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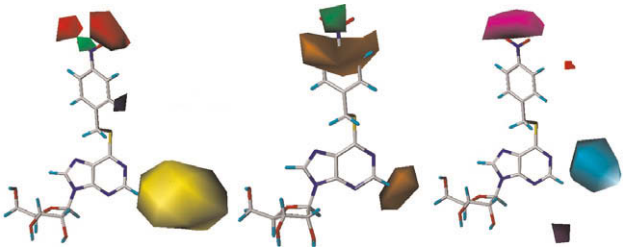
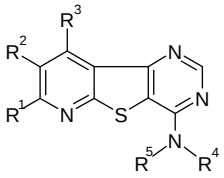
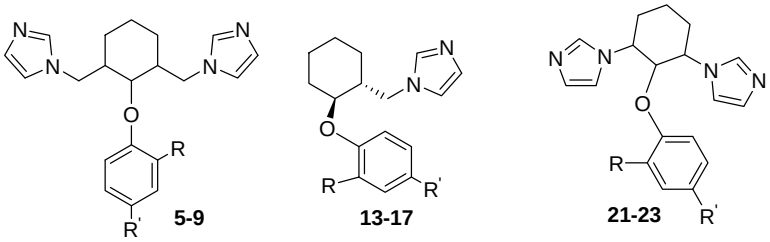
Contents

ARTICLES

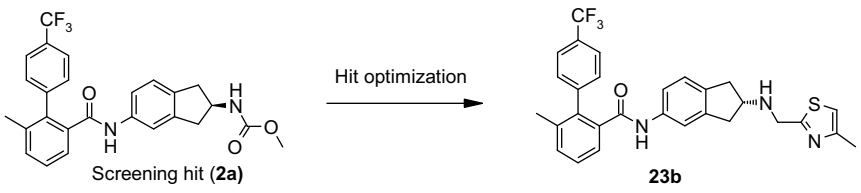


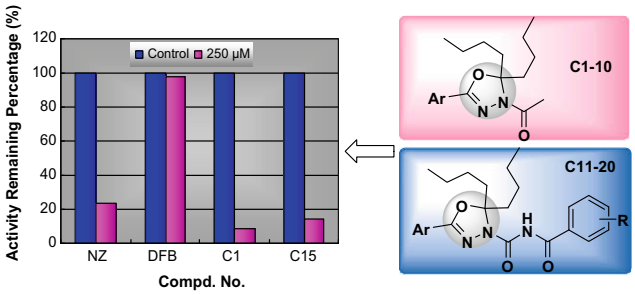
The 3D-QSAR studies involving CoMFA (comparative molecular field analysis) and CoMSIA (comparative molecular similarity indices analysis) on NBMPR analogs developed as human equilibrative nucleoside transporter (hENT1) inhibitors is reported.

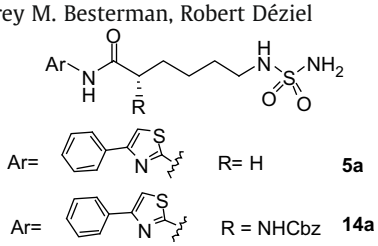




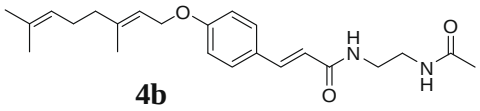
A series of aryloxy cyclohexane-based mono and bis imidazoles were synthesized and evaluated both in vitro and in vivo against *Leishmania donovani*. All the 13 compounds displayed very promising in vitro activity while one compound showed significant in vivo activity.



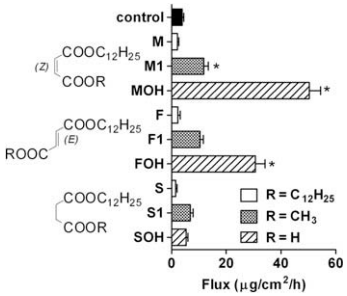




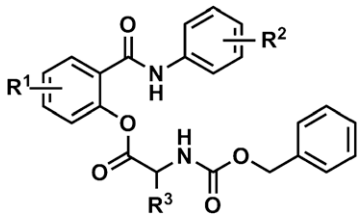
The sulfamide moiety has been utilized to design novel HDAC inhibitors. The potency and selectivity of these inhibitors were influenced both by the nature of the scaffold, and the capping group. Linear long-chain-based analogs were primarily HDAC6-selective, while analogs based on the lysine scaffold resulted in potent HDAC1 and HDAC6 inhibitors.



