ELSEVIER

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Medicinal
Chemistry
Letters

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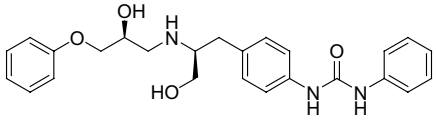
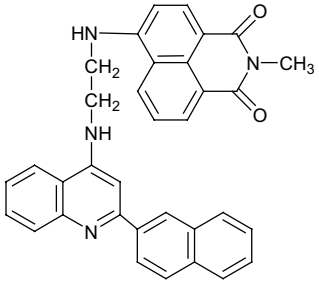
Contents

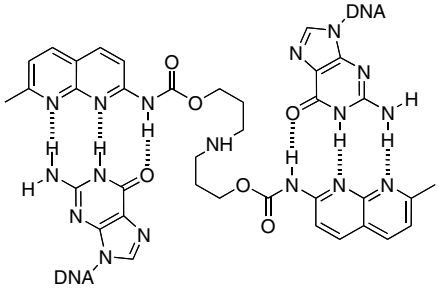
COMMUNICATIONS



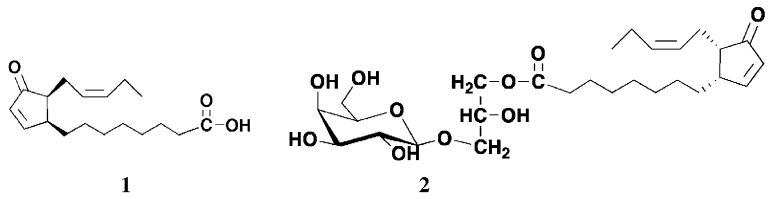
Design and structure–activity relationships of a novel β_3-adrenergic receptor agonist are described.

A novel triplex DNA fluorescent sensor which takes 4-aminonaphthalimide as a reporting group and a triplex-select intercalator as a recognizing group has been synthesized. The results show that the fluorescence of the sensor increases greatly upon addition of T·AT triplex, but the response to single strand DNA and duplex DNA is weak in PIPES 20 buffer (pH7.0).



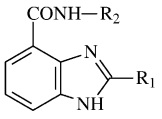


A new ligand possessing 2-amino-1,8-naphthyridines and a carbamate linker strongly binds to G–G mismatch in DNA.



1 2

Two oxylipins, *cis*-12-oxophytodienoic acid (**1**) and a novel monogalactosylmonoacylglyceride (**2**), that acted as inducers of stomatal opening were isolated.

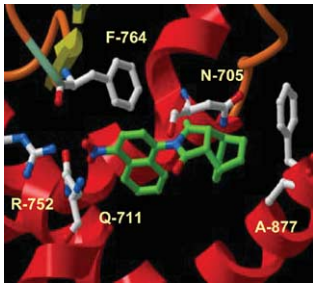


R_1= 2-, 3- and 4-pyridyl

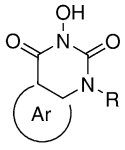
R_2= H, hydroxyethyl and aryl

1

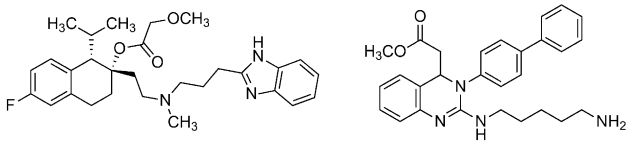
Some benzimidazole derivatives were synthesized and the antiviral evaluation against Coxsackie virus B_3 is reported. These compounds are proved to be excellent inhibitors of CVB_3.



A novel series of isoindoledione based compounds were identified as potent antagonists of the androgen receptor (AR). Co-crystallization of members of this family of inhibitors was successfully accomplished with the T877A AR LBD. A working model of how this class of compounds functions to antagonize the AR was created. Based on this model, it was proposed that expanding the bicyclic portion of the molecule should result in analogs which function as effective antagonists to a variety of AR isoforms. In contrast to what was predicted by the model, SAR around this new series was dictated by the aniline portion rather than the bicyclic portion of the molecule.

