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Synthesis, Anticancer Activity, and Molecular Modeling of New Halogenated Spiro[pyrrolidine-thiazolo-oxindoles] Derivatives

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Abstract: A one-pot, single-step, and an atom-economical process towards the synthesis of highly functionalized spirooxindoles analogues was efficiently conducted to produce a satisfactory chemical yields (70–93%) with excellent relative diastereo-, and regio-selectivity. An in vitro antiproliferative assay was carried out on different cancer cell lines to evaluate the biological activity of the synthesized tetrahydro-1′*H*-spiro[indoline-3,5′-pyrrolo[1,2-*c*]thiazol]-2-one **5a–n.** The prepared hybrids were then tested *in vitro* for their antiproliferative effects against three cancer cell lines, namely, HepG2 (liver cancer), MCF-7 (breast cancer), and HCT-116 (colon cancer). The spirooxindole analogue **5g** exhibited a broad activity against HepG2, MCF-7, and HCT-116 cell lines of liver, breast, and colorectal cancers when compared to *cis*platin. Modeling studies including shape similarity, lipophilicity scores, and physicochemical parameters were calculated. The results of this study indicated that spirooxindole analogue **5g** retained a good physiochemical parameters with acceptable lipophilicity scores.

Keywords: spirooxindole; 1,3-dipolar cycloaddition; eco-friendly chemistry; ROCS; shape alignment; lipophilicity; anticancer activity

1. Introduction

The design of highly complex spiro-heterocycles with multifunctional and potential pharmaceutical efficacy has attracted considerable attention from synthetic and medicinal chemists [1]. One of the most privileged *aza*-heterocyclic scaffolds is spiro[pyrrolidine-oxindole] [2], which is present in natural products and useful as a building block for the synthesis of significant biologically active compounds. This class of *aza*-heterocyclic compounds has gained great interest, owing to several reports of its pharmaceutical potency, including anticancer [3], antitumor [4], 5-HT3 receptor antagonist [5],

acetylcholinesterase-inhibitory [6], antibacterial [7], antibiotic [8], and MDM2–p53 inhibitor [9] effects; selective cyclooxygenase COX-1 with TNF-α and IL-6 inhibitors [10]; and potential hypoglycemic dual inhibitory activity against α-amylase and α-glucosidase [11] (Figure 1). To date, prolonged efforts have been exerted to expand divergent complexity and to develop efficient synthetic routes for these valuable privileged *aza*-heterocyclic scaffolds, which would remarkably enhance their bioactivity [1,12]. In particular, [3+2] cycloaddition is one of the most efficient synthetic approaches to produce these valuable scaffolds with stereoselective method and high yield [13]. To extend our previous research, we explored the effect of halogen substitution on the isatin ring.

