Title: N-Pyrazinyl-phenylsulphonamides and their use in the treatment of chemokine-mediated diseases

Abstract: The invention provides N-pyrazinyl-phenylsulphonamides of formula (I) for use in the treatment of chemokine-mediated diseases. Particularly inflammatory diseases, such as asthma.
N-PYRAZINYL-PHENYLSULPHONAMIDES AND THEIR USE IN THE TREATMENT OF CHEMOKINE MEDIATED DISEASES

The present invention relates to a sulphonamide compound, processes and intermediates used in their preparation, pharmaceutical compositions containing them and their use in therapy.

Certain sulphonamide compounds are known in the art, for example see GB2295616, US patent 2002143024, WO 01/44239, EP 749964 and Esche, J; Wojahn, H. Arch. Pharm. (1966), 299(2), 147-153.

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small-secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. At the present time, the chemokine superfamily comprises three groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C), Cys-Cys (C-C) and Cys-X3-Cys (C-X3-C) families. The C-X-C and C-C families have sequence similarity and are distinguished from one another on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues. The C-X3-C family is distinguished from the other two families on the basis of having a triple amino acid insertion between the NH-proximal pair of cysteine residues.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils. Examples include human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β), Thymus and Activation Regulated Chemokine (TARC, CCL17) and Macrophage Derived Chemokine (MDC, CCL22).

The C-X3-C chemokine (also known as fractalkine) is a potent chemoattractant and activator of microglia in the central nervous system (CNS) as well as of monocytes, T cells, NK cells and mast cells.
Studies have demonstrated that the actions of chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX3CR1 for the C-X3-C family. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

The present invention therefore provides a compound of formula (I) and pharmaceutically acceptable salts, solvates or N-oxides thereof:

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

(1)

in which:

R^1, R^2 and R^3 are independently hydrogen, halogen, cyano, CF₃, OCF₃, OC₁₋₆ alkyl or C₁₋₆ alkyl;

R^4 is halogen, CO₂R₁²;

C₁₋₆ alkoxy where the alkyl group may form a 3-6 membered saturated ring or may be substituted with 1-3 fluorine atoms or a cyano group;

C₃₋₆ alkenyloxy or C₃₋₆ alkynyloxy where either may be optionally substituted with hydroxy or NR¹⁴R¹⁵;

OC₁₋₆ alkyl-X-C₁₋₆ alkyl where the alkyl groups may form a 3-6 membered saturated ring;

OC₁₋₆ alkylR¹¹, or OC₂₋₆ alkyl-X-R¹¹ where the alkyl group may form a 3-6 membered saturated ring and is optionally substituted with 1-3 groups selected from hydroxy, halogen, NR¹⁴R¹⁵, SR¹³, S(O)₂R¹³, S(O)R¹³ or COR¹³;
OC\textsubscript{1-6} alkylR\textsuperscript{16};

R\textsuperscript{5} and R\textsuperscript{6} are independently hydrogen, cyano, halogen, CO\textsubscript{2}R\textsuperscript{12}, CONR\textsuperscript{14}R\textsuperscript{15};

C\textsubscript{1-6} alkyl optionally substituted by hydroxy, NR\textsuperscript{14}R\textsuperscript{15}, or 1-3 fluorines;

C\textsubscript{1-6} alkylR\textsuperscript{11} or XCH(R\textsuperscript{11})C\textsubscript{1-6} alkyl or XCH(R\textsuperscript{16})C\textsubscript{1-6} alkyl where the alkyl group may be optionally substituted with 1-3 groups selected from hydroxy, and NR\textsuperscript{14}R\textsuperscript{15};

NR\textsuperscript{14}R\textsuperscript{15}, N(R\textsuperscript{11})R\textsuperscript{11}, X-(CH\textsubscript{2})\textsubscript{q}NR\textsuperscript{14}R\textsuperscript{15}, (CH\textsubscript{2})\textsubscript{n}NR\textsuperscript{14}R\textsuperscript{15}; NHC(O)C\textsubscript{1-6} alkyl optionally substituted by one or more hydroxy groups,

C\textsubscript{3-6} alkynyl or C\textsubscript{3-6} alkenyl optionally branched and optionally substituted with 1-3 groups selected from hydroxy, cyano, halogen and -O;

R\textsuperscript{11}, X-R\textsuperscript{11}; X-R\textsuperscript{12}; X-C\textsubscript{1-6}alkylR\textsuperscript{16}; X-R\textsuperscript{16}; X-(CH\textsubscript{2})\textsubscript{n}CO\textsubscript{2}R\textsuperscript{12}; X-(CH\textsubscript{2})\textsubscript{n}CONR\textsuperscript{14}R\textsuperscript{15};
X-(CH\textsubscript{2})\textsubscript{n}R\textsuperscript{11}; X-(CH\textsubscript{2})\textsubscript{n}CN; X-(CH\textsubscript{2})\textsubscript{q}OR\textsuperscript{12}; (CH\textsubscript{2})\textsubscript{n}OR\textsuperscript{12};
(CH\textsubscript{2})\textsubscript{n}-X-R\textsuperscript{11}; X-(CH\textsubscript{2})\textsubscript{q}NHC(O)NHR\textsuperscript{12}; X-(CH\textsubscript{2})\textsubscript{q}NHC(O)R\textsuperscript{12};
X-(CH\textsubscript{2})\textsubscript{q}NHS(O)\textsubscript{2}R\textsuperscript{12}; X-(CH\textsubscript{2})\textsubscript{q}NHS(O)\textsubscript{2}R\textsuperscript{11}; X-C\textsubscript{3-6}alkenyl; X-C\textsubscript{3-6}alkynyl;

n is 1, 2, 3, 4 or 5;

q is 2, 3, 4, 5 or 6;

X is NR\textsuperscript{13}, O, S, S(O), S(O)\textsubscript{2};

R\textsuperscript{11} is an aryl group or a 5-7 membered heteraromatic ring containing 1-4 heteroatoms selected from nitrogen, oxygen or sulphur each of which can be optionally substituted by 1-3 groups selected from halogen, C(O)NR\textsuperscript{14}R\textsuperscript{15}, C(O)OR\textsuperscript{12}, hydroxy, =O, =S, CN, NO\textsubscript{2}, COR\textsuperscript{13}, NR\textsuperscript{14}R\textsuperscript{15}, X(CH\textsubscript{2})\textsubscript{q}NR\textsuperscript{14}R\textsuperscript{15}, (CH\textsubscript{2})\textsubscript{n}NR\textsuperscript{14}R\textsuperscript{15}, (CH\textsubscript{2})\textsubscript{n}OH, SR\textsuperscript{13}, S(O)R\textsuperscript{13}, S(O)\textsubscript{2}R\textsuperscript{13}
C\textsubscript{1-6} alkyl-X-C\textsubscript{1-6} alkyl, C\textsubscript{1-6} alkyl or C\textsubscript{1-6} alkoxy where the alkyl group may form a 3-6 membered ring or is optionally substituted with 1-3 groups selected from hydroxy, halogen, NR\textsuperscript{14}R\textsuperscript{15}, SR\textsuperscript{13}, S(O)R\textsuperscript{13}, S(O)\textsubscript{2}R\textsuperscript{13};
R^{12} and R^{13} are independently hydrogen or C_{1-6} alkyl where the alkyl group may be substituted with 1-3 fluorine atoms or may form a saturated 3-6 membered ring;

R^{14} and R^{15} are independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or \((\text{CH}_2)q\text{OH}\), or \(R^{14}\) and \(R^{15}\) together with the nitrogen atom to which they are attached form a 4-8 membered saturated ring containing 1-3 heteroatoms selected from nitrogen, oxygen and sulphur and optionally substituted by C_{1-6} alkyl, C_{1-6} alkyl-OH, or hydroxy; and

\(R^{16}\) is a 4-8 membered saturated ring containing 1-3 heteroatoms selected from nitrogen, oxygen or sulphur and optionally substituted with 1-3 groups selected from hydroxy, cyano, halogen and =O,

provided that:

- when \(R^4\) is halogen or C_{1-4}alkoxy and \(R^5\) is hydrogen, halogen, C_{1-4}alkyl, C_{1-2}alkoxy, C_{1-2}alkylthio, trifluoromethyl or ethynyl and when one of \(R^1\), \(R^2\) or \(R^3\) is C_{1-4}alkyl or C_{1-4}alkoxy and is meta to the sulphonamide group then the group ortho to both the sulphonamide group and the C_{1-6}alkyl or C_{1-6}alkoxy group is not hydrogen,

- when \(R^4\) is halogen or C_{1-4}alkoxy and \(R^5\) is hydrogen, halogen, C_{1-4}alkyl, C_{1-2}alkoxy, C_{1-2}alkylthio, trifluoromethyl or ethynyl and when one of \(R^1\), \(R^2\) or \(R^3\) is C_{1-6}alkyl or C_{1-6}alkoxy and is ortho to the sulphonamide group then the group ortho to the C_{1-6}Alkyl or C_{1-6}alkoxy and also meta to the sulphonamide group is not hydrogen,

- when two of \(R^1\), \(R^2\), \(R^3\) are hydrogen and the other is a methyl group para to the sulphonamide and \(R^4\) is methoxy then \(R^5\) is not hydrogen or bromo, and

- when \(R^5\) is methyl and \(R^6\) is methoxy and one of \(R^1\), \(R^2\) or \(R^3\) is bromo or iodo and the other two are both hydrogen, then the bromo or iodo group is not ortho to the sulphonamide group.

The term aryl includes phenyl and naphthyl. The term alkyl, whether alone or as part of another group, includes straight chain and branched chain alkyl groups. Examples of 5- to 7-membered heteroaromatic ring containing 1 to 4 heteroatoms include thiienyl, furanyl, pyrrolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl, triazinyl, oxazolyl, thiazolyl, isoxazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl.

Examples of saturated 4- to 8-membered rings containing 1 to 3 heteroatoms include
morpholine, piperidine and azetidine. Substituents on any rings can be present in any suitable ring position including suitable substituents on nitrogen atoms.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

Preferred halogen groups for $R^1$, $R^2$ and $R^3$ are chloro, bromo and fluoro. Preferably one of $R^1$, $R^2$ and $R^3$ is hydrogen and the other is chloro, bromo or methyl. More preferably $R^1$ and $R^2$ are chloro at the 2- and 3-positions of the phenyl ring and $R^3$ is hydrogen (i.e. 2,3-dichlorophenyl), $R^1$ and $R^3$ are chloro at the 2- and 4-positions of the phenyl ring and $R^2$ is hydrogen (i.e. 2,4-dichlorophenyl) or $R^1$ is chloro at the 2-position and $R^2$ is methyl at the 3-position of the phenyl ring and $R^3$ is hydrogen (i.e 2-chloro-3-methylphenyl). Most preferably $R^1$ and $R^2$ are chloro at the 2- and 3-positions of the phenyl ring and $R^3$ is hydrogen (i.e. 2,3-dichlorophenyl).

In a further aspect the invention provides a compound of formula (I) as defined above but without the provisos where $R^1$ and $R^2$ are chloro at the 2- and 3-positions of the phenyl ring and $R^3$ is hydrogen (i.e. 2,3-dichlorophenyl), $R^1$ and $R^3$ are chloro at the 2- and 4-positions of the phenyl ring and $R^2$ is hydrogen (i.e. 2,4-dichlorophenyl) or $R^1$ is chloro at the 2-position and $R^2$ is methyl at the 3-position of the phenyl ring and $R^3$ is hydrogen (i.e 2-chloro-3-methylphenyl).

For the group $R^4$ examples of $C_{3-6}$ alkenyloxy include OCH$_2$CH=CH$_2$, examples of $C_{3-6}$ alkynlyloxy include OCH$_2$CCH, examples of $OC_{1-6}$ alkyl-O-C$_{1-6}$ alkyl include OCH$_2$CH$_2$OMe, examples of $OC_{1-6}$ alkylR$^1$ include OCH$_2$R$^1$, and examples of $OC_{1-6}$ alkylR$^1$ include OCH$_2$pyrrolidine.

Preferred groups for $R^4$ include $C_{1-6}$ alkoxy such as methoxy, 2-furanylmethoxy, bromo, chloro, 2-methoxyethoxy, (5-methyl-3-isoxazolyl)methoxy, 2-, 3- or 4-pyridylmethoxy, 3-pyridazinylmethoxy, methoxy, 2-(1-imidazolyl)ethoxy, (2-methyl-4-oxazolyl)methoxy and 4-methoxyphenylmethoxy. More preferably $R^4$ is methoxy.

For $R^5$ and $R^6$ examples of NR$^{14}$R$^{15}$ includes morpholine, pyrrolidine, NMe$_2$, NHCH$_2$CH$_2$OMe, NHMe, and the groups below:
Examples of X-(CH$_2$)$_n$NR$_{14}$R$_{15}$ include SCH$_2$CH$_2$NH$_2$ and SCH$_2$CH$_2$NMe$_2$, examples of (CH$_2$)$_n$NR$_{14}$R$_{15}$ include CH$_2$morpholine, examples of X-R$_{12}$ includes SMe, OMe, OEt, OH, SO$_2$Me, examples of X-C$_1$-alkylR$_{16}$ includes OCH$_2$pyrrolidine, examples of X-(CH$_2$)$_n$CO$_2$R$_{12}$ includes SCH$_2$CO$_2$H, SCH$_2$CO$_2$Me, SCH$_2$CH$_2$CO$_2$Me, examples of X-(CH$_2$)$_n$CONR$_{14}$R$_{15}$ includes SCH$_2$CONH$_2$, SCH$_2$CONHMe, OCH$_2$CONEt$_2$, examples of X-(CH$_2$)$_n$R$_{11}$ includes the groups below:

Examples of X-(CH$_2$)$_n$CN, includes SCH$_2$CN, examples of X-(CH$_2$)$_n$OR$_{12}$ includes OCH$_2$CH$_2$OMe, examples of (CH$_2$)$_n$OR$_{12}$ includes CH$_2$OH, CH$_2$OMe, examples of X-(CH$_2$)$_n$NHC(O)NHR$_{12}$ includes SCH$_2$CH$_2$NHC(O)NHEt, and examples of X-(CH$_2$)$_n$NHC(O)R$_{12}$ includes NHCH$_2$CH$_2$NHC(O)Me. Examples of NHC(O)C$_{1-6}$ alkyl optionally substituted by one or more hydroxy groups includes NHCOCH$_2$OH.

Preferred groups for R$^5$ include hydrogen, halogen such as bromo and chloro, phenyl, C$_{1-6}$ alkyl such as methyl, CH$_2$OH, cyano and 2-aminothanol. More preferably R$^5$ is hydrogen, methyl, CH$_2$OH or halogen such bromo or chloro.

Preferred groups for R$^6$ include hydrogen, C$_{1-6}$ alkyl, CH$_2$OH and halogen, more preferably hydrogen, methyl, CH$_2$OH or chloro.

In a further aspect the invention provides a compound of formula (IA):
in which

R₁, R² and R³ are independently hydrogen, halogen, cyano, CF₃, OCF₃, C₁₋₆ alkenyl or C₁₋₆ alkyl;
R⁴ is halogen, C₁₋₆ alkoxy or OR⁹;
R⁵ and R⁶ are independently hydrogen, halogen, C₁₋₆ alkoxy, C₁₋₆ alkylthio, cyano, R⁹,
OR⁹, NR⁹R¹⁰, SR⁹, S(CH₂)ₙCO₂H, S(CH₂)ₙCO₂R¹₂, S(CH₂)ₙCONR¹²R¹³, S(CH₂)ₙR¹¹ or a
5- to 7-membered heteroaromatic or saturated ring containing 1 to 3 heteroatoms selected
from nitrogen, oxygen and sulphur;
n is 1, 2 or 3;
R⁹ and R¹⁰ are independently hydrogen, C₁₋₆ alkyl optionally substituted by hydroxy, C₁₋₆
alkoxy or NHCOC₁₋₆ alkyl, or R⁹ and R¹⁰ are optionally substituted aryl, C₁₋₆ alkyl-aryl or
C₁₋₆ alkyl-R¹¹ or R⁹ and R¹⁰ together with the nitrogen atom to which they are attached
form a 4- to 8-membered saturated ring containing 1 to 3 heteroatoms selected from
nitrogen, oxygen and sulphur and optionally substituted by C₁₋₆ alkyl or C₁₋₆ alkyl-OH; and
R¹¹ is a 5- to 7-membered heteroaromatic ring containing 1 to 3 heteroatoms selected from
nitrogen, oxygen and sulphur and optionally substituted by C₁₋₆ alkyl; and
R¹² and R¹³ are independently hydrogen or C₁₋₆ alkyl.

For compounds (IA) R₁, R² and R³ are independently hydrogen, halogen, cyano, CF₃,
OCF₃, C₁₋₆ alkenyl or C₁₋₆ alkyl, preferred halogen groups being chloro. Preferably one of
R₁, R² and R³ is methyl, ethenyl, cyano, chloro, fluoro, iodo or two are chloro or all three
are fluoro. More preferred are compounds where R¹ – R³ together with the phenyl group to
which they are attached form a 3-chloro-2-methylphenyl or a 2,3-dichlorophenyl group.

For compounds (IA) preferred groups for R⁴ include halogen such as bromo and chloro,
C₁₋₆ alkoxy such as methoxy and ethoxy, C₁₋₆ alkyl or OR⁹ where R⁹ is CH₃R¹¹ where R¹¹
is a 5- or 6-membered heteroaromatic ring containing 1 or 2 heteroatoms.
More preferably $R^4$ is methoxy, halogen, such as chloro, or $OR^8$ where $R^8$ is $CH_2R^{11}$ where $R^{11}$ is furanyl, 5-methyl-3-isoxazolyl, pyridyl optionally substituted by methyl, pyridazinyl, pyrazinyl, 1-methyl-6-oxo-1,6-dihydro-3-pyridinyl.

For compounds (IA) preferably $R^5$ is hydrogen, methyl, bromo, chloro, methoxy, morpholinyl, pyrrolinyl, dimethylamino, hydroxy, 2-methoxyethoxy, pyrazinyl, pyrimidinyl, O-Ph-CO$_2$H, 2-hydroxyethylamino, 2-methoxyethylamino, NHCH$_2$CH$_2$NHCOMe, cyano, 4-hydroxymethyl-1-piperidinyl, SMe, NHMe, or 2,4-difluorophenyl.

For compounds (IA) preferably $R^6$ is hydrogen or chloro.

Preferred compounds of formula (I)/(IA) include those exemplified herein both in free base form and as pharmaceutically acceptable salts.

According to the invention there is also provided a process for the preparation of compound (I) which comprises reaction of a compound of formula (II):

\[
\begin{array}{c}
\text{R}^5 \\
\text{N} \\
\text{R}^4 \\
\text{R}^6 \\
\text{N} \\
\text{NH}_2
\end{array}
\]

(II)

where $R^4$, $R^5$ and $R^6$ are as defined in formula (I) or are protected derivatives thereof with a compound of formula (III):

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{S} \\
\text{O} \\
\text{LG}
\end{array}
\]

(III)

where $R^1$, $R^2$ and $R^3$ are as defined in formula (I) or are protected derivatives thereof and LG is a leaving group,

and optionally thereafter
removing any protecting groups,
forming a pharmaceutically acceptable salt.

Preferred leaving groups LG include halogen such as chloro. Preferably the reaction
between compounds (II) and (III) is carried out by treating compound (II) with a base such
as sodium hydride or potassium tert-butoxide in a suitable solvent such as 1,2-
dimethoxyethane or tetrahydrofuran.

Where R^4 is C_{1-6} alkoxy where the alkyl group may form a 3-6 membered saturated ring or
may be substituted with 1-3 fluorine atoms or a cyano group;
C_{3-6} alkenyloxy or C_{3-6} alkynyloxy where either may be optionally substituted with
hydroxy or NR^{14}R^{15};
OC_{1-6} alkyl-X-C_{1-6} alkyl where the alkyl groups may form a 3-6 membered saturated ring;
OC_{1-4} alkylR^{11}, or OC_{2-6} alkyl-X-R^{11} where the alkyl group may form a 3-6 membered
saturated ring and is optionally substituted with 1-3 groups selected from hydroxy,
halogen, NR^{14}R^{15}, SR^{13}, S(O)R^{13}, S(O)R^{13}; or
OC_{1-6} alkylR^{16};
compounds of formula (II) can be prepared by treating a compound of the formula (IV),
where LG is a leaving group (such as chlorine or bromine):

\[
\begin{array}{c}
\text{N} \\
\text{R}^5 \\
\text{LG} \\
\text{N} \\
\text{R}^6 \\
\text{NH}_2
\end{array}
\]

(IV)

with a compound of formula (V)

R^4-H

(V)

in a suitable solvent (such as 1,2-dimethoxyethane, N,N-dimethylformamide or
tetrahydrofuran) with a suitable base such as sodium hydride or potassium tert-butoxide
at a suitable temperature such as 25°C to 60°C.
Where R is C₁₋₆ alkoxy where the alkyl group may form a 3-6 membered saturated ring or may be substituted with 1-3 fluorine atoms or a cyano group; C₃₋₆ alkenyloxy or C₃₋₆ alklynyloxy where either may be optionally substituted with hydroxy or NR₁⁴R₁⁵; OC₁₋₆ alkyl-X-C₁₋₆ alkyl where the alkyl groups may form a 3-6 membered saturated ring; OC₁₋₆ alkylR₁¹, or OC₂₋₆ alkyl-X-R₁¹ where the alkyl group may form a 3-6 membered saturated ring and is optionally substituted with 1-3 groups selected from hydroxy, halogen, NR₁⁴R₁⁵, SR₁³, S(O)₂R₁³, S(O)R₁³, or OC₁₋₆ alkylR₁⁶; compounds of formula (I) can be prepared by treating a compound of the formula (VI), where LG is a leaving group (such as chlorine or bromine):

\[
\begin{align*}
R^5 & \quad N \quad LG \\
R^8 & \quad NH
\end{align*}
\]

(VI)

with a compound of formula (V)

in a suitable solvent (such as 1,2-dimethoxyethane, N,N-dimethylformamide or tetrahydrofuran) with a suitable base such as sodium hydride or potassium tert-butoxide at a suitable temperature such as 25°C to 60°C.

Compounds of structure (VIII) can be prepared by taking a compound of formula (VII) where LG is a leaving group (such as chlorine or bromine) and protecting the sulfonamide as for example the trimethylsilyloxyethyl methyl ether (SEM) or methoxymethyl ether (MOM) by the standard literature methods (such as SEM-chloride or MOM-chloride) in a suitable solvent (such as tetrahydrofuran) with a suitable base (such as triethylamine) at a suitable temperature (such as 0-20°C) to afford compound of the formula (VIII):
Compound of formula (VIII) could then be treated with compounds of formulae (IX):

\[ R^5 \cdot H \]  

(IX)

where \( R^5 \cdot H \) is a primary or secondary amine, thiol or alcohol as defined above (i.e. where \( R^5 \) is a group containing an X moiety where X is NR\(^{13} \), O or S), in a suitable solvent (such as tetrahydrofuran or acetonitrile) with or without a suitable base (such as sodium hydride, caesium carbonate or triethylamine) at a suitable temperature ranging from 25-85\(^{\circ}\)C to afford compound of the formula (X):

\[ \text{(X)} \]

The protecting group (P) can then be removed by standard methods to afford compound of formula (I).

Compounds of structure (II) or (I), where \( R^5 \) is an optionally substituted aryl or heteroaryl ring as defined in the claims, can be prepared by taking a compound of formula (XI) or (VII) where LG is a suitable leaving group such as bromine, chlorine or iodine and reacting
it with an aryl or heteroaryl boronic acid such as phenyl boronic acid, a palladium catalyst such as \([1,1'-\text{bis(diphenylphosphino)}\text{ferrocene}]\text{palladium (II)}\) chloride, a suitable base such as caesium fluoride, sodium acetate or caesium carbonate and a suitable solvent such as methanol or ethanol and heating between 40-80°C.

\[ \text{LG} \begin{array}{c} \text{R}^4 \\ \text{N} \\ \text{N} \\ \text{NH}_2 \\ \text{R}^6 \end{array} \rightarrow \begin{array}{c} \text{R}^4 \\ \text{N} \\ \text{N} \\ \text{NH}_2 \\ \text{R}^6 \end{array} \]

\(\text{XI}\)  \(\text{II}\)

\[ \text{LG} \begin{array}{c} \text{R}^4 \\ \text{N} \\ \text{NH} \\ \text{O=S=O} \\ \text{R}^1 \\ \text{R}^2 \\ \text{R}^3 \end{array} \rightarrow \begin{array}{c} \text{R}^4 \\ \text{N} \\ \text{NH} \\ \text{O=S=O} \\ \text{R}^1 \\ \text{R}^2 \\ \text{R}^3 \end{array} \]

\(\text{VII}\)  \(\text{I}\)

Compounds of formula (II) and (I) where \(R^5\) or \(R^6\) is \(\text{CO}_2\) can be prepared by reacting a compound of formula (II) or (I), where \(R^5\) or \(R^6\) is bromine or iodine, in a suitable solvent such as \(\text{R}^{13}\)OH or dioxane containing \(\text{R}^{13}\)OH, a suitable tertiary amine such as triethylamine, a suitable palladium catalyst such as \([1,1'-\text{bis(diphenylphosphino)}\text{ferrocene}]\text{palladium (II)}\) chloride under an atmosphere of carbon monoxide usually at 2-10 bar, ideally at 4-6 bar and at a temperature of 70-120 °C.

Compounds of formula (II) and (I) where \(R^5\) or \(R^6\) is \(\text{CONR}^{14}\text{R}^{15}\) can be prepared by reacting a compound of formula (II) or (I), where \(R^5\) or \(R^6\) is bromine or iodine, in a suitable solvent such as dioxane containing \(\text{NHR}^{14}\text{R}^{15}\), a suitable tertiary amine such as triethylamine, a suitable palladium catalyst such as \([1,1'-\text{bis(diphenylphosphino)}\text{ferrocene}]\text{palladium (II)}\) chloride under an atmosphere of carbon monoxide usually at 2-10 bar, ideally at 4-6 bar and at a temperature of 70-120 °C.

Compounds of formula (I) where \(R^5\) or \(R^6\) is \(\text{CH}_2\)OH can be prepared from compounds of formula (I) where \(R^5\) or \(R^6\) is \(\text{CO}_2\) by reduction using a suitable reducing agent such as
lithium triethylborohydride in a suitable solvent such as tetrahydrofuran at a temperature of 0-10°C.

Compounds of formula (I) where \( R^5 \) or \( R^6 \) is CHO can be prepared from compounds of formula (I) where \( R^5 \) or \( R^6 \) is \( \text{CH}_2\text{OH} \) by oxidation using a suitable oxidising agent such as manganese dioxide or pyridinium chlorochromate (PCC) in a suitable solvent such as tetrahydrofuran or dichloromethane at a temperature of 0-50°C.

Compounds of formula (I) where \( R^5 \) or \( R^6 \) is \( \text{CH} (\text{OH}) R^{11} \) or \( \text{CH} (\text{OH}) (\text{C} 1-5) \text{alkyl} \) can be prepared from compounds of formula (I) where \( R^5 \) or \( R^6 \) is CHO by reaction with a compound of formula (XII) where M is a metal such as magnesium or lithium in a suitable solvent such as tetrahydrofuran or diethyl ether at a temperature of 0-10°C.

\[ \text{C}_{1-5} \text{ alkylM or R}^{11} \text{M} \]

![Diagram](image)

A compound of formula (XV) can be made by reacting a compound of formula (XIII), where \( R^4 \) is preferably chloro, bromo or alkoxy and LG is a suitable leaving group such as chloro or bromo, with a compound of formula (XIV) using a suitable base such as potassium carbonate or caesium carbonate in a suitable solvent such as \( N, N \)-dimethylformamide at a temperature of 40-90°C.

Intermediate compounds of formula (II) and (III) can be prepared using standard chemistry or are available commercially.

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 in the starting reagents or intermediate compound may need to be protected by protecting groups. Thus, the preparation of the compound of formula (I) may involve, at an appropriate stage, the
removal of one or more protecting groups. The protection and deprotection of functional
groups is fully described in ‘Protective Groups in Organic Chemistry’, edited by J. W. F.
McOmie, Plenum Press (1973), and ‘Protective Groups in Organic Synthesis’, 2nd edition,

The compounds of formula (I) above may be converted to a pharmaceutically acceptable
salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium,
aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline,
diethanolamine, ethanolamine, ethylamine, meglumine, tromethamine or procaine, or an
acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate,
maleate, tartrate, citrate, oxalate, methanesulphonate or p-toluenesulphonate.

Certain compounds of formula (II) and (III) are believed to be novel and form a further
aspect of the invention.

The compounds of formula (I) above may be converted to a pharmaceutically acceptable
salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium,
aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline,
diethanolamine, ethanolamine, ethylamine, meglumine, tromethamine or procaine, or an
acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate,
maleate, tartrate, citrate, oxalate, methanesulphonate or p-toluenesulphonate.

