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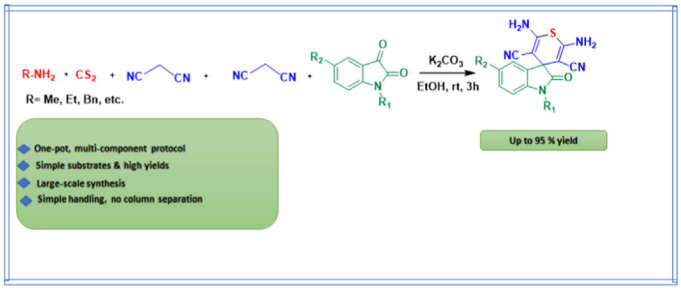
Research article

Facile one-pot, multi-component reaction to synthesize spirooxindole-annulated thiopyran derivatives under environmentally benevolent conditions

F. Matloubi Moghaddam *, Bagher Aghamiri

Laboratory of Organic Synthesis and Natural Products, Department of Chemistry, Sharif University of Technology, Azadi Street, PO Box 111559516, Tehran, Iran

GRAPHICAL ABSTRACT



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Multi-component reaction

ABSTRACT

An efficient and facile one-pot, five-component reaction for the synthesis of 2,6-diamino-1-alkyl-2-oxospiro [indoline-3,4′-thiopyran]-3,5-dicarbonitrile derivatives has been reported by a reaction between primary amines, carbon disulfide, malononitrile, and isatin derivatives. The major advantages of this procedure are high yields of products in relatively short reaction time, scalability, mild conditions, multi-component synthetic procedure, low catalyst loading, no column separation and simple reaction work-up. As a consequence, this synthetic procedure provided an efficient access to spirooxindole-annulated thiopyran derivatives.

1. Introduction

One of the main issues today is reducing environmental pollution in the chemical process that has been addressed with the advent of green chemistry, initiated in the 1990s. Green chemistry and clean processes are common ways of keeping the organic pollution down [1]. Today, sulfur-containing heterocycles are attractive scaffolds in organic chemistry and therefore have created tremendous appetite among organic chemists to make efforts to construct them, especially under environmentally friendly conditions. Dithiocarbamates have become particularly valuable due to their large utility in construction of *S*-containing heterocyclic compounds [2, 3, 4, 5, 6]. Among the *S*-containing heterocyclic compounds, thiopyran scaffolds have been carefully examined by scientists, and studies have validated their notable features, such as antiviral and antimicrobial properties. Moreover, one of the striking features of these motifs is their application in the treatment of cancer [7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18]. In consequence, chemists are hunting new ways to create various thiopyran-containing heterocycles. For example, Rajabi et al. investigated the influence of some novel thiopyran analogs on breast and colon cancer cells [19]. Recently, Asghari and co-workers developed

* Corresponding author.
E-mail address: matloubi@sharif.edu (F. Matloubi Moghaddam).

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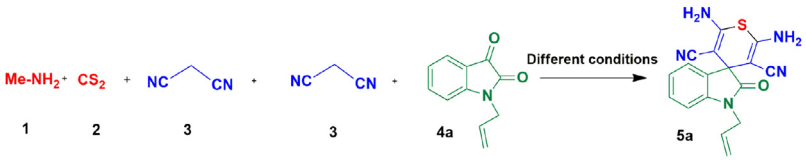
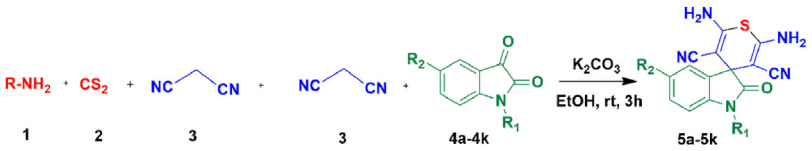
Table 1. Screening the optimal reaction conditions.

