Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

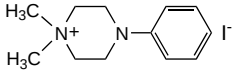
Monitor Editor: Steve Carney

Monitor Authors:
Daniela Barlocco, *University of Milan*
David Barrett, *Fujisawa Pharmaceutical Company*
Paul Edwards, *Pfizer*
Steven Langston, *Millennium Pharmaceuticals*
María Jesús Pérez-Pérez, *Instituto de Química Médica*
Michael Walker, *Bristol-Myers Squibb*
John Weidner, *Emisphere*
Andrew Westwell, *Nottingham University*

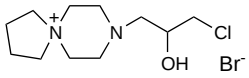
Molecules

Spirocyclopiperazinium salts as analgesics

Selective neuronal nicotinic acetylcholine receptor (nAChR) agonists are considered as useful agents in the treatment of pain. N_1,N_1-dimethyl-N_4-phenylpiperazinium iodide (DMPP, **i**) is a unique ligand in that it does not fit any proposed pharmacophore for nicotinic binding [1]. In the course of their studies on quaternary piperazinium salts [2,3], Li and collaborators found that compound **ii**, which is structurally related to DMPP, had significant analgesic activity. As an extension of this project, these workers have now presented [4] a series of spirocyclopiperazinium derivatives (**iii a–n; iv a–h)**, which have been tested for their *in vivo* analgesic and sedative properties, according to a previously reported method [5]. There is evidence that the anion of the quaternary salt influences biological activity. Therefore, all of the compounds were prepared as bromide salts. In series **iii**, only **iii f** (R = allyl) displayed significant analgesic activity (100% and 45% inhibition in the acetic acid writhing test at the doses of 20 mg kg^{-1} and 10 mg kg^{-1}, respectively). In

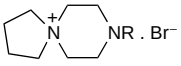


(i)

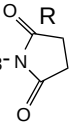


(ii)

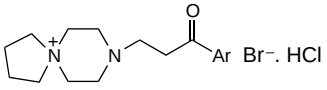
addition, at the tested doses, **iii f** showed no sedative effects. By contrast, all of the series **iv** compounds showed interesting analgesic activity, the most potent being **iv c** (Ar = *p*-hydroxyphenyl; 100% and 77% inhibition at doses of 20 mg kg^{-1} and 10 mg kg^{-1}, respectively). However, **iv c** also showed a significant sedation (85% at 20 mg kg^{-1}). The data obtained in this series clearly indicate that the nature and the position of the substituent



(iii a-n)

(a) R = $CH_2CHOHCH_2Cl$
(b) R = CH_2CH_3
(c) R = $CH_2C(CH_3)=CH_2$
(d) R = CH_2CH_2OH
(e) R = $(CH_2)_4OC_6H_5$
(f) R = $CH_2CH=CH_2$
(g) R = CH_2CH_2- 
(h) R = $(CH_2)_3$- 
(i) R = $CH_2CH=CHC_6H_5$
(j) R = $CH_2CH=CHC_6H_4$.Cl-*o*
(k) R = $CH_2CH=CHC_6H_4$.Cl-*m*
(l) R = $CH_2CH=CHC_6H_4$.Cl-*p*

on the aromatic ring can influence the activity of the spirocyclopiperazinium derivatives. In particular, electron-releasing groups are more favourable than electron-withdrawing substituents. However, the relationships between substituent position and compound activity are not so clear. Nevertheless, these results could be useful for elucidating the factors that influence the interactions between non-traditional ligands and neuronal nicotinic acetylcholine receptors.



(iv a-h)

(a) Ar = Phenyl
(b) Ar = *m*-hydroxyphenyl
(c) Ar = *p*-hydroxyphenyl
(d) Ar = *p*-methylphenyl
(e) Ar = thiophenyl
(f) Ar = furanyl
(g) Ar = *m*-nitrophenyl
(h) Ar = *p*-nitrophenyl

1 de Fiebre, C.M. *et al.* (1995) Characterization of a series of anabaseine-derived compounds reveals that the 3-(4)-dimethylaminocinnamylidine derivative is a selective agonist at neuronal nicotinic alpha 7/125I-alpha-bungarotoxin receptor subtypes. *Mol. Pharmacol.* 47, 164–171
2 Li, R.T. *et al.* (1996) *Acta Pharm. Sinica* 31, 757
3 Li, R.T. *et al.* (1998) *Acta Pharm. Sinica* 33, 28
4 Gao, F.L. *et al.* (2003) Unique spirocyclopiperazinium salt I: Synthesis and structure–activity relationship of spirocyclopiperazinium salts as analgesics. *Biorg. Med. Chem. Lett.* 13, 1535–1537

  PII: S1359-6446(03)02808-3

5 Li, R.T. *et al.* (1999) Synthesis and biological activities of dibenzyl dipiperazine diquaternary ammonium salts. *Arch. Pharm. Pharm. Med. Chem.* 332, 179–181

