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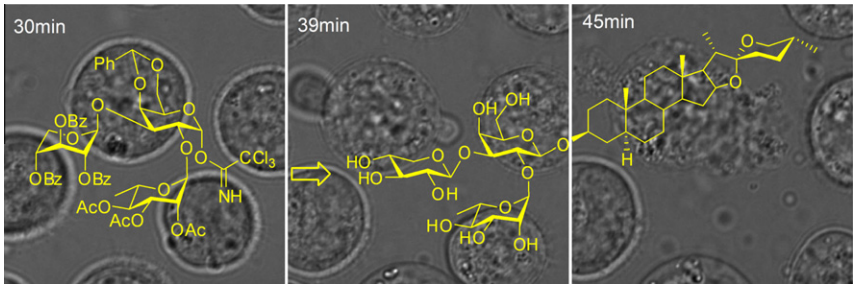
# Bioorganic & Medicinal Chemistry Letters Volume 21, Issue 2, 2011

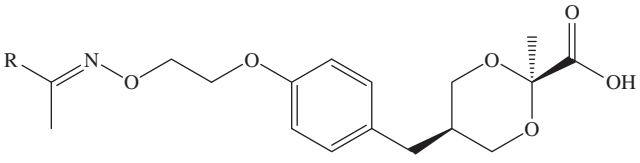
# Contents

## REGULAR ARTICLES







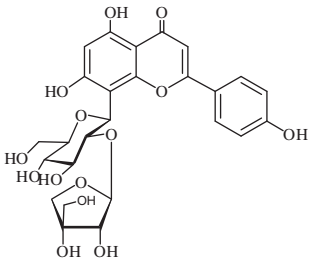



**6a-k**

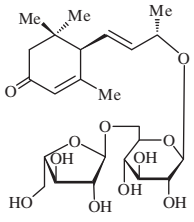
A novel series of oxime containing benzyl-1,3-dioxane-*r*-2-carboxylic acid derivatives are reported as selective PPARα agonists. Some of the test compounds exhibited good selectivity towards PPARα over PPARγ in vitro and the lead compound **6c** showed excellent antihyperglycemic and antihyperlipidemic activity in vivo.



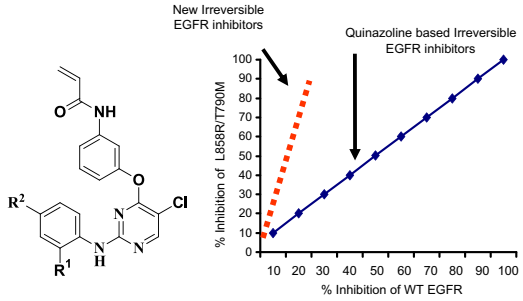
By bioactive-guided fractionation of methanol extract of the *Ficus microcarpa* leaves, one new *C*-glucosylflavone, ficuflavoside (**1**), one new megastigmane glycoside, ficumegasoside (**8**), and twelve known compounds were isolated. The antioxidant activities of these compounds were measured using the oxygen radical absorbance capacity methods. Flavonoids **1**–**6** exhibited potent antioxidant activity of 6.6–9.5 μM Trolox equivalents at the concentration of 2.0 μM. The results also indicated **2**, **3**, and **5** having meaningful reducing capacity of copper (I) ions concentration of 6.1–8.4 çM.



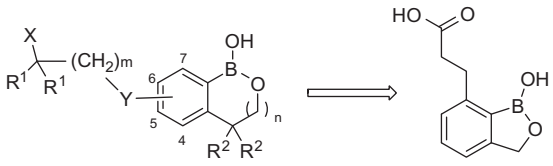
**1**



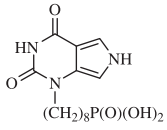
**8**





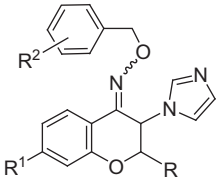





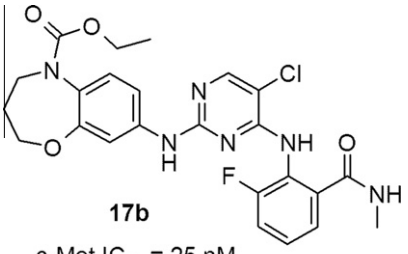



| | |
|---|---|
| TP from Escherichia coli | $IC_{50}$ = 6.8 μM |
| Human TP expressed in V79 | $IC_{50}$ = 27 μM |
| TP from human placenta | $IC_{50}$ = 17 μM |

