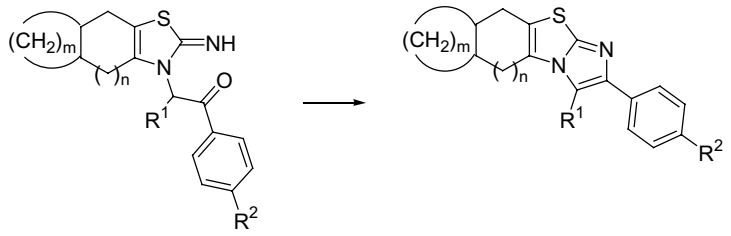
ELSEVIER

Bioorganic & Medicinal Chemistry Letters

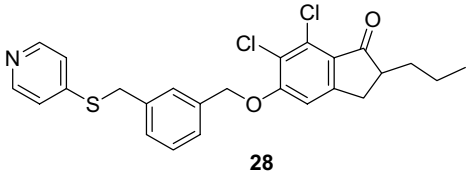
Bioorganic & Medicinal Chemistry Letters Vol. 15, No. 6, 2005

Contents

COMMUNICATIONS

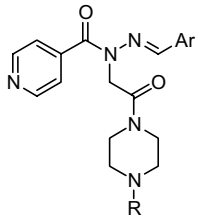


We have identified and synthesized a series of phenyl-tetrazolyl and 4-thiopyridyl indanones as allosteric potentiators of the metabotropic glutamate receptor 2. Structure activity relationship studies directed toward improving the potency and level of potentiation, as well as PK properties, led to the discovery of **28** (EC_{50} = 186 nM), which displayed activity in a rodent model for schizophrenia.



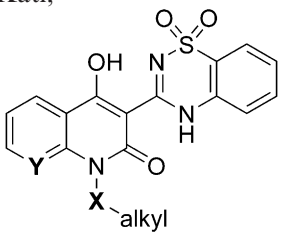
28

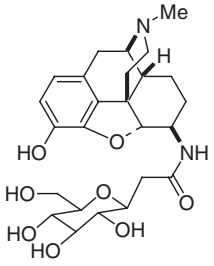
Synthesis and in vitro antituberculosis activity of new series of isonicotinic acid *N′*-arylidene-*N*-[2-oxo-2-(4-aryl-piperazin-1-yl)-ethyl]-hydrazide derivatives **6**–**9** has been described.

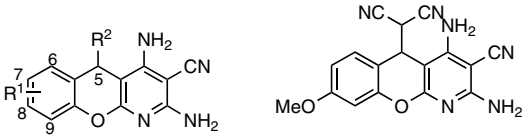


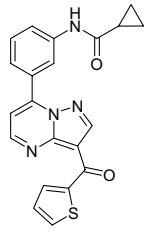
6–9

N-1-Alkylamino and *N*-1-alkyloxy-4-hydroxyquinolon-3-yl benzothiadiazines were evaluated as inhibitors of genotype 1 HCV polymerase.









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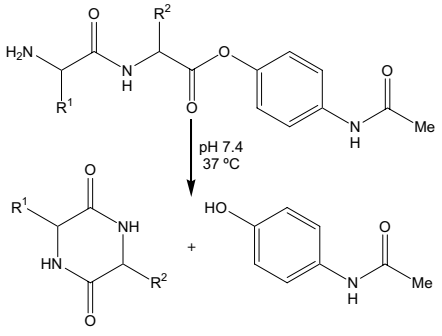
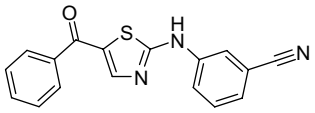
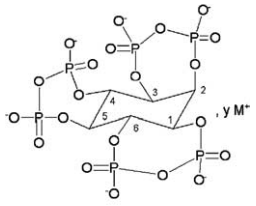




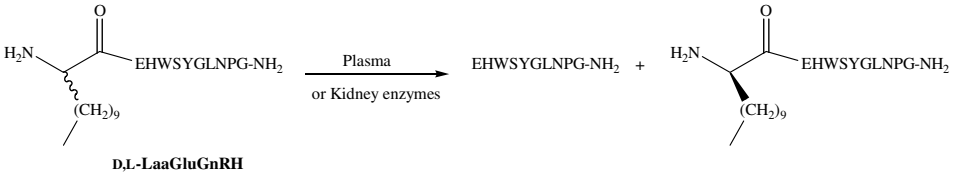
4

A novel 4-aminothiazole hit class was discovered by virtual screening, and the SAR was explored in two rounds of iterative optimisation.

