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Bioorganic & Medicinal Chemistry Letters

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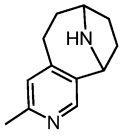
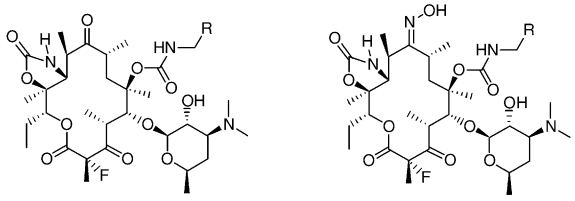
Contents

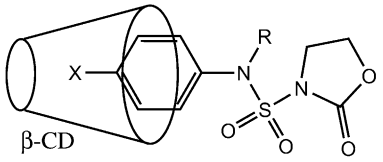
COMMUNICATIONS

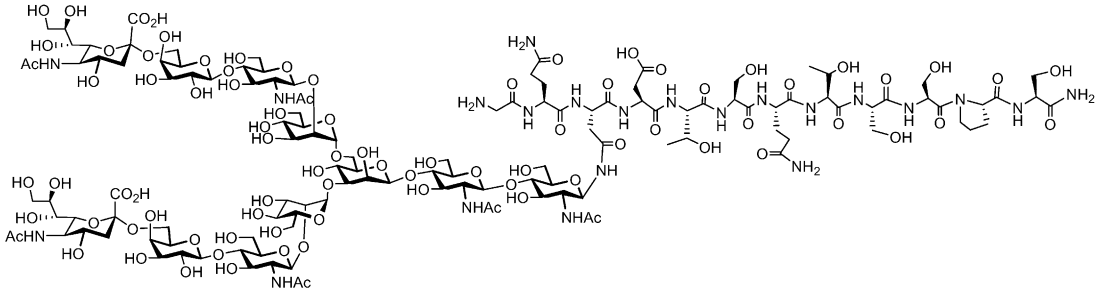


The racemic (±) compound is more potent at the α4β2 nicotinic receptor (K_i = 0.39 nM) than any previously reported bridged nicotinoid, establishing an important role of the 6′-methyl substituent in this pharmacopore model.

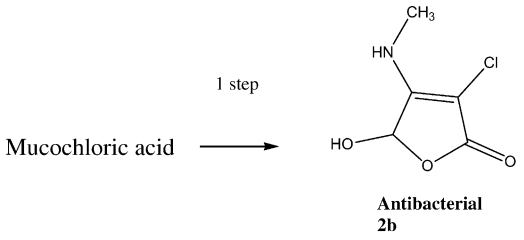


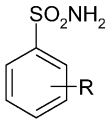
A series of C6-carbamate ketolides with C2-fluorination and C9-oximation was synthesized and shown to have in vitro activity that is superior to erythromycin and comparable to telithromycin. In vivo activity was adversely affected by fluorination, possibly as a result of increased serum protein binding.



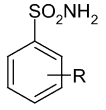


The synthesis of the CD52 glycoproteins was achieved using endoglycosidase-catalyzed oligosaccharide transfer as the key step.

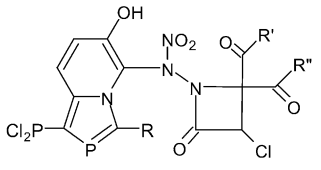




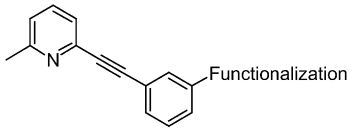
The binding constants (log *K*) of benzene sulfonamides to human CA-II have been modeled using a large series of distance-based topological indices. The need or otherwise of the hydrophobic parameter (log *P*) for such topological modeling of log *K* has been examined critically. In both the cases excellent results have been obtained. In multiparametric models involving indicator parameters we observed that introduction of hydrophobic parameter (log *P*) yields much improved statistics. The results are discussed on the basis of statistical parameters and also by using cross-validation method.



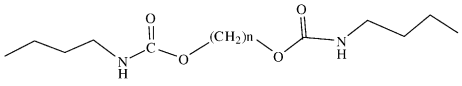
A novel use of NMR chemical shift of the SO_2NH_2 protons (in dioxane as solvent) as a molecular descriptor is described for modeling the inhibition constant for benzene sulfonamides against the zinc enzyme carbonic anhydrase (CA, EC 4.2.1.1). The methodology is extended to model diuretic activity and lipophilicity of benzene sulfonamide derivatives. The regression analysis of the data has shown that the NMR chemical shift is incapable of modeling lipophilicity. However, it is quite useful for modeling the diuretic activity of these derivatives. The results are compared with those obtained using distance-based topological indices: Wiener (W)-, Szeged (Sz)-, and PI (Padmakar-Ivan) indices.



