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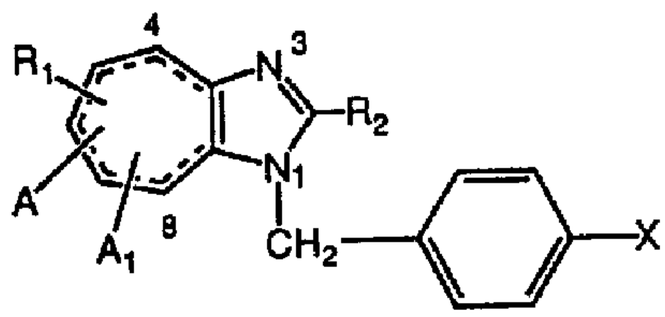
(54) Titre : METHODE DE PREPARATION DE DERIVES DU CYCLOHEPTIMIDAZOLE
(54) Title: METHOD OF MANUFACTURING THE CYCLOHEPTIMIDAZOLE DERIVATIVES



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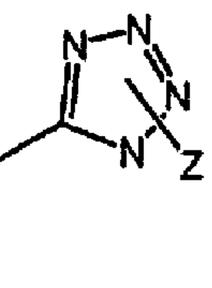

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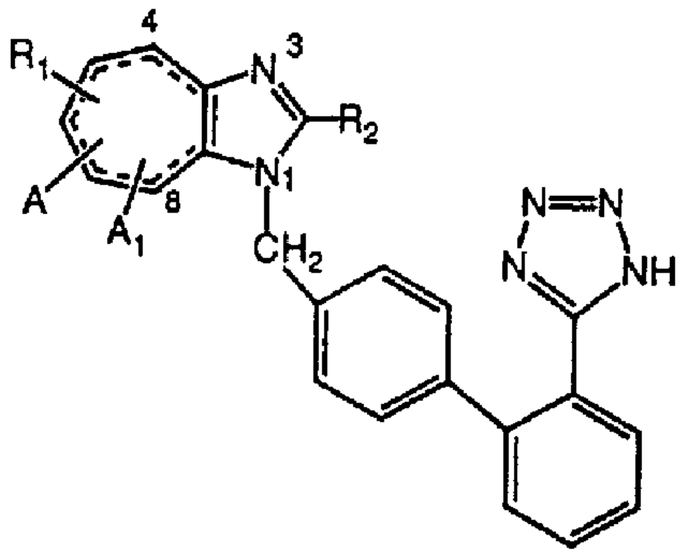

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(57) Abrégé/Abstract:
Disclosed is a method in which a compound of general formula (1) is reacted with a compound of general formula (2), followed by deprotection of protective group Z to give the cycloheptimidazole derivative (4) wherein $R_1$ is hydrogen or isopropyl; $R_2$ is a lower

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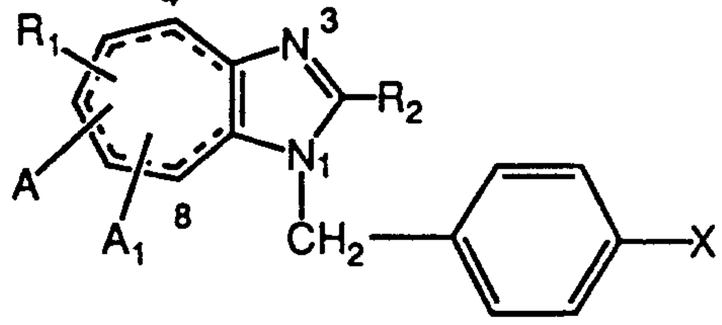
(57) **Abrégé(suite)/Abstract(continued)**:
alkyl; A and $A_1$ are each a substituent at the 4- or 8-position, $A_1$ is hydrogen or hydroxyl when A is a hydrogen or A and $A_1$ together form an oxo group or =CHCOOR$_3$ ($R_3$ represents a lower alkyl); the dotted line means two double bonds or saturated single bonds; X is halogen atom or trifluoromethanesulfonate group; Y is $B(OH)_2$ or -Sn($R_5$)$_3$ ($R_5$ represents a lower alkyl group). The cycloheptimidazole derivative (4) is useful as antihypertensive agent. (see formula 1) (see formula 2) (see formula 4).

## ABSTRACT

Disclosed is a method in which a compound of general formula (1) is reacted with a compound of general formula (2), followed by deprotection of protective group Z to give the cycloheptimidazole derivative (4) wherein $R_1$ is hydrogen or isopropyl; $R_2$ is a lower alkyl; A and $A_1$ are each a substituent at the 4- or 8-position, $A_1$ is hydrogen or hydroxyl when A is a hydrogen or A and $A_1$ together form an oxo group or $=CHCOOR_3$ ($R_3$ represents a lower alkyl); the dotted line means two double bonds or saturated single bonds; X is halogen atom or trifluoromethanesulfonate group; Y is $B(OH)_2$ or $-Sn(R_5)_3$ ($R_5$ represents a lower alkyl group). The cycloheptimidazole derivative (4) is useful as antihypertensive agent.

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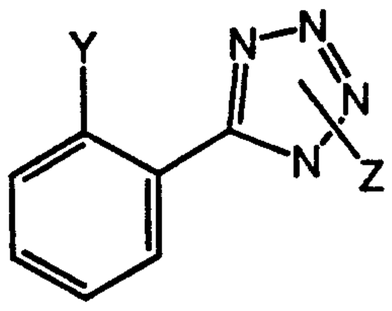


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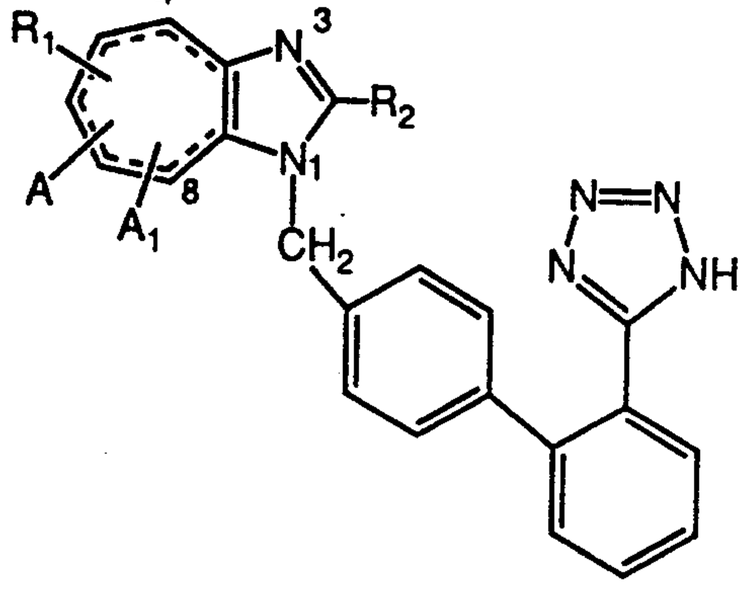


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SPECIFICATION

TITLE OF THE INVENTION

Method of Manufacturing the Cycloheptimidazole Derivatives.

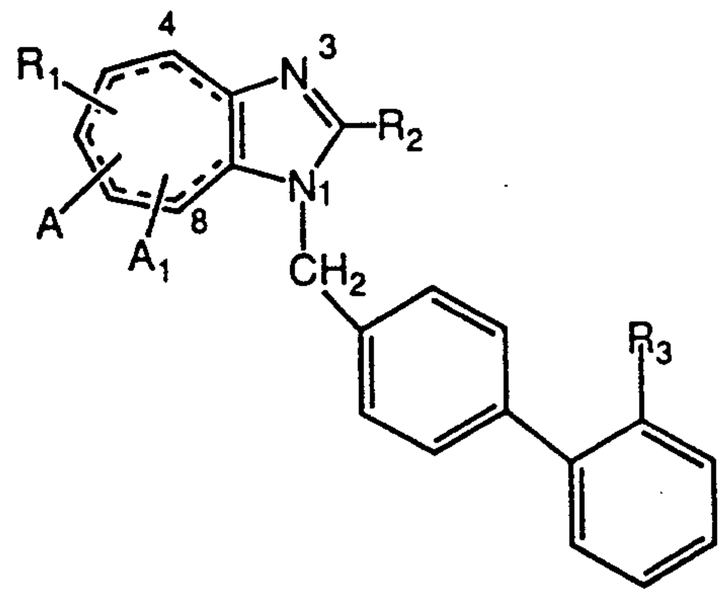
BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a new method of synthesizing cycloheptimidazole derivatives which are active angiotensin II receptor antagonists and are useful for treating hypertension and congestive heart failure.

