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ORIGINAL PAPER

# Convenient and sequential one-pot route for synthesis of 2-thioxoquinazolinone and quinazolinobenzothiazinedione derivatives

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**Abstract** A new and efficient synthetic process has been developed for preparation of 2-thioxoquinazolinone and quinazolinobenzothiazinedione derivatives. The related products were synthesized through reaction of isatoic anhydride, amines/anthranilic acids, and carbon disulfide ($CS_2$) in the presence of potassium hydroxide in ethanol at reflux.

**Keywords** 2-Thioxoquinazolinones · Quinazolinobenzothiazinedione · Isatoic anhydride · Anthranilic acids

## Introduction

Quinazolinone derivatives have attracted extensive interest owing to their biological activities [1–4]. Fused quinazolinone derivatives such as 2-thioxoquinazolinones comprise a large group of biologically active and medicinally important compounds. They have displayed remarkable antiinflammatory and analgesic activity [5] and have also been used as plant growth regulators and fungicides [6–9]. Altanserin and nitroaltanserin (Fig. 1) belong to this class of heterocycles and are utilized as 5-$HT_{2A}$ receptor antagonist drugs [10].

While literature survey reports various procedures for the synthesis of 2-thioxoquinazolinones [1, 5, 11–18], synthesis of quinazolinobenzothiazinedione and their properties have been discussed rarely [19]. In view of the fact that 2-thioxoquinazolinones and quinazolinobenzothiazinediones can possess important biological activities, their significance attracted our attention. In continuation of our efforts towards synthesis of heterocycles [20–22] and especially promising biologically active compounds [23, 24], we present herein a new, efficient, and easy work-up procedure for synthesis of 2-thioxoquinazolinones **4** and quinazolinobenzothiazinedione **6** via sequential one-pot three-component reaction of isatoic anhydride **1**, amines **2** or anthranilic acids **5**, and carbon disulfide (**3**) in the presence of potassium hydroxide in ethanol at reflux (Schemes 1, 2).

## Results and discussion

Focusing on designing a new one-pot multicomponent reaction in the absence of expensive catalysts and microwave irradiation for synthesis of 2-thioxoquinazolinones, isatoic anhydride attracted our attention as an available starting material [25–28]. In this research, not only an efficient and facile protocol for the synthesis of 2-thioxoquinazolinone explained, but synthesis of quinazolinobenzothiazinediones is disclosed (Schemes 1, 2).

Our synthetic process started with investigation of reaction between isatoic anhydride **1** (1 mmol), benzylamine (**2a**, 1 mmol), and carbon disulfide (1 mmol) in a variety of different solvents, e.g., EtOH, MeOH, $CH_2Cl_2$,

**Electronic supplementary material** The online version of this article (doi:10.1007/s00706-013-1110-8) contains supplementary material, which is available to authorized users.

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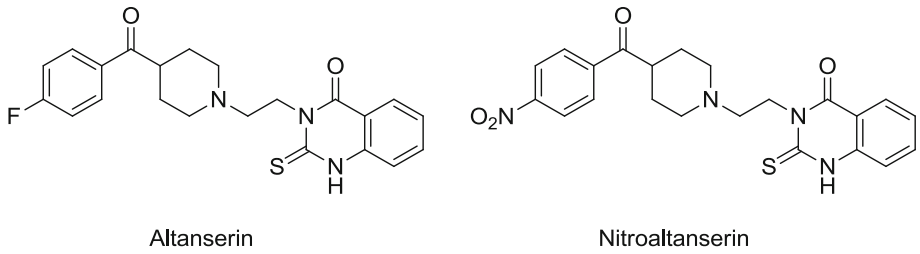
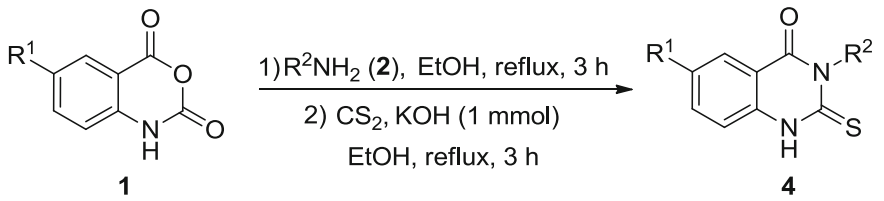
**Fig. 1** Altanserin and nitroaltanserin




