

638096

FORM 1

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

Laboratoires U P S A, Societe Anonyme, of 1 bis, rue Docteur Camille Bru, 47000 Agen, FRANCE, hereby apply for the grant of a standard patent for an invention entitled:

Novel Benzimidazole and Azabenzimidazole Derivatives which are Thromboxane Receptor Antagonists, their Methods of Preparation, Synthesis Intermediates and Pharmaceutical Compositions in which they are Present.

which is described in the accompanying complete specification.

Details of basic application(s):-

<u>Basic Applic. No:</u>	<u>Country:</u>	<u>Application Date:</u>
90 01925	FR	16 February 1990

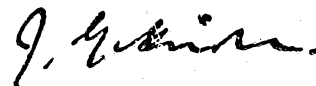
The address for service is:-

Spruson & Ferguson
Patent Attorneys
Level 33 St Martins Tower
31 Market Street
Sydney New South Wales Australia

DATED this SEVENTH day of FEBRUARY 1991

Laboratoires U P S A

By:



Registered Patent Attorney

5019818 07/02/91

TO: THE COMMISSIONER OF PATENTS
OUR REF: 154294
S&F CODE: 51230

5845/3

AUSTRALIAN — PATENT DECLARATION FORM (CONVENTION OR NON-CONVENTION)

(Note: This is a comprehensive form, and parts inappropriate to a particular case must be deleted. This declaration must be signed by the applicant(s), if individual. If applicant is a Company, this declaration must be signed by a person on its behalf and the Company seal or stamp should not be applied. No legalization is required).

Forms 7 and 8

AUSTRALIA

Patents Act 1952

INSTRUCTIONS

- (a) Insert No. if available
(b) Insert full name(s) of applicant(s)

(c) Insert title of invention
EAST AND NAME
ID TITLE OF PERSON
SPINING, LEGIBLY,

- (d) Insert full name(s) of declarant(s) who must be PERSONS, NOT a corporate body (See head note)
(e) Insert address(es) of declarant(s)

- (f) Delete entirely if applicant is corporate body
(g) Delete entirely if applicant is person or persons

- (h) Delete entirely if Convention priority NOT claimed
(i) Insert country in which first basic application was filed.
(j) Insert date of first basic application.
(k) Insert full name(s) of basic applicant(s).
(l) Delete entirely if applicant(s) NOT inventor(s).

- (m) Insert full name(s) of actual inventor(s) if applicant(s) NOT inventor(s)
(n) Insert address(es) of actual inventor(s) if applicant(s) NOT inventor(s).

- (o) Insert manner in which applicant(s) derived title from actual inventor(s) and/or from basic applicant(s).

- (p) Delete entirely if Convention priority NOT claimed
(q) Signature(s) of declarant(s).

(N.B. In seal or stamping)

In support of the application No. (a)
made by (b) Laboratoires U.P.S.A.

for a patent/~~patent of addition~~ for an invention entitled (c) Novel Benzimidazole and Azabenzimidazole Derivatives which are Thromboxane Receptor Antagonists, their Methods of Preparation, Synthesis Intermediates and Pharmaceutical Compositions in which they are Present.

I, (d) Guy Bourdin
of (e) Laboratoires U.P.S.A.
1 bis, rue Docteur Camille Bru, 47000 Agen France

do solemnly and sincerely declare as follows:—

~~1. (f) I am/We are the applicant(s) for the patent/patent of addition.~~

1. (g) I am authorized by the abovementioned applicant for the patent/~~patent of addition~~ to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141 of the Act was/~~were~~ made in the following country or countries on the following date(s) by the following applicant(s) namely:—

(h) in (i) FRANCE on (j) 16 February 19 90
by (k) Laboratoires U.P.S.A.
in (i) on (j) 19
by (k)
in (i) on (j) 19
by (k)

3. ~~(l) I am/We are the actual inventor(s) of the invention.~~

3. (m) Nicole Bru-Magniez, Eric Nicolai and Jean-Marie Teulon

of (n) 24-26, Avenue Raphael, 75016 Paris, France
52, rue St-Ouen, Residence Le Hameau Bt. C, 14000 Caen, France and
13, Avenue Guibert, 78170 La Celle St Cloud, France (respectively)

is/~~are~~ the actual inventor(s) of the invention and the facts upon which the applicant(s) is/~~are~~ entitled to make the application are as follows:—

(o) By virtue of a contract of employment between the inventors as employees and the Applicant as employer, the Applicant is a person who would be entitled to have the patent assigned to it if a patent were granted upon an application made by the inventors.

4. (p) The basic application(s) referred to in paragraph 2 of this Declaration was/~~were~~ the first application(s) made in a Convention country in respect of the invention the subject of the application.

(N.B. In seal or stamping)
Laboratoires U.P.S.A.
SA au Capital de 5.000.000 F
R.C.S. AGEN B 025 820 089
1 bis, rue Docteur Camille Bru
47000 AGEN

this 23rd day of January 1991

PLEASE ADD NAME
AND TITLE OF PERSON
SPINING, LEGIBLY, —

(q) Guy BOURDIN
Directeur Général



AU9170874

(12) PATENT ABRIDGMENT (11) Document No. AU-B-70874/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 638096

(54) Title
NOVEL BENZIMIDAZOLE AND AZABENZIMIDAZOLE DERIVATIVES WHICH ARE THROMBOXANE RECEPTOR ANTAGONISTS, THEIR METHODS OF PREPARATION, SYNTHESIS INTERMEDIATES AND PHARMACEUTICAL COMPOSITIONS IN WHICH THEY ARE PRESENT

international Patent Classification(s)
(51)⁵ C07D 235/16 A61K 031/44 C07D 235/28 C07D 471/04
A61K 031/415

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(71) Applicant(s)
LABORATOIRES U P S A SOCIÉTÉ ANONYME

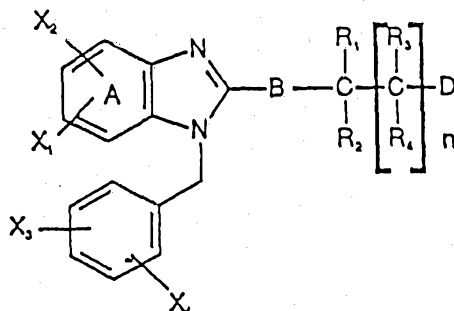
(72) Inventor(s)
NICOLE BRU-MAGNIEZ; ERIC NICOLAI; JEAN-MARIE TEULON

(74) Attorney or Agent
SPRUSON & FERGUSON, GPO Box 3898, SYDNEY NSW 2001

(57) The novel compounds according to the invention possess remarkable pharmacological properties as thromboxane receptor antagonists and can be used in therapy for the treatment of myocardial infarction, angina pectoris, stroke, migraine, cerebral hemorrhages, atherosclerosis, pulmonary embolism, bronchial asthma, bronchitis, pneumonia, circulatory shocks of various origins, nephritis, graft rejection and cancerous metastases.

Claim

1. A benzimidazole derivative of formula (I):



Formula (I)

in which:

A is an aromatic ring or a nitrogen hetero-cycle;

X_1 , X_2 , X_3 and X_4 are independently a hydrogen atom, a halogen atom, a lower alkyl radical, a C_3 - C_7 cycloalkyl radical, an alkoxy radical, an alkylthio radical, a sulfone group, SO_2 -lower alkyl, a sulfoxide group, SO -lower alkyl, a trifluoromethyl group, a hydroxyl group, a nitro group, a methylene alcohol radical or a group $COOR'$, in which R' is a hydrogen or a lower alkyl; X_3 and X_4 can also form a naphthalene with the phenyl;

B is CR_5R_6 , R_5 and R_6 being a hydrogen atom, a lower alkyl radical or a C_3 - C_7 cycloalkyl radical, or the sulfur atom;

R_1 , R_2 , R_3 and R_4 are independently a hydrogen atom, a lower alkyl radical or a C_3 - C_7 cycloalkyl radical; CR_1R_2 or CR_3R_4 can form with B, when the latter is CR_5R_6 , a cycloalkyl or a cycloalkene having 3 to 7 carbon atoms; R_1R_2 and R_3R_4 can also form a ring having 3 to 7 carbon atoms;

n is an integer from 1 to 4 and can be 0 if R_1 and R_2 are other than hydrogen; and

D is a chemical group which can be $COOR_7$, $CONHR_8$ or CN , wherein R_7 and R_8 are a hydrogen atom, a lower alkyl radical or a C_3 - C_7 cycloalkyl radical and its addition salts, in particular the pharmaceutically acceptable addition salts.

16. A pharmaceutical composition which comprises a pharmaceutically effective amount of at least one compound of formula (I) as defined in any one of claims 1 to 14, or one of its pharmaceutically acceptable addition salts, together with a pharmaceutically acceptable excipient, vehicle or carrier.

21. A process for preparing a 1-benzyl-benzimidazole or azabenzimidazole derivative substantially as hereinbefore described with reference to any one of the Examples.

638096

S & F Ref: 154294

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:

Accepted:

Published:

Priority:

Related Art:

Name and Address
of Applicant:

Laboratoires U P S A
1 bis, rue Docteur Camille Bru
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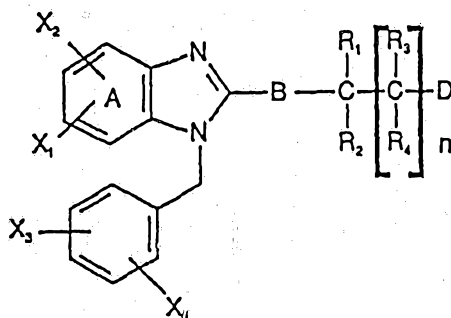
Complete Specification for the invention entitled:

Novel Benzimidazole and Azabenzimidazole Derivatives which
are Thromboxane Receptor Antagonists, their Methods of
Preparation, Synthesis Intermediates and Pharmaceutical
Compositions in which they are Present.

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

ABSTRACT OF THE DISCLOSURE

The present invention relates to the derivatives of the formula



Formula (I)

in which:

A is an aromatic ring or a nitrogen heterocycle;

X_1 , X_2 , X_3 and X_4 are independently a hydrogen atom, a halogen atom, a lower alkyl radical, a C_3 - C_7 cycloalkyl radical, an alkoxy radical, an alkylthio radical, a sulfone group, SO_2 -lower alkyl, a sulfoxide group, SO -lower alkyl, a trifluoromethyl group, a nitro group, a hydroxyl group, a methylene alcohol radical or a group $COOR'$, in which R' is a hydrogen or a lower alkyl; X_3 and X_4 can also form a naphthalene with the phenyl;

B is CR_5R_6 , R_5 and R_6 being a hydrogen atom, a lower alkyl or a C_3 - C_7 cycloalkyl radical, or the sulfur atom;

R_1 , R_2 , R_3 and R_4 are independently a hydrogen atom, a lower alkyl radical or a C_3 - C_7 cycloalkyl radical; CR_1R_2 or CR_3R_4 can form with B , when the latter is CR_5R_6 , a cycloalkyl or a cycloalkene having 3 to 7 carbon atoms; R_1R_2 and R_3R_4 can also form a ring having 3 to 7 carbon atoms;

n is an integer from 1 to 4 and can be 0 if R_1 and R_2 are other than hydrogen; and

D is a chemical group which can be:

$COOR_7$, R_7 being the hydrogen atom, a lower alkyl radical or a C_3 - C_7 cycloalkyl radical,

$CONH-R_8$, R_8 being the hydrogen atom, a lower alkyl radical or a C_3 - C_7 cycloalkyl radical, or

CN ,

and to their addition salts.

Novel benzimidazole and azabenzimidazole derivatives which are thromboxane receptor antagonists, their methods of preparation, synthesis intermediates and pharmaceutical compositions in which they are present

05

The present invention relates, by way of novel products, to the benzimidazole and azabenzimidazole derivatives of general formula (I) below and to their salts.

10

The compounds in question have a very valuable pharmacological profile insofar as they possess thromboxane receptor antagonist properties. Thromboxane A₂ (or TXA₂) affects a variety of tissues or cells. A constrictive action is observed on the vascular, bronchial and uterine smooth musculature. The blood platelets are aggregated by TXA₂, while the membranes of the circulating cells are modified and can thus adhere to each other. The different properties described for thromboxane A₂ are such that a TXA₂ receptor antagonist may be envisaged as having a favorable role in the following pathological conditions: myocardial infarction, angina pectoris, stroke, migraine, brain hemorrhage, atherosclerosis, pulmonary embolism, bronchial asthma, bronchitis, pneumonia, circulatory shock of various origins (hemorrhage, septicemia, heart failure, trauma, acute pancreatitis, burn, bacterial origin), nephritis, graft rejection and cancerous metastases.

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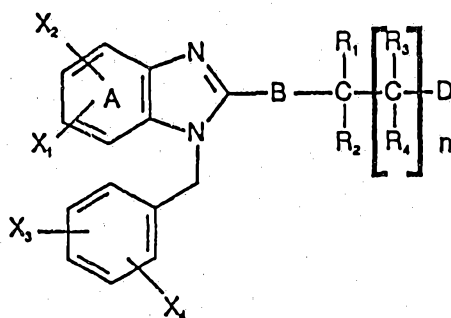
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The present invention further relates to the method of preparing said products and to their applications in therapy. It further relates to the novel intermediates which make it possible to synthesize said products.

35

These benzimidazole and azabenzimidazole derivatives have general formula (I):



Formula (I)

in which:

A is an aromatic ring or a nitrogen heterocycle;

X_1 , X_2 , X_3 and X_4 are independently a hydrogen atom, a halogen atom, a lower alkyl radical, a C_3 - C_7 lower cycloalkyl radical, an alkoxy radical, an alkylthio radical, a sulfone group, SO_2 -lower alkyl, a sulfoxide group, SO -lower alkyl, a trifluoromethyl group, a nitro group, a hydroxyl group, a methylene alcohol radical or a group $COOR'$, in which R' is a hydrogen or a lower alkyl; X_3 and X_4 can also form a naphthalene with the phenyl;

B is CR_5R_6 , R_5 and R_6 being a hydrogen atom, a lower alkyl or a C_3 - C_7 cycloalkyl radical, or the sulfur atom;

R_1 , R_2 , R_3 and R_4 are independently a hydrogen atom, a lower alkyl radical or a C_3 - C_7 cycloalkyl radical; CR_1R_2 or CR_3R_4 can form with B, when the latter is CR_5R_6 , a cycloalkyl or a cycloalkene having 3 to 7 carbon atoms; R_1R_2 and R_3R_4 can also form a ring having 3 to 7 carbon atoms;

n is an integer from 1 to 4 and can be 0 if R_1 and R_2 are other than hydrogen; and

D is a chemical group which can be:

COOR₇, R₇ being the hydrogen atom, a lower alkyl radical or a C₃-C₇ cycloalkyl radical,
CONH-R₈, R₈ being the hydrogen atom, a lower alkyl radical or a C₃-C₇ cycloalkyl radical, or
05 CN.

In the description and the claims, lower alkyl radical is understood as meaning a linear or branched hydrocarbon chain having 1 to 6 carbon atoms. A lower alkyl radical is, for example, a methyl, ethyl, propyl,
10 isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl or isohexyl radical.

C₃-C₇ cycloalkyl radical is understood as meaning a saturated cyclic radical, preferably a cyclopropane, cyclobutane, cyclopentane, cyclohexane or
15 cycloheptane radical.

C₃-C₇ cycloalkene radical is understood as meaning a cyclic radical possessing an unsaturation, preferably a cyclobutene, cyclopentene, cyclohexene or cycloheptene radical.

20 Alkoxy radical is understood as meaning an O-lower alkyl group and alkylthio radical is understood as meaning an S-lower alkyl group, lower alkyl being as defined above.

In the description and the claims, halogen is understood as meaning a chlorine, bromine, iodine or
25 fluorine atom.

Aromatic ring is understood as meaning any aromatic ring such as benzene or naphthalene.

Nitrogen heterocycle is understood as meaning
30 any aromatic ring containing from one to four nitrogens in the ring. Pyridine will be preferred in particular among the nitrogen-containing rings.

The derivatives most similar to these compounds which have so far been disclosed in the literature are
35 described in patent n° 1.580.823 filed in France on 1

December 1967 under US priority of 2 December 1966, n° 598 607, in the name of T.Y. SHEN, A.R. MATZUK and H. SHAM (MERCK and CO.). Said patent describes benzimidazoles substituted in either the 1-position or the 2-position by a lower alkanolic acid residue and in the other position by an aromatic or heteroaromatic group having fewer than three fused rings.

The lower alkanolic acid residue is limited to a chain length of two carbons and can be: $-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)-\text{CH}_2-$.

These derivatives are described as antiinflammatories and antipyretics.

The Applicant has found that these compounds are only slightly active, if at all, as thromboxane receptor antagonists.

In fact, the length of the chain which carries the acid group, namely one or two carbon atoms, is insufficient to exhibit a suitable affinity for the receptor.

On the other hand, surprisingly, the Applicant has demonstrated that if this chain possesses more than three carbon atoms or a heteroatom such as sulfur and at least three carbon atoms, and optimally if it is a branched chain having five carbons, the affinity for the receptor is such that it makes it possible to obtain very good TXA_2 antagonists.

Variants of the invention form the subject of the sub-claims. In particular, according to these variants, A can be a phenyl ring or a pyridine ring and X_1 can be a fluorine atom or a chlorine atom. Likewise, X_2 can be a chlorine atom, a methoxy group or a methylthio group; X_4 can be a chlorine atom; D can advantageously be an acid group.

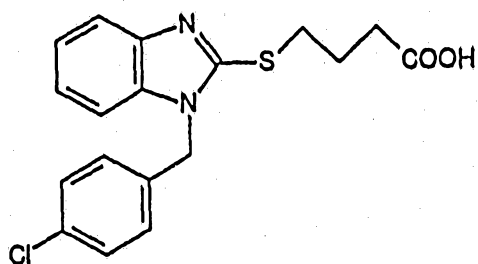
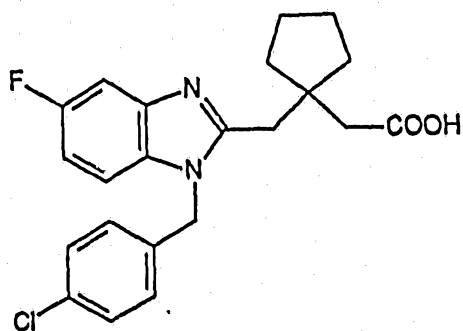
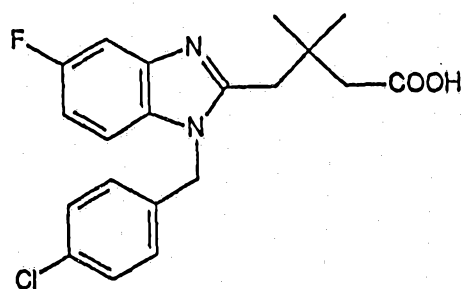
Also according to a particular variant, B can be a methylene group, R_1 and R_2 are each a methyl, R_3

and R_4 are hydrogen and n is equal to 1.

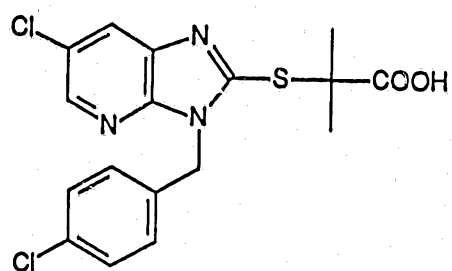
According to another advantageous variant, B is the sulfur atom.

According to yet another variant, C and R_1 and R_2 are a cyclopentane.

