Issue 91 October 2024

The I.S.H.C. Bulletin

Recent Publications of Members

Issue 91 October 2024

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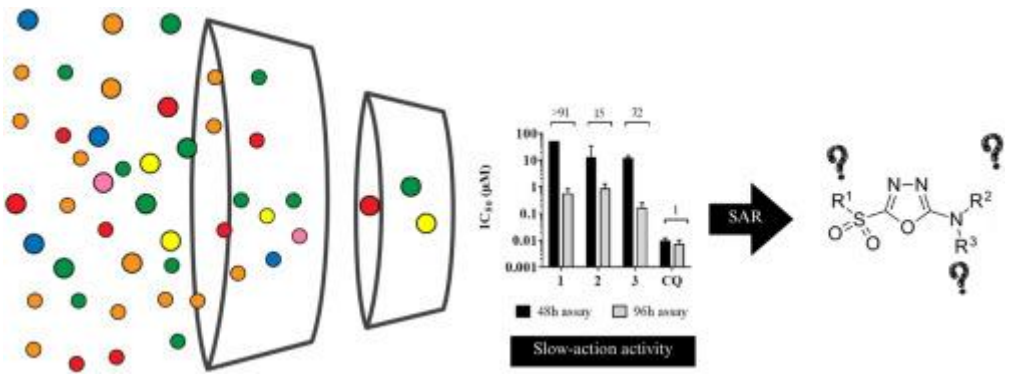
Discovery of 1,3,4-oxadiazoles with slow-action activity against *Plasmodium falciparum* malaria parasites

Katherine T. Andrews*, Gillian M. Fisher, Meaghan Firmin, Andris J. Liepa, Tony Wilson, James Gardiner, Yacine Mohri, Emmanuel Debele, Anjana Rai, Andrew K. Davey, Antoine Masurier, Alix Delion, Alexandros A. Mouratidis, Oliver E. Hutt, Craig M. Forsyth, Jeremy N. Burrows, John H. Ryan*, Andrew G. Riches*, Tina S. Skinner-Adams.*

Eur. J. Med. Chem. **2024**, *278*, 116796. DOI:10.1016/j.ejmech.2024.116796



To achieve malaria eradication, new preventative agents that act differently to front-line treatment drugs are needed. To identify potential chemoprevention starting points we screened a sub-set of the CSIRO Australia Compound Collection for compounds with slow-action *in vitro* activity against Plasmodium falciparum. This work identified N,N-dialkyl-5-alkylsulfonyl-1,3,4-oxadiazol-2-amines as a new antiplasmodial chemotype (*e.g.*, 1 96 h IC50 550 nM; 3 96 h IC50 160 nM) with a different action to delayed-death slow-action drugs. A series of analogues were synthesized from thiotetrazoles and carbomoyl derivatives using Huisgen 1,3,4-oxadiazole synthesis followed by oxidation of the resultant thioethers to target sulfones. Structure activity relationship analysis of analogues identified compounds with potent and selective *in vitro* activity against drug-sensitive and multi-drug resistant Plasmodium parasites (*e.g.*, 31 and 32 96 h IC50 <40 nM; SI > 2500). Subsequent studies in mice with compound **1**, which had the best microsomal stability of the compounds assessed (T1/2 >255 min), demonstrated rapid clearance and poor oral *in vivo* efficacy in a *P. berghei* murine malaria model. These data indicate that while N,N-dialkyl-5-alkylsulfonyl-1,3,4-oxadiazol-2-amines are a novel class of slow-acting antiplasmodial agents, the further development of this chemotype for malaria chemoprophylaxis will require pharmacokinetic profile improvements.

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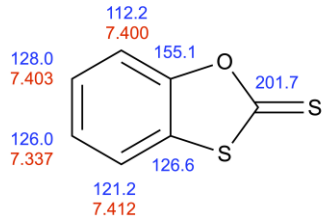
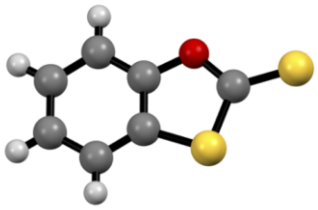
Benzo[*d*][1,3]oxathiole-2-thione

R. Alan Aitken, David B. Cordes, Lauryne Cottineau and Aidan P. McKay

Molbank **2024**, *2024*, M1891 (1–6). DOI: 10.3390/M1891



^{1}H and ^{13}C NMR fully assigned



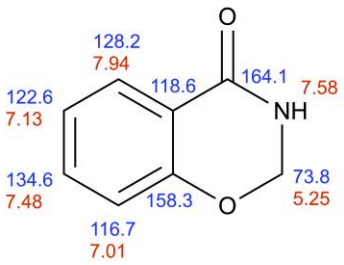
X-Ray structure determined

Although known for 120 years, the title compound has not been adequately characterised before. In this paper, it is fully characterised by ^{1}H and ^{13}C NMR and IR spectroscopy and its X-ray structure has been determined for the first time.

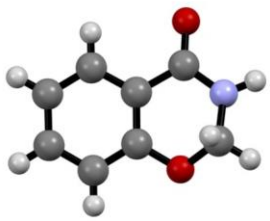
2,3-Dihydrobenzo[*e*][1,3]oxazin-4-one

R. Alan Aitken, David B. Cordes, Mhairi R. Kinahan and Aidan P. McKay

Molbank **2024**, *2024*, M1878 (1–6). DOI: 10.3390/M1878



^{1}H and ^{13}C NMR fully assigned



X-Ray structure shows H-bonded dimers

The title compound and its hydroxymethyl precursor have been fully characterised for the first time. The IR spectra, fully assigned ^{1}H and ^{13}C NMR spectra, and X-ray structures are presented for both compounds. Both compounds form hydrogen-bonded dimers in the crystal structures.

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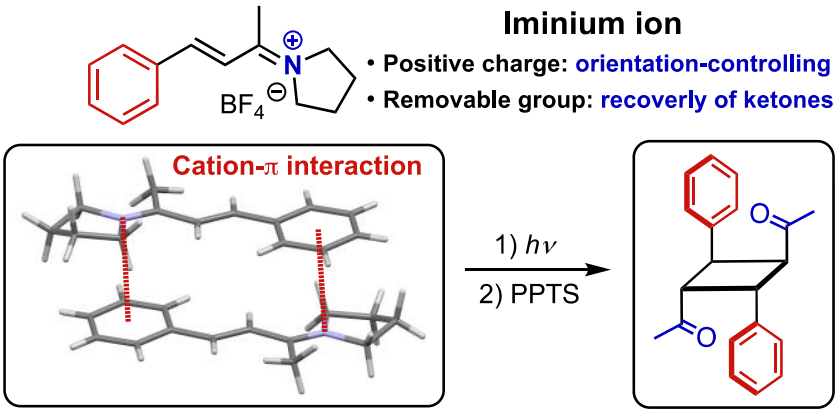
Solid-state [2+2] photodimerization of eniminium salts: stereoselective syntheses of 1,3-diacetylcyclobutanes

Shinji Yamada* and Yuka Honda

Chem. Commun., 2024, 60, 9821. DOI: 10.1039/d4cc03691c



Solid-state [2+2] photodimerization of eniminium ions oriented in a head-to-tail manner controlled by cation-π interactions produced *syn*HT dimers in high yields. As the resulting dimer is readily converted to 1,3-diacetylcyclobutane, the iminium serves as a removable orientation-controlling group for the conjugated ketones.