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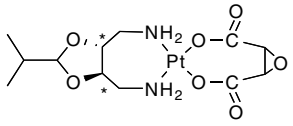
Bioorganic & Medicinal Chemistry Letters

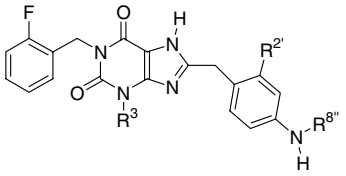
Bioorganic & Medicinal Chemistry Letters Vol. 17, No. 14, 2007

Contents

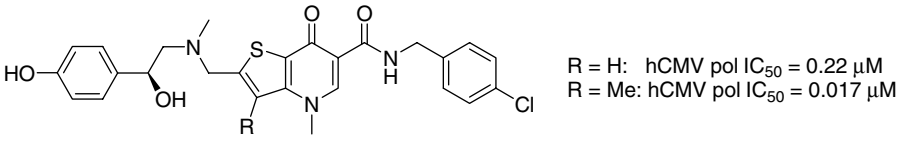
ARTICLES



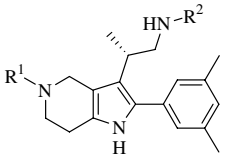
Ten new cisplatin-type platinum complexes with epoxysuccinates as leaving groups have been synthesized and structurally characterized. The in vitro cytotoxic activities of compounds toward SPC-A1 human lung adenocarcinoma cell line and BGC823 human stomach adenocarcinoma cell line have been determined.



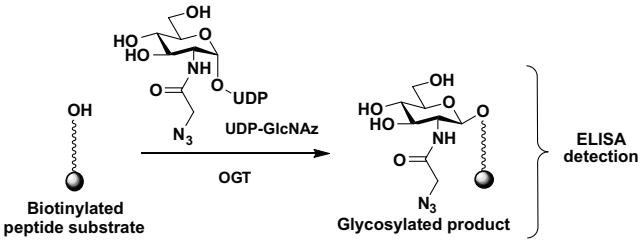
Enzyme and cellular assay results for a number of new modifications on the *C*-8 aminobenzyl unit are reported. Pyrazole sulfonic acid amide analogs are shown to provide improved inhibitors of cPEPCK and a new π–π interaction with the protein.

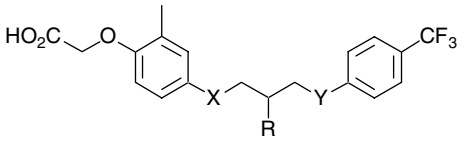


A new class of non-nucleoside antivirals is reported, wherein a C-3 methyl group confers dramatic improvement in potency, perhaps due to conformational restriction of the C-2 sidechain.

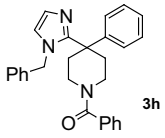


SAR of a series of novel and potent non-peptide GnRH receptor antagonists is disclosed.

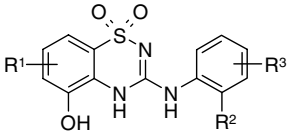




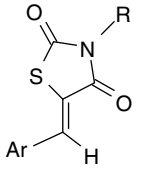
A series of *para*-alkylthiophenoxyacetic acids was prepared and found to be potent and selective PPARδ agonists.

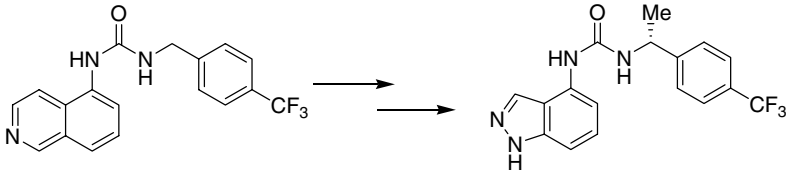


Selective δ-opioid agonists based on the 4-phenyl-4-[1*H*-imidazol-2-yl]-piperidine scaffold are reported. Compound **3h** has shown anxiolytic-/antidepressant-like effects in two mouse animal models.



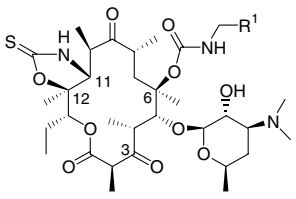
Synthesis, structure and activity relationships, selectivity and developability properties for a new class of CXCR2 receptor antagonists are described.



