Bioorganic & Medicinal Chemistry Letters 19 (2009) 2369–2382

Contents lists available at ScienceDirect

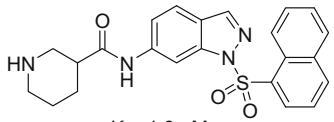
Bioorganic & Medicinal Chemistry Letters

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

Bioorganic & Medicinal Chemistry Letters Vol. 19, No. 9, 2009

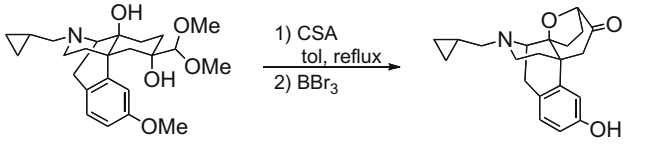
Contents

ARTICLES



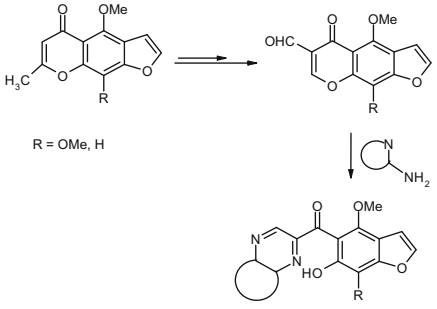
K_i = 1.3 nM
IC_{50} = 10 nM
Full 5-HT$_6$ antagonist
Oral F = 24% (rats)
Efficacious @ 10 mp/kg in NOR (rats)

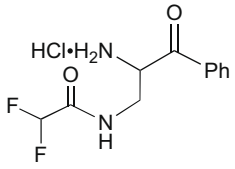
Identification and SAR of a series of 1-sulfonlyindazole derivatives as potent and selective 5-HT$_6$ antagonists are reported.

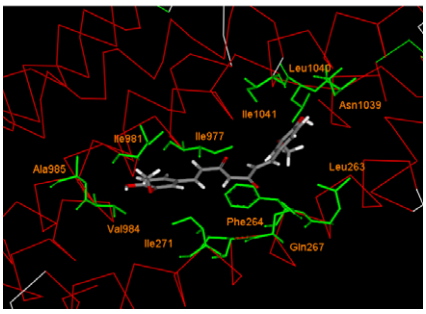


K_i (μ) = 0.397 nM
K_i (κ) = 0.233 nM

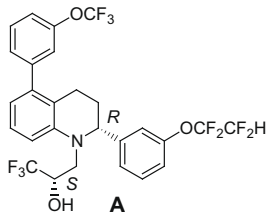
Novel morphinan derivative having oxabicyclo[3.2.1]octane skeleton was prepared from dimethyl acetal derivative. The novel compound showed strong affinity for μ and κ opioid receptor types.





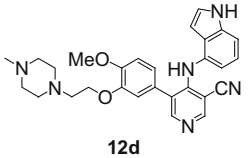


The efficient inhibition of curcumin to PfATP6 may be involved in its antimalarial mechanism.



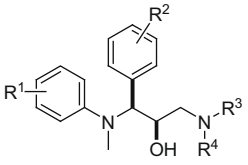
A

Tetrahydroquinoline A is a potent inhibitor of the cholesterol ester transfer protein (CETP), a target for the treatment of low HDL-C and atherosclerosis. Compound A inhibits partially purified CETP with an IC_{50} of 39 nM. The structure–activity relationship of a series of inhibitors of CETP is described herein.

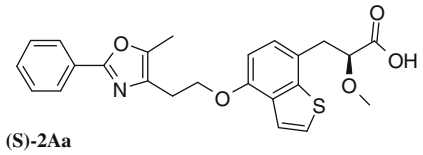


12d

The synthesis and PKCθ inhibitory activity of a series of 4-indolylamino-5-phenyl-3-pyridinecarbonitriles is described. SAR studies led to the identification of compound **12d** as a potent inhibitor of PKCθ.



