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Base-mediated one-pot synthesis of 3,4,5,6-tetrahydro-4-substituted benzo[*h*]quinazoline-2(1*H*)-thione derivatives and evaluation of their antioxidant activity

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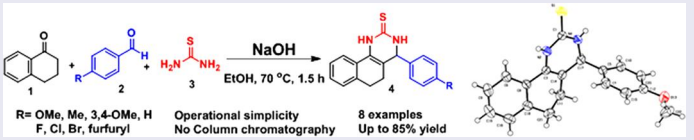
ABSTRACT

One-pot three-component Beginelli-like reactions of a ketone **1**, an aryl aldehyde **2**, and thiourea **3** in the presence of sodium hydroxide are described. In this reaction, 3,4,5,6-tertrahydro-4-substituted quinazoline-2(1*H*)-thione derivatives **4a–h** were obtained in good yields (73–85%). The compound **4a** has been characterized by single crystal X-ray analysis. All the synthesized compounds **4a–h** and **5a–b** were screened for their *in vitro* antioxidant activity. Compounds **4c, 4e,** and **4h** have exhibited an excellent than the standard ascorbic acid. Compounds **4d, 4f,** and **4g** have also shown good activity. Remaining compounds show moderate antioxidant activity.

GRAPHICAL ABSTRACT



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KEYWORDS
α-Tetralone; aldehyde; antioxidant activity; IC_{50} value; quinazoline-2(1*H*)-thione; thiourea

Introduction

The compound-containing quinazoline-2(1*H*)-thione moieties are important classes of bioactive molecules that can show a wide variety of properties such as antibacterial, antiviral, and anti-inflammatory activities.[1] Also, these compounds act as antihypertensives, anticancer agents, calcium-channel blockers, and neuropeptide γ antagonists.[2] One of the well-established synthetic procedures available for quinazoline-2(1*H*)-thione scaffold is the Biginelli reaction, which combines an aromatic aldehyde **2**, thiourea **3**, and carbonyl compound **1** under acidic conditions in ethanol, gives a 3,4,5,6-tetrahydro 4-substituted benzo[*h*]quinazoline-2(1*H*)-thione **4**. It has seen widespread use for generating large collections of molecules in combinatorial synthesis (Fig. 1).[3]

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data (full experimental detail, IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra, and microanalysis) can be accessed on the publisher's website.

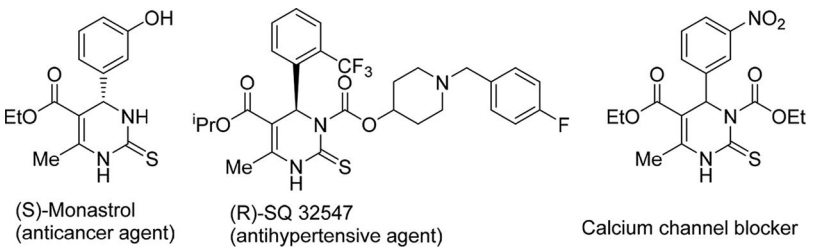
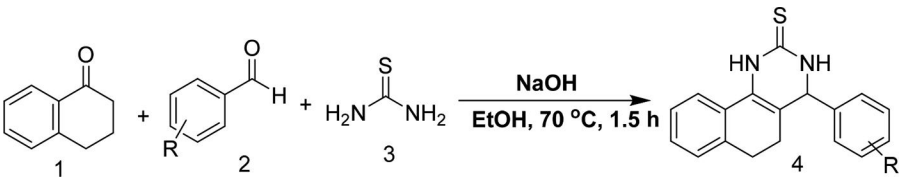


Figure 1. Some examples of biologically active dihydropyrimidinthiones.

