EUROPEAN PATENT APPLICATION

BENZIMIDAZOLE-4-CARBOXAMIDE DERIVATES, THEIR PREPARATION METHODS, PHARMACEUTICAL COMPOSITIONS AND THEIR USES

The present invention relates to the benzimidazole-4-carboxamide derivatives of Formula (I) or pharmaceutically acceptable salts thereof,

X represents thienyl monosubstituted by nitro or amino, unsubstituted thienyl;
Y represents hydroxymethyl, hydroxyethyl, aminophenyl, hydroxyphenyl, C$_1$-C$_6$ alkylphenyl, phenyl monosubstituted by -F, -Cl, -Br or -I, phenyl bisubstituted by hydroxyl and carboxyl, hydroxyethyl bisubstituted by hydroxyethylmethyl or C$_1$-C$_6$ alkyl and monosubstituted phenyl, piperazinyl monosubstituted or bisubstituted or trisubstituted by C$_1$-C$_6$ alkyl or unsubstituted piperazinyl, pyrrol monosubstituted or bisubstituted or trisubstituted by C$_1$-C$_6$ alkyl or unsubstituted pyrrol, pyrazinyl monosubstituted or bisubstituted or unsubstituted by C$_1$-C$_6$ alkyl, piperazinyl monosubstituted or bisubstituted or trisubstituted by C$_1$-C$_6$ alkyl or unsubstituted piperazinyl, pyrrol monosubstituted or bisubstituted or trisubstituted by C$_1$-C$_6$ alkyl or unsubstituted pyrrol, thiazolyl monosubstituted by C$_1$-C$_6$ alkyl, pyrimidinyl monosubstituted or bisubstituted by C$_1$-C$_6$ alkyl or unsubstituted pyrimidinyl, pyrimidinyl monosubstituted by C$_1$-C$_6$ alkyl and bisubstituted by hydroxyl, pyrimidinyl monosubstituted by C$_1$-C$_6$ alkyl and bisubstituted or trisubstituted by -F, -Cl, -Br or -I, purinyl monosubstituted or bisubstituted by C$_1$-C$_6$ alkyl or unsubstituted purinyl, purinyl monosubstituted by hydroxyl.

![Chemical structure of Formula (I)]
FIELD OF THE INVENTION

[0001] The present invention relates to benzimidazole carboxamide derivatives, in particular, relates to the benzimidazole-4-carboxamide derivatives, their preparation methods, pharmaceutical compositions and their uses.

BACKGROUND OF THE INVENTION

[0002] The diseases caused by virus infections severely threaten human health and life and have become major problems in the medical fields. Almost 70% of epidemic diseases are caused by viruses infections statistically. The infectious diseases caused by enteroviruses have often occurred all over the world. The enteroviruses belong to picornaviridae comprising polio viruses, cosxackie viruses, enteric cytopathogenic human orphan virus(ECHO) and new enteroviruses. Each viruses has many serums, at least more than 70 types, which can violate many kinds of tissues, such as nerves, cardiac muscles, muscles, skins and eye conjunctiva etc and can cause lots of infectious diseases all over the world. There are lots of categories of the cosxackie viruses, whose transmission route and pathogenesis are similar to that of poliomyelitis virus, and often occurs latent infections. Their symptom shows slight upper respiratory infections or diarrhea, and occasionally infects central nervous systems, damages spinal cord anterior horn motor neurons, and causes flaccid paralysis of limbs, however, this symptom is relatively light. The cosxackie viruses can violate many tissues and systems, such as respiratory tracts, intestinal tracts, skins, muscles, hearts, livers, adrenal gland and central nervous systems, Clinical manifestations have various of symptoms such as (1) respiratory tract infection, (2) herpangina, (3) febrile rush, (4) hand-foot-and-mouth disease, (5) diarrhea of children, (6) central nervous system syndrome, (7) myocarditis and pericarditis, (8) epidemic chest pain or epidemic myalgia, (9) epidemic conjunctivitis, (10) cosxackie virus hepatitis and so on.

SUMMARY OF THE INVENTION

[0003] The purpose of the present invention is to provide benzimidazole-4-carboxamide derivatives having anti-cosxackie viruses or a pharmaceutically acceptable salts thereof as shown in Formula (I).

\[
\begin{align*}
\text{Y} & \quad \text{N} \\
\text{O} & \quad \text{X}
\end{align*}
\]

