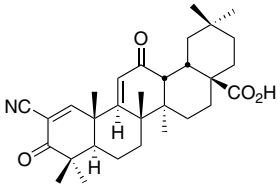
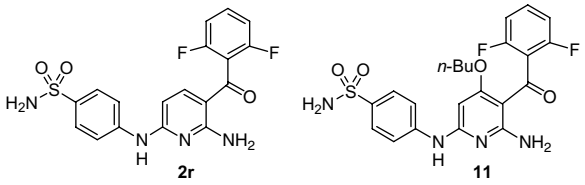
ELSEVIER

Bioorganic & Medicinal Chemistry Letters

Bioorganic & Medicinal Chemistry Letters Vol. 15, No. 9, 2005

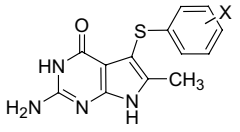
Contents





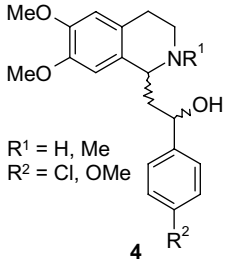
A novel series of 2,6-diamino-3-acylpyridines were designed and synthesized as cyclin-dependent kinase (CDK) inhibitors. The representative compounds **2r** and **11** showed potent CDK1 and CDK2 inhibitory activities and inhibited cellular proliferation in HeLa, HCT116, and A375 tumor cells.

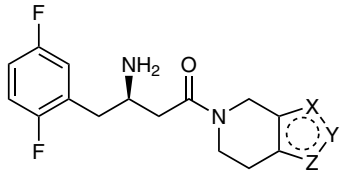
A series of 17 novel 2-amino-4-oxo-5-[(substituted phenyl)thio]pyrrolo[2,3-*d*]-pyrimidines were synthesized as potential inhibitors of thymidylate synthase (TS) and as antitumor agents. The analogues contain a variety of electron withdrawing substituents on the phenyl ring of the side chain and were evaluated as inhibitors of human TS (hTS) and *Escherichia coli* TS and of human and *E. coli* dihydrofolate reductase (DHFR). The analogues **14**, **17**, and **18** were potent inhibitors of hTS with IC_{50} values of 0.28, 0.21, and 0.22 μM, respectively, and were more potent than the clinically used ZD1694, **2** and LY231514, **3** against human TS.



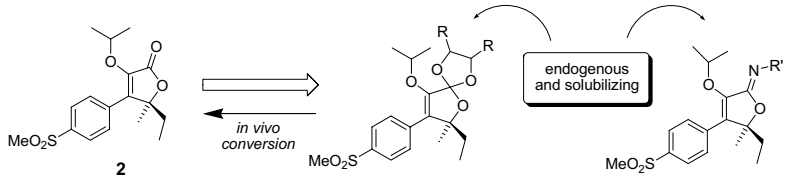
X = F, Cl, Br, CN, NO_2, CF_3, OCF_3

The enantiopure 2-(1,2,3,4-tetrahydro-1-isoquinolyl)ethanol derivatives **4** were evaluated for their affinity to the ifenprodil binding site of the NMDA receptor, their potency to inhibit [^{3}H]MK801 binding, their NMDA-NR2B subtype selectivity and their affinity to HERG K+ channels.

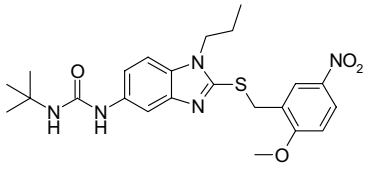


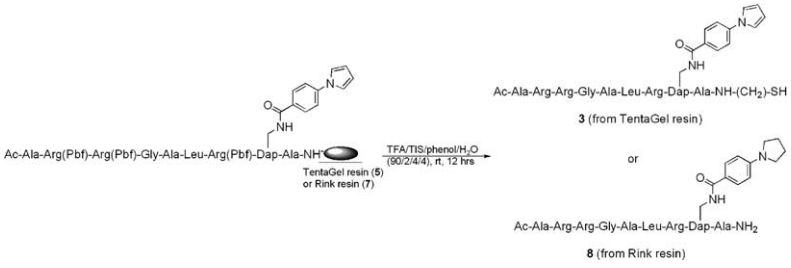


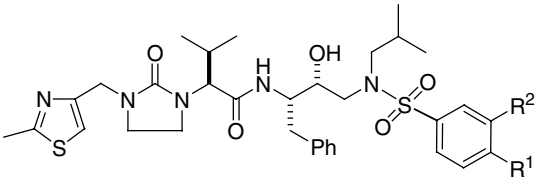
A series of β-aminoacylpiperidines bearing various fused five-membered heterocyclic rings was synthesized as dipeptidyl peptidase IV inhibitors. Potent and relatively selective inhibition could be obtained, depending on the choice of heterocycle, regioisomerism, and substitution.



