Pharmaceutical Compositions Comprising N-(3,5-Dimethoxyphenyl)-N'-(1-Methylethyl)-N-[3-(1-Methyl-1H-Pyrazol-4-Yl)Quinoxalin-6-Yl]Ethane-1,2-Diamine

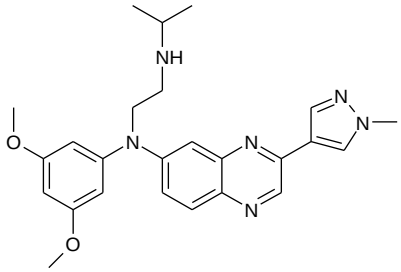
FIELD OF THE INVENTION

The invention relates to pharmaceutical compositions comprising N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, or a pharmaceutically acceptable salt thereof or a solvate thereof; to processes for the preparation of said compositions and to the use of said compositions for the manufacture of a medicament for the prophylaxis of or the treatment, in particular the treatment, of diseases, e.g. cancer.

BACKGROUND OF THE INVENTION

N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine is described in WO2011/135376, which is incorporated herein by reference.

The chemical structure of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine (compound A herein) is :



SUMMARY

According to an aspect of the disclosure there is provided a pharmaceutical composition comprising N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a solvate thereof, a formaldehyde scavenger and a pharmaceutically acceptable carrier.

According to the disclosure there is provided the use of a formaldehyde scavenger, in particular meglumine, to increase the stability, in particular the chemical stability of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a solvate thereof, in particular N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine base, in a pharmaceutical

composition, in particular a solid pharmaceutical composition, in particular a capsule or a tablet.

According to another aspect of the disclosure there is provided use of a formaldehyde scavenger in a pharmaceutical composition to increase the chemical stability of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a solvate thereof, contained in said composition.

According to another aspect of the disclosure there is provided use of a formaldehyde scavenger in a pharmaceutical composition to prevent, postpone, slow down or diminish the tranformation of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a solvate thereof, contained in the composition, into 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine, a pharmaceutically acceptable salt thereof or a solvate thereof.

According to another aspect of the disclosure there is provided a method of preventing, postponing, slowing down or diminishing the transformation of N-(3,5-dimethoxyphenyl)-N’-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxaline-6-yl]ethane-1,2-diamine, a pharmaceutically acceptable salt thereof or a solvate thereof, contained in a pharmaceutical composition, into 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxaline-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine, a pharmaceutically acceptable salt thereof or a solvate thereof, comprising adding a formaldehyde scavenger to said composition.

According to another aspect of the disclosure there is provided a method of treating cancer in a patient, comprising administering to the patient a pharmaceutical composition as defined herein daily for 3 weeks (3 weeks on), followed by 1 week wherein the composition is not administered (1 week off), and repeating this cycle of 3 weeks on, 1 week off.

According to another aspect of the disclosure there is provided use of a pharmaceutical composition as defined herein for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered daily for 3 weeks (3 weeks on), followed by 1 week wherein the composition is not administered (1 week off), and repeating this cycle of 3 weeks on, 1 week off.

According to another aspect of the disclosure there is provided a method of treating cancer in a patient, comprising administering to the patient a pharmaceutical composition as defined herein daily for 1 week (1 week on), followed by 1 week wherein the composition is not administered (1 week off), and repeating this cycle of 1 week on, 1 week off.

According to another aspect of the disclosure there is provided use of a pharmaceutical composition as defined herein for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered daily for 1 week (1 week on), followed by 1 week wherein the composition is not administered (1 week off), and repeating this cycle of 1 week on, 1 week off.

FIGURES

Fig.1 : Experimental set-up of formaldehyde stress test in solid state (N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine = compound A)

Fig. 2 : Degradation of N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine (compound A) in powder blends comprising various concentrations of meglumine in a formaldehyde stress test : ♦ represents a starting powder blend of 2% w/w of compound A, mannitol, microcrystalline cellulose, croscarmellose sodium and magnesium stearate; ■ represents a starting powder blend of 2% w/w of compound A, 1% w/w of meglumine, mannitol, microcrystalline cellulose, croscarmellose sodium and magnesium stearate; ▲represents a starting powder blend of 2% w/w of compound A, 9% w/w of meglumine, mannitol, microcrystalline cellulose, croscarmellose sodium and magnesium stearate. Compound B is 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine.

DETAILED DESCRIPTION OF THE INVENTION

It was found that N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine is sensitive to degradation, especially when incorporated in a solid pharmaceutical composition. In particular, N-(3,5-dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]ethane-1,2-diamine is sensitive, especially when incorporated in a solid pharmaceutical composition, to transformation into a cyclized product, 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine.

The chemical structure of 6,8-dimethoxy-4-(1-methylethyl)-1-[3-(1-methyl-1H-pyrazol-4-yl)quinoxalin-6-yl]-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (compound B herein) is: