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Spirooxindoles: reaction of 2,6-diaminopyrimidin-4(3*H*)-one and isatins

Khosrow Jadidi, Ramin Ghahremanzadeh, Ayoob Bazgir *

Department of Chemistry, Shahid Beheshti University, G.C., PO Box 19396-4716, Tehran, Iran

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ABSTRACT

A simple and efficient cyclocondensation reaction of 2,6-diaminopyrimidin-4(3*H*)-one and isatins for the synthesis of spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine] and spiro[indoline-pyrido[2,3-*d*:6,5-*d*′]dipyrimidine] derivatives is reported.

1. Introduction

Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process, and analysis of drugs in late development or on the market shows that 68% of them are heterocycles.[1,2] Therefore, it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received significant attention.

Benzo- and hetero-fused pyrimidines are known to exhibit promising antiviral,[3] antibacterial,[4] anti-AIDS[5] and antinociceptive[6] activities. Fused pyrimidines are selective inhibitors for multidrug resistance (MDR).[7] The relevance of fused pyrimidines as antiplatelet and antithrombotic drugs[8] has been firmly established by clinical trials. Thus, further exploration of pyrimidine chemistry appears to be worthwhile.

Spirocyclic systems containing one carbon atom common to two rings are structurally interesting.[9] The asymmetric characteristic of the molecule due to the chiral spiro carbon is one of the important criteria of the biological activities. The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds.[10] Spiro compounds represent an important class of naturally occurring substances characteristic by their highly pronounced biological properties.[11,12] Similarly, functionalized spiro cycloalkyloxindoles are found in a variety of natural products and bioactive molecules.[13,14] Consequently, many synthetic methodologies have been developed for constructing these spirocycles, most of which were based on cycloaddition or condensation reactions.[15–23]

Considering the above reports, the development of new and simple synthetic methods for the efficient preparation of spiro heterocycles containing pyrimidine ring fragments is therefore an interesting challenge. Very recently, we have reported a synthesis of spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine] derivatives by the reaction of 6-amino-uracils and isatins in refluxing ethanol.[24] Due to the biological activity of fused pyrimidines, and our interest in the synthesis of heterocyclic compounds,[25–31] herein, we report a simple and efficient method for the preparation of new spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*] pyrimidine] derivatives. To the best of our knowledge, this is the second report on the synthesis of spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine]s.

2. Results and discussion

After some preliminary experimentation, it was found that a mixture of 2,6-diaminopyrimidin-4(3*H*)-one **1** and isatin **2a**, in the presence of a catalytic amount of *p*-toluene sulfuonic acid (*p*-TSA) as an inexpensive and readily available catalyst, afforded 2,2′-diamino-3*H*-spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine]-4,4′,6′(3′*H*,7′*H*,10*H*)-trione **3a** in 85% yield after refluxing in ethanol for 8 h (Scheme 1).

Encouraged by this success, we have extended this reaction to various isatins **2b–d** under similar conditions (using EtOH/*p*-TSA), furnishing the respective 2,2′-diamino-3*H*-spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine]-4,4′,6′(3′*H*,7′*H*,10*H*)-triones **3b–d** in good yields (Scheme 2). The optimized results are summarized in Table 1.

* Corresponding author. Fax: +98 21 22431661.
E-mail address: a_bazgir@sbu.ac.ir (A. Bazgir).

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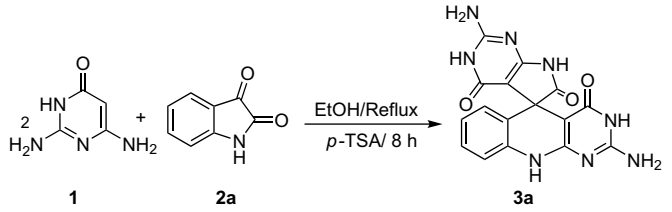
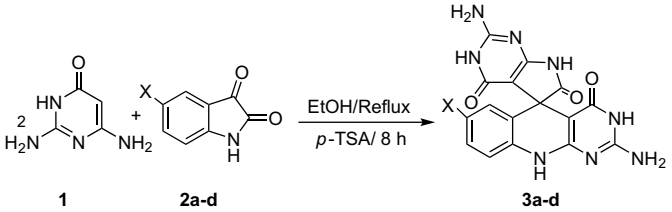


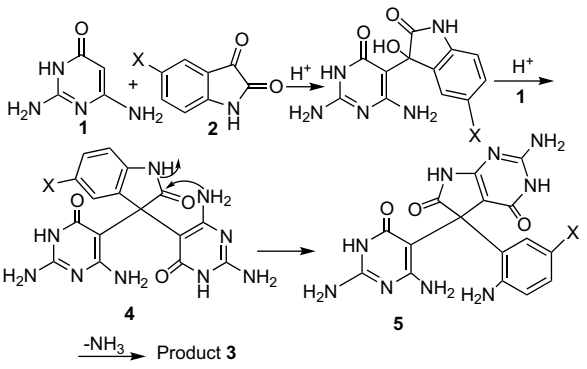
1 2a 3a

Scheme 1.

