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Bioorganic & Medicinal Chemistry Letters

Bioorganic & Medicinal Chemistry Letters Vol. 16, No. 19, 2006

Contents

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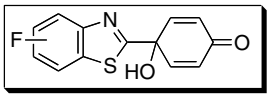
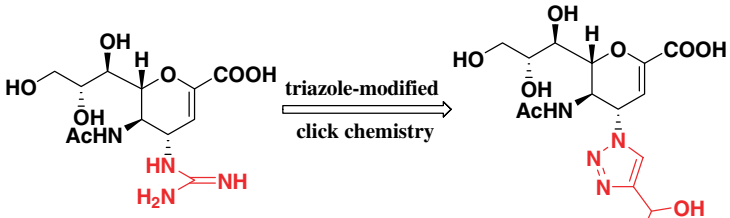
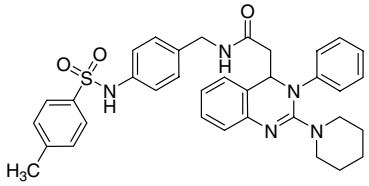


The synthesis and in vitro antitumour evaluation of a new series of fluorinated benzothiazole-substituted 4-hydroxycyclohexa-2,5-dienones ('quinols') is reported.

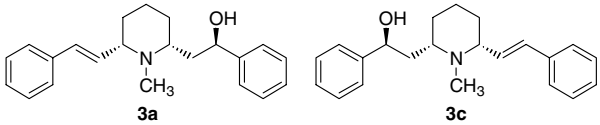
Compound **3b**, 4-triazole-modified zanamivir analogue, shows anti-AIV (H5N1) activity with EC_{50} of 6.4 μM, which is very close to that of zanamivir (EC_{50} = 2.8 μM).



zanamivir **3b**

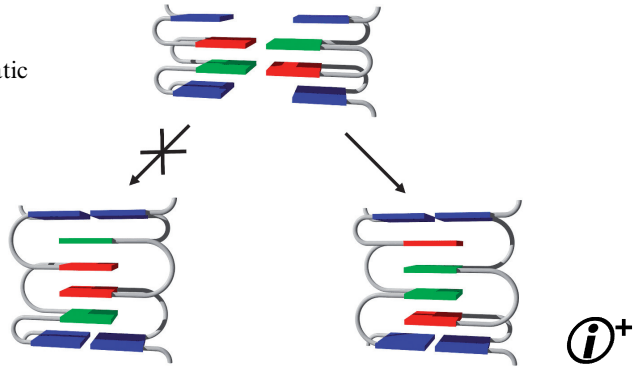


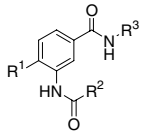
9c (KYS05041): GI_{50} = 2.70 ~ 3.06 μM against human cancer cells

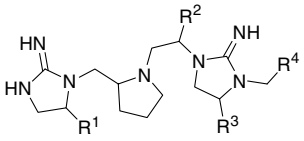


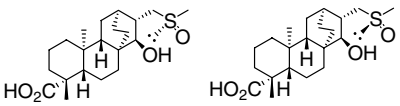
3a **3c**

A series of *des*-keto lobeline analogs has been synthesized and evaluated for their ability to inhibit the dopamine transporter (DAT), the serotonin transporter (SERT) function and for their affinity for the synaptic vesicle monoamine transporter (VMAT2), as well as for α4β2 and α7 neuronal nicotinic acetylcholine receptors (nAChRs). The enantiomers 8*R*-hydroxylobel-9-ene (**3a**) and 10*S*-hydroxylobel-7-ene (**3c**) exhibited high potency and selectivity at SERT and DAT, respectively.

