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Bis(indoline-2,3-diones): versatile precursors for novel bis(spirooxindoles) incorporating 4*H*-chromene-3-carbonitrile and pyrano[2,3-*d*]pyrimidine-6-carbonitrile derivatives

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Abstract: Multicomponent reaction of dimedone or 1,3-dimethylbarbituric acid and malononitrile with a series of bis(indoline-2,3-diones) afforded the corresponding bis(2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile) and bis(7'-amino-1',3'-dimethyl-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano [2,3-d]pyrimidine]-6'-carbonitrile) derivatives in good to excellent yield.

Key words: Bis(indoline-2,3-diones), bis(spirooxindole), 4*H*-chromene-3-carbonitrile, pyrano[2,3-*d*]pyrimidine-6-carbonitrile

1. Introduction

Spirooxindoles are interesting synthetic molecules in heterocyclic chemistry because of their wide variety of applications.[1–3] They represent essential substructures of many natural and biologically active molecules such as horsfiline,[4] spirotryprostatin B, pteropodine,[5] and gelsemine[6] (Figure 1). Moreover, $C-C$ bond formation via the Michael addition reactions of cinnamonitriles with compounds containing active methylenes is an interesting route for the synthesis of chromene and fused chromene derivatives.[7–10] 4*H*-chromenes are an important class of heterocyclic compounds of considerable interest, due to their wide range of biological activities (Figure 2) including anticancer,[11–14] antimicrobial,[15,16] and antiinflammatory activities.[17] Some chromene derivatives were used in the treatment of neurodegenerative diseases.[18] 2-Amino-4*H*-chromene derivatives bearing nitrile functionality also have numerous applications in the treatment of human inflammatory diseases, such as psoriatic and rheumatoid arthritis.[19,20] They have also been studied for the potential treatment of neurodegenerative disease, such as Parkinson disease, Huntington disease, Alzheimer disease, and AIDS-associated dementia as well as for the treatment of schizophrenia and myoclonus.[21] Pyrano[2,3-*d*]pyrimidine-6-carbonitrile derivatives are recognized as a result of their bioactivity.[22,23] Furthermore, derivatized heterocycles with a suitable spacer are reported to exhibit various pharmacological activities such as fungicidal, antibacterial, anticancer, and plant growth regulation.[24–29] They have also numerous applications as electrical conducting materials, chelating agents, and metal ligands.[30,31]

In addition, multicomponent reactions (MCRs), which provide easy and rapid access to plenty of heterocyclic compounds, have the advantages of both atom economy and selectivity.[32–41] As a part of an ongoing re-

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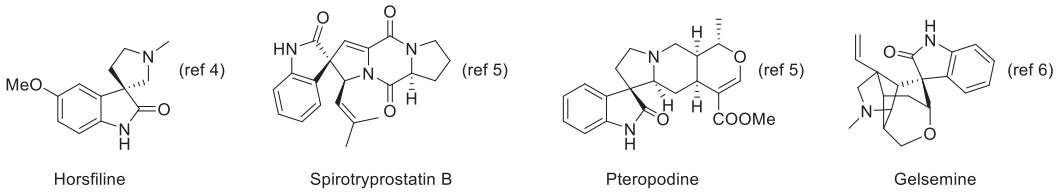


Figure 1. Some drugs incorporating spirooxindole rings.

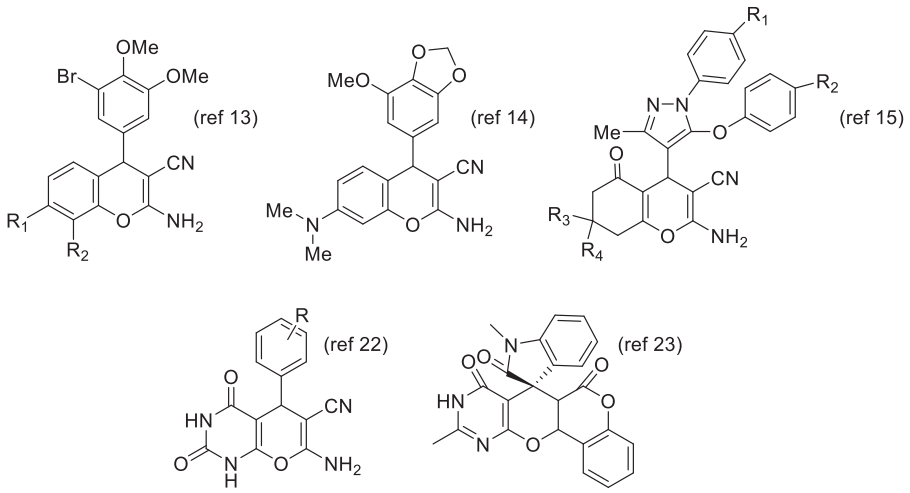
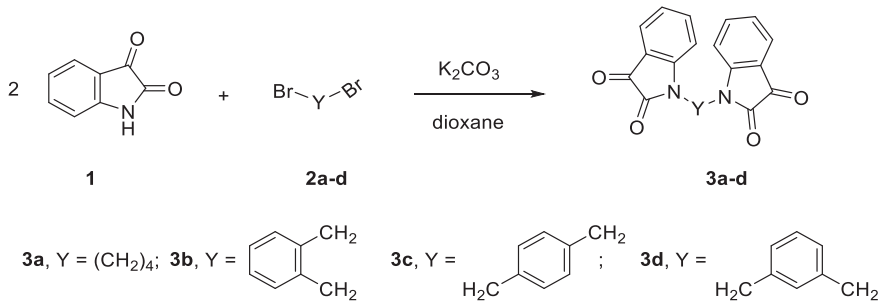