The compounds of formula (I) has activity as pharmaceuticals, in particular as modulators
of chemokine receptor (especially CCR4) activity, and may be used in the treatment
(therapeutic or prophylactic) of conditions/diseases in human and non-human animals
which are exacerbated or caused by excessive or unregulated production of chemokines.
Examples of such conditions/diseases include:

(1) \textbf{(the respiratory tract)} obstructive airways diseases including chronic
obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic,
intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma
(e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic,
atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic
rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa;
membranous rhinitis including croupous, fibrinous and pseudomembranous
rhinitis and scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa
(hay fever) and vasomotor rhinitis; sarcoidosis, farmer’s lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** gout, rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter’s disease), Behcet’s disease, Sjogren’s syndrome and systemic sclerosis;

(3) **(skin)** pruritus, scleroderma, otitis, psoriasis, atopical dermatitis, contact dermatitis and other eczematous demmitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angioderma, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis, lupus;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, inflammatory bowel diseases such as Crohn’s disease, ulcerative colitis, ileitis and enteritis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(central and peripheral nervous system)** Neurodegenerative diseases and dementia disorders, e.g. Alzheimer’s disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob’s disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington’s disease, frontotemporal dementia, Lewy body dementia and vascular dementia; polyneuropathies, e.g. Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, plexopathies; CNS demyelination, e.g. multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis; neuromuscular disorders, e.g. myasthenia gravis and Lambert-Eaton syndrome; spinal disorders, e.g. tropical spastic paraparesis, and stiff-man syndrome: paraneoplastic syndromes, e.g. cerebellar degeneration and encephalomyelitis; CNS trauma; migraine; stroke and rectumx diseases such as meningitis;

(6) **(other tissues and systemic disease)** hepatitis, vasculitis, spondyoarthropathies, vaginitis, glomerulonephritis, myositis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus,
systemic lupus, erythematosus, Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, and idiopathic thrombocytopenia purpura; post-operative adhesions, and sepsis.

(7) (allograft and xenograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(8) Cancer, carcinoma & tumour metastasis, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin, especially non-small cell lung cancer (NSCLC), malignant melanoma, prostate cancer and squamous sarcoma. Hematopoietic tumors of lymphoid lineage, including acute lymphocytic leukemia, B cell lymphoma and Burkets lymphoma, Hodgkins Lymphoma, Acute Lymphoblastic Leukemia. Hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia. Tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma, and other tumors, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma.

(9) All diseases that result from a general imbalance of the immune system and resulting in increased atopic inflammatory reactions.

(10) Cystic fibrosis, re-perfusion injury in the heart, brain, peripheral limbs and other organs.

(11) Burn wounds & chronic skin ulcers

(12) Reproductive Diseases (e.g. Disorders of ovulation, menstruation and implantation, Pre-term labour, Endometriosis)

(13) thrombosis

(14) infectious diseases such as HIV infection and other viral infections, bacterial infections.
Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compound of the invention are used to treat diseases in which the chemokine receptor belongs to the CC chemokine receptor subfamily, more preferably the target chemokine receptor is the CCR4 receptor.

Particular conditions which can be treated with the compound of the invention are asthma, rhinitis and inflammatory skin disorders, diseases in which there are raised TARC, MDC or CCR4 levels. It is preferred that the compound of the invention is used to treat asthma and rhinitis, especially asthma.

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

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity, particularly CCR4 activity, is beneficial.

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.

The invention still further provides a method of treating a chemokine mediated disease wherein the chemokine binds to a chemokine (especially CCR4) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

The invention also provides a method of treating a respiratory disease, such as asthma and rhinitis, especially asthma, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate 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 compound of formula (I) and pharmaceutically acceptable salts and solvates 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/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. 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 or solvate 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 or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; 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. Preferably the compound of the invention is administered orally.

In a further aspect, the present invention provides the use of a compound or formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy in combination with drugs used to treat asthma and rhinitis (such as inhaled and oral steroids, inhaled β2-receptor agonists and oral leukotriene receptor antagonists).
The following examples illustrate the invention.
Example 1
2,3-Dichloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-benzenesulphonamide

Sodium hydride (0.1g of 60%) was added to 3-methoxy-5-methyl-2-pyrazinamine (0.07g) in 1,2-dimethoxyethane (3mL) under nitrogen at room temperature. After 1 hour at 50°, 2,3-dichlorobenzenesulphonyl chloride (0.15g) was added. After stirring for 30 minutes, 5% aqueous citric acid was added and the product extracted with ethyl acetate (X3). The combined extracts were washed with saturated brine, dried (MgSO4) and the solvent was evaporated. Chromatography on silica eluting with dichloromethane/methanol mixtures gave the title compound as a white solid (0.08g).

m/e 346/8/350 (M-1+, 100%)
1H NMR (D6-DMSO) δ 11.27 (1H, s), 8.06 (1H, d), 7.93 (1H, d), 7.60-7.55 (1H, br s), 7.58 (1H, t), 3.87 (3H, s), 2.28 (3H, s).

Example 2
N-(6-Chloro-3-methoxy-2-pyrazinyl)-2,3,4-trifluorobenzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.16g) and 2,3,4-trifluorobenzenesulphonyl chloride (0.25g). Yield 0.08g.

m/e 352/4 (M-1+, 100%)
$^1$H NMR (D6-DMSO) $\delta$ 7.93-7.80 (1H, m), 7.89 (1H, s), 7.60-7.50 (1H, m), 3.91 (3H, s).

Example 3
3-Chloro-$N$-(6-chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.16g) and 3-chloro-2-methylbenzenesulphonyl chloride (0.23g). Yield 0.15g.

m/e 346/8/50 (M-1$^+$, 100%)

$^1$H NMR (D6-DMSO) $\delta$ 8.05 (1H, d), 7.85 (1H, s), 7.75 (1H, d), 7.47 (1H, t), 3.92 (3H, s), 2.66 (3H, s).

Example 4
2,3-Dichloro-$N$-(6-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

a) 3-Bromo-6-chloro-2-pyrazinamine

$N$-bromosuccinimide (6.9g) was added portionwise over 0.5h to a stirred solution of 6-chloro-2-pyrazinamine (5.0g) in chloroform (200mL) heated under reflux. After the addition was complete the reaction mixture was allowed to cool, washed with water and evaporated to give a 3:1 mixture of 5-bromo-6-chloro-2-pyrazinamine and the subtitle compound which were separated by silica gel chromatography eluting with dichloromethane. Yield 2.0g. Used directly.

b) 6-Chloro-3-methoxy-2-pyrazinamine and 3-bromo-6-methoxy-2-pyrazinamine
3-Bromo-6-chloro-2-pyrazinamine (1.0 g), sodium methoxide (3 mL of 25% solution in methanol) and methanol (10 mL) were heated at reflux for 3 hours. The solvent was evaporated and the residue was dissolved in ethyl acetate and brine. The organic layer was separated dried (MgSO₄) and the solvent was evaporated to give a mixture of the sub-title compounds (ratio 10:1). Purification was by silica gel chromatography eluting with dichloromethane. Yield 0.5 g. Used directly.

c) 2,3-Dichloro-N-(6-Chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.24 g) and 2,3-dichlorobenzenesulphonyl chloride (0.32 g). Yield 0.24 g.
m/e 366/8370/2 (M-1⁺, 100%)
¹H NMR (D6-DMSO) δ 8.14 (1H, d), 7.96 (1H, d), 7.89 (1H, s), 7.62 (1H, t), 3.91 (3H, s).

Example 5
2,3-Dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.1g) and 2,3-dichlorobenzenesulphonyl chloride (0.15g). Yield 0.05g.

m/e 366/8/370/2 (M-1+, 100%)

1H NMR (D6-DMSO) δ 8.15 (1H, d), 7.93 (1H, d), 7.79 (1H, s), 7.58 (1H, t), 3.93 (3H, s).

Example 6

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,5-dichlorobenzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.2g) and 2,5-dichlorobenzenesulphonyl chloride (0.24g). Yield 0.14g.

m/e 410/2/4/6 (M-1+, 100%)

1H NMR (D6-DMSO) δ 8.04 (1H, d), 7.86 (1H, s), 7.73 (1H, dd), 7.66 (1H, dd), 3.91 (3H, s).

Example 7

N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,5-dichlorobenzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.2g) and 3,5-dichlorobenzenesulphonyl chloride (0.24g). Yield 0.012g.

m/e 410/2/4/6 (M-1+, 100%)
$^1$H NMR (D6-DMSO) $\delta$ 7.96-7.91 (4H, m), 3.93 (3H, s).

Example 8

$N$-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide

![Chemical Structure](image)

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.1g) and 2,3-dichlorobenzenesulphonyl chloride (0.2g). Yield 0.045g.
m/e 410/2/4/6 (M-1$^+$, 100%)

$^1$H NMR (D6-DMSO) $\delta$ 8.06 (1H, dd), 7.93 (1H, dd), 7.82 (1H, s), 7.57 (1H, t), 3.92 (3H, s).

Example 9

$N$-(5-Bromo-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide

![Chemical Structure](image)

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.2g) and 2,4-dichlorobenzenesulphonyl chloride (0.24g). Yield 0.059g.
m/e 410/2/4/6 (M-1$^+$, 100%)

$^1$H NMR (D6-DMSO) $\delta$ 8.07 (1H, d), 7.85 (2H, d), 7.64 (1H, dd), 3.92 (3H, s).

Example 10

$N$-(5-Bromo-3-methoxy-2-pyrazinyl)-3,4-dichlorobenzenesulphonamide
Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.15g) and 3,4-dichlorobenzenesulphonyl chloride (0.15g). Yield 0.09g.

m/e 410/2/4/6 (M-1\(^+\), 100%)

\(^1\)H NMR (D6-DMF) \(\delta\) 8.14 (1H, s), 8.00-7.85 (3H, m), 3.94 (3H, s).

Example 11
N-(5-Bromo-3-methoxy-2-pyrazinyl)-4-chlorobenzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.1g) and 4-chlorobenzenesulphonyl chloride (0.13g). Yield 0.13g.

m/e 376/8/380 (M-1\(^+\), 100%)

\(^1\)H NMR (D6-DMF) \(\delta\) 11.3 (1H, br s), 7.97 (2H, d), 7.91 (1H, s), 7.66 (2H, d), 3.93 (3H, s).
Example 12
N-(5-Bromo-3-methoxy-2-pyrazinyl)-3-chlorobenzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.1g) and 3-chlorobenzenesulphonyl chloride (0.13g).
Yield 0.14g.
m/e 376/8/380 (M+1\(^+, 100\%
\(^{1}\)H NMR (D6-DMSO) \(\delta\) 8.00-7.90 (3H, m), 7.75 (1H, d), 7.64 (1H, t), 3.94 (3H, s).

Example 13
N-(3-Methoxy-5-methyl-2-pyrazinyl)-2-fluorobenzenesulphonamide

Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 2-fluorobenzenesulphonyl chloride.
m/e 298 (M+1\(^+, 100\%
\(^{1}\)H NMR (D6-DMSO) \(\delta\) 11.05 (1H, br s), 7.85-7.95 (1H, m), 7.65-7.75 (1H, m), 7.50-7.60 (1H, m), 7.35-7.45 (1H, m), 3.90 (3H, s), 2.30 (3H, s).
MP 150-152\(^\circ\)C

Example 14
N-(3-Methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide
Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and benzenesulphonyl chloride.

MP 138-139°C

**Example 15**

*N-(3-Methoxy-5-methyl-2-pyrazinyl)-2-iodobenzencesulphonamide*

Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 2-iodobenzencesulphonamide.

$^1$H NMR (D6-DMDSO) δ 10.75 (1H, br s), 8.05-8.15 (2H, m), 7.65-7.75 (2H, m), 7.30 (1H, dt), 3.90 (3H, s), 2.30 (3H, s).

MP 140-141°C

**Example 16**

*N-(3-Methoxy-5-methyl-2-pyrazinyl)-3-fluorobenzencesulphonamide*
Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 3-fluorobenzenesulphonyl chloride.
MP 95-97°C

**Example 17**

2-[[3-Methoxy-5-methyl-2-pyrazinyl)amino]sulphonyl]benzonitrile

Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 2-cyanobenzenesulphonyl chloride.
m/e 305 (M+1<sup>+</sup>, 100%)

$^1$H NMR (D6-DMSO) $\delta$ 8.15 (1H, dd), 8.05 (1H, dd), 7.85 (1H, dt), 7.80 (1H, dt), 7.60 (1H, s), 3.85 (3H, s), 2.30 (3H, s).

**Example 18**

$N$-(5-Bromo-3-methoxy-2-pyrazinyl)benzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine and benzenesulphonyl chloride
m/e 344 (M+1<sup>+</sup>, 100%)
Example 19

*N-(5-Bromo-3-methoxy-2-pyrazinyl)2-iodobenzenesulphonamide*

\[
\text{\[I\]}\quad \text{\[O\]}\quad \text{\[N\]}\quad \text{\[O\]}\quad \text{\[N\]}\quad \text{\[Br\]}
\]

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine and 2-iodobenzenesulphonyl chloride.

m/e 470 (M+1\(^+\), 100%)

\(^1\)H NMR (D6-DMSO) \(\delta\) 11.30 (1H, br s), 8.0-8.1 (2H, m), 7.80 (1H, s), 7.60 (1H, dt), 7.30 (1H, dt), 3.95 (3H, s).

Example 20

2,3-Dichloro-*N-*[3-(2-furanylmethoxy)-5-methyl-2-pyrazinyl]benzenesulphonamide

a) \(N-(3\)-Bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide

\[
\text{\[Cl\]}\quad \text{\[Cl\]}\quad \text{\[NH\]}\quad \text{\[Br\]}
\]

Prepared by the method of Example 1 using 3-bromo-5-methyl-2-pyrazinamine (0.84g) and 2,3-dichlorobenzenesulphonyl chloride (1.1g). Yield 0.92g.

b) 2,3-Dichloro-*N-*[3-(2-furanylmethoxy)-5-methyl-2-pyrazinyl]benzenesulphonamide
Sodium hydride (0.04g of a 60% dispersion in oil) was added to furfurylalcohol (0.034g) in 1,2-dimethoxyethane (1mL). After 5 minutes N-(3-Bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 20 part a) (0.1g) was added and the mixture heated at 40 °C. After 16h, 5% aqueous citric acid (10mL) was added and the mixture extracted with ethyl acetate (2x50mL). The combined extracts were washed with brine, dried (MgSO₄) and the solvent evaporated. Chromatography on silica gel eluting with dichloromethane gave the title compound as a white solid (0.02g) m/e 412 (M-1⁺, 100%)

1H NMR (D6-DMSO) δ 11.33 (1H, br s), 8.01 (1H, d), 7.90 (1H, d), 7.70 (1H, s), 7.62 (1H, br s), 7.54 (1H, t), 6.61-6.58 (1H, m), 6.50-6.45 (1H, m), 5.33 (2H, s), 2.32 (3H, s) MP 127-129°C

Example 21

2,3-Dichloro-N-[5-methyl-3-(5-methyl-3-isoxazolylmethoxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 20 using (5-methyl-3-isoxazolyl)methanol (0.05g) and N-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.1g). Yield 0.05g.
m/e 429 (M+1⁺, 100%)

1H NMR (D6-DMSO) δ 11.39 (1H, br s), 8.03 (1H, d), 7.91 (1H, d), 7.64 (1H, br s), 7.47 (1H, t), 6.33 (1H, s), 5.37 (2H, s), 2.41 (3H, s), 2.29 (3H, s)

MP 155-156°C

Example 22

2,3-Dichloro-N-[5-methyl-3-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 20 using pyridine-2-methanol (0.05g) and N-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.1g). Yield 0.07g.

m/e 425 (M+1⁺, 100%)

1H NMR (D6-DMSO) δ 8.57-8.54 (1H, m), 8.05 (1H, d), 7.89 (1H, d), 7.83 (1H, dt), 7.65-7.50 (2H, m), 7.56 (1H, t), 7.35-7.30 (1H, m), 5.44 (2H, s), 2.26 (3H, s)

Example 23

2,3-Dichloro-N-[5-methyl-3-(6-methyl-2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 20 using 6-methylpyridine-2-methanol (0.05g) and N-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.1g). Yield 0.023g.
m/e 439 (M+1⁺, 100%)

\( ^1H \) NMR (D6-DMSO) \( \delta \) 8.05 (1H, dd), 7.89 (1H, dd), 7.70 (1H, t), 7.59 (1H, br s), 7.54 (1H, t), 7.34 (1H, d), 7.19 (1H, d), 5.39 (2H, s), 2.47 (3H, s), 2.26 (3H, s)

MP 164-165°C

**Example 24**

2,3-Dichloro-N-[5-methyl-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 20 using pyridine-3-methanol (0.05g) and \( N \)-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.1g). Yield 0.023g.

m/e 425 (M+1⁺, 100%)

\( ^1H \) NMR (D6-DMSO) \( \delta \) 8.74 (1H, d), 8.55 (1H, dd), 8.03 (1H, dd), 7.95-7.85 (2H, m), 7.59 (1H, br s), 7.54 (1H, t), 7.42 (1H, dd), 5.41 (2H, s), 2.29 (3H, s)

MP 160-161°C

**Example 25**

2,3-Dichloro-N-[5-methyl-3-(4-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
Prepared by the method of Example 20 using pyridine-4-methanol (0.05g) and N-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.1g). Yield 0.009g. m/e 425 (M+1\(^+\), 100%) 
\(^1\)H NMR (D6-DMSO) \(\delta 8.57\) (2H, d), \(8.05\) (1H, dd), \(7.89\) (1H, dd), \(7.60\) (1H, s), \(7.55\) (1H, t), \(7.50\) (2H, d), \(5.43\) (2H, s), \(2.26\) (3H, s) 
MP 183-184\(^\circ\)C

**Example 26**

2,3-Dichloro-N-[5-methyl-3-(3-methyl-2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

![Chemical structure](image)

Prepared by the method of Example 20 using 3-methylpyridine-2-methanol (0.05g) and N-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.1g). Yield 0.021g. m/e 439 (M+1\(^+\), 100%) 
\(^1\)H NMR (D6-DMSO) \(\delta 8.36\) (1H, d), \(8.05\) (1H, dd), \(7.83\) (1H, dd), \(7.64\) (1H, d), \(7.60\) (1H, br s), \(7.49\) (1H, t), \(7.31\) (1H, dd), \(5.40\) (2H, s), \(2.33\) (3H, s), \(2.29\) (3H, s) 
MP 137-138\(^\circ\)C

**Example 27**

2,3-Dichloro-N-[5-methyl-3-(pyridazinylmethoxy)-2-pyrazinyl]benzenesulphonamide
Prepared by the method of Example 20 using pyridazine-3-methanol (0.1g) and N-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.15g). Yield 0.038g. m/e 424 (M-1+, 100%)

$^1$H NMR (D6-DMSO) $\delta$ 11.47 (1H, br s), 9.21 (1H, dd), 8.05 (1H, dd), 8.00-7.95 (1H, m), 7.88 (1H, d), 7.80-7.75 (1H, m), 7.62 (1H, br s), 7.54 (1H, t), 5.65 (2H, s), 2.27 (3H, s)

MP 119-124°C

**Example 28**

2,3-Dichloro-N-[3-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

a) 2,3-Dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide

2,3-Dichloropyrazine (2.6g), 2,3-dichlorobenzenesulphonamide (4.0g) and potassium carbonate (10.0g) in $N,N$-dimethylformamide (50mL) was heated at 75°C.

After 16h, 5% aqueous citric acid (30mL) was added and the mixture extracted with ethyl acetate (2x100mL). The combined extracts were washed with brine, dried (MgSO$_4$) and the solvent evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound (1.5g).

b) 2,3-Dichloro-N-[3-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
Sodium hydride (0.05g of a 60% dispersion in oil) was added to pyridine-2-methanol (0.088g) in 1,2-dimethoxyethane (3.0mL). After 5 minutes, 2,3-dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (0.1g) was added and the mixture heated at 70°C. After 4h, 5% aqueous citric acid (10mL) was added and the mixture extracted with ethyl acetate (2x50mL). The combined extracts were washed with brine, dried (MgSO₄) and the solvent evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.06g).

\[ m/e \ 411 (M+1^+, \ 100\%) \]

\[ ^1H \text{ NMR (D6-DMSO)} \delta 8.57 (1H, d), 8.13 (1H, d), 7.93 (1H, d), 7.90-7.75 (2H, m), 7.75-7.65 (1H, m), 7.65-7.55 (2H, m), 7.40-7.30 (1H, m), 5.49 (2H, s) \]

MP 167-168°C

**Example 29**

2,3-Dichloro-N-[3-(pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 28 using pyridine-3-methanol (0.09g) and 2,3-dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (0.1g). Yield 0.042g.

\[ m/e \ 409 (M-1^+, \ 100\%) \]
\[ \text{Example 30} \]

2,3-Dichloro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide

\[
\begin{array}{c}
\text{Cl} \\
\text{Cl} \\
\text{O=S=O} \\
\text{N} \\
\text{O} \\
\text{N} \\
\text{Cl}
\end{array}
\]

2,3-Dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28 part a) (0.2g) in 10% sodium methoxide in methanol (10mL) was heated at 85°C. After 4h, 5% aqueous citric acid (50mL) was added and the mixture extracted with ethyl acetate (2x150mL). The combined extracts were washed with brine, dried (MgSO\(_4\)) and the solvent evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.12g)

m/e 334 (M+1\(^+\), 100%)

\[ \text{\(^1\)H NMR (D6-DMF) \(\delta\) 11.54 (1H, br s), 8.10 (1H, d), 7.94 (1H, d), 7.85-7.75 (1H, m), 7.70-7.55 (1H, m), 7.59 (1H, t), 3.90 (3H, s)} \]

MP 183-184°C

\[ \text{Example 31} \]

\[ N\text{-[5-Bromo-3-(2-pyrazinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide} \]

\[ \text{a) 2,3-Dichloro-N-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide} \]

\[
\begin{array}{c}
\text{Cl} \\
\text{Cl} \\
\text{O=S=O} \\
\text{N} \\
\text{Br} \\
\text{N} \\
\text{Br}
\end{array}
\]
Prepared by the method of Example 1 (reaction performed at room temperature) using 3,5-dibromo-2-pyrazinamine (2.9g) and 2,3-dichloro benzenesulphonyl chloride (2.8g). Yield 4.4g.

b) N-(5-Bromo-3-(2-pyrazinylmethoxy)-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide

Sodium hydride (0.05g of a 60% dispersion in oil) was added to pyrazine-2-methanol (0.04g) in 1,2-dimethoxyethane (3ml). After 5 minutes, 2,3-Dichloro-N-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (0.12g) was added. After 0.5h, 5% aqueous citric acid (10mL) was added and the mixture extracted with ethyl acetate (2x30mL). The combined extracts were washed with brine, dried (MgSO₄) and the solvent evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.06g).

m/e 489 (M⁺, 100%)

¹H NMR (D6-DMSO) δ 9.00 (1H, s), 8.66 (2H, s), 8.08 (1H, dd), 7.92 (1H, dd), 7.91 (1H, s), 7.56 (1H t), 5.53 (2H, s)

Example 32

N-(5-Bromo-3-(1-methyl-6-oxo-1,6-dihydro-3-pyridinylmethoxy)-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide
Prepared by the method of Example 31 using 5-hydroxymethyl-1-methyl-1H-pyridin-2-one (0.1g) and 2,3-dichloro-N-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (0.16g). Yield 0.035g.

m/e 521 (M+1+, 100%)

\(^1\)H NMR (D6-DMSO) 阝 8.04 (1H, dd), 7.91 (1H, dd), 7.90-7.87 (2H, m), 7.60-7.50 (2H, m), 6.42 (1H, d), 5.10 (2H, s), 3.41 (3H, s)

MP 169-170°C

Example 33

\(N\)-[5-Bromo-3-(3-pyridazinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

Prepared by the method of Example 31 using pyridazine-3-methanol (0.07g) and 2,3-dichloro-\(N\)-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (0.15g). Yield 0.06g.

m/e 489 (M-1+, 100%)
1H NMR (D6-DMSO) δ 9.23 (1H, d), 8.08 (1H, dd), 7.99 (1H, dd), 7.92 (1H, dd), 7.91 (1H, s), 7.80 (1H, dd), 7.56 (1H, t), 5.67 (2H, s)
MP 115-120°C

Example 34

N-[5-Bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

Prepared by the method of Example 31 using pyridine-3-methanol (0.44g) and 2,3-dichloro-N-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (1.0g). Yield 0.6g.
m/e 491 (M+1+, 100%)
1H NMR (D6-DMSO) δ 8.78 (1H, d), 8.58 (1H, dd), 8.06 (1H, d), 7.99 (1H, dt), 7.91 (1H, d), 7.88 (1H, s), 7.55 (1H, t), 7.55-7.50 (1H, m), 5.44 (2H, s)
MP 204-206°C

Example 35

N-[5-Bromo-3-(5-pyrimidinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
Prepared by the method of Example 31 using pyrimidine-5-methanol (0.035g) and 2,3-dichloro-N-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (0.16g). Yield 0.028g.
m/e 490 (M-1+, 100%)
$^1$H NMR (D6-DMSO) δ 9.21 (1H, s), 9.02 (2H, s), 8.07 (1H, dd), 7.92 (1H, dd), 7.91 (1H, s), 7.56 (1H, t), 5.45 (2H, s)
MP 208-209°C

Example 36
$N$-[5-Chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

Prepared by the method of Example 31 using pyridine-3-methanol (0.13g) and 2,3-dichloro-$N$-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.3g). Yield 0.19g.
m/e 447 (M+1+, 100%)
$^1$H NMR (D6-DMSO) δ 8.78 (1H, s), 8.59 (1H, dd), 8.06 (1H, dd), 7.96 (1H, dt), 7.91 (1H, dd), 7.83 (1H, s), 7.55 (1H, t), 7.47 (1H, dd), 5.44 (2H, s)
MP 200-204°C

Example 37
$N$-[5-Chloro-3-(5-pyrimidinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
Prepared by the method of Example 31 using pyrimidine-5-methanol (0.035g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.07g). Yield 0.015g.

m/e 448 (M+1⁺, 100%)

1H NMR (D6-DMSO) δ 9.21 (1H, s), 9.02 (2H, s), 8.08 (1H, dd), 7.92 (1H, dd), 7.86 (1H, s), 7.56 (1H, t), 5.46 (2H, s)

MP 205-206°C

Example 38
2-Chloro-N-(6-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.1g) and 2-chlorobenzenesulphonyl chloride (0.13g).

Yield 0.11g.

m/e 332 (M-1⁺, 100%)

1H NMR (D6-DMSO) δ 8.15 (1H, d), 7.86 (1H, s), 7.70-7.50 (3H, m), 3.91 (3H, s)

MP 172-173°C

Example 39
3-Chloro-N-(6-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.1g) and 3-chlorobenzenesulphonyl chloride (0.13g).

Yield 0.14g.

m/e 332 (M-1\(^+\), 100%)

\(^1\)H NMR (D6-DMSO) \(\delta\) 8.05 (1H, d), 7.93 (1H, dd), 7.90 (1H, s), 7.76 (1H, dd), 7.65 (1H, t) 3.92 (3H, s)

MP 126-127\(^\circ\)C

**Example 40**

4-Chloro-N-(6-chloro-3-methoxy-2-pyrazinyl)benezenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.1g) and 4-chlorobenzenesulphonyl chloride (0.13g).

