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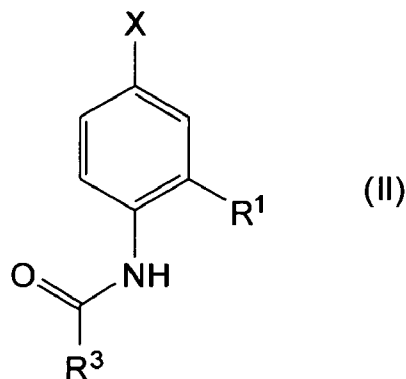
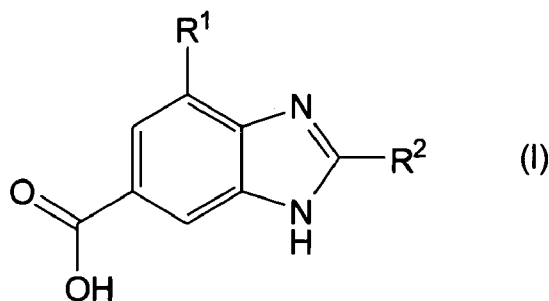
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(54) Title: PROCESS AND INTERMEDIATES FOR THE PREPARATION OF BENZIMIDAZOLECARBOXYLIC ACIDS

(57) Abstract: Substituted benzimidazolecarboxylic acids of formula (I), wherein R¹ and R² independently are hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl, are prepared in a four-step synthesis starting from *N*-acyl-4-haloanilines of formula (II), wherein R¹ is as defined above, R³ is C₁₋₄ alkyl and X is chlorine or bromine.



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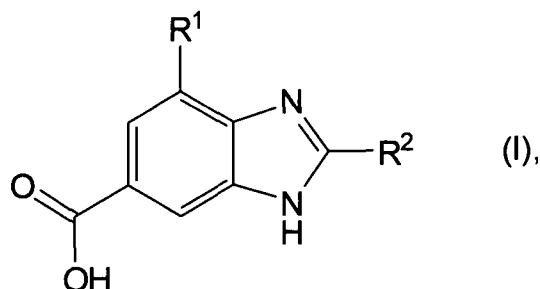
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Process and intermediates for the preparation of benzimidazolecarboxylic acids

The invention relates to a process for the production of substituted benzimidazole-6-carboxylic acids of formula

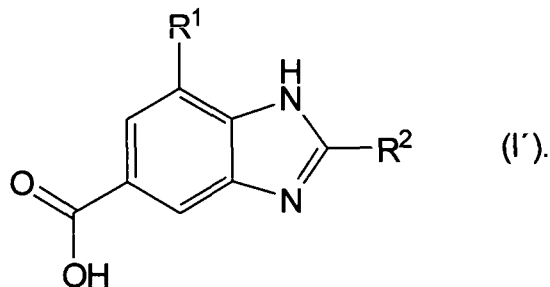


wherein R^1 and R^2 independently are hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl. It further relates to novel intermediates in the process of the invention.

Herein the term " C_{1-n} alkyl", e.g. " C_{1-6} -alkyl", represents any linear or branched alkyl group having 1 to n carbon atoms. C_{1-6} -alkyl represents for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, and the various isomeric pentyls and hexyls. The term " C_{3-6} cycloalkyl" represents cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

20 Benzimidazoles of formula I are useful as intermediates in the synthesis of pharmaceutically active compounds. In particular, 4-methyl-2-propylbenzimidazole-6-carboxylic acid (R^1 = methyl, R^2 = propyl) is a key intermediate in the industrial synthesis of telmisartan, an angiotensin II receptor antagonist used in the therapy of hypertension.

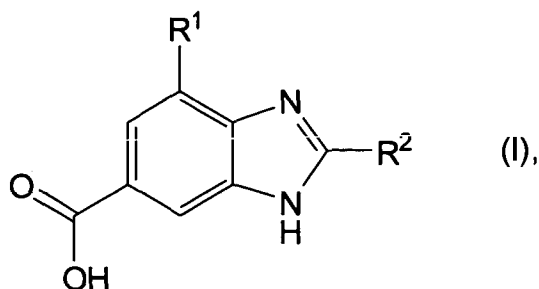
25 The benzimidazolecarboxylic acids of formula I can exist in two tautomeric forms, namely the 1*H* form depicted above and the 3*H* form (I') depicted below:



All compound names and structural formulas used hereinbelow are intended to encompass both tautomeric forms, although, for the sake of simplicity, only the 1*H* form will be mentioned and/or depicted.

