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Indole-Containing Amidinohydrazones as Nonpeptide, Dual RXFP3/4 Agonists: Synthesis, Structure–Activity Relationship, and Molecular Modeling Studies

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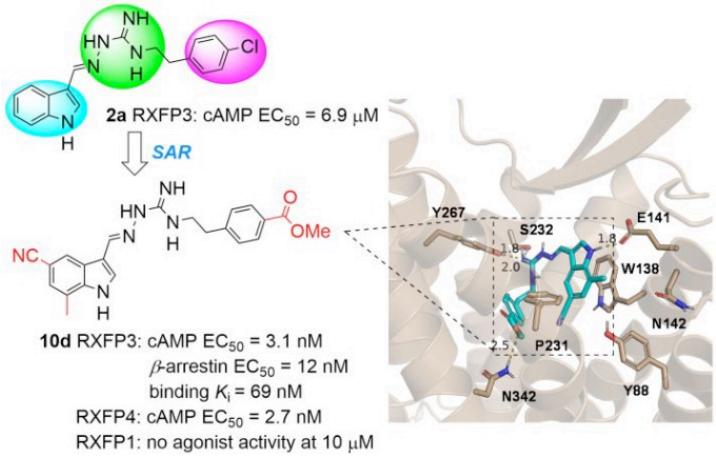
J. Med. Chem. **2021**, *64*, 17866–17886. **DOI:** 10.1021/acs.jmedchem.1c01081

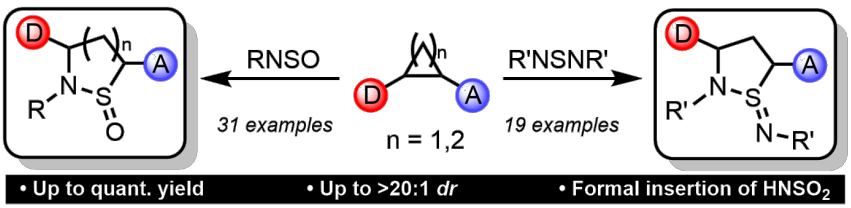


Abstract: The central relaxin-3/RXFP3 system plays important roles in stress responses, feeding, and motivation for reward. However, exploration of its therapeutic applications has been hampered by the lack of small molecule ligands and the cross-activation of RXFP1 in the brain and RXFP4 in the periphery. Herein, we report the first structure–activity relationship studies of a series of novel nonpeptide amidinohydrazone-based agonists, which were characterized by RXFP3 functional and radioligand binding assays. Several potent and efficacious RXFP3 agonists (e.g., 10d) were identified with EC50 values <10 nM. These compounds also had high potency at RXFP4 but no agonist activity at RXFP1, demonstrating > 100-fold selectivity for RXFP3/4 over RXFP1. *In vitro* ADME and pharmacokinetic assessments revealed that the amidinohydrazone derivatives may have limited brain permeability. Collectively, our findings provide the basis for further optimization of lead compounds to develop a suitable agonist to probe RXFP3 functions in the brain.

Cycloadditions of Donor–Acceptor Cyclopropanes and Cyclobutanes Using S=N-Containing Reagents: Access to Cyclic Sulfinamides, Sulfonamides, and Sulfinamidines

Gwyndaf A. Oliver, Maximilian N. Loch, André U. Augustin, Pit Steinbach, Mohammed Sharique, Uttam K. Tambar, Peter G. Jones, Christoph Bannwarth, and Daniel B. Werz* (d.werz@tu-braunschweig.de)

Angew. Chem. Int. Ed. **2021**, *60*, 25825–25831. **DOI:** 10.1002/anie.202106596

