



Issue 96

December 2025

The I.S.H.C. Bulletin
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Issue 96 December 2025

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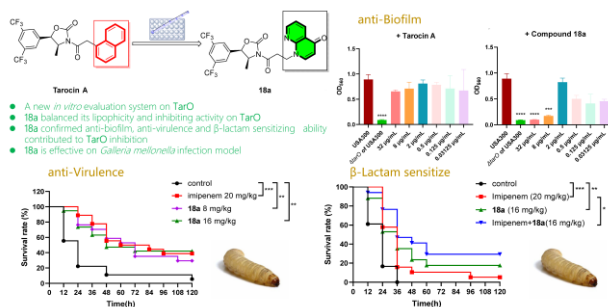
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Call for nominations for the **2026 ISHC E. C. Taylor Senior Award**, the **2026 ISHC A. R. Katritzky Junior Award**, and the **2026 ISHC Industrial Award**, is now open. Closing Date: **15th January 2026**.

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Design, synthesis and optimization of TarO inhibitors as multifunctional antibiotics against Methicillin-resistant *Staphylococcus aureus*.

Yuanchen Zhong, Feifei Chen, Dianyan Chen, Qian He, Xiaofei Zhang*, Lefu Lan*, and Chunhao Yang
npj Antimicrobials and Resistance. 2025, 3: 28 . DOI: 10.1038/s44259-025-00098-z



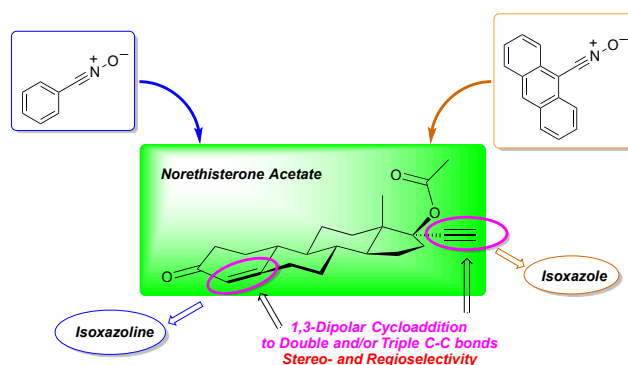
UDP-*N*-acetylglucosamine-undecaprenyl-phosphate *N*-acetylglucosaminophospho-transferase (TarO) has been found to simultaneously contribute to β-lactam resistance and virulence of Methicillin resistant *Staphylococcus aureus* (MRSA). However, optimization of hit compounds targeting TarO has been hindered due to their high lipophilicity and the poor correlation between the enzyme activity inhibition and β-lactam sensitization. In this study, 31 analogues of Tarocin A were designed, synthesized and evaluated by a luminescence-based reporter preliminary screening. In the subsequent β-lactams synergy test, a good correlation was observed between the results obtained from these two methods. Finally, analog **18a** with more potential against TarO and an improved hydrophilicity ($clogP = 3.2$) was obtained. Compared with Tarocin A, **18a** shows stronger β-lactam sensitizing and anti-biofilm activities *in vitro*, as well as potent anti-virulence and synergistic potency with imipenem *in vivo*. These results suggest that TarO is a promising target for combating MRSA, and **18a** can serve as a lead molecule.

Stereo- and regioselectivity in nitrile oxide cycloaddition reactions to norethisterone acetate as dipolarophile

Giuseppe Faita, Mariella Mella and Paolo Quadrelli

Steroids, 2025, 217, 109598.

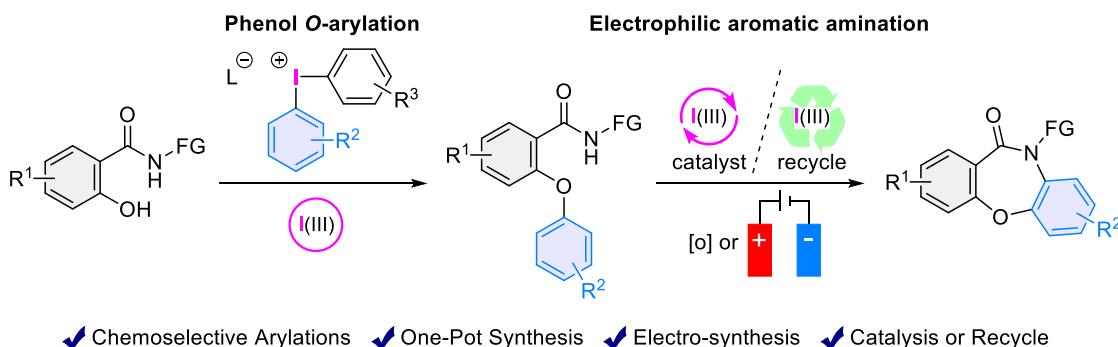
DOI: 10.1016/j.steroids.2025.109598



Benzo- and anthracenenitrile oxides undergo 1,3-dipolar cycloaddition reactions with 17α-acetate norethisterone affording the expected isoxazoline and isoxazoles derivatives in good yields and as single regioisomers. The structures of all the new compounds were elucidated on the basis of the corresponding analytical and spectroscopic data, which were presented and discussed. The stereo- and regiochemical outcome of the cycloadditions were also accounted on the basis of 1,3-dipolar cycloaddition theory and computational investigations. Electronic (Frontier Orbital theory) and steric effects are at work in orienting selectively the cycloaddition to specific regioisomeric steroids.

Transition-Metal-Free Dibenzoxazepinone Synthesis by Hypervalent Iodine-Mediated Chemoselective Arylcyclizations of *N*-Functionalized Salicylamides

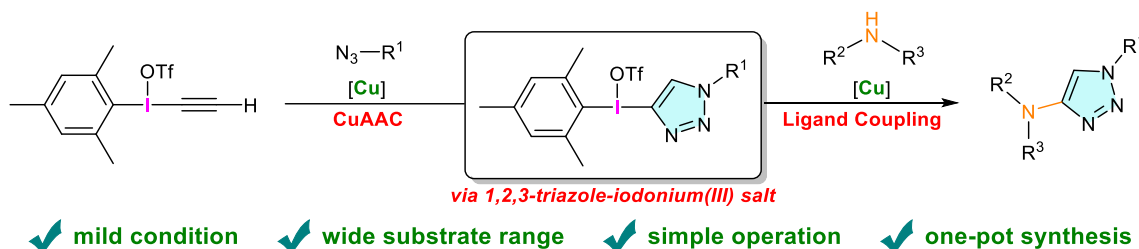
Naoki Miyamoto, Kotaro Kikushima, Hirotaka Sasa, Ten Katagiri, Naoko Takenaga, Yasuyuki Kita,* Toshifumi Dohi*
Chem. Commun. **2025**, 61, 1882-1885. DOI: <https://doi.org/10.1039/D4CC05165C>



We have developed transition-metal-free synthetic methodologies for dibenzoxazepinones utilizing salicylamides as starting materials and employing two distinct types of successive hypervalent iodine-mediated arylocyclizations. This synthetic protocol encompasses selective phenol *O*-arylation of salicylamides with diaryliodonium salts, followed by electrophilic aromatic amination utilizing chemically or electronically generated hypervalent iodine reagents in the second stage of the process.

Divergent Synthesis of 4-Aminotriazoles Through Click Cycloaddition and Generation of Iodonium(III) Triazoles

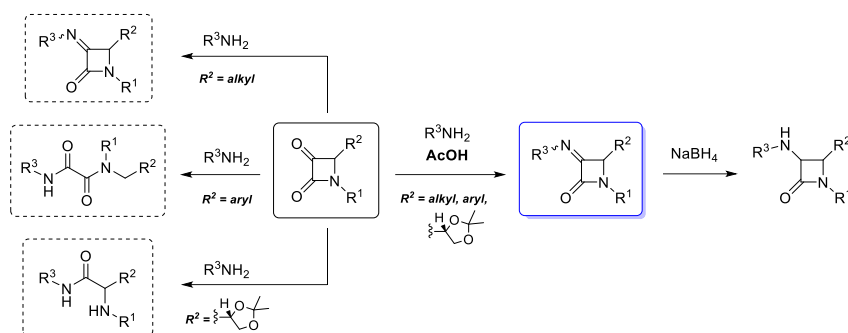
Takumi Hayashi, Elghareeb E. Elboray, Hina Sudo, Naoko Takenaga, Hiroyuki Satake, Toshifumi Dohi*
Eur. J. Org. Chem. **2025**, 28, e202401273. DOI: <https://doi.org/10.1002/ejoc.202401273>



A strategy for synthesizing 4-amino-1,2,3-triazoles was established through sequential click cycloaddition and aminations mediated by triazolyl(Mes)iodonium salts. This method employs a copper-catalyzed process, characterized by mild conditions, a broad substrate scope, and straightforward operational procedures. The method facilitates the efficient construction of substituted aminotriazoles through both stepwise and one-pot syntheses. The practical synthesis of triazolyliodonium salts as stable solids is expected to enable further derivatizations.