A new series of 5-[(3′-chloro-4′,4′-disubstituted-2-oxoazetidinyl)(*N*-nitro)amino]-6-hydroxy-3-alkyl/aryl[1,3]azaphospholo[1,5-*a*]pyridin-1-yl-phosphorus dichlorides has been synthesized and subjected to acute antibacterial and antifungal screening studies. All the derivatives belonging to this series delineated remarkable activity as compared to standard drugs (ampicillin and clotrimazole). Compounds are quantitatively analyzed in relation to their different physicochemical parameters. Significant correlations were obtained between biological activity and polarizability parameter MR. Apart from this, indicator variables had also played a significant role.

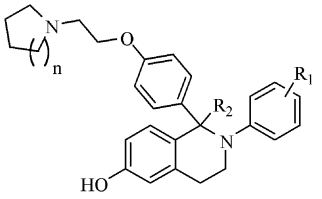


We described the synthesis and biological evaluation of MPEP analogs functionalized at the position 3 of the phenyl ring. The results point out the limitation in the choice of a functional group at this position; the only substituents leading to retention of activity are NO_2 (IC_{50} = 13 nM) and CN (IC_{50} = 8 nM).

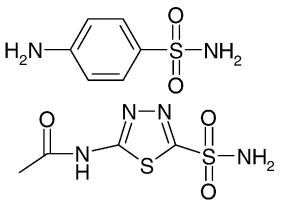


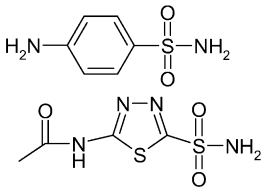
tether inhibitors **8-14**

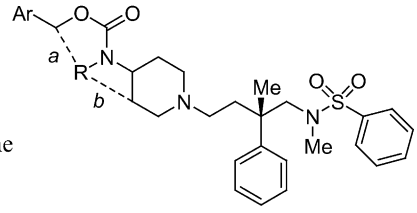
A discontinuity of the pre-steady state $-\log K_s$, values for the acetylcholinesterase inhibitions by tether inhibitors **8–14** versus the tether lengths plot, concave downwards, is indicative of a rate determining change in the K_s step.

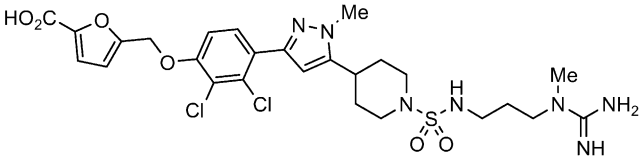


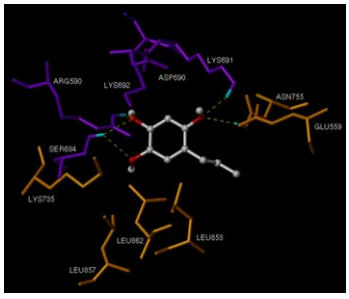
Considering importance of developing selective estrogen receptor modulators (SERMs), the present paper explores selectivity requirements of tetrahydroisoquinoline derivatives for binding with ER_α versus ER_β receptors using E-state index and physicochemical parameters.

