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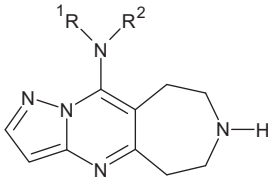
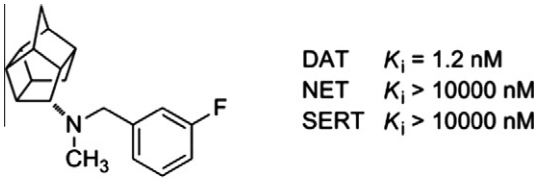
Bioorganic & Medicinal Chemistry Letters Volume 21, Issue 1, 2011

Contents

REGULAR ARTICLES

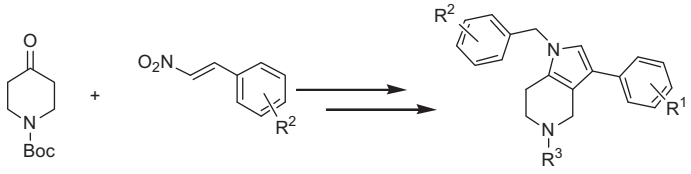


A new class of potent and selective 5-HT$_{2C}$ agonists for the treatment of metabolic disorders is described. Optimization of selectivity, permeability and hERG interaction is discussed.

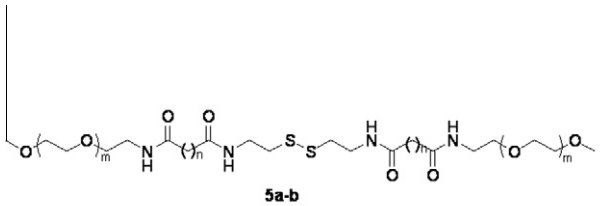


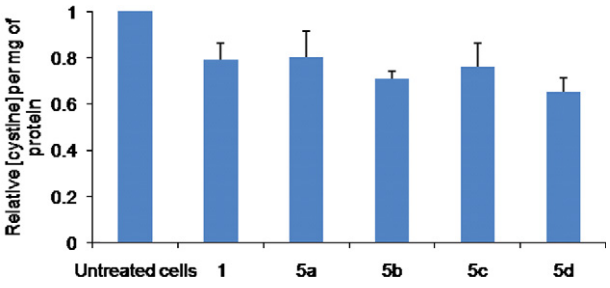
12

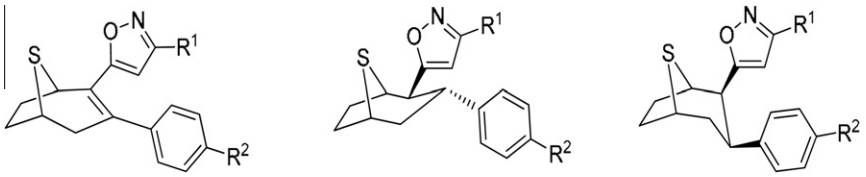
The in vitro affinity of a series of N-substituted *N*-methyl-8-aminopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes for monoamine transporters DAT, NET, and SERT, is reported. Compound **12** was identified as a high affinity DAT ligand with excellent selectivity over the NET and SERT.



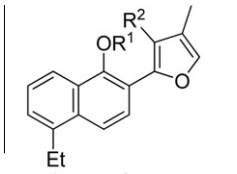
The synthesis and SAR for a novel series of tetrahydropyrido[3,2-*c*]pyrroles is described. Representative compounds are functional antagonists at the 5-HT$_7$ receptor and demonstrate activity in a rat pharmacodynamic model of 5-HT$_7$ activity.



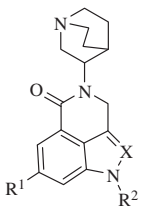




The 2-(3-methylisoxazol-5-yl)-3-aryl-8-thiabicyclo[3.2.1]octanes are potent and selective inhibitors of the Dopamine Transporter (DAT). Isoxazoles **6c** (3β-(4-fluorophenyl)) and **6d** (3β-(4-chlorophenyl)) inhibit the DAT (IC_{50} = 7 nM) and are inactive at Serotonin Transporter inhibition (IC_{50} >1000 nM).

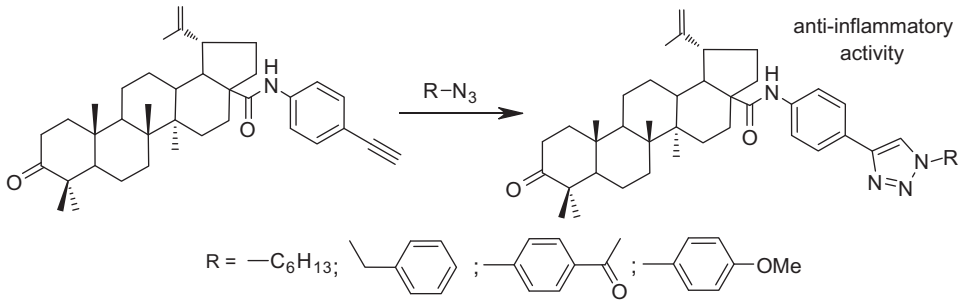


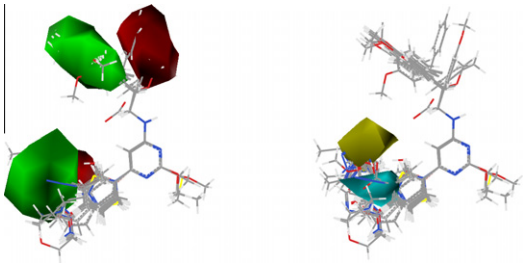
3: R^1 = H, R^2 = CO_2H
7: R^1 = Me, R^2 = CO_2Et
14: R^1 = Me, R^2 = CH_2OH
15: R^1 = Et, R^2 = CH_2OH
19: R^1 = Me, R^2 = CH_2Br



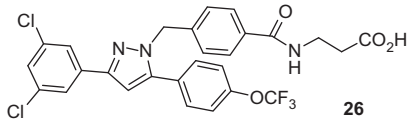
X = N or CH

Selective, low intrinsic activity 5-HT_3 receptor partial agonists with good oral activity are described.



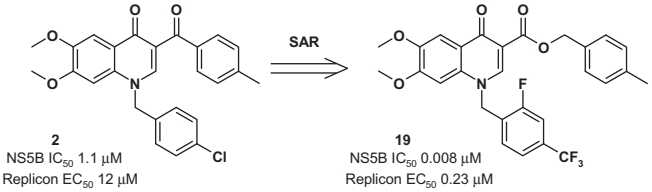


CoMSIA model of 2,6-substituted-4-monosubstituted aminopyrimidine antagonists of prostaglandin D_2 receptor (DP1) is reported. The utility of this QSAR model in chemical lead optimization is discussed.



26

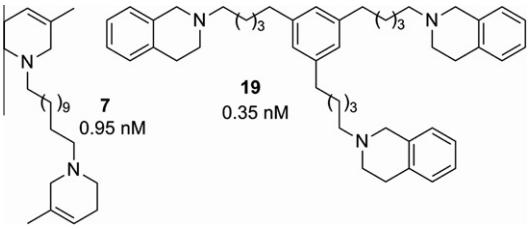
The discovery and SAR study of a novel 1,3,5-pyrazole series of human glucagon receptor antagonists represented by **26** are presented. Compound **26** was selective and orally active in several in vivo preclinical models of type II diabetes.



