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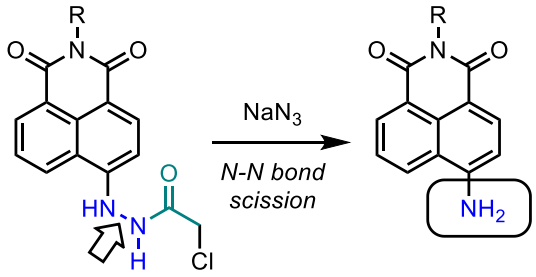
Neighbouring Nitrogen Atom-Induced Reactions of Azidoacetyl Hydrazides, Including Unexpected Nitrogen-Nitrogen Bond Cleavage of the Hydrazide

Hiroki Tanimoto, Ryo Adachi, Aoi Otsuki, Takenori Tomohiro

Organics **2022**, *3*, 520–533. (DOI: 10.3390/org3040035)

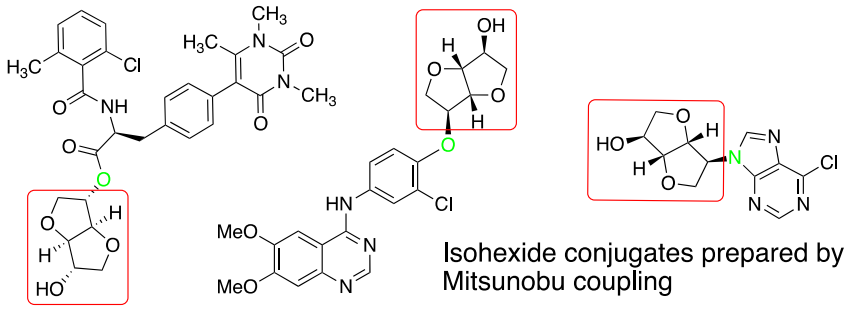


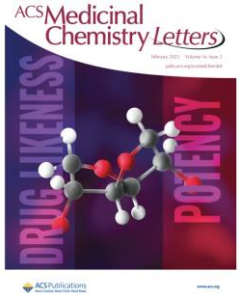
We studied the hydrazide compounds of the α-azidoacetyl group, which showed specific click reactivity by the intramolecular hydrogen bonding between the azido group and the N-H of the hydrazide moiety. In the competitive click reactions with a general alkyl azide, both traceless and non-traceless Staudinger-Bertozzi ligation occurred azide-site-selectively by the acceleration effect of the hydrogen bonding. However, the product obtained from the traceless reaction was further transformed into heterocyclic compounds. In addition, in an attempt at a synthesis of naphthalimide-possessing azidoacetyl hydrazide, nitrogen-nitrogen bond cleavage of the azidoacetyl hydrazides occurred to give the reduced amine product. These unexpected results could help design molecules for the successful Staudinger-Bertozzi ligation of the hydrazide compounds and develop a new nitrogen-nitrogen bond cleavage method.

Incorporation of an Isohexide Subunit Improves the Drug-like Properties of Bioactive Compounds

Achyutharao Sidduri, Mark J. Dresel, and Spencer Knapp

ACS Med. Chem. Lett. 2023, 14, 2, 176–182 (https://doi.org/10.1021/acsmedchemlett.2c0047)





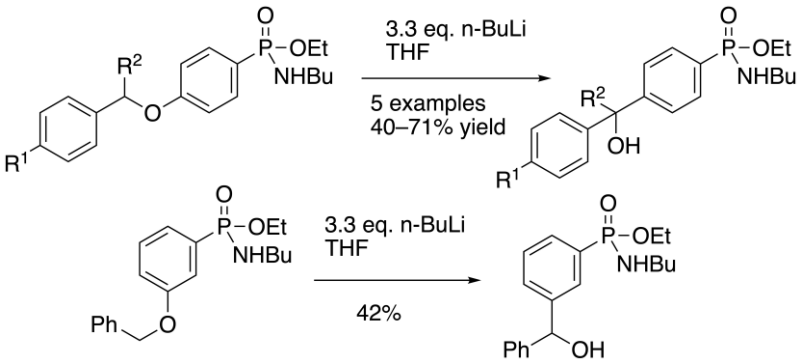
An enhanced ability to pre-engineer favourable drug likeness qualities into bioactive molecules would focus and streamline the drug development process. We find that phenols, carboxylic acids, and a purine react with isosorbide (“GRAS” designated) under Mitsunobu coupling conditions to deliver the isoidide conjugates selectively and efficiently. Such conjugates show improved solubility and permeability properties compared with the bare scaffold compounds themselves, and the purine adduct may have