2. Description of the Prior Art

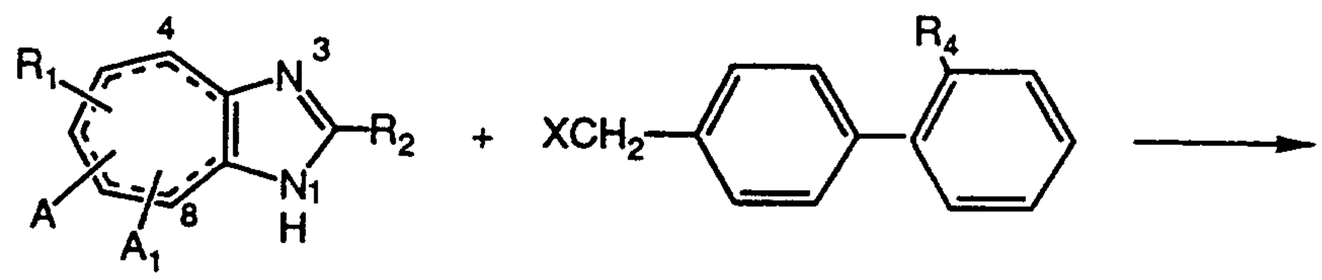
We have synthesized a number of cycloheptimidazole derivatives in order to develop novel agents possessing potent antihypertensive activities. Recently we proposed a new class of cycloheptimidazole derivative compounds of the following general formula:

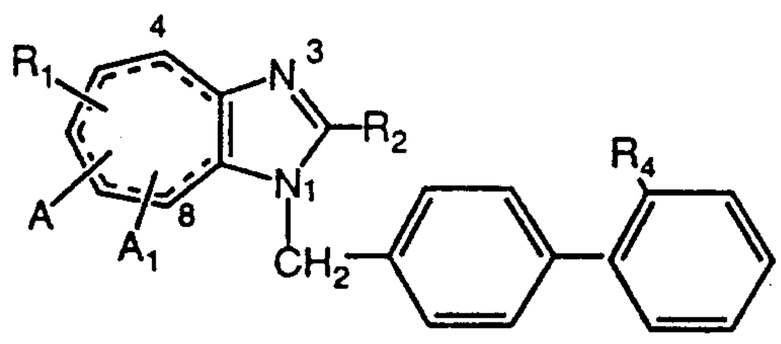



(wherein $R_1$ is hydrogen or isopropyl; $R_2$ represents a lower alkyl; $R_3$ represents a carboxyl or tetrazoyl; A and $A_1$ are individually a substituent at the 4- or 8-position, $A_1$ is a hydrogen or hydroxy when A is a hydrogen or A and $A_1$ may form an oxo group or $=CHCOOR_3$ ($R_3$ represents a lower alkyl); the

dotted line is two double bonds or saturated single bonds); and a method of their synthesis and their use as potent anti-hypertensive, anticongestive heart failure agents and intraocular pressure lowering agents (Japanese Unexamined Patent Publication No. 5-320139 (1993) and Japanese Patent Application No. 5-190153 (1993)).

In preparation of the above cycloheptimidazole derivatives, cycloheptimidazole compounds are reacted with halomethylbiphenyl compounds under the basic condition to give the cycloheptimidazole derivatives, and nitrile group ($R_4$=CN) is then converted into carboxy group or tetrazol group (as shown below).




(wherein $R_4$ is nitrile, X represents halogen atom).

However, in the method we previously reported we must take two step synthetic reactions and further must use an expensive and hard to handle reagent such as $SnN_3$ (Tin azide) and there are some difficulties in the process.

3. Object of the Invention

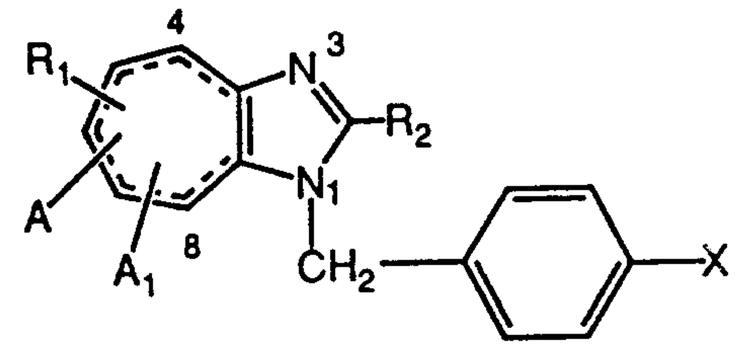
A primary object of the present invention is to find an alternative process for the preparation of the cyclohept-

imidazole derivatives, which method is simple, does not use toxic or expensive reagents and gives a good yield of the cycloheptimidazole derivatives.

SUMMARY OF THE INVENTION

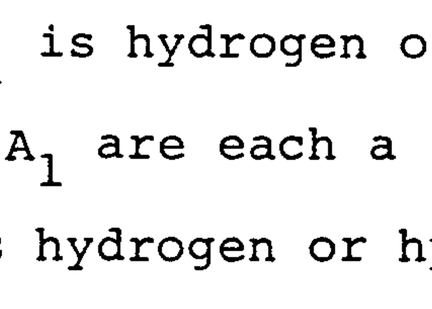
The inventors have conducted intensive studies, and found a new simple and good yield synthetic method involving a palladium catalyzed cross-coupling reaction.

In accordance with the present invention, a compound of general formula (1):



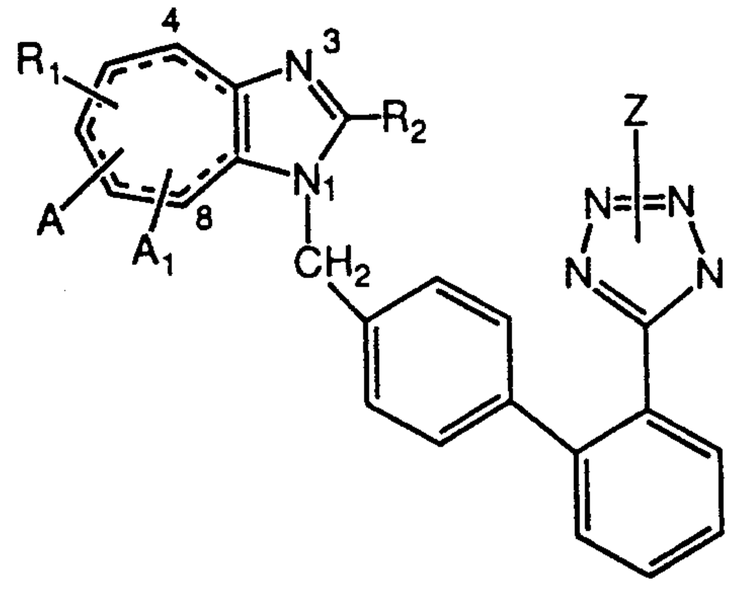
(1)

(wherein $R_1$ is hydrogen or isopropyl; $R_2$ represents a lower alkyl; A and $A_1$ are each a substituent at the 4- or 8-position, and $A_1$ is hydrogen or hydroxy when A is hydrogen or A and $A_1$ together form an oxo group or $=CHCOOR_3$ ($R_3$ represents a lower alkyl); the dotted line represents two double bonds or saturated single bonds; X is halogen atom or trifluoromethanesulfonate) is reacted with a compound of the following general formula (2):



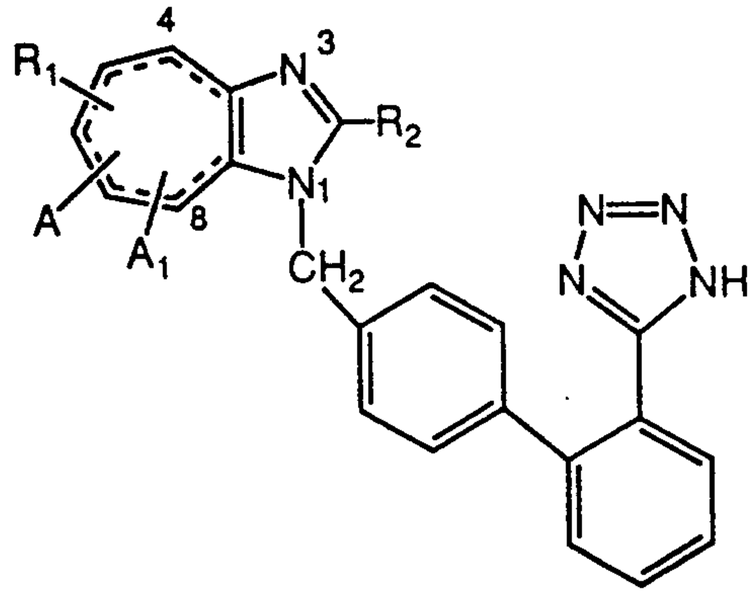
(2)

(wherein Y is $-B(OH)_2$ or $-Sn(R_5)_3$ ($R_5$ represents a lower alkyl group; and Z is a protecting group for the tetraolyl group) to give the compound of following general formula (3):



(3)

(wherein the symbols are as defined above), then the compound (3) is deprotected to give the compound of general formula (4):



(4)

(wherein the symbols are as defined above).

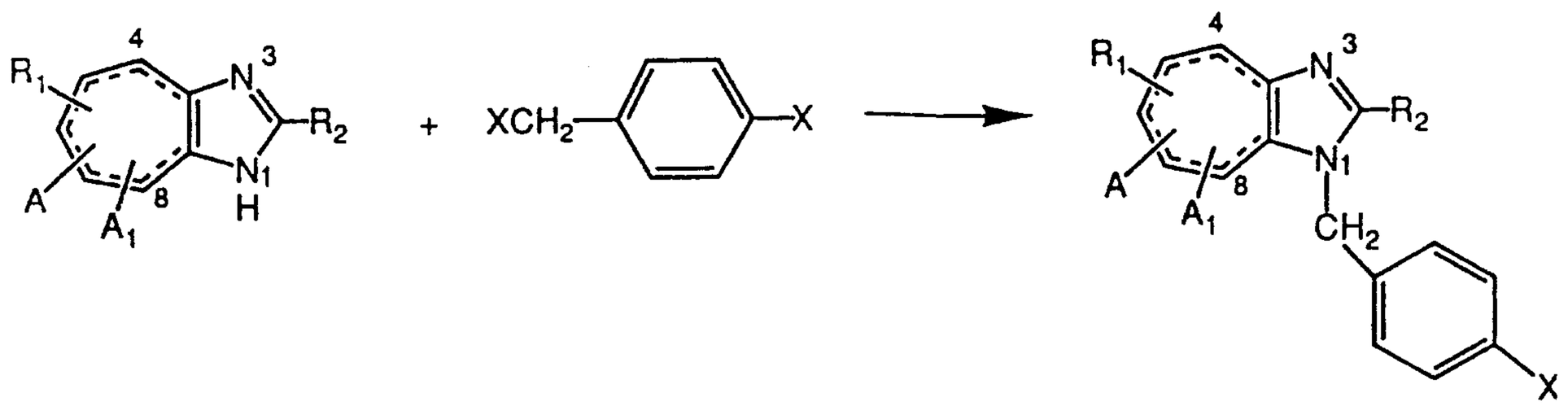
Preferably Z represents tert-butyl, trityl ($-C(Ph)_3$), methoxymethyl, benzylmethyl, p-nitrophenyl group and $R_2$ represents a $C_1$-$C_4$ alkyl group.

