Issue 85 April 2024

# The I.S.H.C. Bulletin

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## Issue 85 April 2024

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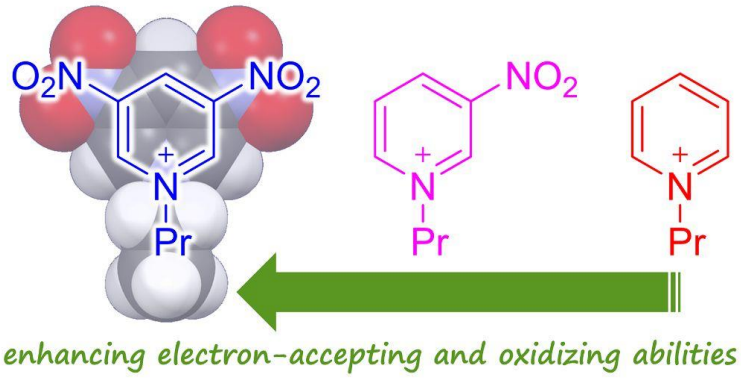
### Highly Electron-Deficient 1-Propyl-3,5-dinitropyridinium: Evaluation of Electron-Accepting Ability and Application as an Oxidative Quencher for Metal Complexes

Akitaka Ito, Yasuyuki Kuroda, Kento Iwai, Soichi Yokoyama, Nagatoshi Nishiwaki
*RSC Advances* **2024**, *14*, 5846–5850. DOI: https://doi.org/10.1039/d4ra00845f




Impacts of the nitro groups on the electron-accepting and oxidizing abilities of N-propylpyridinium were evaluated quantitatively. A 3,5-dinitro derivative has efficiently quenched emission from photosensitizing Ru(II) and Ir(III) complexes owing to the thermodynamically-favored electron transfer to the pyridinium whose LUMO is greatly lowered by the presence of electron-withdrawing nitro groups.

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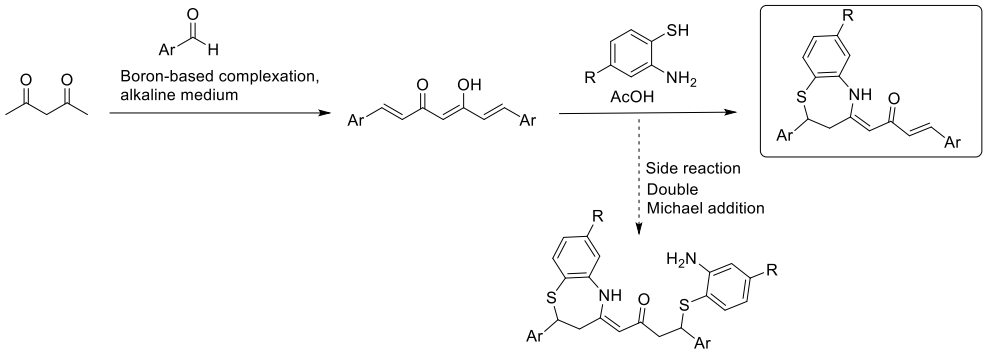
**Issue 85** **April 2024**

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

Katarina Magdalenić, Felien Morlion, Steven De Jonghe, Leentje Persoons, Dominique Schols, Charlotte Grootaert, John Van Camp, Matthias D'hooghe*

*Tetrahedron* **2024**, 133884 DOI: 10.1016/j.tet.2024.133884




The natural product curcumin is often presented as a source of inspiration in the field of drug development because of its therapeutic diversity and safety for human consumption. However, although curcumin indeed shows an interesting profile in terms of *in vitro* biological activity, its low oral bioavailability, poor stability and unclear mechanism of action considerably weakens its case as a marketable drug. In that context, several modifications to the curcumin structure have previously been realized in our lab, culminating in i.a. benzothiazepane-based derivatives with improved drug-like properties and significant cancer cell cytotoxicity. To further explore their structure-activity relationships and to improve their antitumoral activity, we synthesized a library of new 2-heteroaryl-4-(4-heteroaryl-2-oxobut-3-en-1-ylidene)benzothiazepanes, which were evaluated for cytotoxicity against 8 different cancer cell lines. From this screening, pyridine substituted benzothiazepanes emerged as broad-spectrum anticancer agents, whereas 2-thienyl benzothiazepanes and a side product, formed through a double Michael addition, surfaced as promising structures for further elaboration because of their highly selective activity against the NCI-H460 lung cancer cell line.

