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Recyclization of 2-iminocoumarin-3-carbonitriles with 2-aminothiobenzamide: a new synthetic route to substituted 2-(2-iminocoumarin-3-yl)quinazoline-4(3*H*)-thiones

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Recyclization of 2-iminocoumarin-3-carbonitriles with 2-aminothiobenzamide: a new synthetic route to substituted 2-(2-iminocoumarin-3-yl)quinazoline-4(3*H*)-thiones

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The reaction of 2-aminothiobenzamide with either 2-iminocoumarin-3-carbonitrile or 2-iminocoumarin-3-thiocarboxamides has been studied. It has been established that in both cases, 2-(2-iminocoumarin-3-yl)quinazoline-4(3*H*)-thiones are formed as the result of a two-step procedure. The reactions of 2-(2-iminocoumarin-3-yl)quinazoline-4(3*H*)-thiones with arylamines and alkylating agents have been studied.

Keywords: iminocoumarin, quinazoline, thiobenzamide, rearrangement, recyclization

1. Introduction

3-Substituted 2-iminocoumarins have versatile biological activities such as anti-inflammatory (*1*, *2*), antimicrobial, antitumor (*3–6*) and antifungal (*7, 8*). Also, they can be used in the synthesis of 2-substituted 2*H*-1-benzopyrans (*9*).

On the other hand, among 3,4-dihydroquinazolin-4-thione derivatives, selective estrogen receptor beta modulators (*10*) as well as aurora 2 kinase inhibitors (*11*) and antiulcer agents (*12*) had been found. Similar compounds have been also reported as fungicides (*13*) and herbicides (*14*). Some *S*-alkylquinazolin-4-thiones display antimicrobial activity (*15–19*). 3,4-Dihydroquinazolin-4-thiones can be successfully applied as the precursors for annulated heterocyclic systems syntheses (*18*, *20–25*).

As the part of our research work on the synthesis of 3-heteroaryl-2-iminocoumarins (*26*, *27*), we focused our efforts on the synthesis of 2-(2-iminocoumarin-3-yl)quinazoline-4(3*H*)-thiones.

2. Results and discussion

Most of quinazolin-4-thiones synthetic methods involve reactions of quinazolin-4-ones with thionating reagents (*28–34*) or the cyclization 2-aminothiobenzamides (*35–38*). Some other methods which are less common were also reported (*23*, *39*).

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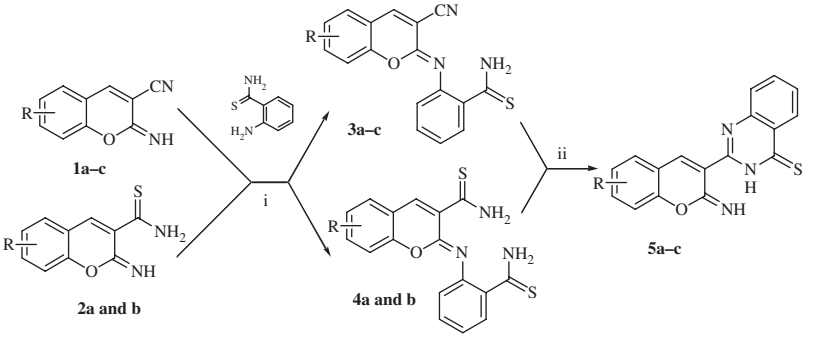
Recently, the advantages of 2-iminocoumarin-3-carboxamides rearrangement (*26*, *27*, *40–45*) under the action of 2-aminothiobenzamide for synthesis of 2-(coumarin-3-yl)quinazolin-4(3*H*)-thiones, which can be easily performed in glacial acetic acid (15 min) have been approved (*38*). According to the proposed mechanism of these rearrangement, the carboxamide group of 2-iminocoumarin-3-carboxamide serves as a precursor of lactone C=O group of the resulting 3-heteroarylcoumarin. Thus, it was worthy to assume that utilization of 2-iminocoumarin-3-carbonitriles in the similar rearrangement will lead to the formation of the products with imino-group (C=NH) in the 2-position of benzopyran ring and the products should be 2-(2-iminocoumarin-3-yl)quinazoline-4(3*H*)-thiones. While the rearrangement of 2-iminocoumarin-3-carbothioamide under the action of 2-aminothiobenzamide could be the way for 2-(2-thioxocoumarin-3-yl)quinazolin-4(3*H*)-thiones.

We performed the interaction of 2-iminocoumarin-3-carbonitrile **1a** with 2-aminothiobenzamide in boiling glacial acetic acid; likewise, it was previously applied for one-step synthesis of 2-(coumarin-3-yl)quinazolin-4(3*H*)-thiones (*38*). The isolated product appeared to be the same as in the case of 2-iminocoumarin-3-carboxamide interaction with 2-aminothiobenzamide – 2-(coumarin-3-yl)quinazolin-4(3*H*)-thione **7a**. Possibly, the traces of water in glacial acetic acid promoted the hydrolysis of imino group of the target product.

