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], antimitic [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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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 $\delta$ 3.09 ppm corresponding to the OCH$_3$ group, a singlet at $\delta$ 6.87 ppm...
equivalent to the pyridine CH₂, and a multiplet at δ 7.23-7.42 ppm corresponding to the two phenyl groups. In addition, the 13C NMR spectrum showed a signal at δ 50.6 due to the OCH₃ group, a signal at δ 89.6 indicating the pyridine CH₃ group, two signals at δ 88.1, 89.5 for the ylidene C=CH 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 C₆H₅ 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-hydrazone derivatives 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 νmax 3473-3318 cm⁻¹ for the NH group, a signal at νmax 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 CH₂ 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 C₆H₅ groups and a singlet at δ 8.42 ppm (D₂O exchangeable) equivalent to the NH group.

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

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The reaction of either compound 13a or 13b with acetylphenone (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-chlorobenzaldehyde (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 \( \delta \) 4.72 ppm (D\(_2\)O exchangeable) equivalent to the NH group, two singlets at \( \delta \) 6.11, 6.24 ppm confirming the CH=CH moiety, a singlet \( \delta \) 6.93 confirming the pyran H-4, a multiplet at \( \delta \) 7.27-7.37 equivalent to the three C\(_2\)H\(_2\) groups and a singlet at \( \delta \) 8.25 (D\(_2\)O exchangeable) for the NH group. In addition, the \( ^{13} \)C NMR spectrum showed a signal at \( \delta \) 88.3 for the pyran C-4, two signals at \( \delta \) 90.4, 92.4 for the CH=CH moiety, signals at \( \delta \) 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\(_2\)H\(_2\) groups, four signals at \( \delta \) 128.6, 129.2, 130.8, 131.7 for the pyran C-2, C-3, C-5, C-6 and a signal at \( \delta \) 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 methylenecarbonyl 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 thiazol[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).

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 route. 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.](image-url)
Uses of chalcone acetophenone to synthesize compounds with c-Met kinase activities

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 °C in a humidified atmosphere containing 5% CO₂. 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% (IC₅₀), 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 concentrations that were able to cause 50% of cell growth inhibition (IC₅₀) 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, 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 | IC₅₀(µmol 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       | 33.1 ± 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 | 0.20 ± 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   | 30.84 ± 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 ± 1.04      | 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      | 30.6 ± 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 ± 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 ± 8.08 | >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

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    | IC₅₀ (nM) c-Met |
|-----------------|-----|-----|------|-----------------|
| 6a              | H   | H   | -    | 8.52 ± 2.419    |
| 6b              | Cl  | OCH₃| -    | 0.41 ± 0.29     |
| 8b              | Cl  | OCH₃| -    | 0.63 ± 0.25     |
| 11a             | H   | H   | -    | 7.13 ± 1.82     |
| 11b             | Cl  | OCH₃| -    | 0.39 ± 0.12     |
| 13a             | H   | H   | -    | 5.36 ± 1.52     |
| 13b             | Cl  | OCH₃| -    | 0.47 ± 0.21     |
| 15a             | H   | H   | -    | 2.62 ± 1.31     |
| 15b             | Cl  | OCH₃| -    | 0.42 ± 0.19     |
| 16a             | H   | H   | -    | 2.34 ± 1.29     |
| 16b             | Cl  | OCH₃| -    | 0.29 ± 0.13     |
| 17a             | H   | H   | -    | 1.73 ± 0.69     |
| 17b             | Cl  | OCH₃| -    | 0.29 ± 0.11     |
| 19a             | H   | H   | -    | 3.80 ± 1.25     |
| 19b             | Cl  | OCH₃| -    | 1.31 ± 0.92     |
| 20a             | H   | H   | -    | 6.84 ± 1.27     |
| 20b             | Cl  | OCH₃| -    | 0.30 ± 0.13     |
| 23a             | H   | H   | -    | 5.78 ± 2.17     |
| 23b             | Cl  | OCH₃| -    | 0.37 ± 0.15     |
| 25a             | H   | H   | OCH₃| 6.31 ± 2.46     |
| 25b             | H   | H   | OCH₃| 0.21 ± 0.09     |
| 25c             | Cl  | H   | Cl   | 0.14 ± 0.06     |
| 25d             | Cl  | OCH₃| H    | 1.21 ± 0.65     |
| 25e             | Cl  | OCH₃| OCH₃| 10.24 ± 2.72    |
| 25f             | Cl  | OCH₃| Cl   | 0.14 ± 0.02     |
| 27a             | H   | H   | -    | 8.36 ± 2.41     |
| 27b             | Cl  | OCH₃| -    | 0.62 ± 0.31     |
| 27c             | Cl  | OCH₃| H    | 2.62 ± 0.82     |
| 28a             | Cl  | OCH₃| OCH₃| 8.32 ± 2.51     |
| 28b             | Cl  | OCH₃| OCH₃| 0.25 ± 0.13     |
| 29a             | Cl  | OCH₃| H    | 4.35 ± 2.18     |
| 29b             | Cl  | OCH₃| OCH₃| 1.36 ± 0.81     |
| 29c             | Cl  | OCH₃| Cl   | 0.84 ± 0.52     |
| 31b             | Cl  | OCH₃| -    | 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 IC₅₀ were summarized in Table 2. The IC₅₀ 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 IC₅₀ values ranging from 0.14 to 10.24 nM.
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, 29e 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 °C