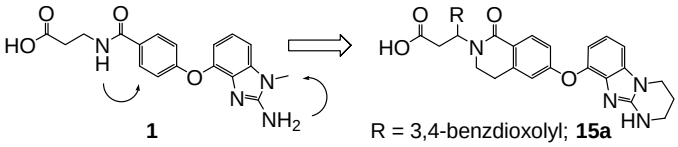
4b TB MIC : 0.1 μg/mL, CLogP : 4.81

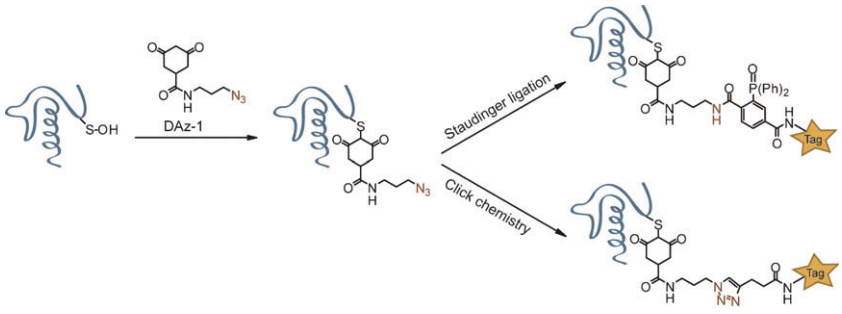


Transdermal permeation enhancers based on dicarboxylic acid esters were studied.

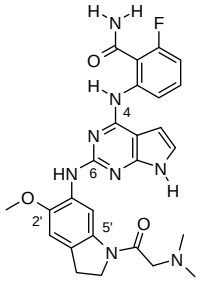


Synthesis of new highly antimicrobial active salicylanilide esters of *N*-protected amino acids is described.



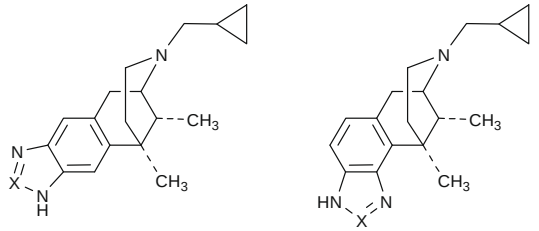


The SAR of C5′ functional groups with terminal basic amines at the C6 aniline of 4,6-bis-anilino-1*H*-pyrrolo[2,3-*d*]pyrimidines is reported. Examples demonstrate potent inhibition of IGF-1R in enzymatic and cellular assays with 1000-fold selectivity over JNK1 and 3.



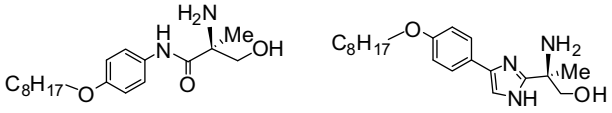
23

IGF-1R Enzyme IC_{50} 1 nM
JNK1 Enzyme IC_{50} 1585 nM
Phospho IGF-1R Cellular IC_{50} 56 nM



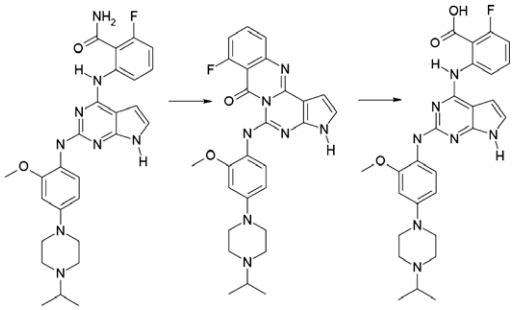
3 **4**

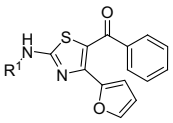
Members of a novel series of 7,8- and 8,9-fused triazole and imidazole analogues of cyclazocine display very high affinity for opioid receptors.



