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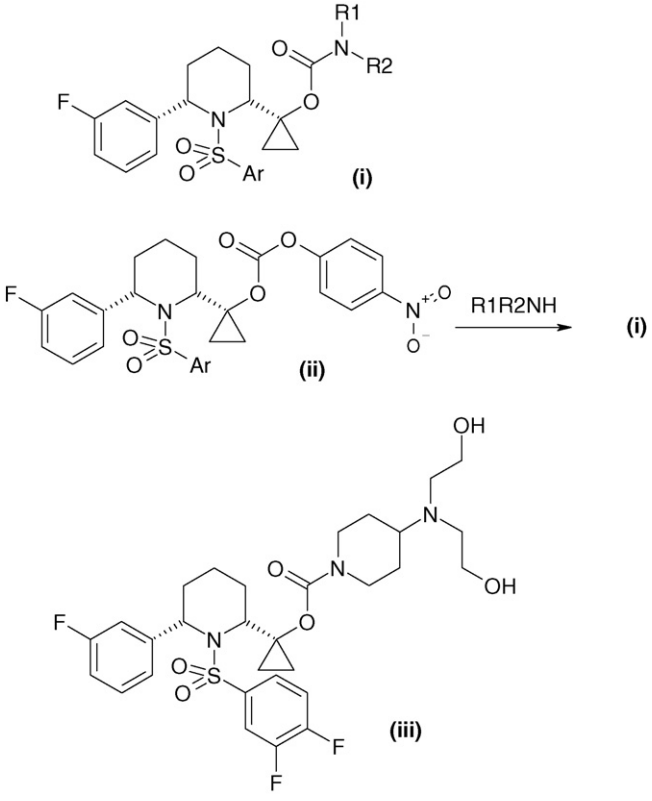
Application of technologies and parallel chemistry for the generation of actives against biological targets

Solution phase synthesis of carbamates as γ-secretase inhibitors

The carbamate moiety is often found in biologically active compounds. Attachment of the carbamate side chain to a known biologically active molecule may improve its physicochemical properties, which makes carbamates useful as prodrugs. Carbamates, therefore, remain an active element in the field of drug research for diverse medicinal chemistry programs throughout the world, including antitumor [1], anti-infective [2] and central nervous system [3]. The synthesis of carbamate derivatives has also been used in drug discovery program targeted to Alzheimer's disease. Alzheimer's disease is a common degenerative brain disorder which accounts for up to 70% of all cases of dementia and is the third most-common cause of death in the United States [4]. One of the major pathological hallmarks of AD is an abnormal extracellular deposition of β-amyloid peptide (Aβ) in the form of plaques in the brains of Alzheimer patients. Although the exact cause of Alzheimer's disease is unknown, a large body of evidence suggests that overproduction of Aβ is central to its pathogenesis. Aβ is produced by the proteolysis of the larger amyloid precursor protein (APP) by sequential action of β- and γ-secretases. γ-Secretase plays a central role in the generation of Aβ peptide. Inhibition of this enzyme was proposed as a target for the treatment of Alzheimer's disease [5]. Further to explore rapidly the SAR of γ-secretase inhibitors containing the carbamate moiety, the parallel synthesis of libraries of carbamates would be useful. Recent work [6] has disclosed a new and practical method for the liquid-phase parallel synthesis of sterically hindered carbamates, exemplified by the synthesis of a targeted library of γ-secretase inhibitors of generic structure (**i**). Synthesis proceeded by the utilization of 4-nitrophenylcarbamate intermediates in their reaction with amines, typified by the conversion of (**ii**) into (**i**). Synthesis also utilized scavenging resins to clean up the final products: using polystyrene isocyanate resin (PS-NCO) and polystyrene benzaldehyde (PS-PhCHO) resin to remove amines, and Amberlyst A26 basic resin (Amberlyst is a registered trademark of Rohm and Haas Co.) to remove 4-nitrophenol from the library members. Utilizing this methodology, a library of 144 compounds was synthesized as singletons.

