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Original article

# Synthesis, molecular docking study and antitumor activity of novel 2-phenylindole derivatives

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ABSTRACT

The starting material, 4-(1-indol-2-yl)phenol **1** was obtained via Fischer synthesis. Vilsmeir Haack's formylation of **1** gave the carboxaldehyde derivative **2** which was subjected to different reactions affording the 3-substituted compounds **3**–**10**. Compound **1** reacted with halo esters to give **11** and **12a**,**b**. The reaction of **12a** with various amino derivatives gave compounds **13**–**16**. The hydrazide derivative **15a** reacted with 1,3-diketones, ethyl acetoacetate and aromatic carboxylic acid derivatives to give **17a**,**b**, **18** and **19a**–**e**, respectively. Antitumor activity of target compounds were tested against breast cancer cell lines (MCF-7) and (MDA-MB-231). The most potent compound was **3e** with $IC_{50} = 1.60$ nM against (MCF-7). Docking was performed on colchicine binding site of tubulin to study the binding mode of the designed compounds.



## 1. Introduction

Today, more than ever, scientists are doing a great deal of research to help prevent or beat cancer. Although there are a large number of anticancer drugs currently used, many new chemical classes of anticancer agents affecting a variety of biological targets have emerged and are under clinical trials for the production of novel effective and less toxic drugs.

Microtubules, cylindrical protein polymers composed of α- and β-tubulin heterodimers, are the basic components of cell structure, which take part in a wide number of pivotal cellular functions [1,2]. Inhibition of microtubule formation leads to mitotic arrest promotes vascular disruption and eventually leads to cell death by apoptosis [3,4]. Hence, tubulin is a common target of attack for many anticancer drugs [5]. Vinca alkaloid, taxanes and other antimitotic agents are used for the treatment of cancer, however, difficulty in synthesis and high cost limited their uses [6]. Therefore, searching for new antimitotic agents with better activity is still in progress.

The indole nucleus emerged as a versatile skeleton for the development of compounds with promising antiproliferative activity [7–9]. A variety of 2-phenylindoles **I** was found to inhibit the growth of human breast cancer cells by different mechanisms depending on the type and position of the substituents [10–13]. Recently, 2-phenylindole-3-carboxaldehydes **II** proved to exert an antimitotic activity in human breast cancer cells by inhibition of tubulin polymerization (Fig. 1) [14,15]. Furthermore, several modifications on the 3-formyl group were carried out in order to overcome the *in-vivo* instability of the aldehyde functional group. These modifications included the formation of oximes, methylamine, propanedinitriles, hydrazones and other derivatives that proved to possess high stability and good antimitotic activity [15–17]. Some of these indole derivatives were structurally optimized through 3D-QSAR and docking studies on tubulin [18]. These findings encouraged us for further exploration of novel anticancer drugs possessing the 2-phenylindole scaffold and bearing different substituents on the 2-phenyl moiety. Furthermore, it was of our interest to focus on the synthesis of the 3-carboxaldehyde phenylindole and perform several modifications on the formyl group aiming to give rise to new potent and stable anticancer agents. Docking studies were performed to assess the binding mode of the active compounds into the colchicine binding site of tubulin.

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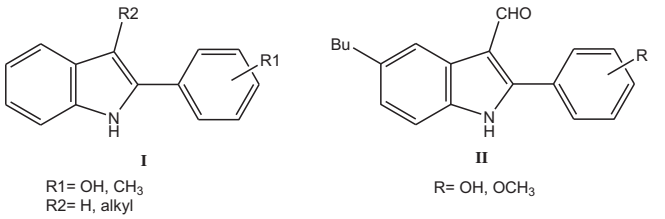



**Fig. 1.** Examples of 2-phenylindole derivatives with anticancer activity.

## 2. Results and discussion

### 2.1. Chemistry

The synthetic pathways adopted for the preparation of the desired new compounds are illustrated in Schemes 1–3. The known starting material **1** was reported to be obtained via Fischer synthesis [19,20]. Scheme 1 illustrates the synthesis of the 3-formyl derivative **2** from the starting material **1** via Vilsmeir Haack's formylation using $POCl_3$ and dimethylformamide (DMF) [15,21]. The IR spectrum of **2** revealed C=O stretching band of formyl group at 1696 $cm^{-1}$ $^1H$ NMR spectrum showed an exchangeable signal at 8.35 assigned to the OH proton and a non exchangeable signal at 9.94 ppm corresponding to the formyl proton, in addition to the indole and phenyl protons.

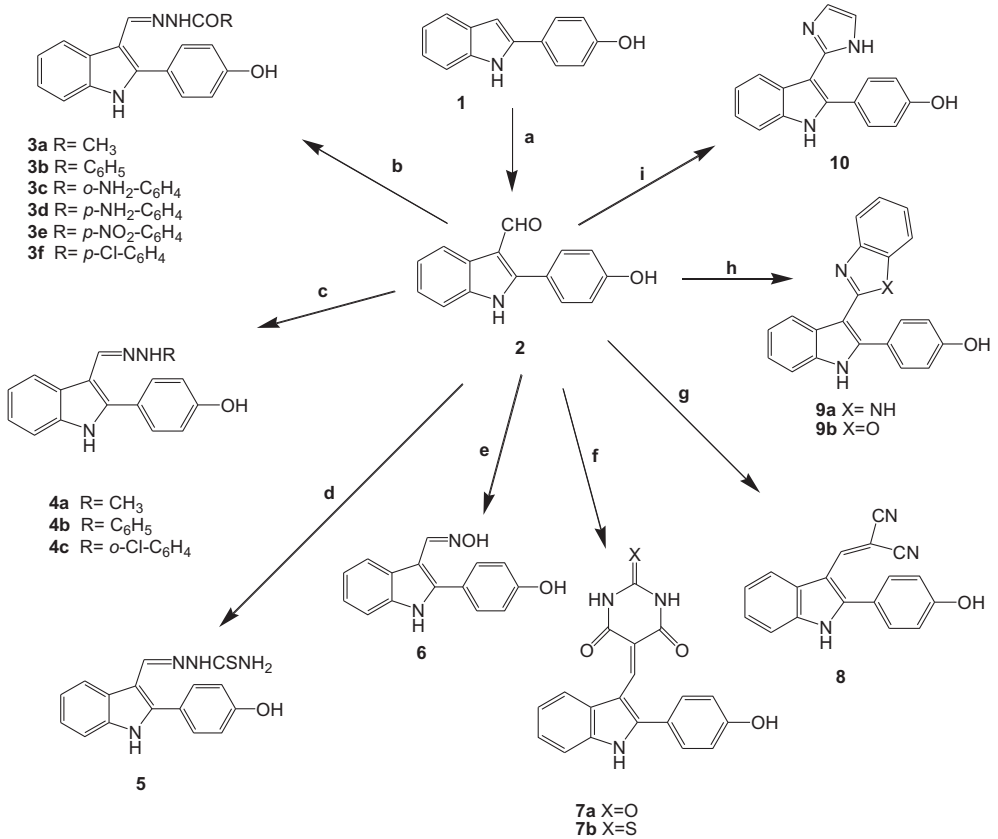
The hydrazides **3a**–**f** and the hydrazones **4a**–**c** were obtained by the reaction of the formyl derivative **2** with different substituted acid hydrazides and hydrazines, respectively.

The hydrazinecarbothioamide derivative **5** was prepared by the reaction of the formyl derivative **2** with thiosemicarbazide. The $^1H$ NMR displayed 2 signals at 8.04 and 9.91 ppm corresponding to $NH_2$ and N–NH protons respectively. The carboxaldehyde oxime derivative **6** was obtained by condensation of the starting formyl derivative **2** with hydroxylamine hydrochloride. $^1H$ NMR of **6** showed a new exchangeable signal at 11.30 ppm corresponding to OH proton of the oxime group.

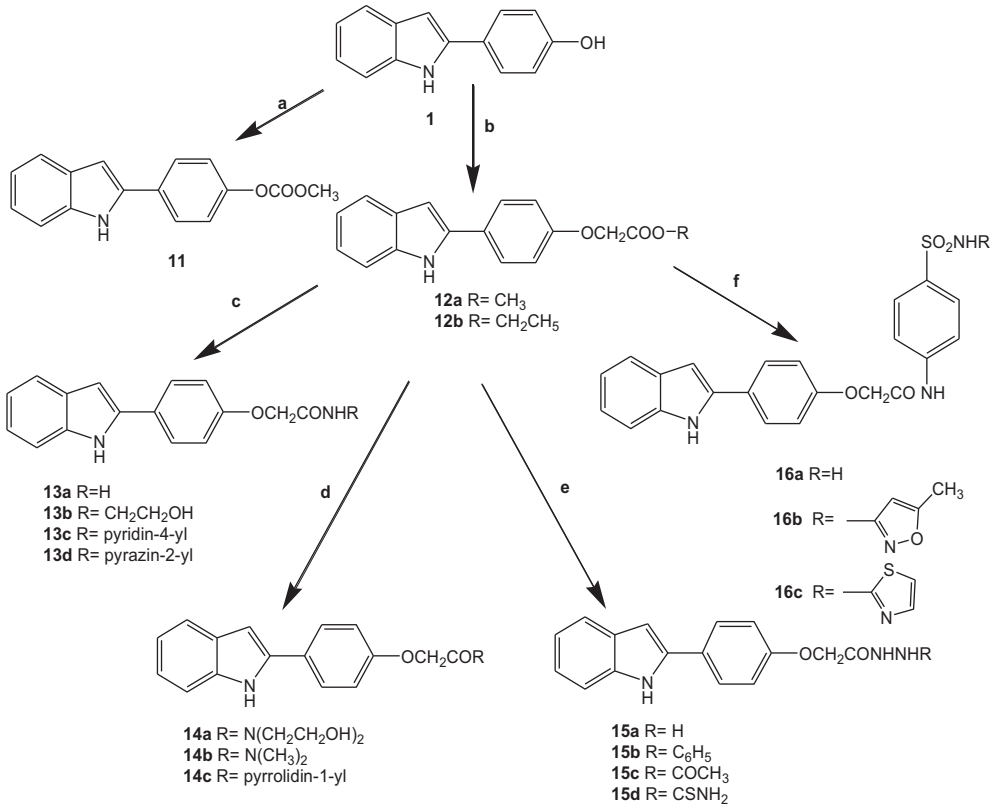
Reaction of the formyl derivative **2** with the active methylene of barbituric and thiobarbituric acids gave the heterocyclic derivatives **7a**,**b** respectively. IR spectrum of **7b** revealed the presence of 3 stretching bands at 3417, 3371 $cm^{-1}$ and 3123 $cm^{-1}$ assigned for OH, indole NH and pyrimidine NH, respectively, in addition to a broad band at 1652 $cm^{-1}$ attributed to the 2C=O groups. $^1H$ NMR of **7b** showed a new exchangeable signal at 12.51 ppm corresponding to the 2 NH protons of the pyrimidine ring.

The propanedinitrile derivative **8** was obtained by the reaction of the starting formyl derivative **2** with malononitrile. IR spectrum of **8** revealed a new stretching band of the nitrile groups at 2214 $cm^{-1}$. $^1H$ NMR showed a signal at 7.93 ppm corresponding to the vinyl proton CH=C.

The 3-substituted indole derivatives **9a**,**b** and **10** were prepared via the reaction of the formyl derivative **2** with the appropriate amine namely, *o*-phenylenediamine, *o*-aminophenol and ethylenediamine, respectively. $^1H$ NMR of **9a** showed 2 multiplets at 7.12–7.19 ppm and 7.55–7.61 ppm and an exchangeable singlet at 12.21 ppm corresponding to the aromatic protons and NH proton of benzimidazole respectively. $^1H$ NMR of **10** showed a multiplet at 7.07 ppm attributed to imidazole protons and a new exchangeable singlet at 8.40 ppm corresponding to imidazole NH.




