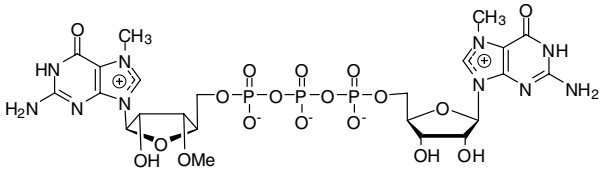
ELSEVIER

Bioorganic &
Medicinal
Chemistry
Letters

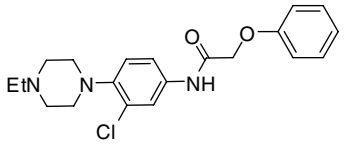
Bioorganic & Medicinal Chemistry Letters Vol. 18, No. 3, 2008

Contents

ARTICLES

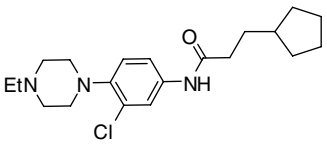


Design, synthesis, and biological evaluation of trimethyl-substituted cap analog $m_2^{7,3'O}$G[5′]ppp[5′]m7G was reported.



9g

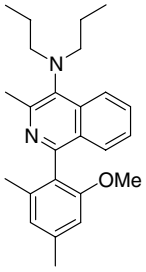
rM1 IC_{50} = 3.3 μM
rM2 IC_{50} >150 μM
rM3 IC_{50} >150 μM
rM4 IC_{50} >150 μM
rM5 IC_{50} >150 μM



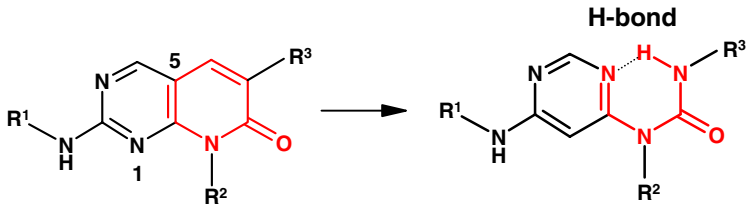
9i

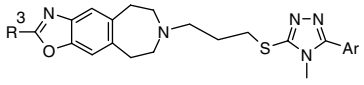
rM1 IC_{50} = 0.44 μM
rM2 IC_{50} = 3.5 μM
rM3 IC_{50} = 3.1 μM
rM4 IC_{50} >150 μM
rM5 IC_{50} = 1.1 μM

The synthesis and SAR of selective rM1 antagonists, such as **9g** (>45-fold selective versus rM2–rM5) and **9i** (>340-fold selective versus rM4), are described as part of a chemical probe development program for the Molecular Library Screening Network.

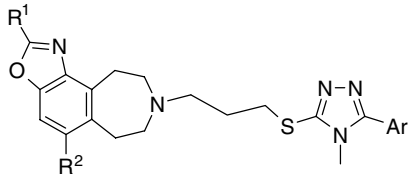


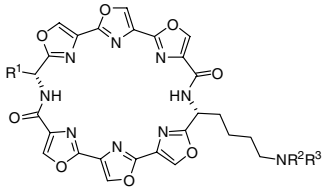
26j, CRF-1 K_i = 6 nM





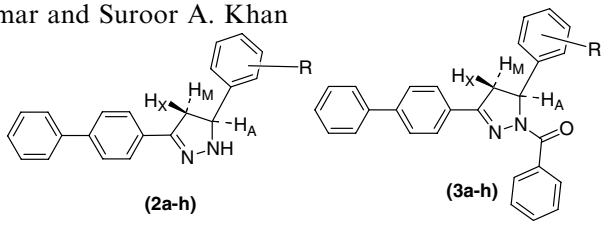
The synthesis of a new class of potent and selective D_3 antagonists is reported.



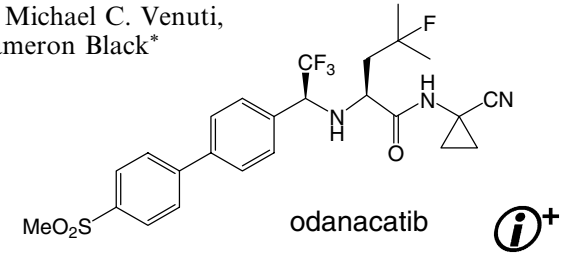


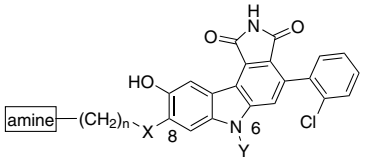
1a R^1 = i-Pr,R^2,R^3 = H
1b R^1 = i-Pr,R^2 = H, R^3 = Ac
1c R^1 = i-Pr,R^2,R^3 = Me
2 R^1 = $(CH_2)_4NH_2$,R^2 R^3 = H

The synthesis of 24-membered macrocyclic hexaoxazoles incorporating one or two lysine residues is reported. Each compound was evaluated for selective stabilization of G-quadruplex DNA.