(1)

wherein X represents thienyl monosubstituted by nitro or amino, unsubstituted thienyl; Y represents hydroxymethyl, hydroxyethyl, aminophenyl, hydroxyphenyl, C1-C6 alkylphenyl, phenyl monosubstituted by -F, -Cl, -Br or -I, phenyl bisubstituted by hydroxyl and carboxyl, hydroxyethyl bisubstituted by hydroxymethyl or C1-C6 alkyl and monosubstituted phenyl, piperazinyl monosubstituted or bisubstituted or trisubstituted by C1-C6 alkyl or unsubstituted piperazinyl, pyridyl monosubstituted or bisubstituted or trisubstituted by C1-C6 alkyl or unsubstituted pyridyl, pyrazinyl monosubstituted or bisubstituted or trisubstituted by C1-C6 alkyl or unsubstituted pyridazinyl, pyrrolyl monosubstituted or bisubstituted or trisubstituted by C1-C6 alkyl or unsubstituted pyrrolyl, thiazolyl monosubstituted by C1-C6 alkyl, pyrimidinyl monosubstituted or bisubstituted or trisubstituted by C1-C6 alkyl or unsubstituted pyrimidinyl, pyrimidinyl monosubstituted by C1-C6 alkyl and bisubstituted by hydroxyl, pyrimidinyl monosubstituted by C1-C6 alkyl and bisubstituted by -F, -Cl, -Br or -I, purinyl monosubstituted or bisubstituted by C1-C6 alkyl or unsubstituted purinyl, purinyl monosubstituted by hydroxyl.

[0004] Most preferably, the benzimidazole-4-carboxamide derivatives as shown in Formula (1) includes the following compounds:

(1)(L)-2-(5-nitro-2-thienyl)-1H-benzimidazole-4-[N-(1-hydroxymethyl-2-p-nitrophenyl hydroxyethyl)]amide

(2)(L)-2-(5-amino-2-thienyl)-1H-benzimidazole-4-[N-(1-hydroxymethyl-2-p-nitrophenyl hydroxyethyl)] amide
(3)(L)-2-(5-amino-2-thienyl)-1H-benzimidazole-4-[N-(1-hydroxymethyl-2-p-aminophenyl hydroxyethyl)]amide
(4)2-(5-amino-2-thienyl)-1H-benzimidazole-4-[N-(1-methyl-2-p-chlorophenylhydroxyethyl)]amide
(5)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-o-fluorophenyl)amide
(6)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-o-chlorophenyl)amide
(7)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-o-bromophenyl)amide
(8)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-m-fluorophenyl)amide
(9)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-m-chlorophenyl)amide
(10)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-m-bromophenyl)amide
(11)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-m-fluorophenyl)amide
(12)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-m-chlorophenyl)amide
(13)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-m-bromophenyl)amide
(14)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-p-fluorophenyl)amide
(15)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-p-chlorophenyl)amide
(16)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-p-bromophenyl)amide
(17)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-o-methylphenyl)amide
(18)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-o-hydroxylphenyl)amide
(19)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-o-aminophenyl)amide
(20)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-o-chlorophenyl)amide
(21)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-o-fluorophenyl)amide
(22)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-o-chlorophenyl)amide
(23)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-2-hydroxyl-4-pyrimidinyl)amide
(24)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-6-purinyl)amide
(25)2-(5-amino-2-thienyl)-1H-benzimidazole-4-(N-6-hydroxyl-2-purinyl)amide
(26)2-(5-nitro-2-thienyl)-1H-benzimidazole-4-(N-(1-methyl-2-p-chlorophenylhydroxyethyl)amide
(27)2-(5-nitro-2-thienyl)-1H-benzimidazole-4-(N-6-hydroxyl-2-purinyl)amide
(28)2-(5-nitro-2-thienyl)-1H-benzimidazole-4-(N-o-fluorophenyl)amide(Refer to Figure 3)
(29)(L)-2-(2-thienyl)-1H-benzimidazole-4-[N-(1-hydroxymethyl-2-p-nitrophophenylhydroxyethyl)]amide
(30)(L)-2-(2-thienyl)-1H-benzimidazole-4-[N-(1-hydroxymethyl-2-p-aminophenylhydroxyethyl)]amide
(31)2-(2-thienyl)-1H-benzimidazole-4-[N-(1-methyl-2-p-chlorophenylhydroxyethyl)]amide
Preferably, the pharmaceutically acceptable salts of benzimidazole-4-carboxamide derivatives are inorganic acid salts thereof selected from sulfate, hydrochloride, nitrate, phosphate or borate, or organic acid salts thereof selected from citrate, succinate, tartrate, lactate or mesylate.

Another purpose of the present invention is to provide anti-cosxackie-viruses pharmaceutical compositions. The pharmaceutical compositions comprise a therapeutically effective amount of the benzimidazole-4-carboxamide derivatives or a pharmaceutically acceptable salts thereof according to any one of claims 1 ~ 7, and one or more pharmaceutically acceptable thinner, excipient and/ or inert carrier.

Another purpose of the prevent invention is to provide uses of the benzimidazole-4-carboxamide derivatives or a pharmaceutically acceptable salt for for preparation of antivirus medications, wherein the viruses are Coxsackie-Virus, echovirus and enterovirus which belong to picornaviridae.