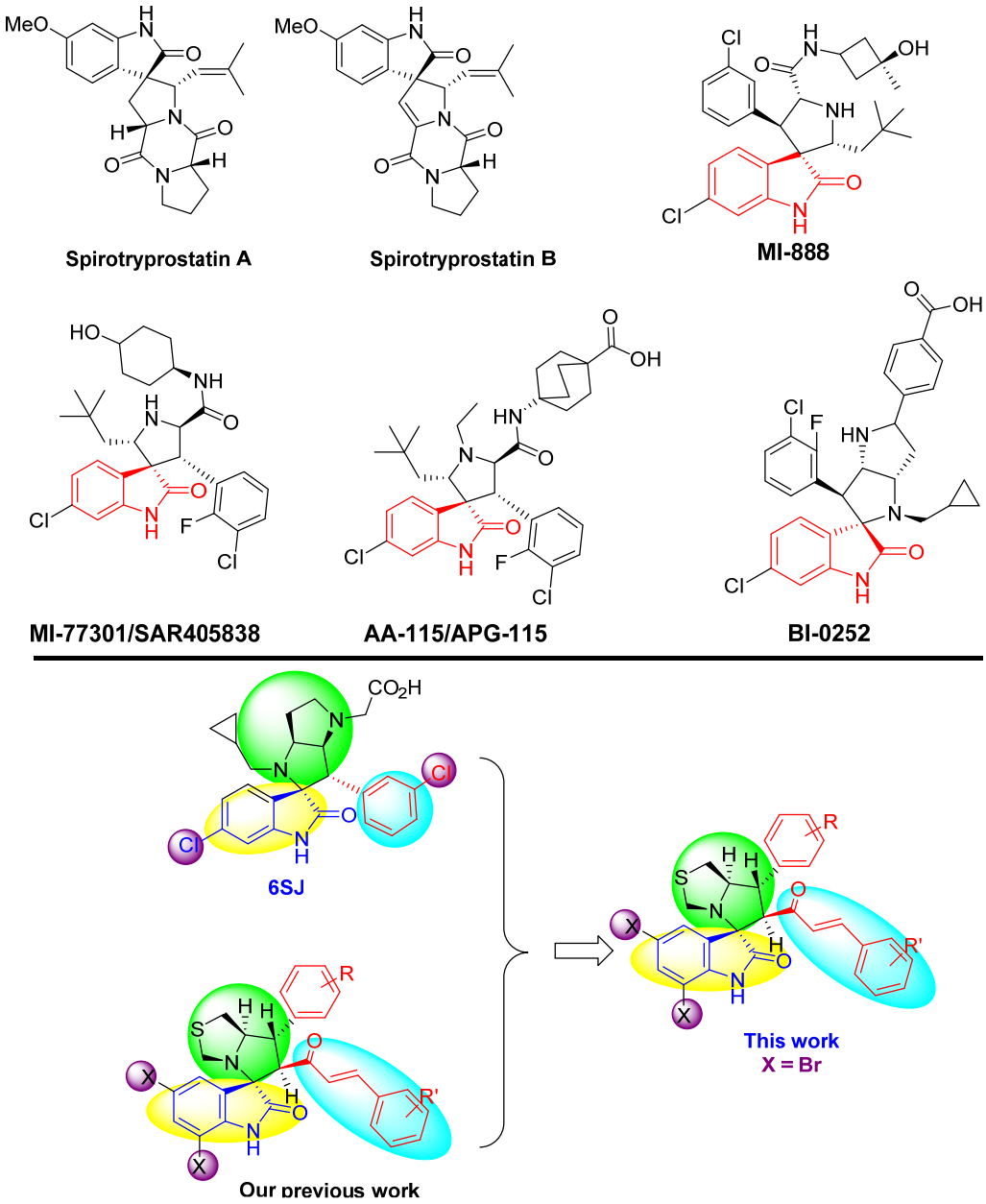


Figure 1. Natural (Spirotryprostatin A and B) and other synthetic spirooxindole scaffolds with high biological importance and structure-activity relationship.

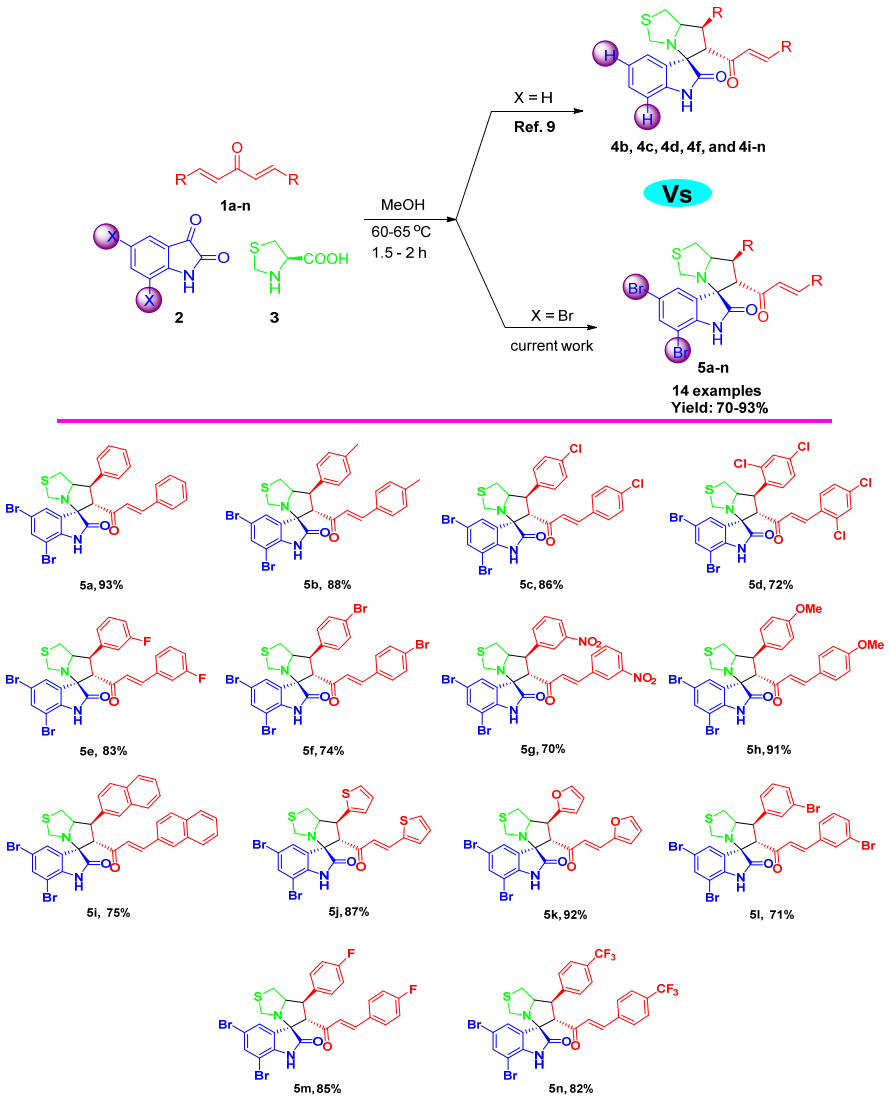
Our previous studies [9] revealed that the presence of dihalide substitution on acyl moiety substantially increased the anticancer activity of the resulting product(s). Moreover, it was reported [9] that chlorinated indole moiety retained better activity, as illustrated in Figure 1a.