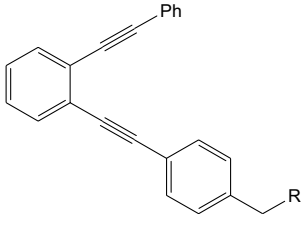
A series of 3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines (**2a**–**h**) and 1-benzoyl-3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines (**3a**–**h**) were synthesized by condensation of chalcones with hydrazine hydrate in solvent system ethanol and DMF. The newly synthesized compounds were screened for their anti-inflammatory and analgesic activity, and were compared with standard drug flurbiprofen.

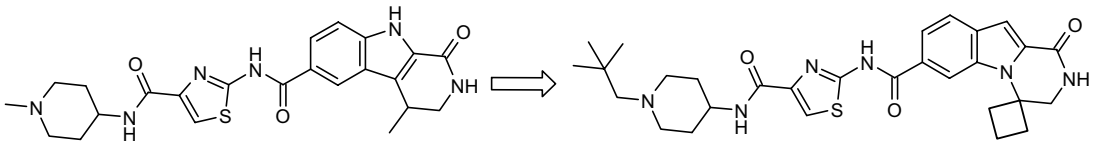




8-Substituted 4-(2-chlorophenyl)-9-hydroxypyrrolo[3,4-*c*]carbazole-1,3(2*H*,6*H*)-diones are potent, soluble inhibitors of Wee1 and Chk1 kinases. They inhibited the alkylator-induced phosphorylation of Cdc2 Tyr15 and abrogated the G2/M checkpoint in HT-29 cells, thus substantially enhancing the cytotoxicity of the DNA-damaging agent cisplatin.

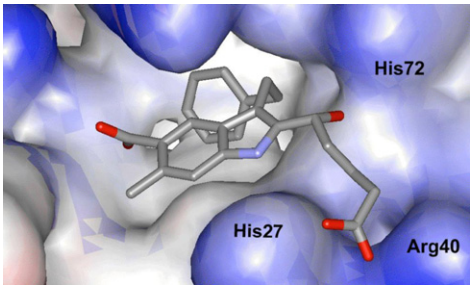
A readily accessible enediyne building block was transformed into a number of conjugates, and photoactivation of the core via the photo-Bergman cyclization effected. Application in the form of immunoconjugates and nanoparticles is demonstrated.

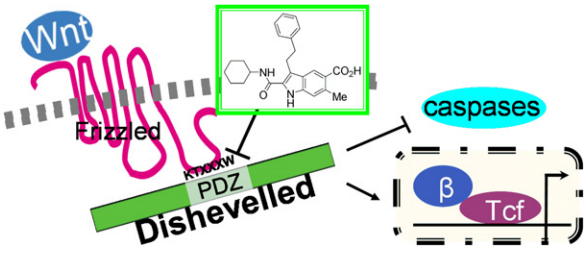


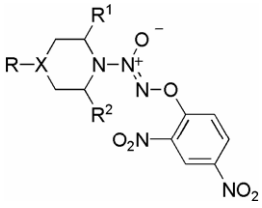


MAPKAP-k2 IC_{50}: 5 nM
THP-1 IC_{50}: >5,000 nM

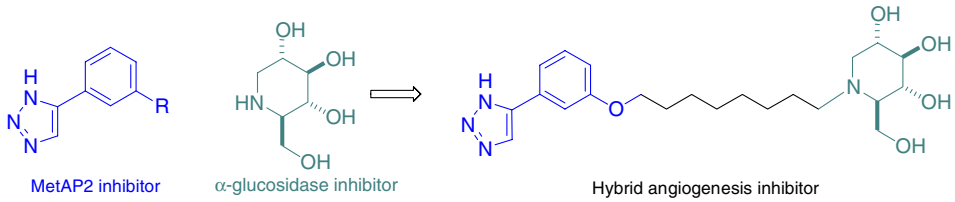
MAPKAP-k2 IC_{50}: 2 nM
THP-1 IC_{50}: 300 nM

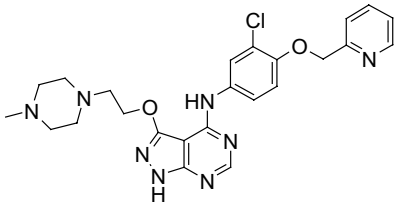






Synthesis and anti-leukemic activity of structural analogues of JS-K, an anti-cancer lead compound, are reported.

