Issue 75 March 2023

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Issue 75 March 2023

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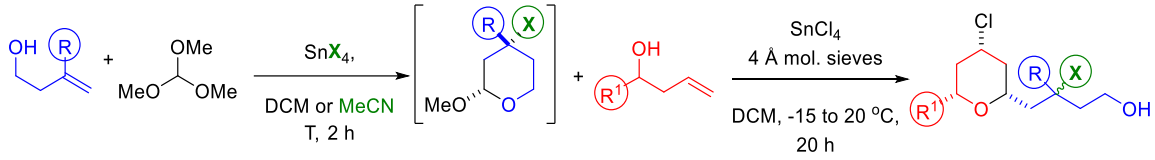
Double Prins Cyclisation Enabled Rapid Access to α,ω-Hydroxytetrahydropyrans

Jonathan Trevorrow, Anne O'Kearney-McMullan, Lucie Miller Potucka, Adrian Dobbs (2022)

European Journal of Organic Chemistry, **2022**, e202200810 (https://doi.org/10.1002/ejoc.202200810)

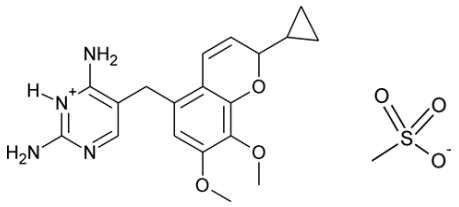


The spiroketal moiety is an important substructure within many biological natural products. One method to access them is via the oxidative cyclisation of a pendant hydroxyl group on to a pre-formed pyran. However access to such precursors has hitherto been challenging and requires multistep syntheses frequently with considerable protecting group manipulation. Herein we report a novel and high yielding method for the preparation of hydroxydi- and hydroxytetra-hydropyrans, as spiroketal precursors, utilizing a novel double-Prins cyclisation approach.

Iclaprim mesylate displaying a hydrogen-bonded molecular tape

Sandro Neuner, Thomas Gelbrich*, Klaus Wurst, Josef Spreitz, Sven Nerdinger, Ulrich J. Griesser, Marijan Stefinovic, and Herwig Schottenberger

Acta Cryst. **2023**, *E79*, 24-27 (https://doi.org/10.1107/S2056989022011689)



The title compound, 2,6-diamino-5-[(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl)methyl]pyrimidin-1-ium methanesulfonate, $C_{19}H_{23}N_4O_3^+$ $CH_3O_3S^-$, is a salt made up from a protonated iclaprim molecule and a mesylate anion. The pyrimidine and chromene units of the iclaprim molecule form an orthogonal arrangement [interplanar angle of 89.67 (6)°], and the 3-nitrogen position of the pyrimidine ring is protonated. Four distinct N—H···O interactions and an additional N— H···N hydrogen bond connect iclaprim and mesylate molecules to one another, resulting in an infinite hydrogen-bonded molecular tape structure. The central section of the tape is formed by a sequence of fused hydrogen-bonded rings involving four distinct ring types.

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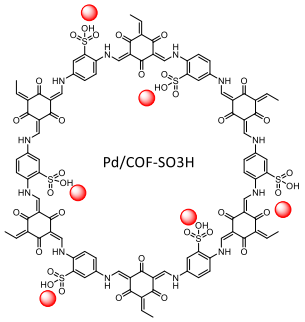
Covalent Organic Framework supported Palladium Catalysts

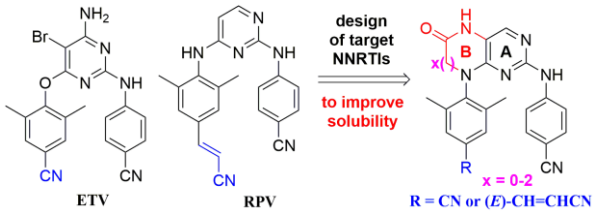
Hadi Salemi, Maarten Debruyne, Veronique Van Speybroeck, Pascal Van Der Voort, Matthias D'hooghe, and Christian V. Stevens
J. Mater. Chem. A, 2022, **10**, 20707-20729 (https://doi.org/10.1039/D2TA05234B)



Covalent organic frameworks (COFs), as highly porous crystalline structures, are newly emerging materials designed with tuneable features. They have a high potential to be a host to immobilize metal catalysts. The unique property of these materials, such as their high surface area, oriented channels, and heteroatom enrichment, make them promising materials to improve some disadvantages of heterogeneous metal catalysts. In this review, the fabrication and application of Pd anchored COFs as one of the most critical transition-metal catalysts that play a crucial role in a wide range of reactions is summarized.

