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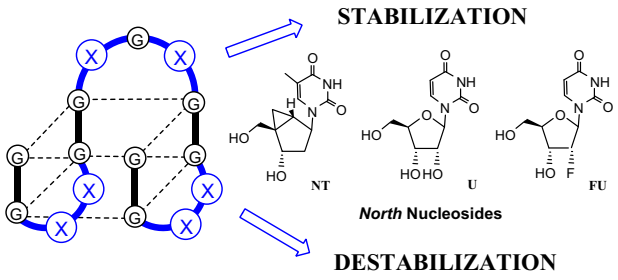
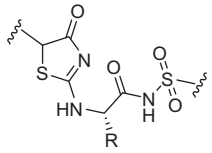
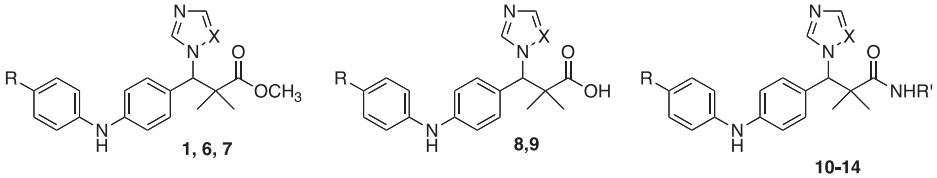
Contents

ARTICLES

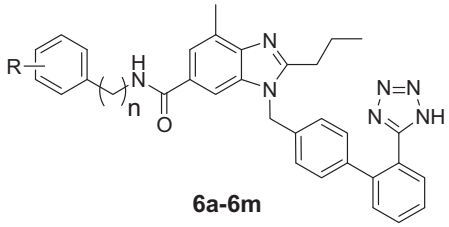




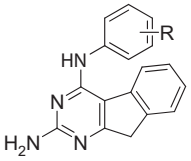
Rhodanine-based sulfonamides were developed as antagonists of anti-apoptotic Bcl-2 protein.



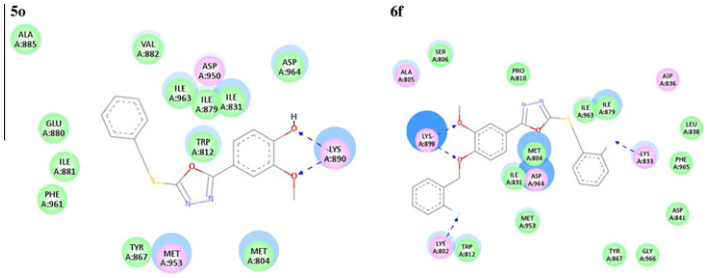
The synthesis and inhibitory activity of novel 3-(1*H*-imidazol- and triazol-1-yl)-2,2-dimethyl-3-(4-(phenylamino)phenyl)propyl derivatives in a MCF-7 CYP26A1 microsomal assay are described. The most promising inhibitor methyl 2,2-dimethyl-3-(4-(phenylamino)phenyl)-3-(1*H*-1,2,4-triazol-1-yl)propanoate (**6**, R = H, X = N) exhibited an IC_{50} of 13 nM (compared with standards Liarozole IC_{50} 540 nM and R116010 IC_{50} 10 nM) and >100-fold selectivity for CYP26 compared with CYP1A2, 2C9 and 2D6 observed and 15-fold selectivity compared with CYP3A4. The results demonstrate the potential for further development of these potent inhibitors.

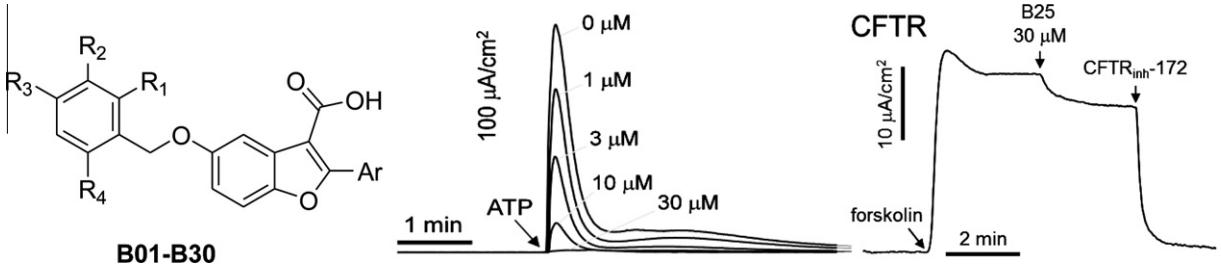


A series of 6-substituted carbamoyl benzimidazoles were designed and synthesised. The in vitro and in vivo evaluation results showed that compound **6g** is an orally active AT_1 receptor antagonist with low toxicity.