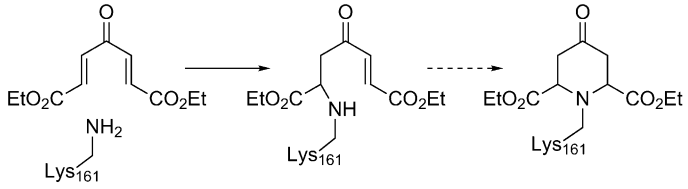




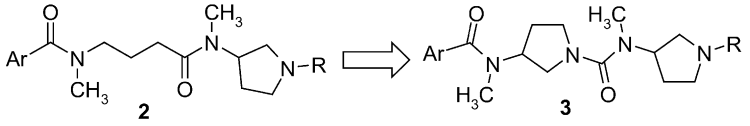




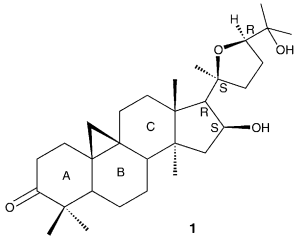




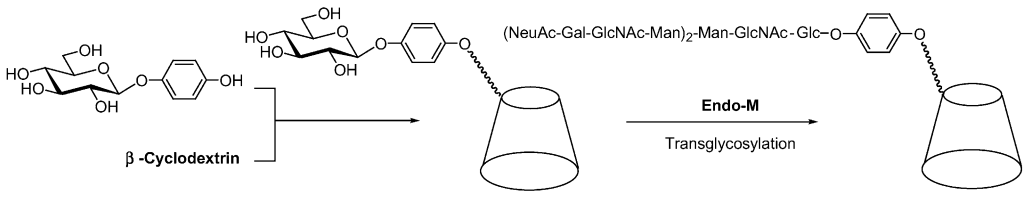
Two new irreversible inhibitors of dihydrodipicolinate synthase, a key enzyme in lysine biosynthesis and an important antibiotic target, are reported.

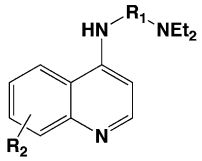


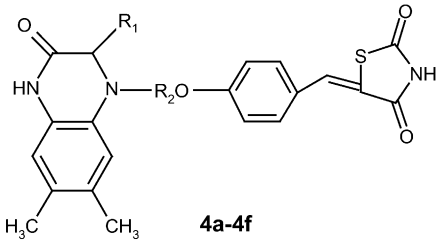
Ureas derived from two substituted 3-aminopyrrolidine subunits were prepared as constrained analogs of a linear lead compound and tested as antagonists of the MCH_1 receptor.

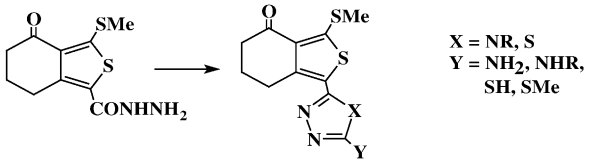


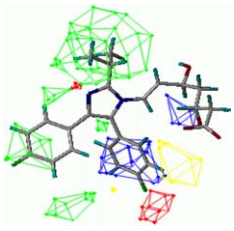
The syntheses of nine argentatin A (**1**) analogs are described. These compounds were assessed for their ability to inhibit growth in vitro in four human cancer cell lines. In addition, an X-ray study of (16*S*,17*R*,20*S*,24*R*)-3-oxime-20,24-epoxy-16,25-dihydroxy-cycloartan-3-one led to the determination of the correct stereochemistry of argentatin A.

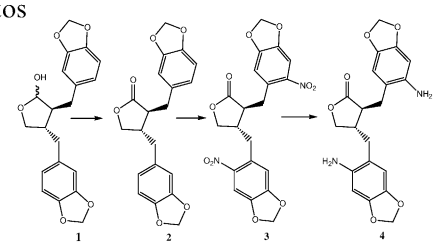




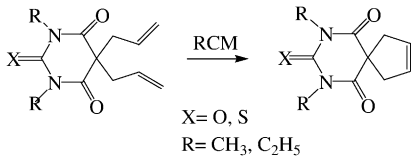




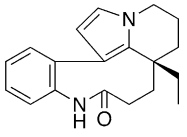




The anti-inflammatory and analgesic activities of three dibenzylbutyrolactone lignans obtained by partial synthesis starting from (−)-cubebin (**1**), which was isolated from the seeds of *Piper cubeba*, were evaluated using different animal models.



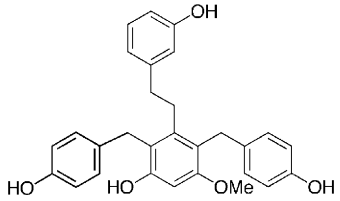
Barbituric acid **1** and related β-dicarbonyl compounds were dialkenylated under the phase-transfer catalyst [e.g., benzyltriethylammonium chloride (BTEAC)] conditions to generate the diallylated products. These diallylated products were subjected to the ring-closing metathesis (RCM) reaction to deliver the corresponding spiro-annulated derivatives.



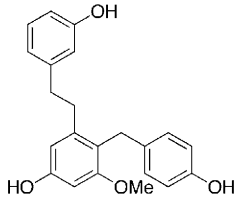
1

Most probable conformation in solution of rhazinilam (**1**) was analyzed and CoMFA results have been applied successfully to rationalize the inhibitory activities of tubulin disassembly of rhazinilam and its analogues in terms of their steric and electrostatic properties.

