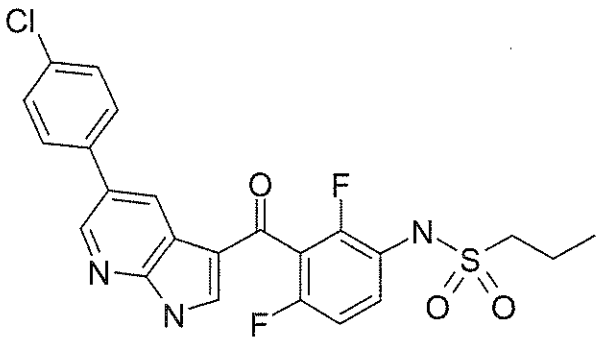
PROCESS FOR THE MANUFACTURE OF PHARMACEUTICALLY ACTIVE COMPOUNDS

The present invention is related to synthesis routes to obtain the compound Propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide (formula 1).



Formula (1)

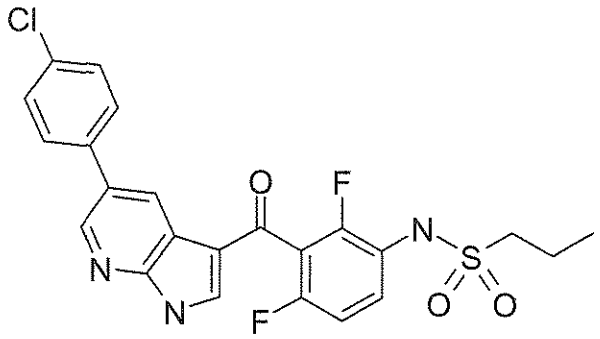
The synthesis of the compound of formula (1) has been described before in WO 2007002433 and WO 2007002325.

However, the known synthesis routes may not be readily adapted for use on an industrial scale.

The present ~~invention~~disclosure provides new and improved synthesis routes for the compound of formula (1), which employ reaction conditions which are particularly amenable to being carried out on an industrial scale. In particular, the process according to the present ~~invention~~disclosure efficiently uses starting materials, avoids formation of high quantities of undesirable by-products, provides high throughput and good product yields and can safely be carried out in large scale production. It is also less expensive, and, due to the

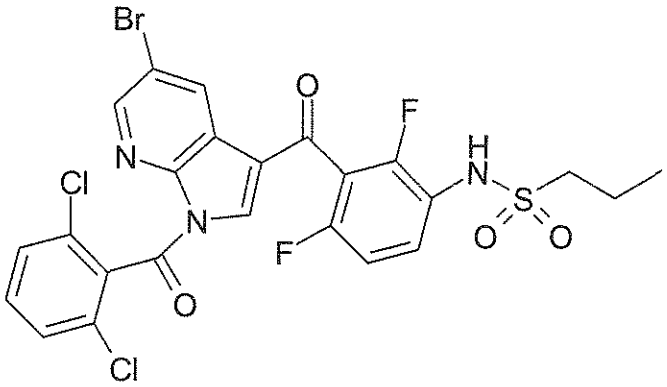
efficient use of starting materials, environmentally friendlier than processes disclosed in the prior art.

In one aspect, there is provided a process for the manufacture of the compound of formula (1),



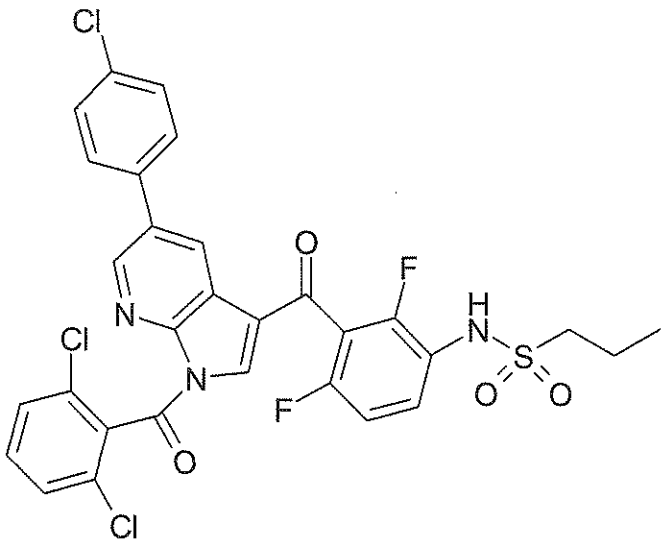
(1),

characterized in that the compound of formula (5)



(5)

is reacted in the presence of 4-Chlorophenylboronic acid and a Palladium Catalyst to give the compound of formula (6)



(6); and

the 2,6-Dichlorobenzamide group in said compound of formula (6) is cleaved to give the compound of formula (1).

