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Recyclization of 2-imino-2H-1-benzopyrans under the action of nucleophilic reagents: the novel approach for 2-(coumarin-3-yl)-3H-quinazolin-4-thiones

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Recyclization of 2-imino-2H-1-benzopyrans under the action of nucleophilic reagents: the novel approach for 2-(coumarin-3-yl)-3H-quinazolin-4-thiones

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The series of approaches for synthesis of 2-(coumarin-3-yl)-3H-quinazolin-4-thiones were evaluated and it was established that the 'recyclization' of 2-iminocoumarin-3-carboxamides under the action of 2-aminothiobenzamide appeared to be the preferable approach compared to the thionation of 2-(coumarin-3-yl)-3H-quinazolin-4-ones. The proposed method allowed us to obtain the desired 2-(coumarin-3-yl)-3H-quinazolin-4-thiones in a short time with excellent yields using a one-pot synthetic procedure.

Keywords: thionation; coumarins; qinazoline; amides; imines

1. Introduction

It is known that 3,4-dihydroquinazolin-4-thiones and their S-alkylanalogs display antimicrobial activity (*1–5*) or amplify the activity of phleomycin-G *in vitro* (*6*). They were also reported as anticonvulsant agents (*7*), and their functionalized derivatives were patented as hypolipemics, antihypertensives and antidiabetics (*8*). Some 4-alkylthioquinazolines are known to be antiulcer agents that appeared to be more effective than cimetidine (*9*). Among the 3,4-dihydroquinazolin-4-thiones, that have no substituent at position 3, the compounds which inhibit the enzyme thymidylate synthetase and possess antitumor activity against murine leukemia cell culture were found (*10*).

On the other hand, the compounds with coumarin moiety are interesting as the matter for biological assays, because some 3-substituted coumarins showed antiallergic, antiarthritic (*11*) and antiasthmatic activities (*12*). Coumarins are also highly potent DNA-gyrase B inhibitors (*13, 14*). The 7-alkoxycoumarins can be applied as biomarkers to characterize cytochrome P450 activity (*15*).

However, the coumarin derivatives substituted at position 3 in the 3,4-dihydroquinazolin-4-thion heterocyclic system have not been reported yet, whereas their oxoanalogs, 2-(coumarin-3-yl)-3H-quinazolin-4-ones, were widely investigated in a series of works (*16–20*). With regard to

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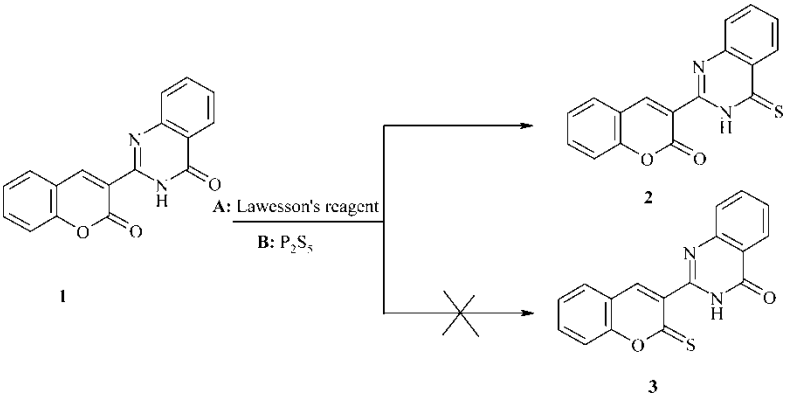
this fact, we focused our efforts on an efficient methodology for the development of synthesis of 2-(coumarin-3-yl)-3H-quinazolin-4-thiones.

