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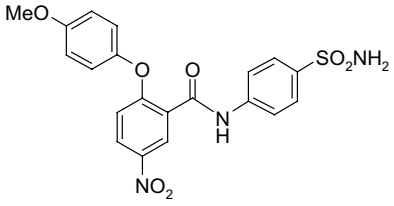
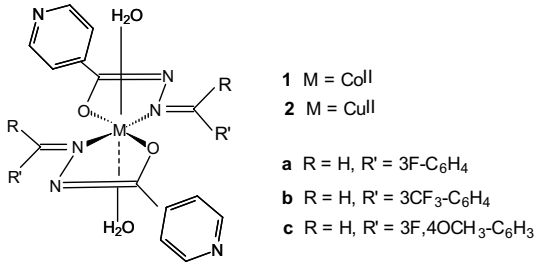
Bioorganic & Medicinal Chemistry Letters

Bioorganic & Medicinal Chemistry Letters Vol. 14, No. 23, 2004

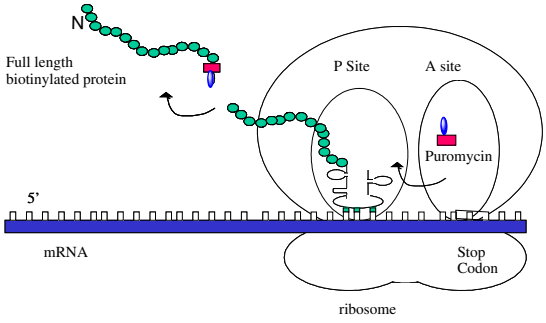
Contents

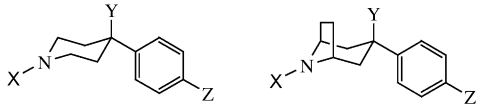
COMMUNICATIONS



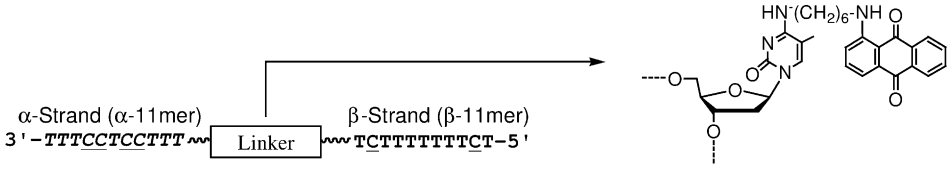


The in vitro antimycobacterial activities of metalcomplexes **1**, **2** are reported.

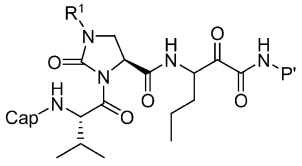




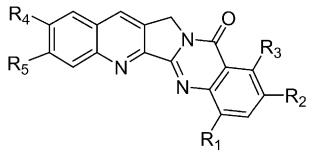
We report a generally applicable PEGylation methodology based on the site-specific incorporation of *para*-azidophenylalanine into proteins in yeast. The azido group was used in a mild [3+2] cycloaddition reaction with an alkyne derivatized PEG reagent to afford selectively PEGylated protein. This strategy should be useful for the generation of selectively PEGylated proteins for therapeutic applications.

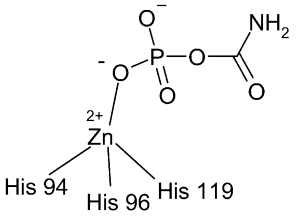


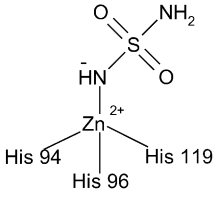
The triple helical DNA formed between the novel α–β chimeric oligodeoxynucleotides bearing an intercalator-conjugated nucleobase located at the internal 4-nt linker region and double-stranded DNA exhibited remarkable thermal stability.

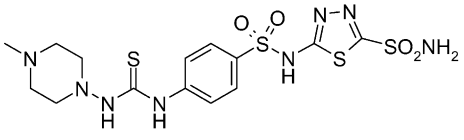


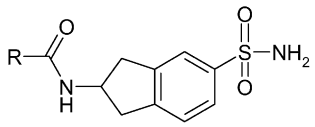
Synthesis and HCV NS3 serine protease inhibitory activity of some novel 2-oxoimidazolidine-4-carboxylic acid derivatives are reported. X-ray structure of an inhibitor, **15c** bound to the protease is presented.

