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Bioorganic & Medicinal Chemistry Letters

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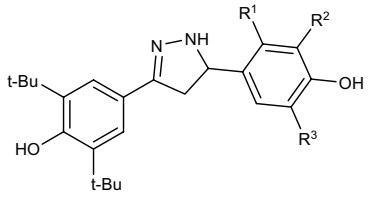
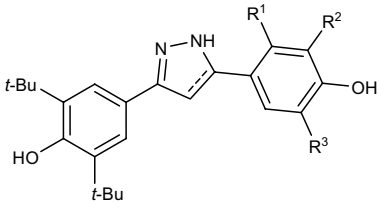
Contents

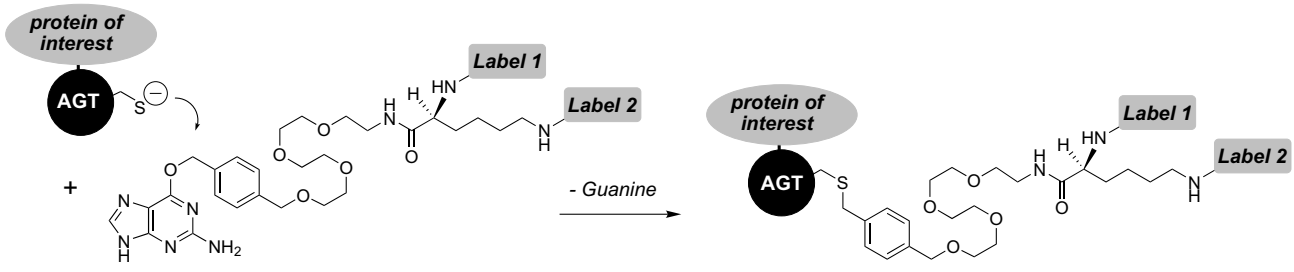
COMMUNICATIONS

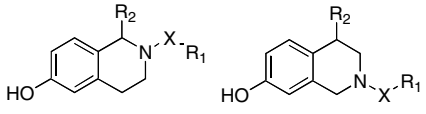


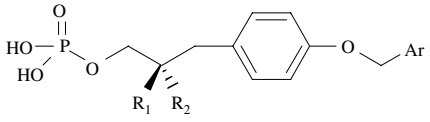
A series of 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-(multi-substituted 4-hydroxyphenyl)-2-pyrazolines **4a**–**i** have been synthesized and demonstrated to be moderate inhibitors of hACAT-1 and -2.



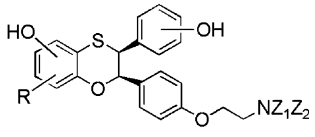
A series of 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-(multi-substituted 4-hydroxyphenyl)-2-pyrazolines **4a**–**j** and pyrazole **5** were synthesized and evaluated for LDL-antioxidant activity. Some derivatives exhibited high potency comparable to probucol.

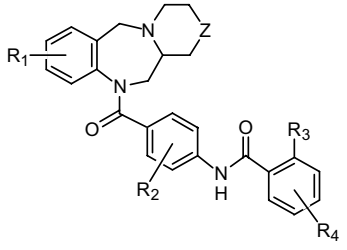


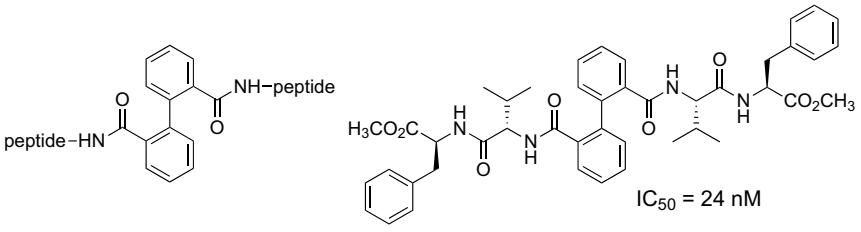


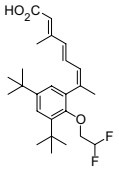


1: R_1 = H; R_2 = $NHC(O)C_{17}H_{33}$; Ar = Ph (K_i = 137 nM LPA_1)
10t: R_1 = $NHC(O)C_{17}H_{33}$; R_2 = H; Ar = 2-pyr (K_i = 18 nM LPA_1)



