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Bioorganic & Medicinal Chemistry Letters

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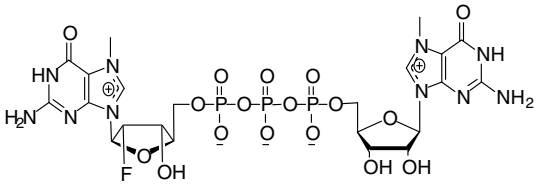
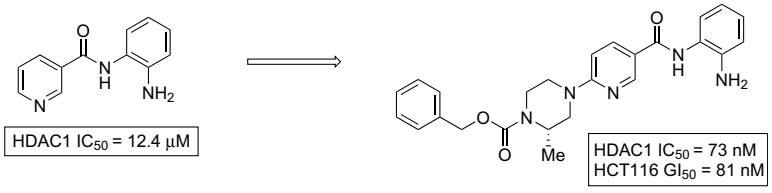
Contents

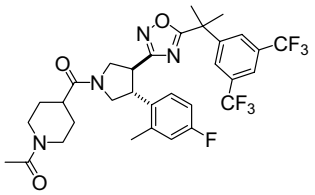
ARTICLES



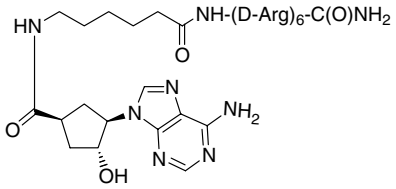
Design, synthesis, and biological evaluation of 2′-fluoro-substituted cap analogs i.e., $m^{7,2'F}G[5']ppp[5']G$ and $m^{7,2'F}G[5']ppp[5']m^7G$ are reported.



The preparation and structure–activity-relationships of novel pyrrolidine-carboxamides and oxadiazoles are described. Compounds in this series were found to be potent hNK_1 antagonists in vitro and efficacious in vivo with minimal interactions with P_{450} liver enzymes. Oxadiazole **22** was determined to have excellent hNK_1 binding affinity, functional activity, and a good PD response in vivo.

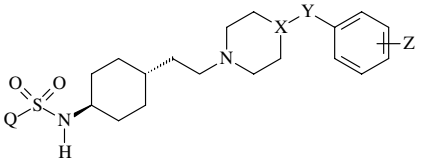


22: hNK_1 IC_{50} = 0.03 nM
ED_{50} (24 hr) = 6 mpk



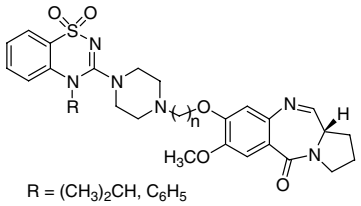
ARC-659-1b. cAPK, K_i < 1 nM

Conjugation of a nucleoside analog and a transport peptide led to a highly potent inhibitor of basophilic protein kinases.

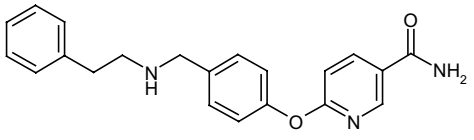


Novel arylsulfonamides were identified as high-affinity dopamine D3 and D2 receptor ligands. Some derivatives were found to be active in antipsychotic tests in vivo.

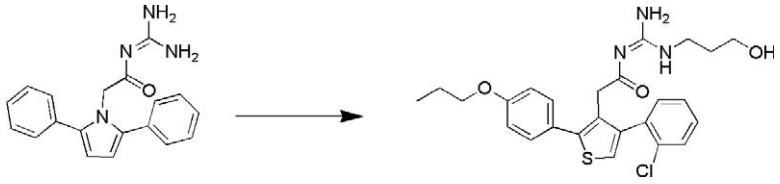
Novel 1,2,4-benzothiadiazine–PBD conjugates were synthesized and displayed significant anticancer activity against selected human cancer cell lines.

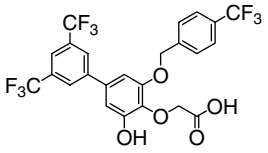


R = $(CH_3)_2CH$, C_6H_5
n = 4,5



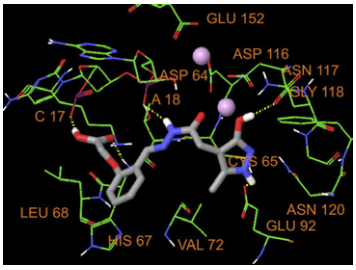
A structurally unique and new class of opioid receptor antagonists (OpRAs) that bear no structural resemblance with morphine or endogenous opioid peptides has been discovered. A series of carboxamido-biaryl ethers were identified as potent receptor antagonists against mu, kappa, and delta opioid receptors.

