Arabian Journal of Chemistry (2014) 7, 630–638

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

1st Heterocyclic Update

Efficient synthesis of new oxindol-based heterocyclic entities via indolin-2-one derivatives

Howida T. Zaky *, Mansoura I. Mohamed, Nadia G. Kandile

Chemistry Department, Faculty of Women, Ain Shams University, Heliopolis 11757, Cairo, Egypt

Received 30 June 2013; accepted 11 January 2014
Available online 21 January 2014

KEYWORDS

3 (2H)-furanone;
Perkin reaction;
Oxindol-based heterocyclic entities;
Microwave;
Anticancer;
Isatin

Abstract New series of oxindol-based heterocyclic entities (**2**–**11**) have been designed and synthesized using indolin-2-one derivatives as key materials (**1a**–**d**). The chemical structures of the new synthesized compounds were characterized by FTIR, ^{1}HNMR, ^{13}CNMR, MS spectroscopy and elemental analyses. Three of the newly synthesized compounds were tested for anticancer activity in the National Cancer Institute (NCI) against human panel breast cancer cell line ***MCF7***, from the *in vitro* assays compound **6c** presented promising anti-cancer activity using Doxorubicin as a reference. Compound **6c** could be a lead compound for discovery of new anticancer agent.

1. Introduction

Medicinal chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level. Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their structures. An important aspect of medicinal chemistry has been to establish a relationship between chemical structure and pharmacological activity (Delgado et al., 1998). It has been established that half of the therapeutic agents consists of heterocyclic compounds. The heterocyclic ring comprises of very core of the active moiety or the pharmacophore (Miller and Remington, 1995). In recent years multicomponent reactions (**MCR's**) (Domling, 2006; Cariou et al., 2008, Umkeherer et al., 2006; Alizadeh et al., 2006; Domling et al., 2000) leading to interesting heterocyclic scaffolds have emerged as powerful tools for incorporating the molecular diversity needed in combinatorial approaches for the synthesis of bioactive compounds and producing diverse chemical libraries of drug-like compounds for biological screening (Weber, 2002, Drug Disc. Today). Indolin-2-one and its derivatives have been designed as a novel class of tyrosine kinase inhibitors, which exhibit selectivity towards different receptor tyrosine kinases (RTK's] (Sun et al., 1998; Lackey et al., 2000; Cho et al., 2010; Kiefer et al., 2010; Mologni et al., 2010).

Various indolin-2-ones have been identified as pharmacologically active compounds in extracts of the traditional anti-inflammatory herb *Isatis tinctoria*. Furthermore; it has been shown that they inhibit compound 48/80-induced mast cell degranulation *in vitro*. Since indolinone systems are useful and important in the field of medicinal chemistry, the development of simple, convenient, and high-yielding protocols is desirable.

* Corresponding author. Tel.: +20 1001140715.
E-mail address: htzaky_h@hotmail.com (H.T. Zaky).

Peer review under responsibility of King Saud University.

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http://dx.doi.org/10.1016/j.arabjc.2014.01.005

The indolin-2-one ring system belongs to the privileged structure in modern medicinal chemistry, particularly in the discovery of new antitumor and anti-angiogenic agents. Indolin-2-one derivatives, especially those with heterocyclic methylene substituents attached to the C-3 position of the indolin-2-one ring, have been disclosed as potent inhibitors of RTK *in vitro* and demonstrated anti-angiogenic properties *in vivo*. The 3-[(3, 5-dimethyl-1*H*-pyrrol-2-yl) methylene] indolin-2-one structure is found in many antitumor drugs (Lv et al., 2011; Uddin et al., 2010). Also it was reported that indolin-2-ones in Clinical Trials act as Potential Kinase Inhibitors (Chinnasamy et al., 2012). Cancer is one of the global health problems and the most frightening and fatal disease of human (Demirayak et al., 2011). Development and discovery of new anticancer agents are one of the main goals in medicinal chemistry. A variety of 3-substituted indolin-2-ones have been utilized as anticancer drugs or drug candidates as shown in Fig. 1 (Krug and Hilgeroth, 2008; Underiner et al., 2004; Chow and Gail Eckhardt 2007; Sandrine et al., 2007; Kumar et al., 2013).The indolin-2-one based Sunitinib is a small-molecule inhibitor of multiple RTK involved in cancer, including VEGFR and PDGFR. It was approved by the USFDA for the treatment of GIST and advanced renal-cell carcinoma in January 2006 and European Union approval in January 2007. Sunitinib is the first anti-cancer drug which received simultaneous FDA approval for two different indications. It has potent anti-angiogenic effects and direct antitumor activities due to the selective inhibition of VEGFR-1 (also known as FLT1), VEGFR-2 (also known as FLK1/KDR), VEGFR3 (also known as FLT4), PDGFRα, PDGFRβ, c-kit, FLT3, RET, and CSF1R (Sandrine et al., 2007; Chow and Gail, 2007).

In continuation of our studies in the synthesis of novel biologically important heterocyclic compounds incorporated with oxindole moiety (El Abbady et al., 1974; Kandile et al., 1991a,b; Hamad et al., 2003; Elgazwy et al., 2006; Zaky 2006, 2007; Kandile et al., 2012,2013), we herein report efficient methods for the synthesis of new oxindol-based heterocyclic entities' derivatives using indolin-2-one derivatives as key materials.

2. Materials and methods

2.1. General

All melting points are uncorrected and were determined on a Gallenkamp melting point apparatus Model MFB 595-0366. Infrared spectra were measured on a Perkin–Elmer spectrophotometer model 1430 using potassium bromide pellets and frequencies are reported in cm^{-1}. The ^1H NMR and ^{13}C NMR were measured in DMSO-d_6 on a Varian Genini-300 MHz spectrometer and chemical shifts δ are in ppm. The mass spectra (m/z) values were measured on a mass spectrophotometer HP model GC MS-QPL000EX (Shimadzu) at 70 eV. Elemental analyses were carried out at the Microanalytical Centre, Cairo University. Explorer Automated Microwave Synthesis Workstation (CEM) was used for the synthesis of compounds.

2.2. Chemistry

2.2.1. Synthesis of 3-[2-oxo-5-(2-methoxyphenyl) furan-3(2H)-ylidene] indolin-2-one (*1b*)

Furanone derivative was prepared via condensation of finely powdered β-(2-methoxybenzoyl) propionic acid (0.01 mol), fused sodium acetate (0.01 mol) and isatin (0.01 mol) in acetic anhydride (10 ml) via microwave irradiation at 200 °C for 2 min. The reaction mixture was cooled, filtered off and the precipitate was washed with water and petroleum ether (b.p. 40–60 °C). The solid product was crystallized from acetic acid to give (**1b**).

2.2.2. 3-[2-Oxo-5-(2-methoxyphenyl) furan-3(2H)-ylidene] indolin-2-one 1b

Dark brown solid, yield 77%; mp 120 °C; IR: 3315 for (NH), 1699 for (C═$O_{lactone}$) 1680-1645 for (C═O_{amide}) cm^{-1}. ^1H NMR: δ 10.00 (s, 1H, NH), 7.85-6.99 (m, 8H, 2Ar-H), 6.89 (s, 1H, CH), 3.25 (s, 3H, CH3 of CH_3O-Ar) ppm, ^{13}C NMR δ: 170.3, 167.4, 159.9, 146.2, 146.1, 144.0, 136.3, 128.2, 127.4, 126.6, 124.3, 122.7, 121.5, 114.2, 99.2, 55.9. Anal. $C_{19}H_{13}NO_4$ (319.304): Calcd: C, 71.46; H, 4.10; N, 4.39; Found: C, 71.53; H, 3.99; N, 4.53. Ms: m/z 319 M^+.

