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Bioorganic & Medicinal Chemistry Letters

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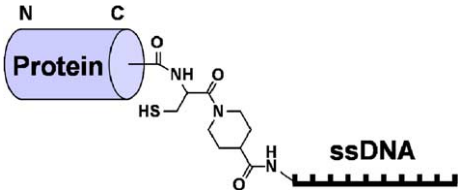
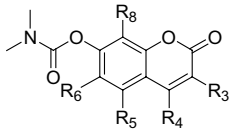
Contents

COMMUNICATIONS

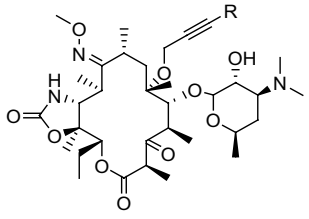


A simple method for conjugating recombinant protein with DNA is reported.

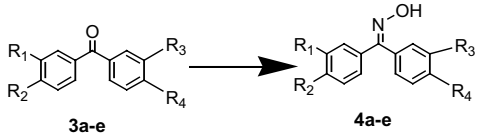


1

A series of coumarin-based TNF-α inhibitors 1 has been synthesized to establish structure–activity relationship.

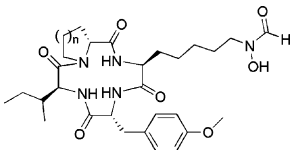


A series of novel 6-*O*-arylpropargyl-9-oxime-ketolides was synthesized and evaluated against various pathogens. These new compounds show promising in vitro antibacterial potency and in vivo efficacy against macrolide resistant strains.

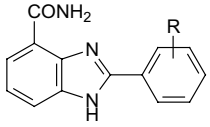


3a-e 4a-e

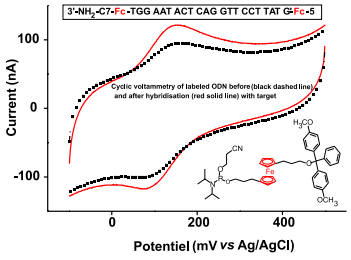
A series of substituted benzophenone oxime analogues has been synthesized and evaluated for in vitro PLA_2 enzyme inhibitory activity and in vivo anti-inflammatory activity using mice.



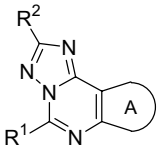
Cyclic tetrapeptide retrohydroxamates were synthesized as HDAC inhibitors with potential as anticancer drugs.



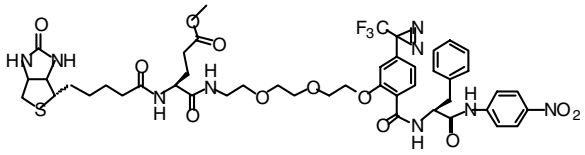
The synthesis and biological evaluation of a new series of amine-substituted 2-arylbenzimidazole-4-carboxamide inhibitors of the DNA-repair enzyme poly(ADP-ribose) polymerase-1 (PARP-1) is reported. The introduction of an amine substituent at the 2-aryl position is not detrimental to activity, with most inhibitors exhibiting K_i values for PARP-1 inhibition in the low nanomolar range. Two compounds in this series were found to potentiate the cytotoxicity of the DNA-methylating agent temozolomide by 4–5-fold in a human colorectal cancer cell line.

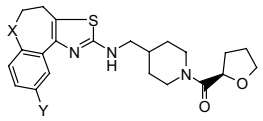


A new type of di-functionalized ferrocene is used directly as reactive synthons for DNA/RNA synthesizer to elaborate electronic DNA probes.

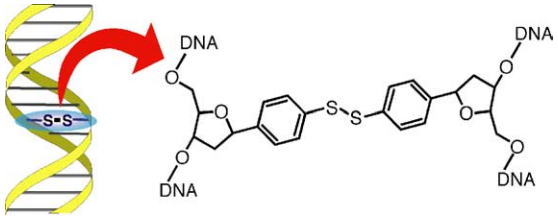


A facile synthetic method for fused triazolopyrimidine derivatives having high affinity and selectivity for human adenosine A_3 receptors is reported.

