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MOLECULES

Recent developments in the production of ligands directed against the group III metabotropic glutamate and the VLA-4 receptors

Aminopyrrolidinetricarboxylic acids: new group iii metabotropic glutamate receptor-selective ligands

The most commonly occurring neurotransmitter in the central nervous system is glutamate, which is thought to have a crucial role in many pathological processes. Glutamate exerts its effects through two families of receptors: the metabotropic (mGlu) and the ionotropic (iGlu) receptors. mGlu receptors have been further divided into three groups according to their sequence homologies, pharmacological properties and signal transduction pathways. Group III mGlu receptors include the mGlu4, mGlu6, mGlu7 and mGlu8 receptors. So far, only a few orthosteric agonists have been described for group III mGlu receptors. Typically, these agonists have low-micromolar to sub-micromolar potencies for mGlu4, mGlu6 and mGlu8, whilst displaying much less potency at the mGlu7 receptor.

Recent work [1] has demonstrated the utility of parallel chemistry for the rapid synthesis of polar amino acid derivatives that are agonists of group III mGlu receptors. Specifically, this work focused on aminopyrrolidine-tricarboxylic acid derivatives (APTC) and the design was based on the family of APTCs that are known to provide selective group III agonists [2]. The aim was to have a rigid template that would enable placement of polar functionality around the core, thus encouraging interaction of these polar groups with distal binding pockets of the receptors.

Following solution phase synthesis of diastereoisomerically pure protected cores, exemplified by generic structure **(i)**, a library of 65 compounds was constructed in solution resulting from capping of the pyrrolidine nitrogen with various (R)-groups, followed by deprotection of the Boc-group. The nitrogen was capped with electrophilic reagents using solid supported reagents and scavengers. The compounds prepared synthetically were screened against three group III mGlu rat receptors (mGlu4, mGlu6 and mGlu8) in functional assays at 450 μM and 300 μM for their agonist and antagonist activities, respectively.

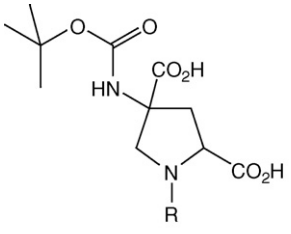
Following this screen, one of the most potent compounds obtained was **(ii),** which displayed an agonist response to mGlu4 with an EC50 of 48 μM. This compound displayed sevenfold selectivity against mGlu6 and was equally active against mGlu8. Compound (ii) was also inactive (EC50 >5000 μM) against group I receptors (mGlu1 and mGlu5) and the group II receptor mGlu2. Interestingly, compound (ii) is a full agonist for mGlu4 but a partial agonist for mGlu8, despite the compound having a similar EC50 value against both mGlu4 and mGlu8.

This work is important because it identifies an agonist for the group III mGlu receptor (mGlu4) with differing efficacies for the subtypes mGlu4 and mGlu8. Therefore, this ligand [compound (ii)] will be of use in furthering our understanding of the pharmacological role and therapeutic potential of the mGlu4 subtype.

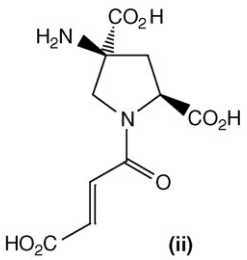
Solid-phase synthesis of 2,3-diphenylpropionic acid derivatives as VLA-4 antagonists

There exists a range of structural templates that have been exploited successfully in medicinal chemistry. One such template is the phenylalanine skeleton **(i)**, which is found within, for example, the angiotensin converting enzyme inhibitor 'alacepril' [3] and the insulin promoter 'nateglinide' [4]. A further structurally related chemical class is represented by recently synthesized VLA-4 antagonists [5]. The integrin, very late antigen-4 (VLA-4), is a heterodimeric adhesion molecule ($\alpha 4\beta 1$) expressed on the surface of leukocytes, binding vascular cell adhesion molecule-1 (VCAM-1) on endothelial cell surfaces.

Small molecule antagonists for VLA-4 are reputed to be useful in the treatment of chronic inflammatory diseases, such as asthma [6] and multiple sclerosis [7]. Recent work [8] has sought to examine the ability of the 2,3-diphenylpropionic acid template to replace phenylalanine moieties in lead compounds, themselves requiring peptide backbone modification, with the intent of improving the overall pharmacokinetic profile of the leads. In this regard, these workers chose to develop an efficient solid phase library synthesis of diverse substituted 2,3-diphenylpropionic acids as potential VLA-4 antagonists.



(i)



(ii)

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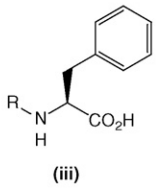
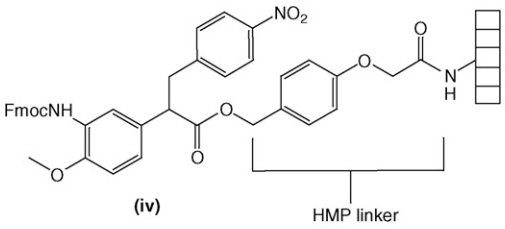
Synthesis of 96 compounds occurred on SynPhase™ Lanterns through a 4-hydroxymethyl phenoxyacetic acid (HMP) linker. The pivotal intermediate **(ii)** was prepared and derivatized through either route: (1) nitro group reduction followed by acylation, then (2) Fmoc-group deprotection, reductive alkylation followed by acylation, or the inverse of this synthetic route (2) then (1). Both routes were attempted to deliver compounds of general structure **(iii)**, obtained after cleavage of compound from the solid phase. The compounds thus obtained were assayed for their ability to inhibit the binding of VLA-4 expressing human leukemia cells (HL-60) to human VCAM-1 expressed on Chinese hamster ovary (CHO) cells. One of the most potent compounds isolated was **(iv)**, which had an IC_{50} of 5 nM for inhibition of VLA-4 binding.

This work is of interest because a general solid-phase library synthesis of substituted 2,3-diphenylpropionic acids has now been developed. Several members of the set of compounds synthesized as part of this library were active as VLA-4 antagonists. Further work is warranted as the synthetic routes developed during this current research are applicable to the synthesis of various propionic acid derivatives decorated with two aromatic residues; derivatives that themselves represent a medicinally useful pharmacophore.



(iii)



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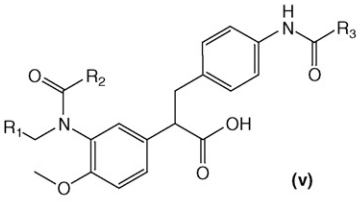

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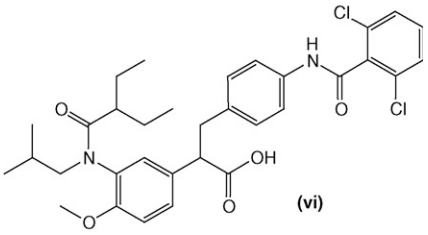

(vi)

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