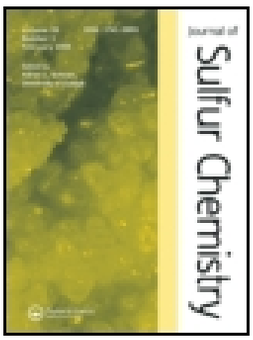


Journal of Sulfur Chemistry

ISSN: 1741-5993 (Print) 1741-6000 (Online) Journal homepage: http://www.tandfonline.com/loi/gsrp20

A green and efficient synthesis of 2-thioxoquinazolinone derivatives in water using potassium thiocyanate

Ghasem Rezanejade Bardajee, Aseyeh Ghaedi, Shohreh Hekmat, Ghazale Abarashi, Mohammad Mahdavi & Tahmineh Akbarzadeh

To cite this article: Ghasem Rezanejade Bardajee, Aseyeh Ghaedi, Shohreh Hekmat, Ghazale Abarashi, Mohammad Mahdavi & Tahmineh Akbarzadeh (2017): A green and efficient synthesis of 2-thioxoquinazolinone derivatives in water using potassium thiocyanate, Journal of Sulfur Chemistry, DOI: 10.1080/17415993.2017.1325891

To link to this article: http://dx.doi.org/10.1080/17415993.2017.1325891

Published online: 17 May 2017.

JOURNAL OF SULFUR CHEMISTRY, 2017
https://doi.org/10.1080/17415993.2017.1325891

Taylor & Francis
Taylor & Francis Group

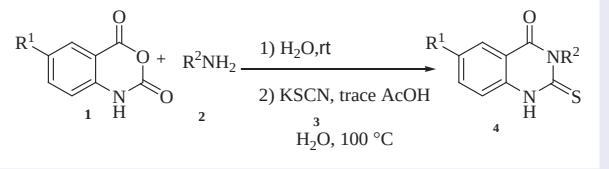
A green and efficient synthesis of 2-thioxoquinazolinone derivatives in water using potassium thiocyanate

Ghasem Rezanejade Bardajee[a], Aseyeh Ghaedi[a], Shohreh Hekmat[a], Ghazale Abarashi[a], Mohammad Mahdavi[b] and Tahmineh Akbarzadeh[c,d]

[a]Department of Chemistry, Payame Noor University (PNU), Tehran, Iran; [b]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran; [c]Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran; [d]Drug Design & Development Research Center, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Green chemistry is one of the most important routes for the synthesis of heterocyclic compounds. In this regard, the synthesis of 2-thioxoquinazolinone derivatives was achieved by condensation of versatile materials including isatoic anhydride, amine and potassium thiocyanate in the green medium of water. This convenient and efficient method affords the desired products with good to excellent yields.



ARTICLE HISTORY
Received 15 January 2017
Accepted 27 April 2017

KEYWORDS
Thioxoquinazolinone; green chemistry; water; isatoic anhydride; potassium thiocyanate

1. Introduction

Providing greener chemical processes and synthetic approaches has become one of the aims of research during the past decade in efforts designed to produce chemical compounds [1–3]. In this regard, new procedures were designed by chemists to reduce environmental pollution and to save energy [4]. Optimizing the reaction conditions in the presence of environmental friendly solvents (*e.g.* water and ethanol) instead of toxic solvents is desirable for green synthesis of organic compounds especially heterocycles [5]. Quinazolinone derivatives are classified as N-rich fused heterocycles which have widespread biological activities [6], including anti-inflammatory [7], anti-parkinsonism [8], anticonvulsant [9],

CONTACT Ghasem Rezanejade Bardajee rezanejad@pnu.ac.ir, ghrezanejad@yahoo.com Department of Chemistry, Payame Noor University (PNU), PO BOX 19395-3697, Tehran, Iran; Tahmineh Akbarzadeh akbarzad@tums.ac.ir Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

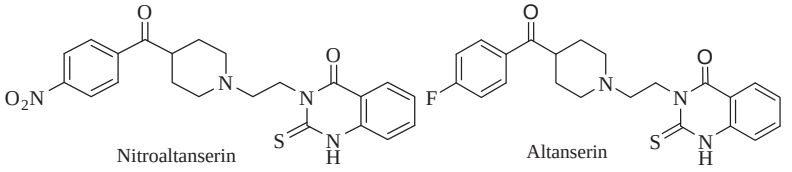


Figure 1. Chemical structures of altanserin and nitroaltanserin.

antimicrobial [10], anticancer and analgesic properties [11]. The 2-thioxoquinazolinone framework is also a favorable unit in drug design since many commercial pharmaceuticals contain this structure [12] such as Altanserin and Nitroaltanserin (Figure 1) as 5-HT2A receptor antagonist drugs [13].

