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Bioorganic &
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Chemistry

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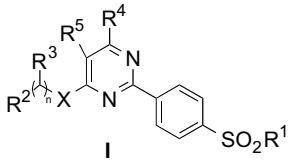
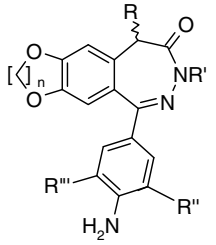
Contents

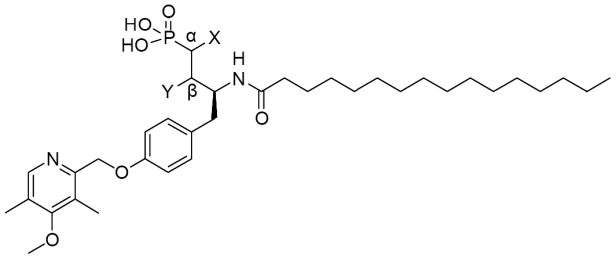
ARTICLES



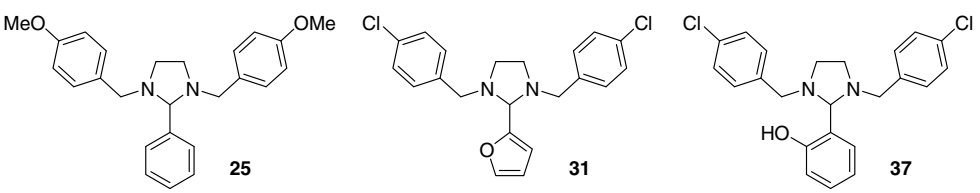
I

New series of pyrimidines **I** were synthesized and evaluated as cyclooxygenase-2 (COX-2) inhibitors. Compounds **8**, **67**, **69**, **71**, **82** and **83** were highly potent and specific COX-2 inhibitors (HWB COX-2 IC_{50} = 2.4–0.3 nM and 80- to 780-fold more selective than rofecoxib).

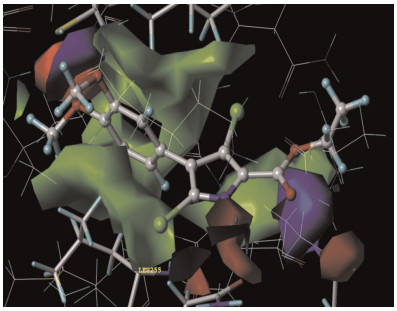




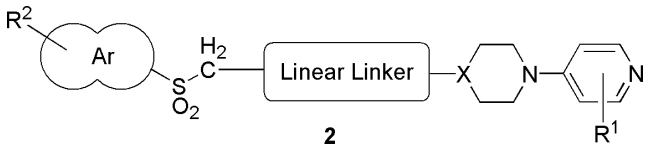
A series of α- and β-substituted phosphonate analogs of LPA were synthesized and evaluated for ATX inhibitory activity.



A series of imidazolidines with relevant in vitro activity against *Trypanosoma cruzi* are described. Activity is related to imidazolidines' lipophilicity.

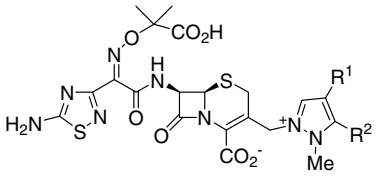


HINT Interaction maps of JG-03-14 bound at the colchicine site of tubulin. Blue contours: favorable polar (H-bond); red: unfavorable polar; green: hydrophobic.



2

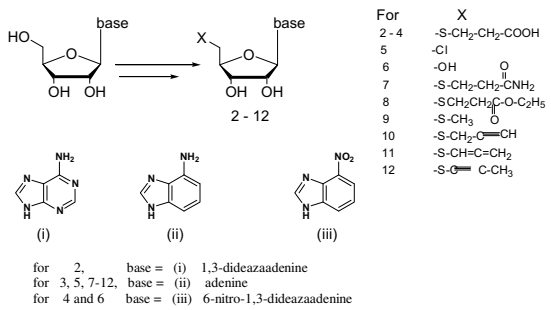
Synthesis, structure–activity relationships, ex vivo anticoagulant activities, selectivity, and pharmacokinetics of sulfonylalkylamides **2** as novel non-amidine FXa inhibitors are reported.