2.2.3. Synthesis of 1-[4-(1-acetyl-2-oxoindolin-3-ylidene)-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl] thiourea 2

A mixture of (1d) (0.01 mol) and thiosemicarbazide (0.01 mol) in absolute ethyl alcohol (30 ml) was heated under reflux for 3 h. The reaction mixture after cooling was poured upon cold water. The solid that separated was filtered off and crystallized from benzene to give (**2**).

Dark red solid, yield 55%; mp 205-7 °C; IR: 3285 for (NH), 3183 for (NH of NH_2), 1690-1675 for (C═O), 1606 for (C═N) cm^{-1}. ^1H NMR: δ 10.40 (s, 1H, NH), 9.6 (s, 2H, NH_2), 7.52-7.28 (m, 9H, 2Ar-H) and 3.07 (s, 3H, CH_3 of $COCH_3$) ppm, Anal. $C_{20}H_{15}N_5O_3S$ (405.37): Calcd: C, 59.25; H, 3.73; N, 17.28, S, 7.89 Found: C, 59.02; H, 3.87; N, 16.98; S, 8.12. Ms: m/z 405 M^+.

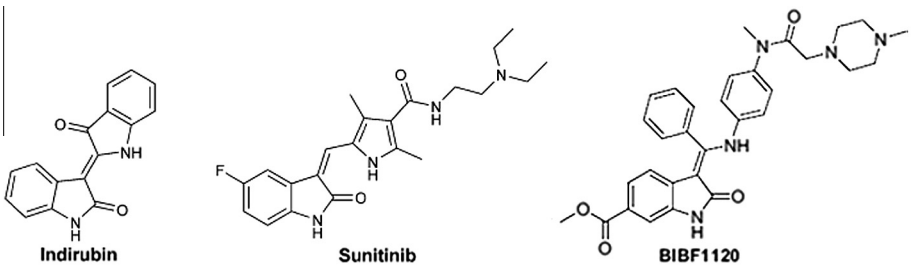


Figure 1 Structures of indolin-2-one derivatives.

2.2.4. Synthesis of 1-acetyl-3-(5-phenyl-2-thioxo-2,3-dihydroimidazo [1,5-b][1,2,4]-triazol-7-ylidene) indolin-2-one 3

Method A:

A solution of (1d) (0.01 mol) and thiosemicarbazide (0.01 mol) in glacial acetic acid (30 ml) was heated under reflux for 2 h. The reaction mixture after cooling was poured upon cold water. The solid product formed was filtered off and crystallized from ethyl alcohol to give (**3**).

Method B:

Heat (2) (0.01 mol) in glacial acetic acid (30 ml) for 2 h. The reaction mixture after cooling was poured upon cold water. The solid product formed was filtered off and crystallized from ethyl alcohol to give (3).

Dark violet solid, yield 65%; mp 188-90 °C; IR: 3202 for (NH), 1666-1621 for (C═O) cm^{-1}. ^1H NMR: δ 10.82 (s, 1H, NH), 7.96-7.11 (m, 9H, 2Ar-H) and 3.32 (s, 3H, CH_3 of $COCH_3$) ppm, ^{13}C NMR δ: 210.93, 209.44, 189.16, 172.22, 168.69, 129.31, 127.98, 114.96, 107.43, 83.07, 82.27, 55.54, 40.34, 39.79, 38.95, 32.52, 26.55, 14.66. Anal. $C_{20}H_{13}N_5O_2S$ (387.354): Calcd: C, 62.01; H, 3.38; N, 18.08; S, 8.26; Found: C, 61.95; H, 3.42; N, 17.65; S, 7.99. Ms: m/z 387 M^+.

*2.2.5. General procedure for synthesis of 3-[1amino-2-oxo-5-aryl-1,2-dihydropyrrol-3-Ylidene]indolin-2-ones **4a,b**, 3-[1-amino-5-oxo-2phenyl-1H imidazole 4(5H) Ylidene]indolin-2-one 4c and 1-acetyl-3[1-amino-5-oxo-2-phenyl-1H- imidazol-4(5H)-Ylidene]indolin-2-one (**4d**)*

A solution of (1a–d) (0.01 mol) and hydrazinehydrate (0.01 mol) in pyridine (50 ml) and few drops of phosphorus oxychloride were refluxed for 6 h. The solid product that separated after cooling was filtered off and crystallized from benzene to give (4a–d).

*2.2.5.1. 3-[1-Amino-2-oxo-5-(2-methylphenyl)-1, 2-dihydropyrrol-3-ylidene]indolin-2-one (**4a**)*. Yellow solid, yield 56%; decomp. at 140 °C mp165 °C; IR: 3260 for (NH), 3190 for (NH of NH_2), 1674-1655 for (C═O) cm^{-1} .^1H NMR: δ 10.43 (s, 1H, NH), 9.10 (s, 2H, NH_2), 7.69-7.02 (m, 8H, 2Ar-H), 6.40 (s, 1H, CH), 3.80 (s, 3H, CH_3 of CH_3-Ar) ppm, Anal. $C_{19}H_{15}N_3O_2$ (317.34): Calcd: C, 71.91; H, 4.76; N, 13.24; Found: C, 72.10; H, 4.85; N, 12.98.Ms: m/z 317 M^+.

*2.2.5.2. 3-[1-Amino-2-oxo-5-(2-methoxyphenyl)-1, 2-dihydropyrrol-3-ylidene]indolin -2-one (**4b**)*. Brown solid, yield 53%; decomp. at 110 °C mp 160 °C; IR: 3254 for (NH), 3179 for (NH of NH_2), 1670-1645 for (C═O) cm^{-1} .^1H NMR: δ 10.22 (s, 1H, NH), 8.99 (s, 2H, NH_2), 7.85-7.13 (m, 8H, 2Ar-H), 6.67 (s, 1H, CH), 3.24 (s, 3H, CH_3 of CH_3O-Ar) ppm, ^{13}C NMR δ: 159.12, 127.34, 127.09, 126.49, 124.27, 121.03, 114.27, 109.09, 101.24, 55.12, 40.32, 40.09, 39.76, 39.21, 38.93, 38.65, 35.65. Anal. $C_{19}H_{15}N_3O_3$ (333.34): Calcd: C, 68.46; H, 4.54; N, 12.61; Found: C, 68.23; H, 4.63; N, 12.73.Ms: m/z 333 M^+.

*2.2.5.3. 3-[1-Amino-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene]indolin -2-one (**4c**)*. Brown solid, yield 67%; decomp. at 120 °C mp 140 °C; IR: 3342 for (NH), 3203 for (NH of NH_2), 1670-1649 for (C═O) and 1601 for (C═N) cm^{-1}. ^1H NMR δ: 0.35 (s, 1H, NH), 9.25 (s, 2H, NH_2) and 8.01-7.32 (m, 9H, 2Ar-H) ppm, Anal. $C_{18}H_{14}N_4O_2$ (318.334): Calcd: C, 67.91; H, 4.43; N, 17.60; Found: C, 67.83; H, 4.03; N, 17.63.Ms: m/z 318 M^+.

*2.2.5.4. 1-Acetyl-3-[1-amino-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene]indolin -2-one (**4d**)*. Brown solid, yield 70%; decomp. at 100 °C mp 120 °C; IR: 3200 for (NH_2), 1671-1642 for (C═O) and 1599 for (C═N) cm^{-1}. ^1H NMR: δ 9.43 (s, 2H, NH_2), 7.95-7.18 (m, 9H, 2Ar-H) and 2.85 (s, 3H, CH_3 of $COCH_3$) ppm, Anal. $C_{19}H_{14}N_4O_3$ (346.342): Calcd: C, 65.89; H, 4.07; N, 16.18; Found: C, 65.53; H, 4.12; N, 16.43. Ms: m/z 346 M^+.