2. Results and discussion

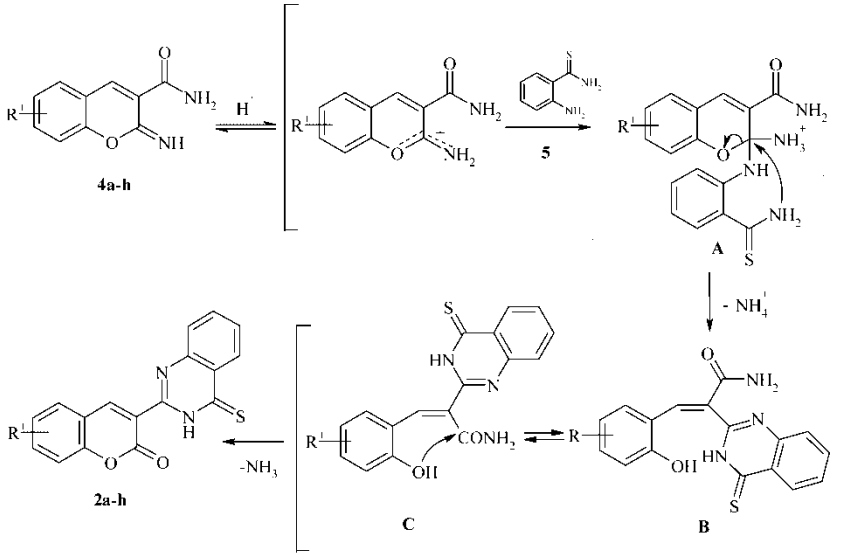
The most common method for synthesis of 3,4-dihydroquinazolin-4-thiones is the thionation of the starting 3,4-dihydroquinazolin-4-ones with phosphorous pentasulfide or Lawesson's reagent (LR) (*21–27*). Since the LR is often employed in the milder conditions it was chosen to convert 2-(coumarin-3-yl)-3H-quinazolin-4-one **1** to its thioanalog. The main problem for this synthesis was the presence of lacton moiety of coumarin, which is known to react with LR to form coumarin-2-thiones (*28–31*), so the strict stoichiometric ratio of **1** and LR (2:1) was used (Method **A**). The monitoring of the reaction by thin-layer chromatography (TLC) (chloroform) showed that the interaction proceeded very slowly and takes about 72 h at refluxing in 1,4-dioxane. As a result, the individual product of monothionation has been isolated (LC/MS m/z 307 $[MH]^+$) with 73% yield, but the formation of desired 2-(coumarin-3-yl)-3H-quinazolin-4-thion **2** still was not the proven fact, though the structure of 2-(2-thioxocoumarin-3-yl)-3H-quinazolin-4-one **3** was pertinent. The later experiments also showed that the same product had been obtained in the reaction of **1** and triple molar excess of phosphorous pentasulfide in refluxing pyridine (Method **B**) (yield 53%) Scheme 1.



Scheme 1.

The other known approach for 2-substituted-3,4-dihydroquinazolin-4-thiones is the cyclization of 2-aminothiobenzamides using acyl halides in strongly basic media (*32–34*). With the aim to develop a more convenient synthetic procedure for **2** and also to prove (distinguish) the selectivity of 2-(coumarin-3-yl)-3H-quinazolin-4-one **1** thionation, we examined the route for **2** *via* 'recyclization' of 2-iminocoumarin-3-carboxamide **4a** under the action of 2-aminothiobenzamibe **5**. It is notable that this approach, based on the rearrangement of 2-iminocoumarin-3-carboxamides in the reactions with binucleofiles, showed good results for pyrimidin-containing 3-heterylcoumarins synthesis (*16, 17, 35–37*). It was recently reported that the reaction between 2-iminocoumarin-3-carboxamides and anthranilamide in glacial acetic acid at reflux leads to 2-(coumarin-3-yl)-3H-quinazolin-4-ones **1** (*16, 17*). We analogously performed the reaction of 2-iminocoumarin-3-carboxamide **4a** with 2-aminothiobenzamibe **5** (Method **C**) and as a result of short-term refluxing (5–10 min) in glacial acetic acid, the bright-yellow

precipitate of the product **2a** (R^1 = H), identical to the previously obtained, was formed with 94% yield (Scheme 2).



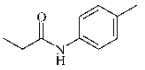
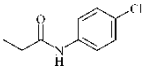
2a R^1 = H; 2b R^1 = 6-Cl; 2c R^1 = 8-OMe; 2d R^1 = 7-OMe; 2e R^1 = 8-OEt; 2f R^1 = 8-OH; 2g R^1 = 6-Br; 2h R^1 = 6-NO_2;

Scheme 2.

The interaction of 2-iminocoumarin-3-carboxamides **4** with 2-aminothiobenzamide **5** in the 'recyclization' conditions proceeds as follows: at the first step the protonated acetic acid molecule **4** is attacked at position 2 with an aminogroup of 2-aminothiobenzamide **5**, which produces the unstable tetrahedral intermediate **A**, which is stabilized by the cleavage of ammonia and pyrimidine ring closure with the formation of **B**; the further *cis,trans*-isomerization of **B** into **C** and later lactone formation completes the process of 2-(coumarin-3-yl)-3H-quinazolin-4-thion **2** synthesis. Since the mechanism of 'recyclization' excludes the possibility of 2-(2-thioxocoumarin-3-yl)-3H-quinazolin-4-one **3** formation, the results obtained evidently illustrate that the thionation of 2-(coumarin-3-yl)-3H-quinazolin-4-one **1** selectively leads to 2-(coumarin-3-yl)-3H-quinazolin-4-thione **2a**, although the 'recyclization' appeared to be the best way for the synthesis of **2**. The analysis of ^{1}H NMR (nuclear magnetic response) spectra of the compounds **2** also displays some favorable evidence for their 2-(coumarin-3-yl)-3H-quinazolin-4-thion structure. The broad singlet of NH proton of **2a–h** observed at 13.49–13.61 ppm is strongly shifted downfield comparatively with the similar signal in the spectrum of 2-(coumarin-3-yl)-3H-quinazolin-4-one **1** (12.07 ppm), at the same time the position of coumarin H-4 signal for compounds **2** at 9.03–8.98 ppm much resembles the chemical shift of **1** H-4 8.97 ppm (*17*), thus it can be established that the structural changes have mostly concerned the 3,4-dihydroquinazolin part of the molecule.

