

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

APPLICATION FOR A STANDARD PATENT

I/We BEECHAM GROUP P.L.C.

of Beecham House, Great West Road, Brentford, Middlesex TW8 9BD,
England

hereby apply for the grant of a Standard Patent for an invention
entitled:

"NOVEL COMPOUNDS"

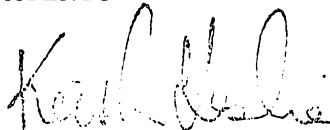
which is described in the accompanying complete specification.

This application is made under the provisions of Section 51 of
the Patents Act 1952 in respect of Australian Patent Application
No.67121/87 made by Beecham Group P.L.C.

The address for service is care of DAVIES & COLLISON, Patent
Attorneys, o 1 Little Collins Street, Melbourne, in the State of
Victoria, Commonwealth of Australia.

DATED this 18th day of May, 1990

To: THE COMMISSIONER OF PATENTS



(a member of the firm of Davies & Collison
for and on behalf of the Applicant)

Davies & Collison, Melbourne and Canberra

DIVISIONAL APPLICATION

No. 67121/87 Lodged 5/1/87

AUSTRALIA

635024

Patents Act 1990

NOTICE OF ENTITLEMENT

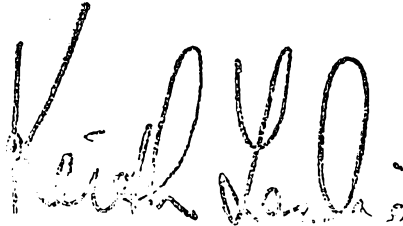
I/We, **Beecham Group p.l.c.** the applicant in respect of Application No. 55147/90,
state the following:-

Francis David KING and Karen Anne JOINER are the actual inventors in respect of
the invention.

The Nominated person(s) is/are entitled to the grant of the patent because the
Nominated person(s) would, on the grant of a patent for the invention, be entitled to
have the patent assigned to him/her/them/it.

The Nominated person is/are the applicant(s)/patentee(s) of the original
application/patent with respect to which the present application is a further complete
application under S.39 of the Patents Act 1990.

Dated this 12th day of January, 1993



(A member of the firm of DAVIES COLLISON CAVE for
and on behalf of the applicant)



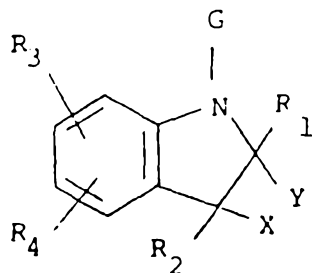
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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 635024

- (54) Title
NOVEL COMPOUNDS
- International Patent Classification(s)
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- (21) Application No. : 55147/90 (22) Application Date : 18.05.90
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- (62) Related to Division(s) : 67121/87
- (71) Applicant(s)
BEECHAM GROUP P.L.C.
- (72) Inventor(s)
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- (74) Attorney or Agent
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- (56) Prior Art Documents
AU 58019/90 C07D 209/08
- (57) Intermediates for compounds which are 5-HT-M-receptor antagonists (anti-emetic and/or gastric motility enhancing).

Claim

1. A compound of the formula (V):



wherein

G is COQ₁, where Q₁ is a leaving group selected from halogen, C₂₋₄ alkoxy, phenoxy, activated hydrocarbyloxy, succinimidylloxy and imidazolylloxy;

X and Y are independently selected from hydrogen or C₁₋₄ alkyl, or together are a bond;

R₁ and R₂ are independently selected from hydrogen, C₁₋₆

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(11) AU-B-55147/90
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alkyl, C₂₋₆ alkenyl-C₁₋₄ alkyl, or together are C₂₋₄ polymethylene; and

R₃ and R₄ are independently selected from hydrogen; halogen; CF₃; C₁₋₆ alkyl; C₁₋₆ alkoxy; C₁₋₆ alkylthio; C₁₋₇ acyl; C₁₋₇ acylamino; C₁₋₆ alkylsulphonylamino; N-(C₁₋₆ alkylsulphonyl)-N-C₁₋₄ alkylamino; C₁₋₆ alkylsulphinyl; hydroxy; nitro; and amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-C₁₋₄ alkylamino optionally N-substituted by one or two group selected from C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl C₁₋₄ alkyl, phenyl or phenyl C₁₋₄ alkyl groups or optionally N-disubstituted by C₄₋₅ polymethylene, excluding the compound 1-(2,3-dihydro)-indolylcarbonyl chloride.

