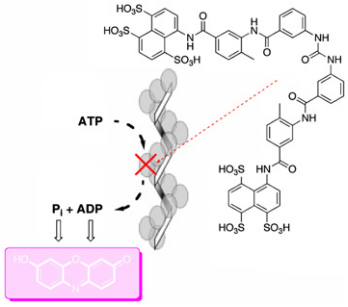
ELSEVIER

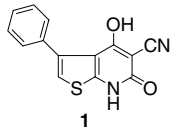
Bioorganic & Medicinal Chemistry Letters

Bioorganic & Medicinal Chemistry Letters Vol. 17, No. 12, 2007

Contents

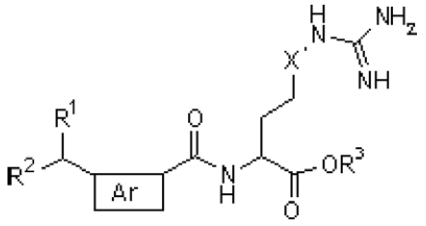
ARTICLES

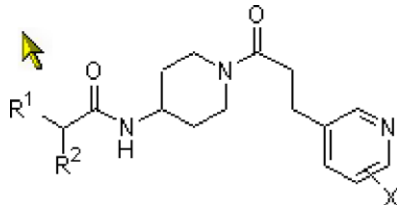


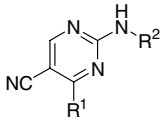


1

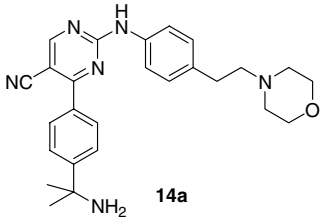
AMPK Rat Liver EC 50 38 uM



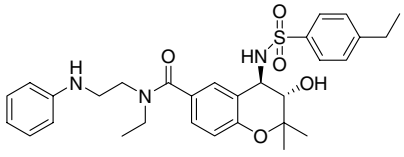




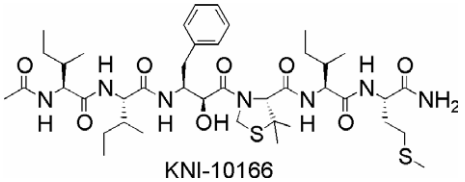
2



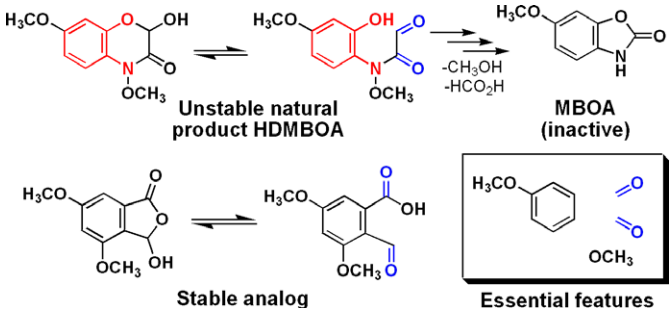
14a

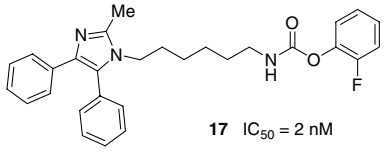


5f IC_{50} = 0.077 μM

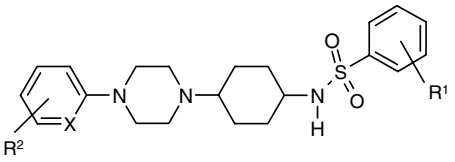


KNI-10166



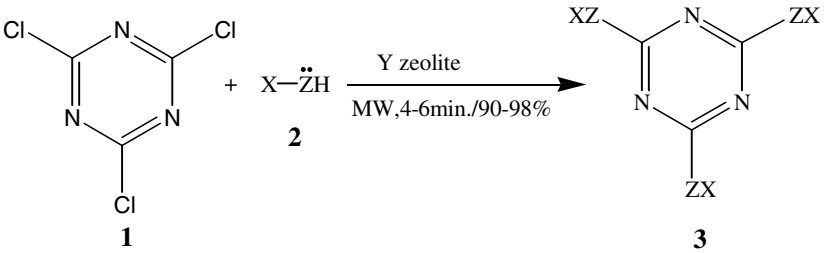


A class of bisarylimidazole derivatives are identified as potent inhibitors of the enzyme fatty acid amide hydrolase (FAAH).