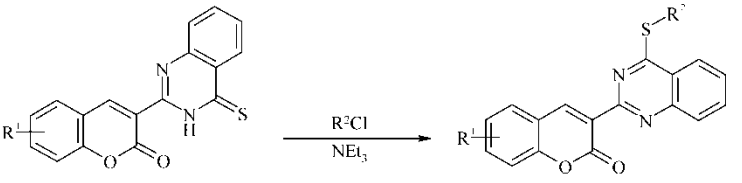
Probably, the low activity of coumarin oxogroup for thionation can be explained by its hydrogen binding with NH of 3,4-dihydroquinazolin moiety, which complicates the reaction. The preferable existence of **2** in the form of thion, which is confirmed with ^{13}C NMR spectra of **2**, where the signals at 185.8–186.1 ppm (C=S) are present, is also very likely caused by the hydrogen bond between 3H-quinazolin-4-thione substituent and carbonyl oxygen of coumarin. The lactone C=O signal for compounds **2** is observed at 158.9–160.5 ppm. In the infrared (IR) spectra of **2** the

Table 1. 3-(4-Alkylthioquinazolin-2-yl)coumarins **6**.

Number	R^1	R^2	Melting point (°C)	Yield (%)
6a	H	Me	164–165	74
6b	H	2-Cl-4-F-Bn	253–154	86
6c	8-OMe		241–243	78
6d	7-OMe		261–263	83
6e	8-OEt	3-Me-Bn	162–164	72
6f	8-OEt	2-Cl-4-F-Bn	201–203	93

intensive broad absorption bands at 3241–3201 cm^{-1} (νN–H) and the characteristic bands of coumarin νC=O at 1712–1662 cm^{-1} are present.

To modify the obtained 2-(coumarin-3-yl)-3H-quinazolin-4-thiones **2**, we alkylated them with iodomethane, some benzylchlorides and chloroacetamides (Scheme 3). The reaction was carried out in dimethylformamide (DMF) in the presence of triethylamine and resulted in the formation of 3-(4-alkylthioquinazolin-2-yl)coumarins **6** in a short time (30–40 min) with the excellent yields. The obtained melting points and yields of compounds **6a–e** are shown in Table 1.



2a, c-e **6a-f**

Scheme 3.

In the ^{1}H NMR spectra of the compounds **6** comparatively with the spectra of **2**, there are no signals of quinazoline NH observed, but the signals of R^2 groups are present for **6a** at 2.73 ppm. (CH_3); for **6b–6f** at 4.21–4.83 ppm (CH_2) ppm and in the case of **6c** and **6d** the signals of amide NH are at 10.27–10.51 ppm. In the ^{13}C NMR spectra of the compounds **6**, the signal of quinazolin C-4 is strongly shifted downfield and its position cannot be surely determined; but the signal of S-CH_2 at 30.4–34.5 ppm for compounds **6b**, **6c**, **6e**, **6f** cleanly confirms the formation of S-alkylation product. For compound **6a** SCH_3 carbon signal is at 12.5 ppm.

3. Experimental section

The melting points (°C) were measured with a Koeffler melting point apparatus and were not corrected. IR spectra were recorded on a FT-IR Bruker Tensor-27 spectrometer in KBr. TLC was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254). Liquid chromatography/mass spectra (LC/MS) were recorded with a PE SCIEX API 150EX liquid chromatograph equipped with a UV detector (λ_{max}215 and 254 nm) and using a C_{18} column (100 × 4 mm). Elution started with water and ended with acetonitrile/water (95:5, v/v) and used a linear gradient at a flow rate of 0.15 mL/min and an analysis cycle time of 25 min. ^{1}H NMR spectra were recorded on a Varian Mercury (200 MHz) spectrometer in DMSO-d_6 using tetramethylsilane

(TMS) as an internal standard (chemical shifts are reported in ppm). ^{13}C NMR spectra were recorded on a Bruker DRX-300 (75 MHz) spectrometer in DMSO-d_6 using (TMS) as an internal standard (chemical shifts are reported in ppm). UV–Vis (ultraviolet–visible) absorption spectra were registered on a Specord M-40 spectrophotometer in 1,4-dioxane. Elemental analyses were within ±0.4% of the theoretical value.

3.1. *2-(Coumarin-3-yl)-3H-quinazolin-4-one(1) and 2-iminocoumarine-3-carboxamides(4a–h)*

These were prepared according to the reported methods (*16, 17, 38–40*).

