Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2337248 C 2011/04/19

(11)(21) 2 337 248

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 1999/07/13
(87) Date publication PCT/PCT Publication Date: 2000/01/27
(45) Date de délivrance/Issue Date: 2011/04/19
(85) Entrée phase nationale/National Entry: 2001/01/12
(86) N° demande PCT/PCT Application No.: EP 1999/004943
(87) N° publication PCT/PCT Publication No.: 2000/003983
(30) Priorité/Priority: 1998/07/16 (GB9815483.4)

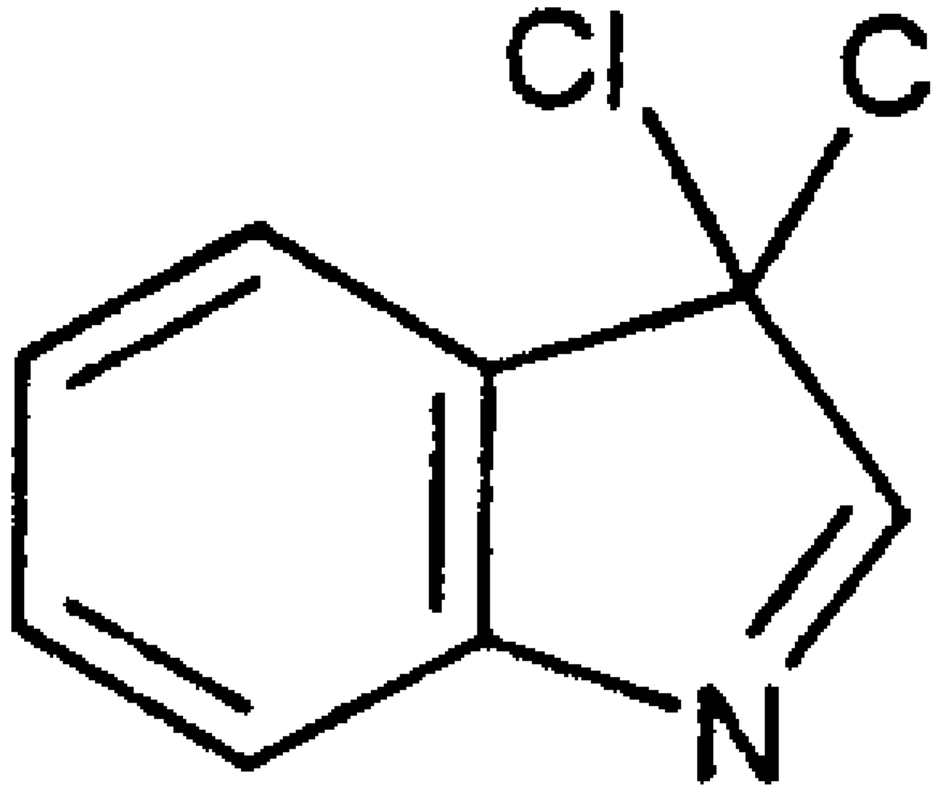
(51) Cl.Int./Int.Cl. *C07D 209/42* (2006.01)

(72) Inventeurs/Inventors:
FEDOULOFF, MICHAEL, GB;
STRACHAN, JOHN BRYCE, GB

(73) Propriétaire/Owner:
SMITHKLINE BEECHAM P.L.C., GB

(74) Agent: GOWLING LAFLEUR HENDERSON LLP

(54) Titre : PROCEDE DE PREPARATION D'UN DERIVE D'INDOLE
(54) Title: PROCESS FOR THE PREPARATION OF AN INDOLE DERIVATIVE



(C)

(57) Abrégé/Abstract:
A process for the preparation of methyl 3-chloro-3H-indole-3-carboxylate, which comprises reacting an appropriate 3-carboxylate indole compound with N-chlorosuccinimide in the presence of a tertiary amine which is less nucleophilic than DABCO and which has a pK_b of from 8 to 11.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 209/42

