Organic Preparations and Procedures International
The New Journal for Organic Synthesis

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/uopp20

Catalyst-free Facile Synthesis of Novel Fused Spiro[benzo[4,5]thiazolo[3,2-*a*]pyrano[2,3-*d*]pyrimidine-4,3'-indoline]-3-carbonitrile Derivatives *via* One-pot Three-Component Reaction

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To cite this article: Maryam Khalili, Abbas Ali Esmaeili & Amir Khojastehnezhad (2022): Catalyst-free Facile Synthesis of Novel Fused Spiro[benzo[4,5]thiazolo[3,2-*a*]pyrano[2,3-*d*]pyrimidine-4,3'-indoline]-3-carbonitrile Derivatives *via* One-pot Three-Component Reaction, Organic Preparations and Procedures International, DOI: 10.1080/00304948.2021.2011577

To link to this article: https://doi.org/10.1080/00304948.2021.2011577

ORGANIC PREPARATIONS AND PROCEDURES INTERNATIONAL
https://doi.org/10.1080/00304948.2021.2011577

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EXPERIMENTAL PAPER

Catalyst-free Facile Synthesis of Novel Fused Spiro[benzo[4,5]thiazolo[3,2-*a*]pyrano[2,3-*d*]pyrimidine-4,3′-indoline]-3-carbonitrile Derivatives *via* One-pot Three-Component Reaction

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ARTICLE HISTORY Received 27 May 2021; Accepted 3 November 2021

These days, multicomponent reactions (MCRs) are attracting considerable attention in medicinal, combinatorial and organic chemistry, owing to their great benefits. These benefits include high efficiency and selectivity, short reaction times, and simplicity.[1–4] Several starting materials combine in a single synthetic operation to form complex organic structures that may have the potential to be used in chemical products and pharmaceuticals.[5–8] As powerful synthetic tools, MCRs provide a wide variety of biologically active heterocyclic compounds and are useful in organic total synthesis. [9–12]

Spirooxindole compounds are a promising class of spiro heterocyclic compounds with unique three dimensional structural features, and they are found in synthetic biologically active compounds as well as natural products.[13–15] As examples, they have demonstrated antimalarial, antifungal, antitubercular and anticancer activities.[16–18] Representative spirooxindoles are NITD609 (antibacterial agent and antimalarial drug),[19] MK-1602 (reported to treat migraine),[20] and MI-77301 (with anticancer activity)[21] (Figure 1).

Thiazolopyrimidines exhibit a diverse range of pharmaceutical and biological activities. Among these, we may note antibacterial,[22] antimicrobial,[23] anti-inflammatory,[24,25] antihypertensive,[26] antinociceptive,[27] and anticancer[28] properties.

In continuation of our ongoing efforts for the synthesis of novel heterocycles from readily available starting materials,[29–36] we now report on the preparation of the new thiazolopyrimidine dione (**3**, Scheme 1), and the dione has been used for the synthesis of novel 2-amino-2′,5-dioxo-7,8,9,10-tetrahydro-5*H*-spiro[benzo[4,5]thiazolo[3,2-*a*]pyrano[2,3-*d*]pyrimidine-4,3′-indoline]-3-carbonitrile derivatives (**6a-m**). This was accomplished *via* a one-pot three-component condensation reaction among **3**, isatin derivatives (**4a-m**), and malononitrile (**5**). To the best of our knowledge, this is the first report for the synthesis of compounds **6** from the dione Scheme 2).

Initially, in order to find the optimized reaction conditions, we chose the three-component reaction of **3**, isatin (**4a**), and malononitrile (**5**) as a model (Table 1). The model reaction was examined in toluene, DMF, THF, MeCN, PEG (400), glycerin, EtOH and H_2O and also under solvent-free conditions without the use of any acidic or

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/00304948.2021.2011577.

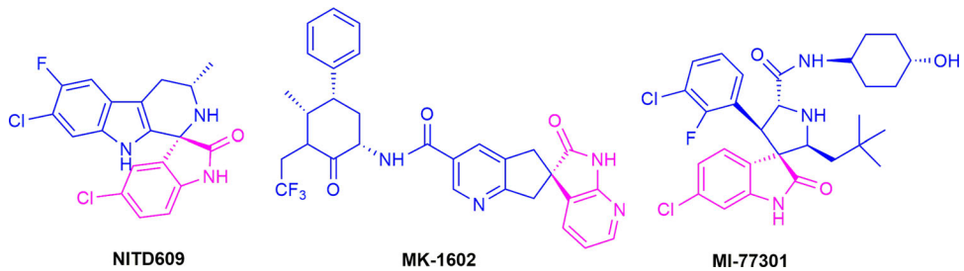
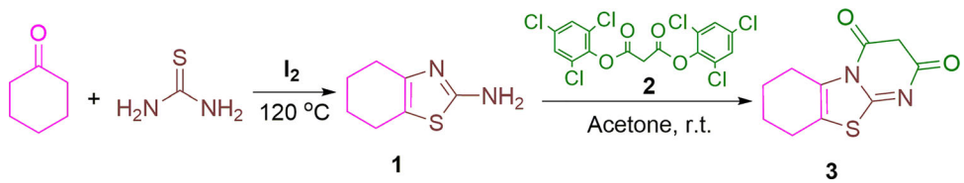
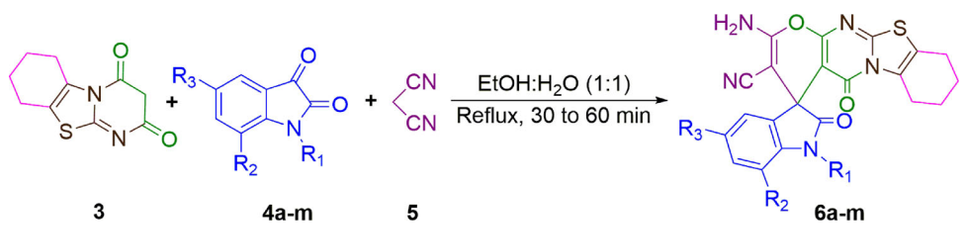