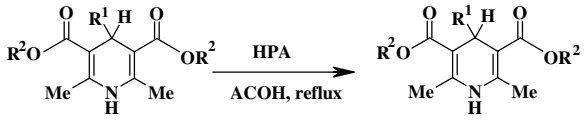
A series of (arylpiperazinyl)cyclohexylsulfonamides that show selectivity to human $\alpha_{1a/1d}$-adrenergic receptors was developed. These compounds have potential for the treatment of BPH/LUTS.

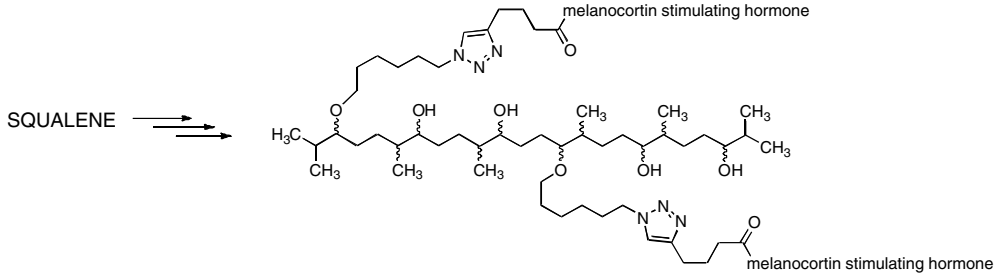
A simple and environmentally friendly procedure has been developed for the synthesis of 2,4,6-trisubstituted-1,3,5-triazines using HY zeolite under microwaves and synthesized compounds screened for cytotoxic, antimicrobial, and photosynthesis-inhibiting activities.



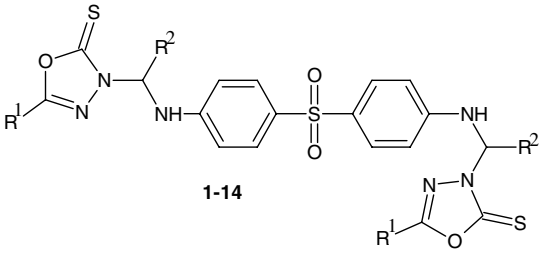
1 2 3

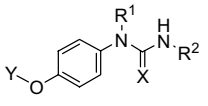
X = Ar/CH_3Ar/$(C_2H_5)_2$/$(CH_3)_2$/CH_3CO/CH_3/OCH_3Ar/NO_2Ar/ClAr/H, Z= O, NH



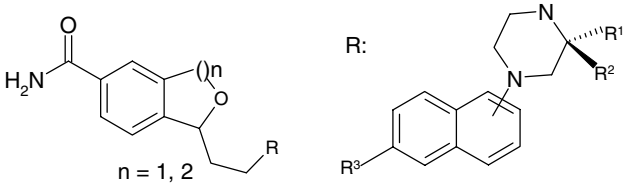


A series of oxadiazole mannich bases were synthesized by reacting oxadiazole derivatives, dapsone and appropriate aldehyde in the presence of methanol. The synthesized compounds were evaluated for antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$ and INH resistant *M. tuberculosis*. Among the synthesized compounds, compound (**4**) 3-{2-furyl[4-(4-{2-furyl[5-(2-naphthyloxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3-yl]methylamino}-phenylsulfonyl)anilino]methyl}-5-(2-naphthyloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione was found to be the most promising compound active against *M. tuberculosis* $H_{37}Rv$ and isoniazid (INH) resistant *M. tuberculosis* with minimum inhibitory concentration (MIC) 0.1 μM & 1.10 μM respectively.



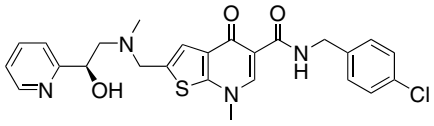


Synthesis of series of ureas and thioureas and their inhibitory activities of NO production in lipopolysaccharide-activated macrophages are reported.



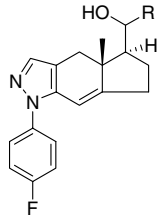
A series of compounds with dual activity as 5-HT$_{1D}$ antagonists and 5-HT reuptake inhibitors were prepared by incorporating naphthylpiperazines to substituted isochromans and dihydroisobenzofurans.

