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Short communication

"On water" expedient synthesis of 3-indolyl-3-hydroxy oxindole derivatives and their anticancer activity *in vitro*

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ABSTRACT

A series of 3-indolyl-3-hydroxy oxindole derivatives ($n = 41$) were synthesized by the green aminocatalytic method with excellent yields under mild reaction conditions. All the newly synthesized derivatives were subjected to evaluate their cytotoxic properties against different human cancer cell lines. Results indicated that about 73% of the derivatives exhibited significant anti-proliferative activities against leukemia (U937, THP-1), lung (A549) and breast cancer (MCF7) cell lines. Among them a few of the derivatives exhibited the most potent and effective cytotoxic activities on U937 (**34**, **36**, **38** and **41**) and MCF7 (**12**, **35**, **40** and **41**) cell lines, and their anti-proliferation activities are better than the positive control, Etoposide.

1. Introduction

C3 functionalised oxindole is featured heterocyclic nucleus in a number of natural products as well as medicinally relevant compounds [1]. In particular 3-substituted-3-hydroxyoxindole is an emerging new scaffold for drug discovery with a broad spectrum of biological activities including antiviral, antibacterial, antitubercular, anti-inflammatory, antiangiogenic, antifungal, anticonvulsant and new targets for cancer chemotherapy [2]. Notably these derivatives have been served as potential synthons for complex natural product synthesis [3]. Several pharmacologically active alkaloids such as Maremycin A and B, Flustramnol, Arundaphine, Donaxaridine, CPC-1, Welwitindoline C in addition to several others contain 3-hydroxyoxindole moiety as shown in (Fig. 1) [4]. Recently 3-hydroxy-3,3′-bisindolin-2-one **1** has been reported as potential synthon for the enantioselective total synthesis of optically pure(+)-folicanthine [5].

Isatins are well-known biological manifolds with a reactive keto-carbonyl group that readily undergoes condensations, resulting in C-3 functionalised oxindole derivatives. Increasing demands for more efficient and scalable synthetic processes, which are both economical and environmentally responsible in terms of feedstock, energy consumption and waste production, require the use of "green" solvents especially water.

Owing to the significance of 3-substituted-3-hydroxy-2-oxindoles and intense research activity of medicinal chemists in the construction of small bioactive chemical entities, we envisioned the combination of both indole and oxindole motif with a hydroxy-bearing C3 substitution to generate biologically attractive architectures (Fig. 2). The use of readily available isatins **1a** and indoles **1b** through a Friedel–Crafts type reaction represents an attractive one-step entry to the valuable targets (Scheme 1) [6]. The literature survey reveals that direct Friedel–Crafts reactions of isatins for the selective synthesis of 3-indolyl-3-hydroxy oxindole derivatives are less explored compared to the methods for synthesis of 3,3′-di(indolyl)oxindoles [7]. Of the developed strategies for the synthesis of target **1** organocatalysis provides an efficient protocol due to its ease of operation, tolerance of wide array of functional groups [8]. As part of our current studies on the design of new routes for C-

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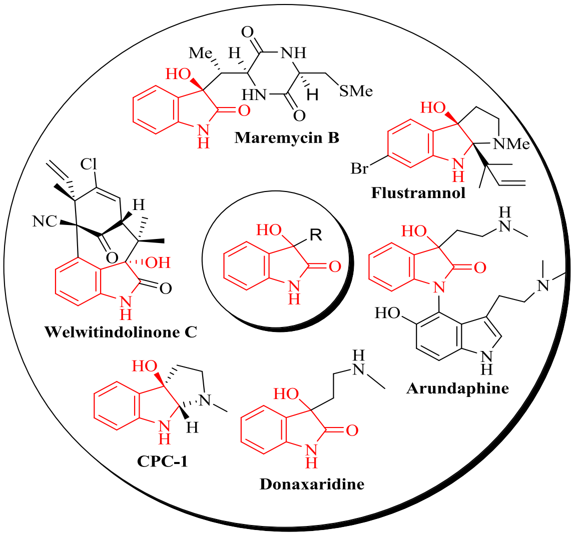


Fig. 1. Bioactive natural products built with 3-substituted-3-hydroxy-2-oxindole core scaffold.

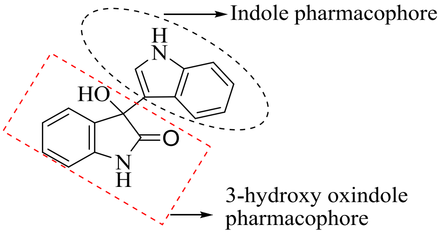
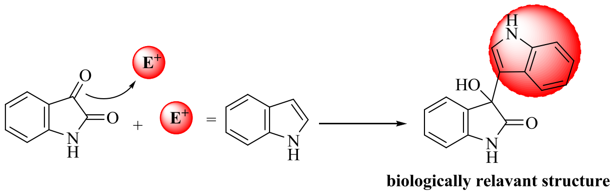


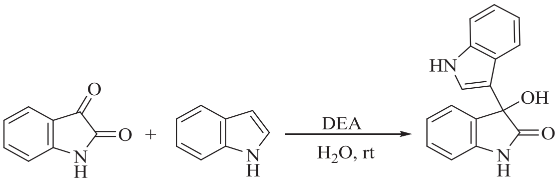
Fig. 2. Oxindole motif bearing hydroxy-group and indole at C3 position.