Figure 1. Examples of biologically active spiroxindoles.



Scheme 1. Synthesis of 6,7,8,9-tetrahydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-2,4(3*H*)-dione (3).

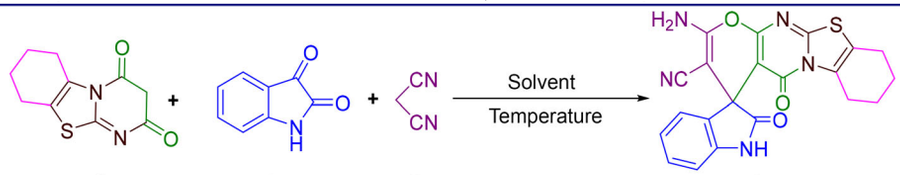


Scheme 2. Synthesis of 2-amino-2′,5-dioxo-7,8,9,10-tetrahydro-5*H*-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-*d*]pyrimidine-4,3′-indoline]-3-carbonitrile derivatives (**6a-m**).

basic catalysts (Table 1, entries 1-9). The yield of the model reaction was low (30%) under solvent-free conditions, after 24 h at 90 °C (Table 1, entry 1). The yield of the reaction in EtOH and H_2O (Table 1, entries 8 and 9) was better compared to other solvents (Table 1, entries 2-7). As a consequence, in the next experiments, we examined the model reaction in mixtures of ethanol and water at different temperatures (Table 1, entries 11-16). In ethanol:water (1:1), the yield of the reaction was increased significantly after only 30 min at reflux (Table 1, entry 10). With other ratios of ethanol and water and lower temperatures (25 and 50 °C), the yields and times of the reaction were less desirable (Table 1, entries 11-16). Thus, the best result was the use of EtOH:H_2O (1:1) at reflux. It was gratifying that the best results were obtained in a greener solvent mixture.

After finding the optimized reaction conditions, the generality of this reaction was investigated for the synthesis of compounds **6a-m** (Table 2). All isatin derivatives, including those with electron-withdrawing or electron-donating groups, gave the final products with excellent yields (mean 92%) in short reaction times (30 to 60 min) (Table 2).

Table 1. Optimization of reaction conditions for the synthesis of compound 6a.



3 **4a** **5** **6a**

Entry	Solvent	Temperature (°C)	Yield (%)	Time (h)
1	Solvent free	90	30	24
2	Toluene	reflux	50	24
3	DMF	100	30	24
4	THF	reflux	50	24
5	MeCN	reflux	40	24
6	PEG	120	55	3.0
7	Glycerin	140	65	3.0
8	EtOH	reflux	80	3.0
9	H_2O	reflux	90	3.0
10	EtOH:H_2O (1:1)	reflux	98	30 (min)
11	EtOH:H_2O (1:1)	25	30	24
12	EtOH:H_2O (1:1)	50	40	24
13	EtOH:H_2O (1:2)	reflux	85	30 (min)
14	EtOH:H_2O (1:3)	reflux	70	30 (min)
15	EtOH:H_2O (2:1)	reflux	50	30 (min)
16	EtOH:H_2O (3:1)	reflux	30	30 (min)