Subsequently, this study was designed to introduce two bromo atoms on the indole ring, presumably to enhance the activity of the examined spirooxindole compounds shown in Figure 1. The *aza*-heterocyclic compounds were prepared via a multicomponent eco-friendly strategy using oxindole as a core structure. The resulting hybrids were biologically evaluated using an *in vitro* antiproliferative assay against three different cell lines for liver, breast, and colorectal cancer. In addition, molecular properties and lipophilicity studies were conducted to get insight about "drug properties consideration" and to discover the compounds' structure-property relationship (SPR).

2. Results and Discussion

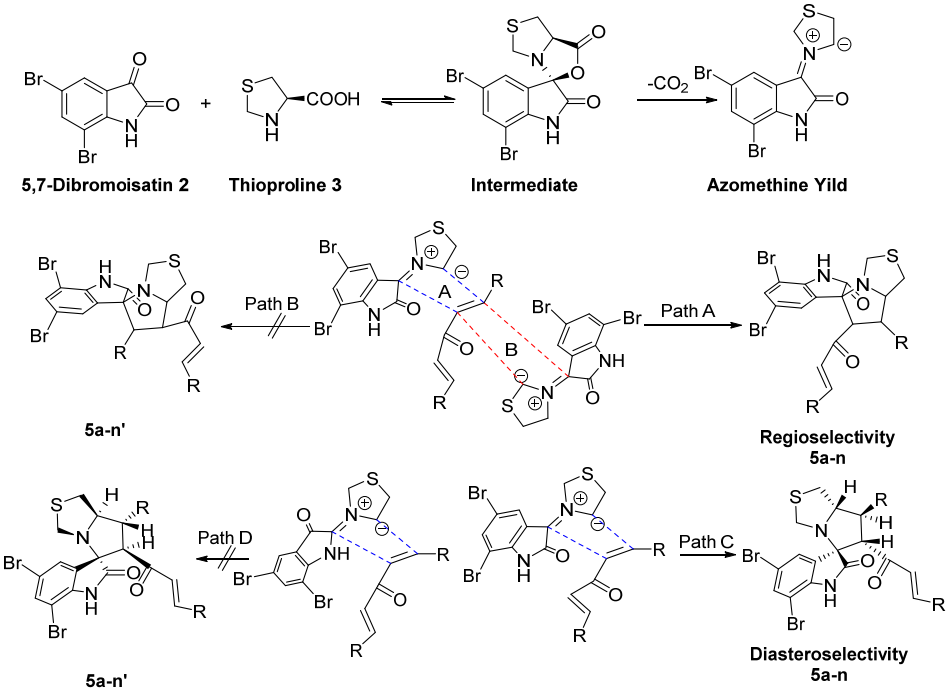
2.1. Synthesis of *5a–n*

The requisite spirooxindoles analogous were prepared by a multicomponent reaction (Scheme 1). The advantages of this efficient method were low-cost and readily available synthons for the synthesis of highly divergent compounds with high-importance applications. Fourteen analogues were prepared through the reactions of *bis*-benzylidine **1a–n,** which had been prepared according to our previous publication [9] with thioproline and 5,7-dibromoisatin, to afford the requisite target compounds. The chemical features of the requisite compounds were assigned based on HNMR, CNMR, IR, and CHN analysis.



