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Bioorganic & Medicinal Chemistry Letters

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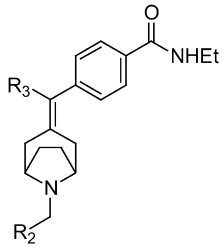
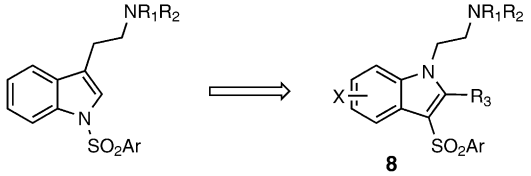
Contents

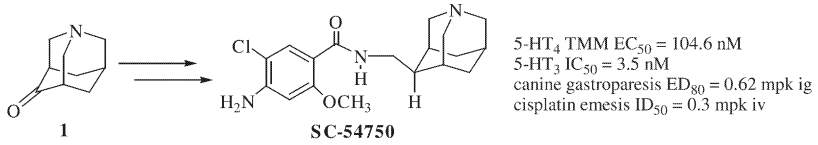
COMMUNICATIONS



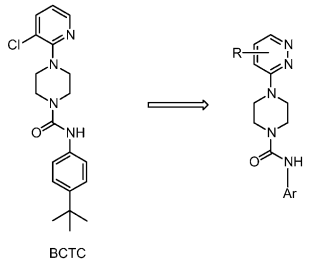


Novel 1-(2-aminoethyl)-3-(arylsulfonyl)-1*H*-indoles were prepared. Binding assays indicated they are 5-HT$_6$ receptor ligands, among which *N*,*N*-dimethyl-*N*-{2-[3-(1-naphthylsulfonyl)-1*H*-indol-1-yl]ethyl}amine **8t** and *N*-methyl-*N*-{2-[3-(1-naphthylsulfonyl)-1*H*-indol-1-yl]ethyl}amine **8u** showed high affinity for 5-HT$_6$ receptors with K_i = 3.7 and 5.7 nM, respectively.

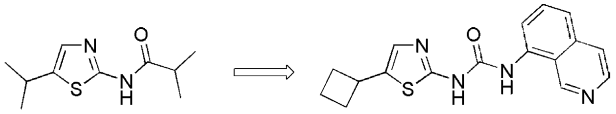
Compounds that contain an α,β-unsaturated carbonyl moiety are often flagged as potential Michael acceptors. All α,β-unsaturated carbonyl moieties are not equivalent, however, and we sought to better understand this system and its potential implications in drug-like molecules. Measurement of the ^{13}C NMR shift of the β-carbon and correlation to in vitro results allowed compounds in our collection to be categorized as potential Michael acceptors, potential substrates for NADPH, or as photoisomerizable.

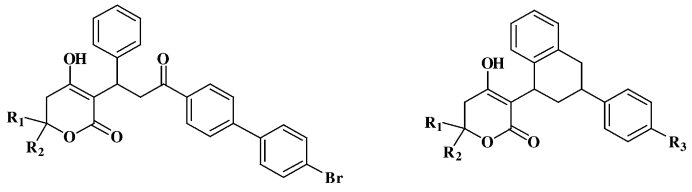


Azaadamantanone **1** was converted to a series of aminoazaadamantane benzamides **9a–d**, which were profiled for serotonin receptor activity. Aminomethylazaadamantane **SC-54750** is a potent 5-HT$_4$ agonist and 5-HT$_3$ antagonist with in vivo efficacy in gastroparesis models and also inhibits cisplatin-induced emesis.

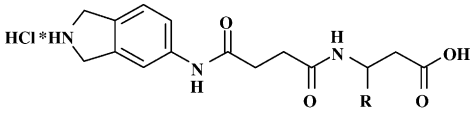


A series of pyridazinylpiperazines were synthesized and evaluated for VR1 antagonist activity in order to improve upon the pharmaceutical and pharmacological properties of BCTC.

