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# Novel Synthesis of Isatin-Thiazole Pharmacophores and their Cytotoxicity Evaluation

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**Abstract**

Novel synthesis of isatin-thiazole pharmacophores was developed which involves condensation of isatin or halo substituted isatins with phenyl hydrazine, 2-hydrazino-benzothiazole or 2-hydrazino-4-phenyl benzothiazole yielded the corresponding hydrazones which on further di-benzylation or di-methylation yielded 1,2'-dibenzyl or 1,2'-dimethyl substituted hydrazones. Furtherisatin or 7-Chloroisatin on condensation with 1,2-diaminobenzene yielded corresponding 6H-indolo2,3-bquinoxalines. One of the compound 1-benzyl-5-bromo-7-chloroindoline-2,3-dione (23) shows cytotoxicity activity against breast cancer cell line (MCF7) with $IC_{50}$ value 27.23 $\pm$ 3 µM and also in colorectal cancer cell line (CT26) with $IC_{50}$ value 17.7 $\pm$ 8 µM, which was comparable to that of standard Doxorubicin.

**Keywords:** Halo substituted isatins, Phenylhydrazine, 2-hydrazino benzothiazole, 6H-indolo 2,3-bquinoxalines, MTT ASSAY.

## Introduction

Although there is considerable advance in the field of combinational chemistry related to drug discovery, the success rate of generating new leads is yet to be achieved. Therefore, there is a necessity to explore focused set of library of compounds starting from therapeutically active heterocycles and make step by step modifications or design hybrid pharmacophore heterocyclic –heterocyclic analogs to make promising molecules.

Isatin (Indolin-1H-2, 3-Dione) is the most promising heterocyclic molecule from the point of exhibiting biological activity. In the past several modifications of isatin molecule were synthesized to study their biological activity. It has chemically three reactive centers, 1-NH, 3-carbonyl and in some reactions 2-carbonyl also. Due to electrophilic character of 3-carbonyl group, isatin or its halo substituted on benzenoid ring have been transformed to 3-substituted-indolin-2-ones like 3-imines (Schiff's bases), 3-hydrazones which on further Mannich reactions by using formaldehyde and secondary amines like diethyl amine, piperidines, morpholines yielded 1-substitueted Mannich bases -3-imines/3-hydrazones. Alternatively, isatins were subjected first to Mannich reaction at position 1- of isatin and then 3-imines (schiff bases)/3-thiosemicarbazones or 3-arylhydrazones

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were prepared (1-3).

Many of such isatin analogues were reported to possess anti-bacterial (4), anti-fungal (5,6), anti-viral (7), anti-HIV (8), antihelmintic (9), anti-inflammatory (10) and anti-convulsant (11).A novel isatin derivative 6-butyl-9-fluoro-2,3-dimethyl-6H-indolo-2,3-b quinoxaline, obtained by the condensation of 7-fluoro-1- butylisatin with 1,2-diamino-3,5-dimethylbenzene displayed significant in-vitro cytotoxicity against HeLa cells (human cervical cancer cells) (12).

IsatinMannich bases and Schiff bases analogues, obtained .by condensation of Isatin-1- Mannich bases with 2-amino -1- methyl benzothiazole were synthesized and studied for anti-breast cancer activity. For example, 9-chloro-1-dimethylaminomethyl-3-(6-methyl-enzothiazol-2-yl imino)-1,3-dihydro-indol-2-one had the highest activity (13). A spiroisatin derivative, 3H-spiro1,3-benzothiazole-2-3'-indol-2'(1'H)-one obtained by the condensation of isatin with 2-aminothiophenol showed anticancer activity (14). Very recently, after our work was completed the synthesis of spiroimidazopyridineoxindoles multicyclic spirooxindole pyrans and etc., were reported (15,16). Thus synthetic modification of isatin skeleton continues to draw the attention of the chemists and biologists.

