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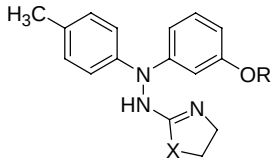
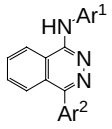
Bioorganic & Medicinal Chemistry Letters

Bioorganic & Medicinal Chemistry Letters Vol. 15, No. 21, 2005

Contents

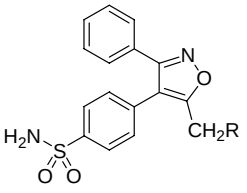


The synthesis and biological evaluation of a new series of bioisosteric phentolamine analogs are described.

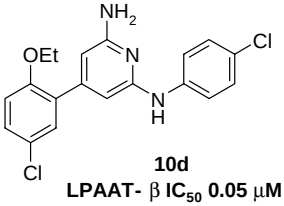


The synthesis and structure–activity relationships for a new class of arylphthalazine derivatives, which have found use as inhibitors of VEGFR-2 kinase, are reported.

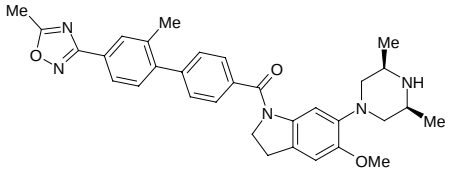
The [^{18}F]fluoromethyl analogue of valdecoxib (~2000 Ci/mmol) was synthesized by [^{18}F]fluoride-ion displacement of the corresponding tosylate in ~40% decay-corrected radiochemical yield within ~120 min from end of bombardment.



Valdecoxib R = H
[^{18}F/^{19}F]Fluoromethyl analogue R = ^{18}F/^{19}F

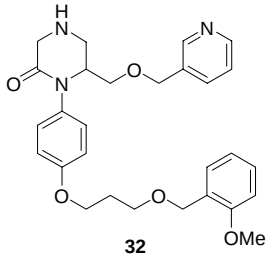


10d
LPAAT-β IC_{50} 0.05 μM
LPAAT-α IC_{50} >40 μM



Introduction of *cis*-2,6-dimethyl substitution onto the piperazine ring of a mixed 5-HT$_{1ABD}$ receptor antagonist offers a combination of both excellent selectivity over 5-HT$_{1A}$ and 5-HT$_{1D}$ receptors and low intrinsic activity.

Inhibition of renin enzymatic activity by a series of ketopiperazine-based compounds containing a C6 benzyloxymethyl substituent correlated with a $+(\pi+\sigma)$ effect. A 3-pyridinyloxymethyl substituent was also found to be equipotent as higher molecular weight analogs, and exhibited decreased CYP3A4 inhibition levels and improved pharmacokinetic properties.



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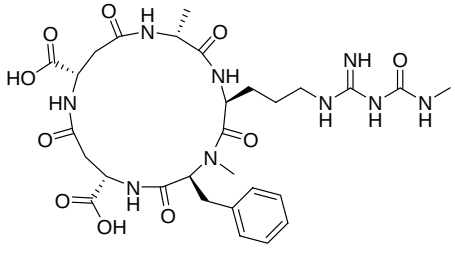
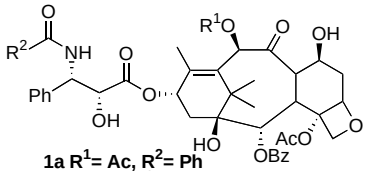
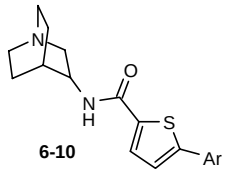
Argifin



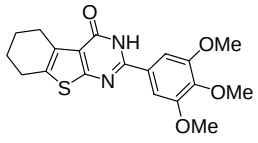


1a R^1= Ac, R^2= Ph
1b R^1= H, R^2= O*t*Bu

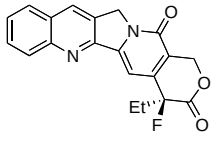
The synthesis and biological activities of docetaxel analogues possessing a peptide side chain at the C3′-N position are described. The chosen amino acids are part of the α-tubulin loop that is equivalent to the paclitaxel binding pocket in β-tubulin.



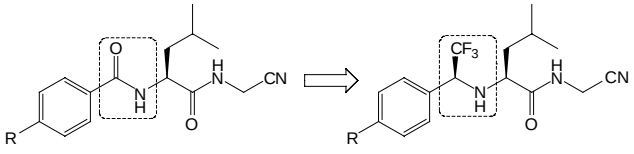
Certain quinuclidine 3-biarylcarboxamides are high affinity nicotinic α7 ligands with an excellent binding selectivity over the 5-HT$_3$ receptor.



