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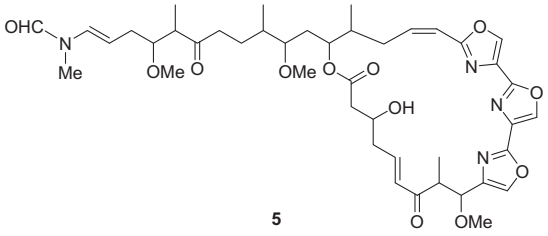
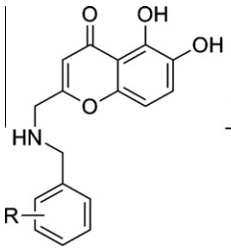
Contents

ARTICLES

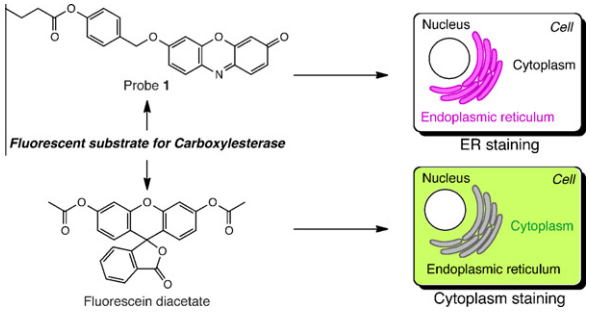


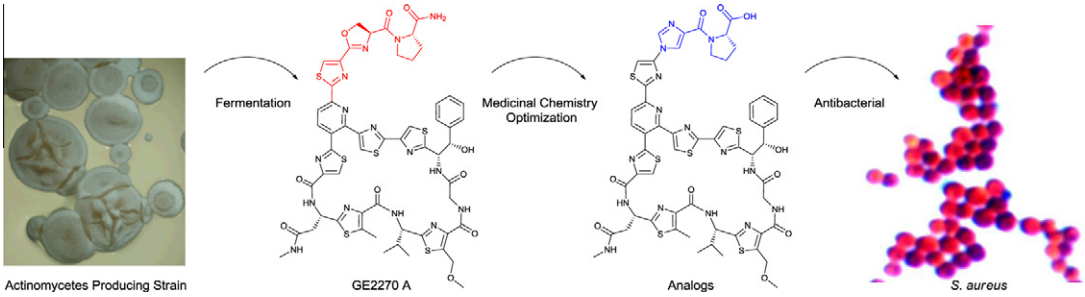
5

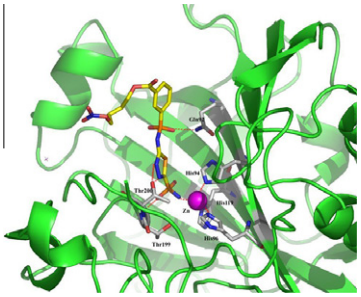
(19*Z*)-Halichondramide (**5**) with enhanced actin depolymerizing activity and potent antifungal activity.

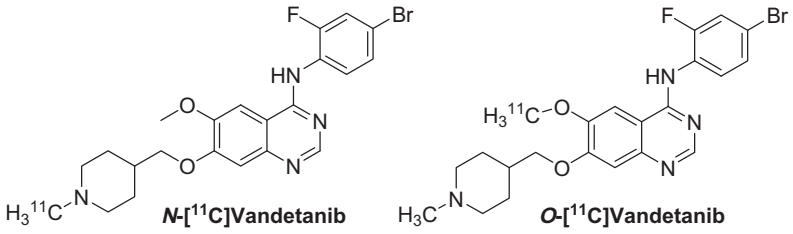


Compd	R	EC_{50} (μM)	CC_{50} (μM)
3i	3-Cl	14.0	>100
3j	3-Br	3.6	>100
3k	3-I	7.3	>100
3n	3-Me	2.0	>100