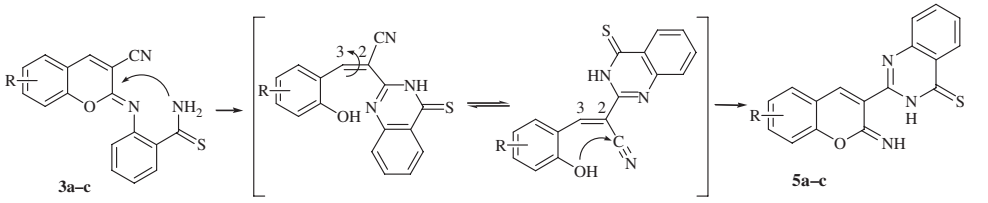
Thus, we had to improve the procedure. First, we performed the interaction of either 2-iminocoumarin-3-carbonitriles **1a**–**c** or 2-iminocoumarin-3-carbothioamides **2a** and **b** with 2-aminothiobenzamide in glacial acetic acid at relatively low temperature (40–50°C) at stirring. As a result, 2-[(3-cyanocoumarin-2-ylidene)amino]benzenecarbothioamides **3a**–**c** and 2-{[2-(aminocarbonothioyl)phenyl]imino}-coumarin-3-carbothioamides **4a** and **b** were precipitated out from acetic acid as yellow solids in high yields. The rearrangements of **3** and **4** have been performed in boiling anhydrous DMF in order to avoid any possibility of hydrolytic processes at the second step of the reaction (Scheme 1).

The rearrangement of 2-[(3-cyanocoumarin-2-ylidene)amino]benzenecarbothioamides **3a**–**c** is likely to proceed according to the mechanism represented in Scheme 2. It involves an intramolecular nucleophilic attack of thioamide NH_2 group on the carbon atom at position 2 of the iminolactone ring followed by a ring opening to produce the corresponding quinazoline-4(3*H*)-thione. The *cis–trans*-isomerization of the quinazoline-4(3*H*)-thione followed by a nucleophilic attach of the OH group at the carbon of the nitrile group afforded the most thermodynamically stable product **5** (Scheme 2).

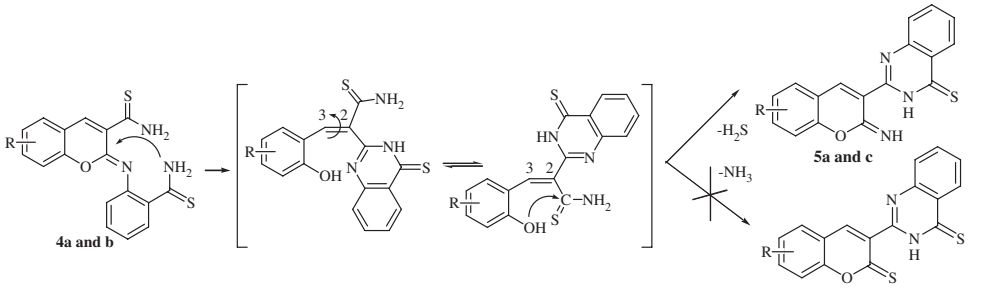
It is noteworthy that the rearrangement of **4a** and **b** in DMF unexpectedly resulted in 2-(2-iminocoumarin-3-yl)quinazoline-4(3*H*)-thiones **5a** and **c** but not 2-(2-thioxo-coumarin-3-yl)quinazolin-4(3*H*)-thiones (Scheme 3). Thus, it can be deduced that in this case the hydrogen



Scheme 1. Reagents and conditions: (i) AcOH, 40–50°C, 30 min; (ii) DMF, 140-150°C, 20 min. Substituents R are given in Table 1 and Section 4.



Scheme 2. The suggested mechanism of 2-[(3-cyanocoumarin-2-ylidene)amino]benzene-carbothioamides **3a-c** rearrangement.



Scheme 3. The suggested mechanism of 2-{[2-(aminocarbonothioyl)phenyl]imino}-coumarin-3-carbothioamides **4a** and **b** rearrangement.

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sulfide cleavage, at the lactone-closure step of the proposed mechanism, is the preferable way for 2-{[2-(aminocarbonothioyl)phenyl]imino}-coumarin-3-carbothioamides **4a** and **b** recyclization (Scheme 3).