applications as a 2'-deoxyadenosine isostere. We anticipate additional benefits, implied by their structures, in metabolic stability and reduced toxicity of the isoidide conjugates as well.

Synthesis and Wittig rearrangement of 3- and 4-benzyloxyphenylphosphonamidates

R. Alan Aitken* and Ryan A. Inwood

Organics **2023**, *4*, 59–69 (DOI: 10.3390/org4010005)

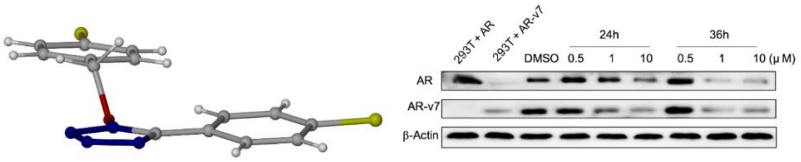


A series of seven *O*-ethyl-*N*-butylphenylphosphonamidates with benzyl ether substituents at the *para* or *meta* position have been prepared and fully characterised. Upon treatment with *n*-butyllithium in THF at RT, these undergo Wittig rearrangement in six cases to give the novel phosphonamidate-substituted diarylmethanols in moderate to good yield.

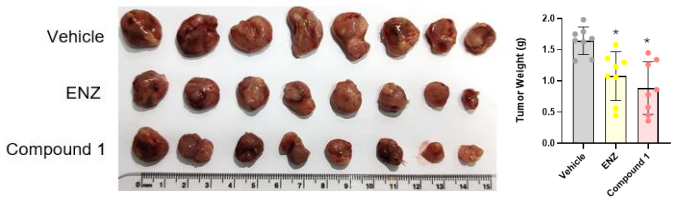
1-Benzyloxy-5-phenyltetrazole derivatives highly active against androgen receptor-dependent prostate cancer cells

Shiting Zhao, Abdelsalam S. Ali, Xinyu Kong, Yan Zhang, Xiaomin Liu, Melissa A. Skidmore, Craig M. Forsyth, G. Paul Savage, Donghai Wu, Yong Xu, Craig L. Francis

European Journal of Medicinal Chemistry **2023**, *246,* 114982 (https://doi.org/10.1016/j.ejmech.2022.114982)



Compound **1**



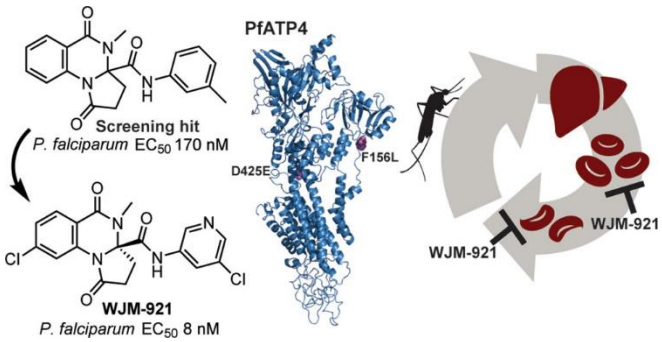
A series of 1-benzyloxy-5-phenyltetrazole derivatives and similar compounds were synthesized and evaluated for their in vitro inhibitory activity against androgen-receptor-dependent (22Rv1) and androgen-receptor independent (PC3) prostate cancer cells. The most active compounds had in vitro IC_{50} values against 22Rv1 cells of <50 nM and showed apparent selectivity for this cell type over PC3 cells; however, these active compounds had short half-lives when incubated with mouse liver microsomes and/or when plasma concentration was monitored during in vivo pharmacokinetic studies in mice or rats. Importantly, lead compound 1 exhibited promising inhibitory effects on cell proliferation, expression of AR and its splicing variant AR-v7 as well as AR regulated target genes in 22Rv1 cells, which are so called castration-resistant prostate cancer (CRPC) cells, and a 22Rv1 CRPC xenograft tumour model in mice. Structural changes which omitted the N–O-benzyl moiety led to dramatic or total loss of activity and S-