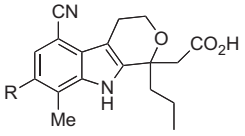




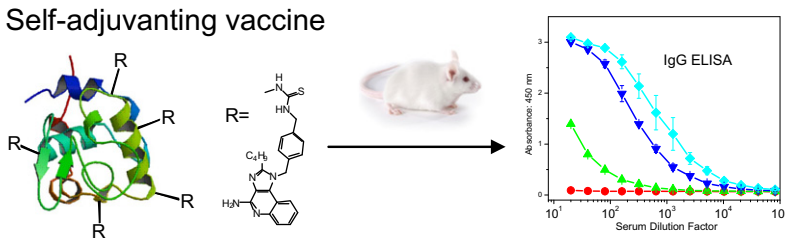


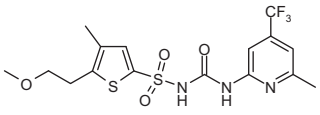


Radiosynthesis of [^{11}C]Vandetanib and [^{11}C]chloro-Vandetanib, new potential PET agents for imaging of VEGFR in cancer, is first reported.



We describe the structure–activity relationship of the C7-position of pyrano[3,4-b]indole-based inhibitors of HCV NS5B polymerase. Further exploration of the allosteric binding site led to the discovery of the significantly more potent compounds 13 and 14.

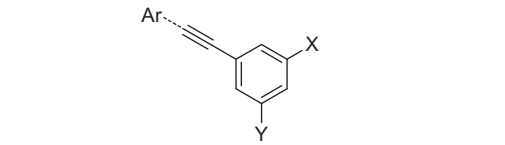




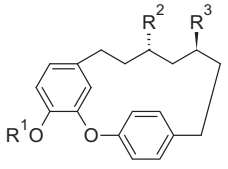
19

Mouse FBPase EC_{50}	5.9 μM
Glucose reduction at 6 hr	38% [100 mg/kg po]
Glycogen reduction at 6 hr	33% [100 mg/kg po]

Compound **19** is representative of a novel sulfonylureido pyridine series that yielded potent inhibitors of fructose-1,6-bisphosphatase, showing significant glucose reduction and modest glycogen lowering in the acute db/db mouse model for Type-2 diabetes.

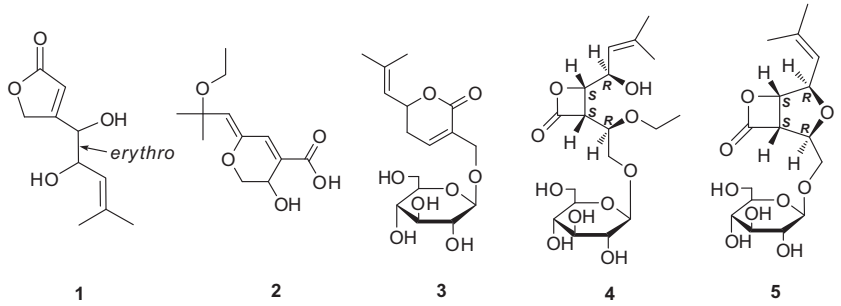


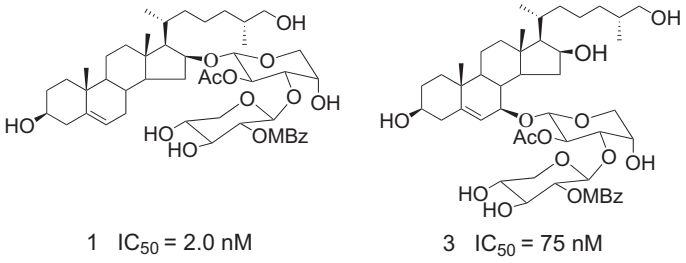
	a	b	c	d	e	f	g	h	i	j
X	CN	NO_2	CN	CN	CN	CN	NO_2	NO_2	Br	Br
Y	NO_2	Br	Cl	F	Br	I	F	I	F	Br