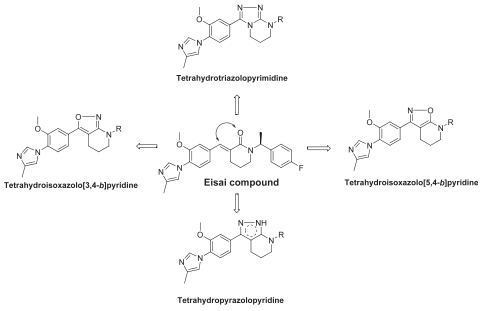




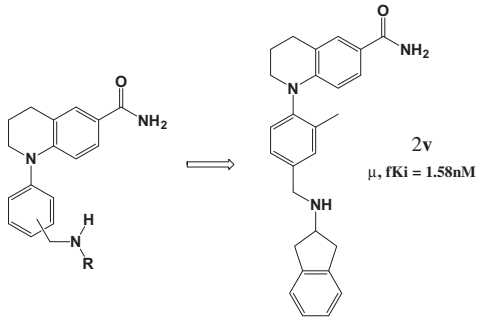
R = H; $CH_3$ $R^1$ = H; Cl
$R^2$ = H; Cl; Br; F; 2,4-$Cl_2$, 3,4-$Cl_2$





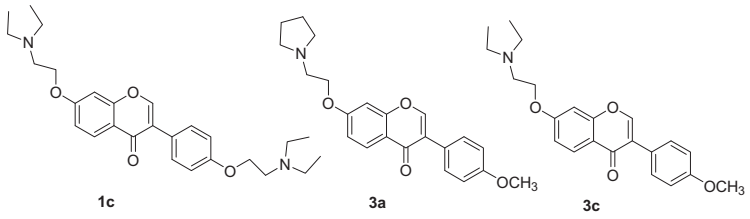





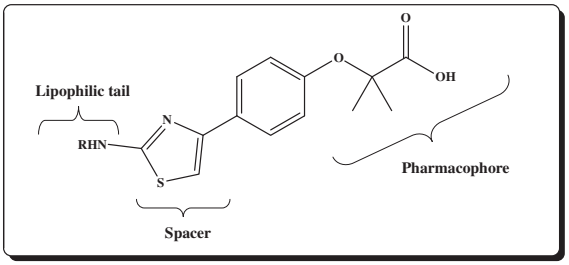




A series of tetrahydroquinoline derivatives was discovered as opioid receptor antagonists.



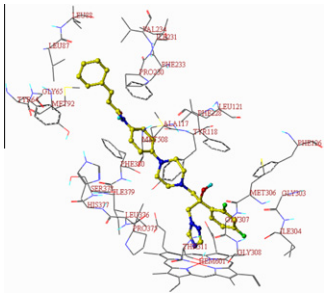



Series of daidzein derivatives were designed, synthesized, and assessed for stimulation of osteoblast function using primary culture of rat calvarial osteoblasts *in vitro*. Compounds **1c**, **3a** and **3c**, each of 10.0 nM concentrations, were several folds more potent than daidzein of 1.0 μM concentration, in stimulating differentiation and mineralization of osteoblasts. At 10 mg $kg^{-1}$ $day^{-1}$ dose for three consecutive days showed anti-estrogenic effect of the same molecules.



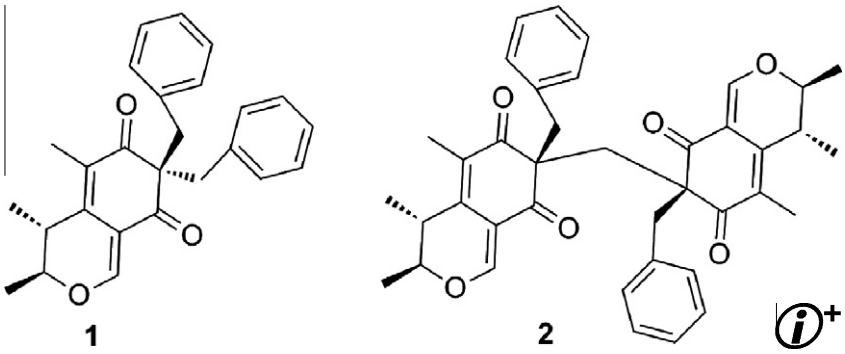

A novel series of 2-(4-(2-substituted aminothiazole-4-yl) phenoxy)-2-methyl propanoic acid derivatives has been developed and evaluated for their hypolipidemic and hypoglycemic activity.



