L.A.15

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Potent Triazolopyridine and Pyrazolopyrimidine Inhibitors of PLK1 and the Structural Basis for Divergent SAR Between the Series.

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Polo-like kinase 1 (PLK1) is a serine/threonine kinase which functions in mitosis and cytokinesis and as such is a target for anti-cancer therapeutics. Here we describe the discovery of 2 classes of potent PLK1 inhibitors: namely, the [1,2,4]triazolo[1,5-a]pyridine series and the 1H-pyrazolo[3,4-d]pyrimidine series. In this poster, we will show SAR comparisons and X-ray crystallographic analysis for the two series. The two chemical series have highly similar R-group trajectories and interactions, however the 5/6- ring systems bind in opposing orientations. We have identified, and will discuss, how intramolecular sterics originating from the inhibitor core in combination with steric effects from the PLK1 binding pocket contribute to the observed conformational differences.

Keywords: kinase, inhibitor, plk1

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SSNMR spectroscopy and X-ray crystallography of fluorinated indazolinones

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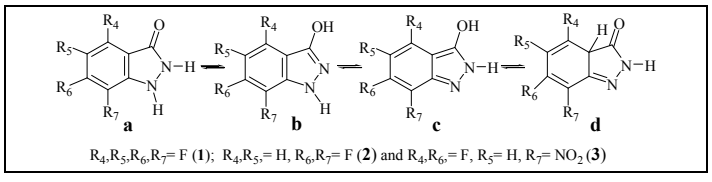
Fluorinated indazoles are good inhibitors of Nitric Oxide Synthase (NOS) [1-8]. This work deals with tautomerism studies in solid state of 3-hydroxy-4,5,6,7-tetrafluoro-1*H*-indazole (**1**), 3-hydroxy-6,7-difluoro-1*H*-indazole (**2**) and 3-hydroxy-4,6-difluoro-7-nitro-1*H*-indazole (**3**).

Between the four possible tautomeric forms **a**-**d**, we have established by ^{13}C and ^{15}N Solid State NMR (SSNMR) that **1** and **2** exist as indazolinones **a**, and **3** in the hydroxy form **b**.

Single-crystal X-ray diffraction analyses indicates that compound **1** crystallizes in the *P2(1)/c* monoclinic space group and the molecular structure corresponds to the tautomer **1a**. Assays to obtain crystals of enough quality for **2** and **3,** to solve their structures, are now being attempted.

Both techniques (SSNMR and X-ray) are complementary and their combined use is becoming a powerful tool for establishing the molecular structures of these indazole derivatives, the starting point to further understand their biological properties.



R_4,R_5,R_6,R_7= F (**1**); R_4,R_5,= H, R_6,R_7= F (**2**) and R_4,R_6,= F, R_5= H, R_7= NO_2 (**3**)

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Polymorphism in 8-Hydroxyquinolin-2(1*H*)-one by X-ray Crystallography, Solid-State NMR and DFT Calculations

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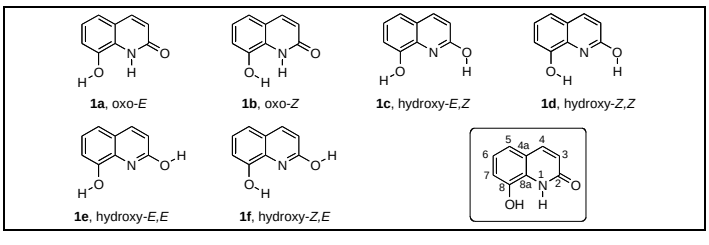
The title compound also known as 8-hydroxycarbostyril or 2,8-quinolinediol (**1**) has found its main application in medicinal chemistry.

Two powerful β_2-adrenergic receptor agonists used for the treatment of asthma, one old (Procaterol) [1-4] and the other very recent (Indacaterol) [5-7] are 8-hydroxyquinolin-2(1*H*)-one derivatives and some of their preparations uses 8-hydroxycarbostyril as starting material. **1** has been reported as a metabolite in rat urine after being fed a diet containing corn [8]; it was also reported that **1** could be formed from quinoline by bacteria. [9,10] Finally, compound **1** was studied in relation with transmissible spongiform encephalopathies [11].

Experimental (NMR, X-ray and DSC) and theoretical studies [DFT B3LYP/6-311++G(d,p)] have permitted to establish the structure of the tautomeric form as 8-hydroxyquinolin-2(1*H*)-one **1a**. In solid state two polymorphs of this tautomer have been identified and their structures elucidated. Polymorph **A** which crystallizes in *Pccn* orthorhombic group and polymorph **B** in the $P2_1/c$ monoclinic group. The arrangement of molecules in both structures is characterized by intermolecular N-H···O and O-H···O hydrogen bonds.



