Bioorganic & Medicinal Chemistry Letters 19 (2009) 1541–1558

Contents lists available at ScienceDirect

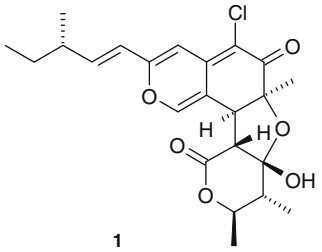
Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Bioorganic & Medicinal Chemistry Letters Vol. 19, No. 6, 2009

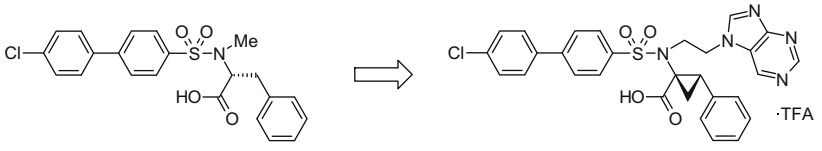
Contents

ARTICLES

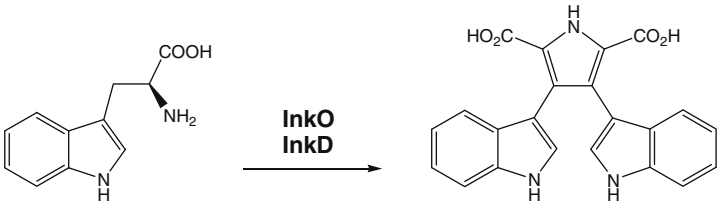


1

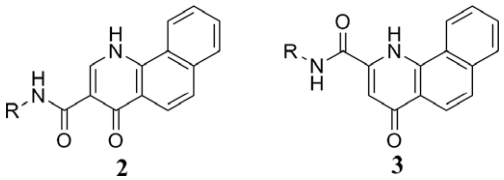
A novel chlorinated azaphilone analogue named chaetomugilin D (**1**) together with three known compounds **2**–**4** has been isolated from the cultures of *Chaetomium globosum*, an endophytic fungus present in *Ginkgo biloba*. The isolates displayed significant growth inhibitory activity against the brine shrimp and *Mucor miehei*.



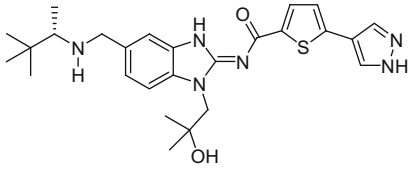
IC_{50} = 8.0 μM IC_{50} = 0.071 μM



Tryptophan Chromopyrrolic acid (CPA)

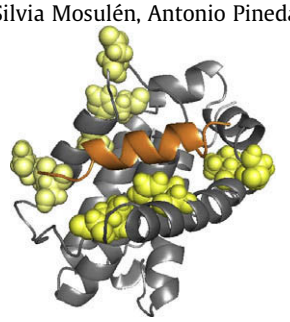


2 3

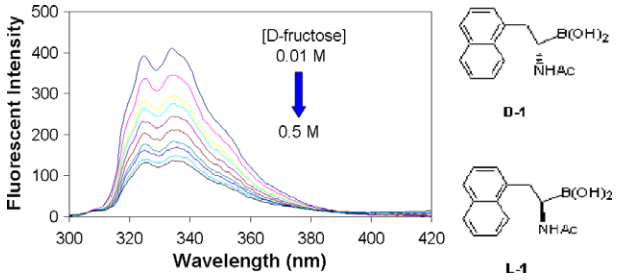


10n

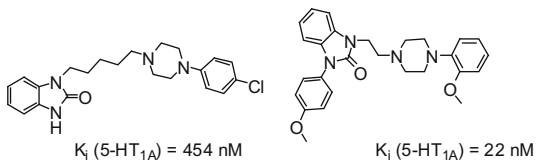
SAR studies around the 5-aminomethylbenzimidazoles and identification of tool compounds such as **10n** for proof-of-concept studies are described.



Bcl-xL residues undergoing chemical shift changes upon binding to quinacrine (yellow spheres) form a patch resembling the interaction reported between Bcl-xL (grey) and the BH3 domain (orange) of a Bak-derivative peptide.