**Scheme 1**




**Scheme 2**

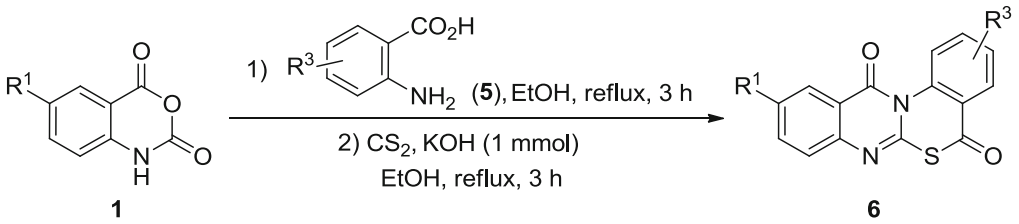



**Table 1** Investigation of various conditions for synthesis of **4a**

| Entry | Solvent | Base | Yield/%[a] |
|---|---|---|---|
| 1 | EtOH | KOH | 85 |
| 2 | MeOH | KOH | 40 |
| 3 | $CH_2Cl_2$ | KOH | 5 |
| 4 | $PhCH_3$ | KOH | 10 |
| 5 | EtOH | NaOH | 25 |
| 6 | MeOH | NaOH | 10 |
| 7 | EtOH | $NEt_3$ | 20 |
| 8 | EtOH | $K_2CO_3$ | 0 |

The reaction times were the same as the optimized conditions

[a] Isolated yield

and toluene, under various conditions. Some results are presented in Table 1. Our results revealed that use of a strong base is essential to obtain the corresponding product **4a** (Table 2, entry 1). It was found that carrying out the reaction in ethanol at reflux offers the best conditions. Also, the influence of different bases was studied, and the results showed that the best performance was obtained with potassium hydroxide (KOH). Hence, KOH was selected as an optimum, available, and inexpensive base. To prevent complications due to possible reaction of amine and $CS_2$, it should be added after complete reaction of isatoic anhydride and amine. Using the optimized condition, a series of reactions using different kinds of amines were performed to synthesize 2-thioxoquinazolinone derivatives **4** (Table 1).

During our investigation, we took anthranilic acid derivatives **5** in the above three-component reaction and directly accessed quinazolinobenzothiazinedione derivatives **6** (Scheme 2). It was found that they could be synthesized under the same optimized conditions in good yield. The results are summarized in Table 3.

Although we have not established the mechanism of reactions in an experimental manner, a possible explanation is proposed in Scheme 3. On the basis of the established chemistry of isatoic anhydride [29–31], it involves the addition of primary amine **2** to isatoic anhydride **1**, resulting in the formation of anthranilamide **7**. Then, in the presence of base, the intermediate **8** is easily obtained by nucleophilic attack of nitrogen to $CS_2$. Cyclization reaction (formation of **9**) followed by elimination of $H_2S$ affords the corresponding compounds **4**. In the case of preparation of quinazolinobenzothiazinedione **6**, the same mechanism is assumed, and in the last step, nucleophilic attack of S (C=S, thiocarbonyl group) at carbonyl group of carboxylic acid leads to the formation of products **6** (Scheme 4).

**Table 2** Synthesis of 2-thioxoquinazolinone derivatives **4** (Scheme 1)

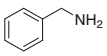
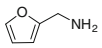
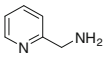
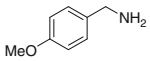
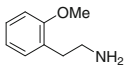
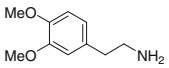
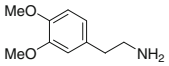
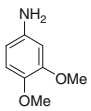
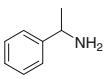
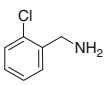
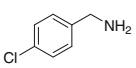
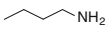
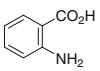
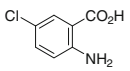
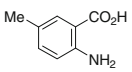
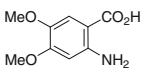
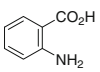
| Entry | $R^1$ | $R^2$-$NH_2$ | Product **4** | M.p./°C | | Yield/%[a] |
|---|---|---|---|---|---|---|
| | | | | Observed | Reported | |
| 1 | H |  | **4a** | 247–248 | 248 [13] | 85 |
| 2 | H |  | **4b** | 233–234 | – | 90 |
| 3 | H |  | **4c** | 265–268 | – | 85 |
| 4 | H |  | **4d** | 233–235 | – | 79 |
| 5 | H |  | **4e** | 202–205 | – | 75 |
| 6 | Cl |  | **4f** | 245–248 | – | 75 |
| 7 | H |  | **4g** | 230–232 | – | 85 |
| 8 | H |  | **4h** | 234–235 | >260 [13] | 75 |
| 9 | H |  | **4i** | 245–247 | – | 77 |
| 10 | H |  | **4j** | 237–239 | – | 80 |
| 11 | H |  | **4k** | 231–233 | 262 [17] | 80 |
| 13 | H |  | **4l** | 227–229 | 230 [17] | 85 |

**Table 2** continued

| Entry | $R^1$ | $R^2$-$NH_2$ | Product **4** | M.p./°C | | Yield/%[a] |
|---|---|---|---|---|---|---|
| | | | | Observed | Reported | |
| 14 | H |  | **4m** | 175–178 | 191 [32] | 80 |
| 15 | H |  | **4n** | 202–204 | 177.5–178.5 [33] | 80 |
| 16 | H |  | **4o** | 183–185 | 175–176 [34] | 78 |

[a] Isolated yield

**Table 3** Synthesis of quinazolinobenzothiazinedione derivatives **6** (Scheme 2)

| Entry | $R^1$ | Anthranilic acid **5** | Product **6** | M.p./°C | | Yield/%[a] |
|---|---|---|---|---|---|---|
| | | | | Observed | Reported | |
| 1 | H |  | **6a** | 299–300 | 300 [19] | 85 |
| 2 | H |  | **6b** | >300 | 306 [19] | 85 |
| 3 | H |  | **6c** | 298–300 | 296 [19] | 80 |
| 4 | H |  | **6d** | >300 | – | 80 |
| 5 | Cl |  | **6e** | >300 | – | 75 |

[a] Isolated yield

All products were characterized by their spectra and physical data. $^1$H nuclear magnetic resonance (NMR) and $^{13}$C NMR spectra of all synthesized compounds associated with this article can be found in the Electronic Supplementary Material.