Over past few years, many Biginelli-like scaffolds have been reported, and substantial efforts have been made to build up new methods for the synthesis of such compounds because of their therapeutic and pharmacological properties.[2c,4] There are several reports on the synthesis of derivatives containing quinazoline-2(1*H*)-thione moieties using protic acids,[5] Lewis acids,[6] triflates,[7] microwave irradiation,[8] ionic liquids,[9] ultra sound,[10] metallic/ammonium salts,[11] Dowex-50 W,[12] and dodecyl hydrogen sulfate.[13a] Unfortunately, many of these methods have used expensive or toxic reagents and strong acidic conditions. Therefore, the development of a less expensive, high-yielding protocol for the synthesis of compounds containing a quinazoline-2(1*H*)-thione **4** moiety remains of great attention and stand for a considerable challenge. However, despite of extensive studies on the Biginelli-like reactions reported in the literature[13b], to best of our knowledge, there are few reports focusing on the development of base-mediated one-pot Biginelli-like reactions.[3c]

Results and discussion

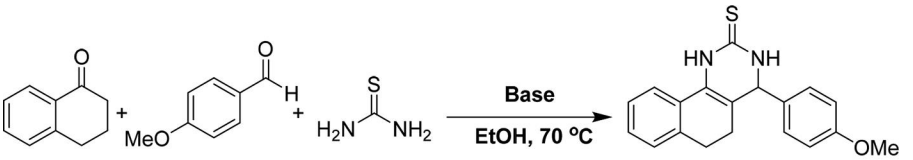
To pursue our interest in the synthesis and antioxidant activity of quinazoline-2(1*H*)-thione, **4** We report herein the sodium hydroxide mediated, one-pot synthesis of 3,4,5,6-tertrahydro-4-substituted quinazoline-2(1*H*)-thione **4** derivatives through three-component condensation of ketone **1**, an aromatic aldehydes **2** and thiourea **3**. The reaction proceeded smoothly in the presence of NaOH (1 eq) to afford 3,4,5,6-tertrahydro-4-substituted quinazoline-2(1*H*)-thione **4** derivatives in good yields (Scheme 1). The pure products **4** were obtained without any additional column chromatography. In addition, through a detailed mechanistic study, (E)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one **6** was suggested as reaction intermediate.



Scheme 1. General scheme for synthesis of 3,4,5,6-tetrahydro-4-substituted benzo[*h*]quinazoline-2(1*H*)-thione derivatives.

Very recently,[14] it has been reported that the cyclocondensation of 2-arylidene-1-tetralonene with thiosemicarbazide under alkaline medium through two step (chalcone preparation followed by cyclocondensation). We have examined the reaction of α-tetralone **1**, anisaldehyde **2a** with thiourea **3** in the presence of NaOH at reflux temperature, gives 85% yield. To optimize the reaction conditions, the reaction was examined with various bases (Table 1). It was found that using of α-tetralone **1** (1 mmol), anisaldehyde **2a** (1 mmol) with thiourea **3** (1 mmol), and NaOH (1 mmol) in 5 mL of in ethanol at 70 °C for 1.5 h, the quinazoline 2 (1*H*)-thione **4a** was obtained in 85% yield (Table 1, Entry 1).

Table 1. Optimization of reaction conditions using various bases.



1 **2a** **3** **4a**

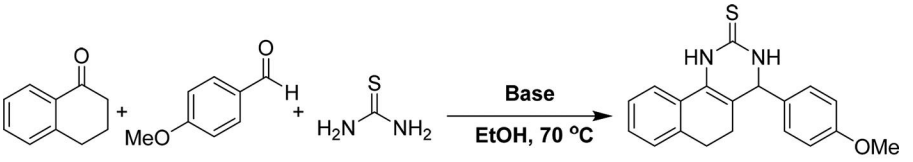
Entry[a]	Base[b]	Time (h)	Yield (%)[c]
1	NaOH	1.5	85[d]
2	KOH	1.5	82[d]
3	LiOH	2.5	80[d]
4	NaOEt	7	76[e]
5	Na^tOBu	7	61[e]
6	K_2CO_3	24	Trace
7	Pyridine	7	64[e]
8	Et_3N	24	Trace
9	DABCO	7	11[e]

[a]Unless otherwise mentioned, the reactions were performed using α-tetralone **1** (1 mmol), anisaldehyde **2a** (1 mmol) with thiourea **3** (1 mmol), and base (1 mmol) in 5 mL of ethanol at 70 °C.
[b]All these cases, **1** mmol of base is used.
[c]Yields are of isolated product.
[d]The products are thrown out from the reaction mixture.
[e]The products are purified using column chromatography.