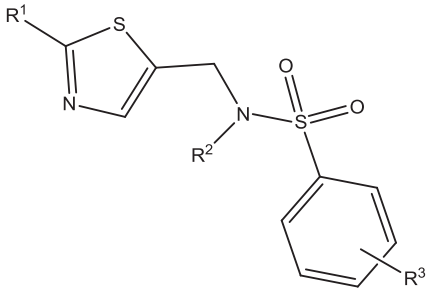
2
NS5B IC_{50} 1.1 μM
Replicon EC_{50} 12 μM

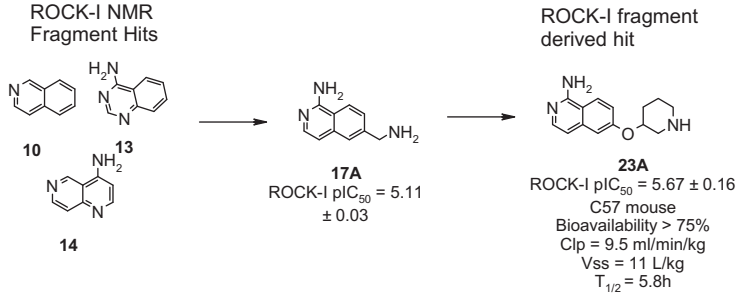
19
NS5B IC_{50} 0.008 μM
Replicon EC_{50} 0.23 μM

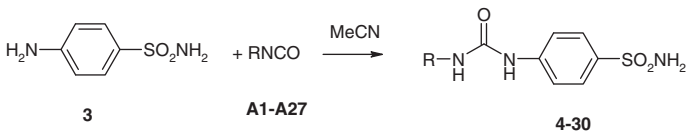
Hepatitis C virus (HCV) infection is treated with a combination of peginterferon alfa-2a/b and ribavirin. To address the limitations of this therapy, numerous small molecule agents are in development, which act by directly affecting key steps in the viral life-cycle. Herein we describe our discovery of quinolone derivatives, novel small-molecules that inhibit NS5b polymerase, a key enzyme of the viral life-cycle. Our SAR led us from keto-quinolones such as **2** to benzyl esters such as **19** with attractive enzyme inhibition and cell-based replicon activity. This class of compounds binds to an allosteric site of NS5B polymerase (NNI-2) as confirmed through a co-crystal structure of a representative compound to NS5B.



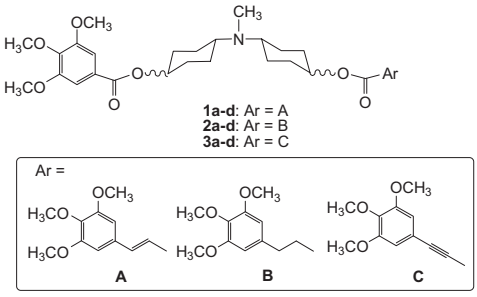
A series of tertiary amine analogs derived from lead azaaromatic quaternary ammonium salts has been designed and synthesized. The bis-tertiary amine analog **7** exhibited an IC_{50} of 0.95 nM, while the tris-tertiary amine analog **19** had an IC_{50} of 0.35 nM at nAChRs mediating nicotine-evoked dopamine release.

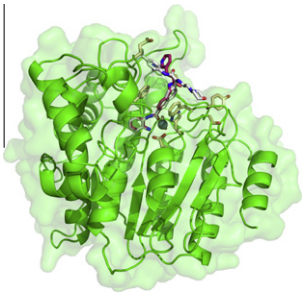


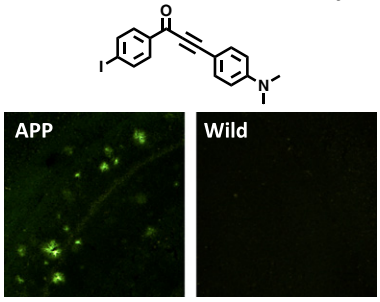


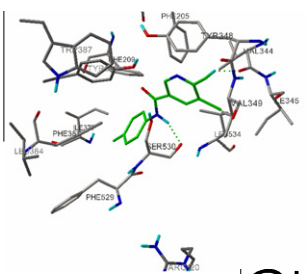


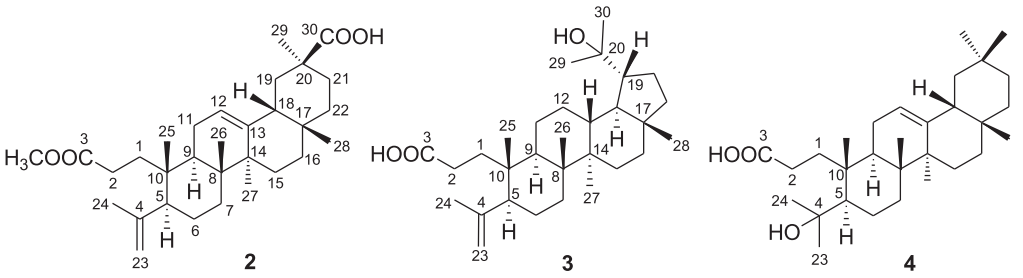
K_i (hCA II) = 2.1–9600 nM; K_i (*C. albicans*) = 3.4–3970 nM; K_i (Rv1284) = 4.8–6500 nM; K_i (Rv3273) = 6.4–6850 nM.



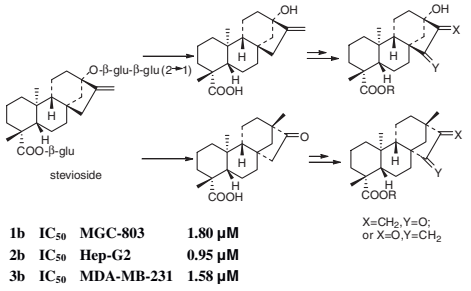


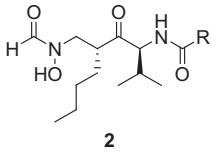




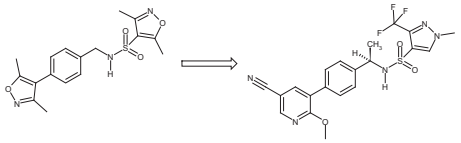


Five new ring A-*seco* triterpenoids, dysoxyhainic acids F–J (**1**–**5**), along with a known ring A-*seco* triterpenoid koetjapic acid (**6**) were isolated from the twigs and leaves of *Dysoxylum hainanense*. Compounds **2**–**4** and **6** exhibited significant antimicrobial activity against Gram-positive bacteria.

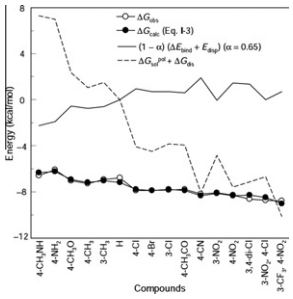


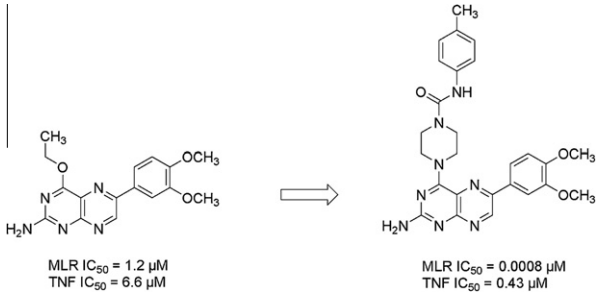


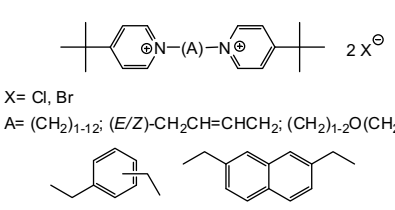
The synthesis and structure–activity relationship studies of peptide deformylase inhibitor **2** are reported.

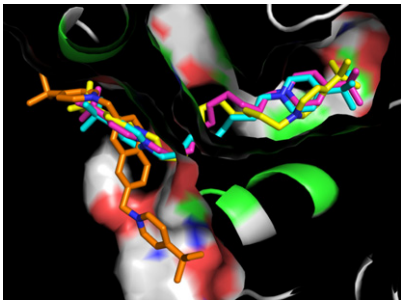


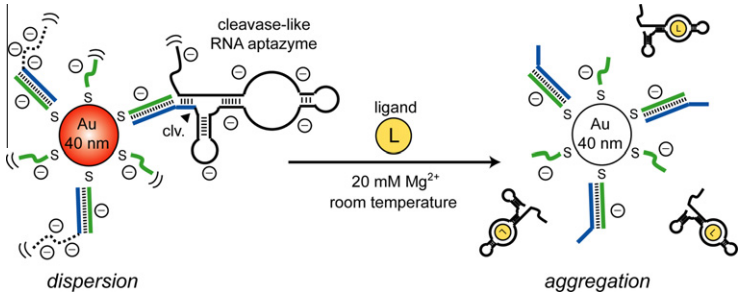
High-throughput screening of 3.87 million compounds delivered a novel series of non-steroidal GR antagonists. Subsequent rounds of optimisation allowed progression from a non-selective ligand with a poor ADMET profile to an orally bioavailable, selective, stable, glucocorticoid receptor antagonist.