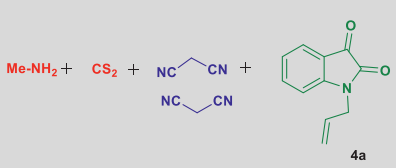
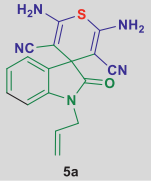
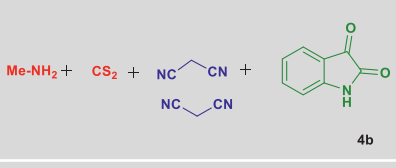
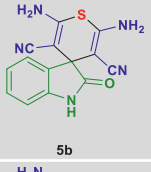
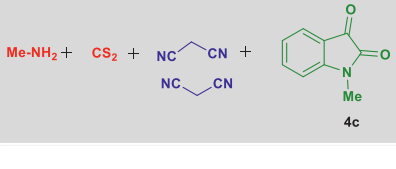
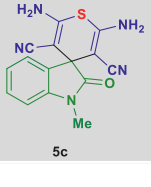


Entry[a]	Cat. (20 mol%)	Solvent	Temp. (°C)	Time	Yield[b] (%)
1	–	PEG-400	25	3h	20
2	–	H_2O	25	3h	-
3	–	CH_3CN	25	3h	30
4	–	THF	25	3h	20
5	–	DCM	25	3h	60
6	K_2CO_3	DCM	25	3h	70
7	Et_3N	DCM	25	3h	65
8	pyridine	DCM	25	3h	67
9	–	$CHCl_3$	25	3h	55
10	K_2CO_3	$CHCl_3$	25	3h	65
11	Et_3N	$CHCl_3$	25	3h	60
12	pyridine	$CHCl_3$	25	3h	65
13	–	EtOH	25	3h	65
14	Et_3N	EtOH	25	3h	80
15[c]	**K_2CO_3**	**EtOH**	**25**	**3h**	**85**
16	pyridine	EtOH	25	3h	80
17	DABCO	EtOH	25	3h	75
18	NaOH	EtOH	25	3h	80

[a] Reaction conditions: Reaction of **1** (0.6 mmol), **2** (0.7 mmol), **3** (1.4 mmol) and **4a** (0.57 mmol) was performed in the presence of 20% mole of catalyst.
[b] Isolated yields of **5**a after filtering of reaction mixture. Simple dispersing of the reaction mixture in water and its subsequent filtering and washing with EtOH afforded desired product.
[c] optimal reaction condition.

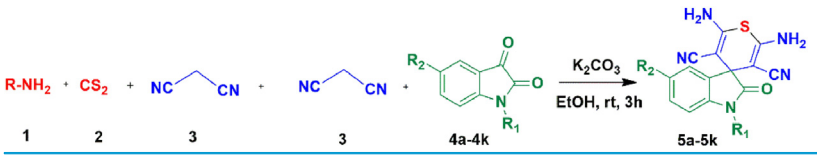
Table 2. One-pot, five-component reaction of methyl amine (1), carbon disulfide (2), malononitrile (3) and isatin derivatives (4a-k) catalyzed by K_2CO_3 under the optimized conditions.[a]



En.	Starting materials	Product	Time (h)	Yield[b](%)	M.P (°C)
1			3h	85	228–230
2			3h	95	220–222
3			3h	85	238–240

(*continued on next page*)

Table 2 (*continued*)