Synthesis of 3-amino- β -lactams through selective imination of 3-oxo- β -lactams

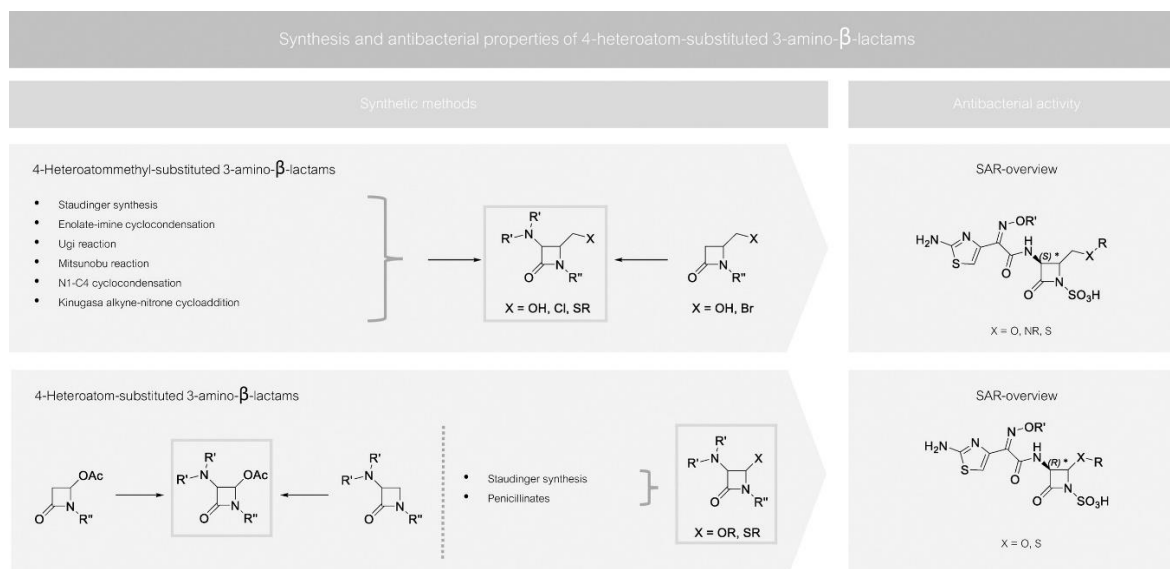
Sari Deketelaere, Emma Vandenheede, Nicola Piens, Lore Cools, Lieselotte Crul, Lotte Demeurisse, Karen Mollet, Christian V. Stevens and Matthias D'hooghe*
Journal of Organic Chemistry **2025**, 90, 5903-5916 DOI: 10.1021/acs.joc.5c00205



3-Oxo- β -lactams are known to deliver different types of reaction products upon treatment with primary amines, predominantly governed by the nature of the C4 substituent. In this work, a C4 substituent-independent protocol for the conversion of 3-oxo- β -lactams to the corresponding 3-imino- β -lactams was developed. By using primary amine hydrochloric acid salts in combination with 2,4,6-collidine, or free primary amines in combination with acetic acid, the undesired ring opening of 4-aryl- and (S)-4-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)azetidione-2,3-diones toward ethanediamides or α -aminoamides, respectively, is avoided, enabling the smooth transformation of any 3-oxo- β -lactam into its imine counterpart. As demonstrated by the ensuing synthesis of 3-alkylamino- β -lactams, 3-imino- β -lactams serve as building blocks for the construction of functionalized 3-amino- β -lactams, the latter being key motifs in drug discovery.

Synthesis and antibacterial properties of 3-amino- β -lactams bearing a heteroatom-containing C4 substituent

Kato Bredael, Fien Vanhecke, Emma Vandenheede, Christian V. Stevens, Stanislav Gobec and Matthias D'hooghe*
ChemMedChem **2025**, 20, e202400994 DOI: 10.1002/cmdc.202400994



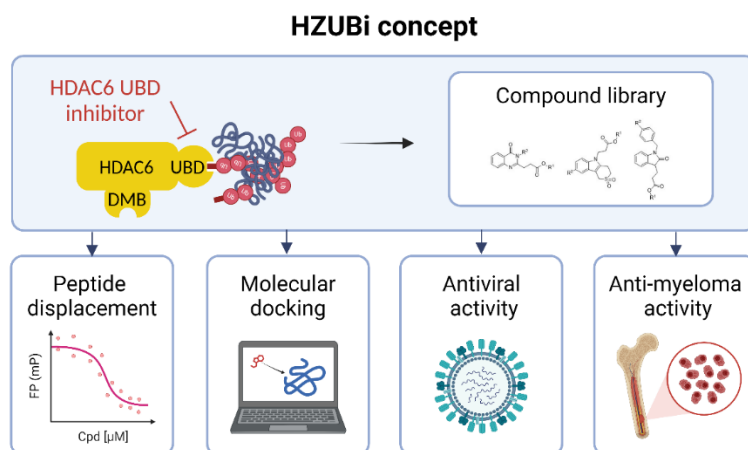
The rise of antimicrobial resistance has spurred the search for innovative antibiotics, with monocyclic 3-amino- β -lactams – aztreonam standing out as key example – showing significant potential. In particular, C4-functionalized 3-amino- β -lactams have emerged as a promising subclass that can potentially improve the activity, stability and cellular permeability of the compounds. This review outlines various synthetic methodologies available for the construction of 3-amino- β -lactams bearing a heteroatom-containing substituent at C4, with the heteroatom connected to the ring system either directly or via a methylene bridge. Special attention is devoted to 3-amino-4-hydroxymethyl- β -lactams and 3-amino-4-acetoxy- β -lactams as versatile synthetic intermediates. Moreover, the effect of these C4 substituents on the biological activity of the corresponding 3-amino- β -lactams is discussed in detail. A better understanding of synthetic protocols and antibacterial properties related to this underexplored class of monocyclic 3-amino- β -lactams might contribute to address the current antibiotics problems we are facing more efficiently.

Synthesis and functional screening of novel inhibitors targeting the HDAC6 zinc finger ubiquitin-binding domain

Silke Geurs, Eleni Staessens, Kato Bredael, Stefaan Borghgraef, Jordy De Ridder, Leentje Persoons, Steven De Jonghe, Dominique Schols, Mandeep K. Mann, Rachel J. Harding, Jorick Franceus, Tom Desmet, Kristof Van Hecke, Dorien Clarisse, Karolien De Bosscher and Matthias D'hooghe*

European Journal of Medicinal Chemistry **2025**, *285*, 117208

DOI: 10.1016/j.ejmech.2024.117208



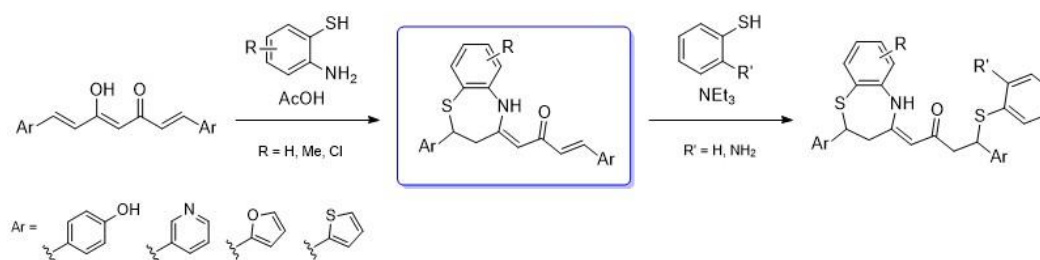
Histone deacetylase 6 (HDAC6) is a promising target for treating neurodegenerative disorders, several cancer types and viral infections. Unique among HDACs, the HDAC6 isoform possesses a zinc finger ubiquitin-binding domain (UBD) crucial for managing misfolded protein aggregates and facilitating viral infection. HDAC6 binds aggregated polyubiquitinated proteins through its UBD, mediating their transport to the aggresome and subsequent removal via autophagy. Despite the importance of the UBD in proteostasis and viral infection, its pharmacological inhibition has been minimally explored thus far, with research largely focused on the deacetylase domain. We synthesized a diverse library of new compounds designed to target the HDAC6-UBD, termed HZUBi, with varied core structures including quinazolinone, oxindole and tetrahydrothiopyrano[4,3-b]indole, aimed at enhancing UBD interaction and extending into the side pocket. New structure-activity relationships were established, computational docking and molecular dynamics studies were performed and the functional impact of selected inhibitors was assessed in the context of multiple myeloma and viral infection. Several new HZUBi could displace a ubiquitin peptide from HDAC6-UBD in a differential manner, although to a lower extent than the literature reference compound HZUBi-3e. Despite exhibiting in vitro target engagement, neither HZUBi-3e nor its ester prodrug HZUBi-1e enhanced proteasome inhibitor-mediated multiple myeloma cell killing. Finally, none of the screened HZUBi triggered anti-viral activity.

Synthesis and cancer cell cytotoxicity of 6-, 7- or 8-substituted 2-(hetero)aryl-4-(4-(hetero)aryl-2-oxobut-3-en-1-ylidene)benzothiazepanes

Katarina Magdalenic, Donatien Morillon, Steven De Jonghe, Leentje Persoons, Dominique Schols, Kristof Van Hecke, Charlotte Grootaert, John Van Camp and Matthias D'hooghe*

Journal of Heterocyclic Chemistry **2025**, *62*, 249-256

DOI: doi.org/10.1002/jhct.4936



Cancer chemotherapy is continuously challenged by serious complications like pronounced side effects and multidrug resistance (MDR). Natural products, such as curcumin, offer promising alternatives due to their diverse biological applications and low toxicity. However, curcumin's clinical utility is limited by poor bioavailability, rapid metabolism and non-specific (PAINS) activity.

