Compositions of formula (I), wherein R<sup>1</sup> represents a substituent selected from: a hydrogen or halogen atom; a hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethanesulfonyloxy, C<sub>1</sub>-alkyl, C<sub>1</sub>-alkoxy, arylC<sub>1</sub>-alkoxy, C<sub>1</sub>-alkythio, C<sub>1</sub>-alkoxyC<sub>1</sub>-alkyl, C<sub>1</sub>-alkoxycycloalkylC<sub>1</sub>-alkoxy, C<sub>1</sub>-alkanoyl, C<sub>1</sub>-alkoxycarbononyl, C<sub>1</sub>-alkylsulphonyl, C<sub>1</sub>-alkylsulphonyloxy, C<sub>1</sub>-alkylsulphonamidoC<sub>1</sub>-alkyl, C<sub>1</sub>-alkylamido, C<sub>1</sub>-alkylsulphonamidoC<sub>1</sub>-alkyl, arylalkylamido, arylcarboxamido, aryIcarboxamidoC<sub>1</sub>-alkyl, aryl, arylC<sub>1</sub>-alkyl, or arylC<sub>1</sub>-alkanoyl group; a group R<sup>3</sup>COCH<sub>2</sub>R<sup>4</sup>, R<sup>3</sup>CONHCH<sub>2</sub>R<sup>4</sup>, R<sup>3</sup>NCOCH<sub>2</sub>R<sup>4</sup>, R<sup>3</sup>CONHCH<sub>2</sub>R<sup>4</sup> is a part of a C<sub>5</sub>-azacycloalkane or C<sub>5</sub>-azacycloalkane ring and p represents zero or an integer from 1 to 4; or a group Ar<sub>r</sub> where Ar<sub>r</sub> represents an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered aromatic heterocyclic ring and Z represents a bond, O, S, or CH<sub>2</sub>; R<sup>2</sup> represents a hydrogen atom or a C<sub>1</sub>-alkyl group; q is 1 or 2; Ar represents an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered aromatic heterocyclic ring; or an optionally substituted bicyclic aromatic or heteroaromatic ring system; and salts thereof. Compounds of formula (I) and their salts have affinity for dopamine receptors, in particular the D<sub>3</sub> receptor, and thus potential in the treatment of conditions wherein modulation of the D<sub>3</sub> receptor is beneficial, e.g. as antipsychotic agents.
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TETRAHYDROISOQUINOLINE DERIVATIVES AND THEIR PHARMACEUTICAL USE

The present invention relates to novel tetrahydroisoquinoline derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy, as modulators of dopamine D3 receptors, in particular as antipsychotic agents.

US Patent No. 5,294,621 describes tetrahydropyridine derivatives of the formula:

(wherein is an optionally substituted thieryl or optionally substituted phenyl ring; R\(^1\), R\(^2\) and R\(^3\) are each inter alia hydrogen; X is inter alia (CH\(_2\))\(^m\)NR\(^7\)CO; m is 2-4; and Ar\(^1\) is an optionally substituted heterocyclic ring or an optionally substituted phenyl ring. The compounds are said to be useful as antiarrhythmic agents.

We have now found a class of tetrahydroisquinoline derivatives which have affinity for dopamine receptors, in particular the D\(_3\) receptor, and thus potential in the treatment of conditions wherein modulation of the D\(_3\) receptor is beneficial, eg as antipsychotic agents.

In a first aspect the present invention provides compounds of formula (I):

(wherein:

R\(^1\) represents a substituent selected from: a hydrogen or halogen atom; a hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethanesulfonyloxy, C\(_{1-4}\)alkyl, C\(_{1-4}\)alkoxy, arylC\(_{1-4}\)alkoxy, C\(_{1-4}\)alkylthio, C\(_{1-4}\)alkoxyC\(_{1-4}\)alkyl, C\(_3-6\)cycloalkylC\(_{1-4}\)alkoxy, C\(_{1-4}\)alkanoyl, C\(_{1-4}\)alkoxycarbonyl, C\(_{1-4}\)alkylsulphonyl, C\(_{1-4}\)alkylsulphonyloxy, C\(_{1-4}\)alkylsulphonylC\(_{1-4}\)alkyl, arylsulphonyl, arylsulphonyloxy, arylsulphonylC\(_{1-4}\)alkyl, C\(_{1-4}\)alkylsulphonamido, C\(_{1-4}\)alkylamido, 

\( \text{Ar} \))
C_{1-4}alkylsulphonamidoC_{1-4}alkyl, C_{1-4}alkylamidoC_{1-4}alkyl, arylsulphonamido, arylcarboxamido, arylsulphonamidoC_{1-4}alkyl, arylcarboxamidoC_{1-4}alkyl, aroyl, aroylC_{1-4}alkyl, or arylC_{1-4}alkanoyl group; a group R^3{CO(CH_2)_poseconds R^3R^4NCO(CH_2)_p or R^3R^4NSO_2(CH_2)_p where each of R^3 and R^4 independently represents a hydrogen atom or a C_{1-4}alkyl group or R^3R^4 forms part of a C_{3-6}azacycloalkane or C_{3-6}(2-oxo)azacycloalkane ring and p represents zero or an integer from 1 to 4; or a group Ar^1Z, wherein Ar^1 represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring and Z represents a bond, O, S, or CH_2;

R^2 represents a hydrogen atom or a C_{1-4}alkyl group;

q is 1 or 2;

Ar represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; or an optionally substituted bicyclic aromatic or heteroaromatic ring system;

and salts thereof.

In the compounds of formula (I) above an alkyl group or moiety may be straight or branched. Alkyl groups which may be employed include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl and any branched isomers thereof such as isopropyl, t-butyl, sec-pentyl, and the like.

When R^1 represents an arylC_{1-4}alkoxy, arylsulphonyl, arylsulphonyl oxy, arylsulphonylC_{1-4}alkyl, arylsulphonamido, arylcarboxamido, arylsulphonamidoC_{1-4}alkyl, arylcarboxamidoC_{1-4}alkyl, aroyl, aroylC_{1-4}alkyl, or arylC_{1-4}alkanoyl group, the aryl moiety may be selected from an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered heterocyclic ring. In the group

R^1 an aryl moiety may be optionally substituted by one or more substituents selected from hydrogen, halogen, amino, cyano, C_{1-4}alkyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, C_{1-4}alkylamido, C_{1-4}alkanoyl, or R^5R^6NCO where each of R^5 and R^6 independently represents a hydrogen atom or C_{1-4}alkyl group.

A halogen atom present in the compounds of formula (I) may be fluorine, chlorine, bromine or iodine.

When q is 2, the substituents R^1 may be the same or different. Preferably q represents 1.

An optionally substituted 5- or 6-membered heterocyclic aromatic ring, as defined for either of the groups Ar or Ar^1 may contain from 1 to 4 heteroatoms selected from O, N or S. When the ring contains 2-4 heteroatoms, one is preferably selected from O, N and S and the remaining heteroatoms are preferably N. Examples of 5 and 6-membered heterocyclic groups include furyl, thiényl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl,
oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl and pyrazolyl.

Examples of bicyclic aromatic or heteroaromatic ring systems for Ar include naphthyl, quinolinyl, indolyl, indazolyl, benzofuranyl, benzothiényl, benzimidazolyl, benzoxazolyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzothiazolyl and pyridopyrrolyl.

The rings Ar and Ar¹ may each independently be optionally substituted by one or more substituents selected from: a hydrogen or halogen atom, a hydroxy, cyano, nitro, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkylenedioxy, C₁₋₄alkanoyl, C₁₋₄alkylsulphonyl, C₁₋₄sulphonamido, R⁷R⁸N⁻, -CONR⁷R⁸, R⁷R⁸NSO₂⁻, or R⁷CON(R⁸)- group wherein each of R⁷ and R⁸ independently represents a hydrogen atom or a C₁₋₄ alkyl group, or R⁷R⁸ together form a C₃₋₆ alkylene chain.

Alternatively, Ar and Ar¹ may be optionally substituted by one or more 5- or 6-membered heterocyclic rings, as defined above, optionally substituted by a C₁₋₂ alkyl or R⁷R⁸N⁻ group; wherein R⁷ and R⁸ are as defined above.

In the rings Ar and Ar¹ substituents positioned ortho to one another may be linked to form a 5- or 6-membered ring.

It will be appreciated that for use in medicine the salts of formula (I) should be physiologically acceptable. Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids eg. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid; and organic acids eg. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulphonic, methanesulphonic or naphthalenesulphonic acid. Other non-physiologically acceptable salts eg. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

Particular compounds according to the invention include:

(E)-7-Methoxy-2-(4-(3-phenylpropenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;
(E)-7-Hydroxy-2-(4-(3-phenylpropenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-Phenylpropenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-Nitrophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-Methoxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-Bromophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;

(E)-2-(4-(3-(3-Chlorophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(3-(2-Thienyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(3-Furyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(4-Chlorophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(4-Dimethylaminophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(3,4-Methylenedioxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(3-(1-Methyl)indolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(1-Naphthyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(2-Methylphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(3-Cyanophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(2-Quinolinyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(2-Methoxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(3-Indolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(2-Benzofuranyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(4-Acetyllphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(3-Methoxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(3-(3-Quinolinyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
\( (E) \)-2-(4-(3-(2,3-Dihydro)benzofuranyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(6-(1,4-benzodioxanyl))propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(Acetyl)phenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(Acetamidophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(3-Dimethylaminophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
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(E)-2-(4-(3-(3,4-Dichlorophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(2-(1-Methyl)pyrrolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(5-Pyrido[2,3-b]indolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(5-(2-Dimethylamino)pyrimidyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(2-Benzoxazolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(4-(1-Pyrrolidinyl)phenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(3-Methylaminocarbonylphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(3,4-Methylenedioxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(Aminocarbonylphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(2-Acetamidophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-(2-thiophene)sulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(4-Dimethylaminophenyl)propenoyl)aminobutyl)-7-(2-thiophene)sulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl-7-methylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(4-Dimethylaminophenyl)propenoyl)aminobutyl)-7-methylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-acetyl-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-bromo-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-(4-cyanophenyl)sulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-Phenylsulfonylmethyl-2-(4-(3-(2-naphthyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-Methylsulfonamido-2-(4-(3-(2-naphthyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-phenylsulfonamido-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-(4-Cyanophenyl)sulfonamido-2-(4-(3-(2-naphthyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(5-Indolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(5-Benzimidazolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-Methylsulfonylmethyl-2-(4-(3-(2-naphthyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-Cyano-2-(4-(3-(2-naphthyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(3-Indolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(4-Dimethylaminophenyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(4-Aminophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(4-Nitrophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-Cyano-2-(4-(3-(3-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-Cyano-2-(4-(3-(3-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(7-Methyl)indolyl)propenoyl)aminobuty1)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(2-(6-Acetyl)naphthyl)propenoyl)aminobuty1)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(3-(7-Methyl)indolyl)propenoyl)aminobuty1)-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(5-benzimidazolyl)propenoyl)aminobuty1)-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(5-indolyl)propenoyl)aminobuty1)-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(6-Acetyl)naphthyl)propenoyl)aminobuty1)-7-cyano-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-Cyano-2-(4-(3-(6-indolyl)propenoyl)aminobuty1)-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-Cyano-2-(4-(3-(7-fluoro)indolyl)propenoyl)aminobuty1)-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(7-Bromo)indolyl)propenoyl)aminobuty1)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(7-Bromo)indolyl)propenoyl)aminobuty1)-7-cyano-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(7-Cyano)indolyl)propenoyl)aminobuty1)-7-cyano-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-Cyano-2-(4-(3-(5-(2-methyl)indolyl)propenoyl)aminobuty1)-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(5-(2-Methyl)indolyl)propenoyl)aminobuty1)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(7-Acetyl)indolyl)propenoyl)aminobuty1)-7-cyano-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-Cyano-2-(4-(3-(6-(2-methyl)indolyl)propenoyl)aminobuty1)-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-Cyano-2-(4-(3-(5-(2,3-dihydro-2-oxo)-1H-indolyl)propenoyl)aminobuty1)-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(6-(1,2-Dihydro-2-oxo)quinolinyl)propenoyl)aminobuty1)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;  
(E)-2-(4-(3-(5-(2-Acetyl)indolyl)propenoyl)aminobuty1)-7-cyano-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-Chloro-2-(4-(3-(6-indolyl)propenoyl)aminobuty1)-1,2,3,4-tetrahydroisoquinoline;  
(E)-7-Cyano-2-(4-(3-(5-(3-methyl)indolyl)propenyl)aminobuty1)-1,2,3,4-tetrahydroisoquinoline;
(E)-2-((4-(3-(6-(3-Methyl)indolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;
(E)-7-Cyano-2-((4-(3-(5-(1-methyl)indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-((3-(2-(1-Methyl)indolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-((4-((3-(5-Indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;
(E)-7-Cyano-2-((4-(3-(5-(2-methyl)benzimidazolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;
(E)-2-((4-(3-(5-(2-Methyl)benzimidazolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-((4-(3-(5-Indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;
(E)-2-((4-(3-(5-Indolyl)propenoyl)aminobutyl)-7-methylsulfonamido-1,2,3,4-tetrahydroisoquinoline;
(E)-2-((4-(3-(5-Indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;
(E)-2-((4-(3-(7-Methyl)indolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;
(E)-7-Cyano-2-((4-(3-(5-(3-dimethyloxazolinyl)indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;
and salts thereof.

The present invention also provides a process for preparing compounds of formula (I) which process comprises:

(a) reacting a compound of formula (II):

```
  R\^1\_q
  \[\text{NH}\]
```

Formula (II)

wherein R\^1 and q are as hereinbefore defined;

with a compound of formula (III):
wherein $R^2$ and $Ar$ are as hereinbefore defined;

(b) reaction of a compound of formula (IV):

Formula (IV)

wherein $R^1$ and $R^2$ are as hereinbefore defined;

with a compound of formula (V):

Formula (V)

wherein $Ar$ is as hereinbefore defined and $X$ is a halogen atom or the residue of an activated ester;

(c) to prepare a compound of formula (I) wherein $R^1$ is $Ar^1$-$Z$ and $Z$ is a bond, reacting a compound of formula (VI):

Formula (VI)
wherein one R\textsuperscript{1\text{a}} represents a group W wherein W is a halogen atom or a
trifluoromethylsulphonyloxy group, or W is a group M selected from a boron derivative
e.g. a boronic acid function B(OH)\textsubscript{2} or a metal function such as trialkylstannyl e.g.
SnBu\textsubscript{3}, zinc halide or magnesium halide, and when q is 2 the other R\textsuperscript{1\text{a}} is R\textsuperscript{1};
with a compound Ar\textsuperscript{1}-W\textsuperscript{1}, wherein W\textsuperscript{1} is a halogen atom or a trifluoromethylsulphonyloxy
group when W is a group M or W\textsuperscript{1} is a group M when W is a halogen atom or a
trifluoromethylsulphonyloxy group;

(d) to prepare a compound of formula (I) wherein R\textsuperscript{1} is Ar\textsuperscript{1}-Z and Z is O or S,
reacting a compound of formula (VII):

![Formula (VII)](image)

wherein one R\textsuperscript{1\text{b}} represent a group ZH and when q is 2 the other R\textsuperscript{1\text{b}} represents R\textsuperscript{1}; with
a reagent serving to introduce the group Ar\textsuperscript{1};

(e) interconversion of one compound of formula (I) to a different compound of
formula (I) e.g. (i) alkylation of a compound (I) wherein R\textsuperscript{2} represents hydrogen, (ii)
conversion of one R\textsuperscript{1} from alkoxy (e.g. methoxy) to hydroxy, or (iii) conversion of R\textsuperscript{1}
from hydroxy to sulphonyloxy, eg alkylsulphonyloxy or trifluoromethanesulphonyloxy;
and optionally thereafter forming a salt of formula (I).

Process (a) requires the presence of a reducing agent. Suitable reducing agents
which may be employed include sodium borohydride, cyanoborohydride or
triacetoxyborohydride under acidic conditions, or catalytic hydrogenation. The reaction
may conveniently be effected in a solvent such as ethanol.

Process (b) may be effected by methods well known in the art for formation of an
amide bond.

Reaction of a compound of formula (VI) with Ar\textsuperscript{1}W\textsuperscript{1}, according to process (c)
may be effected in the presence of a transition metal eg palladium catalyst such as bis-
triphenyolphosphinepalladium dichloride or tetrakis-triphenylphosphinepalladium (0).
When M represents a boronic acid function such as B(OH)\textsubscript{2} the reaction may be carried
out under basic conditions, for example using aqueous sodium carbonate in a suitable
solvent such as dioxane. When M is trialkylstannyl the reaction may be carried out in an
inert solvent, such as xylene or dioxane optionally in the presence of LiCl. When M is a zinc or magnesium halide the reaction may be effected in an aprotic solvent such as tetrahydrofuran. The substituent W is preferably a halogen atom such as bromine, or a sulphonyloxy group such as trifluoromethylsulphonyloxy; and W¹ is preferably a group M, such as trialkylstannyl or B(OH)₂.

In process (d) the reagent serving to introduce the group Ar¹ is preferably a compound of formula Ar¹-Hal, wherein Hal is a halogen atom. The reaction may be effected in the presence of a base, such as potassium carbonate, in a solvent such as dimethylformamide.

Interconversion reactions according to process (e) may be effected using methods well known in the art.

Compounds of formula (II) may be prepared by methods known in the art.

Compounds of formula (III) are known or may be prepared using standard procedures.

A compound of formula (IV) may be prepared by alkylation of a compound (II) by standard methods. Thus, for example a compound of formula (II) may be reacted with N-(4-bromobutylphthalimide) followed by removal of the phthalimide group to give a compound of formula (IV) where R² is hydrogen. Compounds where R² is alkyl may be prepared by subsequent reaction with the appropriate aldehyde using conditions analogous to process (a) above.

Compounds of formula (VI), and (VII) may be prepared by processes analogous to (a) or (b) described above. Compounds Ar¹W¹ and Ar¹-Hal are commercially available or may be prepared by standard methods.

Compounds of formula (I) have been found to exhibit affinity for dopamine receptors, in particular the D³ receptor, and are expected to be useful in the treatment of disease states which require modulation of such receptors, such as psychotic conditions. Compounds of formula (I) have also been found to have greater affinity for dopamine D³ than for D² receptors. The therapeutic effect of currently available antipsychotic agents (neuroleptics) is generally believed to be exerted via blockade of D² receptors; however this mechanism is also thought to be responsible for undesirable extrapyramidal side effects (EPS) associated with many neuroleptic agents. Without wishing to be bound by theory, it has been suggested that blockade of the recently characterised dopamine D³ receptor may give rise to beneficial antipsychotic activity without significant EPS. (see for example Sokoloff et al, Nature, 1990; 347: 146-151; and Schwartz et al, Clinical Neuropharmacology, Vol 16, No. 4, 295-314, 1993). Preferred compounds of the present invention are therefore those which have higher affinity for dopamine D³ than dopamine D² receptors (such affinity can be measured using standard methodology for
example using cloned dopamine receptors). Said compounds may advantageously be used as selective modulators of D₃ receptors.