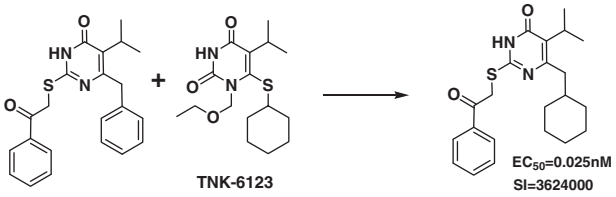


A number of novel triazole derivatives have been synthesized and compound **5a** was studied with molecular docking to get the insight of structural requirements for better enzyme inhibition.

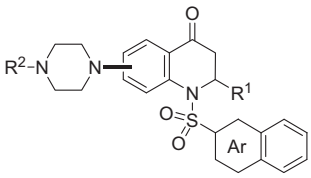




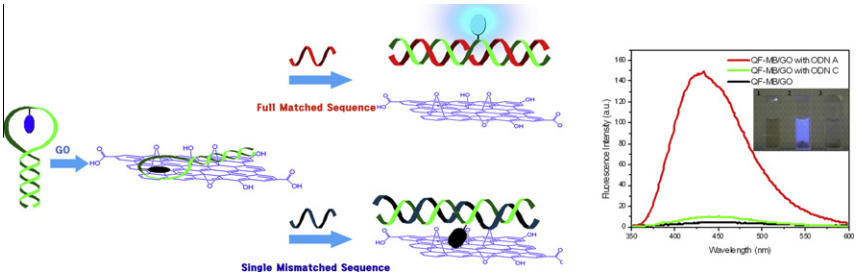


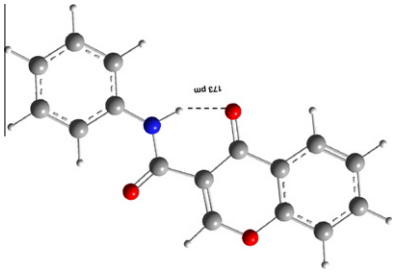

A series of novel dihydro-aryl/alkylsulfanyl-cyclohexylmethyl-oxopyrimidines (*S*-DACOs) were designed, synthesized and evaluated for anti-HIV-1 activity in vitro.





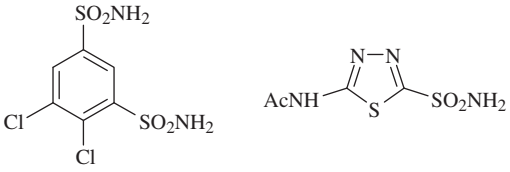





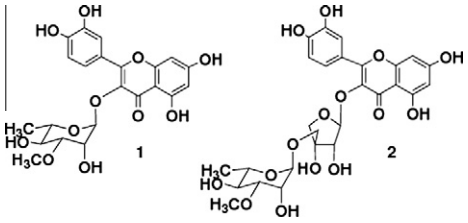
The present project has been focused on the discovery of new chemical entities (NCEs) for MAO inhibition, based on the development of chromone carboxamides. The chromone-3-carboxamides show high selectivity to MAO-B, with compounds **9** and **12** displaying IC$_{50}$ values in nanomolar range.