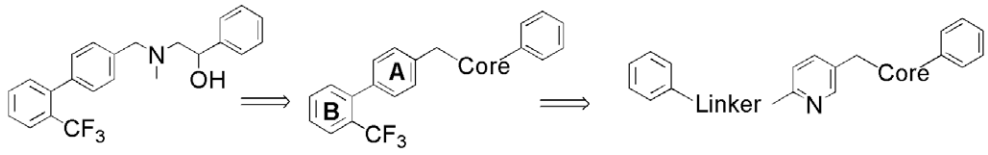


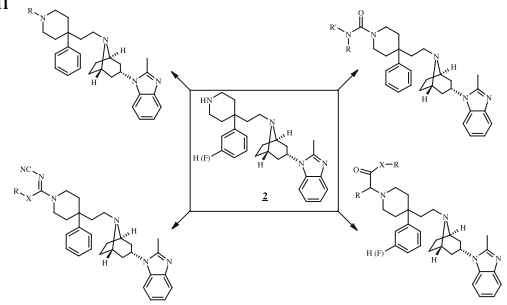
The first amidoboronic acids were identified that show significant fluorescent property changes upon binding with various carbohydrates.

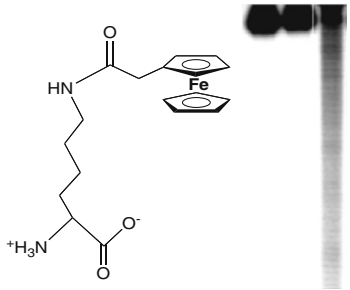


K_i (5-HT$_{1A}$) = 454 nM
K_i (5-HT$_7$) = 7 nM

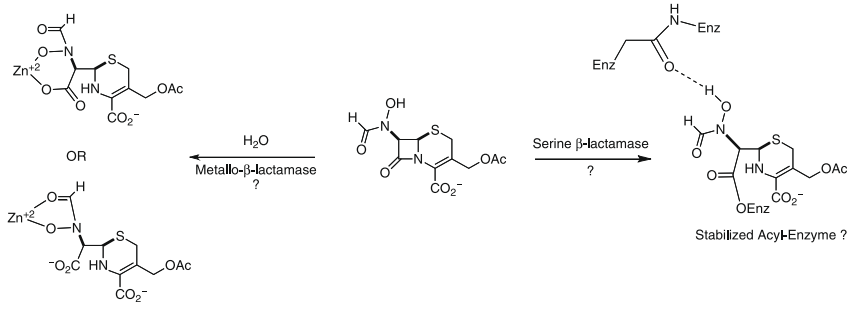
K_i (5-HT$_{1A}$) = 22 nM
K_i (5-HT$_7$) = 296 nM

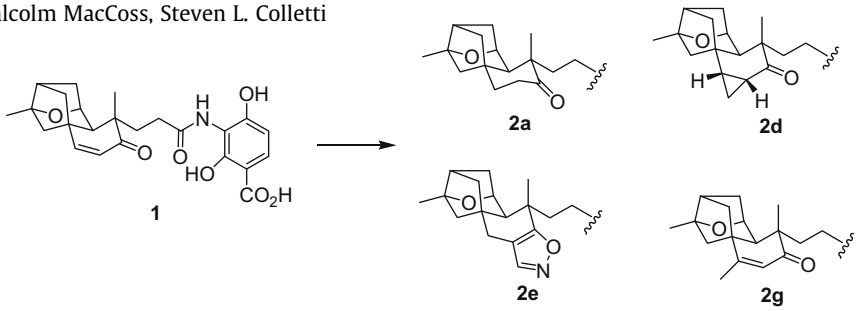


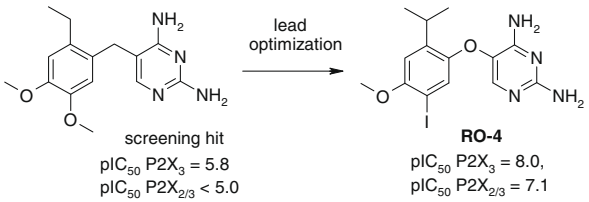




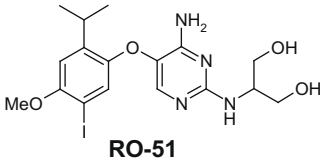
The nucleolytic activity exhibited by an unnatural ferrocenyl amino acid is non-specific along the DNA backbone and can be significantly enhanced under reducing and Fenton conditions.



