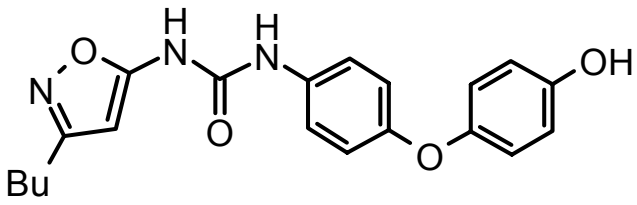
IMPROVED SYNTHESIS OF THE P38 KINASE INHIBITOR 1-(3-BUTYLISOXAZOL-5-YL)-3-[4-(4-HYDROXYPHENOXY)-PHENYL]UREA

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

[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. Compounds similar to the urea **1** are potent p38 and raf kinase inhibitors[1,2]. P38 kinase belongs to the family of mitogen-activated protein (MAP) kinases, and has been implicated in cytokine signaling. Members of the MAP kinase family are implicated of a wide variety of transcription factors and proteins involved in the control of cytokine production. Raf kinase is a downstream effector of the ras signal transduction pathway which transmits signals from groth factor and cytokine receptors on the cell surface to the nucleus, resulting in the regulation of cell differentiation and division. Inhibitors are potentially useful treatments against diseases of inflammation and cancer. In the context of the ongoing collaboration with the DrugMatrix program[2] we needed a reference sample of **1**. Analogous procedures disclosed in Bayer patents[1a] **1** were unsatisfactory in our hands.



1

[1] (a) Dumas, J.; Khire, U.; Lowinger, T. B.; Paulsen, H.; Riedl, B.; Scott, W. J.; Smith, R. A.; Wood, J. E.; Hatoum-Mokdad, H.; Johnson, J.; Lee, W.; Redman, A., **Inhibition of p38 kinase activity using substituted heterocyclic ureas.** WO 9932111 **1999**; (b) Dumas, J.; Khire, U.; Lowinger, T. B.; Paulsen, H.; Riedl, B.; Scott, W. J.; Smith, R. A.; Wood, J. E.; Hatoum-Mokdad, H.; Johnson, J.; Lee, W.; Redman, A., **Inhibition of raf kinase using substituted heterocyclic ureas.** WO 9932106 **1999**
[2] (a) Redman, A. M.; Johnson, J. S.; Dally, R.; Swartz, S.; Wild, H.; Paulsen, H.; Caringal, Y.; Gunn, D.; Renick, J.; Osterhout, M.; Kingery-Wood, J.; Smith, R. A.; Lee, W.; Dumas, J.; Wilhelm, S. M.; Housley, T. J.; Bhargava, A.; Ranges, G. E.; Shrikhande, A.; Young, D.; Bombara, M.; Scott, W. J., **p38 Kinase inhibitors for the treatment of arthritis and osteoporosis: thienyl, furyl, and pyrrolyl ureas.** *Bioorg. Med. Chem. Lett.* **2001**, *11*, 9-12; (b) Dumas, J.; Sibley, R.; Riedl, B.; Monahan, M. K.; Lee, W.; Lowinger, T. B.; Redman, A. M.; Johnson, J. S.; Kingery-Wood, J.; Scott, W. J.; Smith, R. A.; Bobko, M.; Schoenleber, R.; Ranges, G. E.; Housley, T. J.; Bhargava, A.; Wilhelm, S. M.; Shrikhande, A., **Discovery of a new class of p38 kinase inhibitors.** *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2047-2050; (c) Smith, R. A.; Barbosa, J.; Blum, C. L.; Bobko, M. A.; Caringal, Y. V.; Dally, R.; Johnson, J. S.; Katz, M. E.; Kennure, N.; Kingery-Wood, J.; Lee, W.; Lowinger, T. B.; Lyons, J.; Marsh, V.; Rogers, D. H.; Swartz, S.; Walling, T.; Wild, H., **Discovery of heterocyclic ureas as a new class of raf kinase inhibitors: identification of a second generation lead by a combinatorial chemistry approach.** *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2775-2778
[2] http://www.iconixpharm.com/products/products_main.html