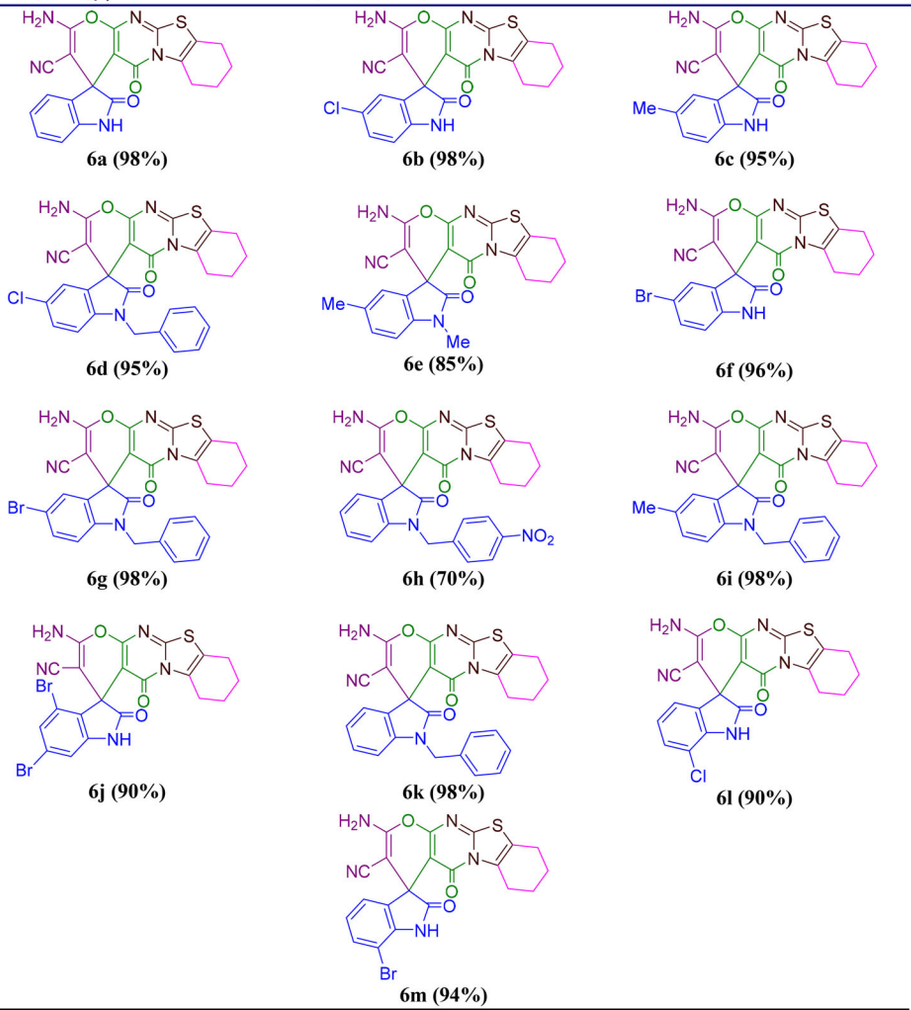
Reaction conditions: isatin (1.0 mmol), malononitrile (1.2 mmol), 6,7,8,9-tetrahydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-2,4(3*H*)-dione (1.0 mmol).

A proposed mechanism is drawn (Scheme 3) for the novel title compounds. In the first step, the condensation reaction of isatin (**4**) with malononitrile (**5**), forms intermediate **(A)**. This intermediate can react with dione **3** *via* Michael addition to produce the intermediate (**B**). Subsequently, after the 6-exo-dig-cyclization reaction of intermediate (**B**), the observed product **(6)** was generated. The mechanism is consistent with the fact that the reaction can be carried out without use of any catalysts.

The chemical structures of all products have been characterized with MS, FT-IR, ^{1}H NMR, ^{13}C NMR, and CHN analysis. For example, the ^{1}H NMR spectrum of product **6a** showed a multiplet with four protons for two central –CH_2– units in the cyclohexane ring at δ 1.67-1.76, a doublet with two protons for another –CH_2– unit at δ 2.62, a multiplet with two protons for yet another –CH_2– at δ 2.87-3.05, a doublet for CHAr with one proton at δ 6.82-6.84, a triplet for CHAr with one proton at δ 6.89-6.94, a doublet for CHAr with one proton at δ 7.06-7.08, a triplet for CHAr with one proton at δ 7.16-7.21, a singlet for NH_2 at δ 7.37, and finally a singlet for NH at δ 10.53. The IR absorption peaks at 3419 and 3328 cm^{-1} are assigned to the NH_2 group, the peak at 2204 cm^{-1} belongs to the CN moiety and the peaks at 1733 and 1657 are attributed to carbonyl groups. Moreover, the carbon NMR spectrum of **6a** exhibited 21 distinct ^{13}C NMR signals, particularly the carbonyls at δ 178 and 182 ppm, the nitrile at δ 117.9 ppm and the spiro carbon at 48.5 ppm.

In summary, a catalyst-free and facile procedure has been described for the synthesis of novel spiro heterocycles **6** *via* a one-pot three-component condensation reaction among dione **3**, isatins and malononitrile in ethanol/water. The short reaction times,

Table 2. Synthesis of different 2-amino-2′,5-dioxo-7,8,9,10-tetrahydro-5*H*-spiro[benzo[4,5]thiazolo[3,2-*a*]pyrano[2,3-*d*]pyrimidine-4,3′-indoline]-3-carbonitrile derivatives.