The reaction of the α-tetralone **1** (1 mmol), anisaldehyde **2a** (1 mmol), and thiourea **3** (1 mmol) with KOH or LiOH in 5 mL of in ethanol, at 70 °C for 1.5 or 2.5 h, gave the quinazoline 2 (1*H*)-thione **4a** in 82 and 80% yields, respectively (Table 1, Entries 2, 3). We have performed the reaction in identical conditions except time 7 h, where the bases NaOEt or NatOBu were used, the quinazoline 2 (1*H*)-thione **4a** was obtained in 76 and 61% yields, respectively (Table 1, Entries 4, 5). The reaction of the α-tetralone **1** (1 mmol), anisaldehyde **2a** (1 mmol) with thiourea **3** (1 mmol) and organic bases such as pyridine or DABCO in 5 mL of ethanol, at 70 °C for 7 h gave the quinazoline 2 (1*H*)-thione **4a** in 64 and 11% yields, respectively (Table 1, Entries 7, 9), whereas, under the same conditions, the weak bases such as K_2CO_3, Et_3N gave only traces of yield even after 24 h (Table 1, Entries 6, 8).

Furthermore, efforts were undertaken to optimize solvent, and the results are summarized (Table 2). We have chosen alcoholic solvent such as methanol, ethanol, isopropanol, THF, ACN, DMF, and DMSO for our study.

Table 2. Optimization study of solvent for reaction condition.



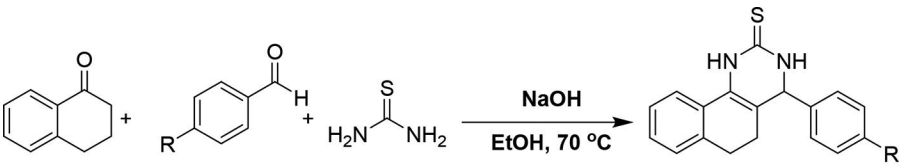
1 **2a** **3** **4a**

Entry	Solvent	Time (h)	Yield (%)[c]
1[a]	Methanol	1.5	75
2[a]	Ethanol	1.5	85
3[a]	IPA	1.5	73
4[b]	THF	14	43
5[b]	ACN	14	19
6[b]	DMF	14	60
7[b]	DMSO	14	72

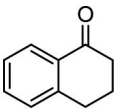
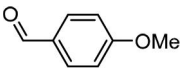
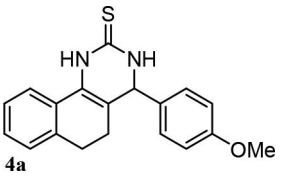
[a]The reactions were performed using α-tetralone **1** (1 mmol), anisaldehyde **2a** (1 mmol) with thiourea **3** (1 mmol), and NaOH (1 mmol) in 5 mL of respective solvent at 70 °C for 1.5 h.
[b]The reactions were performed using α-tetralone **1** (1 mmol), anisaldehyde **2a** (1 mmol) with thiourea **3** (1 mmol), and NaOH (1 mmol) in 5 mL of respective solvent at 70 °C for 14 h.
[c]Yields are of isolated product and are thrown out from the reaction mixture.