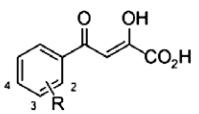




The discovery and structure–activity relationships of a novel series of diaminopyrimidine based dual $P2X_3/P2X_{2/3}$ antagonists is described.

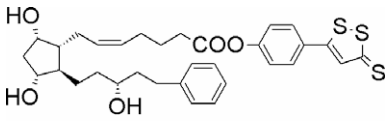


This paper describes the SAR and optimization of diaminopyrimidine template based $P2X_3/P2X_{2/3}$ antagonists. Discovery and the synthesis a highly potent and drug-like dual $P2X_3/P2X_{2/3}$ antagonists **RO-51** is presented.



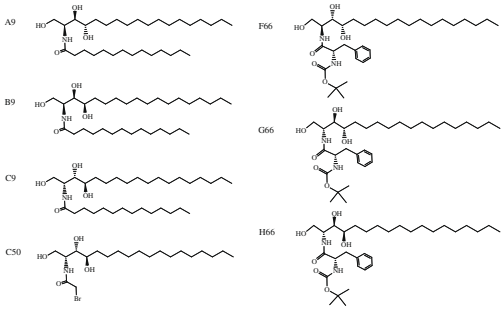
1 R = 4-OCH_2Ph **5** R = 2-OCH_2Ph
2 R = 4-OCH_2(4-ClPh) **6** R = 2-OCH_2(4-ClPh)
3 R = 3-OCH_2Ph **7** R = 3-$NHCH_2Ph$
4 R = 3-OCH_2(4-ClPh) **8** R = 3-$NHCH_2$(4-ClPh)

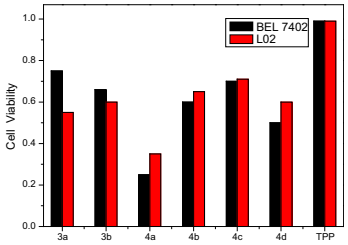
Compd	SCV Hel. IC_{50} (μM)	
	ATPase	Duplex DNA-Unwinding
1	41.3 ± 2.7	39.9 ± 0.5
2	> 50	> 50
3	> 50	> 50
4	24.4 ± 1.0	13.6 ± 0.3
5	> 50	> 50
6	> 50	28.7 ± 2.3
7	> 50	5.4 ± 0.1
8	> 50	11.0 ± 0.6



ACS 67

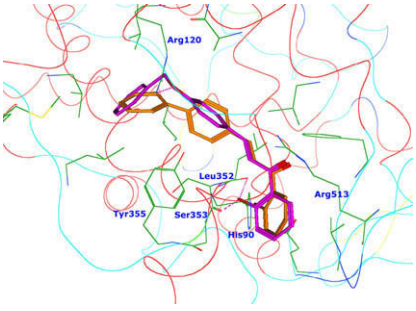
A hydrogen sulphide-releasing derivative of latanoprost acid (ACS 67) was synthesized and showed in rabbit a reduction of intraocular pressure and good tolerability.

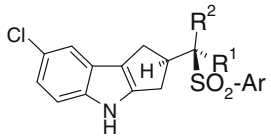




Four porphyrins with NO donors were synthesized, and the cancer cell-oriented accumulation and NO release from the porphyrins were found. The porphyrins with NO donor had more effective killing of BEL-7402 liver cancer cells than L-02 liver normal cells.

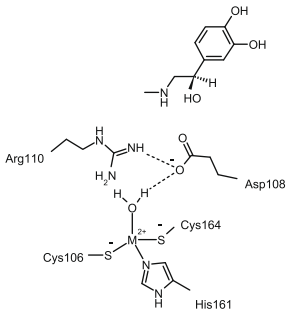
A series of 2′-hydroxychalcones has been synthesized and screened for their in vitro inhibitory activities of cyclooxygenase-2 catalyzed prostaglandin production from lipopolysaccharide-treated RAW 264.7 cells and docked into cyclooxygenase-2.