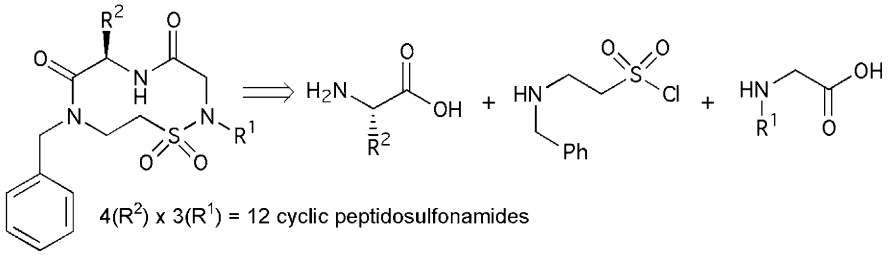


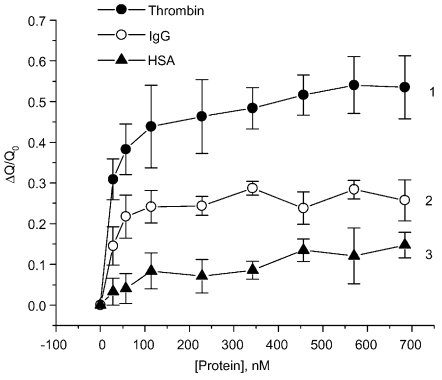
We describe the identification and SAR of a series of low nanomolar inhibitors of FEN1, an enzyme involved in DNA repair pathways. These inhibitors have been shown to sensitize certain cell lines to DNA damage.

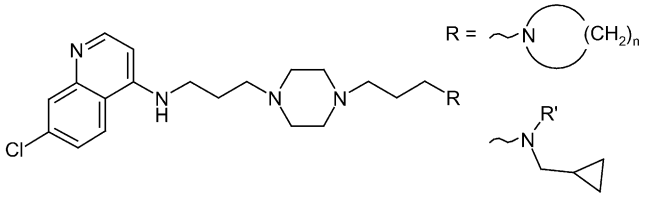


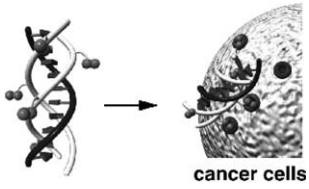
mibefradil (IC_{50} = 1.34 ± 0.49 μM)*
*against T-type Ca_2^+ Channel

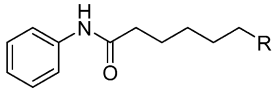
5b (**KYS05044**; IC_{50} = 0.56 ± 0.10 μM)*





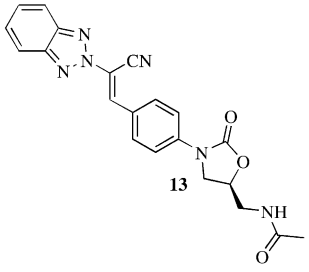


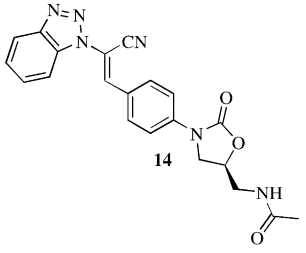




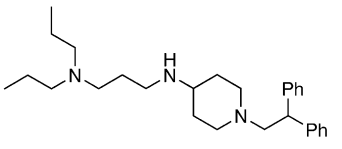
SAHA: R = -$CH_2CONHOH$
5b : R = -$NHCOCH_2SH$

In order to find novel non-hydroxamate histone deacetylase (HDAC) inhibitors, we synthesized several suberoylanilide hydroxamic acid (SAHA)-based compounds designed on the basis of the catalytic mechanism of HDACs. Among these compounds, mercaptoacetamide **5b** was found to be as potent as SAHA. Kinetic enzyme assays and molecular modeling are also reported.

