SYNTHESIS OF SOME NOVEL BENZIMIDAZOL-2-ONE DERIVATIVES

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Abstract. *For the development of medical and pharmaceutical chemistry is essential to optimize and change relevant structures, possessing biological activity. Herein we report the synthesis of some novel 1H-benzimidazolon-2-one derivatives using aza-Michael addition.*

Keywords*: benzimidazole-2-one, aza-Michael addition.*

The benzimidazol-2-one plays essential role in the medicinal chemistry as building block of many biological active compounds as Droperidol, Domeperidone, Pimozid and HY-10355, that are used in clinical practice. Droperidrol is with general properties similar to those of Haloperidol and is used in conjunction with an opioid analgesic such as Fentanyl. Pimozid represents an antipsychotic drug and D2 dopamine receptor antagonist th binds with high affinity to the cloned 5-HT7 receptor. HY-10355 is a cell-permeable quinoxaline compound that has been shown to potently, selectively, allosterically, and reversibly inhibit Akt1, Akt2, and Akt3 activity (IC_{50} = 58 nM, 210 nM, and 2.12 μM respectively).

A series of novel benzimidazolones and their analogues, characterized by the presence of one or more methyl groups or other bioisosteric moieties at different positions of the phenyl ring at N-1 (**1**), were synthesized and evaluated as inhibitors of human immunodeficiency virus type-1 (HIV-1) [1].

Many of these compounds and especially 1,3-dihydro-2H-benzimidazole-2-one ring system have served as a basis for the design and synthesis of new compounds, possessing broad spectrum of biological activity as: potent NK1 antagonists [1], CGRP receptor antagonists [2], farnesyl transferase inhibitors [3], p38 inhibitors [4], cathepsin S inhibitors [5], 5-HT4 agonists and antagonists [6], progesterone receptor antagonist [7], respiratory syncytial virus (RSU) inhibitors [8].

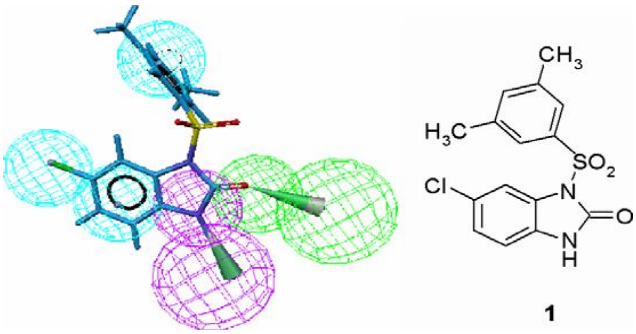

Fig.1

The development of efficient and practical methods for construction of this important heterocycle remains as an active area of synthetic research. The Michael addition reaction is a versatile synthetic methodology for the efficient coupling of electron poor olefins with a vast array of nucleophiles [9]. The nitrogen-donor version of the Michael addition is often referred to as the aza-Michael reaction. Since amines can act as both nucleophiles and bases, no additional base is typically needed in these reactions. Here we report an approach for the use of the reaction of Michael for creating new benzimidazol-2-one derivatives [10].

The synthesis of the target compounds was performed as it is outlined in Fig.2, 3.

The starting benzimidazol-2-ones were synthesized in one step synthesis by heating the mixture of appropriated 4-sunstituted-1,2-diaminobenzenes with urea at 130-140 oC for one hour. The melt was treated with water solution of sodium hydroxide, the solid obtained was filtered and the filtering was neutralized to afford the target benzimidazol-2-one.

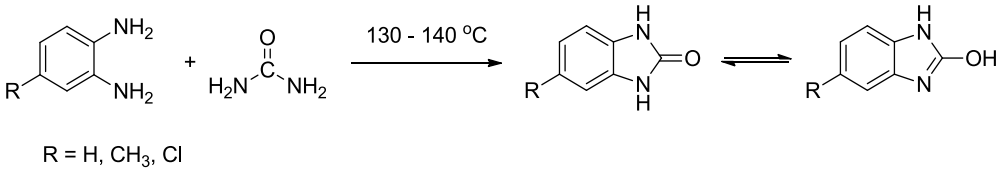

Fig. 2. Synthesis of 1H-benzimidazol-2-ones

It is well known that the H-atoms linked to N-atoms of imidazole heterocycle possess prototropic properties, moreover there is an equilibrium between the hydroxy-form and the oxo-form of benzimidazol-2-one. In polar medium exists predominantly the oxo-form. Therefore the aza-Michael addition of benzimidazolones to α,β-unsaturated carbonyl compounds was performed in DMF medium in molar ratio 1:2.5 under reflux. The reaction was monitored by use of TLC. The reaction was completed for 4-5 hours and after cooling the reaction mixture was poured in water, whereat the target compound crystallized.

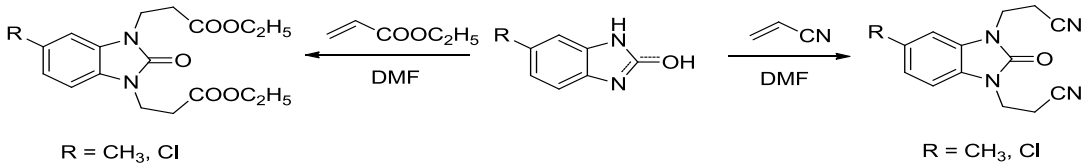

Fig. 3. Synthesis of 1,3-dihydro-substituted-1H-benzimidazol-2-ones

The reactions were monitored by thin layer chromatography. The structures of all products were confirmed by melting points (m.p.), FT-IR - and ^{1}H NMR spectroscopy.

In conclusion, we have developed one pot synthetic method using aza-Mickael addition for the generation of novel 2,3-dihydro-1,3-disubstituted-1H-benzimidazol-2-one derivatives, which can serve as precursors for the preparing other new benzimidazole compounds.

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