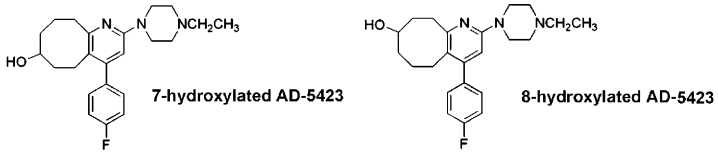
Eight stilbenoids **1**–**8** have been isolated by the guidance of inhibitory effect of tubulin polymerization from the tubers of *Bletilla striata* (Orchidaceae). Among them, both of bisbenzyls **4** and **5** inhibited the polymerization of tubulin at IC_{50} of 10 μM, while bisbenzyl **4** potentiated the cytotoxicity of SN-38 in BCRP-transduced K562 (K562/BCRP) cells.



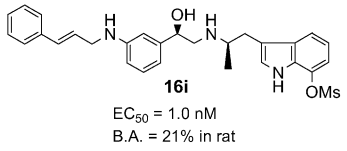
4



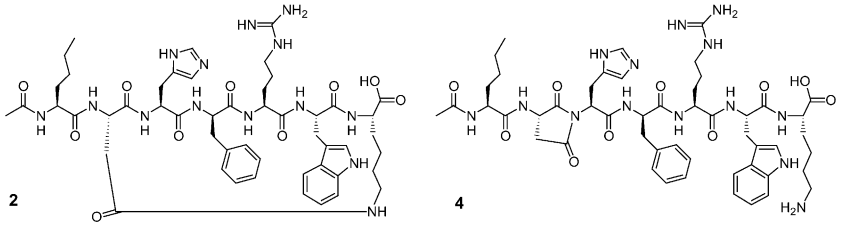
5



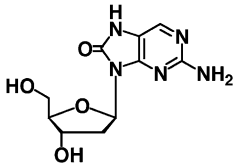
Two hydroxy metabolites in humans of blonanserin was synthesized. The optical resolution, structure, and biological results of these metabolites were also reported.



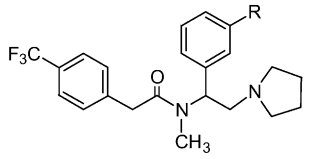
A series of tryptamine-based human β_3-adrenergic receptor (AR) agonists were synthesized in an effort to improve oral bioavailability. Cinnamylamine analog **16i** exhibited an excellent agonistic profile in vitro and good oral bioavailability in rats.



A method was developed to diagnose and minimize aspartimide formation during the synthesis of cyclic peptides on solid phase. Peptide **2** was prepared with minimal byproduct **4**.

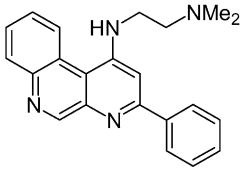


The synthesis of 2-amino-9-(2-deoxy-β-D-ribofuranosyl)-7,8-dihydro-8-oxo-purine (dJ) and its incorporation into DNA via a convertible phosphoramidite are reported. The thermal stability of heteroduplexes containing J has been studied by UV thermal-denaturation experiments.

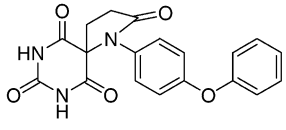


3

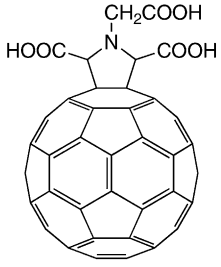
Analogs (**3**) of parent compound **1** (R = H) were prepared as novel potent kappa receptor agonists with improved peripheral restriction indices (platform sedation ED_{50}/writhing ED_{50}).



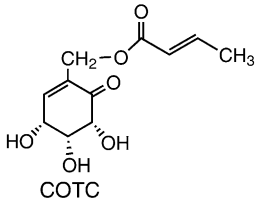
ΔT_m = 27.5 °C for polydA·2polydT; ΔT_m = 0.0 °C for polydA·polydT.



4a

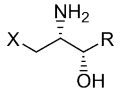


We examined the human immunodeficiency virus-reverse transcriptase and hepatitis C virus RNA-dependent RNA polymerase inhibition activities of cationic, anionic, and amino acid-type fullerene derivatives. Among the fullerene derivatives, the amino acid-type fullerene derivative was the most efficient in human immunodeficiency virus-reverse transcriptase inhibition.



