Issue 81 September 2023

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Issue 81 September 2023

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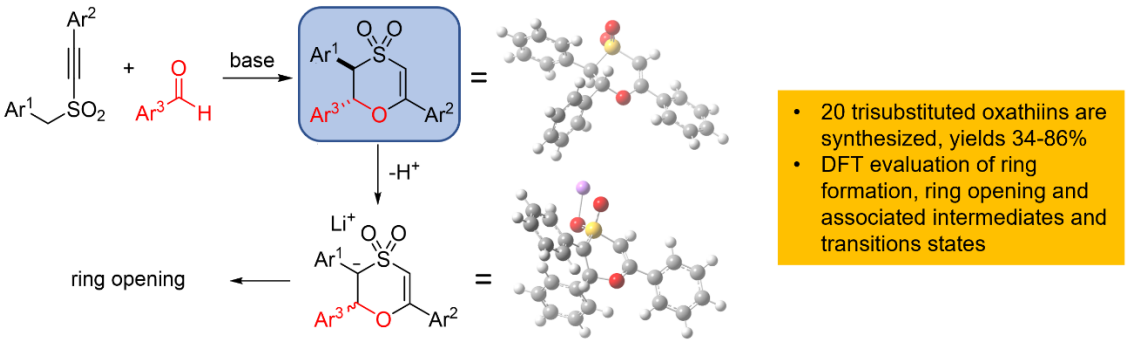
The Synthesis and Base-Induced Breakdown of Triaryl 1,4-Oxathiins—An Experimental and DFT Study

Eric A. Nicol, Matthew Sing, Lilly U. Luu, Erwin J. Remigio, Michelle B. Mills and Adrian L. Schwan*

Molecules **2023**, *28*(17), 6180; https://doi.org/10.3390/molecules28176180

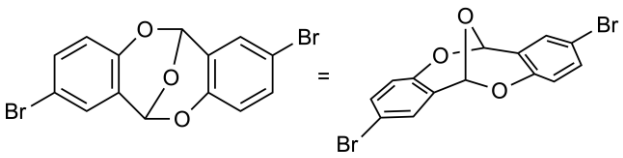


1,4-Oxathiins are valued for a breadth of bioactivities and are known commercial fungicides. This article explores a novel preparation of 2,3,6-trisubstituted 1,4-oxathiin-S,S-dioxides via the reaction of benzyl 1-alkynyl sulfones and aryl aldehydes under basic conditions. A total of 20 examples possessing exclusively a trans arrangement of the 2,3-diaryl substituents are exhibited; the products demonstrate a variation of functional groups on the aryl ring attached to the heterocyclic ring system. The preparation is hindered by the base sensitivity of the products, and a ring-opened by-product typically contaminates the reaction mixture. A DFT assessment of the overall system includes a lithium counterion and offers possible pathways for the incorporation of the aldehyde, the cyclization step and the requisite proton transfers. In addition, the DFT work reveals options for the ring opening chemistry. It appears the trans 2,3-diaryl selectivity is set during the cyclization stage of the reaction sequence. The practical work uncovers a new reaction pathway to create a family of novel 1,4-oxathiin-S,S-dioxides whereas the computational work offers an understanding of the structures and possible mechanisms involved.

2,8-Dibromo-6*H*,12*H*-6,12-epoxydibenzo[*b*,*f*][1,5]dioxocine

R. Alan Aitken, David B. Cordes, An Jie Ler and Aidan P. McKay

Molbank **2023**, *2023*, M1729 (1–5). DOI: 10.3390/M1729



IR, ^{1}H NMR, ^{13}C NMR, X-ray structure

The title dibromodisalicylaldehyde, obtained as a by-product in the m-chloroperoxybenzoic acid oxidation of 5-bromo-2-(methoxymethoxy)benzaldehyde, has been characterised by IR and NMR spectroscopy and X-ray diffraction. The structure features two independent molecules with a π–π stacking interaction between them.