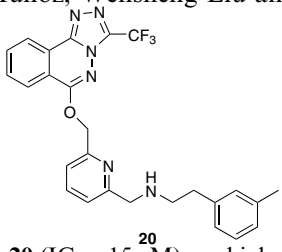




X = CH_2, Y = F hY5 IC50: 2 nM
X = O, Y = F or Me hY5 IC50: 5 nM

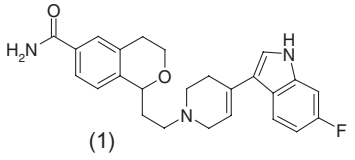


Unnatural mercapto β-C-nucleoside incorporated into DNA. This nucleobase analogue has a reversible redox-active thiol group and formed base pairing with disulfide covalent bonding.



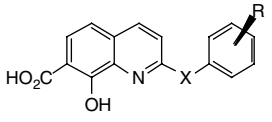
20

[1,2,4]Triazolo[3,4-*a*]phthalazine derivatives such as **20** (IC_{50}=15 nM) are high-affinity ligands of the $\alpha_2\delta$-1 subunit of voltage gated calcium channel.



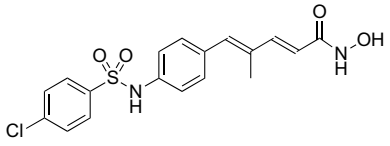
(1)

Incorporation of an SRI pharmacophore onto a selective 5-HT_{1D} agonist leads to a molecule having both 5-HT_{1D} antagonist and SRI activity. RPS techniques were employed to identify potential SAR approaches to ameliorating undesired cross-reactivities.

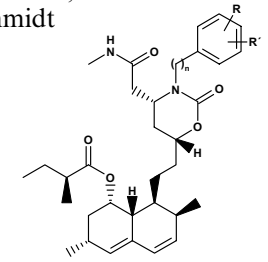


X = CONH, CONHNH, HNCO, NHCONH, COCH=C(OH)

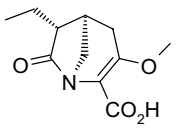
A series of quinoline derivatives linked to an aromatic ring by functionalized spacers was synthesized. The anti-HIV-1 integrase potency was evaluated in both in vitro and ex vivo assays.



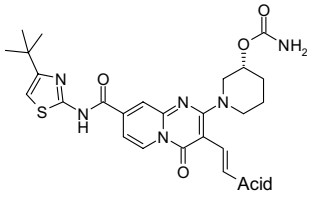
Synthesis and evaluation of unsaturated inhibitors of histone deacetylase are described. Inhibition of histone deacetylase IC_{50}=49 nM.



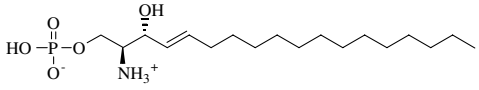
The synthesis, biological activity, and microsomal stability of a series of potent LFA-1/ICAM-1 binding inhibitors of the statin family are presented.



Anti-Bredt bridged bicyclo[3.2.1] γ-lactams were designed as inhibitors of penicillin binding proteins (PBPs). The compounds were prepared by a carbenoid insertion into a lactam N–H bond. Their weak antibacterial activity could either be explained by a poor chemical stability or by unfavorable steric interactions of the methylene bridge of the γ-lactam with the targeted enzymes.

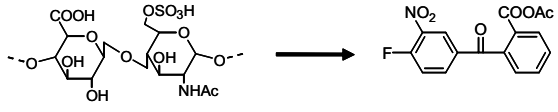


Acid: COOH MPC8: 0.5μg/mL
tetrazole MPC8: <0.25μg/mL
Efflux Pump Inhibitor in *P. aeruginosa*



D-*erythro* sphingosine-1-phosphate

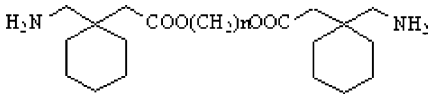
Sphingosine-1-phosphate (S1P) is an important regulator of a wide variety of biological processes acting as an endogenous ligand to EDG/S1P receptors. In an effort to establish structure–activity relationship between EDG/S1P and ligands, we report herein homology modeling study of EDG-1/S1P$_1$, syntheses of S1P analogues, and cell based binding affinity study for EDG/S1P receptors.