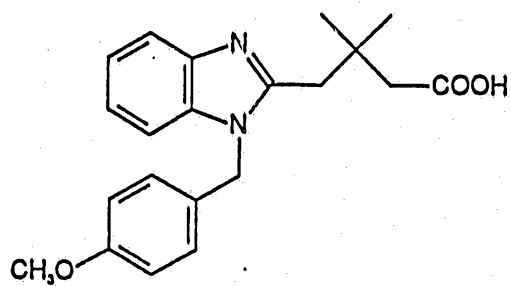
The particularly preferred compounds of the invention are those selected from the products of the formulae



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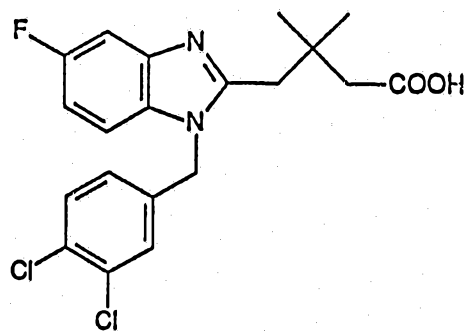


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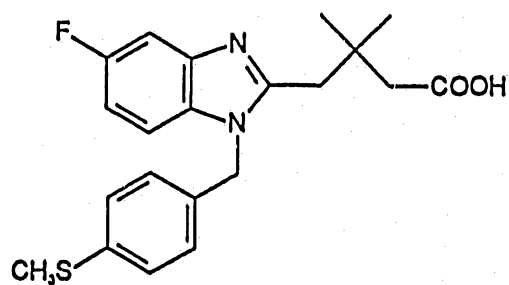
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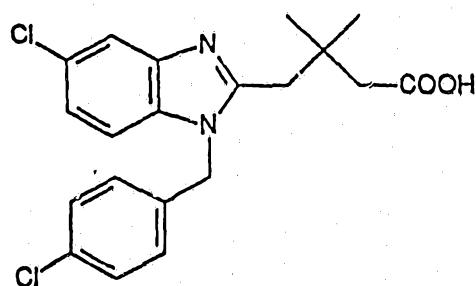
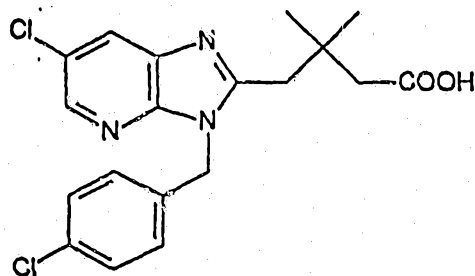


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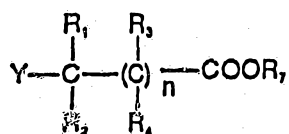


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A - Method of preparing the compounds of formula (I) in which B is the sulfur atom

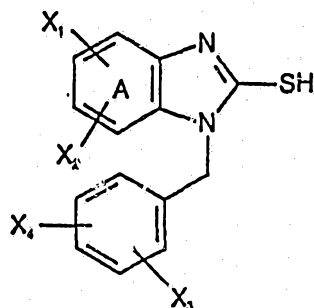
According to the invention, the compounds of formula (I) in which B is the sulfur atom and D is a group COOR_7 , A, X_1 , X_2 , X_3 , X_4 , R_1 , R_2 , R_3 , R_4 and n being as defined above and R_7 being a lower alkyl radical, can be synthesized by reacting an alkyl halogenoalkanoate of formula (II):



Formula (II)

in which R_1 , R_2 , R_3 , R_4 , n and R_7 are as defined above and Y is a halogen, optimally chlorine or bromine, with

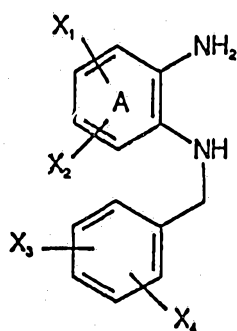
a mercaptobenzimidazole or mercaptoazabenzimidazole derivative of formula (III):



Formula (III)

in which A, X₁, X₂, X₃ and X₄ are as defined above, in the presence of a base such as a sodium or potassium alcoholate in an alcohol, sodium hydride in dimethylformamide or potassium carbonate in acetone or butan-2-one.

The compounds of formula (III) are synthesized by reacting carbon disulfide or potassium xanthogenate with diamine compounds of formula (IV):

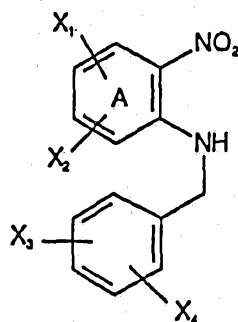


Formula (IV)

in which A, X₁, X₂, X₃ and X₄ are as defined above, under reflux in a solvent such as an alcohol.

The compounds of formula (IV) can be obtained

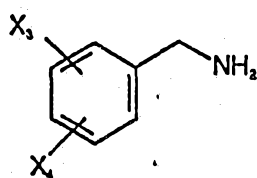
by catalytic hydrogenation of the nitro derivatives of formula (V):



Formula (V)

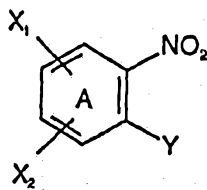
in which A, X₁, X₂, X₃ and X₄ are as defined above, in the presence of Raney nickel for example, in solvents such as an alcohol, tetrahydrofuran or 2-methoxyethanol, under pressure or at atmospheric pressure and at a temperature of between 20 and 120°C.

These nitro derivatives of formula (V) can be synthesized by reacting a substituted benzylamine of formula (VI):



Formula (VI)

in which X₃ and X₄ are as defined above, with a halogenated nitro derivative of formula (VII):



Formula (VII)

05 in which A, X₁ and X₂ are as defined above and Y is a
10 halogen atom, optimally chlorine or fluorine.

In the case where A is a phenyl, the reaction
can be carried out in a solvent such as an alcohol or
tetrahydrofuran, in the presence of potassium carbo-
nate, or simply by heating the reactants at 135°C,
15 without a solvent or a base, according to the method
described in Belgian patent 667,333 of 24 January 1966.

In the case where A is a nitrogen heterocycle,
for example pyridine or pyrimidine, the reaction may be
carried out in solvents such as toluene or xylene, in
20 the presence or absence of pyridine or 2-methyl-5-
ethylpyridine.

The benzylamines of formula (VI) are
commercially available or can be prepared by:
- hydrogenation of the corresponding Schiff base
25 obtained by reacting ammonia with the corresponding
aldehyde under pressure;
- hydrogenation of the corresponding oxime obtained by
reacting hydroxylamine with the corresponding aldehyde;
or
30 - Hofmann degradation of the corresponding phenylacet-
amide, i.e. treatment with a solution of a hypohalite,
for example sodium hypobromite.

The orthohalogenated nitro derivatives of
formula (VII) are commercially available or can be
35 synthesized according to methods described in the

literature, for example in the following references:
in the case where A is a phenyl:

- HOLLEMAN; REIDING; Rec. Trav. Chim. Pays Bas 1904,
23, 361

05 - SWARTS; Rec. Trav. Chim. Pays Bas 1916, 35, 155

in the case where A is a nitrogen heterocycle:

- BATKOWSKI, T.; Roczn. Chem. 1968, 42 (12), 2079-88

- BEBENBURG, W.; STEIMMETZ, S.; THIELE, K.; Chemiker
Zeitung 1979, 103 (12), 387-99

10 - BOON, W.R.; JONES, W.G.M.; RAMAGE, G.R.; J. Chem.
Soc. 1951, 96

- KRUGER, S.; MANN, F.G.; J. Chem. Soc. 1955, 2755

- FUJIMATO, M.; Pharm. Bull. (Tokyo) 1956, 4, 340

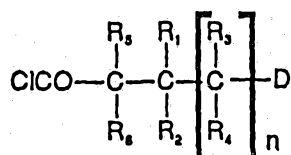
15 The nitro compounds of formula (V) in which A
is a phenyl can also be prepared in several steps from
nitroanilines of formula (VII) in which A is a phenyl
and Y = NH₂. In a first stage, these nitroanilines are
treated with tosyl chloride in pyridine. The resulting
sulfonamide is then alkylated with an appropriately
20 substituted benzyl chloride in the presence of a
metalating agent such as sodium hydride, in a solvent
such as dimethylformamide. The tosylate (4-methylben-
zenesulfonyl) group is then hydrolyzed in propionic
acid, in the presence of concentrated sulfuric acid, to
25 give the corresponding nitro derivatives of formula
(V).

30 Another variant of the method of synthesizing
these compounds of formula (V) in which A is a phenyl
consists in heating the same nitroanilines with approp-
riately substituted benzyl chlorides or bromides to a
temperature of between 100 and 130°C, without a solvent
and in the presence of dry sodium acetate and iodine.

B - Method of preparing the compounds of formula (I) in
which B is a group CR₂R₂

35 The derivatives of formula (I) in which B is a

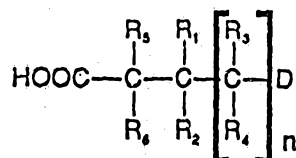
group CR_5R_6 and D is a group CN or $COOR_7$, A, X_1 , X_2 , X_3 , X_4 , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and n being as defined above and R_7 being a lower alkyl group, can be synthesized by reacting derivatives of formula (IV) with derivatives of formula (VIII):



Formula (VIII)

in which D, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and n are as defined above and R_7 is a lower alkyl radical.

These derivatives of formula (VIII) can be prepared, according to a classical method of forming acid chlorides, by treating the corresponding acid ester or cyano acid derivatives of formula (IX):



Formula (IX)

in which D, R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and n are as defined above and R_7 is a lower alkyl radical, with thionyl chloride or phosphorus oxychloride for example, in a solvent such as toluene for example, or without a solvent.

These compounds of formula (IX) are obtained by different routes:

- by monosaponification of the corresponding diesters

or hydrolysis of the corresponding cyano esters in the presence of one equivalent of sodium hydroxide, according to a procedure described for example in the following reference:

- 05 LE MOAL H.; FOUCAUD A.; CARRIE R.; DANION D. and FAYAT C.; Bull. Soc. Chim. Fr. 1964, 828

- in another route for the preparation of the acid ester derivatives, by treatment of the corresponding acid anhydride derivatives with an alcohol. The acid

- 10 anhydrides are obtained by dehydration of the corresponding diacids with acetic anhydride under reflux, or by treatment with half an equivalent of dicyclohexylcarbodiimide. The preparation of the diacid derivatives used which are not commercially available may be found in the following references:

15 HOWARD E. ZIMMERMAN; DAVID N. SCHISSEL; J. Org. Chem. 1986, 51, 196-207

H. NAJER; R. GIUDICELLI; J. SETTE; Bull. Soc. Chim. Fr. 1964, 2572-2581

- 20 J. SEYDEN PENNE; M.C. ROUX-SCHMITT; Bull. Soc. Chim. Fr. 1968, 3812

N.L. ALLINGER; M. NAKAZAKI; V. ZALKOW; J. Am. Chem. Soc. 1959, 81, 4074-4080

J. MEINWALD; J.J. TUFARIELLO; J.J. HURST; J. Am. Chem. Soc. 1964, 86, 2914-2920

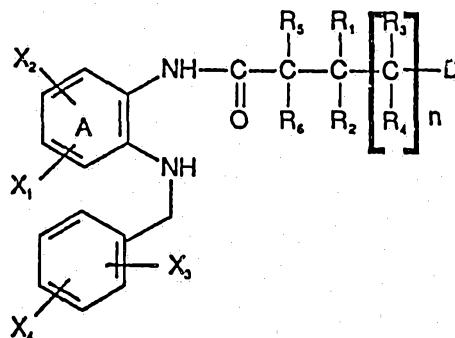
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This reaction between the acid chloride esters or the cyano acid chlorides of formula (VIII) and the diamino derivatives of formula (IV) is performed in two steps.

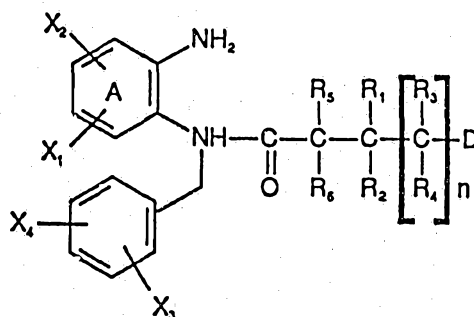
30

In a first stage, in a solvent such as chloroform or tetrahydrofuran for example, in the presence of triethylamine or pyridine, it yields a mixture of amide compounds of formulae (X) and (X bis):

35



Formula (X)



Formula (X bis)

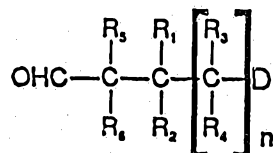
in which A, D, X₁, X₂, X₃, X₄, R₁, R₂, R₃, R₄, R₅, R₆ and n are as defined above.

This mixture of amide compounds of formulae (X) and (X bis) is then treated in an acid medium, either with concentrated hydrochloric acid in an alcohol under reflux, or with concentrated sulfuric acid, or with polyphosphoric acid, to give the compounds of formula (I) in which B is a group CR₅R₆ and D is a group CN or CO₂R₇, R₇ being a lower alkyl radical.

The compounds of formula (I) in which B is a group CR₅R₆ and D is a group CO₂R₇ or CN, R₇ being a lower alkyl radical and R₅ and R₆ being as defined

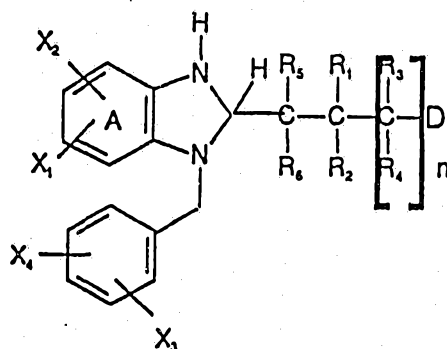
above, can also be prepared in the following manner:

Reaction of aldehydes of formula (VIII'):



Formula (VIII')

in which R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , n and D are as defined above, with the compounds of formula (IV) in a mixture of acetic acid and ethanol gives derivatives of formula (X'):



Formula (X')

in which X_1 , X_2 , X_3 , X_4 , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , n and D are as defined above.

Treatment of these compounds of formula (X') with an oxidizing agent such as iodine or barium manganate for example, at a temperature ranging from room temperature to 100°C , will give the compounds of formula (I) in which B is a group CR_5R_6 and D is a group CO_2R_7 or CN , R_7 being a lower alkyl radical and R_5 and R_6 being as defined above. Examples of this

kind of reaction may be found in the following references:

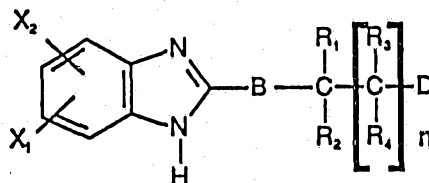
- Srivastava, R.G.; Venkataramani, P.S.; Synt. Comm. 1988, 18 (13), 1537-1544

05 - Perumattam, G.; Synt. Comm. 1989, 19 (19), 3367-3370

The aldehydes of formula (VIII') can be prepared by catalytic hydrogenation of the acid chloride derivatives (VIII) in which D is an ester group, in the presence of palladium-on-charcoal and lutidine in
10 tetrahydrofuran.

This method is particularly advantageous when the ring A is a pyridine ring.

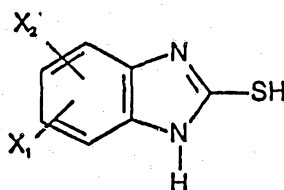
The compounds of formula (I) in which A is a phenyl and D is the group CN or CO₂R₇, R₇ being a lower alkyl radical, can also be synthesized by reacting an
15 appropriately substituted benzyl chloride with derivatives of formula (XI):



Formula (XI)

25 in which D, X₁, X₂, R₁, R₂, R₃, R₄, B and n are as defined above, in a solvent such as dimethylformamide, in the presence of a metalating agent such as sodium hydride.

30 The compounds of formula (XI) in which B is the sulfur atom can be synthesized from the compounds of formula (XII):



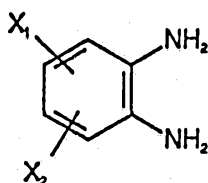
05

Formula (XII)

in which X_1 and X_2 are as defined above, with alkyl
halogenoalkanoate compounds of formula (II) in the
10 presence of a base such as sodium ethylate in alcohol
or potassium carbonate in acetone or tetrahydrofuran.

The compounds of formula (XII) are commercially
available or are synthesized according to methods des-
cribed in BEILSTEIN 24, 119 and 24, supplement (3),
15 293.

The compounds of formula (XI) in which B is a
group CR_5R_6 , R_5 and R_6 being as defined above, can be
synthesized by reacting an acid chloride ester compound
of formula (VIII) with an orthophenylenediamine com-
pound of formula (XIII):
20



25

Formula (XIII)

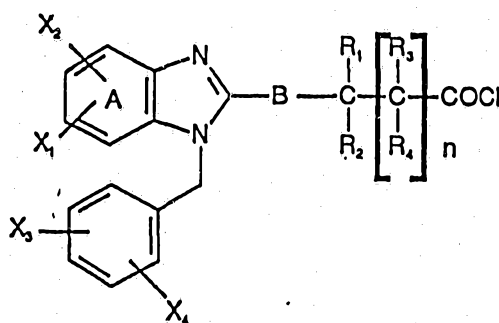
in which X_1 and X_2 are as defined above, under con-
ditions identical to those described above for reacting
30 the compounds of formula (IV) with the derivatives of
formula (VIII).

The compounds of formula (XIII) are commercial-
ly available.

35 The compounds of formula (I) in which D is the

group COOR_7 , and R_7 is the hydrogen atom are obtained by classical hydrolysis of the compounds of formula (I) in which D is the group COOR_7 , and R_7 is a lower alkyl radical, or D is the group CN , either in an acid medium or in a basic medium.

The compounds of formula (I) in which D is a group CONH-R_8 are obtained by reacting amines of the formula $\text{R}_8\text{-NH}_2$, R_8 being as defined above, with acid chlorides of formula (XIV):



Formula (XIV)

in which A, X_1 , X_2 , X_3 , X_4 , R_1 , R_2 , R_3 , R_4 , B and n are as defined above, in a solvent such as chloroform or tetrahydrofuran, in the presence of excess amine or of triethylamine or pyridine. In the case where R_8 is hydrogen, it will be possible quite simply to react the acid chloride of formula (XIV) with a solution of ammonia.

The compounds of formula (XIV) can be prepared according to a classical method for acid chlorides, namely by reacting thionyl chloride, oxalyl chloride or phosphorus oxychloride with the corresponding compounds of formula (I) in which D is the group CO_2H .

The compounds of formula (I) in which D is the group CN can also be prepared by dehydration of the corresponding amide compounds, in which D is CONH_2 , by

treatment with phosphorus oxychloride for example, in a solvent such as dimethylformamide or without a solvent.

05 Addition salts of some of the compounds of formula (I) can be obtained, especially pharmaceutically acceptable addition salts. The sodium, potassium and calcium salts may be mentioned in particular when D is an acid group.

10 The novel compounds according to the invention possess remarkable pharmacological properties as thromboxane receptor antagonists and can be used in therapy for the treatment of myocardial infarction, angina pectoris, stroke, migraine, cerebral hemorrhages, atherosclerosis, pulmonary embolism, bronchial asthma, bronchitis, pneumonia, circulatory shocks of various
15 origins, nephritis, graft rejection and cancerous metastases.

Thus the invention also covers a pharmaceutical composition which comprises a pharmaceutically effective amount of at least one compound of formula (I) as
20 defined above, as well as its pharmaceutically acceptable addition salts if appropriate, which may or may not be incorporated in a pharmaceutically acceptable excipient, vehicle or carrier.

25 The invention also covers a pharmaceutical composition active as a thromboxane receptor antagonist, with which the following diseases in particular can be favorably treated: myocardial infarction, angina pectoris, stroke, migraine, cerebral hemorrhage, atherosclerosis, pulmonary embolism, bronchial asthma, bronchitis, pneumonia, circulatory shocks of various
30 origins such as hemorrhage, septicemia, heart failure, trauma, acute pancreatitis, burn or bacterial origin, nephritis, graft rejection and cancerous metastases, said composition comprising a pharmaceutically effective amount of at least one compound of formula (I)
35

mentioned above, or one of its pharmaceutically acceptable addition salts, which may or may not be incorporated in a pharmaceutically acceptable excipient, vehicle or carrier.

05 The invention also covers a method of preparing a pharmaceutical composition, which comprises incorporating a pharmaceutically effective amount of at least one compound of formula (I) as defined above, as well as its pharmaceutically acceptable addition salts
10 if appropriate, into a pharmaceutically acceptable excipient, vehicle or carrier.