benzylation of a cysteine derivative, as a surrogate for in vivo S-nucleophiles, by representative highly active compounds, suggested a possible chemical reactivity basis for this "activity cliff" and poor pharmacokinetic profile. However, representative highly active compounds did not inhibit a cysteine protease, indicating that the mode of activity is unlikely to be protein modification by S-benzylation. Despite our efforts to elucidate the mode of action, the mechanism remains unclear.

Optimization of 2,3-Dihydroquinazolinone-3-carboxamides as Antimalarials Targeting PfATP4

Trent D. Ashton, Madeline G. Dans, Paola Favuzza, Anna Ngo, Adele M. Lehane, Xinxin Zhang, Deyun Qiu, Bikash Chandra Maity, Nirupam De, Kyra A. Schindler, Tomas Yeo, Heekuk Park, Anne-Catrin Uhlemann, Alisje Churchyard, Jake Baum, David A. Fidock, Kate E. Jarman, Kym N. Lowes, Delphine Baud, Stephen Brand, Paul F. Jackson, Alan F. Cowman, and Brad E. Sleebs

J. Med. Chem. **2023**, *66*, 5, 3540–3565. (DOI:10.1021/acs.jmedchem.2c02092)

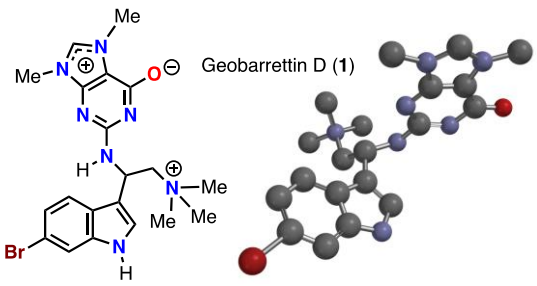


There is an urgent need to populate the antimalarial clinical portfolio with new candidates because of resistance against frontline antimalarials. To discover new antimalarial chemotypes, we performed a high-throughput screen of the Janssen Jumpstarter library against the *Plasmodium falciparum* asexual blood-stage parasite and identified the 2,3-dihydroquinazolinone-3-carboxamide scaffold. We defined the SAR and found that 8-substitution on the tricyclic ring system and 3-substitution of the exocyclic arene produced analogues with potent activity against asexual parasites equivalent to clinically used antimalarials. Resistance selection and profiling against drug-resistant parasite strains revealed that this antimalarial chemotype targets PfATP4. Dihydroquinazolinone analogues were shown to disrupt parasite Na^+ homeostasis and affect parasite pH, exhibited a fast-to-moderate rate of asexual kill, and blocked gametogenesis, consistent with the phenotype of clinically used $PfATP_4$ inhibitors. Finally, we observed that optimized frontrunner analogue WJM-921 demonstrates oral efficacy in a mouse model of malaria.

Geobarrettin D, a Rare Herbipoline-containing 6-Bromoindole Alkaloid from *Geodia barretti*

Xiaxia Di, Ingibjorg Hardardottir, Jona Freysdottir, Dongdong Wang, Kirk R. Gustafson, Sesselja Omarsdottir and Tadeusz F. Molinski

Molecules **2023**, *28*, 2937-2945. doi.org/10.3390/molecules28072937

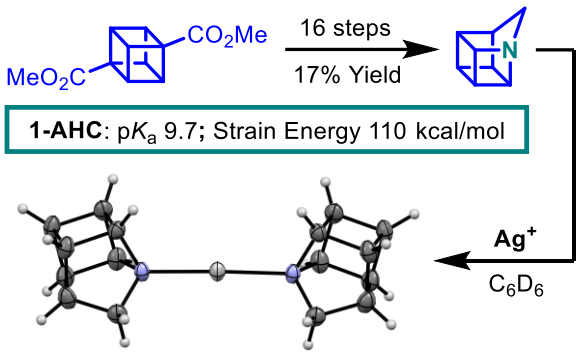


Geobarrettin D (**1**), a new bromoindole alkaloid, was isolated from the marine sponge *Geodia barretti* collected from Icelandic waters. Its structure was elucidated by 1D, and 2D NMR (including ^1H-^{15}N HSQC, ^1H-^{15}N HMBC spectra), as well as HRESIMS data. Geobarrettin D (**1**) is a new 6-bromoindole featuring an unusual purinium herbipoline moiety. Geobarrettin D (**1**) decreased

