ELSEVIER

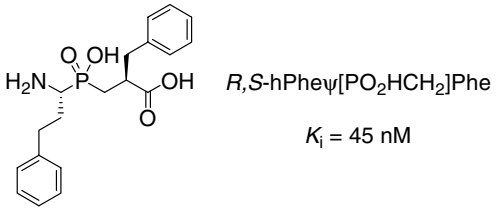
Bioorganic &
Medicinal
Chemistry
Letters

Bioorganic & Medicinal Chemistry Letters Vol. 18, No. 5, 2008

# Contents

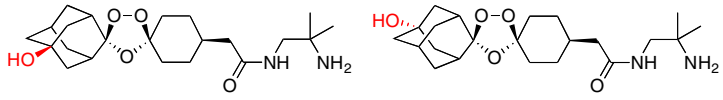
## ARTICLES






First successful separation of all four stereoisomers of a phosphinic acid pseudodipeptide allowed to determine the inhibitory activity of the homophenylalanyl-phenylalanine analogue towards leucine aminopeptidase stereoselectively.

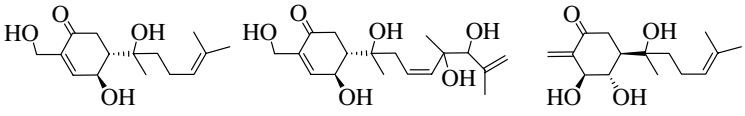





major metabolite
*cis.cis*

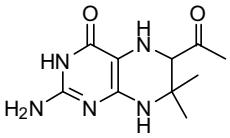
minor metabolite
*trans,cis*





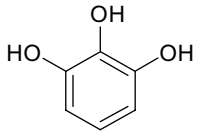

**1** **2** **3**

Three new compounds, antheminones A (**1**), B (**2**), and C (**3**) were isolated from the leaves of *Anthemis maritima*. These compounds exhibited significant antiproliferative activity against leukemia cells.



6-Acetyl-7,7-dimethyl-5,6,7,8-tetrahydropterin activates nitric oxide synthase in tissue, cell, and enzyme preparations as a substitute for the natural cofactor, tetrahydrobiopterin.

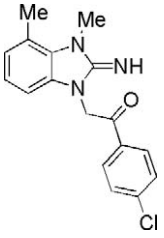




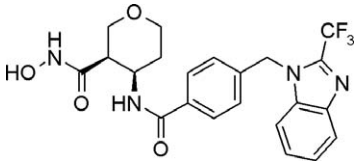
**2** $IC_{50}$ = 2 ± 1 μM

Discovery of several pyrogallol compounds as single digit micromolar inhibitors of bacterial quorum sensing in *Vibrio harveyi*.

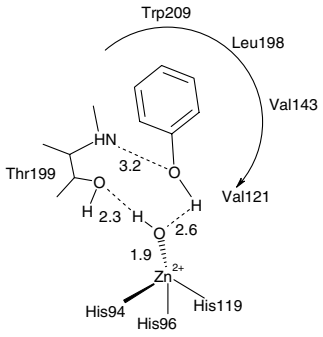






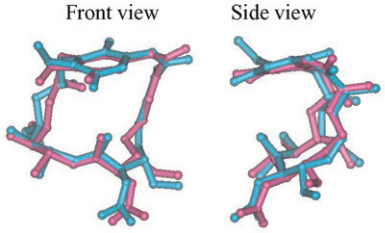


Novel ((2-substituted-1*H*-benzo[*d*]imidazol-1-yl)methyl)benzamides were found to be excellent P1′ substituents in conjunction with unique constrained β-amino hydroxamic acid scaffolds for the discovery of potent, exceptionally selective inhibitors of TNF-α Converting Enzyme (TACE).



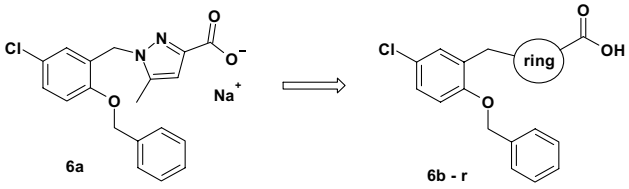



EH21A1–A4, phenolic derivatives of geldanamycin were isolated from *Streptomyces* sp. Their native structures are similar to the active form of geldanamycin. The conformational character is a probable reason for their high affinity to Hsp90 protein.