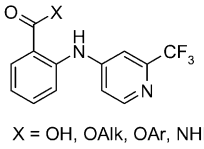




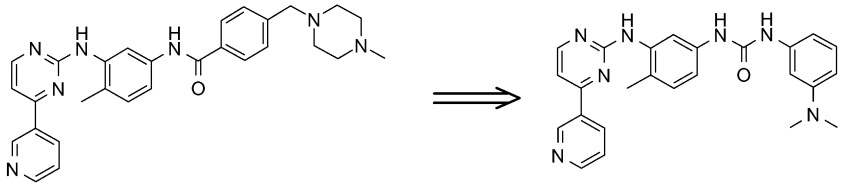




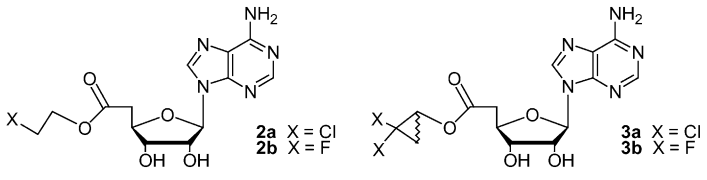




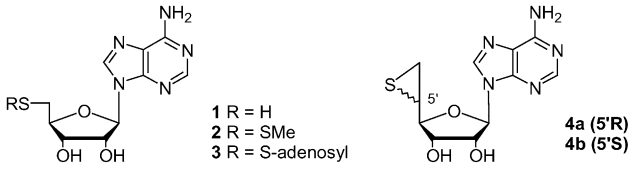
A series of *N*-(2-(trifluoromethyl)pyridin-4-yl)anthranilic acid derivatives was prepared and tested for the in vitro cytotoxic activity against human cancer cell lines. Some aryl esters exhibit antiproliferative activity with GI_{50} values at nanomolar concentrations.



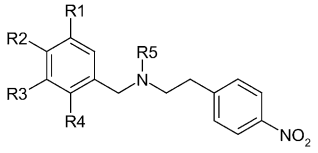
Urea-based analogues of STI571 are described possessing structural features which can differentiate between Abl/Bcr-Abl and PDGFR kinase inhibition.



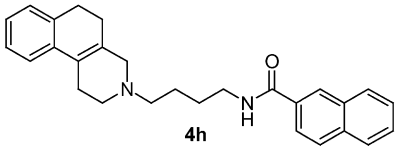
Inactivation of AdoHcy hydrolase with **2**–**3** resulted in time-dependent loss of enzyme activity. The mechanism of inactivation is discussed.



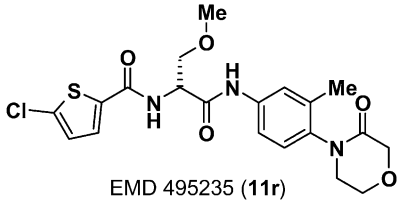
Thionucleosides **1–4** were synthesized for selectively targeting ^{195}Cys of human placental AdoHcy hydrolase.



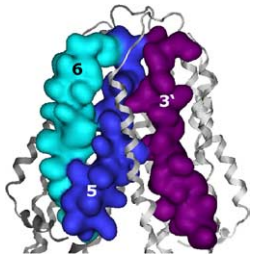
A targeted library of 2-(4-nitrophenyl)ethylbenzylamines has been prepared to optimize the biological activity of BN82002, our initial lead compound, recently described as an original inhibitor of CDC25 phosphatases. The most potent of these compounds inhibit CDC25 in the micromolar range.



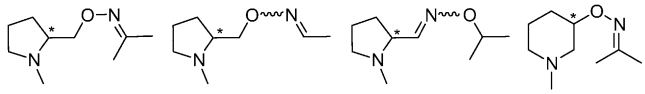
K_i = 6.1 nM to the D_3 receptor
Selectivity of 163 and 133-fold over the D_1 and D_2 receptors

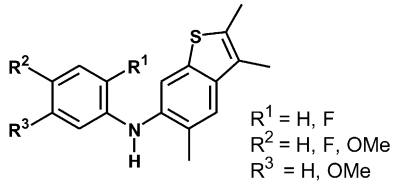


EMD 495235 (**11r**)

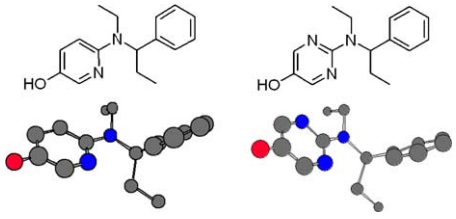


Starting from the dimeric crystal structure of *Vibrio cholerae* MsbA, two homology models of the ATP-dependent multidrug transporter LmrA were generated.