We have found that certain compounds of formula (I) are dopamine D₃ receptor antagonists, others may be agonists or partial agonists. The functional activity of compounds of the invention (i.e. whether they are antagonists, agonists or partial agonists) can be readily determined using the test method described hereinafter, which does not require undue experimentation. D₃ antagonists are of potential use as antipsychotic agents for example in the treatment of schizophrenia, schizo-affective disorders, psychotic depression and mania. Conditions which may be treated by dopamine D₃ receptor agonists include dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias; depression; anxiety, memory disorders, sexual dysfunction and drug (e.g. cocaine) dependency.

In a further aspect therefore the present invention provides a method of treating conditions which require modulation of dopamine D₃ receptors, for example psychoses such as schizophrenia, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

The invention also provides the use of a compound of formula (I) or a physiologically acceptable salt thereof in the manufacture of a medicament for the treatment of conditions which require modulation of dopamine D₃ receptors, for example psychoses such as schizophrenia.

A preferred use for D₃ antagonists according to the present invention is in the treatment of psychoses such as schizophrenia.

A preferred use for D₃ agonists according to the present invention is in the treatment of dyskinetic disorders such as Parkinson's disease.

For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a novel compound of formula (I) or a physiologically acceptable salt thereof and a physiologically acceptable carrier.

The compounds of formula (I) may be administered by any convenient method, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their physiologically acceptable salts which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.
A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.
Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

5 Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base.

The physiologically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.
Biological Test Methods

The ability of the compounds to bind selectively to human D3 dopamine receptors can be demonstrated by measuring their binding to cloned receptors. The inhibition constants (K_i) of test compounds for displacement of [125I]iodosulpride binding to human D3 dopamine receptors expressed in CHO cells were determined as follows. The cell lines were shown to be free from bacterial, fungal and mycoplasmal contaminants, and stocks of each were stored frozen in liquid nitrogen. Cultures were grown as monolayers or in suspension in standard cell culture media. Cells were recovered by scraping (from monolayers) or by centrifugation (from suspension cultures), and were washed two or three times by suspension in phosphate buffered saline followed by collection by centrifugation. Cell pellets were stored frozen at -40°C. Crude cell membranes were prepared by homogenisation followed by high-speed centrifugation, and characterisation of cloned receptors achieved by radioligand binding.

Preparation of CHO cell membranes

Cell pellets were gently thawed at room temperature, and resuspended in about 20 volumes of ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), 20mM EDTA, 0.2 M sucrose. The suspension was homogenised using an Ultra-Turrax at full speed for 15 sec. The homogenate was centrifuged at 18,000 r.p.m for 20 min at 4°C in a Sorvall RC5C centrifuge. The membrane pellet was resuspended in ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), using an Ultra-Turrax, and recentrifuged at 18,000 r.p.m for 15 min at 4°C in a Sorvall RC5C. The membranes were washed two more times with ice-cold 50 mM Tris salts (pH 7.4 @ 37°C). The final pellet was resuspended in 50 mM Tris salts (pH 7.4 @ 37°C), and the protein content determined using bovine serum albumin as a standard


Binding experiments on cloned dopamine receptors

Crude cell membranes were incubated with 0.1 nM [125I]iodosulpride (~2000 Ci/mmol; Amersham, U. K.), and the test compound in a buffer containing 50 mM Tris salts (pH 7.4 @ 37°C), 120 mM NaCl, 5 mM KCl, 2 mM CaCl_2, 1 mM MgCl_2, 0.1% (w/v) bovine serum albumin, in a total volume of 1 ml for 30 min at 37°C. Following incubation, samples were filtered using a Brandel Cell Harvester, and washed three times with ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), 120 mM NaCl, 5 mM KCl, 2 mM CaCl_2, 1 mM MgCl_2. The radioactivity on the filters was measured using a Cobra gamma counter (Canberra Packard). Non-specific binding was defined as the radioligand binding remaining after incubation in the presence of 100 μM iodosulpride. For competition curves, 14 concentrations (half-log dilutions) of competing cold drug were used.
Competition curves were analysed simultaneously whenever possible using non-linear least-squares fitting procedures, capable of fitting one, two or three site models.

Compounds of Examples had pKi values of between 7.0 and 9.0 at the dopamine D3 receptor.

Functional Activity at cloned dopamine receptors
The functional activity of compounds at human D2 and human D3 receptors (i.e. agonism or antagonism) may be determined using a Cytosensor Microphysiometer (McConnell HM et al. Science 1992 257 1906-1912) In Microphysiometer experiments, cells (hD2_CHO or hD3_CHO) were seeded into 12mm Transwell inserts (Costar) at 300000 cells/cup in foetal calf serum (FCS)-containing medium. The cells were incubated for 6h at 37°C in 5% CO₂, before changing to FCS-free medium. After a further 16-18h, cups were loaded into the sensor chambers of the Cytosensor Microphysiometer (Molecular Devices) and the chambers perfused with running medium (bicarbonate-free Dulbecco's modified Eagles medium containing 2 mM glutamine and 44 mM NaCl) at a flow rate of 100 ul/min. Each pump cycle lasted 90s. The pump was on for the first 60s and the acidification rate determined between 68 and 88s, using the Cytosoft programme. Agonists and antagonists were diluted in running medium. In experiments to determine agonist activity, cells were exposed (4.5 min for hD2, 7.5 min for hD3) to increasing concentrations of putative agonist at half hour intervals. Seven concentrations of agonist were used. Peak acidification rate to each agonist concentration was determined and concentration-response curves fitted using Robofit [Tilford, N.S., Bowen, W.P. & Baxter, G.S. Br. J. Pharmacol. (1995) in press]. In experiments to determine antagonist potency, cells were treated at 30 min intervals with five pulses of a submaximal concentration of quinpirole (100 nM for hD2 cells, 30 nM for hD3 cells), before exposure to the lowest concentration of putative antagonist. At the end of the next 30 min interval, cells were pulsed again with quinpirole (in the continued presence of the antagonist) before exposure to the next highest antagonist concentration. In all, five concentrations of antagonist were used in each experiment. Peak acidification rate to each agonist concentration was determined and concentration-inhibition curves fitted using Robofit.
Pharmaceutical Formulations

The following represent typical pharmaceutical formulations according to the present invention, which may be prepared using standard methods.

IV Infusion

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound of formula (I)</td>
<td>1-40 mg</td>
</tr>
<tr>
<td>Buffer</td>
<td>to pH ca 7</td>
</tr>
<tr>
<td>Solvent/complexing agent</td>
<td>to 100 ml</td>
</tr>
</tbody>
</table>

Bolus Injection

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound of formula (I)</td>
<td>1-40 mg</td>
</tr>
<tr>
<td>Buffer</td>
<td>to pH ca 7</td>
</tr>
<tr>
<td>Co-Solvent</td>
<td>to 5 ml</td>
</tr>
</tbody>
</table>

Buffer: Suitable buffers include citrate, phosphate, sodium hydroxide/hydrochloric acid.

Solvent: Typically water but may also include cyclodextrins (1-100 mg) and cosolvents such as propylene glycol, polyethylene glycol and alcohol.

Tablet

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
<td>1 - 40 mg</td>
</tr>
<tr>
<td>Diluent/Filler*</td>
<td>50 - 250 mg</td>
</tr>
<tr>
<td>Binder</td>
<td>5 - 25 mg</td>
</tr>
<tr>
<td>Disintegrant*</td>
<td>5 - 50 mg</td>
</tr>
<tr>
<td>Lubricant</td>
<td>1 - 5 mg</td>
</tr>
<tr>
<td>Cyclodextrin</td>
<td>1 - 100 mg</td>
</tr>
</tbody>
</table>

* may also include cyclodextrins

Diluent: e.g. Microcrystalline cellulose, lactose, starch

Binder: e.g. Polyvinylpyrrolidone, hydroxypropylmethylcellulose

Disintegrant: e.g. Sodium starch glycollate, crospovidone

Lubricant: e.g. Magnesium stearate, sodium stearyl fumarate.
Oral Suspension

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
<td>1 - 40 mg</td>
</tr>
<tr>
<td>Suspending Agent</td>
<td>0.1 - 10 mg</td>
</tr>
<tr>
<td>Diluent</td>
<td>20 - 60 mg</td>
</tr>
<tr>
<td>Preservative</td>
<td>0.01 - 1.0 mg</td>
</tr>
<tr>
<td>Buffer</td>
<td>to pH ca 5 - 8</td>
</tr>
<tr>
<td>Co-solvent</td>
<td>0 - 40 mg</td>
</tr>
<tr>
<td>Flavour</td>
<td>0.01 - 1.0 mg</td>
</tr>
<tr>
<td>Colourant</td>
<td>0.001 - 0.1 mg</td>
</tr>
</tbody>
</table>

Suspending agent: e.g. Xanthan gum, microcrystalline cellulose
Diluent: e.g. sorbitol solution, typically water
Preservative: e.g. sodium benzoate
Buffer: e.g. citrate
Co-solvent: e.g. alcohol, propylene glycol, polyethylene glycol, cyclodextrin

The invention is further illustrated by the following non-limiting examples:

Description 1

4-Phthalimidobutyraldehyde diethyl acetal
A solution of 4-aminobutyraldehyde diethyl acetal (48.5g, 0.3mol) in tetrahydrofuran (60ml) was added dropwise to a stirred slurry of N-(ethoxycarbonyl) phthalimide (65.93g, 0.3mol) in tetrahydrofuran (250ml) at 0°C. After stirring at 0°C for 0.16h and at room temperature for 18h the solvent was removed in vacuo and the residue distilled at 1mmHg to remove the ethyl carbamate by-product. The residual brown oil was allowed to cool to afford the title compound (91g, 93%).
Mass spectrum (API): 218 (MH⁺ for aldehyde).
¹H NMR (CDCl₃) δ: 1.20 (6H, t, J = 7 Hz), 1.70 (4H, m), 3.35 - 3.85 (6H, m), 4.55 (1H, t, J = 5 Hz), 7.70 (2H, m), 7.85 (2H, m).

Description 2

4-Phthalimidobutyraldehyde
A solution of 4-phthalimidobutyraldehyde diethyl acetal (125g, 0.43 mol) in a 1:1 mixture of tetrahydrofuran and 2N hydrochloric acid (800ml) was heated at reflux for 0.75h. The mixture was cooled, concentrated to 400ml and extracted into dichloromethane (3×200ml). Combined organics were dried (Na₂SO₄) and evaporated in
vacuo to afford the title compound as a brown oil that solidified on standing (95g, 100%).

Mass spectrum (API): 218 (MH⁺), C₁₁H₁₁NO₃ requires 217.

¹H NMR (CDCl₃) δ: 2.00 (2H, m), 2.55 (2H, t, J = 5 Hz), 3.75 (2H, t, J = 5 Hz), 7.70 (2H, m), 7.85 (2H, m), 9.30 (1H, s).

Description 3
7-Methoxy-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline

To a stirred solution of 4-phthalimidobutyraldehyde (15.96g, 0.074 mol) and 7-methoxy-1,2,3,4-tetrahydroisoquinoline (10g, 0.061 mol) in 1,2-dichloroethane (100 ml) was added sodium triacetoxyborohydride (19.3g, 0.091 mol) in three equal portions over 10 mins, followed by glacial acetic acid (3.72 ml, 0.061 mol). The resultant mixture was stirred at room temperature for 3h, then at 45 °C for 1h, and poured into saturated aqueous potassium carbonate (600 ml). The mixture was extracted into dichloromethane (2x400 ml) and the combined extracts dried (Na₂SO₄) and evaporated in vacuo.

Trituration of the residue with hexane afforded the title compound as a pale brown gum (13.5g, 60%).


¹H NMR (CDCl₃) δ: 1.70 (4H, m), 2.50 (2H, m), 2.70 (2H, m), 2.80 (2H, m), 3.55 (2H, s), 3.55 - 3.80 (5H, m), 6.55 (1H, d, J = 2 Hz), 6.70 (1H, dd, J = 2 Hz, 8 Hz), 7.00 (1H, d, J = 8 Hz), 7.70 (2H, m), 7.85 (2H, m).

The following compounds were prepared in a similar manner to Description 3:

(a) 7-Nitro-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline


(b) 7-Bromo-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline


(c) 7-Phenylsulfonfylmethyl-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline


(d) 7-Methanesulfonfylmethyl-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline


(e) 2-(4-Phthalimidobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline

Description 4
2-(4-Aminobutyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline
A solution of 7-methoxy-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline (17.4g 0.0478 mol) and hydrazine monohydrate (4.6ml, 0.095mol) in ethanol (300ml) were stirred at room temperature for 18h and at reflux for 1h. The cooled reaction mixture was filtered and the filtrate evaporated in vacuo. The residue was dissolved in 2.5N hydrochloric acid, filtered through Kieselguhr and the filtrate basified with 0.880 ammonia. The product was extracted into dichloromethane (4×200ml), the combined extracts were dried (Na₂SO₄) and evaporated in vacuo to afford the title compound as a brown oil (7g, 63%).
Mass spectrum (API'): 235 (MH') C₁₄H₁₄N₂O requires 234.
¹H NMR (CDCl₃) δ: 1.30 - 1.90 (4H, m), 2.50 (2H, m), 2.60 - 2.90 (8H, m), 3.60 (2H, s), 3.75 (3H, s), 6.55 (1H, d, J = 2 Hz), 6.70 (1H, dd, J = 2 Hz, 8 Hz), 7.00 (1H, d, J = 8 Hz).

Description 5
7-Hydroxy-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline
Prepared from 7-methoxy-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline (1.45g, 3.98 mmol) using a procedure similar to that of Example 2 (1.31g, 94%).
Mass spectrum (API'): 351 (MH') C₁₄H₁₄N₂O₃ requires 350.
¹H NMR (CDCl₃) δ: 1.70 (4H, m), 2.25 - 2.85 (1H, br s), 2.50 (2H, t, J = 7 Hz), 2.70 (2H, d, J = 4 Hz), 2.85 (2H, d, J = 4 Hz), 3.50 (2H, s), 3.75 (2H, t, J = 7 Hz), 6.45 (1H, d, J = 2 Hz), 6.60 (1H, dd, J = 2 Hz, 8 Hz), 6.90 (1H, d, J = 8 Hz), 7.70 (2H, m), 7.85 (2H, m).

Description 6
2-(4-Phthalimidobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline
Trifluoromethanesulfonic anhydride (0.53ml, 3.14 mmol) was added dropwise with stirring to an ice-cooled solution of 7-hydroxy-2-(4-phthalimidobutyl)-1,2,3,4- tetrahydroisoquinoline (1g, 2.86 mmol) in anhydrous pyridine (10ml). After stirring at room temperature for 18h the reaction mixture was added to 10% aqueous Copper (II) sulfate (100ml) and extracted into ethyl acetate (200ml). The organic layer was separated, washed with 10% aqueous copper (II) sulfate (2×50ml), dried (Na₂SO₄) and evaporated in vacuo. Chromatography on silica gel using 10-100% ethyl acetate-hexane gradient elution gave the title compound as a green oil (0.45g, 33%).
Mass spectrum (API'): 483 (MH'). C₂₃H₁₄F₃N₂O₂S requires 482.
\( ^1 \)H NMR (CDCl\(_3\)) \( \delta: \) 1.75 (4H, m), 2.55 (2H, \( t, J = 7 \) Hz), 2.75 (2H, \( t, J = 6 \) Hz), 2.90 (2H, \( t, J = 6 \) Hz), 3.60 (2H, s), 3.75 (2H, \( t, J = 7 \) Hz), 6.90 (1H, d, \( J = 2 \) Hz), 7.05 (1H, dd, \( J = 2 \) Hz, \( 9 \) Hz), 7.15 (1H, d, \( J = 9 \) Hz), 7.70 (2H, m), 7.85 (2H, m).

5 Description 7

2-(4-Aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Prepared from 2-(4-phthalimidobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline (0.44g, 0.91 mmol) using a procedure similar to that of Description 4 (0.26g, 81%).

Mass spectrum (API\(^+\)): 353 (MH\(^+\)). \( C_{14}H_{14}F_3N_2O_3S\) requires 352.

\( ^1 \)H NMR (CDCl\(_3\)) \( \delta: \) 1.50 (6H, m), 2.50 (2H, \( t, J = 7 \) Hz), 2.75 (4H, m), 2.90 (2H, \( t, J = 6 \) Hz), 3.60 (2H, s), 6.90 (1H, d, \( J = 2 \) Hz), 7.0 (1H, dd, \( J = 2 \) Hz, 9 Hz), 7.15 (1H, d, \( J = 9 \) Hz).

The following compounds were prepared in a similar manner to Description 7:

(a) 2-(4-Aminobutyl)-7-methylsulfonamido-1,2,3,4-tetrahydroisoquinoline

\( ^1 \)H NMR (CDCl\(_3\)) \( \delta: \) 1.36 (4H, m), 2.50 (2H, m), 2.70 (4H, m), 2.82 (2H, m), 2.91 (3H, s), 3.39 (3H, m), 3.54 (2H, s), 6.85 (1H, d, \( J = 2 \)Hz), 6.89 - 7.06 (2H, m).

(b) 2-(4-Aminobutyl)-7-phenylsulfonamido-1,2,3,4-tetrahydroisoquinoline

\( ^1 \)H NMR (CDCl\(_3\)) \( \delta: \) 1.39 (4H, m), 2.09 (2H, br s), 2.48 (2H, \( t, J = 7 \)Hz), 2.60 - 2.92 (6H, m), 3.50 (2H, s), 6.76 (2H, m), 6.95 (1H, d, \( J = 8 \)Hz), 7.37 - 7.62 (4H, m), 7.73 (2H, m).

(c) 2-(4-Aminobutyl)-7-(4-cyanophenyl)sulfonamido-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API\(^+\)): Found 385 (MH\(^+\)). \( C_{20}H_{20}N_2O_3S\) requires 384.

(d) 2-(4-Aminobutyl)-7-bromo-1,2,3,4-tetrahydroisoquinoline

\( ^1 \)H NMR (CDCl\(_3\)) \( \delta: \) 1.30 - 1.67 (6H, m), 2.48 (2H, d, \( J = 7 \) Hz), 2.60 - 2.87 (6H, m), 3.55 (2H, s), 6.94 (1H, d, \( J = 9 \) Hz), 7.15 (1H, d, \( J = 2 \) Hz), 7.23 (1H, dd, \( J = 9, 2 \) Hz).

