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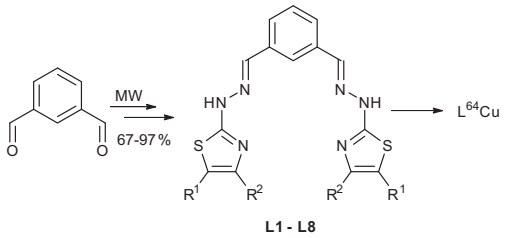
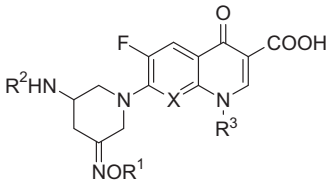
Contents

ARTICLES



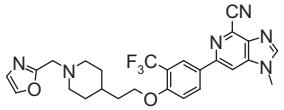


A series of novel 7-(3-alkoxyimino-5-amino/methylaminopiperidin-1-yl)fluoroquinolone derivatives were designed, synthesized and evaluated for their in vitro antibacterial activity compared with gemifloxacin, ciprofloxacin and levofloxacin. All of the target compounds **10**–**27** have good activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, and *Escherichia coli*. In particular, some compounds showed useful activity against several fluoroquinolone-resistant strains, and the most active compound **15** was found to be 16–128, 2–32, and 4–8-fold more potent than the three reference drugs against fluoroquinolone-resistant MSSA, MRSA, and MRSE.

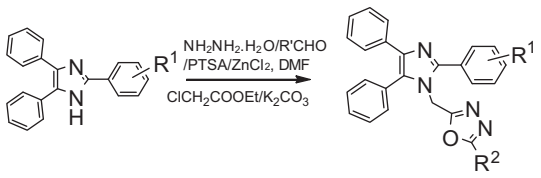
Based on the theoretical understanding of the in vivo lysosomotropism, by manipulating the pk_a of the cathepsin S inhibitors, a set of compounds with pk_a 6–8 were identified to have excellent cell based Lip10 activity, yet avoiding undesired sequestration in spleen.

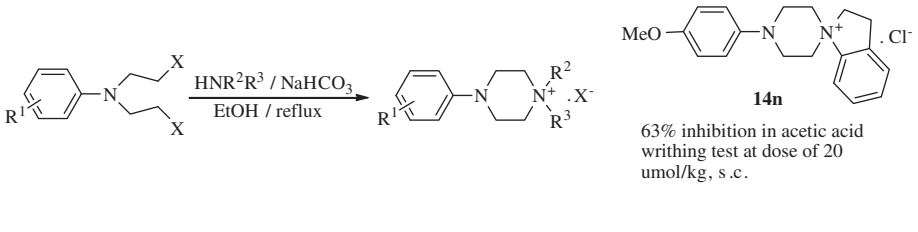
Quantitative description of unbound compound lysosomotropism:

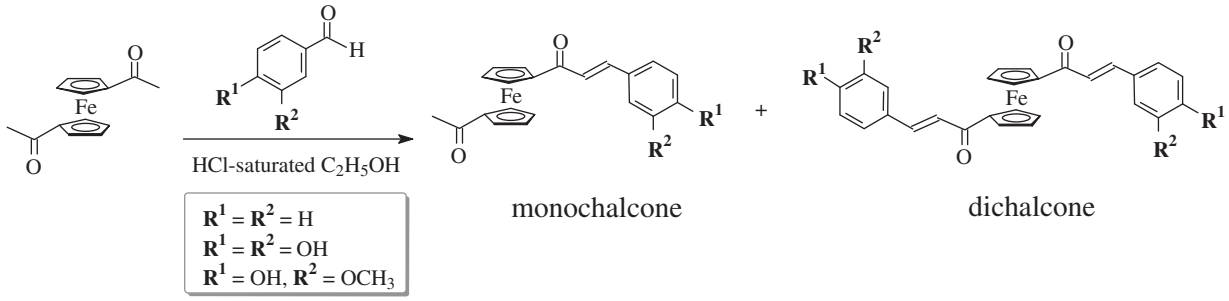
$$f = \frac{10^{pH_M}}{10^{pH_L}} x \frac{10^{pK_a} + 10^{pH_L}}{10^{pK_a} + 10^{pH_M}} = \frac{10^{7.4}}{10^{4.8}} x \frac{10^{pK_a} + 10^{4.8}}{10^{pK_a} + 10^{7.4}}$$



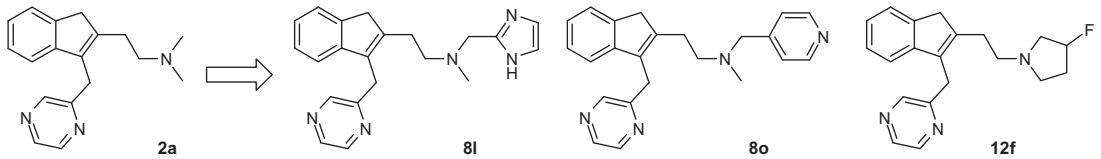
hCatS IC_{50}: 7.9nM
Lip10 IC_{50}: 39nM
F%: 112 (C57 mice)
pK_a: 6.3
Spleen/Plasma ratio: 1.9