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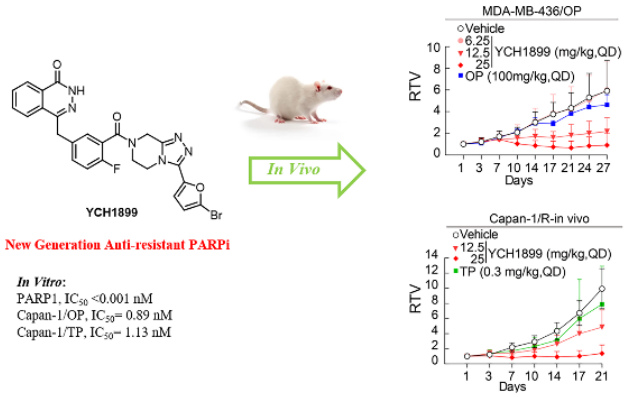
YCH1899, a Highly Effective Phthalazin-1(2*H*)-one Derivative that Overcomes Resistance to Prior PARP Inhibitors

Yuting Sun, Hui Yang, Jiaqi Yuan, Limin Wang, Shanshan Song, Rongrong Chen, Xubin Bao, Li Jia, Tiantian Yang, Xiaofei Zhang, Qian He, Yong Gan, Zehong Miao*, Jinxue He*, and Chunhao Yang*

J. Med. Chem. **2023**, 66, 17, 12284–12303. DOI: 10.1021/acs.jmedchem.3c00821

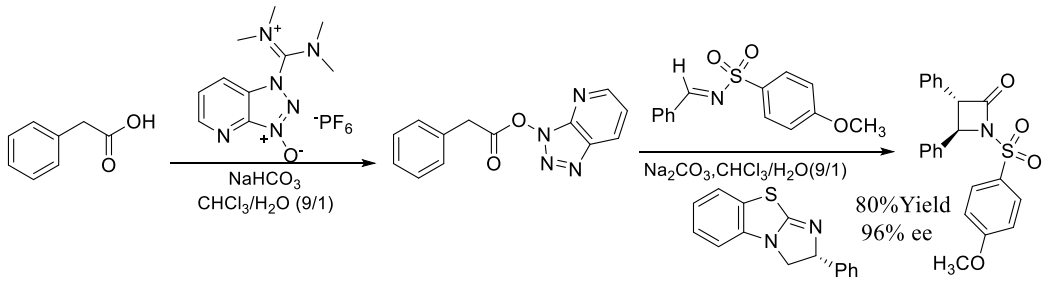


Poly (ADP-ribose) polymerase inhibitors (PARPi) have significant efficacy in treating BRCA-deficient cancers, although resistance development remains an unsolved challenge. Herein, a series of phthalazin-1(2*H*)-one derivatives with excellent enzymatic inhibitory activity was designed and synthesized, and the structure–activity relationship was explored. Compared with olaparib and talazoparib, compound **YCH1899** exhibited distinct antiproliferation activity against olaparib- and talazoparib-resistant cells with IC50 values of 0.89 and 1.13 nM, respectively. Studies on the cellular mechanism revealed that **YCH1899** retained sensitivity in drug-resistant cells with BRCA1/2 restoration or 53BP1 loss. Furthermore, **YCH1899** had acceptable pharmacokinetic properties in rats and showed prominent dose-dependent antitumor activity in olaparib- and talazoparib-resistant cell-derived xenograft models. Overall, this study suggests that **YCH1899** is a new-generation antiresistant PARPi that could provide a valuable direction for addressing drug resistance to existing PARPi drugs.