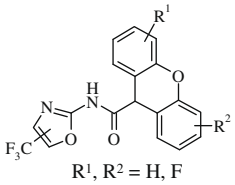




A novel series of selective LXRs modulator derived from a high throughput screening hit is reported.

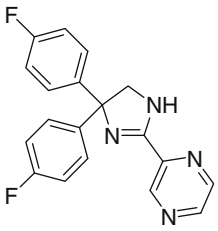
GSH $t_{1/2}$ = 315 min GSH $t_{1/2}$ = 2000 min



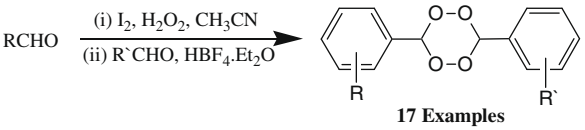


R^1, R^2 = H, F

The synthesis of a new class of selectively fluorinated small molecule mGluR1 enhancers with improved pharmacokinetic properties is presented. Their potential use as pharmacological tools for the study of the physiological roles mediated by mGlu1 receptors is discussed.

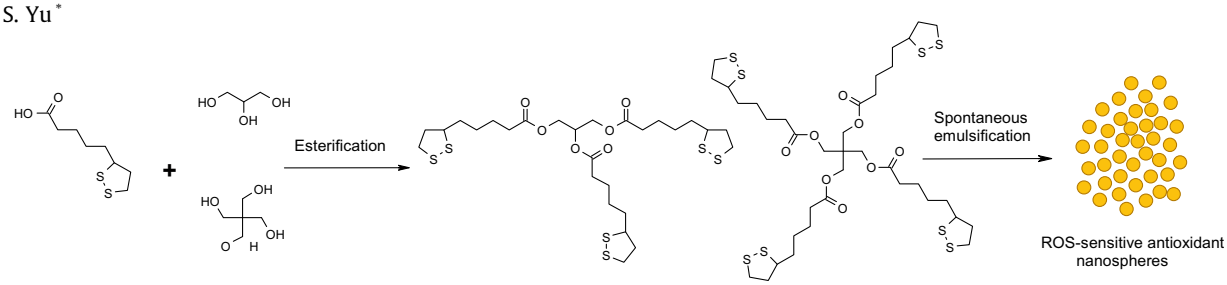


Novel imidazoline derivatives were discovered to be potent neuropeptide Y Y5 receptor antagonists.

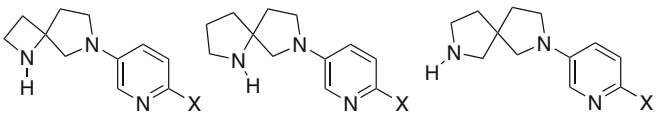


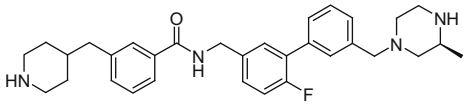
17 Examples

P. falciparum (D6 Clone); IC_{50} = 0.38 - 3.79 μM
P. falciparum (W2 Clone); IC_{50} = 0.45 - 6.01 μM



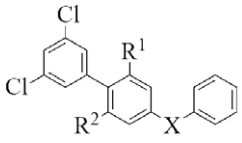
Reactive oxygen species (ROS)-sensitive antioxidant nanospheres were prepared from multiple α-lipoic acid-containing antioxidant compounds (mALAs) by using spontaneous emulsification.



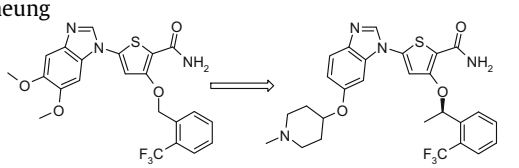


14, M_3 FLIPR pA_2 = 11.0

Exploration of multiple regions of a bi-aryl amine template led to the identification of highly potent M_3 muscarinic acetylcholine receptor antagonists such as **14** possessing good sub-type selectivity for M_3 over M_2. The structure–activity relationships and optimization of the bi-aryl amine series are described.

