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Bioorganic & Medicinal Chemistry Letters

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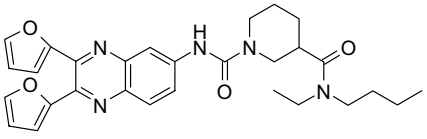
Contents

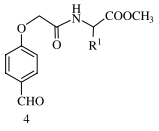
ARTICLES



Compound A17 $IC_{50} = 2.35 \pm 0.65 \mu M$

A series of quinoxalinylurea-based inhibitors are synthesized and shown to be the novel and potent inhibitors against JSP-1. Compound **A17** showed the most potent activity to inhibit JSP-1.

A new class of inhibitors of acetylcholinesterase (methyl 2-(2-(4-formylphenoxy)acetamido)-2-substituted acetate derivatives) is described. Compounds **4b** and **4i** were found to be more potent than galanthamine in inhibiting acetylcholinesterase.

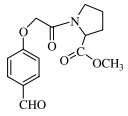


4

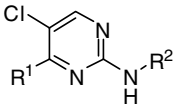
4a R^1 = H 4b R= CH_3 4c $R^1 = CH(CH_3)_2$ 4d $R^1 = CH_2CH_2SCH_3$ 4e $R^1 = CH(CH_3)C_2H_5$

4f $R^1 = CH_2CH(CH_3)_2$ 4g $R^1 = CH_2Ph$ 4h $R^1 = CH_2CH_2COOCH_3$

4i R^1 = 

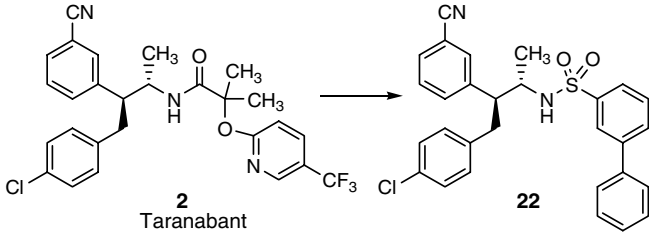
4j R^1 = p-CH_2PhOH 4k 

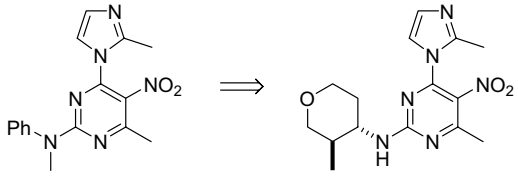
Three-dimensional pharmacophore hypothesis was built. The model was then employed as 3D search query to screen the database for other potential lead compounds.



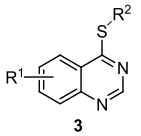
The novel series of 2-amino-4-aryl-5-chloropyrimidines was identified to be potent for both VEGFR-2 and CDK1. SAR at the 2- and 4-positions of the 5-chloropyrimidien core was studied, resulting in many potent analogues with (2-aminoethyl)phenylamino at the 2-position and cumylamino, indol-3-yl, or indol-6-yl at the 4-position. Several derivatives showed good bioavailability in rat PK study.

Sulfonamide analogues of the potent CB1R inverse agonist **2** (Taranabant) were optimized for CB1R activity.





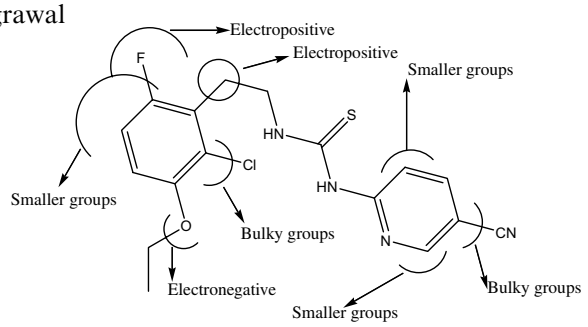
A novel series of imidazolylpyrimidines were found to possess inhibitory activity against the human CMV UL70 primase. Extensive SAR studies on an HTS lead led to potent, orally bioavailable compounds with anti-CMV IC_{50} values of 150 nM in both viral yield and viral DNA replication assays and with a much reduced cytotoxicity compared to marketed treatments ganciclovir and cidofovir.



