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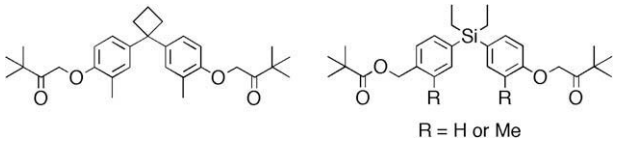
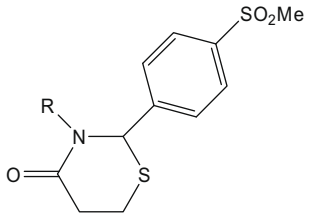
Bioorganic & Medicinal Chemistry Letters Vol. 19, No. 12, 2009

Contents

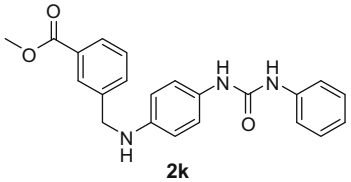
ARTICLES



1,1-Diphenylcyclobutane analog and diethyldiphenylsilane analogs have been identified as superior lead compounds with potent anti-bovine viral diarrhea activity.

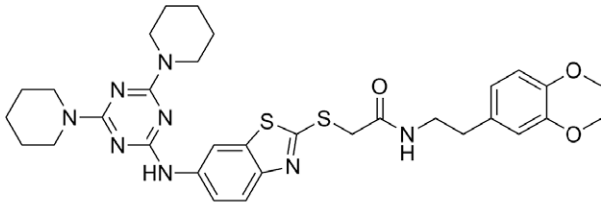


The design, synthesis and evaluation of a series of 3-alkyl-2-aryl-1,3-thiazinan-4-ones, possessing a methylsulfonyl pharmacophore, as potent and selective COX-2 inhibitors are described.

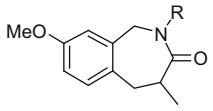


2k

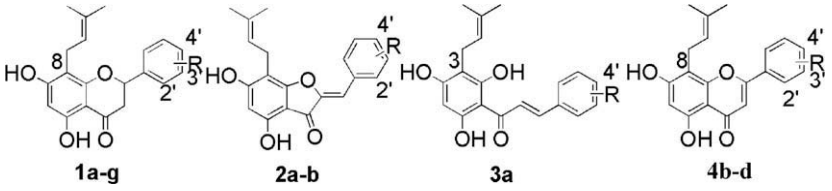
Compound **2k** was found to be a potent inhibitor against HIF-1α accumulation under hypoxic condition without affecting the mRNA expression level of HIF-1α.



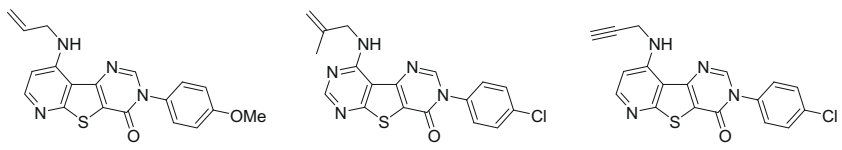
Fifteen new compounds with novel chemical skeleton have been successfully discovered as β-secretase inhibitors through molecular docking in combination with bioassay. Molecular docking reveals that the compounds, for example, compound **12** with IC_{50} value of 2.8 μM, spans the interaction through almost all the sub-sites of BACE-1.



N-alkyl-2-benzazepine derivatives are prepared and their structure and activity relationship are examined.



A series of prenylflavonoids possessed potent vasorelaxant activities and neuroprotective activities were developed. The prenyl group at A-ring of prenylflavonoids, as well as hydroxyl groups at B-ring was important for their activities.

