Issue 77 May 2023

The I.S.H.C. Bulletin

Recent Publications of Members

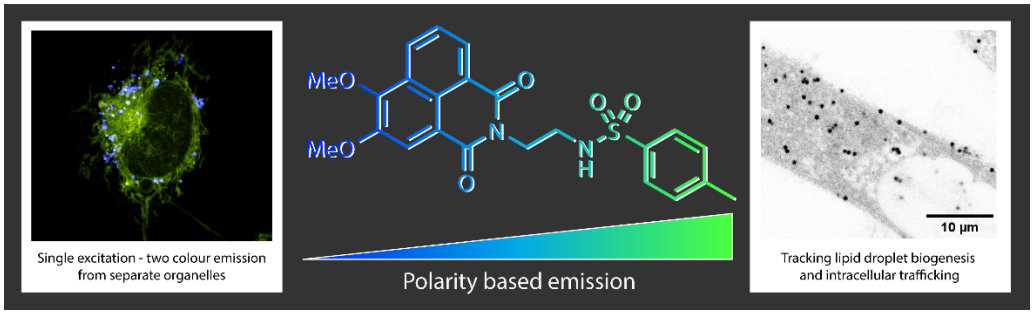
Issue 77 May 2023

Please send any articles for inclusion in future publications to ishc@surrey.ac.uk

If you wish to advertise any conferences or vacant positions, please email ishc@surrey.ac.uk

A fluorescent and solvatochromic 1,8-naphthalimide probe for detection of lipid droplet trafficking and biogenesis

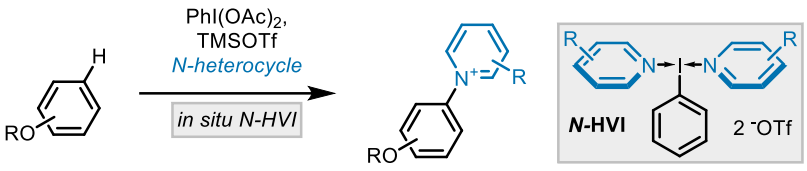
Shane M. Hickey, Ian R.D. Johnson, Elena Dallerba, Mark J. Hackett, Massimiliano Massi, Joanna Lazniewska, Lauren A. Thurgood, Frederick M. Pfeffer, Douglas A. Brooks, Trent D. Ashton,
Dyes and Pigments, 2023, 217, 111382. https://doi.org/10.1016/j.dyepig.2023.111382.



We present a highly fluorescent, solvatochromic, 1,8-naphthalimide for simultaneous imaging of lipid droplets and endoplasmic reticulum, with distinguishable emission maxima. By delineating organelles based on their emission profiles, lipid droplet biogenesis and intercellular trafficking events are visualised. The probe also stains myelin lipids in *ex vivo* brain tissue, indicating histochemical applications.

I(III)-Mediated Arene C–H Amination Using (Hetero)Aryl Nucleophiles

Bill J. Motsch, Jasjit Y. Kaur, and Sarah E. Wengryniuk*
Org. Lett. 2023, 25, 14, 2548–2553



- "oxidatively masked" amination strategy - mild conditions, metal free
- versatile derivatizations of *N*-aryl pyridinium salts

Herein, we report the metal-free oxidative C−H amination of arenes *via* a “heterocyclic group transfer” reaction from an I(III) N-HVI reagent. *N*-Heterocycles serve as oxidatively masked amine nucleophiles, and the resulting *N*-arylpyridinium salts are inert to further oxidation. The reaction proceeds under mild conditions, and mechanistic studies indicate the intermediacy of an arene radical cation. Derivatizations of the resulting pyridinium salts to diverse aryl amine scaffolds are demonstrated.

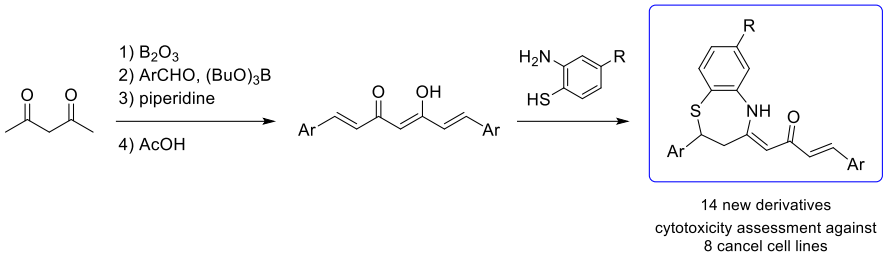
International Society of Heterocyclic Chemistry
ISHC

