Chem. Chem. Technol. 2017.
Vol. 11, No. 1, pp. 19– 24

Chemistry

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CORRELATION BETWEEN *IN SILICO* AND *IN VITRO* RESULTS OF 1-(BENZOYLOXY)UREA AND ITS DERIVATIVES AS POTENTIAL ANTI-CANCER DRUGS

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Received: January 26, 2016 / Revised: February 22, 2016 / Accepted: June 20, 2016

DOI:

Abstract. 1-(Benzoyloxy)urea and its derivatives were synthesized by modified Scotten-Bauman reaction with adding benzoyl chloride or homologs to hydroxyurea in tetrahydrofuran. Structure characterization was conducted based on ultra-violet (UV-VIS) spectrum, infrared (FT-IR), H nucleus magnetic resonance (^{1}H NMR), C nuclear magnetic resonance (^{13}C NMR) and mass spectrometry (MS). *In silico* test to predict anti-cancer activity of 1-(benzoyloxy)urea and its derivatives in ribonucleotide reductase enzyme (PDB: 2EUD) was done using Molegro Program. The anti-cancer activity test was performed *in vitro* by using MTT method to HeLa cell lines. *In silico* test result (Rerank Score) was correlated relative to anti-cancer activity ($\log 1/IC_{50}$). There was a significant linear relationship between *in vitro* and *in silico* anti-cancer activity.

Keywords: 1-(benzoyloxy)urea, derivatives, *in silico* test, *in vitro* test, rerank score.

1. Introduction

In Indonesia cancer is the fifth leading cause of death after heart disease, stroke, respiratory disease and diarrhea. Nearly six percent or 13.2 million of Indonesian people suffer from cancer and need early treatment. According to WHO, one person is dying every 11 minutes in the world because of cancer, and there is one new cancer patient every 3 minutes [1]. Based on the Report of National Basic Health Research 2013, the prevalence of tumor/cancer in Indonesia is 1.4 % per 1,000 people [2].

Cancer treatment can be carried out in several forms: surgery, radiation photo, immunotherapy, stem cell and chemotherapy [3]. Chemotherapy still remains one of the alternatives in cancer treatment, whether it can be done alone or collectively with other forms of treatment. There are some anti-cancer drugs used, including hydroxyurea.

Hydroxyurea was first synthesized in 1869, and its effect in slowing down the growth of leukocyte cells was first observed in 1928. Its clinical use as an anti-cancer compound began in the 1960s [4]. Hydroxyurea is antineoplastic that performs an activity to slow down the work of ribonucleotide reductase enzyme. The enzyme function is to convert ribonucleotide into deoxyribonucleotide. If the enzyme's work slows down, DNA biosynthesis will also slow down. The activities of hydroxyurea are called cytotoxic and antineoplastic that exhibits a special effect on S phase and disturbs cell cycle in phases of G2 and S [5]. Hydroxyurea is a derivative of urea that is used in myeloproliferative syndrome, chronic myelogenous leukemia (CML), polycythemia vera, and essential thrombocytosis [6].

To predict the activity of the compound, *in silico* test is carried out *via* computer simulation. *In silico* test is the method used to initiate discovery of new medicines and improve efficiency in the optimization of the main compounds activity [7]. The activity of synthesized medicinal compound can be predicted from the energy of molecular interaction between a receptor and ligand. The interaction energy can be illustrated with rerank score. *In silico* test is administered by docking molecule of the potential medicinal compound with the selected receptor. Docking is an attempt to streamline ligand that is a small molecule into the receptor that is a big protein by