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# USES OF CHALCONE ACETOPHENONE TO SYNTHESIS HETEROCYCLIC COMPOUNDS WITH CYTOTOXIC AND C-MET KINASE ACTIVITIES

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**ABSTRACT**. The aim of present study was the uses of a series of α,β-unsaturated carbonyl compounds (chalcones), in the synthesis of pyridine, pyran, thiophene, thiazole, together with their uses in heterocyclic synthesis. The work has resulted in the synthesis of a variety of 2,5-dihydropyridine, hydrazide-hydrazone, thiophene derivatives, coumarin, pyran and thiazolo[4,5-*d*]thiazole derivatives. The antitumor activities of the newly synthesized products were carried out against three cancer cell lines namely MCF-7, NCI-H460 and SF-268 and normal human cell line WI38. In addition, the inhibitions of most of the synthesized compounds against c-Met kinase were studied and results showed that many compounds were of high inhibitions, and these are considered as promising anticancer agents. The results obtained encouraged further work in the future.

**KEY WORDS**: Chalcones, Heterocyclic, Pyridine, Pyran, Thiophene, Thiazole, Antitumor

## INTRODUCTION

Chalcones constitute an important group of natural products and their pharmacological values received much interest in recent years. Chemically, they consist of an open chain flavanoids in which the two aromatic rings are joined by a three carbon α,β-unsaturated carbonyl system. The presence of a reactive α,β-unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity [1]. In recent years a variety of chalcones have been reviewed for their cytotoxic, anticancer, chemopreventive, mutagenic as well as antiviral, insecticidal and enzyme inhibitory properties [2, 3].

A number of chalcones having hydroxy, alkoxy groups in different position have been reported to possess anti-bacterial [4], antiulcer [5], antifungal [6], antioxidant [7], vasodilatory [8], antimitotic [9], antimalarial [10], antileishmanial [11] and inhibition of chemical mediators release. In addition of their inhibition of leukotriene B4 [12], inhibition of tyrosine kinase [13, 14] and inhibition of aldose reductase [15] activities. Appreciation of these findings motivated us to synthesize chalcones as a potential template for anticancer agents as a continuation for our previous work [16-18]. It must be noted that this scaffold provides substitution pattern on benzylideneacetophenones nucleus. In this work, we present the synthesis of a series of α,β-unsaturated carbonyl compounds (chalcones), and report the cytotoxic evaluations of the newly synthesized together with the c-Met kinase inhibitions.

## RESULTS AND DISCUSSION

In the present work, we demonstrate the uses of some chalcones of acetophenone for different heterocyclization reactions to produce compounds that showed cytotoxic and c-Met kinase activities. Thus, chalcones **3a,b** (Scheme 1) were synthesized via Claisen-Schmidt condensation

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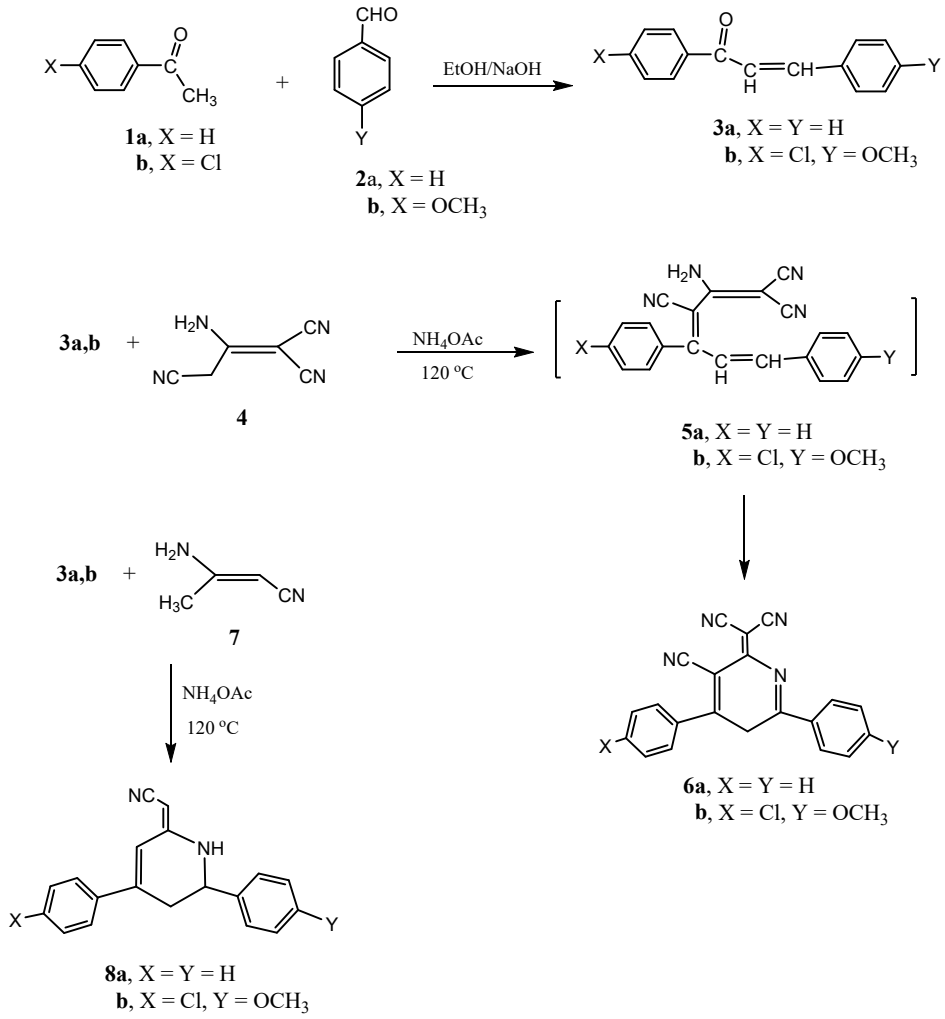


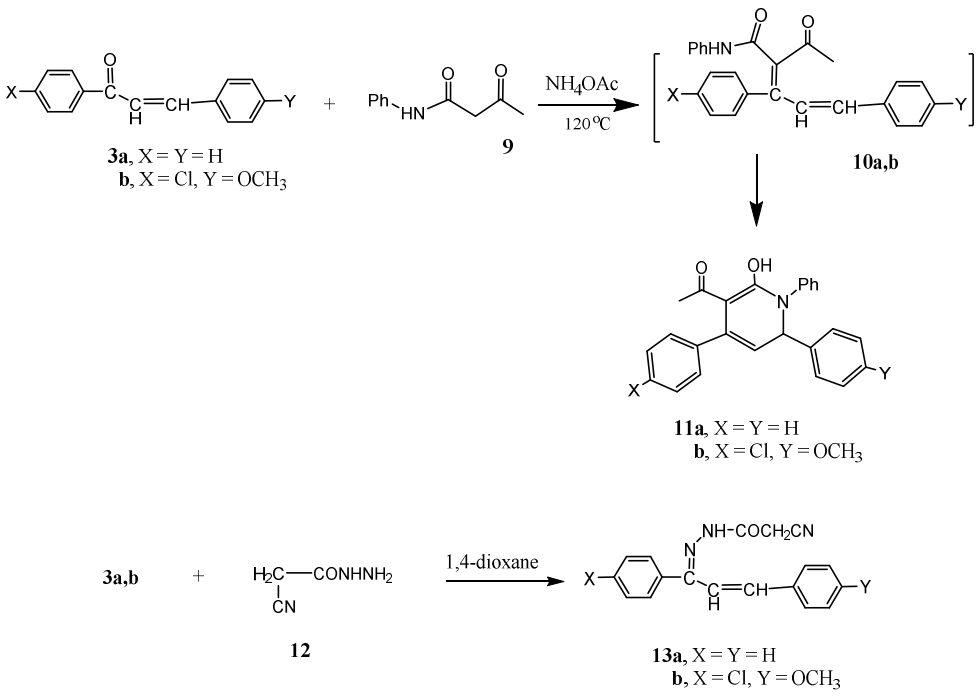

Scheme 1. Synthesis of compounds **3a**,**b**; **6a**,**b** and **8a**,**b**.

reaction of either acetophenone (**1a**) with benzaldehyde (**2a**) or 4-chloroacetophenone (**1b**) with 4-methoxybenzaldehyde (**2b**), in aqueous NaOH (0.05 M) and ethanol, at room temperature (r.t.). After completion of the reaction, the mixture was filtered to collect the precipitates and purification by re-crystallization affords the pure chalcones **3a** and **3b**, respectively. Compounds **3a** and **3b** were the key starting compounds for different heterocyclic derivatives. Thus, the reaction of either compound **3a** or **3b** with 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**4**) in the presence of a catalytic amount of ammonium acetate gave the 2,5-dihydropyridine derivatives **6a** and **6b**, respectively. Formation of **6a,b** took place through the intermediate formation of the acyclic intermediates **5a,b** followed by ring closure. The structures of compounds **6a,b** were established on the basis of analytical and spectral data. Thus, the $^1$H NMR spectrum of **6b** showed the presence of a singlet at δ 3.09 ppm corresponding to the $OCH_3$ group, a singlet at δ 6.87 ppm

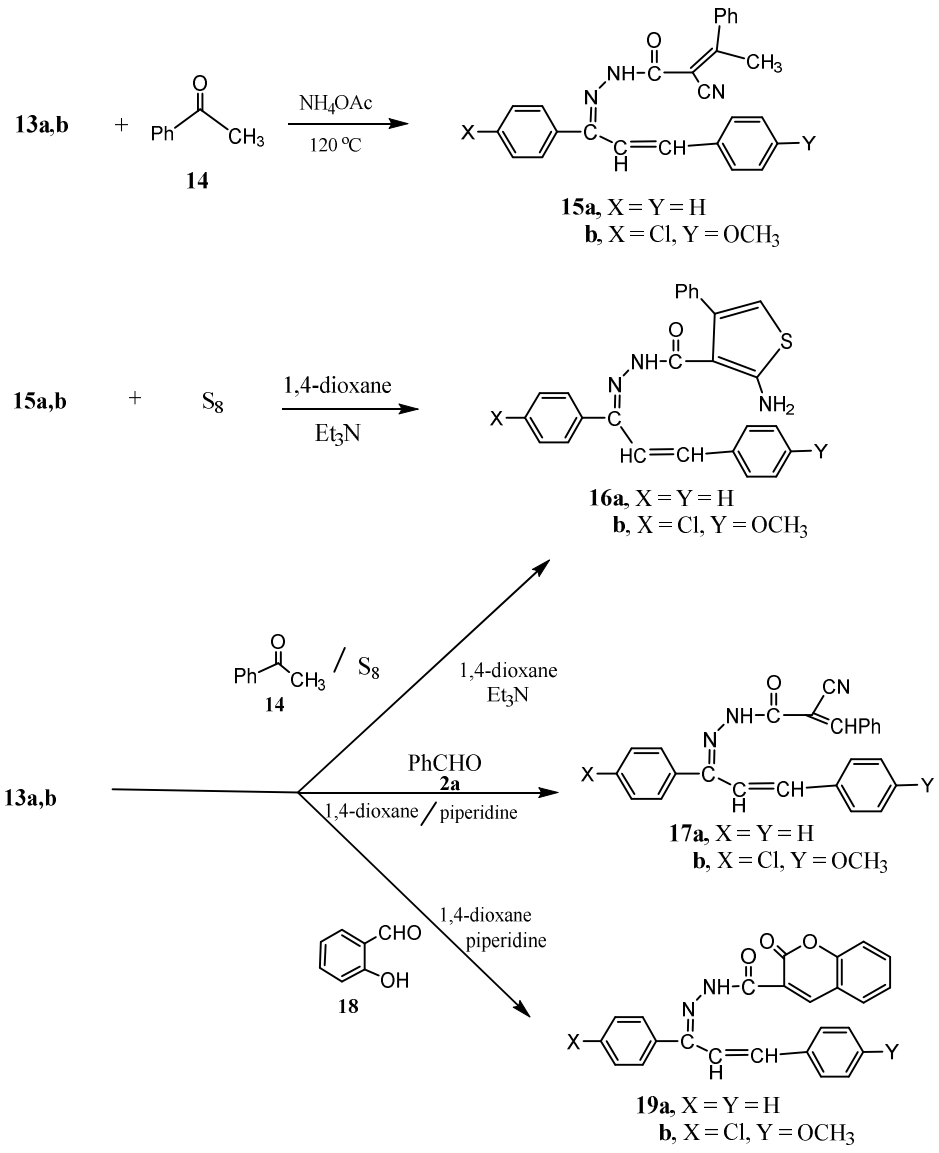
equivalent to the pyridine $CH_2$, and a multiplet at δ 7.23-7.42 ppm corresponding to the two phenyl groups. In addition, the $^{13}C$ NMR spectrum showed a signal at δ 50.6 due to the $OCH_3$ group, a signal at δ 89.6 indicating the pyridine $CH_2$ group, two signals at δ 88.1, 89.5 for the ylidene C=C moiety, three signals at δ 116.8, 117.2, 117.5 for the three CN groups, eight signals at δ 120.3, 120.5, 121.2, 122.9, 122.5, 123.4, 123.8, 124.4 equivalent to the two $C_6H_4$ groups and a signal at δ 173.5 for the C=N. In a similar manner, the reaction of either compound **3a** or **3b** with 3-aminobut-2-enenitrile (**7**) gave the condensation product **8a** and **8b**, respectively (Scheme 1).

