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SYNTHESIS, SPECTRAL CHARACTERIZATION AND PHARMACOLOGICAL EVALUATION OF NOVEL THIAZOLE-OXOINDOLE HYBRID COMPOUNDS AS POTENTIAL ANTICANCER AGENTS

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ABSTRACT

*In the present study, a series of thiazole derivatives bearing 5-morpholinosulfonylindole were designed and synthesized through condensation of 5-(morpholinosulfonyl)isatin **(1)** with some thiazolidinone derivatives as carbon nucleophiles to afford the corresponding arylidene derivatives **(2-5, 7, 8)**. Furthermore, many thiazole derivatives **(11-15)** were obtained through the reaction of thiosemicarbazone derivative **(10)** with many reagents such as dimethyl acetelenedicarboxylate, phencylbromide derivatives, chloroacetonitrile, chloroacetylchloride as well as chloroacetanilide. The newly synthesized compounds were characterized based on spectral (FT-IR,[1]H NMR, [13]C NMR, MS) analysis. Cytotoxicity effects of all synthesized products were tested against three cancer cell lines, MCF-7, HepG-2, HCT-116 and they showed moderate to good cytotoxic activity against the three tested cell lines. The study showed that compounds **(2a, 12b and 12c)** were less or almost equipotent as doxorubicin against the three cell lines HepG-2, HCT-116.*

Keywords: Isatin; thiazol-4(*5H*)-one; 4-thiazolidinone; thiosemicarbazone derivatives.

1- INTRODUCTION

Despite chemotherapy, surgery, radiotherapy, biotherapy and other adjuvant therapy are common treatments for tumor therapy [1] but chemotherapy is still the preferred and most significant treatment for cancer patients in the clinical application [2]. In the recent years there has been a surge of interest in heterocyclic compounds containing nitrogen and sulfur mainly because of their promising medicinal properties especially thiazole. Thiazoles are one of the most intensively investigated classes of aromatic five membered heterocycles and immense attention because it used as building block for the synthesis of many biologically active molecules as Sulfathiazole (antimicrobial drug), Nitazoxanide (antiprotozoal agent), Nizatidine (ulcer therapeutic), Abafungin (antifungal drug), Tiazofurin (antineoplastic agent), Meloxicam (non-steroidal, anti-inflammatory drug), epothilones and Antiarrhythmic, Anticoagulant activities [3-8] as shown in **figure (1).** Also, some natural products containing thiazole ring have been isolated as thiamine (vitamin B1), thiamine pyrophosphate (TPP, a coenzyme important in respiration in the Krebs cycle) [9,10] and most of them exhibited significant cytotoxicity and antitumor potential [11-13]. Thus, the thiazole nucleus has been much studied in the field of organic and medicinal chemistry.

On the other hand, isatin is an endogenous compound identified in many organisms and possess diverse biological activities such as anti-bacterial [14], anticancer [15,16], anti-HIV [17], antimalarial [18], and anti TB activities [19], anti-oxidant [20] etc.

Also, sulfonamide derivatives display extensive biological properties, which are very popular among pharmaceutical chemists working on the design and synthesis of biologically active compounds in the pharmaceutical and agrochemical industry. This attractive scaffold displays a wide variety of pharmacological activities like anticancer [21], antibacterial [22] and anti-inflammatory [23] activities.

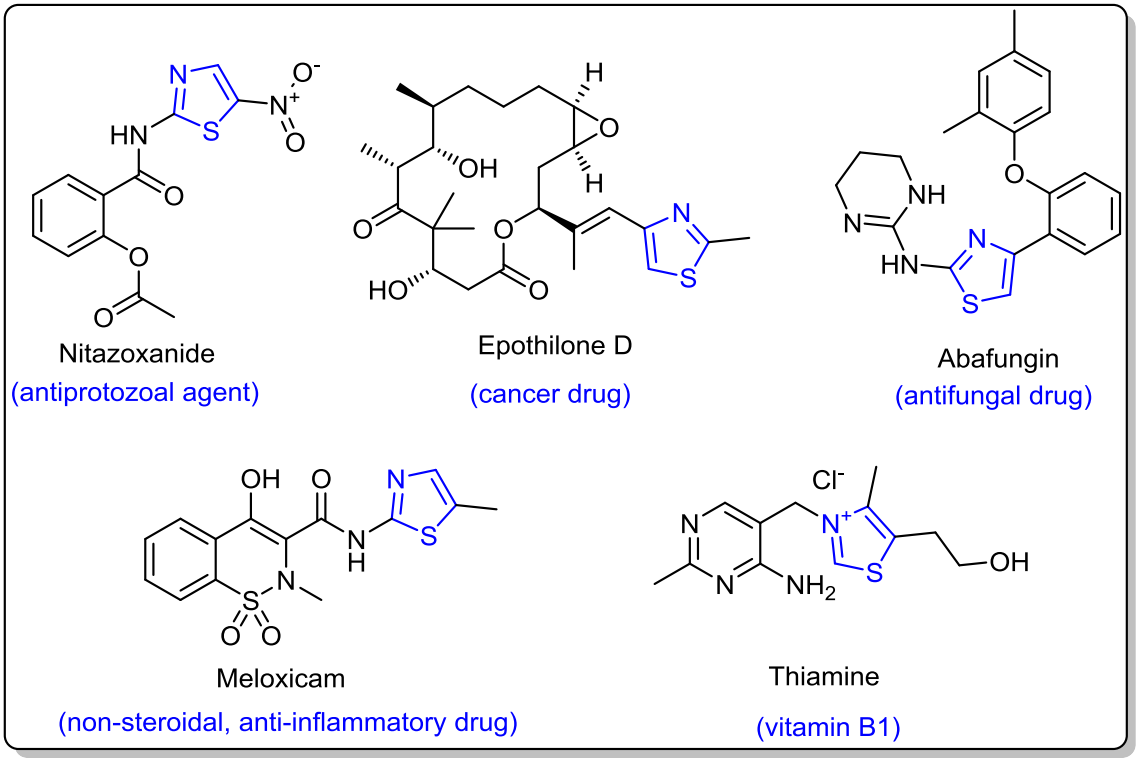


Fig. (1); Some reported drugs containing thiazoles.

In addition, the morpholine scaffold had found to be an outstanding pharmacophore in medicinal chemistry and several molecules having morpholine skeleton are the clinically approved drugs [24]. N-substituted morpholines used in the treatment of inflammatory diseases, like migraine and asthma [25]. Morpholine derivatives have been reported as platelet aggregation inhibitors, anti-emetics, and bronchodilators [26]. Morpholine analogs establish a new antifungal chemical entity not allied with other presently available medications with antifungal potential [27].

Molecular hybridization is a valuable structure modification approach that comprises the incorporation of two or more pharmacophores into single entity. In view of the importance of thiazole and isatin derivatives and as part of our continued interest [28-31] in developing new active therapeutic agent (hybrid drug). We herein report the synthesis of novel thiazole based isatin sulphonamide.