**Scheme 1.** Reagents and solvents: a: $POCl_3$, DMF; b: R–CO–$NHNH_2$, absolute ethanol; c: R-$NHNH_2$, absolute ethanol; d: $NH_2CSNHNH_2$, absolute ethanol; e: $NH_2OH$. HCl, absolute ethanol, pyridine; f: thio/barbituric acid(s), absolute ethanol; **g**: malononitrile, absolute ethanol; h: *o*-phenylenediamine or *o*-aminophenol, absolute ethanol; i: ethylenediamine, absolute ethanol.



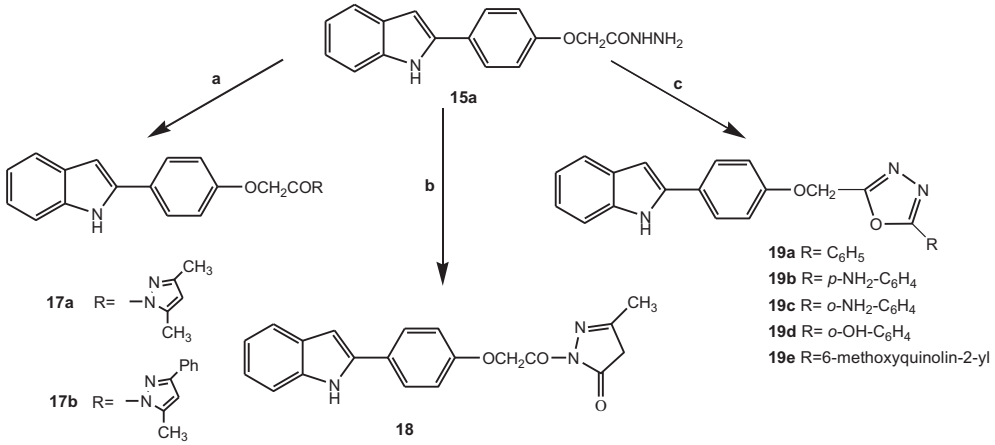

**Scheme 2.** Reagents and solvents: a: Cl–COO–$CH_3$, dry acetone, $K_2CO_3$ anhydrous; b: Br–$CH_2$COO–R, dry acetone, $K_2CO_3$ anhydrous; c: $RNH_2$, absolute ethanol; d: secondary amines, absolute ethanol; e: R–NH–$NH_2$, absolute ethanol; f: sulfonamides, dry acetone, $K_2CO_3$ anhydrous.

Other targeted 2-phenylindole derivatives were prepared as shown in Scheme 2. Methyl chloroformate reacted with **1** to give the methyl carbonate derivative **11**. The $^1$H NMR of **11** revealed a signal at 4.02 ppm corresponding to the methyl protons. The ester derivative **12a** was obtained by the reaction of the starting material **1** with methyl bromoacetate adopting the same procedure used for preparation of **12b** [22,23]. The $^1$H NMR of **12a** displayed 2 new signals at 3.51 ppm and 4.37 ppm corresponding to the methyl and methylene protons respectively.

Aminolysis of the ester derivative **12a** was carried out using different primary and secondary amines affording **13a**–**d** and **14a**–**c**, respectively. $^1$H NMR of **14b** revealed 2 singlets at 3.35 and 3.36 ppm corresponding to the 2 methyl protons.

Reaction of **12a** with hydrazines, acetohydrazide and thiosemicarbazide afforded derivatives **15a**–**d**, respectively. $^1$H NMR of **15a** showed the presence of new exchangeable signals at 4.40 ppm and 9.41 ppm corresponding to the $NH_2$ and NH hydrazide, respectively.

The ester derivative **12a** reacted also with different sulfonamides to give the corresponding sulfonamido derivatives **16a**–**c**. IR spectrum of **16c** revealed a stretching band of the amidic C=O group at 1630 $cm^{-1}$ and absorption bands at 1324 $cm^{-1}$ and 1137 $cm^{-1}$ attributed to the $SO_2$ group. $^1$H NMR of **16c** revealed the presence of 2 multiplets at 6.67–6.69 ppm and 7.12–7.14 ppm corresponding to the thiazole protons and an exchangeable signal at 10.50 ppm corresponding to the NH–$SO_2$ proton. $^{13}$C NMR




**Scheme 3.** Reagents and solvents: a: acetylacetone or benzoylacetone, absolute ethanol; b: ethyl acetoacetate, absolute ethanol; c: RCOOH, $POCl_3$.

spectrum of **16c** showed 2 signals at 124.50 ppm and 152.24 ppm corresponding to the thiazole carbon atoms and a signal at 168.50 ppm corresponding to the C=O carbon atom.

Cyclization of the hydrazide derivative **15a** with different diketones; acetylacetone and benzoylacetone was achieved resulting in the pyrazolo-indole derivatives **17a**,**b** (Scheme 3). $^1$H NMR of **17b** revealed a new signal at 2.05 ppm corresponding to the methyl protons in addition to the aromatic protons of the phenyl groups.

Furthermore, the pyrazolone derivative **18** was obtained by cyclization of the hydrazide derivative **15a** with ethyl acetoacetate. $^1$H NMR of **18** revealed a singlet at 1.21 ppm corresponding to the methyl protons and singlet at 2.25 attributed to the pyrazole protons.

The hydrazide derivative **15a** reacted with different aromatic carboxylic acid derivatives in $POCl_3$ to give the corresponding oxadiazole derivatives **19a**–**e**. $^1$H NMR of **19e** showed a characteristic singlet at 3.93 ppm corresponding to the methoxy protons in addition to the signals assigned for the quinoline protons and the other usual protons of the basic structure.

### 2.2. Antitumor activity

All the newly synthesized compounds and the starting material **1** were tested for their cytotoxic activity against MCF-7 (human breast cancer cell line) using the method of Skehan et al [24–26] and were compared to vincristine as reference drug. The most active compounds **2**, **3b**, **3c**, **3d**, **3e**, **3f**, **4a**, **4b**, **4c**, **9b**, **14c**, **16b**, **16c** and **19a**, revealing $IC_{50} < 20$ nM against MCF-7 were further tested against MDA-MB-231 cell line.

Cytotoxic activities of the tested compounds were expressed as $IC_{50}$ in nM and were recorded in Table 1. Most of the tested compounds showed good anticancer activity against the 2 breast cell lines.

Regarding the activity against MCF-7, the 3-formyl derivative **2** was found to be more potent than the starting phenylindole derivative **1**. Most of the prepared hydrazide-based indole derivatives **3a**–**f** revealed good activity when compared with the reference drug. Compound **3e** exhibited the best activity showing $IC_{50} = 1.60$ nM being more active than vincristine ($IC_{50} = 2.00$ nM). The 4-amino and 4-chloro benzohydrazides **3d** and **3f**, respectively, revealed similar $IC_{50}$ values, indicating that the activity is not related to the electronic nature of the substituent. On the other hand, aliphatic substitution **3a** decreased the activity. Among the hydrazone-based indole derivatives **4a**–**c** compounds **4b** and **4c** were found to be the most potent in this series. Some modifications performed on the 3-formyl derivative **2** led to decrease in activity as shown in hydrazinecarbothioamide, carboxaldehyde oxime, methylene hybrids and propanedinitrile derivatives **5**, **6**, **7a**,**b** and **8**, respectively. Introduction of a heterocyclic moiety at position 3 displayed good activity, the 3-benzoxazole derivative **9b** revealed better activity than the benzimidazole isostere **9a**, while the imidazole derivative **10** showed a slight decrease in activity.

The methyl acetate derivative **12a** was found to be more potent than the methyl carbonate analog **11** which may be attributed to the presence of the methylene spacer in **12a**. Furthermore, compound **12a** exhibited better activity than its ethyl ester analog **12b** that showed a marked decrease in activity suggesting an optimum chain length in the ester moiety. The amide derivatives **13a**–**d** and **14a**–**c** showed good to moderate activity except the hydroxyethyl acetamide derivative **13b** that exhibited a marked drop in activity. However, the pyrido derivative **13c** and the pyrrolidino derivative **14c** were the most active of these series. The hydrazide derivative **15a** revealed higher activity than the other substituted hydrazide **15b**,**c** and thiosemicarbazide **15d**. Sulfonamide derivatives **16a**–**c**, in general showed good activity. The *N*-thiazolesulfonamido derivative **16c** was the most potent, while; the unsubstituted sulfanilamido derivative **16a** was the least.

The pyrazolone derivative **18** exhibited better activity than the pyrazolo derivatives **17a**,**b**. Furthermore, most of the indolyl oxadiazole derivatives **19a**–**e** were found to be good anticancer agents. However, changing the position of amino group in the aniline moiety from the *ortho* position **19c** to the *para* position **19b** decreased the activity.

Regarding the activity against MDA-MB-231, all the tested compounds revealed good cytotoxic profile, however, it was lower than that recorded against MCF-7 except for compounds **9b** and **16b** especially the latter that was as twice as potent against MDA-MB-231. It is noteworthy that the reference drug vincristine also showed lower activity against MDA-MB-231 (IC 50 = 6.00 nM) than MCF-7 (IC 50 = 2.00 nM).

### 2.3. Molecular docking

Molecular Operating Environment (MOE) based molecular docking was done for the starting compound **1**, the target compounds having $IC_{50} < 25$ nM (MCF-7): **2**, **3b**, **3c**, **3d**, **3e**, **3f**, **4a**, **4b**, **4c**, **9a**, **9b**, **13c**, **14c**, **15a**, **16a**, **16b**, **16c**, **19a**, **19e** and vincristine on tubulin co-crystallized with colchicine obtained from the protein

**Table 1**
$IC_{50}$ values of the tested compounds on MCF-7 and MDA-MB-231 cell lines.

| Cpd. | $IC_{50}$ nM ± SE | | Cpd. | $IC_{50}$ nM ± SE | | Cpd. | $IC_{50}$ nM ± SE | |
|---|---|---|---|---|---|---|---|---|
| | MCF-7 | MDA-MB-231 | | MCF-7 | MDA-MB-231 | | MCF-7 | MDA-MB-231 |
| **1** | 71.80 ± 0.19 | n.d. | **8** | 87.70 ± 0.15 | n.d. | **15b** | 28.00 ± 0.23 | n.d. |
| **2** | 9.00 ± 0.13 | 42.19 ± 0.23 | **9a** | 23.50 ± 0.17 | n.d. | **15c** | 92.90 ± 0.25 | n.d. |
| **3a** | 32.30 ± 0.18 | n.d. | **9b** | 17.50 ± 0.23 | 15.34 ± 0.19 | **15d** | 44.70 ± 0.23 | n.d. |
| **3b** | 18.70 ± 0.13 | 28.17 ± 0.14 | **10** | 28.40 ± 0.17 | n.d. | **16a** | 24.20 ± 0.17 | n.d. |
| **3c** | 17.90 ± 0.23 | 29.73 ± 0.12 | **11** | 93.60 ± 0.17 | n.d. | **16b** | 17.50 ± 0.22 | 9.56 ± 0.11 |
| **3d** | 3.70 ± 0.11 | 37.84 ± 0.23 | **12a** | 35.00 ± 0.18 | n.d. | **16c** | 7.40 ± 0.20 | 28.97 ± 0.25 |
| **3e** | 1.60 ± 0.20 | 32.50 ± 0.18 | **12b** | 101.70 ± 0.13 | n.d. | **17a** | 43.20 ± 0.12 | n.d. |
| **3f** | 3.80 ± 0.14 | 37.20 ± 0.26 | **13a** | 37.60 ± 0.24 | n.d. | **17b** | 48.90 ± 0.20 | n.d. |
| **4a** | 17.70 ± 0.19 | 47.55 ± 0.11 | **13b** | 96.80 ± 0.25 | n.d. | **18** | 31.80 ± 0.25 | n.d. |
| **4b** | 6.70 ± 0.17 | 25.08 ± 0.13 | **13c** | 21.10 ± 0.21 | n.d. | **19a** | 13.70 ± 0.23 | 18.33 ± 0.23 |
| **4c** | 5.70 ± 0.15 | 31.58 ± 0.18 | **13d** | 36.30 ± 0.25 | n.d. | **19b** | 48.00 ± 0.10 | n.d. |
| **5** | 32.00 ± 0.24 | n.d. | **14a** | 27.50 ± 0.22 | n.d. | **19c** | 26.00 ± 0.21 | n.d. |
| **6** | 27.60 ± 0.19 | n.d. | **14b** | 34.30 ± 0.25 | n.d. | **19d** | 39.00 ± 0.25 | n.d. |
| **7a** | 41.80 ± 0.25 | n.d. | **14c** | 14.80 ± 0.24 | 42.19 ± 0.21 | **19e** | 22.10 ± 0.18 | n.d. |
| **7b** | 55.10 ± 0.23 | n.d. | **15a** | 20.00 ± 0.21 | n.d. | **Vincristine** | 2.00 ± 0.22 | 6.00 ± 0.14 |

n.d.: Not determined.