The reaction of either **3a** or **3b** with 3-oxo-N-phenylbutanamide (**9**) gave the 6-hydropyridine derivatives **11a** and **11b**, respectively, the reaction took place through the intermediate formation of **10a,b**.

Recently, our research group has been involved through the synthesis of a series of hydrazide-hydrazone derivatives. The hydrazide-hydrazones have been demonstrated to possess antibacterial [19], anticonvulsant [20] and antitubercular activities [21]. These observations led us to synthesize novel hydrazide-hydrazones and to investigate their possible antitumor activities. Thus, the reaction of 2-cyanoacetohydrazide **12** with either compound **3a** or **3b** in 1,4-dioxane under reflux gave the hydrazide-hydrazone derivatives **13a** and **13b**, respectively (Scheme 2). The IR and $^1H$ NMR spectra were the tools of their structural elucidation. Thus, compound **13a** showed in its IR spectrum the presence $\nu_{max}$ 3473-3318 $cm^{-1}$ for the NH group, a signal at $\nu_{max}$ 2253 $cm^{-1}$ equivalent to the cyano group and a signal at 1686 $cm^{-1}$ confirming the presence of the carbonyl group. In addition, the $^1H$ NMR spectrum revealed the presence of a singlet at δ 5.24 for the $CH_2$ group, a doublet at δ 6.09 and 6.29 ppm for the CH=CH group, a multiplet at δ 7.29-7.38 ppm for the two $C_6H_5$ groups and a singlet at δ 8.42 ppm ($D_2O$ exchangeable) equivalent to the NH group.




Scheme 2. Synthesis of compounds **11a**,**b** and **13a**,**b**.

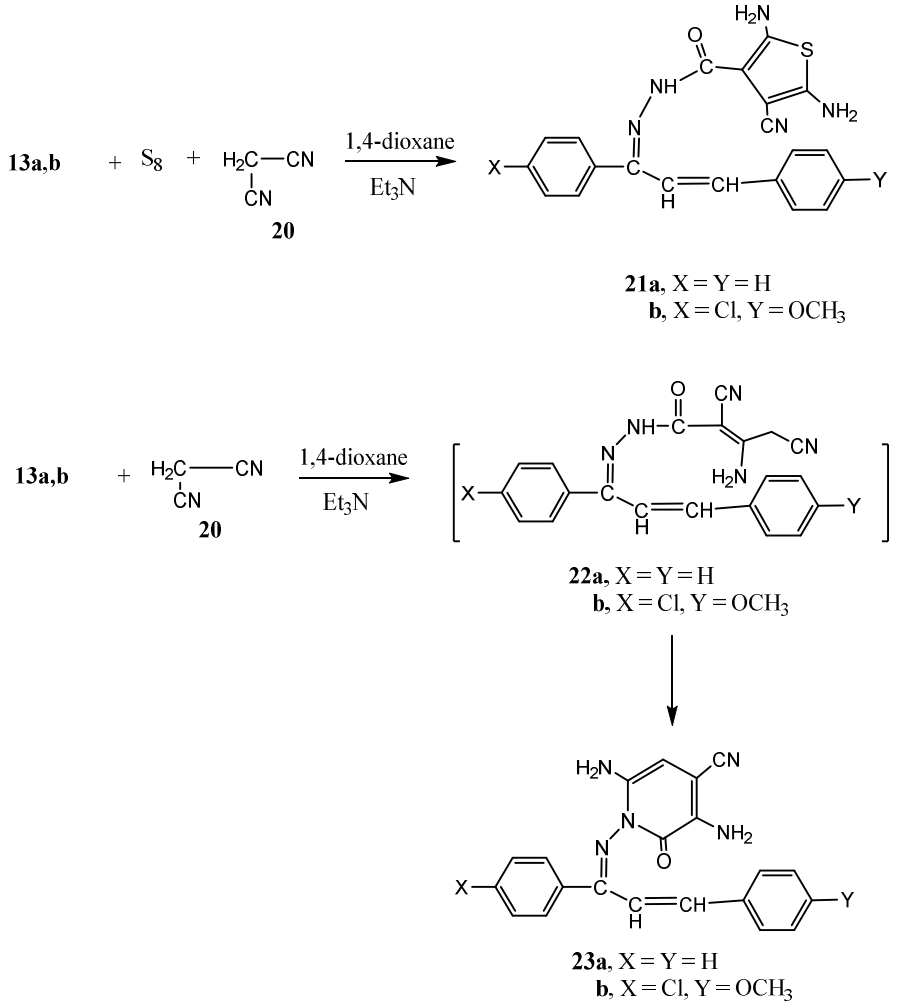



Scheme 3. Synthesis of compounds **15a**,**b**; **16a**,**b**; **17a**,**b** and **19a**,**b**.

The reaction of either compound **13a** or **13b** with acetophenone (**14**) in the presence of ammonium acetate in an oil bath at 120 °C gave the condensation products **15a** and **15b**, respectively. Moreover, the reaction of either compound **15a** or **15b** with elemental sulfur, as a method of Gewald's thiophene synthesis [22-24], in 1,4-dioxane containing triethylamine gave the thiophene derivatives **16a** and **16b**, respectively. The analytical and spectral data were in

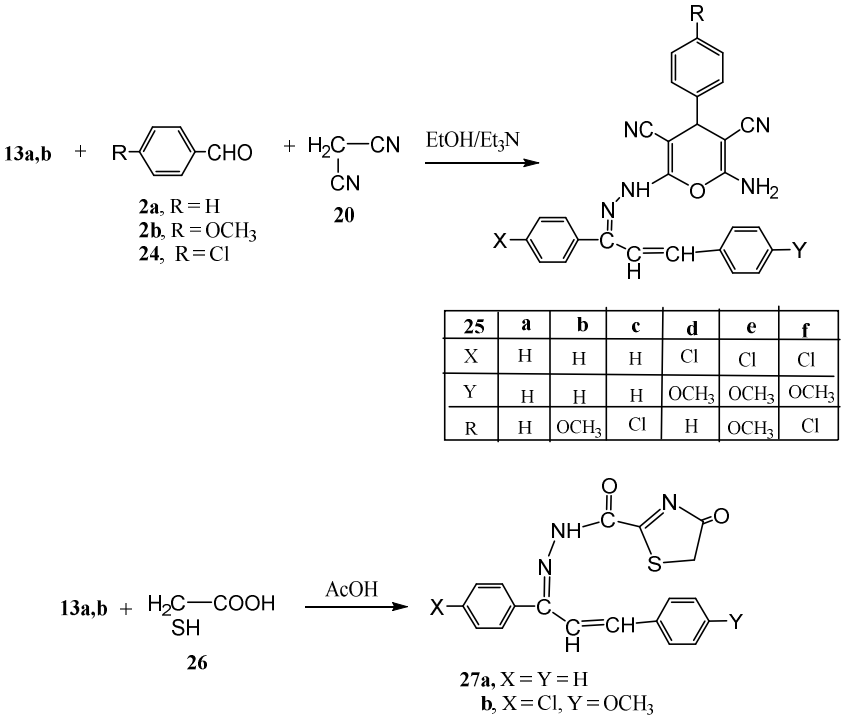
agreement with their respective structures. The same products were obtained through the reaction of either of compound **13a** or **13b** with acetophenone and elemental sulfur in 1,4-dioxane containing triethylamine (m.p., mixed m.p. and fingerprint IR). The reaction of either of **13a** or **13b** with benzaldehyde (**2a**) gave the benzylidene derivatives **17a** and **17b**, respectively. On the other hand, the reaction of either of compound **13a** or **13b** with salicylaldehyde (**18**) gave the coumarin derivatives **19a** and **19b**, respectively (Scheme 3).

The reaction of either compound **13a** or **13b** with malononitrile (**20**) and elemental sulfur gave the thiophene derivatives **21a** and **21b**, respectively. On the other hand, the reaction of either **13a** or **13b** with malononitrile in 1,4-dioxane containing a catalytic amount of triethylamine gave the pyridine-6-one derivatives **23a** and **23b**, respectively. The reaction took place through the intermediate formation of **22a** and **22b** followed by ring closure (Scheme 4).




Scheme 4. Synthesis of compounds **21a**,**b** and **23a**,**b**.

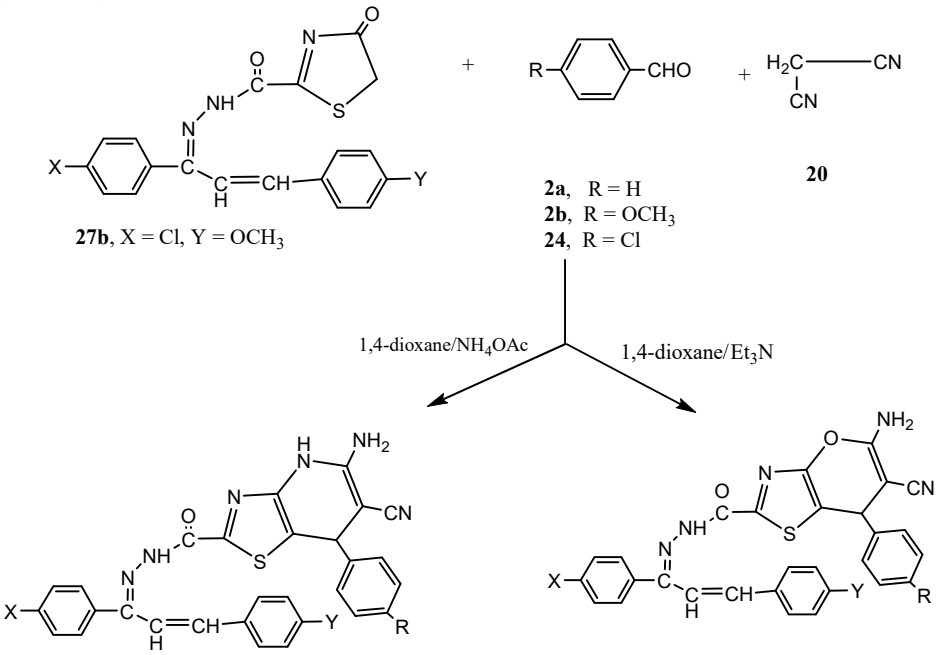
Next, we moved towards studying the reactivity of compounds **13a,b** via the multi-component reactions through their reactions with malononitrile and aromatic aldehydes to afford biologically active polyfunctionally substituted pyran derivatives. Thus, the reaction of either **13a** or **13b** with malononitrile (**20**) and either benzaldehyde (**2a**), 4-methoxybenzaldehyde (**2b**) or 4-chloro-benzaldehyde (**24**) in ethanol containing triethylamine gave the pyran derivatives **25a-f**, respectively. The analytical and spectral data of the latter products were consistent with their respective structures. Thus, the $^1$H NMR spectrum of **25a** (as an example) showed a singlet at δ 4.72 ppm ($D_2O$ exchangeable) equivalent to the $NH_2$ group, two singlets at δ 6.11, 6.24 ppm confirming the CH=CH moiety, a singlet δ 6.93 confirming the pyran H-4, a multiplet at δ 7.27-7.37 equivalent to the three $C_6H_5$ groups and a singlet at δ 8.25 ($D_2O$ exchangeable) for the NH group. In addition, the $^{13}$C NMR spectrum showed a signal at δ 88.3 for the pyran C-4, two signals at δ 90.4, 92.4 for the CH=CH moiety, signals at δ 119.3, 119.5, 120.6, 120.9, 121.3, 121.5, 121.8, 122.0, 122.3, 123.4, 123.6, 125.8 equivalent to the three $C_6H_5$ groups, four signals at δ 128.6, 129.2, 130.8, 131.7 for the pyran C-2, C-3, C-5, C-6 and a signal at δ 168.8 for the C=N group. The reaction of either compound **13a** or **13b** with thioglycollic acid (**26**) gave the thiazol-4-one derivatives **27a** and **27b**, respectively (Scheme 5).




Scheme 5. Synthesis of compounds **25a-f** and **27a**,**b**.

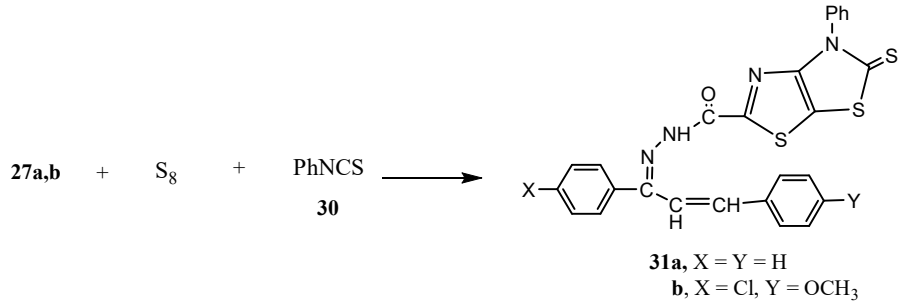
Compounds **27a,b** with their methylenocarbonyl moiety were found to be good candidates for multi-component reactions. Thus, the reaction of either compound **27b** with malononitrile (**20**) and either benzaldehyde (**2a**), 4-methoxybenzaldehyde (**2b**) or 4-chlorobenzaldehyde (**24**) in 1,4-dioxane containing triethylamine gave the thiazolo[4,5-*b*]pyran derivatives **28a-c**, respectively. Moreover, the reaction of either of compound **27b** with malononitrile (**20**) and either benaldehyde (**2a**), 4-methoxybenzaldehyde (**2b**) or 4-chlorobenzaldehyde (**24**) in 1,4-dioxane containing

amount of ammonium acetate gave the thiazolo[4,5-*b*]pyridine derivatives **29a-c**, respectively. On the other hand, the reaction of either **27a** or **27b** with elemental sulfur and phenylisothiocyanate (**30**) gave the thiazolo[4,5-*b*]thiazole derivatives **31a** and **31b**, respectively (Scheme 6).