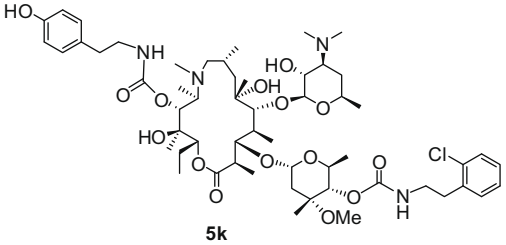


4 R^1= OCH_3; R^2= OCH_3; X= CHOH
5 R^1= OH; R^2= OH; X= C=O
6 R^1= OH; R^2= OCH_3; X= C=O
7 R^1= OH; R^2= OH; X= $C(CH_3)_2$



PLK1 IC_{50} = 2 nM
PLK3 IC_{50} = 9 nM
poor solubility
highly protein bound

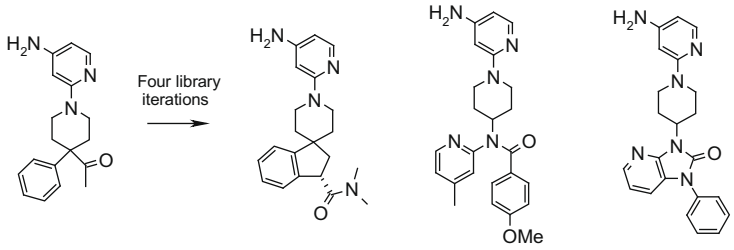
PLK1 IC_{50} = 2 nM
PLK3 IC_{50} = 270 nM
improved solubility
reduced protein binding



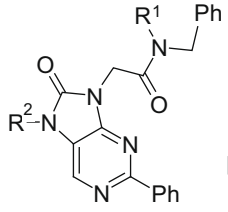
5k

MIC = 0.06μg/mL

A series of new 4,11-di-*O*-arylalkylcarbamoyl azithromycin derivatives were designed, synthesized and evaluated for their in vitro antibacterial activities. Some derivatives exhibited greatly improved activity against erythromycin-resistant *Streptococcus pneumoniae* encoded by the *erm* or *mef* gene.

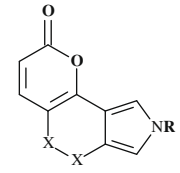


A δ-opioid agonist hit was converted into potent and selective analogues using library chemistry.



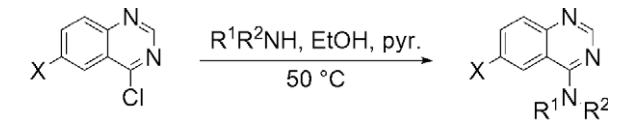
FEAC (**4a**): R^1=CH_2CH_3, R^2=CH_2CH_2F
[18F]FEAC ([18F]**4a**): R^1=CH_2CH_3, R^2=$CH_2CH_2{}^{18}F$
FEDAC (**4b**): R^1=CH_3, R^2=CH_2CH_2F
[18F]FEDAC ([18F]**4b**): R^1=CH_3, R^2=$CH_2CH_2{}^{18}F$

[18F]FEAC ([18F]**4a**) and [18F]FEDAC ([18F]**4b**), two potent PET ligands for peripheral-type benzodiazepine receptor, were synthesized and evaluated.

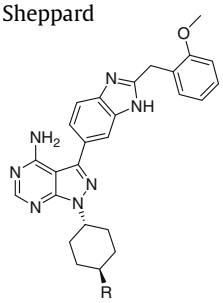


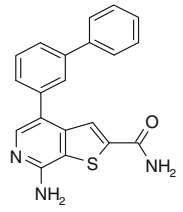
X-X= CH_2-CH_2 or CH=CH

A versatile and convenient pathway for the synthesis of pyrano[2,3-*e*]isoindol-2-one derivatives and their photochemotherapeutic activity are reported.