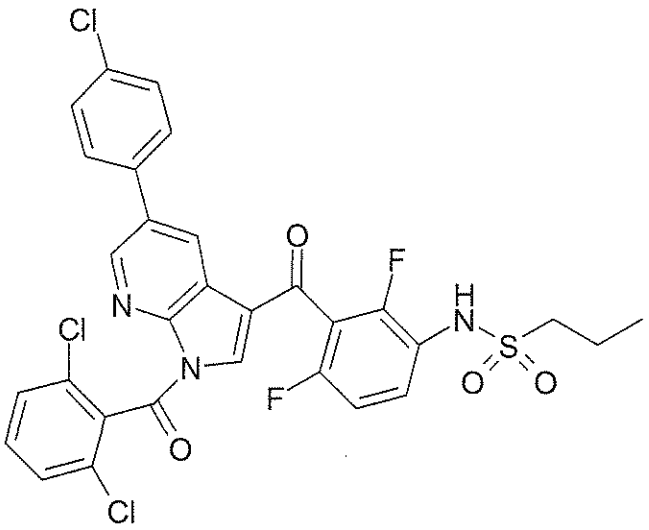
In another embodiment of the present ~~invention~~disclosure there are identified specific compounds (compounds (A) and (B) as specified below) which are by-products of the present synthesis method. Trace amounts of compound (B), obtained by deprotection, i.e. cleavage of 2,6-dichlorobenzamide from compound (A) during the last step of the synthesis of the compound of formula (1), are typically found in the final product (formula (1)) as pharmaceutically acceptable impurity and in amounts of maximum 0.30%, but usually in about 0.02% to about 0.15%, as identified by HPLC, provided said compound of formula (1) had been synthesized according to the present method. Therefore, while the impurity/trace amounts of formula (B) will not affect the pharmacological- or toxicity profile of any potential, future medicament or pharmaceutical preparation containing the compound of formula (1), they may nevertheless serve as fingerprint in order to detect whether the present process has been used to manufacture the compound of formula (1). It will therefore allow for an unambiguous identification as to whether the present process has been used in the manufacture of the compound of formula (1).

Therefore, in another embodiment the present ~~invention~~disclosure provides an analytical method for detecting whether the process according to the present invention has been used, characterized in that said analytical method detects the compound of formula (B) in a pharmaceutical preparation of the compound of formula (1).

Detailed Description of the Invention

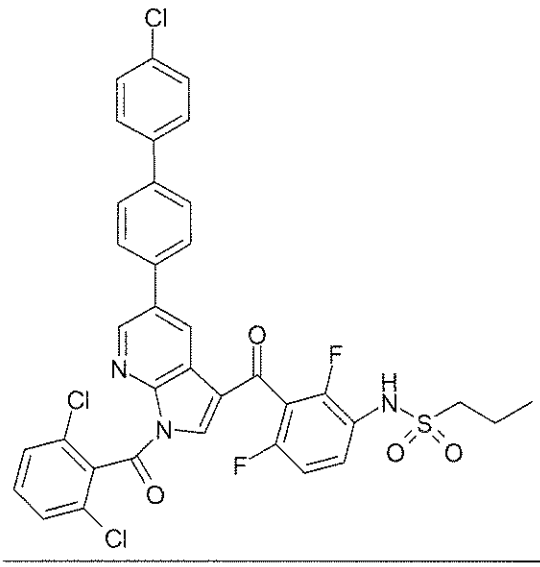
According to the present invention, there is provided a process for the manufacture of the compound of formula (1),

c) said compound of formula (5) is further reacted in the presence of 4-Chlorophenylboronic acid and a Palladium Catalyst to give the compound of formula (6)



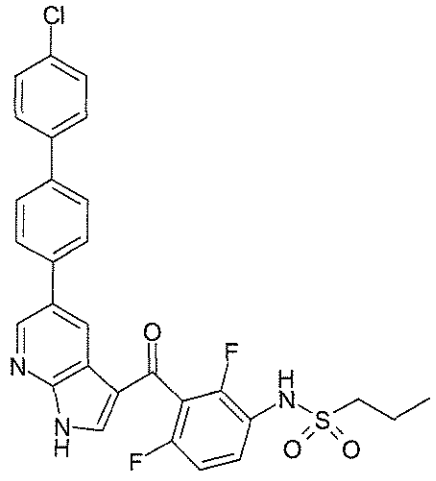
(6);

and the compound of formula (A)



~~according to claim 4~~ (A) as by-product; and

d) said compound of formula (6) is finally reacted with ammonia (NH_3) in methanol or ethanol solution diluted with a polar aprotic solvent such as DMA or DMF to give the compound of formula (1) according to claim 1 as main product, and the compound of formula (B)



~~according to claim 5~~ (B) as by-product.