EH21A1 (**3**) in a native crystalline state
Geldanamycin (**1**) in a cocrystal with Hsp90 protein

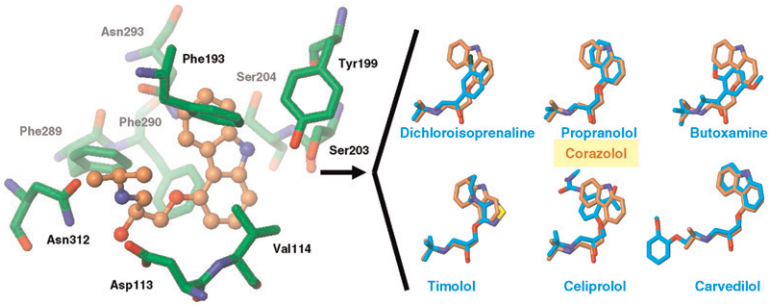


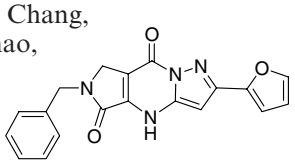



The synthesis and biological activity of a series of novel methylene-linked heterocyclic $EP_1$ receptor antagonists is described.

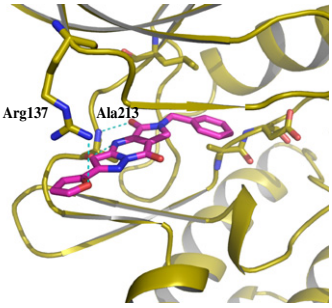


We explore the utility of the Beta2-adrenergic receptor's X-ray structure in drug design including high-throughput docking. Results validate the approach and project its usefulness in finding and designing novel compounds.

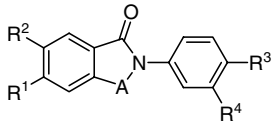




**8a**



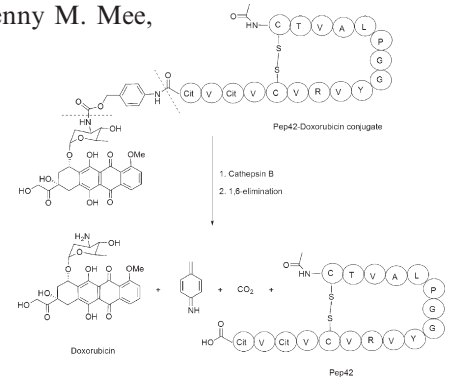


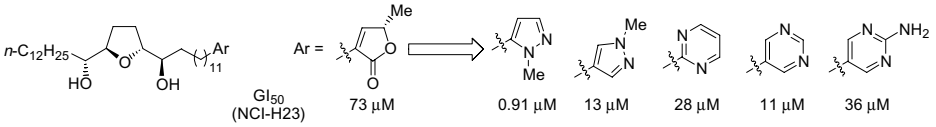
**1a-k:** A=CO
**2a-l:** A=$CH_2$

Based on the structural features of Indoprofen and PIB, a series of isoindol-1,3-diones **1a**–**k** and isoindol-1-ones **2a**–**l** were designed and synthesized. All the isoindolone derivatives showed very good binding affinities with $K_i$ values in the subnanomolar range (0.42–0.94 nM) against aggregated Aβ42 fibrils. Among them, several compounds exhibited excellent binding affinities ($K_i$ = 0.42–0.49 nM) than those of Indoprofen ($K_i$ = 0.52 nM) and PIB ($K_i$ = 0.70 nM).

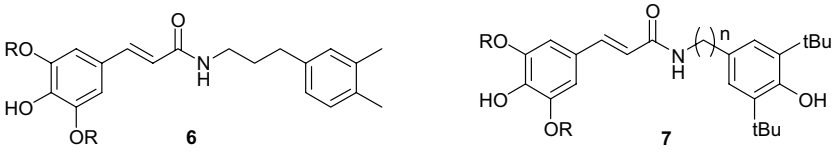




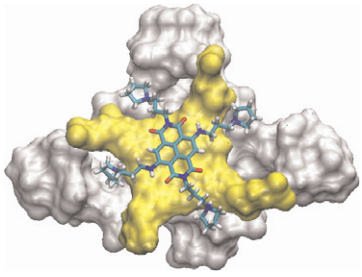


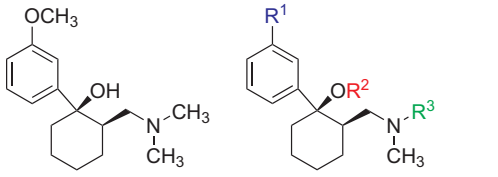

A series of nitrogen-containing heterocyclic analogues of solamin, a natural mono-THF acetogenin, have been synthesized and investigated for their cytotoxicity against 39 tumor cell lines.



