ELSEVIER

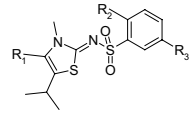
Bioorganic & Medicinal Chemistry

Bioorganic & Medicinal Chemistry Vol. 13, No. 4, 2005

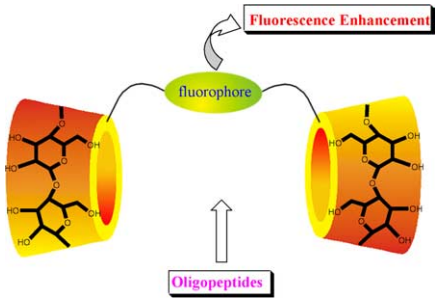
Contents

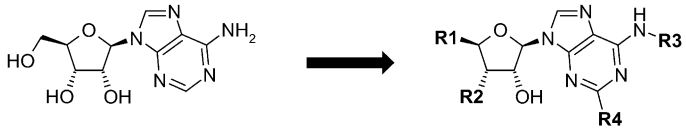
REVIEW

ARTICLES

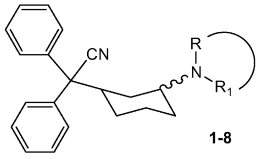


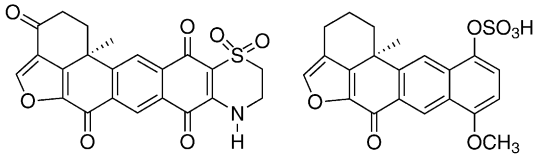
10l : R_1 = Me, R_2 = CN, R_3 = Cl
11g (YM-215389)
: R_1 = Cl, R_2 = OH, R_3 = Br
18b (YM-228855)
: R_1 = Me, R_2 = CN, R_3 = CN



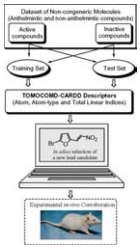


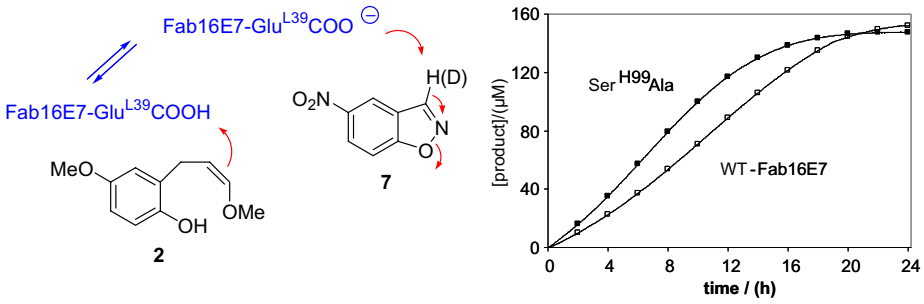
A series of compounds with a diphenylmethyl cyclohexyl skeleton, loosely related to verapamil, has been synthesized and tested as MDR modulators on anthracycline-resistant erythroleukemia K 562 cells. Their residual cardiovascular action (negative inotropic and chronotropic activity as well as vasorelaxant activity) was evaluated on guinea-pig isolated atria preparations and on guinea-pig aortic strip preparations. Most compounds of the series possess a good MDR-reverting activity together with a low cardiovascular action. Among them, three compounds are more potent than verapamil as MDR reverters and lack any cardiovascular action; they can represent useful leads for the development of new safe MDR reversing drugs.