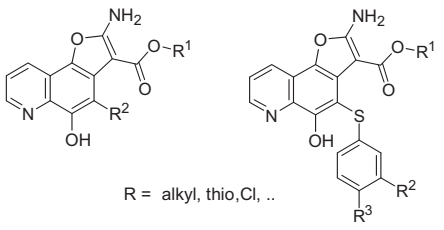




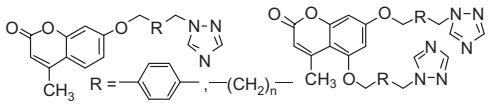
ABTS+, DPPH, and galvinoxyl radical-scavenging evaluations revealed that both Fe(II) in ferrocene and hydroxyl groups in ferrocenyl chalcones played radical-scavenging role.



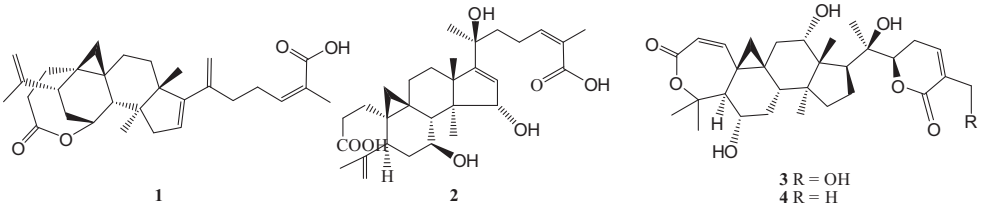
Near exclusive CYP2D6 metabolism in early lead **2a** was addressed by reduction in pK_a of the basic amine. Incorporation of a heteroaryl moiety or a β-fluoro substituent led to the identification of **8l**, **8o**, and **12f**, with promising primary in vitro profiles and reduced biotransformation via CYP2D6.



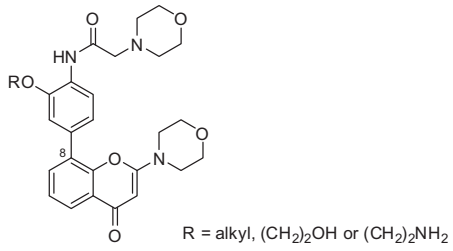
Furo[2,3-*f*]quinolin-5-ols were synthesized and tested for in vitro antifungal activity against pathogenic fungi. Among them tested, many of furo[2,3-*f*]quinolin-5-ols exhibited potent antifungal activity.

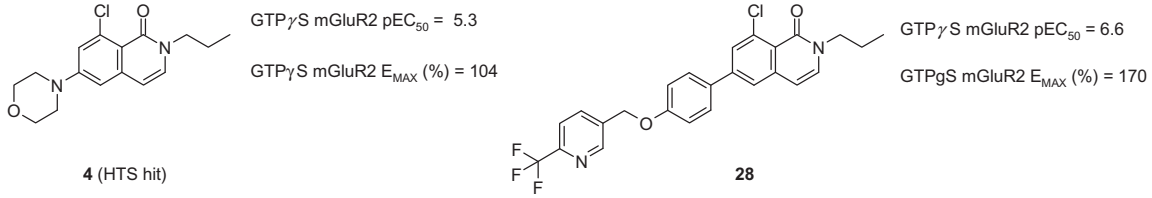


A series of new coumarin-based 1,2,4-triazoles were synthesized and some of them displayed comparable or even better antibacterial and antifungal efficacy compared to reference drugs Enoxacin, Chloromycin and Fluconazole.

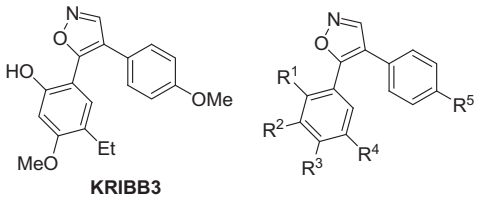


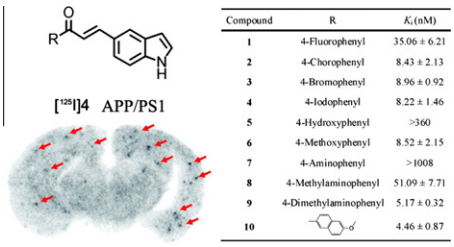
Introduction of an *O*-alkoxyphenyl substituent at the 8-position of the 2-morpholino-4*H*-chromen-4-one pharmacophore enabled regions of the ATP-binding site of DNA-dependent protein kinase (DNA-PK) to be probed further.