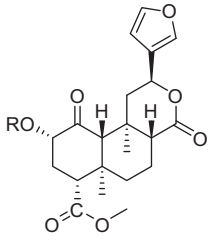


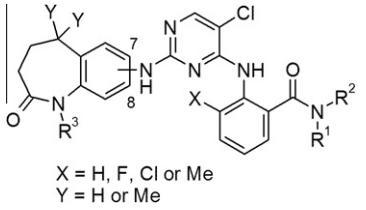


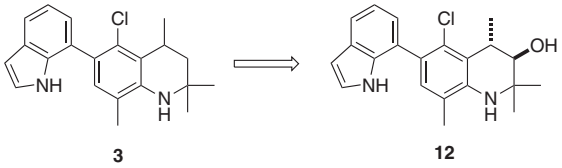


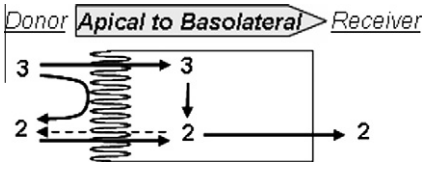


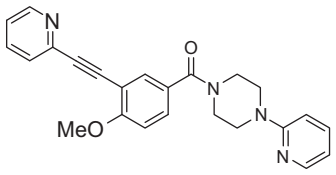




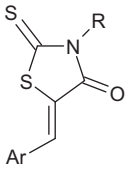




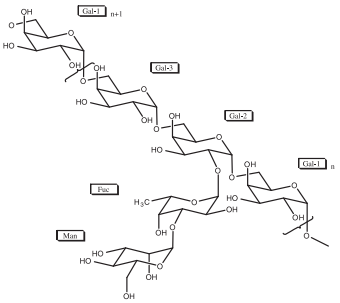


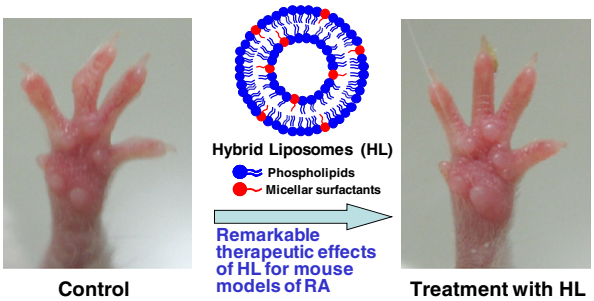


26
mGluR5 Ki: 21 nM
mGluR5 IC_{50}: 8 nM
po activity in 4-Plate and SIH

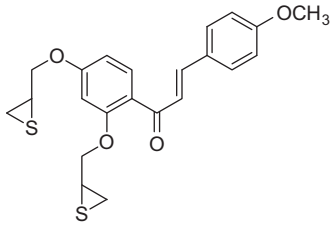


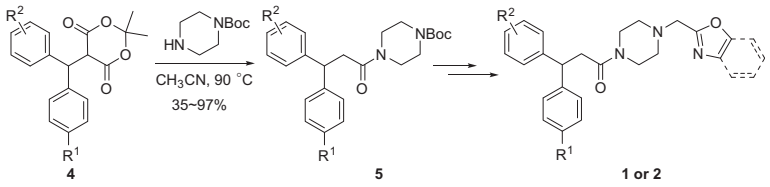
Chemical structure of fomitellan A, a polysaccharide with a mitogenic effect isolated from the fruiting bodies of *Fomitella fraxinea*, has been assigned as a mannofucogalactan with a repeating unit of penta-saccharide, which was composed of a (1→6)-linked D-galactopyranosyl backbone having a C-2 position substituted with disaccharide units of 3-*O*-D-mannopyranosyl-L-fucopyranosyl residue. The ^{1}H and ^{13}C NMR signals of fomitellan A have been completely assigned by extensive NMR experiments.

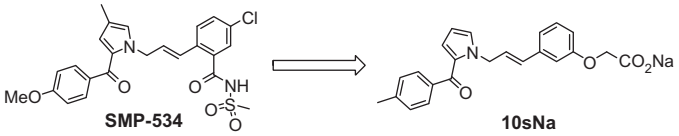




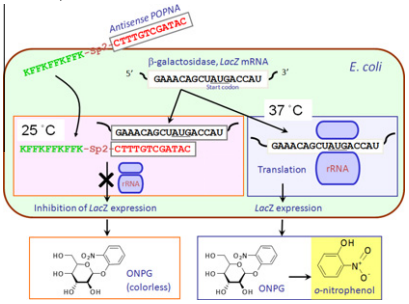
Remarkably high therapeutic effects without joint swelling were obtained in mouse models of RA treated with HL.



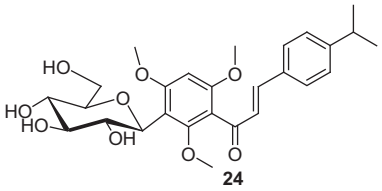




TGF-β signaling pathway inhibitor and potential anti-nephropathic agent SMP-534 was successfully converted to a new class of benzoylpyrrole-based PPARα/γ activators as an anti-diabetic agent. Compound **10sNa** showed a favorable blood glucose-lowering effect without body weight gain.

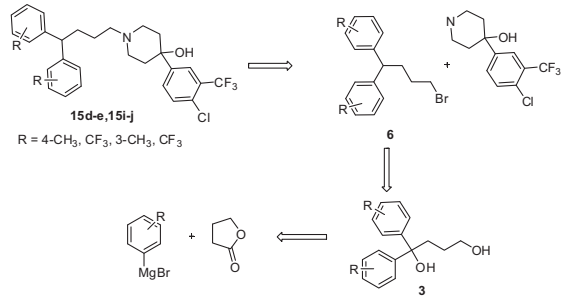


The antisense effect of the pyrrolidine-based oxy-peptide nucleic acid (POPNA) was equivalent to that of a Nielsen-type PNA. The POPNA could switch its antisense effect (*LacZ* activity) over a wide range of ambient temperatures.

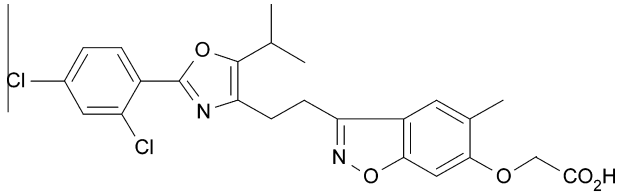


24

Various phenolic C-glycosides were evaluated for their in vitro and in vivo antihyperglycemic activity employing glucose uptake by rat muscle cell lines (L-6) and low dosed-streptozotocin-induced diabetic rats, respectively. The compound **24** lowered the blood glucose levels by 34.9% and 33.6% during 5 h and 24 h, respectively, at the dose of 25 mg/kg body weight which is comparable to standard antidiabetic drug metformin.

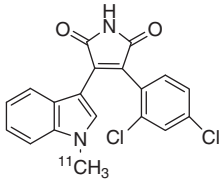


A novel type of diphenylbutylpiperidines as autophagy inducers has been synthesized via new route and some of them showed 10-fold greater activity comparable to lead compound.



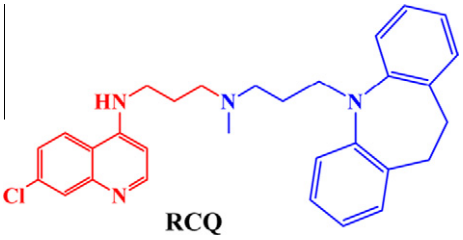
20

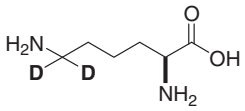
We have succeeded in synthesizing a novel PPARδ selective agonist, compound **20**, characterized by a benzisoxazole ring. Compound **20** exhibited a potent hPPARδ transactivation activity and high δ selectivity. Compound **20** stimulated oligodendrocyte differentiation of primary oligodendrocyte precursors cells in vitro, indicating that it may be an effective drug to treat demyelinating disorders, such as multiple sclerosis.

