ELSEVIER

Bioorganic & Medicinal Chemistry Letters

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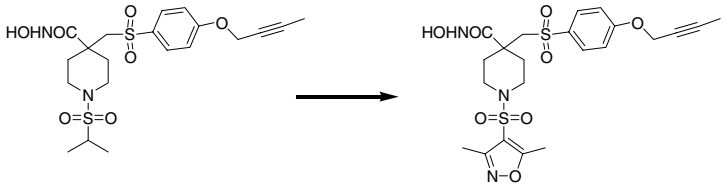
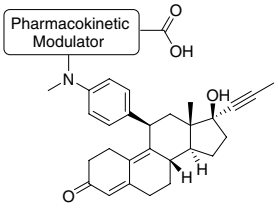
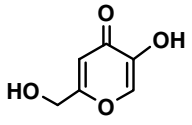
Contents



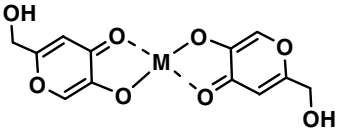
Libraries of mifepristone analogs, MP-Acids, were shown to be potent GR antagonists in binding and cell-based functional screens. A high-throughput pharmacokinetic selection strategy was devised to identify MP-Acids with liver-targeting profiles. These conjugates were tested in in vivo models to evaluate liver versus systemic GR antagonism.



MP-Acid Conjugates



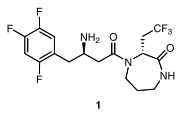
Kojic acid



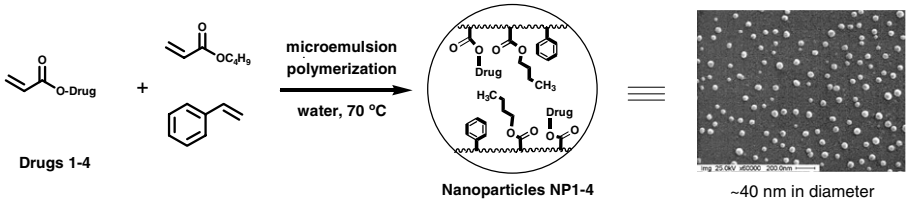
M= Mn (II) or Zn

The naturally occurring fungal metabolite kojic acid and its manganese and zinc complexes have been evaluated as potential radioprotectors in mice. Their toxicity and radioprotective activity (survival rate) have been determined and compared with that of WR-2721 (amifostine). The results of in vivo radioprotection showed that these compounds exhibited significant radioprotective effects against lethal dose of γ-irradiation in mice.

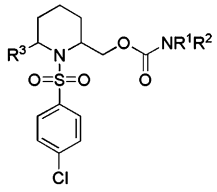

sitagliptin


1

Replacement of the triazolopiperazine ring of sitagliptin (DPP-4 IC_{50} = 18 nM) with 3-(2,2,2-trifluoroethyl)-1,4-diazepan-2-one gave dipeptidyl peptidase IV (DPP-4) inhibitor **1** which is potent (DPP-4 IC_{50} = 2.6 nM), selective, and efficacious in an oral glucose tolerance test in mice. It was selected for extensive preclinical development as a potential back-up candidate to sitagliptin.

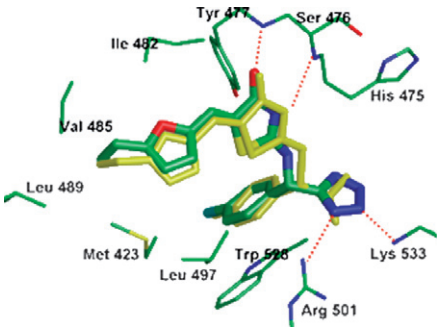


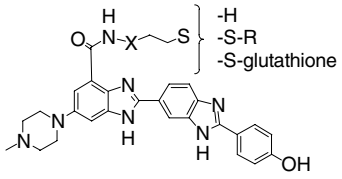
Antibacterially active polyacrylate nanoparticles in the range of 30–50 nm have been synthesized in water by emulsion polymerization of an *N*-thiolated β-lactam acrylate pre-dissolved in a mixture of butyl acrylate and styrene (7:3). The resulting emulsions display potent in vitro activity against MRSA.