secretion of the pro-inflammatory cytokine IL-12p40 by human monocyte derived dendritic cells, without affecting secretion of the anti-inflammatory cytokine IL-10. Thus, compound **1** showed anti-inflammatory activity.

1-Azahomocubane

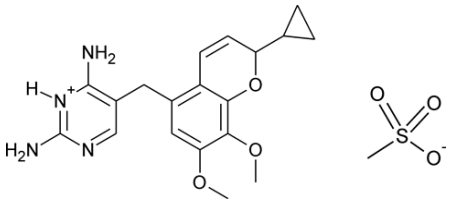
Tyler Fahrenhorst-Jones, David L. Marshall, Jed M. Burns, Gregory K. Pierens, Robert E. Hormann, Allison M. Fisher, Paul V. Bernhardt, Stephen J. Blanksby, G. Paul Savage, Philip E. Eaton, and Craig M. Williams
Chem. Sci. **2023**, *14* (11), 2821–2825. **DOI:** 10.1039/D3SC00001J



The preparation of 1-azahomocubane is reported along with chemical and physical property data (e.g. reactivity, X-ray crystallography, pK_a, proton affinity, and ^{15}N NMR). This highly constrained *N*-heterocyclic cage is the first and only parent azacubane homologue to be synthesised. The nitrogen atom tolerated the strained environment remarkably well and displayed properties consistent with enhanced nitrogen lone pair *s*-character. The key steps to access 1-azahomocubane include Schmidt and aza-Favorskii type rearrangements as well as methylene bridge assembly *via* nucleophilic displacement.

Iclaprim mesylate displaying a hydrogen-bonded molecular tape

Sandro Neuner, Thomas Gelbrich*, Klaus Wurst, Josef Spreitz, Sven Nerdinger, Ulrich J. Griesser, Marijan Stefinovic, and Herwig Schottenberger
Acta Cryst. **2023**, *E79*, 24-27 https://doi.org/10.1107/S2056989022011689

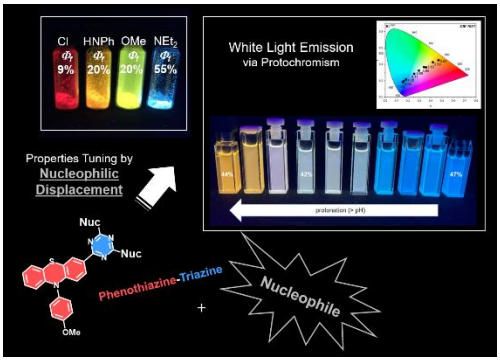


The title compound, 2,6-diamino-5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]pyrimidin-1-ium methanesulfonate, $C_{19}H_{23}N_4O_3^+$ $CH_3O_3S^-$, is a salt made up from a protonated iclaprim molecule and a mesylate anion. The pyrimidine and chromene units of the iclaprim molecule form an orthogonal arrangement [interplanar angle of 89.67 (6)°], and the 3-nitrogen position of the pyrimidine ring is protonated. Four distinct N—H···O interactions and an additional N— H···N hydrogen bond connect iclaprim and mesylate molecules to one another, resulting in an infinite hydrogen-bonded molecular tape structure. The central section of the tape is formed by a sequence of fused hydrogen-bonded rings involving four distinct ring types.