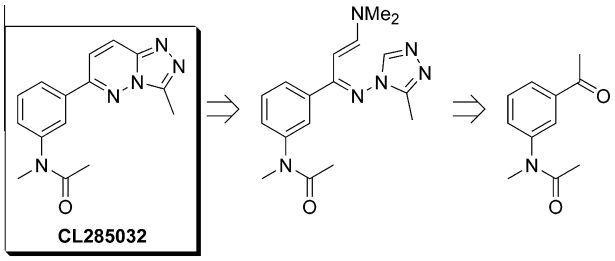


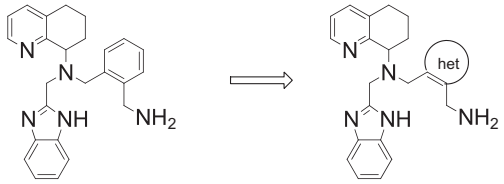
[^{11}C]SB-216763

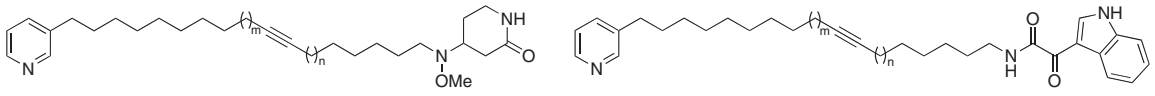
Radiosynthesis of [^{11}C]SB-216763, a new potential PET agent for imaging of glycogen synthase kinase (GSK-3), is first reported.

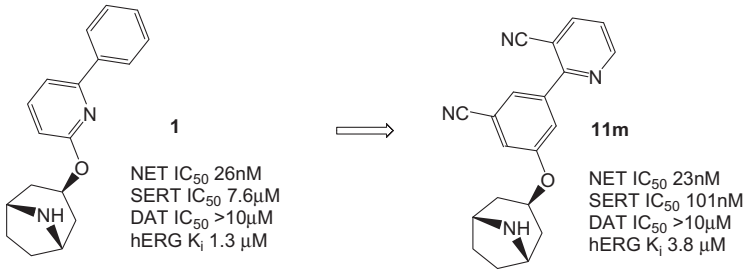


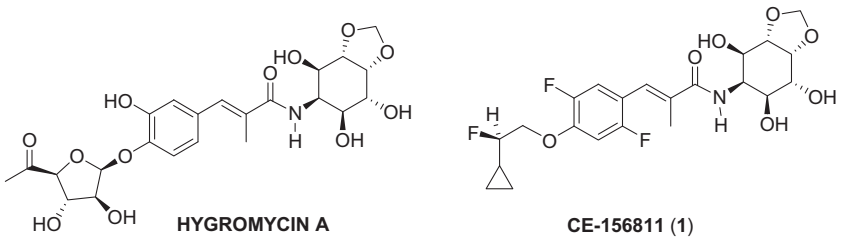


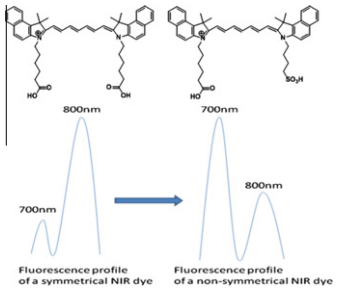


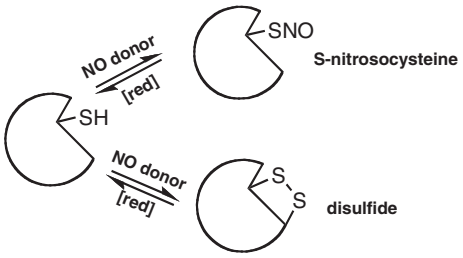


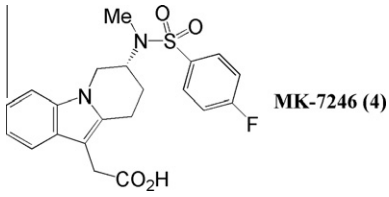


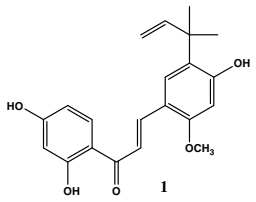


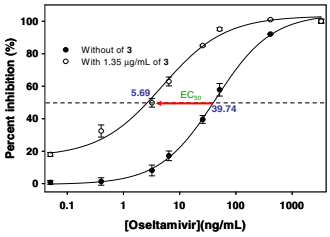




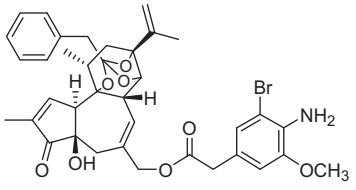




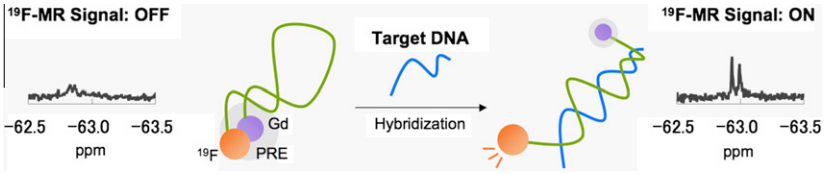


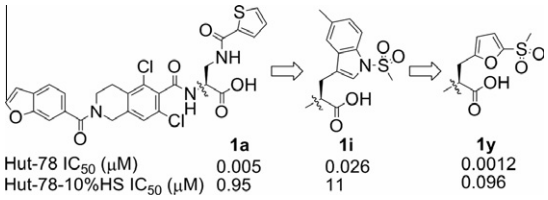


One new licochalcone G (**1**) and seven known (**2**–**8**) chalcones were isolated as inhibitory principles on influenza A virus from the acetone extract of *Glycyrrhiza inflata*. Compounds **3** and **6** without prenyl group showed strong inhibitory effects on various neuraminidases from influenza viral strains, H1N1 and H9N2, and more novel H1N1 (WT) and oseltamivir-resistant novel H1N1 (H274Y) expressed in 293T cells. In addition, the efficacy of oseltamivir with the presence of compound **3** (5 μM) was increased against H274Y neuraminidase.

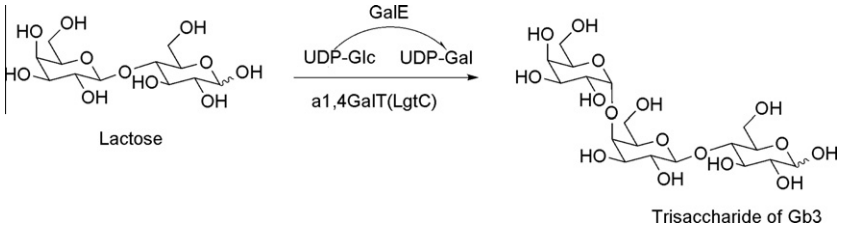


39 Ki(ant) = 2.81 nM

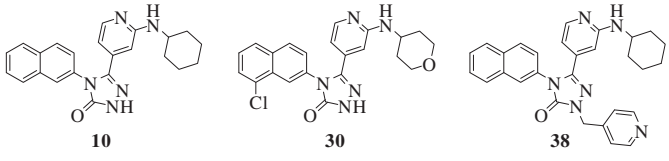


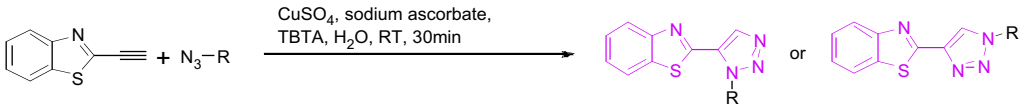


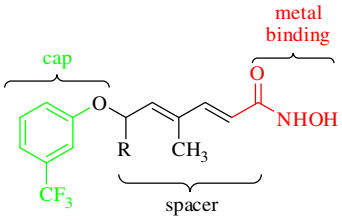
Structure–activity relationship (SAR) of the α-amino acid residue and identification of (*S*)-2,3-diaminopropanoic acid (DAP) replacements of potent tetrahydroisoquinoline (THIQ)-derived LFA-1/ICAM-1 antagonists are described.



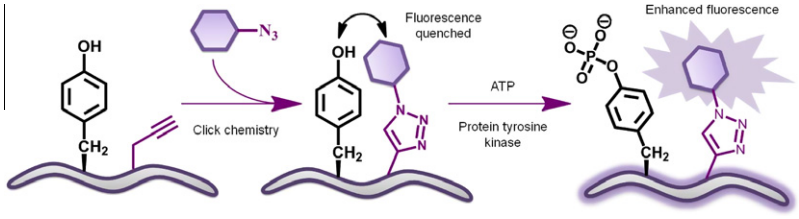
In this Letter, we describe the discovery of selective JNK2 and JNK3 inhibitors, such as **10**, that routinely exhibit >10-fold selectivity over JNK1 and >1000-fold selectivity over related MAPKs, p38α and ERK2. Substitution of the naphthalene ring affords an isoform selective JNK3 inhibitor, **30**, with approximately 10-fold selectivity over both JNK1 and JNK2. A naphthalene ring penetrates deep into the selectivity pocket accounting for the differentiation amongst the kinases. Interestingly, the gatekeeper Met146 sulfide interacts with the naphthalene ring in a sulfur-π stacking interaction. Compound **38** ameliorates neurotoxicity induced by amyloid-β in human cortical neurons. Lastly, we demonstrate how to install propitious in vitro CNS-like properties into these selective inhibitors.

