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Medicinal
Chemistry

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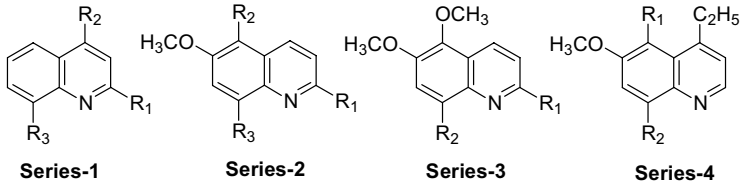
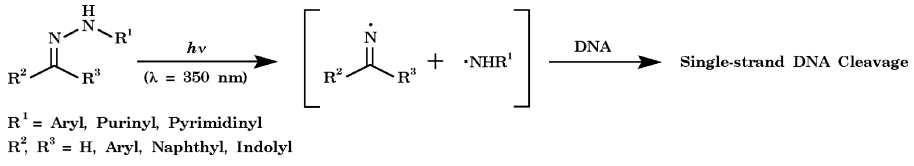
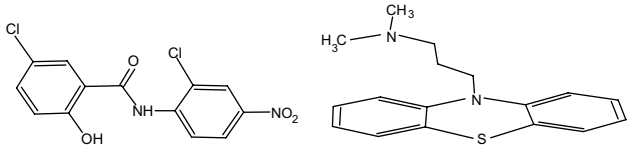
Contents

ARTICLES

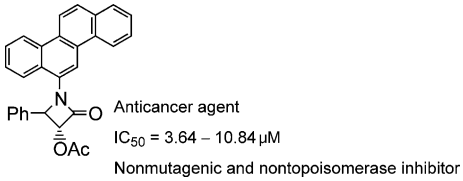


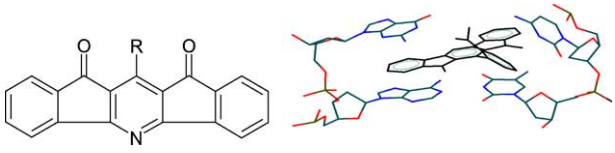
The anti-tuberculosis activities of ring-substituted quinolines (series 1–4) against drug-sensitive and drug-resistant *M. tuberculosis H37Rv* strains are described. The most effective analogues have exhibited potent efficacy (MIC = 1.0 μg/mL).



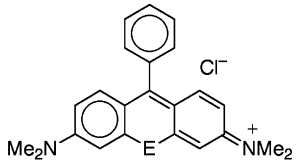


The binding analysis of SARS-CoV main proteinase with HIV, psychotic and parasite drugs (lopinavir, ritonavir, niclosamide and promazine) suggests that these existing drugs can be used as starting points for designing SARS-CoV proteinase inhibitors.

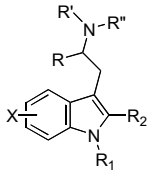




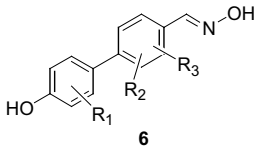
Several diindenopyridine derivatives were synthesized and evaluated for their antitumor activity on cell lines. Effect of structural parameters on the cytotoxicity was evaluated by QSAR analysis. The molecular modeling method was employed to study the DNA-intercalator complex.



TMR-O, E = O, λ_{max} 552 nm, $\phi(^1O_2)$ 0.08
TMR-S, E = S, λ_{max} 571 nm, $\phi(^1O_2)$ 0.21
TMR-Se, E = Se, λ_{max} 582 nm, $\phi(^1O_2)$ 0.87



The binding of >40 tryptamine-related analogs at human 5-HT$_{1E}$ receptors was examined for the purpose of formulating structure–affinity relationships (SAFIR). SAFIR and QSAR studies (CoMFA, QsarIS) implicated important roles for hydrogen bonding in the interaction of these ligands with the receptor.



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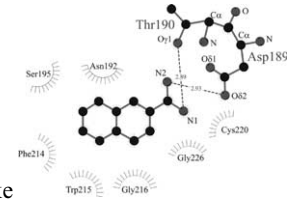
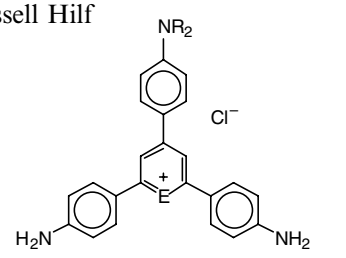
A series of biphenyl carbaldehyde oximes (**6**) was prepared and shown to have significant affinity and selectivity for ERβ. SAR and modeling suggested the oxime moiety was mimicking the C-ring of genistein.

