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Bioorganic &
Medicinal
Chemistry
Letters

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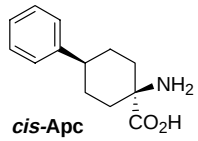
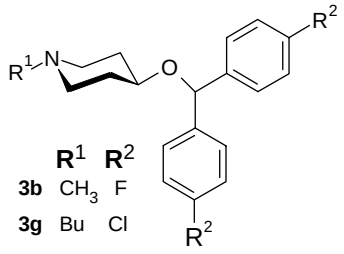
Contents

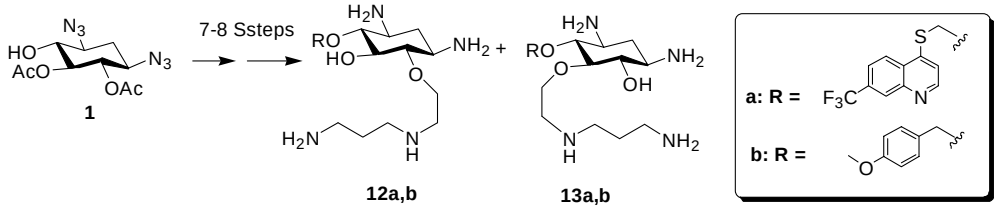
ARTICLES



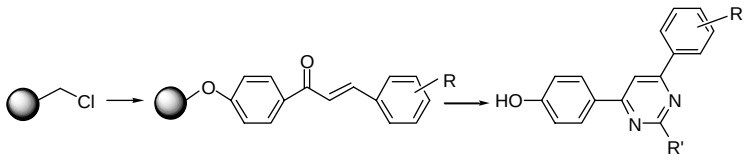
A design and synthesis of *cis*-Apc as new histidine surrogate and its incorporation into linear pentapeptides (Penta-*cis*-Apc-DPhe-Arg-Trp-Gly-NH_2) and related analogs leading to potent and selective hMC4R agonists are reported.



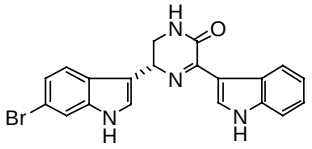
The development of potent 4-(arylmethoxy)-1-alkylpiperidine inhibitors of the dopamine transporter is described. Symmetrical *para* substituents of the benzene rings are important for high potency in binding to the dopamine transporter. **3b** has an IC_{50} = 22.1±5.73 nM and elevates locomotor activity in mice, and **3g** has an IC_{50} = 12.1±7.51 nM and is inactive in this test.



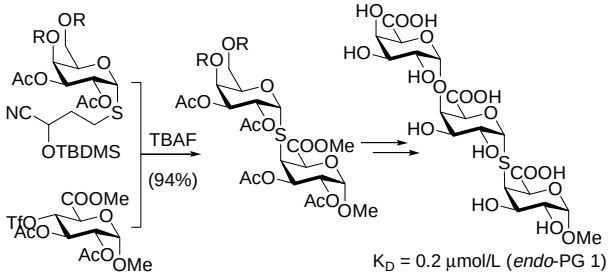
The first carbohydrate-free aminoglycoside analogs bearing the 2-deoxystreptamine moiety were synthesized from asymmetrically protected 2-deoxystrepamine and subsequently demonstrated to have significant binding to the 16S A-site rRNA target and moderate functional activity.



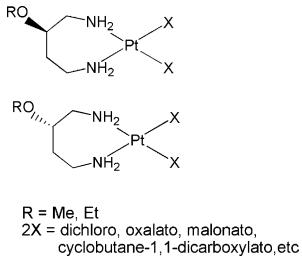
Out of the 30 compounds synthesized, 23 compounds have shown in vitro antimalarial activities against *Plasmodium falciparum* in the range of 0.25–2 μg/mL and 16 compounds have shown antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Ra$, at a concentration of 25 μg/mL.

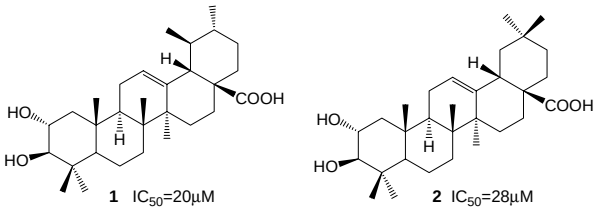


The isolation, structure identification, and bioactivity of nine bis(indole) alkaloids are described.

