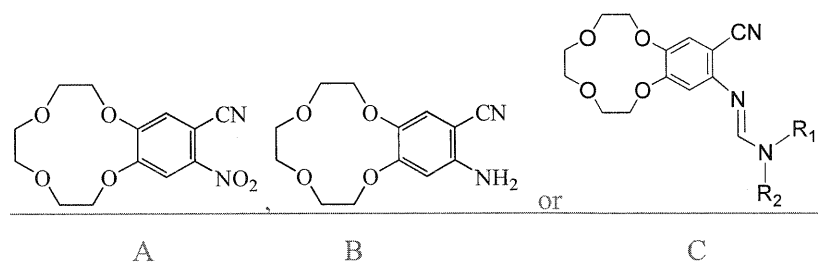


disclosed by US7078409B2 and CN130568C require use of highly toxic reagent, i.e., Chlorinating agent, such as $(\text{COCl})_2$ or phosphorus oxychloride. These highly toxic Chlorinating agents, especially Chlorinating agent containing phosphorus, are very difficult or costly to be completely removed in the later reactions. Therefore, the existing synthetic methods not only are very costly but also cause severe environment pollution problems, and present a significant threat to the health of producers and users. The preparation method disclosed in WO2010/003313 uses metal catalysts, which are also costly and difficult to be separated or recovered. Furthermore, any direct emission of such metal and phosphine ligand will cause severe environment pollutions.

The intermediary compounds designed by the present invention are used for preparing Icotinb or Icotinib hydrochloride. These preparation methods avoid use of high-toxic reagents, proceed in mild reaction conditions, and thus are easier, more economic, lower-toxic and safer than synthetic methods currently known in the art.

Summary of the Invention

In one aspect, there is provide a compound of formula A, B, or C:

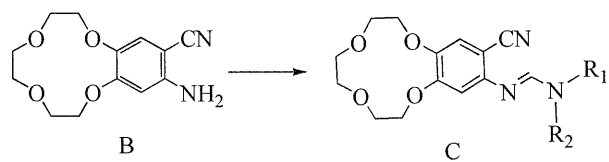


wherein:

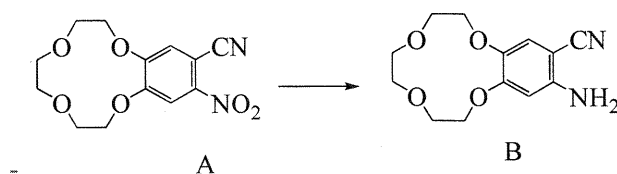
each of R_1 and R_2 independently is methyl, ethyl, propyl, or isopropyl; or

R_1 and R_2 , together with the N atom to which they are attached, form a 3 to 7-membered ring.

In one aspect, there is provide a method for preparing a compound as described herein, wherein compound C is prepared from compound B, and the method comprises the step of:



In one aspect, there is provide a method for preparing a compound as described herein, wherein compound B is prepared from compound A, and the method comprises the step of:



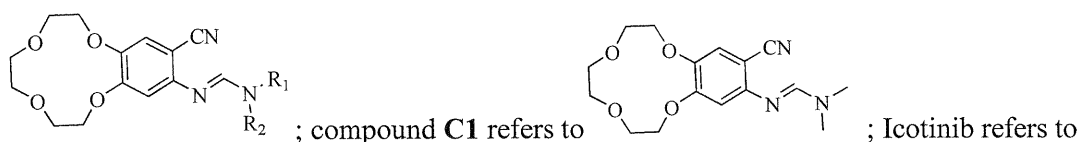
In one aspect, there is provide a method for preparing Icotinib from a compound as described herein, wherein the reaction between compound C and m-aminophenyl acetylene occurs in an organic acid.

In one aspect, there is provide a method for preparing Icotinib hydrochloride from a compound as described herein, wherein compound C is a raw material, and the method comprises using a method as described herein to prepare Icotinib, dissolving the Icotinib in a lower alcohol, adding hydrogen chloride gas or hydrochloric acid while stirring, and then filtering the Icotinib after the reaction is complete.

