl, COR\textsubscript{5}, (SO\textsubscript{2})NR\textsubscript{5}R\textsubscript{6}, NR\textsubscript{5}SO\textsubscript{2}R\textsubscript{5}, SO\textsubscript{2}R\textsubscript{5}, SOR\textsubscript{5}, (CO)C\textsubscript{i-6} alkylNR\textsubscript{5}R\textsubscript{6}, (SO\textsubscript{2})C\textsubscript{i-6} alkylNR\textsubscript{5}R\textsubscript{6}, OSO\textsubscript{2}R\textsubscript{5}, Ci\textsubscript{6} alkyl, C\textsubscript{2-6} alkenyl, Co\textsubscript{6} alkylC\textsubscript{3-8}cycloalkyl, Co\textsubscript{6} alkylaryl, Co\textsubscript{6} alkylheteroaryl and Co\textsubscript{6} alkylheterocyclyl;

m = 0,1,2,3,4;

n = 0,1,2;

for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of microsomal prostaglandin E synthase-1 activity is beneficial.
In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for use in the treatment of an inflammatory disease or condition.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for use in treating osteoarthritis, rheumatoid arthritis, acute or chronic pain, neuropathic pain, apnea, SID, wound healing, cancer, benign or malignant neoplasias, stroke, atherosclerosis or Alzheimer's disease.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for use in treating acute or chronic pain, nociceptive pain, neuropathic pain, apnea, sudden infant death (SID), atherosclerosis, cancer, aneurysm, hyperthermia, myositis, Alzheimer's disease or arthritis.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for use in treating osteoarthritis, rheumatoid arthritis, benign or malignant neoplasias or acute or chronic pain.

In another aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined for use as a medicament.

In another aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined for the treatment of diseases or conditions in which modulation of microsomal prostaglandin E synthase-1 activity is beneficial.

In another aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined for the treatment of an inflammatory disease or condition.

In another aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined for the treatment of osteoarthritis, rheumatoid arthritis, acute or chronic pain, neuropathic pain, apnea, SID, wound healing, cancer, benign or malignant neoplasias, stroke, atherosclerosis or Alzheimer's disease.
In another aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined for the treatment of osteoarthritis, rheumatoid arthritis, benign or malignant neoplasias or acute or chronic pain.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

The invention also provides a method of treating, or reducing the risk of, a disease or condition in which modulation of microsomal prostaglandin E synthase-1 activity is beneficial which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

The invention still further provides a method of treating, or reducing the risk of, an inflammatory disease or condition which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

The invention still further provides a method of treating, or reducing the risk of, osteoarthritis, rheumatoid arthritis, acute or chronic pain, neuropathic pain, apnea, SID, wound healing, cancer, benign or malignant neoplasias, stroke, atherosclerosis or Alzheimer's disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

The invention still further provides a method of treating, or reducing the risk of, osteoarthritis, rheumatoid arthritis, benign or malignant neoplasias or acute or chronic pain which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.
For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of the invention may be in the range from 0.05 mg/kg to 100 mg/kg.

The compounds of formula (I) and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin) in the form, e.g., of creams, solutions or suspensions; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

For oral administration the compound of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into
If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above-mentioned excipients for tablets. Also liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of the above conditions.

Thus, the invention further relates to combination therapies wherein a compound of formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of formula (I) is administered concurrently, simultaneously, sequentially or separately with another pharmaceutically active compound or compounds selected from the following:

(i) neuropathic pain therapies including for example gabapentin, lidoderm, pregablin and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(ii) nociceptive pain therapies such as celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib, diclofenac, loxoprofen, naproxen, paracetamol and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

(iii) migraine therapies including for example almotriptan, amantadine, bromocriptine, butalbital, cabergoline, dichloralphenazone, eletriptan, frovatriptan, lisuride, naratriptan,
pergolide, pramipexole, rizatriptan, ropinirole, sumatriptan, zolmitriptan, zomitriptan, and equivalents and pharmaceutically active isomer(s) and metabolite(s) thereof.

Such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active compound or compounds within approved dosage ranges and/or the dosage described in their respective publication reference(s).

Chemical names were generated by CambridgeSoft MedChem ELN v2.1.

The present invention will now be further explained by reference to the following illustrative examples.

**General Methods**

All solvents used were analytical grade and commercially available anhydrous solvents were routinely used for reactions. Reactions were typically run under an inert atmosphere of nitrogen or argon.

$^1$H, $^{19}$F and $^{13}$C NMR spectra were recorded on a Varian Unity+ 400 NMR Spectrometer equipped with a 5mm BBO probehead with Z-gradients, or a Varian Gemini 300 NMR spectrometer equipped with a 5mm BBI probehead, or a Bruker Avance 400 NMR spectrometer equipped with a 60 µl dual inverse flow probehead with Z-gradients, or a Varian Mercury Plus 400 NMR Spectrometer equipped with a Varian 400 ATB PFG probe, or a Bruker DPX400 NMR spectrometer equipped with a 4-nucleus probehead equipped with Z-gradients, or a Bruker Avance 600 NMR spectrometer equipped with a 5mm BBI probehead with Z-gradients, or Bruker 500MHz Avance III NMR spectrometer, operating at 500 MHz for $^1$H, 125 MHz for $^{13}$C, and 50 MHz for $^{15}$N equipped with a 5mm TXI probehead with Z-gradients.

Unless specifically noted in the examples, spectra were recorded at 400 MHz for proton, 376 MHz for fluorine-19 and 100 MHz for carbon-13.

The following reference signals were used: the middle line of DMSO-$d_6$ δ 2.50 (IH), δ 39.51 (13C); the middle line of CD$_3$OD δ 3.31 (IH) or δ 49.15 (13C); CDCl$_3$ δ 7.26 (IH)
and the middle line of CDCl$_3$ $\delta$ 77.16 (13C) (unless otherwise indicated). NMR spectra are
either reported from high to low field or from low to high field.

Mass spectra were recorded on a Waters LCMS consisting of an Alliance 2795 (LC),
Waters PDA 2996 and a ZQ single quadrupole mass spectrometer. The mass spectrometer
was equipped with an electrospray ion source (ESI) operated in a positive or negative ion
mode. The capillary voltage was 3 kV and cone voltage was 30 V. The mass spectrometer
was scanned between $m/z$ 100-700 with a scan time of 0.3s. Separations were performed on
either Waters X-Terra MS C8 (3.5 µm, 50 or 100 mm x 2.1 mm i.d.) or an ACE 3 AQ (100
mm x 2.1 mm i.d.) obtained from ScantecLab. Flow rates were regulated to 1.0 or 0.3
mL/min, respectively. The column temperature was set to 40 °C. A linear gradient was
applied using a neutral or acidic mobile phase system, starting at 100% A (A: 95:5 10 mM
NH$_4$OAc:MeCN, or 95:5 8 mM HCOOH:MeCN) ending at 100% B (MeCN).

Alternatively, mass spectra were recorded on a Waters LCMS consisting of an Alliance
2690 Separations Module, Waters 2487 Dual 1 Absorbance Detector (220 and 254 nm) and
a Waters ZQ single quadrupole mass spectrometer. The mass spectrometer was equipped
with an electrospray ion source (ESI) operated in a positive or negative ion mode. The
capillary voltage was 3 kV and cone voltage was 30 V. The mass spectrometer was
scanned between $m/z$ 97-800 with a scan time of 0.3 or 0.8 s. Separations were performed on
a Chromolith Performance RP-18e (100 x 4.6 mm). A linear gradient was applied
starting at 95% A (A: 0.1% HCOOH (aq.)) ending at 100% B (MeCN) in 5 minutes. Flow
rate: 2.0 mL/min.

Alternatively, LC-MS analyses were performed on a LC-MS system consisting of a Waters
Alliance 2795 HPLC, a Waters PDA 2996 diode array detector, a Sedex 85 ELS detector
and a ZQ single quadrupole mass spectrometer. The mass spectrometer was equipped with
an electrospray ion source (ESI) operated in positive and negative ion mode. The capillary
voltage was set to 3.3 kV and the cone voltage to 28 V, respectively. The mass
spectrometer scanned between $m/z$ 100-800 with a scan time of 0.3s. The diode array
detector scanned from 200-400 nm. The temperature of the ELS detector was adjusted to
40 °C and the pressure was set to 1.9 bar. Separation was performed on an Gemini C18,
3.0 mm x 50 mm, 3 µm, (Phenomenex) run at a flow rate of 1 ml/min. A linear gradient
was applied starting at 100% A (A: 10mM NH$_4$OAc in 5% CH3CN) ending at 100% B (B:
CH₃CN) in 4.0 min followed by 100 % B until 5.5 min. The column oven temperature was set to 40 °C.
Alternatively, LC-MS analyses were performed on a LC-MS consisting of a Waters sample manager 2777C, a Waters 1525 µl binary pump, a Waters 1500 column oven, a Waters ZQ single quadrupole mass spectrometer, a Waters PDA2996 diode array detector and a Sedex 85 ELS detector. The mass spectrometer was configured with an atmospheric pressure chemical ionisation (APCI) ion source which was further equipped with atmospheric pressure photo ionisation (APPI) device. The mass spectrometer scanned in the positive mode, switching between APCI and APPI mode. The mass range was set to m/z 100-800 using a scan time of 0.1 s. The APPI repeller and the APCI corona were set to 0.58 kV and 0.70 µA, respectively. In addition, the desolvation temperature (350°C), desolvation gas (450 L/Hr) and cone gas (0 L/Hr) were constant for both APCI and APPI mode. Separation was performed using a Gemini column C18, 3.0 mm x 50 mm, 3 µm, (Phenomenex) and run at a flow rate of 0.8 ml/min. A linear gradient was used starting at 100 % A (A: 10 mM NH₄OAc in 5% MeOH) and ending at 100% B (MeOH) in 4.0 min followed by 100 % B until 5.5 min. The column oven temperature was set to 55 °C.
Microwave irradiation was performed in a Creator™, Initiator™ or Smith Synthesizer™ single-mode microwave cavity producing continuous irradiation at 2450 MHz.
HPLC analyses were performed on an Agilent HPIIOO system consisting of G1379A Micro Vacuum Degasser, G1312A Binary Pump, G1367A Well plate auto-sampler, G1316A Thermostatted Column Compartment and G1315B Diode Array Detector.
Column: X-Terra MS, Waters, 3.0 x 100 mm, 3.5 µm. The column temperature was set to 40 °C and the flow rate to 1.0 ml/min. The Diode Array Detector was scanned from 210-300 nm, step and peak width were set to 2 nm and 0.05 min, respectively. A linear gradient was applied, starting at 100 % A (A: 95:5 10 mM NH₄OAc:MeCN) and ending at 100% B (B: MeCN), in 4 min.
Alternatively, HPLC analyses were performed on a Gynkotek P580 HPG consisting of gradient pump with a Gynkotek UVD 170S UV-vis.-detector equipped with a Chromolith Performance RP column (C18, 100 mm x 4.6 mm). The column temperature was set to 25 °C. A linear gradient was applied using MeCN/0. 1 trifluoroacetic acid in MilIIQ water, run from 10% to 100% MeCN in 5 minutes. Flow rate: 3 ml/min.
Thin layer chromatography (TLC) was performed on Merck TLC-plates (Silica gel 60 F254) and UV visualized the spots. Flash chromatography was performed on a Combi Flash™ Companion™ using RediSep™ normal-phase flash columns or using Merck Silica gel 60 (0.040-0.063 mm). Typical solvents used for flash chromatography were mixtures of chloroform/methanol, dichloromethane/methanol, heptane/ethyl acetate, chloroform/methanol/ammonia (aq.) and dichloromethane/methanol/ NH3 (aq.). SCX ion exchange columns were performed on Isolute™ columns. Chromatography through ion exchange columns were typically performed in solvents such a methanol.

Preparative chromatography was run on a Waters autopurification HPLC with a diode array detector. Column: XTerra MS C8, 19 x 300 mm, 10 μm. Narrow gradients with MeCN/(95:5 0.1M NH₄OAc:MeCN) were used at a flow rate of 20 ml/min. Alternatively, purification was achieved on a semi preparative Shimadzu LC-8A HPLC with a Shimadzu SPD-IOA UV-vis.-detector equipped with a Waters Symmetry® column (C18, 5 μm, 100 mm x 19 mm). Narrow gradients with MeCN/0.1% trifluoroacetic acid in MilliQ Water were used at a flow rate of 10 ml/min.

GCMS compound identification was performed on a GC/DIP-MS system supplied by Agilent Technologies consisting of a GC 6890N, G1530N, a G2614A Autosampler, G2613A injector and a G2589N mass spectrometer. The mass spectrometer was equipped with a Direct Inlet Probe (DIP) interface manufactured by SIM GmbH. The mass spectrometer was equipped with an electron impact (EI) ion source and the electron voltage was set to 70 eV. The mass spectrometer scanned between m/z 50-550 and the scan speed was set to 2.91 scan/s. Solvent delay was set from 0 min to 2.3 min. The column used was a VF-5 MS, ID 0.25 mm x 15m, 0.25 μm (Varian Inc.). When introduced by GC, a linear temperature gradient was applied starting at 40-1 10 °C (hold 1 min) and ending at 200-300 °C (hold 1 min), 25 °C/minute, depending on method used.

Preparative chromatography was run on a Waters FractionLynx system with a Autosampler combined Automated Fraction Collector (Waters 2767), Gradient Pump (Waters 2525), Column Switch (Waters CFO) and PDA (Waters 2996). Column; XTerra® Prep MS C8 10 μm OBD™ 19 x 300 mm, with guard column; XTerra® Prep MS C8 10
µm 19 x 10 mm Cartridge. A gradient from 100% A (95% 0.1M NH₄OAc in MiIIIQ water and 5% MeCN) to 100% B (100% MeCN) was applied for LC-separation at flow rate 20 mL/min. The PDA was scanned from 210-350 nm. UV triggering determined the fraction collection.

Alternatively, preparative chromatography was run on a Waters FractionLynx system with a Autosampler combined Automated Fraction Collector (Waters 2767), Gradient Pump (Waters 2425), Make Up Pump (Waters 515), Waters Passive Splitter, Column Switch (Waters SFO), PDA (Waters 2996) and Waters ZQ mass spectrometer. Column; XBridge™ Prep C8 5 µm OBD™ 19 x 250 mm, with guard column; XTerra ® Prep MS C8 10 µm 19 x 10 mm Cartridge. A gradient from within 100% A (95% 0.1 M NH₄OAc in MiIIIQ water and 5% MeCN) to 100% B (100% MeCN) was applied for LC-separation at flow rate 20 mL/min. The PDA was scanned from 210-350 nm. The ZQ mass spectrometer was run with ESI in positive or negative mode. The Capillary Voltage was 3kV and the Cone Voltage was 30V. Mixed triggering, UV and MS signal, determined the fraction collection.

Abbreviations:

PPSE  trimethylsilylpolyphosphate ester
DMAP  4-(dimethylamino)pyridine
DMF  7V,7V-dimethylformamide
DMSO  dimethyl sulfoxide
EDC  1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
RT  room temperature
Rt  retention time
tert  tertiary
DCM  dichloromethane
THF  tetrahyrofuran
Example 1

5-Benzofuran-2-yl-N-(2-sulfamoylphenyl)sulfonyl-pyridine-2-carboxamide

![Chemical Structure]

5-Bromo-N-(2-sulfamoylphenyl)sulfonyl-pyridine-2-carboxamide (57 mg, 0.14 mmol) was dissolved in DMF (800 µl), then benzofuran-2-boronic acid (24 mg, 0.15 mmol) was added followed by the addition of 2M sodium carbonate solution (400 µl). The mixture was subjected to vacuum / argon (x 3); tetrakis(triphenylphosphine)palladium (8 mg, 0.05 mol %) was added and the reaction was allowed to stir at 90 °C overnight. Water was added to the cooled mixture that was then acidified (HCl). The resulting solid was filtered off, washed with water and was then purified by preparative HPLC (XTerra MS C8 column, acetonitrile / ammonium acetate buffer) to give the title compound as a solid (15 mg, 24% yield).

1H NMR (400 MHz, MeOH) δ ppm 9.08 (d, 1 H), 8.38 (dd, 1 H), 8.33 (dd, 1 H), 8.17 - 8.24 (m, 2 H), 7.62 - 7.74 (m, 3 H), 7.58 (d, 1 H), 7.44 (s, 1 H), 7.31 - 7.39 (m, 1 H), 7.27 (t, 1 H).

MS m/z M-H 455.7, M+H 457.7.

a) 5-Bromo-N-(2-sulfamoylphenyl)sulfonyl-pyridine-2-carboxamide

Benzene-1,2-disulfonamide (1.0 g, 4.2 mmol), 5-bromopicolinic acid (1.3 g, 6.3 mmol), EDC (1.22 g, 6.3 mmol) and DMAP (1.3 g, 10.5 mmol) were mixed in DMF (25 ml) and the reaction mixture was stirred for 3 hours. The reaction mixture was diluted with water and washed twice with ethyl acetate. The aqueous layer was acidified (HCl) and the resulting solid was filtered off, washed with water then dried (high vacuum over P₂O₅) to give the title compound as a solid (1.4 g, 79% yield).
\( ^1H \) NMR (400 MHz, DMSO-\( \text{d}_6 \)) \( \delta \) ppm 8.87 (dd, 1 H), 8.36 (dd, 1 H), 8.30 (dd, 1 H), 8.16 (dd, 1 H), 7.87 - 7.97 (m, 3 H), 7.57 (br. s., 2 H); MS m/z M-H 417.6, 419.6, M+H 419.6, 421.6.

Example 2

5-(2,3-Dichlorophenyl)-N-[(2-sulfamoylphenyl)sulfonyl]pyridine-2-carboxamide

The title compound was synthesized using 2,3-dichlorophenylboronic acid and following an analogous preparation to that described for Example 1 (4 mg, 6% yield).

\( ^1H \) NMR (400 MHz, MeOH) \( \delta \) ppm 8.60 (d, 1 H), 8.39 (dd, 1 H), 8.17 - 8.23 (m, 2 H), 7.95 (dd, 1 H), 7.65 - 7.76 (m, 2 H), 7.62 (dd, 1 H), 7.33 - 7.46 (m, 2 H); MS m/z M-H 483.7, 485.7, M+H 485.9, 487.9.

Example 3

4-Benzofuran-2-yl-N-[(2-sulfamoylphenyl)sulfonyl]benzamide

Benzene-1,2-disulfonamide (118 mg, 0.5 mmol), 4-benzofuran-2-ylbenzoic acid (153 mg, 0.65 mmol), EDC (124 mg, 0.65 mmol) and DMAP (183 mg, 1.5 mmol) were mixed in DMF (3 ml) and the reaction mixture was stirred for 3 hours. The reaction mixture was diluted with water (0.5 ml) and filtered. The filtrate was purified by HPLC to give the product as a solid (70 mg, 15% yield).
example 4

4-Benzothiophen-2-yl-N-(2-sulfamoylphenyl)sulfonyl-benzamide

\[
\begin{align*}
\text{O} & \quad \text{NH}_2 \\
\text{S} & \quad \text{O} \\
\text{O} & \\
\text{S} & \quad \text{O} \\
\end{align*}
\]

The title compound was synthesized using the appropriate benzoic acid derivative and following an analogous preparation to that described for Example 3 (7 mg, 30% yield).

\[ ^1\text{H NMR (400 MHz, MeOH) } \delta \text{ ppm 8.48 (br. s., 1 H) 8.28 (dd, 1 H) 7.96 (d, 2 H) 7.79 - 7.89 (m, 7 H) 7.31 - 7.40 (m, 2 H).} \]

MS m/z M-H 471.2.

example 5

4-Benzothiazol-2-yl-N-(2-sulfamoylphenyl)sulfonyl-benzamide

\[
\begin{align*}
\text{O} & \quad \text{NH}_2 \\
\text{S} & \quad \text{O} \\
\text{O} & \\
\text{S} & \quad \text{N} \\
\end{align*}
\]

Benzene- 1,2-disulfonamide (50 mg, 0.21 mmol), 4-benzothiazol-2-ylbenzoic acid (81 mg, 0.32 mmol), DMAP (65 mg, 0.53 mmol) and EDC (61 mg, 0.32 mmol) were mixed in DMF (1.8 ml) and the reaction mixture was stirred until a clear solution was obtained (2 h). The crude product was purified by preparative HPLC (XTerra MS C8 column, acetonitrile / ammonium acetate buffer) to give the title compound as a solid (28 mg, 28% yield).
1H NMR (400 MHz, MeOH)  δ ppm 8.34 (dd, 1 H), 8.19 (dd, 1 H), 8.14 - 8.17 (m, 2 H), 8.08 - 8.12 (m, 2 H), 8.01 - 8.06 (m, 2 H), 7.67 - 7.72 (m, 1 H), 7.62 - 7.67 (m, 1 H), 7.52 - 7.57 (m, 1 H), 7.42 - 7.48 (m, 1 H).

MS m/z M-H 472.0, M+H 473.7.

Example 6

4-(7-Oxa-3,9-diazabicyclo[43.0]nona-2,4,8,10-tetraen-8-yl)-N-(2-sulfamoylphenyl)-sulfonyl-benzamide

[Chemical structure image]

The title compound was obtained as a solid (40 mg, 21 % yield) using the appropriate benzoic acid derivative and following an analogous procedure to that described for Example 5 except the reaction was heated to 50 °C for 2 h to give a clear solution.

1H NMR (400 MHz, DMSO-J 6)  δ ppm 9.21 (s, 1 H), 8.65 (d, 1 H), 8.25 - 8.33 (m, 3 H), 8.07 - 8.15 (m, 3 H), 8.00 (d, 1 H), 7.75 - 7.86 (m, 2 H), 7.47 (br. s., 2 H).

MS m/z M-H 457.0, M+H 459.0.

a) 4-(1,3]Oxazolo[4,5-c]pyridin-2-yl)benzoic Acid

To a solution of methyl 4-(oxazolo[4,5-c]pyridin-2-yl)benzoate (1.27 g, 5.0 mmol) in MeOH (20 ml) and THF (20 ml), was added an 2N aqueous solution of LiOH (5 ml, 10.0 mmol). The reaction mixture was stirred at RT for 20h and then concentrated to one third volume. The solid was filtered off, washed with CH3CN (3 x) and diethyl ether, and dried over P2O5 at 50 °C under reduced pressure to give lithium 4-(1,3]oxazolo[4,5-c]pyridin-2-yl)benzoate (0.98 g, 80%).

1H NMR (DMSO-J 6 ACOH)  δ 7.93 (d, IH), 8.17 (d, 2H), 8.33 (d, 2H), 8.63 (d, IH), 9.17 (s, IH).

b) Methyl 4-(oxazolo[4,5-c]pyridin-2-yl)benzoate

A solution of PPSE was prepared by heating to reflux a mixture of P₂O₅ (4.26 g, 15 mmol) and hexamethyldisiloxane (12.75 ml, 60 mmol) in 1,2-dichlorobenzene (30 ml) under an argon atmosphere until the solution becomes clear (~ 5 min.).

Methyl 4-(4-hydroxyppyridin-3-ylcarbamoyl)benzoate (2.91 g, 10 mmol) was added to PPSE at 180 °C (oil bath temperature) and the mixture was refluxed with vigorous stirring for 2h. After cooling, a precipitate appeared. Diethyl ether was added to the reaction mixture, the solid was collected by filtration and washed with diethyl ether. The solid was then suspended in DCM - MeOH and the mixture was neutralised with aqueous saturated NaHCO₃ solution. The aqueous layer was back extracted with DCM, the organic layers were combined and washed with brine, dried over MgSO₄ and concentrated. The remaining solid was triturated with diethyl ether, filtered, washed with diethyl ether and dried under vacuo at 50 °C to afford methyl 4-(oxazolo[4,5-c]pyridin-2-yl)benzoate (1.00 g, 79%).

1H NMR (DMSO-δ₆): δ 3.88 (s, 3H), 6.31 (d, 1H), 7.71 (d, 1H), 8.01 (d, 2H), 8.09 (d, 2H), 8.75 (s, 1H), 9.43 (s, 1H).

LCMS (EIC) for C₁₄H₁₀N₂O₃ (M = 254.25): 254 [Mf⁺].

c) Methyl 4-(hydroxyppyridin-3-ylcarbamoyl)benzoate

A mixture of terephthalic acid monomethyl ester (7.20 g, 40 mmol), SOCl₂ (60 ml) and DMF (50 µl) was stirred at reflux for 1h. After removal of the excess SOCl₂, the residue was azeotroped with toluene (3 x) to remove the residual SOCl₂. The crude acid chloride was dissolved in DCM (10 ml) and added dropwise at 0 °C to a solution of 3-amino-4-hydroxyppyridine (7.32 g, 40 mmol) in pyridine (40 ml). The reaction mixture was stirred at RT during 2.5 days. Pyridine was evaporated and water was added to the residue. The solid was filtered off, washed with water (3 x), a mixture 1:3 of CH₃CN - diethyl ether, diethyl ether and dried under vacuo at 60 °C to afford methyl 4-(4-hydroxyppyridin-3-ylcarbamoyl)benzoate (9.70 g, 89%) which was used without further purification.

1H NMR (DMSO-δ₆): δ 3.88 (s, 3H), 6.31 (d, 1H), 7.71 (d, 1H), 8.01 (d, 2H), 8.09 (d, 2H), 8.75 (s, 1H), 9.43 (s, 1H).
Example 7

4-(7-Oxa-5,9-diazabicyclo[43.0]nona-2,4,8,10-tetraen-8-yl)-N-(2-sulfamoylphenyl)-
sulfonyl-benzamide

The title compound was obtained as a solid (12 mg, 11 % yield) using the appropriate
benzoic acid derivative and following an analogous procedure to that described for
Example 5 except the reaction was heated to 50 °C for 2 h to give a clear solution.

\[^1\text{H} \text{NMR (400 MHz, MeOH)} \delta \text{ ppm 8.32 - 8.40 (m, 2 H), 8.28 (d, 2 H), 8.15 - 8.24 (m, 4 H), 7.60 - 7.74 (m, 2 H), 7.49 (dd, 1 H).}\]
\[\text{MS m/z M-H 457.0, M+H 458.7.}\]

a) 4-(Oxazolo[5,4-b]pyridin-2-yl)benzoic Acid

To a solution of methyl 4-(oxazolo[5,4-b]pyridin-2-yl)benzoate (1.016 g, 4.0 mmol) in
MeOH (12 ml) and THF (12 ml), was added an 2N aqueous solution of LiOH (4 ml, 8.0
mmol). The reaction mixture was stirred at RT for 15h. The solvents were evaporated off,
the residue diluted with CH$_2$CN to afford a solid, which was filtered off, washed with
CH$_2$CN and diethyl ether. The solid was then added to 6M HCl (15 ml) giving a white
precipitate which was filtered off, washed with water and dried over P2O$_5$ at 50 °C under
reduced pressure to give 4-(oxazolo[5,4-b]pyridin-2-yl)benzoic acid (0.60 g, 63%).

\[^1\text{H} \text{NMR (DMSO-D}_6\): \delta 7.53 (m, IH), 8.15 (d, 2H), 8.32 (m, 3H), 8.41 (d, 1H).}\]

LCMS (EIC) for C$_{13}$H$_8$N$_2$O$_3$ (M = 240.22): 240 [Mf$^+$.]

b) Methyl 4-(oxazolo[5,4-b]pyridin-2-yl)benzoate

A solution of PPSE (trimethylsilylpolypophosphate ester) was prepared according to the
literature (Aizpurua, J.M., Paloma, C. Bull Soc. Chim. Fr. 1984,142) by heating to reflux a
mixture OfP$_2$O$_5$ (3.124 g, 11 mmol) and hexamethyldisiloxane (9 ml, 42.3 mmol) in 1,2-
dichlorobenzene (20 ml) under an argon atmosphere until the solution became clear (~ 5 min.).

After cooling, methyl 4-(2-chloropyridin-3-ylcarbamoyl)benzoate (2.91 g, 10 mmol) was added to PPSE and the mixture was refluxed with vigorous stirring for 24 h. After cooling, diethyl ether was added to the reaction mixture, the precipitate was collected by filtration and washed with petroleum ether. The solid was then dissolved in DCM, the solution was washed with an aqueous saturated NaHCO₃ solution, dried over MgSO₄ and concentrated. A crystalline solid precipitate which was collected, washed with petroleum ether and dried under vacuo to afford methyl 4-(oxazolo[5,4-b]pyridin-2-yl)benzoate (2.06 g, 81%).

1H NMR (CDCl₃): δ 3.98 (s, 3H), 7.39 (dd, IH), 8.12 (d, IH), 8.22 (d, 2H), 8.22 (d, 2H), 8.39 (dd, IH).


c) Methyl 4-(2-chloropyridin-3-ylcarbamoyl)benzoate

A mixture of terephthalic acid monomethyl ester (2.70 g, 1.5 mmol), SOCl₂ (25 ml) and 5 drops of DMF was stirred at RT overnight. After removal of the excess SOCl₂, the residue was azeotroped with toluene (3 x) to remove the residual SOCl₂. The crude acid chloride was dissolved in THF (10 ml) and added dropwise to a solution of 2-chloropyridin-3-amine (1.93 g, 1.5 mmol) and triethylamine (2.8 ml, 2.0 mmol) in THF (30 ml) at 0 ºC. The reaction mixture was stirred at RT overnight; the precipitate was filtered off and the filtrate was concentrated. The crude solid was triturated with diethyl ether, filtered, washed with diethyl ether and dried under vacuo to afford methyl 4-(2-chloropyridin-3-ylcarbamoyl)benzoate (2.68 g, 61%) as a white solid. The filtrate was evaporated and the residue was purified by flash chromatography (DCM/EtOAc 95:5) to afford a second batch of methyl 4-(2-chloropyridin-3-ylcarbamoyl)benzoate (0.63 g, 14%).

1H NMR (CDCl₃): δ 4.02 (s, 3H), 7.35 (dd, IH), 7.98 (d, 2H), 8.18 (dd, IH), 8.21 (d, 2H), 8.45 (s, IH), 8.91 (dd, IH).

Example 8

4-Benzoxazol-2-yl-N-(2-sulfamoylphenyl)sulfonyl-benzamide

\[
\text{Benzene-1,2-disulfonamide (50 mg, 0.21 mmol), 4-benzoxazol-2-ylbenzoic acid (51 mg, 0.21 mmol), DMAP (65 mg, 0.53 mmol) and EDC (57 mg, 0.29 mmol) were mixed in DMF (1.8 ml) and the reaction mixture was stirred for 1 h at RT, then at 50 °C until a clear solution was obtained (30 min). The crude material was purified by preparative HPLC (XTerra MS C8 column, acetonitrile/ammonium acetate buffer) to give the title compound as a solid (40 mg, 42% yield).}
\]

\[^1\text{H NMR (400 MHz, MeOH) }\delta \text{ ppm 8.51 (dd, 1 H), 8.33 (d, 2 H), 8.25 - 8.30 (m, 1 H), 8.07 (d, 2 H), 7.82 - 7.89 (m, 2 H), 7.75 - 7.80 (m, 1 H), 7.71 (dd, 1 H), 7.38 - 7.51 (m, 2 H).} \]

\[\text{MS m/z M-H 456.0, M+H 457.8.}\]

Example 9

2-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-benzofuran-6-carboxamide

\[
\text{Benzene-1,2-disulfonamide (50 mg, 0.21 mmol), 2-phenylbenzofuran-6-carboxylic acid (Example 29a) (53 mg, 0.21 mmol), DMAP (57 mg, 0.46 mmol) and EDC (45 mg, 0.23 mmol) were mixed in DMF (1.8 ml) and the reaction mixture was stirred at RT until a clear solution was obtained (2 h). The crude material was purified by preparative HPLC}
\]
(XTerra MS C8 column, acetonitrile / ammonium acetate buffer) to give the title compound as a film (82 mg, 61% yield).

\[^1\text{H} \text{NMR} \ (400 \text{ MHz, MeOH}) \delta \text{ ppm} \ 8.34 \ (dd, 1 \text{ H}), 8.16 - 8.22 \ (m, 2 \text{ H}), 7.89 - 7.97 \ (m, 3 \text{ H}), 7.66 - 7.71 \ (m, 1 \text{ H}), 7.61 - 7.66 \ (m, 1 \text{ H}), 7.56 \ (d, 1 \text{ H}), 7.44 - 7.51 \ (m, 2 \text{ H}), 7.35 - 7.41 \ (m, 1 \text{ H}), 7.22 \ (s, 1 \text{ H}).\]

MS m/z M-H 455.0.

a) l-Phenyl-benzofuran-6-carboxylic acid

A mixture of 2-phenyl-benzofuran-6-carboxylic acid methyl ester (490 mg, 1.94 mmol) and LiOH.H\textsubscript{2}O (326 mg, 7.26 mmol) in ethanol (20 mL) was heated at reflux for 1 hour. The ethanol was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The aqueous layer was then separated and acidified to pH 4 using citric acid. The precipitated solid was isolated by filtration and dried under high vacuum to give 2-phenyl-benzofuran-6-carboxylic acid (240 mg, 52% yield).

\[^1\text{H} \text{NMR} \ (400 \text{ MHz, DMSO-d\textsubscript{6}}): \delta \ (ppm) \ 12.8 \ (br \ s, \text{ IH}), 8.14 \ (s, \text{ IH}), 8.02-7.96 \ (d, 2\text{ H}), 7.92-7.86 \ (d, \text{ IH}), 7.80-7.74 \ (dd, \text{ IH}), 7.60-7.52 \ (m, 3\text{ H}), 7.50-7.44 \ (m, \text{ IH}); \ ^{19}\text{F} \text{NMR} \ (400 \text{ MHz, DMSO-de}): \delta \ (ppm) \ -57.5.\]

ESMS: m/z [M+1] 238.89.

b) l-Phenyl-benzofuran-6-carboxylic acid methyl ester

A mixture of 3-hydroxy-4-iodo-benzoic acid methyl ester (2 g, 7.20 mmol), phenylacetylene (3.68 g, 36.02 mmol), CuI (68 mg, 0.35 mmol), Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (253 mg, 36.04 mmol) and tetramethylguanidine (8.3 g, 72.06 mmol) in DMF was heated at 60 °C for 10 minutes and then at RT overnight. The reaction mixture was poured into aqueous 2N HCl (70 mL) and the product was extracted with ethyl acetate. The combined extracts were washed with water, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography using 10-30% ethyl acetate/hexane as eluent afforded 2-phenyl-benzofuran-6-carboxylic acid methyl ester (430 mg, 24% yield).
1H NMR (400 MHz, CDCl₃): δ (ppm) 8.22 (s, 1H), 7.98-7.94 (m, 1H), 7.93-7.88 (m, 2H),
7.64-7.6 (m, 1H), 7.52-7.46 (m, 2H), 7.44-7.38 (s, 1H), 7.08 - 7.06 (s, 1H), 3.97 (s, 3H).
ESMS: m/z [M+H] 253.07.

Example 10

4-Bromo-N-(2-sulfamoylphenyl)sulfonyl-benzamide

Benzene-1,2-disulfonamide (118 mg, 0.5 mmol), 4-bromobenzoic acid (131 mg, 0.65 mmol), EDC (124 mg, 0.65 mmol) and DMAP (183 mg, 1.5 mmol) were mixed in DMF (3 ml) and the reaction mixture was stirred for 3 hours. The reaction mixture was diluted with water (0.5 ml) and filtered. The filtrate was purified by HPLC to give the product as a solid (91 mg, 43%).

1H NMR (400 MHz, DMSO- J₆) δ ppm 8.14 (d, 1H), 7.98 (d, 1H), 7.80 (d, 2H), 7.54 -
7.67 (m, 2H), 7.51 (d, 2H), 7.42 (s, 2H).

MS m/z M+H 419, 421, M-H 417, 419.

Example 11

4-Bromo-2-chloro-N-(2-sulfamoylphenyl)sulfonyl-benzamide

Benzene-1,2-disulfonamide (42 mg, 0.18 mmol), 2-chloro-4-bromobenzoic acid (131 mg, 0.65 mmol), EDC (48 mg, 0.25 mmol) and DMAP (76 mg, 0.63 mmol) were mixed in
DMF (1 ml) and the reaction mixture was stirred for 3 hours. The reaction mixture was
diluted with water (0.2 ml) and filtered. The filtrate was purified by HPLC to give the
product as a solid (42 mg, 51%).

$^1$H NMR (400 MHz, DMSO-$_d$$_6$) δ ppm 8.20 (dd, 1 H), 8.03 (d, 1 H), 7.59 - 7.72 (m, 3 H),
7.56 (d, 1 H), 7.48 (dd, 1 H), 7.36 (s, 2 H).

MS m/z, M-H 451, 453.

The compounds of Examples 12 to 21 and 23 were prepared using the appropriate
carboxylic acid derivative and following an analogous procedure to that described for
Example 11.

**Example 12**

4-Bromo-3-methyl-N-(2-sulfamoylphenyl)sulfonyl-benzamide

![Chemical Structure](attachment:image.png)

46 mg, 59%

$^1$H NMR (400 MHz, DMSO-$_d$$_6$) δ ppm 8.18 (d, 1 H), 8.03 (d, 1 H), 7.84 (s, 1 H), 7.62 -
7.74 (m, 2 H), 7.51 - 7.62 (m, 2 H), 7.42 (s, 2 H), 2.35 (s, 3 H).

MS m/z M+H 433, 435, M-H 431, 433.
Example 13

4-Bromo-3-fluoro-N-(2-sulfamoylphenyl)sulfonyl-benzamide

44 mg, 56%.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.15 (dd, 1 H), 7.99 (dd, 1 H), 7.54 - 7.71 (m, 5 H), 7.40 (s, 1 H).

MS m/z M-H 435, 437.

Example 14

4-Bromo-2-fluoro-N-(2-sulfamoylphenyl)sulfonyl-benzamide

40 mg, 51%.

$^1$H NMR (400 MHz, MeOH) $\delta$ ppm 8.34 (dd, 1 H), 8.19 (dd, 1 H), 7.75 (t, 1 H), 7.67 - 7.72 (m, 1 H), 7.62 - 7.67 (m, 1 H), 7.28 - 7.34 (m, 2 H).

MS m/z M-H 435, 437.
Example 15

4-Bromo-2-methyl-N-(2-sulfamoylphenyl)sulfonyl-benzamide

\[\begin{align*}
\text{S} & \quad \text{S} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{S} & \quad \text{S} \\
\text{O} & \quad \text{O} \\
\text{Ar} & \quad \text{Ar} \\
\end{align*}\]

48 mg, 62%.