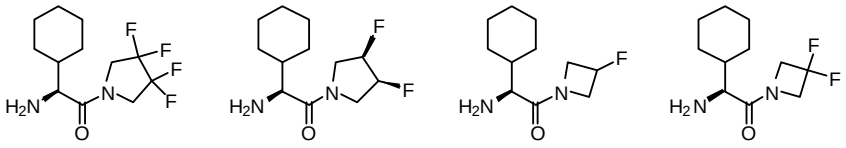
A novel series of anti-proliferative agents containing the thieno[2,3-*d*]pyrimidin-4-one scaffold and the structure–activity relationship studies to improve potency is described.

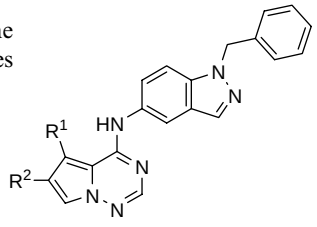


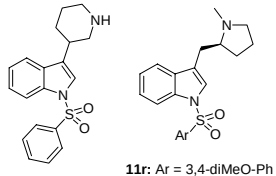
Both enantiomers of 20-fluorocamptothecin and the racemate have been prepared by total synthesis. The (*R*)-enantiomer is essentially inactive in a topoisomerase-I/DNA assay, while the (*S*)-enantiomer is much less active than 20(*S*)-camptothecin. The lactone ring of 20-fluorocamptothecin hydrolyzes more rapidly than that of camptothecin in PBS.



Replacing an amide bond with a trifluoroethylamine leads to potent and selective inhibitors of cathepsin K. The CF_3 group provides a non-basic amine that makes a good hydrogen bond with the enzyme active site.



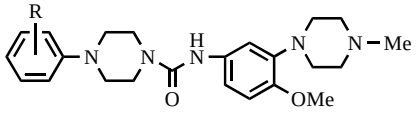




9a

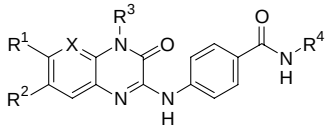
11r: Ar = 3,4-diMeO-Ph
11t: Ar = 5-Cl-thienyl

The discovery of N_1-arylsulfonyl-3-piperidin-3-yl-, -3-(1-methylpyrrolidin-2-ylmethyl)-, and -3-pyrrolidin-3-yl-1*H*-indoles as high affinity 5-HT$_6$ receptor ligands is described. N_1-Benzenesulfonyl-3-piperidin-3-yl-1*H*-indole **9a** is a 24 nM full agonist, while N_1-arylsulfonyl-3-(1-methylpyrrolidin-2-ylmethyl)-1*H*-indole derivatives **11r** and **11t** behave as very potent antagonists.

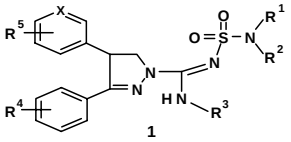


6a: R = 2-Cl; **6e**: R = 4-Ph
6b: R = 2-F; **6f**: R = 4-CF_3
6c: R = 4-Cl; **6g**: R = 4-SMe
6d: R = 4-F;

A series of serotonin 5-HT$_{1B}$ ligands were synthesized and evaluated for their potency and selectivity against other 5-HT receptor subtypes. Many of these new compounds displayed high affinity and selectivity for the 5-HT$_{1B}$ receptor and compound **6c** was found to have the in vitro binding profile necessary for development as a PET radioligand.

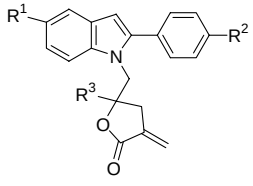


A series of 3-anilino-quinoxalinones has been identified as a new class of glycogen phosphorylase inhibitors.

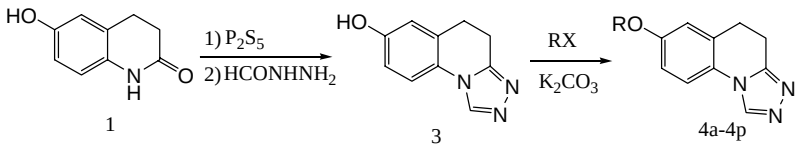


1

Novel 3,4-diaryldihydropyrazoles **1** as potent CB_1 receptor antagonists with lower lipophilicity are described. The key change is the replacement of the arylsulfonyl group in the original series by a dialkylaminosulfonyl moiety.

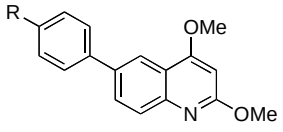


A novel series of indole α-methylene-γ-lactones with remarkable inhibition ability on phosphorylation of AKT, mTOR, p70S6 kinase, and 4E-BP1 has been synthesized.

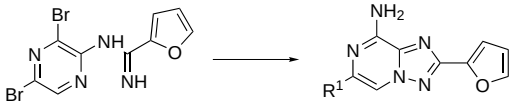


1 3 4a-4p

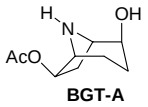
A series of new 7-alkoxyl-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinolines has been synthesized and evaluated as anticonvulsant agents. The MES and scMet tests show that 7-(4-fluorobenzyloxy)-4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinoline **4l** was found to be the most potent, with ED_{50} values of 11.8 and 6.7 mg kg^{-1}, respectively.