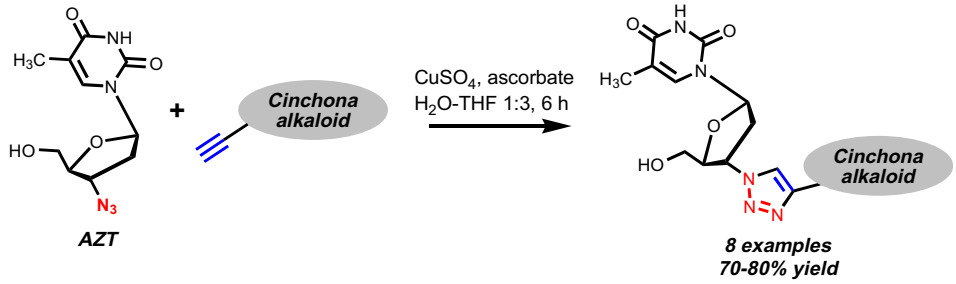

Ki(STPCA-2)=79 nM Ki(STPCA-2)=74 nM



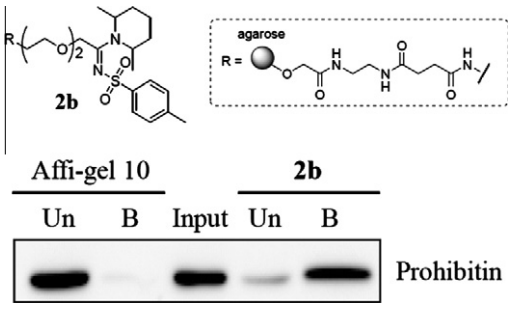

Hedgehog/GLI1-mediated transcriptional inhibitors (**1**, **2**, and **8**) were isolated and their cytotoxicity against cancer cells were described. Treatment with **1** led to a significant decrease in the level of nuclear GLI1 protein and Ptch mRNA expression of PANC1 in an Smo-independent manner.

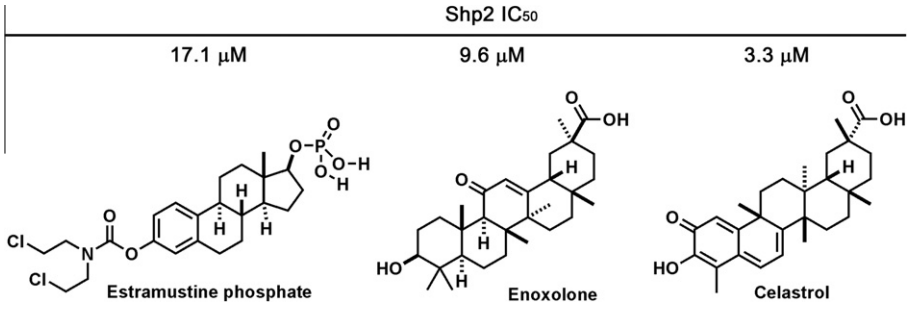




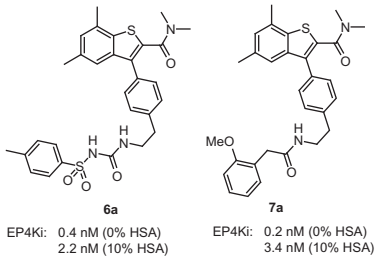



In order to identify the binding proteins to anti-resorptive 5-chloro-1-(2,6-dimethylpiperidin-1-yl)-*N*-tosylpentan-1-imine (**1**), the chemical affinity matrix for the compound **1** (**2b**) was designed and synthesized. Using **2b**-based chemical proteomics, prohibitin was identified as one of strong binding proteins for **2b**.

