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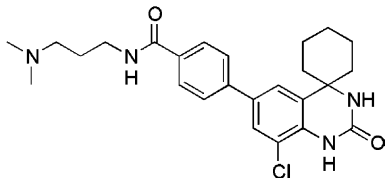
Bioorganic & Medicinal Chemistry Letters

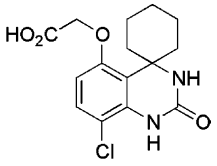
Bioorganic & Medicinal Chemistry Letters Vol. 14, No. 18, 2004

# Contents

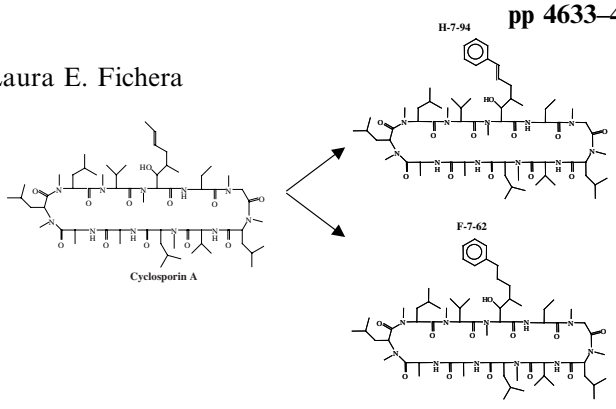
## COMMUNICATIONS



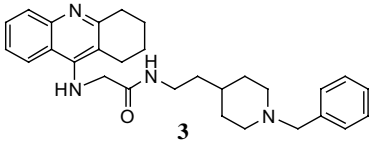






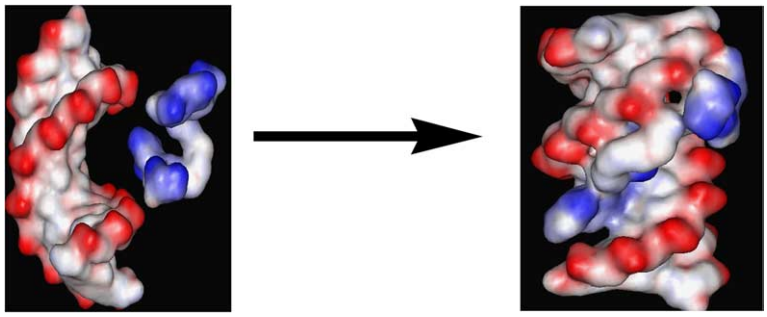




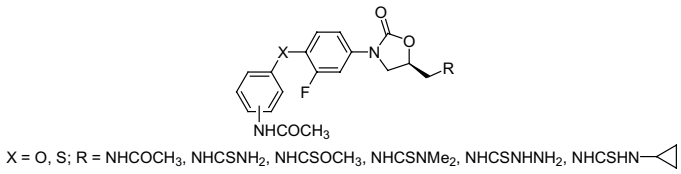



**3** $IC_{50}$=6.0 nM

Tacrine-E2020 hybrids and some related compounds were prepared and their bioactivities on the Alzheimer's Disease were assayed. The optimum hybrid inhibitor **3** is much more potent and selective than tacrine *in vitro*.

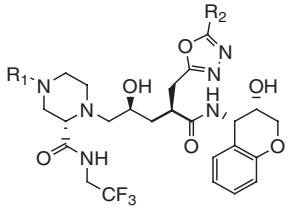






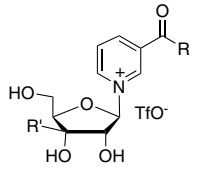

A series of aryloxy/thioaryloxy oxazolidinones has been synthesized and their antibacterial activity in vitro were evaluated and compared with linezolid.



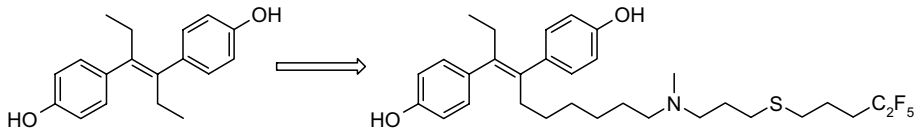


HIV-1 protease inhibitors bearing 1,3,4-oxadiazoles at the P1′ position are highly active against native and PI-resistant HIV-1.