Figure 2. Some drugs incorporating 4-aryl-4*H*-chromene and pyrano[2,3-*d*]pyrimidine-6-carbonitrile.

search program on Michael addition reactions[42–47] as well as on bis-heterocyclic synthesis,[33,48–53] we report the results of our investigations concerning the reactivity patterns of bis(2-oxoindoline-1-yl-3-ylidene)dimalononitrile derivatives towards dimedone or 1,3-dimethylbarbituric acid aiming at synthesis of the respective bis(spirooxindoles) incorporating 4*H*-chromene-3-carbonitrile and pyrano[2,3-*d*]pyrimidine-6-carbonitrile derivatives. It is expected that the synthesis of these molecules in the form of bis(spirooxindoles) can lead to the discovery of new active drugs.

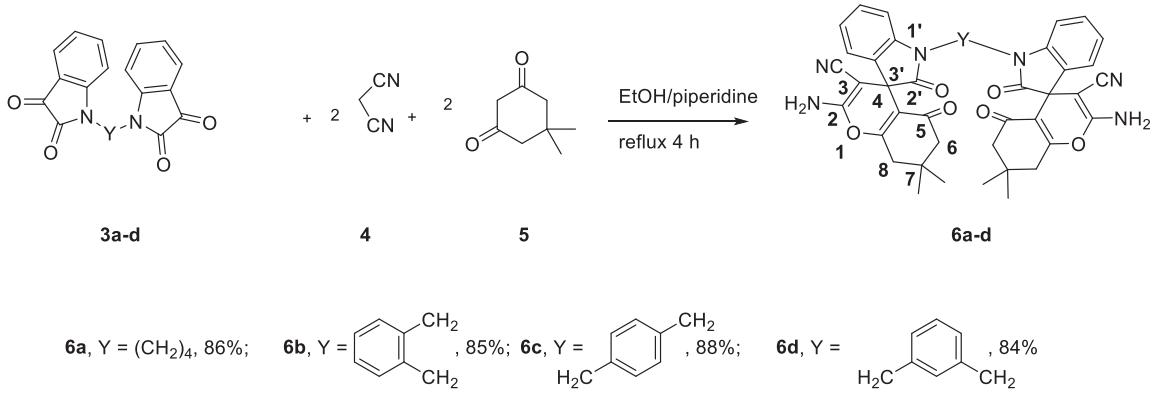
2. Results and discussion

The bis(indoline-2,3-diones) **3a**–**d** were chosen as precursors. In the first step, they were prepared via the direct reaction of 1*H*-indol-2,3-dione **1** with the appropriate dibromo compounds **2a**–**d** in the presence of anhydrous K_2CO_3 (Scheme 1).[54–56]



Scheme 1. Synthesis of bis(indoline-2,3-diones) **3a**–**d**. Reaction conditions: isatin **1** (25 mmol), dibromo derivatives **2a**–**d** (10 mmol), K_2CO_3 (30 mmol), dioxane (10 mL), reflux 30 min. Yields: 75%–84%.

In the second step, the three-component reaction of **3a**–**d** with malononitrile **4** and dimedone **5** was investigated. Thus, reaction of the bis(indoline-2,3-diones) **3a**–**d** with two equivalents of both **4** and **5** afforded the respective bis(2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile) **6a**–**d**, which are tethered to alkyl or aryl linkage (Scheme 2).



Scheme 2. Synthesis of compounds **6a**–**d**. Reaction conditions: bis(indoline-2,3-diones) **3a**–**c** (1 mmol), malononitrile (2 mmol), dimedone (2 mmol), EtOH (15 mL)/piperidine (0.2 mL), reflux 4 h. Yields: 84%–88%.