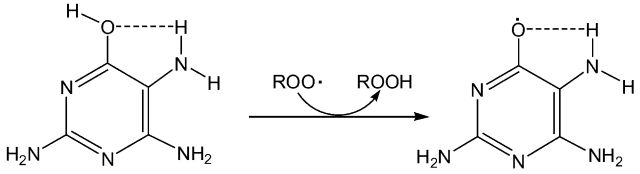




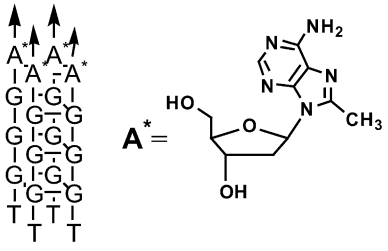
Nine quinones, including the new natural products **6** and **9**, were isolated from a sponge of the genus *Xestospongia*. All the isolated compounds were inhibitory to the dual specificity phosphatase Cdc25B, and five were active at the nanomolar level.

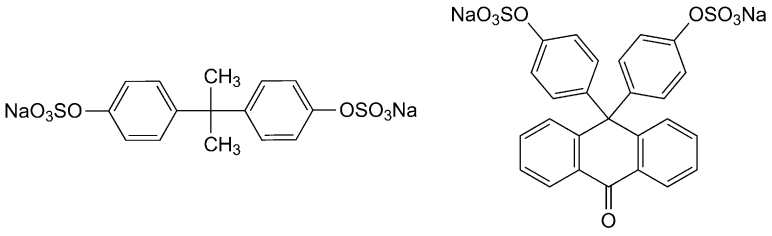


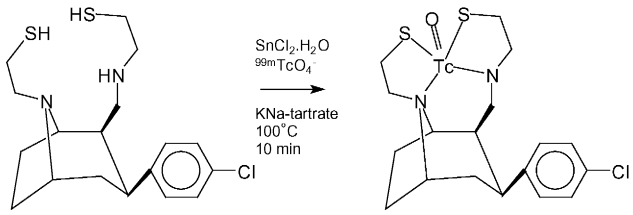


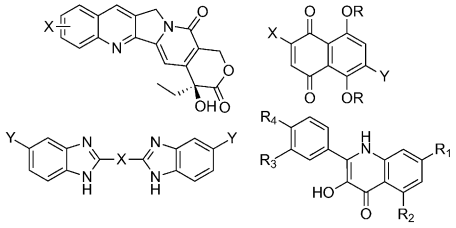


By means of DFT calculation, the structure–activity relationships of metabolites of folates as antioxidants was elucidated and the potential of 4-hydroxypyrimidine as a novel lead antioxidant was evaluated as well.

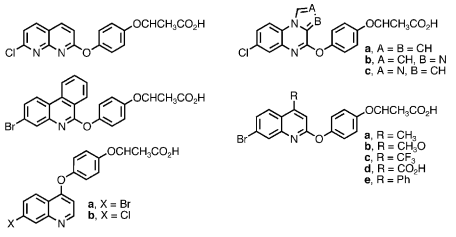


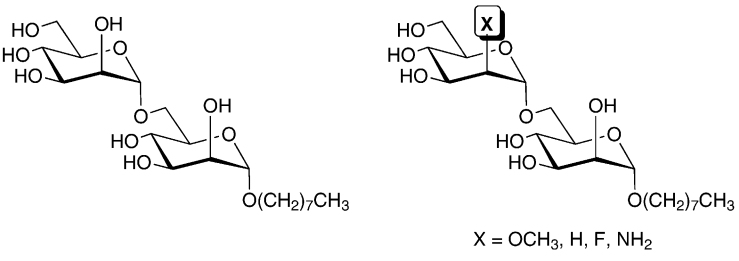


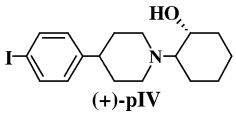




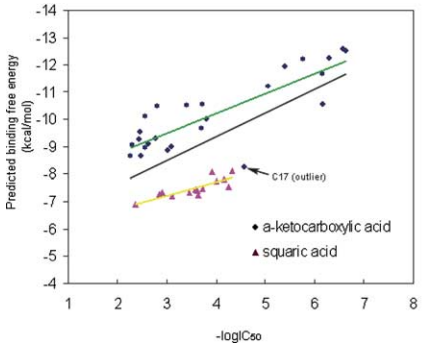
Quantitative structure–activity relationships have been performed for different sets of compounds with respect to their inhibitory activities towards topoisomerase I and II. Activities of these compounds are found to be largely dependent on their hydrophobicity for topoisomerase I and, polarizability and molar volume for topoisomerase II.