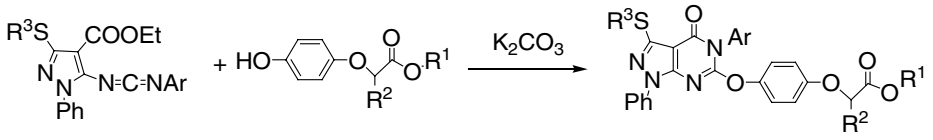
3

3a: R^1=H, R^2=5-(3, 4, 5-trimethoxyphenyl)-1, 3, 4-oxadiazol-2-yl; **3b**: R^1=H, R^2=3-methoxyphenyl; **3c**: R^1= 6, 7, 8-trimethoxyl, R^2=5-(3, 4, 5-trimethoxyphenyl)-1, 3, 4-oxadiazol-2-yl; **3d**: R^1=6, 7, 8-trimethoxyl; R^2=3-methoxyphenyl; **3e**: R^1=H, R^2=5-(3, 4, 5-trimethoxyphenyl)-1, 3, 4-thiadiazol-2-yl; **3f**: R^1=6, 7, 8-trimethoxyl, R^2=5-(3, 4, 5-trimethoxyphenyl)-1, 3, 4-thiadiazol-2-yl; **3g**: R^1=H, R^2=allyl; **3h**: R^1=6-I, R^2=Et; **3i**: R^1=6-I, R^2=*n*-Pr; **3j**: R^1=6-I, R_2=allyl; **3k**: R^1=6-I, R^2=*n*-Bu; **3l**: R^1=6-I, R^2=5-(3, 4, 5-trimethoxyphenyl)-1, 3, 4-oxadiazol-2-yl; **3m**: R^1=6-I, R^2=5-(3, 4, 5-trimethoxyphenyl)-1, 3, 4-thiadiazol-2-yl

A series of S′-substituted 4-alkyl(aryl)thioquinazoline derivatives were synthesized through thioetherification of 4-chloroquinazolines and thiol compounds refluxed in acetone in the presence of K_2CO_3. And their inhibitory activities against cancer cells were bioassayed.

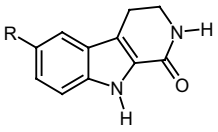


The parameters indicated in the substitution position of compound are responsible for anti-HIV activity.



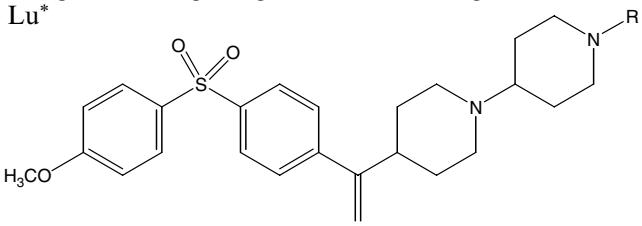
Phosph(on)ate as a zinc-binding group in metalloenzyme inhibitors: X-ray crystal structure of the antiviral drug foscarnet complexed to human carbonic anhydrase I.

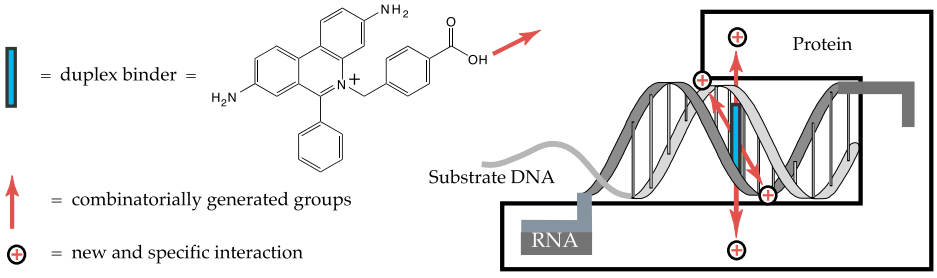
The synthesis and biological evaluation of a small library of C2-substituted SAHA analogs is reported.

