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ORIGINAL PAPER

Synthesis and docking studies of pyran, pyridine and thiophene derivatives and their antitumor evaluations against cancer, hepatocellular carcinoma and cervical carcinoma cell lines

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Abstract
This work aimed to produce novel heterocyclic compounds such as chromene, thieno[3,2-f]chromene, chromeno[5,6-d] thiazole and quinoline derivatives. The newly synthesized heterocyclic compounds were evaluated against cancer cell lines aiming to get new anticancer agents. Dimedone underwent different multi-component reactions to produce fused thiophene, thiazole, coumarin, pyran and pyridine derivatives. Some reactions were catalyzed by effective magnetically separable nano-catalyst. The anti-proliferative activity of the newly synthesized compounds toward six cancer cell was studied. In addition, inhibitions of the most active compounds the thieno[3,2-*f*]chromene derivatives **16a–f** toward cancer cell lines classified according to the disease were also studied. Moreover, the newly synthesized compounds were screened for their anticancer potentials against hepatocellular carcinoma HepG2 and cervical carcinoma HeLa cell lines. Anti-proliferative evaluations, inhibitions were performed for all of the synthesized compounds where the varieties of substituent through the aryl ring and the heterocyclic ring afforded compounds with high activities. Inhibitions toward cancer cell lines classified according to the disease together with inhibitions toward HepG2 and cervical carcinoma HeLa cell lines were measured. Molecular docking of compounds **15c** and **18c** was performed.

Keywords Dimedone · Pyran · Pyridine · Thiophene · Anti-proliferative · Molecular docking

Introduction

The multi-component reactions (MCRs) was considered as an elegant and rapid way to synthesize structurally diverse bioactive heterocyclic compounds in a single synthetic operation from simple reagents through. In the field of drug discovery and medicinal chemistry, multi-component reactions were the most applicable reactions. Due to the advantages of multi-component reactions like high atom-economy, simplification of reagents, high yields of products and high selectivity of products many researches were directed through their applications in recent years [1–4]. One of the most important classes of compounds produced via the multi-component reactions was the 4*H*-benzo[*b*]pyran derivatives. Such group of compounds exhibited numerous pharmacological and biological activities [5]. They showed pronounced biological activities among which diuretic, anti-allergic, antibacterial, anticoagulant, anticancer and anti-anaphylactic activities, as well as their use in therapy [6–9]. There are different methods for the synthesis of 4*H*-benzo[*b*] pyran derivatives depending on the catalyst used through the reaction of aromatic aldehydes, malononitrile (or ethyl cyanoacetate) and dimedone. Some reactions were achieved using tetra-alkyl ammonium salts, acidic salts, tricarboxylic acid salts, organo-metallic catalyst, acidic ionic liquids and some silica salts [10–22]. The yield of products were varied from catalyst to another as some of them gave high yield and others showed lower yields, in additions, some of these catalysts with necessity of use toxic solvents especially during the work-up procedures [23]. To overcome such difficulties,

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other alternating and clean procedures were adopted for the synthesis of 4*H*-benzo[*b*]pyran derivatives. According to WHO Cancer is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumors and neoplasm's. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs; the latter process is referred to as metastasis. Widespread and metastases are the primary cause of death from cancer. Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 (1). The most common in 2020 (in terms of new cases of cancer) were breast, lung, colon, prostate, skin and stomach [24–26]. As the result of the large spread of cancer and the anticancer activities of 4*H*-benzo[*b*]pyran derivatives we were concerned with the synthesis of such compounds [27–29]. Moreover, the 4*H*-pyran derivatives were known to be good anti-cancer agents this appeared in many reports [30–32]. Due to the large applications of 4*H*-pyran derivatives we were involved through a comprehensive program for the synthesis of such group of compounds. As a continuation of that work and in view of our ongoing efforts to explore newer reactions for synthesis of heterocyclic compounds, in this work, in regard we report here different muti-component reactions of dimedone with different active ethylene compounds and 1,3-dicarbonyl compounds. The products underwent further heterocyclization reactions to give annulated products. Apart from that, some of the inhibitors identified were subjected to molecular docking study using Saccharomyces cerevisiae isomaltase crystal structure obtained from the protein data bank. This in silico analysis can help to visualize the binding mode and interaction between the inhibitors and the proteins that cause the inhibitory activity [33–35]. The computer-aided QSAR modeling, molecular docking simulation and ADMET predictions were employed to develop a validated QSAR model through different statistical parameters, elucidating molecular interactions between the 3D structure of the receptor and ligands with their binding modes and also to predict the Pharmacokinetics and ADMET properties of the compounds as inhibitors of serotonin transporter (SERT) [36]. Consequently, the information obtained from this study could be used as a reliable framework and rational template for structural modifications/adjustments of the compounds in developing potential inhibitors of the serotonin transporter (SERT) as novel antidepressant agents with the improved inhibitory potency. The antitumor evaluations of the newly synthesized products were measured in the aim of producing anticancer agents.

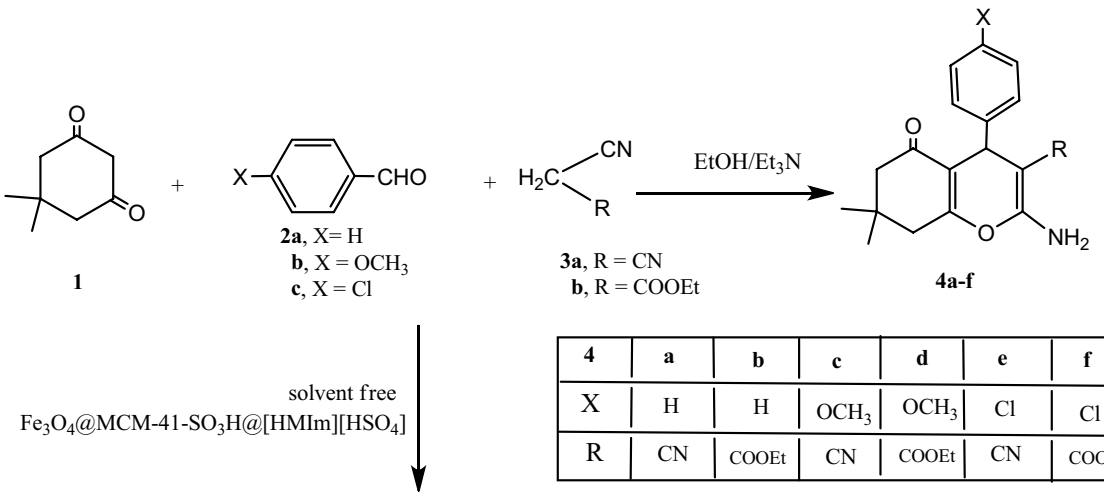
Results and discussion

The reaction sequences for the synthesized compounds were demonstrated through Schemes 1, 2, 3 and 4 starting with dimedone. The multi-component reaction of dimedone (**1**) with either benzaldehyde (**2a**), 4-methoxybenzaldehyde (**2b**) or 4-chlorobenzaldehyde (**2c**) and either maononitrile (**3a**) or ethyl cyanoacetate (**3b**) gave the 7,8-dihydro-4H-chromen-5(6*H*)-one derivatives **4a–f**, respectively. Compounds **4a**, **4c** or **4a** reacted with elemental sulfur and either of malononitrile (**3a**) or ethyl cyanoacetate (**3b**) in 1,4-dioxane containing tiethylamine to give the thieno[3,2-*f*]chromene-8-carbonitrile derivatives **5a–f**, respectively (Scheme 1). The reaction took place through Gewald's thiophene synthesis [37–39]. The structures of the latter products were based on their respective analytical and spectral data. Thus, the ^{1}H NMR spectrum of compound **5a** showed the presence of two NH_2 groups at δ 4.87, 5.22 ppm (D_2O exchangeable) and a singlet at δ 2.40 ppm indicating one CH_2 group. In addition, the ^{13}C NMR spectrum revealed the presence of two signals at δ 116.8 and 117.0 due to the presence of two CN groups and signals at δ 136.0, 138.2, 139.8, 140.1, 142.8, 143.2, 143.8 and 145.8 due to the presence of the thiophene and pyran carbons.

On the other hand, the multi-component reactions of dimedone (**1**), the 3-methyl-1*H*-pyrazol-5(4H)-one (**6**) and either benzaldehyde (**2a**), 4-methoxybenzaldehyde (**2b**) or 4-chlorobenzaldehyde (**2c**) in ethanol containing a catalytic amount of triethylamine gave the tetrahydrochromeno[2,3-*c*]pyrazol-5(1*H*)-one derivatives **7a–c**, respectively. In addition, the multi-component reactions of dimedone (**1**), cyanothioacetamide (**8**) and either benzaldehyde (**2a**), 4-methoxybenzaldehyde (**2b**) or 4-chlorobenzaldehyde (**2c**) in 1,4-dioxane containing a catalytic amount of triethylamine gave the hexahydroquinoline-3-carbonitrile derivatives **9a–c**, respectively (Scheme 2).

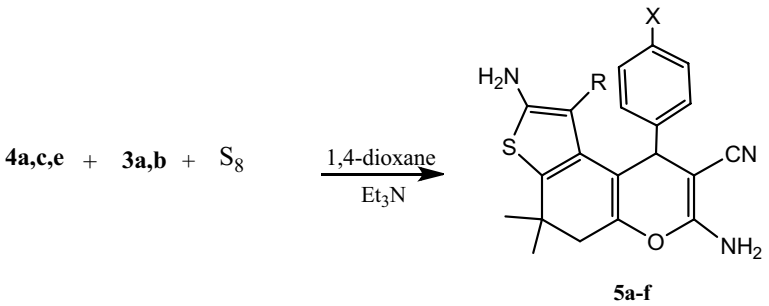
In continuation of such series of reactions, the multi-component reactions of dimedone (**1**), with either ethyl benzoylacetate (**10a**) or ethyl acetoacetate (**10b**) and salicylaldehyde (**11**) in ethanol containing a catalytic amount of triethylamine gave the dihydrochromeno[3,4-*c*]chromene **12a** and **12b**, respectively. Structures of the latter products were based on their respective analytical data. Thus, the ^{1}H NMR spectrum of **12a** showed a singlet at δ 6.52 ppm indicating CH of pyran, and ^{13}C NMR spectrum revealed the presence of a signal at δ 166.5, 168.4 due to the presence of two C=O groups and signals at δ 139.3, 140.2, 142.8 and 145.2 due to the pyran carbons.

On the other hand, the multi-component reactions of dimedone (**1**), with either of malononitrile (**3a**) or ethyl



4	a	b	c	d	e	f
X	H	H	OCH_3	OCH_3	Cl	Cl
R	CN	COOEt	CN	COOEt	CN	COOEt

4a, 88%; **4b**, 90 %; **4c**, 86 %; **4d**, 79 %' **4e**, 85 %; **4f**, 93 %



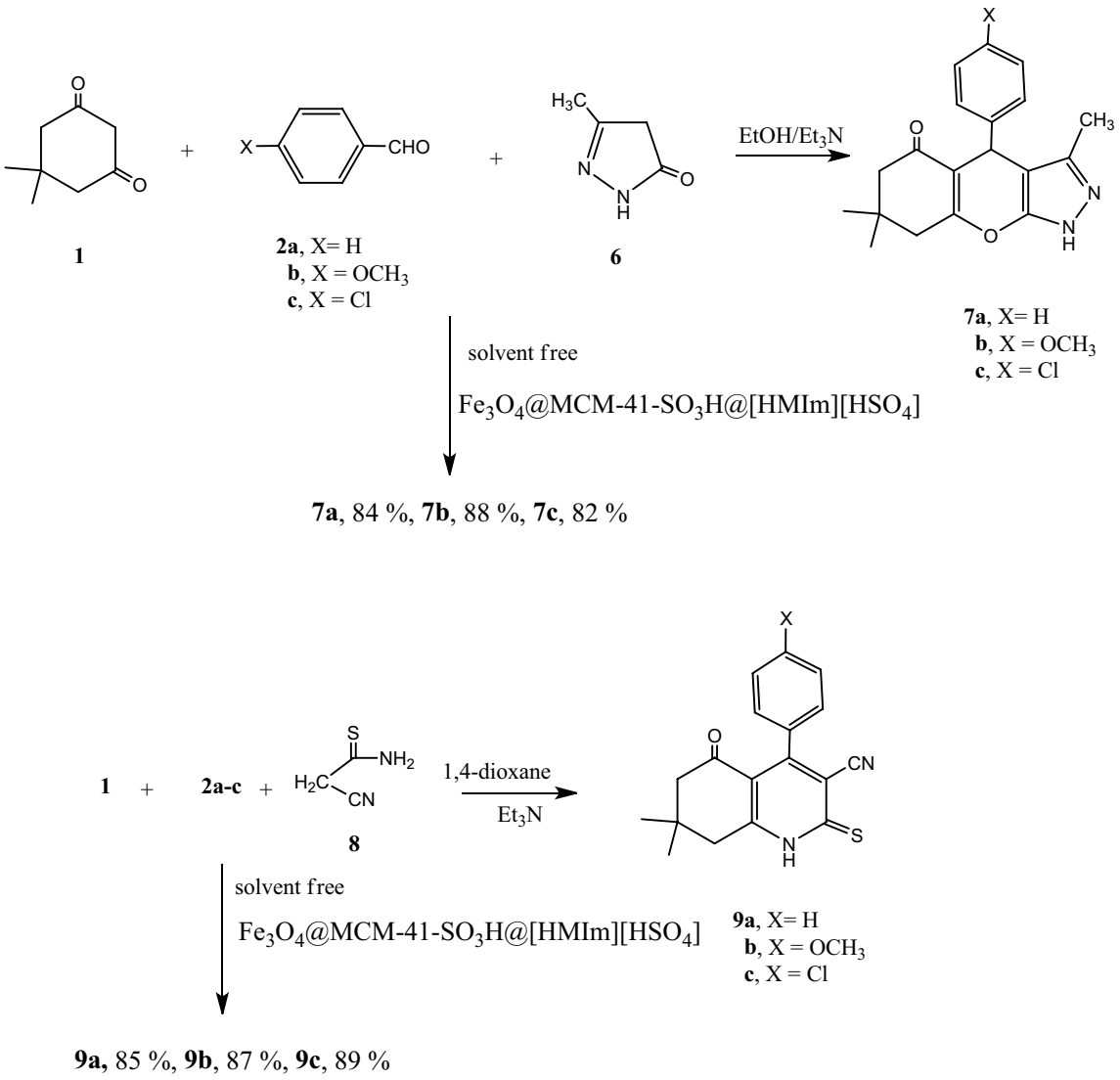
5	a	b	c	d	e	f
X	H	H	OCH_3	OCH_3	Cl	Cl
R	CN	COOEt	CN	COOEt	CN	COOEt

Scheme 1 Synthesis of compounds **4a–f** and **5a–f**

cyanoacetate (**3b**) and salicylaldehyde (**11**) gave the same dihydrochromeno[3,4-*c*]chromene (**13**). Formation of the same product can be explained through the intermediate formation of the imino product in case of the reaction with malononitrile followed by hydrolysis of the C=NH group into C=O. On the other extreme, in case of ethyl cyanoacetate ethanol elimination took place to give directly the C=O.

The multi-component reaction of dimedone (**1**), with either benzaldehyde (**2a**), 4-methoxybenzaldehyde (**2b**) or 4-chlorobenzaldehyde (**2c**) and ethyl benzoylacetate (**10a**) in ethanol containing a catalytic amount of triethylamine yielded the pyran derivatives **14a–c**. However, carrying the same reaction but using ammonium acetate instead of triethylamine gave the pyridine derivatives **15a–c**, respectively (Scheme 3).