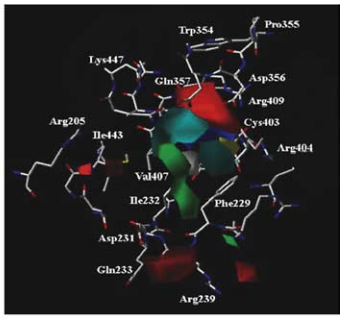


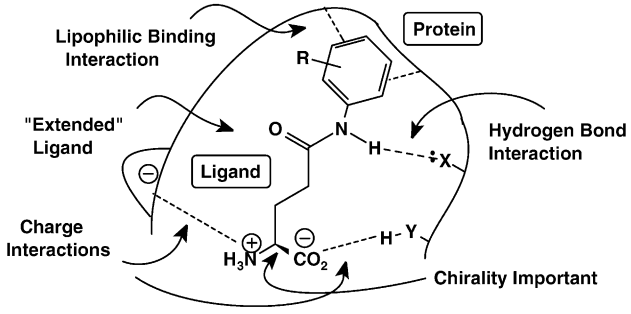


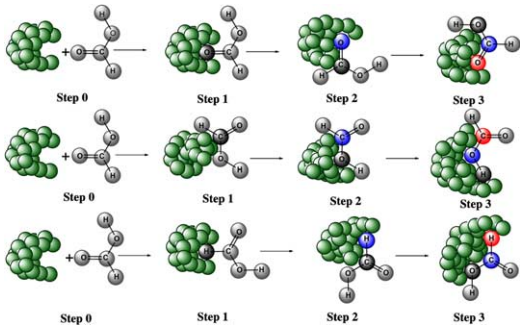


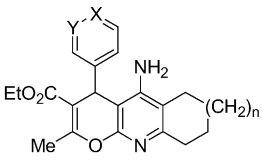
Molecular docking and 3D-QSAR approaches were applied to investigate the interactions of two series of compounds, α-ketocarboxylic acid and squaric acid, with the target protein *Yersinia* protein tyrosine phosphatase YopH. The studies demonstrate the power of combined docking/QSAR approach to explore the probable binding conformations of YopH inhibitors, and further develop reliable quantitative models for rational drug design.