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-1,3-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 °C 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 °C. IR (KBr) νmax 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$_{6}$H$_4$). $^{13}$C NMR (DMSO-d$_6$, 75 MHz): δ 89.1 (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$_{6}$H$_4$), 132.4, 133.0 (pyridine C-3, C-4), 173.2 (C=N). Analysis calcd for C$_{22}$H$_2$_{18}N$_4$: 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 °C. IR (KBr) νmax 3055 (CH aromatic), 2973, 2877 (CH$_3$), 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$_{6}$H$_4$). $^{13}$C NMR (DMSO-d$_6$, 75 MHz): δ 80.56 (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$_{6}$H$_4$), 132.1, 133.3 (pyridine C-3, C-4), 173.5 (C=N). Analysis calcd for C$_{22}$H$_1$_{13}ClN$_4$: 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-enitrile (7) (0.82 g, 0.01 mol) together with ammonium acetate (0.50 g) were heated in an oil bath at 120 °C 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 °C. IR (KBr) νmax 3053 (CH aromatic), 2983 (CH$_3$),

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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) νmax 3436-3329 (NH), 3053 (CH aromatic), 2974, 2879 (CH3, CH2), 2221 (CN), 1635 (C=C). 1H NMR (DMSO-d6, 300 MHz): δ = 2.69 (s, 3H, CH3), 6.29 (t, 1H, J = 6.03 Hz, pyridine H-2), 5.98 (s, 1H, pyridine H-3), 6.96 (s, 1H, CH=C), 7.23-7.74 (m, 8H, 2C6H4), 8.33 (s, 1H, D2O exchangeable, NH). 13C NMR (DMSO-d6, 75 MHz): δ = 50.8 (OCH3), 89.5 (pyridine CH2), 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 (C2H4), 131.2, 133.8 (pyridine C-2, C-3). Analysis calcd for C20H17ClNO3 (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) acetoacetonitrile (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)ethanol (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 (CH3, CH2), 1688 (CO), 1631 (C=C). 1H NMR (DMSO-d6, 300 MHz): δ = 2.86 (s, 3H, CH3), 6.28, 6.93 (2d, 2H, pyridine H-2, H-3), 7.26-7.36 (m, 15H, 3C6H4), 10.21 (s, 1H, D2O exchangeable, OH). 13C NMR (DMSO-d6, 75 MHz): δ = 36.8 (CH3), 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 (C6H4), 132.1, 132.8, 133.8, 134.1 (pyridine C-3, C-4, C-5, C-6), 166.2 (C=O). Analysis calcd for C25H26NO (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)ethanol (11b). Yellow crystals from ethanol, yield 57% (2.45 g) m.p. 81-84 °C. IR (KBr) νmax 3552-3331 (OH), 3055 (CH aromatic), 2982, 2889 (CH3), 1687 (CO), 1628 (C=C). 1H NMR (DMSO-d6, 300 MHz): δ = 2.69 (s, 3H, CH3), 3.13 (s, 3H, OCH3), 6.21, 6.83 (2d, 2H, pyridine H-2, H-3), 7.21-7.48 (m, 15H, 3C6H4, 2C2H4), 10.26 (s, 1H, D2O exchangeable, OH). 13C NMR (DMSO-d6, 75 MHz): δ = 36.5 (CH3), 50.8 (OCH3), 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, 126.5 (C6H4, 2C2H4), 132.0, 132.6, 133.9, 134.5 (pyridine C-3, C-4, C-5, C-6), 166.7 (C=O). Analysis calcd for C26H25ClNO2 (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) cyanoacetyldiazidine (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) νmax 3473-3318 (NH), 3055 (CH aromatic), 2877 (CH=, CH2). Bull. Chem. Soc. Ethiop. 2022, 36(1)
Method (B) added. The reaction mixture was heated under reflux for 2 h then poured onto ice/water containing 

\[ N, 8.93\% \].