2. RESULTS AND DISCUSSION

2.1. Chemistry

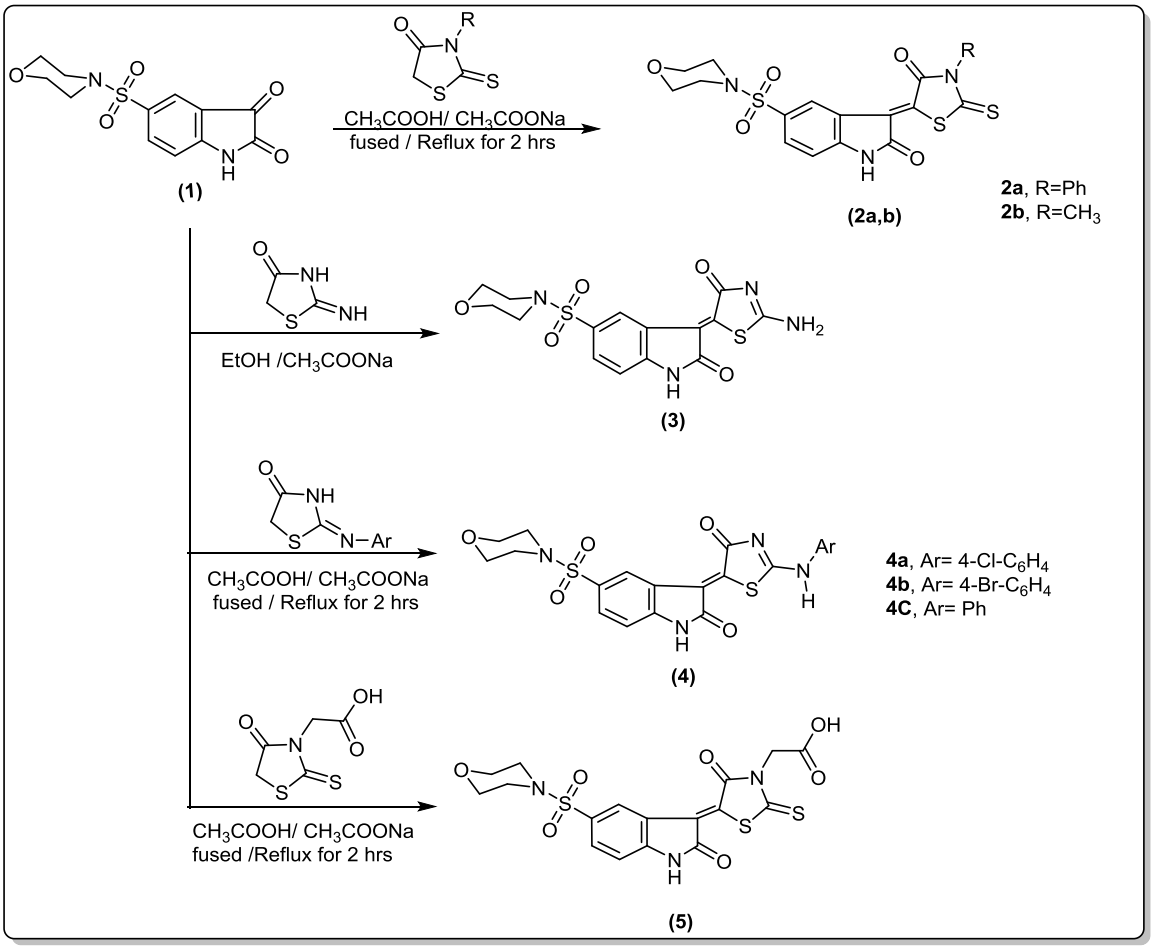
The synthetic pathway leading to the title compounds is outlined in Schemes 1–3. The key starting material 5-(morpholinosulfonyl) isatin **(1)** was prepared as previous described [28]. Thus, reaction of **(1)** with 3-alkyl-2-thioxothiazolidin-4-one as carbon nucleophile in the presence of acetic acid containing fused sodium acetate furnished 5-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene)-3-alkyl-2-thioxo- thiazolidin-4-one **(2a,b)**. The structures of compounds **2a,b** were established on the basic of elemental analysis and spectral data. For example, the IR spectra of compounds **2a** revealed absorption bands at υ 3160 and 1696 cm^{-1} characterized for NH and C=O groups, respectively. Its ^{1}H-NMR spectra (DMSO-d_6) showed, in addition to the aromatic protons between 7.40-7.60 ppm related to eight protons, two triplet signals and one singlet signals at δ 2.84, 3.61 and 11.77 ppm assignable to two $-CH_2$ of morpholinyl moiety and one NH protons, respectively.

Furthermore, the reaction of 5-(morpholinosulfonyl)isatin **(1)** with 2-iminothiazolidin-4-one afforded the corresponding 2-imino-5-(5-(morpholino-sulfonyl)-2-oxoindolin-3-ylidene) thiazolidin-4-one **(3)**. The structure was assigned based on analytical and spectral data. IR spectra of compounds **3**, displayed absorption bands for NH, NH_2 at υ 3510, 3222 and 3114 cm^{-1} in addition to absorption bands at 1699 and 1612 cm^{-1} characterizing C=O and C=N functional groups, respectively. ^{1}H NMR spectra (DMSO-d_6) of compounds **3** exhibited two triplet signals at δ 2.90 and 3.66 ppm indicating morpholinyl protons, three aromatic protons in region 7.17-9.43 ppm as well as two broad signals at δ 9.75, 11.56 ppm related to NH_2, NH groups.

On the same manner, 2-(arylamino)-5-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene) thiazol-4(*5H*)-ones **(4a-c)** were obtained through the reaction of compound **(1)** with 2-(arylimino) thiazolidin-4-ones. Structure of the latter products was elucidated based on analytical and spectral data. IR spectrum of **4a** revealed absorption bands at υ 3163, 3129 and 1699, 1650 cm^{-1} corresponding to two NH and 2C=O functional groups, respectively.

^{1}H NMR spectrum (DMSO-d_6) exhibited two singlet signals at δ 9.42 and 11.61 ppm assignable to two NH, in addition to a multiplet signal at δ 7.10-7.81 ppm distinctive for aromatic protons. In addition, ^{13}C NMR spectrum of **4c** displayed signals at δ 46.34 and 65.67 ppm for CH_2-morpholinyl, also two signals were observed at 154.17 and 168.89 ppm corresponding to the two carbonyl groups.

Also, treatment of **(1)** with 2-(4-oxo-2-thioxothiazolidin-3-yl) acetic acid produces 2-