## Result and Discussion

In recent year's pharmacophore heterocyclic–heterocyclic hybrids gaining importance as practical medicinal agents. For example, several "NIBS" anti-cancer agents are now availablecommercially. Cytotoxicity evaluation of several heterocyclic compounds for their activity against breast cancer cell line and colorectal cancer cell line are also in progress. NIBS contain two or more than heterocyclic hybrids connected through N=N, NH-NH, =N-NH, -O-CH2, NH-C and also contain aromatic rings. Some examples are imatinib, erlotinib, dasatinib and importantly sunitinib. Sunitinib featured isatin ring substituted at position-3. For testing biological activity, N-Mannich bases and 3-Arylhydrazones are common but N-alkyl, N-benzyl isatins with substituted 3-aryl- or heteryl- hydrazones do not seem to have been investigated. Therefore, in the present study, 2-hydrazinobenzothiazole, 2-hydrazino-4-phenylthiazole or phenyl- hydrazine and further the resulting 3-hydrazones were successively condensed with 2 moles of benzyl bromide or methyl iodide was studied (Figure 1).

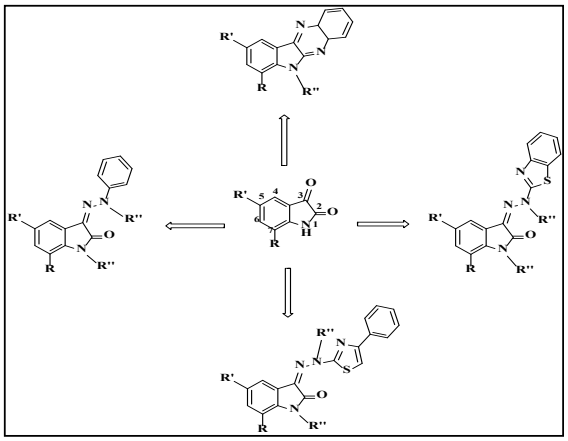
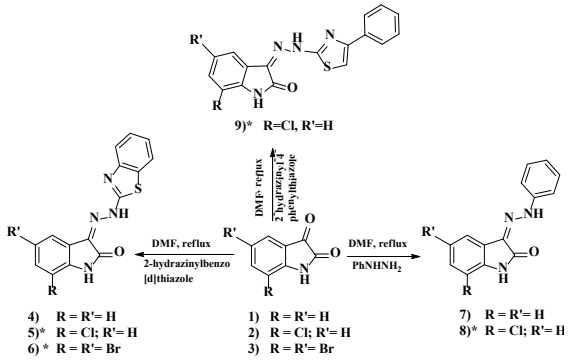


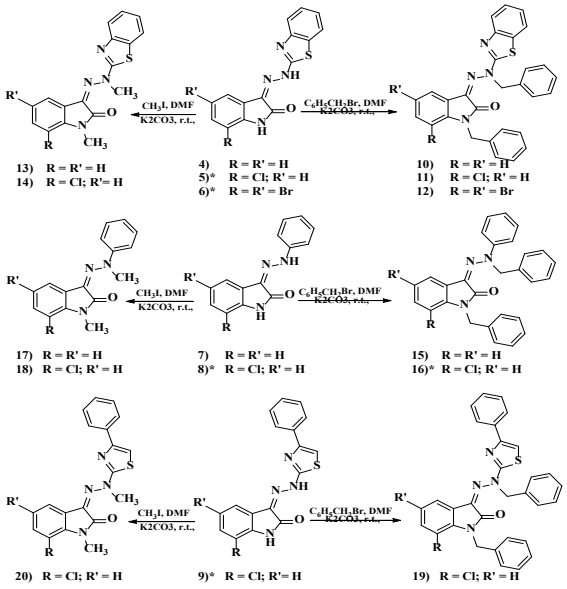
**Fig 1**: Isatin analogues

The condensation of isatin with heterocyclic hydrazines does not seem to have explored. Benzothiazoles are also well known to exhibit various biological activities. Benzothiazole skeleton show various biological activities such as analgesic (17), antitubercular+ (18), antibacterial (19) activities.




**Scheme 1**: Synthesis of hydrazone derivatives of substituted isatins (*not isolated. The crude compound is used for next step).

The several structural variants developed as a result of this study are (*Z*)-3-(2-(benzodthiazol-2-yl)hydrazono)indolin-2-one, (*Z*)-7-chloro-3-(2-(4-phenylthiazol-2-yl)hydrazono)indolin-2-one and (*E*)-3-(2-phenylhydrazono)indolin-2-one were obtained by successive condensation of isatin (or halo substituted isatins) with 2-hydrazino benzothiazole, 2-hydrazino-4-phenyl-thiazoles or phenyl hydrazine ( Scheme 1 ).