The reaction of the α-tetralone **1** (1 mmol) and anisaldehyde **2a** (1 mmol) with thiourea **3** (1 mmol) in 5 mL of alcoholic solvents such as MeOH, EtOH, and IPA in the presence of NaOH (1 mmol), under reflux conditions for 1.5 h gave the quinazoline 2 (1*H*)-thione **4a** in 75, 85, and 73% yields, respectively (Table 2, Entries 1–3). When we examined the reaction with the same condition, the solvents such as THF, ACN, DMF, and DMSO, gave the quinazoline 2 (1*H*)-thione **4a** in 43, 19, 60, and 72% yields, respectively (Table 2, Entries 4–7). It was found that the reaction proceeds better in protic solvents than in aprotic solvent. With the optimized condition in hand, this transformation (Scheme 1) was examined using ketone **1, 1a** aldehyde **2a–h**, and thiourea **3** in the presence of NaOH. As shown in Table 3, the NaOH mediated one-pot condensation of substituted aromatic aldehydes **2**, cyclic ketone **1,** and thiourea **3** proceeded smoothly to furnish the corresponding quinazoline **2** (1*H*)-thione **4** in good yields. It is noted that the methodology worked well even for heterocyclic aldehyde **2 h** (Table 3, Entry 8).

Table 3. Synthesis of quinazoline-2(1*H*)-thione **4a–4h**.

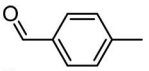
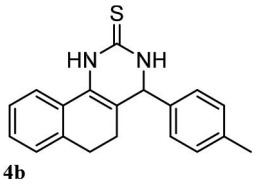
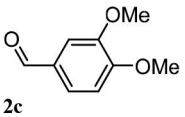
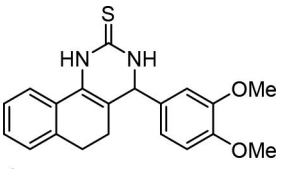
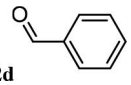
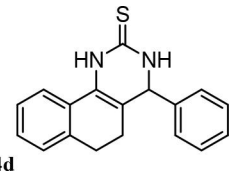
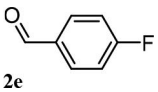
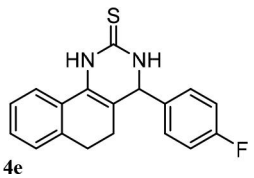
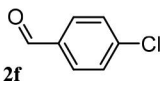
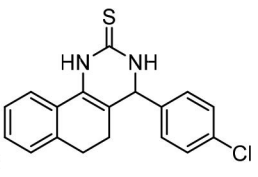
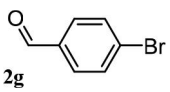
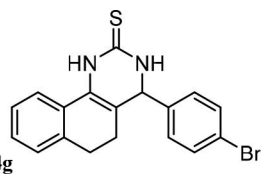
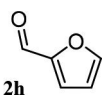
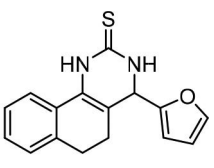


1 **2** **3** **4**

Entry[a]	Ketone 1	Aldehyde 2	Product[b] 4	Time (h)	Yield (%)[c]
1	 **1**	 **2a**	 **4a**	1.5	85

(*Continued*)

Table 3. Continued.

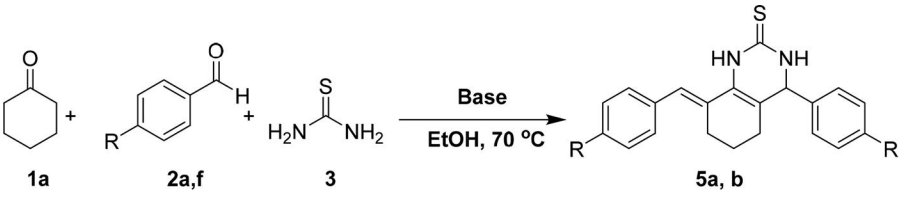
Entry[a]	Ketone 1	Aldehyde 2	Product[b] 4	Time (h)	Yield (%)[c]
2		 **2b**	 **4b**	1.5	82
3		 **2c**	 **4c**	1.5	73
4		 **2d**	 **4d**	2.0	80
5		 **2e**	 **4e**	1.5	81
6		 **2f**	 **4f**	1.5	83
7		 **2g**	 **4g**	1.5	79
8		 **2h**	 **4h**	2.0	77