Scheme 1. Synthesis of tetrahydro-1′*H*-spiro[indoline-3,5′-pyrrolo [1,2-*c*]thiazol]-2-one **5a–n**.

According to Scheme 2 and based on our previous study [9], the reaction proceeds *via* one pot reaction, in which initially 5,7-dibromoisatin **2** reacted with thioproline **3** affording the azomethine ylide after the removal of carbon dioxide from the intermediate. Subsequently, the azomethine ylide reacted with the *bis*-benzylidine **1a–n** to provide the target compounds in a regioselective and diastereoselective manner. The reaction proceeded *via* path A regio-selectively to afford the regioisomer products **5a–n**, while the second regio-isomers **5a–n'** did not occur (path B). There are possible diastereoselective products that could be formed, but in this case only diastereoselective compounds **5a–n** occurred *via* the path C not D.



Scheme 2. Plausible reaction mechanism of the synthesized compounds.

2.2. Biological Activity

The compounds were subjected to an initial evaluation for potential cytotoxic activity against different cancer cell lines, namely, HepG2, MCF-7, and HCT-116 cells, at 50 μM. Cell viability was measured using MTT assay. Among the screened 14 compounds, 3 (**5h**, **5i**, and **5j**) did not show any cytotoxic activity against HepG2 cells. The concentration of the active compounds that killed 50% of the cells (IC_{50}) was evaluated against HepG2 cells. Compound **5g** (IC_{50} = 5.00 ± 0.66 μM) was the most potent active compound, showing more potent activity than that of the standard chemotherapeutic drug *cis*platin (IC_{50} = 9.00 ± 0.76 μM) (Table 1). Moderate anticancer activity against HepG2 cells was observed for compounds **5a** and **5m** (IC_{50} = 10.00 ± 0.47 and 17.00 ± 0.68 μM, respectively).

The same three inactive compounds (**5h**, **5i**, and **5j**) did not show activity against MCF-7 or HCT-116 cells (Table 1). The other 11 tested compounds ($IC_{50} \leq 9.00$ μM) showed superior activity to that of cisplatin (IC_{50} = 9.00 ± 0.29 μM) against MCF-7 cells (Table 1); only compounds (**5c**, **5f**, **5g**, and **5l**) ($IC_{50} < 3.00$ μM) were more potent than cisplatin (IC_{50} = 3.00 ± 0.24 μM) against colon cancer cells (Table 1). The present study showed that compound **5g** retained broad anticancer activity against the three tested cell lines of liver, breast, and colorectal cancers; HepG2, MCF-7, and HCT-116 cells, respectively.

Table 1. Results of anticancer activity against HepG2, MCF-7, and HCT-116 cells.

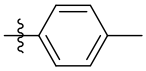
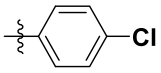
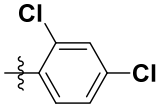
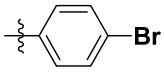
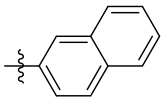
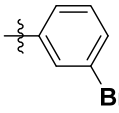
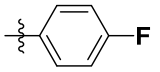
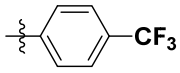
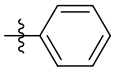
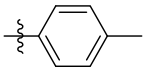
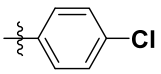
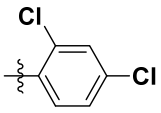
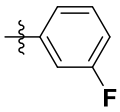
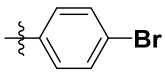
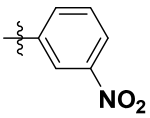
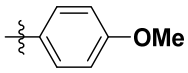
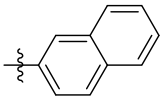
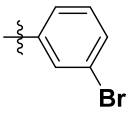
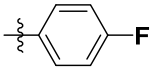
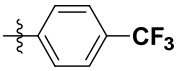
Compound	R	Cancer Type/Cell Line		
		Liver HepG2 (IC_{50} [a], μM)	Breast MCF-7 (IC_{50}, μM)	Colon HCT-116 (IC_{50}, μM)
4b		3.57 ± 0.50	NT [c]	8.00 ± 1.20
4c		2.00 ± 0.50	NT	3.00 ± 0.50
4d		0.85 ± 0.20	NT	2.00 ± 0.60
4f		0.80 ± 0.10	NT	3.00 ± 0.50
4i		2.40 ± 1.00	NT	8.00 ± 0.30
4j		>50.00	NT	14.50 ± 1.50
4k		>50.00	NT	19.00 ± 2.00
4l		0.90 ± 0.10	NT	1.57 ± 0.30
4m		2.40 ± 0.40	NT	5.00 ± 0.30
4n		0.90 ± 0.20	NT	2.90 ± 0.40
5a		10.00 ± 0.47	6.00 ± 0.13	4.50 ± 0.05
5b		30.00 ± 0.38	5.50 ± 0.47	5.00 ± 0.30
5c		25.00 ± 0.09	3.00 ±1.26	2.90 ± 0.25
5d		>50.00 ± 0.28	9.00 ± 0.05	8.50 ± 0.10
5e		22.00 ± 1.02	3.00 ± 0.32	5.00 ± 0.12
5f		50.00 ± 0.38	2.50 ± 1.66	2.20 ± 0.15
5g		5.00 ± 0.66	4.00 ± 0.29	2.80 ± 0.20
5h		NA [b]	NA	NA