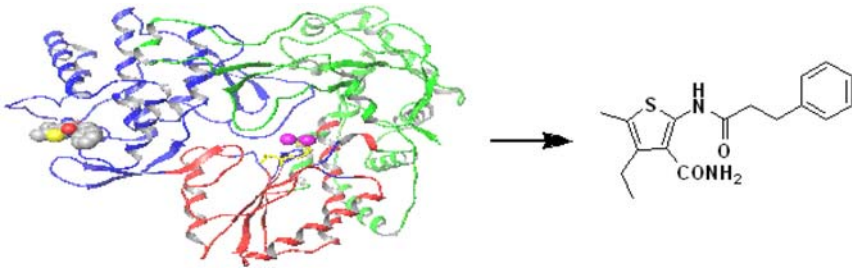


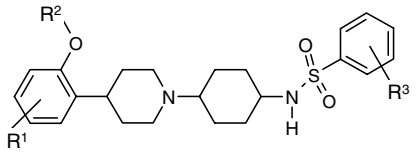
Better PK and higher efficacy in animal model of inflammatory pain

A series of 3-keto-6-*O*-carbamoyl-11,12-cyclic thiocarbamate erythromycin A derivatives has been synthesized. The best compounds in this series possess potent in vitro antibacterial activity against erythromycin-susceptible and erythromycin-resistant bacteria.

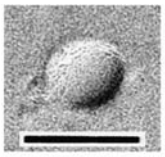


6-*O*-Carbamoyl-11,12-Cyclic Thiocarbamate Ketolides



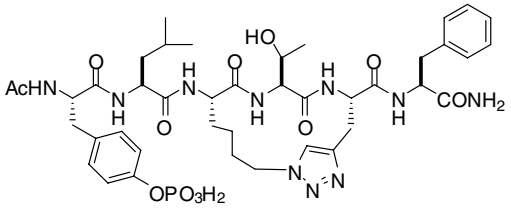


A series of (phenylpiperidinyl)cyclohexylsulfonamides that show selectivity to human $\alpha_{1a/1d}$ adrenergic receptors were developed. These compounds have potential for the treatment of BPH/LUTS.



scale bar = 100 nm

Cerasome can be used as a viral-size siRNA-carrier for RNAi silencing of exogenous and endogenous genes.



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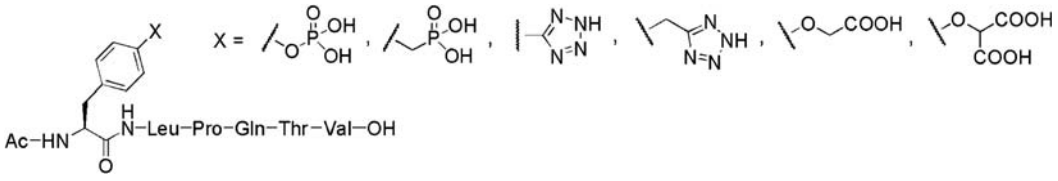
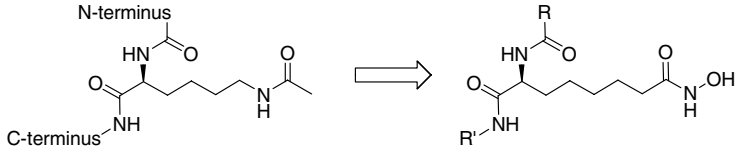
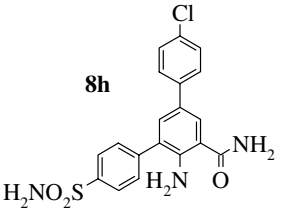


The novel syntheses of two pTyr mimetics, L-tetrazolylmethylphenylalanine (L-Tmp) and L-*O*-malonyltyrosine (L-OMT) are reported. Incorporation into a high affinity ligand of the STAT3 SH2 domain identified L-OMT as the first non-phosphorus pTyr mimetic reported so far against the STAT3 SH2 domain.

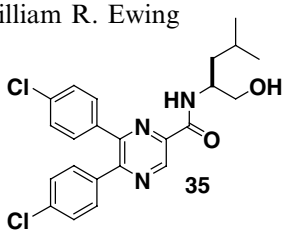


HDAC Peptide Substrate Substrate based inhibitor

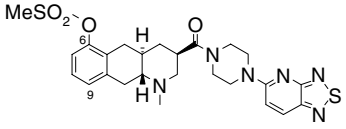
Exploring branched substrate-like HDAC inhibitors, mimicking the peptide substrate, lead to a series of aminosuberoyl hydroxamic acids (ASHAs) with remarkable HDAC inhibitory activity.