Design and Synthesis of Novel HIV-1 NNRTIs with Bicyclic Cores and with Improved Physicochemical Properties

Ladislav Prener, Ondřej Baszczyňski, Martin M. Kaiser, Martin Dračínský, George Stepan, Yu-Jen Lee, Boris Brumshtein, Helen Yu, Petr Jansa, Eric B. Lansdon* and Zlatko Janeba*
Journal of Medicinal Chemistry, 2023, **66**, 1761−1777 (doi.org/10.1021/acs.jmedchem.2c01574)

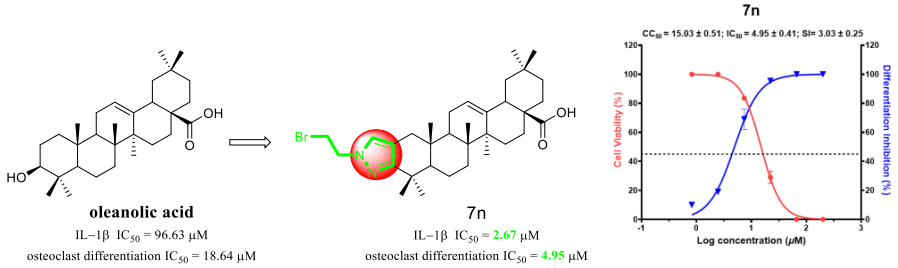


Non-nucleoside reverse transcriptase inhibitors (NNRTIs) represent cornerstones of current regimens for treatment of human immunodeficiency virus type 1 (HIV-1) infections. However, NNRTIs usually suffer from low aqueous solubility and the emergence of resistant viral strains. In the present work, novel bicyclic NNRTIs derived from etravirine (ETV) and rilpivirine (RPV), bearing modified purine, tetrahydropteridine, and pyrimidodiazepine cores, were designed and prepared. Compounds **2**, **4**, and **6** carrying the acrylonitrile moiety displayed single-digit nanomolar activities against the wild-type (WT) virus (EC_{50} = 2.5, 2.7, and 3.0 nM, respectively), where the low nanomolar activity was retained against HXB2 (EC_{50} = 2.2–2.8 nM) and the K103N and Y181C mutated strains (fold change, 1.2–6.7×). Most importantly, compound **2** exhibited significantly improved phosphate-buffered saline solubility (10.4 μM) compared to ETV and RPV (≪1 μM). Additionally, the binding modes of compounds **2**, **4**, and **6** to the reverse transcriptase were studied by X-ray crystallography.

Synthesis and Biological Evaluation of Pyrazole-Fused Oleanolic Acid Derivatives as Novel Inhibitors of Inflammatory and Osteoclast Differentiation.

Yuanyuan Yu, Wenlong Yuan, Jiaqi Yuan, Wenhui Wei, Qian He, Xiaofei Zhang, Shijun He*, and Chunhao Yang*

Bioorg. Med. Chem. **2023**, 80, 117177. (DOI: 10.1016/j.bmc.2023.117177)

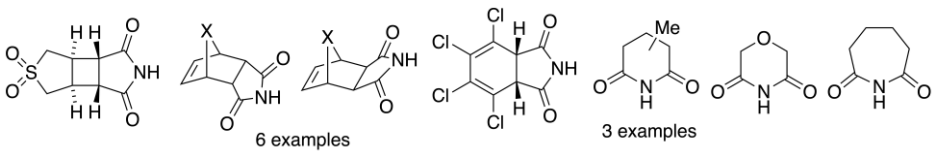


A series of pyrazole-fused oleanolic acid derivatives were designed and synthesized. The modification of these analogues focused on the substituents screening on the pyrazole ring. The cytotoxicity of these compounds and their anti-inflammatory activities *via* inhibiting interleukin-1β (IL-1β) production were evaluated in RAW264.7 cells. Most of the derivatives showed significantly improved potency compared with oleanolic acid. Among them, compound **7n** exhibited the most potent anti-inflammatory activity on decreasing IL-1β production with low cytotoxicity. Moreover, the further study found 7n could inhibit RANKL-induced osteoclast differentiation on bone marrow-derived macrophages (BMMs). These findings may provide a potential direction for the drug development of osteoarthritis.