(e) 2-(4-Aminobutyl)-7-methylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API\(^+\)): Found 299 (MH\(^+\)). \( C_{18}H_{22}N_2O_3S\) requires 298.
(f) 2-(4-Aminobutyl)-7-(2-thiophenesulfonylethoxy)-1,2,3,4-tetrahydropyridine

(g) 2-(4-Aminobutyl)-7-(4-cyanophenylsulfonylethoxy)-1,2,3,4-tetrahydropyridine

(h) 2-(4-Aminobutyl)-7-phenylsulfonylmethyl-1,2,3,4-tetrahydropyridine

(i) 2-(4-Aminobutyl)-7-Methylsulfonylmethyl-1,2,3,4-tetrahydropyridine

(j) 2-(4-Aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydropyridine

Description 8

(E)-3-(5-(2-Dimethylamino)pyrimidinyl)propenoic acid, methyl ester

A solution of (2-dimethylamino)pyrimidine-5-carboxaldehyde [Gupton J.T. et al, J. Het. Chem 28, 1281-5 (1991)] (250mg, 1.66 mmol) and carbomethoxymethylenetriphenyl phosphorane (554mg, 1.66 mmol) in chloroform (100ml) was refluxed for 2h. The reaction mixture was concentrated to 10ml and chromatographed on a silica column topped with neutral alumina using 10-30% ethyl acetate-hexane gradient elution to afford the title compound (280mg, 82%).

¹H NMR (CDCl₃) δ: 3.25 (6H, s), 3.80 (3H, s), 6.25 (1H, d, J = 15Hz), 7.50 (1H, d, J = 15Hz), 8.50 (2H, s).

The following compounds were prepared in a similar manner to Description 8:

(a) (E)-3-(4-(1-Pyrrolidinyl)phenyl)propenoic acid, methyl ester
¹H NMR (CDCl₃) δ: 2.00 (4H, m), 3.30 (4H, m), 3.80 (3H, s), 6.20 (1H, d, J = 15Hz), 6.50 (2H, d, J = 8Hz), 7.40 (2H, d, J = 8Hz), 7.65 (1H, d, J = 15Hz).

(b) (E)-3-(5-(2,3-Dihydro)benzofurananyl)propenoic acid, methyl ester
Mass spectrum (API): Found 205 (MH⁺). C₁₃H₁₂O₂ requires 204.
Description 9

(E)-3-(5-(2-Dimethylamino)pyrimidyl)propenoic acid

A mixture of (E)-3-(5-(2-dimethylamino)pyrimidyl)propenoic acid, methyl ester (250mg, 1.2mmol) and sodium hydroxide (98mg, 2.45mmol) in water (30ml) was heated at reflux for 3h. The resultant solution was cooled, washed with ethyl acetate (50ml) and adjusted to pH6 with 5N HCl. The resultant precipitate was filtered, washed with water and dried in vacuo (195mg, 84%).

\(^1\)H NMR (DMSO) δ: 3.20 (6H, s), 6.40 (1H, d, J = 15Hz), 7.45 (1H, d, J = 15Hz), 8.70 (2H, s), 12.25 (1H, br s).

The following compounds were prepared in a similar manner to Description 9:

(a) (E)-3-(4-(1-Pyrrolidinyl)phenyl)propenoic acid
Mass spectrum (API): Found 216 (M-H)^-. C\(_{13}\)H\(_{12}\)NO\(_2\) requires 217.

(b) (E)-3-(5-(2,3-Dihydrobenzofuranyl)propenoic acid
Mass spectrum (API): Found 189 (M-H)^-. C\(_{11}\)H\(_{10}\)O\(_2\) requires 190.

Description 10

1-(4-Bromophenyl)-2-pyrrolidinone

To a solution of 4-bromoaniline (10g, 58 mmol) in dry THF (150ml), under argon was added triethylamine (6g, 59mmol) and 4-chlorobutyrylchloride (8.2g 58mmol) at 5°C. The mixture was stirred at 5°C for 40 mins and potassium tert-butoxide (16g, 142mmol) added in one portion. After 10 mins the mixture was warmed to 25°C and stirred for 4 hours, then left to stand overnight. Water (10ml) was added and the mixture stirred for 30 mins. The mixture was diluted with ethyl acetate (200ml) and 3% Na\(_2\)CO\(_3\) (aq) (120ml). The aqueous layer was reextracted with ethyl acetate (100ml) and the combined extracts dried over Na\(_2\)SO\(_4\). The solvent was evaporated in vacuo to give a brown solid (12g).

Chromatography on silica gel (~200g) using 30-60% ethyl acetate/hexane gradient elution gave the title compound as a yellow crystalline solid (10.24g, 74%).

Mass spectrum (API'): Found 240 (MH'). C\(_{16}\)H\(_{12}\)BrNO requires 239.

Description 11

(E)-3-(4-(1-(2-Oxo)pyrrolidinyl)phenyl)propenoic acid
A mixture of 1-(4-bromophenyl)-2-pyrrolidinone (2.39g, 10mmol), acrylic acid (0.8g, 11.1mmol), palladium acetate (1.1mg, 0.005mmol), triphenylphosphine (26mg, 0.1mmol) and tri-n-butylamine (5ml), was heated at 150°C for 2.5hrs.

The mixture was allowed to cool to room temperature and then water (20ml) was added, followed by careful addition of sodium hydrogen carbonate (2g) with vigorous stirring. The mixture was then filtered and the filtrate washed with dichloromethane (10ml). The aqueous layer was acidified to pH1 using 5N HCl, and the resultant precipitate filtered, washed with ether (10ml), and dried to give the title compound as a yellow solid (1.24g, 5.4 mmol), 54%.

Mass spectrum (API): Found 230 (M-H)'. C_{15}H_{13}NO requires 231.

The following compounds were prepared in a similar manner to Description 11:

(a) (E)-3-(3-Acetamidophenyl)propenoic acid

\[ \delta: \begin{align*}
1^H NMR (DMSO) & \quad 2.05 (3H, s), 6.40 (1H, d, J = 15Hz), 7.35 (2H, m), 7.55 \quad (1H, d, J = 15Hz), 7.60 (1H, m), 7.85 (1H, br s), 10.10 (1H, s), 12.50 (1H, br s).
\end{align*} \]

(b) (E)-3-(3-Dimethylaminophenyl)propenoic acid

\[ \delta: \begin{align*}
1^H NMR (CDCl₃) & \quad 2.95 (6H, s), 6.45 (1H, d, J = 15Hz), 6.80 (1H, dd, J = 8Hz, 2Hz), 6.85 (1H, br s), 6.95 (1H, d, J = 8Hz), 7.25 (2H, m), 7.75 (1H, d, J = 15Hz).
\end{align*} \]

Description 12

2-(4-Phthalimidobutyl)-7-(2-thiophenesulfonyloxy)-1,2,3,4-tetrahydroisoquinoline

A stirred mixture of 7-hydroxy-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline (2.94g, 8.4mmol) and triethylamine (1.4ml, 10mmol) in dichloromethane (75ml) was treated with 2-thiophenesulfonyl chloride (1.69g, 9.2mmol). After stirring at room temperature for 18h the mixture was washed with saturated aqueous sodium bicarbonate (100ml). The aqueous layer was separated and extracted with dichloromethane (2x50ml). The combined extracts were washed with brine, dried (Na₂SO₄) and evaporated in vacuo. The residue was chromatographed on silica using 30-100% ethyl acetate-pentane gradient elution to afford the title compound as a pale yellow oil (3.45g, 83%).

\[1^H NMR (CDCl₃) \delta: \begin{align*}
1.50 - 1.75 (4H, m), 2.52 (2H, t, J = 7Hz), 2.68 (2H, t, J = 7Hz), 2.84 (2H, t, J = 7Hz), 3.50 (2H, s), 3.74 (2H, t, J = 7Hz), 6.68 (1H, d, J = 7Hz).
\end{align*} \]
3Hz), 6.75 (2H, dd, J = 3, 8 Hz), 7.00 (1H, d, J = 10Hz), 7.08 (1H, m), 7.55 (1H, m), 7.70 (2H, m), 7.85 (2H, m).

The following compounds were prepared in a similar manner to Description 12:

(a) 7-Methylsulfonyloxy-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API\(^+\)): Found: 429 (MH\(^+\)). \(C_{22}H_{24}N_4O_3S\) requires 428.

(b) 7-(4-Cyanophenylsulfonyloxy)-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline
\(^1\)H NMR (CDCl\(_3\)) \(\delta\): 1.50 - 1.85 (4H, m), 2.55 (2H, t, J = 5Hz), 2.70 (2H, t, J = 5Hz), 2.85 (2H, t, J = 5Hz), 3.50 (2H, s), 3.75 (2H, t, J = 5Hz), 6.65 (2H, m), 7.00 (1H, d, J = 10Hz), 7.70 (2H, m), 7.75 - 7.90 (4H, m), 7.95 (2H, m).

Description 13
7-Methylsulfonylamido-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline
7-Amino-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline (3g, 8.6mmol) was dissolved in dichloromethane (100ml), and 2,6-lutidine (1.2ml, 10.32mmol) was added. To this methylsulfonyl chloride (0.73ml, 9.46mmol) was added dropwise. A further portion of 2,6-lutidine (0.6ml, 5.16 mmol) and methylsulfonyl chloride (0.37ml, 4.78 mmol) were later added. The mixture was partitioned between sodium bicarbonate solution (100ml) and dichloromethane (3x50ml). The combined extracts were dried (Na\(_2\)SO\(_4\)) and evaporated in vacuo.

Chromatography of the residue on alumina with ethyl acetate + 0-1% methanol gradient elution gave the title compound as an oil (1.8g, 49%).

Mass spectrum (API\(^+\)): Found 428 (MH\(^+\)). \(C_{22}H_{24}N_4O_3S\) requires 427.

The following compounds were prepared in a similar manner to Description 13:

(a) 7-(4-Cyanophenyl)sulfonylamido-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API\(^+\)): Found 515 (MH\(^+\)). \(C_{22}H_{24}N_4O_3S\) requires 514.

(b) 7-Phenylsulfonylamido-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API\(^+\)): Found 490 (MH\(^+\)). \(C_{27}H_{27}N_4O_4S\) requires 489.
Description 14
7-Bromo-1,2,3,4-tetrahydroisoquinoline
A mixture of 7-bromo-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (G.E.
Stokker, Tetrahedron Letters 1996, 37, 5453) (43.4g, 0.14 mol), potassium
carbonate (104.3g, 0.75 mol), methanol (1L) and water (150ml) was heated at
reflux for 1h, then cooled and evaporated in vacuo. Residue was partitioned
between water (1L) and dichloromethane (4 x 200ml). Combined extracts were
dried (Na₂SO₄) and evaporated in vacuo to give an oil which was dissolved in
hexane. The mixture was filtered and the filtrate evaporated in vacuo to give the
title compound as an oil (17.7g, 60%).
¹H NMR (CDCl₃) δ:  1.77 (1H, br s), 2.73 (2H, t, J = 7Hz), 3.13 (2H, t, J = 7Hz),
3.98 (2H, s), 6.96 (1H, d, J = 9Hz), 7.16 (1H, d, J = 2Hz), 7.26 (1H, dd, J = 9,
2Hz).

The following compounds were prepared in a similar manner to Description 14:

(a) 7-Trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline

(b) 7-Cyano-1,2,3,4-tetrahydroisoquinoline

Description 15
7-Nitro-1,2,3,4-tetrahydroisoquinoline
Prepared from 7-Nitro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (G.E.
Stokker, Tetrahedron Letters 1996, 37, 5453) using a procedure similar to
Description 14 in 80% yield.
¹H NMR (CDCl₃) δ:  1.72 (1H, s), 2.89 (2H, t, J = 6Hz), 3.18 (2H, t, J = 6Hz),
4.09 (2H, s), 7.24 (1H, d, J = 10Hz), 7.89 - 8.06 (2H, m).

Description 16
7-Amino-2-(4-phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline
A mixture of 5% palladium on carbon paste (3.44g), 7-nitro-2-(4-
phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline (19.15g, 0.05mol), ethanol
(791ml) and water (69ml) was hydrogenated at 50psi and 30°C for 6 days. The
reaction mixture was then filtered through Kieselguhr and evaporated in vacuo to
give the title compound as an oil (18.04g, 100%).
Mass spectrum (API\(^{+}\)): Found 350 (MH\(^{+}\)). \( \text{C}_{11}\text{H}_{21}\text{N}_{3}\text{O}_{2} \) requires 349.

**Description 17**

(4-Trifluoroacetamido)butyraldehyde

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To a solution of 4-aminobutyraldehyde diethyl acetal (16.10g, 0.10mmol) and triethylamine (18.06ml, 0.12mol) in dichloromethane (150ml) at 0°C was added a solution of trifluoroacetic anhydride (16.9ml, 0.11mol) in dichloromethane (60ml). The reaction mixture was warmed to room temperature and stirred for 3h, then partitioned between 5% aq NaHCO\(_3\) (400ml) and dichloromethane (400ml). The aqueous layer was extracted further with dichloromethane (3x100ml), the combined extracts were dried (\(\text{Na}_2\text{SO}_4\)) and evaporated in vacuo to afford a pale yellow oil which was added to a stirred mixture of THF (300ml) and water (500ml). 5N Sulfuric acid (2.27ml) was added and the reaction mixture left to stir at room temperature for 18h. Saturated aqueous sodium bicarbonate (500ml) was added and the product was extracted into dichloromethane (4x100ml). The combined organic extracts were dried (\(\text{Na}_2\text{SO}_4\)) and evaporated in vacuo to afford the title compound as a yellow oil (15.42g, 65%).

\(^{1}\text{H} \text{NMR (CDCl}_3\): 1.95 (2H, m), 2.62 (2H, t, \( J = 8\text{Hz} \)), 3.38 (2H, m), 7.54 - 7.80 (1H, br s), 9.77 (1H, s).

**Description 18**

7-Acetyl-2-(4-trifluoroacetamidobutyl)-1,2,3,4-tetrahydroisoquinoline

The title compound was prepared in 37% yield by treating 7-acetyl-1,2,3,4-tetrahydroisoquinoline with (4-trifluoroacetamido)butyraldehyde using a procedure similar to that of Description 3.

Mass spectrum (API\(^{+}\)): Found 343 (MH\(^{+}\)). \( \text{C}_{17}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_2 \) requires 342.

*The following compounds were prepared in a similar manner to Description 18:*

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(a) 7-Cyano-2-(4-trifluoroacetamidobutyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API\(^{+}\)): Found 326 (MH\(^{+}\)). \( \text{C}_{16}\text{H}_{19}\text{F}_3\text{N}_2\text{O} \) requires 325.

(b) 2-(4-Trifluoroacetamidobutyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API\(^{+}\)): Found 301 (MH\(^{+}\)). \( \text{C}_{15}\text{H}_{17}\text{F}_3\text{N}_2\text{O} \) requires 300.

(c) 7-Methylaminosulfonyl-2-(4-trifluoroacetamidobutyl)-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API'): Found 394 (MH'). $C_{16}H_{17}F_9N_4O_3S$ requires 393.

Description 19
7-Acetyl-2-(4-aminobutyl)-1,2,3,4-tetrahydroisoquinoline

A solution of 7-acetyl-2-(4-trifluoroacetamidobutyl)-1,2,3,4-
tetrahydroisoquinoline (0.360g, 1.05mmol) was added to a stirred mixture of
methanol (10ml), water (1.5ml) and potassium carbonate (0.769g, 5.56mmol) and
heated at reflux for 1h. The mixture was cooled then evaporated in vacuo and the
residue partitioned between water (100ml) and dichloromethane (50ml). The aqueous
phase was washed with dichloromethane (2x50ml). The combined organic extracts were dried
(Na$_2$SO$_4$) and evaporated in vacuo to afford the title compound as a yellow oil (0.178g, 68%).

$^1$H NMR (CDCl$_3$) δ: 1.44 - 1.70 (4H, m), 1.75 - 1.92 (2H, br s), 2.56 (5H, m),
2.73 (4H, m), 2.95 (2H, t, J = 4Hz), 3.67 (2H, s), 7.18 (1H, d, J = 6Hz), 7.63 (1H,
s), 7.71 (1H, d, J = 6Hz).

The following compounds were prepared in a similar manner to Description 19:

(a) 2-(4-Aminobutyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API'): Found 230 (MH'). $C_{14}H_{19}N_3$ requires 229.

(b) 2-(4-Aminobutyl)-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API'): Found 205 (MH'). $C_{13}H_{18}N_3$ requires 204.

(c) 2-(4-Aminobutyl)-7-methylaminosulfonyl-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API'): Found 298 (MH'). $C_{16}H_{23}N_3O_2S$ requires 297.

Description 20
7-Bromo-2-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline

To a mixture of 7-bromo-1,2,3,4-tetrahydroisoquinoline (19.33g, 0.091 mol) and
triethylamine (16.6ml, 0.119 mol) in dichloromethane (300ml) was added a solution of methyl chloroformate (8.5 ml; 0.109 mol) in dichloromethane (30ml),
dropwise with ice cooling. Mixture was stirred for 3h at room temperature then partitioned between saturated aqueous NaHCO$_3$ (100ml) and dichloromethane (100ml). Organic phase was dried (Na$_2$SO$_4$) and evaporated in vacuo to give an oil. Chromatography on silica with 30% ethyl acetate - hexane as eluant gave the title compound as an oil (15.25g, 62%).
\(^{1}\)H NMR (CDCl\(_3\)) \(\delta\):  2.80 (2H, m), 3.69 (2H, m), 3.76 (3H, s), 4.59 (2H, s), 7.00 (1H, d, \(J = 9\) Hz), 7.28 (2H, m).

**Description 21**

7-Cyano-2-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline

A mixture of 7-bromo-2-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (12.0g, 0.044 mol), copper (I) cyanide (8.7g, 0.097 mol) and N-methyl-2-pyrrolidinone (100ml) was heated at reflux for 4h, cooled, then partitioned between dilute aqueous ammonia (500ml) and ethyl acetate (300ml). Organic phase was washed with dilute aqueous ammonia (100ml), water (4x100ml), then dried (Na\(_2\)SO\(_4\)) and evaporated in vacuo to give the title compound as an oil (7.89g, 83%).

Mass spectrum (API): Found 217 (MH\(^{+}\)). C\(_{13}\)H\(_{16}\)N\(_2\)O requires 216.

The following compound was prepared in a similar manner to **Description 21**:

(a) 7-Cyano-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API): Found 253 (M-H\(^{-}\)). C\(_{13}\)H\(_{14}\)F\(_3\)N\(_2\)O requires 254.