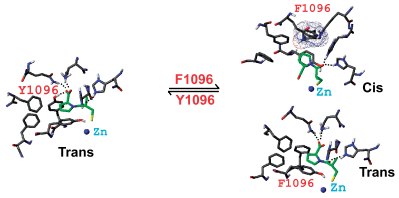






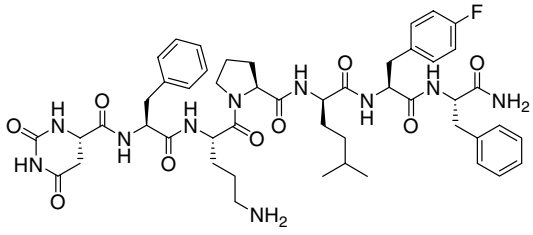


1: serofendic acid A **2: serofendic acid B**

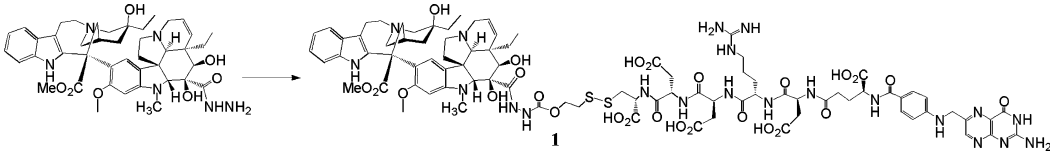


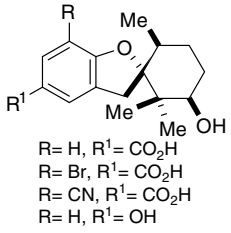
A combinatorial approach through NMR, flexible docking calculations, mutagenesis, and enzymatic studies rationalized the selectivity mechanism of the isomerization states of captopril from the ACE enzyme.

New C5a receptor antagonists characterized by C-terminal amino acids with hydrophobic substitutions are presented.



JPE1375 (**36**)



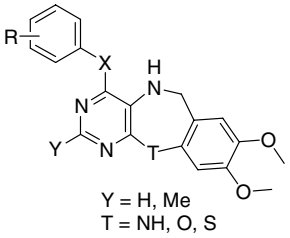


R= H, R^1= CO_2H
R= Br, R^1= CO_2H
R= CN, R^1= CO_2H
R= H, R^1= OH

The synthesis of six filifolinol derivatives as classical complement pathway inhibitors is reported.

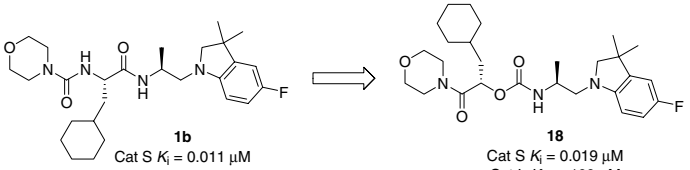
Novel tricyclic azepine derivatives: Biological evaluation of pyrimido[4,5-*b*]-1,4-benzoxazepines, thiazepines, and diazepines as inhibitors of the epidermal growth factor receptor tyrosine kinase **pp 5102–5106**
Leon Smith, II,* Wai C. Wong, Alexander S. Kiselyov, Sabina Burdzovic-Wizemann, Yunyu Mao, Yongjiang Xu, Matthew A.J. Duncton, Ki Kim, Evgueni L. Piatnitski, Jacqueline F. Doody, Ying Wang, Robin L. Rosler, Daniel Milligan, John Columbus, Chris Balagtas, Sui Ping Lee, Andrey Konovalov and Yaron R. Hadari

The synthesis and SAR studies of oxazepines, thiazepines, and diazepines as novel EGFR inhibitor classes are reported.



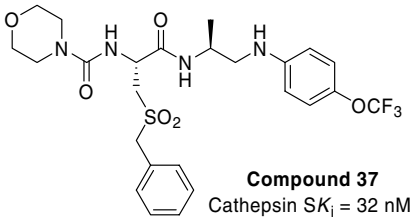
Arylaminoethyl carbamates as a novel series of potent and selective cathepsin S inhibitors **pp 5107–5111**
David C. Tully,* Hong Liu, Arnab K. Chatterjee, Phil B. Alper, Jennifer A. Williams, Michael J. Roberts, Daniel Mutnick, David H. Woodmansee, Thomas Hollenbeck, Perry Gordon, Jonathan Chang, Tove Tuntland, Christine Tumanut, Jun Li, Jennifer L. Harris and Donald S. Karanewsky

The synthesis and SAR of a novel series of arylaminoethyl carbamates is reported as potent, highly selective, and orally bioavailable noncovalent inhibitors of cathepsin S.

