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Benzo[*b*]phospholes

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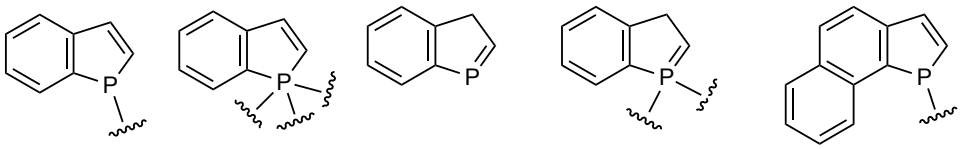
Science of Synthesis Knowledge Updates, **2022**, *2*, 1–42. **DOI:** 10.1055/sos-SD-110-02138



Abstract: This chapter is a complete revision and update of the earlier *Science of Synthesis* contribution from 2000 describing methods for the synthesis of benzo[*b*]phospholes. Half the references describe newer methods reported between 2000 and 2021 and, as well as extensions to the previously described approaches, several completely new approaches are included. Among the strategies covered are reactions of metalated phenylalkyne derivatives with phosphorus halides, cyclizations of (2-alkynylphenyl)phosphorus compounds, direct reactions of phenylphosphorus compounds with alkynes, and aromatization of dihydro derivatives. In addition, the initially obtained compounds can be converted into a variety of derivatives by modification at phosphorus by oxidation, substitution, or reduction.

Benzo[*c*]phospholes

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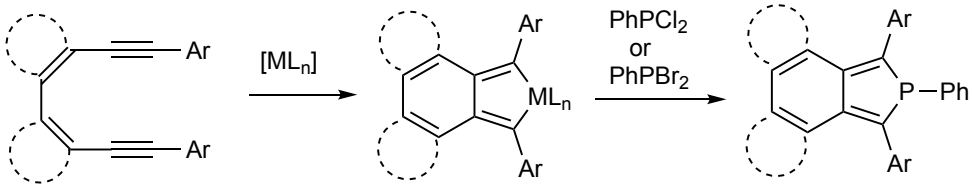
Science of Synthesis Knowledge Updates, **2022**, *2*, 43–53. **DOI:** 10.1055/sos-SD-110-02186



Abstract: This chapter is a complete revision and update of the earlier *Science of Synthesis* contribution from 2000 describing methods for the synthesis of benzo[*c*]phospholes. A third of the references describe newer methods reported between 2000 and 2021 and several completely new approaches are included. Synthetic strategies for preparing these ring systems include metal-mediated reactions of 2,2 bis(arylalkynyl)biaryls with phosphorus dihalides, reaction of *ortho*-disubstituted benzenes with phosphorus compounds, and aromatization of dihydrobenzo[*c*]phospholes.

Phosphorus Analogues of Indolizines

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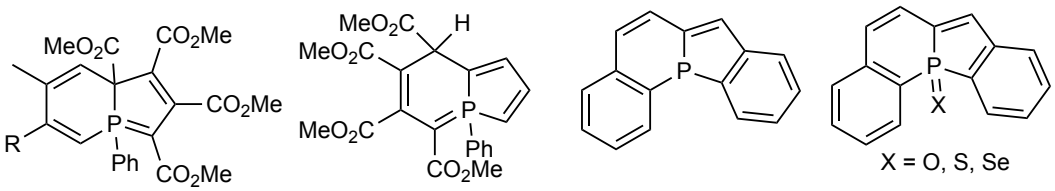
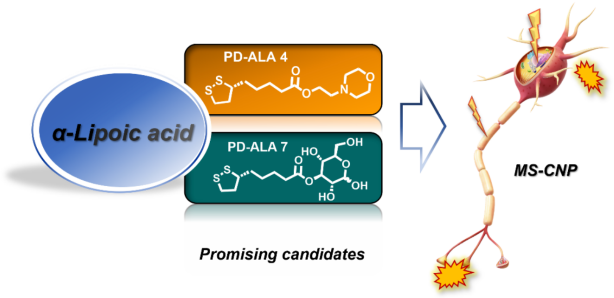
Science of Synthesis Knowledge Updates, **2022**, *2*, 55–61. **DOI:** 10.1055/sos-SD-110-02196



Abstract: This chapter is a complete revision and update of the earlier *Science of Synthesis* contribution from 2000 describing methods for the synthesis of phosphorus analogues of indolizines. The previous route to this rare ring system has now been joined by a second metathesis-based method leading to the parent dibenzophosphindolizine and its chalcogen derivatives.