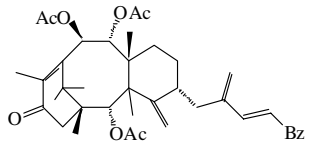


In addition to identifying the set of residues involved in molecular recognition of inhibitors bound to the S1 subsite of snake venom thrombin-like enzymes (SVTLEs), our calculations have indicated that nonpolar (van der Waals) intermolecular interactions and ligand's hydrophobicity are the most important factors affecting binding affinities to the S1 subsite of a SVTLE isolated from the venom of *Lachesis muta muta* (Lmm-TLE). Consequently, we have proposed that S1 subsite lipophilicity may be used to sort binding affinities of trypsin-like enzymes to small molecules by showing that the inhibitory potency of several S1-directed compounds follows subsite lipophilicity among Lmm-TLE and other three trypsin-like serine proteases. Noteworthy, in the course of our analyses we determined that thrombin's S1 subsite should, in fact, be considered less lipophilic than that of trypsin if we account for the presence of the sodium-controlled water channel communicating with the S1 subsite in the coagulant enzyme.



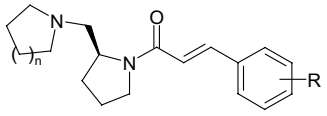
AA1, E = S; **AA1-Se**, E = Se, $NR_2 = NMe_2$

1, E = S; **2**, E = Se; NR_2 = –N O

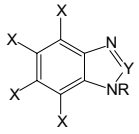


1 IC_{50} = 27 and 36 μM (pol.α and β)

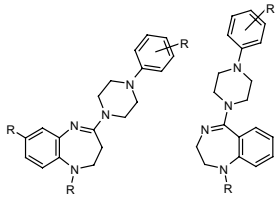
Taxinine was found to selectively inhibit DNA polymerase α (pol.α) and β (pol.β) and Cephalomannine, and five intermediates synthesized chemically inhibited only the pol.α activity in vitro.



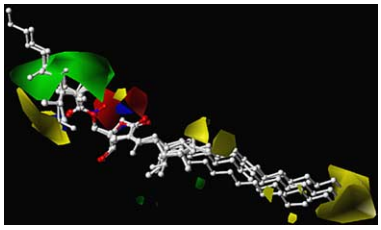
New imidazole-free H_3 antagonists have been found in a series of cinnamic amides of (*S*)-(aminomethyl)pyrrolidines. The influence of the substituent on the aromatic moiety on the potency and the inhibition of three cytochrome P450 subtypes are also described.

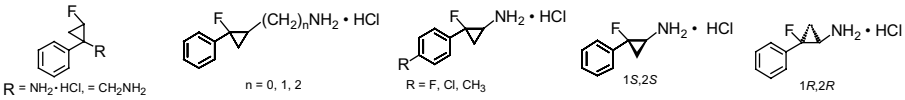


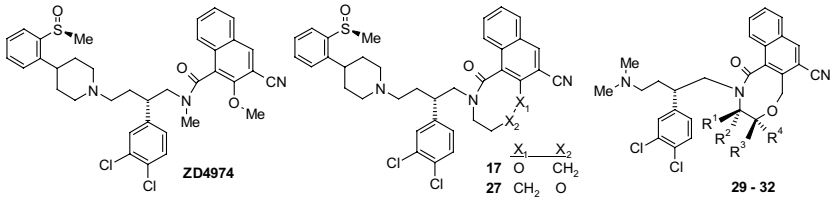
A number of chloro-, bromo- and methyl- analogues of 1*H*-benzimidazole and 1*H*-benzotriazole and their *N*-alkyl derivatives have been synthesized and tested in vitro against *Acanthamoeba castellanii*. Some compounds showed high inhibitory activity at tested concentrations.



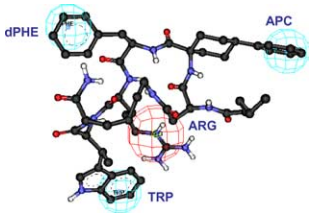
4-Arylpiperazinyl-1-yl-substituted 2,3-dihydro-*1H*-1,4- and 1,5-benzodiazepines and their aza-analogues were synthesized. Some of the title compounds show an impressively high selectivity for the dopamine D4 receptor subtype. In a mitogenesis assay the most promising compounds showed partial agonistic effects.



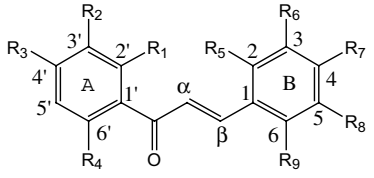




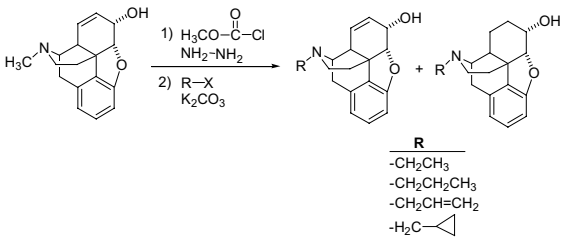
A series of stepwise structural modifications of the NK_1-selective ZD4974 enabled further refinement of a previously reported NK_1 pharmacophore model.

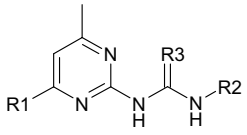


A predictive pharmacophore model of human melanocortin-4 receptor (hMC4R) was derived from the NMR structures of a series of rigidified MT-II related cyclic peptide agonists. The model successfully identified reported hMC4R small molecule ligands from a library of 1000 drug-like compounds.

