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Recent Publications of ISHC Members

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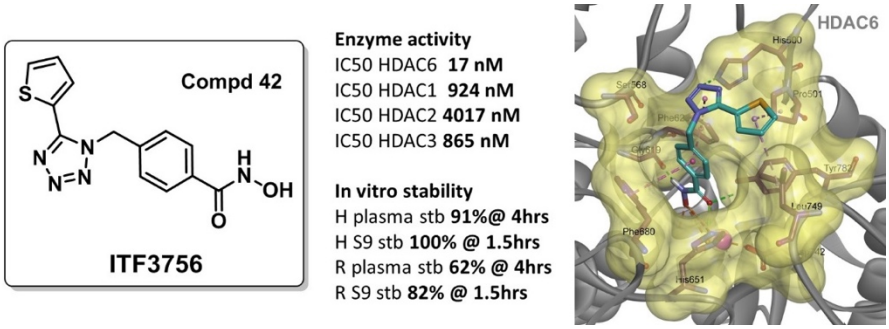
Novel Benzohydroxamate-Based Potent and Selective Histone Deacetylase 6 (HDAC6) Inhibitors Bearing a Pentaheterocyclic Scaffold: Design, Synthesis, and Biological Evaluation

Barbara Vergani, Giovanni Sandrone, Mattia Marchini, Chiara Ripamonti, Edoardo Cellupica, Elisabetta Galbiati, Gianluca Caprini, Gianfranco Pavich, Giulia Porro, Ilaria Rocchio, Maria Lattanzio, Marcello Pezzuto, Malgorzata Skorupska, Paola Cordella, Paolo Pagani, Pietro Pozzi, Roberta Pomarico, Daniela Modena, Flavio Leoni, Raffaella Perego, Gianluca Fossati, Christian Steinkühler, and Andrea Stevenazzi* (a.stevenazzi@italfarmaco.com)

J. Med. Chem. **2019**, *62*, 10711–10739. **DOI:** 10.1021/acs.jmedchem.9b01194

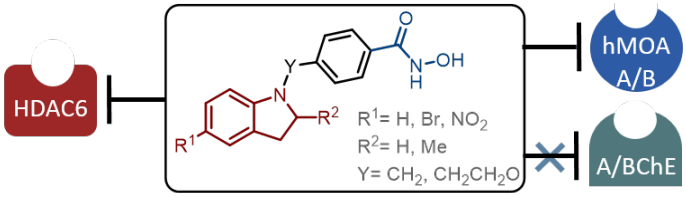


Abstract: Histone deacetylase 6 (HDAC6) is a peculiar HDAC isoform whose expression and functional alterations have been correlated with a variety of pathologies such as autoimmune disorders, neurodegenerative diseases, and cancer. It is primarily a cytoplasmic protein, and its deacetylase activity is focused mainly on non-histone substrates such as tubulin, heat shock protein (HSP)90, Foxp3 and cortactin, to name a few. Selective inhibition of HDAC6 does not show cytotoxic effects in healthy cells, normally associated with the inhibition of Class I HDAC isoforms. Here we describe the design and synthesis of a new class of potent and selective HDAC6 inhibitors that bear a pentaheterocyclic central core. These compounds show a remarkably low toxicity both in vitro and in vivo and are able to increase the function of regulatory T cells (Tregs) at well-tolerated concentrations, suggesting a potential clinical use for the treatment of degenerative or auto-immune diseases and organ transplantation.

