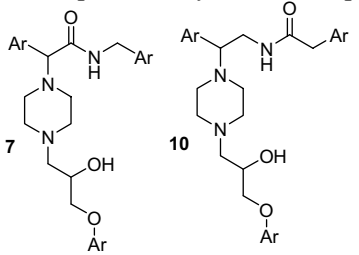
ELSEVIER

Bioorganic & Medicinal Chemistry Letters

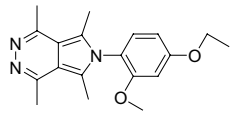
Bioorganic & Medicinal Chemistry Letters Vol. 14, No. 9, 2004

Contents

COMMUNICATIONS

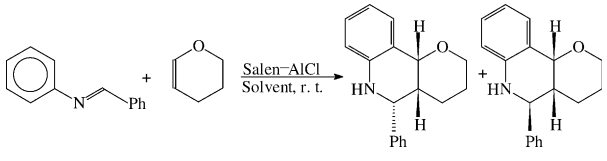


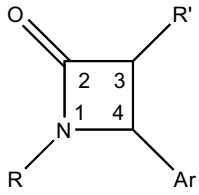
A parallel strategy incorporating predictive modeling and parallel chemistry has led to the identification of two new structural motifs (**7** and **10**) with potent sodium both sodium site **2** blocking activity and favorable eADME profile.



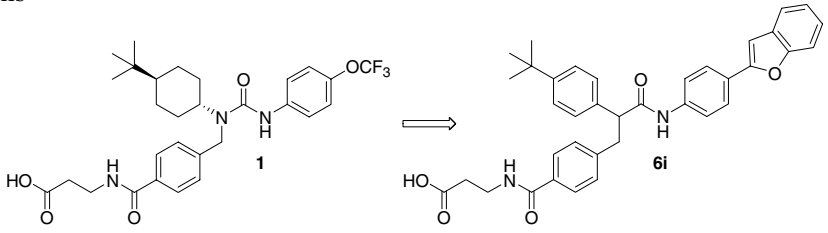
4a

Compounds such as **4a** ($IC_{50} = 4$ nM) are high-affinity ligands of the $\alpha_2\delta$ subunit of voltage-gated calcium channels.

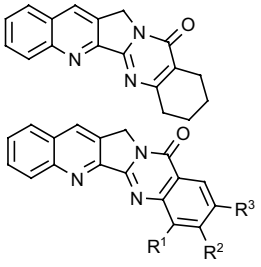




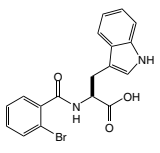
Synthesis, cytotoxicity, tubulin polymerization inhibition, anti-tumor activity, and serum and buffer stability of new 1,4-diaryl-2-azetidinones are reported.



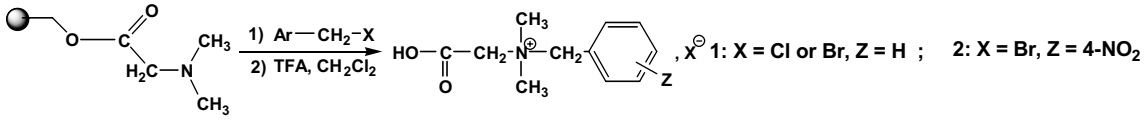
Biaryl amides derived from a reported series of ureas **1** were evaluated and found to be potent human glucagon receptor antagonists. The benzofuran analogue **6i** was administered in Sprague–Dawley rats and blocked the effects of an exogenous glucagon challenge.



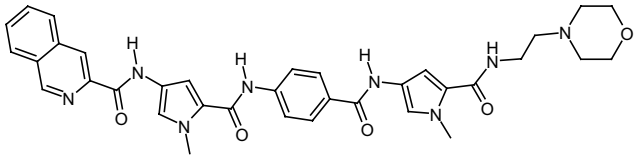
o-Bromobenzoyl L-tryptophan **1** inhibits the association of LFA-1 with ICAM-1 with an IC_{50} of 1.7 μM. Evaluation of the structure–activity relationship of the benzoyl moiety shows that 2,6-di-substitutions greatly enhance potency of this class of inhibitors. Electronegative substitutions that favor a 90° angle between the benzoyl ring and the amide bond yield the most potent compounds. There is a strong correlation between the potency of the compounds and the difference between the ab initio energy at 90° and the global minima energy for given compounds. Combining the favored benzoyl substitutions with L-histidine and L-asparagine resulted in a 15-fold increase in potency over compound **1**.