Yield 0.13g.

m/e 332 (M-1\(^+\), 100%)

\(^1\)H NMR (D6-DMSO) \(\delta\) 7.99 (2H, dt), 7.89 (1H, s), 7.70 (2H, dt), 3.92 (3H, s)

MP 174-175\(^\circ\)C

**Example 41**
N-(6-Chloro-3-methoxy-2-pyrazinyl)-2,4-dichlorobenezesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.05g) and 2,4-dichlorobenzencesulphonyl chloride (0.1g). Yield 0.07g.
m/e 368 (M-1⁺, 100%)

^1H NMR (D6-DMSO) δ 8.13 (1H, d), 7.86 (1H, s), 7.85 (1H, d), 7.70 (1H, dd), 3.91 (3H, s)

MP 189-190°C

Example 42

N-(6-Chloro-3-methoxy-2-pyrazinyl)-3,4-dichlorobenzencesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.05g) and 3,4-dichlorobenzencesulphonyl chloride (0.09g). Yield 0.08g.
m/e 368 (M-1⁺, 100%)

^1H NMR (D6-DMSO) δ 8.21 (1H, s), 7.93-7.90 (3H, m), 3.92 (3H, s)

MP 176-177°C
**Example 43**

3-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-2-methylbenezesulphonamide

![Chemical structure](image)

Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine (0.1g) and 3-chloro-2-methylbenezesulphonyl chloride (0.19g). Yield 0.08g.

m/e 328 (M+H, 100%)

$^1$H NMR (D6-DMSO) δ 11.09 (1H, br s), 7.95 (1H, d), 7.72 (1H, d), 7.54 (1H, br s), 7.41 (1H, t), 3.88 (3H, s), 2.64 (3H, s), 2.27 (3H, s)

MP 133-135°C

**Example 44**

2-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)benezesulphonamide

![Chemical structure](image)

Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine (0.1g) and 2-chlorobenzesulphonyl chloride (0.15g). Yield 0.06g.

m/e 314 (M+H, 100%)
1H NMR (D6-DMSO) δ 11.07 (1H, br s), 8.06 (1H, d), 7.69-7.46 (4H, m), 3.90 (3H, s), 2.24 (3H, s)

Example 45
3-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide

Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine (0.1g) and 3-chlorobenzencesulphonyl chloride (0.18g). Yield 0.042g.

m/e 314 (M+1⁺, 100%)

1H NMR (D6-DMSO) δ 10.89 (1H, br s), 7.97 (1H, d), 7.92 (1H, d), 7.73 (1H, d), 7.65-7.58 (2H, m), 3.90 (3H, s), 2.29 (3H, s)

MP 123-125°C

Example 46
4-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide

Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine (0.1g) and 4-chlorobenzencesulphonyl chloride (0.18g). Yield 0.06g.

m/e 314 (M+1⁺, 100%)

1H NMR (D6-DMSO) δ 10.83 (1H, br s), 7.96 (2H, d), 7.65 (2H, d), 7.60 (1H, s), 3.88 (3H, s), 2.28 (3H, s)
MP 155-156°C

Example 47
2,4-Dichloro-\(N\)-(3-methoxy-5-methyl-2-pyrazinyl)benezesulphonamide

\[
\begin{array}{c}
\text{Cl} \\
\text{O=S=O} \\
\text{N} \\
\text{O}
\end{array}
\]

Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine (0.1g) and 2,4-dichlorobenzenesulphonyl chloride (0.21g). Yield 0.041g.
m/e 348 (M\(^{+1}\), 100%)

\(^1\)H NMR (D6-DMSO) δ 8.05 (1H, d), 7.83 (1H, d), 7.64 (1H, dd), 7.54 (1H, br s), 3.87 (3H, s), 2.27 (3H, s)

MP 135-136°C

Example 48
3,4-Dichloro-\(N\)-(3-methoxy-5-methyl-2-pyrazinyl)benezesulphonamide

\[
\begin{array}{c}
\text{Cl} \\
\text{O=S=O} \\
\text{N} \\
\text{O}
\end{array}
\]

Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine (0.1g) and 3,4-dichlorobenzenesulphonyl chloride (0.21g). Yield 0.046g.
m/e 348 (M\(^{+1}\), 100%)

\(^1\)H NMR (D6-DMSO) δ 10.97 (1H, s), 8.14 (1H, d), 7.91 (1H, dd), 7.88 (1H, d), 7.63 (1H, s), 3.89 (3H, s), 2.27 (3H, s)
MP 148-149°C

**Example 49**

*N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-trifluoromethoxybeneznesulphonamide*

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.1g) and 2-trifluoromethoxybenzenesulphonyl chloride (0.13g). Yield 0.097g

m/e 428 (M-1⁺, 100%)

\(^1\)H NMR (D6-DMSO) δ 8.03 (1H, dd), 7.87 (1H, s), 7.82-7.74 (1H, m), 7.60-7.52 (2H, m), 3.92 (3H, s)

MP 156-157°C

**Example 50**

3-Chloro-*N-(5-chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide*

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.1g) and 3-chloro-2-methylbenzenesulphonyl chloride (0.15g). Yield 0.085g.

m/e 346 (M-1⁺, 100%)
$^1$H NMR (CDCl$_3$) $\delta$ 8.17 (1H, d), 7.69 (1H, br s), 7.64 (1H, s), 7.61 (2H, d), 7.30 (1H, t), 4.04 (3H, s), 2.73 (3H, s)

MP 150-152°C

Example 51
2-Chloro-$N$-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.1g) and 2-chlorobenzenesulphonyl chloride (0.13g).

Yield 0.082g.

m/e 332 (M+1$^+$, 100%)

$^1$H NMR (CDCl$_3$) $\delta$ 8.33 (1H, d), 7.82 (1H, s), 7.64-7.62 (1H, m), 7.61 (1H, s), 7.50-7.42 (2H, m), 4.04 (3H, s)

MP 190-192°C

Example 52
3-Chloro-$N$-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.1g) and 3-chlorobenzenesulphonyl chloride (0.13g). Yield 0.095g.

m/e 332 (M+1<sup>+</sup>, 100%)

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.14 (1H, s), 8.03 (1H, d), 7.76 (1H, s), 7.68-7.53 (2H, m), 7.46 (1H, t), 4.02 (3H, s)

MP 129-130°C

**Example 53**

4-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

[Chemical structure image]

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.1g) and 4-chlorobenzenesulphonyl chloride (0.13g).

Yield 0.05g.

m/e 332 (M+1<sup>+</sup>, 100%)

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.07 (2H, d), 7.75 (1H, s), 7.56 (1H, s), 7.49 (2H, d), 4.02 (3H, s)

MP 179-180°C

**Example 54**

N-(5-Chloro-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide
Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.1 g) and 2,4-dichlorobenzenesulphonyl chloride (0.13 g). Yield 0.045 g.

m/e 368 (M-1\(^+\), 100%)

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.27 (1H, d), 7.78 (1H, s), 7.63 (1H, s), 7.48 (1H, s), 7.43 (1H, d), 4.05 (3H, s)

MP 170-171°C

Example 55

2,3-Dichloro-\(N\)-[3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide

a) \(N\)-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-\(N\)-[2-(trimethylsilyl)ethoxy]methyl] benzenesulphonamide

A mixture of \(N\)-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 8) (0.40 g), diisopropylethylamine (0.26 g) and [2-(chloromethoxy)ethyl]trimethylsilane (0.25 g) in dichloromethane (50 mL) was stirred at room temperature. After 2 h, the solution was washed with water, dried (MgSO\(_4\)) and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.40 g).
b) 2,3-Dichloro-N-[3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{O} & \quad \text{SO} \\
\text{N} & \quad \text{NH} \\
\text{O} & \quad \text{N}
\end{align*}
\]

\(N\)-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-\{(2-\text{trimethylsilyl})\text{ethoxy}\}\text{methyl}\text{benzenesulphonamide}

(0.30g) and morpholine (0.45g) in acetonitrile (10mL) was heated at 50\(^\circ\)C. After 16h, the solution was evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound with SEM group attached, as a white solid. The solid was dissolved in trifluoroacetic acid (5.0mL) and dichloromethane (5.0mL). After 2h, the solution was evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.06g).

\(m/e\ 417\ (M^{+}, 100\%)

\(^1\text{H NMR (CDCl}_3) \ \delta\ 8.17 (1\text{H, d}, 7.65 (1\text{H, d}, 7.41 (1\text{H, s), 7.34 (1H, t), 7.16 (1H, s),} \\
3.89 (3\text{H, s), 3.80-3.75 (4H, m), 3.40-3.35 (4H, m)\)}

\text{MP\ 167-168^\circ\text{C}}

**Example 56**

2,3-Dichloro-N-[3,5-dimethoxy-2-pyrazinyl]benzenesulphonamide
**Example 57**

2,3-Dichloro-N-[3-methoxy-5-(1-pyrrolyl)2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 55 using pyrrolidine (0.4g) and N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-2,3-N-[2-(trimethylsilyl)ethoxy]methyl]benzenesulphonamide (0.3g). Yield 0.045g. m/e 403 (M+1{sup+}, 100%)
\( ^1\text{H NMR} (\text{CDCl}_3) \delta 8.08 (1\text{H, d}), 7.64 (1\text{H, d}), 7.30 (1\text{H, t}), 7.21 (1\text{H, s}), 6.99 (1\text{H, s}), 3.81 (3\text{H, s}), 3.40-3.35 (4\text{H, m}), 2.00-1.95 (4\text{H, m}) \)

MP 179-180\(^\circ\)C

**Example 58**

3-Chloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 3-chloro-2-methylbenzenesulphonyl chloride (0.14g). Yield 0.13g.

m/e 381 (M-1\(^+\), 100%)

\( ^1\text{H NMR} (\text{CDCl}_3) \delta 8.25 (1\text{H, d}), 7.65 (1\text{H, br s}), 7.62 (1\text{H, d}), 7.35 (1\text{H, t}), 4.04 (3\text{H, s}), 2.73 (3\text{H, s}) \)

MP 177-178\(^\circ\)C

**Example 59**

2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 2,3-dichlorobenzenesulphonyl chloride (0.15g). Yield 0.12g.
m/e 402 (M-1+, 100%)

$^1$H NMR (CDCl$_3$) δ 8.31 (1H, d), 7.81 (1H, br s), 7.72 (1H, d), 7.45 (1H, t), 4.05 (3H, s)

MP 172-173°C

**Example 60**
2-Chloro-\(N\)-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

\[
\begin{align*}
\text{O} & \text{SO} \\
\text{Cl} & \text{N} & \text{NH} \\
\text{Cl} & \text{N} & \text{O} \\
\end{align*}
\]

Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 2-chlorobenzenesulphonyl chloride (0.13g). Yield 0.096g.
m/e 367 (M-1+, 100%)

$^1$H NMR (CDCl$_3$) δ 8.39 (1H, d), 7.79 (1H, br s), 7.58-7.45 (3H, m), 4.04 (3H, s)

MP 217-218°C

**Example 61**
3-Chloro-\(N\)-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

\[
\begin{align*}
\text{O} & \text{SO} \\
\text{Cl} & \text{N} & \text{NH} \\
\text{Cl} & \text{N} & \text{O} \\
\end{align*}
\]

Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 3-chlorobenzenesulphonyl chloride (0.13g). Yield 0.047g.
m/e 367 (M-1+, 100%)
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.19 (1H, s), 8.07 (1H, d), 7.61 (1H, d), 7.59 (1H, br s), 7.50 (1H, t), 4.02 (3H, s)

MP 171-172\(^{\circ}\)C

**Example 62**

4-Chloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

\[
\begin{array}{c}
\text{Cl} \\
O-S-\\n\text{Cl} \\
\text{NHN} \\
O \\
\end{array}
\]

Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 4-chlorobenzenesulphonyl chloride (0.13g). Yield 0.09g.

m/e 367 (M-1\(^+\), 100%)

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.11 (2H, d), 7.57 (1H, br s), 7.50 (2H, d), 4.02 (3H, s)

MP 186-187\(^{\circ}\)C

**Example 63**

2,4-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

\[
\begin{array}{c}
\text{Cl} \\
\text{Cl} \\
\text{O}-S-\\
\text{Cl} \\
\text{NHN} \\
\text{Cl} \\
\text{Cl} \\
\end{array}
\]

Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 2,4-dichlorobenzenesulphonyl chloride (0.15g). Yield 0.076g.
m/e 402 (M-1+, 100%) 
$^1$H NMR (CDCl$_3$) δ 8.30 (1H, d), 7.76 (1H, br s), 7.50 (1H, s), 7.48 (1H, d), 4.05 (3H, s) 
MP 171-172°C

Example 64
3,4-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 3,4-dichlorobenzenesulphonyl chloride (0.15g). Yield 0.11g. 

m/e 402 (M-1+, 100%) 
$^1$H NMR (CDCl$_3$) δ 8.30 (1H, s), 8.01 (1H, d), 7.63 (1H, d), 7.58 (1H, br s), 4.03 (3H, s) 
MP 189-191°C

Example 65
2,3-Dichloro-N-(3-methoxy-5,6-dimethyl-2-pyrazinyl)benzenesulphonamide

Prepared by the method of Example 1 using 3-methoxy-5,6-dimethyl-2-pyrazinamine (0.07g) and 2,3-dichlorobenzenesulphonyl chloride (0.12g). Yield 0.04g. 
m/e 360 (M-1+, 100%)
1H NMR (CDCl₃) δ 8.32 (1H, d), 7.67 (1H, s), 7.65 (1H, d), 7.39 (1H, t), 3.95 (3H, s), 2.28 (3H, s), 2.14 (3H, s)
MP 165-166°C

Example 66
2,3-Dichloro-N-(6-chloro-3,5-dimethoxy-2-pyrazinyl)benzenesulphonamide

a) 2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide

To a stirred solution of 2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide (0.68g) in dichloromethane (20mL) was added triethylamine (0.491mL) followed by 2-(trimethylsilyl)ethoxymethyl chloride (0.328g) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water (50mL) and extracted into ethyl acetate (3x20mL). The combined extracts were dried (MgSO₄), filtered and concentrated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the sub-title compound as a white solid (0.74g).

1H NMR (CDCl₃) δ 8.02 (1H, dd), 7.70 (1H, dd), 7.34 (1H, t), 5.22 (2H, s), 3.96 (3H, s), 3.73 (2H, dd), 0.91-0.79 (2H, m), -0.03 (9H, s).

b) 2,3-Dichloro-N-(6-chloro-3,5-dimethoxy-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[[2-(trimethylsilyl)ethoxy]methyl]benzenesulfonamide (0.10g) was dissolved in methanol (1.0mL) and a solution of sodium methoxide in methanol (0.1mL of a 25% solution in methanol) was added. The reaction was stirred at room temperature for 30 min and was concentrated. The residue was dissolved in trifluoroacetic acid (2.0mL) and was stirred at room temperature for 30 min. The reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.028g).

m/e 397 (M-1⁺, 100%)

1H NMR (CDCl₃) δ 8.26 (1H, d), 7.69 (1H, d), 7.41 (1H, t), 7.41 (1H, br s), 4.02 (3H, s), 3.91 (3H, s)

MP 163-165°C

**Example 67**

2,3-Dichloro-N-[6-chloro-3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide

2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[[2-(trimethylsilyl)ethoxy]methyl]benzenesulfonamide (Example 66 part a) (0.10 g) was dissolved in THF (1.0mL) and a solution of morpholine (0.05g) in THF (0.1mL) was added. The reaction was stirred at room temperature for 30 min and was concentrated.
The residue was dissolved in trifluoroacetic acid (2.0mL) and dichloromethane (2.0mL) and was stirred at room temperature for 30 min. The reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.042g).

m/e 452 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 8.28 (1H, dd), 7.69 (1H, dd), 7.49 (1H, br s), 7.43 (1H, t), 3.96 (3H, s), 3.79 (4H, dd), 3.28 (4H, dd)

MP 150-151°C

Example 68
2,3-Dichloro-N-[6-chloro-5-(2-hydroxyethylamino)-3-methoxy-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 67 using 2-aminoethanol (0.05g) and 2,3-dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (0.1g). Yield 0.015g.

m/e 426 (M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 10.31 (1H, s), 7.91 (2H, dd), 7.52 (1H, t), 6.89 (1H, br s), 4.71 (1H, t), 3.63 (3H, s), 3.53 (2H, dd), 3.40 (2H, dd)

Example 69
2,3-Dichloro-N-[6-chloro-5-dimethylamino-3-methoxy-2-pyrazinyl]benzenesulphonamide
Prepared by the method of Example 67 using dimethylamine (5mL of a 2M solution in tetrahydrofuran) and 2,3-dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide (0.1g). Yield 0.015g.

\[ m/e \text{ 410 (M-1}\text{, 100\%)} \]

\(^1\text{H NMR (D6-DMSO)} \delta \text{ 7.99-7.93 (2H, m), 7.56 (1H, t), 3.74 (3H, s), 2.99 (6H, s)} \]

\text{MP 145-146}\text{°C}

**Example 70**

2,3-Dichloro-N-[6-chloro-3-methoxy-5-(2-methoxyethoxy)-2-pyrazinyl]benzenesulphonamide

Sodium hydride (0.019g of 60% dispersion in oil) was added to a solution of 2,3-dichloro-
\( N\)-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide (0.25g) in 2-methoxyethanol (3.0mL) at room temperature. After 16h, the solvent was evaporated and trifluoroacetic acid (2.0mL) added. After 1h, the reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.08g).

\[ m/e \text{ 442 (M+1}\text{, 100\%)} \]

\(^1\text{H NMR (CDCl}_3\text{)} \delta \text{ 8.24 (1H, dd), 7.70 (1H, dd), 7.41 (1H, t), 4.50-4.40 (2H, m), 3.96 (3H, s), 3.80-3.70 (2H, m), 3.42 (3H, s)} \]

\text{MP 193-194}\text{°C}
Example 71

2,3-Dichloro-N-[6-chloro-5-hydroxy-3-methoxy-2-pyrazinyl]benzenesulphonamide

5 tetrabutylammonium hydroxide (0.28g of 40% aqueous solution) was added to a solution of 2,3-dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[(2-(trimethylsilyl)ethoxy)methyl] benzenesulfonamide (0.25g) in 1,2-dimethoxyethane (3.0mL) at room temperature. After 16h, the solution was diluted with ethyl acetate (20mL). The organic solution was washed with aqueous citric acid (10mL) and brine, dried (MgSO₄) and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.08g). The solid was dissolved in trifluoroacetic acid (2.0mL) and dichloromethane (2.0mL) and stirred at room temperature for 1h. The reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.027g).

m/e 384 (M+1⁺, 100%)

1H NMR (CDCl₃) δ 12.56 (1H, s), 10.87 (1H, s), 7.96 (2H, t), 7.56 (1H, t), 3.74 (3H, s)

Example 72

2,3-Dichloro-N-[6-methoxy-5-[(2,2')bipyrazinyl)]benzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-[(2-(trimethylsilanyl)ethoxy)methyl]benzenesulphonamide (Example 55 part a) (0.70g), tetrakis(triphenylphosphine)palladium(0) (0.1g) and 2-(tributylstannanyl)pyrazine (0.50g) in toluene (20mL) was heated under nitrogen at 100°C. After 16h, chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound protected with the SEM group as a white solid. The solid was dissolved in trifluoroacetic acid (2.0mL) and dichloromethane (2.0mL) and stirred at room temperature for 1h. The reaction mixture was concentrated, toluene added and evaporated. The title compound crystallised from acetonitrile to give a white solid (0.38g).

m/e 410 (M-1\(^\dagger\), 100%)

\( ^1H \text{ NMR (D6 DMSO)} \delta 9.35 (1H, s), 8.69 (1H, d), 8.67 (1H, d), 8.40 (1H, br s), 8.14 (1H, d), 7.96 (1H, d), 7.61 (1H, t), 4.07 (3H, s) \)

MP 199-200°C

**Example 73**

4-[5-(2,3-Dichlorobenzenesulphonamino)-6-methoxy-2-pyrazinloyloxy]benzoic acid

![Chemical Structure](image)

4-Hydroxybenzoic acid *tert* butyl ester (0.13g), N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-[(2-(trimethylsilanyl)ethoxy)methyl]benzenesulphonamide (Example 55 part a) (0.35g) and caesium carbonate (0.42g) in acetonitrile (10mL) was heated at 50°C. After 12h, the mixture was diluted with ethyl acetate, washed with water, dried (MgSO\(_4\)) and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound protected with the SEM group and *tert* butyl group as an oil. The oil was dissolved in trifluoroacetic acid (2.0mL) and *tert* butyl group as an oil. The reaction mixture was concentrated, toluene added and evaporated to give the title compound as a white solid (0.19g).

m/e 468 (M-1\(^\dagger\), 100%)
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.28 (1H, d), 8.11 (2H, d), 7.80 (1H, br s), 7.71 (1H, d), 7.45 (2H, m), 7.12 (2H, d), 3.89 (3H, s)  
MP 186-187\(^\circ\)C

**Example 74**

2,3-Dichloro-\(\text{N-}(3,5\)-dichloro-2-pyrazinyl\)benzenesulphonamide

\[
\begin{array}{c}
\text{Cl} \\
\text{S=O} \\
\text{Cl} \\
\text{O} \\
\text{Cl} \\
\text{N} \\
\text{NH} \\
\text{Cl} \\
\text{Cl} \\
\end{array}
\]

Prepared by the method of Example 1 (reaction performed at room temperature) using 3,5-dichloro-2-pyrazinamine (2.0g) and 2,3-dichloro benzenesulphonyl chloride (2.94g). Yield 3.0g.  
m/e 372 (M-1\(^+\), 100%)  
\(^1\)H NMR (D6 DMSO) \(\delta\) 8.29 (1H, s), 8.06 (1H, dd), 7.94 (1H, dd), 7.57 (1H, t)  
MP 181-182\(^\circ\)C

**Example 75**

2,3-Dichloro-\(\text{N-}(6\text{-chloro-3-methoxy-5-}\{2\text{-methoxyethylamino}\}\text{-2-pyrazinyl}\)benzenesulphonamide

\[
\begin{array}{c}
\text{Cl} \\
\text{S=O} \\
\text{Cl} \\
\text{O} \\
\text{Cl} \\
\text{N} \\
\text{NH} \\
\text{O} \\
\end{array}
\]

Prepared by the method of Example 67 using 2-methoxyethylamine (3mL) and 2,3-dichloro-\(\text{N-}(5,6\)-dichloro-3-methoxy-2-pyrazinyl)-\(\text{N-}\{2\text{-}(\text{trimethylsilyl})\text{ethoxy}\}\text{methyl}\)benzenesulphonamide (0.24g). Yield 0.08g.
m/e 439 (M+1⁺, 100%)

\(^1\)H NMR (D6-DMSO) δ 10.32 (1H, s), 7.93-7.88 (2H, m), 7.52 (1H, t), 7.10 (1H, s), 3.65 (3H, s), 3.40-3.10 (4H, m), 1.75 (3H, s)

**Example 76**

\(N\)-[2-[3-Chloro-5-(2,3-dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylamino]ethyl]acetamide

![Chemical structure](image)

2,3-Dichloro-\(N\)-[5,6-dichloro-3-methoxy-2-pyrazinyl]-\(N\)-[[2-(trimethylsilyl)ethoxy]methyl]benzenesulphonamide (Example 66 part a) (0.26g) was dissolved in acetonitrile (1.0mL) and \(N\)-acetylenediamine (0.055mL) and triethylamine (0.19mL) added. After 48h, the reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate gave the title compound protected with the SEM group, as an oil (0.13g). The oil was dissolved in dichloromethane (2.0mL) and boron trifluoride etherate (0.14mL) added. After 2h, ethyl acetate (20mL) was added and the mixture washed with 5% aqueous citric acid (5mL), dried (MgSO₄) and evaporated. Chromatography on silica gel eluting with ethyl acetate gave the title compound as a solid (0.031g).

m/e 470 (M+1⁺, 100%)

\(^1\)H NMR (D6-DMSO) δ 10.32 (1H, s), 7.93-7.88 (2H, m), 7.52 (1H, t), 7.10 (1H, s), 3.65 (3H, s), 3.40-3.10 (4H, m), 1.75 (3H, s)

MP 150-152°C

**Example 77**

2,3-Dichloro-\(N\)-[5-(4-hydroxymethyl-1-piperidinyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide
Prepared by the method of Example 55 using 4-(hydroxymethyl)piperidine (0.4g) and N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (0.3g). Yield 0.012g.

\[ m/e \text{ 447 (M}^+\text{, 100\%)} \]

\[ ^1H \text{ NMR (CDCl}_3\text{) } \delta 8.14 \text{ (1H, dd), 7.65 (1H, dd), 7.33 (1H, t), 7.20 (1H, s), 4.20 -4.10 (2H, m), 3.86 (3H, s), 3.60-3.50 (2H, m), 2.90-2.70 (2H, m), 1.90-1.70 (3H, m), 1.40-1.20 (3H, m)} \]

**Example 78**

2,3-Dichloro-N-[5-cyano-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

\[ N-[5-\text{Bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl}-2,3-\text{dichlorobenzenesulphonamide}
\]

(Example 34) (0.15g), tetrakis(triphenylphosphine)palladium(0) (0.04g) and zinc cyanide (0.03g) in N,N-dimethylformamide (5.0mL) was heated at 70°C. After 5h, the mixture was diluted with ethyl acetate (30mL) and washed with 5% aqueous citric acid (5mL), dried (MgSO\(_4\)) and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures containing 1% acetic acid gave the title compound as a white solid (0.058g).

\[ m/e \text{ 436 (M}^+\text{, 100\%) } \]
\[^1H\] NMR (D6 DMSO) \(\delta\) 7.65 -7.6 (2H, m), 8.29 (1H, dd), 7.99 (1H, s), 7.78 (1H, d), 7.73 (1H, dd), 7.46 (1H, t), 7.40-7.35 (1H, m), 5.45 (2H, s)

MP 222-224°C

Example 79
2,3-Dichloro-\(N\)-(6-chloro-3-methoxy-5-methylamino-2-pyrazinyl)benzenesulphonamide

\[
\begin{array}{c}
\text{Cl} \\
\text{O=S=O} \\
\text{Cl} \\
\text{NH} \\
\text{O} \\
\text{Cl} \\
\text{N} \\
\text{N} \\
\end{array}
\]

3-Dichloro-\(N\)-(5,6-dichloro-3-methoxy-2-pyrazinyl)-\(N\)-\{(2-(trimethylsilyl)ethoxy)methyl\}benzenesulphonamide (Example 66 part a) (0.25 g) was dissolved in methanol (1.0mL) and methylamine (2.0mL of 40% aqueous solution) was added. After 16h, the solution was partitioned between water and ethyl acetate. The organic layer was dried (MgSO\(_4\)) and evaporated. The residue was dissolved in dichloromethane (2.0 mL) and boron trifluoride etherate (0.25mL) added. After 1h, ethyl acetate (20mL) was added and the solution washed with 5% aqueous citric acid (5mL), dried (MgSO\(_4\)) and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.05g).

m/e 395 (M\(^{+}\), 100%)
\[^1H\] NMR (D6-DMSO) \(\delta\) 10.27 (1H, s), 7.95-7.87 (2H, m), 7.51 (1H, dd), 7.10-7.00 (1H, m), 3.64 (3H, s), 2.84 (3H, s)

MP 185-186°C

Example 80
2,3-Dichloro-\(N\)-(3-methoxy-5-methylsulphonyl-2-pyrazinyl)benzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-[[2-(trimethylsilanyl)ethoxy]methyl]benzenesulphonamide (0.30g) and sodium thiomethoxide (0.05g) in acetonitrile (10mL) was stirred at room temperature. After 2h, the solution was evaporated. Chromatography on silica gel eluting with ethyl acetate/isoheptane mixtures gave the title compound with SEM group attached. The compound was dissolved in trifluoroacetic acid (5mL). After 2h, toluene (20mL) was added and the solution evaporated. Chromatography on silica gel eluting with ethyl acetate/isoheptane mixtures gave the title compound as a white solid (0.16g).

mass 380 (M+H+ , 100%) 

1H NMR (CDCl3) δ 8.25 (1H, d), 7.70 (1H, s), 7.68 (1H, d), 7.52 (1H, s), 7.39 (1H, t), 4.03 (3H, s), 2.48 (3H, s) 

MP 141-142°C

Example 81

2,3-Dichloro-N-[5-(2,4-difluorophenyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide

a) 5-(2,4-difluorophenyl)-3-methoxy-2-pyrazinamine

5-Bromo-3-methoxy-2-pyrazinamine (0.3g), cesium fluoride (0.8g), 2,4-difluorobenzeneboronic acid (0.4g) and [1,1’-bis(diphenylphosphino)ferrocene]palladium (II) chloride (0.04g) in methanol (20mL) was heated at 70°C. After 6h, the solvent was evaporated and the residue purified by chromatography on silica eluting with ethyl acetate/isoheptane mixtures to give the sub-title compound (0.2g).
b) 2,3-Dichloro-N-[5-(2,4-difluorophenyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 1 using 5-(2,4-difluorophenyl)-3-methoxy-2-
pyrazinamine (0.2g) and 2,3-dichlorobenzenesulphonyl chloride (0.2g). Yield 0.06g.  
m/e 444 (M-1\(^+\), 100\%)
\(^1\)H NMR (D6-DMSO) \(\delta\): 15 (1H, d), 8.05 -7.95 (2H, m), 7.93 (1H, d), 7.60 (1H, t), 7.45-
7.35 (1H, m), 7.30-7.20 (1H, m), 4.03 (3H, s)
MP 169-170°C

**Example 82**
[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphanyl]acetic acid  
methyl ester

\(N\)-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-\(N\)-[\{2-
(trimethylsilyl)ethoxy\}methyl]benzenesulphonamide
(0.40g), mercaptoacetic acid methyl ester (0.1g) and caesium carbonate (0.6g) in  
acetonitrile (10mL) was stirred at room temperature. After 16h, the solution was diluted  
with dichloromethane, filtered and evaporated. Chromatography on silica gel eluting with  
ethyl acetate/isohexane mixtures gave the title compound with SEM group attached. The  
compound was dissolved in trifluoroacetic acid (5mL). After 2h, toluene (20mL) was
added and the solution evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.15g). m/e 438 (M+1⁺, 100%)

\[ \text{H NMR (CDCl}_3\text{)} \delta \text{2.62 (1H, dd), 7.73 (1H, s), 7.68 (1H, dd), 7.59 (1H, s), 7.41 (1H, t), 3.99 (3H, s), 3.80 (2H, s), 3.71 (3H, s)} \]

MP 152-153°C

Example 83
[5-(2,3-Dichlorobenzenesulphonylamo)-6-methoxy-2-pyrazinylsulphonyl]acetic acid

\[
\begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{S} \\
\text{O} \\
\text{NH} \\
\text{HO} \text{-} \text{S} \\
\end{array}
\]

[5-(2,3-Dichlorobenzenesulphonylamo)-6-methoxy-2-pyrazinylsulphonyl]acetic acid methyl ester (Example 82) (0.1g) and lithium hydroxide (0.04g) in methanol (5mL) and water (1mL) was stirred at room temperature. After 2h, the mixture was evaporated and saturated aqueous citric acid (5mL) added. The white solid was collected, washed with water and dried. Yield 0.07g.

m/e 424 (M+1⁺, 100%)

\[ \text{H NMR (CDCl}_3\text{)} \delta \text{2.72 (1H, dd), 7.90 (1H, br s), 7.70 (1H, dd), 7.61 (1H, s), 7.40 (1H, t), 3.98 (3H, s), 3.80 (2H, s)} \]

MP 138-140°C

Example 84
2,3-Dichloro-N-[5-(2-chlorobenzylsulphonyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide
Prepared by the method of Example 82 using 2-chlorobenzylmercaptan (0.15g) and N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-[2-(trimethylsilyl)ethoxy]methyl]benzenesulphonamide (0.4g). Yield 0.18g.
m/e 492 (M+1⁺, 100%)
¹H NMR (CDCl₃) δ 8.26 (1H, dd), 7.73 (1H, s), 7.69 (1H, dd), 7.53 (1H, s), 7.40-7.30 (3H, m), 7.20-7.10 (2H, m), 4.39 (2H, s), 4.02 (3H, s)
MP 119-120°C