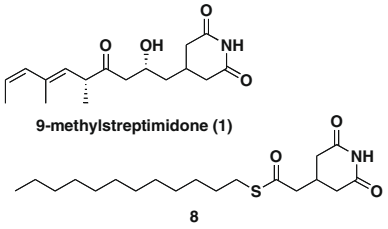


X = Br, Cl, F, H



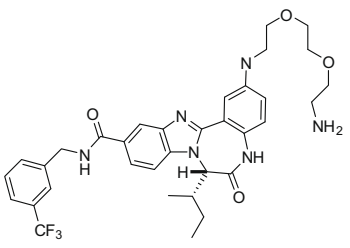


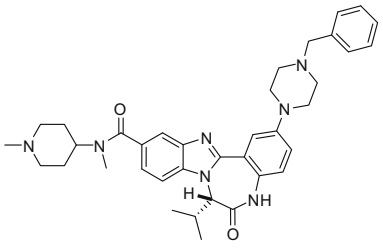
COT (Tpl2 in mice) is a serine/threonine MAP3 kinase that regulates production of TNF-α and other pro-inflammatory cytokines such as IL-1β via theERK/MAP kinase pathway. As TNF-α and IL-1β are clinically validated targets for therapeutic intervention in rheumatoid arthritis (RA), blocking COT provides a potential avenue for amelioration of disease. Herein we describe identification of a cellular active selective small molecule inhibitor of COT kinase.

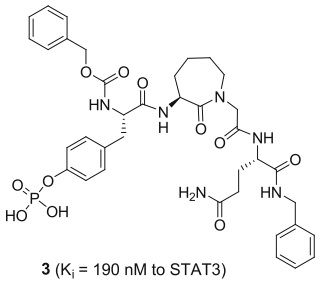


Synthesis and biological evaluation on analogs of 9-methylstreptimidone, an inhibitor of NF-κB, are reported. Simplified compound **8** exhibited inhibitory activity against LPS-induced NO production comparable to that of 9-methylstreptimidone.

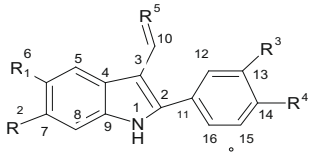
A class of small molecules displaying comparable activities with peptide ligands BAM22 and corticostatin-14 at both the human and rhesus monkey MrgX1 and MrgX2, respectively, receptors was discovered.



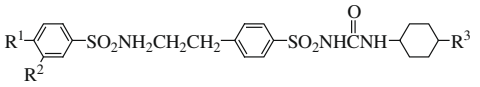




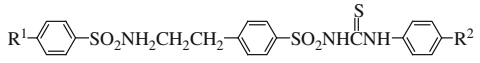
3 (K_i = 190 nM to STAT3)



Comparative QSAR modelling was performed on 2-phenylindole-3-carbaldehydes to find more active antimitotic agents. Stepwise regression, FA-MLR, PVRA and PLS techniques were adopted for QSAR study.

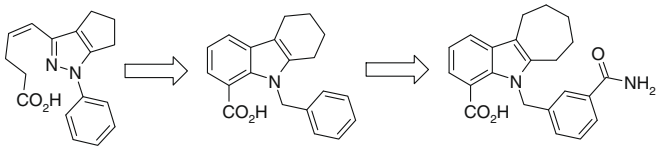


7-16



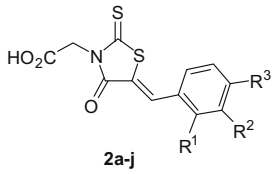
17-25

Compound **10** (R^1 = Br, R^2 = H, R^3 = CH_3) with excellent hypoglycemic and antithrombotic properties, might be useful in the treatment of diabetics with cardiovascular and nephropathy complications.



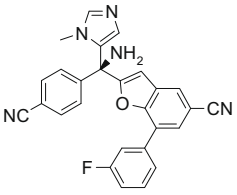
1 **2a** **30**

A novel class of hexahydrocyclohepta[b]indole-based A-FABP inhibitors have been synthesized and evaluated. The potency, selectivity profile, and structure–activity relationship trends of this class of compounds are discussed.



