

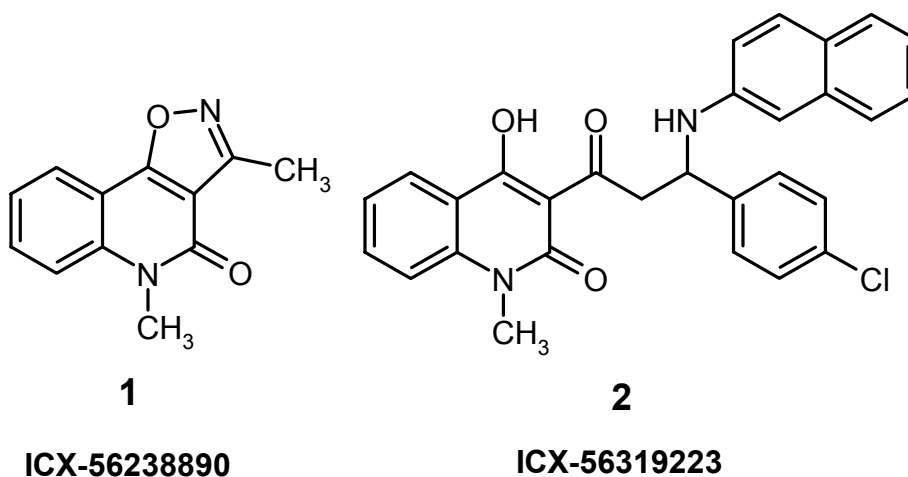
IMPROVED SYNTHESIS OF THE P38 INHIBITOR 3-[3-(4-CHLOROPHENYL)-3-(NAPHTHALEN-2-YLAMINO)-PROPANOYL]-4-HYDROXY-1-METHYLQUINOLIN-2(1H)-ONE

Christian Kühn^a, Ving J. Lee^b, and Ulrich Jordis^a

^a Institute of Applied Synthetic Chemistry, Vienna University of Technology
Getreidemarkt 9, 1060 Vienna, Austria, ujordis@pop.tuwien.ac.at

^b Iconix Pharmaceuticals, 325 East Middlefield Road, Mountain View, CA 94043 USA

Abstract. P38 mitogen-activated protein (MAP) kinase is supposed to be responsible for inflammatory and neurological diseases. Inhibitors of this key enzyme are suitable pharmaceutical targets as potential drugs. P38 MAP kinase is a specific member of the MAP kinase family which is involved in signal transduction and the amplification of cellular responses to stimuli and it is associated with the onset and progression of inflammation. The heterocyclic compounds **1** and **2** are known p38 MAP kinase inhibitors. While **1** has an assigned CAS registry number [2] with no associated references, the literature procedure for **2** was inadequate for preparation of multi-gram quantities. [3]. We will report an optimized synthesis of **1** and **2** that we developed in the context of the collaboration with the DrugMatrix program [4], the world's largest chemogenomics reference database and informatics system.



Leading references: [1]. (a) Ambrosino, C.; Nebreda, A. R., *Cell cycle regulation by p38 MAP kinases. Biology of the Cell* **2001**, *93*, 47-51; (b) Adams, J. L.; Gallagher, T. F.; Boehm, J. C.; Kassis, S.; Gorycki, P. D.; Gum, R. J.; Webb, E. F.; Sorenson, M. E.; Smietana, J. M.; Garigipati, R. S.; Hall, R. F.; Ayrton, A.; Badger, A.; Griswold, D. E.; Young, P. R.; Lee, J. C., **P38 MAP kinase inhibitors: Progress, pitfalls and possibilities. Special Publication - Royal Society of Chemistry** **2001**, *264 (Medicinal Chemistry into the Millennium)*, 163-173; (c) Underwood, D. C.; Griswold, D. E., **Inhibition of p38 MAP kinase. Progress in Respiratory Research** **2001**, *31 (New Drugs for Asthma, Allergy and COPD)*, 342-345

[2]. CAS [359907-66-7].

[3] Melese, Teri; Perkins, Edward L.; Nguyen, Allen T. Q.; Sun, Dongxu. **Quinolin-2-ones and isoxazolo[3,4-c]quinolin-2-ones as modulators of phosphoinositide 3-kinase.** *PCT Int. Appl.* **2003** WO 0335618 CAN 138:353971.

[4] http://www.iconixpharm.com/products/products_main.html