A1

(11) International Publication Number: WO 00/03983

(43) International Publication Date: 27 January 2000 (27.01.00)

(21) International Application Number: PCT/EP99/04943

(22) International Filing Date: 13 July 1999 (13.07.99)

(30) Priority Data:
9815483.4 16 July 1998 (16.07.98) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: FEDOULOFF, Michael [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). STRACHAN, John, Bryce [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: GARRETT, Michael; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: PROCESS FOR THE PREPARATION OF AN INDOLE DERIVATIVE

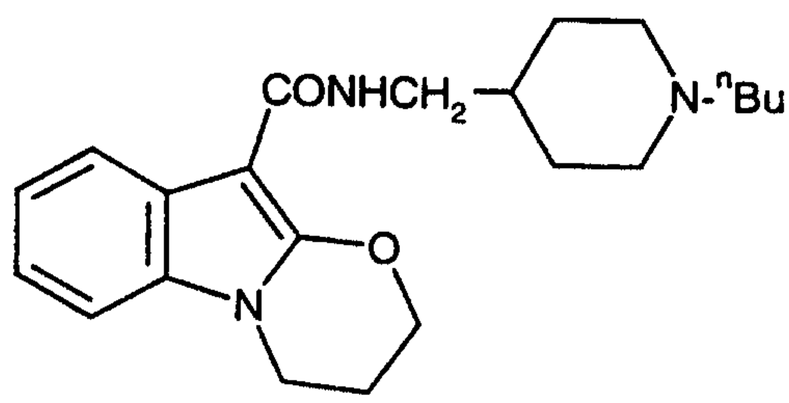
(57) Abstract

A process for the preparation of methyl 3–chloro–3H–indole–3–carboxylate, which comprises reacting an appropriate 3–carboxylate indole compound with N–chlorosuccinimide in the presence of a tertiary amine which is less nucleophilic than DABCO and which has a pK_b of from 8 to 11.

PROCESS FOR THE PREPARATION OF AN INDOLE DERIVATIVE

This invention relates to a new synthetic process to a compound having pharmacological activity.

WO 93/18036 (SmithKline Beecham plc) describes certain indole compounds having 5-HT_4 receptor antagonist activity including the compound of formula (I)

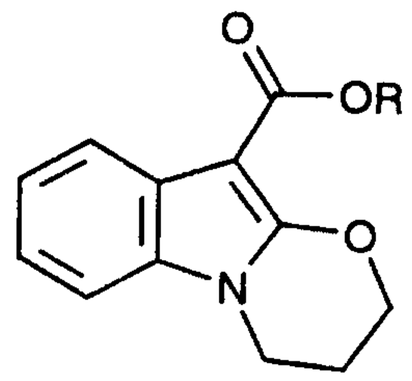


(I)

and its pharmaceutically acceptable salts. This compound is N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide, referred to herein by its code number SB-207266, (the hydrochloride salt is SB-207266-A), which is being developed by SmithKline Beecham plc as the active ingredient in a medicament for treatment of irritable bowel syndrome.

Example 3 of WO 93/18036 describes a method of preparation of SB-207266-A from N-[(1-^{n}butyl-4-piperidyl)methyl]indole-3-carboxamide (i.e. the compound corresponding to SB-207266, without the oxazino moiety), by reacting with N-chlorosuccinimide and 3-bromo-1-propanol, followed by treatment with sodium carbonate. N-[(1-^{n}butyl-4-piperidyl)methyl]indole-3-carboxamide is prepared by coupling N-(1-^{n}butyl-4-piperidyl)methylamine with a indole-3-carboxylic acid.