Compounds **14a–c** were capable for the Gewald's thiophene synthesis due to the presence of cyclohexenone moiety. Thus, either compounds **14a**, **14b** or **14c** reacted with elemental sulfure and either malononitrile (**3a**) or ethyl cyanoacetate (**3b**) to produce the thieno[3,2-*f*]chromene-8-carboxylate derivatives **16a–f**, respectively. The analytical and spectral data of the latter products were in agreement with their respective structures. Thus, the ^{1}H NMR spectrum of **16a** as an example) showed the presence of one NH_2 group at δ 5.18 ppm (D_2O exchangeable) and a singlet at δ 6.50 ppm indicating pyran CH, and the ^{13}C NMR spectrum showed the presence of a signal at δ 116.8 due to the presence of CN group and signals at δ 136.3, 138.8, 139.4, 141.4, 142.5, 143.0, 143.2, 144.5 due to the thiophene and pyran carbons. On the other hand, the reaction of either of compounds **14a–c** with elemental

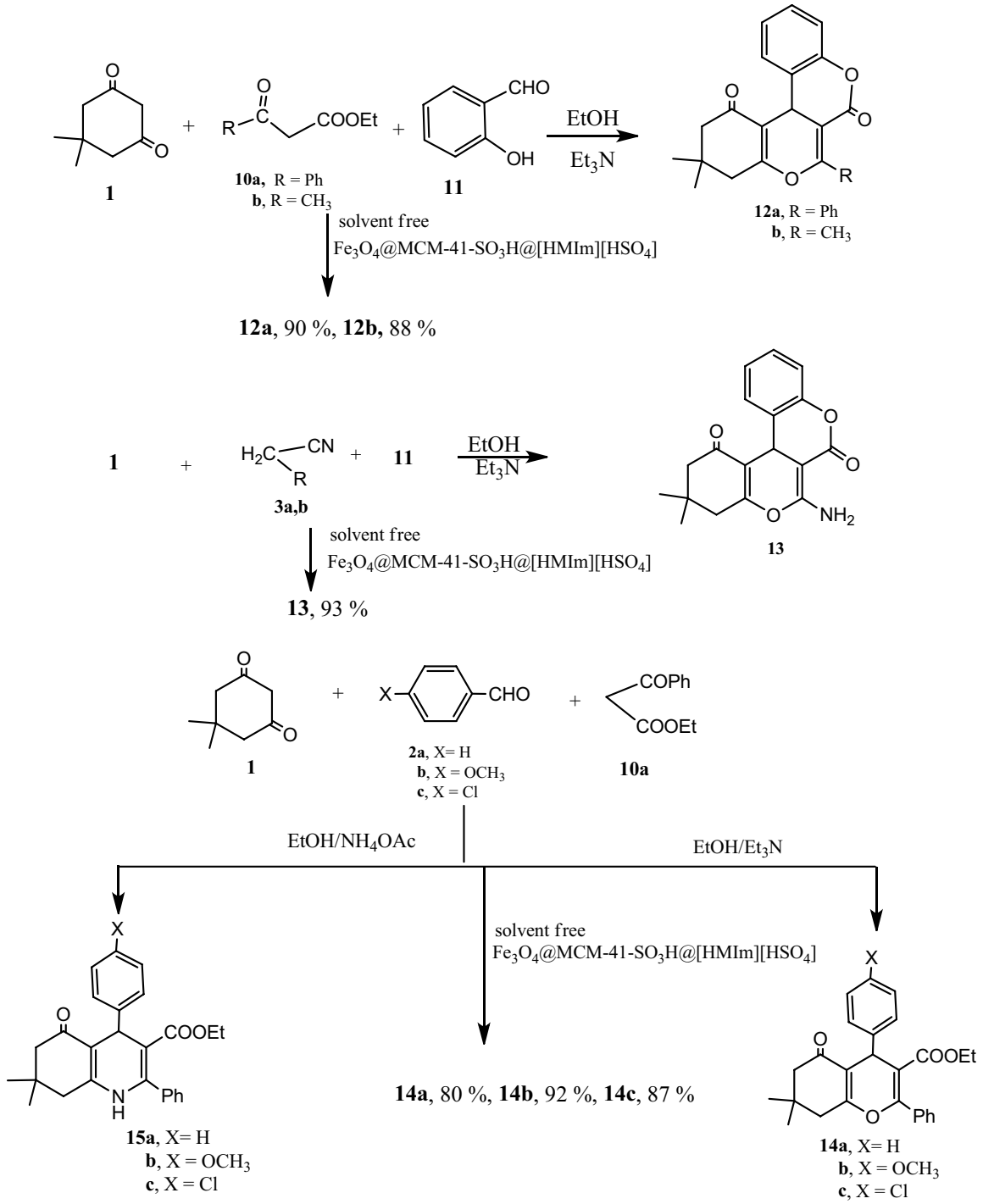


Scheme 2 Synthesis of compounds **7a–c** and **9a–c**

sulfur and phenylisothiocyanate gave the 2,4,5,9-tetrahydro-1*H*-chromeno[5,6-*d*]thiazole derivatives **18a–c**, respectively. Either of the latter compounds **18a–c** reacted with two fold of hydrazine hydrate or phenylhydrazine to give the 2-hydrazono-chromeno[5,6-*d*]thiazole-8-carbohydrazide derivatives **20a–f**, respectively (Scheme 4). Structures of compounds **18a–c** and **20a–f** were based on analytical and spectral data (see experimental section). It is of a great value to mention that the multi-component reactions producing compounds **4a–f**; **7a–c**; **9a–c; 12a,b**; **13** and **14a–c** took place by two methods. The first method was the regular solvent method using a catalytic amount of triethylamine and the second method was the solvent free using by nanoparticle-immobilized ionic liquid [40]. Table 1 showed a comparison between yields of the two methods where the second method in all cases of higher yields than the first method.

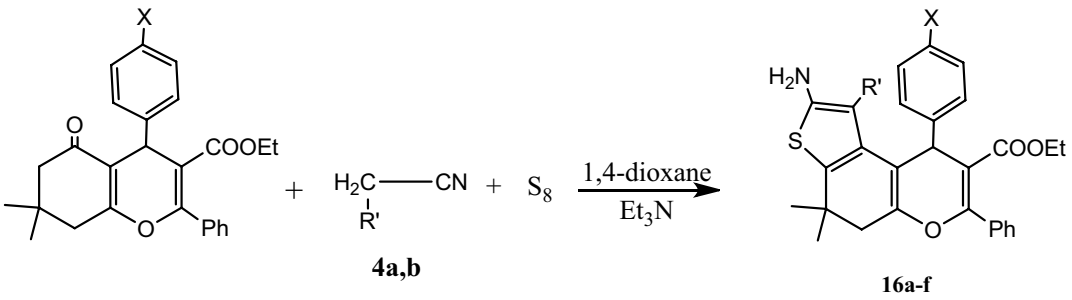
Ionic liquids immobilized on MNPs in multicomponent reactions

Recent studies represent that magnetic nanoparticles (MNPs) are excellent supports for ILs owing to their good stability, easily preparation and functionalization, high surface special features have made MNPs a convenient alternative to catalyst supports. As an example, a magnetically Fe_3O_4@SiO_2 nanoparticle-immobilized ionic liquid (MNPs@SiO_2-IL) was prepared by Azgomi and Mokhtary [41]. The Fe_3O4@MCM-41-SO_3H@[HMIm][HSO_4] efficiently catalyzed the one-pot three-component condensation reactions for the synthesis of **4a–f**; **7a–c**; **9a–c; 12a,b**; **13** and **14a–c** (Schemes 1, 2 and 3). The yields and purity of obtained compounds were much better than the same compounds obtained using ethanol and triethylamine.



Scheme 3 Synthesis of compounds **12a,b**; **13**, **14a–c** and **15a–c**

Table 1 showed a comparison between the reactions catalyzed by Et_3N and those catalyzed by nanoparticle-immobilized ionic liquid. Furthermore, the catalyst was able to be good distributed in the reaction media, simply retrived from the reaction mixture by using a magnet, and reused for several times with no significant loss in activity. This procedure offered several advantages including mild reaction conditions, cleaner reaction, and satisfactory yields of products, as well as a simple experimental and isolated procedure, which make it a useful and attractive protocol for the synthesis of these compounds.

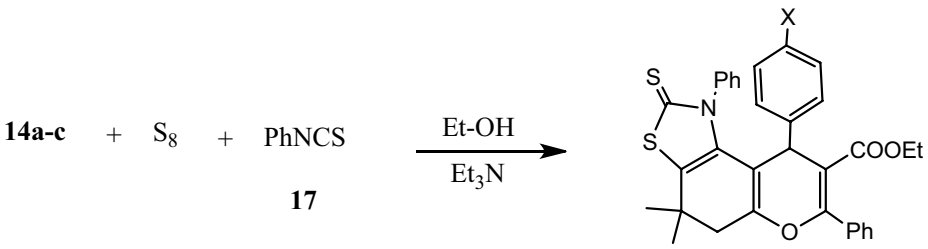


4a,b

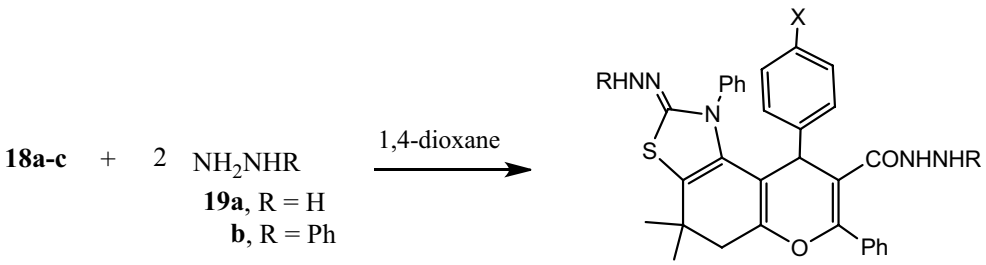
16a-f

14a, X= H
b, X = OCH_3
c, X = Cl

16	a	b	c	d	e	f
X	H	H	OCH_3	OCH_3	Cl	Cl
R'	CN	COOEt	CN	COOEt	CN	COOEt



18a, X= H
b, X = OCH_3
c, X = Cl



20a-f

20	a	b	c	d	e	f
X	H	H	OCH_3	OCH_3	Cl	Cl
R	H	Ph	H	Ph	H	Ph

Scheme 4 Synthesis of compounds **16a–f, 18a–c** and **20a–f**

Biology assay

Cell proliferation assay

The six cancer cell lines namely A549, HT-29, MKN-45, U87MG, SMMC-7721 and H460 were used for the valuation of the newly synthesized compounds using Foretinib as the positive control [42]. The in-vitro assay was carried out using standard MTT procedure. $IC_{50's}$ (inhibitory concentrations 50%) were measured for each compound

Table 1 Yields of products **4a–f**; **7a–c**; **9a–c**; **12a,b**; **13** and **14a–c** catalyzed by Et_3N and those by nanoparticle-immobilized ionic liquid

Compound	X	R	Yield[a]	Yield[b]
4a	H	CN	68	88
4b	H	COOEt	60	90
4c	OCH_3	CN	73	86
4d	OCH_3	COOEt	64	79
4e	Cl	CN	73	85
4f	Cl	COOEt	72	93
7a	H	–	72	84
7b	OCH_3	–	76	88
7c	Cl	–	66	82
9a	H	–	68	85
9b	OCH_3	–	73	87
9c	Cl		58	89
12a	–	Ph	55	90
12b	–	CH_3	68	88
13	–	–	70	93
14a	H	–	64	80
14b	OCH_3	–	65	92
14c	Cl	–	70	87

[a]Reactions were carried in ethanol catalysed by Et_3N

[b]Reactions solvent free catalyzed by Fe_3O_4@MCM-41-SO_3H@[HMIm][HSO_4]

and determined as the result of the average of three determinations.

The mean values of three independent experiments, expressed as IC_{50} values, were presented in Table 2. Most of the synthesized compounds exhibited potent anti-proliferative activity with IC_{50} values less than 30 µM. Generally, the variations of substituent's within the aryl and the heterocycle ring being attached have a notable influence on the anti-proliferative activity.

Structure activity relationship

It was clear from Table 1 that compounds **4e**, **4f**, **5e**, **5f**, **7c**, **9c**, **13**, **14c**, **15c**, **16e**, **16f**, **18c**, **20c** and **20f** were the most cytotoxic compounds against the six cancer cell lines. Considering the pyran derivatives **4a–f**, it was clear that compounds **4e** and **4f** were the most cytotoxic compounds exhibiting $IC_{50} < 1.0$. Considering the 5,9-dihydro-4*H*-thieno[3,2-*f*]chromene derivatives **5a–f**, it was clear that compound **5a** showed the lowest activities among the tested compounds while compound **5c** eexhibited moderate inhibitions toward the six cancer cell lines. In addition compounds **5e** and **5f** exhibited the highest inhibitions toward the six cancer cell lines. Considering the tetrahydrochromeno[2,3-*c*]pyrazole derivatives **7a–c**, interestingly compound **7a** (X = H) exhibited moderate inhibitions while compound **7c** (X = Cl) exhibited high inhibitions toward the six cancer cell lines. For the hexahydroquinoline derivatives **9a–c**, compound **9c** (X = Cl) exhibited the highest inhibitions toward the six cancer cell lines among the three compounds. Both of the two compounds **12a** and **12b** exhibited from moderate to high inhibitions this is due to the presence of the chromeno[3,4-*c*]chromene nucleus within the structure of both compounds. However compound **12a** exhibited high inhibitions than compound **12b** due to the presence of the phenyl substituent. Similarly, for the 3,4-dihydrochromeno[3,4-*c*]chromene derivative **13** exhibited high inhibitions toward the six cancer cell lines. Considering the pyran derivatives **14a–c** and the pyridine derivatives **15a–c** where compound **14a** and **15a** showed relatively high inhibitions than **14b** and **15b** since the latter compounds have an electron donating substituent (X = OCH_3) in their structures. In addition, compounds **14c** (X = Cl) and **15c** (X = Cl) exhibited the highest cytotoxicity among the six compounds, this was attributed to the presence of the electronegative substituent Cl group in their structures. On the other hand for the thieno[3,2-*f*]chromene derivatives **16a–f**, compound **16c** although it contains an electron donating substituent (X = OCH_3) showed moderate activities toward the six cancer cell lines. Moreover, compounds **16e** and **16f** exhibited the highest inhibitions among the six compounds. This was attributed to the presence of the thiophene moiety together of the electron withdrawn substituent the Cl group in their structures. However, for the thiazole derivatives **18a–c** and **19a–f** compounds **18b** and **19c** although they contain an electron donating group, they showed high cytotoxicities toward the six cancer cell lines. This was attributed to the conjugation of the methoxy group with the aryl group. In addition, compounds **18c**, **19e** and **19f** were the most cytotoxic among the nine compounds and this was attributed to the presence of the electron withdrawn substituent Cl group within their structures.

Mechanism of action

It is clear from Table 1 that compounds **4e, 7c** and **20f** were the most cytotoxic compounds among the tested compounds towards the six cancer cell lines. From the structure point of view, it is clear that the high activity of compound **4e** was attributed to the presence of the 4-chlorophenyl moiety beside the CO and CN groups. Similarly, the high activity of compound **7c** was due to not only 4-chlorophenyl but also the carbonyl and pyrazole moieties. Moreover, the reactivity of **20f** was attributed to the 4-chlorophenyl together to the hydrazone and hydrazide moieties. A large number of points of contact are favorable from a pharmacodynamic perspective since it enables a more specific and unique drug-receptor interaction, concomitantly decreasing the likelihood of toxicity. However, a large number of points of contact are

Table 2 Cytotoxicity of the newly synthesized compounds against cancer cell lines (IC_{50})

Compound No	$IC_{50} \pm SEM$ (μM)					
	A549	H460	HT29	MKN-45	U87MG	SMMC-7721
4a	8.41 ± 2.53	10.09 ± 2.32	8.50 ± 2.73	8.42 ± 3.09	7.69 ± 2.52	8.71 ± 2.74
4b	7.63 ± 2.28	8.03 ± 3.17	6.59 ± 1.83	8.91 ± 2.72	5.48 ± 1.25	6.931.37
4c	12.95 ± 3.62	8.42 ± 2.39	10.09 ± 2.73	8.93 ± 3.28	10.43 ± 2.75	10.11 ± 2.74
4d	10.93 ± 2.26	8.82 ± 3.35	8.73 ± 2.28	10.83 ± 2.36	8.64 ± 2.65	8.58 ± 2.27
4e	0.23 ± 0.05	0.24 ± 0.06	0.18 ± 0.02	0.35 ± 0.18	0.36 ± 0.15	0.19 ± 0.04
4f	0.37 ± 0.08	0.42 ± 0.14	0.59 ± 0.13	0.20 ± 0.06	0.46 ± 0.21	0.39 ± 0.25
5a	8.62 ± 2.65	9.52 ± 3.06	9.35 ± 2.92	10.05 ± 2.53	8.32 ± 2.31	8.47 ± 2.04
5b	5.93 ± 1.38	3.28 ± 1.26	4.07 ± 2.31	6.29 ± 1.54	5.92 ± 1.36	6.20 ± 1.17
5c	2.66 ± 0.94	3.06 ± 1.15	2.73 ± 0.84	4.27 ± 1.06	3.52 ± 1.17	3.62 ± 1.02
5d	2.30 ± 0.96	2.48 ± 0.47	2.63 ± 0.59	1.08 ± 0.41	1.62 ± 0.86	1.80 ± 0.53
5e	0.23 ± 0.04	0.19 ± 0.08	0.48 ± 0.05	0.32 ± 0.03	0.42 ± 0.17	0.17 ± 0.03
5f	0.35 ± 0.12	0.28 ± 0.13	0.38 ± 0.16	0.34 ± 0.12	0.38 ± 0.19	0.50 ± 0.17
7a	3.34 ± 1.20	2.62 ± 1.50	2.83 ± 1.13	2.58 ± 0.89	1.15 ± 0.94	2.64 ± 1.07
7b	8.52 ± 2.46	9.14 ± 2.24	9.02 ± 1.73	8.45 ± 2.38	7.53 ± 2.21	6.98 ± 2.421
7c	0.22 ± 0.14	0.25 ± 0.18	0.36 ± 0.23	0.29 ± 0.26	0.35 ± 0.12	0.34 ± 0.25
9a	5.34 ± 1.69	4.80 ± 1.73	6.07 ± 1.47	5.38 ± 1.38	3.84 ± 1.71	5.80 ± 1.49
9b	10.52 ± 2.53	9.85 ± 2.68	8.47 ± 2.38	9.27 ± 2.51	8.24 ± 2.39	10.33 ± 3.62
9c	0.38 ± 0.16	0.29 ± 0.13	0.42 ± 0.15	3.40 ± 1.09	1.02 ± 0.49	0.32 ± 0.16
12a	3.23 ± 1.58	2.56 ± 1.83	0.65 ± 0.29	5.61 ± 1.47	1.17 ± 0.59	1.88 ± 0.87
12b	4.62 ± 1.45	3.60 ± 1.35	2.38 ± 1.69	4.29 ± 1.68	2.44 ± 0.38	3.63 ± 1.62
13	0.48 ± 0.20	0.36 ± 0.15	0.27 ± 0.11	0.30 ± 0.19	0.41 ± 0.15	0.68 ± 0.25
14a	8.53 ± 2.23	9.47 ± 2.62	8.95 ± 2.69	8.93 ± 2.37	10.22 ± 2.57	9.93 ± 2.52
14b	12.37 ± 2.40	10.82 ± 3.69	9.04 ± 2.52	10.33 ± 2.68	7.72 ± 2.83	9.53 ± 2.05
14c	0.36 ± 0.27	0.26 ± 0.06	0.29 ± 0.15	0.36 ± 0.15	0.42 ± 0.28	0.36 ± 0.16
15a	7.26 ± 2.42	7.15 ± 1.57	8.24 ± 2.83	6.37 ± 1.59	5.80 ± 1.32	6.94 ± 1.68
15b	8.69 ± 1.47	7.93 ± 2.53	8.94 ± 2.92	6.93 ± 1.33	7.79 ± 1.58	8.93 ± 2.40
15c	0.25 ± 0.16	0.35 ± 0.15	0.42 ± 0.26	0.39 ± 0..15	0.42 ± 0.09	0.53 ± 0.18
16a	6.73 ± 1.63	7.48 ± 2.40	8.63 ± 2.62	9.72 ± 2.48	7.44 ± 1.74	5.90 ± 1.16
16b	9.36 ± 1.65	8.42 ± 1.48	8.05 ± 2.32	7.04 ± 1.80	9.31 ± 2.42	10.17 ± 2.52
16c	5.83 ± 1.23	4.27 ± 1.63	3.63 ± 1.26	4.61 ± 1.58	6.29 ± 1.63	4.30 ± 1.31
16d	4.20 ± 1.13	5.42 ± 2.25	6.39 ± 1.25	4.25 ± 1.18	5.32 ± 1.18	6.29 ± 1.13
16e	0.52 ± 0.21	0.63 ± 0.42	0.41 ± 1.01	0.98 ± 0.36	1.88 ± 0.79	0.79 ± 0.37
16f	0.43 ± 0.23	0.34 ± 0.18	0.28 ± 0.16	0.34 ± 0.19	0.38 ± 0.16	0.23 ± 0.08
18a	10.23 ± 2.18	10.36 ± 2.31	8.27 ± 2.52	7.42 ± 1.45	8.72 ± 2.30	7.08 ± 2.35
18b	10.33 ± 2.53	8.78 ± 2.53	5.26 ± 1.28	6.58 ± 2.59	8.39 ± 2.28	10.46 ± 2.53
18c	1.28 ± 0.85	0.68 ± 0.29	0.52 ± 1.76	0.52 ± 0.27	0.62 ± 0.16	0.39 ± 0.17
20a	8.37 ± 2.51	9.39 ± 2.42	7.32 ± 2.07	8.70 ± 1.49	7.85 ± 2.39	10.21 ± 3.51
20b	12.22 ± 2.92	10.27 ± 3.45	8.16 ± 2.48	9.36 ± 2.69	8.28 ± 2.57	6.62 ± 1.92
20c	0.59 ± 0.26	0.22 ± 0.06	0.49 ± 0.21	0.62 ± 0.23	0.23 ± 0.13	0.53 ± 0.15
20d	8.84 ± 1.52	8.36 ± 1.93	7.26 ± 1.35	8.52 ± 2.29	8.70 ± 2.62	5.62 ± 1.40
20e	1.08 ± 0.69	1.73 ± 0.89	1.55 ± 0.63	2.25 ± 0.56	1.73 ± 0.59	1.83 ± 0.72
20f	0.28 ± 0.12	0.32 ± 0.21	0.29 ± 0.22	0.36 ± 0.18	0.48 ± 0.19	0.33 ± 0.13
Foretinib	0.08 ± 0.01	0.18 ± 0.03	0.15 ± 0.023	0.03 ± 0.0055	0.90 ± 0.13	0.44 ± 0.062