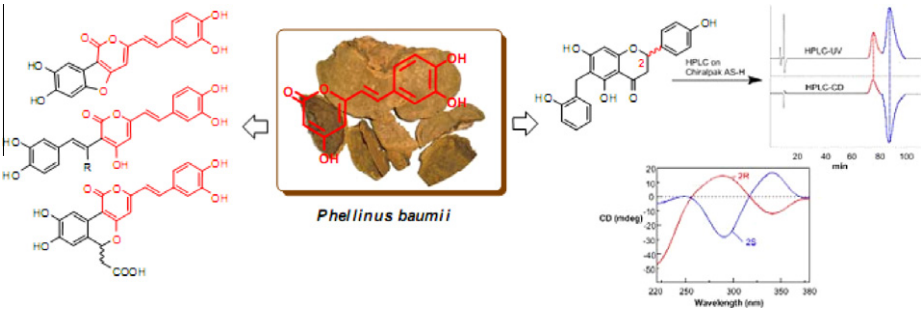
1:R^1=H	R^2=H	R^3=OH
2:R^1=H	R^2=OH	R^3=H
3:R^1=Glc	R^2=H	R^3=OH
4:R^1=Glc	R^2=OH	R^3=H
5:R^1=H	R^2=H	R^3=Glc-(6←1)-Api

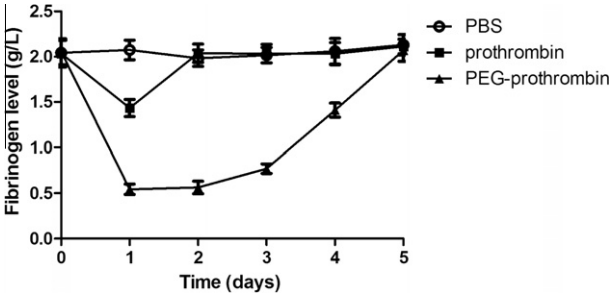
Effect on osteoblastogenesis of eight compounds isolated from the stem bark of *Acer nikoense* was investigated. Diphenyl ether-type cyclic diarylheptanoids **1**–**5** showed osteogenic activity in vitro.



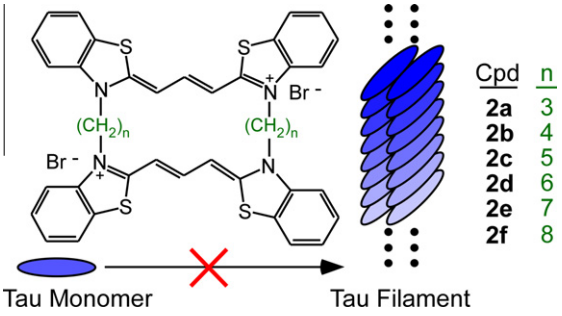


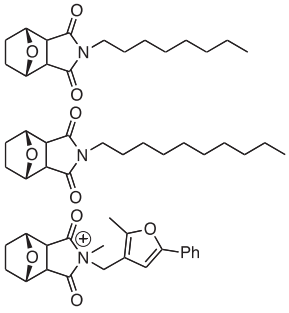
Six cholestane saponins, as mimics of OSW-1, were synthesized and tested for the cytotoxic activities. Compounds **1** and **3** exhibited potent cytotoxicities against five types of human tumor cells, with minimum IC_{50} of 2.0 and 75 nM, respectively.

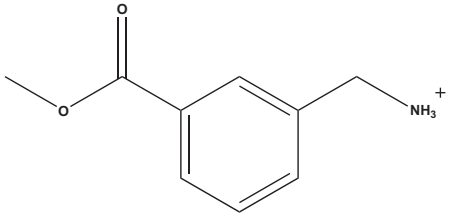




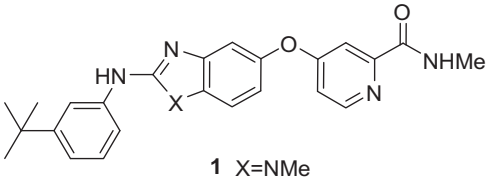
Biological activity assay of prothrombin. The capabilities of fibrinogen-lowering after subcutaneous administration of prothrombin or PEG-prothrombin at a dose of 50 μg/kg. Plasma levels of the fibrinogen were measured by ELISA kit, data are means ± SD for five mice per group.





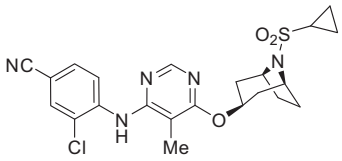


K_{ic} = 0.89 mM
K_{iuc} = 0.41 mM



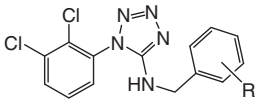
1 X=NMe
2 X=O
3 X=S

Two scaffolds based on 5,6-fused heterocyclic backbones were designed and synthesized as Raf kinase inhibitors. The scaffolds were assessed for in vitro pan–Raf inhibition, activity in cell proliferation and target modulation assays, and pharmacokinetic parameters.

