Issue 82 October 2023

The I.S.H.C. Bulletin

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Issue 82 October 2023

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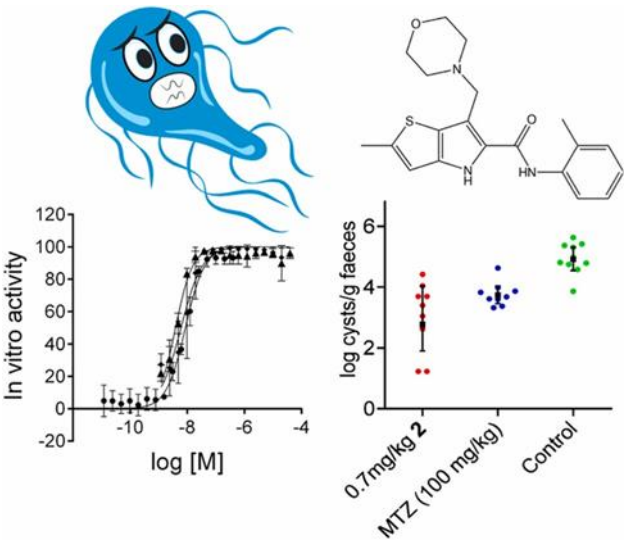
**** SAVE THE DATE: 29th ISHC CONGRESS: 21-26 JULY 2024 in Aveiro, Portugal ****

Thieno[3,2-b]pyrrole 5-carboxamides as potent and selective inhibitors of *Giardia duodenalis*

Christopher JS. Hart, Andrew G. Riches, Snigdha Tiash, Rebecca Abraham, Keely Fayd'Herbe, Ellis Joch, Bilal Zulfiqar, Melissa L. Sykes, Vicky M. Avery, Jan Šlapeta, Sam Abraham, John H. Ryan and Tina S. Skinner-Adams*

Int. J. Parasitol.: Drugs and Drug Resistance, **2023**, 23, 54-62. https://doi.org/10.1016/j.ijpddr.2023.09.002



Giardia duodenalis is the causative agent of the neglected diarrhoeal disease giardiasis. While often self-limiting, giardiasis is ubiquitous and impacts hundreds of millions of people annually. It is also a common gastro-intestinal disease of domestic pets, wildlife, and livestock animals. However, despite this impact, there is no vaccine for Giardia currently available. In addition, treatment relies on chemotherapies that are associated with increasing failure rates. To identify new treatment options for giardiasis we recently screened the Compounds Australia Scaffold Library for new chemotypes with selective anti-Giardia activity, identifying three compounds with sub-μM activity and promising selectivity. Here we extended these studies by examining the anti-Giardia activity of series CL9569 compounds. This compound series was of interest given the promising activity (IC50 1.2 μM) and selectivity demonstrated by representative compound, SN00798525 (1). Data from this work has identified an additional three thieno [3,2-b]pyrrole 5-carboxamides with anti-Giardia activity, including 2 which displayed potent cytocidal (IC50 ≤ 10 nM) and selective activity against multiple Giardia strains, including representatives from both human-infecting assemblages and metronidazole resistant parasites. Preclinical studies in mice also demonstrated that 2 is well-tolerated, does not impact the normal gut microbiota and can reduce Giardia parasite burden in these animals.

International Society of Heterocyclic Chemistry
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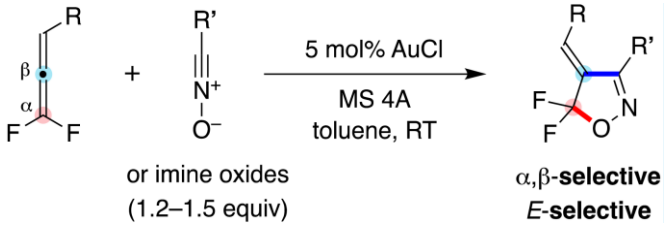
Issue 82 **October 2023**

Fluorine-Activated and -Directed Allene Cycloadditions with Nitrile/Imine Oxides: Synthesis of Ring-Fluorinated Isoxazole Derivatives

Kohei Fuchibe,* Kazuki Sakon, Kyosuke Suto, Reo Eto, Sho Nakazono, and Junji Ichikawa*