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C O M M O N W E A L T H O F A U S T R A L I A

PATENTS ACT 1952

COMPLETE SPECIFICATION

(Original)

FOR OFFICE USE

Class

Int. Class

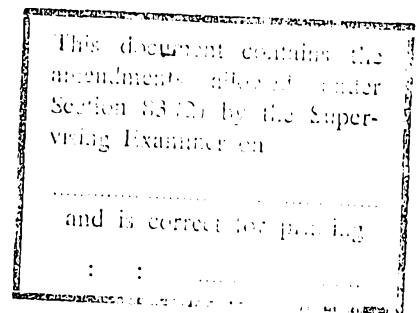
Application Number:

Lodged:

Complete Specification Lodged:

Accepted:

Published:



• Priority:

• Related Art:

Name of Applicant: BEECHAM GROUP P.L.C.

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Actual Inventor(s): Francis David KING
Karen Anne JOINER

Address for Service: DAVIES & COLLISON, Patent Attorneys,
1 Little Collins Street, Melbourne, 3000.

Complete specification for the invention entitled:

"NOVEL COMPOUNDS"

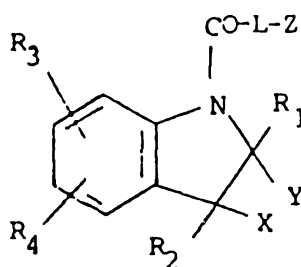
The following statement is a full description of this invention,
including the best method of performing it known to us :-

NOVEL COMPOUNDS

This invention relates to novel compounds useful as intermediates for the preparation of compounds having pharmaceutical properties.

GB 2100259A and 2125398A, and EP-A-158265 describe benzoates and benzamides having an azabicyclic side chain and possessing 5-HT antagonist activity.

In Australian Patent Application No.67121/87 (from which the subject matter of the present invention has been divided), we describe a class of novel, structurally distinct compounds which have 5-HT M-receptor antagonist activity, anti-emetic activity and/or gastric motility enhancing activity. These compounds are represented by the formula (I):



(I)

wherein

L is NH or O;

X and Y are independently selected from hydrogen or C₁₋₄ alkyl, or together are a bond;

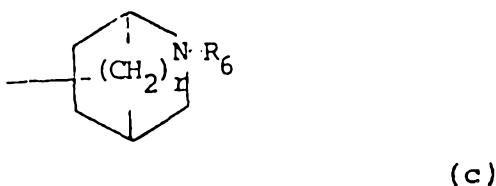
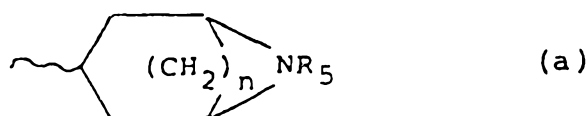
5

R₁ and R₂ are independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl-C₁₋₄ alkyl, or together are C₂₋₄ polymethylene;

- 10 R₃ and R₄ are independently selected from hydrogen; halogen; CF₃; C₁₋₆ alkyl; C₁₋₆ alkoxy; C₁₋₆ alkylthio; C₁₋₇ acyl; C₁₋₇ acylamino; C₁₋₆ alkylsulphonylamino; N-(C₁₋₆ alkylsulphonyl)-N-C₁₋₄ alkylamino; C₁₋₆ alkylsulphonyl; hydroxy; nitro; and amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or
- 15 N-(aminosulphonyl)-C₁₋₄ alkylamino optionally N-substituted by one or two groups selected from C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl C₁₋₄ alkyl, phenyl or phenyl C₁₋₄ alkyl groups or optionally N-disubstituted by C₄₋₅ polymethylene;

20

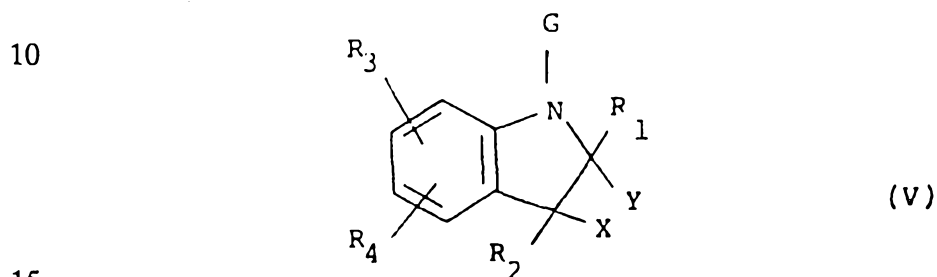
Z is a group of formula (a), (b) or (c)



wherein n is 1 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3;
and

R₅ or R₆ is C₁₋₇ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₂
5 alkyl or C₂₋₇ alkenyl-C₁₋₄ alkyl.