The ^{1}H NMR spectra of compounds **3** and **4** showed that the protons at position 4 of the coumarin ring resonated at δ 8.49–8.96 region. Also, the carbothioamide group protons and the aromatic protons resonated with the regions at δ 9.4–11.4 and 7.1–7.9, respectively. In the ^{1}H NMR spectra of compounds **5a**–**c**, the signal of proton in position 4 of coumarin in the range δ 8.88–8.97 ppm, as well as the signal of imino-group proton (δ 9.55–9.61 ppm) and the signal of quinazoline-4(3*H*)-thione fragment NH (δ 15.77–16.00 ppm) are present. The LC-MS spectra for compounds **3**, **4** and **5** show their high purity. Compounds **5** are slightly soluble in solvents and therefore their ^{13}C NMR spectra were not measured.

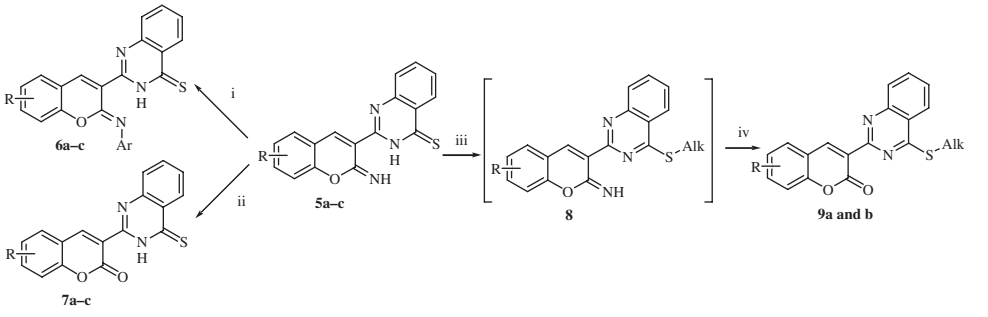
The structures compounds **5** were further confirmed by their reactions with anilines in glacial acetic acid to produce the corresponding **6** (Scheme 4) as yellow solids in high yields (Table 1). Also, compounds **5** could be easily converted to their oxoanalogues **7**, previously described in our work (*38*), by acidic hydrolysis with hydrochloric acid and glacial acetic acid (Scheme 4).

The ^{1}H NMR spectra of compounds **6** do not have the signal of imino-group proton, but they have more signals of aromatic protons than the spectra of compounds **5**. The substituents of phenylimino fragment resonated at 1.21 (t, 3H $CH_2C\underline{H}_3$) and 2.63 (q, 2H $C\underline{H}_2CH_3$) for **6b** and at 3.72 (s, 6H, $2OC\underline{H}_3$) for **6c**. The signals of the proton in position 4 (δ 8.93–8.95 ppm) and quinazoline-4(3*H*)-thione fragment NH (δ 15.55–16.06 ppm) for compounds **6** are almost similar to the same signals of compounds **5**.

The alkylation of compounds **5** with alkyl halides in absolute aprotic solvents should be a convenient approach for synthesis of 3-(4-alkylthioquinazolin-2-yl)-2-iminocoumarins **8**. However, the spectra of the solids obtained after the alkylation of compounds **5** showed the mixture of different products. Most likely, compounds **8** are extremely unstable due to the high reactivity of imino group as well as their ability for pyran ring opening (especially in DMSO or DMSO-d_6) (*46*). The instability of *S*-alkyl compounds **8** relatively with the starting thione **5**, which are stable

Table 1. Synthesis of compounds **3**–**7** and **9**.

X	No.	R	Ar	Alk	Yield (%)
CN	**3a**	H	–	–	80
	3b	8-OMe	–	–	86
	3c	8-OEt	–	–	85
$CSNH_2$	**4a**	H	–	–	76
	4b	8-OEt	–	–	79
	5a	H	–	–	70 (A), 61 (B)
	5b	8-OMe	–	–	88(A)
	5c	8-OEt	–	–	85 (A), 69 (B)
	6a	H	4-FC_6H_4	–	62
	6b	H	4-EtC_6H_4	–	66
	6c	8-OEt	3,5-di-$OMeC_6H_3$	–	70
	7a	H	–	–	89
	7b	8-OMe	–	–	82
	7c	8-OEt	–	–	88
	9a	8-OMe	–	$CH_2C(O)NH(4\text{-}MeC_6H_4)$	61
	9b	8-OEt	–	3-$MeC_6H_4CH_2$	65



Scheme 4. Reagents and conditions: (i) anilines, AcOH, 70–80°C, 30 min; (ii) HCl, AcOH; (iii) AlkHal, DMF, triethylamine, 70°C, 40 min; (iv) HCl, i-PrOH. Substituents R, Ar and Alk are given in Table 1 and Section 4.

in DMSO-d_6, can be possibly explained by the break of intramolecular bound between the NH fragment of quinazoline-4-thione and imino group specific for **5**. The absence of hydrogen binding makes 2-iminopyran cycle of compounds **8** less stable and increases imino-group reactivity. The hydrolysis of the isolated compounds **8** with hydrochloric acid allowed us to obtain the previously reported 3-(4-alkylthioquinazolin-2-yl)coumarins **9a** and **b** (*38*) with high yields.