**Analysis**

\[ \text{N', exchangeable, NH}. \]

\[ 3H, CH_2 220 (CN), 2220 (CH_3), 6.09, 6.26 (2d, 2H, CH=CH), 7.29-7.38 (m, 10H, 2C_6H_4), 8.42 (s, 1H, D_2O exchangeable, NH). \]

\[ ^1\text{C} NMR (DMSO-d_6, 75 MHz): \delta 46.5 (CH_2), 90.4, 92.4 CH=CH), 117.2 (CN), 119.6, 120.4, 120.8, 121.6, 122.3, 123.4, 123.8, 125.5 (2C_6H_4), 165.4 (C=O), 168.3 (C=\text{C}). \]

Analysis calcd for C_{15}H_{27}N_2O (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%).

\[ N'(1-(4-Chlorophenyl)-3-(4-methoxyphenyl)allylidene)-2-cyanoacetohydrazide (13b) \]

Yellow crystals from ethanol, yield 98% (3.46 g) m.p. 102-104 °C. IR (KBr) ν_{max} 3462-3340 (NH), 3053 (CH aromatic), 2893 (CH_2), 2258 (CN), 1687 (CO), 1650 (C=\text{N}), 1632 (C=C). \[ ^1\text{H} NMR (DMSO-d_6, 300 MHz): \delta = 3.09 (s, 3H, OCH_3), 5.31 (s, 2H, CH_2), 6.04, 6.28 (2d, 2H, CH=CH), 7.28-7.46 (m, 8H, 2C_6H_4), 8.21 (s, 1H, D_2O exchangeable, NH). \]

\[ ^1\text{C} NMR (DMSO-d_6, 75 MHz): \delta 46.7 (CH_2), 50.9 (OCH_3), 90.1, 92.6 (CH=CH), 117.1 (CN), 119.3, 120.1, 120.6, 121.3, 122.7, 123.0, 123.6, 125.8 (2C_6H_4), 165.6 (C=O), 168.6 (C=\text{N}). \]

Analysis calcd for C_{15}H_{18}ClN_2O_3 (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) acetoephone (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 °C for 1 h then left to cool. The remaining product was boiled in ethanol (40 mL) and formed solid product was collected by filtration.

\[ 2-Cyano-N'(1,3-diphenylallylidene)-3-phenylbut-2-enyldrazide (15a) \]

Yellow crystals from ethanol, yield 52% (2.03 g) m.p. 177-179 °C. IR (KBr) ν_{max} 3449-3332 (NH), 3058 (CH aromatic), 2220 (CN), 1689 (CO), 1655 (C=\text{N}), 1628 (C=C). \[ ^1\text{H} NMR (DMSO-d_6, 300 MHz): \delta = 2.82 (s, 3H, CH_3), 6.13, 6.29 (2d, 2H, CH=CH), 7.31-7.40 (m, 15H, 3C_6H_4), 8.38 (s, 1H, D_2O exchangeable, NH). \]

\[ ^1\text{C} NMR (DMSO-d_6, 75 MHz): \delta 36.8 (CH_2), 88.3, 89.5 (CH=CH), 95.2, 97.4 C=C), 117.4 (CN), 119.5, 120.2, 120.5, 121.2, 121.5, 121.9, 122.7, 123.1, 123.5, 124.3m, 124.6, 124.8 (3C_6H_4), 165.6 (C=O), 168.6 (C=\text{N}). \]

Analysis calcd for C_{26}H_{21}N_2O (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%).

\[ N'(1-(4-Chlorophenyl)-3-(4-methoxyphenyl)allylidene)-2-cyano-3-phenylbut-2-enyldrazide (15b) \]

Brown crystals from ethanol, yield 60% (2.73 g) m.p. 188-191 °C. IR (KBr) ν_{max} 3447-3317 (NH), 3056 (CH aromatic), 2221 (CN), 1686 (CO), 1653 (C=\text{N}), 1630 (C=C). \[ ^1\text{H} NMR (DMSO-d_6, 300 MHz): \delta = 2.85, 3.08 (s, 6H, CH_3, OCH_3), 6.13, 6.30 (2d, 2H, CH=CH), 7.25-7.29 (m, 13H, 2C_6H_4), 8.28 (s, 1H, D_2O exchangeable, NH). \]

\[ ^1\text{C} NMR (DMSO-d_6, 75 MHz): \delta 36.4 (CH_2), 50.6 (OCH_3), 88.1, 89.2 (CH=CH), 95.5, 97.8 C=C), 117.1 (CN), 119.1, 120.4, 120.5, 121.4, 122.8, 123.3, 123.4, 123.8, 125.4 (C_6H_4, 2C_6H_4), 165.8 (C=O), 169.3 (C=N). \]

Analysis calcd for C_{26}H_{21}ClN_2O_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 acetoephone (1.20 g, 0.01 mol) were added. The reaction mixture was heated under reflux