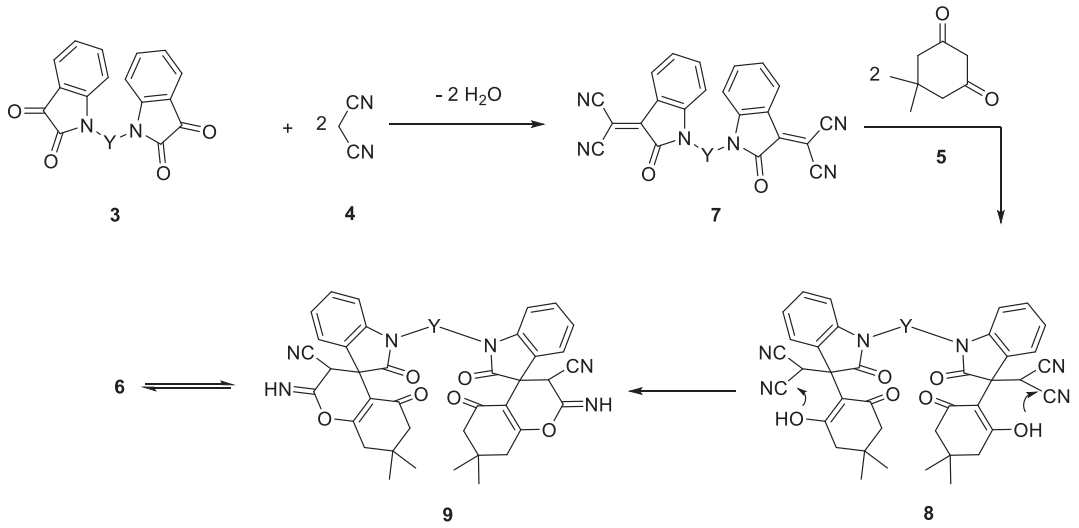
The structure of compounds **6a**–**d** was supported based on spectral data. Thus, the ^{1}H NMR spectrum of **6b** revealed two singlet signals at δ1.04 and 1.05 ppm for the four methyl groups. It also showed characteristic multiplets in the region δ2.18–2.44 ppm for the dimedones H6 and H8. The multiplet at δg5.10 ppm is assigned to the NCH_2 group. The other signals appeared at their expected positions. Furthermore, the ^{13}C NMR spectrum of **6b** was found to be in agreement with the proposed structure; it showed the methyl signals at δ27.1 and 27.5 ppm. The spiro carbon appeared at δ41.0 ppm. It also featured a CN signal at δ117.5 ppm. The two carbonyl groups appeared at δ179 and 195 ppm. All other carbons appeared at their expected positions. The formation of **6** could be explained by the following plausible mechanism. The reaction occurs via an initial Knoevenagel condensation of **3** with malononitrile **4** to yield **7**. The Michael addition reaction occurs via an initial addition of the dimedone CH to the activated double bond in **7** to yield **8**, which cyclizes into **9**. Intermediate **9** tautomerizes into the final isolable product **6** (Scheme 3).

In support of this mechanism, we managed to isolate the Knoevenagel condensation products **7** in some cases. Thus, Knoevenagel condensation of one mole of **3a**–**c** with two moles of malononitrile **2** in ethanol in the presence of piperidine as a basic catalyst afforded the corresponding bis(2-oxoindoline-1-yl-3-ylidene))dimalononitrile derivatives **7a**–**c** in good yields. Subsequent reaction of **7a**–**c** with two moles of dimedone **5** in ethanol in the presence of piperidine afforded **6a**–**c** in good yields (Scheme 4).

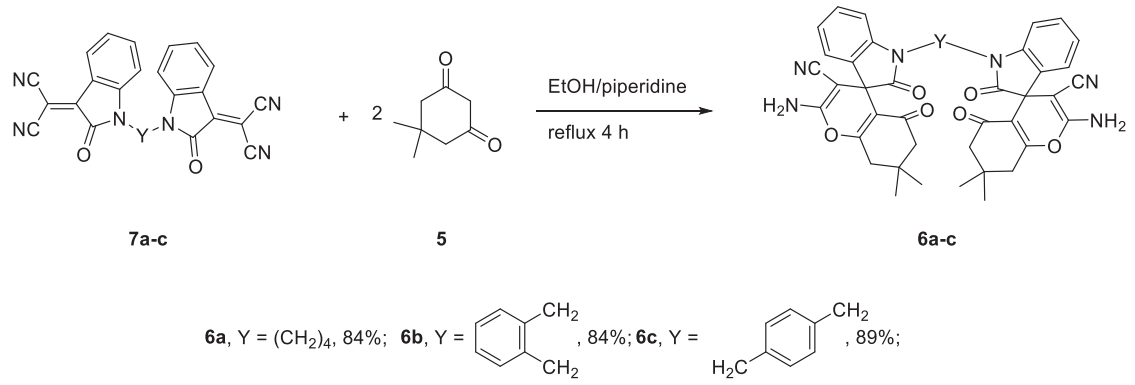
Encouraged by the above results, bis(spirooxindoles) incorporating pyrano[2,3-*d*]pyrimidine derivatives **11a**–**d** were prepared via the three-component reaction of one equivalent of the bis(indoline-2,3-diones) **3a**–**c** with two moles of both malononitrile **4** and 1,3-dimethylbarbituric acid **10** (Scheme 5).

Moreover, alternative synthesis of **11a-c** via the direct reaction of compound **10** with **7a**–**c** was also performed in good yields (Scheme 6).

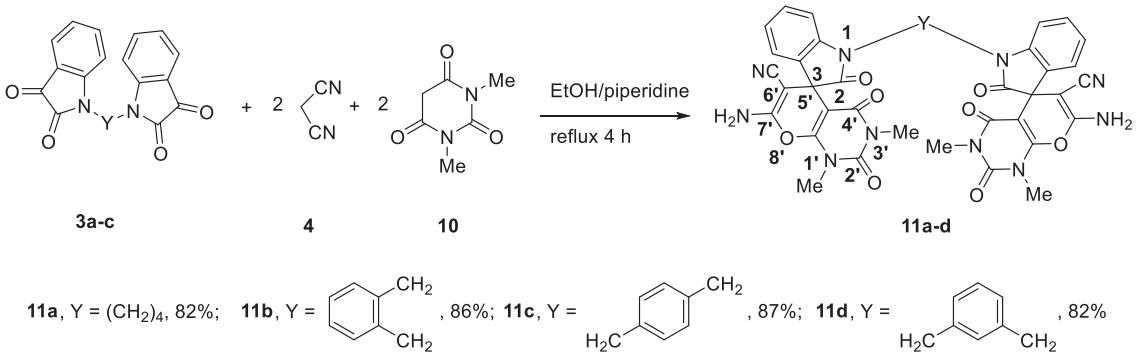
The chemical structure of compound **11** is well established based on spectral tools. Thus, the ^{1}H NMR spectra of compound **11c** revealed two singlets at δ 3.04 and 3.41 ppm for the two types of *N*-methyl groups. The multiplet at δ 4.86 ppm was assigned to the methylene groups. Moreover, the multiplets at δ 6.68–7.62 were assigned to aromatic protons.



