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Cytotoxic and Anticancer Activities of Indoline-2,3-dione (Isatin) and Its Derivatives

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Authors' contributions

This work was carried out in collaboration between both authors. Authors SAI and TE designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Author SAI managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Isatin (1*H*-indolin-2,3-dione) is a versatile bioactive and heterocyclic scaffold with an indole nucleus. For the past decades, isatin and its derivatives have shown tremendous interest among researchers (organic and medicinal chemists). Hence, their extensive structural modification has result in different analogues of isatin depicting wide range of biological and pharmacological activities including antimicrobial, anticancer, anti-inflammatory and analgesic, anticonvulsant, anti-viral, anti HIV and antiplasmodial activity. In this present review, we focus on isatin and its derivatives possessing cytotoxic and anticancer activity against different cancer cell lines from the period 2002 to 2015.

Keywords: 1H-indolin-2; 3-dione; scaffold; cytotoxic activity; medicinal chemists; cancer cell lines.

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ABBREVIATIONS

TKIs : tyrosine Kinase inhibitors;
DNA : deoxy ribonucleic acid;
EC_{50} : half maximal effective concentration;
ERK : extracellular signal-related protein kinase;
GI_{50} : concentration required to inhibit the growth a cellular population by 50%;
IC_{50} : concentration required for 50% inhibition of a biological or biochemical process in vitro;
CDK : cyclin dependent kinase;
FDA : Food and Drug Administration;
Ppm : part per million;

1. INTRODUCTION

Isatin (1*H*-indolin-2,3-dione) (**1**) [1-3], is an endogenous indole molecule found in human (as a metabolite of adrenaline), which shows diverse pharmacological and biological activities. In 1840, Erdmann and Laurent discovered isatin (**1**) as product resulting from the oxidation of indigo dye (**2**) by nitric acid and chromic acid. On the other hand, Isatin (**1**) has been found to be present in plants from the *Isatis* genus, in fruits of the cannon ball tree, *Couroupita guianensis* Aubl., and *Calanthe discolor* Lindl., and was also found to be secreted from the parotid gland of *Bufo* frogs[4-13].

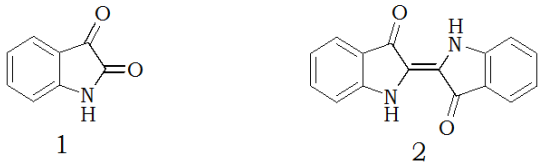


Fig. 1. Structures of isatin (1) and indigo (2)

Numerous publications revealed that isatin (**1**) and its derivatives exhibit various pharmacological and biological activities such as antimicrobial [14-18], anticancer [19-28], anti-inflammatory and analgesic [29-32], anticonvulsant [14,33,34], antioxidant [35-37], antifungal [15-17,38] anti-TB [39,40], anti-viral [38,41-48], anti HIV[46-49], and antiplasmodial activity [38,50,51].

Structurally, isatin(**1**) is a heterocyclic compound [5, 53], which possesses indole (**3**) (benzene ring fused with pyrrole ring) nucleus with keto group (at position 2 and 3) and lactam moiety [1,9,53, 54].

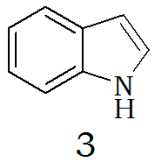


Fig. 2. Structure of indole (3) nucleus

The proposed mechanisms by which isatin (**1**) exerts it cytotoxic activities have been revealed. Isatin (**1**) has been found to exhibit; tyrosine kinase inhibition (act as tyrosine Kinase inhibitors [TKIs]), inhibition of cyclin-dependent kinases (CDKs), and inhibition of the phosphorylation of extracellular signal-related protein kinases (ERK-2) in different cancer cell lines. In addition, it (isatin (**1**)) induces apoptosis via interaction with ERKs, and also induces DNA fragmentation and chromatin condensation [1,10,55-57].

Furthermore, an isatin (**1**) derivative (2-oxoindole), Sunitinib maleate (**4**), (*N*-[2-(diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-1,2-dihydro-2-oxo-*3H*-indol-3-ylidine)methyl]-2,4-dimethyl-*1H*-pyrrole-3-carboxamide) (Sutent®, Pfizer, New York.) is an example of TKIs which has gained approval from Food and Drug Administration, USA (FDA) in the treatment of different malignancies such as advanced renal-cell carcinoma, pancreatic neuroendocrine tumors and gastrointestinal stromal tumors [58-64].

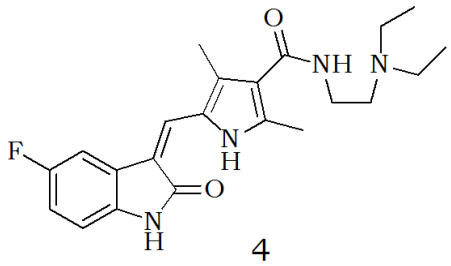


Fig. 3. Structure of sunitinib maleate (4)

2. ISATIN DERIVATIVES WITH CYTOTOXIC EFFECTS

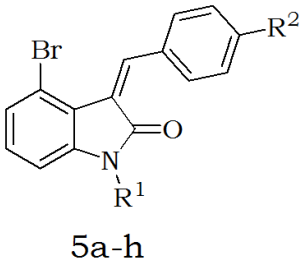
In recent years, enormous studies on the anticancer activities of isatin (**1**) scaffold, its derivatives, Schiff's bases and Mannich bases have been reported [52,55,65-68].

2.1 3-Arylidene Derivatives

A series of 3-benzylidene 4-bromo isatin derivatives (**5a-h**) were synthesized. The anticancer activities of the title compounds were evaluated against two human cancer cell line K562 and HepG2 using MTT assay. The anticancer activity reveals compound **5g** depicted higher potent anticancer activity with IC_{50} value 4.39 μM against human leukemia HepG2 cell line and IC_{50} value = 6.18 μM against K562 cells line [69].