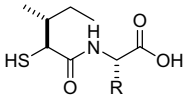


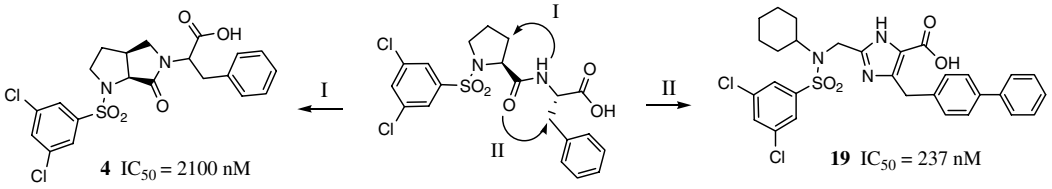




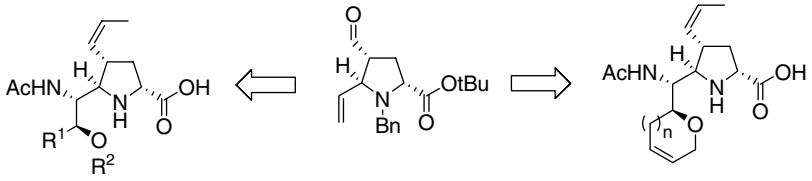


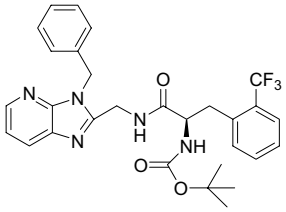

Explorations of the $S^{1'}$ subsite of ACE2 via modifications of the $P^{1'}$ methylene biphenyl moiety of thiol-based metalloprotease inhibitors led to improvements in ACE2 selectivity versus ACE and NEP, while maintaining potent ACE2 inhibition.



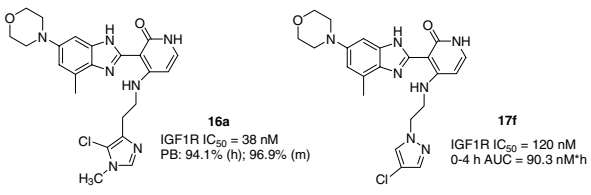


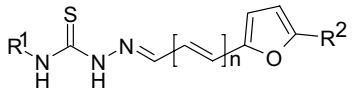







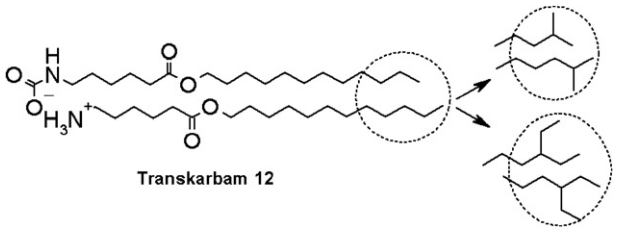






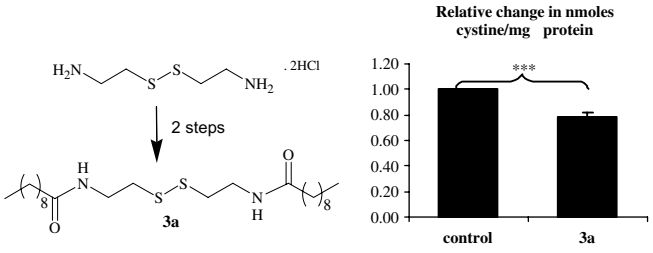
The synthesis and screening of a set of antimicrobial thiosemicarbazones is reported.






Series of Transkarbam 12 derivatives with terminal methyl or ethyl branching was prepared and their permeation-enhancing activity was compared to that of their linear analogues.

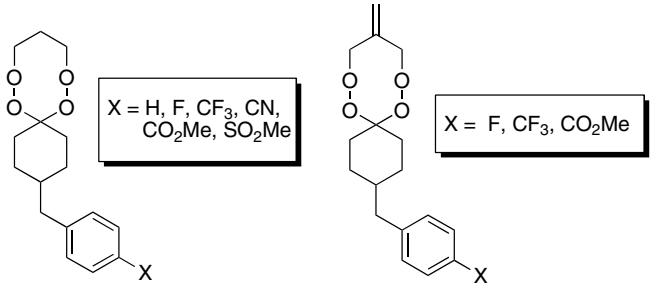





Prodrug **3a** has been shown to deplete levels of lysosomal cystine with negligible toxicity to cultured cells.



Here we present an efficient route into the synthetically challenging bridged 1,2,4,5-tetraoxanes. These achiral derivatives display nanomolar antimalarial activity ($IC_{50}$ = 40–100 nM).



*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

## COVER

Overlay of Corazolol (aqua carbon atoms, ball and stick) and the top-ranked hits from docking a database of proprietary compounds into the X-ray structure of the β2-Adrenergic receptor. Structures shown (grey carbon atoms, stick) are taken from the top-ranked 100 hits after removal of compounds with the traditional β-blocker alkyl motif. [Topiol, S.; Sabio, M. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 1598].



Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE

ELSEVIER

ISSN 0960-894X