Scheme 1. Electrophilic addition of indoles to isatins.

3 functionalization of isatins [9] to biologically active heterocyclic compounds, we herein disclose a simple, green aminocatalytic method for the efficient synthesis of 3-indolyl-3-hydroxy oxindoles in water and their evaluation for anticancer activity.

Initially, we examined the reaction of isatin **1a** and indole **1b** for the synthesis of 3-indolyl-3-hydroxy oxindole **1** with various amine based catalysts, including triethylamine, pyrrolidine, ethylene diamine, piperidine, pyridine, imidazole and diethanolamine using water as solvent. However the reaction proceeded spontaneously at ambient temperature with diethanolamine in water and the corresponding 3-indolyl-3-hydroxy oxindole **1** was obtained in 98%



1a **1b** **1**

Scheme 2. Synthesis of 3-indolyl-3-hydroxy oxindoles from isatin.

Table 1
Synthesis of 3-indolyl-3-hydroxy oxindole derivatives[a].

Compds	R	R^1	R^2	R^3	R^4	Yield [%][b]
1	H	H	H	H	H	98
2	H	Cl	H	H	H	92
3	H	Br	H	H	H	91
4	H	I	H	H	H	83
5	H	F	H	H	H	86
6	H	Me	H	H	H	88
7	H	H	H	Cl	H	89
8	H	OCF_3	H	H	H	94
9	$PhCH_2$	H	H	H	H	81
10	Me	H	H	H	H	84
11	H	H	Br	H	H	81
12	H	OCF_3	Br	H	H	91
13	H	H	Me	H	H	89
14	H	Cl	Br	H	H	91
15	H	Br	Br	H	H	90
16	H	I	Me	H	H	81
17	H	F	Me	H	H	92
18	H	Me	Me	H	H	84
19	$PhCH_2$	H	Br	H	H	81
20	H	H	H	H	Me	83
21	H	H	OMe	H	H	91
22	H	F	OMe	H	H	94
23	H	Cl	OMe	H	H	92
24	H	I	OMe	H	H	92
25	H	F	Br	H	H	91
26	H	I	F	H	H	90
27	H	Br	OMe	H	H	92
28	H	OCF_3	Me	H	H	81
29	H	F	F	H	H	91
30	H	H	F	H	H	93
31	4-Br-$PhCH_2$	Cl	Br	H	H	89
32	2-Br-$PhCH_2$	H	Br	H	H	81
33	2-Cl-$PhCH_2$	H	Br	H	H	80
34	2-Cl-$PhCH_2$	Cl	Br	H	H	84
35	$PhCH_2$	Cl	Br	H	H	80
36	$PhCH_2$	Cl	H	H	H	88
37	2-Cl-$PhCH_2$	H	H	H	H	84
38	2-Cl-$PhCH_2$	Cl	H	H	H	88
39	2-Br-$PhCH_2$	H	OMe	H	H	86
40	2-Cl-$PhCH_2$	H	OMe	H	H	89
41	2-Cl-$PhCH_2$	Cl	OMe	H	H	85

[a] Reaction conditions: Isatin (0.5 mmol), Indole (0.5 mmol), diethanolamine (0.02 mmol) and water (2 mL) at room temperature.
[b] Overall yield of the product.

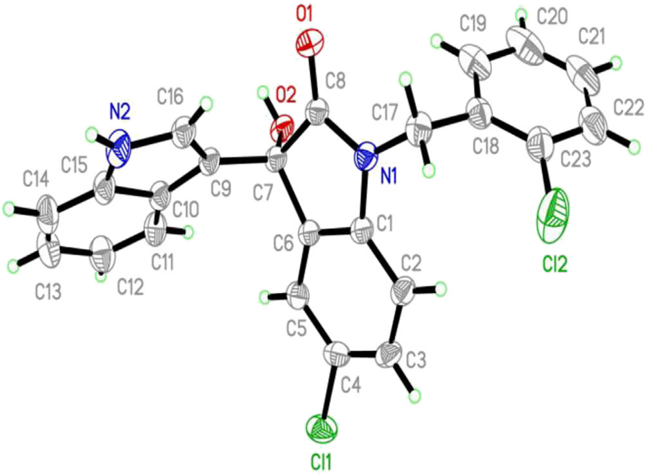


Fig. 3. ORTEP drawing of **38** (30% thermal ellipsoids).