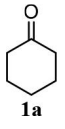
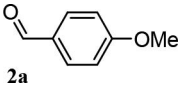
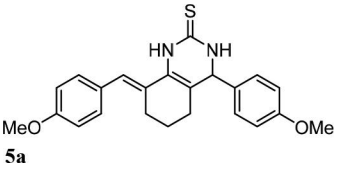
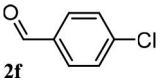
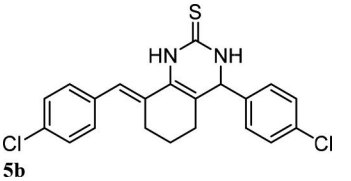
[a]The reactions were performed using α-tetralone **1** (3 mmol), aldehyde **2a–h** (3 mmol) with thiourea **3** (3 mmol), and NaOH (3 mmol) in 5 mL of EtOH at 70 °C.
[b]The products are characterized by Mass, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.
[c]Yields are of isolated product and are thrown out from the reaction mixture.

The versatility of the reaction was investigated with a variety of aldehyde derivatives. According to Table 3, the aldehydes **2a–h** containing both electron-releasing and electron-withdrawing substituents proved to be suitable substrate for this reaction (Table 3, Entries 1–8).

Recently,[15] the two step preparation of quinazoline-2(1*H*)-thione **5a** and **5b** has been reported through the cyclocondensation of bis(arylmethylene)cyclohexanone with thiourea in the presence of sodium methoxide and gave 50–70% yield. It was of our interest to examine the reaction in one pot in the presence of sodium hydroxide as a base. Accordingly, we have performed the reaction of cyclohexanone **1a** (3 mmol), aldehyde **2a, 2f** (6 mmol), and thiourea **3** (3 mmol) in 5 mL ethanol in the presence of NaOH (3 mmol) at 70 °C for 6 h gave the quinazoline-2(1*H*)-thione **5a** and **5b** in 58 and 66% yields, respectively (Table 4, Entries 1, 2). All the structures **4a–h** and **5a–b** were characterized by physical and spectroscopic techniques such as mp, Mass, IR, ^{1}H NMR, and ^{13}C NMR. Compound **4a** ^{1}H NMR spectrum, as an example, revealed the presence of two singlet signals delta 9.00 and 9.69 due to two –NH group of quinozoline-2(1*H*)-thione scaffold. The two singlet signals delta 3.73 (3*H*) and 4.87 (1*H*) correspond to –OCH3 and asymmetric benzylic proton. The doublet at 6.91, multiplet at 7.41, and triplet at 7.66 correspond to aromatic protons. The multiplet at 1.70–2.80 corresponds to aliphatic protons. Structure of compound **4a** was further confirmed by single crystal X-ray analysis. The single crystal X-ray structure of compound **4a** is shown in Fig. 2.

Table 4. Preparation of quinazoline-2(1*H*)-thione **5a–5b**.



Entry[a]	Ketone 1	Aldehyde 2	Product[b] 4	Time (h)	Yield (%)[c]
1				6	58
2				6	66

[a]The reactions were performed using cyclohexanone **1** (3 mmol), aldehyde **2a** or **2f** (6 mmol) with thiourea **3** (3 mmol), and NaOH (3 mmol) in 5 mL of EtOH at 70 °C.
[b]The products are characterized by Mass, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.
[c]Yields are of isolated product and are thrown out from the reaction mixture.

