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Bioorganic & Medicinal Chemistry Letters

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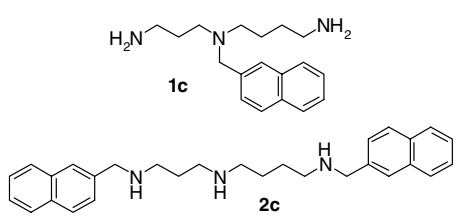
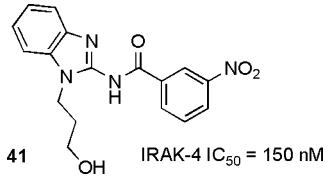
Contents

ARTICLES



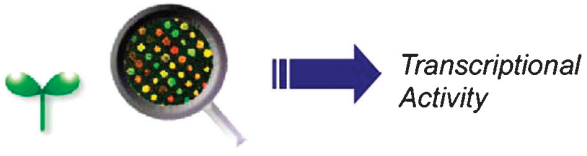
	IC_{50} (μM)	attenuation by 30 μM SPM
1c	9.8	13.1
2c	4.4	2.1

The inhibiting effects of 34 spermidine and spermine derivatives on the binding of [^{3}H]MK-801 to NMDA receptors on rat brain membranes were investigated. Several compounds, including **1c**, appeared to inhibit radioligand binding via the polyamine regulatory site, whereas others, including **2c**, more likely acted directly at the channel.

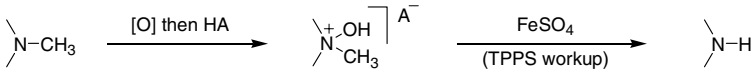


41 IRAK-4 IC_{50} = 150 nM

High-throughput screening of a small-molecule compound library resulted in the identification of a novel series of *N*-acyl 2-aminobenzimidazoles that are potent inhibitors of interleukin-1 receptor-associated kinase-4.

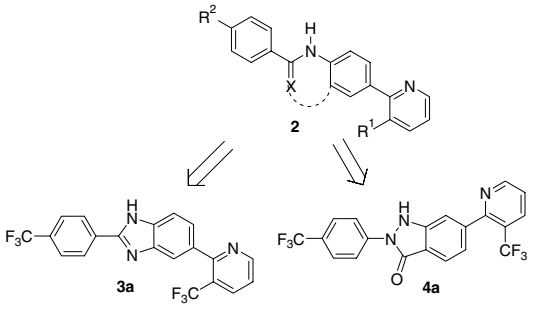


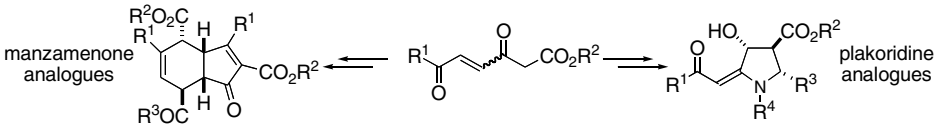
A new screening methodology was developed to uncover natural products that can regulate cellular transcription.

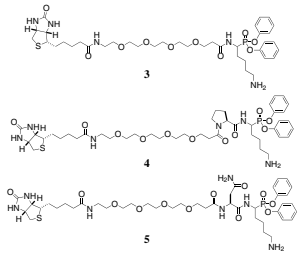


The iron salt-mediated Polonovski reaction efficiently N-demethylates certain opiate alkaloids. In this process, the use of the hydrochloride salt of the tertiary *N*-methyl amine oxide was reported to give better yields of the desired N-demethylated product. Herein, we report further investigation into the use of *N*-oxide salts in the iron salt-mediated Polonovski reaction. An efficient approach for the removal of iron salts that greatly facilitates isolation and purification of the *N*-nor product is also described.

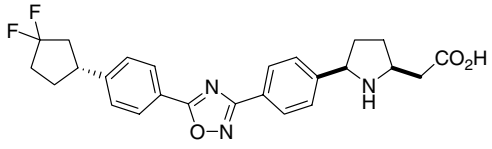
Based on a series of diaryl amides the corresponding inverse amides **2** have been found to be potent TRPV1 receptor antagonists. Benzimidazole (**3**) and indazolone derivatives (**4**) retained good potency in vitro and indazolone **4a** was identified as a novel TRPV1 receptor antagonist suitable for evaluating orally in animal models of analgesia.