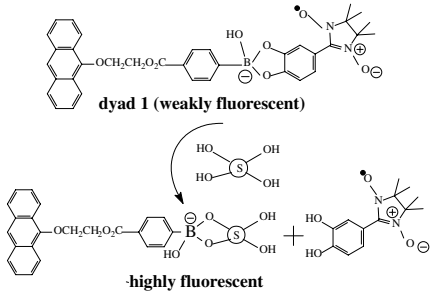
A novel piperidine series of γ-secretase inhibitors, potentially useful for the treatment of Alzheimer's disease, is disclosed.

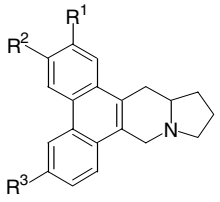
The follow-up designs and more detailed SAR of thiazolone derivatives as novel inhibitors of HCV NS5B polymerase were described. The X-ray complex structure for the new inhibitor was obtained at a resolution of 2.2 Å, and confirmed the design.





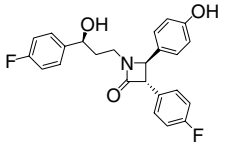
The equilibrium constructed of the Hoechst-thiol and the disulfide derivatives in the presence of glutathione was shifted by the addition of the template DNA to produce higher-affinity compounds.





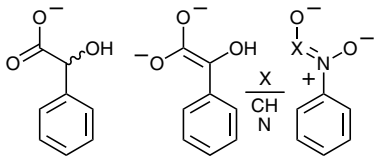
1 (R^1 = OMe, R^2 = OMe, R^3 = OMe)
10 (R^1 = O^{i}Pr, R^2 = OMe, R^3 = OMe)
11 (R^1 = OMe, R^2 = O^{i}Pr, R^3 = OMe)
12 (R^1 = OMe, R^2 = OMe, R^3 = O^{i}Pr)
13 (R^1 = OH, R^2 = OMe, R^3 = OMe)
14 (R^1 = OMe, R^2 = OH, R^3 = OMe)
15 (R^1 = OMe, R^2 = OMe, R^3 = OH)
16 (R^1 = OMe, R^2 = OMe, R^3 = H)
17 (R^1 + R^2 = OCH_2O, R^3 = OMe)

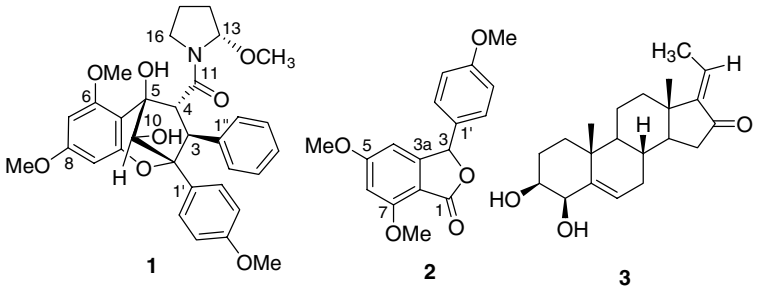
To define the features of the molecule that are essential for cytotoxicity, we have synthesized and evaluated a series of phenanthroindolizidine alkaloid, antofine (**1**), analogues (**10**–**17**).

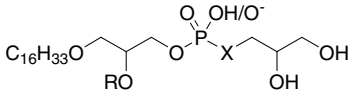


Four individual isomers of backbone re-organized ezetimibe analogs were designed, synthesized, and evaluated for cholesterol absorption inhibition in rats.

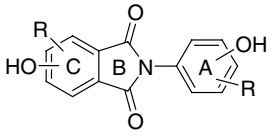
Mandelate racemase (MR) catalyzes the interconversion of the enantiomers of mandelate and has been studied as a paradigm for enzyme-catalyzed proton abstraction from carbon acids. Intermediate analogues *N*-hydroxyformanilide (HFA; X = CH; $K_i = 2.79 \pm 0.19$ μM) and cupferron (X = N; $K_i = 2.67 \pm 0.09$ μM) are identified as potent competitive inhibitors of MR. The pH–pK_i profile indicates that MR can bind either the protonated or deprotonated forms of HFA, with a 10-fold greater affinity for the latter form.