Interest in water soluble COX-2 inhibitors that can be administered intravenously led to the development of novel pro-drugs of a furanone based COX-2 inhibitor **2**. Transforming the lactone moiety of the furanone to an imidate or an *ortho*-ester with a hydrophilic, endogenous appendage resulted in water soluble pro-drugs that converted to the parent drug in vivo.

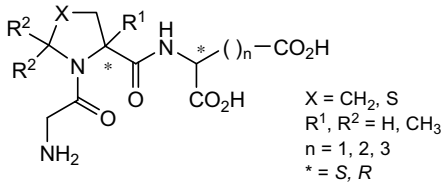


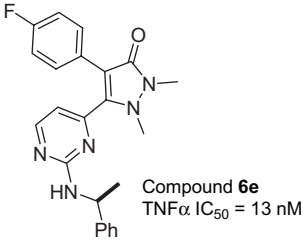


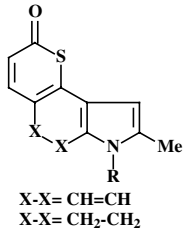


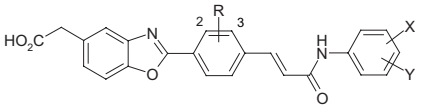
A novel series of arylsulfonamides with various R^1 and R^2 groups were prepared and evaluated as HIV protease inhibitors against both the wild type and A17 resistant viruses. The X-ray crystal structure of the most active oxime analog bound in the enzyme active site is presented.

A series of Pro and/or Glu modified GPE analogues is described. Compounds incorporating P^{Me} and dmP showed higher affinity for glutamate receptors than GPE and neuroprotective effects similar to those of this endogenous tripeptide in culture hippocampal neurons exposed to NMDA.

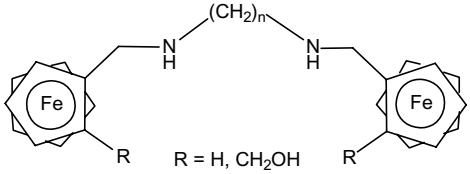




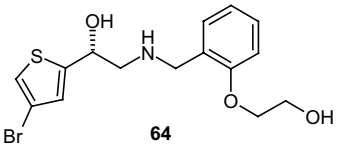




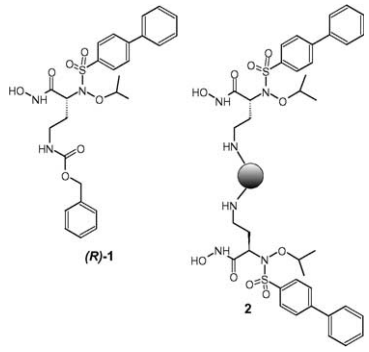
Using a furanylthiazole acetic acid as a starting point, a novel series of benzoxazol-5-yl acetic acid derivatives have been identified as heparanase inhibitors. Several compounds possess an IC_{50} of ~200 nM against heparanase.



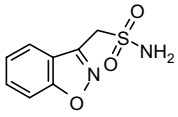
The synthesis and initial in vitro evaluation of ferrocenyl diamino alcohols and diamines as a new class of antimycobacterial ethambutol analogues are reported.