3.2. *2-(Coumarin-3-yl)-3H-quinazolin-4-thione (2a) (Method A)*

The mixture of 2-(coumarin-3-yl)-3H-quinazolin-4-one 0.15 g (0.51 mmol) and Lewesson's reagent 0.105 g (0.25 mmol) in 20 mL of anhydrous 1,4-dioxane was refluxed for 72 h (the reaction progress was monitored by TLC – chloroform). Then the excess of 1,4-dioxane was distilled off under the reduced pressure and the residue was dissolved in a minimal amount of chloroform. The chloroform solution was filtered through a small pad of silica gel and eluted with chloroform (15 mL × 3). The excess chloroform was distilled and the oily residue crystallized from 1,4-dioxane. Yield: 73%.

3.3. *2-(Coumarin-3-yl)-3H-quinazolin-4-thione (2a) (Method B)*

To the mixture of 0.3 g (1 mmol) of 2-(coumarin-3-yl)-3H-quinazolin-4-one and 0.7 g (1.6 mmol) of phosphorous pentasulfide, 5 mL of piperidine was added. Then the mixture was refluxed for 4 h. The bright-yellow transparent solution that formed was cooled and then poured into 50 mL of cold water. The precipitate of **2a**, which had been formed from the oil at stirring, was separated by filtration and washed with propanol-2. Yield: 53%.

3.4. *General procedure for synthesis of 2a–h (Method C)*

To the warm solution of 2-aminothiobenzamide **5** (2 mmol) in the minimal amount of glacial acetic acid, 2-iminocoumarine-3-carboxamide **2** (2 mmol) was added. The mixture was refluxed until the formation of the product **2** precipitate (5–7 min) and then additionally for 3–5 min. Then the mixture was cooled and the precipitate was filtered off and washed with propanol-2.

3.5. *Physical and spectral data of the products 2*

3.5.1. *2-(Coumarin-3-yl)-3H-quinazolin-4-thione (**2a**)*

Yield 94%; mp 275–276 °C; bright-yellow solid. IR(KBr): 3198, 3059, 1708, 1639, 1609, 1554 cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): δ = 7.55 (m, 3H), 7.80 (m, 2H), 8.00 (m, 2H, 5-H+7′-H), 8.58 (d, J = 8.1 Hz, 1H, H-5′), 9.03 (s, 1H, H-4), 13.62 (br s, 1H, NH).

^{13}C NMR (75 Hz, DMSO-d_6): δ = 116.1, 118.9, 119.1, 125.8, 128.2, 128.6, 128.9, 129.7, 130.6, 134.7, 136.1, 144.7, 146.2, 147.5, 154.24, 160.5, 186.0.

LC/MS m/z 307 ([MH]$^+$).

Analysis calculated for $C_{17}H_{10}N_2O_2S$: C, 66.65; H, 3.29; N, 9.14; S, 10.47. Found: C, 66.67; H, 3.15; N, 9.22; S, 10.62.

3.5.2. *2-(6-Chlorocoumarin-3-yl)-3H-quinazolin-4-thione (**2b**)*

Yield 87%; mp 291–293 °C; bright-yellow solid.

IR(KBr): 3250, 3101, 3052, 3034, 2895, 1713, 1637, 1618, 1552 cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): $\delta = 7.62$ (m, 2H, H-8+H6′), 7.80 (m, 2H, H-7+H-8′), 7.95 (t, $J = 8.0$ Hz, 1H, H-7′), 8.15 (d, $J = 2.9$ Hz, 1H, H-5), 8.57 (d, $J = 9.2$ Hz, 1H, H-5′), 9.03 (s, 1H, H-4), 13.55 (br s, 1H, NH).

^{13}C NMR (75 Hz, DMSO-d_6): $\delta = 118.8$, 120.2, 120.6, 128.2, 128.7, 129.2, 129.5, 129.6, 129.7, 134.1, 136.3, 144.6, 144.8, 147.4, 152.8, 160.0, 186.0.

LC/MS m/z 341 ([MH]$^+$).

UV/Vis (dioxane): $\lambda_{max}(\log \varepsilon) = 225$ (4.77), 291 (4.52), 369 nm (4.54).

Analysis calculated for $C_{17}H_9ClN_2O_2S$ (340.79): C, 59.92; H, 2.66; N, 8.22; S, 9.41. Found: C, 59.73; H, 2.72; N, 9.59; S, 9.37.

3.5.3. *2-(8-Methoxycoumarin-3-yl)-3H-quinazolin-4-thione (**2c**)*

Yield 83%; mp 295 °C; dark-yellow solid.

IR(KBr): 3215, 3048, 3008, 2972, 2935, 1702, 1638, 1608, 1554 cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): $\delta = 3.95$ (s, 3H, OCH_3), 7.5 (m, 4H Cou-H+H-6′), 7.79 (d, $J = 7.4$ Hz, 1H, H-8′), 7.94 (t, $J = 7.4$ Hz, 1H, H-7′), 8.57 (d, $J = 8.6$ Hz, 1H, H-5′), 9.03 (s, 1H, H-4), 13.62 (br s, 1H, NH).

