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The piperazine core of tricyclic farnesyltransferase inhibitors

Farnesyltransferase (FTase) is a heterodimeric protein that transfers the isoprenoid moiety of farnesyl pyrophosphate (FPP) to C-terminal CAAX box sequences [1]. CAAX prenylation is needed for the activation of oncogenic Ras proteins and it is believed that Ras activity could be modulated through FTase inhibition. However, several studies indicate that FTase inhibitors (FTIs) can suppress the growth of transformed cells and tumours regardless of Ras activation status [2]. Despite these apparent ambiguities, FTIs promote clinical regression of several solid tumour types with a modest toxicity profile when used as single agents or in combination with cytotoxic agents.

Lonafarnib **(i)** is an FTI currently in phase III clinical trials. Structure–activity relationships (SARs) targeting the N-1 position of the piperidine core of Lonafarnib have been explored, but most derivatives produce IC_{50}s only in the micromolar range. Chemical development of tricyclic FTIs containing a piperazine core has been largely limited to substitution with either pyridine or piperidine functionalities.

To more thoroughly understand the SAR at the piperazine core, recent work [3] has examined the variation of 63 distinct substituents on the N-1 (R3) position in conjunction with variation of 31 substituents at the C-2 (R1) position. In this work, an 11,718-member ECLiPS® (Encoded Combinatorial Library on Polymeric Support) library was synthesized in mixtures on TentaGel™ solid-phase resin derivatized with a 4-bromomethyl-3-nitrobenzamide photolabile linker. The library was built up from coupling of a set of R1 amines with a piperazine carboxylic acid core to deliver **(ii)**. This was then acylated with one nitrogen (using R3 acids) and subsequently coupled to aryl chlorides, giving **(iii)**, see Scheme. The library compounds were then screened at a concentration of 500 nM. Upon screening, several active components were discovered. Following deconvolution and re-synthesis of components within the active mixtures, one of the most potent compounds isolated was **(iv)**, which had an Ftase enzyme IC_{50} of 30 nM.

This work is important in that it demonstrates, for the first time, that substitution at R1 is tolerated, revealing a new sub-site that can be explored through synthesis, thereby enabling new SAR to be generated. Thus, further work in this area is warranted.

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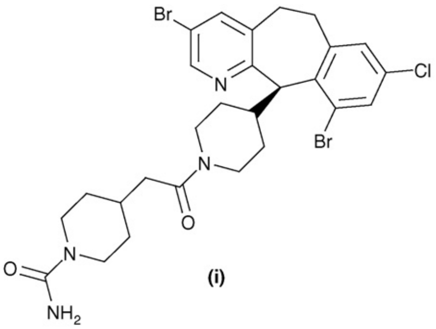
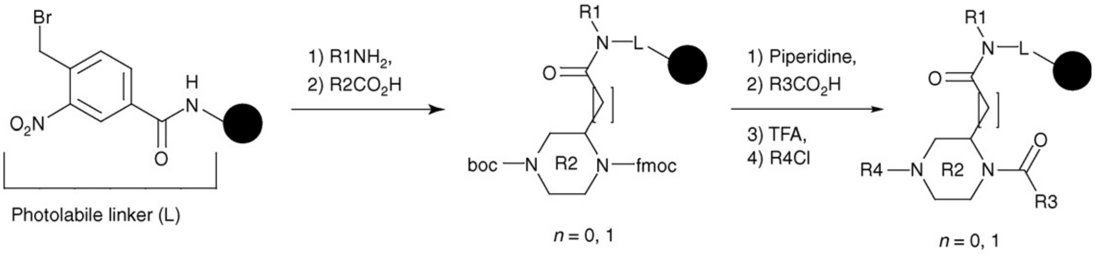


(i)



(ii)

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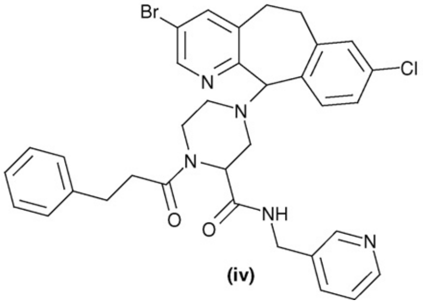

(iv)

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