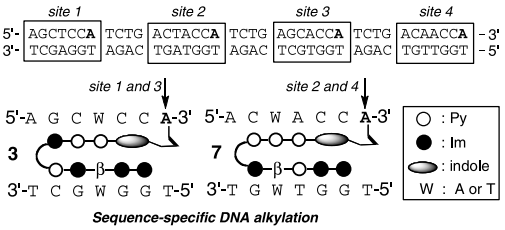


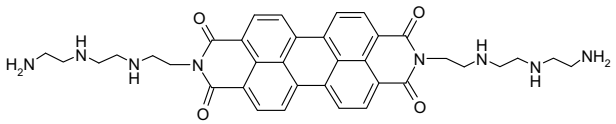
FR259647 derivatives

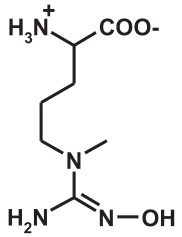
We propose novel structural requirements that FR259647 derivatives with lower probability of entry into the binding pocket of AmpC β-lactamase are more stable to the enzyme.

A series of 11 AdoHcy analogues were synthesized and evaluated for their modulating effects on DNA methylation catalyzed by DNA methyltransferases.

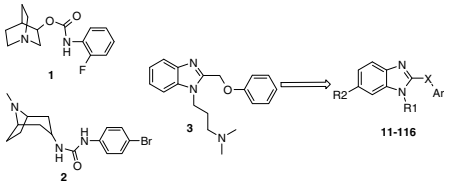




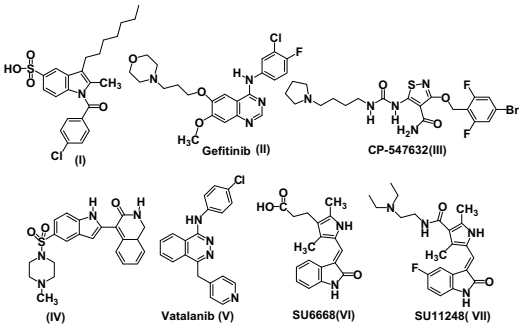


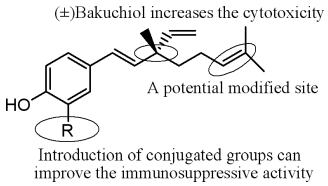


The influence of *N*δ-methyl-L-arginine and its presumed metabolites by NOS catalysis was investigated on the whole nitric oxide generating system including NOSs, arginase and DDAH. *N*ω-Hydroxy-*N*δ-methyl-L-arginine presents a strong inhibitor of arginase with a K_i of 17 μM.



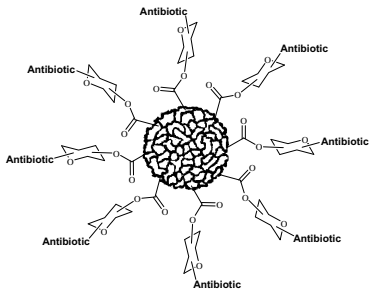
Alpha7 agonists were identified via GOLD (CCDC) docking in the putative agonist binding site of an alpha7 homology model and a series of aminoalkyl benzoimidazoles was synthesised to obtain potentially brain penetrant drugs. The array was prepared starting from the reaction of *ortho*-fluoronitrobenzenes with a selection of diamines, followed by reduction of the nitro group to obtain a series of monoalkylated phenylene diamines. *N*,*N*′-Carbonyldiimidazole (CDI) mediated acylation, followed by a parallel automated work-up procedure, afforded the monoacylated phenylenediamines which were cyclised under acidic conditions. Parallel work-up and purification afforded the array products in good yields and purities with a robust parallel methodology which will be useful for other libraries. Screening for alpha7 activity revealed compounds with agonistic activity for the receptor.



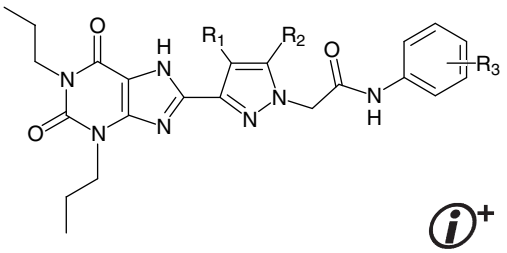


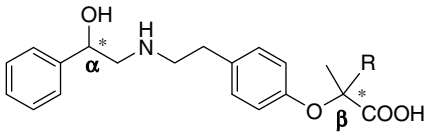
A series of derivatives of bakuchiol were synthesized and tested in vitro for their cytotoxicity, and inhibition of T cell proliferation and B cell proliferation. The data obtained provided preliminary structure–activity relationships of the compounds as immunosuppressive activity.