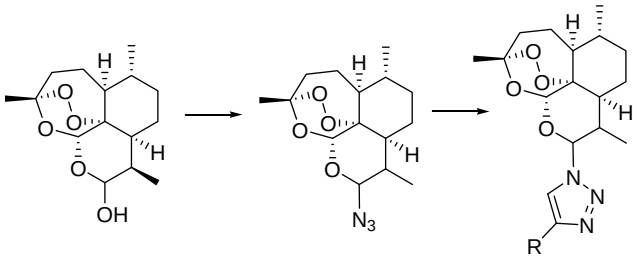
4b (PPI-4621) **10a** (PPI-4691)

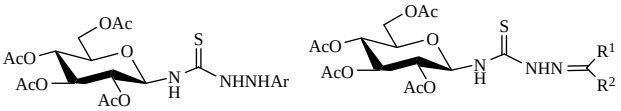
Discovery of two potent and selective sphingosine-1-phosphate receptor agonist chemotypes, alkoxy-phenylamide and alkoxy-phenylimidazole, with potent in vivo oral activity in mouse.





The discovery and synthesis of a series of 2-amino-5-benzoyl-4-(2-furyl)thiazoles as adenosine A_{2A} receptor antagonists are reported.

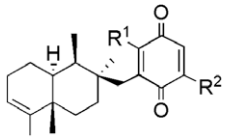




5a-e

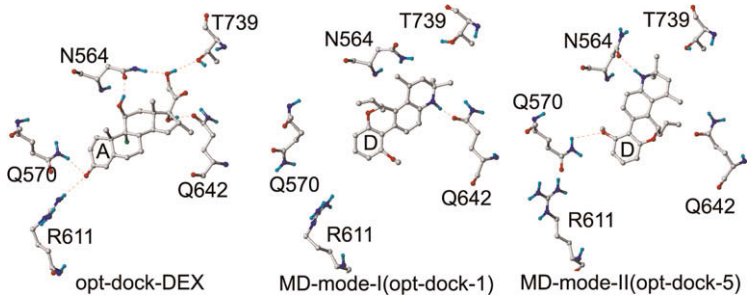
R^1= H, methyl; R^2 = Aryl

4a-k

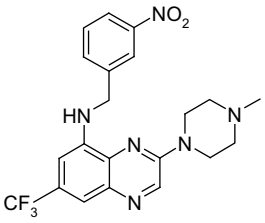


5 R^1 = H R^2 = OCH_3 IC_{50} = 39.50 μM and 19.45 μM
6 R^1 = OH R^2 = OCH_3 IC_{50} = 5.45 μM.
7 R^1 = OH IC_{50} = 6.70 μM.
R^2 = $NHCH_2CH_2SO_3H$

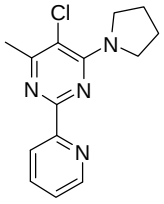
One new sesquiterpene Quinone **5**, together with two known analogues **6** and **7**, had been isolated from the Hainan sponge *Dysidea villosa* with a rare further rearranged drimane skeleton. Compound **7** exhibited the strongest hPTP1B inhibitory activity with an IC_{50} value of 6.70 μM, **6** had significant cytotoxic activity against Hela cell line with an IC_{50} value of 5.45 μM, and new compound **5** showed moderate PTP1B inhibitory activity and cytotoxicity with IC_{50} values of 39.50 and 19.45 μM, respectively.



The AL-438 binding mode in GR ligand binding domain is predicted.

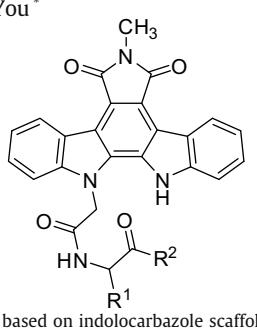


The SAR of a series of quinoxaline inhibitors of c-Met kinase is reported.