Synthesis of Indoline-Based Benzhydroxamic Acids as Potential HDAC6 Inhibitors

Yves Depetter, Silke Geurs, Jorick Franceus, Damijan Knez, Tom Desmet, Karolien De Bosscher, Oliver De Wever, Stanislav Gobec, and Matthias D'hooghe* (matthias.dhooghe@ugent.be)

ChemistrySelect **2019**, *4*, 12308–12312. **DOI:** 10.1002/slct.201902042

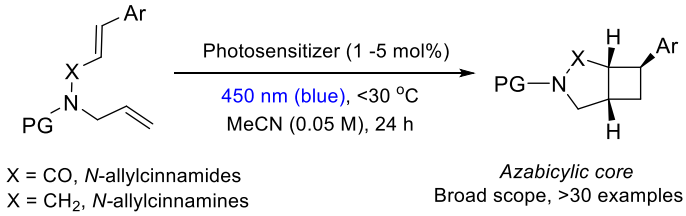


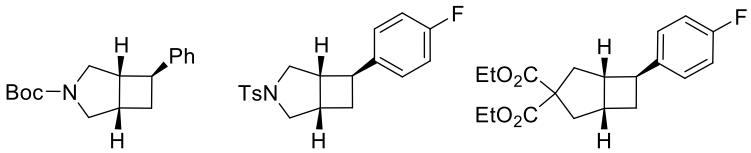
Abstract: The synthesis of HDAC6 inhibitors has attracted considerable interest in medicinal chemistry because of their drug potential in different therapeutic areas. In this paper, the preparation of two classes of indoline-based benzhydroxamic acids is presented, bearing either the classical 4-hydroxycarbamoylbenzyl or a hitherto unexplored 2-[4-(hydroxycarbamoyl)phenoxy]ethyl group, which were shown to exhibit complete HDAC6 inhibition at 10 μM. Furthermore, evaluation of these compounds for interaction with cholinesterases (AChE and BChE) and monoamine oxidases (A and B) revealed some of them to be moderate inhibitors in that respect as well.

Intramolecular [2+2] Cycloaddition of *N*-Allylcinnamamines and *N*-Allylcinnamamides by Visible-Light Photocatalysis

Martins S. Oderinde,* James Kempson, Daniel Smith, Nicholas A. Meanwell, Edna Mao, Joseph Pawluczyk, Muthalagu Vetrichelvan, Manivel Pitchai, Ananta Karmakar, Richard Rampulla, Jianqing Li, T. G. Murali Dhar, and Arvind Mathur (martin.oderinde@bms.com)

Eur. J. Org. Chem. **2020**, 41–46. **DOI:** 10.1002/ejoc.201901482





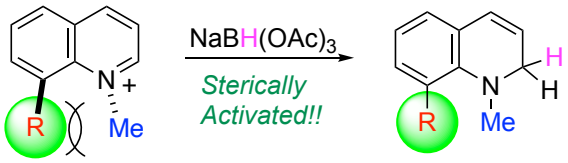
4b, 71% yield **4g**, 79% yield **4u,** 78% yield

Abstract: The visible light-promoted intramolecular [2+2] cycloaddition of *N*-allylcinnamamines and *N*-allylcinnamamides in the presence of catalytic amounts of [Ir{dF(CF$_3$)ppy}$_2$(dtbpy)]-PF$_6$ is reported. Low energy visible light and a high triplet energy iridium-photosensitizer were efficient at promoting the cycloaddition reaction of *N*-allylcinnamamides and *N*-allylcinnamamines to the corresponding aryl-3-azabicyclo[3.2.0]-heptanones and aryl-3-azabicyclo[3.2.0]heptanes, respectively, with high diastereoselectivity and under mild conditions. Azabicyclic fused rings have been employed as surrogates for piperidine motifs in drug discovery. Functional groups useful for deployment and/or elaboration in drug discovery campaigns were all shown to be tolerated, including halides, CF$_3$, cyanide, ester, acetamide, acetate, CH$_3$O, pyridyl, furan, carbamate, tosyl, benzyl, and benzoate.