WO 98/07728 (SmithKline Beecham plc) describes a process for preparing SB-207266-A which involves the use of the N-(1-^{n}butyl-4-piperidyl)methylamine intermediate at a later stage in the process thus resulting in an increased yield of SB-207266-A relative to the amount of this intermediate, which is relatively expensive to produce. In particular, the alternative process comprises the reaction of of N-(1-^{n}butyl-4-piperidyl)methylamine with a compound of formula (A):

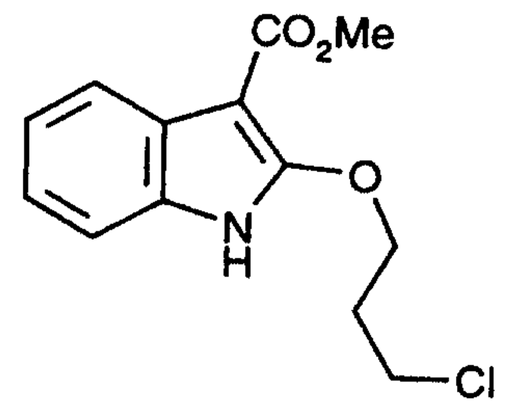


(A)

wherein R is alkyl, such as methyl or ethyl.

The compound of formula (A) wherein R is methyl is methyl 3,4-dihydro-2*H*-[1,3]-oxazino[3,2-*a*]indole-10-carboxylate.

WO98/07728 also describes the preparation of the oxazinoindole compound of the formula (A) from the corresponding indole by reaction with N-chlorosuccinimide and a 3-halo-propanol, such as 3-chloropropanol or 3-bromopropanol followed by cyclisation of the intermediate (B) by treatment with base in a suitable solvent.



(B)

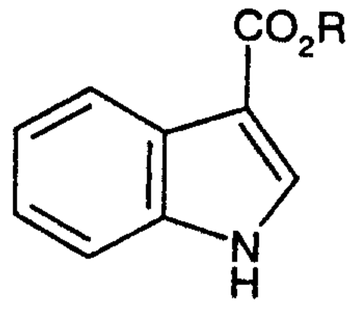
The Description in the latter specification describes in more detail the preparation of compound (B) from the corresponding methyl indole-3-carboxylate by reaction of the latter with N-chlorosuccinimide in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to form an intermediate of formula (C):

(C)

and subsequent reaction of (C) with 3-chloropropanol in the presence of methane sulphonic acid.

We have now found that the replacement of DABCO by a tertiary amine which is less nucleophilic than DABCO and which has a pK_b of from 8 to 11, especially 1,4-dimethylpiperazine, results in significant advantages for the commercial operation of the above reaction.

According to a feature of the present invention we provide a process for the preparation of the compound of formula (C) above, namely methyl 3-chloro-3H-indole-3-carboxylate, which comprises reacting a compound of formula (D) :



(D)

(in which R is as hereinbefore defined)

with N-chlorosuccinimide in the presence of a tertiary amine which is less nucleophilic than DABCO and which has a pK_b of from 8 to 11, especially 1,4-dimethylpiperazine (DMP).

Other examples of preferred bases for use in accordance with the invention are tetramethylethylenediamine and N-methylpiperidine.

The use of the above amine in place of DABCO has been found to increase significantly the overall yield of the process. The former amine also has the following advantages over DABCO:-

a) it is non-hygroscopic;

b) it does not react with dichloromethane, a preferred solvent for the reaction;

c) the product (C) is more stable allowing extended addition times and better temperature control;

d) quicker wash separations are possible during commercial manufacture; and

e) levels of the corresponding 2-methoxy compound, as an impurity, do not increase with extended process times.

The reaction is conveniently effected in an organic solvent such as dichloromethane or chloroform at a temperature in the range -20° C to +20° C.

The resulting product of formula (C) can be used for the next step in the synthesis of SB-207266 e.g as described in WO 98/07728 without any need for isolation or purification.

The following Example illustrates the invention.