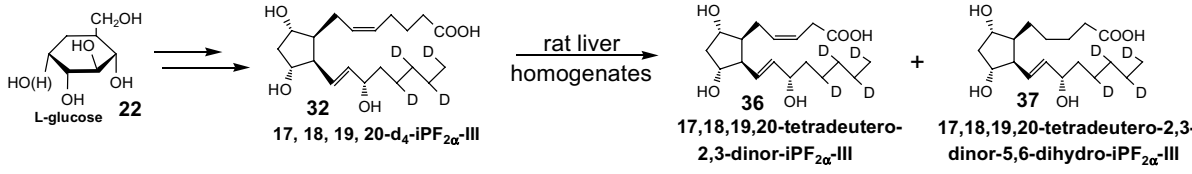


Inositol Tripyrophosphate Salts

Inositol tripyrophosphate (ITPP) salts were found to serve as allosteric effectors of haemoglobin giving a significant P_{50} shift of the oxygen–haemoglobin dissociation curve, with free haemoglobin and whole blood, in vitro.

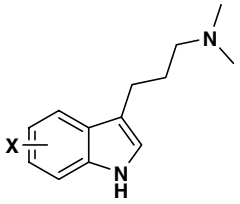


D,L-LaaGluGnRH

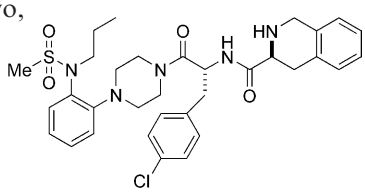


L-glucose 22 — 32 17, 18, 19, 20-d_4-iPF$_{2\alpha}$-III — 36 17,18,19,20-tetradeutero-2,3-dinor-iPF$_{2\alpha}$-III — 37 17,18,19,20-tetradeutero-2,3-dinor-5,6-dihydro-iPF$_{2\alpha}$-III

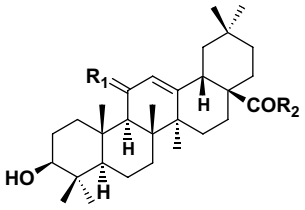
We described herein the total synthesis and metabolism studies of 17,18,19,20-d_4-iPF$_{2\alpha}$-III.

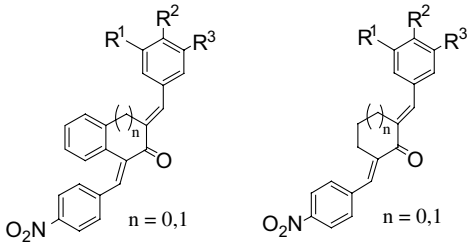


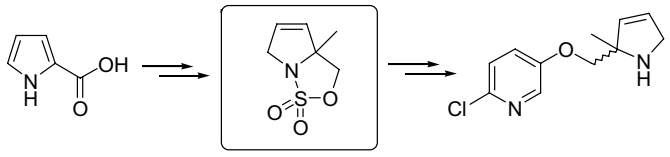
2 A-L



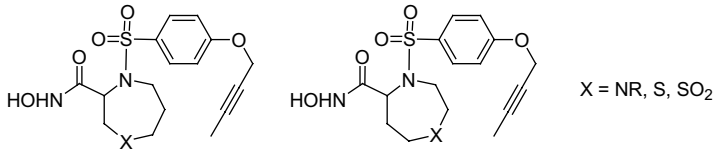
MC4R EC_{50} = 0.4 nM
MC3R EC_{50} >10,000 nM
MC5R EC_{50} = 210 nM
orally active in mouse feeding model



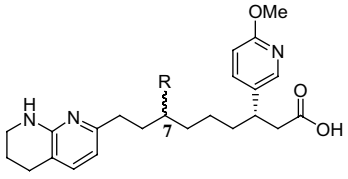




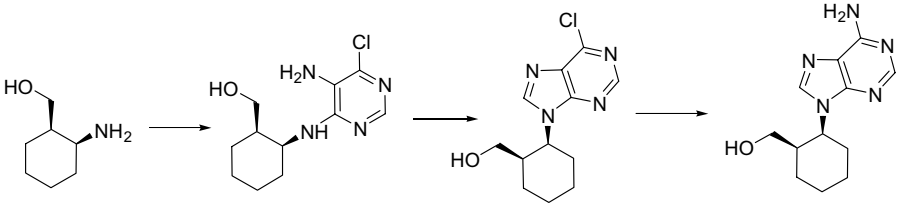
We describe herein the synthesis and analgesic evaluation of a new series of 3-pyridyl ethers which are analogs of the nicotinergic compound tebanicline (ABT-594).