2-Thioxoquinazolinone derivatives have been produced using different methodologies; however low yields, hazardous chemicals and harsh reaction conditions are some of their drawbacks. For example, CS_2 or isothiocyanates were used in these reactions and are flammable, high toxic, stinky and noxious. Despite the mentioned disadvantages, some reported procedures have opened new prospects for the synthesis of 2-thioxoquinazolinones [14–23]. For instance, one-pot three-component reactions of isatoic anhydride, amines and carbon disulfide were accomplished in ethanol with potassium hydroxide under reflux and microwave irradiation conditions [24]. Additionally, 2-thioxoquinazolinones were obtained by the use of isothiocyanates in DMSO/H_2O in the absence of any catalyst under microwave irradiation [24, 25]. Hence, in this article, a more efficient, greener and rapid way for the synthesis of 2-thioxoquinazolinone derivatives is described. According to our previous syntheses based on isatoic anhydride and amines [25–31], we have designed the current synthesis using isatoic anhydrides, amines and potassium thiocyanate in acetic acid and water to give 2-thioxoquinazolinones in high yields within shorter reaction times.

2. Results and discussion

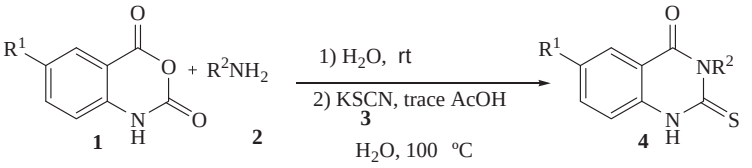
Primarily, we designed a new one-pot process for the synthesis of 2-thioxoquinazolinone derivatives under mild and green conditions. The synthetic procedure was performed through the reaction of isatoic anhydride **1** (1 mmol), potassium thiocyanate (1 mmol) and amine **2a** (1 mmol) in various solvents including EtOH, MeOH, CH_2Cl_2 and H_2O under

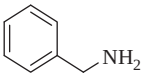
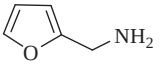
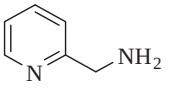
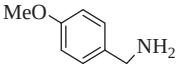
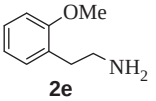
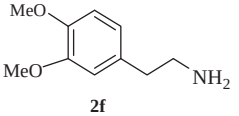
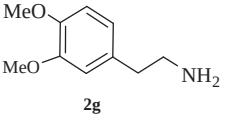
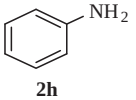
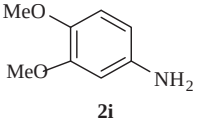
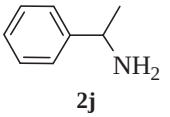
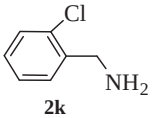
Table 1. Investigation on various conditions for synthesis of **4a–4o**.

Entry	Solvent	Acid	Time (h)	Yield (%)[a]
1	EtOH	AcOH	12	30
2	MeOH	AcOH	10	25
3	H_2O	AcOH	3	85
4	H_2O	–	15	trace
5	CH_2Cl_2	HCl	10	15
6	EtOH	HCl	10	15
7	MeOH	HCl	12	10
8	H_2O	HCl	13	20
9	CH_2Cl_2	HCl	10	trace

[a]Isolated yield.

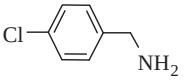
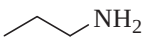
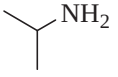
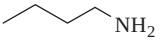
Table 2. Synthesis of 2-thioxoquinazolinone derivatives **4** (Scheme 1).



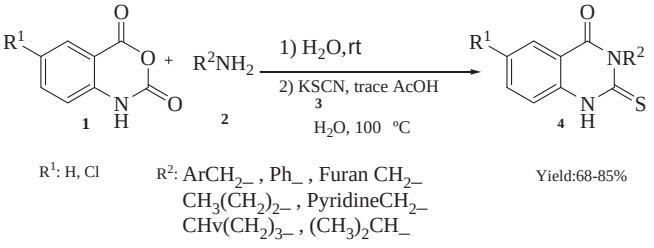
Entry	R^1	R^2 NH_2	Product **4**	Yield (%)[a]
1	H	 **2a**	**4a**	80
2	H	 **2b**	**4b**	85
3	H	 **2c**	**4c**	58
4	H	 **2d**	**4d**	75
5	H	 **2e**	**4e**	75
6	Cl	 **2f**	**4f**	78
7	H	 **2g**	**4g**	83
8	H	 **2h**	**4h**	85
9	H	 **2i**	**4i**	77
10	H	 **2j**	**4j**	78
11	H	 **2k**	**4k**	85

(*continued*)

Table 2. Continued.

