Issue 97 **February 2026**

The I.S.H.C. Bulletin

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Issue 97 February 2026

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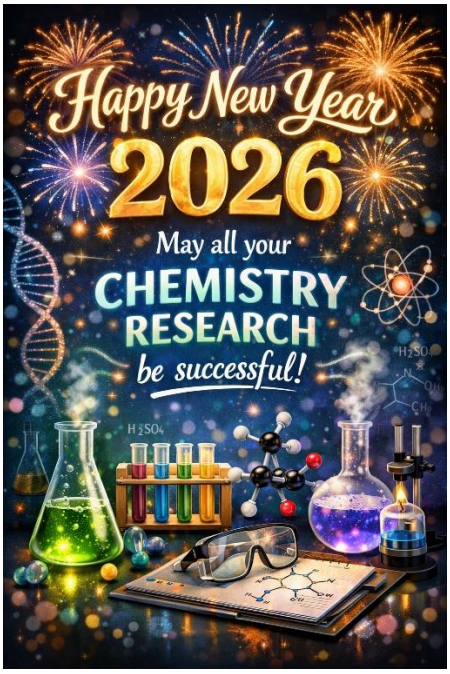

(the Secretary apologies for any errors in the chatgpt-generated image!)

**** SAVE THE DATE: 30th ISHC CONGRESS: July 19–24, 2026**, at **USP São Carlos, Brazil**
Congress Website now open: https://ishc-brazil2026.com/
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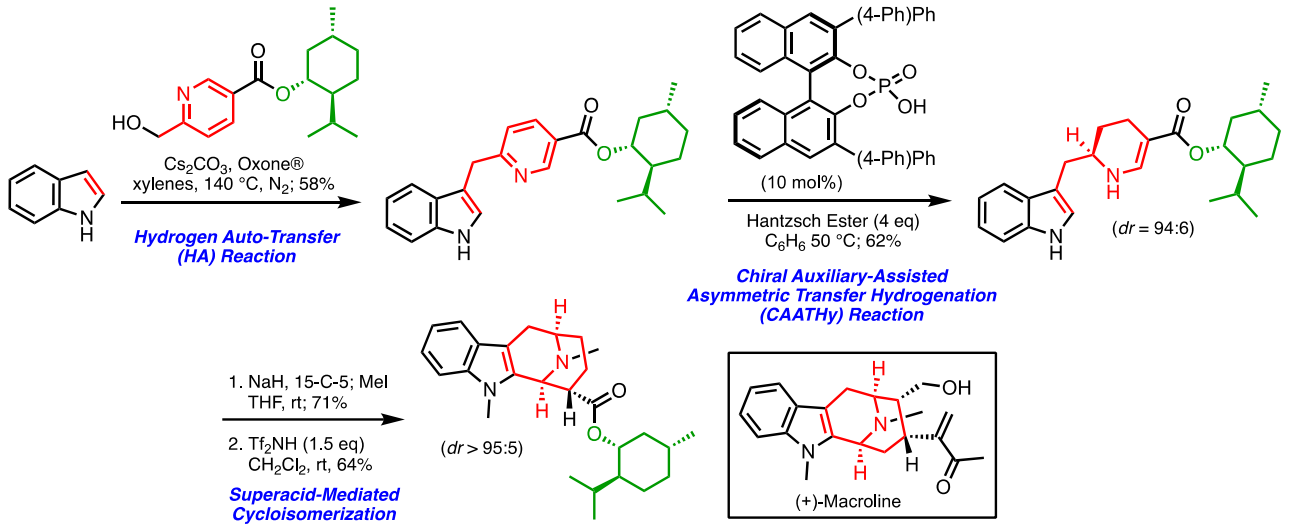
Asymmetric Synthesis of the 9-Azabicyclo[3.3.1]nonane Core of Macroline-Type Alkaloids