$^1$H NMR (400 MHz, MeOH) $\delta$ ppm 8.40 - 8.44 (m, 1 H), 8.22 - 8.27 (m, 1 H), 7.74 - 7.82 (m, 2 H), 7.50 (d, 1 H), 7.33 - 7.40 (m, 2 H), 2.33 (s, 3 H).

MS m/z M-H 431, 433.

Example 16

2-(l-Adamantyl)-N-(2-sulfamoylphenyl)sulfonyl-acetamide

\[\begin{align*}
\text{S} & \quad \text{S} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{S} & \quad \text{S} \\
\text{O} & \quad \text{O} \\
\text{Ar} & \quad \text{Ar} \\
\end{align*}\]

35 mg, 47%.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 11.93 (br. s., 1 H), 8.25 (d, 1 H), 8.14 (d, 1 H), 7.79 - 7.96 (m, 2 H), 7.27 (s, 2 H), 1.98 (s, 2 H), 1.85 (br. s., 3 H), 1.56 - 1.66 (m, 3 H), 1.40 - 1.54 (m, 9 H).

MS m/z M+H 413, M-H 411.
Example 17

N-(2-Sulfamoylphenyl)sulfonylnorbornane-2-carboxamide

\[
\begin{align*}
\text{O} & \text{S} \quad \text{NH}_2 \\
\text{S} & \text{O} \\
\text{O} & \text{S} \quad \text{N} \quad \text{O} \\
\text{H} & \text{N}
\end{align*}
\]

22 mg, 34%.

MS m/z, M-H 357; Rt HPLC (XTerra) 1.85 min.

Example 18

l-Phenyl-N-(2-sulfamoylphenyl)sulfonylcyclohexane-l-carboxamide

\[
\begin{align*}
\text{O} & \text{S} \quad \text{NH}_2 \\
\text{S} & \text{O} \\
\text{O} & \text{S} \quad \text{N} \quad \text{O} \\
\text{H} & \text{N}
\end{align*}
\]

12 mg, 16%.

\(^1\text{H NMR (400 MHz, MeOH)}\) \(\delta\) ppm 8.08 - 8.27 (m, 2 H), 7.65 - 7.86 (m, 2 H), 7.16 - 7.28 (m, 5 H), 2.24 - 2.35 (m, 2 H), 1.69 - 1.79 (m, 2 H), 1.48 - 1.62 (m, 3 H), 1.35 - 1.48 (m, 2 H), 1.20 - 1.34 (m, 1 H).

MS m/z M-H 421.
Example 19

3-(Difluoromethoxy)-N-(2-sulfamoylphenyl)sulfonyl-benzamide

\[
\begin{align*}
\text{O} & \text{S} & \text{NH}_2 \\
\text{O} & \text{S} & \text{O} & \text{O} & \text{F} & \text{F} \\
\text{O} & \text{S} & \text{O} & \text{N} & \text{H} & \text{N} & \text{H} & \text{N}
\end{align*}
\]

40 mg, 55 %.

\(^1\text{H}\) NMR (400 MHz, MeOH) \(\delta\) ppm 8.34 - 8.40 (m, 1 H), 8.19 - 8.24 (m, 1 H), 7.81 (d, 1 H), 7.68 - 7.78 (m, 3 H), 7.43 (t, 1 H), 7.27 (dd, 1 H), 6.85 (t, 1 H).

MS m/z M+H 407, M-H 405.

Example 20

3-Bromo-4-fluoro-N-(2-sulfamoylphenyl)sulfonyl-benzamide

\[
\begin{align*}
\text{O} & \text{S} & \text{NH}_2 \\
\text{O} & \text{S} & \text{O} & \text{O} & \text{Br} & \text{F} \\
\text{O} & \text{S} & \text{O} & \text{N} & \text{H} & \text{N} & \text{H} & \text{N}
\end{align*}
\]

27 mg, 34 %.

\(^1\text{H}\) NMR (400 MHz, MeOH) \(\delta\) ppm 8.33 - 8.38 (m, 1 H), 8.19 - 8.24 (m, 2 H), 7.93 - 7.98 (m, 1 H), 7.68 - 7.77 (m, 2 H), 7.22 (t, 1 H).

MS m/z M-H 335, 337.
Example 21

N-(2-Sulfamoylphenyl)sulfonyl-3-(2,2,3,3-tetrafluoropropoxymethyl)benzamide

\[ \text{N-(2-Sulfamoylphenyl)sulfonyl-3-(2,2,3,3-tetrafluoropropoxymethyl)benzamide} \]

56 mg, 64%.

\[^{1}\text{H NMR (400MHz, DMSO-\text{d}6 \text{)} \delta ppm 8.31 - 8.35 (m, 1 H), 8.12 - 8.16 (m, 1 H), 7.82 - 7.93 (m, 4 H), 7.57 (d, 1 H), 7.48 (t, 1 H), 7.40 (s, 2 H), 6.54 (tt, 1 H), 4.66 (s, 2 H), 3.98 (t, 2 H).} \]

MS m/z M+H 485, M-H 483.

Example 22

4-Methyl-N-(2-sulfamoylphenyl)sulfonyl-2-[3-(trifluoromethyl)phenyl]l,3-thiazole-5-carboxamide

Benzene-1,2-disulfonamide (84 mg, 0.36 mmol), 4-methyl-2-[3-(trifluoromethyl)phenyl]l,3-thiazole-5-carboxylic acid (142 mg, 0.5 mmol), EDC (96 mg, 0.5 mmol) and DMAP (152 mg, 1.26 mmol) were mixed in DMF (2 ml) and the reaction mixture was stirred for 3 hours. The reaction mixture was diluted with water (0.5 ml) and filtered. The filtrate was purified by HPLC to give the product as a solid (77 mg, 42%).
1H NMR (400 MHz, MeOH) δ ppm 8.35 (dd, 1 H), 8.26 (s, 1 H), 8.15 - 8.23 (m, 2 H), 7.77 (d, 1 H), 7.64 - 7.75 (m, 3 H), 2.67 (s, 3 H).

MS m/z M+H 506.6, M-H 504.6.

Example 23

4-Chloro-2-fluoro-N-(2-sulfamoylphenyl)sulfonyl-benzamide

33 mg, 46%.

1H NMR (400 MHz, DMSO-Δ6) δ ppm 8.27 - 8.36 (m, 1 H), 8.13 - 8.19 (m, 1 H), 7.83 - 7.94 (m, 2 H), 7.68 (t, 1 H), 7.51 - 7.58 (m, 1 H), 7.33 - 7.47 (m, 3 H).

MS m/z M-H 391.

General procedure for Examples 24 - 25

To a solution of the appropriate carboxylic acid (1 mmol) in dry DMF (15 mL), benzene-1,2-disulfonamide (0.9 mmol), EDC (1 mmol) and DMAP (1 mmol) were added. The reaction mixture was heated at 40-45 °C for 4 to 17 hours. Most of the DMF was then removed under reduced pressure and the crude product was purified without further work-up using preparative HPLC. Alternatively, after removal of DMF, the residue was partitioned between ethyl acetate and aqueous IN HCl. The organic layer was separated, washed with water, dried over sodium sulfate and concentrated in vacuo. The crude product was then purified by flash column chromatography or recrystallization.
Example 24

2-Benzyl-4-chloro-N-(2-sulfamoylphenyl)sulfonyl-benzamide

Following the general procedure, 2-benzyl-4-chlorobenzoic acid (330 mg, 1.34 mmol) was reacted with benzene-1,2-disulfonamide (285 mg, 1.21 mmol), EDC (257 mg, 1.34 mmol) and DMAP (164 mg, 1.34 mmol) for 17 hours. Purification of the crude product by preparative HPLC afforded the title compound (60 mg, 11%).

$^1$H NMR (400 MHz, MeOH- $d_4$): $\delta$ (ppm) 8.48 (dd, 1H), 8.28 (dd, 1H), 7.76 - 7.95 (m, 2H), 7.56 (d, 1H), 7.08 - 7.34 (m, 5H), 7.03 (d, 2H), 4.03 (s, 2H).

ESMS: $m/z$ [M-I]: 463 and 465.

Example 25

2-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-benzofuran-5-carboxamide

Following the general procedure, 2-phenyl-benzofuran-5-carboxylic acid (200 mg, 0.83 mmol) was reacted with benzene-1,2-disulfonamide (179 mg, 0.75 mmol), EDC (161 mg, 0.84 mmol) and DMAP (103 mg, 0.84 mmol) for 4 hours. The crude product was purified by preparative HPLC to afford the title compound (62 mg, 16%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 9.53 (br s, 1H), 8.60 (d, 1H), 8.28 (d, 1H) 8.07 (br s, 1H), 7.92-7.79 (m, 4H), 7.76 (d, 1H), 7.56 (d, 1H), 7.47 (t, 2H), 7.4 (d, 1H), 7.07 (s, 1H), 5.73 (br s, 2H).

ESMS: $m/z$ [M-I] 454.92.
a) 1-Phenyl-benzofuran-S-carboxylic acid
A mixture of 2-phenyl-benzofuran-5-carboxylic acid methyl ester (1.7 g, 6.73 mmol) and LiOH.H₂O (1.14 g, 27.16 mmol) in ethanol (50 mL) was heated to reflux for 45 minutes. Most of the ethanol was then removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The aqueous layer was separated and acidified with citric acid to pH 4. The precipitated white solid was filtered off, washed with water and dried to afford 2-phenyl-benzofuran-5-carboxylic acid (710 mg, 44%).

¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 12.95 (br s, 1H), 8.29 (s, 1H), 7.96 (d, 2H), 7.74 (d, 1H), 7.60-7.50 (m, 3H), 7.50-7.41 (m, 2H).

ESMS: m/z [M+1] 238.96.

b) 1-Phenyl-benzofuran-S-carboxylic acid methyl ester
A mixture of methyl 4-hydroxy-3-iodobenzoate (1 g, 3.59 mmol), CuI (35 mg, 0.183 mmol), Pd(PPh₃)₂Cl₂ (127 mg, 0.180 mmol), tetramethylguanidine (4.14 g, 35.9 mmol) in DMF (20 mL) was stirred at RT for 10 minutes. Phenylacetylene (1.83 g, 17.98 mmol) was then added and the mixture was stirred for 2 hours at 60 °C and then at RT overnight. The reaction mixture was poured into 2N HCl (100 mL) and the product was extracted with ethyl acetate. The organic layer was washed with water, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 30% ethyl acetate/hexane to afford 2-phenyl-benzofuran-5-carboxylic acid methyl ester as a yellow solid (700 mg, 77%).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.33 (s, 1H) 8.03 (d, 1H) 7.89 (d, 2H) 7.56 (d, 1H) 7.48 (t, 2H) 7.41 (d, 1H) 7.09 (s, 1H) 3.96 (s, 3H).
Example 26

4-Methyl-N-(2-sulfamoylphenyl)sulfonyl-2-[4-(trifluoromethyl)phenyl]l,3-thiazole-5-carboxamide

4-Methyl-2-[4-(trifluoromethyl)phenyl]l,3-thiazole-5-carboxylic acid (122 mg, 0.42 mmol), triethylamine (42 mg, 0.42 mmol) and O-(lH-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium (HBTU) (160 mg, 0.42 mmol) were mixed in MeCN/DMF (3 ml, 2:1). After 10 minutes, benzene-1,2-disulfonamide (100 mg, 0.42 mmol) was added and the reaction mixture was stirred for 12-14 hours. The reaction mixture was filtered and purified by HPLC (XTerra MS C8 column, acetonitrile/ammonium acetate buffer) (138 mg, 65%).

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.09 - 8.21 (m, 3 H), 7.99-8.06 (d, 1 H), 7.80-7.89 (d, 2 H), 7.57-7.74 (m, 2 H), 7.35 (br s, 2 H), 2.56 (s, 3 H).

MS (ES-) 504, 505.

Example 27

2-(2,3-Dihydrobenzofuran-5-yl)-4-methyl-N-(2-sulfamoylphenyl)sulfonyl-l,3-thiazole-5-carboxamide

Benzene-1,2-disulfonamide (100 mg, 0.42 mmol), the carboxylic acid (110 mg, 0.42 mmol), EDC (80 mg, 0.42 mmol) and DMAP (103 mg, 0.84 mmol) were mixed in DMF (3
ml) and the reaction mixture was stirred for 12-15 hours. The reaction mixture was filtered and purified by HPLC (XTerra MS C8 column, acetonitrile / ammonium acetate buffer) to give the product as a solid (19 mg, 15%).

$^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.09 (d, 1 H), 7.88 (d, 1 H), 7.67-7.79 (m, 2 H), 7.47-7.65 (m, 3 H), 7.38 (s, 2 H), 6.86 (dd, 2 H), 3.07 (m, 2 H), 2.54 (s, 3 H).

MS (ES-) 478, 479.

The compounds of Examples 28 to 30 were prepared using the appropriate carboxylic acid derivative and following an analogous procedure to that described for Example 27.

**Example 28**

2-(4-Chlorophenyl)-4-methyl-N-(2-sulfamoylphenyl)sulfonyl-1,3-thiazole-5-carboxamide

![Chemical Structure](image)

22mg, 11%.

$^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.15 (dd, 1 H), 8.01 (dd, 1 H), 7.90-7.96 (m, 2 H), 7.64 - 7.70 (m, 1 H), 7.58 - 7.64 (m, 1 H), 7.51 - 7.56 (m, 2 H), 7.39 (s., 2 H), 2.57 (s, 3 H).
Example 29

4-Methyl-2-phenyl-N-(2-sulfamoylphenyl)sulfonyl-1,3-thiazole-5-carboxamide

\[
\begin{align*}
\text{NH}_2 & \\
\text{S} & \text{O} & \text{O} & \text{O} & \text{S} & \text{NH}_2
\end{align*}
\]

20mg, 11%.

\[^1H\text{ NMR (400 MHz, DMSO-}\delta\text{) } \delta \text{ ppm 8.15 (dd, 1 H), 8.01 (dd, 1 H), 7.88 - 7.95 (m, 2 H), 7.64 - 7.71 (m, 1 H), 7.57 - 7.64 (m, 1 H), 7.44 - 7.52 (m, 3 H), 7.39 (br. s., 2 H), 2.57 (s, 3 H).}\]

Example 30

4-Phenylmethoxy-N-(2-sulfamoylphenyl)sulfonyl-benzamide

\[
\begin{align*}
\text{O} & \text{S} & \text{NH} & \text{O} & \text{O} & \text{S} & \text{NH}_2
\end{align*}
\]

13mg, 14%.

\[^1H\text{ NMR (400 MHz, DMSO-}\delta\text{) } \delta \text{ ppm 8.28 (dd, 1 H), 8.18 (dd, 1 H), 7.92 - 7.98 (m, 2 H), 7.58 - 7.69 (m, 2 H), 7.40 - 7.45 (m, 2 H), 7.34 - 7.39 (m, 2 H), 7.27 - 7.33 (m, 1 H), 6.92 - 6.98 (m, 2 H), 5.11 (s, 2 H).}\]

General procedure for Examples 31-41

Stock solutions of carboxylic acids/acid chlorides in DMF were treated with EDC and DMAP. To these were added stock solutions of benzene-1,2-disulfonamide in DMF in 48 wells and the reaction was put on a shaker overnight. The solvent was removed.
(centrifuge) and preparative chromatography was run on a Waters FractionLynx system with a Autosampler combined Automated Fraction Collector (Waters 2767), Gradient Pump (Waters 2525), Regeneration Pump (Waters 600), Make Up Pump (Waters 515), Waters Active Splitter, Column Switch (Waters CFO), PDA (Waters 2996) and Waters ZQ mass spectrometer. Column; XBridge™ Prep C8 5µm OBD™ 19 x 100mm, with guard column; XTerra ® Prep MS C8 10µm 19 x 10mm Cartridge. A gradient from 100% A (95% 0.1M NH₄OAc in MilliQ water and 5% MeCN) to 100% B (100% MeCN) was applied for LC-separation at flow rate 25ml/min. The PDA was scanned from 210-350nm. The ZQ mass spectrometer was run with ESI in positive mode. The Capillary Voltage was 3kV and the Cone Voltage was 30V. Mixed triggering, UV and MS signal, determined the fraction collection.

Purity analysis was run on a Water Acquity system with PDA (Waters 2996) and Waters ZQ mass spectrometer. Column; Acquity UPLC™ BEH C₈ 1.7µm 2.1 x 50mm. The column temperature was set to 65°C. A linear 2 min 15sec gradient from 100% A (A: 95% 0.01M NH₄OAc in MilliQ water and 5% MeCN) to 100% B (5% 0.01M NH₄OAc in MilliQ water and 95% MeCN) was applied for LC-separation at flow rate 1.0ml/min. The PDA was scanned from 210-350nm and 254nm was extracted for purity determination. The ZQ mass spectrometer was run with ESI in pos/neg switching mode. The Capillary Voltage was 3kV and the Cone Voltage was 30V.

Alternatively, preparative chromatography was carried out on an HPLC (XTerra MS C8 column, acetonitrile / ammonium acetate buffer).

Example 31

4-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-benzamide
\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 8.2 (d, 1 H), 7.93-8.03 (m, 3 H), 7.55 - 7.73 (m, 6 H), 7.45 - 7.54 (m, 2 H), 7.33 - 7.43 (m, 1 H), 6.97-7.32 (s, 3 NH).

MS (ES-) 415, 416 Rt HPLC (XTerra) 4.23 min.

**Example 32**

N-(2-Sulfamoylphenyl)sulfonyl-4-tert-butyl-benzamide

\[\text{\includegraphics[width=0.3\textwidth]{example32}}\]

MS (ES-) 395 Rt HPLC (Xterra) 3.54 min.

**Example 33**

4-Methyl-N-(2-sulfamoylphenyl)sulfonyl-indole-2-carboxamide

\[\text{\includegraphics[width=0.3\textwidth]{example33}}\]

MS (ES-) 392 HPLC Rt (Xterra) 3.54 min.

**Example 34**

5-Pyridin-2-yl-N-(2-sulfamoylphenyl)sulfonyl-thiophene-2-carboxamide

\[\text{\includegraphics[width=0.3\textwidth]{example34}}\]
Example 35

5-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-thiophene-2-carboxamide

MS (ES-) 422, Rt HPLC (XTerra) 5.37 min.

Example 36

5-(3,4-Dichlorophenyl)-N-(2-sulfamoylphenyl)sulfonyl-furan-2-carboxamide

MS (ES-) 421 HPLC Rt (Xterra) 4.12 min.

Example 37

N-(2-Sulfamoylphenyl)sulfonyl-5-[3-(trifluoromethyl)phenyl]furan-2-carboxamide

MS (ES-) 474, 475 Rtl HPLC (Xterra) 4.13 min.

Example 37

N-(2-Sulfamoylphenyl)sulfonyl-5-[3-(trifluoromethyl)phenyl]furan-2-carboxamide

MS (ES-) 474, Rt HPLC 4.77 min.
Example 38

1-(3,5-Dichlorophenyl)-5-propyl-N-(2-sulfamoylphenyl)sulfonyl-pyrazole-4-carboxamide

\[
\text{MS } m/z, \text{ M+H } 516.8, 518.8, \text{ M-H } 515.0, 517.1; \text{ Rt HPLC (FractionLynx) } 0.62 \text{ min.}
\]

Example 39

3,6-Dichloro-N-(2-sulfamoylphenyl)sulfonyl-benzothiophene-2-carboxamide

\[
\text{MS } m/z, \text{ M+H } 464.7, 466.7; \text{ Rt HPLC (FractionLynx) } 0.86 \text{ min.}
\]

Example 40

N-(2-Sulfamoylphenyl)sulfonylbenzothiophene-3-carboxamide

\[
\text{MS (ES-) } 395 \text{ Rt HPLC (FractionLynx) } 0.65 \text{ min.}
\]
**Example 41**

Ethyl 4-[5-[(2-Sulfamoylphenyl)sulfonylcarbamoyl]-2-furyl]benzoate

![Chemical structure of Ethyl 4-[5-[(2-Sulfamoylphenyl)sulfonylcarbamoyl]-2-furyl]benzoate]

**MS (ES-) 477** R\textsubscript{t} HPLC (FractionLynx) 0.76 min.

**Example 42**

2-(3-Chlorophenyl)-4-methyl-N-(2-sulfamoylphenyl)sulfonyl-1,3-thiazole-5-carboxamide

![Chemical structure of 2-(3-Chlorophenyl)-4-methyl-N-(2-sulfamoylphenyl)sulfonyl-1,3-thiazole-5-carboxamide]

The title compound (57 mg, 42%) was synthesized by a procedure analogous to that described for Example 27.

\(^1\text{H NMR (400 MHz, MeOH-}^\text{d})\text{ }\delta\text{ ppm }8.32\text{ (dd, }1\text{ H)}, 8.19\text{ (dd, }1\text{ H)}, 7.96 - 7.98\text{ (m, }1\text{ H)}, 7.85\text{ (dt, }1\text{ H)}, 7.63 - 7.72\text{ (m, }2\text{ H)}, 7.43 - 7.49\text{ (m, }2\text{ H)}, 2.66\text{ (s, }3\text{ H}).

**Example 43**

4-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

![Chemical structure of 4-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide]
4-Bromo-N-(2-sulfamoylphenylsulfonyl)benzamide (80 mg, 0.19 mmol), (2-tert-butyl-1-ethynyl)diisopropoxyborane (100 mg, 0.48 mmol), sodium carbonate (81 mg, 0.76 mmol) and (1,r-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (15.70 mg, 0.02 mmol) were suspended in DMF (2.5 mL) and water (0.2 mL) and the reaction mixture was stirred for 3 hours at 90 °C under an atmosphere of argon. The reaction mixture was filtered and purified by HPLC to give the product as a solid (40 mg, 49%).

$^1$H NMR (DMSO-$d_6$) $\delta$ ppm 8.27 - 8.38 (m, 1 H), 8.10 - 8.18 (m, 1 H), 7.80 - 7.94 (m, 4 H), 7.37 - 7.47 (m, 3 H), 1.29 (s, 9 H).

MS m/z M-H 419, M+H 421.

**Example 44**

4-(3-Hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

![Chemical Structure](image)

4-Bromo-N-(2-sulfamoylphenylsulfonyl)benzamide (80 mg, 0.19 mmol), 2-methyl-3-butyn-2-ol (0.018 mL, 0.19 mmol), copper(I) iodide (9.08 mg, 0.05 mmol), tetrakis(triphenylphosphine)palladium(0) (28.7 mg, 0.02 mmol) and triethylamine (0.080 mL, 0.57 mmol) were dissolved in THF (2 mL) and stirred under an atmosphere of argon at 50 °C for 3 hours and then stirred at RT for another 10 hours. The reaction mixture was filtered and purified by HPLC. The fractions containing the product were collected and the solvent was removed in vacuum. The residue was again purified by HPLC to yield the product as a solid (16 mg, 20%).

$^1$H NMR (MeOH) $\delta$ ppm 8.31 (dd, 1 H), 8.18 (dd, 1 H), 7.93 (d, 2 H), 7.60 - 7.72 (m, 2 H), 7.37 (d, 2 H), 1.55 (s, 6 H).

MS m/z M-H 421, M+H 423.
Example 45
4-(Benzofuran-2-yl)-3-methyl-N-(2-sulfamoylphenylsulfonyl)benzamide

4-Bromo-3-methyl-N-(2-sulfamoylphenyl)sulfonyl-benzamide (198 mg, 0.46 mmol), benzofuran-2-ylboronic acid (111 mg, 0.69 mmol) and (1,1’-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (18.80 mg, 0.02 mmol) were dissolved in N,N-dimethylformamide (2.5 mL) (solvent was bubbled with argon). To this was added 2 M aqueous sodium carbonate (0.685 mL) and the resulting mixture was heated to 120 °C for 1 hour in a microwave. The reaction mixture was filtered through a pad of celite which was rinsed with ethyl acetate. The filtrate was concentrated in vacuo. The residue was dissolved in dimethyl sulfoxide (1.5 mL) and purified by preparative HPLC to give 89 mg (41% yield) of the title compound.

1H NMR (400 MHz, DMSO-δ6) δ ppm 8.16 (d, 1 H), 8.01 (d, 1 H), 7.80 - 7.90 (m, 3 H), 7.55 - 7.73 (m, 4 H), 7.23 - 7.38 (m, 3 H), 2.57 (s, 3 H), 1.89 (s, 2 H); MS (ESI) m/z All [M+H]+

Example 46
4-(Benzofuran-2-yl)-2-methyl-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 45 in 6% yield, starting from 4-bromo-2-methyl-N-(2-sulfamoylphenyl)sulfonyl-benzamide.
\[ ^1 \text{H NMR (400 MHz, CD}_3\text{OD)} \delta \text{ppm 8.38 (dd, 1 H), 8.22 (dd, 1.39 Hz, 1 H), 7.65 - 7.76 (m, 5 H), 7.60 (d, 1 H), 7.52 (d, 1 H), 7.18 - 7.32 (m, 3 H), 2.48 (s, 3 H), 1.97 (s, 2 H); MS (ESI) m/z 471 [M+H]^+} \]

**Example 47**

4-(Benzofuran-2-yl)-3,5-dimethoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

![Chemical Structure](image)

The title compound was synthesized as described for Example 45 in 39% yield, starting from 4-bromo-3,5-dimethoxy-N-(2-sulfamoylphenylsulfonyl)benzamide.

\[ ^1 \text{H NMR (400 MHz, DMSO-}d_6) \delta \text{ppm 8.33 (br. s., 1 H), 8.14 (dd, 1 H), 7.84 (br. s., 2 H), 7.66 (d, 1 H), 7.57 (d, 1 H), 7.46 (s, 2 H), 7.33 (s, 1 H), 7.20 - 7.34 (m, 4 H), 6.96 (d, 1 H), 3.81 (s, 6 H); MS (ESI) m/z 517 [M+H]^+} \]

a) 4-Bromo-3,5-dimethoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

![Chemical Structure](image)

Benzene-1,2-disulfonamide (0.2 g, 0.85 mmol), 4-bromo-3,5-dimethoxybenzoic acid (0.221 g, 0.85 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.227 g, 1.19 mmol) and 4-dimethylaminopyridine (0.259 g, 2.12 mmol) were dissolved in N,N-dimethylforamide (3 mL) and the reaction mixture was stirred at room temperature for 1.5 hour. Water was added and the solution was washed with ethyl acetate. The aqueous phase was acidified with 2 M hydrochloric acid and the product precipitated. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried
over magnesium sulfate and concentrated to give 0.225 g (56% yield) of the title compound.

$^1$H NMR (400 MHz, DMSO-$_d_6$) $\delta$ ppm 8.33 - 8.40 (m, 1 H), 8.17 (dd, 1 H), 7.84 - 8.00 (m, 3 H), 7.42 (br. s., 1 H), 7.24 (s, 2 H), 2.89 (s, 3 H), 2.73 (s, 3 H); MS (ESI) $m/z$ 479, 481

[M+H]$^+$

Example 48

4-(Benzofuran-2-yl)-2-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 45 in 4% yield, starting from 4-bromo-3,5-dimethoxy-N-(2-sulfamoylphenylsulfonyl)benzamide.

$^1$H NMR (400 MHz, DMSO-$_d_6$) $\delta$ ppm 8.17 (d, 1 H), 7.81 (s, 1 H), 7.55 - 7.74 (m, 6 H), 7.48 (s, 1 H), 7.38 (t, 1 H), 7.29 (t, 1 H), 4.06 (s, 3 H); MS (ESI) $m/z$ 487.2 [M+H]$^+$

a) 4-Bromo-2-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 47 a) in 26.5% yield, starting from 4-bromo-2-methoxybenzoic acid.

MS (ESI) $m/z$ 449, 451 [M+H]$^+$
Example 49

4-(Benzofuran-2-yl)-2-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 45 in 73% yield, starting from 4-bromo-2-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.24 (dd, 1.39 Hz, 1 H), 8.05 (dd, 1.39 Hz, 1 H), 7.83 (d, 1 H), 7.61 - 7.77 (m, 4 H), 7.50 (s, 1 H), 7.24 - 7.37 (m, 6 H); MS (ESI) $m/z$ 473.1 [M+H]$^+$

Example 50

4-(Benzofuran-2-yl)-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 47 a) in 4.3% yield, starting from 4-bromo-2-hydroxybenzoic acid.

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ ppm 8.33 (dd, 1 H), 8.21 (dd, 1 H) 7.64 - 7.76 (m, 3 H), 7.00 (d, 1 H); MS (ESI) $m/z$ 433.2, 435.2 [M-H]$^-$
The title compound was synthesized as described for Example 45 in 34% yield, starting from 4-bromo-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide.

\(^1\text{H NMR}\) (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 8.32 - 8.40 (m, 1 H), 8.12 - 8.19 (m, 1 H), 8.02 (d, 1 H), 7.84 - 7.93 (m, 2 H), 7.60 - 7.67 (m, 2 H), 7.57 (s, 1 H), 7.45 (s, 2 H), 7.32 - 7.39 (m, 1 H), 7.27 (t, 1 H), 4.05 (s, 3 H); MS (ESI) \(m/z\) 487.1 [M+H]

a) 4-Bromo-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 47 a) in 80% yield, starting from 4-bromo-3-methoxybenzoic acid.

\(^1\text{H NMR}\) (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 8.36 (dd, 1.64 Hz, 1 H), 8.17 (dd, 1 H), 7.86 - 7.97 (m, 4 H), 7.70 (d, 1 H), 7.59 (d, 1 H), 7.44 (s, 1 H), 7.40 (dd, 1 H), 3.90 (s, 3 H); MS (ESI) \(m/z\) 449, 451 [M+H]

Example 51

4-(Benzofuran-2-yl)-3-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 45 in 9% yield, starting from 4-bromo-3-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide.

\(^1\text{H NMR}\) (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 8.17 (d, 1 H), 8.03 (d, 1 H), 7.84 (d, 1 H), 7.67 (d, 2 H), 7.60 (d, 2 H), 7.46 - 7.50 (m, 2 H), 7.44 (s, 1 H), 7.30 (t, 1 H), 7.24 (t, 1 H); MS (ESI) \(m/z\) 473.1 [M+H]

\[ \text{NH}_2 \]
\[ \text{SO} \]
\[ \text{O} \]
\[ \text{Br} \]

\[ \text{NH}_2 \]
\[ \text{SO} \]
\[ \text{O} \]
\[ \text{Br} \]

\[ \text{NH}_2 \]
\[ \text{SO} \]
\[ \text{O} \]
\[ \text{Br} \]

\[ \text{NH}_2 \]
\[ \text{SO} \]
\[ \text{O} \]
\[ \text{Br} \]
a) 4-Bromo-3-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide

\[
\begin{align*}
\text{NH}_2 \\
\text{SO}-0 \\
\text{SO}-0 \\
\text{OH} \\
\text{Br}
\end{align*}
\]

4-Bromo-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide (200 mg, 0.45 mmol) was dissolved in dichloromethane (3 mL) and cooled to 0°C. Boron tribromide (0.210 mL, 2.23 mmol) was added and mixture was stirred at 0°C for 2 hours. The reaction mixture was allowed to reach room temperature and was stirred overnight. The reaction mixture was washed with water and the combined aqueous phases were extracted with ethyl acetate. The combined organic phases were dried over magnesium sulfate and concentrated to give 190 mg (98% yield) of the title compound.

\[^1H\text{ NMR (400 MHz, DMSO-}^6\text{)}\delta \text{ ppm 10.70 (br. s., 1 H), 8.33 (dd, 1 H), 8.16 (dd, 1 H), 7.85 - 7.96 (m, 2 H), 7.61 (d, 1 H), 7.41 (s, 2 H), 7.35 (d, 1 H), 7.30 (dd, 1 H); MS (ESI) m/z 435, 437 [M+H]^+}\]

Example 52

4-(Benzofuran-2-yl)-2,6-dimethyl-N-(2-sulfamoylphenylsulfonyl)benzamide

\[
\begin{align*}
\text{NH}_2 \\
\text{SO}-0 \\
\text{SO}-0 \\
\text{O} \\
\text{O}
\end{align*}
\]

The title compound was synthesized as described for Example 45 in 14% yield, starting from 4-bromo-2,6-dimethyl-N-(2-sulfamoylphenylsulfonyl)benzamide.

\[^1H\text{ NMR (400 MHz, CD}_3\text{OD) }\delta \text{ ppm 8.46 - 8.52 (m, 1 H), 8.28 (dd, 1 H), 7.82 (dd, 2 H), 7.47 - 7.62 (m, 4 H), 7.28 (t, 1 H), 7.21 (t, 1 H), 7.18 (s, 1 H), 2.27 (s, 5 H); MS (ESI) m/z 483.4 [M-H]^+}\]
a) 4-Bromo-2,6-dimethyl-N-(2-sulfamoylphenylsulfonyl)benzamide

4-Bromo-2,6-dimethylbenzoic acid (0.2 g, 0.87 mmol), fluoro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (0.254 g, 0.96 mmol) and triethylamine (0.487 mL, 3.49 mmol) were dissolved in N,N-dimethylformamide (4.5 mL). Benzene-1,2-disulfonamide (0.248 g, 1.05 mmol) was added and the reaction mixture was stirred at room temperature over night. The reaction mixture was diluted with water and washed with ethyl acetate. The aqueous phase was acidified using 2 M hydrochloric acid and extracted with ethyl acetate. The combined organic phases were dried over magnesium sulfate and concentrated to give 450 mg of the title compound, used in next step without further purification.

MS (ESI) m/z 445.2, 447.2 [M-H]⁻

Example 53

4-(3-Methoxyprop-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

Copper(I) iodide (2.85 µL, 0.08 mmol) was added to a stirred solution of 3-methoxyprop-1-yn-2-ol (0.035 mL, 0.41 mmol), 4-iodo-N-(2-sulfamoylphenylsulfonyl)benzamide (0.1723 g, 0.37 mmol), tetrakis(triphenylphosphine)palladium(0) (0.0305 g, 0.03 mmol) and triethylamine (0.50 mL, 3.59 mmol) in N,N-dimethylformamide (5 mL) under an atmosphere of nitrogen. The resulting mixture was heated at 65°C over night. Water and ethyl acetate was added, the aqueous phase was acidified (pH ~1) with 2 M hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with water,
water/brine (1:1) and brine, dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC gave 0.079 g (52% yield) of the title compound, 

\[ ^1 \text{H NMR (400 MHz, DMSO-} \text{D}_6) \delta \text{ ppm} \]

8.27 - 8.37 (m, 1 H) 8.09 - 8.19 (m, 1 H) 7.81 - 7.94 (m, 4 H) 7.54 (d, 2 H) 7.42 (s, 2 H) 4.35 (s, 2 H) 3.33 (s, 3 H); MS (ESI) m/z 407.0

[M-H]-

**Example 54**

4-(3-Methylbut-3-en-l-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

![Chemical structure of 4-(3-Methylbut-3-en-l-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide]

The title compound was synthesized as described for Example 53 in 60% yield, starting from 2-methylbut-l-en-3-yne.

\[ ^1 \text{H NMR (400 MHz, DMSO-} \text{D}_6) \delta \text{ ppm} \]

8.28 - 8.36 (m, 1 H) 8.13 (d, 1 H) 7.80 - 7.92 (m, 4 H) 7.52 (d, 2 H) 7.42 (s, 2 H) 5.29 - 5.53 (m, 2 H) 1.96 (s, 3 H); MS (ESI) m/z 403.0 [M-H]-

**Example 55**

6-(Phenylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide

![Chemical structure of 6-(Phenylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide]

The title compound was synthesized as described for Example 53 in 99% yield, starting from 6-bromo-N-(2-sulfamoylphenylsulfonyl)nicotinamide and phenylacetylene.
Purification by column chromatography, using 0-10% methanol in dichloromethane as the eluent. The residue was washed with dichloromethane.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 9.01 (d, 1 H) 8.29 - 8.39 (m, 1 H) 8.24 (dd, 1 H) 8.12 (dd, 1 H) 7.84 (d, 2 H) 7.73 (d, 1 H) 7.57 - 7.70 (m, 2 H) 7.38 - 7.55 (m, 5 H); MS (ESI) m/z 403.0 [M-H]$
$

**Example 56**

4-(3-Ethyl-3-hydroxypent-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

![Chemical Structure](image)

Bis(triphenylphosphine)palladium(II) chloride (50.2 mg, 0.07 mmol) and copper(I) iodide (13.63 mg, 0.07 mmol) were added to a solution of 4-bromo-N-(2-sulfamoylphenyl)sulfonyl-benzamide (300 mg, 0.72 mmol), 3-ethylpent-1-yn-3-ol (0.184 mL, 1.43 mmol) and diisopropylamine (0.306 mL, 2.15 mmol) in degased N,N-dimethylformamide (1.5 mL). The reaction mixture was heated at 100 °C in a microwave for 1 hour. The reaction mixture was filtered through a pad of celite which was rinsed with ethyl acetate. The filtrate was concentrated *in vacuo*. The residue was dissolved in dimethyl sulfoxide (1.5 mL) and purified by preparative HPLC to give 88 mg (27% yield) of the title compound.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ ppm 8.13 (dd, 1 H), 7.99 (dd, 1 H), 7.85 (d, 2 H), 7.54 - 7.67 (m, 2 H), 7.34 (d, 2 H), 1.54 - 1.70 (m, 4 H), 0.99 (t, 6 H); MS (ESI) m/z 451.2 [M+H]^+
Example 57

4-(3-Hydroxy-3-methylpent-l-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 56 in 10% yield, starting from 3-methylpent-l-yn-3-ol.

$^1$H NMR (400 MHz, DMSO-$_6$) $\delta$ ppm 8.32 - 8.37 (m, 1 H), 8.15 (dd, 1 H), 7.86 (d, 2 H), 7.84 - 7.94 (m, 2 H), 7.48 (d, 2 H), 7.42 (br. s., 2 H), 1.56 - 1.73 (m, 2 H), 1.41 (s, 3 H), 0.99 (t, 3 H); MS (ESI) m/z 435.1 [M-H]$^-$

Example 58

4-((1-Hydroxycyclopentyl)ethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 45 in 34% yield, starting from 1-ethynylcyclopentanol.