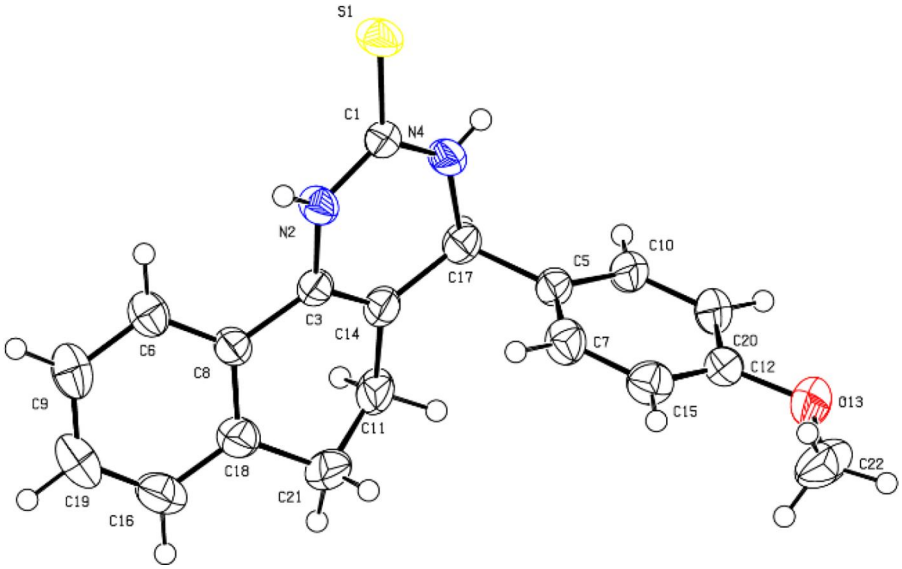
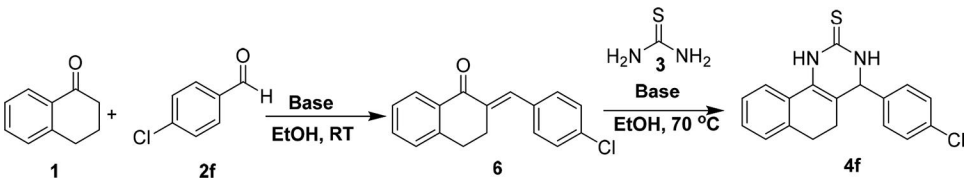


Figure 2. Single crystal X-ray structure of compound **4a** (CCDC No. 1472495).

Previously, Kappe et al.[16] proposed that Lewis acid or protic acid promoted Biginelli reaction proceeded through the formation of an iminium ion (acid catalyzed condensation of aldehyde with urea) as a key intermediate rather than the carbenium ion intermediate (acid catalyzed Knoevenagel reaction of aldehyde and ethyl acetoacetate). The current methodology and the basic condition using NaOH, we visualized that the reaction proceed through Knoevenagel followed by aza-Michel reaction.

To probe the mechanism, we have examined the reaction of α-tetralone **1** with *p*-chlorobenzaldehyde **2f** in ethanol in the presence of 4N NaOH, the formed (E)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one **6**[17] was isolated and characterized by NMR. Then the **6** was treated with thiourea in the presence of NaOH at 70 °C for 5 h (Scheme 2) to afford **4f** in 80% yield. Also, we have investigated the reaction of three-component, one-pot base-mediated reaction of α-tetralone **1**, *p*-chlorobenzaldehyde **2f** with thiourea **3** in ethanol in the presence of NaOH. It was observed that after 15 min of addition of the reagent, it formed a yellow precipitate which was characterized by ^{1}H NMR and confirmed as (E)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one **6**. Furthermore, the yellow precipitate slowly dissolved in another 15 min formed as white precipitate which was filtered and characterized by ^{1}H NMR and confirmed as quinazoline-2(1*H*)-thione **4f**, it was clearly seen that the reaction intermediate formed in the one-pot reaction is (E)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one **6**.



Scheme 2. Preparation of 3,4,5,6-tetrahydro-4-Substituted benzo[*h*]quinazoline-2(1*H*)-thiones through the intermediate **6**.