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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) ν_max 3472-3317 (NH, NH), 3056 (CH aromatic), 1692 (CO), 1653 (C=O), 1632 (C=C). 1H NMR (DMSO-d_6, 300 MHz): δ = 4.82 (s, 2H, D_2O exchangeable, NH), 6.11, 6.23 (2d, 2H, CH=CH), 6.71 (s, 1H, thiophene H-5), 7.27-7.38 (m, 15H, 3C_H) 8.38 (s, 1H, D_2O exchangeable, NH). 13C NMR (DMSO-d_6, 75 MHz): δ 88.4, 89.5 (CH=CH), 119.4, 119.8, 120.4, 120.7, 121.4, 121.6, 122.3, 123.4, 123.6, 125.2, 125.8 (3C_H), 130.4, 132.5, 133.9, 134.2 (thiophene C), 165.7 (C=O), 169.6 (C=N). Analysis calcd for C_{28}H_{22}N_{2}O_{5}S (423.53): C, 73.73; H, 5.00; N, 9.92; S, 7.73%. 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) ν_max 3460-3325 (NH, NH), 3058 (CH aromatic), 1690 (CO), 1653 (C=O), 1630 (C=C). 1H NMR (DMSO-d_6, 300 MHz): δ = 3.08 (s, 3H, OCH_3), 4.84 (s, 2H, D_2O exchangeable, NH), 6.12, 6.24 (2d, 2H, CH=CH), 6.70 (s, 1H, thiophene H-5), 7.21-7.48 (m, 13H, 3C_H, 2C_H), 8.35 (s, 1H, D_2O exchangeable, NH). 13C 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_H, 2C_H), 130.2, 132.6, 133.4, 134.8 (thiophene C), 165.5 (C=O), 169.9 (C=N). Analysis calcd for C_{27}H_{21}ClN_{2}O_{5}S (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) ν_max 3474-3324 (NH), 3056 (CH aromatic), 2222 (CN), 1690 (CO), 1653 (C=O), 1626 (C=C). 1H 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_H), 8.36 (s, 1H, D_2O exchangeable, NH). 13C 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_H), 165.5 (C=O), 170.3 (C=N). Analysis calcd for C_{25}H_{20}ClN_{2}O (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) ν_max 3463-3323 (NH), 3058 (CH aromatic), 2223 (CN), 1689 (CO), 1651 (C=O), 1632 (C=C). 1H 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, 3C_H, 2C_H), 8.33 (s, 1H, D_2O exchangeable, NH). 13C 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_H, 2C_H), 165.7 (C=O), 170.5 (C=N). Analysis calcd for C_{26}H_{22}ClN_{2}O (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-carboxyhydrazide (19a). Brown crystals from ethanol, yield 68% (2.68 g) m.p. 58-60 °C. IR (KBr) νmax 3474-3324 (NH), 3055 (CH aromatic), 1684, 1692 (2CO), 1650 (C=N), 1622 (C=C). 1H NMR (DMSO-d6, 300 MHz): δ = 6.13, 6.29 (2d, 2H, CH=CH), 6.89 (s, 1H, coumarin H-4), 7.26-7.32 (m, 14H, 2C6H5, C6H4), 8.29 (s, 1H, D2O exchangeable, NH). 13C NMR (DMSO-d6, 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 (2C6H5, C6H4), 165.8, 166.4 (2C=O), 169.5 (C=N). Analysis calcd for C22H16N2O3 (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-methoxyphenylallylidene)-2-oxo-2H-chromene-3-carboxyhydrazide (20b). Yellow crystals from ethanol, yield 80% (3.69 g) m.p. 110-112 °C. IR (KBr) νmax 3469-3319 (NH), 3058 (CH aromatic), 1686, 1690 (2CO), 1652 (C=N), 1628 (C=C). 1H NMR (DMSO-d6, 300 MHz): δ = 3.20 (s, 3H, OCH3), 6.16, 6.26 (2d, 2H, CH=CH), 6.87 (s, 1H, coumarin H-4), 7.22-7.49 (m, 12H, 3C6H4), 8.26 (s, 1H, D2O exchangeable, NH). 13C NMR (DMSO-d6, 75 MHz): δ 50.6 (OCH3), 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 (3C6H4), 165.5, 166.7 (2C=O), 169.8 (C=N). Analysis calcd for C22H16ClN2O3 (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) 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.

2,5-Diamo-4-cyano-N’-(1,3-diphenylallylidene)thiophene-3-carboxyhydrazide (21a). Grey crystals from ethanol, yield 58% (2.24 g) m.p. 113-115 °C. IR (KBr) νmax 34780-3326 (2NH2, NH), 3054 (CH aromatic), 2220 (CN), 1688 (CO), 1650 (C=N), 1628 (C=C). 1H NMR (DMSO-d6, 300 MHz): δ = 4.80, 5.23 (2s, 4H, D2O exchangeable, 2NH2), 6.09, 6.22 (2d, 2H, CH=CH), 7.28-7.39 (m, 10H, 2C6H4), 8.27 (s, 1H, D2O exchangeable, NH). 13C NMR (DMSO-d6, 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 (2C6H4), 130.6, 132.8, 133.5, 134.6 (thiophene C), 165.9 (C=O), 169.4 (C=N). Analysis calcd for C22H13N2OS (387.46): C, 65.10; H, 4.42; N, 8.09%. Found: C, 64.88; H, 4.62; N, 8.30% S, 8.09%. MS: m/z 387 (M+, 64%).

