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Synthesis of diverse novel compounds with anticipated antitumor activities starting with biphenyl chalcone

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Abstract

The chalcone as (*E*)-1-([1,1′-biphenyl]-4-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (**3**) was reacted with various active methylene compounds via Michael addition reaction under different conditions. In one hand, chalcone **3** reacted with isatin and glycine in one pot reaction via 1,3-dipolar cycloaddition reaction. On the other hand, chalcone **3** was also reacted with different *N*-nucleophiles via direct addition on the carbonyl group to award cyclic and/or acyclic products. Meanwhile, the reaction of chalcone **3** with *S*-benzylthiuronium chloride afforded the thio-Michael addition product. Chalcone **3** and 10 novel synthesized compounds were screened against two cell lines (HepG2 and MCF-7). Among of them, thiosemicarbazone **16**, oxime **14** and pyrimidine-2(1*H*)-thione **19** derivatives revealed an excellent activity against both cell lines (IC_{50} values = 6.79-12.91 μM), whereas thiosemicarbazone **16** (6.79 ± 0.5 and 7.58 ± 0.6 μM) showed the highest activity.

1 | INTRODUCTION

Compounds bearing biphenyl motif possess an enormous variety of biological activities[1,2] such as antiinflammatory,[3] antihypertensive,[4,5] antiviral,[6] antibreast cancer,[7] antiproliferative,[8] diuretic,[9] antidiabetic,[10,11] antipsychotic, anxiolytic,[12] and antimicrobial[13] activities. Previously, biphenyl derivatives were vastly used as pesticides in the formula of polychlorinated biphenyls (PCBs).[14,15] These biological activities paved an idea for us to synthesize heterocyclic compounds bearing biphenyl moiety.

From the chemical point of view, a chalcone is one of some interesting functionalized compounds due to, structurally, it has α,β-unsaturated carbonyl system (enone moiety) flanked by two aryl groups at positions C-1 and C-3. So that, chalcone is a privileged structure and it can be utilized as a starting building unit for synthesis of numerous heterocyclic compounds[16,17] such as pyrrolone,[18] pyrazoline,[19,20] pyrazole,[21] pyridine,[22] isoxazole,[16] pyranone,[23] pyrimidine,[24] pyrimidine-2(1*H*)-one,[16,25] and pyrimidine-2(1*H*)-thione.[23,25]

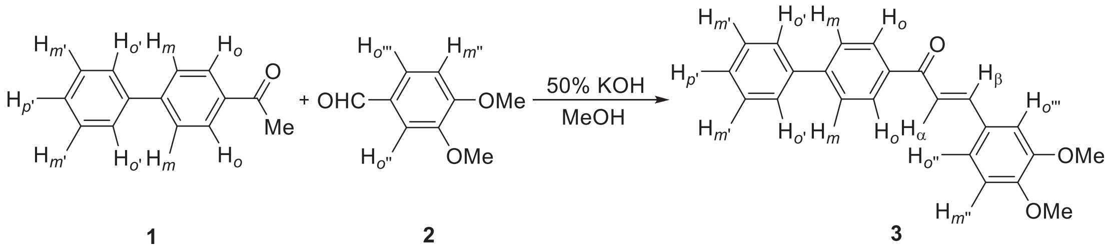
In addition, literature survey manifested that the pyrazoline derivatives were reported to have antiinflammatory and analgesic activities.[19] Pyrimidine derivatives showed a good antimicrobial activity[16] and some heterocyclic moieties also showed a remarkable pharmaceutical importance as antitumor and antimicrobial activities.[20,26–29]

In view of all the aforementioned facts and as a continuation of the global interest in the development of new antitumor agents, the essential target of this work is to synthesize a new heterocyclic sets belonging to biphenyl scaffold that could have antitumor efficacy.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

(*E*)-1-([1,1′-biphenyl]-4-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (**3**)[19,21,30] was synthesized via Claisen-Schmidt condensation reaction between two core structural components (a) a ketone namely, 4-acetyl biphenyl **1**, and



SCHEME 1 Synthesis of (*E*)-chalcone **3**

(b) an aldehyde namely, 3,4-dimethoxybenzaldehyde **2** as depicted in Scheme 1.

The spectral data of chalcone **3** laid a strong foundation for a confirmation of the chemical structure and stereochemistry of **3**. The IR spectrum exhibited absorption bands at 1652 and 1604 cm^{-1} characteristic for functionalities of C=O and C=C, respectively. Moreover, the ^1H NMR spectrum of chalcone **3** indicated the presence of two doublets at 7.80 and 7.47 ppm corresponding to β and α protons of C=C, respectively, with $J = 15.6$ Hz. The *E*-configuration structure (thermodynamically most stable) has been established by this higher value of the coupling constant of vinylic protons.

In this paper, we demonstrate the behavior of chalcone **3** towards some *C*- and *N*- nucleophilic reagents. So that, we exploited chalcone **3** as a starting building unit to build new compounds most of them possessing heterocycles.

At the outset, the synthesis of pyridine derivative **4** was commenced by the reaction of chalcone **3** with malononitrile in the presence of ammonium acetate in ethanolic solution. While, repeating the same reaction in the presence of piperidine as a base instead of ammonium acetate afforded 2,6-dicyanoaniline derivative **5** instead of the pyran derivative **6** as the desired product.[31,32] (Scheme 2).

The structures of compounds **4** and **5** were unambiguously ascertained on the basis of analytical and spectroscopic data. For example, the IR spectrum of compound **4** displayed υ_{NH2} at 3433, 3343 and 3228 cm^{-1} and $\upsilon_{C\equiv N}$ at 2208 cm^{-1}. As well, the ^1H NMR spectrum of **4** exhibited the presence of two singlet characteristic peaks, one of them at 7.34 ppm corresponding to C_5–$H_{(pyridine)}$ and the other at 6.94 ppm corresponding to NH_2 protons (exchangeable with D_2O). On the other hand, the IR spectrum of compound **5** showed the presence of stretching absorption bands for NH_2 at 3381 and 3206 cm^{-1} and C≡N at 2184 and 2147 cm^{-1}. Moreover, the ^1H NMR spectrum of **5** revealed the existence of a broad singlet peak at 8.41 ppm corresponding to NH_2 protons (exchangeable with D_2O).

A speculated mechanistic scenario for the formation of compound **5** is illustrated in Scheme 3.

Afterwards, the reaction of the privileged chalcone **3** with ethyl cyanoacetate in the presence of ammonium acetate in an absolute ethanol gave pyridone **7**. While, repeating this reaction in the presence of piperidine as a base instead of ammonium acetate afforded ethyl 5-([1,1′-biphenyl]-4-yl)-2-cyano-3-(3,4-dimethoxyphenyl)-5-oxopentanoate (**8**) instead of the pyran derivative **9** as the predicted product.[33] (Scheme 2).

