ELSEVIER

Bioorganic & Medicinal Chemistry Letters

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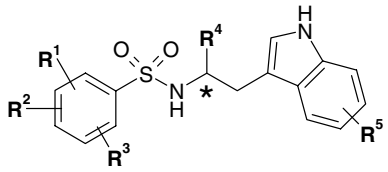
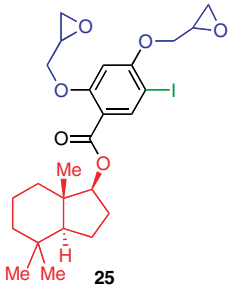
Contents

ARTICLES

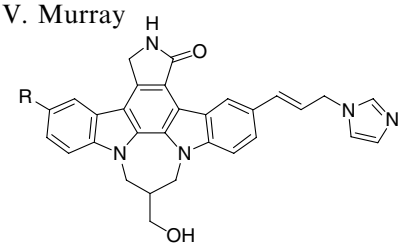


α-Methyltryptamine sulfonamides were identified as human glucocorticoid receptor (hGR) ligands. The SAR and selectivity will be discussed.

The synthesis of norrisolide probes and their effect on the Golgi complex is presented. The studies led to the identification of probe **25**, that contains a Golgi localization motif attached to a bisepoxide crosslinking unit and an iodine tag. This probe induced efficient and irreversible vesiculation of the Golgi membranes and could be used for the isolation of the cellular target of norrisolide.

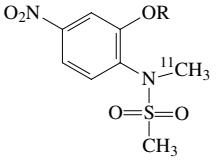


25

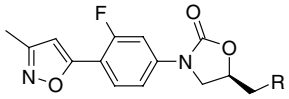


22n, R= H, JAK3 IC_{50} = 11 nM
22r, R= -CH_2OH, JAK3 IC_{50} = 3 nM

The modification of staurosporine led to a new series of potent JAK3 inhibitors is described.

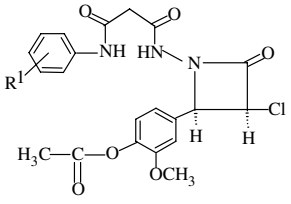


[^{11}C]**3a**: R=$CH_2CH_2CH_3$
[^{11}C]**3b**: R=$CH(CH_3)_2$
[^{11}C]**3c**: R=$CH(CH_2CH_3)_2$
[^{11}C]**3d**: R=C_5H_9
[^{11}C]**3e**: R=C_6H_{11}
[^{11}C]**3f**: R=$CH_2CH_2C_6H_{11}$

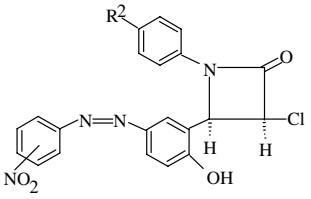


The synthesis, and the in vitro and in vivo evaluation of a new series of potent oxazolidinones are reported.

A new series of 3-chloro-4-(3-methoxy-4-acetyloxyphenyl)-1-[3-oxo-3-(phenylamino)propanamido] azetidin-2-ones **3** and 3-chloro-4-[2-hydroxy-5-(nitro substituted phenylazo)phenyl]-1-phenylazetidin-2-ones **6** have been synthesized. The synthesized compounds were screened to antimicrobial activity against several microbes, in vitro. Significant antimicrobial activity and structure–activity relationship (SAR) trends are obtained for the tested compounds.