*2.2.6. General procedure for synthesis of 3-[1-(-2-methoxybenzylideneamino)-2-oxo-5-(2-methyl phenyl)-1,2-dihydropyrrol-3-ylidene]indolin-2-one (**5a**) and 3-[1-(2-methoxybenzylideneamino)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene]indolin-2-one (**5b**)*

An equimolar ratio of **4a**, **c** (0.01 mol) and o-methoxybenzaldehyde in ethanol (30 ml) and few drops of piperidine were refluxed for 6 h. The reaction mixture was concentrated and cooled. The solid that separated was filtered off and crystallized from ethyl alcohol to give (5a,b).

*2.2.6.1. 3-[1-(2-Methoxybenzylideneamino)-2-oxo-5-(p-tolyl)-1,2-dihydropyrrol-3-ylidene]indolin-2-one (**5a**)*. Orange solid, yield 50%; mp 102 °C; IR: 3207 for (NH), 1668-1650 for (C═O) cm^{-1}. ^1H NMR: δ 10.16 (s, 1H, NH), 8.33 (s, 1H, CH═N), 7.78-7.01 (m, 12H, 3Ar-H), 6.59 (s, 1H, CH), 3.85 (s, 3H, CH_3 of CH_3O-Ar) and 2.35 (s, 3H, CH_3 of CH_3-Ar) ppm, Anal. $C_{27}H_{21}N_3O_3$ (435.468): Calcd: C, 74.46; H, 4.86; N, 9.65; Found: C, 74.14; H, 4.34; 9.67.Ms: m/z 435 M^+.

*2.2.6.2. 3-[1-(2-Methoxybenzylideneamino)-5-oxo-2-phenyl-1H-imidazol-4(5H) -ylidene]indolin -2- one (**5b**)*. Brown solid, yield 45%; mp 158-60 °C; IR: 3195 for (NH), 1692-1668 for (C═O), 1615 for (C═N) cm^{-1}. ^1H NMR: δ 10.54 (s, 1H, NH), 8.21 (s, 1H, CH═N), 7.98-7.11 (m, 13H, 3Ar-H) and 3.67 (s, 3H, CH_3 of CH_3O-Ar) ppm, ^{13}C-NMR δ: 171.75, 157.57, 156.38, 141.05, 138.13, 132.92, 131.65, 131.23, 130.98, 129.43, 128.33, 127.51, 126.49, 125.10, 124.26, 121.96, 120.96, 120.62, 115.31, 112.00, 111.74, 109.97, 55.60 .Anal. $C_{25}H_{18}N_4O_3$ (422.434): Calcd: C, 71.08; H, 4.30; N, 13.27; Found: C, 70.86; H, 4.54; N, 13.65. Ms: m/z 422 M^+.

*2.2.7. General procedure for synthesis of 3-(1-[2-(2-methoxyphenyl)-5-oxo-2H-imidazol-1(5H)-yl)-2-oxo-5-(2-3-(1-[2-(2methoxyphenyl)-4-oxothiazolidin-3-yl)-2-oxo-5-(2-methyl phenyl)-1, methyl phenyl)-1,2-dihydropyrrol-3-ylidene]indolin-2-one(**6a**), 3-(1-[2-(2methoxyphenyl)-5-oxo-2H-imidazol-1(5H)-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H-ylidene] indolin-2-one (**6b**) and 2-dihydopyrrol-3-ylidene] indolin-2-one (**6c**)*

A mixture of 3-[1-(methoxybenzylideneamino)-2-oxo-5-aryl-1 and 2-dihydro-pyrrol-3-ylidene] indolin-2-ones (5a, b) (0.01 mol) was heated above its melting point with appropriate acetic acid derivatives (0.01 mol) in sand bath for 3 h. The product which solidified on cooling was triturated with pet. ether (b.p. 40–60 °C), filtered off and crystallized from benzene to give (6a–c).

*2.2.7.1. 3-(1-[2-(2-Methoxyphenyl)-5-oxo-2H-imidazol-1(5H)-yl)-2-oxo-5-(p-tolyl)-1,2-dihydropyrrol-3-ylidene] indolin-2-one (**6a**)*. Pale brown solid, yield 47%; decomp. at 104 °C; IR: 3205-3190 for (2NH) and 1661-1634 for (C═O) cm^{-1}. ^1H NMR: δ 10.52 (s, 1H, NH), 9.88 (quartet, 1H, NH), 8.01-7.20 (m, 12H, 3Ar-H), 6.80 (s, 1H, CH), 6.73 (d, 1H, CH), 4.12 (d, 2H, CH2), 3.73 (s, 3H, CH_3 of CH_3O-Ar) and 2.93 (s, 3H, CH_3 of CH_3-Ar) ppm, Anal. $C_{29}H_{24}N_4O_4$ (492.522): Calcd: C, 70.72; H, 4.91; N, 11.38; Found: C, 71.00; H, 4.62; N, 11.65. Ms: m/z 492 M^+.

*2.2.7.2. 3-(1-[2-(2-Methoxyphenyl)-5-oxo-2H-imidazol-1(5H)-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene]indolin-2-one (**6b**)*. Pale brown solid, yield 50%; mp.230 °C; IR: 3213-3185 for (2NH), 1670-1643 for (C═O) and 1600 for (C═N) cm^{-1}. ^1H NMR: δ 10.88 (s, 1H, NH), 9.99 (quartet, 1H, NH), 7.98-7.05 (m, 13H, 3Ar-H), 6.78 (d, 1H, CH), 4.20 (d, 2H, CH_2) and 3.70 (s, 3H, CH_3 of CH_3O-Ar) ppm, Anal. $C_{27}H_{21}N_5O_4$ (479.488): Calcd: C, 67.63; H, 4.41.; N, 14.61; Found: C, 67.54; H, 4.68; N, 14.65. Ms: m/z 479 M^+.

*2.2.7.3. 3-(1-[2-(2-Methoxyphenyl)-4-oxothiazolidin-3-yl)-2-oxo-5-(p-tolyl)1,2-dihydropyrrol-3 ylidene] indolin-2-one (**6c**)*. Brown solid, yield 48%; mp 90-2 °C; IR: 3213 for (NH) and 1670-1660 for (C═O) cm^{-1}. ^1H NMR: δ 8.94 (s, 1H, NH), 7.98-7.14 (m, 12H, 3Ar- H), 6.19-6.03 (s, 2H, 2CH), 3.90 (s, 2H, CH_2), 3.18 (s, 3H, CH3 of CH3O-Ar) and 2.51 (s, 3H, CH_3 of CH_3-Ar) ppm, ^{13}C NMR δ: 170.3, 168.8, 160.5, 158.4, 144.0, 142.1, 139.2, 137.6, 136.8, 131.3, 129.8, 129.0, 128.2, 126.6, 126.3, 124.3, 122.7, 121.5, 121.0, 116.6, 114.2, 100.1, 56.5, 45.6, 36.1, 24.3. Anal. $C_{29}H_{23}N_3O_4S$ (509.504): Calcd: C, 68.36; H, 4.55.; N, 8.25; S, 6.28, Found: C, 68.65; H, 4.35; N, 8.65; S, 6.54. Ms: m/z 509 M^+.

*2.2.7. General procedure for synthesis of 3-oxo-N-[2-oxo-3-(2-oxoindolin-3-ylidene)-5-aryl-2, 3-dihydropyrrol-1-yl] butanamides (**7a, b**) and N-[4-(1-acetyl-2-oxoindolin-3-ylidene)-5-oxo-2-phenyl-4, 5-dihydroimidazol-1-yl]-3oxobutanamide (**7c**)*

A solution of (4a, b, d) (0.01 mol) and ethyl acetoacetate (0.01 mol) in ethyl alcohol (50 ml) was refluxed for 3 h. The solid product that separated after cooling was filtered off and crystallized from benzene to give (**7a**–**c**).