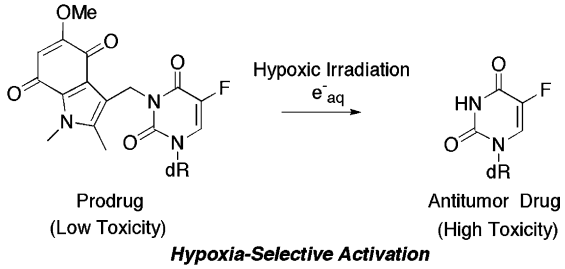


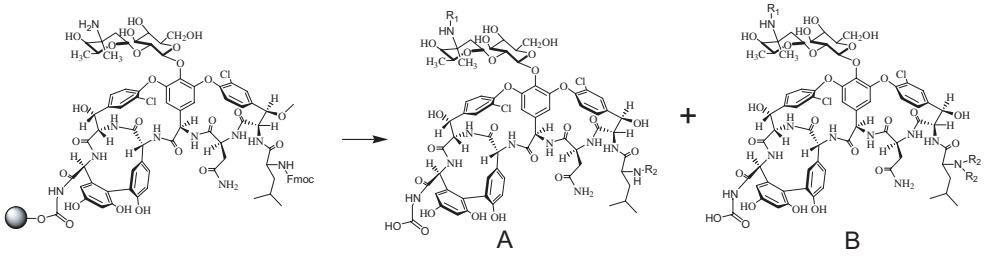
High throughput screening of *Staphylococcus aureus* phenylalanyl tRNA synthetase (FRS) identified an ethanolamine as a sub-micromolar hit. Optimisation studies led to the enantiospecific lead **64**, a single-figure nanomolar inhibitor. The inhibitor series shows selectivity with respect to the mammalian enzyme and the potential for broad spectrum bacterial FRS inhibition.

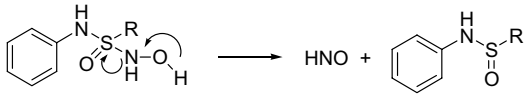


Starting from the potent MMP-2/MMP-14 inhibitor (*R*)-**1** we describe new dimeric compounds of type **2**, which are able to give an inhibitor–enzyme interaction more complex than that allowed for monomeric compounds of type **1** potentially, thus influencing positively the potency and/or selectivity of the new compounds, if compared with those of (*R*)-**1**.

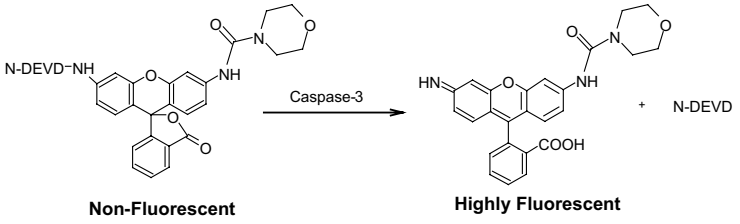




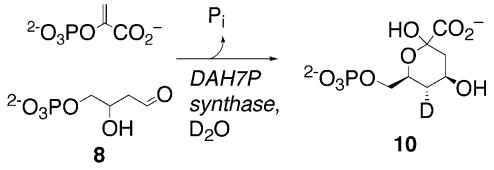




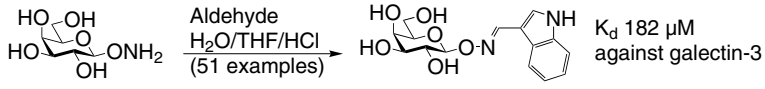
Chlorination and condensation of simple sulfinamides with *O*-benzyl and *O*-*tert*-butyl dimethyl siloxy hydroxylamine gives *O*-protected *N*-hydroxy sulfonimidamides. Deprotection of these compounds produces the corresponding sulfinamide and nitrous oxide, which provides evidence for the intermediacy of nitroxyl (HNO) and identifies these compounds as new potential HNO donors.

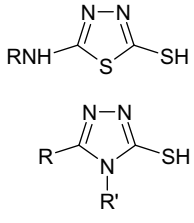


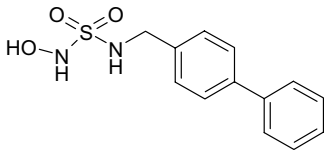
The title compound is a single step cleavage fluorogenic substrate and has significantly higher enzyme turnover rate and sensitivity than existing fluorogenic substrates for detecting caspase-3 activity both in solution and living cells.

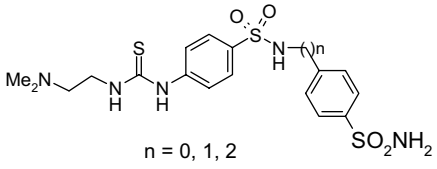


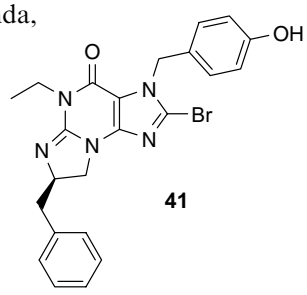
The synthesis of racemic 2-deoxyerythrose 4-phosphate and the selection of one enantiomer of this compound as a substrate for 3-deoxy-D-*arabino*-heptulosonate 7-phosphate synthase are reported. When the enzyme reaction was carried out in deuterium oxide stereospecific deuteration of the product was observed.