- 5 Several processes for the preparation of benzimidazolecarboxylic acids of formula I or related compounds are known in the art. Typically used processes comprise the preparation of nitro-acylaminobenzoates and their ring closure to obtain the corresponding benzimidazoles. From early patents such as US 4 880 804, US 5 591 762, DE-A 199 17 524 up to more recently published patent applications such as
- 10 WO-A 2006/044754 the known processes to prepare benzimidazole intermediates for the preparation of telmisartan and derivatives thereof have not been substantially changed. Similar strategies can be found in scientific literature, such as Ries, U.J. et al., *J. Med. Chem.* 1993, 36, 4040–4051, or Teramoto, S. et al., *J. Med. Chem.* 2003, 46, 3033–3044. Although most of their steps are high-yielding, the syntheses known in
- 15 the art are lengthy and difficult to perform on a large scale. Thus, a shorter synthesis to provide the intermediate of formula I was desired. Furthermore, common syntheses comprise two nitration and two nitro group reduction steps, which are difficult to conduct safely.
- 20 It was an object of the instant invention to provide a shorter, cheaper, more efficient and environmentally sound process that is suitable for large scale production of compounds of formula I, for the preparation of telmisartan and derivatives thereof.

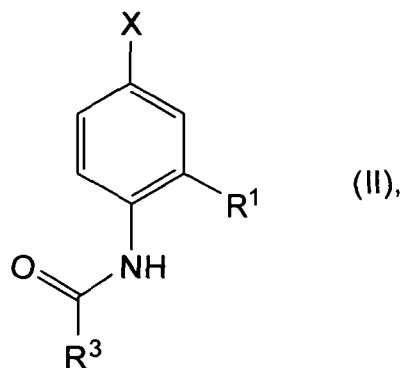
According to the invention, substituted benzimidazolecarboxylic acids of formula



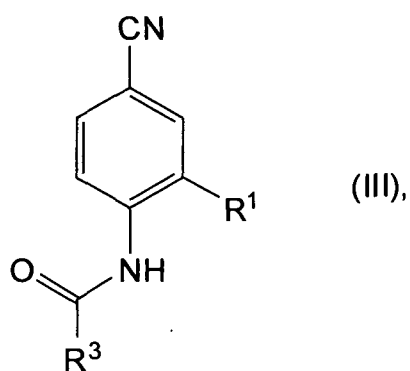
wherein R¹ and R² independently are hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl, are prepared in a process comprising the steps of

(i) cyanating an *N*-acyl-4-haloaniline of formula

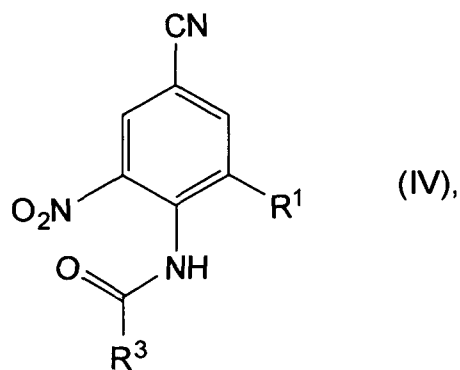
- 3 -



wherein R¹ is as defined above, R³ is C₁₋₄ alkyl and X is chlorine or bromine, to obtain the corresponding cyano compound of formula



wherein R¹ and R³ are as defined above,
nitrating the cyano compound obtained in step (i) to obtain the corresponding nitro compound of formula

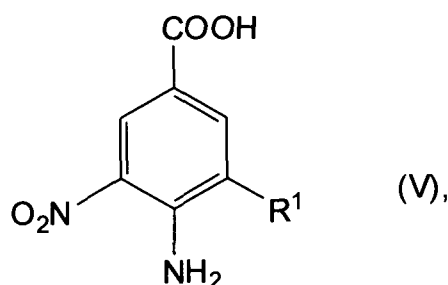


wherein R¹ and R³ are as defined above,

- (ii) hydrolyzing the cyano and acylamino groups of the nitro compound obtained in step (i) to obtain the corresponding *p*-aminobenzoic acid of formula

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- 4 -



wherein R¹ is as defined above, and

- (iii) reacting said *p*-aminobenzoic acid in the presence of a reducing agent with an aldehyde of formula



wherein R² is as defined above,

to obtain the target compound of formula I.

In a preferred embodiment, the cyanation in step (i) is effected with potassium hexacyanoferrate(II) in a polar aprotic solvent and in the presence of a palladium phosphine complex as catalyst. This embodiment is particularly advantageous since potassium hexacyanoferrate(II) is much less toxic than the cyanides usually employed in cyanation reactions. Suitable polar aprotic solvents are for example the commonly used amides, ureas or sulfoxides, such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidone, *N,N,N',N'*-tetramethylurea or dimethyl sulfoxide.