Another purpose of the prevent invention is to provide a method of the benzimidazole-4-carboxamide derivatives or a pharmaceutically acceptable salt thereof as shown in Formula (I), comprising the following steps:

(1) 2-aminoacetyl-3-nitrobenzoic acid is undergoing reactions of ammonolysis, Hoffman degradation and reduction in turn, to produce 2,3- diamino benzoic acid.

(2) 2,3-diamino benzoic acid is condensed with aldehydes X-CHO in the presence of catalyst of cupric acetate, to produce benzimidazole-4-carboxylic acid of Formula (II).
(3) benzimidazole-4-carboxylic acid is reacted with thionyl chloride to produce acyl chloride, and then condensing the acyl chloride and an amine NH₂-Y, to produce the benzimidazole-4-carboxamide derivative of Formula (I).

[0009] The above reaction conditions are as follows: benzimidazole-4-carboxylic acid is reacted with thionyl chloride at temperature of 0~80°C in a molar molecular ratio of thionyl chloride to benzimidazole-4-carboxylic acid is 1~20 times, to produce benzimidazole-4-carbonyl chloride, and then benzimidazole-4-carbonyl chloride is reacted with an amine in an organic solvent at temperature of 0~100°C to produce benzimidazole-4-carboxamide derivatives. Wherein the organic solvent comprises dichloroethane, 1,1,2-trichloroethane, chloroform, tetrachloroethylene, benzene, toluene, xylene, chlorobenzene or dichlorobenzene, and so on.

[0010] The benzimidazole-4-carboxamide derivatives or a pharmaceutically acceptable salt thereof of the present invention may be administered orally or not. The dosage varies with different drugs, the dosage is 10~300 mg per day in general conditions.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Fig. 1 shows ¹HNMR spectrogram of 2-(2,3,4-trihydroxyphenyl)-1H-benzimidazole-4-carboxylic acid in Example 9.
Fig. 2 shows ¹HNMR spectrogram of 2-(5-nitro-2-thienyl)-1H-benzimidazole-4-(N-(1-hydroxymethyl-2-p-nitrophenoxyethyl)amide in Example 21.
Fig. 3 shows ¹HNMR spectrogram of 2-(5-nitro-2-thienyl)-1H-benzimidazole-4-(N-o-fluorophenyl)amide in Example 28.
Fig. 4 shows ¹HNMR spectrogram of (L)-2-(2-pyridyl)-1H-benzimidazole-4-(N-(1-hydroxymethyl-2-p-nitrophenylhydroxyethyl)amide in Example 194.
Fig. 5 shows ¹HNMR spectrogram of 2-(4-hydroxyphenyl)-1H-benzimidazole-4-(N-o-fluorophenyl)amide in Example 663.
Fig. 6 shows ¹HNMR spectrogram of (L)-2-(3-hydroxyphenyl)-1H-benzimidazole-4-(N-(1-hydroxymethyl-2-p-nitrophenylhydroxyethyl)amide in Example 664.

DETAILED DESCRIPTION OF THE PRESENT INVENTION AND PREFERRED EMBODIMENTS THEREOF

[0012] Hereafter, the present invention will be described specifically with reference to examples. The examples are given only for illustration of the technical solution of the present invention and should not be construed to limit the present invention.

[0013] The method of preparing for benzimidazole-4-amide derivatives of the present invention is as follows: using 2-aminoacetyl-3-nitrobenzoic acid as an initiating raw material, 2-aminoacetyl-3-nitrobenzoic acid in turn is undergoing ammonolysis, Hoffman degradation and reduction, to produce 2,3-diamino benzoic acid; and then condensing 2,3-diamino benzoic acid and aldehydes X-CHO in the presence of catalyst of cupric acetate, to produce benzimidazole-4-carboxylic acid; and then reacting benzimidazole-4-carboxylic acid with thionyl chloride to produce acyl chloride, and then condensing the acyl chloride and an amine NH₂-Y, to produce the benzimidazole-4-carboxamide derivative.
**Example 1: Synthesis of 2,3-diamino benzoic acid**

**Step 1: Synthesis of 2-aminoacetyl-3-nitrobenzoic acid**

[0014] 30g of 3-nitro phthalic anhydride is added into 45ml of concentrated ammonia with 28g/g% concentration; and heat it to 60°C under stirring for 30 minutes; and then to cool it to 10°C till precipitate needle shape crystals; and to acidize the needle shape crystals with concentrated chlorhydric acid to produce white solids; and then to filter and dry it to obtain 29.4g of 2-aminoacetyl-3-nitrobenzoic acid.

**Step 2: Synthesis of 2-amino-3-nitrobenzoic acid**

[0015] 13.9g of bromine is dropped into 100ml of sodium hydroxide aqueous-solution containing 7.3g of sodium hydroxide to a solution. Then 17 g of 2-aminoacetyl-3-nitrobenzoic acid is added into the above solution; and to heat it to 80°C to precipitate a large amount of red solids; to filter and then acidize it with the concentrated chlorhydric acid to produce yellow solid products; to dry it to obtain 13.7g of 2-amino-3-nitrobenzoic acid; and then recrystallize the yellow solid products by adding hot water to obtain the yellow needle shape crystals.