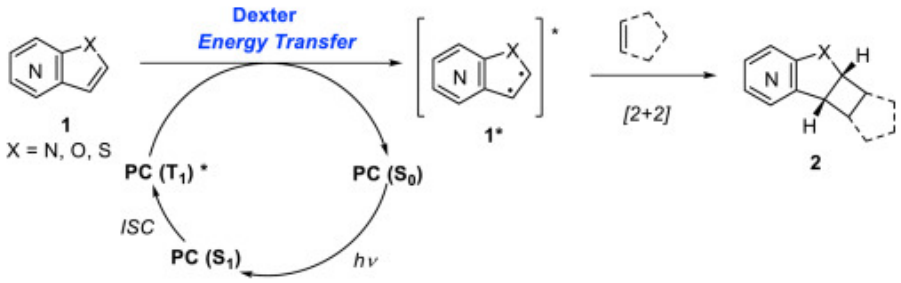


Abstract: By employing (3+2)-and (4+2)-cycloadditions of donor-acceptor (D-A) cyclopropanes and cyclobutanes with *N*-sulfinylamines and sulfur diimides, a variety of isothiazolidines and thiazinanes were synthesized. Use of a sulfinylamine bearing a leaving group, followed by oxidation, lead to formal insertion of $HNSO_2$ providing γ-sultams with no *N*-substitution.

Advances in the Synthesis of Three-Dimensional Molecular Architectures by Dearomatizing Photocycloadditions

Martins S. Oderinde,* Soomin Jin, T. G. Murali Dhar, Nicholas A. Meanwell, Arvind Mathur, James Kempson (martin.oderinde@bms.com)

Tetrahedron **2022**, *103*, 132087 (1–24). **DOI:** 10.1016/j.tet.2021.132087



Abstract: The dearomatizing photocycloaddition reaction is a powerful and effective strategy for synthesizing complex, three-dimensional, polycyclic scaffolds from simple aromatic precursors. Generally, the dearomatizing photocycloaddition reaction is promoted by visible light and occurs via an energy transfer (EnT) process. This mini-review provides an overview of recent advances in this area (2018–2020), encompassing both intramolecular and intermolecular transformations. While the majority of the studies are centered on intramolecular processes due to their predictable regio- and stereo-selectivity, intermolecular transformations that show an exceptionally broad substrate scope are beginning to emerge.

Bioisosteres of the Phenyl Ring: Recent Strategic Applications in Lead Optimization and Drug Design

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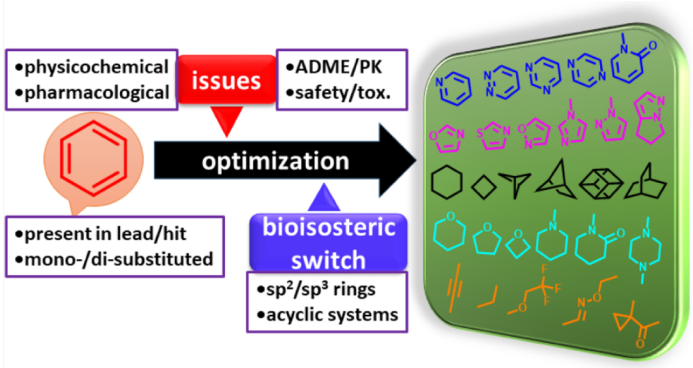
J. Med. Chem. **2021**, *64*, 14046–14128. **DOI:** 10.1021/acs.jmedchem.1c01215