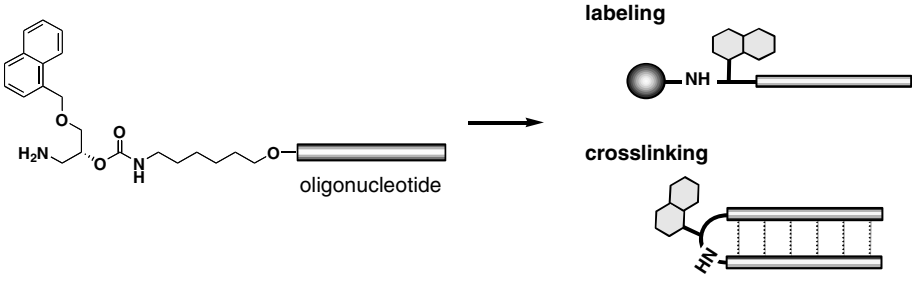


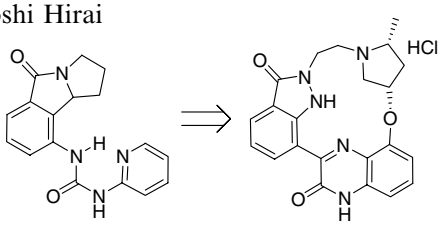
Synthesis and SAR of arylaminoethyl amides as noncovalent inhibitors of cathepsin S: P3 cyclic ethers **pp 5112–5117**
David C. Tully,* Hong Liu, Arnab K. Chatterjee, Phil B. Alper, Robert Epple, Jennifer A. Williams, Michael J. Roberts, David H. Woodmansee, Brian T. Masick, Christine Tumanut, Jun Li, Glen Spraggon, Michael Hornsby, Jonathan Chang, Tove Tuntland, Thomas Hollenbeck, Perry Gordon, Jennifer L. Harris and Donald S. Karanewsky

The synthesis and SAR a series of arylaminoethyl amide cathepsin S inhibitors are reported, focusing on the optimization of P3 and P2 subunits. An X-ray co-crystal structure of compound **37** bound to the active site of cathepsin S is also disclosed.

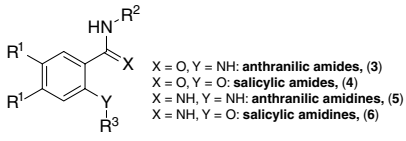


Enhanced reactivity of amino-modified oligonucleotides by insertion of aromatic residue **pp 5118–5121**
Naoshi Kojima, Maiko Sugino, Akiko Mikami, Ken Nonaka, Yumi Fujinawa, Isamu Muto, Kenichi Matsubara, Eiko Ohtsuka and Yasuo Komatsu*

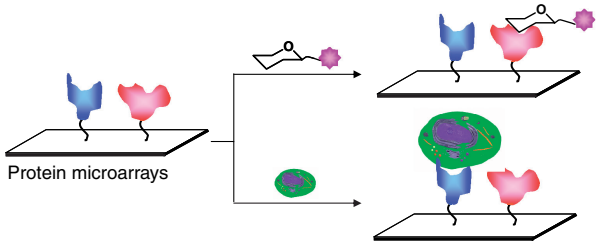




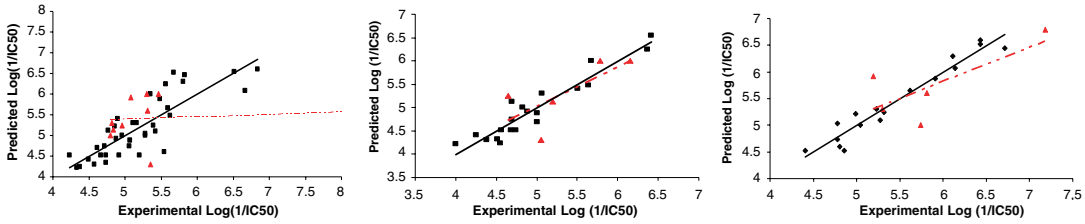
Identification of a novel series of CDK1,2,4,6 inhibitor with macrocyclic quinoxalin-2-one is reported. The structure-based designs and optimizations led to the potent CDK1,2,4,6 inhibitor that could be available as iv administration for in vivo studies from the lead compound with diarylurea scaffold.



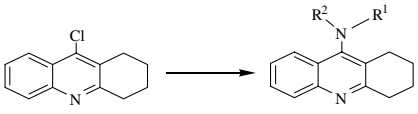
A series of benzamidines and benzamides was synthesized as selective inhibitors of vascular endothelial growth factor receptor (VEGFR) tyrosine kinases, and tested for inhibitory activity toward autophosphorylation by the enzyme assay.



Protein microarrays are applied for studying carbohydrate-recognition events.