data bank (code, 1SA0.pdb). Docked structures for 4 selected compounds (**3e**, **3f**, **4c** and **16b**) are shown in Fig. 2. From previous report about the binding mode of antitubulin agents into the cochicine-binding site and from the experimental docking of vincristine, it was noted that the amino acids involved in the interaction were Cys-$\beta$241, Lys-$\beta$254, Asn-$\alpha$101, Thr-*A*179, Tyr-*A*224, Gn-*A*176. Furthermore, the main interaction of certain arylthioindoles bearing an ester moiety at position 2 of the indole included a hydrogen bond between the carbonyl group of the ester function and lysine in the binding site [27–29]. Our target compounds were successfully docked in the colchicine binding pocket of tubulin as referred from the surrounding amino acids. H-bonding interaction with amino acids in the binding pocket was observed for most compounds in addition to hydrophobic interactions. The most common interaction encountered in all docked structures is that between the phenolic OH, which acted as H-bond acceptor, and lys$\beta$254. For instance, compound **3b**, **3c**, **3d**, **3f**, **4b**, **4c** and **9a** formed an H bond with lys$\beta$254 through the phenolic OH. Additional hydrophobic interaction through the 2-phenyl ring of **3b** and **3f** was also observed. Compounds substituted at the phenolic OH **13c**, **14c** and **16b** were also capable of forming this type of interaction since the OH group is not H bond donor but H bond acceptor group. Moreover, other heteroatoms in the side chain could participate in the same interaction as acceptor groups as displayed by the docked compound **16b** and **16c**. On the other hand, the most active compound **3e** showed a hydrogen bond between the indole NH and Asn-$\alpha$101. According to this docking study, the importance of the presence of a free or substituted phenolic OH group on the 2-phenyl ring of the indole core was established. At the same time, it could be concluded that the binding mode of our target compounds in the colchicine binding site of tubulin suggested that they might act through inhibition of tubulin.

## 3. Experimental

### 3.1. Chemistry

Melting points are uncorrected and were recorded by Open Capillary tube method using on Electro-thermal Melting Point apparatus. Infra red spectra (KBr discs) were recorded on Jasco FT/IR 6100 Fourier Transformer spectrophotometer in the Central Services Unit at the National Research Centre (NRC). $^{1}$H NMR spectra were recorded on JEOL EX-270 spectrometer at 500 MHz and $^{13}$C NMR at 125 MHz in the Central Services Unit at the (NRC). Chemical shifts values ($\delta$) are given in parts per million. Mass spectra were recorded on GC/MS FINNIGAN MAT SSQ 7000 digital DEC 3000 and JEOL JMS-AX 500 mass spectrometers at in the Central Services Unit at the (NRC) as well as GC/MS Shimadzu QP-2010 plus mass spectrometer at the Microanalytical Centre-Cairo University. Elemental analyses were performed on Vario El Elementar in the MicroAnalytical Unit of the Central Services Unit at the (NRC).

#### 3.1.1. 2-(4-Hydroxyphenyl)-1H-indole-3-carboxaldehyde **2**

Phosphorous oxychloride (11 ml, 72.40 mmol) was added dropwise to dimethylformamide (DMF) (10 ml) while cooling in an ice bath and the reaction mixture was stirred for 1 h. A solution of compound **1** (5 g, 2.40 mmol) in (DMF) (5.25 ml, 72 mmol) was added dropwise to the formylating mixture with continuous stirring and kept at room temperature for 2 h. The mixture was then poured onto ice cold water and neutralized with dilute ammonia solution whereby; the formed precipitate was collected by vacuum filtration and crystallized from absolute ethanol to give greenish brown crystals, 90% yield, m.p. 160 °C. IR: $\nu_{max}$/cm$^{-1}$ 3400–3155 (OH, NH stretching); 3063 (CH aromatic); 1696 (C=O); 1580 (C=C).

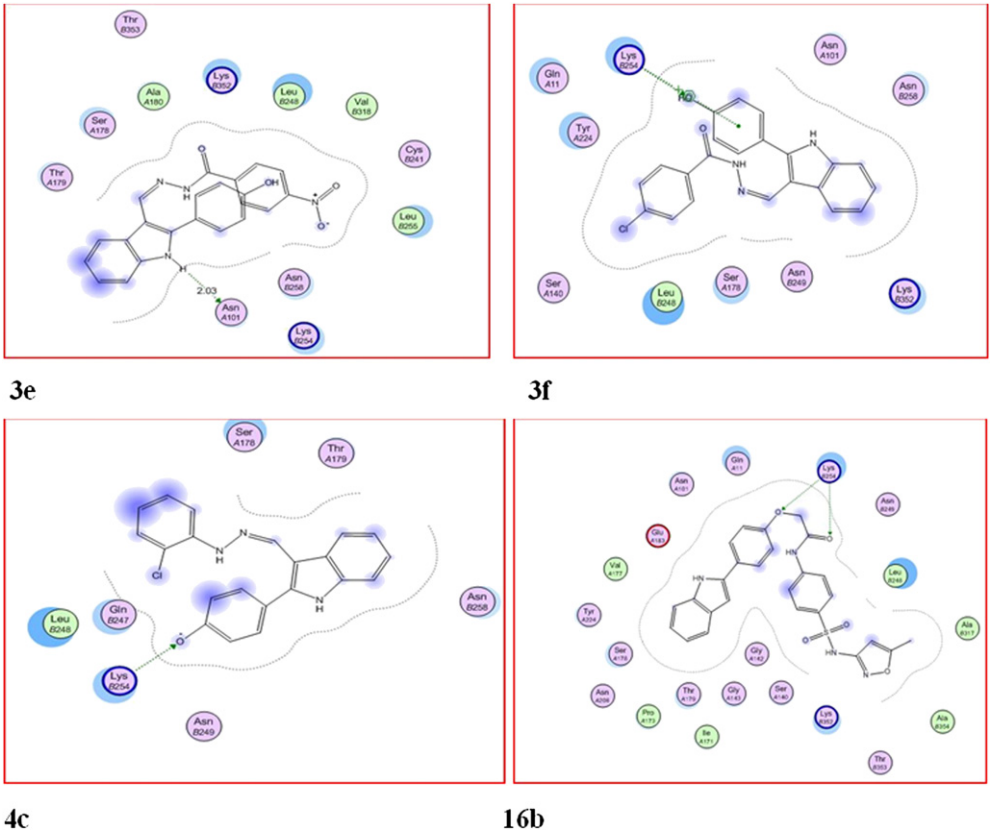



**Fig. 2.** Simplified structures of compounds **3e**, **3f**, **4c** and **16b** docked in the colchicine binding site of tubulin.

$^1$H NMR (DMSO-$d_6$,): $\delta$ 6.96–6.99 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.18–7.28 (m, 2H, indole proton); 7.45–7.48 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.59–7.62 (d, $J$ = 8.10 Hz, 1H, indole proton); 8.16–8.19 (d, $J$ = 8.10 Hz, 1H, indole proton); 8.35 (br s, 1H, OH exchanged by $D_2O$); 9.94 (s, 1H, CHO); 12.21 (s, 1H, NH exchanged by $D_2O$). MS: $m/z$ (%): 237 ($M^+$, 100%). Anal. calcd. for $C_{15}H_{11}NO_2$ (237.25): C, 75.94; H, 4.67; N, 5.90. Found: C, 75.90; H, 4.61; N, 5.71.

*3.1.2. General procedure for the preparation of **3a–f***

Compound **2** (1 g, 4.22 mmol) and the carboxylic acid hydrazide derivative (5.10 mmol) were refluxed for 2 h in absolute ethanol (20 ml) in the presence of 2–3 drops of glacial acetic acid. Cold water was then added to the hot mixture and the formed precipitate, was filtered and crystallized from the appropriate solvent.

*3.1.2.1. N′-{[2-(4-Hydroxyphenyl)-1H-indol-3-yl]methylene} acetohydrazide **3a**.* Brown solid, 70% yield, m.p. 240 °C (absolute ethanol). IR: $\nu_{max}$/cm$^{-1}$ 3393 (OH stretching); 3200 (NH stretching); 3064 (CH aromatic); 2922 (CH aliphatic); 1641(C=O); 1608 (C=N); 1554 (C=C).$^1$H NMR (DMSO-$d_6$,): $\delta$ 2.24 (s, 3H, =N–CH$_3$); 6.95–7.10 (m, 2H, aromatic protons); 7.15–7.18 (d, $J$ = 8.10 Hz, 2H, indole protons); 7.42–7.45 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 8.16–8.18 (d, $J$ = 5.40 Hz, 1H, indole proton); 8.28 (s, 1H, CH=N); 8.37 (m, 1H, indole proton); 10.82 (s, 1H, OH exchanged by $D_2O$); 11.00 (s, 1H, NH exchanged by $D_2O$); 11.64 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{17}H_{15}N_3O_2$ (293.32): C, 69.61; H, 5.15; N, 14.33. Found: C, 69.58; H, 4.85; N, 14.01.

*3.1.2.2. N′-{[2-(4-Hydroxyphenyl)-1H-indol-3-yl] methylene} benzohydrazide **3b**.* White solid, 65% yield, m.p. 135–137 °C (pet.ether 60–80 °C). IR: $\nu_{max}$/cm$^{-1}$ 3431–3110 (OH, NH stretching); 3051 (CH aromatic); 1644 (C=O); 1610 (C=N); 1576 (C=C). $^1$H NMR (DMSO-$d_6$): $\delta$ 4.31 (s, 1H, OH exchanged by $D_2O$); 6.76 (m, 2H, aromatic protons); 7.02 (m, 2H, indole protons); 7.36 (m, 2H, aromatic protons); 7.48 (m, 3H, aromatics and indole proton); 7.78–7.90 (m, 3H, aromatic and indole proton); 8.55 (s, 1H, OH exchanged by $D_2O$); 8.88 (s, 1H, CH=N); 10.82 (s, 1H, NH exchanged by $D_2O$); 11.82 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{22}H_{17}N_3O_2$ (355.39): C, 74.35; H, 4.82; N, 11.82. Found: C, 74.62; H, 4.89; N, 11.51.

*3.1.2.3. 2-Amino-N′-{[2-(4-hydroxyphenyl)-1H-indol-3-yl]methylene} benzohydrazide **3c**.* White solid, 75% yield, m.p. >300 °C (absolute ethanol). IR: $\nu_{max}$/cm$^{-1}$ 3396–3231 (NH$_2$, OH, NH stretching); 3057 (CH aromatic); 1643 (C=O); 1603 (C=N); 1585 (C=C). $^1$H NMR (DMSO-$d_6$): $\delta$ 4.1 (s, 2H, NH$_2$ exchanged by $D_2O$); 6.8–7.02 (m, 6H, aromatic and indole protons); 7.16 (m, 1H, aromatic proton); 7.41 (m, 2H, aromatic protons); 7.50–7.53 (m, 2H, aromatic and indole protons); 8.37 (m, 1H, indole proton); 8.55 (s, 1H, OH exchanged by $D_2O$); 8.88 (s, 1H, CH=N); 10.82 (s, 1H, NH exchanged by $D_2O$); 11.82 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{22}H_{18}N_4O_2$ (370.40): C, 71.34; H, 4.90; N, 15.13. Found: C, 71.20; H, 4.98; N, 14.89.

