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ORIGINAL ARTICLE

Green synthesis of some tetrahydroquinoline derivatives and evaluation as anticancer agents

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Abstract This study demonstrates the design and synthesis of heterocyclic compounds with diverse biological effects. Using an ionic liquid catalyst, a sonosynthetic approach for the assembly of bis-arylidene cycloalkanone derivatives (bis-chalcones) has been reported. Three cancer cell lines Hepatocellular carcinoma cells (HepG-2), Breast carcinoma cells (MCF-7), and Lung carcinoma cells (A-549) were utilized to investigate the antiproliferative effects of some selected samples. Many evaluated drugs exhibited good to moderate cytotoxicity against the examined cell lines. Notably, the IC_{50} values for the *S*-alkyl derivatives ranged from 2.86 to 13.14 μg/mL.

1. Introduction

The building of diverse organic molecule structures from easily available reactants while taking economic and environmental factors into account is crucial from either an industrial or scholarly viewpoint (Wagner et al., 1993). The development of chemical methods that employ more eco-sustainable materials, atom-efficient operations, and energy-saving approaches to decrease waste creation is a crucial requirement considering rising environmental pollution and its substantial impact on biological processes (Patil et al., 2020). Environmental

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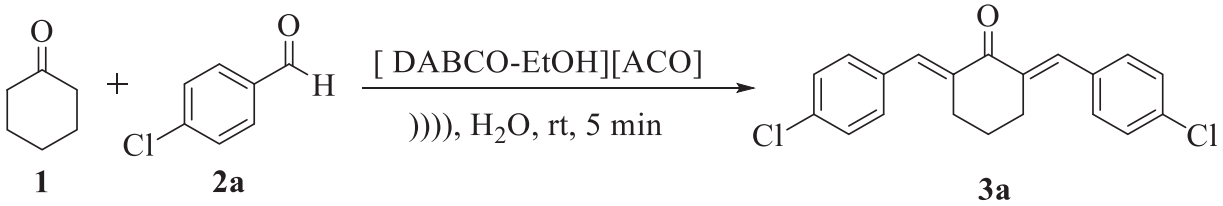
solvents, such as water, are preferred for chemical reactions because they are widely available, non-toxic, and non-combustible (Simbera et al., 2014). In addition, the Claisen–Schmidt reaction is a well-established method for forming carbon–carbon bonds and synthesizing α, and β-unsaturated carbonyl compounds (Gawande et al., 2013). It is also a suitable approach for the assembly of, α,α‘-bis(arylidene)cycloalka nones, which have a variety of applications in biotechnology and pharmaceuticals (Song et al., 2009), quinine reductase enzymes (Eiden et al., 1984), anti-parasitic (Dinkova-Kostova et al., 1998), cholesterol regulators (Piantadosi et al., 1973); pyrrolidines (Braga et al., 2014), cytotoxicity (Raj et al., 2003), and acetyltransferase enzymes (Dimmock et al., 1976). Utilizing a multicomponent reaction technique, Also the benefit the advantage of green chemistry, we will keep on developing eco-friendly synthetic facility methods (Tolba et al., 2022; Tolba et al., 2021; Tolba et al., 2021). So, herein a simple multicomponent reaction approach was given for producing tetrahydroquinoline derivatives with promising biological activities.

2. Results and discussion

Due to the diverse applications of bis-benzylidene cycloalkanones, much effort has been devoted to creating safe, effective, and environmentally friendly techniques for synthesizing these compounds utilizing one-pot, three-component procedures. Several procedures (Costi et al., 2007; Wang et al., 2002; Li et al., 2003; Hosoya et al., 2012; Javanshir et al., 2014; Vashishtha et al., 2015; Ghasemzadeh and Akhlaghinia, 2019; Abaee et al., 2006) for the assembly of bis-arylidene cycloalkanones have been published. Even though several of these methods appear to have distinct advantages, some of them have downsides, such as the use of dangerous solvents, poisonous chemicals, time-consuming procedures, and frequently non-recyclable catalysts. Ionic liquids (ILs) have been identified as eco-friendly dual reagents (solvent and catalyst) due to their excellent properties, such as low cost, accessibility, reusability, and high solubility, as well as their capacity for gram-scale production (An et al., 2008; Egorova and Ananikov, 2018). Recently, various new ILs based on DABCO have been effectively utilized as catalysts in the Claisen–Schmidt reaction (Shirini et al., 2017) and the synthesis of imidazoles. We show the creation of a variety of α,α′-bis[(*aryl or allyl*)*idene*]cycloalkanone derivatives employing DABCO-based IL through ultrasound-assisted Claisen–Schmidt reaction as part of our effort to investigate novel approaches for heterocyclic design (Shirini et al., 2017; Arafa, 2018; Arafa, 2018; Arafa and Ibrahim, 2018). Our first objective was to investigate the IL's catalytic performance in the assembly of, α,α′-bis(substituted benzylidene)cycloalkanones under the following conditions: environmentally friendly solvents, decreased catalyst quantity, low reaction temperature, and rapid pioneer reaction yield. Using modeled reagents, the reaction parameters were optimized with these aims in mind: 4-chlorobenzaldehyde **(2a)** (2.0 mmol) with cyclohexanone **(1)** (1.0 mmol) (Scheme 1), the obtained results were reported in Table 1. Subsequently, several variables, including the energy source, reaction rate, IL dose, and solvent type, were exhaustively examined to determine the optimal reaction conditions.

The 2,6-bis((*E*)-4-chlorobenzylidene)cyclohexane-1-one **(3a)** was produced in 65 % yield under conventional conditions by stirring the reactants in a NaOH/EtOH solution at ambient temperature. A few unreacted starting materials were also observed, despite the reaction being performed for an extended period (Table 1, entry 1). The reaction yield was increased by increasing the reaction temperature (Table 1, entry 2). However, the use of such strong bases resulted from side reactions (such as the self-condensation of aldehydes and ketones), which decreased the yields of the desired products (Egorova and Ananikov, 2018). Even after 3 h of refluxing the reactants under catalyst-free conditions, the needed product**, (3a)** was not observed (TLC) in the reaction profile (Table 1, entry 3). In addition, by executing the reaction under ultrasonic irradiation for 3 h, 85 % of the desired product was produced (Table 1, entry 4). In addition, sonicating the model reactants in aqueous NaOH resulted in a little increase in reaction yield (Table 1, entry 5). Next, a variety of bases, including KOH, LiOH, and 1,4-diazobicyclo [2.2.2] octane (DABCO), were screened to produce a distinct reaction profile and a sped-up reaction rate (Table 1, entries 6–8). None of the previously suggested bases performed better than DABCO, which had the greatest yield (92 %, Table 1, entry 8). Such observations prompted us to examine the reaction in the context of several catalytic strategies. Considering the utilization of ILs enhanced the efficiencies of reactions and considering the acceptable yield achieved employing DABCO in the aforesaid template reaction, we decided to extend our research to the utilization of IL comprised DABCO. [DABCO-EtOH] [AcO], a DABCO-based IL, was designed using the widely obtainable DABCO (**A**) and 2-chloroethan-1-ol (**B**), then refluxed with NaOAc as an ion exchange salt (Scheme 2) (Abaee et al., 2006). Interestingly, the reaction progressed effectively with 1.0 mol% [DABCO-EtOH] [AcO] (**D**) and yielded the desired product in superior yield (95 %) in approximately 10 min (Table 1, entry 9). Several concentrations of catalyst have been utilized on the template reaction to explore the influence of catalyst dosage on this condensation process. The maximum yield (97 %) of the intended product was obtained with 2.0 mol% of the IL catalyst in 5 min (this is might because as the active sites accessible for the reaction increased, both reaction yield and rate were improved as well, (Table 1, entry 10).

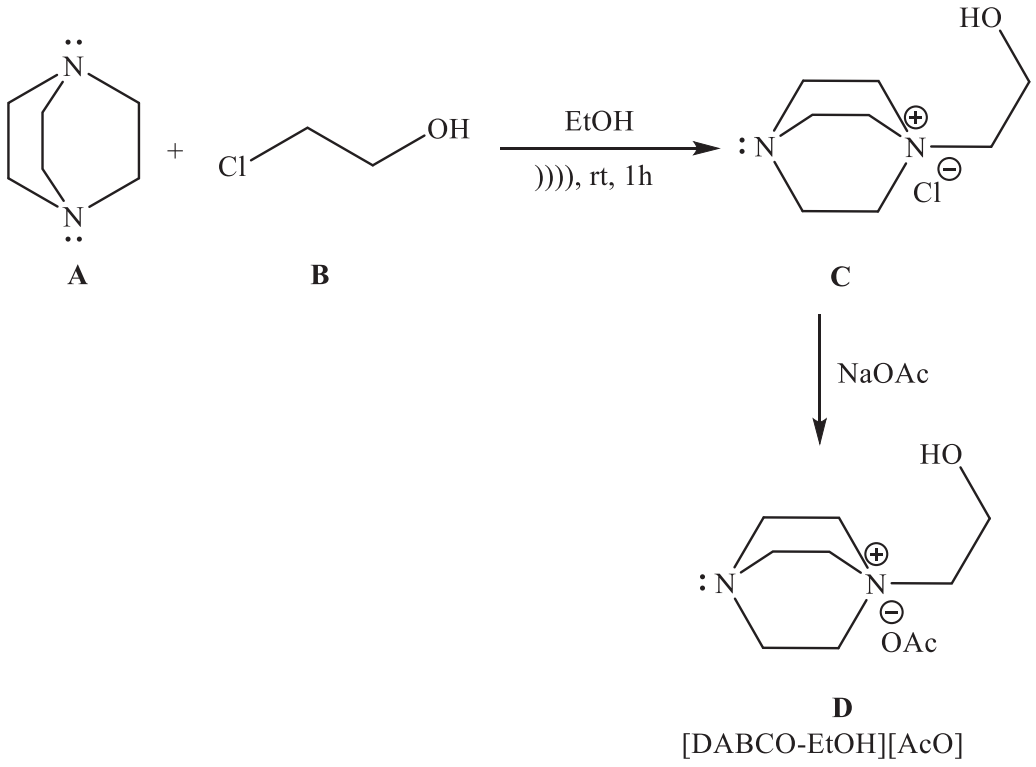


Scheme 1 The synthetic route for bis-chalcone (**3a**).