Ashlyn Bohn, Benjamin M. Cipriano, Nikhil R. Tasker, and Peter Wipf

Synthesis **2026**, eFirst **DOI**: 10.1055/a-2779-1148

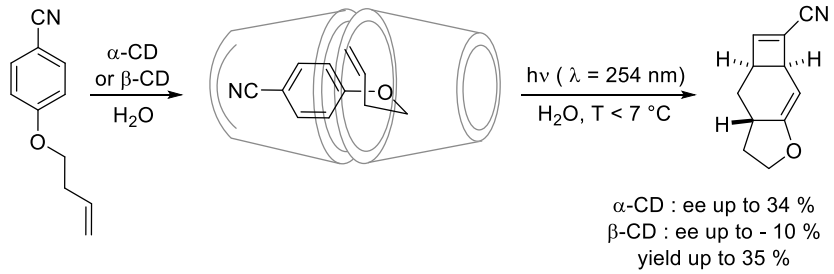


The macroline/sarpagine/ajmaline class of natural products comprises >300 structurally related monoterpene indole alkaloids, with an indole-fused 9-azabicyclo[3.3.1]nonane (9-ABN) core representing the structural hallmark of this class of natural products. A sequential application of three key reactions – hydrogen auto-transfer, chiral auxiliary-assisted asymmetric transfer hydrogenation, and superacid-mediated cycloisomerization – provides an efficient access to the 9-ABN core. The bridged tetracyclic product is thus obtained in 4 steps and 16% overall yield from 1*H*-indole. The chiral pool auxiliary, L-menthol, is used to improve the conversion in the HA reaction and increase the diastereoselectivity in the CAATHy process, thus showcasing a rare example for the synergistic combination of a chiral Brønsted acid catalyst and a chiral auxiliary.

Intramolecular [2 + 2] Photocycloaddition of Benzene Derivatives–Chiral Induction in Cyclodextrin Inclusion

Arthur Desvals, Corentin Lefebvre, Agathe Martinez, N. Hoffmann

J. Org. Chem. **2025**, *90*, 17635–17643. **DOI:** https://doi.org/10.1021/acs.joc.5c01616

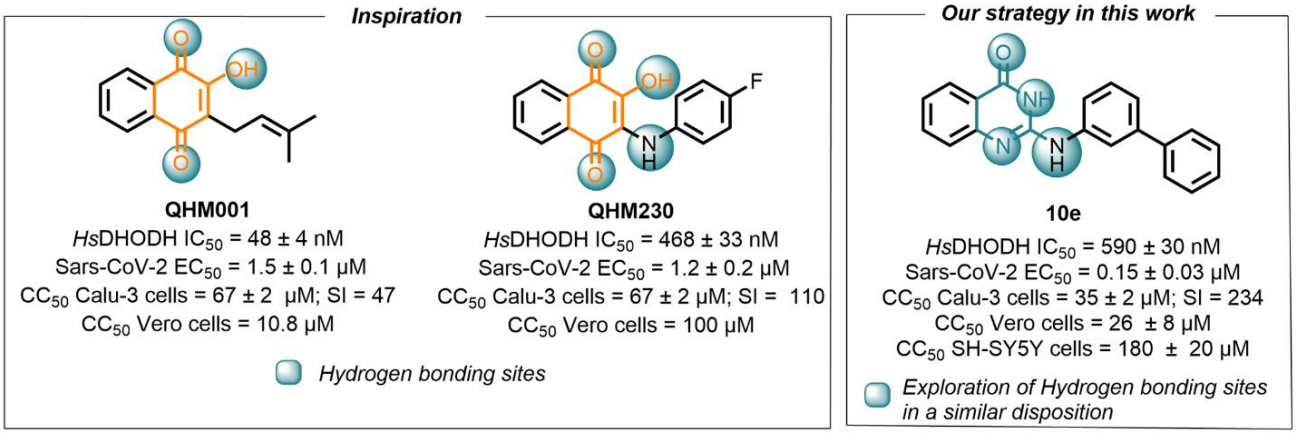


The cyclodextrin (CD) complexes of several butenyloxybenzonitriles were synthesized and irradiated as aqueous suspensions. An enantioselective intramolecular [2 + 2] or ortho photocycloaddition in such inclusion complexes is described. α-Cyclodextrin and β-cyclodextrin induce chirality in the opposite direction. At the reaction temperature (<7 °C), the enantiomeric excess (ee) is significantly increased (34% for α-CD, −10% for β-CD). The product yield in the cyclodextrin complex (35%) was close to that one of the racemic reaction in solution (42%). A topological analysis describes C_2-symmetric chiral induction in a C_6-symmetric host structure (α-Cyclodextrin). In a computational study, the energies of the inclusion complex were calculated for different conformations of compound **3a**.

