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ARTICLE

Cytotoxicity, tyrosine kinase inhibition of novel pyran, pyridine, thiophene, and imidazole derivatives

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Abstract

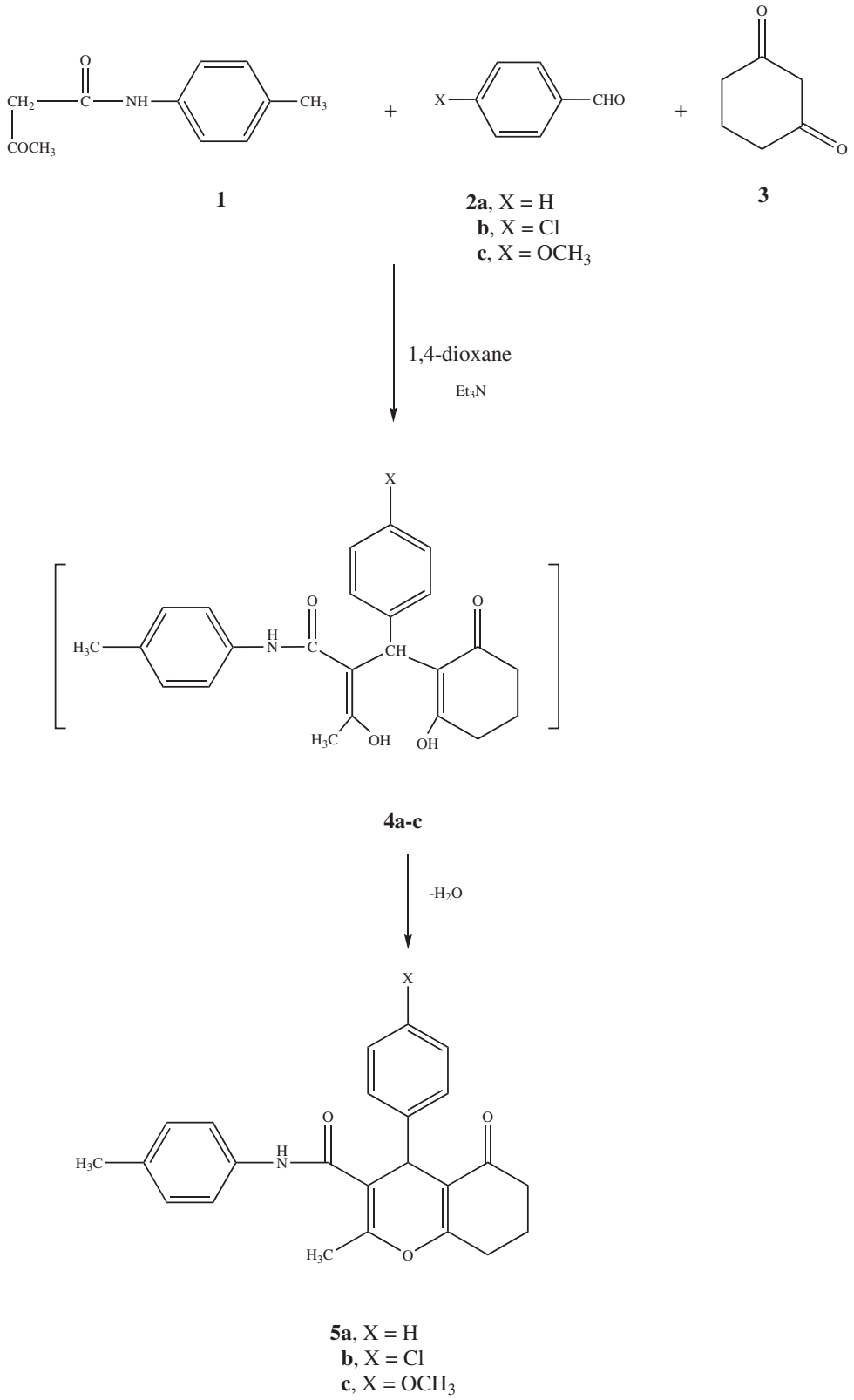
In this work, we are interested to use multicomponent reactions of cyclohexan-1,3-dione with different reagents for synthesizing new derivatives of pyran, pyridine, thiophene, and imidazole with antitumor activities. Twenty-two newly synthesized derivatives were selected and tested for their anticancer potency. Several of these compounds exhibited quite interesting potencies toward three human tumor cell lines, namely NCI-H460 (non-small cell lung cancer), SF-268 (CNS cancer), and MCF-7 (breast adenocarcinoma), especially when compared to that of reference drugs, doxorubicin and 5-Fu. Compounds **5b**, **5c**, **7b**, **9b**, **14a**, **16c**, **18a**, **19c**, **20b**, and **22b**, were found to be the most cytotoxic compounds toward the selected cell lines. On the other hand, **7b**, **14a**, **16c**, **19c**, and **22b** revealed high inhibitions toward the tyrosine kinases. Active compounds against VEGFR-2, **14a**, **16c**, and **19c,** were docked inside VEGFR-2enzyme to show the interaction between the tested compounds and the amino acids of the active site.

1 | INTRODUCTION

Recently, multicomponent reactions (MCRs) have gained a major interest due to their ability to produce final products in the same reaction vessel, resulting from different components. This has the major advantage of shortening the time, as well as the efforts, normally required for multistep synthesis.[1,2] This type of reactions has found a great application in the area of drug discovery in modern organic synthesis.[3–5] In addition, these reactions are characterized by high atom economy and high selectivity products.[6] The one-step synthesis process also allows for the production of great number of molecular structures with divers functionalities, which is the reason they are labeled environmentally friendly.[7] Furthermore, nitrogen-containing heterocyclic rings can be found in a variety of organic molecules, which make them quite valuable in organic synthesis, such as quinoxalines, which is found in applications such as anti-HIV drugs,[8] anticancer agents,[9] and anti-inflammatory drugs.[10] So far, pyrrolo[1,2-*a*]quinoxalines and its derivatives show excellent activities[11] and broad medical potency as antitumor agents,[12] adenosine A3 receptor modulator,[13] anti-HIV drugs,[8] and antiparasitic medicines.[14] These compounds are known to be quite important for building 5-HT3 receptor agonist agents.[15] Due to such great challenge, recently our research group reported several reactions of cyclic β-diketones to produce thaizoles and thiophene derivatives. The produced compounds showed high antiproliferative activities against cancer cell lines together with high inhibitions toward tyrosine kinases.[16–18] This encouraged us to make further studies through the synthesis of new heterocyclic compounds followed by studying their antiproliferative activities. Thus, the current study discusses the use of the variety of multicomponent reactions, starting with active methylene reagents, cyclohexan-1,3-dione, and aromatic aldehydes to afford either pyran or pyridine derivatives with potential antitumor activities.

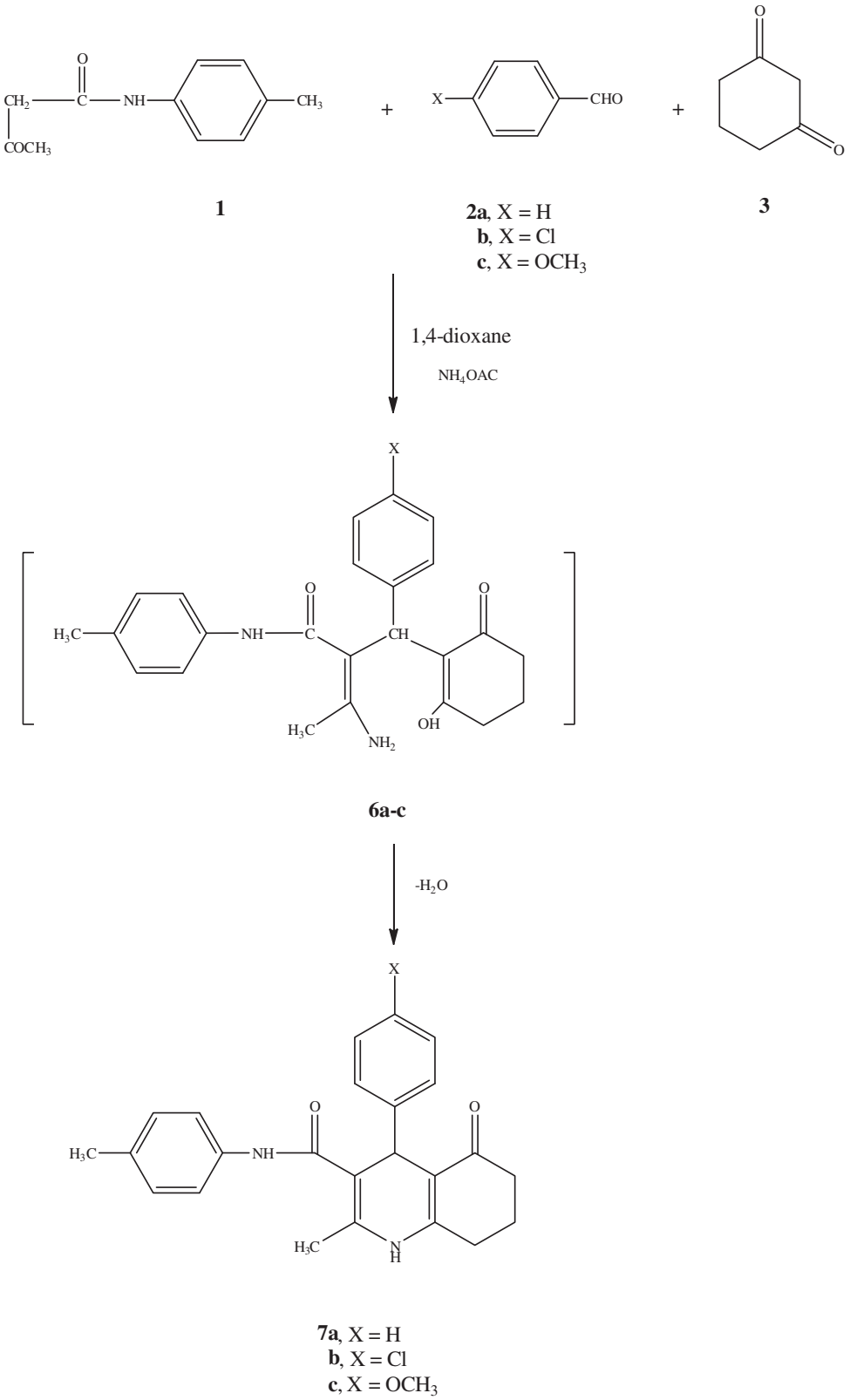
2 | RESULTS AND DISCUSSION

In this work, multicomponent reactions are utilized to produce, potentially, biologically active compounds. 4-Methylacetoacetanilide **1** was allowed to react with any of the aromatic aldehydes, **2a–c**, along with cyclohexan-1,3-dione, **3**, in a medium of ethanol and triethylamine to yield the 5,6,7,8-tetrahydro-4*H*-chromenederivatives, **5a–c** (Scheme 1). The reactions proceeded through the intermediate formation of