*3.1.2.4. 4-Amino-N′-{[2-(4-hydroxyphenyl)-1H-indol-3-yl]methylene} benzohydrazide **3d**.* Brown solid, 80% yield, m.p. >300 °C (pet.ether 60–80 °C). IR: $\nu_{max}$/cm$^{-1}$ 3386–3149 (NH$_2$, OH, NH stretching); 3050 (CH aromatic); 1642 (C=O); 1600 (C=N); 1596 (C=C). $^1$H NMR (DMSO-$d_6$): $\delta$ 4.10 (s, 2H, NH$_2$ exchanged by $D_2O$); 6.96–6.98 (m, 4H, aromatic protons); 7.16 (m, 2H, indole protons); 7.47 (m, 2H, aromatic protons); 7.49–7.60 (m, 3H, aromatic and indole protons); 8.15 (s, 1H, OH); 8.31–8.33 (m, 1H, indole proton); 8.84 (s, 1H, CH=N); 10.20 (s, 1H, NH=N exchanged by $D_2O$); 11.77 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{22}H_{18}N_4O_2$ (370.40): C, 71.34; H, 4.90; N, 15.13. Found: C, 71.05; H, 5.03; N, 15.36.

*3.1.2.5. N′-{[2-(4-Hydroxyphenyl)-1H-indol-3-yl]methylene}-4-nitrobenzohydrazide **3e**.* Compound **3e** was prepared from **2** and *p*-nitrobenzoic acid hydrazide and crystallized from petroleum ether (60–80 °C). Orange solid, 83% yield, m.p. 220 °C. IR: $\nu_{max}$/cm$^{-1}$ 3385–3172 (OH, NH stretching); 3055 (CH aromatic); 1645(C=O); 1602 (C=N); 1582 (C=C); 1491, 1339 (NO$_2$). $^1$H NMR (DMSO-$d_6$): $\delta$ 7.01 (m, 2H, aromatic protons); 7.16–7.19 (d, $J$ = 8.10 Hz, 2H, indole protons); 7.42 (m, 2H, aromatic protons); 7.50–7.53 (m, 1H, indole proton); 8.17 (m, 2H, aromatic protons); 8.34–8.37 (m, 2H, aromatic protons); 8.60 (br s, 1H, OH exchanged by $D_2O$); 8.86–8.89 (m, 2H, indole proton and CH=N); 9.05 (s, 1H, NH=N exchanged by $D_2O$); 11.80 (s, 1H, NH exchanged by $D_2O$). MS: $m/z$ (%): 400 ($M^+$, 20.91%), 209 (100%). Anal. calcd. for $C_{22}H_{16}N_4O_4$ (400.39): C, 66.00; H, 4.03; N, 13.99. Found: C, 66.36; H, 4.43; N, 14.25.

*3.1.2.6. 4-Chloro-N′-{[2-(4-hydroxyphenyl)-1H-indol-3-yl]methylene} benzohydrazide **3f**.* Compound **3f** was prepared from **2** and *p*-chlorobenzoic acid hydrazide. Yellow solid, 76% yield, m.p. 275 °C (absolute ethanol). IR: $\nu_{max}$/cm$^{-1}$ 3392–3151 (OH, NH stretching); 3056 (CH aromatic); 1642 (C=O); 1604 (C=N); 1570 (C=C); 670 (C–Cl). $^1$H NMR (DMSO-$d_6$): $\delta$ 6.92–6.94 (d, $J$ = 10 Hz, 2H, aromatic protons); 7.17–7.33 (m, 2H, indole protons); 7.41–7.43 (d, $J$ = 10 Hz, 2H, aromatic protons); 7.55–7.57 (d, $J$ = 10 Hz, 2H, aromatic protons); 7.76 (m, 1H, indole proton); 8.10–8.20 (m, 3H, aromatic protons and CH=N); 8.12–8.14 (d, $J$ = 10 Hz, 1H, indole proton); 10.01 (s, 1H, OH exchanged by $D_2O$); 10.15 (s, 1H, NH=N exchanged by $D_2O$); 12.16 (s, 1H, NH exchanged by $D_2O$). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 107.22 (indole carbon); 111.22 (indole carbon); 115.78 (aromatic carbons); 120.68 (aromatic carbon); 121.62 (indole carbon); 122.29 (indole carbons); 122.49 (indole carbon); 125.93 (aromatic carbons); 130.62 (aromatic carbons); 136.21 (aromatic carbon); 143.78 (CH=N); 155.00 (C–NH$_2$); 158.34 (C–OH); 168.0 5 (C=O).MS: $m/z$ (%): 389 ($M^+$, 12%), 57(100%). Anal. calcd. for $C_{22}H_{16}N_3O_2Cl$ (389.83): C, 67.78; H, 4.14; Cl, 9.09; N, 10.7. Found: C, 67.53; H, 4.35; Cl, 9.25; N, 10.56.

*3.1.3. General procedure for the preparation of **4a–d***

Compound **2** (1 g, 4.22 mmol) and the hydrazine derivative (5.10 mmol) were refluxed in absolute ethanol (20 ml) in the presence of 2–3 drops of glacial acetic acid for the appropriate time. Cold water was then added to the hot mixture and the formed precipitate, was filtered and crystallized from petroleum ether (60–80 °C).

*3.1.3.1. 4-{3-[(2-Methylhydrazono)methyl]-1H-indol-2-yl} phenol **4a**.* Compound **4a** was prepared from **2** and methylhydrazine for 2 h. Brown solid, 68% yield, m.p. 135 °C. IR: $\nu_{max}$/cm$^{-1}$ 3395 (OH stretching); 3250 (NH stretching); 3057 (CH aromatic); 2920 (CH aliphatic); 1606 (C=N); 1590 (C=C). $^1$H NMR (DMSO-$d_6$): $\delta$ 3.29 (s, 3H, CH$_3$); 6.71(m, 2H, aromatic protons); 6.93 (m, 1H, indole proton); 7.19 (m, 1H, indole proton); 7.40–7.41 (m, 2H, aromatic protons); 7.56 (m, 1H, indole proton); 8.12 (s, 1H, CH=N); 8.35 (m, 1H, indole proton); 9.80 (s, 1H, OH exchanged by $D_2O$); 10.20 (s, 1H, NH–CH$_3$ exchanged by $D_2O$); 12.15 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{16}H_{15}N_3O$ (265.31): C, 72.43; H, 5.70; N, 15.84. Found: C, 72.21; H, 5.88; N, 15.74.

*3.1.3.2. 4-{3-[(2-Phenylhydrazono)methyl]-1H-indol-2-yl}phenol **4b**.* Compound **4b** was prepared from **2** and phenyl hydrazine for 4 h. Dark brown solid, 80% yield, m.p. 110 °C. IR: $\nu_{max}$/cm$^{-1}$ 3393 (OH stretching); 3256 (NH stretching); 3053 (CH aromatic); 1599 (C=N); 1588–1589. (C=C). $^1$H NMR (DMSO-$d_6$): $\delta$ 6.64–6.66 (m, 1H, aromatic proton); 6.68–6.87 (m, 2H, aromatic protons); 6.93–6.96

(m, 2H, indole protons); 6.99–7.35 (m, 2H, aromatic protons); 7.17–7.35 (m, 4H, aromatic protons); 7.44–7.47 (m, 1H, indole proton); 8.20 (s, 1H, CH=N); 8.31 (m, 1H, indole proton); 9.86 (s, 1H, OH exchanged by $D_2O$); 11.44 (s, 2H, NH=N, NH exchanged by $D_2O$). Anal. calcd. for $C_{21}H_{17}N_3O$ (327.38): C, 77.04; H, 5.23; N, 13.84. Found: C, 77.19; H, 5.01; N, 13.56.

*3.1.3.3. 4-{3-[(2-(2-Chlorophenyl) hydrazono) methyl]-1H-indol-2-yl} phenol **4c**.* Compound **4c** was prepared from **2** and o-chlorophenyl hydrazine for 5 h. Light brown solid, 77% yield, m.p. 120–122 °C. IR: $\nu_{max}/cm^{-1}$ 3355 (OH, NH stretching); 3055 (CH aromatic); 1597 (C=N); 1565 (C=C); 593 (C–Cl). $^1H$ NMR (DMSO-$d_6$): $\delta$ 4.42 (s, 1H, NH=N exchanged by $D_2O$); 6.74–6.77 (m, 2H, aromatic protons); 6.80 (m, 2H, aromatic protons); 7.00–7.03 (m, 2H, indole protons); 7.22–7.25 (d, $J = 8.10$ Hz, 1H, aromatic proton); 7.44–7.46 (m, 1H, aromatic proton); 7.54–7.57 (d, $J = 8.10$ Hz, 2H, aromatic protons); 7.59–7.62 (d, $J = 8.10$ Hz, 1H, indole proton); 8.38–8.39 (m, 1H, indole proton); 8.67 (s, 1H, CH=N); 9.58 (s, 1H, OH exchanged by $D_2O$); 11.57 (s, 1H, NH exchanged by $D_2O$). MS: *m/z* (%): 361 ($M^+$, 100%); 362 ($M^+ + 1$, 27.65%). Anal. calcd. for $C_{21}H_{16}ClN_3O$ (361.82): C, 69.71; H, 4.46; Cl, 9.80; N, 11.61. Found: C, 69.32; H, 4.22; Cl, 9.78; N, 11.25.

### *3.1.4. 2-{[2-(4-Hydroxyphenyl)-1H-indol-3-yl]methylene} hydrazinecarbothioamide **5***

Compound **2** (1 g, 4.22 mmol) and thiosemicarbazide (0.5 g, 5.50 mmol) were refluxed in absolute ethanol (20 ml) in the presence of 2–3 drops of glacial acetic acid for 2 h. Cold water was then added to the hot mixture and the precipitate was filtered and crystallized from absolute ethanol. Off white solid, 73% yield, m.p. 233–235 °C. IR: $\nu_{max}/cm^{-1}$ 3393–3251 ( $NH_2$, OH, NH stretching); 3131 (NH=N stretching); 3037 (CH aromatic); 1591 (C=N); 1588 (C=C); 1268 (C=S). $^1H$ NMR (DMSO-$d_6$): $\delta$ 6.94–6.97 (d, $J = 8.10$ Hz, 2H, aromatic protons); 7.13–7.20 (m, 2H, indole protons); 7.35–7.38 (m, 1H, indole proton); 7.45–7.48 (d, $J = 8.10$ Hz, 2H, aromatic protons); 8.04 (s, 2H, $NH_2$ exchanged by $D_2O$); 8.27–8.30 (d, $J = 8.10$ Hz, 1H, indole proton); 8.46 (s, 1H, CH=N); 9.91 (s, 1H, OH exchanged by $D_2O$); 11.14 (s, 1H, NH=N exchanged by $D_2O$); 11.73 (s, 1H, NH exchanged by $D_2O$). MS: *m/z* (%): 310 ($M^+$, 0.44%); 312 ($M^+ + 2$, 1.85%); 209 (100%). Anal. calcd. for $C_{16}H_{14}N_4OS$ (310.37): C, 61.92; H, 4.55; N, 18.05; S, 10.33. Found: C, 61.87; H, 4.78; N, 18.17; S, 10.25.

