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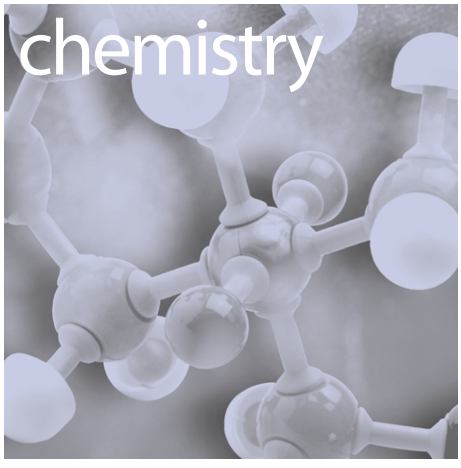
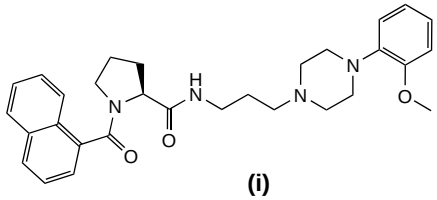


MOLECULES

Carboxamide proline derivatives as CNS agents

The 5-HT$_7$ receptor (5-HT$_7$R) is the most recently identified subtype of the serotonin G-protein-coupled receptor superfamily. It possesses about 36–53% homology with the other human 5-HT receptors. The 5-HT$_7$R has been found to be positively coupled to adenylate cyclase, that is, agonists at the receptor cause a dose-dependant increase in intracellular cyclic AMP (cAMP). Using *in situ* hybridization techniques, it has been shown that 5-HT$_7$R is found both centrally and peripherally. The prominent expression of 5-HT$_7$ receptor in the thalamus, limbic and cortical regions of the brain, in addition to its having a high affinity for several antipsychotic and antidepressant agents, suggest that it could be involved in mental disorders such as schizophrenia [1] and depression [2].

There are many different compound classes capable of binding to the 5-HT$_7$R. A relatively large group of these ligands contain several fragments that additionally bind to other GPCRs (e.g. 5-HT$_{1A}$, 5-HT$_{2A}$, D$_2$). For example, an amine moiety (mostly 4-N-arylpiperazine,tetrahydroisoquinoline or 4-substituted tetrahydropyridine), which is connected by a different length alkyl chain (2–5 carbon atoms) to a terminal aromatic fragment [3]. Recently, workers have applied solid phase parallel chemistry for the generation of a focused arylpiperazine library[4], targeted at 5-HT$_7$ receptors on a solid support (SynPhase Lanterns: www.mimotopes.com, mimotopes, Pty). These authors designed a structurally related 64-member library of sulphonamide and carboxamide L- and D-proline derivatives. The library synthesis was carried out on BAL linker functionalized polyamide SynPhase Lanterns (Mimotopes, Pty) using a split-and-pool approach. The lanterns were equipped with coloured cogs and spindles (corresponding to building blocks) to produce a convenient visual tagging system [5]. The library members were evaluated for their *in vitro* affinity at central serotonin 5-HT$_7$ receptors; additionally, the affinity of 12 compounds for D$_2$ receptors was assessed, and 17 selected compounds were tested for their ability to bind to 5-HT$_{1A}$ receptors.

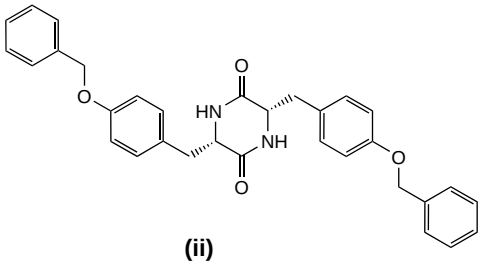


(i)

The compounds selected were screened in radioligand binding assays. One of the most potent compounds against 5-HT$_7$ discovered was **(i)**, which possessed a Ki of 183 nM at the 5-HT$_7$ receptor. This library also uncovered a number of compounds with good potency at the 5-HT$_{1A}$ receptor: **(i)**, for example, has a K$_i$ of 29 nM for 5-HT$_{1A}$. Thus, this work has developed an efficient solid supported method for the synthesis of novel sulfonamide and carboxamide proline derivatives. A 64-member library was obtained on SynPhase Lanterns and screened for the compounds biological evaluation for 5-HT$_7$ and 5-HT$_{1A}$ serotonin, and D$_2$ dopamine receptor affinities. Further work is warranted as this study provides initial data for further investigations concerning 5-HT$_7$ receptor agents.

Diketopiperazines as potential inhibitors of calpain

Calpains are a class of intracellular cytoplasmic non-lysosomal cysteine proteases expressed ubiquitously in mammalian cells. Of the 16 different kinds of calpain identified to date, two of the most studied are μ-calpain (calpain I) and m-calpain (calpain II). They differ in their sensitivity with respect to calcium ion activation: Calpain I requires micromolar concentrations of calcium, in contrast with calpain II, which responds only to millimolar concentrations [6]. Both isoforms are heterodimers with identical 30 kDa subunits, but differing 80 kDa subunits.



(ii)

Calpain overactivation is implicated in many conditions, particularly stroke and myocardial infarction [7]. Thus, selective calpain inhibitors might represent useful pharmacological probes and possibly therapeutic agents. Recent work [8] has centred on the identification of selective non-peptide inhibitors of calpain. These authors developed a one-pot cyclization procedure for the synthesis of diketopiperazine derivatives as calpain inhibitors. A small library of diketopiperazines was synthesized in solution and evaluated for inhibition of calpain I in a continuous fluorescence assay, using recombinant calpain I produced by the

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baculovirus expression system, and Suc-Leu-Tyr-AMC23 as the fluorogenic substrate. When the library compounds were tested, only neglibible activity against calpain I was observed: one of the most potent compounds isolated **(ii)** displayed an IC_{50} of 0.1 mM. Compounds screened possessed IC_{50}s in the range 0.1–1.0 mM. This work has identified a small library of 2,5-diketopiperazines with potentially promising activity as calpain inhibitors. However, no potent calpain analogues were discovered from this methodology. Further work, as indicated by the authors, can now proceed in this important search for calpain inhibition using structure-based methods and an HTS approach.

1 Pouzet, B. *et al.* (2002) J. Effect of the 5-HT_7 receptor antagonist SB-258741 in animal models for schizophrenia. *Pharmacol. Biochem. Behav*. 71, 655–665
2 Middlemiss, D.N. *et al.* (2002) Serotonergic targets in depression. *Curr. Opin. Pharmacol*. 2, 18–22
3 Zajdel, P. *et al.* (2004) Serotonin7 receptors (5-HT_7Rs) and their ligands. *Curr. Med. Chem*. 11, 629–661
4 Leopoldo, M. (2005) Parallel solid-phase synthesis and characterization of new sulfonamide and carboxamide proline derivatives as potential CNS agents. *Bioorg. Med. Chem*. 13, 3029–3035
5 Feliu, L. *et al.* (2003) Spiroimidazolidinone library derivatives on SynPhase lanterns. *Comb. Chem*. 5, 356–361
6 Sorimachi, H. *et al.* (1997). Structure and physiological function of calpains. *Biochem. J*. 1997, 328, 721–732
7 Goll, D.E. *et al.* (2003)The calpain system. *Physiol. Rev*. 83, 731–801
8 Zeng, Y. *et al.* (2005) Synthesis of a small library of diketopiperazines as potential inhibitors of calpain. *J. Bioorg. Med. Chem. Lett*. 15, 3034–3038

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