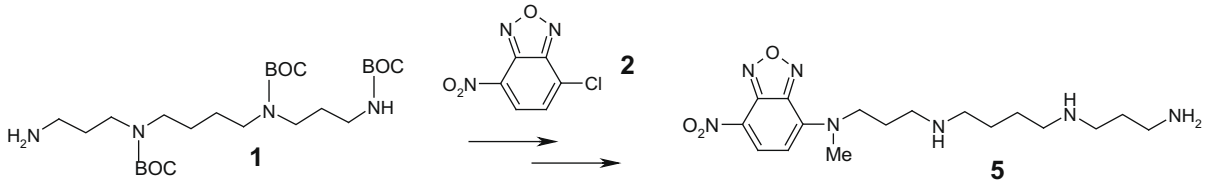
A series of 3-(arylamino)-3-phenylpropan-2-olamines was prepared. A number of analogues displayed significant dual norepinephrine and serotonin reuptake inhibition. Compounds in this class exhibited minimal affinity for the dopamine transporter.



Aleglitazar

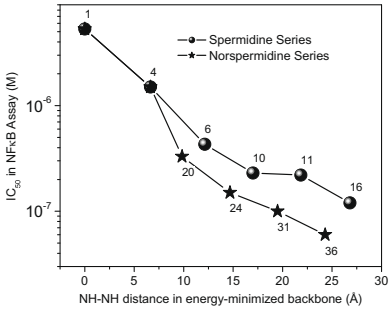
PPAR α IC50 (μM) 0.038 EC50 (μM) 0.050

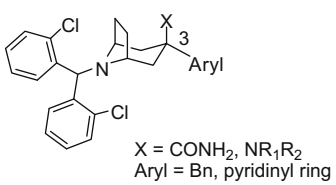
PPARγ IC50 (μM) 0.019 EC50 (μM) 0.021

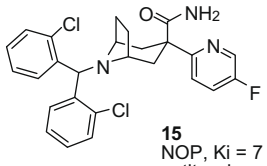


N_1-Methylspermine NBD **5** was synthesized from 4-chloro-7-nitrobenzo[1,2,5]oxadiazole (NBD) **2** and protected spermine **1**. **5** was used as a fluorescent probe to select polyamine transport system (PTS) expressing cells, sensitive to cytotoxic compounds vectored through the PTS.

In exploring the relationship between variously elongated *N*-alkyl spermidine and norspermidine, norspermine-type compounds consistently showed higher lipopolysaccharide-sequestering activities.

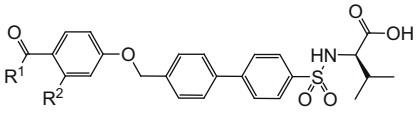




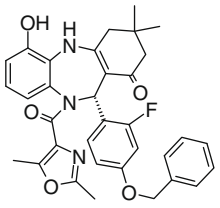


15
NOP, Ki = 7 nM
antitussive activity (GP): ED_{50} 0.02 mg/kg (2h)
anxiolytic-likeactivity (GPPV): ED_{50} 0.3 mg/kg

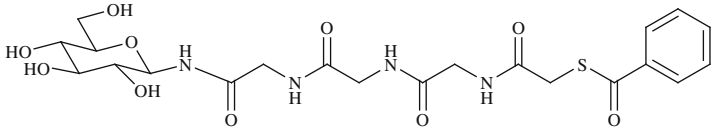
A series of 3-disubstituted-nortropane analogs have been identified to bind to the nociceptin receptor with high affinity. The syntheses and structure–activity relationships of these analogs are described. Compound **15** was identified to possess potent oral antitussive and anxiolytic-like activities in the guinea pig models.



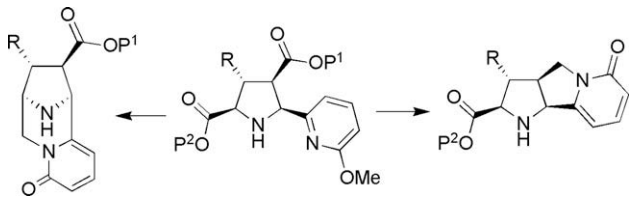
A subset of ((4-keto)-phenoxy)methyl biphenyl-4-sulfonamides were identified as potent Agg-1, MMP-2 and MMP-13 inhibitors through the synthesis of a series of (Phenoxy)methyl biphenylsulfonamide carboxylates.