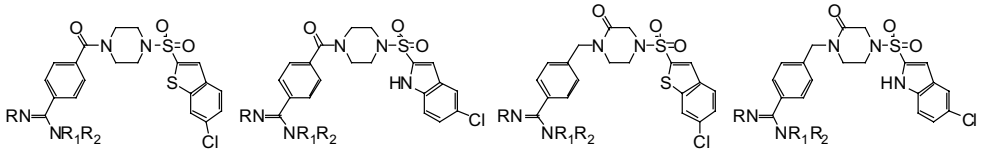
1



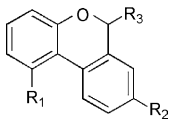
Glycine betaine (GB) analogues were obtained by SPOS using Wang resin and assayed for their toxic activity against 15 Gram positive and Gram negative bacteria. Four benzyl derivatives of GB were selected to determine their effect on bacterial growth. Bacteriostatic and lethal effects were observed for compound **1** and compound **2**, respectively. The importation of the two GB analogues into bacterial cells appeared strictly dependent on the powerful betaine membrane osmoporters; their capacity to be amassed intracellularly at molar levels from extremely diluted solutions might constitute a basis to design a new class of antimicrobial agents.



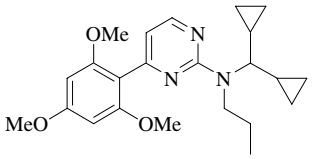
DNA binding ligands with potent antimicrobial activity against Gram-positive bacteria were further optimized by variation of the internal aromatic amino acids to successfully achieve in vivo efficacy in murine models of bacterial infection with methicillin-resistant *S. aureus* (MRSA).



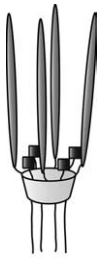
A class of N,N-dialkylated 4-(4-arylsulfonylpiperazine-1-carbonyl)-benzamidines and 4-((4-arylsulfonyl)-2-oxo-piperazin-1-ylmethyl)-benzamidines has been discovered as potent factor Xa inhibitors with desirable in vitro and in vivo anticoagulant activity, but with low oral bioavailability. The 5-chloroindole and 6-chlorobenzo[*b*]thiophene groups are optimal as the factor Xa S1 binding elements.



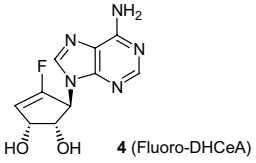
We report the discovery of a novel class of glucocorticoid receptor (GR) antagonists based on the chromene molecular scaffold. The compounds exhibit good functional potency and an improved receptor selectivity profile for GR over other steroid receptors when compared to the classical steroidal GR-antagonist, RU-486.



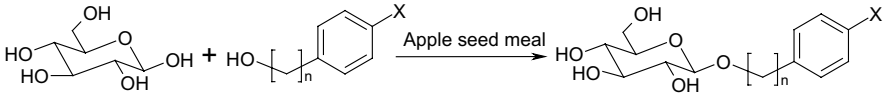
7b

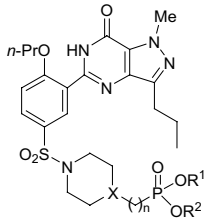


1d

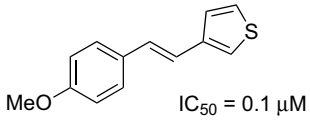


4 (Fluoro-DHCeA)

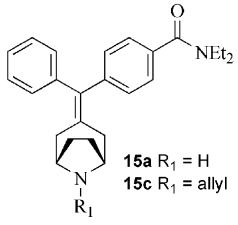




12a–e,13a–d, 14a–d

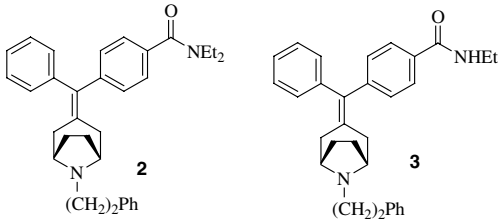


The inhibitory effects of a series of styrylheterocycles on the production of COX-2 mediated PGE_2 were evaluated in a cell culture system. A new series of potential inhibitors, including 3-[2-(4-methoxy-phenyl)-vinyl]-thiophene, have been identified.