unfavorable from a pharmacokinetic perspective, since the resulting increased polarity of the drug molecule tends to decrease the pharmacological half-life and also to decrease the ability of the drug to diffuse across membranes during its distribution throughout the body. In general, most neuroactive drugs have 2–4 points of contact, while most non-neuroactive drugs have 3–6 points of contact. Through our study, it is clear that most of the synthesized molecules with two carbonyl groups (toxicophores) together with the heteroatom sites that enables 2–4 points of contact. A

relationship between chemical structure or chemical properties and biological action, SAR, is in the nature of things and undeniable, not with standing the fact that it is not always easily recognized. Firstly, the functional group approachs: This takes into account the significance of particular groups in the molecule for particular aspects, part processes, in the biological action. Examples are groups described aspharmacophores or toxicophores [43, 44]. Secondly, the integral approach: In this case the overall properties of the molecules count. When these two approaches were applicable through our synthesized molecule increases their applicability as good anticancer agents.

In vitro evaluation of the anticancer activity

A panel of approximately seventeen tumor cell lines at tenfold dilutions of five concentrations (100 µM, 10 µM, 1.0 µM, 0.1 µM and 0.01 µM) [45, 46] were used for testing the thieno[3,2-*f*]chromene derivatives **16a–f** (Table 3)+. The percentage of growth was evaluated spectrophotometrically versus controls not treated with test agents after 48-h exposure and using SRB protein assay to estimate cell viability or growth. Dose–response parameters were calculated for each cell line: GI_{50}-molarconcentration of the compound that inhibits 50% net cell growth. The tested compounds showed inhibition activity ($GI_{50} < 5$ µM) against the selected cancer cell lines that are classified into groups according to the type of disease, the data were shown through Table 3. Throughout compounds **16a–f**, there are three factors, the substituent at C-3 of the thiophene ring and the substituent at the 4-position of the aryl group. It is clear from Table 2 that all tested compounds exhibited high inhibitions toward the cell lines categorized according to the type of the disease. Compound **16a** (X = H, R′ = CN) exhibited high inhibition toward HOP-62, MDA-MB-435 and UACC-62 cell lines with IG_{50}'s 0.42, 0.41 and 0.88 µM, respectively. On the other hand, compound **16b** (X = H, R' = COOEt) showed high inhibitions toward HOP-62, HCT-15, UACC-62, OVCAR-3 cell lines with IG_{50}'s 0.31, 0.59, 0.39 and 0.25 µM, respectively. Compound **16c** (X = OCH_3, R′ = CN) showed high inhibitions toward RPMI-8262, HOP-62, HCT-15, KM12, UACC-62 and 786-0 cancer cell lines with IG_{50}'s 0.85, 0.29, 0.32, 0.35, 0.27 and 0.42 µM, respectively. Moreover, compound **16d** (X = OCH_3, R′ = COOEt) exhibited high inhibitions toward HI-60 (TB), HOP-62, HOP-62, NCI-H460, HCT-116, HCT-15, KM12, SF-295, UACC-62, OVCAR-3 and 786-0 cell lines with IG_{50}'s 0.47, 0.37, 0.22, 0.73, 0.40 and 0.31 µM, respectively. Interestingly, compounds **16e** (X = Cl, R′ = CN) and **16f** (X = Cl, R′ = COOEt) exhibited high inhibitions toward all cancer cell lines except compound **16e** showed moderate inhibitions toward NCI-H460 and MDA-MB-435 cell lines with IG_{50}'s 2.31 and 1.52 µM, respectively.

Cytotoxic activity

Hepatocellular carcinoma HepG2 and cervical carcinoma HeLa were used for screening of the newly synthesized compounds. The cytotoxicity of the compounds was determined using MTT assay and Doxorubicin as a positive control [47–51]. In general, it can be seen that all synthesized compounds exhibited cytotoxic activities against both tested cancer cell lines. Moreover, it can be seen that both cells

Table 3 The influence of compounds **16a–f** on the growth of individual tumor cell lines ($GI_{50} < 5$ µM)

	GI_{50}µM						
Disease	Cell line	16a	16b	16c	16d	16e	16f
Leukemia	CCRF-CEM	2.53	2.41	1.80	2.56	0.25	0.19
Leukemia	RPMI-8262	2.39	2.59	0.85	2.17	0.37	0.48
Leukemia	SR	3.72	2.83	1.79	2.50	0.26	0.18
Leukemia	HI-60 (TB)	2.48	3.21	2.59	0.47	0.31	0.27
Leukemia	K-526	2.53	1.27	2.77	3.17	0.53	0.24
NCS-Lung cancer	HOP-62	0.42	0.31	0.29	0.37	0.25	0.19
NCS-Lung cancer	NCI-H460	2.05	2.93	1.74	0.22	2.31	0.27
Colon cancer	HCT-116	2.64	2.72	1.06	0.73	0.82	0.25
Colon cancer	HCT-15	1.80	0.59	0.32	0.40	0.35	0.42
Colon cancer	KM12	3.68	4.09	0.35	0.31	0.33	2.26
CNS cancer	SF-295	2.04	3.64	2.80	0.59	0.19	0.27
CNS cancer	U251	2.38	3.05	2.95	1.41	0.38	0.26
Melanoma	LOX IMVI	2.43	2.26	1.58	2.44	0.22	0.37
Melanoma	MDA-MB-435	0.41	2.81	1.03	2.63	1.52	0.25
Melanoma	UACC-62	0.88	0.39	0.27	0.46	0.27	0.32
Ovarian cancer	OVCAR-3	2.90	0.25	2.53	0.80	0.22	0.50
Renal cancer	786-0	1.74	1.95	0.42	0.22	0.46	0.30

reacted in a dose-dependent manner toward the applied concentrations. Additionally, both tested cell lines varied in their response toward different synthesized compounds. Furthermore, based on the IC_{50} values (Table 4) obtained for the tested compounds, it can be seen that cytotoxic activities ranged from very strong to non-cytotoxic. Most of the tested compounds exhibited high cytotoxicity except compounds **4c**, **4d**, **5a**, **5c**, **7a**, **9b**, **12b**, **14a** and **16a**. The cytotoxic compounds exhibited higher inhibitions than the reference doxorubicin. For compounds **4a–c** and **5a–f** it was surprisingly that compound **4d** and **5d** exhibited the high cytotoxicity although they contain the electron donating OCH_3 group. On the other hand, compounds **4e**, **4f**, **5e** and **5f** (X = Cl) exhibited the highest inhibitions among the twelve compounds. Considering compounds **7a–c** and **9a–c** it was clear that compounds **7c** and **9c** exhibited the highest inhibitions toward and HeLa cell lines. The 3,4-dihydrochromeno[3,4-*c*]chromene derivative **13** exhibited high inhibitions against HepG2 and HeLa cell lines. For compounds **14a–c** and **15a–c** it was obvious compounds **14b**, **14c**, **15a** and **15c** showed highest inhibitions with IC_{50}'s 3.25, 1.68, 2.18 and 0.49 µM, respectively, against HepG2 cell line and IC_{50}'s 2.39, 3.14, 3.26 and 0.58 µM, respectively, against the HeLa cell line. For the thieno[3,2-*f*]chromene **16a–f**, compounds **16d**, **16e** and **16f** exhibited the highest inhibitions among the six compounds. Interestingly, the three compounds of the chromeno[5,6-*d*]thiazole derivatives **18a–c** and **20a–f** exhibited high inhibitions toward the HepG2 and HeLa cell lines.

In silico study for compounds 15c and 18c

EGFR

Docking study of compounds **15c** and **18c** was prepared by using AutoDock suite 4.2.6 softwar. Due to the structural similarities between the synthesized compounds and reference drugs presented in both EGFR and PIM-1 enzymes that may give promising molecular docking or at least give hint about expecting the antitumor activity of compounds we studied the molecular docking results of compounds **15c** and **18c**. The molecular docking study was done at first at ATP binding site of EGFR and PIM-1 kinases to surmise if these compounds have similar binding mode to the EGFR PIM-1 kinase inhibitors (Figs. 1, 2).

Many anticancer agents were designed to inhibit the tumor cells by diminishing the replication and transcription of DNA.EGFR (epidermal growth factor receptor) is a cellular trans-membrane tyrosine kinase significantly, secreted in elevated levels in many types of human tumors e.g. ovarian, colon, breast, renal and prostate [52, 53]. Irregular EGFR signaling probably play substantial role in the pathogenesis of cancer, and thus, the mechanisms of EGFR-mediated oncogenic signaling are of concern. The amplification of EGFR gene and over expression are a predominantly attractive feature of glioblastoma (GBM), which found in nearly 40% of tumors. In adults, GBM is most widespread primary

Table 4 Evaluations of the newly synthesized compounds against HepG2 and Hela cell lines

Compound	IC_{50} (µM)	
	HepG2	Hela cell
4a	4.59 ± 1.20	6.26 ± 2.31
4b	3.25 ± 1.63	2.04 ± 1.04
4c	7.27 ± 2.35	9.42 ± 2.56
4d	1.57 ± 0.62	2.37 ± 1.14
4e	0.32 ± 0.29	0.45 ± 0.18
4f	0.53 ± 0.20	0.29 ± 0.13
5a	7.62 ± 2.71	4.27 ± 1.53
5b	3.52 ± 1.08	2.52 ± 0.96
5c	5.72 ± 2.82	4.92 ± 1.65
5d	3.32 ± 1.26	5.72 ± 1.70
5e	0.42 ± 0.18	0.32 ± 0.18
5f	0.35 ± 0.16	0.22 ± 0.08
7a	6.42 ± 1.72	4.02 ± 1.63
7b	3.92 ± 1.79	2.62 ± 0.17
7c	0.28 ± 0.07	0.48 ± 0.29
9a	3.32 ± 1.94	2.91 ± 0.79
9b	6.48 ± 1.58	4.51 ± 1.72
9c	0.25 ± 0.09	0.35 ± 0.16
12a	3.60 ± 1.28	2.51 ± 1.72
12b	5.35 ± 1.47	3.15 ± 1.32
13	0.25 ± 0.08	0.53 ± 0.23
14a	8.16 ± 2.47	6.39 ± 2.62
14b	3.25 ± 1.18	4.45 ± 2.30
14c	1.68 ± 0.57	2.39 ± 1.01
15a	2.18 ± 1.32	3.14 ± 1.70
15b	4.37 ± 1.23	3.26 ± 1.14
15c	0.49 ± 0.27	0.58 ± 0.27
16a	6.53 ± 2.50	7.82 ± 2.50
16b	5.13 ± 1.27	4.72 ± 1.85
16c	8.66 ± 2.70	7.49 ± 2.35
16d	3.62 ± 1.53	4.57 ± 1.72
16e	0.52 ± 0.19	0.62 ± 0.15
16f	0.36 ± 0.18	0.42 ± 0.18
18a	1.85 ± 0.79	1.32 ± 0.92
18b	2.52 ± 0.58	3.76 ± 1.58
18c	0.42 ± 0.16	0.38 ± 0.20
20a	1.39 ± 0.75	2.40 ± 1.16
20b	2.30 ± 1.14	1.24 ± 0.72
20c	0.67 ± 0.38	1.37 ± 0.73
20d	2.62 ± 1.07	1.55 ± 0.84
20e	1.13 ± 0.67	0.85 ± 0.24
20f	0.64 ± 0.23	0.35 ± 0.12
Doxorubicin	4.50 ± 0.20	5.57 ± 0.40

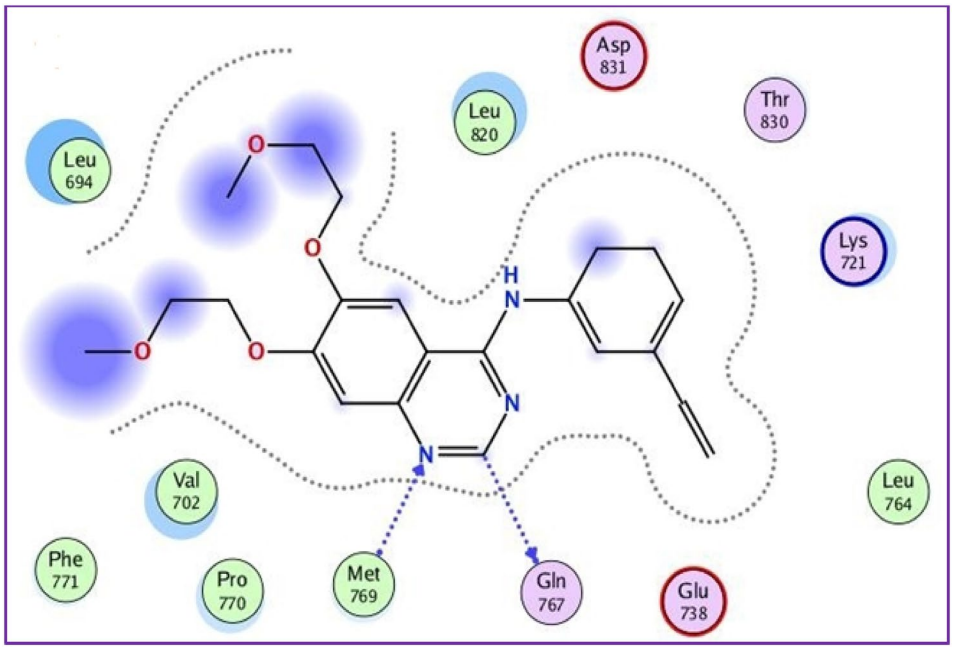


Fig. 1 Two dimensions Erlotinib ligand

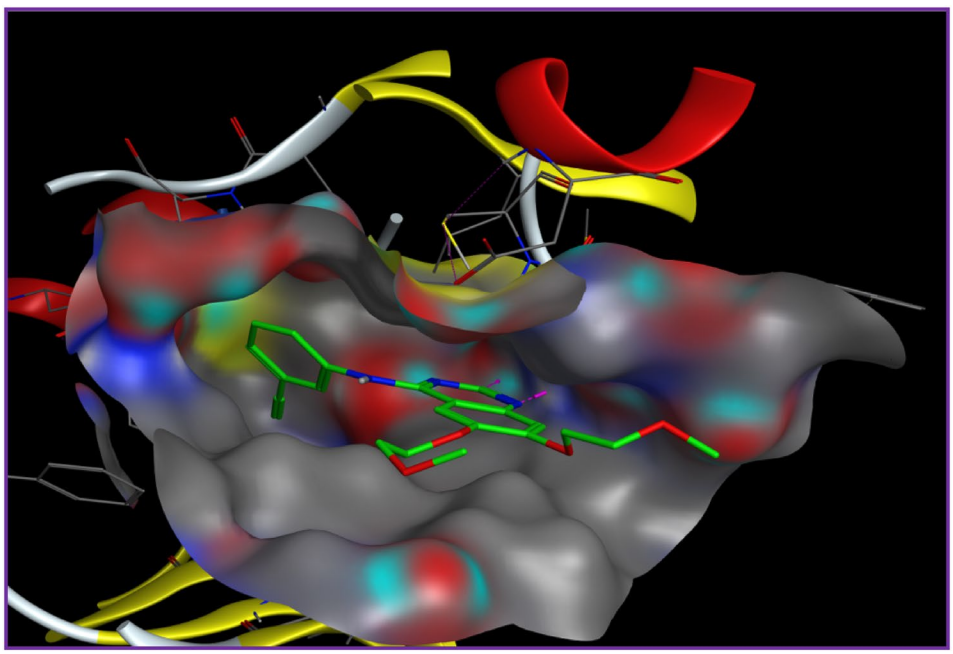


Fig. 2 Three dimensions Erlotinib ligand

malignant tumor of the central nervous system (CNS) [54]. The EGFR coding network donates an attractive objective for therapeutic intervention, and massive effort is converged on the trials to deactivating or blocking the receptor in different cancer types by using antibodies, tyrosine kinase inhibitors (TKIs) or even vaccines [55].