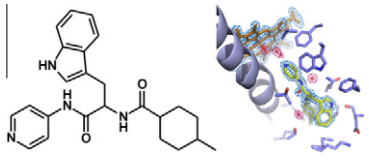


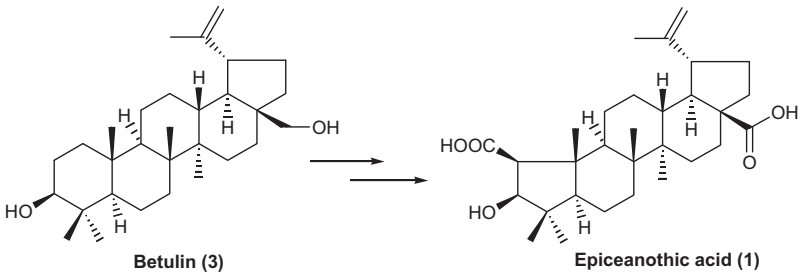




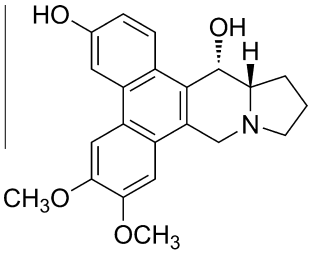
19f
HDAC Inhibition IC_{50} = 18 nM



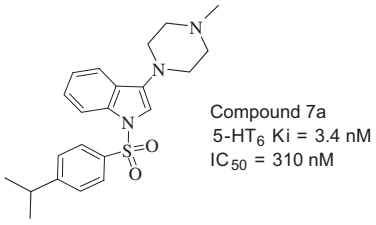




The asymmetric total synthesis of the strongly cytotoxic phenanthroindolizidine alkaloid **3** was achieved. Using the same route, various derivatives were also synthesized. Cytotoxicity of those synthetic compounds and the in vivo antitumor efficacy of selected compounds were evaluated.

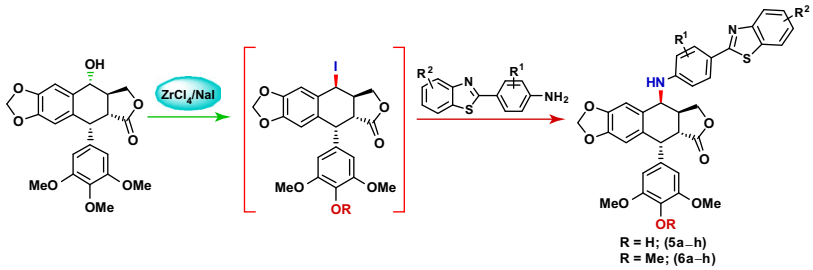


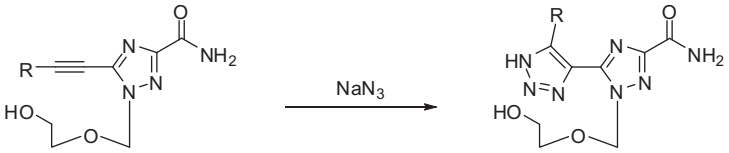
3



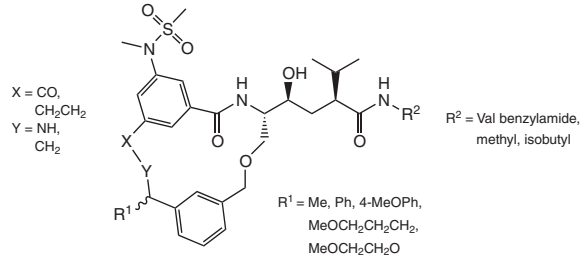
Design, synthesis and SAR of a novel series of N_1-arylsulfonyl-3-piperazinyl indole derivatives as 5-HT6 receptor ligands are reported.

A facile one-pot zirconium tetrachloride and sodium iodide mediated iodination protocol has been applied for the synthesis of benzothiazolo-4β-anilino-podophyllotoxin (**5a**–**h**) and benzothiazolo-4β-anilino-4-*O*-demethylepipodophyllotoxin (**6a**–**h**) congeners. Some of these compounds have shown significant in vitro cytotoxicity on selected human cancer cell lines apart from DNA topoisomerase-II inhibition activity.

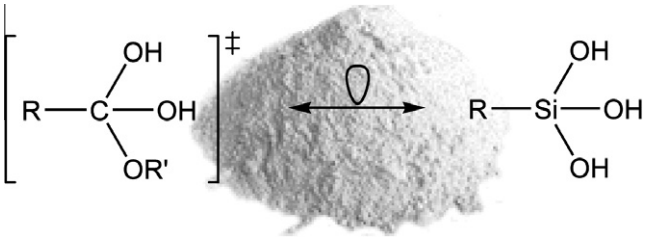




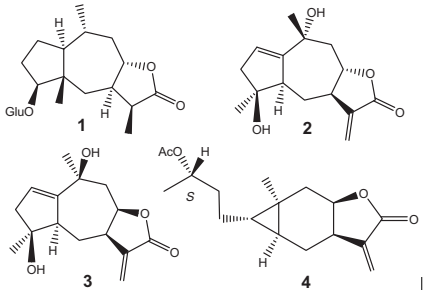
A family of novel bitriazolyl acyclonucleosides were synthesized via the Huisgen reaction by addition of NaN_3 onto the triazole nucleosides bearing internal alkynyl groups introduced at the 5-position of the triazole ring. Some of the synthesized compounds exhibited interesting antiviral activity against tobacco mosaic virus.

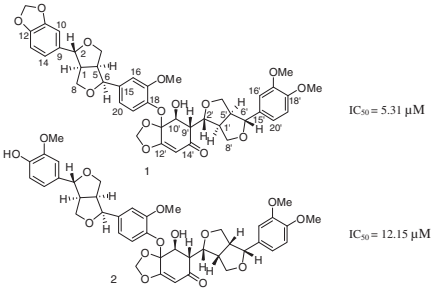


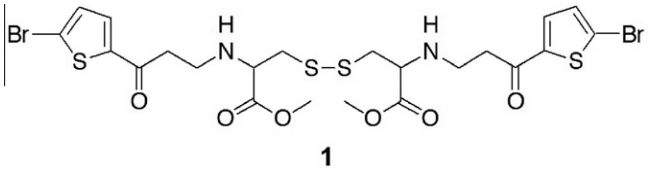
Eight 15–16-membered peptidomimetic macrocycles with the HE scaffold were synthesized and evaluated for their in vitro renin inhibitory activities.



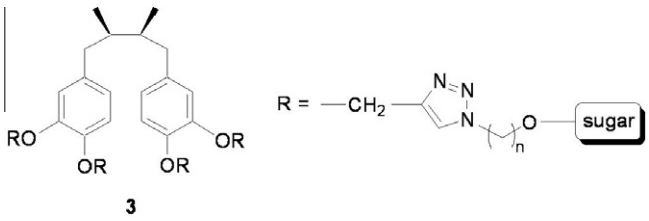
Four new (**1**–**4**) and 13 known sesquiterpene lactones together with two known diterpenes were isolated from *Carpesium faberi*. All isolated compounds were evaluated for their antiproliferative activities against MCF-7 human breast cancer cells using the MTT assay. The sesquiterpene lactones (except tomentosin **17**) possessing an α-methylene-γ-lactone moiety were found to have significant antiproliferative activities. The cell cycle-specific inhibition and apoptosis induced by selected compounds were investigated using flow cytometry (FCM).