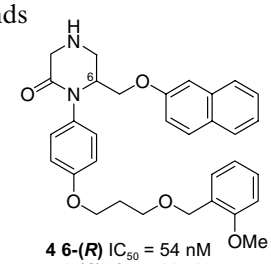




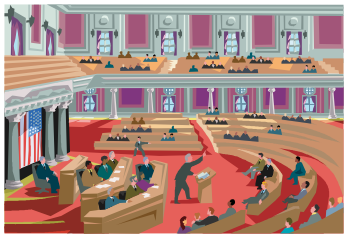




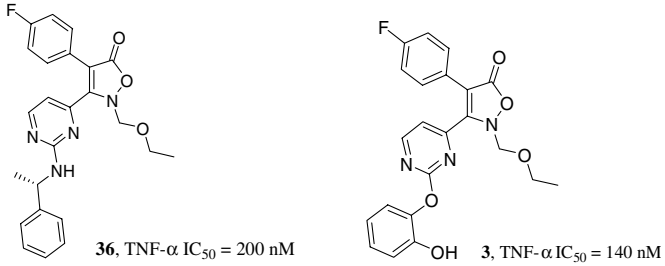
In search of a PDE5 inhibitor for erectile dysfunction, an SAR was developed from a PDE1/PDE5 purine series of leads, which had modest PDE5 potency and poor isozyme selectivity. A compound (**41**) with PDE5 inhibition and in vivo activity similar to sildenafil was discovered from this effort. In addition, purine **41** demonstrated superior overall PDE isozyme selectivity when compared to the approved PDE5 inhibitors sildenafil, vardenafil, and tadalafil, which may result in a more favorable side-effect profile.



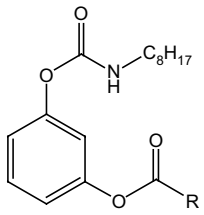
Both enantiomeric configurations of the 6-alkoxymethyl-1-aryl-2-piperazinone scaffold display equipotent renin inhibition activity and similar SAR patterns.



Session adjourned! DPD analogs fail to produce quorum.

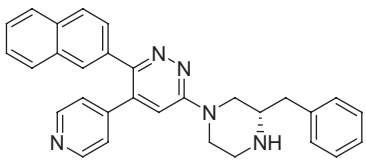


36, TNF-α IC_{50} = 200 nM **3**, TNF-α IC_{50} = 140 nM

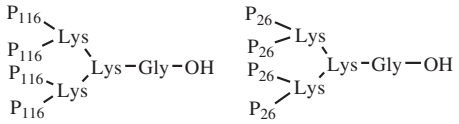


1-9

For the steady state inhibitions of PLA2 by **1–9**, $pK_i = 3.88 \pm 0.06 - (0.08 \pm 0.03)\sigma^* + (0.15 \pm 0.02)\pi$. For the pre-steady state inhibitions of PLA2 by **1–9**, $\log(k_1/k_{-1}) = 5.21 \pm 0.01 - (0.09 \pm 0.01)\sigma^*$ and $\log(k_2/k_{-2}) = -1.29 \pm 0.07 - (0.13 \pm 0.02)\pi$.



Novel potent trisubstituted pyridazine inhibitors of p38 MAP (mitogen activated protein) kinase are described that have activity in both cell-based assays of cytokine release and animal models of rheumatoid arthritis. They demonstrated potent inhibition of LPS-induced TNF-α production in mice and exhibited good efficacy in the rat collagen induced arthritis model.



$(P_{116})_4$-MAP $(P_{26})_4$-MAP

P_{116}: Pro-Gln-Glu-Glu-Lys-Ile-Thr-Lys-Glu-Ile-Leu-Asn-Gly-Lys

P_{26}: Ala-Ala-Gly-Val-Asp-Tyr-Glu-Asp-Glu-Arg-Ile-Ser-Phe-Gln-Asp-Trp-Pro-Lys

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Trisubstituted pyridazines derivatives (gold and blue) modeled in the active site of p38α MAP kinase crystal structure. A structure-based design approach was used to guide the evolution of the original class resulting in a novel p38α inhibitor series. [Tamayo, N.; Liao, L.; Goldberg, M.; Powers, D.; Tudor, Y.-Y.; Yu, V.; Wong, L. M.; Henkle, B.; Middleton, S.; Syed, R.; Harvey, T.; Jang, G.; Hungate, R.; Dominguez, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2409.]

Indexed/Abstracted in: Adis LMS Drug Alerts, Beilstein, Biochemistry & Biophysics Citation Index, BIOSIS previews, CAB Abstracts, CAB Health, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/Elsevier BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE

ELSEVIER

ISSN 0960-894X