Design, Synthesis and Evaluation of Alpha Lipoic Acid Derivatives to Treat Multiple Sclerosis-Associated Central Neuropathic Pain

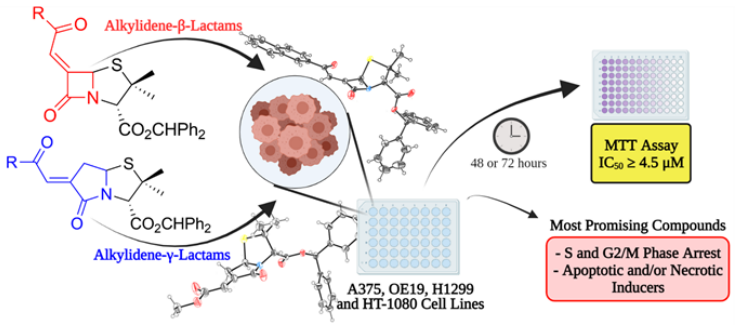
Dehui Kong, Alaa A. Saqer, Matheus Carpinelli de Jesus, Nemat Khan, Alun Jones, Joanne T. Blanchfield, Maree T. Smith, Craig M. Williams* (c.williams3@uq.edu.au)
Bioorg. Med. Chem. **2022**, *69*, 116889 (1–10). **DOI:** 10.1016/j.bmc.2022.116889



Abstract: Multiple sclerosis-associated central neuropathic pain (MS-CNP) is a result of chronic autoimmune inflammation of the nervous system by the disease. This pain indication is difficult to alleviate with clinically used pain-killers. Recently, (*R*)-alpha lipoic acid (ALA), a natural antioxidant, was shown to eliminate oxidative stress in MS-CNP pathological cascades, thus providing an analgesic effect. Unfortunately, ALA suffers from poor oral bioavailability due to poor gastrointestinal stability. A compound library of eight (*R*)-ALA ester prodrugs encompassing a range of biocompatible hydrophobic and hydrophilic acyl functionalities was designed and synthesized in an effort to identify a prodrug candidate with good gastrointestinal stability, and which can rapidly release (*R*)-ALA into the blood stream. The subsequent comprehensive preliminary screening utilizing enzyme-free gastric and intestinal stability assessments, LogP evaluation, *in vitro* plasma stability and caco-2 cell permeability, identified PD-ALA 4 HCl as a desirable candidate. PD-ALA 7 could be a viable substitute should long plasma stability be required.

Insights into the Anticancer Activity of Chiral Alkylidene-β-Lactams and Alkylidene-γ-Lactams: Synthesis and Biological Investigation

Américo J. S. Alves, Nuno G. Alves, Mafalda Laranjo, Clara S. B. Gomes, Ana Cristina Gonçalves, Ana Bela Sarmento-Ribeiro, M. Filomena Botelho, Teresa M. V. D. Pinho e Melo* (tmelo@ci.uc.pt)
Bioorg. Med. Chem. **2022**, *63*, 116738 (1–11). **DOI:** 10.1016/j.bmc.2022.116738

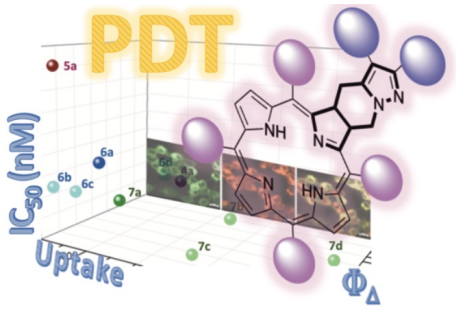


Abstract: Chiral alkylidene-β-lactams and alkylidene-γ-lactams were synthesized and screened for their *in vitro* activity against four human cancer cell lines (melanoma, esophageal, lung and fibrosarcoma carcinoma). Alkylidene-β-lactams were synthesized via Wittig reaction of diverse phosphorus ylides with benzhydryl 6-oxopenicillanate, derived from 6-aminopenicillanic acid. Moreover, novel chiral alkylidene-γ-lactams were synthesized through a multistep strategy starting from a chiral substrate (D-penicillamine). The *in vitro* assays allowed the identification of four compounds with IC_{50} values < 10 μM for A375 cell line, and three compounds with IC_{50} values < 10 μM for OE19 cell line. The effect of the most promising compounds on cell death mechanism, reactive oxygen species generation as well as the evaluation of their ability to act as MMP-9 inhibitors were studied. The reported results unveil the potential of alkylidene-β-lactams as anticancer agents.