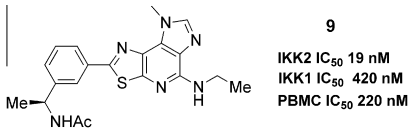




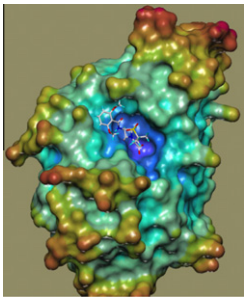
Potent transglutaminase inhibitors were obtained from disulfide compounds, cystamine, dimethyl cystine, and dimethyl homocystine. The disulfide bond and thiophene ring play an important role in inhibitory activity of synthesized aryl β-amino ketones.

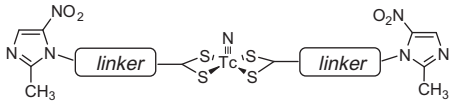


Perglycosylated nordihydroguaiaretic acids were synthesized through the Huiseng 1,3-dipolar cycloaddition reaction, which possessed good water solubility and activity against Hep3B cell line.

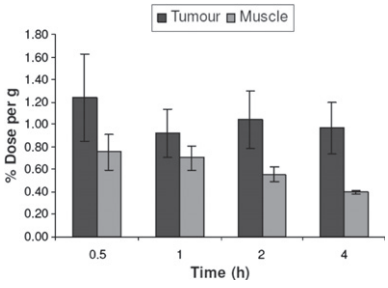


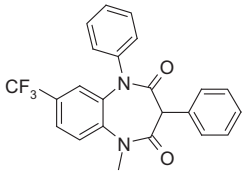
The synthesis, structure–activity relationships (SAR) and biological evaluation of thiazole based tricyclic inhibitors of IKK2 are described. Compound **9** was determined to be efficacious in a murine model for rheumatoid arthritis.





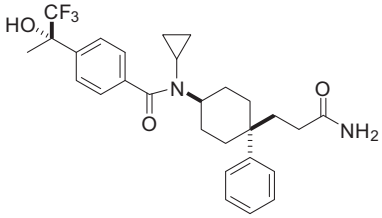
dtcTc1, dtcTc2





48

IC_{50} 1.2 μM
EC_{50} 3.0 μM
CC_{50} >20 μM



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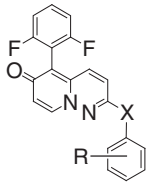
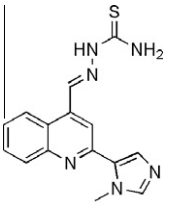
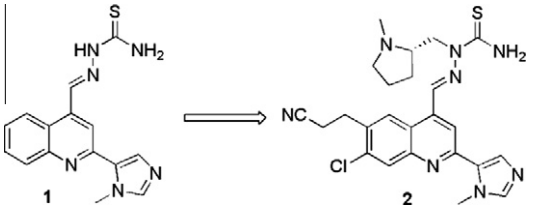
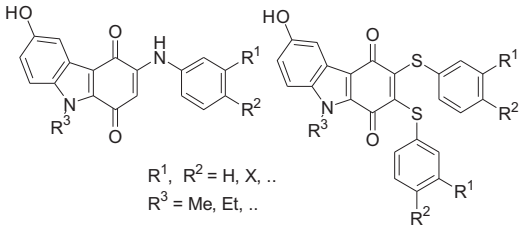


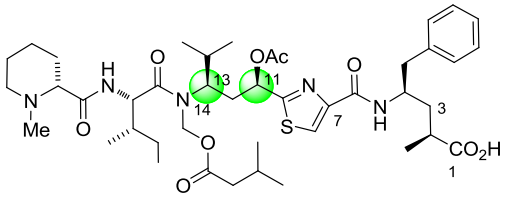


1

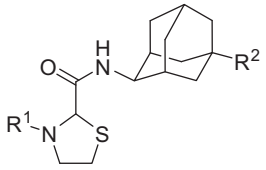


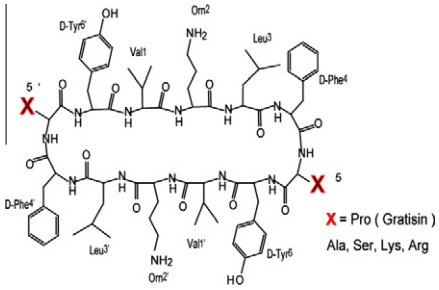


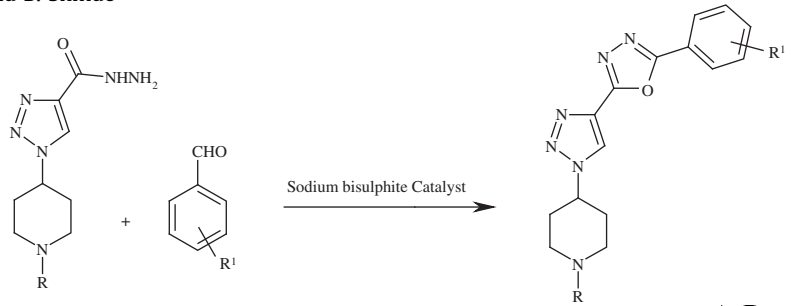
6-Hydroxy-1*H*-carbazole-1,4(9*H*)-diones were synthesized and tested for in vitro antifungal activity against fungi. Many of these tested compounds exhibited potent antifungal activity.

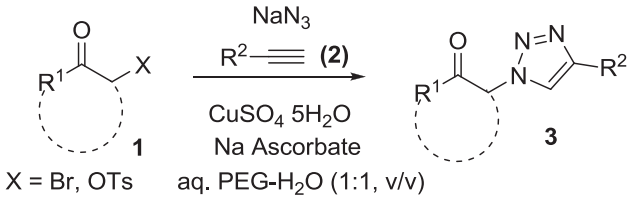


Tubulysin D

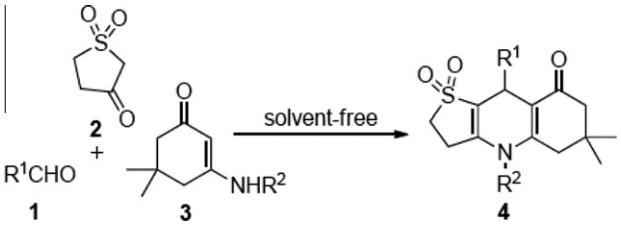






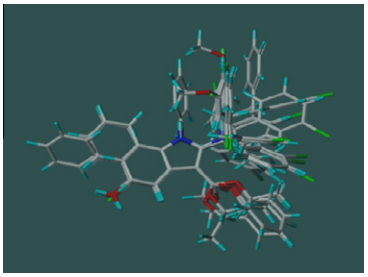


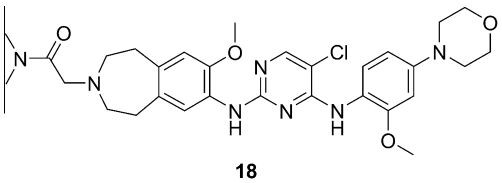
The synthesis and Src kinase inhibitory activity of two classes of 1,4-disubstituted 1,2,3-triazoles are reported.



A series of thieno[3,2-*b*]quinoline derivatives designed based on A-278637 scaffold, were synthesized efficiently via one-pot three-component reaction under solvent-free and catalyst-free conditions. This work provides a new compound library with potential biological activity for biomedical screening.

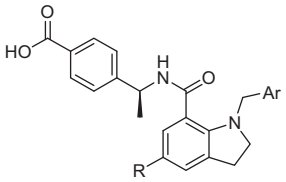
In this Letter, CoMFA and CoMSIA were performed on a series of 2-substituted 5-hydroxyindole-3-carboxylate derivatives as potent 5-LOX inhibitors. The data generated from the present study will further help design and validate novel and potent 5-LOX inhibitors.