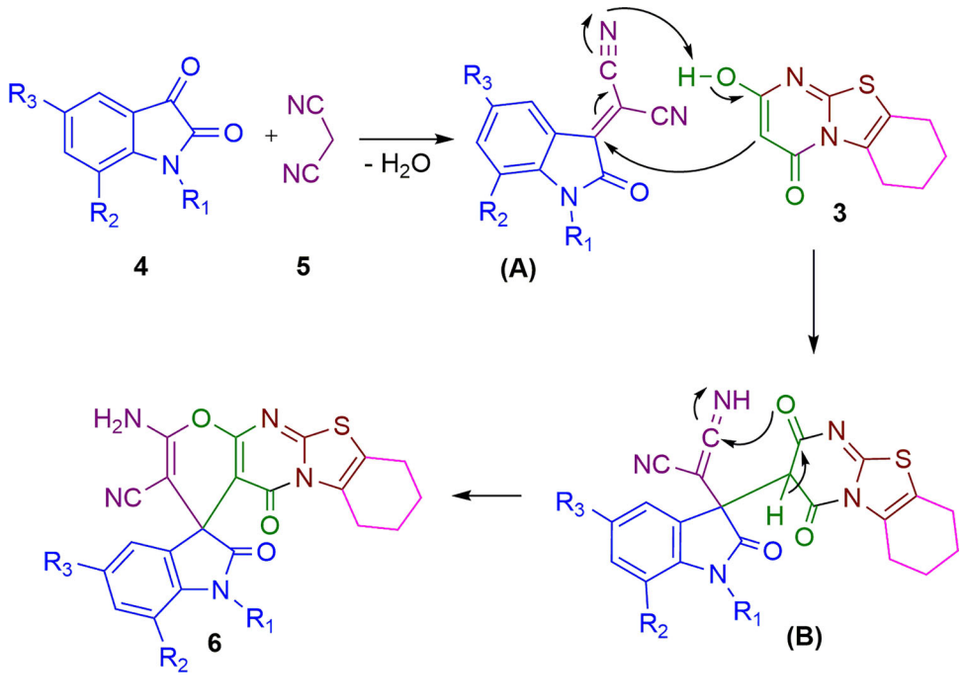


Reaction conditions: Isatin (1.0 mmol), malononitrile (1.2 mmol), 6,7,8,9-tetrahydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-2,4(3*H*)-dione (1.0 mmol) at reflux in EtOH:H_2O (1:1, 5 ml).

high isolated yields and absence of any need for catalyst are advantages of this method. We hope that the ready availability of these new spiro heterocycles will spur the further investigation of their intriguing structures and potential for biological activity.

Experimental section

All the starting materials were purchased from Sigma-Aldrich and Merck and were used without any further purification. Isatin derivatives were prepared by known methods.[37,38] Melting points were recorded on an Electrothermal type 9100 melting point apparatus and are uncorrected. Fourier transform infrared (FT-IR) spectra were recorded with a Nicolet Avatar 370 FT-IR Therma spectrometer. ^{1}H and ^{13}C NMR



Scheme 3. Proposed mechanism for the synthesis of compounds **6**.

spectra were measured with a Bruker DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. Elemental analyses were performed using a Thermo Finnegan Flash EA 1112 series instrument. Mass spectra were recorded with Agilent Technologies (HP) 5973 Network Mass Selective Detector and Shimadzu GC-MS-QP 5050 instrument at 70 eV. Thin layer chromatography (TLC) was carried out on silica gel using *n*-hexane/ethyl acetate as solvent.

6,7,8,9-Tetrahydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidine-2,4(3H)-dione (3)

The enamine **1** was prepared according to the literature.[39] Then the enamine (5.0 mmol) was added to a solution of bis(2,4,6-trichlorophenyl) malonate **2** (5.0 mmol) in 10 mL acetone, and this mixture was stirred at room temperature for 3 h. After completion of the reaction, the resultant precipitate was separated from the reaction mixture by simple filtration and recrystallized from chloroform/ethanol (10:10 mL) to afford the final product of 6,7,8,9-tetrahydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-2,4(3*H*)-dione (**3**).

6,7,8,9-Tetrahydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidine-2,4(3H)-dione (3)

Yellow Powder; yield 85%; mp: 243-244 °C, IR (KBr) (υ max/cm^{-1}): 2238-2658 (broad OH), 3080 (CH), 2949 (CH), 1652 (C = O), 1595 (C = N); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.75-1.78 (s, 4H), 2.57-2.60 (m, 2H), 3.14 (s, 2H), 5.17 (s, 1H, HCH), 11.57 (1H, brs, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.8, 21.9, 23.5, 26.7, 84.7, 118.1,

133.3, 161.9, 163.5, 167.9 ppm; MS (m/z, %) 222 (M, 16), 28 (98), 44 (65), 69 (90), 125 (87), 153 (83), 180 (85).

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 53.98; H, 4.45; N, 12.39.

General procedure for the synthesis of 2-amino-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile derivatives (6a-m)

A mixture of **3** (1.0 mmol), the appropriate isatin derivative (**4a-m**) (1.0 mmol), and malononitrile **5** (1.2 mmol) was refluxed in EOH:H_2O (1:1, 5 mL) for 30 to 60 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and thereafter the precipitated product was separated from the reaction mixture by simple filtration, then washed three times with EtOH (20 mL). The obtained crude compounds were further purified by recrystallization (EtOH) to afford the corresponding final product **6a-m**.