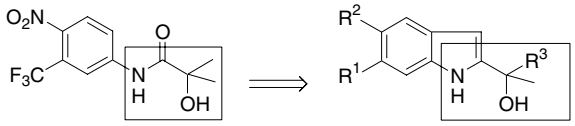


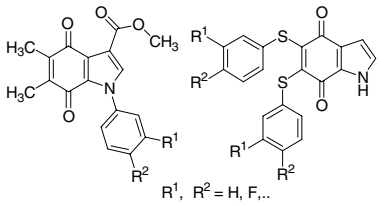


R = hexadecyl, X = O
R = hexadec-9-enyl, X = O
R = hexadecyl, X = CH_2

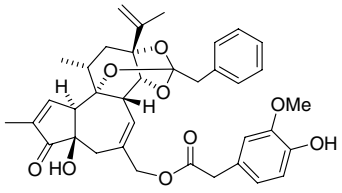


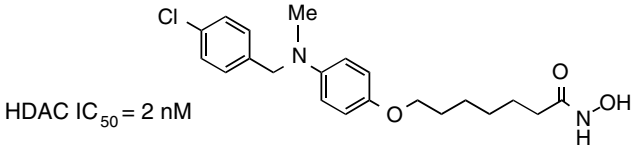
The design, synthesis and biological evaluation of the 2-phenyl-isoindole-1,3-diones will be discussed. Detailed modeling studies with X-ray support were used to understand the ligand binding orientation and observed selectivity.



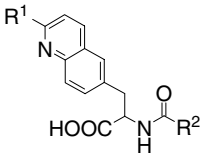


1*H*-Indole-4,7-diones were synthesized and tested for in vitro antifungal activity against fungi. Many of tested them exhibited potent antifungal activity.

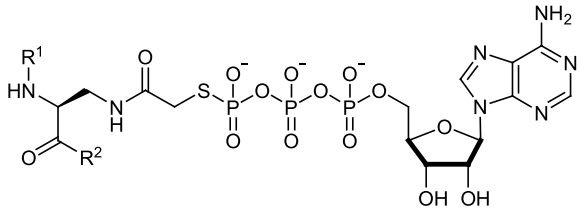




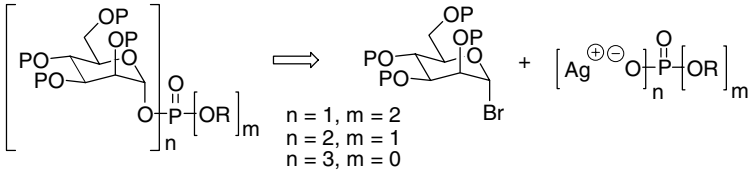
Aryl ether inhibitors of histone deacetylase are described.

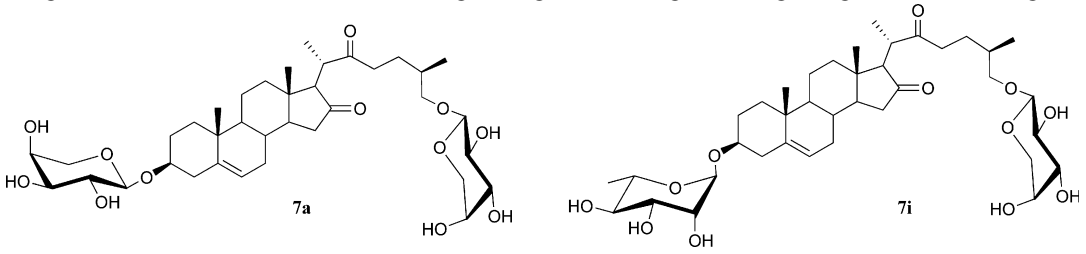


The synthesis and SAR around 2,6-quinolinyl derivatives as potent orally bioavailable VLA-4 antagonists is reported.

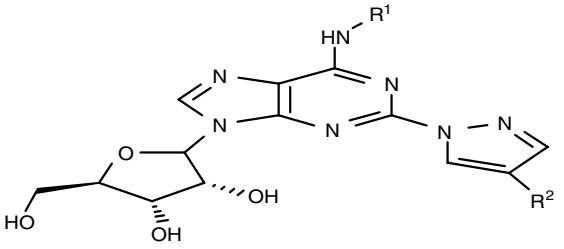


Conjugation of AIP peptide inhibitors to ATPγS by considering a phosphoryl transfer mechanism led to improved potency in CaMKII (calmodulin-dependent protein kinase II) inhibition, which was ATP-competitive and substrate-uncompetitive.

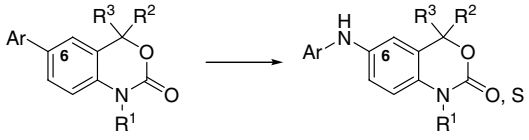




A library of 16 novel bisdesmosidic kryptogenyl saponins was built for investigation of antitumor activity, wherein two compounds showed inhibition against HeLa cells (IC_{50} = 4.25 μM for **7a** and 8.36 μM for **7i**).