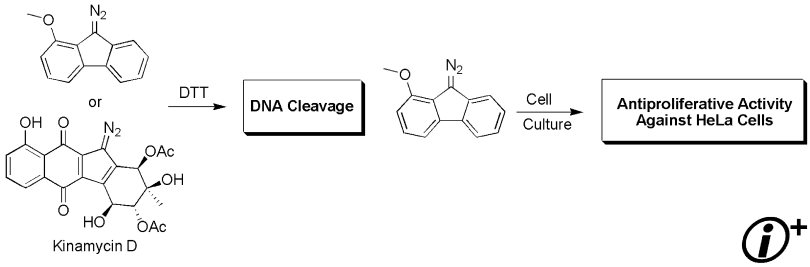


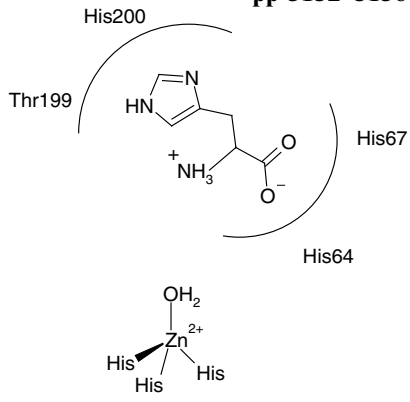
Conventional and cluster analysis based methods for QSAR development have been analysed and compared for their predictability on a set of *Pseudomonas aeruginosa* Deacetylase LpxC inhibitors. Cluster analysis based approach proved to be better than the conventional technique.

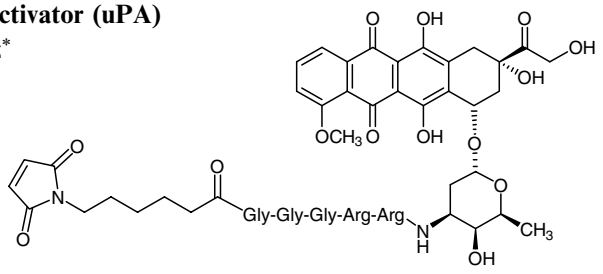


A series of 9-aminotetrahydroacridines were synthesized starting from anthranilic acid and cyclohexanone. Few of the compounds possess potent in vitro antitubercular activities with MIC as low as 0.78 μg/mL.

The synthesis, DNA cleaving, and anti-proliferative properties of electronically modulated diazofluorenes are reported.

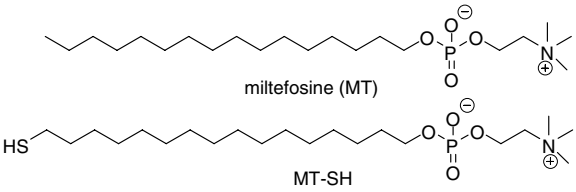






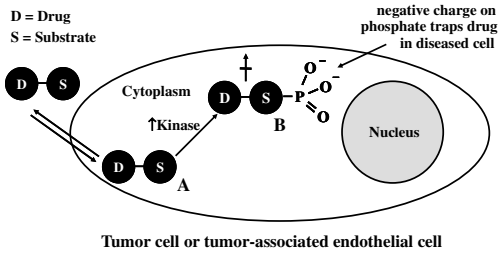
1

A water-soluble albumin-binding prodrug of doxorubicin (**1**) was developed that is cleaved specifically by the tumor-associated protease urokinase-type plasminogen activator (uPA).

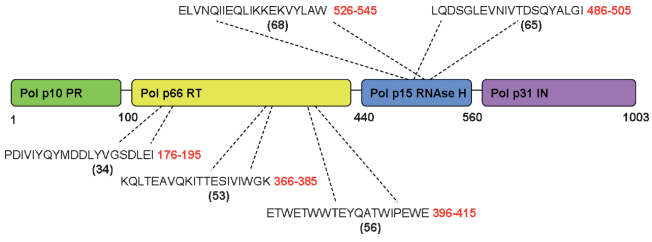


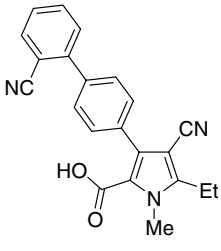
A miltefosine analog capped with a versatile terminal mercapto group presents the same very high leishmanicidal activity as the parent drug, opening new ways for the study of the unknown antiparasite mechanism of alkylphospholipids.

In the present work, we explore the possibility of introducing selectivity to existing chemotherapeutics via the design of non-pro-drug, bi-functional molecules comprising a microtubule-binding agent and a substrate for a disease-associated kinase. The design, synthesis, and in vitro biological evaluation of paclitaxel–thymidine and vinblastine–thymidine bi-functional conjugates are reported here. This work provides the first account of 'kinase-mediated trapping' of cancer therapeutics.