3. Conclusion

Reactions of thioanthranilamide with 2-iminocoumarin-3-carbonitriles and 2-iminocoumarin-3-carbothioamides according to the two-step procedure gave 2-(2-iminocoumarin-3-yl)quinazoline-4(3*H*)-thiones. The procedure is simple and high yielding and therefore provides an alternative for the Knoevenagel reaction. Reactions of quinazoline-4(3*H*)-thiones with phenylamines gave the corresponding 2-(2-phenylimino-coumarin-3-yl)quinazolin-4(3*H*)-thiones. Alkylations of 2-(2-iminocoumarin-3-yl)quinazoline-4(3*H*)-thiones produce the corresponding iminocoumarins which are highly unstable. The structures of iminocoumarins were confirmed by their hydrolysis to the corresponding 3-(4-alkylthioquinazolin-2-yl)coumarins.

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4. Experimental section

Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. Elemental analysis was within ±0.4% of the theoretical value. IR spectra were recorded on Specord M80 spectrometers in KBr. ^{1}H and ^{13}C NMR spectral data were reordered at 200 and 75 MHz, respectively, on Varian Mercury-200 and Varian Geminy-300 spectrometers using TMS as an internal standard. Mass spectral analyses were obtained on a PE SCIEX API 150EX mass spectrometer.

4.1. *2-Iminocoumarin-3-carbonitriles 1 and 2-iminocoumarin-3-carbothioamides 2*

2-Iminocoumarin-3-carbonitriles 1 and 2-iminocoumarin-3-carbothioamides were obtained from corresponding salicylic aldehydes, malononitrile and 2-cyanoacetothioamide according to the Knoevenagel reaction (*47–52*).

4.1.1. *2-Iminocoumarin-3-carbonitrile (**1a**)*

Yield 65%; m.p. 160–162°C, lit. m.p. 160°C (*48*), 164°C (*49*); yellow solid. IR (cm^{-1}): 3293, 3038, 2228 (CN), 1651, 1601, 1450. ^{1}H NMR (200 Hz, $CDCl_3$): δ 7.12 (m, 2 H), 7.32 (d, $J = 6.4$ Hz, 1 H), 7.46 (t, $J = 7.6$ Hz, 1 H), 7.64 (br.s, 1 H), 7.70 (br.s, 1 H). Anal. calcd. for $C_{10}H_6N_2O$: H, 3.34; C, 55.36; N, 10.33. Found: H, 3.20; C, 55.08; N, 10.14.

4.1.2. *2-Imino-8-methoxy-coumarin-3-carbonitrile (**1b**)*

Yield 70%; m.p. 165–167°C, lit. m.p. 170°C (*50*); yellow solid. IR (cm^{-1}): 3287, 3054, 2226 (CN), 1651, 1607, 1477. ^{1}H NMR (200 Hz, $CDCl_3$): δ 3.84 (s, 3 H), 6.89 (d, $J = 6.7$ Hz, 1 H), 7.05 (m, 2 H), 7.67 (br.s, 1 H), 7.78 (br.s, 1 H). Anal. calcd. for $C_{11}H_8N_2O_2$: H, 3.44; C, 54.95; N, 10.05. Found: H, 3.40; C, 54.70; N, 9.82.

4.1.3. *8-Ethoxy-2-iminocoumarin-3-carbonitrile (**1c**)*

Yield 78%; m.p. 161–163°C; yellow solid. IR (cm^{-1}): 3320, 3036, 2228 (CN), 1655, 1604, 1467. ^{1}H NMR (200 Hz, $CDCl_3$): δ 1.36 (t, $J = 6.7$ Hz, 3 H), 4.03 (q, $J = 6.7$ Hz, 2 H), 6.84 (m, 1 H), 6.98 (m, 2 H), 7.61 (br.s, 1 H), 7.71 (br.s, 1 H). Anal. calcd. for $C_{12}H_{10}N_2O_2$: H, 3.57; C, 55.33; N, 9.93. Found: H, 3.31; C, 55.25; N, 9.67.

4.1.4. *2-Iminocoumarine-3-carbothioamide (**2a**)*

Yield 72%; m.p. 140–142°C, lit. m.p. 146°C (*52*); orange solid. IR (cm^{-1}): 3286, 3231, 3013, 1649, 1626, 1562, 1406. ^{1}H NMR (200 Hz, $CDCl_3$): δ 7.17 (m, 2 H), 7.52 (m, 2 H), 7.72 (br.s, 1 H), 8.22 (br.s, 1 H), 9.10 (s, 1 H), 12.14 (br.s, 1 H). Anal. calcd. for $C_{10}H_8N_2OS$: H, 3.95; C, 58.81; N, 13.72; S, 15.70. Found: H, 3.91; C, 58.68; N, 13.65; S, 15.59.