^{13}C NMR (75 Hz, DMSO-d_6): $\delta = 56.8$, 117.2, 119.2, 119.6, 121.7, 125.8, 128.3, 128.6, 128.9, 129.7, 136.1, 143.7, 144.7, 146.4, 147.0, 147.4, 160.3, 186.1.

LC/MS m/z 337 ([MH]$^+$).

UV/Vis (dioxane): $\lambda_{max}(\log \varepsilon) = 249$ (4.60), 306 (4.54), 334 (4.63), 369 nm (4.61).

Analysis calculated for $C_{18}H_{12}N_2O_3S$ (336.37): C, 64.27; H, 3.60; N, 8.33; S, 9.53. Found: C, 64.19; H, 3.45; N, 8.52; S, 9.66.

3.5.4. *2-(7-Methoxycoumarin-3-yl)-3H-quinazolin-4-thione (**2d**)*

Yield 97%; mp 289–291 °C; yellow solid.

IR(KBr): 3234, 3147, 3083, 2980, 2944, 1701, 1608, 1549 cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): $\delta = 3.89$ (s, 3H, OCH_3), 7.07 (dd, $J = 9.0$; 1.4 Hz, 1H, H-6) 7.16 (d, $J = 1.4$ Hz, 1H, H-8), 7.59 (t, $J = 8.6$ Hz, 1H, H-6′), 7.78 (d, $J = 8.5$ Hz, 1H, H-8′), 7.95 (m, 2H, H-5+H-7′), 8.57 (d, $J = 8.6$ Hz, 1H, H-5′), 9.07 (s, 1H, H-4), 13.49 (br s, 1H, NH).

LC/MS m/z 337 ([MH]$^+$).

UV/Vis (dioxane): $\lambda_{max}(\log \varepsilon) = 249$ (4.60), 290 (4.35), 303 (4.32), 370 nm (4.85).

Analysis calculated for $C_{18}H_{12}N_2O_3S$ (336.37): C, 64.27; H, 3.60; N, 8.33; S, 9.53. Found: C, 64.27; H, 3.84; N, 8.39; S, 9.77.

3.5.5. *2-(8-Ethoxycoumarin-3-yl)-3H-quinazolin-4-thione (**2e**)*

Yield 85%; mp 269–271 °C; yellow solid.

IR(KBr): 3209, 2938, 2888, 1702, 1640, 1608, 1544 cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): $\delta = 1.42$ (t, $J = 8.6$ Hz, 3H, OCH_2CH_3); 4.22 (q, $J = 8.6$ Hz, 2H, OCH_2CH_3), 7.25–7.70 (m, 4H, Cou-H+H-6′), 7.82 (d, $J = 7.9$ Hz, 1H, H-8′), 7.96 (t, $J = 7.6$ Hz, 1H, H-7′), 8.58 (d, $J = 8.8$ Hz, 1H, H-5′), 9.03 (s, 1H, H-4), 13.61 (br s, 1H, NH).

^{13}C NMR (75 Hz, DMSO-d_6): $\delta = 14.5$, 65.2, 118.2, 119.4, 121.5, 125.4, 128.0, 128.2, 128.4, 129.3, 135.6, 143.8, 144.3, 145.8, 146.1, 147.0, 160.0, 185.8.

UV/Vis (dioxane): $\lambda_{max}(\log \varepsilon) = 250$ (4.55), 306 (4.48), 336 (4.59), 369 (4.57).

Analysis calculated for $C_{19}H_{14}N_2O_3S$ (350.40): C, 65.13; H, 4.03; N, 7.99; S, 9.15. Found: C, 65.35; H, 4.11; N, 8.02; S, 9.21.

3.5.6. *2-(8-Hydroxycoumarin-3-yl)-3H-quinazolin-4-thione (**2f**)*

Yield 63%; mp > 300 °C; yellow solid.

IR(KBr): 3238, 2879, 1662, 1610, 1555, 1500 cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): $\delta = 7.25$–7.40 (m, 3H, Cou-H), 7.62 (t, $J = 8.2$ Hz, 1H, H-6′), 7.79 (d, $J = 7.6$ Hz, 1H, H-8′), 7.94 (t, $J = 7.6$ Hz, 1H, H-7′), 8.54 (d, $J = 8.2$ Hz, 1H, H-5′), 8.97 (s, 1H, H-4), 10.50 (s, 1H, OH), 13.57 (br s, 1H, NH).

^{13}C NMR (75 Hz, DMSO-d_6): $\delta = 118.0$, 119.6, 120.3, 120.9, 125.4, 128.1, 128.4, 129.3, 135.5, 142.8, 144.3, 144.7, 146.4, 147.0, 160.2, 185.9.