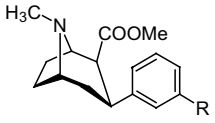


15a R_1 = H
15c R_1 = allyl

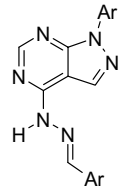
Compounds such as **15a** and **15c** are potent and selective δ opioid agonists.



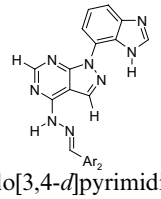
Compound **2**, a potent and selective δ opioid agonist is metabolically converted to **3**, a potent and selective μ opioid agonist.



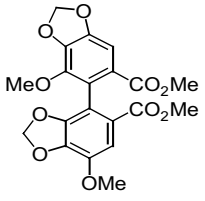
A series of novel 3β-substituted 3′-substituted phenyltropanes was synthesized and evaluated by selective radioligand binding assays for affinity to monoamine transporters.

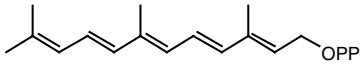


A series of [1-aryl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]arylhydrazones were discovered as novel inhibitors glycogen synthase kinase-3 (GSK-3).

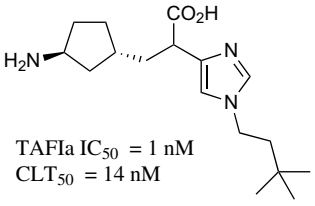


A novel series of [1-(1*H*-benzimidazol-7-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl] arylhydrazones was synthesized and shown to potently inhibit glycogen synthase kinase-3 (GSK-3). In light of detailed structure–activity relationships and structural knowledge of the GSK-3 binding pocket, a benzimidazole substituent was incorporated onto the pyrazolopyrimidine core resulting in improved potency over previous analogs. More importantly, these derivatives show low nanomolar efficacy for stimulating glycogen synthesis in vitro and therefore may be useful in the treatment of type 2 diabetes mellitus.

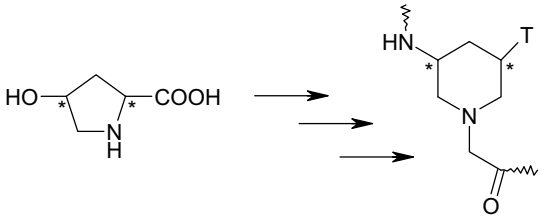




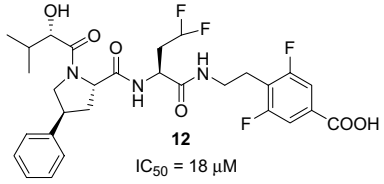
All-*trans* ΔΔFPP



TAFIa IC_{50} = 1 nM
CLT_{50} = 14 nM

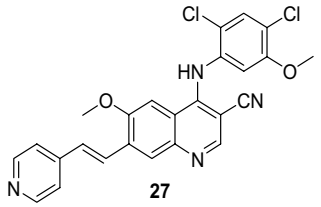


2*S*, 4*R* 3*S*,5*S*



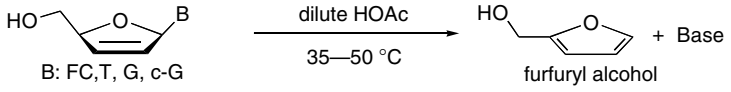
12
IC_{50} = 18 μM

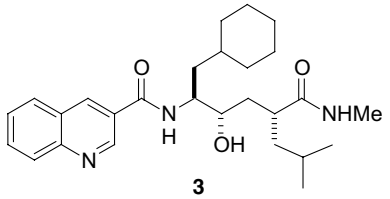
The N-terminal aminoacid of phenethylamide tripeptide inhibitors of the hepatitis C virus NS3 protease can be replaced with an α-hydroxy acid to obtain more drug like inhibitors with low micromolar activity. The highest affinity of the capping residue with *S*-configuration has been explained by molecular modeling studies.