Issue 77 **May 2023**

Synthesis and cancer cell cytotoxicity of 2-aryl-4-(4-aryl-2-oxobut-3-en-1-ylidene)-substituted benzothiazepanes

Katarina Magdalenić, Ulrike Ronse, Steven De Jonghe, Leentje Persoons, Dominique Schols, Julie De Munck, Charlotte Grootaert, John Van Camp, Matthias D'hooghe*

Phytochem. Lett. **2023**, 117-123 DOI: 10.1016/j.phytol.2023.04.008

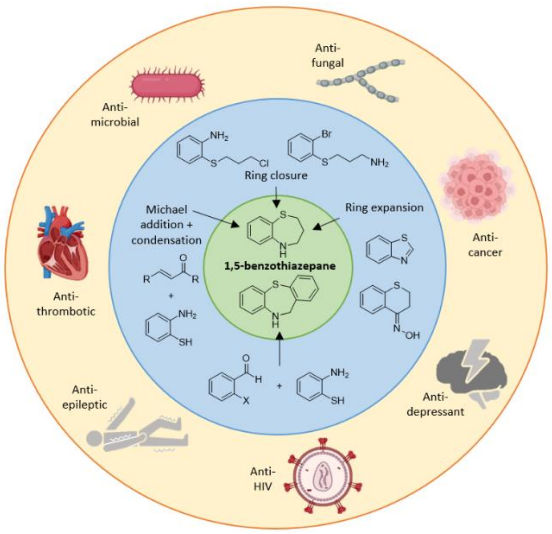


Curcumin is a natural product displaying a broad range of biological activities, including anticancer properties. It is, however, poorly absorbed by the human body and, as a so-called pan-assay interference compound, it exhibits non-specific activity leading to false positive results in biological assays. Nonetheless, different structural modifications of the curcumin scaffold have previously shown to lead to an improved biological and specificity profile without losing antiproliferative activity. In that respect, recent research in our group culminated in unprecedented benzothiazepane-based hit molecules with promising biological and drug-like properties. In the present hit expansion study, 14 new 2-aryl-4-(4-aryl-2-oxobut-3-en-1-ylidene)benzothiazepanes were successfully synthesized through the implementation of various aromatic ring modifications and subsequently tested for cancer cell cytotoxicity using eight different cancer cell lines, revealing useful structure-activity relationship insights for this new class of compounds.

Synthesis of the 1,5-benzothiazepane scaffold – established methods and new developments

Ulrike Ronse, Katarina Magdalenić, John Van Camp, Matthias D'hooghe*

Chemistry Open **2023**, e202200262 DOI: 10.1002/open.202200262

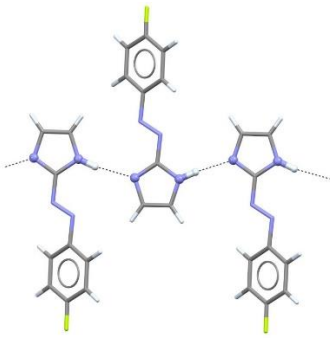


1,5-Benzothiazepane is an important heterocyclic moiety present in a variety of commercial drugs and pharmaceuticals. This privileged scaffold exhibits a diversity of biological activities, including antimicrobial, antibacterial, anti-epileptic, anti-HIV, antidepressant, antithrombotic and anticancer properties. Its important pharmacological potential renders research into the development of new and efficient synthetic methods of high relevance. In the first part of this review, an overview of different synthetic approaches toward 1,5-benzothiazepane and its derivatives is provided, ranging from established protocols to recent (enantioselective) methods that promote sustainability. In the second part, several structural characteristics influencing biological activity are briefly explored, providing a few insights into the structure-activity relationships of these compounds.