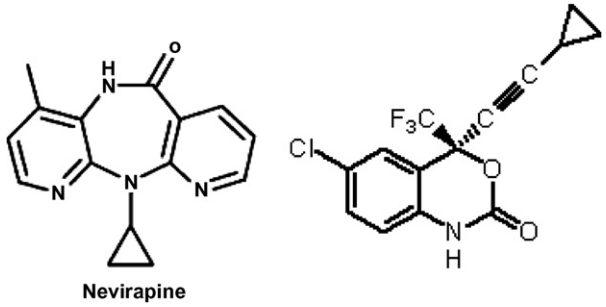


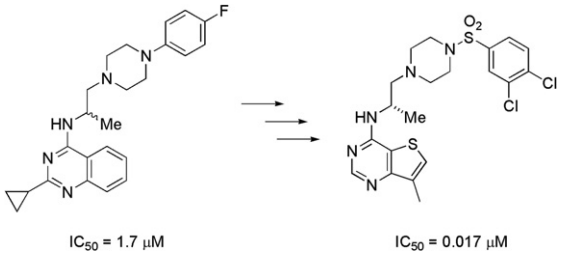


Novel 4-anilino-1*H*-pyrazolo[3,4-*d*]pyrimidines have been synthesized and evaluated in vitro for erbB2 and EGFR kinase inhibition. A representative compound displaying oral bioavailability in rat and dog illustrates the potential of this series to provide orally active erbB2 inhibitors.

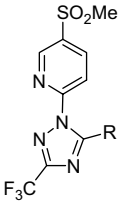
Design, synthesis and conformational analysis of few imidazole and oxazole as bioisosters of 4*S*-(−)-3-(4-chlorophenyl)-*N*-methyl-*N*′-[(4-chlorophenyl)-sulfonyl]-4-phenyl-4,5-dihydro-1H-pyrazole-1-caboxamidine (SLV-319) **2** is reported. Computer assisted conformational analysis gave a direct clue for the loss of CB1 antagonistic activity without a fine docking simulation for the homology model.

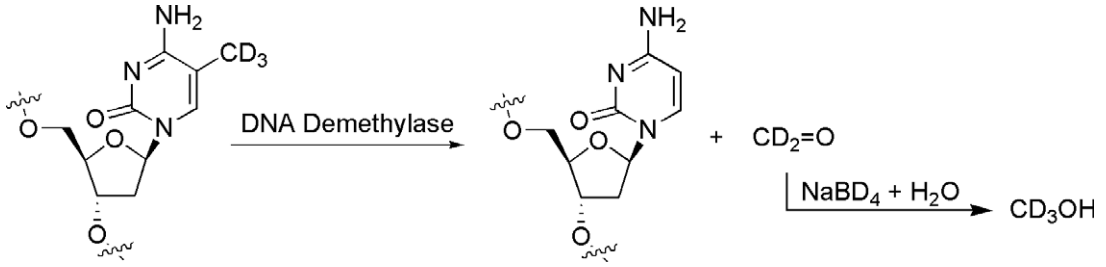
Computer modeling of nevirapine and efavirenz with HIV-1 reverse transcriptase variants.



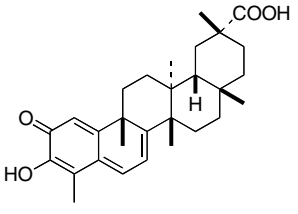


Structure–activity relationship (SAR) studies of novel 5-alkyl and 5-aryl/heteroaryl substituted 1,2,4-triazoles are described. The in vitro activity is compared to that of the pyrazole class of compounds with analogous side chains to delineate the contribution of the triazole ring nitrogen in binding to the active site. Both series are quite potent and selective in the canine whole blood (CWB) COX-2 assay, suggesting the increased binding contribution of the hydrophobic side chains.