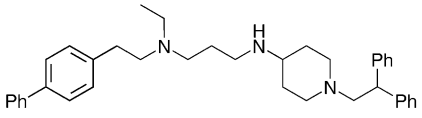




Some novel oxazolidinone derivatives have been synthesized and tested for antibacterial activity. Compound **13** was found to be active against Gram-positive pathogens whereas compound **14** was less active. Either less active or inactive molecules were obtained, when benzotriazole was replaced with benzimidazole, benzthiazole, or benzoxazole. However, thioacetamide analogue of **13** produced a potent molecule similar to linezolid in vitro.

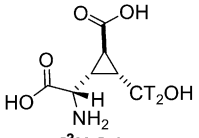


IC_{50} <60 nM (Dd2)



IC_{50} = 75 nM (Dd2)

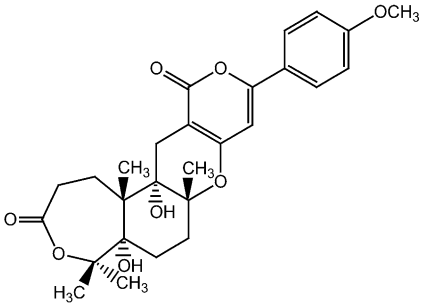
This paper describes potent antimalarial compounds effective against a multi-drug-resistant strain of *P. falciparum* (Dd2) with minimized toxicity, acceptable log *D* values, and stability to hepatocytic metabolism.

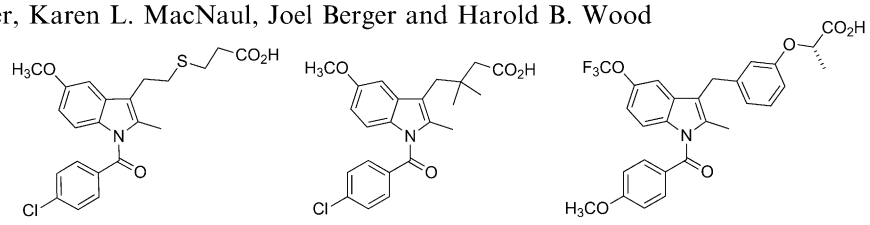


[$^3H_2$]-1

The synthesis of a radiolabeled ligand ([$^3H_2$-1]) and its use in the labeling of mGlu8 receptors is reported.

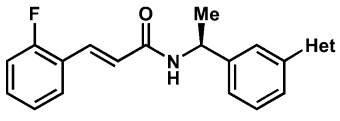
A new seven-membered lactone type meroterpenoid, isoterreulactone A, was isolated from the solid state fermentation of *Aspergillus terreus* and its structure was established by various spectral analysis. Isoterreulactone A inhibited acetylcholinesterase with an IC_{50} value of 2.5 μM while did not inhibit butyrylcholinesterase even at 500 μM.



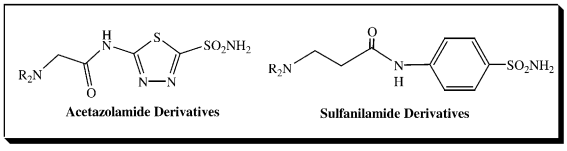


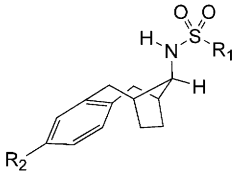
1 2 24

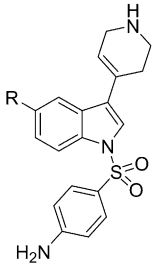
A series of selective PPARγ modulators (SPPARγMs) and their development from hPPARγ active screening leads **1** and **2** is described. SPPARγM **24** displayed robust anti-diabetic activity with an improved therapeutic window in comparison to a PPARγ full agonist in a rodent efficacy model.