According to above observations, the plausible reaction mechanism was proposed. As shown in Fig. 3, the reaction using thiourea is initiated through base-mediated Knoevenagel condensation of aldehyde **2** with α-tetralone **1** to give the intermediate **6**. Subsequently, base-mediated aza-Michel addition of thiourea **3** to (E)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one **6** leads to the formation of Michel adduct **7**. Finally, amino group of intermediate **7** attacked on the carbonyl group in an intramolecular fashion gave the intermediate **9**, followed by elimination of the hydroxyl group gave the desired product **4**.

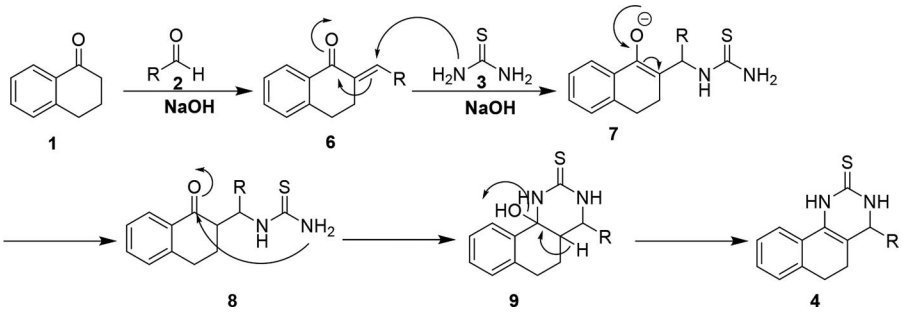


Figure 3. Proposed mechanism.

Antioxidant activity

The DPPH radicals react with suitable reducing agents as a result of which the electrons become paired off forming the corresponding hydrazine. The solution, therefore, loses color stoichiometrically depending on the number of electrons taken up. Substances capable of donating electrons/hydrogen atoms are able to convert DPPH (purple) into their nonradical form 1,1-diphenyl-2-picrylhydrazine (Yellow), a reaction which can be followed spectrophotometrically.[18]

In the DPPH Free radical scavenging activity, compounds **4a–4h** and **5a, 5b** were evaluated for their free radical scavenging activity with ascorbic acid as standard compound. The IC_{50} value was calculated for each compound as well as ascorbic acid are summarized in Table 5 and shown in figures (see supplementary material). The scavenging effect increased with the increasing concentrations of test compounds. The IC_{50} values for compounds **4c, 4e, 4h** were 1.77×10^{-4} M, 1.73×10^{-4} M, and 1.55×10^{-4} M, respectively, which are comparatively lower than the IC_{50} value (1.80×10^{-4} M) of ascorbic acid. The compounds **4d, 4f**, and **4g** were comparable IC_{50} value with ascorbic acid. The IC_{50} value of compounds **4a, 5a**, and **5b** were slightly higher than the standard (Table 5). DPPH is relatively stable nitrogen-centered free radical that easily accepts an electron or hydrogen radical to become a stable diamagnetic molecule. Free radical scavenging activity of the quinazoline-2(1*H*)-thione derivatives are concentration dependent, as the concentration of the test compounds increases, the radical scavenging activity increases and lower IC_{50} value reflects better protective action. From results, it may be postulated that compounds **4c, 4e, 4h** were able to reduce the stable free radical DPPH to the yellow-colored diphenylpicrylhydrazine exhibiting better free radical scavenging activity than the standard antioxidant ascorbic acid.

Table 5. IC_{50} Values for compounds **4a–h** and **5a–b**.

Entry	Product	IC_{50} Value ($\times 10^{-4}$)M
1	**4a**	2.47
2	**4b**	3.14
3	**4c**	1.77
4	**4d**	1.87
5	**4e**	1.73
6	**4f**	1.85
7	**4g**	1.85
8	**4h**	1.55
9	**5a**	2.01
10	**5b**	1.99
11	Ascorbic acid	1.80

Among the synthesized compounds, the kinetic study were performed for the most potent compound **4h** to verify the complete quenching time for DPPH radicals as shown in Fig. 4. As time increases, the intensity at 517 nm decreases, and at 54 min, the DPPH radicals were quenched completely.