Non-Electronic Aromatic Ring Activation by Simple Steric Repulsion between Substituents in 1-Methylquinolinium Salt Systems

Kento Iwai, Soichi Yokoyama, Haruyasu Asahara, and Nagatoshi Nishiwaki* (nishiwaki.nagatoshi@kochi-tech.ac.jp)

Bull. Chem. Soc. Jpn. **2020**, *93*, 50–57. **DOI:** 10.1246/bcsj.20190263

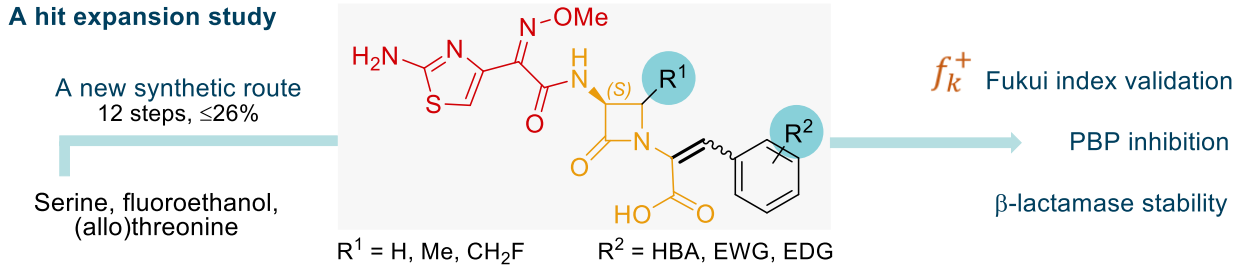


Abstract: A systematic study for non-electronic activation of an aromatic ring was performed using a series of 8-substituted 1-methylquinolinium salts. As the 8-substituent became bulkier, the quinoline framework was distorted by steric repulsion between substituents at the 1- and 8-positions. This was accompanied by lack of coplanarity, which brought about the dearomatization. Consequently, quinolinium ion possessing a bulky 8-substituent exhibited high reactivity undergoing nucleophilic addition at the 2-position efficiently. We demonstrate that the activation was achieved sterically and not electronically.

α-Unsaturated 3-Amino-1-carboxymethyl-β-lactams as Bacterial PBP Inhibitors: Synthesis and Biochemical Assessment

Lena Decuyper, Katarina Magdalenić, Marie Verstraete, Marko Jukič, Izidor Sosič, Eric Sauvage, Ana Maria Amoroso, Oliver Verlaine, Bernard Joris, Stanislav Gobec, and Matthias D'hooghe* (matthias.dhooghe@ugent.be)