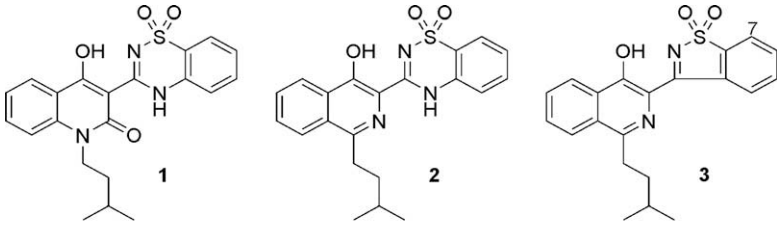


L. donovani IC_{50} 0.53 μM
clogP 2.9

A series of 2-pyridyl pyrimidines has been shown to possess potent in vitro activity against leishmania parasites.

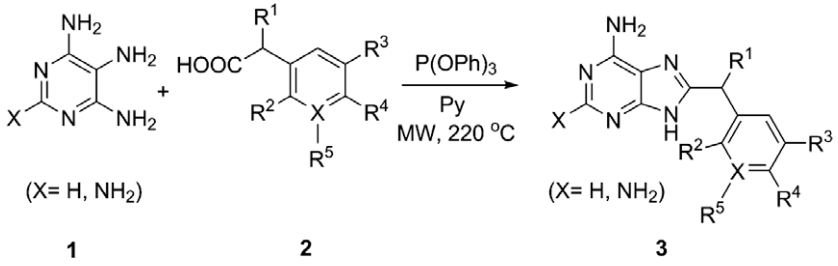


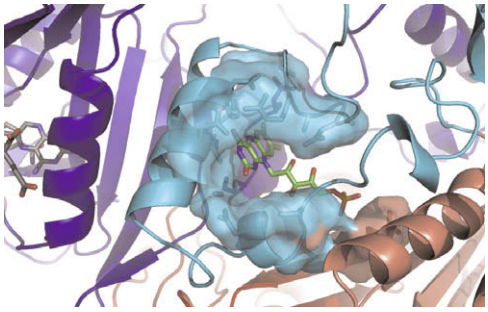
The preparation and evaluation of a novel class of TOPO I inhibitors based on indolocarbazole scaffold are reported.

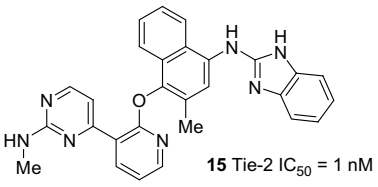


NS5b IC50: 1.1 μM NS5b IC50: 51 μM NS5b IC50: 4.5 μM

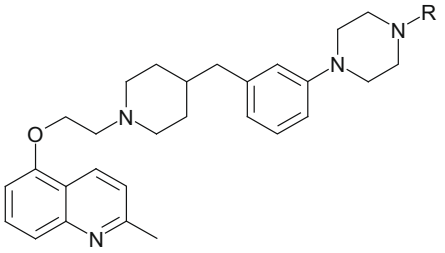
New isoquinoline-based non-nucleoside inhibitors (**2**, **3**) of HCV NS5b RNA-dependent RNA-polymerase are described. Their syntheses and structure–activity relationships are detailed, along with enzyme and cellular activities.



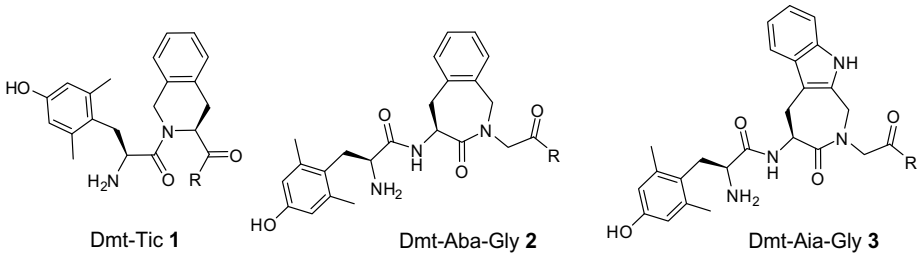


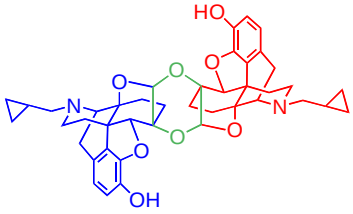


The optimization of a nonselective scaffold into **15**, a potent inhibitor of Tie-2 kinase with selectivity against VEGFR2 kinase, is reported.