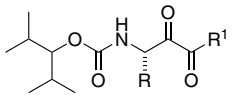
A heparan sulfate disaccharide unit
[HexUA-GlcNAc(6S)]

KI-111

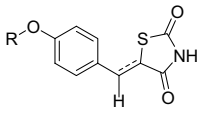
Novel heparan sulfate mimetic compounds (**KI**-compounds) were designed and synthesized as antiadhesive agents.



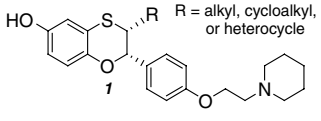
A series of mutual prodrugs were synthesized and their pharmacological properties to treat allodynia were investigated.



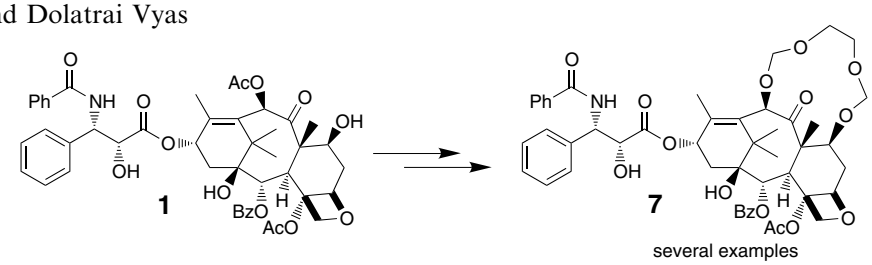
An orally available series of ketoamide-based inhibitors of cathepsin K has been identified. Starting from a potent inhibitor with poor oral bioavailability, modifications to P^1 and $P^{1'}$ elements led to enhancements in solubility and permeability. These improvements resulted in orally available cathepsin K inhibitors.



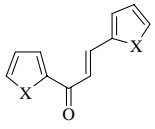
The minimum structural requirements for troglitazone-like compounds to retain their biological activities were reported.



A class of dihydrobenzoxathiins **1** exhibiting a high degree of selectivity for ERα over ERβ has been discovered. The SAR of dihydrobenzoxathiins with modifications at the C-3 position is presented.



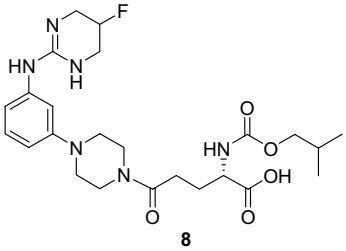
A series of paclitaxel analogues possessing a macrocyclic structure between the 7 and 10 positions has been prepared. These compounds possess in vitro activity against a paclitaxel resistant cell line and have in vivo activity comparable to paclitaxel.



X = S, O, CH=CH, CH=N

For the development of safer anti-inflammatory agents, simple aromatic compounds containing propenone moiety were prepared and evaluated for their dual COX/5-LOX inhibitory activities. Among the 17 prepared compounds, most compounds exhibited considerable COX/5-LOX inhibitory activities. Especially compound **C_{15}** showed the most significant dual COX/5-LOX inhibitory activities.

Using a pore- and channel-forming peptide, TV-XIIa, which is an 11-residual peptaibol isolated from the fungus *Trichoderma viride*, we developed a vehicle for cellular delivery of antisense oligodeoxynucleotides (ODNs). The designed carrier peptide is able to translocate ODNs into NIH3T3 cells at both 4 and 37 °C, and the translocation does not seem to involve an energy-dependent endocytic process.
Carrier peptide: Ac-U-N-I-I-U-P-L-L-U-P-I-K-K-K-K-K-K-K-K-K-K-OH (U: α-aminoisobutyric acid)



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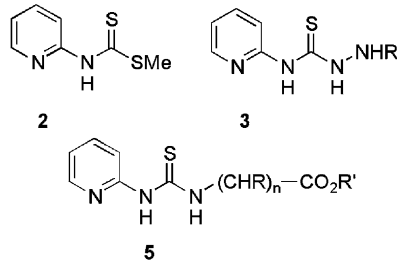
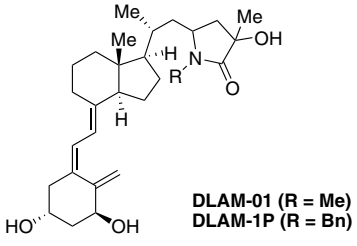
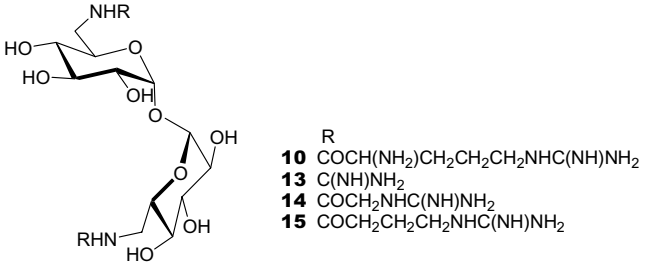
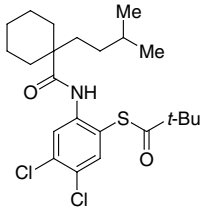