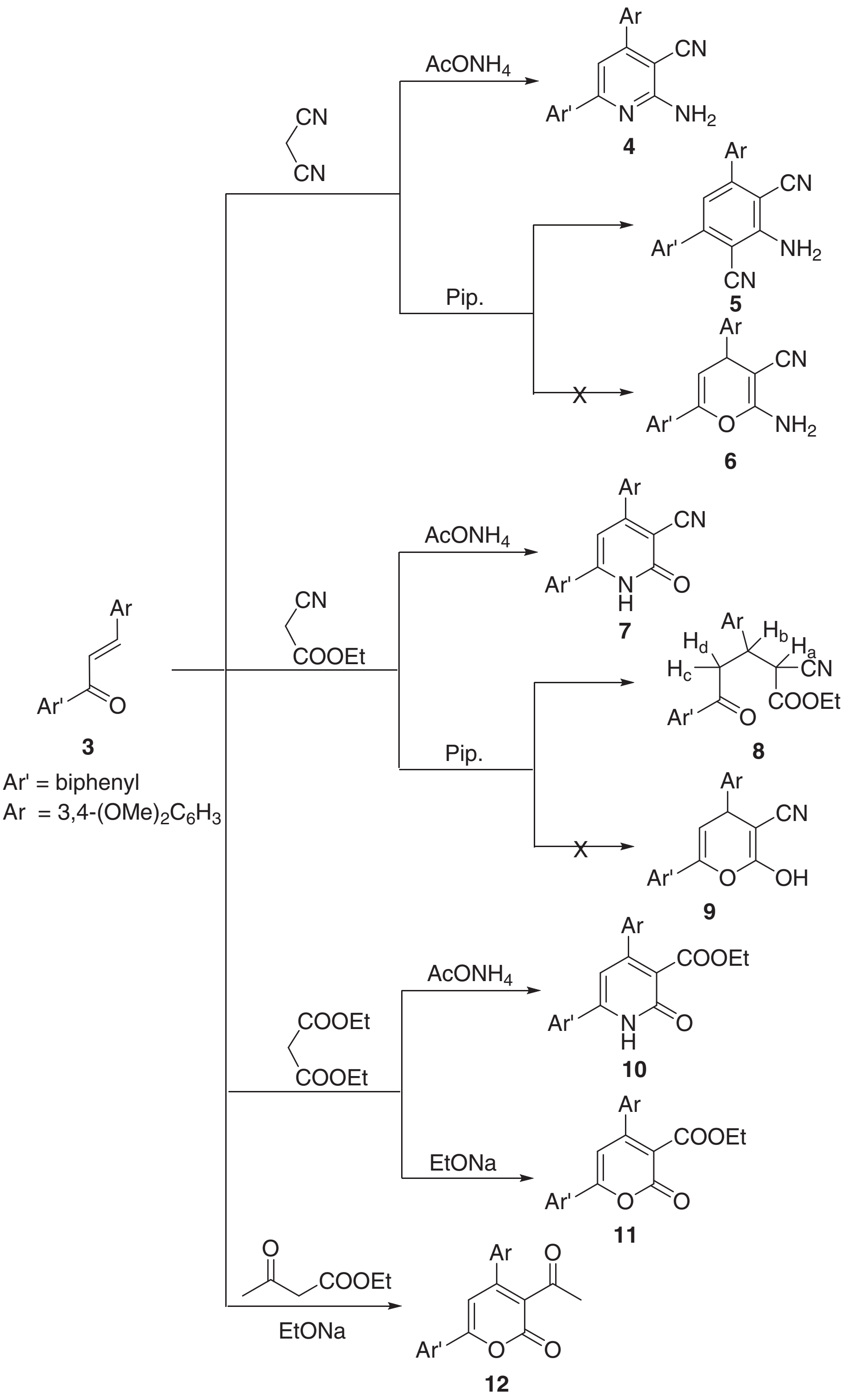
Unequivocally, the structure of **7** was proven via explication of the IR spectrum, which exhibited the presence of υ_{NH} at 3271 cm^{-1}, $\upsilon_{C\equiv N}$ at 2216 cm^{-1} and $\upsilon_{C=O}$ at 1649 cm^{-1}. Furthermore, the ^1H NMR spectrum refer to the presence of two singlet characteristic peaks at 12.71 and 6.90 ppm compatible with NH proton (exchangeable with D_2O) and C_5–$H_{(pyridone)}$, respectively. Whereas, the unexpected structure of compound **8** was elucidated by spectral and elemental analyses. (c.f exp.)

Refluxing of an ethanolic solution of chalcone **3** with diethyl malonate in the presence of ammonium acetate afforded the pyridone derivative **10**. Meanwhile, repeating the later reaction with sodium ethoxide solution in ethanol instead of ammonium acetate furnished the α-pyrone derivative **11**. (Scheme 2).

The predictable structures of compounds **10** and **11** were interpreted by their spectral data. The IR spectrum of **10** exhibited the presence of stretching absorption bands at 3297, 3199, 1737, and 1681 cm^{-1} corresponding to NH, $C=O_{(ester)}$ and $C=O_{(pyridone)}$ groups, respectively. Furthermore, the ^1H NMR spectrum revealed the presence of four characteristic peaks at 10.02, 6.78, 4.01, and 1.04 ppm corresponding to NH (exchangeable with D_2O), C_5–$H_{(pyridone)}$, CH_2 and CH_3 protons of the ethyl ester group, respectively.

While, the IR spectrum of **11** showed three absorption bands at 1747 and 1673 cm^{-1} $(C=O_{pyrone})$[34] and 1701 cm^{-1} $(C=O_{ester})$, respectively. As a proof for the chemical structure of **11**, the ^1H NMR spectrum revealed a singlet peak for C_5–$H_{(pyrone)}$ at 6.73 ppm.

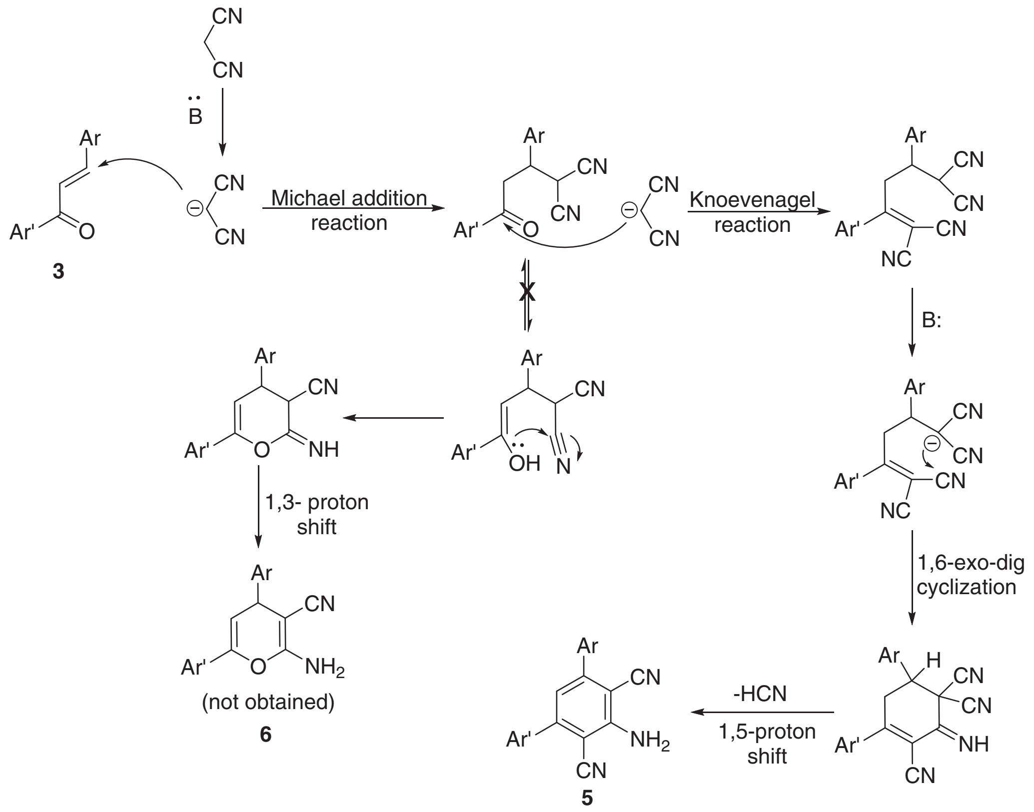
The reaction of a mixture of chalcone **3** and ethyl acetoacetate in ethanol in the presence of sodium ethoxide as a base awarded the α-pyrone derivative **12**. (Scheme 2) The proposed structure of compound **12** is in keeping with its spectral data and the elemental analysis. (c.f exp.)



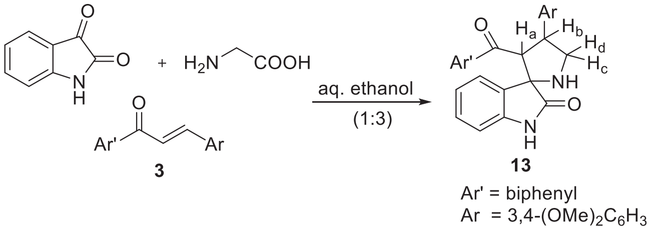
SCHEME 2 Reaction of Chalcone **3** with various *C*-Nucleophiles

The regioselective three-component condensation of azomethine ylides, which derived from isatins and α-amino acids with dipolarophiles have been emerged via a one-pot 1,3-dipolar cycloaddition protocol.[35–38] Therefore, the synthesis of spiroindoline-pyrrolidine derivative **13** was emanated from refluxing a three-component system formed by an aqueous ethanolic solution of chalcone **3**, isatin and glycine. (Scheme 4).

