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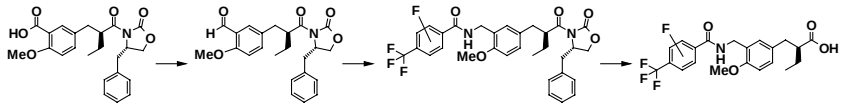
Bioorganic & Medicinal Chemistry Letters

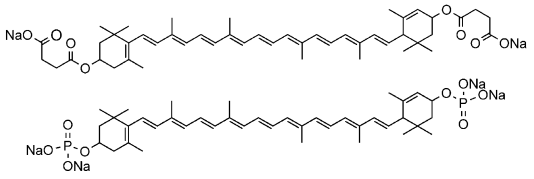
Bioorganic & Medicinal Chemistry Letters Vol. 16, No. 4, 2006

Contents

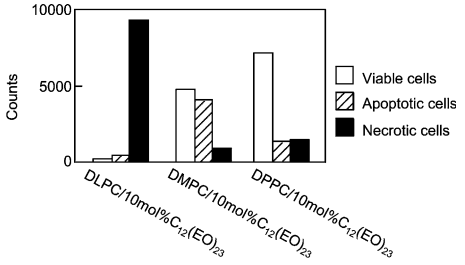
ARTICLES



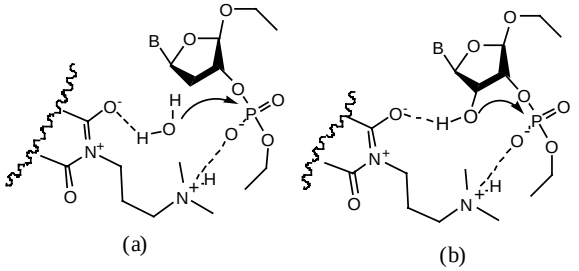
Optically active (*S*)-2-ethylphenylpropanoic acid derivatives, dual agonists for human peroxisome proliferator-activated receptor (PPAR) α and δ, were efficiently prepared.

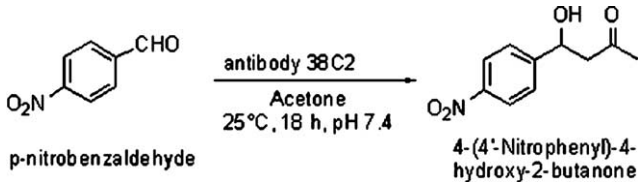


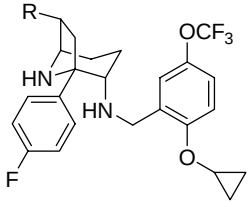
Novel water-dispersible lutein esters were prepared, which demonstrated potent, direct superoxide scavenging ability in an in vitro isolated human neutrophil assay.



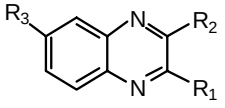
It was found that two methylene groups in phospholipids having the same head group could clearly distinguish between apoptosis and necrosis for human leukemia cells.



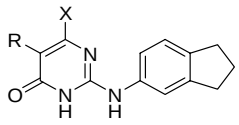




A series of 8-azabicyclo[3.2.1]octane benzylamine hNK_1 antagonists has been explored. Substitution with acidic moieties at the 6-*exo* position leads to high affinity hNK_1 antagonists which are selective over the hERG channel.

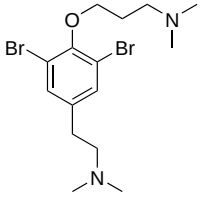


A series of substituted quinoxalines (29 compounds) was synthesized and evaluated against several protozoa. Some of them showed promising antileishmanial activity against *Leishmania donovani*.

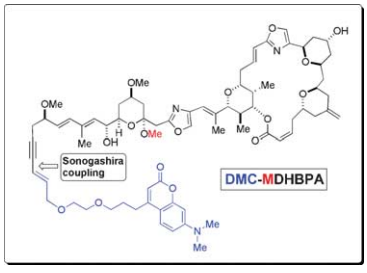


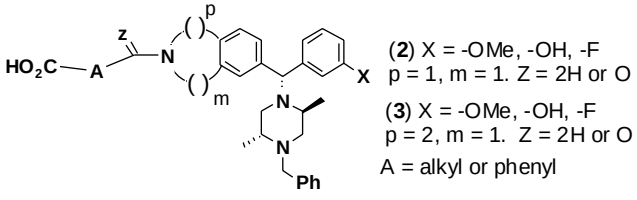
X = OH, NH_2

The preparation and biological evaluation of 5-substituted-6-hydroxy-2-(anilino)pyrimidinones as a new class of DNA polymerase IIIC inhibitors, required for the replication of chromosomal DNA in Gram-positive bacteria, are described. These new dGTP competitive inhibitors displayed good levels of in vitro inhibition and antibacterial activity against *Staphylococcus aureus*. A new class of dATP competitive inhibitors, 6-substituted-2-amino-5-alkyl-pyrimidin-4-ones, whose antibacterial activity was unaffected by serum, were identified.