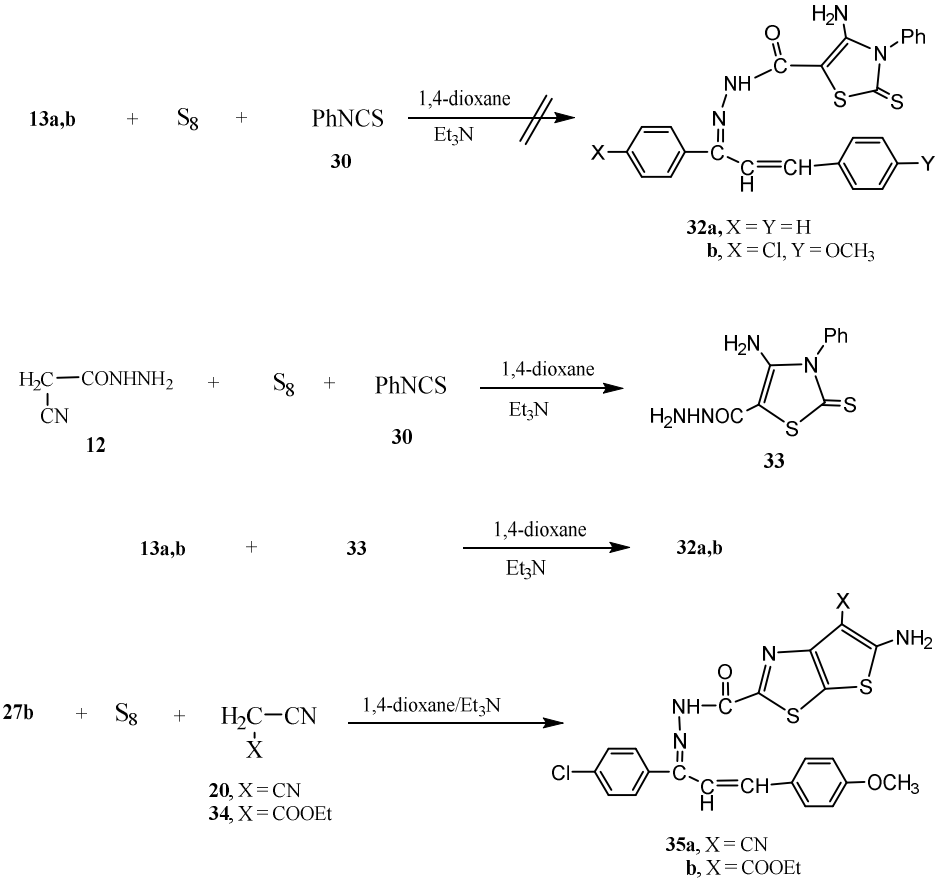

| **29** | X | Y | R |
|---|---|---|---|
| **a** | Cl | $OCH_3$ | H |
| ***b*** | Cl | $OCH_3$ | $OCH_3$ |
| **c** | Cl | $OCH_3$ | Cl |

| **28** | X | Y | R |
|---|---|---|---|
| **a** | Cl | $OCH_3$ | H |
| ***b*** | Cl | $OCH_3$ | $OCH_3$ |
| **c** | Cl | $OCH_3$ | Cl |




Scheme 6. Synthesis of compounds **28a-c**; **29a-c** and **31a**,**b**.

Our trials for the reaction of either compound **13a** or **13b** with elemental sulfur and phenylisothiocyanate to form the thiazol-5-hydrazidohydrazone derivatives **32a** and **32b** in a similar manner like the reaction of compounds **27a** and **27b** were unsuccessful; for that reason we tried to synthesis them through another reaction root. Thus, the reaction of cyanoacetylhydrazine (**12**) with elemental sulfur and phenylisothiocyanate gave the thiazole-2-thione derivative **33** which intern reacted with either compound **13a** or **13b** to give the thiazole-2-hydrazidohydrazone derivatives **32a** and **32b**, respectively (Scheme 7). The structures of the latter products were confirmed on the basis of their respective analytical and spectral data (see experimental section). The presence of the α-carbonylmethylene moiety in compound **27b** showed interesting reactivity towards the Gewald's thiophene synthesis. Thus, the reaction of compound **27b** with elemental sulfur and either malononitrile (**20**) or ethyl cyanoacetate (**34**) gave the thieno[2,3-*b*] thiazole derivatives **35a** and **35b**, respectively. The structures of the latter compounds were elucidated on the basis of their respective analytical and spectral data (see experimental section)




Scheme 7. Synthesis of compounds **32a**,**b**; **33** and **35a**,**b**.

*Antitumor evaluations*

*Antitumor and normal cell lines activity tests*

*Reagents*. Fetal bovine serum (FBS) and L-glutamine, were from Gibco Invitrogen Co. (Scotland, UK). RPMI-1640 medium was from Cambrex (New Jersey, USA). Dimethyl sulfoxide (DMSO), doxorubicin, penicillin, streptomycin and sulforhodamine B (SRB) were from Sigma Chemical Co. (Saint Louis, USA).

*Cell cultures*. Three human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), and SF-268 (CNS cancer) were used. MCF-7 was obtained from the European Collection of Cell Cultures (ECACC, Salisbury, UK), NCI-H460, SF-268 and normal fibroblast cells (WI 38) were kindly provided by the National Cancer Institute (NCI, Cairo, Egypt). They grow as monolayer and routinely maintained in RPMI-1640 medium supplemented with 5% heat inactivated FBS, 2 mM glutamine and antibiotics (penicillin 100 U/mL, streptomycin 100 µg/mL), at 37 ºC in a humidified atmosphere containing 5% $CO_2$. Exponentially growing cells were obtained by plating 1.5 x 105 cells/mL for MCF-7 and SF-268 and 0.75 x 104 cells/mL for NCI-H460, followed by 24 h of incubation. The effect of the vehicle solvent (DMSO) on the growth of these cell lines was evaluated in all the experiments by exposing untreated control cells to the maximum concentration (0.5 %) of DMSO used in each assay.

*Tumor cell growth assay*

The effects of the synthesized compounds on the in vitro growth of human tumor cell lines were evaluated according to the procedure adopted by the National Cancer Institute (NCI, USA) in the 'In vitro Anticancer Drug Discovery Screen' that uses the protein-binding dye sulforhodamine B to assess cell growth. Briefly, exponentially, cells growing in 96-well plates were then exposed for 48 h to five serial concentrations of each compound, starting from a maximum concentration of 150 µM. Following this exposure period adherent cells were fixed, washed, and stained. The bound stain was solubilized, and the absorbance was measured at 492 nm in a plate reader (Bio-Tek Instruments Inc., Power wave XS, Wincoski, USA). For each test compound and cell line, a dose–response curve was obtained and the inhibition of 50% ($IC_{50}$), corresponding to the concentration of the compounds that inhibited 50% of the net cell growth. Doxorubicin was used as a positive control and tested in the same manner.

Results are given in cconcentrations that were able to cause 50% of cell growth inhibition ($IC_{50}$) after a continuous exposure of 48 h and show means ± SEM of three-independent experiments performed in duplicate.

The effect of the newly synthesized compounds on the *in vitro* growth of the three human tumor cell lines representing different tumor namely (MCF-7), (NCI-H460), (SF-268) and normal cell line (WI 38) after continuous exposure for 48h was demonstrated through Table 1.

*Structure activity relationship*

Compounds **19a** and **29c** showed the highest inhibitory effect against the three human tumor cell lines. Compounds **6a**, **11b**, **16b**, **25e**, **25b**, **25c**, **25f**, **35a** and **35b** showed high inhibitory effect against the three human cancer cell lines. Compound **11b** showed high inhibitory effect against (MCF-7), (NCI-H460) and compounds **23a**, **25e** and **35a** moderate inhibitor effect. Compounds **11a** and **29a** showed high inhibitory effect against (SF-268). Compounds **6b, 8b, 11a, 13a, 13b, 15a, 15b, 16a, 17a, 17b, 19b, 21a, 21b, 23b, 25a, 25d, 27a, 27b, 28a, 28b, 28c, 29a, 29b, 31b, 32a** and **33** showed lowest inhibitory effect against the three human tumor cell lines. The highest inhibitory effect of compound **29c** against the three human tumor cell lines was attributed

Table 1. Effect of newly synthesized compounds on the growth of three human tumor cell lines.

| Compound | $IC_{50}$ (μ mol $L^{-1}$) | | | |
|---|---|---|---|---|
| | MCF-7 | NCI-H460 | SF-268 | WI 38 |
| **6a** | 0.06 ± 0.006 | 0.06 ± 0.006 | 0.02 ± 0.008 | >100 |
| **6b** | 33.61 ± 8.15 | 40.32 ± 12.43 | 30.40 ± 2.83 | 62.12 ± 2.03 |
| **8b** | 36.58 ± 1.26 | 22.67 ± 1.64 | 20.18 ± 8.85 | 79.80±10.68 |
| **11a** | 14.26 ± 1.37 | 16.92 ± 1.04 | 0.24 ± 4.12 | 20.38 ± 4.99 |
| **11b** | 0.02 ± 0.002 | 0.01 ± 0.003 | 20.20 ±3.46 | 49.22 ±6.88 |
| **13a** | 23.55 ± 4.06 | 34.6 ± 12.06 | 45.41 ± 2.16 | >100 |
| **13b** | 22.02 ± 7.33 | 22.34 ± 2.18 | 32.64 ± 2.37 | 66.16 ± 8.54 |
| **15a** | 60.01 ± 8.25 | 42.36 ± 10.13 | 30.40 ± 6.06 | >100 |
| **15b** | 13.64 ± 2.72 | 15.05 ± 4.63 | 30.16 ± 8.08 | >100 |
| **16a** | 21.23 ± 2.47 | 23.96 ± 2.86 | 20.68 ± 8.35 | >100 |
| **16b** | 1.28 ± 0.4 | 0.35 ± 0.16 | 2.80 ± 0.06 | 22.4 ± 1.6 |
| **17a** | 70.20 ± 22.20 | 61.30 ± 10.24 | 19.39 ±2.19 | 50.2 ± 10.22 |
| **17b** | 32.23 ± 3.36 | 31.32 ± 12.35 | 40.66 ± 8.78 | 30.24 ± 8.02 |
| **19a** | 0.01 ± 0.002 | 0.02 ± 0.001 | 0.01 ± 0.003 | >100 |
| **19b** | 20.22 ± 2.26 | 30.8± 4.29 | 26.20 ± 4.06 | >100 |
| **21a** | 34.52 ± 2.24 | 28.67 ± 2.68 | 18.38 ± 8.65 | >100 |
| **21b** | 20.8 ± 8.30 | 22.8 ± 4.32 | 22.8 ± 6.23 | >100 |
| **23a** | 2.63 ± 0.01 | 2.66 ± 0.06 | 1.43 ± 0.36 | >100 |
| **23b** | 24.1 ± 10.4 | 30.8 ± 10.8 | 26.1 ± 2.8 | 25.2 ± 0.8 |
| **25a** | 10.33 ± 2.16 | 13.36 ± 2.26 | 12.20 ± 5.28 | >100 |
| **25b** | 0.08 ± 0.002 | 0.08 ± 0.003 | 0.02 ± 0.002 | >100 |
| **25c** | 0.06 ± 0.006 | 0.06 ± 0.006 | 0.2 ± 0.08 | >100 |
| **25d** | 30.0 ± 1.4 | 20.8 ± 4.3 | 20.3 ± 2.8 | >100 |
| **25e** | 0.65 ± 0.082 | 0.86 ± 0.02 | 2.19 ± 0.83 | 64.11 ± 1.22 |
| **25f** | 0.21 ± 0.04 | 0.12 ± 0.04 | 0.08 ± 0.006 | 40.0 ± 1.3 |
| **27a** | 31.22 ± 4. 18 | 30.03 ± 8.01 | 20.59 ± 4.01 | >100 |
| **27b** | 22.4 ± 5.8 | 26.7 ± 8.2 | 31.4 ± 2.4 | 18.6 ± 4.0 |
| **28a** | 26.6 ± 8.5 | 29.3 ± 12.3 | 18.4 ± 2.8 | 68.2 ± 2.0 |
| **28b** | 10.43 ± 1.24 | 10.40 ± 2.86 | 0.43 ± 0.06 | >100 |
| **28c** | 23.55 ± 4.06 | 34.6 ± 12.06 | 45.41 ± 2.16 | >100 |
| **29a** | 22.4 ± 2.10 | 10.42 ± 3.01 | 8.63 ± 2.83 | >100 |
| **29b** | 38.2 ± 3.6 | 36.3 ± 12.5 | 40.6 ± 8.8 | >100 |
| **29c** | 0.01 ± 0.001 | 0.02 ± 0.006 | 0.06 ± 0.002 | >100 |
| **31b** | 36.6 ± 10.2 | 33.0 ± 8.6 | 38.6 ± 8.0 8 | >100 |
| **32a** | 36.09 ± 1.44 | 20.8 ± 4.32 | 28.3 ± 2.8 | 38.4 ± 2.90 |
| **33** | 20.81 ± 8.30 | 18.81 ± 4.32 | 16.83 ± 6.23 | >100 |
| **35a** | 0.68 ± 0.20 | 0.70 ± 0.18 | 2.43 ± 0.51 | 22.45 ± 2.40 |
| **35b** | 0.08 ± 0.004 | 0.05 ± 0.002 | 0.06 ± 0.001 | 28.0 ± 4.94 |
| **Doxorubicin** | 0.04 ± 0.008 | 0.09±0.008 | 0.09±0.007 | > 100 |

to the presence of pyridine heterocyclic ring, thiazole ring, 4-methoxy and chlorine groups. Considering coumarin derivative **19a** showed that highest inhibitory effect against all three human tumor cell lines. High inhibitory effect of compound **6a** against all three human tumor cell lines was attributed to the presence of pyridine heterocyclic ring. Also compounds **25b, 25c, 25e** and **25f** have high inhibitory effects against the three human tumor cell lines this was attributed to the presence of pyran heterocyclic ring, 4-methoxy and chlorine groups. Compounds **35a** and **35b** showed high inhibitory effects against the three human tumor cell lines and this was attributed to the presence of thiazole ring, 4-methoxy and chlorine groups. Compound **11b** showed high inhibitory effect against (MCF-7), (NCI-H460) due to the presence of pyridine heterocyclic ring, OH and chlorine groups, respectively. Compound **28b** showed high inhibition against (SF-268)

and this was attributed to the presence of coumarin, thiazole ring and the hydrazide-hydrazone moiety.