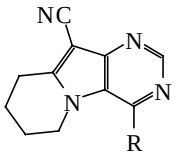


Twenty-six new hydrophilic chiral 2-alkoxy-1,4-butanediamine platinum (II) complexes have been synthesized and most of them were evaluated for their in vitro cytotoxicity toward two human tumor cell lines. The cytotoxicities of platinum complexes are related to the nature of the carrier ligand and leaving group. Complex **5′b** exhibits the greatest potency among those 21 tested platinum complexes in both cell lines.



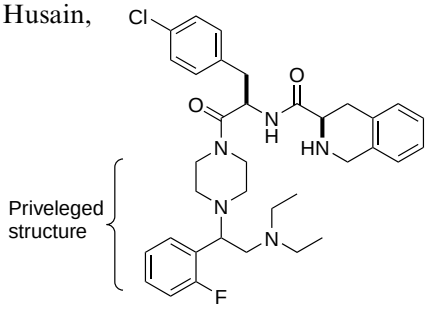


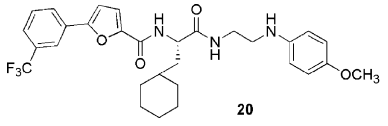
The semi-synthesis, in vitro and in vivo biological evaluation of corosolic acid (**1**) and maslinic acid (**2**) are described. Compounds **1** and **2** represent a new class of inhibitors of glycogen phosphorylases.



Wiener's index—a distance-based topological descriptor has been successfully employed for development of a model for prediction of MRP1 inhibitory activity of pyrrolopyrimidines and their derivatives. Active range of the proposed model possesses vast potential for providing lead structures for development of potent inhibitors of MRP1.

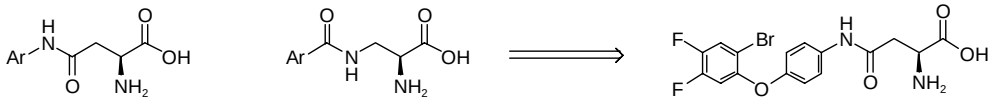
A variety of substituted benzylic piperazines provide useful privileged structures for the construction of ligands with affinity for melanocortin 4 receptors.



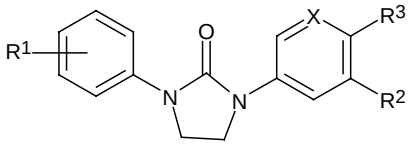


20

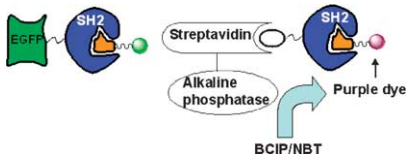
K_i cathepsin S = 3.3 nM
K_i cathepsin K > 65,000 nM
K_i cathepsin L > 17,400 nM



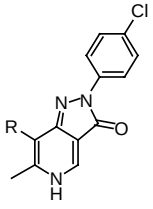
An extensive SAR study of a series of aspartic and 2,3-diaminopropionic acid amides led to the discovery of 2-bromo-4,5-difluorophenoxy)phenyl]-L-asparagine—one of the most potent, selective, competitive non-substrate inhibitors of EAAT-2 identified to date.



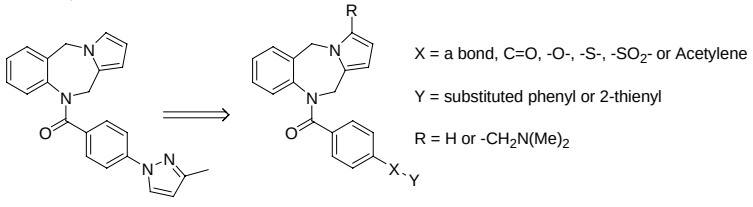
A series of novel bisaryl imidazolidinones have been prepared and evaluated both in vitro and in vivo for their 5-HT_{2C} receptor antagonist activity.



Two solid-phase binding assays were evaluated for potential use in the screening of peptides as the Src SH2 domain inhibitors.



2,5-Dihydro-3*H*-pyrazolo[4,3-*c*]pyridin-3-ones are $GABA_A$ receptor benzodiazepine binding site ligands, which can exhibit functional selectivity for the α_3 subtype over the α_1 subtype. SAR studies to optimize this functional selectivity are described.