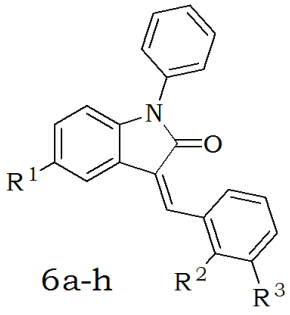
5-Bromo-*N*-phenyl substituted isatin derivatives (**6a-h**) were synthesized and their antitumor activities were screened against HepG2 and HT-29 human tumor cell lines. Compound **6c, 6d** and **6e** were found to exhibit higher antitumor activity against HT-29 cancer cell lines with the IC_{50} values **6c=** 16.10 μM, **6d=** 17.87 μM and **6e=** 16.13 μM. In addition, compound **6d** and **6g** were also active against HepG2 cell lines with the IC_{50} values 19.00 μM and 19.03 μM respectively [54].

In continuation of the previous study, another series of *N*-phenyl substituted isatin derivatives (**7a-g**) were synthesized. The synthesized compounds were screened against K562, HepG2, HT-29 and cell lines. Compound **7a, 7d, 7e,** and **7f** showed significant anticancer activities against all the three cancer cell lines. Hence, Compound **7e** was found to be most potent compound with the IC_{50} values of 24.09 μM, 20.27 μM, and 6.10 μM against cancer cell lines HepG2, HT-29, K562 respectively [70].



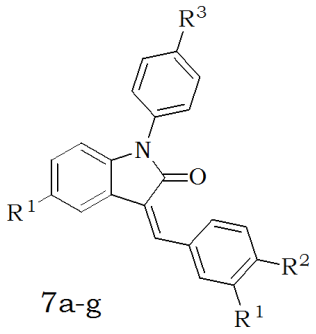
Comp.	R^1	R^2
5a	H	H
5b	CH_3	H
5c	H	Cl
5d	CH_3	Cl
5e	H	OCH_3
5f	CH_3	OCH_3
5g	H	$CH(CH_3)_2$
5h	CH_3	$CH(CH_3)_2$

Fig. 4. Structure of 3-benzylidene 4-bromo isatin derivatives (5a-h)



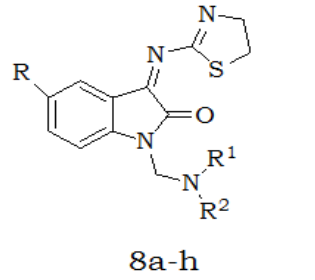
Comp.	R^1	R^2	R^3
6a	H	H	H
6b	H	H	Cl
6c	Br	H	Cl
6d	Br	H	F
6e	Br	H	Br
6f	Br	H	CN
6g	Br	H	NO_2
6h	Br	Cl	Cl

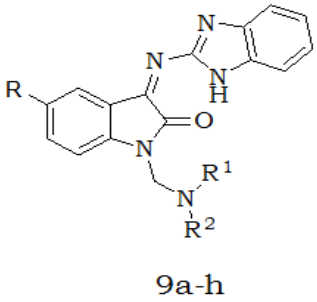
Fig. 5. Structure of 5-Bromo-N-phenyl substituted isatin derivatives (6a-h)



Comp.	R^1	R^2	R^3
7a	H	OCH_3	H
7b	H	Cl	H
7c	Cl	Cl	H
7d	H	Cl	H
7e	Cl	Cl	H
7f	Cl	Cl	CH_3
7g	Cl	Cl	CF_3

Fig. 6. Structure of N-phenyl substituted isatin derivatives (7a-g)





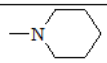
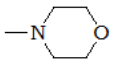
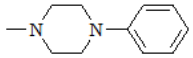
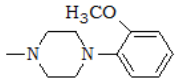
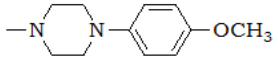
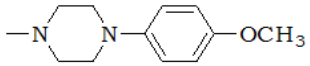
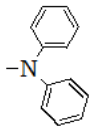
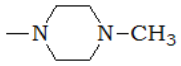
Comp.	R	R^1, R^2
8a, 9a	H	
8b, 9b	H	
8c, 9c	H	
8d, 9d	H	
8e, 9e	H	
8f, 9f	Br	
8g, 9g	H	
8h, 9h	H	

Fig. 7. Structures of isatin-thiazoline (8a-h) and isatin-benzimidazole (9a-h) Schiff's bases

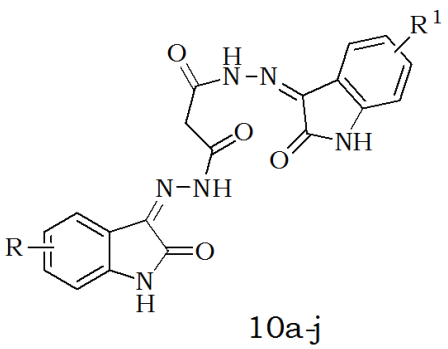
2.2 Hydrazone, Imine and Mannich Bases Derivatives

The anti-breast cancer activities of novel isatin (**1**) Mannich bases coupled with 2-aminothiazoline or 2-aminobenzimidazole moieties to produce isatin-thiazoline (**8a-h**), isatin-benzimidazole (**9a-h**) Schiff's bases respectively [52]. Only eleven Schiff's bases (**8a,8b,8c,8d,8g,9a,9b,9c,9d,9e,** and **9g**) were tested against a human breast adenocarcinoma cell line (MCF-7) and were found to inhibit the proliferation of MCF-7 human breast cancer cells with IC_{50} ranging from 22.59-64.14 **nM**. The cytotoxic screening revealed that compound (**9a-e** and **9g**) showed higher cytotoxic activity than compound (**8a-d,** and **8g**). **9b, 9d**, and **9g** Schiff's bases were the most potent compounds and showed the best anti-breast cancer activity against MCF-7 human breast cancer cells [52].