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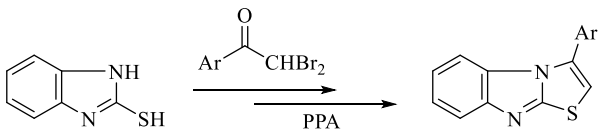
## α,α-Dibromoketones as Synthetic Equivalents of α-Bromoketones for the Synthesis of Thiazolo[3,2-a]benzimidazoles

Ravi Kumar,* Reshmi R. Nair, Richa Prakash, Taeho Bae, Toshifumi Dohi,* and Om Prakash*

*Lett. Org. Chem.* **2024**, *21*, 209- 212. DOI: 10.2174/1570178620666230803123511




**Excellent example illustrating α,α-bromoketones as synthetic equivalents of α-bromoketones**

- Two-Step Synthesis of Thiazolo[3,2-a]benzimidazoles
- Good Yields (71-82%)
- Avoiding Lachrymatory α-Bromoketones

Utilization of α,α-dihalocarbonyl compounds as synthetic equivalents to α-halocarbonyl compounds have been explored in the syntheses of a wide range of highly useful heterocycles and α-functionalized ketones. Continuously growing demand of α,α-dibromoketones, as highly reactive and mild synthetic precursors/intermediates, to carry out selective organic transformations, prompted us to investigate their potential application for the synthesis of thiazolo[3,2-a]benzimidazoles. In this paper, a remarkable application of α,α-dibromoacetophenones in the development of a facile protocol for the synthesis of thiazolo[3,2-a]benzimidazoles, avoiding the use of lachrymatory α-haloketones, is described. Although the mechanism for the debromination from the intermediate compound under these conditions is not confirmed, possible pathways have been suggested.

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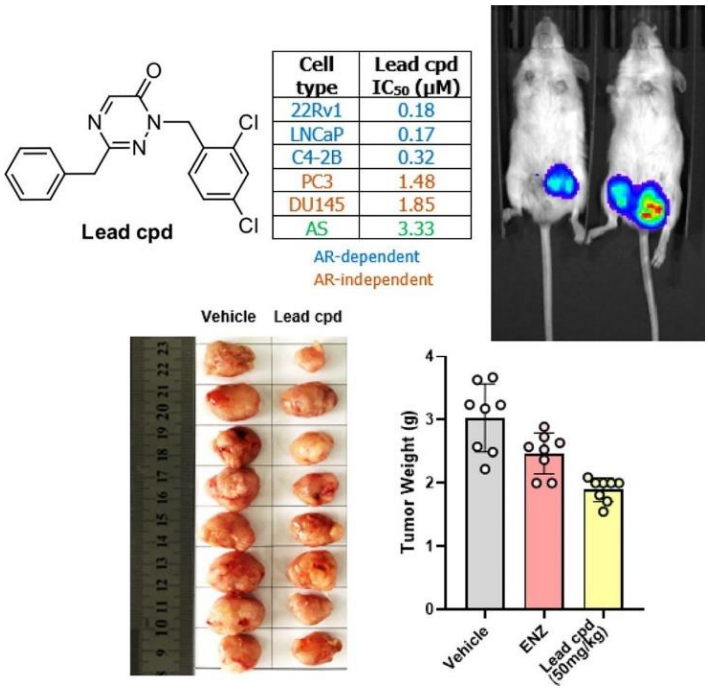
**Issue 85** **April 2024**

## 1,3-Disubstituted-1,2,4-triazin-6-ones with potent activity against androgen receptor-dependent prostate cancer cells

Shiting Zhao, Abdelsalam S. Ali, Xiaomin Liu, Zhiwei Yu, Xinyu Kong, Yan Zhang, G. Paul Savage, Yong Xu, Bin Lin, Donghai Wu,* and Craig L. Francis*

*Bioorganic and Medicinal Chemistry* **2024**, *101*, 117634. https://doi.org/10.1016/j.bmc.2024.117634