More preferably, the palladium phosphine complex is tetrakis(triphenylphosphine)-palladium(0)

In another preferred embodiment, the nitration in step (ii) is effected using an alkali metal nitrate in sulfuric acid as nitrating agent. This embodiment is particularly advantageous since the usage of large amounts of nitric acid is avoided.

In still another preferred embodiment, the hydrolysis in step (iii) is effected using an aqueous hydrohalic acid such as hydrochloric, hydrobromic or hydriodic acid. Hydrochloric acid is particularly preferred.

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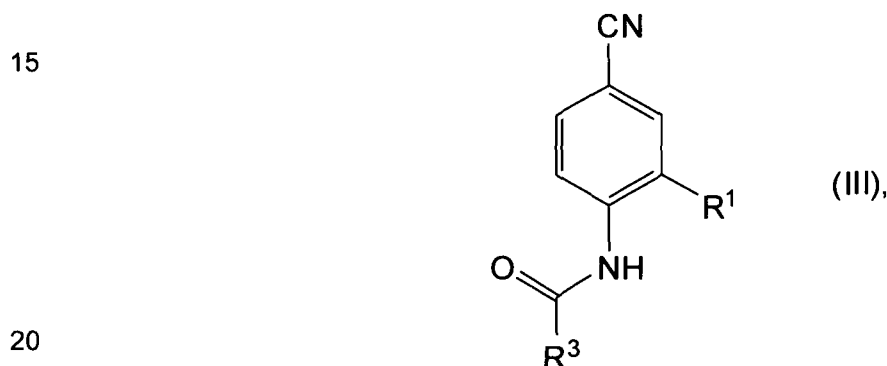
In still another preferred embodiment, an alkali metal dithionite is used as reducing agent in step (iv), sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$) being particularly preferred.

5 In a preferred embodiment, R^1 in the final product (I), the starting material (II) and the intermediates (III) through (V) is methyl.

In another preferred embodiment, R^2 in the final product (I) and the aldehyde (VI) is propyl.

10 In still another preferred embodiment, R^3 in the starting material (II) and the intermediates (III) and (IV) is methyl or propyl.

The compounds of formula

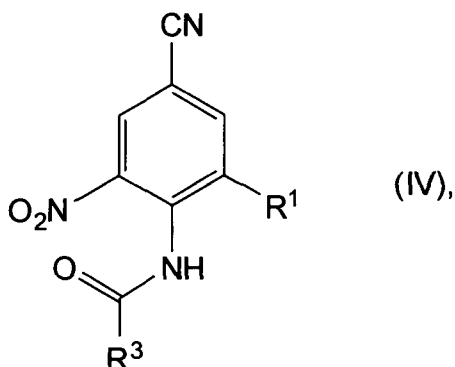


wherein R^1 is C_{1-6} alkyl or C_{3-6} cycloalkyl and R^3 is propyl, are novel and also an embodiment of the invention.

25 In a preferred embodiment, R^1 is methyl.

The compounds of formula

5



(IV),

- 10 wherein R¹ is C₁₋₆ alkyl or C₃₋₆ cycloalkyl and R³ is C₁₋₄ alkyl, are likewise novel and an embodiment of the invention.

In a preferred embodiment, R¹ is methyl.

- 15 In another preferred embodiment, R³ is methyl or propyl.

The following non-limiting examples will further illustrate the invention.

20 **Example 1**

***N*-(4-Bromo-2-methylphenyl)acetamide (II, R¹ = R³ = CH₃, X = Br)**

- A mixture of 2-methylaniline (5 g, 47 mmol, 1 eq.), acetic anhydride (5 g, 49 mmol, 1.1 eq.) and hexamethylphosphoramide (trace) was stirred at room temperature. The reaction was monitored by TLC or HPLC. After completion of amide formation, aqueous hydrobromic acid (40%, 9.53 g, 47 mmol, 1.0 eq.) was added to the resulting solution of *N*-(2-methylphenyl)acetamide and the mixture was cooled to 0 °C. Aqueous hydrogen peroxide (30%, 5.48 g, 47 mmol, 1.0 eq.) was then added slowly within 30 min and stirring was continued overnight. A white precipitate formed and was collected by filtration. The filtrate was concentrated using a rotary evaporator and a second crop of white solid was collected by filtration. The combined white solid was washed with water and aqueous sodium carbonate and dried to give *N*-(4-bromo-2-methylphenyl)acetamide as a white solid.

Yield: 8.50 g (80%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.32 (s, 1H), 7.41 (d, $J = 2.0$ Hz, 1H), 7.40 (d, $J = 8.8$ Hz, 1H), 7.32 (dd, $J = 2.0$ Hz, $J = 8.8$ Hz, 1H), 2.19 (s, 3H), 2.05 (s, 3H).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 168.8, 136.4, 134.5, 133.1, 129.1, 127.0, 117.4, 23.8, 18.0.