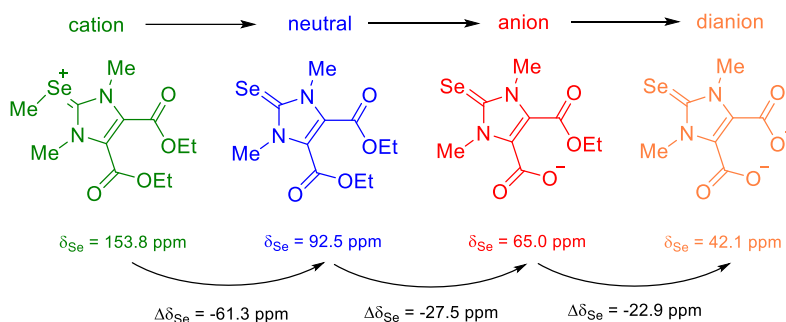
Building on previous findings, this study explored the structural modification of curcumin-inspired benzothiazepane derivatives in an attempt to enhance their therapeutic potential through modifications of the two peripheral (hetero)aromatic rings and the benzothiazepane scaffold. In this way, eight new 2-(hetero)aryl-4-(4-(hetero)aryl-2-oxobut-3-en-1-ylidene)benzothiazepanes and two 4-thiobutan-2-one 'double Michael addition' derivatives were synthesized and tested for cytotoxicity against a panel of eight cancer cell lines. The screening results indicated that bis-(4-hydroxyphenyl) analogs bearing a chlorinated benzothiazepane ring exhibited the highest potency and broad-spectrum activity at the low micromolar range. Bis-substitutions with 3-pyridinyl and 2-furyl groups showed less potent but more specific activity profiles, potentially reducing PAINS effects. 2-Aminothiophenol-derived double Michael addition products demonstrated increased broad-spectrum activity, highlighting the importance of the free aniline amino group for targeted effects. This study underscores the potential of benzothiazepane derivatives as viable cancer cell cytotoxic agents and provides useful insights for future optimization and evaluation.

Studies on the effect of positive and negative charges on the ^{77}Se NMR shifts of selenones and selenenyls of N-heterocyclic carbenes of imidazolium-4,5-dicarboxylates.

Lucas Pruschinski, Sean Ray Kahnert, Colin Herzberger, Jan C. Namyslo, Andreas Schmidt*

J. Org. Chem. **2025**, *90*, 2201–2213.

DOI: 10.1021/acs.joc.4c02581.



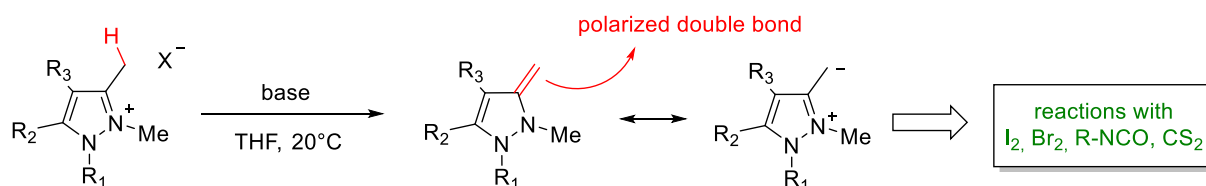
^{77}Se NMR shifts of selenones (selones) are considered a measure of the p-properties of the underlying N-heterocyclic carbenes. However, the shifts are very sensitive to external (solvent, pH, temperature, reference reagent, reference method) and internal parameters (substituent effects, steric effects, nonclassical hydrogen bonds, anisotropy, type of conjugation), which can lead to difficulties in reliably interpreting these values. The Se adducts of 1,3-imidazole-4,5-dicarboxylic acid derivatives were therefore prepared as diesters, monoesters, as well as dianionic dicarboxylates, and methylations to cationic selenenyls were carried out. Thus, these model compounds allow systematic investigation of the influence of charges on the ^{77}Se NMR shifts, as both structural changes and changes in the measurement conditions were minimized. The signals show considerable pH and solvent dependence (MeOD, CDCl_3 , CD_2Cl_2 , CD_3COOD , CD_3CN , acetone- d_6 , THF- d_8 , pyridine- d_5 , toluene- d_8 , DMSO- d_6). Linear relationships between the HOMO and LUMO energies and the ^{77}Se NMR shifts were found.

N-Heterocyclic Olefins of Pyrazole and Indazole

Bolin Zhu, Rouven Woyciechowski, Eike G. Hübner, Felix Lederle and Andreas Schmidt*

Org. Lett. **2025**, *27*, 5572–5577.

DOI: 10.1021/acs.orglett.5c00775



easy synthesis: deprotonation of heteranium salts

polarised olefin: upfield shifts in NMR

stable: no inert atmosphere necessary

nucleophile: adducts with electrophiles

superbase: calculated proton affinity > 260 kJ/mol

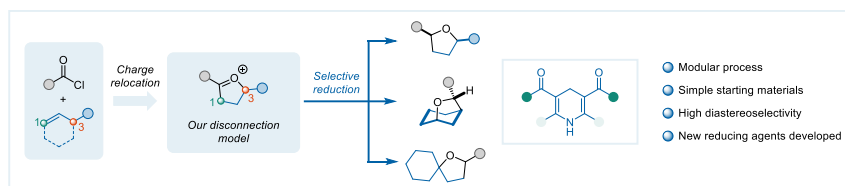
Pyrazole and indazole N-heterocyclic olefins (NHOs) were synthesized in excellent yields by deprotonation of 3-methylpyrazolium and 3-methylindazolium salts with KH or LiHMDS. Reactions were performed with isocyanates, halogens, and carbon disulfide. The measured NMR chemical shifts of the exocyclic methylene group of the NHOs are in the range of 3.2 to 4.5 ppm for the hydrogen atoms and 67 to 77 ppm for the carbon atom, which are less shielded and less polar than those of imidazole NHOs. The calculated proton affinities are 261 kcal/mol (indazole NHOs) and 272 kcal/mol (pyrazole NHOs). The calculated pK_a values are between 14.8 and 25.2, and the bond lengths of the exocyclic double bond are slightly shorter than those of imidazole NHOs. As expected, the highest occupied molecular orbitals (HOMO) show significant atomic orbital coefficients at the exocyclic carbon atom, around 10 percentage points higher for the pyrazole-NHOs.

Charge Relocation Enables a Modular and Diastereoselective Synthesis of *cis*-Substituted Tetrahydrofurans

Zhi-Jie Niu, Bogdan R. Brutiu, Margaux Riomet, Daniel Kaiser and Nuno Maulide*

Angew. Chem. Int. Ed. **2025**, *64* (29), e202503750;

DOI: 10.1002/anie.202503750

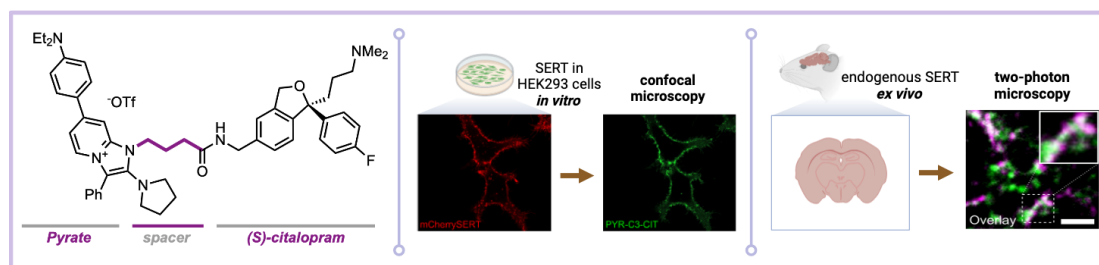


A disconnection model in which acylium ions generated from acyl chlorides are treated with variety of alkenes is reported for the synthesis of 2,5-*cis*-disubstituted tetrahydrofurans (THFs) and other THF derivatives. A charge relocation process leads to the formation of oxocarbenium ions, which are reduced to the desired THF structures. The development of sterically encumbered Hantzsch esters was crucial to the success of this highly diastereoselective process.