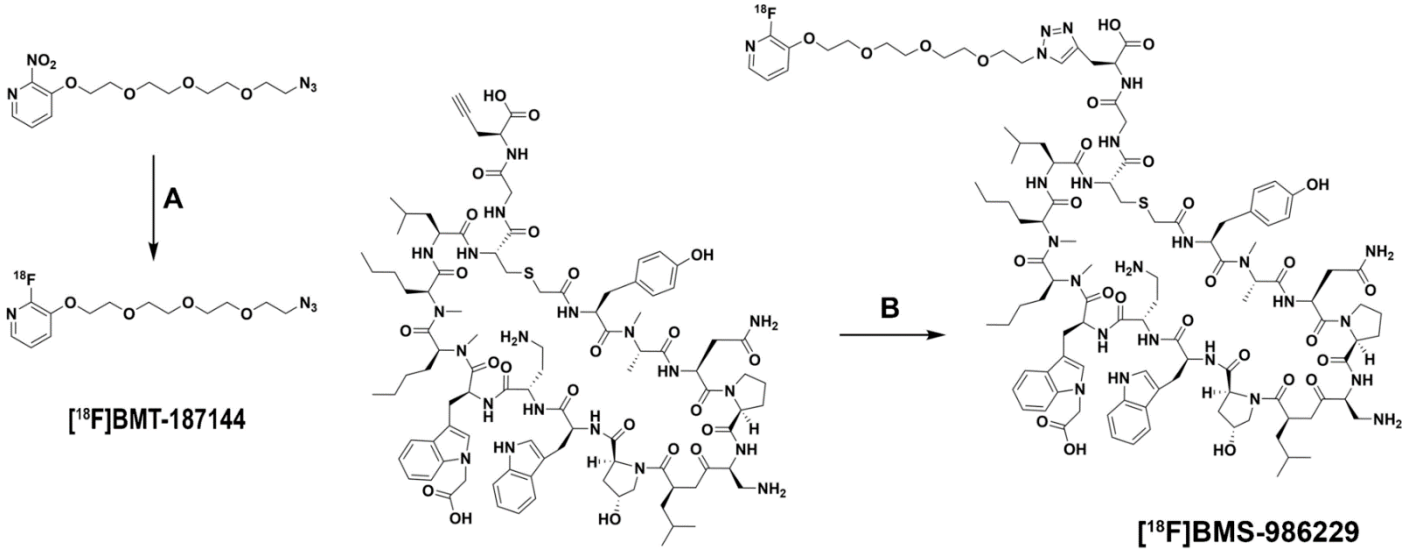



Synthesis and biological evaluation of a small, focused library of 1,3-disubstituted-1,2,4-triazin-6-ones for *in vitro* inhibitory activity against androgen-receptor-dependent (22Rv1) and androgen-receptor independent (PC3) castration-resistant prostate cancer (CRPC) cells led to highly active compounds with *in vitro* $IC_{50}$ values against 22Rv1 cells of <200 nM, and with apparent selectivity for this cell type over PC3 cells. From metabolic/PK evaluations of these compounds, a 3-benzyl-1-(2,4-dichlorobenzyl) derivative had superior properties and showed considerably stronger activity, by nearly an order of magnitude, against AR-dependent LNCaP and C4-2B cells compared to AR-independent DU145 cells. This lead compound decreased AR expression in a dose and time dependent manner and displayed promising therapeutic effects in a 22Rv1 CRPC xenograft mouse model. Computational target prediction and subsequent docking studies suggested three potential known prostate cancer targets: p38a MAPK, TGF-β1, and HGFR/c-Met, with the latter case of c-Met appearing stronger, owing to close structural similarity of the lead compound to known pyridazin-3-one derivatives with potent c-Met inhibitory activity. RNA-seq analysis showed dramatic reduction of AR signalling pathway and/or target genes by the lead compound, subsequently confirmed by quantitative PCR analysis. The lead compound was highly inhibitory against HGF, the c-Met ligand, which fitted well with the computational target prediction and docking studies. These results suggest that this compound could be a promising starting point for the development of an effective therapy for the treatment of CRPC.

## The Discovery and Evaluation of [$^{18}$F]BMS-986229, A Novel Macrocyclic Peptide PET Radioligand for the Measurement of PD-L1 Expression and In-Vivo PD-L1 Target Engagement

David J. Donnelly,* Joonyoung Kim, Tritin Tran, Paul M. Scola, Daniel Tenney, Adrienne Pena,·Thomas Petrone, Yunhui Zhang, Kenneth. M. Boy, Michael A. Poss, Erin L. Cole, Matthew G. Soars, Benjamin M. Johnson, Daniel Cohen, Daniel Batalla, Patrick L. Chow,·Andrea Olga Shorts, Shuyan Du,·Nicholas A. Meanwell, Samuel J. Bonacorsi Jr.