Table 1 Optimization of the model reaction (Scheme 1).

Entry	Catalyst	Conditions	Solvent	Temp (°C)	Time (min)	Yield (%)
1.	NaOH (10 %)	Stirring	EtOH	rt	180	65
2.	NaOH (10 %)	Stirring	EtOH	90	180	82
3.	None	Stirring	EtOH	90	180	0
4.	NaOH (10 %)	)))) [a]	EtOH	rt	180	85
5.	NaOH (10 %)	))))	H_2O	rt	180	87
6.	KOH (10 %)	))))	H_2O	rt	180	85
7.	LiOH (10 %)	))))	H_2O	rt	180	87
8.	DABCO (3.0 mol%)	))))	H_2O	rt	180	92
9.	IL (1.0 mol%)	))))	H_2O	rt	10	95
10.	IL (2.0 mol%)	))))	H_2O	rt	5	97
11.	IL (3.0 mol%)	))))	H_2O	rt	8	95

[a]))))): ultrasonic irradiation (intensity of 80%).



Scheme 2 Synthesis of ionic liquid, [DABCO-EtOH] [AcO] (**D**).

Nonetheless, catalyst loadings greater than 2.0 mol% resulted in a reduction in reaction effectiveness (Table 1, entry 11). This might be due to the catalyst dosage increased, similarly does the reaction viscosity, lowering the ultrasonic strength in certain parts of the reaction solution (Arafa et al., 2018). Consistently, the bubbles in particular reactor locations may not be properly created (Nakano et al., 1987). Thence, 2.0 mol% was recommended as the best catalyst molar ratio (Table 1, Entry 10).

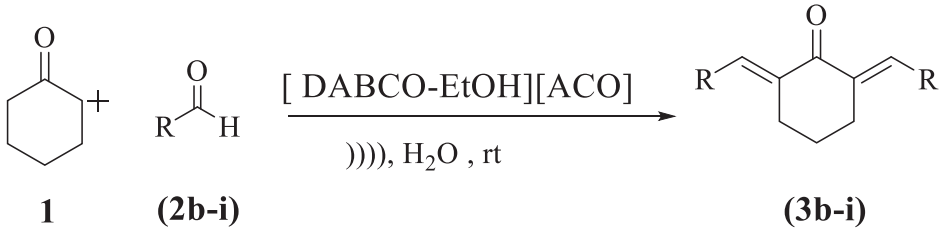
The scope of the current protocol has been also evaluated for assembling bis-chalcones starting with various aldehydes (Scheme 2). In general, the electronic properties of motifs attached to aldehydes have a minimal influence on reaction efficacy. The reaction was exceptionally adaptable to both electron-releasing motifs, including *p*-methyl (**3c**, 96 %) and *p*-methoxy (**3d**, 97 %), as well as electron-accepting motifs, including *p*-nitro (**3e**, 98 %), *o*-nitro (**3f**, 95 %), *p*-chloro (**3a**, 99 %), *o*-cyano (**3 g**, 97 %), and *p*-flouro (**3b**, 96 %). Gratifyingly, heterocyclic aldehydes namely thiophene carboxaldehyde and furfural, similarly had a successful and smooth reaction with cyclohexanone, yielding the condensed products **3 h** and **3i** in 96 % and 93 % yields, respectively (Scheme 2). The melting point and spectral data of all the assembled compounds are matched to those mentioned in the research (Wagner et al., 1993; Costi et al., 2007; Wang et al., 2002; Li et al., 2003; Hosoya et al., 2012; Javanshir et al., 2014). For

example, ^{1}H NMR of derivative **3 h** exhibited a singlet at δ = 7.97 ppm assigned for the vinylic proton. The aromatic protons appeared as multiples in the range of 7.51–7.09 ppm. In addition, the two multiples at δ = 2.91–2.89 and 1.95–1.703 ppm are assigned to the aliphatic protons. Additionally, the ^{13}C NMR of derivative 3 h demonstrated distinguished signals at δ = 189.1, 28.2, and 21.7 ppm attributed for the *C*═O, and CH_2 motifs, respectively (see Scheme 3).

To assess the practicality of scaling up the current approach, the model reaction was carried out on a gram scale using optimum conditions, yielding the anticipated compound **3a** in superior yield (97 %; Scheme 4). Diverse sustainable measurements such as process mass intensity (**PMI**), E-factor (**EF**), reaction mass efficiency (**RME**), and atom economy (**AE**) also have been addressed (Scheme 4).[31] The greater environmental adaptability criteria, such as lower **PMI** (1.12) and **EF** (0.017), as well as high values of **YE** (12.2 %), **CE** (100 %), **AE** (90.5 %), and **RME** (88.8 %), verified the established protocol's eco-sustainable approach.

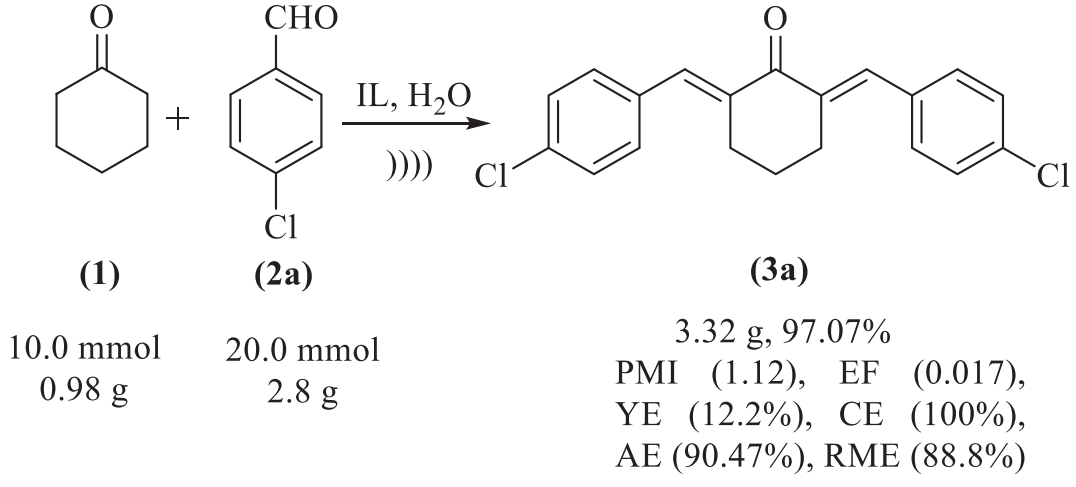
Whereas we could not examine the mechanism of the current reaction, Scheme 5 depicts a probable approach enabling the synthesis of bis-chalcones (**3a-i**). Firstly, the IL active centers (OH & nitrogen lone pair of electrons) could be efficiently activated the reactant molecules to undergo the condensation reaction in an appropriate manner (Scheme 4). Thereby, both aldehyde and ketone are stimulated by such active sites, thus facilitating the removal of a water molecule, yielding the non-isolable intermediate (**I**). This intermediate underwent another condensation reaction with the second molecule of aldehyde and afforded the required products (**3a-i**) in excellent yields. It may be inferred that the ionic liquid enhanced both the yield and the rate of the reaction.

The compounds comprising the quinoline motif have been used in several biological applications in the last decade. For example, employed as an immune regulator, anti-inflammatory, analgesic, anti-allergic, and memory enhancer (Show et al., 2007; Gogate et al. 2003). Thus, our next endeavor turned out to be the design and synthesis of a library of hitherto unreported heterocyclic compounds containing such a significant nucleus; quinoline. The target tetrahydroquinoline-2-thione derivatives (**5a, b**) were smoothly obtained *via* the reaction of 2,6-bis-4-chlorobenzylidenecyclo hexanones (**3a, b**) with cyanothioacetamide (**4**) utilizing EtONa as a catalyst (Scheme 6).

