Bioorganic & Medicinal Chemistry Letters 19 (2009) 1837–1850

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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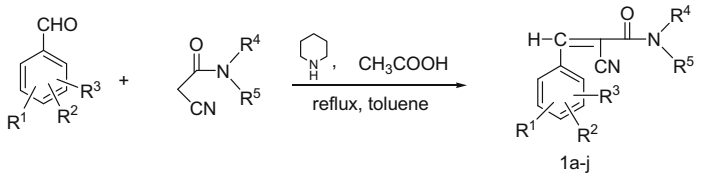
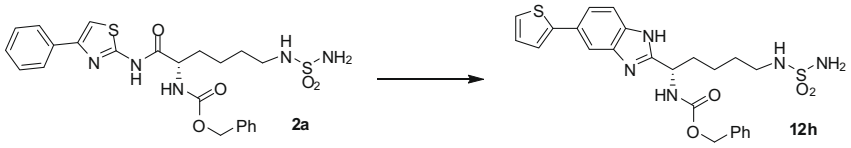
Bioorganic & Medicinal Chemistry Letters Vol. 19, No. 7, 2009

Contents

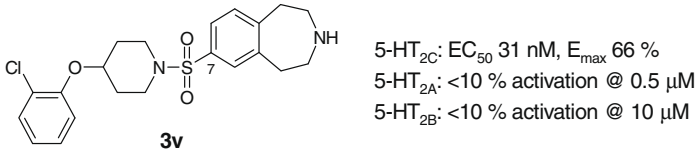
ARTICLES



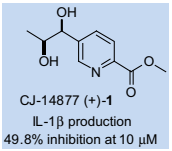
A series of caffeic acid amide derivatives *E*-2-cyano-(3-substituted phenyl) acrylamides were synthesized via Knoevenogal condensation. Some preliminary structure–activity relationships are described.



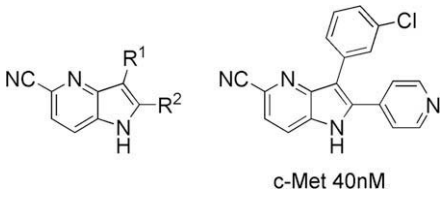
SAR investigation around compound **2a** lead to **12h** with equal HDAC1 and HDAC6 inhibitory activity and enhanced metabolic stability and PK profile.

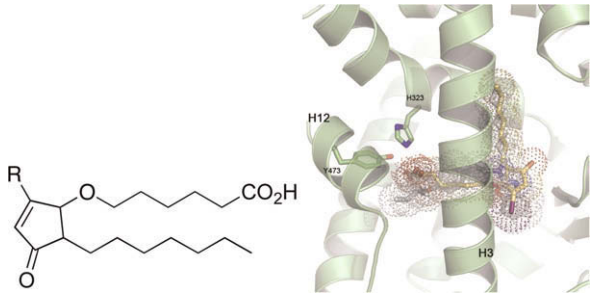


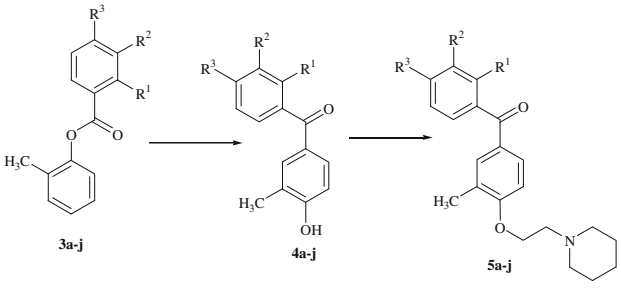
New 7-sulfonamido-3-benzazepines 3 are disclosed as 5-HT$_{2C}$ receptor agonists. Appropriate substitution of the amino group (R^1R^2N-) identified compounds that were potent 5-HT$_{2C}$ agonists with minimal activation of the 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors. Furthermore, representative examples had excellent in vitro ADME properties and good selectivity over ion channel activity.



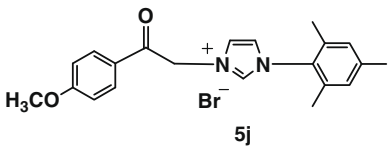
A potent antiinflammatory methyl picolinate alkaloid CJ-14877 [(+)-**1**] and its enantiomer (−)-**1** were synthesized via two steps. (+)-**1** strongly inhibited LPS-stimulated IL-1β production but (−)-1 did not.