*European Journal of Nuclear Medicine and Molecular Imaging*, **2024**, *51*, 978-990
DOI: 10.1007/s00259-023-06527-3




**Purpose**: A same-day PET imaging agent capable of measuring PD-L1 status in tumors is an important tool for optimizing PD-1 and PD-L1 treatments. Herein we describe the discovery and evaluation of a novel, fluorine-18 labeled macrocyclic peptide-based PET ligand for imaging PD-L1.**Method:** [$^{18}$F]BMS-986229 was synthesized via copper-mediated click-chemistry to yield a PD-L1 PET ligand with picomolar affinity and was tested as an *in vivo* tool for assessing PD-L1 expression.
**Results**: Autoradiography showed an 8:1 binding ratio in L2987 (PD-L1 (+)) vs. HT-29 (PD-L1 (-)) tumor tissues, with >90% specific binding. Specific radioligand binding (>90%) was observed in human non-small-cell lung cancer (NSCLC) and cynomolgus monkey spleen tissues. Images of PD-L1 (+) tissues in primates were characterized by high signal-to-noise, with low background signal in non-expressing tissues. PET imaging enabled clear visualization of PD-L1 expression in a murine model *in vivo*, with 5-fold higher uptake in L2987 (PD-L1 (+)) than in control HT-29 (PD-L1 (-)) tumors. Moreover, this imaging agent was used to measure target engagement of PD-L1 inhibitors (peptide or mAb), in PD-L1 (+) tumors as high as 97%.
**Conclusion**: A novel $^{18}$F-labeled macrocyclic peptide radioligand was developed for PET imaging of PD-L1 expressing tissues that demonstrated several advantages within a nonhuman primate model when compared directly to adnectin- or mAb-based ligands. Clinical studies are currently evaluating [$^{18}$F]BMS-986229 to measure PD-L1 expression in tumors

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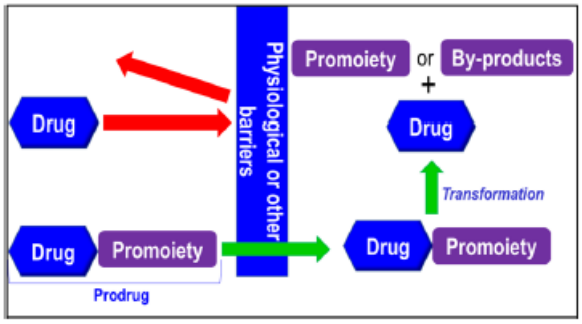
**Issue 85** **April 2024**

## Prodrugs as Empowering Tools in Drug Discovery and Development: Recent Strategic Applications of Drug Delivery Solutions to Mitigate Challenges Associated With Lead Compounds and Drug Candidates

Murugaiah A. M. Subbaiah,* Jarkko Rautio and Nicholas A. Meanwell

*Chem. Soc. Rev.*, **2024**, *53*, 2099 DOI: 10.1039/d2cs00957a




The delivery of a drug to a specific organ or tissue at an efficacious concentration is the pharmacokinetic (PK) hallmark of promoting effective pharmacological action at a target site with an acceptable safety profile. Sub-optimal pharmaceutical or ADME profiles of drug candidates, which can often be a function of inherently poor physicochemical properties, pose significant challenges to drug discovery and development teams and may contribute to high compound attrition rates. Medicinal chemists have exploited prodrugs as an informed strategy to productively enhance the profiles of new chemical entities by optimizing the physicochemical, biopharmaceutical, and pharmacokinetic properties as well as selectively delivering a molecule to the site of action as a means of addressing a range of limitations. While discovery scientists have traditionally employed prodrugs to improve solubility and membrane permeability, the growing sophistication of prodrug technologies has enabled a significant expansion of their scope and applications as an empowering tool to mitigate a broad range of drug delivery challenges. Prodrugs have emerged as successful solutions to resolve non-linear exposure, inadequate exposure to support toxicological studies, pH-dependent absorption, high pill burden, formulation challenges, lack of feasibility of developing solid and liquid dosage forms, first-pass metabolism, high dosing frequency translating to reduced patient compliance and poor site-specific drug delivery. During the period 2012–2022, the US Food and Drug Administration (FDA) approved 50 prodrugs, which amounts to 13% of approved small molecule drugs, reflecting both the importance and success of implementing prodrug approaches in the pursuit of developing safe and effective drugs to address unmet medical needs.