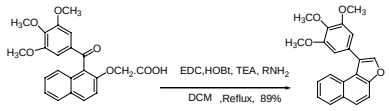


Aplysamine-1

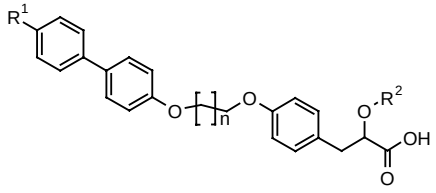




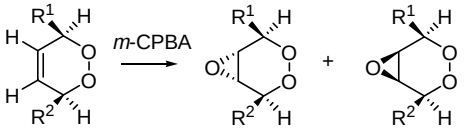
A series of potent and selective zwitterionic δ-opioid agonists (**2**) and (**3**) are described.



3′,4′,5′-Trimethoxy benzoyl-naphthalene 2-*O*-acetic acid (**5**) underwent base catalysed intramolecular condensation to yield exclusively 1-(3′,4′,5′-trimethoxy) phenyl naphtho[2,1-*b*]furan **8**, which has been characterised by spectroscopy. The reaction has been further extended to two more similar compounds **6** and **7** to get aryl naphtho[2,1-*b*]furans **9** and **10**, respectively. These aryl naphthofurans (**8** and **9**) showed significant anticancer activity against various human cancer cell lines in the in vitro MTT assay.

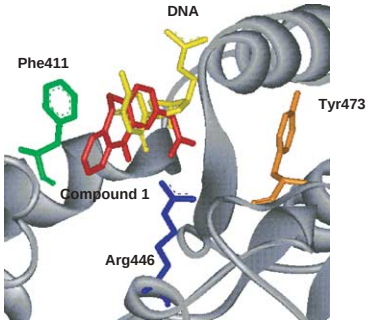


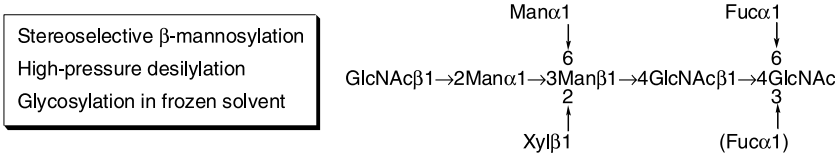
A series of 2-alkoxydihydrocinnamates as PPARγ and PPARα dual agonists with substituted biphenyl tailpiece were synthesized and tested for their functional activity in vitro.



R^1 = cycloalkyl
R^2 = cycloalkyl or H

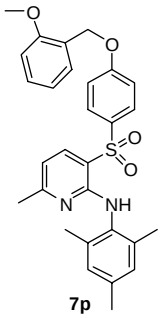
A series of novel endoperoxides were synthesised and tested for inhibitory activity against *Candida* growth. Despite structural similarities, their activity varied considerably. Several endoperoxides demonstrated potential for development as antifungal agents.

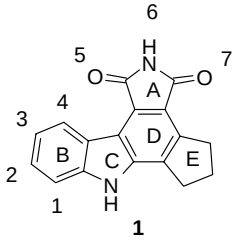




Synthesis of branched complex-type glycans derived from helminth glycoproteins is described.

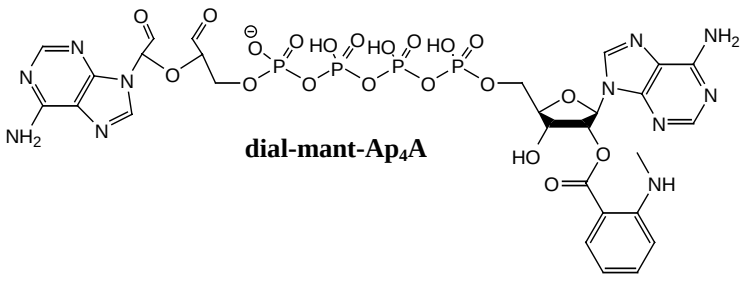
A novel series of 2-anilino-3-phenylsulfonyl-6-methylpyridines was synthesized and evaluated as corticotropin-releasing factor receptor ligands.

