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Medicinal
Chemistry
Letters

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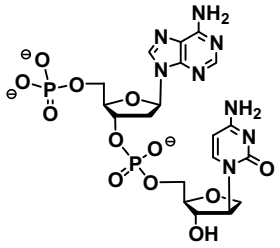
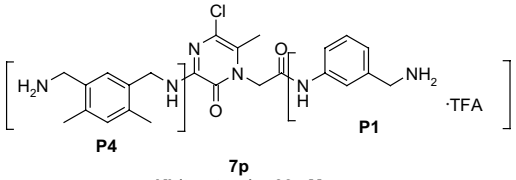
Contents

COMMUNICATIONS

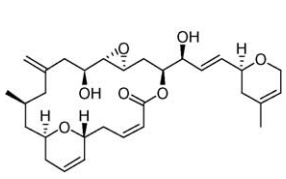


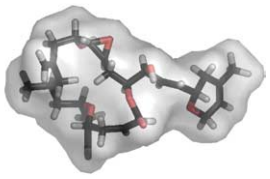
Remarkable selectivity for inhibition of the strand transfer step of HIV-1 integrase by novel dinucleotides.

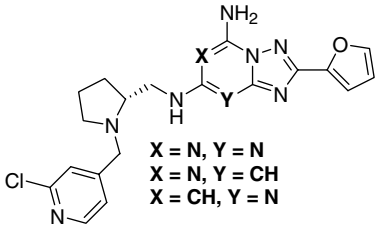


7p
Ki (tryptase) = 93 nM

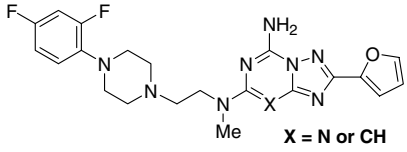
Microtubule-stabilising agents laulimalide and peloruside have been compared with tubulin-interacting drugs paclitaxel and colchicine by different computational approaches. Docking and QSAR-based programs point to a favourable interaction with the β tubulin paclitaxel binding site, although an additional, preferred binding site has been found at the α subunit of tubulin. All together provides a plausible rationalisation of the singular binding features of these microtubule stabilisers and paves the way for future structural studies.







A comparison of the adenosine A_{2a} receptor antagonist activity of three heterocyclic series showed that the core deriving from [1,2,4]triazolo[1,5-*a*]triazine (X = N and Y = CH) afforded compounds with oral activity in the mouse catalepsy model.

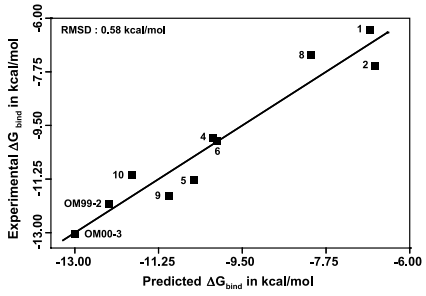


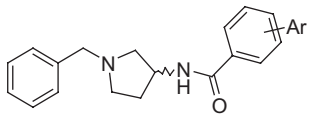
Derivatives of triazolotriazine and triazolopyrimidine have been found to be potent and selective adenosine A_{2a} receptor antagonists with oral activity in the mouse catalepsy model.

LK-71 CH_3NHCO-(4-Cl)Phe-D-Phe-Arg-Trp-NH_2 (**19**)

LK-75 $NCCH_2CO$-(4-Cl)Phe-D-Phe-Arg-Trp-NH_2 (**16**)

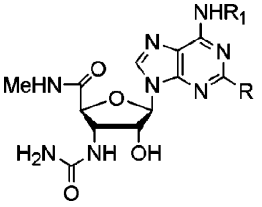
Of the 42 R′-X-(*p*-Cl)Phe-D-Phe-Arg-Trp-NH_2 (X = CO, SO_2, PO, PS) tested on the human (h)MC1, hMC3, and hMC4 receptors (R), the most potent MC4R agonists (EC_{50} of 8–20 nM) were obtained by end-capping with R′ = CH_2=$CHCH_2$ (**9**), $NCCH_2$ (**16**), NH_2COCH_2 (**17**), $HCONHCH_2$ (**18**), CH_3NH (**19**), CH_2=$CHCH_2NH$ (**21**), 2-Th (**23**), $PhCH_2$ (**30**) and X = CO. These compounds possess 35–60-fold hMC4 versus hMC1Rs selectivity with urea LK-71 (**19**) being the most potent and selective at hMC4R (EC_{50} = 8.5 nM, MC4/1R = 100). LK-75 (**16**) combines high potency at hMC4R and MC4/3R selectivity (EC_{50} = 10.5 nM, MC4/3R = 290). SAR is discussed.