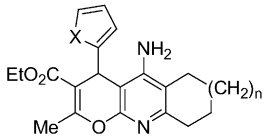


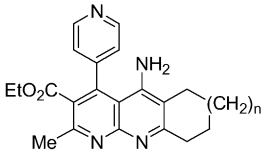


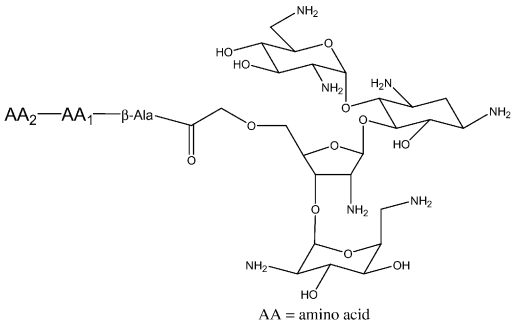


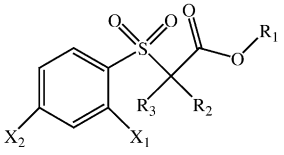






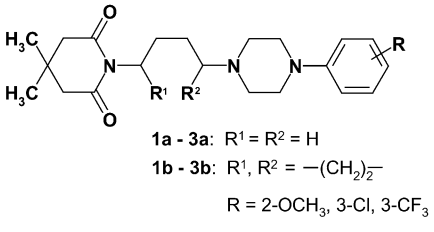


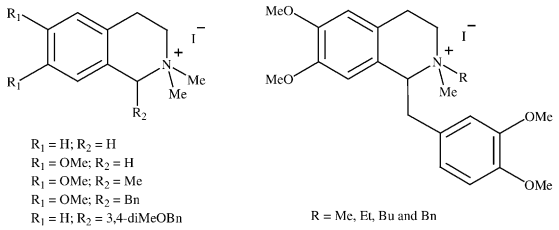


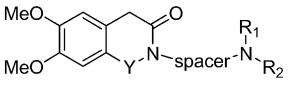


In continuation of our recent efforts to model the acute toxicity of 56 phenylsulfonyl carboxylates to *Vibrio fischeri* using principal component factor analysis, the present paper deals with modeling of the same data set with extended topochemical atom (ETA) indices using genetic function approximation (GFA) as the statistical tool.

Novel, flexible arylpiperazine gepirone analogs (**1a**–**3a**) with a mixed 5-HT$_{1A}$/5-HT$_{2A}$ receptor profile, low D$_2$ receptor affinity, and agonistic (**2a**) or partial agonistic (**1a**, **3a**) activity toward 5-HT$_{1A}$ receptor sites were synthesized. Their conformationally restricted counterparts (**1b**–**3b**) were selective 5-HT$_{1A}$ ligands (over 5-HT$_{2A}$ and D$_2$ receptors), which turned out to be agonists (**2b**, **3b**), or partial agonist (**1b**) of 5-HT$_{1A}$ receptors.

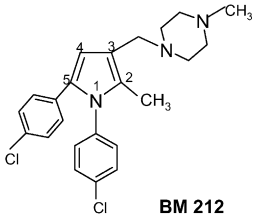




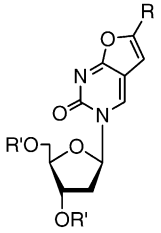


Y = CH_2CH_2, CH=CH;
Spacer = saturated or unsaturated alkyl chain
R_1, R_2 = H, CH_3, cycloalkyl or aryl-cycloalkyl groups

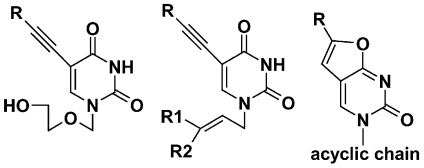
Previously we have identified **BM 212**, a pyrrole derivative with good in vitro activity against mycobacteria and a four-feature pharmacophore model derived from it and many other antimycobacterial compounds synthesized by us. On SAR and molecular modeling considerations, we prepared new pyrrole derivatives in the hope of increasing the activity. The microbiological data showed interesting in vitro activity against *Mycobacterium tuberculosis*.



