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Medicinal
Chemistry
Letters

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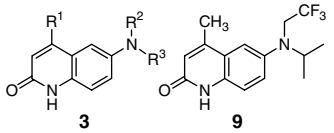
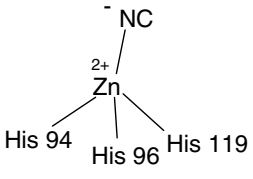
Contents

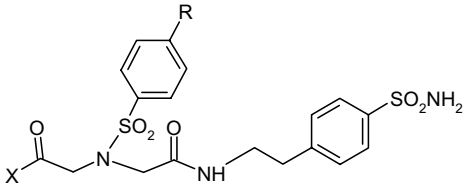
ARTICLES



3 9

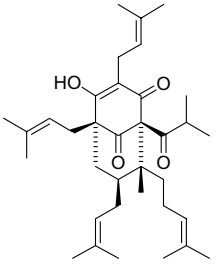
A series of selective androgen receptor modulators (SARMs) with a wide spectrum of receptor modulating activities was developed based on optimization of the 4-substituted 6-bisalkylamino-2-quinolinones (**3**). Significance of the trifluoromethyl group on the side chains and its interactions with amino acid residues within the androgen receptor (AR) ligand binding domain are discussed. A representative analog (**9**) was tested orally in a rodent model of hypogonadism and demonstrated desirable tissue selectivity.



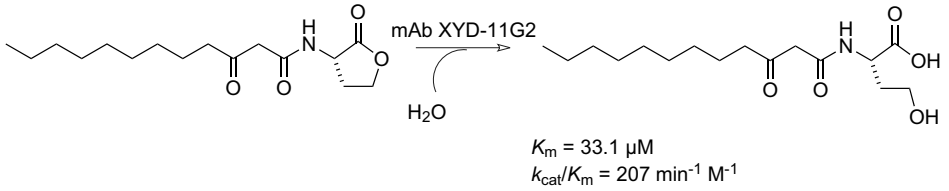


R = OMe, OPhe, Ph; X = OH, NHOH

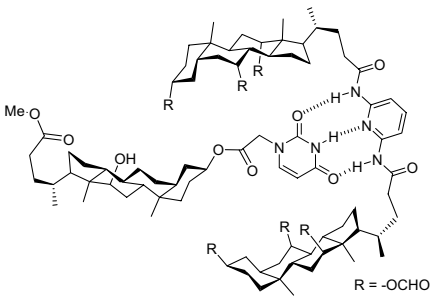
The antimalarial activity of hyperforin and a series of derivatives variously modified on the cyclohexatrienone system was investigated. Hyperforin was active against *Plasmodium falciparum* with an IC_{50} value in the micromolar range, and the activity was not critically dependent on either its phenol-like sensitivity to autooxidation or the presence of unsaturation on the prenyl residues.



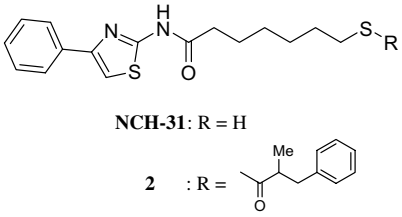
hyperforin

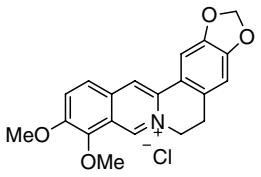


The binding ability of acyclic and cyclic bile acid-based receptors containing 2,6-bis(acylamino)pyridine for different uracil derivatives has been studied.



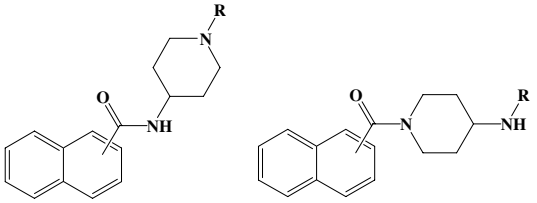
To identify prodrugs of a thiolate histone deacetylase inhibitor NCH-31 that show potent antiproliferative activity and are stable in human plasma, we synthesized several *S*-acyl derivatives of NCH-31. Among these compounds, *S*-2-methyl-3-phenylpropanoyl compound **2** showed potent antiproliferative activity and high stability in human plasma.



