

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, plkl

SSNMR spectroscopy and X-ray crystallography of fluorinated indazolinones

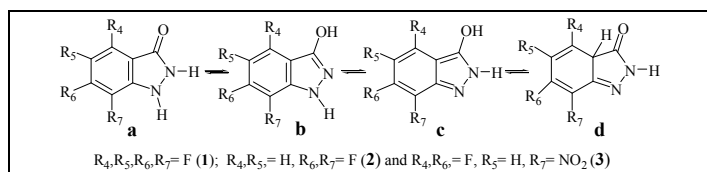
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Fluorinated indazoles are good inhibitors of Nitric Oxide Synthase (NOS) [1-8]. This work deals with tautomerism studies in solid state of 3-hydroxy-4,5,6,7-tetrafluoro-1H-indazole (**1**), 3-hydroxy-6,7-difluoro-1H-indazole (**2**) and 3-hydroxy-4,6-difluoro-7-nitro-1H-indazole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

Between the four possible tautomeric forms **a-d**, we have established by ¹³C and ¹⁵N 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.



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[1] J. Teichert, P. Oulié, K. Jacob, L. Vendier, M. Etienne, R. M. Claramunt, C. López, C. Pérez-Medina, I. Alkorta, J. Elguero, *New J. Chem.* **2007**, *31*, 936.

[2] R. M. Claramunt, C. López, C. Pérez-Medina, M. Pérez-Torralba, J. Elguero, G. Escames, D. Acuña-Castroviejo, *Bioorg. Med. Chem.* **2009**, *17*, 6180. [3] J. Elguero, I. Alkorta, R. M. Claramunt, C. López, D. Sanz, D. Santa María, *Bioorg. Med. Chem.* **2009**, *17*, 8027. [4] C. Pérez-Medina, C. López, R. M. Claramunt, J. Elguero, *J. Heterocycl. Chem.* **2009**, *46*, 1408. [5] C. Pérez-Medina, C. López, R. M. Claramunt, J. Elguero, *Eur. J. Org. Chem.* **2010**, 890. [6] M. Pérez-Torralba, C. López, C. Pérez-Medina, R. M. Claramunt, E. Pinilla, M. R. Torres, I. Alkorta, J. Elguero, *Cryst. Eng. Comm.* **2010**, *12*, 4052. [7] R. M. Claramunt, C. López, A. López, C. Pérez-Medina, M. Pérez-Torralba, I. Alkorta, J. Elguero, G. Escames, D. Acuña-Castroviejo, *Eur. J. Med. Chem.* **2011**, *46*, 1439. [8] P. Cabildo, R. M. Claramunt, C. López, M. A. García, M. Pérez-Torralba, E. Pinilla, M. R. Torres, I. Alkorta, J. Elguero, *J. Mol. Struct.* **2011**, 985, 75.

Keywords: NOS inhibitors, tautomerism, solid state NMR

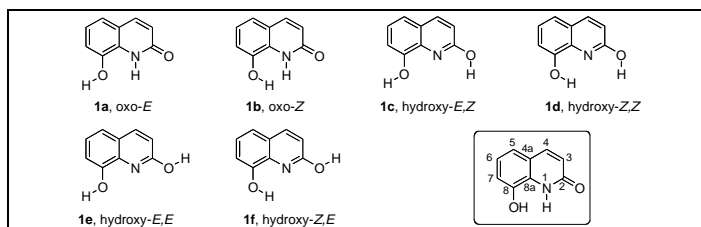
Polymorphism in 8-Hydroxyquinolin-2(1H)-one by X-ray Crystallography, Solid-State NMR and DFT Calculations

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The title compound also known as 8-hydroxycarbostryl 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(1H)-one derivatives and some of their preparations uses 8-hydroxycarbostryl 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(1H)-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 *P2₁/c* monoclinic group. The arrangement of molecules in both structures is characterized by intermolecular N-H \cdots O and O-H \cdots O hydrogen bonds.



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[1] T. Shimizu, H. Mori, E. Tabusa, K. Nakagawa, *Xenobiotica* **1978**, *8*, 705. [2] T. J. Visser, E. A. van der Wouden, A. van Waarde, P. Doze, P. H. Elsinga, W. Vallburg, *Appl. Rad. Isotopes* **2000**, *52*, 857. [3] S. Sirichai, P. Khanatharana, *Talanta* **2008**, *76*, 1194. [4] M. D. Deyrup, S. T. Nowicki, N. G. J. Richards, D. H. Otero, J. K. Harrison, S. P. Baker, *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1999**, *359*, 168. [5] M. Prashad, B. Hu, D. Har, O. Repic, T. J. Blacklock, *Org. Proc. Res. Develop.* **2006**, *10*, 135.