**Description 22**

7-Hydroxymethyl-2-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline

A mixture of 7-cyano-2-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (6.06g, 28 mmol), Raney nickel (50%, 12.2g) and aqueous formic acid (75%; 80ml) was heated at reflux for 1h. Mixture was filtered through kieselguhr and the filtrate partitioned between water (300ml) and dichloromethane (4x100ml). Combined organic extracts were washed with saturated aqueous NaHCO\(_3\) (200ml), dried (Na\(_2\)SO\(_4\)) and evaporated in vacuo to give an oil (4.85g). The latter was dissolved in methanol (100ml) and treated with sodium borohydride (0.84g, 22.1 mmol). Mixture was stirred at room temperature for 3h then treated with 5N HCl (5ml). Resulting mixture was partitioned between saturated aqueous NaHCO\(_3\) (200ml) and dichloromethane (4x50ml). Combined extracts were dried (Na\(_2\)SO\(_4\)) and evaporated in vacuo to give the title compound as an oil (4.65g, 75%).

\(^{1}\)H NMR (CDCl\(_3\)) \(\delta\):  1.96 (1H, br t, \(J = 6\) Hz), 2.83 (2H, t, \(J = 7\) Hz), 3.69 (2H, m), 3.75 (3H, s), 4.60 (2H, s), 4.65 (2H, d, \(J = 6\) Hz), 7.12 (3H, m).
Description 23

2-Methoxycarbonyl-7-phenylsulfonylmethyl-1,2,3,4-tetrahydroisoquinoline
To a stirred solution of 7-hydroxymethyl-2-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (4.65g, 20.9mmol) and triethylamine (3.26ml, 22.1mmol) in dichloromethane (200ml) at 0°C was added a solution of methanesulfonyl chloride (1.67ml; 22.1 mmol) in dichloromethane (20ml). Mixture was stirred at room temperature for 18h then partitioned between saturated aqueous NaHCO₃ (200ml) and dichloromethane (3x50ml). Combined extracts were dried (Na₂SO₄) and evaporated in vacuo to give an oil (6.1g). The latter was dissolved in acetone (200ml) and treated with sodium iodide (3.35g, 22.4 mmol). Resulting mixture was stirred at room temperature for 3h, then ether (300ml) was added and the resulting solid filtered off. The filtrate was evaporated in vacuo to give a solid (6.1g). An aliquot of the latter (3.0g) was dissolved in dimethylformamide (60ml) and treated with sodium phenylsulfinate (1.65g, 10mmol). Resulting solution was stirred at room temperature for 18h then partitioned between ethyl acetate (300ml) and water (5x100ml). Organic phase was dried (Na₂SO₄) and evaporated in vacuo to give an oil. Chromatography on silica with 10-100% ethyl acetate - hexane gradient elution gave the title compound as a colourless solid (2.3g, 65%).


Description 24

7-Phenylsulfonylmethyl-1,2,3,4-tetrahydroisoquinoline
A mixture of 2-methoxycarbonyl-7-phenylsulfonylmethyl-1,2,3,4-tetrahydroisoquinoline (21.5g, 6.2 mmol), sodium hydroxide (20g, 0.5mol) and methanol (250ml) was heated at reflux for 64h. The mixture was cooled and evaporation in vacuo, then the residue was partitioned between water (100ml) and dichloromethane (5x50ml). Combined organic extracts were dried (Na₂SO₄) and evaporated in vacuo to give the title compound as a colourless solid (1.77g, 99%).


The following compound was prepared in a similar manner to Description 24:

(a) 7-Methylsulfonylmethyl-1,2,3,4-tetrahydroisoquinoline
Description 25

2-Methoxycarbonyl-7-methylthiomethyl-1,2,3,4-tetrahydroisoquinoline

To a stirred solution of 7-hydroxymethyl-2-methoxycarbonyl-1,2,3,4-
tetrahydroisoquinoline (4.65g, 20.9mmol) and triethylamine (3.26 ml, 22.1 mmol) in
dichloromethane (200 ml) at 0°C was added a solution of methanesulfonyl chloride (1.67
ml; 22.1 mmol) in dichloromethane (20 ml). Mixture was stirred at room temperature for
18h then partitioned between saturated aqueous NaHCO₃ (200ml) and dichloromethane
(3 x 50 ml). Combined extracts were dried (Na₂SO₄) and evaporated in vacuo to give an
oil (6.1g). The latter was dissolved in acetone (200ml) and treated with sodium iodide
(3.35g, 22.4 mmol). Resulting mixture was stirred at room temperature for 3h, then ether
(300ml) was added and the resulting solid filtered off. The filtrate was evaporated in
vacuo to give a solid (6.1g). An aliquot of the latter (2.64g, 7.98 mmol) was dissolved in
dimethylformamide (20 ml) and treated with sodium methylthiolate (0.59g, 8.38 mmol),
then stirred at room temperature for 4h. The mixture was evaporated in vacuo and the
residue partitioned between water (100 ml) and dichloromethane (4 x 30 ml). The
combined organic extracts were dried (Na₂SO₄), then evaporated in vacuo to give an oil.
Chromatography on silica with 10-50% ethyl acetate - hexane gradient elution gave the
title compound (1.01g, 44%).

¹H NMR (CDCl₃) δ: 2.02 (3H, s), 2.73 (2H, t, J = 7 Hz), 3.63 (2H, s), 3.69 (2H, m),
3.74 (3H, s), 4.62 (2H, br s), 7.00 - 7.13 (3H, m).

Description 26

2-Methoxycarbonyl-7-methylsulfonylmethyl-1,2,3,4-tetrahydroisoquinoline

To a stirred solution of 2-methoxycarbonyl-7-methylthiomethyl-1,2,3,4-
tetrahydroisoquinoline (0.90g, 3.59 mmol) in acetic acid (10 ml) was added a solution of
peracetic acid in acetic acid (36% w/w; 1.4 ml; 7.6 mmol) with ice cooling. Reaction
mixture was stirred at room temperature for 18h, then partitioned between saturated
aqueous NaHCO₃ (200 ml) and dichloromethane (3 x 50 ml). Combined organic extracts
were dried (Na₂SO₄) and evaporated in vacuo to give an oil (1.1g). Chromatography on
silica with 20 - 100% ethyl acetate-hexane gradient elution gave the title compound
(0.23g, 23%).


Description 27

2-Trifluoroacetyl-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline

Prepared in two steps from 4-trifluoromethoxyphenethylamine using a method similar to

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Mass spectrum (API') : Found 314 (MH'). C_{13}H_{14}F_{4}NO_{4} requires 313.

Description 28
7-Methylaminosulfonyl-1,2,3,4-tetrahydroisoquinoline, hydrochloride

To a solution of 2-acetyl-1,2,3,4-tetrahydroisoquinoline (73g) in dry dichloromethane (500ml) under argon at -75°C, was added chlorosulfonic acid (120ml) dropwise. The resulting brown solution was allowed to stir from -75°C to room temperature over 20h. It was then poured into 2L of crushed ice and extracted with dichloromethane (2x500ml). The combined organic layers were washed with brine (2x500ml), dried (Na_{2}SO_{4}) and evaporated to dryness *in vacuo* to give an amber oil (115g). To a solution of the latter (51g) in dry THF (200ml) at 0°C, was added a 2M methylamine solution in THF (200ml). The resulting solution was allowed to stir at room temperature for 18h. Solvent was evaporated *in vacuo* to give an oil which was dissolved in dichloromethane (800ml) and washed with brine (500ml), dried (Na_{2}SO_{4}) and evaporated to give an amber oil. The latter was treated with hot ethyl acetate (300ml) to give a colourless solid precipitate which was filtered and dried *in vacuo* (12g). The solid (6g) was stirred at reflux in 3.7M hydrochloric acid (190ml) for 18h. The solution was cooled to room temperature and neutralised with aqueous potassium carbonate. The water was removed on a freeze-dryer and the resulting solid was repeatedly washed with dichloromethane (4x500ml). The combined organic washings were evaporated *in vacuo* to afford a colourless solid (4.8g) which was treated with ethereal HCl in methanol. Recrystallisation from ethanol gave the title compound (3.5g).

Mass spectrum (API') : Found 227 (MH'). C_{14}H_{14}N_{2}O_{2}S requires 226.

1H NMR (MeOH-d_{4}) δ: 2.33 (3H, s), 2.82 (2H, m), 3.07 (2H, m), 3.97 (2H, br s), 7.19 (1H, d, J = 8 Hz), 7.40 - 7.50 (2H, m)

Example 1
(E)-7-Methoxy-2-(4-(3-phenylpropenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.41g, 2.14 mmol) was added to a solution of *trans*-cinnamic acid (0.317g, 2.14 mmol), 2-(4-aminobutyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (0.5g, 2.14 mmol) and 1-hydroxybenzotriazole (0.1g, 0.7 mmol) in dichloromethane (8ml). The mixture was shaken for 18h, saturated aqueous potassium carbonate (5ml) added and shaking continued for a further 1h. The organic layer was chromatographed on silica gel using 10-100% ethyl acetate-hexane gradient elution to afford the title compound as a yellow gum (0.53g, 68%).

Mass spectrum (API') : 365 (MH'). C_{29}H_{34}N_{2}O_{2} requires 364.
Example 2

(E)-7-Hydroxy-2-(4-(3-phenylpropenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

(E)-7-Methoxy-2-(4-(3-phenylpropenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

(0.46g, 1.25 mmol) in dichloromethane (3ml) was treated with 1N hydrogen chloride in diethyl ether (3ml) and the mixture evaporated in vacuo to afford the hydrochloride salt. The hydrochloride salt (0.5g, 1.25 mmol) in dichloromethane (40ml) was ice cooled as a solution of boron tribromide in dichloromethane (10ml, 1M solution, 10 mmol) was added dropwise. After stirring at room temperature for 18h, the mixture was added to ice and .880 ammonia (100ml) and the mixture stirred for 1h then extracted into dichloromethane (2×100ml). Combined organics were washed with brine (50ml), dried (Na$_2$SO$_4$) and evaporated in vacuo to afford the beige solid (0.43g).

Mass spectrum (API$^+$): 351 (MH$^+$). C$_{18}$H$_{23}$N$_3$O$_2$ requires 350.

$^1$H NMR (CDCl$_3$) δ: 1.70 (4H, m), 2.55 (2H, t, J = 7 Hz), 2.75 (2H, t, J = 7 Hz), 2.90 (2H, t, J = 7 Hz), 3.40 (2H, m), 3.65 (2H, s), 3.75 (3H, s), 6.0 (1H, d, J = 15 Hz), 6.60 (1H, d, J = 2 Hz), 6.75 (1H, dd, J = 2 Hz, 8 Hz), 7.05 (1H, d, J = 8 Hz), 7.15 (2H, m), 7.25 (3H, m), 7.50 (1H, d, J = 15 Hz), 7.95 (1H, br m).

Example 3

(E)-2-(4-(3-Phenylpropenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Trifluoromethanesulfonic anhydride (0.26ml, 1.52 mmol) was added dropwise with stirring to an ice cooled solution of (E)-7-hydroxy-2-(4-(3-phenylpropenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline (0.41g, 1.17 mmol) in anhydrous pyridine (5ml). After stirring at room temperature for 18h the reaction mixture was poured into 10% aqueous copper (II) sulfate (100ml). The mixture was extracted with ethyl acetate (2×75ml).

Combined extracts were washed with 10% aqueous copper (II) sulfate (2×50ml), water (50ml), dried (Na$_2$SO$_4$) and evaporated in vacuo. The residue was chromatographed on silica using 10-100% ethyl acetate-hexane gradient elution to afford the title compound (0.205g, 43%).

Mass spectrum (API$^+$): 483 (MH$^+$). C$_{24}$H$_{26}$F$_3$N$_3$O$_3$S requires 482.

$^1$H NMR (CDCl$_3$) δ: 1.70 (4H, m), 2.60 (2H, t, J = 7 Hz), 2.75 (2H, t, J = 7 Hz), 2.95 (2H, t, J = 7 Hz), 3.40 (2H, m), 3.65 (2H, s), 6.20 (1H, d, J = 15 Hz), 6.70 (1H, br m).
6.95 (1H, d, J = 2 Hz), 7.15 (1H, dd, J = 2 Hz, 8 Hz), 7.15 (1H, d, J = 8 Hz), 7.35 (5H, s), 7.60 (1H, d, J = 15 Hz).

Example 4

(E)-2-(4-(3-(3-Nitrophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Prepared from 2-(4-aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline (0.4g, 1.14 mmol) and trans-3-nitrocinnamic acid (0.22g, 1.14 mmol) using a procedure similar to that of Example 1 (0.362g, 60%).

Mass spectrum (API'): 528 (MH'). C_{22}H_{22}F_{2}N_{2}O_{5}S requires 527.

$^1$H NMR (CDCl$_3$) $\delta$: 1.75 (4H, br s), 2.60 (2H, t, J = 7 Hz), 2.80 (2H, t, J = 7 Hz), 3.00 (2H, t, J = 7 Hz), 3.45 (2H, m), 3.70 (2H, s), 6.30 (1H, d, J = 15 Hz), 6.85 (1H, m), 6.95 (1H, s), 7.05 (1H, dd, J = 8 Hz, 2 Hz), 7.20 (1H, d, J = 8 Hz), 7.50 - 7.70 (2H, m), 7.65 (1H, d, J = 15 Hz), 8.20 (1H, dd, J = 8 Hz, 2 Hz), 8.35 (1H, br s).

The following compounds were prepared in a similar manner to Example 4:

(a) (E)-2-(4-(3-(4-Methoxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): 513 (MH'). C_{23}H_{24}F_{2}N_{2}O_{5}S requires 512.

$^1$H NMR (CDCl$_3$) $\delta$: 1.70 (4H, m), 2.60 (2H, t, J = 7 Hz), 2.75 (2H, t, J = 7 Hz), 2.95 (2H, t, J = 7 Hz), 3.40 (2H, m), 3.65 (2H, s), 3.85 (3H, s), 6.10 (1H, d, J = 15 Hz), 6.60 (1H, br t, J = 6 Hz), 6.85 (2H, d, J = 8 Hz), 6.95 (1H, d, J = 2 Hz), 7.05 (1H, dd, J = 8 Hz, 2 Hz), 7.20 (1H, d, J = 8 Hz), 7.30 (2H, d, J = 8 Hz), 7.55 (1H, d, J = 15 Hz).

(b) (E)-2-(4-(3-(4-Bromophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): 561, 563 (MH'). C_{23}H_{23}BrF_{2}N_{2}O_{5}S requires 560, 562.

$^1$H NMR (CDCl$_3$) $\delta$: 1.70 (4H, m), 2.60 (2H, t, J = 7 Hz), 2.75 (2H, t, J = 7 Hz), 2.95 (2H, t, J = 7 Hz), 3.40 (2H, m), 3.70 (2H, s), 6.15 (1H, d, J = 15 Hz), 6.75 (1H, br m), 6.95 (1H, d, J = 2 Hz), 7.05 (1H, dd, J = 8 Hz, 2 Hz), 7.20 (3H, m), 7.45 - 7.55 (3H, m).

(c) (E)-2-(4-(3-(2-Thienyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum: (API'): 489 (MH'). C_{23}H_{24}F_{2}N_{2}O_{5}S requires 488.

$^1$H NMR (CDCl$_3$) $\delta$: 1.70 (4H, m), 2.55 (2H, t, J = 7 Hz), 2.75 (2H, t, J = 7 Hz), 2.95 (2H, t, J = 7 Hz), 3.40 (2H, m), 3.65 (2H, s), 6.05 (1H, d, J = 15 Hz), 6.60 (1H, br m), 7.05 (3H, m), 7.20 (2H, m), 7.30 (1H, m), 7.70 (1H, d, J = 15 Hz).

(d) (E)-2-(4-(3-(2-Naphthyl)propenyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline
(e) (E)-2-(4-(3-(3-Furyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline
¹H NMR (CDCl₃) δ: 1.70 (4H, m), 2.57 (2H, m), 2.64 (2H, t, J = 7 Hz), 2.94 (2H, m), 3.41 (2H, m), 3.66 (2H, s), 5.94 (1H, d, J = 15 Hz), 6.33 (1H, m), 6.50 (1H, m), 6.97 (1H, m), 7.05 (1H, dd, J = 9 Hz, 3 Hz), 7.18 (1H, d, J = 8 Hz), 7.38 (1H, s), 7.48 (1H, d, J = 15 Hz), 7.56 (1H, s).

(f) (E)-2-(4-(3-(4-Chlorophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline
¹H NMR (CDCl₃) δ: 1.69 (4H, m), 2.56 (2H, m), 2.76 (2H, t, J = 7 Hz), 2.92 (2H, m), 3.43 (2H, m), 3.66 (2H, s), 6.13 (1H, d, J = 15 Hz), 6.70 (1H, m), 7.02 (2H, m), 7.21 (5H, m), 7.52 (1H, d, J = 15 Hz).

(g) (E)-2-(4-(3-(4-Dimethylaminophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline
¹H NMR (CDCl₃) δ: 1.69 (4H, m), 2.57 (2H, m), 2.76 (2H, t, J = 7 Hz), 2.94 (2H, m), 3.01 (6H, s), 3.42 (2H, m), 3.66 (2H, s), 5.98 (1H, d, J = 16 Hz), 6.44 (1H, m), 6.64 (2H, d, J = 8 Hz), 6.98 (1H, m), 7.06 (1H, dd, J = 8 Hz, 2 Hz), 7.21 (3H, m), 7.52 (1H, d, J = 16 Hz).

(h) (E)-2-(4-(3-(3-Methylenedioxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline
¹H NMR (CDCl₃) δ: 1.70 (4H, m), 2.18 (2H, s), 2.56 (2H, m), 2.76 (2H, m), 2.95 (2H, m), 3.42 (2H, m), 3.66 (2H, s), 5.99 (1H, d, J = 16 Hz), 6.67 (1H, m), 6.76 (2H, d, J = 8 Hz), 6.86 (1H, m), 6.96 (1H, m), 7.06 (1H, dd, J = 8 Hz, 2 Hz), 7.19 (1H, d, J = 8 Hz), 7.47 (1H, d, J = 16 Hz).

(i) (E)-2-(4-(3-(3-1-Methylindolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline
¹H NMR (CDCl₃) δ: 1.6 (4H, m), 2.6 (2H, m), 2.75 (2H, t, J = 7Hz), 2.95 (2H, m), 3.45 (2H, m ), 3.67 (2H, s), 3.81 (3H, s), 6.0 (1H, m), 6.28 (1H, d, J = 15Hz), 6.94 (1H, d, J = 2Hz), 7.02 (1H, dd, J = 9, 2Hz), 7.1 - 7.4 (5H, m), 7.8 (2H, m).
(j) (E)-2-(4-(3-(1-Naphthyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline


1H NMR (CDCl₃) δ: 1.74 (4H, m), 2.58 (2H, m), 2.76 (2H, m), 2.92 (2H, m), 3.47 (2H, m), 3.67 (2H, s), 6.23 (1H, d, J = 15Hz), 6.80 (1H, m), 6.95 (2H, m), 7.10 (1H, d, J = 8Hz), 7.44 (2H, m), 7.54 (2H, m), 7.86 (2H, m), 8.21 (1H, m), 8.41 (1H, d, J = 15Hz).

