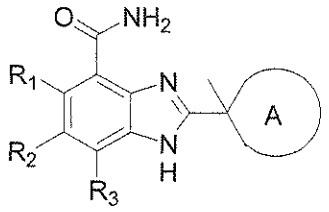
[0012] The present invention relates to a method for mitigating neurotoxic effects of a chemotherapeutic agent, comprising administering to a subject an effective amount of a compound of formula (II).

[0013] The present invention relates to a method for treating chemotherapy-induced neuropathic pain in a subject, comprising administering to the subject an effective amount of a compound of formula (II).

[0013a] The present invention relates to the use of a compound of Formula (I) in the manufacture of a medicament for the prophylactic treatment of chemotherapy-induced peripheral neuropathy in a subject,



(I),

wherein

R_1, R_2, and R_3 are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxycarbonyl, alkyl, alkynyl, cyano, haloalkoxy, haloalkyl, halogen, hydroxy, hydroxyalkyl, nitro, NR_AR_B, and (NR_AR_B)carbonyl;

A is a nonaromatic 4, 5, 6, 7, or 8-membered ring that contains 1 or 2 nitrogen atoms and, optionally, one sulfur or oxygen atom, wherein the nonaromatic ring is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cyano, haloalkoxy, haloalkyl, halogen, heterocycle, heterocyclealkyl, heteroaryl, heteroarylalkyl, hydroxy, hydroxyalkyl, nitro, NR_CR_D, (NR_CR_D)alkyl, (NR_CR_D)carbonyl, (NR_CR_D)carbonylalkyl, (NR_CR_D)sulfonyl, and oxo; and

R_A, R_B, R_C, and R_D are independently selected from the group consisting of hydrogen, alkyl, and alkycarbonyl;

or a pharmaceutically acceptable salt or solvate thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] FIG. 1 shows the prophylactic effect of 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide (Compound A) on vincristine-mediated neuropathy manifested by the prevention of vincristine-mediated pain.

[0015] FIG. 2 shows the prophylactic effect of 6-fluoro-2-(2-methylpyrrolidin-2-yl)-1H-benzimidazole-4-carboxamide (Compound B) on vincristine-mediated neuropathy manifested by the prevention of vincristine-mediated pain.

[0016] FIG. 3 shows the prophylactic effect of 2-[(2S)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide (Compound C) on oxaliplatin-mediated neuropathy manifested by the attenuation of oxaliplatin-mediated mechanical allodynia.

[0017] FIG. 4 shows the prophylactic effect of 2-[(2S)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide (Compound C)on oxaliplatin-mediated neuropathy manifested by the attenuation of oxaliplatin-mediated cold allodynia.

[0018] FIG. 5 shows the prophylactic effect of 2-[(2S)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide (Compound C) on cisplatin-mediated neuropathy manifested by the attenuation of cisplatin-mediated mechanical allodynia.

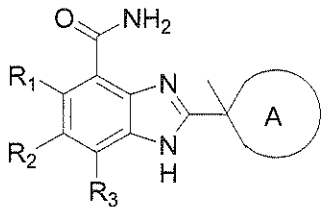
[0019] FIG. 6 shows the prophylactic effect of 2-[(2S)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide (Compound C) on cisplatin-mediated neuropathy manifested by the attenuation of cisplatin-mediated heat hyperalgesia.

[0020] FIG. 7 shows the prophylactic effect of 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide (Compound A) on vincristine-mediated neuropathy manifested by the prevention of vincristine-mediated pain.

[0021] FIG. 8 shows the prevention of vincristine-mediated increase in PAR levels in skin by treatment with 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide (Compound A).

CLAIMS

1. Use of a compound of Formula (I) in the manufacture of a medicament for ~~use in a method of~~ the prophylactic treatment of chemotherapy-induced peripheral neuropathy in a subject,



(I),

wherein

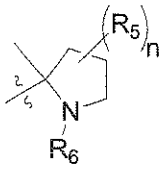
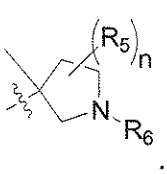
R_1, R_2, and R_3 are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxycarbonyl, alkyl, alkynyl, cyano, haloalkoxy, haloalkyl, halogen, hydroxy, hydroxyalkyl, nitro, NR_AR_B, and (NR_AR_B)carbonyl;

A is a nonaromatic 4, 5, 6, 7, or 8-membered ring that contains 1 or 2 nitrogen atoms and, optionally, one sulfur or oxygen atom, wherein the nonaromatic ring is optionally substituted with 1, 2, or 3 substituents selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cyano, haloalkoxy, haloalkyl, halogen, heterocycle, heterocyclealkyl, heteroaryl, heteroarylalkyl, hydroxy, hydroxyalkyl, nitro, NR_CR_D, (NR_CR_D)alkyl, (NR_CR_D)carbonyl, (NR_CR_D)carbonylalkyl, (NR_CR_D)sulfonyl, and oxo; and

R_A, R_B, R_C, and R_D are independently selected from the group consisting of hydrogen, alkyl, and alkycarbonyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. The use of claim 1, wherein A is selected from the group consisting of


and

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