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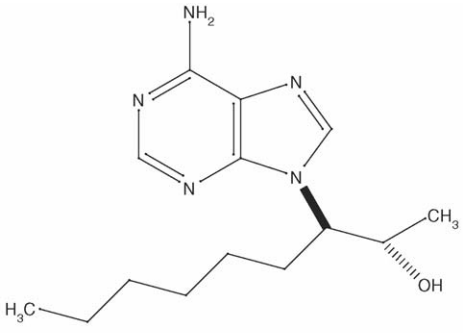
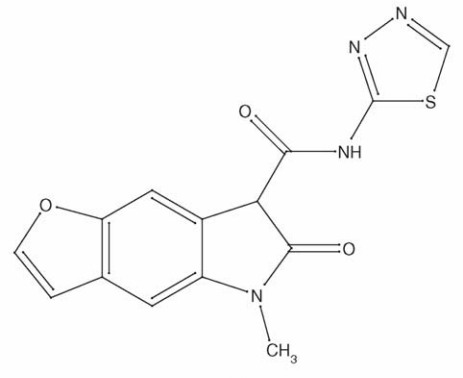
MOLECULES

A novel selective inhibitor of the phosphodiesterase type 2 isozyme

The phosphodiesterase (PDE) enzyme family controls intercellular levels of secondary messengers, cyclic AMP (cAMP) or cGMP, by regulating their hydrolysis. In particular, PDE type 2 (PDE2) possesses a low-affinity catalytic domain and an allosteric domain that is specific for cGMP. It is expressed throughout the body and, therefore, has a broad array of functions and potential therapeutic utility [1]. To date, several PDE2 inhibitors have been described, for example erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA) **(i)**, which is also a potent adenosine deaminase inhibitor [2,3], analogues of the phosphatidylinositol 3-kinase (PI3K) inhibitor LY294002 [4], and Bay 60-7550 [5]. Recently, Chambers *et al.* [6] reported on the oxindole **(ii)**, which was found to be over an order of magnitude more-potent than EHNA as a PDE2 inhibitor (IC_{50} 40 nM and 635 nM, respectively), EHNA also lacked significant inhibition towards other isozymes. In addition, compound **(ii)** showed higher potency than was reported for LY294002 analogues and better PDE1 selectivity than Bay 60-7550 [4,5]. When compound **(ii)** was assayed for interaction against a collection of 54 receptors and ion channels, no significant level of binding was found with respect to its PDE2 potency. Furthermore, the compound showed no inhibition of 5-lipoxygenase (5-LO) or cyclooxygenase-1 (COX-1), enzymes that are inhibited by other oxindole derivatives, and no significant inhibition against a panel of 30 kinases (relative to its PDE2 inhibition). Finally, compound **(ii)** had a suitable solubility (turbidimetric solubility at pH 7 = 55 $\mu g\ ml^{-1}$) and a favourable *in vitro* ADME–Tox profile. On these bases, oxindole **(ii)** could be regarded as a useful tool in defining the role of PDE2 in a broad range of disease states.



EHNA **(i)**



(ii)

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