4.1.5. *8-Etoxy-2-iminocoumarine-3-carbothioamide (**2b**)*

Yield 75%; m.p. 174–176°C; orange solid. IR (cm^{-1}): 3302, 3237, 3042, 1650, 1626, 1594, 1469. ^{1}H NMR (200 Hz, $CDCl_3$): δ 1.47 (t, $J = 7.0$ Hz, 3 H), 4.14 (q, $J = 7.0$ Hz, 2 H), 7.11 (m, 3 H),

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8.14 (br.s, 2 H), 9.09 (s, 1 H), 12.14 (br.s, 1 H). Anal. calcd. for $C_{12}H_{12}N_2O_2S$: H, 4.87; C, 58.05; N, 11.28; S, 12.91. Found: H, 4.81; C, 57.88; N, 11.18; S, 12.77.

4.2. *General procedure for the synthesis of 3 and 4*

A solution of 2-aminothiobenzamide (2 mmol) in glacial acetic acid (3 ml) was added to a suspension of **1** or **2** (2 mmol) in glacial acetic acid (3 ml). The mixture was stirred at 40–50°C for 30 min and the reaction mixture was left to cool. The solid obtained was filtered and dried.

4.2.1. *2-[(3-Cyanocoumarin-2-ylidene)amino]benzenecarbothioamide (**3a**)*

Yield 80%; m.p. 165–167°C; yellow solid. IR (cm^{-1}): 3245, 3129, 2229, 1639, 1553, 1453. ^1H NMR (200 Hz, DMSO-d_6): δ 7.13 (m, 3 H), 7.35 (m, 2 H), 7.61 (m, 3 H), 8.52 (s, 1 H), 9.35 (br.s, 1 H), 9.93 (br.s, 1 H). ^{13}C NMR (75 Hz, DMSO-d_6): δ 185,63, 156.04, 147.35, 145.94, 144.64, 140.04, 135.31, 133.54, 130.19, 129.24, 128.13, 127.99, 124.56, 118.7, 117.42, 116.36, 115.20. LC-MS: m/z (MH^+) 306. Anal. calcd. for $C_{17}H_{11}N_3OS$: H, 3.63; C, 66.87; N, 13.76; S, 10.50. Found: H, 3.42; C, 66.76; N, 13.50; S, 10.42.

4.2.2. *2-[(3-Cyano-8-methoxycoumarin-2-ylidene)amino]benzenecarbothioamide (**3b**)*

Yield 86%; m.p. 223–225°C; yellow solid. IR (cm^{-1}): 3207, 2229, 1644, 1603, 1470. ^1H NMR (200 Hz, DMSO-d_6): δ 3.75 (s, 3 H), 7.27 (m, 6 H), 7.81 (d, J = 7.6 Hz, 1 H), 8.49 (s, 1 H), 9.37 (br.s, 1 H), 9.99 (br.s, 1 H). LC-MS: m/z (MH^+) 336. Anal. calcd. for $C_{18}H_{13}N_3O_2S$: H, 3.91; C, 64.46; N, 12.53; S, 9.56. Found: H, 3.88; C, 64.32; N, 12.40; S, 9.38.

4.2.3. *2-[(3-Cyano-8-ethoxycoumarin-2-ylidene)amino]benzenecarbothioamide (**3c**)*

Yield 85%; m.p. 210–212°C; yellow solid. IR (cm^{-1}): 3198, 2978, 2228, 1645, 1604, 1450. ^1H NMR (200 Hz, DMSO-d_6): δ 1.21 (t, J = 6.7 Hz, 3 H), 4.05 (q, J = 6.7 Hz, 2 H), 7.23 (m, 6 H), 7.87 (d, J = 7.7 Hz, 1 H), 8.50 (s, 1 H), 9.42 (br.s, 1 H), 10.08 (br.s, 1 H). ^{13}C NMR (75 Hz, DMSO-d_6): δ 185.12, 155.28, 146.86, 144.85, 144.13, 142.71, 139.82, 134.80, 128.73, 127.62, 127.58, 127.49, 123.97, 121.18, 118.96, 117.67, 116.92, 64.61, 14.13. LC-MS: m/z (MH^+) 350. Anal. calcd. for $C_{19}H_{15}N_3O_2S$: H, 4.33; C, 65.31; N, 12.03; S, 9.18. Found: H, 4.20; C, 65.12; N, 11.88; S, 9.12.