Malonic acid bisisatin hydrazones (**10a-i**) were synthesized and tested for cytotoxic activity against HLB-100 cell lines. All the synthesized compounds exhibited IC_{50} ranging from 31 µM to 171 µM against HLB-100 cell lines, which were compared to Cisplatin (standard compound). **10e**

was found to be most active compound exhibiting relatively high cytotoxic effect (IC_{50} 31 μM). Compound **10c**, **10d**, and **10g** were also found to be active exhibiting IC_{50} values of 42μM, 56μMand 66μM respectively. Compound **10i** was the least active compound showing IC_{50} value 171 μM [71].

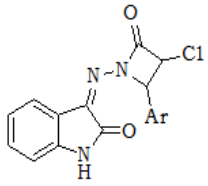
A series of substituted azetidinone containing isatin scaffolds (**11a-j**) were synthesized and tested against two cancer cell lines (MCF-7 and L929). The synthesized compounds showed a lesser activity than the standard drugs (Doxorubin and Paclitaxel). Among the tested compounds, compound **11h** showed significant anticancer activity against L929 cell line with growth percentage inhibition of 41%, 52%, 60%, 69%, 74%, at the conc. of 10 μg/ml, 100 μg/ml, 250 μg/ml, and 500 μg/ml respectively [11].



10a-j

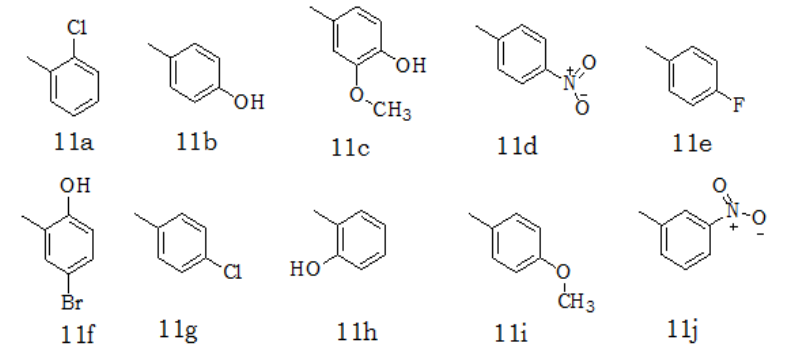
Comp.	R	R¹
10a	F	F
10b	Cl	Cl
10c	Br	Br
10d	CH_3	CH_3
10e	NO_2	NO_2
10f	F	Cl
10g	OH	OH
10h	F	Cl
10i	F	Br
10j	Cl	Br

Fig. 8. Structure of malonic acid bisisatin hydrazones derivatives (10a-i)



11a-j

Ar



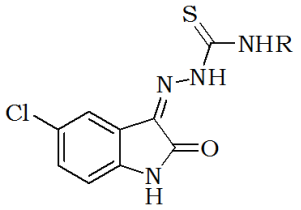
11a 11b 11c 11d 11e

11f 11g 11h 11i 11j

Fig. 9. Structure of substituted azetidinone analogue of isatin

A 5-chloro-1*H*-indole-2,3-dione 3-thiosemicarbazones derivatives (**12a-g**) were synthesized and the antitumor activities of the titled compounds were investigated against HeLa cells derived from human cervix carcinoma. Sunitinib (**4**) was used as a reference drug. The cytotoxic investigation reveals that compound **12a**, **12b** and **12d** were most active compounds showing percentage inhibition values **12b**=50.41%, **12a**=38.19% and **12d**=40.55% [72].

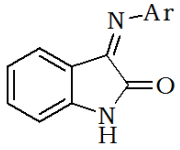
A novel series of isatin (**1**) Schiff's bases (**13a-s**) were synthesized. The cytotoxic activity of some of the synthesized compounds were investigated against HeLa, Raji and LS-180 human cancer cell lines, using Cisplatin as a reference compound. Half of the synthesized compounds exhibited superior cytotoxic activity against HeLa cell. Compound **13b** 3-(2-(4-nitrophenyl) hydrazono) indolin-2-one was found to be most potent with IC_{15} values 3.0±0.5 µM and IC_{30} value of 12.2±3.1 against HeLa cells [65].



12a-g

Comp.	R
12a	$-CH_3$
12b	$-CH_2-CH_3$
12c	$-CH_2-CH=CH_2$
12d	$n-C_4H_9$
12e	$-CH_2-C_6H_5$
12f	$4-F-C_6H_4$
12g	$4-NO_2-C_6H_4$

Fig. 10. Structure of 5-Chloro-1*H*-indole-2,3-dione 3-thiosemicarbazones derivatives (12a-g)



13a-s

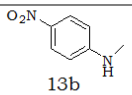
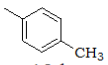
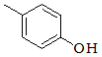
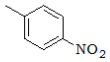
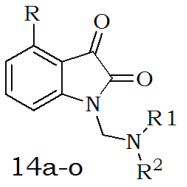
Ar				
 13a	 13b	 13c	 13d	 13e
 13f	 13g	 13h	 13i	 13j
 13k	 13l	 13m	 13n	 13o
 13p	 13q	 13r	 13s	

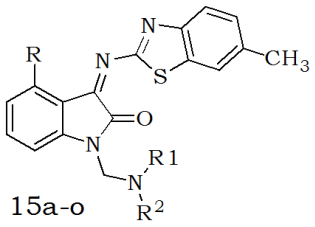
Fig. 11. Structure hydrazono indolin-2-one derivatives (13a-s)

A series of isatin-linked benzothiazole Mannich bases (**14a-o**) and Schiff's bases (**15a-o**) were synthesized. The synthesized compounds were evaluated against three human breast cancer cell lines MCF-7, MDA-MB231, MDA-MB468 and two non-cancer breast epithelial cell lines, 184B5 and MCF10A. Cisplatin and Chloroquine were used as reference drugs. Fourteen out of the synthesized compounds (**14a-o**) and (**15a-o**) exhibited GI_{50} values in the range between 11.68 µM - 28.32 µM. In the Mannich bases series compound **14l** was found to be most active, showing GI_{50} values 20.22 µM, 11.68 µM, and 20.20 µM against MDA-MB231, MDA-MB468 and MCF-7 respectively. Thus, compound **14l** exhibited in vitro cytotoxicity similar to that of Cisplatin. Furthermore, compound **15e** (Schiff's bases series) emerged the most active, exhibiting GI_{50} values 19.76 µM, 17.61 µM, and 14.56 µM against MDA-MB468, MDA-MB231, and MCF-7 respectively. Moreover, the cytotoxic effects of the Schiff's bases series (**15a-o**) were more active compare to those of the Mannich bases series (**14a-o**) [73].