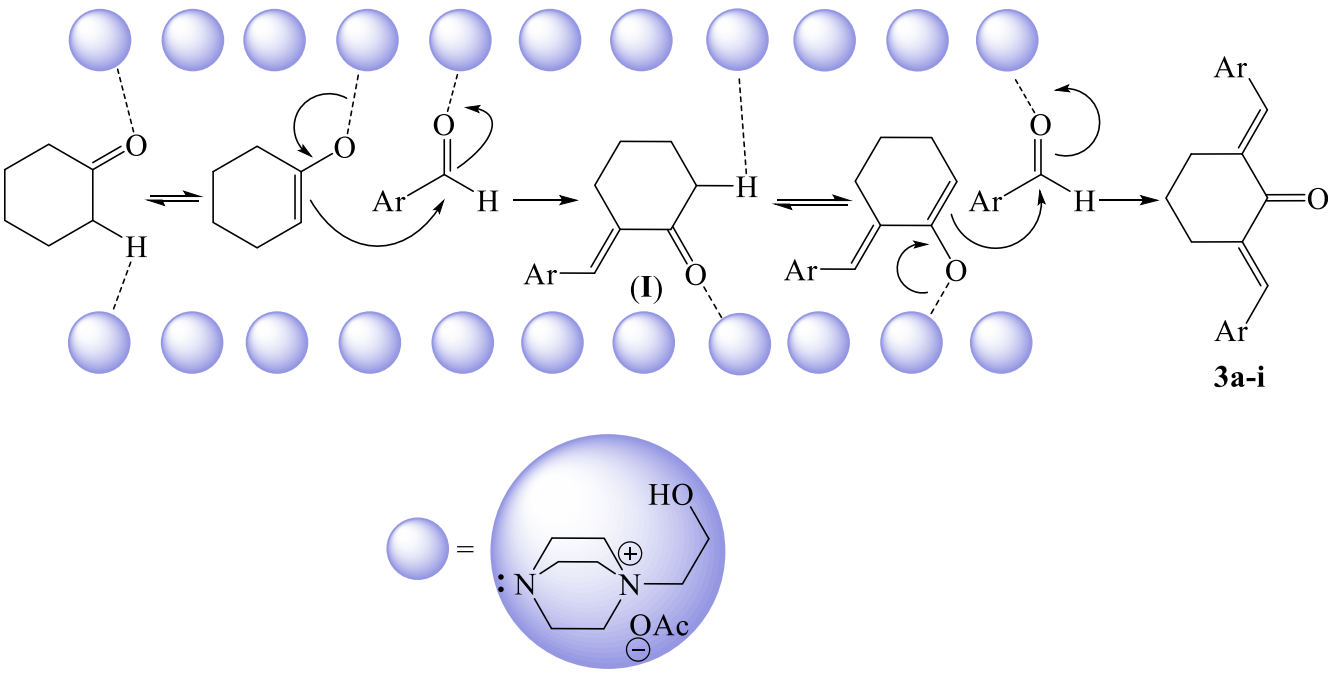


b, R= 4-FC_6H_4, c, R= 4-$CH_3C_6H_4$, d, R= 4-$OCH_3C_6H_4$, e, R= 4-$NO_2C_6H_4$, f, R= 2-$NO_2C_6H_4$, g, R= 2-CNC_6H_4, h, R= thiophen-2-yl , i, R= furan-2-yl

Scheme 3 [DABCO-EtOH] [AcO]-catalyzed preparation of bis chalcones (**3a–i**) [a] (Costi et al., 2007; Wang et al., 2002; Li et al., 2003; Hosoya et al., 2012; Javanshir et al., 2014; Vashishtha et al., 2015; Ghasemzadeh and Akhlaghinia, 2019; Abaee et al., 2006) [a]Reaction conditions: cyclohexanone and aryl aldehyde, IL (2.0 mol%), water (5.0 mL) at rt.



Scheme 4 Scaled-up assembly of compound **3a**.



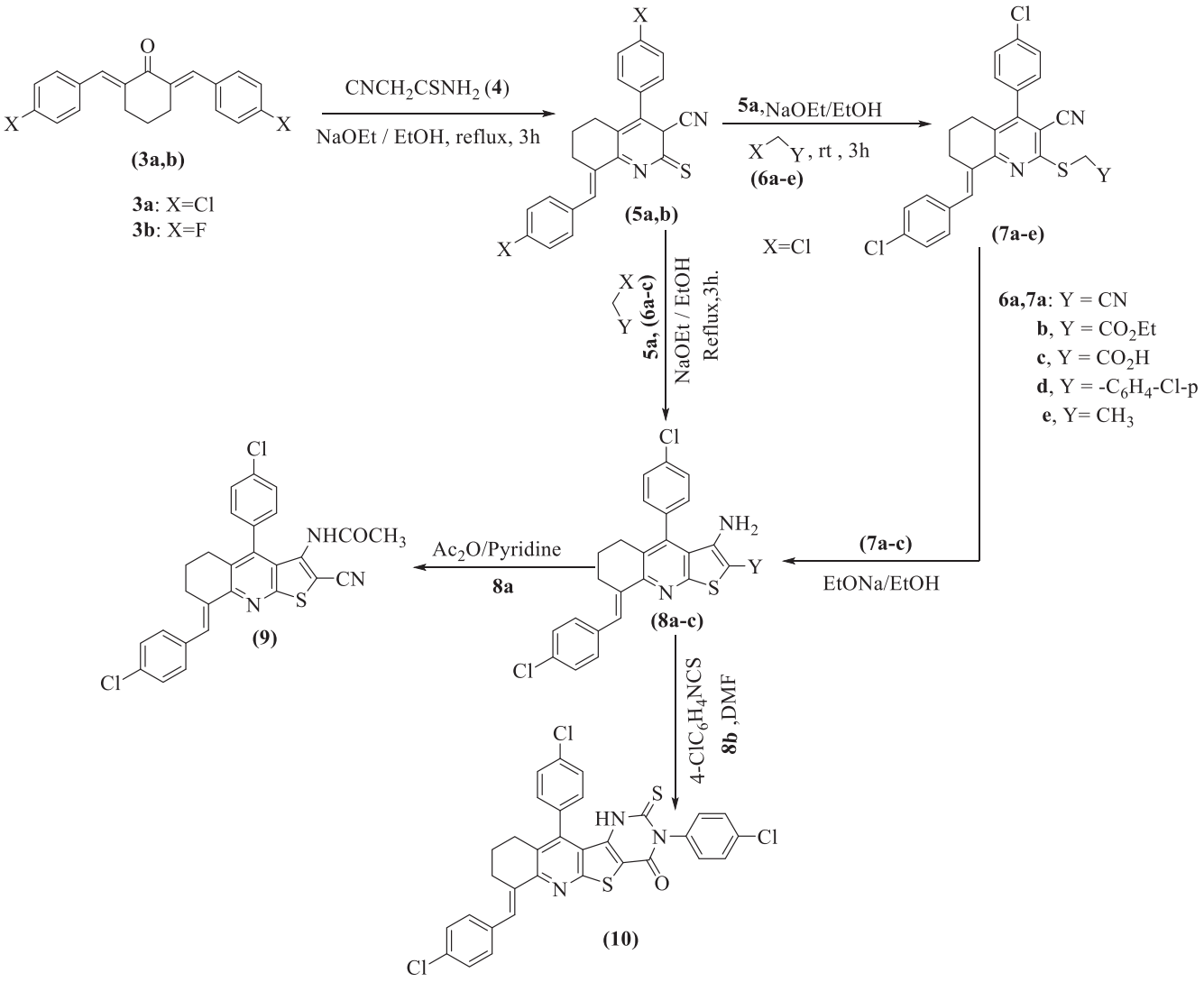
Scheme 5 A tentative mechanism for the assembly of derivatives **3a-i**.

FT-IR, NMR spectroscopy, and MS were used to deduce the chemical structure of the newly synthesized compound **5a**. For example, the FT-IR spectrum of derivative **5a** demonstrated absorption bands at 2214 cm^{-1} attributed to the stretching frequencies of the C≡N group. Further, the mass spectrum of the isolated compound **5a** revealed the required molecular ion peak, as well as its elemental analyses, were compatible with the calculated values. Compound **5a** displayed a molecular ion peak at *m*/*z* 422 corresponding to $C_{23}H_{16}Cl_2N_2S$, with a base peak at *m*/*z* 388 corresponding to the spelling of the H_2S molecule.

Alkylated heterocyclic compounds are essential precursors that may be employed to synthesize polysubstituted fused heterocyclic derivatives (Jiménez-González et al., 2012). Such alkylated derivatives have prospective applications as recyclable agrochemicals (El-Taweel, 2010), medicines, and dye precursors (Jubeen et al., 2018; Kumar and Narasimhan, 2018). Consequently, our next target is to evaluate the possibility of one of the designed thiol derivatives for the *S*-alkylation reaction. To achieve this target, quinoline-2-thione.