SCHEME 1 Synthesis of compounds, **5a–c**

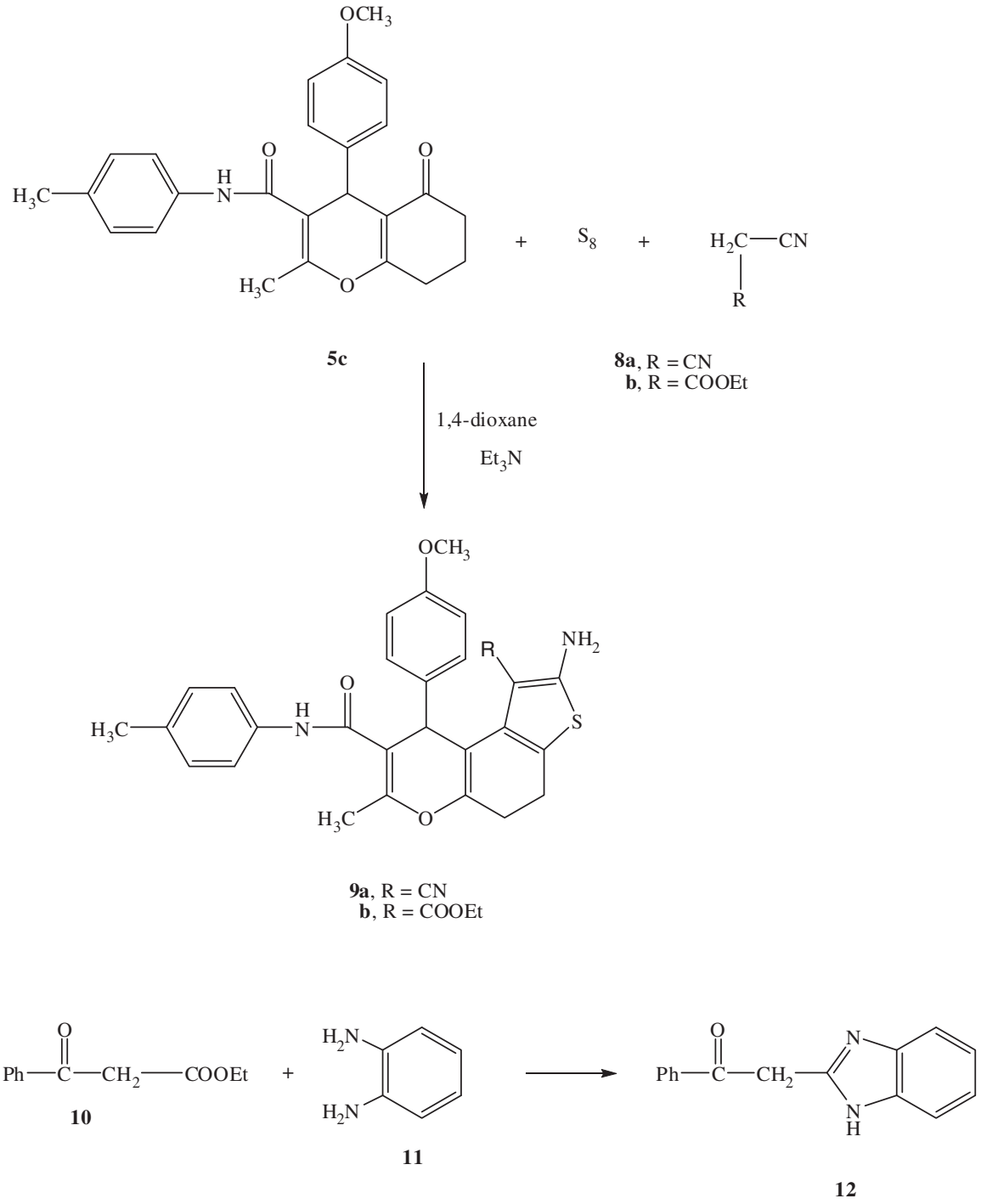
acyclic, **4a–c**. Chemical structures of compounds, **5a–c**, were confirmed using analytical and spectral data. ^{1}H NMR spectrum of compound, **5a**, for example, showed multiplet signals at δ 1.86 to 2.21 ppm corresponding to the three CH_2 groups, two singlets atδ 2.24 and 2.34 ppm corresponding to two CH_3 groups, a singlet at δ 4.50 ppm corresponding to the pyran CH, a multiplet at δ 6.83 to 7.20 ppm corresponding to the C_6H_5 and C_6H_4 groups, and a singlet at δ 9.50 ppm for the NH group. In addition, the ^{13}C NMR spectrum revealed the presence of three



SCHEME 2 Synthesis of compounds, **7a–c**

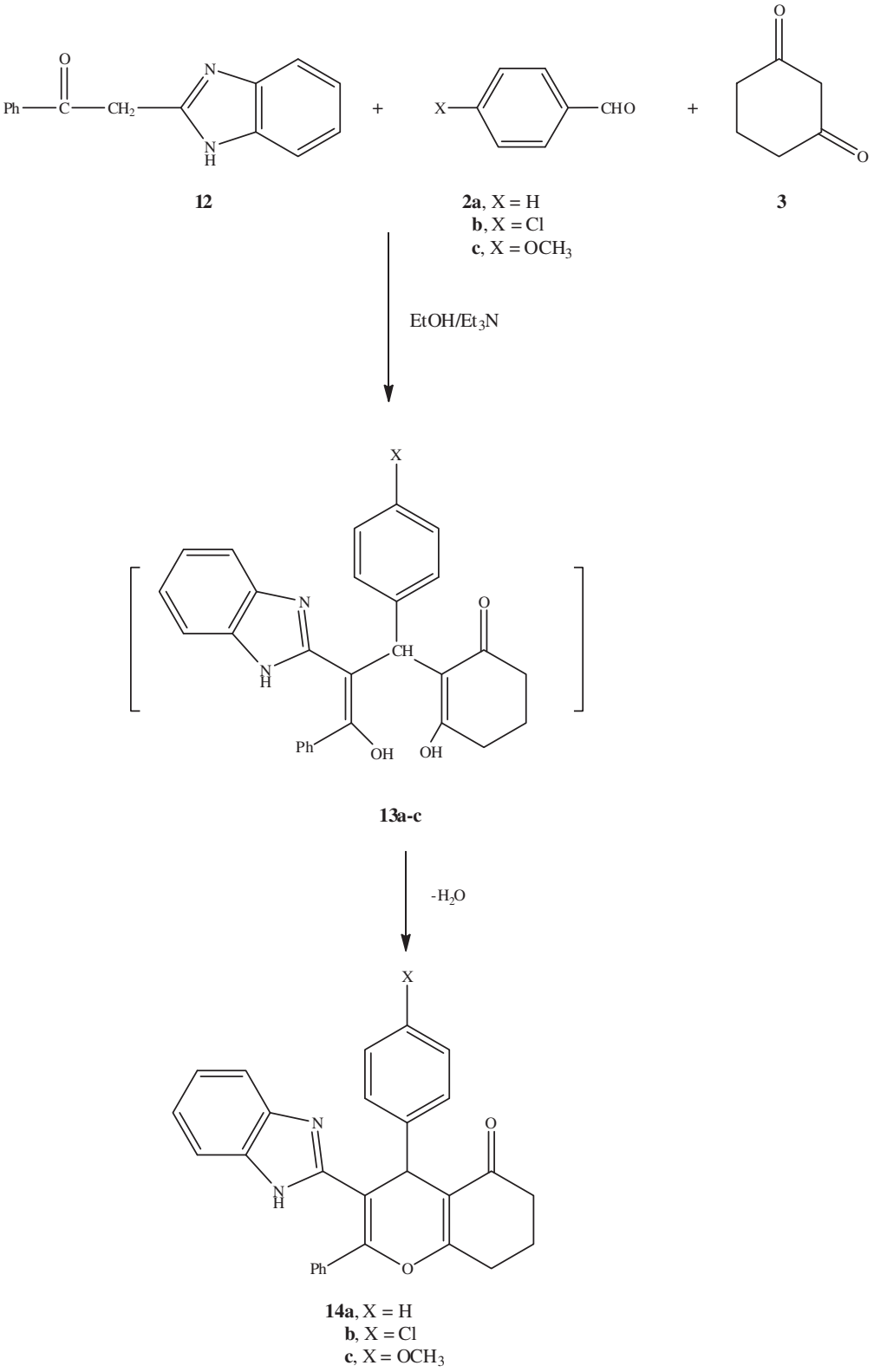
signals at 18.6, 36.9, and 39.6 ppm due to the presence of the three CH_2 groups, five signals at 48.5, 139.8, 140.3, 143.2, and 146.8 ppm indicating the presence of the pyran C, signals at 128.3, 127.0, 126.3, 125.8, 124.8, 123.2, 122.9, and 122.3 ppm for the C_6H_5 and C_6H_4, and two signals at 166.3 and 164.2 ppm for the two CO groups.

Alternatively, the reaction of 4-methylacetoacetanilide **1** with any of the aromatic aldehydes, **2a–c**, along with cyclohexan-1,3-dione, **3** in 1,4-dioxane containing ammonium acetate, yielded the 4,6,7,8-tetrahydroquinoline derivatives, **7a–c** (Scheme 2). The reactions proceeded through the intermediate formation of **6a–c**. The chemical reaction of **5c** with sulfur and either malononitrile or ethyl cyanoacetate reagents, **8a** or **8b**, afforded thieno [3,2-*f*]chromene-8-carboxamide derivatives, **9a** and **9b**, respectively (Scheme 3).



SCHEME 3 Synthesis of compounds, **9a**,**b** and **12**

β-Diketones were used to synthesize benzo[*d*]imidazole derivatives by the reaction of ethyl benzoylacetate **10** with *o*-phenylenediamine **11** at 120°C, using an oil bath to afford the 2-(1*H*-benzo[*d*]imidazol-2-yl)-1-phenylethanone **12** in a good yield. Compound **12** was used in a multicomponent reaction, involving one of the aromatic aldehydes, **2a–c**, along with cyclohexan-1,3-dione in a medium of 1,4-dioxane with triethylamine to produce the corresponding 3-(1*H*-benzo[*d*]imidazol-2-yl)-7,8-dihydro-4*H*-chromene derivatives, **14a–c** (Scheme 4). The chemical structures of **14a–c** were confirmed using both spectral and analytical data. For example, ^{1}H NMR spectrum of **14a**

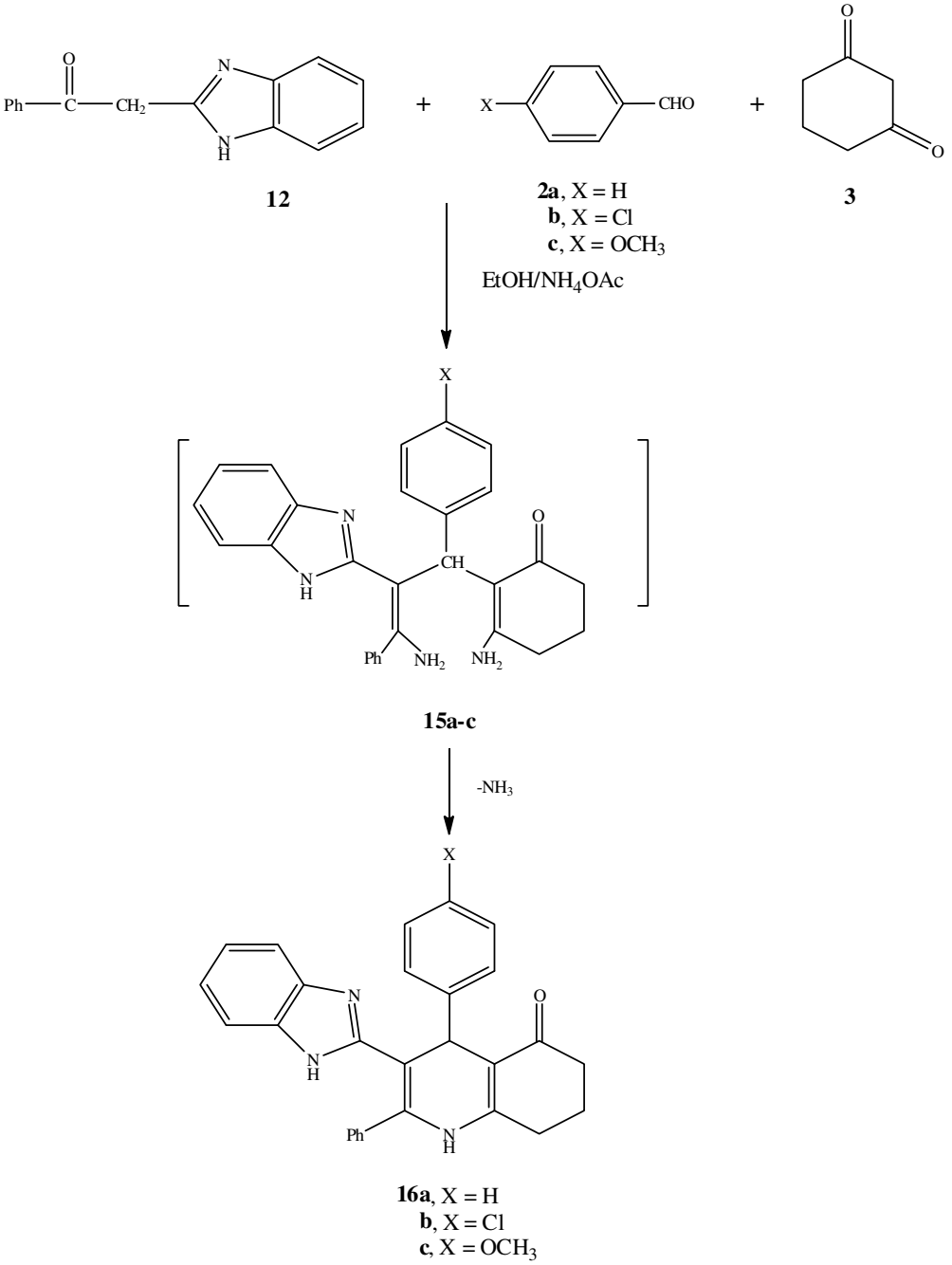


SCHEME 4 Synthesis of compounds, **14a–c**

revealed a multiplet at δ 2.24 to 2.28 ppm corresponding to the three CH_2 groups, a singlet at δ 4.58 ppm corresponding to the pyran CH group, a multiplet at δ 7.18 to 7.55 ppm corresponding to the two C_6H_5 groups, and a singlet signal at δ 10.55 ppm indicating the presence of the NH group. Moreover, the ^{13}C NMR spectrum of compound **14a** showed three signals at 18.1, 36.7, and 39.7 ppm corresponding to the three CH_2 groups, signals at 119.3, 121.5, 122.0, 122.6, 123.6, 124.1, 124.7, 125.2, 126.3, 126.8, 127.1, 128.0, 139.8, 140.2, 140.8, 142.4, 142.6, and 142.8 ppm due to the presence of two C_6H_5, C_6H_4, imidazole and pyran carbons, and two signals at 164.6 and 167.7 ppm confirming the presence of CO and CN groups, respectively.