Quinazolinones as Bioisosteres of Naphthoquinones: A Path to Potent HsDHODH Inhibitors with Optimized Properties

Bruna F. Godoi, Jéssica D. Bueno, Wemenes J. L. Silva, Aline D. da Purificacao, Pedro I. P. Leite, Thiago dos Santos, Murillo Freitas, Daniel G. Silva, Tais C. Silva, Josué de Moraes, Caroline S. Freitas, Mayara Mattos, Thiago M. L. Souza, Bianca A. Martin, Renata F. V. Lopez, M. Cristina Nonato*, Carolina H. Andrade,* and Flavio S. Emery*

ACS Medicinal Chemistry Letters **2026**, *17*, 99–108 https://doi.org/10.1021/acsmedchemlett.5c00237

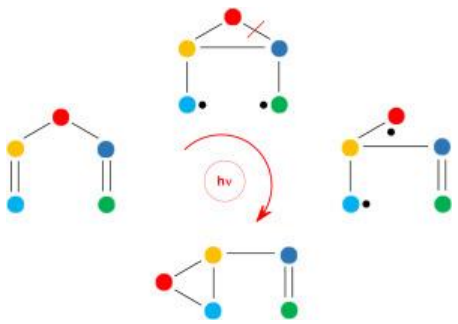


Human dihydroorotate dehydrogenase (*Hs*DHODH) is a key enzyme in pyrimidine biosynthesis and a target for antiviral therapies against RNA viruses like SARS-CoV-2. Building on prior quinone-based inhibitors, we explored quinazolinones as bioisosteric replacements to reduce cytotoxicity and off-target effects. Through structure-based design, we synthesized quinazolinone derivatives aimed at maintaining critical binding interactions. First-generation compounds showed moderate *Hs*DHODH inhibition (up to 60% at 250 µM), with compound **10c** having an IC_{50} of 25 µM. Using computational modeling, we optimized second-generation derivatives, with **10e** showing the highest potency (IC_{50} = 0.59 ± 0.03 µM) and significant antiviral activity against SARS-CoV-2 (EC_{50} = 0.15 ± 0.03 µM). These compounds demonstrated improved selectivity compared to naphthoquinone analogs, though challenges with aqueous solubility remain. These results highlight quinazolinones as promising scaffolds for further development of anti-SARS-CoV-2 therapies targeting *Hs*DHODH.

Di-π-methane, Oxa-di-π-methane, and Aza-di-π-methane Photoisomerization

Norbert Hoffmann

Comprehensive Organic Synthesis, 3rd Edition (G. Molander, P. Knochel, Eds.), *Vol. 5* (D. Trauner, S. Ma, W. Kong, Eds.), Elsevier, Amsterdam **2025**, 340-350.
DOI: https://doi.org/10.1016/B978-0-323-96025-0.00103-4



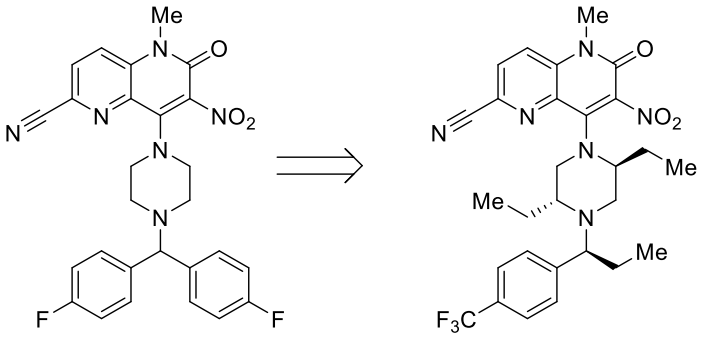
The chromophore of a di-π-methane photoisomerization, also called di-π-methane rearrangement, is composed of two alkene moieties which are connected by a sp^3 carbon atom. In such reactions, vinyl cyclopropane compounds are generated and a high degree of molecular complexity is generated, which makes them particularly interesting for application in organic synthesis, for example, of natural products. The reaction has frequently been carried out with a variety of barrelene derivatives. The di-π-methane photoisomerization is often carried out using triplet sensitization. In this context, visible light and appropriate sensitizer

are used. Recent investigations also deal with complex photochemical reaction sequences in which a di-π-methane rearrangement is involved. Different carbon atoms of the chromophore can be replaced by heteroatoms. Thus, the sp^3 carbon was replaced by a boron or a phosphorous atom. The oxa-di-π-methane photoisomerization is observed when one of the alkenes is replaced by a carbonyl function. These reactions are also applied to the synthesis of complex natural products. Visible light can induce the reaction when Lewis acid complexation of the substrates is applied.