The synthesis and biological activity of carbohydrate-derivatized polyacrylate nanoparticles (right) against methicillin-resistant *Staphylococcus aureus* and *Bacillus anthracis* is described.

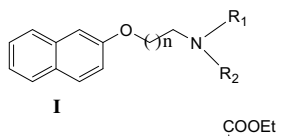


In the present study, synthesis of a new series of 1,3-dipropyl-8-(1-phenylacetamide-1*H*-pyrazol-3-yl)-xanthine derivatives and evaluation of their biological activity as A_{2B} adenosine receptor antagonists are described.

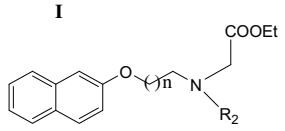




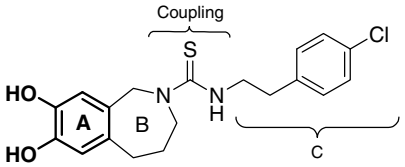
ω-(2-Naphthyloxy) amino alkanes, obtained as major by-product during course of synthesis of carbamate esters from ω-(2-naphthyloxy) alkyl halides and amines, showed significant anti-hyperglycemic and lipid lowering activities in various test models as a novel class of compounds. Compounds were tested in rat GLM, SLM, STZ, and STZ-S models at 100 mg/kg dose. Of these compound **13** was found to be the most active which caused lowering of sugar by 33.6%, 31.0%, 28.5%, and 73.8% in GLM, SLM, STZ, STZ-S, and db/db mice models, respectively. It also significantly effected lowering of LDL in rat model and also in hamster model without reducing HDL. Most of the compounds showing anti-diabetic and lipid lowering activity have shown promising PPAR-α/γ/δ-agonistic activity. Compounds **6**, **13**, and **19** have shown very good PPAR-α/γ/δ-agonistic activity.



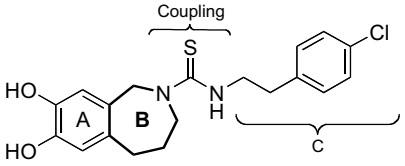
I



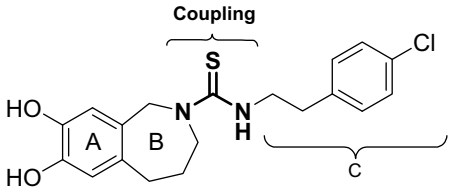
II



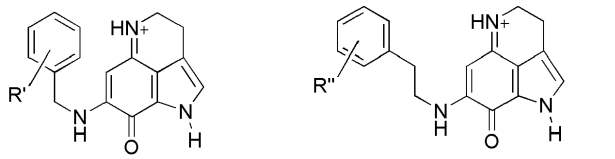
A series of capsazepinoids with different number/position of hydroxyl groups in the A-ring and B-ring size/substitution were prepared, and assayed for bronchorelaxing activity in human small airway preparations.



The dependence of the bronchodilating activity in human small airways of capsazepine derivatives on the chlorination of the A-ring and the replacement of the catechol moiety with bioisosteric groups has been investigated.

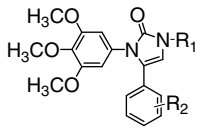


Capsazepine derivatives with various coupling- and C-regions were synthesized and assayed as part of a SAR study of the bronchorelaxing activity in human small airways.