Catalytic Enantioselective Gilman-Speeter Synthesis of β-Lactams by Nucleophilic Activation of Carboxylic Acids

Vasileios Demos, Adriana Karakoula, Minas Paraskeva, Konstantina Moraiti, Konstantina Petrou, Paraskevi Kermanou, and Plato A. Magriotis*

Results in Chemistry, **2023**, *6*, 101067 https://doi.org/10.1016/j.rechem.2023.101067



A novel Gilman-Speeter synthesis of β-lactams has been developed that was rendered highly enantioselective by virtue of isothiourea catalyst's nucleophilicity. This process depends upon the HATU conversion of carboxylic acids to activated esters which then undergo attack by the homochiral catalyst and subsequently deprotonated by inorganic base to furnish catalytic quantities of the corresponding enolate ions that react with imines to provide the requisite β-lactams in good yields and enantiomeric excesses.

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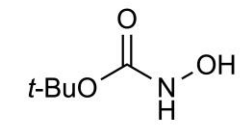
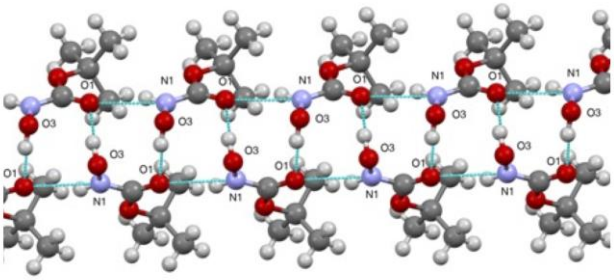
tert-Butyl *N*-Hydroxycarbamate (*N*-Boc-Hydroxylamine)

R. Alan Aitken, David B. Cordes, Aidan P. McKay and Dheirya K. Sonecha

Molbank **2023***, 2023*, M1728 (1–5). DOI: 10.3390/M1728



hydrogen bonding in crystal

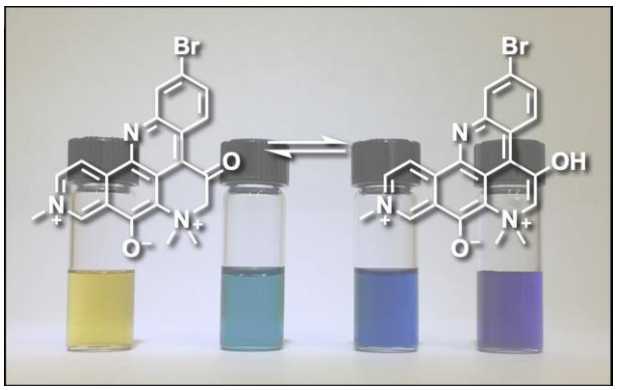


The X-ray structure of the title compound has been determined for the first time. This features ribbons formed by two parallel chains of molecules joined by C=O···H–N hydrogen bonding, which are then cross-linked by C=O···H–O hydrogen bonds. The structure is compared to those of closely related compounds.

Petrosamine Revisted. Experimental and Computational Investigation of Solvatochromism, Tautomerism and Free Energy Landscapes of a Pyridoacridinium Quaternary Salt.

Christopher J. Gartshore, Xiao Wang, Yongxuan Su, Tadeusz F. Molinski* (tmolinski@ucsd.edu)

Mar. Drugs **2023**, *21*, 446-458. **DOI:** doi.org/10.3390/md21080446



Petrosamine (**1**) – a colored pyridoacridine alkaloid from the Belizean sponge, *Petrosia* sp. that is also a potent inhibitor of acetylcholine esterase (AChE) – was investigated by spectroscopic and computational methods. Analysis of the petrosamine free energy landscapes, pK_a and tautomerism revealed an accurate electronic depiction of the molecular structure of **1** as the di-keto form, with net charge of q = +1, rather than a dication (q = +2) under ambient conditions of isolation-purification. The pronounced solvatochromism (UV-vis) reported for **1**, and related analogs, was investigated in detail and is best explained by charge delocalization and stabilization of the ground state (HOMO) of **1** rather than an equilibrium of competing tautomers. Refinement of the molecular structure of **1** by QM methods complements published computational docking studies to define the contact points in the enzyme active site that may improve design of new AChE inhibitors based on the pyridoacridine alkaloid molecular skeleton.