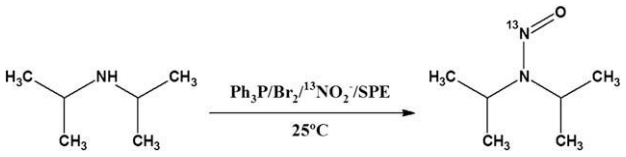




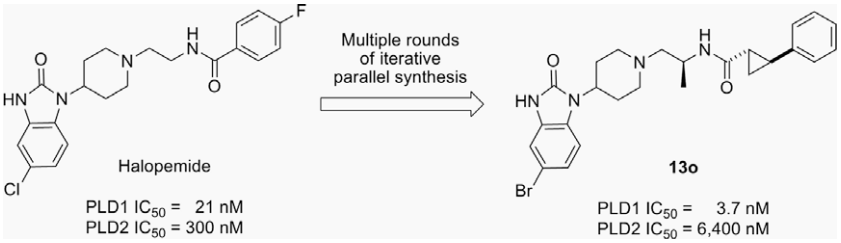
A sequence of substituted benzophenone-*N*-ethyl piperidine ether analogues has been synthesized and evaluated as orally active anti-inflammatory agents with reduced side effects.



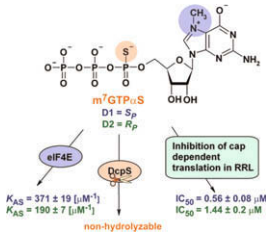
A series of novel phenacylimidazolium derivatives has been prepared and evaluated in vitro against a panel of human tumor cell lines. Phenacylimidazolium bromides bearing a highly sterically hindered aryl group at position-1 and an electron-rich phenacyl or naphthylacyl substituent at position-3 of imidazole ring proved to be more active than imidazolium bromides with other substituted groups. In particular, compound **5j** was found to be the most potent compounds with IC_{50} values lower than 5.0 μM against 8 strains human tumor cell lines and more active than cisplatin.



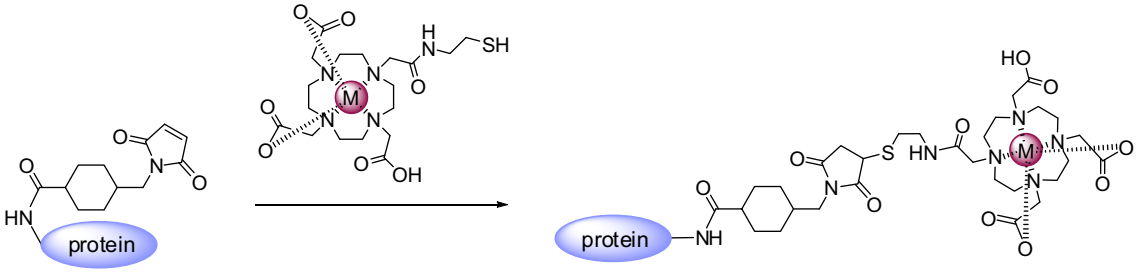
The reaction of resin trapped $[^{13}N]NO_2^-$ with secondary amines in the presence of Ph_3P and Br_2 leads to the formation of the corresponding *N*-[^{13}N]nitrosamines with excellent radiochemical conversion.



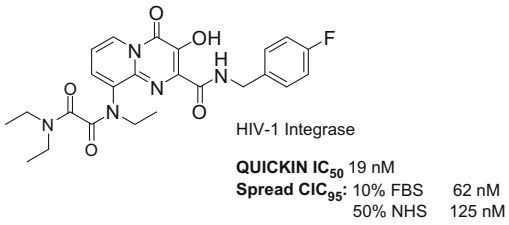
The synthesis and SAR of isoform-selective PLD inhibitors is described. By virtue of the installation of alternative halogenated piperidinyl benzimidazolone privileged structures, in combination with a key (*S*)-methyl group, novel PLD inhibitors with low nM potency and unprecedented levels of isoform selectivity for PLD1 (~1700-fold) over PLD2 were developed.



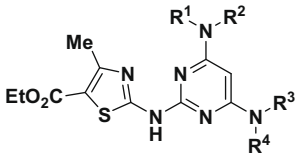
The synthesis and properties of new potent inhibitors of translation, two diastereomers of 7-methylguanosine 5′-(1-thiotriphosphate), are reported. These analogs of mRNA 5′cap are recognized by translational factor eIF4E with high affinity and are resistant to hydrolysis by Decapping Scavenger pyrophosphatase.



Prelabeled thiol-DOTA enables the efficient and simple introduction of radiometals into proteins under mild conditions.