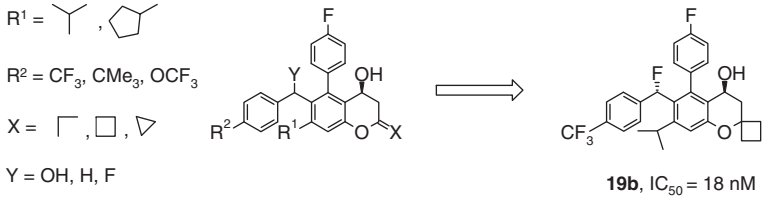




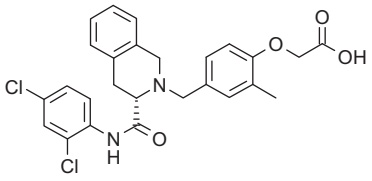
18

ALK IC_{50} = 4 nM



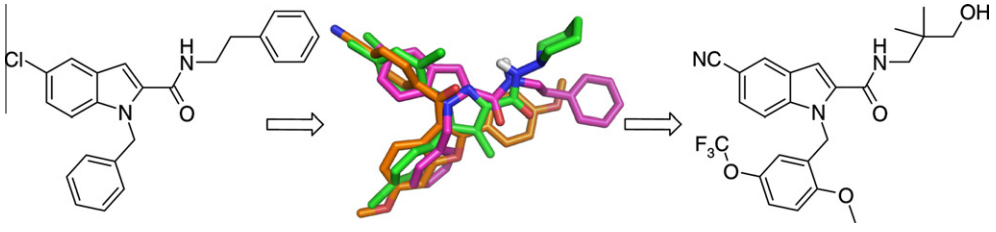


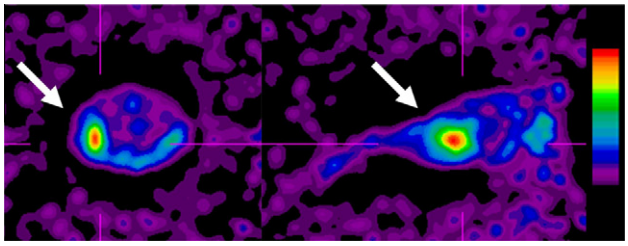
A novel chemical class of active cholesteryl ester transfer protein (CETP) inhibitors were prepared and an evaluation of the structure–activity relationships of these chromanols is described. Compound **19b** was identified as a potent CETP inhibitor with an excellent in vitro and PK-profile.

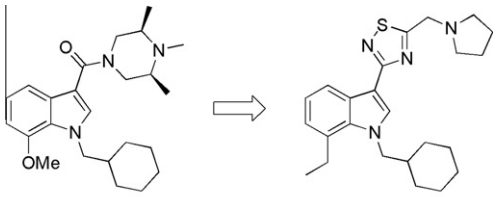


(*S*)-**18**, PPARδ EC_{50} = 5 nM

We describe the discovery of small molecule isoindoline and tetrahydroisoquinoline derivatives as agonists of human peroxisome proliferator-activated receptor δ (PPARδ that displayed excellent selectivity over the PPARα and PPARγ subtypes. Compound **18** demonstrated efficacy in upregulation of PDK4 in human primary myotubes, a biomarker for increased fatty acid oxidation.







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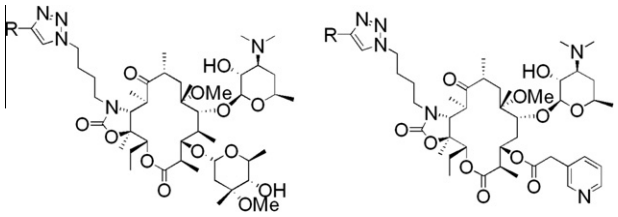
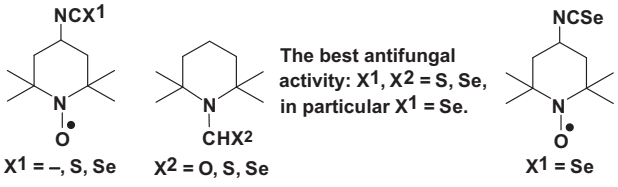
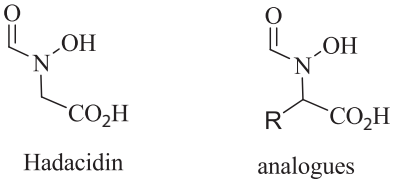
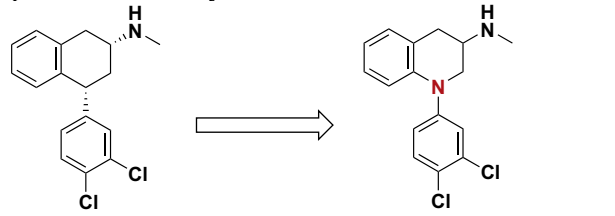


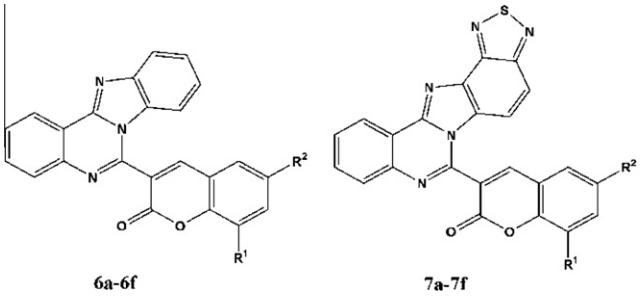
Two series of novel triazole containing 14-member macrolides having either a cladinose or a 3-pyridyl acetate group the 3-position of the macrolide ring were synthesized.

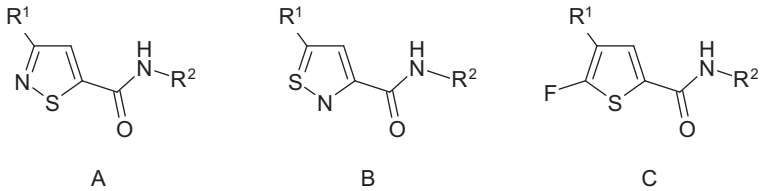


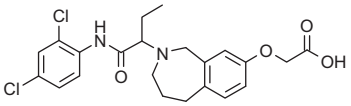




A series of 3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**6a**–**6f**) and 3-[benzothiadiazoleimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one (**7a**–**7f**) derivatives that incorporate a variety of substituents at the 6- and/or 8-positions of the coumarin moieties have been synthesized utilizing cellulose sulfuric acid as an efficient catalyst under both conventional heating and microwave irradiation procedures. These analogs were evaluated for their antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus pyrogenes* (Gram-positive bacteria); *Escherichia coli*, *Klebsiella pneumonia*, *Salmonella typhimurium* (Gram-negative bacteria); and *Aspergillus niger*, *Candida albicans*, and *Aspergillus flavus* (Fungi). Two analogs, **6c** (a 6,8-dichloro analog; $MIC_{[SA]}$ = 2.5 μg/mL; $MIC_{[ST]}$ = 2.5 μg/mL) and **7d** (a 6,8-dibromo analog; $MIC_{[ST]}$ = 2.5 μg/mL) were identified as potent antibacterial agents, and two analogs, **6b** (a 6-bromo analog; $MIC_{[AF]}$ = 10 μg/mL) and **6d** (a 6,8-dibromo analog; $MIC_{[AF]}$ = 15 μg/mL; $MIC_{[CA]}$ = 15 μg/mL), were identified as potent antifungal agents. Based on the MIC data, analogs **6b**, **6c**, **6d**, and **7d** were identified as the most potent antimicrobial agents in the series.



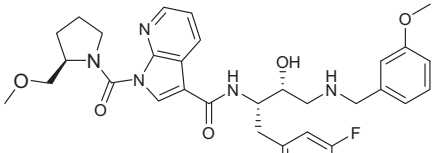




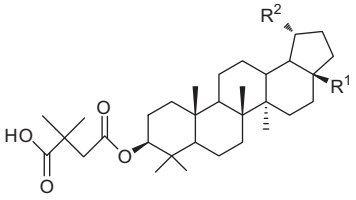
8 (single isomer): PPARδ EC_{50} = 3 nM

We describe the discovery of small molecule benzazepine derivatives as agonists of human peroxisome proliferator-activated receptor δ (PPARδ) that displayed excellent selectivity over the PPARα and PPARγ subtypes. Compound **8** displayed good PK in the rat and efficacy in upregulation of pyruvate dehydrogenase kinase, isozyme 4 (PDK4) mRNA in human primary myotubes, a biomarker for increased fatty acid oxidation.

Indole- and 7-azaindole-1,3-dicarboxamide hydroxyethylamines exhibited potent and selective inhibition of BACE-1. An optimized analog (**10n**) demonstrated good cellular potency and robust reductions in rat plasma Aβ levels after ip administration.

