ELSEVIER

Bioorganic & Medicinal Chemistry

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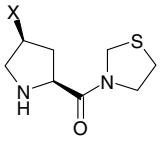
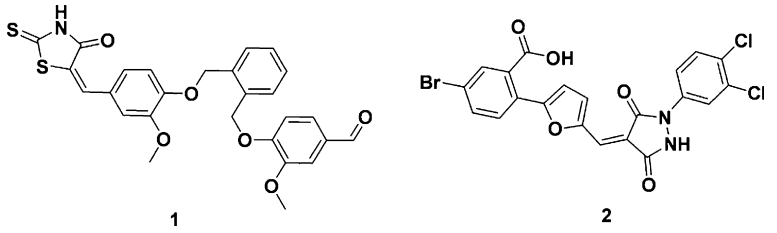
Contents



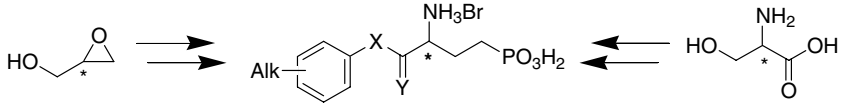
22e: X = 5-MeO-Indolinyl
10 : X = H

Lead optimization of the DPP-IV inhibitor [(*S*)-γ-(arylamino)prolyl]thiazolidine was conducted with focus on the γ-substituent. Compounds with an indoline structure at the γ-position showed potent activity, with the representative compound **22e** 100-fold more potent than the prolylthiazolidine **10** and comparable to NVP-DPP728 despite its lack of an electrophilic group.



1 **2**

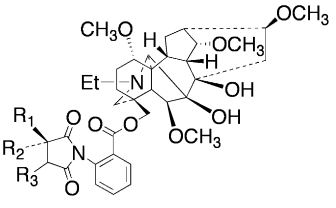
After high-throughput screening against our chemical library, compounds **1** and **2** were identified as *Helicobacter pylori* shikimate kinase inhibitors with IC_{50} values of 5.5 and 6.4 μM, respectively.

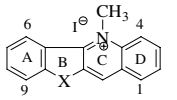


glycidol **γ-amino-phosphonates** **serine**

X = N,O
Y = O,H_2

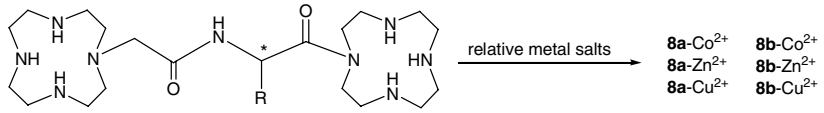
Arylamide, arylether, and arylamine containing γ-aminophosphonates provided potent, subtype-selective agonists and antagonists of the sphingosine 1-phosphate receptors. These phosphate mimetics displayed binding affinities comparable with previously reported phosphate precursors. Two pathways, from glycidol and serine, were pursued for the synthesis of the intermediate phosphonoserine.





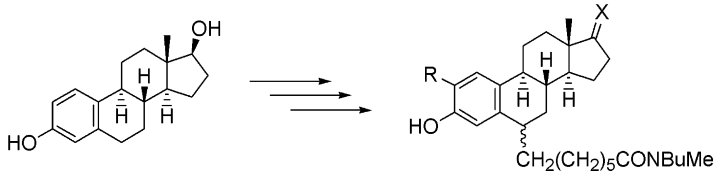
Compd 1; 5-Methyl indolo[3,2-b]quinolinium iodide; X = NH