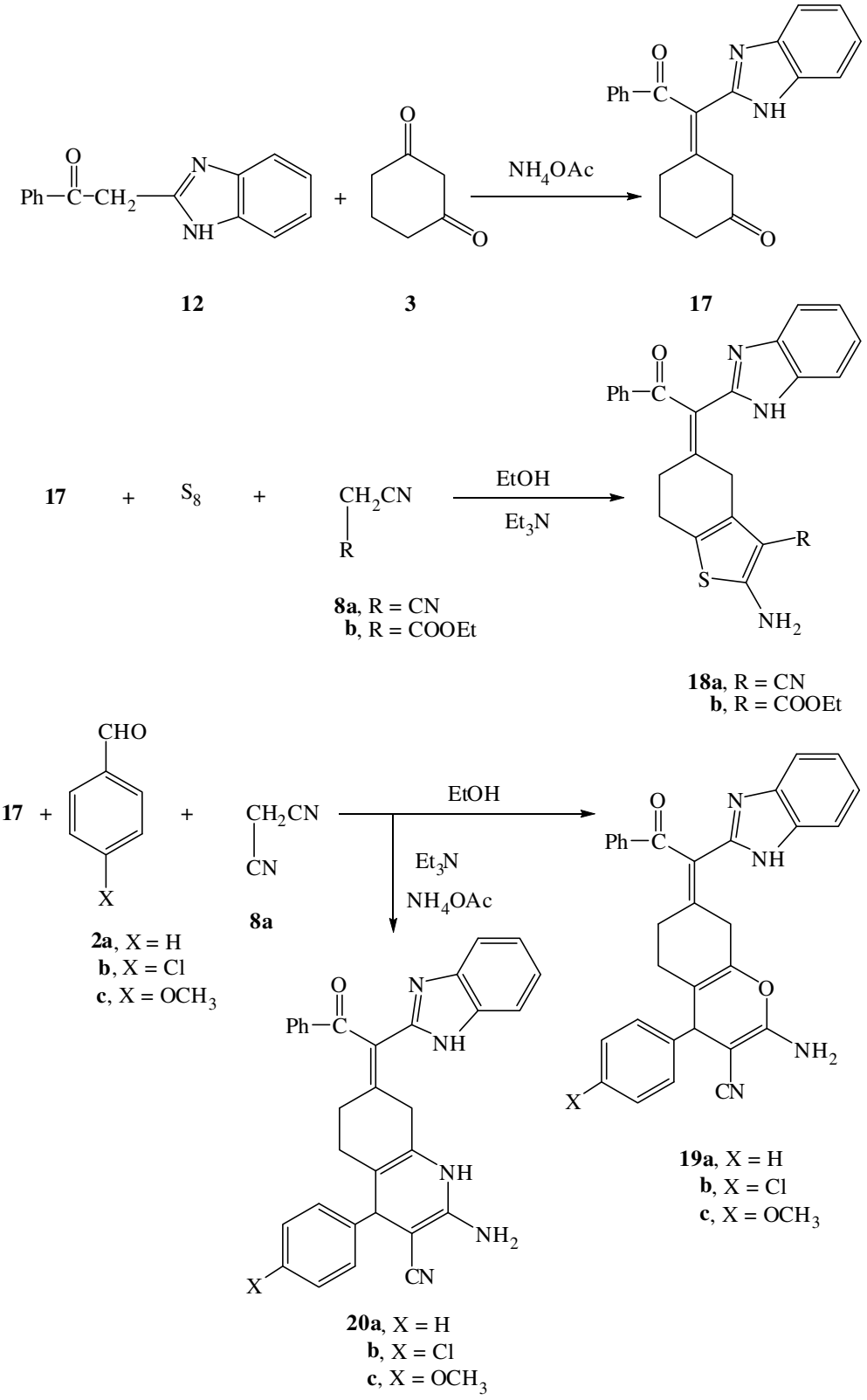
Substituting the triethylamine reagent in the reaction medium with ammonium acetate in a catalytic amount yielded the corresponding 3-(1*H*-benzo[*d*] imidazol-2-yl)-4,6,7,8-tetrahydroquinolinederivatives, **16a–c** (Scheme 5).

The Knoevenagel reaction of compound **12** with cyclohexan-1,3-dione **3** using a catalytic amount of ammonium acetate at 120°C afforded the condensate derivative **17**. Both spectral and analytical data of derivative **17** confirmed its chemical structure. Gewald's thiophene synthesis was then used to synthesize the thiophene derivatives via



SCHEME 5 Synthesis of compounds, **16a–c**

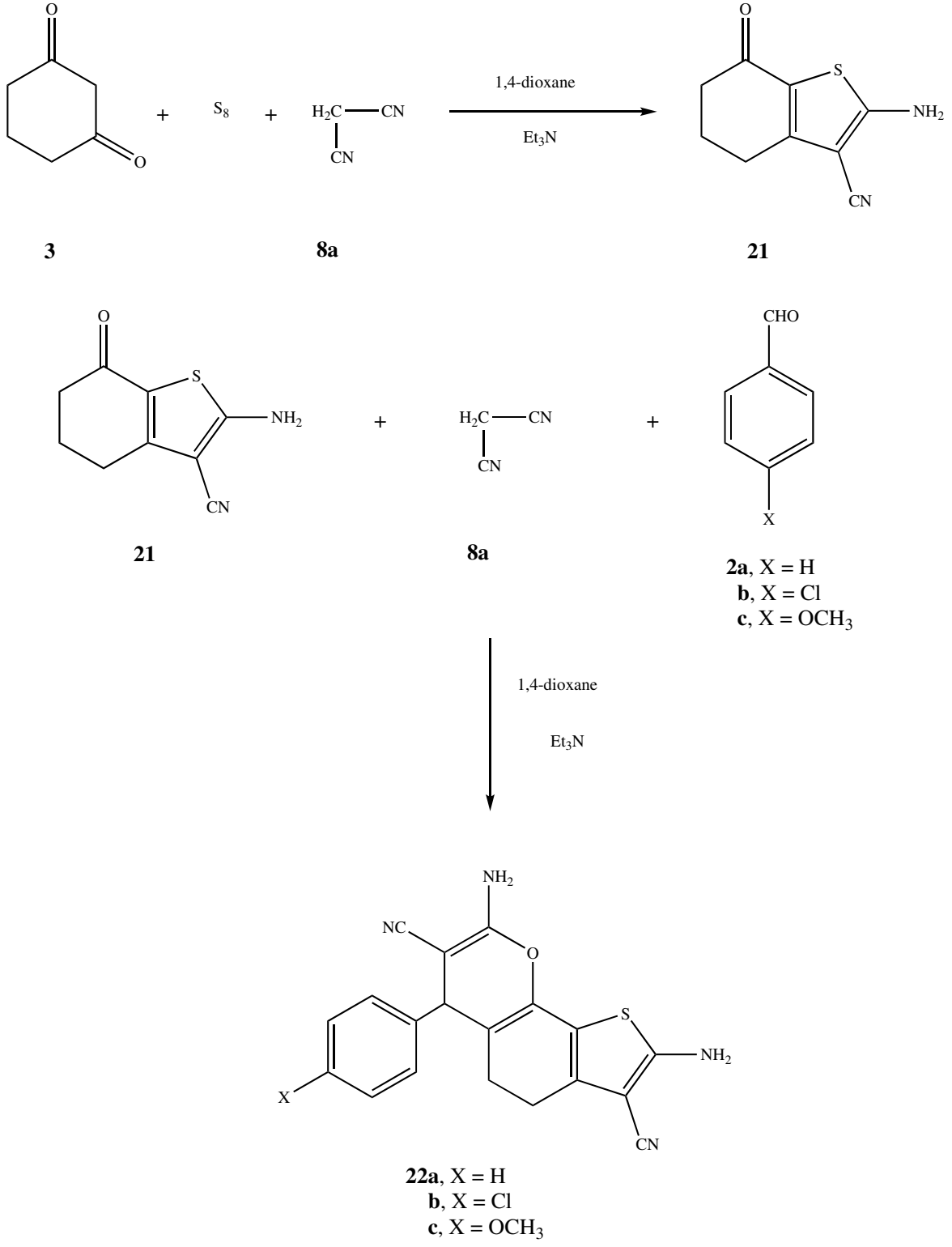
compound **17**.[19–22] Reaction of compound **17** with elemental sulfur and malononitrile **8a** or ethyl cyanoacetate **8b** produced the corresponding 4,5,6,7-tetrahydrobenzo[*b*]thiophene derivatives, **18a**,**b**. Multicomponent reactions of compound **12** with any of the aromatic aldehydes, **2a–c**, along with malononitrile **8a** in 1,4-dioxane medium containing triethylamine afforded the corresponding pyran derivatives **19a–c**. Alternatively, similar reactions were carried out to produce the 1,4,5,6,7,8-hexahydroquinoline derivatives, **20a–c**, using ammonium acetate in place of triethylamine



SCHEME 6 Synthesis of compounds, **17**; **18a**,**b**; **19a–c** and **20a–c**

(Scheme 6). The multicomponent reaction of cyclohexan-1,3-dione **3** with malononitrile **8a** and elemental sulfur produced the corresponding 2-amino-7-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile **21**.

Finally, the multicomponent reaction of 3-carbonitrile **21** with malononitrile **8a** and any of the aromatic aldehydes, **2a–c**, afforded the corresponding 2,6-dihydro-4*H*-thieno[3,2-*h*]chromene-3,7-dicarbonitrile derivatives **22a–c** (Scheme 7).



SCHEME 7 Synthesis of compounds **21** and **22a–c**

The chemical structures of derivatives **22a–c** were confirmed using spectral and analytical data (see experimental section).

2.1 | Biology section

2.1.1 | Antitumor evaluation

Three human tumor cell lines, namely NCI-H460 (non-small cell lung cancer), SF-268 (CNS cancer), and MCF-7 (breast adenocarcinoma) were used to prepare the cell cultures. NCI-H460 and SF-268 cell lines were kindly provided by the National Cancer Institute (NCI, Cairo, Egypt). The MCF-7 cell line was obtained from the European Collection of Cell Cultures (ECACC, Salisbury, UK). To evaluate the influence of DMSO solvent on the cell line growth, untreated control cells were exposed to a maximum concentration of 0.5% DMSO that was used in each assay.

2.1.2 | Tumor cell growth assay

In vitro evaluation of the antitumor activity of the synthesized compounds was carried out by following the growth of tumor cell lines according to the National Cancer Institute (NCI, USA) protocol. The anticancer drugs, doxorubicin and 5-flourouracil, were used as the positive control and subjected to the same protocol.

2.1.3 | Structure-activity relationship

Table 1 clearly shows that compounds **5b**, **5c**, **7b**, **9b**, **14a**, **16c**, **18a**, **19c**, **20b**, and **22b** were the most active compounds.