Fluorescent PyrAte-(S)-citalopram conjugates enable imaging of the serotonin transporter in living tissue

Oliver J. V. Belleza, Iakovos Saridakis, Nadja K. Singer, Xavier Westergaard, Sergio Armentia Matheu, Miran Lemmerer, Margaux Riomet, Pedro A. Sánchez-Murcia, Nina Kastner, Stefanie Rukavina, Yi Xiao, Kathrin Jäntschi, Marco Niello, Klaus Schicker, David Sulzer, Leticia González*, Nuno Maulide* and Harald H. Sitte*

Chem. Sci. **2025**, *16*, 6003–6013; DOI: [10.1039/D4SC06949H](https://doi.org/10.1039/D4SC06949H)



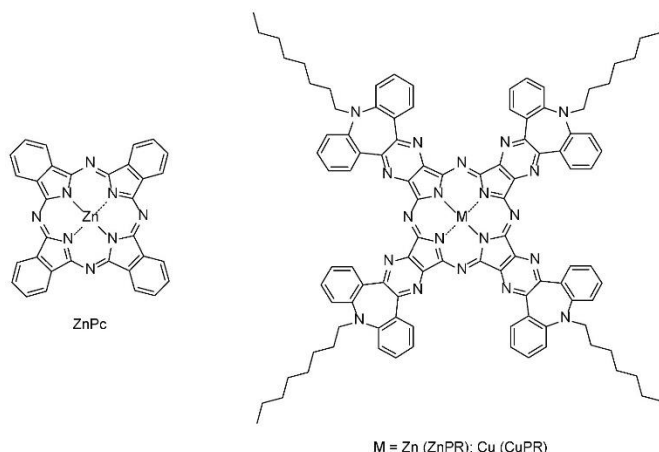
A recently developed class of fluorophores, termed PyrAtes, displays optimal brightness and large Stokes shifts that are ideal for fluorescence microscopy. Herein, we report the development of PyrAte-based fluorescently labeled ligands that bind to the serotonin transporter (SERT), a membrane transport protein important for neurotransmitter homeostasis, which hitherto has not been visualized in its native environment using fluorescent small molecules. The design of a PyrAte fluorophore attached to (S)-citalopram, a selective serotonin reuptake inhibitor, resulted in the synthesis of two fluorescent drug conjugates varying in linker length: PYR-C6-CIT and PYR-C3-CIT. Docking and molecular dynamics experiments are performed to estimate their binding affinities to SERT. Our *in vitro* experiments confirm both compounds are effectively binding to SERT overexpressed in human embryonic kidney 293 cells, with the shorter conjugate displaying improved SERT affinity and membrane staining properties. Furthermore, *ex vivo* imaging of endogenous SERT was demonstrated in acute mouse brain slices using two-photon microscopy.

The large Stokes shift of the PyrAte fluorophore enables simultaneous detection of its own fluorescence signal at 500 nm along with that of a yellow fluorescent protein-based serotonergic marker.

A Minimal Electronic Nose Based on Graphene Functionalized with Metalated Pyrazinoporphyrazines and Phthalocyanines for Ammonia, Benzene, and Hydrogen Sulfide Discrimination

Sonia Freddi, Luca Vaghi, Andrea Penoni, Luca Scapinello and Luigi Sangaletti

Chemosensors. **2025**, 13(5), Article # 165 DOI: 10.3390/chemosensors13050165



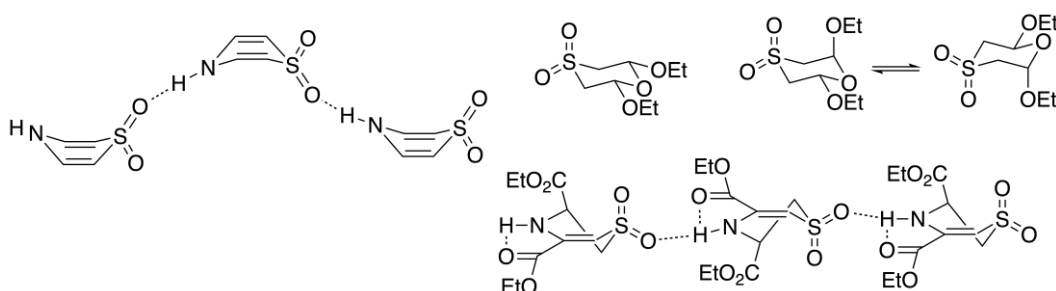
The development of electronic noses is, nowadays, essential for several applications, including breath analysis and industrial security. Ammonia, benzene, and hydrogen sulfide are particularly important due to their environmental and health impacts. Here, graphene-based sensors, functionalized with unconventional in-house synthesized zinc and copper octyl-pyrazinoporphyrazines and commercially available zinc phthalocyanine, have been prepared. Enhanced solubility given by the octyl chains allowed us to exploit drop-casting as a straightforward functionalization technique. The sensors demonstrated excellent performance for detecting ammonia, benzene, and hydrogen sulfide as a single sensor, with a competitive detection limit and a high sensitivity compared to the state of the art. In particular, functionalization enabled the detection of hydrogen sulfide, for which no response is observed with bare graphene, and lowered the detection limit for all the gases compared to bare graphene. Additionally, the prepared sensors have been assembled into an e-nose that shows promising potentiality to be used for both industrial and medical applications thanks to its excellent discrimination capability of single gases and mixtures.

X-Ray Structures of Some Heterocyclic Sulfones

R. Alan Aitken, David B. Cordes, Aidan P. McKay, Alexandra M. Z. Slawin and Dheirya K. Sonecha

Crystals **2025**, 15, 750 (1–13).

DOI: 10.3390/cryst15090750



1,4-Thiazine *S,S*-dioxide **1**, the *cis*- and *trans*-isomers **2** and **3** of its precursor 2,6-diethoxy-1,4-oxathiane *S,S*-dioxide, and diethyl 2,3-dihydro-1,4-thiazine-3,5-dicarboxylate *S,S*-dioxide **4** have been fully characterised, both in solution by ^1H and ^{13}C NMR and in the solid state by X-ray diffraction. Simulation has been used to model the unexpectedly complex ^1H NMR spectra and arrive at a full assignment of all chemical shifts and coupling constants. The crystal structures of both **1** and **4**, which adopt, respectively,

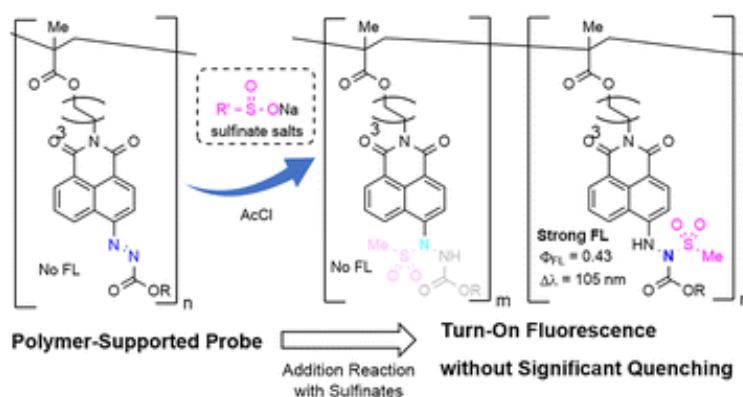
boat and half-chair conformations, are dominated by strong NH to O=S hydrogen bonding leading to chains of molecules. In the case of **4**, the NMR data point to an equatorial position of the C(2)-ester group in solution, while in the crystal, this adopts an axial orientation. Compounds **2** and **3** adopt chair conformations both in solution and in the solid state with ring inversion on the NMR timescale leading to unexpected simplification of the spectra in the case of **3**.

Synthesis of a Naphthalimide-Functionalized Polymethacrylate: A Turn-on Fluorescent Probe for Sulfinic Acids via Covalent Bond Formation

*Hiroki Tanimoto, Aoi Otsuki, Takenori Tomohiro

Org. Biomol. Chem. **2025**, 23(34), 7759–7765.

DOI: 10.1039/D5OB00967G



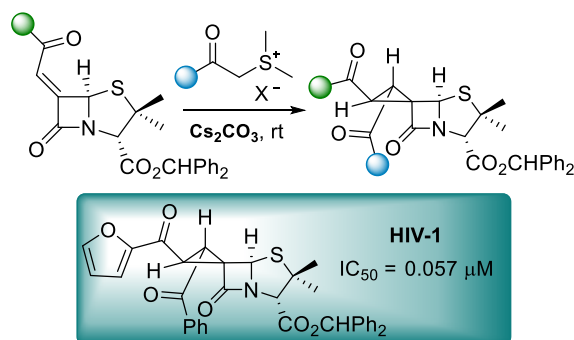
A fluorescent naphthalimide azocarboxylate was successfully tethered to a polymethacrylate backbone. The resulting polymeric material exhibits efficient turn-on fluorescence upon sulfinate addition onto the azo moiety forming covalent bonding, with minimal quenching effects from non-emissive isomeric units.

Synthesis of Chiral Spirocyclopropanepenicillanates via [2+1] Annulation of 6-Alkylidenepenicillanates and Sulfur Ylides

João V. R. Gonçalves, Ricardo M. Carvalho, Jéssica Macedo, Paloma Gonçalves, Inês Bárto, Américo J. S. Alves, José A. Paixão, Nuno Taveira, Teresa M. V. D. Pinho e Melo*

J. Org. Chem. **2025**, 90, 10225-10234

<https://doi.org/10.1021/acs.joc.5c00743>



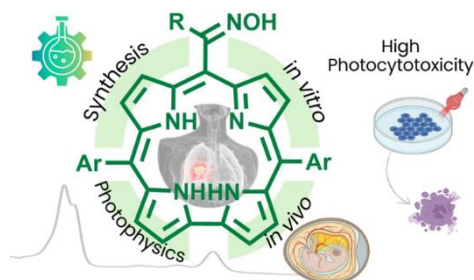
An unexplored reactivity of 6-(Z)-alkylidenepenicillanates was unveiled, describing the synthesis of compounds having a cyclopropane ring spiro-fused to the penicillanic core. This was achieved via the in situ generation of sulfur ylide intermediates from the corresponding sulfur salts, which react with 6-(Z)-alkylidenepenicillanates, leading to spirocyclopropanepenicillanates. The formal [2+1] cycloaddition, which involved the creation of three new chiral centers, proved to be diastereoselective, affording the new chiral spirocyclopropanepenicillanates in good yields. Notably, one spiro-β-lactam exhibited excellent anti-HIV-1 activity.

trans-A₂B-Corroles Containing an Oxime Moiety: Novel Photosensitizers for Photodynamic Therapy of Lung Cancer

João Braz, Catarina Mestre, Bruna D. P. Costa, Susana M. M. Lopes, Ana Clara B. Rodrigues, Ana Cristina Gonçalves, Maria F. Botelho, J. Sérgio Seixas de Melo, Mafalda Laranjo, Marta Pineiro, Teresa M. V. D. Pinho e Melo*

Eur. J. Med. Chem. **2025**, *298*, 117946.