A potent and selective series of 2-amino-3,5-diarylbenzamide inhibitors of IKK-α and IKK-β is described. The most potent compounds are **8h**, **8r** and **8v**, with IKK-β inhibitory potencies of pIC_{50} 7.0, 6.8 and 6.8, respectively. The series has excellent selectivity, both within the IKK family over IKK-ε, and across a wide variety of kinase assays. The potency of **8h** in the IKK-α and IKK-β enzyme assay translates to significant cellular activity (pIC_{50} 5.7–6.1) in assays of functional and mechanistic relevance.

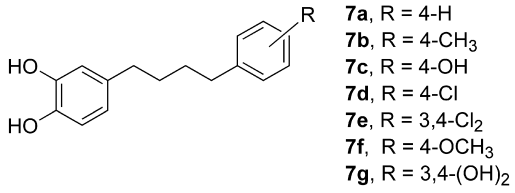


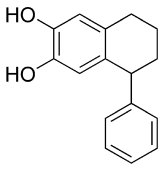
Structure–activity relationships for a series of pyrazine carboxamide CB1 antagonists are reported. Pharmaceutical properties of the series are improved via inclusion of hydroxyl-containing sidechains. This structural modification sufficiently improved ADME properties of an orally inactive series such that food intake reduction was achieved in rat feeding models. Compound **35** elicits a 46 in ad libidum fed rats 4-h post-dose.



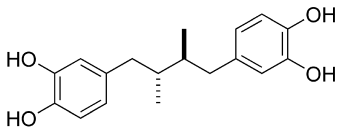
4g: pK_d (sst_1) = 9.67, (sst_2) = 5.29

The identification of a novel class of non-peptide somatostatin sst_1 receptor ligands is described. Optimization of positions 6 and 9 in these obeline-type compounds leads to functional antagonists with sub-nanomolar affinities to sst_1 and >10,000-fold selectivities over the sst_2 receptor subtype.

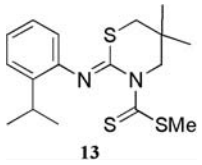




7h

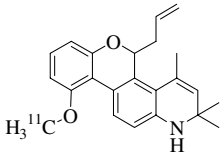


NDGA



13

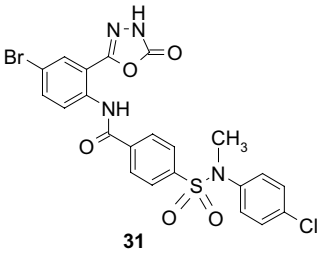
Among the 2-arylimino-5,6-dihydro-4*H*-1,3-thiazines, the most potent compound **13** displays K_i values of >5000 and 9 nM to CB_1 and CB_2 receptors, respectively.



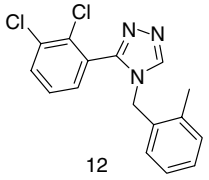
[^{11}C]AL-438

The radiosynthesis and the radiopharmacological characterization of **[^{11}C]AL-438** as a nonsteroidal ligand for the glucocorticoid receptor (GR) is reported.

To improve potency and reduce protein binding in a novel series of antibacterial translation inhibitors, the SAR of carboxylic acid replacements and bioisosteres such as in compound **31** was explored.

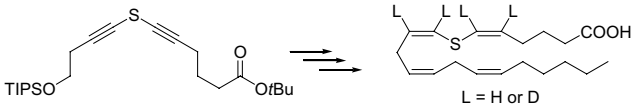


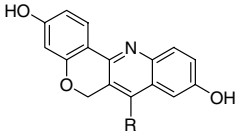
31



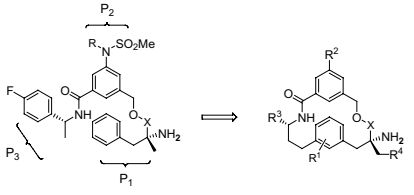
12

The synthesis and in vitro characterization of a series of phenyltriazole $P2X_7$ antagonists are described. Compound **12** was discovered to be active in a rat model of neuropathic pain.





A series of 6*H*-chromeno[4,3-*b*]quinolines has been prepared and displayed high affinity and moderate selectivity for estrogen receptor beta.



This Letter describes the design and synthesis of tertiary carbinamine macrocyclic inhibitors of the β-secretase (BACE-1) enzyme. These macrocyclic inhibitors, some of which incorporate novel P2 substituents, display a 2- to 100-fold increase in potency relative to the previously described acyclic analogs while affording greater stability.

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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