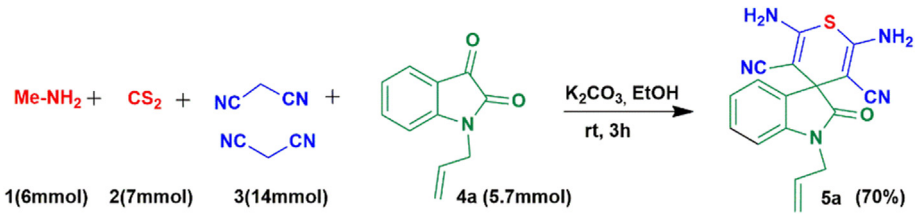


1 2 3 3

En.	Starting materials	Product	Time (h)	Yield[b](%)	M.P (°C)
4	MeNH2 + CS2 + malononitrile + 4d	5d	3h	80	232–234
5	Me-NH2 + CS2 + malononitrile + 4e	5e	3h	78	240–242
6	Me-NH2 + CS2 + malononitrile + 4f	5f	3h	85	224–226
7	Me-NH2 + CS2 + malononitrile + 4g	5g	3h	75	242–244
8	Me-NH2 + CS2 + malononitrile + 4h	5h	3h	80	210–212
9	Me-NH2 + CS2 + malononitrile + 4i	5i	3h	76	248–250
10	Me-NH2 + CS2 + malononitrile + 4j	5j	6h	trace	–
11	Me-NH2 + CS2 + malononitrile + 4k	5k	3h	87	238–240

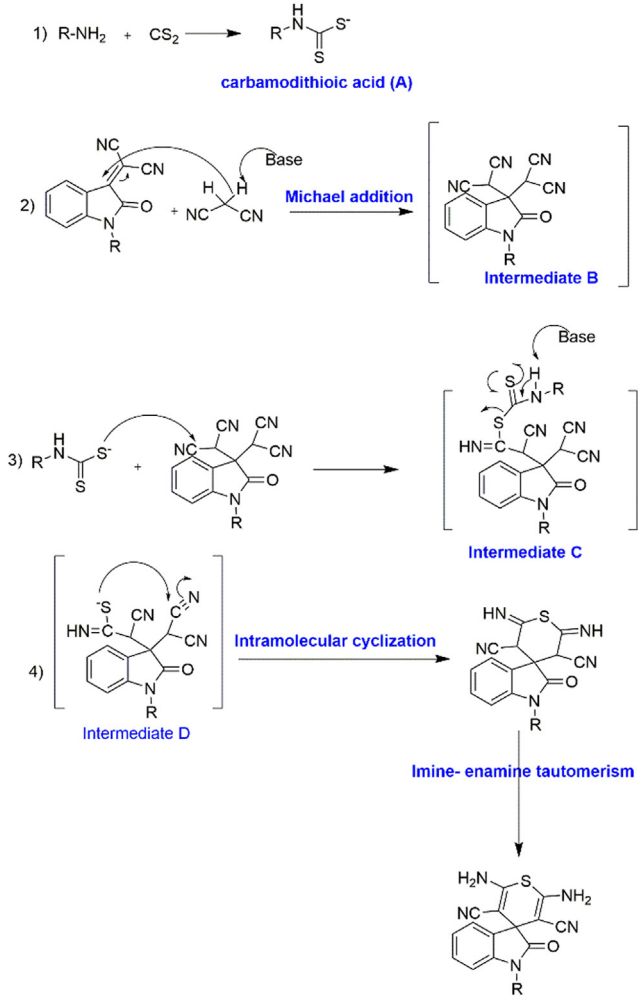
[a] Reaction conditions: Reaction of methyl amine (0.6 mmol), carbon disulfide (0.7 mmol), malononitrile (1.4 mmol) and isatin derivatives (0.57 mmol) was performed in EtOH (1 ml).

[b] The yields refer to the isolated pure products. Simple dispersing of the reaction mixture in water and its subsequent filtering and washing with EtOH afforded desired product.



Scheme 1. Scale-up reaction.