2-Amino-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile (6a)

White Powder; yield 98%; mp: 317 °C, IR (KBr) (υ max/cm^{-1}): 3419, 3328 (NH_2), 2204 (CN), 1733, 1657 (2C = O); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.67-1.76 (m, 4H), 2.62 (s, 2H) 2.87-3.05 (m, 2H), 6.82-6.84 (d, $^3J_{HH}$= 7.8 Hz, 1H, H_{Ar}), 6.89-6.94 (t, $^3J_{HH}$= 7.2 Hz, 1H, H_{Ar}), 7.06-7.08 (d, $^3J_{HH}$ = 7.6 Hz, 1H, H_{Ar}), 7.16-7.21 (dt, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.5, 1H, H_{Ar}), 7.37 (s, 2H, NH_2), 10.53 (s, ^{1}H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.6, 21.8, 23.7, 26.4, 48.5 (C_{spiro}), 57.3, 94.3, 109.7, 117.9, 120.9, 122.3, 124.1, 128.9, 133.3, 134.1, 142.7, 158.6, 158.7, 159.9, 162.5, 178.1 ppm; MS (m/z, %): 417 (M+, 16), 28 (100), 68 (8), 179 (22), 207 (50), 387 (18).

Anal. Calcd for $C_{21}H_{15}N_5O_3S$: C, 60.42; H, 3.62; N, 16.78. Found: C, 60.21; H, 3.87; N, 16.99.

2-Amino-5′-choloro-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile (6b)

White Powder; yield 98%; mp: 308 °C, IR (KBr) (υ max/cm^{-1}): 3430, 3314 (NH_2), 2201 (CN), 1718, 1658 (2C = O); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.70 (s, 4H), 2.62 (s, 2H), 2.90-3.05 (m, 2H), 6.83-6.86 (d, $^3J_{HH}$ = 7.2 Hz, 1H, H_{Ar}), 7.22-7.25 (m, 2H, H_{Ar}), 7.46 (s, 2H, NH_2), 10.67 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.7, 21.8, 23.7, 26.4, 48.8 (C_{spiro}), 56.5, 93.8, 111.1, 117.8, 120.9, 124.5, 126.2, 128.7, 133.3, 136.0, 141.6, 158.7, 158.8, 160.1, 162.7, 178.1 ppm; MS (m/z, %): 451 (M, 16), 43 (100), 65 (8), 178 (47), 239 (88), 419 (55).

Anal. Calcd for $C_{21}H_{14}ClN_5O_3S$: C, 55.82; H, 3.12; N, 15.50. Found: C, 55.60; H, 3.33; N, 15.31.

2-Amino-5′-methyl-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile (6c)

White Powder; yield 95%; mp: 297 °C, IR (KBr) (υ max/cm^{-1}): 3427, 3317 (NH_2), 2201 (CN), 1713, 1657 (2C = O); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.67-1.73 (m, 4H), 2.21 (s, 3H, CH_3) 2.61 (s, 2H), 2.89-3.04 (m, 2H), 6.71-6.73 (d, $^3J_{HH}$ = 7.8Hz, 1H, H_{Ar}), 6.89 (s, 1H, H_{Ar}), 6.97-7.00 (d, $^3J_{HH}$ = 7.5 Hz, 1H, H_{Ar}), 7.36 (s, 2H, NH_2), 10.43 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.1, 21.7, 21.8, 23.70, 26.4, 48.5 (C_{spiro}), 57.5, 94.4, 109.4, 117.9, 120.9, 124.7, 129.1, 131.0, 133.3, 134.1, 140.2, 158.6, 158.7, 159.9, 162.5, 178.0 ppm; MS (m/z, %): 431 (M, 16), 43 (28), 125 (15), 179 (37), 221 (100), 400 (42).

Anal. Calcd for $C_{22}H_{17}N_5O_3S$: C, 61.24; H, 3.97; N, 16.23. Found: C, 61.11; H, 4.01; N, 16.02.

2-Amino-1′-benzyl-5′-chloro-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile (6d)

White Powder; yield 95%; mp: 320 °C, IR (KBr) (υ max/cm^{-1}): 3460, 3343 (NH_2), 2195 (CN), 1723, 1648 (2C = O); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.72 (s, 4H), 2.64 (s, 2H), 2.91-3.08 (m, 2H), 4.90-4.95(d, 1H, $^2J_{HH}$ = 16.2 Hz, Ph-CH_AH_B), 5.0-5.05 (d, 1H, $^2J_{HH}$ = 16.2 Hz, Ph-CH_AH_B), 6.78-6.81 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H_{Ar}), 7.23-7.24 (d, 1H, H_{Ar}), 7.26-7.28 (t, 1H, H_{Ar}), 7.30 (s, 1H, H_{Ar}), 7.33 (s, 1H, H_{Ar}), 7.35 (d, 2H, H_{Ar}), 7.48 (s, 1H, H_{Ar}), 7.51 (s, 1H, H_{Ar}), 7.55 (s, 2H, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.6, 21.8, 23.7, 26.3, 43.9, 48.5, 56.2, 93.4, 110.7, 116.8, 117.9, 121.1, 124.4, 127.3, 127.6, 127.6, 127.8, 128.8, 128.8, 133.4, 135.2, 136.1, 142.2, 158.8, 158.9, 160.3, 162.9, 176.7 ppm; MS (m/z, %): 541 (M, 25), 45 (28), 125 (9), 179 (24), 219 (35), 314 (65), 448 (34).