This invention provides compounds of the formula (V):



wherein

G is COQ₁, where Q₁ is a leaving group selected from halogen,
C₂₋₄ alkoxy, phenoxy, activated hydrocarbyloxy,
20 succinimidyloxy and imidazolyloxy; and

R₁, R₂, R₃, R₄, X and Y have the same designation as for
compounds of the formula (I) defined previously;

25 with the proviso that 1-(2,3-dihydro)-indolylcarbonyl chloride
is specifically excluded.

Examples of leaving groups Q₁, displaceable by a nucleophile,
include halogen such as chloro and bromo; C₂₋₄ alkoxy, such
30 as CH₃O and C₂H₅O-; PhO-; activated hydrocarbyloxy, such as
Cl₅C₆O- or Cl₃CO-; succinimidyloxy; and imidazolyloxy.
Preferably Q₁ is halogen, most preferably chloro.



1
2 Suitable values for X and Y include hydrogen, methyl,
3 ethyl, n- and iso-propyl; or together are a bond.
4
5 Often X and Y are both hydrogen.
6
7 Suitable values for R₁ or R₂ include hydrogen, methyl,
8 ethyl, n- and iso-propyl; prop-2-enyl, but-2-enyl,
9 but-3-enyl, 1-methylenepropyl and 1-methylprop-2-yl in
10 their E and Z forms where stereoisomerism exists; or R₁
11 and R₂ together are as defined in formula (I). Often
12 R₁ and R₂ are both hydrogen.
13
14 Values for R₃ and/or R₄ include hydrogen, fluoro,
15 chloro, bromo, CF₃, methyl, ethyl, methoxy, ethoxy,
16 methylthio, ethylthio, acetyl, propionyl, acetylamino,
17 methylsulphonylamino, methylsulphinyl, hydroxy, nitro;
18 and amino, aminocarbonyl, aminosulphonyl,
19 aminosulphonylamino or N-(aminosulphonyl)-methylamino
20 any of which may be optionally substituted by one or
21 two methyl groups or by a cyclopentyl or cyclohexyl
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1 group or disubstituted by C₄ or C₅ polymethylene; R₃ is
2 often hydrogen and R₄ is hydrogen or a 5-substituent,
3 such as halo or methoxy.

4
5 Preferably n is 2 or 3 and p, q and r are 1 or 2.

6
7 Examples of R₅/R₆ when C₁₋₇ alkyl include as groups of
8 interest C₁₋₃ alkyl such as methyl, ethyl and n- and
9 iso-propyl. Within C₁₋₇ alkyl, C₄₋₇ alkyl are also of
10 interest, especially those of the formula (CH₂)_uR₉
11 wherein u is 1 or 2 and R₉ is a secondary or tertiary
12 C₃₋₆ alkyl group. Examples of C₄₋₇ alkyl include n-,
13 sec- and tert-butyl, n-pentyl, n-heptyl, and iso-butyl,
14 3-methylbutyl, and tert-butylmethyl.

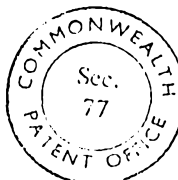
15
16 Examples of R₅/R₆ when C₃₋₈ cycloalkyl-C₁₋₂ alkyl
17 include in particular those wherein the cycloalkyl
18 moiety is cyclohexyl or cyclopropyl. Examples ~~of~~
19 include cyclopropylmethyl, cyclobutylmethyl,
20 cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl,
21 cyclobutylethyl, cyclopentylethyl, cyclohexylethyl,
22 tert-butylmethyl, iso-propylmethyl, iso-propylethyl and
23 tert-butylethyl.

24
25 R₅/R₆ may in particular be cyclopropylmethyl,
26 cyclohexylmethyl, iso-propylmethyl, tert-butylmethyl or
27 iso-propylethyl, preferably tert-butylmethyl.

28
29 Examples of R₅/R₆ when C₂₋₇ alkenyl-C₁₋₄ alkyl include
30 prop-2-enyl, but-2-enyl, but-3-enyl, 1-methylenepropyl
31 and 1-methyl-prop-2-enyl in their E and Z forms when
32 stereoisomerism exists.