A series of *N*-propyl-8-chloro-6-substituted isoquinolones was identified as positive allosteric modulators of metabotropic glutamate receptor 2 (mGluR2 PAM) via high throughput screening (HTS). The subsequent synthesis and initial SAR exploration that led to the identification of compound **28** is described.

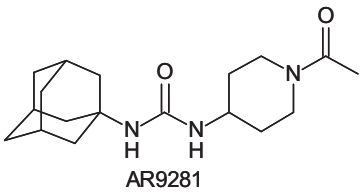


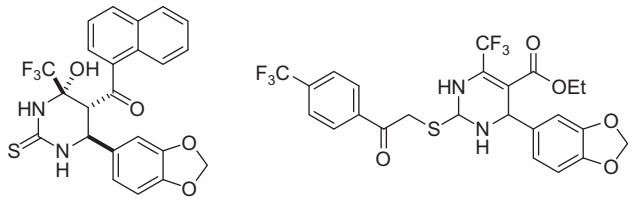


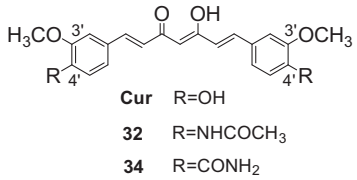
Compound	R	K_i(nM)
1	4-Fluorophenyl	35.06 ± 6.21
2	4-Chorophenyl	8.43 ± 2.13
3	4-Bromophenyl	8.96 ± 0.92
4	4-Iodophenyl	8.22 ± 1.46
5	4-Hydroxyphenyl	>360
6	4-Methoxyphenyl	8.52 ± 2.15
7	4-Aminophenyl	>1008
8	4-Methylaminophenyl	51.09 ± 7.71
9	4-Dimethylaminophenyl	5.17 ± 0.32
10		4.46 ± 0.87

A series of novel indole-chalcone derivatives were synthesized and evaluated as Aβ imaging probes.

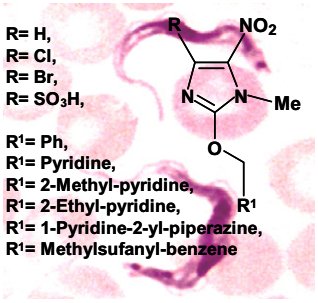
1-(1-Acetyl-piperidin-4-yl)-3-adamantan-1-yl-urea (AR9281) attenuated the enhanced glucose excursion following an intraperitoneal glucose tolerance test and the increase in blood pressure in angiotensin-II-induced hypertension in rats. These effects were dose-dependent and well correlated with inhibition of the soluble epoxide hydrolase (sEH) activity in whole blood.



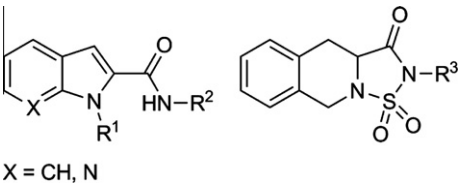




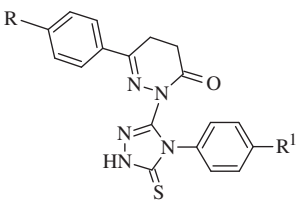
Several synthetic curcumin analogues, especially **32** and **34**, exhibited highly selective cytotoxicity against human epidermoid carcinoma cell line A-431 and human glioblastoma cell line U-251, suggesting their specific potential in the chemoprevention and chemotherapy of skin cancer and glioma.



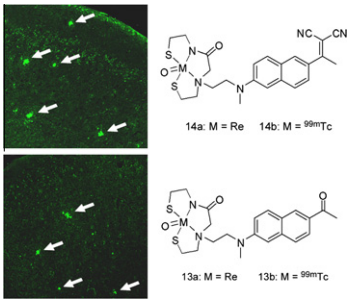
A series of compounds containing a 2-substituted imidazole ring has been synthesized from imidazole and tested for its biological activity against human African trypanosomiasis (HAT) along with its cytotoxicity and solubility.

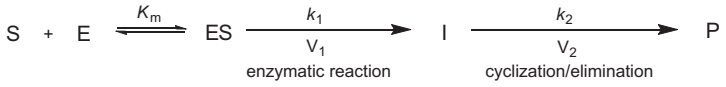


Several thalidomide analogues were synthesized and compared to thalidomide and its more active analogue, lenalidomide, for their ability to inhibit the production of the pro-inflammatory cytokine tumour necrosis factor (TNF)-α and interleukin (IL)-6 by LPS-activated peripheral blood mononuclear cells (PBMCs).



The current work describes the design and synthesis of novel triazole incorporated pyridazinones derivatives with encouraging in vivo antihypertensive activity by non-invasive method using Tail Cuff method.





*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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