Design, Synthesis, and T Cell Checkpoint Combination Potential of First-In-Class DGK*α/ξ* Inhibitor BMS-986408

Denise C. Grünenfelder,* Upender Velaparthi, Jayakumar S. Warrier, Louis Chupak, Chetan Padmakar Darne, Bireshwar Dasgupta, T. G. Murali Dhar, Min Ding, Robert Gentles, Yazhong Huang, Prasada R. Jalagam, Manjunatha Narayana Rao Kamble, Raju Mannoori, Scott Martin, Shana L. Posy, Hasibur Rahaman, Thiruvenkadam Raja, Kotha Rathnakar Reddy, Saumya Roy, Amy Sarjeant, John S. Tokarski, Gopikishan Tonukunuru, Sivasudar Velaiah, Xiaofan Zheng, Aravind Anandam, Gopal Dhar, Shailesh Dudhgaonkar, R. Marcus Fancher, Siddheshwar Layane, Si-Qi Liu, Swagatam Ray, Hongchen Qiu, Susan Wee, Sagnik Chatterjee, Myrtle Davis, Elizabeth Dierks, Anoop Kumar, Thanga Mariappan, Robin Moore, Bokka Venkata Murali, Ramola Sane, Dana Banas, Deepa Calambur, Erica Cook, Priya Dehal, Hua Fang, Gregory Locke, Joseph G. Naglich, Madhu Sudhan Ravindran, Lumelle Schneeweis, Debarati M. Tagore, Mark Witmer, Abigail E. Witt, Dianlin Xie, Emma Lees, Michael Wichroski, Nicholas A. Meanwell, Robert Borzilleri, and Richard E. Olson.

Journal of Medicinal Chemistry, **2025**, *68*, 21840-21859. DOI: 10.1021/acs.jmedchem.5c02240



BMS-502 **BMS-408**

DGK*α* and DGK*ζ* are intracellular T cell checkpoints that negatively regulate T cell signaling, activation, and tumor immunity. Inhibition of DGK*α/ζ* is an attractive mechanism for next-generation immunotherapy, with the potential to broaden the response to existing cancer treatments, including anti-PD-1 and anti-CTLA-4. The lead molecule BMS-502 was optimized to the first-in-class dual DGK*α/ζ* inhibitor BMS-986408 (BMS-408), starting with the replacement of an aryl nitro group that posed a potential liability. Subsequent improvement in cellular potency, cross-species oral pharmacokinetic profile, and optimization of physicochemical properties led to the identification of the development candidate BMS-408. In preclinical studies, BMS-408 demonstrated dose-proportional pharmacokinetics and pharmacodynamics in mice, as well as robust efficacy in combination with either anti-PD-1 and/or anti-CTLA-4 in MC-38 and 1956 tumor models. Given the favorable *in vitro* and *in vivo* profiles, as well as *in vivo* pharmacology, BMS-408 was advanced to clinical development.

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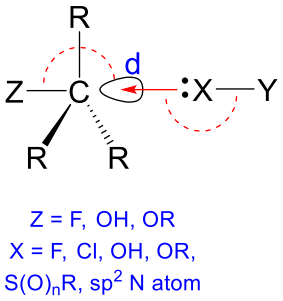
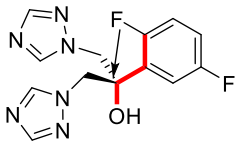
Carbon Atom σ-Hole Tetrel Bonding – A Non-Bonded Interaction with Potential Application in Drug Design