2,5-Diamo-N’-(1-(4-chlorophenyl)-3-(4-methoxyphenylallylidene)-4-cyano-thiophene-3-carboxyhydrazide (21b). Yellow crystals from ethanol, yield 95% (4.29 g) m.p. 120-123 °C. IR (KBr) νmax 3482-3361 (2NH2, NH), 3056 (CH aromatic), 2220 (CN), 1688 (CO), 1650 (C=N), 1636 (C=C). 1H NMR (DMSO-d6, 300 MHz): δ = 3.11 (s, 3H, OCH3), 4.86, 5.22 (2s, 4H, D2O exchangeable, 2NH2), 6.11, 6.24 (2d, 2H, CH=CH), 7.21-7.48 (m, 8H, 2C6H4), 8.31 (s, 1H, D2O exchangeable, NH). 13C NMR (DMSO-d6, 75 MHz): δ 50.6 (OCH3), 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 (2C6H4), 130.3, 132.5, 133.7, 134.8

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(thiophene C), 165.4 (C=O), 169.7 (C=N). Analysis calcd for C$_2$H$_2$ClN$_2$O$_2$S (451.93): C, 58.47; H, 4.01; N, 15.70; 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°C. 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): $\delta = 4.82, 5.31$ (2s, 4H, D$_2$O 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$_6$H$_5$). $^1$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 88.1, 90.2 (CH=CH), 117.1 (CN), 120.0, 120.6, 121.1, 122.5, 124.6, 125.3, 125.5 (2C$_6$H$_5$), 129.4, 130.8, 132.3, 133.1 (pyridine C), 166.9 (C=O), 170.8 (C=N). Analysis calcd for C$_2$H$_2$ClN$_2$O$_2$S (419.86): C, 58.62; H, 4.24; N, 19.49%. Found: C, 58.62; H, 4.24; N, 19.71%. 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-((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°C. IR (KBr) $\nu_{max}$ 3459-3373 (NH$_2$), 3055 (CH aromatic), 2227, 2220 (2CN), 1652 (C=N), 1636 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): $\delta = 4.72$ (s, 2H, D$_2$O 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$_6$H$_5$), 8.25 (s, 1H, D$_2$O exchangeable, NH). $^1$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 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$_6$H$_5$), 128.6, 129.2, 130.8, 131.7 (pyran C2, C-3, C-5, C-6), 168.8 (C=N). Analysis calcd for C$_{38}$H$_{27}$N$_2$O$_4$ (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-((1,3-diphenylallylidene)hydrazinyl)-4-(4-methoxyphenyl)-4H-pyran-3,5-dicarbonitrile (25b)