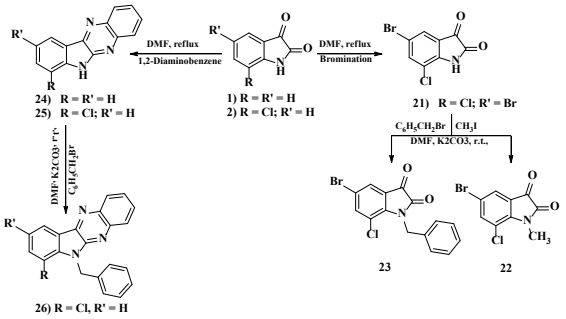

**Scheme 2**: Synthesis of methylated or benzylated derivatives of isatin hydrazones.

In these compounds isatin-benzothiazole pharmacophores are connected through -C=N-N-H group. Further these compounds were di-benzylated or di-methylated at the two available -NH groups to yield novel compounds (Scheme2).

Thus condensation of isatin with phenylhydrazine yielded isatin -3-phenylhydrazone (20) which on reaction with 2 moles of benzyl bromide yielded (*E*)-1-benzyl-3-(2-benzyl-2-phenylhydrazono) indolin-2-one. Likewise, (*Z*)-1-methyl-3-(2-methyl-2-phenyl hydrazono) indolin-2-one was synthesized in good yield (Scheme-2). Further starting from 7-chloro isatin the corresponding (*Z*)-7-chloro-1-methyl-3-(2-methyl-2-phenylhydrazono)indolin-2-one was synthesized (Scheme-2). The condensation of 7-chloroisatin-2-hydrazinobenzothiazole with 2 moles of benzyl bromide or 2 moles of methyl iodide furnished (*E*)-3-(2-(benzodthiazol-2-yl)-2-benzylhydrazono)-1-benzyl-7-chloroindolin-2-one or (*Z*)-3-(2-(benzodthiazol-2-yl)-2-methylhydrazono)-7-chloro-1-methylindolin-2-one respectively, were described. Scheme 2 also depicts the synthesis of (*E*)-3-(2-(benzodthiazol-2-yl)-2-benzylhydrazone)-1-benzyl-5,7-dibromo indolin-2-one.

In $^{1}$H NMR of (*E*)-3-(2-(benzodthiazol-2-yl)-2-benzylhydrazono)-1-benzylindolin-2-one, the aromatic protons resonated at δ = 7.76 (dd, *J* = 11.1, 7.9 Hz, 2H), 7.64 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.39 (td, *J* = 8.2, 4.9 Hz, 1H), 7.32-7.22 (m, 6H), 7.22-7.14 (m, 6H), 7.03 (td, *J* = 7.6, 0.9 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 1H). Two N-$CH_2$ at δ = 6.57 (s, 2H), 4.92 (s, 2H). In $^{13}$C NMR, 1-N-$CH_2$-Ph carbon atoms resonate at δ = 43.7 ppm and 2-(2'-N-$CH_2$-Ph) carbon atom at δ = 56.5 ppm. Isatin 2C=O at δ 170.9 ppm, thiazole ring C=N at δ = 151.9 ppm and 3C=N of isatin at δ = 157.3 ppm. The aromatic carbons found in the region of δ = 108.8 to 141.5 ppm.

Isatin and 7-Chloroisatin (21) are available in our Laboratory. Further 2-hydrazinobenzothiazole (22), 2-hydrazino-4-phenylthiazole (23) and 5,7dibromoisatin (24) are also synthesized as per literature procedure (Scheme-1). 7-chloro-5-bromo isatin (25) was synthesized by bromination of 7-chloroisatin (Scheme-3).




**Scheme 3:** Synthesis of methylated or benzylated derivatives of isatin and 6*H*-indolo 2,3-bquinoxalines

In scheme 3, the conversion of 7-chloro-5-bromoisatin to 5-bromo-7-chloro-1-benzyl isatin or 5-bro-

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**Table 1: Synthesis of hydrazone derivatives of substituted isatins, methylated or benzylated derivatives of isatin hydrazones, methylated or benzylated derivatives of isatin and 6H-indolo2,3-bquinoxalines.**