$^1$H NMR (400 MHz, DMSO-$_6$) $\delta$ ppm 8.13 (dd, 1 H), 7.99 (dd, 1 H), 7.84 (d, 2 H), 7.55 - 7.66 (m, 2 H), 7.44 (br. s., 2 H), 7.33 (d, 2 H), 5.36 (br. s., 1 H), 1.82 - 1.95 (m, 4 H), 1.61 - 1.79 (m, 4 H); MS (ESI) m/z 449.1 [M+H]$^+$
Example 59

3-(3-Hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 56 in 14% yield, starting from 3-bromo-N-(2-sulfamoylphenylsulfonyl)benzamide.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.14 (dd, 1 H), 7.99 (dd, 1 H), 7.93 (s, 1 H), 7.80 (d, 1 H), 7.55 - 7.67 (m, 2 H), 7.36 - 7.41 (m, 1 H), 7.31 (t, 1 H), 2.19 (br. s., 1 H), 1.46 (s, 6 H); MS (ESI) m/z 421.3 [M-H]$^-$

Example 60

3-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 47 a) in 86% yield, starting from 3-bromobenzoic acid.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.36 (dd, 1 H), 8.17 (dd, 1 H), 8.10 (s, 1 H), 7.77 - 7.98 (m, 5 H), 7.39 - 7.48 (m, 3 H); MS (ESI) m/z 417, 419 [M-H]$^-$. 

![Diagram](image)
3-Bromo-N-(2-sulfamoylphenylsulfonyl)benzamide (200 mg, 0.48 mmol), (2-tert-butyl-1-ethynyl)diisopropoxyborane (0.135 mL, 0.57 mmol) and (1,1’-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) (19.62 mg, 0.02 mmol) were dissolved in N,N-dimethylformamide (2.0 mL) (the solvent was bubbled with argon).

Aqueous 2 M sodium carbonate (0.685 mL) was added and the resulting mixture was heated at 120 °C for 40 min in a microwave. The reaction mixture was filtered through a pad of celite which was rinsed with ethyl acetate. The filtrate was concentrated in vacuo. The residue was dissolved in dimethyl sulfoxide (1.5 mL) and purified by preparative HPLC to give 9 mg (4% yield) of the title compound.

**Example 61**

4-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)-1-naphthamide

Diisopropyl 3,3-dimethylbut-1-ynylboronate (0.100 mL, 0.43 mmol), 4-bromo-N-(2-sulfamoylphenylsulfonyl)-1-naphthamide (200 mg, 0.43 mmol), [1,1’-bis(diphenylphosphino)ferrocene]dichloropalladium (35 mg, 0.04 mmol) and potassium carbonate (353 mg, 2.56 mmol) were dissolved in tetrahydrofuran (5 mL) and water (1 mL) in a microwave vial. The reaction was irradiated for 60 minutes at 150°C in a microwave oven, filtered through a plug of celite and concentrated in vacuo. Purification by preparative HPLC gave 19 mg (9% yield) of the title compound.

**1H NMR (CD$_3$OD) δ ppm 8.45 - 8.40 (m, 2 H) 8.29 - 8.22 (m, 2 H) 7.80 (d, 1 H) 7.74 (dd, 1 H) 7.72 - 7.68 (m, 1 H) 7.55 - 7.47 (m, 3 H) 1.42 (s, 9 H); MS (ESI) m/z 469 [M-I]$^-$**
a) 4-Bromo-N-(2-sulfamoylphenylsulfonyl)-l-naphthamide

\[
\begin{align*}
\text{Benzene-1,2-disulfonamide (750 mg, 3.17 mmol), } & \text{4-bromo-l-naphthoic acid (797 mg, 3.17 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (852 mg, 4.44 mmol) and 4-dimethylaminopyridine (970 mg, 7.94 mmol) were dissolved in anhydrous N,N-dimethylformamide (15 mL) and the reaction was stirred at room temperature over night. Water (100 mL) was added and the solution was extracted with ethyl acetate. The aqueous phase was acidified with hydrochloric acid (2 M) and extracted with ethyl acetate. The combined organic phases were washed with water, dried over magnesium sulfate and concentrated in vacuo, to give 1.515 g (80% yield) of the title compound.} \\
\text{MS (ESI) } m/z \ 469, \ 467 \ [M-I]^-
\end{align*}
\]

**Example 62**

4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)-l-naphthamide

\[
\begin{align*}
\text{The title compound was synthesized as described for Example 61 in 31% yield, starting from benzofuran-2-ylboronic acid.} \\
\text{\textsuperscript{1}H NMR (DMSO-\textit{d}_6) } \delta \text{ ppm } 13.19 \text{ (br. s., 2 H)} \ 8.51 \text{ (d, 1 H)} \ 8.48 - 8.44 \text{ (m, 1 H)} \ 8.25 - 8.22 \text{ (m, 1 H)} \ 8.18 \text{ (br. s., 1 H)} \ 8.01 - 7.93 \text{ (m, 4 H)} \ 7.78 \text{ (d, 1 H)} \ 7.74 \text{ (d, 1 H)} \ 7.72 - 7.64 \text{ (m, 2 H)} \ 7.51 \text{ (s, 1 H)} \ 7.46 \text{ (s, 2 H)} \ 7.44 - 7.39 \text{ (m, 1 H)} \ 7.35 \text{ (t, 1 H); MS (ESI) } m/z \ 505 \ [M-I]^-
\end{align*}
\]
Example 63

2-(Benzofuran-2-yl)-4-methyl-N-(2-sulfamoylphenylsulfonyl)thiazole-5-carboxamide

The title compound was synthesized as described for Example 61 in 6% yield, starting from 2-bromo-4-methyl-N-(2-sulfamoylphenylsulfonyl)thiazole-5-carboxamide and benzofuran-2-ylboronic acid.

\[ ^1H \text{NMR (CD}_3\text{OD)} \delta 8.14-8.1 \text{ (m, 1 H)} \ 8.0-7.9 \text{ (m, 1 H)} \ 7.52-7.42 \text{ (m, 3 H)} \ 7.37 \text{ (d, 1 H)} \ 7.27 \text{ (s, 1 H)} \ 7.22 - 7.17 \text{ (m, 1 H)} \ 7.09 \text{ (t, 1 H)} \ 2.47 \text{ (s, 3 H)}; \text{ MS (ESI) m/z 476 [M-I]}^+ \]

a) 2-Bromo-4-methyl-N-(2-sulfamoylphenylsulfonyl)thiazole-5-carboxamide

The title compound was synthesized as described for Example 61 a) in 90% yield, starting from 2-bromo-4-methylthiazole-5-carboxylic acid.

\[ \text{MS (ESI) m/z 440, 438 [M-I]}^+ \]
Example 64

3\((3\text{-Hydroxy-3-methylbut-1-ynyl})\text{-N-(2-sulfamoylphenylsulfonyl)biphenyl-2-carboxamide}

\[
\begin{align*}
2\text{-Bromo-N-(2-sulfamoylphenylsulfonyl)benzamide} & \quad (370 \text{ mg, 0.88 mmol}), \\
[1,1'\text{-bis(diphenylphosphino)ferrocene}]\text{dichloropalladium} & \quad (71 \text{ mg, 0.09 mmol}) \text{ and potassium carbonate} (732 \text{ mg, 5.29 mmol}) \text{ and 2-methyl-4-}(3\text{-}(4,4,5,5\text{-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl})\text{but-3-yn-2-ol} & \quad (328 \text{ mg, 1.15 mmol}) \text{ were dissolved in}
\end{align*}
\]

\[
\begin{align*}
tetrahydrofurane & \quad (4 \text{ mL}) \text{ and water} & \quad (1 \text{ mL}) \text{ in a microwave vial. The reaction was heated for 120 min at 150 }^\circ\text{C in a microwave, filtered through a plug of celite and concentrated } \textit{in vacuo}. \text{ Purification by preparative HPLC gave 7 mg (2% yield) of the title compound:}
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{NMR (CD}_3\text{OD)} \delta \text{ ppm 8.23 - 8.18 (m, 2 H) 7.79 - 7.72 (m, 1 H) 7.68 - 7.63 (m, 1 H) 7.53 - 7.43 (m, 2 H) 7.38 - 7.32 (m, 1 H) 7.27 (d, 1 H) 7.21 (t, 1 H) 7.16 - 7.12 (m, 1 H) 7.10 - 7.040 (m, 1 H) 6.94 (t, 1 H) 1.47 (s, 6 H); MS (ESI) m/z 497 [M-I]\)}}
\end{align*}
\]

a) 2-Methyl-4-\((3\text{-}(4,4,5,5\text{-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl})\text{but-3-yn-2-ol}

\[
\begin{align*}
\end{align*}
\]
Bis(dibenzylideneacetone)palladium (186 mg, 0.32 mmol) and tricyclohexylphosphine (212 mg, 0.76 mmol) were dissolved in anhydrous dioxane (10 mL) and stirred for 30 min. A solution of bis(pinacolato)diboron (2.877 g, 11.33 mmol), potassium acetate (1.588 g, 16.19 mmol) and 4-(3-bromophenyl)-2-methylbut-3-yn-2-ol (2.580 g, 10.79 mmol) in anhydrous dioxane (10 mL), was added and the reaction was heated at 130°C for 60 min in a microwave. Purification by column chromatography, using 0 to 100% ethyl acetate in heptane as the eluent, gave 2.72 g (88% yield) of the title compound:

$^1$H NMR (CD$_3$OD) $\delta$ ppm 7.76 (s, 1 H) 7.71 - 7.66 (m, 1 H) 7.52 - 7.47 (m, 1 H) 7.34 (t, 1 H) 1.58 (s, 6 H) 1.37 (s, 12 H)

### Example 65

4-(Cyclopentylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

![Chemical Structure](image)

4-Bromo-N-(2-sulfamoylphenyl)sulfonyl-benzamide (200 mg, 0.48 mmol), copper(I) iodide (5 g, 0.02 mmol), bis(triphenylphosphine)palladium(II) chloride (17 mg, 0.02 mmol), ethynylcyclopentane (0.055 mL, 0.48 mmol) and diisopropylamine (0.202 mL, 1.43 mmol) were slurried in anhydrous N,N-dimethylformamide (3 mL) in a microwave vial. The reaction was heated for 90 min at 100 °C in a microwave, filtered through a plug of celite and concentrated *in vacuo*. Purification by preparative HPLC gave 34 mg (16% yield) of the title compound:

$^1$H NMR (CD$_3$OD) $\delta$ ppm 8.29 (d, 1 H) 8.18 (d, 1 H) 7.90 (d, 2 H) 7.71 - 7.56 (m, 2 H) 7.32 (d, 2 H) 2.91 - 2.79 (m, 1 H) 2.06 - 1.93 (m, 2 H) 1.83 - 1.73 (m, 2 H) 1.73 - 1.57 (m, 4 H); MS (ESI) m/z 431 [M-I]−
Example 66

3-(Cyclopentylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 65 in 6% yield, starting from 3-bromo-N-(2-sulfamoylphenylsulfonyl)benzamide.

$^1$H NMR (CD$_3$OD) $\delta$ ppm 8.28 (dd, 1 H) 8.18 (dd, 1 H) 7.97 (s, 1 H) 7.90 (d, 1 H) 7.71 - 7.59 (m, 2 H) 7.41 - 7.37 (m, 1 H) 7.28 (t, 1 H) 2.89 - 2.80 (m, 1 H) 2.05 - 1.96 (m, 4 H) 1.83 - 1.59 (m, 4 H); MS (ESI) m/z 431 [M-I] -

Example 67

4-(Cyclopentylethynyl)-2-methyl-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 65 in 10% yield, starting from 4-bromo-2-methyl-N-(2-sulfamoylphenylsulfonyl)benzamide.

$^1$H NMR (CD$_3$OD) $\delta$ ppm 8.33 (d, 1 H) 8.20 (d, 1 H) 7.73 - 7.51 (m, 3 H) 7.12 - 7.08 (m, 2 H) 2.88 - 2.77 (m, 1 H) 2.34 (s, 3 H) 2.03 - 1.94 (m, 2 H) 1.81 - 1.721 (m, 2 H) 1.72 - 1.58 (m, 4 H); MS (ESI) m/z 445 [M-I] -
Example 68

4-(3,3-Dimethylbut-1-ynyl)-3-methoxy-2-methyl-N-(2-sulfamoylphenylsulfonyl)-benzamide

The title compound was synthesized as described for Example 61 in 14% yield, starting from diisopropyl 3,3-dimethylbut-1-ynylboronate and 4-bromo-3-methoxy-2-methyl-N-(2-sulfamoylphenylsulfonyl)benzamide.

$^{1}H$ NMR (CD$_3$OD) $\delta$ ppm 8.39 - 8.31 (m, 1 H) 8.24 - 8.15 (m, 1 H) 7.77 - 7.64 (m, 4 H) 7.24 (d, 1 H) 7.11 (d, 1 H) 3.83 (s, 3 H) 2.25 (s, 3 H) 1.33 (s, 9 H); MS (ESI) $m/z$ 465 [M+1]$^+$

a) 4-Bromo-3-methoxy-2-methyl-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 61 a) in 87% yield, starting from 4-bromo-3-methoxy-2-methylbenzoic acid.

MS (ESI) $m/z$ 463, 461 [M-I]$^-$

b) 4-Bromo-3-methoxy-2-methylbenzoic acid
Methyl 4-bromo-3-methoxy-2-methylbenzoate (1.3 g, 5.02 mmol) was dissolved in 15% sodium hydroxide (20 mL) and heated at 100 °C for 1 hour. The mixture was allowed to cool to room temperature, acidified using hydrochloric acid (4 M) and was extracted with dichloromethane. The combined organic phases were dried over magnesium sulfate and concentrated in vacuo to give 1.15 g (94% yield) of the title compound:

\[ \text{MS (ESI) } m/z \ 245, 243 [\text{M-I}]^- \]

Methyl 4-bromo-3-hydroxy-2-methylbenzoate (1.51 g, 6.16 mmol), iodomethane (1.161 mL, 18.48 mmol) and potassium carbonate (2.55 g, 18.48 mmol) were dissolved in N,N-dimethylformamide (10 mL) and acetone (10 mL) and stirred at room temperature overnight. Water was added and the aqueous phase was extracted with ethyl acetate and dichloromethane. The combined organic phases were washed with water, dried over magnesium sulfate and concentrated in vacuo to gave 1.3 g (81% yield) of the title compound.

\[ ^1H \text{ NMR (CDCl}_3) \delta \text{ ppm } 7.56 - 7.49 (m, 1 \text{ H}) \ 7.47 - 7.38 (m, 1 \text{ H}) \ 3.90 (s, 3 \text{ H}) \ 3.81 (s, 3 \text{ H}) \ 2.57 (s, 3 \text{ H}) \]

Methyl 4-bromo-3-hydroxy-2-methylbenzoate
A solution of bromine (1.608 mL, 31.29 mmol) in dichloromethane (20 mL) was added dropwise over 30 min to a solution of 2-methylpropan-2-amine (3.30 mL, 31.29 mmol) in dichloromethane (100 mL) at -78°C. The solution was stirred for 30 min at -78°C. A solution of methyl 3-hydroxy-2-methylbenzoate (5.2 g, 31.29 mmol) in dichloromethane (30 mL) was added over 30 min. The reaction was allowed to reach room temperature, stirred overnight and water was added. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with water, dried over magnesium sulphate and concentrated in vacuo. Purification by column chromatography, using a gradient of 0 to 10% ethyl acetate in heptane as the eluent, gave 1.51 g (20% yield) of the title compound:

**Example 69**

4-(Benzofuran-2-yl)-3-methoxy-2-methyl-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 61 in 48% yield, starting from benzofuran-2-ylboronic acid and 4-bromo-3-methoxy-2-methyl-N-(2-sulfamoylphenylsulfonyl)benzamide.

\[ ^1H \text{NMR (DMSO-}J_{6}\text{)} \delta \text{ ppm } 8.19 \text{ (dd, } 1 \text{ H}) \text{ 8.02 (dd, } 1 \text{ H}) \text{ 7.73 - 7.57 (m, } 5 \text{ H}) \text{ 7.50 (d, } 1 \text{ H}) \text{ 7.42 (d, } 1 \text{ H}) \text{ 7.36 - 7.29 (m, } 1 \text{ H}) \text{ 7.30 - 7.22 (m, } 1 \text{ H}) \text{ 3.69 (s, } 3 \text{ H}) \text{ 2.33 (s, } 3 \text{ H}); \text{ MS (ESI) } m/2 499 \text{ [M-I]}^- \]
Example 70

4-(Pyridin-3-ylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

Copper(I) iodide (3.56 µL, 0.11 mmol) was added to a stirred solution of 4-iodo-N-(2-sulfamoylphenylsulfonyl)benzamide (0.2129 g, 0.46 mmol), 3-ethynylpyridine (0.0545 g, 0.53 mmol), tetrakis(triphenylphosphine)palladium(0) (0.0346 g, 0.03 mmol) and triethylamine (1 mL, 7.17 mmol) in 7V,7V-dimethylformamide (5 mL) under an atmosphere of nitrogen. The resulting mixture was heated at 65 °C over night. Water was added and the mixture was acidified (pH~1) using 2 M hydrochloric acid. The formed solid was removed by filtration, stirred with warm methanol, filtered and dried. Dissolved in boiling acetonitrile, allowed to cool down to room temperature, filtered, washed with acetonitrile and dried in vacuo to give 0.066 g (33% yield) of the title compound.

1H NMR (400 MHz, DMSO-\(\text{d}_6\)) \(\delta\) ppm 8.82 (s, 1 H) 8.64 (d, 1 H) 8.37 (dd, 1 H) 8.17 (dd, 1 H) 8.04 - 8.10 (m, 1 H) 7.86 - 7.98 (m, 4 H) 7.70 (d, 2 H) 7.53 (dd, 1 H) 7.43 (br. s., 2 H); MS (ESI) \(m/z\) 442.0 [M+H]+, MS (ESI) \(m/z\) 440.2 [M-H]-

Example 71

4-(Pyridin-2-ylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

Synthesized as described for Example 70 in 31% yield, starting from 2-ethynylpyridine. The aqueous phase was acidified using hydrochloric acid 2M, extracted with ethyl acetate and the combined organic phases were dried over magnesium sulfate and concentrated.
The residue was washed with dichloromethane/methanol (9:1), filtered and dried *in vacuo.*

1H NMR (400 MHz, DMSO-\(\text{d}_6\)) \(\delta\) ppm 8.63 (d, 1 H) 8.35 (dd, 1 H) 7.94 (d, 2 H) 7.84 - 7.91 (m, 3 H) 7.70 (t, 3 H) 7.39 - 7.48 (m, 3 H); MS (ESI) \(m/z\) 442.0 [M+H]+, MS (ESI) \(m/z\) 440.2 [M-H].

**Example 72**

4-(Phenylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

![Chemical structure of Example 72](image)

Copper(I) iodide (2.349 µL, 0.07 mmol) was added to a stirred solution of 4-iodo-N-(2-sulfamoylphenylsulfonyl)benzamide (0.200 g, 0.43 mmol), phenylacetylene (0.060 mL, 0.55 mmol), tetrakis(triphenylphosphine)palladium(0) (0.0283 g, 0.02 mmol) and triethylamine (1.5 mL, 10.76 mmol) in N,N-dimethylformamide (5 mL) under an atmosphere of nitrogen. The resulting mixture was heated at 65°C for 3.5 h. Ethyl acetate and water was added. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with water and brine, dried over magnesium sulfate and concentrated. Dichloromethane was added and the precipitated product was filtered off to give 0.035 g. The residue was purified by column chromatography, using a gradient of 0-10% methanol in dichloromethane as the eluent, to give 0.024 g. The two fractions were combined to give 0.059 g (31% yield) of the title compound.

1H NMR (400 MHz, DMSO-\(\text{d}_6\)) \(\delta\) ppm 8.20 (d, 1 H) 8.03 (d, 1 H) 7.92 (d, 2 H) 7.63 - 7.73 (m, 2 H) 7.52 - 7.60 (m, 4 H) 7.41 - 7.47 (m, 5 H); MS (ESI) \(m/z\) 439.2 [M-H].
Example 73

4-(3,3-Dimethylbut-1-ynyl)-3-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide

A mixture of 4-bromo-3-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide (0.10 g, 0.23 mmol), diisopropyl 3,3-dimethylbut-1-ynylboronate (0.11 mL, 0.46 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (0.019 g, 0.020 mmol), N,N-dimethylformamide (2 mL) and 2 M sodium carbonate (0.34 mL, 0.69 mmol) under an atmosphere of argon was heated at 120 °C for 1 hour in a microwave. The reaction mixture was partitioned between ethyl acetate and water, the organic phase was dried over magnesium sulfate and evaporated. Purification by preparative HPLC, gave 0.023 g (23% yield) of the title compound.

$^1$H NMR (DMSO-$d_6$) $\delta$ ppm 8.19 - 8.27 (m, 1 H) 8.00 - 8.07 (m, 1 H) 7.72 - 7.82 (m, 2 H) 7.63 (dd, 1 H) 7.57 (dd, 1 H) 7.41 (t, 1 H) 7.33 (br. s., 2 H) 1.20 (s, 9 H); MS (ESI) $m/z$ 437 [M-I]-.

a) 4-Bromo-3-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide

To a solution of benzene-1,2-disulfonamide (0.47 g, 2.00 mmol) and 4-bromo-3-fluorobenzoic acid (0.44 g, 2.00 mmol) in $\Lambda,\Lambda$-dimethylformamide (20 mL) was $\Lambda$-(3-dimethylaminopropyl)-$\Lambda'$-ethylcarbodiimide hydrochloride (0.58 g, 3.00 mmol) and $\Lambda$-(dimethylamino)pyridine (0.37 g, 3.00 mmol) added, the resulting mixture was stirred at room temperature over night. Water was added and the mixture was washed with ethyl acetate. The aqueous phase was acidified by addition of 1 M hydrochloric acid and
extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and evaporated to give 0.77 g (88% yield) of the title compound.

\[ ^1H \text{NMR (DMSO-}d_6) \delta \text{ ppm 8.30 - 8.37 (m, 1 H) 8.14 (d, 1 H) 7.78 - 7.94 (m, 4 H) 7.66 (dd, 1 H) 7.45 (br. s., 2 H); MS (ESI) } m/z 435, 437 \ [\text{M-I}]^- \.

**Example 74**

2-(3-Methoxyphenyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide

![Chemical structure](image)

The title compound was synthesized as described for Example 73 a) in 11% yield, starting from 2-(3-methoxyphenyl)benzofuran-5-carboxylic acid. Purification by preparative HPLC.

\[ ^1H \text{NMR (DMSO-}d_6) \delta \text{ ppm 8.34 - 8.44 (m, 1 H) 8.29 (d, 1 H) 8.13 - 8.21 (m, 1 H) 7.81 - 7.97 (m, 3 H) 7.72 (d, 1 H) 7.63 (s, 1 H) 7.52 - 7.58 (m, 1 H) 7.48 - 7.51 (m, 1 H) 7.39 - 7.48 (m, 3 H) 7.02 (dd, IH) 3.86 (s, 3 H); MS (ESI) } m/z 485 \ [\text{M-I}]^- \.

a) 2-(3-Methoxyphenyl)benzofuran-5-carboxylic acid

![Chemical structure](image)

A solution of lithium hydroxide (0.066 g, 2.74 mmol) in water (1 mL) was added to a solution of methyl 2-(3-methoxyphenyl)benzofuran-5-carboxylate (0.13 g, 0.46 mmol) in tetrahydrofuran (3 mL). The resulting mixture was stirred at room temperature over night, water was added, the mixture was acidified by the addition of 1 M hydrochloric acid and
extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and evaporated to give 0.12 g (95% yield) of the title compound.

**1H NMR (DMSO-đ) δ ppm** 8.28 (d, 1 H) 7.94 (dd, 1 H) 7.74 (d, 1 H) 7.60 (d, 1 H) 7.51 - 7.56 (m, 1 H) 7.42 - 7.50 (m, 2 H) 7.00 - 7.06 (m, 1 H) 3.87 (s, 3 H); MS (ESI) m/z 267 [M-I]-.

**b) Methyl 2-(3-methoxyphenyl)benzofuran-5-carboxylate**

A mixture of methyl 4-hydroxy-3-iodobenzoate (0.14 g, 0.50 mmol), 3-ethynylanisole (0.19 mL, 1.50 mmol), bis(triphenylphosphine)palladium(II) chloride (0.035 g, 0.050 mmol), copper(I) iodide (9.5 mg, 0.050 mmol) and 1,1,3,3-tetramethylguanidine (0.63 mL, 5.00 mmol) in N,N-dimethylformamide (5 mL) under an atmosphere of argon was heated at 70 °C for 3 days. The reaction mixture was diluted with ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by column chromatography, using heptane:ethyl acetate (9:1) as the eluent, gave 0.13 g (91% yield) of the title compound.

**1H NMR (CDCl₃) δ ppm** 8.35 (dd, 1 H) 8.04 (dd, 1 H) 7.57 (d, 1 H) 7.49 (ddd, 1 H) 7.37 - 7.45 (m, 2 H) 7.10 (d, 1 H) 6.96 (ddd, 1 H) 3.98 (s, 3 H) 3.93 (s, 3 H); MS (EI) m/z 282 [M]+.

**Example 75**

2-(4-Methoxyphenyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide
The title compound was synthesized as described for Example 74 in 27% yield, starting from 2-(4-methoxyphenyl)benzofuran-5-carboxylic acid.

1H NMR (DMSO-d6) δ ppm 8.36 - 8.41 (m, 1 H) 8.25 (d, 1 H) 8.15 - 8.20 (m, 1 H) 7.87 - 7.97 (m, 4 H) 7.81 (dd, 1 H) 7.69 (d, 1 H) 7.42 (d, 3 H) 7.07 - 7.13 (m, 2 H) 3.84 (s, 3 H);

MS (ESI) m/z 485 [M-I]−.

a) 2-(4-Methoxyphenyl)benzofuran-5-carboxylic acid

The title compound was synthesized as described for Example 74 a) in 94% yield, starting from methyl 2-(4-methoxyphenyl)benzofuran-5-carboxylate.

1H NMR (DMSO-d6) δ ppm 12.81 (br. s., 1 H) 8.18 (d, 1 H) 7.80 - 7.88 (m, 3 H) 7.64 (d, 1 H) 7.34 (d, 1 H) 7.02 - 7.09 (m, 2 H) 3.78 (s, 3 H) 3.90 (s, 3 H);

MS (ESI) m/z 267 [M-I]−.

b) Methyl 2-(4-methoxyphenyl)benzofuran-5-carboxylate

The title compound was synthesized as described for Example 74 b) in 98% yield, starting from 1-ethynyl-4-methoxybenzene.

1H NMR (CDCl3) δ ppm 8.31 (d, 1 H) 8.01 (dd, 1 H) 7.79 - 7.87 (m, 2 H) 7.54 (d, 1 H) 6.99 - 7.06 (m, 2 H) 6.96 (d, 1 H) 3.97 (s, 3 H) 3.90 (s, 3 H);

MS (EI) m/z 282 [M]⁺.
Example 76

2-tert-Butyl-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide

The title compound was synthesized as described for Example 74 in 46% yield, starting from 2-tert-butylbenzofuran-5-carboxylic acid.

\(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) ppm: 8.36 (d, 1 H), 8.12 - 8.21 (m, 2 H), 7.86 - 7.97 (m, 2 H), 7.77 (dd, 1 H), 7.60 (d, 1 H), 7.43 (s, 2 H), 6.69 (s, 1 H), 1.35 (s, 9 H); MS (ESI) \(m/z\) 435 [M-I]⁻.

a) 1-tert-Butylbenzofuran-S-carboxylic acid

The title compound was synthesized as described for Example 74 a) in 94% yield, starting from methyl 2-tert-butylbenzofuran-5-carboxylate.

\(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) ppm: 12.77 (br. s., 1 H), 8.08 - 8.15 (m, 1 H), 7.78 (dd, 1 H), 7.54 (d, 1 H), 6.63 (d, 1 H), 1.30 (s, 9 H); MS (ESI) \(m/z\) 217 [M-I]⁻.

b) Methyl 2-tert-butylbenzofuran-5-carboxylate

The title compound was synthesized as described for Example 76 b) in 95% yield, starting from 3,3-Dimethyl-1-butyne as described.
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) ppm 8.09 (d, 1 H) 7.81 (dd, 1 H) 7.30 (d, 1 H) 6.28 (d, 1 H) 3.80 (s, 3 H) 1.26 (s, 9 H); MS (EI) \(m/z\) 232 [M]\(^+\).

**Example 77**

2-(1-Hydroxycyclopentyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide

![Chemical Structure](image)

The title compound was synthesized as described for Example 74 in 29% yield, starting from 2-(1-hydroxycyclopentyl)benzofuran-5-carboxylic acid.

\(^1\)H NMR (DMSO-\(\text{d}_6\)) \(\delta\) ppm 8.30 - 8.40 (m, 1 H) 8.12 - 8.23 (m, 2 H) 7.84 - 7.96 (m, 2 H) 7.75 - 7.81 (m, 1 H) 7.60 (d, 1 H) 7.42 (s, 2 H) 6.82 (s, 1 H) 5.40 (br. s., 1 H) 1.94 - 2.05 (m, 2 H) 1.80 - 1.94 (m, 4 H) 1.65 - 1.78 (m, 2 H); MS (ESI) \(m/z\) 463 [M-I] \(^-\).

**a)** 2-(1-Hydroxycyclopentyl)benzofuran-5-carboxylic acid

![Chemical Structure](image)

The title compound was synthesized as described for Example 74 a) in 99% yield, starting from methyl 2-(1-hydroxycyclopentyl)benzofuran-5-carboxylate.

\(^1\)H NMR (DMSO-\(\text{d}_6\)) \(\delta\) ppm 12.84 (br. s., 1 H) 8.21 (d, 1 H) 7.85 (dd, 1 H) 7.61 (d, 1 H) 6.84 (s, 1 H) 5.38 (s, 1 H) 1.95 - 2.07 (m, 2 H) 1.66 - 1.95 (m, 6 H); MS (ESI) \(m/z\) 245 [M-I] \(^-\).
b) Methyl 2-(1-hydroxycyclopentyl)benzofuran-5-carboxylate

![Methyl 2-(1-hydroxycyclopentyl)benzofuran-5-carboxylate](image)

The title compound was synthesized as described for Example 74 b) in 95% yield, starting from 1-ethynylcyclopentanol.

$^1$H NMR (CDCl$_3$) $\delta$ ppm 8.19 (dd, 1 H) 7.92 (dd, 1 H) 7.39 (d, 1 H) 6.61 (d, 1 H) 3.87 (s, 3 H) 2.06 - 2.20 (m, 2 H) 1.73 - 2.00 (m, 6 H); MS (EI) $m/z$ 260 [M]$^+$.

Example 78

2-Cyclopentyl-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide

![2-Cyclopentyl-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide](image)

The title compound was synthesized as described for Example 74 in 38% yield, starting from 2-cyclopentylbenzofuran-5-carboxylic acid.

$^1$H NMR (DMSO-$d_6$) $\delta$ 8.15 - 8.28 (m, 1 H) 7.97 - 8.06 (m, 2 H) 7.75 (br. s., 2 H) 7.62 (dt, 1 H) 7.39 - 7.49 (m, 1 H) 7.29 (s, 2 H) 6.59 (s, 1 H) 3.07 - 3.17 (m, 1 H) 1.86 - 1.96 (m, 2 H) 1.47 - 1.67 (m, 6 H); MS (ESI) $m/z$ 447 [M-I]$^-$.

a) 2-Cyclopentylbenzofuran-5-carboxylic acid

![2-Cyclopentylbenzofuran-5-carboxylic acid](image)

The title compound was synthesized as described for Example 74 a) in 83% yield, starting from methyl 2-cyclopentylbenzofuran-5-carboxylate.
Methyl 1-cyclopentylbenzofuran-S-carboxylate

The title compound was synthesized as described for Example 74 b) in 97% yield, starting from cyclopentylacetylene.

\[
\text{Example 79}
\]

3-Cyano-4-[(3,3-dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

A mixture of 4-bromo-3-cyano-N-(2-sulfamoylphenylsulfonyl)benzamide (0.11 g, 0.25 mmol), 3,3-dimethyl-1-butyn (0.046 mL, 0.37 mmol), copper(I) iodide (4.72 mg, 0.020 mmol), bis(triphenylphosphine)palladium(II) chloride (0.017 g, 0.020 mmol), and diisopropylamine (0.11 mL, 0.74 mmol) in 7V.7V-dimethylformamide(2 mL) under an atmosphere of argon was heated at 100 °C for 2 hours in a microwave. The reaction mixture was partitioned between ethyl acetate and diluted hydrochloric acid, the organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC followed by column chromatography, using 5% methanol in chloroform as the eluent, gave 0.020 g (18% yield) of the title compound.
\( ^1 \text{H NMR (DMSO-} \text{d}_6 \text{) \( \delta \) ppm} \)

- 8.00 - 8.06 (m, 2 H)
- 7.94 (dd, 1 H)
- 7.86 (dd, 1 H)
- 7.50 - 7.56 (m, 1 H)
- 7.45 - 7.50 (m, 1 H)
- 7.41 (d, 1 H)
- 7.28 (s, 2 H)
- 1.19 (s, 9 H); MS (ESI) m/z 444 [M-I]-

a) 4-Bromo-3-cyano-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 73 a) in 25% yield, starting from 4-bromo-3-cyano benzoic acid. Purification by column chromatography using a step-wise gradient of methanol (10-20%) in chloroform as the eluent. MS (ESI) m/z 442, 444 [M-I]-.

Example 80

4-(Benzofuran-2-yl)-3-cyano-N-(2-sulfamoylphenylsulfonyl)benzamide

A mixture of 4-bromo-3-cyano-N-(2-sulfamoylphenylsulfonyl)benzamide (0.24 g, 0.54 mmol), 2-benzofuranboronic acid (0.11 g, 0.70 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (0.044 g, 0.050 mmol), N,N-dimethylformamide (4 mL) and 2 M sodium carbonate (0.81 mL, 1.62 mmol) under an atmosphere of argon was heated at 120 °C for 0.5 hour in a microwave. The reaction mixture was partitioned between ethyl acetate and diluted hydrochloric acid, the organic phase was dried over magnesium sulfate and evaporated. Purification by preparative HPLC gave 0.071 g (27% yield) of the title compound.
Example 81

4-Chloro-2-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide

![Chemical Structure]

The title compound was synthesized as described for Example 61 a) in 1% yield, starting from 4-chloro-2-hydroxybenzoic acid.

1H NMR (CD3OD) δ ppm 8.21 (dd, 1 H) 8.09 (dd, 1 H) 7.69 (d, 1 H) 7.63 - 7.50 (m, 2 H) 6.71 (d, 1 H) 6.64 (dd, 1 H); MS (ESI) m/z 389 [M-I]−

Example 82

4-Bromo-2-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide

![Chemical Structure]

The title compound was synthesized as described for Example 61 a) in 1% yield, starting from 4-bromo-2-hydroxybenzoic acid.

1H NMR (6274 (m, 3 H) 6.98 (d, 1 H) 6.90 (dd, 1 H) MS (ESI) m/z 435, 433 [M-I]−
Example 83

4-(Benzofuran-2-yl)-2-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide

4-Bromo-2-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide (200mg, 0.46 mmol), benzofuran-2-ylboronic acid (81 mg, 0.50 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (37 mg, 0.05 mmol) and potassium carbonate (379 mg, 2.74 mmol) were dissolved in tetrahydrofuran (5 mL) and water (1 mL) in a microwave vial. The reaction was heated at 150 °C for 60 min in a microwave, filtered through a plug of celite and concentrated in vacuo. Purification by preparative HPLC gave 84 mg (39% yield) of the title compound.

\(^{1}\text{H} \text{NMR (DMSO-}\text{D}_6\text{)} \delta \text{ ppm} 7.29 (t, 1 \text{H}) 7.39 - 7.34 (m, 1 \text{H}) 7.46 (s, 2 \text{H}) 7.61 (s, 1 \text{H}) 7.65 (d, 1 \text{H}) 7.76 - 7.67 (m, 9 \text{H}) 7.85 (t, 1 \text{H}) 8.07 (d, 1 \text{H}) 8.23 (d, 1 \text{H}); \text{MS (ESI) } m/z 473 [M-I]^-}

a) 4-Bromo-2-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide

Benzene- 1,2-disulfonamide (1.0 g, 4.23 mmol), 4-bromo-2-fluorobenzoic acid (0.93 g, 4.23 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.14 g, 5.93 mmol) and 4-dimethylaminopyridine (1.29 g, 10.6 mmol) were dissolved in anhydrous N,N-dimethylformamide (15 mL) and the reaction was stirred at room temperature over night. Water was added and the solution was extracted with ethyl acetate. The aqueous phase was acidified using hydrochloric acid (2 M) and extracted with ethyl acetate. The
combined organic phases were washed with water, dried over magnesium sulfate, filtered and concentrated in vacuo to give 1.69 g (91% yield) of the title compound. MS (ESI) m/z 435, 437 [M-I].

Example 84

4-(3,3-Dimethylbut-1-ynyl)-2-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide

4-Bromo-2-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide (200 mg, 0.46 mmol), cuprous iodide (4 mg, 0.02 mmol), bis(triphenylphosphine)palladium(II) chloride (16 mg, 0.02 mmol), 3,3-dimethyl-1-butyne (0.169 mL, 1.37 mmol) and diisopropylamine (0.193 mL, 1.37 mmol) were slurried in anhydrous N,N-dimethylformamide (3 mL) in a microwave vial. The reaction was heated at 100 °C for 60 min in a microwave, filtered through a plug of celite and concentrated in vacuo. Purification by preparative HPLC gave 101 mg (50% yield) of the title compound. ³H NMR (DMSO-δ) δ ppm 8.17 - 8.13 (m, 1 H) 8.00 (dd, 1 H) 7.72 - 7.52 (m, 6 H) 7.10 - 7.04 (m, 2 H) 1.28 (s, 9 H); MS (ESI) m/z 437 [M-I].

Example 85

4-(Cyclopentylethynyl)-2-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide
The title compound was synthesized as described for Example 84 in 42% yield, starting from 4-bromo-2-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide and ethynylcyclopentane.