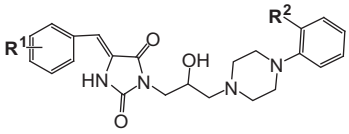


A series of 1,3,4-oxadiazole derivatives (**5a–5q**, **6a–6q**) have been first synthesized for their potential immunosuppressive activity. Among them, compound **5o** and **6f** displayed the most potential biological activity against T cells (IC_{50} = 1.25 μM and 4.75 μM for T cells) and the IC_{50} of positive control (csa) is 2.12 μM. The preliminary mechanism of compound **5o** and **6f** inhibition effects was also detected by flow cytometry (FCM) and the compounds exerted immunosuppressive activity via inducing the apoptosis of activated lymph node cells in a dose dependent manner. Docking simulation was performed to position compound **5o** and **6f** into the PI3Kγ structure active site to determine the probable binding model.

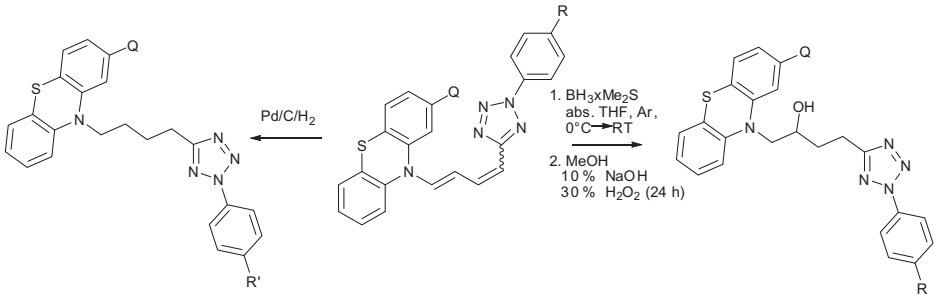


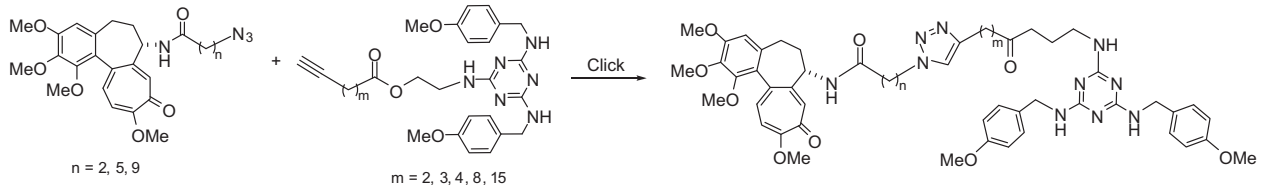


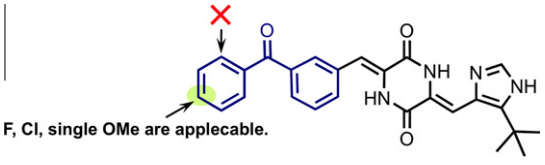
Thirty novel 5-substituted benzyloxy-2-arylbenzofuran-3-carboxylic acids (**B01**–**B30**) were synthesized and evaluated for their TMEM16A inhibitory activity by using short circuit current measurements in Fischer rat thyroid (FRT) cells expressing human TMEM16A. Eight of the novel compounds exhibit excellent CaCCs inhibition with IC_{50} value <6 μM, with compound **B25** exhibiting the lowest IC_{50} value of 2.8 μM.