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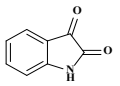
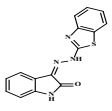
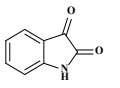
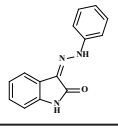
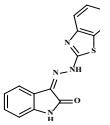
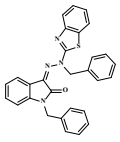
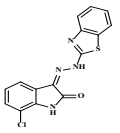
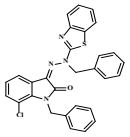
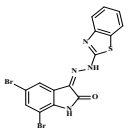
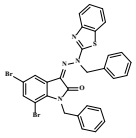
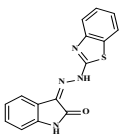
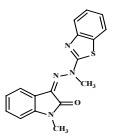
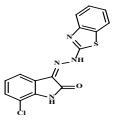
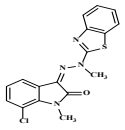
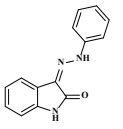
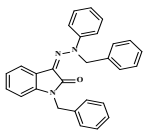
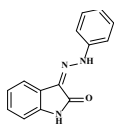
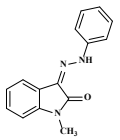
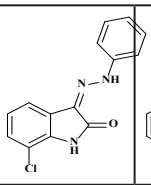
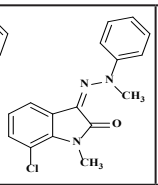
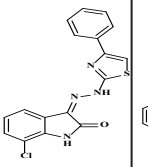
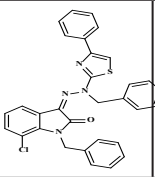
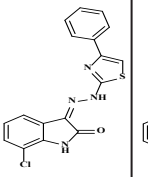
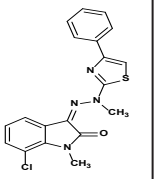
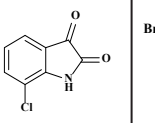
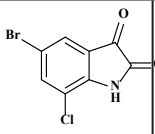
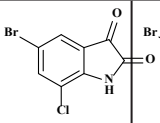
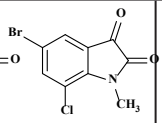
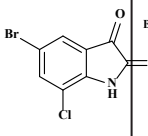
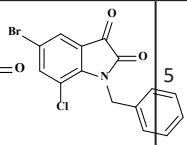
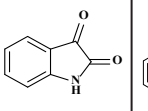
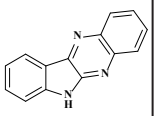
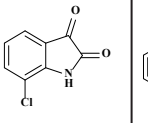
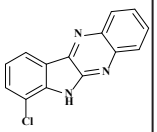
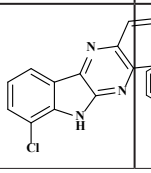
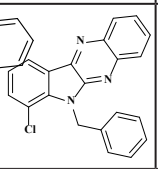
| 1 |  |  | 8 | 68 |
| 2 |  |  | 8 | 69 |
| 3 |  |  | 5 | 62 |
| 4 |  |  | 5 | 66 |
| 5 |  |  | 6 | 58 |
| 6 |  |  | 5 | 67 |
| 7 |  |  | 5 | 64 |
| 8 |  |  | 5 | 62 |
| 9 |  |  | 5 | 59 |
| 10 |  |  | 5 | 61 |
| 11 |  |  | 5 | 63 |
| 12 |  |  | 5 | 60 |
| 13 |  |  | 2 | 70 |
| 14 |  |  | 5 | 67 |
| 15 |  |  | 5 | 71 |
| 16 |  |  | 10 | 65 |
| 17 |  |  | 5 | 67 |
| 18 |  |  | 5 | 69 |

mo-7-chloro-1-methyl isatin were shown. Further fused isatin-quinoxalines were synthesized as shown in scheme-3. Thus isatin or 7-chloroisatin were condensed with 1,2-diaminobenzene (OPDA) to yield fused isatin-quinoxalines, 6*H*-indolo2,3-bquinoxaline or 7-chloro-6H-indolo2,3-bquinoxaline respectively. To our knowledge only one such compound was reported earlier [12].In Isatin-quinoxaline fused compound, *6H*-indolo2,3-bquinoxaline*,* in $^{13}C$ NMR, two C=N appeared at δ = 145.2, 143.2 and 3C=O which normally appears at δ = 158 is absent. This confirms the compound is a fused one. Rest of the aromatic protons appeared at δ =139.4, 139.3, 137.9, 130.0, 128.0, 127.4, 126.5, 124.8, 121.3, 119.6, 118.4 and 111.0.

The typical methods of synthesis of various compounds are given in experimental and in supplementary information. In table 1 the structures and yields are given after chromatography.