## Conclusions

We have developed a novel protocol for the synthesis of 2-thioxoquinazolinone and quinazolinobenzothiazinedione derivatives via sequential one-pot reaction of isatoic anhydride, amines/anthranilic acids, and carbon disulfide. Short reaction time, good product yield, use of simple starting materials, and absence of complex and expensive catalysis and microwave irradiation are the key advantages of this method. The simplicity of the present procedure makes it an interesting alternative to complex, multistep approaches. This protocol does not need tedious workup to isolate the products and can emerge as a novel replacement for previous procedures for the synthesis of the mentioned compounds.

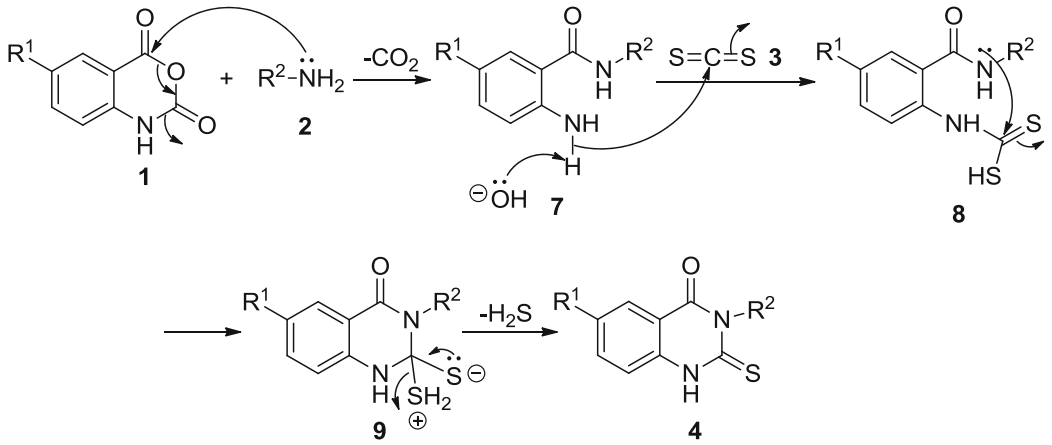
## Experimental

All chemicals were purchased from Merck and Sigma-Aldrich and used without further purification. Melting points were taken on a Kofler hot-stage apparatus. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker FT-500, using tetramethylsilane (TMS) as internal standard. Infrared (IR) spectra were obtained on a Nicolet Magna FTIR 550 spectrophotometer (in KBr). Mass spectra were determined on an Agilent Technology (HP) mass spectrometer operating at ionization potential of 70 eV. Elemental analysis was performed with an Elementar Analysensystem GmbH VarioEL CHNS mode.

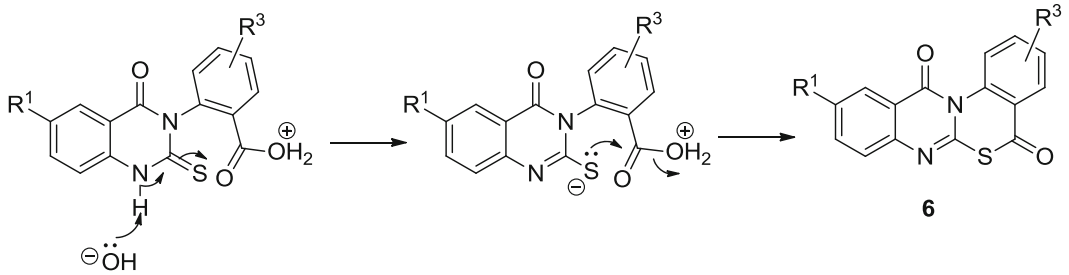
### *General procedure for synthesis of 2-thioxoquinazolinones **4** and quinazolinobenzothiazinediones **6***

A solution of isatoic anhydride **1** (1 mmol) and appropriate amine **2** or **5** (1 mmol) in 10 cm$^3$ EtOH was stirred at reflux for 3 h. Then, a mixture of carbon disulfide (2 mmol) and KOH (1 mmol) was added to the reaction mixture and stirring continued under the same conditions for 3 h. The reaction mixture was cooled to room temperature and poured into 20 cm$^3$ water. The precipitate

**Scheme 3**



**Scheme 4**



was collected by filtration, washed with water, and recrystallized using EtOH to give **4** or **6** as colorless crystals.

