L.A.15

Acta Cryst. (2011) A**67,** C816

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

Philip Chamberlain[a], Sogole Bahmanyar[a], Barbra Pagarigan[a], Palka Patel[a], Jeff Muir[a], Mahan Abbasian[a], Afshin Mahmoudi[a], Dan Zhu[a], and Jennifer R. Riggs[a]. [a]*Celgene Corporation, 4550 Towne Centre Ct., San Diego, California 92121 (USA).* E-mail: pchamberlain@celgene.com

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

L.A.16

Acta Cryst. (2011) A**67,** C816

SSNMR spectroscopy and X-ray crystallography of fluorinated indazolinones

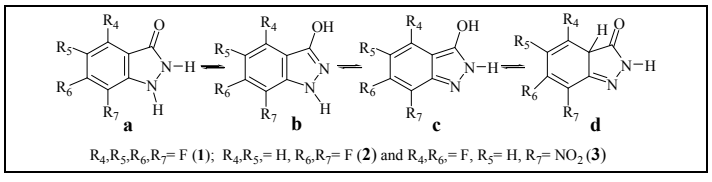
Concepción López,[a] Rosa M. Claramunt,[a] M. Pilar Cabildo,[a] Carlos Pérez-Medina,[a] M. Carmen Torralba,[b] M. Rosario Torres,[b] [a]*Química Orgánica y Bio-Orgánica, Facultad de Ciencias, UNED, 28040 Madrid.* [b]*Química Inorgánica I, CAI de Difracción de Rayos-X, Facultad de Ciencias Químicas, UCM, 28040 Madrid (Spain).* E-mail: clopez@ccia.uned.es

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**)

This work has been financed by the Spanish MICINN (CTQ2010-16122)

[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

L.A.17

Acta Cryst. (2011) A**67,** C816-817

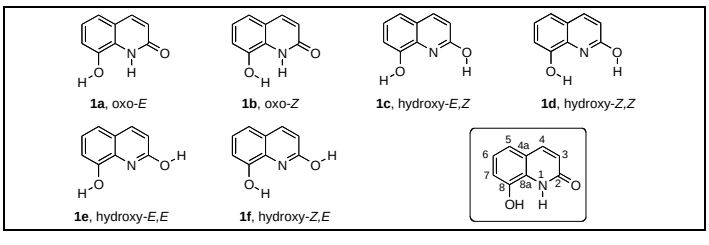
Polymorphism in 8-Hydroxyquinolin-2(1*H*)-one by X-ray Crystallography, Solid-State NMR and DFT Calculations

Rosa M. Claramunt,[a] M. Ángeles García,[a] M. Ángeles Farrán,[a] Carla I. Nieto,[a] M. Carmen Torralba,[b] M. Rosario Torres,[b] Ibon Alkorta,[c] José Elguero,[c] [a]*Química Orgánica y Bio-Orgánica, Facultad de Ciencias, UNED, 28040 Madrid.* [b]*Química Inorgánica I, CAI de Difracción de Rayos-X, Facultad de Ciencias Químicas, UCM, 28040 Madrid. Instituto de Química Médica, Centro de Química Orgánica "Manuel Lora-Tamayo", CSIC, 28006 Madrid (Spain).* E-mail: rclaramunt@ccia.uned.es

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.



This work has been financed by the Spanish MICINN (CTQ2009-13129-C02-02 and CTQ2010-16122) and CAM (MADRISOLAR2, S2009/PPQ-1533)

[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.