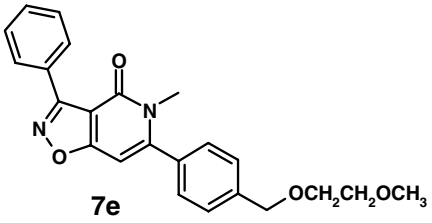


The synthesis, binding affinity and selectivity of 2,6-disubstituted adenosine derivatives for the A_1-AdoR is reported.



6-Aryl benzoxazinones **1-25**

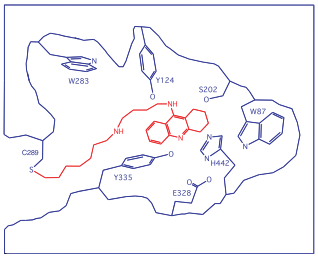
Insertion of a NH linker at the 6-position of 6-aryl benzoxazinones, the progesterone receptor (PR) modulators, led to exclusively PR antagonists (**1**–**25**) in a progesterone induced alkaline phosphatase assay in the T47D cells.

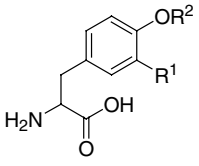


7e

Hit identification and SAR studies leading to the isoxazolo-pyridinone **7e**, a highly potent, brain penetrable activator of the Nurr1 signaling pathway, are described.

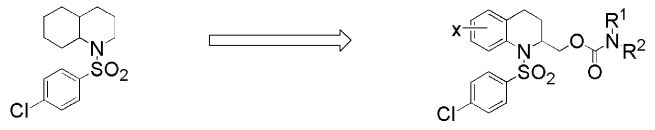
Current anticholinesterase pesticides are toxic to mammals as they target a catalytic serine residue of acetylcholinesterases (AChEs) in insects and in mammals. This article reports a cysteine residue present at the active sites of greenbug and aphid AChEs but absent at those of mammalian AChEs. This discovery enables the design of novel and safe pesticides that target the cysteine residue rather than the ubiquitous serine residue.



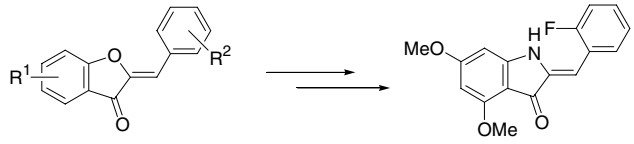


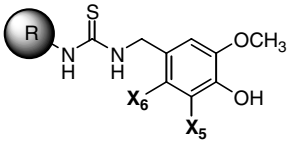
1, $R^1 = CH_2CH_2F$, $R^2 = H$
2, $R^1 = CH_2CH_2CH_2F$, $R^2 = H$
3, $R^1 = CH_2CH_2F$, $R^2 = CH_3$
4, $R^1 = CH_2CH_2CH_2F$, $R^2 = CH_3$

The syntheses of F-18 labeled fluoroalkyltyrosine derivatives and their biological evaluation are reported.

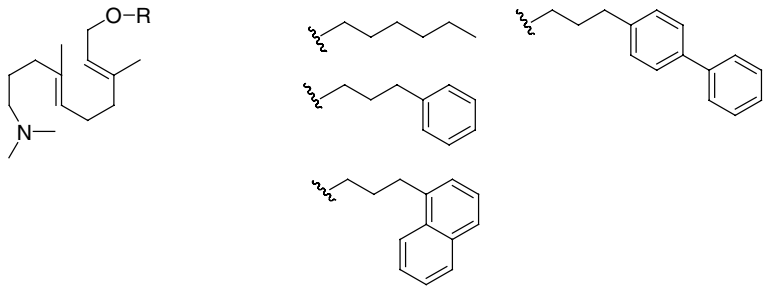


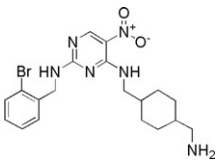
The development of a novel series of tetrahydroquinoline-derived γ-secretase inhibitors for the potential treatment of Alzheimer's disease is described.