(k) (E)-2-(4-(3-(2-Methylphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (APCI): Found 497 (MH⁺). C₈₈H₈₈F₃N₂O₅S requires 496.

1H NMR (CDCl₃) δ: 1.71 (4H, m), 2.40 (3H, s), 2.58 (2H, m), 2.76 (2H, m), 2.95 (2H, m), 3.43 (2H, m), 3.66 (2H, s), 6.08 (1H, d, J = 15Hz), 6.62 (1H, m), 6.95 (1H, m), 7.02 (1H, m), 7.22 (5H, m), 7.87 (1H, d, J = 15Hz).

(l) (E)-2-(4-(3-(3-Cyanophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline


1H NMR (CDCl₃) δ: 1.72 (4H, m), 2.59 (2H, m), 2.78 (2H, m), 2.96 (2H, m), 3.43 (2H, m), 3.67 (2H, s), 6.18 (1H, d, J = 15Hz), 6.84 (1H, m), 6.96 (1H, d, J = 2Hz), 7.07 (1H, dd, J = 7, 2Hz), 7.22 (1H, d, J = 7Hz), 7.49 (3H, m), 7.62 (2H, m).

(m) (E)-2-(4-(3-(2-Quinoliny1)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline


1H NMR (CDCl₃) δ: 1.71 (4H, m), 2.58 (2H, m), 2.77 (2H, m), 2.96 (2H, m), 3.47 (2H, m), 3.66 (2H, s), 6.58 (1H, m), 6.95 (3H, m), 7.15 (1H, d, J = 7Hz), 7.44 (1H, d, J = 8Hz), 7.55 (1H, m), 7.77 (3H, m), 8.06 (1H, d, J = 8Hz), 8.16 (1H, d, J = 8Hz).

(n) (E)-2-(4-(3-(2-Methoxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline


1H NMR (CDCl₃) δ: 1.68 (4H, m), 2.56 (2H, m), 2.75 (2H, m), 2.93 (2H, m), 3.43 (2H, m), 3.65 (2H, s), 3.86 (3H, s), 6.34 (1H, d, J = 15Hz), 6.90 (4H, m), 7.02 (1H, dd, J = 8, 2Hz), 7.16 (1H, d, J = 8Hz), 7.31 (2H, m), 7.83 (1H, d, J = 15Hz).

(o) (E)-2-(4-(3-(3-Indolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

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(p) (E)-2-(4-(3-(2-Benzofuranyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline


1H NMR (CDCl₃) δ: 1.65 (4H, m), 2.51 (2H, m), 2.69 (2H, t, J = 7Hz), 2.89 (2H, t, J = 7Hz), 3.45 (2H, m), 3.58 (2H, s), 6.35 (1H, d, J = 16Hz), 6.36 (1H, m), 6.90 (1H, d, J = 2Hz), 7.00 (1H, dd, J = 9, 2Hz), 7.05 - 7.46 (5H, m), 7.85 (2H, m), 9.20 (1H, br s).

(q) (E)-2-(4-(3-(4-Acetylphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline


1H NMR (CDCl₃) δ: 1.70 (4H, m), 2.60 (2H, m), 2.65 (3H, s), 2.75 (2H, t, J = 6Hz), 2.95 (2H, t, J = 6Hz), 3.45 (2H, m), 3.65 (2H, s), 6.25 (1H, d, J = 15Hz), 6.90 (1H, m), 6.95 (1H, d, J = 2Hz), 7.05 (1H, dd, J = 8, 2Hz), 7.20 (1H, d, J = 8Hz), 7.40 (2H, d, J = 8Hz), 7.55 (1H, d, J = 15Hz), 7.90 (2H, d, J = 8Hz).

(r) (E)-2-(4-(3-(3-Methoxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline


1H NMR (CDCl₃) δ: 1.70 (4H, m), 2.55 (2H, m), 2.75 (2H, t, J = 6Hz), 2.95 (2H, t, J = 6Hz), 3.45 (2H, m), 3.65 (2H, s), 3.80 (3H, s), 6.20 (1H, d, J = 15Hz), 6.55(1H, m), 6.90 (4H, m), 7.05 (1H, dd, J = 8, 2Hz), 7.20 (2H, m), 7.55 (1H, d, J = 15Hz).

(s) (E)-2-(4-(3-(3-Quinolinyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline


1H NMR (CDCl₃) δ: 1.75 (4H, m), 2.60 (2H, m), 2.75 (2H, t, J = 6Hz), 2.95 (2H, t, J = 6Hz), 3.50 (2H, m), 3.65 (2H, s), 6.45 (1H, d, J = 15Hz), 6.65 (1H, m), 6.95 (1H, d, J = 2Hz), 7.00 (1H, dd, J = 8, 2Hz), 7.15 (1H, d, J = 8Hz), 7.55 (1H, m), 7.75 (3H, m), 8.10 (2H, m), 9.00 (1H, d, J = 2Hz).

(t) (E)-2-(4-(3-(2,3-Dihydrobenzofuranyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API’): Found 525 (MH’). C_{23}H_{32}F_{5}N_{5}O_{5}S requires 524.

^1H NMR (CDCl₃): δ: 1.70 (4H, m), 2.60 (2H, m), 2.75 (2H, t, J = 6Hz), 2.95 (2H, t, J = 6Hz), 3.20 (2H, t, J = 8Hz), 3.40 (2H, m), 3.65 (2H, s), 4.60 (2H, t, J = 8Hz), 6.05 (1H, d, J = 15Hz), 6.40 (1H, m), 6.75 (1H, d, J = 7Hz), 6.95 (1H, d, J = 2Hz), 7.05 (1H, dd, J = 8, 2Hz), 7.20 (2H, m), 7.25 (1H, d, J = 7Hz), 7.50 (1H, d, J = 15Hz).

(u) (E)-2-(4-(3-(6-(1,4-benzodioxanyl))propenoyl)aminobutyl)-7-trifluoromethylsulfonfolyoxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API’): Found 541 (MH’). C_{23}H_{32}F_{5}N_{5}O_{5}S requires 540.

^1H NMR (CDCl₃): δ: 1.70 (4H, m), 2.60 (2H, m), 2.75 (2H, t, J = 6Hz), 2.95 (2H, t, J = 6Hz), 3.40 (2H, m), 3.65 (2H, s), 4.30 (4H, s), 6.00 (1H, d, J = 15Hz), 6.65 (1H, m), 6.85 (3H, m), 6.95 (1H, d, J = 2Hz), 7.05 (1H, dd, J = 8, 2Hz), 7.20 (1H, d, J = 8Hz), 7.45 (1H, d, J = 15Hz).

(v) (E)-2-(4-(3-(3-Acetylphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfolyoxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API’): Found 525 (MH’). C_{23}H_{32}F_{5}N_{5}O_{5}S requires 524.

^1H NMR (CDCl₃): δ: 1.70 (4H, m), 2.55 (2H, m), 2.60 (3H, s), 2.75 (2H, t, J = 7Hz), 2.95 (2H, t, J = 7Hz), 3.45 (2H, m), 3.65 (2H, s), 6.30 (1H, d, J = 15Hz), 6.65 (1H, m), 6.95 (1H, d, J = 2Hz), 7.00 (1H, dd, J = 8, 2Hz), 7.20 (1H, d, J = 8Hz), 7.45 (2H, m), 7.60 (1H, d, J = 15Hz), 7.90 (1H, d, J = 7Hz), 8.0 (1H, br s).

(w) (E)-2-(4-(3-(3-Acetamidophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfolyoxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API’): Found 540 (MH’). C_{23}H_{32}F_{5}N_{5}O_{5}S requires 539.

^1H NMR (CDCl₃): δ: 1.75 (4H, m), 2.20 (3H, s), 2.55 (2H, m), 2.75 (2H, t, J = 6Hz), 2.90 (2H, t, J = 6Hz), 3.40 (2H, m), 3.65 (2H, s), 6.25 (1H, d, J = 15Hz), 6.65 (1H, m), 6.95 (1H, d, J = 2Hz), 7.05 (2H, m), 7.15 (1H, d, J = 8Hz), 7.25 (1H, m), 7.45 (1H, br d, J = 8Hz), 7.50 (1H, d, J = 15Hz), 7.65 (2H, m).

(x) (E)-2-(4-(3-(3-Dimethylaminophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfolyoxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API’): Found 526 (MH’). C_{23}H_{32}F_{5}N_{5}O_{5}S requires 525.

^1H NMR (CDCl₃): δ: 1.70 (4H, m), 2.55 (2H, m), 2.75 (2H, t, J = 6Hz), 2.90 (2H, m), 2.95 (6H, s), 3.45 (2H, m), 3.65 (2H, s), 6.20 (1H, d, J = 15Hz), 6.40 (1H, m), 6.75 (3H, m), 6.95 (1H, d, J = 2Hz), 7.05 (1H, dd, J = 8, 2Hz), 7.20 (2H, m), 7.55 (1H, d, J = 15Hz).
(y) (E)-2-(4-(3-(2-Quinoxalinyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API): Found 535 (MH'). C_{22}H_{27}F_{2}N_{2}O_{2}S requires 534.

$^1$H NMR (CDCl$_3$) δ: 1.70 (4H, m), 2.60 (2H, m), 2.75 (2H, t, J = 6Hz), 2.95 (2H, t, J = 6Hz), 3.50 (2H, m), 3.65 (2H, s), 6.70 (1H, m), 7.00 (2H, m), 7.05 (1H, d, J = 15Hz), 7.15 (1H, m), 7.75 (3H, m), 8.10 (2H, m), 8.95 (1H, s).

(z) (E)-2-(4-(3-(2-Benzothiazolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API): Found 540 (MH'). C_{22}H_{27}F_{2}N_{2}O_{2}S requires 539.

$^1$H NMR (CDCl$_3$) δ: 1.70 (4H, m), 2.60 (2H, m), 2.75 (2H, t, J = 6Hz), 2.95 (2H, t, J = 6Hz), 3.45 (2H, m), 3.65 (2H, s), 6.65 (1H, d, J = 15Hz), 6.95 (3H, m), 7.15 (1H, d, J = 8Hz), 7.45 (2H, m), 7.75 (1H, d, J = 15Hz), 7.85 (1H, d, J = 8Hz), 8.05 (1H, d, J = 8Hz).

(a1) (E)-2-(4-(3-(3,4-Dichlorophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API): Found 551 (MH'). C_{22}H_{27}Cl_{2}F_{2}N_{2}O_{2}S requires 550.

$^1$H NMR (CDCl$_3$) δ: 1.70 (4H, m), 2.60 (2H, m), 2.75 (2H, t, J = 6Hz), 2.95 (2H, t, J = 6Hz), 3.40 (2H, m), 3.65 (2H, s), 6.15 (1H, d, J = 15Hz), 6.75 (1H, m), 6.95 (1H, d, J = 2Hz), 7.05 (1H, dd, J = 8, 2Hz), 7.15 (2H, m), 7.40 (3H, m).

(b1) (E)-2-(4-(3-(2-(1-Methyl)pyrrolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API): Found 486 (MH'). C_{22}H_{27}F_{2}N_{2}O_{2}S requires 485.

$^1$H NMR (CDCl$_3$) δ: 1.70 (4H, m), 2.55 (2H, m), 2.75 (2H, t, J = 6Hz), 2.95 (2H, t, J = 6Hz), 3.40 (2H, m), 3.65 (5H, 2xs), 5.95 (1H, d, J = 15Hz), 6.15 (1H, t, J = 3Hz), 6.30 (1H, m), 6.50 (1H, m), 6.70 (1H, br s), 6.95 (1H, d, J = 2Hz), 7.05 (1H, dd, J = 8, 2Hz), 7.20 (1H, d, J = 8Hz), 7.55 (1H, d, J = 15Hz).

(c1) (E)-2-(4-(3-(5-Pyrido[2,3-b]indolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API): Found 523 (MH'). C_{22}H_{27}F_{2}N_{2}O_{2}S requires 522.

$^1$H NMR (CDCl$_3$) δ: 1.70 (4H, m), 2.60 (2H, m), 2.80 (2H, t, J = 6Hz), 3.00 (2H, m), 3.40 (2H, m), 3.60 (2H, m), 6.40 (1H, d, J = 15Hz), 6.90 (1H, br s), 7.05 (1H, m), 7.20 (2H, m), 7.55 (1H, m), 7.70 (1H, d, J = 15Hz), 7.90 (1H, m), 8.25 (3H, m).
(d1) \((E)-2-(4-(3-(5-(2-Dimethylamino)pyrimidyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline\)

Mass spectrum (API'): Found 528 (MH'). \(C_{24}H_{23}F_{3}N_{3}O_{3}S\) requires 527.

\(^1H\) NMR (CDCl\(_3\)) \(\delta\): 1.75 (4H, m), 2.55 (2H, m), 2.75 (2H, t, \(J = 6\) Hz), 2.95 (2H, t, \(J = 6\) Hz), 3.20 (6H, s), 3.40 (2H, m), 3.65 (2H, s), 6.05 (1H, d, \(J = 15\) Hz), 6.50 (1H, m), 6.95 (1H, d, \(J = 2\) Hz), 7.05 (1H, dd, \(J = 8, 2\) Hz), 7.15 (1H, d, \(J = 8\) Hz), 7.40 (1H, d, \(J = 15\) Hz), 8.30 (2H, s).

(e1) \((E)-2-(4-(3-(2-Benzoxazolyl)propenoyl)aminobutyl)-7-trifluoromethylosulfonyloxy-1,2,3,4-tetrahydroisoquinoline\)

Mass spectrum (API'): Found 524 (MH'). \(C_{24}H_{22}F_{3}N_{3}O_{3}S\) requires 523.

\(^1H\) NMR (CDCl\(_3\)) \(\delta\): 1.75 (4H, m), 2.60 (2H, m), 2.75 (2H, t, \(J = 6\) Hz), 2.95 (2H, t, \(J = 6\) Hz), 3.40 (2H, m), 3.65 (2H, s), 6.80 (1H, d, \(J = 15\) Hz), 6.85 (1H, m), 6.95 (2H, m), 7.15 (1H, d, \(J = 8\) Hz), 7.35 (2H, m), 7.45 (1H, d, \(J = 15\) Hz), 7.50 (1H, m), 7.75 (1H, m).

(f1) \((E)-2-(4-(3-(4-(1-Pyrrolidinyl)phenyl)propenoyl)aminobutyl)-7-trifluoromethylosulfonyloxy-1,2,3,4-tetrahydroisoquinoline\)

Mass spectrum (API'): Found 552 (MH'). \(C_{25}H_{23}F_{3}N_{3}O_{3}S\) requires 551.

\(^1H\) NMR (CDCl\(_3\)) \(\delta\): 1.70 (4H, m), 2.05 (4H, m), 2.55 (2H, m), 2.75 (2H, t, \(J = 6\) Hz), 2.95 (2H, t, \(J = 6\) Hz), 3.30 (4H, m), 3.40 (2H, m), 3.65 (2H, s), 5.95 (1H, d, \(J = 15\) Hz), 6.35 (1H, m), 6.50 (2H, d, \(J = 8\) Hz), 6.95 (1H, d, \(J = 2\) Hz), 7.05 (1H, dd, \(J = 8, 2\) Hz), 7.20 (1H, d, \(J = 8\) Hz), 7.25 (2H, d, \(J = 8\) Hz), 7.50 (1H, d, \(J = 15\) Hz).

(g1) \((E)-2-(4-(3-(3-Methylaminocarbonylphenyl)propenoyl)aminobutyl)-7-trifluoromethylosulfonyloxy-1,2,3,4-tetrahydroisoquinoline\).

Mass spectrum (API'): Found 540 (MH'). \(C_{25}H_{24}N_{3}F_{3}O_{3}S\) requires 539.

\(^1H\) NMR (CDCl\(_3\)) \(\delta\): 1.60 - 1.72 (4H, m), 2.52 (2H, t, \(J = 6\) Hz), 2.73 (2H, t, \(J = 6\) Hz), 2.92 (2H, t, \(J = 6\) Hz), 3.00 (3H, d, \(J = 5\) Hz), 3.37 - 3.48 (2H, m), 3.64 (2H, br s), 6.29 (1H, d, \(J = 13\) Hz), 6.49 (1H, m), 6.75 (1H, m), 6.95 (1H, d, \(J = 3\) Hz), 7.03 (1H, dd, \(J = 5\) Hz), 7.17 (1H, d, \(J = 5\) Hz), 7.3 - 7.49 (2H, m), 7.54 (1H, d, \(J = 13\) Hz), 7.69 (1H, m), 7.87 (1H, s).

(h1) \((E)-2-(4-(3-(3,4-Methylenedioxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylosulfonyloxy-1,2,3,4-tetrahydroisoquinoline\)

Mass spectrum (API'): Found 527 (MH'). \(C_{24}H_{21}N_{3}F_{3}O_{3}S\) requires 526.

\(^1H\) NMR (CDCl\(_3\)) \(\delta\): 1.55 - 1.80 (4H, m), 2.55 (2H, t, \(J = 6\) Hz), 2.75 (2H, t, \(J = 6\) Hz), 2.93 (2H, t, \(J = 6\) Hz), 3.44 (2H, m), 3.62 (2H, s), 6.01 (2H, s), 6.22 (1H, m), 6.51 (1H, d,
$J = 13\text{Hz}$, 6.82 (3H, s), 6.95 (1H, d, $J = 2\text{Hz}$), 7.03 (1H, dd, $J = 2, 7\text{Hz}$), 7.15 (1H, d, $J = 7\text{Hz}$), 7.5 (1H, d, $J = 13\text{Hz}$).

(II) (E)-2-((4-(3-Aminocarbonylphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 526 (MH'). $C_{24}H_{28}F_2N_2O_S$ requires 525.

$^1H$ NMR (CDCl$_3$, $\delta$): 1.55 - 1.79 (4H, m), 2.55 (2H, t, $J = 5\text{Hz}$), 2.75 (2H, t, $J = 5\text{Hz}$), 2.90 (2H, t, $J = 5\text{Hz}$), 3.30 - 3.45 (2H, m), 3.65 (2H, s), 5.95 (2H, br s), 6.32 (1H, d, $J = 13\text{Hz}$), 6.70 (1H, t, $J = 6\text{Hz}$), 6.95 (1H, d, $J = 3\text{Hz}$), 7.02 (1H, dd, $J = 3, 6\text{Hz}$), 7.16 (1H, d, $J = 6\text{Hz}$), 7.30 - 7.48 (2H, m), 6.57 (1H, d, $J = 7\text{Hz}$), 7.73 (1H, d, $J = 5\text{Hz}$), 8.90 (1H, s).

(j1) (E)-2-((4-(3-Acetamidophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 540 (MH'). $C_{24}H_{28}F_2N_2O_S$ requires 539.