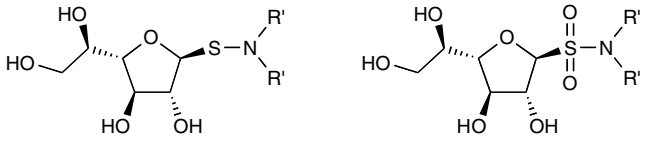


A new class of orally available mGluR1 antagonists was identified by replacement of the known pyrrole core with a β-carboline template suitably substituted at the position C-6.

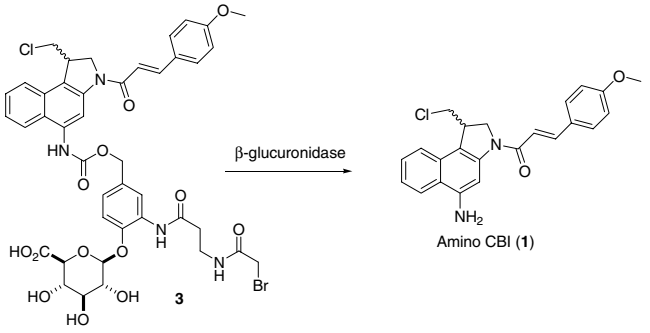
A new M2/M1 quantitative structure–selectivity relationship (QSSR) model of piperidinyl piperidine derivatives as muscarinic M2 subtype receptor antagonists was constructed, discussed, and examined. This model could provide solid basis for designing novel molecules with higher antagonistic selectivity to muscarinic receptors.

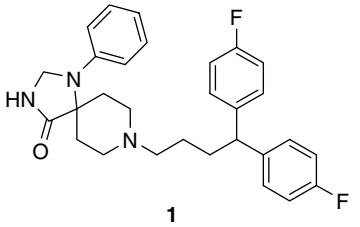




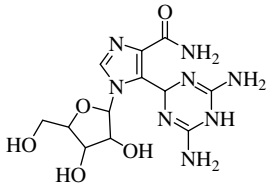


R' = $CH_2(CH_2)_nCH_3$ [n = 2, 4, 6, 8], CH_2Ph

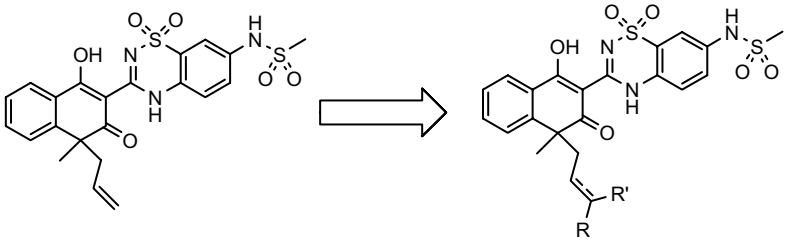


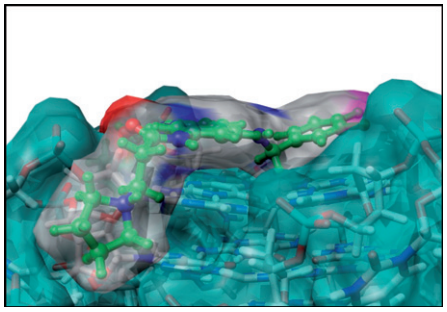


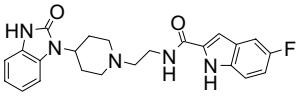
A series of N-substituted analogs based upon the spiropiperidine core of **1** was synthesized and exhibited high binding affinity to the nociceptin (NOP) receptor. The selectivities against other known opioid receptors were determined.