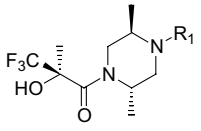


A series of 10 structurally related 2′-oxygenated chalcone derivatives, all of which bearing either hydroxyl and/or methoxy substituents on the A and B rings, were synthesized and evaluated for their cytotoxic activities against the human tumor cells such as Jurkat, U937 cells, and normal cells PHA stimulated PBMCs.

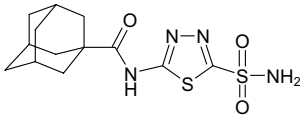


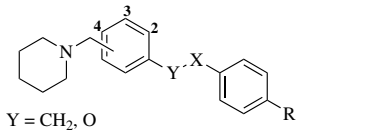


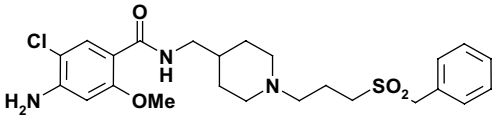
A series of bis-aryl substituted guanidines have been discovered as potent NPY Y5 antagonists. The SAR and in vitro metabolic stability of these compounds are discussed.



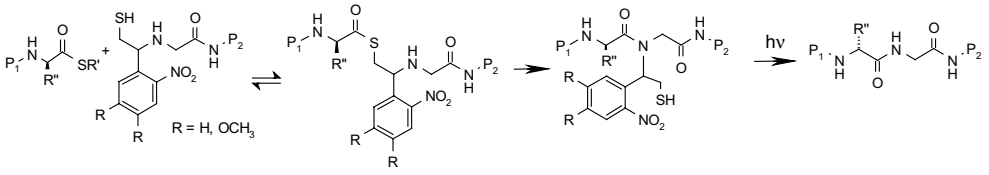
CoMFA study of pyruvate dehydrogenase kinase inhibitors based on a divide and conquer approach for alignment is reported.



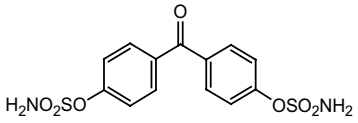




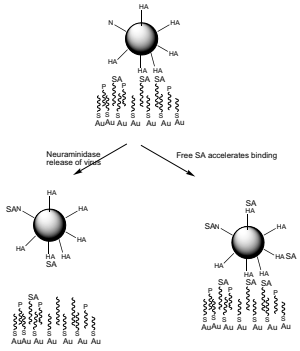
4-Amino-*N*-[1-[3-(benzylsulfonyl)propyl]piperidin-4-ylmethyl]-5-chloro-2-methoxybenzamide (**13a**, **Y-36912**) was a selective 5-HT_4 receptor agonist offering potential as a novel prokinetic agent with reduced side effects derived from 5-HT_3- and dopamine D_2 receptor-binding affinity. In the oral route of administration, this compound enhanced gastric emptying and defecation in mice, and has a possibility as a prokinetic agent, which is effective on both the upper and the lower gastrointestinal tract.



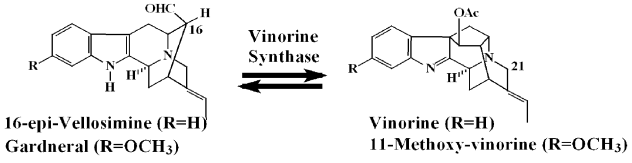
Two photolabile auxiliaries for extended ligation with thioester peptides are described. Post-ligation photolysis from the newly formed peptide bond liberates the native amide structure at the ligation junction. Synthesis of the auxiliaries, ligation properties, photolysis and compatibility with peptide sequence functionalities are reported.



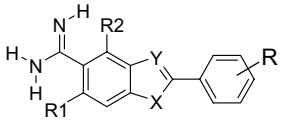
Benzophenone-4,4′-*O*,*O*-bis-sulfamate, is a potent nonsteroidal steroid sulfatase inhibitor with in vivo activity.



The isolation, enrichment, partial amino acid sequences and sequence comparison of vinorine synthase to other acetyltransferases from higher plants were reported.



A cDNA clone encoding vinorine synthase was isolated from *Rauvolfia serpentina* and functionally expressed in *Escherichia coli*. The heterologously expressed enzyme was thoroughly characterized by molecular analysis, mainly by site-directed mutagenesis.



Statistically significant 3D-QSAR CoMFA/CoMSIA models were generated for a series of indole/benzoimidazole-5-carboxamidines. The 3D-CoMFA, CoMSIA contour maps can be used as putative pharmacophore for the design of novel uPA inhibitors as cancer therapeutics.

OTHER CONTENTS

*Corresponding author

COVER

2004: Overlaps of the eight known aldolase alpha-beta barrels in 2-deoxyribose-5-phosphate aldolase (DERA). Ribbon model for DERA is shown in green, with key Lys residues capable of Schiff base formation highlighted in stick figure. Reactive Lys167 is shown in yellow. DeSantis, G.; Liu, J.; Clark, D. P.; Heine, A.; Wilson, I. A.; and Wong, C.-H. *Bioorganic & Medicinal Chemistry* **2003**, *11*, 43–52.

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