The compounds of the general formulae (1) and (2) are also novel and are aspects of the present invention as well as their production processes.

DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

(A) A method for preparing a compound of general formula (1).

(I) A compound of general formula (1) (wherein A and $A_1$ are each a substituent at the 4- or 8-position, and $A_1$ is hydroxy when A is hydrogen or A and $A_1$ may form an oxo group) may be prepared by the following reaction:




(5) (6) (1)

(wherein $R_1$, A, $A_1$, $R_2$, X are the same as mentioned above).

The reaction of cycloheptimidazole (5) and halogenobenzylhalogene compound (6) can be generally carried out in the presence of a base. A base is used in this reaction such as sodium hydride, sodium hydroxide and potassium carbonate. As a solvent used in this reaction, dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), acetone and dioxane may be employed. Furthermore a phase transfer catalyst such as tetra - n - butylammonium hydrogensulfate is applicable in this reaction and $H_2O$ and benzene are used as a solvent. Cycloheptimidazole (5) (the above described) may be prepared by a method described in Japanese Unexamined Patent Publication No. 5-320139 (1993).

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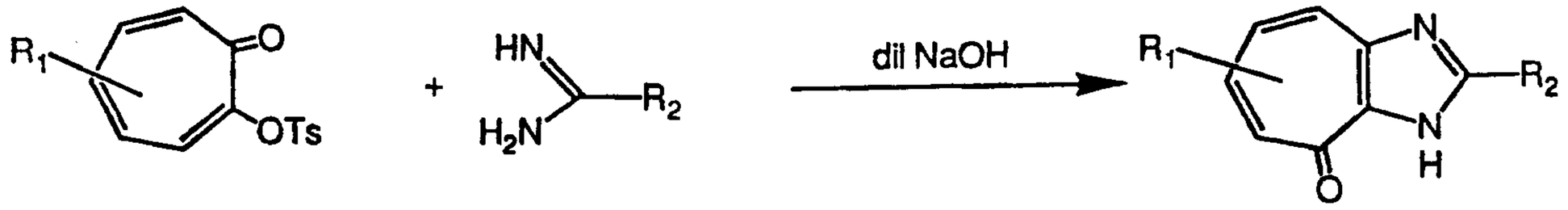
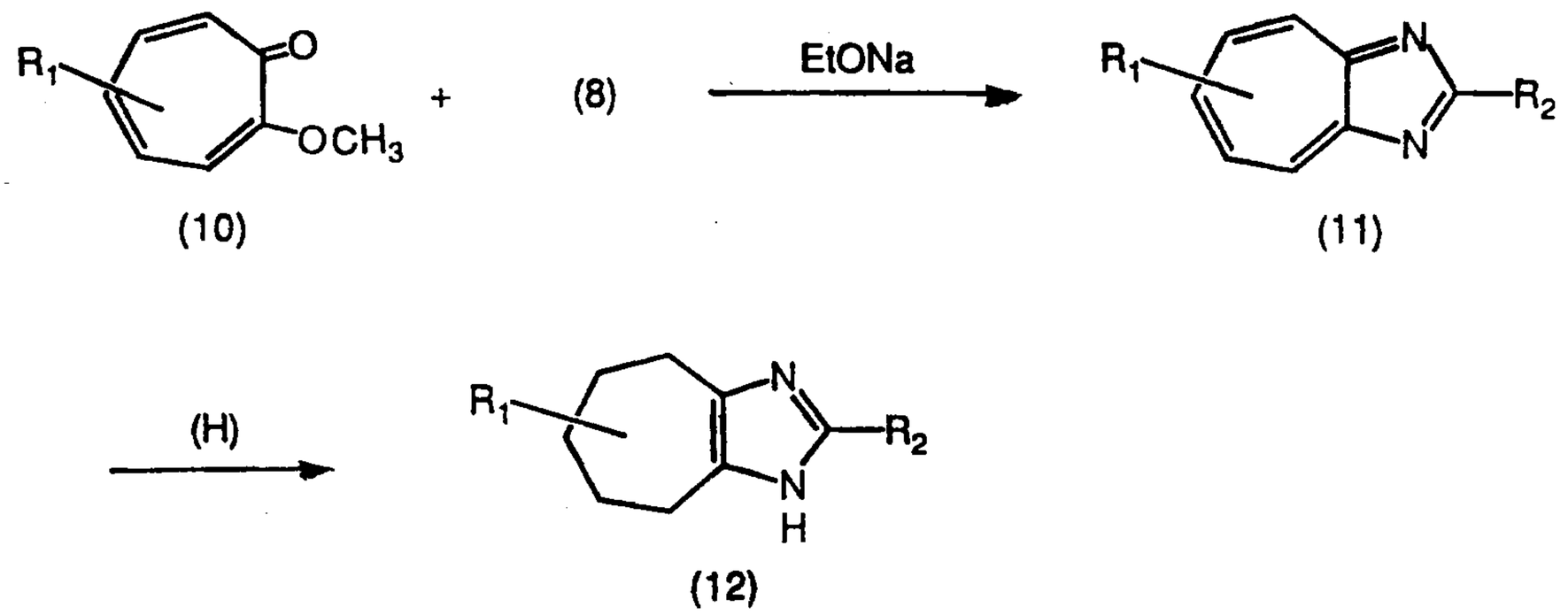
(i) The cycloheptimidazole (5) in which A and $A_1$ together form an oxo group and the dotted line represents two double bonds, i.e., compounds of general formula (9), are prepared by the following reaction:




(7) (8) (9)

(wherein $R_1$ is hydrogen or isopropyl; $R_2$ represents a lower alkyl). Tosyl tropolone (7) is reacted with amidine (8) in the presence of a base to yield oxoimidazole (9) (C.A. 74,53785u, Japanese Examined Patent Publication JP-B-45-31,171).

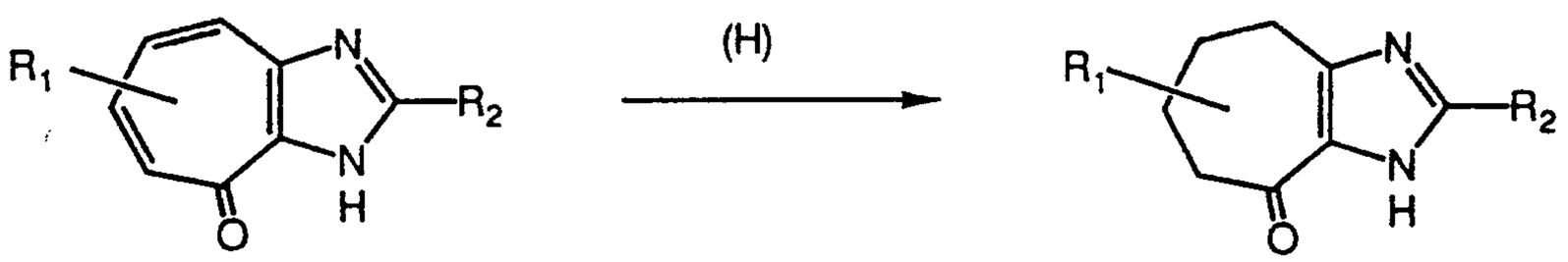
(ii) The cycloheptimidazole (5) in which A and $A_1$ are each hydrogen and the dotted line represents single bonds, i.e., compounds of the general formula (12), are prepared by the following reaction:



(wherein $R_1$, $R_2$ are the same as mentioned above).

Methyl tropolone (10) is reacted with amidine (8) in the presence of EtONa to give cycloheptimidazole (11), and (11) is hydrogenated over $PtO_2$ etc. to 1, 4, 5, 6, 7, 8-hexahydro-cycloheptimidazole (12).

(iii) The cycloheptimidazoles (5) in which A and $A_1$ together form an oxo group and the dotted line represents single bonds, i.e., compoundsof the general formula (13), are prepared by the following reaction:



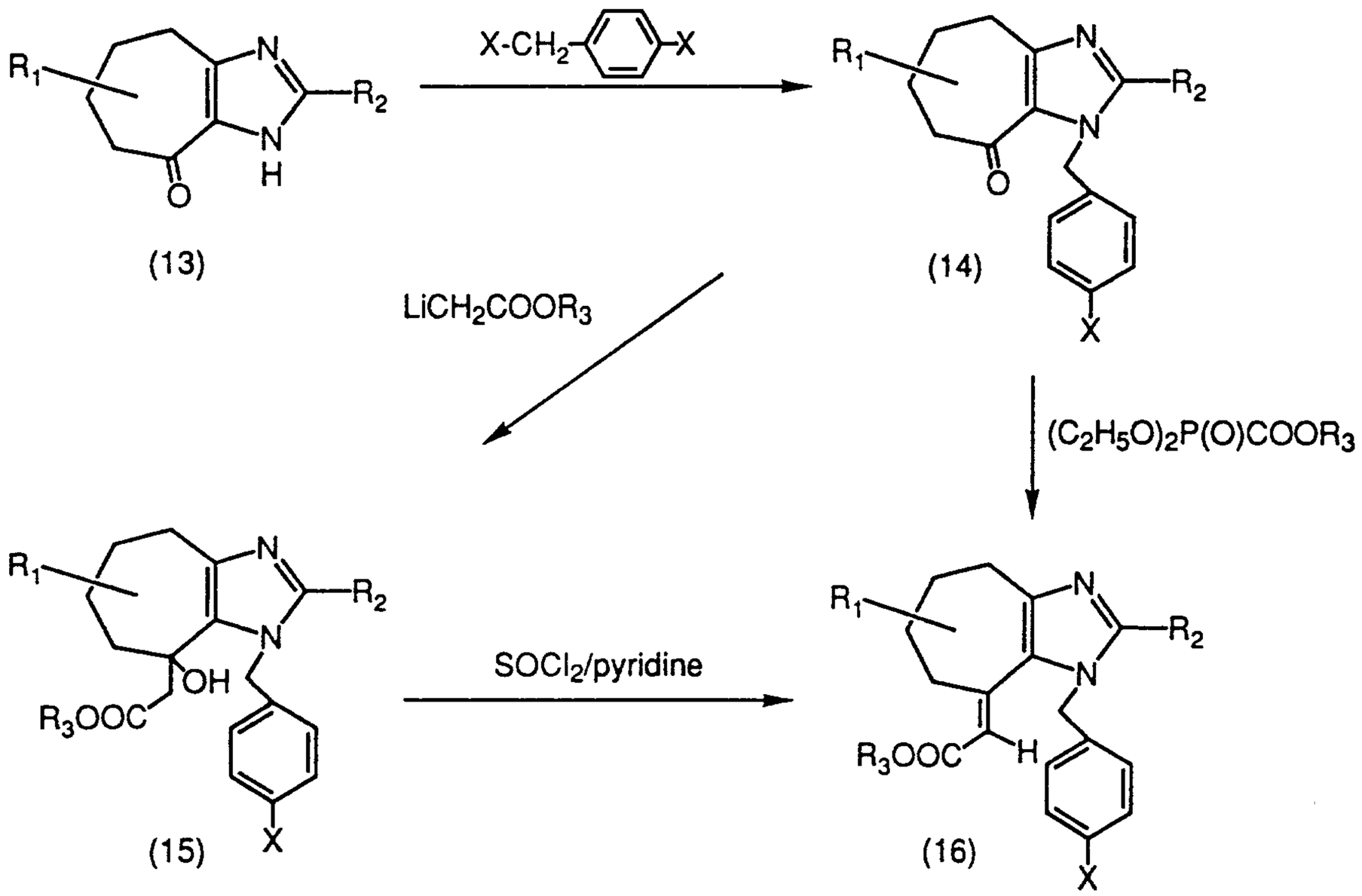

(9) (13)

(wherein $R_1$, $R_2$ are the same as mentioned above).

The oxocycloheptimidazole compound (9) is hydrogenated over Pd/c or $PtO_2$ etc. to give the compound (13).

(iv) The cycloheptimidazole compound (5) in which A is hydrogen and $A_1$ is hydroxyl is obtained from the compound (13) by using a reducing agent such as sodium borohydride and lithium aluminum hydride.

(II) The compounds of general formula (1) (wherein A or $A_1$ $=CHCOOR_3$ and $R_3$ represents a lower alkyl) are prepared by the following reactions:




(wherein $R_1$, $R_2$, $R_3$, X are the same as mentioned above).

The compound (13) is reacted with p-halogenobenzyl-halogen compound (6) in the presence of a base and a phase transfer catalyst such as tetra - n - butylammonium hydrogen-sulfate to give the compound (14). The obtained compound (14) is reacted with $LiCH_2COOR_3$ to give the compound (15), and then followed by the dehydration with $SOCl_2$/pyridine to give the compound (16). Also the reaction of the compound (14) with $(C_2H_5O)_2P(O)CH_2COOR_3$ in the presence of base gives the compound (16).

(B) A method for preparing a compound of general formula (2).

(I) Boronic acids of general formula (2) are

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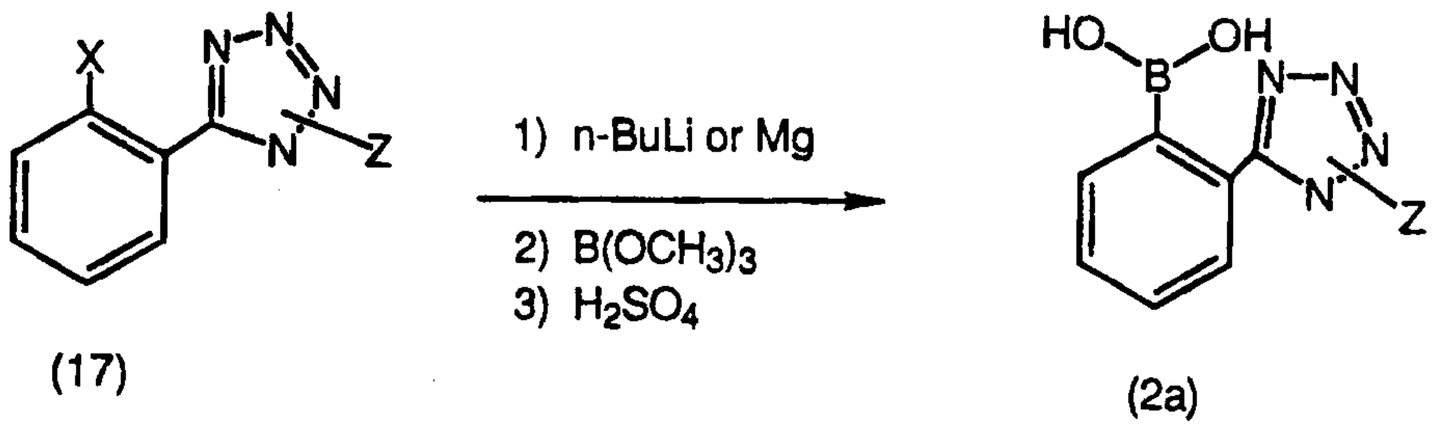
prepared by the following reaction:

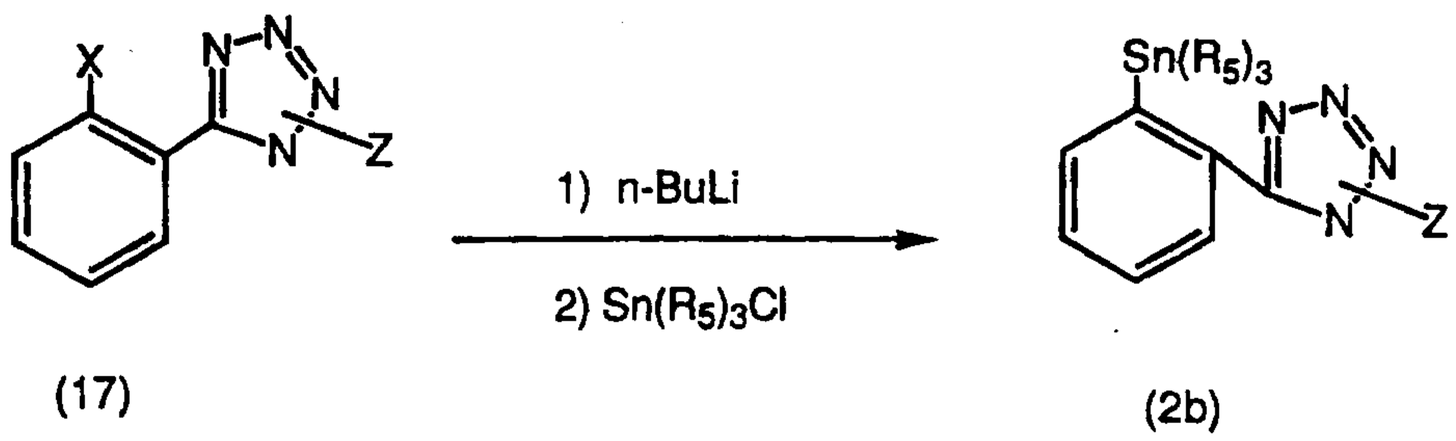



(17) (2a)

(wherein X is halogen atom, Z represents protecting group).

The compound of (17) is reacted with n-BuLi or Mg and then added $B(OCH_3)_3$ followed by hydrolysis with dilute $H_2SO_4$ to give the boronic acid (2a). (Jikken Kagakukouza (Experimental Chemistry) 24, Yuukigousei (Organic Synthesis) VI, Maruzen (KK), Japan, 1992, P. 61-90.)

(II) Tin compounds of general formula (2) are prepared by the following reaction:




(17) (2b)

(wherein X is halogen atom, Z represents protecting group, $R_5$ represents a lower alkyl group).

The compound (17) is reacted with n-BuLi and then $Sn(R_5)_3Cl$ to give the tin compound (2b).

(C) A method for preparing a compound of general formula (3).

In accordance with the present invention, the compound of general formula (1) is reacted with the compound of general formula (2) to give the compound of general formula (3).

(I) In the case of Y is $-B(OH)_2$ in the compound of general formula (2), the compound of the general formula (1) is reacted with the compound of the general formula (2) in the presence of a base and a catalyst to give the compound of the general formula (3). (Suzuki; Synthetic Communication, 11(7), 513 (1981).) The catalyst used in this reaction may be a palladium catalyst, such as $Pd(PPh_3)_4$, $PdCl_2$ and Pd/C. The base used in this reaction is for example sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide. A solvent may be used in this reaction such as water, ethanol, methanol, benzene and toluene. The reaction is conducted preferably at room temperature or at a temperature at which the solvent refluxes.

(II) In the case of Y is $-Sn(R_5)_3$ (wherein $R_5$ is a lower alkyl group) in the compound of general formula (2), the compound of the general formula (1) is reacted with the compound of the general formula (2) in the presence of a catalyst to give the compound of the general formula (3). (Shille; Angew. Chem. Int. Ed. Engl, 25, 508-524 (1988).) The catalyst used in this reaction may be a palladium, copper or lithium catalyst such as $Pd(PPh_3)_4$, $PdCl_2$, Pd/C, CuI and LiCl. A solvent may be used in this reaction such as tetra-

hydrofuran (THF), dimethoxyethane (DME) and dimethyl formamide (DMF). The reaction is conducted preferably at room temperature or at a temperature at which the solvent refluxes.