The five most potent peptides derive from different regions of the HIV-1 HXB2 Pol genome. Numbers adjacent to each peptide sequence indicate amino acid spans of the respective subunits on the Pol polypeptide (Numbering according to the HXB2 Numbering Engine nomenclature, Los Alamos National Laboratory). Numbers in parentheses indicate the number of the peptide (domains not drawn to scale).





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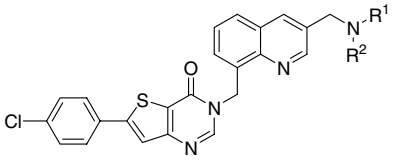
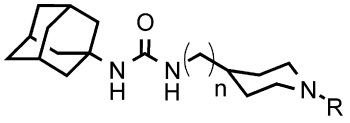
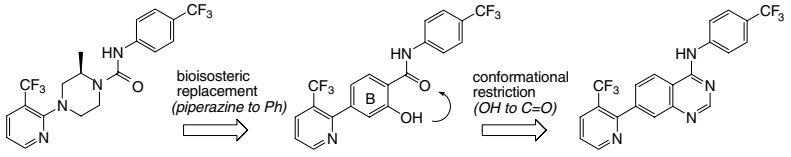
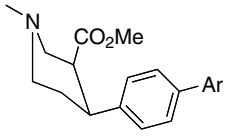




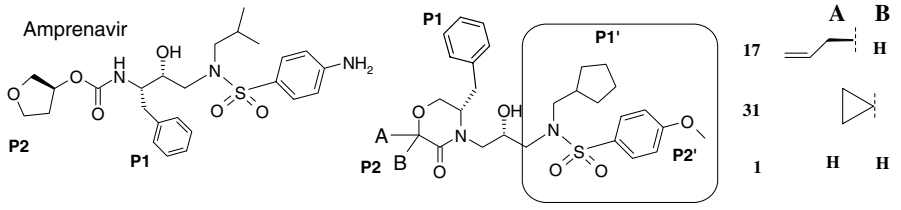
n = 0,1
R = H, alkyl, acyl



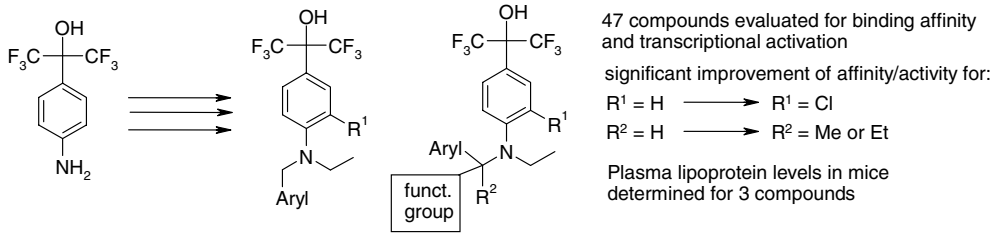
A novel VR1 antagonist template (4-aminoquinazoline) exhibits improved in vitro potency and oral bioavailability relative to the corresponding urea or carboxamide compounds.

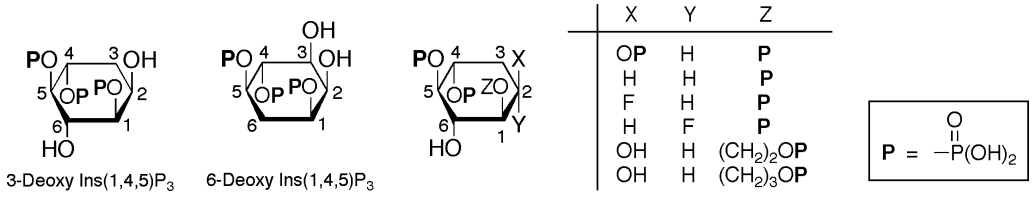


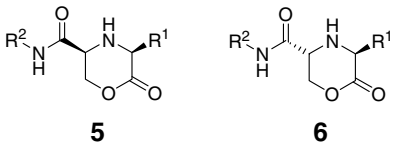
A series of novel piperidine based analogs of cocaine was synthesized and evaluated in vitro against the three monoamine transporters to develop new potential selective SERT radiotracers.



Morpholinone-based P1/P2 derivatives have been discovered to provide a new and promising scaffold toward potent mimetics of the HIV-1 protease inhibitor Amprenavir. In particular, allyl- and spiro-cyclopropyl—P2-substituted inhibitors **17** and **31** were found 500× more potent than the parent inhibitor **1**.







Morpholin-2-one-5-carboxamide derivatives were prepared by using a one-pot Ugi multicomponent reaction and showed potent and selective T-type calcium channel blocking activities.

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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