### *3.1.5. 2-(4-Hydroxyphenyl)-1H-indole-3-carboxaldehyde oxime **6***

Compound **2** (1 g, 4.22 mmol) and the hydroxylamine hydrochloride (1 g, 14.50 mmol) were refluxed in absolute ethanol (20 ml) in the presence of 3 ml pyridine for 10 h. The mixture was then poured onto cold water. The obtained light brown precipitate was collected by filtration and crystallized from petroleum ether (60–80 °C). 90% yield, m.p. 228–230 °C. IR: $\nu_{max}/cm^{-1}$ 3410 (OH stretching); 3289 (NH stretching); 3059 (CH aromatic); 1611 (C=N); 1597 (C=C). $^1H$ NMR (DMSO-$d_6$): $\delta$ 6.94–6.97 (d, $J = 8.10$ Hz, 2H, aromatic protons); 7.03–7.13 (m, 2H, indole protons); 7.14–7.43 (m, 3H, aromatic and indole protons); 8.03–8.06 (d, $J = 8.10$ Hz, 1H, indole proton); 8.23 (s, 1H, CH=N); 10.59 (s, 1H, OH exchanged by $D_2O$); 11.30 ( br s, 1H, OH exchanged by $D_2O$); 11.59 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{15}H_{12}N_2O_2$ (252.27): C, 71.42; H, 4.79; N, 11.10. Found: C, 71.22; H, 4.57; N, 11.26.

### *3.1.6. General procedure for the preparation of **7a**–**b***

Compound **2** (1 g, 4.22 mmol) and barbituric or thiobarbituric acid (4.22 mmol) were refluxed in absolute ethanol (30 ml) in the presence of 2–3 drops piperidine for 2 h. The mixture was then poured onto cold water and the precipitate was filtered and crystallized from petroleum ether (60–80 °C).

*3.1.6.1. 5-{[2-(4-Hydroxyphenyl)-1H-indol-3-yl] methylene} pyrimidine-2,4,6 (1H,3H,5H)-trione **7a**.* Compound **7a** was prepared from **2** and barbituric acid. Brown solid, 85% yield, m.p. 175 °C. IR: $\nu_{max}/cm^{-1}$ 3419 (OH stretching); 3370–3157 (NH stretching); 3050 (CH aromatic); 2950 (CH aliphatic); 1684 (C=O); 1612 (C=N); 1582 (C=C). $^1H$ NMR (DMSO-$d_6$): $\delta$ 6.97 (m, 2H, aromatic protons); 7.13 (m, 2H, indole protons); 7.22 (m, 1H, indole proton); 7.40 (m, 2H, aromatic protons); 7.95 (m, 1H, indole proton); 8.13 (s, 1H, CH=C); 8.72 (s, 2H, NH pyrimidine exchanged by $D_2O$); 9.43 (s, 1H, OH exchanged by $D_2O$); 10.92 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{19}H_{13}N_3O_4$ (347.32): C, 65.70; H, 3.77; N, 12.10. Found: C, 65.79; H, 3.64; N, 12.31.

*3.1.6.2. 5-{[2-(4-Hydroxyphenyl)-1H-indol-3-yl]methylene}-2-thioxodihydropyrimidine-4,6 (1H,5H)-dione **7b**.* Compound **7b** was prepared from **2** and thiobarbituric acid. Green solid, 73% yield, m.p. 210 °C. IR: $\nu_{max}/cm^{-1}$ 3417 (OH stretching); 3371–3123 (NH stretching); 3049 (CH aromatic); 2950 (CH aliphatic); 1652 (C=O); 1611 (C=N); 1572 (C=C); 1253 (C=S). $^1H$ NMR (DMSO-$d_6$): $\delta$ 6.98 (m, 2H, aromatic protons); 7.13–7.16 (d, $J = 8.1$ Hz, 2H, indole protons); 7.23–7.25 (m, 1H, indole proton); 7.53–7.56 (d, $J = 8.10$ Hz, 2H, aromatic protons); 7.63–7.66 (d, $J = 8.10$ Hz, 1H, indole proton); 7.78 (s, 1H, CH=C); 9.92 (s, 1H, OH exchanged by $D_2O$); 11.62 (s, 1H, NH exchanged by $D_2O$); 12.51 (br s, 2H, NH exchanged by $D_2O$). MS: *m/z* (%): 364 ($M^+ + 1$, 1.50%); 365 ($M^+ + 2$, 1.65%); 209 (100%). Anal. calcd. For $C_{19}H_{13}N_3O_3S$ (363.39): C, 62.80; H, 3.61; N, 11.50; S, 8.82. Found: C, 62.65; H, 3.95; N, 11.78; S, 8.59.

### *3.1.7. 2-{[2-(4-Hydroxyphenyl)-1H-indol-3-yl] methylene} propanedinitrile **8***

Compound **2** (1 g, 4.22 mmol) and malononitrile (0.4 g, 5.10 mmol) were refluxed in absolute ethanol (30 ml) in the presence of 2–3 drops piperidine for 2 h. The mixture was then poured onto cold water and the precipitate was collected and crystallized from petroleum ether (60–80 °C). Dark brown, 46% yield, m.p. 150–152 °C. IR: $\nu_{max}/cm^{-1}$ 3453 (OH stretching); 3266 (NH stretching); 3055 (CH aromatic); 2214 (C≡N); 1553 (C=C). $^1H$ NMR (DMSO-$d_6$): $\delta$ 6.97–7.05 (d, $J = 8.10$ Hz, 2H, aromatic protons); 7.24–7.33 (m, 2H, indole protons); 7.50–7.70 (m, 3H, indole and aromatic protons); 7.93 (s, 1H, CH=C vinyl); 8.05–8.08 (d, $J = 8.10$ Hz, 1H, indole proton); 12.22 (s, 1H, OH exchanged by $D_2O$); 12.89 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{18}H_{11}N_3O$ (285.30): C, 75.78; H, 3.89; N, 14.73. Found: C, 75.54; H, 3.75; N, 14.96.

### *3.1.8. General procedure for the preparation of **9a**,**b***

Compound **2** (1 g, 4.22 mmol) and the appropriate aniline derivative (6.33 mmol) were refluxed in absolute ethanol (30 ml) at 70 °C for 7 h. The reaction mixture was then poured onto water and the precipitate was filtered, collected and crystallized from petroleum ether (60–80 °C).

*3.1.8.1. 2-{[2-(4-Hydroxyphenyl)-1H-indol-3-yl]}-1H-benzo[d] imidazole **9a**.* Compound **9a** was prepared from **2** and *o*-phenylenediamine. Orange solid, 80% yield, m.p. 200 °C (dec.). IR: $\nu_{max}/cm^{-1}$ 3374–3155 (OH, NH stretching); 3057 (CH aromatic); 1611 (C=N); 1561 (C=C). $^1H$ NMR (DMSO-$d_6$): $\delta$ 6.81–6.84 (d, $J = 8.10$ Hz, 2H, aromatic protons); 6.90–6.93 (d, $J = 8.10$ Hz, 2H, indole protons); 7.12–7.19 (m, 2H, aromatic protons); 7.44–7.47 (d, $J = 8.10$ Hz, 2H, aromatic protons); 7.55–7.61 (m, 2H, aromatic protons); 7.82–7.84 (d, $J = 5.40$ Hz, 1H, indole proton); 8.14–8.17 (d, $J = 8.10$ Hz, 1H, indole proton); 9.81 (s, 1H, OH exchanged by $D_2O$); 11.81 (s, 1H, NH

exchanged by $D_2O$); 12.21 (s, 1H, NH exchanged by $D_2O$). MS: *m*/*z* (%):325 ($M^+$, 19.20%); 209 (100%). Anal. calcd. for $C_{21}H_{15}N_3O$ (325.36): C, 77.52; H, 4.65; N, 12.91. Found: C, 77.31; H, 4.42; N, 12.88.

*3.1.8.2. 2-{[2-(4-Hydroxyphenyl)-1H-indol-3-yl]}-1H-benzo[d] oxazole* ***9b***. Compound **9b** was prepared from **2** and *o*-aminophenol. Brown solid, 75% yield, m.p. 210 °C. IR: $\nu_{max}/cm^{-1}$ 3363–3184 (OH, NH stretching); 3055 (CH aromatic); 1608 (C=N); 1572 (C=C). $^1H$ NMR (DMSO-$d_6$,): $\delta$ 6.90–7.00 (m, 2H, phenyl protons); 6.19 (m, 2H, indole protons); 7.23 (m, 2H, phenyl protons); 7.38 (m, 2H, benzoxazole protons); 7.46 (m, 1H, indole proton); 7.60 (m, 2H, benzoxazole protons); 8.16 (m, 1H, indole proton); 10.08 (s, 1H, OH exchanged by $D_2O$); 12.23 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{21}H_{14}N_2O_2$ (326.35): C, 77.29; H, 4.32; N, 11.58. Found: C, 77.44; H, 4.15; N, 11.36.

*3.1.9. 2-{[2-(4-Hydroxyphenyl)-1H-indol-3-yl]}-1H-imidazole* ***10***

Compound **10** was prepared from **2** (1 g, 4.22 mmol) and ethylenediamine (0.40 g, 6.67 mmol) according to the procedure used for the preparation of **9a**,**b**. The precipitate was filtered and crystallized from petroleum ether (60–80 °C). Green solid, 82% yield, m.p. 195–196 °C. IR: $\nu_{max}/cm^{-1}$ 3390–3183 (OH, NH stretching); 3061 (CH aromatic); 1611 (C=N); 1596 (C=C). $^1H$ NMR (DMSO-$d_6$): $\delta$ 6.90 (m, 2H, phenyl protons); 6.95–6.98 (d, $J$ = 8.10 Hz, 2H, indole protons); 7.07 (m, 2H, imidazole protons); 7.44 (m, 2H, phenyl protons); 7.58–7.61 (m, 1H, indole proton); 8.17 (m, 1H, indole proton); 8.31 (s, 1H, OH exchanged by $D_2O$); 8.40 (br s, 1H, NH exchanged by $D_2O$); 11.43 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{17}H_{13}N_3O$ (275.30): C, 74.17; H, 4.76; N, 15.26. Found: C, 74.41; H, 4.55; N, 15.41.

*3.1.10. 4-(1H-Indol-2-yl) phenyl methyl carbonate* ***11***

Compound **1** (2 g, 9.60 mmol) and methyl chloroformate (0.90 ml, 9.60 mmol) were refluxed in the presence of anhydrous potassium carbonate (3 g, 14.50 mmol) in dry acetone (100 ml) for 10 h. The mixture was then cooled, filtered and the filtrate was poured onto crushed ice. The buff precipitate formed was collected by filtration and crystallized from absolute ethanol. 68% yield, m.p. 180 °C. IR: $\nu_{max}/cm^{-1}$ 3388–3362 ($NH_2$, NH stretching); 3051 (CH aromatic); 2915 (CH aliphatic); 1741 (C=O) ester; 1552 (C=C). $^1H$ NMR (DMSO-$d_6$): $\delta$ 4.02 (s, 3H, $CH_3$); 6.87 (s, 1H, indole proton); 7.20–7.35 (m, 4H, indole and aromatic protons); 7.47–7.50 (d, $J$ = 8.10 Hz, 1H, indole proton); 7.75–7.78 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.69–7.72 (d, $J$ = 8.10 Hz, 1H, indole proton); 8.78 (s, 1H, NH exchanged by $D_2O$). MS: *m*/*z* (%): 267 ($M^+$, 100%). Anal. calcd. for $C_{16}H_{13}NO_3$ (267.28): C, 71.90; H, 4.90; N, 5.24. Found: C, 71.74; H, 4.62; N, 5.33.

*3.1.11. General procedure for the preparation of* ***12a**,**b***

Compound **1** (2 g, 9.60 mmol) and alkyl bromoacetate (9.60 mmol) were treated similarly as in the experimental procedure adopted for the synthesis of **11**. The obtained solid was crystallized from absolute ethanol.

*3.1.11.1. Methyl 2-[4-(1H-indol-2-yl)phenoxy]acetate* ***12a***. Compound **12a** was prepared from **1** and methyl bromoacetate. Buff solid, 80% yield, m.p. 170 °C. IR: $\nu_{max}/cm^{-1}$ 3433 (NH stretching); 3056 (CH aromatic); 2922–2854 (CH aliphatic); 1758 (C=O) ester; 1520 (C=C). $^1H$ NMR (DMSO-$d_6$): $\delta$ 3.51 (s, 3H, $CH_3$); 4.37 (s, 2H, O–$CH_2$); 6.40 (s, 1H, indole proton); 6.64–6.68 (d, $J$ = 8.10 Hz, 2H, indole protons); 6.76–6.88 (m, 2H, aromatic protons); 6.87–6.95 (m, 1H, indole proton); 7.05–7.08 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.28–7.31 (d, $J$ = 8.10 Hz, 1H, indole proton); 8.26 (s, 1H, NH exchanged by $D_2O$). MS: *m*/*z* (%):281 ($M^+$, 100%). Anal. calcd. for $C_{17}H_{15}NO_3$ (281.31): C, 72.58; H, 5.37; N, 4.98. Found: C, 72.76; H, 5.19; N, 4.76.