The docking results revealed good binding ability with highly energetically stable score of compounds **15c** and **18c** for EGFR. Molecular docking results of the compounds **15c** and **18c** into the ATP binding site of EGFR kinases were demonstrated. The targets compounds were docked into ATP of EGFR (1m17, from PDB: code 1M17 [56, 57] receptor active site pocket, which contain Erlotinib as co-crystallized ligand (Figs. 1, 2). A two hydrogen bonds showed clearly, and they expounded as, N-1 of the quinazoline ring binds to the hydrophobic pocket of N-terminal domain of Epidermal growth factor receptor tyrosine kinase (EGFR-TK) with NH Of Met-769 (backbone interaction) and C-2 of the quinazoline ring binds to C=O of Gln-767 (backbone interaction) via hydrog-en bonding. That interactions showed how quinazoline ring bindings explicating inhibitory effect EGFR. Similarly, **15c** and **18c** docking results showed that

compounds **15c** with two hydrogen bond with good bond length 3.22 and with very good harmony to the reference drug (RMSD = 1.32 and energy score of -6.60) (Figs. 3, 4). Whereas, compound **18c** gave one hydrogen bond supported with one aromatic interaction shown in (Table 5) (Figs. 5, 6).

PIM1 receptor

PIM1 crystal structure complex with its inhibitor uploaded from Protein Data Bank (PDB ID code: 2OBJ) [58–60]. Like EGFR, targets **15c** and **18c** were docked into the pocket of receptor active site shown in Figs. 3, 4, 5 and 6. Docking profiles do not differ from the practical data and revealed excellent RMSD &binding scores. Compound **18c** binds to the active amino acid residue with H-bonding and hydrophobic (aromatic) interaction typically as the co-crystalline ligand (6-(5-BROMO-2-HYDROXYPHENYL)-2-OXO-4-PHENYL-1,2-DIHYDRO-PYRIDINE-3-CARBONITRILE or VRV as named in PDB) as in Figs. 5 and 6. Compound **18c** showed two hydrogen bonds with 0.91 RMSD value confirming the superimposition fitness of **18c** interior the active site pocket similarly to VRVco-crystallized ligand.

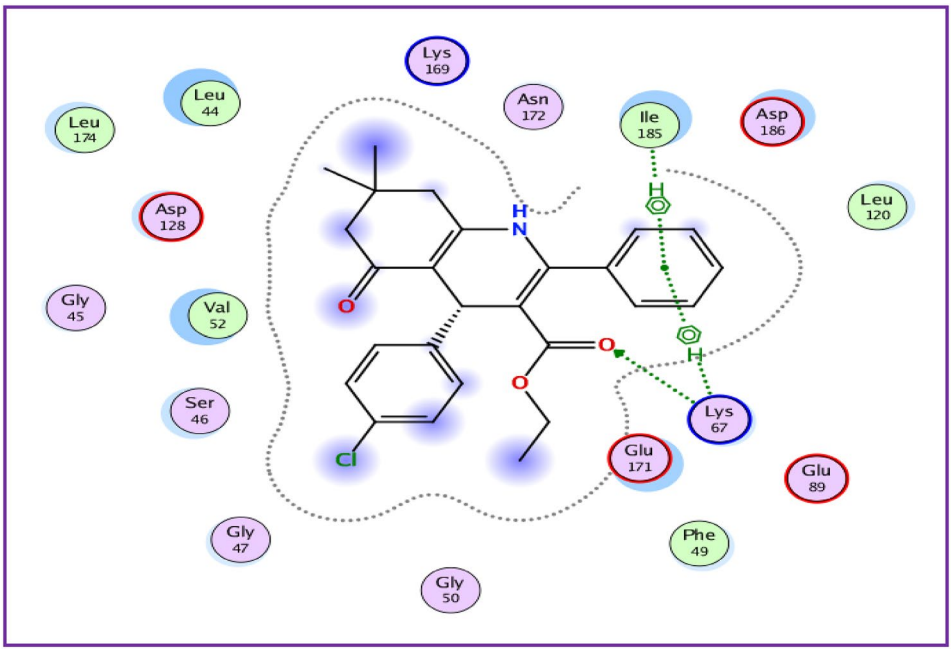


Fig. 3 Two dimensions of compound **15c**

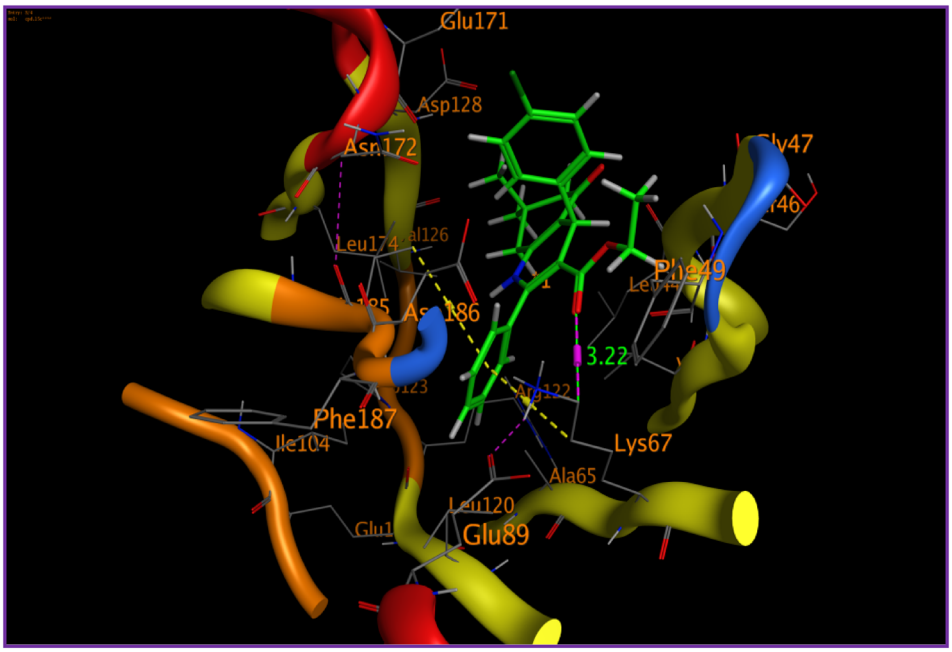


Fig. 4 Three dimensions of compound **15c** and Erlotinib (green)

Table 5 Docking results of compounds **15c** and **18a** onto PIM-1

Compound	Interactions	Type	Distance (A°)	Score	RMSD
Ref drug	Lys 67	Hydrogen bond	2.06	−6.646	0.9739
	Leu 174	aromatic	–		
15c	Lys 67	Hydrogen bond	3.22	−6.60	1.32
	Ile185	aromatic	–		
	Lys 67	Aromatic	–		
18c	Pro770	Hydrogen bond	4	−6.62	0.91
	Lue694	aromatic	–		

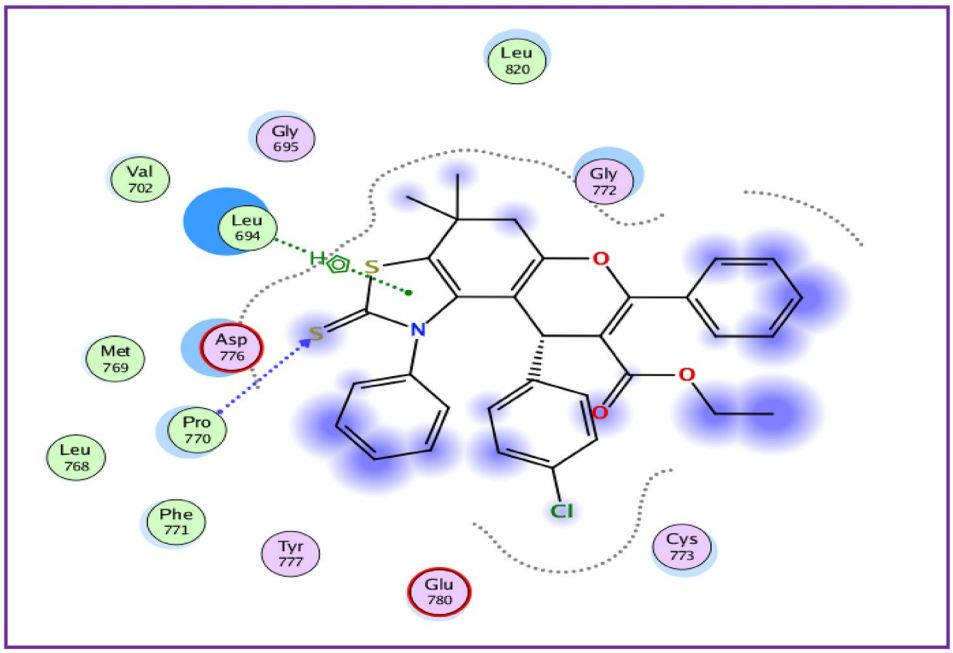


Fig. 5 Two dimensions of **18c**

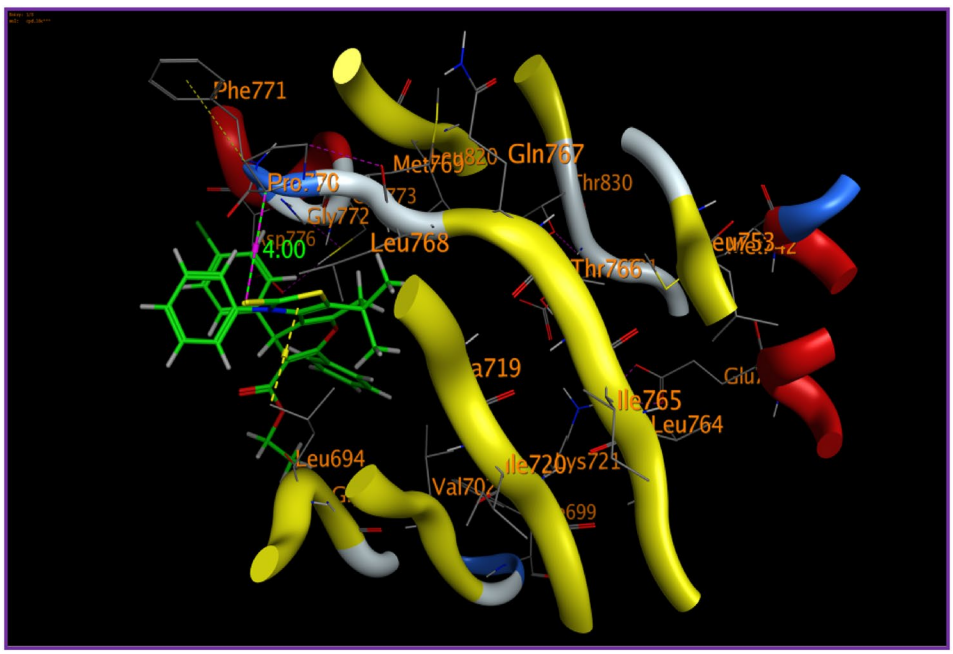


Fig. 6 Three dimensions of **18c** and Erlotinib (green)

Whereas, VRV itself displayed two interactions one of them is strong hydrogen bonding between Lys 67 and C=O with bond length of 4.0 angstrom and the other is aromatic interaction with Val52.

Docking procedure of EGFR kinase and PIM-1 kinase

The reference (co-crystallized) compounds in both 1M17 & 2OBJ were labeled as colored structure. The binding sites were recognized automatically from surfaces and maps options and docking proceeded directly after ligand and protein preparation. Default settings were done to perform molecular docking using MOE-Dock options through "Rotate Bonds" selection to permit flexible ligand-rigid receptor docking. The scoring function fitted to be London G with a replacement of Triangle matcher. 30Conformers of the highest score ligand were retained. The top five scoring of ligand-receptor docking was then viewed by 2D and 3D ligand-receptor interactions.

Enzyme inhibition

Based on the data obtained from the antitumor results listed in Tables 2 and 3 and molecular docking study consequences, compounds **15c** and **18c** were chosen to be *in-vitro* tested against both EGFR and Pim-1 enzymes and the equivalent Table 5 especially, these two compounds were chosen to study their enzyme inhibitions using ELISA-based EGFR-TK and Pim kinase kits. Based on the data of Table 5 compounds **15c** and **18c** showed high inhibitions toward EGFR and Pim-1 enzymes and such inhibitions were close to the references used Erlotinib and Qurecitin (Table 6).

Experimental

Dry solvents were used through this work and all Melting points of the synthesized compounds were recorded on Buchi melting point apparatus D-545. The IR spectra (KBr discs) were recorded on Bruker Vector 22 instrument. ^{13}C NMR and ^{1}H NMR spectra were measured on Bruker DPX300 instrument in DMSO-d_6 with TMS as internal standard. Mass spectra were measured using EIMS (Shimadzu) and ESI-esquire 3000 Bruker Daltonics instrument. Elemental analyses were measured using the Micro-analytical Data center at Cairo University. All reactions was monitored by TLC on 2 × 5 cm pre-coated silica gel 60 F254 plates of thickness of 0.25 mm (Merck) for getting complete reactions.

Table 6 In-vitro enzyme inhibition of **15c** and **18c** relative to positive standards of EGFR and Pim-1

Compound	IC_{50} EGFR (ng/mL)	IC_{50} Pim-1(ng/mL)
15c	20.37 ± 2.81	342.51 ± 19.32
18c	24.3 ± 3.51	316.27 ± 12.80
Erlotinib	20.1 ± 1.02	Not tested
Qurecitin	Not tested	300.57 ± 14.40

General procedure for the synthesis of the 7,8-dihydro-4H-chromen-5-one derivatives 4a–c

Method (A): Each of either benzaldehyde (1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) or chlorobenzaldehyde (1.40 g, 0.01 mol) and either malononitrile or ethyl cyanoacetate were added to a solution of dimedone (1.40 g, 0.01 mol) in ethanol (40 mL) containing triethylamine (0.50 mL). The reaction mixture was heated under reflux for 3 h then left to cool and the formed solid product, in each case was collected by filtration.

Method (B): Each of either benzaldehyde (1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) or chlorobenzaldehyde (1.40 g, 0.01 mol) and either malononitrile or ethyl cyanoacetate were added to dimedone (1.40 g, 0.01 mol). To the reaction mixture the Fe_3O_4@MCM-41-SO_3H@[HMIm][HSO_4] catalyst was added. The whole reaction mixture was reacted in a test tube with a glass bar at 110 °C under solvent-free condition for the appropriate time. When the reaction was completed, checked by TLC, the reaction mixture was dissolved in ethanol (5 mL) and the catalyst was isolated by applying the magnetic field. Then, the filtrate was concentrated on a rotary evaporator under reduced.pressure and the solid crude product created was washed with water and recrystallized from ethanol to afford pure products.

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4a)

Yellow crystals from 1,4-dioxane, yield (1.99 g, 68%), m.p.195–197 °C. IR (KBr) ν max (cm^{-1}): 3480–3320 (NH_2), 3050 (CH-aromatic), 2953 (CH-aliphatic), 2220 (CN), 1703 (CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.09, 1.03 (2s, 6H, $2CH_3$), 2.27, 2.39 (2s, 4H, $2CH_2$), 4.80 (s, 2H, D_2O exchangeable, NH_2), 6.50 (s, 1H, CH- pyran), 7.26–7.40 (m, 5H, C_6H_5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.3 ($2CH_3$), 36.3, 56.2 ($2CH_2$), 24.5 ($2CH_3$), 90.8 (pyran C-4), 116.8 (CN), 120.4, 121.8, 123.3, 124.2 (C_6H_5), 139.6, 140.3, 142.6, 145.8 (pyran C-2, C-3, C-5, C-6), 168.3 (C=O). Analysis Calculated for: $C_{18}H_{18}N_2O_2$ (294.35): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.58; H, 6.22; N, 9.69%. EIMS: m/z 294 $[M]^+$ (40%).

Ethyl 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4b)

Yellow crystals from 1,4-dioxane, yield (2.04 g, 60%), m.p. 145–147 °C. IR (KBr) ν max (cm^{-1}): 3490–3342 (NH_2), 3050 (CH-aromatic), 2953 (CH-aliphatic), 1703, 1690 (2CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.04 (2s, 6H, $2CH_3$), 1.12 (t, 3H, *J* = 6.88 Hz, CH_3), 2.27, 2.38 (2s, 4H, $2CH_2$), 4.20 (q, 2H, *J* = 6.88 Hz, CH_2), 4.83 (s, 2H, D_2O exchangeable, NH_2), 6.52 (s, 1H, CH- pyran), 7.25–7.42 (m, 5H, C_6H_5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.1 ($OCH_2\underline{CH_3}$), 24.4 ($2CH_3$), 36.1, 56.5 ($2CH_2$), 24.6 ($2CH_3$), 52.3 ($O\underline{CH_2}CH_3$), 90.7 (pyran C-4), 120.1, 120.9, 122.5, 124.9 (C_6H_5), 139.3, 140.2, 142.5, 144.3 (pyran C-2, C-3, C-5, C-6), 165.3, 168.1 (2C=O). Analysis Calculated for: $C_{20}H_{23}NO_4$ (341.40): C, 70.36; H, 6.79; N, 4.10. Found: C, 70.58; H, 6.72; N, 4.37%. EIMS: m/z 341 $[M]^+$ (40%).