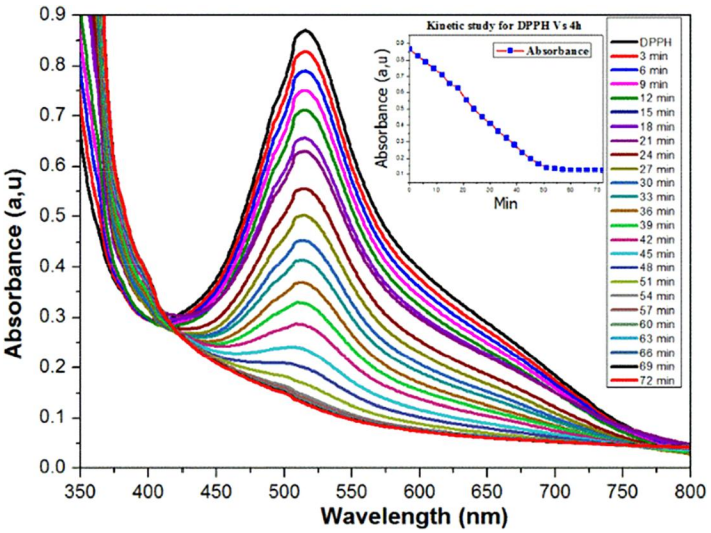


Figure 4. Kinetic study for DPPH Vs **4h**.

Conclusions

In this study, we have developed the sodium hydroxide-mediated one-pot synthesis of 3,4,5,6-tertrahydro-4-substituted quinazoline-2(1*H*)-thione derivatives **4a–h,** and the compound **4a** has been characterized by single crystal X-ray analysis. This method provides several advantages such as inexpensive reagents, short reaction times, easy synthetic procedure, good yields, simple workup procedure, and easy isolation. It is expected to be useful synthetic procedure for the synthesis of wide variety of drug-like molecules contains quinazoline-2(1*H*)-thione **4** moiety. All the synthesized compounds **4a–h** and **5a–b** were screened for antioxidant activity. Among the synthesized compound, **4h** exhibits an excellent antioxidant activity.

General procedure for synthesis of 3,4,5,6-tetrahydro-4-substituted benzo[h] quinazoline-2(1H)-thione derivatives

To a stirred solution of ketone **1** (3 mmol) in EtOH (5 mL), aryl aldehyde **2** (3 mmol), thiourea **3** (3 mmol), and NaOH (3 mmol) were added and were heated at 70 °C for respective time (Table 3). After 15 min, yellow solid was thrown out from the reaction mixture. The heating was continued, the yellow solid was slowly dissolved, and a white solid was precipitated from the reaction mixture. The white solid was filtered and washed twice with cold ethanol (10 mL) to afford 3,4,5,6-tetrahydro-4-substituted benzo[*h*]quinazoline-2(1*H*)-thione **4** in 73–85% yields.

3,4,5,6-tetrahydro-4-(4-methoxyphenyl)benzo[h]quina-zoline-2(1H)-thione (4a)[8f]

Yield: 0.82 g, (85%); White solid; mp 219–221 °C.[8f] IR (KBr): 3436, 3209, 2927, 2860, 1619, 1572, 1477, 1176, 1032 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.69 (s, 1H), 9.00 (s, 1H), 7.66 (m, 1H), 7.41 (m, 5H), 6.91 (d, 2H, $J = 8.40$ Hz), 4.87 (s, 1H), 3.73 (s, 3H), 2.70 (m, 1H), 2.57 (m, 1H), 2.11 (m, 1H), 1.81 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.4, 159.4, 135.8, 135.4, 128.7, 128.2, 128.0, 126.9, 122.0, 114.4, 111.9, 58.3, 55.5, 27.8, 24.0; MS (EI): $m/z = 323$ [M + 1].

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