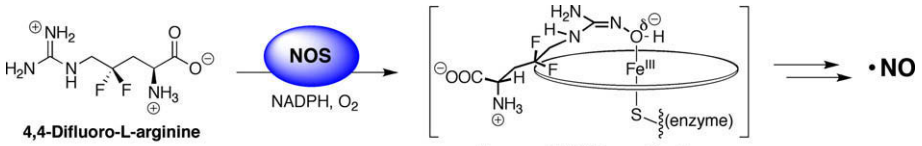
2a-j

The development of thiazolidinones as dolicholphosphate mannose synthase (DPMS) inhibitors and novel trypanocidal agents (ED50 < 100 μM) is reported.



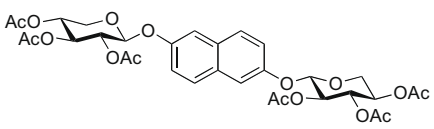
11f

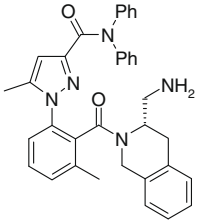
The synthesis and biological activity of benzofuran derivatives as farnesyltransferase inhibitor is described.



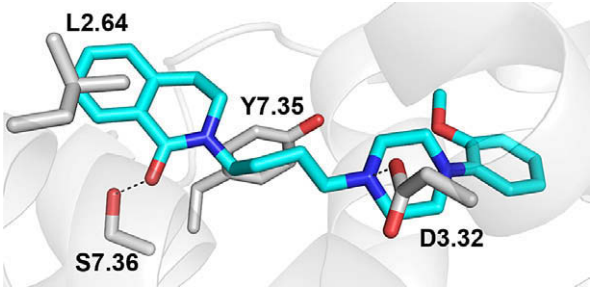
4,4-Difluoro-L-arginine

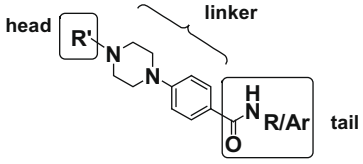
Proposed NOS heme ligation by N^G-hydroxy intermediate



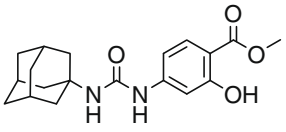


Determination of the bioactive conformation of a series of atropisomeric Bcl-2 inhibitors is reported.





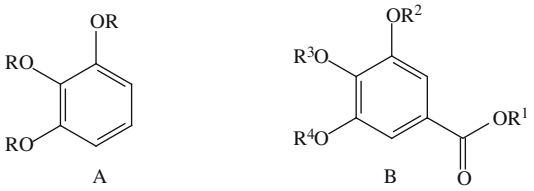
We report here synthesis and SAR of substituted piperazinyl-*N*-(aryl)benzamides as potent inhibitors of HCV replication exerted via modulation of the dimerization of NS5A.



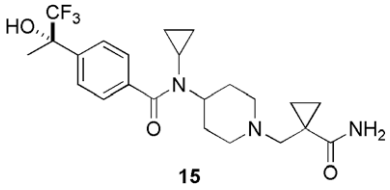
28

The methyl salicylate-based urea **28** was synthesized as a soluble epoxide hydrolase inhibitor. This compound had not only strong inhibitory activity but also relatively high metabolic and chemical stabilities.

Bacteria isolated from the parotoid gland of the cane toad (*Bufo marinus*) have the ability to biotransform steroid toxins (bufadienolides), suggesting a possible new strategy for cane toad control.

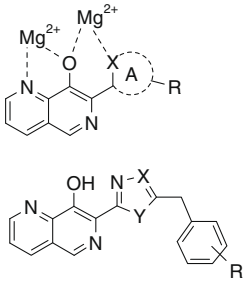


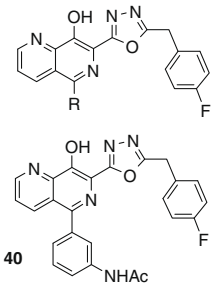
When the log*P* of each gallate was calculated and related to the different values of MIC against *Microsporum gypseum* it was observed that hexyl, heptyl, octyl and nonyl gallates exhibit a significant positive deviation from the curve corresponding to a polynomial equation obtained for the other gallates. This suggests that these compounds have a further mode of action besides their hydrophobicity, possibly the inhibition of some enzyme involved in ergosterol biosynthesis.