Entry	R^1	R^2 NH_2	Product **4**	Yield (%)[a]
12	H	 **2l**	**4l**	84
13	H	 **2m**	**4m**	74
14	H	 **2n**	**4n**	70
15	H	 **2o**	**4o**	68

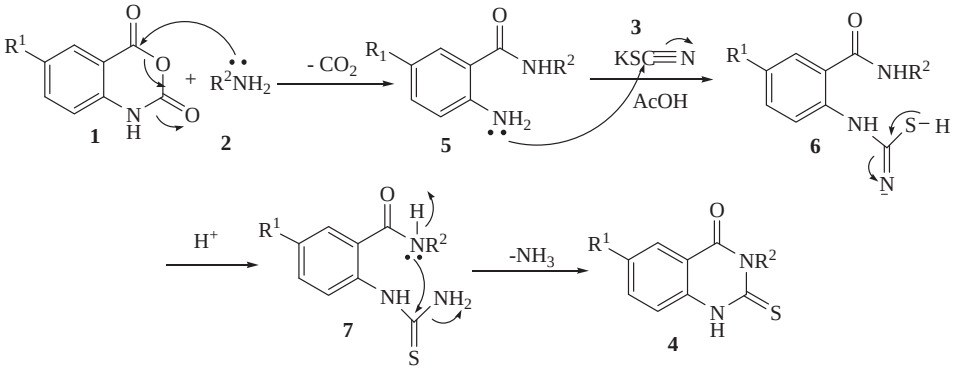
[a]Isolated yield.



Scheme 1. General outline for the synthesis of 2-thioxoquinazolinones (**4a–4o**).

different conditions. Also, the impact of different acidic catalysts was studied on this reaction and the best results were obtained in acetic acid (AcOH), which is a safe, green and available organic acid. To prevent side reactions of amine with KSCN **3**, it should be added to the mixture after completion of the reaction between isatoic anhydride and the amine. However, the results showed that the use of acid catalyst is important to successfully obtain the product **4a** (Table 1, Entries 3 and 4). In addition, water was selected as the best solvent for this reaction (Table 1, Entry 3). By applying the optimized conditions (Table 1, Entry 3), a series of 2-thioxoquinazolinone derivatives **4** were obtained using different kinds of amines (Table 2). Initially, a mixture of isatoic anhydride **1** and amine **2** was stirred in H_2O at room temperature. Then potassium thiocyanate was added to the mixture and the reaction was continued in H_2O at 80°C in the presence of acetic acid (Scheme 1).

To investigate generality of this procedure, various primary aliphatic and aromatic amines were applied in this reaction and a range of 2-thioxoquinazolinone derivatives (**4a–4o**) were obtained in 68–85% yields (Table 2). Generally, benzylamine derivatives bearing both electron-donating and electron-withdrawing groups on the aromatic ring gave the corresponding products in high yields (Table 2, Entries 4–12). Furthermore, aniline, primary and secondary alkyl amines produced the desired products in good yields (Table 2, Entries 13–15). A plausible reaction mechanism for the formation of product **4** is proposed in Scheme 2. According to the chemistry of isatoic anhydride [32–36],



Scheme 2. The proposed mechanism for the formation of 2-thioxoquinazolinone 4.

nucleophilic addition of amine **2** to the carbonyl group of isatoic anhydride **1**, resulted in the removal of a carbon dioxide molecule and formation of anthranilamide **5**. Then, nucleophilic attack of amino group of intermediate **5** on KSCN achieved intermediate **6**. In the final step, intermediate **7** is obtained and after elimination of NH_3 following an intramolecular cyclization, the corresponding compound **4** is obtained. Characterization of the products was achieved by their physical and spectral data. Although there are several methods for the synthesis of the entitled heterocycles, due to the importance of introducing green methods for the preparation of heterocycles in organic synthesis, the present methodology can be regarded as a versatile strategy for the synthesis of 2-thioxoquinazolinone derivatives. The advantages of using water as the solvent in organic reactions include simplifying of the work-up procedure, the improvement of selectivity and reactivity, and moderate reaction conditions. Moreover, unusual reactivity and reverse selectivity can happen in the presence of water in comparison with organic solvents during synthesis of organic compounds. In the present study, acetic acid and potassium thiocyanate are highly soluble in water while they have low solubility in methanol or ethanol solvents. Moreover, the ring opening reaction of isatoic anhydride in aqueous medium is a highly desirable reaction. For these reasons, applying water as the reaction medium is the best condition for this methodology. Herein, we report an efficient and environmentally benign method for the preparation of 2-thioxoquinazolinone derivatives **4** in high yields. This method can be considered as an interesting alternative to other complex and multi-step procedures reported in the literature. The present method is simple with no need of tedious work-up procedures. It is an appropriate replacement for previous approaches reported for the synthesis of the mentioned products. Considering the fact that most 2-thioxoquinazolinone derivatives show interesting biological activities, the new compounds synthesized in this paper are valuable for further pharmaceutical research.