\(^1\)H NMR (DMSO-\(\text{d}_6\)) \(\delta\) ppm 8.15 (dd, 1 H) 8.00 (dd, 1 H) 7.71 - 7.52 (m, 6 H) 7.14 - 7.00 (m, 2 H) 2.86 (t, 1 H) 2.02 - 1.91 (m, 2 H) 1.70 (ddd, 2 H) 1.49 - 1.65 (m, 4 H); MS (ESI) \(m/z\) 449[M-I]~

**Example 86**

4-(Cyclopentylethynyl)-2-fluoro-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 84 in 9% yield, starting from 4-bromo-2-fluoro-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide and ethynylcyclopentane.

\(^1\)H NMR (CD\(_3\)OD) \(\delta\) ppm 8.35 (dd, 1 H) 8.21 (dd, 1 H) 7.76 - 7.66 (m, 2 H) 7.39 (t, 1 H) 7.07 (d, 1 H) 3.91 (s, 3 H) 2.96 - 2.85 (m, 1 H) 2.07 - 1.97 (m, 2 H) 1.84 - 1.61 (m, 6 H); MS (ESI) \(m/z\) 479 [M-I]~

a) 4-Bromo-2-fluoro-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 83 a) in 91% yield, starting from 4-bromo-2-fluoro-3-methoxybenzoic acid.
MS (ESI) $m/z$ 465, 467 [M-I]$^-$

**Example 87**

4-(Benzofuran-2-yl)-2-fluoro-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 83 in 14% yield, starting from 4-bromo-2-fluoro-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide.

$^1$H NMR (DMSO-$d_6$) $\delta$ ppm 12.78 (br. s., 1 H) 8.35 (dd, 1 H) 8.19 (dd, 1 H) 7.97 - 7.88 (m, 2 H) 7.77 (dd, 2 H) 7.66 (d, 1 H) 7.60 (s, 1 H) 7.49 (dd, 1 H) 7.45 (s, 2 H) 7.42 - 7.37 (m, 1 H) 7.31 (t, 1 H) 4.01 (s, 3 H); MS (ESI) $m/z$ 503 [M+I]$^+$

**Example 88**

5-(Cyclohexylethynyl)-N-(2-sulfamoylphenylsulfonyl)picolinamide

The title compound was synthesized as described for Example 84 in 4% yield, starting from 5-bromo-N-(2-sulfamoylphenylsulfonyl)picolinamide and ethynylcyclohexane.

$^1$H NMR (CDCl$_3$) $\delta$ ppm 8.21 (s, 1 H) 8.12 (d, 1 H) 7.90 (d, 1 H) 7.73 (d, 1 H) 7.46 (d, 1 H) 7.38 (t, 1 H) 7.33 (t, 1 H) 2.39 - 2.27 (m, 1 H) 1.56 - 1.63 (m, 2 H) 1.50 - 1.40 (m, 2 H) 1.29 - 1.20 (m, 2 H) 1.13 - 1.02 (m, 4 H); MS (ESI) $m/z$ 446 [M-I]$^-$
a) 5-Bromo-N-(2-sulfamoylphenylsulfonyl)picolinamide

The title compound was synthesized as described for Example 83a) in 57% yield, starting from 5-bromopicolinic acid made acidic.

MS (ESI) m/z 418, 420 [M-I]−

**Example 89**

5-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)picolinamide

The title compound was synthesized as described for Example 84 in 4% yield, starting from 5-bromo-N-(2-sulfamoylphenylsulfonyl)picolinamide and 3,3-dimethylbut-1-yne.

$^1$H NMR (CDCl$_3$) δ ppm 8.24 (s, 1 H) 8.16 (d, 1 H) 7.92 (d, 1 H) 7.69 (d, 1 H) 7.51 - 7.41 (m, 3 H) 1.02 (s, 9 H); MS (ESI) m/z 420 [M-I]−

**Example 90**

4-(3,3-Dimethylbut-1-ynyl)-2-fluoro-3-methoxy-N-(2-sulfamoylphenylsulfonyl)-benzamide
The title compound was synthesized as described for Example 84 in 8% yield, starting from 4-bromo-2-fluoro-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide and 3,3-dimethylbut-1-yne but was heated at 100 °C for 180 min in a microwave.

\[ ^1H \text{ NMR (CDCl}_3) \delta \text{ ppm} \]

8.22 - 8.16 (m, 1 H) 8.00 - 7.95 (m, 1 H) 7.57 - 7.50 (m, 2 H) 7.10 (t, 1 H) 6.84 (d, 1 H) 3.66 (s, 3 H) 1.02 (s, 9 H); MS (ESI) \text{ m/z 467 [M-I]}^{-}

**Example 91**

4-(Benzofuran-2-yl)-2-chloro-N-(2-sulfamoylphenylsulfonyl)benzamide

![Image of the compound]

The title compound was synthesized as described for Example 83 in 8% yield, starting from 4-bromo-2-chloro-N-(2-sulfamoylphenylsulfonyl)benzamide but was heated at 150 °C for 15 min in a microwave.

\[ ^1H \text{ NMR (CD}_3\text{OD)} \delta \text{ ppm} \]

8.53 (dd, 1 H) 8.33 (dd, 1 H) 8.01 (d, 1 H) 7.93 - 7.88 (m, 3 H) 7.70 (d, 1 H) 7.66 (d, 1 H) 7.58 (d, 1 H) 7.37 (t, 1 H) 7.28 (t, J=7.25 Hz, 1 H); MS (ESI) \text{ m/z 489 [M-I]}^{-}

**a)** 4-Bromo-2-chloro-N-(2-sulfamoylphenylsulfonyl)benzamide

![Image of the compound a)]

The title compound was synthesized as described for Example 83 a) in 80% yield, starting from 4-bromo-2-chlorobenzoic acid.

MS (ESI) \text{ m/z 451, 453 [M-I]}^{-}
Example 92

4-(Cyclopentylethynyl)-2-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 83 in 35% yield, starting from 4-bromo-2-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide and ethynylcyclopentane but was heated at 100 °C for 30 min in a microwave: ¹H NMR CD₃OD δ ppm 8.33 (dd, 1 H) 8.20 (dd, 1 H) 7.75 (d, 1 H) 7.69 (ddd, 2 H) 6.78 - 6.72 (m, 2 H) 2.88 - 2.82 (m, 1 H) 2.05 - 1.98 (m, 2 H) 1.835 - 1.75 (m, 2 H) 1.71 - 1.62 (m, 4 H);

MS (ESI) m/z 447 [M-1]⁻

Example 93

6-(Cyclopentylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide

Copper(I) iodide (0.267 µL, 7.88 µmol) was added to a stirred solution of 6-bromo-N-(2-sulfamoylphenylsulfonyl)nicotinamide (0.177 g, 0.42 mmol), cyclopentylacetylene (0.050 mL, 0.43 mmol), tetrakis(triphenylphosphine)palladium(0) (0.0301 g, 0.03 mmol) and triethylamine (1 mL, 7.2 mmol) in N,N-dimethylformamide (5 mL) under an atmosphere of nitrogen. The resulting mixture was heated at 65 °C over night. Water and ethyl acetate was added and the aqueous phase was washed with ethyl acetate. The aqueous phase was acidified (pH ~ 2) with 2 M hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with water/brine (1:1) and brine, dried over magnesium sulfate and the solvent was evaporated. Dissolved in dichloromethane and the organic phase was washed
with water and water/brine (1:1), dried over magnesium sulfate and the solvent was evaporated to give 0.090 g (49% yield) of the title compound.

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) ppm 8.92 (d, 1 H) 8.27 - 8.38 (m, 1 H) 8.07 - 8.21 (m, 2 H) 7.78 - 7.90 (m, 2 H) 7.51 (d, 1 H) 7.45 (br. s., 2 H) 2.85 - 2.99 (m, 1 H) 1.90 - 2.07 (m, 2 H) 1.52 - 1.78 (m, 6 H). MS (ESI) \(m/z\) 434.1 [M+H]^+, 432.2 [M-H].

\textbf{Example 94}

6-(Pyridin-2-ylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide

\begin{align*}
\text{1H NMR (400 MHz, DMSO-} \_\_\text{)} & \delta\text{ ppm 8.80 (d, 1 H) 8.29 - 8.37 (m, 1 H) 8.08 - 8.16 (m, 2 H) 7.81 - 7.92 (m, 2 H) 7.78 (d, 1 H) 7.46 (m, 1 H); MS (ESI) } m/z \text{ 420.0 [M+H]^+, 421.8 [M-H]^\text{.}}
\end{align*}
The title compound was synthesized as described for Example 93 in 46% yield, starting from 2-ethynylpyridine.

\[ \text{H NMR (400 MHz, DMSO-d_6) \delta ppm 9.04 (d, 1 H) 8.67 (d, 1 H) 8.30 - 8.37 (m, 1 H) 8.27 (dd, 1 H) 8.09 - 8.16 (m, 1 H) 7.87 - 7.97 (m, 1 H) 7.73 - 7.88 (m, 4 H) 7.41 - 7.53 (m, 3 H); MS (ESI) } m/z 443.0 [M+H]^+, 441.2 [M-H].\]

**Example 95**

6-(Pyridin-3-ylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide

![Chemical Structure](image)

The title compound was synthesized as described for Example 93 in 17% yield, starting from 3-ethynylpyridine.

\[ \text{H NMR (400 MHz, DMSO-d_6) \delta ppm 9.03 (d, 1 H) 8.85 (d, 1 H) 8.67 (dd, 1 H) 8.31 - 8.38 (m, 1 H) 8.27 (dd, 1 H) 8.07 - 8.16 (m, 2 H) 7.82 - 7.90 (m, 2 H) 7.79 (d, 1 H) 7.54 (dd, 1 H) 7.47 (br. s., 2 H); MS (ESI) } m/z 443.0 [M+H]^+, 441.2 [M-H].\]

**Example 96**

2-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)pyrimidine-5-carboxamide

![Chemical Structure](image)

The title compound was synthesized as described for Example 93 a) in 59% yield, starting from of 2-(3,3-dimethylbut-1-ynyl)pyrimidine-5-carboxylic acid. The residue was dissolved in warm dichloromethane/methanol (9: 1), a small amount of dichloromethane
was added and the mixture was allowed to cool down. The formed precipitate was removed by filtration, washed with dichloromethane and dried in vacuo.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.99 (s, 2 H) 8.18 (dd, 1 H) 8.00 (dd, 1 H) 7.57 - 7.72 (m, 2 H) 7.39 (s, 2 H) 1.31 (s, 9 H); MS (ESI) $m/z$ 423.0 [M+H]$^+$, 421.2 [M-H]$^-$. 

**a) 2-(3,3-Dimethylbut-1-ynyl)pyrimidine-5-carboxylic acid**

![Chemical Structure Image]

A solution of lithium hydroxide monohydrate (0.047 g, 1.13 mmol) in water (1 mL) was added to a solution of methyl 2-(3,3-dimethylbut-1-ynyl)pyrimidine-5-carboxylate (0.080 g, 0.37 mmol) in tetrahydrofuran (4 mL) and the mixture was stirred at room temperature overnight. Water was added and the pH was set to ~1 with 2 M hydrochloric acid. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with water and brine, dried over magnesium sulfate and concentrated to give 0.061 g (82% yield) of the title compound.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 13.65 (s, 1 H) 8.85 (d, 1 H) 8.16 (dd, 1 H) 7.80 (d, 1 H); MS (ESI) $m/z$ 205.0 [M+H]$^+$, 203.1 [M-H]$^-$. 

**b) Methyl 2-(3,3-dimethylbut-1-ynyl)pyrimidine-5-carboxylate**

![Chemical Structure Image]

Water (2 mL) was added to a stirred suspension of methyl 2-chloropyrimidine-5-carboxylate (0.306 g, 1.77 mmol), (2-tert-butyl-1-ethynyl)diisoproxyborane (0.45 mL,
1.91 mmol), [l,r-bis(diphenylphosphino)ferrocene]palladium(II) chloride (0.111 g, 0.14 mmol) and potassium carbonate (0.770 g, 5.57 mmol) in tetrahydrofuran (8 mL) and the resulting mixture was heated at 60°C over night. Water and ethyl acetate was added. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with water and brine, dried over magnesium sulfate and the solvent was evaporated. Purification by column chromatography, using 0-10% methanol in dichloromethane as the eluent, gave 0.082 g (21% yield) of the title compound.

1H NMR (400 MHz, DMSO-J6) δ ppm 9.16 (s, 2 H) 3.91 (s, 3 H) 1.33 (s, 9 H).

Example 97

N-(2-Sulfamoylphenylsulfonyl)-4-((3,3,3-trifluoropropoxy)methyl)benzamide

![Chemical structure](image)

The title compound was synthesized as described for Example 93 a) in 43% yield, starting from 4-((3,3,3-trifluoropropoxy)methyl)benzoic acid. Purification by column chromatography, using a gradient of 0-10% methanol in dichloromethane as the eluent.

1H NMR (400 MHz, DMSO-J6) δ ppm 8.35 (dd, 1 H) 8.16 (dd, 1 H) 7.85 - 7.96 (m, 4 H) 7.36 - 7.46 (m, 4 H) 4.57 (s, 2 H) 3.66 (t, 2 H) 2.53 - 2.68 (m, 2 H); MS (ESI) m/z 465.2 [M-H]-.

a) 4-((3,3,3-Trifluoropropoxy)methyl)benzoic acid

![Chemical structure](image)

The title compound was synthesized as described for Example 96 a) in 82% yield, starting
from methyl 4-((3,3,3-trifluoropropoxy)methyl)benzoate.

1H NMR (400 MHz, CDCl3) δ ppm 8.12 (d, 2 H) 7.45 (d, 2 H) 4.63 (s, 2 H) 3.74 (t, 2 H) 2.38 - 2.61 (m, 2 H); MS (ESI) m/z 247.2 [M-H]⁻.

b) Methyl 4-((3,3,3-trifluoropropoxy)methyl)benzoate

3,3,3-Trifluoropropan-l-ol (0.200 mL, 2.27 mmol) was added dropwise to a stirred suspension of sodium hydride (0.084 mL, 2.52 mmol, prewashed with heptane) in tetrahydrofuran (2 mL) and the resulting mixture was stirred at room temperature for 5 min. A solution of methyl 4-(bromomethyl)benzoate (0.519 g, 2.27 mmol) in tetrahydrofuran (2.5 mL) was added dropwise followed by addition of tetrabutylammonium iodide (0.083 g, 0.22 mmol). The mixture was heated at 65°C for 2.5 hours and was then allowed to cool down to room temperature. Water was added and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried over magnesium sulfate and the solvent was evaporated. Purification by column chromatography, using 0-100% ethyl acetate in n-heptane as the eluent, gave 0.435 g (73% yield) of the title compound.

1H NMR (400 MHz, CDCl3) δ ppm 8.04 (d, 2 H) 7.37 - 7.46 (m, 2 H) 4.60 (s, 2 H) 3.93 (s, 3 H) 3.72 (t, 2 H) 2.37 - 2.55 (m, 2 H); MS (ESI) m/z 261.2 [M-H]⁻.

Example 98

4-(Cyclopentylethynyl)-3-(hydroxymethyl)-N-(2-sulfamoylphenylsulfonyl)benzamide
Copper(I) iodide (0.89 µL, 0.03 mmol) was added to a stirred solution of 4-bromo-3-(hydroxymethyl)-N-(2-sulfamoylphenylsulfonyl)benzamide (0.1970 g, 0.44 mmol), cyclopentylacetylene (0.050 mL, 0.43 mmol), tetrakis(triphenylphosphine)palladium(0) (0.0251 g, 0.02 mmol) and triethylamine (0.92 mL, 6.60 mmol) in N,N-dimethylformamide (6 mL) under an atmosphere of nitrogen. The resulting mixture was heated at 65°C over night. Another portion of cyclopentylacetylene (0.050 mL, 0.43 mmol) was added, and the mixture was stirred at 65 °C over night. Water and ethyl acetate was added and the aqueous phase was washed with ethyl acetate. The aqueous phase was acidified (pH ~ 2) with 2 M hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with water/brine (1:1) and brine, dried over magnesium sulfate and the solvent was evaporated. Purification by column chromatography, using a gradient of 0-10% methanol in dichloromethane as the eluent, followed by purification by preparative HPLC gave 0.045 g (22% yield) of the title compound.

1H NMR (400 MHz, DMSO-Δ) δ ppm 8.22 - 8.34 (m, 1 H) 8.05 - 8.16 (m, 1 H) 8.00 (s, 1 H) 7.76 - 7.91 (m, 2 H) 7.70 - 7.76 (m, 1 H) 7.40 (s, 2 H) 7.31 - 7.38 (m, 1 H) 4.59 (s, 2 H) 2.86 - 2.98 (m, 1 H) 1.99 (s, 2 H) 1.68 - 1.78 (m, 2 H) 1.51 - 1.68 (m, 4 H); MS (ESI) m/z 463.1 [M+H]+, 461.3 [M-H].

a) 4-Bromo-3-(hydroxymethyl)benzoic acid

The title compound was synthesized as described for Example 96 a) in 98% yield, starting from methyl 3-(acetoxymethyl)-4-bromobenzoate.

1H NMR (400 MHz, DMSO-Δ) δ ppm 13.12 (br. s., 1 H) 8.11 (d, 1 H) 7.64 - 7.78 (m, 2 H) 5.59 (br. s., 1 H) 4.54 (br. s., 2 H); MS (ESI) m/z 229 and 231 [M-H].
b) Methyl 3-(acetoxymethyl)-4-bromobenzoate

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{O} & \quad \text{Br}
\end{align*}
\]

Potassium acetate (1.89 g, 19.3 mmol) was added to a solution of methyl 4-bromo-3-(bromomethyl)benzoate (3.015 g, 9.79 mmol) in acetic acid (12 mL) and the mixture was heated at 100 °C for 5 hours. Water and ethyl acetate was added. The aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, saturated sodium hydrogen carbonate and brine, dried over magnesium sulfate and the solvent was evaporated. Purification by column chromatography, using 0-30% ethyl acetate in n-heptane as the eluent, gave 1.61 g (57% yield from methyl 4-bromo-3-methylbenzoate).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 8.07 (d, 1 H) 7.86 (dd, 1 H) 7.67 (d, 1 H) 5.23 (s, 2 H) 3.94 (s, 3 H) 2.18 (s, 3 H).

c) Methyl 4-bromo-3-(bromomethyl)benzoate

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{O} & \quad \text{Br}
\end{align*}
\]

N-Bromosuccinimide (1.0 mL, 12 mmol) and 2,2'-azobisisobutyronitrile (0.005 g, 0.03 mmol) was added to a stirred solution of methyl 4-bromo-3-methylbenzoate (2.190 g, 9.56 mmol) in carbon tetrachloride (50 mL) and the resulting mixture was stirred at 70 °C for 2.5 days. Water and chloroform was added. The aqueous phase was extracted with chloroform and the combined organic phases were washed with water and 5% aqueous sodium hydrogen carbonate, dried over magnesium sulfate and the solvent was evaporated to give 3.015 g of the title compound.

GC MS (EI) \(m/z\) 308 [M]+.
Example 99

6-(3-Methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide

The title compound was synthesized as described for Example 93 in 40% yield, starting from 6-bromo-N-(2-sulfamoylphenylsulfonyl)nicotinamide and 3-methyl-1-butyn but the mixture was heated at 65 °C for 1.5 hours. Purification by column chromatography, using dichloromethane/methanol (85:15) as the eluent.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.93 (d, 1 H) 8.30 - 8.39 (m, 1 H) 8.09 - 8.21 (m, 2 H) 7.80 - 7.94 (m, 2 H) 7.54 (d, 1 H) 7.45 (br. s., 2 H) 2.79 - 2.94 (m, 1 H) 1.23 (d, 6 H); MS (ESI) $m/z$ 408.1 [M+H]$^+$, 406.3 [M-H]$^-$. 

Example 100

3-(Hydroxymethyl)-4-(phenylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 93 in 29% yield, starting from 4-bromo-3-(hydroxymethyl)-N-(2-sulfamoylphenylsulfonyl)benzamide and phenylacetylene but was heated at 65 °C for 2 days. Purification by preparative HPLC.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.29 - 8.40 (m, 1 H) 8.11 - 8.19 (m, 1 H) 8.05 (s, 1 H) 7.86 - 7.93 (m, 2 H) 7.84 (dd, 1 H) 7.56 - 7.63 (m, 3 H) 7.43 - 7.50 (m, 3 H) 7.42 (br. s., 2 H) 4.73 (s, 2 H); MS (ESI) $m/z$ 471.1 [M+H]$^+$, 469.3 [M-H]$^-$. 


Example 101

4-(Cyclohexylethynyl)-3-(hydroxymethyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 93 in 32% yield, starting from 4-bromo-3-(hydroxymethyl)-N-(2-sulfamoylphenylsulfonyl)benzamide and cyclohexylacetylene but was heated at 65 °C for 3 days. Purification by preparative HPLC.  

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.33 (dd, 1 H) 8.10 - 8.20 (m, 1 H) 7.99 (s, 1 H) 7.82 - 7.95 (m, 2 H) 7.76 (dd, 1 H) 7.32 - 7.46 (m, 3 H) 4.61 (s, 2 H) 2.68 - 2.81 (m, 1 H) 1.81 (dd, 2 H) 1.59 - 1.74 (m, 2 H) 1.44 - 1.59 (m, 3 H) 1.28 - 1.44 (m, 3 H); MS (ESI) $m/z$ 477.1 [M+H]$^+$, 475.3 [M-H].

Example 102

2-((4-chlorophenyl)ethynyl)-N-(2-sulfamoylphenylsulfonyl)pyrimidine-5-carboxamide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.0857 g, 0.45 mmol) was added to a solution of benzene-1,2-disulfonamide (0.0753 g, 0.32 mmol), 2-((4-chlorophenyl)ethynyl)pyrimidine-5-carboxylic acid (0.080 g, 0.31 mmol) and 4-dimethylaminopyridine (0.0567 g, 0.46 mmol) in N,N-dimethylformamide (15 mL) at room temperature and the mixture was stirred overnight. Water was added and the aqueous phase was washed with ethyl acetate. The aqueous phase was acidified to pH ~ 1 with 2 M hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over magnesium sulfate and the solvent was
evaporated. Purification by preparative HPLC gave 0.042 g (29% yield) of the title compound.

\[^1^H\text{NMR}\ (400\ \text{MHz, DMSO}-\text{J}_6)\ \delta\ \text{ppm} \ 9.12\ (s,\ 2\ H)\ 8.26\ (dd,\ 1\ H)\ 8.06\ (dd,\ 1\ H)\ 7.67 - 7.78\ (m,\ 4\ H)\ 7.52 - 7.61\ (m,\ 2\ H)\ 7.44\ (br.\ s.,\ 2\ H);\ MS\ (ESI)\ m/z\ 477.0\ [M+H]^+, 475.2 [M-H].

a) 2-((4-Chlorophenyl)ethynyl)pyrimidine-5-carboxylic acid

The title compound was synthesized as described for Example 96 a) in 85% yield, starting from methyl 2-((4-chlorophenyl)ethynyl)pyrimidine-5-carboxylate.

\[^1^H\text{NMR}\ (400\ \text{MHz, DMSO}-\text{J}_6)\ \delta\ \text{ppm} \ 13.71 - 14.20\ (br.\ s.,\ 1\ H)\ 9.22\ (s,\ 2\ H)\ 7.68 - 7.85\ (m,\ 2\ H)\ 7.49 - 7.67\ (m,\ 2\ H);\ MS\ (ESI)\ m/z\ 259.0\ [M+H]^+, 257.1 [M-H].

b) Methyl 2-((4-chlorophenyl)ethynyl)pyrimidine-5-carboxylate

The title compound was synthesized as described for Example 93 in 26% yield, starting from methyl 2-chloropyrimidine-5-carboxylate and 1-chloro-4-ethynylbenzene but was heated at 65 °C for 3 hours. Purification by preparative HPLC.

\[^1^H\text{NMR}\ (400\ \text{MHz, DMSO}-\text{J}_6)\ \delta\ \text{ppm} \ 9.26\ (s,\ 2\ H)\ 7.68 - 7.82\ (m,\ 2\ H)\ 7.53 - 7.65\ (m,\ 2\ H)\ 3.93\ (s,\ 3\ H);\ MS\ (ESI)\ m/z\ 273.0\ [M+H]^+. 
Example 103

4-(Benzofuran-2-yl)-3-(hydroxymethyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

![Chemical structure](image)

4-Bromo-3-(hydroxymethyl)-N-(2-sulfamoylphenylsulfonyl)benzamide (0.1912 g, 0.43 mmol), benzofuran-2-ylboronic acid (0.0783 g, 0.48 mmol), potassium carbonate (0.2428 g, 1.76 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride (0.0385 g, 0.05 mmol) in tetrahydrofuran (10 mL) and water (2 mL) was heated at 65 °C overnight. Water and ethyl acetate was added and the aqueous phase was acidified with hydrochloric acid (2 M). The aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, water/brine (1:1) and brine, dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC gave 0.042 g (20% yield) of the title compound.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 8.29 - 8.39 (m, 1 H) 8.18 (s, 1 H) 8.11 - 8.17 (m, 1 H) 7.92 - 8.02 (m, 2 H) 7.82 - 7.92 (m, 2 H) 7.72 (s, 1 H) 7.65 (s, 1 H) 7.42 (d, 3 H) 7.38 (s, 1 H) 7.30 (s, 1 H) 4.78 (s, 2 H); MS (ESI) m/z 487.1 [M+H]$^+$, 485.3 [M-H]$^-$.  

Example 104

4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide

![Chemical structure](image)

4-(Benzofuran-2-yl)cyclohexanecarboxylic acid (0.337 g, 1.38 mmol), N-(3-dimethylaminopropyl)-N'-ethylecarbodiimide hydrochloride (0.264 g, 1.38 mmol) and 4-(dimethylamino)pyridine (0.234 g, 1.92 mmol) were added to a solution of benzene-1,2-
disulfonamide (0.181 g, 0.77 mmol) in N,N-dimethylformamide (10 mL) at room temperature. The reaction mixture was stirred for 3 hours and the solvent was evaporated. Purification by preparative HPLC gave 0.14 g (38% yield) of the title compound as a mixture of regioisomers.

a) 4-(Benzofuran-2-yl)cyclohexanecarboxylic acid

A solution of sodium hypochlorite (0.147 g, 1.97 mmol and sulfamic acid (0.191 g, 1.97 mmol) in water (5 mL) was added dropwise to a cooled (0°C) solution of 4-(benzofuran-2-yl)cyclohexanecarbaldehyde (0.300 g, 1.31 mmol) in tetrahydrofuran (15 mL). The reaction mixture was stirred at 0°C for 10 min and was then allowed to reach 10°C before the reaction was quenched with solid sodium thiosulphate. The resulting mixture was partitioned between brine and ethyl acetate, the organic phase was dried over magnesium sulfate and the solvent was evaporated to give 0.38 g (quantitative yield) of the title compound.

b) 4-(Benzofuran-2-yl)cyclohexanecarbaldehyde

A solution of potassium tert-butoxide (1.006 g, 8.96 mmol) dissolved in tetrahydrofuran (15 mL) was added dropwise to a cooled (0°C) solution of (methoxymethyl)triphenylphosphonium chloride (3.07 g, 8.96 mmol) in tetrahydrofuran (15 mL) under an atmosphere of argon. The reaction mixture was stirred for 15 min at 0°C and was then allowed to reach room temperature. A solution of 4-(benzofuran-2-yl)cyclohexanone (0.960 g, 4.48 mmol, WO 2004099191 A2) in tetrahydrofuran (15 mL) was added dropwise and the mixture was stirred over night. The reaction mixture was cooled to 0°C and water (10 mL) and 6 M aqueous hydrochloric acid (10 mL) were added.
dropwise. The resulting mixture was stirred for 1 hour at room temperature and was then extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and the solvent was evaporated. Purification by column chromatography, using heptane/ethyl acetate (13:1-10:1) as the eluent, gave 0.31 g (30% yield) of the title compound.

GC MS (EI) m/z 228 [M]+.

Example 105

(ls,4s)-4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide

The regioisomers of 4-(benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl) cyclohexanecarboxamide (0.125 g, 0.27 mmol) were separated by preparative chromatography was run on a SFC Berger Multigram system with a Knauer K-2501 UV detector. Column; Chiracel AD 10µm 21.2 x 250mm. The column temperature was set to 35°C. An isocratic condition of 40% ethanol and 60% C₂O was applied at flow rate 50.0 mL/min. The UV detector scanned at 220 nm. The UV signal determined the fraction collection, to give 0.033 g (26% yield) of the title compound.

¹H NMR (400 MHz, CD₃OD) δ ppm 8.37 (dd, 1 H), 8.09 - 8.30 (m, 1 H), 7.72 - 7.92 (m, 2 H), 7.40 - 7.54 (m, 1 H), 7.34 (d, 1 H), 7.03 - 7.27 (m, 2 H), 6.39 (s, 1 H), 2.82 - 3.07 (m, 1 H), 2.53 (d, 1 H), 1.87 - 2.12 (m, 2 H), 1.73 - 1.89 (m, 4 H), 1.56 - 1.74 (m, 2 H); MS (ESI) m/z 461 [M-I]−
Example 106
(lr,4r)-4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide

The regioisomers of 4-(benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide (0.125 g, 0.27 mmol) were separated by preparative chromatography was run on a SFC Berger Multigram system with a Knauer K-2501 UV detector. Column: Chiralcel AD 10 µm 21.2 x 250mm. The column temperature was set to 35°C. An isocratic condition of 40% ethanol and 60% C₂O was applied at flow rate 50.0 mL/min. The UV detector scanned at 220 nm. The UV signal determined the fraction collection, to give 0.065 g (52% yield) of the title compound.

1H NMR (400 MHz, CD₃OD) δ ppm 8.41 (dd, 1 H), 8.26 (dd, 1 H), 7.71 - 7.96 (m, 2 H), 7.40 - 7.57 (m, 1 H), 7.35 (d, 1 H), 7.03 - 7.28 (m, 2 H), 6.41 (s, 1 H), 2.54 - 2.86 (m, 1 H), 2.28 - 2.47 (m, 1 H), 2.18 (dd, 2 H), 1.80 - 2.07 (m, 2 H), 1.21 - 1.66 (m, 4 H); MS (ESI) m/z 461 [M-I]⁻.

Example 107
4-(Benzofuran-2-yl)-l-methyl-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide

4-(Benzofuran-2-yl)-l-methylcyclohexanecarboxylic acid (0.158 g, 0.61 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.176 g, 0.92 mmol) and 4-dimethylaminopyridine (0.156 g, 1.27 mmol) were added to a solution of benzene-1,2-disulfonamide (0.120 g, 0.51 mmol) in N,N-dimethylformamide (10 mL) at room
temperature and stirred over night. More of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.076 g, 0.40 mmol) and 4-dimethylaminopyridine (0.056 g, 0.46 mmol) were added. The reaction mixture was stirred for another 2 hours and was then partitioned between water and ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC gave 0.112 g (46% yield) of the title compound as a mixture of regioisomers.

MS (ESI) m/z 475 [M-I].

\[ \text{a) 4-(Benzofuran-2-yl)-1-methylcyclohexanecarboxylic acid} \]

The title compound was synthesized as described for 104 b) in 86% yield, starting from 4-(benzofuran-2-yl)-1-methylcyclohexanecarbaldehyde.

MS (ES-) m/z 257 [M-I].

\[ \text{b) 4-(Benzofuran-2-yl)-1-methylcyclohexanecarbaldehyde} \]

Potassium tert-butoxide (0.151 g, 1.34 mmol) was added to a cooled solution (0 °C) of 4-(benzofuran-2-yl)cyclohexanecarbaldehyde (0.216 g, 1.02 mmol) in dichloromethane (15 mL) followed by addition of iodomethane (0.193 mL, 3.10 mmol). The mixture was stirred at 0 °C for 30 min, the cooling was removed and the mixture was stirred at room temperature for another 1.5 hour. The reaction mixture was partitioned between brine and dichloromethane. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by column chromatography, using heptane/ethyl acetate (10:1) as the eluent, gave 0.173 g (69% yield) of the title compound.

GC MS (EI) m/z 242 [M]+.
Example 108

(lr,4r)-4-(Benzofuran-2-yl)-1-methyl-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide

The regioisomers 4-(benzofuran-2-yl)-1-methyl-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide (0.111g, 0.23 mmol) were separated by preparative chromatography was run on a SFC Berger Multigram system with a Knauer K-2501 UV detector. Column; Chiralcel OD 10μm 21.2 x 250mm. The column temperature was set to 35 °C. An isocratic condition of 40% methanol + 0.1% DEA and 60% C₂O was applied at flow rate 50.0 mL/min. The UV detector scanned at 220nm. The UV signal determined the fraction collection, to give 0.064 g (58% yield) of the title compound.

¹H NMR (400 MHz, CD₃OD) δ ppm 8.20 (d, 1 H), 8.15 (dd, 1 H), 7.54 - 7.65 (m, 2 H), 7.44 - 7.51 (m, 1 H), 7.36 (d, 1 H), 7.07 - 7.21 (m, 2 H), 6.34 (s, 1 H), 2.59 - 2.74 (m, 1 H), 2.37 (d, 2 H), 1.93 (d, 2 H), 1.65 (d, 2 H), 1.17 - 1.25 (m, 2 H), 1.14 (s, 3 H); MS (ESI) m/z 461 [M-I].

Example 109

(ls,4s)-4-(Benzofuran-2-yl)-1-methyl-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide

The regioisomers of 4-(benzofuran-2-yl)-1-methyl-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide (0.111g, 0.23 mmol) were separated by preparative
chromatography was run on a SFC Berger Multigram system with a Knauer K-2501 UV detector. Column; Chiralcel OD 10µm 21.2 x 250mm. The column temperature was set to 35 °C. An isocratic condition of 40% methanol + 0.1% DEA and 60% C₂O was applied at flow rate 50.0 mL/min. The UV detector scanned at 220nm. The UV signal determined the fraction collection, to give 0.011 g (10% yield) of the title compound.

\[ ^1H \text{NMR} (400 \text{ MHz, CD}_3\text{OD}) \delta \text{ ppm 8.14 - 8.30} (m, 2 \text{ H}), 7.61 - 7.76 (m, 2 \text{ H}), 7.46 - 7.54 (m, 1 \text{ H}), 7.34 - 7.43 (m, 1 \text{ H}), 7.10 - 7.23 (m, 2 \text{ H}), 6.44 - 6.51 (m, 1 \text{ H}), 2.75 (br. s., 1 \text{ H}), 1.99 (br. s., 2 \text{ H}), 1.84 - 1.96 (m, 2 \text{ H}), 1.79 (br. s., 4 \text{ H}), 1.20 - 1.24 (m, 3 \text{ H}), MS (ESI) m/z 475 [M-I]. \]

**Example 110**

4-(3,3-Dimethylbut-1-ynyl)-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

\[
\text{4-Bromo-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide} \quad (0.227 \text{ g}, 0.51 \text{ mmol}), \\
\text{diisopropyl 3,3-dimethylbut-1-ynylboronate} \quad (0.238 \text{ mL}, 1.01 \text{ mmol}), 1,1'-
\text{bis(diphenylphosphino)ferrocene-palladium dichloride} \quad (0.042 \text{ g}, 0.05 \text{ mmol}) \text{ were dissolved in N,N-dimethylformamide (3 mL) under an atmosphere of argon and a solution of aqueous sodium carbonate (0.758 mL, 1.52 mmol) was added. The reaction mixture was heated in a microwave at 120 °C for 20 min under argon atmosphere. The reaction mixture was partitioned between water and ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC and gave 0.019 g (8% yield) of the title compound.} \\
^1H \text{NMR} (400 \text{ MHz, CD}_3\text{OD}) \delta \text{ ppm 8.35 (d, 1 H), 8.16 - 8.28} (m, 1 \text{ H}), 7.67 - 7.79 (m, 2 \text{ H}), 7.53 - 7.63 (m, 1 \text{ H}), 7.46 (d, 1 \text{ H}), 7.27 (d, 1 \text{ H}), 3.87 (s, 3 \text{ H}), 1.27 - 1.37 (m, 9 \text{ H}); MS (ESI) m/z 449 [M-I].
\]

\[
\text{MS (ESI) m/z 475 [M-I].}
\]
Example 111

4-(Cyclopropylethynyl)-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

Ethynylcyclopropane (0.215 mL, 2.54 mmol), tetrakis(triphenylphosphine)palladium(0) (0.049 g, 0.04 mmol) and triethylamine (1.763 mL, 12.69 mmol) was added to a solution of 4-bromo-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide (0.190 g, 0.42 mmol) in N,N-dimethylformamide (13 mL) under an atmosphere of argon. The reaction mixture was stirred at room temperature for 5 min, copper(I) iodide (0.012 g, 0.06 mmol) was added and the reaction mixture was heated at 65 °C. After 4 days was the reaction mixture filtered and the solvent was evaporated. Purification by preparative HPLC gave 0.088 g (48% yield) of the title compound.

$^1$H NMR (400 MHz, CD$_3$OD) δ ppm 8.30 (d, 1 H), 8.19 (d, 1 H), 7.57 - 7.74 (m, 3 H), 7.47 (d, 1 H), 7.24 (d, 1 H), 3.87 (s, 3 H), 1.42 - 1.56 (m, 1 H), 0.83 - 0.94 (m, 2 H), 0.69 - 0.80 (m, 2 H); MS (ESI) m/z 433 [M-I]$^-$. 

Example 112

4-(3-Methoxy-3-methylbut-1-ylnyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 111 in 36% yield, starting from 3-methoxy-3-methylbut-1-yne (Jackson, W. Roy et al, Aust. J. Chem., 1988, 41(2), 251-61) and 4-bromo-N-(2-sulfamoylphenylsulfonyl)benzamide.