an effective method for forming thiopyran derivatives and then evaluated their antibacterial and antifungal activities [20]. Furthermore, Vliet et al. reported the synthesis and biological evaluation of thiopyran analogues [21]. On the other hand, oxindole motifs are introduced as important organic scaffolds because these molecules show unprecedented benefits to medicinal chemistry. In addition to this, oxindole motifs are present in many natural products and agrochemicals. Also, sulfur-containing spiro heterocyclic oxindoles are of considerable importance in treatment of cancer disease and therefore chemists have carried out various studies into sulfur-containing spiro heterocyclic oxindole scaffolds [22, 23]. For example, Sheng et al. reported an efficient method for the synthesis of spiro-tetrahydrothiopyran-oxindoles with good antitumor activity [24]. Majumdar and coworkers reported One-pot efficient route for the synthesis of spirooxindole-annulated thiopyran derivatives [25]. Synthesis and pharmacological evaluation of novel antitumor spirodihyd rothiopyran-oxindole derivatives was also reported by Sheng et al. [26] Considering all these facts, the resulting molecules bearing oxindole and thiopyran scaffolds have provided some tangible benefits to medicinal chemistry and therefore have found application as scaffolds for drug discovery. Encouraged by this reality, we began our initial investigations into the synthesis of sulfur-containing spiro heterocyclic oxindoles in green condition. To obtain molecules containing these two important scaffolds, our initial hypothesis was tested by employing a reaction between primary amines, carbon disulfide, malononitrile, and isatin derivatives. In this publication, we would like to report a scalable high-yielding synthesis of 2, 6-diamino-1-alkyl-2oxospiro[indoline-3,4′-thiopyran]-3,5-dicarbonitrile derivatives in the mild condition.



Scheme 2. Anticipated mechanism for the formation of final products.

2. Result and discussion

Initially, we investigated the reaction of methylamine (**1**), carbon disulfide (**2**), malononitrile (**3**) and 1-allylindoline-2,3-dione (**4a**) as the model reaction (Table 1). Hence, a mixture of **1** (0.6 mmol), **2** (0.7 mmol) in EtOH (1 ml) was mixed and stirred at room temperature for 2 min, then **3** (1.4 mmol)) and **4a** (0.57 mmol) were added in the presence of K_2CO_3 and stirred for more 3h to afford the corresponding 1-allyl-2′,6′-diamino-2-oxospiro[indoline-3,4′-thiopyran]-3′,5′-dicarbonitrile (**5a**) in high yield. Then, different solvents and bases were screened to achieve the optimal reaction conditions. The influence of different bases on the reaction was first checked. The reaction was found to proceed better in the presence of base as catalyst (Table 1, entries 6–18). For better results, different reaction solvents were also assessed. EtOH was selected not only as a green but also as an efficient solvent in this reaction and found to be suitable for the model reaction (Table 1, entries 13–18). All in all, the best results were obtained with K_2CO_3 as the catalyst and EtOH as solvent at 25 °C and 3h of stirring.

Encouraged by this green and simple approach for the synthesis of 2,6-diamino-1-alkyl-2-oxospiro[indoline-3,4′-thiopyran]-3,5-dicarbonitrile derivatives, the general scope of the reaction was investigated using various isatin derivatives (Table 2). The reaction proceeded well with a variety of substituents on the nitrogen atom as well as the aromatic ring of the isatin derivatives. To our delight, the desired sulfur-containing spiro heterocyclic oxindoles were obtained in high yields.

The solid products were obtained in high yields (up to 95%). The structure of final products were characterized through NMR, elemental and FT-IR spectral analysis. Due to the lack of chiral inducing agents, the products were racemic mixtures with 0% ee value.

For further investigation of the potential practicability of this designed synthetic procedure as a useful tool in organic synthesis, we enlarged the reaction into a gram scale (Scheme 1). We were delighted to provide the product 5a in 70% yield.

Subsequently, to define the sequence of steps in the reaction, the reaction mechanism was investigated (Scheme 2). In the beginning, the primary amine **1** reacts with carbon disulfide **2** to generate carbamodithioic acid A. Afterward, under the basic media, carbanion of malononitrile is generated and attacks to isatin derivatives to afford cyano-substituted alkenyl oxindoles. Another attack of malononitrile on cyano-substituted alkenyl oxindoles lead to generation of the intermediate B. Next, the Michael addition of carbamodithioic acid A to intermediate B produce intermediate C. A hydrogen transfer and carbon-sulfur bond disconnection leads to formation of intermediate D. Another attack on C≡N, cyclization and then imine-enamine tautomerization leads to provide the final products.