<https://doi.org/10.1016/j.ejmech.2025.117946>



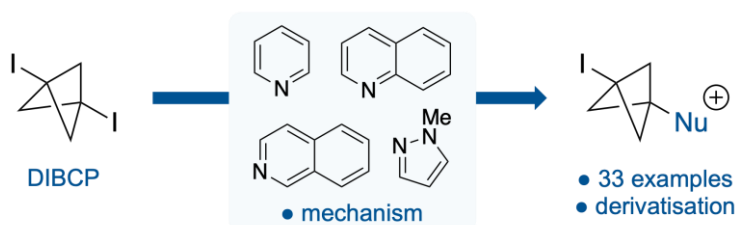
A series of fourteen *trans*-A₂B-corroles containing an oxime moiety were synthesized based on the reactivity of nitrosoalkenes towards dipyrromethanes, to evaluate their potential as a safe therapeutic option for photodynamic therapy (PDT) of lung cancer (LC). These macrocycles exhibited photophysical and acid-base properties suitable for use as photosensitizers (PS) in biological systems. Structure-photodynamic activity relationships were established by evaluating the photodynamic effects of the compounds on human lung cancer cell lines (A549 and H1299). The strong photodynamic activity observed demonstrated that the oxime group plays a crucial role in enhancing biological activity. In fact, the model corrole without an oxime moiety (5,10,15-triphenylcorrole) showed no photodynamic activity against any of the studied LC cell lines (IC₅₀>10 μM), whereas all fourteen oxime-functionalized corroles exhibited significantly lower IC₅₀ values. Among them, triazole-oxime derivatives displayed the highest activity, followed by phenyl-oxime and methyl-oxime corroles. The lead photosensitizers, with IC₅₀ values below 50 nM and no cytotoxicity *per se*, outperformed Temoporfin, the active compound in Foscan®, a clinically approved PS. This highlights oxime-functionalized *trans*-A₂B-corroles as promising candidates for photodynamic therapy of LC. The *in vivo* efficacy of one oxime-corrole based PDT was also evaluated using the chick embryo chorioallantoic membrane model demonstrating its potential as an effective photosensitizer *in vivo*.

Nucleophilic substitution of 1,3-diiodobicyclo[1.1.1]pentane: synthesis of bicyclo[1.1.1]pentyropyridinium, quinolinium, isoquinolinium and pyrazolium salts

Harvey J. C. Monroe,^a Dolapo J. Bello,^a Bradley J. Duff,^a Mark R. J. Elsegood,^a Kohei Watanabe,^b Gareth J. Pritchard*^a and Marc C. Kimber*^a

Journal of Organic Chemistry, **2025**, *90*, 23, 7712-7722

DOI: <https://doi.org/10.1021/acs.joc.5c00565>



In this study, we describe the synthesis of bicyclo[1.1.1]pentane salts by the nucleophilic reaction of 1,3-diiodobicyclo[1.1.1]pentane (DIBCP) with several classes of nucleophiles. The bicyclo[1.1.1]pentane fragments are an established isostere for the ^tbutyl, alkynyl and 1,4-diaryl structural units, whose synthesis is typically achieved by addition to the unstable, cryogenically stored, [1.1.1]propellane precursor. In contrast, DIBCP is a stable crystalline solid, with the potential to be a feedstock in the synthesis of BCP fragments. This work provides a straightforward, practical synthetic route to bicyclo[1.1.1]pentyropyridinium, quinolinium, isoquinolinium and pyrazolium salts. This transformation displays a broad substrate scope, good yield profile, with several of the BCP products being fully characterised by single-crystal X-ray crystallography. The reaction proceeds by nucleophilic substitution on 1,3-diiodobicyclo[1.1.1]pentane (DIBCP), and we provide detailed computational

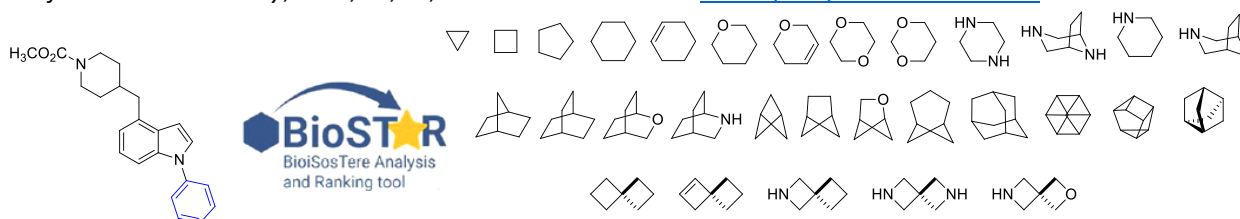
analysis, showing the role of two nucleophiles in stabilising a key carbocation intermediate. The synthesised salts are isosteres of existing arylpyridinium and arylquinolinium salts used within pharmaceuticals and high-value commodity chemicals within the industrial chemical sector. Finally, the synthetic utility of these salts is examined, providing practical synthetic routes to *N*-pyridin-4-one and *N*-quinolin-4-one substituted bicyclo[1.1.1]pentanes.

A Data-Driven Perspective on Bioisostere Evaluation: Mapping the Benzene Bioisostere Landscape with BioSTAR

Pol Hernández-Lladó, Nicholas A. Meanwell, and Angela J. Russell

Journal of Medicinal Chemistry, 2025, 68, 16, 16921–16939

DOI: [0.1021/acs.jmedchem.5c01641](https://doi.org/10.1021/acs.jmedchem.5c01641)

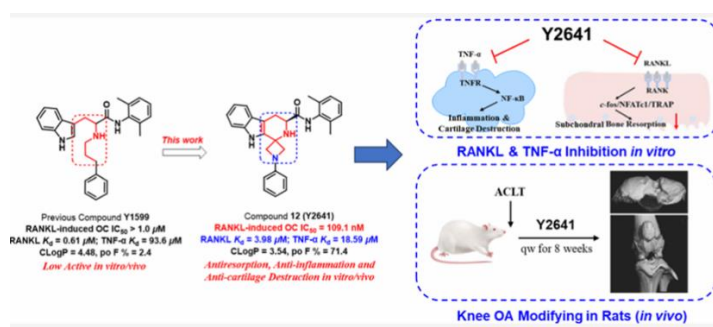


The bioisostere landscape is continually expanding, with new scaffolds emerging as alternatives in drug design. Increasingly, medicinal chemists face the challenge of selecting and prioritising these bioisosteres, often relying on personal experience and anecdotal evidence. In this Perspective, we lay out a data-driven approach to analyze the bioisostere landscape, using benzene bioisosteres as a representative example, and quantitatively compare replacements based on their impact on bioactivity, solubility, and metabolic stability. To support the findings of the analysis, we highlight recent and particularly elegant examples of benzene bioisostere applications while identifying areas where further development could significantly benefit the community. By providing this Perspective and associated data-mining workflow (BioSTAR), we aim to support more informed decision-making in bioisosteric replacement selection in drug design and inspire future innovations in bioisostere design.

Identification of a RANKL/TNF- α Dual-inhibitor as a Potential Disease Modifying Agent for the Treatment of Knee Osteoarthritis.

Zhenguang Shao, Tianqi Wang, Xueming Yan, Ruonan Ning, Xing Xu, Qian He, Xiaofei Zhang*, Min Jiang*, Chunhao Yang.*

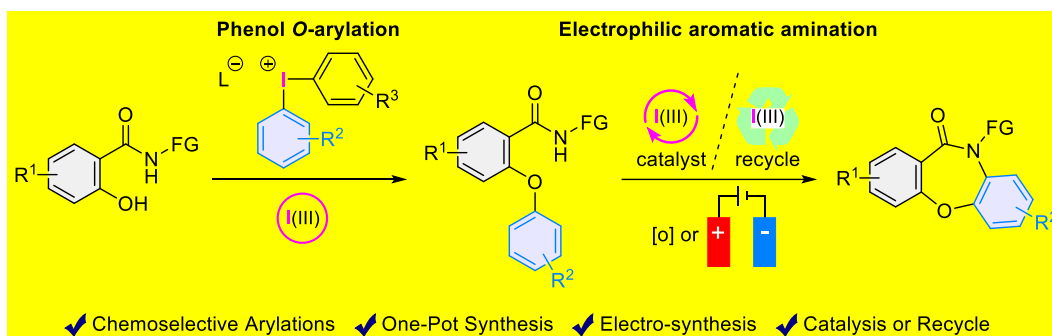
J. Med. Chem. 2025, 68(10), 10216-10237. DOI: [10.1021/acs.jmedchem.5c00394](https://doi.org/10.1021/acs.jmedchem.5c00394).