Example 2

N-(4-Bromo-2-methylphenyl)butyramide (II, $\text{R}^1 = \text{CH}_3$, $\text{R}^3 = n\text{-C}_3\text{H}_7$, $\text{X} = \text{Br}$)

Butyryl chloride (36.0 g, 0.338 mol, 1.2 eq.) was added to a solution of 2-methylaniline (30.0 g, 0.28 mol, 1.0 eq.) and triethylamine (31.2 g, 0.308 mol, 1.1 eq.) in dichloromethane (250 mL) within 35 min at room temperature. The mixture was stirred at room temperature for another 3.5 h and then washed with water and aqueous sodium carbonate solution. The organic layer was dried with anhydrous sodium sulfate and concentrated to give *N*-(2-methylphenyl)butyramide as a white solid (45.27 g, 90%) which was used in the next step without further purification.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.23 (s, 1H), 7.37 (d, $J = 7.6$ Hz, 1H), 7.20 (d, $J = 7.5$ Hz, 1H), 7.15 (t, $J = 7.6$ Hz, 1H), 7.07 (t, $J = 6.8$ Hz, 1H), 2.31 (t, $J = 7.3$ Hz, 2H), 2.20 (s, 3H), 1.63 (m, $J = 7.4$ Hz, $J = 7.3$ Hz, 2H), 0.95 (t, $J = 7.4$ Hz, 3H).

The crude *N*-(2-methylphenyl)butyramide (5.01 g, 28 mmol, 1.0 eq.) was dissolved in methanol (50 mL). Aqueous hydrobromic acid (40%, 5.87 g, 29 mmol, 1.0 eq.) was added in one portion. The mixture was cooled (ice-water bath), aqueous hydrogen peroxide (30%, 3.67 g, 29 mmol, 1.0 eq.) was added slowly within 15 min and stirring was continued overnight. After removal of excess methanol, a white solid was obtained by filtration. The wet cake was washed with aqueous sodium carbonate and water and dried under vacuum to give a white solid.

Yield: 6.22 g (85%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.26 (s, 1H), 7.42 (d, $J = 2.0$ Hz, 1H), 7.36 (d, $J = 8.5$ Hz, 1H), 7.32 (dd, $J = 2.0$ Hz, $J = 8.5$ Hz, 1H), 2.30 (t, $J = 7.2$ Hz, 2H), 2.18 (s, 3H), 1.61 (m, $J = 7.2$ Hz, $J = 7.4$ Hz, 2H), 0.92 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 171.6, 136.4, 134.8, 133.1, 129.1, 127.3, 117.5, 38.2, 19.2, 18.0, 14.1.

5 Example 3

N-(4-Chloro-2-methylphenyl)butyramide (II, $\text{R}^1 = \text{CH}_3$, $\text{R}^3 = n\text{-C}_3\text{H}_7$, $\text{X} = \text{Cl}$)

n-Butyryl chloride (18.64 g, 0.175 mol, 1.2 eq.) was added to a mixture of 4-chloro-2-methylaniline (20 g, 0.141 mol, 1.0 eq.) and triethylamine (17.41 g, 0.172 mol, 1.2 eq.) in dichloromethane (250 mL) within 25 min at room temperature. The reaction mixture was stirred at room temperature for another 18 h. Iced water was then added and the mixture was extracted with dichloromethane. The combined organic layer was washed with aqueous sodium carbonate and water, dried over anhydrous sodium sulfate, and concentrated to give a white solid.

Yield: 25 g (80%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.27 (s, 1H), 7.41 (d, $J = 8.5$ Hz, 1H), 7.28 (d, $J = 2.3$ Hz, 1H), 7.20 (dd, $J = 8.5$ Hz, $J = 2.3$ Hz, 1H), 2.30 (t, $J = 7.4$ Hz, 2H), 2.10 (s, 3H), 1.61 (m, $J = 7.4$ Hz, $J = 7.4$ Hz, 2H), 0.92 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 171.6, 135.9, 134.4, 130.2, 129.2, 127.0, 126.1, 38.1, 19.2, 18.1, 14.0.

Example 4

N-(4-Chloro-2-methylphenyl)butyramide (II, $\text{R}^1 = \text{CH}_3$, $\text{R}^3 = n\text{-C}_3\text{H}_7$, $\text{X} = \text{Cl}$)

A mixture of *N*-(2-methylphenyl)butyramide (1.0 g, 6 mmol, 1.0 eq.), hydrochloric acid (36%, 0.6 mL, 7 mmol, 1.2 eq.) and aqueous hydrogen peroxide (30%, 0.7 mL, 7 mmol, 1.2 eq.) in methanol (10 mL) in an open system equipped with a reflux condenser was heated to 40 °C for 18 h. Preparative TLC isolated *N*-(4-chloro-2-methylphenyl)butyramide as a white solid (119 mg, 10%).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 172.1, 141.6, 134.5, 131.2, 130.6, 124.5, 119.4, 106.8, 38.3, 19.1, 18.0, 14.0.