Development and applications of a series of diphenylphosphonate-based probes for the trypsin-like serine proteases are reported.



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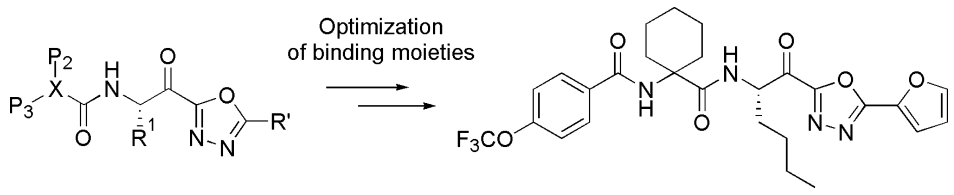
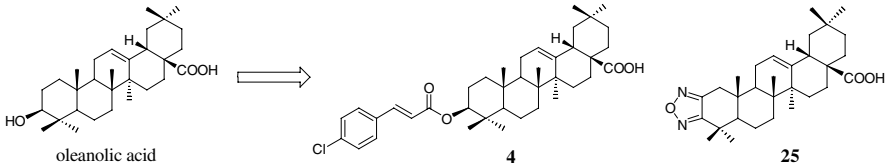
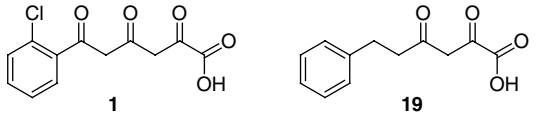




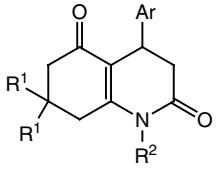
oleanolic acid
(IC_{50} = 14 μM)

4
(IC_{50} = 3.3 μM)

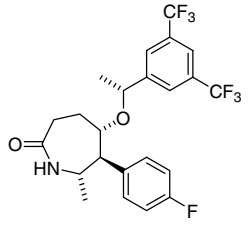
25
(IC_{50} = 11.2 μM)



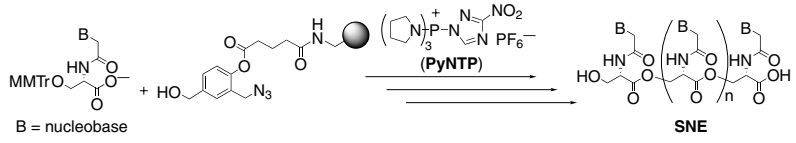
1 19



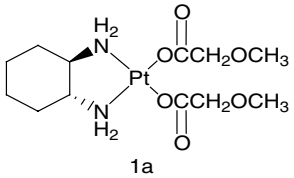
A series of N-substituted 4-aryl-4,6,7,8-tetrahydroquinoline-2,5(1*H*,3*H*)-dione derivatives for biomedical screening were synthesized under microwave irradiation.



9c hNK_1R IC_{50} 0.09 nM



A novel analog of nucleic acids bearing an optically active serine ester backbone: serine-based nucleobase-linked polyester (SNE) was synthesized.

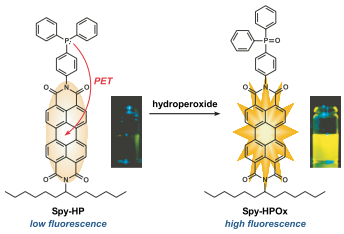


1a

Twelve new cisplatin-type platinum complexes, characteristic of alkoxyacetate as carboxylato ligands, have been synthesized, structurally characterized, and evaluated for their in vitro cytotoxicity against a panel of cultured cell lines. Most of them showed better cytotoxic activity than carboplatin against those selected cell lines.

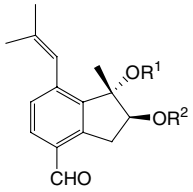
Novel fluorescent probe for detecting hydroperoxides with strong emission in the visible range pp 2943–2946
Nobuaki Soh,* Tomoyuki Ariyoshi, Tuyoshi Fukaminato, Koji Nakano, Masahiro Irie and Toshihiko Imato*

A novel fluorescent probe, a swallow-tailed perylene derivative for detecting hydroperoxides (Spy-HP), containing perylene 3,4,9,10-tetracarboxyl bisimide as the main skeleton in the structure, was developed. Spy-HP quantitatively reacted with hydroperoxides to form its oxidized derivative, Spy-HPOx, and emitted an extremely strong fluorescence ($\Phi \sim 1$) in visible range (λ_{ex} = 524 nm and λ_{em} = 535 nm), as the result of cancelling the photoinduced electron transfer (PET) effect.