 In another embodiment, a pharmaceutical composition active as a thromboxane receptor antagonist is prepared with which the following diseases in particular can be favorably treated: myocardial infarction,
15 angina pectoris, stroke, migraine, cerebral hemorrhage, atherosclerosis, pulmonary embolism, bronchial asthma, bronchitis, pneumonia, circulatory shocks of various origins such as hemorrhage, septicemia, heart failure,
20 trauma, acute pancreatitis, burn or bacterial origin, nephritis, graft rejection and cancerous metastases.

 In another variant, a pharmaceutical composition is formulated as gelatin capsules or tablets containing from 1 to 200 mg of active ingredient, or as
25 injectable preparations containing from 0.01 to 10 mg of active ingredient.

 The invention also covers a method of therapeutic treatment for mammals, which comprises administering to said mammal a therapeutically effective amount
30 of at least one compound of formula (I) as defined above, or one of its pharmaceutically acceptable addition salts, which may or may not be incorporated in a pharmaceutically acceptable excipient, vehicle or carrier. In a variant of this method of treatment, the
35 compound of formula (I), either by itself or in associ-

ation with a pharmaceutically acceptable excipient, is formulated as gelatin capsules or tablets containing from 1 to 200 mg of active ingredient for oral administration, or as injectable preparations containing from
05 0.01 to 10 mg of active ingredient for parenteral administration.

In human and animal therapy, the compounds of formula (I) and their salts can be administered, by themselves or in association with a physiologically
10 acceptable excipient, in any form, in particular in the form of gelatin capsules and tablets for oral administration or in the form of an injectable solution for parenteral administration.

As will become clearly apparent from the pharmacology tests given at the end of the description, the compounds according to the invention can be administered in human therapy, for the above-mentioned indications, orally in the form of tablets or gelatin capsules containing from 1 to 200 mg of active ingredient,
15 or parenterally in the form of injectable preparations containing from 0.01 to 10 mg of active ingredient, in one or more dosage units per day for an adult with an average weight of 60 to 70 kg.

In animal therapy, the daily dose which can be used should normally be between 1 and 100 mg per kg.
25

Further characteristics and advantages of the invention will be understood more clearly from the following description of some Preparatory Examples, which in no way imply a limitation but are given by way
30 of illustration.

Example 1:

2-(4-Chlorophenylmethylamino)-5-fluoronitrobenzene

Formula (V): $X_1 = 5-F$, $X_2 = X_3 = H$, $X_4 = 4-Cl$, $A =$
phenyl

05

30 g of 2,5-difluoronitrobenzene and 26.7 g of
4-chlorobenzylamine are dissolved in 300 ml of tetra-
hydrofuran. 40 g of potassium carbonate are added to
10 this solution and the mixture is refluxed for 8 hours.
After cooling, the reaction mixture is added to 1.7 l
of water and 50 ml of concentrated hydrochloric acid.
The crystals obtained are filtered off and washed with
water and then with isopropyl ether to give 41.9 g of
15 2-(4-chlorophenylmethylamino)-5-fluoronitrobenzene in
the form of crystals melting at 160°C.

The following Example was synthesized by this
procedure:

20 Example 2:

2-(3,4-Dichlorophenylmethylamino)-5-fluoronitrobenzene

Formula (V): $X_1 = 5-F$, $X_2 = H$, $X_3 = 3-Cl$, $X_4 = 4-Cl$,
 $A =$ phenyl

25

Crystals melting at 110°C.

Example 3:

2-(4-Chlorophenylmethylamino)-5-chloronitrobenzene

30

Formula (V): $X_1 = 5-Cl$, $X_2 = H$, $X_3 = 4-Cl$, $X_4 = H$, $A =$
phenyl

25 g of 2,5-dichloronitrobenzene and 36.9 g of
35 4-chlorobenzylamine are heated for two hours at 135°C,

it being necessary for the temperature always to be kept below 140°C. After cooling, the mixture is taken up with water and extracted with ethyl acetate. After drying over magnesium sulfate and evaporation under vacuum, the residue is taken up with ether and the crystals obtained are filtered off and washed with ether to give 22.3 g of 2-(4-chlorophenylmethylamino)-5-chloronitrobenzene in the form of crystals melting at 120°C.

10

Example 4:

2-(4-Chlorophenylmethylamino)-5-methoxynitrobenzene

15

Formula (V): $X_1 = 5\text{-OMe}$, $X_2 = \text{H}$, $X_3 = 4\text{-Cl}$, $X_4 = \text{H}$, A = phenyl

A) 2-(4-Methylphenylsulfonylamino)-5-methoxynitrobenzene

20

50 g of 4-methoxy-2-nitroaniline are stirred at 0°C in 300 ml of pyridine. 56.7 g of tosyl chloride are added in portions at 0°C and the mixture is then stirred for two hours at room temperature, left to stand overnight and poured into an ice/water mixture.

25

The crystals obtained are filtered off and washed with water and then with isopropyl ether to give 72.8 g of 2-(4-methylbenzenesulfonylamino)-5-methoxynitrobenzene in the form of crystals melting at 99°C.

30

B) N-(4-Chlorobenzyl)-N-(4-methylbenzenesulfonyl)-2-nitro-4-methoxyaniline

35

72.8 g of 2-(4-methylbenzenesulfonylamino)-5-methoxynitrobenzene, prepared in A), are added to 56.5 ml of 4 N sodium hydroxide solution and 29.2 g of 4-

chlorobenzyl chloride. The mixture is refluxed for 4 hours, a further 43.7 g of 4-chlorobenzyl chloride are then added and the resulting mixture is refluxed for another 45 minutes. After cooling, 12.2 ml of 35% sodium hydroxide solution are added to the reaction mixture, the latter is refluxed for three hours 45 minutes and then cooled and water and ether are added. The insoluble material is filtered off and washed with water and ether to give 98 g of N-(4-chlorobenzyl)-N-(4-methylbenzenesulfonyl)-2-nitro-4-methoxyaniline in the form of crystals melting at 124°C. Evaporation of the ether phase yields an additional 10 g of crystals melting at 124°C.

15 C) 2-(4-Chlorophenylmethylamino)-5-methoxynitrobenzene

108 g of N-(4-chlorobenzyl)-N-(4-methylbenzenesulfonyl)-2-nitro-4-methoxyaniline, prepared in B), are added to 940 ml of propionic acid and 102 ml of concentrated sulfuric acid. The mixture is heated at 95°C for 1 h 30 min and the solution is concentrated to half its volume by evaporation under vacuum and then poured on to ice and neutralized with ammonium hydroxide.

The crystals obtained are filtered off and washed with water and then with isopropyl ether to give 60 g of 2-(4-chlorophenylmethylamino)-5-methoxynitrobenzene in the form of crystals melting at 135°C.

Example 5:

30 2-(4-Chlorophenylmethylamino)-3-nitropyridine

Formula (V): $X_3 = 4\text{-Cl}$, $X_1 = X_2 = X_4 = \text{H}$, A = 2-pyridine

35 A solution of 26.5 g of 2-chloro-3-nitropyri-

dine, 23.7 g of 4-chlorobenzylamine and 25 ml of 2-methyl-5-ethylpyridine in 200 ml of xylene is refluxed for 12 hours. The reaction mixture is then cooled, water and acetic acid are added and the resulting mixture is then extracted with ether. The organic phase is dried over magnesium sulfate, filtered and then evaporated under vacuum to give an oil which crystallizes from isopropyl ether. The crystals are filtered off and then dried to give 27 g of 2-(4-chlorophenylmethylamino)-3-nitropyridine in the form of crystals melting at 100°C.

Example 6:

2-(4-Chlorophenylmethylamino)-3-nitro-5-chloropyridine

Formula (V): $X_1 = 5\text{-Cl}$, $X_2 = \text{H}$, $X_3 = 4\text{-Cl}$, $X_4 = \text{H}$, A = 2-pyridine

A solution of 20.9 g of 4-chlorobenzylamine and 15.7 g of 2,5-dichloro-3-nitropyridine in 250 ml of xylene and 20 ml of 2-methyl-5-ethylpyridine is refluxed for 30 hours. After cooling, water is added to the reaction mixture, the resulting mixture is then extracted with ethyl acetate and the organic phase is washed with a dilute solution of hydrochloric acid and dried over magnesium sulfate. The solvent is evaporated off under vacuum and the residue obtained crystallizes from isopropyl ether to give 21.1 g of 2-(4-chlorophenylmethylamino)-3-nitro-5-chloropyridine in the form of crystals melting at 120°C.

Example 7:

2-(2-Fluoro-4-bromophenylmethylamino)-3-nitro-5-chloro-pyridine

05 Formula (V): $X_1 = 5\text{-Cl}$, $X_2 = \text{H}$, $X_3 = 2\text{-F}$, $X_4 = 4\text{-Br}$,
A = 2-pyridine

Prepared by the procedure of Example 6.

Crystals melting at 75-77°C.

10

Example 8:

2-(4-Chlorophenylmethylamino)-5-fluoroaniline

15 Formula (IV): $X_1 = 5\text{-F}$, $X_2 = \text{H}$, $X_3 = 4\text{-Cl}$, $X_4 = \text{H}$, A =
phenyl

41.7 g of 2-(4-chlorophenylmethylamino)-5-fluoronitrobenzene, prepared in Example 1, are dissolved in 1 l of tetrahydrofuran and hydrogenated at ordinary temperature and pressure in the presence of 5 g of Raney nickel. When the theoretical amount of hydrogen has been absorbed, the catalyst is filtered off and the solvent is evaporated off under vacuum to give 34.1 g of 2-(4-chlorophenylmethylamino)-5-fluoroaniline in the form of crystals melting at 99°C.

25

The following Examples were prepared by the same procedure:

Example 9:

30 2-(4-Chlorophenylmethylamino)-5-methoxyaniline

Formula (IV): $X_1 = 5\text{-MeO}$, $X_2 = \text{H}$, $X_3 = 4\text{-Cl}$, $X_4 = \text{H}$,
A = phenyl

35

Crystals melting at 90°C.

Example 10:

2-(3,4-Dichlorophenylmethylamino)-5-fluoroaniline

Formula (IV): $X_1 = 5-F$, $X_2 = H$, $X_3 = 3-Cl$, $X_4 = 4-Cl$,
A = phenyl

05

Crystals melting at 104°C.

Example 11:

10 2-(4-Chlorophenylmethylamino)-5-chloroaniline

Formula (IV): $X_1 = 5-Cl$, $X_2 = H$, $X_3 = 4-Cl$, $X_4 = H$, A =
phenyl

15

Crystals melting at 138°C.

Example 12:

2-(2-Fluoro-4-bromophenylmethylamino)-3-amino-5-chloro-
pyridine

20

Formula (IV): $X_1 = 5-Cl$, $X_2 = H$, $X_3 = 2-F$, $X_4 = 4-Br$,
A = 2-pyridine

Crystals melting at 97°C.

25

Example 13:

2-(4-Chlorophenylmethylamino)-3-aminopyridine

Formula (IV): $X_1 = H$, $X_2 = H$, $X_3 = 4-Cl$, $X_4 = H$, A = 2-
pyridine

30

Crystals melting at 132°C.

35

Example 14:

2-(4-Chlorophenylmethylamino)-3-amino-5-chloropyridine

Formula (IV): $X_1 = 5\text{-Cl}$, $X_2 = \text{H}$, $X_3 = 4\text{-Cl}$, $X_4 = \text{H}$, A =
2-pyridine

Oil used as such for the next step.

Example 15:

1-(4-Chlorophenylmethyl)-2-mercapto-5-fluorobenzimidazole

Formula (III): $X_1 = 5\text{-F}$, $X_2 = \text{H}$, $X_3 = 4\text{-Cl}$, $X_4 = \text{H}$, A =
phenyl

25 ml of carbon disulfide are added to 35.2 g of 2-(4-chlorophenylmethylamino)-5-fluoroaniline, prepared in Example 8, dissolved in 500 ml of ethanol. The mixture is refluxed for 12 hours and allowed to return to room temperature. After standing for a few hours, the crystals are filtered off and washed with ethanol and then with isopropanol and ether to give 33 g of 1-(4-chlorophenylmethyl)-2-mercapto-5-fluorobenzimidazole in the form of crystals melting at 215°C.

The following Examples were prepared by the same procedure:

Example 16:

1-(4-Chlorophenylmethyl)-2-mercaptoimidazo[4,5-b]-pyridine

Formula (III): $X_3 = 4\text{-Cl}$, $X_1 = X_2 = X_4 = \text{H}$, A = 2-pyridine

Crystals melting at 216°C.

1-(4-Chlorophenyl)ethyl)-2-mercapto-5-chloroimidazo-
[4,5-b]pyridine

05 Formula (III): X₁ = 5-Cl, X₂ = H, X₃ = 4-Cl, X₄ = H,
 A = 2-pyridine

Crystals melting at 260°C.

10 Example 18:

**1-(2-Fluoro-4-bromophenylmethyl)-2-mercapto-5-chloro-
pyridine**

Formula (III): $X_1 = 5\text{-Cl}$, $X_2 = \text{H}$, $X_3 = 2\text{-F}$, $X_4 = 4\text{-Br}$,
A = 2-pyridine

Crystals melting at 240°C.

Example 19:

20 Ethyl 4-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]-
mercaptobutanoate

Formula (I): $X_1 = 5\text{-F}$, $X_2 = \text{H}$, $X_3 = 4\text{-Cl}$, $X_4 = \text{H}$, $\text{A} =$
phenyl, $\text{B} = \text{S}$, $\text{D} = \text{CO}_2\text{Et}$, $\text{R}_1 = \text{R}_2 = \text{R}_3 =$
 $\text{R}_4 = \text{H}$, $n = 2$

9 g of 1-(4-chlorophenylmethyl)-2-mercapto-5-fluorobenzimidazole, prepared in Example 15, and 4.4 ml of ethyl 4-bromobutyrate are refluxed for 5 hours in 100 ml of acetone in the presence of 6.3 g of potassium carbonate. The solvent is evaporated off under vacuum, the residue is taken up with water and then extracted with ethyl acetate and the extract is washed with a dilute solution of sodium hydroxide. The organic phase is dried over magnesium sulfate and evaporated under

vacuum to give 11.9 g of ethyl 4-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]mercaptobutanoate in the form of an oil, which is used as such for the next step.

05 The following Examples were prepared by the same procedure:

Example 20:

Ethyl 5-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]-mercaptopentanoate

10

Formula (I): $X_1 = 5-F$, $X_2 = H$, $X_3 = 4-Cl$, $X_4 = H$, $A =$
phenyl, $B = S$, $D = CO_2Et$, $R_1 = R_2 = R_3 =$
 $R_4 = H$, $n = 3$

15

Oil used as such for the next step.

Example 21:

Ethyl 4-[1-(2-fluoro-4-bromobenzyl)-5-chloroimidazo-
[4,5-b]pyridin-2-yl]mercaptobutanoate

20

Formula (I): $X_1 = 5-Cl$, $X_2 = H$, $X_3 = 2-F$, $X_4 = 4-Br$,
 $A = 2\text{-pyridine}$, $D = CO_2Et$, $B = S$, $R_1 =$
 $R_2 = R_3 = R_4 = H$, $n = 2$

25

Crystals melting at 94°C.

Example 22:

Ethyl 2-[1-(4-chlorobenzyl)-5-chloroimidazo[4,5-b]-
pyridin-2-yl]mercapto-2-methylpropionate

30

Formula (I): $X_1 = 5-Cl$, $X_2 = H$, $X_3 = 4-Cl$, $X_4 = H$, $A =$
2-pyridine, $D = CO_2Et$, $B = S$, $R_1 = R_2 =$
 CH_3 , $n = 0$

35

Oil used as such for the next step.

Example 23:

Ethyl 4-[1-(4-chlorobenzyl)imidazo[4,5-b]pyridin-2-yl]-mercaptobutanoate

05 Formula (I): $X_1 = H$, $X_2 = X_3 = H$, $X_4 = 4-Cl$, $A = 2$ -
pyridine, $D = CO_2Et$, $B = S$, $R_1 = R_2 = R_3 =$
 $R_4 = H$, $n = 2$

Oil used as such for the next step.

10

Example 24:

Ethyl 4-(benzimidazol-2-yl)mercaptobutanoate

Formula (XI): $X_1 = X_2 = H$, $B = S$, $D = CO_2Et$, $R_1 = R_2 =$
15 $R_3 = R_4 = H$, $n = 2$

50 g of 2-mercaptobenzimidazole are dissolved
in 300 ml of ethanol, and a solution of 7.65 g of
sodium in 150 ml of ethanol is added at room tempera-
20 ture, with stirring. The mixture is stirred for a few
minutes at room temperature and 64.3 g of ethyl 4-
bromobutyrate are added rapidly. The reaction mixture
is refluxed for 6 hours and then cooled. The solvents
are evaporated off to dryness under vacuum, the residue
25 is taken up with water and the crystals obtained are
filtered off, washed with water and then with ether and
dried to give 85 g of ethyl 4-(benzimidazol-2-yl)mer-
captobutanoate in the form of crystals melting at 70-
72°C.

30

Example 25:

Ethyl 5-(benzimidazol-2-yl)mercaptopentanoate

Formula (XI): $X_1 = X_2 = H$, $B = S$, $D = CO_2Et$, $R_1 = R_2 =$
35 $R_3 = R_4 = H$, $n = 3$

Prepared by the procedure of Example 24.
Crystals melting at 100°C.

Example 26:

05 Ethyl 4-[1-(4-chlorobenzyl)benzimidazol-2-yl]mercapto-
butanoate

Formula (I): $X_1 = H$, $X_2 = X_3 = H$, $X_4 = 4-Cl$, $A =$
phenyl, $D = CO_2Et$, $B = S$, $R_1 = R_2 = R_3 =$
10 $R_4 = H$, $n = 2$

20 g of ethyl 4-(benzimidazol-2-yl)mercapto-
butanoate, prepared in Example 24, are added to a
suspension of 2.9 g of 60% sodium hydride in 150 ml of
15 anhydrous dimethylformamide. The mixture is stirred
for 30 minutes at 80°C and then cooled to room tempera-
ture and a solution of 12.7 g of 4-chloro-chloromethyl-
benzene in 20 ml of anhydrous dimethylformamide is
added dropwise.

20 The mixture is refluxed for 5 hours and the
solvent is evaporated off to dryness. The residue is
taken up with water and extracted with ethyl acetate
and the organic phase is dried and then evaporated
under vacuum to give 27 g of ethyl 4-[1-(4-chloro-
25 benzyl)benzimidazol-2-yl]mercaptobutanoate in the form
of an oil, which is used as such for the next step.
The following Example was prepared by the same proce-
dure:

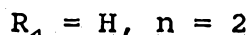
30 Example 27:

Ethyl 4-[1-(2,4-dichlorobenzyl)benzimidazol-2-yl]
mercaptobutanoate

Formula (I): $X_1 = H$, $X_2 = H$, $X_3 = 2-Cl$, $X_4 = 4-Cl$, $A =$
phenyl, $D = CO_2Et$, $B = S$, $R_1 = R_2 = R_3 =$

35





Crystals melting at 92°C.

05 Example 28:

Acid chloride ethyl ester of 3,3-dimethylglutaric acid

Formula (VIII): $R_5 = R_6 = H, R_1 = R_2 = CH_3, R_3 = R_4 =$
H, $n = 1, D = CO_2Et$

10

50 g of 3,3-dimethylglutaric anhydride are dissolved in 500 ml of absolute ethanol and the mixture is refluxed for 12 hours. The alcohol is evaporated off to dryness under vacuum, 250 ml of toluene are added to the residue and 45 ml of thionyl chloride are then added dropwise at room temperature, with stirring.

15

The mixture is heated at 80°C for two hours, the solvents are then evaporated off and the residue is distilled at between 115 and 125°C under 20 mm of mercury to give 58.2 g of the acid chloride ethyl ester of 3,3-dimethylglutaric acid.

20

The following Examples were prepared by the same procedure:

25 Example 29:

Acid chloride ethyl ester of 3-methylglutaric acid

Formula (VIII): $R_5 = R_6 = H, R_1 = CH_3, R_2 = R_3 = R_4 =$
H, $n = 1, D = CO_2Et$

30

Oil used as such for the next step.