33
34 R₅/R₆ is preferably methyl or ethyl, most preferably
35 methyl.

36
37
38



1
2 Preferred compounds of the present invention may be
3 selected from the following:

4
5 1-(2,3-Dihydro)-indolyltrichloromethyl carbamate,

6
7 1-(2,3-dihydro-3-methyl)indolyl-O-(1-
8 succinimidyl)carbamate,

9
10 1-(2,3-dihydro-5-fluoro)indolyl-O-(1-
11 succinimidyl)carbamate,

12
13 1-(2,3-dihydro-5-methoxy)indolyl trichloromethyl
14 carbamate,

15
16 ~~1-(2,3-dihydro)indolylcarbonyl chloride,~~

17
18 1-(2,3-dihydro-3-ethyl)indolylcarbonyl chloride,

19
20 1-(2,3-dihydro-5-nitro)indolyl-trichloromethyl
21 carbamate,

22
23 1-[1-(2,3-dihydro-6-nitro)indolylcarbonyl]-imidazole,
24 or

25
26 1-(2,3-dihydro-3,3-dimethyl)indolylcarbonyl chloride.

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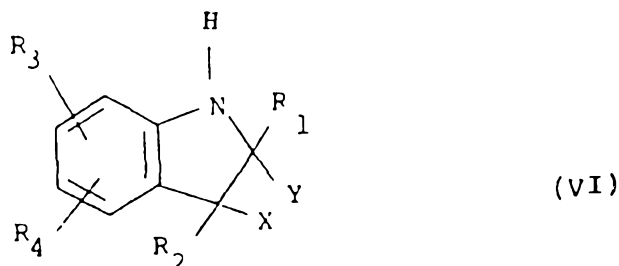
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38



1 Compounds of the formula (V) may be prepared by reacting a
2 compound of the formula (VI):



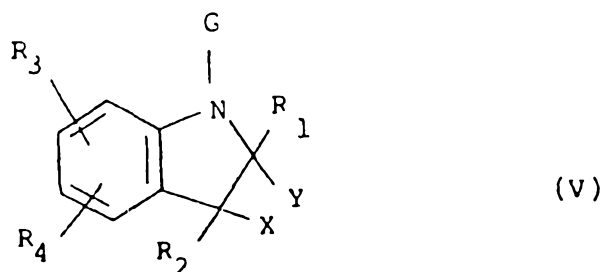
10
11 with a compound of the formula (VII):



14
15 wherein

16
17 R is a leaving group which may be the same as Q_1 or
18 different; and Q_1 , R_1 , R_2 , R_3 , R_4 , X and Y are as
19 hereinbefore defined.

20
21 Compounds of the formula (V) are useful as intermediates in
22 the preparation of compounds of the formula (I) as
23 previously mentioned. As described in our co-pending patent
24 application No.67121/87, compounds of the formula (I) may be
25 prepared by reacting a compound of formula (V):



33 with a compound of formula (VI):



36
37
38 wherein

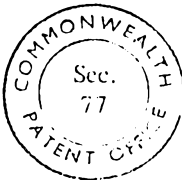
or hydrogen
1 G is COQ_{1A} where Q₁ is a leaving group ~~or hydrogen~~; and,
2 when G is COQ₁, J is NH₂, or OH or a reactive derivative
3 thereof or, when G is hydrogen, J is a group containing an
4 activated carbonyl group capable of forming a CO-L-linkage
5 with the compound of formula (V); Z¹ is Z as defined or
6 wherein R₅/R₆ is replaced by a hydrogenolysable protecting
7 group; and the remaining variables are as hereinbefore
8 defined; and thereafter optionally converting any R₃ and R₄
9 group to another R₃ and R₄ group respectively, converting
10 Z¹, when other than Z, to Z; converting X and Y to other X
11 and Y; and optionally forming a pharmaceutically acceptable
12 salt of the resultant compound of formula (I).

13
14 Further details of reaction conditions are set forth in
15 application No.67121/87 which is incorporated herein by
16 reference.