*3-Benzyl-2,3-dihydro-2-thioxoquinazolin-4(1H)-one* (**4a**, $C_{15}H_{12}N_2OS$)
White crystals; m.p.: 247–248 °C ([13] 248 °C).

*3-[(Furan-2-yl)methyl]-2,3-dihydro-2-thioxoquinazolin-4(1H)-one* (**4b**, $C_{13}H_{10}N_2O_2S$)
White crystals; m.p.: 233–234 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 5.65$ (s, 2H, $NCH_2$), 6.34 (dd, $J = 3.2$, 0.7 Hz, 1H, furan), 6.37 (dd, $J = 3.2$, 1.8 Hz, 1H, furan), 7.34 (t, $J = 7.5$ Hz, 1H, $H_6$), 7.39 (d, $J = 7.5$ Hz, 1H, $H_8$), 7.53–7.54 (m, 1H, furan), 7.73 (td, $J = 7.5$, 1.3 Hz, 1H, $H_7$), 7.97 (dd, $J = 7.5$, 1.3 Hz, 1H, $H_5$), 13.03 (s, 1H, NH) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta = 42.2$, 108.3, 110.5, 115.3, 115.7, 124.6, 127.3, 135.7, 136.0, 139.0, 142.0, 159.0, 175.0 ppm; IR (KBr): $\bar{\nu} = 3{,}246$, 3,044, 1,658, 1,621, 1,533, 1,488 cm$^{-1}$; MS (70 eV): *m/z* (%) = 257.05 (2, [M-1]$^+$), 167 (41), 149 (53), 113 (21), 104 (14), 91 (19), 83 (27), 69 (94), 43 (100).

*2,3-Dihydro-3-[(pyridin-2-yl)methyl]-2-thioxoquinazolin-4(1H)-one* (**4c**, $C_{14}H_{11}N_3OS$)
White crystals; m.p.: 265–268 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 5.77$ (s, 2H, $NCH_2$), 7.22 (t, $J = 7.5$ Hz, 1H, $H_6$), 7.27 (d, $J = 7.2$ Hz, 1H, $H_{3'}$), 7.36 (t, $J = 7.2$ Hz, 1H, $H_{5'}$), 7.45 (d, $J = 7.2$ Hz, 1H, $H_8$), 7.71 (t, $J = 7.2$ Hz, 1H, $H_{4'}$), 7.78 (t, $J = 7.5$ Hz, 1H, $H_7$), 7.96 (d, $J = 7.5$ Hz, 1H, $H_5$), 8.41 (t, $J = 7.2$ Hz, 1H, $H_{3'}$), 13.04 (s, 1H, NH) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta = 50.0$, 115.4, 115.7, 120.7, 121.9, 124.5, 127.4, 135.6, 136.5, 139.2, 148.8, 155.4, 159.4, 175.6 ppm; IR (KBr): $\bar{\nu} = 3{,}268$, 3,071, 1,664, 1,623, 1,596, 1,532, 1,481 cm$^{-1}$; MS (70 eV): *m/z* (%) = 269.06 (7, M$^+$), 263 (11), 236 (100), 225 (23), 189 (15), 183 (25), 170 (16), 162 (54), 149 (98), 118 (32), 109 (61), 97 (15), 71 (46), 57 (92).

*2,3-Dihydro-3-(4-methoxybenzyl)-2-thioxoquinazolin-4(1H)-one* (**4d**, $C_{16}H_{14}N_2O_2S$)
White crystals; m.p.: 233–235 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 3.71$ (s, 3H, $OCH_3$), 5.77 (s, 2H, $NCH_2$), 6.85 (d, $J = 6.7$ Hz, 2H, $H_{3'}$, $H_{5'}$), 7.33–7.36 (m, 3H, $H_6$, $H_{2'}$, $H_{6'}$), 7.42 (d, $J = 8.0$ Hz, 1H, $H_8$), 7.76 (t, $J = 8.0$ Hz, 1H, $H_7$), 7.96 (d, $J = 8.0$ Hz, 1H, $H_5$), 13.05 (s, 1H, NH) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$):

$\delta$ = 48.0, 55.0, 113.5, 115.4, 115.7, 124.6, 127.3, 128.6, 129.0, 135.6, 139.1, 158.3, 159.3, 175.4 ppm; IR (KBr): $\bar{\nu}$ = 3,250, 3,070, 1,665, 1,625, 1,590, 1,535, 1,480 $cm^{-1}$.