5 Example 7

N-(4-Cyano-2-methylphenyl)butyramide (III, $\text{R}^1 = \text{CH}_3$, $\text{R}^3 = n\text{-C}_3\text{H}_7$)

A mixture of *N*-(4-chloro-2-methylphenyl)butyramide (0.504 g, 2.38 mmol, 1.0 eq.), potassium hexacyanoferrate(II) trihydrate (0.40 g, 0.95 mmol, 0.4 eq.), sodium carbonate (0.304 g, 2.87 mmol, 1.2 eq.), palladium(II) acetate (12.2 mg, 0.05 mmol, 0.02 eq.), triphenylphosphine (62.2 mg, 0.24 mmol, 0.1 eq.) in *N,N*-dimethylacetamide (7 mL) was heated to 140 °C for 18 h. *N*-(4-Cyano-2-methylphenyl)butyramide was obtained in 40% yield and unreacted starting material was fully recovered. NMR spectra were found identical to those of the product prepared from *N*-(4-bromo-2-methylphenyl)-butyramide.

Example 8

N-(4-Cyano-2-methyl-6-nitrophenyl)acetamide (IV, $\text{R}^1 = \text{R}^3 = \text{CH}_3$)

A mixture of sodium nitrate (4.87 g, 57 mmol, 2 eq) and concentrated sulfuric acid (98%, 25 mL) was stirred in an ice-water bath for 25 min. *N*-(4-Cyano-2-methylphenyl)acetamide (5.00 g, 29 mmol, 1 eq.) was then added in portions slowly. The reaction mixture was stirred in an ice-water bath for 3.5 h before it was poured into ice water to give a yellow precipitate. Ethyl acetate was added. The organic phase was separated and washed with aqueous sodium carbonate. Removal of ethyl acetate by rotary evaporator afforded a yellow solid.

Yield: 5.20 g (80%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.19 (s, 1H), 8.30 (d, $J = 1.68$ Hz, 1H), 8.11 (m, 1H), 2.34 (s, 3H), 2.07 (s, 3H).

^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 169.1, 138.4, 137.9, 133.5, 126.9, 117.5, 108.8, 23.2, 18.1.

Example 5***N*-(4-Cyano-2-methylphenyl)acetamide (III, R¹ = R³ = CH₃)**

A mixture of *N*-(4-bromo-2-methylphenyl)acetamide (20.08 g, 88 mmol, 1.0 eq.) potassium hexacyanoferrate(II) trihydrate (14.86 g, 35 mmol), tetrakis(triphenylphosphine)palladium(0) (506.6 mg, 0.44 mmol, 0.5% eq), sodium carbonate (11.23 g, 106 mmol, 1.2 eq) and DMF (200 mL) was heated to 120 °C for 20 h under nitrogen protection. The reaction mixture was then cooled to room temperature and the precipitated solid was filtrated off. The organic layer was diluted with ethyl acetate, washed with water, and dried with anhydrous sodium sulfate. Volatiles were removed by rotary evaporator to give a white solid.

Yield: 10.74 g (72%).

¹H NMR (400 MHz, DMSO-*d*₆): δ 9.46 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.60 (dd, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H), 2.26 (s, 3H), 2.12 (s, 3H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ 169.3, 141.6, 134.4, 131.5, 130.6, 124.2, 119.4, 106.8, 24.1, 18.0.

Example 6***N*-(4-Cyano-2-methylphenyl)butyramide (III, R¹ = CH₃, R³ = *n*-C₃H₇)**

A mixture of *N*-(4-bromo-2-methylphenyl)butyramide (20.04 g, 78 mmol, 1.0 eq.), potassium hexacyanoferrate(II) trihydrate (13.17 g, 31 mmol, 0.4 eq.), tetrakis(triphenylphosphine)palladium(0) (454 mg, 0.39 mmol, 0.005 eq.), sodium carbonate (9.94 g, 94 mmol, 1.2 eq.) in DMF (200 mL) was heated to 120 °C for 21 h. The reaction mixture was cooled to room temperature and the precipitated solid was filtrated off. The organic layer was diluted in dichloromethane and washed with water. Volatiles were removed to give the crude product. Ethyl ether was used to dilute the crude product and insoluble solid was filtrated off. The filtrate was concentrated to give a light yellow solid.

Yield: 12.0 g (75%).