*2.2.7.1. 3-Oxo-N-[2-oxo-3-(2-oxoindolin-3-ylidene)-5-(2-methylphenyl)-2,3-dihydropyrrol-1-yl] butanamide (**7a**)*. Orange solid, yield 55%; mp 180 °C; IR: 3267-3199 for (2NH), 1670-1645 for (C═O) cm^{-1}. ^1H NMR: δ 10.22 (s, 1H, NH), 9.99 (s, 1H, NH), 7.85- 7.13 (m, 8H, 2Ar-H), 6.67 (s, 1H, CH), 3.84 (s, 2H, CH_2 of $COCH_2$), 3.12 (s, 3H, CH_3 of $COCH_3$) and 2.89 (s, 3H, CH_3 of CH_3-Ar) ppm. ^{13}C NMR δ: 176.26, 143.60, 138.80, 137.98, 132.36, 129.45, 129.39, 128.97, 127.34, 125.69, 125.55, 125.12, 124.27, 122.35, 121.04, 115.61, 109.48, 109.02, 106.75, 60.40, 29.46. Anal. $C_{23}H_{19}N_3O_4$ (401.412): Calcd: C, 68.81; H, 4.77; N, 10.47; Found: C, 69.21; H, 4.42; N, 10.76. Ms: m/z 401 M^+.

*2.2.7.2. 3-Oxo-N-[2-oxo-3-(2-oxoindolin-3-ylidene)-5-(2-methoxyphenyl)-2,3-dihydropyrrol-1-yl] butanamide (**7b**)*. Pale brown solid, yield 50%; mp 178-80 °C; IR: 3325-3278 for (2NH), 1685-1645 for (C═O) cm^{-1}. ^1H NMR: δ 10.15 (s, 1H, NH), 9.40 (s, 1H, NH), 7.88-7.12 (m, 8H, 2Ar-H), 6.81 (s, 1H, CH), 3.99 (s, 2H, CH_2 of $COCH_2$), 3.38 (s, 3H, CH_3 of $COCH_3$) and 3.02 (s, 3H, CH_3 of CH_3O-Ar) ppm, Anal. $C_{23}H_{19}N_3O_5$ (417.412): Calcd: C, 66.18; H, 4.59; N, 10.07; Found: C, 66.21; H, 4.42; N, 10.46.Ms: m/z 417 M^+.

*2.2.7.3. 3-N-[4-(1-Acetyl-2-oxoindolin-3-ylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl]-3-oxobutanamide (**7c**)*. Brown solid, yield 62%; mp 98-100 °C; IR: 3225 for (NH), 1670-1645 for (C═O) and 1617 for (C═N) cm^{-1}. ^1H NMR: δ 9.98 (s, 1H, NH), 7.98-7.32 (m, 9H, 2Ar-H), 3.87 (s, 2H, CH_2 of $COCH_2$) 3.25-2.98 (s, 6H, $2CH_3$ of $2COCH_3$) ppm, Anal. $C_{23}H_{18}N_4O_5$ (430.414): Calcd: C, 64.18; H, 4.22; N, 13.02; Found: C, 64.01; H, 4.34; N, 12.83. Ms: m/z 430 M^+.

*2.2.9. General procedure for synthesis of 3-[1-(3-methylisoxazol-5-ylamino)-2-oxo-5-aryl-1,2-dihydropyrrol-3-ylidene] indolin-2-ones (**8a, b**)*

A mixture of (7a, b) (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) in pyridine (30 ml) was heated under reflux for 2 h. The reaction mixture was evaporated under reduced pressure. The solid product formed was crystallized from benzene to give (8a,b).

*2.2.9.1. 3-[1-(3-Methylisoxazol-5-ylamino)-2-oxo-5-(2-methyl phenyl)-1,2-dihydropyrrol-3-ylidene]indolin-2-one (**8a**)*. Yellow solid, yield 65%; mp 128-30 °C; IR: 3300-3211 for (2NH), 1689-1651 for (C═O) and 1600 for (C═N) cm^{-1}. ^1H NMR: δ 10.51 (s, 1H, NH), 9.80 (s, 1H, NH), 7.82-7.35 (m, 8H, 2ArH), 6.736.54 (s, 2H, 2CH), 3.53 (s, 3H, CH_3 of CH_3-Ar) and 3.10 (s, 3H, CH_3) ppm, Anal. $C_{23}H_{18}N_4O_3$ (398.414): Calcd: C, 69.33; H, 4.55.; N, 14.07; Found: C, 69.21; H, 4.67; N, 13.98. Ms: m/z 398 M^+.

*2.2.9.2. 3-[1-(3-Methylisoxazol-5-ylamino)-2-oxo-5-(2-methoxyphenyl)-1,2-dihydropyrrol-3- ylidene]indolin-2-one (**8b**)*. Orange solid, yield 57%; mp 195-7 °C; IR: 3400-3173 for (2NH), 1680-1651 for (C═O) and 1607 for (C═N) cm^{-1}. ^1H NMR: δ 10.33 (s, 1H, NH), 8.99 (s, 1H, NH), 7.98-7.23 (m, 8H, 2Ar-H), 6.88-6.63 (s, 2H, 2CH), 3.72 (s, 3H, CH_3 of CH_3O-Ar) and 2.93 (s, 3H, CH_3) ppm, ^{13}C NMR: δ 170.3, 160.7, 160.5, 159.0, 158.9, 144.0, 142.1, 139.2, 136.8, 128.2, 127.4, 126.6, 124.3, 122.7, 121.5, 114.2, 100.2, 1001, 55.9, 17.6. Anal. $C_{23}H_{18}N_4O_4$ (414.414): Calcd: C, 66.66; H, 4.38.; N, 13.52; Found: C, 67.00; H, 4.58; N, 13.45. Ms: m/z 414 M^+.

*2.2.10. General procedure for synthesis of 3-[1-(3-methyl-1H-pyrazol-5-ylamino)-2-oxo-5-aryl-1,2-dihydropyrrol-3-ylidene] indolin-2-ones (**8c,d**) and 1-acetyl-3-[1-(3-methyl-1H-pyrazol-5-ylamino)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene] indolin-2-one (**8e**)*

A solution of (7a, b, d) (0.01 mol) and hydrazine hydrate (0.01 mol) in pyridine (50 ml) and few drops of phosphorus oxychloride were refluxed for 6 h. The solid that separated after cooling was filtered off and crystallized from benzene to give (8c–e).

*2.2.10.1. 3-[1-(3-Methyl-1H-pyrazol-5-ylamino)-2-oxo-5-(2-methyl phenyl)-1,2-dihydropyrrol-3-ylidene] indolin-2-one (**8c**)*. Green solid, yield 50%; mp 246-8 °C; IR: 3208-3180

for (3NH), 1741-1651 for (C═O) and 1601 for (C═N) cm^{-1}. ^1H NMR: δ 10.34 (s, 1H, NH), 10.12 (s, 1H, NH), 9.49 (s, 1H, NH), 7.73-7.01 (m, 8H, 2Ar-H), 6.40-6.23 (s, 2H, 2CH), 3.34 (s, 3H, CH_3 of CH_3-Ar) and 3.12 (s, 3H, CH_3) ppm, Anal. $C_{22}H_{18}N_6O_3$ (414.432): Calcd:C, 63.76; H, 4.38.; N, 20.28; Found: C, 63.86; H, 4.55; N, 20.45. Ms: *m/z* 414 M^+.