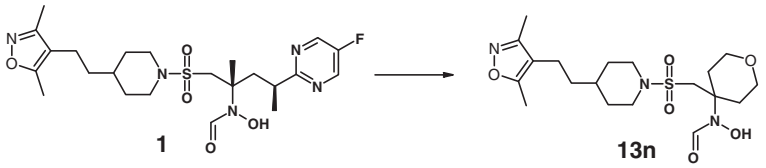


36j
hEC$_{50}$ = 3 nM
h% max = 96%

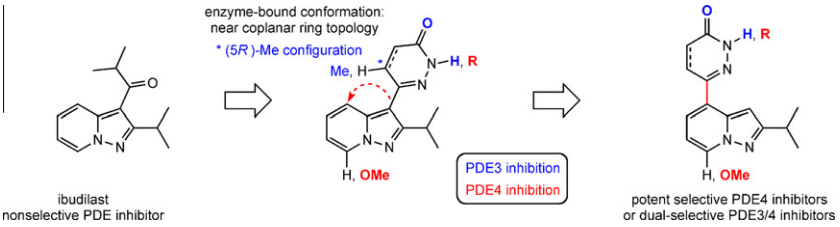
The lead optimization studies of a series of GPR119 agonists incorporating a nortropanol scaffold led to the identification of compound **36j** as a potent and orally active GPR119 agonist with high agonist activity.

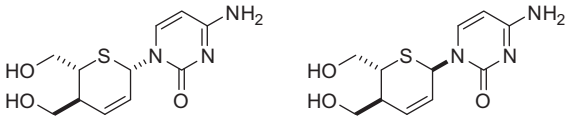


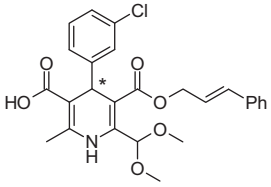
The synthesis and structure–activity relationship studies of P2X$_7$ antagonists are reported.



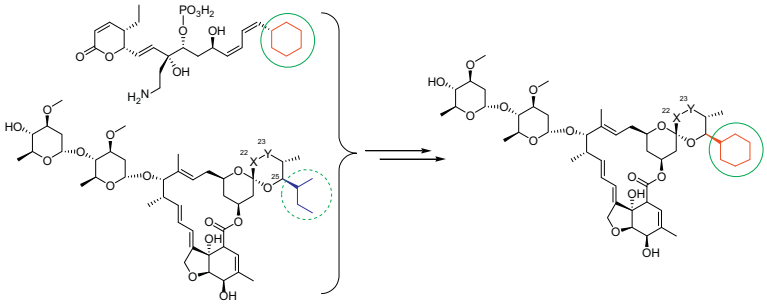
ADAM-TS4 IC_{50} = **26 nM**
MMP-13 IC_{50} = **>31000 nM**
MMP-2/14/9 IC_{50} = **>23000 nM**
Dog $t_{1/2}$ **19 h**
Dog F% **52%**

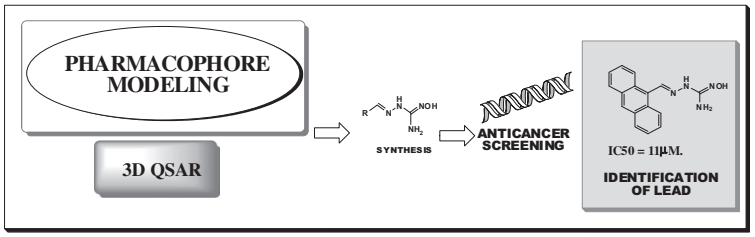


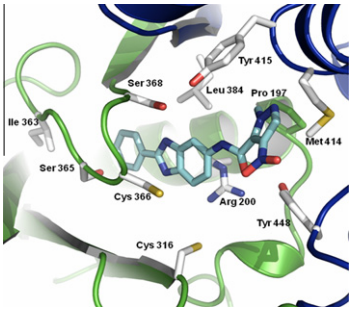


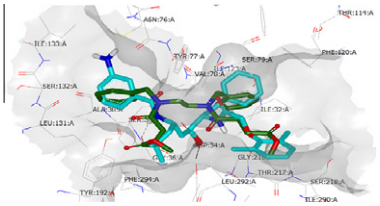


The novel asymmetric synthesis is reported for the preparation of optically pure (+)-4-(3-chlorophenyl)-6-dimethoxymethyl-2-methyl-1,4-dihydropyridine-3,5-dicarboxilic acid cinnamyl ester ((+)-**3**) as a promising blocker for the N-type calcium channels.