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Keywords: tautomerism, polymorphism, hydrogen bonding

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Cation ordering at the nanoscale

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We describe a new mechanism of microstructure formation occurring during cation ordering processes under non-equilibrium conditions: a fully coherent and regular array of nanosized domains develops in columbite crystals through separation into discrete phases which have the same composition but different degree of long-range cation order. Such pattern of microstructure can be created by high temperature annealing of crystals which grew with an initially metastable state of cation disorder. Size and distribution of the domains remain more or less constant over a prolonged period of annealing.

High-resolution and contrast TEM images revealed microstructural features, and synchrotron X-ray powder diffraction allowed the evolution of cation ordering and domain sizes to be observed *in situ* [1]. Progressive ordering takes place within the ordered domains and the disordered matrix without significant changes in microstructure. At some late stage, when the ordering is advanced, the ordered domains again grow until the equilibrium is achieved. Analysis of IR and Raman spectra collected on samples with different compositions and degrees of order together with the real space analysis of the diffraction data using the Pair Distribution Function technique provide new information on the evolution of the local and mesoscopic structure of columbite, as well as an estimation of the spatial extent of the ordered/disordered domains, thus allowing to gain further insights and a better understanding of the factors controlling the ordering process in columbite.

We can speculate that a new family of such microstructures might appear during ordering under metastable conditions of other oxide phases. The new decomposition mechanism observed in columbite might offer another alternative toward self-organizing systems.

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Keywords: ordering, microstructure, oxide

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Experimental and theoretical charge density studies of lidocaine barbiturate.

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The major goal of crystal engineering is the prediction of structure-property relationship. Nowadays, high resolution, low temperature X-ray diffraction experiments enable the extraction and analysis of the charge density distribution in crystals. Electron density and its properties can be considered as a valuable tool for the analysis of chemical bonding, in particular hydrogen bonding.
Recently, comparative experimental and theoretical charge density analysis was carried out for two out of the polymorphic forms of urea barbituric acid co-crystals [1]. Herein we report the charge density analysis results for polar structure of lidocaine barbiturate: space group $P2_1$, a=11.1322(5), b=11.4604(6), c=14.8607(8)Å, β=92.712(3)°. The experimental charge density was evaluated using the XD2006 [2], the multipole refinement was carried out using the Hansen–Coppens formalism [3] implemented in XD2006. Periodic single-point quantum calculations were performed using CRYSTAL06 [4] with the DFT method at the B3LYP/6-31G** level. The multipole refinement based on the amplitude of the theoretical static structure factors was carried out with the XD2006. In the structure there are two symetrically independent barbiturate ions and two lidocaine cations. Molecular recognition and the formation of specific hydrogen patterns in the examined structure will be discussed. In addition an attempt was made to calculate the static polarizabillity and first hyperpolarizability tensors for the crystalline system [5], [6].

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Keywords: crystal engineering, charge density, non-linear optical materials

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Synthesis of new Cu(III) substituted dithiolate complexes $(CH_3P(Ph)_3)[Cu(bdtCl_2)_2]$

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Coordination compounds of copper in the oxidation state Cu(III) are quite unusual. The series of several dithiolate complexes of general formula $R[M(bdt)_2]$ with benzene-1,2-dithiol (bdt), M = Ni, Co and Cu as the central atom and various ammonium (phosphonium) derivatives R = Me_4N^+, Et_4N^+, Pr_4N^+, Me_3PhN^+, $MePh_3P^+$, Ph_4P^+ , were prepared [1]. A wide range of technical applications (e.g. superconductors, resins, polarization filters, vulcanization accelerators) of the dithiolate complexes, as well as their biological activity (anticholinesterase activity, pesticides) makes them interesting subjects for the research. Our previous attempt to study the electronic structure of these complexes from diffraction data was not successful due to large anisotropic displacement parameters (ADPs) [2]. In order to reduce the thermal motion in the complex, chloro-substituted ligand, 3,6-dichloro-1,2-benzenedithiol ($bdtCl_2$) was used for the synthesis.
Preparation of $(MePh_3P)[Cu(bdtCl_2)_2]$: Solution of Na (0.08 g, 3.3 mmol) in MeOH (10 cm^3) was added to 3,6-dichloro-1,2-benzenedithiole (0.34 g, 1.6 mmol). To this mixture, $CuCl_2{\cdot}2H_2O$ (0.13g, 0.76 mmol) in MeOH (10 cm^3) was added. Finally, $MePh_3PBr$ (0.57 g, 1.6 mmol) in MeOH (10 cm^3) was added. The resulting solution was stirred for 24 hours. The complex was precipitated by the slow addition of water, with vigorous stirring. The green crystalline powder was filtered off, washed with diethyl ether, and then recrystallized from acetone/methanol solution (40:5) (yield 99%). Crude product was purified by column using eluent mixture toluene/methanol (10:1). Two products were obtained by this method – a complex with methylated and with non-methylated dithiolate ligand. After crystalization a single crystal suitable for X-ray analysis was selected.