**Step 3: Synthesis of 2,3-diaminobenzoic acid**

[0016] 3g of the above mentioned 2-amino-3-nitrobenzoic acid is added into 30ml of methanol, 20% sodium hydroxide aqueous solution with the same molar as 2-amino-3-nitrobenzoic acid is dropped into the above methanol solution till dissolve completely. 0.2g of Raney nickel at the moment is added in to the methanol solution, and to heat it to 65°C and reflux it at the temperature; and then drop 80g/g% hydrazine hydrate (about 1.5 equivalent weight × 1.1) till the yellow disappears completely. Hot Raney nickel is filtered; and then heat and concentrate the mother liquid and acidize it with the concentrated chlorhydric acid to produce 2.3g of red 2,3-diaminobenzoic acid; afterwards isolate and purify the crude product of red 2,3-diaminobenzoic acid by column chromatography.

**Example 2: Synthesis of 2-(5-nitro-2-thienyl)-1H-benzimidazole-4-carboxylic acid**

[0017] 2.0g of 2,3-diaminobenzoic acid is dissolved into 60ml of methanol, and methanol solution of 5-nitrofurfural is added into the methanol under stirring. Then 0.5g of cupric acetate (Cu(Ac)2•H2O) is added into the above methanol, and then to heat and reflux it; and then to filter hot solution after 2,3-diaminobenzoic acid disappears. 20% sodium sulfide aqueous solution is added into the filtrate and heat it till boiling; and then filtrate the copper sulfide deposition while it is hot; and then to evaporate the filtrate to dry, purify it through column chromatography to obtain 2-(5-nitro-2-thienyl)-1H-benzimidazole-4-carboxylic acid. The yield is about 65%.

**Examples 5: synthesis of intermediates of benzimidazole-4-carboxylic acid**

[0018] Synthesize the benzimidazole-4-carboxylic acid as shown in Formula (II) according to the method of Example 2. The difference is to use aldehydes with different X group as listed in Table 1.

![Formula (II)](image)

<table>
<thead>
<tr>
<th>No. of Products</th>
<th>Compounds</th>
<th>X</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-carboxylic acid</td>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>
Structure Identification of Products:

(5) 2-(2-thienyl)-1H-benzimidazole-4-carboxylic acid

Example 21: Synthesis of (L)-2-(5-nitro-2-thienyl)-1H-benzimidazole-4-(N-(1-hydroxymethyl-2-p-nitrophenylhydroxyethyl)amide

Example 22: Synthesis of 2-(5-nitro-2-thienyl)-1H-benzimidazole-4-(N-(1-methyl -2-p-chlorophenylhydroxyethyl)amide

Examples 27, 28, 56-78:

[0024] Use the same process as Example 22 to synthesize the compound as shown in Table 2.
<table>
<thead>
<tr>
<th>No.</th>
<th>Compounds</th>
<th>X</th>
<th>Y</th>
<th>Field %</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>2-(5-nitro-2-thienyl)-1H-benzimidazole-4-(N-6-hydroxyl-2-purinyl)amide</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>90</td>
</tr>
<tr>
<td>28</td>
<td>2-(5-nitro-2-thienyl)-1H-benzimidazole-4-(N-o-fluorophenyl)amide</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>89</td>
</tr>
<tr>
<td>56</td>
<td>(L)-2-(2-thienyl)-1H-benzimidazole-4-[N-(1-hydroxymethyl-2-p-nitrophosphorylhydroxyethyl)]amide</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>90</td>
</tr>
<tr>
<td>57</td>
<td>(L)-2-(2-thienyl)-1H-benzimidazole-4-[N-(1-hydroxymethyl-2-p-aminophenylhydroxyethyl)]amide</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td>92</td>
</tr>
<tr>
<td>58</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-[N-(1-methyl-2-p-chlorophenylhydroxyethyl)]amide</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
<td>92</td>
</tr>
<tr>
<td>59</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-N'-piperidinyl)amide</td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
<td>91</td>
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<tr>
<td>60</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-2-piperazinyl)amide</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td>88</td>
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<tr>
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<td><img src="image15.png" alt="Image" /></td>
<td><img src="image16.png" alt="Image" /></td>
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<td><img src="image18.png" alt="Image" /></td>
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<td>No.</td>
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<td>Y</td>
<td>Field %</td>
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<td>---------------------------------------------------------------------------</td>
<td>------------</td>
<td>------------------</td>
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</tr>
<tr>
<td>63</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-5-benzimidazolonyl)amide</td>
<td><img src="image1" alt="Structure" /></td>
<td><img src="image2" alt="Structure" /></td>
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<tr>
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<td><img src="image3" alt="Structure" /></td>
<td><img src="image4" alt="Structure" /></td>
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<tr>
<td>65</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-4'-pyrazolyl)amide</td>
<td><img src="image5" alt="Structure" /></td>
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<td>66</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-(N'-piperazinyl))amide</td>
<td><img src="image7" alt="Structure" /></td>
<td><img src="image8" alt="Structure" /></td>
<td>94</td>
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<td>67</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-2-pyrazinyl)amide</td>
<td><img src="image9" alt="Structure" /></td>
<td><img src="image10" alt="Structure" /></td>
<td>94</td>
</tr>
<tr>
<td>68</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-2-pyrimidinyl)amide</td>
<td><img src="image11" alt="Structure" /></td>
<td><img src="image12" alt="Structure" /></td>
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<td>69</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-2-pyridyl)amide</td>
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<td><img src="image14" alt="Structure" /></td>
<td>90</td>
</tr>
<tr>
<td>70</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-4-methyl-5-thiazolyl)amide</td>
<td><img src="image15" alt="Structure" /></td>
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<td>91</td>
</tr>
<tr>
<td>71</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-2,4-dihydroxyl-5-pyrimidinyl)amide</td>
<td><img src="image17" alt="Structure" /></td>
<td><img src="image18" alt="Structure" /></td>
<td>93</td>
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</table>
Structure Identification of Product (refer to Figures 3-6):

