cytokines and TNF-α. It is well documented that pirfenidone inhibits excessive biosynthesis or release of various fibrogenic cytokines such as TGF-β1, bFGF, PDGF, and EGF. Zhang S et al., *Australian New Eng. J. Ophthal.*, 26:S74-S76 (1998). Experimental reports also show that pirfenidone blocks the synthesis and release of excessive amounts of TNF-α from macrophages and other cells. Cain et al., *Int. J. Immunopharm.*, 20:685-695 (1998).

[0006] Pirfenidone has been studied in clinical trials for use in treatment of IPF. Thus, there is a need for a synthetic scheme that provides pirfenidone having sufficient purity as an active pharmaceutical ingredient (API) and involves efficient and economical processes. Prior batches of pirfenidone were shown to have residual solvent traces of ethyl acetate (e.g., about 2 ppm) and butanol.

SUMMARY

[0007] Disclosed herein are methods of preparing pirfenidone. More specifically, disclosed herein is a method of synthesizing pirfenidone comprising admixing bromobenzene, 5-methyl-2-pyridone, cuprous oxide, and an organic solvent under conditions sufficient to form pirfenidone, wherein the bromobenzene comprises less than about 0.15% by weight dibromobenzene. The admixing can be performed under elevated temperatures, for example at least about 100°C. The organic solvent can comprise dimethyl formamide.

[0007a] In a first aspect, there is provided a method of synthesizing pirfenidone comprising admixing bromobenzene, 5-methyl-2-pyridone, cuprous oxide, and an organic solvent under conditions sufficient to form pirfenidone, wherein the bromobenzene comprises less than 0.15% by weight or molar ratio dibromobenzene.

[0007b] In a second aspect, there is provided pirfenidone prepared by the method as defined herein, having a purity of at least 98% by weight or molar ratio and essentially free of ethyl acetate and butanol.

[0007c] In a third aspect, there is provided pirfenidone having less than 0.1% by weight or molar ratio of a di(5-methyl-2-pyridinone)benzene impurity.

[0007d] In a fourth aspect, there is provided pirfenidone having less than 0.1% by weight or molar ratio of an impurity which elutes at a relative retention time of 1.95 compared to the retention time of pirfenidone, when analyzed by liquid chromatography.

[0007e] In a fifth aspect, there is provided pirfenidone having less than 0.1% by weight or molar ratio of an impurity which elutes at a relative retention time of 1.24 compared to the retention time of pirfenidone, when analyzed by liquid chromatography.

[0007f] In a sixth aspect, there is provided a pharmaceutical composition comprising the pirfenidone as defined herein and a pharmaceutically acceptable excipient.

[0008] In some embodiments, the method further comprises washing the pirfenidone with a saline solution. The saline solution can comprise about 10 wt% to about 15 wt% sodium chloride. In various embodiments, the method further comprises extracting the pirfenidone with an extracting solvent. The extracting solvent can comprise toluene.

[0009] In various embodiments, the method further comprises admixing a base with the bromobenzene, 5-methyl-2-pyridone, cuprous oxide, and organic solvent. The base can be an inorganic base. In a specific embodiment, the inorganic base comprises a carbonate, and more specifically, potassium carbonate.

[0010] In some embodiments, the method further comprises crystallizing the pirfenidone from a solvent mixture comprising heptanes and toluene to form purified pirfenidone. The method can also further comprise recrystallizing the purified pirfenidone by dissolving at least a portion of the purified pirfenidone in an acidic aqueous solution at an elevated temperature to form a pirfenidone solution; adding a basic solution to the pirfenidone solution until the pH is at least about 11; and cooling the basic pirfenidone solution to a temperature below about 20°C to form recrystallized pirfenidone. In some cases, the elevated temperature is at least about 40°C. In various cases, the acidic aqueous solution comprises hydrochloric

acid. In some cases, the basic solution comprises sodium hydroxide. In various cases, the basic pirfenidone solution is cooled to a temperature below about 10°C. In some cases, the purifying of the pirfenidone is performed in the absence of ethyl acetate and butanol. In a specific case, the pirfenidone prepared by the methods disclosed herein has a purity of at least 98% by weight or molar ratio and is essentially free of or free of ethyl acetate and butanol, where essentially free of describes a product where neither ethyl acetate nor butanol is intentionally added during the synthetic processes, as described herein. A pirfenidone composition essentially free of ethyl acetate and/or butanol can permit the presence of trace amounts of ethyl acetate and/or butanol which are carry-over impurities, e.g. present in the reagents or starting materials used in a synthetic process such as one described herein. The pirfenidone prepared can have a purity of at least 99%, and more preferably, at least 99.9% by weight or molar ratio.

[0011] In another embodiment~~aspect~~, disclosed herein is pirfenidone having less than about 0.1% by weight or molar ratio of a di(5-methyl-2-pyridone)benzene impurity, and preferably less than about 0.05% by weight or molar ratio of a di(5-methyl-2-pyridone)benzene impurity.

[0012] In yet another embodiment~~aspect~~, disclosed herein is pirfenidone having less than about 0.1% by weight or molar ratio of an impurity which elutes at a relative retention time of about 1.95 compared to the retention time of pirfenidone, when analyzed by liquid chromatography. Preferably, the pirfenidone has less than about 0.05% by weight or molar ratio of the impurity with the relative retention time of 1.95.

[0013] In still another embodiment~~aspect~~, disclosed herein is pirfenidone having less than about 0.1% by weight or molar ratio of an impurity which elutes at a relative retention time of about 1.24 compared to the retention time of pirfenidone, when analyzed by liquid chromatography. Preferably, the pirfenidone has less than about 0.05% by weight or molar ratio of the impurity with the relative retention time of 1.24.

[0014] In another embodiment~~aspect~~, pharmaceutical compositions comprising pirfenidone as disclosed herein and a pharmaceutically acceptable excipient are described.

DETAILED DESCRIPTION

[0015] Disclosed herein is an improved process for preparing pirfenidone. The process involves using a cuprous oxide catalyst to couple 5-methyl-2-pyridone and bromobenzene in an organic solvent. Without intending to be limited by any particular theory, it is believed that the purity of the bromobenzene is important, as amounts of a dibromobenzene impurity in the bromobenzene can lead to dimer-type byproducts, which can complicate the