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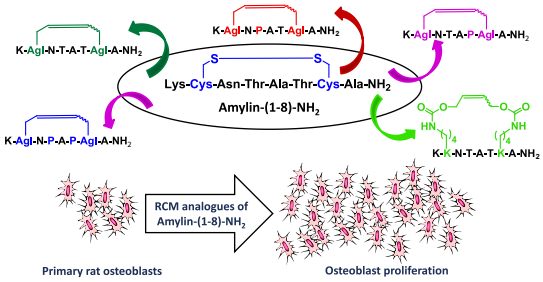
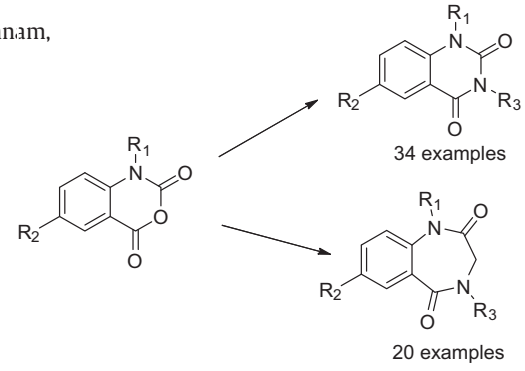
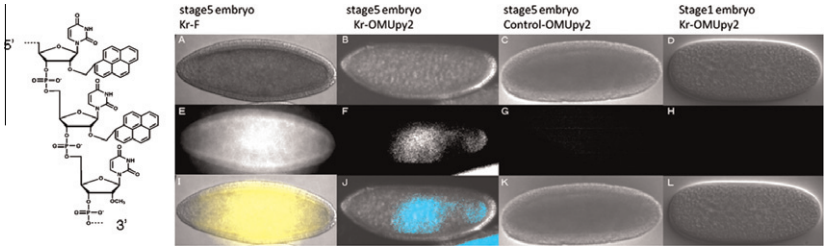
Contents

ARTICLES

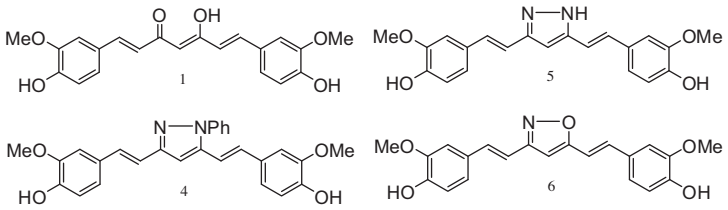




A library of 1,4-benzodiazepines and quinazoline-2,4-diones has been synthesised that display MIC values as low as 0.97 μM against *Trypanosoma brucei*.

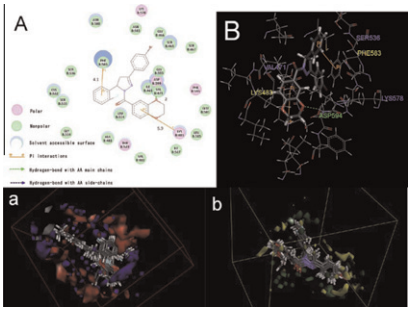


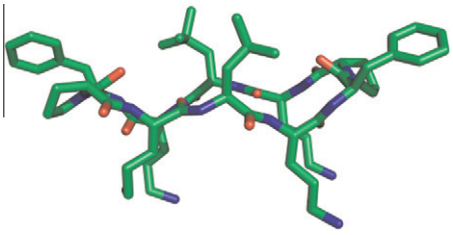
RNA-specific probe (OMUpy2) was found to be applicable to the detection of specific mRNA in *Drosophila* embryos from the view point of temporal and spatial localization in multi cellar specimens.

