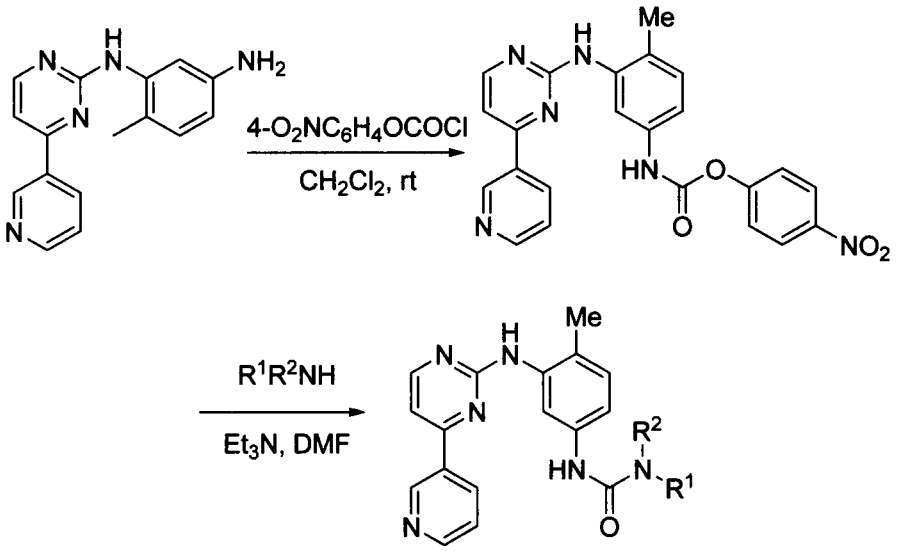

In the investigation to evaluate hypothesis that the potency of the molecule might be enhanced by replacing *N*-methylpiperazine group with an alternative binding group,[45] such as a urea moiety. The reasoning is that this group would maintain the H-bond interactions to human protein kinases. Compounds were prepared by the route in which the phenylamino-pyrimidine core structure was prepared using a variation of the principal synthesis, involving reaction of the enamine derivative of the β-aldehydoketone with guanidine. The guanidine was readily available from the commercially available aniline derivative, via reaction with cyanamid, followed by catalytic hydrogenation. Aminoformylation of 3-acetylpyridine with DMF–dimethylacetal furnished the enone intermediate. For the parallel synthesis of the urea library, the 4-nitrophenylcarbamate derivative was selected on the basis of its reactivity, together with the stability and crystallinity of the hydrochloride salt. The addition of a variety of amines to a solution of in DMF containing triethylamine provided the desired urea derivatives.

13.3.4 Bosentan

The endothelins are a family of structurally related 21-amino acid peptides that are the most potent vasoconstrictors identified so far in vascular preparations in both animals and humans. An endothelin receptor antagonist, bosentan, is a new drug for treating cardiovascular pathology, especially congestive heart failure.[46] Two generations of processes were established aiming at reducing the bulk drug manufacturing cost.