Anal. Calcd. for $C_{28}H_{20}ClN_5O_3S$: C, 62.05; H, 3.72; N, 12.92. Found: C, 62.28; H, 3.81; N, 12.78.

2-Amino-1′,5′-dimethyl-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile (6e)

White Powder; yield 85%; mp: 280-281 °C, IR (KBr) (υ max/cm^{-1}): 3533, 3407 (NH_2), 2197 (CN), 1714, 1667 (2C = O); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.67-1.71 (m, 4H), 2.24 (s, 3H, CH_3), 2.62 (s, 2H), 2.85-3.03 (m, 2H), 3.17 (s, 3H, CH_3), 6.91-6.94 (d, $^3J_{HH}$ = 9Hz, 1H, H_{Ar}), 6.96 (s, 1H, H_{Ar}), 7.08-7.11 (d, $^3J_{HH}$ = 9 Hz, 1H, H_{Ar}), 7.40 (s, 2H, NH_2), ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.1, 21.7, 21.8, 23.70, 26.4, 27.14, 48.5 (C_{spiro}), 57.4, 94.5, 109.4, 118.0, 121.0, 124.7, 129.2, 131.0, 133.3, 134.1, 140.2, 158.6, 158.7, 159.9, 162.5, 178.1 ppm; ppm; MS (m/z, %): 445 (M, 5), 29 (100), 41 (34), 76 (28), 124 (12), 180 (24), 220 (16), 234 (76), 413 (18).

Anal. Calcd for $C_{23}H_{19}N_5O_3S$: C, 62.01; H, 4.30; N, 15.72. Found: C, 61.90; H, 4.13; N, 15.57.

2-Amino-5′-bromo-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile (6f)

White Powder; yield 96%; mp: 279-280 °C, IR (KBr) (υ max/cm^{-1}): 3452, 3321 (NH_2), 2206 (CN), 1738, 1666 (2C = O); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 1.68-1.72 (m, 4H), 2.63 (s, 2H), 2.90-3.05 (m, 2H), 6.79-6.82 (d, $^3J_{HH}$ = 9 Hz, 1H, H_{Ar}), 7.34 (s, 1H, H_{Ar}), 7.35-7.38 (d, $^3J_{HH}$ = 9 Hz, 1H, H_{Ar}), 7.46 (s, 2H, NH_2), 10.68 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 21.7, 21.8, 23.7, 26.4, 48.7 (C_{spiro}), 56.5, 93.8, 111.6, 113.9, 117.7, 120.9, 127.1, 131.6, 133.3, 136.4, 142.0, 158.7, 158.8, 160.1, 162.7, 177.8 ppm; MS (m/z, %): 496 (M, 23), 43 (29), 125 (16), 179 (100), 219 (10), 283 (75), 465 (70).

Anal. Calcd for $C_{21}H_{14}BrN_5O_3S$: C, 50.82; H, 2.84; N, 14.11. Found: C, 50.51; H, 2.93; N, 13.97.

2-Amino-1′-benzyl-5′-bromo-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile (6g)

White Powder; yield 98%; mp: 311-312 °C, IR (KBr) (υ max/cm^{-1}): 3456, 3346 (NH_2), 2200 (CN), 1719, 1650 (2C = O); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 1.72 (s, 4H), 2.53 (s, 2H), 2.91-3.08 (m, 2H), 4.90-4.95 (d, 1H, $^2J_{HH}$ = 15.9 Hz, Ph-CH_AH_B), 5.0-5.05 (d, 1H, $^2J_{HH}$ = 15.9 Hz, Ph-CH_AH_B), 6.73-6.76 (d, $^3J_{HH}$ = 9 Hz, 1H, H_{Ar}), 7.30 (s, 1H, H_{Ar}), 7.33 (s, 1H, H_{Ar}), 7.35-7.37 (m, 1H, H_{Ar}), 7.40 (s, 1H, H_{Ar}), 7.45 (s, 1H, H_{Ar}), 7.48 (s, 1H, H_{Ar}), 7.51 (s, 1H, H_{Ar}), 7.56 (s, 2H, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 21.7, 21.8, 23.7, 26.3, 43.9, 48.4, 56.2, 93.6, 111.2, 115.0, 117.9, 127.1, 127.6, 127.7, 127.8, 128.8, 128.8, 131.6, 133.4, 135.6, 136.1, 142.6, 158.8, 158.9, 160.3, 162.9, 176.6 ppm; MS (m/z, %): 586 (M, 39), 64 (41), 179 (52), 219 (36), 360 (32), 495 (84), 557(18).

