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Bioorganic & Medicinal Chemistry Letters

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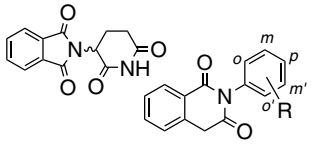
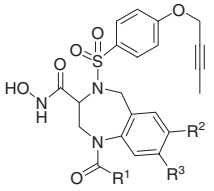
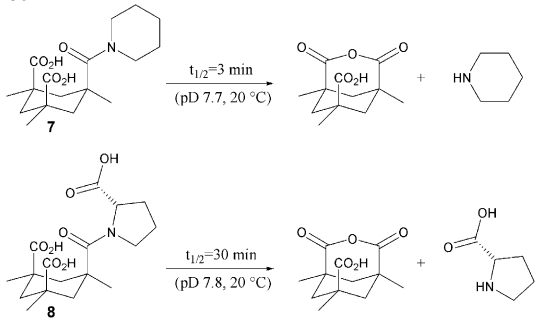
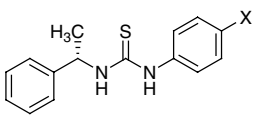
Contents

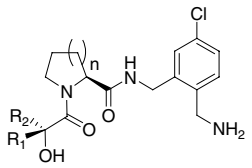
COMMUNICATIONS



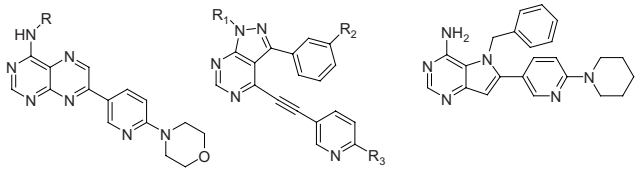


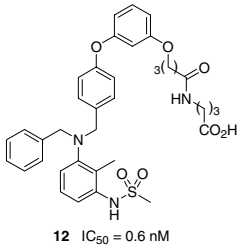






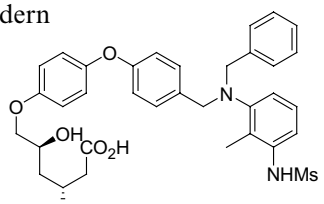
In order to overcome several limitations of our lead compound, which possessed a fluorenyl side chain in P3, we synthesized a series of analogs where we systematically truncated this fluorenyl side chain. This resulted in a series of compounds with progressively smaller aliphatic side chains inhabiting P3. These changes dialed out the undesired properties of the fluorenyl side chain while maintaining thrombin inhibition and desired pharmacokinetics. Subsequent elaboration of the proline P2 unit with an azetidine unit maintained these effects while increasing metabolic stability.





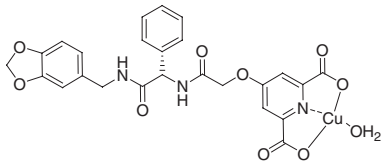
12 IC_{50} = 0.6 nM

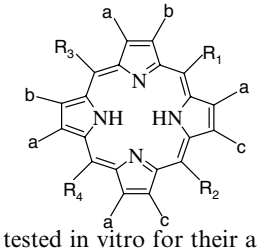
The synthesis and biochemical profile of the potent glucocorticoid receptor modulator **12** (h-GR binding $IC_{50} = 0.6$ nm) is reported.



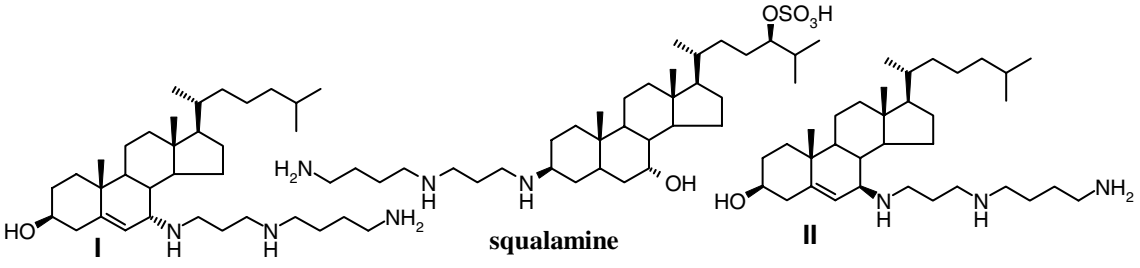
16 IC_{50} = 2 nM

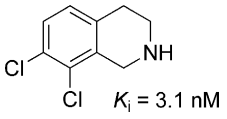
The synthesis and hepatic selectivity of steroidal and nonsteroidal glucocorticoid receptor modulator–statin hybrids (e.g., **16** h-GR binding IC_{50}=2 nm) is reported.