*2,3-Dihydro-3-(2-methoxyphenethyl)-2-thioxoquinazolin-4(1H)-one* (**4e**, $C_{17}H_{16}N_2O_2S$)
White crystals; m.p.: 202–205 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 2.98 (t, $J$ = 7.8 Hz, 2H, $NCH_2CH_2$), 3.73 (s, 3H, $OCH_3$), 4.63 (t, $J$ = 7.8 Hz, 2H, $NCH_2CH_2$), 6.87 (t, $J$ = 7.5 Hz, 1H, $H_{3'}$), 6.93 (d, $J$ = 7.5 Hz, 1H, $H_{6'}$), 7.17–7.22 (m, 2H, $H_{4'}$, $H_{5'}$), 7.33 (td, $J$ = 7.8, 1.2 Hz, 1H, $H_6$), 7.39 (d, $J$ = 7.8 Hz, 1H, $H_8$), 7.78 (td, $J$ = 7.8, 1.2 Hz, 1H, $H_7$), 7.95 (dd, $J$ = 7.8, 1.2 Hz, 1H, $H_5$), 12.92 (s, 1H, NH) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 26.8, 45.4, 55.2, 110.7, 115.5, 120.3, 124.4, 126.5, 127.2, 127.8, 129.8, 135.4, 136.2, 139.0, 157.4, 159.1, 175.0 ppm; IR (KBr): $\bar{\nu}$ = 3,265, 3,080, 1,667, 1,629, 1,593, 1,530, 1,481 $cm^{-1}$; MS (70 eV): $m/z$ (%) = 312.09 (45, $M^+$), 257 (11), 229 (20), 178 (24), 134 (100), 111 (25), 91 (40), 69 (98).

*6-Chloro-3-(3,4-dimethoxyphenethyl)-2,3-dihydro-2-thioxoquinazolin-4(1H)-one* (**4f**, $C_{18}H_{17}ClN_2O_3S$)
White crystals; m.p.: 245–248 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 2.90 (t, $J$ = 8.1 Hz, 2H, $NCH_2CH_2$), 3.73 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$), 4.50 (t, $J$ = 8.1 Hz, 2H, $NCH_2CH_2$), 6.80 (dd, $J$ = 8.1, 1.9 Hz, 1H, $H_{6'}$), 6.86 (d, $J$ = 1.9 Hz, 1H, $H_{2'}$), 6.89 (d, $J$ = 8.1 Hz, 1H, $H_{5'}$), 7.40 (d, $J$ = 8.8 Hz, 1H, $H_8$), 7.80 (dd, $J$ = 8.8, 2.4 Hz, 1H, $H_7$), 7.89 (d, $J$ = 2.4 Hz, 1H, $H_5$), 13.15 (s, 1H, NH) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 31.7, 47.2, 55.3, 55.5, 112.0, 112.3, 116.9, 117.9, 120.4, 126.1, 128.3, 130.8, 135.4, 137.9, 147.5, 148.7, 158.2, 174.8 ppm; IR (KBr): $\bar{\nu}$ = 3,260, 3,081, 1,669, 1,625, 1,591, 1,528, 1,479 $cm^{-1}$.

*3-(3,4-Dimethoxyphenethyl)-2,3-dihydro-2-thioxoquinazolin-4(1H)-one* (**4g**, $C_{18}H_{18}N_2O_3S$)
White crystals; m.p.: 230–232 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 2.91 (t, $J$ = 8.0 Hz, 2H, $NCH_2CH_2$), 3.73 (s, 3H, $OCH_3$), 3.74 (s, 3H, $OCH_3$), 4.58 (t, $J$ = 8.0 Hz, 2H, $NCH_2CH_2$), 6.80 (d, $J$ = 8.5 Hz, 1H, $H_{5'}$), 6.87–6.90 (m, 2H, $H_{2'}$, $H_{6'}$), 7.34 (t, $J$ = 8.0 Hz, 1H, $H_6$), 7.40 (d, $J$ = 8.0 Hz, 1H, $H_8$), 7.74 (t, $J$ = 8.0 Hz, 1H, $H_7$), 7.96 (d, $J$ = 8.0 Hz, 1H, $H_5$), 12.96 (s, 1H, NH) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 31.8, 47.1, 55.3, 55.5, 112.0, 112.3, 115.5, 115.6, 120.5, 124.5, 127.2, 130.9, 135.4, 139.0, 147.5, 148.7, 159.1, 174.9 ppm; IR (KBr): $\bar{\nu}$ = 3,180, 3,040, 1,686, 1,622, 1,589, 1,541, 1,484 $cm^{-1}$; MS (70 eV): $m/z$ (%) = 342.10 (3, $M^+$), 282 (67), 167 (82), 149 (100), 120 (25), 104 (41), 71 (31), 57 (41).

*2,3-Dihydro-3-phenyl-2-thioxoquinazolin-4(1H)-one* (**4h**, $C_{14}H_{10}N_2OS$)
White crystals; m.p.: 234–235 °C ([13] >260 °C); $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 7.27–7.28 (m, 2H, ArH), 7.35 (t, $J$ = 7.7 Hz, 1H, $H_6$), 7.40–7.49 (m, 4H, $H_8$, ArH), 7.79 (td, $J$ = 7.7, 1.0 Hz, 1H, $H_7$), 7.96 (dd, $J$ = 8.0, 1.0 Hz, 1H, $H_5$), 13.03 (s, 1H, NH) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 115.6, 116.1, 124.3, 127.4, 128.0, 128.8, 128.9, 135.5, 139.3, 139.6, 159.7, 176.0 ppm; IR (KBr): $\bar{\nu}$ = 3,247, 3,031, 1,664, 1,622, 1,530, 1,488 $cm^{-1}$; MS (70 eV): $m/z$ (%) = 254.05 (5, $M^+$), 167 (53), 149 (84), 113 (17), 104 (16), 91 (10), 83 (38), 69 (70), 57 (100), 43 (98).