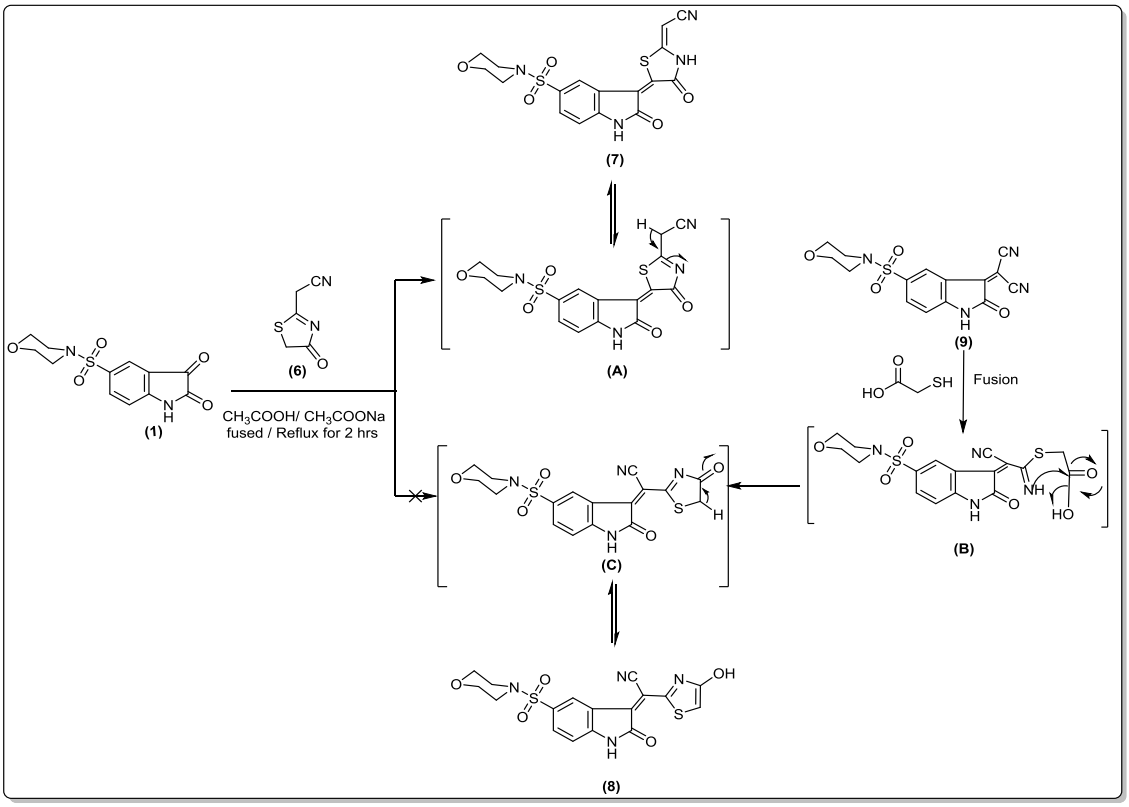


Scheme (1); Reaction of starting material 5-(morpholinosulfonyl)isatin (1) with different thiazole derivatives as carbon nucleophiles.

(5-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetic acid **(5)** based on elemental analysis and spectral data. The IR spectrum of that product revealed intense absorption broad band at υ 3453 for hydroxyl and NH groups and 1705, 1613 cm^{-1} related to carbonyl and C=N groups. ^1H NMR spectra (DMSO-d_6) of compounds (**5**) exhibited two triplet signals at δ 2.92 and 3.66 ppm indicating morpholinyl protons, 4.65 ppm due to CH_2 of acetic acid, three aromatic proton in region 7.22-9.22 ppm as well as 11.85 ppm related to NH; **Scheme (1).**

2-(4-Oxothiazolidine-2-ylidene)acetonitrile **(6)** [32] characterized by the presence of two active methylene as well as presence of nitrile and carbonyl groups which make it chemically very active, so it can be used as a precursor to synthesize many biologically and chemically active ring systems. So, regioselective condensation was occurred through the reaction of acetonitrile derivatives **(6)** with the starting material **(1)** in acetic acid containing catalytic amount of fused sod. acetate, where the condensation occurred at the methylene group number 5 to afford a single product which was formulated as 2-(5-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene)-4-oxo-4,5-dihydrothiazol-2-yl)acetonitrile **(7)**. The structure of **(7)** was confirmed on the basis of analytical and spectroscopic data. Thus, IR spectrum showed stretching significance absorption bands at υ 3336, 3219, 2205, and 1703 cm^{-1} attributed to two imine, nitrile, and carbonyl moieties. ^1H NMR spectra (DMSO-d_6) of compounds **(7)** exhibited two triplet signals at δ 2.89 and 3.64 ppm indicating morpholinyl protons, 5.12 ppm due to at exocyclic methylene of acetonitrile derivative **(6)**, three aromatic proton in reign 7.10- 7.62 ppm as well as 9.6, 11.34 ppm related to two NH, This, prove that, 5-(morpholinosulfonyl) isatin condensed first with 4-thiazolidinone ring **(6)** at endocyclic methylene at position **5** rather than the most active methylene exocyclic methylene at position number **2**. Scheme 2.

On the other hand, compound 2-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene)-2-(4-oxo-4, 5-dihydrothiazol-2-yl) acetonitrile **(8)** has been synthesized through another route

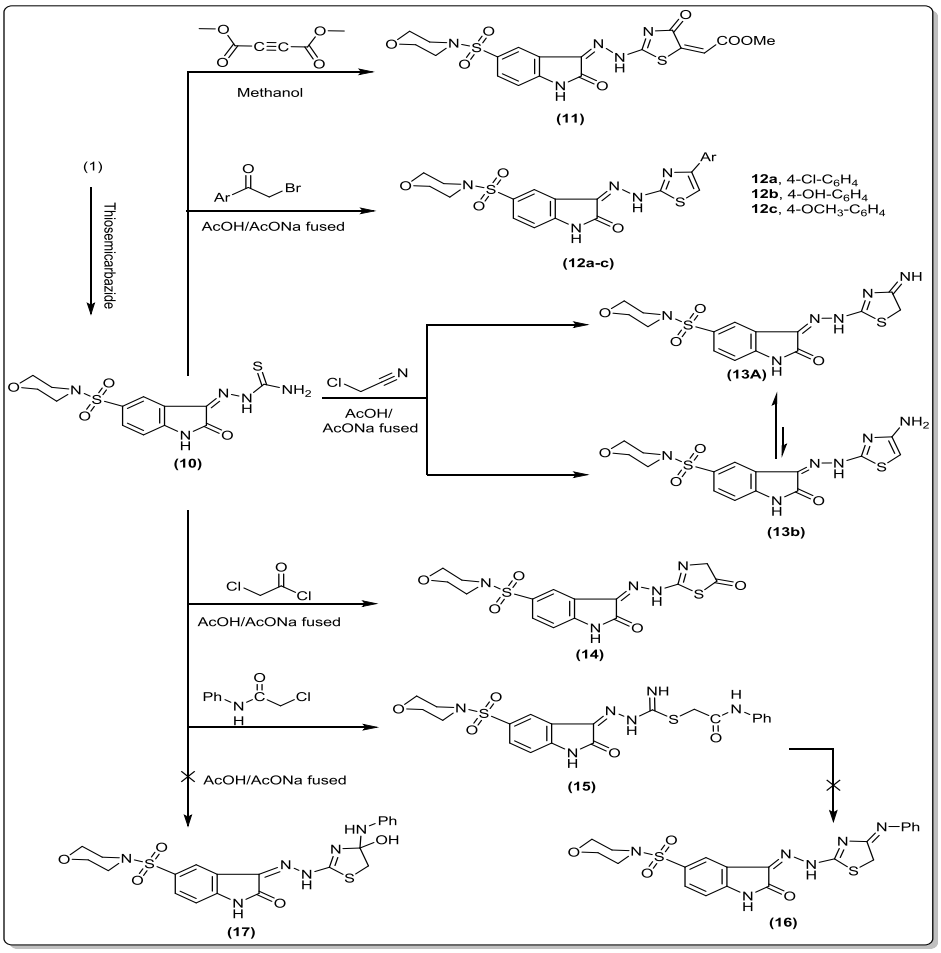


Scheme (2); Regioselective condensation of acetonitrile derivatives (6) with the starting material (1).

via the reaction of 2-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene) malononitrile [28] with thioglycolic acid and the structure of the latter product was confirmed by spectroscopic studies and elemental analysis. The IR spectrum of compound **(8)** revealed absorption bands at υ 3349, 3217, 2207 and 1740 cm^{-1} corresponding to an OH, NH, cyano and carbonyl groups. Its ^{1}H NMR spectrum (DMSO-d_6) revealed signals at δ 8.65 and 11.56, 12.08 ppm due to methine-H, NH and OH protons where NH, OH signals exchangeable by D_2O.