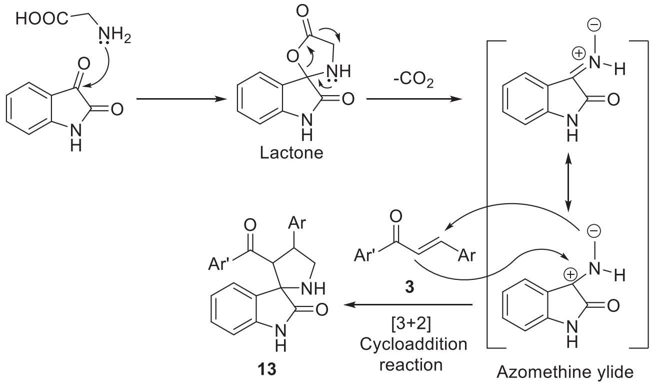
The IR spectrum of compound **13** displayed bands for NH at 3294 cm^{-1}, C=O$_{\text{(indolinone)}}$ at 1721 cm^{-1} and C=O$_{\text{(ketone)}}$ 1675 cm^{-1}. As well, the ^{1}H NMR spectrum of compound **13** is in keeping with the proposed structure. Meanwhile, it revealed the presence of two singlet peaks at 10.34 and 2.27 ppm corresponding to two NH protons (exchangeable with D_2O) and four characteristics peaks, one of them as a doublet peak at 4.42 ppm corresponding to H$_a$



SCHEME 3 Proposed putative mechanism for the formation of 2,6-dicyanoaniline derivative **5**



SCHEME 4 Formation of spiroindoline-pyrrolidine derivative **13**



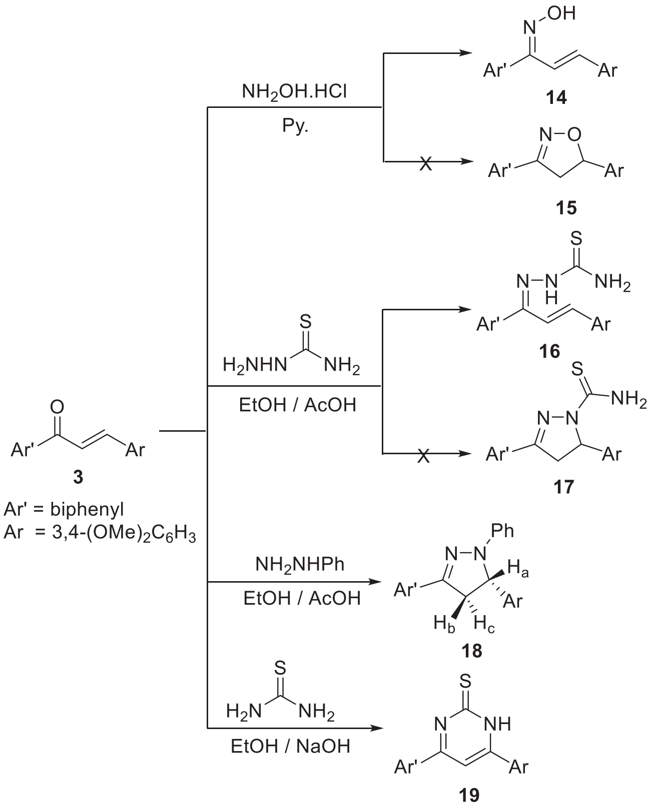
SCHEME 5 Proposed putative mechanism for the formation of spiroindoline-pyrrolidine derivative **13**

with $J_{ab} = 10.0$ Hz and the other three peaks as a multiplet at 4.16, 3.45, and 3.35 ppm corresponding to H$_b$, H$_c$, and H$_d$.

The putative mechanism for the formation of spiroindoline-pyrrolidine derivative **13** is outlined in Scheme 5. The key azomethine ylide intermediate was performed through the formation of lactone intermediate. Then the azomethine ylide underwent the 1,3-dipolar cycloaddition reaction with dipolarophile chalcone **3** in a regioselective manner. The regioselectivity of the reaction is explicable by the preference of the electron-rich carbon of the 1,3-dipole which added to the electron-deficient β-carbon of the α,β-unsaturated carbonyl moiety of chalcone **3**.

At this juncture, we demonstrated the reaction of chalcone **3** with variant *N*-nucleophiles, as refluxing of chalcone **3** with hydroxyl amine hydrochloride in dry pyridine afforded the unexpected oxime derivative **14** as the sole product instead of the desired product isoxazoline derivative **15**.[39] (Scheme 6).

The IR spectrum of **14** indicated the absence of the stretching absorption band for the carbonyl group. After profound investigation of the ^{1}H NMR spectrum of compound **14** which revealed the presence of a singlet peak at 11.53 ppm corresponding to OH proton (exchangeable with D$_2$O) and two doublet peaks at 7.47 and 6.73 ppm with $J = 16.8$ Hz corresponding to β and α vinylic



SCHEME 6 Reaction of Chalcone **3** with various *N*-Nucleophiles

protons, respectively. The higher value of the coupling constant of the vinylic protons manifested the established of them in *E*-configuration.

Similarly, refluxing of an ethanolic solution of chalcone **3** with thiosemicarbazide in the presence of a catalytic amount of acetic acid gave the thiosemicarbazone derivative **16** instead of the pyrazoline derivative **17**[40,41] (Scheme 6). The ^{1}H NMR spectrum of thiosemicarbazone derivative **16** elucidated the *E*-configuration of it.

Pleasingly, by the same later way, heating a mixture of compound **3** with phenyl hydrazine in an absolute ethanol containing a catalytic amount of acetic acid awarded the anticipated Δ^2-pyrazoline derivative **18**. (Scheme 6) The chemical structure of compound **18** was inferred from the spectral and elemental analyses. The IR spectrum of **18** displayed the absence of the absorption band for the carbonyl group. Moreover, the ^{1}H NMR spectrum manifested the presence of doublet-doublet peaks at δ = 5.40, 5.37 ppm with J_{ab} = 12.0 and J_{ac} = 6.8 ppm corresponding to H_a (attached to chiral carbon), doublet-doublet peaks at δ = 3.91, 3.87 ppm with J_{bc} = 17.4 and J_{ba} = 12.0 ppm corresponding to H_b (H_b cis to H_a) and doublet-doublet peaks at δ = 3.15, 3.11 ppm with J_{cb} = 17.2 and J_{ca} = 6.8 ppm corresponding to H_c (H_c trans to H_a).

The synthesis of 2-pyrimidinethione derivative **19** was commenced from the reaction of chalcone **3** with thiourea in ethanol under basic condition (aqueous NaOH). (Scheme 6) Interestingly, the ^{1}H NMR spectrum of compound **19** revealed the existence of a broad peak at 11.89 ppm exchangeable with D_2O corresponding to NH proton and a singlet peak at 6.65 ppm corresponding to C_5–$H_{(pyrimidinethione)}$.

Expectedly, refluxing of chalcone **3** with *S*-benzylthiuronium chloride in ethanol in the presence of sodium hydroxide as a base affords the 2-benzylthio pyrimidine derivative **21** as described in our literature.[42] Meanwhile, in this study the thio-Michael addition product[43]**20** was smoothly achieved instead. (Scheme 7).