Considering compounds **5a–c**, it is clear that compounds, **5b** (X = Cl) and **5c** (X = OCH_3), were the most cytotoxic compounds among the three compounds. Such high cytotoxicity of these compounds resulted from the impact of Cl and OCH_3 groups present in these compounds, respectively. It is apparent that among all 4,6,7,8-tetrahydroquinoline derivatives, **7a-c**, compound **7b** (X = Cl) had the highest activity with GI_{50}, 0.64, 0.72, and 1.43 μmol^{-1}. For the annulated compounds, **9a** and **9b**, it is clear that compound **9b** (R = COOEt), showed higher cytotoxicity than derivative **9a** (R = CN) and its high potency was due to COOEt moiety present within the compound. However, it is apparent that derivative **14a** (X = H) had the highest cytotoxicity among all the pyran derivatives, **14a–c**, although compounds, **14b** and **14c**, with (X = Cl) and (X = OCH_3), respectively, showed low cytotoxicity. For the benzo[*b*]imidazole derivatives, **18a** and **18b**, it is obvious that **18a** (R = CN) is more cytotoxic than **18b** (R = COOEt). Multicomponent reactions of derivative **17** with any of the aromatic aldehydes, **2a–c**, along with malononitrile **8a** afforded the chromen-7(8*H*)-ylidene)-2-oxo-2-phenylethyl)-1*H*-benzo[*d*]imidazole derivatives **19a–c**. It is clear from table 1 that compound **19c** had the highest cytotoxicity among the other derivatives, possibly due to the presence of OCH_3 group. However, in the case of the pyridine derivatives, **20a–c**, it was noticed that compound **20b** (X = Cl) had the highest cytotoxicity.4,5,6,7-Tetrahydrobenzo[*b*]thiophene derivative, **21**, showed moderate inhibition against the three

TABLE 1 Influence of the newly synthesized compounds on the growth of the three human tumor cell lines

Compound	GI_{50} ($\mu molL^{-1}$) MCF-7	NCI-H460	SF-268
5a	2.64 ± 0.18	4.52 ± 1.27	6.28 ± 1.31
5b	0.23 ± 0.13	0.62 ± 0.18	0.75 ± 0.21
5c	0.69 ± 0.32	0.81 ± 0.22	0.43 ± 0.15
7a	32.31 ± 2.26	34.8 ± 0.38	30.5 ± 1.26
7b	0.64 ± 0.40	0.72 ± 0.08	1.43 ± 0.09
7c	36.32 ± 6.82	26.36 ± 6.41	22.83 ± 3.61
9a	70.5 ± 18.9	40.6 ± 12.18	50.4 ± 8.26
9b	0.06 ± 0.005	0.08 ± 0.004	0.04 ± 0.003
14a	0.08 ± 0.006	0.04 ± 0.003	0.01 ± 0.05
14b	44.13 ± 8.27	23.53 ± 4.18	6.14 ± 8.53
14c	22.28 ± 10.28	14.16 ± 4.26	12.24 ± 4.16
16a	36.26 ± 6.51	22.08 ± 8.27	0.41 ± 0.17
16b	2.09 ± 0.67	1.86 ± 0.85	1.06 ± 0.69
16c	0.26 ± 0.07	0.36 ± 0.19	0.36 ± 0.16
17	4.52 ± 1.58	3.73 ± 0.16	3.62 ± 1.52
18a	0.06 ± 0.002	0.03 ± 0.004	0.02 ± 0.01
18b	18.32 ± 2.46	14.53 ± 2.54	12.43 ± 1.72
19a	10.53 ± 2.26	4.35 ± 1.38	8.28 ± 1.48
19b	20.4 ± 2.82	36.1 ± 5.28	16.83 ± 4.58
19c	0.08 ± 0.002	0.07 ± 0.003	0.09 ± 0.002
20a	22.4 ± 1.32	22.63 ± 2.68	21.28 ± 3.69
20b	0.01 ± 0.005	0.06 ± 0.008	0.05 ± 0.006
20c	22.8 ± 2.36	14.93 ± 2.48	20.9 ± 3.68
21	8.59 ± 2.16	6.73 ± 1.58	5.93 ± 1.32
22a	16.39 ± 4.08	20.61 ± 8.25	18.22 ± 6.35
22b	0.46 ± 0.12	0.16 ± 0.02	0.84 ± 0.08
22c	31.21 ± 2.63	20.40 ± 4.53	18.42 ± 3.62
Doxorubicin	0.04 ± 0.008	0.09 ± 0.008	0.09 ± 0.007
5-Fu	0.71 ± 0.04	0.33 ± 0.06	0.28 ± 0.08

TABLE 2 Inhibitory impact of compounds **5b**, **5c**, **7b**, **9b**, **14a**, **16c**, **18a**, **19c**, **20b**, and **22b** toward tyrosine kinases [Enzyme IC_{50} (nM)]

Compound	c-Kit	Flt-3	VEGFR-2	EGFR	PDGFR
5b	4.38	6.82	5.03	6.26	8.96
5c	1.70	1.26	1.17	1.53	1.28
7b	0.48	0.25	0.61	0.32	0.26
9b	4.31	6.42	5.96	8.53	3.31
14a	0.24	0.56	0.26	0.42	0.29
16c	0.25	0.28	0.15	0.83	0.62
18a	2.26	3.28	4.62	5.38	3.26
19c	0.36	0.48	0.25	0.41	0.54
20b	1.08	1.13	1.42	2.36	1.29
22b	0.23	0.29	0.46	0.35	0.31
Sorafenib	0.19	0.20	0.31	0.28	0.39

different cancer cell lines. Similarly, compound **22b** (X = Cl) showed the highest cytotoxicity among the three derivatives **22a–c**. The study clearly shows that, in most cases, the presence of an electronegative group, such as Cl atom or OCH_3 group, resulted in high cytotoxic reactivity of the compounds. It is of great value to mention that compounds **5b**, **5c**, **7b**, **9b**, **14a**, **16c**, **18a**, **19c**, **20b**, and **22b** showed inhibitions higher than 5-Fu toward MCF-7 cell line. On the other hand, compounds **9b**, **14a**, **20b**, and **22b** revealed higher inhibitions than 5-Fu toward NCI- H460 cell line.

2.1.4 | Inhibitory impact of compounds 5b, 5c, 7b, 9b, 14a, 16c, 18a, 19c, 20b, and 22b toward tyrosine kinase enzymes

Tyrosine kinase enzyme assay protocol

Poly (Glu, Tyr) 4:1 (Sigma) 20 μg/mL was used as a substrate in 384-well plates. Then, 50 μL of 10 mMATP (Invitrogen) solution, diluted in kinase reaction buffer (50 μM HEPES, Ph 7.0, 1 M DTT, 1 M $MgCl_2$, 1 M $MnCl_2$, and 0.1% NaN_3), was added to each well. Various concentrations of the tested compounds, diluted in 10 μL of 1% DMSO (v/v), were used as the negative control. The kinase reaction was started by the addition of purified tyrosine kinase proteins diluted in 39 μL of kinase reaction buffer solution. The incubation time for the reactions was 30 minutes at 25°C and ceased by the addition of 5 μL of streptavidin-XL665 and 5 μL Tk Antibody Cryptate working solution to all of wells. The plates were read using Envision (PerkinElmer) at 320 and 615 nM. The inhibition rate (%) was calculated using the mathematical equation:

$$\%\text{inhibition} = 100 - [(\text{Activity of enzyme with tested compounds} - \text{Min})/(\text{Max} - \text{Min})] \times 100.$$

Max refers to the observed enzyme activity measured in the presence of enzyme, substrates, and cofactors; Min refers to the observed enzyme activity in the presence of substrates, cofactors, and in the absence of enzyme. IC_{50} values were calculated using the inhibition curves.

The active compounds **5b**, **5c**, **7b**, **9b**, **14a**, **16c**, **18a**, **19c**, **20b**, and **22b**, were additionally assessed as enzyme inhibitors against five tyrosine kinase enzymes (c-Kit, Flt-3, VEGFR-2, EGFR, and PDGFR), using a similar protocol (see experimental section), using Sorafenib as the positive control drug. Results of the study for the different compounds against the five tyrosine kinases are shown in Table 2.

It is apparent from Table 2 that derivatives, **7b** (X = Cl), **14a** (X = H), **16c** (X = OCH_3), **19c** (X = OCH_3), and **22b** (X = OCH_3), revealed high inhibitions toward the tyrosine kinases with IC_{50}'s 0.48, 0.24, 0.25, 0.36, and 0.23 nM, respectively. On the other hand, derivatives, **5b** and **14a**, show low inhibitions while compounds, **5c**, **18a**, and **20b**, had moderate inhibition impact.

3 | MOLECULAR DOCKING STUDY

3.1 | Molecular docking

The molecular studies were carried out using Molecular Operating Environment (MOE 2014). All the

minimizations were performed with MOE until an RMSD gradient of 0.01 K Cal/mol Å, with MMFF94X force field, and the partial charges were automatically calculated. Docking simulations were performed using the crystal structure of VEGFR-2 (PDB ID: 4ASD) that was obtained from Protein Data Bank. Enzyme structure was checked for missing atoms, bonds, and contacts. Water molecules were removed. Protonate 3D application of MOE was used to add the missing hydrogens and properly assign the ionization states. The ligand molecules were constructed using the builder molecule and were energy minimized. The active site was generated using the MOE-Alpha site finder. Ligands were docked within the active sites using the MOE-Dock, and the generated poses were energy minimized using the MMFF94x force field. Finally, the optimized poses were ranked using the GBVI/WSA DG free-energy estimates. Docking poses were visually inspected and interactions with binding pocket residues were analyzed.

Docking simulation was carried out to illustrate the binding mode and the interaction of the active compounds, **14a**, **16c**, and **19c**, with the amino acids in the active site of the VEGFR-2. Docking study was performed using the crystal structure of VEGFR-2 (PDB ID: 4ASD)[23] which has a co-crystallized ligand (sorafenib, BAX) as inhibitor inside its active site. In the beginning,

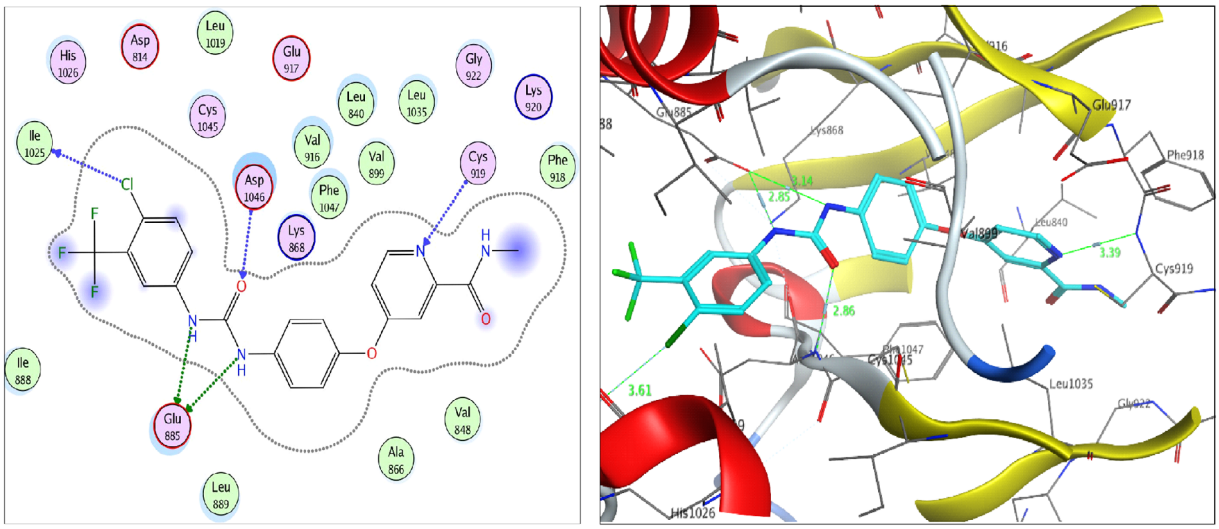


FIGURE 1 A, 2D diagram; B, 3D diagram representation of co-crystallized ligand (sorafenib BAX) showing its interaction with the VEGFR-2 receptor active site

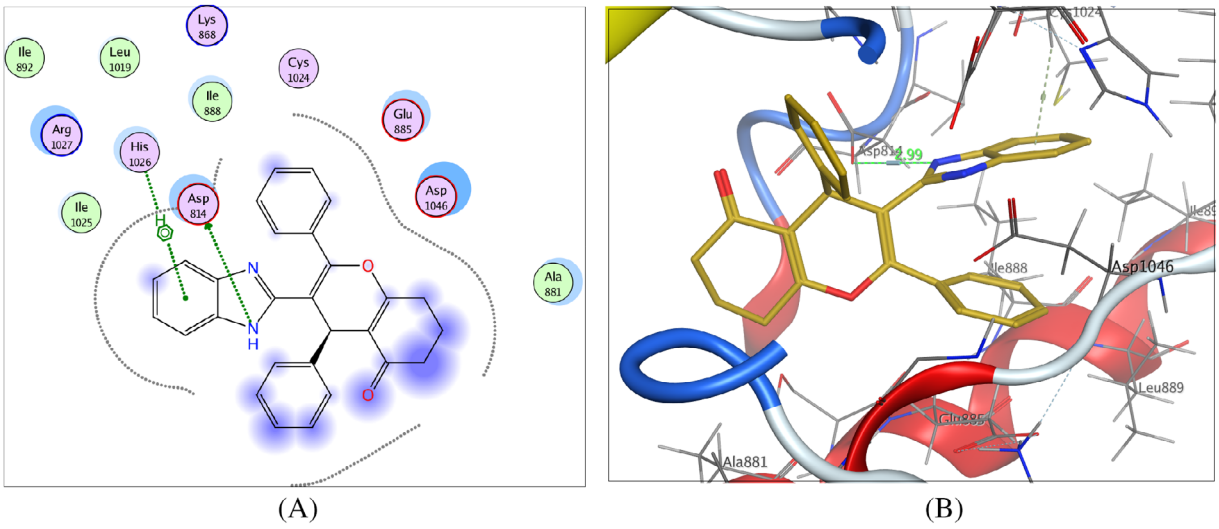


FIGURE 2 A, 2D diagram; B, 3D diagram representation of compound, **14a**, showing its interaction with the VEGFR-2 receptor active site