Anal. Calcd for $C_{28}H_{20}BrN_5O_3S$: C, 56.90; H, 3.44; N, 11.94. Found: C, 57.3x; H, 3.41; N, 11.59.

2-Amino-1′-(4-nitrobenzyl)-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile (6h)

White Powder; yield 70%; mp: 302-304 °C, IR (KBr) (υ max/cm^{-1}): 3405, 3325 (NH_2), 2200 (CN), 1740, 1661 (2C = O); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ_H 1.71-1.75 (m, 4H), 2.62 (s, 2H) 2.87-3.08 (m, 2H), 5.15 (s, 2H, CH_2-benzyl), 6.83-6.86 (d, $^3J_{HH}$ = 9 Hz, 1H, H_{Ar}), 6.99-7.04 (t, $^3J_{HH}$ = 7.8 Hz, 1H, H_{Ar}), 7.18-7.23 (t, $^3J_{HH}$ = 7.5 Hz, 2H, H_{Ar}), 7.52 (s, 2H, NH_2), 7.79-7.78 (d, $^3J_{HH}$ = 9 Hz, 2H, H_{Ar}), 8.17-8.20 (d, $^3J_{HH}$ = 9 Hz, 2H, H_{Ar}), ppm; ^{13}C NMR (75 MHz, DMSO-d$_6$): δ_C 21.7, 21.8, 23.7, 25.6, 26.3, 43.4, 48.3, 56.8, 67.50, 94.0, 109.1, 118.0, 121.1, 123.4, 123.8, 123.8, 124.3, 129.0, 129.0, 133.2, 133.4, 142.8, 144.7, 147.3, 158.7, 158.8, 160.1, 162.7, 176.9 (C = Oisatin) ppm; MS (m/z, %): 552 (M, 8), 43 (32), 78 (69), 105 (31), 179 (45), 219 (70), 325 (100), 413 (60), 523(28).

Anal. Calcd for $C_{28}H_{20}N_6O_5S$: C, 60.86; H, 3.65; N, 15.21. Found: C, 60.90; H, 3.43; N, 14.98.

2-Amino-1′-benzyl-5′-methyl-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile (6i)

White Powder; yield 98%; mp: 290 °C, IR (KBr) (υ max/cm^{-1}): 3452, 3342 (NH_2), 2202 (CN), 1714, 1651 (2C = O); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.69-1.73 (m, 4H), 2.21 (s, 3H, H_{Me}), 2.62 (s, 2H), 2.89-3.02 (m, 2H), 4.86-4.91(d, 1H, $^2J_{HH}$ = 16.2 Hz, Ph-CH_AH_B), 4.98-5.03 (d, 1H, $^2J_{HH}$ = 16.2 Hz, Ph-CH_AH_B), 6.63-6.65 (d, $^3J_{HH}$ = 7.8 Hz, 1H, H_{Ar}), 6.96-7.0 (td, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.8 Hz, 2H, H_{Ar}), 7.26-7.34 (m, 3H, H_{Ar}), 7.46 (s, 2H, NH_2), 7.50 (s, 1H, H_{Ar}), 7.53 (s, 1H, H_{Ar}), ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.1,21.7, 21.8, 23.7, 26.4, 43.9, 48.3, 57.1, 94.3, 109.1, 118.0, 121.0, 123.0, 124.7, 127.6, 127.7, 128.7, 129.1, 132.1, 133.3, 133.4, 136.6, 140.9, 158.7, 158.8, 160.1, 162.7, 176.7 (C = O isatin) ppm; MS (m/z, %): 521 (M, 58), 64 (68), 179 (42), 219 (38), 295 (73), 430 (85), 494 (28).

Anal. Calcd for $C_{29}H_{23}N_5O_3S$: C, 66.78; H, 4.44; N, 13.43. Found: C, 67.03; H, 4.41; N, 13.29.

2-Amino-4′,6′-dibromo-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile (6j)

White Powder; yield 90%; mp: 307-308 °C, IR (KBr) (υ max/cm^{-1}): 3435, 3322 (NH_2), 2201 (CN), 1724, 1657 (2C = O); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.70-1.72 (m, 4H), 2.63 (s, 2H), 2.96-3.0 (m, 2H), 7.42 (d, $^4J_{HH}$ = 1.8 Hz, 1H, H_{Ar}), 7.56 (s, 2H, NH_2), 7.64 (d, $^4J_{HH}$ = 1.8 Hz, 1H, H_{Ar}), 11.05 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.7, 21.8, 23.7, 26.4, 49.9, 56.1, 93.5, 102.9, 114.5, 117.7, 121.1, 126.5, 133.4, 133.6, 137.5, 141.8, 158.8, 158.9, 160.1, 162.9, 177.8 (C = O_{isatin}) ppm; MS (m/z, %): 575 (M, 25), 56 (36), 179 (62), 219 (15), 361 (79), 547 (65).

Anal. Calcd for $C_{21}H_{13}Br_2N_5O_3S$: C, 43.85; H, 2.28; N, 12.17. Found: C, 43.62; H, 2.33; N, 11.89.