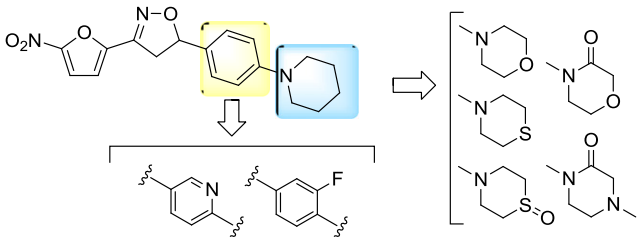


The inhibition of CaMKII kinase activity by natural curcumin I (**1**) and its two pyrazole derivatives (**4, 5**) and one isoxazole derivative (**6**) is reported.

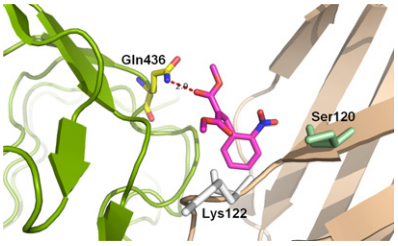
Two series of novel 2,3-dihydrobenzo[*b*][1,4]dioxin-containing 4,5-dihydro-1*H*-pyrazole derivatives **C1**–**C15** and **D1**–**D15** have been synthesized and evaluated for their B-Raf inhibitory and anti-proliferation activities. Compound **C14** ((3-(4-bromophenyl)-5-(2-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)methanone) showed the most potent biological activity against B-Raf^{V600E} (IC_{50} = 0.11 μM) and WM266.4 human melanoma cell line (GI_{50} = 0.58 μM), being comparable with the positive control Erlotinib and more potent than our previous best compound, while **D10** ((2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)(5-(3-fluorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)methanone) performed the best in the **D** series (IC_{50} = 1.70 μM; GI_{50} = 1.45 μM). The docking simulation was performed to analyze the probable binding models and poses and the QSAR model was built for reasonable design of B-Raf inhibitors in future. The introduction of 2,3-dihydrobenzo[*b*][1,4]dioxin structure reinforced the combination of our compounds and the receptor, resulting in progress of bioactivity.

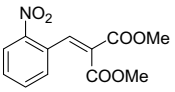






A series of tetracyclic nitrofuran isoxazoline antimicrobial agents was designed and synthesized to increase pharmacokinetic properties including solubility and metabolic stability over on an initial lead.





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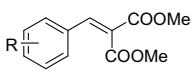

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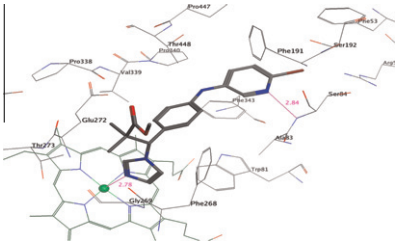
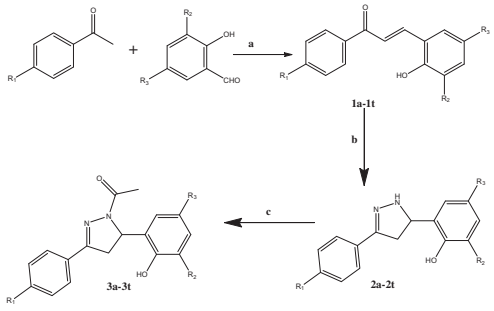
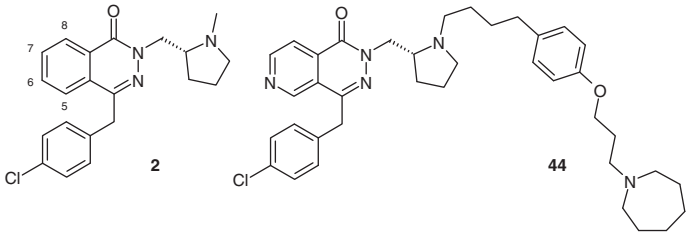


A series of 3-[4-(arylamino)phenyl]-3-(azole)-2,2-dimethylpropanoates were prepared and evaluated for their inhibitory activity against CYP26A1 with molecular modeling studies to determine key binding interactions within the CYP26A1 active site.