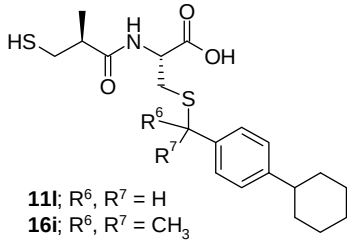


SAR studies on a series of substituted phenyl piperazines and piperidines are described. Several examples are disclosed as potent 5-HT_1 receptor ligands and their PK profiles presented.

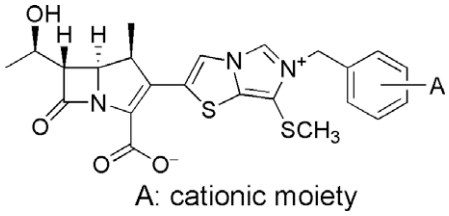




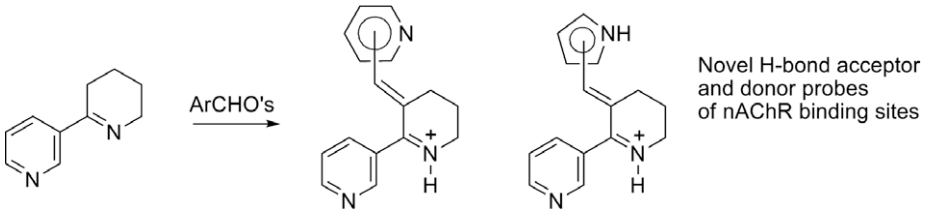
Novel dimeric morphinan derivative with a 1,4-dioxane spacer was synthesized, and showed μ, κ, and putative ε opioid receptor antagonist activities.

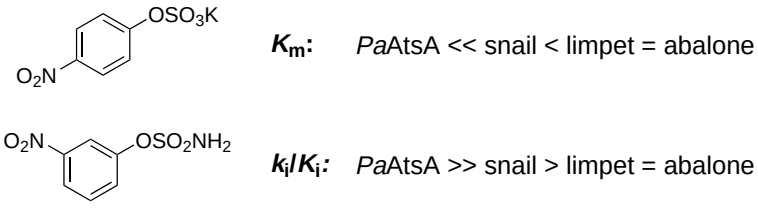


The design, synthesis, and biological evaluation of a new class of *N*-mercaptoacyl-L-cysteine derivatives as leukotriene A_4 (LTA_4) hydrolase inhibitors are reported. Modification at the *para*-substituent of the phenyl ring of *S*-benzyl-L-cysteine moiety improved LTA_4 hydrolase inhibitory activity as well as selectivity over ACE. In particular, compounds **11l** and **16i** having cyclohexyl group exhibited superior features about the two enzymes.

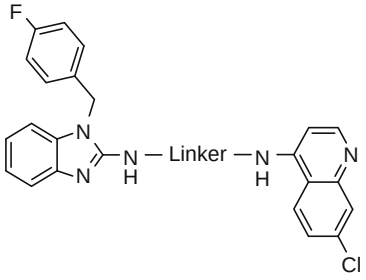


A new series of 1β-methyl carbapenems possessing a 6,7,-disubstituted imidazo[5,1-*b*]thiazol-2-yl group was prepared. Among them, introduction of cationic benzyl moiety to the 6 position of imidazo[5,1-*b*]thiazole resulted in excellent anti-MRSA activity.

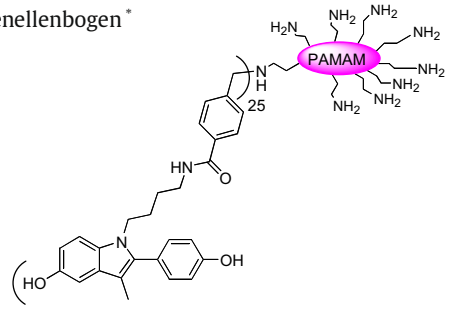




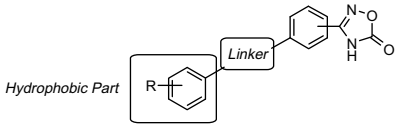
Aryl sulfamates were identified as versatile active-site directed inactivators for a range of sulfatases. They are promising tools for analysis of sulfatase-related processes and for the treatment of associated dysfunctions in vivo.