Crystal Structure of 2-[(1*E*)-2-(4-Fluorophenyl)diazenyl]-*1H*-imidazole

Thomas Gelbrich, Klaus Wurst, Paul Mayer, Sven Nerdinger * and Herwig Schottenberger *

Molbank **2023**, *2023(1)*, M1571. DOI: https://doi.org/10.3390/M1571

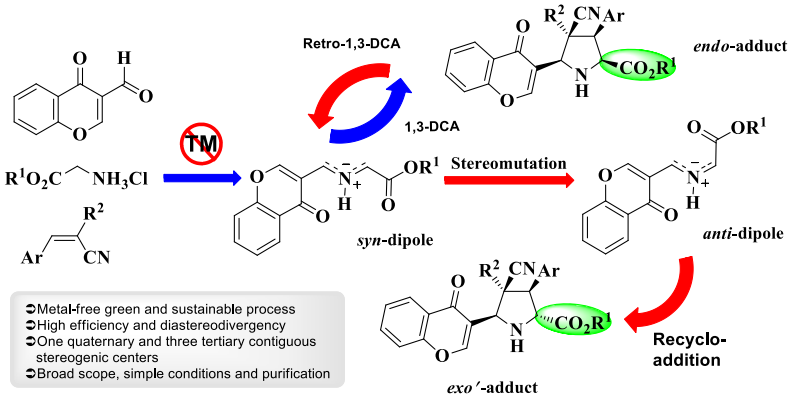


The molecule of the title compound adopts a twisted geometry with a rotation of approximately 30° between the mean planes of the imidazole and phenyl rings. The crystal structure displays hydrogen bonded chains as a result of N–H···N interactions between the imidazole rings of neighboring molecules. These H-bonded chains are assembled into flat molecular layers parallel to the (121) plane. Two intermolecular interactions, involving inversion-related molecules belonging to adjacent molecular layers, contribute significantly to the stabilization of the crystal.

1,3-Dipolar Cycloaddition of 3-Chromonyl-Substituted Glycine Imino Esters with Arylidenes and *in situ* Diastereodivergent *via* Retrocycloaddition

Mohammed F. Radwan, Elghareeb E. Elboray,* Hemat M. Dardeer, Yusuke Kobayashi, Takumi Furuta, Shohei Hamada, Toshifumi Dohi, and Moustafa F. Aly*

Chem.-Asian J. **2023**, *18*, e202300215(1)- e202300215(15). DOI: https://doi.org/10.1002/asia.202300215



1,3-Dipolar cycloaddition through *in situ* generation of azomethine ylide provides a straightforward and critically important sustainable approach for access to diverse pyrrolidine chemical space. Herein, we developed a metal-free AcOH-activated 1,3-dipolar cycloaddition protocol that permits the synthesis of uncommon pyrrolidine cycloadducts with excellent diastereoselectivity. The challenging substrates of 3-formylchromone, glycine ester.HCl and arylidene dipolarophile were reacted in the presence of AcONa, which played a dual role as a base and AcOH source, to deliver firstly *endo*cycloadduct. Under prolonged reaction time at room temperature or heating; the *endo*-adduct underwent diastereodivergent *via* a sequence of retro-cycloaddition, stereomutation of the generated syn-dipole into *anti*-dipole and recycloaddition; to furnish the scarcely known *exo*'-cycloadduct with high diastereodivergency. The reaction worked well with a broad range of substrates and the stereochemistry of the obtained cycloadducts was determined without ambiguity using NMR- and X-ray analysis. Experimental and theoretical DFT calculation studies were performed to support the proposed reaction mechanism and elucidate the key role of AcOH in the process which seems more beneficial than other transition metal-catalyzed processes.

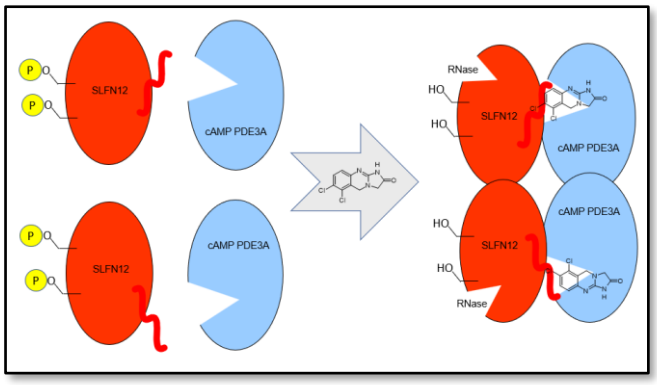
International Society of Heterocyclic Chemistry
ISHC

Issue 77 **May 2023**

Anagrelide: A Clinically Effective cAMP Phosphodiesterase 3A Inhibitor with Molecular Glue Properties