3



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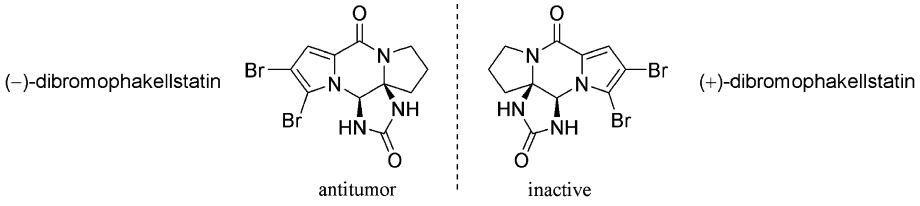
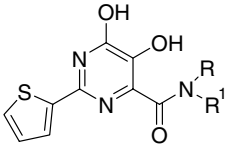
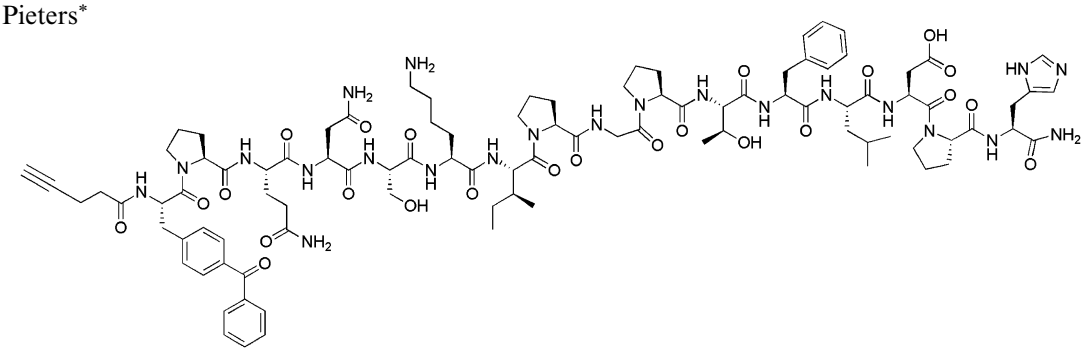
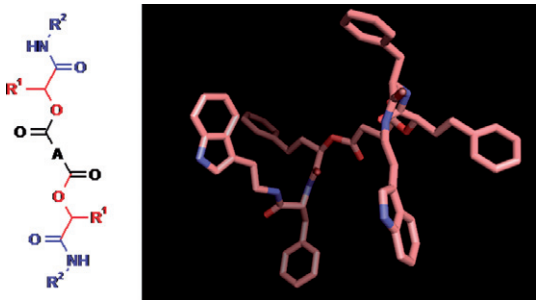
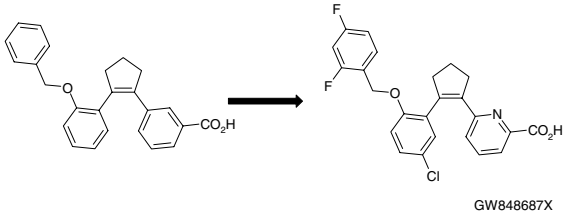
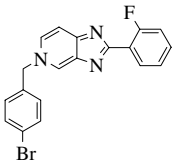


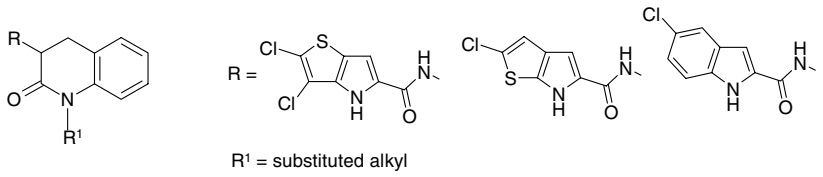




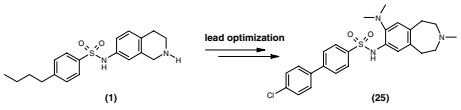




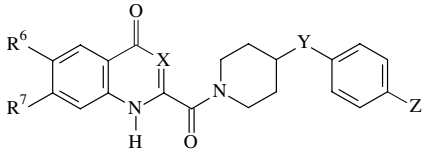




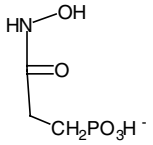
Optimisation of R^1 led to 2,3-dihydroxypropyl compounds which showed good in vitro potency and improved physical properties, together with good DMPK profiles and acute in vivo efficacy.