35

Example 30:

Acid chloride ethyl ester of 3,3-diethylglutaric acid

05 Formula (VIII): $R_5 = R_6 = H$, $R_1 = R_2 = C_2H_5$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$

Oil used as such for the next step.

Example 31:

10 Acid chloride ethyl ester of 3-methyl-3-ethylglutaric acid

15 Formula (VIII): $R_5 = R_6 = H$, $R_1 = CH_3$, $R_2 = C_2H_5$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$

Oil used as such for the next step.

Example 32:

20 Acid chloride ethyl ester of cyclohexane-1,1-diacetic acid

Formula (VIII): $R_5 = R_6 = H$, $R_1 + R_2 = CH_2-CH_2-CH_2-CH_2-CH_2$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$

25 Oil boiling at 170-175°C under 25 mm of mercury.

Example 33:

30 Acid chloride ethyl ester of cyclopentane-1,1-diacetic acid

Formula (VIII): $R_5 = R_6 = H$, $R_1 + R_2 = CH_2-CH_2-CH_2-CH_2$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$

35 Oil boiling at 165-170°C under 25 mm of mer-

cury.

Example 34:

05 Ethyl 4-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]-
3,3-dimethylbutanoate

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D =$
 CO_2Et , $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5-F$, $X_2 =$
 H , $X_3 = 4-Cl$, $X_4 = H$

10

10 g of 2-(4-chlorobenzylamino)-5-fluoroani-
line, prepared in Example 8, are dissolved in 100 ml of
chloroform, stabilized with amylene, and 6 ml of tri-
ethylamine. A solution of 8.25 g of the acid chloride
15 ethyl ester of 3,3-dimethylglutaric acid, prepared in
Example 28, in 20 ml of chloroform, stabilized with
amylene, is added dropwise. The mixture is stirred for
two hours at room temperature, the crystals formed are
filtered off and the solvents are evaporated off under
20 vacuum. The residue obtained is dissolved in 200 ml of
ethanol and 30 ml of concentrated hydrochloric acid and
the mixture is refluxed for 10 hours. The solvents are
evaporated off to dryness and the residue is taken up
with water and then extracted with ethyl acetate. The
25 organic phase is dried and evaporated under vacuum to
give 14 g of ethyl 4-[1-(4-chlorobenzyl)-5-fluorobenz-
imidazol-2-yl]-3,3-dimethylbutanoate in the form of an
oil, which is used as such for the next step.

30 The following Examples were synthesized by the
same procedure:

Example 35:

Ethyl [1-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]methylcyclopent-1-yl]acetate

- 05 Formula (I): $R_1 + R_2 = \text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2$, $R_3 = R_4 = \text{H}$,
 $n = 1$, $D = \text{CO}_2\text{Et}$, $A = \text{phenyl}$, $B = \text{CH}_2$,
 $X_1 = 5\text{-F}$, $X_2 = \text{H}$, $X_3 = 4\text{-Cl}$, $X_4 = \text{H}$

Oil used as such for the next step.

10

Example 36:

Ethyl [1-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]methylcyclohex-1-yl]acetate

- 15 Formula (I): $R_1 + R_2 = \text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{Et}$, $A = \text{phenyl}$, $B = \text{CH}_2$,
 $X_1 = 5\text{-F}$, $X_2 = \text{H}$, $X_3 = 4\text{-Cl}$, $X_4 = \text{H}$

Oil used as such for the next step.

20

Example 37:

Ethyl 4-[1-(3,4-dichlorobenzyl)-5-fluorobenzimidazol-2-yl]-3,3-dimethylbutanoate

- 25 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{Et}$, $A = \text{phenyl}$, $B = \text{CH}_2$, $X_1 = 5\text{-F}$, $X_2 = \text{H}$, $X_3 = 3\text{-Cl}$, $X_4 = 4\text{-Cl}$

Oil used as such for the next step.

30

Example 38:

Ethyl 4-[1-(4-chlorobenzyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoate

- 35 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D =$

CO_2Et , A = phenyl, B = CH_2 , $\text{X}_1 = 5\text{-Cl}$,
 $\text{X}_2 = \text{H}$, $\text{X}_3 = 4\text{-Cl}$, $\text{X}_4 = \text{H}$

Oil used as such for the next step.

05

Example 39:

Ethyl 4-[1-(4-chlorobenzyl)-5-methoxybenzimidazol-2-yl]-3,3-dimethylbutanoate

10

Formula (I): $\text{R}_1 = \text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{R}_4 = \text{H}$, $n = 1$, D =
 CO_2Et , B = CH_2 , A = phenyl, $\text{X}_1 = 5\text{-MeO}$,
 $\text{X}_2 = \text{H}$, $\text{X}_3 = 4\text{-Cl}$, $\text{X}_4 = \text{H}$

Oil used as such for the next step.

15

Example 40:

Ethyl 4-(benzimidazol-2-yl)-3,3-dimethylbutanoate

20

Formula (XI): B = CH_2 , $\text{R}_1 = \text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{R}_4 = \text{H}$, $n =$
1, D = CO_2Et , $\text{X}_1 = \text{X}_2 = \text{H}$

25

A solution of 139.2 g of the acid chloride ethyl ester of 3,3-dimethylglutaric acid, prepared in Example 28, in 125 ml of chloroform, stabilized with amylene, is added dropwise, at a temperature of between 5°C and 10°C, to a solution of 72.8 g of orthophenylenediamine and 112 ml of triethylamine in 1 l of anhydrous tetrahydrofuran. The mixture is stirred at 0°C for two hours and then at 50°C for one hour; the crystals are filtered off and the solvents are evaporated off under vacuum. The residue is taken up in 4.4 l of ethanol and 444 ml of concentrated hydrochloric acid and the mixture is refluxed for 12 hours. The solvents are evaporated off and the residue is taken up with water and then neutralized with a 1 N solution of

35

sodium hydroxide and extracted with ether. The ether phase is dried and then evaporated under vacuum to give 99 g of ethyl 4-(benzimidazol-2-yl)-3,3-dimethylbutanoate in the form of crystals melting at 123°C.

05 The following Examples were prepared by the same procedure:

Example 41:

10 Ethyl 4-(5,6-dichlorobenzimidazol-2-yl)-3,3-dimethylbutanoate

Formula (XI): $B = CH_2$, $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$, $X_1 = 5-Cl$, $X_2 = 6-Cl$

15 Crystals melting at 128°C.

Example 42:

Ethyl 4-(benzimidazol-2-yl)-3-methyl-3-ethylbutanoate

20 Formula (XI): $B = CH_2$, $R_1 = CH_3$, $R_2 = C_2H_5$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$, $X_1 = X_2 = H$

Oil used as such for the next step.

25 Example 43:

Ethyl 4-(benzimidazol-2-yl)-3,3-diethylbutanoate

Formula (XI): $B = CH_2$, $R_1 = R_2 = C_2H_5$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$, $X_1 = X_2 = H$

30 Crystals melting at 81°C.

35

Example 44:

Ethyl 4-(benzimidazol-2-yl)-3-methylbutanoate

Formula (XI): $B = CH_2$, $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$, $X_1 = X_2 = H$

Crystals melting at 105°C.

Example 45:

Ethyl 4-[1-(4-chlorobenzyl)benzimidazol-2-yl]-3,3-dimethylbutanoate

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$, $A = \text{phenyl}$, $B = CH_2$, $X_1 = H$, $X_2 = X_3 = H$, $X_4 = 4-Cl$

9 g of ethyl 4-(benzimidazol-2-yl)-3,3-dimethylbutanoate, prepared in Example 40, are added to a suspension of 21.5 g of 60% sodium hydride in 50 ml of anhydrous dimethylformamide. The mixture is stirred for 1 hour at 50°C, 5.6 g of 4-chlorobenzyl chloride are then added and the solution obtained is heated for 5 hours at 90°C. The solvents are concentrated under vacuum and the residue is taken up with water and then extracted with ether. The ether phase is washed with water and then dried over magnesium sulfate and the ether is evaporated off to dryness to give 12.9 g of ethyl 4-[1-(4-chlorobenzyl)benzimidazol-2-yl]-3,3-dimethylbutanoate in the form of an oil, which is used as such for the next step.

The following Examples were prepared by the same procedure:

Example 46:

Ethyl 4-[1-(2-fluoro-4-bromobenzyl)benzimidazol-2-yl]-3,3-dimethylbutanoate

05 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$, $A = \text{phenyl}$, $B = CH_2$, $X_1 = H$, $X_2 = H$, $X_3 = 2-F$, $X_4 = 4-Br$

Oil used as such for the next step.

10

Example 47:

Ethyl 4-(1-benzylbenzimidazol-2-yl)-3,3-dimethylbutanoate

15 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$, $A = \text{phenyl}$, $B = CH_2$, $X_1 = X_2 = X_3 = X_4 = H$

Oil used as such for the next step.

20

Example 48:

Ethyl 4-[1-(4-methylbenzyl)benzimidazol-2-yl]-3,3-dimethylbutanoate

25 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$, $B = CH_2$, $A = \text{phenyl}$, $X_1 = X_2 = X_3 = H$, $X_4 = 4-Me$

Oil used as such for the next step.

30

Example 49:

Ethyl 4-[1-(4-fluorobenzyl)benzimidazol-2-yl]-3,3-dimethylbutanoate

35 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D =$

CO_2Et , A = phenyl, B = CH_2 , $\text{X}_1 = \text{X}_2 = \text{X}_3 = \text{H}$, $\text{X}_4 = 4\text{-F}$

Oil used as such for the next step.

05

Example 50:

Ethyl 4-[1-(4-methoxybenzyl)benzimidazol-2-yl]-3,3-dimethylbutanoate

10

Formula (I): $\text{R}_1 = \text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{R}_4 = \text{H}$, $n = 1$, D = CO_2Et , B = CH_2 , A = phenyl, $\text{X}_3 = 4\text{-MeO}$, $\text{X}_1 = \text{X}_2 = \text{X}_4 = \text{H}$

Oil used as such for the next step.

15

Example 51:

Ethyl 4-[1-(4-bromobenzyl)benzimidazol-2-yl]-3,3-dimethylbutanoate

20

Formula (I): $\text{R}_1 = \text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{R}_4 = \text{H}$, $n = 1$, D = CO_2Et , B = CH_2 , A = phenyl, $\text{X}_3 = 4\text{-Br}$, $\text{X}_1 = \text{X}_2 = \text{X}_4 = \text{H}$

Oil used as such for the next step.

25

Example 52:

Ethyl 4-[1-(4-chlorobenzyl)-5,6-dichlorobenzimidazol-2-yl]-3,3-dimethylbutanoate

30

Formula (I): $\text{R}_1 = \text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{R}_4 = \text{H}$, $n = 1$, D = CO_2Et , B = CH_2 , A = phenyl, $\text{X}_1 = 5\text{-Cl}$, $\text{X}_2 = 6\text{-Cl}$, $\text{X}_3 = 4\text{-Cl}$, $\text{X}_4 = \text{H}$

Oil used as such for the next step.

35

Example 53:

Ethyl 4-[1-(3-trifluoromethylbenzyl)benzimidazol-2-yl]-3,3-dimethylbutanoate

- 05 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{Et}$, $B = \text{CH}_2$, $A = \text{phenyl}$, $X_1 = \text{H}$, $X_2 = \text{H}$, $X_3 = \text{H}$, $X_4 = 3\text{-CF}_3$

Oil used as such for the next step.

10

Example 54:

Ethyl 4-[1-(4-chlorobenzyl)benzimidazol-2-yl]-3-methyl-3-ethylbutanoate

- 15 Formula (I): $R_1 = \text{CH}_3$, $R_2 = \text{C}_2\text{H}_5$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{Et}$, $B = \text{CH}_2$, $A = \text{phenyl}$, $X_1 = \text{H}$, $X_2 = \text{H}$, $X_3 = \text{H}$, $X_4 = 4\text{-Cl}$

Oil used as such for the next step.

20

Example 55:

Ethyl 4-[1-(4-chlorobenzyl)benzimidazol-2-yl]-3,3-diethylbutanoate

- 25 Formula (I): $R_1 = R_2 = \text{C}_2\text{H}_5$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{Et}$, $B = \text{CH}_2$, $A = \text{phenyl}$, $X_1 = \text{H}$, $X_2 = \text{H}$, $X_3 = 4\text{-Cl}$, $X_4 = \text{H}$

Oil used as such for the next step.

30

Example 56:

Ethyl 4-[1-(4-chlorobenzyl)benzimidazol-2-yl]-3-methylbutanoate

- 35 Formula (I): $R_1 = \text{CH}_3$, $R_2 = \text{H}$, $R_3 = R_4 = \text{H}$, $n = 1$, $D =$

CO_2Et , $\text{B} = \text{CH}_2$, $\text{A} = \text{phenyl}$, $\text{X}_1 = \text{X}_2 = \text{X}_3 = \text{H}$, $\text{X}_4 = 4\text{-Cl}$

Oil used as such for the next step.

05

Example 57:

Ethyl 4-[1-(naphth-2-ylmethyl)benzimidazol-2-yl]-3,3-dimethylbutanoate

10

Formula (I): $\text{R}_1 = \text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{R}_4 = \text{H}$, $n = 1$, $\text{D} = \text{CO}_2\text{Et}$, $\text{B} = \text{CH}_2$, $\text{A} = \text{phenyl}$, $\text{X}_3 + \text{X}_4$ form a phenyl ring in the 3,4-position, $\text{X}_1 = \text{X}_2 = \text{H}$

15

Oil used as such for the next step.

Example 58:

4-(1-Benzylbenzimidazol-2-yl)-3,3-dimethylbutanoic acid

20

Formula (I): $\text{R}_1 = \text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{R}_4 = \text{H}$, $n = 1$, $\text{D} = \text{CO}_2\text{H}$, $\text{B} = \text{CH}_2$, $\text{A} = \text{phenyl}$, $\text{X}_1 = \text{X}_2 = \text{X}_3 = \text{X}_4 = \text{H}$

25

9 g of ethyl 4-(1-benzylbenzimidazol-2-yl)-3,3-dimethylbutanoate, prepared in Example 47, are dissolved in a mixture composed of 90 ml of concentrated hydrochloric acid, 270 ml of water and 250 ml of acetic acid. The mixture is refluxed for 4 hours and the solvents are concentrated under vacuum. The residue is taken up with a 1 N solution of sodium hydroxide and the resulting mixture is washed with ether; the aqueous phase is acidified by having sulfur dioxide bubbled through it until the pH is 5-6, and the crystals formed are filtered off and washed with water and isopropyl ether to give 5.3 g of 4-(1-benzylbenzimidazol-2-yl)-

35

3,3-dimethylbutanoic acid in the form of crystals melting at 160-1°C.

The following compounds were prepared by the same procedure:

05

Example 59:

5-[1-(4-Chlorobenzyl)-5-fluorobenzimidazol-2-yl]mercaptopentanoic acid

10

Formula (I): $R_1 = R_2 = R_3 = R_4 = H$, $n = 3$, $D = CO_2H$,
 $B = S$, $A = \text{phenyl}$, $X_1 = 5-F$, $X_2 = X_3 = H$,
 $X_4 = 4-Cl$

Crystals melting at 184-186°C.

15

Example 60:

4-[1-(2-Fluoro-4-bromobenzyl)-5-chloroimidazo[4,5-b]-pyridin-2-yl]mercaptobutanoic acid

20

Formula (I): $R_1 = R_2 = R_3 = R_4 = H$, $n = 2$, $D = CO_2H$,
 $B = S$, $A = \text{pyridine}$, $X_1 = 5-Cl$, $X_2 = H$,
 $X_3 = 2-F$, $X_4 = 4-Br$

Crystals melting at 156-158°C.

25

Example 61:

2-[1-(4-Chlorobenzyl)-5-chloroimidazo[4,5-b]pyridin-2-yl]mercapto-2-methylpropanoic acid

30

Formula (I): $R_1 = R_2 = CH_3$, $n = 0$, $D = CO_2H$, $B = S$, $A =$
 pyridine , $X_1 = 5-Cl$, $X_2 = H$, $X_3 = 4-Cl$,
 $X_4 = H$

Crystals melting at 188-189°C.

35

Example 62:

4-[1-(4-Chlorobenzyl)imidazo[4,5-b]pyridin-2-yl]mercaptobutanoic acid

05 Formula (I): $R_1 = R_2 = R_3 = R_4 = H$, $n = 2$, $D = CO_2H$,
 $B = S$, $A = \text{pyridine}$, $X_1 = X_2 = H$, $X_3 =$
 4-Cl, $X_4 = H$

 Crystals melting at 121-122°C.

10

Example 63:

4-[1-(4-Chlorobenzyl)benzimidazol-2-yl]mercaptobutanoic acid

15 Formula (I): $R_1 = R_2 = R_3 = R_4 = H$, $n = 2$, $D = CO_2H$,
 $B = S$, $A = \text{phenyl}$, $X_1 = X_2 = X_3 = H$, $X_4 =$
 4-Cl

 Crystals melting at 187-190°C.

20

Example 64:

4-[1-(2,4-Dichlorobenzyl)benzimidazol-2-yl]mercaptobutanoic acid

25 Formula (I): $R_1 = R_2 = R_3 = R_4 = H$, $n = 2$, $D = CO_2H$,
 $B = S$, $A = \text{phenyl}$, $X_1 = X_2 = H$, $X_3 = 2\text{-Cl}$,
 $X_4 = 4\text{-Cl}$

 Crystals melting at 117-120°C.

30

Example 65:

4-[1-(4-Chlorobenzyl)-5-fluorobenzimidazol-2-yl]mercaptobutanoic acid

35 Formula (I): $R_1 = R_2 = R_3 = R_4 = H$, $n = 2$, $D = CO_2H$,

B = S, A = phenyl, $X_1 = 5\text{-F}$, $X_2 = X_3 = \text{H}$,
 $X_4 = 4\text{-Cl}$

Crystals melting at 176-178°C.

05

Example 66:

4-[1-(4-Methylbenzyl)benzimidazol-2-yl]-3,3-dimethyl-
butanoic acid

10 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, D =
 CO_2H , B = CH_2 , A = phenyl, $X_1 = X_2 = X_3 =$
H, $X_4 = 4\text{-Me}$

Crystals melting at 147-148°C.

15

Example 67:

4-[1-(4-Fluorobenzyl)benzimidazol-2-yl]-3,3-dimethyl-
butanoic acid

20 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, D =
 CO_2H , B = CH_2 , A = phenyl, $X_1 = X_2 = X_3 =$
H, $X_4 = 4\text{-F}$

Crystals melting at 180-181°C.

25

Example 68:

4-[1-(4-Methoxybenzyl)benzimidazol-2-yl]-3,3-dimethyl-
butanoic acid

30 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, D =
 CO_2H , B = CH_2 , A = phenyl, $X_1 = X_2 = X_3 =$
H, $X_4 = 4\text{-MeO}$

Crystals melting at 149-150°C.

35

Example 69:

4-[1-(4-Bromobenzyl)benzimidazol-2-yl]-3,3-dimethyl-
butanoic acid

- 05 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D =$
 CO_2H , $B = \text{CH}_2$, $A = \text{phenyl}$, $X_1 = X_2 = X_3 =$
 H , $X_4 = 4\text{-Br}$

Crystals melting at 171-172°C.

10

Example 70:

4-[1-(4-Chlorobenzyl)-5,6-dichlorobenzimidazol-2-yl]-
3,3-dimethylbutanoic acid

- 15 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D =$
 CO_2H , $B = \text{CH}_2$, $A = \text{phenyl}$, $X_1 = 5\text{-Cl}$, $X_2 =$
 6-Cl , $X_3 = \text{H}$, $X_4 = 4\text{-Cl}$

Crystals melting at 197-199°C.

20

Example 71:

4-[1-(3-Trifluoromethylbenzyl)benzimidazol-2-yl]-3,3-
dimethylbutanoic acid

- 25 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D =$
 CO_2H , $B = \text{CH}_2$, $A = \text{phenyl}$, $X_1 = X_2 = X_3 =$
 H , $X_4 = 3\text{-CF}_3$

Crystals melting at 163-164°C.

30

Example 72:

[1-[1-(4-Chlorobenzyl)-5-fluorobenzimidazol-2-yl]-
methylcyclopent-1-yl]acetic acid

- 35 Formula (I): $R_1 + R_2 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, $R_3 = R_4 = \text{H}$, $n =$

1, D = CO₂H, B = CH₂, A = phenyl, X₁ =
5-F, X₂ = X₃ = H, X₄ = 4-Cl

Crystals melting at 164-165°C.