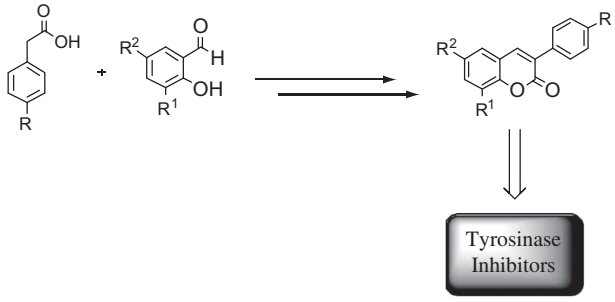


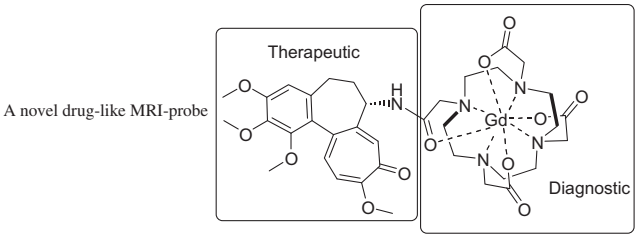


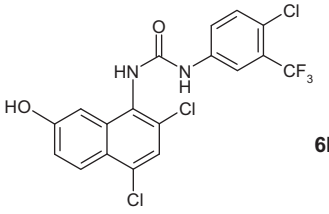




With the aim to find out structural features for the tyrosinase inhibitory activity, in the present communication we report the synthesis and pharmacological evaluation of a new series of phenylcoumarin derivatives with different number of hydroxyl or ether groups and bromo substituent in the scaffold. The synthesized compounds **5**–**12** were evaluated as mushroom tyrosinase inhibitors showing, two of them, lower IC_{50} than the umbelliferone. Compound **12** (IC_{50} = 215 μM) is the best tyrosinase inhibitor of this series.

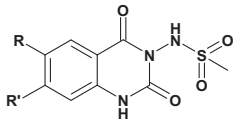






6b: 5.9 nM

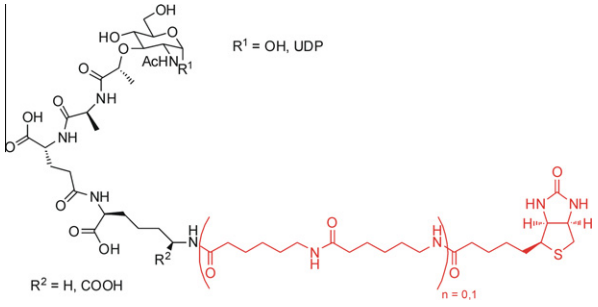
We have identified naphthol derivatives as inhibitors of the vanilloid receptor TRPV1 by high throughput screening. The initial lead showed high clearance in rats and has been optimized by enhancing the acidity of the phenol group. Compound **6b** has reduced clearance, improved potency and is active in rat cystometry models of urinary incontinence after intravenous administration.