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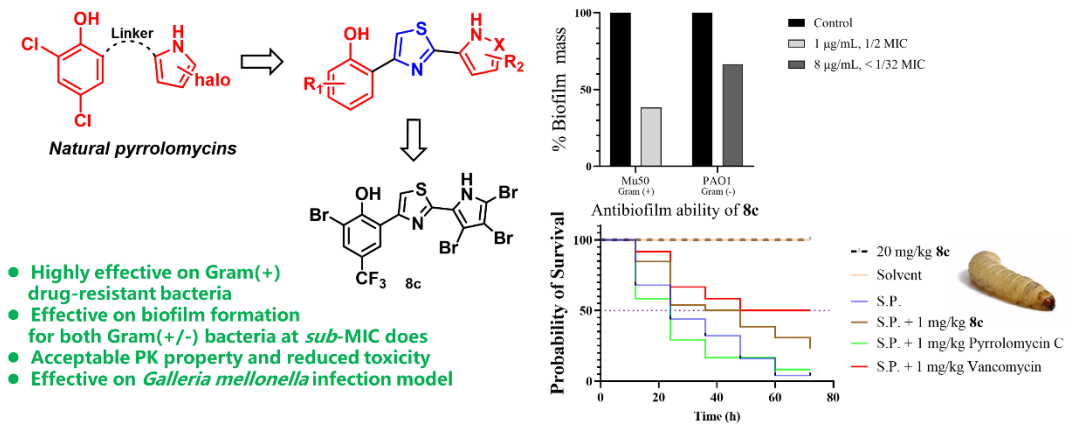
## Design, synthesis and biological evaluation of thiazolyl-halogenated pyrroles or pyrazoles as novel antibacterial and antibiofilm agents.

Yuanchen Zhong, Huan Liu, Feifei Chen, Qian He, Xiaofei Zhang,* Lefu Lan,* and Chunhao Yang.*

*Eur. J. Med. Chem.* **2024**, *268, 116221.* DOI: 10.1016/j.ejmech.2024.116221



The formation of biofilm is one of the important factors for bacteria to develop drug-resistant. A series of halogenated-pyrroles or pyrazoles containing thiazole groups as antibacterial agents were designed and synthesized to target biofilms. Among them, compound **8c** showed antibacterial activity against various Gram-positive bacteria, particularly against vancomycin-resistant *Enterococcus faecalis* (MIC ≤0.125 μg/mL). Additionally, this compound significantly inhibited biofilm formation of *Staphylococcus aureus* and *Pseudomonas aeruginosa* at sub-MIC doses. Furthermore, compound **8c** exhibited significantly lower mammalian cell toxicity compared to pyrrolomycin C and its hepatic microsomal metabolic stability in various species was also evaluated. Further experiment on the infection model of Galleria mellonella proved that the compound was effective *in vivo*.

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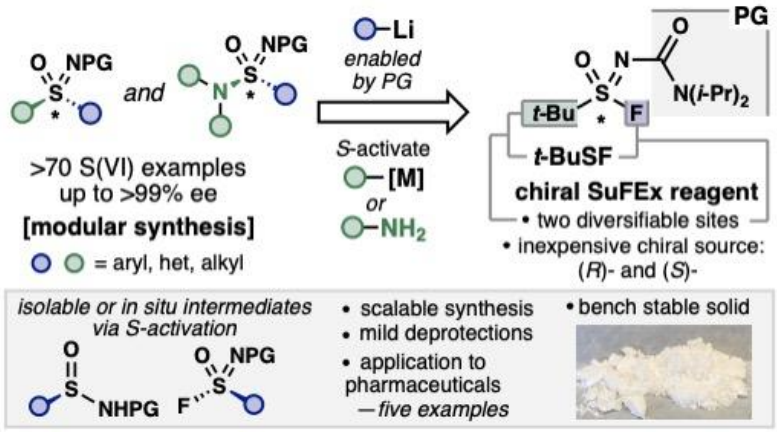
## Asymmetric Synthesis of Sulfoximines, Sulfonimidoyl Fluorides, and Sulfonimidamides Enabled by an Enantiopure Bifunctional S(VI) Reagent

Shun Teng, Zachary P. Shultz, Chuan Shan, Lukasz Wojtas, Justin Lopchuk*

*Nat. Chem.* **2024**, *16*, 183-192. https://doi.org/10.1038/s41557-023-01419-3




An increased interest to expand three-dimensional chemical space for the design of new materials and medicines has created a demand for isosteric replacement groups of commonly used molecular functionality. The structural and chemical properties of chiral S(VI) functional groups provide unique spatial and electronic features compared to their achiral sulfur- and carbon-based counterparts. Manipulation of the S(VI) center to introduce structural variation with stereochemical control has remained a synthetic challenge. The stability of sulfonimidoyl fluorides and the efficiency of sulfur fluorine exchange (SuFEx) chemistry has enabled the development of an enantiopure bifunctional S(VI) transfer reagent (***t*-BuSF**) to overcome current synthetic limitations. Here, this reagent platform serves as a chiral SuFEx template for the rapid asymmetric synthesis of over seventy different sulfoximines, sulfonimidoyl fluorides and sulfonimidamides with excellent enantiopurity and good overall yields. Furthermore, the practical utility of ***t*-BuSF** was demonstrated in the syntheses of enantiopure pharmaceutical intermediates and analogs.

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