



Synthesis, SAR elucidations and molecular docking study of newly designed isatin based oxadiazole analogs as potent inhibitors of thymidine phosphorylase

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ABSTRACT

Thymidine phosphorylase is an enzyme involved in pyrimidine salvage pathway that is identical to platelet-derived endothelial cell growth factor (PD-ECGF) and gliostatin. It is enormously up regulated in a variety of solid tumors. Furthermore, surpassing of TP level protects tumor cells from apoptosis and helps cell survival. Thus TP is identified as a prime target for developing novel anticancer therapies. A new class of exceptionally potent isatin based oxadiazole (1–30) has been synthesized and evaluated for thymidine phosphorylase inhibitory potential. All analogs showed potent thymidine phosphorylase inhibition when compared with standard 7-Deazaxanthine, 7DX (IC₅₀ = 38.68 ± 1.12 μM). Molecular docking study was performed in order to determine the binding interaction of these newly synthesized compounds, which revealed that these synthesized compounds established stronger hydrogen bonding network with active site of residues as compare to the standard compound 7DX.

1. Introduction

Cancer is the leading cause of premature mortality worldwide [1], which ultimately led vast interest in exploring several potential angiogenic modulators in order to develop new therapies for cancer treatment [2–4]. Among various angiogenic activators, thymidine phosphorylase (TP, EC 2.4.2.4) has been identified as a crucial angiogenic protein [5]. TP is found in many normal tissues and cells present in both cytoplasm and nucleus [6]. TP causes a variety of pathological complications such as psoriasis, rheumatoid arthritis, inflammatory bowel disease and atherosclerosis etc [7]. TP is a major contributor in tumor angiogenesis as it facilitates proliferation of endothelial cells during cancer metastasis [7,8]. TP has been shown to be identical to platelet-derived endothelial cell growth factor (PDECGF) [9–12], which has been implicated in angiogenesis and chemotaxis in human tumors

[13,14]. Increased hypoxia correlates with elevated TP activity, and increased levels of this enzyme have been observed in colorectal, ovarian, pancreatic, and breast tumors [15,16]. In the last few years, hybrid drug design has emerged as a prime tool for the discovery of innovative anticancer therapies that can potentially overcome most of the pharmacokinetic drawbacks encountered when using conventional anticancer drugs (see Table 1).

Isatin as an indole derivative widely distributed endogenously in human and other mammalian tissues and fluids probably due to tryptophan metabolic pathway. The versatility of isatin molecular architecture makes it as an ideal platform for structural modification and derivatization and many isatin derivatives exhibit a broad range of biological activities such as anticancer [17], antidepressant [18], anticonvulsant [19], antifungal [20], anti-HIV [21] and anti-inflammatory activity [22]. In the last several decades, many researchers

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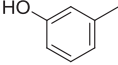
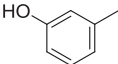
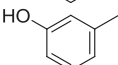
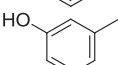
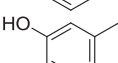
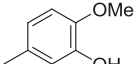
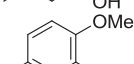
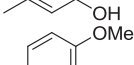
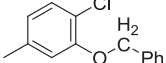
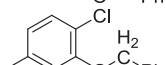
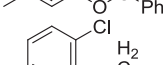
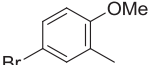
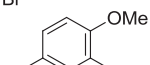
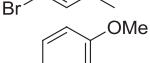
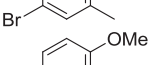
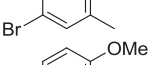
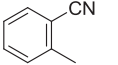
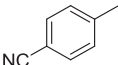
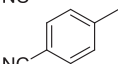
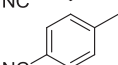
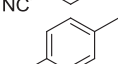
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Table 1

Synthesis of various analogs of isatin based oxadiazole derivatives (1–30) and its thymidine phosphorylase inhibition.

Comp. No.	R	R ₁	R ₂	IC ₅₀ (μM ± SEM ^a)
<i>Category-A</i>				
1		<i>N</i> -Isopropyl	H	7.80 ± 0.20
2		<i>N</i> -Butyl	H	9.40 ± 0.20
3		H	5-isopropyl	5.30 ± 0.10
4		<i>N</i> -Pentyl	H	16.50 ± 0.30
5		H	H	19.40 ± 0.40
<i>Category-B</i>				
6		H	5-isopropyl	6.20 ± 0.10
7		<i>N</i> -Isopropyl	H	4.70 ± 0.10
8		<i>N</i> -Butyl	H	5.30 ± 0.10
<i>Category-C</i>				
9		H	5-isopropyl	14.60 ± 0.3
10		<i>N</i> -Isopropyl	H	11.30 ± 0.30
11		<i>N</i> -Butyl	H	17.60 ± 0.40
<i>Category-D</i>				
12		H	5-isopropyl	48.50 ± 1.20
13		<i>N</i> -Isopropyl	H	29.10 ± 0.90
14		<i>N</i> -Butyl	H	38.60 ± .90
15		<i>N</i> -Pentyl	H	46.20 ± 1.20
16		H	H	49.40 ± 1.30
<i>Category-E</i>				
17		<i>N</i> -Isopropyl	H	25.10 ± 0.50
18		<i>N</i> -Butyl	H	19.70 ± 0.40
19		<i>N</i> -Pentyl	H	34.60 ± 0.60
20		H	5-isopropyl	26.80 ± 0.60
21		<i>N</i> -Isopropyl	H	18.40 ± 0.40

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