Monitor: molecules and profiles

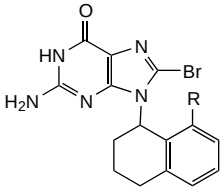
Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and 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.

Molecules

Guanine analogues as phosphodiesterase 7 (PDE7) inhibitors

The secondary messengers cAMP and cGMP are regulated by phosphodiesterases (PDEs), which hydrolyze them to the corresponding inactive 5′-monophosphate nucleotides. To date, 11 PDE gene families have been identified, varying in substrate specificity, inhibitor sensitivity and regulatory characteristics[1]. In particular, PDE7 is a cAMP-specific enzyme with a low K_m (0.2 μM), which is insensitive to the standard PDE4 inhibitor, rolipram[2]. The PDE7 mRNA is widely distributed, although the active protein has been identified predominantly in T-cells. It is suggested that selective inhibitors of PDE7 could have benefits in the treatment of T-cell-mediated diseases. In addition, the presence of PDE7 in airway epithelial cells implies that inhibitors could be beneficial in airway disease therapy.

To date, only two series of synthetic PED7 inhibitors have been described[3], which lack selectivity over the PDE4 and PDE3 isozymes. Because this could result in several side effects (e.g. emesis and cardiotoxicity), selective PDE7 inhibitors are highly desired. In a recent paper[4], Davenport and coworkers report on a series of guanine analogues that possess PDE7 inhibitory activity *in vitro* and demonstrate some evidence of selectivity over PDE4 and PDE3 isoenzymes. Their initial guanine-based hit [compound **(i)**; R = H] was identified as a result of screening internal and external databases. Extended SAR studies on compound **(i)** showed that the removal of the bromine and the amino group, as well as the replacement of the saturated six-membered ring with a five-membered and a seven-membered ring, reduced its activity. On the contrary, when a substituent (e.g. bromine, methoxy or nitro group) was inserted into the tetralin ring, improved activity was seen. In particular, compound **(ii)** (R = Br) was the most potent (IC_{50} = 1.31 μM) and selective (<14% inhibition for PDE3 and PDE4 at 10 μM).



(i) R = H
(ii) R = Br

Finally, because the natural ligand for PDE7 contains an adenine base, several compounds, in which the guanine was substituted with an adenine, were prepared. However, none of these analogues was found to offer any advantage over compound **(ii)**.

1 Rascon, A. (1997) Cyclic nucleotide phosphodiesterases: diversity, classification, structure and function. *Acta Cient. Venez.* 48, 145–153

2 Kaulen, P. *et al.* (1989) Autoradiographic mapping of a selective cyclic adenosine monophosphate phosphodiesterase in rat brain with the anti-depressant [^{3}H] rolipram. *Brain Res.* 503, 229–245

3 Martinez, I. *et al.* (2000) Benzyl derivatives of 2,1,3-benzo- and benzothieno[3,2-a]thiadiazine 2,2-dioxides: first phosphodiesterase 7 inhibitors. *J. Med. Chem.* 43, 683–689

4 Barnes, M.J. (2001) Synthesis and structure-activity relationships of guanine analogues as phosphodiesterase 7 (PDE7) inhibitors. *J. Med. Chem.* 11, 1081–1083

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Novel antiviral molecules

Anti-HIV activity of betulinic acid analogue YKFH312

Highly active antiretroviral therapy (HAART) has proven to be beneficial in the treatment of HIV, however, it has become increasingly clear that the therapy needs to be improved. One of the principal problems has been the emergence of viral resistance and several approaches are being pursued to slow down or overcome this resistance. One approach is to discover agents that attack viral targets, other than HIV polymerase and HIV protease, which form the basis of existing

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