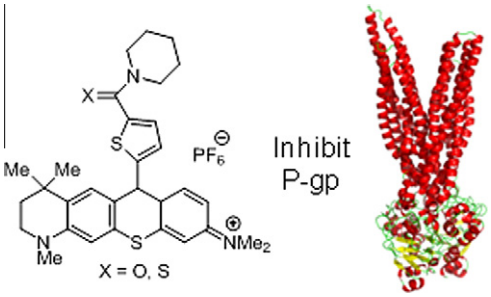


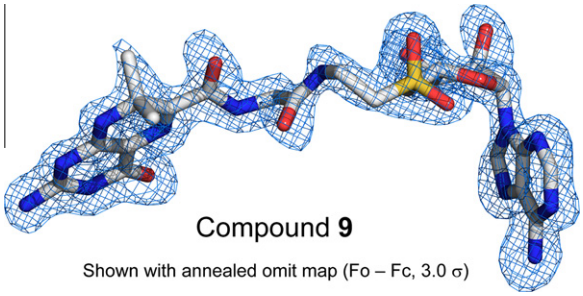
A series of novel arylidenehydantoin phenylpiperazine derivatives were synthesized and evaluated towards α_1-adrenoceptor antagonistic properties in vitro. SAR-analysis, basing on crystallographic and molecular modelling studies, was performed.

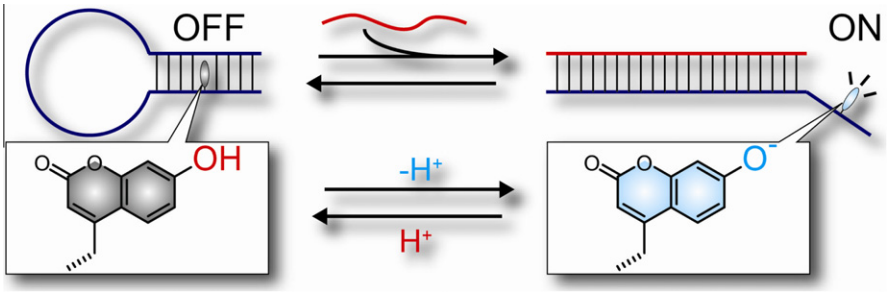




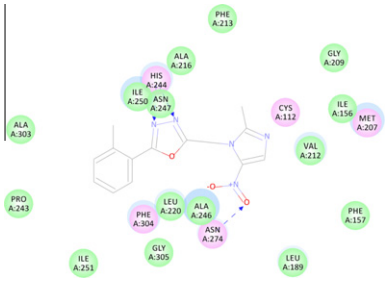


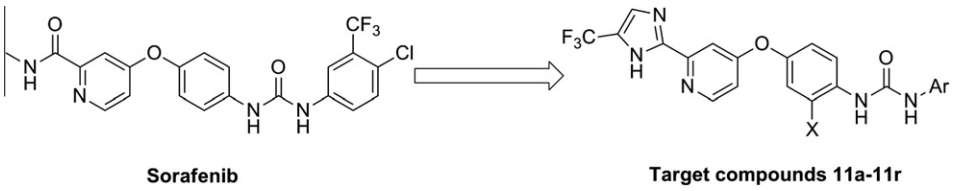




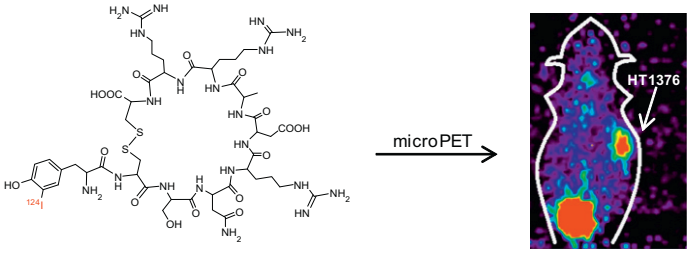


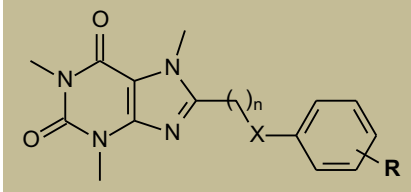
Nitroimidazoles and their derivatives have drawn continuing interest over the years because of their varied biological activities, recently found application in drug development for antimicrobial chemotherapeutics and antiangiogenic hypoxic cell radiosensitizers. In order to search for novel antibacterial agents, we designed and synthesized a series of secnidazole analogs based on oxadiazole scaffold (**4**–**21**). Among these compounds, **4** and **7**–**21** were reported for the first time. These compounds were tested for antibacterial activities against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Staphylococcus aureus*. This new nitroimidazole derivatives class demonstrated strong antibacterial activities. *Escherichia coli* β-ketoacyl-acyl carrier protein synthase III (FabH) inhibitory assay and docking simulation indicated that the compounds 2-(2-methoxyphenyl)-5-((2-methyl-5-nitro-1*H*-imidazol-1-yl)methyl)-1,3,4-oxadiazole (**11**) with MIC of 1.56–3.13 μg/mL against the tested bacterial strains and 2-((2-methyl-5-nitro-1*H*-imidazol-1-yl)methyl)-5-(2-methylbenzyl)-1,3,4-oxadiazole (**12**) with MIC of 1.56–6.25 μg/mL were most potent inhibitors of *Escherichia coli* FabH.