A series of novel 4,5-dihydropyrazole derivatives (**3a**–**3t**) containing hydroxyphenyl moiety as potential V600E mutant BRAF kinase ($BRAF^{V600E}$) inhibitors were designed and synthesized. Docking simulation was performed to insert compounds **3d** and **3m** into the crystal structure of $BRAF^{V600E}$ to determine the probable binding model, respectively. Based on the preliminary results, compound **3d** and **3m** with potent inhibitory activity in tumor growth may be a potential anticancer agent. Results of the bioassays against $BRAF^{V600E}$, MCF-7 human breast cancer cell line and WM266.4 human melanoma cell line all showed several compounds had potent activities IC_{50} value in low micromolar range, among them, compound **3d** and compound **3m** showed strong potent anticancer activity, which were proved by that **3d**: IC_{50} = 1.31 μM for MCF-7 and IC_{50} = 0.45 μM for WM266.5, IC_{50} = 0.22 μM for $BRAF^{V600E}$, **3m**: IC_{50} = 0.97 μM for MCF-7 and IC_{50} = 0.72 μM for WM266.5, IC_{50} = 0.46 μM for $BRAF^{V600E}$, which were comparable with the positive control Erlotinib.





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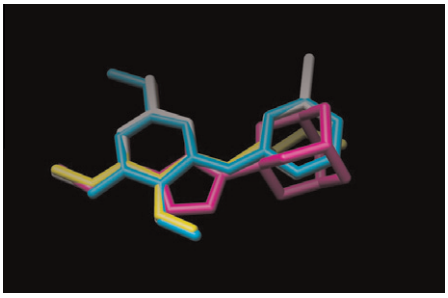
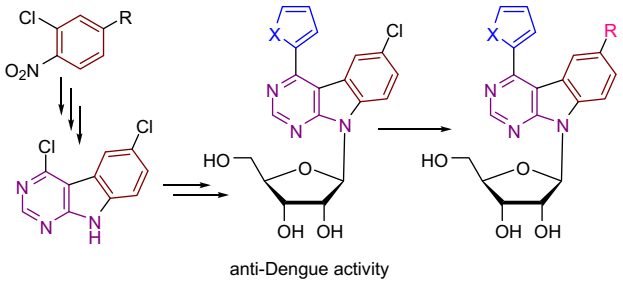
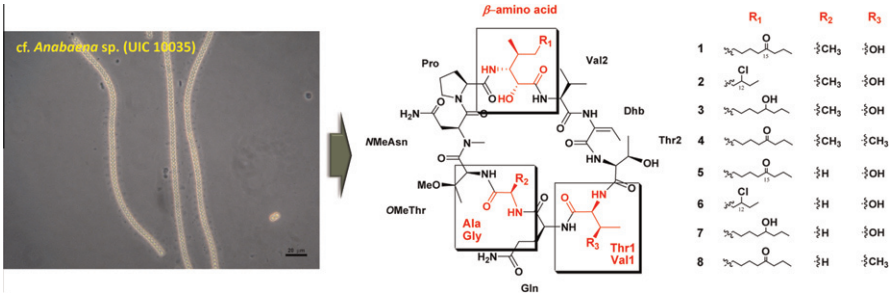
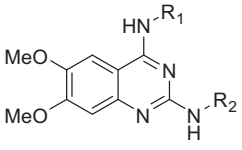
Synthesis and SAR of novel 5-, 6-, 7-, 8-aza, 5,8-diazaphthalazinone derivatives **2,** and dual H_1 H_3 receptor antagonist **44**.