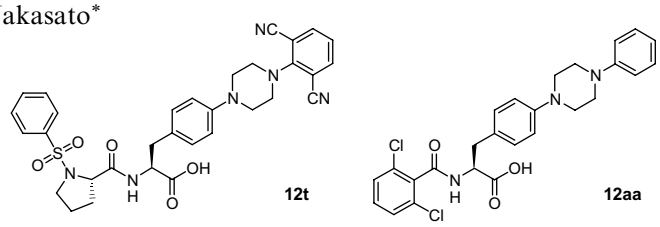


The $^2H_3$-methyl group in DNA 5-[Me–$^2H_3$ is removed by MBD2 as dideuteroformaldehyde.

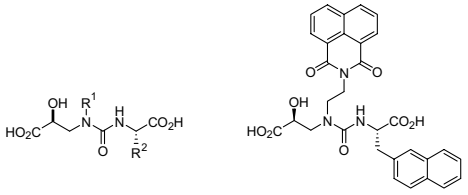


4

Four cytotoxic quinoid triterpenes, tingenone (**1**), 22β-hydroxytingenone (**2**), pristimerin (**3**), and celastrol (**4**), isolated from *Maytenus chuchuhuasca*, potently inhibit the polymerization of tubulin.

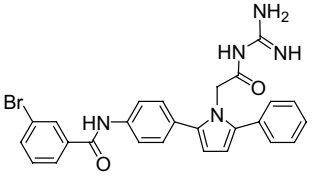


To improve poor pharmacokinetic characters of the preceding VLA-4 inhibitors, novel piperazinylphenylalanine derivatives were designed and optimized for oral bioavailability.

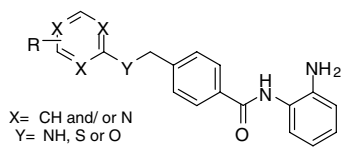


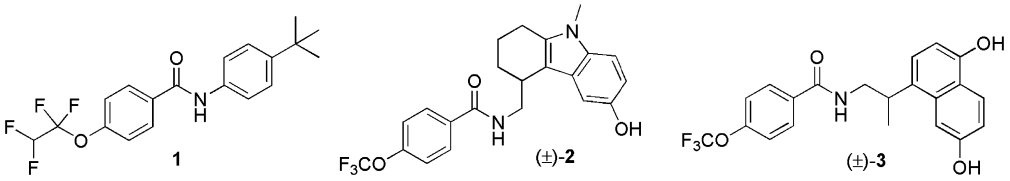
A series of urea analogues related to SA6817 and a GSK phosphonic acid with reported ACE inhibitory activity were prepared and tested for dual ACE and ECE activities. Although excellent ACE and NEP inhibition was achieved, only modest ECE inhibition was observed with one analogue.

Hit-to-lead optimization of a series of acyl guanidines by optimization of the interactions with the S_1–S_3 and S2′ enzyme binding pockets led to submicromolar BACE-1 inhibitors.

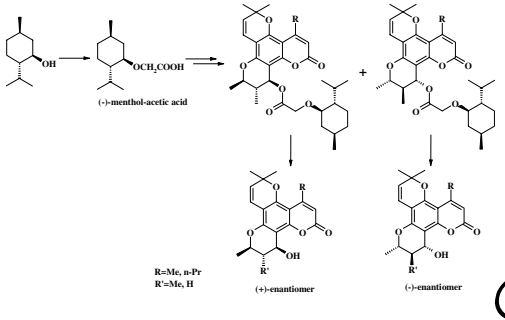


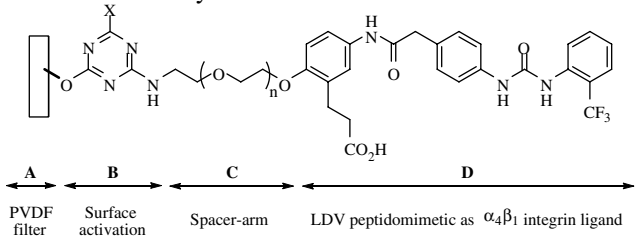
The synthesis and biological evaluation as histone deacetylase (HDACs) inhibitors of a variety of 4-(heteroarylaminomethyl)-*N*-(2-aminophenyl)-benzamides of the general structure shown is presented herein.





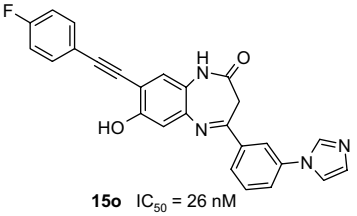
The chemical resolution of (±)-calanolide A and (±)-cordatolide A into their corresponding optically active enantiomers is described in this paper. Their inhibitory activities against HIV-1 are also tested in vitro.