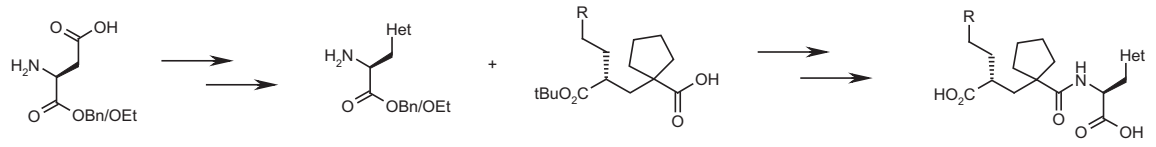


AMPA receptor antagonists

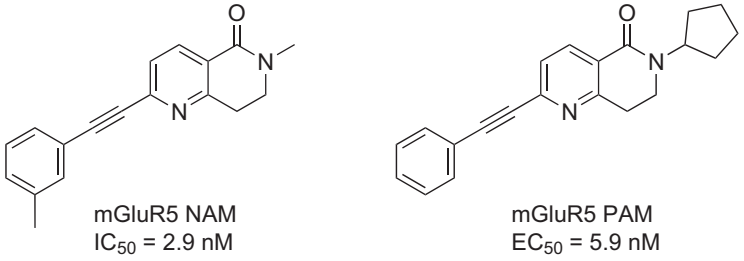
R = 1-imidazolyl, R' = NO_2: IC_{50} ([^{3}H]CNQX binding) = 82 nM

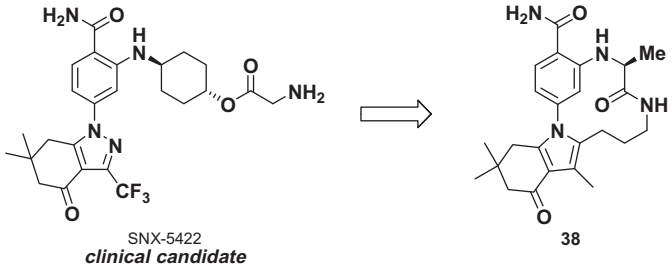
R = H, R' = Cl: E-shock mouse, oral administration: IC_{50} = 23 mg/kg



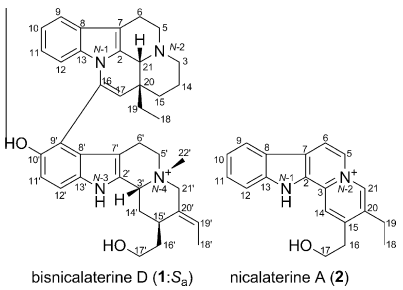


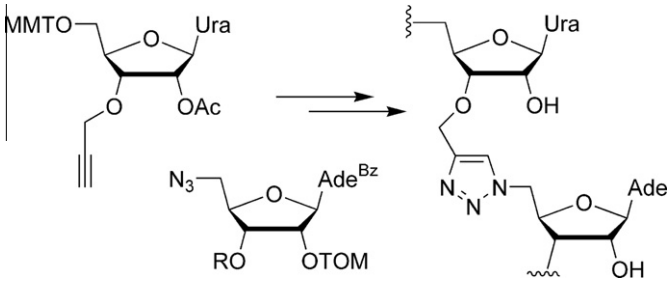
Novel heteroarylalanines derived from L-aspartic acid were designed and synthesised as potential inhibitors of Neutral Endopeptidase (NEP).