(D) Deprotection.

The compound of the general formula (3) is deprotected with a strong acid such as HCl and $CH_3SO_3H$ in benzene or toluene at reflux to give the object compound (4).

For better understanding the present invention, the following working examples are presented. By no means, however, the present invention should not be considered to be restricted to these working examples.

Example 1:

5-[2-4-(2-Propyl-8-oxo-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazolyl)methylbiphenylyl)]tetrazole.

(a) 1-(4-Iodobenzyl)-2-propyl-8-oxo-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazole.

2-Propyl-8-oxo-4,5,6,7-tetrahydro-cycloheptimidazole (5.0g) was dissolved in toluene (150ml) and 30% NaOH aqueous solution (60ml) was added. The mixture was stirred at room temperature for 30 min. 4-Iodobenzylbromide (9.2g) and tetra-n-butylammonium hydrogensulfate (2.0g) were then added and the reaction mixture was stirred at room temperature for 8hrs. The solution was filtered, and the filtrate was extracted with ethyl acetate (50mlx2), and the organic layer was washed with water and brine and dried ($Na_2SO_4$), filtered, and concentrated under vacuum. The resulting product was purified by silica gel column chromatography ($SiO_2$ 120g). Elution was carried out with n-hexane/ethyl acetate (1/1). The object compound was obtained

as a yellow color crystal (8.69g): mp (°C) 64-65; Mass (m/e): $M^+$=408, 217 (BP): IR ($cm^{-1}$): 2926, 1632, 1464, 1428. $^1$H-NMR ($CDCl_3$): 0.95 (3H, t, $-CH_2CH_2\underline{CH}_3$), 1.70 (2H, m, $-CH_2\underline{CH}_2CH_3$), 1.87 (2H, m, Cyclo), 1.92 (2H, m, Cyclo), 2.58 (2H, m, Cyclo), 2.65 (2H, m, Cyclo), 2.96 (2H, t, $-\underline{CH}_2CH_2CH_3$), 5.47 (2H, s, $-\underline{CH}_2-C_6H_5$), 6.71 (2H, d, aromatic), 7.62 (2H, d, aromatic).

(b) 2-tert-Butyl-5-[2-(4-(2-propyl-8-oxo-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazolyl)methylbiphenyl)]tetrazole.

A solution of the compound (150mg) which was obtained by the method as described above (a) in toluene (10ml) and ethanol (1ml) was added to [2-(2-tert-butyl-2H-tetrazol-5-yl)-phenyl] boronic acid (96mg) (example 3), $Pd(PPh_3)_4$ (35mg) and 2M $Na_2CO_3$ (0.7ml). The mixture was stirred at reflux for 3 hrs. The solution was concentrated under vacuum. The resulting product was purified by silica gel column chromatography. Elution was carried out with ethyl acetate/n-hexane (10:1). The object compound was obtained as a yellow color oil. IR ($cm^{-1}$): 2926, 1632, 1464, 1428. Mass (m/e) : $M^+$=482, 426,178 (BP). $^1$H-NMR ($CDCl_3$): 0.96 (3H, t, $-CH_2CH_2\underline{CH}_3$), 1.55 (9H, s, $-(\underline{CH}_3)_3$), 1.75 (2H, m, $-CH_2\underline{CH}_2CH_3$), 1.80~2.00 (4H, m, Cyclo), 2.59 (2H, t, Cyclo), 2.68 (2H, m, Cyclo), 3.01 (2H, q, $-\underline{CH}_2CH_2CH_3$), 5.57 (2H, s, $-\underline{CH}_2C_6H_5$), 6.90 (2H, d, aromatic), 7.09 (2H, d, aromatic), 7.35~7.60 (3H, m, aromatic), 7.89 (2H, d, aromatic).

(c) 5-[2-(4-(2-Propyl-8-oxo-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazolyl)methylbiphenylyl)]tetrazole.

A solution of the compound (100mg) which was obtained by the method as described above (b) in toluene 10ml and

methanesulfonic acid (200mg) was refluxed for 3hrs. The solution was concentrated under vacuum, and poured into ice water. The aqueous solution was adjusted pH8 with 10% NaOH. The resulting precipitate was collected by filtration, and was recrystallized with ethanol. The product was obtained as white crystal (77.4mg): mp (°C) 214-216; Mass (m/e): $M^+$=426, 383, 355, 178 (BP), 152. $^1$H-NMR ($CDCl_3$): 0.90 (3H, t, $-CH_2CH_2\underline{CH}_3$), 1.58 (2H, m, $-CH_2\underline{CH}_2CH_3$), 1.68 (2H, m, Cyclo), 1.75 (2H, m, Cyclo), 2.30 (2H, m, Cyclo), 2.47 (2H, m, Cyclo), 2.53 (2H, t, $-\underline{CH}_2CH_2CH_3$), 5.45 (2H, s, $-\underline{CH}_2C_6H_5$), 6.75 (2H, d, aromatic), 7.00 (2H, d, aromatic), 7.42 (2H, d, aromatic), 7.52 (2H, d, aromatic), 7.60 (2H, d, aromatic), 7.85 (2H, d, aromatic).

Example 2:

5-[2-(4-(2-Propyl-8-oxo-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazolyl)methylbiphenylyl)]tetrazole.

To a solution of 1-(4-iodobenzyl)-2-propyl-8-oxo-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazole (100mg) which was prepared in a similar manner as described in step (a) of Example 1 and 2-(2-tert.-butyl-2H-tetrazol-5-yl)phenyl]tri-n-butylstanano (120mg) (Example 4) in THF 8ml, added were lithium chloride (31.15mg) and $Pd(PPh_3)_4$ 1.4mg. The reaction mixture was refluxed for 48hrs. The reaction mixture was filtered, and filtrate was concentrated under vacuum. After the addition of ethyl acetate, the mixture was washed with brine, dried ($Na_2SO_4$), filtered, and organic solvent was evaporated under vacuum. The resulting oil was purified by silica gel column chromatography eluting with ethyl acetate/n-

hexane (1/1), 2-tert.-butyl-5-[2-(4-(2-propyl-8-oxo-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazolyl)methylbiphenylyl)]tetrazole was obtained as a yellow oil (45mg): Mass (m/e): $M^+$=482, 426, 369, 178 (BP). IR ($cm^{-1}$): 2926, 1632, 1464, 1428, 1389. $^1$H-NMR ($CDCl_3$): 0.96 (3H, t, $-CH_2CH_2\underline{CH}_3$), 1.55 (9H, s, $-(CH_3)_3$), 1.74 (2H, m, $-CH_2\underline{CH}_2CH_3$), 1.80~2.00 (4H, m, Cyclo), 2.59 (2H, t, Cyclo), 2.68 (2H, m, Cyclo), 3.01 (2H, q, $-\underline{CH}_2CH_2CH_3$), 5.57 (2H, s, $-\underline{CH}_2C_6H_5$), 6.90 (2H, d, aromatic), 7.09 (2H, d, aromatic), 7.35~7.60 (3H, m, aromatic), 7.89 (2H, d, aromatic).

According to the procedure described in Example 1, tert.-butyl group of 2-tert.-butyl-5-[2-(4-(2-propyl-8-oxo-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazolyl]methylbiphenylyl)]-tetrazole was deprotected to give the target compound of 5-[2-(4-(2-propyl-8-oxo-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazolyl)-methylbiphenylyl)]tetrazole.

Example 3:

[2-(2-tert.-Butyl-2H-tetrazole-5-yl)phenyl] boronic acid.

To a cooled (-78°C) solution of 5-(2-bromophenyl)-2-(1,1-dimethylethyl)-2H-tetrazole (3.3g) in THF (20ml) was added 1.6M n-BuLi in hexane (7.80ml) and triisopropyl borate (2.30g) was added. The cooling bath was removed, and the mixture was stirred at room temperature for 1h. HCl (0.5N) was added, and the mixture was stirred vigorously for 30min. The layers were separated, and the aqueous phase was extracted with ether. The combined organic phases were extracted with 1N KOH (3x10ml). The aqueous extracts were acidified (pH1) with 2N HCl (20ml), and the precipitate was collected by

filtration to give 1.87g of the boronic acid as a white solid: mp=117~122°C. $^1$H-NMR ($CDCl_3$): 1.72 (9H, s, $-C(CH_3)_3$), 7.46 (2H, m, aromatic), 7.90 (2H, m, aromatic).

Example 4:

[2-(2-tert.-Butyl-2H-tetrazole-5-yl)phenyl] tri-n-butylstanane.

To a cooled (-78°C) solution of 5-(2-bromophenyl)-2-(1,1-dimethylethyl)-2H-tetrazole (1.23g) in THF 8ml was added to 1.6M n-BuLi in hexane (3.27ml). After 1h., tri-n-butyltin chloride (1.71g) was added, and stirring was continued for 3hr at -78°C. The mixture was warmed to room temperature and stirred for 18h. Water was added, and the mixture was extracted with ether (30mlx2). The combined extracts were washed with water and brine, dried, and concentrated. The resulting oil was purified by silica gel column chromatography eluting with n-hexane, the butylstanane was obtained as a yellow oil (1.0g). $^1$H-NMR ($CDCl_3$): 0.78 (9H, t, $-(CH_3)_3$), 0.93 (6H, t, $-(CH_2-)_3$), 1.21 (6H, m, $-(CH_2-)_3$), 1.43 (6H, m, $-(CH_2-)_3$), 1.80 (9H, s, $(CH_3)_3$), 7.43 (1H, d, aromatic), 7.45 (1H, d, aromatic), 7.60 (1H, m, aromatic), 8.00 (1H, m, aromatic).