*3-(3,4-Dimethoxyphenyl)-2,3-dihydro-2-thioxoquinazolin-4(1H)-one* (**4i**, $C_{16}H_{14}N_2O_3S$)
White crystals; m.p.: 245–248 °C: $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 3.71 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 6.80 (dd, $J$ = 8.5, 2.3 Hz, 1H, $H_{6'}$), 6.93 (d, $J$ = 2.3 Hz, 1H, $H_{2'}$), 7.02 (d, $J$ = 8.5 Hz, 1H, $H_{5'}$), 7.34 (t, $J$ = 7.8 Hz, 1H, $H_6$), 7.44 (d, $J$ = 7.8 Hz, 1H, $H_8$), 7.78 (td, $J$ = 7.8, 1.2 Hz, 1H, $H_7$), 7.95 (dd, $J$ = 7.8, 1.2 Hz, 1H, $H_5$), 13.00 (s, 1H, NH) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 55.5, 55.6, 111.4, 112.7, 115.6, 116.1, 121.0, 124.2, 127.4, 132.0, 135.5, 139.5, 148.4, 148.9, 159.8, 176.4 ppm; IR (KBr): $\bar{\nu}$ = 3,180, 3,030, 1,696, 1,648, 1,623, 1,537, 1,488 $cm^{-1}$; MS (70 eV): $m/z$ (%) = 314.07 (100, $M^+$), 297 (27), 268 (16), 240 (14), 180 (10), 162 (74), 145 (43), 111 (23), 83 (41), 57 (41).

*2,3-Dihydro-3-(1-phenylethyl)-2-thioxoquinazolin-4(1H)-one* (**4j**, $C_{16}H_{14}N_2OS$)
White crystals; m.p.: 237–239 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 1.86 (d, $J$ = 6.5 Hz, 3H, $CH_3$), 7.20 (q, $J$ = 6.5 Hz, 1H, CH), 7.28–7.34 (m, 6H, $H_6$, ArH), 7.42 (d, $J$ = 7.5 Hz, 1H, $H_8$), 7.72 (t, $J$ = 7.5 Hz, 1H, $H_7$), 7.99 (d, $J$ = 7.5 Hz, 1H, $H_5$), 13.06 (s, 1H, NH) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 14.9, 56.6, 115.6, 116.4, 124.5, 125.6, 126.4, 127.0, 128.0, 135.4, 138.9, 140.3, 158.3, 176.5 ppm; IR (KBr): $\bar{\nu}$ = 3,310, 3,025, 1,666, 1,623, 1,526, 1,492 $cm^{-1}$; MS (70 eV): $m/z$ (%) = 282.08 (56, $M^+$), 178 (100), 149 (55), 134 (11), 120 (34), 104 (57), 77 (45), 57 (27).

*3-(2-Chlorobenzyl)-2,3-dihydro-2-thioxoquinazolin-4(1H)-one* (**4k**, $C_{15}H_{11}ClN_2OS$)
White crystals; m.p.: 231–233 °C ([17] 262 °C); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 5.88 (s, 2H, $NCH_2$), 6.97 (d, $J$ = 7.5 Hz, 1H, $H_{6'}$), 7.13–7.17 (m, 2H, $H_{3'}$, $H_{4'}$), 7.20 (t, $J$ = 7.7 Hz, 1H, $H_6$), 7.36 (t, $J$ = 7.5 Hz, 1H, $H_{5'}$), 7.43 (d, $J$ = 7.7 Hz, 1H, $H_8$), 7.70 (t, $J$ = 7.7 Hz, 1H, $H_7$), 8.17 (d, $J$ = 7.7 Hz, 1H, $H_5$), 10.12 (s, 1H, NH) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 48.0, 114.4, 125.2, 125.9, 126.8, 128.2, 128.9, 129.7, 131.1, 132.9, 135.0, 135.8, 138.3,

159.5, 176.2 ppm; IR (KBr): $\bar{\nu}$ = 3,182, 3,033, 1,690, 1,620, 1,540, 1,488 $cm^{-1}$.

*3-(4-Chlorobenzyl)-2,3-dihydro-2-thioxoquinazolin-4(1H)-one* (**4l**, $C_{15}H_{11}ClN_2OS$)
White crystals; m.p.: 227–229 °C ([17] 230 °C).