3. Conclusion

In conclusion, we have reported a rapid, efficient and environmentally benign method for the preparation of 2-thioxoquinazolinones via the ring opening reaction of isatoic anhydrides, amines and potassium thiocyanate using acetic acid in aqueous medium.

The advantages of the present method are the eco-friendly approach and simple work-up procedure that make this method applicable for medical researchers to make progress during their drug discovery investigations based on thioxoquinazolinones.

4. Experimental

Merck and Sigma Aldrich chemicals were used in this protocol with no further purification. Melting points were measured on a Kofler hot-stage device. ^{1}H and ^{13}C NMR spectra were taken on a Bruker FT-500 instrument, using tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Nicolet Magna FTIR550 spectrophotometer using KBr plate. Mass spectra were obtained on an Agilent Technology (HP) mass spectrometer with an ionization potential of 70 eV. Elemental analysis was accomplished with an Elementar Analysen system GmbH VarioEL CHNS.

5. General procedure for the preparation of 2-thioxoquinazolinone derivatives 4a–4o

A mixture of isatoic anhydride **1** (1 mmol) and the corresponding amine **2** (1 mmol) in H_2O (5 mL) was stirred for 1 h at ambient temperature. Then, KSCN (1 mmol) in acetic acid (1 mL) and H_2O (5 mL) was added to the mixture and the reaction was continued for 3 h at 80°C. After completion of the reaction, the crude product was filtered, washed well with water and recrystallized in hot water to gain the pure colorless product **4.**

5.1. 3-benzyl-2,3-dihydro-2-thioxoquinazolin-4(1H)-one (4a).

White crystals; yield: 214 mg (80%), mp 247–249°C ([18] lit. 248°C).

5.2. 3-((furan-2-yl) methyl)-2,3-dihydro-2-thioxoquinazolin-4(1H)-one (4b).

White crystals; yield: 219 mg (85%), mp 233–234°C; IR (KBr): 3346, 3034, 1658, 1625, 1523, 1498 cm^{-1}; ^{1}HNMR (500 MHz, DMSO-d_6): 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, Ar, 7.39 (d, J = 7.5 Hz, 1H, Ar), 7.53–7.54 (m, 1H, furan), 7.73 (td, J = 7.5, 1.3 Hz, 1H, Ar), 7.97 (dd, J = 7.5, 1.3 Hz, 1H, Ar), 13.03 (s, 1H, NH);^{13}C NMR (125 MHz, DMSO-d_6): 42.2, 108.3, 110.5, 115.3, 115.7, 124.6, 127.3, 135.7, 136, 139.0, 142.0, 159.0, 175.0. Mass *m/z* (%): 258 [M^+] (2), 167 (41), 149 (53), 113 (21), 104 (14), 91 (19), 83 (27), 69 (94), 43 (100). Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.85%. Found: C, 60.65; H, 4.15; N, 10.66.

5.3. 2,3-Dihydro-3- (pyridin-2-yl)methyl-2-thioxoquinazolin-4(1H)-one (4c).

White crystals; yield: 156 mg (58%), mp 265–268°C; IR (KBr): 3278, 3071, 1684, 1613, 1596 1532, 1481 cm^{-1}, ^{1}HNMR (500 MHz, DMSO-d_6): 5.70 (s, 2H, NCH_2), 7.22 (t, J = 7.5 Hz, 1H, H_6), 7.27 (d, J = 7.2 Hz, 1H, $H_{2'}$), 7.36 (t, J = 7.2 Hz, 1H,$H_{5'}$), 7.45 (d, J = 7.2 Hz, 1H, H_8), 7.70 (t, J = 7.2 Hz, 1H, $H_{4'}$), 7.75 (t, J = 7.5 Hz, 1H, H_7), 7.96 (d, J = 7.5 Hz,

1H, H_5), 8.40 (t, $J = 7.2$ Hz, 1H, $H_{3'}$), 13.04 (s, 1H, NH);^{13}C NMR (125 MHz, DMSO-d_6): 50.0, 115.4, 115.7, 120.7, 121.9, 124.5, 127.4, 135.6, 136.5, 139.2, 148.8, 155.0, 159.0, 175.6. Mass *m/z* (%): 269 [M^+] (7), 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); Anal. Calcd for $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60%. Found: C, 62.70; H, 4.25; N, 15.75.