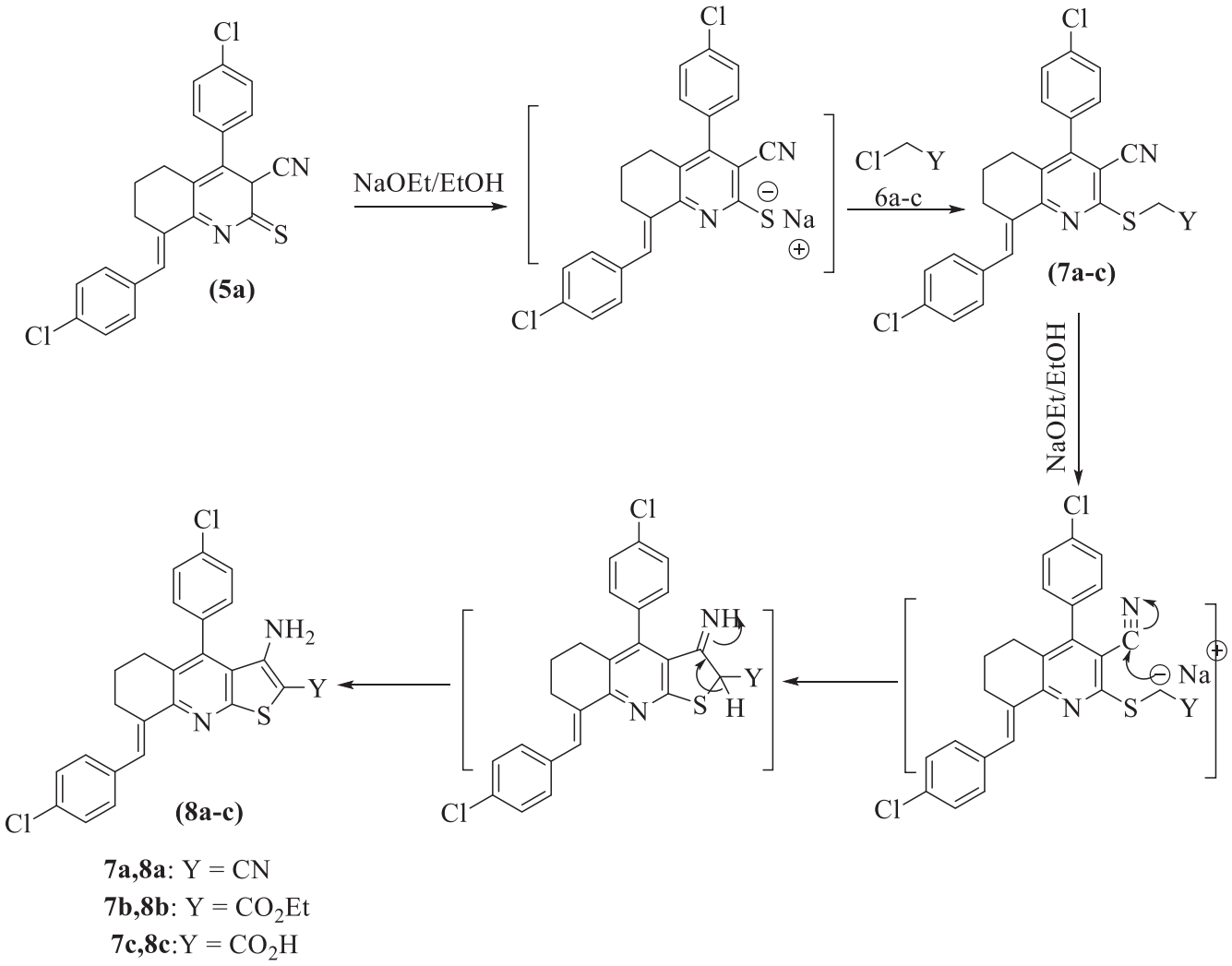
5a was permitted to react with a diversified of halo-derivatives including chloroaceonitrile, ethyl bromoacetate, chloroacetic acid, 4-chlorobenzyl chloride, and ethyl iodide **6a-e** using sodium ethoxide and/or K_2CO_3 as a base to afford the expected 2-alkylated compounds **7a-e**. The molecular structure of the *S*-alkylated derivatives **7a-e** was interpreted from their mass spectrometric analyses, FT-IR, and NMR. For example, the FT-IR spectrum of derivative **7b** demonstrated a distinguished stretching band at 2214 cm^{-1} assigned to the absorption frequencies of the C≡N group. Besides, the absorption band at 1743 cm^{-1} is assigned to the C=O motif. Additionally, the ^{1}H NMR spectrum of **7d** exhibited two singlet signals that related to the S-CH_2 group at δ = 4.54 ppm and vinyl proton at δ = 7.96 ppm. Besides, the aromatic protons appeared as a multiplet at δ = 7.45–7.27 ppm, and three multiplets at δ = 2.80–1.70 ppm for the methylene protons (CH_2). The existence of distinguished signals in the ^{13}C NMR spectrum of derivative **7d** is compatible with the suggested structure. The resonances owing to the carbons of the four CH_2, which emerge at δ = 33.9, 27.6, 27.4, and 22.3 ppm, are the most essential part of the spectrum. In addition, the mass spectra of the isolated compounds **7a-d** revealed the required molecular ion peak, and their elemental analyses were compatible with the calculated values. For example, derivative **7b** presented a molecular ion peak at *m*/*z* 508 equivalent to $C_{27}H_{22}Cl_2N_2O_2S$; in agreement with the molar mass of the proposed structure. The synthesized *S*-alkylated derivatives **7a-c** possessed two distinctive function groups, active methylene, and cyano motifs, that could be used for the design of various fused heterocycles under cyclization conditions. Interestingly, when the *S*-alkylated derivatives **7a-c** boiled in ethanol containing a catalytic amount of NaOEt, underwent a cyclization reaction and afforded the thieno[2,3-*b*]quinolines **8a-c** in excellent outcomes. Surprisingly, the thieno[2,3-*b*] quinolines **8a-c** could be also obtained in quantitative yields directly by refluxing the thiol derivative **5a** with appropriate halo-derivatives **6a-c** using two equivalents of NaOEt (Scheme 6). The reaction starts with a sulfur-nucleophilic attack to the halo-derivatives **6a-c** to afford the *S*-alkyl derivatives **7a-c** which in turn undergoes another carbon-nucleophilic attack to the cyano group followed by aromatization to finally afford the thieno[2,3-*b*] quinolines **8a-c** (Scheme 7).

FT-IR, NMR, and mass spectra were utilized to demonstrate the molecular structure of derivatives **8a-c**. For example, the FT-IR spectrum of derivative **8b** exhibits bands in the frequency of 3487, 3340, and 1666 cm^{-1} corresponding to NH_2 and C=O, respectively. The absence of the stretching frequency belongs to the cyano motif and the decrease in the absorption value of the carbonyl group indicates the cyclization of *S*-alkyl derivatives. The ^{1}H NMR spectral analysis of the obtained compounds (for example, **8b**), showed two distinctive singlets at δ = 5.35 and 8.09 ppm attributed to the



Scheme 6 Synthetic pathway for the preparation of the target tetrahydroquinoline derivatives (**5a-10**). (Madkour et al., 2018).

amino (NH_2; this is strong evidence to prove the cyclization) and vinyl (C = CH) protons, respectively. Additionally, the quartet-triplet pattern appeared at δ = 4.29–4.25 and 1.34–1.32 ppm, respectively. The other protons appeared in their respective regions. Besides, in the ^{13}C NMR, the ring closure may be observed by the disappearance of the signals at 112 and 30 ppm corresponding to the *C*≡N and *C*H_2-S groups, respectively. In addition, the MS of the isolated derivatives **8a-c** revealed the required molecular ion peaks, and their elemental analyses were compatible with the calculated values. For example, derivatives **8b, c** displayed molecular ion peaks at *m*/*z* 508 equivalent to $C_{27}H_{22}Cl_2N_2O_2S$ **8b**, and at *m*/*z* 480 equivalent to $C_{25}H_{18}C_{l2}N_2O_2S$ **8c**: in agreement with the molar mass of the proposed structure. On refluxing the amino-cyano derivative **8a** in dry pyridine containing an equimolar amount of acetic anhydride, (*E*)-*N*-(8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-2-cyano-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-3-yl) acetamide **9** was obtained in quantitative yield (Scheme 6). Further, the amino ester derivative **8b** could be reacted with the 1-chloro-4-isothiocyanatobenzene in DMF under refluxing conditions to provide the unreported pyrimidine-2-thione derivative **10** in an acceptable yield (Scheme 6). The chemical structure of derivative **10** was elucidated *via* FT-IR, and MS. The MS of the isolated derivative **10** presented the required molecular ion peak (*m*/*z* 632) with a base peak at *m*/*z* 125 corresponding to 4-chlorocyclohepta-2,4,6-trien-1-ylium. Besides, the elemental analysis was compatible with the calculated value. Furthermore, when derivative **5a** was reacted with dialkylacetylenedicarboxylates (DMAD and DEAD, **(11a**, **b)** in dichloromethane (DCM) afforded after purification, yellow and orange crystalline products **14a**, **b** respectively (Scheme 8). From the obtained results of the elemental analyses and mass spectrum (*m*/*z* 594) of the reaction product **14b**, the molecular formula could be estimated to be: $C_{31}H_{26}Cl_2N_2O_4S$ **14b** which is compatible with the suggested compound **12** (supposing that the NH added to the CBC in DEAD). Besides, the IR spectrum of the obtained product **14b** demonstrated two absorption bands at υ_{max} 1720 and 1714 assigned to the C═O motifs (ester), a distinguished band at 2222 cm^{-1} attributed to the cyano group, and no absorption bands corresponding to the amide C═O (for derivative **12**). Thus, the proposed structure **12** was excluded. The ^{1}H and ^{13}C NMR demonstrated a pattern, which cannot be justified for either of the derivatives **12** or **13**. The existence of signals for the two ester



Scheme 7 A tentative mechanism for the assembly of derivatives **8a-c**.

carbonyl groups in the ^{13}C NMR, and two ethyl signals (quartet/triplet pattern) in the ^{1}H NMR spectrum of derivative **14b**, as well as the complete lack of the amide carbonyl absorption band in the FT-IR spectrum, gave us the assumption that a Michael addition occurred from the SH nucleophile in the tautomer mercaptopyridine to the activated CBC of DEAD. Moreover, the ^{13}C NMR showed no signals attributed to the C═S motifs. As a result, the molecular structures of **14a, b** have been proposed for these compounds.