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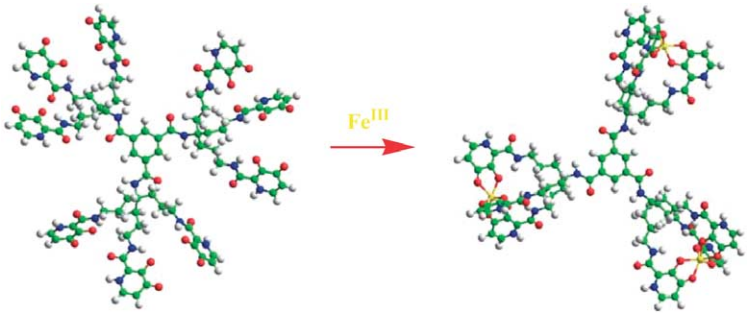
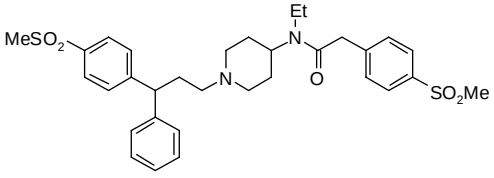
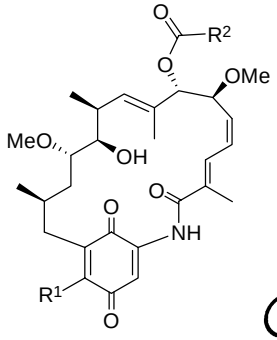
Synthesis and structure–activity relationships (SAR) of arginine vasopressin (AVP) receptor modulators are described.

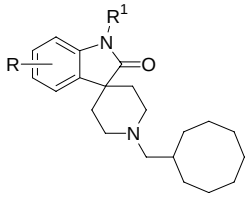




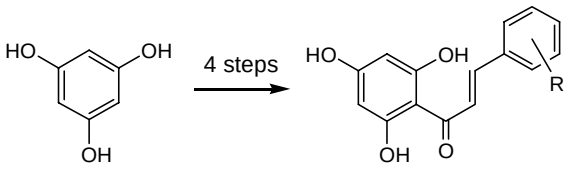
SAR and DMPK studies led to the identification of substituted *N*-alkyl-*N*-[1-(3,3-diphenylpropyl)piperidin-4-yl]-2-phenylacetamides as potent and orally bioavailable ligands for the human CCR5 receptor.

The structure-based design, synthesis, Hsp90 inhibitions, and cytotoxicity of a series of 7-derivatives of 17-alkyl geldanamycins are described.



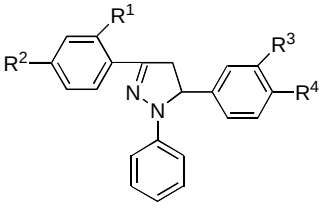


Synthesis and SAR of a series of indolin-2-ones provided compounds with high affinity for the ORL-1 receptor.

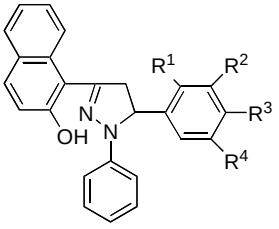


A series of trihydroxychalcones was synthesized and screened in vitro for their inhibitory effects on washed rabbit platelet aggregation induced by arachidonic acid (100 μM) and collagen (10 μg/ml). Compound **4e** exhibited a potent inhibitory effect on arachidonic acid- and collagen-induced platelet aggregation. The structure–activity relationships were also discussed in this paper.

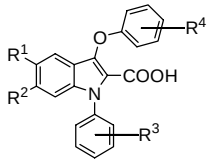
The synthesis of different substituted 2-pyrazolines from the corresponding chalcones by condensation with phenyl hydrazine hydrochloride is reported. The chalcones employed in this reaction were prepared by condensing appropriate acetophenones with benzaldehyde derivatives in dilute ethanolic potassium hydroxide solution. The majority of the compounds synthesised possessed significant antidepressant activity in mice ($P < 0.05$) in the Porsolt behavioural despair test.