Example 85

2,3-Dichloro-N-[6-chloro-5-(3-hydroxy-1-azetidinyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide

2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[(2-(trimethylsilyl)ethoxy]methyl]benzenesulphonamide (Example 66 part a) (0.20 g), azetidin-3-ol hydrochloride (0.082g) and triethylamine (0.25mL) in acetonitrile (3mL) and water (0.5mL) was stirred at room temperature. After 2h, the mixture was evaporated and triturated with diethyl ether. The ethereal solution was evaporated and the residue dissolved in a 1molar solution of tetrabutylammonium fluoride in THF (6mL). After 16h,
the reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.024g).

m/e 442 (M+1\(^+\), 100%)

\(^1\)H NMR (D6-DMF) \(\delta\) 10.58 (1H, s), 7.92 (2H, d), 7.54 (1H, t), 5.66 (1H, s), 4.49 (1H, s), 4.36 (2H, t), 3.88 (2H, m), 3.67 (3H, s)

MP 93-95°C

**Example 86**

2,3-Dichloro-\(\text{N-}[5\text{-methyl-3-(1-oxy-3-pyrazinylmethoxy)-2-pyrazinyl}]benzenesulphonamide\)

![Chemical Structure](image)

2,3-Dichloro-\(\text{N-}[5\text{-methyl-3-(3-pyridinylmethoxy)-2-pyrazinyl}]benzenesulphonamide\) (Example 24) (0.2g) and 3-chloroperbenzoic acid (0.35g) in dichloromethane (4mL) was stirred at room temperature. After 0.5h, chromatography on silica gel eluting with 5% methanol in ethyl acetate containing 1% acetic acid gave the title compound as a white solid (0.16g).

m/e 441 (M+1\(^+\), 100%)

\(^1\)H NMR (D6-DMF) \(\delta\) 11.56 (1H, br s), 8.60 (1H, br s), 8.18 (1H, dt), 8.06 (1H, dd), 7.90 (1H, dd), 7.61 (1H, br s), 7.56 (1H, t), 7.50-7.40 (2H, m), 5.36 (2H, s), 2.28 (3H, s)

MP 223-228°C

**Example 87**

2,3-Dichloro-\(\text{N-}[5\text{-chloro-3-(4-pyridinylmethoxy)-2-pyrazinyl}]benzenesulphonamide\)
Prepared by the method of Example 31b using pyridine-4-methanol (0.4g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.4g). Yield 0.47g.

m/e 445 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.63 (2H, d), 8.08 (1H, dd), 7.91 (1H, dd), 7.83 (1H, s), 7.60 (2H, d), 7.55 (1H, t), 5.47 (2H, s)

MP 226-229°C decomposes

Example 88

2,3-Dichloro-N-[5-chloro-3-(1-oxy-4-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 86 using 2,3-dichloro-N-[5-chloro-3-(4-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 87) (0.1g). Yield 0.4g.

m/e 462 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.27 (2H, dt), 8.07 (1H, dd), 7.92 (1H, dd), 7.85 (1H, s), 7.60 (2H, d), 7.57 (1H, t), 5.38 (2H, s)

MP 208-211°C decomposes

Example 89

2,3-Dichloro-N-[5-chloro-3-(2-pyridinylmethoxy)-2-pyrazinyl]
Prepared by the method of Example 31b using pyridine-2-methanol (0.2g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.2g). Yield 0.1g.

m/e 445 (M+1⁺, 100%)

$^1$H NMR (D6-DMSO) δ 8.58 (1H, dt), 8.08 (1H, dd), 7.92 (1H, dd), 7.80-7.90 (2H, m), 7.64 (1H, d), 7.56 (1H, t), 7.18-7.20 (1H, m), 5.47 (2H, s)

MP 147-148°C

**Example 90**

2,3-Dichloro-N-[5-chloro-3-(2-methylsulphonylethoxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 31 using 2-methylsulphonylethanol (0.05g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.1g). Yield 0.06g.

m/e 427 (M-1⁺, 100%)

$^1$H NMR (D6-DMSO) δ 11.50-12.00 (1H, br s), 8.09 (1H, d), 7.95 (1H, d), 7.81 (1H, s), 7.60 (1H, t), 4.47 (2H, t), 2.86 (2H, t), 2.14 (3H, s)

MP 140-141°C

**Example 91**
N-(3-Butoxy-5-chloro-2-pyraziny1)-2,3-dichlorobenzenesulphonamide

Prepared by the method of Example 31 using 1-butanol (0.05g) and 2,3-dichloro-N-(3,5-dichloro-2-pyraziny1)benzenesulphonamide (Example 74) (0.1g). Yield 0.037g.

m/e 410 (M+1⁺, 100%)

\[ ^1H \text{ NMR (D6-DMSO)} \delta 8.08 (1H, d), 7.96 (1H, d), 7.79 (1H, s), 7.57 (1H, t), 4.29 (2H, t), 1.60-1.75 (2H, m), 1.40-1.50 (2H, m), 0.95 (3H, t) \]

MP 133-134°C

Example 92

2,3-Dichloro-N-[5-chloro-3-(2-methyl-3-pyridinylmethoxy)-2-pyraziny1]benzenesulphonamide

Prepared by the method of Example 31 using (2-methyl-3-pyridinyl)methanol (0.15g) and 2,3-dichloro-N-(3,5-dichloro-2-pyraziny1)benzenesulphonamide (Example 74) (0.15g).

Yield 0.06g

m/e 458 (M+1⁺, 100%)

\[ ^1H \text{ NMR (D6-DMSO)} \delta 8.45 (1H, dd), 8.05 (1H, dd), 7.94 (1H, dd), 7.88 (1H, dd), 7.80 (1H, s), 7.53 (1H, t), 7.32 (1H, dd), 5.40 (2H, s), 2.56 (3H, s) \]

MP 214-216°C decomposes

Example 93
2,3-Dichloro-N-[5-chloro-3-(6-methyl-2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 31 using (6-methyl-2-pyridinyl)methanol (0.15g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.15g).
Yield 0.06g.
m/e 461 (M+1⁺, 100%)
¹H NMR (D6-DMSO) δ 8.08 (1H, dd), 7.91 (1H, dd), 7.84 (1H, s), 7.75 (1H, t), 7.55 (1H, t), 7.42 (1H, d), 7.24 (1H, d), 5.42 (2H, s), 2.52 (3H, s)

Example 94
2,3-Dichloro-N-[5-chloro-3-(1-oxy-2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 86 using 2,3-dichloro-N-[5-chloro-3-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 89) (0.2g). Yield 0.1g.
m/e 462 (M+1⁺, 100%)
¹H NMR (D6-DMSO) δ 8.35-8.40 (1H, m), 8.09 (1H, dd), 7.80-7.90 (2H, m), 7.88 (1H, s), 7.58 (1H, t), 7.40-7.50 (2H, m), 5.51 (2H, s)
MP 222-224°C decomposes

Example 95
3-Chloro-N-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2-methylbenzenesulphonamide

a) 5-Chloro-3-(3-pyridinylmethoxy)-2-pyrazinamine

3,5-Dichloro-2-pyrazinamine (1.0g) was added to a stirred suspension of pyridine-3-methanol (1.3g) and sodium hydride (0.70g of 60% dispersion in oil) in 1,2-dimethoxyethane (10mL). After 0.5h, 5% aqueous citric acid was added and the mixture extracted with ethyl acetate. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.2g). Used directly.

b) 3-Chloro-N-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2-methylbenzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinamine (Example 95a) (0.1g) and 3-chloro-2-methylbenzenesulphonyl chloride (0.09g). Yield 0.012g,
m/e 425 (M+1+, 100%)
$^1$H NMR (D6-DMSO) δ 8.78 (1H, d), 8.58 (1H, dd), 7.96 (2H, dt), 7.83 (1H, s), 7.72 (1H, d), 7.46 (1H, dd), 7.40 (1H, t), 5.44 (2H, s), 2.63 (3H, s)
MP 192-193°C

Example 96
3-Chloro-N-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2-fluorobenzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinamine (Example 95a) (0.1 g) and 3-chloro-2-fluorobenzenesulphonyl chloride (0.1 g). Yield 0.034 g.

m/e 429 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.78 (1H, d), 8.60 (1H, dd), 7.99 (1H, dt), 7.80-7.90 (3H, m), 7.48 (1H, dd), 7.40 (1H, t), 5.43 (2H, s)

MP 177-178°C

Example 97

2,3-Dichloro-N-[5-chloro-3-(4-methoxyphenylmethoxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 31 using 4-methoxybenzylalcohol (0.3 g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.5 g). Yield 0.4 g.

m/e 475 (M+1⁺, 100%)
**Example 98**

**N-[5-Bromo-6-chloro-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide**

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

Prepared by the method of Example 1 (reaction performed at room temperature) using 3-bromo-5-chloro-2-pyrazinamine (Example 4a) (1.2g) and 2,3-dichlorobenzenesulphonyl chloride (1.4g). Yield 1.5g.

m/e 418 (M+1⁺, 100%)

**H NMR (D6-DMSO) δ 8.07 (1H, dd), 7.90-7.80 (2H, m), 7.53 (1H, t)**

MP 123-124⁰C

**Example 99**

**2,3-Dichloro-N-[6-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide**

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

Prepared by the method of Example 31 using pyridine-3-methanol (0.22g) and N-(3-bromo-6-chloro-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 98) (0.2g).

Yield 0.04g.

m/e 445 (M+1⁺, 100%)

**H NMR (D6-DMSO) δ 8.77 (1H, br s), 8.59 (1H, dd), 8.12 (1H, dd), 8.00 (1H, dt), 7.92 (1H, dd), 7.84 (1H, s), 7.58 (1H, t), 7.55-7.50 (1H, m), 5.44 (2H, s)**

MP 203-204⁰C
Example 100

2,3-Dichloro-N-[6-chloro-3-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 31 using pyridine-2-methanol (0.22g) and N-(3-bromo-6-chloro-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 98) (0.2g). Yield 0.13g.

m/e 445 (M+1<sup>+</sup>, 100%)  
<sup>1</sup>H NMR (D6-DMSO) δ 8.56 (1H, dd), 8.15 (1H, dd), 7.94 (1H, dd), 7.90-7.80 (2H, m), 7.65-7.60 (1H, m), 7.58 (1H, s), 7.40-7.35 (1H, m), 5.48 (2H, s)

MP 201-203°C

Example 101

N-[5-(2-Aminoethylsulphonyl)-3-(2-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

a) 2,3-Dichloro-N-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-N-[2-trimethylsilylethoxymethyl]benzenesulphonamide
Prepared by the method of Example 66a using 2,3-dichloro-N-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 36) (0.5g). Yield 0.68g. Used directly.

b) N-[5-(2-Aminoethylsulphonyl)-3-(2-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

A mixture of 2,3-dichloro-N-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-N-[2-trimethylsilylthioethylmethyl]benzenesulphonamide (Example 101a) (0.68g), caesium carbonate (1.9g) and 2-aminoethanethiol hydrochloride (0.2g) in acetonitrile (5mL) was stirred at room temperature for 5h. Ethyl acetate was added and the mixture washed with water and brine. The organic layer was dried (MgSO₄) and evaporated. The residue was dissolved in trifluoroacetic acid. After 1h, toluene was added and the mixture evaporated to dryness. HCl (1M in dioxane) was added and the solid collected by filtration (0.2g).

m/e 484 (M⁺, 100%)

¹H NMR (D6-DMSO) δ 8.65 (1H, s), 8.52 (1H, d), 8.20-7.60 (2H, br s), 7.96 (1H, dd), 7.82 (1H, d), 7.62 (1H, d), 7.42-7.38 (1H, m), 7.35 (1H, t), 7.30 (1H, s), 5.24 (2H, s), 3.05-3.00 (2H, m), 2.85-2.80 (2H, m)

Example 102

2,3-Dichloro-N-[5-chloro-3-(6-methoxy-3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
Prepared by the method of Example 31 using (6-methoxy-3-pyridinyl)methanol (0.3g) and 2,3-dichloro-\(N\)-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.3g). Yield 0.15g.

m/e 474 (M+1\(^+\), 100%)

\(^1\)H NMR (D6-DMSO) \(\delta\) 8.32 (1H, d), 8.04 (1H, dd), 7.91 (1H, dd), 7.85-7.80 (2H, m), 7.86 (1H, d), 7.55 (1H, t), 6.86 (1H, dd), 5.33 (2H, s), 3.87 (3H, s)

**Example 103**

\(N\)-[3-(3-Bromophenylmethoxy)-5-chloro-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide.

Prepared by the method of Example 31b using 3-bromobenzylalcohol (1.3g) and 2,3-dichloro-\(N\)-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (1.1g). Yield 1.1g.

m/e 522 (M+1\(^+\), 100%)

\(^1\)H NMR (D6-DMSO) \(\delta\) 8.07 (1H, dd), 7.92 (1H, dd), 7.85 (1H, s), 7.78 (1H, s), 7.60-7.50 (3H, m), 7.37 (1H, t), 5.40 (2H, s)
Example 104
3-[6-Chloro-3-(2,3-dichlorobenzensulphonylamino)-2-pyrazinyl]oxymethyl|benzoic acid methyl ester

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

\[N-[3-(3-Bromophenylmethoxy)-5-chloro-2-pyrazinyl]-2,3-dichlorobenzesulphonamide\] (Example 103) (1.0g) and \(\text{bis(triphenylphosphine)palladium dichloride}\) (0.4g) in methanol (15mL) and triethylamine (7mL) was heated at 100°C under an atmosphere of carbon monoxide (6 barr). After 20h, the mixture was filtered and evaporated. The residue was dissolved in ethyl acetate. The organic solution was washed with brine, aqueous citric acid, dried (MgSO₄) and evaporated. Chromatography on silica gel eluting with ethyl acetate/iso-hexane mixtures gave the title compound as a white solid (0.65g).

\[\text{m/e 503 (M}^{+}\text{, 100%)}\]

\[1^\text{H NMR (D6-DMSO)} \delta 8.11 (1H, s), 8.05 (1H, dd), 7.95 (1H, d), 7.90 (1H, dd), 7.84 (1H, s), 7.80 (1H, d), 7.60-7.50 (2H, m), 5.46 (2H, s), 3.88 (3H, s)\]

MP 175-176°C

Example 105
3-[6-Chloro-3-(2,3-dichlorobenzensulphonylamino)-2-pyrazinyl]oxymethyl|benzoic acid
A mixture of 3-[[6-chloro-3-(2,3-dichlorobenzensulphonylamino)-2-
pyrazinyl]oxy]methyl]benzoic acid methyl ester (Example 104) (0.3g) and lithium hydroxide
hydrate (0.2g) in water (5mL) and methanol (5mL) was stirred at room temperature. After
3h, hydrochloric acid (2M) was added to acidify the mixture and the solid product was
collected by filtration and dried (0.25g).
m/e 489 (M+1", 100%)
"H NMR (D6-DMSO) δ 13.10-13.00 (1H, br s), 12.00-11.80 (1H, br s), 8.10 (1H, s), 8.05
(1H, dd), 7.85-7.95 (2H, m), 7.82 (1H, s), 7.76 (1H, d), 7.54 (2H, t), 5.46 (2H, s)
MP 218-224°C decomposes

Example 106
2,3-Dichloro-N-[5-chloro-3-(3-hydroxymethylphenylmethoxy)-2-
pyrazinyl]benzenesulphonamide
a) 2,3-Dichloro-N-[[5-chloro-3-[3-(tetrahydro-2-pyran-2-yl)methyl]phenylmethoxy]-2-
pyrazinyl]benzenesulphonamide
Prepared by the method of Example 31 using [3-(tetrahydro-2-
pyran-2-ylloxymethyl)phenyl]methanol (1.99g) and 2,3-dichloro-N-(3,5-dichloro-2-
pyrazinyl)benzenesulphonamide (Example 74) (1.0g). Yield 1.0g. Used directly.

b) 2,3-Dichloro-N-[5-chloro-3-(3-hydroxymethylphenylmethoxy)-2-
pyrazinyl]benzenesulphonamide

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
O & \quad \text{S=O} \\
\text{Cl} & \quad \text{NH} \\
\text{Cl} & \quad \text{O} \\
\text{OH} & \\
\end{align*}
\]

2,3-Dichloro-N-{5-chloro-3-[3-(tetrahydro-2-pyran-2-ylloxymethyl)phenylmethoxy]-2-
pyrazinyl} benzenesulphonamide (Example 106a) (1.0g) in acetic acid (40mL), water
(10mL) and tetrahydrofuran (20mL) was heated at 45°C for 16h and the solution was
evaporated to dryness. Chromatography on silica gel eluting with ethyl acetate/iso-hexane
mixtures gave the title compound as a white solid (0.6g).

m/e 475 (M+1^+, 100%)

^1^H NMR (D6-DMSO) δ 8.05 (1H, dd), 7.91 (1H, dd), 7.82 (1H, s), 7.55 (1H, t), 7.43 (1H,
s), 7.40-7.25 (3H, m), 5.39 (2H, s), 4.52 (2H, s)

MP 162-163°C

Example 107

2,3-Dichloro-N-[5-chloro-3-(3-methylaminomethylphenylmethoxy)-2-
pyrazinyl]benzenesulphonamide

a) 2,3-Dichloro-N-[5-chloro-3-(3-formylphenylmethoxy)-2-
pyrazinyl]benzenesulphonamide
2,3-Dichloro-\(N\)-[5-chloro-3-(3-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 106) (0.6g) and manganese dioxide (1.0g) in tetrahydrofuran (5mL) was stirred at room temperature for 16h. The mixture was diluted with dichloromethane and filtered through celite. The solution was evaporated to dryness and the product crystallised from diethyl ether (0.4g). Used directly.

b) 2,3-Dichloro-\(N\)-[5-chloro-3-(3-methylaminomethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide

A mixture of 2,3-dichloro-\(N\)-[5-chloro-3-(3-formylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 107a) (0.1g), methylamine (2mL of a 2M solution in tetrahydrofuran) and acetic acid (0.2mL) in methanol (2mL) was stirred at room temperature. After 2h, sodium cyanoborohydride (0.03g) was added. After 0.5h, water (2mL) was added and the mixture evaporated to dryness. Chromatography on silica gel eluting with methanol/dichloromethane mixtures gave the title compound as a white solid (0.035g).
m/e 487 (M+1\(^+\), 100%)
Example 108
2,3-Dichloro-N-[5-chloro-3-[(2-hydroxyethylamino)methyl]phenylmethoxy]-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 107b using 2,3-dichloro-N-[5-chloro-3-(3-formylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 107a) (0.1g) and 2-aminoethanol (0.05g). Yield 0.035g.

\[ ^1\text{H NMR (D6-DMSO) } \delta \text{ 9.00-8.80 (2H, br s), 7.93 (1H, d), 7.80-7.20 (7H, m), 5.28 (2H, s), 5.21 (1H, t), 4.20 (2H, s), 3.80-3.60 (2H, m), 3.05-2.95 (2H, m) }\]

MP 196-198°C

Example 109
2,3-Dichloro-N-[5-chloro-3-(4-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide
Prepared by the method of Examples 106a and 106b using [4-(tetrahydro-2-pyran-2-yl)methyl]phenyl)methanol (2.0g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzensulphonamide (Example 74) (1.0g). Yield 0.7g.

m/e 474 (M-1\(^+\), 100%)

\(^1\)H NMR (D6-DMSO) δ 8.05 (1H, dd), 7.91 (1H, dd), 7.83 (1H, s), 7.55 (1H, t), 7.46 (2H, d), 7.33 (2H, d), 5.38 (2H, s), 4.51 (2H, s)

MP 177-178°C

**Example 110**

2,3-Dichloro-N-[5-chloro-3-{4-[(2-hydroxyethylamino)methyl]phenylmethoxy}-2-pyrazinyl]benzensulphonamide

a) 2,3-Dichloro-N-[5-chloro-3-(4-formylphenylmethoxy)-2-pyrazinyl]benzensulphonamide

Prepared by the method of Example 107a using 2,3-dichloro-N-[5-chloro-3-(4-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzensulphonamide (Example 109) (0.65g). Yield 0.64g. Used directly.
b) 2,3-Dichloro-\(N\)-(5-chloro-3-{4-[(2-hydroxyethylamino)methyl]phenylmethoxy}-2-pyrazinyl)benzenesulphonamide

\[
\text{\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\text{O=S=O}};
  \node (b) at (0.5,0) {\text{NN}};
  \node (c) at (1,0) {\text{O}};
  \node (d) at (1.5,0) {\text{Cl}};
  \node (e) at (2,0) {\text{Cl}};
  \node (f) at (2.5,0) {\text{Cl}};
  \node (g) at (3,0) {\text{HNN}};
  \node (h) at (3.5,0) {\text{OH}};
  \node (i) at (4,0) {\text{HNN}};
  \node (j) at (4.5,0) {\text{OH}};
  \node (k) at (5,0) {\text{HNN}};
  \node (l) at (5.5,0) {\text{OH}};
\end{tikzpicture}
\end{center}}
\]

Prepared by the method of Example 107b using 2,3-dichloro-\(N\)-(5-chloro-4-(3-formylphenylmethoxy)-2-pyrazinyl)benzenesulphonamide (Example 110a) (0.1g) and 2-aminoethanol (0.05g). Yield 0.028g.

m/e 517 (M+H\(^{+}\), 100%)

\(^1\)H NMR (D6-DMSO) \(\delta\) 8.75 (2H, br s), 7.93 (1H, dd), 7.61 (1H, dd), 7.54 (4H, s), 7.35 (1H, t), 7.26 (1H, s), 5.26 (2H, s), 5.18 (1H, t), 4.18 (2H, s), 3.70-3.60 (2H, m), 3.00-2.95 (2H, m)

MP 202-205°C

Example 111
2,3-Dichloro-\(N\)-(3-{4-hydroxymethylphenylmethoxy}-2-pyrazinyl)benzenesulphonamide

a) 2,3-Dichloro-\(N\)-(3-{4-(tetrahydro-2-pyranyloxymethyl)phenylmethoxy}-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28a) (0.1g), [4-(tetrahydro-2-pyranloxyethyl)phenyl]methanol (0.27g) and potassium tert-butoxide (2mL of a 1M solution in tetrahydrofuran) in N-methylpyrrolidinone (1mL) was stirred at 50°C. After 2h, aqueous citric acid was added and the mixture extracted with ethyl acetate. The organic solution was washed with water and brine and evaporated to dryness. Used directly.

b) 2,3-Dichloro-N-[3-(4-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide

2,3-Dichloro-N-{3-[4-(tetrahydro-2-pyranloxyethyl)phenylmethoxy]-2-pyrazinyl}benzenesulphonamide (Example 111a) in acetic acid (10mL), water (2.5mL) and tetrahydrofuran (5mL) was heated at 45°C for 16h and the solution was evaporated to dryness. Chromatography on silica gel eluting with ethyl acetate/iso-hexane mixtures gave the title compound as a white solid (0.022g). m/e 440 (M+1⁺, 100%)
Example 112

2,3-Dichloro-N-[5-chloro-3-(2-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide

\[
\text{Cl} \quad \text{Cl} \\
\text{N} \quad \text{S} \quad \text{O} \\
\text{Cl} \quad \text{Cl} \\
\text{O} \quad \text{H} \\
\text{HO} \\
\text{Cl} \\
\text{Cl}
\]

2,3-Dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74).

(0.15g), (2-hydroxymethylphenyl)methanol (0.27g) and potassium tert-butoxide (3mL of a 1M solution in tetrahydrofuran) in N-methylpyrrolidinone (2mL) was stirred at room temperature. After 1h, aqueous citric acid was added and the mixture extracted with ethyl acetate. The organic solution was washed with water and brine and evaporated to dryness.

Chromatography on silica gel eluting with ethyl acetate/iso-hexane mixtures gave the title compound as a white solid (0.027g).

m/e 474 (M+1\(^+\), 100%)

\(^1\)H NMR (D6-DMSO) δ 8.06 (1H, dd), 7.90 (1H, dd), 7.81 (1H, s), 7.60-7.40 (3H, m), 7.37 (1H, t), 7.29 (1H, t), 5.45 (2H, s), 4.64 (2H, s)

Example 113

5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxypyrazine-2-carboxylic acid, methyl ester
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 8) (6.5g) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.7g) in methanol (30mL) and triethylamine (10mL) was heated at 100°C under an atmosphere of carbon monoxide (6 bar). After 5h, the mixture was filtered and evaporated. The residue was dissolved in ethyl acetate. The organic solution was washed with brine, aqueous citric acid, dried (MgSO₄) and evaporated. Chromatography on silica gel eluting with ethyl acetate/iso-hexane mixtures gave the title compound as a white solid (4.8g). m/e 392 (M+1⁺, 100%)  

³H NMR (D6-DMSO) δ 8.13 (2H, dd), 7.95 (1H, dd), 7.60 (1H, t), 3.95 (3H, s), 3.82 (3H, s)  

MP 120-121°C

Example 114

2,3-Dichloro-N-[5-(1-hydroxy-1-methylethyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide

Methylinmagnesium bromide (3mL of a 3M solution in diethyl ether) was added over 3 minutes to a stirred solution of 5-(2,3-dichlorobenzenesulphonylamino)-6-methoxypyrazine-2-carboxylic acid, methyl ester (Example 113) (0.3g) in tetrahydrofuran (10mL) cooled in an ice/water bath. After a further 5 minutes, aqueous citric acid was added and the mixture extracted with ethyl acetate. The organic solution was evaporated to
dryness. Chromatography on silica gel eluting with methanol/dichloromethane mixtures gave the title compound as a white solid (0.15g).

m/e 392 (M+1\(^+\), 100%)

\(^1\)H NMR (D\(_6\)-DMSO) \(\delta\) 11.40-11.30 (1H, br s), 8.07 (1H, dd), 7.93 (1H, d), 7.90-7.80 (1H, br s), 7.59 (1H, t), 5.10-5.05 (1H, br s), 3.88 (3H, s), 1.39 (6H, s)

MP 192-193\(^\circ\)C

**Example 115**

\(\text{N-}[5-(2\text{-Aminoethoxy})-3\text{-methoxy-2-pyrazinyl}]-2,3\text{-dichlorobenzenesulphonamide}\)

\(\text{a) 2,3\text{-Dichloro-N-[5-chloro-3-methoxy-2-pyrazinyl]}-N-\{2-(trimethylsilyl)ethoxy\}methyl\text{-benzenesulphonamide}\)

Prepared by the method of Example 66a using 2,3-dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide (Example 5) (7.0g). Yield 9.8g. Used directly.

b) \(\text{N-}[5-(2\text{-aminoethoxy})-3\text{-methoxy-2-pyrazinyl}]-2,3\text{-dichlorobenzenesulphonamide}\)

2,3-Dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-N-\{2-(trimethylsilyl)ethoxy\}methyl \text{-benzenesulphonamide} (Example 115a) (0.25g) was added to a mixture of ethanolamine (0.05mL) and sodium hydride (0.035g of a 60% dispersion in oil) in 1,2-dimethoxyethane (15mL) at room temperature. After 2h, the mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried (MgSO\(_4\)) and evaporated to dryness. Chromatography on silica gel eluting with
methanol/dichloromethane mixtures gave the title compound containing the SEM ([2- (trimethylsilyl)ethoxy]methyl) protecting group as an oil (0.14g). Trifluoroacetic acid (1mL) and dichloromethane (3mL) were added. After 0.5h at room temperature, toluene was added and the solution evaporated to dryness. HCl (4M in dioxane) was added and the mixture evaporated to dryness. The product was crystallised from diethyl ether (0.075g).

m/e 393 (M+1+, 100%)

$^1$H NMR (D6-DMSO) δ 10.90 (1H, br s), 8.07 (2H, br s), 7.99-7.92 (2H, m), 7.56 (1H, t), 7.49 (1H, s), 4.45 (2H, t), 3.84 (3H, s), 3.25-3.20 (2H, m)

MP 200-205°C

**Example 116**

$N$-$\{5-$\{2$-$Aminoethylthio\}$-6$-$chloro$-3$-$methoxy$-2$-$pyrazinyl\}$-$2$,$3$-$dichlorobenzencesulfonamide$

Prepared by the method of Example 101b using 2,3-dichloro-$N$-$\{5$,$6$-$chloro$-3$-$methoxy$-2$-$pyrazinyl\}$-$2$-$pyrazinyl$-$2$,$3$-$dichlorobenzencesulfonamide (Example 66a) (0.27g). Yield 0.055g.

m/e 443 (M+1+, 100%)

$^1$H NMR (D6-DMSO) δ 8.09 (1H, d), 7.90 (1H, d), 7.58 (1H, t), 3.95 (3H, s), 3.33 (2H, t), 3.14 (2H, t).

MP 185-190°C

**Example 117**

3-$\{5$-$\{2$,$3$-$Dichlorophenyl$-sulphonyl$]a $mino\}$-6$methoxy$-2$-$pyrazinyl$]thio$]propanoic acid, methyl ester
Prepared by the method of Example 101b using 2,3-dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-N-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (Example 115a) (0.25 g) and 3-mercaptopropionic acid, methyl ester (0.06mL). Yield 0.1g. m/e 452 (M+H+, 100%)  

$^1$H NMR (D6-DMSO) δ 11.35 (1H, br s), 8.03 (1H, d), 7.93 (1H, d), 7.66 (1H, s), 7.57 (1H, t), 3.90 (3H, s), 3.58 (3H, s), 3.29 (2H, t), 2.72 (2H, t).  