$^1$H NMR (400 MHz, CD$_3$OD) δ ppm 8.29 (dd, 1 H), 8.19 (dd, 1 H), 7.98 (d, 2 H), 7.58 - 7.73 (m, 2 H), 7.39 (d, 2 H), 3.41 (s, 3 H), 1.52 (s, 6 H); MS (ESI) m/z 435 [M-I]$^-$. 
Example 113

4-(3-Methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

3-Methylbut-1-ynyl (0.085 g, 1.25 mmol), tetrakis(triphenylphosphine)palladium(0) (0.072 g, 0.06 mmol) and triethylamine (2.60 mL, 18.68 mmol) were added to a solution of 4-bromo-N-(2-sulfamoylphenylsulfonyl)benzamide (0.261 g, 0.62 mmol) in N,N-dimethylformamide (10 mL) under an atmosphere of argon. The reaction mixture was stirred at room temperature for 5 min, copper(I) iodide (0.018 g, 0.09 mmol) was added and the reaction mixture was heated at 65 °C over night. The reaction mixture was partitioned between water (set to pH~2 with aqueous 2 M hydrochloric acid) and ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC gave 0.058 g (23% yield) of the title compound.

$^1$H NMR (500 MHz, CD$_3$OD) δ ppm 8.38 (d, 1 H) 8.17 (d, 1 H) 7.73 - 7.80 (m, 2 H) 7.70 (d, 2 H) 7.32 (d, 2 H) 2.61 - 2.79 (m, 1 H) 1.16 (s, 3 H) 1.15 (s, 3 H); MS (ESI) m/z 405 [M-I]-.

Example 114

3-Methoxy-4-(3-methoxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 111 in 33% yield, starting from 4-bromo-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide and 3-methoxy-3-

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ ppm 8.29 (dd, 1 H), 8.21 (dd, 1 H), 7.62 - 7.76 (m, 3 H), 7.55 (d, 1 H), 7.30 (d, 1 H), 3.88 (s, 3 H), 3.43 (s, 3 H), 1.52 (s, 6 H); MS (ESI) m/z 465 [M-I]-.

Example 115

3-Hydroxy-4-(3-methoxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)-benzamide

![Chemical Structure](image)

The title compound was synthesized as described for Example 111 in 31% yield, starting from 4-bromo-3-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide and 3-methoxy-3-methylbut-1-yn (Jackson, W. Roy et al., Aust. J. Chem., 1988, 41(2), 251-61). Purification by preparative HPLC followed by column chromatography, using ethyl acetate/methanol (50:1 -30:1 + 1% triethylamine) as the eluent.

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ ppm 8.28 (dd, 1 H), 8.19 (dd, 1 H), 7.57 - 7.75 (m, 2 H), 7.48 (s, 1 H), 7.43 (d, 1 H), 7.24 (d, 1 H), 3.44 (s, 3 H), 1.53 (s, 6 H); MS (ESI) m/z 451 [M-I]-.

Example 116

6-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide

![Chemical Structure](image)

The title compound was synthesized as described for Example 110 in 25% yield, starting
Example 117
6-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide

The title compound was synthesized as described for Example 110 in 25% yield, starting from 6-bromo-N-(2-sulfamoylphenylsulfonyl)nicotinamide and benzofuran-2-ylboronic acid.

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ ppm 9.20 (br. s., 1 H), 8.47 (d, 1 H), 8.35 (dd, 1 H), 8.22 (dd, 1 H), 7.99 (d, 1 H), 7.63 - 7.78 (m, 3 H), 7.54 - 7.62 (m, 2 H), 7.33 - 7.45 (m, 1 H), 7.28 (t, 1 H); MS (ESI) m/z 456 [M-I]$^-$.

Example 118
4-(3,3-Dimethylbut-1-ynyl)-3-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 110 in 28% yield, starting from 4-bromo-3-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)benzamide and diisopropyl 3,3-dimethylbut-1-ynylboronate. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ ppm...
8.12 (dd, 1 H) 7.98 (dd, 1 H) 7.60 - 7.68 (m, 1 H) 7.53 - 7.60 (m, 1 H) 7.40 - 7.48 (m, 4 H)
7.21 (d, 1 H) 4.02 - 4.13 (m, 2 H) 3.73 - 3.82 (m, 2 H) 3.67 (dd, 2 H) 3.46 (dd, 2 H) 3.24 (s, 3 H) 1.27 (s, 9 H); MS (ESI) m/z 438 [M-I].

a) 4-Bromo-3-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfbnyl)-benzamide

2-(2-Methoxyethoxy)ethanol (0.309 mL, 2.60 mmol), triphenylphosphine (0.681 g, 2.60 mmol) and diisopropyl azodicarboxylate (0.511 mL, 2.60 mmol) were added to a solution of methyl 4-bromo-3-hydroxybenzoate (0.4 g, 1.7 mmol) in tetrahydrofuran (20 mL) and the reaction mixture was stirred at room temperature for 2 days. A solution of lithium hydroxide monohydrate (0.124 g, 5.19 mmol) in water (2 mL) was added and the reaction mixture was stirred for another 4 days. The reaction mixture acidified with 2.0 M aqueous hydrochloric acid and partitioned between water and ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated. The product 4-bromo-3-(2-(2-methoxyethoxy)ethoxy)benzoic acid (0.562 g, 1.76 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.506 g, 2.64 mmol) and 4-dimethylaminopyridine (0.323 g, 2.64 mmol) were added to a solution of benzene-1,2-disulfonamide (0.546 g, 2.31 mmol) in N,N-dimethylformamide (30 mL) at room temperature and stirred over night. Water was added and the solution was extracted with ethyl acetate. The aqueous phase was acidified with 2 M aqueous hydrochloric acid and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by column chromatography, using ethyl acetate/methanol (50:1 + 1% triethylamine) as the eluent, gave 0.55 g (60% yield) of the title compound.

1H NMR (400 MHz, CD3OD) δ ppm 8.45 - 8.55 (m, 1 H), 8.22 - 8.31 (m, 1 H), 7.81 - 7.89 (m, 2 H), 7.62 (d, 1 H), 7.53 (d, 1 H), 7.35 (dd, 1 H), 4.18 - 4.29 (m, 2 H), 3.83 - 3.91 (m, 2 H), 3.72 (dd, 2 H), 3.51 - 3.58 (m, 2 H), 3.27 - 3.35 (m, 3 H); MS (ES) m/z 435 and 437 [M-I].
Example 119

4-(Benzofuran-2-yl)-3-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)-benzamidine

The title compound was synthesized as described for Example 110 in 21% yield, starting from 4-bromo-3-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)benzamide and benzofuran-2-ylboronic acid.

\(^1\)H NMR (400 MHz, CD\(_2\)OD) \(\delta\) ppm 8.43 (d, 1 H), 8.20 - 8.30 (m, 1 H), 8.06 (d, 1 H), 7.73 - 7.84 (m, 3 H), 7.59 - 7.71 (m, 3 H), 7.53 (d, 1 H), 7.32 (td, 1 H), 7.15 - 7.27 (m, 1 H), 4.42 (dd, 2 H), 3.98 - 4.08 (m, 2 H), 3.77 - 3.84 (m, 2 H), 3.59 - 3.68 (m, 2 H), 3.36 - 3.40 (m, 3 H); MS (ESI) \(m/z\) 573 [M-I]⁻.

Example 120

2-(2-Methoxyphenyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide

2-(2-Methoxyphenyl)benzofuran-5-carboxylic acid (0.058 g, 0.22 mmol) N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride (0.062 g, 0.32 mmol) and 4-dimethylaminopyridine (0.026 g, 0.22 mmol) were added to a solution of benzene-1,2-disulfonamide (0.051 g, 0.22 mmol) in N,N-dimethylformamide (4 mL). The reaction mixture was stirred at room temperature over night and the solvent was evaporated. Purification by column chromatography, using ethyl acetate/methanol (40:1 +1% triethylamine) as the eluent, gave 0.042 g (83% yield) of the title compound.

\(^1\)H NMR (400 MHz, DMSO-J\(_6\)) \(\delta\) ppm 8.21 (d, 1 H), 8.17 (dd, 1 H), 8.00 (dd, 1 H), 7.95
(dd, 1 H), 7.90 (dd, 1 H), 7.61 - 7.69 (m, 1 H), 7.54 - 7.61 (m, 1 H), 7.46 - 7.54 (m, 3 H), 7.36 - 7.45 (m, 2 H), 7.20 (d, 1 H), 7.06 - 7.15 (m, 1 H), 3.99 (s, 3 H); MS (ESI) m/z 485 [M-I].

a) 2-(2-Methoxyphenyl)benzofuran-5-carboxylic acid

A solution of lithium hydroxide monohydrate (0.028 g, 0.67 mmol) in water (1 mL) was added to a solution of methyl 2-(2-methoxyphenyl)benzofuran-5-carboxylate (0.063 g, 0.22 mmol) in tetrahydrofuran (3 mL). The reaction mixture was stirred overnight, acidified with 2.0 M aqueous hydrochloric acid and partitioned between water and ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated to give 0.058 g (97% yield) of the title compound.

$^1$H NMR (400 MHz, CD$_3$OD), $\delta$ ppm 13.68 (br. s., 1 H), 9.11 (d, 1 H), 8.76 (ddd, 2 H), 8.50 (d, 1 H), 8.31 (s, 1 H), 8.19 - 8.29 (m, 1 H), 8.03 (d, 1 H), 7.87 - 7.98 (m, 1 H), 4.76 - 4.87 (m, 3 H); MS (ESI) m/z 267 [M-I].

b) Methyl 2-(2-methoxyphenyl)benzofuran-5-carboxylate

Methyl 4-hydroxy-3-iodobenzoate (0.111 g, 0.40 mmol), 2'-methoxyphenyl acetylene (0.052 ml, 0.40 mmol) 1,1,3,3-tetramethylguanidine (0.502 mL, 4.00 mmol) bis(triphenylphosphine)palladium(II)chloride (0.028 g, 0.04 mmol) and copper(I) iodide (1.36 $\mu$L, 0.04 mmol) were dissolved in N,N-dimethylformamide (5 mL). The reaction
mixture was heated at 50 °C under an atmosphere of argon over night and the solvent was evaporated. Purification by column chromatography, using heptane/ethyl acetate (9:1) as the eluent gave 0.064 g (57% yield) of the title compound. 

1^H NMR (400 MHz, CDCl₃), δ ppm 8.34 (d, 1 H), 8.07 (dd, 1 H), 8.01 (dd, 1 H), 7.53 (d, 1 H), 7.40 (s, 1 H), 7.33 - 7.39 (m, 1 H), 7.06 - 7.14 (m, 1 H), 7.02 (d, 1 H), 4.01 (s, 3 H), 3.96 (s, 3 H).

Example 121

2-(l-tert-Butoxyethyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide

The title compound was synthesized as described for Example 120 in 64% yield, starting from 2-(l-tert-butoxyethyl)benzofuran-5-carboxylic acid.

1^H NMR (400 MHz, DMSO-J₆), δ ppm 8.12 - 8.17 (m, 2 H), 7.99 (dd, 1 H), 7.83 (dd, 1 H), 7.53 - 7.67 (m, 2 H), 7.41 (d, 1 H), 6.76 (s, 1 H) 4.88 (q, 1 H), 1.41 (d, 3 H), 1.16 - 1.22 (m, 9 H); MS (ESI) m/z 479 [M-I].

a) 2-(l-tert-Butoxyethyl)benzofuran-5-carboxylic acid

The title compound was synthesized as described for Example 120 a) in 44% yield, starting from methyl 2-(l-tert-butoxyethyl)benzofuran-5-carboxylate.

1^H NMR (400 MHz, CD₃CD₂OD) δ ppm 13.61 (br. s., 1 H) 9.02 (d, 1 H) 8.67 (dd, 1 H)
The title compound was synthesized as described for Example 120 b) in 53% yield, starting from 3-tert-butoxybut-1-yne.

MS (ES) m/z 276 [M]+.

Example 122

2-(Pyridin-2-yl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide

The title compound was synthesized as described for Example 120 in 35% yield, starting from 2-(pyridin-2-yl)benzofuran-5-carboxylic acid.

\[ ^1 \text{H NMR (500 MHz, CD}_{3}\text{OD), } \delta \text{ ppm 8.64 (dt, 1 H), 8.46 - 8.54 (m, 1 H), 8.30 (d, 1 H), 8.23 - 8.29 (m, 1 H), 8.00 - 8.07 (m, 1 H), 7.97 (td, 1 H), 7.92 (s, 1 H), 7.79 - 7.89 (m, 2 H), 7.66 (d, 1 H), 7.60 (s, 1 H), 7.43 (ddd, 1 H); MS (ESI) m/z 456 [M-I]^-}. \]

a) 2-(Pyridin-2-yl)benzofuran-5-carboxylic acid
The title compound was synthesized as described for Example 120 a) in 91% yield, starting from methyl 2-(pyridin-2-yl)benzofuran-5-carboxylate.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 8.71 (d, 1 H) 8.40 (d, 1 H) 8.08 (dd, 1 H) 7.93 (d, 1 H) 7.83 (td, 1 H) 7.60 (d, 1 H) 7.51 (s, 1 H) 7.30 (ddd, 1 H); MS (ESI) m/z 239 [M-I]$^-$. 

b) Methyl 2-(pyridin-2-yl)benzofuran-5-carboxylate

The title compound was synthesized as described for Example 120 b) in 87% yield, starting from 2-ethynylpyridine.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 8.71 (d, 1 H) 8.40 (d, 1 H) 8.08 (dd, 1 H) 7.93 (d, 1 H) 7.83 (td, 1 H) 7.60 (d, 1 H) 7.51 (s, 1 H) 7.30 (ddd, 1 H); GC MS (EI) m/z 253 [M$^+$].

Example 123

2-(Pyridin-3-yl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide

The title compound was synthesized as described for Example 120 in 24% yield, starting from 2-(pyridin-3-yl)benzofuran-5-carboxylic acid.

$^1$H NMR (500 MHz, CD$_3$OD), $\delta$ ppm 9.11 (s, 1 H) 8.56 (d, 1 H), 8.47 - 8.54 (m, 1 H), 8.36 (dt, 1 H), 8.22 - 8.30 (m, 2 H), 7.91 (dd, 1 H), 7.84 (dd, 2 H), 7.65 (d, 1 H), 7.57 (dd, 1 H), 7.52 (s, 1 H); MS (ESI) m/z 456 [M-I]$^-$. 
a) 2-(Pyridin-2-yl)benzofuran-5-carboxylic acid

The title compound was synthesized as described for Example 120 a) in 83% yield, starting from methyl 2-(pyridin-2-yl)benzofuran-5-carboxylate.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm 13.02 (br. s., 1 H) 9.17 (d, 1 H) 8.63 (dd, 1 H) 8.31 (td, 2 H) 7.96 (dd, 1 H) 7.68 - 7.82 (m, 2 H) 7.56 (dd, 1 H); MS (ESI) $m/z$ 238[M-I] $^-$. 

b) Methyl 2-(pyridin-3-yl)benzofuran-5-carboxylate

The title compound was synthesized as described for Example 120 b) in 83% yield, starting from 3-ethynylpyridine.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 9.14 (d, 1 H) 8.63 (dd, 1 H) 8.37 (d, 1 H) 8.15 (dt, 1 H) 8.07 (dd, 1 H) 7.59 (d, 1 H) 7.37 - 7.48 (m, 1 H) 7.19 (d, 1 H); GC MS (EI) $m/z$ 253[M]$^+$. 

Example 124

2-(2-Hydroxypropan-2-yl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide

The title compound was synthesized as described for Example 120 in 85% yield, starting from 2-(2-hydroxypropan-2-yl)benzofuran-5-carboxylic acid.

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ ppm 8.10 - 8.19 (m, 2 H) 7.99 (dd, 1 H) 7.82 (dd, 1 H)
The title compound was synthesized as described for Example 120 a) in 46% yield, starting from methyl 2-(2-hydroxypropan-2-yl)benzofuran-5-carboxylate.

The title compound was synthesized as described for Example 120 b) in 79% yield, starting from 2-methylbut-3-yen-2-ol.

**Example 125**

2-(2-Methoxypropan-2-yl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide
The title compound was synthesized as described for Example 120 in 85% yield, starting from 2-(2-methoxypropan-2-yl)benzofuran-5-carboxylic acid.

\[ \text{H NMR (500 MHz, DMSO-} \delta, \text{ ppm 8.17 (d, 1 H), 8.14 (dd, 1 H), 7.98 (dd, 1 H), 7.85 (dd, 1 H), 7.62 (dd, 1 H), 7.58 (dd, 1 H), 7.49 (br. s., 2 H), 7.46 (d, 1 H), 6.91 (d, H), 2.98 (s, 3 H) 1.51 - 1.58 (m, 6 H); MS (ESI) } m/z 451 \ [\text{M-I}^-]. \]

a) 2-(2-Methoxypropan-2-yl)benzofuran-5-carboxylic acid

\[ \text{The title compound was synthesized as described for Example 120 a) in 65% yield, starting from methyl 2-(2-methoxypropan-2-yl)benzofuran-5-carboxylate.} \]

\[ \text{H NMR (400 MHz, CD}_3\text{OD) } \delta \text{ ppm 8.30 (d, 1 H) 7.99 (dd, 1 H) 7.53 (d, 1 H) 6.87 (s, 1 H) 3.12 (s, 3 H) 1.62 (s, 6 H); MS (ESI) } m/z 233 \ [\text{M-I}^-]. \]

b) Methyl 2-(2-methoxypropan-2-yl)benzofuran-5-carboxylate

\[ \text{The title compound was synthesized as described for Example 120 b) in 65% yield, starting from 3-methoxy-3-methylbut-1-yne.} \]

\[ \text{GC MS (EI) } m/z 248 \ [\text{M}^+]. \]
Example 126

2-Cyclopropyl-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide

The title compound was synthesized as described for Example 120 in 36% yield, starting from 2-cyclopropylbenzofuran-5-carboxylic acid.

1H NMR (500 MHz, CD3OD) δ ppm 8.33 - 8.43 (m, 1 H) 8.09 - 8.20 (m, 1 H) 7.94 (d, 1 H) 7.73 (dd, 2 H) 7.64 (dd, 1 H) 7.30 (dd, 1 H) 6.36 - 6.47 (m, 1 H) 1.95 - 2.05 (m, 1 H) 0.90 - 1.00 (m, 2 H) 0.80 - 0.90 (m, 2 H); MS (ESI) m/z 419 [M-I]⁻.

a) 2-Cyclopropylbenzofuran-5-carboxylic acid

The title compound was synthesized as described for Example 120 a) in 46% yield, starting, from methyl 2-cyclopropylbenzofuran-5-carboxylate.

1H NMR (400 MHz, CD3OD) δ ppm 8.15 (d, 1 H) 7.85 - 7.93 (m, 1 H) 7.34 - 7.47 (m, 1 H) 6.52 (s, 1 H) 2.09 (tt, 1 H) 0.99 - 1.07 (m, 2 H) 0.90 - 0.99 (m, 2 H); MS (ESI) m/z 201 [M-I]⁻.

b) Methyl 2-cyclopropylbenzofuran-5-carboxylate

The title compound was synthesized as described for Example 120 b) in 73% yield,
starting from ethynylcyclopropane.

GC MS (EI) m/z 216 [M]+.

Example 127

4-(Benzofuran-2-yl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

4-Bromo-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide (0.14 g, 0.24 mmol), benzofuran-2-ylboronic acid (0.077 g, 0.48 mmol) and 1,1′-bis(diphenylphosphino)ferrocene-palladium dichloride (0.020 g, 0.02 mmol) were dissolved in N,N-dimethylformamide under an atmosphere of argon followed by addition of aqueous sodium carbonate (0.358 mL, 0.72 mmol). The reaction mixture was heated in a microwave at 120 °C for 20 min under an atmosphere of argon and was then partitioned between water and ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (2 M) and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC gave 0.064 g (52% yield) of the title compound.

1H NMR (500 MHz, DMSO-δ6), δ ppm 8.35 (d, 1 H) 8.15 (d, 1 H), 8.01 (d, 1 H), 7.88 (br. s., 2 H), 7.69 - 7.78 (m, 2 H), 7.62 (d, 1 H), 7.53 - 7.60 (m, 2 H), 7.46 (s, 2 H), 7.31 - 7.40 (m, 1 H) 7.23 - 7.31 (m, 1 H), 4.91 - 5.03 (m, 1 H), 1.46 (s, 3 H), 1.45 (s, 3 H); MS (ESI) m/z 513 [M-I]-.

a) 4-Bromo-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide
4-bromo-3-isopropoxybenzoic acid (0.621 g, 2.40 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.689 g, 3.60 mmol) and 4-dimethylaminopyridine (0.439 g, 3.60 mmol) were added to a solution of benzene-1,2-disulfonamide (0.566 g, 2.40 mmol) in N,N-dimethylformamide (30 mL). The reaction mixture was stirred at room temperature over night and was then partitioned between water and ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (2 M) and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by column chromatography, using ethyl acetate as the eluent, gave 0.944 g (83% yield) of the title compound.

\[ ^1\text{H NMR (500 MHz, CD}_2\text{OD) } \delta \text{ ppm 8.39 (d, 1 H), 8.20 - 8.28 (m, 1 H), 7.73 - 7.79 (m, 2 H), 7.61 (s, 1 H), 7.56 (d, 1 H), 7.39 (dd, 1 H), 4.72 (dt, 1 H), 1.37 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z Al 5, All [M-I]^-.} \]

b) 4-Bromo-3-isopropoxybenzoic acid

![Chemical Structure]

A solution of lithium hydroxide (0.355 g, 8.46 mmol) in water (3 mL) was added to a solution of methyl 4-bromo-3-isopropoxybenzoate (0.770 g, 2.82 mmol) in tetrahydrofuran (20 mL) and the reaction mixture was stirred at room temperature over night. The reaction mixture was acidified with 2.0 M aqueous hydrochloric acid and partitioned between water and ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated to give 0.621 g (85% yield) of the title compound.

\[ ^1\text{H NMR (500 MHz, CDCl}_3\text{) } \delta \text{ ppm 7.66 (d, 1 H), 7.61 (d, 1 H), 7.53 - 7.58 (m, 1 H), 4.68 (dt, 1 H), 1.43 (d, 6 H); MS (ESI) m/z 257, 259 [M-I]^-.} \]
c) **Methyl 4-bromo-3-isopropoxybenzoate**

2-Propanol (0.348 mL, 4.54 mmol), triphenylphosphine (1.192 g, 4.54 mmol) and diisopropyl azodicarboxylate (0.895 mL, 4.54 mmol) were added to a solution of methyl 4-bromo-3-hydroxybenzoate (0.7 g, 3.03 mmol) in tetrahydrofuran (20 mL). The reaction mixture was stirred at room temperature overnight and the solvent was evaporated. Purification by column chromatography, using heptane/ethyl acetate (8:1) as the eluent, gave 0.775 g (94% yield) of the title compound.

\[ ^1H \text{NMR (500 MHz, CDCl}_3) \delta \text{ppm 7.61 (d, 1 H), 7.56 (d, 1 H), 7.49 (dd, 1 H), 4.67 (dt, 1 H), 3.92 (s, 3 H), 1.42 (s, 3 H), 1.41 (s, 3 H); GC MS (ES) m/z 272, 274 [M]^+.}\]

**Example 128**

4-(3,3-Dimethylbut-1-ynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 127 in 30% yield, starting from 4-bromo-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide and diisopropyl 3,3-dimethylbut-1-ynylboronate.

\[ ^1H \text{NMR (500 MHz, CD}_3\text{OD), } \delta \text{ppm 8.34 (dd, 1 H), 8.15 (dd, 1 H), 7.67 - 7.80 (m, 2 H), 7.38 (s, 1 H), 7.29 (dd, 1 H), 7.21 (d, 1 H), 4.57 (dt, 1 H), 1.24 (s, 3 H), 1.23 (s, 3 H), 1.18 - 1.22 (m, 9 H); MS (ESI) m/z 477 [M-I]^{-}.}\]
Example 129

4-(3-Hydroxy-3-methylbut-1-ynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonlyl)benzamide

[Chemical structure image]

2-Methylbut-3-yn-2-ol (0.068 g, 0.81 mmol), tetrakis(triphenylphosphine)palladium(0) (0.047 g, 0.04 mmol) and triethylamine (1.699 ml, 12.19 mmol) were added to a solution of 4-bromo-3-isopropoxy-N-(2-sulfamoylphenylsulfonlyl)benzamide (0.194 g, 0.41 mmol) in N,N-dimethylformamide (8 ml) under an atmosphere of argon. The reaction mixture was stirred at room temperature for 5 min, copper (I) iodide (0.012 g, 0.06 mmol) was added and the reaction mixture was heated at 65 °C over night. More 2-methylbut-3-yn-2-ol (0.068 g, 0.81 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.047 g, 0.04 mmol) were added and the heating continued over the weekend. The reaction mixture was partitioned between water and ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (2 M) and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC followed by column chromatography, using heptane/ethyl acetate (1:1) followed by ethyl acetate/methanol (100:1 + 1% triethylamine) as the eluent, gave 0.044 g (23% yield) of the title compound.

1H NMR (500 MHz, CD3OD) δ ppm 8.28 (dd, 1 H), 8.20 (dd, 1 H), 7.61 - 7.74 (m, 3 H), 7.50 - 7.58 (m, 1 H), 7.30 (d, 1 H), 4.60 - 4.74 (m, 1 H), 1.56 (s, 6 H), 1.34 (s, 3 H), 1.33 (s, 3 H); MS (ESI) m/z 479 [M-I]−.
Example 130

4-(Cyclopentylethynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

Ethynylcyclopentane (0.060 g, 0.64 mmol), tetrakis(triphenylphosphine)palladium(0) (0.049 g, 0.04 mmol) and triethylamine (1.787 mL, 12.82 mmol) were added to a solution of 4-bromo-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide (0.204 g, 0.43 mmol) in N,N-dimethylformamide (9 mL) under an atmosphere of argon. The reaction mixture was stirred at room temperature for 5 min, copper(I) iodide (0.012 g, 0.06 mmol) was added and the reaction mixture was heated at 65 °C over night. Ethynylcyclopentane (0.028 g, 0.3 mmol) was added and the reaction mixture was heated for an additional 24 hours. The reaction mixture was partitioned between water and ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (2 M) and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC gave 0.023 g (11% yield) of the title compound.

1H NMR (500 MHz, CD3OD) δ ppm 1.31 (d, 6 H) 1.58 - 1.68 (m, 2 H) 1.68 - 1.77 (m, 2 H) 1.76 - 1.87 (m, 2 H) 1.92 - 2.08 (m, 2 H) 2.89 (t, 1 H) 4.55 - 4.71 (m, 1 H) 7.24 (d, 1 H) 7.55 (dd, 1 H) 7.64 (d, 1 H) 7.65 - 7.73 (m, 2 H) 8.21 (d, 1 H) 8.26 (d, 1 H); MS (ESI) m/z A16 [M-I]⁻.

Example 131

4-(Cyclohexylethynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide
The title compound was synthesized as described for Example 130 in 16% yield, starting from 4-bromo-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide and ethynylcyclohexane.

\[ ^1H \text{ NMR (500 MHz, CD}_3\text{OD)} \delta \text{ ppm 8.27 (dd, 1 H) 8.19 - 8.24 (m, 1 H) 7.62 - 7.74 (m, 3 H) 7.56 (dd, 1 H) 7.26 (d, 1 H) 4.59 - 4.73 (m, 1 H) 2.67 (br. s., 1 H) 1.73 - 1.94 (m, 4 H) 1.49 - 1.67 (m, 3 H) 1.36 - 1.49 (m, 3 H) 1.32 (s, 3 H) 1.31 (s, 3 H); MS (ESI) } m/z 503 [M-I]^- . \]

**Example 132**

4-(Cyclopropylethynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 130 in 16% yield, starting from 4-bromo-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide and ethynylicyclopropane.

\[ ^1H \text{ NMR (500 MHz, CD}_3\text{OD)} \delta \text{ ppm 8.39 - 8.53 (m, 1 H) 8.16 - 8.34 (m, 1 H) 7.72 - 7.93 (m, 2 H) 7.42 - 7.52 (m, 1 H) 7.34 - 7.41 (m, 1 H) 7.24 - 7.34 (m, 1 H) 4.57 - 4.76 (m, 1 H) 1.43 - 1.56 (m, 1 H) 1.33 (s, 3 H) 1.32 (s, 3 H) 0.86 - 0.94 (m, 2 H) 0.71 - 0.78 (m, 2 H); MS (ESI) } m/z 461 [M-I]^- . \]
Example 133

4-((1-Hydroxycycloheptyl)ethynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)-
benzamide

1-Ethynylcycloheptanol (0.105 g, 0.76 mmol, Verkruijsse, H D.; De Graaf, W.; Brandsma, L. Synth. Commun., 1988, 18(2), 131-4) tetrakis(triphenylphosphine)palladium(0) (0.044 g, 0.04 mmol) and triethylamine (1.594 mL, 11.44 mmol) was added to a solution of 4-
bromo-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide (0.182 g, 0.38 mmol) in
N,N-dimethylformamide (8 mL) under an atmosphere of argon. The reaction mixture was
stirred at room temperature for 5 min, copper(I) iodide (10.9 mg, 0.06 mmol) was added
and the reaction mixture was heated at 65 °C for 2 days. The reaction mixture was
partitioned between water and ethyl acetate. The aqueous phase was acidified with aqueous
hydrochloric acid (2 M) and extracted with ethyl acetate. The organic phase was dried over
magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC gave
0.060 g (29% yield) of the title compound.

1H NMR (500 MHz, CD3OD) δ ppm 8.43 - 8.51 (m, 1 H) 8.23 - 8.31 (m, 1 H) 7.80 - 7.90
(m, 2 H) 7.50 (s, 1 H) 7.39 (s, 2 H) 4.69 - 4.79 (m, 1 H) 2.03 - 2.16 (m, 2 H) 1.80 - 1.92
(m, 2 H) 1.66 - 1.79 (m, 6 H) 1.55 - 1.66 (m, 2 H) 1.36 (s, 3 H) 1.34 (s, 3 H); MS (ESI) m/z
533 [M-I].
Example 134

6-(3,3-Dimethylbut-1-ynyl)-5-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)nicotinamide

6-Chloro-5-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)nicotinamide (0.162 g, 0.33 mmol), diisopropyl 3,3-dimethylbut-1-ynylboronate (0.155 mL, 0.66 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (0.027 g, 0.03 mmol) were dissolved in N,N-dimethylformamide under a atmosphere of argon followed by addition of aqueous sodium carbonate (0.492 mL, 0.98 mmol). The reaction mixture was heated in a microwave at 120 °C for 40 min under an atmosphere of argon and was then partitioned between water and ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (2 M) and extracted with ethyl acetate. The organic phase were dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC gave 0.028 g (16% yield) of the title compound.

1H NMR (500 MHz, CD3OD), δ ppm 8.50 (s, 1 H), 8.46 (dd, 1 H), 8.25 (dd, 1 H), 7.94 (s, 1 H) 7.82 (dd, 2 H), 4.24 - 4.30 (m, 2 H), 3.90 (dd, 2 H), 3.71 - 3.78 (m, 2 H), 3.52 - 3.58 (m, 2 H), 3.33 (s, 3 H), 1.35 (s, 9 H); MS (ESI) m/z 538 [M-I]-.

a) 6-Chloro-5-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)nicotinamide

6-Chloro-5-(2-(2-methoxyethoxy)ethoxy)nicotinic acid (0.516 g, 1.87 mmol) N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.466 g, 2.43 mmol) and 4-
dimethylaminopyridine (0.297 g, 2.43 mmol) were added to a solution of benzene-1,2-
disulfonamide (0.420 g, 1.78 mmol) in N,N-dimethylformamide (20 mL) at room
temperature and the reaction mixture was stirred over night. The reaction mixture was
partitioned between water and ethyl acetate. The aqueous phase was acidified with aqueous
hydrochloric acid (2 M) and extracted with ethyl acetate, the organic phase was dried over
magnesium sulfate and the solvent was evaporated. Purification by column
chromatography, using ethyl acetate/methanol (100:1 + 1% triethyamine) as the eluent,
gave 0.74 g (81% yield) of the title compound.
MS (ESI) m/z 492, 494, 496 [M-I]^-.  

b) 6-Chloro-5-(2-(2-methoxyethoxy)ethoxy)nicotinic acid

2-(2-Methoxyethoxy)ethanol (0.333 mL, 2.80 mmol), triphenyolphosphine (0.734 g, 2.80
mmol) and diisopropyl azodicarboxylate (0.551 mL, 2.80 mmol) were added to a solution
of methyl 6-chloro-5-hydroxycotinate (0.350 g, 1.87 mmol) in tetrahydrofuran (15 mL).
The reaction mixture was stirred at room temperature over night. A solution of lithium
hydroxide monohydrate (0.134 g, 5.60 mmol) in water (2 mL) was added and the reaction
mixture was stirred for 3 days at room temperature. The aqueous phase was acidified with
aqueous hydrochloric acid (2 M) and extracted with ethyl acetate. The organic phase was
dried over magnesium sulfate and the solvent was evaporated to give the title compound.
MS (ESI) m/z 276, 278, 280 [M+H]^+. 
c) Methyl 6-chloro-S-hydroxynicotinate

N-Chlorosuccinimide (2.093 g, 15.67 mmol) was added to a solution of methyl 5-hydroxynicotinate (2.0 g, 13.06 mmol) in N,N-dimethylformamide (20 mL). The reaction mixture was heated at 80 °C over night and the solvent was evaporated. Purification by column chromatography, using heptane/ethyl acetate (3:1 -1:1) as the eluent, gave 0.957 g of the title compound.

MS (ESI) m/z 186, 188, 190 [M-I]⁻.

**Example 135**

6-(Benzofuran-2-yl)-5-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)-nicotinamide

The title compound was synthesized as described for Example 134 in 31% yield, starting from 6-chloro-5-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)nicotinamide and benzofuran-2-ylboronic acid. The reaction mixture was heated in a microwave at 120 °C for 20 min.

¹H NMR (500 MHz, CD₃OD) δ ppm 8.60 (d, 1 H), 8.34 - 8.46 (m, 1 H) 8.13 - 8.24 (m, 1 H) 7.98 (d, 1 H), 7.84 (d, 1 H), 7.70 - 7.80 (m, 2 H), 7.61 (d, 1 H), 7.51 (d, 1 H), 7.30 (td, 1 H), 7.14 - 7.23 (m, 1 H), 4.29 - 4.42 (m, 2 H), 3.86 - 3.98 (m, 2 H), 3.63 - 3.74 (m, 2 H), 3.45 - 3.56 (m, 2 H), 3.23 - 3.27 (m, 3 H); MS (ESI) m/z 574 [M-I]⁻.
Example 136

6-(Cyclopentylethynyl)-5-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)nicotinamide

Ethynylcyclopentane (0.054 g, 0.58 mmol), tetrakis(triphenylphosphine)palladium(0) (0.044 g, 0.04 mmol) and triethylamine (1.608 mL, 11.54 mmol) were added to a solution of 6-chloro-5-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)nicotinamide (0.190 g, 0.38 mmol) in N,N-dimethylformamide (8 mL) under an atmosphere of argon. The reaction mixture was stirred at room temperature for 5 min, copper(I) iodide (10.99 mg, 0.06 mmol) was added and the reaction mixture was heated at 65 °C over night. The reaction mixture was partitioned between water and ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (2 M) and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC gave 0.063 g (30% yield) of the title compound.

^1H NMR (500 MHz, CD$_3$OD) δ ppm 8.43 - 8.55 (m, 2 H), 8.21 - 8.31 (m, 1 H), 7.93 (s, 1 H), 7.77 - 7.89 (m, 2 H), 4.23 - 4.35 (m, 2 H), 3.86 - 3.96 (m, 2 H), 3.74 (dd, 2 H), 3.54 (dd, 2 H), 3.33 (s, 3 H), 2.91 - 3.01 (m, 1 H), 1.96 - 2.08 (m, 2 H), 1.71 - 1.87 (m, 4 H), 1.59 - 1.70 (m, 2 H); MS (ESI) m/z 550 [M-I].

Example 137

6-(Cyclopentylethynyl)-5-methoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide
The title compound was synthesized as described for Example 136 in 34% yield, starting from 6-chloro-5-methoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide and ethynylcyclopentane.

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ ppm 8.31 - 8.46 (m, 2 H) 8.12 - 8.20 (m, 1 H) 7.81 (s, 1 H) 7.70 - 7.78 (m, 2 H) 3.84 (s, 3 H); MS (ESI) m/z 462 [M-I]$^-$. 

a) 6-Chloro-5-methoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide

![Chemical Structure](image)

The title compound was synthesized as described for Example 127 a) in 62% yield, starting from 6-chloro-5-methoxynicotinic acid.

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ ppm 8.45 - 8.57 (m, 1 H) 8.38 (d, 1 H) 8.20 - 8.34 (m, 1 H) 7.81 - 7.98 (m, 3 H) 3.98 (s, 3 H); MS (ESI) m/z 404, 406, 408 [M-I]$^-$. 

b) 6-Chloro-S-methoxynicotinic acid

![Chemical Structure](image)

The title compound was synthesized as described for Example 127 b) in 74% yield, starting from methyl 6-chloro-5-methoxynicotinate.

$^1$HNMR (500 MHz, CD$_3$OD), $\delta$ ppm 8.51 (d, 1 H), 7.94 (d, 1 H), 4.00 (s, 3 H); MS (ESI) m/z 186, 188, 190 [M-I]$^-$. 
c) Methyl 6-chloro-S-methoxynicotinate

Potassium carbonate (2.59 g, 18.71 mmol) and iodomethane (1.031 mL, 16.55 mmol) were added to a solution of methyl 6-chloro-5-hydroxynicotinate (2.7 g, 14.4 mmol) in N,N-dimethylformamide (40 mL) at room temperature and the resulting mixture was stirred overnight. The reaction mixture was partitioned between water and ethyl acetate. The organic phase was washed with water, dried over magnesium sulfate and the solvent was evaporated to give 2.48 g (85% yield) of the title compound.

MS (ESI) m/z 202, 204, 206 [M+1]+.

Example 138

6-(Cyclohexylethynyl)-5-methoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide

The title compound was synthesized as described for Example 136 in 11% yield, starting from 6-chloro-5-methoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide and ethynylcyclohexane.

1H NMR (500 MHz, CD3OD) δ ppm 1.36 - 1.48 (m, 3 H) 1.51 - 1.67 (m, 3 H) 1.76 - 1.86 (m, 2 H) 1.86 - 1.97 (m, 2 H) 2.63 - 2.78 (m, 1 H) 3.92 (s, 3 H) 7.63 - 7.75 (m, 2 H) 8.00 (d, 1 H) 8.21 (dd, 1 H) 8.30 (dd, 1 H) 8.59 (d, 1 H); MS (ESI) m/z 476 [M-I].
Example 139

5-Methoxy-N-(2-sulfamoylphenylsulfonyl)-6-((4-(trifluoromethyl)phenyl)-
ethynyl)nicotinamide

The title compound was synthesized as described for Example 136 in 28% yield, starting from 6-chloro-5-methoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide and 1-ethynyl-4-(trifluoromethyl)benzene.