Table 1. *Cont.*

Compound	R	Cancer Type/Cell Line		
		Liver HepG2 (IC_{50} [a], μM)	Breast MCF-7 (IC_{50}, μM)	Colon HCT-116 (IC_{50}, μM)
5i		NA	NA	NA
5j		NA	NA	NA
5k		40.00 ± 0.57	8.00 ± 0.20	13.00 ± 0.72
5l		35.00 ± 0.45	3.00 ± 0.04	2.80 ± 0.19
5m		17.00 ± 0.678	4.50 ± 0.08	4.00 ± 0.52
5n		30.00 ± 0.79	5.00 ± 0.16	3.70 ± 1.04
	*cis*platin	9.00 ± 0.76	9.00 ± 0.29	3.00 ± 0.24

[a] IC_{50} (μM) was evaluated using MTT assay and ± is the standard deviation from three independent experiments. [b] NA: means that the tested compound did not show anticancer activity at 50 μM. [c] NT: did not tested against the MCF-7 cells.

2.3. Effect of the Dibromo on the Anticancer Activity

The structure-activity relationship between the previously reported spirooxindole analogues **4b**, **4c**, **4d**, **4f**, and **4i-n** [9] and the diboromo-substituted spiroxindoles **5b**, **5c**, **5d**, **5f**, and **5i-n** is described. In fact, the IC_{50} values of Table 1 clearly show that the replacement of the H atoms of the previously reported compounds **4b**, **4c**, **4d**, **4f**, and **4i-n** with that of its analogues with the Br produced a significant decrease in the inhibitory growth effect on the HEPG2 cell line. On the other hand, compounds **5b**, **5c**, **5f**, **5k,** and **5m** (dibromo-substituted) showed better activity against HCT-116 cells than their dibromo-unsubstituted indole counterparts. Compounds **5d**, **5l**, and **5n** showed less activity than the compounds **4d**, **4l**, and **4n,** respectively. Compounds **5i** and **5j** were not active and compounds **4i** and **4j** presented some activity (Table 1).

2.4. Shape Alignment by Rapid Overlay Chemical Structure (ROCS) Analysis

Shape and electrostatic potential are two fundamental molecular descriptors for computational drug discovery, because in protein ligand binding, the shape of a ligand has to conform in large degree to the shape of a protein binding site. The electrostatic potentials presented in the binding site have to complement the electrostatic potential of the protein. Accordingly, it is very important to model and understand protein ligand bindings correctly. The 3D shape structure exhibits good neighborhood behavior, in which high similarity in shape reflects high similarity in biology. Shape similarity can have different applications, such as virtual screening, lead-hopping, molecular alignment, pose generation, and predictions.

ROCS is a tool used in shape similarity studies. ROCS requires a query, which is an active molecule with some biological activities in at least one 3D conformation. It also requires a database of the molecules of the compounds of interest. Consistent with these standards, our compounds (database set) showed similarity to standard compound **BI-0225** (Figure 2). Compound **5g** showed high similarity to **BI-0225** in terms of its oxindole moiety and oxoindole ring.