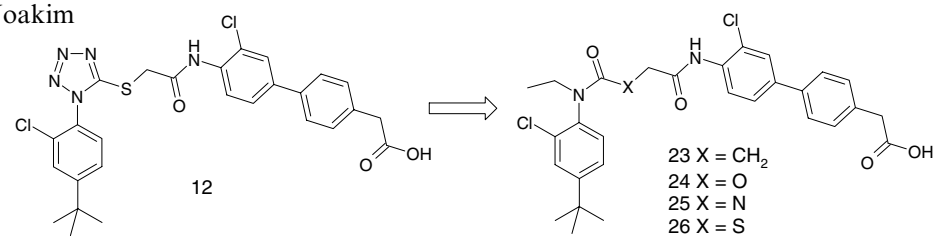
A potent series of broad-spectrum antivirals against human herpesviruses has been identified which inhibit HCMV, HSV-1, EBV, and VZV polymerases.



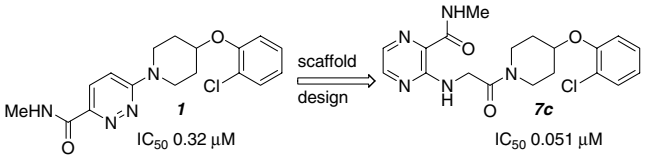
5d

Compounds containing the depicted core were synthesized. These compounds were evaluated for binding to the glucocorticoid receptor in cell based transactivation and transrepression assays. Molecular modeling and in vivo data are also provided.

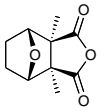




Tetrazole thioacetanilides such as **12** were identified as potent NNRTIs via high-throughput screening. Analysis of the binding mode of these inhibitors permitted the successful scaffold hop to tertiary amides (**23**), carbamates (**24**), and thiocarbamates (**26**).

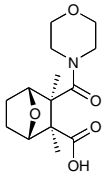


In this work, we report the first improvement in protein phosphatase inhibition by a cantharidin analogue. Compound **19** is approximately twice as potent as cantharidin against both PP1 and PP2A. Additionally **19** displays excellent broad spectrum cytotoxicity.



2

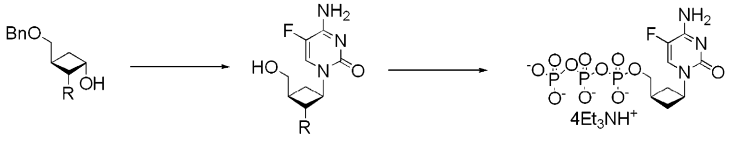
PP2A IC_{50} = 1.2 ± 0.1 μM
PP1 IC_{50} = 11.3 ± 1.97 μM



19

PP2A IC_{50} = 0.79 ± 0.1 μM
PP1 IC_{50} = 5.9 ± 2.2 μM

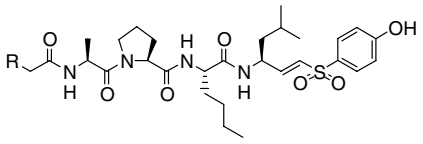
Several 2′-substituted cyclobutyl nucleosides were synthesized and evaluated as anti-HIV agents. Whereas the cyclobutyl nucleosides were not active against HIV in culture, the triphosphate forms were quite active against wild-type and mutant forms of HIV reverse transcriptase (RT).



R = H, F, Me

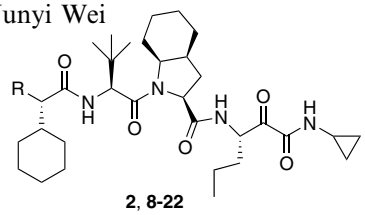
IC_{50} >100 μM in cell assay

IC_{50} = 6.1 μM in cell-free assay



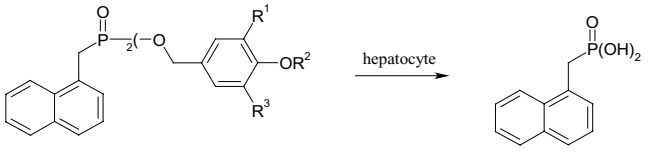
R = H or R = N_3

A subunit-specific proteasome inhibitor was developed and its specificity was assayed both by fluorescent substrate hydrolysis and by visualization of the targeted subunits via an activity-based probe approach.



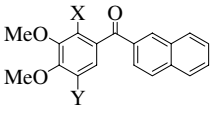
2, **8-22**

A series of tetrapeptide HCV NS34A protease inhibitors with varying P4 capping groups were prepared. The SAR and pharmacokinetic properties of these inhibitors are discussed.

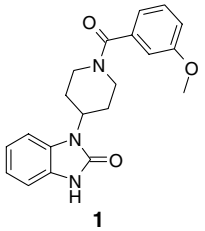


A series of bis[(para-methoxy)benzyl] phosphonate esters were synthesized and evaluated as phosphonate prodrugs. Two esters (**4b** and **4c**) were identified with significantly improved aqueous stability and enhanced penetration to primary rat hepatocytes.