Org. Lett. **2023**, *25*, 7258. **DOI: 10.1021/acs.orglett.3c02879**

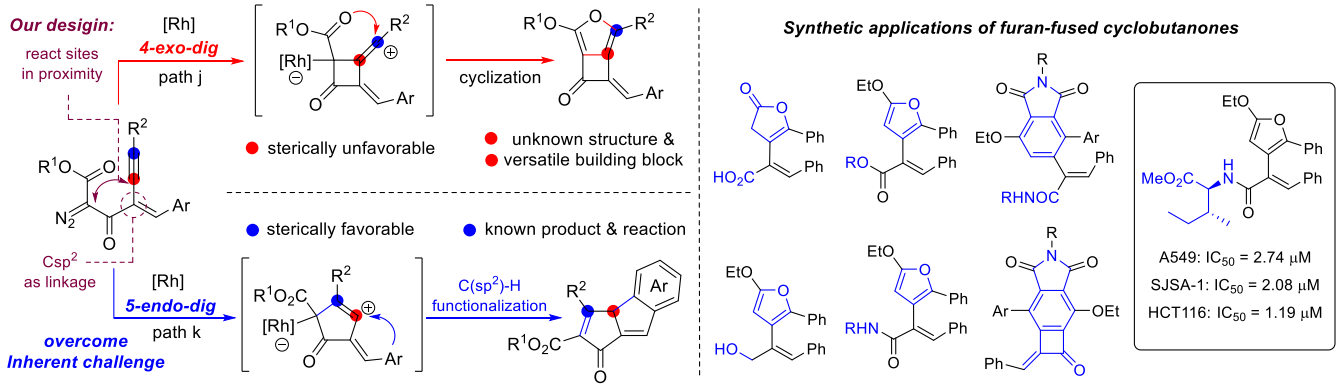


1,1-Difluoroallenes underwent a regioselective [2 + 3] cycloaddition with nitrile oxides and imine oxides in the presence of a AuCl catalyst. (*E*)-4-Alkylidene-5,5-difluoroisoxazolines and -isoxazolidines were obtained in regioselective and diastereoselective manners by employing aurated difluoroallylic cation intermediates. The synthesized 5,5-difluoroisoxazolines were readily aromatized through dehydrofluorination or allylic fluorine substitution to provide 5-fluoroisoxazoles.

Catalytic *4-exo-dig* carbocyclization for the construction of furan-fused cyclobutanones and synthetic applications

Kemiao Hong, Yi Zhou, Haoxuan Yuan, Zhijing Zhang, Jingjing Huang, Shanliang Dong, Wenhao Hu, Zhi-Xiang Yu and Xinfang Xu**

Nat. Commun. **2023**, ***14***, 6378; https://doi.org/10.1038/s41467-023-42032-9

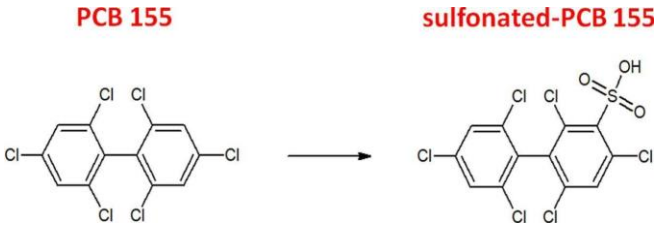


Cyclobutanone is a strained motif with broad applications, while direct assembly of the aromatic ring fused cyclobutanones beyond benzocyclobutenone (BCB) skeletons remains challenging. Herein, we report a Rh-catalyzed formal [3+2] annulation of diazo group tethered alkynes involving a *4-exo-dig* carbocyclization process, providing a straightforward access to furan-fused cyclobutanones. DFT calculations disclose that, by comparison to the competitive 5-*endo-dig* process, 4-*exo-dig* carbocyclization is mainly due to lower angle strain of the key *sp*-hybridized vinyl cationic transition state in the cyclization step. Using less reactive catalysts Rh_2(carboxylate)$_4$ is critical for high selectivity, which is explained as catalyst-substrate hydrogen bonding interaction. This method is proved successful to direct access previously inaccessible and unknown furan-fused cyclobutanone scaffolds, which can participate in a variety of post-functionalization reactions as versatile synthetic blocks. In addition, preliminary antitumor activity study of these products indicates that some molecules exhibited significant anticancer potency against different human cancer cell lines.

Synthesis of a new sulfonated-hexachlorobiphenyl standard for environmental analysis, ecotoxicological, and toxicological studies

Maspero Angelo, Vavassori Federico, Penoni Andrea, Galli Simona, Palmisano Giovanni, Bagnati Renzo, Passoni Alice, Davoli Enrico, Palladini Jessica, Terzaghi Elisa, Di Guardo, Antonio