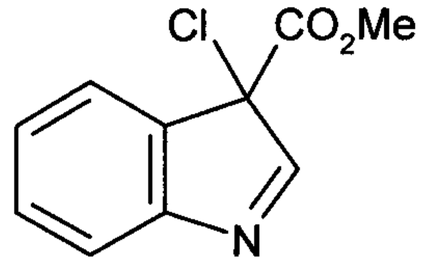
Example

Methyl 2-(3-chloropropoxy)-indole-3-carboxylate (formula (B))

A mixture of methyl indole-3-carboxylate and dichloromethane is cooled to 0° C. 1,4-dimethylpiperazine (0.55eq.) and N-chlorosuccinimide (1.1 eq) are added and the mixture left to stir for two hours to give slurry containing the compound of formula (C) above. The resulting slurry is added to a solution of 3-chloropropanol (1.1 eq) and trichloroacetic acid (0.12 eq) in dichloromethane, maintaining the temperature below 0° C. The reaction mixture is left to stir for half an hour, then washed with 10% aqueous sodium carbonate, 0.5 M hydrochloric acid and water. The organic solution is dried over sodium sulphate, filtered and the solvent evaporated. Toluene is added and the mixture stirred at 0-5° C for one hour. The product is then filtered, washed with toluene and dried to give the title product in 83 % yield.

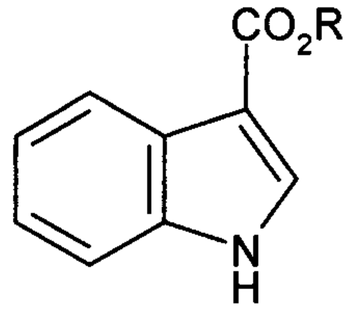
Claims

1. A process for the preparation of methyl 3-chloro-3H-indole-3-carboxylate, namely the compound of formula (C):



(C)

, which process comprises reacting a compound of formula (D):



(D)

in which R is methyl

with N-chlorosuccinimide in the presence of a tertiary amine which is less nucleophilic than DABCO and which has a pK_b of from 8 to 11.

2. A process as claimed in claim 1 in which the tertiary amine is 1,4-dimethylpiperazine, tetramethylethylenediamine or N-methylpiperidine.

3. A process as claimed in claim 1 in which the tertiary amine is 1,4-dimethylpiperazine or tetramethylethylenediamine.

4. A process as claimed in claim 1 in which the tertiary amine is 1,4-dimethylpiperazine.

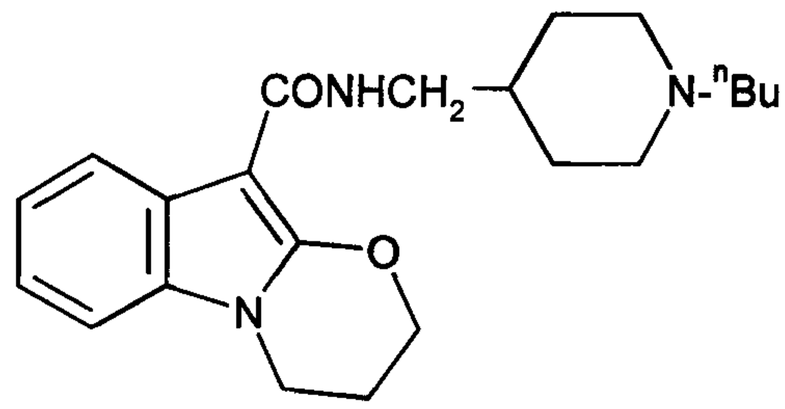
5. A process as claimed in any one of claims 1 to 4 in which the reaction is effected in an organic solvent at a temperature in the range –20 °C to +20 °C.

6. A process as claimed in claim 5 wherein the organic solvent is dichloromethane or chloroform.

7. A process as claimed in any one of claims 1 to 4, wherein dichloromethane is used as a solvent for the reaction.

8. A process as claimed in any one of claims 1 to 7, wherein: a mixture of methyl indole-3-carboxylate and dichloromethane is cooled to 0 °C; 1,4-dimethylpiperazine (0.55 eq.) and N-chlorosuccinimide (1.1 eq.) are added; and the mixture is left to stir for two hours to give a slurry containing the compound of formula (C).