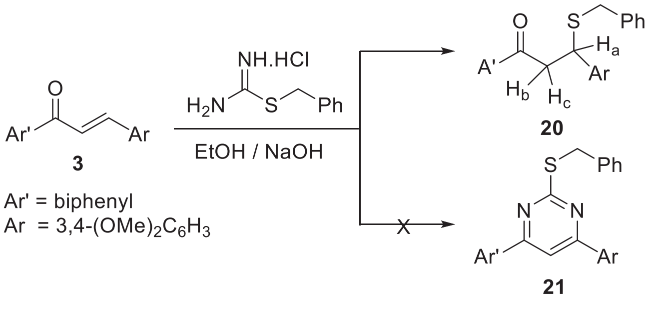
The thio-Michael adduct **20** was unequivocally ascertained by spectral data and elemental analysis. The IR spectrum of **20** showed a band for $\upsilon_{C=O}$ at 1681 cm^{-1}. Furthermore, the ^{1}H NMR spectrum exhibited the presence of extra peaks in aromatic region corresponding to five Ar–H for the phenyl ring of S-benzyl and a singlet peak at 3.66 corresponding to $\underline{SCH_2}$Ph beside the appearance of doublet-doublet peaks at 4.29, 4.27 ppm with J = 8.0 and J = 6.4 Hz corresponding to H_a of the chiral carbon and a multiplet peak at 3.60 to 3.49 ppm corresponding to the methylene protons (H_b and H_c) which adjacent to the chiral carbon.

In the light of encouraging results, we suggested a putative mechanism, where *S*-benzylthiuronium chloride serves only as the source of benzyl mercaptan, by exploitation the nucleophilicity and basicity of NaOH solution. Subsequently, benzyl mercaptan is involved in thio-Michael addition reaction through its attacking by the lone pair of sulfur atom on β-carbon of chalcone **3** to award 1,4-addition adduct in first, followed by 1,3-proton shift to furnish the 1,2-adduct as exemplified in Scheme 8.

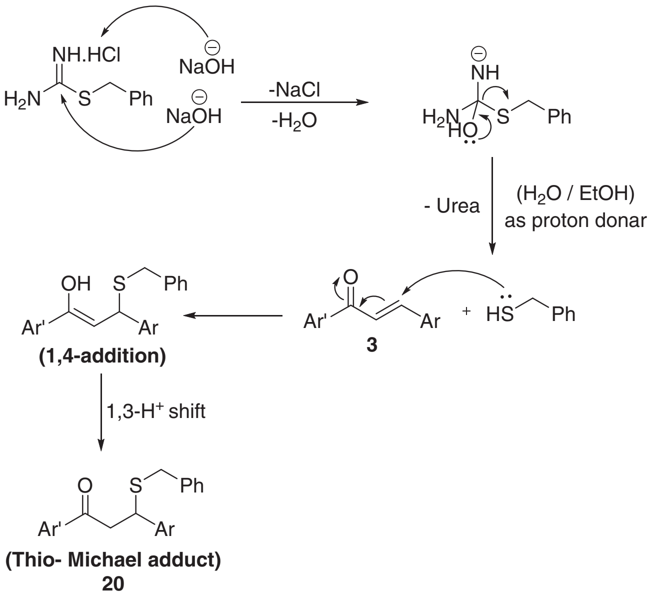
2.2 | Pharmacology

2.2.1 | In-vitro cytotoxicity assay

The in vitro antitumor activities of the chalcone **3** as a parent material and 10 novel synthesized compounds against a panel of two human tumor cell lines, including



SCHEME 7 Formation of the thio-Michael adduct **20**



SCHEME 8 Proposed putative mechanism for the formation of the thio-Michael adduct **20**

TABLE 1 Cytotoxic activity of the selected compounds against human tumor cells

	In vitro cytotoxicity IC_{50} (μM)	
Compounds	**HepG2**	**MCF-7**
DOX	4.50 ± 0.3	4.17 ± 0.2
3	37.62 ± 2.8	44.70 ± 2.9
4	53.78 ± 3.5	49.06 ± 3.1
7	73.65 ± 4.0	65.01 ± 3.8
10	42.38 ± 3.1	27.95 ± 2.1
11	30.42 ± 2.4	38.53 ± 2.5
12	18.06 ± 1.6	15.42 ± 1.4
13	23.14 ± 1.9	19.76 ± 1.7
14	9.48 ± 0.9	10.39 ± 1.0
16	6.79 ± 0.5	7.58 ± 0.6
18	62.70 ± 3.8	54.17 ± 3.6
19	12.91 ± 1.3	11.31 ± 1.2

Note: IC_{50} (μM): 1 to 10 (very strong); 11 to 20 (strong); 21 to 50 (moderate); 51 to 100 (weak) and above 100 (non-cytotoxic).
Abbreviation: DOX, Doxorubicin.

(HepG2) hepatocellular carcinoma and (MCF-7) mammary gland breast cancer were examined by using MTT method according to the previous method,[44,45] Doxorubicin (DOX) was used as the standard anticancer drug due to its accessibility and ubiquitous use. The inhibitory activities IC_{50} (μM) are outlined in Table 1.

Conspicuously, in Table 1 compounds **14** and **16** exhibited an excellent cell potency against HepG2 cell line compared to that of doxorubicin. Meanwhile, compounds **16** manifested a promising potent activity against MCF-7 cell line. Additionally, in case of HepG2 cell line, two compounds **12** and **19** exhibited strong cytotoxic activity. Compounds **3**, **10**, **11**, and **13** showed moderate activities, while, the rest of compounds exhibited weak activities. On the other hand, the activity against MCF-7 cell line revealed that compounds **12**, **13**, **14**, and **19** have strong percentage viability. Compounds **3**, **4**, **10**, and **11** showed moderate activities. Meanwhile, compounds **7** and **18** exhibited weak activities.

2.2.2 | Structure activity relationship's (SAR's)

To study the structure activity relationship's (SAR's) of these novel compounds and discover the most potency, we synthesized, selected, and evaluated 11 compounds against two human tumor cell lines (HepG2 and MCF-7). The results of the antitumor screening imply the following general structural requirements:

1. Compounds **16** and **14** have a remarkable potency nearby to doxorubicin against both cell lines. Briefly, the higher activity of compounds **16** and **14** may be attributable to the intermolecular H-bonding interactions and the hydrophobicity characters which resulted from the presence of thiosemicarbazone **16** and oxime **14** moieties beside of a delocalization of the л electrons between the groups Ar′ and Ar.
2. The presence of the double bond between the Ar′ and Ar groups allowing the delocalization of the л electrons between these two aromatic rings. For example, in compound **13** and, in particular, compound **18** (which also does not have a hydrogen bond donor in the area between the Ar′ and Ar groups), this delocalization is broken because of the absence of the double bond cited above. Compound **18** lacking the phenyl group on the dihydrodiazole ring could have had better activity, and could have been at least as active as compound **19** if it had a diazole ring in place of dihydrodiazole ring because of the presumed presence of double bond (in this case it becomes the analogue of compound **19** but without the C═S group), which could ensure a delocalization of the л electrons between the groups Ar′ and Ar.
3. There must be a certain freedom of motion for Ar′ group, relatively, to Ar. For example, compound **19** is good but remains less active than compounds **14** and **16**. Although it is structurally close to compound **16** and, it is a hydrogen bond donor (–N[C═S]NH), but it is less flexible than compounds **14** and **16** because of diazine ring on which are linked the Ar′ and Ar groups. The same remark can

be done about compounds **4**, **7**, **10**, **11**, and **12**. Indeed, although the presence of delocalization of л electrons between Ar′ and Ar groups, these molecules are less flexible than compounds **3**, **14**, and **16**.

3 | CONCLUSION

Chalcone **3** was reacted in three ways. First, it reacted with various active methylene compounds (AMC) via Michael addition reaction under different conditions. Second, chalcone **3** reacted with isatin and glycine in one pot reaction via 1,3-dipolar cycloaddition reaction. Third, chalcone **3** was also reacted with different *N*-nucleophiles via direct addition on the carbonyl group to award cyclic and/or acyclic products. Meanwhile, reaction of chalcone **3** with *S*-benzylthiuronium chloride afforded the thio-Michael addition product. The structures of all novel synthesized compounds were characterized by their elemental analyses and spectral data. Among the examined compounds, thiosemicarbazone **16**, oxime **14**, and pyrimidine-2(1*H*)-thione **19** derivatives were revealed excellent cell potency with IC_{50} values (6.79-12.91 μM) against both cell lines (HepG2 and MCF-7). Noteworthy, thiosemicarbazone derivative **16** was manifested the best antitumor activity against both cell lines, which represents a good starting point for the development of novel antitumor agents. The results of this investigation have prompted us on persistent the development and prospection of novel thiosemicarbazone derivatives.