3. Biological evaluation

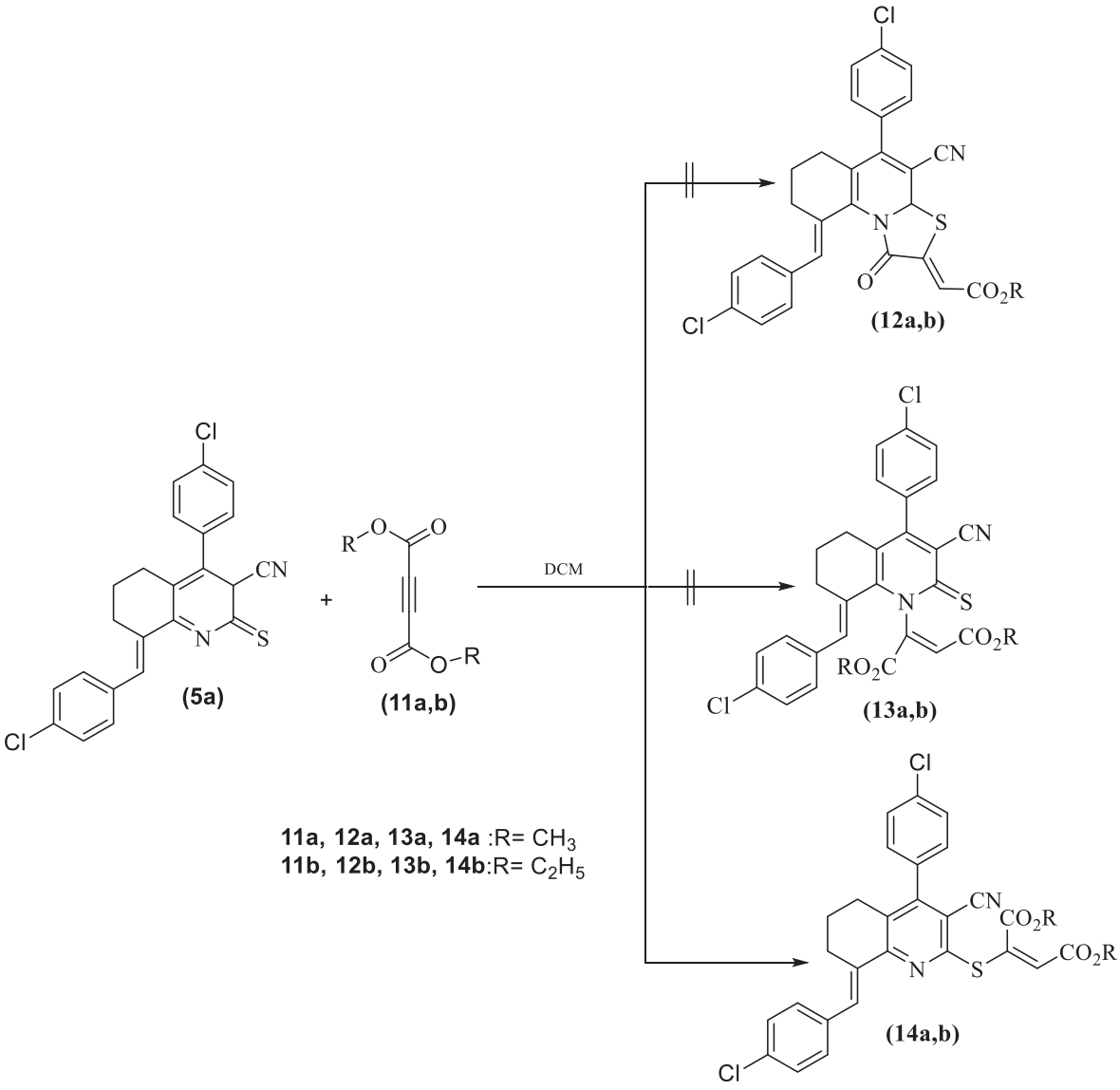
3.1. Cytotoxicity activities

The *in vitro* cytotoxicity activities applications of some of these selected compounds (**5a, 5b, 7d, 7e, 8b**, and **10**) were investigated against HepG-2, MCF-7, and A-549 cell lines employing MTT (3-(4,5)- dimethylthiahiazo(-zy1)-3,5-di-phenytetrazo liumromide) assay and utilizing Doxorubicin as a reference compound (Table 2). Interestingly, the antitumor activity of these selected compounds (Table 2) showed significant differences depending on the molecular structures. In general, derivatives **5a** and **5b** exhibited superior activities against both HepG-2 and MCF-7 with IC_{50} ranged 2.86–13.14 μg/mL. However, these derivatives displayed moderate activities towards A-549 (25.54 and 28.45 μg/mL, respectively). Besides, derivatives **7d, 7e**, and **8b** showed moderate activities in comparison with the reference material (Doxorubicin, Table 2).

4. Experimental section

4.1. Materials

Electrothermal IA9100 melting point apparatus (UK) was used to monitor the melting points that were reported incorrectly. On a Shimadzu DR-8001 spectrometer, IR spectra were measured. As an inner standard, TMS was employed using either $CDCl_3$ or DMSO d_6 as a solvent to obtain the NMR data, which were done using a Jeol 600 MHz NMR scanner. A Hewlett Packard MS-5988-USA spectrometer has been employed to record mass spectra at 70 eV. Organic solvents and fine chemicals were received and utilized without purification from Aldrich, Fluka, or Across chemicals manufacturers.



Scheme 8 Synthesis of derivatives **14a, b.**

Table 2 IC_{50} values for compounds **5a, 5b, 7d, 7e, 8b, 10**, and Doxorubicin.

Compound	IC_{50} values (μg/mL)		
	HepG-2	MCF-7	A-549
5a	2.86 ± 0.22	3.17 ± 0.39	25.54 ± 1.15
5b	11.23 ± 0.55	13.14 ± 0.86	28.45 ± 1.03
7d	29.40 ± 1.28	59.35 ± 2.41	42.81 ± 1.37
7e	56.52 ± 2.04	60.21 ± 1.97	116.02 ± 2.94
8b	51.42 ± 1.96	79.81 ± 2.05	55.78 ± 2.34
10	108.97 ± 3.81	157.82 ± 3.96	121.96 ± 3.12
Doxorubicin	0.75 ± 0.11	1.02 ± 0.14	1.27 ± 0.35

4.2. Synthesis of the catalyst [DABCO-EtOH][AcO].

A mixture of 2-chloro-1-ethanol (0.067 mL, 1.0 mmol) and 1,4-diazobicyclo[2.2.2]octane (DABCO) (0.112 g, 1.0 mmol) in EtOH (20.0 mL) was sonicated for 1 h. After the completion of the reaction (confirmed by TLC), the solvent was evaporated under reduced pressure, and the intermediate A was obtained and used in the next step without any purification. Then, sodium acetate (0.0820 g, 1.0 mmol) was added to a solution of A (0.192 g, 1.0 mmol) in EtOH (20 mL). The mixture was sonicated for another 1 h, and the solvent was removed under reduced pressure to give the corresponding IL catalyst (**B**).

4.3. General methods for synthesis of bis-chalcone derivatives (3a-i)

4.3.1. Conventional method:

A mixture of cyclohexanone (**1**) (1.0 mmol), aromatic aldehydes (**2a-i**) (2.0 mmol), and five drops of NaOH (10 %) were dissolved in ethanol (20.0 mL) at room temperature with continuous stirring for three hours to get the target products α, α'-bis chalcone derivatives(**3a-i**), which was recrystallized

from ethanol. **4.3.2. Ultrasonic protocol using [DABCO-EtOH][AcO] as a catalyst**.

A 25.0 mL round flask had been charged with cyclohexanone (**1**) (1.0 mmol), aldehydes (**2a-i**) (2.0 mmol), [DABCO-EtOH][AcO] (2.0 mol%), and 10.0 mL water. The reaction vessel had been immersed in the ultrasonic bath and sonicated at room temperature for an adequate period. After completion of the reaction (established by TLC, eluent: MeOH/DCM = 1:9 vol), the solid component that isolated out had been filtered out and washed with H_2O, dried, and crystallized from ethanol to afford the pure compounds. The catalyst had been recovered from the aqueous layer under vacuum, washed with *n*-hexane, and reused for the next reactions. The authenticity samples of the products (**3a–i**) was elucidated by comparing their melting points with literature and their data on FT-IR.[15–22] **4.3.3. 2,6-Bis((*E*)-4-chlorobenzylidene) cyclohexan-1-one (3a).**

Yellow plates; yield: 99 %; m.p. 195–198 °C; FT-IR (KBr, cm^{-1}): ν_{max} 1666 (C═O), 1604 and 1573 (C═C). ^{1}H NMR ($CDCl_3$), δ_H (ppm): 7.78–6.96 (m, 10*H*; 2 = C*H* and 8 Ar-*H*), 2.75 (br, 4H, 2CH_2), 1.83 (br, 2H, CH_2); ^{13}C NMR, δ_C (ppm): 187.8 (*C*═O), 159.4, 137.2, 133.9, 131.9, 128.7, 113.0 (2 = *C*H and Ar-*C*), 28.5, 23.1(3*C*H_2). Analysis calculated for $C_{20}H_{16}Cl_2O$ (343.25); C, 69.98; H, 4.70; Cl, 20.66 %, Found; C, 69.94; H, 4.73; Cl, 20.62 %.

4.3.2. 2,6-Bis((E)-4-fluorobenzylidene) cyclohexan-1-one (3b).

Yellow needles; yield: 96 %; m.p. greater than 400 °C; FT-IR (KBr, cm^{-1}): ν_{max} 1666 (C═O), 1604 and 1566 (C═C). ^{1}H NMR ($CDCl_3$), δ_H (ppm): 7.76–6.93 (m, 10*H*; 2 = C*H* and 8 Ar-*H*), 2.72 (br, 4H, 2CH_2), 1.82 (br, 2H, CH_2); ^{13}C NMR, δ_C (ppm): 184.4 (*C*═O), 158.3, 138.4, 132.2, 132.7, 129.1, 113.1 (2 = *C*H and Ar-*C*), 27.4, 22.8 (3*C*H_2). Analysis calculated for $C_{20}H_{16}F_2O$ (310.34); C, 77.40; H, 5.20; F, 12.24 %, Found; C, 77.43; H, 5.24; F, 12.27.