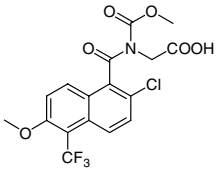




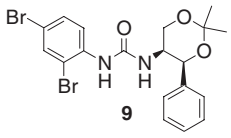
Twenty four aminoporphyrin derivatives have been tested in vitro for their antibacterial photoactivity against *Escherichia coli* and *Staphylococcus aureus*. Two of these compounds, bearing polyamine units (**17**–**18**) exhibited a significant activity especially against Gram-negative bacteria. For **17**, **18**: R_1=R_2=R_3=R_4=H, a=CH_3, b=CH=CH_2 and c=$(CH_2)_2$COspermidine for **17**, c=$(CH_2)_2$CO-spermine for **18**.





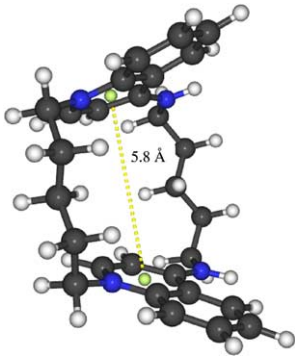


A novel series of HCV NS5B RNA dependent RNA polymerase inhibitors containing a naphthalene carboxamide scaffold and the structure–activity relationship studies to improve potency are described.

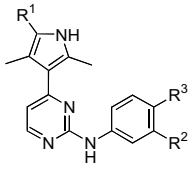


9

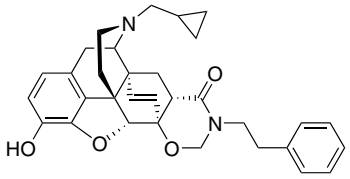
A series of novel, selective orexin receptor 2 antagonists consisting of substituted 4-phenyl-[1,3]dioxanes is reported (e.g. **9**).



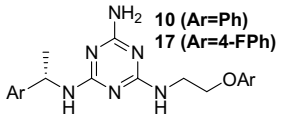
Two important elements of the pharmacophore are a distance of ca. 5.8 Å between the centroids of the pyridinium rings and a high population of synperiplanar conformations.



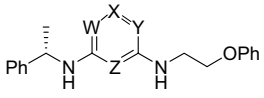
A series of 2-anilino-4-(1*H*-pyrrol-3-yl) pyrimidines were prepared and evaluated for their ability to inhibit cyclin-dependent kinases (CDKs). These inhibitors also exhibit potent anti-proliferative activity against human tumour cell lines. Structure–activity relationships and biochemical characterization are discussed.



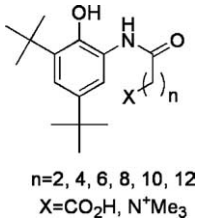
The rational drug design of a selective ε opioid receptor antagonist from an agonist for putative ε opioid receptor on the basis of the accessory site concept was described.



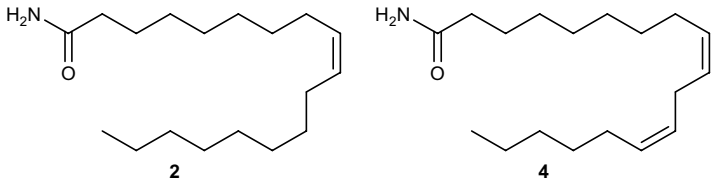
A series of aminotriazines as novel 5-HT$_7$ receptor antagonists are discussed. Compounds **10** and **17** have high affinity for the 5-HT$_7$ receptor, produce no agonist effects by themselves, and shift the dose–response curve of 5-CT to the right in the manner of an antagonist.



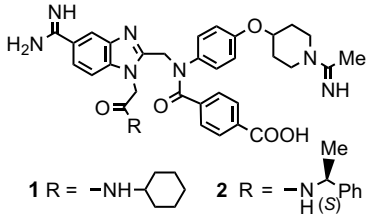
The present studies have identified a series of diaminopyrimidines and diaminopyridines as novel 5-HT$_7$ receptor ligands. Three regiosiomeric classes of pyrimidines and four regioisomeric classes of pyridines were synthesized and analyzed for binding to the 5-HT$_7$ receptor. The 5-HT$_7$ binding affinities of different regioisomers show clearly the structure–activity relationship with position of ring nitrogens.

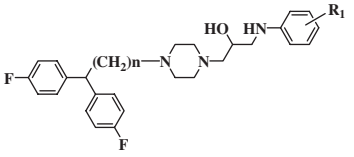


Synthesis and structure–antioxidant activity relationships of novel membrane-addressed antioxidants are reported.