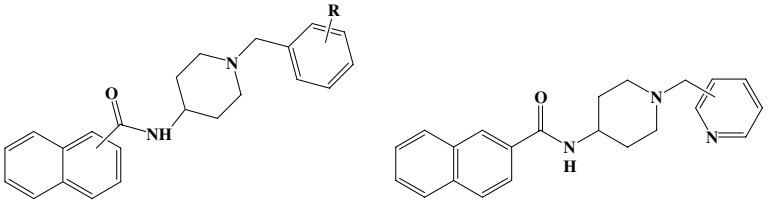


1

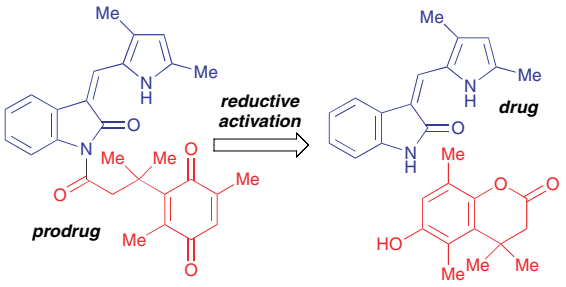
Berberine chloride (**1**) inhibited the human cytomegalovirus replication at IC_{50} 0.68 μM, which was equivalent to that (0.91 μM) for ganciclovir. The selectivity index of **1**, the ratio of 50% cytotoxic concentration to IC_{50}, was 110.



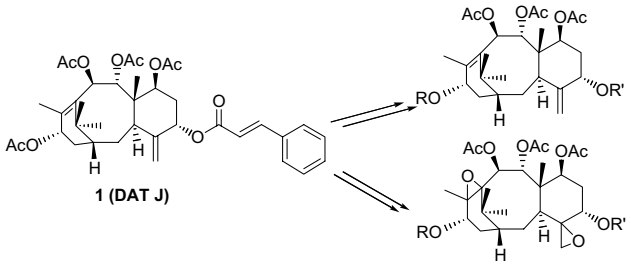
R = benzyl, 2-phenethyl, 1-phenethyl, 3-phenylpropyl, (*S*)-3-(1-hydroxy-1-phenyl)propyl, (*R*)-3-(1-hydroxy-1-phenyl)propyl, 4-phenylbutyl.

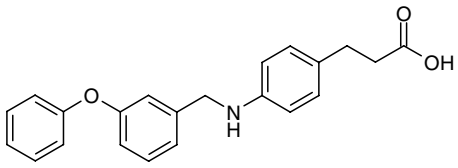


1- and 2-Naphthamide derivatives: **R** = H, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 3-CF_3, 4-CF_3, 2,3,4,5,6-F, 4-NO_2, 3-MeO, 4-MeO, 2-Me, 3-Me, 4-Me.



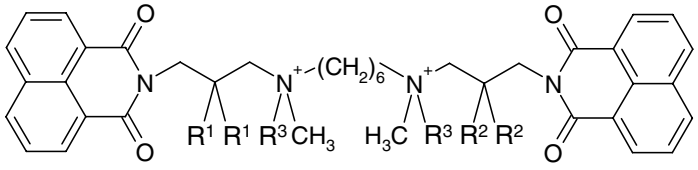
A small library of 2-deacetoxytaxinine J (DAT-J) **1** derivatives was synthesised and tested in vitro for their reversal activity in human mammary carcinoma MDR cell line MCF7-R. One of the new taxoids showed to be active at 0.1 μM when tested in combination with paclitaxel.





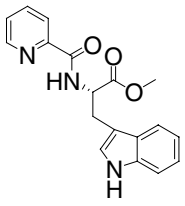
GPR40 pEC_{50} = 7.3

The discovery, solid phase synthesis and structure–activity relationships of novel carboxylic acid agonists for the GPR40 receptor are described.

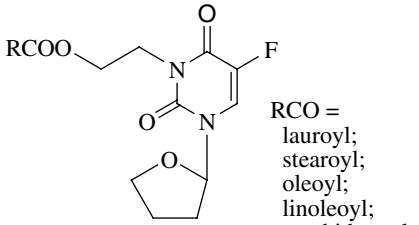


Pharmacophore mapping has been performed on farnesyltransferase inhibitors (FTIs) to quantitatively explore common chemical features among a considerable number of structures with great diversity.

Synthesis and biological activity of pseudopeptides based L-tryptophan are described. L-*o*-TrpPA being less toxic could be an effective antimicrobial broad-spectrum drug, and has a good activity against methicillin-resistant *Staphylococcus aureus* and fluconazole-resistant *Candida* spp. from clinical isolates.

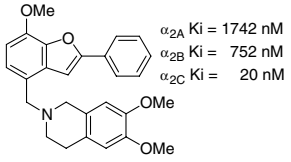


L-*o*-TrpPA (82%)

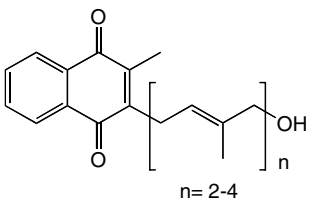


5a-5e

Syntheses and structure-activity relationships of novel fatty acid-nucleoside conjugates **5a**–**5e** are reported.