3. Conclusion

In summary, regarding the potential value of sulfur-containing spiro heterocyclic oxindoles in medicinal chemistry, we have introduced a facile and efficient green protocol for the synthesis of 2,6-diamino-1-alkyl-2-oxospiro[indoline-3,4′-thiopyran]-3,5-dicarbonitrile derivatives. The green parameters of this synthetic protocol are high yields of products in relatively short reaction time, mild reaction conditions, multi-component synthetic approach, low catalyst loading, no column separation and simple reaction work-up. Needless to say, the above-mentioned features are of paramount importance for industrial applications. In addition to this, to demonstrate the promising applicability of this synthetic procedure, a large scale preparation of the products was also effectively done.

4. Experimental section

General Remarks. All solvents and starting materials were purchased from Merck and Sigma-Aldrich used without any additional purification. Analytical TLC was carried out using Merck 0.2 mm silica gel 60 F-254 Al-plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-400 machine using DMSO-d6 as solvent and TMS as an internal standard at room temperature (DMSO-d6 1HNMR: δ (ppm) = 2.50 ppm;^{13}C-NMR: δ (ppm) = 39.9 ppm). Chemical shifts were reported in ppm scale. FT-IR spectra of samples were obtained on ABB Bomem MB100 spectrometer with potassium bromide (KBr) pellets. Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected.

4.1. Experimental procedure for the synthesis of 5a-5k

To a solution of primary amines (0.6 mmol) in EtOH (1 ml), Carbon disulfide (0.7 mmol) was added and stirred at room temperature for 2 min. Then isatin derivatives (0.57 mmol) and malononitrile (1.4 mmol) were added to the previous mixture in the presence of K_2CO_3 (20 mol%) and stirred for more 3 h. Upon completion of the reaction, a little amount of water (3 ml) was added to the reaction mixture until the organic products separated from ethanol as a solid precipitate. After final filtration, the pure products **5a-5k** were dried in air and directly characterized by ^{1}H NMR, ^{13}C NMR, elemental and FT-IR analysis.

4.1.1. 1-Allyl-2′,6′-diamino-2-oxospiro[indoline-3,4′-thiopyran]-3′,5′-dicarbonitrile (5a)

yellowish solid; yield 90%; m.p. 228–230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.32 (2H, br s), 5.15 (2H, q, J = 4.0 Hz), 5.81 (1H, m), 6.96 (1H, d, J = 8.0 Hz), 7.10 (1H, t, J = 8.0 Hz), 7.23 (4H, br s), 7.28 (2H, m) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 42.1, 52.2, 69.8, 110.0, 116.7, 117.2, 123.7, 125.1, 129.8, 131.7, 132.5, 142.3, 153.1, 176.3 ppm; IR (KBr) ν = 3315, 3208, 2190, 1710, 1591 cm^{-1}; Anal. Calcd. for $C_{17}H_{13}N_5OS$: C, 60.88; H, 3.91; N, 20.88; Found: C, 60.69; H, 3.97; N, 20.66%.

4.1.2. 2′,6′-Diamino-2-oxospiro[indoline-3,4′-thiopyran]-3′,5′-dicarbonitrile (5b)

yellowish solid; yield 95%; m.p. 220–222 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.85 (1H, d, J = 8.0 Hz), 7.02 (1H, t, J = 8.0 Hz), 7.16 (4H, br s), 7.24 (2H, t, J = 8.0 Hz), 10.56 (1H, s) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 52.6, 70.1, 110.3, 117.2, 123.0, 125.2, 129.7, 133.5, 141.8, 152.7, 178.0 ppm; IR (KBr) ν = 3318, 3199, 2190, 1715, 1591 cm^{-1}; Anal. Calcd. for $C_{14}H_9N_5OS$: C, 56.94; H, 3.07; N, 23.71; Found: C, 56.87; H, 3.16; N, 23.56%.