4.3.3. 2,6-Bis((E)-4-methylbenzylidene) cyclohexan-1-one (3c).

Yellow plats; yield 96 %; m.p. 174 °C; FT-IR (KBr, cm^{-1}): ν_{max} 1658 (C═O), 1566 and 1597 (C═C). ^{1}H NMR ($CDCl_3$), δ_H (ppm): 7.74–6.97 (m, 10*H*; 2 = C*H* and 8 Ar-*H*), 2.76 (br, 4H, 2CH_2), 2.01 (br, 2H, CH_2), 1.87 (s, 6H, 2CH_3); ^{13}C NMR, δ_C (ppm): 187.0 (*C*═O), 159.2, 137.8, 133.2, 131.7, 128.8, 113.6 (2 = *C*H and Ar-*C*), 28.3, 23.4 (3*C*H_2), 14.3 (2 CH_3). Analysis calculated for $C_{22}H_{22}O$ (302.42): C, 87.38; H, 7.33 %, Found: C, 87.35; H, 7.36 %.

4.3.4. 2,6-Bis((E)-4-methoxybenzylidene) cyclohexan-1-one (3d).

Yellow flaxes; yield: 97 %; m.p. 165–167 °C; FT-IR (KBr, cm^{-1}): ν_{max} 1658 (C═O), 1589 and 1543 (C═C). ^{1}H NMR ($CDCl_3$), δ_H (ppm): 7.74–6.90 (m, 10*H*; 2 = C*H* and 8 Ar-*H*), 3.82 (s, 6H, 2OCH_3), 2.89 (br, 4H, 2CH_2), 1.78 (br, 2H, CH_2); ^{13}C NMR, δ_C (ppm): 190.6 (*C*═O), 159.5, 136.5, 133.9, 131.9, 128.7, 113.0 (2 = *C*H and Ar-*C*), 54.3 (2 OCH_3), 28.3, 22.2 (3*C*H_2). Analysis calculated for $C_{22}H_{22}O_3$ (334.42): C, 79.02; H, 6.63 %, Found: C, 79.06; H, 6.60 %.

4.3.5. 2,6-Bis((E)-4-nitrobenzylidene) cyclohexan-1-one (3e).

Brown; yield: 98 %; m.p. 213 °C; FT-IR (KBr, cm^{-1}): ν_{max} 1666 (C═O), 1512 and 1589 (C═C). ^{1}H NMR ($CDCl_3$), δ_H (ppm): 7.76–6.92 (m, 10*H*; 2 = C*H* and 8 Ar-*H*), 2.71 (br, 4H, 2CH_2), 1.98 (br, 2H, CH_2); ^{13}C NMR, δ_C (ppm): 186.3 (*C*═O), 158.3, 136.9, 134.2, 132.3, 129.4, 113.5 (2 = *C*H and Ar-*C*), 28.8, 24.5 (3*C*H_2). Analysis calculated for $C_{20}H_{16}N_2O_5$ (364.36): C, 65.93; H, 4.43; N, 7.69 %, Found: C, 65.97; H, 4.48; N, 7.65 %.

4.3.6. 2,6-Bis((E)-2-nitrobenzylidene) cyclohexan-1-one (3f).

Coffee; yield: 95 %; m.p. 96 °C; FT-IR (KBr, cm^{-1}): ν_{max} 1697 (C═O), 1519 and 1566 (C═C). ^{1}H NMR ($CDCl_3$), δ_H (ppm): 7.69–6.92 (m, 10*H*; 2 = C*H* and 8 Ar-*H*), 2.74 (br, 4H, 2CH_2), 2.21 (br, 2H, CH_2); ^{13}C NMR, δ_C (ppm): 186.5 (*C*═O), 159.7, 137.4, 133.6, 131.3, 128.4, 113.1 (2 = *C*H and Ar-*C*), 28.5, 23.1 (3*C*H_2). Analysis calculated for $C_{20}H_{16}N_2O_5$ (364.36): C, 65.93; H, 4.43; N, 7.69 %, Found: C, 65.96; H, 4.47; N, 7.65 %.

4.3.7. 2,6-Bis(E)-4-cyanobenzylidenecyclohexan-1-one (3 g).

Yellow plates; yield: 97 %; m.p. 232 °C; FT-IR (KBr, cm^{-1}): ν_{max} 2222 (C≡N), 1666 (C═O), 1597 and 1581 (C═C). ^{1}H NMR ($CDCl_3$), δ_H (ppm): 7.73–7.01 (m, 10*H*; 2 = C*H* and 8 Ar-*H*), 2.73 (br, 4H, 2CH_2), 2.15 (br, 2H, CH_2); ^{13}C NMR, δ_C (ppm): 187.0 (*C*═O), 159.2, 137.8, 133.2, 131.7, 128.8, 113.6 (2 = *C*H and Ar-*C*), 105 (2*C*≡N), 28.3, 23.4 (3*C*H_2). Analysis calculated for $C_{22}H_{16}N_2O$ (324.38): C, 81.46; H, 4.97; N, 8.64 %, Found: C, 81.49; H, 4.94; N, 8.68 %.

4.3.8. (2E,6E)-2,6-Bis(thiophen-2-ylmethylene)cyclohexan-1-one (3 h).

Yellow flaxes; yield: 96 %; m.p. 164 °C. FT-IR (KBr, cm^{-1}): ν_{max} 1643 (C═O) and 1589 (C═C); ^{1}H NMR ($CDCl_3$), δ_H (ppm): 7.97 (s, 2H, =C*H*), 7.51–7.09 (m, 6H, thiophene-*H*), 2.91–2.89 (br, 4H, 2*C*H_2), 1.95–1.703 (br, 2H, CH_2); ^{13}C NMR δ_C (ppm): 189.1 (C═O), 139.6, 133.1, 132.9, 130.0, 129.8, 127.7 (Ar-*C* and CH = *C*), 28.2, 21.7 (3*C*H_2). Analysis calculated for $C_{16}H_{14}OS_2$ (286.41): C, 67.10; H, 4.93; S, 22.39 %, Found: C, 67.07; H, 4.90; S, 22.43 %.

4.3.9. ((2E,6E)-2,6-Bis(furan-2-ylmethylene)cyclohexan-1-one (3i).

Brown flakes; yield: 95 %; m.p. 223 °C; FT-IR (KBr, cm^{-1}): ν_{max} 1643 (C═O), 1543 and 1589 (C═C); ^{1}H NMR ($CDCl_3$), δ_H (ppm): 7.53–6.49 (m, 8H, 2 = C*H* and 6 furan-*H*), 2.99 (br, 4H, 2CH_2) and 1.88 (br, 2H, CH_2). ^{13}C NMR δ_C (ppm): 188.8 (*C*═O), 152.6, 152.2, 144.6, 133.0, 132.7, 116.1, 112.4 (CH = *C* and, Ar-*C*), 27.8, 21.2 (3*C*H_2). Analysis calculated for $C_{16}H_{14}O_3$ (254.29): C, 75.58; H, 5.55 %, Found: C C, 75.54; H, 5.52 %.

4.4. Synthesis of derivatives 5a, b

A solution of bis-chalcone derivatives (**3a**, and/or **3b,** 1.0 mmol), cyanothioacetamide (1.0 mmol), and sodium ethoxide (2.0 mmol, prepared by mixing 0.32 g Na in 30.0 mL absolute EtOH) was boiled for 7 h. To the resulting solution, a few drops of HCl (36.0 %) was added, and the obtained solid was separated, and crystallized from a proper solvent.

4.4.1. (E)-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-2-thioxo-2,3,5,6,7,8-hexahydroquinoline-3-carbonitrile (5a)

Orange crystals; yield: 67 %; m.p. 288–289 °C; IR (V_{max}, cm^{-1}): 2214 (C≡N); ^{1}H NMR (DMSO d_6), δ_H (ppm): 8.13–7.45 (m, 9H, Ar*H*& =C*H*), 2.82–1.72 (m, 7H, C*H*& 3CH_2); ^{13}C NMR δ_C (ppm): 105 (*C*≡N), 117 (*C*H =) and 158.6 (C=S). Analysis calculated for $C_{23}H_{16}Cl_2N_2S$ (423.4); C, 65.25; H, 3.81; N, 6.62 %, Found; C, 65.28; H, 3.80; N, 6.64 %; EI-MS (*m*/*z*): 422.1 [M^+-1].

4.4.2. (E)-8-(4-fluorobenzylidene)-4-(4-fluorophenyl)-2-thioxo-2,3,5,6,7,8-hexahydroquinoline-3-carbonitrile (5b)

Yellow crystals; yield: 77 %; m.p. 201–203 °C; IR (V_{max}, cm^{-1}): 2191 (C≡N); ^{1}H NMR (DMSO d_6), δ_H (ppm): 8.21–7.51 (m, 9H, Ar*H*& =C*H*), 2.84–1.76 (m, 7H, C*H*& 3CH_2); ^{13}C NMR δ_C (ppm): 105 (*C*≡N), 115 (*C*H =) and 159.7 (C=S). Analysis calculated for $C_{23}H_{16}F_2N_2S$ (390.5); C, 70.75; H, 4.13; N, 7.17 %; Found; C, 70.76; H, 4.16; N, 7.19 %.