DESCRIPTION OF THE INVENTION

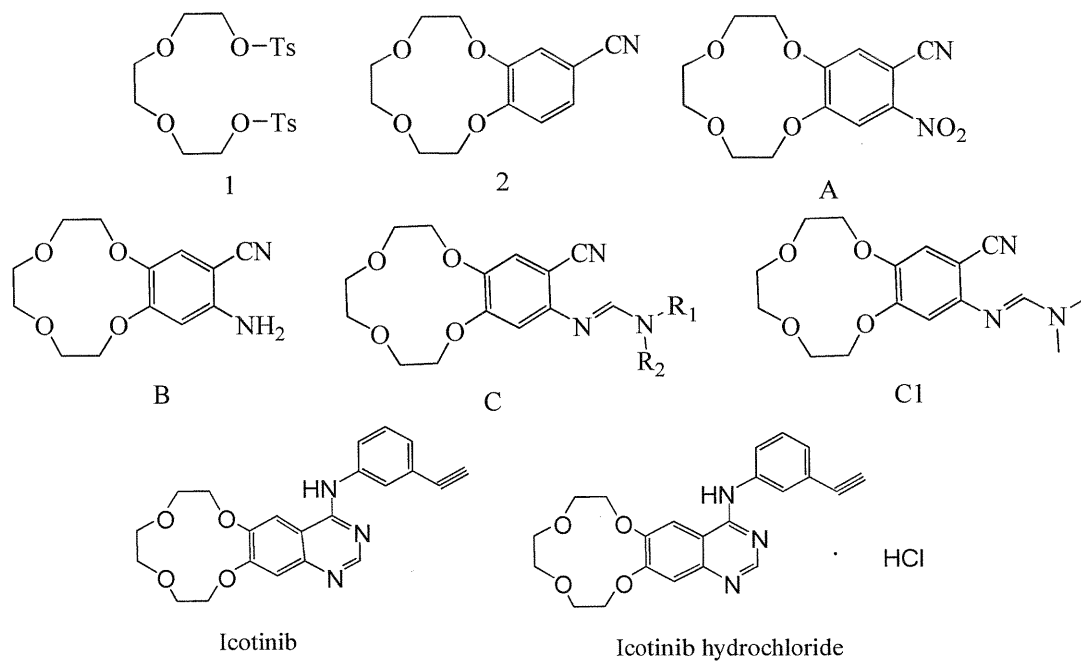
The present invention overcomes the problems of the existing technology and provides methods for preparing intermediates of Icotinib, i.e., compound **A**, compound **B**, and compound **C**, as well as methods for preparing Icotinib and Icotinib hydrochloride using those intermediates. These novel methods are more environmental friendly and economic, and can proceed in relatively mild reaction conditions and reduce environment pollutions.

For the convenience of illustration in the present application, compound **1** refers to 1,8-bis-(para-toluenesulfonate)-3,6-dioxo-octane is named; compound **2** refers to 3,4-benzo-12-crown-4-benzonitrile ; compound **A** refers to 6-nitro-3,4-benzo-12-crown-4-benzonitrile ; compound **B** refers to 6-amino-3,4-benzo-12-crown-4-benzonitrile ; compound **C** refers to

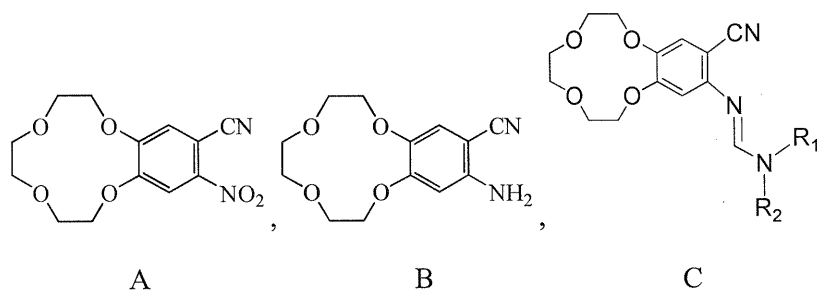


4-[(3-ethynylphenyl)amino]-quinazoline and [6,7-b]-12-crown-4; Icotinib hydrochloride refers to 4-[(3-ethynylphenyl)amino]-quinazoline and [6,7-b]-12-crown-4 hydrochloride. For these compounds, compound **A** can be used to prepare compound **B**, compound **B** can be used to prepare compound **C**, compound **C** can be used to prepare Icotinib or Icotinib hydrochloride, and all of the compounds **A**, **B**,

and **C** can be used to prepare Icotinib and Icotinib hydrochloride. Chemical structures of Compounds **1**, **2**, **A**, **B**, **C**, and **C1**, Icotinib and Icotinib hydrochloride are shown below, respectively:



The present invention firstly provides a compound of formula **A**, **B** or **C**:



wherein,

each R_1 and R_2 independently is methyl, ethyl, propyl, or isopropyl; or,

R_1 and R_2 , together with the N atom to which they are attached, form a 3 to 7-membered ring.

Preferably, each of R_1 and R_2 independently is methyl or ethyl.

The present invention further provides some preferred technical solutions with regard to compound

C:

Preferably, R_1 and R_2 are methyl.

Preferably, R_1 and R_2 are ethyl.

Preferably, R_1 and R_2 , together with the N atom to which they are attached, form a 3, 4 or 5-membered ring.