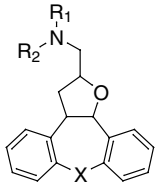




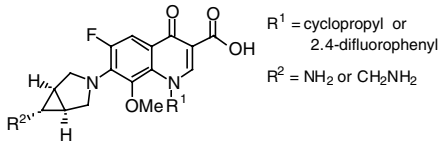


1

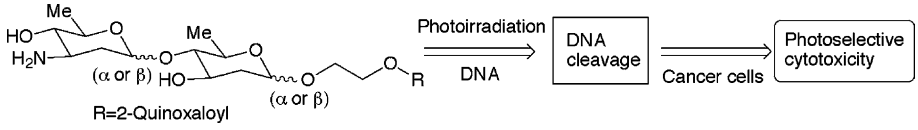
Benzofused heterocyclic analogs of the RXR selective modulator **1** (LG101506) were synthesized, and tested for their ability to bind RXRα and activate RXR homo and heterodimers. Potency and efficacy were observed to be dependent upon the choice of heterocycle as well as the sidechain employed.

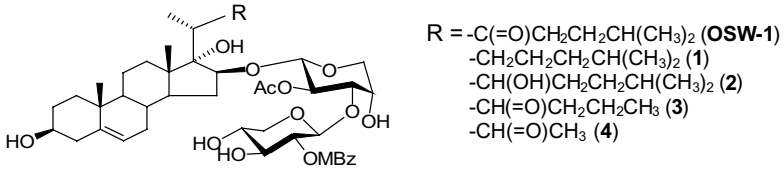


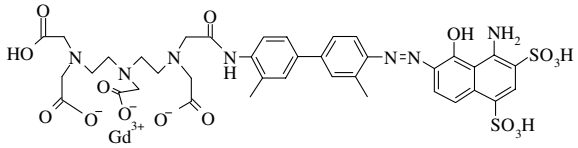
The synthesis of a series of substituted 2-(aminoalkyl)-3,3a,8,12b-tetrahydro-2*H*-dibenzocyclohepta[1,2-*b*]furan derivatives as 5-$HT_{2A/2C}$ antagonists is reported. The mCPP antagonistic activity of a set of selected compounds is also disclosed.

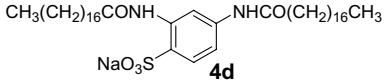


	1	4
	R^1 = cyclopropyl	R^1 = 2.4-difluorophenyl
	R^2 = NH_2	R^2 = CH_2NH_2
IC_{50}	2.1 μM	37 μM (*T. gondii*)
	73.1 μM	not active (*P. yoelii yoelii*)
	92 μM	40 μM (*P. falciparum*)

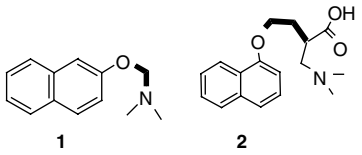




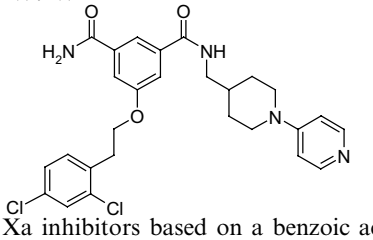




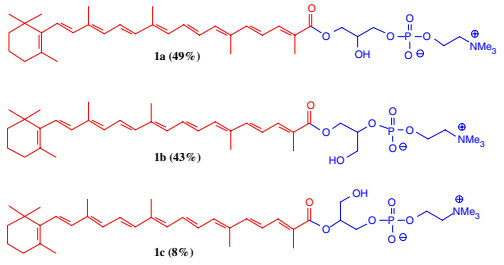
This paper describes novel scavenger receptor inhibitors bearing two long chains whose orientations are fixed by the presence of benzene ring.



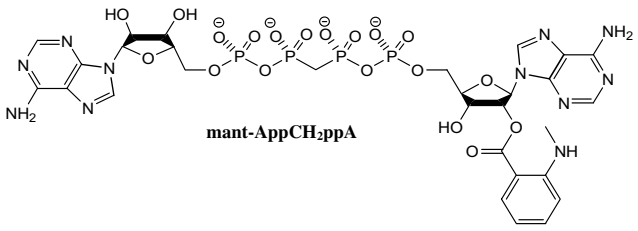
A series of **1** and **2** were synthesized for evaluation for their hypotensive activity.