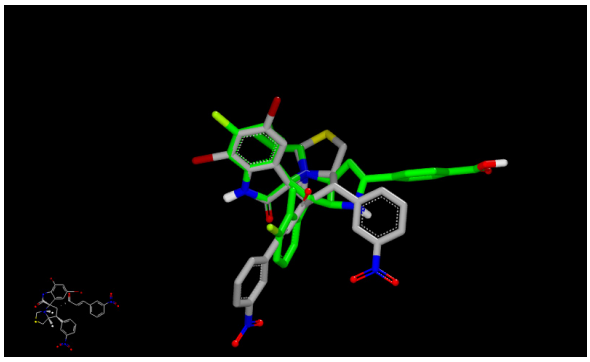


Figure 2. Shape similarity of **5g** with **BI-0252** as analyzed by Rapid Overlay Shape Chemical Structure (ROCS) and visualized by VIDA application.

2.5. Predicted Pharmacokinetics and Pharmacodynamics Parameters

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction for drug candidates is mandatory in the drug design process, as these parameters contribute to determining the failure of approximately 60% of all drugs in the development and approval phases. It is well-known that ADMET prediction is performed at the last stage of the drug development process with high cost and effort. At present, ADMET is determined at the beginning of drug discovery stages in order to eliminate molecules with poor ADMET properties from the drug discovery pipeline with the aim to save research costs. In this regard, computational tools were used to predict ADMET properties in this study [14].

The Caco-2 cell, percentage of human intestinal absorption (HIA), and skin permeability models have all been suggested as reliable in vitro models to estimate oral drug absorption and transdermal delivery [15]. Drug penetration to the blood brain barrier (BBB) provides insight into drugs that act on the central nervous system and on plasma protein binding (PPB). Compared to the other compounds, **5g** showed the lowest BBB penetration value (0.017) and a low value in the Caco-2 cell model (18.80). All compounds showed high PPB and HIA values, as well as very low skin permeability values in the range of −1.80 to −2.79 (Table 2).

Table 2. Predicted pharmacokinetic and pharmacodynamic parameters of the most active compounds.

#	Lipinski's Rule				PreADMET [16] Prediction					
	MW	LogP [17]	HBD	HBA	BBB	PPB	HIA	Caco-2 Value	Skin Permeability	Drug-Likeness Model Score [17]
5a	607.98	5.02	1	4	0.39	100.00	97.99	39.51	−2.45	0.36
5b	636.01	5.82	1	4	0.95	94.44	98.03	41.48	−2.28	0.60
5c	679.25	6.44	1	4	1.64	100.00	98.04	44.04	−2.49	0.83
5e	646.34	5.56	1	4	0.51	100.00	97.99	40.35	−2.75	0.63
5f	768.15	6.72	1	4	1.96	100.00	97.96	46.69	−2.15	0.71
5g	700.35	4.47	1	8	0.017	100.00	98.94	18.80	−2.46	0.44
5l	768.15	6.72	1	4	1.69	100.00	97.96	46.60	−2.15	0.63
5m	646.34	5.56	1	4	0.49	100.00	97.99	40.35	−2.79	0.72
5n	746.34	7.49	1	4	3.33	100.00	98.03	48.45	−1.80	0.47

HBD, hydrogen bond donor; HBA, hydrogen bond acceptor; BBB, blood brain barrier; PPB, plasma protein binding; HIA, percentage human intestinal absorption; Caco-2 value, permeability to Caco-2 (human colorectal carcinoma) cells in vitro.

2.6. Ligand Efficiency (LE) and Lipophilic Efficiency (LipE)

In the current study, for optimization assessment, LE was calculated [18]. The parameter LE has a crucial role in "lead optimization for drug-like candidate" properties [19]. Compounds with the highest activity were selected for evaluation against sensitive cancer cell lines (breast and colon cancer cells).

LE was calculated using the following equation [20]:

$$LE = (pIC_{50} \times 1.37)/NHA$$

IC_{50} = half-maximal inhibitory concentration (in terms of molar concentration); NHA = non-hydrogen atom.

The compounds had an LE value in the range of 0.19–0.26 except for compound **5n** (Table 3). All compounds exhibited higher LE values in breast cancer cells than in colon cancer cells, especially compounds **5c**, **5e**, and **5l** (LE = 0.26), all of which were structural isomers.

The recommended LE value should be in the range of 0.3. The acceptable LE value should be higher than 0.3.