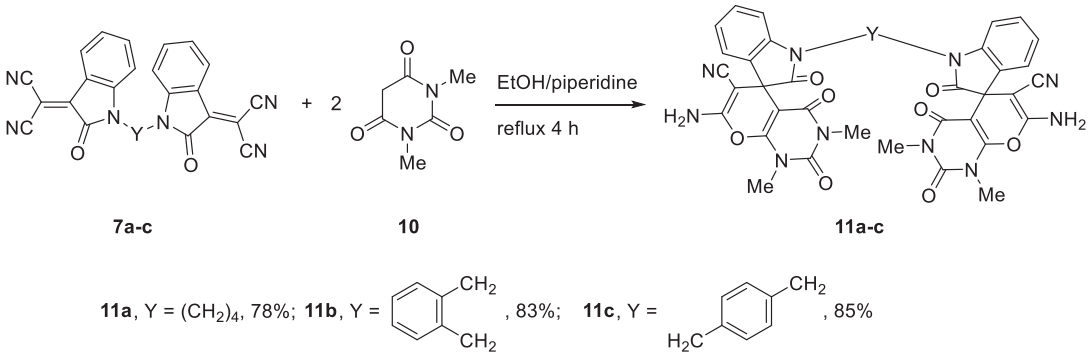
Scheme 3. Proposed pathway for the synthesis of compounds **6a**–**d**.



Scheme 4. Synthesis of compounds **6a**–**c** via stepwise reaction of **7** with **5**. Reaction conditions: (1 mmol) **7a**–**c**, dimedone (2 mmol), EtOH (15 mL)/piperidine (0.2 mL), reflux 2 h. Yields: 84%–89%.



Scheme 5. Synthesis of compounds **11a**–**d**. Reaction conditions: bis(indoline-2,3-diones) **3a**–**c** (1 mmol), malononitrile (2 mmol), 1,3-dimethylbarbituric acid **10** (2 mmol), EtOH (15 mL)/piperidine (0.2 mL), reflux 2 h. Yields: 82%–87%.



Scheme 6. Synthesis of compounds **11a**–**c** via stepwise reaction of **7** with **10**. Reaction conditions: **7a**–**c** (1 mmol), 1,3-dimethylbarbituric acid **10** (2 mmol), EtOH (15 mL)/piperidine (0.2 mL), reflux 2 h. Yields: 78%–85%.

It is noteworthy to mention that our attempts to get compounds **6** and **11** via reaction of monopodal spirooxindole **12**[40] and **13**[41] with the appropriate dihalo compounds **2** using a mild base were unsuccessful (Figure 3).

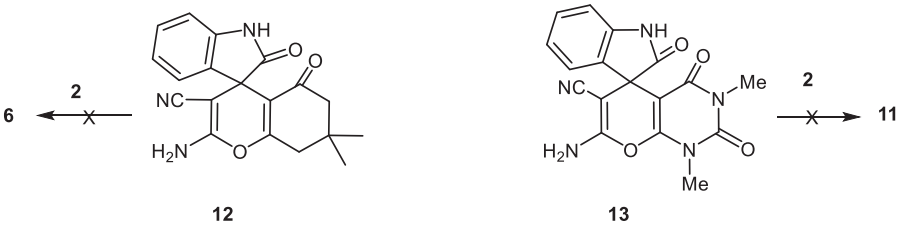


Figure 3. Alternative method for synthesis of compounds **6** and **11**.

3. Conclusions

We developed an efficient synthetic strategy for novel bis(spirooxindoles) incorporating 4 *H* -chromene-3-carbonitrile as well as pyrano[2,3-*d*]pyrimidine-6-carbonitrile derivatives via one-pot three-component reactions of the bis(indoline-2,3-diones), malononitrile and dimedone or 1,3-dimethylbarbituric acid in good to excellent yield. The advantages of the reactions are effortlessly accessible starting materials, operational simplicity, and wide extension to acquire assorted diversity of the products.

4. Experimental

4.1. Apparatus and chemicals

Melting points were measured with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded using a FTIR Bruker–vector 22 spectrophotometer as KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO–d_6 as solvent on a Varian Gemini NMR spectrometer at 300 MHz and 75 MHz, respectively, using TMS as internal standard. Chemical shifts are reported as δ values in ppm. Mass spectra were recorded with a Shimadzu GCMS–QP–1000 EX mass spectrometer in EI (70 eV) model. The elemental analyses were performed at the Micro Analytical Center, Cairo University.