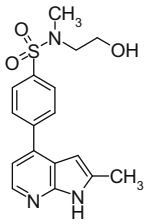


(*R*)-11zk
NS5B IC_{50} = 29 nM
Replicon EC_{50} = 270 nM

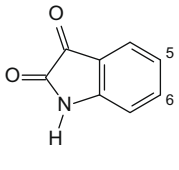


A novel **D-glucose**-MAG_3 derivative was synthesized and evaluated as diagnosis agent for tumor.

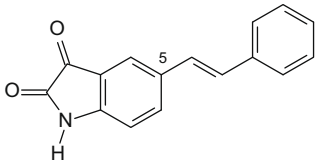




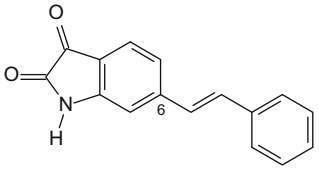
The synthesis and SAR of 4-aryl-7-azaindoles as ATP-competitive IKK2 inhibitors is described. Modification around the hinge binding region of the 7-azaindole led to a series of potent and selective inhibitors with good cellular activity.



Isatin (**1**): K_i = 3 μM (MAO-B)
K_i = 15 μM (MAO-A)

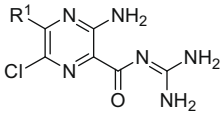


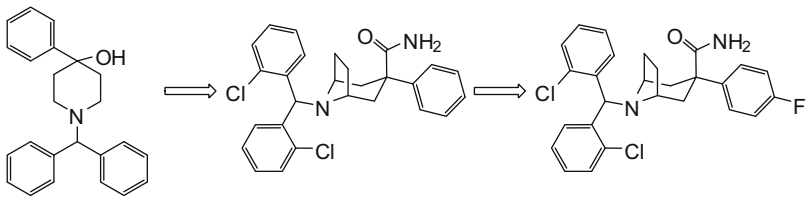
4a: K_i = 0.31 μM (MAO-B)
K_i = 0.78 μM (MAO-A)



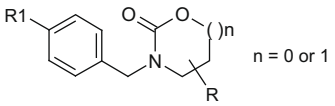
5: K_i = 0.56 μM (MAO-B)
K_i = 22 μM (MAO-A)

Using the small molecule isatin (**1**) as lead compound, (*E*)-5-styrylisatin (**4a**–**c**) and (*E*)-6-styrylisatin (**5**) analogues were synthesized and found to be more potent as inhibitors of MAO-B than was isatin. Similar to isatin, these analogues also inhibited MAO-A.

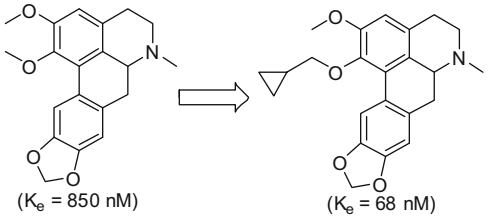




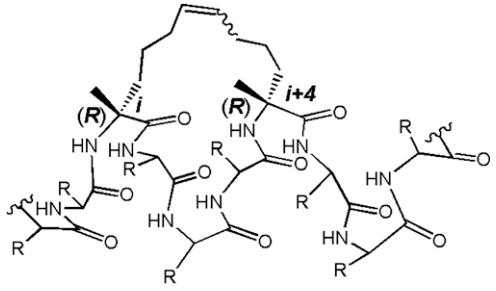
1 **24** **32**



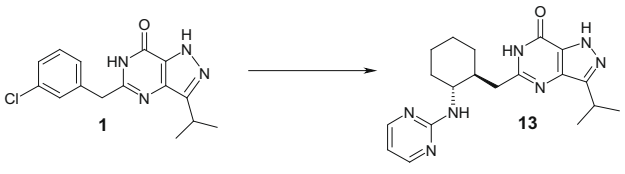
The discovery, synthesis and SAR of a novel series of 3-benzyl-1,3-oxazolidin-2-ones as positive allosteric modulators (PAMs) of mGluR2 is described which led to potent, metabolically stable and orally available mGluR2 PAMs.