$^1H$ NMR (CDCl$_3$, $\delta$): 1.52 - 1.70 (4H, m), 2.17 (3H, s), 2.50 (2H, t, $J = 5\text{Hz}$), 2.71 (2H, t, $J = 5\text{Hz}$), 2.90 (2H, t, $J = 5\text{Hz}$), 3.30 (2H, m), 3.60 (2H, s), 6.17 (1H, d, $J = 13\text{Hz}$), 6.92 (1H, d, $J = 3\text{Hz}$), 7.05 (2H, m), 7.15 (1H, d, $J = 7\text{Hz}$), 7.20 - 7.35 (3H, m), 7.59 (1H, d, $J = 7\text{Hz}$), 7.7 (1H, d, $J = 13\text{Hz}$), 8.58 (1H, s).

(k1) (E)-2-((4-(3-Naphthyl)propenoyl)aminobutyl)-7-(2-thiophene)sulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 547 (MH'). $C_{25}H_{26}N_2O_S$ requires 546.

$^1H$ NMR (CDCl$_3$, $\delta$): 1.70 (4H, m), 2.55 (2H, m), 2.74 (2H, t, $J = 7\text{Hz}$), 3.43 (2H, m), 3.58 (2H, s), 6.26 (1H, d, $J = 16\text{Hz}$), 6.78 (2H, m), 6.86 (1H, m), 7.05 (2H, m), 7.38 (1H, m), 7.50 (2H, m), 7.56 (1H, m), 7.68 (2H, m), 7.80 (4H, m).

(11) (E)-2-((4-(3-(4-Dimethylaminophenyl)propenoyl)aminobutyl)-7-(2-thiophene)sulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 540 (MH'). $C_{26}H_{32}N_2O_S$ requires 539.

$^1H$ NMR (CDCl$_3$, $\delta$): 1.68 (4H, m), 2.55 (2H, m), 2.74 (2H, t, $J = 7\text{Hz}$), 3.00 (6H, s), 3.40 (2H, m), 3.55 (2H, s), 5.95 (1H, d, $J = 13\text{Hz}$), 6.64 (3H, m), 6.74 (1H, d, $J = 3\text{Hz}$), 6.80 (1H, dd, $J = 10, 3\text{Hz}$), 7.05 (2H, m), 7.24 (2H, d, $J = 10\text{Hz}$), 7.50 (1H, d, $J = 13\text{Hz}$), 7.58 (1H, dd, $J = 7, 3\text{Hz}$), 7.70 (1H, dd, $J = 7, 3\text{Hz}$).

(m1) (E)-2-((4-(3-Naphthyl)propenoyl)aminobutyl)-7-methylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

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Mass spectrum (API'): Found 479 (MH'). \( \text{C}_{27}\text{H}_{35}\text{N}_{3}\text{O}_{3} \) requires 478.

\(^1\text{H NMR (CDCl}_3\)} \delta: 1.70 (4H, m), 2.58 (2H, m), 2.75 (2H, t, J = 7Hz), 2.95 (2H, t, J = 7Hz), 3.08 (3H, s), 3.45 (2H, m), 3.66 (2H, s), 6.28 (1H, d, J = 16Hz), 6.90 (1H, m), 7.00 (1H, d, J = 3Hz), 7.06 (1H, dd, J = 10, 3Hz), 7.15 (1H, d, J = 10Hz), 7.36 (1H, m), 7.50 (2H, m), 7.74 (1H, d, J = 16Hz), 7.82 (4H, m).

(n1) \((E)-2-(4-(3-(4-Dimethylaminophenyl)propanoyl)aminobutyl)-7-methylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline\)
Mass spectrum (API'): Found 472 (MH'). \( \text{C}_{28}\text{H}_{37}\text{N}_{3}\text{O}_{3} \) requires 471.

\(^1\text{H NMR (CDCl}_3\)} \delta: 1.70 (4H, m), 2.55 (2H, m), 2.75 (2H, t, J = 7Hz), 2.95 (8H, m), 3.40 (2H, m), 3.64 (2H, s), 5.96 (1H, d, J = 16Hz), 6.64 (3H, m), 7.00 (1H, d, J = 3Hz), 7.02 - 7.30 (4H, m), 7.52 (1H, d, J = 16Hz).

(o1) \((E)-2-(4-(3-(2-Naphthyl)propanoyl)aminobutyl)-7-acetyl-1,2,3,4-tetrahydroisoquinoline\)
Mass spectrum (API'): Found 427 (MH'). \( \text{C}_{27}\text{H}_{35}\text{N}_{3}\text{O}_{2} \) requires 426.

\(^1\text{H NMR (CDCl}_3\)} \delta: 1.75 (4H, m), 2.50 (3H, s), 2.62 (2H, m), 2.75 (2H, t, J = 5Hz), 3.00 (2H, t, J = 5Hz), 3.45 (2H, m), 3.72 (2H, s), 6.24 (1H, d, J = 13Hz), 7.16 - 7.32 (3H, m), 7.48 (2H, m), 7.67 (2H, s), 7.70 - 7.84 (5H, m).

(p1) \((E)-2-(4-(3-(2-Naphthyl)propanoyl)aminobutyl)-7-bromo-1,2,3,4-tetrahydroisoquinoline\)
Mass spectrum (API'): Found 463 (MH'). \( \text{C}_{27}\text{H}_{37}\text{N}_{3}\text{Br} \) requires 462.

\(^1\text{H NMR (CDCl}_3\)} \delta: 1.75 (4H, m), 2.57 (2H, t, J = 5Hz), 2.75 (2H, t, J = 5Hz), 2.90 (2H, t, J = 5Hz), 3.45 (2H, m), 3.65 (2H, s), 6.18 (1H, d, J = 15Hz), 7.00 (1H, d, J = 8Hz), 7.14 - 7.73 (3H, m), 7.45 (3H, m), 7.64 - 7.90 (5H, m).

(q1) \((E)-2-(4-(3-(2-Naphthyl)propanoyl)aminobutyl)-7-(4-cyanophenyl)sulfonyloxy-1,2,3,4-tetrahydroisoquinoline\)
Mass spectrum (API'): Found 566 (MH'). \( \text{C}_{31}\text{H}_{39}\text{N}_{3}\text{O}_{4} \) requires 565.

\(^1\text{H NMR (CDCl}_3\)} \delta: 1.70 (4H, m), 2.55 (2H, t, J = 5Hz), 2.75 (2H, t, J = 5Hz), 2.92 (2H, t, J = 5Hz), 3.45 (2H, m), 3.55 (2H, s), 6.30 (1H, d, J = 15Hz), 6.72 (3H, m), 7.04 (1H, d, J = 8Hz), 7.40 (1H, m), 7.45 - 7.55 (2H, m), 7.68 - 8.00 (9H, m).

(r1) \((E)-2-(4-(3-(2-Naphthyl)propanoyl)aminobutyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline\)
Mass spectrum (API'): Found 415 (MH'). \( \text{C}_{29}\text{H}_{39}\text{N}_{3}\text{O}_2 \) requires 414.
\text{H NMR (CDCl₃)} δ: 1.75 (4H, m), 2.58 (2H, t, J = 7Hz), 2.75 (2H, t, J = 7Hz), 2.90 (2H, t, J = 7Hz), 3.43 (2H, m), 3.67 (2H, s), 3.74 (3H, s), 6.14 (1H, d, J = 17Hz), 6.62 (1H, d, J = 3Hz), 6.76 (1H, dd, J = 3, 10Hz), 7.05 (1H, d, J = 10Hz), 7.15 (1H, dd, J = 3, 10Hz), 7.47 (2H, m), 7.66 (1H, d, J = 10Hz), 7.74 (2H, s), 7.80 (2H, m), 8.00 (1H, m).

(s1) \((E)-7\text{-Phenylsulfonylmethyl}-2-(4-(3-(2-naphthyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline\)

Mass spectrum (API): Found 539 (MH⁺). \(\text{C}_{21}\text{H}_{24}\text{N}_{5}\text{O}_{5}\text{S} \text{requires 538.}\)

\text{H NMR (CDCl₃)} δ: 1.70 (4H, m), 2.54 (2H, m), 2.73 (2H, t, J = 7Hz), 2.91 (2H, t, J = 7Hz), 3.44 (2H, m), 3.53 (2H, s), 4.16 (2H, s), 6.29 (1H, d, J = 15Hz), 6.75 (1H, d, J = 2Hz), 6.85 (1H, dd, J = 9, 2Hz), 6.99 (1H, br s), 7.00 (1H, d, J = 9Hz), 7.35 - 7.88 (13H, m).

(t1) \((E)-7\text{-Methylsulfonylamo}-2-(4-(3-(2-naphthyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline\)

Mass spectrum (API): Found 478 (MH⁺). \(\text{C}_{20}\text{H}_{21}\text{N}_{5}\text{O}_{5} \text{requires 477.}\)

\text{H NMR (CDCl₃)} δ: 1.72 (4H, m), 2.55 (2H, m), 2.75 (2H, t, J = 10Hz), 2.91 (5H, m), 3.44 (2H, m), 3.61 (2H, s), 6.21 (1H, d, J = 15Hz), 6.91 (1H, d, J = 2Hz), 7.00 (1H, dd, J = 8, 2Hz), 7.10 (1H, d, J = 8Hz), 7.32 (1H, dd, J = 8, 2Hz), 7.46 - 7.55 (3H, m), 7.70 (1H, d, J = 15Hz), 7.78 - 7.86 (5H, m).

(u1) \((E)-2-(4-(3-Naphthyl)propenoyl)aminobutyl)-7\text{-phenylsulfonylamido}-1,2,3,4-tetrahydroisoquinoline\)

Mass spectrum (API): Found 540 (MH⁺). \(\text{C}_{21}\text{H}_{22}\text{N}_{5}\text{O}_{5}\text{S} \text{requires 539.}\)

\text{H NMR (CDCl₃)} δ: 1.65 (4H, m), 2.49 (2H, m), 2.71 (2H, m), 2.81 (2H, m), 3.40 (2H, m), 3.49 (2H, s), 6.28 (1H, d, J = 15Hz), 6.71 (1H, d, J = 2Hz), 6.90 (2H, m), 7.19 (1H, m), 7.29 - 7.51 (6H, m), 7.69 - 7.82 (8H, m).

(v1) \((E)-7\text{-}(4\text{-Cyanophenyl)sulfonylamido}-2-(4-(3-(2-naphthyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline\)

Mass spectrum (API): Found 565 (MH⁺). \(\text{C}_{22}\text{H}_{23}\text{N}_{5}\text{O}_{5}\text{S} \text{requires 564.}\)

\text{H NMR (CDCl₃)} δ: 1.58 (4H, m), 2.34 (2H, m), 2.64 (2H, m), 2.76 (2H, m), 3.88 (4H, m), 6.21 (1H, d, J = 16Hz), 6.72 (1H, s), 6.88 - 7.04 (2H, m), 7.18 (1H, d, J = 10Hz), 7.40 - 7.51 (4H, m), 7.58 (2H, d, J = 9Hz), 7.66 - 7.89 (7H, m).

(w1) \((E)-2-(4-(3-(5\text{-Indolyl})propenoyl)aminobutyl)-7\text{-trifluoromethylsulfonyloxy}-1,2,3,4-tetrahydroisoquinoline\)

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Mass spectrum (API'): Found 522 (MH'). \( C_{25}H_{22}F_{3}N_{4}O_{5} \) requires 521.

\(^1\)H NMR (CDCl\(_3\)): \( \delta \): 1.70 (4H, m), 2.55 (2H, t, J = 6 Hz), 2.75 (2H, t, J = 6 Hz), 2.90 (2H, t, J = 6 Hz), 3.45 (2H, m), 3.65 (2H, s), 6.20 (1H, d, J = 16 Hz), 6.45 (1H, m), 6.55 (1H, m), 6.95 (1H, d, J = 2 Hz), 7.05 (1H, dd, J = 8, 2 Hz), 7.15 (1H, d, J = 8 Hz), 7.20 - 7.30 (2H, m), 7.35 (1H, d, J = 8 Hz), 7.65 (1H, s), 7.70 (1H, d, J = 16 Hz), 8.50 (1H, br s).

(x1) (E)-2-(4-(3-(5-Benzimidazolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 523 (MH'). \( C_{28}H_{22}F_{3}N_{4}O_{5} \) requires 522.

\(^1\)H NMR (CD\(_3\)OD): \( \delta \): 1.50 (4H, m), 2.45 (2H, t, J = 7 Hz), 2.65 (2H, t, J = 6 Hz), 2.75 (2H, t, J = 6 Hz), 3.20 (2H, m), 3.50 (2H, s), 6.40 (1H, d, J = 16 Hz), 6.90 (2H, m), 7.10 (1H, d, J = 8 Hz), 7.35 (1H, dd, J = 8, 2 Hz), 7.45 (1H, d, J = 8 Hz), 7.50 (1H, d, J = 16 Hz), 7.60 (1H, s), 8.05 (1H, s).

(y1) (E)-7-Methylsulfonylmethyl-2-(4-(3-(2-naphthyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 477 (MH'). \( C_{27}H_{22}F_{3}N_{4}O_{5} \) requires 476.

\(^1\)H NMR (CDCl\(_3\)): \( \delta \): 1.74 (4H, m), 2.58 (2H, m), 2.70 (3H, s), 2.77 (2H, t, J = 7 Hz), 2.96 (2H, t, J = 7 Hz), 3.44 (2H, m), 3.66 (2H, s), 4.10 (2H, s), 6.29 (1H, d, J = 15 Hz), 6.95 (1H, m), 7.08 (1H, s), 7.16 (2H, s), 7.39 (1H, dd, J = 9, 2 Hz), 7.50 (2H, m), 7.65 - 7.87 (5H, m).

(z1) (E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 469 (MH'). \( C_{25}H_{22}F_{3}N_{4}O_{5} \) requires 468.

\(^1\)H NMR (CDCl\(_3\)): \( \delta \): 1.72 (4H, m), 2.57 (2H, t, J = 6 Hz), 2.75 (2H, t, J = 6 Hz), 2.91 (2H, t, J = 6 Hz), 3.45 (2H, m), 3.65 (2H, s), 6.26 (1H, d, J = 16 Hz), 6.94 (1H, s), 6.96 - 7.17 (3H, m), 7.33 (1H, dd, J = 9, 2 Hz), 7.49 (2H, m), 7.73 (1H, d, J = 9 Hz), 7.75 - 7.87 (4H, m).

(a2) (E)-7-Cyano-2-(4-(3-(2-naphthyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 410 (MH'). \( C_{25}H_{22}F_{3}N_{4}O \) requires 409.

\(^1\)H NMR (CDCl\(_3\)): \( \delta \): 1.69 (4H, m), 2.56 (2H, m), 2.75 (2H, t, J = 7 Hz), 2.97 (2H, t, J = 7 Hz), 3.45 (2H, m), 3.64 (2H, s), 6.27 (1H, d, J = 16 Hz), 6.80 (1H, m), 7.18 (1H, d, J = 9 Hz), 7.30 - 7.45 (3H, m), 7.49 (2H, m), 7.75 (1H, d, J = 16 Hz), 7.76 - 7.87 (4H, m).
(b2) (E)-2-(4-(3-(3-Indolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API\textsuperscript{+}): Found 458 (MH\textsuperscript{+}). C\textsubscript{29}H\textsubscript{28}F\textsubscript{3}N\textsubscript{3}O\textsubscript{2} requires 457.

\(^1\)H NMR (CDCl\textsubscript{3}) \(\delta\): 1.68 (4H, m), 2.56 (2H, m), 2.73 (2H, t, J = 7 Hz), 2.90 (2H, t, J = 7 Hz), 3.45 (2H, m), 3.61 (2H, s), 6.26 - 6.37 (2H, m), 6.90 (1H, br s), 6.98 (1H, m), 7.09 (1H, d, J = 8 Hz), 7.15 - 7.28 (2H, m), 7.33 (1H, d, J = 3 Hz), 7.41 (1H, dd, J = 8, 2 Hz), 7.77 - 7.89 (2H, m), 8.82 (1H, br s).

(c2) (E)-2-(4-(3-Dimethylaminophenyl)propenoyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API\textsuperscript{+}): Found 462 (MH\textsuperscript{+}). C\textsubscript{29}H\textsubscript{28}F\textsubscript{3}N\textsubscript{3}O\textsubscript{2} requires 461.

\(^1\)H NMR (CDCl\textsubscript{3}) \(\delta\): 1.70 (4H, m), 2.67 (2H, m), 2.75 (2H, t, J = 7 Hz), 2.94 (2H, t, J = 7 Hz), 2.99 (6H, s), 3.41 (2H, m), 3.65 (2H, s), 5.95 (1H, d, J = 16Hz), 6.64 (2H, d, J = 9 Hz), 6.77 (1H, m), 6.93 (1H, br s), 7.03 (1H, m), 7.14 (1H, d, J = 9 Hz), 7.21 (2H, d, J = 9 Hz), 7.50 (1H, d, J = 16 Hz).

(d2) (E)-7-Cyano-2-(4-(3-(3-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API\textsuperscript{+}): Found 399 (MH\textsuperscript{+}). C\textsubscript{29}H\textsubscript{28}N\textsubscript{2}O requires 398.

\(^1\)H NMR (CDCl\textsubscript{3}) \(\delta\): 1.70 (4H, m), 2.55 (2H, m), 2.70 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.45 (2H, m), 3.60 (2H, s), 6.25 (1H, m), 6.30 (1H, d, J = 16 Hz), 7.05 - 7.45 (7H, m), 7.80 (1H, m), 7.85 (1H, d, J = 16 Hz), 8.90 (1H, br s).

(e2) (E)-2-(4-(3-(7-Methyl)indolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API\textsuperscript{+}): Found 536 (MH\textsuperscript{+}). C\textsubscript{30}H\textsubscript{29}F\textsubscript{3}N\textsubscript{3}O\textsubscript{2}S requires 535.

\(^1\)H NMR (CDCl\textsubscript{3}) \(\delta\): 1.60 (4H, m), 2.45 (2H, m), 2.50 (3H, s), 2.60 (2H, t, J = 5 Hz), 2.80 (2H, t, J = 5 Hz), 3.40 (2H, m), 3.50 (2H, s), 6.40 (1H, d, J = 16 Hz), 6.65 (1H, t, J = 5 Hz), 6.85 (1H, d, J = 2 Hz), 6.9 - 7.15 (4H, m), 7.30 (1H, m), 7.65 (1H, d, J = 8 Hz), 7.85 (1H, d, J = 16 Hz), 9.70 (1H, br s).

(f2) (E)-2-(4-(3-(2-(6-Acetyl)naphthyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API\textsuperscript{+}): Found 575 (MH\textsuperscript{+}). C\textsubscript{30}H\textsubscript{29}F\textsubscript{3}N\textsubscript{3}O\textsubscript{2}S requires 574.