17
18 ~~The compounds of the present invention may be in the form of~~
19 ~~pharmaceutically acceptable salts. Acid addition salts may~~
20 ~~be formed conventionally, for example, by reaction of the~~
21 ~~base compound of the formula (V) with a pharmaceutically~~
22 ~~acceptable organic or inorganic acid.~~

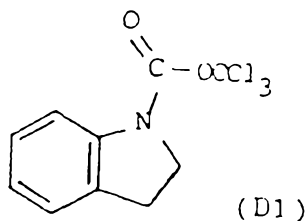
23
24 This invention also provides a pharmaceutical composition
25 comprising a compound of the formula (V), or a
26 pharmaceutically acceptable salt thereof, and a
27 pharmaceutically acceptable carrier. The preparation of
28 pharmaceutical compositions and nature of pharmaceutically
29 acceptable carriers are well known in the art, and are
30 ~~described, for example, in application No.67121/87.~~

31
32 The following Examples illustrate the preparation of
33 compounds of the formula (V):



Example 1

1-(2,3-Dihydro)-indolyltrichloromethyl carbamate (D1)



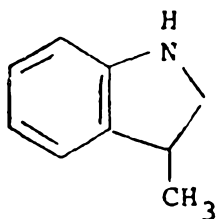
To 2,3-dihydroindole (5g) in dry dichloromethane (140ml) and triethylamine (5.85ml) at 0° was added dropwise trichloromethyl chloroformate (5ml) in dry dichloromethane (20ml). The reaction mixture was stirred at room temperature for 2h, then washed with water (5ml) and 5N hydrochloric acid solution (5ml). The organic phase was dried (Na₂SO₄), the solvent evaporated in vacuo and the residue purified by filtration through a short alumina column, eluting with dichloromethane to give the title compound (D1) (8.5g, 72%) as a buff solid m.p. 59-60°.

¹H-NMR (CDCl₃) 60MHz

δ	7.85-7.55 (m, 1H)
	7.30-6.70 (m, 3H)
	4.25-3.70 (m, 2H)
	3.25-2.80 (m, 2H)

Example 2

2,3-Dihydro-3-methylindole (D2)



Following the procedure outlined by G.W. Gribble and J.H. Hoffman, Synthesis 859, 1977, ethyl indole (5g) was converted to the title compound (D2) (4.17g, 32%).

^1H NMR (CDCl_3) 60MHz

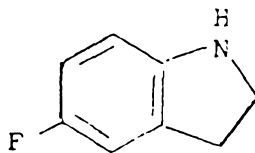
δ 7.30-6.30 (m, 4H)

3.80-2.80 (m, 4H)

1.30 (d, 3H)

Example 3

2,3-Dihydro-5-fluoroindole (D3)



(D3)

Following the procedure outlined in Example 2, 5-fluoroindole (3g) was converted to the title compound (D3) (2.54g, 84%).

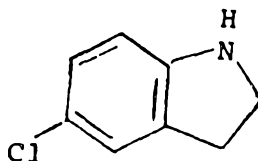
^1H -NMR (CDCl_3) 60MHz

δ 7.05-6.10 (m, 3H)

4.10-2.60 (m, 5H)

Example 4

2,3-Dihydro-5-chloroindole (D4)



(D4)

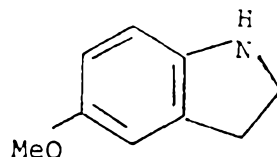
Following the procedure outlined in Example 2, 5-chloroindole (0.86g) was converted to the title compound (D4) (0.84g, 97%).

¹H-NMR (CDCl₃) 60MHz

δ 7.30-6.65 (m, 2H)
 6.60-6.25 (m, 1H)
 4.10-3.25 (m, 3H)
 3.20-2.70 (m, 2H)

Example 5

2,3-Dihydro-5-methoxyindole (D5)



(D5)

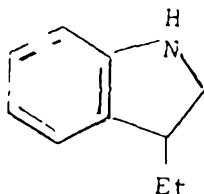
A solution of 5-methoxyindole (1g) in glacial acetic acid (20ml) was hydrogenated over platinum oxide (0.27g) at room temperature. After absorption of the theoretical amount of hydrogen (153ml), the catalyst was filtered off and the solvent evaporated in vacuo. The residue was basified with saturated potassium carbonate solution and extracted with diethyl ether. The organic phase was dried (Na₂SO₄), the solvent evaporated in vacuo to give the title compound (D5) (0.43g, 42%).

¹H-NMR (CDCl₃) 60MHz

δ 6.85-6.35 (m, 3H)
 3.65 (s, 3H)
 3.60-2.70 (m, 5H)

Example 6

2,3-Dihydro-3-ethylindole (D6)



(D6)

Following the procedure outlined in Example 2, 3-ethylindole (2.3g) (J.T. Fitzpatrick and R.D. Hiser, J. Org. Chem., 22, 1703-4, 1957) was converted to the title compound (D6) (1.3g, 56%).