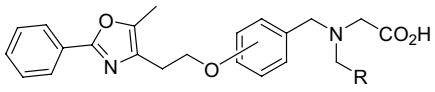
Synthesis and in vitro screening results of the title compound against *Flaviviridae* enzymes have been reported. The target compound exhibited anti-helicase activity against WNV and HCV NTPase/helicase with an IC_{50} of 23 and 37 μM, respectively.





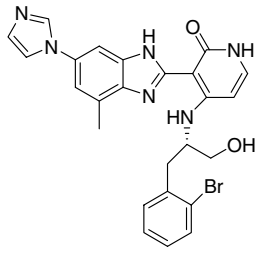


Halopemide, which was identified by HTS to inhibit phospholipase D2 (PLD2), provided the basis for an exploratory effort to identify potent inhibitors of PLD2 for use as inflammatory mediators. Parallel synthesis and purification were utilized to rapidly identify orally available amide analogs derived from indole 2-carboxylic acids with superior potency versus PLD2.



1,3- and 1,4-Alkoxybenzylglycines

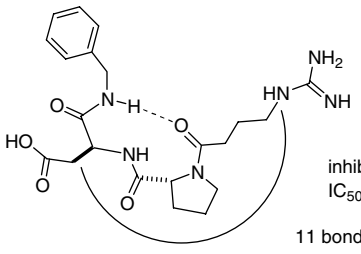
A novel series of potent dual agonists of PPARα and PPARγ, the oxybenzylglycines, were identified and explored using a solution-phase library approach. The synthesis and structure–activity relationships of this series of dual PPARα/γ agonists are described.



IGF1R IC_{50} = 0.29 μM

The discovery and synthesis of 3-(1*H*-benzo[*d*]imidazol-2-yl)pyridin-2(1*H*)-one inhibitors of insulin-like growth factor receptor-1 (IGF-1R) are presented. Installing amine containing side chains at the 4-position of pyridone ring significantly improved the enzyme potency. SAR and biological activity of these compounds are presented.

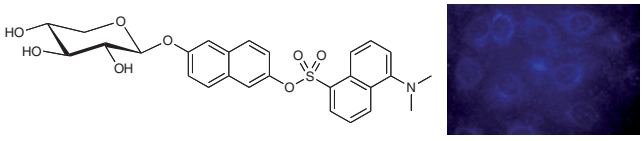
A novel class of indole ligands for estrogen receptor α have been discovered which exhibit potent affinity and high selectivity. Substitution of the bazedoxifene skeleton to the linker present in the HTS lead **1a** provided **22b** which was found to be 130-fold α-selective and acted as an antagonist of estradiol activity in uterine tissue and MCF-7 cancer cells.

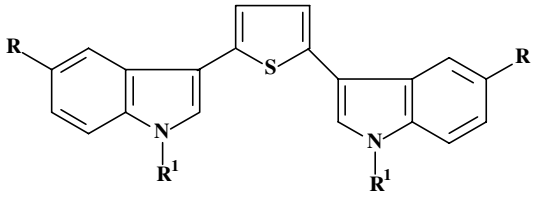


4

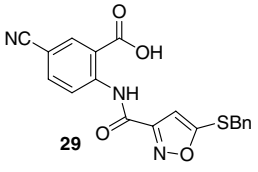
inhibition of SK-MEL-24 cells adhesion to fibronectin: IC_{50} = 26 nM

11 bonds





The synthesis and antitumor activity of novel 2,5-bis(3′-indolyl)thiophene derivatives are reported.



29

This paper describes the discovery of anthranilic acid derivatives as potent antibacterial agents against Gram-positive organisms.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Typical snapshot of **7b** bound to HIV-RT from an MC simulation. Carbon atoms of **7b** are gold; from the left, Tyr181, Tyr188, Phe227, Leu100, Lys101; Trp229 at the top, Val106 at the bottom. H-bond with Lys101 O on right. Some residues in front including Glu138 have been removed for clarity. The water on N5 is also H-bonded to a carboxylate O of Glu138. [Thakur, V. T.; Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domaoal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5664.]

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