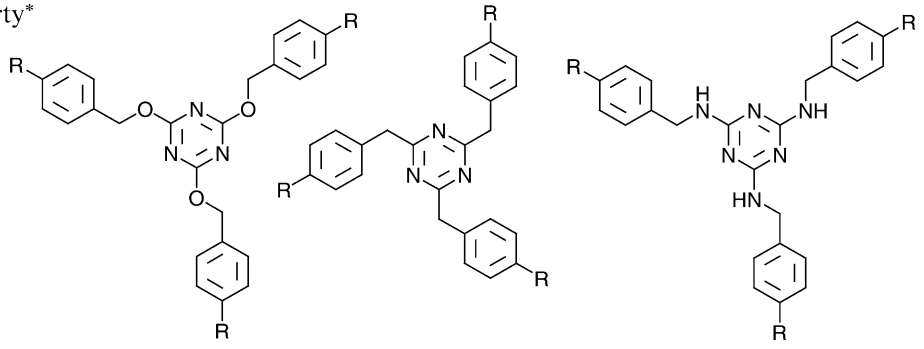
COTC

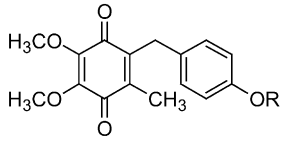
Inhibitor of Glyoxalase I



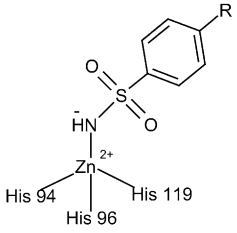
(R: *n*-alk-1-enyl, styryl, aryl; X: OPO_3H_2, Br)

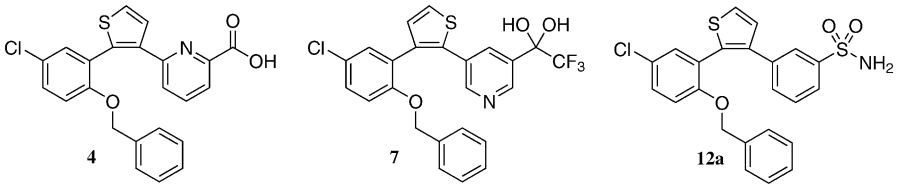
Sphingosine-1-phosphate (S-1P) derivatives such as *threo*-(2*S*,3*S*)-S-1Ps and *threo*-(1*S*,2*R*)-2-amino-1-aryl-3-bromopropanols have been prepared. These *threo*-amino alcohols have shown potent inhibitory activity against Ca^{2+} ion increases in HL60 cells induced by natural *erythro*-S-1P.



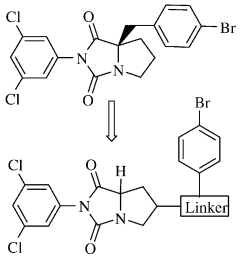


Anti-glycation activity of our anti-oxidant quinone library was measured and several 2,3-dimethoxy-5-methyl-1,4-benzoquinones and 2-methyl-1,4-naphthoquinones were identified as novel inhibitors of glycation.

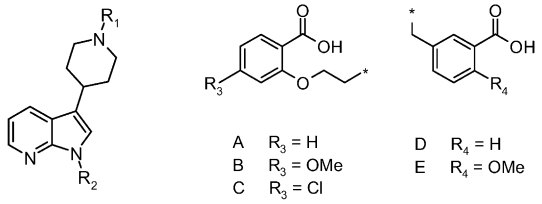




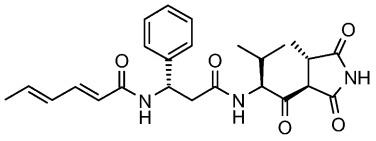
The synthesis and biological activity of a novel series of EP_1 receptor antagonists is reported. SAR studies in this series led to the identification of optimized inhibitors **4**, **7**, and **12a**.



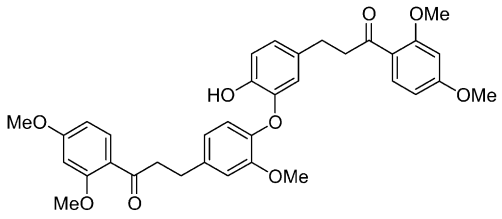
LFA-1 is a member of the β2-integrin family and is expressed on all leukocytes. This paper describes the de novo design, synthesis, and in vitro activity of LFA-1 antagonists based on a bicyclic[5.5]hydantoin scaffold.