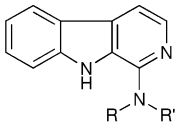




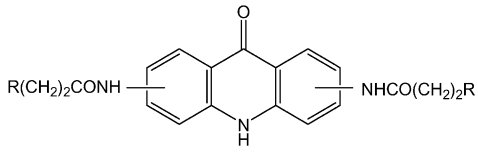
In vitro antimicrobial data against Gram positive, Gram negative bacteria, and *Candida albicans* are presented.



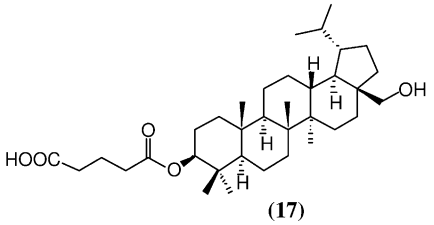
Pyridine and pyrimidine analogs of the nonsteroidal estrogen deoxyhexestrol were synthesized. Their low affinity for the estrogen receptor is ascribed, in part, to resonance enforcement of a conformation unfavorable for binding.



A selection of amino-substituted β-carbolines have been prepared and show anticancer and antimalarial activities.

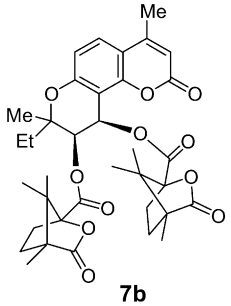


3-*O*-Glutaryl-dihydrobetulin (**17**) demonstrated extremely potent anti-HIV activity with an EC_{50} value of 2×10^{-5} μM and a TI value of 1.12×10^{6}. 3-*O*-(3′,3′-Dimethylsuccinyl)- and 3-*O*-(3′,3′-dimethylglutaryl)-dihydrobetulins (**15**, **16**) were also potent anti-HIV compounds with EC_{50} values of 0.0017 and 0.00131M, respectively, and TI values of 16,160 and 19,530, respectively.

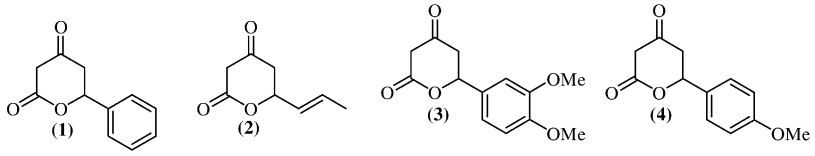


(**17**)

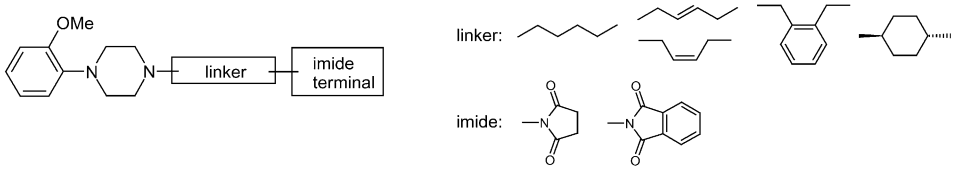
Four 4-methyl-3′,4′-di-*O*-(−)-camphanoyl-(+)-*cis*-khellactone (4-methyl DCK) analogs (**7a**–**d**) with different alkyl substituents at the 2′-position were synthesized and evaluated for inhibition of HIV-1 replication in H9 lymphocytes. 2′-Methyl-2′-ethyl-4-methyl DCK (**7b**) was more potent (EC_{50} = 0.22 μM, TI > 175) than the other three compounds (**7a**, **7c**, and **7d**), but significantly less potent than 4-methyl DCK (**2**, EC_{50} = 0.0059 μM, TI > 6600).

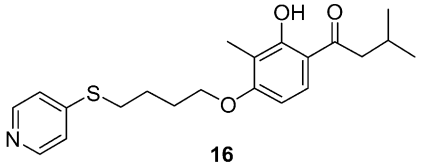


7b



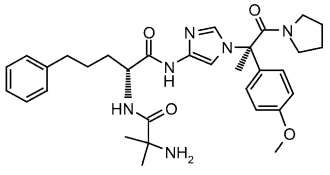
The capacities of the dihydropyran-2,4-diones **1**–**4** to inhibit the stable free radical DPPH have been determined. All four compounds exhibited high inhibition percentages but 6-phenyl-dihydropyran-2,4-dione (**1**) was the most active. The antioxidant activity for this class of compound is reported for the first time.