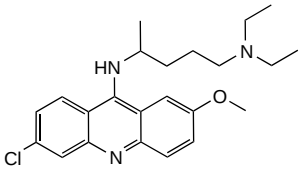
Daniela Barlocco
University of Milan
Viale Abruzzi 42
Milano 20131, Italy
e-mail: daniela.barlocco@unimi.it

Combinatorial chemistry

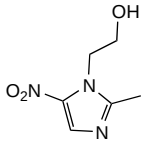
Isoflavones as antigiardial agents

Giardia lamblia is a flagellated, unicellular protozoan that causes the acute or chronic gastrointestinal disease, giardiasis, in humans. Among the most common of parasitic infections, over 200 million people are infected with *G. lamblia* throughout the world. The prevalence of diarrhoea caused by giardiasis in AIDS patients is higher than those without AIDS, due to the suppressed immunity of patients. Until 1988, quinacrine (**i**) was used to treat the disease; the current mainstay of treatment is now metronidazole (**ii**), which yields high cure rates, but also produces general toxicity and occasional drug resistance. Thus, safe efficacious novel antigiardial agents are required.

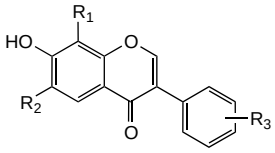
Biological evaluation of various natural products has indicated that molecules possessing a flavonoid skeleton exhibit antigiardial activity. Hence, the development of a library of isoflavone derivatives, of general structure **iii**, was envisaged as an approach to discover potent leads, while simultaneously developing SARs: Avery and co-workers prepared a library of 174 isoflavone derivatives in solution [1]. A selection of potent compounds were obtained from this library upon screening for inhibition of giardial growth, with one of the most potent compounds synthesized being **iv,** with an IC_{50} value of $<1.1\ \mu g\ mL^{-1}$. This work has provided promising antigiardial leads and, thus, represents a fruitful approach for further investigation.



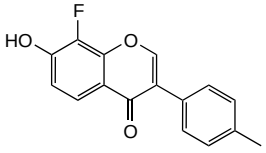
(i)



(ii)



(iii)



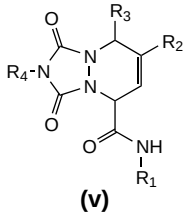
(iv)

Thrombin inhibitors

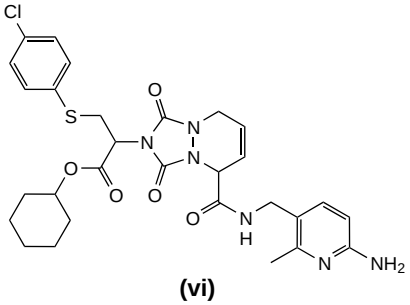
The serine protease, thrombin, has been a dominant subject of pharmaceutical research for several years. This research has produced advances in the development of highly active and selective inhibitors of thrombin. Despite these advances, however, no orally active direct thrombin inhibitor is currently widely available for the treatment of thrombotic diseases.

Recently, bicyclic β-strand mimetics have been disclosed that are useful as scaffolds for the synthesis of protease inhibitors based on the triazolopyridazine structure (**v**) [2].

More recently, new triazolopyridazine chemistry has emerged, that extends the scope of this chemical class into the synthesis of new libraries of bioactive compounds, and into rapid generation and optimization of thrombin inhibitor compounds [3]. More than 600 single compounds have been synthesized on various solid phase resins, such as Wang and chlorotrityl polystyrene resin; these have been screened for inhibition of thrombin and trypsin by fluorometric assay. Several potent inhibitors were found, one of the most potent being **vi**, which possessed a *K*i value of 0.057 nM against thrombin. This work has generated rapid SAR and potent thrombin inhibitor lead compounds.



(v)



(vi)

1 Mineno, T. *et al.* (2002) Solution-phase parallel synthesis of an isoflavone library for the discovery of novel antigiardial agents. *Comb. Chem. High Throughput Screen.* 5, 481–487
2 Ogbu, C.O. *et al.* (1998) Highly efficient and versatile synthesis of libraries of constrained β-strand mimetics. *Bioorg. Med. Chem. Lett.* 8, 2321–2326
3 Boatman, P.D. *et al.* (2003) High-throughput synthesis and optimisation of thrombin inhibitors via urazole α-addition and Michael addition. *Bioorg. Med. Chem. Lett.* 13, 1445–1449

Paul Edwards
Discovery Chemistry
Pfizer Global Research and Development
Sandwich, Kent, UK CT13 9NJ
fax: +44 1304 643555
e-mail: paul_edwards@sandwich.pfizer.com

 1359-6446/03/$ – see front matter PII: S1359-6446(03)02807-1