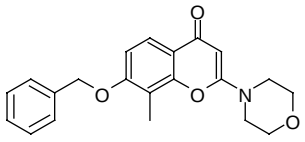




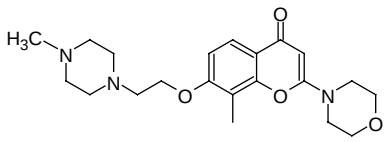
Pyrrolocarbazole **1** was identified as a potent PARP-1 inhibitor (IC_{50} = 36 nM) from our internal database. The synthesis and SAR optimization around this template with the aid of modeling studies led to the identification of the truncated imide.

Synthesis and initial testing of two novel fluorescent labelled affinity probes designed for use in diadenosine-5′,5-P^1,P^4-tetraphosphate (Ap_4A)-binding studies, dial-mant-Ap_4A and azido-mant-Ap_4A.

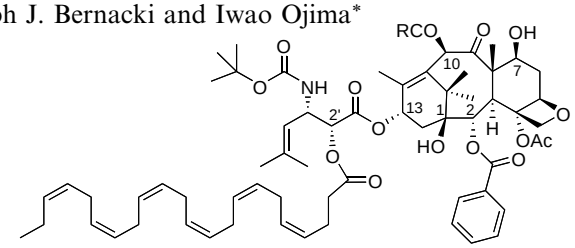




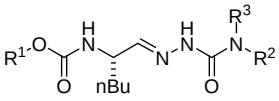
Platelet aggregation inhibitor
v. PDE3 IC_{50} = 0.6 μM



Platelet aggregation inhibitor
Inactive v. PDE3

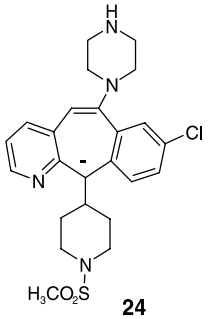


The syntheses and exceptional antitumor activities of a series of novel fatty acid-second-generation taxoid conjugates against human tumor xenografts are reported.



Starting from potent aldehyde inhibitors with poor drug properties, derivatization to semicarbazones led to the identification of a series of semicarbazone-based cathepsin K inhibitors with greater solubility and better pharmacokinetic profiles than their parent aldehydes. Furthermore, a representative semicarbazone inhibitor attenuated bone resorption in an ex vivo rat calvarial bone resorption model. However, based on enzyme inhibition comparisons at neutral pH, semicarbazone hydrolysis rates, and ^{13}C NMR experiments, these semicarbazones probably function as prodrugs of aldehydes.

Novel potent, orally bioavailable Ftase inhibitor targeting catalytic zinc is presented.



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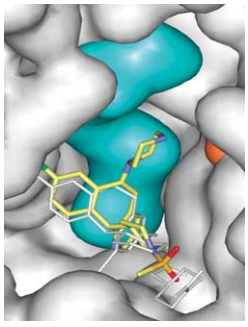
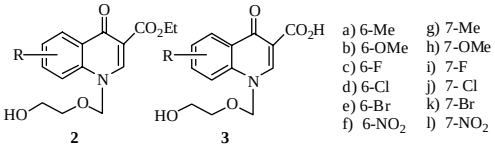
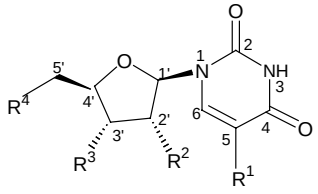
Ftase IC50 = 0.007 μM



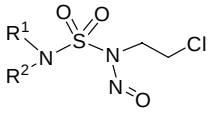


2 3

Several new acyclonucleosides, 1-[(2-hydroxy-ethoxy)methyl]-3-carbethoxy-4(1*H*)quinolones (**2a**–**l**) and 1-[(2-hydroxy-ethoxy)methyl]-4(1*H*)quinolone-3-carboxylic acids (**3a**–**j** and **3l**), were synthesized and evaluated against herpes simplex virus type 1 (HSV-1).



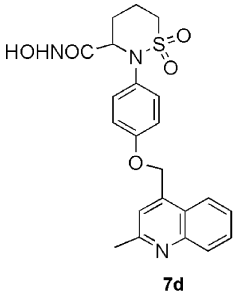
Robust and predictive 3D-QSAR models were developed for dTMP derivatives inhibiting TMP kinase. Three different alignment methods were used and compared with active site residues to explore the nature of substituent.



CENS

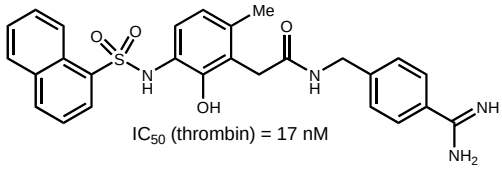
The kinetics of aqueous decomposition of three 2-chloroethylnitrososulfamide are reported.