This investigation was extended to cover the reactivity of isatin thiosemicarbazone **(10)** [33] towards different reagents for the synthesis of many derivatives of thiazole containing indole moiety. Thus, the thiosemicarbazone derivative have tautomeric structure between thione / was discussed react as thiol derivative with the reagent as mentioned in scheme (**3**).

Interaction of compound **(10)** with dimethylacetelenedicarboxylate in methanol afforded one product which was identified as methyl 2-(2-(2-(-5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene)hydrazinyl)-4-oxothiazol-5-(*4H*)-ylidene)acetate**(11).** The structure of **(11)** was eluci-dated by correct spectral data and elemental analyses. Its IR spectrum displayed stretching bands for NH and 2 CO at υ 3190, 1732 & 1701 cm^{-1}. The ^{1}H NMR spectrum (DMSO–d_6) exhibited two singlet signals at δ 3.81, 6.77 due to methoxy and -CH methine exocyclic as well as two singlet signals due to two NH at 11.27, 11.64 ppm in addition to the morpholinyl and aromatic protons. Also, ^{13}C-NMR spectrum showed presence of morpholinyl, methoxy, aromatic and methine carbons at 46.21, 46.32, 65.71 and 65.72, 53.11(OCH_3), 111.60-158.88 ppm in addition to three singlet signals at δ 163.16, 166.35, 168.98 related to carbonyl groups.



Scheme (3); Reaction of thiosemicarbazone with different reagents to afford the thiazole derivatives (11-15).

In addition, 3-(2-(4-arylthiazol-2-yl) hydrazono)-5-(morpholinosulfonyl)indolin-2-ones **(12a-c)** were produced through alkylation of the thiosemicarbazone derivative **(10)** with phencylbromides in acetic acid containing sod.acetate. IR pattern of **(12a-c)** displayed stretching frequencies at υ 3418-3104 and 1698-1691 cm^{-1} for NH, C=O respectivelly. ^{1}H NMR spectra (DMSO-d_6) of compound (**12c)** exhibited two triplet signals at δ 2.90 and 3.65 ppm indicating morpholinyl protons, 3.89 ppm due to methoxy group, seven aromatic protons in reign 7.06- 8.10 ppm, -CH thiazole at δ 8.58 ppm and two singlet signals at δ 10.97, 11.73 ppm related to NH. ^{13}C NMR spectrum of **12b** displayed signals at δ 46.38, 46.43, 65.71 and 65.79 ppm for $CH_{2\text{-morpholinyl,}}$ also signal was observed at 172.53 ppm corresponding to carbonyl groups and aromatic carbon between 112.00- 163.16.

Treatment of thiosemicarbazone derivatives **(10)** with chloroacetonitrile in acetic acid afforded 3-(2-(4-imino-4,5-dihydrothiazol-2-yl) hydrazono)-5-(morpholino-sulfonyl) indolin-2-one **(13a)** which was found to be in tautomeric forms with the isomer **(13b)**, while isomer **13a** was favored on the basis of spectral data. The IR spectrum of compound **(13a)** revealed absorption bands in the zone υ 3288, 3196 and 1700 cm^{-1} corresponding to an imine and carbonyl, respectively. Its ^{1}H NMR spectrum (DMSO-d_6) showed presence of CH_2 of thiazole at 4.02 and lack of amino group and –CH-methine signals, also, three singlet signals were appeared at 8.52, 11.22, 11.65 ppm corresponding for three NH proton which disappeared with D_2O.

In the same way 2-(2-(5-(Morpholinosulfonyl)-2-oxo-indolin-3-ylidene)hydrazinyl)thiazol-5(*4H*)-one **(14)** was obtained as a single product, when compound **(10)** was treated with chloroacetylchloride. Elemental analysis and spectral data were found in good agreement with the expected structure. IR spectrum revealed the absorption bands at υ 3284, 3194 related to 2NH, in addition to υ 1700 and 1613 cm^{-1} corresponding to -C=O and -C=N groups respectively. The ^{1}H NMR spectrum (DMSO-d_6) showed singlet signal at δ 4.04 ppm attributed to methylene group, two triplets at 2.88, 3.65 ppm related to morpholinyl moiety and two singlet signals at 11.23, 11.65 ppm for -NH protons respectively, beside signals at δ 7.17-8.10 ppm, which are distinctive for aromatic protons, that identified as two doubles and one singlet for indolinone moiety.

On another hand, interaction of compound **(10)** with chloroacetanilide derivative produced a product which was formulated as the non-cyclic structure **15** rather than the cyclic structure **16** or **17**. The structure of (**15)** was confirmed based on the elemental analysis and spectral data. Thus, its IR spectrum showed the presence of many bands at υ 3283, 3182 and 1725 cm^{-1} corresponding for NH and C=O. Its ^{1}H NMR spectrum exhibited two triplet signals at δ 2.89 (J = 4.0Hz) and 3.65 (J = 4.2 Hz), singlet signal at δ 4.04 corresponding for the methylene group beside four singlet signals at δ 10.03, 11.23, 11.65, 12.87 ppm due to 4NH as well as eight aromatic protons between 7.08-8.52 ppm. ^{13}C NMR spectrum of **(15)** displayed signals at δ 21.51 for methylene group, 46.37, 46.42, 65.72 and 65.79 ppm related to CH_2 of morpholinyl moiety, also three signals were observed at 174.8, 175.85, 179.26 ppm corresponding to C=N and carbonyl groups beside signals of aromatic proton in the range 111.2-165.30 ppm, also mass spectrum showed a molecular ion peak at m/z 502 corresponding to the molecular formula.

2.2. Biological evaluation

The target compounds were evaluated for the cytotoxicity against three cancer cell lines including HepG-2, HCT-116 and MCF-7 using sulforhodamine B colorimetric (SRB) cell proliferation assay, doxorubicin was used as a reference, the obtained IC_{50} values are expressed in µM and represented in **Table 1.**

The target compounds showed moderate to good cytotoxic activity against the three tested cell lines where most of the tested compounds

have shown broad spectrum towards the selected cell lines HepG-2, HCT-116 and MCF-7 cell line.

Compounds **2a, 12b** and **12c** exhibited the best activity against HepG-2 , HCT-116 and MCF-7 with IC_{50} values of (6.59 ± 2.14, 8.78 ± 2.5, 7.76 ± 0.18) µM for compound **2a**, (4.37 ± 0.22 , 6.86 ± 0.14, 9.77 ± 0.25) µM for compound **12b** and (9.44 ± 1.65, 7.83 ± 0.58, 5.49 ± 0.68) µM for compound **12c** which were less active or equipotent as doxorubicin.

Table 1: Cytotoxic activity of the synthesized compounds against cancerous cell lines.

