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# ISATIN/THIOSEMICARBAZONE HYBRIDS: FACILE SYNTHESIS, AND THEIR EVALUATION AS ANTI-PROLIFERATIVE AGENTS AND METABOLIC ENZYME INHIBITORS

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**ABSTRACT**. We are reporting a novel series of thiosemicarbazone derivatives derived from isatin (**1-6**), structural determination, and investigation of the inhibitory properties against proliferative, carbonic anhydrase, and cholinesterase enzymes. The anti-proliferative effects of the compounds were measured by XTT assay against MCF-7 and MDA-MB-231 cancerous cell lines. Compound **3** showed significant cytotoxic effects on both MCF-7 and MDA-MB-231 cell lines, with $IC_{50}$ values of 8.19 µM and 23.41 µM, respectively. In addition, the compounds (**1-6**) inhibited the hCA I and II, their $K_i$ values 2.01 ± 0.35 – 21.55 ± 2.56 and 1.24 ± 0.33 – 25.03 ± 5.48 µM, respectively. AChE was also successfully inhibited by these compounds (**1-6**), with $K_i$ values ranging from 40.37 ± 8.23 to 125.43 ± 24.93 µM. The best $K_i$ values for **3**, **6**, and **4** for α-glycosidase were 564.35 ± 72.06, 594.38 ± 52.04, and 683.437 ± 66.58 µM, respectively. Binding affinities were determined to be -6.697 kcal/mol, -8.251 kcal/mol, -9.932 kcal/mol, and -4.946 kcal/mol for hCA I, hCA II, AChE, and α-glucosidase enzymes, respectively. These findings reveal that the formed compounds containing isatin moieties were crucial in the enzyme inhibition.

**KEY WORDS**: Isatin, Thiosemicarbazone, Anti-proliferative activity, Enzyme inhibition, Molecular docking

## INTRODUCTION

Cancer, one of the worst diseases in the world, is responsible for the deaths of an increasing number of people. Therefore, the development of novel, safe, and selective anti-cancer compounds has become a major goal for medicinal chemistry researchers as most of the existing anti-cancer drugs are highly hazardous [1-3]. Alzheimer's is an extremely tough disease to manage, especially for the elderly people, and it has a significant impact on quality of life of people. The illness might be categorized as cognitive deterioration with strong executive function difficulties. In addition, this disease is a progressive brain disorder that gradually robs people of their capability for reasoning, memory, and doing basic tasks [4-6]. Although the exact cause of this disease is still unknown, however, several factors, including acetylcholine (ACh) deficiency, excessive amyloid-beta (β-amyloid) peptide development, neurofibrillary node (NFT) formation,

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