4 | EXPERIMENTAL

4.1.1. | Materials and methods

Most solvents and reagents were purchased from the local Egyptian productions and Merck chemical industries and were directly used without purification unless otherwise specified. Melting points were determined in open glass capillaries and without correction. The IR spectra (400-4000 cm^{-1}) were recorded on the Nicolet iS10 FT-IR spectrometer (thermo scientific) using KBr disc and expressed in wavenumber (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on 400 and 100 MHz, respectively, in $CDCl_3$ or DMSO-d_6 as a solvent using TMS as the internal standard and chemical shifts (δ) are quoted in ppm. Mass spectra have been recorded on Shimadzu GC-MS QP1000EX apparatus at 70 eV were recorded at the Faculty of Science, Al-Azhar University, Egypt. Elemental analyses were carried out at the Microanalytical Data Centre at the Faculty of Science, Cairo University, Egypt. The percentages of elements were found to be very near to that of the calculated values. TLC was performed on Merk Silica gel 60 F_{254} aluminum packed plate coated with flourescent. All reactions were monitored by TLC (thin layer chromatography, Merck) on precoated silica gel G plates in petroleum ether/ethyl acetate mixture as the eluting system. Visualization of spots on TLC plates was done by UV lamp (254 nm). Antitumor activity was screened at the drugs department, Faculty of pharmacy, Mansoura University, Egypt.

4.1.2. | (*E*)-1-([1,1′-biphenyl]-4-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one 3

To a mixture of aqueous potassium hydroxide (20 mL, 50%) and methanol (40 mL), 4-acetyl biphenyl **1** (0.01 mol, 1.96 g) was added.[19,30] The reaction mixture was stirred at 0°C in ice bath. After 5 minutes, 3,4-dimethoxybenzaldehyde **2** (0.01 mol, 1.66 g) was added slowly. Stirring was persistent in ice bath for 3 hours. The completion of the reaction was monitored by TLC, and then the reaction mixture was poured slowly into 200 mL of ice water to obtain yellow solid, filtered off, washed several times with cold water then recrystallized from ethanol or petroleum ether 80°C to 100°C to give **3** as bright yellow crystals; m.p.: 120°C to 121°C (Lit. m.p.: 128°C-129°C),[30] yield 95%. IR (KBr, υ/cm^{-1}): 2965, 2937, 2840 (CH_3), 1652 (C═O), 1604 (C═C). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.11 to 8.09 (d, 2H, Ar′–H, H_o, $J = 8$ Hz), 7.82 to 7.78 (d, 1H, β CH═, $J = 15.6$ Hz), 7.74 to 7.72 (d, 2H, Ar′–H, H_m, $J = 8.4$ Hz), 7.66 to 7.64 (d, 2H, Ar′–H, $H_{o'}$, $J = 7.6$ Hz), 7.50 to 7.46 (t, 2H, Ar′–H, $H_{m'}$, $J = 7.2$ Hz, $J = 7.6$ Hz), 7.49 to 7.45 (d, 1H, α CH═, $J = 15.6$ Hz), 7.42 to 7.38 (t, 1H, Ar′–H, $H_{p'}$, $J = 7.6$ Hz, $J = 7.8$ Hz), 7.26, 7.24 (d,d, 1H, Ar–H, $H_{o''}$, $J_m = 1.6$ Hz, $J_o = 8.4$ Hz), 7.18 (d, 1H, Ar–H, $H_{o'}$, $J_m = 1.6$ Hz), 6.92 to 6.90 (d, 1H, Ar–H, $H_{m'}$, $J = 8$ Hz), 3.96 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3). MS m/z (%): 344 (M^+; 100), 329 (14.15), 313 (5.10), 152 (19.4), 77 (11.96). *Anal.* Calcd for $C_{23}H_{20}O_3$ (344.41): C, 80.21; H, 5.85. Found: C, 80.27; H, 5.88.

4.1 | General procedure for the synthesis of 4, 7, 10

A mixture of chalcone **3** (0.01 mol, 3.44 g), with the appropriate active methylene (malononitrile, ethyl cyanoacetate, and/or diethyl malonate) (0.01 mol) and ammonium acetate (2.31 g, 0.03 mol) in an absolute ethanol (50 mL) was heated under stirring for 12 hours. The completion of the reaction was monitored by TLC. After cooling, the reaction mixture was poured into cold water with stirring. The solid product was collected by filtration at the pump, dried well and recrystallized from the proper solvent (ethanol, dioxane, and toluene for compounds **4**, **7** and **10**, respectivety).

4.1.1 | 6-([1,1′-biphenyl]-4-yl)-2-amino-4-(3,4-dimethoxyphenyl)nicotinonitrile 4

Buff crystals; m.p.: 224°C to 226°C, yield 86%. IR (KBr, υ/cm^{-1}): 3433, 3343, 3228 (NH_2), 2958, 2934, 2842 (CH_3), 2208 (C≡N), 1633 (C═N), 1605 (C═C). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.23 to 8.21 (d, 2H, Ar′–H, H_o, J = 8.4 Hz), 7.79 to 7.77 (d, 2H, Ar′–H, H_m, J = 8.4 Hz), 7.74 to 7.72 (d, 2H, Ar′–H, $H_{o'}$, J = 8.8 Hz), 7.49 to 7.45 (t, 2H, Ar′–H, $H_{m'}$, J = 6.8 Hz, J = 8 Hz), 7.39 to 7.36 (t, 1H, Ar′–H, $H_{p'}$, J = 7.6 Hz, J = 7.2 Hz), 7.34 (s, 1H, C_5–$H_{(pyridine)}$), 7.29 to 7.28 (d, 1H, Ar–H, H $_{o''}$, J_m = 2 Hz), 7.27, 7.25 (d,d, 1H, Ar–H, $H_{o'}$, J_m = 2.4 Hz, J_o = 8.2 Hz), 7.12 to 7.10 (d, 1H, Ar–H, $H_{m''}$, J = 8 Hz), 6.94 (s, 2H, NH_2, exchangeable with D_2O), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3). MS m/z (%): 407 (M^+; 100), 392 (5.27), 364 (12.48), 152 (1.67), 77 (0.78). *Anal.* Calcd for $C_{26}H_{21}N_3O_2$ (407.47): C, 76.64; H, 5.19; N, 10.31. Found: C, 76.59; H, 5.16; N, 10.35.

4.1.2 | 6-([1,1′-biphenyl]-4-yl)-4-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile 7

Yellow crystals; m.p.: 280°C to 282°C, yield 83%. IR (KBr, υ/cm^{-1}): 3271 (NH), 2932, 2902, 2837 (CH_3), 2216 (C≡N), 1649 (C═O), 1601 (C═C). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.71 (s, 1H, NH, exchangeable with D_2O), 7.99 to 7.97 (d, 2H, Ar′–H, H_o, J = 8.4 Hz), 7.83 to 7.81 (d, 2H, Ar′–H, H_m, J = 8.4 Hz), 7.75 to 7.73 (d, 2H, Ar′–H, $H_{o'}$, J = 7.6 Hz), 7.50 to 7.46 (t, 2H, Ar′–H, $H_{m'}$, J = 7.6 Hz, J = 8 Hz), 7.42 to 7.38 (t, 1H, Ar′–H, $H_{p'}$, J = 7.6 Hz, J = 6.8 Hz), 7.36, 7.35 (d,d, 1H, Ar–H, $H_{o'}$, J_m = 2 Hz, J_o = 7.6 Hz),7.34 (s, 1H, Ar–H, $H_{o''}$), 7.13 to 7.11 (d, 1H, Ar–H, $H_{m'}$, J = 8 Hz), 6.90 (s, 1H, C_5–$H_{(pyridone)}$), 3.838 (s, 3H, OCH_3), 3.831 (s, 3H, OCH_3). MS m/z (%): 408 (M^+; 100), 392 (7.95), 364 (19.24). *Anal.* Calcd for $C_{26}H_{20}N_2O_3$ (408.46): C, 76.46; H, 4.94; N, 6.86. Found: C, 76.51; H, 4.96; N, 6.83.