*All products were characterised by $^{1}H$, $^{13}C$ NMR, IR and ESI-HRMS spectroscopic techniques

## CYTOTOXICITY EVALUATION

Table 2: $IC_{50}$ values of different isatin derivatives

| Compound No. | MCF7 | CHO |
|---|---|---|
| 4 | >50 | >50 |
| 7 | >50 | 34 ± 6 |
| 10 | >50 | >50 |
| 13 | >50 | >50 |
| 15 | >50 | >50 |
| 17 | >50 | >50 |
| 18 | >50 | >50 |
| 21 | >50 | >50 |
| 22 | 34 ± 5 | 29 ± 4 |
| 23 | 11 ± 5 | 10 ± 5 |
| 25 | >50 | >50 |
| 26 | >50 | >50 |
| Doxorubicin | | |

The inhibitory efficienty ($IC_{50}$ values) was tested for all hydrazone derivatives of substituted isatins, methylated or benzylated derivatives of isatin hydrazones, methylated or benzylated derivatives of isatin and 6H-indolo2,3-bquinoxalines against a panel of two different cancer cell lines such as MCF7 and CT26. This experiment was performed with a positive control in both the cell lines. The results are as follows shown in the following table 2. From the above results we can conclude that compound **23** is cytotoxic on cancer cell lines such as CT26 which is a colorectal cancer and MCF7 which is a breast cancer cell line.

Table 3: $IC_{50}$ values of compound 23 against MCF7 and CT26

| Cell Line | $IC_{50}$ of Compound 23 (μM) | $IC_{50}$ of Doxorubicin (μM) |
|---|---|---|
| MCF7 | 27±3 | 8.067±0.3 |
| CT26 | 17±8 | 7.099±1.43 |

Table 3 showed the $IC_{50}$ values of compound **23** against cancer cell lines such as MCF7 which is a breast cancer cell line and CT26 which is a colorectal cancer cell line. A positive control was also taken with compound **23**. The compound showed more cytotoxicity against colorectal cancer CT26 ($IC_{50}$ = 17.7 ± 8 μM) with a positive control as Doxorubicin ($IC_{50}$=7.099 ± 1.43).

On breast cancer cell line MCF7, compound **15** is cytotoxic ($IC_{50}$ = 27.23 ± 3). Here Doxorubicin have ($IC_{50}$ = 8.067 ± 0.3). Compound **23** includes halogen group and this increases the efficiency of the compound. In fact, the binding efficiency of the compound to its ligand depends on its size.

This leads to a conclusion that compound **23** exhibits cytotoxic nature to different cancer cell lines.

## CONCLUSION

Thus, several isatin-benzothiazole/-thiazole hybrids were synthesized. Such hydrazones were di-benzylated or di-methylated with 2 moles of benzyl bromide or methyl iodide.Di-benzylation or di-methylationtook place at position of 1- of isatin and at position 2- of hydrazones resulted, which is an interesting and which is a nov-

el observation. When isatin on condensation with OPDA, resulted in fused isatin-quinoxaline heterocyclic, 6H-indolo2,3-bquinoxaline which is also an interesting observation . All the compounds are characterized by spectral data which is incorporated in experimental. In these compounds isatin-benzothiazole pharmacophores are connected through -C=N-N- group. Thus, new pharmacophore isatin- thiazole hybrids and isatin 3-hydrazones were generated in the present study. These compounds evaluated for cytotoxicity activity against different cancer cell lines.One of the compound 1-benzyl-5-bromo-7-chloroindoline-2,3-dione(23) showed cytotoxicity activity against breast cancer cell line (MCF7) with $IC_{50}$ value 27.23 $\pm$ 3 µM and also in colorectal cancer cell line (CT26) with $IC_{50}$ value 17.7 $\pm$ 8 µM, which was comparable to that of standard Doxorubicin.

## EXPERIMENTAL SECTION

### *General chemical methods*

All solvents and the reagents were purchased commercially and used without further purification. All moisture sensitive reactions were carried out in anhydrous solvents under $N_2$ atmosphere. Column chromatography was carried out with silica gel (Merck 60–120 mesh). All reactions were monitored by thin layer chromatography (TLC) on silica gel Merck, Kieselgel 60 F254 plates; both starting material and products were visualized with using UV 254 nm and anisaldehyde stain followed by heating. $^1H$ and $^{13}C$ NMR spectra were recorded with an internal deuterium lock on Bruker 300, 400 and 500 MHz instruments, chemical shifts (δ) were measured in parts per million (ppm) and calibrated to the residual proton and carbon resonance of the $CDCl_3$ (δH = 7.26 and δC = 77.0 ppm). TOF analyzer technique was used for the HRMS measurement. FTIR spectra were recorded with a Bruker Alpha spectrophotometer and were reported in $cm^{-1}$.