<table>
<thead>
<tr>
<th>No.</th>
<th>Compounds X Y</th>
<th>Field %</th>
</tr>
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<tbody>
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<td>93</td>
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<tr>
<td>73</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-4-chloro-6-amino-2-pyrimidinyl)amide</td>
<td>88</td>
</tr>
<tr>
<td>74</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-4,6-dichloro-5-pyrimidinyl)amide</td>
<td>89</td>
</tr>
<tr>
<td>75</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-o-fluorophenyl)amide</td>
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<td>76</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-2-hydroxyl-4-pyrimidinyl)amide</td>
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<td>77</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-6-purinyl)amide</td>
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<td>78</td>
<td>2-(2-thienyl)-1H-benzimidazole-4-(N-6-hydroxyl-2-purinyl)amide</td>
<td>91</td>
</tr>
</tbody>
</table>

(27) 2-(5-nitro-2-thienyl)-1H-benzimidazole-4-(N-6-hydroxyl-2-purinyl)amide
1H NMR (DMSO, 400MHz): \( \delta \): 7.43-7.46(t,1H), 7.70-7.72(d,1H), 7.89-7.91(d,1H), 7.93-7.95(d,1H), 8.30-8.33(d,1H), 8.57-8.60(d,1H), 11.53(s,1H);

(28) 2-(5-nitro-2-thienyl)-1H-benzimidazole-4-(N-o-fluorophenyl)amide (refer to Figure 3)
1H NMR (DMSO, 400MHz): \( \delta \): 7.13-7.19(m,1H), 7.23-7.27(t,1H), 7.36-7.41(t,1H), 7.50-7.51 4(m,2H), 7.85-7.87(d,1H), 7.94-7.95(d,1H), 8.05-8.07(d,1H), 8.57-8.61(t,1H), 12.19-12.20(d,1H), 14.25(s,1H);

(56) (L)-2-(2-thienyl)-1H-benzimidazole-4-[N-(1-hydroxymethyl-2-p-nitrophenylhydroxyethyl)]amide
1H NMR (DMSO, 400MHz): \( \delta \): 3.17-3.18(m,1H), 3.25-3.28(m,1H), 3.50-3.52(m,1H), 3.65-3.68(t,1H), 3.70-3.72(d,1H),
7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.43-7.45(t,1H), 7.85-7.87(d,1H), 7.69-7.71(d,1H);
7.85-7.87(d,1H), 7.89-7.91(d,1H);
5
(57) 2-(2-thienyl)-1H-benzimidazole-4-[N-(1-hydroxyethyl-2-p-aminophenylhydroxyethyl)amide]

δ: 3.17-3.18(m,1H), 3.25-3.28(m,1H), 3.65-3.68(t,1H), 3.70-3.72(d,1H);

7.69-7.71(d,1H), 7.89-7.91(d,1H), 7.93-7.95(d,1H), 8.17-8.20(d,2H);

(58) 2-(2-thienyl)-1H-benzimidazole-4-[N-(1-methyl-2-p-chlorophenylhydroxyethyl)amide]

δ: 6.27(s,2H), 6.66-6.68(d,1H), 7.11-7.13(d,2H), 7.17-7.19(t,1H), 7.29-7.30(d,2H), 7.40-7.41(d,2H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.85-7.87(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H);

(59) 2-(2-thienyl)-1H-benzimidazole-4-(N-N'-piperidinyl)amide

δ: 7.69-7.71(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H);

(60) 2-(2-thienyl)-1H-benzimidazole-4-(N-2-piperazinyl)amide

δ: 7.69-7.71(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H);

(61) 2-(2-thienyl)-1H-benzimidazole-4-(N-2'-benzimidazolyl)amide

δ: 7.69-7.71(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H);