R' = 4-Me, 4-OMe, 3,4-di-OMe, 3,4,5-tri-OMe, 3,4-O-CH_2-O-, 4-Cl, 4-F

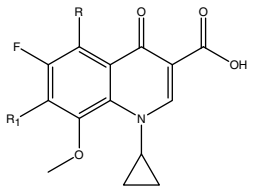
R'' = 4-Me, 4-OMe, 3,4-di-OMe, 3,4-O-CH_2-O-, 3,4-di-Cl, 4-Cl, 4-F

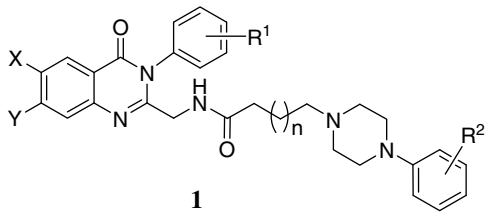


R_1 = H, $COCH_3$, NHCOR
R_2 = H, 4-Br, 4-Cl, 4-NO_2, 4-OCH_3, 2,4-2F, 3,4-$(OCH_3)_2$, 3-NO_2-4-OCH_3, 3-NH_2-4-OCH_3, 3-OH-4-OCH_3

A new series of imidazol-2-one derivatives were prepared and investigated as anticancer agents.

Thirty-four newer 1-cyclopropyl-1,4-dihydro-6-fluoro-7-(substituted secondary amino)-8-methoxy-5-(sub)-4-oxoquinoline-3-carboxylic acids were synthesized and its in vitro and in vivo antimycobacterial activities against *Mycobacterium tuberculosis* H37Rv (MTB), multi-drug resistant *M. tuberculosis* (MDR-TB) and *Mycobacterium smegmatis* (MC^2) and its ability to inhibit the supercoiling activity of DNA gyrase were reported.

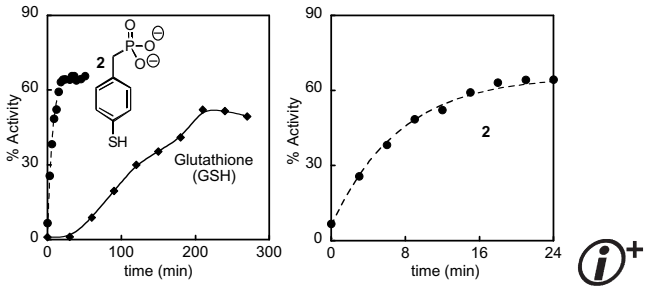




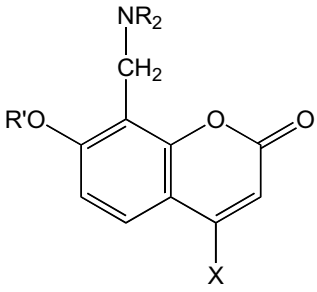
1

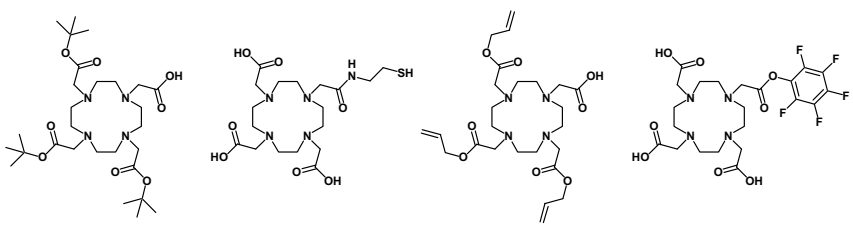
A small molecule library of quinazolinone derivatives **1** was synthesized and biologically evaluated to estimate binding affinity to the 5-HT$_7$ receptor.

The folding rate of reduced lysozyme to native protein was enhanced by a factor of 10 at pH 7 when the standard redox buffer component glutathione was replaced by an aromatic thiol.

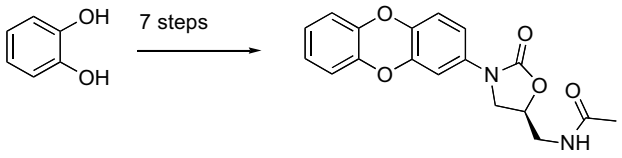


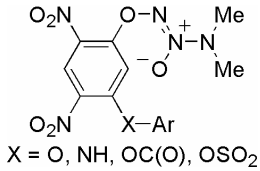
Some Mannich bases of 7-hydroxycoumarin were prepared and tested against viruses containing single-stranded, positive-sense RNA genomes (ssRNA$^+$). When position 7 was propylated, the resulting 7-propyloxy derivatives were in some cases endowed with an interesting activity against BVDV. Therefore, 7-propyloxy derivatives were submitted to a molecular modeling study using DNA polymerase of HCV as a target. The good correlation between calculated molecular modeling IC$_{50}$ and experimental EC$_{50}$ is reasonable proof that DNA polymerase is potentially involved in the inhibition of surrogate HCV viruses.