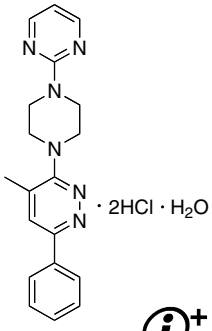
The SAR study around compound (**1**), led to the identification of sulfonamide (**25**), a molecule combining dopamine D_2/D_3 receptor antagonism with serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 receptor antagonism to treat schizophrenia.

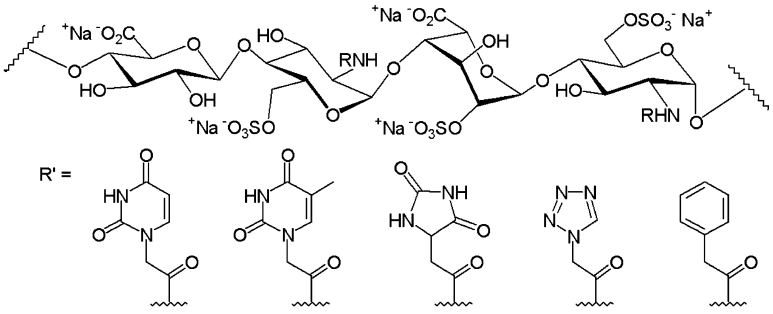


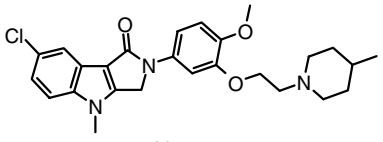
Starting from indole- and benzimidazole-2-carboxamides as lead compounds, a novel series of kynurenic acid amide derivatives was prepared and identified as NR2B selective NMDA receptor antagonists. The synthesis and SAR studies are discussed.



We report the synthesis and biochemical evaluation of new competitive inhibitors of the cytosolic (NADH-dependent) glycerophosphate dehydrogenase. One compound, phosphono-propionohydroxamic acid, with a K_i of 6 μM, might be of interest as an anti-obesity drug.

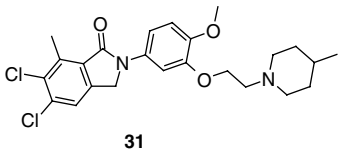






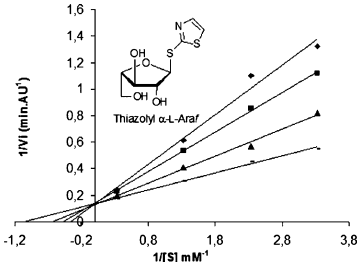
16

pKi 5-HT$_{2C}$ = 8.5, $F_{p.o.}$ = 44%

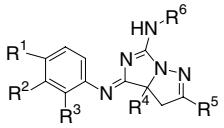


31

pKi 5-HT$_{2C}$ = 8.6, $F_{p.o.}$ = 43%

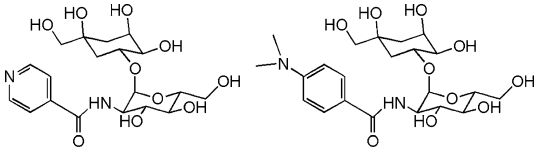


The synthesis and in vitro activity of the powerful furanosidic inhibitors of the arabinofuranosidase AbfD3 are reported.