Nicholas A. Meanwell*

ACS Med. Chem. Lett. **2023**, *14*, 350-361 DOI: 10.1021/acsmedchemlett.3c00092

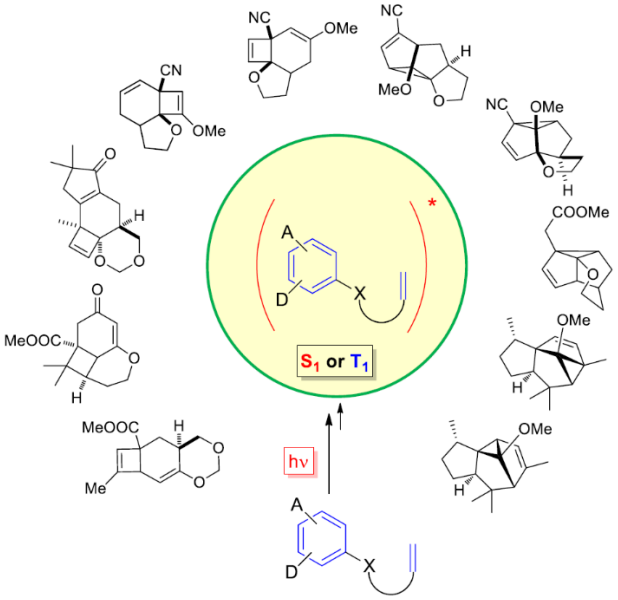


The mode of action by which the orphan drug anagrelide, a potent cAMP phosphodiesterase 3A inhibitor, reduces blood platelet count in humans is not well understood. Recent studies indicate that 1 stabilizes a complex between PDE3A and Schlafen 12, protecting it from degradation while activating its RNase activity.

Photocycloadditions of benzene derivatives and their systematic application to organic synthesis

Arthur Desvals, Norbert Hoffmann*

Aust. J. Chem. **2023**, *76*, 117-129. **DOI:** https://www.publish.csiro.au/ch/CH23029



Photocycloadditions of benzene derivatives with alkenes play an important role as key steps in organic synthesis. Intramolecular reactions have been most frequently studied in this context. Often, meta or [2 + 3] photocycloadditions take place in competition with ortho or [2 + 2] additions. The influence of the substitution pattern and the spin multiplicity of the excited state on the outcome of these reactions is discussed. A topological analysis permitting a systematic application of the [2 + 3] photocycloadditions to the total synthesis of natural products is presented and a selection of corresponding syntheses is discussed. More recently the [2 + 2] photocycloaddition and consecutive rearrangements on organic synthesis have been published. Some approaches in the context of asymmetric synthesis have also been reported.

International Society of Heterocyclic Chemistry
ISHC

Issue 77 **May 2023**

A Bis(imidazole)-based Cysteine Labeling Tool for Metalloprotein Assembly

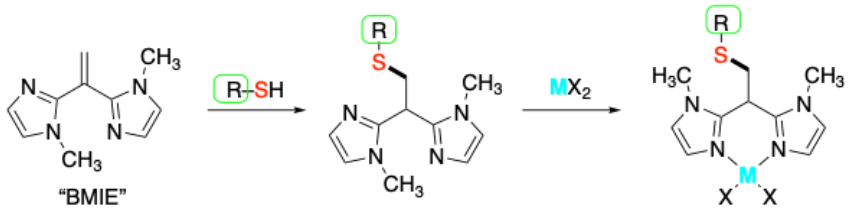
Raheel Ahmad,[1] Alexei M. Tyryshkin,[2] Lingjun Xie[1], William A. Hansen,[1,3] Brahm J. Yachnin,[1,3] Thomas J. Emge,[1] Ashraf Mashrai,[1,3] Sagar D. Khare,[,1,3] and Spencer Knapp[*,1]*

[1]Department of Chemistry & Chemical Biology, Rutgers The State University of New Jersey, 123 Bevier Rd, Piscataway, NJ 08854

[2]Department of Marine and Coastal Sciences, Rutgers The State University of New Jersey, 71 Dudley Road, New Brunswick, NJ 08901

[3]Rutgers Center for Integrative Proteomics Research, 174 Frelinghuysen Rd, Piscataway, NJ 08854