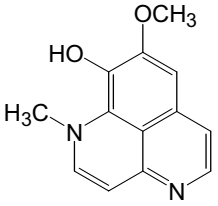




2-*O*-Carboxymethylpyrogallol derivatives were synthesized, with their in vitro inhibitory activities against PTP1B and in vivo antihyperglycemic effects examined. When compound **14** was fed to a high-fat diet-induced diabetic mouse model, significant improvements were observed in both the fasting glucose level and glucose tolerance.

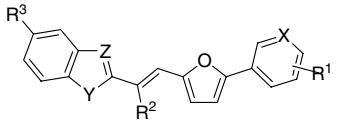
Virtual screening was performed on a model of full-length HIV-1 integrase complexed with viral DNA. Docking into the active site of this model yielded several μM level, structurally novel inhibitors of the strand transfer reaction catalyzed by wild-type HIV-1 integrase.

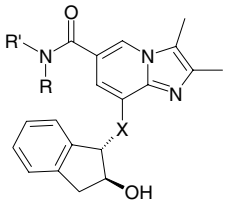




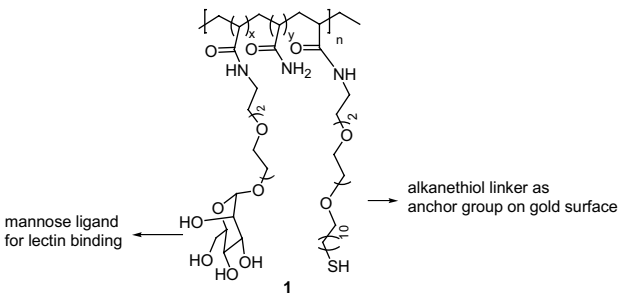
2: IC_{50} = 3.7 μg/mL

The isolation and sortase A inhibitory activity of four aaptamines ares reported.





X = NH, O



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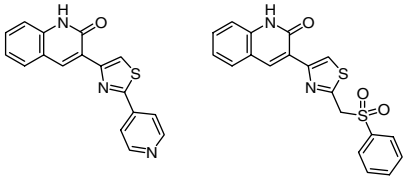
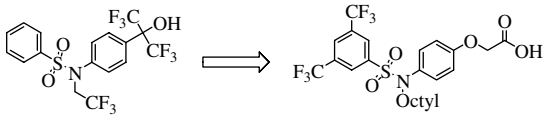


3 IC_{50}: 54 ± 33 nM **17j** IC_{50}: 29 ± 19 nM

A novel series of quinolin-2(1*H*)-one derivatives were synthesized and found to have potent CDK5 inhibitory activities.

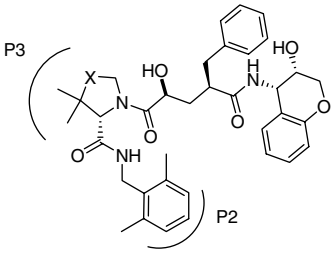


4 TO901317 $A\beta_{38}$ IC_{50} = 4.5; $A\beta_{40}$ IC_{50} = >40; $A\beta_{42}$ EC_{50} = 3.6

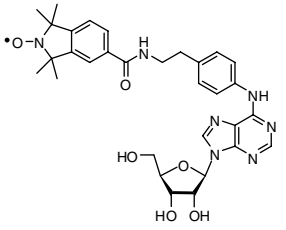
9 $A\beta_{38}$ EC_{50} = 23.7; $A\beta_{40}$ IC_{50} = >40; $A\beta_{42}$ IC_{50} = 19.6

TO-901317 analogue derivatives, where the hexafluorocarbinol moiety was replaced by an oxyacetic acid functionality, switch the mode of action from an inverse modulation to normal modulation of γ-secretase. As anticipated, compound **9** was found to be an effective modulator of γ-secretase and displayed activity at low micromolar concentration.

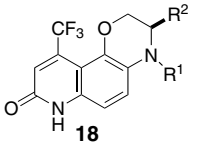
HIV protease inhibitors with modifications on the P3 position have been designed and synthesized. These compounds exhibit excellent antiviral activity against both the wild type enzyme and PI-resistant clinical viral isolates.