MP 146-148°C

**Example 118**

2,3-Dichloro-N-[5-bromo-3-methoxy-6-methyl-2-pyrazinyl]benzenesulphonamide

a) 6-Methyl-2-pyrazinamine

Dimethylzinc (100mL of a 2M solution in toluene) was added dropwise over 0.5h to a stirred solution of 6-chloro-2-pyrazinamine (12.9g) and [1,3-bis(diphenylphosphino)propane]nickel(II) chloride (5.4g) in dioxane (200mL) under a nitrogen atmosphere. The reaction mixture was heated at reflux for 18h, then cooled to room temperature and quenched cautiously with iso-propanol (30mL) and methanol (50mL). After removal of solvent *in vacuo*, the residue was partitioned between dichloromethane and aqueous ammonium chloride. The organic phase was filtered through celite, dried (MgSO$_4$), filtered and evaporated to give the crude product as an orange solid. Chromatography on silica gel eluting with ethyl acetate/methanol mixtures gave the title compound (5.1g). Used directly.

b) 3,5-Dibromo-6-methyl-2-pyrazinamine
A solution of bromine (1.85g) in chloroform (5mL) was added dropwise to a stirred solution of 2-amino-6-methylpyrazine (Example 118a) (0.6g) in chloroform (50mL). The reaction mixture was stirred at room temperature for 0.5h, then washed twice with water, dried (MgSO₄), filtered and evaporated to give the crude product as an orange solid. Chromatography on silica gel eluting with dichloromethane gave the title compound (0.95g). Used directly.

c) 5-Bromo-3-methoxy-6-methyl-2-pyrazinamine

A solution of 3,5-dibromo-6-methyl-2-pyrazinamine (Example 118b) (0.9g) was added to a solution of sodium (0.39g) in methanol (30mL) was heated at reflux for 18h. After removal of solvent in vacuo, the residue was partitioned between water and dichloromethane, and the organic phase dried (MgSO₄), filtered and evaporated to give the title compound as a pale yellow solid (0.58g).

m/e 218/220 (M+1⁺, 100%)

\[^{1}\text{H}\text{ NMR (CDCl}_3\text{)}\delta\ 4.70\ (2\text{H, br s}),\ 3.97\ (3\text{H, s}),\ 2.40\ (3\text{H, s})\]

d) 2,3-Dichloro-N-[5-bromo-3-methoxy-6-methyl-2-pyrazinyl]benzenesulphonamide

Sodium hydride (0.5g of a 60% dispersion in oil) was added to a solution of 5-bromo-3-methoxy-6-methyl-2-pyrazinamine (Example 118c) (0.55g) in N-methylpyrrolidinone (25mL). The resultant dark solution was stirred at room temperature for 0.5h before a solution of 2,3-dichlorobenzenesulphonyl chloride (0.67g) in N-methylpyrrolidinone (5mL) was added dropwise. The reaction mixture was stirred at room temperature for 3h, then quenched with aqueous ammonium chloride and partitioned between ethyl acetate and aqueous ammonium chloride (x5). the organic phase was dried (MgSO₄), filtered and evaporated to give the crude product. Chromatography on silica gel eluting with dichloromethane/ acetic acid (200:1) gave the title compound as a pale yellow solid (0.38g).
m/e 424/426/428 (M-1, 100%)
\(^1\)H NMR (CDCl₃) δ 8.29 (1H, d), 7.69 (2H, d), 7.41 (1H, t), 4.01 (3H, s), 2.27 (3H, s)
MP 146-148\(^\circ\)C

Example 119
5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-3-methylpyrazine-2-carboxylic acid, methyl ester

Prepared by the method of Example 113 using 2,3-dichloro-N-[5-bromo-3-methoxy-6-methylpyrazinyl]benzenesulphonamide (Example 118) (0.35g). Yield 0.27g.
m/e 404/406 (M-1, 100%)
\(^1\)H NMR (CDCl₃) δ 8.32 (1H, br s), 8.10 (1H, br s), 7.70 (1H, d), 7.42 (1H, t) 4.06 (3H, s), 3.90 (3H, s), 2.50 (3H, br s).
MP 149-150\(^\circ\)C

Example 120
2,3-Dichloro-N-[5-(hydroxymethyl)-3-methoxy-6-methyl-2-pyrazinyl]benzenesulphonamide

To a stirred solution of 5-(2,3-dichlorobenzenesulphonylamino)-6-methoxy-3-methylpyrazine-2-carboxylic acid, methyl ester (Example 119) (0.19g) in tetrahydrofuran (10mL) under an atmosphere of nitrogen was added a solution of lithium triethylborohydride (1.7mL of a 1M solution in tetrahydrofuran). The reaction mixture was stirred at room temperature for 1h, before quenching with aqueous ammonium chloride
and extraction into dichloromethane. The organic phase was dried (MgSO₄), filtered and evaporated to give the crude product as a colourless oil. Chromatography on silica gel eluting with dichloromethane/ethyl acetate/acetic acid (150:50:1) gave the title compound as a white solid (0.38 g).

m/e 378 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.31 (1H, br d), 7.77 (1H, br s), 7.68 (1H, d), 7.41 (1H, t), 4.55 (2H, d), 4.03 (3H, s), 3.12 (1H, br s), 2.13 (3H, br s).

MP 175-177°C

**Example 121**

2,3-Dichloro-N-[5,6-dichloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

**a)** 5,6-Dichloro-3-(3-pyridinylmethoxy)-2-pyrazinamine

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

To a stirred suspension of sodium hydride (1.20 g of a 60% dispersion in oil) in dry dimethoxymethane (40 mL) was added pyridine-3-methanol (2.18 g) in 1,2-dimethoxymethane (10 mL). The resulting suspension was stirred at room temperature for 0.5 h and then 3,5,6-trichloro-2-aminopyrazine (1.2 g) was added and the mixture stirred at 70°C for 4 h. The reaction mixture was cooled and cautiously added to water (100 mL) and neutralised with 2 M hydrochloric acid. The mixture was extracted with ethyl acetate (2x50 mL), dried (MgSO₄), filtered and concentrated. The residue was purified by chromatography on silical gel eluting with ethyl acetate to afford the sub-titled compound as a white solid (0.29 g).

¹H NMR (CDCl₃) δ 8.73 (1H, s), 8.63 (1H, d), 7.8 (1H, d), 7.35 (1H, dd), 5.42 (2H, s), 4.92 (2H, br s).

**b)** 2,3-Dichloro-N-[5,6-dichloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-(3-pyridinylmethoxy)-2-pyrazinamine (Example 121a) (0.27g) and 2,3-dichlorobenzenesulphonyl chloride (0.27g). Yield 0.17g.

m/e 479 (M+1⁺, 100%)

\(^1\)H NMR (D6-DMSO) δ 8.8 (1H, s), 8.63 (1H, d), 8.11 (1H, d), 8.06 (1H, d), 7.58-7.52 (2H, m), 5.41 (2H, s).

Example 122

3-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-2-fluorobenzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.16g) and 3-chloro-2-fluorobenzenesulphonyl chloride (0.27g). Yield 0.22g.

m/e 354, 352 (M+1⁺, 100%)

\(^1\)H NMR (D6-DMSO) δ 7.94-7.86 (2H, m), 7.82 (1H, s), 7.43 (1H, dt), 3.92 (3H, s).

MP 156-157°C

Example 123

3-Chloro-2-fluoro-N-[3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

a) 3-(3-Pyridinylmethoxy)-2-pyrazinamine
Prepared as for Example 121a using 3-chloro-2-aminopyrazine (0.5 g), pyridine-3-methanol (0.42g) and sodium hydride (0.31g of a 60% dispersion in oil) in N-methylpyrrolidinone (5 mL) to afford the sub-titled compound as a solid (0.62 g).  
$^1$H NMR (CDCl$_3$) $\delta$ 8.73 (1H, d), 8.60 (1H, d), 7.78 (1H, d), 7.60 (1H, d), 7.42 (1H, d), 7.32 (1H, dd), 5.43 (2H, s), 4.77 (2H, br).  
MP 120-122$^\circ$C

b) 3-Chloro-2-fluoro-N-[3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

To a stirred solution of 3-(3-pyridinylmethoxy)-2-pyrazinamine (Example 122a) (0.404 g) in dichloromethane (5mL) and pyridine (1 mL) was added iso-butylchloroformate (0.3mL) and the resulting solution stirred for 20 hours. The reaction mixture was poured into water (20mL) and extracted into ethyl acetate (2x20mL). The combined extracts were dried (MgSO$_4$), filtered and concentrated to afford an oil (0.51 g) that was used without further purification. A portion of the residue (0.15g) was dissolved in 1,2-dimethoxyethane (2 mL) and sodium hydride (0.030g of 60% dispersion in oil) added. The resulting suspension was stirred for 15 minutes and then 3-chloro-2-fluorobenzenesulfonyl chloride (0.137g) in dimethoxyethane (1 mL) was added. The resulting solution was stirred at room temperature for 6h. The reaction mixture was poured into water (20mL) and extracted into ethyl acetate (2x20mL). The combined extracts were dried (MgSO$_4$), filtered and concentrated to afford an oil that was dissolved into methanol (5mL) and water (2mL) and sodium hydroxide (0.04g) was added. The mixture was heated to 60$^\circ$C for 1 hour, cooled and was poured into water (20mL) and extracted into ethyl acetate (2x20ml). The combined extracts were dried (MgSO$_4$), filtered and concentrated to afford an oil that was purified by chromatography on silica gel eluting with ethyl acetate/iso-hexane mixtures followed by ethyl acetate to afford the title compound (0.067g) as a white solid. m/e 395, 397 (M+1$^+$, 100%)  
$^1$H NMR (CDCl$_3$) $\delta$ 8.69 (1H, s), 8.62 (1H, d), 8.06 (1H, t), 7.78 (1H, d), 7.68 (1H, d), 7.69-7.60 (2H, m), 7.34 (1H, dd), 7.26 (1H, dd), 5.43 (2H, s).
Example 124
3-{[(2,3-Dichlorophenyl)sulphonyl]amino}pyrazine-2-carboxylic acid, methyl ester

![Chemical Structure]

To a stirred solution of 2,3-dichlorobenzenesulphonyl chloride (0.246g) and methyl-3-amino-pyrazine-2-carboxylate (0.153g) in 1,2-dimethoxymethane (3mL) was added portionwise sodium hydride (0.1g of a 60% dispersion in oil) over 1 hour. The mixture was stirred at room temperature for 20h, was poured into water (20mL) and extracted into ethyl acetate (2x20mL). The combined extracts were dried (MgSO₄), filtered and concentrated to afford an oil that was purified by chromatography on silica gel eluting with dichloromethane to afford the titled compound (0.085g) as a white solid.

m/e 362/364 (M+H⁺, 100%)  
1H NMR (CDCl₃) δ 10.97 (1H, s), 8.32 (1H, dd), 8.31 (1H, d), 8.25 (1H, d), 7.68 (1H, dd), 7.42 (1H, t), 4.08 (3H, s).
MP 177-178°C

Example 125
N-(5-Bromo-6-chloro-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide

a) 3-Methoxy-5-bromo-6-chloro-2-pyrazinamine

![Chemical Structure]

A stirred solution of 2-amino-6-chloropyrazine (2.0g) and N-bromosuccinimide (13.71g) in chloroform (100 mL) was heated to reflux for 20 hours. The reaction mixture was cooled and concentrated onto silica gel (20g) and the residue loaded onto a column of silica gel (5cm x 2cm) and the column was eluted with dichloromethane. Concentration afforded 3,5-dibromo-6-chloro-2-pyrazinamide that was dissolved into methanol (200 mL) and sodium methoxide (32g of a 25% solution in methanol) added. The reaction was heated to 70°C for 1.5h, cooled and concentrated to approx. 50 mL capacity. The reaction mixture was poured into water (200mL) and the sub-titled adduct (2.0g) collected as an off-white solid.

m/e 235, 237 (M+H⁺, 100%)
b) \(N\)-(5-Bromo-6-chloro-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide

\[\text{Procedure as for Example 1 (reaction performed at room temperature) using 3-methoxy-5-bromo-6-chloro-2-pyrazinamine (Example 125a) (0.5g) and 2,3-dichlorobenzenesulphonyl chloride (2.21g). Yield 3.2g.}\]
\[m/e 445, 447 (M-1^+ , 100\%)\]
\[^1\text{H NMR (CDCl}_3\text{)} \delta 8.32 (1H, dd), 7.79 (1H, br), 7.72 (1H, dd), 7.45 (1H, t), 4.05 (3H, s).\]
\[\text{MP 177-178°C}\]

\textbf{Example 126}

\textit{3-Chloro-5-\{[(2,3-dichlorophenyl)sulphonyl]amino\}-6-methoxypyrazine-2-carboxylic acid, methyl ester}

\[\text{Prepared by the method of Example 113 using } N\text{-}(5-bromo-6-chloro-3-methoxypyrazin-2-yl)-2,3-dichlorobenzenesulfonamide (Example 125) (1.0g). Yield 0.92g.}\]
\[m/e 426, 428 (M-1^+ , 100\%)\]
\[^1\text{H NMR (CDCl}_3\text{)} \delta 8.36 (1H, dd), 8.05 (1H, br), 7.73 (1H, dd), 7.47 (1H, t), 4.09 (3H, s), 3.92 (3H, s).\]
\[\text{MP 200-201°C}\]

\textbf{Example 127}

\textit{2,3-Dichloro-N-[6-chloro-5-(hydroxymethyl)-3-methoxypyrazin-2-yl]benzenesulphonamide}

\[\text{Prepared as for Example 120 using 3-chloro-5-\{[(2,3-dichlorophenyl)sulphonyl]amino\}-6-methoxypyrazine-2-carboxylic acid, methyl ester (Example 126) (0.105g). Yield 0.072g.}\]
m/e 397, 399 (M-1\(^+\), 100%)

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.34 (1H, dd), 7.84 (1H, br), 7.74 (1H, dd), 7.45 (1H, t), 4.63 (2H, d), 4.07 (3H, s), 2.83 (1H, t).

MP 145-147\(^\circ\)C

Example 128

2,3-Dichloro-N-\{3-[(6-methoxy-3-pyridyl)methoxy]-2-pyrazinyl\}benzenesulphonamide

Prepared by the method of Example 28b using 2,3-dichloro-N-(3-chloro-2-pyrazinyl) benzenesulphonamide (Example 28a) (0.338g) and (6-methoxy-3-pyridyl)methanol (0.21g). Yield 0.23g.

m/e 439, 440 (M-1\(^+\), 100%)

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.28-8.26 (2H, m), 7.70-7.65 (3H, m), 7.60 (1H, br), 7.39 (1H, t), 6.80 (2H, d), 5.36 (2H, s), 3.97 (3H, s).

MP 187-188\(^\circ\)C

Example 129

2,3-Dichloro-N-[6-chloro-3-methoxy-5-(methoxymethyl)-2-pyrazinyl]benzenesulphonamide

To a stirred solution of 2,3-dichloro-N-[6-chloro-5-(hydroxymethyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide (Example 127) (0.1g) in tetrahydrofuran (3mL) was added manganese dioxide (0.131g) and the resulting suspension was stirred for 20h, filtered and concentrated. The residue was taken up into methanol (3mL) and acetic acid (0.1mL). To this solution was added ethylamine hydrochloride (0.081g) and sodium cyanoborohydride (0.051g). The resulting mixture was stirred for 20h and concentrated
onto silical gel (1 g) and eluting with methanol/dichloromethane mixtures to afford the

titled compound (0.029 g) as a white solid.

m/e 412, 414 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 8.35 (1H, dd), 7.72 (1H, d), 7.45 (1H, t), 4.45 (2H, s), 4.05 (3H, s),
3.43 (3H, s).

MP 193-196°C

**Example 130**

2-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-3-fluorobenzenesulphonamide

a) N-(5-Chloro-3-methoxy-2-pyrazinyl)-3-fluorobenzenesulphonamide

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<table>
<thead>
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<tbody>
<tr>
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By the method outlined in Example 1 (reaction performed at room temperature) using 5-
chloro-3-methoxy-2-pyrazinamine (0.798g) and 3-fluorobenzenesulphonyl chloride
(1.17g). Yield 0.64g.

m/e 316 (M-1⁺, 100%)

b) 2-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-3-fluorobenzenesulphonamide.

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<table>
<thead>
<tr>
<th>Cl</th>
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</tbody>
</table>
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A solution of N-(5-chloro-3-methoxy-2-pyrazinyl)-3-fluorobenzenesulphonamide

(Example 130a) (0.159g) in dry tetrahydrofuran (3mL) was added to a stirred solution of
lithium di-iso-propylamide (prepared from di-iso-propylamine (0.151g) and n-butyl
lithium (2.5M in hexanes)) in tetrahydrofuran (7.0mL) at −78°C. The resulting solution
was stirred at −78°C for 15 minutes and then hexachloroethane (0.472g) in tetrahydrofuran
(2mL) was added and the mixture allowed to attain room temperature over a 5 hour period.
The reaction was quenched by the addition of 1N hydrochloric acid (10mL) and extracted
into ethyl acetate (2x20mL). The combined extracts were dried (MgSO₄), filtered and
concentrated to afford an oil that was purified by chromatography on silica gel eluting with
ethyl acetate/iso-hexane mixtures gave the titled compound (0.086 g) as a white solid.
m/e 350, 352 (M-1⁺, 100%)
$^1$H NMR (CDCl$_3$) $\delta$ 8.16 (1H, dd), 7.81 (1H, br), 7.62 (1H, s), 7.48-7.37 (2H, m), 4.06 (3H, s)
MP 159-159.5°C

Example 131
2-Chloro-3-fluoro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide

a) 3-Fluoro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide

By the method outlined in Example 1 (reaction performed at room temperature) using 3-chloro-2-pyrazinamine (1.29g), 3-fluorobenzenesulphonyl chloride (2.13g). The crude adduct was reacted with a solution of sodium methoxide (10mL of a 25% solution in methanol) in methanol (20mL) to afford the sub-titled compound (2.36g) as a solid.
m/e 284 (M+1+, 100%)
MP 142-143°C

b) 2-Chloro-3-fluoro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide

Prepared as for Example 130, 3-fluoro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide (Example 131a) (0.283g), lithium di-iso-propylamine (prepared from di-iso-propylamine (0.30g) and n-butyl lithium (0.96mL of a 2.5M solution in hexanes)) and hexachloroethane (0.994g) in anhydrous tetrahydrofuran (20mL) afforded the titled compound (0.092g) as a white solid after re-crystallisation from tert-butyl methylether.
m/e 318, 320 (M-1, 100%)
$^1$H NMR (CD$_3$OD) $\delta$ 8.11-8.08 (2H, m), 7.57 (1H, d), 7.57-7.50 (3H, m), 4.0 (3H, s).
MP 144-145°C

Example 132
2-Chloro-3-methoxy-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide
a) 3-Methoxy-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide

By the method outlined in Example 1 (reaction performed at room temperature) using 3-chloro-2-aminopyrazine (0.83 g), 3-methoxybenzenesulfonyl chloride (1.44 g). The crude adduct was reacted with a solution of sodium methoxide (10 mL of a 25% solution in methanol) in methanol (20mL) to afford the sub-titled compound (1.41g) as a solid.
m/e 296 (M+1⁺, 100%)
MP 133-134°C

b) 2-Chloro-3-methoxy-N-(3-methoxypyrazin-2-yl)benzenesulphonamide

Prepared as for Example 130, 3-methoxy-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide (Example 132a) (0.295g), lithium di-iso-propylamide (prepared from di-iso-propylamine (0.30g) and n-butyl lithium (0.96mL of a 2.5M solution in hexanes)) and hexachloroethane (0.994g) in anhydrous tetrahydrofuran (20mL) afforded the titled compound (0.152g) as a white solid after re-crystallisation from tert-butyl methylether.
m/e 328, 329 (M-1⁺, 100%)
1H NMR (CDCl₃) δ 7.97 (1H, d), 7.92 (1H, br), 7.65 (1H, d), 7.60 (1H, d), 7.41 (1H, t), 7.15 (1H, t), 3.99 (3H, s), 3.91 (3H, s).
MP 151-152°C

Example 133

N-[5-Bromo-3-[(2S)-2-pyrrolidinylmethoxy]-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
Sodium hydride (0.026g of a 60% dispersion in oil) was added to a mixture of 2,3-dichloro-N-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (Example 31a) (0.1g) and 2-hydroxymethylpyrrolidine-1-carboxylic acid tert-butyl ester (0.088g) in 1,2-dimethoxyethane (2mL). After 0.5h, the reaction mixture was partitioned between 2N hydrochloric acid and ethyl acetate. The organic solution was dried (MgSO₄) and evaporated. Chromatography on silica gel eluting with ethyl acetate/iso-hexane mixtures gave the title compound protected with the BOC (tert-butoxycarbonyl) group (0.11g) as an oil. This product was dissolved in dichloromethane (6mL) and trifluoroacetic acid (2mL). After 2h, toluene was added and the solution evaporated to dryness. Crystallisation from diethyl ether gave the product as a white solid (0.083g).

m/e 482 (M+1⁺, 100%)

¹H NMR (D₆-DMSO) δ 8.99 (1H, br), 8.65 (1H, br s), 8.13 (1H, d), 7.95 (1H, d), 7.84 (1H, s), 7.59 (1H, t), 4.57 (1H, dd), 4.39 (1H, t), 4.0 (1H, br s), 3.3 (2H, d), 2.20-2.05 (1H, m), 2.05-1.90 (2H, m), 1.85-1.75 (1H, m).

MP 199-200°C

**Example 134**

5-(2,3-Dichlorobenzenesulphonylamino)-6-(3-pyrdinylmethoxy)pyrazine-2-carboxylic acid, methyl ester

![Chemical structure](image)
Prepared as for Example 113 using \( N-[5\text{-bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl}]\)-2,3-dichlorobenzenesulphonamide (Example 34) (0.2g) and bis(triphenylphosphine)palladium(II) dichloride (0.1g). Yield 0.14g. m/e 469(M+1\(^+\), 100%)

\(^1\)H NMR (D6-DMSO) \( \delta \) 8.83 (1H, s), 8.61 (1H, d), 8.15-8.05 (3H, m), 7.90 (1H, d), 7.60-7.50 (2H, m), 5.48 (2H, s), 3.82 (3H, s).
MP 209-210\(^0\)C

**Example 135**

5-\{[(2,3-Dichlorophenyl)sulphonyl]amino\}-6-(3-pyridinylmethoxy)-2-pyrazinecarboxamide

![Chemical structure]

5-(2,3-Dichlorobenzenesulphonylamino)-6-(3-pyridinylmethoxy)pyrazine-2-carboxylic acid, methyl ester (Example 134) (0.05g) was heated at 60\(^0\)C in 7M ammonia in methanol for 4 days. The solution was evaporated to dryness and the product crystallised from methyl acetate. Yield 0.027g. m/e 453(M-1\(^+\), 100%)

\(^1\)H NMR (D6-DMSO) \( \delta \) 8.72 (1H, s), 8.52 (1H, d), 7.99 (1H,d), 7.90 (1H, d), 7.83 (1H, s), 7.66 (1H, d), 7.56 (1H, s), 7.45-7.35 (2H, m), 5.49 (2H, s).
MP 174-178\(^0\)C

**Example 136**

2,3-Dichloro-\( N-[5\text{-}(4\text{-pyridinyl})\text{-3-(3-pyridinylmethoxy)-2-pyrazinyl}]\)benzenesulphonamide

a) [5-Bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl][(2,3-dichlorophenyl)sulphonyl]carbamic acid, 2-methylpropyl ester
Sodium hydride (0.045g of a 60% dispersion in oil) was added to \(N\)-[5-bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide (Example 34) (0.5g) in 1,2-dimethoxyethane (3mL). Iso-butylchloroformate (0.15mL) was added. After 2h, the mixture was partitioned between water and ethyl acetate. The organic layer was dried (\(\text{Na}_2\text{SO}_4\)) and evaporated to yield the product (0.65g). Used directly.

b) 2,3-Dichloro-\(N\)-[5-(4-pyridinyl)-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

[5-Bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl][2,3-dichlorophenyl]sulphonyl]carbamic acid, 2-methylpropyl ester (Example 136a) (0.11g), 4-tributylstannanlypyridine (0.067g) and tetrakis(triphenylphosphine)palladium(0) (0.05g) in toluene (3mL) was heated at 95°C for 16h. Chromatography on silica gel eluting with ethyl acetate/ethanol mixtures gave the title compound protected with the 2-methylpropylcarbonyl group (0.09g). The compound was heated at 60°C in methanol (2mL) and 1M sodium hydroxide (0.36mL) for 1h. The solution was evaporated. Purification was by reverse phase preparative high pressure liquid chromatography. Yield 0.015g.

\(m/e\ 488(M+1^+, 100\%)\)
\textsuperscript{1}H NMR (D6-DMSO) δ 9.05 (1H, s), 8.85 (2H, d), 8.78 (1H, d), 8.62 (1H, s), 8.44-8.39 (3H, m), 8.17 (1H, dd), 7.96 (1H, dd), 7.87-7.80 (1H, m), 7.64-7.57 (1H, m), 5.74 (2H, s)

**Example 137**

2,3-Dichloro-N-[(5-hydroxymethyl)-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

\[
\begin{align*}
\text{\begin{tikzpicture}
\draw (0,0) circle (0.5cm);
\draw (0,0) -- (0.5,0.866) -- (1,0) -- (0.5,-0.866) -- (0,0);
\draw (0.5,0.866) -- (0,1.732);
\draw (0.5,-0.866) -- (0,-1.732);
\end{tikzpicture}}
\end{align*}
\]

Lithium aluminium hydride (0.85mL of a 1M solution in tetrahydrofuran) was added dropwise to 5-(2,3-dichlorobenzenesulphonylamino)-6-(3-pyridinylmethoxy)pyrazine-2-carboxylic acid, methyl ester (Example 134) (0.2g) in tetrahydrofuran (10mL) cooled to –65°C. The reaction mixture was allowed to warm to room temperature and stirred for 1h. Aqueous acetic acid was added and the mixture extracted with ethyl acetate. The organic solution was dried (MgSO\textsubscript{4}) and evaporated. Chromatography on silica gel eluting with ethyl acetate/methanol mixtures gave the title compound (0.08g).

m/e 441(M+1\textsuperscript{+}, 100%)

\textsuperscript{1}H NMR (D6-DMSO) δ 8.73 (1H, s), 8.55 (1H, d), 8.06 (1H, dd), 7.95-7.85 (2H, m), 7.65 (1H, s), 7.56 (1H, t), 7.64-7.57 (1H, m), 5.41 (2H, s), 5.36 (1H, t), 4.41 (2H, d)

**Example 138**

2,3-Dichloro-N-[(5-hydroxymethyl)-3-methoxy]-2-pyrazinyl]benzenesulphonamide

\[
\begin{align*}
\text{\begin{tikzpicture}
\draw (0,0) circle (0.5cm);
\draw (0,0) -- (0.5,0.866) -- (1,0) -- (0.5,-0.866) -- (0,0);
\draw (0.5,0.866) -- (0,1.732);
\draw (0.5,-0.866) -- (0,-1.732);
\end{tikzpicture}}
\end{align*}
\]
Prepared as for Example 120 using 5-(2,3-dichlorobenzenesulphonylamino)-6-methoxypyrazine-2-carboxylic acid, methyl ester (Example 113) (0.84g). Yield 0.5g. m/e 364(M+1\(^+\), 100%)  
\(^1\)H NMR (D6-DMSO) \(\delta\) 8.21 (1H, dd), 7.79 (1H, dd), 7.59 (1H, s), 7.51 (1H, t), 4.50 (2H, s), 4.01 (3H, s).  
MP 160-161\(^\circ\)C.

Example 139

\(N\)-(5-Allyloxy-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide

\[
\text{Cl} \quad \text{Cl} \\
\text{O} \quad \text{S}=\text{O} \\
\text{N} \quad \text{Cl}
\]

Procedure as for Example 115 using \(N\)-(5-chloro-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-((2-((trimethylsilyl)oxy)ethoxy)methyl)benzenesulphonamide (Example 115a) (0.25 g), allyl alcohol (0.06g) and sodium hydride (0.035g of a 60% dispersion in oil) in \(N,N\)-dimethylformamide (5mL) stirred at room temperature for 5 days. Purification was by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures to give the title compound with SEM attached. Yield 0.18g. This compound was dissolved in dichloromethane (4mL) and trifluoroacetic acid (1mL). After 2h, toluene was added and the mixture evaporated to dryness. Purification was by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures to give the title compound. Crystallised for diethyl ether/iso-hexane mixtures. Yield 0.026g.  
m/e 390 (M+1\(^+\), 100%)  
\(^1\)H NMR (D6-DMSO) \(\delta\) 10.81 (1H, s), 8.0-7.9 (2H, m), 7.53 (1H, t), 7.49 (1H, s), 6.07-7.02 (1H, m), 5.38 (1H, dd), 5.26 (1H, dd), 4.80 (2H, d), 3.82 (3H, s)  
MP 120-121\(^\circ\)C

Example 140

2,3-Dichloro-N-{3-methoxy-5-{(pyrazinyl)oxy}methyl}-2-pyrazinyl}benzenesulphonamide
Sodium hydride (0.022g of a 60% dispersion in oil) was added to 2,3-dichloro-N-[5-(hydroxymethyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide (Example 138) (0.05g) in N-methylpyrrolidinone (2mL). After 0.5h, chloropyrazine (0.013mL) was added and the mixture heated at 60°C for 3h. Aqueous acetic acid was added and the mixture extracted with ethyl acetate. The organic solution was dried (Na₂SO₄) and evaporated. Chromatography on silica gel eluting with ethyl acetate/iso-hexane mixtures gave the title compound (0.012g).
m/e 442(M⁺, 100%) 

¹H NMR (D₆-DMSO) δ 8.36 (1H, s), 8.23 (2H, d), 8.06 (1H, d), 7.87 (1H, d), 7.68 (1H, s), 7.54 (1H, t), 5.26 (2H, s), 3.86 (3H, s).
MP 155°C (dec).