Fluorescent Phenothiazine-Triazine Donor-Acceptor Conjugates by Facile Consecutive Nucleophilic Displacement – Color Tuning by Substitution and Protochromicity

L. N. Kloeters, L. May, B. Tengen, L. May, T. J. J. Müller

Dyes Pigm. **2022**, *206*, 110564. DOI: 10.1016/j.dyepig.2022.110564

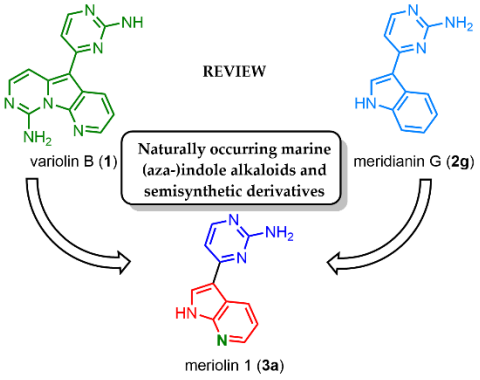


A series of phenothiazine-triazine chromophores is prepared starting from brominated phenothiazine in a one-pot fashion by twofold nucleophilic substitution on cyanuric chloride. The title compounds show high fluorescence quantum yields in solution and in the solid state spanning a color range from deep blue to red by modulating the acceptor strength of the triazine moiety. Electron deficient substituted triazine chromophores exhibit a strong charge transfer character as shown by solvatochromism studies and small singlet-triplet energy gap making them interesting-candidates for thermally activated delayed fluorescence (TADF). Protonation of an electron rich triazine chromophore resulted in shifted spectral emission and showed in one case the formation of complementary emission colors and white light formation. Thus, by substitution of the triazine spectral emission color can be fine-tuned and specific photophysical properties like TADF and white light emission can be addressed.

A survey on the synthesis of variolins, meridianins, and meriolins – Naturally occurring marine (aza)indole alkaloids and their semisynthetic derivatives.

M. Kruppa, T. J. J. Müller

Molecules **2023**, *28*, 947. DOI: 10.3390/molecules28030947

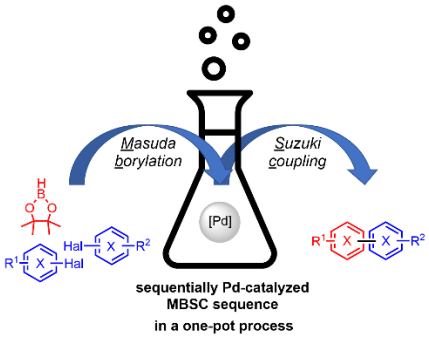


Marine natural products are a source of essential significance due to a plethora of highly diverse biological properties. The naturally occurring (aza)indole alkaloids variolin B (**1**), meridianins (**2**), and their synthetic hybrids meriolins (**3**) exhibit potent kinase inhibitory activities and have aroused considerable interest in the past two decades. Therefore, the immense demand for versatile synthetic accesses to these structures has considerably increased. This review surveys the synthetic pathways to these naturally occurring alkaloids and their semisynthetic derivatives.

Masuda Borylation–Suzuki Coupling (MBSC) Sequence: A One-Pot Process to Access Complex (hetero)Biaryls.

M. Kruppa, T. J. J. Müller

Catalysts **2023**, *13*, 350. DOI: 10.3390/catal13020350

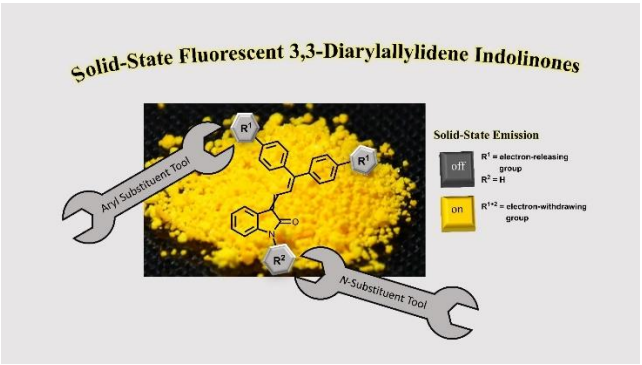


The direct formation of (hetero)biaryls from readily available (hetero)aryl halides under mild reaction conditions can be efficiently achieved through the Masuda borylation–Suzuki coupling (MBSC) sequence. The MBSC sequence catenates Pd-catalyzed Masuda borylation and Suzuki coupling into a one-pot process, giving access to diverse symmetrically and unsymmetrically substituted scaffolds. (Hetero)biaryls are ubiquitous structural motifs that appear in natural products, pharmaceutically relevant scaffolds, functional dyes, and several other structures. This review summarizes the development of the MBSC sequence and its improvements over the past two decades.