4.2.4. *2-{[2-(Aminocarbonothioyl)phenyl]imino}-coumarin-3-carbothioamide (**4a**)*

Yield 76%; m.p. 180–182°C; yellow solid. IR (cm^{-1}): 3439, 3282, 3150, 3030, 1651, 1566, 1404, 1298. ^1H NMR (200 Hz, DMSO-d_6): δ 7.18 (m, 3 H), 7.35 (m, 2 H), 7.56 (m, 2 H), 7.84 (d, J = 7.6 Hz, 1 H), 8.95 (s, 1 H), 9.43 (s, 1 H), 9.82 (s, 1 H), 10.48 (s, 1 H), 11.03 (s, 1 H). LC-MS: m/z (MH^+) 340. Anal. calcd. for $C_{17}H_{13}N_3OS_2$: H, 3.86; C, 60.15; N, 12.38; S, 18.89. Found: H, 3.77; C, 60.02; N, 12.28; S, 18.75.

4.2.5. *2-{[2-(Aminocarbonothioyl)phenyl]imino}-8-ethoxy-coumarin-3-carbothioamide (**4b**)*

Yield 79%; m.p. 140–142°C; yellow solid. IR ($cm^{-1}cm^{-1}$): 3444, 3251, 3149, 2977, 1631, 1620, 1469, 1273. ^1H NMR (200 Hz, DMSO-d_6): δ 1.24 (t, J = 6.7 Hz, 3 H), 4.01 (q, J = 6.7 Hz, 2 H), 7.16 (m, 1 H), 7.33 (m, 4 H), 7.50 (dd, J=7.6, 1.8 Hz, 1 H), 7.61 (d, J=7.9 Hz, 1 H), 8.96 (s, 1 H),

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9.49 (s, 1 H), 9.89 (s, 1 H), 10.43 (s, 1 H), 11.25 (s, 1 H). LC-MS: m/z (MH^+) 384. Anal. calcd. for $C_{19}H_{17}N_3O_2S_2$: H, 4.47; C, 59.51; N, 10.96; S, 16.72. Found: H, 4.40; C, 59.42; N, 10.85; S, 16.47.

4.3. *Synthesis of compounds 5*

A solution of either **3** (method A) or **4** (method B) in DMF (5 ml) was heated at 140–150°C for 20 min. The solid obtained after cooling was filtered, washed with 2-propanol and dried to give **5**.

4.3.1. *2-(2-Iminocoumarin-3-yl)quinazolin-4(3H)-thione (**5a**)*

Yields 70% (Method A) and 61% (Method B); m.p. 238–240°C; yellow solid. IR (cm^{-1}): 3320, 2912, 1655, 1607, 1556, 1498, 1462. ^{1}H NMR (200 Hz, DMSO-d_6): δ 7.33 (t, $J = 7.7$ Hz, 2 H), 7.61 (qd, $J = 8.1$, 1.5 Hz, 2 H), 7.86 (m, 4 H), 8.55 (dd, $J = 8.1$, 1.1 Hz, 1 H), 8.97 (s, 1 H), 9.59 (br.s, 1 H), 15.86 (br.s, 1 H). LC-MS: m/z (MH^+) 306. Anal. calcd. for $C_{17}H_{11}N_3OS$: H, 3.63; C, 66.87; N, 13.76; S, 10.50. Found: H, 3.46; C, 66.75; N, 13.51; S, 10.31.

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4.3.2. *2-(2-Imino-8-methoxycoumarin-3-yl)quinazolin-4(3H)-thione (**5b**)*

Yield 88% (Method A); m.p. 288–290°C; yellow solid. IR (cm^{-1}): 3313, 2834, 1655, 1605, 1559, 1494, 1430. ^{1}H NMR (200 Hz, DMSO-d_6): δ 3.90 (s, 3 H), 7.32 (m, 2 H), 7.56 (t, $J = 7.7$ Hz, 1 H), 7.83 (m, 2 H), 8.55 (d, $J = 8.1$ Hz, 1 H), 8.88 (s, 1 H), 9.55 (br.s, 1 H), 15.77 (br.s, 1 H). LC-MS: m/z (MH^+) 336. Anal. calcd. for $C_{18}H_{13}N_3O_2S$: H, 3.91; C, 64.46; N, 12.53; S, 9.56. Found: H, 3.62; C, 64.74; N, 12.32; S, 9.50.