05

Example 73:

[1-[1-(4-Chlorobenzyl)-5-fluorobenzimidazol-2-yl]-
methylcyclohex-1-yl]acetic acid

10

Formula (I): R₁ + R₂ = CH₂CH₂CH₂CH₂CH₂, R₃ = R₄ = H,
n = 1, D = CO₂H, B = CH₂, A = phenyl, X₁ =
5-F, X₂ = X₃ = H, X₄ = 4-Cl

Crystals melting at 182-184°C.

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Example 74:

4-[1-(4-Chlorobenzyl)-5-fluorobenzimidazol-2-yl]-3,3-
dimethylbutanoic acid

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Formula (I): R₁ = R₂ = CH₃, R₃ = R₄ = H, n = 1, D =
CO₂H, B = CH₂, A = phenyl, X₁ = 5-F, X₂ =
X₃ = H, X₄ = 4-Cl

Crystals melting at 164-165°C.

25

Example 75:

4-[1-(4-Chlorobenzyl)benzimidazol-2-yl]-3-methyl-3-
ethylbutanoic acid

30

Formula (I): R₁ = C₂H₅, R₂ = CH₃, R₃ = R₄ = H, n = 1,
D = CO₂H, B = CH₂, A = phenyl, X₁ = X₂ =
X₃ = H, X₄ = 4-Cl

Crystals melting at 120-123°C.

35

Example 76:

4-[1-(2-Fluoro-4-bromobenzyl)benzimidazol-2-yl]-3,3-dimethylbutanoic acid

- 05 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{H}$, $B = \text{CH}_2$, $A = \text{phenyl}$, $X_1 = X_2 = \text{H}$, $X_3 = 2\text{-F}$, $X_4 = 4\text{-Br}$

Crystals melting at 147-148°C.

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Example 77:

4-[1-(4-Chlorobenzyl)benzimidazol-2-yl]-3,3-dimethylbutanoic acid

- 15 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{H}$, $B = \text{CH}_2$, $A = \text{phenyl}$, $X_1 = X_2 = X_3 = \text{H}$, $X_4 = 4\text{-Cl}$

Crystals melting at 170-171°C.

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Example 78:

4-[1-(4-Chlorobenzyl)-5-methoxybenzimidazol-2-yl]-3,3-dimethylbutanoic acid

- 25 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{H}$, $B = \text{CH}_2$, $A = \text{phenyl}$, $X_1 = 5\text{-MeO}$, $X_2 = X_3 = \text{H}$, $X_4 = 4\text{-Cl}$

Crystals melting at 174-176°C.

30

Example 79:

4-[1-(4-Chlorobenzyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoic acid

- 35 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D =$

CO_2H , $\text{B} = \text{CH}_2$, $\text{A} = \text{phenyl}$, $\text{X}_1 = 5\text{-Cl}$, $\text{X}_2 =$
 $\text{X}_3 = \text{H}$, $\text{X}_4 = 4\text{-Cl}$

Crystals melting at 205-207°C.

05

Example 80:

4-[1-(3,4-Dichlorobenzyl)-5-fluorobenzimidazol-2-yl]-
3,3-dimethylbutanoic acid

10

Formula (I): $\text{R}_1 = \text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{R}_4 = \text{H}$, $n = 1$, $\text{D} =$
 CO_2H , $\text{B} = \text{CH}_2$, $\text{A} = \text{phenyl}$, $\text{X}_1 = 5\text{-F}$, $\text{X}_2 =$
 H , $\text{X}_3 = 3\text{-Cl}$, $\text{X}_4 = 4\text{-Cl}$

Crystals melting at 177-180°C.

15

Example 81:

4-[1-(4-Nitrobenzyl)benzimidazol-2-yl]-3,3-dimethyl-
butanoic acid

20

Formula (I): $\text{R}_1 = \text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{R}_4 = \text{H}$, $n = 1$, $\text{D} =$
 CO_2H , $\text{B} = \text{CH}_2$, $\text{A} = \text{phenyl}$, $\text{X}_1 = \text{X}_2 = \text{X}_3 =$
 H , $\text{X}_4 = 4\text{-NO}_2$

Crystals melting at 192-194°C.

25

Example 82:

4-[1-(4-Chlorobenzyl)benzimidazol-2-yl]-3,3-diethyl-
butanoic acid

30

Formula (I): $\text{R}_1 = \text{R}_2 = \text{C}_2\text{H}_5$, $\text{R}_3 = \text{R}_4 = \text{H}$, $n = 1$, $\text{D} =$
 CO_2H , $\text{B} = \text{CH}_2$, $\text{A} = \text{phenyl}$, $\text{X}_1 = \text{X}_2 = \text{X}_3 =$
 H , $\text{X}_4 = 4\text{-Cl}$

Crystals melting at 139-140°C.

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Example 83:

4-[1-(4-Chlorobenzyl)benzimidazol-2-yl]-3-methyl-
butanoic acid

05 Formula (I): $R_1 = H$, $R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D =$
 CO_2H , $B = CH_2$, $A = \text{phenyl}$, $X_1 = X_2 = X_3 =$
 H , $X_4 = 4-Cl$

Crystals melting at 201-202°C.

10

Example 84:

4-[1-(Naphth-2-ylmethyl)benzimidazol-2-yl]-3,3-di-
methylbutanoic acid

15 Formula (I): $A = \text{phenyl}$, $B = CH_2$, $D = CO_2H$, $R_1 = R_2 =$
 CH_3 , $R_3 = R_4 = H$, $n = 1$, $X_1 = X_2 = H$, $X_3 +$
 X_4 form a phenyl ring in the 3,4-position

Crystals melting at 147-149°C.

20

Example 85:

4-[1-(4-Chlorobenzyl)benzimidazol-2-yl]-3,3-dimethyl-
butanamide

25 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $B =$
 CH_2 , $D = CONH_2$, $A = \text{phenyl}$, $X_3 = 4-Cl$,
 $X_1 = X_2 = X_4 = H$

30 11.7 g of 4-[1-(4-chlorobenzyl)benzimidazol-2-
yl]-3,3-dimethylbutanoic acid, prepared in Example 77,
are added to 100 ml of anhydrous toluene and 3 ml of
thionyl chloride. The mixture is heated at 80°C for 4
hours and the solvents are evaporated off under vacuum.
The residue is taken up in 50 ml of chloroform, stabi-
35 lized with amylene, and added dropwise to 50 ml of 28%

ammonium hydroxide. When the addition is complete, the mixture is stirred at room temperature for 1 hour 30 minutes and then decanted. The organic phase is dried over magnesium sulfate and the solvent is evaporated off to dryness under vacuum. The residue crystallizes from isopropyl ether and is recrystallized from acetonitrile to give 5.1 g of 4-[1-(4-chlorobenzyl)benzimidazol-2-yl]-3,3-dimethylbutanamide in the form of crystals melting at 163-165°C.

Example 86:

4-[1-(4-Chlorobenzyl)benzimidazol-2-yl]-3,3-dimethylbutyronitrile

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $B = CH_2$, $D = CN$, $A = \text{phenyl}$, $X_3 = 4-Cl$, $X_1 = X_2 = X_4 = H$

2.7 g of 4-[1-(4-chlorobenzyl)benzimidazol-2-yl]-3,3-dimethylbutanamide are dissolved in 50 ml of chloroform. 2.3 ml of phosphorus oxychloride are added and the mixture is refluxed for 5 hours. After cooling, the solvents are evaporated off under vacuum and the residue is taken up with water and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and evaporated to dryness under vacuum to give an oil which crystallizes from ether. The crystals are filtered off, washed with ether and then dried to give 2.5 g of 4-[1-(4-chlorobenzyl)benzimidazol-2-yl]-3,3-dimethylbutyronitrile in the form of crystals melting at 110°C.

Example 87:

4-[1-(4-Hydroxybenzyl)benzimidazol-2-yl]-3,3-dimethylbutanoic acid

05 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $B = \text{CH}_2$, $D = \text{CO}_2\text{H}$, $A = \text{phenyl}$, $X_4 = 4\text{-OH}$, $X_1 = X_2 = X_3 = \text{H}$

10 2 g of 4-[1-(4-methoxybenzyl)benzimidazol-2-yl]-3,3-dimethylbutanoic acid, prepared in Example 68, are dissolved in 40 ml of acetic acid and 40 ml of 48% hydrobromic acid. The mixture is refluxed for 3 hours and the solvents are evaporated off under vacuum. The residue is taken up with a 1 N solution of sodium hydroxide so as to adjust the pH to 9-10, and the resulting aqueous phase is washed with ether and then acidified with sulfur dioxide to pH 5.5. The crystals obtained are filtered off, washed with water and then with ether and then chromatographed on silica gel in a 9:1 chloroform/methanol eluent to give 0.4 g of 4-[1-(4-hydroxybenzyl)benzimidazol-2-yl]-3,3-dimethylbutanoic acid in the form of crystals melting at 215-216°C.

Example 88:

25 Acid chloride ethyl ester of trans-cyclobutane-1,2-dicarboxylic acid

Formula (VIII): $R_1 + R_5 = \text{CH}_2\text{-CH}_2$, $R_2 = R_6 = \text{H}$, $D = \text{CO}_2\text{Et}$, $n = 0$

30

14.2 g of ethyl trans-cyclobutane-1,2-dicarboxylate are dissolved in 100 ml of ethanol, and 2.8 g of sodium hydroxide pellets are added together with 30 ml of water. The mixture is refluxed for 1 hour and the solvents are evaporated off under vacuum. The

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residue is taken up with water and washed with ether. The aqueous phase is acidified with dilute hydrochloric acid and extracted with ether. The ether phase is dried over magnesium sulfate and evaporated under vacuum to give 7.5 g of the monoethyl ester of trans-cyclobutane-1,2-dicarboxylic acid. 6 ml of thionyl chloride and 50 ml of toluene are added to these 7.5 g and the mixture is refluxed for two hours. The solvents are evaporated off to dryness to give 9 g of the acid chloride ethyl ester of trans-cyclobutane-1,2-dicarboxylic acid in the form of an oil, which is used as such for the next step.

Example 89:

Ethyl trans-2-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]cyclobutane-1-carboxylate

Formula (I): $B = CR_5R_6$, $R_1 + R_5 = CH_2CH_2$, $R_2 = R_6 = H$,
 $n = 0$, $D = CO_2Et$, $A = \text{phenyl}$, $X_1 = 5-F$,
 $X_2 = H$, $X_3 = 4-Cl$, $X_4 = H$

Prepared by the procedure of Example 34.
Oil used as such for the next step.

Example 90:

Trans-2-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]-cyclobutane-1-carboxylic acid

Formula (I): $B = CR_5R_6$, $R_1 + R_5 = CH_2CH_2$, $R_2 = R_6 = H$,
 $n = 0$, $D = CO_2H$, $A = \text{phenyl}$, $X_1 = 5-F$,
 $X_2 = H$, $X_3 = 4-Cl$, $X_4 = H$

Prepared by the procedure of Example 58.
Crystals melting at 173-175°C.

Example 91:

Ethyl 4-[1-(4-chlorophenylmethyl)-5-chloroimidazo[4,5-b]pyridin-2-yl]-3,3-dimethylbutanoate

05 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D =$
COOEt, $A = 2\text{-pyridine}$, $B = \text{CH}_2$, $X_1 = 5\text{-Cl}$,
 $X_2 = X_3 = \text{H}$, $X_4 = 4\text{-Cl}$

10 16.5 g of 2-(4-chlorobenzylamino)-3-amino-5-chloropyridine, prepared in Example 14, are dissolved in a mixture consisting of 25 ml of ethanol and 25 ml of acetic acid. 12.1 g of ethyl 4-formyl-3,3-dimethylbutanoate are added and the mixture is stirred for 4 hours at room temperature. The solvents are evaporated
15 off to dryness under vacuum and the residue is dissolved in 200 ml of 1,2-dimethoxyethane. 20 g of iodine are added and the solution is heated for 16 hours at 50°C. The solvent is then evaporated off to dryness under vacuum and the residue is taken up with water and
20 extracted with ether. The ether phase is washed with water, dried over magnesium sulfate and evaporated. The oil obtained is chromatographed on silica gel in a 7:3 cyclohexane/ethyl acetate eluent to give 10 g of ethyl 4-[1-(4-chlorophenylmethyl)-5-chloroimidazo[4,5-b]pyridin-2-yl]-3,3-dimethylbutanoate in the form of an
25 oil, which is used as such for the next step.

Preparation of ethyl 4-formyl-3,3-dimethylbutanoate:

30 40 g of the acid chloride ethyl ester of 3,3-dimethylglutaric acid, prepared in Example 28, are dissolved in 400 ml of tetrahydrofuran. 2 g of 5% palladium-on-charcoal and 22.8 ml of 2,6-lutidine are added and the mixture is hydrogenated at normal pressure and room temperature. When the absorption of
35

hydrogen has ceased, the catalyst is filtered off and the solvent is evaporated off under vacuum. The residue is taken up with water and extracted with ether. The ether phase is washed with a dilute solution of hydrochloric acid in the cold, washed with a solution of sodium bicarbonate in the cold, dried over magnesium sulfate and evaporated under vacuum to give, after distillation of the residue, 18 g of ethyl 4-formyl-3,3-dimethylbutanoate in the form of a liquid with a boiling point b.p.₂₀ of 112-118°C.

Example 92:

4-[1-(4-Chlorophenylmethyl)-5-chloroimidazo[4,5-b]pyridin-2-yl]-3,3-dimethylbutanoic acid

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = COOH$, $A = 2$ -pyridine, $B = CH_2$, $X_1 = 5-Cl$, $X_2 = X_3 = H$, $X_4 = 4-Cl$

If the procedure of Example 58 is followed, except that ethyl 4-[1-(4-chlorophenylmethyl)-5-chloroimidazo[4,5-b]pyridin-2-yl]-3,3-dimethylbutanoate, prepared in Example 91, is used as the starting material, 4-[1-(4-chlorophenylmethyl)-5-chloroimidazo[4,5-b]pyridin-2-yl]-3,3-dimethylbutanoic acid is obtained in the form of crystals melting at 120-122°C.

Example 93:

2-(4-Methylthiobenzyl)amino-5-fluoronitrobenzene

Formula (V): $X_1 = 5-F$, $X_2 = X_3 = H$, $X_4 = 4-SCH_3$, $A =$ phenyl

24.8 g of 2-amino-5-fluoronitrobenzene and 27.6 g of 4-methylthiobenzyl chloride are mixed and

14.4 g of anhydrous sodium acetate and 0.3 g of iodine are added. The mixture is heated at 120°C for 12 hours, with stirring, and is then cooled, taken up with a dilute solution of hydrochloric acid and extracted with ethyl acetate. The organic phase is washed with dilute hydrochloric acid and then with water, dried over magnesium sulfate and evaporated to dryness. The oil obtained crystallizes from isopropyl ether to give 23.8 g of 2-(4-methylthiobenzyl)amino-5-fluoronitrobenzene in the form of crystals melting at 117°C.

Example 94:

2-(4-Methylthiobenzyl)amino-5-fluoroaniline

Formula (IV): $X_1 = 5-F$, $X_2 = X_3 = H$, $X_4 = 4-SCH_3$, A = phenyl

Prepared by the procedure of Example 8.

Crystals melting at 112°C.

Example 95:

Ethyl 4-[1-(4-methylthiobenzyl)-5-fluorobenzimidazol-2-yl]-3,3-dimethylbutanoate

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, D = CO_2Et , A = phenyl, B = CH_2 , $X_1 = 5-F$, $X_2 = X_3 = H$, $X_4 = 4-SCH_3$

Prepared by the procedure of Example 34.

Oil used as such for the next step.

Example 96:

4-[1-(4-Methylthiobenzyl)-5-fluorobenzimidazol-2-yl]-
3,3-dimethylbutanoic acid

05 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D =$
 CO_2H , $A = \text{phenyl}$, $B = \text{CH}_2$, $X_1 = 5\text{-F}$, $X_2 =$
 $X_3 = \text{H}$, $X_4 = 4\text{-SCH}_3$

Prepared by the procedure of Example 58.

10 Crystals melting at 154-155°C.

Example 97:

4-[1-(4-Methylsulfonylbenzyl)-5-fluorobenzimidazol-2-
yl]-3,3-dimethylbutanoic acid

15 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D =$
 CO_2H , $A = \text{phenyl}$, $B = \text{CH}_2$, $X_1 = 5\text{-F}$, $X_2 =$
 $X_3 = \text{H}$, $X_4 = 4\text{-SO}_2\text{CH}_3$

20 3 g of 4-[1-(4-methylthiobenzyl)-5-fluorobenz-
imidazol-2-yl]-3,3-dimethylbutanoic acid, prepared in
Example 96, are dissolved in 100 ml of methanol. The
mixture is cooled to 0°C and 3.8 g of 70% metachloro-
perbenzoic acid are added. When the addition is com-
plete, the mixture is stirred at room temperature for
25 10 hours. The crystals formed are filtered off, washed
with methanol and then dried to give 2.4 g of 4-[1-(4-
methylsulfonylbenzyl)-5-fluorobenzimidazol-2-yl]-3,3-
dimethylbutanoic acid in the form of crystals melting
30 at 221-222°C.

Example 98:

2-(3,4-Dichlorobenzyl)amino-5-chloronitrobenzene

35 Formula (V): $X_1 = 5\text{-Cl}$, $X_2 = \text{H}$, $X_3 = 3\text{-Cl}$, $X_4 = 4\text{-Cl}$,

A = phenyl

Prepared by the procedure of Example 3.
Crystals melting at 129°C.

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Example 99:

2-(3,4-Dichlorobenzyl)amino-5-chloroaniline

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Formula (IV): $X_1 = 5\text{-Cl}$, $X_2 = \text{H}$, $X_3 = 3\text{-Cl}$, $X_4 = 4\text{-Cl}$,
A = phenyl

Prepared by the procedure of Example 8.
Crystals melting at 80°C.

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Example 100:

Ethyl 4-[1-(3,4-dichlorobenzyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoate

20

Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{Et}$,
A = phenyl, $B = \text{CH}_2$, $X_1 = 5\text{-Cl}$,
 $X_2 = \text{H}$, $X_3 = 3\text{-Cl}$, $X_4 = 4\text{-Cl}$

Prepared by the procedure of Example 34.
Oil used as such for the next step.

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Example 101:

4-[1-(3,4-Dichlorobenzyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoic acid

30

Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{H}$,
A = phenyl, $B = \text{CH}_2$, $X_1 = 5\text{-Cl}$,
 $X_2 = \text{H}$, $X_3 = 4\text{-Cl}$, $X_5 = 3\text{-Cl}$

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Prepared by the procedure of Example 58.
Crystals melting at 183-184°C.

Example 102:

2-(2-Fluoro-4-bromobenzyl)amino-5-fluoronitrobenzene

Formula (V): $X_1 = 5\text{-F}$, $X_2 = \text{H}$, $X_3 = 2\text{-F}$, $X_4 = 4\text{-Br}$, A =
phenyl

Prepared by the procedure of Example 1.
Crystals melting at 130°C.

Example 103:

2-(2-Fluoro-4-bromobenzyl)amino-5-fluoroaniline

Formula (IV): $X_1 = 5\text{-F}$, $X_2 = \text{H}$, $X_3 = 2\text{-F}$, $X_4 = 4\text{-Br}$,
A = phenyl

Prepared by the procedure of Example 8.
Oil used as such for the next step.

Example 104:

Ethyl 4-[1-(2-fluoro-4-bromobenzyl)-5-fluorobenz-
imidazol-2-yl]-3,3-dimethylbutanoate

Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, D =
 CO_2Et , A = phenyl, B = CH_2 , $X_1 = 5\text{-F}$, $X_2 =$
H, $X_3 = 2\text{-F}$, $X_4 = 4\text{-Br}$

Prepared by the procedure of Example 34.
Oil used as such for the next step.