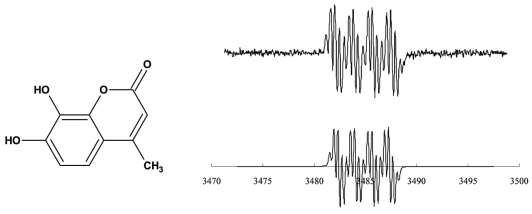


Improved synthesis protocols for several DOTA derivatives. The utility of these and other DOTA derivatives for multimerization reactions is studied with PAMAM dendrimers.



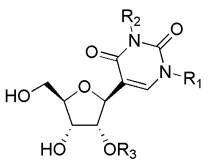


A number of structural analogues of PABA/NO, an anti-cancer lead compound, were synthesized; their nitric oxide release patterns and anti-leukemic activity are reported.

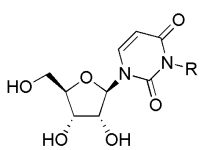


ESR signal of the 7,8-dihydroxy-4-methylcoumarin radical

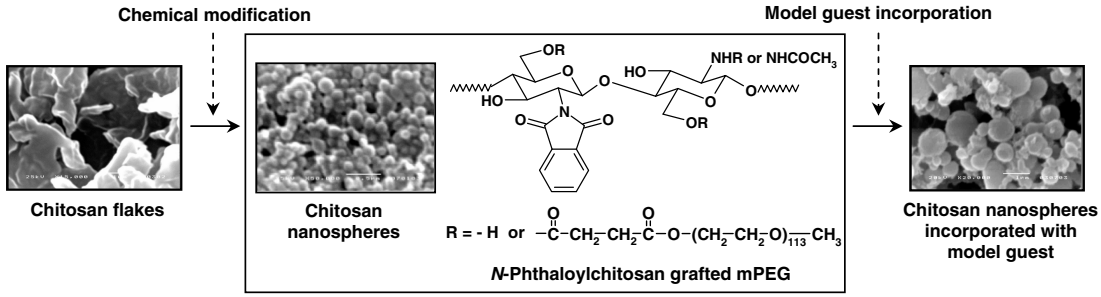
The present work evaluates the structural requirements of related hydroxycoumarins to induce apoptosis in a leukemic cell line, suggesting that reactive oxygen species generation plays a critical role in dihydroxycoumarin-induced apoptosis in U-937 cells.

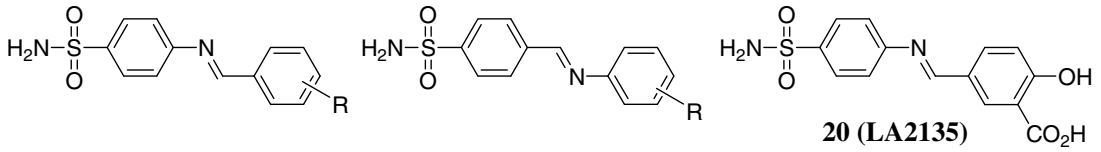


R_1 = H, R_2 = H, R_3 = H
R_1 = CH_3, R_2 = H, R_3 = H
R_1 = CH_3, R_2 = $CH_2CH_2CH(NH_2)(COOH)$, R_3 = H
R_1 = CH_3, R_2 = $CH_2(CH_2)_2CH_2OH$, R_3 = H
R_1 = H, R_2 = H, R_3 = CH_3



R = $CH_2CH_2CH(NH_2)(COOH)$
R = $CH_2(CH_2)_2CH(NH_2)(COOH)$
R = $CH_2(CH_2)_2COOH$
R = $CH_2(CH_2)_2CH_2OH$





The synthesis, evaluation, and structure–activity relationships of two series of benzenesulfonamides as potent and selective COX-2 inhibitors are described.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

An insight into biologically relevant chemical space showing the scaffolds of potential natural-product based inhibitors orbiting their target, the protein structure of protein 11-beta steroid dehydrogenase (PDB code 1xu7). Graphic produced using Pymol (http://www.pymol.org). [M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, Charting biologically relevant chemical space: A structural classification of natural products (SCONP), *PNAS* **2005**, *102*, 17272–17277 and S. Wetzel, H. Waldmann, Cheminformatic analysis of natural products and their chemical space, *Chimia* **2007**, *61*(6), 355–360].

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