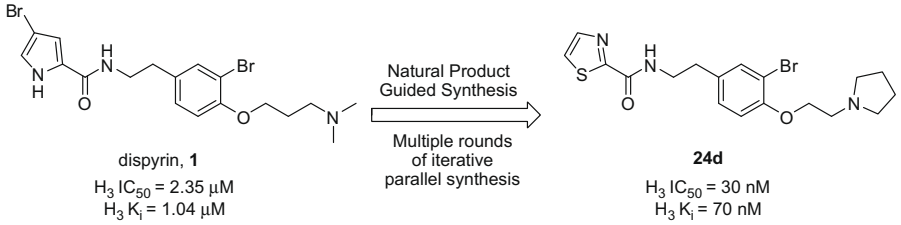


11a; h-mGluR1 IC_{50} = 2.0 nM
r-mGluR1 K_i = 1.1 nM
h-mGluR5 IC_{50} = >3000 nM

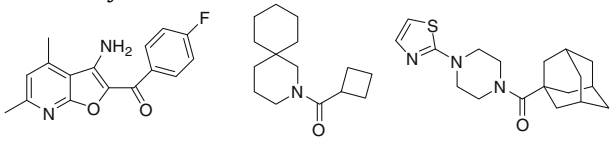
13a; h-mGluR1 IC_{50} = 7.7 nM
r-mGluR1 K_i = 2.2 nM
h-mGluR5 IC_{50} = >3000 nM

11q; h-mGluR1 IC_{50} = 0.9 nM
r-mGluR1 K_i = 0.6 nM
h-mGluR5 IC_{50} = >3000 nM

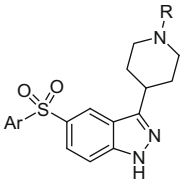
A series of highly potent and selective mGluR1 antagonists have been discovered and demonstrated efficacy in animal model for pain.



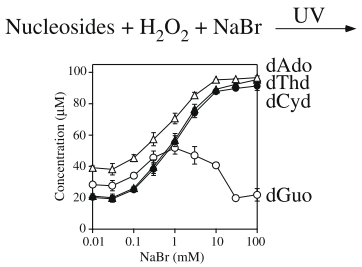
The natural product guided synthesis of analogs of the marine alkaloid dispyrin, and the resulting SAR of H_3 antagonism, is described. Three rounds of iterative parallel synthesis generated **24d**, a potent H_3 antagonist (IC_{50} = 30 nM, K_i = 70 nM) with a novel chemotype based on the bromotyramine motif of dispyrin.

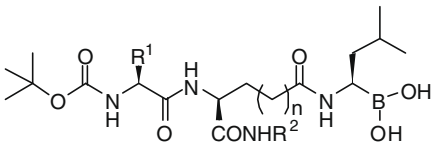


This Letter describes the discovery and SAR of three novel series of mGluR5 non-competitive antagonists/negative allosteric modulators (NAMs) not based on manipulation of an MPEP/MTEP chemotype. This work demonstrates fundamentally new mGluR5 NAM chemotypes with submicromolar potencies, and the first example of a mode of pharmacology 'switch' to provide PAMs with a non-MPEP scaffold.



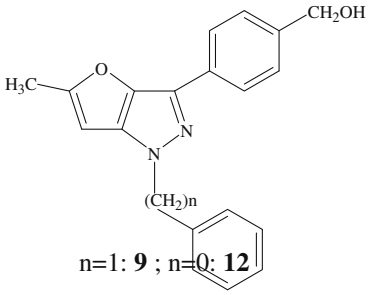
Synthesis and SAR of a novel series of 3-piperidinyl-5-sulfonylindazoles as potent 5-HT_6 ligands are reported.



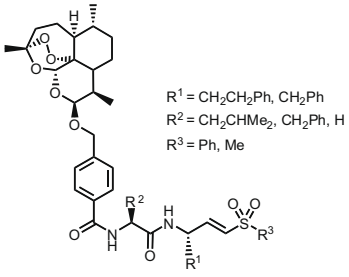


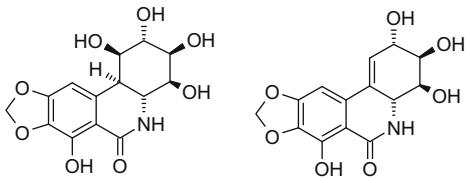
A series of boron peptides were synthesized as inhibitors of the chymotrypsin-like (β5) activity of the 20S proteasome based around the structure of Belactosin C.

Among the 12 furopyrazole derivative of benzylindazole analogs tested, carbinol derivatives (compounds **9** and **12**) exhibited strong neuroprotective against C2 ceramide-induced apoptosis in cultured cortical neurons.

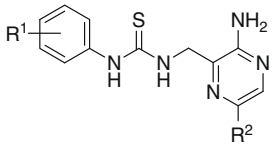


Artemisinin–vinyl sulfone hybrid molecules were active against the *Plasmodium falciparum* W2 strain in the low nanomolar range and those containing the Leu-hPhe core inhibited falcipain-2 in low micromolar range.

