VERSITA

Chemical Papers 67 (3) 305–312 (2013)
DOI: 10.2478/s11696-012-0278-4

ORIGINAL PAPER

Prediction of anti-tuberculosis activity of 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-dione derivatives‡

[a]Peter Nemeček*, [a]Ján Mocák†, [a]Jozef Lehotay, [b]Karel Waisser

[a]*Department of Chemistry, University of Ss. Cyril and Methodius, J. Herdu 2, 917 01 Trnava, Slovakia*

[b]*Faculty of Pharmacy, Charles University, Heyrovského 1203, Hradec Králové, CZ-50005, Czech Republic*

Received 8 December 2011; Revised 13 July 2012; Accepted 3 August 2012

Correlation analysis and, in particular, artificial neural networks (ANN) were used to predict the anti-mycobacterial activity of substituted 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones (PBODs) by quantitative structure – activity relationship (QSAR) calculations. Initially, sixty-four derivatives were synthesised and biologically tested; ten further derivatives were proposed for future synthesis on the basis of the prediction results. The biological activity was originally expressed by minimum inhibitory concentration (MIC) against *Mycobacterium tuberculosis*; however, its transformed pMIC form was found to be more informative. Theoretical molecular descriptors of several types were selected to establish a primary drug model of the species which was expected to exhibit a substantial anti-mycobacterial effect. Lipophilicity and solubility indices, several basic molecular properties, quantum chemistry quantities as well as ^{1}H and ^{13}C NMR chemical shifts, were employed as the descriptors, enabling a very successful prediction of the pMIC values. The utilisation of in silico variables and simulated NMR data is highly advantageous in the first phase of the drug design, as they permit prediction of the compounds with a high expected activity, minimising the risk of synthesising less active species. The MIC values predicted at less than 4 μmol L^{-1} for six of the ten compounds suggested for further synthesis are better than the best value for the original set of compounds.

Keywords: 3-phenyl-2*H*-1,3-benzoxazine-2,4(3*H*)-diones, *Mycobacterium tuberculosis*, minimum inhibitory concentration, QSAR, artificial neural networks

Introduction

The study of compounds inhibiting the growth of mycobacteria is important in respect of their danger to human health. With regard to the role of mycobacteria in human infection, the threat of tuberculosis poses a serious problem for contemporary medicine. Worldwide, tuberculosis (TB) remains the most frequently occurring important infectious disease causing morbidity and death (Tomioka & Namba, 2006). One-third of the world's population is infected with *Mycobacterium tuberculosis*, the etiological agent of TB. The World Health Organization estimates that each year eight to ten million new TB cases occur worldwide; the incidence of TB is currently increasing and two million people die from tuberculosis every year (Frieden et al., 2003). *M. tuberculosis,* together with *M. avium* and *M. kansasii,* are the mycobacteria strains most widely spread among HIV-infected patients (Corbett et al., 1999; Marras et al., 2004; El-Sadr et al., 2000; Mitha et al., 2011) and are the main cause of their mortality. Hence, the search for the optimum molecular structure (with the highest biological activity) of new effective anti-mycobacterial com-

*Corresponding author, e-mail: peter.nemecek@ucm.sk
‡Presented at the International Conference on Applied Natural Sciences 2011, Častá-Papiernička, 5–7 October 2011.
†Professor Mocák passed away on March 1, 2012.