*2.2.10.2. 3-[1-(3-Methyl-1H-pyrazol-5-ylamino)-2-oxo-5-(2-methoxyphenyl)-1,2-dihydropyrrol-3-ylidene] indolin-2-one (**8d**).* Green solid, yield 58%; mp158 °C; IR: 3310-3211 for (3NH), 1740-1660 for (C═O) and 1607 for (C═N) cm^{-1}. ^1H NMR: δ 10.30 (s, 1H, NH), 10.01 (s, 1H, NH), 9.33 (s, 1H, NH), 7.87-7.21 (m, 8H, 2Ar-H), 6.65-6.32 (s, 2H, 2CH), 3.80 (s, 3H, CH_3 of CH_3O-Ar) and 2.52 (s, 3H, CH_3) ppm, Anal. $C_{23}H_{19}N_5O_2$ (397.432): Calcd: C, 69.51; H, 4.82.; N, 17.62; Found: C, 69.71; H, 4.85; N, 17.85. Ms: *m/z* 397 M^+.

*2.2.10.3. 3-1-Acetyl-3-[1-(3-methyl-1H-pyrazol-5-ylamino)-5-oxo-2-phenyl-1H-imidazol-4 (5H) ylidene]indolin-2-one (**8e**).* Green solid, yield 60%; mp 178-80 °C; IR: 3201-3195 for (2NH), 1704-1650 for (C═O) and 1610-1601 for (C═N) cm^{-1}. ^1H NMR: δ 10.20 (s, 1H, NH), 9.40 (s, 1H, NH), 7.92-7.02 (m, 9H, 2Ar-H), 6.41 (s, 1H, CH), 3.74 (s, 3H, $COCH_3$) and 2.92 (s, 3H, CH_3) ppm, ^{13}C NMR δ: 172.1, 166.0, 161.7, 156.5, 145.3, 144.7, 141.0, 140.3, 139.8, 130.2, 128.9, 128.7, 128.2, 126.6, 126.1, 124.3, 122.7, 121.5, 92.9, 20.2, 17.4. Anal. $C_{23}H_{18}N_6O_3$ (426.434): Calcd: C, 64.78; H, 4.25; N, 19.71; Found: C, 64.52; H, 4.32; N, 20.02. Ms: *m/z* 426 M^+.

*2.2.11. General procedure for synthesis of 2-chloro-N-[2-oxo-3-(2-oxo indolin-3-ylidene)-5-(2-methoxyphenyl)-2,3-dihydropyrrol-1-yl] acetamide (**9a**) and N-[4-(1-acetyl-2-oxoindolin-3-ylidene)-5-oxo-2phenyl4,5dihydroimidazol-1-yl]-2-chloroacetamide (**9b**)*

A mixture of (4b, d) (0.01 mol) with chloroacetylchloride (20 ml) was refluxed for 3 h. The reaction mixture was evaporated under reduced pressure. The solid product formed was filtered off and crystallized from ethyl alcohol to give the title compounds.

*2.2.11.1. 2-Chloro-N-[2-oxo-3-(2-oxoindolin-3-ylidene)-5-(2-methoxyphenyl)-2,3-dihydro-pyrrol-1-yl] acetamide (**9a**).* Brown solid, yield 64%; mp 60-62 °C; IR: 3201-3150 for (2NH), 1680-1666 for (C═O) and 1617 for (C═N) cm^{-1}. ^1H NMR: δ 10.53 (s, 1H, NH), 9.80 (s, 1H, NH), 7.99-7.21 (m, 8H, 2Ar-H), 6.95 (s, 1H, CH), 4.23 (s, 2H, CH_2 of $COCH_2$) and 3.30 (s, 3H, CH_3 of CH_3O-Ar) ppm, Anal. $C_{21}H_{16}N_3O_4Cl$ (409.818): Calcd: C, 61.54; H, 3.94; N, 10.26; Cl, 8.65; Found: C, 61.89; H, 4.02; N, 10.56; Cl,8.21.Ms: *m/z* 409 M^+.

*2.2.11.2. 2-N-(4-[1-Acetyl-2-oxoindolin-3-ylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl] 2-chloroacetamide (**9b**).* Brown solid, yield 48%; mp 90-2 °C; IR: 3357-3248 for (2NH), 1663-1635 for (C═O) and 1601 for (C═N) cm^{-1}. ^1H NMR: δ 11.25 (s, 1H, NH), 10.52 (s, 1H, NH), 7.98-7.23 (m, 8H, 2Ar-H), 6.80 (s, 1H, CH), 4.37 (s, 2H, CH_2) and 3.51 (s, 3H, CH_3 of CH_3O-Ar) ppm, Anal. $C_{21}H_{16}N_4O_3$ (372.378): Calcd: C, 67.73; H, 4.33.; N, 15.05; Found: C, 67.87; H, 4.12; N, 14.95. Ms: *m/z* 372 M+.

2.2.12. Synthesis of 8-(2-oxoindolin-3-ylidene)-6-(2-methoxyphenyl) pyrrolo[1,2-b][1,2,4] triazin-3(2H,4H,8H)-one (10)

A mixture of (9a) (0.01 mol) with ammonium acetate (0.01 mol) in glacial acetic acid was refluxed for 6 h. The solid product that separated after cooling was filtered off and crystallized from benzene to give (**10**).

Brown solid, yield 48%; mp 90-2 °C; IR: 3357-3248 for (2NH), 1663-1635 for (C═O) and 1601 for (C═N) cm^{-1}. ^1H NMR: δ 11.25 (s, 1H, NH), 10.52 (s, 1H, NH), 7.98-7.23 (m, 8H, 2Ar-H), 6.80 (s, 1H, CH), 4.37 (s, 2H, CH_2) and 3.51 (s, 3H, CH_3 of CH_3O-Ar) ppm, Anal. $C_{21}H_{16}N_4O_3$ (372.378): Calcd: C, 67.73; H, 4.33; N, 15.05; Found: C, 67.87; H, 4.12; N, 14.95. Ms: *m/z* 372 M+.

*2.2.13. General procedure for synthesis of 1-[2-oxo-3-(2-oxoindolin-3-ylidene)-5-(2-methoxyphenyl)-2,3-dihydropyrrol-1-yl] piperazine-2,6-dione (**11a**) and 4-[2-oxo-3-(2-oxoindolin-3-ylidene)-5-(2-methoxyphenyl)-2,3-dihydropyrrol-1-yl] thiomorpholine-3,5-dione (**11b**)*

A solution of (9a) (0.01 mol) and glycine or thioglycolic acid (0.01 mol) was refluxed for 6 h. in pyridine (50 ml). The reaction mixture after cooling was evaporated under reduced pressure; the residue was poured upon cold water. The solid product formed was filtered off and crystallized from benzene to give (**11a**, **b**).

*2.2.13.1. 1-[2-Oxo-3-(2-oxoindolin-3-ylidene)-5-(2methoxyphenyl)-2,3-dihydropyrrol-1-yl] piperazine-2,6-dione (**11a**).* Brown solid, yield 60%; decomp. at 80, mp 188-90 °C; IR: 3310-3270 for (2NH) and 1663 for (C═O sharp) cm^{-1}. ^1H NMR: δ 10.90 (s, 1H, NH), 10.23 (quin., 1H, NH), 7.99-7.30 (m, 8H, 2Ar-H), 5.05 (s, 1H, CH), 3.89-3.77 (d, 4H, $2CH_2$) and 2.95 (s, 3H, CH_3 of CH_3O-Ar) ppm, Anal. $C_{23}H_{18}N_4O_5$ (430.414): Calcd: C, 64.18; H, 4.22; N, 13.03; Found: C, 64.47; H, 4.53; N, 12.95. Ms: *m/z* 430 M^+.