5.4. 2,3-Dihydro-3-(4-methoxybenzyl)-2-thioxoquinazolin-4(1H)-one (4d).

White crystals; yield: 223 mg (75%), mp 233–235°C; IR (KBr): 3260, 3080, 1655, 1615, 1590, 1525, 1470 cm^{-1}, ^{1}HNMR (500 MHz, DMSO-d_6): 3.71 (s, 3H, OCH_3), 5.77 (s, 2H, NCH_2), 6.8 (d, $J = 6.7$ Hz, 2H, $H_{3'}$, $H_{5'}$), 7.3–7.3 (m, 3H, H_6, $H_{2'}$, $H_{6'}$), 7.4 (d, $J = 8.0$ Hz, 1H, H_8), 7.70 (t, $J = 8.0$ Hz, 1H, H_7), 7.94 (d, $J = 8.0$ Hz, 1H, H_5), 13.05 (s, 1H, NH); ^{13}CNMR (125 MHz, DMSO-d_6): 48.0, 55. 1, 113.5, 115.4, 115.7, 124.8, 127.3, 128.9, 129.0, 135.6, 139.0, 158.3, 159.3, 175.3. Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.01; H, 4.33; N, 8.99.

5.5. 2,3-Dihydro-3-(2-methoxyphenethyl)-2-thioxoquinazolin 4(1H)-one (4e).

White crystals; yield: 234 mg(75%), mp 202–205°C, IR (KBr): 3265, 3081, 1669, 1620, 1580, 1550, 1491 cm^{-1}, ^{1}HNMR (500 MHz, DMSO-d_6): 2.9 (t, $J = 7.8$ Hz, 2H, NCH_2CH_2), 3.63 (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 (dt, $J = 7.8$ 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); ^{13}CNMR (125 MHz, DMSO-d_6): 26.8, 45.4, 55.2, 110.0, 115.5, 120.3, 124.4, 126.5, 127.2, 127.8, 129.8, 135.4, 136.2, 139.0, 157.4, 159.1. *m/z* (%) = 312.09 (45, M^+), 257 (11), 229 (20), 178 (24), 134 (100), 111 (25), 91 (40), 69 (98). Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 64.96; H, 4.96; N, 8.57.

5.6. 6-Chloro-3-(3,4-dimethoxyphenethyl)-2,3-dihydro-2-thioxoquinazolin-4(1H)-one(4f).

White crystals; yield: 293 mg (78%), mp 245–248°C; IR (KBr): 3280, 3091, 1669, 1645, 1580, 1528, 1470 cm^{-1}. ^{1}HNMR (500 MHz, DMSO-d_6): 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, H6′), 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). ^{13}CNMR (125 MHz, DMSO-d_6): 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. Anal. Calcd for $C_{18}H_{17}ClN_2O_3S$: C, 57.37; H, 4.55; N, 7.43. Found: C, 56.97; H, 4.15; N, 7.03.

5.7. 3-(3,4-Dimethoxyphenethyl)-2,3-dihydro-2-thioxoquinazolin-4(1H)-one (4 g) [26].

White crystals; yield: 283 mg (83%), mp 230–232°C; IR (KBr): 3180, 3040, 1686, 1622, 1589, 1541 cm^{-1}. ^{1}HNMR (500 MHz, DMSO-d_6): 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). ^{13}CNMR (125 MHz, DMSO-d_6): 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. Anal. Calcd for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18. Found: C, 62.74; H, 4.90; N, 7.78.

5.8. 2,3-Dihydro-3-phenyl-2-thioxoquinazolin-4(1H)-one (4 h)

White crystals; yield: 156 mg (58%), mp 234–235°C ([18] > 260°C); IR (KBr): 3247, 3031, 1664, 1622, 1530, 1488 cm^{-1}. ^{1}HNMR (500 MHz, DMSO-d_6|): 7.27–7.28 (m, 2H, ArH), 7.35 (t, J = 7.7 Hz, 1H, H_6), 7.40–7.49 (m, 4H, 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). ^{13}CNMR (125 MHz, DMSO-d_6): 115.6, 116.1, 124.3, 127.4, 128.0, 128.8, 128.9, 135.5, 139.3, 139.6, 159.7.176.0. 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). Anal. Calcd for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.02. Found: C, 65.72; H, 3.56; N, 10.62.