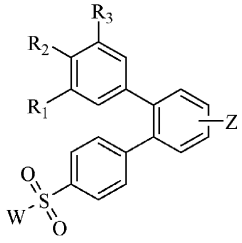



A stereoselective synthesis of β-anomers of nicotinamide riboside (NAR), its deamidated analog (NaR), and of a nicotinamide *C*-methylated riboside derivative (NA3′-*C*-MeR) was developed.




The nonsteroidal estrogen diethylstilbestrol can be converted into potent antiestrogens devoid of agonist activity by introduction of side chains with appropriate functional groups.

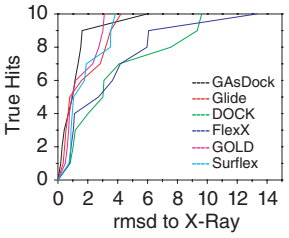


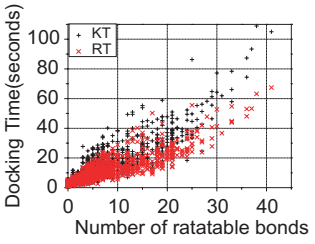



An attempt has been made to explore selectivity requirements for COX-2 versus COX-1 binding of terphenyl methyl sulfones and sulfonamides using electrotopological state (E-state) index and suitable indicator parameters.

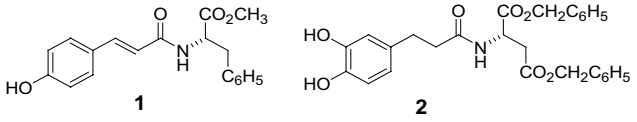


A new rapid accurate flexible docking program, GAsDock, was developed based on an improved multi-population genetic algorithm. Its rapid docking speed and excellent accuracy are efficient enough for virtual screening toward large-scale chemical databases.

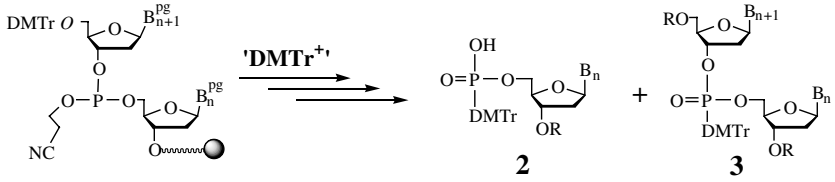




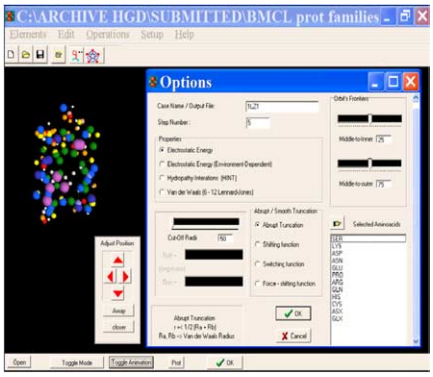




A series of cinnamic acid derivatives were prepared and their biological activities were evaluated in lipoprotein metabolism. Among the tested compounds, 4-hydroxycinnamic acid (L-phenylalanine methyl ester) amide (**1**) and 3,4-dihydroxyhydrocinammic acid (L-aspartic acid dibenzyl ester) amide (**2**) showed potent anti-atherogenic and anti-oxidant activities.

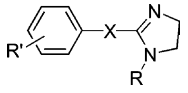



Under suboptimal sulfurization conditions DMTr-*C*-phosphonate monoesters **2** and DMTr-*C*-phosphonate diesters **3** are formed during solid-phase oligonucleotide synthesis.



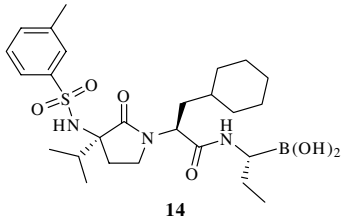




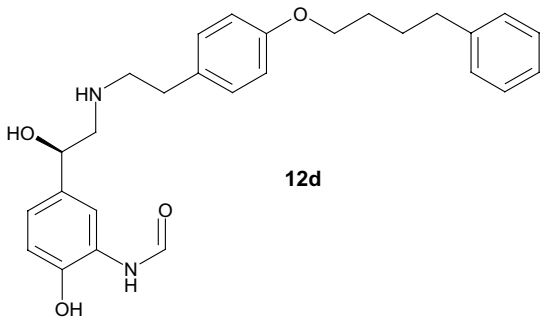

Depending on appended substituents, 2-(anilino)- and 2-(benzyl)imidazoline derivatives (X = NH or $CH_2$) bind at *h*5-HT$_{1D}$ receptors with varying affinities and selectivities over *h*5-HT$_{1B}$ receptors. Functional and pharmacokinetic data are provided for examples of 2-(benzyl)imidazolines and a ring-expanded analog: 2-(benzyl)-3,4,5,6-tetrahydropyrimidine.