¹H NMR (400 MHz, DMSO-*d*₆): δ 9.41 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.62 (dd, *J* = 8.4 Hz, *J* = 1.8 Hz, 1H).

Example 9***N*-(4-Cyano-2-methyl-6-nitrophenyl)butyramide (IV, R¹ = CH₃, R³ = *n*-C₃H₇)**

5 A mixture of sodium nitrate (6.73 g, 79 mmol, 2.0 eq.) and sulfuric acid (98%, 40 mL) was stirred in an ice-water bath for 15 min. *N*-(4-Cyano-2-methylphenyl)butyramide (8.00 g, 40 mmol, 1.0 eq.) was then added in portions within 55 min and the mixture was stirred in an ice-water bath for 3 h. The reaction mixture was poured into iced water and extracted with ethyl acetate. The organic layer was washed with an aqueous solution of sodium carbonate and water. Volatiles were removed under reduced
10 pressure to give an orange solid.

Yield: 8.01 g (80%).

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.12 (s, 1H), 8.30 (d, *J* = 1.7 Hz, 1H), 8.11 (m, 1H), 2.34 (s, 3H), 2.33 (t, *J* = 7.1 Hz, 2H), 1.58 (qd, *J* = 7.3 Hz, *J* = 7.1 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

15 ¹³C NMR (100 MHz, DMSO-*d*₆): δ 171.8, 146.4, 138.3, 138.0, 133.5, 126.8, 117.5, 108.8, 37.6, 18.7, 18.1, 14.0.

Example 10

20 **4-Amino-3-methyl-5-nitrobenzoic acid (V, R¹ = CH₃)**

A mixture of *N*-(4-cyano-2-methyl-6-nitrophenyl)acetamide (1.5 g, 0.07 mol, 1 eq.), concentrated hydrochloric acid (7.5 mL, 88 mmol, 12.8 eq.) and 1,4-dioxane (7.5 mL) was heated to 100 °C for 22 h. The reaction mixture was then cooled to room temperature and water was added. The precipitated solid was collected by filtration and
25 washed with aqueous sodium carbonate and water until the pH of the filtrate reached 7. The filter cake was dried under vacuum to give a brown solid.

Yield: 0.98 g (73%).

¹H NMR (400 MHz, DMSO-*d*₆): δ 12.77 (s, 1H), 8.46 (d, *J* = 2.0 Hz, 1H), 7.79 (d, *J* = 1.0 Hz, 1H), 7.60 (s, 2H), 2.21 (s, 3H).

30 ¹³C NMR (100 MHz, DMSO-*d*₆): δ 166.5, 147.5, 135.6, 130.5, 126.9, 126.4, 117.3, 18.4.

Example 11**4-Amino-3-methyl-5-nitrobenzoic acid (V, R¹ = CH₃)**

A mixture of *N*-(4-cyano-2-methyl-6-nitrophenyl)butyramide (315 mg, 1.27 mmol, 1.0 eq.), concentrated hydrochloric acid (1.3 mL, 12.0 M, 15.27 mmol, 12.0 eq.) and 1,4-dioxane (1.3 mL) was heated to 100 °C for 24 h. The reaction mixture was then cooled to room temperature and water was added. The precipitated solid was collected by filtration and washed with ethyl acetate and water. The solid was dried under vacuum to give a light brown solid.

Yield: 95.5 mg (38%).

¹H NMR (400 MHz, DMSO-*d*₆): δ 12.77 (s, 1H), 8.46 (d, *J* = 2.0 Hz, 1H), 7.79 (d, *J* = 1.0 Hz, 1H), 7.60 (s, 2H), 2.21 (s, 3H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ 166.5, 147.5, 135.6, 130.5, 126.9, 126.4, 117.3, 18.4.

Example 12**4-Methyl-2-propyl-1*H*-benzimidazole-6-carboxylic acid (I, R¹ = CH₃, R² = *n*-C₃H₇)**

A mixture of 4-amino-3-methyl-5-nitrobenzoic acid (0.98 g, 5 mmol, 1 eq.), sodium dithionite (2.47 g, 14 mmol, 2.8 eq.), *n*-butyraldehyde (0.38 g, 5 mmol, 1.0 eq.), ethanol (15 mL) and water (15 mL) was heated to 70 °C for 2 h. The reaction mixture was cooled to room temperature and ethanol was removed by rotary evaporator. The solid precipitated was washed with water, collected by filtration and dried under vacuum to give an off-white solid.