Sample no.	IC_{50}% (µM) ± S.E.**		
	HepG-2	HCT-116	MCF-7
1	28.54 ± 2.5	59.97 ± 0.09	67.93 ± 0.19
2a	6.59 ± 2.14	8.78 ± 2.5	7.76 ± 0.18
2b	18.49 ± 1.28	13.53 ± 0.35	20.61 ± 1.12
3	35.95 ± 2.60	40.51 ± 3.8	34.36 ± 0.85
4a	23.86 ± 0.54	23.82 ± 1.35	28.80 ± .68
4b	40.09 ± 1.68	33.46 ± 0.81	42.09 ± 2.21
4c	47.85 ± 1.35	44.63 ± 0.45	51.59 ± 1.65
5	37.20 ± 0.67	41.27 ± 0.87	32.75 ± 1.02
7	32.87 ± 1.02	36.69 ± 0.28	44.23 ± 2.42
8	41.43 ± 3.86	39.18 ± 2.48	43.28 ± 0.69
10	18.48 ± 0.34	15.51 ± 0.25	18.67 ± 0.65
11	20.61 ± 0.68	23.44 ± 2.81	25.34 ± 1.65
12a	43.33 ± 1.65	26.64 ± 0.31	46.32 ± 2.54
12b	4.37 ± 0.22	6.86 ± 0.14	9.77 ± 0.25
12c	9.44 ± 1.65	7.83 ± 0.58	5.49 ± 0.68
13	20.49 ± 1.87	25.07 ± 1.68	30.27 ± 0.98
14	31.24 ± 0.58	33.17 ± 2.35	37.45 ± 0.71
15	15.72 ± 1.92	17.94 ± 0.57	20.86 ± 2.21
Isatin	32.31 ± 0.45	21.56 ± 0.37	41.83 ± 0.67
Dox.	5.59 ± 0.55	7.03 ± 0.21	4.89 ± 0.47

**Three independent experiments were performed for each concentration.

The results indicated that the 3-alkyl-2-thioxo- thiazolidin-4-one **(2a, b)** derivatives were more active than the corresponding 2-iminothiazolidin-4-one derivatives **(3),** 2-(arylamino)-5-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene) thiazol-4(*5H*)-ones **(4a-c)**, This can be attributed to presence of new thioxo in designed compounds in position 2 **(2a,b)** derivatives also, presence of (-N-Ph) more active than (-N-Me), see Table 1

Presence of acetic acid derivatives as 2-(5-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene)-4-oxo-2-thioxothiazolidin-3-yl) acetic acid **(5)** as well as acetonitrile derivatives (**7,8)** showed moderate anticancer activity, with IC_{50} value less than 50 µM against all the tested cell line (37.20 ± 0.67 , 41.27 ± 0.87, 32.75 ± 1.02) µM for **(5)**, (32.87 ± 1.02, 36.69 ± 0.28, 44.23 ± 2.42) µM for **(7)** and (41.43 ± 3.86, 39.18 ± 2.48, 43.28 ± 0.69) µM for **(8)** respectively and from previous result it's clear that condensation at endocyclic methylene at position **5** at compound **(7)** give slightly significant against all cell lines rather than exocyclic methylene at position number 2 compound **(8)**.

As found in table 1, it is readily observed that there is a significant difference in cytotoxic activity when various alkyl groups are introduced into the phenyl ring of phencylbromide derivatives in (**12a-c)**. The Presence of hydroxy group in 4-arylthiazol-2-yl derivatives **(12b)** affected activity higher than doxorubicin against HepG-2 and HCT-116cell line, so replacement of hydroxyl group is required to study structure activity relationship. Introducing methoxy group to aryl group of 3-(2-(4-(4-aryl) thiazol-2-yl) hydrazono)-5-(morpholinosulfonyl) indolin-2-one **(12a, c)** causes an increase in activity in the cause of **12c** rather than **12a,** which may be attributed to a lipophilic electron withdrawing (Cl atom).

Compounds (**13, 14, 15)** showed moderate anticancer activity, against all the tested cell line and in some causes give result activity better than isatin itself and starting material and that indicate that sulfonyl moiety affected in activity and presence of thiazole derivative in the desired compounds increase activity against all the tested cell lines. Most of synthetized compounds showed good activity than starting material. Finally, the presence of 2-thioxo **(2a, b)** and presence of hydroxy group on 4-position of phenyl ring at 4-arylthiazol-2-yl derivatives **(12b)** enhanced the antitumor activity and led

to results near to or better than the reference drug.

3. EXPERIMENTAL SECTION

3.1. Chemistry

All melting points are recorded on digital Gallen Kamp MFB-595 instrument and may be uncorrected. The IR spectra (KBr) (cm^{-1}) were measured on a Shimadzu 440 spectrophotometer. ^{1}H NMR spectra (δ, ppm) were obtained in deuterated dimethyl sulfoxide on a Bruker spectrometer (400 MHz) spectrometer, using TMS as an internal standard; chemical shifts are reported as δ ppm units. Mass spectra were recorded on Thermo Scientific ISQLT mass spectrometer at the Regional Center for Mycology and Biotechnology, Al-Azhar University. Elemental analyses were carried out at Micro Analytical Unit, Cairo University, Cairo, Egypt.

Synthesis of thiazole derivatives 2a, b, 3, 4,5,7 :-

A mixture of 5-morpholinosulfonylisatin **(1)** (0.01 mol) and 3-phenyl-2-thioxothiazolidin-4-one, 3-methyl-2-thioxothiazolidin-4-one, 2-iminothiazolidin-4-one, 2-(arylamino)thiazol-4(5H)-one derivatives, 2-(4-oxo-4,5-dihydrothiazol-2-yl)acetonitrile and/ or 2-(4-oxo-2-thioxothiazolidin-3-yl)-acetic acid (0.01 mol) in 10 mL acetic acid containing (0.2 g) of fused sodium acetate was heated under reflux for 1-4 h. The solid product formed collected by filtration and washed by water and recrystallized from proper solvent.

5-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene)-3-phenyl-2-thioxothiazolidin-4-one (2a):-

Yield 89.3% as red powder from ethanol; mp: 286-288 °C, IR: ν/cm^{-1}: 3160 (NH), 3060 (CH-Ar), 2974, 2911, 2848 (CH-aliph), 1696 (C=O), 1617 (C=N); ^{1}H NMR: δ/ppm 2.84 (t, 4H, *J*= 4.2 Hz, $N(CH_2)_2$), 3.61(t, 4H, *J*= 3.8 Hz $O(CH_2)_2$), 7.40-7.60 (m, 8H, Ar-H), 11.77 (s, H, NH; exchangeable with D_2O); MS: (Mwt.: 487): m/z,487 [M^{+1}, (34.12%)], 56 (100%); Anal. Calcd for $C_{21}H_{17}N_3O_5S_3$ (487.56): C, 51.73; H, 3.51; N, 8.62; Found C, 51.81; H, 3.43; N, 8.78%.

3-methyl-5-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene)-2-thioxothiazolidin-4-one(2b):-

Yield 92.8% as red powder from methanol; mp: >300°C, IR: ν/cm^{-1}: 3201 (NH), 3075 (CH-Ar), 2975, 2895, 2856 (CH-aliph), 1718, 1693 (C=O), 1613 (C=N); ^{1}H NMR: δ/ppm = 2.92 (t, 4H, *J*=4.0 Hz, $N(CH_2)_2$), 3.48 (s, 3H, -N-CH_3), 3.67 (t, 4H, *J*= 4.2 Hz, -$O(CH_2)_2$), 7.22 (d, 1H, *J*= 8.4 Hz, Ar-H), 7.81 (d, 1H, *J*= 8.4 Hz, Ar-H), 9.26 (s, 1H, Ar-H), 11.78 (s, H, NH; exchangeable with D_2O); MS:(Mwt.: 425): m/z, 425 [M^{+1}, (11.28%)], 56 (100%); Anal. Calcd for $C_{16}H_{15}N_3O_5S_3$ (425.49): C, 45.17; H, 3.55; N, 9.88; Found C, 45.32; H, 3.31; N, 9.94%.