Yellow crystals from ethanol, yield 82% (3.88 g) m.p. 177-179°C. IR (KBr) $\nu_{max}$ 3349-3373 (NH$_2$), 3055 (CH aromatic), 2227, 2220 (2CN), 1652 (C=N), 1636 (C=C). $^1$H NMR (DMSO-$d_6$, 200 MHz): $\delta = 4.72$ (s, 2H, D$_2$O 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$_6$H$_5$), 8.25 (s, 1H, D$_2$O exchangeable, NH). $^1$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 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$_6$H$_5$), 128.6, 129.2, 130.8, 131.7 (pyran C2, C-3, C-5, C-6), 168.8 (C=N). Analysis calcd for C$_{38}$H$_{27}$N$_2$O$_4$ (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-4-(4-chlorophenyl)-6-((2-(1,3-diphenylallylidene)hydrazinyl)-4H-pyran-3,5-dicarbonitrile (25e). Yellow crystals from ethanol, yield 71% (3.39 g) m.p. 136-138 °C. IR (KBr) ν max 3453, 3370 (NH exchangeable, NH). 1H NMR (DMSO-d6, 300 MHz): δ = 2.90 (3H, OCH3), 3.11 (2s, 6H, ClN), 3.78 (s, 2H, CH=CH), 6.67 (2d, 2H, CH=CH), 6.99 (s, 1H, pyran H-4), 7.22-7.39 (m, 14H, 2C6H5, C6H4), 8.28 (s, 1H, D2O exchangeable, NH). 13C NMR (DMSO-d6, 75 MHz): δ 50.8 (OCH3), 88.3 (pyran C-4), 90.4, 92.6 (CH=CH), 116.8, 117.5 (2CN), 119.9, 120.9, 121.4, 121.7, 122.1, 122.5, 123.4, 125.9 (2C6H5, C6H4), 128.4, 129.7, 130.2, 131.8 (pyran C2, C-3, C-5, C-6), 168.8 (C=N). Analysis calc for C20H18ClN3O (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)-4H-pyran-3,5-dicarbonitrile (25d). Yellow crystals from ethanol, yield 83% (4.21 g) m.p. 98 °C. IR (KBr) ν max 3488-3340 (NH, NH), 3057 (CH aromatic), 2987 (CH3), 2225, 2220 (2CN), 1652 (C=N), 1626 (C=C). 1H NMR (DMSO-d6, 300 MHz): δ = 2.90 (3H, OCH3), 3.11 (2s, 6H, ClN), 3.78 (s, 2H, CH=CH), 6.67 (2d, 2H, CH=CH), 6.99 (s, 1H, pyran H-4), 7.22-7.39 (m, 14H, 2C6H5, C6H4), 8.28 (s, 1H, D2O exchangeable, NH). 13C NMR (DMSO-d6, 75 MHz): δ 50.8 (OCH3), 88.3 (pyran C-4), 90.4, 92.6 (CH=CH), 116.8, 117.5 (2CN), 119.9, 120.9, 121.4, 121.7, 122.1, 122.5, 123.4, 125.9 (2C6H5, C6H4), 128.4, 129.7, 130.2, 131.8 (pyran C2, C-3, C-5, C-6), 168.8 (C=N). Analysis calc for C20H18ClN3O (477.97): C, 70.36; H, 4.22; 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) ν max 3480-3322 (NH, NH), 3054 (CH aromatic), 2984 (CH3), 2226, 2221 (2CN), 1648 (C=N), 1629 (C=C). 1H NMR (DMSO-d6, 300 MHz): δ = 2.90, 3.11 (2s, 6H, 2OCH3), 4.75 (s, 2H, D2O exchangeable, NH), 6.08, 6.25 (2d, 2H, CH=CH), 6.93 (s, 1H, pyran H-4), 7.21-7.47 (m, 12H, 3C6H5, C6H4), 8.25 (s, 1H, D2O exchangeable, NH). 13C NMR (DMSO-d6, 75 MHz): δ 50.6, 50.8 (2OCH3), 88.3 (pyran C-4), 90.4, 92.6 (CH=CH), 116.8, 117.0 (2CN), 119.3, 119.5, 120.4, 120.8, 121.0, 121.6, 121.9, 122.3, 122.5, 123.2, 123.9, 125.9 (3C6H3), 128.6, 129.7, 130.2, 131.9 (pyran C2, C-3, C-5, C-6), 168.5 (C=N). Analysis calc for C20H18ClN3O3 (538.00): C, 66.97; H, 4.50; N, 13.03%. 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-(4-methoxy 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) ν max 3462-3352 (NH, NH), 3056 (CH aromatic), 2989 (CH3), 2225, 2220 (2CN), 1651 (C=N), 1627 (C=C). 1H NMR (DMSO-d6, 300 MHz): δ = 3.12 (3H, OCH3), 4.73 (s, 2H, D2O exchangeable, NH), 6.06, 6.27 (2d, 2H, CH=CH), 6.92 (s, 1H, pyran H-4), 7.24-7.49 (m, 12H, 3C6H5, C6H4), 8.22 (s, 1H, D2O exchangeable, NH). 13C NMR (DMSO-d6, 75 MHz): δ 50.9 (OCH3), 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 (3C6H3), 128.4, 129.1, 130.7, 131.5 (pyran