Example 141

2,3-Dichloro-N-[5-(3-hydroxy-1-propynyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide

A mixture of N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-[{2-(trimethylsilyl)ethoxy}methyl]benzenesulphonamide (Example 55a) (0.52g), propargyl alcohol (0.223mL), copper(I)iodide (0.05g) and bis(triphenylphosphine)palladium(II) chloride (0.1g) in triethylamine (3mL) was stirred at room temperature and under nitrogen for 16h. The solvent was evaporated. Chromatography on silica gel eluting with ethyl acetate/iso-hexane mixtures gave the title compound containing the SEM ([2-(trimethylsilyl)ethoxy]methyl) protecting group (0.38g). 0.074g of this compound was
dissolved in dichloromethane (2mL) and trifluoroacetic acid (2mL). After 1h the solvent was evaporated. Chromatography on silica gel eluting with ethyl acetate/isoo-hexane mixtures gave the title compound (0.043g).

m/e 386(M-1⁺, 100%)

^1^H NMR (D6-DMSO) δ 8.07 (1H, d), 7.93 (1H, d), 7.72 (1H, s), 7.58 (1H, t), 4.29 (2H, s), 3.90 (3H, s).

**Example 142**

_N-3-[(5-Bromo-3-pyridinyl)methoxy]-5-chloro-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide_

![Chemical Structure]

Prepared by the method of Example 31 using (5-bromo-3-pyridinyl)methanol (0.2g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.25g). Yield 0.17g.

m/e 523(M-1⁺, 100%)

^1^H NMR (D6-DMSO) δ 8.77 (1H, d), 8.71 (1H, d), 8.28 (1H, s), 8.07 (1H, dd), 7.92 (1H, d), 7.85 (1H, s), 7.55 (1H, t), 5.43 (2H, s).

MP 199-201°C.

**Example 143**

_2,3-Dichloro-N-[5-chloro-3-{[6-(hydroxymethyl)-2-pyridinyl]methoxy}-2-pyrazinyl]benzenesulphonamide_
Prepared by the method of Example 31 using 2,6-bis(hydroxymethyl)pyridine (0.11g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.11g) in N-methylpyrrolidinone (2mL). Yield 0.043g.

m/e 475(M+1^+, 100%)

\(^1\)H NMR (D6-DMSO) δ 7.97 (1H, d), 7.83 (1H, t), 7.68 (1H, d), 7.43-7.35 (4H, m), 5.44 (1H, s), 5.32 (2H, s), 4.58 (2H, s).

MP 220°C

**Example 144**

2,3-Dichloro-N-{5-chloro-3-[(2-methyl-4-oxazolyl)methoxy]-2-pyrazinyl}benzenesulphonamide

Prepared by the method of Example 31b using (2-methyl-4-oxazolyl)methanol (0.08g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.26g).

Yield 0.083g.

m/e 449(M+1^+, 100%)

\(^1\)H NMR (D6-DMSO) δ 8.09 (1H, s), 8.03 (1H, dd), 7.94 (1H, dd), 7.85 (1H, s), 7.55 (1H, t), 5.23 (2H, s), 2.45 (3H, s)

MP 172-173°C.
Example 145
2,3-Dichloro-N-[3-[(2-methyl-4-oxazolyl) methoxy]-2-pyrazinyl] benzenesulphonamide

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{example_145_structure}
\end{center}}
\]

Prepared by the method of Example 28 using (2-methyl-4-oxazolyl)methanol (0.3g) and 2,3-dichloro-N-(3-chloro-2-pyrazinyl) benzenesulphonamide (0.89g). Yield 0.035g. m/e 412(M-1^+, 100%)

\(^1\)H NMR (D6-DMSO) \(\delta\) 8.06 (2H, dd), 7.92 (1H, dd), 7.85 (1H, br s), 7.70 (1H, br s), 7.56 (1H, t), 5.23 (2H, s), 2.41 (3H, s).

MP 207-209\(^\circ\)C.

Examples 146-165 were prepared using the following procedure:

To a solution of \(N\)-(3,5-dibromo-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 31) (0.003g) and primary alcohol (0.026mL of a 0.5M solution in \(N\)-methylypyrrrolidinone) in \(N\)-methylpyrrrolidinone (0.1mL) was added potassium tert-butoxide (0.050mL of a 1M solution in tetrahydrofuran). The solution was allowed to stand for 24 hours. The reaction mixture was diluted with acetic acid (0.010mL) and water (0.10mL) and the solvents were evaporated. The residue was redissolved in dimethylsulphoxide (0.5mL) and purified by mass directed high pressure liquid chromatography. The solvent was evaporated to afford a solid.

Example 146
\(N\)-[5-Bromo-3-(phenylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
Example 147

$N\text{-}[5\text{-Bromo-3-(2-cyclopropylethoxy)pyrazinyl}]\text{-2,3-dichlorobenzenesulphonamide}$

Example 148

$N\text{-}[5\text{-Bromo-3-(3-thienylmethoxy)pyrazinyl}]\text{-2,3-dichlorobenzenesulphonamide}$
m/e 495(M+1\(^+\), 100%)

**Example 149**

\(N\{-5\text{-Bromo-3-\{(2-methyl-3-furanyl)methoxy\}-2-pyrazinyl\}-2,3\text{-dichlorobenzenesulphonamide}\}

![Chemical Structure](image)

m/e 493(M+1\(^+\), 100%)

**Example 150**

\(N\{-5\text{-Bromo-3-\{(3-furanyl)methoxy\}-2-pyrazinyl\}-2,3\text{-dichlorobenzenesulphonamide}\}

![Chemical Structure](image)

m/e 479(M+1\(^+\), 100%)

**Example 151**

\(N\{-5\text{-Bromo-3-\{(4-fluorophenyl)methoxy\}-2-pyrazinyl\}-2,3\text{-dichlorobenzenesulphonamide}\}

![Chemical Structure](image)
Example 152

\[ N^\prime\{-5\text{-Bromo-3-\{3-fluorophenyl\}methoxy}-2\text{-pyrazinyl}-2,3\text{-dichlorobenzenesulphonamide} \} \]

Example 153

\[ N\{-5\text{-Bromo-3-\{3-(2\text{-pyridinyl\})propoxy\}-2\text{-pyrazinyl}-2,3\text{-dichlorobenzenesulphonamide} \} \]
Example 154

5  \(N\)-[5-Bromo-3-(pentyloxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

m/e 518(M+\(^+\), 100%)

Example 155

10 \(N\)-[5-Bromo-3-(propyloxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

m/e 441(M+\(^+\), 100%)
Example 156
\(N\)-[5-Bromo-3-(2-methoxyethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

\[\text{Structure Image}\]

\[\text{m/e 457 (M}^+\text{, 100%)}\]

Example 157
\(N\)-[5-Bromo-3-(2-ethoxyethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

\[\text{Structure Image}\]

\[\text{m/e 471 (M}^+\text{, 100%)}\]

Example 158
\(N\)-[5-Bromo-3-(2-fluoroethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

\[\text{Structure Image}\]
Example 159

\[ N\{-5\text{-Bromo-3-[2-\(\text{1H-imidazol-1-yl}\)ethoxy]-2-pyrazinyl}\}-2,3\text{-dichlorobenzenesulphonamide} \]

m/e 445(M+\(^+\), 100%)

Example 160

\[ N\{-5\text{-Bromo-3-[3-(3-pyridinyl)propoxy]-2-pyrazinyl}\}-2,3\text{-dichlorobenzenesulphonamide} \]

m/e 493(M+\(^+\), 100%)
m/e 516(M-1+ 100%)

Example 161

N-[5-Bromo-3-(2-(methylamino)ethoxy)-2-pyrazinyl]-2,3-
5 dichlorobenzenesulphonamide

m/e 456(M+1+ 100%)

Example 162

N-[5-Bromo-3-[3-(4-hydroxyphenyl)propoxy]-2-pyrazinyl]-2,3-
10 dichlorobenzenesulphonamide

m/e 533(M+1+ 100%)

Example 163

N-[5-Bromo-3-(2-phenoxyethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
Example 164

\[ N-[5\text{-Bromo-3-(cyclopropylmethoxy)-2-pyrazinyl}]-2,3\text{-dichlorobenzenesulphonamide} \]

\[
\text{m/e 517(M-1}^+, 100\%) 
\]

Example 165

\[ N-[5\text{-Bromo-3-(3-phenoxypropoxy)-2-pyrazinyl}]-2,3\text{-dichlorobenzenesulphonamide} \]

\[
\text{m/e 531(M-1}^+, 100\%) 
\]
2,3-Dichloro-N-(5-ethoxy-3-methoxy-2-pyrazinyl)benzenesulphonamide

Prepared as for Example 56 using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (Example 55a) (0.3g) and sodium ethoxide (5mL of a 0.5M solution in ethanol). Yield 0.1g.
m/e 378 (M+1,100%)
$^1$H NMR (CDCl$_3$) δ 8.22 (1H, d), 7.65 (1H, d), 7.49 (1H, s), 7.34 (1H, t), 7.30 (1H, s), 4.24 (2H, q), 3.95 (3H, s), 1.36 (3H, t)
MP 96-97°C

Example 167

2,3-Dichloro-N-[3-methoxy-5-([1,2,4]-1-triazolyl)-2-pyrazinyl]benzenesulphonamide

Prepared as for Example 101b (reaction heated at 50°C) using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (Example 55a) (0.25g) and [1,2,4]triazole (0.1g). The intermediate product containing the SEM (2-[trimethylsilyl]ethoxymethyl) group was purified by silica gel chromatography eluting with ethyl acetate/isoo-hexane mixtures. Deprotection as for Example 101b gave the title compound. Yield 0.035g.
m/e 401 (M+1$, 100%)
$^1$H NMR (CDCl$_3$) δ 8.92 (1H, s), 8.34 (1H, d), 8.24 (1H, s), 8.08 (1H, s), 8.01 (1H, br s), 7.72 (1H, d), 7.43 (1H, t), 4.14 (3H, t)
MP 248-249°C

Example 168
2-[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphonyl]-N-methylacetamide

Prepared as for Example 101b using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-[2-(trimethylsilanyloxy)methyl]benzenesulphonamide (Example 55a) (0.4g) and 2-mercapto-N-methylacetamide (0.1g). The intermediate product containing the SEM (2-[trimethylsilyloxy)methyl] group was purified by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures. Deprotection as for Example 101b gave the title compound. Yield 0.05g.
m/e 437 (M+1+, 100%)

\(^1H\) NMR (CDCl\textsubscript{3}) \(\delta\) 8.25 (1H, dd), 7.76 (1H, s), 7.68 (1H, dd), 7.58 (1H, s), 7.40 (1H, t), 6.62 (1H, br s), 3.99 (3H, s), 3.69 (2H, s), 2.86 (3H, d)

MP 150-152°C

\textbf{Example 169}

2-[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphonyl]acetamide

Prepared as for Example 101b using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-[2-(trimethylsilanyloxy)methyl]benzenesulphonamide (Example 55a) (0.2g) and 2-mercaptoacetamide (0.05g). The intermediate product containing the SEM group was purified by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures. Deprotection as for Example 101b gave the title compound. Yield 0.03g.
m/e 423 (M+1+, 100%)

\(^1H\) NMR (CDCl\textsubscript{3}) \(\delta\) 7.98 (1H, dd), 7.75 (1H, d), 7.46-7.42 (3H, m), 7.06 (1H, s), 3.83 (3H, s), 2.59 (2H, s)

MP 163-164°C
Example 170
2,3-Dichloro-N-[5-(4-fluorobenzylsulphonyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide

Prepared as for Example 101b using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-\{2-(trimethylsilyl)ethoxy\}methyl]benzenesulphonamide (Example 55a) (0.4g) and (4-fluorophenyl)methanethiol (0.13g). The intermediate product containing the SEM group was purified by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures. Deprotection as for Example 101b gave the title compound. Yield 0.2g

m/e 474 (M+1\(^+\), 100%)
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.25 (1H, dd), 7.73 (1H, s), 7.67 (1H, dd), 7.51 (1H, s), 7.38 (1H, t), 7.27 (2H, m), 6.92 (2H, m), 4.24 (2H, s), 4.01 (3H, s)
MP 119-120\(^\circ\)C

Example 171
2,3-Dichloro-N-[5-cyanomethylsulphonyl-3-methoxy-2-pyrazinyl]benzenesulphonamide

See example 172 for preparation.

m/e 403 (M-1\(^+\), 100%)
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.28 (1H, dd), 7.84 (1H, s), 7.69 (1H, dd), 7.63 (1H, s), 7.38 (1H, t), 4.11 (3H, s), 3.78 (2H, s)
MP 158-159\(^\circ\)C

Example 172
2,3-Dichloro-N-[3-methoxy-5-[(1,2,4)-3-oxadiazolymethylsulphonyl]-2-

pyrazinyl]benzenesulphonamide
Prepared as for Example 101b using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-
[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (Example 55a) (0.4g), [1,2,4]-
3-oxadiazolymethanethiol (0.15g) and cesium carbonate (0.5g) at room temperature for
16h. The intermediate products containing the SEM (2-[trimethylsilylethoxymethyl]
group was purified by silica gel chromatography eluting with ethyl acetate/iso-hexane
mixtures. Deprotection as for Example 101b gave the title compound (0.09g) and 2,3-
dichloro-N-[5-cyanomethylsulphonyl-3-methoxy-2-pyrazinyl]benzenesulphonamide
(Example 171) (0.1g) which were separated by silica gel chromatography eluting with
dichloromethane.
m/e 448 (M+1+, 100%)
H NMR (CDCl3) δ 8.64 (1H, s), 8.26 (1H, dd), 7.76 (1H, s), 7.67 (1H, dd), 7.57 (1H, s),
7.37 (1H, t), 4.39 (2H, s), 4.04 (3H, s)
MP 154-156°C

Example 173
N-[5-(2-Aminoethylsulphonyl)-3-methoxy-2-pyrazinyl]-2,3-
dichlorobenzenesulphonamide

Prepared as for Example 101b using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-
[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (Example 55a) (0.45g) and 2-
aminoethanethiol hydrochloride (0.2g). Yield 0.03g
m/e 409 (M+1+, 100%)
H NMR (D6-DMSO) δ 8.02 (1H, dd), 7.94 (1H, dd), 7.87 (1H, s), 7.70 (1H, s), 7.58 (1H,
t), 3.93 (3H, s), 3.48 (2H, br s), 3.28 (2H, t), 3.10-3.03 (2H, m)
Example 174

2,3-Dichloro-N-[3-methoxy-5-(5-methyl-3-isoxazolylmethoxy)]-2-
pyrazinyl]benzenesulphonamide

Prepared as for Example 115b using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-
[2-(trimethylsilanyloxy)methyl]benzenesulphonamide (Example 55a) (0.3g) and (5-
methyl-3-oxazolyl)methanol (0.13g). The intermediate product containing the SEM (2-
[trimethylsilyloxy)methyl] group was purified by silica gel chromatography eluting
with ethyl acetate/isooctane mixtures. Deprotection as for Example 115b gave the title
compound. Yield 0.2g

m/e 445 (M+1+, 100%)

^1H NMR (CDCl_3) δ 8.22 (1H, dd), 7.66 (1H, dd), 7.59 (1H, s), 7.38 (2H, t), 6.01 (1H, t),
5.31 (2H, s), 3.97 (3H, s), 2.43 (3H, s)

MP 142-143°C

Example 175

2,3-Dichloro-N-[5-(5-dimethylaminomethyl-2-furanyl)methoxy]-3-methoxy-2-
pyrazinyl]benzenesulphonamide

Prepared as for Example 115b using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-
[2-(trimethylsilyl)oxy)methyl]benzenesulphonamide (Example 55a) (0.3g) and (5-
dimethylaminomethyl-2-furanyl)methanol (0.2g). After removal of the SEM (2-
[trimethylsilyloxy)methyl] group the title compound was purified by silica gel
chromatography eluting with methanol/dichloromethane mixtures Yield 0.23g
m/e 487 (M+1⁺, 100%)

$^1$H NMR (CDCl₃) δ 8.21 (1H, dd), 7.66 (1H, dd), 7.37 (2H, t), 6.39 (2H, s), 5.20 (2H, s), 4.00 (3H, s), 3.84 (2H, s), 2.51 (6H, s)

MP 114-115°C

Example 176

$N$-[5-Bromo-3-(5-dimethylaminomethyl-2-furanylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

Prepared by the method of Example 31 using (5-dimethylaminomethyl-2-furanyl)methanol (0.2g) and 2,3-dichloro-$N$-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (Example 31a) (0.2g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures and recrystallised from acetonitrile. Yield 0.058g.
m/e 535 (M+1⁺, 100%)

$^1$H NMR (D6-DMSO) δ 7.92 (1H, dd), 7.63 (1H, dd), 7.36 (2H, t), 6.71 (1H, d), 6.68 (1H, d), 5.22 (2H, s), 4.37 (2H, d), 2.75 (6H. s)

MP 206-207°C

Example 177

2,3-Dichloro-$N$-[5-(2-hydroxyethylsulphonyl)-3-methoxy-2-

pyrazinyl]benzenesulphonamide

Prepared as for Example 101b using $N$-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-$N$-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (Example 55a) (0.2g) and 2-mercaptoethanol (0.2g). After removal of the SEM (2-[trimethylsilyl]ethoxymethyl) group
the title compound was purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.015g
m/e 410 (M+1⁺, 100%)
¹H NMR (CDCl₃) δ 8.27 (1H, dd), 7.78 (1H, s), 7.67 (1H, dd), 7.61 (1H, s), 7.39 (1H, t), 4.04 (3H, s), 3.83 (2H, t), 3.24 (2H, t)
MP 180-181°C

Example 178
2,3-Dichloro-N-[5-[2-(ethylureido)ethylsulphonyl]-3-methoxy-2-

pyrazinyl}benzenesulphonamide

Ethylisocyanate (0.016g) was added to N-[5-(2-aminoethylsulphonyl)-3-methoxy-2-
pyrazinyl]-2,3-dichloro-benzenesulphonamide (Example 173) (0.08g) in dichloromethane (5mL). After 1h, the reaction mixture was evaporated to dryness. Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.015g.
m/e 480 (M+1⁺, 100%)
¹H NMR (CDCl₃) δ 8.27 (1H, dd), 7.69 (1H, dd), 7.56 (1H, s), 7.39 (1H, t), 4.60 (1H, br s), 4.18 (1H, br s), 4.04 (3H, s), 3.40-3.30 (2H, m), 3.30-3.2 (2H, m), 3.25-3.20 (2H, m), 1.15 (3H, t)

Example 179
2,3-Dichloro-N-[3-(5-dimethylaminomethyl-2-furanylmethoxy)-2-

pyrazinyl}benzenesulphonamide
Prepared by the method of Example 28 using (5-dimethylaminomethyl-2-furanyl)methanol (0.2g) and 2,3-dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28) (0.4g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.2g.

\[ m/e \ 455\ (M-1^+, \ 100\%) \]

$^1$H NMR (D6-DMSO) $\delta$ 7.96 (1H, dd), 7.66 (1H, dd), 7.40 (1H, t), 7.30 (1H, d), 7.24 (1H, d), 6.65 (1H, s), 6.64 (1H, d), 6.53 (1H, d), 5.23 (2H, s), 4.25 (2H, s), 2.66 (6H, s)

**Example 180**

2,3-Dichloro-N-[6-chloro-3-(5-dimethylaminomethyl-2-furanylmethoxy)-2-

\[
\begin{array}{c}
\text{N} \\
\text{Cl}
\end{array}
\]

pyrazinyl]benzenesulphonamide

Prepared by the method of Example 31 using (5-dimethylaminomethyl-2-furanyl)methanol (0.2g) and N-(3-bromo-6-chloro-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 98) (0.3g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.11g.

\[ m/e \ 491\ (M+1^+, \ 100\%) \]

$^1$H NMR (D6-DMSO) $\delta$ 8.01 (1H, dd), 7.66 (1H, dd), 7.39 (1H, t), 7.11 (1H, s), 6.69 (1H, d), 6.67 (1H, d), 6.52 (2H, s), 4.39 (2H, s), 2.76 (6H, s)

MP 209-210°C

**Example 181**

2,3-Dichloro-N-[6-chloro-3-(5-methyaminomethyl-2-furanylmethoxy)-2-

\[
\begin{array}{c}
\text{N} \\
\text{Cl}
\end{array}
\]

pyrazinyl]benzenesulphonamide
Prepared by the method of Example 31 using (5-methylaminomethyl-2-furanyl)methanol (0.3g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.4g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.03g.

m/e 477 (M+1\(^+\), 100%)

\(^1\)H NMR (D6-DMSO) \(\delta\) 8.98 (2H, br), 7.92 (1H, d), 7.63 (1H, d), 7.35 (1H, t), 7.29 (1H, s), 6.67 (1H, d), 6.64 (1H, d), 5.20 (2H, s), 4.25 (2H, s), 2.59 (3H, s)

MP 211-212°C

Example 182

2,3-Dichloro-N-[5-chloro-3-(5-dimethylaminomethyl-2-furanylmethoxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 31 using (5-dimethylaminomethyl-2-furanyl)methanol (0.3g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.4g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.30g.

m/e 491 (M+1\(^+\), 100%)

\(^1\)H NMR (D6-DMSO) \(\delta\) 7.93 (1H, dd), 7.65 (1H, dd), 7.36 (1H, t), 7.32 (1H, s), 6.71 (1H, d), 6.69 (1H, d), 5.23 (2H, s), 4.38 (2H, s), 2.75 (6H, s)

MP 209-210°C

Example 183

2,3-Dichloro-N-[3-(5-methylaminomethyl-2-furanylmethoxy)-2-pyrazinyl]benzenesulphonamide
Prepared by the method of Example 28 using (5-methylaminomethyl-2-furanyl)methanol (0.2g) and 2,3-dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28) (0.4g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.12g.

m/e 443 (M+1<sup>+</sup>, 100%)

<sup>1</sup>H NMR (D6-DMSO) δ 8.99 (2H, br s), 7.95 (1H, d), 7.62 (1H, d), 7.35 (1H, t), 7.24 (1H, d), 7.15 (1H, d), 6.88 (1H, d), 6.63 (1H, d), 5.20 (2H, s), 4.24 (2H, s), 2.58 (3H, s)

MP 198-199°C

Example 184

N-(5-Bromo-3-methoxypyrazinyl)-2-cyanobenzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.2g) and 2-cyanobenzenesulphonyl chloride (0.24g). Yield 0.059g.

m/e 369/370 (M+1<sup>+</sup>), 307/309 (100%)

<sup>1</sup>H NMR (D6-DMSO) δ 8.14 (1H, d), 8.09 (1H, d), 7.93-7.82 (3H, m), 3.93 (3H, s).

MP 190-191.5°C

Example 185

N-(5-Bromo-3-methoxypyrazinyl)-2,3-dichloro-4-fluorobenzenesulphonamide
a) 2,3-Dichloro-4-fluorobenzencesulphonyl chloride

Chlorosulphonic acid (12.1mL) was added dropwise to a solution of 2,3-dichloro-4-
fluorobenzene (5.0g) in dichloromethane (12mL) at -40°C. The solution was allowed to
slowly warm to room temperature and was stirred for 3 days. The solution was poured
onto crushed ice/water, extracted into dichloromethane and concentrated under reduced
pressure. Purified by silica gel chromatography eluting with dichloromethane/iso-hexane
mixtures. Yield 4.2g
m/e 262/264 (M⁺), 163 (100%).

b) N-(5-Bromo-3-methoxypyrazinyl)-2,3-dichloro-4-fluorobenzencesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-
bromo-3-methoxy-2-pyrazinamine (0.2g) and 2,3-dichloro-4-fluorobenzencesulphonyl
chloride (Example 185a) (0.31g). Yield 0.042g.
m/e 430 (M-1⁺,100%)
1H NMR (D6-DMSO) δ 8.16-8.12 (1H, m), 7.81 (1H, s), 7.68-7.64 (1H, m), 3.92 (3H, s).
MP 208-211°C

Example 186
2,3-Dichloro-N-[3-methoxy-5-(4-morpholinylmethyl)-2-
pyrazinyl]benzenesulphonamide

a) 2,3-Dichloro-N-(5-formyl-3-methoxy-2-pyrazinyl)benzenesulphonamide
Prepared as for Example 107a using 2,3-dichloro-\(N\)-[5-(hydroxymethyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide (Example 138) (0.6g). Yield 0.53g. Used directly.

b) 2,3-Dichloro-\(N\)-[3-methoxy-5-(4-morpholinylmethyl)-2-pyrazinyl]benzenesulphonamide

Prepared as for Example 107b using 2,3-dichloro-\(N\)-[5-formyl-3-methoxy-2-pyrazinyl]benzenesulphonamide (Example 186a) (0.26g) and morpholine (3.7mL). Yield 0.057g.

m/e 433 (M+\(^+\), 100%)

\(^1\)H NMR (D6-DMSO) \(\delta\) 8.12 (1H, d), 7.94(1H, d), 7.59 (1H, t), 4.20 (2H, s), 3.96 (3H, s), 3.85-3.65 (5H, m)

Example 187
\(N\)-(3-Allyloxy-5-chloro-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide
Prepared by the method of Example 31 using allyl alcohol (10mL) as solvent and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.35g). Yield 0.32g.
m/e 393 (M-1⁺, 100%)

1H NMR (D6-DMSO) δ 11.80 (1H, br s), 8.08 (1H, dd), 7.96 (1H, dd), 7.82 (1H, dd), 7.58 (1H, t), 6.10-6.00 (1H, m), 5.49 (1H, dddd), 5.29 (1H, dddd), 4.86 (2H, dddd)
MP 145-146°C

**Example 188**

2,3-Dichloro-N-[5-chloro-3-(2-propynloxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 31 using propargyl alcohol (0.3g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.35g). Yield 0.2g.
m/e 390 (M-1⁺, 100%)

1H NMR (D6-DMSO) δ 8.08 (1H, dd), 7.95 (1H, dd), 7.86 (1H, s), 7.58 (1H, t), 5.02 (2H, d), 3.65 (1H, t)
MP 138-139°C

**Example 189**

2,3-Dichloro-N-[3-(2-propynloxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 28 using propargyl alcohol as solvent (3mL), 2,3-dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28) (0.3g) and sodium hydride (0.2g of a 60% dispersion in oil) at room temperature for 16h. Yield 0.27g.
m/e 356 (M-1⁺, 100%)
1H NMR (D6-DMSO) $\delta$ 11.67 (1H, br s), 8.10 (1H, dd), 7.94 (1H, dd), 7.85 (1H, br), 7.72 (1H, br), 7.59 (1H, t), 5.01 (2H, d), 3.56 (1H, t)
MP 153-154°C

**Example 190**

2,3-Dichloro-N-(5-cyano-3-methoxy-2-pyrazinyl)benzenesulphonamide

Prepared as for Example 78 using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 8) (0.1g). Yield 0.034g.

m/e 357 (M$^+$, 100%)

1H NMR (D6-DMSO) $\delta$ 8.15 (1H, s), 8.14 (1H, dd), 7.95 (1H, dd), 7.59 (1H, t), 3.96 (3H, s)
MP 239-240°C

**Example 191**

2,3-Dichloro-N-{3-methoxy-5-{(2S)-pyrrolidin-2-ylmethoxy)-2-pyrazinyl}benzenesulphonamide hydrochloride

Procedure as for Example 115 using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-\{(2-{[(trimethylsilyl)oxy]ethoxy}methyl)benzenesulphonamide (Example 55a) (0.5 g), tert-butyl (2S)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (0.603 g) and sodium hydride (0.12g of a 60% dispersion in oil) in N-methylpyrrolidinone (20mL). The adduct was deprotected with HCl (4M in dioxane) to afford the titled adduct (0.241g) as a white solid.

m/e 433, 435 (M-HCl$^+$, 100%)

1H NMR (D6-DMSO) $\delta$ 10.92 (1H, s), 9.45 (1H, br), 8.93 (1H, br), 7.98 (1H, d), 7.93 (1H, d), 7.57 (1H, d), 7.52 (1H, d), 4.53 (1H, dd), 4.37 (1H, dd), 3.94-3.86 (1H, m), 3.85 (3H, s), 3.22-3.18 (2H, m), 2.13-2.08 (1H, m), 1.99-1.86 (2H, m), 1.76-1.67 (1H, m).
Example 192

2,3-Dichloro-N-[6-chloro-3-methoxy-5-[(2R)-2-pyrrolidinymethoxy]-2-pyrazinyl]benzenesulphonamide Hydrochloride

Procedure as for Example 115 using 2,3-dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (Example 66a) (0.29g), tert-butyl (2S)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (0.15 g) and sodium hydride (0.04g of a 60% dispersion in oil) in N-methylpyrrolidinone (20mL). The adduct was deprotected with HCl (4M in dioxane) to afford the titled adduct (0.2g) as a white solid. m/e 464 (M+H)<sup>+</sup>, 100%

<sup>1</sup>H NMR (D6-DMSO) δ 11.24 (1H, br s), 9.46 (1H, br s), 8.99 (1H, br s), 8.01 (1H, d), 7.96 (1H, d), 7.59 (1H, m), 4.61 (1H, dd), 4.46 (1H, dd), 3.95 (1H, br s), 3.85 (3H, s), 3.19 (2H, br s), 2.16-2.07 (1H, br s), 2.03-1.94 (1H, br s), 1.92-1.85 (1H, br s), 1.81-1.72 (1H, br s).