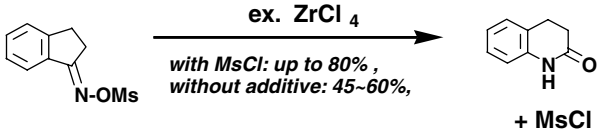


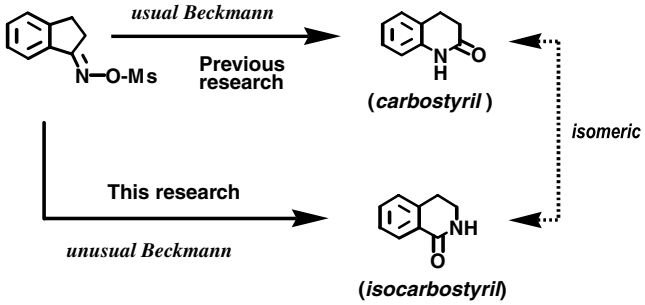
10

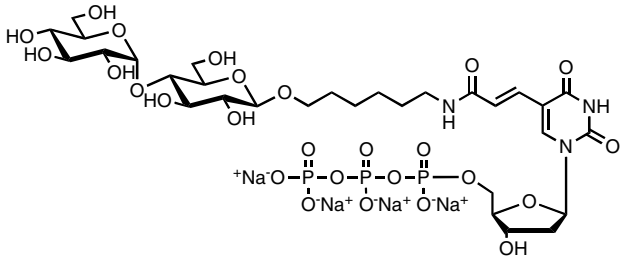
A novel imidazolopyrazole derivative has been fortuitously discovered as potent selective androgen receptor modulator with in vivo efficacy.



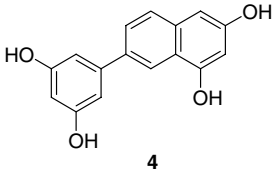
Examples of MCA inhibitors (IC_{50} values ~50 μM)







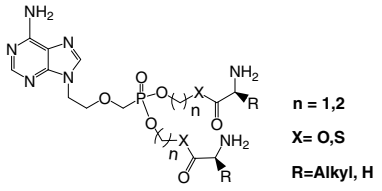
The construction of saccharide-modified DNAs using saccharide-modified dUTPs and DNA polymerase and the characterization of their biophysical properties are reported.



4

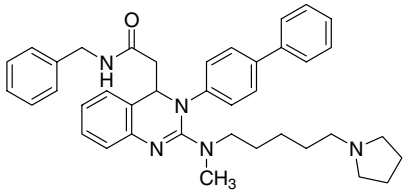
Isosteres of oxyresveratrol and resveratrol and their derivatives with 2-phenyl-naphthalene template were synthesized and evaluated as tyrosinase inhibitors.

A series of novel bis(L-amino acid)ester prodrugs of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) was synthesized and their anti-HBV activity was evaluated in HepG2 2.2.15 cells. Compound **11** exhibited five times more potent anti-HBV activity, 60 times higher selective index (SI) than adefovir dipivoxil. Moreover, compound **11** was more stable than adefovir dipivoxil with $t_{1/2}$ of 270 min.

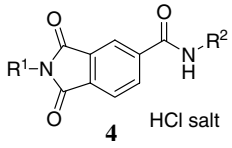


Compound **11** n = 2, X = O, R = 2-Methylpropyl

EC_{50} 0.0952 μM, CC_{50} 6636 μM, SI 69532

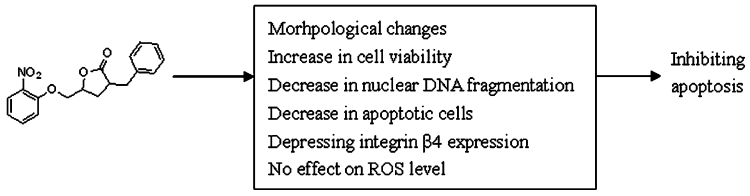


11b (KYS05080)
(IC_{50} = 0.26 ± 0.01 μM against T-type)
(Selectivity = 7.5 for T/N-type channel)