2.7. Lipophilic Efficiency (LipE) or Ligand Lipophilic Efficiency (LEE)

Lip E or LLE is an avenue to determine compound affinity with respect to its lipophilicity.

Nowadays, the lipophilic efficiency (LipE) index (LEE), which includes lipophilicity and potency, is becoming more and more popular in drug design. It allows for the normalization of observed potency with changes in the lipophilicity, and it is considered an effective and practical tool for keeping lipophilicity under control to avoid any "molecular obesity".

LipE or LLE is calculated as the difference between the potency and log P as illustrated in the following equation:

$$Lip\ E = pIC50 - cLog\ P$$

According to data revealed in Table 3, compound **5g** showed best value in comparison to other derivatives between both cell lines.

Table 3. Summary of ligand efficiency scores for the target compounds.

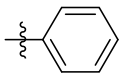
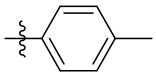
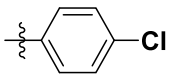
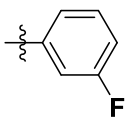
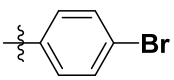
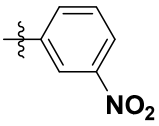
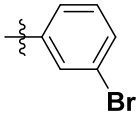
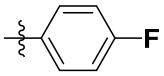
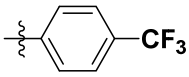
Compounds	R	NHA	cLog P	Breast Cancer Cells			Colon Cancer Cells		
				pIC_{50}	LE	LipE (LEE)	pIC_{50}	LE	LipE (LEE)
5a		35	5.02	5.22	0.2	0.20	5.34	0.2	0.32
5b		37	5.82	5.26	0.19	-0.56	5.3	0.2	-0.52
5c		37	6.44	5.52	0.26	-0.92	5.53	0.26	-0.91
5e		37	5.56	5.52	0.26	-0.04	5.3	0.2	-0.26
5f		37	6.72	5.6	0.2	-1.12	5.66	0.21	-1.06

Table 3. *Cont.*

Compounds	R	NHA	cLog P	Breast Cancer Cells			Colon Cancer Cells		
				pIC_{50}	LE	LipE (LEE)	pIC_{50}	LE	LipE (LEE)
5g		41	4.47	5.39	0.22	0.92	5.55	0.19	1.08
5l		37	6.72	5.52	0.26	-1.2	5.55	0.2	-0.17
5m		37	5.56	5.34	0.2	-0.22	5.39	0.2	-0.17
5n		43	7.49	5.3	0.17	-2.19	5.43	0.17	-2.06

2.8. Structure-Activity Relationship

The activity of the 2,4-dichloro derivative (compound **5c** or **4c**) was better than those of the 4- chloro analogues (compound **5d** or **4d** respectively), emphasizing the geometrical role of aryl moieties in the activities of the compounds. This result was consistent with that of our previous studies, which indicated the effect of such substitution patterns and showed that the 2,4-dichloro substitution was favorable to the activities of the compounds [19,20].

Hetero aryl (compound **5k**, **5j**), bulky (compound **5i**), or EDG (**5h**) reduced the activity indicated the site which was adopted by aryl groups in the side chain. The substitution site on both phenyl rings was important in the activity and physicochemical parameters of the compounds. This was clearly observed in compounds **5c**, **5e**, and **5l** compared to compounds **5f** and **5m**. Strong EWG (**5g**) exhibited the best activity.

3. Materials and Methods

General information of the equipment used in the synthesis and the characterization of the compounds can be found in the supplementary materials. Additionally, the anticancer activity along with shape alignment and ROCS can be found in the supplementary materials.

4. Conclusions

In summary, we synthesized a series of new spirooxindole analogues based on di-substituted isatin. The anticancer activity of the compounds against three different cancer cell lines was explored. Among the analogues, the compound spirooxindole analogue **5g** had an inhibitory growth potency in HCT116 similar to that of cisplatin, but it is ca. 1.8 (in HepP2) or 2.25 (in MCF7) times more potent than the reference drug, and also showed good physicochemical parameters and lipophilicity value. Further investigation of the mechanism of action of compound **5g** is required.

Supplementary Materials: The following are available online at http://www.mdpi.com/2076-3417/10/6/2170/s1, characterization of the synthesized compounds; protocol for anticancer activity; ROCS protocol, Figures of the NMR spectrum.

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Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds **5a–n** are available from the authors.

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