\(^1\)H NMR (CDCl\textsubscript{3}) \(\delta\): 1.70 (4H, m), 2.60 (2H, m), 2.70 (3H, s), 2.75 (2H, m), 2.95 (2H, m), 3.45 (2H, m), 3.65 (2H, s), 6.35 (1H, d, J = 16 Hz), 6.80 (1H, m), 6.95 (1H, d, J = 2
Hz), 7.05 (1H, dd, J = 8, 2 Hz), 7.20 (1H, d, J = 8 Hz), 7.45 (1H, d, J = 8 Hz), 7.75 (1H, d, J = 16 Hz), 7.85 (3H, m), 8.05 (1H, d, J = 9 Hz), 8.40 (1H, s).

(g2) (E)-7-Cyano-2-(4-(3-(3-(methyl)indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API⁺): Found 413 (MH⁺). \(C_{25}H_{28}N_3O\) requires 412.
1H NMR (CDCl₃) \(\delta\): 1.65 (4H, m), 2.45 (3H, s), 2.50 (2H, m), 2.70 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.45 (2H, m), 3.55 (2H, s), 6.25 (1H, m), 6.30 (1H, d, J = 16 Hz), 7.10 (3H, m), 7.25 (1H, m), 7.40 (2H, m), 7.65 (1H, d, J = 8 Hz), 7.85 (1H, d, J = 16 Hz), 8.80 (1H, br s).

(h2) (E)-7-Cyano-2-(4-(3-(5-benzimidazolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API⁺): Found 400 (MH⁺). \(C_{25}H_{28}N_3O\) requires 399.
1H NMR (CDCl₃) \(\delta\): 1.70 (4H, m), 2.55 (2H, m), 2.75 (2H, m), 2.95 (2H, m), 3.45 (2H, m), 3.60 (2H, s), 6.20 (1H, d, J = 16 Hz), 7.15 (3H, m), 7.25 (2H, m), 7.35 (1H, m), 7.60 (2H, m), 7.65 (1H, d, J = 16 Hz), 8.10 (1H, s).

(i2) (E)-7-Cyano-2-(4-(3-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API⁺): Found 399 (MH⁺). \(C_{25}H_{28}N_3O\) requires 398.
1H NMR (CDCl₃) \(\delta\): 1.70 (4H, m), 2.55 (2H, m), 2.65 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.45 (2H, m), 3.65 (2H, s), 6.15 (1H, d, J = 16 Hz), 6.55 (1H, br s), 6.70 (1H, m), 7.20 (3H, m), 7.35 (3H, m), 7.65 (1H, s), 7.70 (1H, d, J = 16 Hz), 8.55 (1H, br s).

(j2) (E)-2-(4-(3-(2-(6-Acetyl)naphthyl)propenoyl)aminobutyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API⁺): Found 452 (MH⁺). \(C_{29}H_{27}N_3O_2\) requires 451.
1H NMR (CDCl₃) \(\delta\): 1.70 (4H, m), 2.60 (2H, m), 2.75 (3H, s), 2.80 (2H, m), 2.95 (2H, m), 3.45 (2H, m), 3.65 (2H, s), 6.30 (1H, d, J = 16 Hz), 6.95 (1H, m), 7.15 - 7.50 (4H, m), 7.75 (1H, d, J = 16 Hz), 7.85 (3H, m), 8.05 (1H, m), 8.45 (1H, br s).

(k2) (E)-7-Cyano-2-(4-(3-(6-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API⁺): Found 399 (MH⁺). \(C_{25}H_{28}N_3O\) requires 398.
1H NMR (CDCl₃) \(\delta\): 1.75 (4H, m), 2.60 (2H, t, J = 6 Hz), 2.80 (2H, t, J = 6 Hz), 3.00 (2H, t, J = 6 Hz), 3.45 (2H m), 3.65 (2H, s), 6.10 (1H, d, J = 16 Hz), 6.55 (1H, m), 6.75
(1H, m), 7.10 (1H, dd, J = 8, 2 Hz), 7.15 (1H, d, J = 8 Hz), 7.25 (1H, m), 7.35 (2H, m), 7.40 (1H, br s), 7.60 (1H, d, J = 8 Hz), 7.70 (1H, d, J = 16 Hz), 8.70 (1H, br s).

(12) (E)-7-Cyano-2-(4-(3-(7-fluoroindolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline


1H NMR (CDCl3) δ: 1.70 (4H, m), 2.55 (2H, m), 2.75 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.45 (2H, m), 3.60 (2H, s), 6.25 (1H, m), 6.30 (1H, d, J = 16 Hz), 6.95 (1H, m), 7.10 (2H, m), 7.25 (1H, m), 7.35 (2H, m), 7.55 (1H, d, J = 8 Hz), 7.75 (1H, d, J = 16 Hz), 9.10 (1H, br s).

(m2) (E)-2-(4-(3-(7-Bromoindolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline


1H NMR (DMSO-d6) δ: 1.70 (4H, m), 2.60 (2H, m), 2.75 (2H, m), 2.95 (2H, m), 3.35 (2H, m), 3.70 (2H, s), 6.70 (1H, d, J = 16 Hz), 7.20 (3H, m), 7.35 (1H, d, J = 8 Hz), 7.55 (1H, d, J = 8 Hz), 7.70 (1H, d, J = 16 Hz), 7.95 (1H, s), 8.05 (2H, m), 11.90 (1H, br s).

(n2) (E)-2-(4-(3-(7-Bromoindolyl)propenoyl)aminobutyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline


1H NMR (DMSO-d6) δ: 1.70 (4H, m), 2.55 (2H, m), 2.75 (2H, m), 2.95 (2H, m), 3.30 (2H, m), 3.60 (2H, s), 6.65 (1H, d, J = 16 Hz), 7.15 (1H, m), 7.35 (1H, d, J = 8 Hz), 7.45 (1H, d, J = 8 Hz), 7.60 (3H, m), 7.80 (1H, s), 7.95 (2H, m), 11.80 (1H, br s).

(o2) (E)-2-(4-(3-(7-Cyanoindolyl)propenoyl)aminobutyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline


1H NMR (DMSO-d6) δ: 1.65 (4H, m), 2.55 (2H, m), 2.70 (2H, m), 2.95 (2H, m), 3.30 (2H, m), 3.60 (2H, s), 6.75 (1H, t, J = 16 Hz), 7.40 (2H, m), 7.65 (3H, m), 7.75 (1H, d, J = 8 Hz), 8.00 (2H, m), 8.30 (1H, d, J = 8 Hz), 12.50 (1H, br s).

(p2) (E)-7-Cyano-2-(4-(3-(5-(2-methylindolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline


1H NMR (DMSO-d6) δ: 1.60 (4H, m), 2.45 (3H, s), 2.55 (2H, m), 2.75 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.25 (2H, m), 3.65 (2H, s), 6.20 (1H, s), 6.55 (1H, d, J = 16 Hz),
7.30 (3H, m), 7.45 (1H, d, J = 16 Hz), 7.60 (3H, br s), 8.00 (1H, t, J = 5 Hz), 11.20 (1H, br s).

(q2) (E)-2-(4-(3-(5-(2-Methylindolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API+): Found 472 (MH+). C_{35}H_{39}F,N_{7}O_{3} requires 471.
1H NMR (DMSO-d_{6}) δ: 1.65 (4H, m), 2.45 (3H, s), 2.55 (2H, m), 2.75 (2H, m), 2.90 (2H, m), 3.30 (2H, m), 3.65 (2H, s), 6.20 (1H, s), 6.55 (1H, d, J = 16 Hz), 7.20 (2H, m), 7.30 (3H, m), 7.55 (1H, d, J = 16 Hz), 7.65 (1H, br s), 8.05 (1H, m), 11.20 (1H, br s).

(r2) (E)-2-(4-(3-(7-Acetylindolyl)propenoyl)aminobutyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API+): Found 441 (MH+). C_{35}H_{38}N_{4}O requires 440.
1H NMR (DMSO-d_{6}) δ: 1.60 (4H, m), 2.55 (2H, m), 2.70 (2H, m), 2.75 (3H, s), 2.95 (2H, m), 3.65 (2H, s), 6.75 (1H, d, J = 16 Hz), 7.35 (2H, m), 7.65 (2H, m), 7.70 (1H, d, J = 16 Hz), 7.80 (1H, d, J = 2 Hz), 7.90 (1H, m), 8.0 (1H, d, J = 7 Hz), 8.25 (1H, d, J = 7 Hz), 11.80 (1H, br s).

(s2) (E)-7-Cyano-2-(4-(3-(6-(2-methylindolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API+): Found 413 (MH+). C_{35}H_{37}N_{4}O requires 412.
1H NMR (DMSO-d_{6}) δ: 1.65 (4H, m), 2.50 (3H, s), 2.60 (2H, m), 2.75 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.30 (2H, m), 3.65 (2H, s), 6.20 (1H, s), 6.60 (1H, d, J = 16 Hz), 7.25 (1H, dd, J = 8, 2 Hz), 7.40 (1H, d, J = 8 Hz), 7.50 (3H, m), 7.60 (1H, d, J = 16 Hz), 7.65 (1H, m), 8.10 (1H, m), 11.20 (1H, br s).

(t2) (E)-7-Cyano-2-(4-(3-(5-(2,3-dihydro-2-oxo)-1H-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API+): Found 415 (MH+). C_{35}H_{38}N_{4}O requires 414.
1H NMR (DMSO-d_{6}) δ: 1.00 (4H, m), 2.70 (2H, m), 2.94 (2H, m), 3.21 (2H, m), 3.36 (2H, s), 3.55 (4H, m), 6.50 (1H, d, J = 16 Hz), 6.85 (1H, d, J = 9 Hz), 7.25 - 7.50 (4H, m), 7.56 (2H, m), 8.03 (1H, m), 10.57 (1H, br s).

(u2) (E)-2-(4-(3-(6-(1,2-Dihydro-2-oxo)quinolinyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API+): Found 486 (MH+). C_{35}H_{39}F,N_{7}O_{3} requires 485.

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H NMR (DMSO-d$_6$) δ: 1.65 (4H, m), 2.50 (2H, m), 2.75 (2H, m), 2.90 (2H, m), 3.30 (2H, m), 3.65 (2H, s), 6.60 (1H, d, $J = 11$ Hz), 6.65 (1H, d, $J = 16$ Hz), 7.20 (2H, m), 7.30 (1H, d, $J = 8$ Hz), 7.40 (1H, d, $J = 8$ Hz), 7.50 (1H, d, $J = 16$ Hz), 7.80 (1H, d, $J = 8$ Hz), 7.90 (1H, s), 8.00 (1H, d, J = 10 Hz), 8.25 (1H, m), 12.00 (1H br s).

(v2) (E)-2-(4-(3-(5-(2-Acetyl)indolyl)propenoyl)aminobutyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 441 (MH$^+$). $C_{27}H_{35}N_7O_2$ requires 440.

H NMR (DMSO-d$_6$) δ: 1.70 (4H, m), 2.60 (2H, m), 2.70 (3H, s), 2.80 (2H, t, J = 6 Hz), 3.00 (2H, t, J = 6 Hz), 3.35 (2H, m), 3.70 (2H, s), 6.65 (1H, d, $J = 16$ Hz), 7.40 (1H, d, J = 8 Hz), 7.55 (1H, d, J = 2 Hz), 7.65 (5H, m), 8.00 (1H, s), 8.20 (1H, m), 12.10 (1H, br s).

(w2) (E)-7-Chloro-2-(4-(3-(6-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API') Found 408 (MH$^+$). $C_{26}H_{25}$ClN$_5$O$_2$ requires 407.

H NMR (CDCl$_3$) δ: 1.72 (4H, m), 2.58 (2H, m), 2.75 (2H, m), 2.91 (2H, m), 3.42 (2H, m), 3.66 (2H, s), 6.05 (1H, d, $J = 15$ Hz), 6.54 (1H, m), 7.04 (2H, m), 7.12 (2H, m), 7.27 (2H, m), 7.41 (1H, m), 7.57 (1H, d, J = 8 Hz), 7.67 (1H, d, J = 15 Hz), 8.38 (1H, m).

(x2) (E)-7-Cyano-2-(4-(3-(5-(3-methyl)indolyl)propenyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 413 (MH$^+$). $C_{28}H_{32}N_4O$ requires 412.

H NMR (CDCl$_3$ + DMSO) δ: 1.51 (4H, m), 2.15 (3H, s), 2.41 (2H, m), 2.58 (2H, m), 2.79 (2H, t, J = 5.8 Hz), 3.22 (2H, m), 3.47 (2H, s), 6.17 (1H, d, J = 15.5 Hz), 6.82 (1H, s), 6.96 (1H, t, J = 5.5 Hz), 7.0 - 7.3 (5H, m), 7.46 (1H, m), 7.52 (1H, d, J = 15.5 Hz), 9.66 (1H, s).

(y2) (E)-2-(4-(3-(6-(3-Methyl)indolyl)propenoyl)aminobutyl)-7-trifluormethoxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 472 (MH$^+$). $C_{25}H_{34}N_5F_3O_2$ requires 471.

H NMR (CDCl$_3$) δ: 1.69 (4H, m), 2.31 (3H, s), 2.55 (2H, m), 2.73 (2H, m), 2.91 (2H, m), 3.40 (2H, m), 3.64 (2H, s), 6.14 (1H, d, J = 15.5 Hz), 6.9 - 7.2 (6H, m), 7.29 (1H, s), 7.48 (1H, d, J = 8.3 Hz), 7.71 (1H, d, J = 15.5 Hz), 8.37 (1H, s).

(z2) (E)-7-Cyano-2-(4-(3-(5-(1-methyl)indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline
Mass spectrum (API'): Found 413 (MH'). $C_{24}H_{22}N_5O$ requires 412.

$^1$H NMR (CDCl$_3$) δ: 1.69 (4H, m), 2.58 (2H, m), 2.75 (2H, t, J = 6 Hz), 2.97 (2H, m), 3.39 (2H, m), 3.65 (2H, s), 3.81 (3H, s), 6.31 (1H, d, J = 15.8 Hz), 6.48 (1H, d, J = 3 Hz), 7.08 (1H, d, J = 3 Hz), 7.1 - 7.4 (6H, m), 7.66 (1H, s), 7.67 (1H, d, J = 15.8 Hz).

(a3) (E)-2-(4-(3-(2-(1-Methyl)indolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 536 (MH'). $C_{38}H_{36}F_N_5O_S$ requires 535.

$^1$H NMR (CDCl$_3$) δ: 1.65 (4H, m), 2.50 (2H, m), 2.65 (2H, t, J = 5 Hz), 2.85 (2H, m), 3.40 (2H, m), 3.55 (2H, s), 3.70 (3H, s), 6.40 (1H, d, J = 15 Hz), 6.65 (1H, s), 6.90 (1H, s), 7.05 (3H, m), 7.20 (3H, m), 7.45 (1H, d, J = 8 Hz), 7.70 (1H, d, J = 15 Hz).

(b3) (E)-2-(4-(3-(5-Indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 374 (MH'). $C_{27}H_{27}N_5O$ requires 373.

$^1$H NMR (CDCl$_3$) δ: 1.75 (4H, m), 2.55 (2H, m), 2.75 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.40 (2H, m), 3.70 (2H, s), 6.05 (1H, d, J = 16 Hz), 6.55 (1H, s), 7.05 (1H, m), 7.20 (7H, m), 7.55 (1H, s), 7.65 (1H, d, J = 16 Hz), 8.25 (1H, br s).

(c3) (E)-7-Cyano-2-(4-(3-(5-(2-methyl)benzimidazolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 414 (MH'). $C_{28}H_{25}N_5O$ requires 413.

$^1$H NMR (CDCl$_3$) δ: 1.70 (4H, m), 2.55 (2H, m), 2.60 (3H, s), 2.75 (2H, t, J = 6 Hz), 3.00 (2H, t, J = 6 Hz), 3.45 (2H, m), 3.65 (2H, s), 6.10 (1H, d, J = 16 Hz), 6.90 (1H, br s), 7.20 (2H, m), 7.35 (3H, m), 7.50 (2H, m), 7.70 (1H, d, J = 16 Hz).

(d3) (E)-2-(4-(3-(5-(2-Methyl)benzimidazolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 473 (MH'). $C_{29}H_{30}F_3N_5O_5$ requires 472.

$^1$H NMR (CDCl$_3$) δ: 1.70 (4H, m), 2.55 (2H, t, J = 6 Hz), 2.65 (3H, s), 2.75 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.40 (2H, m), 3.65 (2H, s), 6.10 (1H, d, J = 16 Hz), 6.95 (1H, br s), 7.00 (1H, m), 7.10 (2H, m), 7.45 (4H, m), 7.70 (1H, d, J = 16 Hz).

(e3) (E)-2-(4-(3-(5-Indolyl)propenoyl)aminobutyl)-7-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 442 (MH'). $C_{25}H_{27}F_3N_5O$ requires 441.
(f3) (E)-2-(4-(3-(5-Indolyl)propenoyl)aminobutyl)-7-methylsulfonamido-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 467 (MH⁺). C₃₅H₃₀N₅O₃S requires 466.

¹H NMR (DCl, δ): 1.72 (4H, m), 2.59 (2H, m), 2.76 (2H, m), 2.16 (2H, m), 3.43 (2H, m), 3.70 (2H, s), 6.61 (1H, d, J = 15.5 Hz), 6.56 (1H, s), 6.66 (1H, m), 7.10 - 7.45 (6H, m), 7.68 (1H, s), 7.71 (1H, d, J = 15.5 Hz), 8.31 (1H, br s).

(g3) (E)-2-(4-(3-(5-Indolyl)propenoyl)aminobutyl)-7-methylaminosulfonyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 467 (MH⁺). C₃₅H₃₀N₅O₃S requires 466.

¹H NMR (CD,OD) δ: 1.60 - 1.80 (4H, m), 2.48 (3H, s), 2.62 (2H, m), 2.82 (2H, m), 3.00 (2H, m), 3.39 (2H, m), 3.73 (2H, s), 6.45 (1H, s), 6.51 (1H, d, J = 17 Hz), 7.25 (1H, d, J = 3 Hz), 7.35 (3H, m), 7.63 (3H, m), 7.73 (1H, m), 7.79 (1H, br s).

(h3) (E)-2-(4-(3-(7-Methylindolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API'): Found 472 (MH⁺). C₅₀H₃₅F₃N₅O₂ requires 471.

¹H NMR (CDCl₃) δ: 1.66 - 1.71 (4H, m), 2.51 (3H, s), 2.56 (2H, m), 2.74 (2H, m), 2.93 (2H, m), 3.44 (2H, m), 3.63 (2H, s), 6.23 (1H, m), 6.31 (1H, d, J = 15.5 Hz), 6.89 (1H, s), 6.90 - 7.20 (4H, m), 7.35 (1H, d, J = 2.75 Hz), 7.67 (1H, d, J = 7.7 Hz), 7.83 (1H, d, J = 15.5 Hz), 8.48 (1H, br s).