5.9. 3-(3,4-Dimethoxyphenyl)-2,3-dihydro-2-thioquinazolin-4(1H)-one (4i) [19].

White crystals; yield: 241 mg (77%), mp 245–248°C; IR (KBr): 3180, 3030, 1696, 1648, 1623, 1537, 1488 cm^{-1}. ^{1}HNMR (500 MHz, DMSO-d_6): 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, H5′), 7.34 (t, J = 7.8 Hz, 1H, H6), 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). ^{13}CNMR (125 MHz, DMSO-d_6): 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. 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). Anal. Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.99; H, 5.20; N, 8.50. Found: C, 61.59; H, 4.60; N, 8.40.

5.10. 2,3-(Dihydro-3-(1-phenylethyl)-2-thioxoquinozolin-4(1H)-one (4j) [19].

White crystals; yield: 219 mg (78%), mp 237–239°C; IR (KBr): 3310, 3045, 1656, 1633, 1526, 1499 cm^{-1}. ^{1}HNMR (500 MHz, DMSO-d_6): 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, 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). ^{13}CNMR (125 MHz, DMSO-d_6): 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. Anal. Calcd for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92. Found: C, 67.66; H, 4.60; N, 9.32.

5.11. 3-(2-Chlorobenzyl)-2,3-dihydro-2-thioxoquinazolin-4(1H)-one (4k).

White crystals; yield: 256 mg (85%), mp 231–233°C ([18] 262°C); IR (KBr): 3182, 3043, 1680, 1630, 1560, 1498 cm^{-1}. ^{1}HNMR (500 MHz, DMSO-d_6): 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, H6), 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). ^{13}CNMR (125 MHz, DMSO-d_6): 48.0, 114.4,

125.2, 125.9, 126.7, 128.2, 128.9, 129.7, 131.1, 132.9, 135.0, 135.8, 138.3, 159.5, 176.2. Anal. Calcd for $C_{15}H_{11}ClN_2OS$: C, 59.50; H, 3.66; N, 9.25. Found: C, 59.10; H, 3.26; N, 8.85.

5.12. 3-(4-Chlorobenzyl)-2,3-dihydro-2-thioxoquinazolin-4(1H)-one (4 l).

White crystals; yield: 253 mg (84%), mp 227–229°C ([18] 230°C).

5.13. 2,3-Dihydro-3-propyl-2-thioxoquinazolin-4(1H)-one (4 m).

White crystals; yield: 162 mg (74%), mp 175–178°C ([35] 191°C); IR (KBr): 3190, 3052, 1699, 1648, 1596, 1435, 1501 cm^{-1}. ^{1}HNMR (500 MHz, DMSO-d_6): 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). ^{13}CNMR (125 MHz, DMSO-d_6): 11.2, 20.1, 48.4, 114.5, 116.2, 125.0, 128.5, 135.3, 138.4, 159.6, 175.7. Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 59.57; H, 5.09; N, 12.32.

5.14. 2,3-Dihydro-3-isopropyl-2-thioxoquinazolin-4(1H)-one (4n).

White crystals; yield: 154 mg (70%), mp 202–204°C ([37,38]177–179°C); IR (KBr): 3191, 3055, 1690, 1628, 1625, 1535, 1480 cm^{-1}. ^{1}HNMR (500 MHz, DMSO-d_6): 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 (t, d, 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). ^{13}CNMR (125 MHz, DMSO-d_6): 18.5, 52.5, 115.3, 116.7, 124.4, 126.9, 135.2, 138.8, 159.4, 175.2. Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72. Found: C, 59.57; H, 5.09; N, 12.32.

5.15. 3-Butyl-2,3-dihydro-2-thioxoquinazolin-4(1H)-one (4o).

White crystals; yield: 159 mg (68%), mp 183–185°C ([34,35,39]175–176°C). [40] ^{1}H NMR (500 MHz, DMSO-d_6): d 0.94 (t, 3H, J = 6.8 Hz), 1.31–1.42(m, 2H), 1.63–1.72 (m, 2H), 4.40 (t, 2H, J = 6.8 Hz), 7.18–7.20 (m, 2H) 7.74 (t, 1H, J = 6.8 Hz), 7.96 (d, 1H, J = 6.8 Hz), 12.90 (brs, 1H,NH). MS (70 eV): m/z (%) = 234 [M^+] (12), 177 (41), 77 (53), 43 (100). Anal. Calcd for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.11; H, 4.62; N, 11.56.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by grants from PNU, INSF and Tehran University of Medical Sciences as research project [Grant No: 33150-33-03-95].