Nicholas A. Meanwell

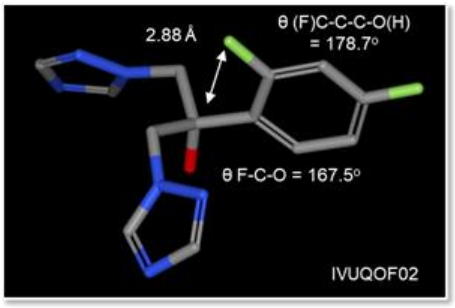
Medicinal Chemistry Research **2025**, *34*, 2414-2471. DOI: 10.1007/s00044-025-03440-2



Z = F, OH, OR
X = F, Cl, OH, OR,
$S(O)_nR$, sp^2 N atom



fluconazole

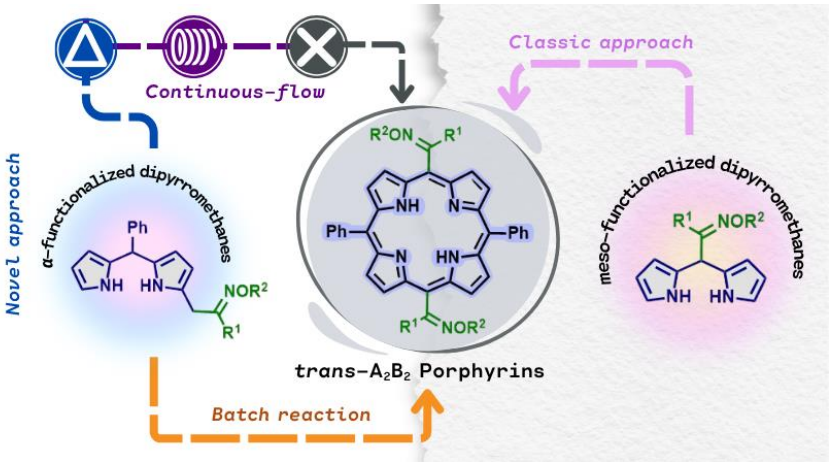


The non-bonded interaction between the positive electrostatic potential associated with a σ *-orbital (the σ hole) of a substituted carbon atom and an atom with a lone pair of electrons is referred to as tetrel bonding and can be expressed in both intermolecular and intramolecular manifolds. Intermolecular tetrel bonding can contribute to the inventory of interactions that convene protein-ligand complexes while intramolecular tetrel bonds can influence the conformation of a molecule. While the energy associated with a carbon-based tetrel bond is calculated to be of a modest value, ranging from ~5 kcal/mole for a close contact between optimal partners to ~1 kcal/mole for a more relaxed and what is perhaps the more typical interaction, the prevalence of carbon tetrel bonding in drug design may be underappreciated. The energy of a carbon-based σ-hole tetrel bonding interaction has been equated with that calculated for the more prominent n→π* multipolar-type of tetrel bonding interaction or a C-H→π bond, both of which are recognized as interactions of value in drug design. In this review, we provide a perspective on the evidence in support of intermolecular and intramolecular σ-hole tetrel bonding interactions in the context of geometric parameters associated with drug and drug-like molecule structures deposited in the Cambridge Structural Database (CSD) and the Protein Data Bank (PDB).

Synthetic Pathway to trans-A2B2-Porphyrins: From Oxime Substituted Dipyrromethanes to Functionalized Macrocycles

João Simões, Bruna Costa, Ana Clara Beltran Rodrigues, Susana M. Lopes, J. Seixas de Melo, M. Pineiro, T. M. V. D. Pinho e Melo*

J. Org. Chem. **2025**, *90*, 16060−16069 https://doi.org/10.1021/acs.joc.5c01907



An unprecedented approach to trans-A2B2-porphyrins from α-oxime-functionalized dipyrromethanes has been disclosed. Initially aimed at BODIPY synthesis, the process serendipitously yielded porphyrins with photophysical properties suitable for use as photosensitizers in photodynamic therapy (PDT), as mirrored by its ΦΔ values which ranged from 66% to 86%. This unexpected discovery paves the way for innovative synthetic approaches to macrocycles via DDQ-mediated metal-free C(sp^3)–C(sp^2) cross-coupling reactions. The synthesis under batch reaction conditions was successfully transposed to the more

sustainable continuous-flow synthesis. Furthermore, meso-oxime-functionalized trans-A2B2-porphyrins were also obtained via the classic [2+2]-type reaction between meso-oxime-functionalized dipyrromethanes and aldehydes.