$^1$H NMR (500 MHz, CD$_3$OD) δ ppm 8.67 (d, 1 H) 8.37 (dd, 1 H) 8.20 (dd, 1 H) 8.10 (d, 1 H) 7.76 - 7.84 (m, 2 H) 7.63 - 7.76 (m, 4 H) 4.01 (s, 3 H); MS (ESI) m/z 538 [M-I]$^-$.  

Example 140

N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride

2-Phenyl-1H-indole-5-carboxylic acid (0.080 g, 0.34 mmol), N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (0.097 g, 0.51 mmol) and 4-dimethylaminopyridine (0.062 g, 0.51 mmol) were added to a solution of benzene-1,2-disulfonamide (0.080 g, 0.34 mmol) in N,N-dimethylformamide (30 mL) at room temperature and the reaction mixture was stirred over night. Water was added and the solution was extracted with ethyl acetate. The aqueous phase was acidified with 2 M aqueous hydrochloric acid and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC gave 0.056 g (37% yield) of the title compound.
H NMR (500 MHz, CD3OD) δ ppm: 8.49 (dd, 1 H) 8.27 (dd, 1 H) 8.15 - 8.22 (m, 1 H) 7.83 - 7.91 (m, 2 H) 7.81 (d, 2 H) 7.64 (dd, 1 H) 7.39 - 7.50 (m, 3 H) 7.27 - 7.39 (m, 1 H) 6.95 (s, 1 H); MS (ESI) m/z 454 [M-I]⁻.

**a) 1-Phenyl-1H-indole-3-carboxylic acid**

![1-Phenyl-1H-indole-3-carboxylic acid structure](image)

A solution of lithium hydroxide monohydrate (0.057 g, 2.36 mmol) in water (2 mL) was added to a solution of methyl 2-phenyl-1H-indole-5-carboxylate (0.198 g, 0.79 mmol) in tetrahydrofuran (10 mL) at room temperature and the resulting mixture was stirred for 5 days. Additional amounts of lithium hydroxide monohydrate (0.057 g, 2.36 mmol) dissolved in water (2 mL) was added and the reaction mixture was stirred over night. The reaction mixture was partitioned between water and ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (2 M) and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated to give 0.085 g (46% yield) of the title compound. MS (ESI) m/z 236 [M-I]⁻.

**b) Methyl 2-phenyl-1H-indole-3-carboxylate**

![Methyl 2-phenyl-1H-indole-3-carboxylate structure](image)

Methyl 3-iodo-4-(2,2,2-trifluoroacetamido)benzoate (0.600 g, 1.61 mmol), ethynylbenzene (0.265 mL, 2.41 mmol), 1,1,3,3-tetramethylguanidine (2.020 mL, 16.08 mmol), bis(triphenylphosphine)palladium(II) chloride (0.133 g, 0.16 mmol) and copper(I) iodide (0.031 g, 0.16 mmol) were dissolved in N,N-dimethylformamide (15 mL), the resulting
mixture was stirred at 50 °C under an atmosphere of argon over night and the solvent was evaporated. Purification by column chromatography, using heptane/ethyl acetate (7:1 to 4:1) as the eluent, gave 0.202 g (50% yield) of the title compound.

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] \( \delta \) ppm 3.92 - 3.98 (m, 3 H) 6.92 (dd, 1 H) 7.33 - 7.40 (m, 1 H) 7.42 (d, 1 H) 7.48 (t, 2 H) 7.69 (d, 2 H) 7.92 (dd, 1 H) 8.40 (d, 1 H) 8.55 (br. s., 1 H);

MS (ESI) \text{m/z 250[M-I] } ^-.

\( \text{c) Methyl 3-iodo-4-(2,2,2-trifluoroacetamido)benzoate} \)

\[ \begin{align*}
\text{O} & \quad \text{O} \\
\text{I} & \quad \text{N} \quad \text{O} \\
\text{F} & \quad \text{F}
\end{align*} \]

A solution of methyl 4-amino-3-iodobenzoate (1.0 g, 3.61 mmol) and triethylamine (1.003 mL, 7.22 mmol) in dichloromethane (20 mL) was added dropwise to a cooled (0 °C) solution of trifluoroacetic anhydride (1.275 mL, 9.02 mmol) in dichloromethane (5 mL). The cooling was removed, the mixture was stirred at room temperature for 3 hours, poured into ice-water and extracted with dichloromethane. The organic phase was dried over sodium sulfate and the solvent was evaporated. Purification by column chromatography, using heptane/ethyl acetate (4:1) as the eluent, gave 1.23 g (91% yield) of the title compound.

\[ ^1H \text{NMR (500 MHz, CD}_3\text{OD} \] \( \delta \) ppm 8.54 (d, 1 H) 8.07 (dd, 1 H) 7.57 (d, 1 H) 3.93 (s, 3 H); MS (ESI) \text{m/z 372 [M-I]^-}. 

\[ \text{a) l-(2-Methoxyethyl)-2-phenyl-IH-indole-5-carboxylic acid} \]

\[ \begin{align*}
\text{O} & \quad \text{O} \\
\text{HO} & \quad \text{N} \quad \text{C} \\
\text{O} & \quad \text{O}
\end{align*} \]
A solution of lithium hydroxide (0.024 g, 0.99 mmol) in water (2 mL) was added to a solution of methyl 1-(2-methoxyethyl)-2-phenyl-lH-indole-5-carboxylate (0.102 g, 0.33 mmol) in tetrahydrofuran (6 mL) at room temperature and the reaction mixture was stirred over the weekend. Another 16 equivalents of lithium hydroxide was added and the reaction was stirred for 3 days. The reaction was partitioned between water and ethyl acetate, the aqueous phase was acidified with 2 M aqueous hydrochloric acid and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated to give 0.029 g (30% yield) of the title compound.

MS (ESI) m/z 294 [M-I].

b) Methyl 1-(2-methoxyethyl)-2-phenyl-lH-indole-5-carboxylate

Potassium hydroxide (0.041 g, 0.74 mmol) was added to a solution of methyl 2-phenyl-lH-indole-5-carboxylate (0.084 g, 0.33 mmol) and 2-bromoethyl methyl ether (0.035 mL, 0.37 mmol) in N,N-dimethylformamide (5 mL) at room temperature and the reaction was stirred over night. 2-Bromoethyl methyl ether (0.035 mL, 0.37 mmol) was added and the reaction mixture was stirred for another 2 hours. More 2-bromoethyl methyl ether (0.035 mL, 0.37 mmol) was added and the mixture was stirred for another 1.5 hours. The reaction was partitioned between water and ethyl acetate, the organic phase was dried over magnesium sulfate and the solvent was evaporated to give the title compound.

MS (ESI) m/z 310 [M+1].
Example 141

1-(2-Methoxyethyl)-2-phenyl-N-(2-sulfamoylphenylsulfonyl)-1H-indole-5-carboxamide

The title compound was synthesized as described for Example 140 in 26% yield, starting from 1-(2-methoxyethyl)-2-phenyl-1H-indole-5-carboxylic acid.

\[
\text{\textsuperscript{1}H NMR (500 MHz, CD}_{3}\text{OD) } \delta \text{ ppm 8.43 - 8.53 (m, 1 H) 8.25 - 8.32 (m, 1 H) 8.21 (d, 1 H) 7.78 - 7.90 (m, 2 H) 7.73 (dd, 1 H) 7.53 - 7.60 (m, 3 H) 7.47 - 7.53 (m, 2 H) 7.39 - 7.47 (m, 1 H) 6.62 (s, 1 H) 4.39 (t, 2 H) 3.57 (t, 2 H) 3.11 (s, 3 H); MS (ESI) m/z 512 [M-I]^{-}.}
\]

Example 142

6-(cyclopropylethynyl)-5-isopropoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide

The title compound was synthesized as described for Example 130 in 37% yield, starting from 6-chloro-5-isopropoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide and ethynylcyclopropane.

\[
\text{\textsuperscript{1}H NMR (500 MHz, CD}_{3}\text{OD) } \delta \text{ ppm 8.41 - 8.49 (m, 2 H) 8.25 (dd, 1 H) 7.90 (s, 1 H) 7.81 (dd, 2 H) 4.68 - 4.78 (m, 1 H) 1.53 - 1.61 (m, 1 H) 1.38 (s, 3 H) 1.36 (s, 3 H) 0.96 - 1.03 (m, 2 H) 0.81 - 0.89 (m, 2 H); MS (ESI) m/z 462 [M-I]^{-}.}
\]
a) 6-Chloro-5-isopropoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide

The title compound was synthesized as described for Example 127 a in 54% yield, starting from 6-chloro-S-isopropoxynicotinic acid.

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ ppm 8.51 (dd, 1 H) 8.36 (d, 1 H) 8.26 - 8.32 (m, 1 H) 7.84 - 7.94 (m, 3 H) 4.74 - 4.85 (m, 1 H) 1.41 - 1.45 (m, 3 H) 1.40 (s, 3 H); MS (ESI) m/z 432, 434, 436 [M-I].

b) 6-Chloro-S-isopropoxynicotinic acid

The title compound was synthesized as described for Example 127 b) in 80% yield, starting from methyl 6-chloro-5-isopropoxynicotinate.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 8.67 (d, 1 H) 7.80 (d, 1 H) 4.66 - 4.73 (m, 1 H) 1.46 (s, 3 H) 1.45 (s, 3 H); MS (ES) m/z 214, 216, 218 [M-I].

c) Methyl 6-chloro-S-isopropoxynicotinate
The title compound was synthesized as described for Example 127 c) in 88% yield, starting from methyl 6-chloro-5-methoxynicotinate.

\[ ^1H \text{NMR} (500 \text{ MHz, CDCl}_3) \delta \text{ ppm} 8.57 (d, 1 \text{ H}) 7.76 (d, 1 \text{ H}) 4.58 - 4.78 (m, 1 \text{ H}) 3.97 (s, 3 \text{ H}) 1.44 (s, 3 \text{ H}) 1.43 (s, 3 \text{ H}); \text{GC MS (El) } m/z 229 [M]^+. \]

**Example 143**

6-(Cyclopentylethynyl)-5-isopropoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide

Ethynylcyclopentane (0.039 g, 0.41 mmol), tetrakis(triphenylphosphine)palladium(0) (0.048 g, 0.04 mmol) and triethylamine (1.735 mL, 12.45 mmol) was added to a solution of 6-chloro-5-isopropoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide (0.180 g, 0.41 mmol) in N,N-dimethylformamide (8 mL) under an atmosphere of argon. The reaction mixture was stirred at room temperature for 5 min, copper(I) iodide (0.012 g, 0.06 mmol) was added and the reaction mixture was heated at 65 °C over night. The reaction mixture was partitioned between water and ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (2 M) and extracted with ethyl acetate. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC gave 0.033 g (16% yield) of the title compound.

\[ ^1H \text{NMR} (500 \text{ MHz, CD}_3\text{OD}) \delta \text{ ppm} 8.50 (d, 1 \text{ H}) 8.39 - 8.45 (m, 1 \text{ H}) 8.20 - 8.26 (m, 1 \text{ H}) 7.94 (d, 1 \text{ H}) 7.72 - 7.82 (m, 2 \text{ H}) 4.69 - 4.77 (m, 1 \text{ H}) 2.90 - 3.02 (m, 1 \text{ H}) 1.97 - 2.07 (m, 2 \text{ H}) 1.73 - 1.89 (m, 4 \text{ H}) 1.62 - 1.73 (m, 2 \text{ H}) 1.38 (s, 3 \text{ H}) 1.37 (s, 3 \text{ H}); \text{MS (ESI) } m/z 490 [M-I]^+. \]
Example 144

6-(Cyclohexylethynyl)-5-isopropoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide

The title compound was synthesized as described for Example 127 a) in 14% yield, starting from ethynylcyclohexane but the reaction mixture was heated at 65 °C over the weekend. 

$^1$H NMR (500 MHz, CD$_3$OD) δ ppm 8.42 - 8.52 (m, 2 H) 8.20 - 8.30 (m, 1 H) 7.91 (s, 1 H) 7.77 - 7.85 (m, 2 H) 4.74 (dt, 1 H) 2.69 - 2.81 (m, 1 H) 1.83 (d, 4 H) 1.50 - 1.68 (m, 3 H) 1.40 - 1.48 (m, 3 H) 1.38 (s, 3 H) 1.36 (s, 3 H); MS (ESI) m/z 504 [M-I]$^-$. 

Example 145

4-(Benzofuran-2-yl)-3-(3-methoxy-3-methylbutoxy)-N-(2-sulfamoylphenylsulfonyl)-benzamide

4-bromo-3 -(3-methoxy-3-methylbutoxy)-N-(2-sulfamoylphenylsulfonyl)benzamide (0.250 g, 0.47 mmol), benzofuran-2-ylboronic acid (0.151 g, 0.93 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (0.038 g, 0.05 mmol) were dissolved in N,N-dimethylformamide (3 mL) under an atmosphere of argon. Aqueous sodium carbonate (0.700 mL, 1.40 mmol) was added, the reaction mixture was heated in a microwave at 120 °C for 20 min under an atmosphere of argon and was then partitioned between water and ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (2 M) and extracted with ethyl acetate. The organic phase were dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC
gave 0.181 g (68% yield) of the title compound.

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ ppm 8.45 - 8.53 (m, 1 H) 8.28 (dd, 1 H) 8.09 (d, 1 H) 7.80 - 7.91 (m, 2 H) 7.71 (s, 1 H) 7.64 (d, 1 H) 7.58 (dd, 1 H) 7.55 (s, 1 H) 7.52 (d, 1 H) 7.28 - 7.36 (m, 1 H) 7.23 (t, 1 H) 4.38 (t, 2 H) 3.29 (s, 3 H) 2.24 (t, 2 H) 1.33 (s, 6 H); MS (ESI) $m/z$ 571 [M-I]$^\cdot$.

a) 4-Bromo-3-(3-methoxy-3-methylbutoxy)-N-(2-sulfamoylphenylsulfonyl)-
benzamide

![Chemical structure of 4-Bromo-3-(3-methoxy-3-methylbutoxy)-N-(2-sulfamoylphenylsulfonyl)-benzamide]

The title compound was synthesized as described for Example 127 a) in 75% yield, starting from 4-bromo-3-(3-methoxy-3-methylbutoxy)benzoic acid.

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ ppm 8.33 (d, 1 H) 8.21 (dd, 1 H) 7.64 - 7.77 (m, 3 H) 7.52 (d, 1 H) 7.44 (dd, 1 H) 4.19 (t, 2 H) 3.24 (s, 3 H) 2.06 (t, 2 H) 1.22 - 1.35 (m, 6 H); MS (ESI) $m/z$ 533, 535 [M-I]$^\cdot$.

b) 4-Bromo-3-(3-methoxy-3-methylbutoxy)benzoic acid

![Chemical structure of 4-Bromo-3-(3-methoxy-3-methylbutoxy)benzoic acid]

The title compound was synthesized as described for Example 127 b) in 99% yield, starting from methyl 4-bromo-3-(3-methoxy-3-methylbutoxy)benzoate.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 7.69 (d, 1 H) 7.64 (d, 1 H) 7.57 (dd, 1 H) 4.25 (t, 2 H) 3.27 (s, 3 H) 2.13 (t, 2 H) 1.31 (s, 6 H); MS (ESI) $m/z$ 315, 317 [M-I]$^\cdot$. 
c) Methyl 4-bromo-3-(3-methoxy-3-methylbutoxy)benzoate

The title compound was synthesized as described for Example 127 c) in 98% yield, starting from methyl 4-bromo-3-hydroxybenzoate.

\[ ^1\text{H NMR (500 MHz, CDCl}_3\text{)} \delta \text{ppm } 7.61 \text{ (d, 1 H)} \ 7.56 \text{ (d, 1 H)} \ 7.50 \text{ (dd, 1 H)} \ 4.19 \text{ (t, 2 H)} \ 3.93 \text{ (s, 3 H)} \ 3.25 \text{ (s, 3 H)} \ 2.10 \text{ (t, 2 H)} \ 1.29 \text{ (s, 6 H)}; \text{ GC MS (EI) m/z 330,332 } [\text{M}]^+ . \]

**Example 146**

4-(Cyclopentylethynyl)-3-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide

A mixture of 4-bromo-3-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide (131 mg, 0.30 mmol), cyclopentylacetylene (0.035 mL, 0.30 mmol), copper(I) iodide (5.7 mg, 0.030 mmol), bis(triphenylphosphine)palladium(II) chloride (21.1 mg, 0.030 mmol) and diisopropylamine (0.13 mL, 0.90 mmol) in N,N-dimethylformamide (2 mL) under an atmosphere of argon was heated at 100 °C for 2 hours in a microwave. The reaction mixture was partitioned between ethyl acetate and aqueous hydrochloric acid. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC gave 0.070 g (52% yield) of the title compound.

\[ ^1\text{H NMR (CD}_3\text{OD)} \delta \text{ppm } 8.34 \text{ - 8.39 (m, 1 H)} \ 8.14 \text{ - 8.18 (m, 1 H)} \ 7.73 \text{ - 7.77 (m, 2 H)} \ 7.49 \text{ - 7.55 (m, 2 H)} \ 7.35 \text{ (t, 1 H)} \ 2.77 \text{ - 2.85 (m, 1 H)} \ 1.87 \text{ - 1.97 (m, 2 H)} \ 1.49 \text{ - 1.75 (m, 6 H)}; \text{ MS (ESI) m/z 449 } [\text{M-I}]^- . \]
Example 147

6-(Benzofuran-2-yl)-5-chloro-N-(2-sulfamoylphenylsulfonyl)nicotinamide

A mixture of 5,6-dichloro-N-(2-sulfamoylphenylsulfonyl)nicotinamide (164 mg, 0.40 mmol), 2-benzofuranboronic acid (84 mg, 0.52 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (32.9 mg, 0.040 mmol), N,N-dimethylformamide (4 mL) and sodium carbonate (2 M, 0.60 mL, 1.20 mmol) under an atmosphere of argon was heated at 120 °C for 0.5 hour in a microwave. The reaction mixture was partitioned between ethyl acetate and diluted hydrochloric acid, the organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by preparative HPLC gave 0.047 g (24% yield) of the title compound.

\[ ^1 \text{H NMR (DMSO-}^6\text{)} \delta \text{ ppm } 8.96 (d, 1 H) 8.37 (s, 1 H) 8.26 (dd, 3.70 Hz, 1 H) 8.05 (dd, 3.39 Hz, 1 H) 7.88 (s, 1 H) 7.73 - 7.80 (m, 3 H) 7.66 (d, 1 H) 7.37 - 7.50 (m, 3 H) 7.26 - 7.31 (m, 1 H); MS (ESI) \text{ m/z } 490 \text{ [M-I]}^- \]

Example 148

5-Chloro-6-(cyclopentylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide

The title compound was synthesized as described for Example 146 in 34% yield, starting from 5,6-dichloro-N-(2-sulfamoylphenylsulfonyl)nicotinamide. Purification by preparative HPLC.
1
H NMR (DMSO-\textsubscript{d}\textsubscript{6}) \(\delta\) ppm 8.76 (d, 1 H) 8.20 - 8.29 (m, 2 H) 8.00 - 8.08 (m, 1 H) 7.73 - 7.81 (m, 2 H) 7.41 (br. s., 2 H) 2.89 - 3.00 (m, 1 H) 1.90 - 1.99 (m, 2 H) 1.48 - 1.71 (m, 6 H); MS (ESI) \textit{m/}z 466 [M-I]\textsuperscript{−}.

a) 5,6-Dichloro-N-(2-sulfamoylphenylsulfonyl)nicotinamide

The title compound was synthesized as described for Example 73 a) in 88\% yield, starting from 5,6-dichloronicotinic acid.

1\textsuperscript{H} NMR (DMSO-\textsubscript{d}\textsubscript{6}) \(\delta\) ppm 8.71 - 8.77 (m, 1 H) 8.36 - 8.43 (m, 1 H) 8.23 - 8.31 (m, 1 H) 8.05 - 8.11 (m, 1 H) 7.72 - 7.81 (m, 2 H) 7.43 - 7.50 (m, 2 H); MS (ESI) \textit{m/}z 408 [M-I]\textsuperscript{−}.

**Example 149**

5-Chloro-6-(3,3-dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide

The title compound was synthesized as described for Example 146 in 34\% yield, starting from 5,6-dichloro-N-(2-sulfamoylphenylsulfonyl)nicotinamide and 3,3-dimethylbut-1-ynyl. Purification by preparative HPLC.

1\textsuperscript{H} NMR (DMSO-\textsubscript{d}\textsubscript{6}) \(\delta\) ppm 8.83 (d, 1 H) 8.27 - 8.35 (m, 2 H) 8.07 - 8.15 (m, 1 H) 7.79 - 7.88 (m, 2 H) 7.48 (br. s., 2 H) 1.34 (s, 9 H); MS (ESI) \textit{m/}z 454 [M-I]\textsuperscript{−}.
Example 150

4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)-2-(trifluoromethyl)benzamide

The title compound was synthesized as described for Example 147 in 39% yield, starting from 4-iodo-N-(2-sulfamoylphenylsulfonyl)-2-(trifluoromethyl)benzamide.

\( ^1H \text{NMR} \) (DMSO-\( \delta \)) \( \delta \) ppm 8.32 - 8.40 (m, 1 H) 8.16 - 8.31 (m, 3 H) 7.85 - 7.99 (m, 2 H) 7.76 - 7.85 (m, 2 H) 7.67 - 7.76 (m, 2 H) 7.36 - 7.46 (m, 3 H) 7.27 - 7.36 (m, 1 H); MS (ESI) m/z 523 [M-I]⁻.

Example 151

4-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)-2-(trifluoromethyl)benzamide

The title compound was synthesized as described for Example 146 in 22% yield, starting from 4-iodo-N-(2-sulfamoylphenylsulfonyl)-2-(trifluoromethyl)benzamide and 3,3-dimethylbut-1-yn (1.5 equiv.). Purification by preparative HPLC.

\( ^1H \text{NMR} \) (DMSO-\( \delta \)) \( \delta \) ppm 8.34 (d, 1 H) 8.18 (d, 1 H) 7.85 - 7.96 (m, 2 H) 7.67 - 7.73 (m, 2 H) 7.62 - 7.66 (m, 1 H) 7.39 (s, 2 H) 1.31 (s, 9 H); MS (ESI) m/z 487 [M-I]⁻.
a) 4-Iodo-N-(2-sulfamoylphenylsulfonyl)-2-(trifluoromethyl)benzamide

![Chemical Structure](image)

The title compound was synthesized as described for Example 73 a) in 14% yield, starting from 4-iodo-2-(trifluoromethyl)benzoic acid.

MS (ESI) m/z 533 [M-I]^-.

b) 4-Iodo-2-(trifluoromethyl)benzoic acid

![Chemical Structure](image)

A solution of sodium nitrite (0.37 g, 5.36 mmol) in water (1.5 mL) was added dropwise to a cooled (0 °C) suspension of 4-amino-2-(trifluoromethyl)benzoic acid (1 g, 4.9 mmol) in hydrochloric acid (37%, 2 mL) and ice (3 g). After 20 min at 0 °C the reaction mixture was slowly added to a stirred solution of potassium iodide (8.09 g, 48.8 mmol) in water (8 mL) at 0 °C. The resulting mixture was stirred at room temperature over night, dichloromethane and sodium sulfite (2.52 g, 20.0 mmol) was added, the organic phase was collected, dried over magnesium sulfate and the solvent was evaporated to give the title compound.

^1H NMR (DMSO-\text{\textit{d}_6}) \delta ppm 13.78 (s, 1 H) 8.11 - 8.24 (m, 2 H) 7.49 - 7.66 (m, 1 H); MS (ESI) m/z 315 [M-I]^-.
Example 152

4-(Benzofuran-2-yl)-2,6-difluoro-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 147 in 26% yield, starting from 4-bromo-2,6-difluoro-N-(2-sulfamoylphenylsulfonyl)benzamide.

$^1$H NMR (DMSO-$d_6$) δ ppm 8.19 - 8.28 (m, 1 H) 8.05 - 8.13 (m, 1 H) 7.75 - 7.86 (m, 2 H) 7.57 - 7.69 (m, 5 H) 7.33 (dt, 1 H) 7.20 - 7.30 (m, 3 H); MS (ESI) $m/z$ 491 [M-I].

Example 153

4-(Cyclopentylethynyl)-2,6-difluoro-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 73 a) in 27% yield, starting from 4-bromo-2,6-difluorobenzoic acid.

MS (ESI) $m/z$ 453, 455 [M-I]⁻.
The title compound was synthesized as described for Example 146 in 43% yield, starting from 4-bromo-2,6-difluoro-N-(2-sulfamoylphenylsulfonyl)benzamide. Purification by preparative HPLC.

$^1$H NMR (DMSO-$d_6$) δ ppm 8.23 - 8.31 (m, 1 H) 8.13 - 8.19 (m, 1 H) 7.83 - 7.94 (m, 2 H) 7.32 (s, 2 H) 7.19 (d, 2 H) 2.85 - 2.94 (m, 1 H) 1.93 - 2.03 (m, 2 H) 1.53 - 1.77 (m, 6 H); MS (ESI) m/z 467 [M-I]$^-$. 

Example 154

4-(Benzofuran-2-yl)-3-(3-hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenyl-sulfonyl)benzamide

The title compound was synthesized as described for Example 146 in 34% yield, starting from 4-(benzofuran-2-yl)-3-bromo-N-(2-sulfamoylphenylsulfonyl)benzamide and 2-Methyl-3-butyn-2-ol (3 equiv.). Purification by preparative HPLC.

$^1$H NMR (DMSO-$d_6$) δ ppm 8.33 (br s, 1 H) 8.04 - 8.20 (m, 3 H) 7.93 - 8.01 (m, 2 H) 7.87 (br s, 2 H) 7.74 (d, 1 H) 7.67 (d, 1 H) 7.47 (s, 2 H) 7.38 - 7.44 (m, 1 H) 7.32 (t, 1 H) 1.59 (s, 6 H); MS (ESI) m/z 537 [M-I]$^-$. 

Example 155

4-(Benzofuran-2-yl)-3-bromo-N-(2-sulfamoylphenylsulfonyl)benzamide
The title compound was synthesized as described for Example 147 in 33% yield, starting from 3-bromo-4-iodo-N-(2-sulfamoylphenylsulfonyl)benzamide and using 2-benzofuranboronic acid (1 equiv.).

\[ ^1H \text{NMR (DMSO-} J_6) \delta \text{ppm 8.30 - 8.39 (m, 2 H) 8.11 - 8.18 (m, 1 H) 7.97 - 8.07 (m, 2 H) 7.86 (br s, 2 H) 7.77 - 7.81 (m, 2 H) 7.65 - 7.72 (m, 1 H) 7.48 (s, 2 H) 7.40 - 7.45 (m, 1 H) 7.31 - 7.36 (m, 1 H); MS (ESI) } m/z 533, 535 \text{ [M-I]}^- \]

a) 3-Bromo-4-iodo-N-(2-sulfamoylphenylsulfonyl)benzamide

![Chemical structure](image)

The title compound was synthesized as described for Example 73 a) in 75% yield, starting from 3-bromo-4-iodobenzoic acid.

\[ ^1H \text{NMR (DMSO-} J_6) \delta \text{ppm 8.26 - 8.34 (m, 1 H) 8.18 (br s, 1 H) 8.09 - 8.15 (m, 1 H) 8.01 - 8.07 (m, 1 H) 7.85 (br s, 2 H) 7.53 (dd, 1 H) 7.46 (br s, 2 H); MS (ESI) } m/z 543, 545 \text{ [M-I]}^- \]

b) 3-Bromo-4-iodobenzoic acid

![Chemical structure](image)

The title compound was synthesized as described for Example 74 a) in 98% yield, starting from methyl 3-bromo-4-iodobenzoate.

\[ ^1H \text{NMR (DMSO-} J_6) \delta \text{ppm 13.46 (s, 1 H) 8.06 - 8.20 (m, 2 H) 7.61 (dd, 1 H); MS (ESI) } m/z 325, 327 \text{ [M-I]}^- \].
c) Methyl 3-bromo-4-iodobenzoate

The title compound was synthesized as described for Example 151 b) in 70% yield, starting from methyl 4-amino-3-bromobenzoate. Purification by column chromatography, using heptane/ethyl acetate (19:1) as the eluent.

$^1$H NMR (CDCl$_3$) δ ppm 8.18 (d, 1 H) 7.88 (d, 1 H) 7.55 (dd, 1 H) 3.85 (s, 3 H).

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Example 156

4-(Benzyloxy)-3-(3-hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)-benzamide

The title compound was synthesized as described for Example 154 in 37% yield, starting from 4-(benzyloxy)-3-iodo-N-(2-sulfamoylphenylsulfonyl)benzamide.

$^1$H NMR (DMSO-$_d_6$) δ ppm 8.24 (br s, 1 H) 8.01 - 8.10 (m, 1 H) 7.90 - 7.94 (m, 1 H) 7.72 - 7.86 (m, 3 H) 7.41 - 7.46 (m, 2 H) 7.30 - 7.39 (m, 4 H) 7.22 - 7.29 (m, 1 H) 7.10 - 7.18 (m, 1 H) 5.19 (s, 2 H) 1.39 (s, 6 H); MS (ESI) m/z 527 [M-I]$^-$. 
Example 157

4-(Benzyloxy)-3-iodo-N-(2-sulfamoylphenylsulfonyl)benzamide

The title compound was synthesized as described for Example 73 a) in 26% yield, starting from 4-(benzyloxy)-3-iodobenzoic acid. Purification by column chromatography, using a gradient of heptane/ethyl acetate (3:1 - 1:3) as the eluent. MS (ESI) m/z 571 [M-I].

a) 4-(Benzyloxy)-3-iodobenzoic acid

The title compound was synthesized as described for Example 74 a), starting from benzyl 4-(benzyloxy)-3-iodobenzoate.

$^1$H NMR (DMSO-$d_6$) $\delta$ ppm 12.91 (s, 1 H) 8.30 (d, 1 H) 7.94 (dd, 1 H) 7.48 - 7.55 (m, 2 H) 7.40 - 7.47 (m, 2 H) 7.33 - 7.39 (m, 1 H) 7.19 (d, 1 H) 5.30 (s, 2 H); MS (ESI) m/z 353 [M-I].

b) Benzyl 4-(benzyloxy)-3-iodobenzoate
Sodium hydride (60% in mineral oil, 0.88 g, 22.0 mmol) was added in portions to a solution of 4-hydroxy-3-iodobenzoic acid (2.64 g, 10.0 mmol) in N,N-dimethylformamide (30 mL), after 0.5 hour benzyl bromide (3.56 mL, 30.0 mmol) was added and the reaction was stirred for 3 days. The reaction mixture was diluted with toluene and washed with water. The organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by column chromatography, using heptane/ethyl acetate (7:1) as the eluent, gave 1.91 g (43% yield) of the title compound.

\[^1\text{H} \text{NMR (CDCl}_3 \text{)} \delta \text{ppm} 8.56 (\text{d, 1 H}) 8.07 (\text{dd, 1 H}) 7.36 - 7.58 (\text{m, 10 H}) 6.92 (\text{d, 1 H}) 5.39 (\text{s, 2 H}) 5.28 (\text{s, 2 H}).\]

**Example 158**

2-Benzyl-N-(2-sulfamoylphenylsulfonyl)-1H-indole-5-carboxamide

![Chemical structure](image)

The title compound was synthesized as described for Example 73 a) in 23% yield, starting from 2-benzyl-1H-indole-5-carboxylic acid. Purification by preparative HPLC.

\[^1\text{H} \text{NMR (DMSO-}d_6\text{)} \delta \text{ppm} 12.15 (\text{br s, 1 H}) 11.42 (\text{br s, 1 H}) 8.28 - 8.38 (\text{m, 1 H}) 8.09 - 8.19 (\text{m, 2 H}) 7.90 (\text{br s, 2 H}) 7.52 - 7.58 (\text{m, 1 H}) 7.40 (\text{br s, 2 H}) 7.27 - 7.35 (\text{m, 5 H}) 7.20 - 7.26 (\text{m, 1 H}) 6.30 (\text{s, 1 H}) 4.09 (\text{s, 2 H}); \text{MS (ESI)} \text{ m/z 468 [M-I]}^{-}.\]

a) 1-Benzyl-1H-indole-5-carboxylic acid

![Chemical structure](image)
The title compound was synthesized as described for Example 74 a), starting from methyl 2-benzyl-1H-indole-5-carboxylate.

MS (ESI) m/z 250 [M-I]⁻.

b) Methyl 2-benzyl-1H-indole-5-carboxylate

A mixture of methyl 3-iodo-4-(2,2,2-trifluoroacetamido)benzoate (0.60 g, 1.61 mmol), 3-phenyl-1-propyne (0.20 ml, 1.61 mmol), 1,1,3,3-tetramethylguanidine (2.02 ml, 16.08 mmol), bis(triphenylphosphine)palladium(II)chloride (0.13 g, 0.16 mmol) and copper(I) iodide (0.031 g, 0.16 mmol) in N,N-dimethylformamide (15 mL) was stirred under an atmosphere of argon at 50 °C over night. The reaction mixture was concentrated and purified by column chromatography, using heptane/ethyl acetate (4:1) as the eluent, to give 0.18 g (82% yield) of the title compound.

¹H NMR (DMSO-J) δ ppm 11.43 (br s, 1 H) 8.14 (d, 1 H) 7.66 (dd, 1 H) 7.29 - 7.38 (m, 5 H) 7.21 - 7.26 (m, 1 H) 6.31 (s, 1 H) 4.09 (s, 2 H) 3.82 (s, 3 H); MS (ESI) m/z 264 [M-I]⁻.

Example 159

7-(Cyclopropylethynyl)-2,2-difluoro-N-(2-sulfamoylphenylsulfonyl)-benzo[d][1,3]dioxole-4-carboxamide
The title compound was synthesized as described for Example 146 in 20% yield, starting from 7-bromo-2,2-difluoro-N-(2-sulfamoylphenylsulfonyl)benzo[d][1,3]dioxole-4-carboxamide and 2-cyclopropylethyn-l-ylum. Purification by preparative HPLC.

$^1$H NMR (DMSO-$d_6$) $\delta$ ppm 8.20 - 8.28 (m, 1 H) 8.03 - 8.11 (m, 1 H) 7.70 - 7.82 (m, 2 H) 7.56 (d, 1 H) 7.44 (br s, 2 H) 7.17 - 7.24 (m, 1 H) 1.61 - 1.70 (m, 1 H) 0.94 - 1.00 (m, 2 H) 0.79 - 0.85 (m, 2 H); MS (ESI) $m/z$ 483 [M-I]$^{-1}$.

**a)** 7-Bromo-2,2-difluorobenzo[d][1,3]dioxole-4-carboxylic acid

![Chemical Structure](image)

The title compound was synthesized as described for Example 73 a), starting from 7-bromo-2,2-difluorobenzo[d][1,3]dioxole-4-carboxylic acid. Purification by column chromatography using chloroform/methanol (9:1) as the eluent. MS (ESI) $m/z$ 497, 499 [M-I]$^{-1}$.

**b)** 7-Bromo-2,2-difluorobenzo[d][1,3]dioxole-4-carboxylic acid

![Chemical Structure](image)

Diisopropylamine (1.18 mL, 8.44 mmol) and 4-bromo-2,2-difluoro-1,3-benzodioxole (2.0 g, 8.44 mmol) were added to a cooled (-100 °C) solution of n-butyllithium (1.6 M, in hexane, 5.27 mL, 8.44 mmol) in tetrahydrofuran (15 mL). The reaction mixture was stirred for 2 hours and was then poured onto freshly crushed dry-ice. When the mixture had reached room temperature, water was added and the mixture was washed with
dichloromethane, the water phase was acidified with 2 M hydrochloric acid and extracted with diethyl ether. The organic phase was dried over magnesium sulfate and the solvent was evaporated to give the crude title compound (contains a des-bromo impurity that was present through the synthesis until the final purification step).

MS (ESI) m/z 279, 281 [M-I]⁻.

**Example 160**

4-(Cyclopropylethynyl)-N-(2-sulfamoylphenylsulfonyl)-3-(3,3,3-trifluoropropoxy)-benzamide

Triethylamine (1.296 mL, 9.30 mmol) was added to a mixture of 4-bromo-N-(2-sulfamoylphenylsulfonyl)-3-(3,3,3-trifluoropropoxy)benzamide (165 mg, 0.31 mmol), cyclopropylacetylene (0.079 mL, 0.93 mmol) and tetrakis(triphenylphosphine)palladium(0) (35.8 mg, 0.030 mmol) in N,N-dimethylformamide (2 mL). The mixture was stirred for 5 min, copper(I) iodide (8.9 mg, 0.050 mmol) was added and the reaction was heated at 65 °C over night. The reaction mixture was partitioned between ethyl acetate and aqueous hydrochloric acid, the organic phase was dried over magnesium sulfate and the solvent was evaporated. Purification by column chromatography, using chloroform/methanol (9:1) as the eluent, gave 37% yield of the title compound.

$^1$H NMR (DMSO-$d_6$) δ ppm 8.21-8.10 (m, 1H) 7.97 - 8.06 (m, 1H) 7.25-7.53 (m, 2H) 7.41 - 7.52 (m, 4H) 7.27 (d, 1H) 4.21 (t, 2H) 2.75 - 2.87 (m, 2H) 1.47 - 1.58 (m, 1H) 0.84 - 0.93 (m, 2H) 0.67 - 0.73 (m, 2H); MS (ESI) m/z 515 [M-I]⁻.
a) 4-Bromo-N-(2-sulfamoylphenylsulfonyl)-3-(3,3,3-trifluoropropoxy)benzamide

The title compound was synthesized as described for Example 73 a), starting from 4-bromo-3-(3,3,3-trifluoropropoxy)benzoic acid. MS (ESI) m/z 529, 531 [M-I]⁻.

b) 4-Bromo-3-(3,3,3-trifluoropropoxy)benzoic acid

The title compound was synthesized as described for Example 74 a) in 96% yield, starting from methyl 4-bromo-3-(3,3,3-trifluoropropoxy)benzoate.