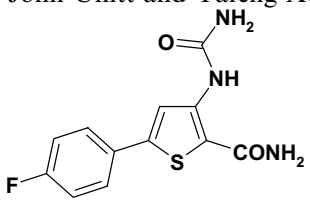
A series of novel, highly potent, achiral factor Xa inhibitors based on a benzoic acid scaffold and containing a chlorophenethyl moiety directed towards the protease S1 pocket is described. The compound shown was found to be the most active in a number of antithrombotic assays.



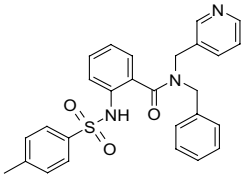
Superoxide scavenging by highly water-dispersible carotenoid derivatives in vitro.



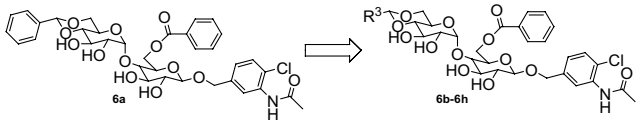
A novel tandem synthetic–biosynthetic procedure is described for the synthesis of four new fluorescent dinucleoside polyphosphates: mant–Ap_4A, mant–$AppCH_2ppA$, TNP–Ap_4A and TNP–$AppCH_2ppA$.

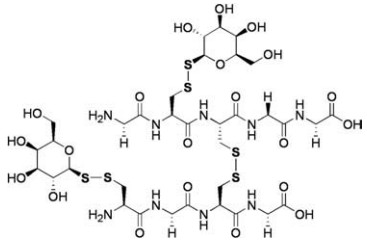


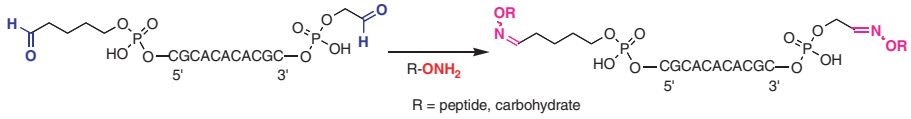
22 IKK-2 IC_{50} 0.063 μM



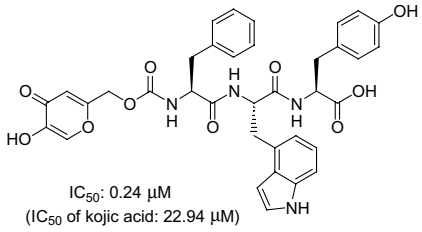
3i



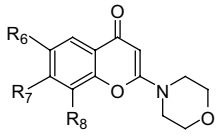




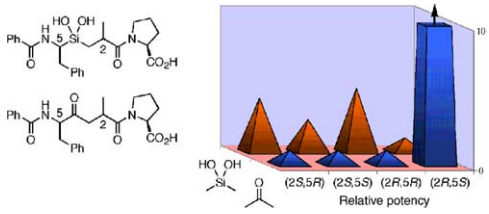
The preparation of oligonucleotide conjugates bearing the same reporter group (i.e., a peptide or a carbohydrate) at both extremity was achieved using chemoselective oxime bond formation.



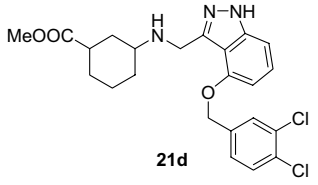
Kojic acid-FWY exhibited 100-fold tyrosinase inhibitory activity compared with kojic acid. The storage stabilities of these kojic acid-tripeptides were 15 times higher and their toxicity was lower than that of kojic acid.



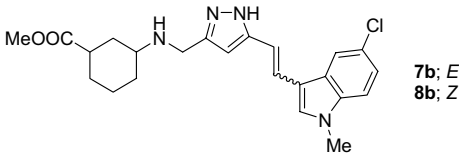
Synthetic 2-morpholinochromones, including the known PI3-kinase inhibitor LY294002, have been evaluated in vitro as inhibitors of isolated human platelet phosphodiesterases. Inhibition of the cAMP-phosphodiesterases, PDE2 and PDE3 by LY294002 is reported for the first time. Preliminary screening across a range of 2-morpholinochromones has revealed structural features for optimised PDE2 inhibition.