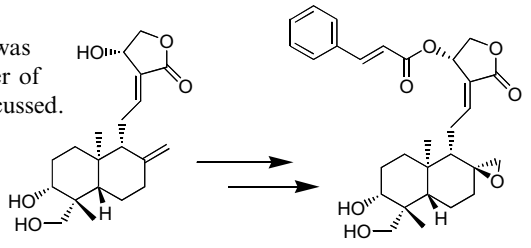

**14**

Synthesis and in vitro characterization of a novel, lactam boronic acid based, selective, and rapidly reversible inhibitor of the 20S-proteasome is presented.




12d



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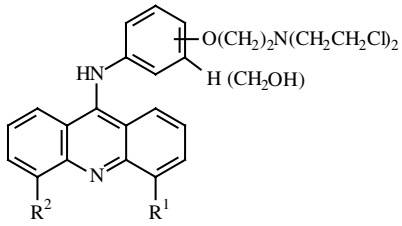
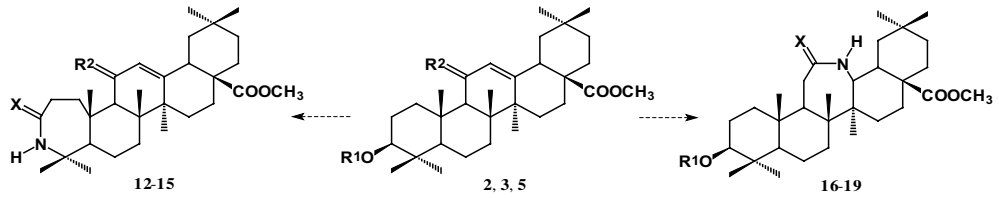
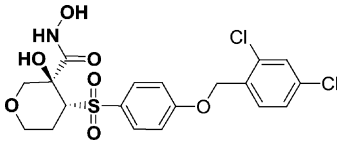




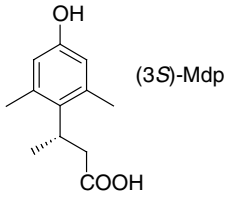

12-15 2, 3, 5 16-19

$R^1$ = H or $CH_3CO$ $R^2$ = $H_2$ or O X = O or S



*N*-Hydroxy-3-hydroxy-4-arylsulfonyltetrahydropyranyl-3-carboxamides were designed as novel inhibitors of MMP-13 and aggrecanase based on known endocyclic hydroxamate inhibitors of matrix metalloproteinases. These compounds offer favorable physicochemical properties and low metabolic clearance. Synthesis and structure–activity relationships are reported.

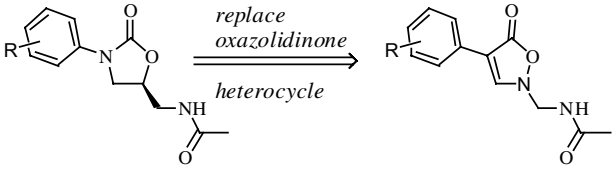





(3*S*)-Mdp-c[D-Cys-Gly-Phe($pNO_2$)-D-Cys]$NH_2$

The synthesis and in vitro activity profile of a potent opioid peptide antagonist lacking an N-terminal amino group are described.

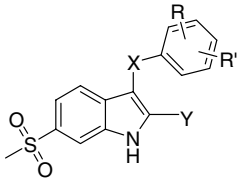


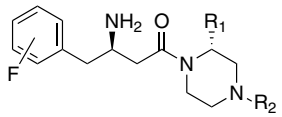



Oxazolidinone Antibacterials Isoxazolinone Antibacterials



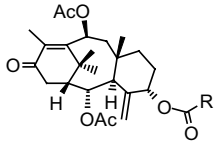
The introduction of 3-arylmethyl, 3-aryloxy and 3-arylthio moieties into a 6-methylsulfonylindole framework using rational drug design led to potent, selective COX-2 inhibitors having efficacy in a rat carrageenan air pouch model. Incorporation of a conformationally more rigid 3-aroyloxy substituent onto the 6-methylsulfonylindole scaffold led to selective, but considerably less potent COX-2 inhibitors. Variation of the hydrophilicity and size of the indole 2-substituent of 3-arylthio-6-methylsulfonylindole inhibitors led to modulation of the COX-2 human whole blood (HWB) potency and selectivity.