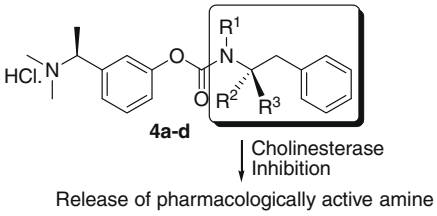




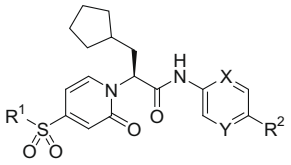
The cytochrome P450 3A4 inhibitory activity of a series of 26 structurally diverse Amaryllidaceae alkaloids and synthetic derivatives is reported. Chemoselective manipulation of the hydroxyl groups in the lycorane series and structure–activity studies provides revealing insight into structural features required for this inhibition.

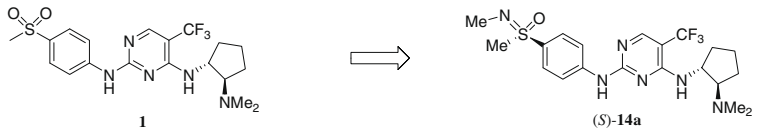


Novel 1-(2-aminopyrazin-3-yl)methyl-2-thioureas are described as inhibitors of MK-2. These compounds demonstrate potent in vitro activity against the enzyme with IC_{50} values as low as 15 nM, and suppress expression of TNFα in THP-1 cells and in vivo in an acute inflammation model in mice.

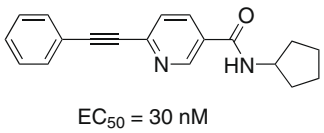


Upon inhibition of cholinesterase by **4a–d**, pharmacologically active amines are released.

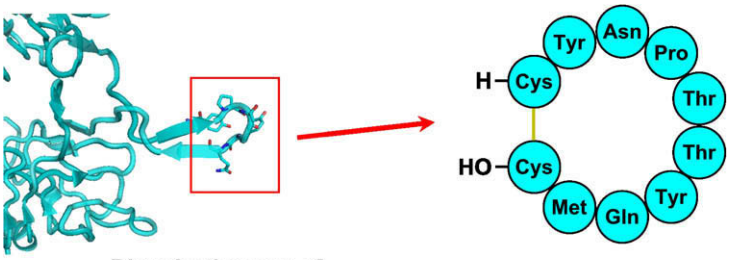




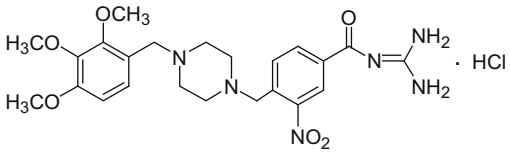
Synthesis and in vitro activity for a series sulfoximine-substituted trifluoromethylpyrimine analogs as inhibitors of PYK2 are described. Compared to the corresponding sulfone analog, the sulfoximines surprisingly showed significantly lower dofetilide binding activity, which is an early indicator of cardiovascular safety.