Osteoarthritis (OA) is a multifactorial degenerative disease involved subchondral bone remodeling, cartilage destruction and synovium inflammation. While receptor activator of nuclear factor- κ B ligand (RANKL), a tumor necrosis factor (TNF) superfamily protein, is a critical regulator in bone metabolism associated with subchondral bone resorption, TNF- α is also an important inflammatory factor involved in the OA inflammation and cartilage destruction. Based on previous compound **Y1599**, we identified a novel tetrahydro- β -carboline derivative **Y2641** with both RANKL and TNF- α inhibition in this study. **Y2641** exhibited potent RANKL-induced osteoclastogenic inhibition ($IC_{50} = 109.1$ nM), and had anti-inflammatory and cartilage destruction inhibiting effects at $10 \mu M$ with low cytotoxicity. SPR assays demonstrated the binding affinity of **Y2641** to RANKL ($K_d = 3.984 \mu M$) and TNF- α ($K_d = 18.59 \mu M$). *In vivo* assay further revealed the disease-modifying effects of **Y2641** in OA rats, establishing **Y2641** as a promising lead compound for the development of disease-modifying osteoarthritis drugs.

Metal-Free Synthesis of Benzimidazolinones via Oxidative Cyclization Under Hypervalent Iodine Catalysis

Mayu Hirashima, Shotaro Hamatani, Hiroataka Sasa, Naoko Takenaga, Tomonori Hanasaki,* Toshifumi Dohi*
Chemistry **2025**, 7, 50. DOI: <https://doi.org/10.3390/chemistry7020050>



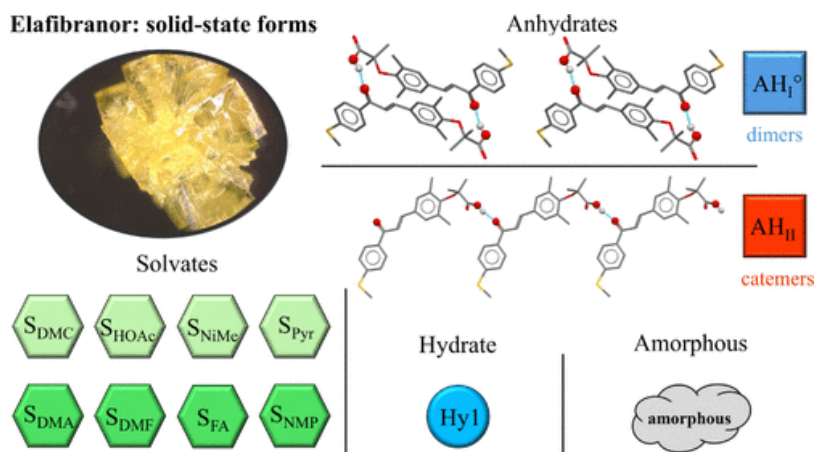
Benzimidazolinones exhibit unique biological activities and serve as building blocks in synthesizing pharmaceutical compounds. Although multiple synthetic approaches involving intermolecular cyclization reactions have been reported, intramolecular cyclization reactions are scarce, and more rational synthetic methods are required. Hypervalent iodine-catalyzed oxidative C–N coupling is a potentially effective approach for synthesizing benzimidazolinones under metal-free conditions. In this study, we present a method utilizing hypervalent iodine catalysis for the oxidative cyclization of N'-aryl urea compounds, resulting in the first metal-free synthesis of various benzimidazolinones.

From Structure to Stability: Exploring the Solid-State Forms of a Novel First-In-Class PPAR Agonist (Elafibranor)

Pascal Pellegrini, Thomas Gelbrich, Marijan Stefinovic, Sven Nerdinger, and Doris E. Braun *

Crystal Growth & Design **2025**, 25, 16, 6892–6907

DOI: [10.1021/acs.cgd.5c00844](https://doi.org/10.1021/acs.cgd.5c00844)



The solid-state landscape of elafibranor (EFR) was systematically investigated using over 40 different solvents, by applying specific crystallization methods according to the solubility of EFR in each case. This screening resulted in 16 distinct solid-state forms. Twelve of these forms (two anhydrate polymorphs, eight solvates, one hydrate, and the amorphous phase) were isolated in phase-pure form and in sufficient quantities to carry out detailed characterization by single-crystal and powder X-ray diffraction, infrared spectroscopy, as well as thermal analytical methods. EFR exhibits a pronounced tendency to form monosolvates, except for a dimethyl carbonate hemisolvate. Notably, none of the solvated forms were found to be isostructural with one another. Controlled desolvation and dehydration enabled the isolation of phase-pure anhydrous forms. The metastable anhydrate (AH_{III}) is most readily obtained by desolvating specific solvates under defined conditions, whereas the stable polymorph (AH_I[°]) can be obtained either through desolvation or by direct crystallization from solution using various solvents. The two polymorphs (AH_I[°] and AH_{III}) display a monotropic relationship. Transformation pathways, particularly desolvation and (de)hydration processes, were correlated with crystal structural features. The hydrogen bond motifs among EFR molecules and the strengths of the EFR-solvent interactions in the solvates significantly influence the mechanism and outcome of the transitions. In combination with systematic

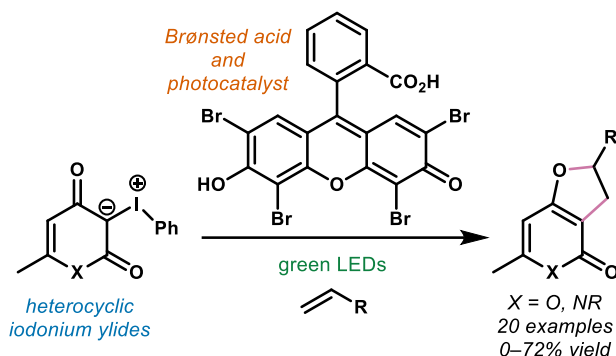
storage experiments under varying temperature and relative humidity conditions, these findings led to a fundamentally better understanding of the relative stability of the (solvate) forms.

Photocatalytic Activation of Heterocyclic Iodonium Ylides for the Synthesis of Dihydrofuropranones and Dihydrofuropyridones

Kelsey T. Sumter, Carly Slough, Hayley E. Johnson, Catherine S. Kesler, and Mary Elisabeth Daub

J. Org. Chem. **2025**, *90* (38), 13488–13495.

DOI: 10.1021/acs.joc.5c01187



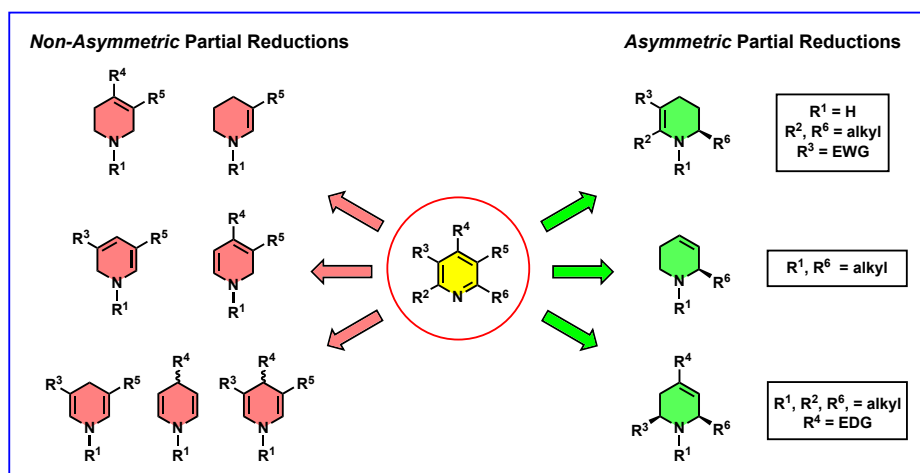
β -Distabilized iodonium ylides undergo photocatalytic activation using neutral eosin Y and visible light to afford dihydrofuropranones, dihydrofuropyridones, and dihydrofurans. Steady-state absorption spectroscopy and application of the method of continuous variations to complexation-induced chemical shifts provide evidence for the binary complexation of eosin Y and β -distabilized iodonium ylides. Preliminary mechanistic studies using transient absorption spectroscopy suggest monoanionic eosin Y as the active photocatalyst functioning *via* an oxidative quenching cycle. This simple approach to enhancing the reactivity of heterocyclic iodonium ylides expands the scope of their use as building blocks in the synthesis of heterocycles.