MP 200-204°C

Example 193

2,3-Dichloro-N-[3-methoxy-5-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide Hydrochloride
Procedure as for Example 115 using \(N\)-(5-chloro-3-methoxy-2-pyrazinyl)-2,3-dichloro-\(N\)-(2-[(trimethylsilyl)oxy]ethoxy)methyl)benzenesulphonamide (Example 115a) (0.5 g), pyridine-3-methanol (0.11 g) and sodium hydride (0.05g of a 60% dispersion in oil) in \(N\)-methylpyrrolidinone (5mL). Yield 0.23g.

m/e 438 (M-\(H^+\), 100%)

\(^1\)H NMR (D6-DMSO) \(\delta\) 10.9 (1H, br s), 8.7 (1H, br s), 8.12 (1H, t), 7.99-7.92 (2H, m), 7.74 (1H, d), 7.61 (1H, s), 7.63-7.53 (2H, m), 5.54 (2H, s), 3.73 (3H, s).

MP 180-183°C.

**Example 194**

2,3-Dichloro-\(N\)-(3-methoxy-6-methyl-2-pyrazinyl)benzenesulphonamide

a) 3-Methoxy-6-methyl-2-pyrazinamine

![Chemical structure of 3-Methoxy-6-methyl-2-pyrazinamine](image)

To a solution of 5-bromo-3-methoxy-6-methyl-2-pyrazinamine (Example 118c) (0.8g) and ammonium formate (0.4g) in methanol (20mL) was added palladium on carbon (0.2g) and the reaction mixture heated at reflux for 5h. After cooling to room temperature, the reaction mixture was filtered through a plug of celite, and the filtrate evaporated. The residue was partitioned between dichloromethane and water, and the organic phase dried (MgSO\(_4\)), filtered and evaporated to give the title compound as a white solid (0.44g).

\(^1\)H NMR (D6-DMSO) \(\delta\) 7.10 (1H, s), 6.15 (2H, br s), 3.83 (3H, s), 2.14 (3H, s)

b) 2,3-Dichloro-\(N\)-(3-methoxy-6-methyl-2-pyrazinyl)benzenesulphonamide

![Chemical structure of 2,3-Dichloro-\(N\)-(3-methoxy-6-methyl-2-pyrazinyl)benzenesulphonamide](image)

A solution of 3-methoxy-6-methyl-2-pyrazinamine (Example 194a) (0.050g) and 2,3-dichlorobenzenesulphonyl chloride (0.098g) in pyridine (0.3mL) was stirred at room temperature for 18h. Solvent was evaporated to give a residue which was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate/acetic acid (200:4:1) giving the title compound as a pale orange solid (0.071g).
m/e 348/350 (M+H\(^+\), 100%)
\(^1\)H NMR (D6-DMSO) \(\delta\) 11.44 (1H, br s), 8.14 (1H, dd), 7.92 (1H, dd), 7.65 (1H, br s), 7.61 (1H, t), 3.85 (3H, s), 2.07 (3H, br s).

MP 50-60\(^\circ\)C

**Example 195**

2,3-Dichloro-N-[3-methoxy-5-(1H-1,2,4-triazol-1-ylmethyl)-2-pyrazinyl]benzenesulphonamide

a) 2,3-Dichloro-N-[5-(hydroxymethyl)-3-methoxy-2-pyrazinyl]-N-{2-(trimethylsilyl)ethoxy[methyl]benzenesulphonamide

![Chemical Structure]

To a suspension of 2,3-dichloro-N-[5-(hydroxymethyl)-3-methoxy-2-pyrazinyl]-benzenesulphonamide (1.0g) in dichloromethane (100mL) was added diisopropylethylamine (0.57mL) and 2-(trimethylsilyl)ethoxymethyl chloride (0.58mL). The reaction mixture was stirred at room temperature for 0.5h, then washed with water. The organic phase was dried (MgSO\(_4\)), filtered and evaporated to give a yellow oil. This was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate mixtures to give the title compound as a colourless oil (0.8g).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.04 (1H, s), 7.99 (1H, d), 7.66 (1H, d), 7.28 (1H, t), 5.27 (2H, s), 4.74 (2H, d), 3.90 (3H, s), 3.78 (2H, m), 2.58 (1H, t), 0.85 (2H, m), 0.00 (9H, s).

b) 2,3-Dichloro-N-[3-methoxy-5-(1H-1,2,4-triazol-1-ylmethyl)-2-pyrazinyl] benzenesulphonamide
To a solution of 2,3-dichloro-N-[5-(hydroxymethyl)-3-methoxy-2-pyrazinyl]-N-[[2-(trimethylsilyl)ethoxy]methyl]benzenesulphonamide (Example 195a) (0.1g) and triethylamine (0.056mL) in dichloromethane (5mL) at 0°C was added methanesulphonyl chloride (0.019mL) and the reaction mixture stirred at 0°C for 1h and room temperature for 1h. The solution was filtered through a plug of silica washing with ethyl acetate and concentrated in vacuo to give a colourless oil (0.082g). This was dissolved in N,N-dimethylformamide (0.5mL) and 1,2,4-triazole (0.013g) and sodium carbonate (0.026g) added. The reaction mixture was heated at 60°C for 18h, then partitioned between ethyl acetate and saturated aqueous ammonium chloride (5x). The organic phase was dried (MgSO₄), filtered and evaporated. The residue was dissolved in trifluoroacetic acid (2mL) and dichloromethane (2mL). After 20min, removal of solvent in vacuo gave a residue which was purified by chromatography on silica gel eluting with ethyl acetate/acetic acid mixtures to give the title compound a pale yellow solid (0.011g).

m/e 413/415 (M-H, 100%)

¹H NMR (CDCl₃) δ 8.27 (2H, m), 8.0 (1H, br s), 7.94 (1H, s), 7.68 (1H, d), 7.58 (1H, br s), 7.41 (1H, t), 5.25 (2H, s), 3.97 (3H, s).

MP 95-105°C

Example 196

N-(3-(5-Aminomethyl-2-furanylimethoxy)-5-chloro-2-pyrazinyl)-2,3-dichloro-benzenesulphonamide
Prepared by the method of Example 31 using (5-aminomethyl-2-furanyl)methanol (0.2g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.3g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.1g.

m/e 463 (M+1^+, 100%)  
^1H NMR (D6-DMSO) δ 8.25 (2H, br s), 7.92 (1H, dd), 7.61 (1H, dd), 7.35 (1H, t), 7.27 (1H, s), 6.66 (1H, d), 6.57 (1H, d), 5.19 (2H, s), 4.14 (2H, s)  
MP 201-202°C

Example 197

N-(3-(5-Aminomethyl-2-furanylmethoxy)-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide

Prepared by the method of Example 28 using (5-aminomethyl-2-furanyl)methanol (0.2g) and 2,3-dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28) (0.3g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.2g.

m/e 427 (M-1^+, 100%)  
^1H NMR (D6-DMSO) δ 8.40 (2H, br s), 7.96 (1H, dd), 7.60 (1H, dd), 7.35 (1H, t), 7.24 (1H, d), 7.15 (1H, d), 6.64 (1H, d), 6.57 (1H, d), 5.20 (2H, s), 4.13 (2H, s)  
MP 199-201°C

Example 198

2,3-Dichloro-N-[3-methoxy-5-(2-propyn-1-ylxy)-2-pyrazinyl]benzenesulphonamide
Procedure as for Example 115 using 2,3-dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-N-((2-[(trimethylsilyl)oxy]ethoxy)methyl)benzenesulphonamide (Example 115a) (0.25g), propargyl alcohol (0.025mL) and sodium hydride (0.035g of a 60% dispersion in oil) in N,N-dimethylformamide (5mL). Yield 0.05g.

m/e 388 (M+1⁺, 100%)

^1^H NMR (D6-DMSO) δ 10.90 (1H, s), 7.98-7.94 (2H, m), 7.55 (1H, t), 7.51 (1H, s), 4.97 (2H, d), 3.85 (3H, s), 3.56 (1H, t)

MP 110-112°C

**Example 199**

{[5-(2,3-Dichlorophenylsulfonylamo)-6-methoxy-2-pyrazinyl]oxy}acetic acid, methyl ester

![Structure of Example 199](image)

Procedure as for Example 115 using 2,3-dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-N-((2-[(trimethylsilyl)oxy]ethoxy)methyl)benzenesulphonamide (Example 115a) (0.26g), methyl glycolate (0.075mL) and sodium hydride (0.035g of a 60% dispersion in oil) in N,N-dimethylformamide (5mL). Yield 0.1g

m/e 422 (M+1⁺, 100%)

^1^H NMR (D6-DMSO) δ 10.89 (1H, s), 7.99-7.92 (2H, m), 7.58-7.53 (2H, m), 4.92 (2H, s), 3.75 (3H, s), 3.68 (3H, s).

MP 185-190°C

**Example 200**

N-[5-(2,3-Dichlorophenylsulphonylamo)-6-methoxy-2-pyrazinyl]-2-hydroxyacetamide
Procedure as for Example 115 using 2,3-dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-N-((2-[(trimethylsilyl)oxy]ethoxy)methyl)benzenesulphonamide (Example 115a) (0.25g), glycolamide (0.066g) and sodium hydride (0.035g of a 60% dispersion in oil) in N,N-dimethylformamide (5mL). Yield 0.075g.

m/e 407 (M+1+, 100%)

1H NMR (D6-DMSO) δ 11.23 (1H, br s), 9.77 (1H, s), 8.36 (1H, s), 8.05 (1H, dd), 7.94 (1H, dd), 7.58 (1H, t), 4.04 (2H, s), 3.86 (3H, s).

MP 153-155°C

Example 201

6-(2,3-Dichlorophenylsulphonylamino)-5-methoxy-2-pyrazinecarboxylic acid, methyl ester

a) 6-chloro-3-methoxy-2-pyrazinamine

A mixture of 5-bromo-6-chloro-3-methoxy-2-pyrazinamine (Example 125a) (0.6g), triethylamine (0.72mL), 10% palladium on carbon (0.05g) and ethyl acetate (50mL) were hydrogenated at 0.5 bar until reaction was complete as judged by hydrogen uptake. The reaction mixture was filtered and washed with water (25mL), dried (MgSO4), filtered and evaporated to afford the sub-titled compound (0.33g). Used Directly.

b) 6-Amino-5-methoxypyrazine-2-carboxylic acid methyl ester
c) 6-(2,3-Dichlorophenylsulphonylamino)-5-methoxy-2-pyrazinecarboxylic acid, methyl ester

Prepared by the method of Example 1 (reaction performed at room temperature) using 6-amino-5-methoxy-2-pyrazinecarboxylic acid methyl ester (Example 201b) (0.3g) and 2,3-dichlorobenzenesulphonyl chloride (0.4g). Yield 0.15g.

m/e 392 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.39 (1H, s), 8.25 (1H, dd), 7.93 (1H, dd), 7.65 (1H, t), 3.99 (3H, s), 3.77 (3H, s)

MP 90-92°C

Example 202

2,3-Dichloro-N-[6-(hydroxymethyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide

Prepared as for example 120 using 6-(2,3-dichlorophenylsulphonylamino)-5-methoxy-2-pyrazinecarboxylic acid, methyl ester (Example 201) (0.12g). Yield 0.03g.

m/e 364 (M+1⁺, 100%)
$^1$H NMR (D6-DMSO) $\delta$ 11.5 (1H, br s), 8.13 (1H, dd), 7.92 (1H, dd), 7.77 (1H, br s), 7.59 (1H, t), 5.25 (1H, br s), 4.19 (2H, s), 3.87 (3H, s).

MP 153-155°C

Example 203

2,3-Dichloro-N-(5-methanesulphonyl-3-methoxy-2-pyrazinyl)benzenesulphonamide

Oxone (potassium peroxymonosulphate) (0.6g) was added to 2,3-dichloro-N-(3-methoxy-5-methylsulphanyl-2-pyrazinyl)benzenesulphonamide (Example 80) (0.3g) in methanol (40mL) and water (10mL) and the mixture heated at 50°C for 4h. After cooling, the mixture was filtered and evaporated. Purified by silica gel chromatography eluting with ethyl acetate/isoo-hexane mixtures containing 1% acetic acid to give the title compound.

Yield 0.2g.

m/e 411 (M+1$, 100%)

$^1$H NMR (CDCl$_3$) $\delta$ 8.33 (1H, s), 8.30 (1H, s), 8.23 (1H, br s), 7.72 (1H, dd), 7.47 (1H, t), 4.14 (3H, s), 3.11 (3H, s)

MP 237-238°C

Example 204

2-[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinyloxy]-N,N-diethylacetamide

Prepared as for Example 115b using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-[[2-(trimethylsilyl)ethoxy]methyl]benzenesulphonamide (Example 55a) (0.35g) and N,N-diethyl-2-hydroxyacetamide (0.13g). Yield 0.2g

m/e 463 (M+1$, 100%)

$^1$H NMR (CDCl$_3$) $\delta$ 8.22 (1H, dd), 7.68 (1H, dd), 7.52 (1H, s), 7.46 (1H, s), 7.37 (1H, t), 4.88 (2H, s), 3.92 (3H, s), 3.38 (2H, q), 3.30 (2H, q), 1.20 (3H, t), 1.11 (3H, t)
Example 205

2,3-Dichloro-N-[5-{2-(dimethylamino)ethylsulphonyl}-3-methoxy-2-pyrazinyl]benzenesulphonamide

Prepared as for Example 101b using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 55a) (0.3g) and 2-(dimethylamino)ethanethiol hydrochloride (0.2g). Yield 0.25g.

m/e 435(M-1+, 100%)

$^1$H NMR (D6-DMSO) δ 8.05 (1H, dd), 7.95 (1H, dd), 7.71 (1H, s), 7.58 (1H, t), 3.98 (3H, s), 3.47 (2H, m), 3.32 (2H, m), 2.77 (6H, s)

MP 117-118°C

Example 206

2,3-Dichloro-N-(5-difluoromethyl-3-methoxy-2-pyrazinyl)benzenesulphonamide

(Diethylamino)sulphur trifluoride (DAST) (0.15g) and 2,3-dichloro-N-(5-formyl-3-methoxy-2-pyrazinyl)benzenesulphonamide (Example 186a) (0.3g) in dichloromethane (20mL) was stirred at room temperature for 4h and then evaporated. Purified by silica gel chromatography eluting with ethyl acetate/isoo-hexane mixtures to give the title compound. Yield 0.06g.

m/e 382(M-1+, 100%)

$^1$H NMR (D6-DMSO) δ 8.14 (1H, dd), 7.96 (1H, dd), 7.84 (1H, s), 7.60 (1H, t), 6.80 (1H, t), 3.95 (3H, s)

MP 117-118°C

Example 207

2,3-Dichloro-4-fluoro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide
Sodium hydride (0.4g of a 60% dispersion in oil) was added to a solution of 3-methoxy-2-pyrazinamine (0.25g) in N-methylpyrrolidinone (10mL). After 0.5h, 2,3-dichloro-4-fluorobenzenesulphonyl chloride (Example 185a) (0.63g) was added. After 16h at room temperature the reaction mixture was quenched with 2M aqueous HCl, extracted with ethyl acetate, dried (MgSO₄) and evaporated. Purification was by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures. Yield 0.16g.

m/e 350/352 (M⁺, 100%)

¹H NMR (D₆-DMSO) δ 8.16 (1H, dd), 7.78 (1H, br s), 7.68 (1H, t), 7.62 (1H, br s), 3.9 (3H, s)

MP 192-194 °C

Example 208
2,3-Dichloro-N-[5-chloro-3-[1-(cyclopropyl)ethoxy]-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 31b using 1-(cyclopropyl)ethanol (0.1g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.1g). Yield 0.04g.

m/e 422 (M+1⁺, 100%)

¹H NMR (D₆-DMSO) δ 11.70-11.50 (1H, br s), 8.07 (1H, dd), 7.94 (1H, dd), 7.77 (1H, s), 7.59 (1H, t), 4.60-4.50 (1H, m), 1.33 (3H, d), 1.1-1.0 (1H, m), 0.6-0.3 (4H, m)

MP 161-162°C
Example 209
2,3-Dichloro-N-[5-chloro-3-(5-formyl-2-furanylmethoxy)-2-pyrazinyl]benzenesulphonamide

5 a) [5-(1,3-Dimethyl-2-imidazolidinyl)-2-furanyl]methanol

5-hydroxymethylfuran-2-carbaldehyde (5.0g) and N,N'-dimethylethane-1,2-diamine (3.8g) in toluene (100mL) was heated under reflux using a Dean and Stark apparatus. After 12h, the toluene was evaporated to give an oil. Yield 8.3g. Used directly.

10 b) 2,3-Dichloro-N-[5-chloro-3-(5-formyl-2-furanylmethoxy)-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 31b (reaction heated at 60°C for 4h) using [5-(1,3-dimethyl-2-imidazolidinyl)-2-furanyl]methanol (2.3g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (3.0g). The reaction was quenched with 2M hydrochloric acid and left for 16h. The solid product was collected. Purified by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures to give the title compound. Yield 2.5g.

m/e 410 (M+1<sup>+</sup>, 100%)

<sup>1</sup>H NMR (D6-DMSO) δ 9.64 (1H, s), 8.06 (1H, dd), 7.94 (1H, dd), 7.87 (1H, s), 7.57 (2H, d+t), 6.93 (1H, d), 5.47 (2H, d)

Example 210
2,3-Dichloro-N-[5-chloro-3-(5-cyclopropylaminomethyl-2-furanylmethoxy)-2-pyrazinyl]benzenesulphonamide
Prepared by the method of Example 107b using 2,3-dichloro-N-[5-chloro-3-(5-formyl-2-furanylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 209) (0.3g) and cyclopropylamine (0.1g). Yield 0.1g.

m/e 503 (M-1, 100%)

$^1$H NMR (D6-DMSO) $\delta$ 7.93 (1H, dd), 7.63 (1H, dd), 7.36 (1H, t), 7.30 (1H, s), 6.66 (1H, d), 6.63 (1H, d), 5.21 (2H, s), 4.34 (2H, s), 2.71 (1H, m), 0.76 (4H, m)

MP 175-176°C

**Example 211**

*N-[5,6-bis-(Hydroxymethyl)-3-methoxy-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide*

a) 2,3-Dichloro-N-(5,6-dicyano-3-methoxy-2-pyrazinyl)benzenesulphonamide

Prepared by the method outlined in Example 1 using 5-amino-6-chloro-2,3-dicyanopyrazine (1.8g) and 2,3-dichlorobenzenesulfonyl chloride (2.7g). The adduct was reacted by the method outlined in example 31b using sodium methoxide to afford the sub-titled compound that was used directly.

m/e 382, 383 (M-1, 100%)

b) 5-{{(2,3-Dichlorophenyl)sulphonyl]amino}-6-methoxypyrazine-2,3-dicarboxylic acid, dimethyl ester
The crude product from above (Example 211a) was dissolved in 10% aqueous sodium hydroxide solution and heated under reflux for 10 hours. The reaction mixture was cooled, concentrated and the residue was treated with thionyl chloride (30mL) and refluxed for 1 hour, cooled and concentrated, azeotroping with dry toluene. The resulting residue was dissolved in methanol (30mL) and allowed to stand for 10 hours and concentrated to afford the sub-titled compound that was used directly.

m/e 448, 450 (M-1^+, 100%)

c) N-[5,6-bis-(Hydroxymethyl)-3-methoxy-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

To a solution of 5-{{(2,3-dichlorophenyl)sulphonyl]amino}-6-methoxypyrazine-2,3-dicarboxylic acid, dimethyl ester (Example 211b, 0.5g) dissolved in anhydrous tetrahydrofuran (20 mL) at 0°C was added a solution of lithium triethylborohydride (Super hydride®) (5.55 mL of a 1M solution in tetrahydrofuran) and the resulting solution was stirred for 1 hour. The reaction was quenched by the addition of 1N hydrochloric acid (10 mL) and extracted into ethyl acetate (2x20mL). The combined extracts were dried (MgSO₄), filtered and concentrated to afford an oil that was purified by chromatography on silica gel eluting with ethyl acetate/dichloromethane mixtures to afford the titled compound (0.201 g) as a foam.

m/e 392, 394 (M-1^+, 100%)

^1H NMR (CDCl₃) δ 8.30 (1H, d); 7.91 (1H, br s), 7.71 (1H, d), 7.46 (1H, t), 4.59 (2H, s), 4.50 (2H, s), 4.0 (3H, s)

Example 212

N-[3-[(2-amino-4-oxazolyl)methoxy]-5-chloro-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

a) (4-Hydroxymethyl-2-oxazolyl)carbamic acid tert-butyl ester
Prepared by the method of Example 120 using 2-{bis[(1,1-dimethylethoxy)carbonyl]amino}-4-oxazolcarboxylic acid, ethyl ester (0.65g) and sodium triethylborohydride (5.5mL of a 1M solution in tetrahydrofuran). Yield 0.24g. Used directly.

b) \(N\)-[3-[(2-amino-4-oxazolyl)methoxy]-5-chloro-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

Prepared by the method of Example 112 using (4-hydroxymethyl-2-oxazolyl)carbamic acid \(\text{tert-}\)butyl ester (Example 212a) (0.12g) and 2,3-dichloro-\(N\)-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.21g). Purification was by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures to give the title compound with the BOC (\(\text{tert-}\)butyl carbonyl) attached (0.11g). This compound was dissolved in trifluoroacetic acid (1.5mL) and dichloromethane (1.5mL). After 2h, the solution was evaporated. Purification was by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures to give the title compound. Yield 0.08g.

\(^1\text{H NMR (D6-DMSO)} \delta 8.04 (1\text{H, dd}), 7.91 (1\text{H, dd}), 7.80 (1\text{H, s}), 7.55 (1\text{H, t}), 7.49 (1\text{H, s}), 6.71 (2\text{H, br s}), 5.10(2\text{H, s}).

\(\text{MP 137°C}\)
Pharmacological Analysis

FMAT Whole cell binding assay

Cells

CHO-K1 cells stably expressing the human recombinant CCR4 receptor (Euroscreen; Brussels, Belgium) were cultured in NUT.MIX.F.12(HAM) medium with glutamax-1, containing 10% (v/v) foetal bovine serum and 400 μg ml⁻¹ geneticin.

Cells were harvested at approximately 70% confluence by treatment with a cell dissociation buffer, and seeded at 5x10⁴ cells/100μl culture medium into wells of a black Costar clear-bottomed 96-well microtitre plates. Plates were incubated overnight at 37°C in 5% CO₂ and used the following day.

ASSAY

Before use, the cell plates were washed twice with 100 μl Hanks balanced salt solution (HBSS). To each well was then added 65μl of HBSS, 10 μL of 10% DMSO in HBSS ± test compound and then 25 μL of 2.8 nM FB-MDC (Applied Biosystems). This fluorescent probe was prepared from a 10μM stock in 0.08% (v/v) TFA/16% (v/v) acetonitrile, diluted into HBSS.

After two hours incubation in the dark at room temperature, the plates were analysed in an FMAT8100 reader (Applied Biosystems) to measure fluorescence that was associated with binding of FB-MDC to the cells. Compound activity was determined as an pIC₅₀ [log(concentration of compound that results in 50% inhibition)], comparing fluorescence in control and background wells.

Typical Data

Fluorescence (ctrl) = 1200
Fluorescence (bkg) = 0

The compounds of the examples all have a pIC₅₀ of greater than 5.0.
Data for specific compounds is given below.

<table>
<thead>
<tr>
<th>Example</th>
<th>pIC$_{50}$</th>
<th>Mean</th>
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<tbody>
<tr>
<td>Example 112</td>
<td>pIC$_{50}$</td>
<td>9.5</td>
</tr>
<tr>
<td>Example 119</td>
<td>pIC$_{50}$</td>
<td>7.2</td>
</tr>
<tr>
<td>Example 186</td>
<td>pIC$_{50}$</td>
<td>6.2</td>
</tr>
</tbody>
</table>
CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:

![Chemical Structure](image)

(I)

in which:

- $R^1$, $R^2$ and $R^3$ are independently hydrogen, halogen, cyano, CF$_3$, OCF$_3$, OC$_{1-6}$ alkyl or C$_{1-6}$ alkyl;
- $R^4$ is halogen, CO$_2$R$_{^{12}}$;
- C$_{1-6}$ alkoxy where the alkyl group may form a 3-6 membered saturated ring or may be substituted with 1-3 fluorine atoms or a cyano group;
- C$_{3-6}$ alkenyloxy or C$_{3-6}$ alkynyloxy where either may be optionally substituted with hydroxy or NR$_{^{14}}$R$_{^{15}}$;
- OC$_{1-6}$ alkyl-X-C$_{1-6}$ alkyl where the alkyl groups may form a 3-6 membered saturated ring;
- OC$_{1-6}$ alkylR$_{^{11}}$, or OC$_{2-6}$ alkyl-X-R$_{^{11}}$ where the alkyl group may form a 3-6 membered saturated ring and is optionally substituted with 1-3 groups selected from hydroxy, halogen, NR$_{^{14}}$R$_{^{15}}$, SR$_{^{13}}$, S(O)$_2$R$_{^{12}}$, S(O)R$_{^{13}}$ or COR$_{^{13}}$;
- OC$_{1-6}$ alkylR$_{^{16}}$. 
R
5
 and R
6
 are independently hydrogen, cyano, halogen, CO
2
R
12,
 CONR
14
R
15;

C
1-6
 alkyl optionally substituted by hydroxy, NR
14
R
15, or 1-3 fluorines;

C
1-6
 alkylR
11
 or XCH(R
11
)C
1-6
 alkyl or XCH(R
16
)C
1-6
 alkyl where the alkyl group may be optionally substituted with 1-3 groups selected from hydroxy, and NR
14
R
15;

NR
14
R
15, N(R
11
)R
11, X-(CH
2
)qNR
14
R
15, (CH
2
)nNR
14
R
15, NHC(O)C
1-6
 alkyl optionally substituted by one or more hydroxy groups,

C
3-6
 alkynyl or C
3-6
 alkenyl optionally branched and optionally substituted with 1-3 groups selected from hydroxy, cyano, halogen and =O;

R
11, X-R
11, X-R
12, X-C
1-6
alkylR
16, X-R
16, X-(CH
2
)nCO
2
R
12, X-(CH
2
)nCONR
14
R
15,

X-(CH
2
)nR
11, X-(CH
2
)nCN; X-(CH
2
)qOR
12, (CH
2
)nOR
12;

(CH
2
)n-X-R
11, X-(CH
2
)qNHC(O)NH
R
12, X-(CH
2
)qNHC(O)R
12;

X-(CH
2
)qNHS(O)R
12, X-(CH
2
)qNHS(O)R
11, X-C
3-6
alkenyl; X-C
3-6
alkynyl;

n is 1, 2, 3, 4 or 5;

q is 2, 3, 4, 5 or 6;

X is NR
13, O, S, S(O), S(O)2;

R
11
 is an aryl group or a 5-7 membered heteraromatic ring containing 1-4 heteroatoms selected from nitrogen, oxygen or sulphur each of which can be optionally substituted by 1-3 groups selected from halogen, C(O)NR
14
R
15, C(O)OR
12, hydroxy, =O, =S, CN, NO
2,
 COR
13, NR
14
R
15, X(CH
2
)qNR
14
R
15, (CH
2
)nNR
14
R
15, (CH
2
)nOH, SR
13, S(O)R
13, S(O)2R
13

C
1-6
 alkyl-X-C
1-6
 alkyl, C
1-6
 alkyl or C
1-6
 alkoxy where the alkyl group may form a 3-6 membered ring or is optionally substituted with 1-3 groups selected from hydroxy, halogen, NR
14
R
15, SR
13, S(O)R
13, S(O)2R
13;

R
12
 and R
13
 are independently hydrogen or C
1-6
 alkyl where the alkyl group may be substituted with 1-3 fluorine atoms or may form a saturated 3-6 membered ring;

R
14
 and R
15
 are independently hydrogen, C
1-6
 alkyl, C
3-6
cycloalkyl or (CH
2
)qOH,
or $R^{14}$ and $R^{15}$ together with the nitrogen atom to which they are attached form a 4-8 membered saturated ring containing 1-3 heteroatoms selected from nitrogen, oxygen and sulphur and optionally substituted by C$_{1-6}$ alkyl, C$_{1-6}$ alkyl-OH, or hydroxy; and

5 $R^{16}$ is a 4-8 membered saturated ring containing 1-3 heteroatoms selected from nitrogen, oxygen or sulphur and optionally substituted with 1-3 groups selected from hydroxy, cyano, halogen and $=O$,

provided that:

- when $R^4$ is halogen or C$_{1-4}$alkoxy and $R^5$ is hydrogen, halogen, C$_{1-4}$alkyl, C$_{1-2}$alkoxy, C$_{1-2}$alkylthio, trifluoromethyl or ethynyl and when one of $R^1$, $R^2$ or $R^3$ is C$_{1-6}$alkyl or C$_{1-6}$alkoxy and is meta to the sulphonamide group then the group ortho to both the sulphonamide group and the C$_{1-6}$alkyl or C$_{1-6}$alkoxy group is not hydrogen,

- when $R^4$ is halogen or C$_{1-4}$alkoxy and $R^5$ is hydrogen, halogen, C$_{1-4}$alkyl, C$_{1-2}$alkoxy, C$_{1-2}$alkylthio, trifluoromethyl or ethynyl and when one of $R^1$, $R^2$ or $R^3$ is C$_{1-6}$alkyl or C$_{1-6}$alkoxy and is ortho to the sulphonamide group then the group ortho to the C$_{1-6}$Alkyl or C$_{1-6}$alkoxy and also meta to the sulphonamide group is not hydrogen,

- when two of $R^1$, $R^2$, $R^3$ are hydrogen and the other is a methyl group para to the sulphonamide and $R^4$ is methoxy then $R^5$ is not hydrogen or bromo, and

- when $R^2$ is methyl and $R^6$ is methoxy and one of $R^1$, $R^2$ or $R^3$ is bromo or iodo and the other two are both hydrogen, then the bromo or iodo group is not ortho to the sulphonamide group.