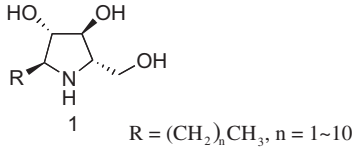






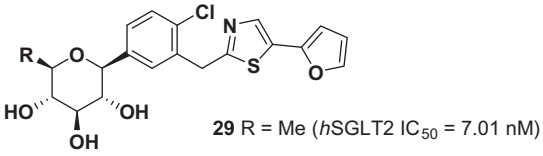





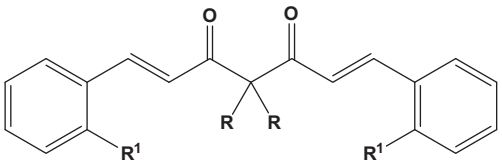




**1-*C*-alkyl-l-arabinoiminofuranoses**



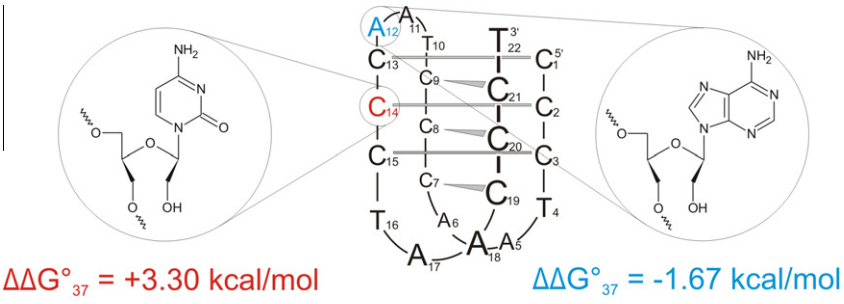



A variety of modifications at the C-6 position on glucose were conducted in the present study to establish SAR on carbohydrate pharmacophore based on structure of potent thiazole **5**. Among the compounds tested, deshydroxy **29** demonstrated the best in vitro inhibitory activity against *h*SGLT2 in this series to date.

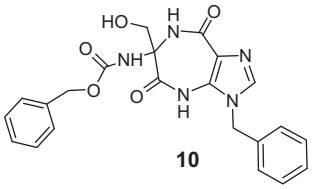



2-Hydroxycurcuminoids inhibited tumor growth and exhibited more potent antitumor activity than 2-hydroxycinnamaldehyde and curcumin. The compound induced apoptosis through ROS generation and cell cycle arrest at G2/M phase.



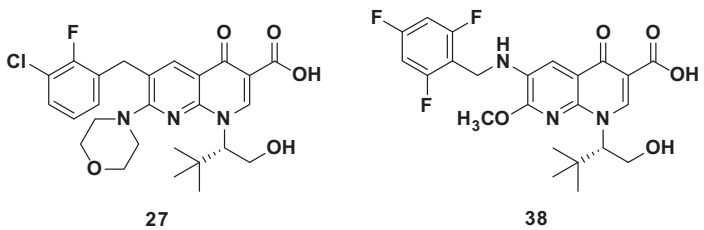




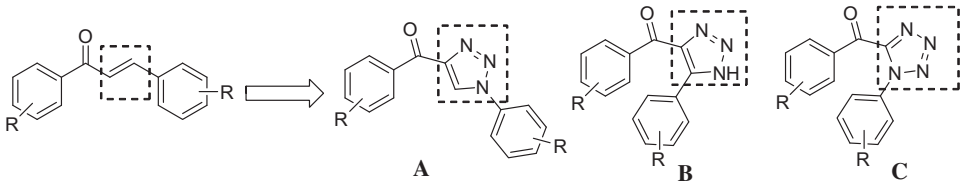




Synthesis and biochemical inhibition studies of a novel transition state analog inhibitor of guanase (**10**) bearing the ring structure of azepinomycin have been reported. The compound was synthesized in five-steps from a known compound and biochemically screened against the rabbit liver guanase. The compound exhibited competitive inhibition profile with a $K_i$ of 16.7 ± 0.5 μM.

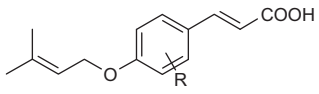





SAR studies on the quinoline carboxylic acid class of HIV-1 integrase inhibitors focused on improving the metabolic stability and led to the discovery of **27** and **38**.



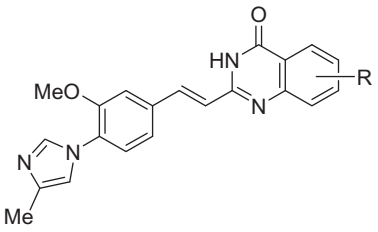



$DI_{50}$ = 0.18 - 0.72 µmol/cm²

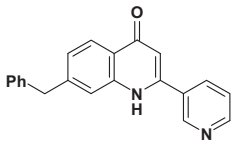
*at the Croton oil ear test in mice



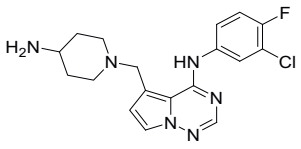



Synthesis, SAR and evaluation of styrenyl quinazolinones as novel gamma secretase modulators are presented in this communication. Starting from literature and in-house leads we evaluated a range of quinazolinones which showed good modulation of γ-secretase activity.





