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Bioorganic &
Medicinal
Chemistry
Letters

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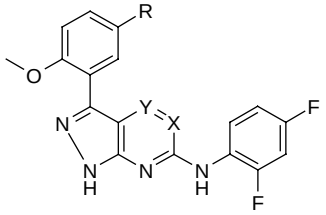
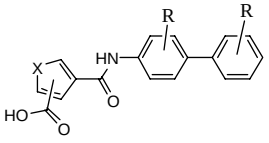
Contents

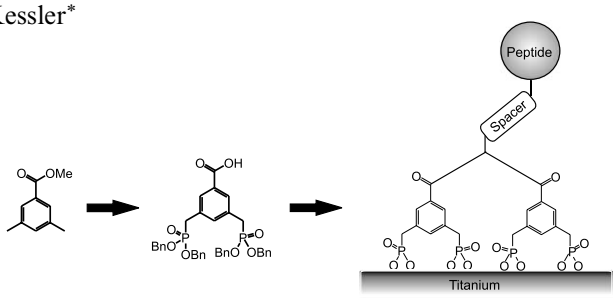
ARTICLES



A test library with three novel p38α inhibitory scaffolds and a narrow set of substituents was prepared. Appropriate combination of substituents and scaffolds generated potent p38α inhibitors, for example, pyrazolo[3,4-*b*]pyridine **9**, pyrazolo[3,4-*d*]pyrimidine **18a** and pyrazolo[3,4-*b*]pyrazine **23b** with potent in vivo activity upon oral administration in animal models of rheumatoid arthritis.

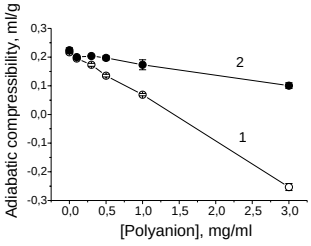


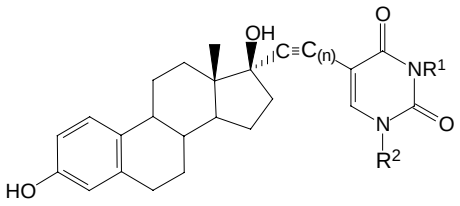
A previously discovered DHODH inhibitor series was improved by replacing a cyclopentene ring by aromatic heterocycles. The compounds were prepared by the directed *ortho*-metallation procedure. Inhibitory activities were in the low nanomolar range and the compounds show potent immunosuppressive effects on stimulated PBMC's.



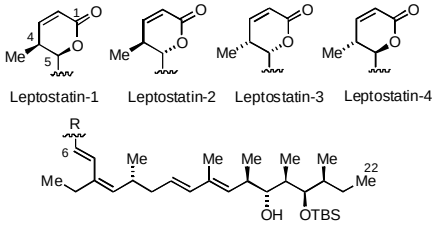
Cyclic RDG-peptides were anchored on titanium with phosphonic acids, protected as benzylesters during synthesis, to enhance osteoblast adhesion.

The ultrasound velocimetry, densitometry, and differential scanning calorimetry have been used to study the formation of the complexes between human serum albumin (HSA) and polyanions heparin (HEP) and/or dextran sulfate (DS). Adiabatic compressibility and phase transition temperature of HSA decreased with increasing concentration of HEP (1) and DS (2). Changes of compressibility can be caused by increase of the hydration due formation of the HSA–polyanion complexes and due to partial unfolding of HSA. HEP more strongly interacts with HSA then DS.





Nucleosides were coupled to estradiol via a 17α-ethynyl spacer group using Pd(II) as a catalyst and evaluated in vitro for estrogen receptor binding affinity and cytotoxicity.