2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4c)

Yellow crystals from 1,4-dioxane, yield (2.36 g, 73%, m.p. 219–221 °C. IR (KBr) ν max (cm^{-1}): 3468–3320 (NH_2), 3050 (CH-aromatic), 2953 (CH-aliphatic), 2220 (CN), 1702 (CO), 1582 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.04 (2s, 6H, $2CH_3$), 2.29, 2.32 (2s, 4H, $2CH_2$), 3.67 (s, 3H, OCH_3), 4.82 (s, 2H, D_2O exchangeable, NH_2), 6.53 (s, 1H, CH- pyran), 7.23–7.42 (m, 4H, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.6 ($2CH_3$), 36.1, 56.0 ($2CH_2$), 24.3 ($2CH_3$), 50.2 (OCH_3), 90.8 (pyran C-4), 116.8 (CN), 120.1, 122.6, 123.8, 125.6 (C_6H_4), 139.4, 140.1, 143.1, 144.5 (pyran C-2, C-3, C-5, C-6), 168.6 (C=O). Analysis Calculated for: $C_{19}H_{20}N_2O_3$ (324.37): C, 70.35; H, 6.21; N, 8.64%. Found: C, 70.51; H, 6.32; N, 8.70%. EIMS: m/z 324 $[M]^+$ (32%).

Ethyl 2-amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4d)

Pale yellow crystals from 1,4-dioxane, yield 64%, m.p. 145–147 °C. IR (KBr) ν max (cm^{-1}): 3479–3322 (NH_2), 3050 (CH-aromatic), 2950 (CH-aliphatic), 1702, 1690 (2CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.09, 1.06 (2s, 6H, $2CH_3$), 1.12 (t, 3H, *J* = 7.11 Hz, CH_3), 2.27, 2.38 (2s, 4H, $2CH_2$), 3.70 (s, 3H, OCH_3), 4.22 (q, 2H, *J* = 7.11 Hz, CH_2), 4.83 (s, 2H, D_2O exchangeable, NH_2), 6.50 (s, 1H, CH- pyran), 7.21–7.48 (m, 4H, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.2 ($OCH_2\underline{CH_3}$), 24.6 ($2CH_3$), 36.8, 56.3 ($2CH_2$), 24.8 ($2CH_3$), 52.1 ($O\underline{CH_2}CH_3$), 90.6 (pyran C-4), 120.2, 120.4, 122.8, 124.2 (C_6H_5), 139.1, 140.6, 142.8, 143.1 (pyran C-2, C-3, C-5, C-6), 165.5, 168.7 (C=O). Analysis Calculated for: $C_{21}H_{25}NO_5$ (371.43): C, 67.91; H, 6.78; N, 3.77%. Found: C, 67.83; H, 6.59; N, 3.80%. EIMS: m/z 371 $[M]^+$ (24%).

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4e)

Yellow crystals from 1,4-dioxane, yield (2.39 g, 73%, m.p. 210–213 °C. IR (KBr) ν max (cm^{-1}): 3469–3372 (NH_2), 3050 (CH-aromatic), 2955 (CH-aliphatic), 2220 (CN), 1703 (CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.03 (2s, 6H, $2CH_3$), 2.29, 2.36 (2s, 4H, $2CH_2$), 4.81 (s, 2H, D_2O exchangeable, NH_2), 6.53 (s, 1H, CH-pyran), 7.21–7.48 (m, 4H, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.6 ($2CH_3$), 36.2, 56.0 ($2CH_2$), 24.8 ($2CH_3$), 90.6 (pyran C-4), 116.7 (CN), 120.2, 121.6, 122.9, 125.6 (C_6H_4), 139.3, 140.1, 143.2, 144.0 (pyran C-2, C-3, C-5, C-6), 168.6 (C=O). Analysis Calculated for: $C_{18}H_{17}ClN_2O_2$ (328.79): C, 65.75; H, 5.21; N, 8.52. Found: C, 65.90; H, 5.41; N, 8.73%. EIMS: m/z 328 $[M]^+$ (46%).

Ethyl 2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4f)

Yellow crystals from ethanol, yield (2.70 g, 72%), m.p. 133–135 °C. IR (KBr) ν max (cm^{-1}): 3487–3361 (NH_2), 3050 (CH-aromatic), 2953 (CH-aliphatic), 1702, 1688 (2CO), 1583 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.05 (2s, 6H, $2CH_3$), 1.12 (t, 3H, *J* = 7.02 Hz, CH_3), 2.24, 2.39 (2s, 4H, $2CH_2$), 4.20 (q, 2H, *J* = 7.02 Hz, CH_2), 4.85 (s, 2H, D_2O exchangeable, NH_2), 6.50 (s, 1H, CH- pyran), 7.23–7.52 (m, 4H, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.2 ($OCH_2\underline{CH_3}$), 24.6 ($2CH_3$), 36.2, 56.3 ($2CH_2$), 24.8 ($2CH_3$), 52.3 ($O\underline{CH_2}CH_3$), 90.6 (pyran C-4), 120.5, 122.9, 123.8, 126.2 (C_6H_4), 139.5, 140.6, 143.2, 144.1 (pyran C-2, C-3, C-5, C-6), 165.6, 168.7 (C=O). Analysis Calculated for: $C_{20}H_{22}ClNO_4$ (375.85: C, 63.91; H, 5.90; N, 3.72%. Found: C, 64.27; H, 6.11; N, 3.59%. EIMS: m/z 375 $[M]^+$ (32%).

General procedure for the synthesis of the thieno[3,2-f]chromene derivatives 5a–f

Each of either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 g, 0.01 mol) were added to a solution of either compounds **4a** (2.94 g, 0.01 mol), **4c** (3.24 g, 0.01 mol) or **4e** (3.28 g, 0.01 mol) in 1,4-dioxane (50 mL) containing triethylamine (0.50 mL). The reaction mixture was heated under reflux for 2 h then poured onto ice/water

containing a few drops of hydrochloric acid and the precipitated solid product was collected by filtration.

2,7-Diamino-4,4-dimethyl-9-phenyl-5,9-dihydro-4*H*-thieno[3,2-*f*]-chromene-1,8-dicarbonitrile (5a)

Orange crystals from ethanol, yield (2.24 g, 60%), m.p. 185–187 °C. IR (KBr) ν max (cm^{-1}): 3497–3340 ($2NH_2$), 3050 (CH-aromatic), 2953 (CH-aliphatic), 2223, 2220 (2CN), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.03 (2s, 6H, $2CH_3$), 2.40 (s, 2H, CH_2), 4.87, 5.22 (2s, 4H, D_2O exchangeable, $2NH_2$), 6.52 (s, 1H, CH- pyran), 7.23–7.42 (m, 5H, C_6H_5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.6 ($2CH_3$), 56.0 (CH_2), 24.5 ($2CH_3$), 90.5 (pyran C-4), 116.8, 117.0 (2CN), 120.2, 121.4, 124.1, 125.6 (C_6H_5), 136.0, 138.2, 139.8, 140.1, 142.8, 143.2, 143.8, 145.8 (thiophene C, pyran C-2, C-3, C-5, C-6). Analysis Calculated for $C_{21}H_{18}N_4OS$ (374.46): C, 67.36; H, 4.85; N, 14.56; S, 8.56%. Found: C, 67.53; H, 5.61; N, 15.23; S, 8.73%. EIMS: m/z 374 $[M]^+$ (28%).

Ethyl 2,7-diamino-8-cyano-4,4-dimethyl-9-phenyl-5,9-dihydro-4*H*-thieno-[3,2-*f*]hromene-1-carboxylate (5b)

Orange crystals from ethanol, yield (2.86 g, 68%, m.p. 215–217 °C. IR (KBr) ν max (cm^{-1}): 3488–3318 ($2NH_2$), 3050 (CH-aromatic), 2953 (CH-aliphatic), 2220 (CN), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.04 (2s, 6H, $2CH_3$), 1.12 (t, 3H, J = 5.92 Hz, CH_3), 2.49 (s, 2H, CH_2), 4.20 (q, 2H, J = 5.92 Hz, CH_2), 4.85, 5.29 (2s, 4H, D_2O exchangeable, $2NH_2$), 6.51 (s, 1H, CH- pyran), 7.25–7.40 (m, 5H, C_6H_5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.2 ($OCH_2\underline{CH_3}$), 24.6 ($2CH_3$), 52.3 ($O\underline{CH_2}CH_3$), 56.3 (CH_2), 24.6 ($2CH_3$), 90.8 (pyran C-4), 116.9 (CN), 120.3, 122.7, 124.8, 126.1 (C_6H_5), 136.4, 137.8, 139.2, 140.6, 142.3, 143.9, 143.3, 144.5 (thiophene C, pyran C-2, C-3, C-5, C-6). Analysis Calculated for $C_{23}H_{23}N_3O_3S$ (421.51): C, 65.54; H, 5.50; N, 9.97; S, 7.61. Found: C, 65.36; H, 5.72; N, 10.13; S, 7.80%. EIMS: m/z 421 $[M]^+$ (36%).

2,7-Diamino-9-(4-methoxyphenyl)-4,4-dimethyl-5,9-dihydro-4*H*-thieno-[3,2-*f*]chromene-1,8-dicarbonitrile (5c)

Orange crystals from ethanol, yield (2.50 g, 62%), m.p.187–189 °C. IR (KBr) ν max (cm^{-1}): 3488–3362 ($2NH_2$), 3050 (CH-aromatic), 2953 (CH-aliphatic), 2222, 2220 (2CN), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.03 (2s, 6H, $2CH_3$), 2.42 (2s, 4H, $2CH_2$), 4.84, 5.25 (2s, 4H, D_2O exchangeable, $2NH_2$), 6.58 (s, 1H, CH-pyran), 7.22–7.46 (m, 5H, C_6H_5). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.6 ($2CH_3$), 50.4 (OCH_3), 56.3 (CH_2), 24.8 ($2CH_3$), 90.6 (pyran C-4), 116.7, 117.1 (2CN), 120.4, 120.8, 123.6, 126.4 (C_6H_4), 136.3, 137.6, 139.5, 140.6, 142.3, 143.6, 143.5, 144.2 (thiophene C, pyran C-2, C-3, C-5, C-6). Analysis Calculated for $C_{22}H_{20}N_4O_2S$ (404.48): C, 65.33; H, 4.98; N, 13.85; S, 7.93%. Found: C, 65.40; H, 5.19; N, 14.02; S, 8.04%. EIMS: m/z 404 $[M]^+$ (22%).

Ethyl 2,7-diamino-8-cyano-9-(4-methoxyphenyl)-4,4-dimethyl-5,9-dihydro-4*H*-thieno[3,2-*f*]chromene-1-carboxylate (5d)

Orange crystals from ethanol, yield (3.47 g, 77%), m.p. 187–189 °C. IR (KBr) ν max (cm^{-1}): 3464–3358 ($2NH_2$), 3050 (CH-aromatic), 2953 (CH-aliphatic), 2220 (CN), 1582 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.03 (2s, 6H, $2CH_3$), 1.12 (t, 3H, J = 6.26 Hz, CH_3), 2.47 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3), 4.21 (q, 2H, J = 6.26 Hz, CH_2), 4.84, 5.26 (2s, 4H, D_2O exchangeable, $2NH_2$), 6.53 (s, 1H, CH-pyran), 7.22–7.45 (m, 4H, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.1 ($OCH_2\underline{CH_3}$), 24.6 ($2CH_3$), 50.4 (OCH_3), 52.3 ($O\underline{CH_2}CH_3$), 56.6 (CH_2), 24.3 ($2CH_3$), 90.8 pyran C-4), 116.8 (CN), 120.1, 122.4, 123.9, 125.2 (C_6H_4), 136.2, 137.6, 138.3, 139.2, 142.6, 143.3, 143.6, 144.1 (thiophene C, pyran C-2, C-3, C-5, C-6). Analysis Calculated for $C_{24}H_{25}N_3O_4S$ (451.54): C, 63.84; H, 5.58; N, 9.31; S, 7.10%. Found: C, 65.03; H, 5.68; N, 9.44; S, 7.29%. EIMS: m/z 451 $[M]^+$ (26%).

2,7-Diamino-9-(4-chlorophenyl)-4,4-dimethyl-5,9-dihydro-4*H*-thien[3,2-*f*]chromene-1,8-dicarbonitrile (5e)

Orange crystals from ethanol, yield (2.69 g, 66%), m.p. 185–188 °C. IR (KBr) ν max (cm^{-1}): 3486–3343 ($2NH_2$), 3050 (CH-aromatic), 2952 (CH-aliphatic), 2222, 2220 (2CN), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.03 (2s, 6H, $2CH_3$), 2.41 (s, 2H, CH_2), 4.89, 5.21 (2s, 4H, D_2O exchangeable, $2NH_2$), 6.50 (s, 1H, CH- pyran), 7.21–7.43 (m, 4H, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 56.2 (CH_2), 24.7 ($2CH_3$), 90.8 (pyran C-4), 116.7, 117.1 (2CN), 120.4, 122.7, 124.6, 126.2 (C_6H_4), 136.2, 137.7, 139.3, 140.6, 142.7, 143.8, 144.2, 145.5 (thiophene C, pyran C-2, C-3, C-5, C-6). Analysis Calculated for $C_{21}H_{17}ClN_4OS$ (408.90): C, 61.68; H, 4.19; N, 13.70; S, 7.84%. Found: C, 61.73; H, 4.35; N, 13.83; S, 9.12%. EIMS: m/z 408 $[M]^+$ (22%).

Ethyl 2,7-diamino-8-cyano-9-(4-methoxyphenyl)-4,4-dimethyl-5,9-dihydro-4*H*-thieno[3,2-*f*]chromene-1-carboxylate (5f)

Orange crystals from ethanol, yield (3.50, 77%), m.p. 197–180 °C. IR (KBr) ν max (cm^{-1}): 3464–3358 ($2NH_2$), 3050 (CH-aromatic), 2953 (CH-aliphatic), 2220 (CN), 1687 (CO), 1582 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.03 (2s, 6H, $2CH_3$), 1.12 (t, 3H, J = 6.26 Hz,

CH_3), 2.47 (s, 2H, CH_2), 4.21 (q, 2H, $J = 6.26$ Hz, CH_2), 4.84, 5.26 (2s, 4H, D_2O exchangeable, $2NH_2$), 6.53 (s, 1H, CH- pyran), 7.22–7.45 (m, 4H, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.1 ($OCH_2\underline{CH_3}$), 52.3 ($O\underline{CH_2}CH_3$), 56.6 (CH_2), 24.3 ($2CH_3$), 90.6 (pyran C-4), 116.8 (CN), 120.1, 122.4, 123.9, 125.2 (C_6H_4), 136.2, 137.6, 138.3, 139.2, 142.6, 143.3, 143.6, 144.1 (thiophene C, pyran C-2, C-3, C-5, C-6). Analysis Calculated for $C_{23}H_{22}ClN_3O_3S$ (455.96): C, 60.59; H, 4.86; N, 9.22; S, 7.03%. Found: C, 60.26; H, 5.02; N, 9.53; S, 7.26%. EIMS: m/z 455 $[M]^+$ (26%).

General procedure for the synthesis of the tetrahydrochromeno[2,3-c]pyrazol-5(1H)-one derivatives 7a–c

Method (A): To a solution of compounds **1** (1.40 g, 0.01 mol) in absolute ethanol (50 mL) containing triethylamine (0.50 mL) each of either benzaldehyde (1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) or chlorobenzaldehyde (1.40 g, 0.01 mol) and the 3-methyl-1H-pyrazol-5(4H)-one (0.98 g, 0.01) were added. The reaction mixture was heated under reflux for 2 h then poured onto ice/water containing a few drops of hydrochloric acid and the precipitated solid product was collected by filtration.

Method (B): Each of either benzaldehyde (1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) or chlorobenzaldehyde (1.40 g, 0.01 mol) and either malononitrile or ethyl cyanoacetate were added to 3-methyl-1H-pyrazol-5(4H)-one (0.98 g, 0.01). To the reaction mixture the Fe_3O_4@MCM-41-SO_3H@[HMIm][HSO_4] catalyst (0.50 g) was added and the whole mixture was reacted in a test tube with a glass bar at 110 °C under solvent-free condition for the appropriate time. When the reaction was completed, checked by TLC, the reaction mixture was dissolved in ethanol (5 mL) and the catalyst was isolated by applying the magnetic field. Then, the filtrate was concentrated on a rotary evaporator under reduced pressure and the solid crude product created was washed with water and recrystallized from ethanol to afford pure products.

3,7,7-Trimethyl-4-phenyl-4,6,7,8-tetrahydrochromeno[2,3-*c*]pyrazol-5(1*H*)-one (7a)

Yellow crystals from 1,4-dioxane, yield (2.21 g, 72%), m.p. 163–167 °C. IR (KBr) ν max (cm^{-1}): 3494–3346 (NH), 3050 (CH-aromatic), 2953 (CH-aliphatic), 1702 (CO), 1580 (C=C). ^1H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.03 (2s, 6H, $2CH_3$), 2.23, 2.36 (2s, 4H, $2CH_2$), 2.68 (s, 3H, CH_3), 6.52 (s, 1H, CH- pyran), 7.24–7.43 (m, 5H, C_6H_5), 8.31 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.4 ($2CH_3$), 36.1, 56.4 ($2CH_2$), 24.7 ($2CH_3$), 90.6 (pyran C-4), 116.6 (CN), 120.2, 121.5, 122.8, 123.8 (C_6H_5), 138.2, 139.3, 140.3, 141.8, 142.4, 143.5 (pyrazole C-4, C-5, pyran C-2, C-3, C-5, C-6), 168.6 (C=O). Analysis Calculated for: $C_{19}H_{20}N_2O_2$ (308.37): C, 74.00; H, 6.54; N, 9.08%. Found: C, 73.92; H, 6.39; N, 9.17%. EIMS: m/z 308 $[M]^+$ (36%).