Table 2. c-Met enzymatic activity of the newly synthesized compounds.

| Compound Number | X | Y | R | $IC_{50}$ (nM) c-Met |
|---|---|---|---|---|
| **6a** | H | H | - | 8.52 ± 2.419 |
| **6b** | Cl | $OCH_3$ | - | 0.41± 0.29 |
| **8b** | Cl | $OCH_3$ | - | 0.63 ± 0.25 |
| **11a** | H | H | - | 7.13 ± 1.82 |
| **11b** | Cl | $OCH_3$ | - | 0.39 ± 0.12 |
| **13a** | H | H | - | 5.36 ± 1.52 |
| **13b** | Cl | $OCH_3$ | - | 0.47 ±0.21 |
| **15a** | H | H | - | 2.62 ± 1.31 |
| **15b** | Cl | $OCH_3$ | - | 0.42 ±0.19 |
| **16a** | H | H | - | 2.34 ± 1.29 |
| **16b** | Cl | $OCH_3$ | - | 0.29 ±0.13 |
| **17a** | H | H | - | 1.73 ± 0.69 |
| **17b** | Cl | $OCH_3$ | - | 0.29 ± 0.11 |
| **19a** | H | H | - | 3.80 ± 1.25 |
| **19b** | Cl | $OCH_3$ | - | 1.31 ±0.92 |
| **21a** | H | H | - | 6.84 ±1.27 |
| **21b** | Cl | $OCH_3$ | - | 0.30 ± 0.13 |
| **23a** | H | H | - | 5.78± 2.17 |
| **23b** | Cl | $OCH_3$ | - | 0.37 ± 0.15 |
| **25a** | H | H | H | 6.31 ± 2.46 |
| **25b** | H | H | $OCH_3$ | 0.21 ± 0.09 |
| **25c** | H | H | Cl | 0.14 ± 0.06 |
| **25d** | Cl | $OCH_3$ | H | 1.21 ± 0.65 |
| **25e** | Cl | $OCH_3$ | $OCH_3$ | 10.24 ± 2.72 |
| **25f** | Cl | $OCH_3$ | Cl | 0.14 ± 0.02 |
| **27a** | H | H | - | 8.36 ± 2.41 |
| **27b** | Cl | $OCH_3$ | - | 0.62 ± 0.31 |
| **28a** | Cl | $OCH_3$ | H | 2.62 ± 0.82 |
| **28b** | Cl | $OCH_3$ | $OCH_3$ | 8.32 ± 2.51 |
| **28c** | Cl | $OCH_3$ | Cl | 0.25 ± 0.13 |
| **29a** | Cl | $OCH_3$ | H | 4.35 ± 2.18 |
| **29b** | Cl | $OCH_3$ | $OCH_3$ | 1.36 ± 0.81 |
| **29c** | Cl | $OCH_3$ | Cl | 0.84 ± 0.52 |
| **31b** | Cl | $OCH_3$ | - | 6.32 ± 2.80 |
| **32a** | H | H | | 8.26 ± 2.39 |
| **33** | - | - | - | 1.38 ± 0.92 |
| **35a** | CN | - | - | 3.64 ± 1.50 |
| **35b** | COOEt | - | - | 0.36 ± 0.16 |
| **Foretinib** | - | - | - | 1.16 ± 0.17 |

*c-Met kinase inhibition*

Most of the newly synthesized compounds were evaluated for their inhibitions toward c-Met enzyme using a homogeneous time-resolved fluorescence (HTRF) assay. Taking foretinib as the positive control, the results expressed as $IC_{50}$ were summarized in Table 2. The $IC_{50}$ values are the average of at least three independent experiments. As illustrated in Table 2, all the tested compounds displayed potent c-Met enzymatic activity with $IC_{50}$ values ranging from 0.14 to 10.24

nM. Compared with foretinib ($IC_{50}$ = 1.16 nM), fifteen of them **6b**, **8b**, **11b**, **13b**, **15b**, **16b**, **17b**, **21b**, **23b**, **25b**, **25f**, **27b**, **28c**, **29c** and **35b** exhibited higher potency than the reference foretinib ($IC_{50}$ = 1.16 nM). In addition, compounds **6a**, **11a**, **13a**, **21a**, **23a**, **25a**, **25e**, **27a**, **28b**, **31b** and **32a** exhibited low inhibitions toward c-Met kinase.

## EXPERIMENTAL

*General*

All melting points were determined on an Electrothermal digital melting point apparatus and are uncorrected. IR spectra (KBr discs) were recorded on a FTIR plus 460 or Pye Unicam SP-1000 spectrophotometer (Pye Unicam, UK, Cambridge). $^1$H NMR and $^{13}$C NMR spectra were recorded with Varian Gemini-200 (200 MHz, Varian UK) and JEOL AS 500 MHz (JEOL, Japan) instruments in DMSO-$d_6$ as solvent, using TMS as internal standard chemical shifts are expressed as δ ppm. The mass spectra were recorded with Hewlett Packard 5988 A GC/MS system (Hewlett Packard, Agilent, USA) and GCMS-QP 1000Ex Shimadzu (EI, 70 eV) (Shimadzu, Japan) instruments. Analytical data were obtained from on Vario EL III Elemental CHNS analyzer. Compounds **3a** and **3b** were synthesized according to the reported literature, with m.p, 55 ºC

*General procedure for the synthesis of the dihydropyridine derivatives **6a,b***

To a dry solid of either of compound **3a** (2.08 g, 0.01 mol) or **3b** (2.72 g, 0.01 mol) 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**4**) (1.32 g, 0.01 mol) and ammonium acetate (0.50 g) was added. The reaction mixture was heated in an oil bath at 120 ºC for 30 min then left to cool. The remaining product was boiled in ethanol (40 mL) and formed solid product was collected by filtration.

*2-(3-Cyano-4,6-diphenylpyridin-2(5H)-ylidene)malononitrile (**6a**).* Brown crystals from ethanol, yield 79% (2.53 g) m.p. 131-134 ºC. IR (KBr) $\nu_{max}$ 3058 (CH aromatic), 2972 ($CH_2$), 2223-2221 (3 CN), 1645 (C=N), 1634 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 6.89 (s, 2H, pyridine $CH_2$), 7.28-7.38 (m, 10H, $2C_6H_5$). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 89.3 (pyridine $CH_2$), 88.3, 89.1 (C=C), 116.5, 117.0, 117.3 (3CN), 120.0, 121.3, 121.6, 122.4, 122.9, 123.2, 123.5, 124.8 ($2C_6H_5$), 132.4, 133.0 (pyridine C-3, C-4), 173.2 (C=N). Analysis calcd for $C_{21}H_{12}N_4$ (320.35): C, 78.73; H, 3.78; N, 17.49%. Found: C, 78.58; H, 4.60; N, 17.38%. MS: *m/z* 320 ($M^+$, 70%).

*2-(4-(4-Chlorophenyl)-3-cyano-6-(4-methoxyphenyl)pyridin-2(5H)-ylidene)malononitrile (**6b**).* Yellow crystals from ethanol, yield 88 % (3.38 g) m.p. 93 ºC. IR (KBr) $\nu_{max}$ 3055 (CH aromatic), 2973, 2877 ($CH_3$, $CH_2$), 2225-2220 (3 CN), 1646 (C=N), 1631 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 3.09 (s, 3H, $OCH_3$), 6.87 (s, 2H, pyridine $CH_2$), 7.23-7.42 (m, 8H, $2C_6H_4$). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.6 ($OCH_3$), 89.6 (pyridine $CH_2$), 88.1, 89.5 (C=C), 116.8, 117.2, 117.5 (3CN), 120.3, 120.5, 121.2, 122.9, 122.5, 123.4, 123.8, 124.4 ($2C_6H_4$), 132.1, 133.3 (pyridine C-3, C-4), 173.5 (C=N). Analysis calcd for $C_{22}H_{13}ClN_4O$ (384.82): C, 68.67; H, 3.41; N, 14.56%. Found: C, 68.42; H, 3.58; N, 14.72%. MS: *m/z* 384 ($M^+$, 58%).

*General procedure for the synthesis of the tetrahydropyridine **8a,b***

Equimolecular amounts of either compound **3a** (2.08 g, 0.01 mol) or **3b** (2.72 g, 0.01 mol), 3-aminobut-2-enenitrile (**7**) (0.82 g, 0.01 mol) together with ammonium acetate (0.50 g) were heated in an oil bath at 120 ºC for 1 h then left to cool. The remaining product was boiled in ethanol (40 mL) and formed solid product was collected by filtration.

*2-(4,6-Diphenyl-5,6-dihydropyridin-2(1H)-ylidene)acetonitrile (**8a**).* Yellow crystals from ethanol, yield 70 % (1.90 g) m.p. 163-165 ºC. IR (KBr) $\nu_{max}$ 3053 (CH aromatic), 2983 ($CH_2$),

2220 (CN), 1636 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 5.73 (d, 2H, J = 5.80 Hz, $CH_2$), 6.21 (t, 1H, J = 5.80 Hz, pyridine H-2), 6.58 (s, 1H, pyridine H-3), 6.93 (s, 1H, CH=C), 7.28-7.38 (m, 10H, $2C_6H_5$), 8.33 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 89.3 (pyridine $CH_2$), 88.3, 89.8 (C=C), 116.9 (CN), 120.1, 120.8, 121.3, 122.4, 122.7, 123.2, 123.5, 124.8 ($2C_6H_5$), 132.3, 133.5 (pyridine C-2, C-3). Analysis calcd for $C_{19}H_{16}N_2$ (272.34): C, 83.79; H, 5.92; N, 10.29%. Found: C, 83.91; H, 5.68; N, 10.41%. MS: *m/z* 272 ($M^+$, 75%).

*2-(4-(4-Chlorophenyl)-6-(4-methoxyphenyl)-5,6-dihydropyridin-2(1H)-ylidene)acetonitrile (**8b**).* Yellow crystals from ethanol, yield 65% (2.35 g) m.p. 143-145 °C. IR (KBr) $\nu_{max}$ 3466-3328 (NH), 3053 (CH aromatic), 2974, 2879 ($CH_3$, $CH_2$), 2221 (CN), 1635 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 3.11 (s, 3H, $OCH_3$), 5.70 (d, 2H, J = 6.03 Hz, $CH_2$), 6.24 (t, 1H, J = 6.03 Hz, pyridine H-2), 5.98 (s, 1H, pyridine H-3), 6.96 (s, 1H, CH=C), 7.23-7.42 (m, 8H, $2C_6H_4$), 8.33 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.8 ($OCH_3$), 89.5 (pyridine $CH_2$), 88.1, 89.5 (C=C), 116.8 (CN), 120.5, 120.7, 121.1, 122.8, 122.9, 123.0, 123.4, 125.5 ($2C_6H_4$), 132.1, 133.8 (pyridine C-2, C-3). Analysis calcd for $C_{20}H_{17}ClN_2O$ (336.81): C, 71.32; H, 5.09; N, 8.32%. Found: C, 71.49; H, 4.92; N, 8.53%. MS: *m/z* 336 ($M^+$, 55%).

*General procedure for the synthesis of the pyridine derivatives **11a,b***

To a dry solid of either of compound **3a** (2.08 g, 0.01 mol) or **3b** (2.72 g, 0.01 mol) acetoacetanilide (**9**) (1.77 g, 0.01 mol) and ammonium acetate (0.50 g) was added. The reaction mixture was heated in an oil bath at 120 °C for 45 min then left to cool. The remaining product was boiled in ethanol (50 mL) and formed solid product was collected by filtration.

*1-(2-Hydroxy-1,4,6-triphenyl-1,6-dihydropyridin-3-yl)ethanone (**11a**).* Yellow crystals from ethanol, yield 54% (1.98 g) m.p. 70 °C. IR (KBr) νmax 3528-3329 (OH), 3053 (CH aromatic), 2980, 2877 ($CH_3$), 1688 (CO), 1631 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 2.86 (s, 3H, $CH_3$), 6.28, 6.93 (2d, 2H, pyridine H-2, H-3), 7.26-7.36 (m, 15H, $3C_6H_5$), 10.21 (s, 1H, $D_2O$ exchangeable, OH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 36.8 ($CH_3$), 90.3 (pyridine C-2), 120.1, 120.8, 121.3, 121.6, 121.8, 122.2, 122.5, 122.9, 123.1, 123.6, 125.8 ($3C_6H_5$), 132.1, 132.8, 133.8, 134.1 (pyridine C-3, C-4, C-5, C-6), 166.2 (C=O). Analysis calcd for $C_{25}H_{21}NO_2$ (367.44): C, 81.72; H, 5.76; N, 3.81%. Found: C, 81.96; H, 5.63; N, 4.14%. MS: *m/z* 367 ($M^+$, 40%).