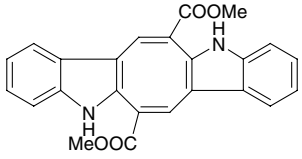


Two novel aromatic valerenane-type sesquiterpenes from the Chinese green alga *Caulerpa taxifolia* pp 2947–2950
Shui-Chun Mao, Yue-Wei Guo* and Xu Shen

Caulerpals A (**2**) and B (**3**), two novel sesquiterpenes possessing an uncommon aromatic valerenane-type carbon skeleton, along with one known metabolite, caulerpin (**4**), have been isolated from the Chinese green alga *Caulerpa taxifolia* (Vahl) C. Agardh. Their structures and relative stereochemistry were elucidated on the basis of extensive spectroscopic analysis. Compounds **2**–**4** were evaluated for their inhibitory activity against hPTP1B and the result showed that only compound **4** had a strong PTP1B inhibitory activity with an IC_{50} value of 3.77 μM.

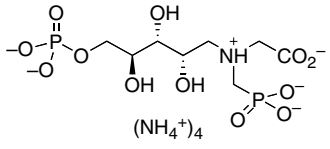


2 R^1 = H, R^2 = Ac
3 R^1 = CH_3, R^2 = H



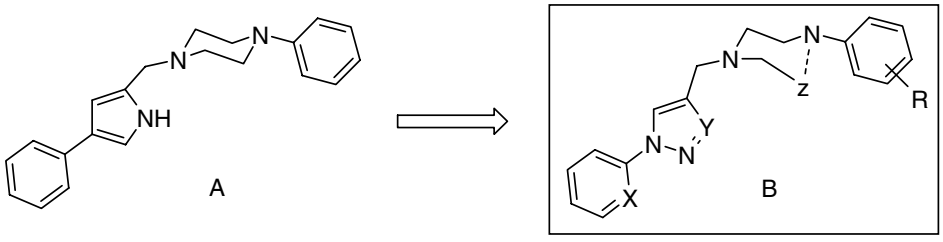
4

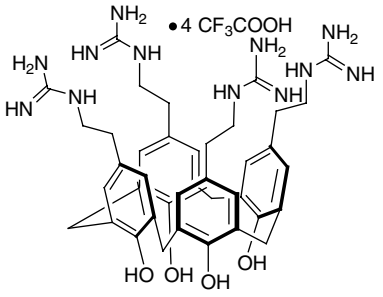
Synthesis and evaluation of a mechanism-based inhibitor of a 3-deoxy-D-*arabino* heptulosonate 7-phosphate synthase pp 2951–2954
Scott R. Walker and Emily J. Parker*

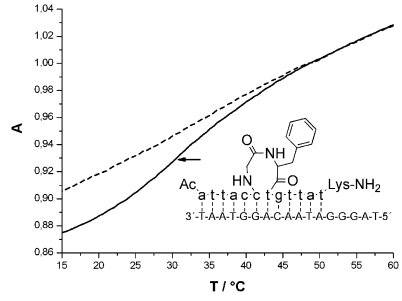


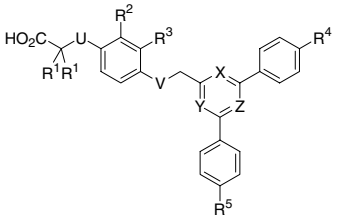
The first mechanism-based inhibitor of a 3-deoxy-D-*arabino* heptulosonate 7-phosphate (DAH7P) synthase has been synthesised in 12 steps from D-arabinose, and has been found to be a very slow binding inhibitor of *Escherichia coli* DAH7P synthase.

Synthesis and biological investigations of dopaminergic partial agonists preferentially recognizing the D4 receptor subtype pp 2955–2959
Stefan Löber, Harald Hübner and Peter Gmeiner*

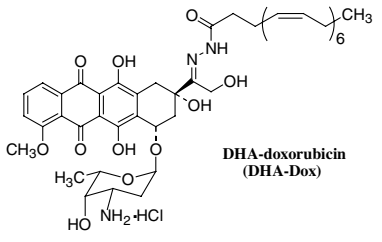




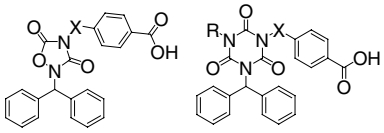




A series of highly potent and selective PPAR agonists is reported.