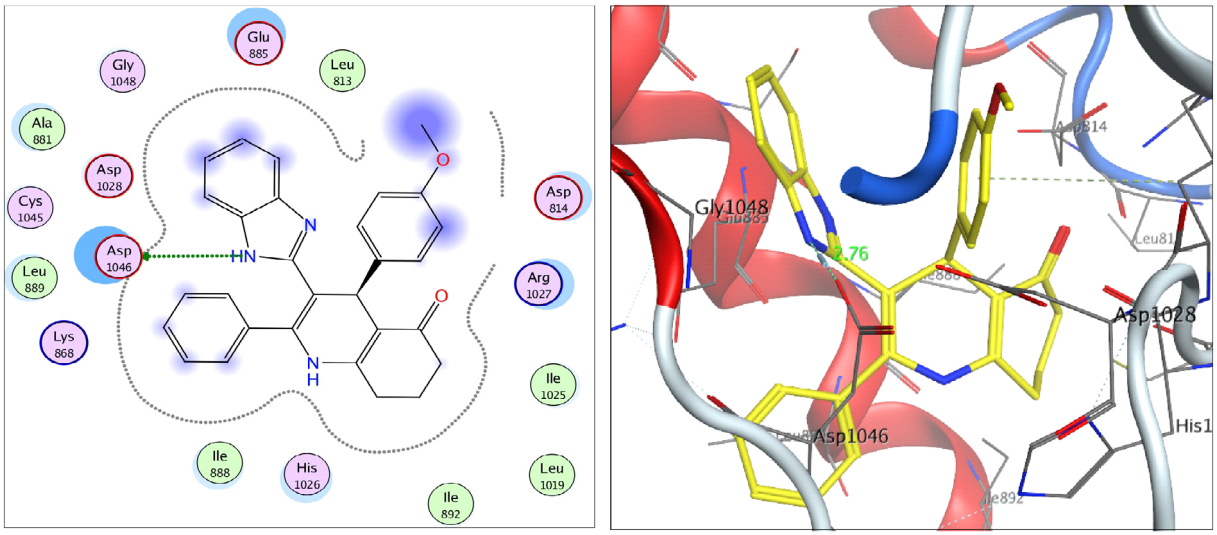


FIGURE 3 A, 2D diagram; B, 3D diagram representation of compound, **16c**, showing its interaction with the VEGFR-2 receptor active site

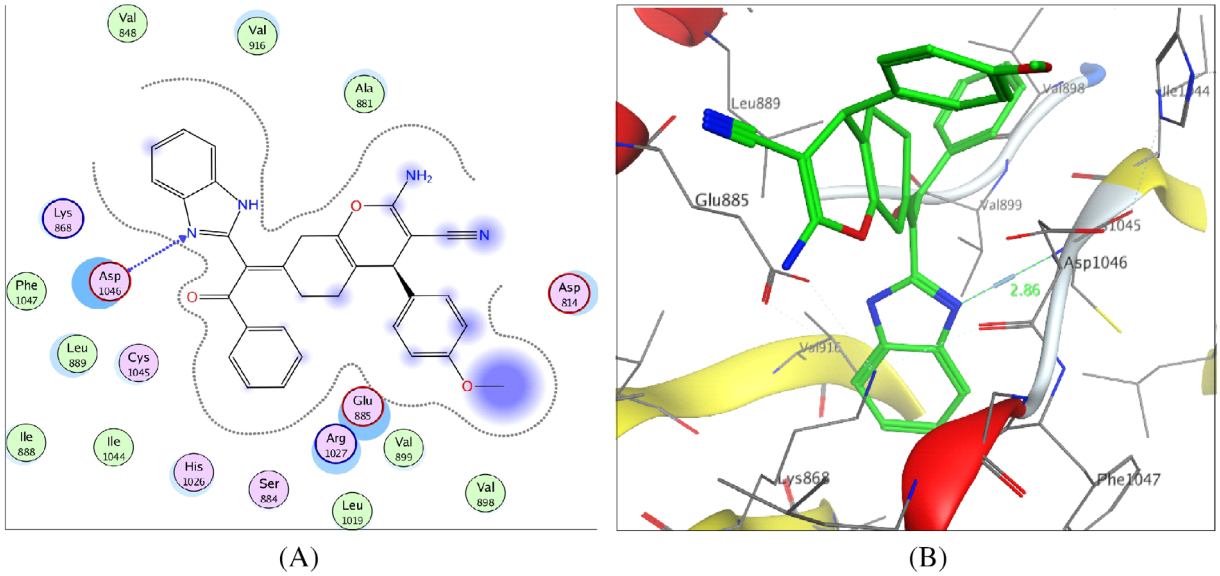


FIGURE 4 A, 2D diagram; B, 3D diagram representation of compound, **19c**, showing its interaction with the VEGFR-2 receptor active site

the docking study was validated by re-docking of the co-crystallized ligand (BAX) inside the active site of VEGFR-2. The re-docking of the co-crystallized ligand, BAX, was carried out to indicate the suitability of the used protocol for the planned docking study. The validation method was achieved by removing the bound ligand from the complex followed by its docking back into the binding site, which yielded root mean square deviation values RMSD of 0.88 Å with energy score (S) -9.94 kcal/mol. The top pose obtained from the MOE docking simulation showed the interactions of the co-crystallized ligand, BAX, with the key amino acids inside the active site (Ile1025, Asp1046, Cys919, and Glu885), Figure 1.

It was clear from the docking study that the three compounds revealed a binding pattern involving the benzoimidazole moiety. The docking results showed that compound, **14a**, has binding energy of −5.64 kcal/mol and exhibited only one hydrogen-bond donor, which is formed between the NH of benzoimidazole ring, and the CO group of Asp814 amino acid with a bond length of 2.99 Å, as shown in Figure 2. Concerning the docking study of compounds, **16c** and **19c**, it showed that these

compounds can fit into VEGFR-2 pocket with one hydrogen bond, with Asp1046, similar to that of the co-crystallized ligand BAX, with bond lengths of 2.76 and 2.86 Å, respectively, shown in Figures 3 and 4. In case of compound, **16c**, the hydrogen-bond donor was between the NH of the benzoimidazole ring and oxygen of Asp1046 amino acid while the hydrogen-bond acceptor in the case of compound, **19c**, was between the N of benzoimidazole ring with NH of Asp1046 amino acid. The binding energy of compounds, **16c** and **19c**, scored −5.79 and−4.39 kcal/mol, respectively.

According to the above-mentioned data, the presence of benzoimidazole moiety has played an important role to bind with amino acids inside the pocket, which has provided a major explanation for the inhibition effect of compounds **14a**, **16c**, and **19c** toward VEGFR-2 enzyme.

4 | CONCLUSIONS

In conclusion, a new series of pyran and thiophene derivatives were developed. The obtained compounds demonstrated greater activity against human tumor cell lines such as SF-268 NCI-H460 and MCF-7 cell lines. The results indicated that derivatives **5b**, **5c**, **7b**, **9b**, **14a**, **16c**, **18a**, **19c**, **20b**, **and 22b**, had the highest activity and were tested for possible enzyme inhibition impact against tyrosine kinase enzymes (c-Kit, Flt-3, VEGFR-2, EGFR, and PDGFR). Compounds **7b**, **14a**, **16c**, **19c**, and **22b** showed the highest inhibition values. Docking simulation of the most potent compounds **14a**, **16c**, and **19c**, against the VEGFR-2 enzyme showed interactions with the Asp1046 and Asp814 amino acids inside the binding pockets of VEGFR-2 enzyme, which explains their inhibition effect.

5 | EXPERIMENTAL

5.1 | Chemistry

The obtained compounds showed their melting points using Electrothermal digital melting point apparatus and are uncorrected. IR spectra (KBr discs) were measured on a FTIR plus 460 or Pye Unicam SP-1000 spectrophotometer (Pye Unicam, UK, Cambridge). ^{1}H NMR spectra were obtained from Varian Gemini-300 (300 MHz, Varian UK) using DMSO-d_6 as a solvent and Tetraethylsilane (TMS) as an internal standard. Chemical shifts are expressed as δ ppm. The mass spectra were measured with Hewlett Packard 5988 A GC/MS system (Hewlett Packard, Agilent, USA) instrument.

Chemicals used for the screening processes were purchased from international companies. RPMI-1640 medium was purchased from Cambrex, New Jersey, USA. L-Glutamine and fetal bovine serum (FBS) were purchased from Gibco Invitrogen Co. (Scotland, UK). Doxorubicin, dimethyl sulfoxide (DMSO), streptomycin, sulforhodamine B (SRB), and penicillin were supplied from Sigma Chemicals, Saint Louis, USA.

5.1.1 | General procedure for the synthesis of chromene derivatives, 5a–c

Either benzaldehyde (1.08 g, 0.01 mol), *p*-chlorobenzaldehyde (1.40 g, 0.01 mol) or *p*-methoxybenzaldehyde (1.36 g, 0.01 mol) and cyclohexan-1,3-dione (1.12 g, 0.01 mol) were added to a solution of 3-oxo-*N*-(*p*-toyl)butanamide (1.91 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (1.0 mL). The reaction mixture was heated under reflux for 3 hours then poured onto ice/water mixture, and the participated product was collected by filtration.

2-Methyl-5-oxo-4-phenyl-N-(p-tolyl)-5,6,7,8-tetrahydro-4H-chromene-3-carboxamide (**5a**). Pale yellow, yield 80%, Mp 179-186°C. IR (KBr) ν max (cm^{-1}): 3480-3316 (NH), 3030 (CH-aromatic), 2953 (CH-aliphatic), 1720 (CO), 1606 (HNCO), 1530 (CC). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.86-2.21 (m, 6H, 3CH_2), 2.34, 2.68 (2s, 6H, 2CH_3), 4.50 (s, 1H, CH- pyran), 6.83-7.20 (m, 9H, C_6H_5, C_6H_4), 9.50 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.8, 18.6, 21.3, 36.9, 39.6 (3CH_2, 2CH_3), 48.5, 139.8, 140.3, 143.2, 146.8 (pyran C),128.3, 127.0, 126.3, 124.8, 124.8, 123.2, 122.9, 122.3 (C_6H_5, C_6H_4), 166.3, 164.2 (2CO). EIMS: m/z 373[M]$^+$(26%); Anal. for $C_{24}H_{23}NO_3$ (373.44): Calcd: C, 77.19; H, 6.21; N, 3.75%. Found: C, 77.28; H, 6.10; N, 3.50%.

4-(4-Chlorophenyl)-2-methyl-5-oxo-4-phenyl-N-(p-tolyl)-5,6,7,8-tetrahydro-4H-chromene-3-carboxamide (**5b**). Light brown, Mp 171-178°C, yield 72%. IR (KBr) ν max (cm^{-1}): 3477-3306 (NH), 3050 (CH-aromatic), 2938 (CH-aliphatic),1664 (CO),1607 (HNCO), 1529 (CC). ^{1}H NMR (DMSO-d_6, 300 MHz): δ1.89-2.26 (m, 6H, 3CH_2), 2.21, 2.32 (2s, 6H, 2CH_3), 4.55 (s, 1H, CH- pyran), 7.11-7.31 (m, 8H, 2C_6H_4), 10.18 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 17.2, 18.9, 21.0, 36.7, 39.8 (3CH_2,2CH_3), 49.1139.5, 140.2, 143.8, 146.4 (pyran C), 122.0, 122.2, 123.6, 124.4, 125.9, 125.8, 127.2, 128.3 (C_6H_5, C_6H_4), 164.1, 166.7 (2CO). EIMS: m/z 407[M]$^+$(23%); Anal. for $C_{24}H_{22}ClNO_3$ (407.89): Calcd: C, 70.67; H, 5.44; N, 3.43%. Found: C, 70.55; H, 5.38; N, 3.32%.

4-(4-Methoxyphenyl)-2-methyl-5-oxo-4-phenyl-N-(p-tolyl)-5,6,7,8-tetrahydro-4H-chromene-3-carboxamide (**5c**). Pale yellow, Mp 99-104°C, yield 65%. IR (KBr) ν max (cm^{-1}): 3417(NH), 3030 (CH-aromatic), 2947 (CH-aliphatic),1658 (CO),1611 (HNCO), 1510 (CC). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.20-2.48 (m, 6H, 2CH_2), 2.49, 2.63 (2s, 6H, 2CH_3), 3.69 (s, 3H, OCH_3), 4.55 (s, 1H, CH-

pyran), 6.74-7.09 (m, 8H, $2C_6H_4$), 10.00 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 17.4, 18.7, 20.3, 36.5, 39.8 ($3CH_2$,$2CH_3$), 52.6 (OCH_3), 50.2, 139.3, 140.4, 143.5, 146.8 (pyran C),122.0, 122.6, 123.2, 124.4, 125.1, 125.2, 126.4, 149.9 ($2C_6H_4$), 164.1, 166.7 (2CO). Anal. For $C_{25}H_{25}NO_4$ (403.47): Calcd: C, 74.42; H, 6.25; N, 3.47%. Found: C, 74.30; H, 6.30; N, 3.20%.