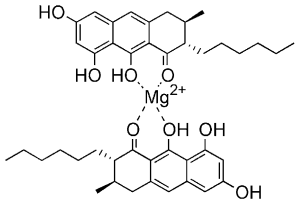
8

A series of *N*-(1-benzylpyrrolidin-3-yl)arylbenzamides **8** has been prepared, and their structure–activity relationships studied. Potent ligands selective for human D_4 (hD_4) over hD_2 and α_1 have been identified. One example was determined to be an antagonist in a cAMP assay, with an IC_{50} of 1500 nM.

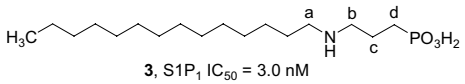


3a (R = H, R_1 = Me)
3b (R = H, R_1 = 3-iodobenzyl)
4a (R = Cl, R_1 = Me)
4b (R = Cl, R_1 = 3-iodobenzyl)

Novel 3′-ureidoadenosine analogues, **3** and **4** were synthesized from 1,2:5,6-di-*O*-isopropylidene-D-glucose in order to cause stronger hydrogen bonding than the corresponding 3′-aminoadenosine derivatives at the A_3 adenosine receptor.

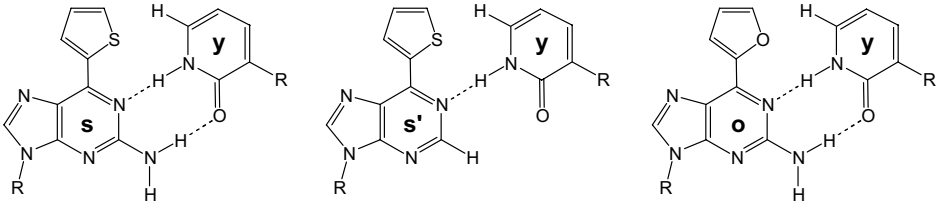


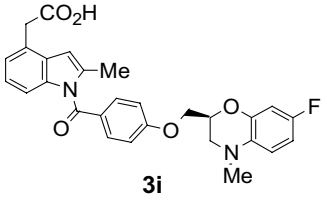
DNA-Binding of Mg^{2+}-Coorinated Dimer Complex



3, $S1P_1$ IC_{50} = 3.0 nM
Letters indicate the postion for tethering.

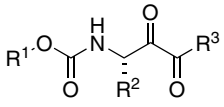
A series of conformationally constrained analogs of **3** were synthesized and evaluated as S1P receptor agonists. Several novel scaffolds were identified as suitable for further investigation.



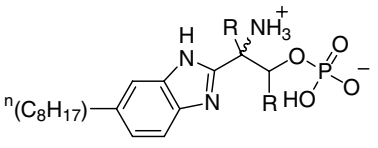


3i

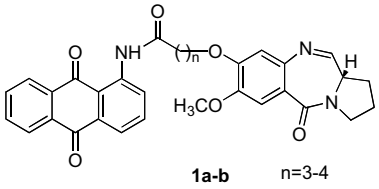
Discovery process of a new PGD_2 receptor antagonists **3i** is reported.



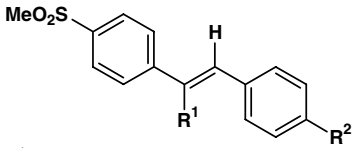
A series of ketoamides were synthesized and evaluated for inhibitory activity against cathepsin K. Exploration of the interactions between achiral P^2 substituents and the cysteine protease based on molecular modeling suggestions resulted in potent cathepsin K inhibitors that demonstrated high selectivity versus cathepsins B, H, and L. Subsequent modifications of the P^3, P^1, and $P^{1\prime}$ moieties afforded orally bioavailable inhibitors.



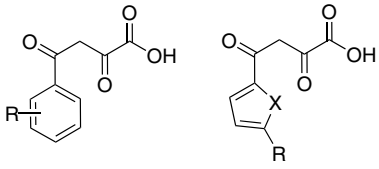
We report the synthesis and potencies of several selective $S1P_4$ receptor agonists.