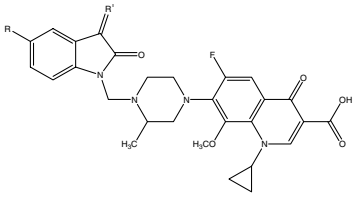


Synthesis of a DHA and doxorubicin conjugate is reported.

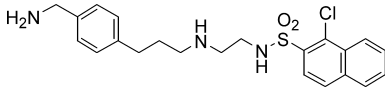


Novel scaffolds based on 1,2,4-oxadiazolidin-3,5-dione and 1,3,5-triazin-2,4,6-trione are described as cytosolic phospholipase $A_2\alpha$ substrate mimetics.

Among the synthesized compounds, 1-cyclopropyl-6-fluoro-8-methoxy-7-[[[N^4-[1′-(5-isatinyl-β-semicarbazo)]methyl]3-methyl]N^1-piperazinyl]-4-oxo-1,4-dihydro-3-quinoline carboxylic acid (**3d**) was found to be the most active compound in vitro with an MIC of 0.0125 μg/mL against MTB and MTR-TB. In the in vivo animal model **3d** decreased the bacterial load in lung and spleen tissues with 3.62- and 3.76-log10 protections, respectively. Compound **3d** was also found to be equally active as gatifloxacin in the inhibition of the supercoiling activity of wild-type *Mycobacterium tuberculosis* DNA gyrase with an IC_{50} of 3.0 μg/mL.

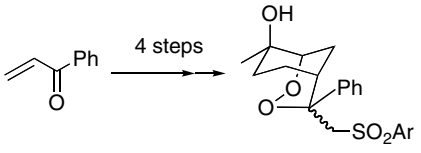


3a-3q

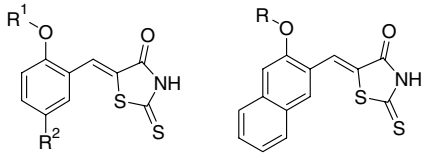


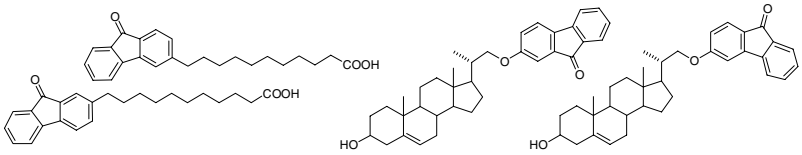
15h IC_{50} = 5 nM

Synthesis and structure–activity relationships of β-tryptase inhibitors are described.



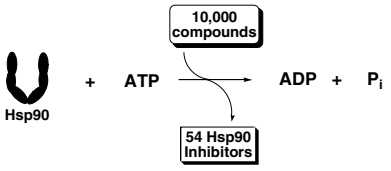
A Diels–Alder/thiol–olefin co-oxygenation approach to the synthesis of novel bicyclic endoperoxides **17a**–**22b** is reported. Some of these bicyclic endoperoxides (e.g., **17b**, **19b**, **22a** and **22b**) have potent nanomolar antimalarial activity equivalent to that of the synthetic antimalarial agent arteflene.



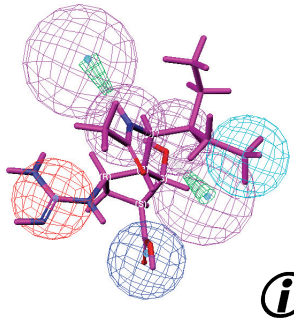


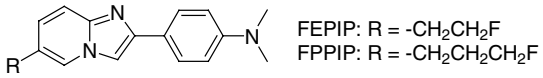
Syntheses are described of analogs of fatty acids and cholesterol containing the fluorenone moiety, which is both photoactivable and fluorescent. Evidence is presented that the sterol analogs can substitute successfully for cholesterol in living cells.