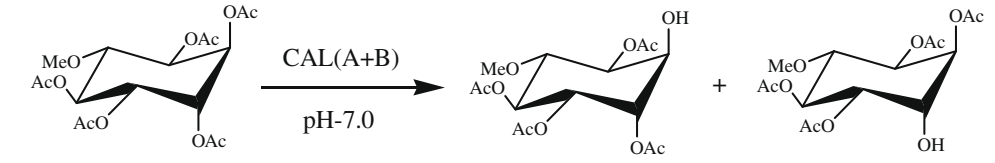


The synthesis and SAR of a new class of HIV-1 integrase inhibitors is reported.



2

A series of pyrimidine based inhibitors of PDE7 are discussed. The synthesis, structure–activity relationships (SAR) and selectivity against several other PDE family members as well as activity in T cells are presented. These compounds were found to have effects on T cell proliferation, however it is not clear whether the mechanism is related to PDE7 inhibition.

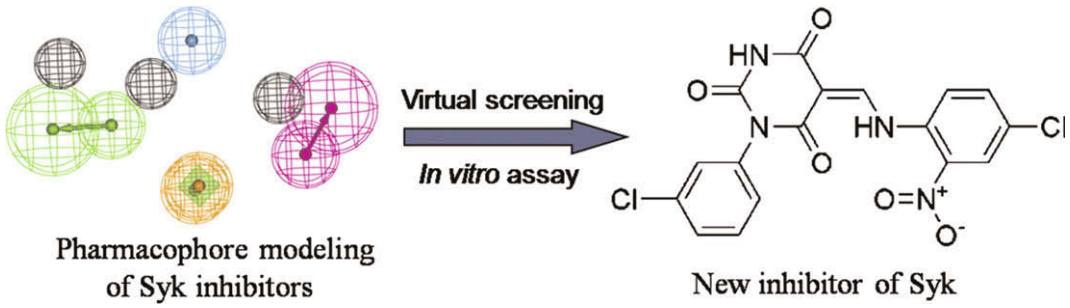


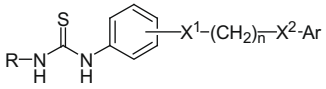
D-1,2,4,5,6-penta-O-acetyl-4-O-methyl-chiro-inositol

D-1, 2, 3, 5-tetra-O-acetyl-4-O-methyl chiro-inositol

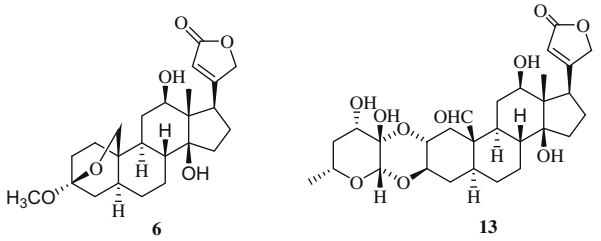
D-1, 2,4, 5-tetra-O-acetyl-3-O-methyl chiro-inositol

Semi-synthetic analogs of pinitol were prepared using chemo-enzymatic approaches and their TNF-α expression in human neutrophils using flowcytometry is reported.



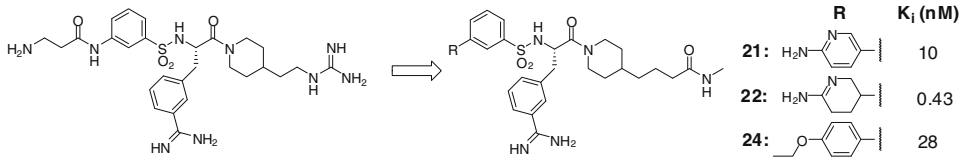


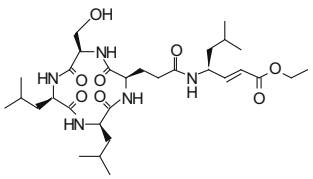
The synthesis and SAR of potent hepatitis C virus inhibitors based on an aryl thiourea scaffold are described.



6 **13**

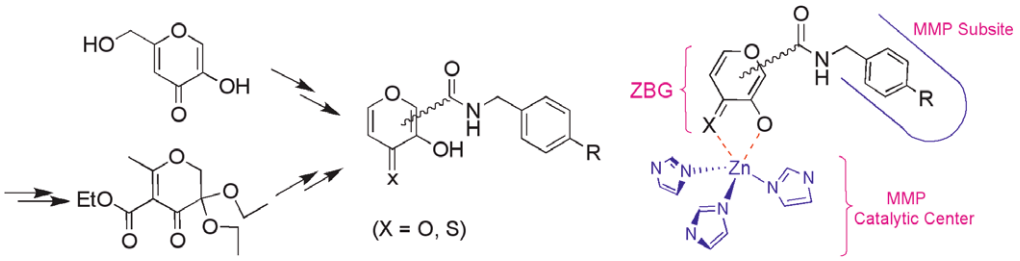
A new cardenolide **6** and a new doubly linked cardenolide glycoside **13** together with eleven known compounds were isolated from the aerial part of *Asclepias curassavica* and their cytotoxic activity was evaluated. The new compound **13** showed significant cytotoxic activity against HepG2 and Raji cell lines with IC_{50} values of 0.69 and 1.46 μM, respectively.