*1-(4-(4-Chlorophenyl)-2-hydroxy-6-(4-methoxyphenyl)-1-phenyl-1,6-dihydropyridin-3-yl)ethanone (**11b**).* Yellow crystals from ethanol, yield 57% (2.45 g) m.p. 81-84 °C. IR (KBr) $\nu_{max}$ 3552-3331 (OH), 3055 (CH aromatic), 2982, 2889 ($CH_3$), 1687 (CO), 1628 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 2.69 (s, 3H, $CH_3$), 3.13 (s, 3H, $OCH_3$), 6.21, 6.83 (2d, 2H, pyridine H-2, H-3), 7.21-7.48 (m, 13H, $C_6H_5$, $2C_6H_4$), 10.26 (s, 1H, $D_2O$ exchangeable, OH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 36.5 ($CH_3$), 50.8 ($OCH_3$), 90.6 (pyridine C-2), 119.3, 120.8, 121.1, 121.5, 121.7, 122.5, 122.7, 123.1, 123.6, 124.2, 124.6, 125.6 ($C_6H_5$, $2C_6H_4$), 132.0, 132.6, 133.9, 134.5 (pyridine C-3, C-4, C-5, C-6), 166.7 (C=O). Analysis calcd for $C_{26}H_{22}ClNO_3$ (431.91): C, 72.30; H, 5.13; N, 3.24%. Found: C, 72.49; H, 5.43; N, 3.66%. MS: *m/z* 431 ($M^+$, 65%).

*General procedure for the synthesis of the hydrazide-hydrazone derivatives **13a,b***

To a solution of either of compound **3a** (2.08 g, 0.01 mol) or **3b** (2.72 g, 0.01 mol) in 1,4-dioxane (50 mL) cyanoacetylhydrazine (1.0 g, 0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 3 h and the formed solid product, upon cooling, was collected by filtration.

*2-Cyano-N'-(1,3-diphenylallylidene)acetohydrazide (**13a**).* Yellow crystals from ethanol, yield 92% (2.66 g) m.p. 130-134 °C. IR (KBr) $\nu_{max}$ 3473-3318 (NH), 3055 (CH aromatic), 2877 ($CH_2$),

2253 (CN), 1686 (CO), 1658 (C=N), 1633 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 5.24 (s, 2H, $CH_2$), 6.09, 6.26 (2d, 2H, CH=CH), 7.29-7.38 (m, 10H, $2C_6H_5$), 8.42 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 46.5 ($CH_2$), 90.4, 92.4 CH=CH), 117.2 (CN), 119.6, 120.4, 120.8, 121.6, 122.3, 123.4, 123.8, 125.5 ($2C_6H_5$), 165.4 (C=O), 168.3 (C=N). Analysis calcd for $C_{18}H_{15}N_3O$ (289.33): C, 74.72; H, 5.23; N, 14.52%. Found: C, 74.61; H, 5.39; N, 14.39%. MS: *m/z* 289 ($M^+$, 50%).

*N'-(1-(4-Chlorophenyl)-3-(4-methoxyphenyl)allylidene)-2-cyanoaceto-hydrazide (**13b**).* Yellow crystals from ethanol, yield 98% (3.46 g) m.p. 102-104 ºC. IR (KBr) $\nu_{max}$ 3462-3340 (NH), 3053 (CH aromatic), 2893 ($CH_2$), 2258 (CN), 1687 (CO), 1650 (C=N), 1632 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 3.09 (s, 3H, $OCH_3$), 5.31 (s, 2H, $CH_2$), 6.04, 6.28 (2d, 2H, CH=CH), 7.28-7.46 (m, 8H, $2C_6H_4$), 8.21 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 46.7 ($CH_2$), 50.9 ($OCH_3$), 90.1, 92.6 (CH=CH), 117.1 (CN), 119.3, 120.1, 120.6, 121.3, 122.7, 123.0, 123.6, 125.8 ($2C_6H_4$), 165.6 (C=O), 168.6 (C=N). Analysis calcd for $C_{19}H_{16}ClN_3O_2$ (353.80): C, 64.50; H, 4.56; N, 11.88%. Found: C, 64.39; H, 4.80; N, 12.09%. MS: *m/z* 353 ($M^+$, 75%).

*General procedure for the synthesis of the hydrazide-hydrazone derivatives **15a,b***

To a dry solid of either of compound **13a** (2.89 g, 0.01 mol) or **13b** (3.53 g, 0.01 mol) acetophenone (**14**) (1.20 g, 0.01 mol) and ammonium acetate (0.50 g) was added. The reaction mixture was heated in an oil bath at 120 ºC for 1 h then left to cool. The remaining product was boiled in ethanol (40 mL) and formed solid product was collected by filtration.

*2-Cyano-N'-(1,3-diphenylallylidene)-3-phenylbut-2-enehydrazide (**15a**).* Yellow crystals from ethanol, yield 52 % (2.03 g) m.p. 177-179 ºC. IR (KBr) $\nu_{max}$ 3449-3332 (NH), 3058 (CH aromatic), 2220 (CN), 1689 (CO), 1655 (C=N), 1628 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 2.82 (s, 3H, $CH_3$), 6.13, 6.29 (2d, 2H, CH=CH), 7.31-7.40 (m, 15H, $3C_6H_5$), 8.38 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 36.8 ($CH_3$), 88.3, 89.5 (CH=CH), 95.2, 97.4 C=C), 117.4 (CN), 119.5, 120.2, 120.5, 121.2, 121.5, 121.9, 122.7, 123.1, 123.5, 124.3m 124.6, 124.8 ($3C_6H_5$), 165.6 (C=O), 168.6 (C=N). Analysis calcd for $C_{26}H_{21}N_3O$ (391.46): C, 79.77; H, 5.41; N, 10.73%. Found: C, 79.59; H, 5.57; N, 10.82%. MS: *m/z* 391 ($M^+$, 80%).

*N'-(1-(4-Chlorophenyl)-3-(4-methoxyphenyl)allylidene)-2-cyano-3-phenylbut-2-enehydrazide (**15b**).* Brown crystals from ethanol, yield 60% (2.73 g) m.p. 188-191 ºC. IR (KBr) $\nu_{max}$ 3447-3317 (NH), 3056 (CH aromatic), 2221 (CN), 1686 (CO), 1653 (C=N), 1630 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 2.85, 3.08 (s, 6H, $CH_3$, $OCH_3$), 6.13, 6.30 (2d, 2H, CH=CH), 7.26-7.49 (m, 13H, $C_6H_5$, $2C_6H_4$), 8.28 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 36.4 ($CH_3$), 50.6 ($OCH_3$), 88.1, 89.2 (CH=CH), 95.5, 97.8 C=C), 117.1 (CN), 119.1, 120.4, 120.5, 121.4, 122.3, 123.4, 123.8, 125.4 ($C_6H_5$, $2C_6H_4$), 165.8 (C=O), 169.3 (C=N). Analysis calcd for $C_{27}H_{22}ClN_3O_2$ (455.94): C, 71.13; H, 4.86; N, 9.22%. Found: C, 70.88; H, 4.68; N, 8.93%. MS: *m/z* 455 ($M^+$, 65 %). MS: *m/z* 455 ($M^+$, 64%).

*General procedure for the synthesis of the thiophene derivatives **16a,b***

*Method (A)*. To a solution of either compound **15a** (3.91 g, 0.01 mol) or **15b** (4.55 g, 0.01 mol) in 1,4-dioxane (50 mL) containing triethylamine (1.0 mL) elemental sulfur (0.32 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

*Method (B).* To a solution of compound **13a** (2.89 g, 0.01 mol), or **13b** (3.35 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL) both of elemental sulfur (0.32 g, 0.01 mol) and acetophenone (1.20 g, 0.01 mol) were added. The reaction mixture was heated under reflux

for 2 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

*2-Amino-N'-(1,3-diphenylallylidene)-4-phenylthiophene-3-carbohydrazide (**16a**).* Brown crystals from ethanol, yield 58 % (2.45 g) m.p. 47 °C. IR (KBr) $\nu_{max}$ 3472-3317 ($NH_2$, NH), 3056 (CH aromatic), 1692 (CO), 1653 (C=N), 1632 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 4.82 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.11, 6.23 (2d, 2H, CH=CH), 6.71 (s, 1H, thiophene H-5), 7.27-7.38 (m, 15H, $3C_6H_5$), 8.38 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 88.4, 89.5 (CH=CH), 119.4, 119.8, 120.4, 120.3, 120.7, 121.4, 121.6, 122.3, 123.4, 123.6, 125.2, 125.8 ($3C_6H_5$), 130.4, 132.5, 133.9, 134.2 (thiophene C), 165.7 (C=O), 169.6 (C=N). Analysis calcd for $C_{26}H_{21}N_3OS$ (423.53): C, 73.73; H, 5.00; N, 9.92; S, 7.57%. Found: C, 73.83; H, 5.22; N, 10.14; S, 7.73%. MS: *m/z* 423 ($M^+$, 70%).

*2-Amino-N'-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)-4-phenylthiophene-3-carbohydrazide (**16b**).* Brown crystals from ethanol, yield 69% (3.36 g) m.p. 103-105 °C. IR (KBr) $\nu_{max}$ 3460-3325 ($NH_2$, NH), 3058 (CH aromatic), 1690 (CO), 1653 (C=N), 1630 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 3.08 (s, 3H, $OCH_3$), 4.84 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.12, 6.24 (2d, 2H, CH=CH), 6.70 (s, 1H, thiophene H-5), 7.21-7.48 (m, 13H, $C_6H_5$, $2C_6H_4$), 8.35 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.8 ($OCH_3$), 88.2, 89.5 (CH=CH), 119.1, 119.5, 120.2, 120.7, 120.3 120.5, 121.4, 122.5, 123.8, 124.3, 125.5, 125.9 ($C_6H_5$, $2C_6H_4$), 130.2, 132.6, 133.4, 134.8 (thiophene C), 165.5 (C=O), 169.9 (C=N). Analysis calcd for $C_{27}H_{22}ClN_3O_2S$ (488.00): C, 66.45; H, 4.54; N, 8.61; S, 6.57%. Found: C, 66.72; H, 4.69; N, 8.80; S, 6.83%. MS: *m/z* 488 ($M^+$, 58%).

*General Procedure for the synthesis of the hydrazide-hydrazone derivatives **17a,b***

To a solution of compound **13a** (2.89 g, 0.01 mol), or **13b** (3.35 g, 0.01 mol) in 1,4-dioxane (40 mL) containing piperidine (0.50 mL) benzaldehyde (1.08 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

*2-Cyano-N'-(1,3-diphenylallylidene)-3-phenylacrylohydrazide (**17a**).* Yellow crystals from ethanol, yield 76% (2.86 g) m.p. 203-206 °C. IR (KBr) $\nu_{max}$ 3474-3324 (NH), 3056 (CH aromatic), 2222 (CN), 1690 (CO), 1653 (C=N), 1626 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 6.63 (s, 1H, CH=C), 6.12, 6.27 (2d, 2H, CH=CH), 7.26-7.32 (m, 15H, $3C_6H_5$), 8.36 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 78.4, 80.5 (CH=C), 88.4, 89.8 (CH=CH), 117.3 (CN), 119.2, 119.5, 120.1, 120.4, 120.7, 121.2, 121.5, 122.3, 122.6, 123.5, 123.4, 125.8 ($3C_6H_5$), 165.5 (C=O), 170.3 (C=N). Analysis calcd for $C_{25}H_{19}N_3O$ (377.44): C, 79.55; H, 5.07; N, 11.13%. Found: C, 79.72; H, 5.29; N, 11.46%. MS: *m/z* 377 ($M^+$, 70%).

*(1-(4-Chlorophenyl)-3-(4-methoxyphenyl)allylidene)-2-cyano-3-phenylacrylohydrazide (**17b**).* Yellow crystals from ethanol, yield 94% (4.15 g) m.p. 58-60 °C. IR (KBr) $\nu_{max}$ 3463-3323 (NH), 3058 (CH aromatic), 2223 (CN), 1689 (CO), 1651 (C=N), 1632 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 3.12 (s, 3H, $OCH_3$), 6.62 (s, 1H, CH=C), 6.13, 6.25 (2d, 2H, CH=CH), 7.23-7.47 (m, 13H, $C_6H_5$, $2C_6H_4$), 8.33 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.5 ($OCH_3$), 78.6, 80.9 (CH=C), 88.1, 89.6 (CH=CH), 117.0 (CN), 119.5, 119.8, 120.3, 120.8, 121.2, 121.4, 121.8, 122.1, 122.5, 123.8, 123.1, 125.5 ($C_6H_5$, $2C_6H_4$), 165.7 (C=O), 170.5 (C=N). Analysis calcd for $C_{26}H_{20}ClN_3O_2$ (441.91): C, 70.67; H, 4.56; N, 9.51%. Found: C, 70.82; H, 4.72; N, 9.72%. MS: *m/z* 441 ($M^+$, 65%).