*2.2.13.2. 4-[2-Oxo-3-(2-oxoindolin-3-ylidene)-5-(2-methoxyphenyl)-2,3-dihydropyrrol-1-yl] thiomorpholine-3,5-dione (**11b**).* Brown solid, yield 48%; mp 100-2 °C; IR: 3190 for (NH) and 1670 for (C═O sharp) cm^{-1}. ^1H NMR: δ 11.60 (s, 1H, NH), 8.00-7.39 (m, 8H, 2Ar-H), 5.15 (s, 1H, CH), 3.91-3.67 (s, 4H, $2CH_2$) and 2.51(s, 3H, CH_3 of CH_3O-Ar) ppm, ^{13}C NMR δ: 170.3, 168.3, 160.5, 159.9, 144.0, 142.1, 139.2, 136.8, 128.2, 127.4, 126.6, 124.3, 122.7, 121.5, 114.2, 100.1, 55.9, 38.7 .Anal. $C_{23}H_{17}N_3O_5S$ (447.396): Calcd: C, 61.74; H, 3.83; N, 9.39; S, 7.15; Found: C, 61.47; H, 3.59 N, 9.56; S, 7.55. Ms: *m/z* 447 M^+.

2.3. Biological screening

The primary evaluation of *in vitro* cytotoxicity against human tumor cell of the complexes under investigation has been tested in the National Cancer Institute (NCI), Cairo University using the method of Skehan and Storeng, 1990. The study also involved the cytotoxicity evaluation of Doxorubicin as antitumor agent reference as follows:

1. Cells were plated in 96-multiwell plate (105 cells/well) for 24 h before treatment with the compound to allow attachment of cell to the wall of the plate.

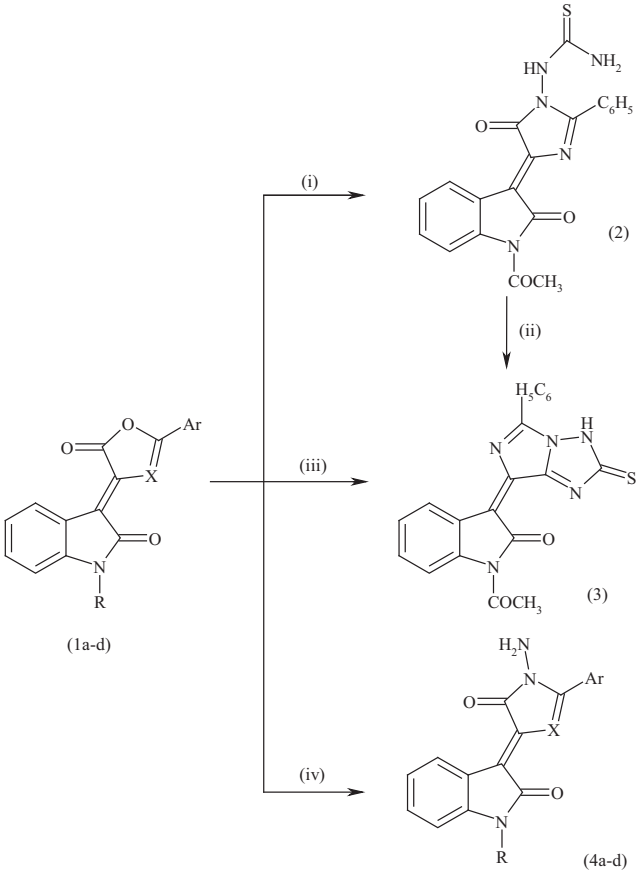
2. Different concentrations of the compound under test (0, 1, 2.5, 5 and 10 μg/mL) were added to the cell monolayer triplicate walls that were prepared for each individual dose.
3. Monolayer cells were incubated with the compound for 48 h at 37 °C and in atmosphere of 5% CO_2.
4. After 48 h, cells were fixed, washed and stained with sulforhodamine-B stain.
5. Excess stain was washed with acetic acid and attached stain was recovered with Tris–EDTA buffer.
6. Color intensity was measured in an ELISA reader.
7. The relation between the surviving fraction and drug concentration is plotted to give survival curve of cancer breast cell line after the specified compound.

The results of the *in vitro* cytotoxicity activity on human tumor cell line MCF7 (breast cell) were determined according to the dose values of the drug exposure required to reduce survival in the cell lines to 50%.

3. Results and discussion

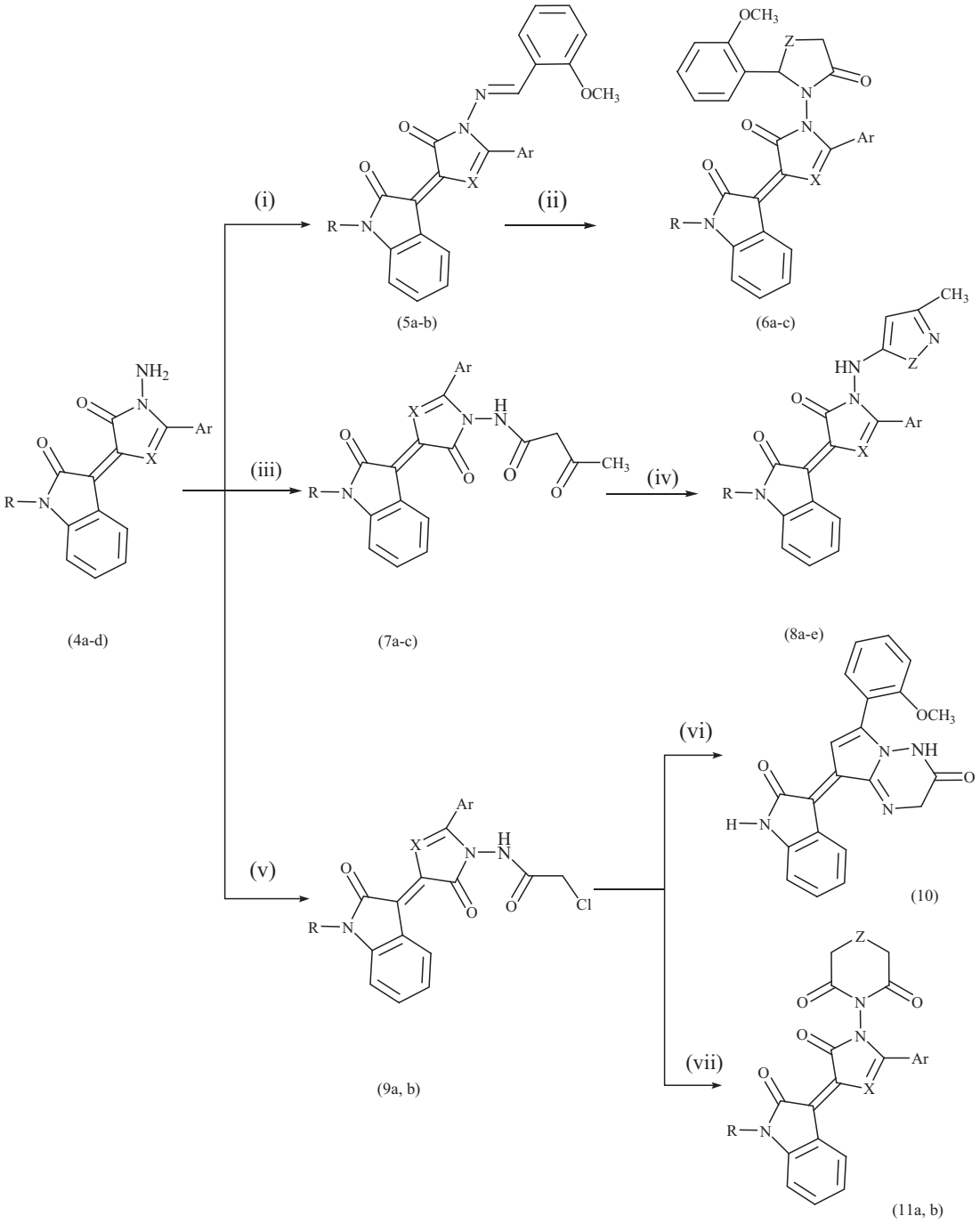
We reported early the traditional Perkin reaction of isatin with β-aroyl propionic acids to give 1-acetyl-3-(2-oxo-5-arylfuran-3(2H)-ylidene) indolin-2-ones (El Abbady et al., 1974), in the present study we apply conventional Perkin reaction under microwave reactor to give 3-(2-oxo-5-arylfuran-3(2H)-ylidene) indolin-2-ones **1a**–**c**. However, 3-(5-oxo-2-phenyloxazol-4(5H)-ylidene) indolin-2-one **1d** was obtained from the reaction of hippuric acid with isatin under traditional Perkin conditions according to the method reported in our previous work (Kandile et al., 1991a,b). The reaction of compound **1d** with thiosemicarbazide was studied. It was noticed that the reaction is solvent dependant. Thus conducting the reaction of compound **1d** with thiosemicarbazide in refluxing absolute ethanol for 3 h produce 1-[4-(1-acetyl-2-oxoindolin-3-ylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl] thiourea **2**. However, ring closure occurred on conducting the reaction in refluxing glacial acetic acid for 3 h to afford the cyclized product 1-acetyl-3-(5-phenyl-2-thioxo-2,3-dihydro-imidazo[1,5-b][1,2,4]triazol-7-ylidene) indolin-2-one **3** as illustrated in Scheme 1. ^{1}H NMR spectrum of compound **2** displayed NH protons of the NH_2 group which disappeared by addition of D_2O. The chemical reactivity of compounds **2a**–**d** towards some nucleophiles such as hydrazine hydrate was investigated. When compounds **2a**–**d** were allowed to react with hydrazine hydrate in refluxing pyridine and few drops of phosphorus oxychloride it afforded 3-[(1-amino-2-oxo-5-(aryl)-1,2-dihydropyrrol-3-ylidene] indolin-2-ones (**4a**–**d**). The structures of these compounds were established from FTIR, ^{1}H NMR, ^{13}C NMR, and MS spectra and elemental analysis. The ^{13}C NMR of 3-[1-amino-2-oxo-5-(2-methoxyphenyl)-1,2-dihydropyrrol-3-ylidene] indolin-2-one (**4b**) showed bands at 159.12, 127.34, 127.09, 126.49, 124.27, 121.03, 114.27, 109.09, 101.24, 55.12, 40.32, 40.09, 39.76, 39.21, 38.93, 38.65, and 35.65. The synthetic route used to synthesize these compounds is outlined in Scheme 1.