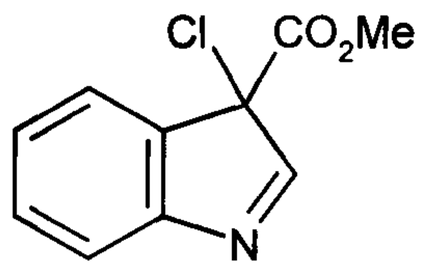
9. A process for preparing N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide, namely the compound of Formula (I):



(I)

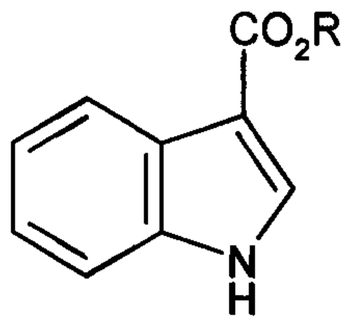
, or a pharmaceutically acceptable salt thereof, which process comprises:

(a) preparing methyl 3-chloro-3H-indole-3-carboxylate, namely the compound of formula (C):



(C)

by reacting a compound of formula (D):

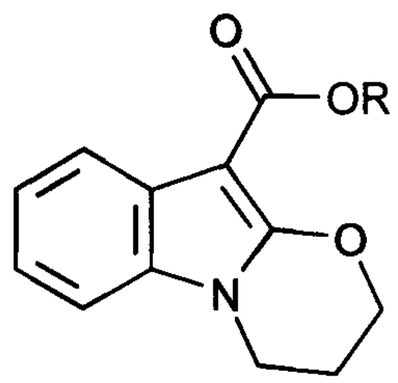


(D)

, in which R is methyl, with N-chlorosuccinimide in the presence of a tertiary amine which is less nucleophilic than DABCO and which has a pK_b of from 8 to 11; and

(b) using the resulting compound of formula (C) in the next step in the synthesis of the N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide or the pharmaceutically acceptable salt thereof, wherein step (b) comprises:

- preparing an oxazinoindole compound of formula (A):



(A)

wherein R is methyl, by reaction of the compound of formula (C) with a 3-halo-propanol in the presence of an acid, followed by cyclisation of the resulting intermediate by treatment with base in a suitable solvent; and

- reacting N-(1-^{n}butyl-4-piperidyl)methylamine with the compound of formula (A) to prepare the N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide.

10. A process as claimed in claim 9, wherein the compound of formula (C) is used without isolation or purification.

11. A process as claimed in claim 9 or 10 wherein the 3-halo-propanol is 3-chloropropanol or 3-bromopropanol.

12. A process as claimed in claim 9, 10 or 11, comprising, in step (b), preparing the oxazinoindole compound of formula (A) by reaction of the compound of formula (C) with the 3-halo-propanol in the presence of trichloroacetic acid or methane sulphonic acid, followed by cyclisation of the resulting intermediate by treatment with base in the suitable solvent.

13. A process as claimed in claim 12, comprising, in step (b), preparing the oxazinoindole compound of formula (A) by reaction of the compound of formula (C) with the 3-halo-propanol in the presence of trichloroacetic acid, followed by cyclisation of the resulting intermediate by treatment with base in the suitable solvent.

14. A process as claimed in claim 9, 10, 11, 12 or 13, in which the tertiary amine is 1,4-dimethylpiperazine, tetramethylethylenediamine or N-methylpiperidine.

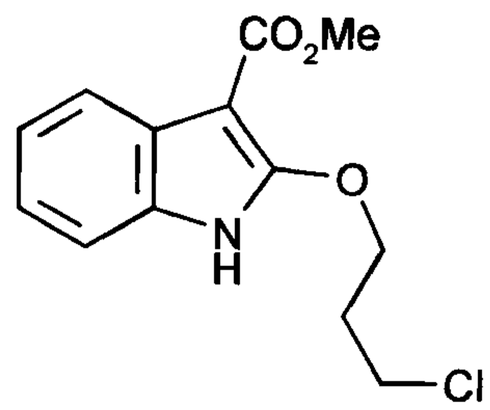
15. A process as claimed in claim 9, 10, 11, 12 or 13, in which the tertiary amine is 1,4-dimethylpiperazine or tetramethylethylenediamine.