(62) 2-(2-thienyl)-1H-benzimidazole-4-(N-o-aminophenyl)amide

δ: 7.69-7.71(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H);

(63) 2-(2-thienyl)-1H-benzimidazole-4-(N-2'-pyridazinyl)amide

δ: 7.69-7.71(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H);

(64) 2-(2-thienyl)-1H-benzimidazole-4-(N-1-methyl-2-p-chlorophenylhydroxyethyl)amide}

δ: 7.69-7.71(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H), 8.37(s,2H), 9.24-9.26(d,1H), 13.00-13.03(d,1H);

(65) 2-(2-thienyl)-1H-benzimidazole-4-(N-4'-pyrazolyl)amide

δ: 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.85-7.87(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H);

(66) 2-(2-thienyl)-1H-benzimidazole-4-(N-N'-piperazinyl)amide

δ: 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.85-7.87(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H);

(67) 2-(2-thienyl)-1H-benzimidazole-4-(N-2'-pyrazinyl)amide

δ: 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.85-7.87(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H);

(68) 2-(2-thienyl)-1H-benzimidazole-4-(N-2'-pyrimidinyl)amide

δ: 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.85-7.87(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H);

(69) 2-(2-thienyl)-1H-benzimidazole-4-(N-2'-pyridyl)amide

δ: 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.85-7.87(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H);

(70) 2-(2-thienyl)-1H-benzimidazole-4-(N-4-methyl-5-thiazolyl)amide

δ: 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.85-7.87(d,1H), 7.89-7.91(d,1H), 8.12(s,1H);

(71) 2-(2-thienyl)-1H-benzimidazole-4-(N-2,4-dihydroxy-5-pyrimidinyl)amide

δ: 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.85-7.87(d,1H), 7.89-7.91(d,1H), 8.32(s,1H);

(72) 2-(2-thienyl)-1H-benzimidazole-4-(N-2,4-dimethoxy-5-pyrimidinyl)amide

δ: 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.74(s,2H), 7.85-7.87(d,1H), 7.89-7.91(d,1H);

(73) 2-(2-thienyl)-1H-benzimidazole-4-(N-4-chloro-L-amino-2-pyrimidinyl)amide

δ: 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.74(s,2H), 7.85-7.87(d,1H), 7.89-7.91(d,1H);

(74) 2-(2-thienyl)-1H-benzimidazole-4-(N-4,6-dichloro-5-pyrimidinyl)amide

δ: 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.85-7.87(d,1H), 7.89-7.91(d,1H), 8.32(s,1H);
7.93-7.94(d,1H), 9.34(s,1H);
(75)2-(2-thienyl)-1H-benzimidazole-4-(N-o-fluorophenyl)amide
1HNMR (DMSO, 400MHz) δ: 6.60-6.61(d,1H), 6.63-6.65(t,1H), 6.96-6.98(t,1H), 6.99-7.01(d,1H), 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.85-7.87(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H);
(76)2-(2-thienyl)-1H-benzimidazole-4-(N-2-hydroxy-4-pyrimidinyl)amide
1HNMR (DMSO, 400MHz) δ: 5.46-5.48(d,1H), 7.10-7.11(d,1H), 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.82(s,1H), 7.85-7.87(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H);
(77)2-(2-thienyl)-1H-benzimidazole-4-(N-6-purinyl)amide
1HNMR (DMSO, 400MHz) δ: 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.85-7.86(d,1H), 7.87-7.88(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H), 8.16-8.18(d,1H);
(78)2-(2-thienyl)-1H-benzimidazole-4-(N-6-hydroxy-2-purinyl)amide
1HNMR (DMSO, 400MHz) δ: 7.17-7.19(t,1H), 7.43-7.45(t,1H), 7.69-7.71(d,1H), 7.85-7.87(d,1H), 7.89-7.91(d,1H), 7.93-7.94(d,1H), 8.57-8.59(d,1H), 11.53(s,1H).

Measures of Properties:

1. Measures of anti-coxsackie B3 viruses activity of the compounds

[0026] The products are applied for measures of antivirus properties of Vero cells. Refer to the results of Table 3: datum of anti-coxsackie B3 viruses activities of some compounds.