Example 5:

2-Ethyl-8-ethoxycarbonylmethylidene-1-[(2'-1H-tetrazole-5-yl)biphenyl-4-yl)methyl]-4,5,6,7-tetrahydro-cycloheptimidazole.

(a) 1-(4-Bromobenzyl)-2-ethyl-8-oxo-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazole.

2-Ethyl-8-oxo-4,5,6,7-tetrahydro-cycloheptimidazole (2.5g) was dissolved in toluene (50ml) and 30% NaOH aqueous

solution (30ml) was added. The mixture was stirred at room temperature for 30min. 4-Bromobenzylbromide (3.6g) and tetra-n-butylammonium hydrogensulfate (0.5g) were then added and the reaction mixture was stirred at room temperature for 8hrs. The solution was filtered, and filtrate was extracted with ethyl acetate (20mlx2), and the organic layer was washed with water and brine and dried ($Na_2SO_4$), filtered, and concentrated under vacuum. The resulting product was purified by silica gel column chromatography ($SiO_2$ 100g). Elution was carried out with n-hexane/ethyl acetate (1/1). The object compound was obtained as a yellow color oil (4.0g). Mass (m/e): $M^+$=347, 319, 169 (BP). IR ($cm^{-1}$): 2950, 1640, 1480, 1400, 1330. $^1H$-NMR ($CDCl_3$): 1.27 (3H, t, $-CH_2\underline{CH_3}$), 1.85 1.87 (2H, m, Cyclo), 1.91~1.94 (2H, m, Cyclo), 2.60~2.65 (4H, m, Cyclo), 3.01 (2H, q, $\underline{CH_2}CH_3$), 5.48 (2H, s, $-\underline{CH_2}C_6H_4$), 6.86 (2H, d, aromatic), 7.41 (2H, d, aromatic).

(b) 1-(4-Bromobenzyl)-2-ethyl-8-ethoxycarbonylmethyl-8-hydroxy-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazole.

To a solution of $(Me_3Si)_2NLi$ (2.88ml) in THF (5ml) was added dry ethyl acetate (0.25ml) at -78°C, and the mixture was stirred for 15min. Then compound (0.5g) which was prepared by Example 5 (a) in dry THF was dropwised. The reaction mixture was stirred at -78°C for 1h, and treated with 6N HCl to adjust the pH5.0. The reaction mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and then brine and dried ($Na_2SO_4$), filtered, and concentrated under vacuum. The resulting product was purified by silica gel column chromatography. Elution was carried out with chloroform/-

methanol (20/1). The object compound was obtained as a yellow oil (388mg). Mass (m/e): $M^+$=435, 348, 169 (BP), 90. IR ($cm^{-1}$): 3300, 2900, 1720, 1170, 1000. $^1H$-NMR ($CDCl_3$): 1.28 (3H, t, $-CH_2\underline{CH}_3$), 1.33 (3H, t, $-CH_2\underline{CH}_3$), 1.80~2.20 (6H, m, Cyclo), 2.71 (2H, m, $-CH_2COOEt$), 2.78 (2H, q, $-\underline{CH}_2CH_3$), 2.97 (2H, m, Cyclo), 4.57 (2H, q, $-\underline{CH}_2CH_3$), 5.81 (2H, s, $-\underline{CH}_2C_6H_5$), 7.20~7.40 (4H, m, aromatic).

(c) 1-(4-Bromobenzyl)-2-ethyl-8-ethoxycarbonyl-methylidene-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazole.

(1) 1-(4-Bromobenzyl)-2-ethyl-8-ethoxycarbonyl-methyl-8-hydroxy-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazole (0.38g) which was prepared in step (b) of Example 5 was dissolved in pyridine (2ml), and $SOCl_2$ (0.32g) was added thereto, and the mixture was stirred at room temperature for 1h. The reaction mixture was poured into 10% HCl (20ml) at 0°C, and extracted with ethyl acetate, and ethyl acetate layer was washed with brine and dried ($Na_2SO_4$), filtered, and concentrated under vacuum. The resulting product was purified by silica gel column chromatography. Elution was carried out with chloroform/-methanol (20/1). The object compound was obtained as a yellow oil (280mg).

(2) KH (0.08g) was dissolved in THF 5ml, and then diethyl phosphonoacetate (0.37g) was added at 5°C. After the mixture was stirred at 10°C for 10min, 1-(4-bromobenzyl)-2-ethyl-8-oxo-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazole (0.5g) in THF 1ml which was prepared in step (a) of Example 5 was added. The mixture was stirred at 40°C for 5hrs. The reaction mixture was poured into ice water (20ml), and extracted

with ethyl acetate. The organic layer was washed with water and then brine and dried ($Na_2SO_4$), filtered, and concentrated under vacuum. The resulting product was purified by silica gel column chromatography. Elution was carried out with chloroform/methanol (20/1). The object compound was obtained as a yellow color oil (60mg). Mass (m/e): $M^+$+1=418, 371, 343, 171 (BP), 90. IR ($cm^{-1}$): 2900, 1710, 1230, 1170, 1000. $^1$H-NMR ($CDCl_3$): 1.26 (3H, t, $-CH_2\underline{CH}_3$), 1.26 (3H, t, $-CH_2\underline{CH}_3$), 1.85 (2H, m, Cyclo), 1.90 (2H, m, Cyclo), 2.91 (2H, q, $\underline{CH}_2CH_3$), 2.92 (2H, q, $\underline{CH}_2CH_3$), 4.05~4.20 (4H, m, Cyclo), 5.28 (2H, s, $-\underline{CH}_2C_6H_5$), 5.68 (1H, s, $=C\underline{H}COOC_2H_5$), 6.80 (2H, d, aromatic), 7.55 (2H, d, aromatic).

(d) 2-tert.-Butyl-5-[2-(4-(2-ethyl-8-ethoxycarbonyl-methylidene-4,5,6,7-tetrahydro-1(4H)-cycloheptimidazolyl)methyl-biphenylyl)]tetrazole.

To a solution of the compound (280mg) which was prepared by Example 5 (c) in toluene (5ml) and ethanol (0.1ml), added were [2-(2-tert.-butyl-2H-tetrazole-5-yl)phenyl] boronic acid (175.5mg), $Pd(PPh_3)_4$ (26.8mg) and 2M $Na_2CO_3$ (1.6ml). The mixture was stirred at reflux for 4.5hrs. The reaction mixture was poured into water (30ml), and extracted with toluene (20mlx3), and toluene layer was washed with brine and dried ($Na_2SO_4$), filtered, and concentrated under vacuum. The resulting product was purified with silica gel column chromatography. Elution was carried out with ethyl acetate/n-hexane (1/1). The object compound was obtained as a yellow oil (230mg). Mass (m/e): $M^+$+1=539, 451, 253, 178 (BP). IR ($cm^{-1}$): 3420, 3000, 1230, 2950, 1720. $^1$H-NMR ($CDCl_3$): 1.25 (3H, s, t-Bu), 1.82 (2H, m,

Cyclo), 1.89 (2H, m, Cyclo), 2.55 (2H, q, $-\underline{CH}_2CH_3$), 2.80～2.83 (2H, m, Cyclo), 3.04～3.07 (2H, m, Cyclo), 4.12 (2H, q, $-\underline{CH}_2CH_3$), 5.17 (2H, s, $-\underline{CH}_2C_6H_5$), 5.56 (1H, s, $=C\underline{H}COOC_2H_5$), 6.82 (2H, d, aromatic), 7.14 (2H, d, aromatic), 7.39～7.88 (4H, m, aromatic).

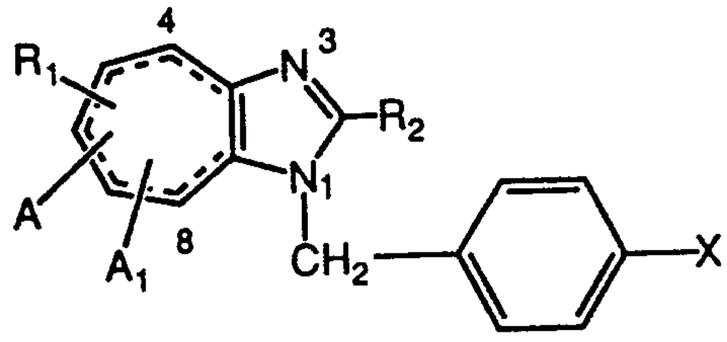
(e) 2-Ethyl-8-carboxymethylidene-1-[(2'-(1H-tetrazole-5-yl)biphenyl-4-yl)methyl]-4,5,6,7-tetrahydro-cycloheptimidazole.

A solution of the compound (200mg) which was obtained by the Example 5 (d) as described above in toluene 20ml and methanesulfonic acid (400mg) was refluxed for 3hrs. The solution was concentrated under vacuum, and poured into ice water. The aqueous solution was adjusted pH4 with 10% NaOH. The resulting precipitate was collected by filtration, and was recrystallized with methanol (2ml). The product was obtained as white crystal (120mg). mp: 191～193°C. Mass (m/e): $M^+$=408 ($M^+$-COOH), 367, 192 (BP), 134. IR ($cm^{-1}$): 2914, 1692, 1611, 1452, 1362, 1197. $^1$H-NMR ($CD_3OD$): 1.30 (3H, t, $-CH_2\underline{CH}_3$), 1.94 (4H, bs, Cyclo), 2.65～3.03 (6H, m, $-\underline{CH}_2CH_3$+Cyclo), 5.43 (2H, s, $-\underline{CH}_2C_6H_5$), 5.92 (1H, s, $=C\underline{H}COOH$), 6.80～7.70 (8H, m, aromatic), 7.96 (1H, s, -NH).