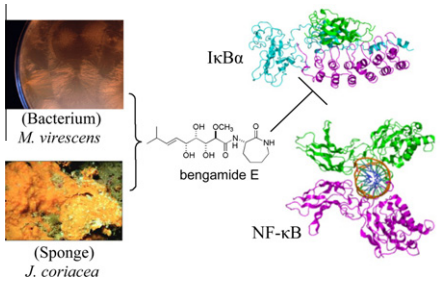
A series of novel bis-aryl ureas derivatives were designed and synthesized as Raf kinase inhibitors based on the lead compound of Sorafenib.

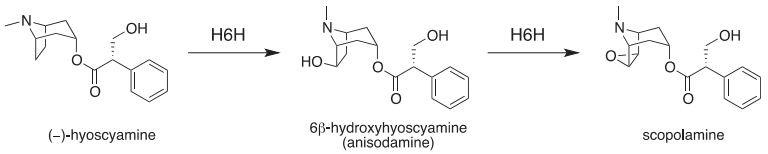


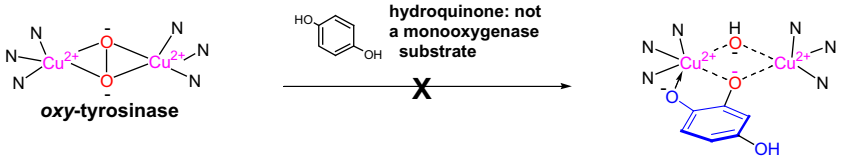


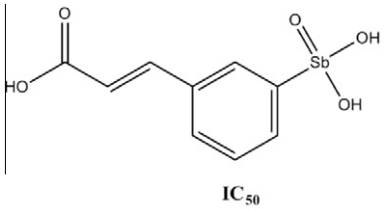
	n	R	X	IC_{50} MAO-A μM	IC_{50} MAO-B μM
3c	1	3-Br	O	34.0	0.148
3i	1	4-Br	O	10.7	0.187
4c	1	3-Br	S	23.8	4.90
5b	2	3-Br	S	No inhibition	5.67

The human MAO inhibition potencies of a synthetic series of caffeine derivatives are reported.







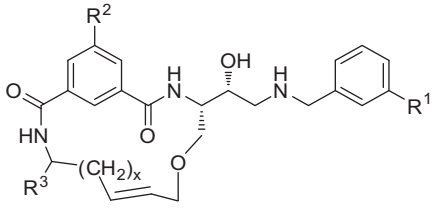


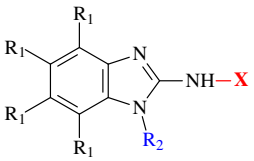
IC_{50}

Cdc25a: **0.11 ± 0.01 μM**

Cdc25b: **0.60 ± 0.07 μM**

Cdc25c: **>>10 μM**



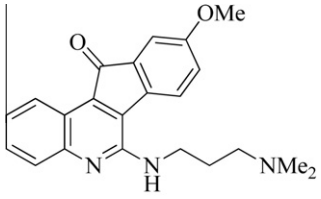


2a: R_1 = Br; R_2 = H, X = $(CH_2)_2$-NH_2; LD_{50} = 7.22±1.05 μM

2d: R_1 = Br; R_2 = H, X = $(CH_2)_2$-$N(CH_3)_2$; LD_{50} = 9.37±1.05 μM

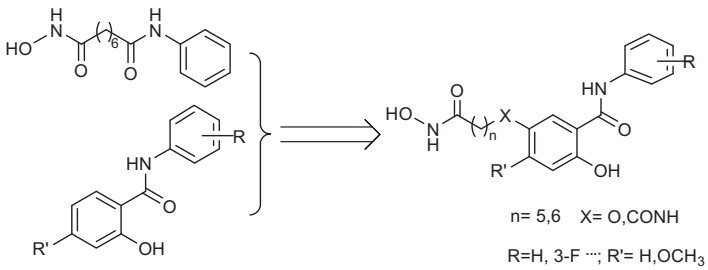
5b: R_1 = I; R_2 = H, X = $(CH_2)_2$-$N(CH_3)_2$; LD_{50} = 7.37±1.02 μM