4.1.3 | Ethyl 6-([1,1′-biphenyl]-4-yl)-4-(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate 10

Yellow crystals; m.p.: 58°C to 60°C, yield 69%. IR (KBr, υ/cm^{-1}): 3297, 3199 (NH), 2996, 2929, 2834 ($CH_{aliph.}$), 1737 (C═O_{ester}), 1681 (C═O $_{pyridinone}$), 1600 (C═C). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.02 (s, 1H, NH, exchangeable with D_2O), 8.39 to 8.37 (d, 2H, Ar′–H, H_o, J = 8.4 Hz), 8.20 to 8.18 (d, 2H, Ar′–H, H_m, J = 8.4 Hz), 7.83 to 7.81 (d, 2H, Ar′–H, $H_{o'}$, J = 8.4 Hz), 7.78 to 7.32 (m, 5H, 3Ar′–H + 2Ar–H), 6.86 (s, 1H, Ar–H, $H_{o''}$), 6.78 (s, 1H, C_5–$H_{(pyridone)}$), 4.03 to 3.98 (q, 2H, $\underline{CH_2}CH_3$$J$ = 7.2 Hz), 3.69 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 1.06 to 1.02 (t, 3H, CH2$\underline{CH_3}$, J = 7.2 Hz). MS m/z (%): 456 (M + 1; 13.41), 455 (22.58), 384 (100), 344 (55.78), 329 (30.84), 193 (5.67), 179 (14.70), 152 (39.17), 77 (36.74). *Anal.* Calcd for $C_{28}H_{25}NO_5$ (455.51): C, 73.83; H, 5.53; N, 3.08. Found: C, 73.79; H, 5.50; N, 3.05.

4.2 | General procedure for the synthesis of 5 and 8

A mixture of chalcone **3** (0.01 mol, 3.44 g), with the appropriate active methylene (malononitrile and/or ethyl cyanoacetate) (0.01 mol) in an absolute ethanol (50 mL) containing drops of piperidine as a base was refluxed under stirring for 12 hours. After the resulting solution was concentrated, set aside to cool, then poured onto acidified cold water. The solid deposited was collected by filtration and purified by recrystallization from the proper solvent (ethanol and petroleum ether 80°C to 100°C for compounds **5** and **8**, respectively).

4.2.1 | 5′-imino-3,4-dimethoxy-[1,1′:3′,1′:4′,1′-quaterphenyl]-4′,6′-dicarbonitrile 5

Brown crystals; m.p.: 134°C to 136°C, yield 47%. IR (KBr, υ/cm^{-1}): 3381, 3206 (NH_2), 2934, 2837 (CH_3), 2184, 2147 (C≡N), 1603 (C═N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.41(br.s, 2H, NH_2, exchangeable with D_2O), 8.25 to 8.23 (d, 2H, Ar′–H, H_o, J = 8.4 Hz), 7.78 to 7.75 (d, 2H, Ar′–H, H_m, J = 8.8 Hz), 7.74 to 7.72 (d, 2H, Ar′–H, $H_{o'}$, J = 8 Hz), 7.49 to 7.45 (t, 2H, Ar′–H, $H_{m'}$, J = 7.2 Hz, J = 7.6 Hz), 7.41 to 7.37 (t, 1H, Ar′–H, $H_{p'}$, J = 7.2 Hz, J = 6.4 Hz), 7.35 (s, 1H, Ar–H), 7.19, 7.18 (d,d, 1H, Ar–H, $H_{o'}$, J_o = 2.4 Hz, J_m = 6.5 Hz), 7.159 to 7.154 (d, 1H, Ar–H, $H_{o''}$, J_m = 2 Hz), 7.08 to 7.06 (d, 1H, Ar–H, $H_{m'}$, J = 8 Hz), 3.82 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3). MS m/z (%): 431 (M^+; 58.38), 407 (100), 392 (87.03), 204 (0.78), 179 (1.85), 77 (1.29). *Anal.* Calcd for $C_{28}H_{21}N_3O_2$ (431.50): C, 77.94; H, 4.91; N, 9.74. Found: C, 77.88; H, 4.89; N, 9.71.

4.2.2 | Ethyl 5-([1,1′-biphenyl]-4-yl)-2-cyano-3-(3,4-dimethoxyphenyl)-5-oxopentanoate 8

Pale yellow crystals; m.p.: 122°C to 123°C, yield 44%. IR (KBr, υ/cm^{-1}): 2960, 2934, 2839 ($CH_{aliph.}$), 2244 (C≡N), 1731 ($C{=}O_{ester}$), 1674 ($C{=}O_{ketone}$), 1603 (C=C). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.05 to 8.03 (d, 2H, Ar′–H, H_o, $J = 8.4$ Hz), 7.70 to 7.68 (d, 2H, Ar′–H, H_m, $J = 8.4$ Hz), 7.63 to 7.61 (d, 2H, Ar′–H, $H_{o'}$, $J = 8.4$ Hz), 7.49 to 7.45 (t, 2H, Ar′–H, $H_{m'}$, $J = 6.8$ Hz, $J = 8$ Hz), 7.42 to 7.38 (t, 1H, Ar′–H, $H_{p'}$, $J = 7.2$ Hz, $J = 7.6$ Hz), 6.98, 6.96 (d,d, 1H, Ar–H, $H_{o'}$, $J_m = 2$ Hz, $J_o = 8.4$ Hz), 6.96 to 6.95 (d, 1H, Ar–H, $H_{o''}$, $J_m = 2.8$ Hz), 6.84 to 6.82 (d, 1H, Ar–H, $H_{m'}$, $J = 8$ Hz), 4.14 to 4.08 (q, 3H, $\underline{CH_2}CH_3$ + H_b, $J = 7.6$ Hz, $J = 6.8$ Hz), 3.96 to 3.95 (d, 1H, H_a, $J_{ab} = 4.4$ Hz), 3.90 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.72, 3.67 (d,d, 1H, H_c, $J_{cd} = 18$ Hz, $J_{cb} = 9.2$ Hz), 3.56, 3.52 (d,d, 1H, H_d, $J_{dc} = 18$ Hz, $J_{db} = 4.8$ Hz), 1.17 to 1.13 (t, 3H, CH2$\underline{CH_3}$, $J = 7.6$ Hz, $J = 7.2$ Hz). *Anal.* Calcd for $C_{28}H_{27}NO_5$ (457.53): C, 73.51; H, 5.95; N, 3.06. Found: C, 73.57; H, 5.97; N, 3.01.

4.3 | General procedure for the synthesis of 11 and 12

A mixture of chalcone **3** (0.01 mol, 3.44 g), with the appropriate active methylene (diethylmalonate and/or ethyl acetoacetate) (0.01 mol) in ethanol (35 mL) in the presence of sodium ethoxide solution (15 mL) was refluxed under stirring on hot plate for 10 hours and left to reach ambient temperature. Then the reaction mixture was poured onto acidified cold water by acetic acid. The precipitated solid was collected by filtration and recrystallized from relevant solvent (ethanol and toluene for compounds **11** and **12**, respectively).

4.3.1 | Ethyl 6-([1,1′-biphenyl]-4-yl)-4-(3,4-dimethoxyphenyl)-2-oxo-2*H*-pyran-3-carboxylate 11

Yellow crystals; m.p.: 166°C to 168°C, yield 63%. IR (KBr, υ/cm^{-1}): 2963, 2934, 2914, 2840 ($CH_{aliph.}$), 1747, 1673 ($C{=}O_{pyrone}$), 1701 ($C{=}O_{ester}$), 1602 (C=C). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.00 to 7.98 (d, 2H, Ar′–H, H_o, $J = 8.4$ Hz), 7.79 to 7.77 (d, 2H, Ar′–H, H_m, $J = 8.4$ Hz), 7.73 to 7.70 (d, 2H, Ar′–H, $H_{o'}$, $J = 8.4$ Hz), 7.50 to 7.46 (t, 2H, Ar′–H, $H_{m'}$, $J = 7.2$ Hz, $J = 7.2$ Hz), 7.42 to 7.38 (t, 1H, Ar′–H, $H_{p'}$, $J = 7.2$ Hz, $J = 7.2$ Hz), 6.899 to 6.896 (d, 1H, Ar–H, $H_{o''}$, $J_m = 1.2$ Hz), 6.80 to 6.75 (m, 2H, Ar–H, $H_{o'}$ + $H_{m'}$), 6.73 (s, 1H, C_5–$H_{(pyrone)}$), 3.70 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.63 to 3.58 (q, 2H, $\underline{CH_2}CH_3 J = 8$ Hz, $J = 6.8$ Hz), 1.05 to 1.02 (t, 3H, CH2$\underline{CH_3}$, $J = 7.2$ Hz, $J = 6.8$ Hz). MS m/z (%): 456 (M^+; 10.86), 407 (46.62), 404 (100), 382 (41.65), 152 (25.88), 77 (10.55). *Anal.* Calcd for $C_{28}H_{24}O_6$ (456.49): C, 73.67; H, 5.30. Found: C, 73.52; H, 5.19.