Compd 5b; 5-Methyl benzothieno[3,2-b]quinolinium iodide; X = S

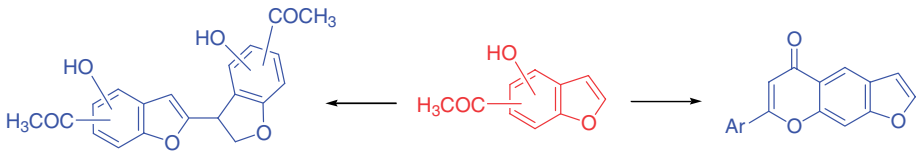


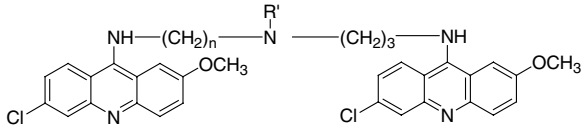
8a R=$CH_2CH(CH_3)_2$
8b R=CH_2OH

The design and synthesis of a small library of 8-amidoflavone, 8-sulfonamidoflavone, 8-amido-7-hydroxyflavone, and heterocyclic analogues of flavopiridol is reported. The potential activity of these compounds as kinase inhibitors was evaluated by cytotoxicity studies in MCF-7, ID-8 cancer cell lines, and inhibition of CDK2-Cyclin A enzyme activity in vitro. The antiproliferative and CDK2-Cyclin A inhibitory activity of these analogues was significantly lower than the activity of flavopiridol. Molecular docking simulations were carried out and these studies suggested a different binding orientation inside the CDK2 binding pocket for these analogues compared to flavopiridol.

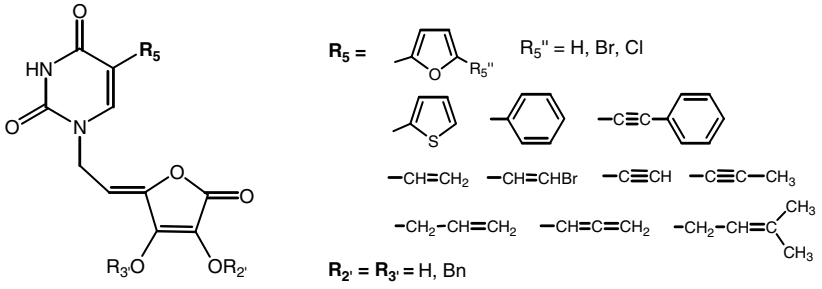


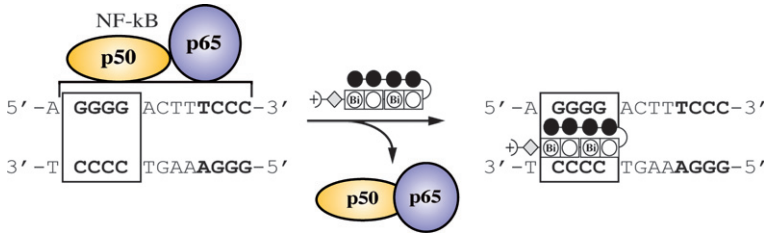
11 (X = O; R = H; C6α)
12 (X = O; R = H; C6β)
13 (X = 17β-OH; R = H; C6α)
14 (X = 17β-OH; R = H; C6β)
15 (X = 17β-OH; R = OMe; C6β)

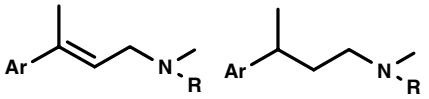




A series of N^{ε}-substituted **6** or **7** carbons of triamine-linked acridine dimers were synthesized and their biological activity was determined. Most acridine dimer derivatives reveal highly potent cancer cell killing activity with COLO205, HAT22T, SK-BR-3 and MOLT-4 human cancer cell lines by in vitro cytotoxicity assays and DNA binding activity. Some acridine dimers also demonstrated various anit-COLO 205 solid tumor activities in vivo. Compound **1** has shown the most potent solid tumor inhibition.