*General procedure for the synthesis of the coumarin derivatives **19a,b***

To a solution of compound **13a** (2.89 g, 0.01 mol), or **13b** (3.35 g, 0.01 mol) in 1,4-dioxane (40 mL) containing piperidine (0.50 mL) salicylaldehyde (1.22 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

*(1,3-Diphenylallylidene)-2-oxo-2H-chromene-3-carbohydrazide (**19a**).* Brown crystals from ethanol, yield 68% (2.68 g) m.p. 58-60 °C. IR (KBr) $\nu_{max}$ 3474-3324 (NH), 3055 (CH aromatic), 1684, 1692 (2CO), 1650 (C=N), 1622 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 6.13, 6.29 (2d, 2H, CH=CH), 6.89 (s, 1H, coumarin H-4), 7.26-7.32 (m, 14H, $2C_6H_5$, $C_6H_4$), 8.29 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 88.4, 89.8 (CH=CH), 90.6, 95.4 (coumarin C-3, C-4), 120.1, 120.6, 120.8, 121.3, 121.8, 122.5, 122.7, 123.9, 124.1, 124.2, 124.8 ($2C_6H_5$, $C_6H_4$), 165.8, 166.4 (2C=O), 169.5 (C=N). Analysis calcd for $C_{25}H_{18}N_2O_3$ (394.42): C, 76.13; H, 4.60; N, 7.10%. Found: C, 76.49; H, 4.83; N, 7.22%. MS: *m/z* 394 ($M^+$, 80%).

*N'-(1-(4-Chlorophenyl)-3-(4-methoxyphenyl)allylidene)-2-oxo-2H-chromene-3-carbohydrazide (**20b**).* Yellow crystals from ethanol, yield 80% (3.69 g) m.p. 110-112 °C. IR (KBr) $\nu_{max}$ 3469-3319 (NH), 3058 (CH aromatic), 1686, 1690 (2CO), 1652 (C=N), 1628 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 3.20 (s, 3H, $OCH_3$), 6.16, 6.26 (2d, 2H, CH=CH), 6.87 (s, 1H, coumarin H-4), 7.22-7.49 (m, 12H, $3C_6H_4$), 8.26 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.6 ($OCH_3$), 88.1, 89.6 (CH=CH), 90.3, 95.8 (coumarin C-3, C-4), 120.2, 120.5, 120.5, 121.0, 121.5, 122.3, 122.8, 123.3, 124.6, 124.2, 125.2 ($3C_6H_4$), 165.5, 166.7 (2C=O), 169.8 (C=N). Analysis calcd for $C_{26}H_{19}ClN_2O_4$ (458.89): C, 68.05; H, 4.17; N, 6.10%. Found: C, 67.92; H, 4.28; N, 6.36%. MS: *m/z* 458 ($M^+$, 72%).

*General procedure for the synthesis of the thiophene derivatives **21a,b***

To a solution of compound **13a** (2.89 g, 0.01 mol), or **13b** (3.35 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL) both of elemental sulfur (0.32 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 2 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

*2,5-Diamino-4-cyano-N'-(1,3-diphenylallylidene)thiophene-3-carbohydrazide (**21a**).* Grey crystals from ethanol, yield 58% (2.24 g) m.p. 113-115 °C. IR (KBr) $\nu_{max}$ 34780-3326 ($2NH_2$, NH), 3054 (CH aromatic), 2220 (CN), 1688 (CO), 1650 (C=N), 1628 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 4.80, 5.23 (2s, 4H, $D_2O$ exchangeable, $2NH_2$), 6.09, 6.22 (2d, 2H, CH=CH), 7.28-7.39 (m, 10H, $2C_6H_5$), 8.27 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 88.2, 89.7 (CH=CH), 116.8 (CN), 120.0., 121.2, 121.3, 121.5, 122.0, 123.4, 125.2, 125.8 ($2C_6H_5$), 130.6, 132.8, 133.5, 134.6 (thiophene C), 165.9 (C=O), 169.4 (C=N). Analysis calcd for $C_{21}H_{17}N_5OS$ (387.46): C, 65.10; H, 4.42; N, 18.08; S, 8.28%. Found: C, 64.88; H, 4.62; N, 18.30; S, 8.09%. MS: *m/z* 387 ($M^+$, 64%).

*2,5-Diamino-N'-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)-4-cyano-thiophene-3-carbohydrazide (**21b**).* Yellow crystals from ethanol, yield 95% (4.29 g) m.p. 120-123 °C. IR (KBr) $\nu_{max}$ 3482-3361 ($2NH_2$, NH), 3056 (CH aromatic), 2220 (CN), 1688 (CO), 1650 (C=N), 1636 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 3.11 (s, 3H, $OCH_3$), 4.86, 5.22 (2s, 4H, $D_2O$ exchangeable, $2NH_2$), 6.11, 6.24 (2d, 2H, CH=CH), 7.21-7.48 (m, 8H, $2C_6H_4$), 8.31 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.6 ($OCH_3$), 88.5, 89.9 (CH=CH), 117.3 (CN), 120.2., 120.5, 121.3, 121.8, 122.7, 124.8, 125.5, 125.9 ($2C_6H_4$), 130.3, 132.5, 133.7, 134.8

(thiophene C), 165.4 (C=O), 169.7 (C=N). Analysis calcd for $C_{22}H_{18}ClN_5O_2S$ (451.93): C, 58.47; H, 4.01; N, 15.50; S, 7.10%. Found: C, 58.62; H, 4.24; N, 15.73; S, 6.96%. MS: *m/z* 451 ($M^+$, 58%).

*General procedure for the synthesis of the pyridine derivatives* ***23a,b***

To a solution of compound **13a** (2.89 g, 0.01 mol), or **13b** (3.35 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL) malononitrile (0.66 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

*4,6-Diamino-1-((1,3-diphenylallylidene)amino)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**23a**).* Yellow crystals from ethanol, yield 61% (2.17 g) m.p. 130-134 ºC. IR (KBr) $\nu_{max}$ 3474-3349 ($2NH_2$), 3056 (CH aromatic), 2220 (CN), 1692 (CO), 1651 (C=N), 1634 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 4.82, 5.31 (2s, 4H, $D_2O$ exchangeable, $2NH_2$), 6.03, 6.42 (2d, 2H, CH=CH), 6.88 (s, 1H, pyridine H-3), 7.26-7.37 (m, 10H, $2C_6H_5$). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 88.1, 90.2 (CH=CH), 117.1 (CN), 120.0., 120.6, 121.1, 121.5, 122.2, 124.6, 125.3, 125.5 ($2C_6H_5$), 129.4., 130.8, 132.3, 133.1 (pyridine C), 166.9 (C=O), 170.8 (C=N). Analysis calcd for $C_{21}H_{17}N_5O$ (355.39): C, 70.97; H, 4.82; N, 19.71%. Found: C, 71.28; H, 4.83; N, 19.49%. MS: *m/z* 355 ($M^+$, 80%).

*4,6-Diamino-1-((1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)amino)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (**23b**).* Yellow crystals from ethanol, yield 69% (2.89 g) m.p. 153-155 ºC. IR (KBr) $\nu_{max}$ 3486-3327 ($2NH_2$), 3054 (CH aromatic), 2222 (CN), 1688 (CO), 1646 (C=N), 1632 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 3.12 (s, 3H, $OCH_3$), 4.80, 5.34 (2s, 4H, $D_2O$ exchangeable, $2NH_2$), 6.05, 6.38 (2d, 2H, CH=CH), 6.84 (s, 1H, pyridine H-3), 7.22-7.42 (m, 8H, $2C_6H_4$). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.7 ($OCH_3$), 88.4, 90.6 (CH=CH), 117.4 (CN), 120.2., 120.9, 121.4, 121.8, 122.5, 123.8, 125.7, 125.8 ($2C_6H_4$), 129.1, 130.4, 132.5, 132.9 (pyridine C), 166.7 (C=O), 170.5 (C=N). Analysis calcd for $C_{22}H_{18}ClN_5O_2$ (419.86): C, 62.93; H, 4.32; N, 16.68%. Found: C, 63.29; H, 4.63; N, 16.73%. MS: *m/z* 419 ($M^+$, 63%).

*General procedure for the synthesis of the pyran derivatives* ***25a-f***

To a solution of compound **13a** (2.89 g, 0.01 mol), or **13b** (3.35 g, 0.01 mol) in ethanol (40 mL) containing triethylamine (0.50 mL) any of benzaldehyde (1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) or 4-chlorobenzaldehyde (1.40 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 3 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

*2-Amino-6-(2-(1,3-diphenylallylidene)hydrazinyl)-4-phenyl-4H-pyran-3,5-dicarbonitrile (**25a**).* Brown crystals from ethanol, yield 66% (2.94 g) m.p. 75-77 ºC. IR (KBr) $\nu_{max}$ 3459-3373 ($NH_2$, NH), 3055 (CH aromatic), 2227, 2220 (2CN), 1652 (C=N), 1636 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 4.72 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.11, 6.24 (2d, 2H, CH=CH), 6.93 (s, 1H, pyran H-4), 7.27-7.37 (m, 15H, $3C_6H_5$), 8.25 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 88.3 (pyran C-4), 90.4, 92.4 (CH=CH), 116.4, 117.2 (2CN), 119.3, 119.5, 120.6, 120.9, 121.3, 121.5, 121.8, 122.0, 122.3, 123.4, 123.6, 125.8 ($3C_6H_5$), 128.6, 129.2, 130.8, 131.7 (pyran C2, C-3, C-5, C-6), 168.8 (C=N). Analysis calcd for $C_{28}H_{21}N_5O$ (443.50): C, 75.83; H, 4.77; N, 15.79%. Found: C, 76.15; H, 4.83; N, 15.68%. MS: *m/z* 443 ($M^+$, 58%).

*2-Amino-6-((2-(1,3-diphenylallylidene)hydrazinyl)-4-(4-methoxyphenyl)-4H-pyran-3,5-dicarbo-nitrile (**25b**).* Yellow crystals from ethanol, yield 82% (3.88 g) m.p. 177-179 ºC. IR (KBr) $\nu_{max}$

3472-3359 ($NH_2$, NH), 3057 (CH aromatic), 2977 ($CH_3$), 2223, 2221 (2CN), 1650 (C=N), 1631 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 2.93 (s, 3H, $OCH_3$), 4.70 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.11, 6.26 (2d, 2H, CH=CH), 6.90 (s, 1H, pyran H-4), 7.26-7.39 (m, 14H, $2C_6H_5$, $C_6H_4$), 8.23 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.6 ($OCH_3$), 88.6 pyran C-4), 90.2, 92.3 (CH=CH), 116.8, 117.5 (2CN), 119.1, 119.4, 119.6, 120.4, 121.3, 121.4, 121.7, 122.2, 122.5, 123.2, 123.4, 125.9 ($2C_6H_5$, $C_6H_4$), 128.4, 129.7, 130.2, 131.8 (pyran C2, C-3, C-5, C-6), 168.4 (C=N). Analysis calcd for $C_{29}H_{23}N_5O_2$ (473.53): C, 73.56; H, 4.90; N, 14.79%. Found: C, 73.29; H, 4.71; N, 14.98%. MS: *m/z* 473 ($M^+$, 72%).

*2-Amino-4-(4-chlorophenyl)-6-((2-(1,3-diphenylallylidene)hydrazinyl)-4H-pyran-3,5-dicarbonitrile (**25c**).* Yellow crystals from ethanol, yield 71% (3.39 g) m.p. 136-138 °C. IR (KBr) $\nu_{max}$ 3442-3370 ($NH_2$, NH), 3053 (CH aromatic), 2227, 2220 (2CN), 1646 (C=N), 1632 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 4.70 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.13, 6.23 (2d, 2H, CH=CH), 6.90 (s, 1H, pyran H-4), 7.22-7.39 (m, 14H, $2C_6H_5$, $C_6H_4$), 8.23 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 88.8 pyran C-4), 90.2, 92.6 CH=CH), 116.8, 117.5 (2CN), 119.3, 119.7, 119.9, 120.1, 121.5, 121.8, 121.9, 122.4, 122.7, 123.1, 123.3, 125.7 ($2C_6H_5$, $C_6H_4$), 128.2, 129.5, 130.4, 131.6 (pyran C2, C-3, C-5, C-6), 168.6 (C=N). Analysis calcd for $C_{28}H_{20}ClN_5O$ (477.94): C, 70.36; H, 4.22; N, 14.65%. Found: C, 70.42; H, 4.31; N, 14.83%. MS: *m/z* 477 ($M^+$, 54%).

*2-Amino-6-(2-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)hydrazinyl)-4-phenyl-4H-pyran-3,5-dicarbonitrile (**25d**).* Yellow crystals from ethanol, yield 83% (4.21 g) m.p. 98 °C. IR (KBr) $\nu_{max}$ 3488-3340 ($NH_2$, NH), 3057 (CH aromatic), 2987 ($CH_3$), 2225, 2220 (2CN), 1652 (C=N), 1626 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 2.92 (s, 3H, $OCH_3$), 4.73 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.11, 6.27 (2d, 2H, CH=CH), 6.91 (s, 1H, pyran H-4), 7.22-7.49 (m, 13H, $C_6H_5$, $2C_6H_4$), 8.26 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.8 ($OCH_3$), 88.3 (pyran C-4), 90.4, 92.6 (CH=CH), 116.5, 117.3 (2CN), 119.6, 119.8, 120.2, 120.4, 121.2, 121.5, 121.8, 122.1, 122.5, 123.5, 123.7, 125.4 ($C_6H_5$, $2C_6H_4$), 128.1, 129.3, 130.5, 131.6 (pyran C2, C-3, C-5, C-6), 168.8 (C=N). Analysis calcd for $C_{29}H_{22}ClN_5O_2$ (507.97): C, 68.57; H, 4.37; N, 13.79%. Found: C, 68.42; H, 4.44; N, 14.01%. MS: *m/z* 507 ($M^+$, 60%).