A series of β-isatin aldehyde-*N,N'*-thiocarbohydrazone (**16a-g**), bis-β-isatinthiocarbohydrazones, bis-β-isatin carbohydrazones (**17a-e**), *N*,2-bis(thiophen-2-ylmethylidene) thiocarbohydrazone (**18a**), *N*,2-bis(thiophen-2-ylmethylidene) carbohydrazone (**18b**) derivatives were synthesized. The cytotoxic activity of the synthesized compounds were evaluated against murine leukemia cells (L1210), human T-lymphocyte cells (CEM) and human cervix carcinoma cells (HeLa) by MTT assay. Compound **18b** and **16f** were found to be more potent with IC_{50} values 10 µM and 13 µM respectively against murine leukemia cells (L1210) cell lines. Also, it was revealed that compound **16g** (IC_{50} value 11 µM), **16f** (IC_{50} value 17 µM) and **18b** (IC_{50} value 17 µM) exhibited more cytotoxic activity against human T-lymphocyte cells (CEM). Compound **16b** and **16g** with IC_{50} values 12 µM and 13 µM respectively were found to be active against human cervix carcinoma cells (HeLa). Finally, compound **17d** (IC_{50} value > 250 µM) was found to be less potent against all the three cell lines [74].



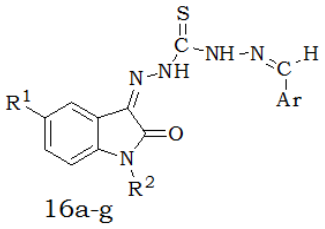
14a-o



15a-o

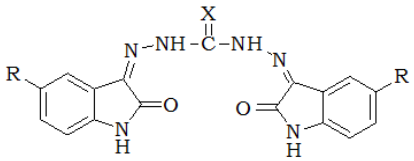
Comp.	R	R^1 R^2	Comp.	R	R^1 R^2
14a	H	$(CH_3)_2$	15a	H	$(CH_3)_2$
14b	H	$(CH_2CH_3)_2$	15b	H	$(CH_2CH_3)_2$
14c	H	$(C_6H_5)_2$	15c	H	$(C_6H_5)_2$
14d	H	Piperidinyl	15d	H	Piperidinyl
14e	H	Morpholinyl	15e	H	Morpholinyl
14f	Cl	$(CH_3)_2$	15f	Cl	$(CH_3)_2$
14g	Cl	$(CH_2CH_3)_2$	15g	Cl	$(CH_2CH_3)_2$
14h	Cl	$(C_6H_5)_2$	15h	Cl	$(C_6H_5)_2$
14i	Cl	Piperidinyl	15i	Cl	Piperidinyl
14j	Cl	Morpholinyl	15j	Cl	Morpholinyl
14k	Br	$(CH_3)_2$	15k	Br	$(CH_3)_2$
14l	Br	$(CH_2CH_3)_2$	15l	Br	$(CH_2CH_3)_2$
14m	Br	$(C_6H_5)_2$	15m	Br	$(C_6H_5)_2$
14n	Br	Piperidinyl	15n	Br	Piperidinyl
14o	Br	Morpholinyl	15o	Br	Morpholinyl

Fig. 12. Structure of isatin-linked benzothiazole Mannich bases (14a-o) and Schiff's bases (15a-o)



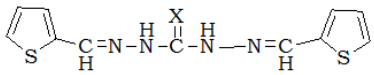
16a-g

Comp.	R^1	R^2	Ar
16a	H	H	16a
16b	H	H	16b
16c	H	H	16c
16d	H	H	16d
16e	H	H	16e
16f	H	H	16f
16g	H	C_6H_5-CH_2-	16g



17a-e

Comp.	X	R
17a	O	H
17b	O	Cl
17c	O	$-CH_3$
17d	O	NO_2
17e	S	H



18a-b

X=O,S

Fig. 13. Structures of β-isatin aldehyde-*N,N'*-thiocarbohydrazone (16a-g), bis-β-isatinthiocarbohydrazones, bis-β-isatin carbohydrazones (17a-e), *N*,2-bis(thiophen-2-ylmethylidene) thiocarbohydrazone (18a), *N*,2-bis(thiophen-2-ylmethylidene) carbohydrazone (18b) derivatives.

Another series of dimethyl-substituted isatin derivatives (**19, 20, 21, 22, 23, 24, 25a-b,** and **26a-b**) were synthesized. The cytotoxic activities of the titled compounds were evaluated against brine shrimp by lethality assay. The study reveals that compound **22, 23, 24** and **26b** were highly active against the brine shrine with the LD_{50} values of 24ppm, 24 ppm, 22 ppm, and 24ppm respectively. Compound **25a**, **25b** and **26a** were moderately active against the brine shrimp depicting LD_{50} values 36 ppm, 31 ppm, and 29 ppm respectively [75].

2.3 Spiro-Oxindole Derivatives

A novel spiro-oxindole (**27a-v**) derivatives were synthesized and tested against A549 lung adenocarcinoma cancer cell line. Compound **27a-v** is a conjugates of isatin (**1**), sarcosine (**28**) and 3-(1*H*-indol-3-yl)-3-oxo-2-(2-oxoindolin-3-ylidene) propanenitrile (**29**). The *N*-alkylated isatin exhibited greater anticancer activity. Compound (**27i**) which is a *N*-propargyl substituted isatin depicted the highest anticancer activity at the dose of 200 µg/mL with IC_{50} value of 50 µg/mL [76].