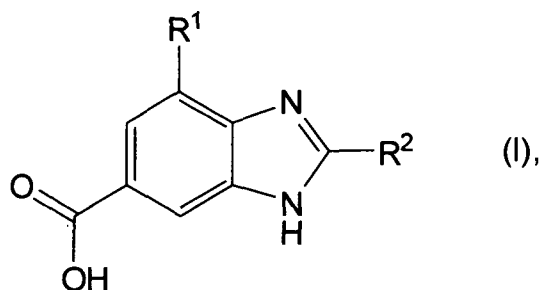
Yield: 0.41 g (37%).

¹H NMR (400 MHz, DMSO-*d*₆): δ 12.42 (s, 1H), 7.82 (s, 1H), 7.56 (s, 1H), 2.80 (t, *J* = 7.4 Hz, 2H), 2.50 (s, 3H), 1.79 (qd, *J* = 7.4 Hz, *J* = 7.32 Hz, 2H), 0.94 (t, *J* = 7.32 Hz, 3H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ 168.6, 157.5, 124.1, 123.3, 31.0, 21.4, 17.1, 14.2.

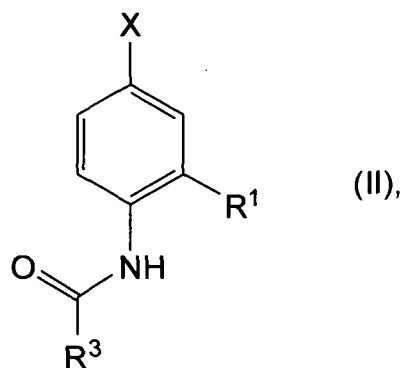
Claims

1. A process for the production of substituted benzimidazolecarboxylic acids of formula

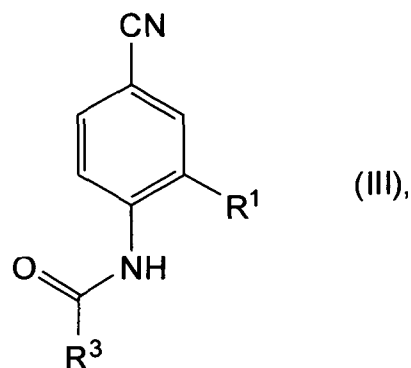


wherein R¹ and R² independently are hydrogen, C₁₋₆ alkyl or C₃₋₆ cycloalkyl, comprising the steps of

- (i) cyanating an *N*-acyl-4-haloaniline of formula

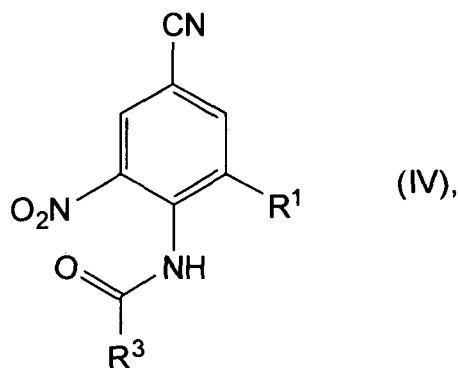


wherein R¹ is as defined above, R³ is C₁₋₄ alkyl and X is chlorine or bromine, to obtain the corresponding cyano compound of formula



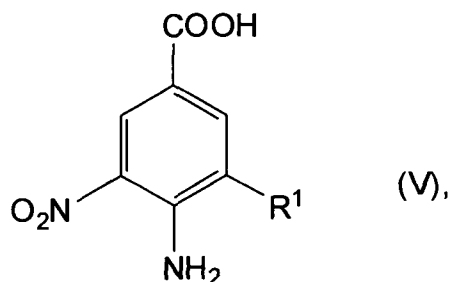
- wherein R¹ and R³ are as defined above,
- (ii) nitrating the cyano compound obtained in step (i) to obtain the corresponding nitro compound of formula

- 14 -



wherein R¹ and R³ are as defined above,

- (iii) hydrolyzing the cyano and acylamino groups of the nitro compound obtained in step (ii) to obtain the corresponding *p*-aminobenzoic acid of formula



wherein R¹ is as defined above, and

- (iv) reacting said *p*-aminobenzoic acid in the presence of a reducing agent with an aldehyde of formula

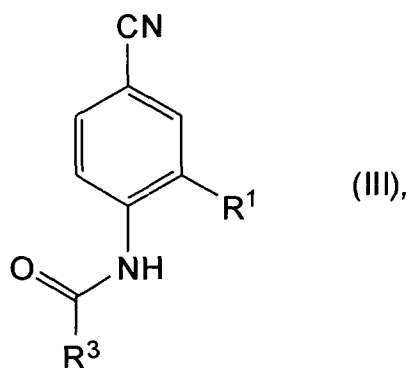


wherein R² is as defined above,

to obtain the target compound of formula I.