6: R_1 = I; R_2 = CH_3, X = $(CH_2)_2$-NH_2; LD_{50} = 4.75±1.02 μM

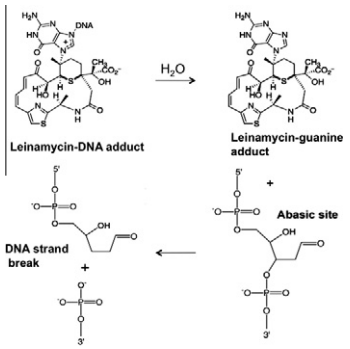


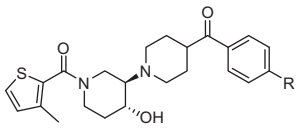
5b

Compound **5b** was the most active with a mean GI_{50} value of 3.39 μM, and intercalates DNA, induces cell cycle arrest at G2/M phase via cleavage of PARP, induces caspase-3 and caspase-8 activities and consequently to cause the cell death.



N-Aryl salicylamide and the pharmacophore of HDAC inhibitor (hydroxamic acid) were incorporated to present a novel class of EGFR–HDAC dual inhibitors.

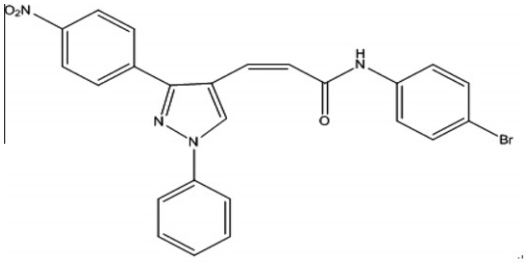




9g, R = F
$K_{i\text{-}VAChT}$ = 11.4 nM
K_i-σ_1 = 12125 nM
K_i-σ_2 = 4219 nM
σ_1/VAChT = 1063
σ_2/VAChT = 370
Log P = 2.53

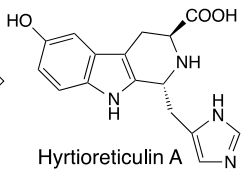
10g, R = OCH_3
Ki-VAChT = 10.2 nM
Ki-σ_1 = 15300 nM
Ki-σ_2 = 20700 nM
σ_1/VAChT = 1500
σ_2/VAChT = 2030
Log P = 2.51

In present study, a series of 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-*N*-phenylacrylamid derivatives (**5a**–**8d**) were designed, synthesized, and evaluated for HDAC inhibition and tumor cell antiproliferation. All of these compounds are reported for the first time, the chemical structures of these compounds were confirmed by means of ^{1}H NMR, ESI-MS and elemental analyzes. Among the compounds, compound **8c** showed the most potent biological activity against HCT116 cancer cell line (IC_{50} of 0.42 ± 0.02 μM for HDAC-1 and IC_{50} = 0.62 ± 0.02 for HCT116). The results of Docking simulation and Western-blot demonstrated that compound **8c** with potent inhibitory activity in tumor growth inhibition may be a potential anticancer agent against HCT116 cancer cell.