1H NMR (DMSO-\textsubscript{d}6) δ ppm 13.28 (br s, 1 H) 7.74 (d, 1 H) 7.58 (d, 1 H) 7.49 (dd, 1 H) 4.37 (t, 2 H) 2.78 - 2.91 (m, 2 H); MS (ESI) m/z 311, 313 [M-I]⁻.
c) Methyl 4-bromo-3-(3,3,3-trifluoropropoxy)benzoate

\[
\begin{align*}
\text{O} & \quad \text{Br} \\
\text{O} & \quad \text{F} \quad \text{F} \\
\end{align*}
\]

Triphenylphosphine (0.51 g, 1.95 mmol) and diisopropyl azodicarboxylate (0.38 mL, 1.95 mmol) were added to a solution of methyl 4-bromo-3-hydroxybenzoate (0.30 g, 1.30 mmol) and 3,3,3-trifluoro-1-propanol (0.17 mL, 1.95 mmol) in tetrahydrofuran (10 mL). The reaction was stirred overnight, concentrated and the residue was purified by column chromatography, using heptane/ethyl acetate (9:1) as the eluent, to give 74% yield of the title compound.

\[^1\text{H NMR (DMSO-}d_6) \delta\text{ ppm 7.71 (d, 1 H) 7.52 (d, 1 H) 7.44 (dd, 1 H) 4.31 (t, 2 H) 3.80 (s, 3 \text{H}) 2.72 - 2.84 (m, 2 \text{H}); MS (El) m/z 326, 328 [M]^+}.

Example 161

4-(Benzofuran-2-yl)-N-(4-(hydroxymethyl)-2-sulfamoylphenylsulfonyl)benzamide

\[
\begin{align*}
\text{O} & \quad \text{S} \\
\text{O} & \quad \text{S} \\
\end{align*}
\]

4-(Benzofuran-2-yl)-N-(4-((tert-butyldimethylsilyloxy)methyl)-2-(N-tert-butylsulfamoyl)phenylsulfonyl)benzamide (241 mg, 0.37 mmol) was dissolved in 2,2,2-trifluoroacetic acid (3 mL, 40.39 mmol) and heated at 90 °C for 1 hour. The 2,2,2-trifluoroacetic acid was evaporated, the residue was diluted in 1 M sodium hydroxide (5 mL) and methanol (5 mL) and was stirred at 60 °C for 10 min. The resulting mixture was
concentrated in vacuo and purified using preparative HPLC to give 137 mg (76% yield) of
the title compound.

\textsuperscript{1}H NMR (CD\textsubscript{3}OD) \(\delta\) ppm: 8.29 (d, 1 H), 8.20 (d, 1 H), 8.09 (d, 2 H), 7.89 (d, 2 H), 7.67 - 7.60 (m, 2 H), 7.53 (d, 1 H), 7.30 (td, 1 H), 7.27 (s, 1 H), 7.25 - 7.21 (m, 1 H), 4.70 (s, 2 H); MS (ESI) \textit{m/z} 485 [M-1]⁻

a) 4-(Benzofuran-2-yl)-N-(4-((tert-butyldimethylsilyloxy)methyl)-2-(N-tert-
butylsulfamoyl)phenylsulfonyl)benzamide

4-bromo-N-(4-((tert-butyldimethylsilyloxy)methyl)-2-(N-tert-
butylsulfamoyl)phenylsulfonyl)benzamide (1.0 g, 1.61 mmol), [1,1'-
bis(diphenylphosphino)ferrocene]dichloropalladium (0.130 g, 0.16 mmol), benzofuran-2-
ylboronic acid (0.287 g, 1.78 mmol) and potassium carbonate (1.338 g, 9.68 mmol) were
dissolved in tetrahydrofuran (14 mL) and water (1 mL). The reaction was irradiated for 15
min at 150 °C in a microwave, filtered through a plug of celite and concentrated in vacuo.
Purification by column chromatography, using a gradient with increasing polarity (0 to 100
% ethyl acetate in heptane) as the eluent, gave 0.266 g (25% yield) of the title compound.

MS (ESI) \textit{m/z} 655 [M-1]⁻
b) 4-Bromo-N-(4-((tert-butyldimethylsilyloxy)methyl)-2-(N-tert-butylsulfamoyl)phenylsulfonyl)benzamide

\[
\text{N}^l\text{-tert-butyl-5-((tert-butyldimethylsilyloxy)methyl)benzene-1,2-disulfonamide (600 mg, 1.37 mmol), 4-bromobenzoic acid (276 mg, 1.37 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (369 mg, 1.92 mmol) and 4-dimethylaminopyridine (420 mg, 3.44 mmol) were dissolved in anhydrous N,N-dimethylformamide (15 mL) and the reaction was stirred at room temperature over night. Water was added and the solution was extracted with ethyl acetate. The aqueous phase was acidified using hydrochloric acid (2 M) and extracted with ethyl acetate. The combined organic phases were washed with water, dried over magnesium sulfate and concentrated in vacuo to give 895 mg (quantitative yield) of the title compound. }
\]

\[\text{MS (ESI) m/z 617, 619 [M-1]^+}\]

c) \(\text{N}^l\text{-tert-Butyl-5-((tert-butyldimethylsilyloxy)methyl)benzene-1,2-disulfonamide}\)

\[
\text{2-(Benzylthio)-N-tert-butyl-5-((tert-butyldimethylsilyloxy)methyl)benzenesulfonamide (500mg, 1.04 mmol) was dissolved in dichloromethane (5 mL), water (5 mL) and formic acid (5 mL). Chlorine gas was bubbled through the vigorously stirred mixture for 1 min at 0 °C. The reaction was allowed to reach room temperature and was stirred for 15 min.}\
\]
Ammonium hydroxide (33%) was added dropwise at 0°C to the mixture until it became basic. The mixture was extracted with dichloromethane and ethyl acetate and the combined organic phases were dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by column chromatography, using a gradient with increasing polarity (0 to 100% ethyl acetate in heptane) as the eluent, gave 172 mg (38% yield) of the title compound.

MS (ESI) m/z 435 [M-I]⁻

d) 2-(Benzylthio)-N-tert-buty1-5-((tert-
butyldimethylsilyloxy)methyl)benzenesulfonamide

2-Bromo-N-tert-butyl-5-((tert-butyldimethylsilyloxy)methyl)benzenesulfonamide (7.7 g, 17.64 mmol), phenylmethanethiol (2.326 mL, 19.41 mmol), N-ethyldiisopropylamine (5.83 mL, 35.28 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (0.510 g, 0.88 mmol) and tris(dibenzylideneacetone)palladium(0) (0.404 g, 0.44 mmol) were dissolved in anhydrous N,N-dimethylformamide (22 mL). The reaction was split into two 20-mL microwave vials each were run in a microwave at 180°C for 30 min. The combined vials were dissolved in 1 M sodium hydroxide (100 mL) and extracted with dichloromethane. The combined organic phases were dried over magnesium sulfate and concentrated in vacuo. Purification by column chromatography, using a gradient with increasing polarity (0 to 100% ethyl acetate in heptane) as the eluent, gave 7.30 g (86% yield) of the title compound.

MS (ESI) m/z 478 [M-1]⁻
e) 2-Bromo-N-tert-butyl-5-((tert-butyldimethylsilyloxy)methyl)benzenesulfonamide

\[
\begin{align*}
\text{Br} & \text{O=S=O} \\
\text{HN} & \\
\text{Si} & \text{CH}_3 \text{CH}_2 \text{Cl}
\end{align*}
\]

2-Bromo-N-tert-butyl-5-(hydroxymethyl)benzenesulfonamide (5.9 g, 18.31 mmol), tert-butylchlorodimethylsilane (5.52 g, 36.62 mmol) and lH-imidazole (2.493 g, 36.62 mmol) were dissolved in anhydrous acetonitrile (100 mL). The reaction was stirred at room temperature over night, diluted with water (100 mL) and extracted with ethyl acetate. The combined organic phases were dried through a plug of celite and concentrated \textit{in vacuo} to give 7.70 g (96% yield) of the title compound.

MS (ESI) \(m/z\) 434, 436 [M-I]-

f) 2-Bromo-N-tert-butyl-5-(hydroxymethyl)benzenesulfonamide

\[
\begin{align*}
\text{Br} & \text{O=S=O} \\
\text{OH} & \\
\text{NH} & \text{CH}_2 \text{CH}_3 \text{CH}_2 \text{Cl}
\end{align*}
\]

Aluminum(III) lithium hydride (47.1 mL, 47.1 mmol) was slowly added dropwise to a solution of methyl 4-bromo-3-(N-tert-butylsulfamoyl)benzoate (11 g, 31.41 mmol) in anhydrous tetrahydrofuran (50 mL) at 0 °C. The reaction was allowed to reach room temperature and was stirred at room temperature for 15 min. Water (5 mL) was added dropwise, followed by 25% aqueous sodium hydroxide (5 mL) and followed by water (15 mL). The reaction was stirred for 5 min and filtered. The filtrate was diluted with water,
extracted with dichloromethane and the solvent was evaporated to give 4.10 g (40.5% yield) of the title compound.

MS (ESI) m/z 320, 322 [M-I]^−

g) Methyl 4-bromo-3-(N-tert-butylsulfamoyl)benzoate

2-Methylpropan-2-amine (28.7 mL, 272.10 mmol) followed by triethylamine (37.7 mL, 272.10 mmol) was added to a solution of 4-bromo-3-(chlorosulfonyl)benzoic acid (40.75 g, 136.05 mmol) in dichloromethane (100 mL). The reaction was stirred at room temperature for 2 hours and was acidified using hydrochloric acid (2 M). The mixture was extracted with ethyl acetate, silica was added and the solvent was evaporated. The silica was placed in a glass filter funnel and rinsed with a mobile phase consisting of ethyl acetate, methanol and formic acid (2:2:1). The resulting mixture was concentrated in vacuo, the residue was dissolved in methanol (50 mL), sulfuric acid (1.213 mL, 12.12 mmol) was added and the reaction was refluxed over night. The solution was concentrated under vacuum until half of the volume remained and water (5 mL) was added. The mixture was extracted with dichloromethane, the combined organic phases were dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by column chromatography, using a gradient with increasing polarity (0 to 100% ethyl acetate in heptane) as the eluent, gave 31.0 g (65% yield) of the title compound.

MS (ESI) m/z 348, 350 [M-I]^−
Example 162

Benzene-1,2-disulfonic acid 1-amide 2[(quinoline-3-carbonyl)-amide]

A mixture of benzene-1,2-disulfonamide (0.20 g, 0.85 mmol), 3-quinoline carboxylic acid (0.15 g, 0.85 mmol), \( \mathcal{N} \)-(3-dimethylaminopropyl)-\( \mathcal{N} \)’-ethylcarbodiimide hydrochloride (0.16 g, 0.85 mmol) and 4-dimethylaminopyridine (0.10 g, 0.85 mmol) in anhydrous N,N-dimethylformamide (5 mL) was stirred at room temperature for 3.5 days. Water (20 mL) and ethyl acetate (10 mL) were added, and the layers were separated. The aqueous phase was concentrated under reduced pressure and the resulting solid was washed with methanol and dried. Purification by preparative HPLC gave 35.1 mg (11% yield) of the title compound.

\(^1\)H NMR (400 MHz, DMSO-4) \( \delta \) (ppm) 9.28 (s, 1H), 9.05 (s, 1H), 8.41-8.32 (m, 1H), 8.21-8.08 (m, 3H), 7.95 (t, 1H), 7.90-7.81 (m, 2H), 7.76 (t, 1H), 7.48 (br.s., 2H);

MS (ESI) \( m/z \) 392.0 [M+1] +

Assays for Determining Biological Activity

Inhibition of prostaglandin E synthase activity

Compounds were tested as inhibitors of microsomal prostaglandin E synthase activity in microsomal prostaglandin E synthase assays and whole cell assays. These assays measure prostaglandin E2 (PGE2) synthesis which is taken as a measure of prostaglandin E synthase activity. Microsomal prostaglandin E synthase biochemical assays used microsomal prostaglandin E synthase-1 in microsomal preparations. The source of the microsomes can be for example interleukin-1 \( \beta \)-stimulated human A549 cells (which express human mPGES-1) or Sf9 cells transfected with plasmids encoding human mPGES-1 cDNA.

The whole blood assay [described by Patrignani, P. et al, Journal of Pharmacology and Experimental Therapeutics, 1994, vol. 271, pp 1705-1712] was used as the whole cell
assay for testing the compounds. Whole blood provides a protein and cell rich milieu for the study of biochemical efficacy of anti-inflammatory compounds such as prostaglandin synthase inhibitors. To study the inhibitory activities of these compounds, human blood was stimulated with lipopolysaccharide (LPS) for typically 16 hours to induce mPGES-1 expression, after which the concentration of produced PGE2 was measured by competitive-immuno assay (homogeneous time-resolved fluorescence, HTRF) as read out for effectiveness against mPGES-1-dependent PGE2 production.

**Microsomal prostaglandin E synthase biochemical assay**

A solution of test compound was added to a diluted microsome preparation containing human mPGES-1 and pre-incubated for 15 minutes in potassium phosphate buffer pH 6.8 with cofactor glutathione (GSH). Corresponding solutions without test compound were used as positive controls, and corresponding solutions without test compound and without microsomes were used as negative controls. The enzymatic reaction was then started by addition of the substrate PGH2 in an organic solution (dry acetonitrile).

The typical reaction conditions of the enzymatic reaction were thus: Test compound: ranging from 60 µM to 0.002 µM, or zero in positive and negative controls; potassium phosphate buffer pH 6.8: 50 mM; GSH: 2.5 mM; mPGES-1-containing microsomes: 2 µg/mL (sample and positive controls) or 0 µg/mL (negative control); PGH2: 10.8 µM; Acetonitrile: 7.7 % (v/v); DMSO: 0.6% (v/v). The reaction was stopped after one minute by adding an acidic solution (pH 1.9) of ferric chloride and citrate (final concentrations 7 mM and 47 mM respectively), by which the PGH2 was sequestered (the PGH2 is reduced to mainly 12-hydroxy heptadecatrienoic acid (12-HHT) which is not detected by the subsequent PGE2 detection step). The resulting solution was then pH neutralized by addition of potassium phosphate buffer, prior to diluting an aliquot of the resulting solution in a weak potassium phosphate buffer (50 mM, pH 6.8) containing 0.2% BSA (w/v).

[Adapted from Jacobsson et al, Proc. Natl. Acad. Sci. USA, 1999, vol. 96, pp. 7220-7225] The PGE2 formed was quantified by use of a commercial HTRF based kit (catalogue #62PG2PEC or #62P2APEC from Cisbio International). 100% activity was defined as the PGE2 production in positive controls subtracted by the PGE2 production in the negative controls. IC50 values were then determined using standard procedures.
Data from this assay for representative compounds is shown in the Table below. The potency is expressed as IC50 and the value indicated is an average of at least n=2. The data indicate that the compounds of the invention are expected to possess useful therapeutic properties.

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<th>Example No.</th>
<th>IC50 (μM)</th>
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Whole blood assay

Human blood collected from human volunteers in heparinized tubes was incubated with 100 µM acetyl salicylic acid, in order to inhibit the constitutively expressed cyclooxygenase (COX)-1/COX-2 enzymes, and then stimulated with 0.1 µg/ml LPS to induce the expression of enzymes along the COX-2 pathway, e.g. COX-2 and mPGES-1. 100 µL of this blood was added to the wells of a 384-well plate containing 1 µL DMSO solutions of compounds typically in the final concentration range 316 µM to 0.01 µM. Naproxen was used as reference compound. The mix was incubated at 37°C for 16 hours.

Plasma was harvested by centrifugation and stored at -70°C until further analysis of PGE2 levels. For the calculations, the 0%-activity value was represented by blood treated with acetyl salicylic acid, LPS and the reference compound (1 mM Naproxen). The 100%-activity value was represented by blood treated with aspirin, LPS and DMSO. [Reference: Patrignani, P. et al, Journal of Pharmacology and Experimental Therapeutics, 1994, vol. 271, pp 1705-1712]. The PGE2 formed was quantified, after dilution in a weak potassium phosphate buffer (50 mM, pH 6.8) containing 0.2% BSA (w/v), by use of a commercial HTRF based kit (catalogue #62PG2PEC or #62P2APEC from Cisbio International). IC50 values were then determined using standard procedures.
1. A compound of formula (I) or a pharmaceutically acceptable salt thereof

wherein:

A is selected from mono- and bicyclic aryl, mono- and bicyclic heteroaryl, cycloalkenyl and mono- and bicyclic heterocyclyl;

$R^1$ is independently selected from halogen, nitro, SF$_5$, CHO, CO$_2$alkylCN, OC$_{1-6}$alkylCN, CO$_2$alkylOR, CO$_2$alkylOR, C$_{0-6}$alkylNR$_5$R, CO$_2$alkylNR$_5$R, CO$_2$alkylCON(R$_5$)$_2$, OC$_{1-6}$alkylCON($R^5$)$_2$, OC$_{2-6}$alkylNR$_5$(CO)R, C$_{0-6}$alkylNR$_5$(CO)R, 0(CO)NR$_5$R, 0(CO)OR, 0(CO)OR, 0(CO)R, C$_{0-6}$alkylCOR, 5, OC$_{1-6}$alkylCOR, 5, NR$_5$(CO)(CO)R, 5, NR$_5$(CO)(CO)NR$_5$R, C$_{0-6}$alkylSR, C$_{0-6}$alkyl(SO$_2$)NR$_5$R, OC$_{1-6}$alkylNR$_5$(SO$_2$)R, C$_{0-6}$alkyl(SO$_2$)NR$_5$R, C$_{0-6}$alkyl(SO$_2$)NR$_5$R, 0(CO)alkyl(ISO$_2$)R, C$_{0-6}$alkyl(ISO$_2$)R, C$_{0-6}$alkyl(SO$_2$), C$_{0-6}$alkyl(ISO$_2$)R, C$_{0-6}$alkyl(SO$_2$), C$_{2}$alkenyl, C$_{2}$alkynyl, CO$_2$alkylC$_{3}$Cycloalkyl, CO$_2$alkylaryl, CO$_2$alkylheteroaryl and CO$_2$alkylheterocyclyl, wherein said CO$_2$alkyl, C$_{2}$alkenyl, C$_{2}$alkynyl, C$_{3}$alkenyl, C$_{3}$alkynyl, CO$_2$alkylC$_{3}$Cycloalkyl, CO$_2$alkylaryl, CO$_2$alkylheteroaryl or CO$_2$alkylheterocyclyl is optionally substituted with one or more B, and wherein any of the individual aryl or heteroaryl groups may be optionally fused with a 4, 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclyl group to form a bicyclic ring system where the bicyclic ring system is optionally substituted with one or more B;
R² is \(-L²₁ -L²₂\);

R³ is hydrogen;

5  \(G^1\) is selected from \(\text{C}_3\)-iocyloalkyl, \(\text{C}_4\)-i₂cycloalkenyl, \(\text{C}_7\)-i₂cycloalkynyl, aryl, heteroaryl, heterocycl, wherein said \(\text{C}_3\)-iocyloalkyl, \(\text{C}_4\)-i₂cycloalkenyl, \(\text{C}_7\)-i₂cycloalkynyl, aryl, heteroaryl or heterocycl is optionally substituted with one or more \(R^{10}\);

\(G^2\) is selected from hydrogen, Cs-s-cycloalkyl, \(\text{C}_4\)-i₂cycloalkenyl, Cy.\(^\wedge\)cycloalkynyl, aryl, heteroaryl, heterocycl, wherein said \(\text{C}_3\_\text{i}_3\)cycloalkyl, \(\text{C}_4\_\text{i}_2\)cycloalkenyl, \(\text{C}_7\_\text{i}_2\)cycloalkynyl, aryl, heteroaryl or heterocycl is optionally substituted with one or more \(R^{10}\);

At each occurrence, \(R^5\) is independently selected from hydrogen, \(\text{C}_{1,6}\)alkyl, \(\text{C}_{2,6}\)alkenyl, \(\text{C}_{2,6}\)alkynyl, \(\text{C}_{0,6}\)alkyl\(\text{C}_{3,8}\)cycloalkyl, \(\text{C}_{0,6}\)alkylaryl, \(\text{C}_{0,6}\)alkylheteroaryl and \(\text{C}_{0,6}\)alkylheterocycl, wherein said \(\text{C}_{1,6}\)alkyl, \(\text{C}_{2,6}\)alkenyl, \(\text{C}_{2,6}\)alkynyl, \(\text{C}_{0,6}\)alkyl\(\text{C}_{3,8}\)cycloalkyl, \(\text{C}_{0,6}\)alkylaryl, \(\text{C}_{0,6}\)alkylheteroaryl or \(\text{C}_{0,6}\)alkylheterocycl is optionally substituted with one or more \(B\);

At each occurrence, \(R^6\) is selected from hydrogen, \(\text{C}_{1,6}\)alkyl, \(\text{C}_{2,6}\)alkenyl, \(\text{C}_{2,6}\)alkynyl, \(\text{C}_{0,6}\)alkylOR\(^5\), \(\text{C}_{0,6}\)alkyl\(\text{C}_{3,8}\)cycloalkyl, \(\text{C}_{0,6}\)alkylaryl, \(\text{C}_{0,6}\)alkylheteroaryl and \(\text{C}_{0,6}\)alkylheterocycl, wherein said \(\text{C}_{1,6}\)alkyl, \(\text{C}_{2,6}\)alkenyl, \(\text{C}_{2,6}\)alkynyl, \(\text{C}_{0,6}\)alkyl\(\text{C}_{3,8}\)cycloalkyl, \(\text{C}_{0,6}\)alkylaryl, \(\text{C}_{0,6}\)alkylheteroaryl or \(\text{C}_{0,6}\)alkylheterocycl is optionally substituted with one or more \(B\); or

\(R^5\) and \(R^6\) may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S that is optionally substituted with \(B\); whenever two \(R^5\) groups occur in the structure then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, that is optionally substituted with one or more \(B\).
L¹ and L² independently represent a bond or a 1-7 membered non-cyclic linking group containing 0-2 heteroatoms selected from O, N, and S, said linking group optionally containing CO, S(O)ₙ, C≡C or an acetylenic group, and optionally being substituted with one or more R⁸;

R⁸ is selected from halogen, nitro, CHO, CN, OH, O(CH₃)₆alkyl, O(C(CH₃)₆alkyl)O(C(CH₃)₆alkyl), C(CH₃)₆alkyl, C(CH₃)₆alkenyl, C(CH₃)₆alkynyl N(C(CH₃)₆alkyl)C(CH₃)₆alkyl, NH₂, NH(C(CH₃)₆alkyl), S(O)ₙ(C(CH₃)₆alkyl), SO₂N(C(CH₃)₆alkyl)(C(CH₃)₆alkyl), SO₂NH₂, SO₂NH(C(CH₃)₆alkyl), CF₃, CHF₂, CFH₂, C(O)(C(CH₃)₆alkyl), C(O)N(C(CH₃)₆alkyl)(C(CH₃)₆alkyl), C(O)NH(C(CH₃)₆alkyl), C(O)NH₂, N(C(CH₃)₆alkyl)(CO)N(C(CH₃)₆alkyl)(C(CH₃)₆alkyl), NH(CO)N(C(CH₃)₆alkyl)(C(CH₃)₆alkyl), N(C(CH₃)₆alkyl)(CO)NH(C(CH₃)₆alkyl), NH(CO)NH₂, N(C(CH₃)₆alkyl)(CO)NH₂.

Whenever two R⁸ groups are connected to the same atom of the linking group L¹, they may optionally together form a 3 to 6 membered non-aromatic, carbocyclic or heterocyclic (containing one or more heteroatoms selected from N, O or S) ring, that is optionally substituted with one or more R⁹;

R⁹ is selected from halogen, nitro, CHO, CN, OH, O(CH₃)₆alkyl, O(C(CH₃)₆alkyl)O(C(CH₃)₆alkyl), C(CH₃)₆alkyl, C(CH₃)₆alkenyl, C(CH₃)₆alkynyl N(C(CH₃)₆alkyl)(C(CH₃)₆alkyl), NH₂, NH(C(CH₃)₆alkyl), S(O)ₙ(C(CH₃)₆alkyl), SO₂N(C(CH₃)₆alkyl)(C(CH₃)₆alkyl), SO₂NH₂, SO₂NH(C(CH₃)₆alkyl), CF₃, CHF₂, CFH₂, C(O)(C(CH₃)₆alkyl), C(O)N(C(CH₃)₆alkyl)(C(CH₃)₆alkyl), C(O)NH(C(CH₃)₆alkyl), C(O)NH₂, N(C(CH₃)₆alkyl)(CO)N(C(CH₃)₆alkyl)(C(CH₃)₆alkyl), NH(CO)N(C(CH₃)₆alkyl)(C(CH₃)₆alkyl), N(C(CH₃)₆alkyl)(CO)NH(C(CH₃)₆alkyl), NH(CO)NH₂, N(C(CH₃)₆alkyl)(CO)NH₂.

B is selected from halogen, nitro, SF₅, OSF₅, CN, OR¹⁵, OC(CH₃)₆alkylNR¹⁵R¹⁶, NR¹⁵R¹⁶, CONR¹⁵R¹⁶, NR¹⁵(CO)R¹⁶, O(CO)(C(CH₃)₆alkyl), (CO)OC(CH₃)₆alkyl, COR¹⁵, (SO₂)NR¹⁵R¹⁶, NR¹⁵SO₂R¹⁵, SO₂R¹⁵, SOR¹⁵, (CO)d(CH₃)₆alkylNR¹⁵R¹⁶, (SO₂)C(CH₃)₆alkylNR¹⁵R¹⁶, OSO₂R¹⁵, C(CH₃)₆alkyl, C(CH₃)₆alkenyl, C(CH₃)₆alkynyl, C(CH₃)₆alkylC₃₈cycloalkyl, C(CH₃)₆alkylaryl, C(CH₃)₆alkylheteroaryl and C(CH₃)₆alkylheterocyclyl;
R\textsuperscript{15} is selected from hydrogen, C\textsuperscript{1} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, Co-6 alkylC\textsubscript{3-8} cycloalkyl, Co-6 alkylaryl, Co-6 alkyllheteroaryl and Co-6 alky1heterocycl1; 

R\textsuperscript{16} is selected from hydrogen, C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{0-6} alkylOR, Co-alkylC\textsubscript{3-8} cycloalkyl, Co-alkylaryl, Co-alkylheteroaryl and Co-alkylheterocycl1; or

R\textsuperscript{15} and R\textsuperscript{16} may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S; whenever two R\textsuperscript{15} groups occur in the structure then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S;

D is selected from halogen, nitro, SF\textsubscript{5}, OSF\textsubscript{5}, CN, OR\textsubscript{13}, OC\textsubscript{2-6} alkylNR\textsuperscript{13}R\textsuperscript{14}, NR\textsuperscript{13}R\textsuperscript{14}, CONR\textsuperscript{13}R\textsuperscript{14}, NR\textsubscript{11}(CO)R\textsuperscript{14}, O(CO)C\textsubscript{i-6} alkyl, (CO)OC\textsubscript{i-6} alkyl, COR\textsuperscript{13}, (SO\textsubscript{2})NR\textsuperscript{13}R\textsuperscript{14}, NR\textsuperscript{13}SO\textsubscript{2}R\textsuperscript{14}, SO\textsubscript{2}R\textsuperscript{13}, SOR\textsuperscript{13}, (CO)d\textsubscript{1-6} alkylNR\textsuperscript{13}R\textsuperscript{14}, (SO\textsubscript{2})C\textsubscript{i-6} alkylNR\textsuperscript{11}R\textsuperscript{14}, OSO\textsubscript{2}R\textsuperscript{13}, Ci\textsubscript{i-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, Co-6 alkylC\textsubscript{3-8} cycloalkyl, and Co-6 alky1heterocycl1;

R\textsuperscript{10} is independently selected from halogen, nitro, SF\textsubscript{5}, OSF\textsubscript{5}, CN, OR\textsuperscript{11}, C\equiv CR\textsuperscript{11}, OC\textsubscript{2-6} alkylNR\textsuperscript{13}R\textsuperscript{12}, NR\textsuperscript{11}R\textsuperscript{12}, CONR\textsuperscript{11}R\textsuperscript{12}, NR\textsuperscript{11}(CO)R\textsuperscript{12}, O(CO)C\textsubscript{i-6} alkyl, (CO)OC\textsubscript{i-6} alkyl, COR\textsuperscript{11}, (SO\textsubscript{2})NR\textsuperscript{11}R\textsuperscript{12}, NR\textsuperscript{11}SO\textsubscript{2}R\textsuperscript{11}, SO\textsubscript{2}R\textsuperscript{11}, SOR\textsuperscript{11}, (CO)C\textsuperscript{1-6} alkylNR\textsuperscript{11}R\textsuperscript{12}, (SO\textsubscript{2})C\textsubscript{i-6} alkylNR\textsuperscript{13}R\textsuperscript{12}, OSO\textsubscript{2}R\textsuperscript{11}, Ci\textsubscript{i-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{0-6} alkylC\textsubscript{3-8} cycloalkyl, Co-6 alkylaryl, Co-6 alky1heteroaryl, Co-6 alky1heterocycl1 and OC\textsubscript{2-6} alkylheterocycl1, wherein said C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{0-6} alkylC\textsubscript{3-8} cycloalkyl, C\textsubscript{0-6} alkylaryl, C\textsubscript{0-6} alky1heteroaryl, Co-6 alky1heterocycl1 or OC\textsubscript{2-6} alkylheterocycl1 is optionally substituted with one or more E, and wherein any of the individual aryl or heteroaryl groups may be optionally fused with a 4, 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocycl1 group to form a bicyclic ring system where the bicyclic ring system is optionally substituted with one or more E;
At each occurrence, \( R^{11} \) is independently selected from hydrogen, \( C_{1-6} \) alkyl, \( C_{2-6} \) alkenyl, \( C_{2-6} \) alkynyl, \( C_{6} \) alkylC\(_{3-8}\) cycloalkyl, \( C_{6} \) alkylaryl, \( C_{6} \) alkylheteroaryl and \( C_{6} \) alkylheterocyclyl, wherein any of the individual \( C_{6} \) alkyl, \( C_{2-6} \) alkynyl, \( C_{6} \) alkylC\(_{3-8}\) cycloalkyl, \( C_{6} \) alkylaryl, \( C_{6} \) alkylheteroaryl and \( C_{6} \) alkylheterocyclyl groups may be optionally substituted with one or more E;

\[ R^{12} \] is selected from hydrogen, \( C_{6} \) alkyl, \( C_{2-6} \) alkenyl, \( C_{2-6} \) alkynyl, \( C_{6} \) alkylC\(_{3-8}\) cycloalkyl, \( C_{6} \) alkylaryl, \( C_{6} \) alkylheteroaryl and \( C_{6} \) alkylheterocyclyl, wherein any of the individual \( C_{6} \) alkyl, \( C_{2-6} \) alkenyl, \( C_{2-6} \) alkynyl, \( C_{6} \) alkylC\(_{3-8}\) cycloalkyl, \( C_{6} \) alkylaryl, \( C_{6} \) alkylheteroaryl and \( C_{6} \) alkylheterocyclyl groups may be optionally substituted with one or more E; or

\( R^{11} \) and \( R^{12} \) may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S that is optionally substituted with B; whenever two \( R^{11} \) groups occur in the structure then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, where the ring system is optionally substituted with one or more E;

\[ R^{13} \] is independently selected from hydrogen, \( C_{1-6} \) alkyl, \( C_{2-6} \) alkenyl, \( C_{2-6} \) alkynyl, \( C_{6} \) alkylC\(_{3-8}\) cycloalkyl, \( C_{6} \) alkylaryl, \( C_{6} \) alkylheteroaryl and \( C_{6} \) alkylheterocyclyl;

\[ R^{14} \] is selected from hydrogen, \( C_{6} \) alkyl, \( C_{2-6} \) alkenyl, \( C_{2-6} \) alkynyl, \( C_{6} \) alkylOR\(^5\), \( C_{6} \) alkylC\(_{3-8}\) cycloalkyl, \( C_{6} \) alkylaryl, \( C_{6} \) alkylheteroaryl and \( C_{6} \) alkylheterocyclyl; or

\( R^{13} \) and \( R^{14} \) may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S; whenever two \( R^{13} \) groups occur in the structure then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S;
E is selected from halogen, nitro, SF₅, OSF₅, CN, OR⁵, OC₂₋₆ alkylNR⁵R⁶, NR⁵R⁶, CONR⁵R⁶, NR₂(CO)R⁶, O(CO)Ci₆ alkyl, (CO)OCi₆ alkyl, COR⁵, (SO₂)NR⁵R⁶, NR⁵SO₂R⁵, SO₂R⁵, SOR⁵, (CO)Ci₆ alkylNR⁵R⁶, (SO₂)Ci₆ alkylNR⁵R⁶, OSO₂R⁵, Ci₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, Co₋₆ alkylCl₃₋₈ cycloalkyl, Co₋₆ alkylaryl, Co₋₆ alkyl heteroaryl and Co₋₆ alkyl heterocyclyl;

m = 0, 1, 2, 3, 4;
n = 0, 1, 2;

provided that the compounds:
1.2-Benzenedisulfonamide, NI-[(4,6-dimethyl-2-pyrimidinyl)amino]carbonyl; or
1.2-Benzenedisulfonamide, NI-[(4,6-dimethoxy-1,3,5-triazin-2-yl)amino]carbonyl; or
1.2-Benzenedisulfonamide, NI-[(4-methoxy-6-methyl-2-pyrimidinyl)amino]carbonyl; or
1.2-Benzenedisulfonamide, NI-[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl] are excluded.

2. A compound according to Claim 1 wherein A represents phenyl.

3. A compound according to claim 1 or 2 wherein m is 0.

4. A compound according to claim 1 or 2 wherein m is 1.

5. A compound according to any one of claims 1-4 wherein R¹ represents halogen, Ci₄ alkyl or Ci₄ alkoxy; said Ci₄ alkyl or Ci₄ alkoxy being optionally substituted by OH or by one or more F atoms.

6. A compound according to any one of claims 1-5 wherein R⁵ and R⁶ independently represents hydrogen or Ci₁₋₆ alkyl being optionally substituted by B.

7. A compound according to any one of claims 1-6 wherein B is OR₁⁵.
8. A compound according to any one of claims 1-7 wherein $R^{11}$ represents hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{6-6}$ alkyl$C_{3-8}$ cycloalkyl, $C_{6-6}$ alkylaryl, $C_{6-6}$ alkylheteroaryl, wherein any of the individual $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{6-6}$ alkyl$C_{3-8}$ cycloalkyl, $C_{6-6}$ alkylaryl, $C_{6-6}$ alkylheteroaryl groups may be optionally substituted with one or more $E$.

9. A compound according to any one of claims 1-8 wherein $R^{12}$ represents hydrogen, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{6-6}$ alkyl$C_{3-8}$ cycloalkyl, $C_{6-6}$ alkylaryl, $C_{6-6}$ alkylheteroaryl, wherein any of the individual $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{6-6}$ alkyl$C_{3-8}$ cycloalkyl, $C_{6-6}$ alkylaryl, $C_{6-6}$ alkylheteroaryl groups may be optionally substituted with one or more $E$.

10. A compound according to any one of claims 1-9 wherein $E$ represents halogen or $OR^5$.

11. A compound according to any one of claims 1-10 wherein $L^1$ is a direct bond.

12. A compound according to any one of claims 1-10 wherein $L^1$ is $-CH_2^\cdot$.

13. A compound according to any one of claims 1-12 wherein $L^2$ is a direct bond.

14. A compound according to any one of claims 1-12 wherein $L^2$ is $-C\equiv C\cdot$, $-OCH_2^\cdot$ or $-CH_2^\cdot$.

15. A compound according to any one of claims 1-14 wherein $G^1$ represents phenyl optionally fused to one further ring selected from phenyl and 5- or 6-membered heteroaryl.

16. A compound according to any one of claims 1-14 wherein $G^1$ represents phenyl, 5- or 6-membered heteroaryl or $C_3$-iocyloalkyl optionally fused to one further ring selected from phenyl and 5- or 6-membered heteroaryl wherein said phenyl, 5- or 6-membered heteroaryl or $C_3$-iocyloalkyl optionally fused to one further ring selected from phenyl and 5- or 6-membered heteroaryl is optionally substituted with one or more $R^{10}$. 


17. A compound according to anyone of claims 1-16 wherein G represents H, phenyl, Cs.scycloalkyl or 5- or 6-membered heteroaryl; said phenyl or 5- or 6-membered heteroaryl being optionally fused to one further ring independently selected from phenyl, a 5- or 6-membered heteroaryl ring wherein said phenyl or 5- or 6-membered heteroaryl being optionally fused to one further ring independently selected from phenyl, a 5- or 6-membered heteroaryl ring is optionally substituted with one or more R\(^1\). 

18. A compound according to anyone of claims 1-17 wherein R\(^1\) is independently selected from halogen, CN, C\(_i\)\(_i\)alkyl, OR\(^1\), C≡CR\(^1\), (CO)OC\(_i\)\(_i\)alkyl, C\(_3\)\(_8\)cycloalkyl or heteroaryl said d \(_6\)alkyl, OR\(^1\), (CO)OC\(_i\)\(_i\)alkyl, C\(_3\)\(_8\)cycloalkyl, Co-\(_6\)alkylaryl or Co-\(_6\)alkylheteroaryl being optionally substituted by OH or by one or more F atoms.

19. A compound according to anyone of claims 1-18 wherein R\(^1\) is selected from hydrogen, C\(_i\)\(_i\)alkyl, C\(_2\)\(_6\)alkenyl, C\(_2\)\(_6\)alkynyl, Co-\(_6\)alkyl Cs-scycloalkyl, Co-\(_6\)alkylaryl, Co-\(_6\)alkylheteroaryl and Co-\(_6\)alkylheterocyclyl.

20. A compound according to anyone of claims 1-19 wherein R\(^1\) is selected from hydrocarborn, C\(_i\)\(_i\)alkyl, C\(_i\)\(_i\)alkenyl, C\(_i\)\(_i\)alkynyl, Co-\(_6\)alkyl Cs-scycloalkyl, Co-\(_6\)alkylaryl, Co-\(_6\)alkylheteroaryl and Co-\(_6\)alkylheterocyclyl.