5.1.2 | General procedure for the synthesis of hexahdroquinoline derivatives 7a–c

Either benzaldehyde (1.08 g, 0.01 mol), *p*-chlorobenzaldehyde (1.40 g, 0.01 mol) or *p*-methoxybenzaldehyde (1.36, 0.01 mol) and cyclohexan-1,3dione (1.12 g, 0.01 mol) were added to a solution of 3-oxo-*N*-(*p*-toyl)butanamide (1.91 g, 0.01 mol) in 1,4-dioxane (40 mL) containing ammonium acetate (1.5 g, 0.01 mol). The reaction mixture was heated under reflux for 5 hours then poured onto ice/water mixture, and the participated product was collected by filtration.

2-Methyl-5-oxo-4-phenyl-N-(p-tolyl)-1,4,5,6,7,8-hexahdroquinoline-3-carboxamide (**7a**). Pale yellow, yield 67%, Mp 145-148°C. IR (KBr) ν max (cm^{-1}): 3488-3361 (NH), 3060 (CH-aromatic), 2940 (CH-aliphatic), 1688 (CO), 1492 (CC).^{1}H NMR (DMSO-d_6, 300 MHz): δ2.03-2.22 (m, 6H, $3CH_2$), 2.48, 2.50 (2s, 6H, $2CH_3$), 4.97 (s, 1H, CH-pyridine), 7.02-7.43 (m, 9H, C_6H_5, C_6H_4), 8.72, 9.41 (2s, 2H, 2NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ17.9, 18.4, 21.8, 36.6, 38.2 ($3CH_2$,$2CH_3$),46.5, 139.5, 139.8, 141.6, 144.3 (pyridine C),120.7, 122.3, 123.7, 124.4, 124.9, 126.1, 127.5, 128.1 (C_6H_5, C_6H_4), 166.8, 164.3(2CO). EIMS: m/z 372 $[M]^+$(35%); Anal. For $C_{24}H_{24}N_2O_2$ (372.46): Calcd: C, 77.39; H, 6.49; N, 7.52%. Found: C, 77.25; H, 6.34; N, 7.60%.

4-(4-Chlorophenyl)-2-methyl-5-oxo-4-phenyl-N-(p-tolyl)-1,4,5,6,7,8-hexahdroquinoline-3-carboxamide (**7b**). Pale yellow, yield 70%, Mp 90-92°C. IR (KBr) ν max (cm^{-1}): 3468-3351 (NH), 3067 (CH-aromatic), 2943 (CH-aliphatic), 1605 (CO), 1489 (CC). ^{1}HNMR (DMSO-d_6, 300 MHz): δ2.03-2.21 (m, 6H, $3CH_2$), 2.48, 2.49 (2s, 6H, $2CH_3$), 4.69 (s, 1H, CH- pyridine), 7.02-7.43 (m, 8H, $2C_6H_4$), 8.78 (s, 1H, NH), 9.46 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ18.0, 18.5, 21.0, 36.8, 38.1 ($3CH_2$, $2CH_3$), 44.9, 138.8, 139.6, 142.5, 143.8 (pyridine C), 121.3, 121.9, 122.3, 124.9, 125.6, 126.2, 127.7, 128.1 (C_6H_5, C_6H_4), 164.4, 166.9 (2CO). EIMS: m/z 406 $[M]^+$ (35%); Anal. for $C_{24}H_{23}ClN_2O_2$ (406.90): Calcd: C, 70.84; H, 5.70; N, 6.88%. Found: C, 70.80; H, 5.75; N, 6.82%.

4-(4-Methoxyphenyl)-2-methyl-5-oxo-4-phenyl-N-(p-tolyl)-1,4,5,6,7,8-hexahdroquinoline-3-carboxamide (**7c**). Pale yellow, yield 71%. Mp 128-130°C. IR (KBr) ν max (cm^{-1}): 3492-3386 (NH), 3067 (CH-aromatic), 2940 (CH-aliphatic), 1604 (CO),1506 (CC).^{1}H NMR (DMSO-d_6, 300 MHz): δ2.03-2.21 (m, 6H, $3CH_2$), 2.48, (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 4.91 (s, 1H, CH-pyridine), 6.72-7.44 (m, 8H, $2C_6H_4$), 8.68 (s, 1H, NH), 9.37 (s, 1H NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.3, 18.4, 21.6, 36.7, 39.8 ($3CH_2$, $2CH_3$), 52.4 (OCH_3), 45.3, 138.5, 139.4, 141.8, 143.6 (pyridine C), 121.5, 122.8, 123.9, 124.2, 125.9, 126.4, 127.1, 147.8 ($2C_6H_4$), 164.3, 166.5 (2CO). Anal. for $C_{25}H_{26}N_2O_3$ (402.49): Calcd: C, 74.60; H, 6.51; N, 6.96%. Found: C, 74.40; H, 6.59; N, 6.77%.

5.1.3 | General procedure for the synthesis of thieno[3,2-*f*]chromene derivatives, 9a,b

Equimolar amounts of compound, **5c** (4.03 g, 0.01 mol), and each of sulfur (0.32 g, 0.01 mol) and either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 g, 0.01 mol) and were dissolved in 1,4-dioxane (50 mL) containing triethylamine (1.0 mL) was heated under reflux for 2 hours. The reaction mixture was left to cool and then poured onto an ice/water mixture, containing a few drops of hydrochloric acid, and the participated product was collected by filtration.

2-Amino-1-cyano-9-(4-methoxyphenyl)-7-methyl-N-(p-tolyl)-5,9-dihydro-4H-thieno[3,2-f]chromene-8-carboxamide (**9a**). Brown crystals, yield: 69%, Mp 134-138°C. IR (KBr) ν max (cm^{-1}): 3420, 3324 (NH, NH_2), 3030 (CH-aromatic), 2946 (CH-aliphatic), 2205 (CN), 1656 (CO), 1509 (CC). ^{1}HNMR (DMSO-d_6, 300 MHz): δ1.91-2.2 (m, 4H, $2CH_2$), 2.25 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.52 (s, 1H, CH- pyran), 4.82 (s, 2H, NH_2), 6.74-7.20 (m, 8H, $2C_6H_4$), 9.50 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ17.6, 18.3, 21.5, 36.7 ($2CH_2$, $2CH_3$), 50.0, 138.1, 139.7, 141.3, 143.3 (pyran C),118.2, 119.5, 120.1, 121.8, 122.9, 124.0, 124.3, 125.2, 126.5, 127.7, 135.0, 136.4 (thiophene and two C_6H_4), 116.5 (CN), 162.5 (CO). Anal. for $C_{28}H_{25}N_3O_3S$ (483.58): Calcd: C, 69.54; H, 5.21; N, 8.69%. Found: C, 69.43; H, 5.15; N, 8.78%.

Ethyl 2-amino-9-(4-methoxyphenyl)-7-methyl-8-(p-tolylcarbomoyl)-5,9-dihydro-4H-thieno[3,2-f]chromene-1-carboxylate (**9b**). Pale yellow, yield 70%, Mp 139-144°C. IR (KBr) ν max (cm^{-1}): 3427-3320 (NH, NH_2), 2945 (CH aromatic), 2838 (CH-aliphatic), 1710, 1657 (2CO), 1509 (CC). (DMSO-d_6, 300 MHz): δ 1.12 (t, 3H, $J = 7.5$ Hz, CH_3), 1.30-1.96 (m, 4H, $2CH_2$), 2.17 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.25 (q, 2H, $J = 7.5$ Hz, CH_2), 4.85 (s, 2H, NH_2), 4.52 (s, 1H, pyran CH), 6.74-7.20 (m, 8H, $2C_6H_4$), 9.50 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.2 ($OCH_2\underline{CH_3}$), 18.0, 18.3, 21.9, 36.7 ($2CH_2$,$2CH_3$), 50.6 ($O\underline{CH_2}CH_3$), 52.1(OCH_3), 50.4, 138.5, 139.4, 141.8, 143.6 (pyran C),118.6, 119.9, 120.2, 121.5, 122.6, 123.7, 124.3, 125.8, 126.0, 127.3,

135.4, 136.8 (thiophene and two C_6H_4), 164.3, 166.9 (2CO). Anal. for $C_{30}H_{30}N_2O_5S$ (530.63): Calcd: C, 67.90; H, 5.70; N, 5.28%. Found: C, 67.69; H, 5.54; N, 5.43%.

5.1.4 | Synthesis of 2-(1*H*-benzo[*d*] imidazol-2-yl)-1-phenylethanone (12)

A dry mixture of equimolar amounts of ethyl benzoylacetate (1.92 g, 0.01 mol) and o-phenylenediamine (1.09 g, 0.01 mol) was heated at 120°C in an oil bath for 10 minutes, and then the reaction mixture was left to cool. The formed solid product was triturated with diethylether, and then collected by filtration.

Pale yellow crystals, yield 72% (1.69 g), Mp 180-183°C. IR (KBr) ν max (cm^{-1}): 3437 (NH), 3053 (CH aromatic), 2974 (CH-aliphatic), 1680 (CO), 1515 (CC). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.50 (s, 2H, CH_2), 7.20-7.55 (m, 9H, C_6H_5, C_6H_4), 10.45 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 49.8 (CH_2), 118.2, 123.8, 124.9, 125.0, 126.0, 127.3, 128.3, 129.6, 130.2, 139.2, 140.3 (two benzene, indole C), 164.8 (CO), 167.2 (CN). EIMS: m/z 236 $[M]^+$ (90). Analysis for $C_{15}H_{12}N_2O$ (236.27): Calcd: C, 76.25; H, 5.12; N, 11.86%. Found: C, 76.39; H, 4.82; N, 11.66%.

5.1.5 | General procedure for the synthesis of 7,8-dihydro-4*H*-chromen-5 (6*H*)-one derivatives 14a–c

Each of either benzaldehyde (1.08 g, 0.01 mol), *p*-chlorobenzaldehyde (1.40 g, 0.01 mol) or *p*-methoxybenzaldehyde (1.36 g, 0.01 mol), and cyclohexan-1,3-dione (1.12 g, 0.01 mol) were added to a solution of compound, **12** (2.36 g, 0.01 mol), in 1,4-dioxane (40 mL) containing triethylamine (1.0 mL). The reaction mixture was heated under reflux for 3 hours and then poured onto an ice/water mixture, and the participated product was collected by filtration.

3-(1H-Benzo[d]imidazol-2-yl)-2,4-diphenyl-7,8-dihydro-4H-chromen-5(6H)-one (**14a**). Pale yellow, yield: 66%, Mp 192-196°C. IR (KBr) ν max (cm^{-1}): 3492 (NH), 3056 (CH-aromatic), 2962 (CH-aliphatic), 1661 (CO),1603 (CC).^{1}H-NMR (DMSO-d_6, 300 MHz): δ 2.24-2.28 (m, 6H, $3CH_2$), 4.58 (s, 1H, CH-pyran),7.18-7.55 (m, 14H, $2C_6H_5$, C_6H_4), 10.55 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.1, 36.7, 39.7 ($3CH_2$), 52.4, 119.3, 121.5, 122.0, 122.6, 123.6, 124.1, 124.7, 125.2, 126.3, 126.8, 127.1, 128.0, 139.8, 140.2, 140.8, 142.4, 142.6, 142.8 ($2C_6H_5$, C_6H_4, imidazole, pyran C), 164.6 (CO), 167.7 (CN). EIMS: m/z 418 $[M]^+$ (68). Anal. for $C_{28}H_{22}N_2O_2$ (418.49): Calcd: C, 80.36; H, 5.30; N, 6.69%. Found: C, 80.28; H, 5.19; N, 6.88%.

3-(1H-Benzo[d]imidazol-2-yl)-4-(4-chlorophenyl)-2-phenyl-7,8-dihydro-4H-chromen-5(6H)-one (**14b**). Pale yellow, yield: 75%, Mp 156-159°C. IR (KBr) ν max (cm^{-1}): 3423 (NH), 3087, 3054 (CH-aromatic), 2932 (CH-aliphatic), 1666 (CO), 1517 (CC). ^{1}H NMR (DMSO-d_6, 300 MHz): δ2.24-2.50 (m, 6H, $3CH_2$), 4.55 (s, 1H, CH-pyran), 7.18-7.54 (m, 13H, $2C_6H_4$, C_6H_5), 10.00 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.3, 36.4, 39.9 ($3CH_2$), 51.5, 120.7, 121.8, 122.5, 122.8, 123.9, 124.3, 124.5, 125.0, 126.8, 126.9, 127.6, 128.3, 139.5, 140.6, 141.3, 141.8, 143.6, 143.8 (C_6H_5, $2C_6H_4$, imidazole, pyran C), 164.9 (CO), 167.8 (CN). EIMS: m/z 452 $[M]^+$ (48). Anal. for $C_{28}H_{21}ClN_2O_2$ (452.93): Calcd: C, 74.25; H, 4.67; N, 6.18%. Found: C, 74.05; H, 6.87; N, 6.30%.