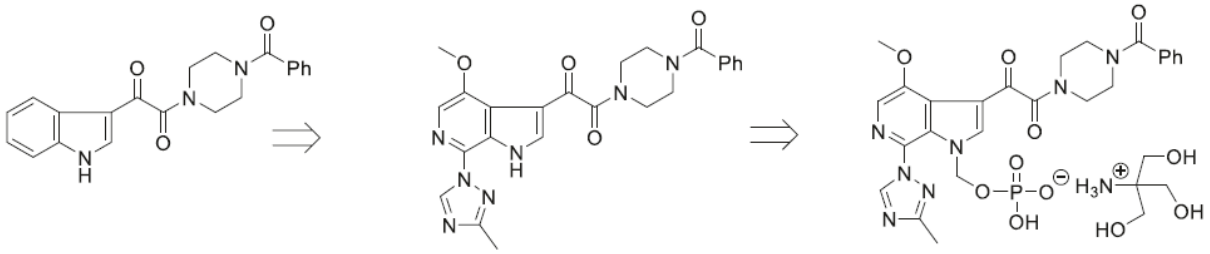


Abstract: The benzene moiety is the most prevalent ring system in marketed drugs, underscoring its historic popularity in drug design either as a pharmacophore or as a scaffold that projects pharmacophoric elements. However, introspective analyses of medicinal chemistry practices at the beginning of the 21st century highlighted the indiscriminate deployment of phenyl rings as an important contributor to the poor physicochemical properties of advanced molecules, which limited their prospects of being developed into effective drugs. This Perspective deliberates on the design and applications of bioisosteric replacements for a phenyl ring that have provided practical solutions to a range of developability problems frequently encountered in lead optimization campaigns. While the effect of phenyl ring replacements on compound properties is contextual in nature, bioisosteric substitution can lead to enhanced potency, solubility, and metabolic stability while reducing lipophilicity, plasma protein binding, phospholipidosis potential, and inhibition of cytochrome P450 enzymes and the hERG channel.

Innovation in the Discovery of the HIV-1 Attachment Inhibitor Temsavir and its Phosphonooxymethyl Prodrug Fostemsavir

Tao Wang, John F. Kadow, and Nicholas A. Meanwell* (wangtao@kawin.com.cn or nicholas.meanwell@bms.com)

Med. Chem. Res. **2021**, *30*, 1955–1980. **DOI:** 10.1007/s00044-021-02787-6

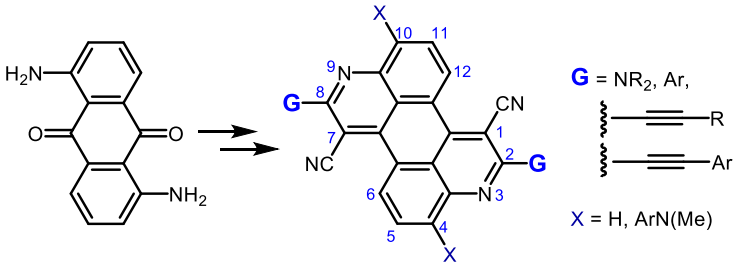


Abstract: The discovery and development of fostemsavir (**2**), the tromethamine salt of the phosphonooxymethyl prodrug of temsavir (**1**), encountered significant challenges at many points in the preclinical and clinical development program that, in many cases, stimulated the implementation of innovative solutions in order to enable further progression. In the preclinical program, a range of novel chemistry methodologies were developed during the course of the discovery effort that enabled a thorough examination and definition of the HIV-1 attachment inhibitor (AI) pharmacophore. These discoveries helped to address the challenges associated with realizing a molecule with all of the properties necessary to successfully advance through development and this aspect of the program is the major focus of this retrospective. Although challenges and innovation are not unusual in drug discovery and development programs, the HIV-1 AI program is noteworthy not only because of the serial nature of the challenges encountered along the development path, but also because it resulted in a compound that remains the first and only example of a mechanistically novel class of HIV-1 inhibitor that is proving to be very beneficial for controlling virus levels in highly treatment-experienced HIV-1 infected patients.

Some New 2,8-Disubstituted-1,7-dicyano-3,9-diazaperylenes

Maxime Ayer, Rico S. Bolli, Anthony S. R. Chesman, Craig M. Forsyth, Justine L. Jeffery, Andris J. Liepa, Karolina M. Morawska, Théo Ozga, and Craig L. Francis* (craig.francis@csiro.au)

Arkivoc **2022**, *part iv,* 24–45. **DOI:** 10.24820/ark.5550190.p011.661



Abstract: Concise synthetic protocols for a range of new 2,8-disubstituted-1,7-dicyano-3,9-diazaperylenes, starting from commercially available 1,5-diaminoanthraquinone, have been developed, which enable the introduction of various tertiary-amino, substituted-ethynyl, and aryl groups at the C2 and C8 positions, as well as incorporation of aryl-amino groups at the C4 and C10 positions, of the rare 3,9-diazaperylene ring system. This methodology should enable tuning of physical and optoelectronic properties and may find use in the discovery of new materials for organic photovoltaic devices or other organic electronic applications.