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C2, C-3, C-5, C-6), 168.7 (C=N). Analysis calculated for C₉H₇Cl₃N₂O₂ (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) thiglycollic 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-carboxhydrazide (27a). Yellow crystals from ethanol, yield 73% (3.02 g) m.p. 103–106 °C. IR (KBr) νmax 3473-3326 (NH), 3054 (CH aromatic), 1686, 1691 (2CO), 1655 (C=N), 1622 (C=C). 1H NMR (DMSO-d₆, 300 MHz): δ = 3.20 (s, 3H, OCH₃), 5.95 (s, 2H, thiazole CH₂), 6.12, 6.29 (2d, 2H, CH=CH), 7.24-7.39 (m, 8H, 2C=CH), 8.36 (s, 1H, D₂O exchangeable, NH). 13C NMR (DMSO-d₆, 75 MHz): δ 50.8 (OCH₃), 90.1, 92.9 (CH=CH), 96.5 (thiazole CH₂), 120.3, 121.6, 121.8, 122.3, 123.5, 124.2, 124.4, 125.8 (2C=CH₂), 165.6, 166.3 (2CO), 168.1, 168.7 (2C=N). Analysis calculated for C₂₉H₂₈ClN₂O₂ (431.88): C, 58.04%; H, 4.30%; N, 9.94%; S, 7.88%. MS: m/z 439 (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-pyran-2,3-diythiazol-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 °C. IR (KBr) νmax 3457-3340 (NH₂, NH), 3053 (CH aromatic), 2987 (CH₃), 2220 (CN), 1680 (CO), 1652 (C=N), 1626 (C=C). 1H NMR (DMSO-d₆, 300 MHz): δ = 2.98 (s, 3H, OCH₃), 4.71 (s, 2H, D₂O exchangeable, NH₂), 6.11, 6.28 (2d, 2H, CH=CH), 6.95 (s, 1H, pyran H-4), 7.20-7.44 (m, 13H, C₆H₅, 2C₆H₅), 8.21 (s, 1H, D₂O exchangeable, NH). 13C NMR (DMSO-d₆, 75 MHz): δ 50.6 (OCH₃), 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 (C₆H₅, 2C₆H₅), 127.8, 128.3, 129.8, 130.4 (pyran C), 164.5 (CO), 168.1, 168.7 (2C=N). Analysis calculated for C₆H₂ClIN(O)S (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-pyran-2,3-diythiazol-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 °C. IR (KBr) νmax 3480-3312 (NH₂, NH), 3056 (CH aromatic), 2984 (CH₃), 2221 (CN), 1680 (CO), 1646 (C=N), 1626 (C=C). 1H NMR (DMSO-d₆, 300 MHz): δ = 2.95, 3.08 (2s, 2H, OCH₃), 4.73 (s, 2H, D₂O exchangeable, NH₂), 6.06, 6.28 (2d, 2H, CH=CH), 3420 (NH), 3054 (CH aromatic), 1686, 1691 (2CO), 1655 (C=N), 1622 (C=C). Bull. Chem. Soc. Ethiop. 2022, 36(1)
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 °C. IR (KBr) \( \nu_{\text{max}} \) 3457-3340 (NH), 3053 (CH aromatic), 2987 (CH3), 2220 (CN), 1680 (CO), 1562 (C=N), 1626 (C=C). 1H NMR (DMSO-\(d_6\), 300 MHz): \( \delta = 2.93 \) (s, 3H, OCH3), 4.72 (s, 2H, D2O exchangeable, NH2), 6.10, 6.31 (2d, 2H, CH=CH), 6.93 (s, 1H, pyridine H-4), 7.27-7.43 (m, 13H, C6H5, 2C6H4). 13C NMR (DMSO-\(d_6\), 75 MHz): \( \delta \) 50.5 (OCH3), 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, 123.3, 124.8, 124.5, 125.8 (C6H5, 2C6H4), 128.5, 128.8, 130.4, 132.8 (pyridine C), 165.7 (CO), 168.4 (2C=O). Analysis calcd for C39H35ClN3O7S: C, 56.44; H, 4.09; N, 14.82; S, 5.65%. Found: C, 56.37; 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 °C. IR (KBr) \( \nu_{\text{max}} \) 3480-3312 (NH2, NH), 3056 (CH aromatic), 2984 (CH3), 2221 (CN), 1680 (CO), 1646 (C=N), 1562 (C=C). 1H NMR (DMSO-\(d_6\), 300 MHz): \( \delta = 2.95, 3.08 \) (2s, 6H, 2OCH3), 4.73 (s, 2H, D2O exchangeable, NH2), 6.09, 6.24 (2d, 2H, CH=CH), 6.90 (s, 1H, pyridine H-4), 7.26-7.45 (m, 12H, 3C6H5), 8.21, 8.28 (2s, 2H, D2O exchangeable, 2NH). 13C NMR (DMSO-\(d_6\), 75 MHz): 50.8, 50.8 (2OCH3), 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 (C6H5), 128.6, 129.8, 130.4, 130.9 (pyridine C), 165.5 (CO), 168.1, 168.8 (2C=O). Analysis calcd for C39H35ClN3O7S: C, 56.44; H, 4.09; N, 14.82; S, 5.65%. Found: C, 56.28; 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) νmax 3449-3362 (NH2, NH), 3055 (CH aromatic), 2989 (CH3), 2222 (CN), 1680 (CO), 1650 (C=N), 1626 (C=C). 1H NMR (DMSO-d6, 300 MHz): δ = 3.10 (s, 3H, OCH3), 4.78 (s, 2H, D2O exchangeable, NH2), 6.14, 6.24 (2d, 2H, CH=CH), 6.92 (s, 1H, pyridine-H-4), 7.25-7.49 (m, 12H, 3C6H5), 8.21 (s, 1H, D2O exchangeable, NH). 13C NMR (DMSO-d6, 75 MHz): 50.8 (2OCH3), 90.8 (pyridine C-4), 90.4, 92.6 (CH=CH), 116.8 (CN), 120.1, 120.2, 120.4, 121.4, 122.5, 123.2, 123.3, 124.1, 124.6, 125.3, 125.7 (3C6H5), 128.3, 128.6, 130.2, 130.6 (pyridine C-4), 165.8 (CO), 168.1, 168.8 (CO=N). Analysis calc'd for C35H32ClN2O5S (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.