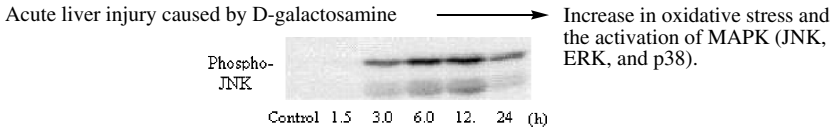
Recently, we reported a useful assay for the determination of Hsp90 ATPase activity. Using this assay, high-throughput screening of ~10,000 compounds was performed to determine the feasibility of this assay on large scale. Results from high-throughput screening indicated that the assay was reproducible (av Z-factor = 0.80) and identified 0.57% of the compounds as Hsp90 inhibitors that exhibited IC_{50}s less than 20 μM. The structures of several of these inhibitory scaffolds are reported along with their IC_{50} values.



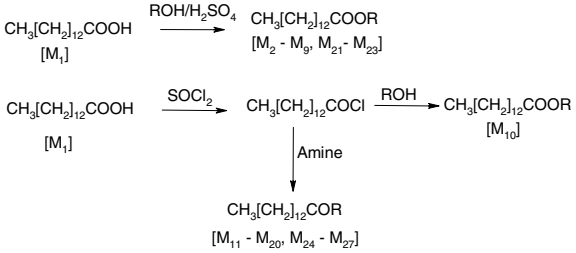
A quantitative pharmacophore hypothesis for AIV neuraminidase inhibitors was built based on 22 compounds with great molecular diversity and bioactivity, and validated using 88 compounds to be highly predictive.



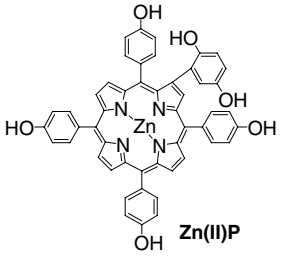




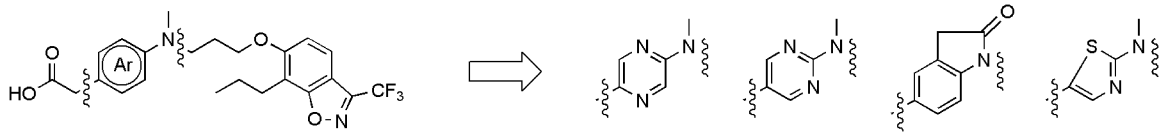
Oxidative stress and the activation of JNK and ERK took place almost simultaneously in the rat liver by intraperitoneal administration of D-galactosamine, followed by the activation of p38 MAPK.

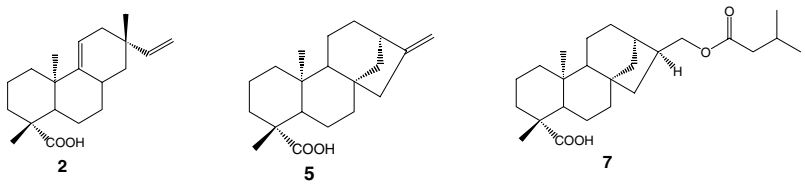


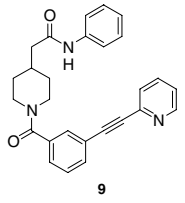
QSAR study of synthesized myristic acid derivatives as antibacterial agents indicated the importance of topological parameters $^{2}\chi^{v}$ and $^{0}\chi^{v}$ in contribution to antibacterial activity.

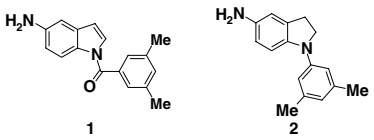


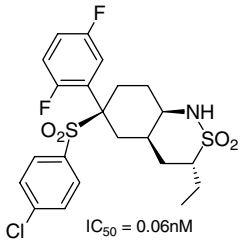
Novel photosensitizers hydroxylporphyrins were synthesized and characterized. The preliminary biological activity studies show that Zn(II)P having high anti-tumor activity(in vitro).











The identification of a potent γ-secretase inhibitor, for example (ED_{50} = 0.06 nM), is reported.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

View of the crystal structure of the DB819-d(CGCGAATTCGCG)$_2$ complex, looking down the minor groove of the DNA (see Campbell, N.H.; Evans, D.A.; Lee, M.P.H.; Parkinson, G.N.; Neidle, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 15.). The DB819 molecule is shown in space-filling mode. Visualisation produced with the VMD program. [Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33.]

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