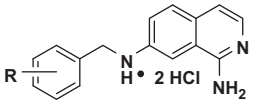

rhinovirus 3C protease $pIC_{50}$ = 5




**8l**

A novel series of 5-((4-aminopiperidin-1-yl)methyl)-pyrrolo[2,1-*f*][1,2,4]triazin-4-amines with small aniline substituents at the C4 position were optimized for dual EGFR and HER2 protein tyrosine kinase inhibition. Compound **8l** exhibited promising oral efficacy in both EGFR and HER2-driven human tumor xenograft models.

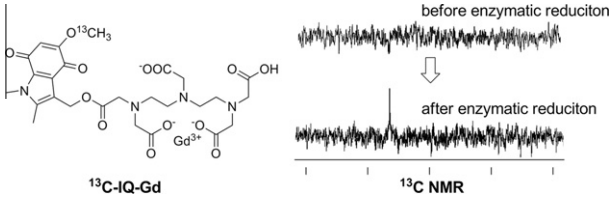





**2a-f**

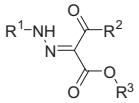
Six 7-benzylamino-1-isoquinolinamines **2** were found to be submicromolar inhibitors in vitro of drug-resistant *Plasmodium falciparum*, with the best possessing activity comparable to chloroquine. Despite being developed from a lead that is a DHFR inhibitor, these compounds do not mediate their antimalarial effects by inhibition of DHFR.






**$^{13}$C-IQ-Gd** **$^{13}$C NMR**



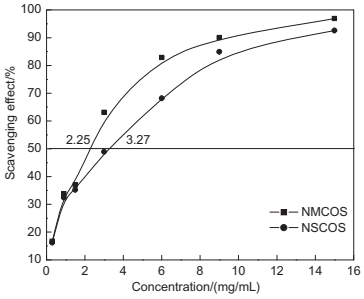



$R^1$ = $C_6H_5$, 4-$NO_2C_6H_4$, 4-$MeC_6H_4$, 4-$HOC_6H_4$, 2-$MeOCC_6H_4$, 2-$HOH_2CC_6H_4$, 4-$MeOCC_6H_4$, 4-$FC_6H_4$, 3-$ClC_6H_4$, 4-$MeOC_6H_4$, naphthalen-1-yl, 4-$EtOOCC_6H_4$

$R^2$ = $CH_3$, $CF_3$

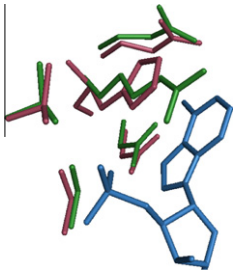
$R^3$ = $CH_3$, $C_2H_5$, $H_2C-CH(CH_3)_2$

A novel series of aryl hydrazono esters (AHE) (1–13) were synthesized (yield 76–98%) to study the oviposition responses in *Aedes albopictus* (Skuse) mosquitoes for the first time. At a concentration of 10 μg $ml^{-1}$ in dual choice experiment, among the screened compounds, AHE-12 showed remarkable oviposition attractant activity with an oviposition activity index (OAI) of +0.299 (greater than 95% confidence limit) comparable to *p*-cresol (OAI +0.320) which is well-reported oviposition attractant for *Aedes aegypti*. Conversely, AHE-10 exhibited highest oviposition deterrent activity with OAI −0.247. The possible utilization of these compounds will be in integrated vector management strategies.



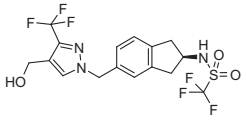

*N*-Maleoyl chitosan oligosaccharide (NMCOS) and *N*-succinyl chitosan oligosaccharide (NSCOS) with the same substituting degree of 0.49 showed different superoxide anion, hydroxyl radical scavenging activity and reducing power. The difference may be related to the fact that maleoyl has stronger electron-withdrawing effect than succinyl.