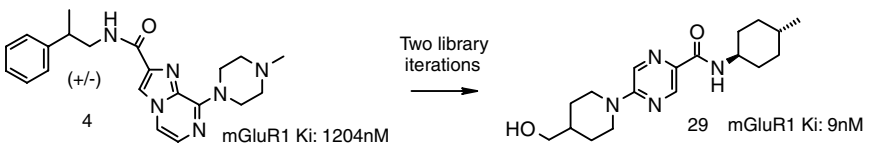


4 HCl salt

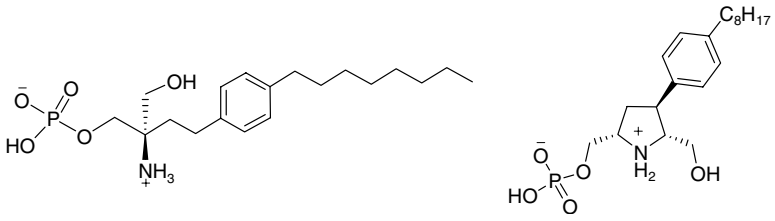
A small molecule library of 1,3-dioxoisoindoline-5-carboxamides **4** was designed, synthesized, and biologically evaluated as potential T-type calcium channel blockers. The most active compound shows blocking activity with IC_{50} value of 0.93 μM.

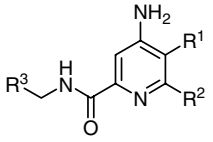


3-Benzyl-5-((2-nitrophenoxy) methyl)-dihydrofuran-2(3H)-one (3BDO) inhibited VEC apoptosis induced by deprivation of serum and FGF-2 and depressed the expression of integrin β4. ROS were not involved in this process.



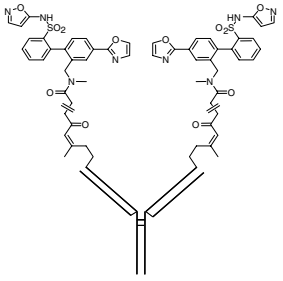
Weakly active (**4**) was converted into low molecular weight, high activity (**29**) using library chemistry.

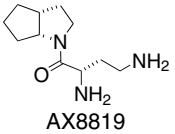




The hemodynamic effects of a series of potent and selective 4-aminopyridine carboxamide-based pan-JNK inhibitors were assessed in an anesthetized rat model. The effects of these agents on mean arterial pressure, heart rate, cardiac contractility, and peripheral vascular resistance are described, and the implication for targeting protein kinases in metabolic diseases is discussed.

β-Diketone containing aryl sulfonamide endothelin antagonists were synthesized and covalently linked to the reactive lysine of the antibody m38C2 to create a series of chemically programmed antibodies. These antibodies, named as CovX-Bodies, behaved as potent endothelin receptor antagonists in vitro and showed anti-tumor effect in vivo.





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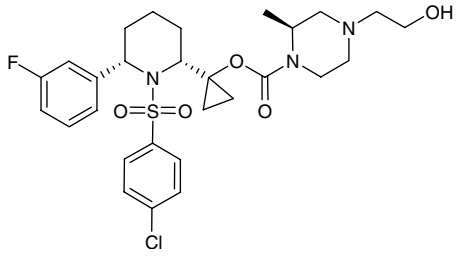
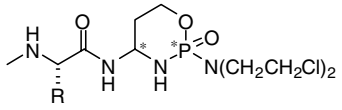
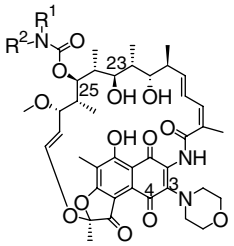
A cell permeable, selective DPP II (also known as DPP2, DPP7, and QPP) inhibitor is reported.





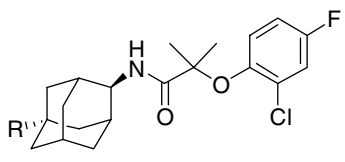
A series of novel phenylalanine-conjugated 4-aminocyclophosphamide isomers were synthesized and evaluated as potential prodrugs for proteolytic activation.



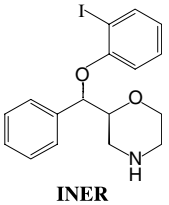
C25- rifamycin carbamate

The synthesis of C25 carbamate derivatives of rifamycins and biological data are reported.

