

its alkoxy side chain; moreover the skilled artisan knew at the same time that sulfamide or *n*-propylaminosulfonamide are poor nucleophiles (mesomeric effect leading to a delocalization of the *N*-lone pair to the sulphur).

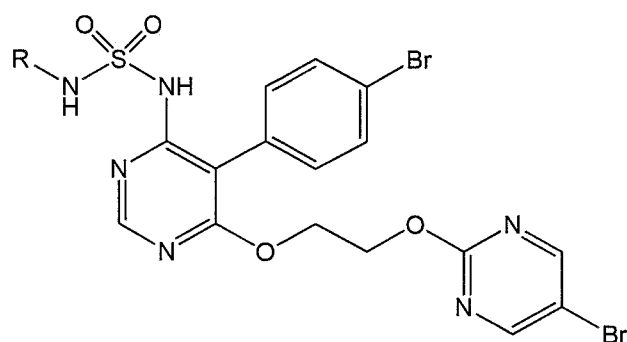
5 In accordance with the expected failure of the nucleophilic aromatic substitution reaction, the inventors could thus observe that reaction of the compound of formula I-1 wherein X is chlorine with standard fluorinating agents such as KF or NaF did not yield the fluorinated intermediate with sufficient purity and yield. Besides it was also observed that reaction of the compound of formula I-1 wherein X is chlorine with sulfamide did not occur at 70°C in DMSO. These findings confirm the fact that the compound of formula I-1 is not suitable
10 for nucleophilic aromatic substitution, in particular if the nucleophile intended to be used in the nucleophilic aromatic substitution is a poor nucleophile like a sulfamide.

Summary

It has now been surprisingly found that an alternative route to the compounds of formula I was nevertheless possible wherein the sulfamide function would be introduced in the last
15 step by nucleophilic substitution on the pyrimidine core. The introduction of the sulfamide function through nucleophilic substitution on the pyrimidine core was however only possible in a satisfactory manner when using the particular reaction conditions found by the inventors and described hereafter.

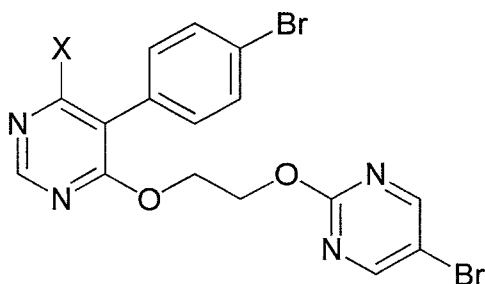
Thus said alternative route required obtaining a fluorinated intermediate with high purity,
20 which result could only be properly achieved using the fluorination agent tetra-*n*-butyl ammonium fluoride hydrate or cesium fluoride.

In one aspect of the disclosure, there is provided a process for manufacturing the compound of formula I



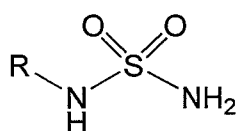
I

wherein R is *n*-propyl, or a salt thereof, said process comprising the reaction of the compound of formula I-1



I-1

5 wherein X is bromine, chlorine or fluorine, with the compound of formula I-2



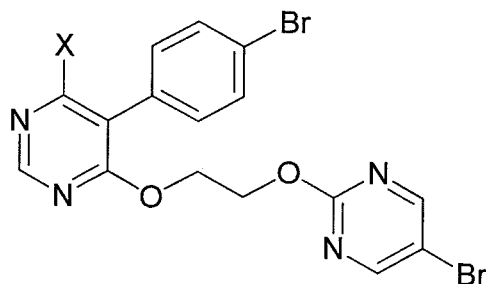
I-2

wherein R is *n*-propyl, or a salt of said compound of formula I-2, said reaction being performed in the presence of a base in a polar aprotic organic solvent or a polar mixture of aprotic organic solvents, and, when X is bromine or chlorine, in the presence of tetra-*n*-butyl ammonium fluoride hydrate or cesium fluoride.

10 A significant advantage of this alternative route is that it allows the use in the last step of a pyrimidine derivative already possessing a functionalised side chain at position 6 (i.e. the 2-(5-bromo-pyrimidin-2-yloxy)-ethoxy side chain), which avoids the use of an excess of ethylene glycol (required at some point to obtain the 2-(5-bromo-pyrimidin-2-yloxy)-

ethoxy side chain - see e.g. WO 02/053557 or Bolli et al., *J. Med. Chem.* (2012), **55**, 7849-7861) in a late stage of the manufacturing process. Besides, this route allows to use a single intermediate for preparing in a single step any compound of formula I wherein R represents H, (C₁-C₆)alkyl or benzyl.