4.2. General procedure for synthesis of compounds 6a-d and 11a-d

Method A: A mixture of bis-isatin derivatives **3a**–**d** (1 mmol), malononitrile **4** (0.07, 1 mmol) and dimedone **5** (0.14 g, 1 mmol) or 1,3-dimethylbarbituric acid **10** (0.16 g, 1 mmol) was heated at reflux in absolute EtOH (15 mL) in the presence of piperidine (0.2 mL) for 4 h. The solvent was evaporated under reduced pressure and the crude products were crystallized from ethanol/dioxane (5 mL, 3:1, v/v).

Method B (for compounds **6a**–**c** and **11a**–**c**): A mixture of bis(2-oxoindoline-1-yl-3-ylidene) dimalononitrile derivatives **7a**–**c** (1 mmol) and dimedone **5** (0.14 g, 1 mmol) or 1,3-dimethylbarbituric acid **10** (0.16 g, 1 mmol) was heated at reflux in absolute EtOH (15 mL) in the presence of piperidine (0.2 mL) for 4 h. The solvent was evaporated under reduced pressure and the crude products were crystallized from ethanol/dioxane (5 mL, 3:1, v/v).

4.2.1. 1',1"'-(Butane-1,4-diyl)bis(2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile) (6a)

Red crystals (0.62 g, 86% (method A); 0.61, 84% (method B)); mp 294–296 °C; IR (KBr): ν 3432 (br, NH_2), 2194 (C≡N), 1715 (dimedone C=O), 1671 (isatin C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.01 (s, 6H, $2CH_3$), 1.05 (s, 6H, $2CH_3$), 1.77 (br, 4H, $2CH_2$), 2.07 (m, 4H, H8), 2.44 (m, 4H, H6), 3.70 (br, 4H, $2NCH_2$), 6.94–7.25 (m, 12H, Ar-H and $2NH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.4, 27.0, 27.7, 32.0, 38.8, 46.5, 50.0, 57.4, 108.6, 110.8, 117.3, 122.3, 122.9, 128.4, 133.7, 143.0, 158.9, 164.3, 176.5, 194.9 ppm; MS (EI, 70 eV): m/z 724 [M^+]; Anal. Calcd for $C_{42}H_{40}N_6O_6$: C, 69.60; H, 5.56; N, 11.59. Found: C, 69.44; H, 5.45; N, 11.73.

4.2.2. 1',1"'-(1,2-Phenylenebis(methylene))bis(2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile) (6b)

Brick red crystals (0.66 g, 85% (method A); 0.65, 84% (method B)); mp 292–294 °C; IR (KBr): ν 3454 (br, NH_2), 2196 (C≡N), 1674 (dimedone C=O), 1608 (isatin C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.04 (s, 6H, $2CH_3$), 1.05 (s, 6H, $2CH_3$), 2.18 (m, 4H, H8), 2.44 (m, 4H, H6), 5.10 (s, 4H, $2CH_2$), 6.84–7.54 (br, 16H, Ar-H and $2NH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.1, 27.5, 31.9, 41.0, 46.7, 50.0, 57.3, 109.1, 110.6, 117.5, 122.6, 122.9, 126.3, 126.9, 128.3, 131.2, 133.1, 133.6, 142.9, 158.9, 164.5, 176.8, 195.0 ppm; MS (EI, 70 eV): m/z 772 [M^+]; Anal. Calcd for $C_{46}H_{40}N_6O_6$: C, 71.49; H, 5.22; N, 10.87. Found: C, 71.61; H, 5.14; N, 10.73.

4.2.3. 1',1"'-(1,4-Phenylenebis(methylene))bis(2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile) (6c)

Deep red crystals (0.68 g, 88% (method A); 0.69, 89% (method B)); mp >300 °C; IR (KBr): ν 3422 (br, NH_2), 2193 (C≡N), 1673 (dimedone C=O), 1608 (isatin C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.01 (s, 6H, $2CH_3$), 1.05 (s, 6H, $2CH_3$), 2.15 (m, 4H, H8), 2.60 (m, 4H, H6), 4.88 (s, 4H, $2CH_2$), 6.67–7.43 (m, 16H, Ar-H and $2NH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.0, 27.6, 31.9, 40.3, 46.5, 49.8, 57.1, 108.9, 110.6, 117.3, 122.5, 122.9, 127.1, 128.3, 133.5, 135.0, 142.5, 158.9, 164.5, 176.7, 195.0 ppm; MS (EI, 70 eV): m/z 772 [M^+]; Anal. Calcd for $C_{46}H_{40}N_6O_6$: C, 71.49; H, 5.22; N, 10.87. Found: C, 71.55; H, 5.34; N, 10.78.

4.2.4. 1',1"'-(1,3-Phenylenebis(methylene))bis(2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile) (6d)

Red crystals (0.65 g, 84% (method A)); mp 266–268 °C; IR (KBr): ν 3435 (br, NH_2), 2197 (C≡N), 1673 (dimedone C=O), 1608 (isatin C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02 (s, 6H, $2CH_3$), 1.06 (s, 6H, $2CH_3$), 2.11 (m, 4H, H8), 2.60 (m, 4H, H6), 4.76 (m, 4H, $2CH_2$), 6.61–7.60 (m, 16H, Ar-H and $2NH_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.1, 27.7, 32.1, 40.3, 46.6, 50.0, 56.1, 109.0, 110.7, 117.7, 122.7, 123.0, 125.9, 126.1, 128.4, 128.6, 133.6, 136.3, 142.6, 159.1, 164.6, 176.8, 195.2 ppm; MS (EI, 70 eV): m/z 772 [M^+]; Anal. Calcd for $C_{46}H_{40}N_6O_6$: C, 71.49; H, 5.22; N, 10.87. Found: C, 71.54; H, 5.13; N, 10.92.