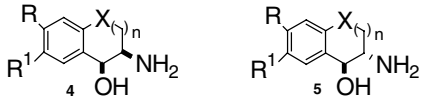
Four diastereomers of a Phe-Ala peptide mimic incorporating a central silanediol group have been individually prepared and tested as inhibitors of angiotensin-converting enzyme (ACE). Three of the silanediols exhibit levels of inhibition that are similar to those of corresponding ketones reported by Almquist. For the fourth diastereomer, with both stereogenic carbons inverted relative to the most active isomer, the ketone gives the least enzyme inhibition whereas the silanediol shows a surprisingly low IC_{50} value.



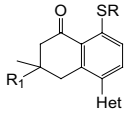
21d



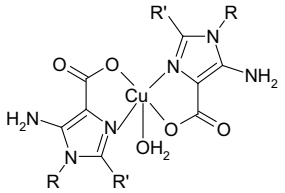
7b; *E*
8b; *Z*



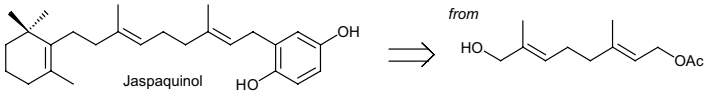
Chemo- and stereoselective synthesis of **4** and **5** is described.

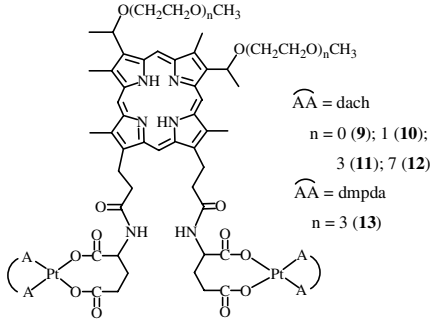


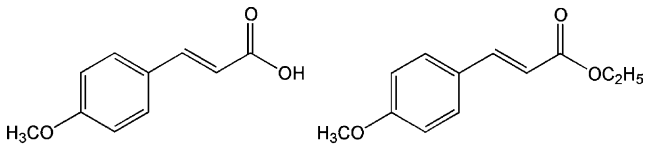
The identification of a novel class of ligands for the benzodiazepine site of α5-containing $GABA_A$ receptors with a range of efficacies is reported.



The copper complexes of 5-amino-imidazole ligands were prepared and characterized by various spectroscopic techniques. Ligands and copper complexes exhibited dose-dependent antiproliferative effects on the growth of B16F10 melanoma cells line but lower IC_{50} values were observed for the copper complexes.

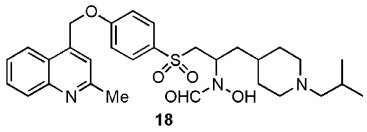






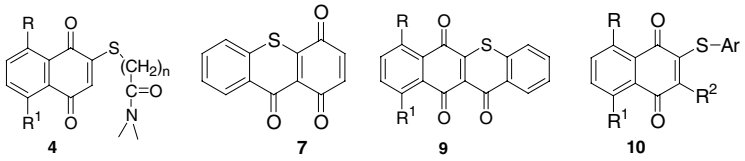
4-methoxy-*trans*-cinnamic acid 4-methoxy-*trans*-cinnamic acid ethyl

The substitution at 4-position in *trans*-cinnamic acid with OH– and OC_2H_5-group increased the α-glucosidase inhibitory activity. Both 4-methoxy-*trans*-cinnamic acid and 4-methoxy-*trans*-cinnamic acid ethyl ester exerted the highest potent inhibitory activity among those of *trans*-cinnamic acid derivatives.