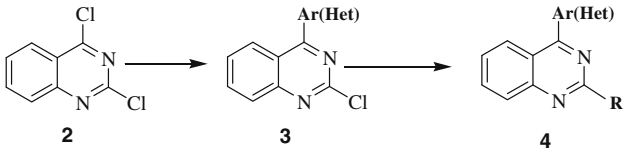
Evaluation of nantenine analogs at human 5-HT$_{2A}$ receptors is reported.

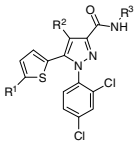


An analysis of stereochemical effects of the hydrocarbon crosslink on the helical stability and cellular uptake of *i*,*i*+4 stapled peptides reveals that *S*,*S* is superior in both respects to *R*,*R*.

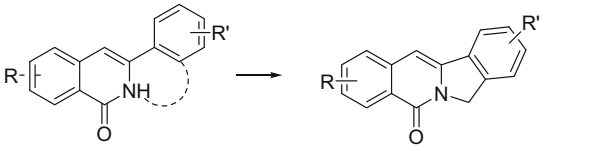


Starting from the non-selective lead **1**, the sequential use of library and directed synthesis led to the optimized PDE9 inhibitor **13**.

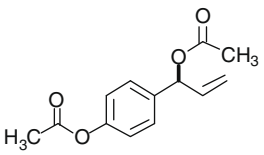




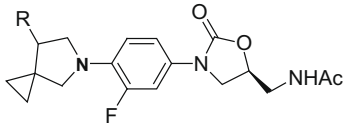
2-11



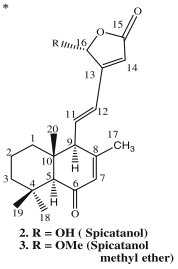
3-Arylisoquinoline (**2**) 7*H*-Isoindolo[2,1-*b*]isoquinolin-5-one (**4**)

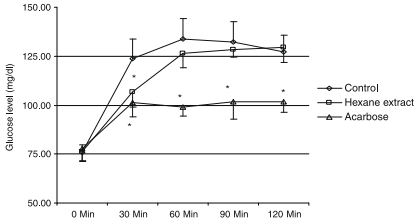


A new Rev export inhibitor, 1′-acetoxychavicol acetate (**1**) was disclosed *Alpina galanga* through bioassy guided separation. Both biotinylated probe (**2**) and several synthesized analogs clarified crucial portions in **1**.

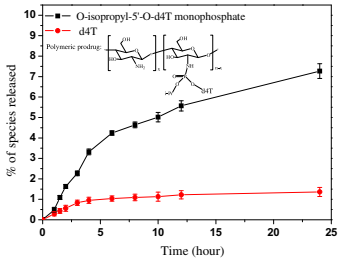


The synthesis of a new series of oxazolidinones having spiro[2,4]heptane moieties is described. Their in vitro antibacterial activities against both Gram-positive and Gram-negative bacteria were tested and the effect of substituents on the oxazolidinone ring was investigated. A particular compound **Ih** having fluoro group showed the most potent antibacterial activity.

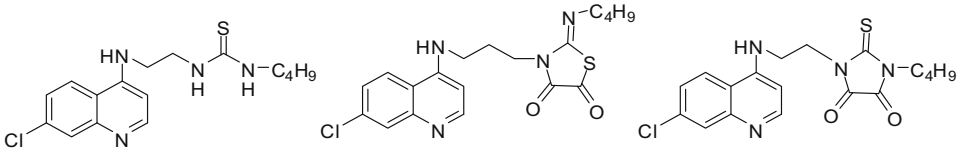




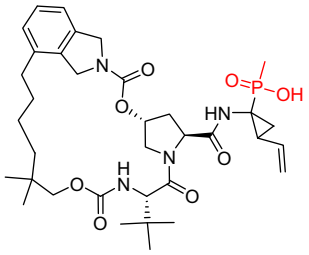
Antihyperglycemic extract of the rhizomes of *Hedychium spicatum* yielded two new labdane diterpenes, spicatanol (**2**) and spicatanol methyl ether (**3**) as novel intestinal α-glucosidase inhibitors along with other known compounds, possessing varying degree of α-glucosidase inhibitory potentials.