4.3.2 | 6-([1,1′-biphenyl]-4-yl)-3-acetyl-4-(3,4-dimethoxyphenyl)-2*H*-pyran-2-one 12

Brown crystals; m.p.: 66°C to 68°C, yield 71%. IR (KBr, υ/cm^{-1}): 2929, 2835 ($CH_{aliph.}$), 1701 (br.) (C=O), 1602 (C=C). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.01 to 6.79 (m, 12H, 9Ar′–H + 3Ar–H), 6.65 (s, 1H, C_5–H_{pyrone}) 3.78 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 2.64 (s, 3H, $COCH_3$). MS m/z (%): 426 (M^+; 8.67), 402 (100), 383 (10.21), 382 (26.60), 178 (8.11), 152 (6.16), 77 (8.33). *Anal.* Calcd for $C_{27}H_{22}O_5$ (426.47): C, 76.04; H, 5.20. Found: C, 76.16; H, 5.27.

4.3.3 | 3′-([1,1′-biphenyl]-4-carbonyl)-4′-(3,4-dimethoxyphenyl)spiro[indoline-3,2′-pyrrolidin]-2-one 13

A mixture consisting of isatin (1.47 g, 0.01 mol), glycine (0.75 g, 0.01 mol) and chalcone **3** (0.01 mol, 3.44 g) in 50 mL aqueous methanol (1:3) was heated under stirring on hot plate for 10 hours. The amount of solvent was reduced by evaporation, set aside to cool. After slow evaporation, the precipitated solid was collected and recrystallized from benzene to award **13** as orange crystals; m.p.: 194°C to 196°C, yield 57%. IR (KBr, υ/cm^{-1}): 3294 (NH), 2953, 2932, 2834 ($CH_{aliph.}$), 1721 ($C{=}O_{indolinone}$), 1675 ($C{=}O_{ketone}$), 1619 (C=C). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.34 (s, 1H, NH, exchangeable with D_2O), 7.85 to 6.81 (m, 15H, 9Ar′–H + 6Ar–H), 6.45 (d, 1H, Ar–H, $J = 7.6$ Hz), 4.42 (d, 1H, H_a, $J_{ab} = 10.0$ Hz), 4.16 (m, 1H, H_b), 3.74 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.45 (m, 1H, H_d), 3.35 (m, 1H, H_c), 2.27 (s, 1H, NH, exchangeable with D_2O). MS m/z (%): 504 (M^+; 30.80), 502 (51.62), 487 (20.06), 486 (65.31), 459 (58.74), 408 (33.09), 407 (98.62), 344 (100), 329 (46.11), 313 (22.85), 152 (49.30), 77 (24.10). *Anal.* Calcd for $C_{32}H_{28}N_2O_4$ (504.59): C, 76.17; H, 5.59; N, 5.55. Found: C, 76.02; H, 5.43; N, 5.69.

4.3.4 | (2*E*)-1-([1,1′-biphenyl]-4-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one oxime 14

A mixture consisting of chalcone **3** (0.01 mol, 3.44 g) and hydroxyl amine hydrochloride (0.01 mol, 0.7 g) in dry pyridine (20 mL) was refluxed under stirring for 10 hours. The reaction mixture was concentrated, set aside to cool. Then the reaction mixture was poured onto acidified cold water by acetic acid. The product deposited was filtered and recrystallized from ethanol to give **14** as orange crystals; m.p.: 162°C to 164°C, yield 78%. IR (KBr, υ/cm^{-1}):3178 (br.) (OH), 2959, 2930, 2835 (CH_3), 1620 (C═N), 1597 (C═C). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.53 (s, 1H, OH, exchangeable with D_2O), 7.74 to 7.72 (d, 2H, Ar′–H, H_o, J = 8.4 Hz), 7.71 to 7.70 (d, 2H, Ar′–H, H_m, J = 7.2 Hz), 7.55 to 7.53 (d, 2H, Ar′–H, $H_{o'}$, J = 8.4 Hz), 7.50 to 7.46 (t, 2H, Ar′–H, $H_{m'}$, J = 6.8 Hz, J = 7.6 Hz), 7.49 to 7.46 (d, 1H, β CH═, J = 16.8 Hz), 7.39 to 7.35 (t, 1H, Ar′–H, $H_{p'}$, J = 6.8 Hz, J = 7.6 Hz), 7.176 to 7.171 (d, 1H, Ar–H, $H_{o''}$, J_m = 2 Hz), 7.10, 7.07 (d,d, 1H, Ar–H, $H_{o'}$, J_m = 2 Hz, J = 8.4 Hz), 6.94 to 6.92 (d, 1H, Ar–H, $H_{m'}$, J = 8.4 Hz), 6.75 to 6.71 (d,1H, α CH═, J = 16.8 Hz), 3.96 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3). MS m/z (%): 359 (M^+; 57.83), 358 (91.49), 342 (100), 326 (9.59), 152 (6.40), 77 (4.35). *Anal.* Calcd for $C_{23}H_{21}NO_3$ (359.43): C, 76.86; H, 5.89; N, 3.90. Found: C, 76.89; H, 5.91; N, 3.89.

4.4 | General procedure for preparation of compounds 16 and 18

To a mixture of chalcone **3** (0.01 mol, 3.44 g), and (thiosemicarbazide and/or phenyl hydrazine) (0.01 mol) in an absolute ethanol (40 mL), a catalytic amount of acetic acid was added (5 drops) and heated under stirring for 6 hours. After cooling, the resulting solution was poured slowly into crushed ice with stirring, the solid deposited was collected by filtration, washed with water several times, dried and further purification was done by recrystallized from relevant solvent (ethanol and dioxane for compounds **16** and **18**, respectively).

4.4.1 | (*E*)-2-(1-([1,1′-biphenyl]-4-yl)-3-(3,4-dimethoxyphenyl)allylidene) hydrazine-1-carbothioamide 16

Yellow crystals; m.p.: 186°C to 188°C, yield 66%. IR (KBr, υ/cm^{-1}):3447, 3328 (NH_2), 3129 (NH), 2959, 2925, 2833 (CH_3), 1600 (C═N), 1587 (C═C), 1264 (C═S). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.87 (s, 1H, NH, exchangeable with D_2O), 8.27 (br.s, 2H, NH_2, exchangeable with D_2O), 8.24 to 8.22 (d, 2H, Ar′–H, H_o, J = 8.4 Hz), 8.02 to 7.99 (d, 2H, Ar′–H, H_m, J = 8.4 Hz), 7.94 to 7.92 (d, 2H, Ar′–H, $H_{o'}$, J = 8.4 Hz), 7.71 to 7.37 (m, 3H, Ar′–H, 2$H_{m'}$ + $H_{p'}$), 7.65 to 7.61 (d,1H, β CH═, J = 15.6 Hz), 7.28, 7.26 (d,d, 1H, Ar–H, $H_{o'}$, J_m = 2 Hz, J_o = 8.4 Hz), 7.10 to 7.09 (d, 1H, Ar–H, $H_{o''}$, J_m = 1.6 Hz), 6.97 to 6.95 (d, 1H, Ar–H, $H_{m'}$, J_o = 8.4 Hz), 6.80 to 6.76 (d,1H, α CH═, J = 15.6 Hz), 3.80 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3). MS m/z (%): 417 (M^+; 100), 416 (75.26), 384 (30.39), 357 (30.54), 221 (6.23), 179 (4.80), 152 (6.08), 77 (5.61), 60 (18.34). *Anal.* Calcd for $C_{24}H_{23}N_3O_2S$ (417.53): C, 69.04; H, 5.55; N, 10.06; S, 7.68. Found: C, 69.16; H, 5.58; N, 10.02; S, 7.61.