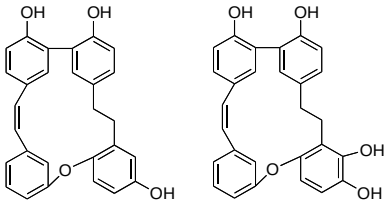
A series of novel hybrids of CQ and astemizole have been shown to possess potent in vitro and in vivo antiplasmodial activity.



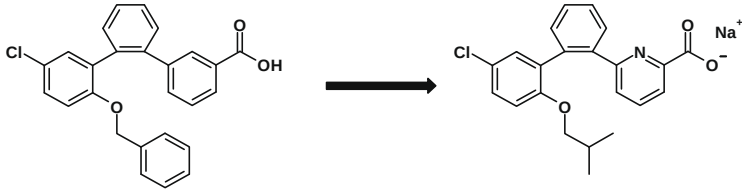
We report the synthesis of *N*-substituted-2-phenylindoles as estrogen receptor ligands. Optimal tether lengths were explored for creating a PAMAM-conjugated indole ligand.



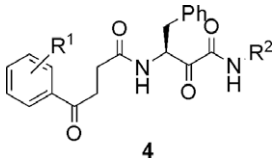
We have successfully obtained 1,2,4-oxadiazol-5-one bioisoteres of Am580 or Tazarotene-like retinoids. In particular compound **4** displays an EC50 of 26 nM on RAR-β.



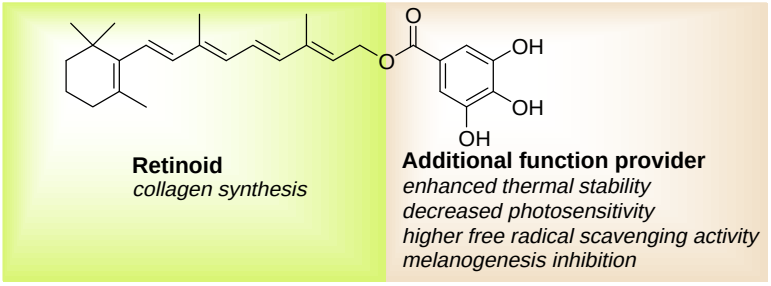
Two bis(bibenzyls), isoplagiochins A (**1**) and B (**2**) have been isolated by the guidance of inhibitory effect of tubulin polymerization from the liverwort *Plagiochila fruticosa* (Plagiochilaceae). Isoplagiochins A and B inhibited the polymerization of tubulin at IC_{50} 50 and 25 μM, respectively. Furthermore structure–activity relationship based on their conformations was discussed.

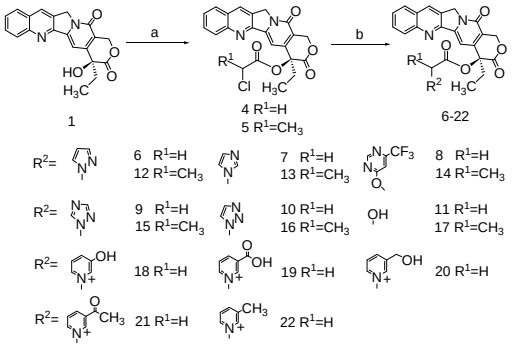


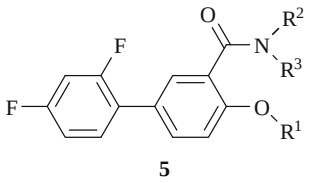
This paper details the discovery and characterization of GSK345931 (**7i**) from the lead compound **4**.