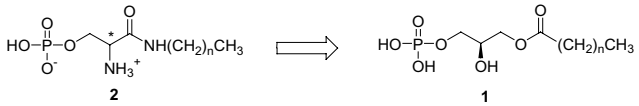
1a-b n=3-4



$\mathbf{R^1}$ = Et, *n*-Propyl, *n*-Hexyl, *n*-Heptyl;
$\mathbf{R^2}$ = H, Me

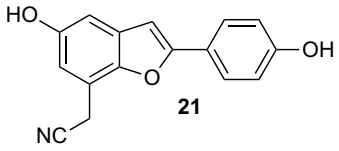


Flap endonuclease 1 (FEN1) is a key enzyme involved in base excision repair (BER), a primary pathway utilized by mammalian cells to repair DNA damage. In this report, we describe the identification and SAR of a series of 2,4-diketobutyric acid FEN1 inhibitors that may be useful as chemopotentiators.



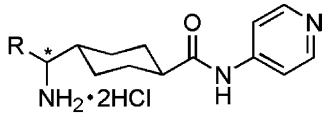
2 **1**

A series of serine amide phosphates (SAPs) and serine amide alcohols (SAAs) were prepared and evaluated for their in vitro cytotoxicity against five human prostate cancer cell lines. The SAR and biological activity of the synthesized compounds is reported.



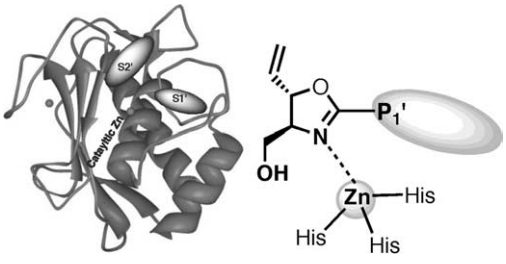
21

Substituted benzofuran **21** is a potent and selective ER ligand.

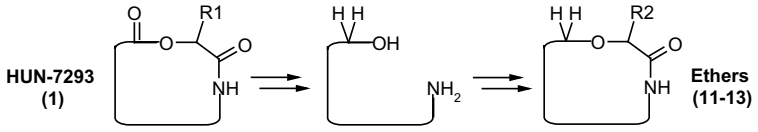


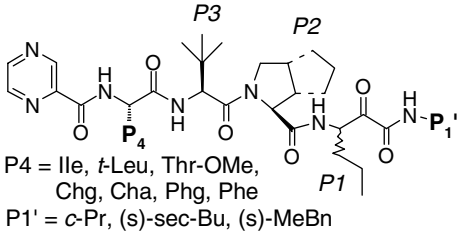
1-3

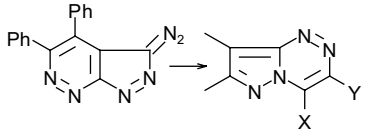
The influence of stereochemistry and alkyl side chain length on the bioactivity of the Rho kinase inhibitor Y-27632 [(+)-**1**, R = Me] was examined by the synthesis of (+)- and (−)-**1**, and two alkyl chain analogs (+)- and (−)-**2** (R = *n*-propyl) and (−)-**3** (R = *n*-octyl) as well as their evaluation in enzymatic and neurite outgrowth assays.



We examined the suppression effect of cleavage of the HIV-1 RNA gene on HIV-1 expression, using the catalytic RNA subunit RNase P and the 3′-half $tRNA^{Try}$ [external guide sequence (EGS)] in vivo. HIV-1 expression was inhibited by the $tRNA^{met}$-EGS-U5 and U6-EGS-U5 from the $tRNA^{met}$ and U6 promoters, respectively. There was no difference in the inhibitory effects on HIV-1 expression between the $tRNA^{met}$ and U6 promoters.







Pyridazinopyrazolotriazine

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Cover figure provided by ***Indraneel Ghosh****, Department of Chemistry, University of Arizona.* The cover depicts the **Dual Surface Selection** methodology developed by the author: the blue helix of htBl (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htBl (center) allows for functional selection against thrombin (right) [Rajagopal, S.; Meza-Romero, R.; Ghosh, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1389].

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