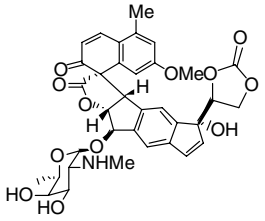




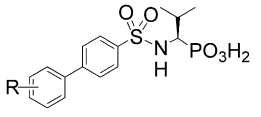


11 Ar=biphen-4-yl, R=CH_3, $K_i\sigma1$ = 1.02±0,2, $K_i\sigma2/K_i\sigma1$ = 157.8
12 Ar=naphth-2-yl, R=$CH_2C_6H_5$, $K_i\sigma1$ = 7.88±0.3, $K_i\sigma2/K_i\sigma1$ = 110.8

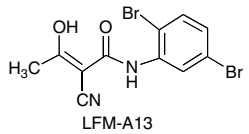
The synthesis, SARs, and molecular modeling studies are reported.



A mimic of the natural product derived DNA bulge-binding agent NCSi-gb was prepared from an accessible compound using an α-fucosylation strategy. The congener shows pronounced affinity for two-base DNA bulges and is active in a functional DNA slippage assay. Fluorescence patterns induced between the agent and synthetic oligos suggest fingerprinting assays may be developed for the detection of bulged sites in DNA.

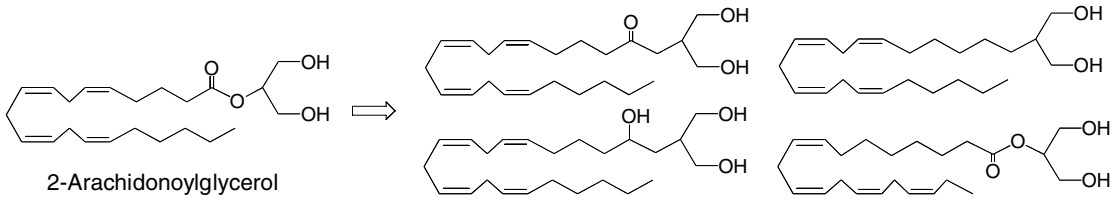


(*R*)-α-Biphenylsulfonylamino 2-methylpropyl phosphonates were synthesized starting from enantiopure (*S*)-*N*-isobutylidene-*p*-bromobenzenesulfinamide as common intermediate. Screening of the new phosphonate inhibitors on MMP-1, -2, -3, -7, -8, -9, -13 and -14 showed IC_{50} in the range of nM in most cases.

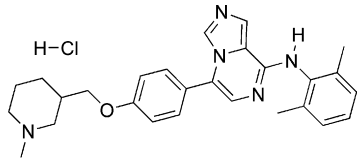


LFM-A13

Molecular modeling studies led to the identification of LFM-A13 (α-cyano-β-hydroxy-β-methyl-*N*-(2,5-dibromophenyl)propenamide) as a potent inhibitor of Polo-like kinase (Plk). LFM-A13 inhibited recombinant purified Plx1, the *Xenopus* homolog of Plk, in a concentration-dependent fashion, as measured by autophosphorylation and phosphorylation of a substrate Cdc25 peptide. LFM-A13 was a selective Plk inhibitor. While the human PLK3 kinase was also inhibited by LFM-A13 with an IC_{50} value of 6 μM, none of the 7 other serine-threonine kinases, including CDK1, CDK2, CDK3, CHK1, IKK, MAPK1 or SAPK2a, none of the 10 tyrosine kinases, including ABL, BRK, BMX, c-KIT, FYN, IGF1R, PDGFR, JAK2, MET, or YES, or the lipid kinase PI3Kγ were inhibited (IC_{50} values > 200–500 μM). The mode of Plk3 inhibition by LFM-A13 was competitive with respect to ATP with a K_i value of 7.2 μM from Dixon plots. Notably, LFM-A13 delayed tumor progression in the MMTV/*neu* transgenic mouse model of HER2 positive breast cancer at least as effectively as paclitaxel and gemcitabine. These results establish LFM-A13 as a small molecule inhibitor of Plk with in vitro and in vivo anti-proliferative activity against human breast cancer.