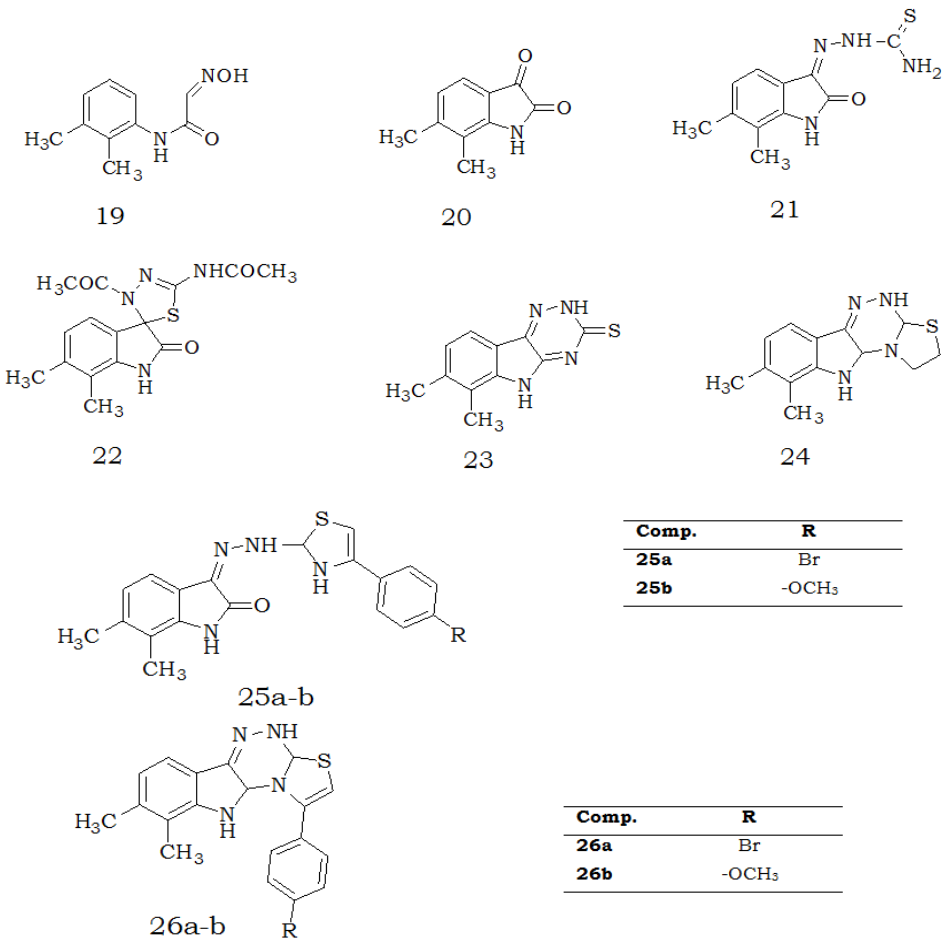
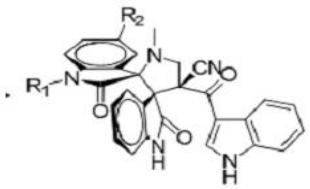


Fig. 14. Structure of dimethyl-substituted isatin derivatives (19, 20, 21, 22, 23, 24, 25a-b, and 26a-b)

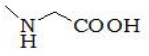
Another series of fluorinated pyranopyrazole substituted spiro-oxindole derivatives (**30a-i**), were synthesized and evaluated for their anticancer activity against **U937** (human histiocytic lymphoma) and **B16F10** (mouse mealanocarcinoma) cancer cell lines. The anticancer activity of the synthesized compounds was found to be significant on **B16F10** cancer cell lines than **U937** cancer cell lines. At 10µg to 200 µg/ml concentration, compound **30g** was found to be most potent. Thus, it possess nitro group in the spiro-oxindole moiety and a chlorine atom in the pyrazole fragment. Compound **30e**, **30f**, and **30i** were less active [2].

2.4 Isatin-Based Conjugates at Position 3

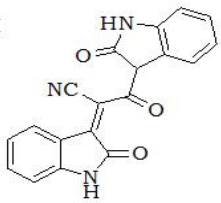
A series of isatin (**1**) based compounds conjugated with 4-thiazolidinone (**31**), and pyrazoline (**32**) fragments were synthesized and tested for their anticancer activities (in vitro and in vivo) against 60 human tumor cell line of 9 different types including: leukemia, melanoma, prostate, ovarian, CNS, renal, breast, and lung cancers(Havrylyuk et al., 2012). The first series of the synthesized compounds 3-[2-(3,5-diaryl-4,5-dihydropyrazol-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-ylidene]-2,3-dihydro-1*H*-indol-2-ones (**33a-w**) are conjugates of isatin(**1**), 4-thiazolidinone (**31**), and pyrazoline (**32**) moieties. The in vitro primary level screening on tested cell lines in **10 µM** concentration revealed that compound (**33a-d**, **33g-l**, **33n**, **33o**, and **33q-t**) showed significant anticancer activity, compound (**33f**) showed moderate activity and compound (**33e, 33m,** and **33p**) were found to be inactive [7].