Solid-state fluorescent 3,3-diarylallylidene indolinones by pseudo-five-component synthesis.

F. Wilbert, T. J. J. Müller

Dyes Pigm. **2023**, *213*, 111139. DOI: 10.1016/j.dyepig.2023.111139

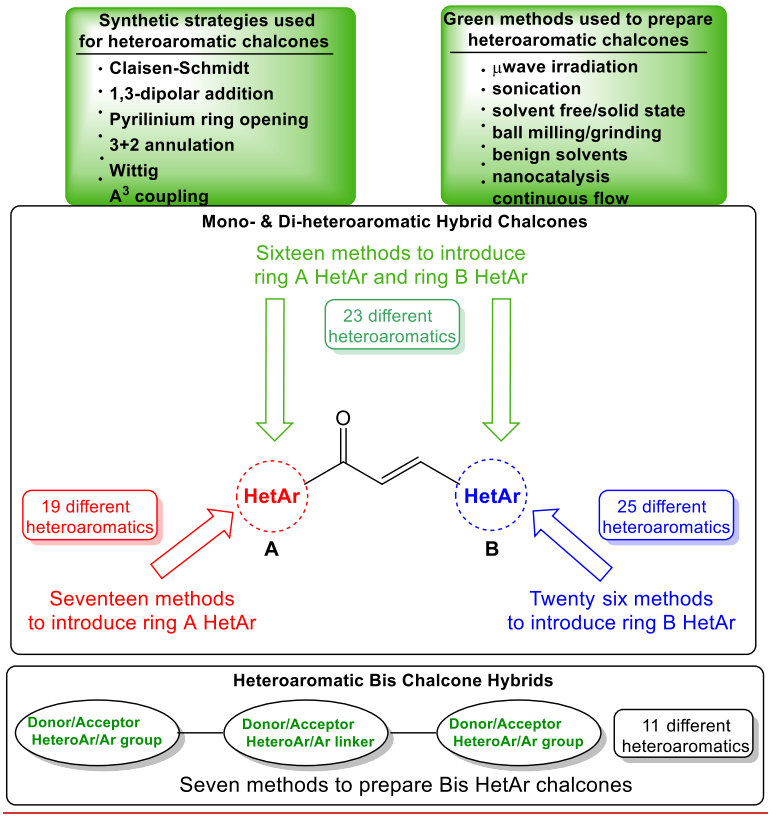


One-pot syntheses of 3,3-diarylallylidene indolinones are achieved by *pseudo*-four- and *pseudo*-five-component reactions. The title compounds are obtained as a mixture of *E*/*Z*-configured isomers. The photophysical characteristics are assessed by absorption and solid-state emission spectroscopy. Irrespective of their configuration, the 3,3-diarylallylidene indolinones fluoresce in the solid state for electron-withdrawing and weakly electron-releasing remote *p*-phenyl substituted dyes with concomitantly Boc substitution of the lactam moiety. DFT and TD DFT calculation reproduce and rationalize the electronic structure of the longest wavelength absorption and emission bands.

Advances in the Synthesis of Heteroaromatic Hybrid Chalcones

Mallia, Ajay; Sloop, Joseph

Molecules **2023**, *28*, 3201. https://doi.org/10.3390/molecules28073201



Abstract: Chalcones continue to occupy a venerated status as scaffolds for the construction of a variety of heterocyclic molecules with medicinal and industrial properties. Syntheses of hybrid chalcones featuring heteroaromatic components, especially those methods utilizing green chemistry principles, are important additions to the preparative methodologies for this valuable class of molecules. This review outlines the advances made in the last few decades toward the incorporation of heteroaromatic components in the construction of hybrid chalcones and highlights examples of environmentally responsible processes employed in their preparation.