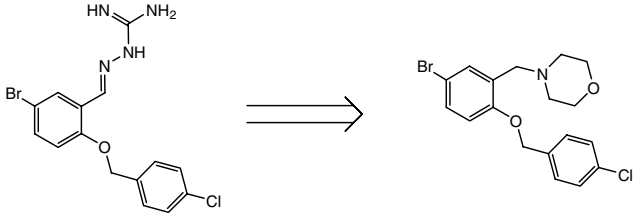


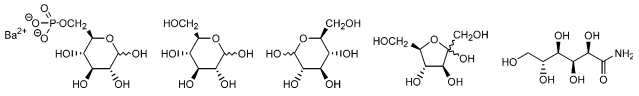


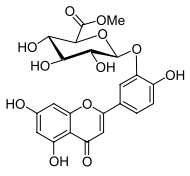
Selected potent TRPV1 agonists have been modified by 5- or 6-halogenation on the aromatic A-region to analyze their effects on potency and efficacy (agonism versus antagonism).

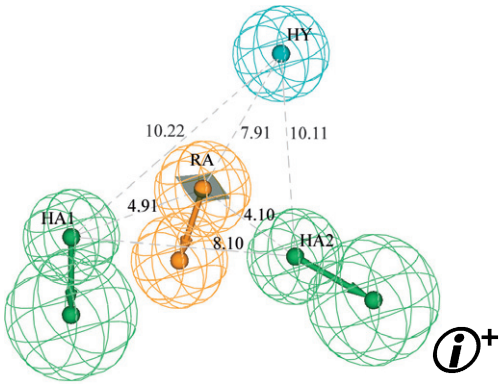


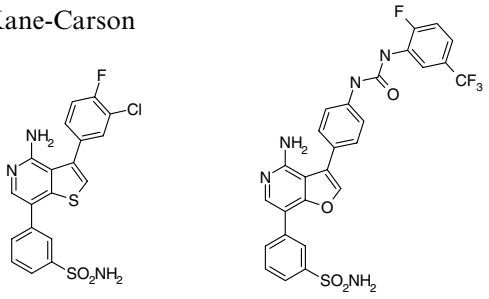


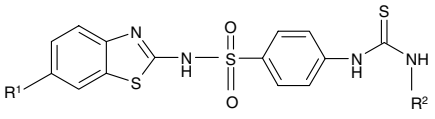




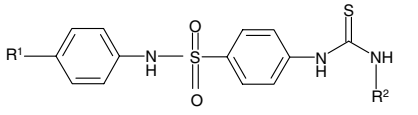








(1-6)



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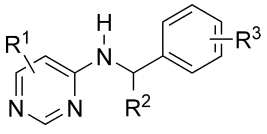
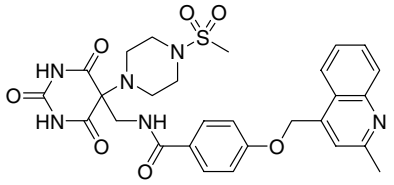
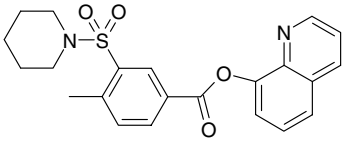


Novel HIV-1 inhibitors

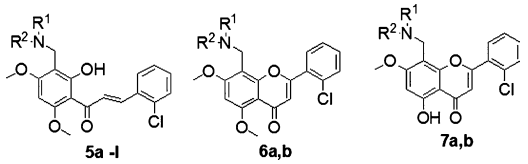


Compound 51
pTACE (IC_{50}): 0.002 μM



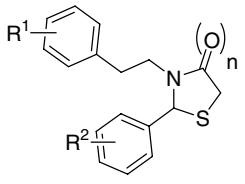
Compound 1

High-throughput screening identified the piperidinyl-sulfonyl benzoic ester **1** as a novel agonist for CB_1 receptor with nanomolar affinity. We report here the pharmacological profile of compound **1** as well as preliminary biological activities in pain model. Analogs were purchased and the structure–affinity relationships among this novel class are discussed.



5a -l **6a,b** **7a,b**

A novel series of nitrogen-containing flavonoids **5a**–**l**, **6a**,**b**, and **7a**,**b** were designed and synthesized as cyclin-dependent kinases inhibitors. The representative compounds **5a**, **5b**, **5e**, and **5g** showed potent CDK1/Cyclin B inhibitory activities.



The synthesis and evaluation of a series of thiazolidine based blockers of human Kv1.5 is described.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Typical snapshot of **7b** bound to HIV-RT from an MC simulation. Carbon atoms of **7b** are gold; from the left, Tyr181, Tyr188, Phe227, Leu100, Lys101; Trp229 at the top, Val106 at the bottom. H-bond with Lys101 O on right. Some residues in front including Glu138 have been removed for clarity. The water on N5 is also H-bonded to a carboxylate O of Glu138. [Thakur, V. T.; Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domaoal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5664.]

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