27

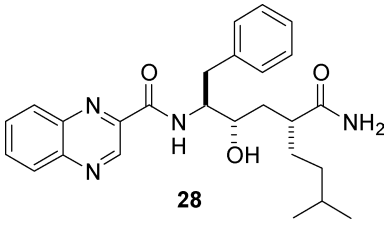
A series of 7-ethynyl and 7-ethenyl-4-anilino-3-quinolinecarbonitriles was synthesized and tested for Src inhibition. The 7-(4-ethenylpyridine) derivative **27** was the most potent inhibitor tested in this series.





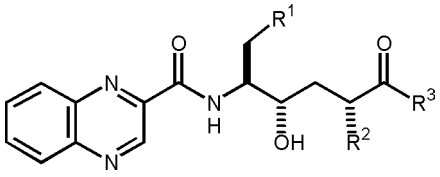
3

This manuscript details fundamental SAR work around compound **3**, a micromolar inhibitor of CCL3 binding to its receptor CCR1.

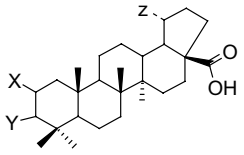


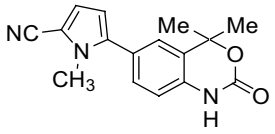
28

This manuscript details the discovery of potent CCR1 antagonists.

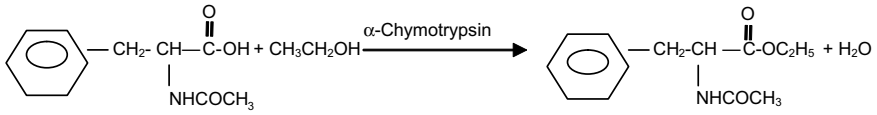


The synthesis, biological activity and pharmacokinetic profile of novel CCR1 antagonists are described.

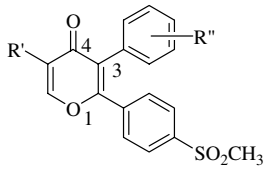


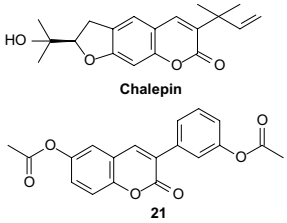


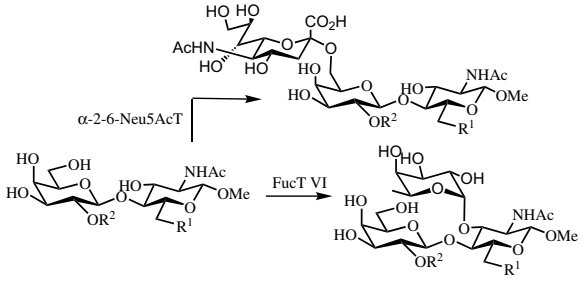
A series of 1,4-dihydro-2*H*-[*d*][3,1]-benzoxazin-2-one and 1,3-dihydro-[3*H*]-indol-2-one containing 6- or 5-, respectively, appended substituted pyrrole moieties were synthesized and evaluated for their ability to modulate the activity of the progesterone receptor (PR).

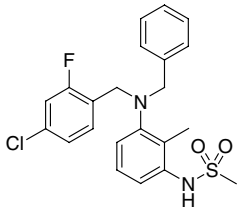


The increase in reaction rates of free α-chymotrypsin-catalyzed esterification was achieved by precipitation of the enzyme from an aqueous solution.



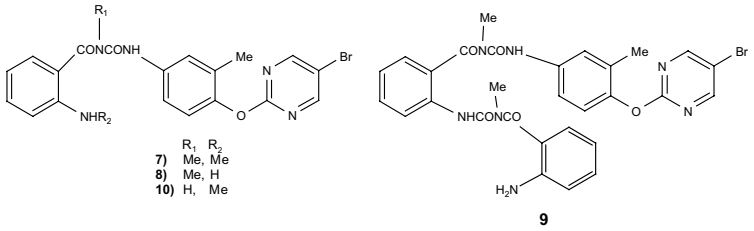


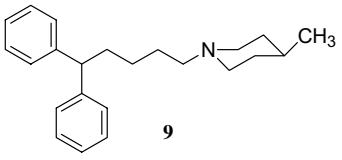




19 IC_{50} = 5.7 nM

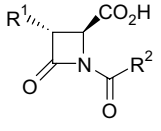
The discovery and synthesis of a novel series of selective glucocorticoid receptor modulators is reported, typified by sulfonamide **19** (h-GR binding IC_{50} = 5.7 nm).