Example 105:

4-[1-(2-Fluoro-4-bromobenzyl)-5-fluorobenzimidazol-2-
yl]-3,3-dimethylbutanoic acid

Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, D =
 CO_2H , A = phenyl, B = CH_2 , $X_1 = 5\text{-F}$, $X_2 =$

H, $X_3 = 2\text{-F}$, $X_4 = 4\text{-Br}$

Prepared by the procedure of Example 58.

Crystals melting at $145\text{-}7^\circ\text{C}$.

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Example 106:

2-(4-Bromobenzyl)amino-5-fluoronitrobenzene

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Formula (V): $X_1 = 5\text{-F}$, $X_2 = \text{H}$, $X_3 = 4\text{-Br}$, $X_4 = \text{H}$, A =
phenyl

Prepared by the procedure of Example 1.

Crystals melting at 163°C .

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Example 107:

2-(4-Bromobenzyl)amino-5-fluoroaniline

Formula (IV): $X_1 = 5\text{-F}$, $X_2 = \text{H}$, $X_3 = 4\text{-Br}$, $X_4 = \text{H}$, A =
phenyl

20

Prepared by the procedure of Example 8.

Crystals melting at 97°C .

Example 108:

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Ethyl 4-[1-(4-bromobenzyl)-5-fluorobenzimidazol-2-yl]-
3,3-dimethylbutanoate

Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, D =
 CO_2Et , A = phenyl, B = CH_2 , $X_1 = 5\text{-F}$, $X_2 =$
30 $X_3 = \text{H}$, $X_4 = 4\text{-Br}$

Prepared by the procedure of Example 34.

Oil used as such for the next step.

35

Example 109:

4-[1-(4-Bromobenzyl)-5-fluorobenzimidazol-2-yl]-3,3-dimethylbutanoic acid

05 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2H$, $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5-F$, $X_2 = X_3 = H$, $X_4 = 4-Br$

Prepared by the procedure of Example 58.

10 Crystals melting at 172-174°C.

Example 110:

2-(4-Methoxybenzyl)amino-5-chloronitrobenzene

15 Formula (V): $X_1 = 5-Cl$, $X_2 = X_3 = H$, $X_4 = 4-OCH_3$, $A = \text{phenyl}$

Prepared by the procedure of Example 3.

Crystals melting at 114°C.

Example 111:

2-(4-Methoxybenzyl)amino-5-chloroaniline

25 Formula (IV): $X_1 = 5-Cl$, $X_2 = X_3 = H$, $X_4 = 4-OCH_3$, $A = \text{phenyl}$

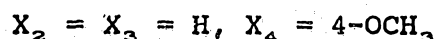
Prepared by the procedure of Example 8.

Crystals melting at 108°C.

30 Example 112:

Ethyl 4-[1-(4-methoxybenzyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoate

35 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$, $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5-Cl$,



Prepared by the procedure of Example 34.

Oil used as such for the next step.

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Example 113:

4-[1-(4-Methoxybenzyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoic acid

10 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2H$, $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5-Cl$, $X_2 = X_3 = H$, $X_4 = 4-OCH_3$

Prepared by the procedure of Example 58.

15 Crystals melting at 144-145°C.

Example 114:

2-(4-Methylthiobenzyl)amino-5-chloronitrobenzene

20 Formula (V): $X_1 = 5-Cl$, $X_2 = X_3 = H$, $X_4 = 4-SCH_3$, $A = \text{phenyl}$

Prepared by the procedure of Example 93.

Crystals melting at 74°C.

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Example 115:

2-(4-Methylthiobenzyl)amino-5-chloroaniline

30 Formula (IV): $X_1 = 5-Cl$, $X_2 = X_3 = H$, $X_4 = 4-SCH_3$, $A = \text{phenyl}$

Prepared by the procedure of Example 8.

Crystals melting at 131°C.

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Example 116:

Ethyl 4-[1-(4-methylthiobenzyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoate

05 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D =$
 CO_2Et , $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5-Cl$,
 $X_2 = X_3 = H$, $X_4 = 4-SCH_3$

Prepared by the procedure of Example 34.

10 Oil used as such for the next step.

Example 117:

4-[1-(4-Methylthiobenzyl)-5-chlorobenzimidazol-2-yl]-
3,3-dimethylbutanoic acid

15 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D =$
 CO_2H , $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5-Cl$,
 $X_2 = X_3 = H$, $X_4 = 4-SCH_3$

20 Prepared by the procedure of Example 58.
Crystals melting at 138-139°C.

Example 118:

4-[1-(4-Methylsulfoxybenzyl)-5-chlorobenzimidazol-2-
25 yl]-3,3-dimethylbutanoic acid

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D =$
 CO_2H , $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5-Cl$,
 $X_2 = X_3 = H$, $X_4 = 4-SOCH_3$

30

5 g of 4-[1-(4-methylthiobenzyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoic acid, prepared in Example 117, are dissolved in 350 ml of methanol. The solution is stirred at 0°C and 2.9 g of 75% metachloro-
35 perbenzoic acid are then added. The mixture is stirred

in the cold for 30 minutes and then at room temperature for 4 hours. The solution is concentrated to dryness, the residue is taken up with water and ether and the crystals formed are filtered off, washed with ether and then chromatographed on silica gel in a 90:10:0.5 ether/methanol/acetic acid eluent to give 2.5 g of 4-[1-(4-methylsulfoxybenzyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoic acid in the form of crystals melting at 161-2°C.

Example 119:

4-[1-(4-Methylsulfonylbzyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoic acid

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2H$, $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5-Cl$, $X_2 = X_3 = H$, $X_4 = 4-SO_2CH_3$

Prepared by the procedure of Example 97.
Crystals melting at 228-30°C.

Example 120:

2-(2-Fluoro-4-chlorobenzyl)amino-5-chloronitrobenzene

Formula (V): $X_1 = 5-Cl$, $X_2 = H$, $X_3 = 2-F$, $X_4 = 4-Cl$, $A = \text{phenyl}$

Prepared by the procedure of Example 3.
Crystals melting at 130°C.

Example 121:

2-(2-Fluoro-4-chlorobenzyl)amino-5-chloroaniline

Formula (IV): $X_1 = 5-Cl$, $X_2 = H$, $X_3 = 2-F$, $X_4 = 4-Cl$, $A = \text{phenyl}$

Prepared by the procedure of Example 8.
Oil used as such for the next step.

Example 122:

05 Ethyl 4-[1-(2-fluoro-4-chlorobenzyl)-5-chlorobenz-
imidazol-2-yl]-3,3-dimethylbutanoate

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D =$
CO₂Et, $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5\text{-Cl}$,
10 $X_2 = H$, $X_3 = 2\text{-F}$, $X_4 = 4\text{-Cl}$

Prepared by the procedure of Example 34.
Oil used as such for the next step.

15 Example 123:

4-[1-(2-Fluoro-4-chlorobenzyl)-5-chlorobenzimidazol-2-
yl]-3,3-dimethylbutanoic acid

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D =$
20 CO₂H, $B = CH_2$, $X_1 = 5\text{-Cl}$, $X_2 = H$, $X_3 = 2\text{-F}$, $X_4 = 4\text{-Cl}$

Prepared by the procedure of Example 58.
Crystals melting at 186-188°C.

25 Example 124:

2-(4-Chlorobenzyl)amino-5-bromonitrobenzene

Formula (V): $X_1 = 5\text{-Br}$, $X_2 = X_3 = H$, $X_4 = 4\text{-Cl}$, $A =$
30 phenyl

Prepared by the procedure of Example 3.
Crystals melting at 118°C.

Example 125:

2-(4-Chlorobenzyl)amino-5-bromoaniline

Formula (IV): $X_1 = 5\text{-Br}$, $X_2 = X_3 = \text{H}$, $X_4 = 4\text{-Cl}$, A =
phenyl

Prepared by the procedure of Example 8.
Crystals melting at 149°C.

10 Example 126:

Ethyl 4-[1-(4-chlorobenzyl)-5-bromobenzimidazol-2-yl]-
3,3-dimethylbutanoate

Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, D =
CO₂Et, A = phenyl, B = CH₂, $X_1 = 5\text{-Br}$,
 $X_2 = X_3 = \text{H}$, $X_4 = 4\text{-Cl}$

Prepared by the procedure of Example 34.
Oil used as such for the next step.

20

Example 127:

4-[1-(4-Chlorobenzyl)-5-bromobenzimidazol-2-yl]-3,3-
dimethylbutanoic acid

25 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, D =
CO₂H, A = phenyl, B = CH₂, $X_1 = 5\text{-Br}$,
 $X_2 = X_3 = \text{H}$, $X_4 = 4\text{-Cl}$

Prepared by the procedure of Example 58.
Crystals melting at 219-221°C.

30

Example 128:

2-(4-Methoxybenzyl)amino-5-fluoronitrobenzene

35 Formula (V): $X_1 = 5\text{-F}$, $X_2 = X_3 = \text{H}$, $X_4 = 4\text{-OMe}$, A =

phenyl

Prepared by the procedure of Example 1.
Crystals melting at 106°C.

05

Example 129:

2-(4-Methoxybenzyl)amino-5-fluoroaniline

Formula (IV): $X_1 = 5-F$, $X_2 = X_3 = H$, $X_4 = 4-OMe$, A =
phenyl

10

Prepared by the procedure of Example 8.
Crystals melting at 123°C.

15

Example 130:

Ethyl 4-[1-(4-methoxybenzyl)-5-fluorobenzimidazol-2-yl]-3,3-dimethylbutanoate

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, D =
 CO_2Et , A = phenyl, $X_1 = 5-F$, $X_2 = X_3 = H$,
 $X_4 = 4-OMe$

20

Prepared by the procedure of Example 34.
Oil used as such for the next step.

25

Example 131:

4-[1-(4-Methoxybenzyl)-5-fluorobenzimidazol-2-yl]-3,3-dimethylbutanoic acid

30

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, D =
 CO_2H , A = phenyl, B = CH_2 , $X_1 = 5-F$, $X_2 =$
 $X_3 = H$, $X_4 = 4-OMe$

35

Prepared by the procedure of Example 58.
Crystals melting at 137-138°C.

Example 132:

2-(2-Fluoro-4-bromobenzyl)amino-5-chloronitrobenzene

Formula (V): $X_1 = 5\text{-Cl}$, $X_2 = \text{H}$, $X_3 = 2\text{-F}$, $X_4 = 4\text{-Br}$,
A = phenyl

Prepared by the procedure of Example 3.
Crystals melting at 130°C.

Example 133:

2-(2-Fluoro-4-bromobenzyl)amino-5-chloroaniline

Formula (IV): $X_1 = 5\text{-Cl}$, $X_2 = \text{H}$, $X_3 = 2\text{-F}$, $X_4 = 4\text{-Br}$,
A = phenyl

Prepared by the procedure of Example 8.
Crystals melting at 89°C.

Example 134:

Ethyl 4-[1-(2-fluoro-4-bromobenzyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoate

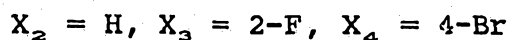
Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{Et}$,
A = phenyl, B = CH_2 , $X_1 = 5\text{-Cl}$,
 $X_2 = \text{H}$, $X_3 = 2\text{-F}$, $X_4 = 4\text{-Br}$

Prepared by the procedure of Example 34.
Oil used as such for the next step.

Example 135:

4-[1-(2-Fluoro-4-bromobenzyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoic acid

Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{H}$,
A = phenyl, B = CH_2 , $X_1 = 5\text{-Cl}$,



Prepared by the procedure of Example 58.
Crystals melting at 176-7°C.

05

Example 136:

2-(4-Bromobenzyl)amino-5-chloronitrobenzene

10

Formula (V): $X_1 = 5-Cl$, $X_2 = X_3 = H$, $X_4 = 4-Br$, A =
phenyl

Prepared by the procedure of Example 3.
Crystals melting at 136°C.

15

Example 137:

2-(4-Bromobenzyl)amino-5-chloroaniline

Formula (IV): $X_1 = 5-Cl$, $X_2 = X_3 = H$, $X_4 = 4-Br$, A =
phenyl

20

Prepared by the procedure of Example 8.
Crystals melting at 152°C.

Example 138:

25

Ethyl 4-[1-(4-bromobenzyl)-5-chlorobenzimidazol-2-yl]-
3,3-dimethylbutanoate

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, D =
 CO_2Et , A = phenyl, B = CH_2 , $X_1 = 5-Cl$,
30 $X_2 = X_3 = H$, $X_4 = 4-Br$

Prepared by the procedure of Example 34.
Oil used as such for the next step.

35

Example 139:

4-[1-(4-Bromobenzyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoic acid

05 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{H}$, $A = \text{phenyl}$, $B = \text{CH}_2$, $X_1 = 5\text{-Cl}$,
 $X_2 = X_3 = \text{H}$, $X_4 = 4\text{-Br}$

Prepared by the procedure of Example 34.

10 Oil used as such for the next step.

Example 140:

2-(Naphth-2-ylmethyl)amino-5-chloronitrobenzene

15 Formula (V): $X_1 = 5\text{-Cl}$, $X_2 = \text{H}$, $A = \text{phenyl}$, $X_3 + X_4$
form a phenyl ring in the 3,4-position

Prepared by the procedure of Example 93.

Crystals melting at 143°C.

20

Example 141:

2-(Naphth-2-ylmethyl)amino-5-chloroaniline

Formula (IV): $X_1 = 5\text{-Cl}$, $X_2 = \text{H}$, $A = \text{phenyl}$, $X_3 + X_4$
25 form a phenyl ring in the 3,4-position

Prepared by the procedure of Example 8.

Crystals melting at 124°C.

30 Example 142:

Ethyl 4-[1-(naphth-2-ylmethyl)-5-chlorobenzimidazol-2-yl]-3,3-dimethylbutanoate

35 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{Et}$, $A = \text{phenyl}$, $B = \text{CH}_2$, $X_1 = 5\text{-Cl}$,

$X_2 = H$, X_3 and X_4 form a phenyl ring in the 3,4-position

Prepared by the procedure of Example 34.

05

Oil used as such for the next step.

Example 143:

4-[1-(Naphth-2-ylmethyl)-5-chlorobenzimidazol-2-yl]-
3,3-dimethylbutanoic acid

10

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2H$, $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5-Cl$,
 $X_2 = H$, X_3 and X_4 form a phenyl ring in the 3,4-position

15

Prepared by the procedure of Example 58.

Crystals melting at 168-169°C.

Example 144:

20

1-(Naphth-2-ylmethyl)amino-5-fluoronitrobenzene

Formula (V): $X_1 = 5-F$, $X_2 = H$, $A = \text{phenyl}$, X_3 and X_4
form a phenyl ring in the 3,4-position

25

Prepared by the procedure of Example 93.

Crystals melting at 170°C.

Example 145:

1-(Naphth-2-ylmethyl)amino-5-fluoroaniline

30

Formula (IV): $X_1 = 5-F$, $X_2 = H$, $A = \text{phenyl}$, X_3 and X_4
form a phenyl ring in the 3,4-position

Prepared by the procedure of Example 8.

35

Crystals melting at 118°C.

Example 146:

Ethyl 4-[1-(naphth-2-ylmethyl)-5-fluorobenzimidazol-2-yl]-3,3-dimethylbutanoate

05 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$, $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5-F$, $X_2 = H$, X_3 and X_4 form a phenyl ring in the 3,4-position

10 Prepared by the procedure of Example 34.
 Oil used as such for the next step.

Example 147:

15 4-[1-(Naphth-2-ylmethyl)-5-fluorobenzimidazol-2-yl]-3,3-dimethylbutanoic acid

20 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2H$, $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5-F$, $X_2 = H$, X_3 and X_4 form a phenyl ring in the 3,4-position

 Prepared by the procedure of Example 58.
 Crystals melting at 157-158°C.

25 Example 148:

 Acid chloride ethyl ester of cyclopropane-1,1-diacetic acid

30 Formula (VIII): $R_5 = R_6 = H$, $R_1 + R_2 = CH_2CH_2$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$

 Prepared by the procedure of Example 28 from cyclopropane-1,1-diacetic anhydride.

 Oil used as such for the next step.

35

Preparation of cyclopropane-1,1-diacetic anhydride:

11 g of cyclopropane-1,1-diacetonitrile (the preparation of which can be found in the references: SEYDEN; PENNE J.; ROUX; SCHMITT M.C.; Bull. Soc. Chim. Fr. 1968, 9, 3810-3812, and CHAMBOUX B.; ETIENNE Y.; PALLAUD R.; C.R. Acad. Science Paris 1962, 255, p. 536-538) are added to 150 ml of 20% potassium hydroxide solution and the mixture is refluxed for 12 hours. After cooling, the mixture is washed with ether and the aqueous phase is acidified with hydrochloric acid and then saturated with sodium chloride and extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and then evaporated to dryness to give 10.5 g of cyclopentane-1,1-diacetic acid melting at 105°C. This acid is dissolved in 50 ml of acetic anhydride and the mixture is refluxed for 5 hours. The solvent is evaporated off to dryness to give 10.2 g of cyclopropane-1,1-diacetic anhydride melting at 102°C.

Example 149:

Ethyl [1-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]methylcycloprop-1-yl]acetate

Formula (I): $R_1 + R_2 = CH_2CH_2$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$, $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5-F$, $X_2 = X_3 = H$, $X_4 = 4-Cl$

Prepared by the procedure of Example 34 from the acid chloride ester of cyclopropane-1,1-diacetic acid prepared in Example 148.

Oil used as such for the next step.

Example 150:

[1-[1-(4-Chlorobenzyl)-5-fluorobenzimidazol-2-yl]-methylcycloprop-1-yl]acetic acid

05 Formula (I): $R_1 + R_2 = CH_2CH_2$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2H$, $B = CH_2$, $A = \text{phenyl}$, $X_1 = 5-F$, $X_2 = X_3 = H$, $X_4 = 4-Cl$

Prepared by the procedure of Example 58.

10 Crystals melting at 181-3°C.

Example 151:

Acid chloride ethyl ester of trans-cyclopentane-1,2-dicarboxylic acid

15 Formula (VIII): $R_1 + R_5 = CH_2CH_2CH_2$, $R_2 = R_6 = H$, $D = CO_2Et$, $n = 0$

Prepared by the procedure of Example 88.

20 Oil used as such for the next step.

Example 152:

Ethyl trans-2-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]cyclopentane-1-carboxylate

25 Formula (I): $B = CR_5R_6$, $R_1 + R_5 = CH_2CH_2CH_2$, $R_2 = R_6 = H$, $n = 0$, $D = CO_2Et$, $A = \text{phenyl}$, $X_1 = 5-F$, $X_2 = H$, $X_3 = 4-Cl$, $X_4 = H$

30 Prepared by the procedure of Example 34 from the acid chloride ethyl ester of trans-cyclopentane-1,2-dicarboxylic acid prepared in Example 151.

Oil used as such for the next step.

35

Example 153:

Trans-2-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]cyclopentane-1-carboxylic acid

05 Formula (I): $B = CR_5R_6$, $R_1 + R_5 = CH_2CH_2CH_2$, $R_2 = R_6 = H$, $n = 0$, $D = CO_2H$, $A = \text{phenyl}$, $X_1 = 5-F$, $X_2 = H$, $X_3 = 4-Cl$, $X_4 = H$

Prepared by the procedure of Example 58.

10 Crystals melting at 210-211°C.

Example 154:

Ethyl 4-[1-(4-chlorobenzyl)imidazo[4,5-b]pyridin-2-yl]-3,3-dimethylbutanoate

15 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2Et$, $A = 2\text{-pyridine}$, $B = CH_2$, $X_1 = X_2 = H$, $X_3 = H$, $X_4 = 4-Cl$

20 Prepared by the procedure of Example 91.

Oil used as such for the next step.

Example 155:

4-[1-(4-Chlorobenzyl)imidazo[4,5-b]pyridin-2-yl]-3,3-dimethylbutanoic acid

25 Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 1$, $D = CO_2H$, $A = 2\text{-pyridine}$, $B = CH_2$, $X_1 = X_2 = H$, $X_3 = H$, $X_4 = 4-Cl$

30

Prepared by the procedure of Example 58.

Crystals melting at 138-140°C.