¹H-NMR (CDCl₃) 60MHz

δ 7.20-6.40 (m, 4H)

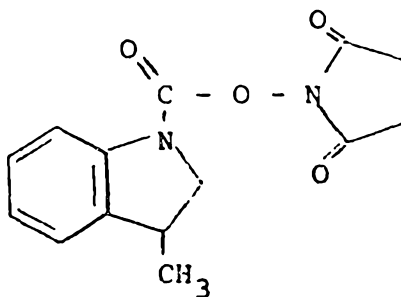
3.90-2.90 (m, 4H)

2.10-0.8 (m, 2H)

0.9 (t, 3H)

Example 7

1-(2,3-Dihydro-3-methyl)indolyl-O-(1-succinimidyl)-
carbamate (D7)



(D7)

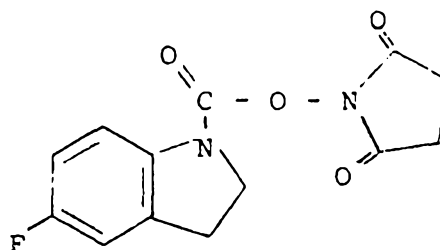
N,N-Disuccinimidyl carbonate (8.03g) and 2,3-dihydro-3-methylindole (D2) (4.17g) in dry toluene (150ml) was stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue dissolved in dichloromethane, washed with 5N hydrochloric acid solution (10ml), saturated potassium bicarbonate (10ml) and brine (30ml). The organic phase was dried (Na₂SO₄), evaporated in vacuo and the residue purified by filtration through a short silica column, eluting with dichloromethane to give the title compound (D7) (6.85g, 80%).

¹H-NMR (CDCl₃) 60MHz

δ 7.85-6.80 (m, 4H)
 4.60-4.00 (m, 1H)
 3.95-3.10 (m, 2H)
 2.75 (s, 4H)
 1.30 (bd, 3H)

Example 8

1-(2,3-Dihydro-5-fluoro)indolyl-O-(1-succinimidyl)-
carbamate (D8)



(D8)

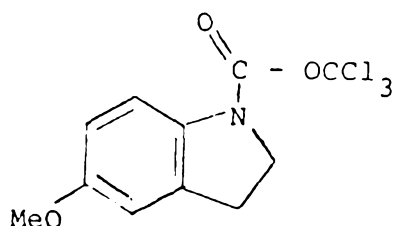
Following the procedure outlined in Example 7, reaction of N,N-disuccinimidyl carbonate (4.75g) with 2,3-dihydro-5-fluoroindole (D3) afforded the title compound (D8) (5g, 97%).

¹H-NMR (CDCl₃) 60MHz

δ 7.90-7.60 (m, 1H)
7.30-6.60 (m, 3H)
4.40-4.00 (m, 2H)
3.40-2.90 (m, 2H)
2.85 (s, 4H)

Example 9

1-(2,3-Dihydro-5-methoxy)indolyl trichloromethyl
carbamate (D9)



(D9)

Following the procedure outlined in Example 1, reaction of 2,3-dihydro-5-methoxyindole (D5) (0.43g) with trichloromethylchloroformate (0.35ml) afforded the title compound (D9) (0.52g, 58%).

¹H-NMR (CDCl₃) 60MHz

δ 7.88-7.58 (m, 1H)
6.85-6.48 (m, 2H)
4.35-3.80 (m, 2H)
3.70 (s, 3H)
3.35-2.80 (m, 2H)

1 Example 10

2

3 1-(2,3-Dihydro)indolylcarbonyl chloride (D10)

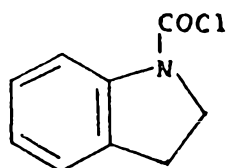
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6

7

8



(D10)

9 To phosgene [110ml (12.5% w/w solution in toluene)] in dry
10 dichloromethane (150ml) at 0° was added dropwise a solution
11 of triethylamine (17ml) and freshly distilled 2,3-dihydro-
12 indole (14.5g) in dry dichloromethane (100ml). The reaction
13 mixture was then stirred at 0° for 1h, and then poured into
14 pentane (2.5l), washed with 5N sulphuric acid solution
15 (100ml) and brine (100ml). The organic phase was dried
16 (Na₂SO₄), the solvent evaporated in vacuo and the residue
17 triturated with 60/80 pet. ether to give the title compound
18 (D10) (18.37g, 83%).