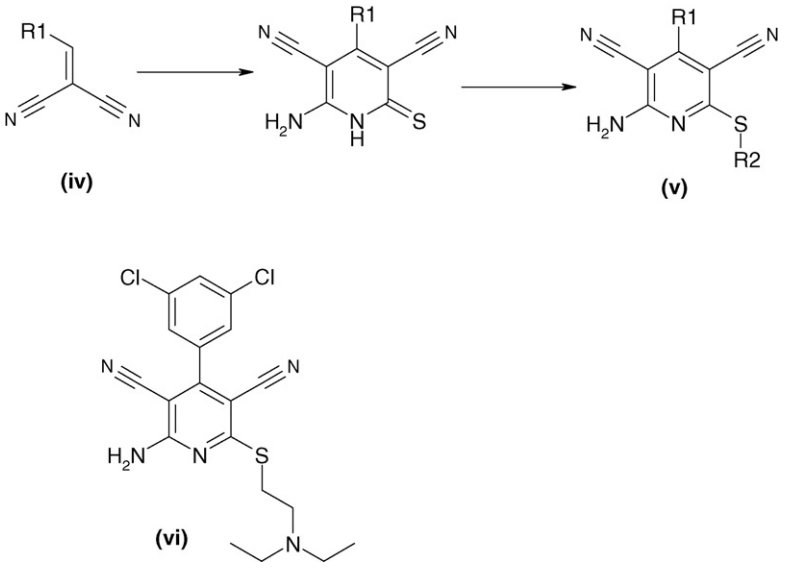
Next, *in vitro* screening of the library was performed against γ-secretase [7] and several inhibitors demonstrated activity, with IC_{50} values in the range from 1 μM to 5 nM. One of the most potent compounds tested was (**iii**) which possessed an IC_{50} of 4.9 nM. This work is of interest because of the combination of resin scavengers and 4-nitrophenylcarbamate intermediates allowing the synthesis of sterically encumbered compounds in a library format that are inhibitors of γ-secretase. Further work in this area is warranted with a view to improve the drug-like properties of compounds within this series.



1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2008.05.002

Prion inhibition by 2-aminopyridine-3,5-dicarbonitrile-based compounds

Misfolding of the cellular prion protein, PrP^{C}, to a β-rich conformation, denoted PrP^{Sc}, is the underlying molecular event that gives rise to the prion diseases [8]. Subsequent deposition of oligomeric PrP^{Sc} in the central nervous system leads to neuronal loss and rapid death in animals and humans. The conversion of PrP^{C} to PrP^{Sc} is believed to proceed via formation of a complex between the PrP isoforms and another, unidentified, molecular chaperone (X). The proposed PrP–X binding may involve an epitope that maps to dominant-negative PrP mutants. Dominant-negative PrP mutants protect from disease, as demonstrated by familial polymorphisms in the human and ovine prion protein gene (*PRNP*) [9], and transfection studies in scrapie-infected cells [10]. Recent work has centered on efforts to identify inhibitors to PrP^{Sc} formation using a structure-based approach. Computational chemistry was used to derive pharmacophore models based on the conformation and electronic space of the dominant-negative mutant PrPs [11]. As part of this work to deduce SAR, a 2-aminopyridine-3,5-dicarbonitrile series of compounds was identified. Several analogs were active at low micromolar concentrations in a scrapie-infected cell model of prion replication. More recent work has disclosed the biological and *in vitro* pharmacokinetic data on a potent subset of 2-aminopyridine-3,5-dicarbonitrile compounds [12]. This new lead of compounds possesses a halobenzene and basic alkyl substituents on a pyridine heterocyclic scaffold. One hundred and fifty-two library members were synthesized in a one-pot, two-step reaction, from 2-(arylidene)-malononitriles (**iv**), which was first reacted with 2-cyanothioacetamide and then with a diverse set of alkyl halides and aryl halides to give final products (**v**). Compounds were purified by HPLC. The isolated compounds were then screened against scrapie-infected neuroblastoma cells (ScN2a). Bioactivity against PrP^{Sc} accumulation was expressed as EC_{50}, the compound concentration at which 50% of PrP^{Sc} had been removed from the culture on exposure to compound. From this work, several potent compounds were obtained. One of the most potent compounds was (**vi**) which possessed an EC_{50} value of 2.2 μM. This work is of interest because compounds have been identified that inhibit accumulation of PrP^{Sc} in a cell model of prion replication at low micromolar concentrations. Additionally, these current compounds are of suitable potency to form the basis of chemical genetics probes which could be used to identify targets that may be implicated in prion replication. Further work in this area is warranted in improving the properties of this series of inhibitors.



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