4.5. Synthesis of S-alkylated derivatives (7a-d).

Method A:

A mixture of **5a** (1.0 mmol) and various alkyl halides (**6a-e**) (1.0 mmol) namely chloroacetonitrile, ethyl bromoacetate, chloroacetic acid, 4-chlorobenzyl chloride, and ethyl iodide, in 20.0 mL ethanol containing 1.0 mmol Na metal were stirred at ambient temperature for 20 min then boiled for 7 h. And then to the resulting solution, few droplets of dilute hydrochloric acid were added, and the obtained precipitate were crystallized from EtOH/dioxane (9:1) and identified as *S*-alkylated derivatives (**7a-e**).

Method B:

A mixture of **5a** (1.0 mmol), various alkyl halides (**6a-e**) (1.0 mmol) namely chloroacetonitrile, ethyl bromoacetate, chloroacetic acid, 4-chlorobenzyl chloride, and ethyl iodide, in 20.0 mL dimethylformamide and 0.5 g K_2CO_3 were stirred at ambient temperature for 4 h. And then the reaction mixture was filtered off, and poured into ice-cold water to furnish precipitate which was separated and recrystallized from the ethanol/-dioxane (9:1) and identified as S-alkylated derivatives (**7a-e**).

4.5.1. (E)-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-2-((cyanomethyl)thio)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (7a)

Coffee crystals; yield 54 %; m.p. decompose at 332 °C; IR (V_{max}, cm^{-1}): 2214, 2207 (2C≡N); ^{1}H NMR ($CDCl_3$), δ_H (ppm): 7.93 (s, 1H, =C*H*), 7.43–7.15 (m, 8H, Ar-*H*), 4.38 (s, 2H, S-CH_2), 2.83–1.87 (m, 6H, 3CH_2). ^{13}C NMR δ_C (ppm): 158.3, 155.0, 130.1, 129.7, 128.8, 128.6 (Ar-*C*), 115.5 (2*C*≡N), 105.6 (=*C*H), 32.8 (*C*H_2), 28.2, 27.7, 23.5(3*C*H_2) Analysis calculated $C_{25}H_{17}Cl_2N_3S$ (462.4) Calcd C, 64.94; H, 3.71; N, 9.09; S, 6.93 %; Found; C, 64.95; H, 3.74; N, 9.10 %. EI-MS (*m*/*z*): 460.2 [M^+-2].

4.5.2. Ethyl(E)-2-((8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-3-cyano-5,6,7,8-tetrahydro-quinolin-2-yl) thio) acetate (7b)

Brown crystals; yield 83 %; m.p. 230–227 °C; IR (V_{max}, cm^{-1}): 2214 (C≡N); 1743 (C=O); ^{1}H NMR (DMSO d_6), δ_H (ppm): 7.97 (s, 1H, =C*H*), 7.44–7.25 (m, 8H, Ar-*H*), 4.42 (s, 2H, S-CH_2), 3.87 (q, J = 7.2 Hz, 2H, CH_2), 2.81–1.81 (m, 6H, 3CH_2),1.36(t, J = 8.1 Hz, 3H, CH_3). ^{13}C NMR δ_C (ppm): 166.76 (C=O), 157.4, 156.2, 132.4, 130.7, 129.4, 128.8 (Ar-*C*), 115.4 (*C*≡N), 105.8 (=*C*H),61.4 (CH_2), 33.2 (*C*H_2), 29.3, 28.6, 24.5(3*C*H_2), 14.6(CH_3). Analysis calculated $C_{27}H_{22}Cl_2N_2O_2S$ (509.4) Calcd. C, 63.66; H, 4.35; N, 5.50 %; Found: C, 63.67; H, 4.38; N, 5.45 %. EI-MS (*m*/*z*): 508.4 [M^+-1].

4.5.3. (E)-2-((8-(4-Chlorobenzylidene)-4-(4-chlorophenyl)-3-cyano-5,6,7,8-tetrahydroquinolin-2- yl)thio)acetic acid (7c)

Yellow crystals; yield 70 %; m.p. 198–200 °C; IR (V_{max}, cm^{-1}): 2206 (C≡N); 1712 (C=O); 2931 (CH_2). ^{1}H NMR (DMSO d_6), δ_H (ppm): 9.65 (s, 1H, OH), 7.95 (s, 1H, =C*H*), 7.51–7.21 (m, 8H, Ar-*H*), 4.43 (s, 2H, S-CH_2), 2.86–1.76 (m, 6H, 3CH_2). ^{13}C NMR δ_C (ppm): 164.3 (C=O), 158.3, 154.1, 131.7, 130.9, 129.5, 128.4 (Ar-*C*), 115.7 (*C*≡N), 105.6 (=*C*H), 32.6 (*C*H_2), 28.3, 27.6, 23.5(3*C*H_2). Analysis calculated $C_{25}H_{18}Cl_2N_2O_2S$ (481.4) Calcd: C, 62.38; H, 3.77; N, 5.82 %; Found: C, 62.40; H, 3.80; N, 5.84 %; EI-MS (*m*/*z*): 480 [M^+-1].

4.5.4. (E)-2-((4-Chlorobenzyl) thio)-8-(4-Chlorobenzylidene)-4-(4-Chlorophenyl)-5,6,7,8-tetr hydroquinoline-3-Carbonitrile (7d)

Yellow crystals; yield 95 %; m.p. 212–214 °C; IR (V_{max}, cm^{-1}): 2214 (C≡N); 2954 (CH_2); ^{1}H NMR ($CDCl_3$), δ_H (ppm): 7.96 (s, 1H, =C*H*), 7.45–7.27 (m, 12H, Ar-*H*), 4.54 (s, 2H, S-CH_2), 2.80–1.70 (m, 6H, 3CH_2). ^{13}C NMR δ_C (ppm): 158.3, 155.1, 155.0, 153.2, 131.0, 130.1, 129.7, 129.3, 128.8, 128.6 (Ar-*C*), 115.4 (*C*≡N), 105.3 (=*C*H), 33.9 (*C*H_2), 27.6, 27.4, 22.3 (3*C*H_2). Analysis calculated $C_{30}H_{21}C_{l3}N_2S$ (547.9) Calcd: C, 65.76; H, 3.86; N, 5.11 %; Found: C, 65.77; H, 3.89; N, 5.12 %. EI-MS (*m*/*z*): 547.4 [M].

4.5.5. (E)-8-(4-Chlorobenzylidene)-4-(4-chlorophenyl)-2-(ethylthio)-5,6,7,8-tetrahydro-quinoline-3- carbonitrile (7e)

Yellow crystals; yield 79 %; m.p. 252–254 °C; IR (V_{max}, cm^{-1}): 2214 (C≡N); 2924 (CH_2). ^{1}H NMR (DMSO d_6), δ_H (ppm): 7.94 (s, 1H, =C*H*), 7.55–7.34(m, 8H, Ar-*H*), 4.47 (q, J = 7.4 Hz, 2H, S-CH_2), 2.85–1.87 (m, 6H, 3CH_2), 1.43(t, J = 7.9 Hz, 3H, CH_3). ^{13}C NMR δ_C (ppm): 158.6, 153.5, 132.6, 130.2, 129.3, 128.8 (Ar-*C*), 115.4 (*C*≡N), 105.1 (=*C*H), 33.1 (*C*H_2), 29.6, 28.2, 24.7(3*C*H_2). Analysis calculated $C_{25}H_{20}Cl_2N_2S$ (451.4) Calcd: C, 66.52; H, 4.47; N, 6.21 %; Found: C, 66.53; H, 4.50; N, 6.22 %; EI-MS (*m*/*z*): 449.3 [M^+-2].

4.6. Synthesis of derivatives (8a-c).

Method A:

Derivatives (**7a-c)** (1.0 mmol) in 30.0 mL ethanol containing 1.0 mmol metallic sodium were refluxed for 5 h, and then the resulting solution was neutralized by using dilute hydrochloric acid to give derivatives **8a-c** with good yield. The resulting products (**8a-c)** were crystallized from the proper solvent.

Method B:

Derivatives **8a-c** were obtained directly on refluxing of the thiol derivative (**5a**) with halo-derivatives (**6a-c**) in ethanol

containing 2.0 mmol of sodium metal for 6 h and then the solution was neutralized by using dilute hydrochloric acid to give derivatives **8a-c** with good yield. The obtained products **8a-c** were crystallized from the proper solvent.

4.6.1. (E)-3-Amino-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-3H-1 l4-thieno[2,3-b] quinoline-2-carbonitrile (8a)

Yellow crystals; yield 55 %; m.p. 313–314 °C; IR (V_{max}, cm^{-1}): 2198 (C≡N); 3479, 3325 (NH_2), ^1H NMR ($CDCl_3$), δ_H (ppm): 8.12 (br, 1H, =C*H*), 7.64–7.2 (m, 8H, Ar-*H*), 4.3 (s, 2H, NH_2), 2.82–1.55 (m, 6H, 3CH_2). Analysis calculated $C_{25}H_{17}Cl_2N_3S$ (462.4) Calcd C, 64.94; H, 3.71; N, 9.09 %; Found; C, 64.96; H, 3.74; N, 9.11 %. EI-MS (*m*/*z*): 460.2 [M^+-2].