Photocatalytic Radical Addition to Levoglucosenone

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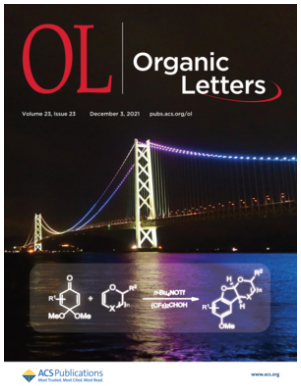
Eur. J. Org. Chem. **2022**, e202101298 (1–9). **DOI:** 10.1002/ejoc.202101298

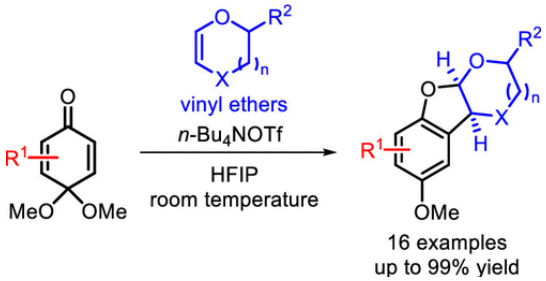
Abstract: Using photocatalysis with tetra-*n*-butylammonium decatungstate (TBADT), alkanes, cyclic acetals, cyclic ethers, formamide and aldehydes were added in a stereoselective way to levoglucosenone (LGO). A hydrogen atom is transferred from the donor compound to the photochemically excited TBADT, and the resulting radicals add onto LGO in a stereoselective way. In the case of the addition of adamantane, two regio-isomers were obtained which form a crystalline solid solution. Cyrene™, obtained by hydrogenation of LGO, was added under the same conditions. In this case, only two of 32 possible isomers of the resulting Cyrene™ dimer were formed. The regio-selectivity of the HAT step is discussed in detail. For this purpose, bond dissociation energies and partial charges have been calculated. Transition state calculations of the radical addition to LGO explain the stereospecificity of this reaction step.

[3 + 2] Coupling of Quinone Monoacetals with Vinyl Ethers Effected by Tetrabutylammonium Triflate: Regiocontrolled Synthesis of 2-Oxygenated Dihydrobenzofurans

Tohru Kamitanaka, Yusuke Tsunoda, Yuriko Fujita, Toshifumi Dohi, and Yasuyuki Kita* (kita@ph.ritsumei.ac.jp)

Org. Lett. **2021**, *23*, 9025–9029. **DOI:** 10.1021/acs.orglett.1c02792

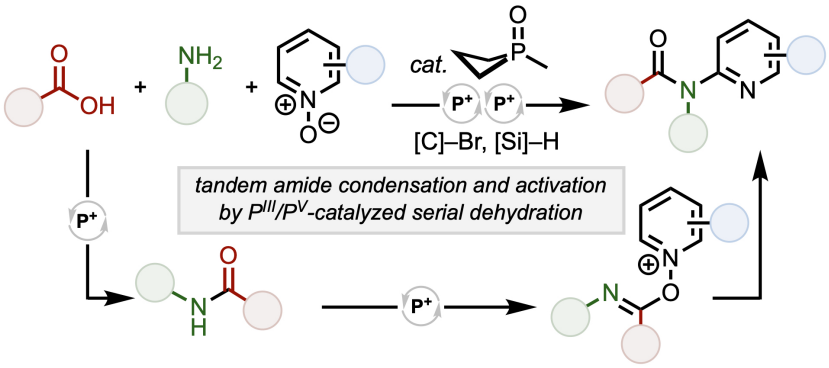




Abstract: The synthesis of 2-oxygenated dihydrobenzofurans involving the [3 + 2] coupling of quinone monoacetals with vinyl ethers has been realized by tetrabutylammonium triflate catalysis. The reaction involves a new activation method of the acetal moiety in quinone monoacetals under acid-free conditions affording the highly oxygenated dihydrobenzofurans. This new activation mode was achieved by using the triflate anion catalyst for stabilization of the highly reactive cationic intermediate.