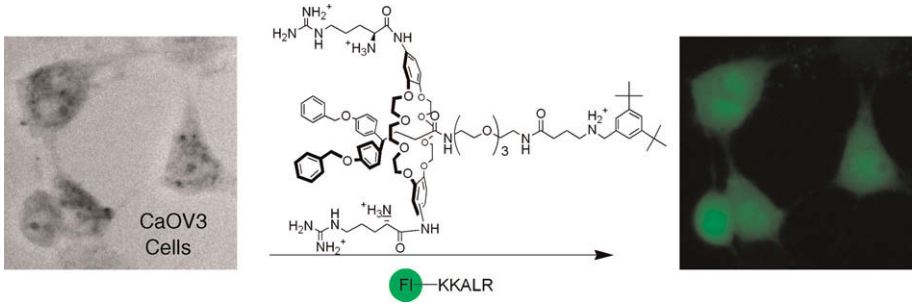
Aryl-4-oxobutanoic acid amide derivatives **4** were designed as acyclic variants of μ-calpain inhibitory chromone and quinolinone derivatives. Of the compounds synthesized, **4c-2**, which possesses a 2-methoxymethoxy group at the phenyl ring and a primary amide at the warhead region of the inhibitor most potently inhibited μ-calpain (IC_{50} = 0.34 μM). Our findings suggest that the 4-aryl-4-oxobutanoic acid amide derivatives should be considered a new family of μ-calpain inhibitors.

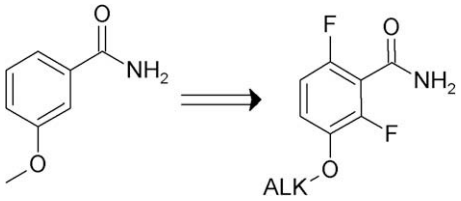


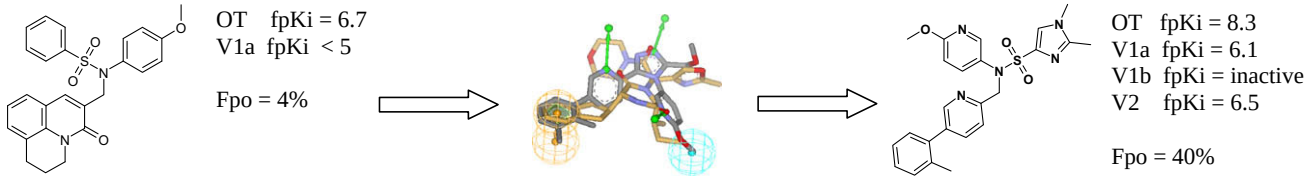


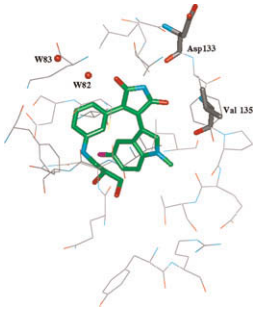


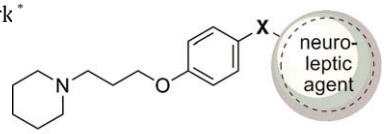
Twenty-one amide derivatives of diflunisal were synthesized starting in three steps. Compound **5m** possesses an excellent anti-inflammatory activity and a good analgesic activity, maybe a potential anti-inflammatory agent.











X = amide, amine, ester
neuroleptic agent = amitriptyline, maprotiline chlorpromazine, chlorprothixene, fluphenazine clozapine

K_i (H_3) = 0.042 - 4.9 nM, D_2 & D_3 ≥ 15 nM

New multiple target drugs based on marketed neuroleptics have been designed, prepared and profiled maintaining dopamine hD_2/hD_3 receptor affinities, reducing histamine hH_1 receptor affinities and introducing high affinity at histamine hH_3 receptors (H_3R). hD_1/hD_5 binding was heterogeneously shifted. The addition of an H_3R pharmacophore to different typical and atypical neuroleptics by amide, amine or ester linkages resulted in a new profile of potential antipsychotics with low nanomolar to subnanomolar H_3R affinities.

OTHER CONTENTS

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Supplementary data available via ScienceDirect

COVER

Overlay of high resolution co-crystal structures of *R*-**22**-ADP (cyan) and **1**-ADP (green) bound in an allosteric binding site of the mitotic kinesin KSP. [Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, J. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5677.]

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