*2,3-Dihydro-3-propyl-2-thioxoquinazolin-4(1H)-one* (**4m**, $C_{11}H_{12}N_2OS$)
White crystals; m.p.: 175–178 °C ([28] 191 °C); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.04 (t, $J$ = 7.5 Hz, 3H, $CH_3CH_2CH_2N$), 1.86 (sextet, $J$ = 7.5 Hz, 2H, $CH_3CH_2CH_2N$), 4.50 (t, $J$ = 7.5 Hz, 2H, $CH_3CH_2CH_2N$), 7.23 (d, $J$ = 7.7 Hz, 1H, $H_8$), 7.34 (t, $J$ = 7.5 Hz, 1H, $H_6$), 7.67 (td, $J$ = 7.7, 1.3 Hz, 1H, $H_7$), 8.15 (dd, $J$ = 7.7, 1.3 Hz, 1H, $H_5$), 10.90 (s, 1H, NH) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 11.2, 20.1, 48.4, 114.6, 116.2, 125.0, 128.5, 135.3, 138.4, 159.6, 175.7 ppm; IR (KBr): $\bar{\nu}$ = 3,190, 3,052, 1,699, 1,648, 1,626, 1,535, 1,481 $cm^{-1}$.

*2,3-Dihydro-3-isopropyl-2-thioxoquinazolin-4(1H)-one* (**4n**, $C_{11}H_{12}N_2OS$)
White crystals; m.p.: 202–204 °C ([29] 177.5–178.5 °C); $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 1.04 (d, $J$ = 7.0 Hz, 6H, $(CH_3)_2CHN$), 6.06 (q, $J$ = 7.0 Hz, 1H, $(CH_3)_2CHN$), 7.32 (t, $J$ = 8.0 Hz, 1H, $H_6$), 7.34 (d, $J$ = 8.0 Hz, 1H, $H_8$), 7.67 (td, $J$ = 8.0, 1.3 Hz, 1H, $H_7$), 8.15 (dd, $J$ = 8.0, 1.3 Hz, 1H, $H_5$), 12.87 (s, 1H, NH) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 18.5, 52.5, 115.3, 116.7, 124.4, 126.9, 135.2, 138.8, 159.4, 175.2 ppm; IR (KBr): $\bar{\nu}$ = 3,191, 3,055, 1,690, 1,628, 1,625, 1,535, 1,480 $cm^{-1}$.

*3-Butyl-2,3-dihydro-2-thioxoquinazolin-4(1H)-one* (**4o**, $C_{12}H_{14}N_2OS$)
White crystals; m.p.: 183–185 °C ([30] 175–176 °C).

*5H,12H-Quinazolino[3,2-a][3,1]benzothiazine-5,12-dione* (**6a**, $C_{15}H_8N_2O_2S$)
White crystals; m.p.: 299–300 °C ([19] 300 °C).

*3-Chloro-5H,12H-quinazolino[3,2-a][3,1]benzothiazine-5,12-dione* (**6b**, $C_{15}H_7ClN_2O_2S$)
White crystals; m.p.: >300 °C ([19] 306 °C); $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 7.10–7.25 (m, 2H, $H_2$, $H_8$), 7.44–7.34 (m, 2H, $H_4$, $H_9$), 7.69 (t, $J$ = 7.5 Hz, 1H, $H_{10}$), 7.88 (d, $J$ = 7.5 Hz, 1H, $H_1$), 8.04 (d, $J$ = 7.5 Hz, 1H, $H_{11}$) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 123.4, 127.2, 128.8, 129.1, 129.7, 131.3, 131.6, 131.8, 134.7, 138.0, 138.5, 139.1, 160.2, 166.6, 175.9 ppm; IR (KBr): $\bar{\nu}$ = 3,023, 1,679, 1,638, 1,621, 1,572 $cm^{-1}$; MS (70 eV): $m/z$ (%) = 315.99 (2, $[M + 2]^+$), 313.99 (7, $M^+$), 262 (100), 236 (31), 183 (71), 109 (69), 97 (52), 69 (69).

*3-Methyl-5H,12H-quinazolino[3,2-a][3,1]benzothiazine-5,12-dione* (**6c**, $C_{16}H_{10}N_2O_2S$)
White crystals; m.p.: 298–300 °C ([19] 296 °C).

*2,3-Dimethoxy-5H,12H-quinazolino[3,2-a][3,1]benzothiazine-5,12-dione* (**6d**, $C_{17}H_{12}N_2O_4S$)
White crystals; m.p.: >300 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ = 3.73 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 6.74 (s, 1H, $H_1$), 7.27 (t, $J$ = 7.5 Hz, 1H, $H_9$), 7.41 (d, $J$ = 7.5 Hz, 1H, $H_8$), 7.64 (s, 1H, $H_4$), 7.71 (t, $J$ = 7.5 Hz, 1H, $H_{10}$), 7.90 (d, $J$ = 7.5 Hz, 1H, $H_{11}$) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ = 55.4, 55.7, 112.9, 114.2, 114.9, 115.5, 116.5, 121.7, 123.6, 127.3, 132.4, 134.9, 147.2, 149.7, 160.0, 167.6, 176.4 ppm; IR (KBr): $\bar{\nu}$ = 3,040, 2,928, 2,830, 1,680, 1,670, 1,640, 1,560 $cm^{-1}$.