A number of aryl-substituted 2,4-dimethoxyquinolines have been synthesized and tested against a range of nematodes. The 6-substituted compounds show significant activity against resistant strains.

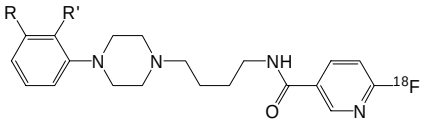


This paper describes the preparation, by a novel route, of A_{2A} receptor antagonists containing the [1,2,4]triazolo[1,5-*a*]pyrazine nucleus, which is isomeric with the [1,2,4]triazolo[1,5-*c*]pyrimidine core of a series of known A_{2A} antagonists with in vivo activity in animal models of Parkinson's disease.

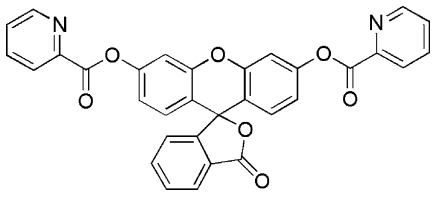


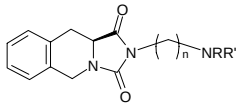
BGT-A

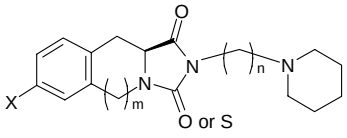
A new CoMFA model of baogongteng A (BGT-A) and its derivatives with agonistic activity to muscarinic receptors was constructed, discussed, and examined. This model could provide solid basis for designing novel molecules with higher agonistic activity to muscarinic receptors.



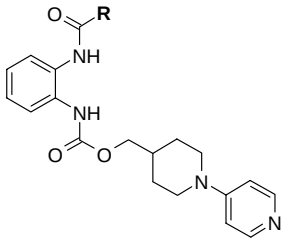
A series of dopamine D3 receptor radioligands were synthesized. The 6-fluoropyridin-3-yl derivative [^{18}F]**8d** displayed good D3 affinity (K_i = 1.1 nM) and was used for receptor autoradiography studies on rat brain slices.

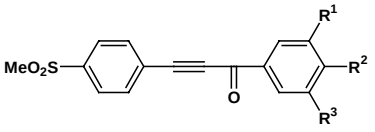




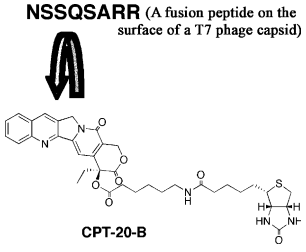


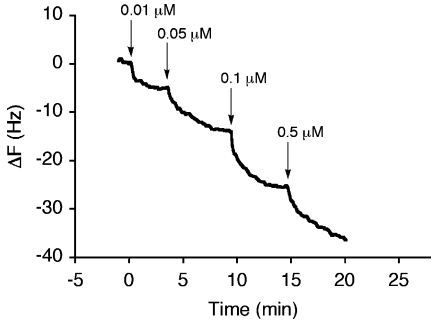
n = 2 or 3
m = 0 or 1
X = H or OH

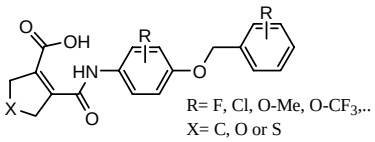




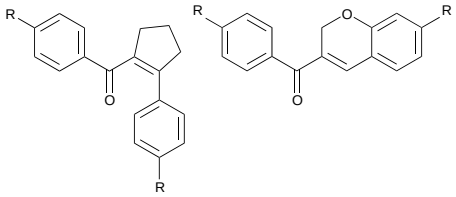
11 (R^1 = H, OMe, F; R^2 = H, Me, CF_3, CN, F; R^3 = H, OMe)

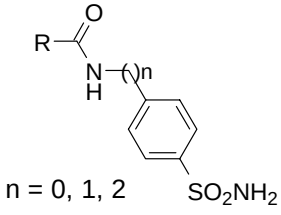


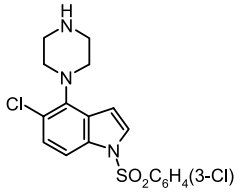




Novel DHODH inhibitors were developed, based on a previously described series by introduction of heteroatoms into the cyclopentene ring and hydroxyl groups attached to it. Also, the hydrophobic biphenyl side chain was replaced with benzyloxy phenyl groups. Activities on human, rat, and mouse enzymes indicate a species specificity of these inhibitors.







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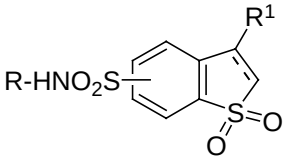

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*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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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ISSN 0960-894X