The structures of 3-[(1-amino-2-oxo-5-(4-aryl)-1,2-dihydropyrrol-3-ylidene]indolin-2-ones (**4a,c**) were confirmed chemically by reaction with 2-methoxybenzaldehyde to form the corresponding Schiff products (**5a,b**) named 3-[1(2-methoxybenzylideneamino)-2-oxo-5-(p-tolyl)-1,2-dihydropyrrol-3-ylidene] indolin-2-one (**5a**) and 3-[1-(2-methoxy-benzylideneamino)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene] indolin-2-one (**5b**) as well as physically by spectral and analytical data. ^{1}H NMR of 3-[1-(2-methoxybenzylidene-amino)-2-oxo-5-(2-methylphenyl)-1,2-dihydropyrrol-3-ylidene] indolin-2-one (**5a**) shows bands at δ 10.16 (s, 1H, NH), 8.33 (s, 1H, CH═N), 7.78-7.01 (m, 12H, 3Ar-H), 6.59 (s, 1H, CH), 3.85 (s, 3H, CH_3 of CH_3O-Ar) and 2.35 (s, 3H, CH_3 of CH_3-Ar) ppm. The Schiff products were utilized as key starting materials for the synthesis of the imidazolo and thiazolo derivatives .Attempts to cyclize the Schiff products 5a,b to the corresponding imidazolo derivatives named 3-[1-(2-(2-methoxyphenyl)-5-oxo-2H-imidazol-1(5H)-yl)-2-oxo-5-(p-tolyl)-1,2-dihydropyrrol-3-ylidene] indolin-2-one (**6a**), and 3-[1-(2(2methoxyphenyl)-5-oxo-2H-imidazol-1(5H)-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene] indolin-2-one (**6b**) respectively by reaction of the Schiff bases (**5a**,**b**) with glycine in the presence of few drops of piperidine as a catalyst were performed. The ^{1}H NMR spectrum of 3-[1-(2-(2-methoxyphenyl)-5-oxo-2H-imidazol-1(5H)-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene] indolin-2-one (**6b**) showed bands at δ 10.88 (s, 1H, NH), 9.99 (t, 1H, NH), 7.98-7.05 (m, 13H, 3Ar-H), 4.20 (d, 2H, CH_2) and 3.70 (s, 3H, CH_3 of CH_3O-Ar) ppm. Also the Schiff product (**5a**) was cyclized to the corresponding thiazolo derivative 3-[1-(2-(2-methoxyphenyl)-4-oxothiazolidin-3-yl)-2-oxo-5-(2-methyl phenyl)-1,2-dihydopyrrol-3-ylidene] indolin-2-one (**6c**) by the same



Scheme 1 Reagents and conditions; (i) $NH_2NHCSNH_2$/EtOH, reflux; (ii) ACOH, reflux; (iii) $NH_2NHCSNH_2$/ACOH, reflux; (iv) $NH_2NH_2H_2O$/pyridine/$POCl_3$, reflux.

manner with thioglycolic acid. The pyrrolones (**4a**–**c**) were treated with different electrophiles in an attempt to obtain different heterocycles. The reaction of (**4a,b,d**) with ethyl acetoacetate afforded the corresponding key products 3-oxo-N-[2-oxo-3-(2-oxoindolin-3-ylidene)-5-aryl-2,3-dihydro-pyrrol-1-yl]butanamide (**7a**,**b**) and N-[4-(1-acetyl-2-oxoindolin-3-ylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl]-3-oxobutanamide (**7c**) which show no bands for the NH_2 group in IR and ^1H NMR spectra. The ^{13}C NMR of 3-oxo-N-[2-oxo-3-(2-oxoindolin-3-ylidene)-5-(2-methyl phenyl)-2,3-dihydropyrrol-1-yl] butanamide (**7a**) showed bands at 176.26, 143.60, 138.80,137.98, 132.36, 129.45, 129.39, 128.97, 127.34, 125.69, 125.55, 125.12, 124.27, 122.35, 121.04, 115.61, 109.48, 109.02, 106.75, 60.40 and 29.46. The oxazolo derivatives 3-[1-(3-methylisoxazol-5-ylamino)-2-oxo-5-aryl-1,2-dihydropyrrol-3-ylidene] indolin-2-ones (**8a**,**b**) were obtained by reaction of (**7a**,**b**) with hydroxylamine hydrochloride in the presence of phosphorus oxychloride .While the pyrozolo derivatives 3-[1-(3-methyl-1H-pyrazol-5-ylamino)-2-oxo-5-aryl-1,2-dihydro-pyrrol-3-ylidene] indolin-2-ones (**8c**,**d**) and 1-acetyl-3-[1-(3-methyl-1H-pyrazol-yl-amino)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene] indolin-2-one



Scheme 2 Reagents and conditions: (i) $CH_3OC_6H_4CHO$/EtOH/piperidine, reflux; (ii) $ZHCH_2COOH$, fusion; (iii) $CH_3COCH_2COOC_2H_5$/EtOH, reflux; (iv) $NH_2NH_2H_2O$ or NH_2OH HCl/pyridine/$POCl_3$; (v) $ClCH_2COCl$/reflux; (vi) CH_3COONH_4/glacial ACOH.

Table 1 New synthesized compounds.