27a-v



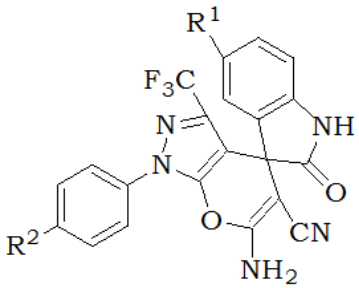
28



29

Comp	R^1	R^2	Comp	R^1	R^2	Comp	R^1	R^2
27a	H	H	27i	propargyl	H	27q	H	I
27b	H	methyl	27j	Ph	H	27r	methyl	NO_2
27c	methyl	H	27k	benzyl	H	27s	methyl	F
27d	methyl	methyl	27l	$-CH_2-COOEt$	H	27t	methyl	Cl
27e	ethyl	H	27m	H	NO_2	27u	methyl	Br
27f	butyl	H	27n	H	F	27v	methyl	I
27g	hexyl	H	27o	H	Cl			
27h	Allyl	H	27p	H	Br			

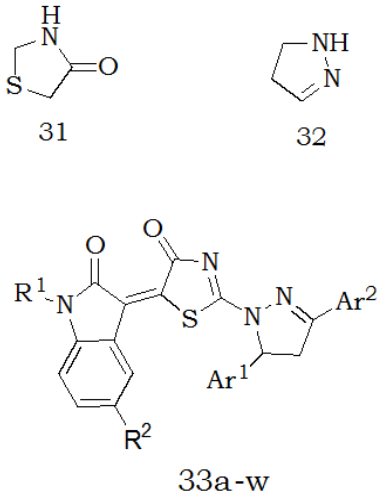
Fig. 15. Structure of spiro-oxindole (27a-v) derivatives



30a-l

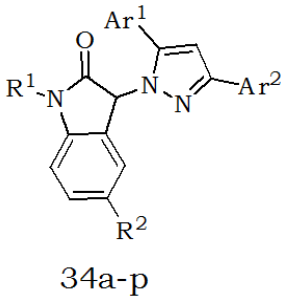
Comp.	R^1	R^2
30a	$-NO_2$	F
30b	Br	F
30c	H	H
30d	Br	H
30e	H	Cl
30f	F	Cl
30g	NO_2	Cl
30h	NO_2	H
30i	Br	Cl
30j	H	F
30k	F	F
30l	F	H

Fig. 16. Structure of fluorinated pyranopyrazole substituted spiro-oxindole derivatives (30a-i)



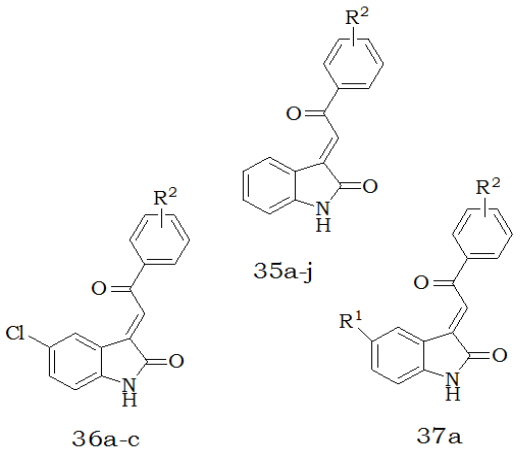
Comp.	Ar^1	Ar^2	R^1	R^2
33a	2-OH-C_6H_4	Ph	H	H
33b	2-OH-C_6H_4	Ph	H	Br
33c	4-OMe-C_6H_4	Ph	H	H
33d	4-OMe-C_6H_4	Ph	H	Br
33e	4-OMe-C_6H_4	Ph	CH_2COOH	H
33f	4-OMe-C_6H_4	4-OMe-C_6H_4	H	H
33g	4-OMe-C_6H_4	4-OMe-C_6H_4	H	Br
33h	4-OMe-C_6H_4	4-OMe-C_6H_4	H	Cl
33i	4-OMe-C_6H_4	naphthalene-2-yl	H	H
33j	4-OMe-C_6H_4	naphthalene-2-yl	H	Br
33k	4-Cl-C_6H_4	Ph	H	H
33l	4-Cl-C_6H_4	Ph	H	Me
33m	4-Cl-C_6H_4	4-OMe-C_6H_4	H	H
33n	4-Cl-C_6H_4	4-OMe-C_6H_4	H	Br
33o	4-Cl-C_6H_4	4-OMe-C_6H_4	H	Cl
33p	4-Cl-C_6H_4	4-OMe-C_6H_4	Me	H
33q	4-Cl-C_6H_4	naphthalene-2-yl	H	H
33r	4-NMe_2-C_6H_4	Ph	H	H
33s	4-NMe_2-C_6H_4	Ph	H	Br
33t	4-NMe_2-C_6H_4	Ph	H	Cl
33u	thiophen-2-yl	Ph	H	H
33v	thiophen-2-yl	Ph	H	Br
33w	thiophen-2-yl	Ph	Me	H

Fig. 17. Structure of 3-[2-(3,5-diaryl-4,5-dihydropyrazol-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-ylidene]-2,3-dihydro-1*H*-indol-2-ones (33a-w)



Comp.	Ar^1	Ar^2	R^1	R^2
34a	2-OH-C_6H_4	Ph	CH_2COOH	H
34b	4-OMe-C_6H_4	4-OMe-C_6H_4	H	H
34c	4-OMe-C_6H_4	4-OMe-C_6H_4	H	Br
34d	4-OMe-C_6H_4	4-OMe-C_6H_4	H	Cl
34e	4-Cl-C_6H_4	Ph	H	H
34f	4-Cl-C_6H_4	Ph	H	Br
34g	4-Cl-C_6H_4	Ph	CH_2COOH	H
34h	4-Cl-C_6H_4	4-OMe-C_6H_4	H	H
34i	4-Cl-C_6H_4	4-OMe-C_6H_4	H	Br
34j	4-Cl-C_6H_4	4-OMe-C_6H_4	H	Cl
34k	4-NMe_2-C_6H_4	Ph	H	H
34l	4-OMe-C_6H_4	naphthalen-2-yl	H	H
34m	4-OMe-C_6H_4	naphthalen-2-yl	H	Cl
34n	4-Cl-C_6H_4	naphthalen-2-yl	H	H
34o	4-Cl-C_6H_4	naphthalen-2-yl	H	Br
34p	4-Cl-C_6H_4	naphthalen-2-yl	CH_2COOH	H

Fig. 18. Structure of 3-(3,5-diarylpyrazol-1-yl)-2,3-dihydro-1*H*-indol-2-one (34a-p)