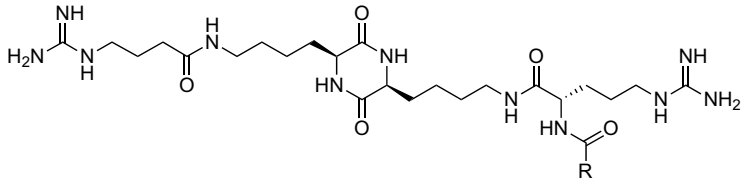


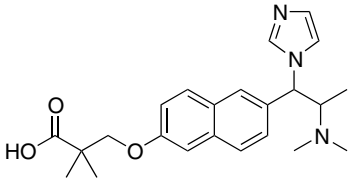
Potent and selective TACE and MMP inhibitors utilizing the diazepine and thiazepine ring systems were synthesized and evaluated for biological activity in in vitro and in vivo models of TNF-α release and arthritis.

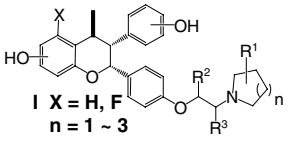


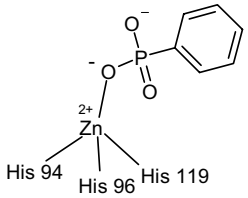
Potent, novel 7-oxo $\alpha_v\beta_3$ antagonists have been prepared. These antagonists offer decreased plasma protein binding and excellent pharmacokinetic profiles.

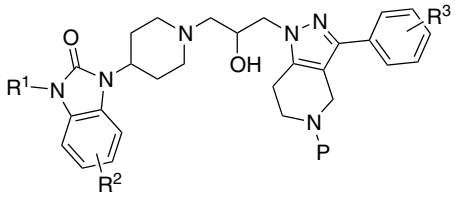




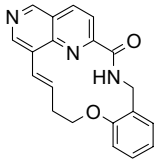




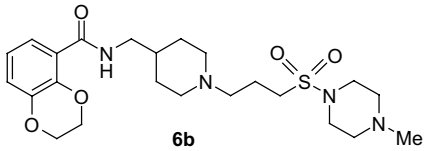




Noncovalent, potent, selective and orally bioavailable inhibitors of the cysteine protease cathepsin S are reported.

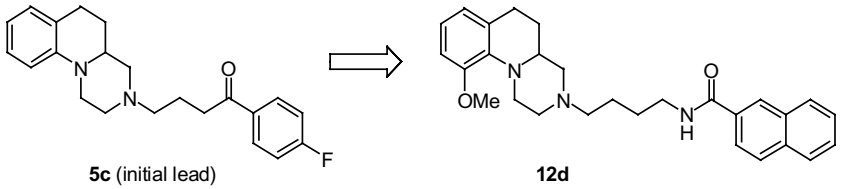


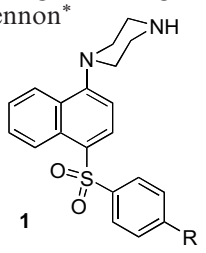
A novel class of macrocyclic 1,6-napthyridines designed to adopt the presumed bioactive conformation of anti-HCMV acyclic 1,6-napthyridines are described. Both 14- and 15-membered macrocycles were shown to be highly potent against HCMV HSV-1 and HSV-2.



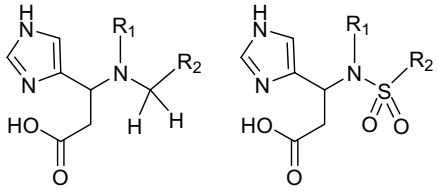
6b

Replacement of the *N*-butyl side-chain of lead 5-HT$_4$ receptor antagonist **2** with propanesulfonylpiperidinyl, morpholinyl, and piperazinyl groups led to higher affinity analogs **4**–**6**. In vitro drug metabolism screens and cassette pharmacokinetic studies in the dog led to identification of the *N*-methylpiperazinyl analog (**6b**), which displayed pharmacokinetic, selectivity, and safety parameters sufficient for advancement to the clinic for the treatment of urinary incontinence.