*2-Amino-6-(2-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)-hydrazinyl)-4-(4-methoxyphenyl)-4H-pyran-3,5-dicarbonitrile (**25e**).* Yellow crystals from ethanol, yield 88% (4.73 g) m.p. 144-146 °C. IR (KBr) $\nu_{max}$ 3480-3322 ($NH_2$, NH), 3054 (CH aromatic), 2984 ($CH_3$), 2226, 2221 (2CN), 1648 (C=N), 1629 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 2.90, 3.11 (2s, 6H, $2OCH_3$), 4.75 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.08, 6.25 (2d, 2H, CH=CH), 6.93 (s, 1H, pyran H-4), 7.21-7.47 (m, 12H, $3C_6H_4$), 8.25 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.6, 50.8 ($2OCH_3$), 88.3 (pyran C-4), 90.4, 92.6 CH=CH), 116.8, 117.0 (2CN), 119.3, 119.5, 120.4, 120.8, 121.3, 121.6, 121.9, 122.3, 122.5, 123.2, 123.9, 125.9 ($3C_6H_4$), 128.6, 129.7, 130.2, 131.9 (pyran C2, C-3, C-5, C-6), 168.5 (C=N). Analysis calcd for $C_{30}H_{24}ClN_5O_3$ (538.00): C, 66.97; H, 4.50; N, 13.02%. Found: C, 66.74; H, 4.61; N, 13.25%. MS: *m/z* 538 ($M^+$, 48%).

*2-Amino-4-(4-chlorophenyl)-6-(2-(1-(4-chlorophenyl)-3-(4methoxy phenyl)-allylidene)hydrazinyl)-4H-pyran-3,5-dicarbonitrile (**25f**).* Yellow crystals from ethanol, yield 85% (4.61 g) m.p. 122-125 °C. IR (KBr) $\nu_{max}$ 3462-3352 ($NH_2$, NH), 3056 (CH aromatic), 2989 ($CH_3$), 2225, 2220 (2CN), 1651 (C=N), 1627 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 3.12 (s, 3H, $OCH_3$), 4.73 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.06, 6.27 (2d, 2H, CH=CH), 6.92 (s, 1H, pyran H-4), 7.24-7.49 (m, 12H, $3C_6H_4$), 8.22 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.9 ($OCH_3$), 88.1 (pyran C-4), 90.2, 92.8 (CH=CH), 116.7, 117.3 (2CN), 119.1, 119.7, 120.4, 120.5, 120.9, 121.2, 121.7, 121.8, 122.1, 122.6, 123.3, 125.7 ($3C_6H_4$), 128.4, 129.1, 130.7, 131.5 (pyran

C2, C-3, C-5, C-6), 168.7 (C=N). Analysis calcd for $C_{29}H_{21}Cl_2N_5O_2$ (542.42): C, 64.21; H, 3.90; N, 12.91%. Found: C, 64.47; H, 4.30; N, 13.26%. MS: *m/z* 542 ($M^+$, 56%).

*General procedure for the synthesis of the thiazole derivatives* ***27a,b***

To a solution of compound **13a** (2.89 g, 0.01 mol), or **13b** (3.35 g, 0.01 mol) in acetic acid (50 mL) thioglycollic acid (0.92 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 4 h then poured onto ice/water and the formed solid product was collected by filtration.

*(N)-N'-(1,3-Diphenylallylidene)-4-oxo-4,5-dihydrothiazole-2-carbohydrazide (**27a**).* Yellow crystals from ethanol, yield 67% (2.34 g) m.p. 83 ºC. IR (KBr) $\nu_{max}$ 3489-3330 (NH), 3058 (CH aromatic), 1689, 1693 (2CO), 1658 (C=N), 1625 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 5.99 (s, 2H, thiazole $CH_2$), 6.14, 6.30 (2d, 2H, CH=CH), 7.23-7.36 (m, 10H, $2C_6H_5$), 8.32 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 90.4, 92.6 (CH=CH), 96.3 (thiazole $CH_2$), 120.6, 121.3, 121.7, 122.8, 123.0, 123.7, 124.5, 125.5 ($2C_6H_5$), 165.4, 166.1 (2CO), 168.2, 168.9 (2C=N). Analysis calcd for $C_{19}H_{15}N_3O_2S$ (349.41): C, 65.31; H, 4.33; N, 12.03; S, 9.18%. Found: C, 65.42; H, 4.42; N, 11.94; S, 9.25%. MS: *m/z* 349 ($M^+$, 70%).

*(N')-N'-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)-4-oxo-4,5-dihydrothiazole-2-carbohydrazide (**27b**).* Yellow crystals from ethanol, yield 73% (3.02 g) m.p. 103-106 ºC. IR (KBr) $\nu_{max}$ 3473-3326 (NH), 3054 (CH aromatic), 1686, 1691 (2CO), 1655 (C=N), 1622 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 3.20 (s, 3H, $OCH_3$), 5.95 (s, 2H, thiazole $CH_2$), 6.12, 6.29 (2d, 2H, CH=CH), 7.24-7.39 (m, 8H, $2C_6H_4$), 8.36 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.8 ($OCH_3$), 90.1, 92.9 (CH=CH), 96.5 (thiazole $CH_2$), 120.3, 121.6, 121.8, 122.3, 123.5, 124.2, 124.4, 125.8 ($2C_6H_4$), 165.6, 166.3 (2CO), 168.1, 168.7 (2C=N). Analysis calcd for $C_{20}H_{16}ClN_3O_3S$ (413.88): C, 58.04; H, 3.90; N, 10.15; S, 7.75%. Found: C, 58.35; H, 4.16; N, 9.94; S, 7.88%. MS: *m/z* 413 ($M^+$, 55%).

*General procedure for the synthesis of the pyran derivatives* ***28a-c***

To a solution of compound **27b** (4.13 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL) any of benzaldehyde (1.08 g, 0.01 mol), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) or 4-chlorobenzaldehyde (1.40 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 3 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

*(N')-2-(5-Amino-6-cyano-7-phenyl-7H-pyrano[2,3-d]thiazol-2-yl)-N'-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)acetohydrazide (**28a**).* Yellow crystals from ethanol, yield 84% (4.88 g) m.p. 185-187 ºC. IR (KBr) $\nu_{max}$ 3457-3340 ($NH_2$, NH), 3053 (CH aromatic), 2987 ($CH_3$), 2220 (CN), 1680 (CO), 1652 (C=N), 1626 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 2.98 (s, 3H, $OCH_3$), 4.71 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.11, 6.28 (2d, 2H, CH=CH), 6.95 (s, 1H, pyran H-4), 7.20-7.44 (m, 13H, $C_6H_5$, $2C_6H_4$), 8.21 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.6 ($OCH_3$), 90.1, 92.9 (CH=CH), 116.9 (CN), 120.3, 120.8, 120.9, 121.6, 121.8, 122.0, 122.1, 122.3, 123.5, 124.2, 124.4, 125.8 ($C_6H_5$, $2C_6H_4$), 127.8, 128.3, 129.8, 130.4 (pyran C), 165.6 (CO), 168.1, 168.7 (2C=N). Analysis calcd for $C_{30}H_{22}ClN_5O_3S$ (568.05): C, 63.43; H, 3.90; N, 12.33; S, 5.64%. Found: C, 63.62; H, 3.76; N, 12.25; S, 5.80%. MS: *m/z* 568 ($M^+$, 55%).

*(N')-2-(5-Amino-6-cyano-7-(4-methoxyphenyl)-7H-pyrano[2,3-d]thiazol-2-yl)-N'-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)acetohydrazide (**28b**).* Brown crystals from ethanol, yield 60% (3.67 g) m.p. 177-179 ºC. IR (KBr) $\nu_{max}$ 3480-3312 ($NH_2$, NH), 3056 (CH aromatic), 2984 ($CH_3$), 2221 (CN), 1680 (CO), 1646 (C=N), 1626 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 2.95, 3.08 (2s, 6H, $2OCH_3$), 4.73 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.06, 6.28 (2d, 2H, CH=CH),

6.91 (s, 1H, pyran H-4), 7.23-7.49 (m, 12H, $3C_6H_4$), 8.22 (s, 1H, $D_2O$ exchangeable, NH). $^{13}C$ NMR (DMSO-$d_6$, 75 MHz): δ 50.6, 50.9 ($2OCH_3$), 88.2 (pyran C-4), 90.3, 92.9 (CH=CH), 116.9 (CN), 120.1, 120.6, 121.4, 121.4, 122.6, 123.0, 123.2, 123.8, 124.1, 124.6, 124.9, 125.5 ($3C_6H_4$), 128.1, 128.6, 130.2, 130.4 (pyran C), 165.5 (CO), 168.3, 168.5 (2C=N). Analysis calcd for $C_{31}H_{24}ClN_5O_4S$ (598.07): C, 62.26; H, 4.04; N, 11.71; S, 5.36%. Found: C, 62.53; H, 4.23; N, 11.64; S, 5.41%. MS: *m/z* 598 ($M^+$, 68%).

*(N')-2-(5-Amino-7-(4-chlorophenyl)-6-cyano-7H-pyrano[2,3-d]thiazol-2-yl)-N'-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)acetohydrazide (**28c**).* Yellow crystals from ethanol, yield 80% (4.93 g) m.p. 198-201 ºC. IR (KBr) $\nu_{max}$ 3449-3362 ($NH_2$, NH), 3055 (CH aromatic), 2989 ($CH_3$), 2222 (CN), 1650 (C=N), 1626 (C=C). $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ = 3.11 (s, 3H, $OCH_3$), 4.72 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.12, 6.27 (2d, 2H, CH=CH), 6.90 (s, 1H, pyran H-4), 7.21-7.47 (m, 12H, $3C_6H_4$), 8.23 (s, 1H, $D_2O$ exchangeable, NH). $^{13}C$ NMR (DMSO-$d_6$, 75 MHz): δ 50.6 ($OCH_3$), 90.1, 92.9 (CH=CH), 116.7 (CN), 120.2, 120.6, 120.9, 121.6, 121.8, 122.3, 122.6, 123.6, 136.7, 124.4, 124.8, 125.4 ($3C_6H_4$), 128.3, 128.6, 130.2, 130.6 (pyran C), 165.8 (CO), 168.1, 168.8 (2C=N). Analysis calcd for $C_{30}H_{21}Cl_2N_5O_3S$ (602.49): C, 59.81; H, 3.51; N, 11.62; S, 5.23%. Found: C, 59.56; H, 3.68; N, 11.49; S, 5.36%. MS: *m/z* 602 ($M^+$, 80%).

*General procedure for the synthesis of the pyran derivatives **29a-c***

To a solution of compound **27b** (4.13 g, 0.01 mol) in 1,4-dioxane (40 mL) containing ammonium acetate (0.50 g) any of benzaldehyde (1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) or 4-chlorobenzaldehyde (1.40 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 3 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

*(N')-2-(5-Amino-6-cyano-7-phenyl-4,7-dihydrothiazolo[4,5-b]pyridin-2-yl)-N'-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)acetohydrazide (**29a**).* Yellow crystals from ethanol, yield 61% (3.54 g) m.p. 161-163 ºC. IR (KBr) $\nu_{max}$ 3457-3340 ($NH_2$, NH), 3053 (CH aromatic), 2987 ($CH_3$), 2220 (CN), 1680 (CO), 1652 (C=N), 1626 (C=C). $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ = 2.93 (s, 3H, $OCH_3$), 4.72 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.10, 6.31 (2d, 2H, CH=CH), 6.93 (s, 1H, pyridine H-4), 7.27-7.43 (m, 13H, $C_6H_5$, $2C_6H_4$), 8.23, 8.27 (2s, 2H, $D_2O$ exchangeable, 2NH). $^{13}C$ NMR (DMSO-$d_6$, 75 MHz): δ 50.5 ($OCH_3$), 90.8 (pyridine C-4), 89.7 (pyridine C-4), 90.3, 92.5 (CH=CH), 116.8 (CN), 119.3, 119.4, 120.4, 121.3, 121.5, 121.7, 122.6, 122.8, 123.3, 124.8, 124.5, 125.8 ($C_6H_5$, $2C_6H_4$), 128.5, 128.8, 130.4, 132.8 (pyridine C), 165.7 (CO), 168.4, 168.4 (2C=N). Analysis calcd for $C_{30}H_{23}ClN_6O_2S$ (567.06): C, 63.54; H, 4.09; N, 14.82; S, 5.65%. Found: C, 63.73; H, 3.91; N, 14.66; S, 5.72%. MS: *m/z* 567 ($M^+$, 67%).