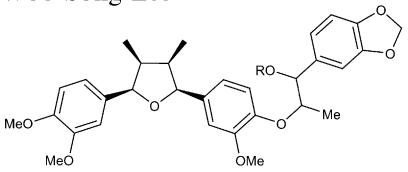
The synthesis and the KCNQ2 opener activity of a novel series of acrylamides are described.



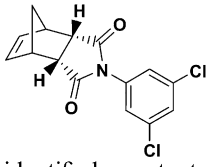




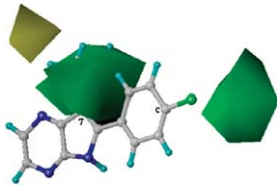
15g: R = H; **15y**: R = OMe



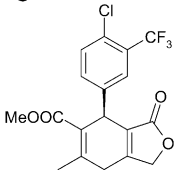
R = Me, Et, *i*-Pr, *n*-Bu, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_8H_{17}, *n*-C_9H_{19}



A novel series of isoindoledione based compounds were identified as potent antagonists of the androgen receptor (AR). SAR around this series revealed dramatic differences in binding and function in mutant variants (MT) of the AR as compared to the wild type (WT) receptor. Optimization of the aniline portion revealed substitution patterns, which yielded potent antagonist activity against the WT AR as well as the MT AR found in the LNCaP and PCa2b human prostate tumor cell lines.

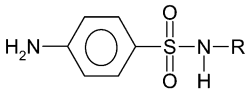


The 3D QSAR studies of GSK-3 inhibition by aloisines is reported.

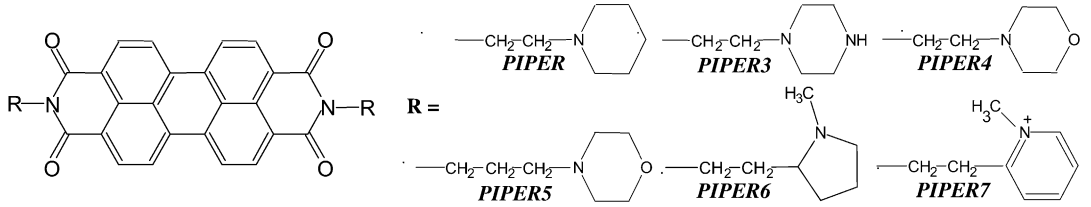


rac-**16**, IC_{50} = 8 nM

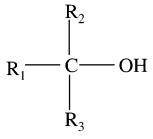
Novel cyclohexadienes have been identified as potent and specific IK_{Ca}-channel blockers. In this communication we describe their synthesis as well as their chemical and biological properties. A selected derivative distributes well into brain and reduces the infarct volume, intracranial pressure as well as the water content in a rat subdural hematoma model of traumatic brain injury after iv administration.



Sulfa drugs are building blockers of several types of Mannich bases. Consequently, the antibacterial activities of sulfa drugs are reported in this paper, which will help in understanding antibacterial activities of Mannich bases. Reported QSAR is carried out using distance-based topological indices and discussed critically on the basis of statistical parameters.

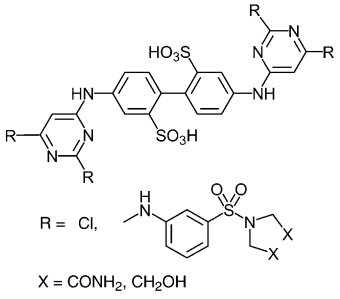


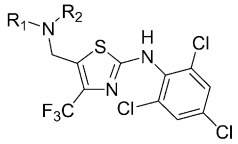
Synthesis of the shown perylene derivatives and their activity in inducing different G-quadruplex structures and in inhibiting telomerase are reported.



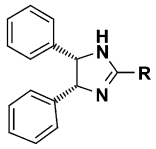
This paper describes the use of ^{13}C NMR chemical shift as molecular descriptor (molecular parameter) for modeling lipophilicity (log *P*). A set of 32 alcohols were chosen for this purpose. The regression analysis of the data showed that ^{13}C NMR chemical shifts of these alcohols can be used as a molecular descriptor (molecular property) for modeling the lipophilicity (log *P*). Better results are obtained by introducing an indicator parameter.