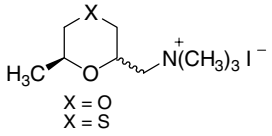


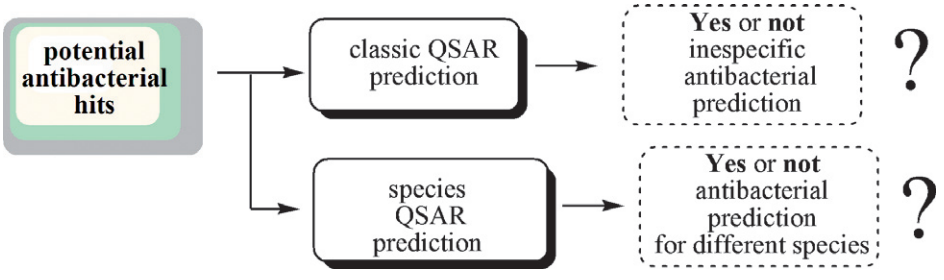
Several structural analogs of 2-arachidonoylglycerol were synthesized and their biological activities as CB1 receptor agonists and CB2 receptor agonists were evaluated.

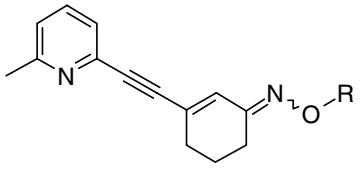


14c·HCl

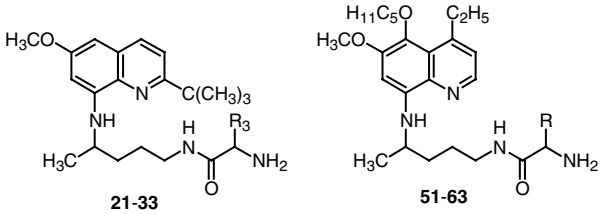
We studied novel c-Src inhibitors as potential therapeutic agents for acute ischemic stroke. Compound **14c·HCl** demonstrated potent c-Src inhibitory activity, remarkable central nervous system (CNS) penetration, and significant neuroprotective efficacy in vivo in rat models.



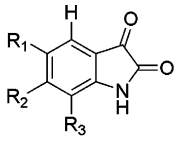




2, ABP688 R = -CH_3
[^{3}H]-ABP688, R = -CT_3



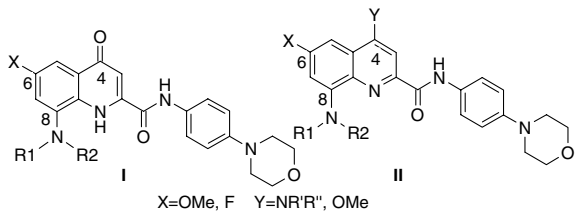
21-33 **51-63**



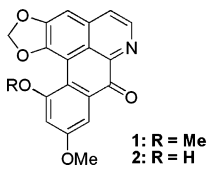
2p R_1, R_2, R_3 = Br

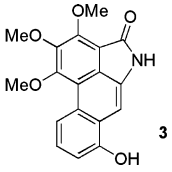
IC_{50} (μM)	U937	Jurkat
	6.67	5.80

MPS amenable syntheses of novel potent 5HT1b antagonists, 6-methoxy-8-amino-4-oxo-1,4-dihydroquinoline-2-carboxylic acid-(4-morpholin-4-yl-phenyl)amides (**I**) and 4-amino-6-methoxy-8-(4-methyl-piperazin-1-yl)-quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amides (**II**), are described.