Comp.	R²
35a	H
35b	4-F
35c	4-Cl
35d	4-Br
35e	4-NO_2
35f	3-NO_2
35g	4-OCH_3
35h	2- OCH_3
35i	3,4-OCH_3
35j	4-CH_3
36a	H
36b	4-F
36c	3,4-OCH_3
37a	H

Fig. 19. Structure of isatin-linked chalcones compounds, 3-(2-oxo-2-phenylethylidene) indolin-2-one (35a-j), (36a-c) and (37a)

The second series of the synthesized compounds 3-(3,5-diarylpyrazol-1-yl)-2,3-dihydro-1H-indol-2-one (**34a-p**) are conjugates of isatin (**1**) and pyrazole (**32**) fragments. The in vitro screening showed that only (**34i-k** and **34o**) exhibited moderate activity in 10 **µM** concentration. However, compounds (**33a-w**) were found to be more active than (**34a-p**). Compound **33a-d, 33f-p, 33q-t, 34i-k** and **34o** were subjected to further screening. At the secondary level assay, compound **33j** was found to be most active, hence it shows a mean GI_{50} value of 0.071 µM and a mean TGI value of 0.76 µM in 60-cell-line screen with a low toxicity and moderate activity level in the in vivo hollow fiber assay [7].

A novel isatin-linked chalcones compounds, 3-(2-oxo-2-phenylethylidene)indolin-2-one (**35a-j**), (**36a-c**) and (**37a**) were synthesized and investigated for growth inhibitory against three breast cancer cell lines (MDA-MB468, MDA-MB231 and MCF-7). At (**< 20 µM**) most of the compounds were found to exhibit grater anticancer activity against all the studied cancer cell lines. Thus, compound **36c** was found to be most potent with GI_{50} values of 8.54, 4.76 and 3.59 **µM** against MDA-MB231, MDA-MB468 and MCF7 cells, respectively [10].

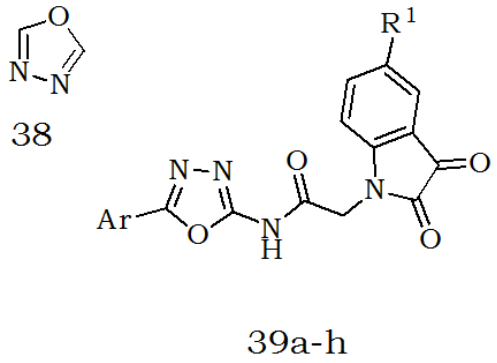
2.5 Miscellaneous

The novel series (**39a-h**) (conjugates of isatin (**1**) and oxadiazole (**38**) fragments), were synthesized and evaluated for their antitumor activities against 60 human cancer cell lines which were derived from nine different cancer types: leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers. Compounds **39a, 39c, 39e, 39g, 39h** were selected and tested against the 60 cancer cell lines. At the single concentration of 10^{-5} M, the tested compounds depicted low antitumor activity in the in vitro screening on the tested cell lines with average values of GP = 89.90–104.31%. Compound **39a** (GP = 70.33 %), **39c** (GP = 70.06 %), **39g** (GP = 61.78 %), and **39h** (GP = 70.09 %) were moderately active against a renal cancer UO-31 cell line. In addition, compound **39g** was active on a prostate cancer PC-3 cell line (GP =55.54 %) [3].

A new series of uracil-isatin scaffold hybrids (**40a-l**) were synthesized. The cytotoxic activities of the titled compounds were evaluated against DU145 (prostate), HeLa (cervix), and MCF-7 (breast) cancer cell lines using MTT assay. Compound **40g** and **40k** were found to be most active against DU145 at a lower conc. (between 13 and 19 µM) hence, shown IC_{50} values 18.21 µM and 13.90 µM respectively. Compound **40h** was found to be most active on MCF-7 cell lines with the IC_{50} value of 38.16 µM. most compounds were inactive against HeLa cell lines [57].

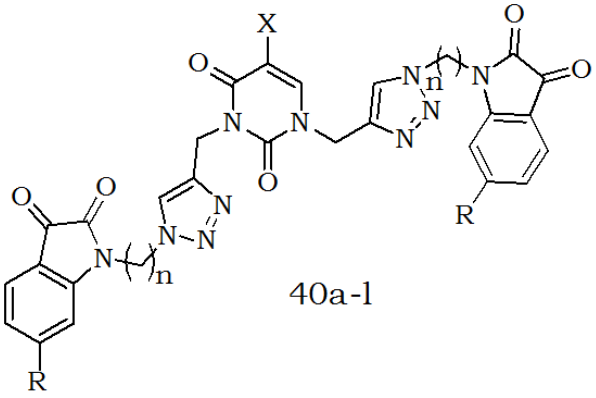
A novel 2-(2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)-*N*-phenylacetamide derivatives (**41a-j**) were synthesized and evaluated against breast cancer cell lines (MCF-7) and non-cancer African green monkey cell line VERO (using Vinblastine as standard drug). The tested compounds exhibited IC_{50} ranging from 1.96-3.91 µM against MCF-7 cancer cell line, compound (**41f- 41j**) were

inactive against both MCF-7 and VERO. Interestingly, compound **41b** emerged to be most active in the series showing IC_{50} value 1.96 μM against MCF-7 cancer cell lines, although Vinblastine (reference drug) exhibited IC_{50} value 1.90 μM against MCF-7 [21].