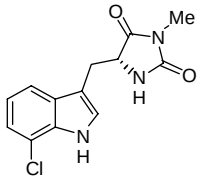
($2_{a\text{-}e}$)

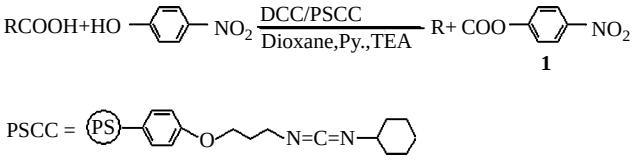


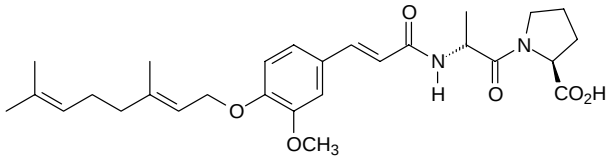
($4_{a\text{-}e}$)



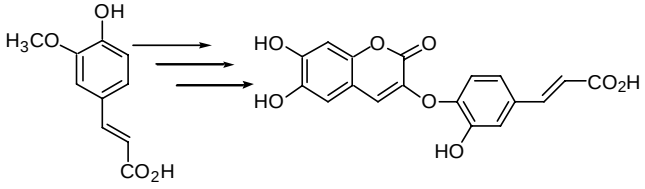
A series of novel aryl indole-2-carboxylic acids has been identified as potent selective PPARγ modulators. Their chemical synthesis and in vitro activities are discussed. An optimized compound was efficacious in the *db*/*db* mouse model of type 2 diabetes.



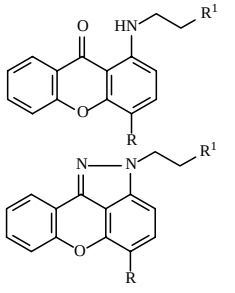


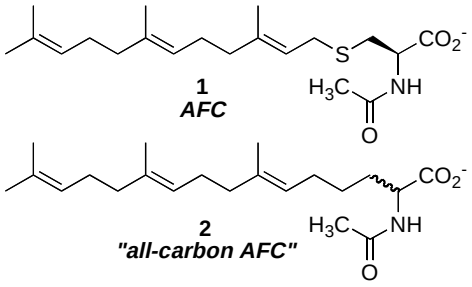


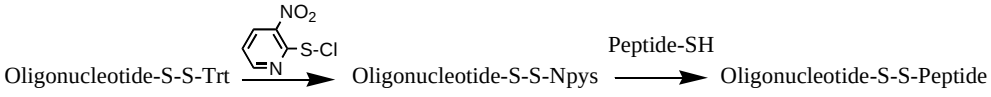
The synthesis of a novel colon ACE targeted prodrug of 3-(4′-geranyloxy-3′-methoxyphenyl)-2-*trans*-propenoic acid is described.



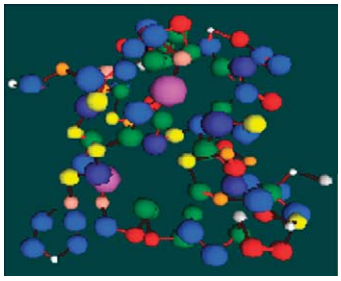
Two caffeoyl-coumarin conjugates derived from sagecoumarin were synthesized and exhibited potent micromolar inhibitory potencies against HIV-1 integrase in 3′-end processing reaction but were less effective against HIV-1 replication.

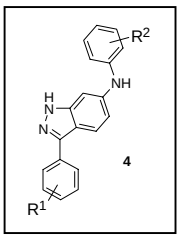






A straightforward method to attach an oligonucleotide to a cell penetrating peptide is developed.





The structure-based design and synthesis of a new series of c-Jun N-terminal kinase-3 inhibitors **4** with selectivity against JNK1 and p38α is reported.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Amerliorating transthyretin amyloidogenesis by native state kinetic stabilization mediated by small molecule binding. Small molecule binding to the amyloidogenic protein transthyretin kinetically stabilizes the native tetrameric state, preventing dissociation to folded monomers that misfold and misassemble into toxic intermediates, amorphous aggregates, and amyloid fibrils. The Kelly laboratory has developed several structurally distinct inhibitor families, depicted in the background, that are undergoing pharmacological evaluation. Created by Steven M. Johnson, graduate student in Professor Jeffery W. Kelly's laboratory, Department of Chemistry, The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, CA 92037, USA.

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