4.2.5. 1,1"-(Butane-1,4-diyl)bis(7'-amino-1',3'-dimethyl-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-6'-carbonitrile) (11a)

Red crystals (0.62 g, 82% (method A); 0.59 g, 78% (method B)); mp 150–152 °C; IR (KBr): ν 3431 (br, NH_2), 2195 (C≡N), 1721 (C=O), 1650 (C=O), 1596 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.63 (m, 4H, $2CH_2$), 2.96 (s, 6H, $2CH_3$-(1')), 3.13 (s, 6H, $2CH_3$-(3')), 3.71 (br, 4H, $2CH_2$), 6.93–7.94 (m, 12H, Ar-H and $2NH_2$) ppm; MS (EI, 70 eV): m/z 756 [M^+]; Anal. Calcd for $C_{38}H_{32}N_{10}O_8$: C, 60.31; H, 4.26; N, 18.51. Found: C, 60.38; H, 4.18; N, 18.47.

4.2.6. 1,1"-(1,2-Phenylenebis(methylene))bis(7'-amino-1',3'-dimethyl-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-6'-carbonitrile) (11b)

Red crystals (0.69 g, 86% (method A); 0.67 g, 83% (method B)); mp 220–224 °C; IR (KBr): ν 3430 (br, NH_2), 2199 (C≡N), 1690 (C=O), 1654 (C=O), 1610 (C=O) cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.06 (s, 6H, $2CH_3$-(1')), 3.42 (s, 6H, $2CH_3$-(3')), 5.13 (m, 4H, $2CH_2$), 6.86–7.64 (m, 16H, Ar-H and $2NH_2$) ppm; MS (EI, 70 eV): m/z 804 [M^+]; Anal. Calcd for $C_{42}H_{32}N_{10}O_8$: C, 62.68; H, 4.01; N, 17.40. Found: C, 62.54; H, 4.14; N, 17.32.

4.2.7. 1,1"-(1,4-Phenylenebis(methylene))bis(7'-amino-1',3'-dimethyl-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-6'-carbonitrile) (11c)

Red crystals (0.70 g, 87% (method A); 0.69 g, 85% (method B)); mp 220–224 °C; IR (KBr): ν 3430 (br, NH_2), 2196 (C≡N), 1688 (C=O), 1648 (C=O), 1612 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.04 (s, 6H, $2CH_3$-(1')), 3.41 (s, 6H, $2CH_3$-(3')), 4.86 (br, 4H, $2CH_2$), 6.68–7.62 (m, 16H, Ar-H and $2NH_2$) ppm; MS (EI, 70 eV): m/z 804 [M^+]; Anal. Calcd for $C_{42}H_{32}N_{10}O_8$: C, 62.68; H, 4.01; N, 17.40. Found: C, 62.61; H, 3.92; N, 17.48.

4.2.8. 1,1"-(1,3-Phenylenebis(methylene))bis(7'-amino-1',3'-dimethyl-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-6'-carbonitrile) (11d)

Red crystals (0.64 g, 82% (method A)); mp 220–224 °C; IR (KBr): ν 3429 (br, NH_2), 2200 (C≡N), 1690 (C=O), 1654 (C=O), 1609 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.04 (s, 6H, $2CH_3$-(1')), 3.11 (s, 6H, $2CH_3$-(3')), 4.83 (br, 4H, $2CH_2$), 6.65–7.64 (m, 16H, Ar-H and $2NH_2$) ppm, MS (EI, 70 eV): m/z 804 [M^+]; Anal. Calcd for $C_{42}H_{32}N_{10}O_8$: C, 62.68; H, 4.01; N, 17.40. Found: C, 62.55; H, 4.11; N, 17.31.

4.3. General method for synthesis of compounds 7a–c

A mixture of bis-isatin derivatives **3a**–**c** (1 mmol) and malononitrile (0.15 g, 2.2 mmol) was heated at reflux in absolute EtOH (15 mL) in the presence of piperidine (0.2 mL) for 30 min. The crude product was collected by filtration and crystallized from EtOH/dioxane (5 mL, 4:1, v/v).

4.3.1. 2,2'-(Butane-1,4-diylbis(2-oxoindoline-1-yl-3-ylidene))dimalononitrile (7a)

Red crystals (0.64 g, 82%); mp >300 °C; IR (KBr): ν 2192 (C≡N), 1648 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.64 (br, 4H, CH_2), 3.63 (br, 4H, $2CH_2$), 6.36–7.33 (m, 8H, Ar-H) ppm; MS (EI, 70 eV): m/z 444 [M$^+$]; Anal. Calcd for $C_{26}H_{16}N_6O_2$: C, 70.26; H, 3.63; N, 18.91. Found: C, 70.33; H, 3.55; N, 18.86.

4.3.2. 2,2'-((1,2-Phenylenebis(methylene))bis(2-oxoindoline-1-yl-3-ylidene))dimalononitrile (7b)

Red crystals (0.38 g, 78%); mp >300 °C; IR (KBr): ν 2191 (C≡N), 1620 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.12 (m, 4H, $2CH_2$), 6.97–8.03 (m, 12H, Ar-H) ppm; MS (EI, 70 eV): m/z 492 [M$^+$]; Anal. Calcd for $C_{30}H_{16}N_6O_2$: C, 73.16; H, 3.27; N, 17.06. Found: C, 73.09; H, 3.22; N, 17.01.