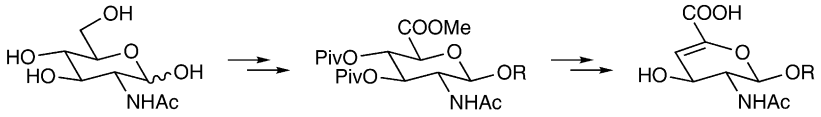




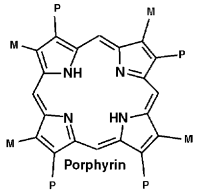
A series of 4-hydroxycoumarin derivatives was prepared and evaluated for antitumor activity against five human tumor cell lines.



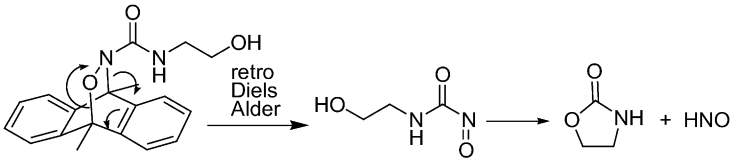
The novel RGDF mimetics **9a** and **9b** were synthesized with the use of 4-(isoindoline-5-yl)amino-4-oxobutyric acid as a surrogate of Arg-Gly motif. The synthesized compounds have demonstrated a high potency to inhibit platelet aggregation in vitro and to block FITC-Fg binding to $\alpha_{IIb}\beta_3$ on washed human platelets.

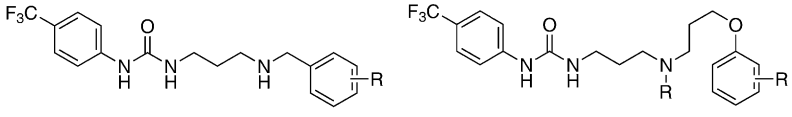


The synthesis of Neu5Ac2en mimetics as inhibitors of *Vibrio cholerae* sialidase is reported.

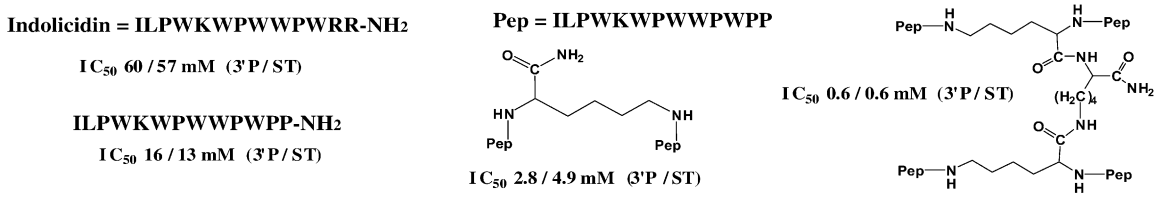


A porphyrin-resin rapidly and effectively separates coproporphyrinogen oxidase from uroporphyrinogen decarboxylase as well as the majority of hemoglobin.

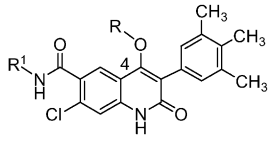




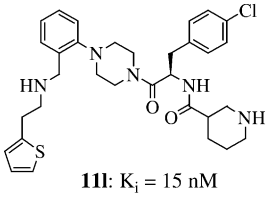
The synthesis and evaluation of aryl urea analogs as broad-spectrum antibacterial agents is described.

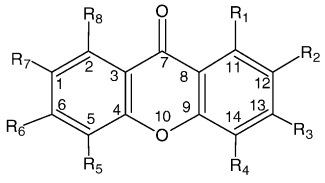


The HIV-1 integrase inhibitory activity of indolicidin and its analogs (including dimeric and tetrameric) are reported.

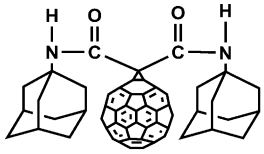


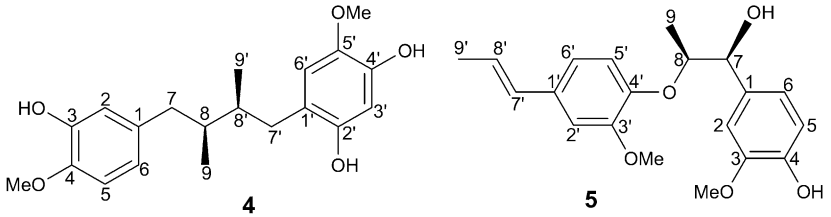
Potent neutral replacements of the basic amine at the 4-position of quinolone non-peptide GnRH antagonists are reported.