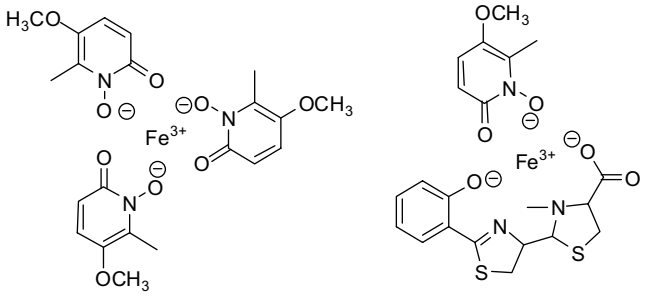


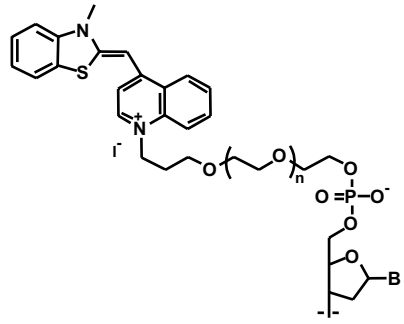
4-Arylsulfone derivatives of 1-(1-naphthyl)piperazine represent a novel class of human 5-HT_6 serotonin receptor ligands. In particular, compounds such as **1f** (**1**; R = H; K_i = 3.8 nM) and **1g** (**1**; R = NH_2; K_i = 0.9 nM) displayed high affinity for this receptor population, and **1f** was shown to behave as a 5-HT_6 antagonist.

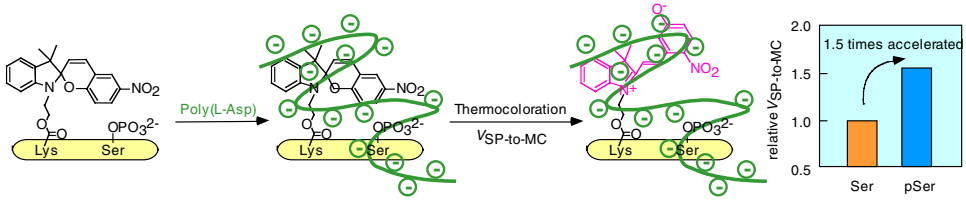


Synthesis and biological evaluation of imidazol-4-yl-β-amino acid derivatives is reported.

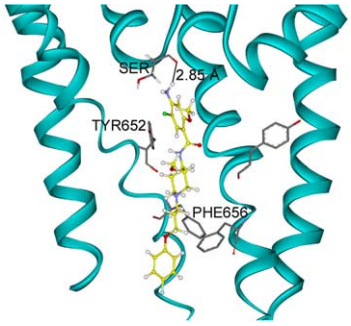
The synthesis of cepabactin and the corresponding iron (III) complex is described. The purification and characterization of a mixed complex between iron (III), pyochelin and cepabactin is also reported.

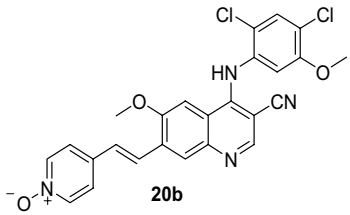






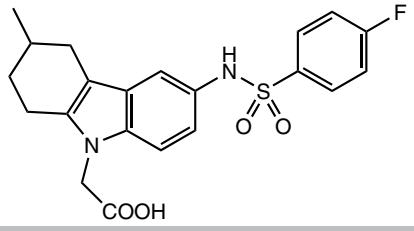
A unique chromism-based assay (CHROBA) technique using photochromic spiropyran-containing peptides has been firstly established for detection of protein kinase A-catalyzed phosphorylation. The promising method has advantages that avoid isolation and/or immobilization of substrates to remove excess nonreactive isotope-labeled ATP or fluorescently-labeled anti-phosphoamino acid antibodies from the reaction mixture.





New ethynyl and ethenyl-4-phenylamino-3-quinolinecarbonitrile derivatives were synthesized and tested for Src inhibition. The *N*-oxide derivative **20b** is the first 3-quinolinecarbonitrile to show subnanomolar inhibitory activity in a Src enzyme assay.

The chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH-2), also found on eosinophils and basophils, is a prostaglandin D_2 receptor involved in the recruitment of these cell types during an inflammatory response. In this report, we describe the synthesis and optimization of a ramatroban isostere that is a selective and potent antagonist of CRTH-2 which may be useful in the treatment of certain diseases.



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Two views of a ribbon representation of the homology model for the pore region of the hERG K^+ channel. The effective size of the pore changes as the channel moves from a closed to open state. Modeling suggests that the hERG channel can use this flexibility to accommodate a wide variety of ligands. The red, yellow, and green structures correspond to increasingly open states for this K^+ channel [Rajamani, R.; Tounge, B. A.; Li, J.; Reynolds, C. H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1737].

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