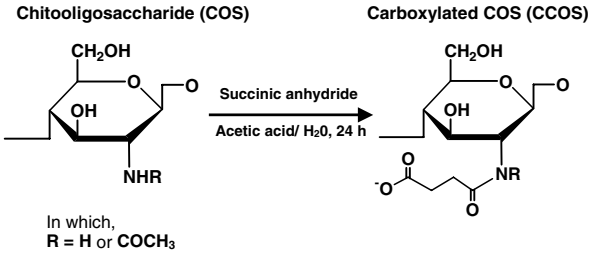


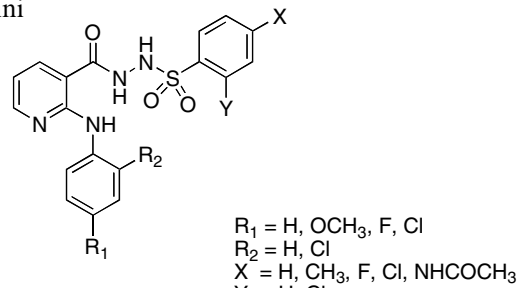
X=OMe, F Y=NR'R'', OMe

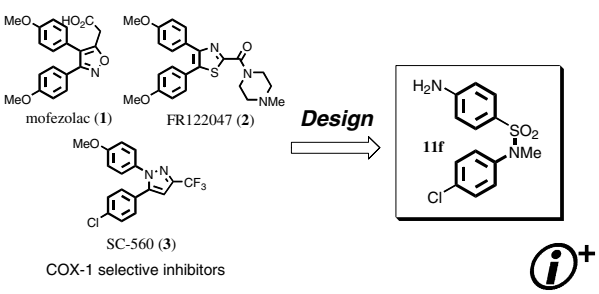


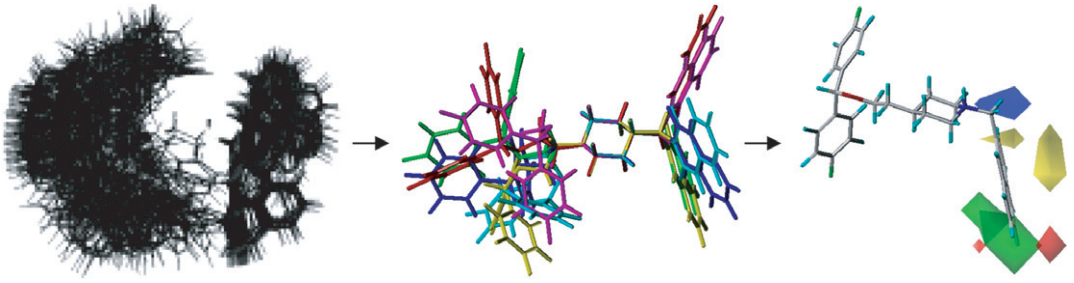


	IC_{50} (ConA-T cell)	IC_{50} (LPS-B cell)
1	3.58 μM	2.15 μM
2	0.81 μM	0.56 μM
3	22.8 μM	41.7 μM



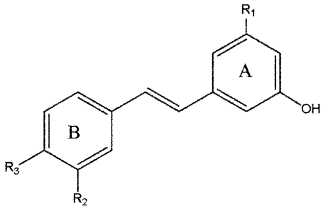






Over 700 low-energy conformers — 6 representative conformers — Predictive & Stable QSAR model

Polymerization of the amyloid β-peptide (Aβ) has been identified as one of the major characteristics of Alzheimer's disease (AD). The inhibitory properties of stilbenes were characterized and compared. These results support the hypothesis that stilbenes could be of therapeutic value in AD.



	R_1	R_2	R_3	
1	OH	H	OH	**resveratrol**
2	OGlc	H	OH	**piceid**
3	OGlc	H	OGlc	**resveratrol diglucoside**
4	OH	OH	OH	**piceatannol**
5	OGlc	OH	OH	**astringine**

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Terfenadine (an antihistamine pulled from the market in 1997) bound to a model of an open form of the homo-tetrameric pore domain of hERG, produced using Schrödinger's "Induced Fit Docking" technology [Farid, R.; Day, T.; Friesner, R. A.; Pearlstein, R. A. *Bioorg. Med. Chem.* **2006,** *14*, 3160–3173].

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