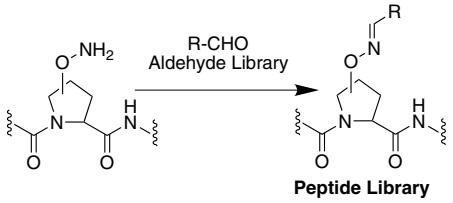


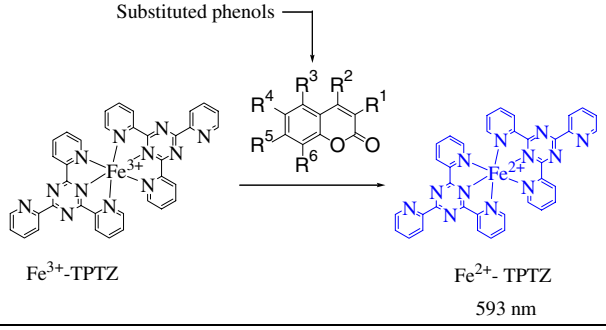


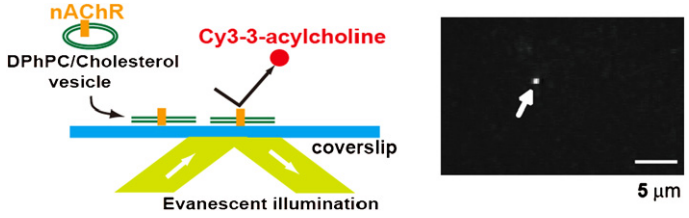
A PVDF hydrophilic membrane was surface modified with a non-peptide mimic of the fibronectin LDV sequence designed as VLA-4 integrin ligand. Leukocyte depletion with such a filter was significantly improved.

In a series of 1,3-dihydro-benzo[*b*][1,4]diazepin-2-ones the replacement of a nitrile by a five-membered heterocycle produced highly potent non-competitive group II mGluR antagonists. Further modification led to compounds with the ability to reverse LY354740-mediated inhibition of field excitatory postsynaptic potentials in the rat dentate gyrus.

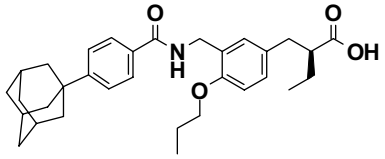




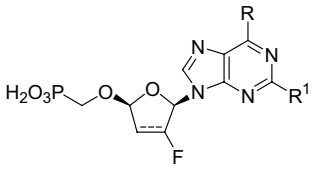




A novel fluorescent analogue of acetylcholine, Cy3-3-acylcholine, was synthesized. Discrete intensity changes of fluorescent spots due to a single ligand binding/unbinding to nicotinic acetylcholine receptors were visualized under microscopy.

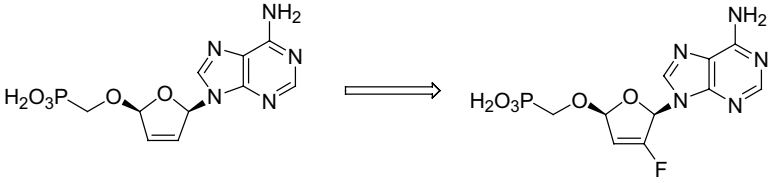


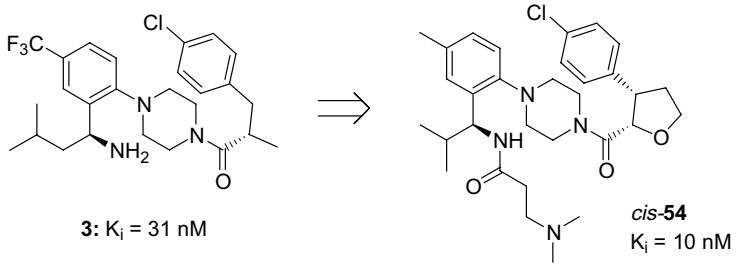
3-(4-Alkoxyphenyl)propanoic acid derivatives were prepared as candidate peroxisome proliferator-activated receptor (PPAR) α/δ/γ pan agonists, based on our previous SAR studies directed toward the development of subtype-selective PPAR agonists.