LC/MS m/z 323 ($[MH]^+$).

UV/Vis (dioxane): $\lambda_{max}(\log \varepsilon) = 254$ (4.53), 307 (4.42), 337 (4.59), 351 (4.58), 368 nm (4.56).

Analysis calculated for $C_{17}H_{10}N_2O_3S$ (322.34): C, 63.35; H, 3.13; N, 8.69; S, 9.95. Found: C, 63.21; H, 3.35; N, 8.87; S, 9.77.

3.5.7. *2-(6-Bromocoumarin-3-yl)-3H-quinazolin-4-thione (**2g**)*

Yield 91%; mp > 300 °C; yellow solid.

IR(KBr): 3241, 3098, 3048, 2885, 1712, 1648, 1612, 1550 cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): $\delta = 7.56$ (d, $J = 9.1$ Hz, 1H, H-8), 7.67 (t, $J = 7.3$ Hz, 1H, H-6′), 7.80 (m, 3H, H-7+H-8′+H-7′), 8.30 (d, $J = 2.5$ Hz, 1H, H-5), 8.58 (d, $J = 7.3$ Hz, 1H, H-5′), 8.96 (s, 1H, H-4), 13.59 (br s, 1H, NH).

^{13}C NMR (75 Hz, DMSO-d_6): $\delta = 117.0$, 118.6, 119.8, 120.4, 128.0, 128.6, 129.3, 132.1, 135.7, 136.5, 144.5, 146.8, 152.9, 159.6, 185.8.

LC/MS m/z 385.3 (M^+).

UV/Vis (dioxane): $\lambda_{max}(\log \varepsilon) = 226$ (4.67), 291 (4.44), 369 nm (4.45).

Analysis calculated for $C_{17}H_9BrN_2O_2S$ (385.24): C, 53.00; H, 2.35; N, 7.27; S, 8.32. Found: C, 53.25; H, 2.56; N, 7.12; S, 8.55.

3.5.8. *2-(6-Nitrocoumarin-3-yl)-3H-quinazolin-4-thione (**2h**)*

Yield 72%; mp 298–299 °C; dark-yellow solid.

IR(KBr): 3233, 3081, 3061, 2881, 2818, 1717, 1618, 1555, 1526, 1344 (ν_s NO_2) cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): $\delta = 7.75$ (m, 4H, H-8+H-6′+H-7′+H-8′), 8.57 (m, 2H, H-7+H-5′), 9.02 (d, $J = 1.8$ Hz, 1H, H-5), 9.07 (s, 1H, H-4), 13.61 (br s, 1H, NH).

LC/MS m/z 352.4 ($[MH]^+$).

^{13}C NMR (75 Hz, DMSO-d_6): $\delta = 117.9$, 118.9, 121.0, 125.8, 128.1, 128.2, 128.7, 129.3, 135.6, 144.1, 144.5, 144.6, 146.6, 157.1, 158.9, 186.1.

UV/Vis (dioxane): $\lambda_{max}(\log \varepsilon) = 247$ (4.36), 278 (4.44), 359 nm (4.28).

Analysis calculated for $C_{17}H_9N_3O_4S$ (351.34): C, 58.12; H, 2.58; N, 11.96; S, 9.13. Found: C, 58.10; H, 2.75; N, 11.81; S, 9.11.

3.6. *General procedure for synthesis of 6a–f*

To the suspension of 2-(coumarin-3-yl)-3H-quinazolin-4-thione **2** (0.5 mmol) and triethylamine (0.525 mmol) in 7 mL of DMF, the alkylating agent (0.525 mol) was added. The mixture was

heated (70 °C) and stirred for 30–40 min. After cooling, the mixture was poured into 30 mL of cold water and the precipitate formed was filtered and recrystallized from propanol-2–DMF mixture.

3.7. *Physical and spectral data of the products 6*

3.7.1. *3-(4-Methylthioquinazolin-2-yl)coumarin (**6a**)*

Yield 74%; mp 164–165 °C; white solid.

IR(KBr): 3058, 2921, 1746, 1604, 1561, 1540, 1483 cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): $\delta = 2.73$ (s, 3H, CH_3S), 7.44 (m, 2H, H-6+H-8), 7.7 (m, 2H, H-6′+H-7), 7.93 (d, $J = 7.6$ Hz, 1H, H-5), 8.04 (m, 2H, H-7′+H-8′), 8.15 (d, $J = 7.7$ Hz, 1H, H-5′), 8.84 (s, 1H, H-4).

^{13}C NMR (75 Hz, DMSO-d_6): $\delta = 12.5$, 116.4, 119.2, 122.2, 123.9, 125.0, 125.9, 128.6, 129.0, 129.9, 133.3, 134.8, 145.1, 148.1, 154.4, 156.7, 157.9, 171.5.