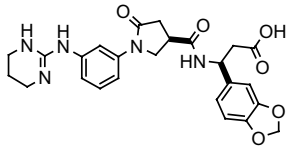


18

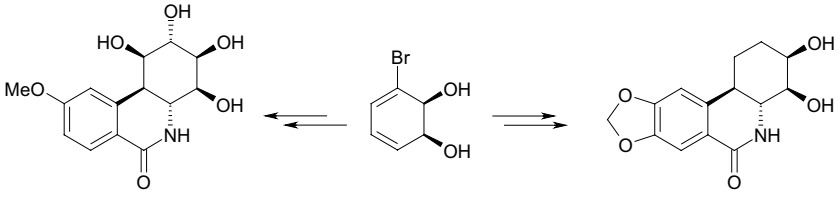
Reverse hydroxamate-based selective TACE inhibitors are described. Compound **18** has a potent TACE inhibitory activity and a high selectivity against MMPs, and has demonstrated an excellent oral inhibitory activity of the lipopolysaccharide (LPS)-stimulated TNF-α production in rats.

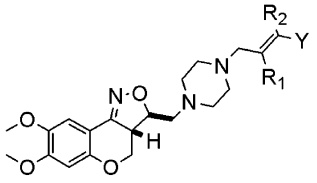


The synthesis, antiviral, antifungal and anticancer activities of **4**–**10** is described.

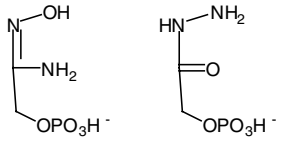


Novel $\alpha_v\beta_3$ antagonists based on the *N*-aryl-γ-lactam scaffold were prepared. SAR studies led to the identification of potent antagonists for $\alpha_v\beta_3$ receptor with excellent selectivity against the structurally related $\alpha_{IIb}\beta_3$ receptor. Additional interactions of *N*-aryl-γ-lactam derivatives with $\alpha_v\beta_3$ were found when compared to c(-RGDf[NMe]V-) peptide antagonist. The effects of the conformation and configuration of the γ-lactam core on the binding were also assessed.





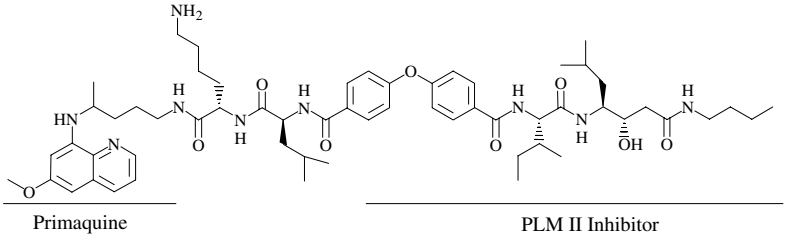
The synthesis and preliminary pharmacological activity of new substituted cinnamyl derivatives of our novel series of 3-piperazinylmethyl-3a,4-dihydro-3*H*-[1]benzopyrano-[4,3-*c*]isoxazoles are reported.



PGA PGHz

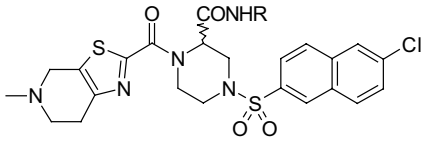
PGA and PGHz, two new derivatives of phosphoglycolic acid, were synthesised and successfully tested as selective inhibitors of class II FBP-aldolase.

Peptide nucleic acids (PNAs) C- or N-modified with dioxime ligands were prepared by solid-phase synthesis using iron(II)-clathrochelates as protected dioxime building blocks. These PNA bind complementary DNA sequence specifically, though with much reduced affinity in comparison with nonmodified PNA. The dioxime–PNA conjugates bind Cu^{2+} and Ni^{2+} at μM concentration.



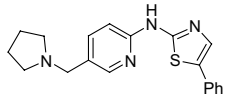
Primaquine PLM II Inhibitor

IC_{50} = 0.59 nM (Plasmepsin II); IC_{50} = 0.4 μM (*P. falciparum*)