Synthesis and glucose-6-phosphatase inhibitory activity of (thiouriedo)alkanoic acid esters are reported.

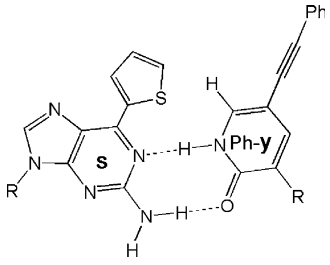
meso- and β-Substituted di(pyridiumyl)porphyrins **3**, **4**, and **7** have been synthesized and their interactions with DNA have been investigated. *meso*-Substituted porphyrins showed the stronger effect on DNA than that of β-substituted porphyrin. Cytoxicity of compound **3** (IC_{50}) to THP-1 tumor cell was up to 0.11 nM.

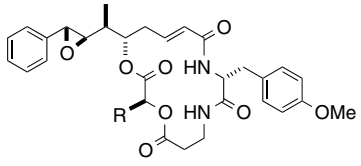






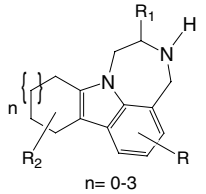
Studies on the relationship between the structure of the benzene moiety of *S*-(2-(acylamino)phenyl) 2,2-dimethylpropanethioates and CETP inhibitory activity were performed. The most potent compound achieved 50% inhibition of CETP activity in human plasma at a concentration of 2 μM.



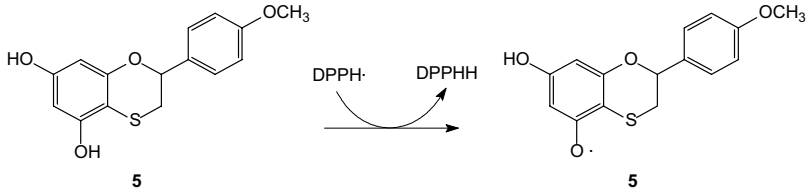


arenastatin A (**1**): R = $CH_2CH(CH_3)_2$
15-*i*-propylanalogue: R = $CH(CH_3)_2$
15-*t*-butylanalogue: R = $C(CH_3)_3$

Two analogues possessing steric hindered substituents on C-15 of arenastatin A (**1**), a potent cytotoxic spongean depsipeptide, were synthesized and shown to enhance the stability in mouse serum. In particular, 15-*tert*-butylanalogue with higher cytotoxicity exhibited anti-tumor activity through iv administration different from **1**.

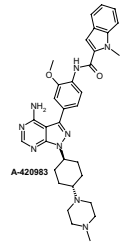


The synthesis and characterization of a new class of human 5-HT_{2C} receptor agonists are described. Potent and selective 5-HT_{2C} receptor agonists have been identified in this class of molecules.

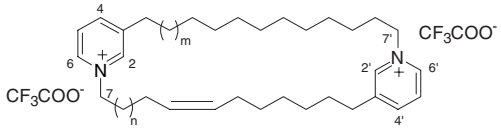


5 5

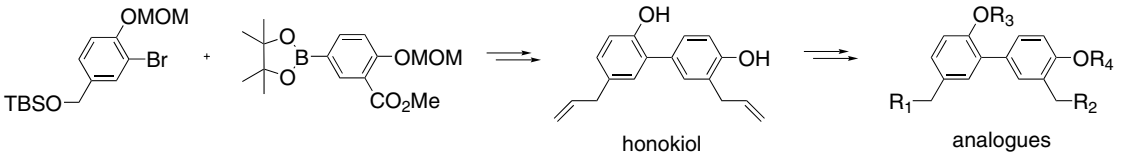
By means of density functional theory calculations, 5-OH in 4-thiaflavans was revealed, unexpectedly, to be more active than 7-OH in scavenging DPPH radical.