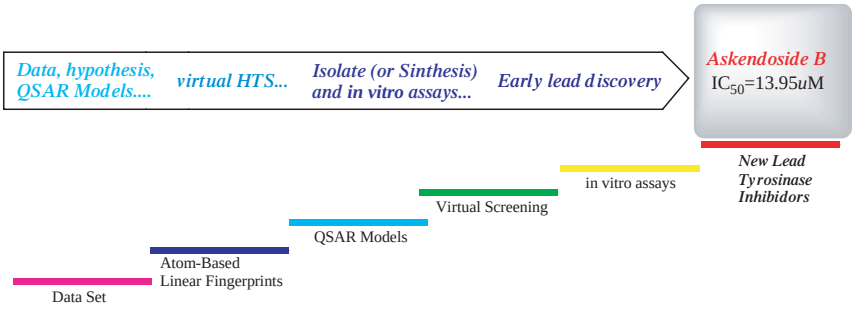


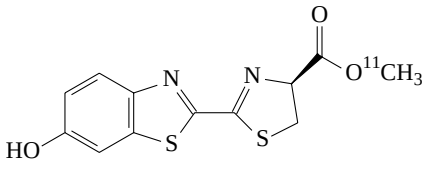
Cytotoxicity Toward HCT-116 Cells

compound	IC_{50}, nM[a]
leptostatin-1	3.0
leptostatin-2	2.0
leptostatin-3	0.2
leptostatin-4	30
callystatin A	0.03

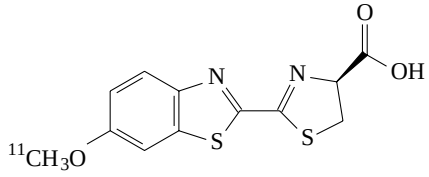
[a] average of two determinations

Four stereoisomeric hybrids of the antitumor natural products callystatin A and leptomycin B have been prepared by total synthesis and evaluated as cytotoxic agents toward H-116 human colon cancer cells.

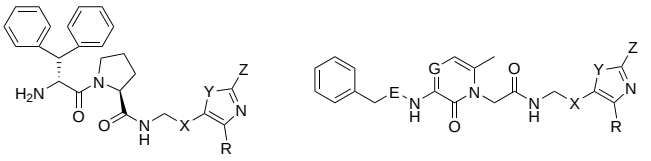




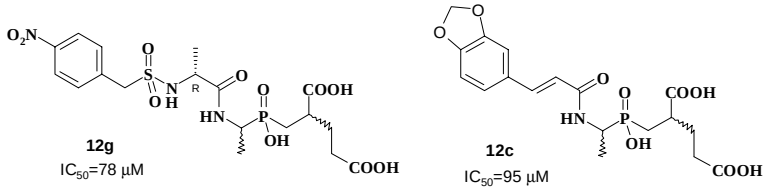
D-luciferin [^{11}C]methyl ester ([^{11}C]LMEster, [^{11}C]**1**)



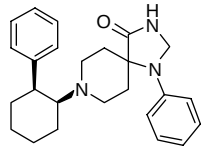
D-luciferin [^{11}C]methyl ether ([^{11}C]LMEther, [^{11}C]**2**)



Imidazoles and aminothiazoles, in spite of their weak basicity, have been optimized to function as potent P1 ligands in both a peptide series and a nonpeptide series of noncovalent small molecule thrombin inhibitors.



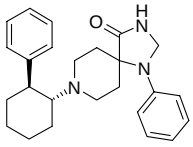
A series of new inhibitors of the D-glutamic acid-adding enzyme (MurD) is presented. Two compounds (**12g** and **12c**) had IC_{50} values near 100 μM and constitute a promising starting point for further development.



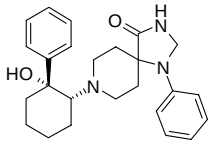
1

Screening of the Roche compound library led to the identification of *cis*-*N*-(2-phenyl-cyclohexyl)-spiropiperidine **1** as structurally novel GlyT1 inhibitor. The SAR, which was developed in this series, resulted in the discovery of highly potent compounds displaying excellent selectivity against the GlyT2 isoform.

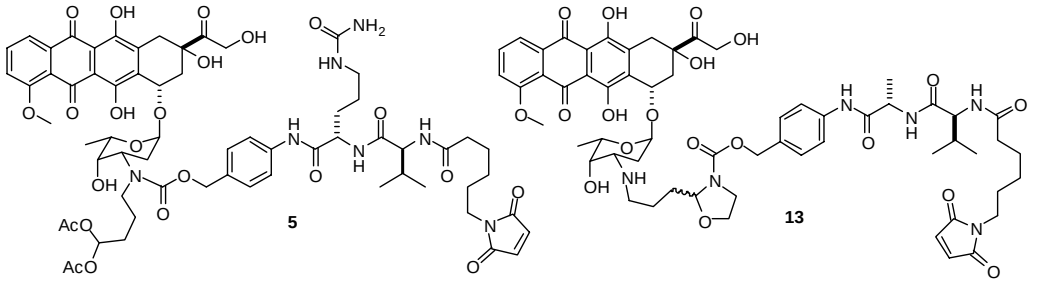
During SAR exploration of *N*-(2-aryl-cyclohexyl) substituted spiropiperidine as GlyT1 inhibitors, it was found that introduction of a hydroxy group in position 2 of the cyclohexyl residue considerably improves the pharmacological profile. In particular, reduction of the binding affinity at the nociceptin/orphanin FQ peptide and the μ opioid receptors was achieved.