The synthesis and biological activity of a new family of phenstatin analogues, carrying a 2-naphthyl moiety, is reported. Compound **7** (IC_{50}[TPI] = 1.1 μM) is more potent than combretastatin A4 (IC_{50}[TPI] = 3 μM) in tubulin polymerization inhibition assays (TPI). The replacement of the 3-hydroxy-4-methoxyphenyl ring by a 2-naphthyl system is more favourable in the phenstatin than in the combretastatin series.

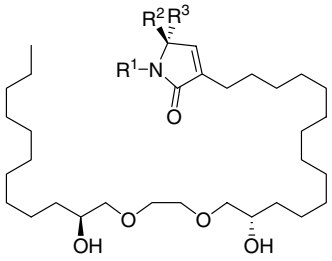


Naphthylphenstatins
X or Y = MeO
7 X = H, Y = OMe
IC_{50} (TPI) = 1.1 μM

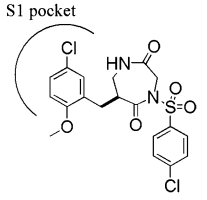


1

Compound **1** was identified as a potent 11β-HSD1 inhibitor in a HTS screen. Synthesis and inhibitory potency of analogs to **1** are reported.

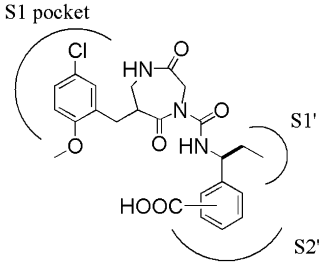


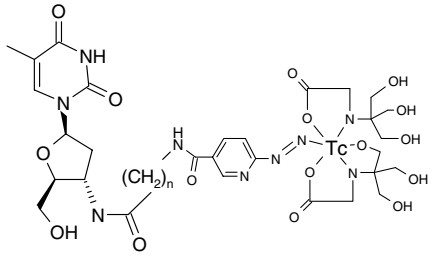
A new series of annonaceous acetogenin mimics containing a terminal lactam were designed, synthesized, and evaluated.



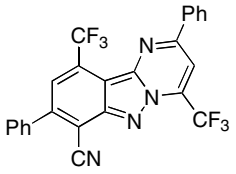
A novel series of 6-substituted 4-sulfonyl-1,4-diazepane-2,5-diones were designed, synthesized, and evaluated as human chymase inhibitors. Structure–activity relationship studies led to the identification of a potent inhibitor, (6*S*)-6-(5-chloro-2-methoxybenzyl)-4-[(4-chlorophenyl)sulfonyl]-1,4-diazepane-2,5-dione, with an IC_{50} of 0.027 μM.

A novel series of 6-benzyl substituted 4-aminocarbonyl-1,4-diazepane-2,5-diones was designed, synthesized, and evaluated as human chymase inhibitors. From this series, we identified several compounds which were effective, via oral administration, in a mouse model of chronic dermatitis.

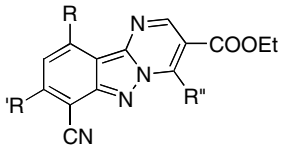




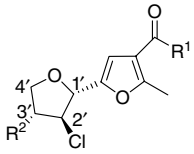
The synthesis and labeling of a series of thymidine analogs were reported.



5f



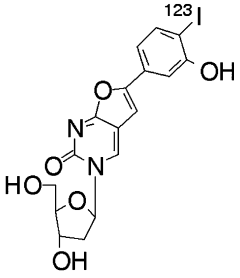
7b: R = Ph, R' = CF_3, R" = OH
7d: R = CF_3, R' = Ph, R" = NH_2
7e: R = Ph, R' = CF_3, R" = NH_2

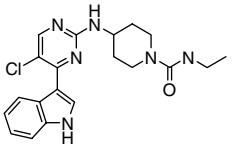


R^1 = CH_3, OC_2H_5

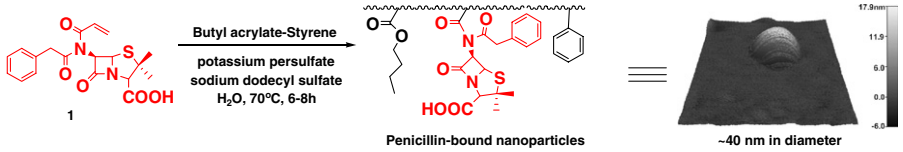
R^2 = OH, OMs, N_3, NH_2, O

Some new furanosyl α-C-glycoside derivatives were synthesized and tested for in vitro cytotoxicity against human lung adenocarcinoma cell lines.