Solid state structure and hydrogen bonding of some cyclic NH carboximides

R. Alan Aitken,* Alexander J. B. Nelson, Alexandra M. Z. Slawin and Dheirya K. Sonecha

Crystals **2023**, *13*, 150 (1–10) (DOI: 10.3390/cryst13010150)



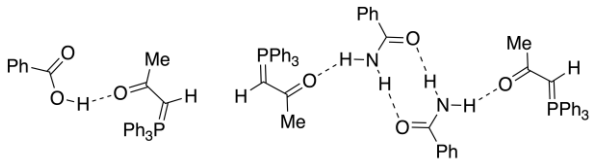
hydrogen bonding patterns for 13 new cyclic NH carboximides

Thirteen new crystal structures of cyclic NH carboximides have been determined and are compared with respect to the mode of intermolecular hydrogen bonding observed in the crystal. The structures include a new cyclobutane-fused succinimide, seven new simple bi- and tricyclic succinimides derived from Diels–Alder reactions of maleimide, three methylated glutarimides, a morpholinedione and adipimide, the first seven-membered ring NH carboximide to be structurally characterised. Overall, seven of the compounds adopt a ribbon structure, five show centrosymmetric dimers, and one has bonding between NH and a remote bridging ether oxygen. Halogen bonding was also detected in one case.

Oxo-stabilised phosphonium ylides as hydrogen bond acceptors

R. Alan Aitken,* Lee P. Cleghorn, Graham Dawson, Ian P. Gray, Anna Lashtabeg and Alexandra M. Z. Slawin

Inorganics **2023**, *11*, 50 (1–14). (DOI: 10.3390/inorganics11020050(



adducts formed in solid state and solution

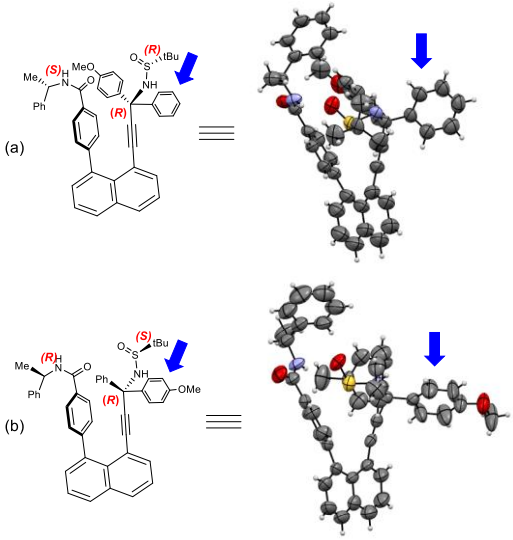
Oxo-stabilised phosphonium ylides are found to form crystalline hydrogen-bonded adducts with aromatic carboxylic acids, as confirmed by X-ray diffraction. There is also strong hydrogen bonding in solution as indicated by ^{13}C NMR spectroscopy and this confirmed adduct formation with acetic acid, benzamide, thiobenzamide, benzyl alcohol, benzenesulfinic acid and

diphenylphosphinic acid. The X-ray structure of the benzamide adduct was also determined, showing a hydrogen-bonded dimeric structure. A bis(stabilised ylide) was also prepared and is found to form a complex hydrogen-bonded adduct with benzoic acid, ethanol and water.

Orientational Chirality, its Asymmetric Control and Computational Study

Shengzhou Jin, Yu Wang, Yao Tang, Jia-Yin Wang, Ting Xu, Junyi Pan, Sai Zhang, Qiankai Yuan, Anis Ur Rahman, James D. McDonald, Guo-Qiang Wang, Shuhua Li and Guigen Li*

Research (Wash D C), **2022**, *2022*, article 0012, https://doi. org/10.34133/research.0012.