21. A compound according to claim 1 wherein G represents phenyl, 5- or 6-membered heteroaryl or C\(_3\)\(_8\)cycloalkyl optionally fused to one further ring selected from phenyl and 5- or 6-membered heteroaryl wherein said phenyl, 5- or 6-membered heteroaryl or C\(_3\) cycloalkyl optionally fused to one further ring selected from phenyl and 5- or 6-membered heteroaryl is optionally substituted with one or more R\(^1\).

22. A compound according to claim 1 wherein; A is selected from phenyl or pyridyl; said phenyl or pyridyl being optionally fused to a phenyl, a 5- or 6-membered heteroaryl, Cs\(^\circ\)cycloalkyl or Cs\(^\circ\)heterocyclyl ring.
$R^1$ is independently selected from halogen, nitro, $SF_5$, CHO, CN, $NR^5R^6$, $CO_2R^5$, $CON(R^5)_2$, $NR^5(CO)R^6$, $0(CO)NR^5R^6$, $NR^5(CO)OR^6$, $0(CO)OR^5$, $0(CO)R^5$, $COR^5$, $NR^5(CO)(CO)R^5$, $NR^5(CO)(CO)NR^5R^6$, $SR^5$, $(SO_2)NR^5R^6$, $(SO)NR^5R^6$, $OSO_2R^5$, $NR^5(SO_2)NR^5R^6$, $NR^5(SO)R^6$, $SO_2R^6$, $SOR^5$, $Ci_6alkyl$, $Ci_6alkoxy$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $Cs.scycloalkyl$, $Co-_alkylaryl$, $Co-_alkylheteroaryl$ and heterocyclyl, wherein said $Ci_6alkyl$, $C_{1-6}alkoxy$, $C_{2-6}alkenyl$, $Cs.scycloalkyl$, $Co-_alkylaryl$, $Co-_alkylheteroaryl$ or heterocyclyl is optionally substituted with one or more $B$, and wherein any of the individual aryl or heteroaryl groups may be optionally fused with a 4, 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclyl group to form a bicyclic ring system where the bicyclic ring system is optionally substituted with one or more $B$;

$m = 0, 1, 2$;

$R^2$ is $-L^1G^1-L^2-G^2$;

$R^3$ is hydrogen;

$R^5$ and $R^6$ is independently selected from hydrogen, $Ci_6alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $Ci_6alkoxy$, $C_{3-8}scycloalkyl$, ary1, $C_{1-6}alkylaryl$, heteroaryl. $C_{1-6}alkylheteroaryl$ and heterocyclyl;

$R^{11}$ and $R^{12}$ are independently selected from hydrogen and $C_{1-6}alkyl$ wherein said $C_{1-6}alkyl$ is optionally substituted with one or more $E$.

$L^1$ represents a direct bond, $-CH_2^-$, $-CH_2CH_2^-$ or $-CH=CH-$;

$L^2$ represents a direct bond, $-O-$, $-OCH_2^-$, $-CH_2^-$, $-CH_2CH_2^-$ or $-C\equiv C-$;

$G^1$ represents phenyl or 5- or 6-membered heteroaryl optionally fused to one further ring independently selected from phenyl and 5- or 6-membered heteroaryl wherein said phenyl or 5- or 6-membered heteroaryl optionally fused to one further ring independently selected
from phenyl and 5- or 6-membered heteroaryl is optionally substituted with one or more \( R^{10} \).

\( 2 \) \( G \) represents H, phenyl or 5- or 6-membered heteroaryl; said phenyl or 5- or 6-membered heteroaryl being optionally fused to one further ring independently selected from phenyl, a 5- or 6-membered heteroaryl, \( C_{5,6} \) carbocyclil or \( C_{5,6} \) heterocyclil ring wherein said phenyl or 5- or 6-membered heteroaryl being optionally fused to one further ring independently selected from phenyl, a 5- or 6-membered heteroaryl, \( C_{5,6} \) carbocyclil or \( C_{5,6} \) heterocyclil ring is optionally substituted with one or more \( R^{10} \).

\( R^{10} \) is independently selected from halogen, nitro, \( SF_5 \), \( OSF_5 \), \( CN \), \( OR^{11} \), \( C=CR^{11} \), \( OC_2 \)
\( 6 \) alkylNR\( ^\pi \)R\(^{12} \), NR\(^{11} \)R\(^{12} \), CONR\(^{11} \)R\(^{12} \), NR\(^{\pi} \)(CO)R\(^{12} \), 0(CO)C\( _i \)alkyl, (CO)OC\( _i \)alkyl, COR\(^{11} \), (SO\(_2\))NR\(^{11} \)R\(^{12} \), NR\(^{11} \)SO\(_2\)R\(^{11} \), SO\(_2\)R\(^{11} \), SOR\(^{11} \), (CO)C\(^\pi\)alkylNR\(^{11} \)R\(^{12} \), (SO\(_2\))C\(_i\)
\( 6 \) alkylNR\( ^\pi \)R\(^{12} \), OSO\(_2\)R\(^{11} \), C\(_i\)alkyl, C\(_{2,6}\)alkenyl, C\(_{2,6}\)alkynyl, C\(_{3,8}\)cycloalkyl, aryl, heteroaryl, heterocyclil and OC\(_{2,6}\)alkylheterocyclil, wherein said \( C_{1,6}\)alkyl, \( C_{2,6}\)alkenyl, \( C_{2,6}\)alkynyl, C\(_{3,8}\)cycloalkyl, aryl, heteroaryl, heterocyclil or OC\(^\pi\)alkylheterocyclil is optionally substituted with one or more E, and wherein any of the individual aryl or heteroaryl groups may be optionally fused with a 4, 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclil group to form a bicyclic ring system where the bicyclic ring system is optionally substituted with one or more E.

23. A compound according to Claim 1 wherein:

A is phenyl or pyridyl;

\( R^1 \) is independently selected from halogen, nitro, \( SF_5 \), \( OH \), \( CHO \), \( C_{1,4}\)alkyl or \( C_{1,4}\)alkoxy; said \( C_{1,4}\)alkyl or \( C_{1,4}\)alkoxy being optionally substituted by \( OH \) or by one or more \( F \) atoms.
\( m = 0, 1, 2 \);

\( R^3 \) is hydrogen;

\( R^5 \) and \( R^6 \) is independently selected from hydrogen and \( C_{1,4}\)alkyl!
L\(^1\) represents a direct bond, -CH\(_2\), -CH\(_2\)CH\(_2\) or -CH=CH-; 
L\(^2\) represents a direct bond, -O-, -OCH\(_2\), -CH\(_2\), -CH\(_2\)CH\(_2\) or 
- C≡C-.

G\(^1\) represents phenyl, 5- or 6-membered heteroaryl or C\(_3\)-iocycloalkyl; optionally fused to one further ring independently selected from phenyl and 5- or 6-membered heteroaryl; 
G\(^2\) represents H, phenyl, Cs-cycloalkyl or 5- or 6-membered heteroaryl; said phenyl or 5- or 6-membered heteroaryl being optionally fused to one further ring independently selected from phenyl, a 5- or 6-membered heteroaryl ring.

R\(^{10}\) is independently selected from halogen, CN, Ci\(_6\)alkyl, C\(_1\)-alkoxy, C≡CR\(^{11}\), (CO)OCi\(_6\)alkyl, C\(_3\)-cycloalkyl or heteroaryl said C\(_1\)-alkyl, (CO)OCi\(_6\)alkyl, C\(_3\)-cycloalkyl, heteroaryl or C\(_6\)alkoxy being optionally substituted by OH or by one or more F atoms.

24. A compound according to Claim 1 wherein:

A is phenyl; 
R\(^1\) is independently selected from halogen, Ci\(_4\)alkyl or Ci\(_4\)alkoxy; said Ci\(_4\)alkyl or Ci\(_4\)alkoxy being optionally substituted by OH or by one or more F atoms; 
m = 0 or 1; 
R\(^3\) is hydrogen; 
R\(^5\) and R\(^6\) is independently selected from hydrogen and C\(_6\)alkyl; 
L\(^1\) represents a direct bond or -CH\(_2\); 
L\(^2\) represents a direct bond, -O-, -OCH\(_2\), -CH\(_2\), -CH\(_2\)CH\(_2\) or 
- C≡C-; 
G\(^1\) represents phenyl, 5- or 6-membered heteroaryl or C\(_3\)-iocycloalkyl; optionally fused to one further ring independently selected from phenyl and 5- or 6-membered heteroaryl;
\(G^2\) represents H, phenyl, Cs-scycloalkyl or 5- or 6-membered heteroaryl; said phenyl or 5- or 6-membered heteroaryl being optionally fused to one further ring independently selected from phenyl, a 5- or 6-membered heteroaryl ring;

\(R^{10}\) is independently selected from halogen, CN, \(d^-\)alkyl, \(C_{1,6}\)alkoxy, C≡CR, \((CO)OCi_{\text{6}}\)alkyl, Cs\(^{c}\)cycloalkyl or heteroaryl said \(C_{1,6}\)alkyl, \((CO)OCi_{\text{6}}\)alkyl, Cs.scycloalkyl, heteroaryl or Ci\(_{6}\)alkoxy being optionally substituted by OH or by one or more F atoms.

25. A compound according to any preceding claim being an entity selected from:

- 5-Benzofuran-2-yl-N-(2-sulfamoylphenyl)sulfonyl-pyridine-2-carboxamide;
- 5-(2,3-Dichlorophenyl)-N-(2-sulfamoylphenyl)sulfonyl-pyridine-2-carboxamide;
- 4-Benzofuran-2-yl-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
- 4-Benzothiophen-2-yl-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
- 4-Benzothiazol-2-yl-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
- 4-(7-Oxa-3,9-diazabicyclo[4.3.0]nona-2,4,8,10-tetraen-8-yl)-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
- 4-(7-Oxa-5,9-diazabicyclo[4.3.0]nona-2,4,8,10-tetraen-8-yl)-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
- 4-Benzooxazol-2-yl-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
- 2-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-benzofuran-6-carboxamide;
- 4-Bromo-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
- 4-Bromo-2-chloro-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
- 4-Bromo-3-methyl-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
- 4-Bromo-3-fluoro-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
- 4-Bromo-2-fluoro-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
- 4-Bromo-2-methyl-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
- 2-(1-Adamantyl)-N-(2-sulfamoylphenyl)sulfonyl-acetamide;
- N-(2-Sulfamoylphenyl)sulfonylnorbornane-2-carboxamide;
- 1-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-cyclohexane-1-carboxamide;
- 3-(Difluoromethoxy)-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
3-Bromo-4-fluoro-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
N-(2-Sulfamoylphenyl)sulfonyl-3-(2,2,3,3-tetrafluoropropoxymethyl)benzamide;
4-Methyl-N-(2-sulfamoylphenyl)sulfonyl-2-[3-(trifluoromethyl)phenyl][3-thiazole-5-carboxamide;
4-Chloro-2-fluoro-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
2-Benzyl-4-chloro-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
2-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-benzofuran-5-carboxamide;
4-Methyl-N-(2-sulfamoylphenyl)sulfonyl-2-[4-(trifluoromethyl)phenyl][3-thiazole-5-carboxamide;
2-(2,3-Dihydrobenzofuran-5-yl)-4-methyl-N-(2-sulfamoylphenyl)sulfonyl-1,3-thiazole-5-carboxamide;
2-(4-Chlorophenyl)-4-methyl-N-(2-sulfamoylphenyl)sulfonyl-1,3-thiazole-5-carboxamide;
4-Methyl-2-phenyl-N-(2-sulfamoylphenyl)sulfonyl-1,3-thiazole-5-carboxamide;
4-Phenylmethoxy-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
4-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
N-(2-Sulfamoylphenyl)sulfonyl-4-tert-butyl-benzamide;
1-Methyl-N-(2-sulfamoylphenyl)sulfonyl-indole-2-carboxamide;
5-Pyridin-2-yl-N-(2-sulfamoylphenyl)sulfonyl-thiophene-2-carboxamide;
5-Phenyl-N-(2-sulfamoylphenyl)sulfonyl-thiophene-2-carboxamide;
5-(3,4-Dichlorophenyl)-N-(2-sulfamoylphenyl)sulfonyl-furan-2-carboxamide;
N-(2-Sulfamoylphenyl)sulfonyl-5-[3-(trifluoromethyl)phenyl]furan-2-carboxamide;
1-(3,5-Dichlorophenyl)-5-propyl-N-(2-sulfamoylphenyl)sulfonyl-pyrazole-4-carboxamide;
3,6-Dichloro-N-(2-sulfamoylphenyl)sulfonyl-benzothiophene-2-carboxamide;
N-(2-Sulfamoylphenyl)sulfonylbenzothiophene-3-carboxamide;
Ethyl 4-[5-(2-Sulfamoylphenyl)sulfonylcarbamoyl]-2-furylbenzoate;
2-(3-Chlorophenyl)-4-methyl-N-(2-sulfamoylphenyl)sulfonyl-1,3-thiazole-5-carboxamide;
4-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
4-(3-Hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
4-(Benzofuran-2-yl)-2-methyl-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
4-(Benzofuran-2-yl)-2-methyl-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
4-(Benzofuran-2-yl)-3,5-dimethoxy-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
4-(Benzofuran-2-yl)-2-methoxy-N-(2-sulfamoylphenyl)sulfonyl-benzamide;
4-(Benzofuran-2-yl)-2-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-3-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-2,6-dimethyl-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3-Methoxyprop-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3-Methylbut-3-en-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
6-(Phenylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
4-(3-Ethyl-3-hydroxypent-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3-Hydroxy-3-methylpent-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-((1-Hydroxycyclopentyl)ethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
3-(3-Hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
3-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)-1-naphthamide;
4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)-1-naphthamide;
2-(Benzofuran-2-yl)-4-methyl-N-(2-sulfamoylphenylsulfonyl)thiazole-5-carboxamide;
3-(3-Hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)biphenyl-2-carboxamide;
4-(Cyclopentylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
3-(Cyclopentylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopentylethynyl)-2-methyl-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3,3-Dimethylbut-1-ynyl)-3-methoxy-2-methyl-N-(2-sulfamoylphenylsulfonyl)-benzamide;
4-(Benzofuran-2-yl)-3-methoxy-2-methyl-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Pyridin-3-ylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Pyridin-2-ylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Phenylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3,3-Dimethylbut-1-ynyl)-3-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
2-(3-Methoxyphenyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(4-Methoxyphenyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-tert-Butyl-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(1-Hydroxycyclopentyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-Cyclopentyl-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
3-Cyano-4-(3,3-dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-3-cyano-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-Chloro-2-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-Bromo-2-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzomaran-2-yl)-2-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3,3-Dimethylbut-1-ynyl)-2-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopentylethynyl)-2-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopentylethynyl)-2-fluoro-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzomaran-2-yl)-2-fluoro-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
5-(Cyclohexylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
5-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
4-(3,3-Dimethylbut-1-ynyl)-2-fluoro-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-2-chloro-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopentylethynyl)-2-hydroxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
6-(Cyclopentylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Pyridin-2-ythynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Pyridin-3-ythynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
2-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)pyrimidine-5-carboxamide;
N-(2-Sulfamoylphenylsulfonyl)-4-((3,3,3-trifluoropropoxy)methyl)benzamide;
4-(Cyclopentylethynyl)-3-(hydroxymethyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
6-(3-Methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
3-(Hydroxymethyl)-4-(phenylethynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclohexylethynyl)-3-(hydroxymethyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
2-((4-chlorophenyl)ethynyl)-N-(2-sulfamoylphenylsulfonyl)pyrimidine-5-carboxamide;
4-(Benzofuran-2-yl)-3-(hydroxymethyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide;
(IS,4S)-4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide;
(IR,4R)-4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide;
4-(Benzofuran-2-yl)-1-methyl-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide;
(IR,4R)-4-(Benzofuran-2-yl)-1-methyl-N-(2-sulfamoylphenylsulfonyl)cyclohexanecarboxamide;
(1S,4S)-4-(Benzofuran-2-yl)-1-methyl-N-(2-sulfamoylphenylsulfonyl) cyclohexane-carboxamide;
4-(3,3-Dimethylbut-1-ynyl)-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopropylethynyl)-3-methoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3-Methoxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3-Methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
3-Methoxy-4-(3-methoxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
3-Hydroxy-4-(3-methoxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)benzamide;
6-(3,3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
4-(3,3-Dimethylbut-1-ynyl)-3-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenyl-sulfonyl)benzamide;
4-(Benzofuran-2-yl)-3-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)benzamide;
2-(2-Methoxyphenyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(1-tert-Butoxyethyl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(Pyridin-2-yl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(Pyridin-3-yl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(2-Hydroxypropan-2-yl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-(2-Methoxypropan-2-yl)-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
2-Cyclopropyl-N-(2-sulfamoylphenylsulfonyl)benzofuran-5-carboxamide;
4-(Benzofuran-2-yl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3,3-Dimethylbut-1-ynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(3-Hydroxy-3-methylbut-1-ynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopentylethynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclohexylethynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopropylethynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-((1-Hydroxycycloheptyl)ethynyl)-3-isopropoxy-N-(2-sulfamoylphenylsulfonyl)benzamide;
6-(3,3-Dimethylbut-1-ynyl)-5-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenyl-sulfonyl)nicotinamide;
6-(Benzofuran-2-yl)-5-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenylsulfonyl)-nicotinamide;
6-(Cyclopentylethynyl)-5-(2-(2-methoxyethoxy)ethoxy)-N-(2-sulfamoylphenyl-
sulfonyl)nicotinamide;
6-(Cyclopentylethynyl)-5-methoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Cyclohexylethynyl)-5-methoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
5-Methoxy-N-(2-sulfamoylphenylsulfonyl)-6-((4-(trifluoromethyl)phenyl)-
ethynyl)nicotinamide;
N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride;
l-(2-Methoxyethyl)-2-phenyl-N-(2-sulfamoylphenylsulfonyl)-1H-indole-5-carboxamide;
6-(cyclopropylethynyl)-5-isopropoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Cyclopentylethynyl)-5-isopropoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
6-(Cyclohexylethynyl)-5-isopropoxy-N-(2-sulfamoylphenylsulfonyl)nicotinamide4-
(Benzofuran-2-yl)-3-(3-methoxy-3-methylbutoxy)-N-(2-sulfamoylphenylsulfonyl)-
benzamide;
4-(Cyclopentylethynyl)-3-fluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
6-(Benzofuran-2-yl)-5-chloro-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
5-Chloro-6-(cyclopentylethynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
5-Chloro-6-(3,3-dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)nicotinamide;
4-(Benzofuran-2-yl)-N-(2-sulfamoylphenylsulfonyl)-2-(trifluoromethyl)benzamide;
4-(4.3-Dimethylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)-2-(trifluoromethyl)
benzamide;
4-(Benzofuran-2-yl)-2,6-difluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Cyclopentylethynyl)-2,6-difluoro-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzofuran-2-yl)-3-(3-hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenyl-
sulfonyl)benzamide;
4-(Benzofuran-2-yl)-3-bromo-N-(2-sulfamoylphenylsulfonyl)benzamide;
4-(Benzyloxy)-3-(3-hydroxy-3-methylbut-1-ynyl)-N-(2-sulfamoylphenylsulfonyl)-
benzamide;
4-(Benzyloxy)-3-iodo-N-(2-sulfamoylphenylsulfonyl)benzamide;
2-Benzyl-N-(2-sulfamoylphenylsulfonyl)-1H-indole-5-carboxamide;
7-(Cyclopropylethynyl)-2,2-difluoro-N-(2-sulfamoylphenylsulfonyl)-benzo[d][1,3]dioxole-4-carboxamide;
4-(Cyclopropylethynyl)-N-(2-sulfamoylphenylsulfonyl)-3-(3,3,3-trifluoropropoxy)-benzamide;
4-(Benzofuran-2-yl)-N-(4-(hydroxymethyl)-2-sulfamoylphenylsulfonyl)benzamide;
Benzene-1,2-disulfonic acid 1-amide 2[(quinoline-3-carbonyl)-amide] and pharmaceutically acceptable salts of any one thereof.

26. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1 which comprises,
(a) reacting a compound of formula (II)

\[
\begin{align*}
\text{(II)} & \quad \text{wherein } R_1, R_3, A \text{ and } m \text{ are as defined in formula (I),} \\
& \text{with a compound of formula (III)} \\
\end{align*}
\]

\[
\begin{align*}
\text{(III)} & \quad \text{wherein } L_1, L_2, G^1 \text{ and } G^2 \text{ are as defined in formula (I) and } X \text{ represents a leaving group such as } \text{OH or halogen; or} \\
& \text{(b) when } L_2 \text{ represents a direct bond and } G^1 \text{ and } G^2 \text{ are both aromatic moieties, reacting a compound of formula (IV)}
\end{align*}
\]
wherein Hal represents a halogen atom and $R^1$, $R^3$, $A$, $m$ and $L^1$ are as defined in formula (I),

with a nucleophile $G^-M$ wherein $M$ represents an organo-tin or organo boronic acid group;

and optionally after (a) or (b) carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

27. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 25 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

28. A process for the preparation of a pharmaceutical composition as claimed in claim 27 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 25 with a pharmaceutically acceptable adjuvant, diluent or carrier.

29. A compound of formula (I) or a pharmaceutically acceptable salt thereof

wherein:

wherein $R^1$, $R^3$, $A$, $m$ and $L^1$ are as defined in formula (I),

and optionally after (a) or (b) carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.
A is selected from mono- and bicyclic aryl, mono- and bicyclic heteroaryl, cycloalkenyl and mono- and bicyclic heterocyclyl;

R¹ is independently selected from halogen, nitro, SF₅, CHO, C₆₋₅alkylCN, OCN₆₋₅alkylCN, C₆₋₅alkylOR, OC₂₋₅alkylOR, C₆₋₅alkylNR₂R₆, OC₂₋₅alkylNR₂R₆,
OC₂₋₅alkylOSO₂R, C₀₋₅alkylCN₂R₆, OCN₂₋₅alkylCN₂R₆, OC₂₋₅alkylCON(R)₂, OC₂₋₅alkylCON(R)₂, C₀₋₅alkylNR₂(CO)R₆, OC₀₋₅alkylNR₂(CO)R₆,
OC₀₋₅alkylSR, C₀₋₅alkylSR, OC₀₋₅alkylSO₂R, C₀₋₅alkylSO₂R, OC₀₋₅alkyl(SO)₂R, C₀₋₅alkyl(SO)₂R,
OC₀₋₅alkyl(SO)NR₆, OCN₀₋₅alkyl(SO)NR₆, C₀₋₅alkyl(SO)NR₆, OC₀₋₅alkyl(SO)NR₆, OCN₀₋₅alkyl(SO)NR₆, C₀₋₅alkyl(SO)NR₆,
OC₀₋₅alkyl(SO)NR₂, C₀₋₅alkyl(SO)NR₂, OC₀₋₅alkyl(SO)NR₂, C₀₋₅alkyl(SO)NR₂,
OC₀₋₅alkyl(SO)NR₂R, C₀₋₅alkyl(SO)NR₂R, OC₀₋₅alkyl(SO)NR₂R, C₀₋₅alkyl(SO)NR₂R,
OC₀₋₅alkyl(SO)NR₂R, C₀₋₅alkyl(SO)NR₂R, OC₀₋₅alkyl(SO)NR₂R, C₀₋₅alkyl(SO)NR₂R,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ, OC₀₋₅alkyl(SO)NR₂Rᵣ, C₀₋₅alkyl(SO)NR₂Rᵣ,
\( G^2 \) is selected from hydrogen, \( C_{3-8}\)cycloalkyl, \( C_{4-12}\)cycloalkenyl, \( C_{7-12}\)cycloalkynyl, aryl, heteroaryl, heterocyclyl, wherein said Cs.scycloalkyl, \( C_{4-12}\)cycloalkenyl, \( C_{7-12}\)cycloalkynyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one or more \( R^{10} \);

At each occurrence, \( R^5 \) is independently selected from hydrogen, \( C_{1-6}\)alkyl, \( C_{2-6}\)alkenyl, \( C_{2-6}\)alkynyl, \( C_{6-10}\)alkylCs.scycloalkyl, \( C_{4-10}\)alkylaryl, \( C_{4-10}\)alkylheteroaryl and \( C_{4-10}\)alkylheterocyclyl, wherein said \( C_{1-6}\)alkyl, \( C_{2-6}\)alkenyl, \( C_{2-6}\)alkynyl, \( C_{6-10}\)alkylC3-gcycloalkyl, \( C_{3-10}\)alkylaryl, \( C_{4-10}\)alkylheteroaryl or \( C_{4-10}\)alkylheterocyclyl is optionally substituted with one or more \( B \);

At each occurrence, \( R^6 \) is selected from hydrogen, \( C_{1-6}\)alkyl, \( C_{2-6}\)alkenyl, \( C_{2-6}\)alkynyl, \( C_{6-10}\)alkylOR \( C_{6-10}\)alkylCs.scycloalkyl, \( C_{4-10}\)alkylaryl, \( C_{4-10}\)alkylheteroaryl and \( C_{4-10}\)alkylheterocyclyl, wherein said \( C_{1-6}\)alkyl, \( C_{2-6}\)alkenyl, \( C_{2-6}\)alkynyl, \( C_{6-10}\)alkylC3-gcycloalkyl, \( C_{4-10}\)alkylaryl, \( C_{4-10}\)alkylheteroaryl or \( C_{4-10}\)alkylheterocyclyl is optionally substituted with one or more \( B \); or

\( R^5 \) and \( R^6 \) may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S that is optionally substituted with \( B \); whenever two \( R^5 \) groups occur in the structure then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, that is optionally substituted with one or more \( B \);

\( L^1 \) and \( L^2 \) independently represent a bond or a 1-7 membered non-cyclic linking group containing 0-2 heteroatoms selected from O, N, and S, said linking group optionally containing CO, S(O)\(_n\), C=O or an acetylenic group, and optionally being substituted with one or more \( R^8 \);

\( R^8 \) is selected from halogen, CHO, CN, CO\(_2\)alkyl, O(C\(_\text{ Ci}_{1-6}\)alkyl)O(C\(_\text{ Ci}_{1-6}\)alkyl), C\(_\text{ Ci}_{1-6}\)alkyl, C\(_\text{ Ci}_{2-6}\)alkenyl, C\(_\text{ Ci}_{2-6}\)alkynyl N(C\(_\text{ Ci}_{1-6}\)alkyl)(C\(_\text{ Ci}_{1-6}\)alkyl), NH\(_2\), NH(C\(_\text{ Ci}_{1-6}\)alkyl), S(O)\(_n\)(C\(_\text{ Ci}_{1-6}\)alkyl), SO\(_2\)N(C\(_\text{ Ci}_{6}\)alkyl)(C\(_\text{ Ci}_{6}\)alkyl), SO\(_2\)NH\(_2\), SO\(_2\)NH(C\(_\text{ Ci}_{6}\)alkyl), CF\(_3\), CHF\(_2\), CFH\(_2\), C(O)(C\(_\text{ Ci}_{6}\)alkyl), C(O)N(C\(_\text{ Ci}_{6}\)alkyl)(C\(_\text{ Ci}_{6}\)alkyl), C(O)NH(C\(_\text{ Ci}_{6}\)alkyl), C(O)NH\(_2\), N(C\(_\text{ Ci}_{6}\)alkyl).
6alkyl)(CO)N(C1-6 alkyl)(C1-6 alkyl), NH(CO)N(C1-6 alkyl)(C1-6 alkyl), N(C1-
6alkyl)(CO)NH(C1-6 alkyl), NH(CO)NH2, N(C1-6 alkyl)(CO)NH2.

Whenever two R8 groups are connected to the same atom of the linking group L1, they
may optionally together form a 3 to 6 membered non-aromatic, carbocyclic or heterocyclic
(containing one or more heteroatoms selected from N, O or S) ring, that is optionally
substituted with one or more R9:

R9 is selected from halogen, nitro, CHO, CN, OH, OC1-6 alkyl, O(C1-6 alkyl)O(C1-6 alkyl),
C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl N(C1-6 alkyl)(C1-6 alkyl), NH2, NH(C1-6 alkyl), S(O)2(C1-
6alkyl), SO2N(Ci6 alkyl)(Ci6 alkyl), SO2NH2, SO2NH(C1-6 alkyl), CF3, CHF2, CFH2,
C(O)(Ci6 alkyl), C(O)(N(Ci6 alkyl)(Ci6 alkyl), C(O)NH(Ci6 alkyl), C(O)NH2, N(Ci-
6alkyl)(CO)N(Ci6 alkyl), NH(CO)N(Ci6 alkyl)(Ci6 alkyl), N(Ci-
6alkyl)(CO)NH(Ci6 alkyl), NH(CO)NH2, N(Ci6 alkyl)(CO)NH2

B is selected from halogen, nitro, SF5, OSF5, CN, OR15, OC2-6 alkylNR15R16, NR15R16,
CONR15R16, NR15(CO)R16, O(CO)Ci6 alkyl, (CO)OCI6 alkyl, COR15, (SO2)NR15R16,
NR15SO2R15, SO2R15, SOR15, (CO)d6 alkylNR15R16, (SO2)Ci6 alkylNR15R16, OSO2R15,
Ci6 alkyl, C2-6 alkenyl, C2-6 alkynyl, CO6 alkylC3-8 cycloalkyl, CO6 alkylaryl,
C0-6 alkylheteroaryl and CO6 alkylheterocycl;

R15 is selected from hydrogen, Ci6 alkyl, C2-6 alkenyl, C2-6 alkynyl, CO6 alkylC3-8 cycloalkyl,
CO6 alkylaryl, CO6 alkylheteroaryl and CO6 alkylheterocycl;

R16 is selected from hydrogen, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C0-6 alkylOR5, C0-
6alkylC3-8 cycloalkyl, CO6 alkylaryl, CO6 alkylheteroaryl and CO6 alkylheterocycl; or

R15 and R16 may together with the linking atom or atoms to which they are bonded form a
4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O
or S; whenever two R15 groups occur in the structure then they may optionally together
with the linking atom or atoms to which they are bonded form a 5 or 6 membered
heterocyclic ring containing one or more heteroatoms selected from N, O or S;
D is selected from halogen, nitro, SF₅, OSF₅, CN, OR, OC₂₋₆alkylNR, NR, CONR, NR(CO)R, O(CO)Ci₆alkyl, (CO)OCi₆alkyl, COR, (SO₂)NR, NRSO₂R, SO₃R, (CO)d₆alkylNR, (SO₂)Ci₆alkylNR, OSO₂R, C₆₆alkyl, C₂₆alkenyl, C₂₆alkynyl, C₅₆alkylC₃₋₈cycloalkyl, and Co₆alkylheterocyclyl;

R₆ is independently selected from halogen, nitro, SF₅, OSF₅, CN, OR, C═CR, OC₂₋₆alkylNR, NR, CONR, NR(CO)R, O(CO)Ci₆alkyl, (CO)OCi₆alkyl, COR, (SO₂)NR, NRSO₂R, SO₃R, (CO)d₆alkylNR, (SO₂)Ci₆alkylNR, OSO₂R, C₆₆alkyl, C₂₆alkenyl, C₂₆alkynyl, C₅₆alkylC₃₋₈cycloalkyl, and OC₆alkylheterocyclyl, wherein said Ci₆alkyl, C₂₆alkenyl, C₂₆alkynyl, C₅₆alkylC₃₋₈cycloalkyl, C₅₆alkylaryl, C₅₆alkylaryl, C₆₆alkylheteroaryler or OC₆alkylheterocyclyl is optionally substituted with one or more E, and wherein any of the individual aryl or heteroaryl groups may be optionally fused with a 4, 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclyl group to form a bicyclic ring system where the bicyclic ring system is optionally substituted with one or more E;

At each occurrence, R₁¹ is independently selected from hydrogen, Ci₆alkyl, C₂₆alkenyl, C₂₆alkynyl, Co₆alkylC₃₋₈cycloalkyl, Co₆alkylaryl, Co₆alkylheteroarylder and Co₆alkylheterocyclyl, wherein any of the individual Ci₆alkyl, C₂₆alkenyl, C₂₆alkynyl, C₅₆alkylC₃₋₈cycloalkyl, Co₆alkylaryl, Co₆alkylheteroarylder and Co₆alkylheterocyclyl groups may be optionally substituted with one or more E;

R₁² is selected from hydrogen, Ci₆alkyl, C₂₆alkenyl, C₂₆alkynyl, Co₆alkylC₃₋₈cycloalkyl, Co₆alkylaryl, Co₆alkylheteroarylder and Co₆alkylheterocyclyl, wherein any of the individual Ci₆alkyl, C₂₆alkenyl, C₂₆alkynyl, C₅₆alkylC₃₋₈cycloalkyl, Co₆alkylaryl, Co₆alkylheteroarylder and Co₆alkylheterocyclyl groups may be optionally substituted with one or more E; or

R₁¹ and R₁² may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O
or S that is optionally substituted with B; whenever two R\textsuperscript{11} groups occur in the structure then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S, where the ring system is optionally substituted with one or more E;

R\textsuperscript{13} is independently selected from hydrogen, Ci\textsubscript{6}-alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, CO\textsubscript{6}alkylC\textsubscript{3-8}cycloalkyl, CO\textsubscript{6}alkylaryl, CO\textsubscript{6}alkylheteroaryl and CO\textsubscript{6}alkylheterocyclyl;

R\textsuperscript{14} is selected from hydrogen, Ci\textsubscript{6}-alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, CO\textsubscript{6}alkylOR\textsuperscript{5}, CO\textsubscript{6}alkylCs\textsubscript{2}gycloalkyl, C\textsubscript{0-6}alkylaryl, C\textsubscript{0-6}alkylheteroaryl and CO\textsubscript{6}alkylheterocyclyl; or

R\textsuperscript{13} and R\textsuperscript{14} may together with the linking atom or atoms to which they are bonded form a 4 to 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S; whenever two R\textsuperscript{13} groups occur in the structure then they may optionally together with the linking atom or atoms to which they are bonded form a 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected from N, O or S;

E is selected from halogen, nitro, SF\textsubscript{5}, OSF\textsubscript{5}, CN, OR\textsuperscript{5}, OC\textsubscript{2-6}alkylNR\textsubscript{5}R\textsubscript{6}, NR\textsubscript{5}R\textsubscript{6}, CONR\textsuperscript{5}R\textsubscript{6}, NR\textsubscript{5}(CO)R\textsubscript{6}, O(CO)Ci\textsubscript{6}alkyl, (CO)OCi\textsubscript{6}alkyl, COR\textsuperscript{5}, (SO\textsubscript{2})NR\textsubscript{5}R\textsubscript{6}, NR\textsubscript{5}SO\textsubscript{2}R\textsubscript{5}, SO\textsubscript{2}R\textsubscript{5}, SOR\textsuperscript{5}, (CO)Ci\textsubscript{6}alkylNR\textsubscript{5}R\textsubscript{6}, (SO\textsubscript{2})Ci\textsubscript{6}alkylNR\textsubscript{5}R\textsubscript{6}, OSO\textsubscript{2}R\textsubscript{5}, Ci\textsubscript{6}alkyl, C\textsubscript{2-6}alkenyl, C\textsubscript{2-6}alkynyl, CO\textsubscript{6}alkylC\textsubscript{3-8}cycloalkyl, CO\textsubscript{6}alkylaryl, CO\textsubscript{6}alkylheteroaryl and CO\textsubscript{6}alkylheterocyclyl;

m = 0,1,2,3,4;

n = 0,1,2;

for use in therapy.

30. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in claim 29 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of microsomal prostaglandin E synthase-1 activity is beneficial.
31. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in claim 29 in the manufacture of a medicament for use in treating osteoarthritis, rheumatoid arthritis, benign or malignant neoplasias or acute or chronic pain.

32. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in claim 29 in the manufacture of a medicament for use in treating acute or chronic pain, nociceptive pain, neuropathic pain, apnea, sudden infant death (SID), atherosclerosis, cancer, aneurysm, hyperthermia, myositis, Alzheimer's disease or arthritis.

33. A method of treating, or reducing the risk of, an inflammatory disease or condition which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 29.
A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

**IPC: C07C, A61K, C07D**

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

SE, DK, FI, NO classes as above

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

**EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS DATA**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>A</td>
<td>WO 0181312 A2 (MERCK FROSST CANADA &amp; CO.), 1 November 2001 (01.11.2001)</td>
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</table>

Further documents are listed in the continuation of Box C.

- See patent family annex.

* Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier application or patent but published on or after the international filing date
  - "h" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - "O" document referring to an oral disclosure, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search: 13 February 2009
Date of mailing of the international search report: 20-02-2009

Name and mailing address of the ISA/
Swedish Patent Office
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Facsimile No. +46 8 666 02 86

Authorized officer
Eva Johansson /ELY
Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 2008)
INTERNATIONAL SEARCH REPORT

<table>
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<td>This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:</td>
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| 1.     | Claims Nos.: 3-3  
|        | because they relate to subject matter not required to be searched by this Authority, namely:  
|        | Claim 33 relates to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic .../...  
| 2.     | Claims Nos.:  
|        | because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically: |
| 3.     | Claims Nos.:  
|        | because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). |

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<td>This International Searching Authority found multiple inventions in this international application, as follows:</td>
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<td>[-J] AS all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.</td>
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<td>r-J AS only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:</td>
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<td>4.</td>
<td>No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:</td>
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**Remark on Protest**  
| The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee. |
| The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation. |
| No protest accompanied the payment of additional search fees. |
methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for this claim. The search has been directed to the technical content of the claim.
International patent classification (IPC)

C07C 311/51 (2006.01)
A61K 31/145 (2006.01)
A61P 19/00 (2006.01)
C07D 209/42 (2006.01)
C07D 213/04 (2006.01)
C07D 213/78 (2006.01)
C07D 231/14 (2006.01)
C07D 263/57 (2006.01)
C07D 277/56 (2006.01)
C07D 277/64 (2006.01)
C07D 307/68 (2006.01)
C07D 307/79 (2006.01)
C07D 333/38 (2006.01)
C07D 333/52 (2006.01)
C07D 405/04 (2006.01)
C07D 409/06 (2006.01)
C07D 417/04 (2006.01)
C07D 498/04 (2006.01)

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Use the application number as username.
The password is PAWNUGUATU.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.
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