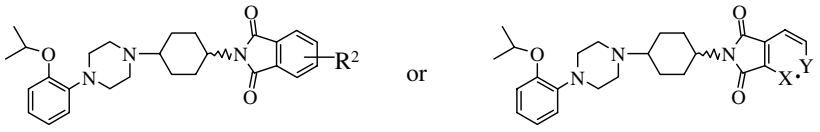


The synthesis and SAR studies of a series of novel 4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)methylbenzofuran derivatives as highly selective α_{2C}-adrenergic receptor antagonists are reported.

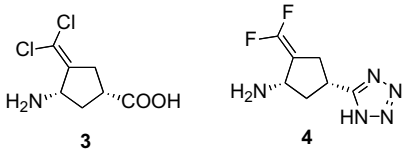


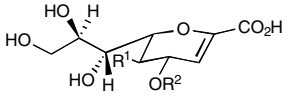
n= 2-4

Novel ω-oxygenated vitamin K_2 analogues, which were candidates for metabolites of vitamin K_2 homologues, were efficiently synthesized and their apoptosis-inducing activity was evaluated.

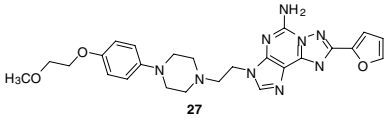


$K_i(\alpha_{1a})$, $K_i(\alpha_{1d})$ values in the range of 0.09 nM ~ 38 nM;
$K_i(\alpha_{1b})/K_i(\alpha_{1a})$ up to 401; $K_i(\alpha_{1b})/K_i(\alpha_{1d})$ up to 3607.

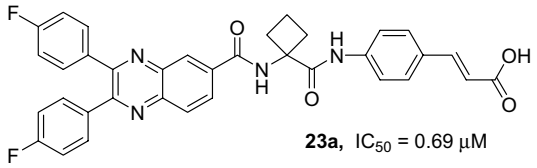




4-O-Alkylated Neu5Ac2en derivatives display micromolar inhibition of hPIV-3 sialidase activity.

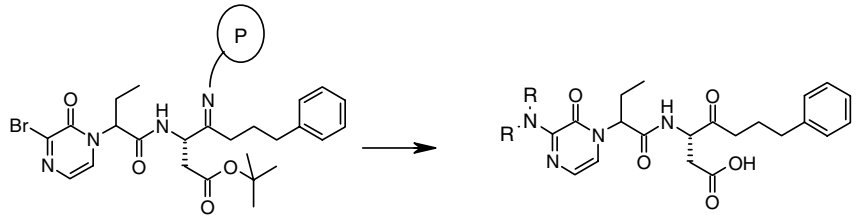


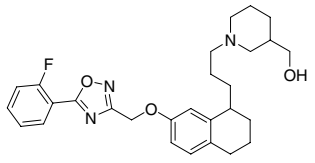
A novel series of 3-substituted-8-aryl-[1,2,4]-triazolo[5,1-*i*]purin-5-amine analogs related to Sch 58261 was synthesized in order to identify potent adenosine A_{2A} receptor antagonists with improved selectivity over the A_1 receptor, physiochemical properties, and pharmacokinetic profiles as compared to those of Sch 58261. As a result of structural modifications, numerous analogs with excellent in vitro binding affinities and selectivities were identified. Moreover, compound **27** displayed both superior in vitro and highly promising in vivo profiles.



23a, IC_{50} = 0.69 μM

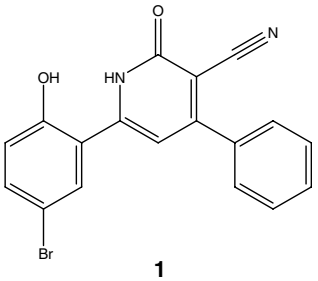
A novel quinoxaline amide was found to be active against HCV NS5B RNA-dependent RNA polymerase through SAR studies.





9, GlyT1 K_i = 10.2 nM

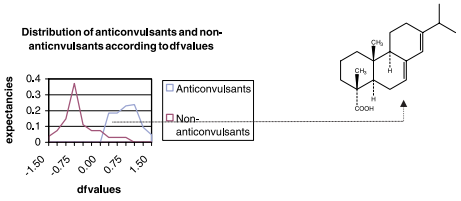
The synthesis and structure-activity relationships (SAR) of a series of indane and tetralin inhibitors of the type 1 glycine transporter, derived from a high-throughput screening (HTS) hit, are described.

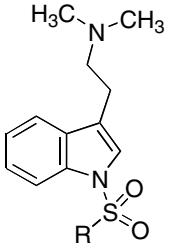


1

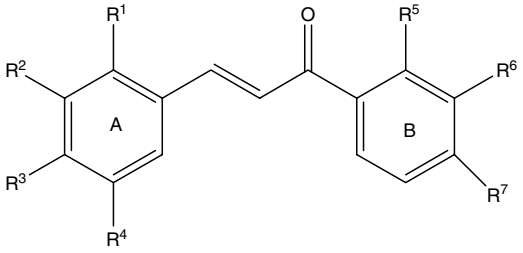
A novel class of pyridone-based inhibitors of Pim-1 kinase is reported. A complex crystal structure of Pim-1/compound **1** (IC_{50} of **1** = 50 nM) defined an inhibitory mechanism of action.