16. A process as claimed in claim 9, 10, 11, 12 or 13, in which the tertiary amine is 1,4-dimethylpiperazine.

17. A process as claimed in any one of claims 9 to 16 in which the reaction in step (a) is effected in an organic solvent at a temperature in the range –20 °C to +20 °C.

18. A process as claimed in claim 17 wherein in step (a) the organic solvent is dichloromethane or chloroform.

19. A process as claimed in claim 9 or 10, comprising, in step (b), preparing the oxazinoindole compound of formula (A) by reaction of the compound of formula (C) with 3-chloropropanol in the presence of an acid, followed by cyclisation of the intermediate (B):



(B)

by treatment with base in a suitable solvent.

20. A process as claimed in claim 19, comprising, in step (b), preparing the oxazinoindole compound of formula (A) by reaction of the compound of formula (C) with the 3-chloropropanol in the presence of trichloroacetic acid or methane sulphonic acid, followed by cyclisation of the intermediate (B) by treatment with base in the suitable solvent.

21. A process as claimed in claim 20, wherein the reaction of (C) with the 3-chloropropanol is in the presence of methane sulphonic acid.

22. A process as claimed in claim 20, comprising, in step (b), preparing the oxazinoindole compound of formula (A) by reaction of the compound of formula (C) with the 3-chloropropanol in the presence of trichloroacetic acid, followed by cyclisation of the intermediate (B) by treatment with base in the suitable solvent.

23. A process as claimed in claim 19, 20, 21 or 22, in which the tertiary amine is 1,4-dimethylpiperazine, tetramethylethylenediamine or N-methylpiperidine.

24. A process as claimed in claim 19, 20, 21 or 22, in which the tertiary amine is 1,4-dimethylpiperazine or tetramethylethylenediamine.

25. A process as claimed in claim 19, 20, 21 or 22, in which the tertiary amine is 1,4-dimethylpiperazine.

26. A process as claimed in any one of claims 19 to 25 in which the reaction in step (a) is effected in an organic solvent at a temperature in the range –20 °C to +20 °C.

27. A process as claimed in claim 26 wherein in step (a) the organic solvent is dichloromethane or chloroform.

28. A process as claimed in claim 22 wherein:

a mixture of methyl indole-3-carboxylate and dichloromethane is cooled to 0 °C;

1,4-dimethylpiperazine (0.55eq.) and N-chlorosuccinimide (1.1 eq) are added and the mixture is left to stir for two hours to give a slurry containing the compound of formula (C);

the resulting slurry is added to a solution of 3-chloropropanol (1.1 eq) and trichloroacetic acid (0.12 eq) in dichloromethane, maintaining the temperature below 0° C;

the reaction mixture is left to stir for half an hour, then washed with 10% aqueous sodium carbonate, 0.5 M hydrochloric acid and water;

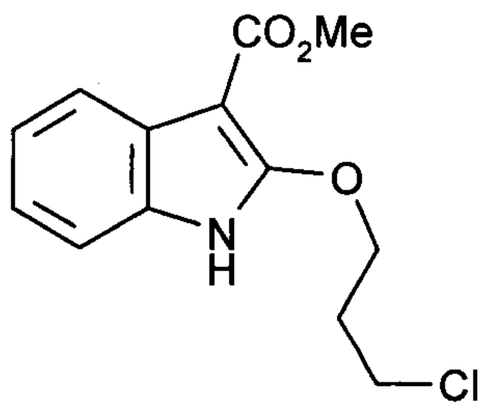
the organic solution is dried over sodium sulphate, filtered and the solvent is evaporated;

toluene is added and the mixture is stirred at 0-5° C for one hour;

and the product is then filtered, washed with toluene and dried to give methyl 2-(3-chloropropoxy)-indole-3-carboxylate of formula (B).

