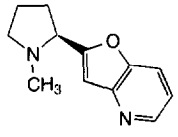
Monitor: molecules and profiles

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.

Neuronal nicotinic acetylcholine receptor ligands

Potent and selective neuronal nicotinic acetylcholine receptor modulators may be useful as therapeutic agents for the treatment of cognitive disorders. Elliott, R.L. and coworkers have described the synthesis and evaluation of a novel series of 2-[2′-furo(3,2-*b*)pyridinyl] pyrrolidines as potent nicotinic acetylcholine receptor ligands [*Bioorg. Med. Chem. Lett.* (1997) 7, 2703–2708]. These compounds have K_i values ranging from 2.7 to 97 nM. The intrinsic activity of these compounds was shown to be 9–58% of that of nicotine in the IMR-32 cell line and 6–81% in the K177 cell line.



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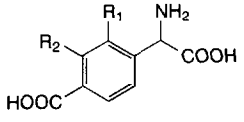
In developing these ligands Elliott *et al.* sought to identify compounds with particular selectivity for individual receptor subtypes. Compound **1** was found to have greater selectivity for the K177 cell line ($\alpha_4\beta_2$ receptor) than the IMR32 cells ($\alpha_3\beta_x$ receptor) and the TE671 cells (α_1 neuromuscular receptor. This agent was shown to act as a partial agonist (EC_{50} = 141 nM) in a rat striatal slice dopamine release assay.

mGluR1 receptor antagonists

There are at least eight metabotropic glutamate receptor proteins (mGluR1–8) that trigger various intracellular events. Clark, B.P. and coworkers have reported the synthesis of novel 4-carboxyphenylglycine derivatives to investigate the effects of aromatic substitution on the antagonistic potency of (*S*)-4-carboxyphenylglycine (**2**) on mGluR1 receptors [*Bioorg. Med. Chem. Lett.* (1997) 2777–2780].

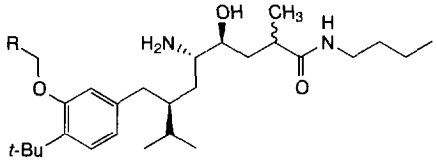
These studies have demonstrated that the addition of a 2-methyl substituent to phenylglycines increases the antagonistic potency on mGluR1 receptors. Compounds **3** [(+)-isomer: LY367385] and **4** are more potent and selective mGluR1 receptor antagonists than any phenylglycine previously reported and may therefore be useful pharmacological tools.



2 R_1 = H, R_2 = H
3 R_1 = CH_3, R_2 = H
4 R_1 = CH_3, R_2 = OH

Renin inhibitors

Renin inhibitors, which specifically block the first rate-limiting step of the blood pressure-regulating renin–angiotensin system, have been widely investigated as potential agents for the treatment of hypertension and other cardiovascular diseases. However, the development of many of these compounds has been hindered by poor oral bioavailability, rapid metabolism and first-pass biliary excretion. In an attempt to overcome these problems a number of groups have been working on the development of structurally distinct renin inhibitors.



5 R = $CO_2C_2H_5$
6 R = $CONH_2$
7 R = SO_2CH_3

Göschke, R. and coworkers have recently reported the evaluation *in vitro* of a series of novel, low-molecular-weight, transition-state, peptidomimetic renin inhibitors characterized by an all-carbon, 8-phenyl substituted, octane carboxamide skeleton [*Biorg. Med. Chem. Lett.* (1997) 7, 2735–2740]. The most potent inhibitors (**5**, **6** and **7**) were shown to have an IC_{50} = 6, 20 and 13 nM, respectively, towards purified human renin.

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