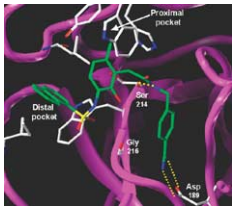
Novel sultam hydroxamates with potent MMP activity were transformed into potent TACE inhibitors, lacking MMP activity. From this effort, compound **7d** was identified as a potent TACE inhibitor (IC_{50} = 3.7 nM) that lacked MMP-1, -2, -9, and -13 activity.



7d

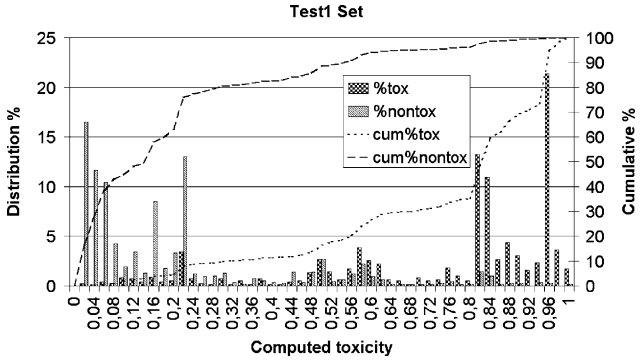
TACE IC_{50} = 3.7 nM



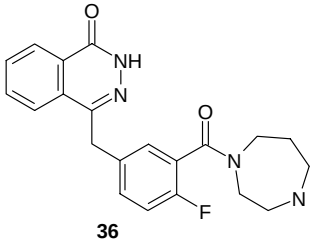


Prototypical thrombin inhibitors were synthesized based on a trisubstituted phenol as a core motif. A naphthylsulfonamide analogue showed excellent antithrombin activity. An X-ray co-crystal structure showed the expected interactions.

A neural network based classification approach using cytotoxicity data measured for 30,000 compounds has been developed to predict cytotoxicity.

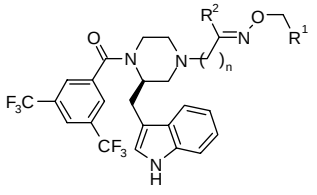


The discovery of novel and cellularly potent PARP-1 inhibitors is described. Compound **36** is effective in specific killing of BRCA2-deficient tumour cells.

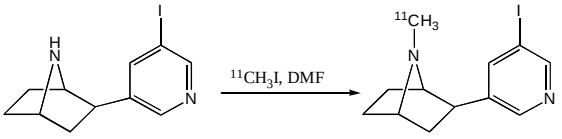


36

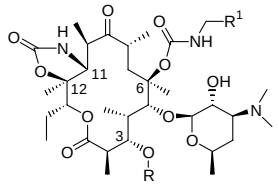
IC_{50} = 7.0 nM, PF_{50} = 12.6, $t_{1/2}$ = 60 min



The synthesis and SAR for a new class of centrally active NK-1 receptor antagonists are described. The new compounds all have a piperazinyl oxime ether functionality. Several new compounds have high affinity for the NK-1 receptor and show good antagonistic activity in the gerbil foot-tapping assay.

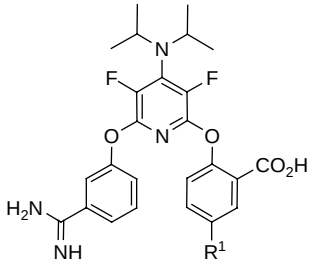


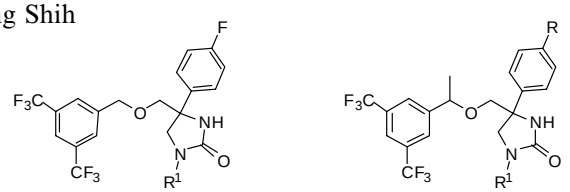
[^{11}C]NMI-EPB



R = COR^2 or $CONR^3R^4$
3-*O*-Acyl-6-*O*-Carbamoyl
Macrolides

A series of 3-*O*-acyl-6-*O*-carbamoyl erythromycin A derivatives has been synthesized. The best compounds in this series possess potent in vitro antibacterial activity against erythromycin-susceptible and erythromycin-resistant bacteria.





2 **3 (R = H)**
4 (R = F)

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Superposition of the X-ray crystal structures of 8 (white) and CVS1695 (magenta) in complexes with thrombin. [Hanessian, S.; Therrien, E.; van Otterlo, W. A. L.; Bayrakdarian, M.; Nilsson, I.; Fjellström, O.; Xue, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1036.]

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ISSN 0960-894X