The synthesis of pyrimidine containing dendrimer-like dianionic inhibitors of the respiratory syncytial virus is described; their biological activity is compared with that of triazine compounds with the similar structure.

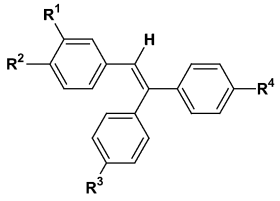




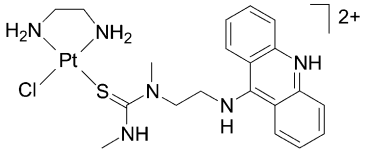
An efficient approach was developed to synthesize 2-(2,4,6-trichlorophenylamino)-4-trifluoromethyl-5-aminomethylthiazoles, corticotropin-releasing factor type 1 receptor (CRF_1R) antagonists, by monoalkylation of amines with chloromethyl intermediate **5**. The effect of variations in aminomethyl side chain of **6** on binding affinity is discussed.



The synthesis and SAR of a series of potent $P2X_7$ receptor antagonists is described. The synthesis featured high-throughput solution- and solid-phase techniques including a microwave induced imidazoline formation.



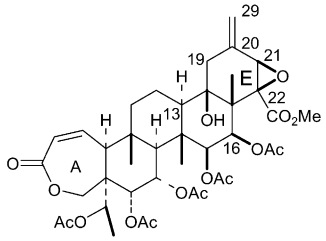
R^1 = H, F; R^2 = H, Me, SO_2Me, F, Cl;
R^3 = H, Me, F, Cl; R^4 = Me, F, Cl, SO_2Me



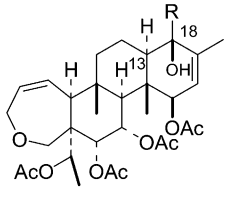
PT–ACRAMTU

The drug conjugate PT-ACRAMTU efficiently kills SNB19 and U87MG brain cancer cells without affecting normal cells. Enhanced caspase-3 levels post treatment indicate that the new agent triggers an apoptotic response.

Correolide (**1**) was converted to a new series of tetracyclic Kv1.3 blockers **2**. SAR for this class of compounds in two functional assays, Rb_Kv and human T cell proliferation, is presented herein.



1 correolide



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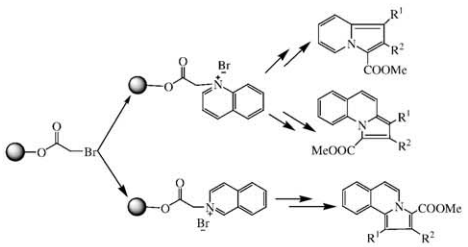

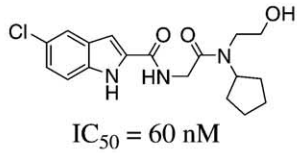

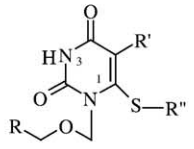

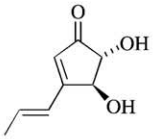

OTHER CONTENTS

*Corresponding author

COVER

2005: The proteolytic enzyme memapsin 2 (β-secretase, BACE-1) is the protease that cleaves the β-amyloid precursor protein (APP) to produce the 40-42 residue amyloid-β peptide (Aβ) in the human brain, a key event in the progression of Alzheimer's disease (AD). The X-ray crystal structure of memapsin 2 complexed with a peptidomimetic cyclic inhibitor is depicted. Inhibitor (green) is in the binding cleft of memapsin 2 shown as a ribbon diagram for the polypeptide backbone [Ghosh, A. K.; Devasamudram, T.; Hong, L.; DeZutter, C.; Xu, X.; Weerasena, V.; Koelsch, G.; Bilcer, G.; Tang, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 15].

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