2. A compound according to claim 1 in which one of $R^1$, $R^2$ and $R^3$ is hydrogen and the other is chloro, bromo or methyl.

3. A compound according to claim 1 or 2 in which $R^4$ is C$_{1-6}$ alkoxy such as methoxy, 2-furanylmethoxy, bromo, chloro, 2-methoxyethoxy, (5-methyl-3-isoxazolyl)methoxy, pyridylmethoxy, 3-pyridazinylmethoxy, methoxy, 2-(1-imidazolyl)ethoxy, (2-methyl-4-oxazolyl)methoxy and 4-methoxyphenylmethoxy.

4. A compound according to any one of claims 1 to 3 in which $R^2$ is hydrogen, halogen such as bromo and chloro, phenyl-C$_{1-6}$ alkyl such as methyl, CH$_3$OH, cyano and
2-aminothanol

5. A compound according to any one of claims 1 to 3 in which \( R^6 \) is hydrogen, \( C_{1-6} \) alkyl, \( \text{CH}_2\text{OH} \) and halogen.

6. A compound according to claim 1 in which is:
2,3-Dichloro-\( N \)-(3-methoxy-5-methyl-2-pyrazinyl)-benzenesulphonamide
\( N \)-(6-Chloro-3-methoxy-2-pyrazinyl)-2,3,4-tifluorobenzenesulphonamide
3-Chloro-\( N \)-(6-chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide
2,3-Dichloro-\( N \)-(6-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-\( N \)-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
\( N \)-(5-Bromo-3-methoxy-2-pyrazinyl)-2,5-dichlorobenzenesulphonamide
\( N \)-(5-Bromo-3-methoxy-2-pyrazinyl)-3,5-dichlorobenzenesulphonamide
\( N \)-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide
\( N \)-(5-Bromo-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide
\( N \)-(5-Bromo-3-methoxy-2-pyrazinyl)-3,4-dichlorobenzenesulphonamide
\( N \)-(5-Bromo-3-methoxy-2-pyrazinyl)-4-chlorobenzenesulphonamide
\( N \)-(5-Bromo-3-methoxy-2-pyrazinyl)-3-chlorobenzenesulphonamide
\( N \)-(3-Methoxy-5-methyl-2-pyrazinyl)-2-fluorobenzenesulphonamide
\( N \)-(3-Methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide
\( N \)-(3-Methoxy-5-methyl-2-pyrazinyl)-2-iodobenzenesulphonamide
\( N \)-(3-Methoxy-5-methyl-2-pyrazinyl)-3-fluorobenzenesulphonamide
2-[(3-Methoxy-5-methyl-2-pyrazinyl)amino]sulphonylbenzonitrile
\( N \)-(5-Bromo-3-methoxy-2-pyrazinyl)benzenesulphonamide
\( N \)-(5-Bromo-3-methoxy-2-pyrazinyl)2-iodobenzenesulphonamide
2,3-Dichloro-\( N \)-[3-(2-furanylmethoxy)-5-methyl-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\( N \)-[5-methyl-3-(5-methyl-3-isoxazolymethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\( N \)-[5-methyl-3-(2-pyridylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\( N \)-[5-methyl-3-(6-methyl-2-pyridylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\( N \)-[5-methyl-3-(3-pyridylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\( N \)-[5-methyl-3-(4-pyridylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\( N \)-[5-methyl-3-(3-methyl-2-pyridylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\( N \)-[5-methyl-3-(3-pyridazylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[3-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide
N-[5-Bromo-3-(2-pyrazinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(1-methyl-6-oxo-1,6-dihydro-3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(3-pyridazinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(5-pyrimidinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Chloro-3-(5-pyrimidinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
2-Chloro-N-(6-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
4-Chloro-N-(6-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
N-(6-Chloro-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide
N-(6-Chloro-3-methoxy-2-pyrazinyl)-3,4-dichlorobenzenesulphonamide
3-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-2-methylbenzenesulphonamide
2-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide
3-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide
4-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide
2,4-Dichloro-N-(3-methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide
3,4-Dichloro-N-(3-methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-trifluoromethoxybenzenesulphonamide
3-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide
2-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
3-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
4-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
N-(5-Chloro-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide
2,3-Dichloro-N-[3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[3,5-dimethoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[3-methoxy-5-(1-pyrrolinyl)-2-pyrazinyl]benzenesulphonamide
3-Chloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide
2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
2-Chloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
3-Chloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
4-Chloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
2,4-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide
3,4-Dichloro-\(N-(5,6\text{-dichloro-3-methoxy-2-pyrazinyl})\)benzenesulphonamide
2,3-Dichloro-\(N-(3\text{-methoxy-5,6-dimethyl-2-pyrazinyl})\)benzenesulphonamide
2,3-Dichloro-\(N-(6\text{-chloro-3,5-dimethoxy-2-pyrazinyl})\)benzenesulphonamide
2,3-Dichloro-\(N-[6\text{-chloro-3-methoxy-5-(4-morpholinyl)-2-pyrazinyl}]\)benzenesulphonamide
2,3-Dichloro-\(N-[6\text{-chloro-5-(2-hydroxyethylamino)-3-methoxy-2-pyrazinyl}]\)benzenesulphonamide
2,3-Dichloro-\(N-[6\text{-chloro-5-dimethylamino-3-methoxy-2-pyrazinyl}]\)benzenesulphonamide
2,3-Dichloro-\(N-[6\text{-chloro-3-methoxy-5-(2-methoxyethoxy)-2-pyrazinyl}]\)benzenesulphonamide
2,3-Dichloro-\(N-[6\text{-chloro-5-hydroxy-3-methoxy-2-pyrazinyl}]\)benzenesulphonamide
2,3-Dichloro-\(N-[6\text{-methoxy-5-([2,2\text{-bipyrazinyl}]\)benzenesulphonamide}
4-[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinyl]oxy]benzoic acid
2,3-Dichloro-\(N-(3,5\text{-dichloro-2-pyrazinyl})\)benzenesulphonamide
2,3-Dichloro-\(N-[6\text{-chloro-3-methoxy-5-([2-methoxyethyl]amino)-2-pyrazinyl}]\)benzenesulphonamide
\(N\)-\{[3-Chloro-5-(2,3-dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylamino]ethyl\} acetamide
2,3-Dichloro-\(N-[5-(4-hydroxymethyl-1-piperidinyl)-3-methoxy-2-pyrazinyl]\)benzenesulphonamide
2,3-Dichloro-\(N-[5\text{-cyano-3-(3-pyridinylmethoxy)-2-pyrazinyl}]\)benzenesulphonamide
2,3-Dichloro-\(N-(6\text{-chloro-3-methoxy-5-methylamino-2-pyrazinyl})\)benzenesulphonamide
2,3-Dichloro-\(N-(3\text{-methoxy-5-methylsulphanil-2-pyrazinyl})\)benzenesulphonamide
2,3-Dichloro-\(N-[5\text{-[2,4-difluorophenyl]-3-methoxy-2-pyrazinyl}]\)benzenesulphonamide
[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazineylsulphanyl]acetic acid methyl ester
[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazineylsulphanyl]acetic acid
2,3-Dichloro-\(N-[5\text{-[2-chlorobenzylsulphanil-3-methoxy-2-pyrazinyl}]\)benzenesulphonamide
2,3-Dichloro-\(N-[6\text{-chloro-5-(3-hydroxy-1-azetidinyl)-3-methoxy-2-pyrazinyl}]\)benzenesulphonamide
2,3-Dichloro-\(N-[5\text{-methyl-3-(1-oxy-3-pyrazinylmethoxy)-2-pyrazinyl}]\)benzenesulphonamide
2,3-Dichloro-\(N-[5\text{-chloro-3-(4-pyridinylmethoxy)-2-pyrazinyl}]\)benzenesulphonamide
2,3-Dichloro-\(N-[5\text{-chloro-3-(1-oxy-4-pyridinylmethoxy)-2-pyrazinyl}]\)benzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-(2-methylsulphonylthoxy)-2-pyrazinyl]benzenesulphonamide
N-(3-Butoxy-5-chloro-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-(2-methyl-3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-(6-methyl-2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-(1-oxo-2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
3-Chloro-N-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2-methylbenzenesulphonamide
3-Chloro-N-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2-fluorobenzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-(4-methoxyphenylmethoxy)-2-pyrazinyl]benzenesulphonamide
N-[5-Bromo-6-chloro-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
2,3-Dichloro-N-[6-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[6-chloro-3-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
N-[5-(2-Aminoethylsulphonyl)-3-(2-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-(6-methoxy-3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
N-[3-(3-Bromophenylmethoxy)-5-chloro-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
3-[6-Chloro-3-(2,3-dichlorobenzenesulphonylamino)-2-pyrazinyl]oxymethyl]benzoic acid methyl ester
3-[6-Chloro-3-(2,3-dichlorobenzenesulphonylamino)-2-pyrazinyl]oxymethyl]benzoic acid
2,3-Dichloro-N-[5-chloro-3-(3-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-(3-methylaminomethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-{3-[(2-hydroxyethylamino)methyl]phenylmethoxy}-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-(4-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-{4-[(2-hydroxyethylamino)methyl]phenylmethoxy}-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[3-(4-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-(2-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide
5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxypyrazine-2-carboxylic acid, methyl ester

2,3-Dichloro-N-[5-(1-hydroxy-1-methylethyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide
N':[5-(2-Aminoethoxy)-3-methoxy-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N'-{5-[(2-Aminoethyl)thio]-6-chloro-3-methoxy-2-pyrazinyl}'-2,3-dichlorobenzenesulphonamide

3-[[{2,3-Dichlorophenyl}sulphonylamino]-6-methoxy-2-pyrazinyl]thio]propanoic acid, methyl ester

2,3-Dichloro-N-[5-bromo-3-methoxy-6-methyl-2-pyrazinyl]benzenesulphonamide
5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-3-methylpyrazine-2-carboxylic acid, methyl ester

2,3-Dichloro-N-[5-(hydroxymethyl)-3-methoxy-6-methyl-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5,6-dichloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
3-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-2-fluorobenzenesulphonamide
3-Chloro-2-fluoro-N-[3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

3-[(2,3-Dichlorophenyl)sulphonylamino]pyrazine-2-carboxylic acid, methyl ester
N-(5-Bromo-6-chloro-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide
3-Chloro-5-[(2,3-dichlorophenyl)sulphonylamino]-6-methoxypyrazine-2-carboxylic acid, methyl ester

2,3-Dichloro-N-[6-chloro-5-(hydroxymethyl)-3-methoxypyrazin-2-yl]benzenesulphonamide
2,3-Dichloro-N-[3-[(6-methoxy-3-pyridinyl)methoxy]-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[6-chloro-3-methoxy-5-(methoxymethyl)-2-pyrazinyl]benzenesulphonamide
2-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-3-fluorobenzenesulphonamide
2-Chloro-3-fluoro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide
2-Chloro-3-methoxy-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide
N-[5-Bromo-3-[(2S)-2-pyrrolidinylmethoxy]-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
5-(2,3-Dichlorobenzenesulphonylamino)-6-(3-pyridinylmethoxy)pyrazine-2-carboxylic acid, methyl ester
5-\{(2,3-Dichlorophenyl)sulphonylamino\}-6-(3-pyridinylmethoxy)-2-pyrazinecarboxamide
2,3-Dichloro-N-[5-(4-pyridinyl)-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5-(hydroxymethyl)-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide
N-(5-Allyloxy-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide
2,3-Dichloro-N-[5-(3-hydroxy-1-propynyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide
N-\{3-[(5-Bromo-3-pyridinyl)methoxy]-5-chloro-2-pyrazinyl\}-2,3-dichlorobenzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-\{6-(hydroxymethyl)-2-pyridinyl\}methoxy]-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-\{(2-methyl-4-oxazolyl)\}methoxy]-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-\{3-\{(2-methyl-4-oxazolyl)\}methoxy\}-2-pyrazinyl]benzenesulphonamide
N-[5-Bromo-3-(phenylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(2-cyclopentyloxy)pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(3-thienylmethoxy)pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-\{(2-methyl-3-furanyl)\}methoxy]-2-pyrazinyl] \{-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-\{(3-furanyl)\}methoxy]-2-pyrazinyl] -2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-\{(4-fluorophenyl)\}methoxy]-2-pyrazinyl] -2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-\{(3-fluorophenyl)\}methoxy]-2-pyrazinyl] -2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-\{(2-pyridinyl)propoxy\}-2-pyrazinyl] -2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(pentyloxy)-2-pyrazinyl] -2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(propoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(2-methoxyethoxy)-2-pyrazinyl] -2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(2-ethoxyethoxy)-2-pyrazinyl] -2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-(2-fluoroethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-[2-(1H-imidazol-1-yl)ethoxy]-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-\{(3-pyridinyl)propoxy\}-2-pyrazinyl] -2,3-dichlorobenzenesulphonamide
N-[5-Bromo-3-\{(2-(methylamino)ethoxy\}]-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-{5-Bromo-3-[3-(4-hydroxyphenyl)propoxy]-2-pyrazinyl}-2,3-
dichlorobenzensulphonamide
N-{5-Bromo-3-(2-phenoxyethoxy)-2-pyrazinyl}-2,3-dichlorobenzensulphonamide
N-{5-Bromo-3-(cyclopropylmethoxy)-2-pyrazinyl}-2,3-dichlorobenzensulphonamide
N-{5-Bromo-3-(3-phenoxypropoxy)-2-pyrazinyl}-2,3-dichlorobenzensulphonamide
2,3-Dichloro-N-(5-ethoxy-3-methoxy-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-N-[3-methoxy-5-([1,2,4]1-triazolyl)-2-pyrazinyl]benzenesulphonamide
2-[5-(2,3-Dichlorobenzensulphonylamino)-6-methoxy-2-pyrazinylsulphonyl]-N-
methylacetamide
2-[5-(2,3-Dichlorobenzensulphonylamino)-6-methoxy-2-pyrazinylsulphonyl]acetamide
2,3-Dichloro-N-[5-(4-fluorobenzylsulphonyl)-3-methoxy-2-
pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5-cyanomethylsulphonyl-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[3-methoxy-5-([1,2,4]-3-oxadiazolylmethylsulphonyl)-2-
pyrazinyl]benzenesulphonamide
N-[5-(2-Aminoethylsulphonyl)-3-methoxy-2-pyrazinyl]-2,3-dichlorobenzensulphonamide
2,3-Dichloro-N-[3-methoxy-5-(5-methyl-3-isoxazolylmethoxy))]-2-
pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5-(5-dimethylaminomethyl-2-furanylmethoxy)-3-methoxy-2-
pyrazinyl]benzenesulphonamide
N-[5-Bromo-3-(5-dimethylaminomethyl-2-furanylmethoxy)-2-pyrazinyl]-2,3-dichloro-
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2,3-Dichloro-N-[5-(2-hydroxyethylsulphonyl)-3-methoxy-2-
pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-{5-[2-(ethylureido)ethylsulphonyl]-3-methoxy-2-
pyrazinyl}benzenesulphonamide
2,3-Dichloro-N-[3-(5-dimethylaminomethyl-2-furanylmethoxy)-2-
pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[6-chloro-3-(5-dimethylaminomethyl-2-furanylmethoxy)-2-
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2,3-Dichloro-N-[6-chloro-3-(5-methylaminomethyl-2-furanylmethoxy)-2-
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2,3-Dichloro-N-[5-chloro-3-(5-dimethylaminomethyl-2-furanylmethoxy)-2-
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2,3-Dichloro-N-[3-(5-methylaminomethyl-2-furanylmethoxy)-2-
pyrazinyl]benzenesulphonamide
\(N\)-(5-Bromo-3-methoxypyrazinyl)-2-cyanobenzenesulphonamide
\(N\)-(5-Bromo-3-methoxypyrazinyl)-2,3-dichloro-4-fluorobenzenesulphonamide
2,3-Dichloro-\(N\)-[3-methoxy-5-(4-morpholinylmethyl)-2-pyrazinyl]benzenesulphonamide
\(N\)-(3-Allyloxy-5-chloro-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide
2,3-Dichloro-\(N\)-[5-chloro-3-(2-propynloxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\(N\)-[3-(2-propynloxy)-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\(N\)-[5-cyano-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\(N\)-[3-methoxy-5-[(2S)-pyrrolidin-2-ylmethoxy]-2-pyrazinyl]benzenesulphonamide hydrochloride
2,3-Dichloro-\(N\)-[6-chloro-3-methoxy-5-[(2R)-2-pyrrolidinylmethoxy]-2-pyrazinyl]benzenesulphonamide Hydrochloride
2,3-Dichloro-\(N\)-[3-methoxy-5-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide Hydrochloride
2,3-Dichloro-\(N\)-[3-methoxy-6-methyl-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\(N\)-[3-methoxy-5-([1H-1,2,4-triazol-1-ylmethyl]-2-pyrazinyl]benzenesulphonamide
\(N\)-(3-(5-Aminomethyl-2-furanylmethoxy)-5-chloro-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide
\(N\)-(3-(5-Aminomethyl-2-furanylmethoxy)-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide
2,3-Dichloro-\(N\)-[3-methoxy-5-(2-propyn-1-yloxy)-2-pyrazinyl]benzenesulphonamide
\{[5-(2,3-Dichlorophenylsulfonylamino)-6-methoxy-2-pyrazinyl]oxy\} acetic acid, methyl ester
\(N\)-[5-(2,3-Dichlorophenylsulphonamino)-6-methoxy-2-pyrazinyl]-2-hydroxyacetamide
6-(2,3-Dichlorophenylsulphonamino)-5-methoxy-2-pyrazinecarboxylic acid, methyl ester
2,3-Dichloro-\(N\)-[6-(hydroxymethyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\(N\)-[5-methanesulphonyl-3-methoxy-2-pyrazinyl]benzenesulphonamide
2-[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinyl]oxy\}-\(N\),\(N\)-diethylacetamide
2,3-Dichloro-\(N\)-[5-[2-(dimethylamino)ethylsulphonyl]-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\(N\)-[5-difluoromethyl-3-methoxy-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-4-fluoro-\(N\)-(3-methoxy-2-pyrazinyl)benzenesulphonamide
2,3-Dichloro-\(N\)-[5-chloro-3-[1-(cyclopropyl)ethoxy]-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-\(N\)-[5-chloro-3-[5-formyl-2-furanylmethoxy]-2-pyrazinyl]benzenesulphonamide
2,3-Dichloro-N-[5-chloro-3-(5-cyclopropylaminomethyl-2-furanylmethoxy)-2-pyrazinyl]-benzenesulphonamide
N-[5,6-bis-(Hydroxymethyl)-3-methoxy-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
N-[3-[(2-amino-4-oxazolyl)methoxy]-5-chloro-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
and pharmaceutically acceptable salts and solvates thereof.

7. A process for the preparation of compound (I) which comprises:
   (a) reaction of a compound of formula (II):

   ![Chemical Structure](image)

   (II)

   where R⁴, R⁵ and R⁶ are as defined in formula (I) or are protected derivatives thereof with a compound of formula (III):

   ![Chemical Structure](image)

   (III)

   where R¹, R² and R³ are as defined in formula (I) or are protected derivatives thereof and LG is a leaving group, or

   (b) for compounds where R⁴ is C₁₋₆ alkoxy where the alkyl group may form a 3-6 membered saturated ring or may be substituted with 1-3 fluorine atoms or a cyano group; C₃₋₆ alkenyloxy or C₃₋₆ alkynyloxy where either may be optionally substituted with hydroxy or NR¹⁴R¹⁵, OC₁₋₆ alkyl-X-C₁₋₆ alkyl where the alkyl groups may form a 3-6 membered saturated ring; OC₁₋₆ alkylR¹¹, or OC₂₋₆ alkyl-X-R¹¹ where the alkyl group may form a 3-6 membered saturated ring and is optionally substituted with 1-3 groups selected from hydroxy, halogen, NR¹⁴R¹⁵, SR¹³, S(O)₂R¹¹, S(O)R¹¹; or
OC_{1-6} \text{alkylR}^{16};

treating a compound of the formula (VI), where LG is a leaving group:

(VI)

with a compound of formula (V) in the presence of a suitable base, or

(c) for compounds of structure (I), where R^5 is an optionally substituted aryl or heteroaryl ring as defined above, reacting a compound of formula (XI) or (VII) where LG is a leaving group with an aryl or heteroaryl boronic acid in the presence of a palladium catalyst and a suitable base at elevated temperature:

(VII) \quad \rightarrow \quad (I)

and optionally thereafter process (a), (b) or (c)

- removing any protecting groups,
- converting a compound of formula (I) to a further compound of formula (I)
- forming a pharmaceutically acceptable salt.
8. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. A process for the preparation of a pharmaceutical composition as claimed in claim 2 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1 with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

11. A method of treating a chemokine mediated disease wherein the chemokine binds to one or more chemokine receptors, which comprises administering to a patient a therapeutically effective amount of a compound of formula (IB), or a pharmaceutically acceptable salt or solvate thereof:

(IB)

where:

R¹, R² and R³ are independently hydrogen, halogen, cyano, CF₃, or C₁₋₆ alkyl;

R⁴ is halogen, CO₂R¹₂,

C₁₋₆ alkoxy where the alkyl group may form a 3-6 membered saturated ring or may be substituted with 1-3 fluorine atoms or a cyano group;

C₃₋₆ alkenyloxy or C₃₋₆ alkynyloxy where either may be optionally substituted with hydroxy or NR¹⁴R¹⁵,
OC₁₋₆ alkyl-X-C₁₋₆ alkyl where the alkyl groups may form a 3-6 membered saturated ring;

OC₁₋₆ alkylR\(^{11}\), or OC₂₋₆ alkyl-X-R\(^{11}\) where the alkyl group may form a 3-6 membered saturated ring and is optionally substituted with 1-3 groups selected from hydroxy, halogen, NR\(^{14}\)R\(^{12}\), SR\(^{13}\), S(O)₂R\(^{13}\), S(O)R\(^{13}\);

OC₁₋₆ alkylR\(^{16}\);

R\(^{5}\) and R\(^{6}\) are independently hydrogen, cyano, halogen, CO₂R\(^{12}\), CONR\(^{14}\)R\(^{15}\);

C₁₋₆ alkyl optionally substituted by hydroxy, NR\(^{14}\)R\(^{15}\), or 1-3 fluorines;

C₁₋₆ alkylR\(^{11}\) or XCH(R\(^{11}\))C₁₋₆ alkyl or XCH(R\(^{16}\))C₁₋₆ alkyl where the alkyl group may be optionally substituted with 1-3 groups selected from hydroxy, and NR\(^{14}\)R\(^{15}\);

NR\(^{14}\)R\(^{15}\), N(R\(^{11}\))R\(^{11}\), X-(CH\(_{2}\))qNR\(^{14}\)R\(^{15}\), (CH\(_{2}\))nNR\(^{14}\)R\(^{15}\);

C₃₋₆ alkenyl or C₃₋₆ alkenyl optionally branched and optionally substituted with 1-3 groups selected from hydroxy, cyano, halogen and =O;

R\(^{11}\), X-R\(^{11}\), X-R\(^{12}\), X-C₁₋₆ alkylR\(^{16}\), X-R\(^{16}\), X-(CH\(_{2}\))nCO₂R\(^{12}\), X-(CH\(_{2}\))nCONR\(^{14}\)R\(^{15}\), X-(CH\(_{2}\))nR\(^{11}\), X-(CH\(_{2}\))nCN; X-(CH\(_{2}\))qOR\(^{12}\), (CH\(_{2}\))nOR\(^{12}\), (CH\(_{2}\))n-X-R\(^{11}\), X-(CH\(_{2}\))qNHCO(O)NHR\(^{12}\), X-(CH\(_{2}\))qNHCO(O)R\(^{12}\), X-(CH\(_{2}\))qNHS(O)₂R\(^{12}\), X-(CH\(_{2}\))qNHS(O)₂R\(^{11}\), X-C₃₋₆ alkenyl; X-C₃₋₆ alkenynyl;

n is 1, 2, 3, 4 or 5;

q is 2, 3, 4, 5 or 6;

X is NR\(^{13}\), O, S, S(O), S(O)₂;

R\(^{11}\) is an aryl group or a 5-7 membered heteraromatic ring containing 1-4 heteroatoms selected from nitrogen, oxygen or sulphur each of which can be optionally substituted by 1-3 groups selected from halogen, C(O)NR\(^{14}\)R\(^{15}\), C(O)OR\(^{12}\), hydroxy, =O, =S, CN, NO₂,

NR\(^{14}\)R\(^{15}\), X(CH\(_{2}\))qNR\(^{14}\)R\(^{15}\), (CH\(_{2}\))nNR\(^{14}\)R\(^{15}\), (CH\(_{2}\))nOH, SR\(^{13}\), S(O)R\(^{13}\), S(O)₂R\(^{13}\).
C_{1-6} alkyl-X-C_{1-6} alkyl, C_{1-6} alkyl or C_{1-6} alkoxy where the alkyl group may form a 3-6 membered ring or is optionally substituted with 1-3 groups selected from hydroxy, halogen, NR^{14}R^{15}, SR^{13}, S(O)R^{13}, S(O)_{2}R^{13};

R^{12} and R^{13} are independently hydrogen or C_{1-6} alkyl where the alkyl group may be substituted with 1-3 fluorine atoms or may form a saturated 3-6 membered ring;

R^{14} and R^{15} are independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or (CH_{2})qOH,

or R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4-8 membered saturated ring containing 1-3 heteroatoms selected from nitrogen, oxygen and sulphur and optionally substituted by C_{1-6} alkyl, C_{1-6} alkyl-OH, or hydroxy; and

R^{16} is a 4-8 membered saturated ring containing 1-3 heteroatoms selected from nitrogen, oxygen or sulphur and optionally substituted with 1-3 groups selected from hydroxy, cyano, halogen and =O,

12. A method according to claim 11 in which the chemokine receptor belongs to the CCR chemokine receptor subfamily.

13. A method according to claim 11 or 12 in which the chemokine receptor is the CCR4 receptor.

14 A method of treating an inflammatory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (IB), or a pharmaceutically acceptable salt or solvate thereof, as defined in claim 11.

15. A method according to claim 14, wherein the disease is asthma.
# INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

- C07D 241/22, 401/12, 403/04, 403/12, 405/12, 409/12, 413/04, 413/12,
- A61K 31/4965, A61P 11/06, 29/00

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

**B. FIELDS SEARCHED**

- Minimum documentation searched (classification system followed by classification symbol)
  - IPC7: C07D, A61K, A61P

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 database consulted during the international search (name of database and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>WO 9526957 A1 (ZENECA LIMITED), 12 October 1995 (12.10.95), see page 55, step(i)</td>
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<td>X</td>
<td>STN International, File CAPPLUS, CAPPLUS accession no. 2000:34745, Document no. 132:93309, Bristol-Myers Squibb Bo.: &quot;Preparation of N-isoxazolyl biphenylsulfonamides and related compounds as dual angiotensin II and endothelin receptor antagonists&quot;; &amp; WO,A1,2000001389, 20000113, see compound with CAS RN 25475-89-9</td>
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<td>GB 2295616 A (ZENECA LIMITED), 5 June 1996 (05.06.96), see particularly page 19, first paragraph; claim 3; examples</td>
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Further documents are listed in the continuation of Box C.

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Date of the actual completion of the international search: 22 April 2003

Date of mailing of the international search report: 24-04-2003

Name and mailing address of the ISA/Swedish Patent Office:
- Box 5055, S-102 42 STOCKHOLM
- Facsimile No. +46 8 666 02 86

Authorized officer:
- Nebil Gecer/E6
- Telephone No. +46 8 782 25 00
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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**INTERNATIONAL SEARCH REPORT**

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **11–15**
   - because they relate to subject matter not required to be searched by this Authority, namely:
     
     *see next sheet*

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).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ 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.:

4. ☐ 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.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant’s protest.

☐ No protest accompanied the payment of additional search fees.

*Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)*
Claims 11-15 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.
<table>
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<td>WO 9526957 A1</td>
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<td>AU 2077795 A</td>
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