Uniting Amide Synthesis and Activation by P^{III}/P^{V}–Catalyzed Serial Condensation: Three-Component Assembly of 2-Amidopyridines

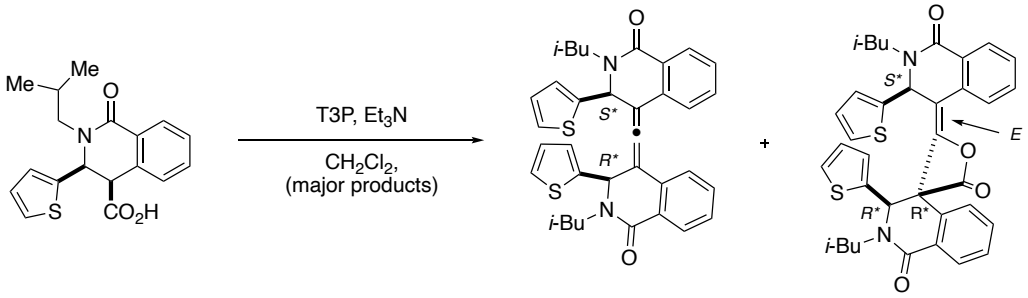
Jeffrey M. Lipshultz and Alexander T. Radosevich* (radosevich@mit.edu)
J. Am. Chem. Soc. **2021**, *143*, 14487–14494. **DOI:** 10.1021/jacs.1c07608



Abstract: An organophosphorus (P^{III}/P^{V} redox) catalyzed method for the three-component condensation of amines, carboxylic acids, and pyridine *N*-oxides to generate 2-amidopyridines via serial dehydration is reported. Whereas amide synthesis and functionalization usually occur under divergent reaction conditions, here a phosphetane catalyst (together with a mild bromenium oxidant and terminal hydrosilane reductant) is shown to drive both steps chemoselectively in an auto-tandem catalytic cascade. The ability to both prepare, and functionalize amides under the action of a single organocatalytic reactive intermediate enables new possibilities for the efficient and modular preparation of medicinal targets.

Stereoelectronic Features of a Complex Ketene Dimerization Reaction

Robert D. Barrows, Mark J. Dresel, Thomas J. Emge, Paul R. Rablen, and Spencer Knapp* (spencer.knapp@rutgers.edu)
Molecules **2022**, *27*, 66 (1–11). **DOI:** 10.3390/molecules27010066

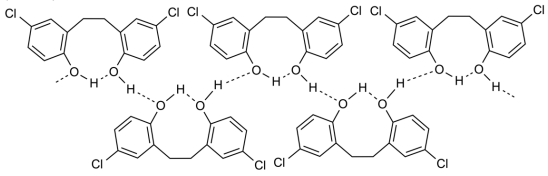


Abstract: The amidation reaction of a tetrahydroisoquinolin-1-one-4-carboxylic acid is a key step in the multi-kilogram scale preparation of the antimalarial drug SJ733, now in phase 2 clinical trials. In the course of investigating THIQ carboxamidations, we found that propanephosphonic acid anhydride (T3P) is an effective reagent, although yield and byproducts vary with the nature and quantity of the base. As a control, the T3P reaction of a 3-(2-thienyl) THIQ was performed in the absence of the amine, and the products were characterized: among them are three dimeric allenes and two dimeric lactones. A nucleophile-promoted ketene dimerization process subject to subtle steric and stereoelectronic effects accounts for their formation. Two novel monomeric products, a decarboxylated isoquinolone and a purple, fused aryl ketone, were also isolated, and mechanisms for their formation from the ketene intermediate are proposed.