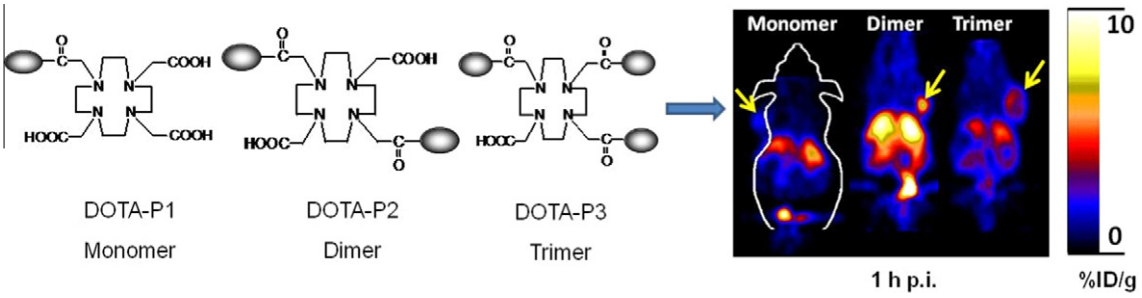


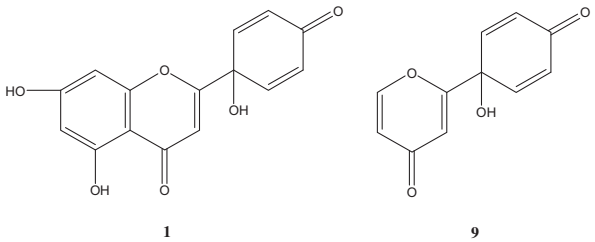


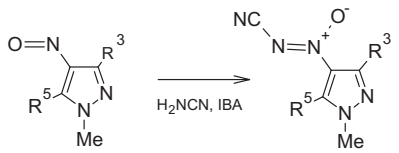
Two new indole alkaloids, bisnicalaterine D (**1**), consisting of an eburnane and a corynanthe type of skeletons, and nicalaterine A (**2**) were isolated from the bark of *Hunteria zeylanica*. Their structures were elucidated by various spectroscopic data such as NMR and CD spectra. A series of bisnicalaterines and nicalaterine A showed potent antiplasmodial activity against *Plasmodium falciparum* 3D7.





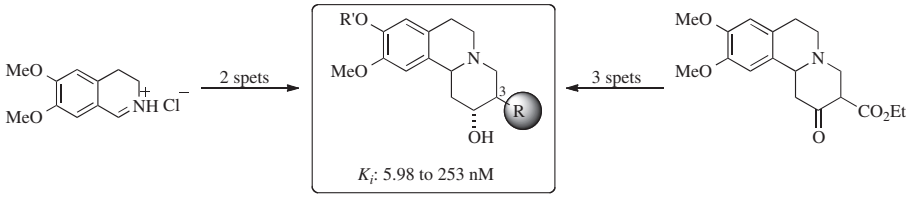


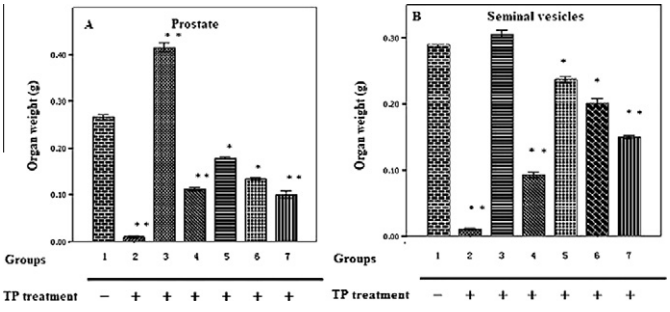


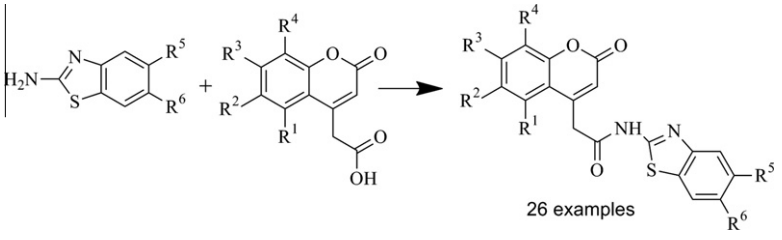


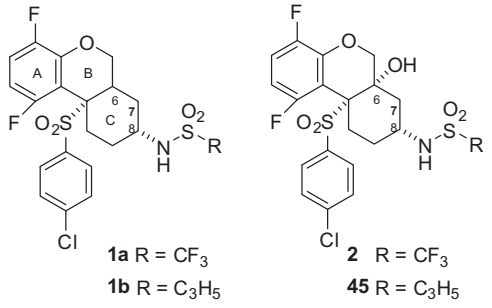
R^3, R^5 = pyridine, pyrazole, isoxazole, thiofene and furan rings

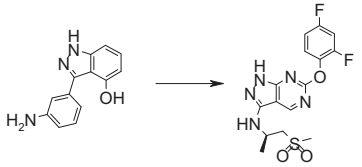
A number of products display interesting activity against *Candida krusei* and *Candida glabrata*, two fungal species resistant to azoles.