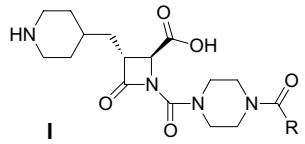


Compound **9**, derived from a thioxanthene analog, binds with very high affinity ($K_i = 0.09$ nM) at σ_1 receptors and with about 190-fold selectivity versus σ_2 receptors. As such, it extends the SAR for σ_1 binding of phenylpentylamines to derivatives bearing a benzylic phenyl group.

The synthesis, via the Ugi reaction, of a library of heparan sulfate mimetics is described. The compounds display micromolar affinities for the heparan sulfate-binding growth factors FGF-1 and FGF-2.

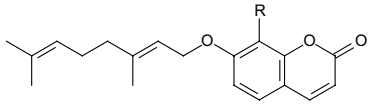


A series of potent azetidinone tryptase inhibitors with primary or secondary amine or aminopyridine functionality incorporated at the R^1 position is described. One analog (**4**, IC_{50}=1.8 nM) was shown to be highly selective against trypsin and most other related serine proteases.

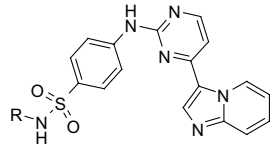


I

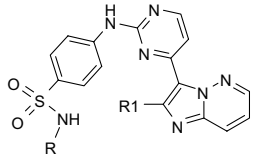
A parallel library based on structure **I** was prepared, which identified potent tryptase inhibitors with improved selectivity against trypsin. A crystal structure of one compound bound to trypsin is shown and a hypothesis is presented to account for the observed SAR.



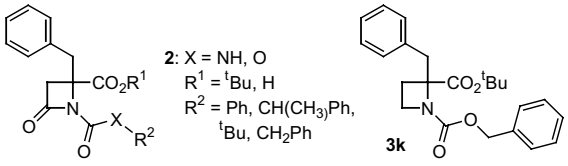
Synthesis and anti-inflammatory activity of some natural and semisynthetic 7-geranyloxy-8-substituted coumarins are described.

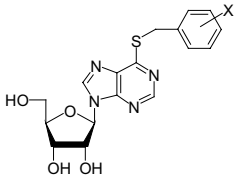


Investigation of detailed SAR and optimisation of imidazo[1,2-*a*]pyridine cyclin-dependent kinase inhibitors has led to the identification of potent and selective inhibitors of CDK2 and CDK1.



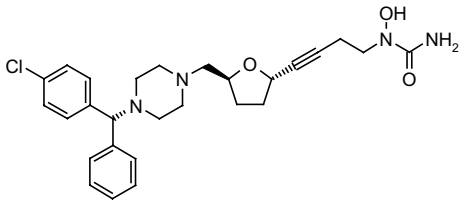
Imidazo[1,2-*b*]pyridazines have been identified and characterised as potent CDK inhibitors. The binding mode and SAR of these compounds has been elucidated and shown to differ from that of the structurally similar imidazo[1,2-*a*]pyridine series. Examples of this series show potent and selective CDK inhibition and give significant blood levels following oral dosing to mice.



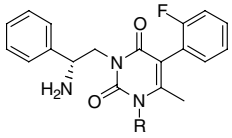


Synthesis and structure–activity relationship of novel halogenated nitrobenzylthioinosine analogs as *es* nucleoside transporter inhibitors is reported.

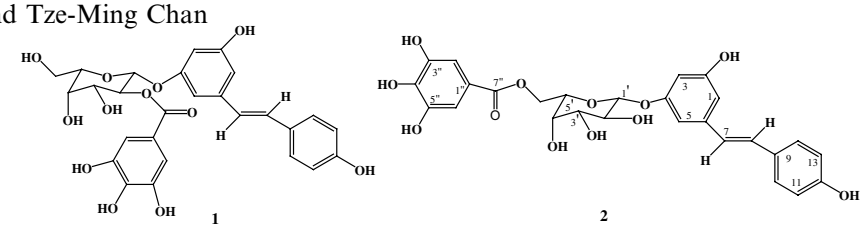
Neuroprotective effects of flavones were examined. Luteolin and apigenin exhibited neuroprotection against oxidative stress-induced cell death in SH-SY5Y cells. Free radical scavenging activity and neuroprotection assays revealed that flavones exerted their neuroprotective effects via the direct interaction with the apoptotic caspase pathway independently of their antioxidant activity.