*3.1.11.2. Ethyl 2-[4-(1H-indol-2-yl)phenoxy]acetate* ***12b*** *[22,23].* Compound **12b** was prepared from **1** and ethyl bromoacetate. Buff solid, 75% yield, m.p. 150 °C. IR: $\nu_{max}/cm^{-1}$ 3392 (NH stretching); 3048 (CH aromatic); 2922–2853 (CH aliphatic); 1732 (C=O) ester; 1576 (C=N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 1.34 (t, 3H, $CH_2$–$\underline{CH_3}$); 4.36 (q, 2H, $\underline{CH_2}$–$CH_3$); 4.75 (s, 2H, O–$CH_2$); 6.80 (s, 1H, indole proton); 7.05–7.07 (d, $J$ = 5.40 Hz, 2H, indole protons); 7.18–7.21 (m, 2H, aromatic protons); 7.21–7.35 (m, 1H, indole proton); 7.46–7.48 (d, $J$ = 5.40 Hz, 2H, aromatic protons); 7.67–7.70 (d, $J$ = 8.10 Hz, 1H, indole proton); 8.65 (s, 1H, NH exchanged by $D_2O$). MS: *m*/*z* (%) 295 ($M^+$, 100). Anal. calcd. for $C_{18}H_{17}NO_3$ (295.33): C, 73.20; H, 5.80; N, 4.74. Found: C, 73.34; H, 5.99; N, 4.88.

*3.1.12. General procedure for the preparation of* ***13a–d***

Compound **12a** (1 g, 3.56 mmol) and the appropriate primary amine (3.56 mmol) were refluxed in absolute ethanol (50 ml) for 8 h. The reaction mixture was then cooled, the formed precipitate was filtered and crystallized from absolute ethanol.

*3.1.12.1. 2-[4-(1H-Indol-2-yl) phenoxy] acetamide* ***13a***. Compound **13a** was prepared from **12a** and ammonia solution. White solid, 80% yield, m.p. 210 °C. IR: $\nu_{max}/cm^{-1}$ 3422–3165($NH_2$, NH stretching); 3049 (CH aromatic); 2921 (CH aliphatic); 1670 (C=O amidic); 1540 (C=C). $^1H$ NMR (DMSO-$d_6$): $\delta$ 4.46 (s, 2H, O–$CH_2$); 6.76 (s, 1H, indole proton); 6.92–6.95 (m, 2H, indole protons); 6.97–7.03 (m, 2H, aromatic protons); 7.20 (s, 2H, $NH_2$ exchanged by $D_2O$); 7.35–7.45 (m, 1H, indole proton); 7.48–7.56 (m, 2H, aromatic protons); 7.78 (m, 1H, indole proton); 11.41 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{16}H_{14}N_2O_2$ (266.29): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.34; H, 5.44; N, 10.34.

*3.1.12.2. 2-[4-(1H-Indol-2-yl) phenoxy]-N-(2-hydroxyethyl) acetamide* ***13b***. Compound **13b** was prepared from **12a** and ethanolamine for 8 h. Green solid, 90% yield, m.p. 163 °C. IR: $\nu_{max}/cm^{-1}$ 3430 (OH stretching); 3340–3231 (NH stretching); 3056 (CH aromatic); 2923 (CH aliphatic); 1651(C=O amidic); 1589 (C=C). $^1H$ NMR (DMSO-$d_6$): $\delta$ 3.23 (m, 2H, N–$CH_2$); 3.43 (m, 2H, $\underline{CH_2}$–OH); 4.52 (s, 2H, O–$CH_2$); 4.75 (s, 1H, OH exchanged by $D_2O$); 6.76 (s, 1H, indole proton); 6.93–6.96 (d, $J$ = 8.10 Hz, 2H, indole protons); 7.03–7.06 (m, 2H, aromatic protons); 7.34–7.37 (d, $J$ = 8.10 Hz, 1H, indole proton); 7.46–7.49 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.78–7.80 (d, $J$ = 5.40 Hz, 1H, indole proton); 8.06 (s, 1H, NH–CO exchanged by $D_2O$); 11.43 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{18}H_{18}N_2O_3$ (310.35): C, 69.66; H, 5.85; N, 9.03. Found: C, 69.79; H, 5.68; N, 8.78.

*3.1.12.3. 2-[4-(1H-Indol-2-yl) phenoxy]-N-(pyridin-4-yl) acetamide* ***13c***. Compound **13c** was prepared from **12a** and *p*-aminopyridine. Green solid 85% yield, m.p. 198–200 °C. IR: $\nu_{max}/cm^{-1}$ 3422–3251(NH stretching); 2948 (CH aromatic); 2919 (CH aliphatic); 1647(C=O amidic).; 1609 (C=N); 1530 (C=C). $^1H$ NMR (DMSO-$d_6$): $\delta$ 4.60 (s, 2H, O–$CH_2$); 6.80 (s, 1H, indole proton); 6.97–7.00 (d, $J$ = 8.10 Hz, 2H, indole protons); 7.03 (m, 2H, aromatic protons); 7.25 (s, 1H, NH–CO exchanged by $D_2O$); 7.50 (m, 3H, aromatic and indole protons); 7.80 (m, 1H, indole proton); 8.45–8.56 (m, 4H, aromatic protons); 11.45 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{21}H_{17}N_3O_2$ (343.38): C, 73.45; H, 4.99; N, 12.24. Found: C, 73.28; H, 5.23; N, 12.53.

*3.1.12.4. 2-[4-(1H-Indol-2-yl) phenoxy]-N-(pyrazin-2-yl) acetamide* ***13d***. Compound **13d** was prepared from **12a** and 2-aminopyrazine. Green solid, 84 %yield, m.p.100–101 °C. IR: $\nu_{max}/cm^{-1}$ 3428–3250

(NH stretching); 2949 (CH aromatic); 2920 (CH aliphatic); 1649 (C=O amidic); 1612 (C=N); 1551 (C=C).$^1$H NMR (DMSO-$d_6$): $\delta$ 4.68 (s, 2H, O–$CH_2$); 6.36 (s, 1H, NH–CO exchanged by $D_2O$); 6.74 (s, 1H, indole proton); 6.97–7.00 (d, $J$ = 8.10 Hz, 2H, indole protons); 7.05 (m, 2H, aromatic protons); 7.34–7.37 (d, $J$ = 8.10 Hz, 1H, indole proton); 7.46–7.49 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.65 (m, 1H, indole proton); 7.75–7.78 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.85 (s, 1H, aromatic proton); 11.40 (s, 1H, NH exchanged by $D_2O$). MS, $m/z$ (%): 344 ($M^+$, 1.50%). Anal. calcd. for $C_{20}H_{16}N_4O_2$ (344.37): C, 69.76; H, 4.68; N, 16.27. Found: C, 69.59; H, 4.62; N, 16.45.

*3.1.13. General procedure for the preparation of* ***14a–c***

Compound **12a** (1 g, 3.56 mmol) and the appropriate secondary amine (3.56 mmol) were refluxed in absolute ethanol (40 ml) for 5 h. The reaction mixture was cooled and the formed precipitate was filtered and crystallized from the absolute ethanol.

*3.1.13.1. 2-[4-(1H-Indol-2-yl) phenoxy]-N, N-bis (2-hydroxyethyl) acetamide* ***14a***. Compound **14a** was prepared from **12a** and diethanolamine. Greenish white, 96% yield, m.p. 188 °C. IR: $\nu_{max}$/cm$^{-1}$ 3436 (OH stretching); 3358 (NH stretching); 3050 (CH aromatic); 2936 (CH aliphatic); 1644 (C=O amidic); 1497 (C=C).$^1$H NMR (DMSO-$d_6$): $\delta$ 3.37 (m, 4H, 2N–$\underline{CH_2}$–$CH_2$); 3.65 (m, 4H, $2CH_2$–$\underline{CH_2}$–OH); 4.81 (s, 1H, OH exchanged by $D_2O$); 4.93 (s, 2H, O–$CH_2$); 5.10 (s, 1H, OH exchanged by $D_2O$); 6.73 (s, 1H, indole proton); 6.95–6.98 (d, $J$ = 8.10 Hz, 2H, indole protons); 7.01–7.04 (m, 2H, aromatic protons); 7.34–7.37 (d, $J$ = 8.10 Hz, 1H, indole proton); 7.46–7.49 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.71–7.74 (d, $J$ = 8.10 Hz, 1H, indole proton); 11.40 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{20}H_{22}N_2O_4$ (354.40): C, 67.66; H, 6.26; N, 7.90. Found: C, 67.58; H, 6.49; N, 7.63.

*3.1.13.2. 2-[4-(1H-Indol-2-yl) phenoxy]-N, N-dimethylacetamide* ***14b***. Compound **14a** was prepared from **12a** and dimethylamine. Yellowish green solid, 95% yield, m.p. 265–267 °C. IR: $\nu_{max}$/cm$^{-1}$ 3389 (NH stretching); 3053 (CH aromatic); 2921–2853 (CH aliphatic); 1633 (C=O amidic); 1586 (C=C). $^1$H NMR (DMSO-$d_6$): $\delta$ 3.35 (s, 3H, N–$CH_3$); 3.36 (s, 3H, N–$CH_3$); 4.80 (s, 2H, O–$CH_2$); 6.97 (s, 1H, indole proton); 7.17–7.25 (m, 2H, indole protons); 7.30–7.41 (m, 2H, aromatic protons); 7.42–7.47 (m, 1H, indole proton); 7.49–7.55 (m, 2H, aromatic protons); 7.91 (m, 1H, indole proton); 11.50 (s, 1H, NH exchanged by $D_2O$). MS, $m/z$ (%): 394 ($M^+$, 1.48%); 105 (100%). Anal. calcd. for $C_{18}H_{18}N_2O_2$ (394.35): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.22; H, 6.37; N, 9.26.

*3.1.13.3. 2-[4-(1H-Indol-2-yl) phenoxy]-1-(pyrrolidin-1-yl) ethanone* ***14c***. Compound **14c** was prepared from **12a** and pyrrolidine. Green solid, 86% yield, m.p. 190–192 °C. IR: $\nu_{max}$/cm$^{-1}$ 3417 (NH stretching); 3051 (CH aromatic); 2923–2857 (CH aliphatic); 1655 (C=O amidic); 1534 (C=C). $^1$H NMR (DMSO-$d_6$): $\delta$ 1.81 (m, 4H, pyrrolidine protons); 3.07 (m, 4H, pyrrolidine protons); 4.57 (s, 2H, O–$CH_2$); 6.75 (s, 1H, indole proton); 6.75–7.01 (d, $J$ = 8.10 Hz, 2H, indole protons); 7.05 (m, 2H, aromatic protons); 7.35–7.37 (d, $J$ = 5.40 Hz, 1H, indole proton); 7.46–7.49 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.75–7.78 (d, $J$ = 8.10 Hz, 1H, indole proton); 11.41 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{20}H_{20}N_2O_2$ (320.38): C, 74.98; H, 6.29; N, 8.74. Found: C, 75.16; H, 6.46; N, 8.67.

*3.1.14. General procedure for the preparation of* ***15a–d***

Compound **12a** (1 g, 3.56 mmol) and the hydrazide or hydrazine derivative (3.56 mmol) were refluxed in absolute ethanol (30 ml) for 2 h. The reaction mixture was then cooled and the precipitate was filtered and crystallized from the appropriate solvent.