*10-Chloro-5H,12H-quinazolino[3,2-a][3,1]benzothiazine-5,12-dione* (**6e**, $C_{15}H_7ClN_2O_2S$)
White crystals; m.p.: >300 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 6.89–7.31 (m, 5H, ArH), 7.77–7.84 (m, 2H, ArH) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 116.0, 118.8, 119.2, 123.6, 127.3, 128.7, 129.5, 130.2, 131.2, 133.0, 134.3, 135.3, 136.5, 160.4, 175.9 ppm.

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## References

1. Xia Y, Yang ZY, Hour MJ, Kuo SC, Xia P, Bastow KF, Nakanishi Y, Nampoothiri P, Hackl T, Hamel E, Lee KH (2001) Bioorg Med Chem Lett 11:193
2. Mukerji DD, Agarwal VR, Nautiyal SR (1985) Indian J Pharm Sci 47:8
3. Kenichi O, Yoshihisa Y, Toyonari O, Toru I, Yoshio I (1985) J Med Chem 28:568
4. Jiang JB, Hesson DP, Dusak BA, Dexter DL, Kang GJ, Hamel E (1990) J Med Chem 33:1721
5. Rajasekaran A, Rajamanickam V, Darlinquine S (2001) Yakugaku Zasshi 131:1079
6. Suesse M, Cleve D, Johne S (1990) Preparation of (3-alkoxycarbonylalkyl-3,4-dihydro-4-oxo-quinazolin-2-ylthio)alkanoic acids and esters as plant growth regulators and fungicides. Ger (East) DD 278788, May 16
7. Suesse M, Cleve D, Johne S (1991) Chem Abstr 114:62116y
8. Suesse M, Schaks A, Johne S (1990) Preparation of [(2-alkoxycarbonylalkylthio-3,4-dihydro-4-oxo-quinazolin-3-yl)alkanoyloxy]alkanoic acid esters as plant growth regulators and fungicides. Ger (East) DD 278789, May 16
9. Suesse M, Schaks A, Johne S (1991) Chem Abstr 114:62115
10. Lemaire C, Cantineau R, Guillaume M, Plenevaux A, Christiaens L (1991) J Nucl Med 32:2266
11. Saeed A, Shaheen U, Bolte M (2010) J Chin Chem Soc 57:82
12. Saeed A, Flörke U (2011) Crystals 1:254
13. Tiwari VK, Singh DD, Hussain HA, Mishra BB, Singh A (2008) Monatsh Chem 139:43

14. Dou GL, Wang MM, Huang ZB, Shi DQ (2009) J Heterocycl Chem 46:645
15. Castro A, Jerez MJ, Gil C, Calderón F, Doménech T, Nueda A, Martínez A (2008) Eur J Med Chem 43:1349
16. Azizian J, Mohammadi AA, Karimi AR (2003) Synth Commun 33:415
17. Satponth PS, Trivedi JP (1971) J Indian Chem Soc 48:1021
18. Lakhan R, Srivastava M (1993) Proc Indian Acad Sci Chem Sci 105:11
19. Singh S, Kaur S, Kaushal AN (1976) J Indian Chem Soc 53:382
20. Mahdavi M, Asadi M, Saeedi M, Rezaei Z, Moghbel H, Foroumadi A, Shafiee A (2012) Synlett 23:2521
21. Hosseini-Zare MS, Mahdavi M, Saeedi M, Asadi M, Javanshir S, Shafiee A, Foroumadi A (2012) Tetrahedron Lett 53:3448
22. Mahdavi M, Asadi M, Saeedi M, Ebrahimi M, Rasouli MA, Ranjbar PR, Foroumadi A, Shafiee A (2012) Synthesis 44:3649
23. Tahghighi A, Razmi S, Mahdavi M, Foroumadi P, Ardestani SK, Emami S, Kobarfard F, Dastmalchi S, Shafiee A, Foroumadi A (2012) Eur J Med Chem 50:124
24. Khalaj A, Nakhjiri M, Negahbani AS, Samadizadeh M, Firoozpour L, Rajabalian S, Samadi N, Faramarzi MA, Adipour N, Shafiee A, Foroumadi A (2011) Eur J Med Chem 46:65
25. Sunder S, Peet NP (1979) J Heterocycl Chem 16:1339
26. Wang M, Zhang TT, Liang Y, Gao JJ (2012) Monatsh Chem 143:835
27. Karimi-Jaberi Z, Arjmandi R (2011) Monatsh Chem 142:631
28. Mahdavi M, Asadi M, Saeedi M, Tehrani MH, Mirfazli SS, Shafiee A, Foroumadi A (2013) Synth Commun 43:2936
29. Clark RH, Wagner EC (1944) J Org Chem 9:55
30. Staiger RP, Wagner EC (1948) J Org Chem 13:347
31. Staiger RP, Miller EB (1959) J Org Chem 24:1214
32. Talukdar PB, Sengupta SK, Datta AK, Roy TK (1977) Indian J Chem B 15B:41
33. Wagner G, Rothe L (1969) Pharmazie 24:513
34. Shafik RM, Hazzaa AAB, Habib NS (1979) Pharmazie 34:148