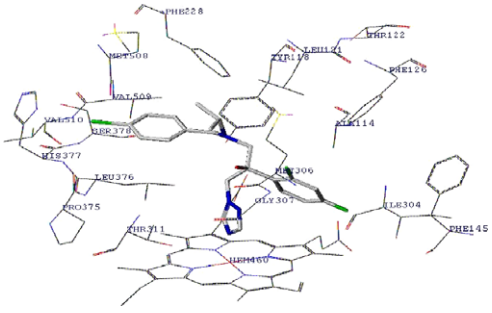


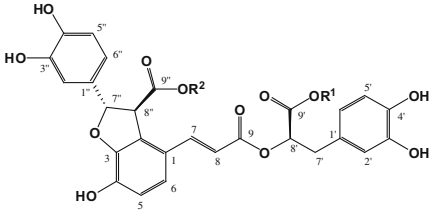
15

The discovery and optimization of a piperidyl benzamide series of 11β-HSD1 inhibitors is reported.

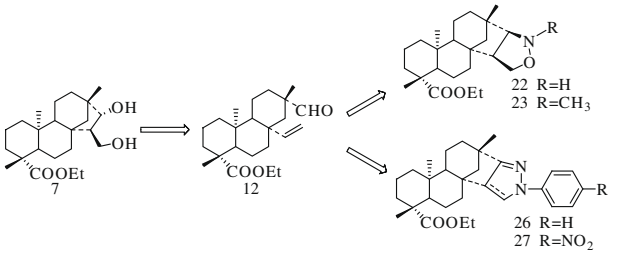




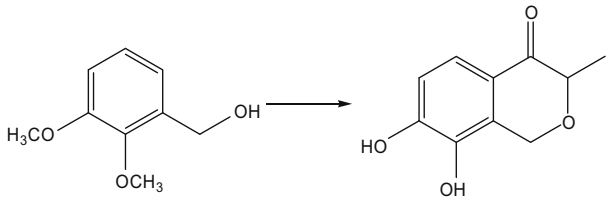




Lithospermic acid (**1**) $R^1 = R^2 = H$
9"-Methyl lithospermate (**2**) $R^1 = H,\ R^2 = CH_3$
9'-Methyl lithospermate (**3**) $R^1 = CH_3,\ R^2 = H$

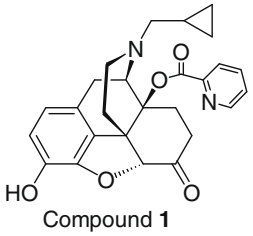


A novel series of 15- and 16-substituted isosteviol derivatives were designed and prepared. Within all compounds, **22** (IC_{50} = 15 μM) showed the most potent cytotoxic activities against B16-F10 melanoma cells.



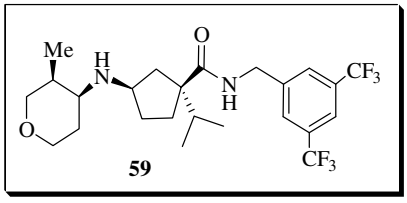
(±)7, 8-dihydroxy-3-methyl- isochromanone-4 (**1**)

The total synthesis of (±)7,8-dihydroxy-3-methyl-isochromanone-4 (**1**) is described and this compound displays potent antihypertensive activity and moderate ACE inhibitory activity.



Compound **1**

A series of 14-*O*-heterocyclic-substituted naltrexone derivatives were designed, synthesized, and evaluated. Among them, compound **1** showed binding affinity at subnanomolar level and highest selectivity for the mu opioid receptor.



59

Discovery of a novel series of 3-aminocyclopentanecarboxamide CCR2 receptor antagonists are presented herein. These compounds demonstrate high affinity and functional inhibition of hCCR2 receptors. A discussion on SAR along with the cross species PK profile for the best analog (**59**) is also included.

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.]

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