2-imino-5-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene) thiazolidin-4-one (3):-

Yield 81.3% as yellowish powder from ethanol; mp: 290-292 °C, IR: ν/cm^{-1}: 3510, 3222, 3114 (NH, NH_2), 3052 (CH-Ar), 2968, 2905, 2859 (CH-aliph), 1699 (C=O), 1612 (C=N); ^{1}H NMR: δ/ppm 2.90 (t, 4H, *J* = 4.2 Hz, $N(CH_2)_2$), 3.66 (t, 4H, *J* = 4.4 Hz $O(CH_2)_2$), 7.17 (d, 1H, *J*= 8.4 Hz, Ar-H), 7.73 (d, 1H, *J*= 8.4 Hz, Ar-H), 9.43 (s, 1H, Ar-H), 9.75(br, 2H, NH_2: exchangeable with D_2O), 11.56 (br, 1H, NH;exchangeable with D_2O); MS:(Mwt.: 394): m/z, 394[M^{+1}, (10.13%)], 152 (100%);Anal. Calcd for $C_{15}H_{14}N_4O_5S_2$ (394.42): C, 45.68; H, 3.58; N, 14.21; Found C, 45.62; H, 3.44; N, 14.35%.

2-((4-Chlorophenyl)amino)-5-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene)thiazol-4(*5H*)-one) (4a) :-

Yield 86.87% as reddish powder from ethanol; mp: >300°C, IR: ν/cm^{-1}: 3166, 3133 (2NH), 3060 (CH-Ar), 2978, 2918, 2859 (CH-aliph), 1699, 1650 (C=O), 1613 (C=N); ^{1}H NMR: δ/ppm 2.91 (t, 4H, J = 4.0 Hz, $N(CH_2)_2$), 3.66 (t, 4H, J = 4.2 Hz $O(CH_2)_2$), 7.1 (d, 1H, *J*= 8.4 Hz, Ar-H), 7.15 (d, 1H, *J*= 8.4 Hz, Ar-H), 7.18 (d, 1H, *J*= 8.0 Hz, Ar-H), 7.47-7.49 (m, 2H, Ar-H), 7.51 (d, 1H, *J*= 8.4 Hz, Ar-H), 7.81

(d, 1H, *J*= 8.4 Hz, Ar-H), 9.42, 11.61 (2s, 2H, 2NH; exchangeable with D_2O); Anal. Calcd for $C_{21}H_{17}ClN_4O_5S_2$ (504.97): C, 49.95; H, 3.39; N, 11.10; Found C, 49.78; H, 3.51; N, 11.03%.

2-((4-Bromophenyl)amino)-5-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene)thiazol4(*5H*)-one(4b):-

Yield 88.54% as red powder from ethanol; mp: 291-293 °C, IR: ν/cm^{-1}: 3163, 3129 (2NH), 3060 (CH-Ar), 2977, 2918, 2857 (CH-aliph), 1699, 1648 (C=O), 1613 (C=N); ^{1}H NMR: δ/ppm 2.95 (t, 4H, *J* = 4.2 Hz, $N(CH_2)_2$), 3.66 (t, 4H, *J* = 3.8 Hz $O(CH_2)_2$), 7.04 (d, 1H, *J*= 8.0 Hz, Ar-H), 7.13-7.19 (m, 2H, Ar-H), 7.62 (d, 1H, *J*= 8.4 Hz, Ar-H), 7.63-7.64 (m, 1H, Ar-H), 7.7-7.72 (m, 1H, Ar-H), 7.77 (d, 1H, *J*= 8.4 Hz, Ar-H), 9.41, 11.63 (2s, 2H, 2NH; exchangeable with D_2O); ^{13}C NMR: 46.37 ($N(CH_2)_2$), 65.80 ($O(CH_2)_2$), 111.03, 120.91, 121.15, 123.49, 124.22, 127.66, 128.06, 131.60, 132.49, 132.77, 141.24, 144.90, 146.62, 147.05, 147.09, 152.84, 169.54 (2C=O); Anal. Calcd for $C_{21}H_{17}BrN_4O_5S_2$ (549.41): C, 45.91; H, 3.12; N, 10.20; Found C, 45.82; H, 3.27; N, 10.33%.

5-(5-(Morpholinosulfonyl)-2-oxoindolin-3-ylidene)-2-(phenylamino)thiazol-4(*5H*)-one(4c):-

Yield 84.34% as orange powder from ethanol; mp: 298-300 °C, IR: ν/cm^{-1}: 3162, (NH), 3058 (CH-Ar), 2980, 2919, 2859 (CH-aliph), 1699, 1648 (C=O), 1613 (C=N); ^{1}H NMR: δ/ppm 2.93 (t, 4H, *J* = 4.0 Hz, $N(CH_2)_2$), 3.64(t, 4H, *J* = 4.2 Hz $O(CH_2)_2$), 7.07 (d, 1H, *J*= 8.4 Hz, Ar-H), 7.14 (d, 1H, *J*= 8.4 Hz, Ar-H), 7.33-7.35 (m, 2H, Ar-H), 7.53 (d, 1H, *J*= 8.4 Hz, Ar-H), 7.66-7.69 (m, 2H, Ar-H), 7.73-7.75 (m, 1H, Ar-H), 9.41, 11.62 (2s, 2H, 2NH; exchangeable with D_2O); ^{13}C NMR: 46.34 ($N(CH_2)_2$), 65.67 ($O(CH_2)_2$), 110.13, 121.21, 122.67, 123.99, 124.27, 126.76, 129.36, 131.32, 133.17, 133.84, 142.38, 145.90, 146.67, 147.10, 147.99, 154.17, 168.89 (2C=O); MS:(Mwt.:470): m/z, 470[M^{+1}, (38.44%)], 407 (100%);Anal. Calcd for $C_{21}H_{18}N_4O_5S_2$ (470.52): C, 53.61; H, 3.86; N, 11.91; Found C, 53.46; H, 3.98; N, 11.84%.

2-(5-(5-(Morpholinosulfonyl)-2-oxoindolin-3-ylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid(5):-

Yield 92% as red powder from ethanol; mp: dec.280 °C, IR: ν/cm^{-1}: 3453 (br. OH,NH), 3069 (CH-Ar), 2969, 2902, 2862 (CH-aliph), 1705 (C=O), 1613 (C=N); ^{1}H NMR: δ/ppm 2.92 (t, 4H, *J* = 4.0 Hz, $N(CH_2)_2$), 3.66 (t, 4H, *J* = 4.0 Hz, $O(CH_2)_2$), 4.65 (s, 2H, CH_2), 7.22 (d, 1H, *J*= 8.4 Hz, Ar-H), 7.81 (d, 1H, *J*= 8.8 Hz, Ar-H), 9.22 (s, 1H, Ar-H), 11.85 (s, 1H, NH; exchangeable with D_2O); MS:(Mwt.: 469): m/z, 469[M^{+1}, (16.97%)], 134 (100%); Anal. Calcd for $C_{17}H_{15}N_3O_7S_3$ (469.50): C, 43.49; H, 3.22; N, 8.95; Found C, 43.35; H, 3.41; N, 8.87%.

2-(5-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene)-4-oxo-4,5-dihydrothiazol-2-yl) acetonitrile (7):-

Yield 68.14% as brown powder from ethanol/ benzene; mp: dec.280 °C, IR: ν/cm^{-1}: 3336, 3219 (2NH), 3086 (CH-Ar), 2976, 2921, 2858 (CH-aliph), 2205 (CN), 1703(br-C=O), 1612 (C=N); ^{1}H NMR: δ/ppm = 2.89 (t, 4H, $N(CH_2)_2$), 3.64 (t, 4H, $O(CH_2)_2$), 5.12 (s, CH-methine), 7.1 (d, 1H, J= 8.4 Hz, Ar-H), 7.12 (s, 1H, Ar-H), 7.62 (d, 1H, 8.0, Ar-H), 9.6, 11.43 (2s, 2H, 2NH; exchangeable with D_2O) ; Anal. Calcd for $C_{17}H_{14}N_4O_5S_2$ (418.44): C, 48.80; H, 3.37; N, 13.39; Found C, 48.65; H, 3.22; N, 13.26%.