***(**N')-2-(5-Amino-6-cyano-7-(4-methoxyphenyl)-4,7-dihydrothiazolo[4,5-b]pyridin-2-yl)-N'-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)-acetohydrazide (**29b**).* Yellow crystals from ethanol, yield 67% (4.09 g) m.p. 180-183 ºC. IR (KBr) $\nu_{max}$ 3480-3312 ($NH_2$, NH), 3056 (CH aromatic), 2984 ($CH_3$), 2221 (CN), 1680 (CO), 1646 (C=N), 1626 (C=C). $^1H$ NMR (DMSO-$d_6$, 300 MHz): δ = 2.95, 3.08 (2s, 6H, $2OCH_3$), 4.73 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.09, 6.24 (2d, 2H, CH=CH), 6.90 (s, 1H, pyran H-4), 7.26-7.45 (m, 12H, $3C_6H_4$), 8.21, 8.28 (2s, 2H, $D_2O$ exchangeable, 2NH). $^{13}C$ NMR (DMSO-$d_6$, 75 MHz): 50.8, 50.8 ($2OCH_3$), 90.8 (pyridine C-4), 90.2, 92.8 (CH=CH), 116.7 (CN), 119.0, 119.2, 120.2, 129.5, 129.7, 121.6, 121.8, 122.3, 123.6, 124.2, 124.6, 125.7 ($3C_6H_4$), 128.6, 129.8, 130.4, 130.9 (pyridine C), 165.5 (CO), 168.1, 168.8 (2C=N). Analysis calcd for $C_{31}H_{25}ClN_6O_3S$ (597.09): C, 62.36; H, 4.22; N, 14.08; S, 5.37%. Found: C, 62.68; H, 4.23; N, 13.94; S, 5.41%. MS: *m/z* 579 ($M^+$, 37%).

*(N')-2-(5-Amino-7-(4-chlorophenyl)-6-cyano-4,7-dihydrothiazolo[4,5-b]pyridine-2-yl)-N'-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)-acetohydrazide (**29c**).* Yellow crystals from

ethanol, yield 75% (4.61 g) m.p. 197-199 °C. IR (KBr) $\nu_{max}$ 3449-3362 ($NH_2$, NH), 3055 (CH aromatic), 2989 ($CH_3$), 2222 (CN), 1680 (CO), 1650 (C=N), 1626 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 3.10 (s, 3H, $OCH_3$), 4.78 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.14, 6.24 (2d, 2H, CH=CH), 6.92 (s, 1H, pyridine H-4), 7.25-7.49 (m, 12H, $3C_6H_4$), 8.21 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): 50.8 ($2OCH_3$), 90.8 (pyridine C-4), 90.4, 92.6 (CH=CH), 116.8 (CN), 120.1, 120.2, 120.4, 121.4, 122.5, 122.8, 123.2, 123.3, 124.1, 124.6, 125.3, 125.7 ($3C_6H_4$), 128.3, 128.6, 130.2, 130.6 (pyridine C-4), 165.8 (CO), 168.1, 168.8 (2C=N). Analysis calcd for $C_{30}H_{22}Cl_2N_6O_2S$ (601.53): C, 59.90; H, 3.93; N, 13.65; S, 5.21%. Found: C, 59.73; H, 3.72; N, 13.77; S, 5.18%. MS: *m/z* 601 ($M^+$, 55%).

*General procedure for the synthesis of the thiazolo[4,5-d]thiazole derivatives* ***31a,b***

To a solution of compound **27a** (3.49 g, 0.01 mol), or **27b** (4.13 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL) each of elemental sulfur (0.32 g, 0.01 mol) and phenylisothiocyanate (1.35 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 2 h then left to cool and the formed solid product, in each case, was collected by filtration.

*(N')-N'-(1,3-Diphenylallylidene)-2-(4-phenyl-5-thioxo-4,5-dihydrothiazolo[4,5-d]thiazol-2-yl)-acetohydrazide (**31a**).* Yellow crystals from ethanol, yield 66% (3.14 g) m.p. 215-218 °C. IR (KBr) $\nu_{max}$ 3482-3329 (NH), 3056 (CH aromatic), 1688 (CO), 1654 (C=N), 1625 (C=C), 1205 (C=S). $^1$H NMR (DMSO-$d_6$, 2300 MHz): δ = 6.11, 6.32 (2d, 2H, CH=CH), 7.28-7.37 (m, 15H, $3C_6H_5$), 8.35 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 89.4, 91.8 (CH=CH), 120.0, 120.5, 120.8, 121.2, 122.6, 123.0, 123.1, 123.4, 124.5, 124.8, 125.7, 125.8 ($3C_6H_5$), 130.2, 130.6 thiazole C), 166.2 (CO), 168.4, 169.1 (2C=N), 180.3 (C=S). Analysis calcd for $C_{26}H_{18}N_4OS_3$ (498.64): C, 62.63; H, 3.64; N, 11.24; S, 19.29%. Found: C, 62.92; H, 3.83; N, 11.20; S, 19.03%. MS: *m/z* 498 ($M^+$, 74%).

*(N')-N'-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)-2-(4-phenyl-5-thioxo-4,5-dihydro-thiazolo[4,5-d]thiazol-2-yl)acetohydrazide (**31b**).* Brown crystals from ethanol, yield 55% (3.09 g) m.p.127-129 °C. IR (KBr) $\nu_{max}$ 3470-3322 (NH), 3054 (CH aromatic), 1686 (CO), 1655 (C=N), 1622 (C=C), 1208 (C=S). $^1$H NMR (DMSO-$d_6$, 200 MHz): δ = 3.18 (s, 3H, $OCH_3$), 6.14, 6.26 (2d, 2H, CH=CH), 7.21-7.44 (m, 13H, $C_6H_5$, $2C_6H_4$), 8.32 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 50.3 ($OCH_3$), 89.6, 92.1 (CH=CH), 120.2, 120.6, 120.8, 121.4, 121.8, 122.6, 123.1, 123.6, 124.7, 124.9, 125.2, 125.6 ($C_6H_5$, $2C_6H_4$), 130.2, 130.8 thiazole C), 166.7 (CO), 168.2, 169.4 (2C=N), 180.1 (C=S). Analysis calcd for $C_{27}H_{19}ClN_4O_2S_3$ (563.11): C, 57.59; H, 3.40; N, 9.95; S, 17.08%. Found: C, 57.29; H, 4.52; N, 9.74; S, 16.88%. MS: *m/z* 563 ($M^+$, 50%).

*General procedure for the synthesis of the 2,3-dihydrothiazole derivatives* ***32a,b***

To a solution of either compound **13a** (2.89 g, 0.01 mol), or **13b** (3.35 g, 0.01 mol) in 1,4-dioxane (50 mL) containing triethylamine (1.0 mL) compound **33** (2.66 g, 0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 2 h and the formed solid product, upon cooling, was collected by filtration.

*(N')-4-Amino-N'-(1,3-diphenylallylidene)-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carbohydrazide (32a).* Black crystals from ethanol, yield 58% (2.64 g) m.p. 171-173 °C. IR (KBr) $\nu_{max}$ 3463-3320 ($NH_2$, NH), 3057 (CH aromatic), 1688 (CO), 1654 (C=N), 1628 (C=C), 1218 (C=S). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 4.72 (s, 2H, (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.13, 6.24 (2d, 2H, CH=CH), 7.26-7.38 (m, 15H, $3C_6H_5$), 8.30 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 90.3, 93.1 (CH=CH), 119.8, 119.9, 120.8, 121.3, 121.4, 121.8, 122.0, 122.4, 123.6, 124.2, 125.2, 125.6 ($3C_6H_5$), 130.5, 132.6 thiazole C), 166.4 (CO), 168.2 (C=N),

180.3 (C=S). Analysis calcd for $C_{25}H_{20}N_4OS_2$ (456.58): C, 65.76; H, 4.42; N, 12.27; S, 14.05%. Found: C, 65.63; H, 4.62; N, 12.33; S, 13.86%. MS: *m/z* 456 ($M^+$, 66%).

*(N')-4-Amino-N'-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carbohydrazide (**32b**).* Brown crystals from ethanol, yield 70% (3.64g) m.p. 191-192 °C. IR (KBr) $\nu_{max}$ 3473-3322 ($NH_2$, NH), 3053 (CH aromatic), 1687 (CO), 1650 (C=N), 1632 (C=C), 1230 (C=S). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 3.17 (s, 3H, $OCH_3$), 4.77 (s, 2H, $D_2O$ exchangeable, $NH_2$), 6.12, 6.28 (2d, 2H, CH=CH), 7.23-7.49 (m, 13H, $C_6H_5$, $2C_6H_4$), 8.23 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): 50.7 ($OCH_3$), 90.3, 93.1 (CH=CH), 119.8, 119.9, 120.4, 120.6, 121.4, 122.1, 123.4, 124.2, 124.3, 124.5, 125.1, 125.8 ($C_6H_5$, $2C_6H_4$), 130.6, 132.8 thiazole C), 166.6 (C), 168.7 (C=N), 180.2 (C=S). Analysis calcd for $C_{26}H_{21}ClN_4O_2S$ (521.05): C, 59.93; H, 4.06; N, 10.75; S, 12.31%. Found: C, 59.77; H, 4.19; N, 10.69; S, 12.28%. MS: *m/z* 521 ($M^+$, 75%).

*4-Amino-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carbohydrazide (**33**).* To a solution of compound **12** (1.00 g, 0.01 mol), in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL) each of elemental sulfur (0.32 g, 0.01 mol) and phenylisothiocyanate (1.30 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 1 h then left to cool and the formed solid product, in each case, was collected by filtration. Yellow crystals from ethanol, yield 75% (1.99 g) m.p. 176-178 °C. IR (KBr) $\nu_{max}$ 3493-3342 ($NH_2$, 2NH), 3056 (CH aromatic), 1688 (CO), 1620 (C=C), 1216 (C=S). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 4.93, 5.21 (2s, 4H, $2NH_2$), 7.31-7.37 (m, 5H, $C_6H_5$), 8.11 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 120.2, 122.4, 123.6, 125.2, 125.6 ($C_6H_5$), 130.6, 132.3 thiazole C), 166.8 (CO), 180.5 (C=S). Analysis calcd for $C_{10}H_{10}N_4OS_2$ (266.34): C, 45.09; H, 3.78; N, 21.04; S, 24.08%. Found: C, 44.83; H, 3.93; N, 20.91; S, 23.72%. MS: *m/z* 266 ($M^+$, 66%).

*General procedure for the synthesis of the thieno[3,2-d]thiazole derivatives **35a,b***

To a solution of compound **27b** (4.13 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (1 mL) elemental sulfur (0.32 g, 0.01 mol) and either of malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 h then poured onto ice/water containing few drops of hydrochloric acid and the formed solid product, in each case, was collected by filtration.

*(N')-5-Amino-N'-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)-6-cyanothieno[3,2-d]thiazole-2-carbohydrazide (**35a**).* Brown crystals from ethanol, yield 95% (4.69 g) m.p. 113-115 °C. IR (KBr) $\nu_{max}$ 3489-3330 ($NH_2$, NH), 3058 (CH aromatic), 2220 (CN), 1688 (CO), 1656 (C=N), 1628 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 3.12 (s, 3H, $OCH_3$), 4.89 (s, 2H, $NH_2$), 6.16, 6.30 (2d, 2H, CH=CH), 7.23-7.44 (m, 8H, $2C_6H_4$), 8.34 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): 50.9 ($OCH_3$), 116.8 (CN), 120.2, 120.7, 121.5, 122.4, 123.4, 124.8, 125.6, 125.9 ($2C_6H_4$), 130.6, 131.6, 131.8, 132.9 thiophene C), 166.8 (CO), 174.6, 176.2 (2C=N). Analysis calcd for $C_{23}H_{16}ClN_5O_2S_2$ (493.99): C, 55.92; H, 3.26; N, 14.18; S, 12.98%. Found: C, 55.60; H, 3.49; N, 14.26; S, 12.69%. MS: *m/z* 493 ($M^+$, 80%).

*Ethyl 5-amino-2-((2-(1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)-hydrazine-carbonyl)thieno[3,2-d]thiazole-6-carboxylate (**35b**).* Yellow crystals from ethanol, yield 80% (4.32 g) m.p. 140-143 °C. IR (KBr) $\nu_{max}$ 3472-3335 ($NH_2$, NH), 3055 (CH aromatic), 1689, 1693 (2CO), 1656 (C=N), 1626 (C=C). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ = 1.13 (t, 3H, *J* = 7.11 Hz, $CH_3$), 3.08 (s, 3H, $OCH_3$), 4.23 (q, 2H, *J* = 7.11 Hz, $CH_2$), 4.89 (s, 2H, $NH_2$), 6.15, 6.31 (2d, 2H, CH=CH), 7.25-7.48 (m, 8H, $2C_6H_4$), 8.34 (s, 1H, $D_2O$ exchangeable, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 16.5 ($OCH_2\underline{CH_3}$), 50.2 ($O\underline{CH_2}CH_3$), 50.8 ($OCH_3$), 120.1, 120.5, 121.3, 122.6, 123.8, 124.3, 125.5, 125.9 ($2C_6H_4$), 130.6, 131.6, 131.8, 132.9 thiophene C), 166.6 (CO), 174.4, 176.5

(2C=N). Analysis calcd for $C_{25}H_{21}ClN_4O_4S_2$ (541.04): C, 55.50; H, 3.91; N, 10.36; S, 11.85%. Found: C, 55.83; H, 3.69; N, 10.41; S, 12.06%. MS: *m/z* 541 ($M^+$, 66%).

## CONCLUSION

The target molecules were synthesized using α,β-unsaturated carbonyl compounds (chalcones) through a series of heterocyclization reactions to produce pyridine, hydrazide-hydrazone derivatives, thiophene, coumarin, pyran and thiazole-6-one derivatives, thiazolo[4,5-*b*]pyran derivatives. The anti-proliferative activity of the newly synthesized compounds toward three cancer cell lines and normal human cell line indicated that many compounds expressed high inhibitions toward the cancer cell lines. The results obtained in this work encourage further work in the future since many compounds were considered as promising anticancer agents.

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