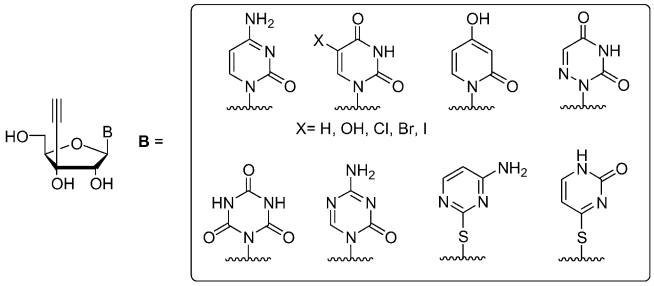
BM 212

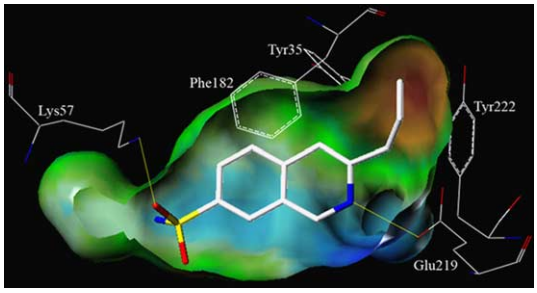


R = *p*-$CH_3C_6H_4$
R' = H, Ac

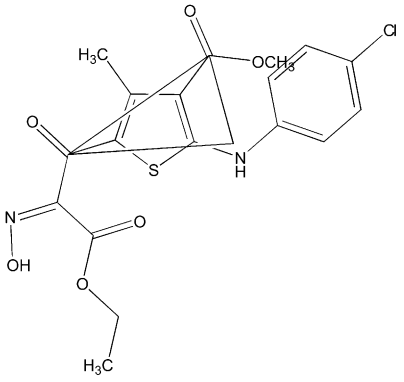


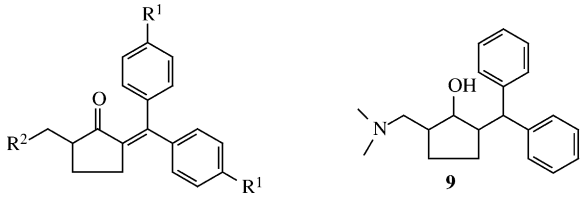
The synthesis of series of *hitherto unknown* 5-alkynyl pyrimidine acyclic nucleosides and their furopyrimidine analogues is described. The in vitro antiviral activity (HIV, HSV-1) and toxicity in different cell lines are reported.





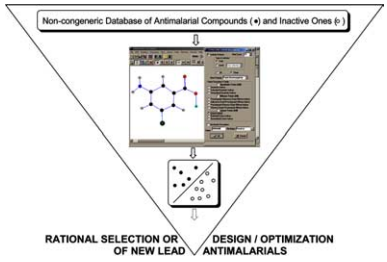
We report the QSAR studies of some thiophene analogs as anti-inflammatory agents. The dominant role played by the electronic parameters, E_{LUMO} and dipole moment in the modulation of the biological activity, help us to propose a novel anti-inflammatory pharmacophore where involvement of oxime is well reflected.

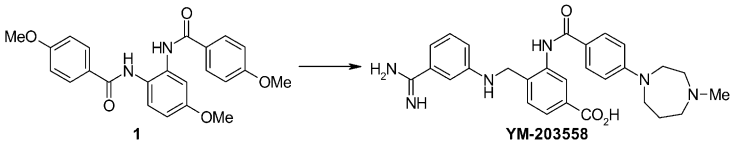




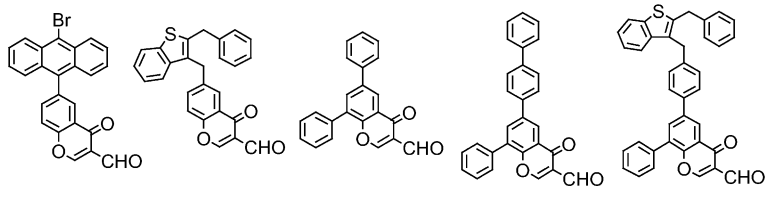
7a ~ 7d R^1 = H R^2 = dimethylamino, 4-morpholinyl, 1-piperidyl, 1-pyrrolidinyl

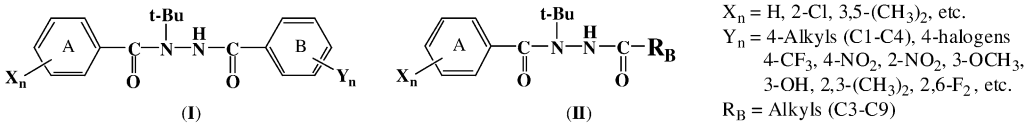
7e ~ 7h $R^1 = CH_3$ R^2 = dimethylamino, 4-morpholinyl, 1-piperidyl, 1-pyrrolidinyl