EC_{50} = 30 nM

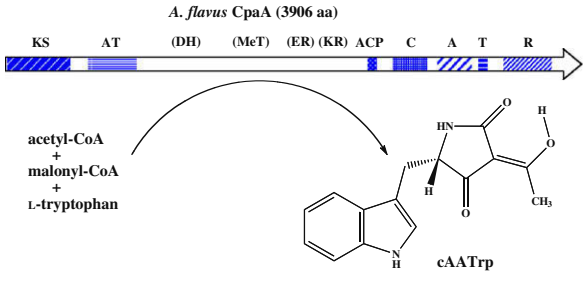


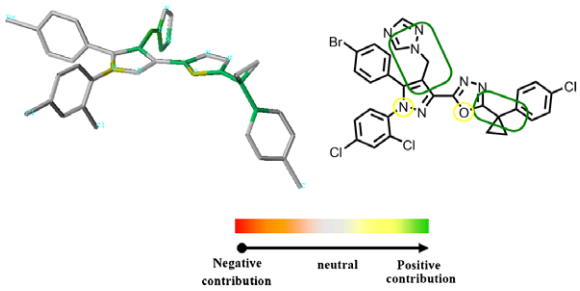
Dimerization arm of the EGF receptor

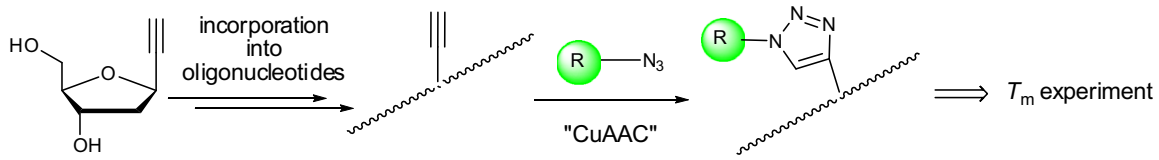


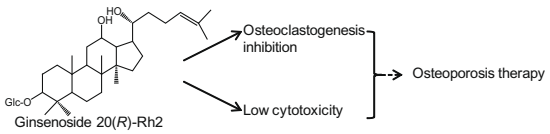
5f (IC_{50}=3.60 nM to NHE1)

A novel series of substituted benzoylguanidine derivatives were designed and synthesized as potent NHE1 inhibitors and cardioprotective agents. Among these compounds, **5f** was found to be the most potent NHE1 inhibitor, with a IC_{50} of 3.60 nM, being 18 times more potent than cariporide. Compound **5f** showed superior cardioprotective efficacy in vivo and in vitro.

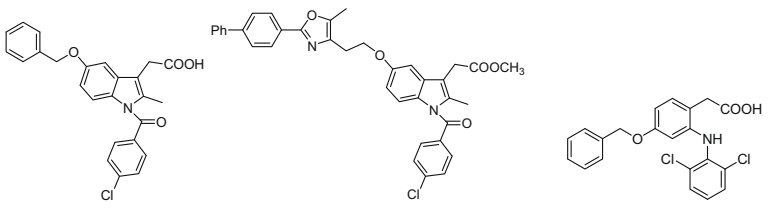






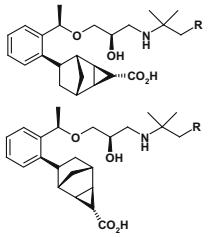


Ginsenoside 20(*R*)-Rh2 and ginsenoside 20(*S*)-Rh2 showed a significant inhibitory effect on osteoclast differentiation. Only ginsenoside 20(*R*)-Rh2 showed no cytotoxicity to osteoclast proliferation. 20(*R*)-Hydroxylation of the aliphatic side chain of Rh2 could be the main target in producing anti-osteoclast agent.



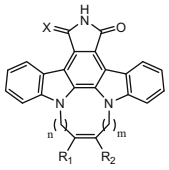
5a **7h** **17**

A series of aromatic acetic acid compounds were designed and synthesized on the basis of Non-steroidal anti-inflammatory drugs indomethacin and diclofenac. Compounds **5a, 7a, 5h, 7h** and **17** could strongly promote insulin-regulated differentiation of 3T3-L1 cells in vitro. They acted as full or partial PPARγ agonist, or improved insulin resistance through non-PPARγ pathway.

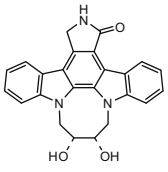


The discovery of a structurally novel, orally bioavailable series of calcium sensing receptor negative allosteric modulators is described.

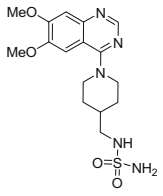
The synthesis and biological evaluation of JAK3 based staurosporine compounds is described. The compounds are constructed using a ring closing metathesis strategy to assemble the sugar mimetic portion (**I**). These analogs show potent JAK3 inhibitory activity against isolated enzyme and in IL-2 stimulated T-cells. One analog (**32**) showed unique biological effects during in vitro and in vivo tests including inhibition of STAT5 phosphorylation, blockade of mast cell degranulation, and reduction of JAK3 effects in mouse models of allergic disease.



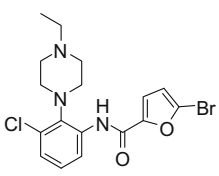
I



32
JAK3
IC_{50} = 6 nM



We describe a series of novel quinazolin-4-piperidin-4-methyl sulfamide PC-1 inhibitors and the utility of a hERG homology model to optimize binding selectivity for PC-1 over the hERG potassium channel.



1

A novel series of c-jun N-terminal kinase (JNK) inhibitors were designed and developed from high-throughput-screening lead **1**.

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.]

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