3-(1H-Benzo[d]imidazol-2-yl)-4-(4-methoxyphenyl)-2-phenyl-7,8-dihydro-4H-chromen-5(6H)-one (**14c**). Pale yellow, yield: 72%, Mp 144-148°C. IR (KBr) ν max (cm^{-1}): 3434 (NH), 3087, 3054 (CH-aromatic), 2932 (CH-aliphatic), 1680 (CO), 1517 (CC). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.22-2.53 (m, 6H, $3CH_2$), 3.65 (s, 3H, OCH_3), 4.58 (s, 1H, CH-pyran), 7.23-7.56 (m, 13H, $2C_6H_4$, C_6H_5), 10.13 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.5, 36.6, 39.9 ($3CH_2$), 52.6 (OCH_3), 52.5, 120.3, 121.2, 122.9, 123.3, 123.9, 124.3, 124.5, 125.6, 126.8, 126.5, 127.9, 128.1, 139.1, 140.2, 141.3, 142.0, 142.8, 143.8 (C_6H_5, $2C_6H_4$, imidazole, pyran C), 164.8 (CO), 167.3 (CN). EIMS: m/z 448 $[M]^+$ (40). Anal. for $C_{29}H_{24}N_2O_3$ (448.51): Calcd: C, 77.66; H, 5.39; N, 6.25%. Found: C, 77.41; H, 5.44; N, 651%.

5.1.6 | General procedure for synthesis of 4,6,7,8-tetrahydroquinolin-5(1*H*)-one derivatives, 16a–c

Each of either benzaldehyde **(**1.08 g, 0.01 mol), *p*-chlorobenzaldehyde (1.40 g, 0.01 mol) or *p*-methoxybenzaldehyde (1.36 g, 0.01 mol), and cyclohexan-1,3-dione (1.12 g, 0.01 mol) were added to a solution of compound, **12** (2.36 g, 0.01 mol), in 1,4-dioxane (40 mL) containing ammonium acetate (1.50 g, 0.02 mol). The reaction mixture was heated under reflux for 3 hours and then poured onto an ice/water mixture, and the participated product was collected by filtration.

3-(1H-Benzo[d]imidazol-2-yl)-2,4-diphenyl-4,6,7,8-tetrahydroquinolin-5(1H)-one (**16a**). Pale yellow, yield: 74%, Mp 185-187°C. IR (KBr) ν max (cm^{-1}): 3387-3328 (2NH), 3056 (CH-aromatic), 2960 (CH-aliphatic), 1661 (CO), 1603 (CC). ^{1}H-NMR (DMSO-d_6, 300 MHz): δ2.22-2.29 (m, 6H, $3CH_2$), 4.56 (s, 1H, CH-pyridine), 7.23-7.58 (m, 14H, $2C_6H_5$, C_6H_4), 9.25, 10.43 (2s, 2H, 2NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.4, 36.8, 39.7 ($3CH_2$), 48.2, 120.6, 121.8, 122.4, 122.2, 122.8, 124.3, 124.5, 125.2, 126.7, 126.8, 127.3, 128.0, 140.3, 140.8, 141.6, 141.9,

142.4, 142.8 ($2C_6H_5$, C_6H_4, imidazole, pyridine C), 164.4 (CO), 167.9 (CN). EIMS: m/z 417 $[M]^+$ (42). Anal. for $C_{28}H_{23}N_3O$ (417.50), Calcd: C, 80.55; H, 5.55; N, 10.06%. Found: C, 80.25; H, 5.46; N, 10.28%.

3-(1H-Benzo[d]imidazol-2-yl)-4-(4-chlorophenyl)-2-phenyl-4,6,7,8-tetrahydroquinolin-5(1H)-one (**16b**). Pale yellow, yield 68%, Mp 205-208°C. IR (KBr) ν max (cm^{-1}): 3423-3380 (2NH) 3087, 3054 (CH-aromatic), 2930 (CH-aliphatic), 1666 (CO), 1517 (CC). ^{1}H NMR (DMSO-d_6, 300 MHz): δ2.23-2.58 (m, 6H, $3CH_2$), 4.53 (s, 1H, CH-pyridine), 7.21-7.54 (m, 13H, $2C_6H_4$, C_6H_5), 9.48, 10.04 (2s, 2H, 2NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.5, 36.2, 39.7 ($3CH_2$), 48.6, 120.5, 121.6, 122.8, 123.4, 123.8, 124.3, 124.6, 125.3, 125.6, 126.2, 126.1, 128.3, 139.5, 140.5, 140.6, 141.3, 142.6, 143.6 (C_6H_5, $2C_6H_4$, imidazole, pyridine C), 164.4 (CO), 167.5 (CN). EIMS: m/z 451 $[M]^+$ (28). Anal. for $C_{28}H_{22}ClN_3O$ (451.95): Calcd: C, 74.41; H, 4.91; N, 9.30%. Found: C, 74.31; H, 4.91; N, 9.47%.

3-(1H-Benzo[d]imidazol-2-yl)-4-(4-methoxyphenyl)-2-phenyl-4,6,7,8-tetrahydroquinoline-5(1H)-one (**16c**). Pale yellow, yield: 72%, Mp 200-204°C. IR (KBr) ν max (cm^{-1}): 3474-3348 (2NH), 3083, 3054 (CH-aromatic), 2932 (CH-aliphatic), 1680 (CO), 1517 (CC). ^{1}H NMR (DMSO-d_6, 300 MHz): δ2.22-2.53 (m, 6H, $3CH_2$), 3.67 (s, 3H, OCH_3), 4.58 (s, 1H, CH-pyridine), 7.25-7.53 (m, 13H, $2C_6H_4$, C_6H_5), 10.13 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.2, 36.6, 39.8 ($3CH_2$), 49.2, 120.8, 121.4, 122.5, 123.7, 123.9, 124.5, 124.3, 125.4, 126.8, 126.8, 127.3, 128.1, 139.5, 140.8, 141.6, 142.3, 142.8, 143.9 (C_6H_5, $2C_6H_4$, imidazole, pyridine C), 164.3 (CO), 167.7 (CN). EIMS: m/z 448 $[M]^+$ (40). Anal. for $C_{29}H_{25}N_3O_2$ (447.53): Calcd: C, 77.83; H, 5.63; N, 9.39%. Found: C, 77.61; H, 5.55; N, 9.45%.

5.1.7 | Synthesis of 3-(1-(1*H*-benzo[*d*]imidazol-2-yl)-2-oxo-2-phenylethylidene)-cyclohexanone (17)

Equimolar amounts of compound, **12** (2.36 g, 0.01 mol), and cyclohexan-1,3-dione (1.12 g, 0.01 mol) were heated at 120°C in dry conditions, in an oil bath, for 10 minutes, and then the reaction mixture was left to cool. The formed solid product was triturated with diethylether and then collected by filtration.

Pale yellow, yield: 78%, Mp 196-198°C. IR (KBr) ν max (cm^{-1}): 3486 (NH), 3080, 3054 (CH-aromatic), 2932 (CH-aliphatic), 1705, 1680 (2CO), 1620 (CC). ^{1}H NMR (DMSO-d_6, 300 MHz): δ2.20-2.58 (m, 6H, $3CH_2$), 2.80 (s, 2H, CH_2), 7.22-7.50 (m, 9H, C_6H_4, C_6H_5), 8.23 (s, 1H, NH). ^{13}C NMR (DMSO-d_6 75 MHz): δ 19.9, 38.4, 40.5, 43.2 ($4CH_2$), 97.2, 110.4 (CC), 120.3, 121.8, 123.7, 123.6, 124.2, 125.3, 126.6, 127.5 (C_6H_5, C_6H_4), 164.8, 166.3 (2CO), 170.3 (CN). EIMS: m/z 330 $[M]^+$ (36). Anal. for $C_{21}H_{18}N_2O_2$ (330.38): Calcd: C, 76.34; H, 5.49; N, 8.48%. Found: C, 76.26; H, 5.61; N, 8.39%.

5.1.8 | General procedure for the synthesis of 6,7-dihydrobenzo[*b*]thiophen-5(4*H*)-ylidene derivatives, 18a–b

Each elemental sulfur and either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 g, 0.01 mol) were added to a solution of compound **17** (3.30 g, 0.01 mol), in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL). The reaction mixture was heated under reflux for 3 hours and then poured onto ice/water mixture, and the participated product was collected by filtration.

5-(1-(1H-Benzo[d]imidazol-2-yl)-2-oxo-2-phenylethyldiene)-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (**18a**). Pale yellow, yield 65%, Mp 150-152°C. IR (KBr) ν max (cm^{-1}): 3462-3353 (NH_2, NH), 3087, 3054 (CH-aromatic), 2930 (CH-aliphatic), 2227 (CN), 1686 (CO), 1540 (CC). ^{1}H NMR (DMSO-d_6, 300 MHz): δ2.21-2.59 (m, 6H, $3CH_2$), 4.84 (s, 2H, NH_2), 7.23-7.46 (m, 9H, C_6H_4, C_6H_5), 9.46 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.2, 36.2, 39.9 ($3CH_2$), 99.2, 111.0 (CC), 116.8 (CN), 120.5, 121.6, 122.8, 123.8, 124.3, 125.3, 125.6, 126.1, 139.9, 140.5, 141.3, 142.6 (C_6H_5, C_6H_4, thiophene C), 164.8 (CO), 168.3 (CN). EIMS: m/z 410 $[M]^+$ (32). Anal. for $C_{24}H_{18}N_4OS$ (410.49): Calcd: C, 70.42; H, 4.42; N, 13.65; S, 7.81%. Found: C, 70.05; H, 4.60; N, 13.76; S, 7.92%.

Ethyl 5-(1-(1H-benzo[d]imidazol-2-yl)-2-oxo-2-phenylethyldiene)-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**18b**). Reddish brown yellow, yield 65%, Mp 150-152°C. IR (KBr) ν max (cm^{-1}): 3482-3337 (NH_2, NH), 3087, 3054 (CH-aromatic), 2930 (CH-aliphatic), 1705, 1686 (2CO), 1540 (CC). ^{1}H NMR (DMSO-d_6, 300 MHz): δ1.12 (t, 3H, J = 6.4 Hz, $OCH_2\underline{CH_3}$), 2.21-2.46 (m, 6H, $3CH_2$), 4.21 (q, 2H, J = 6.4 Hz, $O\underline{CH_2}CH_3$), 4.86 (s, 2H, NH_2), 7.23-7.46 (m, 9H, C_6H_4, C_6H_5), 9.46 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.2 ($OCH_2\underline{CH_3}$), 18.3, 36.2, 39.6 ($3CH_2$), 52.8 ($O\underline{CH_2}CH_3$), 97.5, 110.9 (CC), 120.3, 121.2, 122.6, 123.4, 124.6, 125.8, 125.6, 126.3, 139.9, 140.3, 141.1, 142.8 (C_6H_5, C_6H_4, thiophene C), 165.5, 168.3 (2CO), 168.8 (CN). EIMS: m/z 457 $[M]^+$ (40). Anal. for $C_{26}H_{23}N_3O_3S$ (457.57): Calcd: C, 68.25; H, 5.07; N, 9.18; S, 7.01%. Found: C, 68.36; H, 5.19; N, 9.06; S, 7.12%.

5.1.9 | General procedure for the synthesis of 5,6,7,8-tetrahydro-4*H*-chromenes, 19a–c

Either benzaldehyde (1.08 g, 0.01 mol), *p*-chlorobenzaldehyde (1.40 g, 0.01 mol) or *p*-methoxybenzaldehyde (1.36, 0.01 mol)

and malononitrile (0.66 g, 0.01 mol) were added to a solution of compound, **17** (3.30 g, 0.01 mol), in 1,4-dioxane (40 mL) containing triethylamine (0.50 mL). The reaction mixture was heated under reflux for 3 hours and then poured onto ice/water mixture, and the participated product was collected by filtration.

7-(1-(1H-Benzo[d]imidazol-2-yl)-2-oxo-2-phenylethyldiene)-2-amino-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**19a**). Pale brown, yield: 72%, Mp 123-125°C. R (KBr) ν max (cm^{-1}): 3457-3325 (NH, NH_2), 3055 (CH-aromatic), 2962 (CH-aliphatic), 2221 (CN), 1688 (CO), 1628 (CC).^{1}H-NMR (DMSO-d_6, 300 MHz): δ2.23-2.29 (m, 6H, $3CH_2$), 4.61 (s, 1H, CH-pyran), 4.52 (s, 2H, NH_2), 7.18-7.55 (m, 14H, $2C_6H_5$, C_6H_4), 10.55 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75MHz): δ 18.1, 36.7, 39.7 ($3CH_2$), 98.0, 112.1 (CC), 50.2, 119.3, 121.5, 122.0, 122.6, 123.6, 124.1, 124.7, 125.2, 126.3, 126.8, 127.1, 128.0, 139.8, 140.2, 140.8, 142.4, 142.6, 142.8 ($2C_6H_5$, C_6H_4, imidazole, pyran C), 164.6 (CO), 167.7 (CN). EIMS: m/z 484 $[M]^+$ (46). Anal. for $C_{31}H_{24}N_4O_2$ (484.55): Calcd: C, 76.84; H, 4.99; N, 11.56%. Found: C, 76.61; H, 4.73; N, 11.42%.