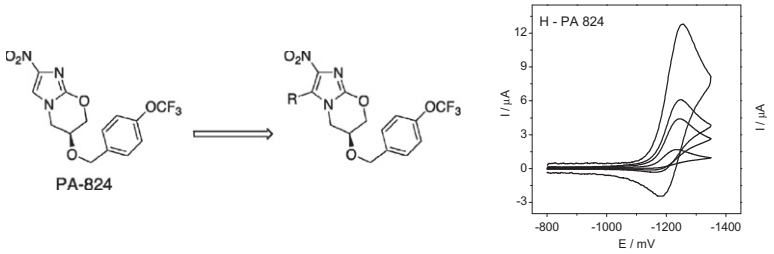
Superimposition of the structures of AKR1B14 (magenta) and AKR1B1 (green) in the vicinity of the 2′-phosphate adenosine moiety of NADPH (blue).

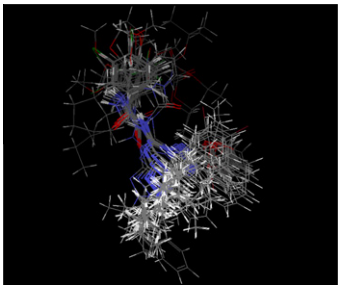




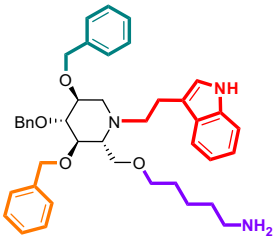
The evolution of an advanced lead compound **19** through a scaffold hopping approach guided by structure-based drug design is described.



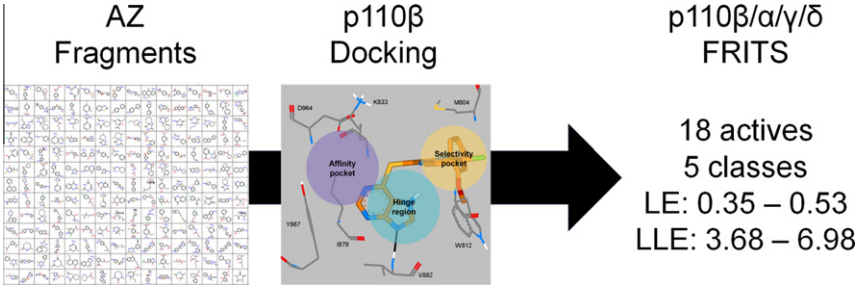






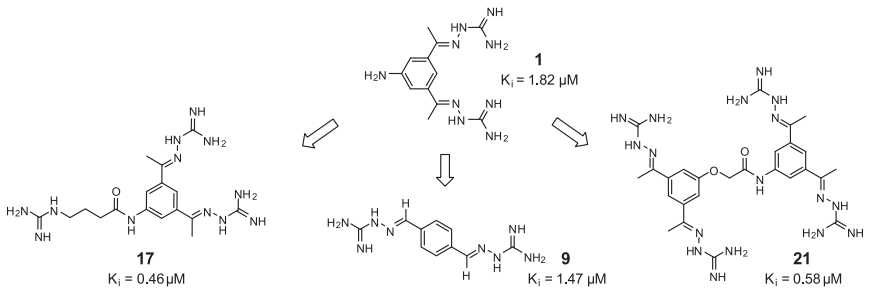


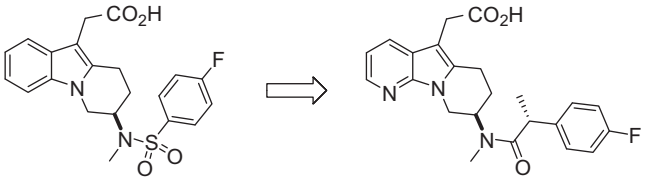


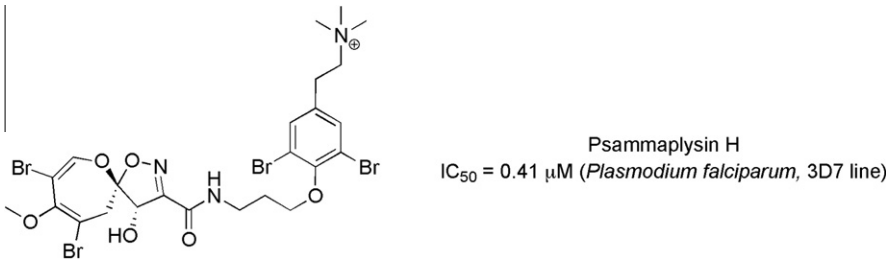

The identification of novel class 1 phosphatidylinositide 3-kinases (PI3K) inhibitors by fragment-based virtual screening is described.