Example 5

(E)-2-(4-(3-(4-Aminophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

A mixture of 2-(4-aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline (440mg, 1.25mmol), trans-4-aminocinnamic acid hydrochloride (250mg, 1.25mmol), triethylamine (0.174ml, 1.25mmol) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (240mg, 1.25mmol) and 1-hydroxybenzotriazole (100mg, 0.74mmol) in dichloromethane (50ml) was stirred at room temperature for 18h. The reaction mixture was washed with saturated aqueous sodium hydrogen carbonate (50ml) and the organic layer dried (Na₂SO₄) and evaporated in
vacuo. The residue was chromatographed on silica using 10 - 100% ethyl acetate-hexane gradient elution to afford the title compound (280mg, 45%).

Mass spectrum (APCI): Found 498 (MH'). C_{27}H_{28}F_{3}N_{3}O_{4}S requires 497.

\(^1\text{H NMR (CDCl}_3\text{)} \delta: \) 1.75 (4H, m), 2.55 (2H, m), 2.75 (2H, t, J = 6Hz), 2.90 (2H, t, J = 6Hz), 3.40 (2H, m), 3.65 (2H, s), 3.85 (2H, br s), 6.00 (1H, d, J = 15Hz), 6.45 (1H, m), 6.60 (2H, d, J = 8Hz), 6.95 (1H, d, J = 2Hz), 7.05 (1H, dd, J = 8, 2Hz), 7.20 (4H, m), 7.50 (1H, d, J = 15Hz).

Example 6

(E)-2-[(4-(3-(4-Nitrophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

A mixture of 2-(4-aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline (400mg, 1.14mmol), \textit{trans}-4-nitrocinnamoyl chloride (240mg, 1.14mmol) and triethylamine (0.2ml, 1.37mmol) in dichloromethane (6ml) was shaken at room temperature for 18h. Saturated aqueous potassium carbonate (5ml) was added and shaking resumed for 15mins. The organic layer was chromatographed on silica using 10-100% ethyl acetate-hexane gradient elution to afford the title compound as a yellow gum (490mg, 82%).

Mass spectrum (APCI): Found 528 (MH'). C_{33}H_{34}F_{3}N_{3}O_{6}S requires 527.

\(^1\text{H NMR (CDCl}_3\text{)} \delta: \) 1.75 (4H, m), 2.60 (2H, m), 2.75 (2H, t, J = 6Hz), 2.95 (2H, t, J = 6Hz), 3.45 (2H, m), 3.65 (2H, s), 6.25 (1H, d, J = 15Hz), 6.95 (2H, m), 7.05 (1H, dd, J = 8, 2Hz), 7.15 (1H, d, J = 8Hz), 7.45 (2H, d, J = 8Hz), 7.60 (1H, d, J = 15Hz), 8.20 (2H, d, J = 8Hz).

Example 7

(E)-7-Cyano-2-[(4-(3-(5-(3-dimethylaminomethyl)indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline

A mixture of (E)-7-cyano-2-(4-(3-(5-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline (0.15g, 0.37 mmol), dimethylamine hydrochloride (0.033g, 0.41 mmol), paraformaldehyde (0.013g, 0.43 mmol) and 1-butanol (10ml) was heated at reflux for 2h. Reaction mixture was evaporated in \textit{vacuo} and the residue partitioned between saturated aqueous NaHCO\textsubscript{3} (50ml) and dichloromethane (3x30ml). Combined organic extracts were dried (Na\textsubscript{2}SO\textsubscript{4}) and evaporated in \textit{vacuo} to give an oil (0.13g). Chromatography on silica using 0 - 10% methanol - ethyl acetate gradient elution gave the title compound (0.017g, 13%).

Mass spectrum (APCI): Found 456 (MH'). C_{38}H_{37}N_{5}O requires 455.
$^1$H NMR (CDCl$_3$) $\delta$: 1.70 (4H, m), 2.60 (2H, m), 2.65 (6H, s), 2.78 (2H, t, $J = 7$ Hz),
2.97 (2H, t, $J = 7$ Hz), 3.43 (2H, m), 3.67 (2H, s), 4.18 (2H, s), 6.32 (1H, d, $J = 16$ Hz),
7.20 (1H, m), 7.23 - 7.48 (6H, m), 7.62 (1H, m), 7.70 (1H, m), 7.78 (1H, m).
Claims:

1. A compound of formula (I):

\[ \text{Formula (I)} \]

wherein:

- \( R^1 \) represents a substituent selected from: a hydrogen or halogen atom; a hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethanesulfonyloxy, \( \text{C}_{1-4} \text{alkyl} \), \( \text{C}_{1-4} \text{alkoxy} \), aryl\( \text{C}_{1-4} \text{alkoxy} \), \( \text{C}_{1-4} \text{alkylthio} \), \( \text{C}_{1-4} \text{alkoxyC}_{1-4} \text{alkyl} \), \( \text{C}_{3-6} \text{cycloalkylC}_{1-4} \text{alkoxy} \), \( \text{C}_{1-4} \text{alkanoyl} \), \( \text{C}_{1-4} \text{alkoxycarbonyl} \), \( \text{C}_{1-4} \text{alkylsulphonyl} \), \( \text{C}_{1-4} \text{alkylsulphonyloxy} \), \( \text{C}_{1-4} \text{alkylsulphonylC}_{1-4} \text{alkyl} \), arylsulphonyl, arylylsulphonyloxy, arylylsulphonylC\( \text{C}_{1-4} \text{alkyl} \), \( \text{C}_{1-4} \text{alkylsulphonamido} \), \( \text{C}_{1-4} \text{alkylamido} \), \( \text{C}_{1-4} \text{alkylsulphonamidoC}_{1-4} \text{alkyl} \), \( \text{C}_{1-4} \text{alkylamidoC}_{1-4} \text{alkyl} \), arylylsulphonamido, arylcarboxamido, arylylsulphonamido\( \text{C}_{1-4} \text{alkyl} \), arylcarboxamido\( \text{C}_{1-4} \text{alkyl} \), aryl, arylC\( \text{C}_{1-4} \text{alkyl} \), or ary\( \text{C}_{1-4} \text{alkanoyl} \) group; a group \( \text{R}^3 \text{OCO(CH}_2)_p \), \( \text{R}^3 \text{CON}\{\text{R}^4\} (\text{CH}_2)_p \), \( \text{R}^3 \text{R}^4 \text{NCO(CH}_2)_p \) or \( \text{R}^3 \text{R}^4 \text{NSO}_2(\text{CH}_2)_p \) where each of \( \text{R}^3 \) and \( \text{R}^4 \) independently represents a hydrogen atom or a \( \text{C}_{1-4} \text{alkyl} \) group or \( \text{R}^3 \text{R}^4 \) forms part of a \( \text{C}_{3-6} \text{azacycloalkane} \) or \( \text{C}_{3-6}(2\text{-oxo})\text{azacycloalkane} \) ring and \( p \) represents zero or an integer from 1 to 4; or a group \( \text{Ar}^1 \text{Z} \), wherein \( \text{Ar}^1 \) represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring and \( Z \) represents a bond, O, S, or \( \text{CH}_2 \):

- \( R^2 \) represents a hydrogen atom or a \( \text{C}_{1-4} \text{alkyl} \) group;
- \( q \) is 1 or 2;
- \( \text{Ar} \) represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; or an optionally substituted bicyclic aromatic or heteroaromatic ring system; or a salt thereof.

2. A compound according to claim 1 wherein \( q \) represents 1.

3. A compound of formula (I) which is:
(E)-7-Methoxy-2-(4-(3-phenylpropenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;
(E)-7-Hydroxy-2-(4-(3-phenylpropenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-Phenylpropenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-Nitrophenoxy)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(4-Methoxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(4-Bromophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Thienyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-Furyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-Chlorophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(4-Dimethylaminophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3,4-Methylenedioxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-(1-Methyl)indolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(1-Naphthyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Methylphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-Cyanophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Quinolinyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Methoxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-Indolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Benzofuranyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonfyl oxy-1,2,3,4-tetrahydroisoquinoline;
1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(4-Acetylphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-Methoxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-Quinolinyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(5-(2,3-Dihydropyrazolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(6-(1,4-benzodioxanoyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-Acetylphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-Acetamidophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-Dimethylaminophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Quinoxalinoyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Benzothiazolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3,4-Dichlorophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-(1-Methylpyrrolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(5-Pyrido[2,3-b]indolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(5-(2-Dimethylamino)pyrimidinyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Benzoxazolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(4-(1-Pyrrolidinyl)phenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-Methylenedioxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-Methylenedioxyphenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(3-Aminocarbonylphenyl)propenoyl)aminobutyl)-7-
trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Acetamido phenyl)propenoyl)aminobutyl)-7-
trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-(2-
thiophene)sulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(4-Dimethylaminophenyl)propenoyl)aminobutyl)-7-
(2-thiophene)sulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-methylsulfonyloxy-
1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(4-Dimethylaminophenyl)propenoyl)aminobutyl)-7-
methylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-acetyl-1,2,3,4-
tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-bromo-1,2,3,4-
tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-(4-cyanophenyl)sulfonyloxy-
1,2,3,4-tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Naphthyl)propenoyl)aminobutyl)-7-methoxy-1,2,3,4-
tetrahydroisoquinoline;
(E)-7-Phenylsulfonylmethyl-2-(4-(3-(2-naphthyl)propenol)aminobutyl)-1,2,3,4-
tetrahydroisoquinoline;
(E)-7-Methylsulfonamido-2-(4-(3-(2-naphthyl)propenol)aminobutyl)-1,2,3,4-
tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Naphthyl)propenol)aminobutyl)-7-phenylsulfonamido-1,2,3,4-
tetrahydroisoquinoline;
(E)-7-(4-Cyanophenyl)sulfonamido-2-(4-(3-(2-naphthyl)propenol)aminobutyl)-1,2,3,4-
tetrahydroisoquinoline;
(E)-2-(4-(3-(5-Indolyl)propenol)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-
tetrahydroisoquinoline;
(E)-2-(4-(3-(5-Benzimidazolyl)propenol)aminobutyl)-7-trifluoromethylsulfonyloxy-
1,2,3,4-tetrahydroisoquinoline;
(E)-7-Methylsulfonylmethyl-2-(4-(3-(2-naphthyl)propenol)aminobutyl)-1,2,3,4-
tetrahydroisoquinoline;
(E)-2-(4-(3-(2-Naphthyl)propenol)aminobutyl)-7-trifluoromethoxy-
1,2,3,4-tetrahydroisoquinoline;
(E)-7-Cyano-2-(4-(3-(2-naphthyl)propenol)aminobutyl)-1,2,3,4-
tetrahydroisoquinoline;
\((E)-2-(4-(3-(3-Indolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-2-(4-(3-(4-Dimethylaminophenyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-2-(4-(3-(4-Aminophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-2-(4-(3-(4-Nitrophenyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-7-Cyano-2-(4-(3-(3-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-2-(4-(3-(3-(7-Methylindolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-2-(4-(3-(2-(6-Acetyl)naphthyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-7-Cyano-2-(4-(3-(3-(7-methylindolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-7-Cyano-2-(4-(3-(5-benzimidazolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-7-Cyano-2-(4-(3-(5-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-7-Cyano-2-(4-(3-(6-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-7-Cyano-2-(4-(3-(7-fluoroindolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-2-(4-(3-(2-(6-Acetyl)naphthyl)propenoyl)aminobutyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-7-Cyano-2-(4-(3-(6-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-7-Cyano-2-(4-(3-(7-fluoroindolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-2-(4-(3-(3-(7-Bromo)indolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-2-(4-(3-(3-(7-Bromo)indolyl)propenoyl)aminobutyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-2-(4-(3-(3-(7-Cyano)indolyl)propenoyl)aminobutyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-7-Cyano-2-(4-(3-(5-(2-methyl)indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-2-(4-(3-(5-(2-Methyl)indolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;\)
\((E)-2-(4-(3-(3-(7-Acetyl)indolyl)propenoyl)aminobutyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;\)
(E)-7-Cyano-2-(4-(3-(6-(2-methyl)indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;

(E)-7-Cyano-2-(4-(3-(5-(2,3-dihydro-2-oxo)-1H-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;

(E)-2-(4-(3-(6-(1,2-Dihydro-2-oxo)quinolinyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;

(E)-2-(4-(3-(5-(2-Acetyl)indolyl)propenoyl)aminobutyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;

(E)-7-Chloro-2-(4-(3-(6-indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;

(E)-7-Cyano-2-(4-(3-(5-(3-methyl)indolyl)propenyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;

(E)-2-(4-(3-(6-(3-Methyl)indolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;

(E)-7-Cyano-2-(4-(3-(5-(1-methyl)indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;

(E)-2-(4-(3-(2-(1-Methyl)indolyl)propenoyl)aminobutyl)-7-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline;

(E)-2-(4-(3-(5-Indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;

(E)-7-Cyano-2-(4-(3-(5-(2-methyl)benzimidazolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;

(E)-2-(4-(3-(5-(2-Methyl)benzimidazolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;

(E)-2-(4-(3-(5-Indolyl)propenoyl)aminobutyl)-7-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline;

(E)-2-(4-(3-(5-Indolyl)propenoyl)aminobutyl)-7-methylsulfonylamido-1,2,3,4-tetrahydroisoquinoline;

(E)-2-(4-(3-(5-Indolyl)propenoyl)aminobutyl)-7-methylaminosulfonyl-1,2,3,4-tetrahydroisoquinoline;

(E)-2-(4-(3-(5-(7-Methyl)indolyl)propenoyl)aminobutyl)-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;

(E)-7-Cyano-2-(4-(3-(5-(3-dimethylaminomethyl)indolyl)propenoyl)aminobutyl)-1,2,3,4-tetrahydroisoquinoline;

or a salt thereof.

4. A process for preparing a compound of formula (I) as defined in any of claims 1 to 3 which process comprises:

(a) reacting a compound of formula (II):
wherein $R^1$ and $q$ are as hereinbefore defined;
with a compound of formula (III):

(b) reaction of a compound of formula (IV):

wherein $R^2$ and $Ar$ are as hereinbefore defined;

wherein $R^1$ and $R^2$ are as hereinbefore defined;
with a compound of formula (V):

wherein $Ar$ is as hereinbefore defined and $X$ is a halogen atom or the residue of an activated ester;

(c) to prepare a compound of formula (I) wherein $R^1$ is $Ar^1.Z$ and $Z$ is a bond, reacting a compound of formula (VI):
wherein one $R^{1a}$ represents a group $W$ wherein $W$ is a halogen atom or a 
trifluoromethylsulphonyloxy group, or $W$ is a group $M$ selected from a boron derivative 
e.g. a boronic acid function $B(OH)_2$ or a metal function such as trialkylstannyl e.g. 
$SnBu_3$, zinc halide or magnesium halide, and when $q$ is 2 the other $R^{1a}$ is $R^1$; with a 
compound $Ar^1-W^1$, wherein $W^1$ is a halogen atom or a trifluoromethylsulphonyloxy 
group when $W$ is a group $M$ or $W^1$ is a group $M$ when $W$ is a halogen atom or a 
trifluoromethylsulphonyloxy group:

(d) to prepare a compound of formula (I) wherein $R^1$ is $Ar^1-Z$ and $Z$ is $O$ or $S$, 
reacting a compound of formula (VII):

wherein one $R^{1b}$ represent a group $ZH$ and when $q$ is 2 the other $R^{1b}$ represents $R^1$; with 
a reagent serving to introduce the group $Ar^1$;

(e) interconversion of one compound of formula (I) to a different compound of 
formula (I) e.g. (i) alkylation of a compound (I) wherein $R^2$ represent hydrogen, (ii) 
conversion of one $R^1$ from alkoxy (e.g. methoxy) to hydroxy, or (iii) conversion of $R^1$ 
from hydroxy to sulphphonyloxy, eg alkylsulphonyloxy or trifluoromethanesulphonyloxy; 
optionally thereafter forming a salt of formula (I).

5. A pharmaceutical composition comprising a compound of formula (I) as 
claimed in any of claims 1 to 3 or a physiologically acceptable salt thereof and a 
physiologically acceptable carrier therefor.
6. The use of a compound of formula (I) as claimed in any of claims 1 to 3 or a physiologically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition which requires modulation of a dopamine receptor.

7. Use according to claim 6 wherein the dopamine receptor is a dopamine D₃ receptor.

8. Use according to claim 6 or claim 7 wherein a dopamine antagonist is required.

9. Use according to any of claims 6 to 8 wherein the condition is a psychotic condition.

10. A method of treating a condition which requires modulation of a dopamine receptor which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as claimed in claim 1 or a physiologically acceptable salt thereof.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D217/04 A61K31/47 C07D405/12 C07D401/12 C07D417/12
C07D471/04 //((C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category * Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.

A CHEMICAL ABSTRACTS, vol. 107, no. 11, 14 September 1987 Columbus, Ohio, US; abstract no. 089337, PATSENKO A A ET AL: "Interaction of simple tetrahydroisoquinolines with opiate and high affinity dopamine (D3) receptors of rat striatum" XP002048675 6-isoquinolino1, 1,2,3,4-tetrahydrol-7-methoxy-l-methyl and 6,7-isoquinolinediol,1,2,3,4-tetrahydro-l-methyl see abstract & FARMAKOL. TOKSIKOL. (MOSCOW) (FATOAO,00148381B);87; VOL.50 (4); PP.33-5, INST. BIOKHIM.;GRODNO; USSR (SU), --- -/--

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another station or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"S" document member of the same patent family

Date of the actual completion of the international search 2 December 1997

Date of mailing of the international search report 16.12.97

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (31-70) 340-2040, Tx: 31 651 epo nl, Fax: (31-70) 340-3016

Authorized officer

Scruton-Evans, I
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<th>Relevant to claim No.</th>
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<td>P,A</td>
<td>BOYFIELD I ET AL: &quot;A novel series of 2-aminotetralins with high affinity and selectivity for the dopamine D3 receptor&quot; BIOORG. MED. CHEM. LETT. (BMCLEB.0960894);97; VOL.7 (15); PP.1995-1998, SMITHKLINE BEECHAM PHARMACEUTICALS, NEW FRONTIERS SCIENCE PARK;ESSEX; CM19 5AW; UK (GB), XP002048674 see compounds of formula 3 and Table 1</td>
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<td>A</td>
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<td>WO 96 02246 A (BASF AG) 1 February 1996 see the whole document</td>
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<td>US 5 294 621 A (R.K.RUSSELL) 15 March 1994 cited in the application see the whole document</td>
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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.: because they relate to subject matter not required to be searched by this Authority, namely:
   Remark: Although claim(s) 10
   is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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.
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