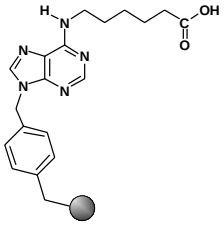


GlyT1 EC_{50} (μM): 0.073
NOP IC_{50} (μM): 0.310
μ IC_{50} (μM): 0.520



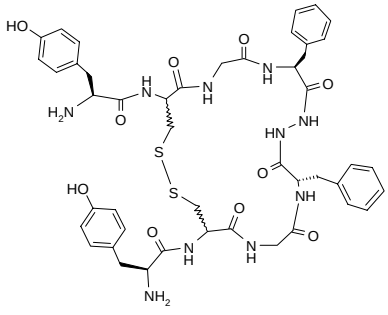
GlyT1 EC_{50} (μM): 0.044
NOP IC_{50} (μM): 15
μ IC_{50} (μM): 2.7

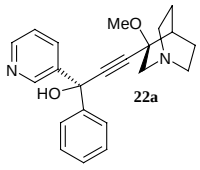




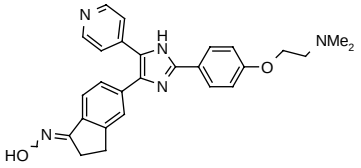
Use of polymer AP-1 for modulated synthesis of apatitic composites is reported.

Design, synthesis, and biological evaluation of the first cyclic biphalin analogues are reported. D-Alanine residues in positions 2, 2′ of the parent peptide were replaced by D- and L-cysteine and an intramolecular disulfide bridge has been established. Two cyclic biphalin analogues, with quite different biological profiles, have been described.



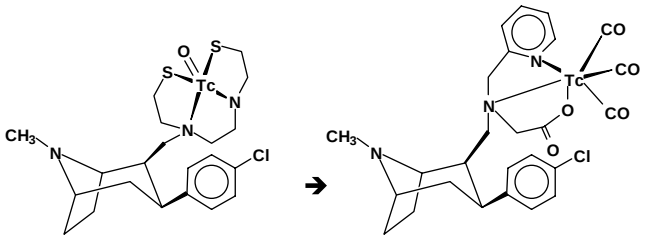


The synthesis and biological evaluation of a novel family of M_3 muscarinic antagonists are described. A systematic modification of the substituents to a novel alkyne-quinuclidine scaffold yielded original compounds displaying potent in vitro anticholinergic properties.

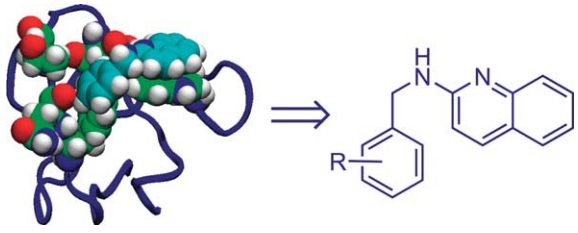


SB-590885 (**33**)

A novel triarylimidazole derivative, SB-590885 (**33**), bearing a 2,3-dihydro-1*H*-inden-1-one oxime substituent has been identified as a potent and extremely selective inhibitor of B-Raf kinase.