Asymmetric Partial Reductions of Pyridines

Ashlyn Bohn, Benjamin M. Cipriano Cipriano, and Peter Wipf

Trends Chem. **2025**, *7*(11), 650–658

DOI: [10.1016/j.trechm.2025.09.007](https://doi.org/10.1016/j.trechm.2025.09.007)

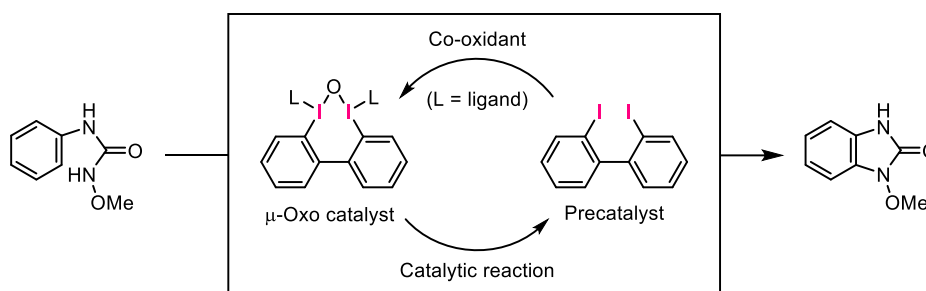


The asymmetric partial reduction of substituted pyridines offers a direct and versatile approach to access chiral dihydropyridines and tetrahydropyridines, valuable intermediates found in numerous natural products and active pharmaceutical ingredients. Despite its potential, this methodology is far less developed than the exhaustive asymmetric reduction of pyridines to piperidines, and current applications are mostly limited to tetrahydropyridines. Challenges persist, such as the necessity for electron-withdrawing groups at the 3-position and limited stereocontrol, with new stereocenter formation largely restricted to the C-6

position. There are no precedents for producing chiral dihydropyridines via this strategy, highlighting significant gaps and opportunities for innovation. Addressing these limitations—particularly by exploring how different substitution patterns at the 4-, 5-, and 6-positions affect selectivity and overall mechanism—could greatly expand the strategic utility of the asymmetric partial reduction of pyridines, enabling the efficient synthesis of highly functionalized, chiral heterocycles for late-stage medicinal chemistry and natural product synthesis.

Metal-Free Synthesis of Benzimidazolinones via Oxidative Cyclization Under Hypervalent Iodine Catalysis

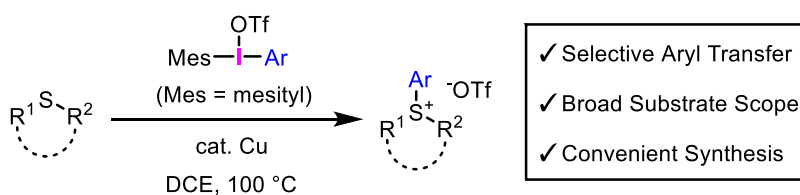
Mayu Hirashima, Shotaro Hamatani, Hiroataka Sasa, Naoko Takenaga, Tomonori Hanasaki,* Toshifumi Dohi*
Chemistry **2025**, 7, 50-59. DOI: <https://doi.org/10.3390/chemistry7020050>



Benzimidazolinones exhibit unique biological activities and serve as building blocks in synthesizing pharmaceutical compounds. Although multiple synthetic approaches involving intermolecular cyclization reactions have been reported, intramolecular cyclization reactions are scarce, and more rational synthetic methods are required. Hypervalent iodine-catalyzed oxidative C–N coupling is a potentially effective approach for synthesizing benzimidazolinones under metal-free conditions. In this study, we present a method utilizing hypervalent iodine catalysis for the oxidative cyclization of *N'*-aryl urea compounds, resulting in the first metal-free synthesis of various benzimidazolinones.

Synthesis of Heterocyclic Sulfonium Triflates by Cu-Catalyzed Selective S-Arylation with Aryl(mesityl)iodonium Salts

Yoto Yusuke, Ryo Hatagochi, Yuto Irie, Naoko Takenaga, Ravi Kumar,* Toshifumi Dohi*
Curr. Org. Synth. **2025**, 22, 531-538. DOI: [10.2174/0115701794298369240607042545](https://doi.org/10.2174/0115701794298369240607042545)

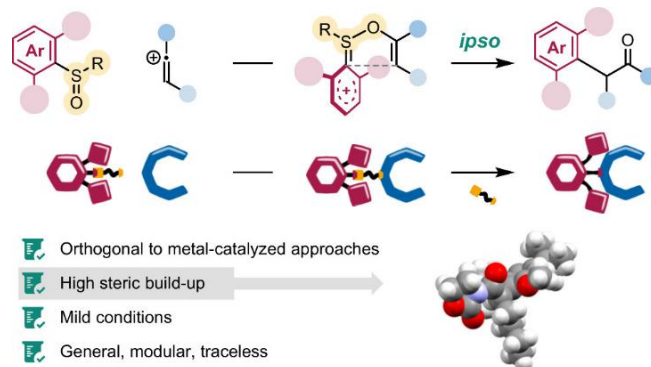


An efficient method for synthesizing cyclic arylsulfonium salts has been developed by selective aryl transfer to the sulfur atom from aryl(mesityl)iodonium triflates, a recyclable series of diaryliodonium salts, in the presence of inorganic copper catalyst.

Synthesis of Sterically Congested Carbonyl Compounds via an *ipso*-Selective Sulfonium Rearrangement

Immo Klose, Christian Knittl-Frank, Nicolas G.-Simonian, Boris Maryasin, Daniel Kaiser, and Nuno Maulide*

J. Am. Chem. Soc. **2025**, *147*, 42, 37899–37906 . DOI: 10.1021/jacs.5c13777



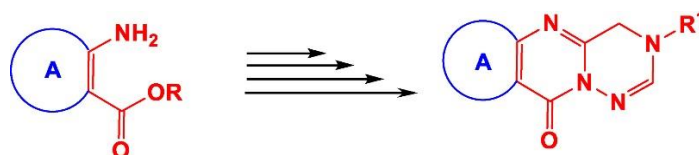
Despite the success of metal-catalyzed cross-coupling strategies to assemble a variety of C–C bonds, the synthesis of sterically congested α -arylated carbonyl compounds remains a difficult task. Herein, we present an *ipso*-rearrangement approach relying on electron redistribution in sulfonium intermediates. This modular method enables the synthesis of a variety of α -arylated carbonyl compounds and is orthogonal to traditional metal-catalyzed cross-coupling strategies. More importantly, it demonstrated remarkable robustness toward steric hindrance and allowed us to efficiently forge congested C–C bonds.

A Universal Method for the Synthesis of new Heterocyclic Systems: Pyrimido[2,1-*f*][1,2,4]triazines

Samvel N. Sirakanyan,* Domenico Spinelli, Athina Geronikaki, Victor G. Kartsev, Elmira K. Hakobyan,* Hasmik V. Jughetsyan, Hasmik A. Yegoryan, and Anush A. Hovakimyan.

ChemistryOpen, **2025**, *14*(6), e202400379

DOI: 10.1002/open.202400379



A = het, arom; R = Me, Et; R¹ = primary amine.

Previously unknown fused heterocycles, specifically pyrido[3'',2'':4',5']thieno[3',2':4,5]pyrimido[2,1-*f*][1,2,4]triazines were synthesized, the preparation of which was carried out through a four-step sequence. First, the starting amino esters of thieno[2,3-*b*]pyridines were acylated, and the resulting products were then allowed to react with different amines. These amine-substituted intermediates were subsequently treated with hydrazine hydrate, which promoted ring closure and produced new aminomethyl-substituted thieno[3,2-*d*]pyrimidines. A final cyclization step transformed these compounds into a series of previously unknown fused heterocycles of titled compounds. These structures are noteworthy because even the fusion of the last two rings forms a heterocyclic arrangement that has not been described before.

1,2,3-Triazine 1-Oxides are a Productive Platform for Synthetic Methodologies

Luca De Angelis and Michael P. Doyle

SynOpen **2025**, 9, 236-246. DOI: 10.1055/a-2722-6531



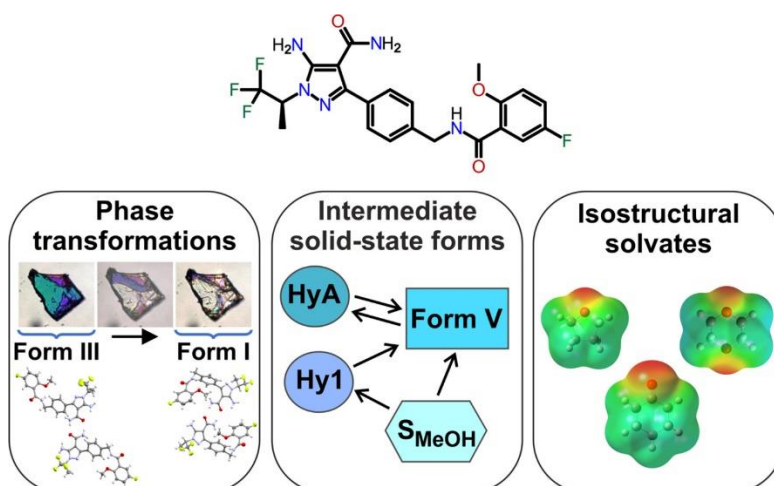
This graphical review provides a concise overview of the synthesis and uses of 4-carboxylato-1,2,3-triazine 1-oxides in diverse syntheses, especially of heterocyclic compounds. Prepared in high yields from reactions between vinyldiazoacetates and tert-butyl nitrite, these triazines undergo nucleophilic substitution reactions, generally at the 6-position with the loss of dinitrogen or nitrous oxide, to form diverse products. Deoxygenation to 1,2,3-triazines, inverse electron demand Diels-Alder reactions, borohydride induced 1,4-hydrogen addition, and syntheses of new diazo compounds are among the new processes that have been uncovered. This review serves as an indicator for future applications.