4-(4-Methoxyphenyl)-3,7,7-trimethyl-4,6,7,8-tetrahydrochromeno[2,3-*c*]pyrazol-5(1*H*)-one (7b)

Yellow crystals from 1,4-dioxane, yield (3.56 g, 76%), m.p.124–126 °C. IR (KBr) ν max (cm^{-1}): 3483–3351 (NH), 3050 (CH-aromatic), 2955 (CH-aliphatic), 1702 (CO), 1581 (C=C). ^1H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.03 (2s, 6H, $2CH_3$), 2.24, 2.39 (2s, 4H, $2CH_2$), 2.66 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 6.54 (s, 1H, CH- pyran), 7.24–7.48 (m, 4H, C_6H_4), 8.31 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 36.3, 56.2 ($2CH_2$), 24.8 ($2CH_3$), 36.8 (CH_3), 50.4 (OCH_3), 90.6 (pyran C-4), 116.8 (CN), 120.6, 121.8, 122.4, 125.2 (C_6H_4), 138.1, 139.5, 141.7, 142.3, 143.1, 143.9 (pyrazole C-4, C-5, pyran C-2, C-3, C-5, C-6), 168.8 (C=O). Analysis Calculated for:$C_{20}H_{22}N_2O_3$ (338.40): C, 70.99; H, 6.55; N, 8.28%. Found: C, 70.73; H, 6.33; N, 8.40%. EIMS: m/z 338 $[M]^+$ (28%).

4-(4-Chlorophenyl)-3,7,7-trimethyl-4,6,7,8-tetrahydrochromeno[2,3-*c*]pyrazol-5(1*H*)-one (7c)

Yellow crystals from 1,4-dioxane, yield (2.25 g, 66%, m.p. 123–126 °C. IR (KBr) ν max (cm^{-1}): 3463–3325 (NH), 3050 (CH-aromatic), 2953 (CH-aliphatic), 1701 (CO), 1583 (C=C). ^1H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.02 (2s, 6H, $2CH_3$), 2.22, 2.38 (2s, 4H, $2CH_2$), 2.66 (s, 3H, CH_3), 6.54 (s, 1H, CH- pyran), 7.24–7.49 (m, 4H, C_6H_4), 8.30 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 36.4, 56.2 ($2CH_2$), 24.8 ($2CH_3$), 36.7 (CH_3), 50.8 (pyran C-4), 116.9 (CN), 120.5, 122.7, 123.2, 124.5 (C_6H_5), 138.5, 139.2, 140.8, 141.6, 142.2, 143.8 (pyrazole C-4, C-5, pyran C-2, C-3, C-5, C-6), 168.8 (C=O). Analysis Calculated for: $C_{19}H_{19}ClN_2O_2$ (342.82): C, 66.57; H, 5.59; N, 8.17. Found: C, 66.39; H, 5.42; N, 8.38%. EIMS: m/z 342 $[M]^+$ (40%).

General procedure of the hexahydroquinoline-3-carbonitrile derivatives 9a–c

Method (A): To a stirred solution of compounds **1** (1.40 g, 0.01 mol) in 1,4-dioxane (50 mL) containing triethylamine (0.50 mL) each of either 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 cyanothioacetamide (1.00 g, 0.01) were added. The reaction mixture was heated under reflux for 3 h then poured onto ice/water containing a few drops of hydrochloric acid and the precipitated solid product was collected by filtration.

Method (B): Each of either benzaldehyde (1.06 g, 0.01 mol), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) or chlorobenzaldehyde (1.40 g, 0.01 mol) and either cyanothioacetamide (1.00 g, 0.01) were added to compounds **1** (1.40 g, 0.01 mol). To the reaction mixture the Fe_3O_4@MCM-41-SO_3H@[HMIm][HSO_4] catalyst was added. The whole reaction mixture was reacted in a test tube with a glass bar at 110 °C under solvent-free condition for the appropriate time. When the reaction was completed, checked by TLC, the reaction mixture was dissolved in ethanol (5 mL) and the catalyst was isolated by applying the magnetic field. Then, the filtrate was concentrated on a rotary evaporator under reduced pressure and the solid crude product created was washed with water and recrystallized from ethanol to afford pure products.

7,7-Dimethyl-5-oxo-4-phenyl-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (9a)

Yellow crystals from ethanol, yield (2.09 g, 68%), m.p. 223–226 °C. IR (KBr) ν max (cm^{-1}): 3479–3331 (NH), 3050 (CH-aromatic), 2950 (CH-aliphatic), 2220 (CN), 1703 (CO), 1582 (C=C), 1206 (C=S). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.04 (2s, 6H, $2CH_3$), 2.25, 2.38 (2s, 4H, $2CH_2$), 7.26–7.41 (m, 5H, C_6H_5), 8.38 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.8 ($2CH_3$), 36.4, 56.3 ($2CH_2$), 94.2 (pyridine C-4), 116.9 (CN), 120.7, 122.8, 124.3, 125.6 (C_6H_5), 138.6, 139.8, 142.9, 143.2 (pyridine C-2, C-3, C-5, C-6), 168.4 (C=O), 180.3 (C=S). Analysis Calculated for: $C_{18}H_{16}N_2OS$ (308.40): C, 70.10; H, 5.23; N, 9.08; S, 10.40. Found: C, 70.38; H, 5.42; N, 9.25; S, 10.29%. EIMS: m/z 308 $[M]^+$ (22%).

4-(4-Methoxyphenyl)-7,7-dimethyl-5-oxo-2-thioxo-1,2,5,6,7,8-hexahydro-quinoline-3-carbonitrile (9b)

Pale yellow crystals from ethanol, yield (2.64 g, 73%), m.p. 180–182 °C. IR (KBr) ν max (cm^{-1}): 3458–3329 (NH), 3050 (CH-aromatic), 2950 (CH-aliphatic), 2220 (CN), 1702 (CO), 1586 (C=C), 1208 (C=S). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.02 (2s, 6H, $2CH_3$), 2.23, 2.37 (2s, 4H, $2CH_2$), 3.66 (s, 3H, OCH_3), 7.21–7.48 (m, 4H, C_6H_4), 8.38 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 36.3, 56.5 ($2CH_2$), 24.8 ($2CH_3$), 50.8 (OCH_3), 94.5 (pyridine C-4), 116.8 (CN), 120.2, 122.4, 124.3, 126.9 (C_6H_5), 138.6, 139.6, 140.8, 143.2 (pyridine C-2, C-3, C-5, C-6), 168.2 (C=O), 180.5 (C=S). Analysis Calculated for:$C_{19}H_{18}N_2O_2S$ (338.42): C, 67.43; H, 5.36; N, 8.28; S, 9.47%. Found: C, 67.58; H, 5.29; N, 8.36; S, 9.52%. EIMS: m/z 338 $[M]^+$ (18%).

4-(4-Chlorophenyl)-7,7-dimethyl-5-oxo-2-thioxo-1,2,5,6,7,8-hexahydro-quinoline-3-carbonitrile (9c)

Yellow crystals from ethanol, yield (1.98 g, 58%), m.p. 166–168 °C. IR (KBr) ν max (cm^{-1}): 3493–3326 (NH), 3050 (CH-aromatic), 2950 (CH-aliphatic), 2220 (CN), 1701 (CO), 1582 (C=C), 1205 (C=S). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.05 (2s, 6H, $2CH_3$), 2.26, 2.37 (2s, 4H, $2CH_2$), 7.21–7.48 (m, 4H, C_6H_4), 8.37 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 36.2, 56.5 ($2CH_2$), 24.6 ($2CH_3$), 116.9 (CN), 120.5, 122.6, 124.6, 126.2 (C_6H_4), 138.8, 139.5, 142.3, 143.6 (pyridine C-3, C-4, C-5, C-6), 168.6 (C=O), 180.5 (C=S). Analysis Calculated for: $C_{18}H_{15}ClN_2OS$ (342.84): C, 63.06; H, 4.41; N, 8.17; S, 9.35%. Found: C, 63.32; H, 4.46; N, 8.25; S, 9.60%. EIMS: m/z 342 $[M]^+$ (28%).

General procedure for the synthesis of the dihydrochromeno[3,4-c]chromene derivatives 12a,b

Method (A): To a solution of compounds **1** (1.40 g, 0.01 mol) in absolute ethanol (50 mL) containing triethylamine (0.50 mL) each of either ethyl benzoylacetate (1.92 g, 0.01 mol) or ethyl acetoacetate (1.30 g, 0.01 mol) and salicylaldehyde (1.22 g, 0.01) were added. The reaction mixture was heated under reflux for 3 h then poured onto ice/water containing a few drops of hydrochloric acid and the precipitated solid product was collected by filtration.

Method (B) Each of either ethyl benzoylacetate (1.92 g, 0.01 mol) or ethyl acetoacetate (1.30 g, 0.01 mol) and salicylaldehyde (1.22 g, 0.01) were added to compounds **1** (1.40 g, 0.01 mol). To the reaction mixture, the Fe_3O_4@MCM-41-SO_3H@[HMIm][HSO_4] catalyst was added. The whole reaction mixture was reacted in a test tube with a glass bar at 110 °C under solvent-free condition for the appropriate time. When the reaction was completed, checked by TLC, the reaction mixture was dissolved in ethanol (5 mL) and the catalyst was isolated by applying the magnetic field. Then, the filtrate was concentrated on a rotary evaporator under reduced pressure and the solid crude product created was washed with water and recrystallized from ethanol to afford pure products.

3,3-Dimethyl-6-phenyl-3,4-dihydrochromeno[3,4-*c*]chromene-1,7-(2*H*,12b*H*)-dione (12a)

Yellow crystals from 1,4-dioxane, yield (2.04 g, 55%), m.p. 186–188 °C. IR (KBr) ν max (cm^{-1}): 3055 (CH-aromatic), 2950 (CH-aliphatic), 1703–1690 (2CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.09, 1.03 (2s, 6H, $2CH_3$), 2.27, 2.41 (2s, 4H, $2CH_2$), 6.52 (s, 1H, CH- pyran), 7.26–7.42 (m, 9H, C_6H_5, C_6H_4). ^{13}C NMR (DMSO-d_6,

75 MHz): δ 36.5, 56.0 ($2CH_2$), 24.8 ($2CH_3$), 90.6 (pyran C-4), 120.6, 120.9, 121.8, 122.3, 125.2, 126.1, 128.3 (C_6H_5, C_6H_4), 139.3, 140.2, 142.8, 145.2 (pyran C-2, C-3, C-5, C-6), 166.5, 168.4 (2C=O). Analysis Calculated for: $C_{24}H_{20}O_4$ (372.41): C, 77.40; H, 5.41%. Found: C, 77.26; H, 5.60%. EIMS: m/z 372 $[M]^+$ (38%).

3,3,6-Trimethyl-3,4-dihydrochromeno[3,4-*c*] chromene-1,7(2*H*,12b*H*)-dione (12b)

Yellow crystals from ethanol/DMF, yield (2.10 g, 68%), m.p. 208–211 °C. IR (KBr) ν max (cm^{-1}): 3055 (CH-aromatic), 2950 (CH-aliphatic), 1701–1690 (2CO), 1582 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.04 (2s, 6H, $2CH_3$), 2.28, 2.43 (2s, 4H, $2CH_2$), 2.69 (s, 3H, CH_3), 6.55 (s, 1H, CH- pyran), 7.24–7.45 (m, 4H, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.8 (CH_3), 36.53, 56.2 ($2CH_2$), 24.7 ($2CH_3$), 28.4 (CH_3), 120.5, 123.2, 125.2, 128.5 (C_6H_4), 139.4, 140.5, 142.3, 144.6 (pyran C-2, C-3, C-5, C-6), 166.3, 168.2 (2C=O). Analysis Calculated for: $C_{19}H_{18}O_4$ (310.34): C, 73.53; H, 5.85. Found: C, 73.70; H, 5.92%. EIMS: m/z 310 $[M]^+$ (26%).

6-Amino-3,3-dimethyl-3,4-dihydrochromeno[3,4-*c*] chromene-1,7-(2*H*,12*b*H)-dione (13)

Mrthod (A): Equimolar amounts of compounds **1** (1.40 g, 0.01 mol) in absolute ethanol (50 mL) containing triethylamine (0.50 mL) and either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 g, 0.01 mol) and salicylaldehyde (1.22 g, 0.01) were mixed. The reaction mixture was heated under reflux for 3 h then poured onto ice/water containing a few drops of hydrochloric acid and the precipitated solid product was collected by filtration.

Method B: Each of either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.07 g, 0.01 mol) and salicylaldehyde (1.22 g, 0.01) were added to compounds **1** (1.40 g, 0.01 mol). To the reaction mixture, the Fe_3O_4@MCM-41-SO_3H@[HMIm][HSO_4] catalyst was added. The whole reaction mixture was reacted in a test tube with a glass bar at 110 °C under solvent-free condition for the appropriate time. When the reaction was completed, checked by TLC, the reaction mixture was dissolved in ethanol (5 mL) and the catalyst was isolated by applying the magnetic field. Then, the filtrate was concentrated on a rotary evaporator under reduced pressure and the solid crude product created was washed with water and recrystallized from ethanol to afford pure products.

Pale yellow crystals from 1,4-dioxane, yield (217 g, 70%), m.p. 196–198 °C. IR (KBr) ν max (cm^{-1}): 3055 (CH-aromatic), 2950 (CH-aliphatic), 1703–1700 (2CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.04 (2s, 6H, $2CH_3$), 2.28, 2.43 (2s, 4H, $2CH_2$), 4.93 (s, 2H, D_2O exchangeable, NH_2), 6.54 (s, 1H, CH- pyran), 7.26–7.42 (m, 4H, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.8 (CH_3), 36.53, 56.2 ($2CH_2$), 24.7 ($2CH_3$), 90.7 (pyran C-4), 120.3, 122.7, 124.5, 127.3 (C_6H_4), 139.9, 141.3, 142.8, 143.4 (pyran C-2, C-3, C-5, C-6), 165.8, 168.6 (2C=O). Analysis Calculated for: $C_{18}H_{17}NO_4$ (311.33): C, 69.44; H, 5.50; N, 4.50%. Found: C, 69.60; H, 5.73; N, 4.69%. EIMS: m/z 311 $[M]^+$ (32%).

General procedure for the synthesis of the pyran derivatives 14a–c

Method (A): Each of either 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 ethyl benzoylacetate (1.92 g, 0.01) were added to a solution of compounds **1** (1.40 g, 0.01 mol) in absolute ethanol (50 mL) containing triethylamine (0.50 mL). The reaction mixture was heated under reflux for 5 h then poured onto ice/water containing a few drops of hydrochloric acid and the precipitated solid product was collected by filtration.

Method (B) Each of either 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 ethyl benzoylacetate (1.92 g, 0.01) were added to a solution of compounds **1** (1.40 g, 0.01 mol). To the reaction mixture, the Fe_3O_4@MCM-41-SO_3H@[HMIm][HSO_4] catalyst was added. The whole reaction mixture was reacted in a test tube with a glass bar at 110 °C under solvent-free condition for the appropriate time. When the reaction was completed, checked by TLC, the reaction mixture was dissolved in ethanol (5 mL) and the catalyst was isolated by applying the magnetic field. Then, the filtrate was concentrated on a rotary evaporator under reduced pressure and the solid crude product created was washed with water and recrystallized from ethanol to afford pure products.

Ethyl 7,7-dimethyl-5-oxo-2,4-diphenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (14a)

Yellow crystals from ethanol, yield (257 g, 64%), m.p. 195–197 °C. IR (KBr) ν max (cm^{-1}): 3050 (CH-aromatic), 2953 (CH-aliphatic), 1705, 1690 (2CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.03 (2s, 6H, $2CH_3$), 1.12 (t, 3H, J = 7.13 Hz, CH_3), 2.25, 2.39 (2s, 4H, $2CH_2$), 4.22 (q, 2H, J = 7.13 Hz, CH_2), 6.52 (s, 1H, CH- pyran), 7.26–7.46 (m, 10H, $2C_6H_5$). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.3 ($OCH_2\underline{CH_3}$), 36.3, 56.7 ($2CH_2$), 24.8 ($2CH_3$), 52.1 ($O\underline{CH_2}CH_3$), 90.6 (pyran C-4), 120.1, 120.6, 121.4, 121.8, 122.5, 123.6, 124.0, 124.8 ($2C_6H_5$), 139.4, 140.2, 142.8, 143.8 (pyran C-2, C-3, C-5, C-6), 165.6, 168.7 (2C=O). Analysis Calculated for: $C_{26}H_{26}O_4$ (402.48): C, 77.59; H,

6.51%. Found: C, 77.80; H, 6.39%. EIMS: m/z 402 $[M]^+$ (36%).