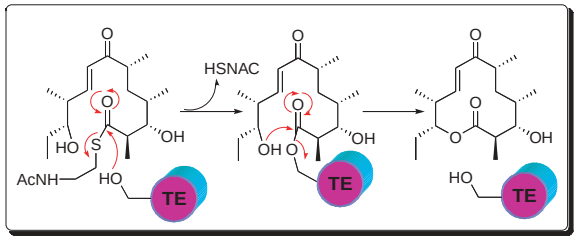


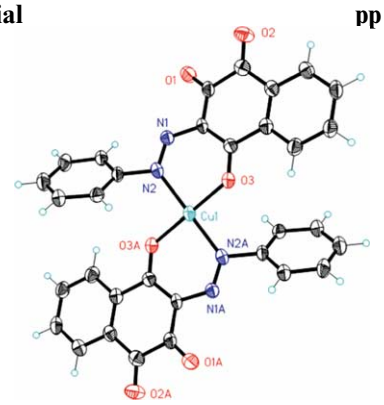
^{99m}Tc-TRODAT-1 ^{99m}Tc-tricarbonyl tropane-PAA

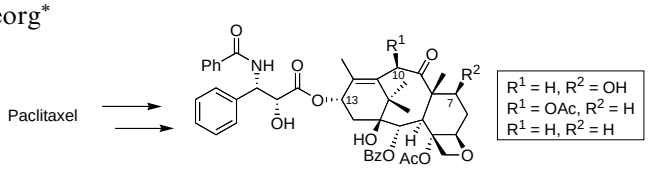


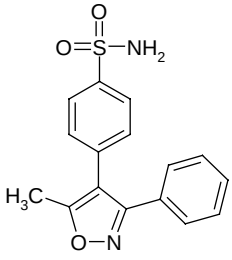
The synthesis of *N*-benzylated-2-aminoquinolines for ligand binding studies with the Tec SH3 domain is described.

The recombinant thioesterase (TE) domain of the picromycin-methymycin synthase (PICS) catalyzes the macrolactonization of **3**, the *N*-acetylcysteamine thioester of seco-10-deoxymethynolide, to generate 10-deoxymethynolide (**1**) with high efficiency. The recombinant TE domain of 6-deoxyerythronolide B synthase (DEBS TE) shows the same reaction specificity as PICS TE, but with significantly lower activity.

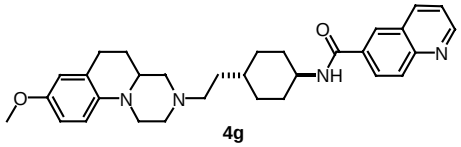






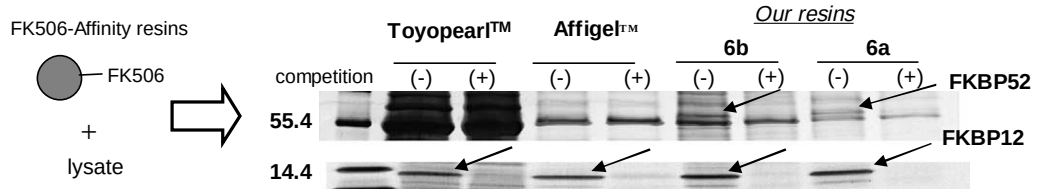


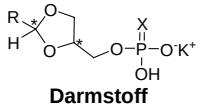
Valdecoxib **1**

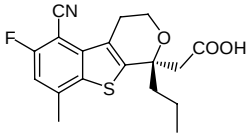


4g

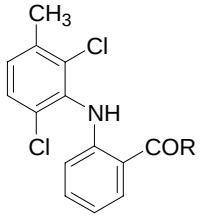
K_i = 9.7 nM to the D_3 receptor
Selectivities of >5000 and 466 times over the D_1-like and D_2-like receptors



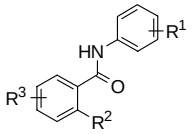




A novel class of HCV NS5B RNA dependent RNA polymerase inhibitors containing 3,4-dihydro-1*H*-[1]-benzothieno [2,3-*c*]pyran and 3,4-dihydro-1*H*-pyrano[3,4-*b*]benzofuran scaffolds and their structure–activity relationship are described.



Quantitative structure–activity relationship studies on a series of meclofenamic acid analogues revealed the importance of molecular flexibility and number of hydrogen bond donor atoms for COX-2 and COX-1 inhibitory activities, respectively.



A series of EGFR PTK inhibitors with an acrylamido moiety at the 4- or 5-position of salicylanilides were synthesized and tested for their inhibitory activity toward the EGFR tyrosine kinase.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

View of the crystal structure of the DB819-d(CGCGAATTCGCG)$_2$ complex, looking down the minor groove of the DNA (see Campbell, N.H.; Evans, D.A.; Lee, M.P.H.; Parkinson, G.N.; Neidle, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 15.). The DB819 molecule is shown in space-filling mode. Visualisation produced with the VMD program. [Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33.]

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