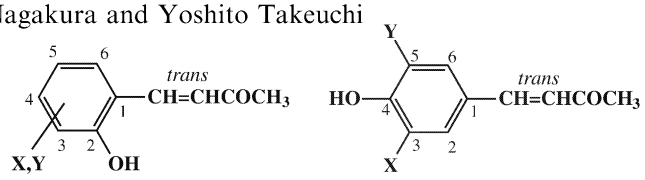
This work presents a QSAR study of the MAO A inhibitory activity (IMAO A) of a set of xanthones resorting to the molecular descriptors E-state index (S_i), molecular connectivity (χ) and shape (k). The xanthones group (9-H-xanton-9-onas), of natural or synthetic origin, present eight positions for the substitution and their IMAO A was reported previously by Gnerre et al. The descriptors included in the adjusted model were selected to describe the molecular structure of the compounds. The model was selected using the leave-one-out method and the cross-validation statistics shows the model is useful for prediction since: $r^2 = 0.847$, $s = 8.069$ and $F = 9.72$, calculated by multiple linear regression.





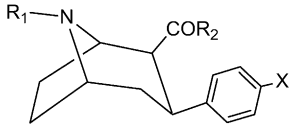
4 **5**

A new diarylbutane lignan, 2′-hydroxy dihydroguaiaretic acid (**4**), and a known 8-*O*-4′-type neolignan, machilin D (**5**) were isolated from the ethyl acetate extracts of *Saururus chinensis* root and exhibited low-density lipoprotein (LDL)-antioxidant activity and radical DPPH scavenging activity.

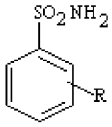


2OH-BZ **4OH-BZ**

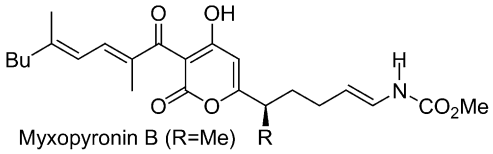
Antioxidant activities for a series of hydroxybenzalacetones, **OH-BZ**, were evaluated by measuring inhibitory potencies of **OH-BZ** against lipid peroxidation induced by *t*-BuOOH or γ-irradiation. Their quantitative structure–activity relationship (QSAR) studies indicated that the activities are mainly governed by electronic and steric factors.



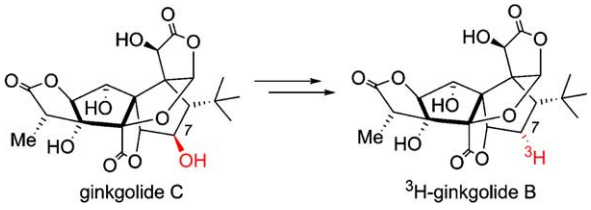
A series of novel fluoroalkyl-containing tropane derivatives were synthesized from cocaine. The binding affinities for DAT, SERT, and NET were determined via competitive binding assays.



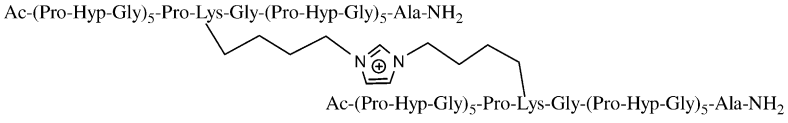
A large series of distance-based topological indices has been used for modeling lipophilicity, diuretic activity, and carbonic anhydrase inhibition activity of a library of simple substituted benzene sulfonamides. The results have shown that the topological approach used is quite useful for modeling carbonic anhydrase inhibition and the use of molecular connectivity is the best for this purpose. Excellent results are obtained in multiparametric regressions. The results are critically discussed on the basis of statistical parameters.



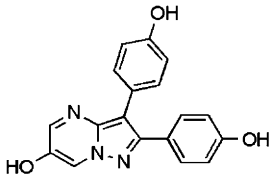
A series of myxopyronin B analogs has been prepared via a convergent synthetic route and were tested for in vitro inhibitory activity against DNA-dependent RNA polymerase and antibacterial activity against *E. coli* and *S. aureus*.