2. The process of claim 1, wherein the cyanation in step (i) is effected with potassium hexacyanoferrate(II) in a polar aprotic solvent and in the presence of a palladium phosphine complex as catalyst.
3. The process of claim 2, wherein the palladium phosphine complex is tetrakis(tri-phenylphosphine)palladium(0).

4. The process of any of claims 1 to 3, wherein the nitration in step (ii) is effected using an alkali metal nitrate in sulfuric acid as nitrating agent.
5. The process of any of claims 1 to 4, wherein the hydrolysis in step (iii) is effected using an aqueous hydrohalic acid.
6. The process of any of claims 1 to 5, wherein in step (iv) an alkali metal dithionite is used as reducing agent.
7. The process of any of claims 1 to 6, wherein R¹ is methyl.
8. The process of any of claims 1 to 7, wherein R² is propyl.
9. The process of any of claims 1 to 8, wherein R³ is methyl or propyl.
10. A compound of formula

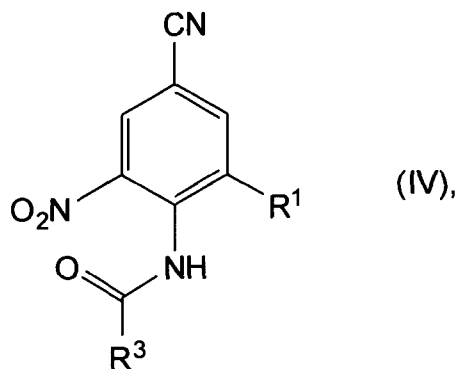


wherein R¹ is C₁₋₆ alkyl or C₃₋₆ cycloalkyl and R³ is propyl.

11. The compound of claim 10 wherein R¹ is methyl.

12. A compound of formula

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10

wherein R¹ is C₁₋₆ alkyl or C₃₋₆ cycloalkyl and R³ is C₁₋₄ alkyl.

13. The compound of claim 12 wherein R¹ is methyl.

14. The compound of claim 12 or 13 wherein R³ is methyl or propyl.

15

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/003787

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D235/08 C07C255/50
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07C

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/044754 A (REDDYS LAB LTD DR [IN]; REDDYS LAB INC DR [US]; VENKATARAMAN SUNDARAM) 27 April 2006 (2006-04-27) cited in the application the whole document	1-14
Y	RANGARAJAN, MEERA ET AL: "Topoisomerase I inhibition and cytotoxicity of 5-bromo- and 5-phenylterbenzimidazoles" BIOORGANIC & MEDICINAL CHEMISTRY, 8(11), 2591-2600 CODEN: BMECEP; ISSN: 0968-0896, 2000, XP002540449 * scheme 1 * ----- -/--	1-9

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

Date of the actual completion of the international search

30 September 2010

Date of mailing of the international search report

06/10/2010

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Fanni, Stefano

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/003787

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CZARNY A ET AL: JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US, vol. 33, 1 January 1996 (1996-01-01), pages 1393-1397, XP000914681 ISSN: 0022-152X page 1394, left-hand column, paragraph 2 page 1393 scheme 1	1-14
A	US 2004/204397 A1 (CHATURVEDULA PRASAD V [US] ET AL CHATURVEDULA PRASAD V [US] ET AL) 14 October 2004 (2004-10-14) page 154, paragraph 1054 - paragraph 1057	1-9
A	WO 2005/080388 A (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; TSANT) 1 September 2005 (2005-09-01) example 28	1-9
Y	NAVARRO-OCANA ARTURO ET AL: "Reductive cyclization with baker's yeast of 4-alkyl-2-nitroacetanili des to 6-alkylbenzimidazoles and 1-hydroxy-2-methyl-6-alkylbenzimidazole" PERKIN TRANSACTIONS 1, ROYAL SOCIETY OF CHEMISTRY, GB LNKD- DOI:10.1039/B107492J, vol. 1, no. 21, 1 January 2001 (2001-01-01), pages 2754-2756, XP002540450 ISSN: 1472-7781 scheme 1	12-14
Y	US 4 018 790 A (PAGET CHARLES J ET AL) 19 April 1977 (1977-04-19) example 9	10-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2010/003787

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9

Process for the preparation of compounds of formula I

2. claims: 10, 11

Compound of fomrula III

3. claims: 12-14

Compound of formula IV

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/003787

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			US 2007149502 A1	28-06-2007
			US 2007232600 A1	04-10-2007
			US 2007149503 A1	28-06-2007
WO 2005080388	A	01-09-2005	AR 047706 A1	08-02-2006
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			BR PI0507861 A	17-07-2007
			CA 2553879 A1	01-09-2005
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			CN 101648944 A	17-02-2010
			EA 200601457 A1	29-06-2007
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			UY 28758 A1	30-09-2005
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US 4018790	A	19-04-1977	NONE	