19

20 Example 11

21

22 1-(2,3-Dihydro-3-ethyl)indolylcarbonyl chloride (D11)

23

24

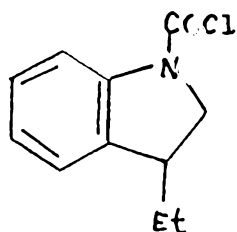
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(D11)

30 Following the procedure outlined in Example 10, reaction of
31 2,3-dihydro-3-ethylindole (D6) (1.25g) with phosgene [7.7ml
32 (12.5% w/w solution in toluene)] afforded the title compound
33 (D11) (1.6g, 90%).

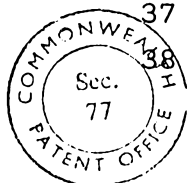
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1 Example 12

2

3 1-(2,3-Dihydro-5-nitro)indolyl-trichloromethyl
4 carbamate (D12)

5

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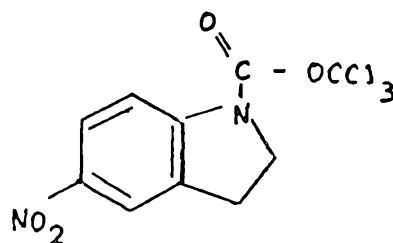
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(D12)

12 Following the procedure outlined in Example 1, reaction of
13 2,3-dihydro-5-nitroindole (4.72g) with trichloromethyl-
14 chloroformate (3.44ml) afforded the title compound (D12)
15 (5.5g, 59%)

16 ¹H-NMR (CDCl₃) 60MHz

17 δ 8.80-7.10 (m, 3H)

18 4.70-3.90 (m, 2H)

19 3.50-2.95 (m, 2H)

20

21 Example 13

22

23 1-[1-(2,3-Dihydro-6-nitro)indolylcarbonyl]imidazole (D13)

24

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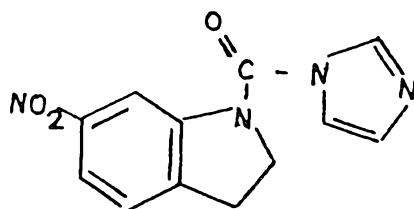
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(D13)

31 2,3-Dihydro-6-nitroindole (3g) and 1,1'-carbonyldi-
32 imidazole (2.96g) in dry toluene (75ml) was heated under
33 reflux for 5h. The reaction mixture was cooled and the
34 solvent evaporated in vacuo. The residue was dissolved in
35 dichloromethane (100ml) and washed with 5N hydrochloric acid
36 solution (10ml) and water (20ml). The organic phase was
37 dried (Na₂SO₄) and the solvent evaporated in vacuo to give
38 the title compound (D13) (4.7g, 100%).

1 Example 14

2

3 1-(2,3-Dihydro-3,3-dimethyl)indolylcarbonyl chloride (D14)

4

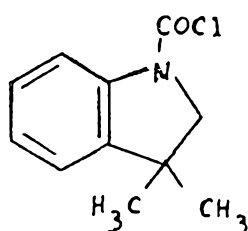
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(D14)

10 Following the procedure outlined in Example 10, reaction of
11 2,3-dihydro-3,3-dimethylindole (2.7g) with phosgene [16.5ml
12 (12.5% w/w solution in toluene)] afforded the title compound
13 (D14) (3.5g, 91%).

14

15 Example 15 - Synthesis of a compound of the Formula (I)

16

17 endo-N-(9-Methyl-9-azabicyclo[3.3.1]non-3-yl)-2,3-
18 dihydroindole-1-carboxamide (E1)

19

20

21

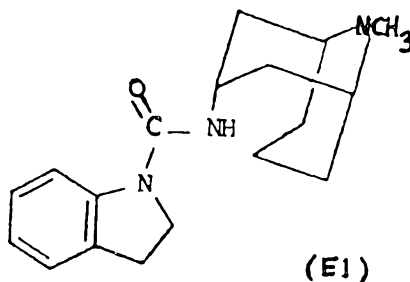
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(E1)