Orientational chirality was discovered and characterized by a C(sp)-C(sp^3) axis-anchored chiral center and a remotely anchored blocker. X-ray structural analysis proved orientatiomers are stabilized by through-space functional groups, making it possible for one *R*- or *S*-chiral center to exhibit three orientational isomers simply by rotating operations. A new model system was proposed, fundamentally different from traditional Felkin-Ahn-type or Cram-type models. In these traditional models, chiral C(sp^3) center and blocking C(sp^2) carbons are connected adjacently, and there exist six energy barriers during rotating along C(sp^2)–C(sp^3) axis. In comparison, the present orientational chirality model shows that a chiral C(sp)-C(sp^3) carbon is remotely located from a blocking group. Thus, it is focused on the steric dialog between a chiral C(sp^3) center and a remotely anchored functional group. There exist three energy barriers for either (*R*)- or (*S*)- C(sp)-C(sp^3) stereogenicity in the new model. Chiral amide auxiliary was proven to be an excellent chiral auxiliary in controlling rotations of orientatiomers to give complete stereoselectivity. The asymmetric synthesis of individual orientatiomers was conducted via multi-step synthesis by taking advantage of the Suzuki-Miyaura cross-coupling and Sonogashira coupling reactions. DFT computational study presented optimized conformers and relative energies for individual orientatiomers. This discovery would be anticipated to result in a new stereochemistry topic, and have a broad impact on chemical, biomedical, and material sciences in the future.

A New Chiral Phenomenon of Orientational Chirality, its Synthetic Control and Computational Study

Shengzhou Jin, Ting Xu, Yao Tang, Jia-Yin Wang, Yu Wang, Junyi Pan, Sai Zhang, Qingkai Yuan, Anis Ur Rahman, Adelia J. A. Aquino, Hans Lischka, and Guigen Li*

Front. Chem., **2022**, 10:1110240 (doi: 10.3389/fchem.2022.1110240)

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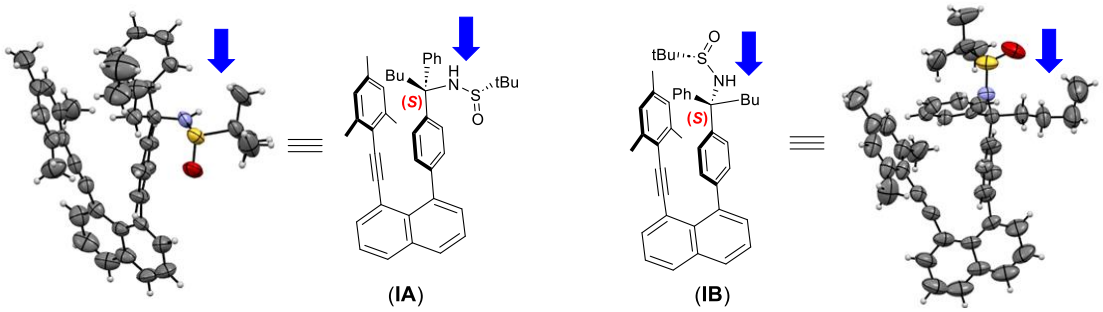

A new type of chirality, orientational chirality, consisting of a tetrahedron center and a remotely anchored blocker, has been discovered. The key structural element of this chirality is characterized by multiple orientations directed by a through-space functional group. The multi-step synthesis of orientational chiral targets was conducted by taking advantage of asymmetric nucleophilic addition, Suzuki-Miyaura cross-coupling and Sonogashira coupling. An unprecedented catalytic species showing a five-membered ring consisting of C(sp^2)-Br-Pd-C(sp^2) bonds was isolated during performing Suzuki-Miyaura cross-coupling. X-ray diffraction analysis confirmed the species structure and absolute configuration of chiral orientation products. Based on X-ray structures, a model was proposed for the new chirality phenomenon to differentiate the present molecular framework from previous others. DFT computational study presented the relative stability of individual orientatiomers.