Ring-Fused *meso*-Tetraarylchlorins as Auspicious PDT Sensitizers: Synthesis, Structural Characterization, Photophysics, and Biological Evaluation

Mafalda Laranjo, Nelson A. M. Pereira, Andreia S. R. Oliveira, Márcia Campos Aguiar, Gonçalo Brites, Bruno F. O. Nascimento, Beatriz Serambeque, Bruna D. P. Costa, João Pina, J. Sérgio Seixas de Melo, Marta Pineiro, M. Filomena Botelho, and Teresa M. V. D. Pinho e Melo* (tmelo@ci.uc.pt)

Front. Chem. (Med. Pharm. Chem.) **2022**, *10*, 873245 (1–14). **DOI:** 10.3389/fchem.2022.873245



Abstract: Novel 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-fused *meso*-tetraarylchlorins, with different degrees of hydrophilicity (with methyl ester, hydroxymethyl and carboxylic acid moieties), have been synthesized and their photophysical characterization as well as *in vitro* photocytotoxicity assessment against human melanoma, esophageal and bladder carcinomas was carried out. An integrated analysis of the photosensitizers' performance, considering singlet oxygen generation data, cell internalization and intracellular localization, allowed to establish relevant structure-photoactivity relationships and the rationalization of the observed photocytotoxicity. In the diacid and monoalcohol series, chlorins derived from *meso*-tetraphenylporphyrin proved to be the most efficient PDT agents, showing IC_{50} values of 68 nM and 344 nM against A375 cells, respectively. These compounds were less active against OE19 and HT1376 cells, the diacid chlorin with IC_{50} values still in the nano-molar range whereas the monohydroxymethyl-chlorin showed significantly higher IC_{50} values. The lead di(hydroxymethyl)-substituted *meso*-tetraphenylchlorin confirmed its remarkable photoactivity with IC_{50} values below 75 nM against the studied cancer cell lines. Subcellular accumulation of this chlorin in mitochondria, endoplasmic reticulum and plasma membrane was demonstrated.

Intramolecular Arylation of 2-Bromobenzenesulfonamides Using DMSO/HCOONa•2H$_2$O System: An Access to Dibenzosultams

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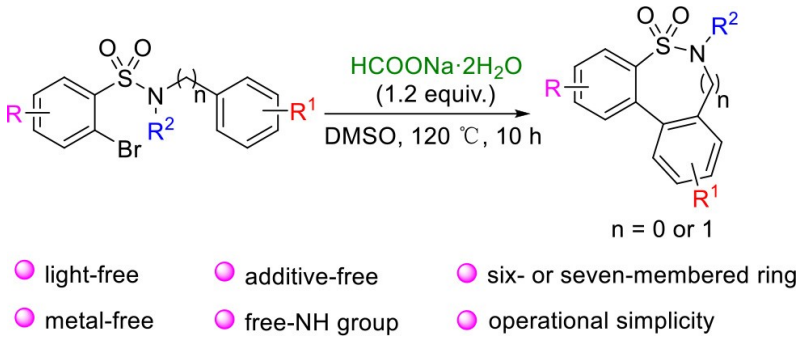
Adv. Synth. Catal. **2022**, *364*, 1889–1895. **DOI:** 10.1002/adsc.202200140



Abstract: Six- or seven-membered dibenzosultams were synthesized upon treatment of *N*-aryl- or *N*-benzyl-2-halobenzenesulfonamides with HCOONa·2H$_2$O in DMSO without using additional measures and additives, such as light irradiation, electrochemical apparatus, transition metals, and oxidants. Further functionalization of the free NH group of the resultant dibenzosultams demonstrates the synthetic practicability of this method.