Anticonvulsant activity of abietic acid at 30 mg/kg in the Maximal Electroshock test was rationally discovered through application of a Discriminant Function based on 2D descriptors in virtual screening of a 10,000 compounds database.

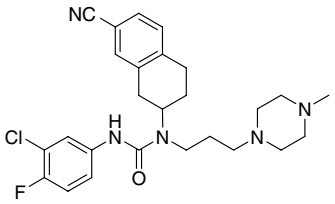




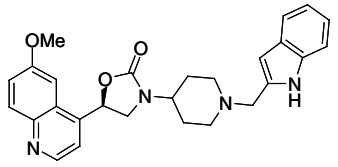
N_1-Alkylsulfonyl- (R = alkyl) and N_1-arylsulfonyltryptamines (R = aryl) bind at h5-HT_6 serotonin receptors. The latter bind with higher affinity than their N_1-benzyltryptamine counterparts, and evidence suggests they might bind in a different manner at h5-HT_6 receptors.



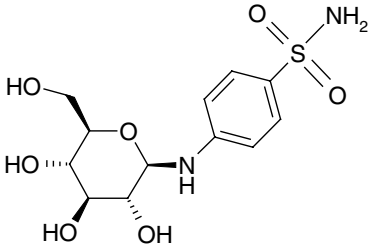
Twenty-five chalcones were synthesized, and their activity was evaluated by luciferase reporter phage (LRP) assay, and quantitative structure–activity relationship (QSAR) was developed.

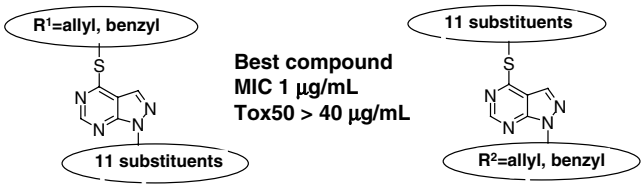


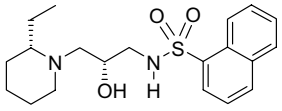
7o
MCH1R K_i = 8.5 nM



SB-649701 (**1a**), hCCR8 FLIPR pIC_{50} = 7.7



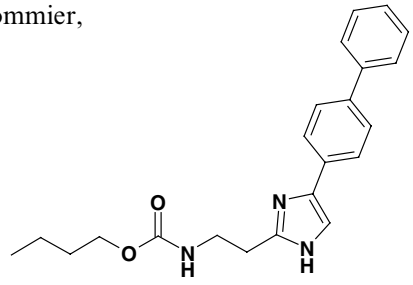




(2) pIC_{50} 7.0 (hGlyT-1c)

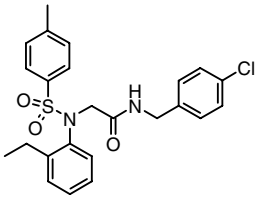
High throughput screening led to the discovery of a novel series of 1,3-diaminopropan-2-ol sulfonamides as selective GlyT-1 inhibitors. Structure–activity relationships of this novel series and optimisation of the initial hit that led to the identification of (**2**), a potent and selective GlyT-1 inhibitor, are also presented.

A series of 4-arylimidazole carbamates was synthesized and their binding affinities to the site-2 sodium (Na^+) channel were determined. SAR studies led to the identification of compound **10**, a potent Na^+ channel blocker which was efficacious in pain models in vivo.

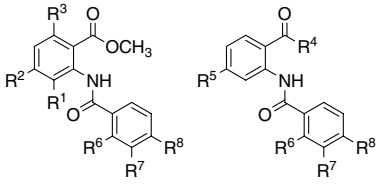


10

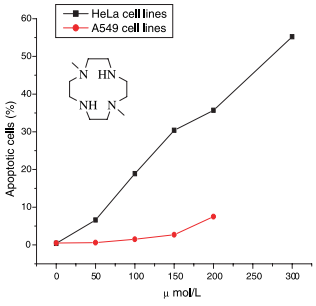
The discovery, synthesis, pharmacokinetic profile and structure–activity relationships of a novel series of non-acidic EP_1 receptor antagonists are described.



EP_1 pKi = 7.9



A series of 2-benzoylaminobenzoic esters were synthesized and subjected to anti-platelet aggregation, inhibition of superoxide anion generation, and inhibition of neutrophil elastase release assays.



OTHER CONTENTS

*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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