(13C-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, 0.01 mol) m.p. 197-199 °C. IR (KBr) νmax 3482-3329 (NH2, NH), 3056 (CH aromatic), 1688 (CO), 1654 (C=N), 1625 (C=C), 1205 (C=S). 1H NMR (DMSO-d6, 300 MHz): δ = 6.11, 6.32 (2d, 2H, CH=CH), 7.27-7.37 (m, 15H, 3C6H5), 8.35 (s, 1H, D2O exchangeable, NH). 13C NMR (DMSO-d6, 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 (3C6H5), 130.2, 130.6 thiazole C), 166.2 (CO), 168.4, 169.1 (CO=N), 180.3 (C=S). Analysis calc'd for C44H37N2O5S (663.63): C, 70.08; H, 4.12; N, 13.65; S, 5.18%. Found: C, 70.06; H, 4.18; N, 13.71; S, 5.12%. MS: m/z 663 (M+, 55%).

**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.

(13C-N'-1-(4-chlorophenyl)-3-(4-methoxyphenyl)allylidene)-2-(4-phenyl-5-thioxo-4,5-dihydrothiazolo[4,5-d]thiazol-2-yl)acetohydrazide (31b). Brown crystals from ethanol, yield 55% (3.09 g) m.p.127-129 °C. IR (KBr) νmax 3470-3322 (NH2, NH), 3054 (CH aromatic), 1686 (CO), 1655 (C=N), 1622 (C=C), 1208 (C=S). 1H NMR (DMSO-d6, 200 MHz): δ = 3.18 (s, 3H, OCH3), 6.14, 6.26 (2d, 2H, CH=CH), 7.21-7.44 (m, 13H, 3C6H5), 8.32 (s, 1H, D2O exchangeable, NH). 13C NMR (DMSO-d6, 75 MHz): δ 50.3 (OCH3), 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 (3C6H5), 130.2, 130.8 thiazole C), 166.7 (CO), 168.2, 169.4 (CO=N), 180.1 (C=S). Analysis calc'd for C35H26ClN2O5S (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%).

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180.3 (C=S). Analysis calcd for C_{10}H_{10}N_{3}O_{2}S (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-carboxyhydrazide (32b). Brown crystals from ethanol, yield 70% (3.64g) m.p. 191-192 °C. IR (KBr) \nu_{max} 3473-3322 (NH_2, NH), 3035 (CH aromatic), 1687 (CO), 1650 (C=N), 1632 (C=C), 1230 (C=S). 1H NMR (DMSO-d_6, 300 MHz): \delta = 4.90 (2s, 4H, 2NH(CH=CH)), 8.73 (s, 1H, D,O exchangeable, NH). 13C NMR (DMSO-d_6, 75 MHz): \delta = 116.8 (CN), 120.2, 120.7, 121.5, 122.4, 123.4, 124.8, 125.6, 125.9 (2C(CH_3)), 131.6, 131.8, 132.9 (thiazole C), 166.6 (CO). Analysis calcd for C_{10}H_{10}ClN_{3}O_{2}S (266.34): C, 59.77; H, 4.19; N, 21.04; S, 24.08%. Found: C, 59.48; H, 4.39; 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 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, 2NH), 3056 (CH aromatic), 1688 (CO), 1620 (C=C), 1216 (C=S). 1H NMR (DMSO-d_6, 300 MHz): \delta = 4.93, 5.21 (2s, 4H, 2NH(CH=CH)), 7.31-7.37 (m, 5H, C(CH_3)), 8.11 (s, 1H, D,O exchangeable, NH). 13C NMR (DMSO-d_6, 75 MHz): \delta = 120.2, 122.4, 123.6, 125.2, 126.5 (C(CH_3)), 130.6, 132.3 (thiazole C), 166.8 (CO). Analysis calcd for C_{10}H_{10}N_{3}O_{2}S (266.34): C, 59.77; H, 4.19; N, 21.04; S, 24.08%. Found: C, 59.48; H, 4.39; N, 20.91; S, 23.72%. MS: m/z 266 (M^+, 66%).

4-Amino-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carboxyhydrazide (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 malononitrile (0.66 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL) 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.
Uses of chalcone acetophenone to synthesize compounds with c-Met kinase activities

(2C=N). Analysis calcd for C_{25}H_{21}ClN_{4}O_{4}S_{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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