29. A process as claimed in any one of claims 9 to 28, in which the hydrochloride salt of N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (SB-207266-A) is prepared.

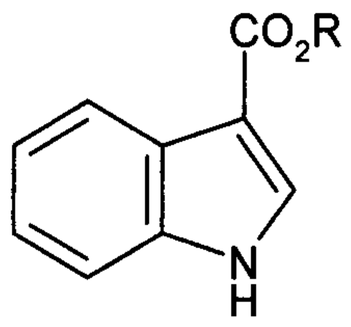
30. A process for the preparation of a compound (B):



(B)

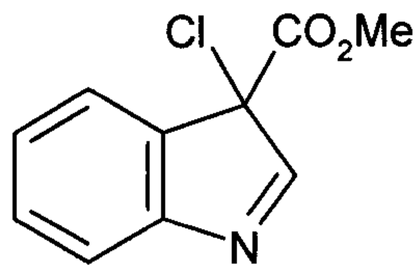
from the corresponding methyl indole-3-carboxylate by:

(a) reaction of methyl indole-3-carboxylate (D):



(D)

, in which R is methyl, with N-chlorosuccinimide in the presence of a tertiary amine which is less nucleophilic than DABCO and which has a pK_b of from 8 to 11, to form an intermediate of formula (C):



(C);

and (b) subsequent reaction of (C) with 3-chloropropanol in the presence of an acid.

31. A process as claimed in claim 30 in which the amine is 1,4-dimethylpiperazine, tetramethylethylenediamine or N-methylpiperidine.

32. A process as claimed in claim 30 in which the amine is 1,4-dimethylpiperazine or tetramethylethylenediamine.

33. A process as claimed in claim 30 in which the amine is 1,4-dimethylpiperazine.

34. A process as claimed in any one of claims 30 to 33 in which the reaction in step (a) is effected in an organic solvent at a temperature in the range –20 °C to +20 °C.

35. A process as claimed in claim 34 wherein in step (a) the organic solvent is dichloromethane or chloroform.

36. A process as claimed in any one of claims 30 to 33, wherein dichloromethane is used as a solvent for the reaction in step (a).

37. A process as claimed in any one of claims 30 to 36, wherein the compound of formula (C) is used without isolation or purification.

38. A process as claimed in any one of claims 30 to 37, wherein the subsequent reaction of (C) with the 3-chloropropanol is in the presence of trichloroacetic acid or methane sulphonic acid.

39. A process as claimed in claim 38, wherein the subsequent reaction of (C) with the 3-chloropropanol is in the presence of methane sulphonic acid.

40. A process as claimed in claim 38, wherein the subsequent reaction of (C) with the 3-chloropropanol is in the presence of trichloroacetic acid.

41. A process as claimed in claim 40, wherein:

a mixture of methyl indole-3-carboxylate and dichloromethane is cooled to 0 °C;

1,4-dimethylpiperazine (0.55eq.) and N-chlorosuccinimide (1.1 eq) are added and the mixture is left to stir for two hours to give a slurry containing the compound of formula (C);