Chem. Eur. J. **2019**, *25*, 16128–16140. **DOI:** 10.1002/chem.201904139

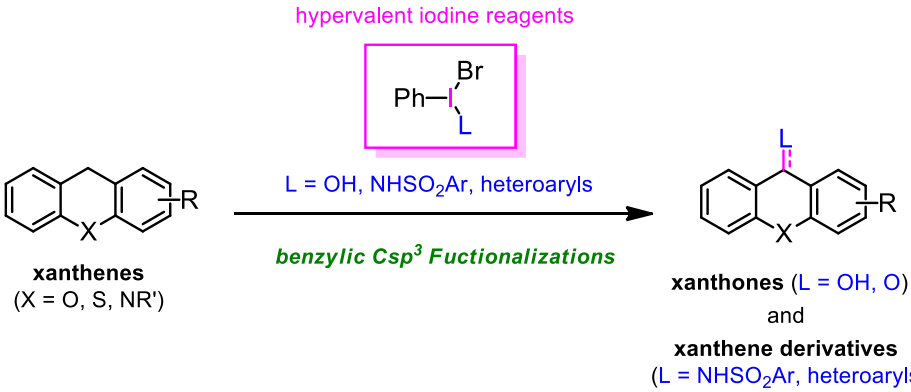


Abstract: Innovative monocyclic β-lactam entities create opportunities in the battle against resistant bacteria because of their PBP acylation potential, intrinsically high β-lactamase stability and compact scaffold. α-Benzylidene-substituted 3-amino-1-carboxymethyl-β-lactams were recently shown to be potent PBP inhibitors and constitute eligible anchor points for synthetic elaboration of the chemical space around the central β-lactam ring. The present study discloses a 12-step synthesis of ten α-arylmethylidenecarboxylates using a microwave-assisted Wittig olefination as the crucial reaction step. The library was designed aiming at enhanced β-lactam electrophilicity and extended electron flow after enzymatic attack. Additionally, increased β-lactamase stability and intermolecular target interaction were envisioned by tackling both the substitution pattern of the aromatic ring and the β-lactam C4-position. The significance of α-unsaturation was validated and the R39/PBP3 inhibitory potency shown to be augmented the most through decoration of the aromatic ring with electron-withdrawing groups. Furthermore, ring cleavage by representative β-lactamases was ruled out, providing new insights in the SAR landscape of monocyclic β-lactams as eligible PBP or β-lactamase inhibitors.

Benzylic Oxidation and Functionalizations of Xanthenes by Ligand Transfer Reactions of Hypervalent Iodine Reagents

Toshifumi Dohi,* Keina Komiyama, Shohei Ueda, Nobutaka Yamaoka, Motoki Ito, and Yasuyuki Kita* (kita@ph.ritsumei.ac.jp)

Heterocycles **2020**, *100*, 85–103. **DOI:** 10.3987/COM-19-14139

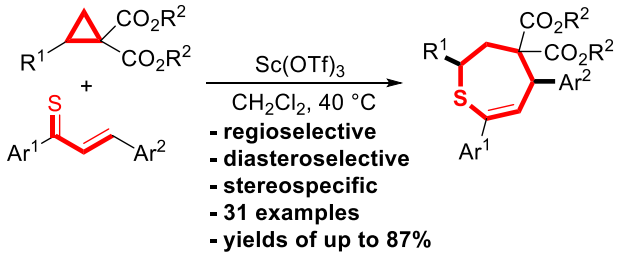


Abstract: The benzylic oxidation, amidation, and unprecedented heteroarylation proceed at room temperature using iodosobenzene, (sulfonylimido)iodobenzenes, and diaryliodonium(III) salts are described for the direct Csp³-H functionalizations of xanthene molecules. This study has demonstrated that hypervalent iodine reagents serve as unified synthetic tools for versatile xanthene Csp³-H transformations based on the radical and SET oxidation processes.

(4 + 3)-Cycloaddition of Donor–Acceptor Cyclopropanes with Thiochalcones: A Diastereoselective Access to Tetrahydrothiepines

André U. Augustin, J. Luca Merz, Peter G. Jones, Grzegorz Mlostón, and Daniel B. Werz* (d.werz@tu-braunschweig.de)

Org. Lett. **2019**, *21*, 9405–9409. **DOI:** 10.1021/acs.orglett.9b03623.