Ethyl 4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-2-phenyl-5,6,7,8-tetra-hydro-4*H*-chromene-3-carboxylate (14b)

Yellow crystals from ethanol, yield (2.80 g, 65%), m.p. 253–256 °C. IR (KBr) ν max (cm^{-1}): 3050 (CH-aromatic), 2955 (CH-aliphatic), 1705, 1692 (2CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.02 (2s, 6H, $2CH_3$), 1.13 (t, 3H, J = 7.42 Hz, CH_3), 2.23, 2.37 (2s, 4H, $2CH_2$), 3.67 (s, 3H, OCH_3), 4.22 (q, 2H, J = 7.42 Hz, CH_2), 6.50 (s, 1H, CH- pyran), 7.24–7.49 (m, 9H, C_6H_5, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.2 ($OCH_2\underline{CH_3}$), 36.6, 56.4 ($2CH_2$), 24.7 ($2CH_3$), 50.8 (OCH_3), 52.2 ($O\underline{CH_2}CH_3$), 90.8 (pyran C-4), 120.2, 120.4, 121.6, 121.9, 122.2, 123.8, 124.0, 125.6 (C_6H_5, C_6H_4), 139.2, 140.8, 142.4, 143.6 (pyran C-2, C-3, C-5, C-6), 165.3, 168.9 (2C=O). Analysis Calculated for: $C_{27}H_{28}O_5$ (432.51): C, 74.98; H, 6.53%. Found: C, 75.26; H, 6.32%. EIMS: m/z 432 $[M]^+$ (25%).$^+$

Ethyl 4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-2-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (14c)

Yellow crystals from 1,4-dioxane, yield (3.05 g, 70%), m.p. 239–242 °C. IR (KBr) ν max (cm^{-1}): 3053 (CH-aromatic), 2953 (CH-aliphatic), 1703, 1689 (2CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.04 (2s, 6H, $2CH_3$), 1.12 (t, 3H, J = 6.40 Hz, CH_3), 2.25, 2.39 (2s, 4H, $2CH_2$), 4.22 (q, 2H, J = 6.40 Hz, CH_2), 6.53 (s, 1H, CH- pyran), 7.24–7.52 (m, 9H, C_6H_5, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.2 ($OCH_2\underline{CH_3}$), 36.2, 56.8 ($2CH_2$), 24.8 ($2CH_3$), 52.3 ($O\underline{CH_2}CH_3$), 90.6 (pyran C-4), 120.4, 120.9, 121.6, 121.5, 122.7, 124.8, 125.6, 126.4 (C_6H_5, C_6H_4), 139.2, 140.5, 142.3, 144.7 (pyran C-2, C-3, C-5, C-6), 165.3, 168.9 (2C=O). Analysis Calculated for: $C_{26}H_{25}ClO_4$ (436.93): C, 71.47; H, 5.77%. Found: C, 71.24; H, 5.92%. EIMS: m/z 436 $[M]^+$ (42%).

General procedure for the synthesis of the pyridine derivatives 15a–c

To a solution of compounds **1** (1.40 g, 0.01 mol) in absolute ethanol (50 mL) containing ammonium acetate (1.0 g mL) each of either 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 ethyl benzoylacetate (1.92 g, 0.01) were added. The reaction mixture was heated under reflux for 5 h then poured onto ice/water containing a few drops of hydrochloric acid and the precipitated solid product was collected by filtration.

Ethyl 7,7-dimethyl-5-oxo-2,4-diphenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (15a)

Yellow crystals from 1,4-dioxane, yield (3.12 g, 78%), m.p. 202–205 °C. IR (KBr) ν max (cm^{-1}): 3570–3329 (NH), 3050 (CH-aromatic), 2950 (CH-aliphatic), 1703, 1690 (2CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.03 (2s, 6H, $2CH_3$), 1.12 (t, 3H, J = 5.80 Hz, CH_3), 2.22, 2.38 (2s, 4H, $2CH_2$), 4.22 (q, 2H, J = 5.80 Hz, CH_2), 6.50 (s, 1H, CH- pyridine), 7.28–7.40 (m, 10H, $2C_6H_5$), 8.38 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.2 ($OCH_2\underline{CH_3}$), 36.4, 56.5 ($2CH_2$), 24.7 ($2CH_3$), 52.2 ($O\underline{CH_2}CH_3$), 94.2 (pyridine C-4), 119.8, 120.4, 121.6, 121.9, 122.3, 122.6, 124.3, 125.2 ($2C_6H_5$), 139.2, 141.1, 143.4, 144.2 (pyridine C-2, C-3, C-5, C-6), 165.4, 168.9 (2C=O). Analysis Calculated for: $C_{26}H_{27}NO_3$ (401.50): C, 77.78; H, 6.78; N, 3.49%. Found: C, 77.85; H, 6.53; N, 3.62%. EIMS: m/z 401 $[M]^+$ (28%).

Ethyl 4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylate (15b)

Yellow crystals from 1,4-dioxane, yield (3.01 g,70%), m.p. 266–268 °C. IR (KBr) ν max (cm^{-1}): 3570–3352 (NH), 3050 (CH-aromatic), 2955 (CH-aliphatic), 1703, 1690 (2CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.03 (2s, 6H, $2CH_3$), 1.12 (t, 3H, J = 7.29 Hz, CH_3), 2.23, 2.37 (2s, 4H, $2CH_2$), 3.67 (s, 3H, OCH_3), 4.22 (q, 2H, J = 7.29 Hz, CH_2), 6.50 (s, 1H, CH- pyridine), 7.24–7.49 (m, 9H, C_6H_5, C_6H_4), 8.28 (s, 1H, NH).. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.2 ($OCH_2\underline{CH_3}$), 36.6, 56.4 ($2CH_2$), 24.8 ($2CH_3$), 50.7 (OCH_3), 52.1 ($O\underline{CH_2}CH_3$), 95.2 (pyridine C-4), 120.1, 120.6, 121.8, 121.3, 122.7, 123.3, 124.2, 126.9 (C_6H_5, C_6H_4), 139.3, 140.2, 141.8, 144.2 (pyridine C-2, C-3, C-5, C-6), 165.3, 168.9 (2C=O). Analysis Calculated for: $C_{27}H_{29}NO_4$ (431.52): C, 75.15; H, 6.77; N, 3.25. Found: C, 75.28; H, 6.49; N, 3.50%. EIMS: m/z 431 $[M]^+$ (32%).

Ethyl 4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylate (15c)

Yellow crystals from 1,4-dioxane, yield (2.87 g, 66%), m.p. 168–170 °C. IR (KBr) ν max (cm^{-1}): 3472–3327 (NH), 3055 (CH-aromatic), 2950 (CH-aliphatic), 1702, 1689 (2CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.04 (2s, 6H, $2CH_3$), 1.12 (t, 3H, J = 6.32 Hz, CH_3), 2.23, 2.38 (2s, 4H, $2CH_2$), 4.21 (q, 2H, J = 6.32 Hz, CH_2), 6.53 (s, 1H, CH- pyridine), 7.22–7.54 (m, 9H, C_6H_5, C_6H_4), 8.30 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.2 ($OCH_2\underline{CH_3}$), 36.4, 56.8 ($2CH_2$), 24.8 ($2CH_3$), 52.6 ($O\underline{CH_2}CH_3$), 94.2 (pyridine C-4), 120.3, 120.6, 121.3, 121.9, 122.2, 124.6, 125.1, 126.8 (C_6H_5, C_6H_4), 139.5, 140.5, 142.7, 143.2 (pyridine C-2, C3, C-5, C-6), 165.3, 168.7 (2C=O). Analysis

Calculated for: $C_{26}H_{26}ClNO_3$ (435.94): C, 71.63; H, 6.01; N, 3.21%. Found: C, 71.42; H, 5.86; N, 3.33%. EIMS: m/z 435 $[M]^+$ (30%).

General procedure for the synthesis of the thieno[3,2-f]chromene-8-carboxylate 16a–f

To a solution of either compounds **14a** (4.02 g, 0.01 mol), **14b** (4.32 g, 0.01 mol) or **14c** (4.36 g, 0.01 mol) in 1,4-dioxane (50 mL) containing triethylamine (0.50 mL) each of either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) were added. The reaction mixture was heated under reflux for 2 h then poured onto ice/water containing a few drops of hydrochloric acid and the precipitated solid product was collected by filtration.

Ethyl 2-amino-1-cyano-4,4-dimethyl-7,9-diphenyl-5,9-dihydro-4*H*-thieno[3,2-*f*]chromene-8-carboxylate (16a)

Pale orange crystals from acetic acid, yield (3.27 g, 68%), m.p. 162–165 °C. IR (KBr) ν max (cm^{-1}): 3474–3328 (NH_2), 3050 (CH-aromatic), 2953 (CH-aliphatic), 2220 (CN), 1689 (CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.04 (2s, 6H, $2CH_3$), 1.12 (t, 3H, J = 5.86 Hz, CH_3), 2.43 (s, 2H, CH_2), 4.22 (q, 2H, J = 5.86 Hz, CH_2), 5.18 (s, 2H, D_2O exchangeable, NH_2), 6.50 (s, 1H, CH-pyran), 7.25–7.40 (m, 10H, $2C_6H_5$). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.2 ($OCH_2\underline{CH_3}$), 24.5 ($2CH_3$), 56.0 (CH_2), 52.1 ($O\underline{CH_2}CH_3$), 90.6 (pyridine C-4), 116.8 (CN), 120.1, 122.6, 123.3, 123.8, 124.7, 125.1, 125.4, 126.4 ($2C_6H_5$), 136.3, 138.8, 139.4, 141.4, 142.5, 143.0, 143.2, 144.5 (thiophene C, pyran C-2, C-3, C-5, C-6), 165.8 (CO). Analysis Calculated for: $C_{29}H_{26}N_2O_3S$ (482.59): C, 72.17; H, 5.43; N, 5.80; S, 6.64%. Found: C, 72.29; H, 5.50; N, 5.71; S, 6.93%. EIMS: m/z 482 $[M]^+$ (44%).

Diethyl 2-amino-4,4-dimethyl-7,9-diphenyl-5,9-dihydro-4*H*-thieno[3,2-*f*]chromene-1,8-dicarboxylate (16b)

Pale orange crystals from acetic acid, yield 78%, m.p. 129–131 °C. IR (KBr) ν max (cm^{-1}): 3458–3341 (NH_2), 3050 (CH-aromatic), 2953 (CH-aliphatic), 1689, 1687 (2CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.04 (2s, 6H, $2CH_3$), 1.11, 1.12 (2t, 6H, J = 5.86, 6.83 Hz, $2CH_3$), 2.43 (s, 2H, CH_2), 4.19, 4.22 (2q, 4H, J = 5.86, 6.83 Hz, $2CH_2$), 5.17 (s, 2H, D_2O exchangeable, NH_2), 6.53 (s, 1H, CH-pyran), 7.23–7.46 (m, 10H, $2C_6H_5$). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.1, 16.2 (two $OCH_2\underline{CH_3}$), 24.7 ($2CH_3$), 56.2 (CH_2), 52.1, 52.3 (two $O\underline{CH_2}CH_3$), 90.5 (pyran C-4), 120.3, 122.7, 123.2, 123.5, 124.9, 125.3, 125.6, 126.8 ($2C_6H_5$), 136.5, 138.7, 139.9, 140.3, 142.8, 143.2, 143.7, 143.3 (thiophene C, pyran C-2, C-3, C-5, C-6), 165.6, 166.2 (2CO). Analysis Calculated for: $C_{31}H_{31}NO_5S$ (529.65): C, 70.30; H, 5.90; N, 2.64; S, 6.05. Found: C, 70.52; H, 5.74; N, 2.83; S, 6.25%. EIMS: m/z 529 $[M]^+$ (26%).

Ethyl 2-amino-1-cyano-9-(4-methoxyphenyl)-4,4-dimethyl-7-phenyl-5,9-dihydro-4*H*-thieno[3,2-*f*]chromene-8-carboxylate (16c)

Pale orange crystals from acetic acid, yield (3.07 g, 60%), m.p. 143–145 °C. IR (KBr) ν max (cm^{-1}): 3483–3342 (NH_2), 3050 (CH-aromatic), 2953 (CH-aliphatic), 2220 (CN), 1688 (CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.05 (2s, 6H, $2CH_3$), 1.13 (t, 3H, J = 7.22 Hz, CH_3), 2.45 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3), 4.23 (q, 2H, J = 7.22 Hz, CH_2), 5.21 (s, 2H, D_2O exchangeable, NH_2), 6.50 (s, 1H, CH- pyran), 7.22–7.48 (m, 9H, C_6H_5, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.1 ($OCH_2\underline{CH_3}$), 24.8 ($2CH_3$), 50.2 (OCH_3), 56.2 (CH_2), 52.2 ($O\underline{CH_2}CH_3$), 90.5 (pyran C-5), 116.8 (CN), 120.3, 121.4, 121.8, 122.5, 123.67, 125.8, 126.8, 127.4 (C_6H_5, C_6H_4), 136.1, 138.6, 139.2, 141.7, 142.6, 142.8, 143.5, 144.8 (thiophene C, pyran C-2, C-3, C-5, C-6), 165.6, 166.3 (2CO). Analysis Calculated for: $C_{30}H_{28}N_2O_4S$ (512.62): C, 70.29; H, 5.51; N, 5.46; S, 6.26. Found: C, 70.42; H, 5.46; N, 5.61; S, 6.38%. EIMS: m/z 512 $[M]^+$ (46%).

Diethyl 2-amino-9-(4-methoxyphenyl)-4,4-dimethyl-7-phenyl-5,9-dihydro-4*H*-thieno[3,2-*f*]chromene-1,8-dicarboxylate (16d)

Yellow crystals from acetic acid, yield (3.91 g, 70%, m.p. 231–233 °C. IR (KBr) ν max (cm^{-1}): 3472–3330 (NH_2), 3050 (CH-aromatic), 2955 (CH-aliphatic), 1688, 1686 (2CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.09, 1.05 (2s, 6H, $2CH_3$), 1.12, 1.13 (2t, 6H, J = 7.22, 7.31 Hz, $2CH_3$), 2.43 (s, 2H, CH_2), 4.19, 3.67 (s, 3H, OCH_3), 4.22 (2q, 4H, J = 7.22, 7.31 Hz, $2CH_2$), 5.18 (s, 2H, D_2O exchangeable, NH_2), 6.51 (s, 1H, CH- pyran), 7.22–7.52 (m, 9H, C_6H_5, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.1, 16.3 (two $OCH_2\underline{CH_3}$), 24.8 ($2CH_3$), 56.3 (CH_2), 50.8 (OCH_3), 52.2, 52.3 (two $O\underline{CH_2}CH_3$), 90.6 (pyran C-4), 120.1, 121.3, 123.7, 123.9, 124.3, 125.1, 125.4, 126.5 (C_6H_5, C_6H_4), 136.3, 138.6, 139.5, 140.7, 143.2, 143.6, 143.3, 143.4 (thiophene C, pyran C-2, C-3, C-54, C-6), 165.3, 166.6 (2CO). Analysis Calculated for: $C_{32}H_{33}NO_6S$ (559.67): C, 68.67; H, 5.94; N, 2.50; S, 5.73%. Found: C, 68.52; H, 5.88; N, 2.71; S, 5.62%. EIMS: m/z 559 $[M]^+$ (33%).

Ethyl 2-amino-9-(4-chlorophenyl)-1-cyano-4,4-dimethyl-7-phenyl-5,9-dihydro-4*H*-thieno[3,2-*f*]chromene-8-carboxylate (16e)

Pale orange crystals from acetic acid, yield (3.72 g, 72%), m.p. 111–113 °C. IR (KBr) ν max (cm^{-1}): 3493–3340 (NH_2),

3050 (CH-aromatic), 2951 (CH-aliphatic), 2220 (CN), 1688 (CO), 1580 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.03 (2s, 6H, $2CH_3$), 1.13 (t, 3H, J = 7.02 Hz, CH_3), 2.46 (s, 2H, CH_2), 4.22 (q, 2H, J = 7.02 Hz, CH_2), 5.21 (s, 2H, D_2O exchangeable, NH_2), 6.54 (s, 1H, CH- pyran), 7.25–7.40 (m, 9H, C_6H_5, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.1 ($OCH_2\underline{CH_3}$), 24.7 ($2CH_3$), 56.3 (CH_2), 52.2 ($O\underline{CH_2}CH_3$), 90.7 (pyran C-4), 116.8 (CN), 120.0, 121.8, 123.6, 124.5, 125.2, 125.7, 126.1, 127.0 (C_6H_5, C_6H_4), 136.4, 138.7, 139.2, 141.1, 142.8, 143.2, 143.6, 144.7 (thiophene C, pyran C-2, C-3, C-5, C-6), 165.5 (CO). Analysis Calculated for: $C_{29}H_{25}ClN_2O_3S$ (517.04): C, 67.37; H, 4.87; N, 5.42; S, 6.20%. Found: C, 67.55; H, 5.04; N, 5.60; S, 6.42%. EIMS: m/z 517 $[M]^+$ (32%).

Diethyl 2-amino-9-(4-chlorophenyl)-4,4-dimethyl-7-phenyl-5,9-dihydro-4*H*-thieno-[3,2-*f*]chromene-1,8-dicarboxylate (16f)

Yellow crystals from acetic acid, yield (33.77 g, 67%), m.p. 85 °C. IR (KBr) ν max (cm^{-1}): 3483–3327 (NH_2), 3050 (CH-aromatic), 2955 (CH-aliphatic), 1688, 1686 (2CO), 1584 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.04 (2s, 6H, $2CH_3$), 1.12, 1.14 (2t, 6H, J = 6.25, 7.51 Hz, $2CH_3$), 2.43 (s, 2H, CH_2), 4.19, 4.22 (2q, 4H, J = 6.25, 7.51 Hz, $2CH_2$), 5.18 (s, 2H, D_2O exchangeable, NH_2), 6.51 (s, 1H, CH- pyran), 7.22–7.52 (m, 9H, C_6H_5, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.1, 16.3 (two $OCH_2\underline{CH_3}$), 24.8 ($2CH_3$), 56.3 (CH_2), 52.1, 52.4 (two $O\underline{CH_2}CH_3$), 90.6 (pyran C-4), 120.5, 120.9, 122.3, 123.5, 124.1, 125.4, 125.8, 127.9 (C_6H_5, C_6H_4), 136.5, 137.8, 139.2, 140.5, 143.9, 143.3, 143.6, 144.1 (thiophene C, pyran C-2, C-3, C-5, C-6), 165.6, 166.9 (2CO). Analysis Calculated for: $C_{31}H_{30}ClNO_5S$ (564.09): C, 66.01; H, 5.36; N, 2.48; S, 5.68%. Found: C, 66.26; H, 5.46; N, 2.62; S, 5.80%. EIMS: m/z 564 $[M]^+$ (26%).