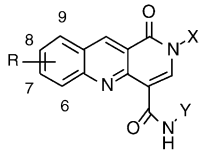




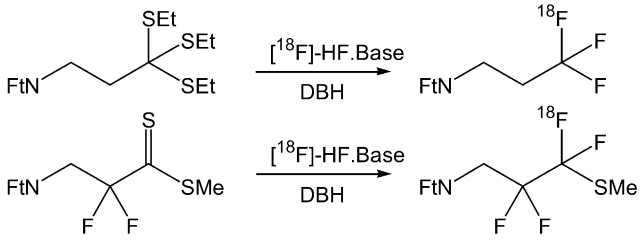
As a result of modification of HTS hit compound **1** to improve both its fXa inhibitory activity and its oral anticoagulant activity, YM-203558 showed nanomolar potency in fXa inhibitory activity and had excellent oral anticoagulant activity.

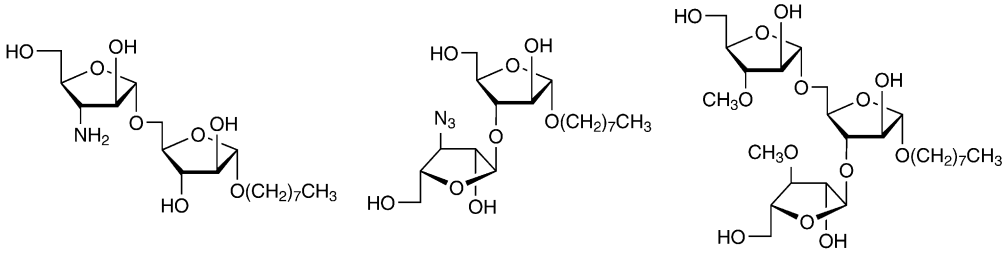


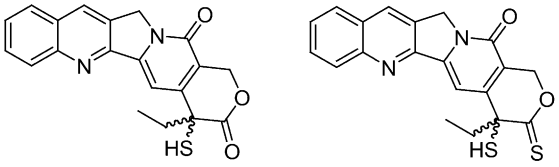


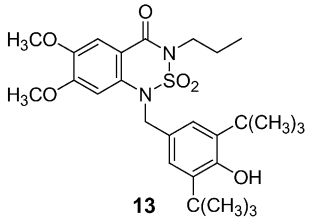


Twenty-six new compounds were prepared and tested. Compound **2t** (R = 6-Me, X = 4-FC_6H_4, Y = $(CH_2)_2NMe_2$) at 1.8 mg kg^{-1} was curative against colon 38 tumors in mice.









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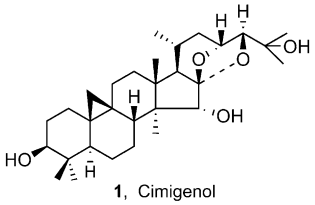
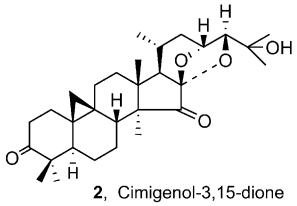
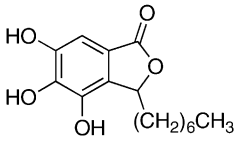


1, Cimigenol



2, Cimigenol-3,15-dione



Cytosporone E

Cytosporone E was synthesized using the Meyers *ortho*-alkylation of a chiral aromatic oxazoline as the key step to form the phthalide backbone. Antibacterial testing demonstrates activity against Gram-positive bacteria and not Gram-negative bacteria.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

2005: Human liver glycogen phosphorylase A (HLGPa) is an attractive target enzyme for discovering anti-type 2 diabetes drugs. This picture shows the interaction model for a series of indole-2-carboxamides to HLGPa derived from molecular docking simulations [Liu, G.; Zhang, Z.; Luo, X.; Shen, J.; Liu, H.; Shen, X.; Chen, K.; Jiang, H. *Bioorg. Med. Chem.* **2004**, *12*, 4147–4157].

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