UV/Vis (dioxane): $\lambda_{max}(\log \varepsilon) = 297$ (4.52), 325 nm (4.50).

Analysis calculated for $C_{18}H_{12}N_2O_2S$ (320.40): C, 67.48; H, 3.78; N, 8.74; S, 10.01. Found: C, 67.80; H, 3.95; N, 8.63; S, 10.27.

3.7.2. *3-[4-(2-Chloro-4-fluorobenzylthio)quinazolin-2-yl]coumarin (**6b**)*

Yield 86%; mp 253–254 °C; white solid.

IR(KBr): 3104, 3049, 2990, 2943, 1726, 1610, 1557, 1561, 1538 cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): $\delta = 4.83$ (s, 2H, $ArCH_2S$), 7.13 (d, $J = 7.4$; 2.5 Hz, 1H, H-6″), 7.46 (m, 3H, H-6+H-8+H-5″), 7.75 (m, 3H, H-6′+H-7+H-3″), 7.95 (d, $J = 7.7$ Hz, 1H, H-5), 8.04 (m, 2H, H-7′+H-8′), 8.13 (d, $J = 7.9$ Hz, 1H, H-5′), 8.82 (s, 1H, H-4).

^{13}C NMR (75 Hz, DMSO-d_6): $\delta = 30.5$, 114.3, 114.6, 116.0, 116.5, 118.9, 121.7, 123.5, 124.6, 125.4, 128.4, 128.7, 129.5, 131.5, 131.6, 132.9, 134.4, 134.7, 144.7, 148.3, 156.3, 157.7, 163.1, 169.6.

LC/MS m/z 449 ($[MH]^+$).

UV/Vis (dioxane): $\lambda_{max}(\log \varepsilon) = 298$ (4.53), 327 nm (4.51).

Analysis calculated for $C_{24}H_{14}ClFN_2O_2S$ (448.91): C, 64.22; H, 3.14; N, 6.24; S, 7.14. Found: C, 64.42; H, 3.20; N, 6.15; S, 7.10.

3.7.3. *N^1-(4-Methylphenyl)-2-[2-(8-methoxycoumarin-3-yl)-4-quinazolinylthio]acetamide (**6c**)*

Yield 78%; mp 241–243 °C; pale-yellow solid.

IR(KBr): 3120, 3060, 2938, 2868, 2836, 1717, 1678, 1609, 1572, 1559, 1539 cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): $\delta = 2.18$ (s, 3H, $ArCH_3$), 3.91 (s, 3H, $CouOCH_3$), 4.33 (s, 2H, $ArCH_2S$), 6.89 (d, $J = 9.5$ Hz, 1H, H-7), 7.01 (d, $J = 10.5$ Hz, 2H, H-3″+H-5″), 7.18 (t, $J = 9.7$ Hz, 1H, H-6), 7.38 (m, 3H, H-5+H-2″+H-6″), 7.75 (m, 1H, H-6′), 8.02 (m, 2H, H-7′+H-8′), 8.19 (d, $J = 8.7$ Hz, 1H, H-5′), 8.62 (s, 1H, H-4), 10.27 (br s, 1H, NH).

^{13}C NMR (75 Hz, DMSO-d_6): $\delta = 20.3$, 34.5, 56.6, 116.0, 119.5, 119.7, 120.8, 121.6, 123.6, 124.4, 125.3, 128.4, 128.8, 129.0, 132.66, 134.7, 136.3, 143.7, 145.2, 146.6, 148.1, 156.1, 157.4, 165.4, 170.0.

LC/MS m/z 484 ($[MH]^+$).

UV/Vis (dioxane): $\lambda_{max}(\log \varepsilon) = 230$ (4.69), 244 (4.66), 314 nm (4.55).

Analysis calculated for $C_{27}H_{21}N_3O_4S$ (483.55): C, 67.07; H, 4.38; N, 8.69; S, 6.63. Found: C, 67.03; H, 4.65; N, 8.91; S, 6.80.

3.7.4. *N^1-(4-Chlorophenyl)-2-[2-(7-methoxycoumarin-3-yl)-4-quinazolinylthio] acetamide (**6d**)*

Yield 83%; mp 261–263 °C; pale-yellow solid.

IR(KBr): 3128, 3057, 2946, 2840, 1737, 1674, 1615, 1557, 1530, 1505 cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): $\delta = 3.94$ (s, 3H, CouOCH_3), 4.34 (s, 2H, ArCH_2S), 6.91 (d, $J = 7.2$ Hz, 1H, H-6), 7.03 (s, 1H, H-8), 7.25 (d, $J = 8.6$ Hz, 2H, H-3″+H-5″), 7.37 (d, $J = 7.2$ Hz, 1H, H-5), 7.55 (d, $J = 8.6$ Hz, 2H, H-2″+H-6″), 7.75 (m, 1H, H-6′), 7.95 (m, 2H, H-7′+H-8′), 8.17 (d, $J = 8.0$ Hz, 1H, H-5′), 8.65 (s, 1H, H-4), 10.51 (br s, 1H, NH).