References

[1] Clark JH. Green chemistry: challenges and opportunities. Green chem. 1999;1:1–8.

[2] Sheldon R. Green solvents for sustainable organic synthesis: state of the art. Green Chem. 2005;7:267–278.
[3] Ghaedi A, Bardajee GR, Mirshokrayi A, et al. Facile, novel and efficient synthesis of new pyrazolo[3,4-b]pyridine products from condensation of pyrazole-5-amine derivatives and activated carbonyl groups. RSC Adv. 2015;5:89652–89658.
[4] Tanaka K, Toda F. Solvent-free organic synthesis. Chem Rev. 2000;100:1025–1074.
[5] Chermahini AN, Teimouri A, Momenbeik F, et al. Clay-catalyzed synthesis of 5-substituent 1-H-tetrazoles. J Heterocycl Chem. 2010;47:913–922.
[6] Ozaki K, Yamada Y, Oine T, et al. Studies on 4(1H)-quinazolinones. 5. synthesis and antiinflammatory activity of 4(1H)-quinazolinone derivatives. J Med Chem. 1985;28:568–576.
[7] Choo HYP, Kim M, Lee SK, et al. Solid-phase combinatorial synthesis and cytotoxicity of 3-aryl-2,4-quinazolindiones. Bioorg Med Chem. 2002;10:517–523.
[8] Castano T, Wang H, Campillo NE, et al. Synthesis, structural analysis, and biological evaluation of thioxoquinazoline derivatives as phosphodiesterase7 inhibitors. Chem Med Chem. 2009;4:866–876.
[9] Ji F, Lv MF, Yi WB, et al. One-pot synthesis of 2-amino-4(3H)-quinazolinones via ring-opening of isatoic anhydride and palladium-catalyzed oxidative isocyanide-insertion. Org Biomol Chem. 2014;12:5766–5772.
[10] Rajasekaran A, Rajamanickam V, Darlinquine S. Synthesis of some new thioxoquinazolinone derivatives and a study on their anticonvulsant and antimicrobial activities. Eur Rev Med Pharmacol Sci. 2013;17:95–104.
[11] Alagarsamy V, Raja Solomon V, Dhanabal K. Synthesis and pharmacological evaluation of some 3-phenyl-2-substituted-3H-quinazolin-4-one as analgesic, anti-inflammatory agents. Bioorg Med Chem. 2007;15:235–241.
[12] Asif M. Chemical characteristics, synthetic methods, and biological potential of quinazoline and quinazolinone derivatives. Int J Med Chem. 2014;2014:1–27.
[13] Lemaire C, Cantineau R, Guillaume M, et al. Fluorine-18-altanserin: a radio ligand for the study of serotonin receptors with PET: radiolabeling and in vivo biologic behavior in rats. J Nucl Med. 1991;32:2266–2272.
[14] Li Z, Huang H, Sun H, et al. Microwave-assisted efficient and convenient synthesis of 2,4(1H,3H)-quinazolinediones and 2-thioxoquinazolines. J Comb Chem. 2008;10:484–486.
[15] Kobayashi H, Yokoi Y, Konishi H. One-pot synthesis of 3-arylquinazoline-2,4 (1*H*,3*H*)-dithiones by the reaction of 2-lithiophenyl isothiocyanates with aryl isothiocyanates. Synthesis (Mass). 2011;2011:1526–1528.
[16] Saeed A, Shaheen U, Bolte M. Synthesis, characterization and crystal structure of some novel 1-aryl-2-thioxo-2,3-dihydro-1h-quinazolin-4-ones. J Chin Chem Soc. 2010;57:82–88.
[17] Saeed A, Florke U. Synthesis and crystal structure of 1-(3-fluorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one. Crystals (Basel). 2011;1:254–259.
[18] Tiwari VK, Singh DD, Hussain HA, et al. One-pot, simple, and convenient synthesis of 2-thioxo-2,3-dihydroquinazolin-4(1H)-ones. Monatsh Chem. 2008;139:43–48.
[19] Hatamjafari F, Rad-Moghadam R. Synthesis of 2-thioxoquinazolin-4(1H)-ones in warer at room temperature. Eur Chem Bull. 2014;3:719–722.
[20] Dou GL, Wang MM, Huang ZB, et al. One-pot synthesis of quinazoline-2,4(1H,3H)-diones and 2-thioxoquinazolinones with the aid of low-valent titanium reagent. J Heterocycl Chem. 2009;46:645–649.
[21] Castro A, Jerez MJ, Gil C, et al. CODES, a novel procedure for ligand-based virtual screening: PDE7 inhibitors as an application example. Eur J Med Chem. 2008;43:1349–1359.
[22] Azizian J, Mohammadi AA, Karimi AR. An efficient one-pot procedure for preparation of 2,4 (1H,3H)-quinazolinediones and 2-thioxoquinazolinone derivatives under microwave irradiation. Synth Commun. 2003;33:415–420.
[23] He L, Li H, Chen J, et al. Recent advances in 4(3H)-quinazolinone syntheses. RSC Adv. 2014;4:12065–12077.