4.4.2 | 3-([1,1′-biphenyl]-4-yl)-5-(3,4-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole 18

Yellow crystals; m.p.: 184°C to 185°C, yield 89%. IR (KBr, υ/cm^{-1}): 2959, 2934, 2833 ($CH_{aliph.}$), 1595 (C═N or C═C). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.82 to 7.80 (d, 2H, Ar′–H, H_o, J = 8.4 Hz), 7.73 to 7.71 (d, 2H, Ar′–H, H_m, J = 8.8 Hz), 7.71 to 7.69 (d, 2H, Ar′–H, $H_{o'}$, J = 8.8 Hz), 7.48 to 7.44 (t, 2H, Ar′–H, $H_{m'}$, J = 7.6 Hz, J = 8 Hz), 7.38 to 7.34 (t, 1H, Ar′–H, $H_{p'}$, J = 6.8 Hz, J = 7.6 Hz), 7.16 to 7.13 (t, 2H, NPh-H, H_m, J = 8.4 Hz, J = 7.2 Hz), 7.04 to 7.02 (d, 2H, NPh-H, H_o, J = 7.6 Hz), 6.93 to 6.92 (d, 1H, Ar–H, $H_{o''}$, J_m = 2.4 Hz), 6.88 to 6.86 (d, 1H, Ar–H, $H_{m'}$, J = 8.4 Hz), 6.77, 6.75 (d,d, 1H, Ar–H, $H_{o'}$, J = 1.6, J = 8.4 Hz), 6.73 to 6.69 (t, 1H, Nph-H, H_p, J = 7.2 Hz, J = 7.6 Hz), 5.40, 5.37 (d,d, 1H, H_a, J_{ab} = 12.0, J_{ac} = 6.8 Hz), 3.91, 3.87 (d,d, 1H, H_b, J_{bc} = 17.4, J_{ba} = 12.0 Hz), 3.69 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.15, 3.11 (d,d, 1H, H_c, J_{cb} = 17.2, J_{ca} = 6.8 Hz). MS m/z (%): 434 (M^+; 100), 297 (0.70), 270 (1.33), 77 (1.90). *Anal.* Calcd for $C_{29}H_{26}N_2O_2$ (434.54): C, 80.16; H, 6.03; N, 6.45. Found: C, 80.12; H, 6.01; N, 6.48.

4.4.3 | 4-([1,1′-biphenyl]-4-yl)-6-(3,4-dimethoxyphenyl)pyrimidine-2(1*H*)-thione 19

To a mixture of chalcone **3** (0.01 mol, 3.44 g), and thiourea (0.76 g, 0.01 mol) in ethanol (40 mL), an aqueous solution of sodium hydroxide (10 mL, 40%) was added and heated under stirring for 6 hours. After cooling, the resulting solution was neutralized by pouring slowly into crushed ice cold water acidified by acetic acid with stirring, The resulting solid was collected, washed with water several times, dried and recrystallized from toluene to give **19** as green crystals; m.p.: 240°C to 242°C, yield 62%. IR (KBr, υ/cm^{-1}): 3387 (NH), 2999, 2932, 2834 (CH_3), 1623 (C═N), 1600 (C═C), 1264 (C═S). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.89 (br.s, 1H, NH, exchangeable with D_2O), 8.38 to 7.09 (m, 12H, 9Ar′–H + 3Ar–H), 6.65 (s, 1H, C_5–$H_{(pyrimidinethione)}$), 3.87 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3). MS m/z (%): 400 (M^+; 100), 399 (91.58), 384 (67.02), 383 (66.36), 341 (23.68), 311 (26.12), 280 (12.38), 193 (22.27), 180 (8.53), 152 (17.69), 77 (11.74), 44 (39.30). *Anal.* Calcd for $C_{24}H_{20}N_2O_2S$ (400.50): C, 71.98; H, 5.03; N, 6.99; S, 8.01. Found: C, 72.07; H, 5.07; N, 7.02; S, 7.92.

4.4.4 | 1-([1,1′-biphenyl]-4-yl)-3-(benzylthio)-3-(3,4-dimethoxyphenyl)propan-1-one 20

To a solution of *S*-benzylthiuronium chloride (2.02 g, 0.01 mol) in water (10 mL), sodium hydroxide (10 mL, 1 N) was added dropwise with shaking, the pale green precipitate was formed, was dissolved in warmed ethanol (10 mL), then a solution of chalcone **3** (0.01 mol, 3.44 g) in ethanol (20 mL) was added and the whole mixture was heated under stirring for 5 hours. The solid formed after cooling was collected by filteration and recrystallized from petroleum ether 80°C to 100°C to give **20** as pale yellow crystals; m.p.: 76°C to 78°C, yield 92%. IR (KBr, υ/cm^{-1}): 2912, 2832 ($CH_{aliph.}$), 1681 (C=O), 1602 (C=C). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.98 to 7.95 (d, 2H, Ar′–H, H_o, $J = 8.4$ Hz), 7.76 to 7.74 (d, 2H, Ar′–H, H_m, $J = 8.4$ Hz), 7.70 to 7.68 (d, 2H, Ar′–H, $H_{o'}$, $J = 8.8$ Hz), 7.49 to 7.45 (t, 2H, Ar′–H, $H_{m'}$, $J = 6.8$ Hz, $J = 8$ Hz), 7.41 to 7.37 (t, 1H, Ar′–H, $H_{p'}$, $J = 6.8$ Hz, $J = 7.6$ Hz), 7.27 to 7.25 (d, 1H, Ar–H, benzyl-H, H_o, $J = 7.6$ Hz), 7.25 to 7.23 (d, 1H, Ar–H, benzyl-H, H_o, $J = 7.2$ Hz), 7.20 to 7.17 (t, 3H, Ar–H, benzyl-H, $2H_m + H_p$), 6.90 (s, 1H, Ar–H), 6.82 (s, 2H, Ar–H), 4.29, 4.27 (d,d, 1H, H_a, $J = 8.0$, $J = 6.4$ Hz), 3.68 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.60 (s, 2H, CH_2S), 3.57 to 3.49 (m, 2H, CH_2CO, H_bH_c). MS m/z (%): 468 (M^+; 9.36), 377 (100), 344 (97.50), 329 (28.21), 313 (17.18), 181 (12.72), 152 (16.05), 91 (40.07), 77 (4.89). *Anal.* Calcd for $C_{30}H_{28}O_3S$ (468.61): C, 76.89; H, 6.02; S, 6.84. Found: C, 76.93; H, 6.00; S, 6.86.

4.5 | Cytotoxicity and antitumor evaluation

The in vitro antitumor activities of the parent chalcone **3** and 10 novelty synthesized compounds against two cell lines (HepG2 and (MCF-7) were performed with the MTT assay according to the previous method.[44,45] Doxorubicin (DOX) was using as the standard anticancer drug. The MTT assay is based on the reduction of the soluble 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) into a purple formazan derivative, mainly by mitochondrial succinate dehydrogenase inside living cells. The cells used in cytotoxicity assay were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum. Antibiotics added were (100 units/mL) penicillin and (100 μg/mL) streptomycin at 37°C in a 5% CO_2 incubator. The cells were plated in a 96-well culture plates at a density of (1.0×10^4 cells/well) and incubated in a humidified atmosphere with 5% CO_2 at 37°C for 48 hours. Test compounds were added to the cells with different concentrations. After they had been incubated for 24 hours. Twenty microlitre of MTT solution (5 mg/mL) was added to each well and the plates were incubated for additional 4 hours. One hundred microlitre of DMSO was added into each well to dissolve the purple formazan formed. The absorbance of each well was recorded by using a microplate reader (EXL 800, USA) at 570 nm. The results were expressed as the IC_{50} (μM). Each experiment was performed three times.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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