This work describes the novel synthesis of chitosan–*O*-isopropyl-5′-*O*-d4T monophosphate conjugate, allowing a sustained release of d4T 5′-(*O*-isopropyl)monophosphate for antiretroviral treatment.



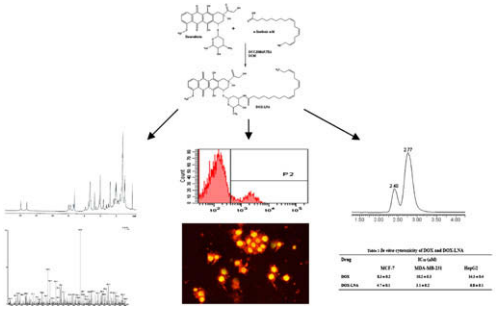
New prototypes of thiourea, thiazolidinedione and thioparabanic acid derivatives of 4-aminoquinoline were synthesized and screened for their antimalarial activities. Among all, compound **3** found to be the most active against both chloroquine sensitive strain 3D7 of *Plasmodium falciparum* and chloroquine resistant strain N-67 of *Plasmodium yoelii* with a suppression of 99.27% on day 4 in an in vivo assay.

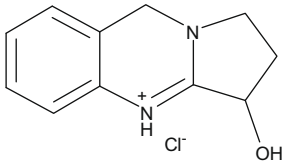


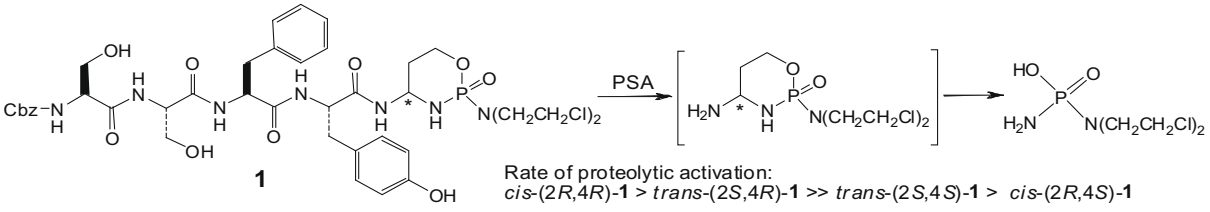
K_i (1b) = 0.0024 μM

EC_{50} (10% FCS) = 0.50 μM

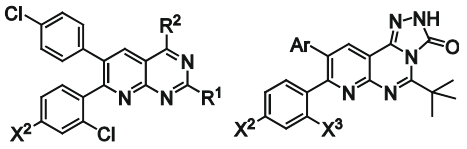
EC_{50} (50% NHS) = 0.25 μM

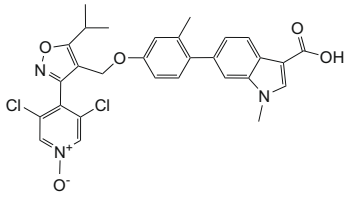




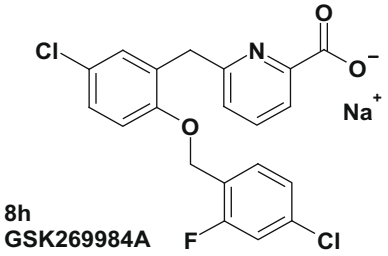


Rate of proteolytic activation:
cis-(2*R*,4*R*)-**1** > *trans*-(2*S*,4*R*)-**1** >> *trans*-(2*S*,4*S*)-**1** > *cis*-(2*R*,4*S*)-**1**





A series of 3-aryl heterocyclic isoxazole analogs were designed and synthesized, N-oxide pyridine analog (**7b**) was identified as a promising FXR agonist with potent binding affinity and good efficacy.



This Letter details the discovery of GSK269984A (**8h**) which was selected as a clinical development candidate for the treatment of inflammatory pain.

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