The synthesis and SAR of a series of piperazines containing a fluorophenyl β-amino amide moiety is reported.



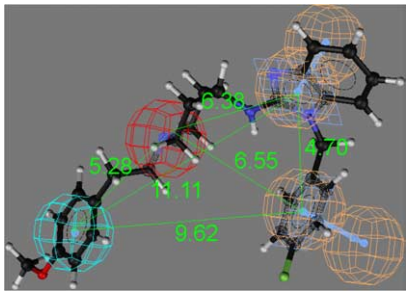



**8:** R = $PhCH_2$
**9:** R = $PhCH_2CH_2$
**10:** R = 2,5- dimethoxyl-$PhCH_2$

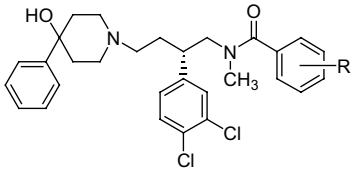
Three novel taxinine analogues were prepared and tested for their activity as multidrug resistance (MDR) reversal agents in comparison with verapamil. In vitro testing demonstrated that compounds **8**–**10** possess MDR-reversal activity in the KB/V cell line. In accumulation assay, the intracellular rhodamine123 concentration increased significantly after treatment with compound **9**, higher than that of verapamil in KB/V cell line. In vivo studies with VCR-resistant KB/V tumor xenografts showed that **9** in combination with VCR significantly inhibited tumor growth. Treatment with VCR or **9** alone did not result in growth inhibition.



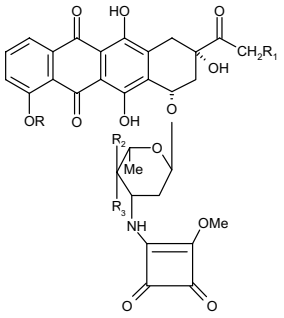
This paper reports a pharmacophore hypothesis for $I_{Kr}$ potassium channel blockers using HypoGen module in Catalyst software. The pharmacophore can be used to in predicting biological activity of compounds by virtual screening.



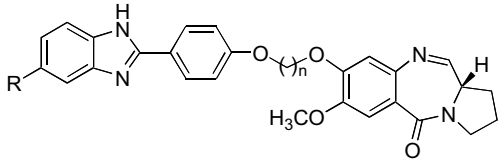



R = H
R = *p*-F
R = *o*-, *m*-, *p*-$NO_2$
R = *o*-, *m*-, *p*-$NH_2$
R = *o*-, *m*-, *p*-NCS
R = *o*-, *m*-, *p*-$NHCOCH_3$
R = *o*-, *m*-, *p*-$NHCOCH_2Br$

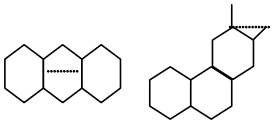






R = H, N-Methylpiperazine n = 3, 4, 5





A novel application of distance-based topological indices have been used for modeling electronic absorption bands of arene absorption spectra as a tool for modeling their toxicity and environment pollution. The statistical analysis of the data have shown that PI index gives better results for modeling $\ln \lambda_{\beta}$; while Sz index proved better for modeling $\ln \lambda_{p}$. The results are critically discussed on the basis of regression parameters and quality of correlation. Such a study will be useful as a tool for modeling toxicity of arene system as well as their environmental pollution.

## OTHER CONTENTS



*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

## COVER

*Cover figure provided by* ***Indraneel Ghosh****, Department of Chemistry, University of Arizona.* The cover depicts the **Dual Surface Selection** methodology developed by the author: the blue helix of htBl (center) allows structural selection with the Fc portion of Immunoglobulin (left), while the residues randomized on the red sheet of htBl (center) allows for functional selection against thrombin (right) [Rajagopal, S.; Meza-Romero, R.; Ghosh, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1389].



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