LC/MS m/z 504 ([MH]$^+$).

UV/Vis (dioxane): λ_{max} (log ε) = 250 (4.77), 324 (4.59), 366 (4.59).

Analysis calculated for $C_{26}H_{18}ClN_3O_4S$ (503.97): C, 61.97; H, 3.60; N, 8.34; S, 6.36. Found: C, 61.79; H, 3.92; N, 8.40; S, 6.39.

3.7.5. *8-Ethoxy-3-[4-(3-methylbenzylthio)quinazolin-2-yl]coumarin (**6e**)*

Yield 82%; mp 162–164 °C; pale-yellow solid.

IR(KBr): 3056, 2981, 2834, 2880, 1744, 1638, 1609, 1573, 1558, 1524 cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): $\delta = 1.42$ (t, $J = 7.8$ Hz, 3H, OCH_2CH_3); 2.15 (s, 3H, ArCH_3), 4.22 (q, $J = 7.8$ Hz, 2H, OCH_2CH_3), 4.69 (s, 2H, ArCH_2S), 6.95–7.40 (m, 7H, Cou-H+Bn-H), 7.71 (m, 1H, H-6′), 7.98 (m, 2H, H-7′+H-8′), 8.08 (d, $J = 8.6$ Hz, 1H, H-5′), 8.77 (s, 1H, H-4).

^{13}C NMR (75 Hz, DMSO-d_6): $\delta = 14.6$, 20.7, 33.3, 65.2, 117.2, 119.7, 120.9, 121.7, 123.5, 124.5, 126.1, 127.9, 128.2, 128.3, 128.7, 129.7, 134.5, 137.3, 137.6, 144.9, 145.8, 148.2, 156.3, 157.4, 170.2.

UV/Vis (dioxane): λ_{max} (log ε) = 223 (4.60), 313 nm (4.44).

Analysis calculated for $C_{27}H_{22}N_2O_3S$ (454.55): C, 71.35; H, 4.88; N, 6.16; S, 7.05. Found: C, 71.31; H, 4.73; N, 6.28; S, 7.31.

3.7.6. *8-Ethoxy-3-[4-(2-chloro-4-fluorobenzylthio)quinazolin-2-yl]coumarin (**6f**)*

Yield 93%; mp 201–203 °C; white solid.

IR(KBr): 3049, 2993, 2912, 2869, 2837, 1731, 1635, 1613, 1581, 1561, 1538 cm^{-1}.

^{1}H NMR (200 Hz, DMSO-d_6): $\delta = 1.41$ (t, $J = 7.1$ Hz, 3H, OCH_2CH_3); 4.21 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 4.85 (s, 2H, ArCH_2S), 7.14 (td, $J = 7.7$; 2.1 Hz, 1H, H-6″), 7.4 (m, 4H, Cou-H+H-5″), 7.8 (m, 2H, H-6′+H-3″), 8.02 (m, 2H, H-7′+H-8′), 8.12 (d, $J = 8.5$ Hz, 1H, H-5′), 8.79 (s, 1H, H-4).

^{13}C NMR (75 Hz, DMSO-d_6): $\delta = 14.6$, 30.4, 65.1, 114.4, 114.6, 116.5, 116.8, 117.2, 119.7, 120.9, 121.7, 123.5, 124.6, 125.5, 128.3, 128.7, 131.5, 131.6, 132.8, 132.9, 134.6, 144.1, 145.0, 145.8, 148.3, 156.3, 157.5, 169.6.

LC/MS m/z 493 ([MH]$^+$).

UV/Vis (dioxane): λ_{max} (log ε) = 224 (4.75), 312 nm (4.60).

Analysis calculated for $C_{26}H_{18}ClFN_2O_3S$ (492.96): C, 63.35; H, 3.68; N, 5.68; S, 6.50. Found: C, 63.58; H, 3.82; N, 5.49; S, 6.68.

4. Conclusion

The series of approaches for synthesis of 2-(coumarin-3-yl)-3H-quinazolin-4-thiones were evaluated and it was established that the ‘recyclization’ of 2-iminocoumarin-3-carboxamides under the

action of 2-aminothiobenzamide appeared to be the preferable approach compared to the common synthetic methods. The proposed method allowed us to obtain the desired 2-(coumarin-3-yl)-3H-quinazolin-4-thiones in a short time with excellent yields using a one-pot synthetic procedure and simple method for the products' isolation. With the application of 'recyclization' as the alternative approach, the selective thionation of 2-(coumarin-3-yl)-3H-quinazolin-4-ones (LR of P_2S_5) that leads to 2-(coumarin-3-yl)-3H-quinazolin-4-thiones has been approved.

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