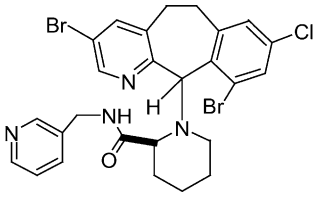


16

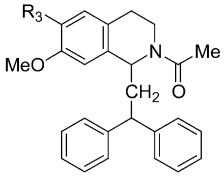
We have identified and synthesized a series of 4-thiopyridyl acetophenones as positive allosteric potentiators of the metabotropic glutamate receptor 2. Structure–activity relationship studies directed toward replacement of the tetrazole in the initial lead led to the discovery of **16** (EC_{50} = 340 nM), which showed improved brain penetration over the initial lead.



LY444711 is an orally active ghrelin agonist that binds with good affinity and is a potent activator of the growth hormone secretagogue receptor 1a (GHS-R1a) receptor. In rat models of feeding behavior and pharmacology, LY444711 creates a positive energy balance and induces adiposity by stimulating food consumption and sparing fat utilization.



Design and synthesis of farnesyl protein transferase inhibitors, targeting catalytic zinc are reported.

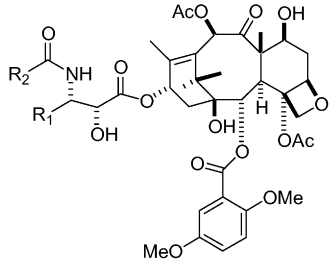


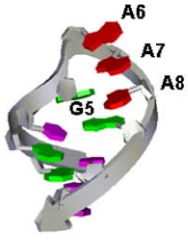
1a (R3= -OMe) MT2 IC_{50} = 9.7 nM

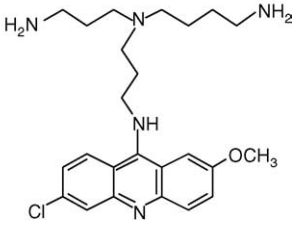
1z (R3= -H) MT2 IC_{50} = 5.5 nM

A series of tetrahydroisoquinolines has yielded potent MT_2 receptor antagonists, which are selective versus the MT_1 receptor.

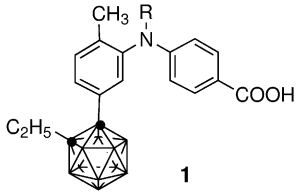
The use of drug–antibody conjugates affords a method for the targeted delivery of anticancer drugs specifically to cancer cells. Monoclonal antibodies alone usually do not possess high therapeutic efficacy, however, they are capable of targeting tumor markers selectively. We have prepared taxoids with significantly higher cytotoxicity than paclitaxel and docetaxel. These taxoids now meet the high potency required for use in a targeted-delivery approach using monoclonal antibodies. The synthesis and biological evaluation of these taxoids are reported.





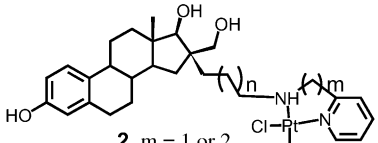


An aminoacridine derivative binds with low micromolar affinity and one to one stoichiometry to the junction between the stem and the loop of a GAAA tetraloop.



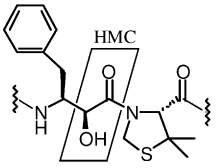
1

We designed and synthesized novel retinoid X receptor (RXR)-selective antagonists such as **1** bearing a carborane moiety.

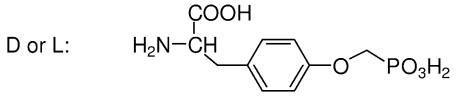


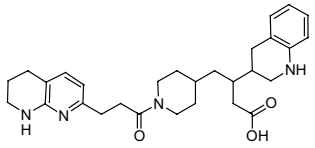
2, m = 1 or 2
n = 2, 4, 6 or 8

The biological activity of hybrids **2** was evaluated in vitro on human uterine and ovarian cancers. The molecules present high affinity for the estrogen receptor alpha. The cytotoxicity and the affinity of **2** are explained by molecular modeling analysis.

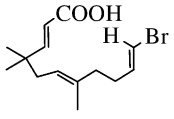


Towards the development of chemotherapy for the infection by human T-cell leukemia virus type I (HTLV-I), we have established evaluation systems for HTLV-I protease (PR) inhibitors using both recombinant and chemically synthesized HTLV-I PRs. Newly synthesized substrate-based inhibitors containing hydroxymethylcarbonyl (HMC) isostere showed potent anti-HTLV-I PR activity.





Selective reduction of the quinoline yielded potent $\alpha_v\beta_3$ antagonists with improved oral bioavailability relative to the corresponding quinoline derivatives.



4E

The synthesis and evaluation of **4*E***, autophosphorylation inhibitor of YycG (histidine–kinase), are reported.

OTHER CONTENTS

*Corresponding author
Supplementary data available via ScienceDirect

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