Synthesis of the chromeno[5,6-d]thiazole derivatives 18a–c

Equimolar amounts of either **14a** (4.02 g, 0.01 mol), **14b** (4.32 g, 0.01 mol) or **14c** (4.36 g, 0.01 mol) in absolute ethanol (50 mL) containing triethylamine (1.0 mL), elemental sulfur (0.32 g, 0.01 mol) and phenylisothiocyanate (1.30 g, 0.01 mol) were mixed together. The reaction mixture, in each case was heated under reflux for 2 h then poured onto ice/water containing a few drops of hydrochloric acid and the formed solid product was collected by filtration.

Ethyl 4,4-dimethyl-1,7,9-triphenyl-2-thioxo-2,4,5,9-tetrahydro-1*H*-chromeno[5,6-*d*]thiazole-8-carboxylate (18a)

Orange crystals from ethanol, yield (3.30 g, 60%), m.p. 221–223 °C. IR (KBr) ν max (cm^{-1}): 3050 (CH-aromatic), 2956 (CH-aliphatic), 1688 (CO), 1580 (C=C), 1210 (C=S). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.03 (2s, 6H, $2CH_3$), 1.16 (t, 3H, J = 7.05 Hz, $OCH_2\underline{CH_3}$), 2.40 (s, 2H, CH_2), 4.22 (q, 2H, J = 7.05 Hz, $O\underline{CH_2}CH_3$), 6.56 (s, 1H, CH- pyran), 7.25–7.42 (m, 15H, $3C_6H_5$). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.2 ($OCH_2\underline{CH_3}$), 24.3 ($2CH_3$), 50.2 (OCH_2CH_3), 56.0 (CH_2), 90.8 (pyran C-4),119.0, 119.6, 120.4, 121.5, 122.2, 122.6, 123.1, 123.6, 124.6, 124.9, 125.1, 125.8 ($3C_6H_5$), 134.1, 136.7, 139.2, 140.1, 142.8, 143.2, 143.8, 145.8 (thiazole C, pyran C-2, C-3, C-5, C-6), 178.7 (C=S). Analysis Calculated for $C_{33}H_{29}NO_3S_2$ (551.72): C, 71.84; H, 5.30; N, 2.54; S, 11.62%. Found: C, 71.96; H, 5.48; N, 2.80; S, 11.80%. EIMS: m/z 551 $[M]^+$ (80%).

Ethyl 9-(4-methoxyphenyl)-4,4-dimethyl-1,7-diphenyl-2-thioxo-2,4,5,9-tetrahydro-1*H*-chromeno[5,6-*d*]thiazole-8-carboxylate (18b)

Orange crystals from 1,4-dioxane, yield (3.83 g, 66%), m.p. 201–204 °C. IR (KBr) ν max (cm^{-1}): 3050 (CH-aromatic), 2955 (CH-aliphatic), 1688 (CO), 1620 (C=C), 1218 (C=S). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.05 (2s, 6H, $2CH_3$), 1.13 (t, 3H, J = 6.95 Hz, $OCH_2\underline{CH_3}$), 2.43 (s, 2H, CH_2), 3.70 (s, 3H, CH_3), 4.22 (q, 2H, J = 6.95 Hz, $O\underline{CH_2}CH_3$), 6.53 (s, 1H, CH- pyran), 7.24–7.56 (m, 14H, $2C_6H_5$, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.5 ($OCH_2\underline{CH_3}$), 24.6 ($2CH_3$), 50.1 (OCH_2CH_3), 50.7 (OCH_3), 56.0 (CH_2), 90.7 (pyran C-4), 119.2, 119.5, 120.3, 120.7, 122.1, 122.8, 123.3, 123.8, 124.2, 124.7, 125.5, 126.4 ($2C_6H_5$, C_6H_4), 133.8, 135.2, 139.1, 140.3, 142.2, 143.5, 143.4, 145.9 (thiazole C, pyran C-2, C-3, C-5, C-6), 178.9 (C=S). Analysis Calculated for $C_{34}H_{31}NO_4S_2$ (581.74): C, 70.20; H, 5.37; N, 2.41; S, 11.02%. Found: C, 70.39; H, 5.43; N, 2.67; S, 11.19%. EIMS: m/z 581 $[M]^+$ (76%).

Ethyl 9-(4-chlorophenyl)-4,4-dimethyl-1,7-diphenyl-2-thioxo-2,4,5,9-tetrahydro-1*H*-chromeno[5,6-*d*]thiazole-8-carboxylate (18c)

Orange crystals from ethanol, yield (2.90 g, 50%), m.p. 156–158 °C. IR (KBr) ν max (cm^{-1}): 3050 (CH-aromatic), 2954 (CH-aliphatic), 1689 (CO), 1580 (C=C), 1212 (C=S). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.03 (2s, 6H, $2CH_3$), 1.16 (t, 3H, J = 6.30 Hz, $OCH_2\underline{CH_3}$), 2.43 (s, 2H, CH_2), 4.22 (q, 2H, J = 6.30 Hz, $O\underline{CH_2}CH_3$), 6.58 (s, 1H, CH- pyran), 7.25–7.56 (m, 14H, $2C_6H_5$, C_6H_4). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.5 ($OCH_2\underline{CH_3}$), 24.6 ($2CH_3$), 50.5 (OCH_2CH_3), 56.3 (CH_2), 90.8 (pyran C-4), 119.3, 120.0, 120.4, 121.8, 122.1, 122.7, 123.1, 123.9, 124.2, 124.5, 125.3, 125.5 ($2C_6H_5$, C_6H_4), 133.6, 136.9, 139.1, 140.1, 142.5, 143.2, 143.7, 145.3 (thiazole C, pyran C-2, C-3, C-5, C-6), 178.9 (C=S). Analysis Calculated for $C_{33}H_{28}ClNO_3S_2$

(586.16): C, 67.62; H, 4.81; N, 2.39; S, 10.94%. Found: C, 67.82; H, 5.02; N, 2.42; S, 11.19%. EIMS: m/z 586 $[M]^+$ (58%).

General procedure for the synthesis of the hydrazide derivatives 20a–f

To a solution of either **18a** (5.51 g, 0.01 mol), **18b** (5.81 g, 0.01 mol) or **18c** (5.85 g, 0.01 mol) in 1,4-dioxane (40 mL) either hydrazine hydrate (1.0 mL, 0.20 mol) or phenylhydrazine (2.16 g, 0.02 mol) was added. The reaction mixture, in each case, was heated under reflux for 3 h then left to cool and the produced solid product was collected by filtration.

2-Hydrazono-4,4-dimethyl-1,7,9-triphenyl-2,4,5,9-tetrahydro-1*H*-chromeno[5,6-*d*]thiazole-8-carbohydrazide (20a)

Orange crystals from ethanol/DMF, yield (3.21 g, 60%), m.p. > 300 °C. IR (KBr) ν max (cm^{-1}): 3520–3342 (NH_2, NH), 3050 (CH-aromatic), 2955 (CH-aliphatic), 1687 (CO), 1623 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.03 (2s, 6H, $2CH_3$), 2.40 (s, 2H, CH_2), 4.58 (s, 4H, D_2O exchangeable, $2NH_2$), 6.53 (s, 1H, CH- pyran), 7.25–7.48 (m, 15H, $3C_6H_5$), 8.20 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.3 ($2CH_3$), 56.2 (CH_2), 90.6 (pyran C-4), 119.5, 119.9, 120.1, 121.4, 121.8, 122.2, 123.5, 123.9, 124.6, 124.8, 125.4, 125.5 ($3C_6H_5$), 134.0, 136.4, 138.6, 140.4, 142.3, 143.6, 143.9, 145.3 (thiazole C, pyran C-2, C-3, C-5, C-6, 164.8 (CO), 174.9 (C=N). Analysis Calculated for $C_{31}H_{29}N_5O_2S$ (535.66): C, 69.51; H, 5.46; N, 13.07; S, 5.99%. Found: C, 69.24; H, 5.49; N, 13.26; S, 6.16%. EIMS: m/z 535 $[M]^+$ (85%).

4,4-Dimethyl-N',1,7,9-tetraphenyl-2-(2-phenylhydrazono)-2,4,5,9-tetrahydro-1*H*-chromeno[5,6-*d*]thiazole-8-carbohydrazide (20b)

Orange crystals from ethanol/DMF, yield (4.25 g, 62%), m.p. 268–271 °C. IR (KBr) ν max (cm^{-1}): 3520–3342 (NH_2, NH), 3050 (CH-aromatic), 2955 (CH-aliphatic), 1689 (CO), 1623 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.06, 1.04 (2s, 6H, $2CH_3$), 2.38 (s, 2H, CH_2), 6.56 (s, 1H, CH- pyran), 7.25–7.48 (m, 25H, $5C_6H_5$), 8.20, 8.24, 8.29 (3 s, 3H, D_2O exchangeable, 3NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.3 ($2CH_3$), 56.2 (CH_2), 90.4 (pyran C-4), 118.7, 119.5, 119.9, 120.1, 120.4, 120.6, 121.4, 121.8, 122.2, 122.4, 122.3, 123.5, 123.9, 124.6, 124.8, 125.1, 125.4, 125.5 ($5C_6H_5$), 133.8, 134.1, 137.2, 139.3, 142.3, 143.4, 143.9, 144.1 (thiazole C, pyran C-2, C-3, C-5, C-6), 164.4 (CO), 174.8 (C=N). Analysis Calculated for $C_{43}H_{37}N_5O_2S$ (687.95): C, 75.08; H, 5.42; N, 10.18; S, 4.66%. Found: C, 74.23; H, 5.60; N, 10.31; S, 4.82%. EIMS: m/z 687 $[M]^+$ (80%).

2-Hydrazono-9-(4-methoxyphenyl)-4,4-dimethyl-1,7-diphenyl-2,4,5,9-tetrahydro-1*H*-chromeno[5,6-*d*]thiazole-8-carbohydrazide (20c)

Orange crystals from ethanol/DMF, yield (3.39 g, 60%), m.p. 245–248 °C. IR (KBr) ν max (cm^{-1}): 3492–3335 (NH_2, NH), 3050 (CH-aromatic), 2955 (CH-aliphatic), 1689 (CO), 1631 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.08, 1.05 (2s, 6H, $2CH_3$), 2.43 (s, 2H, CH_2), 3.69 (s, 3H, OCH_3), 4.58 (s, 4H, D_2O exchangeable, $2NH_2$), 6.53 (s, 1H, CH-pyran), 7.22–7.58 (m, 14H, $2C_6H_5$, C_6H_4), 8.23 (s, 1H, D_2O exchangeable, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.5 ($2CH_3$), 56.6 (CH_2), 50.6 (OCH_3), 90.6 (pyran C-4), 119.2, 119.7, 120.3, 121.6, 121.9, 122.2, 123.5, 123.7, 124.4, 124.8, 125.1, 125.8 ($2C_6H_5$, C_6H_4), 133.8, 135.7, 138.3, 140.2, 142.6, 143.8, 143.9, 144.6 (thiazole C, pyran C-2, C-3, C-5, C-6), 164.8 (CO), 174.6 (C=N). Analysis Calculated for $C_{32}H_{31}N_5O_3S$ (565.69): C, 67.94; H, 5.52; N, 12.38; S, 5.67%. Found: C, 68.25; H, 5.46; N, 12.51; S, 6.43%. EIMS: m/z 565 $[M]^+$ (65%).

9-(4-Methoxyphenyl)-4,4-dimethyl-N',1,7-triphenyl-2-(2-phenylhydrazono)-2,4,5,9-tetrahydro-1*H*-chromeno[5,6-*d*]thiazole-8-carbohydrazide (20d)

Orange crystals from ethanol/DMF, yield (4.44 g, 62%), m.p. 221–225 °C. IR (KBr) ν max (cm^{-1}): 3484–3327 (NH_2, NH), 3050 (CH-aromatic), 2955 (CH-aliphatic), 1687 (CO), 1635 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.04 (2s, 6H, $2CH_3$), 2.35 (s, 2H, CH_2), 3.66 (s, 3H, OCH_3), 6.52 (s, 1H, CH- pyran), 7.26–7.52 (m, 24H, $4C_6H_5$, C_6H_4), 8.22, 8.26, 8.28 (3 s, 3H, D_2O exchangeable, 3NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.6 ($2CH_3$), 56.3 (CH_2), 90.7 (pyran C-4), 119.5, 119.8, 119.9, 120.4, 120.7, 120.8, 121.2, 121.5, 122.5, 122.6, 122.8, 123.3, 123.5, 124.8, 124.8, 125.3, 125.6, 125.8 ($4C_6H_5$, C_6H_4), 133.5, 134.3, 137.5, 138.2, 141.1, 143.8, 143.5, 144.3 (thiazole C, pyran C-2, C-3, C-5, C-6), 164.5 (CO), 174.7 (C=N). Analysis Calculated for $C_{44}H_{39}N_5O_3S$ (717.88): C, 73.62; H, 5.48; N, 9.59; S, 4.47%. Found: C, 73.80; H, 5.32; N, 9.79; S, 4.51%. EIMS: m/z 717 $[M]^+$ (50%).

9-(4-Chlorophenyl)-2-hydrazono-4,4-dimethyl-1,7-diphenyl-2,4,5,9-tetrahydro-1*H*-chromeno[5,6-*d*]thiazole-8-carbohydrazide (20e)

Pale brown crystals from ethanol/DMF, yield (3.30 g, 58%), m.p. 196–197 °C. IR (KBr) ν max (cm^{-1}): 3478–3342 (NH_2, NH), 3050 (CH-aromatic), 2956 (CH-aliphatic), 1687 (CO), 1634 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.06 (2s, 6H, $2CH_3$), 2.45 (s, 2H, CH_2), 4.52 (s, 4H, D_2O exchangeable, $2NH_2$), 6.56 (s, 1H, CH- pyran), 7.24–7.55 (m, 14H, $2C_6H_5$, C_6H_4), 8.24 (s, 1H, D_2O exchangeable,

NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.7 ($2CH_3$), 56.6 (CH_2), 50.8 (OCH_3), 90.8 (pyan C-4), 119.0, 119.4, 120.7, 121.1, 121.9, 122.0, 123.5, 123.9, 124.4, 124.2, 125.3, 125.6 ($2C_6H_5$, C_6H_4), 133.4, 135.4, 138.6, 140.1, 142.3, 143.8, 143.7, 144.2 (thiazole C, pyran C-2, C-3, C-5, C-6), 164.8 (CO), 174.6 (C=N). Analysis Calculated for $C_{31}H_{28}ClN_5O_2S$ (570.10): C, 65.31; H, 4.95; N, 12.28; S, 5.62%. Found: C, 65.52; H, 5.13; N, 12.40; S, 6.39%. EIMS: m/z 570 $[M]^+$ (42%).

9-(4-Chlorophenyl)-4,4-dimethyl-N',1,7-triphenyl-2-(2-phenylhydrazono)-2,4,5,9-tetrahydro-1*H*-chromeno[5,6-*d*]thiazole-8-carbohydrazide (20f)

Orange crystals from ethanol/DMF, yield (3.46 g, 48%), m.p. 195–198 °C. IR (KBr) ν max (cm^{-1}): 3498–3332 (NH), 3050 (CH-aromatic), 2955 (CH-aliphatic), 1687 (CO), 1632 (C=C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.07, 1.04 (2s, 6H, $2CH_3$), 2.38 (s, 2H, CH_2), 6.56 (s, 1H, CH- pyran), 7.25–7.48 (m, 24H, $4C_6H_5$, C_6H_4), 8.20, 8.24, 8.29 (3 s, 3H, D_2O exchangeable, 3NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.3 ($2CH_3$), 56.2 (CH_2), 90.6 (pyran C-4), 118.7, 119.5, 119.9, 120.1, 120.4, 120.6, 121.4, 121.8, 122.2, 122.4, 122.3, 123.5, 123.9, 124.6, 124.8, 125.1, 125.4, 125.5 ($4C_6H_5$, C_6H_4), 133.8, 134.1, 137.2, 139.3, 142.3, 143.4, 143.9, 144.1 (thiazole C, pyran C-2, C-3, C-5, C-6), 164.4 (CO), 174.8 (C=N). Analysis Calculated for $C_{43}H_{36}ClN_5O_2S$ (722.30): C, 71.50; H, 5.02; N, 9.70; S, 4.44%. Found: C, 71.23; H, 5.37; N, 10.01; S, 4.62%. EIMS: m/z 722 $[M]^+$ (80%).

Conclusion

The target molecules were synthesized using dimedone through multi-component reactions reactions to produce fused thiophene, thiazole, coumarin, pyran and pyridine derivatives. Some multi-component reactions were carried out using the effective magnetically separable nanocatalyst Fe_3O_4@MCM-41-SO_3H@[HMIm][HSO_4] could efficiently catalyze the one-pot three-component reaction. The anti-proliferative activity of the newly synthesized compounds toward the six cancer cell lines namely A549, H460, HT-29, MKN-45, U87MG, and S + MMC-7721 was studied. In addition, inhibitions of the most active compounds the thieno[3,2-*f*]chromene derivatives 1**6a–f** toward cancer cell lines classified according to the disease were also studied. Moreover, the newly synthesized compounds were screened for their anticancer potentials against hepatocellular carcinoma HepG2 and cervical carcinoma HeLa 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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Declarations

Conflict of interest The authors declare no conflict of interest, financial, or otherwise.

Ethical approval No related ethical issues.

Informed consent Informed consent was obtained from all participants included in the study.

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Consent to participate The authors promise that the work described has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out.

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