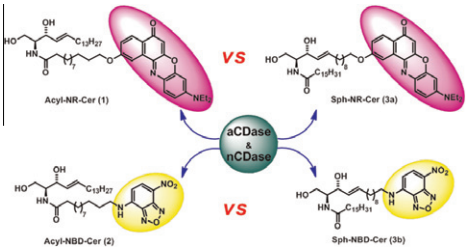






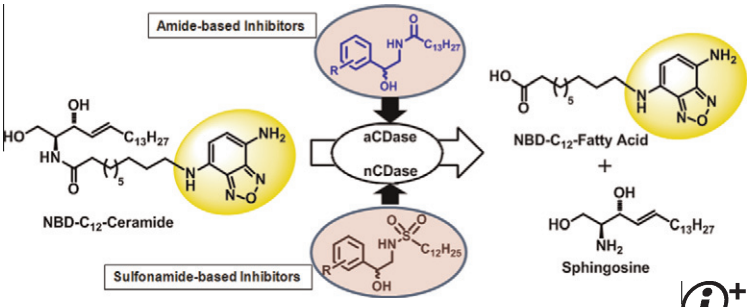


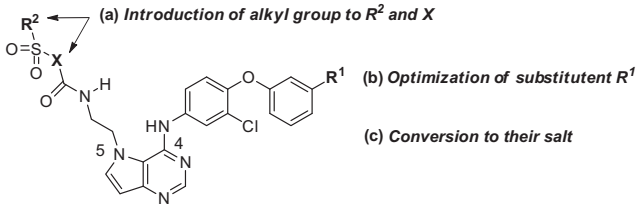
Quinazoline derivatives were synthesized with two steps. These derivatives induced cell apoptosis without the inhibition of EGFR activity. The novel compounds were tested in the ability of CIP2A down-regulation.



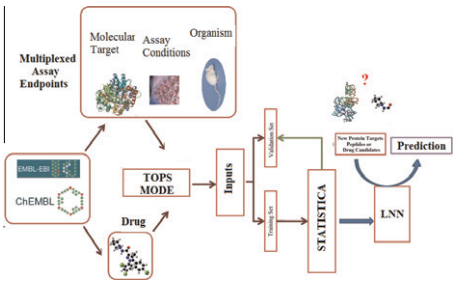
In this study we have synthesized novel Nile Red (NR)-labeled ceramides as substrates of acid and neutral ceramidases. Structure–activity-relationship and kinetic studies with NR- and commercially available NBD-ceramides provide insights into their substrate specificities toward recombinant acid and neutral ceramidases.

In the present study we describe the design and synthesis of series of amide- and sulfonamide-based compounds as inhibitors of recombinant acid and neutral ceramidases. Our results suggest that the electronic effects of the substituents on phenyl ring in B-13 and D-*e*-MAPP analogues have negligible effects either in enhancing the inhibition potencies or for selectivity towards aCDase over nCDase. However, the hydrophobicity and the steric effects of longer alkyl chains (*n*-Pr, *n*-Bu or *t*-Bu groups) at the phenyl ring were found to be important for an enhanced selectivity towards aCDase over nCDase.





1a: $R^1 = CF_3$, $R_2 = CH_3$, X = CH_2
2a: $R^1 = Cl$, $R_2 = CH_3$, X = CH_2



OTHER CONTENT

*Corresponding author

ⓘ+ Supplementary data available via SciVerse ScienceDirect

COVER

The 2011 Nobel Prize in Physiology or Medicine was awarded for the discovery of mechanisms triggering the activation of innate immunity and mediating the communication between innate and adaptive immunity, many of which through the toll-llike receptor (TLR) protein family. Thirteen years after the landmark discovery, targeting TLR signaling has become an important strategy in medicinal chemistry. In this report, we showed that arylidene malonate derivatives (shown in spacefilling representation in magenta) are effective regulators of the horseshoe-shaped TLR4 (shown in ribbon) signaling by targeting the TLR4/MD-2 protein-protein interface. [Zhang, S.; Cheng, K.; Wang, X.; Yin, H. *Bioorg. Med. Chem.* **2012**, *20*, 6074–6080.]

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