The synthesis of potent and selective adamantane sulfone and sulfonamide 11-β-HSD-1 inhibitors represented by **10** and **40** is reported.



10 R = SO_2Me, h-HSD-1 K_i = 7 nM
40 R = SO_2NH_2, h-HSD-1 K_i = 6 nM



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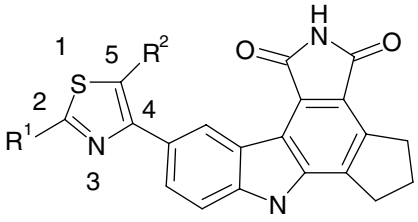
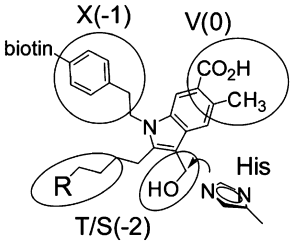
The synthesis and in vivo evaluation of a novel iodo reboxetine analog with subnanomolar affinity for the norepinephrine transporter are described.

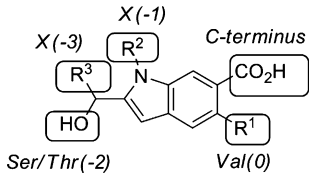
A series of potent and selective NPY2 receptor agonist peptides are described.



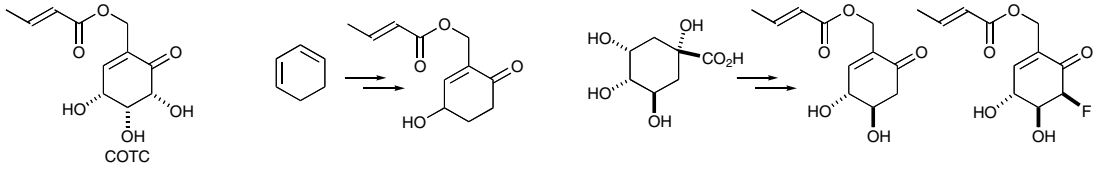
Synthesis and activity of a series of 4-thiazol-yl substituted analogs of a novel pyrrolocarbazole as poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors have been disclosed.

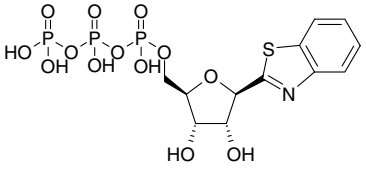


A chemical probe that contained a chemical scaffold mimicking the E/D-T/S-XV peptide differentially visualized the cellular proteome.



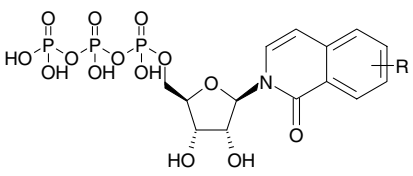
Novel small molecules were designed to specifically target the ligand-binding pocket of a PDZ domain.





The synthesis and $P2Y_2$ activities of some novel C-linked nucleotide triphosphates are reported. These exhibit excellent agonist potency and selectivity for the $P2Y_2$ receptor. Stability studies were carried out on representative compounds from the N-linked and C-linked series; these showed enhanced metabolic stability compared with that of UTP.

The synthesis and $P2Y_2$ activities of a novel series of UTP analogs bearing 'unnatural' bicyclic bases in place of the uracil are described. Many of these compounds were potent and selective agonists of the $P2Y_2$ receptor.



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*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Typical snapshot of **7b** bound to HIV-RT from an MC simulation. Carbon atoms of **7b** are gold; from the left, Tyr181, Tyr188, Phe227, Leu100, Lys101; Trp229 at the top, Val106 at the bottom. H-bond with Lys101 O on right. Some residues in front including Glu138 have been removed for clarity. The water on N5 is also H-bonded to a carboxylate O of Glu138. [Thakur, V. T.; Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domaoal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5664.]

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