Experimental and analytical details of three typical compounds are described below and for rest of the compounds the details are given in supplementary information.

### *Experimental and Analytical data for selected compounds*

(1). A mixture of isatin (1 g, 6.80 mmol), 2-phenylhydrazino benzothiazole (880 mg, 8.16 mmol) in DMF (10 mL) with few drops of acetic acid and refluxed for 8 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into cold water and extracted with ethyl acetate (3 x 20 mL). The combined organic layer dried over $Na_2SO_4$ and the solvent was removed under the reduced pressure. The residue was purified by silica gel chromatography eluting (EtOAc: hexane, 1:49) leading to (*Z*)-3-(2-(benzodthiazol-2-yl)hydrazono)indolin-2-one(1.09 g, 68%) derivative as yellow solid (Scheme 1).

### *(Z)-3-(2-(benzodthiazol-2-yl)hydrazono)indolin-2-one (4).*

Yellow solid; mp 249-251 ˚C; IR (Neat) $v_{max}$ 2956, 2923, 2853, 1693, 1550, 772 $cm^{-1}$; $H^1$ NMR ($CDCl_3$+DMSO, 400 MHz): δ = 9.85-9.76 (brs, 1H), 8.34 (d, *J* = 7.4 Hz, 1H), 7.79-7.60 (m, 1H), 7.51 (dd, *J* = 7.8, 2.2 Hz, 1H), 7.40-7.19 (m, 3H), 7.16-7.05 (m, 1H), 7.01-6.93 (m, 1H), 6.88 (d, *J* = 7.7 Hz, 1H); $C^{13}$ NMR ($CDCl_3$+DMSO, 75 MHz): δ = 173.6, 165.7, 141.7, 141.1, 138.9, 129.7, 126.2, 125.6, 124.5, 121.7, 121.3, 120.7, 117.4, 112.0, 109.2. HRMS(ESI) *m/z* calcd for $C_{15}H_{10}N_4OS$, $M+H^+$ 295.0648, found 295.0631.

(2). To a stirred solution of *Z*)-3-(2-(benzodthiazol-2-yl)hydrazono)-7-chloroindolin-2-one (300 mg, 1.26 mmol) in DMF (8 mL) at 0 ˚C were sequentially added $K_2CO_3$ (524 mg, 3.79 mmol) and benzyl bromide (316 µL, 2.65 mmol) and stirring was continued for 5hat room temperature. The reaction mixture was poured into cold water and extracted with ethyl acetate (3 x 20 mL). The combined organic layer dried over $Na_2SO_4$, filtered and concentrated. The obtained residue was purified by silica gel column chromatography (EtOAc: hexane, 1:19) to give (*E*)-3-(2-(benzodthiazol-2-yl)-2-benzylhydrazono)-1-benzyl-7-chloroindolin-2-one (347 mg,

66%) as a yellowish red solid (Scheme 2).