4.6.2. Ethyl(E)-3-amino-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-thieno [2,3- b] quinoline-2-carboxylate (8b)

Yellow; yield 83 %; m.p. 270–271 °C; IR (V_{max}, cm^{-1}): 3487, 3340 (NH_2); 1666 (C=O). ^1H NMR ($CDCl_3$), δ_H (ppm): 8.09 (s, H, C = C*H*), 7.62–6.609 (m, 8H, Ar-*H*), 5.35 (s, 2H, NH_2), 4.29–4.25 (q, 2H, *C*H_2), 1.346–1.32 (t, 3H, CH_3), 2.84–1.55 (m, 6H, 3CH_2).^{13}C NMR δ_C (ppm): 178 (*C*=O), 136.0, 135.2, 131.1, 130.8, 129.9, 129.8, 129.6, 128.4, 127.7 (Ar-*C*), 60.6 (*C*H_2), 27.2, 23.5, 22.7 (3*C*H_2), 14.59 (*C*H_3). Analysis calculated $C_{27}H_{22}Cl_2N_2O_2S$ (509.4) Calcd: C, 63.66; H, 4.38; N, 5.51 %; Found, C, 63.67; H, 4.41; N, 5.52 %. EI-MS (*m*/*z*): 508.5 [M^+−1].

4.6.3. (E)-3-Amino-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-b] quinoline-2-carboxylic acid (8c)

Dark yellow crystals; yield 70 %; m.p. 178–179 °C; IR (V_{max}, cm^{-1}): 3495–3400 (NH_2); 2500–3200 (OH), 2939 (CH_2); 1635 (C=O). ^1H NMR (DMSO d_6), δ_H (ppm): 7.97 (s, 1H, =CH), 7.62–7.21 (m, 8H, Ar-*H*), 6.63 (s, 1H, O*H*), 5.44 (br, 2H, NH_2), 2.46–1.64 (m, 6H, 3CH_2). Analysis calculated $C_{25}H_{18}Cl_2N_2O_2S$ (481.4) Calcd: C, 62.38; H, 3.77; N, 5.82 %; Found: C, 62.40; H, 3.80; N, 5.84 %. EI-MS (*m*/*z*): 480.3 [M^+−1].

4.7. (E)-N-(8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-2-cyano-5,6,7,8- tetrahydrothieno[2,3-b]quinolin-3-yl)acetamide (9)

To a hot solution of compound **8a** (1.0 mmol) in 20 mL dry pyridine, acetic anhydride (1.0 mmol) was added. After that the reaction was refluxed further to 3 h. After cooling the reaction mixture was poured into crushed ice / water with vigorous stirring to get yellow precipitate which filtered off, dried and recrystallized from ethanol/benzene (9:1) as flaxes crystals; Yield: 68 %; m.p. 236–237 °C; IR (V_{max}, cm^{-1}): 2222 (C≡N); 3325 (N−H); 1535 (C=C); 1720 (C=O), ^1H NMR ($CDCl_3$), δ_H (ppm): 8.15 (s, 1H, =C*H*), 7.55–7.03 (m, 9H, Ar-*H,* N*H*), 2.87–1.76 (m, 9H, 3CH_2, CH_3). Analysis calculated $C_{27}H_{19}Cl_2N_3OS$ (504.4) Calcd: C, 64.29; H, 3.80; N, 8.33 %; Found C, 64.32; H, 3.76; N, 8.30 %.

4.8. (E)-7-(4-Chlorobenzylidene)-3,11-bis(4-chlorophenyl)-2-thioxo-2,3,7,8,9,10-hexahydro pyrimido[4′,5′:4,5]thieno[2,3-b] quinolin-4(1H)-one (10)

A mixture of **8a** (1.0 mmol) and 4-chlorophenylisothiocyanate (1.0 mmol) in DMF (20.0 mL) were refluxed for 4 h. After cooling, the obtained solution poured into crushed ice/water with vigorous stirring to get precipitate, which filtered off, dried, and recrystallized from dioxane as orange plates; Yield: 80 %; m.p. 257–260 °C; IR (V_{max}, cm^{-1}): 3379 (N−H), 1666 (C=O), 1566 (C=C). Analysis calculated $C_{32}H20Cl_3N3OS_2$ (633.0) Calcd: C, 60.72; H, 3.18; N, 6.64 %; Found C, 60.73; H, 3.121; N, 6.65 %. %. EI-MS (*m*/*z*): 632.4 [M^+−1].

4.9. Synthesis of dialkyl 2-((8-((E)-4-chlorobenzylidene)-4-(4-chlorophenyl)-3-cyano-5,6,7,8-tetrahydroquinolin-2-yl) thio) maleate (14a, b).

General method: A solution of dialkylacetylenedicarboxylate **(11a, b)** (1.0 mmol) and **5a** (1.0 mmol) in DCM (20.0 mL) containing a catalytic amount of triethylamine were stirring at ambient temperature for three hours. The formed rigid substance was separated from the mother liquor by a vacuum pump and the obtained product is crystallized from ethanol to afford derivatives **14a, b**.

4.9.1. Dimethyl 2-((8-((E)-4-chlorobenzylidene)-4-(4-chlorophenyl)-3-cyano-5,6,7,8-tetrahydro quinolin-2-yl) thio)maleate (14a).

Yellow flakes; yield: 68 %; m.p. 220–221 °C; IR (V_{max}, cm^{-1}): 2222 (C≡N); 1527 (C=C); 1712,1710 (C=O). ^1H NMR ($CDCl_3$), δ_H (ppm): 8.05 (s, 1H, =*C*H), 7.48 (s, 1H, =CH), 7.46–7.03 (m, 8H, Ar-H), 2.82–2.78 (t, *J* = 7.2 Hz, 2H, CH_2), 2.53–2.50 (t, *J* = 7.2 Hz, 2H, CH_2), 2.22–2.18 (m, 2H, CH_2), 1.97(s, 3H, CH_3) and 1.94 (s, 3H, CH_3), ^{13}C NMR δ_C (ppm): 164.7, 164.5 (2*C* = O), 157.3, 155.6, 153.4, 135.4, 131.7, 129.8,129.45,129.41, 128.5, 106.4 (Ar-*C*), 117.0 (*C*≡N), 28.7, 24.3 (3*C*H_2), 14.56, 13.74 (2*C*H_3). Analysis calculated $C_{29}H_{22}Cl_2N_2O_4S$ (565.5) Calcd: C, 61.60; H, 3.92; N, 4.95 %; Found C, 61.65; H, 3.94; N, 4.97 %.

4.9.2. Diethyl2-((8-((E)-4-chlorobenzylidene)-4-(4-chlorophenyl)-3-cyano-5,6,7,8-tetrahydro-quinolin-2- yl) thio)maleate (14b).

Orange flakes, 0.07 g (57 %) yield; m.p. 297–299 °C; IR (V_{max}, cm^{-1}): 2222 (C≡N); 1720, 1714 (C=O); 3055 (CH_2). ^1H NMR ($CDCl_3$), δ_H (ppm): 8.06 (s, 1H, =*C*H), 7.49 (s, 1H, =CH), 7.47–7.05 (m, 8H, Ar-H), 4.302–4.267 (q, *J* = 7.1 Hz, 2H, CH_2), 4.068–4.033 (q, *J* = 7.1 Hz, 2H, CH_2), 2.81–2.79 (t, *J* = 7.0 Hz, 2H, CH_2), 2.51–2.49 (t, *J* = 7.1 Hz, 2H, CH_2), 1.71–1.68 (m, 2H, CH2), 1.34–1.294 (t, 3H, CH_3) and 0.983–0.960 (t, 3H, CH_3), ^{13}C NMR δ_C (ppm): 164.6, 164.4 (2*C* = O), 157.3, 155.6, 153.4, 135.4, 131.7, 129.8,129.45,129.41, 128.6, 105.7 (Ar-*C*), 115.0 (*C*≡N), 62.4, 61.6 (2*C*H_2), 27.6, 22.1 (3*C*H_2), 14.29, 13.84 (2*C*H_3). Analysis calculated $C_{31}H_{26}Cl_2N_2O_4S$ (593.5) Calcd: C, 61.60; H, 3.92; N, 4.95 %; Found C, 61.63; H, 3.95; N, 4.92 %. EI-MS (*m*/*z*): 594.4 [M^+ + 1].

4.10. ***Cytotoxicity activities against three tumor cell lines for compounds 5a, 5b, 7d, 7e, 8b,*** *and* ***10.***

The *in vitro* cytotoxicity activities of some selected compounds (**5a, 5b, 7d, 7e, 8b,** and **10**) against HepG-2, MCF-7, and A-549 cell lines were tested by MTT 3-(4,5-di methylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay utilizing Doxorubicin as a reference compound (Abo-Ashour et al., 2019).

5. Conclusions

We have reported the design and green synthesis of some heterocyclic molecules with diverse biological properties. A methodology for the construction of bis-arylidene cycloalkanone derivatives (bis-chalcones) using an ionic liquid substance as a catalyst has been provided. Simple multicomponent procedures are outlined for the environmentally friendly production of tetrahydroquinoline(1*H*)thions. Good yields of novel thienoquinolino compounds were also produced. Three cancer cell lines Hepatocellular carcinoma cells (HepG-2), Breast carcinoma cells (MCF-7), and Lung carcinoma cells (A-549) were used to examine the antiproliferative effects of some selected derivatives. The majority of evaluated drugs exhibited moderate to excellent cytotoxicity against the examined cell lines. Notably, the IC_{50} values for the *S*-alkyl derivatives ranged from 2.86 to 13.14 μg/mL.

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Conflicts of interest

There are no conflicts of interest to be declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2023.104543.

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