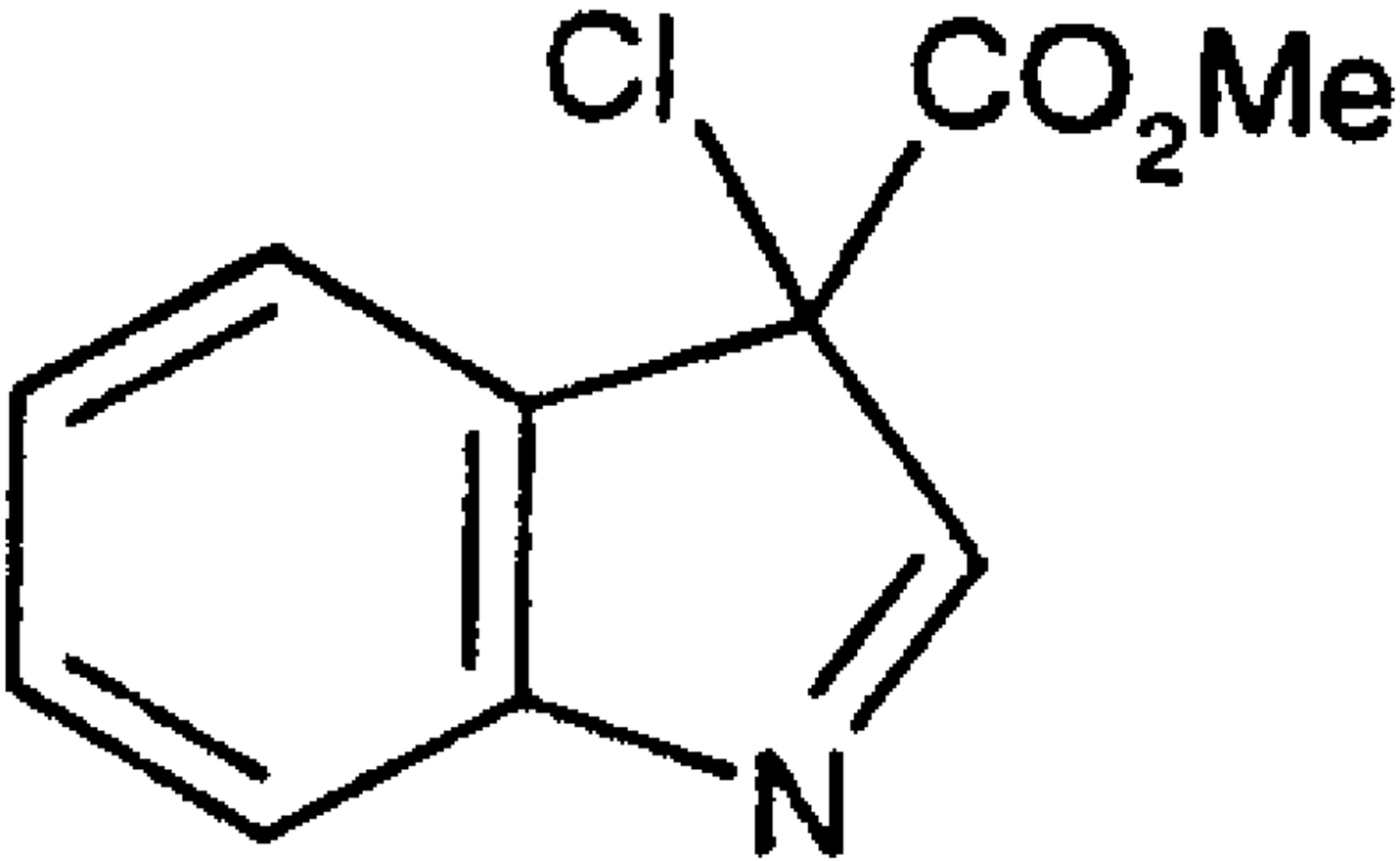
the resulting slurry is added to a solution of 3-chloropropanol (1.1 eq) and trichloroacetic acid (0.12 eq) in dichloromethane, maintaining the temperature below 0° C;

the reaction mixture is left to stir for half an hour, then washed with 10% aqueous sodium carbonate, 0.5 M hydrochloric acid and water;

the organic solution is dried over sodium sulphate, filtered and the solvent is evaporated;

toluene is added and the mixture is stirred at 0-5° C for one hour;

and the product is then filtered, washed with toluene and dried to give methyl 2-(3-chloropropoxy)-indole-3-carboxylate of formula (B).



(C)