Unraveling the solid-state complexity of pirtobrutinib: Polymorphs, solvates, hydrates, and their transformation pathways

Tom L. Petrick, Thomas Gelbrich, Sven Nerdinger, Marijan Stefinovic and Doris E. Braun *

Journal of Molecular Structure **2026**, 1352, 144513

DOI: <https://doi.org/10.1016/j.molstruc.2025.144513>



A comprehensive solid-state screening of pirtobrutinib led to the identification of five anhydrates (I - V), five solvates, two hydrates (**Hy1**, **HyA**), and the amorphous phase. Extensive structural and thermal characterization was performed using hot-stage microscopy, thermogravimetric analysis, differential scanning calorimetry, infrared spectroscopy, and both powder and single-crystal X-ray diffraction. The crystal structures of two anhydrates (I and III) were solved, both crystallizing in the orthorhombic space groups with two molecules in the asymmetric unit and exhibiting pseudosymmetry. In addition, unit cell and space group information were obtained for several other forms. Three solvates were identified as isostructural, one as unstable, and a fifth as a solvate polymorph. Form V was not directly obtained by crystallization but was only accessible through desolvation. **Hy1** was

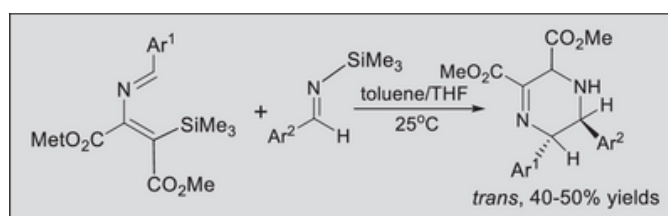
identified as a stoichiometric monohydrate, whereas **HyA** exhibits non-stoichiometric hydration behavior. Structural similarities between **Hy1** and the methanol solvate, as well as between **HyA** and Form **V**, suggest that the formation of these hydrates depends on specific precursor structures. Form **I** emerged as the most frequently obtained and a stable polymorph, crystallizing under a broad range of experimental conditions. It was found to be monotropically related to Forms **II** and **V**, and enantiotropically related to Forms **III** and **IV**. The formation of the latter two forms was linked to the presence of an unidentified impurity. This study highlights the importance of comprehensive solid-form screening, particularly with regard to solvates (hydrates) and the amorphous form, for understanding solid-state transformation pathways, desolvation behavior, and for enabling form selection in pharmaceutical development.

Inverse Electron Demand Formal Dihetero Diels–Alder Reactions: Synthesis of C-Substituted Piperazines and Morpholines

[Maria Sehou](#), [Andreas Tsigilaras](#), [Antonis Asimakopoulos](#), [Prof. Dr. Plato A. Magriotis](#)

ChemistrySelect **2025**, *10*, e02484

DOI: [10.1002/slct.202502484](https://doi.org/10.1002/slct.202502484)



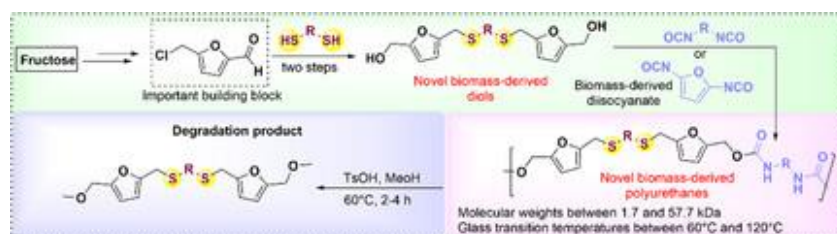
The quest for either normal or inverse electron demand formal dihetero Diels–Alder reactions led to the discovery of a novel formal, inverse electron demand Diaza Diels–Alder Reaction (DADAR) that is both practical and efficient providing access to NH carbon-substituted piperazines. This process proceeds at ambient temperature and does not require the presence of a Lewis acid due to the operation of the β -silicon effect stabilizing the key zwitterion intermediate en route to the desired dehydropiperazines. Piperazine and morpholine are important scaffolds in medicinal chemistry, and the practical and efficient synthesis of their C-substituted analogs is an active area of research with substantial room for improvement. Herein, we present an inverse electron demand formal dihetero Diels–Alder approach to the synthesis of these saturated heterocycles. The first use of trimethylsilyl imines as heterodienophiles in the DiAza Diels–Alder Reaction (DADAR) for the synthesis of C-substituted NH piperazines is also described.

Novel Sulfur-Containing Polyurethanes using 5-(Chloromethyl)Furfural as a Renewable Building Block

[Jorge Andrés Mora Vargas](#), [Jéssica Ribeiro da Silva](#), [Ana Clara Lancarovici Alves](#), [Germán Darío Gómez Higueta](#), [Antonio José Felix Carvalho](#), [Antonio C. B. Burtoloso](#)

ChemSusChem **2025**, *18*, e202500888

DOI: [10.1002/cssc.202500888](https://doi.org/10.1002/cssc.202500888)



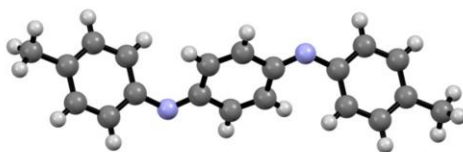
The development of novel polymeric materials with unique properties and applications across various industries, driven by biomass-based molecular platforms, has experienced remarkable growth. Among these, 5-(chloromethyl)furfural (CMF) has emerged as a promising precursor to produce biomass-derived monomers and innovative chemical products. Herein, an efficient method is presented for synthesizing novel biomass-derived diols, achieved in very good yields by reacting CMF with various dithiols, followed by reduction of the resulting dialdehydes. Subsequently, 12 new polyurethanes are synthesized via polyaddition of these diols with commercially available diisocyanates, using an organic base as a catalyst. The resulting polymers exhibit molecular weights ranging from 1.7 to 57.7 kDa, glass transition temperatures between 22 and 120 °C, and degradation

temperatures (Td5%) exceeding 170 °C. Additionally, a nearly fully biomass-derived polymer is synthesized through the reaction of furandiazylazide (FDAz) with one of the obtained diols, via Curtius rearrangement. Recognizing the importance of developing innovative polymers alongside efficient chemical degradation and recycling methods, a synthesized polyurethane is also subjected to chemical degradation studies.

***N,N'*-Di(*p*-tolyl)-1,4-benzoquinondiimine (*N,N'*-Di-*p*-tolylcyclohexa-2,5-diene-1,4-diimine)**

R. Alan Aitken, Rebecca Bascombe and Alexandra M. Z. Slawin

Molbank **2025**, 2025, M2089 (1–6). DOI: 10.3390/M2089



X-Ray structure, only (*E*)

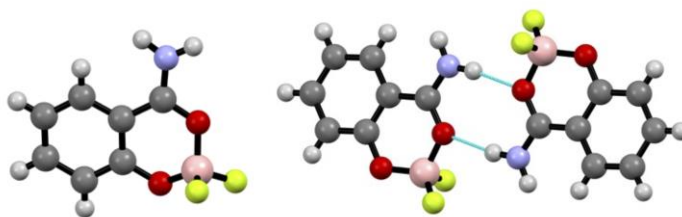
¹H, ¹³C NMR fully assigned for (*E*) and (*Z*) isomers

The title compound has been fully characterised using ¹H and ¹³C NMR spectroscopy, which reveals (*E*) to (*Z*) isomerisation upon dissolution. In the solid state, X-ray diffraction shows exclusively the (*E*)-isomer with two geometrically near-identical independent molecules each with the outer rings tilted with respect to the central ring.

2-(Difluoroboryloxy)benzamide

R. Alan Aitken, Hibet E. M. Akkache, David B. Cordes, Aidan P. McKay and Dorian Moreau

Molbank **2025**, 2025, M2093 (1–6). DOI: 10.3390/M2093



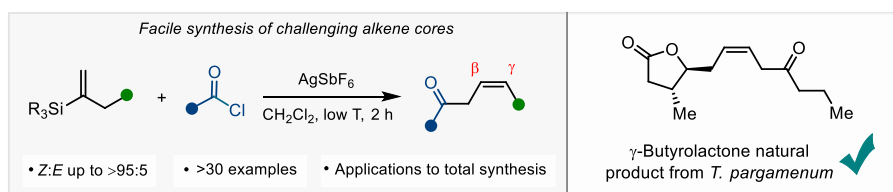
Fully assigned ¹H, ¹³C, ¹¹B and ¹⁹F NMR; Two different polymorphs in crystal

The title compound has been fully characterised by NMR for the first time. Fully assigned ¹H and ¹³C NMR spectra, and the X-ray structure of two different polymorphs are presented. The polymorphs show similar molecular geometries but exhibit significantly different patterns of intermolecular interactions.

Facile (*Z*)-Selective Synthesis of β,γ -Unsaturated Ketones by a Silicon-based Olefination Strategy

Daniya Aynetdinova, Jakub Brzeškiewicz, Nikolaos Skoulikas, and Nuno Maulide *

Angew. Chem. Int. Ed. **2025**, 64(49), e202517069 DOI: 10.1002/anie. 202517069





Issue 96

December 2025

A novel silicon-based olefination strategy to access challenging β,γ -(Z)-unsaturated ketones with high diastereoselectivity in a single step from easily accessible, branched vinyl silanes is presented. This new disconnection resolves many longstanding challenges that have prevented general and efficient synthetic approaches to (Z)-deconjugated enones, affording a broad scope of this type of alkenes with high functional group tolerance. The developed transformation has been applied as a key step in the synthesis of a range of natural products.