Synthesis of 2-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene)-2-(4-oxo-4,5-dihydro-thiazol2-yl) acetonitrile (8):-

A mixture of 2-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene) malononitrile (0.01 mol) and thioglycolic acid (0.01 mol) were heated under reflux for 6h in the presence of (10 ml) of dimethylformamide. The mixture was concentrated and cooled to room temperature then poured on crushed ice, the separated solid was filtered, washed several times with water,

dried and recrystallized to give the title compound.

Yield 71.68% as brown powder from dioxane ; mp: 240-242 °C, IR: ν/cm^{-1}: 3349, 3217 (OH, NH), 3067 (CH-Ar), 2979, 2921, 2860 (CH-aliph), 2207 (CN), 1740(C=O), 1616 (C=N); ^{1}H NMR: δ/ppm 2.91 (t, 4H, *J*= 4.6Hz, N(CH_2)$_2$), 3.65 (t, 4H, *J*= 2.8 Hz, O(CH_2)$_2$), 7.11 (d, 1H, *J*= 8.0 Hz, Ar-H), 7.67 (d, 1H, *J*= 8.0, Ar-H), 8.08 (s, 1H, Ar-H), 8.65 (s, CH-methine), 11.56, 12.08 (2s, 2H, NH-isatin , OH; exchangeable with D_2O); Anal. Calcd for $C_{17}H_{14}N_4O_5S_2$ (418.44): C, 48.80; H, 3.37; N, 13.39; Found C, 48.72; H, 3.29; N, 13.41%.

Synthesis of methyl-2-(2-(2-(-5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene) hydraz-inyl)-4-oxothiazol-5(*4H*)-ylidene) acetate (11):-

Equimolar quantities (0.01 mol) of thiosemicarbazone **(10)** and dimethylethylenedicarboxylate (0.01 mol) were dissolved in methanol (15 mL) and refluxed for 2 h. The solid product formed collected by filtration and washed by hot methanol.

Yield 83.14% as orange powder from methanol ; mp: 262-264 °C, IR: ν/cm^{-1}: 3190 (NH), 3042 (CH-Ar), 2980,2923,2901, 2864, (CH-aliph), 1732, 1701(C=O), 1614 (C=N); ^{1}H NMR: δ/ppm = 2.93 (t, 4H, *J* = 4.2 Hz, N(CH_2)$_2$), 3.66 (t, 4H, *J* = 4.1 Hz, O(CH_2)$_2$), 3.81 (s, 3H, OCH_3), 6.77(s, 1H,-CH=), 7.12 (d,1H, *J* = 8.0 Hz, Ar-H), 7.75 (dd, 1H, *J* = 8.3, 1.9 Hz, Ar-H), 8.1 (s,1H, Ar-H), 11.27, 11.64 (2s, 2H, NH-isatin , NH; exchangeable with D_2O); ^{13}C NMR: 46.32, 46.37 (N(CH_2)$_2$), 53.11 (OCH_3), 65.71, 65.75 (O(CH_2)$_2$), 111.60, 116.18, 120.87, 121.48, 128.06, 133.09, 142.29, 146.37, 147.89, 158.88, 163.16, 166.35, 168.98 (3C=O); Anal. Calcd for $C_{18}H_{17}N_5O_7S_2$ (479.48): C, 45.09; H, 3.57; N, 14.61; Found C, 44.97; H, 3.64; N, 14.45%.

General procedure for preparation of 12a-c, 13, 14, and 15:-

A mixture of thiosemicarbazone derivatives **(10)** (0.01mol) and phenacyl bromide derivatives, chloroacetonitril, chloroacetylchloride and/ or 2-chloro-N-phenylacetamide (0.01 mol) and fused sodium acetate (0. 2 g) in methanol (20 ml) was heated under reflux for 4-6 h. The solid product that formed was collected by filtration and washed with hot water.

3-(2-(4-(4-Chlorophenyl)thiazol-2-yl)hydrazono)-5-(morpholinosulfonyl)indolin-2-one (12a):-

Yield 87.52 % as orange powder from dioxane ; mp: 266-268 °C, IR: ν/cm^{-1}: 3418, 3279 (NH), 3087 (CH-Ar), 2967, 2917, 2858 (CH-aliph), 1698 (C=O), 1615 (C=N); ^{1}H NMR: δ/ppm 2.90 (t, 4H, *J*= 4.4 Hz, N(CH_2)$_2$), 3.66 (t, 4H, O(CH_2)$_2$), 7.15-7.23 (m, 2H, Ar-H), 7.51 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.72 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.76 (m, 1H, Ar-H), 7.95 (d, 1H, *J* = 8.0 Hz, Ar-H), 8.1 (s, 1H, Ar-H), 8.55 (s, 1H, -CH thiazol), 11.08, 11.65, (s, 2H, 2NH, exchangeable with D_2O); ^{13}C NMR: 46.38, 46.43 (N(CH_2)$_2$), 65.71, 65.79 (O(CH_2)$_2$), 111.82, 120.91, 121.43, 127.94, 128.55, 129.23, 130.91, 131.30, 145.33, 146.38, 153.19, 163.16, 179.27 (C=O); Anal. Calcd for $C_{21}H_{18}ClN_5O_4S_2$ (503.98): C, 50.05; H, 3.60; N, 13.90; Found C, 49.82; H, 3.41; N, 14.05%.

3-(2-(4-(4-Hydroxyphenyl)thiazol-2-yl)hydrazono)-5-(morpholinosulfonyl)indolin-2-one (12b):-

Yield 88.94 % as red powder from dioxane ; mp: 255-257 °C, IR: ν/cm^{-1}: 3307, 3245 (NH), 3083 (CH-Ar), 2978, 2918, 2881 (CH-aliph), 1694 (C=O), 1615 (C=N); ^{1}H NMR: δ/ppm 2.89 (t, 4H, *J* = 4.0 Hz, N(CH_2)$_2$), 3.65 (t, 4H, *J* = 4.0, O(CH_2)$_2$), 6.80- 6.84 (m, 2H, Ar-H), 7.03 (s, 1H, Ar-H), 7.15-7.23 (m, 1H, Ar-H), 7.45-7.54 (m, 1H, Ar-H), 7.68 (d, 1H, J= 8.0 Hz, Ar-H),7.74 (d, 1H, J= 8.0 Hz, Ar-H), 8.54 (s, 1H, thiazol-H), 9.62, 11.72,13.3 (3s, 3H, 2NH, OH; exchangeable with D_2O); ^{13}C NMR: 46.37, 46.45 (N(CH_2)$_2$), 65.71, 65.74 (O(CH_2)$_2$),104.9, 112.00, 115.93, 118.99, 120.91, 121.03, 127.66, 127.81, 128.40, 128.55, 130.76, 145.17, 151.90, 152.20, 157.94, 163.7, 172.53; MS:(Mwt.: 485): m/z, 485 [M^{+1}, (49.07%)], 389 (100%); Anal. Calcd

for $C_{21}H_{19}N_5O_5S_2$ (485.53): C, 51.95; H, 3.94; N, 14.42; Found C, 51.83; H, 3.81; N, 14.54%.