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<tr>
<th>NAME OF COMPOUNDS</th>
<th>X</th>
<th>Y</th>
<th>IC50(μg/ml)</th>
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<td>(L)-2-(2-thienyl)-1H-benzimidazole-4-[N-(1-hydroxymethyl-2-p-nitrophensalicyloxyethyl)]amide</td>
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<td>15.90</td>
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<td>2-(2-thienyl)-1H-benzimidazole-4-[N-(1-methyl-2-p-chlorophenylhydroxyethyl)]amide</td>
<td><img src="https://example.com/image3.png" alt="image" /></td>
<td><img src="https://example.com/image4.png" alt="image" /></td>
<td>5.30</td>
</tr>
<tr>
<td>(L)-2-(5-nitro-2-thienyl)-1H-benzimidazole-4-[N-(1-hydroxymethyl-2-p-nitrophensalicyloxyethyl)]amide</td>
<td><img src="https://example.com/image5.png" alt="image" /></td>
<td><img src="https://example.com/image6.png" alt="image" /></td>
<td>10.69</td>
</tr>
<tr>
<td>2-(5-nitro-2-thienyl)-1H-benzimidazole-4-[N-(1-methyl-2-p-chlorophenylhydroxyethyl)]amide</td>
<td><img src="https://example.com/image7.png" alt="image" /></td>
<td><img src="https://example.com/image8.png" alt="image" /></td>
<td>7.12</td>
</tr>
<tr>
<td>2-thienyl-1H-benzimidazole-4-(N-(2-fluorophenyl)-amide</td>
<td><img src="https://example.com/image9.png" alt="image" /></td>
<td><img src="https://example.com/image10.png" alt="image" /></td>
<td>1.06</td>
</tr>
</tbody>
</table>
In the above table: "-" indicates that these samples don’t have anti-coxsackie B3 viruses activities at the maximum nontoxic dose.

IC50 indicates half inhibitory concentration for viruses.

RBV indicates triazole nucleoside, is also called ribavirin, virazole.

It may be seen from the result of test, these compounds have better properties of anti-coxsackie B3 viruses. These compounds of the present invention have better effects on the coxsackie viruses of the picornaviridae and can inhibit coxsackie viruses.

Although the present invention has been described in connection with the above embodiments, it should be understood that the present invention is not limited to such preferred embodiments and procedures set forth above. The embodiments and procedures were chosen and described in order to best explain the principles of the invention and its practical application, to thereby enable others skilled in the art to best utilize the invention. It will be apparent to those skilled in the art that various substitution, modifications and changes may be thereto without departing from the scope and spirit of the invention. Therefore, the intention is intended to cover all alternative constructions and equivalents falling within the spirit and scope of the invention as defined only by the appended claims and equivalents thereto.

Claims

1. The benzimidazole-4-carboxamide derivatives of Formula (I) or pharmaceutically acceptable salts thereof,
wherein X represents thienyl monosubstituted by nitro or amino. unsubstituted thienyl; Y represents hydroxymethyl, hydroxyethyl, aminophenyl, hydroxyphenyl, \( C_1-C_6 \) alkylphenyl, phenyl monosubstituted by -F, -Cl, -Br or -I, phenyl bisubstituted by hydroxyl and carboxyl, hydroxyethyl bisubstituted by hydroxymethyl or \( C_1-C_6 \) alkyl and monosubstituted phenyl, piperazinyl monosubstituted or bisubstituted or trisubstituted by \( C_1-C_6 \) alkyl or unsubstituted piperazinyl, pyridyl monosubstituted or bisubstituted or trisubstituted by \( C_1-C_6 \) alkyl or unsubstituted pyridyl, pyrazinyl monosubstituted or bisubstituted or trisubstituted by \( C_1-C_6 \) alkyl and monosubstituted phenyl, \( C_1-C_6 \) alkyl or unsubstituted pyrrolyl, thiazolyl monosubstituted by \( C_1-C_6 \) alkyl or unsubstituted pyrimidinyl, pyrimidinyl monosubstituted or bisubstituted or trisubstituted by hydroxyl, pyrimidinyl monosubstituted or bisubstituted by \( C_1-C_6 \) alkyl and bisubstituted or trisubstituted by -F, -Cl, -Br or -I, purinyl monosubstituted or bisubstituted by \( C_1-C_6 \) alkyl or unsubstituted purinyl, purinyl monosubstituted or bisubstituted by hydroxyl.

2. The benzimidazole-4-carboxamide derivatives or a pharmaceutically acceptable salt thereof according to claim 1, wherein, the derivatives are as follows:

(1) \((L)-2-(5\text{-nitro-2-thienyl})-1H\text{-benzimidazole-4-[N-(1-hydroxymethyl-2-p-nitrophenyl hydroxyethyl)]amide}\)

(2) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-(1-hydroxymethyl-2-p-nitrophenyl hydroxyethyl)]amide}\)

(3) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-(1-hydroxymethyl-2-p-chlorophenylhydroxyethyl)]amide}\)

(4) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-fluorophenyl]amide}\)

(5) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-chlorophenyl]amide}\)

(6) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-bromophenyl]amide}\)

(7) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-m-fluorophenyl]amide}\)

(8) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-m-chlorophenyl]amide}\)

(9) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-m-bromophenyl]amide}\)

(10) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-methylphenyl]amide}\)

(11) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-m-hydroxylphenyl]amide}\)

(12) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-m-aminophenyl]amide}\)

(13) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-p-fluorophenyl]amide}\)

(14) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-p-chlorophenyl]amide}\)

(15) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-p-bromophenyl]amide}\)

(16) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-aminophenyl]amide}\)

(17) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-hydroxylphenyl]amide}\)