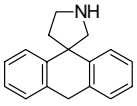
Compounds containing the pharmacophores of known antihistamines and known 5-lipoxygenase inhibitors show both activities in vitro and in animal models.



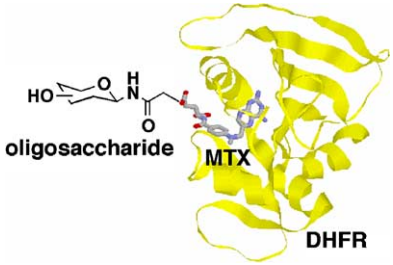
The design and synthesis of this novel class of GnRH receptor antagonists is described. Results from SAR studies carried out around N-1 of the uracil are summarized. The best compound showed $K_i = 0.7$ nM.



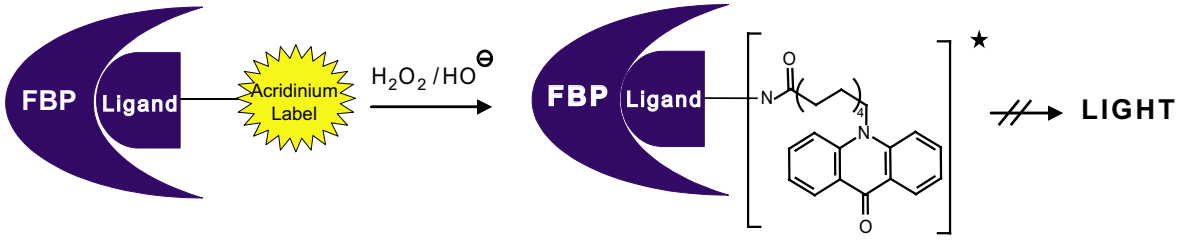
The 70% aqueous methanolic extract of the Peruvian plant *Polygonum cuspidatum* sp. was found to contain two novel phenolic saccharides **1** and **2**, which were identified as inhibitors of the bacterial DNA primase enzyme. Structures of these two compounds were established based on high resolution NMR studies. Compounds **1** and **2** inhibited the primase enzyme with an IC_{50} of 4 and 5 μM, respectively.

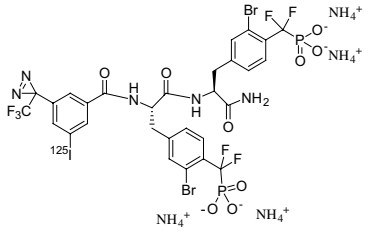


The 5-HT_{2A} receptor affinities of ring altered derivatives of spiro[9,10-dihydroanthracene]-9,3′-pyrrolidine (**4**), a structurally unique tetracyclic 5-HT_{2A} receptor antagonist, are described. Most characteristics of the parent compound prove to be necessary for optimal 5-HT_{2A} receptor affinity. In addition, the parent compound is shown to have high 5-HT_2 receptor selectivity.

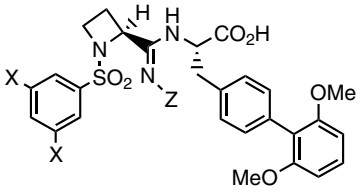


A novel type of artificial glycoprotein was developed, by using dihydrofolate reductase (DHFR) and oligosaccharide–methotrexate (MTX) as a protein–ligand pair.

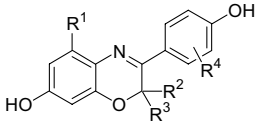




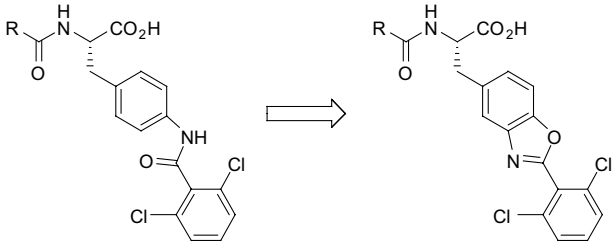
The synthesis of a novel radioactive peptidic photoaffinity probe for the PTP-1B enzyme as well as some SAR leading to the choice of this compound as a photoaffinity probe are presented.