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

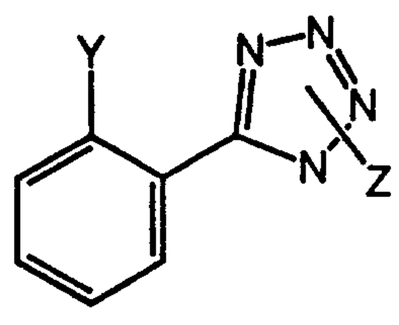
1. A process which comprises:

reacting a compound of the general formula (1):



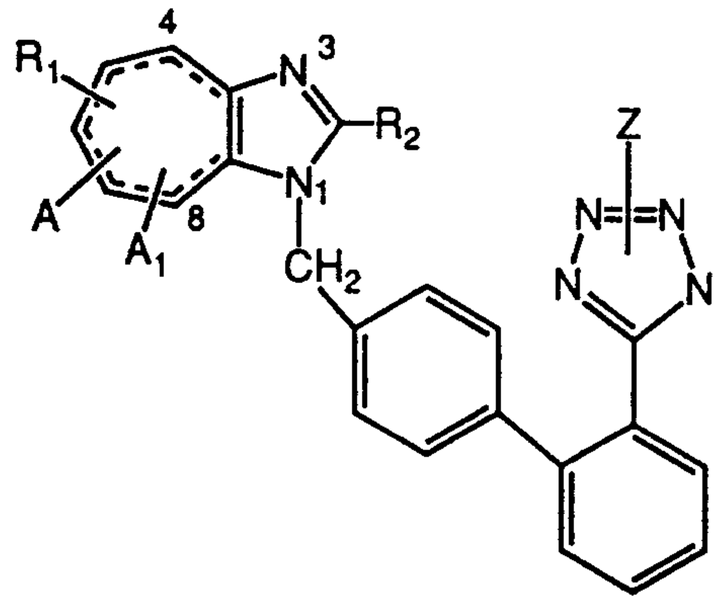
(1)

(wherein $R_1$ is hydrogen or isopropyl; $R_2$ is a lower alkyl; A and $A_1$ are each a substituent at the 4- or 8-position, and $A_1$ is hydrogen or hydroxyl when A is hydrogen, or A and $A_1$ together form an oxo group or $=CHCOOR_3$ (in which $R_3$ is a lower alkyl); the dotted line represents two double bonds or saturated single bonds; and X is halogen atom or trifluoromethanesulfonate) with a compound of the general formula (2):



(2)

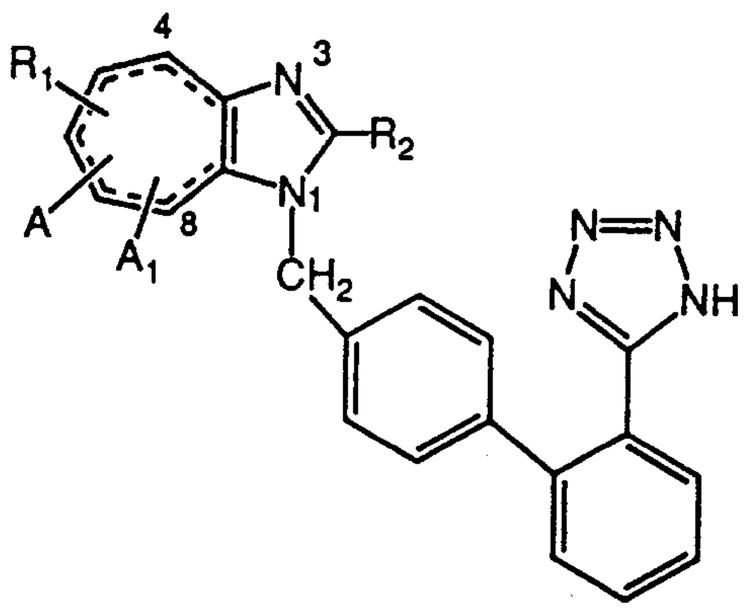
(wherein Y is $-B(OH)_2$ or $-Sn(R_5)_3$ (in which $R^5$ is a lower alkyl); and Z is a protecting group), to give a compound of the general formula (3):



(3)

(wherein $R_1$, $R_2$, A, $A_1$, the dotted line and Z are as defined above), and

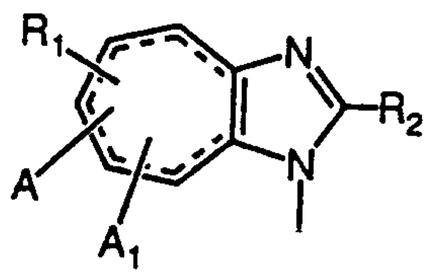
then deprotecting the compound (3) to give a compound of the general formula (4):



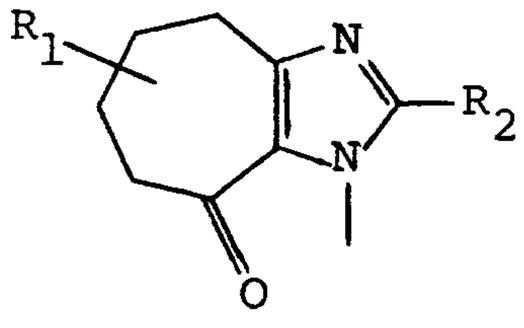
(4)

(wherein $R_1$, $R_2$, A, $A_1$ and the dotted line are as defined above).

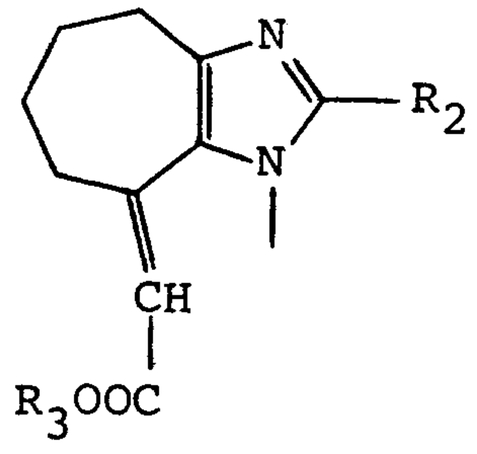
2. The process according to claim 1, wherein the portion



of the formulae (1) and (3) is



or

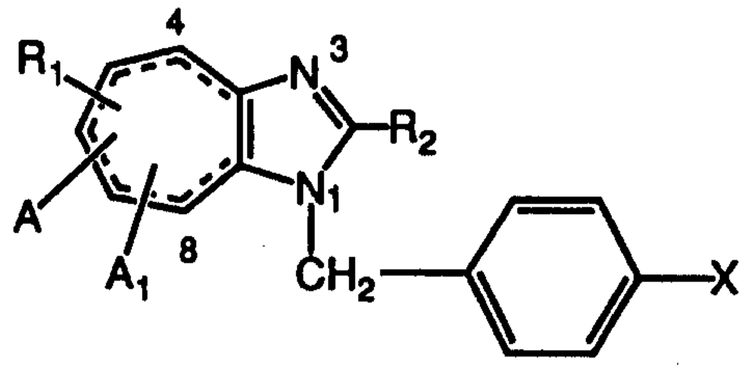


3. The process according to claim 1 or 2, wherein Y in the formula (2) is $-B(OH)_2$; and the reaction of the compound (1) with the compound (2) is carried out in the presence of a base and a catalyst selected from the group consisting of $Pd(PPh_3)_4$, $PdCl_2$ and Pd/C.

4. The process according to claim 1 or 2, wherein Y in the formula is $-Sn(R_5)_3$ in which $R_5$ is a lower alkyl group; and the reaction of the compound (1) with the compound (2) is carried out in the presence of a catalyst selected from the group consisting of $Pd(PPh_3)_4$, $PdCl_2$, Pd/C, CuI and LiCl.

5. The process according to claim 1, 2, 3 or 4, wherein the protective group Z is a member selected from the group consisting of tert-butyl, trityl, methoxymethyl and p-nitrophenyl; and the protective group is removed from the compound (3) by treating the compound (3) with HCl or $CH_3SO_3H$ in benzene or toluene at a reflux temperature.

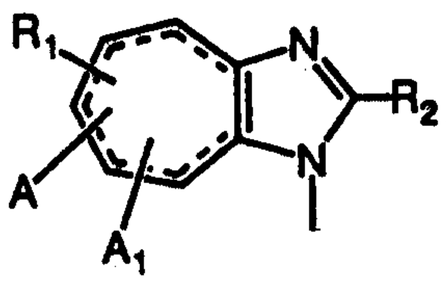
6. A compound of the general formula (1):



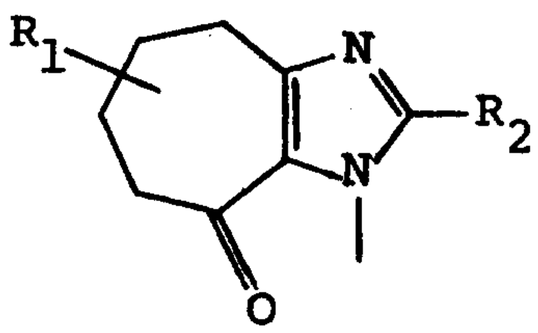
(1)

(wherein $R_1$ is hydrogen or isopropyl; $R_2$ is a lower alkyl; A and $A_1$ are each a substituent at the 4- or 8-position, and $A_1$ is hydrogen or hydroxyl when A is hydrogen, or A and $A_1$ together form an oxo group or $=CHCOOR_3$ (in which $R_3$ is a lower alkyl); the dotted line represents two double bonds or saturated single bonds; and X is halogen atom or trifluoromethanesulfonate).