(18) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-aminophenyl]amide}\)

(19) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-methylphenyl]amide}\)

(20) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-p-methylphenyl]amide}\)

(21) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-p-methylphenyl]amide}\)

(22) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-p-hydroxylphenyl]amide}\)

(23) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-p-aminophenyl]amide}\)

(24) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-aminophenyl]amide}\)

(25) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-hydroxylphenyl]amide}\)

(26) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-hydroxylphenyl]amide}\)

(27) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-fluorophenyl]amide}\)

(28) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-o-fluorophenyl]amide}\)

(29) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-1-hydroxymethyl-2-p-nitrophenylhydroxyethyl]amide}\)

(30) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-1-hydroxymethyl-2-p-nitrophenylhydroxyethyl]amide}\)

(31) \((L)-2-(5\text{-amino-2-thienyl})-1H\text{-benzimidazole-4-[N-1-hydroxymethyl-2-p-chlorophenylhydroxyethyl]amide}\)
(33) 2-(2-thienyl)-1H-benzimidazole-4-(N-2-piperazinyl)amide
(34) 2-(2-thienyl)-1H-benzimidazole-4-(N-2'-benzimidazolyl)amide
(35) 2-(2-thienyl)-1H-benzimidazole-4-(N-o-aminophenyl)amide
(36) 2-(2-thienyl)-1H-benzimidazole-4-(N-5-benzimidazolonyl)amide
(37) 2-(2-thienyl)-1H-benzimidazole-4-(N'-4'-carbonamido-5'-imidazolyl)amide
(38) 2-(2-thienyl)-1H-benzimidazole-4-(N'-4'-pyrazolyl)amide
(39) 2-(2-thienyl)-1H-benzimidazole-4-(N-(N'-piperazinyl))amide
(40) 2-(2-thienyl)-1H-benzimidazole-4-(N-2-pyrazinyl)amide
(41) 2-(2-thienyl)-1H-benzimidazole-4-(N-2-pyrimidinyl)amide
(42) 2-(2-thienyl)-1H-benzimidazole-4-(N-2-pyridyl)amide
(43) 2-(2-thienyl)-1H-benzimidazole-4-(N-4'-methyl-5-thiazolyl)amide
(44) 2-(2-thienyl)-1H-benzimidazole-4-(N-2,4-dihydroxy-5-pyrimidinyl)amide
(45) 2-(2-thienyl)-1H-benzimidazole-4-(N-4,6-dimethoxy-2-pyrimidinyl)amide
(46) 2-(2-thienyl)-1H-benzimidazole-4-(N-4-chloro-6-amino-2-pyrimidinyl)amide
(47) 2-(2-thienyl)-1H-benzimidazole-4-(N-4,6-dichloro-5-pyrimidinyl)amide
(48) 2-(2-thienyl)-1H-benzimidazole-4-(N-o-fluorophenyl)amide
(49) 2-(2-thienyl)-1H-benzimidazole-4-(N-2-hydroxy-4-pyrimidinyl)amide
(50) 2-(2-thienyl)-1H-benzimidazole-4-(N-6-purinyl)amide
(51) 2-(2-thienyl)-1H-benzimidazole-4-(N-6-hydroxyl-2-purinyl)amide.

3. The benzimidazole-4-carboxamide derivatives or a pharmaceutically acceptable salts thereof according to claim 1 or 2, wherein the pharmaceutically acceptable salts of benzimidazole-4-carboxamide derivatives are inorganic acid salts thereof selected from sulfate, hydrochloride, nitrate, phosphate or borate, or organic acid salts thereof selected from citrate, succinate, tartrate, lactate or mesylate.

4. A pharmaceutical composition, comprising a therapeutically effective amount of the benzimidazole-4-carboxamide derivatives or a pharmaceutically acceptable salts thereof according to any one of claims 1~3, and one or more pharmaceutically acceptable thinner, excipient and/ or inert carrier.

5. A use of benzimidazole-4-carboxamide derivatives or a pharmaceutically acceptable salts thereof according to any one of claims 1~3 for preparation of coxsackie virus medications.
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<td>A</td>
<td>CN 1 425 663 A (UNIV SHANGHAI COMMUNICATION [CN]) 25 June 2003 (2003-06-25)</td>
<td>1-5 INV.</td>
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<tr>
<td>A</td>
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<tr>
<td>E</td>
<td>WO 2010/078830 A1 (UNIV SHANGHAI JIAOTONG [CN]; LUO XIANJIN [CN]; XUE FEI [CN]; ZHANG ZHO) 15 July 2010 (2010-07-15)</td>
<td>1-3,5 C07D</td>
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The present search report has been drawn up for all claims

Examiner: Gutke, Hans-Jürgen

1 October 2015
This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on 61-10-2015. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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<tr>
<td>CA 2749174 A1</td>
<td>15-07-2010</td>
<td>CN 101619058 A</td>
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<td>US 2011269766 A1</td>
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