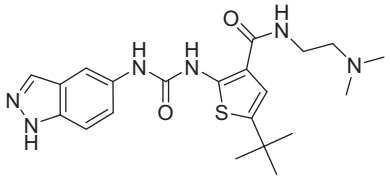




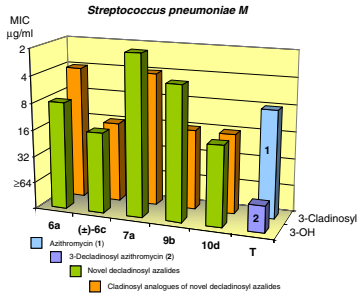



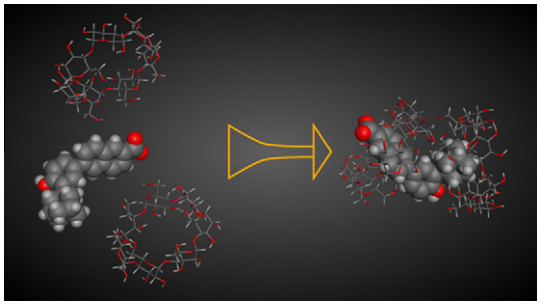

The isolation, structure elucidation and antimalarial activity of a new bromotyrosine alkaloid, psammaplysin H, is reported.



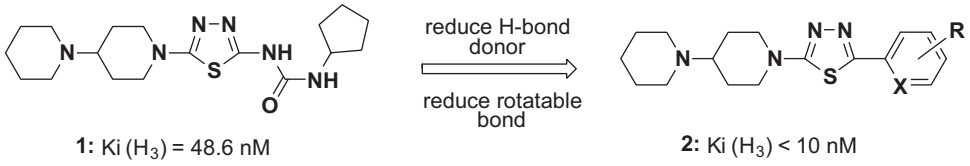






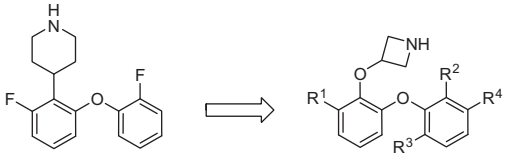




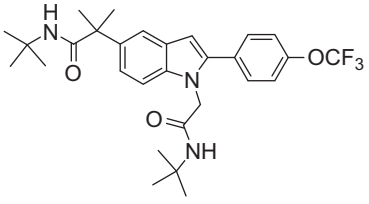

**1:** Ki ($H_3$) = 48.6 nM

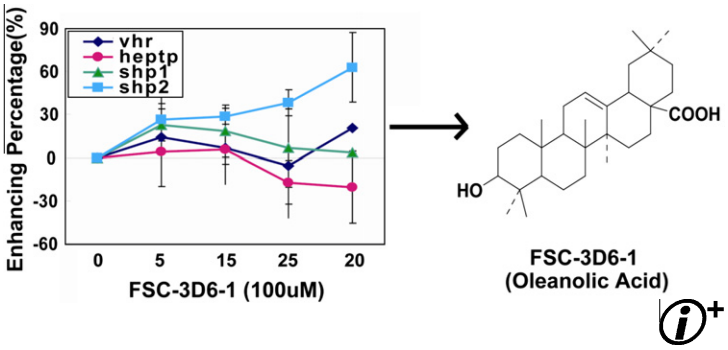
**2:** Ki ($H_3$) < 10 nM














*Corresponding author
Supplementary data available via ScienceDirect

**COVER**

Crystal structure of **2** bound to 3CP. Putative hydrogen bonds indicated with dashed lines. [Baxter, A.; Chambers, M.; Edfeldt, F.; Edman, K.; Freeman, A.; Johansson, C.; King, S.; Morley, A.; Petersen, J.; Rawlins, P.; Spadola, L.; Thong, B.; Van de Poël, H.; Williams, N. *Bioorg. Med. Chem. Lett.* **2011,** *21,* 777.]



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