4.3.3. *2-(2-Imino-8-ethoxycoumarin-3-yl)quinazolin-4(3H)-thione (**5c**)*

Yields 85% (Method A) and 69% (Method B); m.p. 262–264°C; yellow solid. IR (cm^{-1}): 3330, 2927, 1656, 1602, 1557, 1465. ^{1}H NMR (200 Hz, DMSO-d_6): δ 1.40 (t, $J = 7.0$ Hz, 3 H), 4.17 (q, $J = 7.0$ Hz, 2 H), 7.25 (m, 2 H), 7.42 (d, $J = 7.3$ Hz, 1 H), 7.59 (td, $J = 8.1$, 1.1 Hz, 1 H), 7.79 (d, $J = 8.4$ Hz, 1 H), 7.90 (t, $J = 8.1$ Hz, 1 H), 8.55 (d, $J = 8.1$ Hz, 1 H), 8.91 (s, 1 H), 9.61 (br.s, 1 H), 16.00 (br.s, 1 H). LC-MS: m/z (MH^+) 350. Anal. calcd. for $C_{19}H_{15}N_3O_2S$: H, 4.33; C, 65.31; N, 12.03; S, 9.18. Found: H, 4.60; C, 65.11; N, 11.85; S, 9.02.

4.4. *General procedure for the synthesis of 6*

To a solution of corresponding aniline (1 mmol) in glacial acetic acid (5 ml) 2-(2-iminocoumarin-3-yl)quinazoline-4(3*H*)-thione **3** (1mmol) was added at 40–50°C under stirring. The reaction mixture was heated at 70–80°C for 30 min. After cooling down to room temperature, the precipitate formed was filtered, washed with 2-propanol and recrystallized form DMF.

4.4.1. *2-[2-(4-Fluoro-phenylimino)-coumarin-3-yl]quinazolin-4(3H)-thione (**6a**)*

Yield 62%; m.p. 278–280°C; yellow solid. IR (cm^{-1}): 2861, 1641, 1549, 1499, 1461. ^{1}H NMR (200 Hz, DMSO-d_6): δ 7.30 (m, 4 H), 7.57 (m, 4 H), 7.84 (m, 3 H), 8.53 (d, $J = 8.1$ Hz, 1 H), 8.94 (s, 1 H), 15.55 (s, 1 H). LC-MS: m/z (MH^+) 400. Anal. calcd. for $C_{23}H_{14}FN_3OS$: H, 3.53; C, 69.16; N, 10.52; S, 8.03. Found: H, 3.41; C, 68.94; N, 10.43; S, 7.85.

4.4.2. *2-[2-(4-Ethyl-phenylimino)-coumarin-3-yl]quinazolin-4(3H)-thione (**6b**)*

Yield 66%; m.p. 259–261°C; yellow solid. IR (cm^{-1}): 2964, 1640, 1592, 1548, 1493, 1466. ^{1}H NMR (200 Hz, DMSO-d_6): δ 1.21 (t, $J = 7.3$ Hz, 3 H), 2.63 (q, $J = 7.3$ Hz, 2 H), 7.31 (m, 4 H), 7.45 (d, $J = 8.4$ Hz, 2 H), 7.60 (m, 2 H), 7.79 (d, $J = 7.7$ Hz, 1 H), 7.90 (m, 2 H), 8.54 (d, $J = 7.3$ Hz, 1 H), 8.95 (s, 1 H), 15.78 (s, 1 H). LC-MS: m/z (MH^+) 410. Anal. calcd. for $C_{25}H_{19}N_3OS$: H, 4.68; C, 73.33; N, 10.26; S, 7.83. Found: H, 4.60; C, 73.22; N, 10.12; S, 7.77.

4.4.3. *2-[8-Ethoxy-2-(3,5-dimethoxy-phenylimino)-coumarin-3-yl]quinazolin-4(3H)-thione (**6c**)*

Yield 70%; m.p. 218–220°C; yellow solid. IR (cm^{-1}): 2832, 1649, 1589, 1550, 1493, 1468. ^{1}H NMR (200 Hz, DMSO-d_6): δ 1.34 (t, $J = 7.0$ Hz, 3 H), 3.72 (s, 6 H), 4.10 (q, $J = 7.0$ Hz, 2 H), 6.36 (t, $J = 2.2$ Hz, 1 H), 6.97 (d, $J = 2.2$ Hz, 2 H), 7.25 (m, 2 H), 7.40 (dd, $J = 6.6$, 1.8 Hz, 1 H), 7.58 (td, $J = 8.1$, 1.1 Hz, 1 H), 7.75 (d, $J = 8.1$ Hz, 1 H), 7.90 (td, $J = 8.1$, 1.1 Hz, 1 H), 8.50 (dd, $J = 8.1$, 1.1 Hz, 1 H), 8.93 (s, 1 H), 16.06 (s, 1 H). LC-MS: m/z (MH^+) 486. Anal. calcd. for $C_{27}H_{23}N_3O_4S$: H, 4.77; C, 66.79; N, 8.65; S, 6.60. Found: H, 4.66; C, 66.67; N, 8.53; S, 6.42.