2-Amino-1′-benzyl-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile (6k)

White Powder; yield 98%; mp: 320-321 °C, IR (KBr) (υ max/cm^{-1}): 3382, 3317 (NH_2), 2202 (CN), 1721, 1653 (2C = O); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.69-1.72 (m, 4H), 2.63 (s, 2H), 2.88-3.08 (m, 2H), 4.88-4.93 (d, 1H, $^2J_{HH}$ = 15.9 Hz, Ph-CH_AH_B), 5.01-5.06 (d, 1H, $^2J_{HH}$ = 15.9 Hz, Ph-CH_AH_B), 6.75-6.78 (d, $^3J_{HH}$ = 7.8 Hz, 1H, H_{Ar}), 6.96-7.0 (t, $^3J_{HH}$ = 7.8 Hz, 1H, H_{Ar}), 7.15-7.19 (m, 2H, H_{Ar}), 7.29-7.34 (m, 3H, H_{Ar}), 7.47 (s, 2H, NH_2), 7.51 (s, 1H, H_{Ar}), 7.53 (s, 1H, H_{Ar}), ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.6, 21.8, 23.7, 26.3, 43.9, 48.3, 56.9, 94.2, 109.3, 117.7, 121.0, 123.1, 124.1, 127.6, 127.7, 127.7, 128.7, 128.7, 128.9, 133.2, 133.4, 136.5, 143.3, 158.7, 158.8, 160.1, 162.7, 176.9 (C = O isatin) ppm; MS (m/z, %): 507 (M, 38), 65 (41), 179 (45), 220 (18), 281 (36), 415 (88), 478 (27).

Anal. Calcd for $C_{28}H_{21}N_5O_3S$: C, 66.26; H, 4.17; N, 13.80. Found: C, 65.98; H, 4.23; N, 13.71.

2-Amino-7′-chloro-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile (6l)

White Powder; yield 90%; mp: 335-337 °C, IR (KBr) (υ max/cm^{-1}): 3423, 3328 (NH_2), 2201 (CN), 1743, 1657 (2C = O); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.71 (s, 4H), 2.63 (s, 2H), 2.89-3.05 (m, 2H), 6.62-6.67 (t, $^3J_{HH}$ = 7.8 Hz, 1H, H_{Ar}), 7.08-7.10 (d, $^3J_{HH}$ = 7.2 Hz, 1H, H_{Ar}), 7.25-7.28 (d, $^3J_{HH}$ = 8.1 Hz, 1H, H_{Ar}), 7.48 (s, 2H, NH_2), 10.99 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.6, 21.8, 23.7, 26.4, 49.4 (C_{spiro}), 56.6, 93.9, 113.9, 117.7, 121.1, 122.9, 123.6, 128.9, 135.6, 140.4, 158.7, 158.8, 160.1, 162.7, 178.1 ppm; MS (m/z, %) 452 (M + 1, 5), 28 (100), 43 (24), 179 (26), 240 (38), 267 (5), 425 (12).

Anal. Calcd for $C_{21}H_{14}ClN_5O_3S$: C, 55.82; H, 3.12; N, 15.50. Found: C, 55.67; H, 3.23; N, 15.79.

2-Amino-7′-bromo-2′,5-dioxo-7,8,9,10-tetrahydro-5H-spiro[benzo[4,5]thiazolo[3,2-a]pyrano[2,3-d]pyrimidine-4,3′-indoline]-3-carbonitrile (6m)

White Powder; yield 94%; mp: 328-329 °C, IR (KBr)(υ max/cm^{-1}): 3419, 3324 (NH_2), 2198 (CN), 1738, 1655 (2C = O); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.71 (m, 4H), 2.63 (s, 2H), 2.89-3.05 (m, 2H), 6.86-6.92 (t, $^3J_{HH}$ = 7.8 Hz, 1H, H_{Ar}), 7.11-7.13 (d, $^3J_{HH}$ = 7.2 Hz, 1H, H_{Ar}), 7.37-7.40 (d, $^3J_{HH}$ = 8.1 Hz, 1H, H_{Ar}), 7.48 (s, 2H, NH_2), 10.86 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.6, 21.8, 23.7, 26.4, 49.6 (C_{spiro}), 56.7, 93.9, 102.2, 117.7, 121.1, 123.4, 124.0, 127.1, 131.8, 133.3, 135.8, 142.1, 158.7, 158.8, 160.0, 162.7, 178.1 ppm; MS (m/z, %) 497 (M + 1, 10), 28 (100), 41 (23), 125 (15), 180 (25), 284 (24), 469 (15).

Anal. Calcd for $C_{21}H_{14}BrN_5O_3S$: C, 50.82; H, 2.84; N, 14.11. Found: C, 50.67; H, 2.91; N, 13.87.

Supplementary material

Experimental procedures and characterizations of synthesized products are shown; copies of the NMR, IR and mass spectra are available.

Acknowledgments

The Research Council of Ferdowsi University of Mashhad is acknowledged for financial support (Grant No. 3/54469).

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