35

Example 156:

5-Formyl-4,4-dimethylvaleronitrile

Formula (VIII'): $R_1 = R_2 = CH_3$, $R_3 = R_4 = R_5 = R_6 = H$,
n = 2, D = CN

A] Ethyl 4-(dioxolan-2-yl)-3,3-dimethylbutanoate

74 g of ethyl 4-formyl-3,3-dimethylbutanoate, prepared in Example 91, are dissolved in 450 ml of anhydrous toluene in the presence of 0.5 g of para-toluenesulfonic acid and 26.7 g of ethylene glycol. The mixture is heated to the reflux temperature and the water formed during the reaction is removed by means of a Dean-Stark apparatus. After refluxing for two hours, the solvent is evaporated off under vacuum and the residue is distilled to give 86.7 g of ethyl 4-(dioxolan-2-yl)-3,3-dimethylbutanoate in the form of a liquid with a boiling point b.p.¹⁰ of 138-140°C.

B] 4-(Dioxolan-2-yl)-3,3-dimethylbutanol

86.7 g of ethyl 4-(dioxolan-2-yl)-3,3-dimethylbutanoate, prepared above, are dissolved in 720 ml of ether. This solution is added dropwise at 10°C to a suspension of 9 g of lithium aluminum hydride in 700 ml of ether. When the addition is complete, the mixture is stirred for 3 hours at room temperature and then cooled to 10°C. A saturated solution of sodium sulfate is added dropwise at this temperature until a granular precipitate is obtained, which is filtered off. The ether filtrate is evaporated to dryness at a temperature below 30°C to give 81.9 g of 4-(dioxolan-2-yl)-3,3-dimethylbutanol in the form of an oil, which is used as such for the next step.

C] 4-(Dioxolan-2-yl)-3,3-dimethylbutanol mesylate

81.9 g of 4-(dioxolan-2-yl)-3,3-dimethylbutanol, prepared above, are dissolved in 600 ml of chloroform, stabilized with amylene, in the presence of 62 ml of triethylamine. The mixture is cooled to 5°C and 81 ml of mesyl chloride are added dropwise. The mixture is subsequently stirred for 4 hours at 5°C and then left overnight at this temperature, washed with cold water and evaporated at 30°C under vacuum. The residue obtained is taken up with ether and washed with sodium bicarbonate. The ether phase is dried over magnesium sulfate and then evaporated at 30°C under vacuum to give 93.5 g of 4-(dioxolan-2-yl)-3,3-dimethylbutanol mesylate.

D] 5-(Dioxolan-2-yl)-4,4-dimethylvaleronitrile

93.5 g of the mesylate prepared in C] are dissolved in 500 ml of acetonitrile. 50 g of potassium cyanide and 4.8 g of crown ether 18-6 are added. The mixture is refluxed for 8 hours and then taken up with water and extracted with ethyl acetate. The organic phase is washed several times with water and then dried over magnesium sulfate and evaporated under vacuum. The residue obtained is distilled under reduced pressure to give 50 g of 5-(dioxolan-2-yl)-4,4-dimethylvaleronitrile with a boiling point b.p._{0.5} of 90-8°C.

E] 5-Formyl-4,4-dimethylvaleronitrile

50 g of 5-(dioxolan-2-yl)-4,4-dimethylvaleronitrile, prepared in D], are dissolved in 1.3 l of acetone in the presence of 140 ml of concentrated hydrochloric acid and 700 ml of water. The mixture is

stirred at room temperature for 5 hours, the acetone is concentrated under vacuum and the residue is taken up with ether, washed with water and then evaporated to dryness to give 35 g of 5-formyl-4,4-dimethylvaleronitrile.

Example 157:

5-[1-(4-Chlorobenzyl)-5-fluorobenzimidazol-2-yl]-4,4-dimethylvaleronitrile

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 2$, $D = CN$,
 $A = \text{phenyl}$, $B = CH_2$, $X_1 = 5-F$, $X_2 = X_3 = H$, $X_4 = 4-Cl$

Prepared by the procedure of Example 91 from 5-formyl-4,4-dimethylvaleronitrile prepared in Example 156.

Oil used as such for the next step.

Example 158:

5-[1-(4-Chlorobenzyl)-5-fluorobenzimidazol-2-yl]-4,4-dimethylpentanoic acid

Formula (I): $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$, $n = 2$, $D = CO_2H$, $X_1 = 5-F$, $X_2 = H$, $X_3 = H$, $X_4 = 4-Cl$,
 $B = CH_2$, $A = \text{phenyl}$

3 g of 5-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]-4,4-dimethylvaleronitrile, prepared in Example 157, are dissolved in a mixture composed of 30 ml of water and 30 ml of ethanol. 3 g of sodium hydroxide pellets are added and the mixture is refluxed for 15 hours. After cooling, 100 ml of water are added and the solution obtained is washed with ether. The aqueous phase is acidified by having sulfur dioxide

bubbled through it and the crystals obtained are filtered off, washed with water and then with isopropyl ether and dried to give 2.3 g of 5-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]-4,4-dimethylpentanoic acid
05 in the form of crystals melting at 184-6°C.

Example 159:

Acid chloride ethyl ester of cyclohexene-cis-4,5-dicarboxylic acid

10

Formula (VIII): $n = 0$, $D = \text{CO}_2\text{Et}$, $R_1 = R_5 = \text{H}$, $R_6 +$
 $R_2 = \text{CH}_2\text{-CH=CH-CH}_2$

Prepared by the procedure of Example 28 from
15 cyclohexene-cis-4,5-dicarboxylic anhydride.

Oil used as such for the next step.

Example 160:

Ethyl cis-5-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]cyclohexene-4-carboxylate
20

Formula (I): $B = \text{CR}_5\text{R}_6$, $R_1 = R_5 = \text{H}$, $R_2 + R_6 =$
 $\text{CH}_2\text{-CH=CH-CH}_2$, $n = 0$, $D = \text{CO}_2\text{Et}$, $A =$
phenyl, $X_1 = 5\text{-F}$, $X_2 = X_3 = \text{H}$, $X_4 = 4\text{-Cl}$

25

Prepared by the procedure of Example 34.

Crystals melting at 136°C.

Example 161:

Cis-5-[1-(4-chlorobenzyl)-5-fluorobenzimidazol-2-yl]-cyclohexene-4-carboxylic acid
30

Formula (I): $B = \text{CR}_5\text{R}_6$, $R_1 = R_5 = \text{H}$, $R_2 + R_6 =$
 $\text{CH}_2\text{-CH=CH-CH}_2$, $n = 0$, $D = \text{CO}_2\text{H}$, $A =$
phenyl, $X_1 = 5\text{-F}$, $X_2 = X_3 = \text{H}$, $X_4 = 4\text{-Cl}$

35

Prepared by the procedure of Example 58.

Crystals melting at 185-186°C.

Example 162:

05 2-(4-Methylthiobenzyl)amino-3-nitro-5-chloropyridine

Formula (V): $X_1 = 5\text{-Cl}$, $X_2 = \text{H}$, $X_3 = 4\text{-SCH}_3$, $X_4 = \text{H}$,
A = 2-pyridine

10 Prepared by the procedure of Example 6.
Crystals melting at 88°C.

Example 163:

15 2-(4-Methylthiobenzyl)amino-3-amino-5-chloropyridine

Formula (IV): $X_1 = 5\text{-Cl}$, $X_2 = \text{H}$, $X_3 = 4\text{-SCH}_3$, $X_4 = \text{H}$,
A = 2-pyridine

20 Prepared by the procedure of Example 14.
Crystals melting at 116°C.

Example 164:

25 Ethyl 4-[1-(4-methylthiobenzyl)-5-chloroimidazo[4,5-b]-
pyridin-2-yl]-3,3-dimethylbutanoate

Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, D =
 CO_2Et , A = 2-pyridine, B = CH_2 , $X_1 = 5\text{-Cl}$,
 $X_2 = X_3 = \text{H}$, $X_4 = 4\text{-SCH}_3$

30 Prepared by the procedure of Example 91.
Oil used as such for the next step.

35

Example 165:

4-[1-(4-Methylthiobenzyl)-5-chloroimidazo[4,5-b]pyridin-2-yl]-3,3-dimethylbutanoic acid

05 Formula (I): $R_1 = R_2 = \text{CH}_3$, $R_3 = R_4 = \text{H}$, $n = 1$, $D = \text{CO}_2\text{H}$, $A = 2\text{-pyridine}$, $B = \text{CH}_2$, $X_1 = 5\text{-Cl}$,
 $X_2 = X_3 = \text{H}$, $X_4 = 4\text{-SCH}_3$

Prepared by the procedure of Example 92.

10 Crystals melting at 125-126°C.

15

20

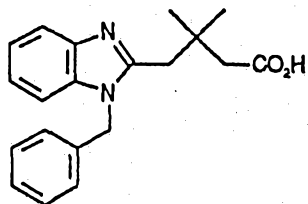
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30

35

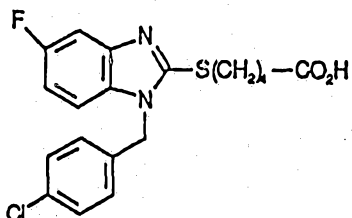
TABLE

Example 58



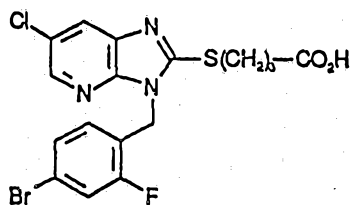
UP 116-52

Example 59



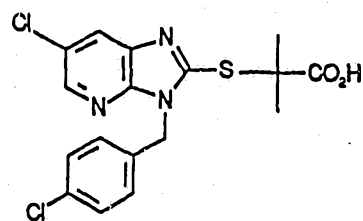
UP 116-11

Example 60



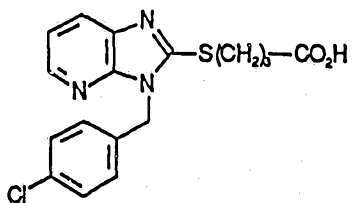
UP 116-17

Example 61



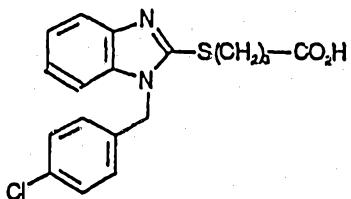
UP 116-21

Example 62



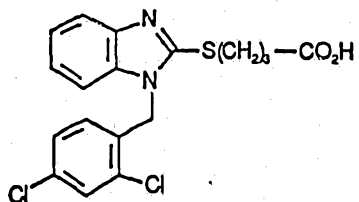
UP 116-13

Example 63



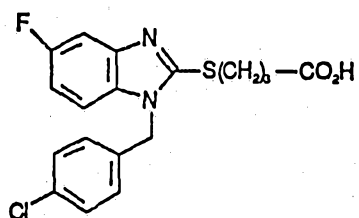
UP 116-16

Example 64



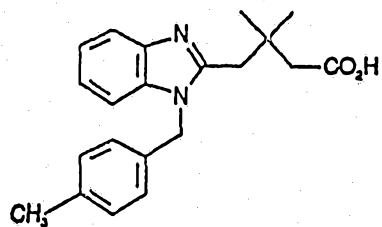
UP 116-18

Example 65



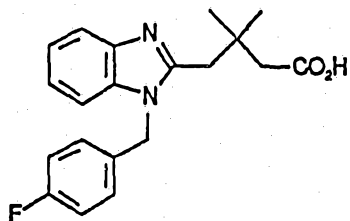
UP 116-1

Example 66



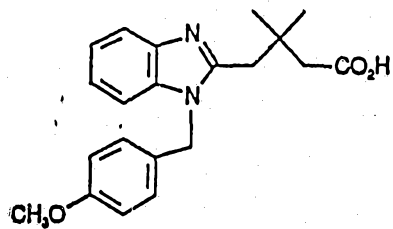
UP 116-57

Example 67



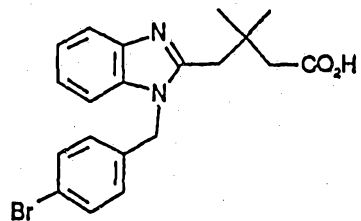
UP 116-56

Example 68



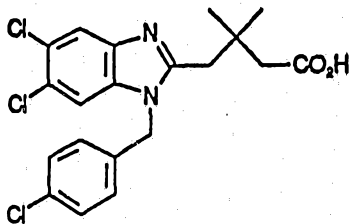
UP 116-55

Example 69



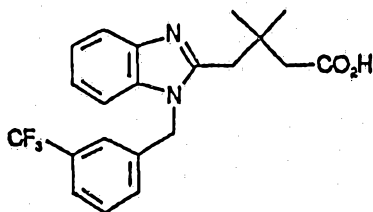
UP 116-59

Example 70



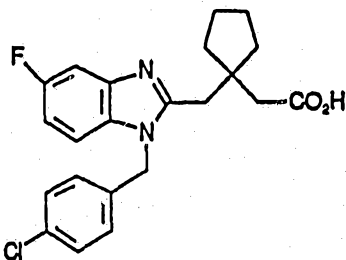
UP 116-63

Example 71



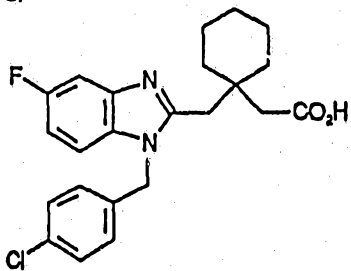
UP 116-67

Example 72



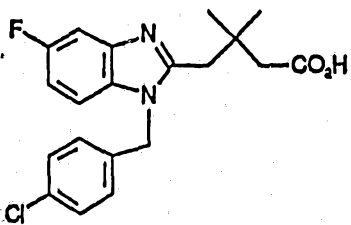
UP 116-53

Example 73



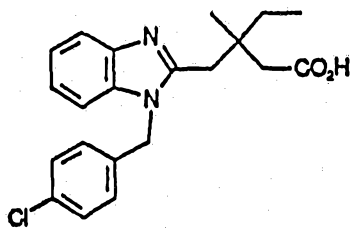
UP 116-54

Example 74



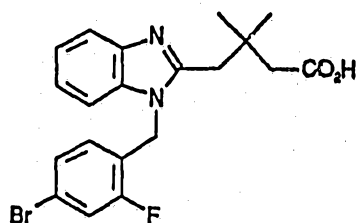
UP 116-47

Example 75



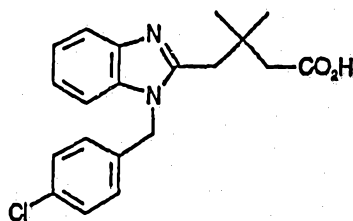
UP 116-65

Example 76



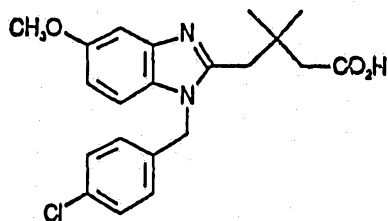
UP 116-51

Example 77



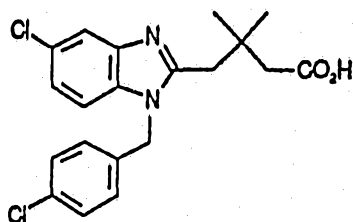
UP 116-58

Example 78



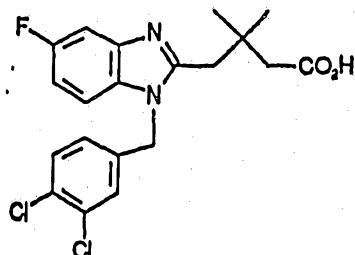
UP 116-64

Example 79



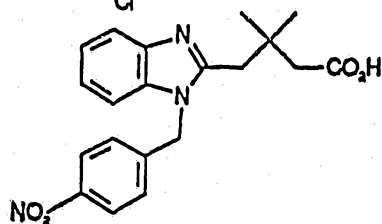
UP 116-60

Example 80



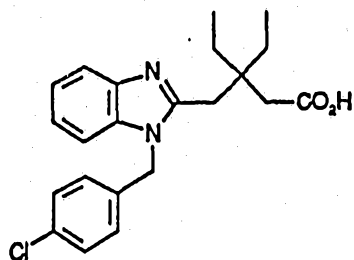
UP 116-62

Example 81



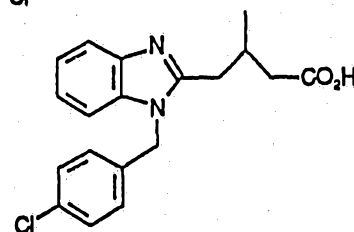
UP 116-66

Example 82



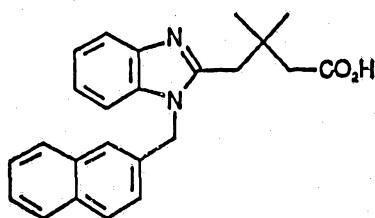
UP 116-68

Example 83



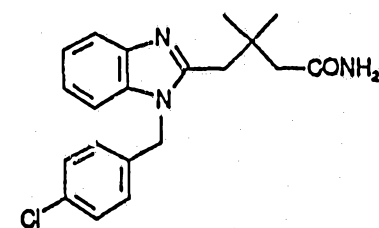
UP 116-70

Example 84



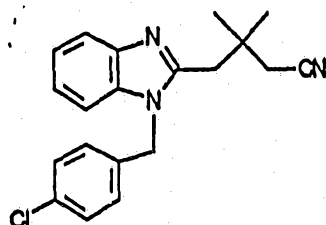
UP 116-71

Example 85



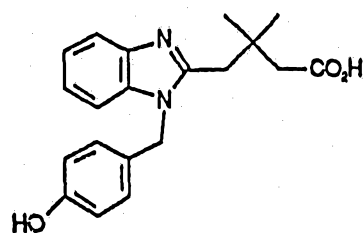
UP 116-72

Example 86



UP 116-73

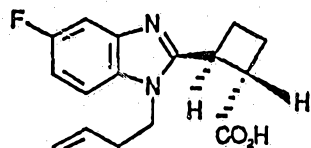
Example 87



UP 116-61

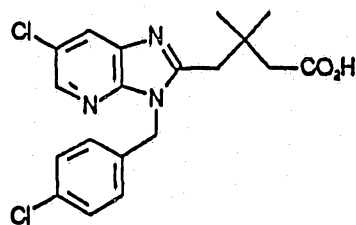
Example 90

UP 116-74



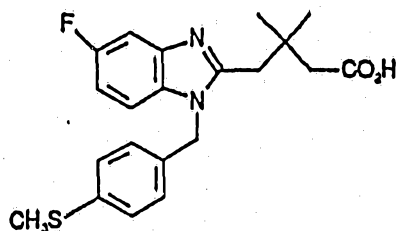
Example 92

UP 116-77



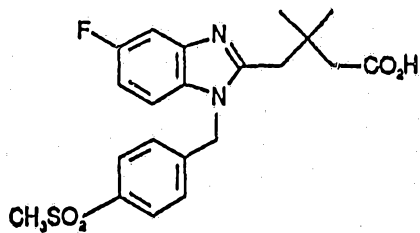
Example 96

UP 116-78



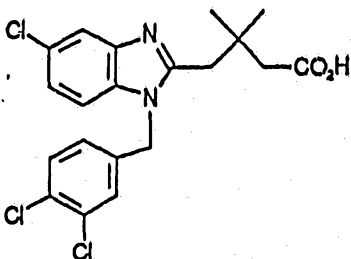
Example 97

UP 116-79



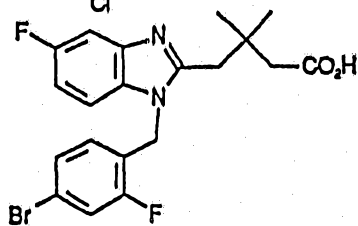
Example 101

UP 116-81

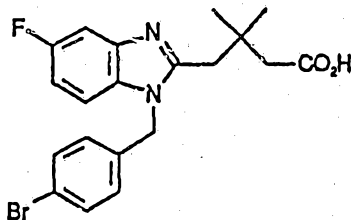


Example 105

UP 116-83

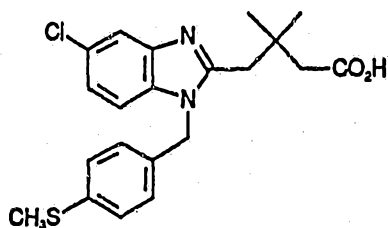


Example 109



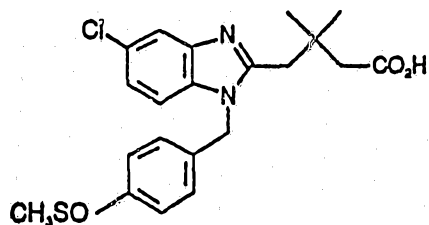
UP 116-84

Example 117



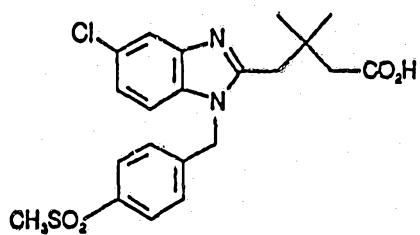
UP 116-87

Example 118



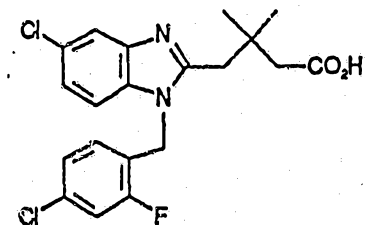
UP 116-86

Example 119



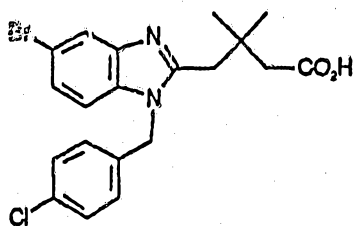
UP 116-89

Example 123



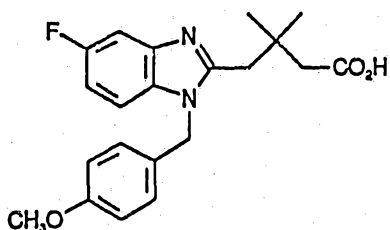
UP 116-88

Example 127



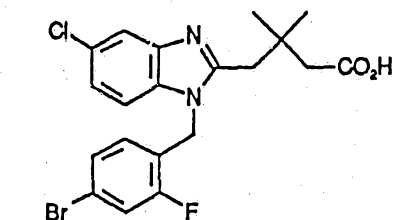
UP 116-90

Example 131



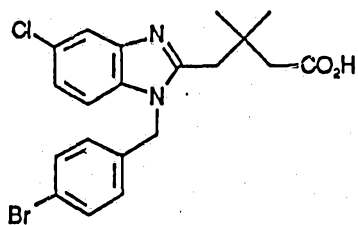
UP 116-91.