Entry	Compound	R	Ar	X	Z
1	1_b	H	$C_6H_4OCH_3$-o	CH	
2	2	$COCH_3$	C_6H_5	N	
3	3	$COCH_3$	C_6H_5	N	
4	4_a	H	$C_6H_4CH_3$-o	CH	
5	4_b	H	$C_6H_4OCH_3$-o	H	
6	4_c	H	$C_6H_4CH_3$-o	N	
7	4_d	$COCH_3$	C_6H_5	N	
8	5_a	H	$C_6H_4CH_3$-o	CH	
9	5_b	H	C_6H_5	N	
10	6_a	H	$C_6H_4CH_3$	CH	NH
11	6_b	H	C_6H_5	N	NH
12	6_c	H	$C_6H_4CH_3$-o	CH	S
13	7_a	H	$C_6H_4CH_3$-o	CH	
14	7_b	H	$C_6H_4OCH_3$-o	CH	
15	7_c	$COCH_3$	C_6H_5	N	
16	8_a	H	$C_6H_4CH_3$-o	CH	O
17	8_b	H	$C_6H_4OCH_3$-o	CH	O
18	8_c	H	$C_6H_4OCH_3$-o	N	NH
19	8_d	H	$C_6H_4CH_3$-o	CH	NH
20	8_e	$COCH_3$	C_6H_5	N	NH
21	9_a	H	$C_6H_4OCH_3$-o	CH	
22	9_b	H	C_6H_5	N	
23	11_a	H	$C_6H_4OCH_3$-o	CH	NH
24	11_b	H	$C_6H_4OCH_3$-o	CH	S

8e were obtained by reaction of (**7a**, **b**, **d**) with hydrazine hydrate in the presence of phosphorus oxychloride in good yield, good analytical and spectral data. The ^{1}H NMR of 3-[1-(3-methyl-1H-pyrazol-5-ylamino)-2-oxo-5-(2-methoxy-phenyl)-1,2dihydropyrrol-3-ylidene] indolin-2-one (**8d**) showed bands at δ 10.30 (s, 1H, NH), 10.01 (s, 1H, NH), 9.33 (s, 1H, NH), 7.87-7.21 (m, 8H, 2Ar-H), 6.65-6.32 (s, 2H, 2CH),3.80 (s, 3H ,CH_3 of CH_3O-Ar) and 2.52 (s, 3H, CH_3) ppm. The reaction of pyrrolono derivatives (**4b**,**d**) with chloroacetylchloride yielded 2-chloro-N-[2-oxo-3-(2-oxoindolin-3-ylidene)-5-(2-methoxyphenyl)-2,3dihydro-pyrrol-1-yl] acetamide (**9a**) and N-[4-(1-acetyl-2-oxoindolin-3-ylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl]-2-chloro-acetamide (**9b**). The IR of 2 -chloro-N-[2-oxo-3-(2-oxoindolin-3-ylidene)-5-(2-methoxyphenyl)-2, 3dihydropyrrol-1-yl] acetamide (**9a**) showed bands at 3201-3150 for (2NH), 1680-1666 for (C═O) and 1617 for (C═N) cm^{-1}. 8-(2-oxo-indolin-3-ylidene)-6-(2-methoxyphenyl) pyrrolo [1,2-b][1,2,4]triazin-3(2H,4H,8H)-one (**10**) have been synthesized via reaction of 2-chloro-N-[2-oxo-3-(2-oxoindolin-3-ylidene)-5-(2-methoxyphenyl)-2,3dihydropyrrol-1-yl] acetamide (**9a**) with ammonium acetate in glacial acetic acid. As indicated in Scheme 2 the title compounds named 1-[2-oxo-3-(2-oxoindolin-3-ylidene)-5-(4-methoxyphenyl)-2, 3-dihydropyrrol-1-yl] piperazine-2,6-dione (**11a**) and 4-[2-oxo-3-(2-oxoindolin-3-ylidene)-5-(2-methoxy-phenyl)-2,3-dihydropyrrol-1-yl] thiomorpholine-3,5-dione (**11b**) were prepared via reaction of (**9a**,**b**) with glycine and thioglycolic acid respectively. Further supports for the structure of these compounds were obtained from IR, ^{1}H NMR, and MS spectra. The synthetic route used to synthesize these compounds is outlined in Scheme 2.

All the newly synthesized compounds are listed in Table 1.

4. *In vitro* cytotoxicity evaluation

Three of the newly synthesized compounds **6c**, **8d** and **11b** were selected as prototypes and screened against a panel human tumor cell line ***MCF-7*** (breast cancer). Primary anticancer assay was performed in accordance with the protocol of the National Cancer Institute, Cairo University, Egypt by the method described in Section 2.

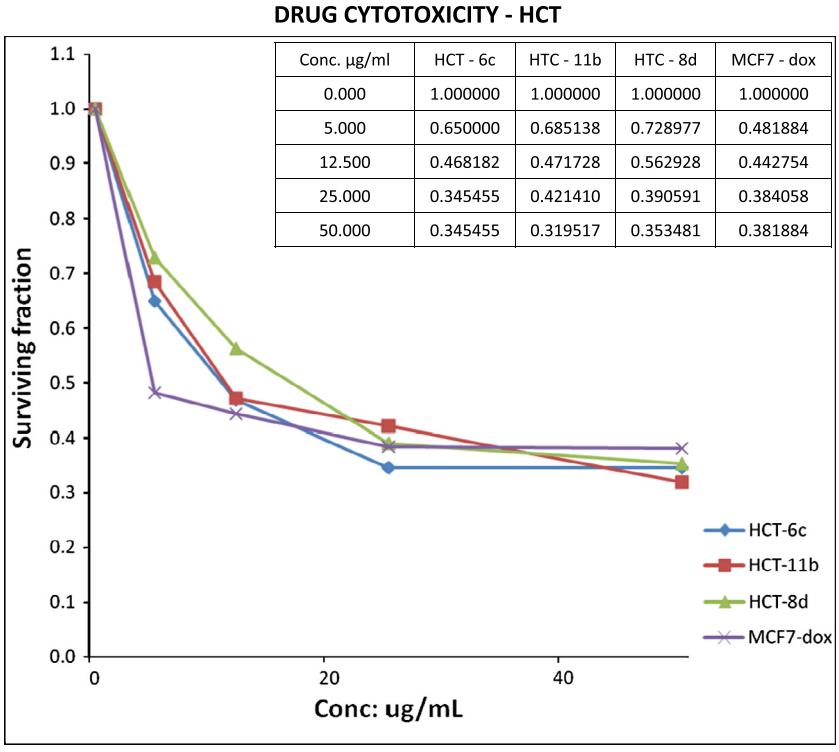


Figure 2 The cytotoxicity data of the activity of compounds **6c**, **8d** and **11b** virus Doxorubicin (in means of IC50 values).

The cytotoxicity data of the activity of compounds **6c**, **8d** and **11b** comparable with that obtained with widely used anticancer drug Doxorubicin (in means of IC50 values) were recorded in Fig. 2. The *in vitro* cytotoxicity results in Fig. 2 deduced good results of these derivatives to Doxorubicin as standard drug. The data showed that the synthesized indolin-2-one compounds **11b** and **6c** showed the high activity towards the breast tumor cell line (MCF7). But the reactivity of compound **6c** is more potent than the remaining compounds towards the breast human cell line (MCF7).

5. Conclusion

In summary, we have reported the synthesis of novel oxindol-based heterocyclic entities generated via the reaction of 3-[2-oxo-5-arylfuran-3(2H)-ylidene] indolin-2-ones (**1a**–**d**) with different chemical reagents, then evaluation of anticancer activity of selected compounds against human panel breast cancer cell line ***MCF7***. The *in vitro* cytotoxicity data revealed that compound **6c** showed the highest activity.

Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article.

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