Herein we report the synthesis and biological evaluation of some potent and selective A_1 adenosine receptor agonists, which incorporate a functionalised linker attached to an antioxidant moiety. N^6-(2,2,5,5-Tetramethylpyrrolidin-1-yloxyl-3-ylmethyl)adenosine (VCP28, **2e**) proved to be an agonist with high affinity (K_i = 50 nM) and good selectivity (A_3/A_1 400) for the A_1AR. N^6-[4-[2-[1,1,3,3-Tetramethylisoindolin-2-yloxyl-5-amido]ethyl]phenyl]adenosine (VCP102, **5a**) has higher binding affinity (K_i = 7 nM), but lower selectivity (A_3/A_1 = ~3). All compounds bind weakly (K_i > 1 μM) to A_{2A} and A_{2B} receptors. The combination of A_1 agonist activity and antioxidant activity has the potential to produce cardioprotective effects.



VCP102 (**5a**)



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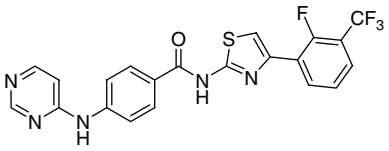
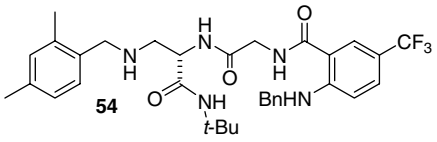
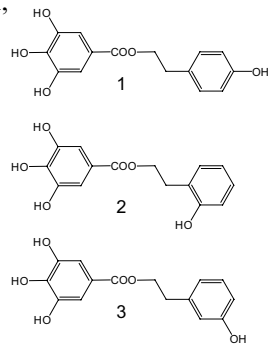
The synthesis and biological evaluation of a selective androgen receptor modulator (SARM) series is reported.



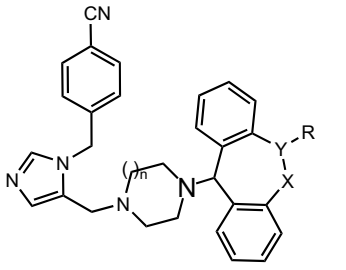


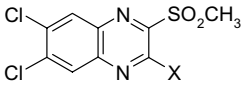
A new series of CCR2 antagonists has been discovered that incorporates intramolecular hydrogen bonding as a strategy for rigidifying the scaffold. The structure–activity relationship was established through initial systematic modification of substitution pattern and chain length, followed by independent optimization of three substituents. Compound **54** exhibited potent activity (CCR2 binding IC_{50} = 19 nM; Chemotaxis IC_{50} = 39 nM) and good selectivity over CCR1 and CCR3.



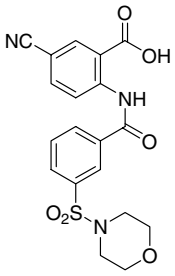
The synthesis of the potent melanin formation inhibitors (**1**–**3**) is reported.

The design, synthesis, inhibitory FTase activity and antiproliferative properties of the title tricyclic compounds are reported.

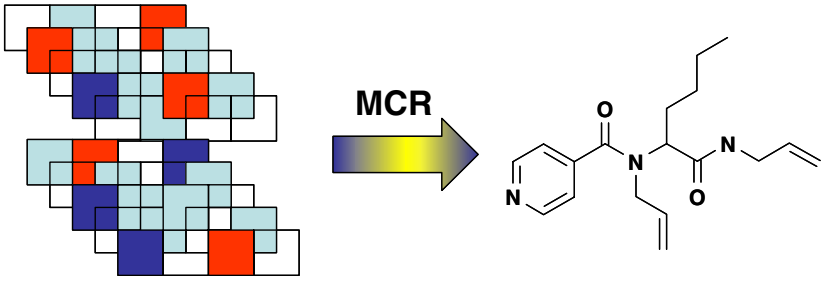


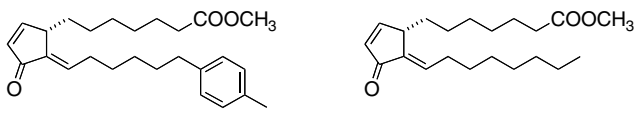


X = alkyl, CF_3, alkylamino



A study of the relationship between pK_a of a compound containing a carboxylic acid, and its antibacterial activity and protein binding is reported.





The synthesis and evaluation for anti- and proapoptotic properties of cyclopentenone prostaglandin analogs are described.

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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