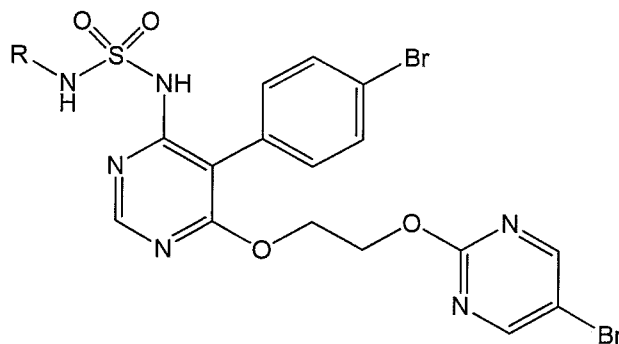
- 5 In another aspect, there is provided a use of a compound of formula I-1



I-1

wherein X is bromine, chlorine or fluorine, or a salt thereof, in a process for manufacturing the compound of formula I as defined in claim 1, or a salt thereof.

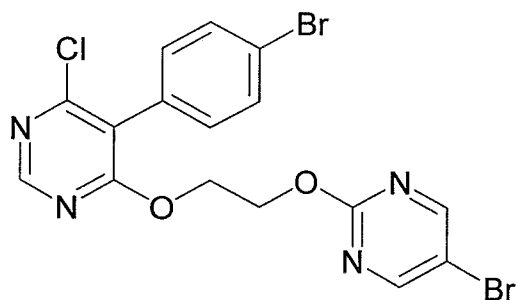
In yet another aspect, there is provided a process for manufacturing the compound of formula I



I

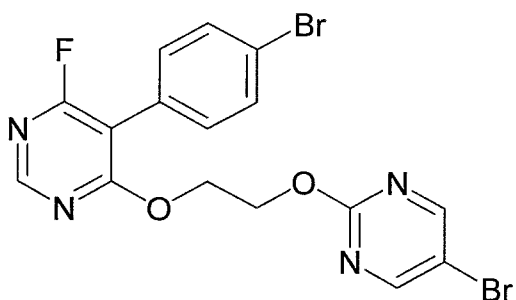
wherein R is *n*-propyl, or for manufacturing a salt thereof, said process comprising the reaction of the compound of formula I-1, said process comprising the following steps:

- a) the reaction of the compound of formula I-1_{Cl}



I-1_{Cl}

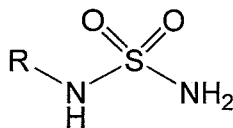
- 5 or a salt thereof, with tetra *n*-butyl ammonium fluoride hydrate or cesium fluoride in the presence of a base in a polar aprotic organic solvent or a polar mixture of aprotic organic solvents, to yield the compound of formula I-1_F



I-1_F

and

- b) the reaction of the compound of formula I-1_F obtained at step a) with a compound of formula I-2



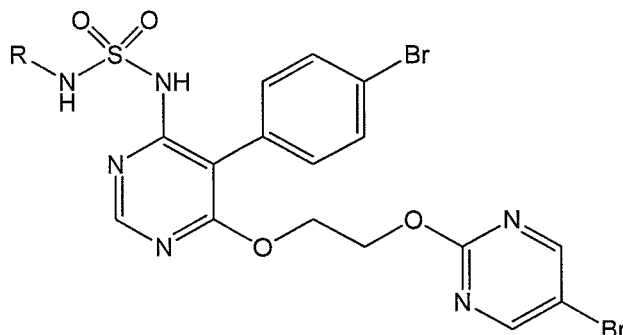
I-2

wherein R is *n*-propyl, or a salt thereof, in the presence of a base in a polar aprotic organic solvent or a polar mixture of aprotic organic solvents, to yield said compound of formula I or a salt thereof.

Detailed Description

Various embodiments of the invention are presented hereafter:

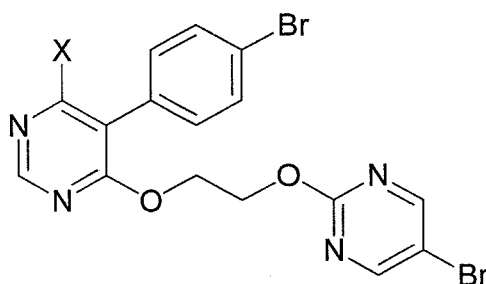
1) The invention firstly relates to a process for manufacturing the compound of formula I



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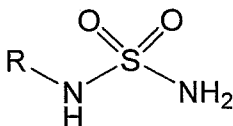
I

wherein R is H, (C₁-C₆)alkyl or benzyl, or a salt thereof, said process comprising the reaction of the compound of formula I-1



I-1

wherein X is bromine, chlorine or fluorine (and in particular chlorine or fluorine), with the compound of formula I-2



I-2

10 wherein R is H, (C₁-C₆)alkyl or benzyl, or a salt of said compound of formula I-2, said reaction being performed in the presence of a base in a polar aprotic organic solvent or a polar mixture of aprotic organic solvents, and, when X is bromine or chlorine, in the presence of tetra-*n*-butyl ammonium fluoride hydrate or cesium fluoride.