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4.5. *General procedure for the synthesis of 7*

A mixture of **5** (0.5 mmol) in acetic acid (5 ml) containing hydrochloric acid (0.5 ml) was heated at 80–90°C for 20 min. The solid obtained after cooling was collected by filtration and dried.

4.5.1. *2-(Coumarin-3-yl)quinazolin-4(3H)-thione (**7a**)*

Yield 89%; m.p. 275–277°C, lit. m.p.. 275–276°C (*38*); yellow solid. ^{1}H NMR (200 Hz, DMSO-d_6): δ 7.55 (m, 3Í), 7.80 (m, 2H), 8.00 (m, 2H), 8.58 (d, $J = 8.1$ Hz, 1H), 9.03 (s, 1H), 13.62 (br s, 1H, NH).

4.5.2. *2-(8-Methoxycoumarin-3-yl)quinazolin-4(3H)-thione (**7b**)*

Yield 82%; m.p. 295–297°C, lit. m.p. 295°C (*38*); yellow solid. ^{1}H NMR (200 Hz, DMSO-d_6): δ 3.95 (s, 3H, OC$\underline{H}_3$), 7.5 (m, 4H), 7.79 (d, $J = 7.4$ Hz, 1H), 7.94 (t, $J = 7.4$ Hz, 1H), 8.57 (d, $J = 8.6$ Hz, 1H), 9.03 (s, 1H), 13.62 (br s, 1H, NH).

4.5.3. *2-(8-Ethoxycoumarin-3-yl)quinazolin-4(3H)-thione (**7c**)*

Yield 88%; m.p. 270–272°C, lit. m.p. 269–271°C (*38*); yellow solid. ^{1}H NMR (200 Hz, DMSO-d_6): δ 1.42 (t., $J = 8.6$ Hz, 3H, $OCH_2C\underline{H}_3$); 4.22 (q, $J = 8.6$ Hz, 2H, $OC\underline{H}_2CH_3$), 7.25–7.70 (m, 4H), 7.82 (d, $J = 7.9$ Hz, 1H), 7.96 (t, $J = 7.6$ Hz, 1H), 8.58 (d, $J = 8.8$ Hz, 1H), 9.03 (s, 1H), 13.61 (br s, 1H, NH).

4.6. *General procedure for the synthesis of 9*

To a suspension of **5** (0.5 mmol) in DMF (5 ml) and TEA (0.53 mmol), an alkylating agent (0.53 mol) was added. The mixture was stirred at 70°C for 40 min and allowed to cool. The mixture was diluted with of 2-propanol (5 ml) and the solid obtained was collected by filtration,

washed with 2-propanol and dried to give **8**. A mixture of **8**, 2-propanole (5 ml) and hydrochloric acid (0.5 ml) was refluxed for 20 min. The solid obtained after cooling was filtered, dried and recrystallized from DMF.

4.6.1. *N-(4-Methylphenyl)-2-[2-(8-methoxycoumarin-3-yl)-4-quinazolinylthio]acetamide (**9a**)*

Yield 61%; m.p. 240–241°C, lit. m.p. 241–243°C (*38*); colorless solid. ^{1}H NMR (200 Hz, DMSO-d_6): δ 2.18 (s, 3H, ArC$\underline{H}_3$), 3,91 (s, 3H, CouOC$\underline{H}_3$), 4.33 (s, 2H, ArC$\underline{H}_2$S), 6,89 (d, $J = 9.5$ Hz, 1H), 7.01 (d, $J = 10.5$ Hz, 2H), 7.18 (t, $J = 9.7$ Hz, 1H), 7.38 (m, 3H, H-5+ H-2$''$ + H-6$''$), 7,75 (m, 1H), 8.02 (m, 2H), 8.19 (d, $J = 8.7$ Hz, 1H), 8.62 (s, 1H), 10.27 (br s, 1H, NH).

4.6.2. *8-Ethoxy-3-[4-(3-methylbenzylthio)quinazolin-2-yl]coumarin (**9b**)*

Yield 65%; m.p. 162–163°C, lit. m.p. 162–164°C (*38*); yellow solid. ^{1}H NMR (200 Hz, DMSO-d_6): δ 1.42 (t, $J = 7.8$ Hz, 3H, OCH$_2$C$\underline{H}_3$); 2.15 (s, 3H, ArC$\underline{H}_3$), 4.22 (q, $J = 7.8$ Hz, 2H, OC$\underline{H}_2$CH$_3$), 4.69 (s, 2H, ArC$\underline{H}_2$S), 6.95–7.40 (m, 7H), 7,71 (m, 1H), 7.98 (m, 2H), 8.08 (d, $J = 8.6$ Hz, 1H), 8.77 (s, 1H).

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