4.1.3. 2′,6′-Diamino-1-methyl-2-oxospiro[indoline-3,4′-thiopyran]-3′,5′-dicarbonitrile (5c)

white solid; yield 85%; m.p. 238–240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.15 (3H, s), 7.10 (1H, t, J = 8.0 Hz), 7.12 (1H, d, 8.0 Hz), 7.19 (4H, br s), 7.25 (1H, d, 8.0 Hz), 7.36 (1H, t, 8.0 Hz) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 26.8, 52.2, 69.8, 109.4, 117.1, 123.7, 124.9, 129.9, 132.6, 143.2, 153.0, 176.4 ppm; IR (KBr) ν = 3318, 3208, 2195, 1709, 1646 cm^{-1}; Anal. Calcd. for $C_{15}H_{11}N_5OS$: C, 58.24; H, 3.58; N, 22.64; Found: C, 58.08; H, 3.69; N, 22.16%.

4.1.4. 2′,6′-Diamino-2-oxo-1-propylspiro[indoline-3,4′-thiopyran]-3′,5′-dicarbonitrile (5d)

white solid; yield 80%; m.p. 232–234 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.89 (3H, t, J = 8.0 Hz), 1.61 (2H, q, J = 8.0 Hz), 3.65 (2H, t, J = 8.0 Hz), 7.11 (2H, d, J = 8.0 Hz), 7.19 (4H, br s), 7.25 (1H, d, J = 8.0 Hz), 7.33 (1H, t, J = 8.0 Hz) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 11.5, 20.7, 41.6, 52.2, 70.0, 109.6, 117.0, 123.5, 125.0, 129.8, 132.8, 142.7, 152.8, 176.4 ppm; IR (KBr) ν = 3345, 3215, 2210, 1700, 1605 cm^{-1}; Anal. Calcd. for $C_{17}H_{15}N_5OS$: C, 60.52; H, 4.48; N, 20.76; Found: C, 60.41; H, 4.54; N, 20.59%.

4.1.5. 2′,6′-diamino-2-oxo-1-(prop-2-yn-1-yl)spiro[indoline-3,4′-thiopyran]-3′,5′-dicarbonitrile (5e)

white solid; yield 78%; m.p. 240–242 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.27 (1H, t, J = 4.0 Hz), 4.53 (2H, d, J = 4.0 Hz), 7.16 (2H, t, J = 8.0 Hz), 7.25 (4H, br s), 7.29 (1H, d, J = 8.0 Hz), 7.39 (1H, t, J = 8.0 Hz) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 29.6, 69.6, 75.1, 78.1, 110.1, 116.9, 124.0, 125.2, 129.8, 132.3, 141.4, 153.3, 175.8 ppm; IR (KBr) ν = 3312, 3220, 2198, 1711, 1596 cm^{-1}; Anal. Calcd. for $C_{17}H_{11}N_5OS$: C, 61.25; H, 3.33; N, 21.01; Found: C, 61.09; H, 3.47; N, 20.76%.

4.1.6. 2′,6′-Diamino-1-benzyl-2-oxospiro[indoline-3,4′-thiopyran]-3′,5′-dicarbonitrile (5f)

white solid; yield 85%; m.p. 224–226 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.93 (2H, s), 6.87 (1H, d, J = 8.0 Hz), 7.10 (1H, t, J = 8.0 Hz), 7.15–7.30 (9H, m), 7.35 (2H, t, J = 8.0 Hz) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 43.5, 52.2, 69.8, 110.0, 117.2, 123.8, 125.2, 127.4, 127.8, 128.9, 129.8, 132.6, 142.3, 153.2, 176.7 ppm; IR (KBr) ν = 3312, 3214, 2195, 1702, 1601 cm^{-1}; Anal. Calcd. for $C_{21}H_{15}N_5OS$: C, 65.44; H, 3.92; N, 18.17; Found: C, 65.32; H, 4.07; N, 17.96%.