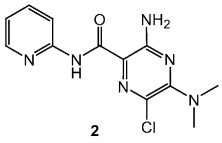


R_1 = A, B, C, D, E



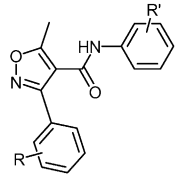
Pyrrolidinediones represent a new class of antibiotics that target bacterial fatty acid biosynthesis. Structure–activity relationships for the pyrrolidinedione group and the fatty acid side chain are described.



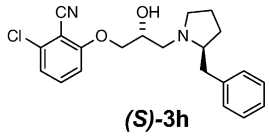


2

The mGlu5 receptor has been implicated in a number of CNS disorders. Herein, we report on the discovery, synthesis, and biological evaluation of dipyridyl amides as small molecules mGluR5 antagonists.

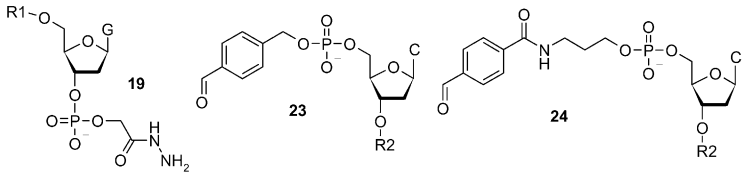


A series of isoxazole carboxamide derivatives has been developed as potent ghrelin receptor antagonists. The synthesis and structure–activity relationships (SAR) are described.

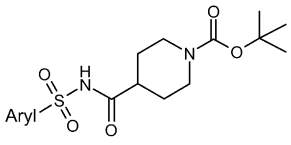


(S)-**3h**

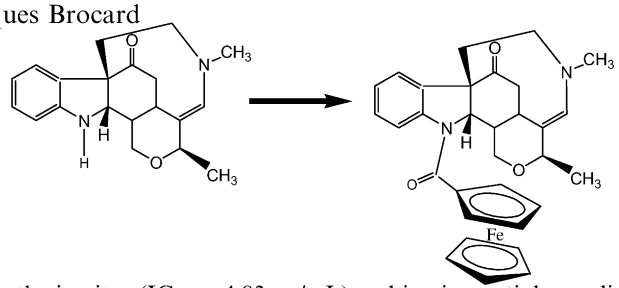
A novel series of calcium-sensing receptor antagonists was prepared as exemplified by (*S*)-**3h**. This new compound showed comparable potency to NPS-2143 as a calcium-sensing receptor antagonist but possessed reduced hERG blocking activity.



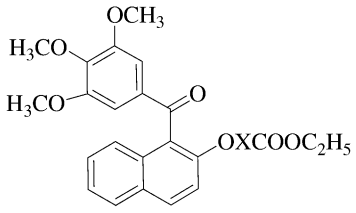
The synthesis of new 3′- and 5′-hydrazide- and aldehyde-modified oligonucleotides and the suitability of hydrazone formation for activator-free ligation of oligonucleotides is reported.



The discovery and structure–activity relationships for this novel class of STS inhibitors are presented.



The synthesis (yield 22%) as well as the in vitro (IC_{50} = 4.83 μg/mL) and in vivo antiplasmodial and chemosensitizing activities of N_a-deacetyl-ferrocenoyl-strychnobrasiline are reported.



Quantitative structure–activity relationship (QSAR) studies on lipophilicity (log *P*) for a series of 1,2-dithiole-3-thiones have been carried out using distance-based topological indices. In addition, we have also reported QSAR study on modeling quinone reductase specific activity (logCDQR) and production of growth hormone (logCDGH). The regression analysis of the data show that this set of compounds exhibit 'familial' relationships in that excellent results are obtained by dividing the data set into two classes (families).

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

2005: The proteolytic enzyme memapsin 2 (β-secretase, BACE-1) is the protease that cleaves the β-amyloid precursor protein (APP) to produce the 40-42 residue amyloid-β peptide (Aβ) in the human brain, a key event in the progression of Alzheimer's disease (AD). The X-ray crystal structure of memapsin 2 complexed with a peptidomimetic cyclic inhibitor is depicted. Inhibitor (green) is in the binding cleft of memapsin 2 shown as a ribbon diagram for the polypeptide backbone [Ghosh, A. K.; Devasamudram, T.; Hong, L.; DeZutter, C.; Xu, X.; Weerasena, V.; Koelsch, G.; Bilcer, G.; Tang, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 15].

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