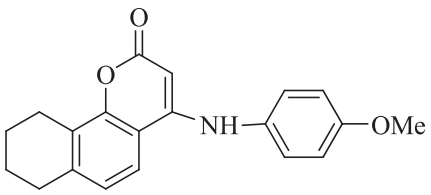


10n
BACE-1 IC_{50} = 10 nM
HEKSw IC_{50} = 26 nM



R^1 = CN, R^2 = $CH_3C{=}CH_2$ (**7**);
R^1 = HCO, R^2 = $HC(CH_3)_2$ (**18**);
R^1 = HCO, R^2 = $CH_3C{=}CH_2$ (**19**)

Newly synthesized triterpene derivatives were tested on HIV-1 activity and cellular toxicity. Compounds **7**, **18** and **19** manifested highest activity and therapeutic index, which are comparable with bevirimat.



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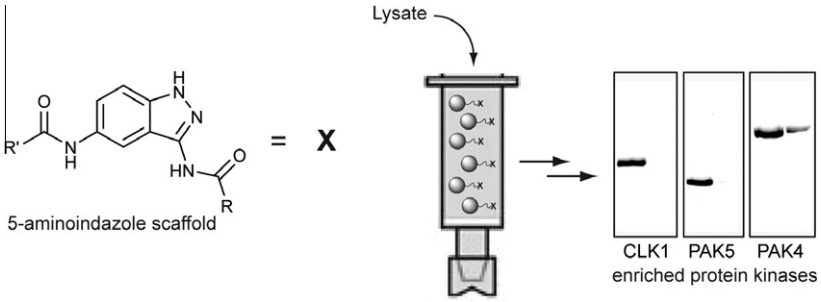
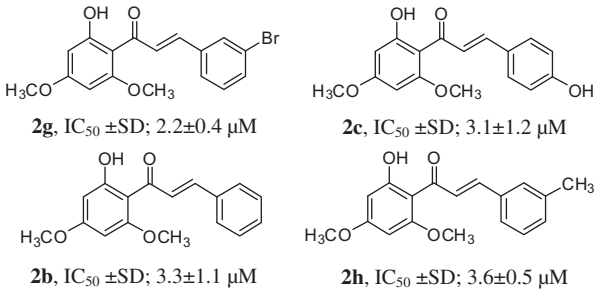
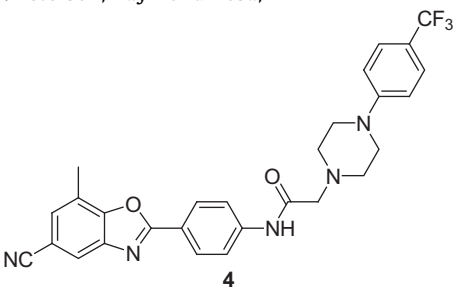
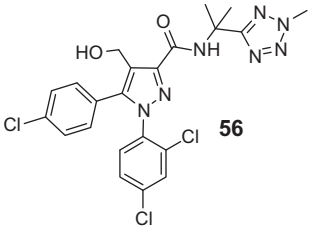
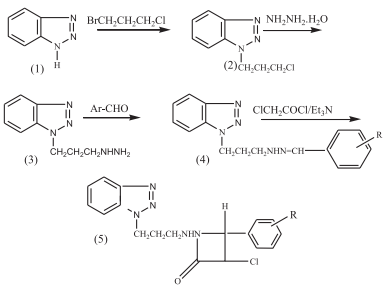


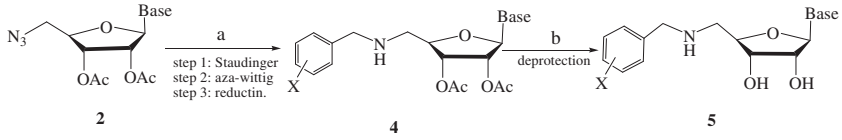


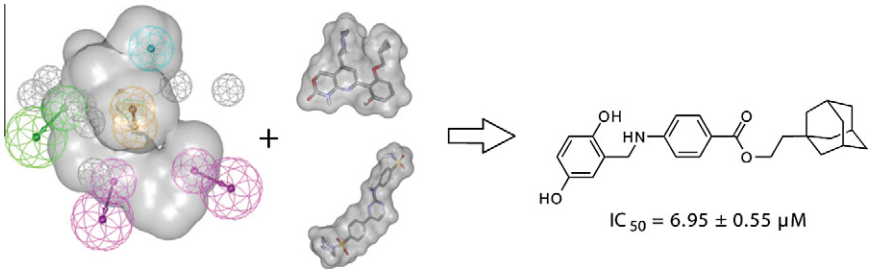


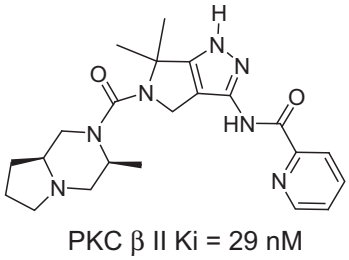




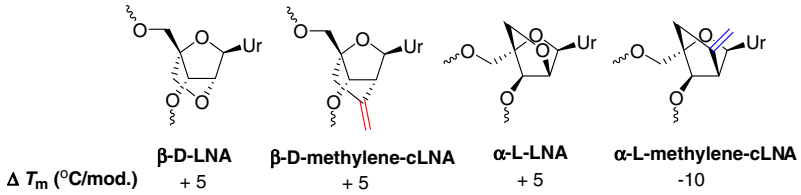
Some new kind of azetidinone derivatives of benzotriazole **5a–i** synthesized from *N*-[(benzylidene hydrazino)-propyl]-benzotriazole **4a–i**. The reaction was carried out by both conventional and microwave methods. Some azetidinone derivatives of benzotriazole displayed better antitubercular and antimicrobial activity.

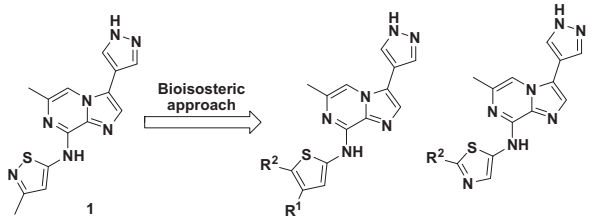




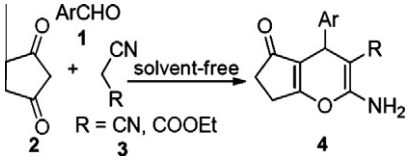


The discovery and initial SAR of a series of novel pyrrolopyrazole PKC β II inhibitors are reported.

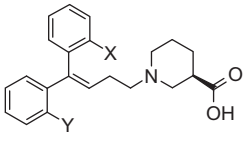




Our continued effort toward the development of the imidazo[1,2-*a*]pyrazine scaffold as Aurora kinase inhibitors is described. Bioisosteric approach was applied to optimize the 8-position of the core. Several new potent Aurora A/B dual inhibitors, such as **25k** and **25l**, were identified.



A series of 4-aryl-cyclopenta[*b*]pyran derivatives, designed based on natural product scaffold, were synthesized efficiently via multi-component reaction under solvent-free and catalyst-free conditions. This chemistry provides a new compound library with potential activity for biomedical screening.



6 X≠Y

Two complementary stereospecific syntheses of unsymmetrical 4,4-diphenylbut-3-enyl derivatives **6** (X ≠ Y) are reported. Structure–activity relationships of compounds **6** at the GAT-1 transporter are presented with the optimal substitution pattern leading to potency (**6ac**, X = Me, Y = F, fpK_i = 7.83) comparable to the clinical standard tiagabine.

OTHER CONTENT

*Corresponding author
Supplementary data available via ScienceDirect

COVER

Botulinum neurotoxins are the most deadly toxins known to man, approximately 10 million times more deadly than cyanide. Botulinum neurotoxins are classified by the US Centers for Disease Control (CDC) as bioterrorism agents. The etiological agent responsible for botulinum intoxication is a metalloprotease; as such this is a key therapeutic target. Currently, there are no approved pharmacological treatments for botulinum intoxication. Discovering molecules that could be used as a path forward for therapeutic development as botulinum protease inhibitors is tantamount. A benzylidene cyclopentenedione-based inhibitor was found to be the first affinity reagent to covalently modify the active site of botulinum neurotoxin A light chain metalloprotease. Its kinetic parameters are reported and such an approach for inhibition of this deadly neurotoxin. [Capková, K.; Hixon, M. S.; Pellett, S.; Barbieri, J. T.; Johnson, E. A.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 206.]

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. Also covered in the abstract and citation database SCOPUS®. Full text available on ScienceDirect®

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ISSN 0960-894X