***(E)-3-(2-(benzodthiazol-2-yl)-2-benzylhydrazono)-1-benzyl-7-chloroindolin-2-one (11).***

Yellowish red solid; mp 192-194 ˚C; IR (Neat) $v_{max}$ 3063, 3031, 2954, 2923, 1697, 1607, 1572, 754 $cm^{-1}$. $H^1$ NMR ($CDCl_3$, 400 MHz): δ = 7.78 (d, *J* = 8.0 Hz, 1H), 7.75 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.58 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.40 (td, *J* = 7.4, 1.2 Hz, 1H), 7.31-7.07 (m, 12H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.56 (s, 2H), 5.37 (s, 2H); $C^{13}$ NMR ($CDCl_3$, 100 MHz): δ = 170.6, 157.7, 151.8, 137.1, 137.1, 134.5, 133.8, 131.8, 129.9, 128.5, 128.4, 127.6, 127.3, 127.1, 126.4, 126.1, 125.8, 123.8, 123.3, 121.8, 121.0, 119.2, 115.3, 56.6, 44.7; HRMS(ESI) *m/z*calcd for $C_{29}H_{21}ClN_4OS$, $M+H^+$ 509.1197, found 509.1178.(3). To a stirred solution of *Z*)-3-(2-(benzodthiazol-2-yl)hydrazono)-7-chloroindolin-2-one (300 mg, 1.26 mmol) in DMF (8 mL) at 0 ˚C were sequentially added $K_2CO_3$ (524 mg, 3.79 mmol) and methyl iodide (206 µL, 2.43 mmol) and stirring was continued for 5h at room temperature. The reaction mixture was poured into cold water and extracted with ethyl acetate (3 x 20 mL). The combined organic layer dried over $Na_2SO_4$, filtered and concentrated. The obtained residue was purified by silica gel column chromatography (EtOAc: hexane, 1:19) to give (*Z*)-3-(2-(benzodthiazol-2-yl)-2-methylhydrazono)-7-chloro-1-methylindolin-2-one (336 mg, 64%) as a red solid (Scheme 2).

***(Z)-3-(2-(benzodthiazol-2-yl)-2-methylhydrazono)-7-chloro-1-methylindolin-2-one (14).***

Red solid; mp 204-206 ˚C; IR (Neat) $v_{max}$ 3059, 2921, 2851, 1694, 1609, 1579, 753 $cm^{-1}$. $H^1$ NMR ($CDCl_3$, 500 MHz): δ = 7.78 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.56 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.40 (td, *J* = 7.3, 1.2 Hz, 1H), 7.29-7.22 (m, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.28 (s, 3H), 3.65 (s, 3H); $C^{13}$ NMR ($CDCl_3$, 100 MHz): δ = 170.1, 157.4, 151.7, 138.0, 133.3, 131.8, 130.0, 126.8, 125.6, 123.7, 123.3, 121.5, 121.0, 119.0, 115.6, 43.3, 29.4; HRMS(ESI) *m/z*calcd for $C_{17}H_{13}ClN_4OS$, $M+H^+$ 357.0571, found 357.0566.

(4). A mixture of 7-chloro isatin (1 g, 5.53 mmol), *o*- phenylenediamine (775 mg, 7.18 mmol) in DMF (10 mL) with few drops of acetic acid and refluxed for 10 h. The reaction mixture was poured in cold water and extracted with EtOAc (3 x 20 mL). The combined organic layer dried over $Na_2SO_4$, filtered and concentrated. The obtained residue was purified by column chromatography (EtOAc: hexane, 1:19) to give quinoxaline (894 mg, 64%) as a light yellow solid. The above obtained qunioxaline (200 mg, 790 µmol) in DMF (2 mL) was treated with $K_2CO_3$ (218 mg, 1.58 mmol) and benzyl bromide (103 µL, 502 µmol) at room temperature and stirring was continued for 5 h. The reaction was poured in cold water and extracted with EtOAc (3 x 20 mL). The combined organic layer dried over $Na_2SO_4$, filtered and concentrated. The obtained residue was purified by column chromatography (EtOAc: hexane, 1:19) to give 26 (184 mg, 68%) as a yellow solid (Scheme 3).

***6-benzyl-7-chloro-6,11a-dihydro-4aH-indolo2,3-bquinoxaline (26)****.*

Yellow solid; mp 242-244 ˚C; IR (Neat) $v_{max}$: 3026, 2954, 2921, 1643, 1597, 1582, 1450, 772 $cm^{-1}$; $H^1$ NMR ($CDCl_3$, 500 MHz): δ = 8.16 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.85 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.48-7.44 (m, 1H), 7.37 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.35-7.32 (m, 2H), 7.32-7.27 (m, 3H), 6.75 (t, *J* = 7.9 Hz, 1H), 6.07 (s, 2H), 5.57 (s, 2H); $C^{13}$ NMR ($CDCl_3$, 125 MHz): δ = 154.6, 143.8, 135.1, 132.4, 132.2, 131.2, 130.4, 129.6, 128.9, 127.7, 126.9, 123.9, 120.6, 119.7, 116.5, 114.4, 46.4; HRMS(ESI) *m/z*calcd for $C_{21}H_{14}ClN_3$, $M+Na^+$ 366.0768, found 366.0779.

***Declaration of Competing Interest***

There are no conflicts to declare. For all the compounds experimental details and spectral data and as well as charts are given in Supplementary information

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