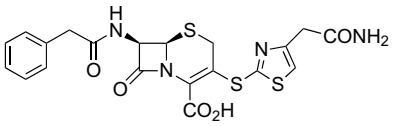
A-420983 (compound **7**) is a potent inhibitor of lck. A-420983 exhibits oral efficacy in animal models of delayed-type hypersensitivity and organ transplant rejection.



cyclostellettamine G (**1**): m=1, n=1
dehydrocyclostellettamine D (**2**): m=1, n=4, Δ^{13}
dehydrocyclostellettamine E (**3**): m=2, n=4, Δ^{13}

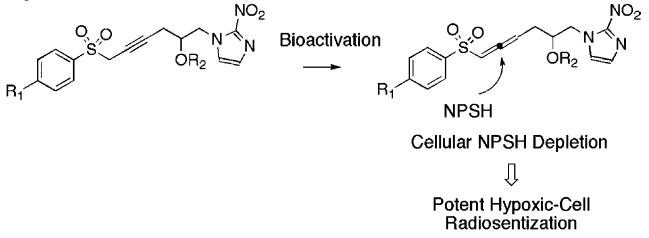


Honokiol has been synthesized by utilizing Pd-catalyzed Suzuki–Miyaura coupling reaction as a key step. The structure–activity relationship between neurite outgrowth-promoting activity and its O-methylated and/or its hydrogenated analogues in the primary cultures of fetal rat cortical neurons suggests that 5-allyl and 4′-hydroxyl groups are essential for affecting the neurotrophic activity of honokiol.

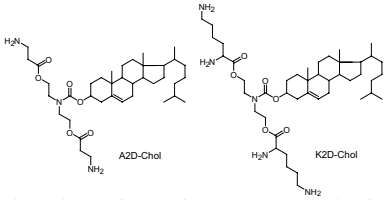


8a (FR193879)

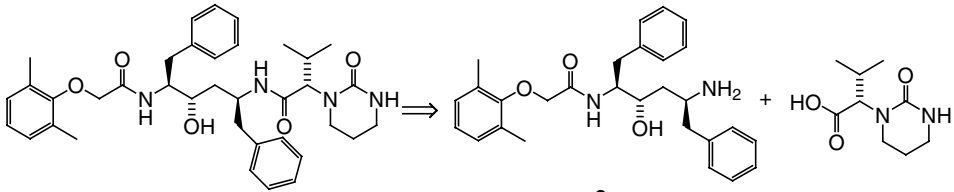
The synthesis, therapeutic efficacy against *Helicobacter pylori*, and preliminary safety of the novel cephem derivative, FR 193879 (**8a**) are described. Compound **8a** having a (4-carbamoylmethylthiazol-2-yl)thio moiety at the 3-position and a phenylacetamido at the 7-position was found to have good safety showing a nontoxic dose of >100 mg/kg in dogs in a 4-week repeat dose toxicity study and extremely potent therapeutic efficacy against *H. pylori*, showing 30 times superior activity compared to AMPC, and did not display cross-resistance with CAM or MNZ.



Propargylic sulfones containing a 2-nitroimidazole function have been synthesized to evaluate their hypoxic-cell radiosensitizing activity toward EMT6/KU tumor cells and intracellular nonprotein thiol (NPSH) depletion reactivity.

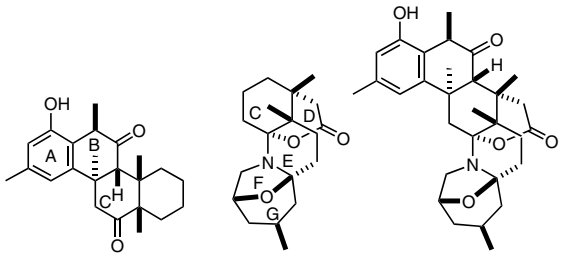


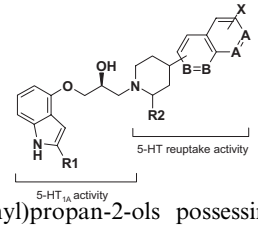
New degradable cationic ester lipids with 'T-shape' configurations were synthesized and tested for gene delivery carrier. Their transfection efficiency and toxicity were compared with commercially available cationic lipids, DOTMA, DOSPA, and DC-Chol. They showed efficient transfection activity and almost no toxicity on mammalian cell lines. Their ester bond degradation was monitored by ^{1}H NMR.