4.1.7. 2′,6′-Diamino-5-chloro-1-methyl-2-oxospiro[indoline-3,4′-thiopyran]-3′,5′-dicarbonitrile (5g)

Yellowish solid; yield 75%; m.p. 242–244 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.15 (3H, s), 7.13 (1H, d, J = 8.0 Hz), 7.30 (4H, br s), 7.33 (1H, s), 7.43 (1H, d, 8.0 Hz) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 27.0, 52.5, 68.9, 111.0, 117.0, 125.0, 127.7, 129.9, 134.5, 142.2, 153.3, 176.1 ppm; IR (KBr) ν = 3305, 3204, 2195, 1711, 1578 cm^{-1}; Anal. Calcd. for $C_{15}H_{10}ClN_5OS$: C, 52.41; H, 2.93; N, 20.37; Found: C, 52.30; H, 3.11; N, 20.19%.

4.1.8. 2′,6′-Diamino-5-chloro-2-oxo-1-propylspiro[indoline-3,4′-thiopyran]-3′,5′-dicarbonitrile (5h)

white solid; yield 80%; m.p. 210–212 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.88 (3H, t, J = 8.0 Hz), 1.60 (2H, q, J = 8.0 Hz), 3.66 (2H, t, J = 8.0 Hz), 7.17 (1H, d, J = 8.0 Hz), 7.28 (4H, br s), 7.32 (1H, s), 7.41 (1H, d, J = 8.0 Hz) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 11.4, 20.6, 41.7, 52.5, 69.0, 111.3, 117.0, 125.0, 127.5, 129.8, 134.8, 141.7, 153.1, 176.1 ppm; IR (KBr) ν = 3314, 3209, 2185, 1713, 1644 cm^{-1}; Anal. Calcd. for $C_{17}H_{14}ClN_5OS$: C, 54.91; H, 3.80; N, 18.83; Found: C, 54.78; H, 3.91; N, 18.64%.

4.1.9. 2′,6′-Diamino-1-benzyl-5-chloro-2-oxospiro[indoline-3,4′-thiopyran]-3′,5′-dicarbonitrile (5i)

white solid; yield 76%; m.p. 248–250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.36 (2H, s), 7.05 (6H, br s), 7.26 (2H, d, J = 8.0 Hz), 7.35 (2H, t, J = 8.0 Hz), 7.42 (1H, s), 7.48 (2H, d, J = 8.0 Hz) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 37.7, 68.7, 116.1, 118.5, 126.5, 127.4, 127.7, 130.5, 130.6, 134.0, 134.7, 151.8, 160.8, 163.4 ppm; IR (KBr) ν = 3330, 3224, 2198, 1705, 1605 cm^{-1}; Anal. Calcd. for $C_{21}H_{14}ClN_5OS$: C, 60.07; H, 3.36; N, 16.68; Found: C, 59.88; H, 3.48; N, 16.51%.

4.1.10. 2′,6′-Diamino-1-ethyl-2-oxospiro[indoline-3,4′-thiopyran]-3′,5′-dicarbonitrile (5k)

white solid; yield 87%; m.p. 238–240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (3H, t, J = 8.0 Hz), 3.72 (2H, q, J = 8.0 Hz), 7.11 (2H, d, J = 8.0 Hz), 7.18 (4H, br s), 7.25 (1H, d, J = 8.0 Hz), 7.33 (1H, t, J = 8.0 Hz) ppm; ^{13}C NMR (176 MHz, DMSO-d_6) δ 12.8, 34.9, 52.2, 69.9, 109.4, 117.0, 123.6, 125.0, 129.9, 133.0, 142.0, 152.7, 175.9 ppm; IR (KBr) ν = 3318, 3211, 2188, 1718, 1640 cm^{-1}; Anal. Calcd. for $C_{16}H_{13}N_5OS$: C, 59.43; H, 4.05; N, 21.66; Found: C, 59.31; H, 4.17; N, 21.48%.

Declarations

Author contribution statement

F. Matloubi Moghaddam: Analyzed and interpreted the data.

Bagher Aghamiri: Conceived and designed the experiments; Wrote the paper.

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The authors declare no conflict of interest.

Additional information

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