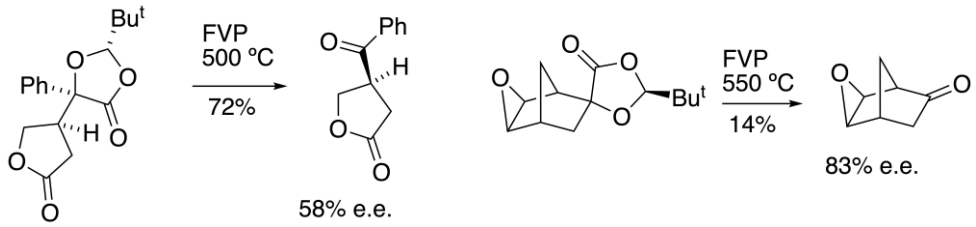
Journal of Inorganic Biochemistry, Volume 244, July 2023, 112206 https://pubmed.ncbi.nlm.nih.gov/37030124/



New Chemistry of Chiral 1,3-Dioxolan-4-ones

R. Alan Aitken, Lynn A. Power and Alexandra M. Z. Slawin

Molecules **2023**, *28*, 3845 (1–18). DOI: 10.3390/molecules28093845



(2*S*,5*S*)-5-Phenyl-2-*t*-butyl-1,3-dioxolan-4-one, readily derived from mandelic acid, undergoes the Michael addition to butenolide and 4-methoxy-β-nitrostyrene with the absolute configuration of the products confirmed by X-ray diffraction in each case. In the former case, thermal fragmentation gives the phenyl ketone, thus illustrating use of the dioxolanone as a chiral benzoyl anion equivalent. The Diels–Alder cycloaddition chemistry of (2*S*)-5-methylene-2-*t*-butyl-1,3-dioxolan-4-one, derived from lactic acid, has been further examined with the X-ray structures of four adducts determined. In one case, thermal fragmentation of the adduct gives a chiral epoxy ketone resulting from the dioxolanone acting as a chiral ketene equivalent, while in others the products give insight into the mechanism of the dioxolanone fragmentation process.

Streptothricin F is a bactericidal antibiotic effective against highly drug-resistant gram negative bacteria that interacts with the 30S subunit of the 70S ribosome

Christopher E. Morgan, Yoon-Suk Kang, Alex B. Gree, Kenneth P. Smith, Matthew G. Dowgiallo, Brandon C. Miller, Lucius Chiaraviglio, Katherine A. Truelson, Katelyn E. Zulauf, Shade Rodriguez, Anthony D. Kang, Roman Manetsch, Edward W. Yu, James E. Kirby

PLoS Biol **21**(5): e3002091. https://doi.org/10.1371/journal.pbio.3002091

The streptothricin natural product mixture (also known as nourseothricin) was discovered in the early 1940s, generating intense initial interest because of excellent gram-negative activity. Here, we establish the activity spectrum of nourseothricin and its main components, streptothricin F (S-F, 1 lysine) and streptothricin D (S-D, 3 lysines), purified to homogeneity, against highly drug-resistant, carbapenem-resistant Enterobacterales (CRE) and *Acinetobacter baumannii*. For CRE, the MIC50 and MIC90 for S-F and S-D were 2 and 4 μM, and 0.25 and 0.5 μM, respectively. S-F and nourseothricin showed rapid, bactericidal activity. SF and S-D both showed approximately 40-fold greater selectivity for prokaryotic than eukaryotic ribosomes in in vitro translation assays. In vivo, delayed renal toxicity occurred at >10-fold higher doses of S-F compared with S-D. Substantial treatment effect of S-F in the murine thigh model was observed against the otherwise pandrug-resistant, NDM-1-expressing *Klebsiella pneumoniae*

Nevada strain with minimal or no toxicity. Cryo-EM characterization of S-F bound to the *A*. *baumannii* 70S ribosome defines extensive hydrogen bonding of the S-F steptolidine moiety, as a guanine mimetic, to the 16S rRNA C1054 nucleobase (*Escherichia coli* numbering) in helix 34, and the carbamoylated gulosamine moiety of S-F with A1196, explaining the high-level resistance conferred by corresponding mutations at the residues identified in single *rrn* operon *E*. *coli*. Structural analysis suggests that S-F probes the A-decoding site, which potentially may account for its miscoding activity. Based on unique and promising activity, we suggest that the streptothricin scaffold deserves further preclinical exploration as a potential therapeutic for drug-resistant, gram-negative pathogens.