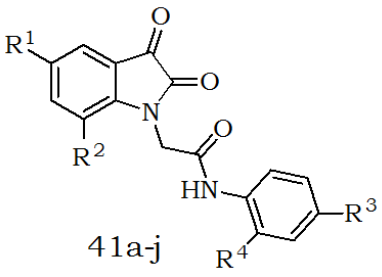
Comp.	Ar	R^1
39a	4-MeO-C_6H_4	H
39b	4-MeO-C_6H_4	Cl
39c	3,4-MeO-C_6H_3	H
39d	3,4-MeO-C_6H_3	Cl
39e	3,4-MeO-C_6H_3	Br
39f	4-Cl-C_6H_4	H
39g	4-Cl-C_6H_4	Cl
39h	4-Cl-C_6H_4	Br

Fig. 20. Structures of conjugates of isatin (1) and oxadiazole (38) fragments (39a-h)



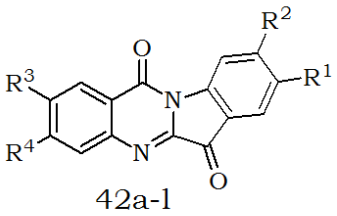
Comp.	R	X	n
40a	H	H	2
40b	F	H	2
40c	Cl	H	2
40d	CH_3	H	2
40e	H	F	2
40f	Cl	F	2
40g	H	Cl	2
40h	Cl	Cl	2
40i	H	H	3
40j	F	H	3
40k	Cl	H	3
40l	CH_3	H	3

Fig. 21. Structure of uracil-isatin scaffold hybrids (40a-l)



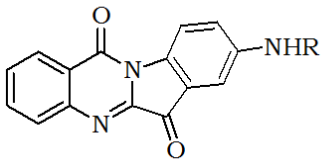
Comp.	R^1	R^2	R^3	R^4
41a	Br	Br	H	H
41b	Br	Br	NO_2	H
41c	Br	Br	CH_3	H
41d	Br	Br	H	NO_2
41e	Br	Br	H	CH_3
41f	H	H	H	H
41g	H	H	NO_2	H
41h	H	H	CH_3	H
41i	H	H	H	NO_2
41j	H	H	H	CH_3

Fig. 22. Structure of 2-(2,3-dioxo-2,3-dihydro-1H-indol-1-yl)-N-phenylacetamide derivatives (41a-j)

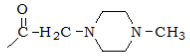


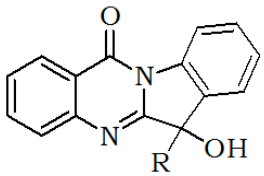
42a-l

Comp.	R^1	R^2	R^3	R^4
42a	H	H	H	H
42b	H	H	Br	H
42c	H	H	NO_2	H
42d	H	H	OMe	OMe
42e	H	H	NH_2	H
42f	Br	H	H	H
42g	$-OCH_2O-$	$-OCH_2O-$	H	H
42h	OMe	H	H	H
342i	Me	H	H	H
42j	Cl	H	H	H



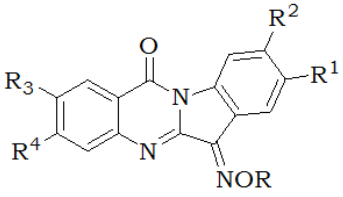
43a-f

Comp.	R
43a	$-C(O)-CH_3$
43b	$-C(O)-CH_2-CH_2-CH3$
43c	$-C(O)-CH_2-CH_3$
43d	$-C(O)-CH_2-CH_3$
43e	
43f	SO_2-CH_3



44a-d

Comp.	R
44a	-CH3
44b	-CH=CH2
44c	$-CH_2-CH_2-CH_2-CH3$
44d	$-OCH_2-CH_2-O-Ph$



45a-n

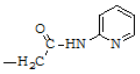
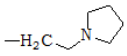
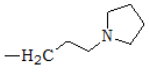
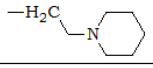
Comp.	R^1	R^2	R^3	R^4	R
45a	H	H	H	H	-
45b	H	H	H	H	$-CH_2-CH_2-OH$
45c	H	H	H	H	$-CH_2-COO-CH_3$
45d	H	H	H	H	
45e	H	H	H	H	$-C(O)-CH=CH-CH-Ph$
45f	H	H	H	H	$-CH_2-CH_2-CH_2-NMe_2$
45g	H	H	H	H	$-CH_2-CH_2-NMe_2$
45h	H	H	H	H	
45i	H	H	H	H	
45j	NO_2	H	H	H	$-CH_2-CH_2-NMe_2$
45k	NO_2	H	H	H	$-CH_2-CH_2-CH_2-NMe_2$
45l	NO_2	H	H	H	$-CH_2-CH_2-OH$
45m	Br	H	H	H	$-CH_2-CH_2-NMe_2$
45n	Br	H	H	H	

Fig. 23. Structure of indolo[2,1-b]quinazoline derivatives (42a-l), (43a-f), (44a-d) and (45a-n)

A novel series of indolo[2,1-b]quinazoline derivatives (**42a-l**), (**43a-f**), (**44a-d**) and (**45a-n**) were synthesized and evaluated for anticancer activity in vitro against eight cancer cell lines colon (SW620), Lung (H522), Ovarian (SKOV3), Prostate (DU145), Renal (A498), CNS (U251) and Breast (MCF7/ADR). Compound **42b**, **42c** showed no significant activities in all human cancer cell lines. Whereas, compound **42f** and **42h** exhibited better activity, with **42f** showing cytotoxic activity at a concentration less than 1 μM in four out of the eight cancer cell lines. Compound **43d** was found to be more potent in the **43a-f** series (Amide derivatives) showing average GI_{50} value of 1 μM. However, none of the **44a-d** series (12-hydroxy-12alkyl/aryl derivatives) were found to be active. The study reveals that 12-ketoxime ethers derivatives (**45b-45d, 45f-45n**) are more active than 12-ketoxime esters (**45e**) with the exception of compound **45c** and **45d** [77].

3. CONCLUSION

This present review collects some of the reports that revealed the anticancer activity and cytotoxic activity of isatin and its derivatives between 2002 and 2015. The isatin scaffold is synthetically important as well possess wide range of promising cytotoxic activity. It has been observed so far that some of the isatin derivatives show better cytotoxic activity than the standard drugs. The quest to explore more active isatin derivatives against different cancer cell lines is of paramount. Thus, modification of the isatin scaffold can be utilized to develop potentially active cytotoxic agents in future studies.

ETHICAL APPROVAL AND CONSENT

These are not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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