4.3.3. 2,2'-((1,4-Phenylenebis(methylene))bis(2-oxoindoline-1-yl-3-ylidene))dimalononitrile (7c)

Red crystals (0.42 g, 85%); mp >300 °C; IR (KBr): ν 2193 (C≡N), 1611 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.88 (m, 4H, $2CH_2$), 6.94–7.96 (m, 12H, Ar-H) ppm; MS (EI, 70 eV): m/z 492 [M$^+$]; Anal. Calcd for $C_{30}H_{16}N_6O_2$: C, 73.16; H, 3.27; N, 17.06. Found: C, 73.11; H, 3.22; N, 17.01.

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References

1. Lin, H.; Danishefsky, S. J. *Angew. Chemie Int. Ed.* **2003**, *42*, 36-51.
2. Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, *2003*, 2209-2219.
3. Galliford, C. V; Scheidt, K. A. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 8748-8758.
4. Palmisano, G.; Annunziata, R.; Papeo, G.; Sisti, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1-4.
5. Da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Brazilian Chem. Soc.* **2001**, *12*, 273-324.
6. Kates, M.; Marion, L. *Can. J. Chem.* **1951**, *29*, 37-45.
7. Rostamnia, S.; Nuri, A.; Xin, H.; Pourjavadi, A.; Hosseini, S. H. *Tetrahedron Lett.* **2013**, *54*, 3344-3347.
8. Nemouchi, S.; Boulcina, R.; Carboni, B.; Debache, A. *Comptes Rendus Chim.* **2012**, *15*, 394-397.
9. Borhade, A. V.; Uphade, B. K.; Tope, D. R. *J. Chem. Sci.* **2013**, *125*, 583-589.
10. Albadi, J.; Mansournezhad, A.; Darvishi-Paduk, M. *Chinese Chem. Lett.* **2013**, *24*, 208-210.
11. Gourdeau, H.; Leblond, L.; Hamelin, B.; Desputeau, C.; Dong, K.; Kianicka, I.; Custeau, D.; Boudreau, C.; Geerts, L.; Cai, S. X.; et al. *Mol. Cancer Ther.* **2004**, *3*, 1375-1384.
12. Mohr, S. J.; Chirigos, M. A.; Fuhrman, F. S.; Pryor, J. W. *Cancer Res.* **1975**, *35*, 3750-3754.
13. Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Zhao, J.; Crogan-Grundy, C.; Xu, L.; Lamothe, S.; Gourdeau, H.; Denis, R.; et al. *J. Med. Chem.* **2007**, *50*, 2858-2864.

14. Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Crogan-Grundy, C.; Labreque, D.; Bubenick, M.; Attardo, G.; Denis, R.; Lamothe, S.; et al. *J. Med. Chem.* **2008**, *51*, 417-423.
15. Sangani, C. B.; Shah, N. M.; Patel, M. P.; Patel, R. G. *J. Serbian Chem. Soc.* **2012**, *77*, 1165-1174.
16. Thareja, S.; Verma, A.; Kalra, A.; Gosain, S.; Rewatkar, P. V.; Kokil, G. R. *Acta Pol.* **2010**, *67*, 423-427.
17. Thomas, N.; Zachariah, S. *Asian J. Pharm. Clin. Res.* **2013**, *6*, 11-15.
18. Albiston, A. L.; Diwakarla, S.; Fernando, R. N.; Mountford, S. J.; Yeatman, H. R.; Morgan, B.; Pham, V.; Holien, J. K.; Parker, M. W.; Thompson, P. E.; et al. *Br. J. Pharmacol.* **2011**, *164*, 37-47.
19. Skommer, J.; Wlodkowic, D.; Mättö, M.; Eray, M.; Pelkonen, J. *Leuk. Res.* **2006**, *30*, 322-331.
20. Kemnitzer, W.; Kasibhatla, S.; Jiang, S.; Zhang, H.; Zhao, J.; Jia, S.; Xu, L.; Crogan-Grundy, C.; Denis, R.; Barriault, N.; et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4745-4751.
21. Konkoy, C.; Fick, D.; Cai, S.; Lan, N.; Keana, J. *Chem. Abstr 2001, 134, 29313a.* **2001**.
22. Bhat, A. R.; Dongre, R. S.; Shalla, A. H.; Naikoo, G. A.; Ul Hassan, I. *J. Assoc. Arab Univ. Basic Appl. Sci.* **2016**, *20*, 19-25.
23. Jiang, X.; Sun, Y.; Yao, J.; Cao, Y.; Kai, M.; He, N.; Zhang, X.; Wang, Y.; Wang, R. *Adv. Synth. Catal.* **2012**, *354*, 917-925.
24. Raasch, A.; Scharfenstein, O.; Tränkle, C.; Holzgrabe, U.; Mohr, K. *J. Med. Chem.* **2002**, *45*, 3809-3812.
25. Jain, M.; Sakhuja, R.; Khanna, P.; Bhagat, S.; Jain, S. *Arkivoc* **2008**, *xv*, 54-64.
26. Yang, G. Y.; Oh, K. A.; Park, N. J.; Jung, Y. S. *Bioorg. Med. Chem.* **2007**, *15*, 7704-7710.
27. Di Giacomo, B.; Bedini, A.; Spadoni, G.; Tarzia, G.; Fraschini, F.; Pannacci, M.; Lucini, V. *Bioorg. Med. Chem.* **2007**, *15*, 4643-4650.
28. Antonini, I.; Polucci, P.; Magnano, A.; Gatto, B.; Palumbo, M.; Menta, E.; Pescalli, N.; Martelli, S. *J. Med. Chem.* **2003**, *46*, 3109-3115.
29. Antonini, I.; Polucci, P.; Magnano, A.; Sparapani, S.; Martelli, S. *J. Med. Chem.* **2004**, *47*, 5244-5250.
30. Wang, C.; Jung, G. Y.; Hua, Y.; Pearson, C.; Bryce, M. R.; Petty, M. C.; Batsanov, A. S.; Goeta, A. E.; Howard, J. A. K. *Chem. Mater.* **2001**, *13*, 1167-1173.
31. Wang, C.; Jung, G. Y.; Batsanov, A. S.; Bryce, M. R.; Petty, M. C. *J. Mater. Chem.* **2002**, *12*, 173-180.
32. Jieping Zhu, H. B. *Multicomponent Reactions*; Wiley: Weinheim, Germany, 2006.
33. Shaaban, M. R.; Elwahy, A. H. M. *Curr. Org. Synth.* **2015**, *11*, 471-525.
34. Khoobi, M.; Ramazani, A.; Foroumadi, A.; Souldozi, A.; Ślepokura, K.; Lis, T.; Mahyari, A.; Shafiee, A.; Joo, S. W. *Helv. Chim. Acta* **2013**, *96*, 906-918.
35. Zareai, Z.; Khoobi, M.; Ramazani, A.; Foroumadi, A.; Souldozi, A.; Ślepokura, K.; Lis, T.; Shafiee, A. *Tetrahedron* **2012**, *68*, 6721-6726.
36. Ramazani, A.; Rouhani, M.; Joo, S. W. *Ultrason. Sonochem.* **2016**, *28*, 393-399.
37. Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083-3135.
38. Biggs-Houck, J. E.; Younai, A.; Shaw, J. T. *Curr. Opin. Chem. Biol.* **2010**, *14*, 371-382.
39. Brauch, S.; van Berkel, S. S.; Westermann, B. *Chem. Soc. Rev.* **2013**, *42*, 4948-4962.
40. Nasseri, M. A.; Zakerinasab, B.; Allahresani, A. *Iran. J. Catal.* **2015**, *5*, 161-167.
41. Elinson, M. N.; Ilovaisky, A. I.; Merkulova, V. M.; Demchuk, D. V.; Belyakov, P. A.; Ogibin, Y. N.; Nikishin, G. I. *Electrochim. Acta* **2008**, *53*, 8346-8350.
42. Abdelhamid, I. A.; Darwish, E. S.; Nasra, M. A.; Abdel-Gallil, F. M.; Fleita, D. H. *Synthesis (Stuttg).* **2010**, 1107-1112.
43. Ghozlan, S. A. S.; Abdelhamid, I. A.; Hassaneen, H. M.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2007**, *44*, 105-108.

44. Abdelhamid, I. A. *Synlett* **2008**, *10*, 625-627.
45. Ghozlan, S. A. S.; Abdelmoniem, A. M.; Butenschön, H.; Abdelhamid, I. A. *Tetrahedron* **2015**, *71*, 1413-1418.
46. Ghozlan, S. A. S.; Mohamed, M. H.; Abdelmoniem, A. M.; Abdelhamid, I. A. *Arkivoc* **2009**, *x*, 302-311.
47. Ghozlan, S. A. S.; Mohamed, M. F.; Ahmed, A. G.; Shouman, S. A.; Attia, Y. M.; Abdelhamid, I. A. *Arch. Pharm. (Weinheim).* **2015**, *348*, 113-124.
48. Mekky, A. E. M.; Elwahy, A. H. M. *J. Heterocycl. Chem.* **2014**, *51*, E34-E41.
49. Sayed, O. M.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. *J. Sulfur Chem.* **2014**, *36*, 124-134.
50. Sayed, O. M.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. *J. Heterocycl. Chem.* **2015**, DOI: 10.1002/jhet.2373.
51. Elwahy, A. H. M. .; Abbas, A. A. *Tetrahedron* **2000**, *56*, 885-895.
52. Elwahy, A. H. M.; Abbas, A. A.; Kassab, R. M. *Synthesis (Stuttg).* **2002**, 260-264.
53. Elwahy, A. H. M.; Abbas, A. A. *Synth. Commun.* **2000**, *30*, 2903-2921.
54. Wang, Y.; Cao, S. L.; Wan, C. Q.; Yuan, J. L. *Acta Cryst* **2010**, *E66*, o1569-o1570.
55. Nikpassand, M.; Zare Fekri, L.; Jamshidi, N. *J. Heterocycl. Chem.* **2015**, *52*, 1580-1583.
56. Tayade, Y. A.; Padvi, S. A.; Wagh, Y. B.; Dalal, D. S. *Tetrahedron Lett.* **2015**, *56*, 2441-2447.