Example 135



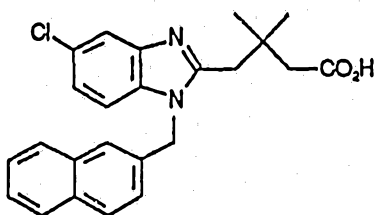
UP 116-93

Example 139



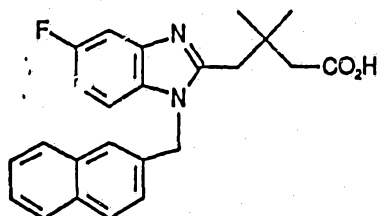
UP 116-95

Example 143



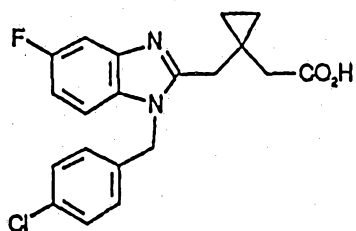
UP 116-97

Example 147



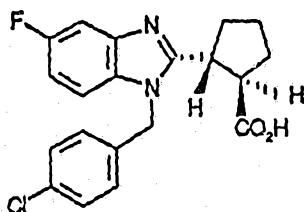
UP 116-96

Example 150



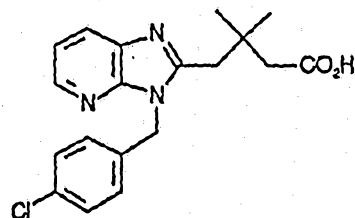
UP 116-75

Example 153



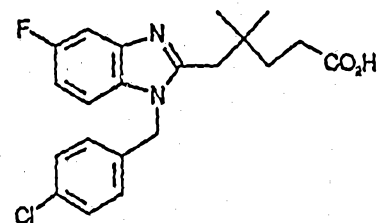
UP 116-80

Example 155



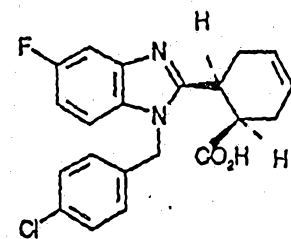
UP 116-82

Example 158



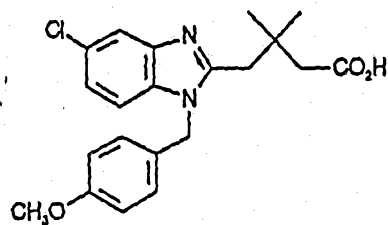
UP 116-92

Example 161



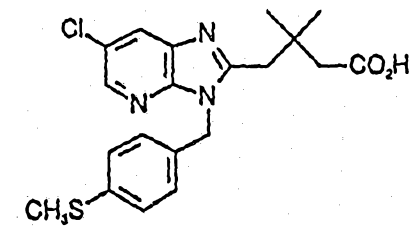
UP 116-76

Example 113



UP 116-85

Example 165



UP 116-99

PHARMACOLOGY

Principle

05 The affinity of the products of the Examples described for thromboxane A_2 receptors is evaluated by the technique of displacing a radioligand specifically bound to the TXA_2 receptors of human platelets.

10 Technique

Human platelets incubate in the presence of a single concentration of [^{125}I]PTA-OH (9,11-dimethyl-methano-11,12-methano-16-(3-[^{125}I]iodo-4-hydroxy-phenyl)-13,14-dihydro-13-aza-15 α - ω -tetranor- TXA_2), a TXA_2 /PGH₂ receptor antagonist, and two concentrations of competing agents (10^{-5} M, 10^{-7} M) for 30 minutes at 37°C.

20 The reaction is completed by the addition of a buffer, followed by rapid filtration through glasspaper filters.

25 The non-specific binding is determined in the presence of U 46619 (9,11-dideoxy-11 α ,9 α -epoxymethano-prostaglandin F_{2 α} ; mimetic thromboxane A_2).

Results

30 The results are expressed, for the doses tested, as the percentage displacement of the radioligand specifically bound to the TXA_2 receptors of human platelets. For certain products of the Examples, the inhibition constant K_i was determined according to the formula of CHENG and PRUSOFF:

$$K_i = \frac{IC_{50}}{1 + \frac{L}{K_D}}$$

05 in which IC denotes the 50% inhibitory concentration, L the concentration of radioactive ligand and K_D the dissociation constant of the radioactive ligand.

10 Toxicology

15 Preliminary toxicity studies were able to show that the 50% lethal doses determined after oral administration to rats were greater than 300 mg/kg, representing an advantageous therapeutic index.

Conclusion

20 In conclusion, the molecules described in the present patent application, or their non-toxic addition salts, exhibit a substantial affinity for TXA_2 receptors and can be advantageously and profitably used in the treatment of the following pathological conditions:

25 - myocardial infarction, angina pectoris, stroke, migraine, cerebral hemorrhage, atherosclerosis, pulmonary embolism, bronchial asthma, bronchitis, pneumonia, circulatory shock of various origins (hemorrhage, septicemia, heart failure, trauma, acute pancreatitis, burn, bacterial origin), nephritis, 30 graft rejection and cancerous metastases,

35 by oral administration in the form of tablets or gelatin capsules containing from 1 to 200 mg of active ingredient, or by parenteral administration in the form

of injectable preparations containing from 0.01 to 10 mg of active ingredient, preferably in several dosage units (2 to 4) or administrations per day.

05

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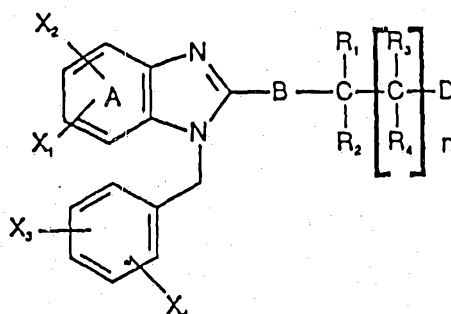
35

% displacement			
	Example	Concentration	
		1E-7 M	1E-5 M
05			
	58	13	95
	59	28	100
	60	24	60
	61	30	100
	62	27	64
10	63	37	97
	64	34	97
	65	8	93
	66	52	100
	67	66	100
	68	89	100
	69	86	96
15	70	14	100
	71	49	100
	72	71	100
	73	0	98
	74	94	100
	75	57	100
	76	88	99
	77	85	100
20	78	44	100
	79	74	99
	80	89	92
	81	83	100
	82	35	97
	83	10	100
	84	85	98
	85	7	90
25	87	50	96
	90	2	97
	92	97	100
	96	100	100
	97	100	100
	101	71	92
	105	100	98
30	109	95	92
	117	87	89
	118	54	92
	119	61	82
	123	77	87
	127	38	67
	131	79	100
35			

35

The claims defining the invention are as follows:

1. A benzimidazole derivative of formula (I):



Formula (I)

in which:

A is an aromatic ring or a nitrogen heterocycle;

X₁, X₂, X₃ and X₄ are independently a hydrogen atom, a halogen atom, a lower alkyl radical, a C₃-C₇ cycloalkyl radical, an alkoxy radical, an alkylthio radical, a sulfone group, SO₂-lower alkyl, a sulfoxide group, SO-lower alkyl, a trifluoromethyl group, a hydroxyl group, a nitro group, a methylene alcohol radical or a group COOR', in which R' is a hydrogen or a lower alkyl; X₃ and X₄ can also form a naphthalene with the phenyl;

B is CR₅R₆, R₅ and R₆ being a hydrogen atom, a lower alkyl radical or a C₃-C₇ cycloalkyl radical, or the sulfur atom;

R₁, R₂, R₃ and R₄ are independently a hydrogen atom, a lower alkyl radical or a C₃-C₇ cycloalkyl radical; CR₁R₂ or CR₃R₄ can form with B, when the latter is CR₅R₆, a cycloalkyl or a cycloalkene having 3 to 7 carbon atoms; R₁R₂ and R₃R₄ can also form a ring having 3 to 7 carbon atoms;

n is an integer from 1 to 4 and can be 0 if R_1 and R_2 are other than hydrogen; and

D is a chemical group which can be COOR_7 , CONHR_8 or CN , wherein R_7 and R_8 are a hydrogen atom, a lower alkyl radical or a $\text{C}_3\text{-C}_7$ cycloalkyl radical and its addition salts, in particular the pharmaceutically acceptable addition salts.

2. A derivative according to claim 1, wherein A is a phenyl ring.

3. A derivative according to claim 1, wherein A is a pyridine ring.

10 4. A derivative according to any one of claims 1 to 3, wherein X_1 is the fluorine atom.

5. A derivative according to any one of claims 1 to 3, wherein X_1 is the chlorine atom.

15 6. A derivative according to any one of claims 1 to 5, wherein X_3 is the chlorine atom.

7. A derivative according to any one of claims 1 to 5, wherein X_3 is the methoxy group.

8. A derivative according to any one of claims 1 to 5, wherein X_3 is the methylthio group.

20 9. A derivative according to any one of claims 1 to 8, wherein X_4 is the chlorine atom.

10. A derivative according to any one of claims 1 to 9, wherein D is an acid group.

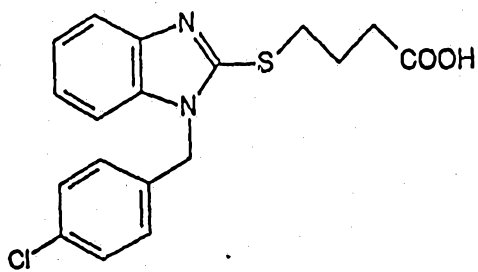
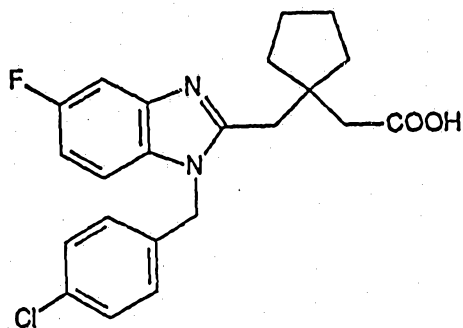
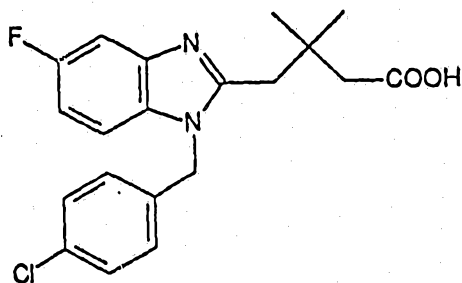
25 11. A derivative according to any one of claims 1 to 10, wherein B is a methylene group, R_1 and R_2 are each a methyl, R_3 and R_4 are hydrogen and n is equal to 1.

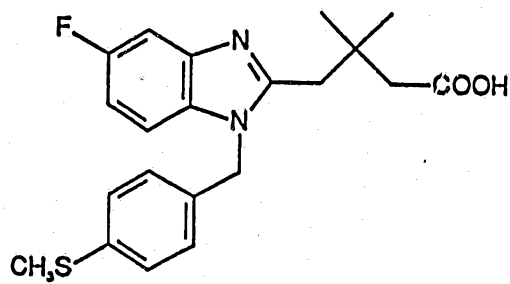
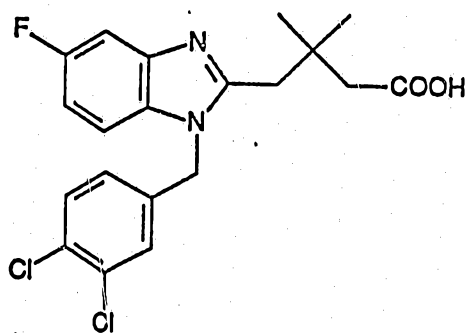
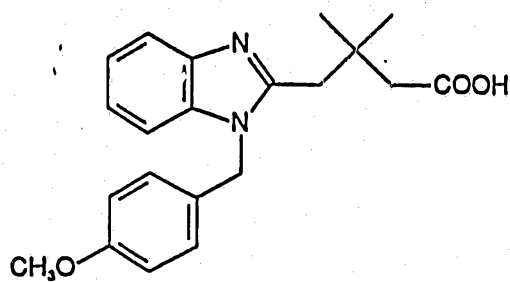
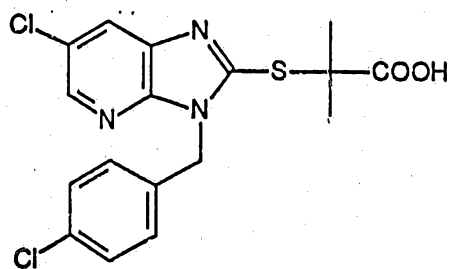
12. A derivative according to any one of claims 1 to 10, wherein B is the sulfur atom.

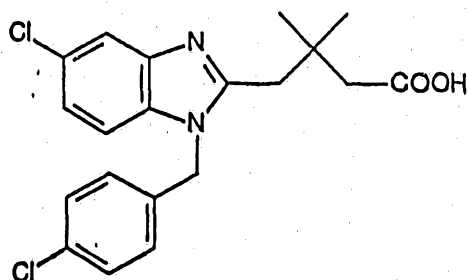
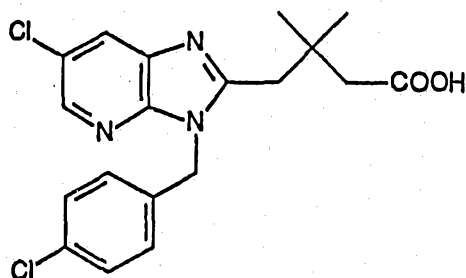
30 13. A derivative according to any one of claims 1 to 10 or 12, wherein CR_1R_2 is a cyclopentane.



14. A derivative according to any one of claims 1 to 11 which is selected from the derivatives of the formulae:



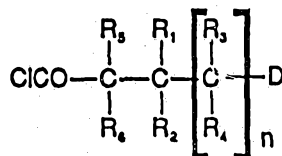




15. A method of preparing the compounds of formula (I) according to any one of claims 1 to 14, wherein said compounds are prepared:

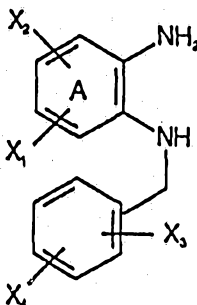
A/ if B is a sulfur atom: by reacting an alkyl halogenoalkanoate with a mercaptobenzimidazole or mercaptoazabenzimidazole in the presence of a base such as a sodium or potassium alcoholate, sodium or lithium hydride or potassium carbonate, in an alcohol, dimethylformamide, acetone or butan-2-one; or

B/ if B is a group CR_5R_6 : in two steps by reacting an acid chloride of formula (VIII):



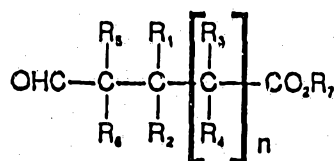
Formula (VIII)

in which $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5, \text{R}_6$ and n are as defined above and D is ~~an ester or nitrile group, with a di-~~ ^{CN or COOR₇, in which R₇ is as defined in Claim 1} amine of formula (IV):



Formula (IV)

in which $\text{A}, \text{X}_1, \text{X}_2, \text{X}_3$ and X_4 are as defined above, this being followed in a second stage by cyclization in an acid medium, or by reacting the diamine of formula (IV) with an aldehyde of formula (VIII'):



Formula (VIII')



in which R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and n are as defined above and R_7 is a lower alkyl radical, in an acetic acid and alcohol medium, it being possible for said alcohol to be methanol, ethanol or methoxyethanol for example, the derivative obtained then being oxidized
5 with an oxidizing agent such as iodine or barium manganate, acid or basic hydrolysis of the ester or nitrile derivatives yielding compounds of formula (I).

16. A pharmaceutical composition which comprises a pharmaceutically effective amount of at least one compound of formula (I)
10 as defined in any one of claims 1 to 14, or one of its pharmaceutically acceptable addition salts, together with a pharmaceutically acceptable excipient, vehicle or carrier.

17. A pharmaceutical composition active as a thromboxane receptor antagonist, with which the following diseases in particular can be
15 favorably treated: myocardial infarction, angina pectoris, stroke, migraine, cerebral hemorrhage, atherosclerosis, pulmonary embolism, bronchial asthma, bronchitis, pneumonia, circulatory shocks of various origins (hemorrhage, septicemia, heart failure, trauma, acute pancreatitis, burn, bacterial origin), nephritis, graft rejection and
20 cancerous metastases, said composition containing a pharmaceutically effective amount of at least one compound of formula (I) as defined in any one of claims 1 to 14, or one of its pharmaceutically acceptable addition salts, together with a pharmaceutically acceptable excipient, vehicle or carrier.

25 18. A method of preparing a pharmaceutical composition, which comprises incorporating a pharmaceutically effective amount of at least one compound of formula (I) as

defined in any one of claims 1 to 14, or one of its pharmaceutically acceptable addition salts, into a pharmaceutically acceptable excipient, vehicle or carrier.

19. A method according to claim 18, wherein the pharmaceutical composition is formulated as gelatin capsules or tablets containing from 1 to 200 mg of active ingredient, or as injectable preparations containing from 0.01 to 10 mg of active ingredient.

20. A 1-benzyl-benzimidazole or azabenzimidazole derivative substantially as hereinbefore described with reference to any one of the Examples.

21. A process for preparing a 1-benzyl-benzimidazole or azabenzimidazole derivative substantially as hereinbefore described with reference to any one of the Examples.

22. A method for the treatment or prophylaxis of myocardial infarction, angina pectoris, stroke, migraine, cerebral hemorrhages, atherosclerosis, pulmonary embolism, bronchial asthma, bronchitis, pneumonia, circulatory shocks of various origins, nephritis, graft rejection or cancerous metastases in a mammal requiring said treatment or prophylaxis, which method comprises administering to said mammal an effective amount of at least one compound according to any one of claims 1 to 14 or 20, or of a composition according to claim 16 or claim 17.

DATED this FIFTH day of FEBRUARY 1991

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