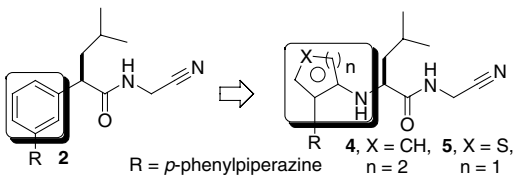


Unsaturated fatty acid amides **2** and **4**, isolated from *Mylabris phalerate* Pallas, inhibited rat liver microsomal ACAT, hACAT-1, and -2 activities.

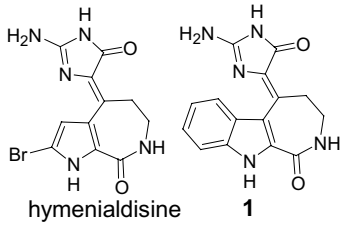




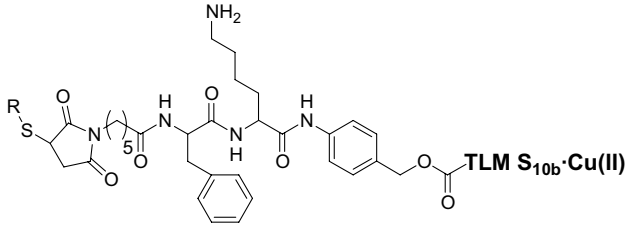
n=0-4; R_1=H, 3,4-diCl, 4-Cl, 4-Me, 4-OMe, 4-N$(CH_3)_2$, 4-NO_2, 3,4,5-triOMe, 4-NH_2, 4-OH, 3,5-di-*tert*-Bu-4-OH

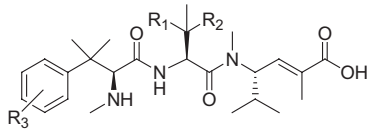


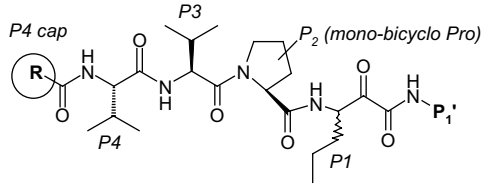
Modelling studies suggested that the introduction of a NH linker between the P3 aryl and P2 leucinamide moieties of our previously reported inhibitor **2** would allow the formation of an H-bond with the Gly66 residue of Cat K. Aniline **4** and thiophene **5** were prepared and confirmed this hypothesis by showing increased potency against Cat K and good selectivity.



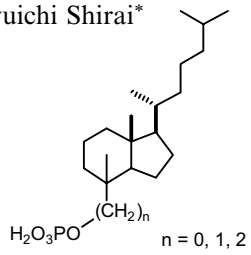
The inhibition of kinase activity by a hymenialdisine-derived indoloazepine is reported. Compound **1** was found to be a potent inhibitor of Chk2 ($IC_{50} = 8$ nM).





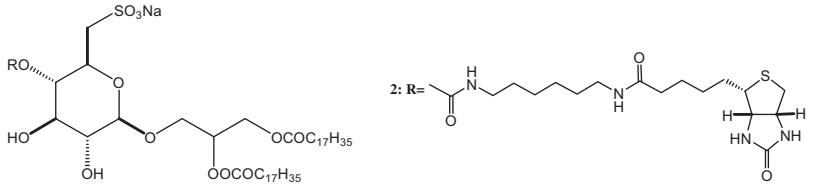


The design, syntheses, and biological evaluation of new series of P4 tetrazole, adipic acid, ester, amide capped tetrapeptidyl α-ketoamide based HCV NS3 protease inhibitors are discussed.

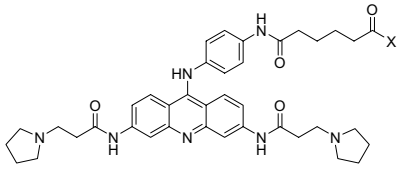


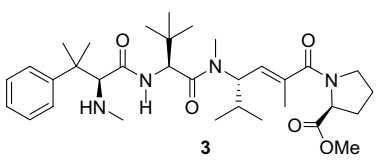
6a-6e

Compounds (**6a**–**e**) were synthesized by phosphorylation of hydrophobic perhydroindan derivatives derived from vitamin D_3, and were found to show strong inhibitory activity towards dual-specificity phosphatase Cdc25A (IC_{50}=0.7–24.5 μM).



The synthesis of the biotinylated immunosuppressant and the determination of its binding peptide are reported.





3

Modifications of the D-piece carboxylic acid group of HTI-286 gave tubulin inhibitors that were potent cytotoxic agents. For example, the amide analog derived from L-proline (**3**) had an IC_{50} = 1.5 nM in KB-3-1 cells and was effective in a human xenograft model in athymic mice.

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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