3-(2-(4-(4-Methoxyphenyl)thiazol-2-yl)hydrazono)-5-(morpholinosulfonyl)indolin-2-one (12c):-

Yield 85.69 % as orange powder from dioxane ; mp: 264-266 °C, IR: ν/cm^{-1}: 3250, 3104 (2NH), 3087 (CH-Ar), 2967, 2907, 2858 (CH-aliph), 1691 (C=O), 1616 (C=N); ^{1}H NMR: δ/ppm = 2.90 (s, 4H, N$(CH_2)_2$), 3.65 (s, 4H, O$(CH_2)_2$), 3.89 (s, 3H, OCH_3), 7.06 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.23 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.52-7.54 (m, 1H, Ar-H), 7.66- 7.73 (m, 1H, Ar-H), 7.75-7.77 (m, 1H, Ar-H), 7.86 (d, 1H, *J* = 8.6 Hz, Ar-H), 8.1 (s, 1H, Ar-H), 8.58 (s, 1H, -CH thiazol), 10.97, 11.73, (2s, 2H, 2NH ,exchangeable with D_2O); Anal. Calcd for $C_{22}H_{21}N_5O_5S_2$ (499.56): C, 52.89; H, 4.24; N, 14.02; Found C, 52.96; H, 4.36; N, 14.18%.

3-((-4-Iminothiazolidin-2-ylidene) hydrazono)-5-(morpholinosulfonyl) indolin-2-one (13a):-

Yield 63.24 % as brown powder from ethanol ; mp: >300 °C, IR: ν/cm^{-1}: 3288, 3196 (2NH), 3097 (CH-Ar), 2969, 2923, 2857 (CH-aliph), 1700 (C=O), 1613 (C=N); ^{1}H NMR: δ/ppm 2.88 (t, 4H, *J* = 3.6 Hz, N$(CH_2)_2$), 3.65 (s, 4H, *J* = 4.0 Hz, O$(CH_2)_2$), 4.02 (s, 2H, CH_2), 7.1 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.17 (d, 1H, *J* = 8.0 Hz, Ar-H), 8.11 (s, 1H, Ar-H), 8.52 , 11.22, 11,65 (3s, 3H, NH-isatin, 2NH ,exchangeable with D_2O); Anal. Calcd for $C_{15}H_{16}N_6O_4S_2$ (408.45): C, 44.11; H, 3.95; N, 20.58; Found C, 44.02; H, 4.06; N, 20.69%.

2-((-5-(Morpholinosulfonyl)-2-oxoind-olin-3-ylidene)hydrazono)thiazolidin-5-one (14):-

Yield 65.21 % as red powder from ethanol ; mp266-268 °C, IR: ν/cm^{-1}: 3284, 3194 (2NH), 3094, 3051 (CH-Ar), 2978, 2855, 2781 (CH-aliph), 1700 (C=O), 1613 (C=N); ^{1}H NMR: δ/ppm = 2.88 (t, 4H, *J* = 3.6 Hz, N$(CH_2)_2$), 3.65 (m, 4H, O$(CH_2)_2$), 4.04 (s, 2H, CH_2), 7.17 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.72 (d, 1H, *J* = 7.2 Hz, Ar-H), 8.10 (s, 1H, Ar-H), 11.23, 11.65 (2s, 2H, 2NH, exchangeable with D_2O; MS:(Mwt.: 409): m/z, 409[M^{+1}, (29.65%)], 402 (100%);Anal. Calcd for $C_{15}H_{15}N_5O_5S_2$ (409.44): C, 44.00; H, 3.69; N, 17.11; Found C, 39.89; H, 3.59; N, 17.42%.

2-oxo-2-(phenylamino)ethyl-2-(5-(morpholinosulfonyl)-2-oxoindolin-3-ylidene)hydrazine-1-carbimidothioate (15):-

Yield 85.69 % as orange powder from dioxane ; mp: >300 °C, IR: ν/cm^{-1}: 3283, 3182 (2NH), 3072 (CH-Ar), 2983, 2920, 2859 (CH-aliph), 1725 (C=O), 1614 (C=N); ^{1}H NMR: δ/ppm 2.89 (t, 4H, *J* = 4.0Hz, N$(CH_2)_2$), 3.65 (s, 4H, *J* = 4.2 Hz, O$(CH_2)_2$), 4.04 (s, 2H, CH_2), 7.08-7.11 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.17 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.42 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.60-7.64 (m, 2H, Ar-H), 7.69- 7.73 (m, 2H, Ar-H), 8.11 (s, 1H, Ar-H), 8.52 (s, 1H, Ar-H), 10.03, 11.23, 11,65, 12.87 (4s, 4H, NH-isatin, NH ,exchangeable with D_2O; ^{13}C NMR: 21.51 (CH_2), 46.37, 46.42 (N$(CH_2)_2$), 65.72, 65.79 (O$(CH_2)_2$), 111.2, 117.67, 120.91, 121.43, 128.55, 130.92, 131.29, 132.88, 137.91, 146.38, 148.16, 163.16, 165.30, 174.8, 175.85, 179.26 ; MS: (Mwt.: 502): m/z, 502 [M^{+1}, (9.05%)], 57 (100%); Anal. Calcd for $C_{21}H_{22}N_6O_5S_2$ (502.11): C, 50.19; H, 4.41; N, 16.72; Found C, 50.68; H, 4.31; N, 16.34%.

3.2. Antiproliferative activity

In vitro cytotoxicity of all synthetized compounds were evaluated by using colorimetric assay method (SRB) against three human tumor cell lines including mammary gland breast cancer cell line (MCF-7), human hepatocellular carcinoma cell line (HepG-2), colon carcinoma cell line (HCT-116), they were obtained from VACSERA-Cell Culture Unit, Cairo, Egypt. For comparison, doxorubicin was used as a standard reference drug. RPMI-1640 medium, SRB (SulphoRhodamine-B), DMSO (Dimethyl sulfoxide) and doxorubicin were purchased from (sigma co., St. Louis, USA). Fetal bovine serum was obtained from (GIBCO, UK). The cells were cultured in RPMI-1640 medium with 10% fetal bovine serum. Antibiotics (penicillin 100 units/mL and streptomycin 100µg/mL)

were added at 37 °C in a 5% CO_2 incubator. The cells were seeded in a 96-well plate at a density of 1.0x104 cells/well at 37 °C for 48 h under 5% CO_2. After incubation, the cells were treated with different concentrations of the tested compounds and incubated for 24 h. Then the medium was discarded. Fixation was carried out by 10% trichloroacetic acid (TCA) 150 µL/well for 1 h at 4 °C, then wash by water 3 times (TCA reduce SRB protein binding). Wells were stained by SRB 70 µL/well for 10 min at room temperature with 0.4% 70 µL/well (keep in dark place). Then washed with acetic acid 1% to remove unbound dye (end point: colorless drainage). The plates were subjected to air drying for 24 h. The dye were solubilized with 50 µL/well of 10 mMtris base (PH 7.4) for 5 min on a shaker at 1600 rpm. The optical density (OD) of each well was measured at 570 nm with an ELISA microplate reader (EXL 800 USA). The inhibitory concentration at 50% (IC_{50}) was determined from the exponential curve of viability versus concentration. The viability was calculated, as (A570 of treated samples/A570 of untreated sample) X 100 and The IC50 values were calculated using the Microsoft Excel. The data were recorded and analyzed to estimate the effects of the tested compounds on cell viability and growth; IC_{50} values for the tested compounds are reported in Table 1, three independent experiments for each concentration were performed. as previously reported [28].

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