7-(1-(1H-Benzo[d]imidazol-2-yl)-2-oxo-2-phenylethyldiene)-2-amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**19b**). Pale brown, yield: 66%, Mp 145-148°C. IR (KBr) ν max (cm^{-1}): 3457-3325 (NH, NH_2), 3055 (CH-aromatic), 2962 (CH-aliphatic), 2223 (CN), 1688 (CO), 1628 (CC).^{1}H-NMR (DMSO-d_6, 300 MHz): δ2.21-2.28 (m, 6H, $3CH_2$), 4.64 (s, 1H, CH-pyran), 4.50 (s, 2H, NH_2), 7.18-7.55 (m, 13H, C_6H_5, $2C_6H_4$), 10.58 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.1, 36.7, 39.7 ($3CH_2$), 97.6, 111.3 (CC), 51.3, 120.6, 121.1, 122.3, 123.2, 123.8, 124.3, 124.9, 125.6, 126.1, 126.6, 127.3, 128.2, 139.6, 140.7, 140.5, 142.1, 142.9, 143.2 (C_6H_5, $2C_6H_4$, imidazole, pyran C), 164.8 (CO), 167.9 (CN). EIMS: m/z 518 $[M]^+$ (26). Anal. for $C_{31}H_{23}ClN_4O_2$ (518.99): Calcd: C, 71.74; H, 4.47; N, 10.80%. Found: C, 71.85; H, 4.26; N, 10.47%.

7-(1-(1H-Benzo[d]imidazol-2-yl)-2-oxo-2-phenylethyldiene)-2-amino-4-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**19c**). Pale brown, yield: 66%, Mp 145-148°C. IR (KBr) ν max (cm^{-1}): 3457-3325 (NH, NH_2), 3055 (CH-aromatic), 2962 (CH-aliphatic), 2219 (CN), 1688 (CO), 1628 (CC).^{1}H-NMR (DMSO-d_6, 300 MHz): δ2.21-2.28 (m, 6H, $3CH_2$), 3.67 (s, 3H, OCH_3), 4.64 (s, 1H, CH-pyran), 4.50 (s, 2H, NH_2), 7.18-7.55 (m, 13H, C_6H_5, $2C_6H_4$), 10.58 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.1, 36.7, 39.7 ($3CH_2$), 50.4 (OCH_3), 97.1, 110.8 (CC), 52.3, 120.6, 121.1, 122.5, 123.1, 123.8, 124.3, 124.6, 125.6, 126.4, 126.6, 127.3, 128.2, 139.6, 140.3, 140.6, 142.1, 142.3, 142.8 (C_6H_5, $2C_6H_4$, imidazole, pyran C), 164.5 (CO), 167.6 (CN). EIMS: m/z 514 $[M]^+$ (38). Anal. for $C_{32}H_{26}N_4O_3$ (514.57): Calcd: C, 74.69; H, 5.09; N, 10.98%. Found: C, 74.78; H, 4.94; N, 10.76%.

5.1.10 | General procedure for the synthesis of 1,4,5,6,7,8-hexahydroquinoline, 20a–c

Each of either benzaldehyde (1.08 g, 0.01 mol), *p*-chlorobenzaldehyde (1.40 g, 0.01 mol) or *p*-methoxybenzaldehyde (1.36, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) were added to a solution of compound **17** (3.30 g, 0.01 mol) in 1,4-dioxane (40 mL) containing ammonium acetate (1.50 g, 0.02 mol). The reaction mixture was heated under reflux for 3 hours and then poured onto ice/water mixture, and the participated product was collected by filtration.

7-(1-(1H-Benzo[d]imidazol-2-yl)-2-oxo-2-phenylethyldiene)-2-amino-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**20a**). Pale yellow, yield: 62%, Mp 146-148°C. IR (KBr) ν max (cm^{-1}): 3479-3336 (NH, NH_2), 3055 (CH-aromatic), 2962 (CH-aliphatic), 2220 (CN), 1702 (CO), 1628 (CC).^{1}H-NMR (DMSO-d_6, 300 MHz): δ2.21-2.29 (m, 6H, $3CH_2$), 4.63 (s, 1H, CH-pyridine), 4.58 (s, 2H, NH_2), 7.18-7.59 (m, 14H, $2C_6H_5$, C_6H_4), 11.06 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.6, 36.5, 39.4 ($3CH_2$), 97.0, 110.5 (CC), 49.3, 120.6, 121.8, 122.8, 122.9, 123.4, 124.6, 124.9, 125.0, 126.8, 126.3, 127.5, 128.6, 138.3, 140.6, 141.5, 142.8, 142.9, 143.8 ($2C_6H_5$, C_6H_4, imidazole, pyridine C), 165.8 (CO), 168.3 (CN). EIMS: m/z 482 $[M]^+$ (40). Anal. for $C_{31}H_{25}N_5O$ (483.56): Calcd: C, 77.00; H, 5.21; N, 14.48%. Found: C, 76.77; H, 5.05; N, 14.25%.

7-(1-(1H-Benzo[d]imidazol-2-yl)-2-oxo-2-phenylethyldiene)-2-amino-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**20b**). Pale yellow, yield: 64%, Mp 128-131°C. IR (KBr) ν max (cm^{-1}): 3473-3339 (NH, NH_2), 3055 (CH-aromatic), 2962 (CH-aliphatic), 2220 (CN), 1702 (CO), 1624 (CC).^{1}H-NMR (DMSO-d_6, 300 MHz): δ2.24-2.50 (m, 6H, $3CH_2$), 4.64 (s, 1H, CH-pyridine), 4.50 (s, 2H, NH_2), 7.22-7.55 (m, 13H, C_6H_5, $2C_6H_4$), 10.58 (s, 1H, NH). ^{13}C NMR (DMSO-d_6 75 MHz): δ 18.2, 36.8, 39.5 ($3CH_2$), 97.5, 111.2 (CC), 49.9, 120.8, 122.2, 122.6, 123.7, 123.2, 124.1, 124.5, 125.3, 126.0, 126.8, 127.5, 128.3, 139.4, 140.3, 140.6, 142.6, 142.3, 143.8 (C_6H_5, $2C_6H_4$, imidazole, pyridine C), 165.3 (CO), 167.5 (CN). EIMS: m/z 518 $[M]^+$ (36). Anal. for $C_{31}H_{24}ClN_5O$ (518.01): Calcd: C, 71.88; H, 4.67; N, 13.52%. Found: C, 71.61; H, 4.98; N, 13.58%.

7-(1-(1H-Benzo[d]imidazol-2-yl)-2-oxo-2-phenylethyldiene)-2-amino-4-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**20c**). Yellow, yield: 66%, Mp 120-123°C. IR (KBr) ν max (cm^{-1}): 3467-3310 (NH, NH_2), 3055 (CH-aromatic), 2962 (CH-aliphatic), 2219 (CN), 1703 (CO), 1568 (CC).^{1}H-NMR (DMSO-d_6, 300 MHz): δ2.28-2.51 (m, 6H, $3CH_2$), 3.56 (s, 3H, OCH_3), 5.51 (s, 1H, CH-pyridine), 4.59 (s, 2H, NH_2), 7.21-7.59 (m, 13H, C_6H_5, $2C_6H_4$), 10.58 (s, 1H, NH). ^{13}C NMR (DMSO-d_6 75 MHz): δ 18.3, 36.7,

39.5 ($3CH_2$), 50.8 (OCH_3), 98.0, 111.6 (CC), 50.6, 120.6, 121.9, 122.2, 123.8, 123.6, 124.00, 124.3, 125.6, 126.4, 126.8, 127.3, 128.2, 139.6, 140.3, 140.8, 142.0, 142.6, 143.2 (C_6H_5, $2C_6H_4$, imidazole, pyridine C), 164.5 (CO), 167.6 (CN). EIMS: m/z 513 $[M]^+$ (28). Anal. for $C_{32}H_{27}N_5O_2$ (513.01): Calcd: C, 74.83; H, 5.30; N, 13.64%. Found: C, 74.64; H, 5.24; N, 13.79%.

5.1.11 | General procedure for the synthesis of 5,6-dihydro-4*H*-thieno[3,2-*h*] chromene derivatives, 22a–c

To a solution of compound, **21** (1.92 g, 0.01 mol), in 1,4-dioxane (40 mL), containing triethylamine (0.50 mL), each of either benzaldehyde (1.08 g, 0.01 mol), *p*-chlorobenzaldehyde (1.40 g, 0.01 mol) or *p*-methoxybenzaldehyde (1.36 g, 0.01 mol), and malononitrile (0.66 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 3 hours and then poured onto ice/water mixture, and the participated product was collected by filtration.

2,8-Diamino-4-phenyl-5,6-dihydro-4H-thione[3,2-h] chromene-3,7-dicarbonitril (**22a**). Pale brown, yield 72%, Mp 98-101°C. IR (KBr) ν max (cm^{-1}): 3458-3349 (NH_2), 3060 (CH-aromatic), 2940 (CH-aliphatic), 2221 (CN), 1688 (CO), 1580 (CC).^{1}H NMR (DMSO-d_6, 300 MHz): δ2.13-2.39(m, 4H, $2CH_2$), 4.90, 5.13 (2s, 4H, $2NH_2$), 5.98 (s, 1H, CH-pyran), 7.18-7.46 (m, 5H, C_6H_5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ23.6, 39.9 ($2CH_2$), 116.3, 117.0 (2CN), 49.8, 124.9, 126.1, 127.5, 128.1, 132.6, 133.8, 135.0, 136.3, 139.7, 139.5, 141.8, 143.6 (C_6H_5, thiophene, pyran C). EIMS: m/z 346 $[M]^+$(32%); Anal. for $C_{19}H_{14}N_4OS$ (346.41): Calcd: C, 65.88; H, 4.07; N, 16.17; S, 9.26%. Found: C, 65.51; H, 3.88; N, 16.30; S, 9.11%.

2,8-Diamino-4-(4-chlorophenyl)-5,6-dihydro-4H-thione[3, 2-h]chromene-3,7-dicarbonitrile (**22b**). Orange, yield 74%, Mp 108-110°C. IR (KBr) ν max (cm^{-1}): 3493-3325 (NH_2), 3060 (CH-aromatic), 2940 (CH-aliphatic), 2223, 2192 (2CN), 1688 (CO), 1580 (CC).^{1}H NMR (DMSO-d_6, 300 MHz): δ2.13-2.39 (m, 4H, $2CH_2$), 4.90, 5.13 (2s, 4H, $2NH_2$), 5.98 (s, 1H, CH-pyran), 7.18-7.46 (m,4H, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 32.6, 39.9 ($2CH_2$), 116.3, 116.9 (2CN), 50.0, 121.2, 123.2, 126.9, 127.5, 132.3, 133.3, 134.3, 136.3, 139.7, 140.3, 142.3, 143.3 (C_6H_4, thiophene, pyran C). EIMS: m/z 380 $[M]^+$(32%); Anal. for $C_{19}H_{13}ClN_4OS$ (380.85): Calcd: C, 59.92; H, 3.44; N, 14.71; S, 8.42%. Found: C, 60.15; H, 3.60; N, 14.93; S, 8.61%.

2,8-Diamino-4-(4-methoxyphenyl)-5,6-dihydro-4H-thione[3,2-h]chromene-3,7-dicarbonitrile (**22c**). Yellow, yield: 66%, Mp 120-123°C. IR (KBr) ν max (cm^{-1}): 3467-3310 (NH), 3055 (CH-aromatic), 2962 (CH-aliphatic), 2219 (CN), 1703 (CO), 1568 (CC).^{1}H-NMR (DMSO-d_6, 300 MHz): δ2.28-2.51 (m, 4H, $2CH_2$), 3.62 (s, 3H, OCH_3), 5.54 (s, 1H, CH-pyridine), 4.88, 5.16 (2s, 4H, $2NH_2$), 7.24-7.53 (m, 4H, C_6H_4), 10.22 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 36.2, 39.5 ($2CH_2$), 50.8 (OCH_3), 116.8, 117.1 (2CN), 50.8, 120.5, 122.6, 126.4, 127.1, 132.6, 133.3, 134.7, 136.1, 139.3, 140.5, 142.7, 143.9 (C_6H_4, thiophene, pyran C). EIMS: m/z 376 $[M]^+$ (24). Anal. for $C_{20}H_{16}N_4O_2S$ (376.43): Calcd: C, 63.81; H, 4.28; N, 14.88; S, 8.52%. Found: C, 63.48; H, 4.00; N, 14.61; S, 8.68%.

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