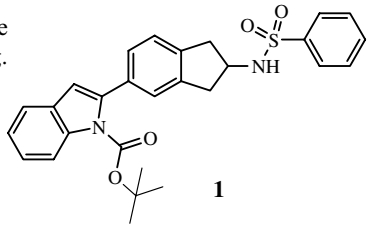


A series of novel aminopyrimidines is reported which exhibits JNK1 and JNK2 inhibitory activity.



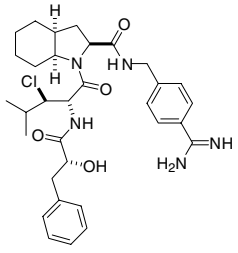
Polyacrylate nanoparticles bearing penicillin antibiotics attached to the polymeric matrix have been prepared in water by emulsion polymerization. The nanoparticles are uniformly 25–40 nm in diameter and are stable over a wide range of pH values and in blood serum. The nanoparticle emulsions display potent in vitro activity against *Staphylococcus aureus* and retain their full antibiotic capabilities against β-lactamase producing, methicillin-resistant *S. aureus*, suggesting their use as therapies for drug-resistant bacterial infections.

A structurally novel LXR agonist (**1**) was identified utilizing the combination of virtual screening and high-throughput gene profiling. Structure–activity relationship studies on **1** are described.

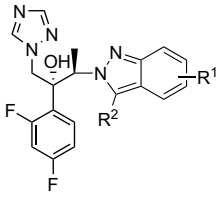


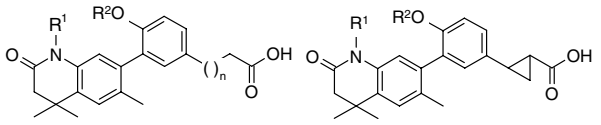
Fold induction @ 10 μM:
ABCA1: 8.4
SREBP1c: 3.1
EC_{50} (μM): 0.21 (LXRβ)
1.42 (LXRα)

The synthesis of a series of unnatural aeruginosin hybrids and their structure–activity relationships against thrombin are reported. The D-3*R*-chloroleucine hybrid **16** was found as one of the most active thrombin inhibitors in this series.

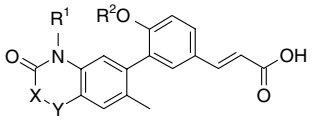


16
Thrombin IC_{50} = 0.0016 μM

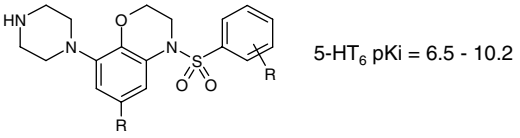




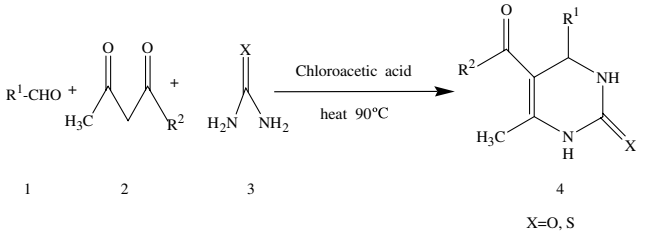
A number of RXR modulators with novel structural features were synthesized and screened in the functional assays. The synthesis and the structure–activity relationship within the series of compounds will be presented. Some in vivo data generated in the models for dyslipidemia and diabetes will also be presented.



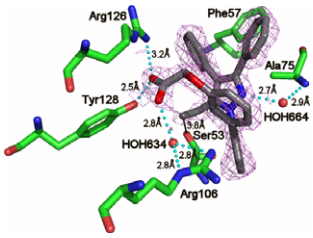
A number of RXR agonists were synthesized and screened in functional assays. The synthesis and the structure–activity relationship (SAR) within the series of compounds will be presented. Some in vivo data in rodent models for dyslipidemia and diabetes will also be presented.



The synthesis and structure–activity relationships of a series of 3,4-dihydro-2*H*-benzo[1,4]oxazine based 5-HT$_6$ antagonists are described.



A simple and effective synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives from aldehydes, 1,3-dicarbonyl compounds and urea or thiourea using chloroacetic acid as catalyst under solvent-free conditions is reported.



X-ray crystal structure of an FABP inhibitor bound to the active site of aFABP.

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.]

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