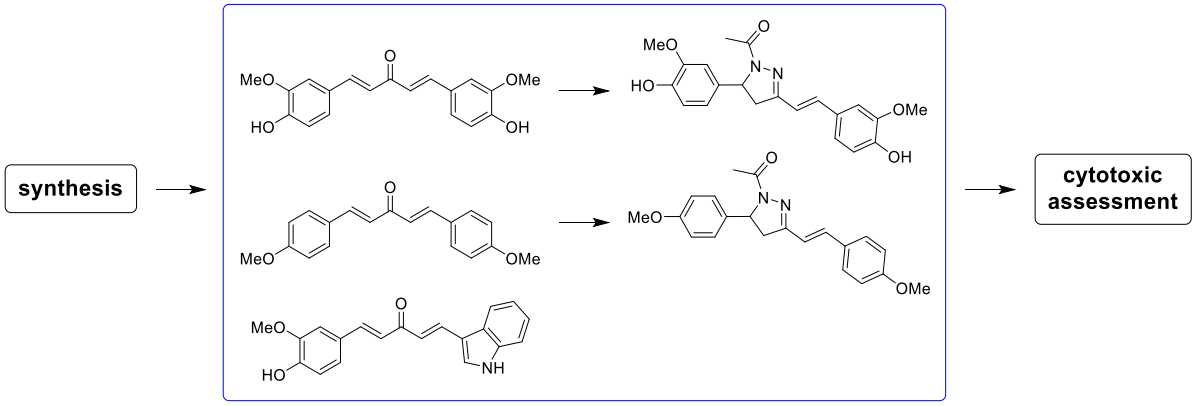


Abstract: A general approach is described for the formation of tetrahydrothiepines using donor–acceptor cyclopropanes. Thiochalcones, functioning as sulfur-containing four-atom building blocks, were reacted in a Lewis acid catalyzed formal (4 + 3)-cycloaddition reaction with donor–acceptor cyclopropanes as three-atom building blocks. Under mild conditions various tetrahydrothiepines were synthesized in good yields in a stereospecific reaction with high functional group tolerance.

Synthesis and Cytotoxic Evaluation of Monocarbonyl Curcuminoids and Their Pyrazoline Derivatives

Tim Van de Walle, Atiruj Theppawong, Charlotte Grootaert, Steven De Jonghe, Leentje Persoons, Dirk Daelemans, Kristof Van Hecke, John Van Camp,* Matthias D'hooghe* (john.vancamp@ugent.be or matthias.dhooghe@ugent.be)

Monatshefte Chem. **2019**, *150*, 2045–2051. **DOI:** 10.1007/s00706-019-02516-1



Abstract: A small set of structurally different monocarbonyl curcuminoids was prepared and screened for cytotoxic activity. In particular, bis-3-methoxy-4-hydroxy- and bis-4-methoxyphenyl-substituted monocarbonyls were synthesized and transformed into the corresponding three-dimensional N-acetylpyrazoline derivatives. In addition, a non-symmetrical indole-based monocarbonyl curcumin was prepared as well. Preliminary cytotoxic evaluation revealed significant effects for 4-hydroxy (pyrazoline) monocarbonyl curcuminoids, whereas the non-phenolic variants displayed rather poor activity.

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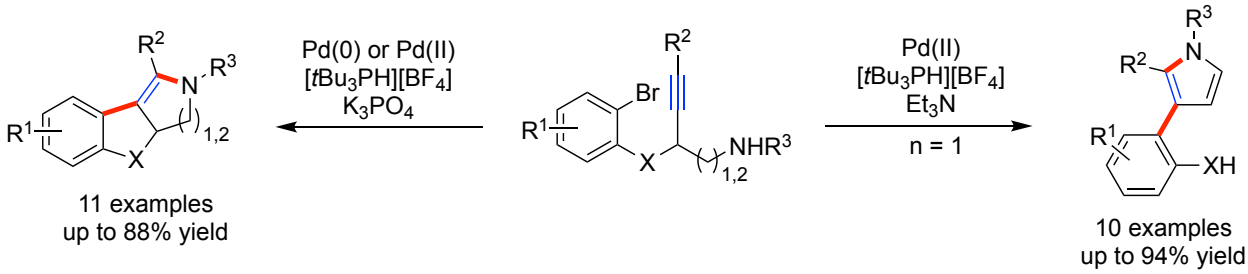
An *anti*-Carbopalladation/Amination Cascade with Alkynes: Access to Tetrasubstituted Enamines and Pyrroles

Theresa Schitter, Simon Stammwitz, Peter G. Jones, and Daniel B. Werz* (d.werz@tu-braunschweig.de)
Org. Lett. **2019**, *21*, 9415–9419. **DOI:** 10.1021/acs.orglett.9b03625



Abstract: A palladium-catalyzed intramolecular formal anti-carboamination of internal alkynes for the synthesis of tetrasubstituted enamines and pyrroles is reported. A broad range of different aniline derivatives, and also alkylated and benzylated amines, were used for the termination of the cascade. In the follow-up chemistry, we demonstrate that the TBS-protected pyrrole can be converted to a variety of other substituted pyrroles.