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Small Heterocyclic Molecules as Anticancer Agents: Design, Synthesis, and Evaluation Against MCF-7 Cell Lines

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Abstract—Isatin and substituted isatin derivatives possess a broad spectrum of biological activities. These moieties also have a wide scope for substitution, particularly at positions N-1 and C-3. Therefore, the study focused on design of some novel isatin/substituted isatin Schiff's bases. The compounds were screened based on their binding energies, and only the low-energy compounds were subjected to synthesis. All the compounds were synthesized by conventional methods in a two-step synthesis. Mannich bases of isatin were synthesized by reacting secondary amines and 37% formalin, which were then reacted with primary aromatic amines in the presence of glacial acetic acid to yield the title compounds. All the compounds were characterized by physical, chromatographic and spectroscopic methods. The synthesized compounds were tested for anti-cancer activity against the MCF-7 cell lines. The compounds showed good activity against MCF-7 cell lines in comparison to the standard drug, Doxorubicin. The compounds, **IDF 3B**, **IDF 3G**, **IDF 3H**, and **IDF 3I** showed IC_{50} values of 7.08, 5.78, 4.73, and 5.73 μg/mL, respectively. The obtained data indicated that the analogues were effective against the tested breast cancer. The in silico ADMET prediction study was also carried out, and the compounds were predicted to be safe. The study, therefore, concludes that the isatin moiety could serve as the lead to the development of new anti-breast cancer agents.

Keywords: ɯsatin, substituted isatin, Mannich base, breast cancer, molecular docking, MCF-7 cell line, in vitro testing, in silico ADMET prediction

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INTRODUCTION

Cancer is a collection/group of cells characterized by their uncontrolled growth and division. It is the second leading cause of death worldwide and exerts tremendous burden on the health care system [1, 2]. In Asian countries, more than 60% breast cancer cases are diagnosed as estrogen receptor α positive (ER-α) cancers. In normal mammary gland development, ER-α plays a significant role in breast cancer development [3]. Among all types of cancer, breast cancer is one of the most common cancers occurring especially in the females.

Heterocyclic rings have great significance in biological activity of compounds [4–6]. Isatin (1*H*-Indole-2,3-dione), an indole oxidized derivative is one such molecule [7]. It possesses several biological activities *viz.* anti-fungal [8], anti-tubercular [9], anti-HIV, anti-viral [8], anti-cancer [10–12], anti-convulsant [13], anti-bacterial [14], anti-inflammatory [15], and anti-oxidant [16]. A number of isatin analogues may be obtained by substitutions at different positions to potentiate the cytotoxic and anticancer effectiveness [17] (Fig. 1).

Also, benzothiazole possesses a wide variety of biological activities [18–25]. 2-Aminobenzothiazole

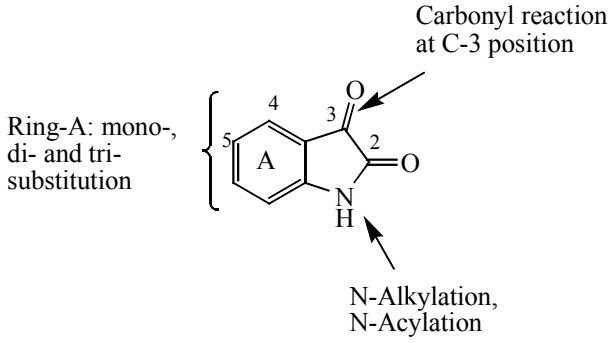

Fig. 1. Isatin scaffold containing various substitution sites.