[24] Liu W, Zhang Q, Gong F, et al. A convenient and efficient synthesis of 2-thioxoquinazolinone derivatives via microwave irradiation. J Heterocycl Chem. 2015;52:317–321.
[25] Asadi M, Masoomi S, Ebrahimi SM, et al. Convenient and sequential one-pot route for synthesis of 2-thioxoquinazolinone and quinazolinobenzothiazinedione derivatives. Monatsh Chem. 2014;145:497–504.
[26] Numadate A, Mita Y, Matsumoto Y, et al. Development of 2-thioxoquinazoline-4-one derivatives as dual and selective inhibitors of dynamin-related protein 1 (Drp1) and puromycin-sensitive aminopeptidase (PSA). Chem Pharm Bull. 2014;62, 979–988.
[27] Mahdavi M, Asadi M, Saeedi M, et al. Synthesis of novel 1, 4-benzodiazepine-3, 5-dione derivatives: reaction of 2-aminobenzamides under bargellini reaction conditions. Synlett. 2012;23:2521–2525.
[28] Hosseini-Zare MS, Mahdavi M, Saeedi M, et al. Synthesis of 2,3-diaryl-5*H*-imidazo[2,1-*a*]isoindol-5-ones via the one-pot reaction of 1,2-diketones, 2-formylbenzoic acids, and ammonium acetate. Tetrahedron Lett. 2012;53:3448–3451.
[29] Mahdavi M, Asadi M, Saeedi M, et al. One-pot, four-component synthesis of novel imidazo[2,1-*b*]thiazol-5-amine derivatives. Synthesis (Mass). 2012;44:3649–3654.
[30] Tahghighi A, Razmi S, Mahdavi M, et al. Synthesis and anti-leishmanial activity of 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-amines containing *N*-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl] moieties. Eur J Med Chem. 2012;50:124–128.
[31] Khalaj A, Nakhjiri M, Negahbani AS, et al. Discovery of a novel nitroimidazolyl–oxazolidinone hybrid with potent antigram-positive activity: synthesis and antibacterial evaluation. Eur J Med Chem. 2011;46:65–70.
[32] Sunder S, Peet NP. Preparation of novel heterocyclic systems from isatoic anhydrides. J Heterocycl Chem. 1979;16:1339–1344.
[33] Wang M, Zhang TT, Liang Y, et al. Efficient synthesis of mono- and disubstituted 2,3-dihydroquinazolin-4(1H)-ones using copper benzenesulfonate as a reusable catalyst in aqueous solution. Monatsh Chem. 2012;143:835–839.
[34] Karimi-Jaberi Z, Arjmandi R. Acetic acid-promoted, efficient, one-pot synthesis of 2,3-dihydroquinazolin-4(1H)-ones. Monatsh Chem. 2011;142:631–635.
[35] Mahdavi M, Asadi M, Saeedi M, et al. Green synthesis of new boron-containing quinazolines: preparation of benzo[d][1,3,2]diazaborinin-4(1H)-one derivatives. Synth Commun. 2013;43:2936–2942.
[36] Clark RH, Wagner EC. Isatoic anhydride. I. Reactions with primary and secondary amines and with some amides1. J Org Chem. 1944;9:55–67.
[37] Staiger RP, Wagner EC. Isatoic anhydride. II. Reactions of isatoic anhydride with ammonia. J Org Chem. 1948;13:347–352.
[38] Monirah A, Danah A, Fatima E. Synthesis of some-2-thioxo-3-substituted-2,3-dihydro-1H-quinazolin-4-one derivatives as potential antibacterial and antifungal agents. Res J Chem Environ. 2013;17:48–52.
[39] Staiger RP, Miller EB. Isatoic anhydride. IV. Reactions with various nucleophiles. J Org Chem. 1959;24:1214–1219.
[40] Azizi N, Edrisi M. Practical approach to 2-thioxo-2,3-dihydroquinazolin-4(1H)-one via dithiocarbamate-anthranilic acid reaction. Chines Chem Lett. 2017;28:109–112.