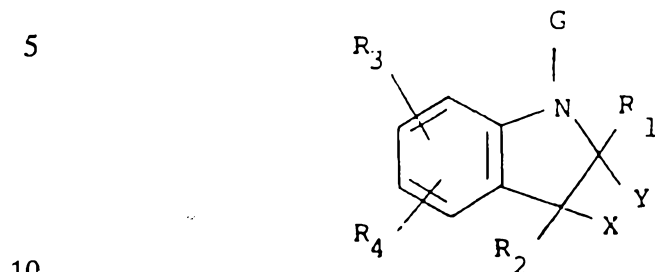
27 To 1-(2,3-dihydro)-indolyltrichloromethyl carbamate (D1)
28 (3.64g) in dry toluene (100ml) was added endo-3-amino-9-
29 methyl-9-azabicyclo[3.3.1]nonane (2g) in dry toluene (20ml).
30 The reaction mixture was heated under reflux for 24h, then
31 the solvent evaporated in vacuo. The residue was extracted
32 with dichloromethane (200ml) and washed with saturated
33 potassium carbonate solution (2 x 20ml). The organic phase
34 was dried (Na₂SO₄) concentrated and the residue purified by
35 column chromatography on alumina, eluting with CHCl₃ to
36 give, after crystallisation from ethyl acetate, the title
37 compound (E1) (2g, 52%) m.p. 176-8°.

38 ¹H-NMR (CDCl₃) 270MHz

1	
2	δ 7.85 (d, 1H)
3	7.25-7.05 (m, 2H)
4	6.95-6.85 (m, 1H)
5	4.45-4.25 (m, 2H)
6	4.00-3.80 (t, 2H)
7	3.25-3.05 (m, 4H)
8	2.65-2.40 (m, 2H)
9	2.50 (s, 3H)
10	2.15-1.85 (m, 3H)
11	1.65-1.00 (m, 5H)
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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula (V):



wherein

G is COQ₁, where Q₁ is a leaving group selected from halogen, C₂₋₄ alkoxy, phenoxy, activated hydrocarbyloxy, succinimidyloxy and imidazolyloxy;

15

X and Y are independently selected from hydrogen or C₁₋₄ alkyl, or together are a bond;

20 R₁ and R₂ are independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl-C₁₋₄ alkyl, or together are C₂₋₄ polymethylene; and

R₃ and R₄ are independently selected from hydrogen; halogen; CF₃; C₁₋₆ alkyl; C₁₋₆ alkoxy; C₁₋₆ alkylthio; C₁₋₇ acyl; C₁₋₇ acylamino; C₁₋₆ alkylsulphonylamino; N-(C₁₋₆ alkylsulphonyl)-N-C₁₋₄ alkylamino; C₁₋₆ alkylsulphonyl; hydroxy; nitro; and amino, aminocarbonyl, aminosulphonyl, aminosulphonylamino or N-(aminosulphonyl)-C₁₋₄ alkylamino optionally N-substituted by one or two group selected from C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl C₁₋₄ alkyl, phenyl or phenyl C₁₋₄ alkyl groups or optionally N-disubstituted by C₄₋₅ polymethylene, excluding the compound 1-(2,3-dihydro)-indolylcarbonyl chloride.

25

30

35

2. A compound according to claim 1 wherein Q₁ is selected from halogen, C₁₋₄ alkoxy, activated hydrocarbyloxy, succinimidyloxy, and imidazolyloxy.



1 3. A compound according to claim 1 selected from:

2

3 1-(2,3-Dihydro)-indolyltrichloromethyl carbamate,

4

5 1-(2,3-dihydro-3-methyl)indolyl-0-(1-succinimidyl)-

6 carbamate,

7

8 1-(2,3-dihydro-5-fluoro)indolyl-0-(1-succinimidyl)-

9 carbamate,

10

11 1-(2,3-dihydro-5-methoxy)indolyl trichloromethyl carbamate,

12

13 1-(2,3-dihydro-3-ethyl)indolylcarbonyl chloride,

14

15 1-(2,3-dihydro-5-nitro)indolyl-trichloromethyl carbamate,

16

17 1-[1-(2,3-dihydro-6-nitro)indolylcarbonyl]-imidazole, or

18

19 1-(2,3-dihydro-3,3-dimethyl)indolylcarbonyl chloride.

20

21 4. A compound according to claim 1 substantially as

22 hereinbefore described with reference to any one of the

23 Examples.

24

25 DATED this 18th day of May, 1990

26 BEECHAM GROUP P.L.C.

27 By its Patent Attorneys:

28 DAVIES & COLLISON

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