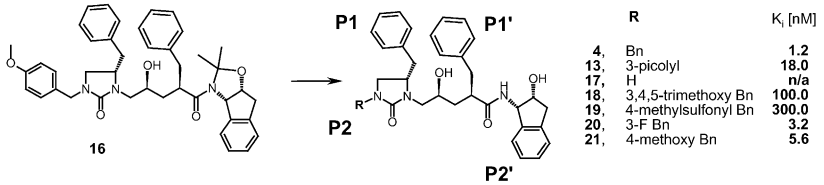
A radiolabeled constituent of *Ginkgo biloba*, [^{3}H]-ginkgolide B, was prepared in high specific radioactivity, providing a tool for studying neuromodulatory properties of ginkgolides.



Glycation reactions using a model peptide of collagen and glucose or ribose resulted in detection of carboxylmethyl-lysine in the peptide; and treatment with glyoxal provided a dimer of the peptide linked with glyoxal lysine dimer (GOLD).

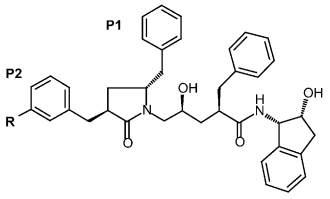


We investigated the pyrazolo[1,5-*a*]pyrimidine system as a novel heterocyclic scaffold for the development of estrogen receptor (ER) ligands. By altering the pattern of hydroxyl substitution, we established the orientation that is most favorable for ER binding, thus enabling further development of this ER ligand core.



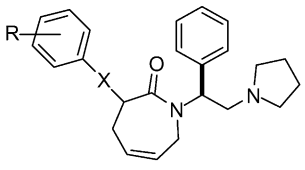
	R	K_i [nM]
4,	Bn	**1.2**
13,	3-picolyl	**18.0**
17,	H	**n/a**
18,	3,4,5-trimethoxy Bn	**100.0**
19,	4-methylsulfonyl Bn	**300.0**
20,	3-F Bn	**3.2**
21,	4-methoxy Bn	**5.6**

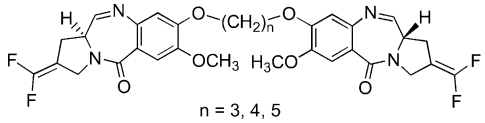
We have developed an efficient synthetic approach to analogues of potent HIV-protease inhibitor (PI) **4**. Key chemistry includes TFA-mediated deprotection of MOB-protected **16** to precursor **17**. Alkylation of **17** enabled the synthesis of many PIs, as exemplified here by **13**, **19**–**21**, in excellent yields and purity, and thus overcoming bottlenecks of our prior synthetic approach to these PIs. These results allowed to rapidly evaluate the SAR in P1–P2 cyclic urea-based HIV-1 PIs as well as provided a strong rationale towards P1–P2 pyrrolidone scaffold-based PIs, ultimately leading to subnanomolar PIs (follow-up communication).

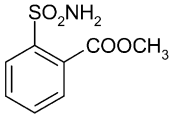


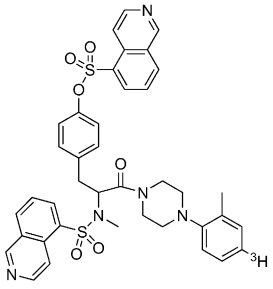
	R	K_i [nM]
4	H	0.067
17b	NH_2	0.10
19b	OH	0.05

SAR around the HIV-1 protease inhibitor lead **4**, which utilizes the (3*S*,5*R*)-3,5-bis(phenylmethyl)-2-pyrrolidinone as P1–P2 scaffold, led to discovery of *meta*-amino- and *meta*-hydroxy inhibitors **17b** and **19b**, which while equipotent to **4**, in addition offered an improved aqueous solubility. The SAR was further rationalized with the aid of X-ray crystallography and suggested specific role assumed by the *meta*-substituent, which can uniquely support high enzyme potency and which can be utilized as a platform for further chemical manipulations to fine–tune other drug-like properties in this series. This finding enables additional chemistry manipulations in search for other potential HIV-1 protease inhibitor drug candidates.









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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