Science of the Total Environment 2023, 882, Article number 163445

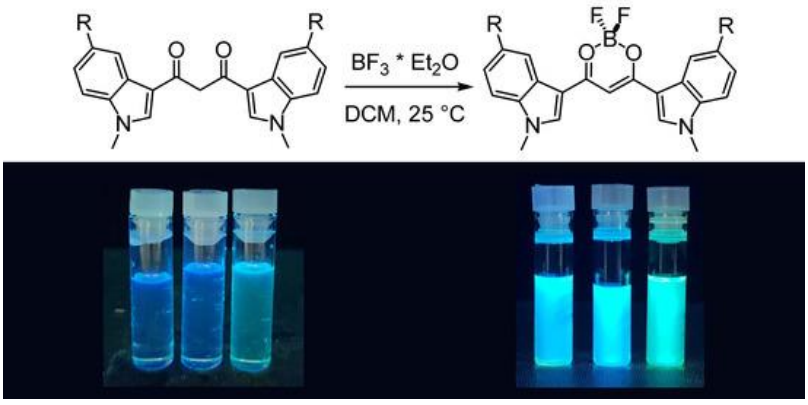


Sulfonated-polychlorinated biphenyls (sulfonated-PCBs) are a newly discovered class of PCB metabolites. They were observed for the first time in polar bear serum and lately, in soil, together with hydroxy-sulfonated-PCBs. Their presence is ubiquitous in soils, and their estimated physical chemical properties show high mobility in water, compared to the parent compounds. However, no single pure standards exist so far and therefore their quantification in the environmental matrices is not accurate. Additionally, pure standards are needed to experimentally determine their physical chemical properties, as well as the ecotoxicological and toxicological characteristics. In the present work, the challenging goal of preparing a polychlorinated biphenyl monosulfonic acid was achieved exploring different synthetic approaches, along which the selection of the starting material resulted in a crucial point. Using PCB-153 (2,2′-4,4′-5,5′-hexachloro-1,1′-biphenyl) the synthesis afforded, as the major species, a side compound. On the contrary, the use of PCB-155 (2,2′-4,4′-6,6′-hexachloro-1,1′-biphenyl), a symmetric hexachlorobiphenyl derivative showing chlorine atoms at all the ortho positions, gave the target sulfonated-PCB compound. In this case, sulfonation was successfully carried out through a two-step procedure, involving chlorosulfonylation and the subsequent hydrolysis of the chlorosulfonyl intermediate.

Synthesis, Characterization, Fluorescence Properties, and DFT Modeling of Difluoroboron Biindolediketonates

Maspero Angelo, Vavassori Federico, Nardo Luca, Vesco Guglielmo, Vitillo Jenny G., Penoni Andrea

Molecules 2023, 28, Article number 4688



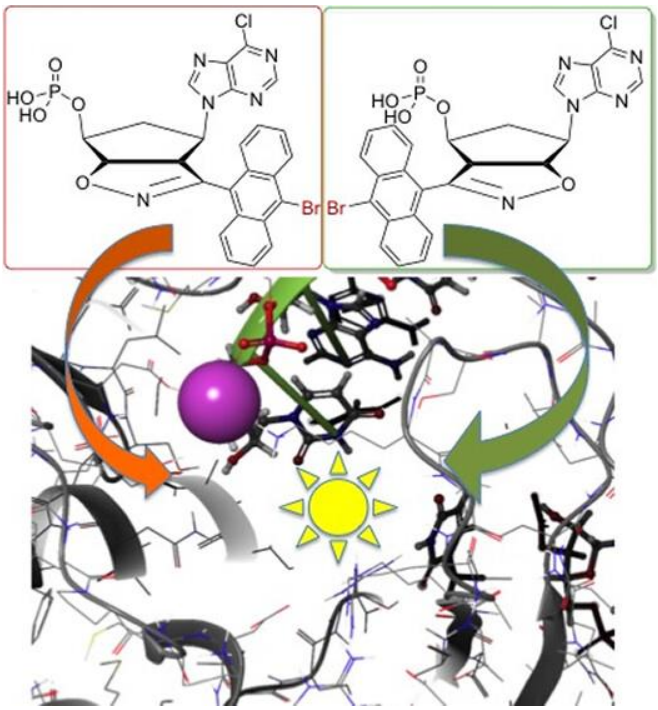
We report a simple and efficient strategy to enhance the fluorescence of biocompatible biindole diketonates (bdks) in the visible spectrum through difluoroboronation (BF_2bdks complexes). Emission spectroscopy testifies an increase in the fluorescence quantum yields from a few percent to as much as >0.7. This massive increment is essentially independent of substitutions at the indole (-H, -Cl, and -OCH_3) and corresponds to a significant stabilization of the excited state with respect to non-radiative decay mechanisms: the non-radiative decay rates are reduced by as much as an order of magnitude, from 10^9 s^{-1} to 10^8 s^{-1}, upon difluoroboronation. The stabilization of the excited state is large enough to enable sizeable $^1O_2$ photosensitized production. Different time-dependent (TD) density functional theory (DFT) methods were assessed in their ability to model the electronic properties of the compounds, with TD-B3LYP-D3 providing the most accurate excitation energies. The calculations associate the

first active optical transition in both the bdks and BF_2bdks electronic spectra to the $S_0 \rightarrow S_1$ transition, corresponding to a shift in the electronic density from the indoles to the oxygens or the O-BF_2-O unit, respectively.

Inhibition of the RNA-Dependent RNA-Polymerase from SARS-CoV-2 by 6-Chloropurine Isoxazoline-Carbocyclic Monophosphate Nucleotides

Marco Leusciatti, Beatrice Macchi, Francesca Marino-Merlo, Antonio Mastino, Giulia Morra and Paolo Quadrelli

ACS Omega, **2023***, 8,* 36311−36320. **DOI**: 10.1021/acsomega.3c04918



Isoxazoline-carbocyclic monophosphate nucleotides were designed and synthesized through the chemistry of nitrosocarbonyl intermediates and stable anthracenenitrile oxide. Docking and molecular dynamics studies were first conducted for determining the best candidate for polymerase SARS-CoV-2 inhibition. The setup phosphorylation protocol afforded the nucleotides available for the biological tests. Preliminary inhibition and cytotoxicity assays were then performed, and the results showed a moderate activity of the nucleotides accompanied by cytotoxicity.