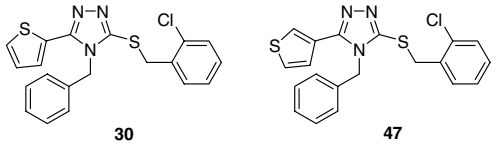


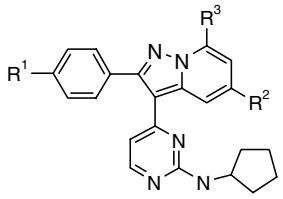
Modified purine analogs of nucleoside phosphonate GS-9148 (2′F-d4AP) were synthesized and their anti-HIV activity evaluated.

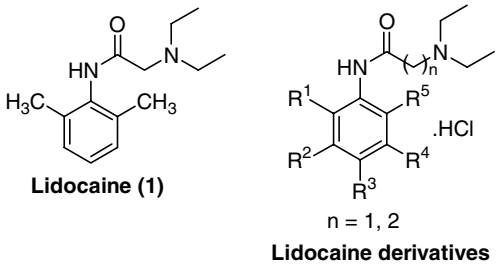
Compound **4** (2′-Fd4AP) was synthesized and maintained the favorable anti-HIV properties of **2** while demonstrating a marked reduction in mitochondrial toxicity to HepG2 cells.

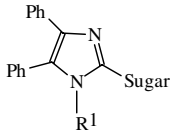


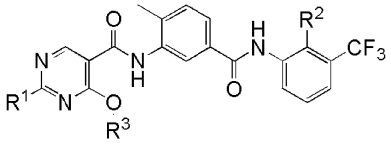


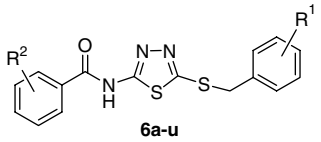






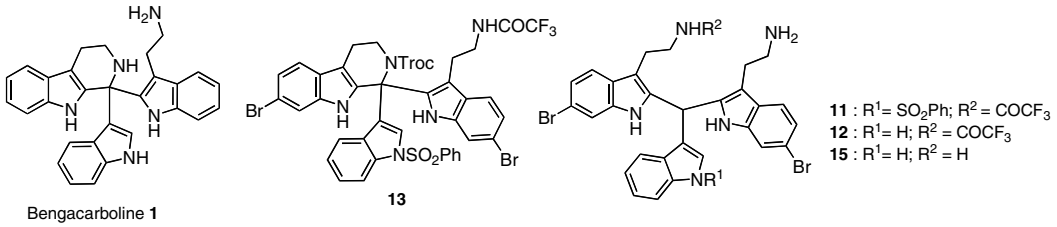




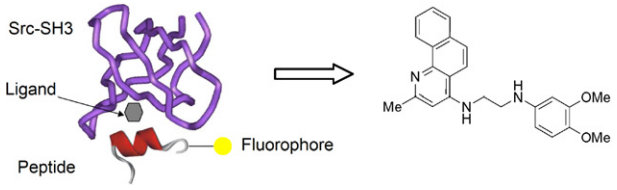


6a-u

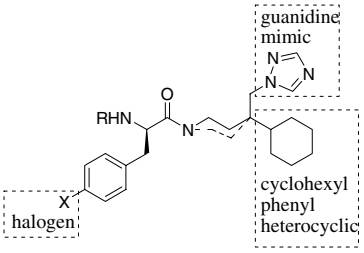
A series of substituted benzoylamino-2-[(4-benzyl)thio]-1,3,4-thiadiazoles (**6a**–**u**) has been discovered as potent Abl tyrosine kinase inhibitors showing an interesting inhibitory activity on murine myeloid 3B clone and drug resistant subclones.



Bengacarboline derivatives (**11**–**13** and **15**) were synthesized. Seco derivatives **11** and **12** display a cytotoxic activity by inducing an accumulation of cells in the S phase of DNA synthesis.



The design, synthesis, and biological activity of a series of peptidomimetic melanocortin receptor agonists is reported. Some binding affinity at the melanocortin receptors MC_3 and MC_4 was noted. In silico docking indicated that the relative positions of the hydrogen-bonding sites and hydrophobic regions of the compounds are reasonably well matched to the receptor-binding site. This may present a lead entry into a selective series of MC_4R agonists.



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Overlay of high resolution co-crystal structures of *R*-**22**-ADP (cyan) and **1**-ADP (green) bound in an allosteric binding site of the mitotic kinesin KSP. [Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, J. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5677.]

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE

ELSEVIER

ISSN 0960-894X