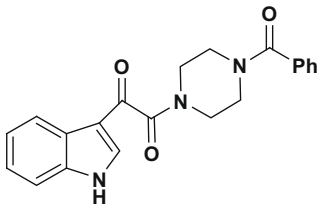




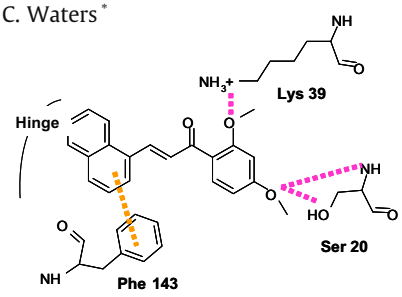
c[Ser-Leu-Leu-Glu(Leu-VE)]

New vinyl ester cyclopeptide, derivatives were synthesized and tested as proteasome inhibitors. Some analogues showed selective inhibition of the β1 proteasome catalytic subunit.

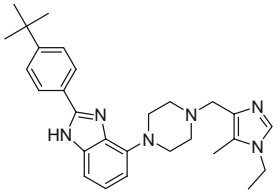




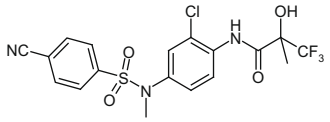
The effects of introducing simple halogen, alkyl, and alkoxy substituents to the 4, 5, 6 and 7 positions of 1-(4-benzoylpiperazin-1-yl)-2-(1*H*-indol-3-yl)ethane-1,2-dione, an inhibitor of the interaction between HIV gp120 and host cell CD4 receptors, on activity in an HIV entry assay was examined. Small substituents at C-4 generally resulted in increased potency whilst substitution at C-7 was readily tolerated and uniformly produced more potent HIV entry inhibitors. Substituents deployed at C-6 and, particularly, C-5 generally produced a modest to marked weakening of potency compared to the prototype. Small alkyl substituents at N-1 exerted minimal effect on activity whilst increasing the size of the alkyl moiety led to progressively reduced inhibitory properties. These studies establish a basic understanding of the indole element of the HIV attachment inhibitor pharmacophore.



Various 1,3-diaryl-2-propenones which inhibit Pfmrk in the low micromolar range are identified. Modeling reveals two amino acid residues within the active site responsible for the selectivity over other CDKs.

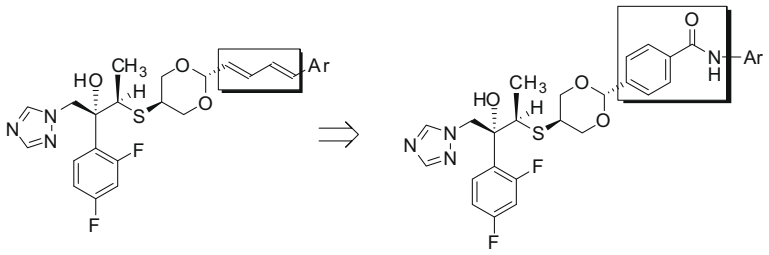


The potent GnRH antagonist template, 2-(4-*tert*-butylphenyl)-4-(1-piperazinyl)benzimidazole was appended to several small heterocycles. The *N*-ethylimidazole **32** was screened for in vivo pharmacokinetic and GnRH activity in rats.



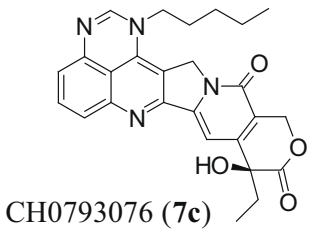
20

The synthesis and SAR of new liver X receptor agonists is reported. The effort to optimize these hits into LXRβ selectivity is described. Compound **20** displayed desirable pharmacokinetic profile and was evaluated in vivo.