*3.1.14.1. 2-[4-(1H-Indol-2-yl) phenoxy] acetohydrazide* ***15a***. Compound **15a** was prepared from **12a** and methylhydrazine. Buff solid, 93% yield, m.p. 230 °C (absolute ethanol). IR: $\nu_{max}$/cm$^{-1}$ 3435 (NH stretching); 3317 and 3263 (–$NH_2$ stretching); 3049 (CH aromatic); 2921 (CH aliphatic); 1668 (C=O amidic); 1523 (C=C).$^1$H NMR (DMSO-$d_6$): $\delta$ 4.40 (s, 2H, $NH_2$); 4.55 (s, 2H, O–$CH_2$); 6.79 (s, 1H, indole proton); 6.98–7.01 (d, $J$ = 8.10 Hz, 2H, indole protons); 7.04–7.07 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.37–7.39 (d, $J$ = 5.40 Hz, 1H, indole proton); 7.49–7.51 (d, $J$ = 5.40 Hz, 2H, aromatic protons); 7.78–7.82 (d, $J$ = 8.10 Hz, 1H, indole proton); 9.41 (s, 1H, NH exchanged by $D_2O$); 11.44 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{16}H_{15}N_3O_2$ (281.31): C, 68.31; H, 5.37; N, 14.94. Found: C, 68.08; H, 5.59; N, 14.72.

*3.1.14.2. 2-[4-(1H-Indol-2-yl) phenoxy]-N′-phenylacetohydrazide* ***15b***. Compound **15b** was prepared from **12a** and phenyl hydrazine. Brown solid 60% yield, m.p. 200 °C (pet. ether 60–80 °C). IR: $\nu_{max}$/cm$^{-1}$ 3430 (OH stretching); 3340–3231 (NH stretching); 3056 (CH aromatic); 2923 (CH aliphatic); 1651 (C=O amidic); 1510 (C=C). $^1$H NMR (DMSO-$d_6$): $\delta$ 3.71 (s, 1H, N–NH exchanged by $D_2O$); 4.85 (s, 2H, $CH_2$); 6.76 (s, 1H, indole proton); 6.94–7.01 (m, 3H, aromatic and indole protons); 7.03–7.08 (m, 4H, aromatic protons); 7.35–7.38 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.47–7.50 (d, $J$ = 8.10 Hz, 3H, indole and aromatic protons); 7.76–7.79 (d, $J$ = 8.10 Hz, 1H, indole proton); 11.41 (s, 2H, $CH_2$–NH, NH exchanged by $D_2O$). Anal. calcd. for $C_{22}H_{19}N_3O_2$ (357.41): C, 73.93; H, 5.36; N, 11.76. Found: C, 73.74; H, 5.56; N, 11.56.

*3.1.14.3. 2-[4-(1H-Indol-2-yl) phenoxy]-N′-acetylacetohydrazide* ***15c***. Compound **15c** was prepared from **12a** and acetohydrazide. Brown solid, 75% yield, m.p. 140 °C (absolute ethanol). IR: $\nu_{max}$/cm$^{-1}$ 3432 (NH stretching); 3052 (CH aromatic); 2923–2855 (CH aliphatic); 1662 (C=O amidic, acetyl); 1546 (C=C).$^1$H NMR (DMSO-$d_6$): $\delta$ 1.30 (s, 3H, CO–$CH_3$); 4.25 (s, 2H, (NH–NH) exchanged by $D_2O$); 4.88 (s, 2H, O–$CH_2$); 6.82 (s, 1H, indole proton); 7.02 (m, 2H, indole protons); 7.06–7.09 (m, 2H, aromatic protons); 7.41–7.43 (m, 1H, indole proton); 7.53–7.56 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.82–7.85 (d, $J$ = 8.10 Hz, 1H, indole proton); 11.47 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{18}H_{17}N_3O$ (323.35): C, 66.86; H, 5.30; N, 13.00. Found: C, 66.53; H, 5.07; N, 13.39.

*3.1.14.4. 2-{2-[4-(1H-Indol-2-yl) phenoxy] acetyl}hydrazinecarbothioamide* ***15d***. Compound **15d** was prepared from **12a** and thiosemicarbazide. Brown solid, 80% yield, m.p. 118–120 °C (absolute ethanol). IR: $\nu_{max}$/cm$^{-1}$ 3431–3367 (NH, $NH_2$ stretching); 3052 (CH aromatic); 2922 (CH aliphatic); 1669 (C=O amidic); 1558 (C=C); 1212 (C=S).$^1$H NMR (DMSO-$d_6$): $\delta$ 1.19 (s, 2H, NH–NH exchanged by $D_2O$); 4.14 (s, 2H, $NH_2$ exchanged by $D_2O$); 4.80 (s, 2H, O–$CH_2$); 6.73 (s, 1H, indole proton); 6.93–6.98 (m, 2H, indole protons); 7.02–7.05 (m, 2H, aromatic protons); 7.32 (m, 1H, indole proton); 7.45–7.50 (m, 2H, aromatic protons); 7.74 (m, 1H, indole protons); 11.38 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{17}H_{16}N_4O_2S$ (340.40): C, 59.98; H, 4.74; N, 16.46; S, 9.42. Found: C, 59.62; H, 4.57; N, 16.33; S, 9.16.

*3.1.15. General procedure for the preparation of* ***16a–c***

Compound **12a** (1 g, 3.56 mmol) and the appropriate sulfonamide (3.56 mmol) were stirred in dry acetone (50 ml) in the presence of anhydrous potassium carbonate (1 g, 4.83 mmol) for 10 h. The reaction mixture was then filtered while hot. Upon cooling, crystals separated out and were filtered and recrystallized from absolute ethanol.

*3.1.15.1. 2-[4-(1H-Indol-2-yl) phenoxy]-N-(4-sulfamoylphenyl) acetamide* ***16a***. Compound **16a** was prepared from **12a** and

sulfanilamide. Light yellow crystals, 75% yield, m.p. 190 °C. IR: $\nu_{max}$/cm$^{-1}$ 3460–3376 ($NH_2$ stretching); 3246 (–NH stretching); 3052 (CH aromatic); 2923 (CH aliphatic); 1636 (C=O); 1598 (C=N); 1504 (C=C); 1312–1147 ($SO_2$).$^1$H NMR (DMSO-$d_6$): $\delta$ 5.88 (s, 2Hs, O–$CH_2$); 6.61–6.64 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 6.75 (s, 1H, indole proton); 6.95–7.05 (m, 4H, indole protons, aromatic protons); 7.15 (br 2s, 2H, $SO_2$–$NH_2$ exchanged by $D_2O$); 7.48–7.51 (d, $J$ = 8.10 Hz, 3H, indole and aromatic protons); 7.81–7.87 (m, 3H, aromatic and indole protons); 11.40 (s, 2H, NH exchanged by $D_2O$). Anal. calcd. for $C_{22}H_{19}N_3O_4S$ (421.47): C, 62.69; H, 4.54; N, 9.97; S, 7.61. Found: C, 62.49; H, 4.78; N, 10.23; S, 7.69.

*3.1.15.2. 2-[4-(1H-Indol-2-yl) phenoxy]-N-{4-[N-(5-methylisoxazol-3-yl) sulfamoyl] phenyl} acetamide* ***16b***. Compound **16c** was prepared from **12a** and sulfamethoxazole. Gray crystals, 90% yield, m.p. 250–252 °C. IR: $\nu_{max}$/cm$^{-1}$ 3465–3179 (NH stretching); 3051 (CH aromatic); 2921 (CH aliphatic); 1620 (C=O); 1597(C=N); 1547 (C=C); 1363–1148 ($SO_2$).$^1$H NMR (DMSO-$d_6$): $\delta$ 2.21 (s, 3H, $CH_3$); 5.90 (s, 2H, O–$CH_2$); 6.48–6.51 (d, $J$ = 8.1 Hz, 2H, aromatic protons); 6.65 (s, 2H, thiazole and indole protons); 6.95 (m, 4H, indole and aromatic protons); 7.37–7.40 (d, $J$ = 8.1 Hz, 3H, indole and aromatic protons); 7.75 (m, 3H, indole and aromatic protons); 10.25 (s, 1H, NH–$SO_2$ exchanged by $D_2O$); 11.32 (s, 2H, NH exchanged by $D_2O$). MS ($m/z$ %): 502 ($M^+$, 0.03%); 145 (100%). Anal. calcd. for $C_{26}H_{22}N_4O_5S$ (502.54): C, 62.14; H, 4.41; N, 11.15; S, 6.38. Found: C, 62.33; H, 4.79; N, 11.44; S, 6.09.

*3.1.15.3. 2-[4-(1H-Indol-2-yl) phenoxy]-N-[4-(N-thiazol-2-ylsulfamoyl) phenyl] acetamide* ***16c***. Compound **16c** was prepared from **12a** and sulfathiazole. Yellow crystals, 93% yield, m.p. 210 °C. IR: $\nu_{max}$/cm$^{-1}$ 3432–3189 (NH stretching); 3092 (CH aromatic); 2919 (CH aliphatic); 1630 (C=O); 1581 (C=N); 1530 (C=C); 1324–1137 ($SO_2$).$^1$H NMR (DMSO-$d_6$): $\delta$ 5.78 (s, 2H, O–$CH_2$); 6.48–6.50 (m, 2H, aromatic protons); 6.67–6.69 (m, 2H, indole and thiazole protons); 6.95 (m, 4H, indole and aromatic protons); 7.12–7.14 (m, 1H, thiazole proton); 7.36–7.39 (m, 3H, indole and aromatic protons); 7.71 (m, 3H, indole and aromatic protons); 10.50 (s, 1H, NH–$SO_2$ exchanged by $D_2O$); 11.35 (s, 2H, NH indole, NH–CO exchanged by $D_2O$). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 62.50 (O–$CH_2$); 107.45 (indole carbon); 112.43 (indole and aromatic carbons); 124.50 (indole and thiazole carbons); 127.78 (indole, thiazole and aromatic carbons); 152.24 (aromatic and thiazole carbons); 168.50 (C=O). MS ($m/z$ %): 504 ($M^+$, 1.78%). Anal. calcd. for $C_{25}H_{20}N_4O_4S_2$ (504.58): C, 59.51; H, 4.00; N, 11.10; S, 12.71. Found: C, 59.89; H, 3.87; N, 11.45; S, 12.52.

*3.1.16. General procedure for the preparation of* ***17a,b***

Compound 15a (1 g, 3.56 mmol) and corresponding diketones (3.56 mmol) were refluxed in absolute ethanol (30 ml) for 5 h. The reaction mixture was cooled and the precipitate was filtered and crystallized from the appropriate solvent.

*3.1.16.1. 2-[4-(1H-Indol-2-yl) phenoxy]-1-(3,5-dimethyl-1H-pyrazol-1-yl) ethanone* ***17a***. Compound **17a** was prepared from **15a** and acetylacetone. White solid, 85% yield, m.p. 260 °C. (pet. ether 60–80 °C). IR: $\nu_{max}$/cm$^{-1}$ 3234 (NH stretching); 3056 (CH aromatic); 2921–2855 (CH aliphatic); 1699 (C=O); 1612 (C=N); 1556 (C=C). $^1$H NMR (DMSO-$d_6$): $\delta$ 1.21 (s, 3H, –N=C–$CH_3$); 1.69 (s, 3H, N–C–$CH_3$); 4.16 (s, 2H, O–$CH_2$); 4.82 (s, 1H, pyrazole proton); 6.76 (s, 1H, indole proton); 6.86 (m, 2H, indole protons); 6.99–7.02 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.35–7.47 (m, 2H, aromatic protons); 7.69–7.72 (d, $J$ = 8.10 Hz, 1H, indole proton); 7.77–7.79 (d, $J$ = 8.10 Hz, 1H, indole proton); 11.46 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{21}H_{19}N_3O_2$ (345.39): C, 73.03; H, 5.54; N, 12.17. Found: C, 72.62; H, 5.89; N, 12.23.