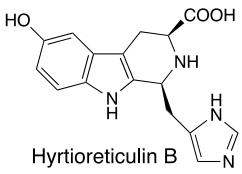


8c

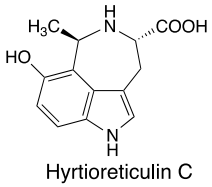
Hyrtios reticulatus



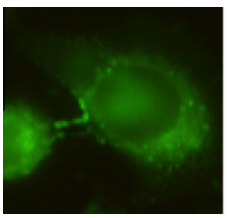
Hyrtioreticulin A

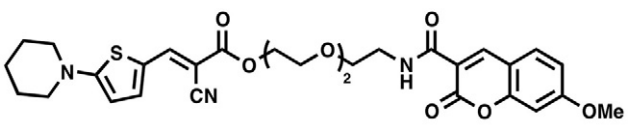


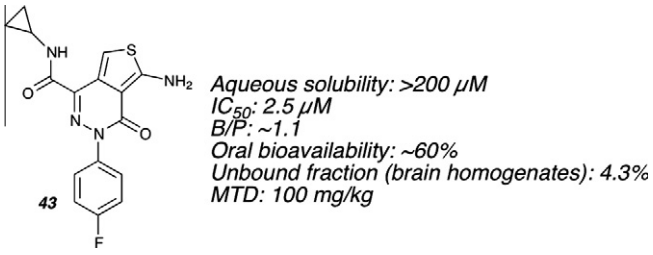
Hyrtioreticulin B

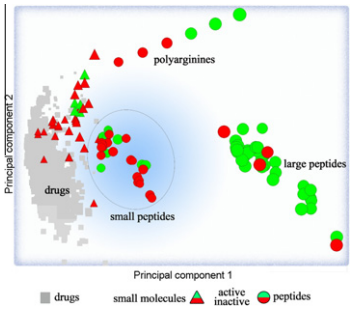


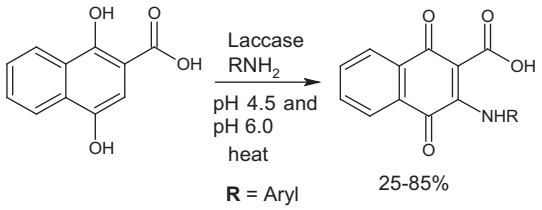
Hyrtioreticulin C

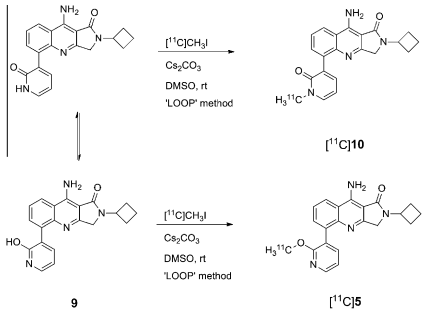


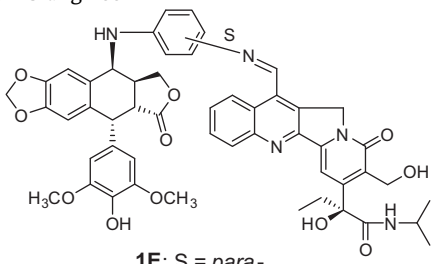




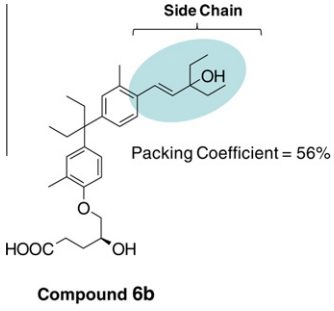




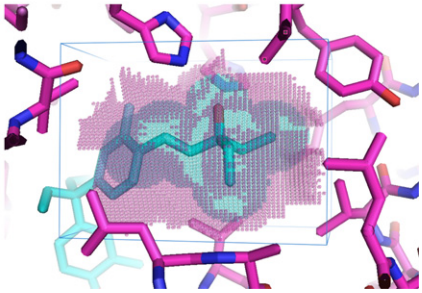


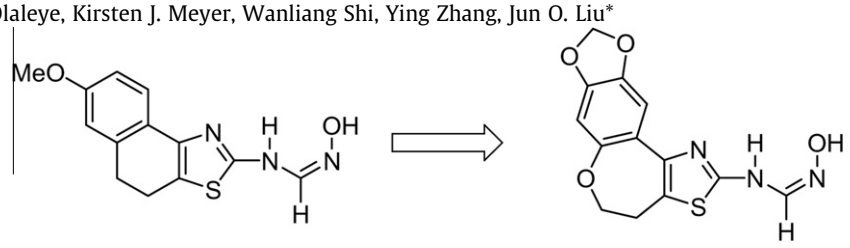


1E: S = *para*-
2E: S = *ortho*-



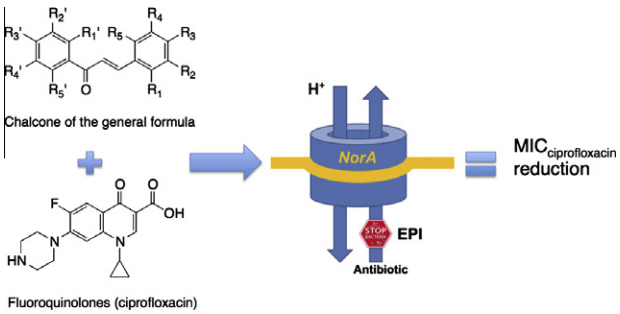
Compound 6b

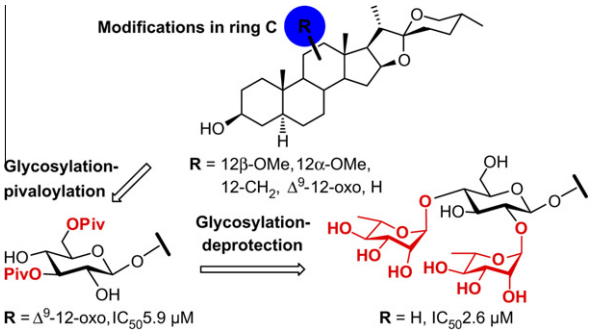


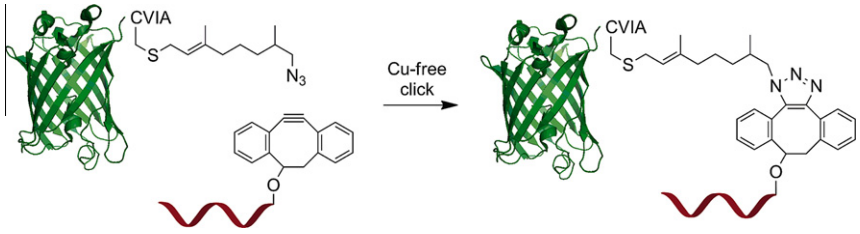


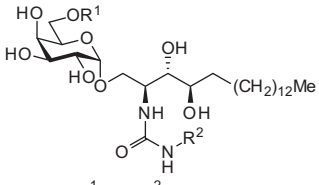
A hit
Mtb-MetAP1a/1c: 5.35/1.33 μM

After SAR
Mtb-MetAP1a/1c: 1.26/0.38 μM

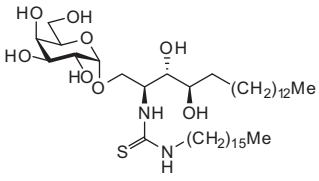




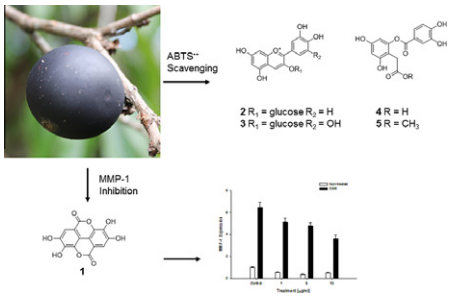




RCAI-105: R^1 = H, R^2 = -$(CH_2)_{23}$Me highly bioactive (Th1-type)
RCAI-84: R^1 = H, R^2 = -$(CH_2)_{15}$Me bioactive
RCAI-107: R^1 = H, R^2 = -$(CH_2)_7$Me almost inactive
RCAI-106: R^1 = Me, R^2 = -$(CH_2)_{23}$Me highly bioactive (Th1-type)
RCAI-108: R^1 = H, R^2 = -$(CH_2)_5$Ph almost inactive



RCAI-91 almost inactive



*Corresponding author
Supplementary data available via SciVerse ScienceDirect

COVER

Dipyrone (metamizol) is a common antipyretic drug and the most popular non-opioid analgesic in many countries. In spite of its long and widespread use, molecular details of its fate in the body are not fully known. Two unknown metabolites were now found, viz. arachidonoyl amides, and positively tested for cannabis receptor binding (CB1 and CB2) and cyclooxygenase inhibition. Two more puzzle pieces of the dipyrone story found! (Rogosch, T.; Sinning, C.; Podlewski, A.; Watzer, B.; Schlosburg, J.; Lichtman, A.H.; Cascio, M.G.; Bisogno, T.; Di Marzo, V.; Nüsing, R.; Imming, P. *Bioorg. Med. Chem.* **2012,** *20,* 103–109.]

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