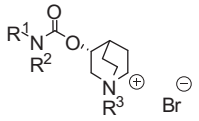




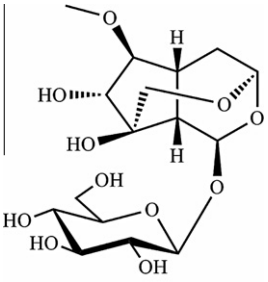








SAR around R^1, R^2 and R^3 are reported



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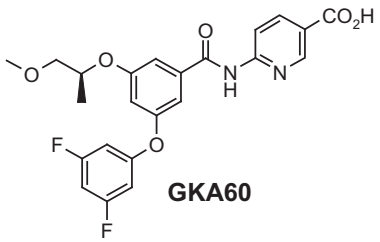
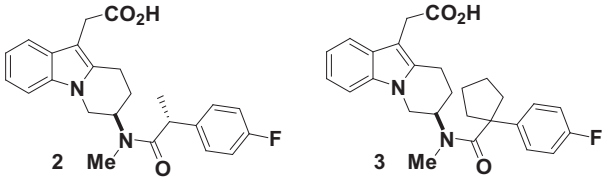
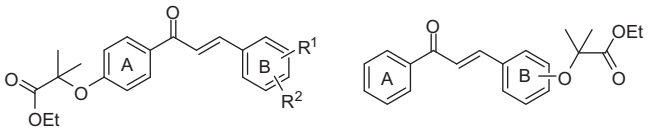
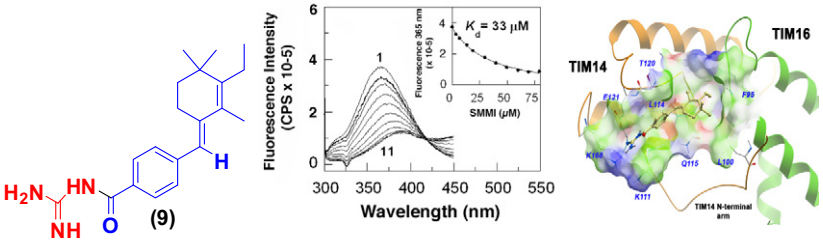


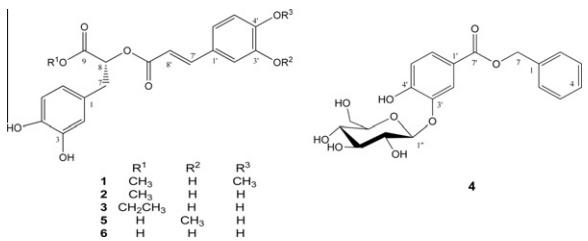
GKA60

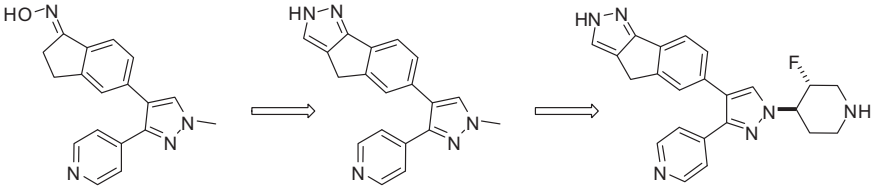






We designed and synthesized novel Magmas inhibitors, and tested their biological activity in yeast proliferation assays. We found that the most active compound **9** inhibited growth at the 4 μM scale. This compound was shown by fluorometric titration to bind to Magmas with a K_d = 33 μM. Molecular modeling suggested that the inhibitor bound at the predicted site in Magmas.





Compound 1a
BRaf IC_{50} = 0.02 nM

Compound 2a
BRaf IC_{50} = 2.2 nM

Compound 38
BRaf IC_{50} = 1.4 nM

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Botulinum neurotoxins are the most deadly toxins known to man, approximately 10 million times more deadly than cyanide. Botulinum neurotoxins are classified by the US Centers for Disease Control (CDC) as bioterrorism agents. The etiological agent responsible for botulinum intoxication is a metalloprotease; as such this is a key therapeutic target. Currently, there are no approved pharmacological treatments for botulinum intoxication. Discovering molecules that could be used as a path forward for therapeutic development as botulinum protease inhibitors is tantamount. A benzylidene cyclopentenedione-based inhibitor was found to be the first affinity reagent to covalently modify the active site of botulinum neurotoxin A light chain metalloprotease. Its kinetic parameters are reported and such an approach for inhibition of this deadly neurotoxin. [Capková, K.; Hixon, M. S.; Pellett, S.; Barbieri, J. T.; Johnson, E. A.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 206.]

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