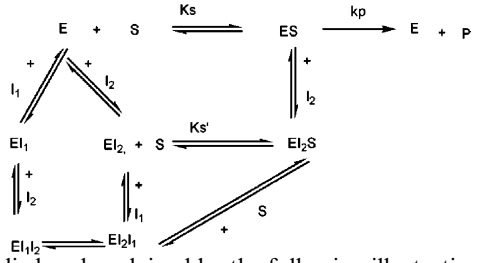


3c: R = H, **3d**: R = Me

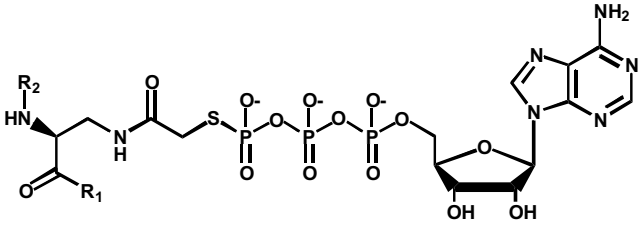
4,5,6,7-Tetrahydrothiazolo[5,4-*c*]pyridine derivatives were found to be potent and selective fXa inhibitors. Compound **3c** or **3d** exhibited potent anti-fXa activity and evident prolongation with the good intestinal absorption.



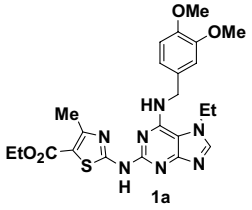
KDR IC_{50} = 6 ± 2 nM
Cell IC_{50} = 28 nM

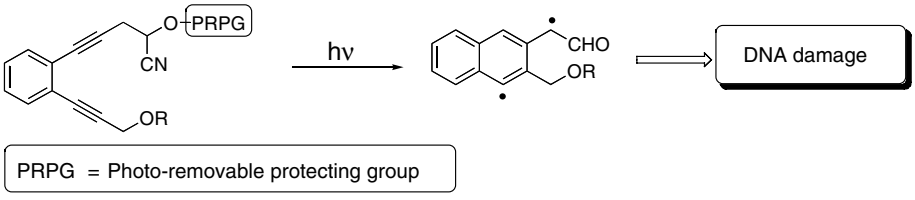


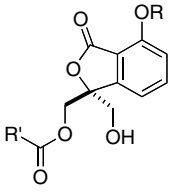
The mode of synergetic inhibition was studied and explained by the following illustration, when D-glucose, a reversible competitive inhibitor (I_1), and genistein (I_2), a reversible noncompetitive inhibitor were added to the reactant solution containing substrate and enzyme at the same time.

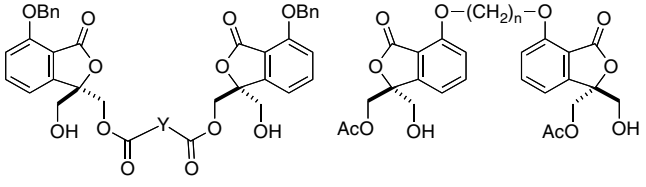


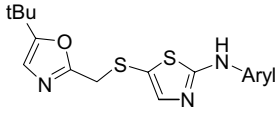
A bisubstrate analogue inhibitor of protein kinase A was designed and synthesized. Kinetic characterization provides novel evidence for the dissociative transition state of protein serine/threonine kinases and illustrates a simple method to convert a low affinity peptide substrate to a selective and modest affinity ligand for these enzymes.



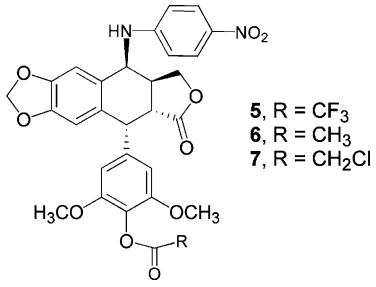


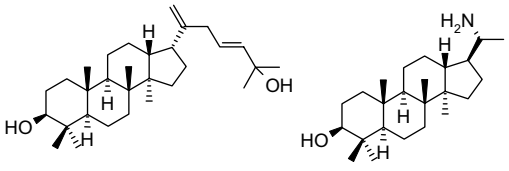




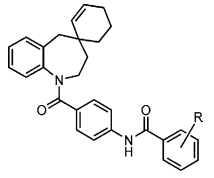


N-Aryl-2-aminothiazoles (structure above) were prepared and found to be inhibitors of CDK1/CDK2/CDK4 in vitro. Modification of the aryl group afforded analogues with in vivo anticancer activity.





The synthesis and in vivo activity of new potent anti-inflammatory triterpenoids are described.



Spirobenzazepines as V_{1a} selective as well as V_{1a}/V_2 dual vasopressin receptor antagonists have been described.

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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