*3.1.16.2. 2-[4-(1H-Indol-2-yl) phenoxy]-1-(5-methyl-3-phenyl-1H-pyrazol-1-yl) ethanone* ***17b***. Compound **17b** was prepared from **15a** and benzoylacetone. White solid, 60% yield, m.p. 208–209 °C. (absolute ethanol). IR: $\nu_{max}$/cm$^{-1}$ 3498 (NH stretching); 3055 (CH aromatic); 2922–2855 (CH aliphatic); 1667 (C=O); 1610 (C=N); 1546 (C=C). $^1$H NMR (DMSO-$d_6$): $\delta$ 2.05 (s, 3H, $CH_3$); 4.52 (s, 2H, O–$CH_2$); 5.04 (s, 1H, pyrazole proton); 6.73 (s, 1H, indole proton); 6.95 (m, 2H, indole protons); 7.05 (m, 2H, aromatic protons); 7.25 (m, 3H, aromatic protons); 7.36 (m, 2H, aromatic protons); 7.48 (m, 1H, indole proton); 7.53 (m, 2H, aromatic protons); 7.73 (m, 1H, indole proton); 11.38 (s, 1H, NH exchanged by $D_2O$). MS ($m/z$ %): 408 ($M + 1^+$, 1.78%). Anal. calcd. for $C_{26}H_{21}N_3O_2$ (407.46): C, 76.64; H, 5.19; N, 10.31. Found: C, 76.34; H, 5.54; N, 10.18.

*3.1.17. 1-{2-[4-(1H-Indol-2-yl) phenoxy] acetyl}-3-methyl-1H-pyrazol-5(4H)-one* ***18***

Compound **18** was prepared from **15a** and ethyl acetoacetate by the same procedure used for the preparation of **17a**,**b**. Off white solid, 80% yield, m.p. 140 °C (dec.). (pet. ether 60–80 °C). IR: $\nu_{max}$/cm$^{-1}$ 3429–3285 (NH stretching); 3052 (CH aromatic); 2923–2857 (CH aliphatic); 1696–1665 (2C=O); 1612 (C=N); 1537 (C=C). $^1$H NMR (DMSO-$d_6$): $\delta$ 1.21 (s, 3H, $CH_3$); 2.25 (s, 2H, pyrazole protons); 4.69 (s, 2H, O–$CH_2$); 6.77 (s, 1H, indole proton); 6.96–6.99 (d, $J$ = 8.10 Hz, 2H, indole protons); 7.03–7.05 (d, $J$ = 5.40 Hz, 2H, aromatic protons); 7.35–7.38 (d, $J$ = 8.10 Hz, 1H, indole proton); 7.47–7.50 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.79 (m, 1H, indole proton); 11.42 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{20}H_{17}N_3O_3$ (347.37): C, 69.15; H, 4.93; N, 12.10. Found: C, 68.66; H, 5.36; N, 12.25.

*3.1.18. General procedure for the preparation of* ***19a–e***

Compound **15a** (1 g, 3.56 mmol), the appropriate carboxylic acid derivative (3.56 mmol) and phosphorous oxychloride (4 ml, 26 mmol) were refluxed on a water bath for 2 h at 80 °C. The reaction mixture was then poured onto ice/cold water and neutralized by $NaHCO_3$ solution. The so formed precipitate was filtered and crystallized from the appropriate solvent.

*3.1.18.1. 2-{[4-(1H-Indol-2-yl) phenoxy] methyl}-5-phenyl-1,3,4-oxadiazole* ***19a***. Compound **19a** was prepared from **15a** and benzoic acid. Green solid, 63% yield, m.p. 160 °C (dec.). (pet. ether 60–80 °C). IR: $\nu_{max}$/cm$^{-1}$ 3421 (NH stretching); 3054 (CH aromatic); 2921 (CH aliphatic); 1609 (C=N); 1544 (C=C). $^1$H NMR (DMSO-$d_6$): $\delta$ 4.55 (m, 2H, O–$CH_2$); 6.76 (s, 1H, indole proton); 6.96–6.99 (d, $J$ = 8.1 Hz, 2H, indole protons); 7.03–7.05 (d, $J$ = 8.10 Hz, 2H, aromatic protons); 7.35–7.37 (m, 5H, aromatic protons); 7.50–7.52 (d, $J$ = 5.40 Hz, 1H, indole proton); 7.56–7.59 (m, 2H, aromatic protons); 7.78–7.80 (m, 1H, indole proton); 11.43 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{23}H_{17}N_3O_2$ (367.40): C, 75.19; H, 4.66; N, 11.44. Found: C, 74.82; H, 4.85; N, 11.49.

*3.1.18.2. 4-{5-[(4-(1H-Indol-2-yl) phenoxy) methyl]-1,3, 4-oxadiazol-2-yl}aniline* ***19b***. Compound **19b** was prepared from **15a** and *p*-aminobenzoic acid. Dark violet solid, 86% yield, m.p. 140–142 °C. (pet. ether 60–80 °C). IR: $\nu_{max}$/cm$^{-1}$ 3328–3215 ($NH_2$, NH stretching); 3055 (CH aromatic); 2924 (CH aliphatic); 1604 (C=N); 1498 (C=C). $^1$H NMR (DMSO-$d_6$): $\delta$ 4.52 (m, 2H, O–$CH_2$); 6.78 (s, 1H, indole proton); 6.97 (m, 2H, indole protons); 7.03–7.06 (m, 2H, aromatic protons); 7.20–7.36 (m, 4H, aromatic protons); 7.48 (m, 1H, indole proton); 7.76 (m, 2H, aromatic protons); 7.79 (m, 1H, indole proton); 8.00 (s, 2H, $NH_2$ exchanged by $D_2O$); 11.42 (s, 1H, NH exchanged by $D_2O$). MS ($m/z$ %): 382 ($M^+$, 0.71%); 209 (100%). Anal. calcd. for $C_{23}H_{18}N_4O_2$ (382.41): C, 72.24; H, 4.74; N, 14.65. Found: C, 72.34; H, 4.88; N, 14.45.

*3.1.18.3. 2-{5-[(4-(1H-Indol-2-yl) phenoxy) methyl]-1,3, 4-oxadiazol-2-yl}aniline **19c**.* Compound **19c** was prepared from **15a** and anthranilic acid. Brown solid, 89% yield, m.p. 100–102 °C. (absolute ethanol). IR: $\nu_{max}/cm^{-1}$ 3422–3250 ($NH_2$, NH stretching); 3057(CH aromatic); 2922 (CH aliphatic); 1612 (C=N); 1542 (C=C). $^1H$ NMR (DMSO-$d_6$): $\delta$ 4.50 (s, 2H, O–$CH_2$); 6.85 (s, 1H, indole proton); 6.97–7.00 (m, 2H, indole protons); 7.03–7.07 (m, 2H, aromatic protons); 7.23–7.36 (m, 4H, aromatic protons); 7.42 (m, 1H, indole proton); 7.48 (m, 2H, aromatic protons); 7.80 (m, 1H, indole proton); 8.18 (s, 2H, $NH_2$ exchanged by $D_2O$); 11.46 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{23}H_{18}N_4O_2$ (382.41): C, 72.24; H, 4.74; N, 14.65. Found: C, 72.59; H, 4.63; N, 14.57.

*3.1.18.4. 2-{5-[(4-(1H-Indol-2-yl) phenoxy) methyl]-1,3,4-oxadiazol-2-yl} phenol **19d**.* Compound **19d** was prepared from **15a** and salicylic acid. Dark green solid, 75% yield, m.p. 250 °C. (pet. ether 60–80 °C). IR: $\nu_{max}/cm^{-1}$ 3393 (OH stretching); 3265 (NH stretching); 3054 (CH aromatic); 2923(CH aliphatic); 1607 (C=N); 1541 (C=C). $^1H$ NMR (DMSO-$d_6$): $\delta$ 4.54 (s, 2H, O–$CH_2$); 6.77 (s, 1H, indole proton); 6.97 (m, 2H, indole protons); 7.04 (m, 2H, aromatic protons); 7.38 (m, 4H, aromatic protons); 7.40 (m, 1H, indole proton); 7.50 (m, 2H, aromatic protons); 7.72 (m, 1H, indole proton); 9.65 (s, 1H, –OH exchanged by $D_2O$); 11.41 (s, 1H, NH exchanged by $D_2O$). Anal. calcd. for $C_{23}H_{17}N_3O_3$ (383.40): C, 72.05; H, 4.47; N, 10.96. Found: C, 71.99; H, 4.26; N, 10.80.

*3.1.18.5. 2-{[4-(1H-Indol-2-yl) phenoxy] methyl}-5-(6-methoxyquinolin-2-yl)-1,3,4-oxadiazole **19e**.* Compound **19e** was prepared from **15a** and 6-methoxyquinolinic acid. Dark violet solid, 80% yield, m.p. >300 °C. (absolute ethanol). IR: $\nu_{max}/cm^{-1}$ 3396 (NH stretching); 3059 (CH aromatic); 2923–2853 (CH aliphatic); 1614 (C=N); 1548 (C=C). $^1H$ NMR (DMSO-$d_6$): $\delta$ 3.93 (s, 3H, O–$CH_3$); 4.60 (m, 2H, O–$CH_2$); 6.72 (s, 1H, indole proton); 6.92 (m, 2H, indole protons); 7.10 (m, 3H, aromatic protons); 7.23 (m, 1H, aromatic proton); 7.37 (m, 1H, aromatic proton); 7.51 (m, 3H, indole and aromatic protons); 7.64 (m, 2H, indole and aromatic protons); 8.22–8.24 (m, 1H, aromatic proton); 11.45 (s, 1H, NH exchanged by $D_2O$). MS (*m/z* %): 448 ($M^+$, 1.23%); 150 (100%). Anal. calcd. for $C_{27}H_{20}N_4O_3$ (448.47): C, 72.31; H, 4.49; N, 12.49. Found: C, 72.55; H, 4.39; N, 12.54.

### *3.2. Antitumor activity against MCF-7 and MDA-MB-231*

Antitumor activity was performed in the National Cancer Institute Cairo University.

1. Cells were plated in 96-multiwell plates ($10^4$ cells/well) for 24 h before treatment with the compounds to allow the attachment of cells to the wall of the plate.
2. Different concentrations of the compounds under test (0, 1, 2.5, 10 μg/ml) were added to the cell monolayer.
3. Triplicate wells were prepared for each individual dose.
4. Monolayer cells were incubated with the compounds for 48 h at 37 °C and in 5% $CO_2$ atmosphere.
5. After 48 h, cells were fixed, washed and stained with Sulforhodamine B (SRB) stain.
6. Excess stain was washed with acetic acid and the attached stain was recovered with Tris EDTA buffer.
7. Color intensity was measured in an ELISA reader.

The relation between the surviving fraction and drug concentration was plotted to get the survival curve of the tumor cell line after the specified compound was added.

$IC_{50}$ and standard errors (S.E) for the $IC_{50}$ values were calculated by Graph Pad Prism 5 software.

### *3.3. Molecular docking*

All molecular modeling calculations and docking studies were performed using 'Molecular Operating Environment (MOE) version 2008.10 release of Chemical Computing Group's'. The program operated under 'Windows XP' operating system installed on an Intel Pentium IV PC with a 2.8 MHz processor and 512 RAM.

The target compounds were built using the MOE builder interface and subjected to energy minimization using the included MOPAC. The produced model was subjected to Systematic Conformational Search where all items were set as default with RMS gradient of 0.01 kcal/mol and RMS distance of 0.1 Å.

The X-ray crystallographic structure of tubulin co-crystallized with colchicine was obtained from the Protein Data Bank; code "1SAO.pdb". The enzyme was prepared for docking studies as follows:

a. The ligand molecule was removed form the enzyme active site.
b. Hydrogen atoms were added to the isolated target with their standard geometry.
c. A connect and type procedure was run for automatic completion of missed bonds during isolation and crystallization.
d. The target was fixed to be dealt as a rigid structure.
e. The active site was isolated by the Alpha site finder tool using the binding amino acids as key elements in isolation.
f. Dummies were created around the active site.

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