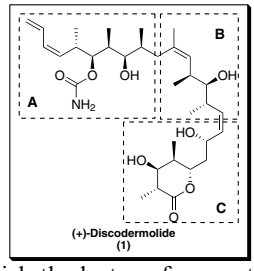


The preparation and SAR of amidines as small molecule antagonists of VLA-4 is discussed.

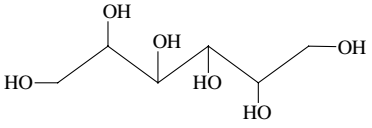


A series of 3-aryl-7-hydroxybenzoxazine analogues have been prepared and evaluated as ligands for the two estrogen receptor subtypes. Compounds with more than a 10-fold selectivity toward the ERβ subtype have been identified in both binding and functional assays.

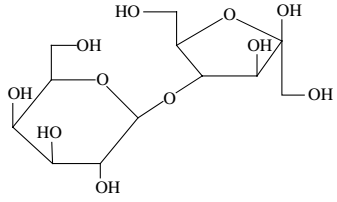




A series of 7-deoxy discodermolide analogues in which the lactone fragment '**C**' was replaced by aryl substituents were designed, synthesized, and evaluated for cytotoxicity.

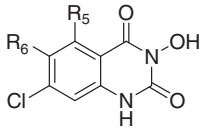


Mannitol ($C_6H_{14}O_6$, Mw 182.17)

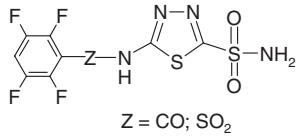


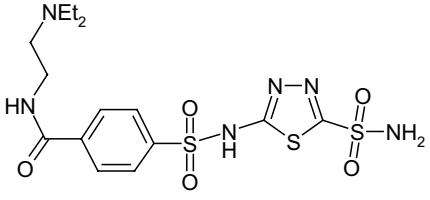
Lactulose ($C_{12}H_{22}O_{11}$, Mw 342.29)

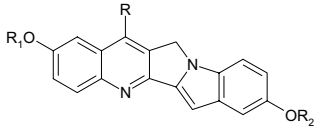
The contents of mannitol (M), lactulose (L), and the L/M ratio in urine were determined by HPLC/RID/MS, and the ratios of L/M were used for evaluation of intestinal permeability for cirrhotic patients.



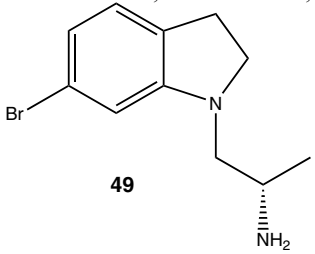
The synthesis and Gly/NMDA, AMPA and KA receptor binding activities of some 3-hydroxy-quinazoline-2,4-dione derivatives are reported. The binding data showed that introduction of chlorine atom(s) on precise position(s) of the benzofused moiety yielded Gly/NMDA selective antagonists, while the presence of the 6-(1,2,4-triazol-4-yl) group shifted the affinity and selectivity towards the AMPA receptor.







A series of ethers of the dihydroxybenzo[5,6]pyrrolizino[1,2-*b*]quinoline skeleton, a new heterocyclic pattern, was synthesised and evaluated for its cytotoxic activity against three cancer cell lines.



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A series of 1-(1-indolinyl)-2-propylamines was synthesised and evaluated as 5-HT$_{2C}$ receptor agonists for the treatment of obesity. A number of compounds, including **49**, were found to reduce food intake in rats after oral administration.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Cover figure provided by ***Indraneel Ghosh,*** *Department of Chemistry, University of Arizona.* The cover depicts the **Dual Surface Selection** methodology developed by the author: the blue helix of htBl (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htBl (center) allows for functional selection against thrombin (right) [Rajagopal, S.; Meza-Romero, R.; Ghosh, I. *Bioorg. Med. Chem. Lett.* **2004**, *14,* 1389].

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ISSN 0960-894X