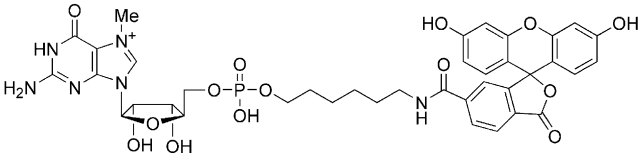


1a (ABT-378, lopinavir) **2** **3a**

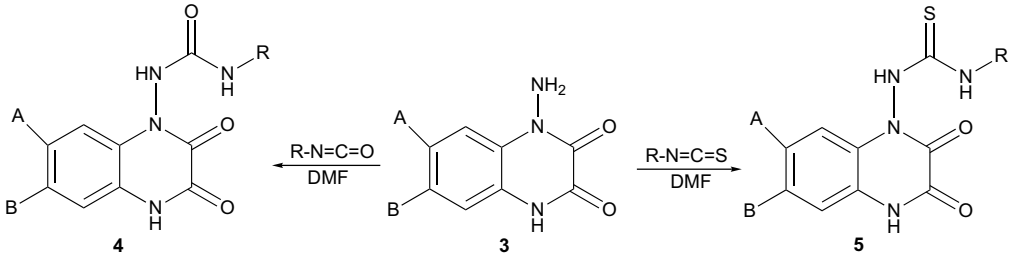
The HIV protease inhibitor ABT-378 (lopinavir) has a six-member cyclic urea in the P-2 position. A series of analogues in which the six-member cyclic urea is replaced by various heterocycles was synthesized and the structure–activity relationships explored.

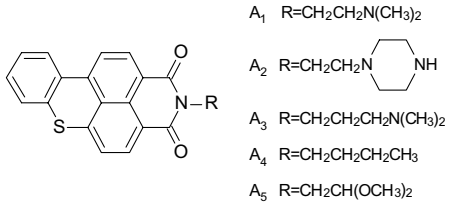




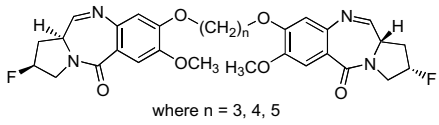


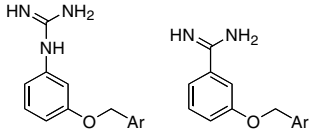
Synthesis of fluorescein labeled 7-methylguanosinemonophosphate.

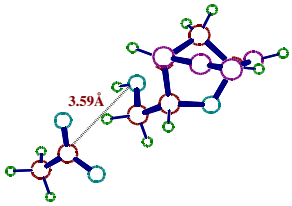




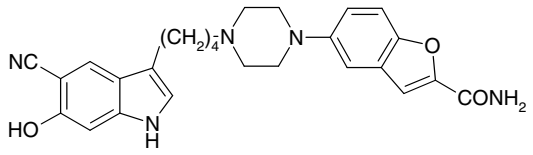
Several photocleavers of thio-heterocyclic fused naphthalimides are designed, synthesized and evaluated.



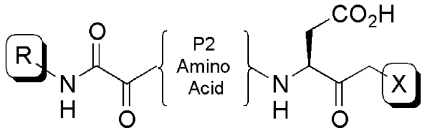




Ab initio Hartree Fock supermolecule calculations (with BSSE) have been carried out to evaluate interaction energies between the drug and the asp 185 of catalytic triad. The study indicates that minor conformational changes may lead to significant differences in interaction energies. The correlation of interaction energies with potency data indicates requirement of ~13 kcal/mol threshold interaction energy for the drug to undergo efficient competitive inhibition.



Japp–Klingemann type Fischer-indole synthesis protocols were used to build indole-5-carboxylic acids and derivatives.



Structural modifications were made to a previously described acyl dipeptide caspase inhibitor, leading to the oxamyl dipeptide series. Subsequent SAR studies directed toward the warhead, P2, and P4 regions of this novel peptidomimetic are described herein.

OTHER CONTENTS

*Corresponding author

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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