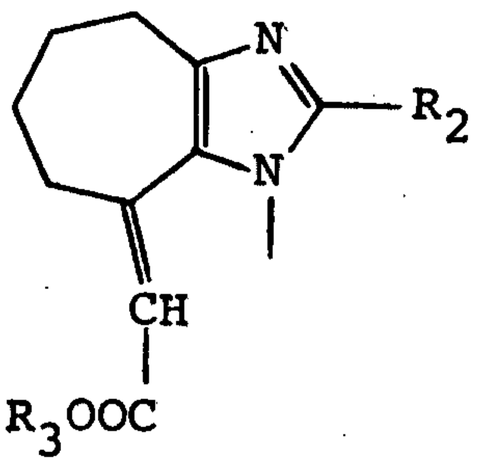
7. The compound according to claim 6, wherein the portion



of the formula (1) is



or



8. A process for producing a compound of the general formula (1) as defined in claim 6, which comprises:

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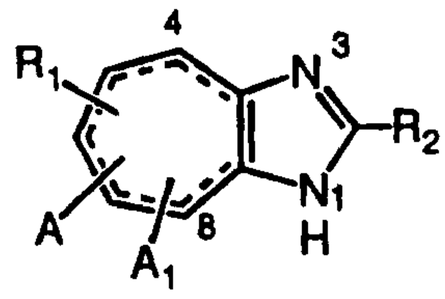
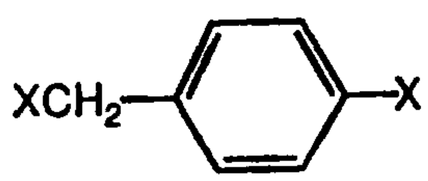
reacting a compound of the general formula (5):



(5)

(wherein $R_1$, $R_2$, A, $A_1$ and the dotted line are as defined in claim 6) with a halogenobenzylhalogene of the formula (6):



(6)

in the presence of a base.

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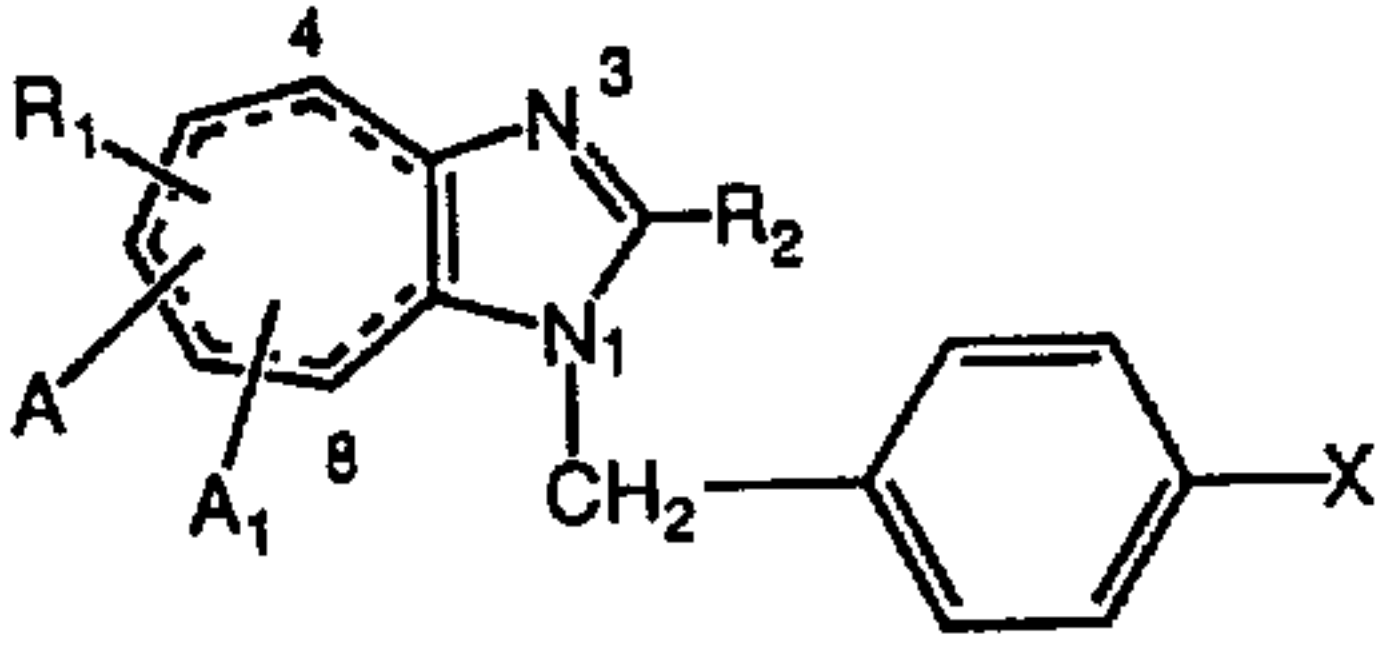
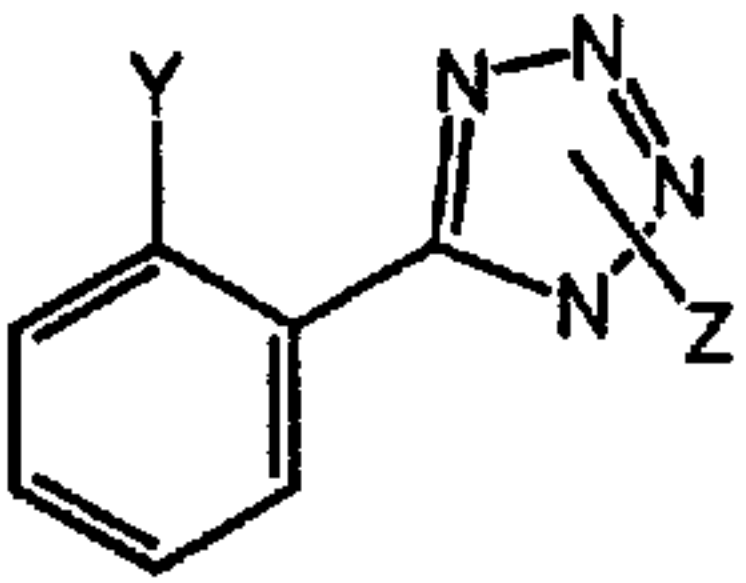
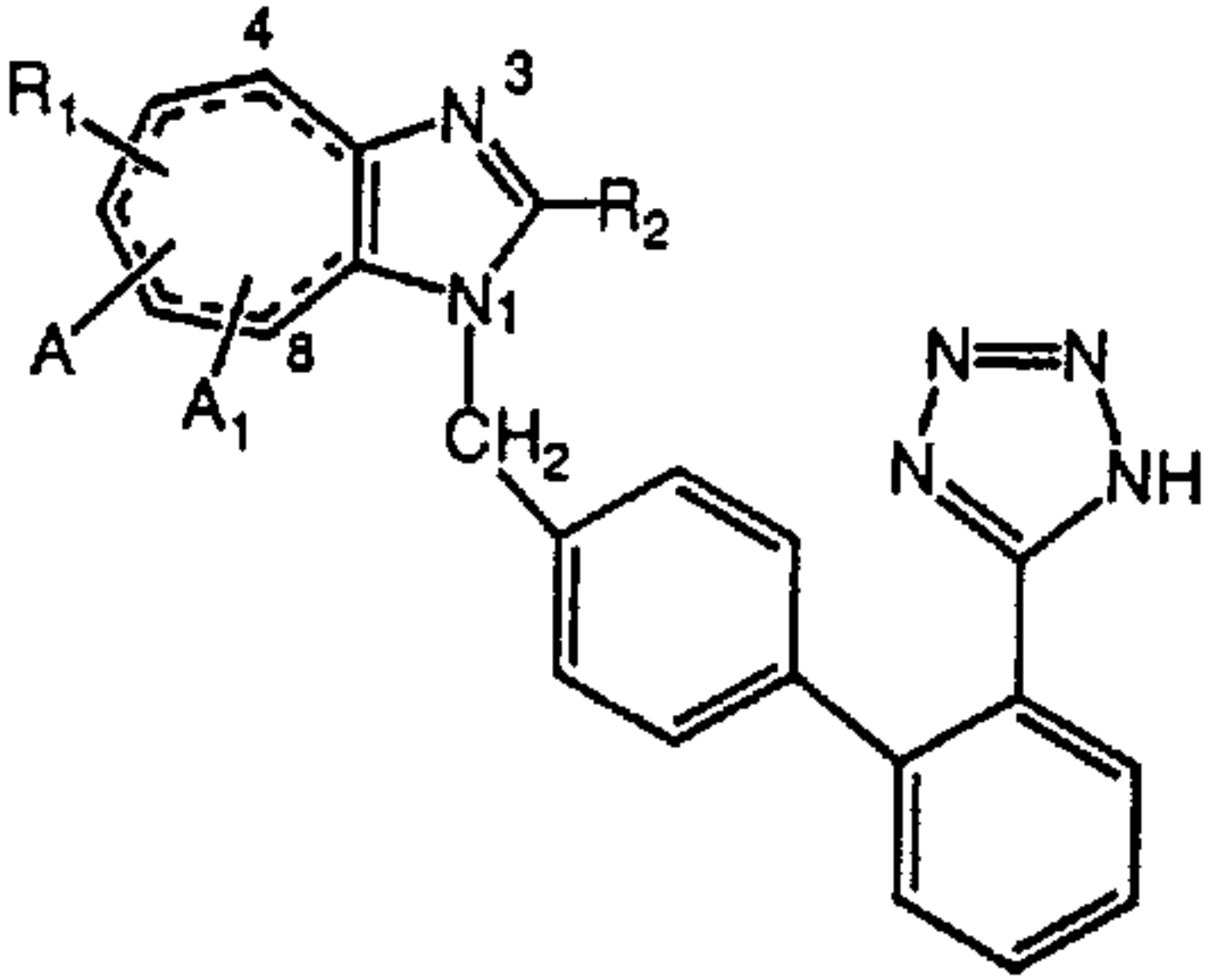
Patent Agents



(1)



(2)



(4)