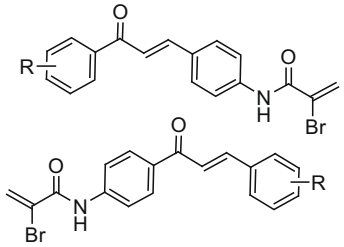


Synthesis and in vitro antifungal activities of a novel series of triazole antifungal agents wherein the diene part of CS-758 was replaced by an aryl-amide group are described.

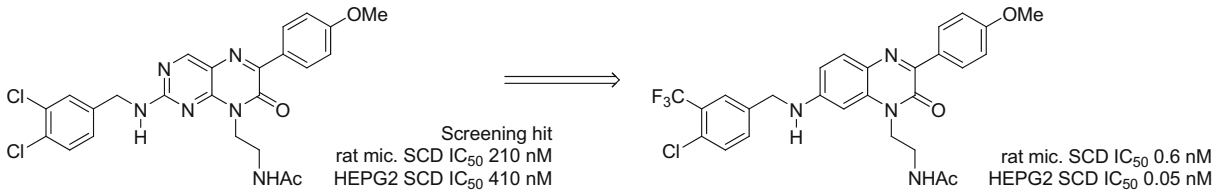
Design and synthesis of new topoisomerase I inhibitor, **7c** and its analogs, as well as their antitumor activities are described. Compound **7c** was effective against BCRP positive tumors.

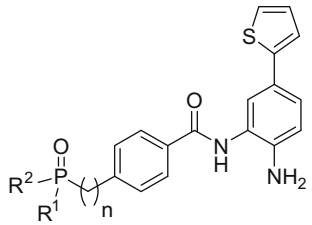


CH0793076 (**7c**)

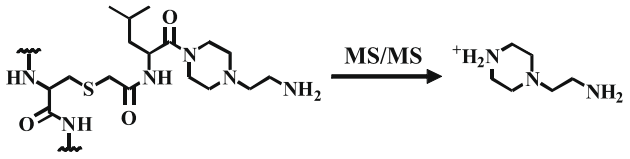


R=H, OMe, Me, $N(CH_3)_2$, halogen

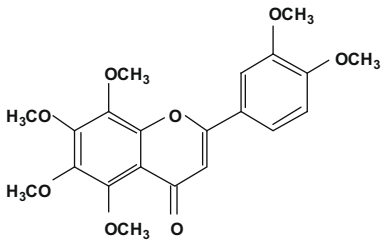




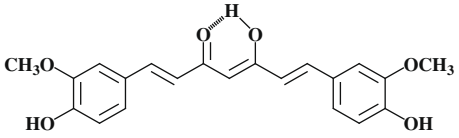
Preparation and structure–activity relationships of phosphorus-containing histone deacetylase inhibitors are detailed. A strong trend between decreasing phosphorus functional group size and superior mouse pharmacokinetic properties was identified. In addition, optimized candidates showed tumor growth inhibition in xenograft studies.

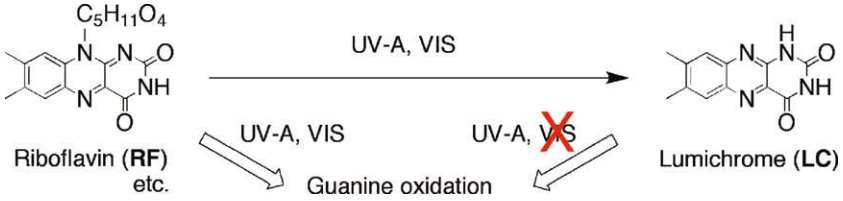


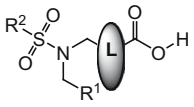
Novel stable isotope labeled reagents are synthesized, providing a robust tool for MS-based quantitative proteomics.



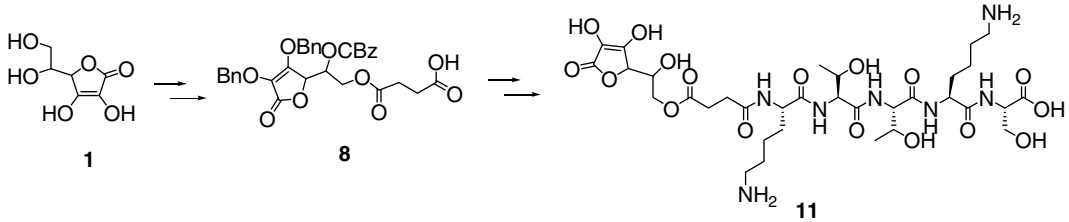
The identification of nobiletin as an enhancer of adiponectin secretion is reported.







We describe the synthesis, SAR, and in vivo efficacy of a series of EP_2-selective sulfonamide derivatives.



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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ISSN 0960-894X