2,2′-(Ethane-1,2-diyl)bis(4-chlorophenol)

R. Alan Aitken,* Anna L. G. Gidlow, Russel S. Ramsewak, and Alexandra M. Z. Slawin (raa@st-and.ac.uk)

Molbank **2022**, *2022*, M1318 (1–4). **DOI:** 10.3390/M1318



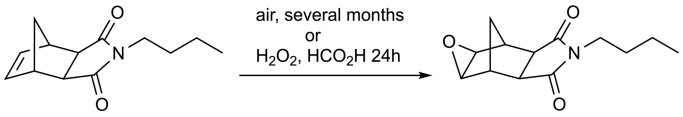
X-Ray structure

Abstract: The X-ray structure of the title compound, obtained as a byproduct in a natural product synthesis, has been determined and shows an unusual pattern featuring chains of molecules with both intra- and intermolecular hydrogen bonding of the OH groups.

2,6-*exo*-8,10-*exo*-4-Butyl-9-oxa-4-azatetracyclo[5.3.1.$0^{2,6}$.$0^{8,10}$]undecane-3,5-dione

R. Alan Aitken,* Fiona M. Fotherby, and Alexandra M. Z. Slawin (raa@st-and.ac.uk)

Molbank **2022**, *2022*, M1320 (1–7). **DOI:** 10.3390/M1320



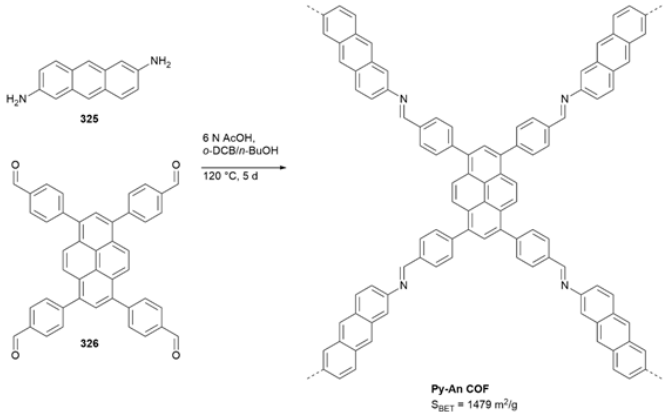
^{1}H,^{13}C NMR ^{1}H,^{13}C NMR, X-ray structure

Abstract: The title epoxide was obtained by spontaneous epoxidation of the corresponding unsaturated imide in air or by peracid oxidation. Unambiguous assignment of the ^{1}H and ^{13}C NMR spectra is achieved by comparison between analogous compounds and its X-ray structure confirms the *exo,exo*-configuration.

Porous Organic Polymers as Metal Free Heterogeneous Organocatalysts

Maarten Debruyne,* Veronique Van Speybroeck, Pascal Van Der Voort, and Christian V. Stevens (mgadbruy.debruyne@ugent.be)

Green Chem. **2021**, *23*, 7361–7434. **DOI:** 10.1039/d1gc02319e



Abstract: Efficient catalysis is essential from a green chemistry perspective. Porous organic polymers (POPs) have recently emerged as highly effective materials for catalytic applications. POPs possess controllable compositions and functionalities, high surface areas and can be very stable. In this review we focus on the application of POPs as metal free heterogeneous organocatalysts, a booming field in green chemistry. Acid, base, combined acid-base and hydrogen bonding catalysis are addressed. In addition, chiral catalysis and CO_2 utilization with POPs are discussed. The aim is to provide a comprehensive overview of the field, exploring all different types of POPs as metal free catalysts. Special attention is given to the synthesis conditions to provide the reader more insight in the construction of these types of materials.