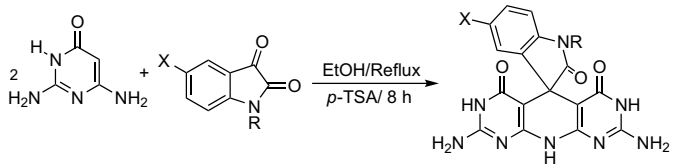


1 2a-d 3a-d

Scheme 2.



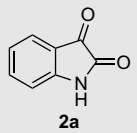
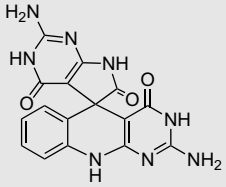
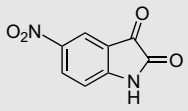
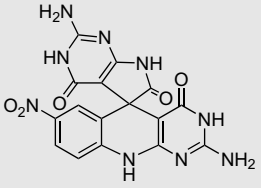
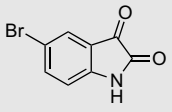
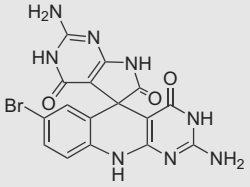
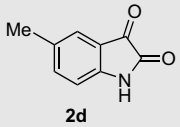
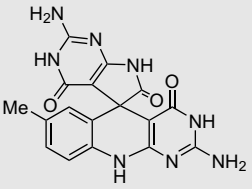
Scheme 3.



1 6a-g 7a-g

Scheme 4.

Table 1
Synthesis of spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine]-trione **3**

Entry	Isatin **2**	Product **3**	Yield[a] (%)
1	 **2a**	 **3a**	85
2	 **2b**	 **3b**	90
3	 **2c**	 **3c**	88
4	 **2d**	 **3d**	85

[a] Isolated yields.

We have not established the exact mechanism for the formation of spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine]-triones **3**, however, a reasonable suggestion is offered in Scheme 3. The reaction may have proceeded through intermediate **4**, formed in situ by reaction of isatins **2** with 2,6-diaminopyrimidin-4(3*H*)-one **1**, then, intermediate **4** was converted to intermediate **5** and which cyclized to afford the corresponding product **3** and ammonia (Scheme 3).

Finally, to further explore the potential of this protocol for spiro-heterocyclic synthesis, we investigated the reaction of 2,6-di aminopyrimidin-4(3*H*)-one **1** and *N*-alkylisatins **6a**–**g**. Surprisingly, it was found that under similar conditions, different products 2′, 8′-diamino-spiro[indoline-3,5′-pyrido[2,3-*d*:6,5-*d*′]dipyrimidine]-2,4′,6′(3′*H*,7′*H*,10′*H*)-triones **7a**–**g** were formed in 78–87% yields (Scheme 4, Table 2). In previous work, we found that *N*-alkylisatin and isatins reacted similarly.[24] To the best of our knowledge, this new procedure provides the first example of an efficient method for the synthesis of spiro[indoline-3,5′-pyrido[2,3-*d*:6,5-*d*′]-dipyrimidine]triones.

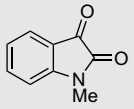
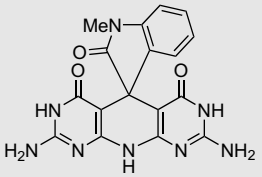
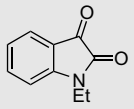
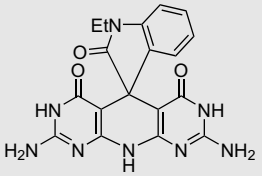
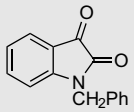
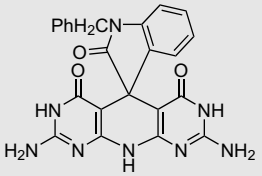
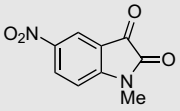
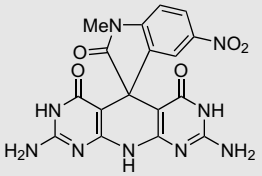
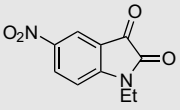
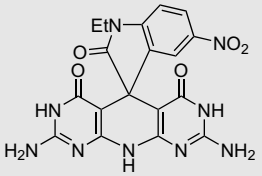
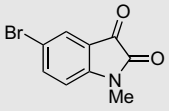
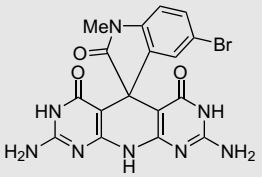
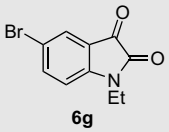
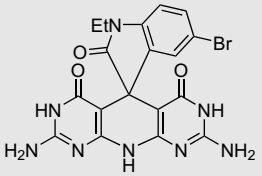
Compounds **7** may result from the initial addition of 2,6-di-aminopyrimidin-4(3*H*)-one **1** to *N*-alkylisatins **6** to yield intermediate **8**, which reacted further with another molecule of **1** and cyclized to afford the corresponding product **7** (Scheme 5).

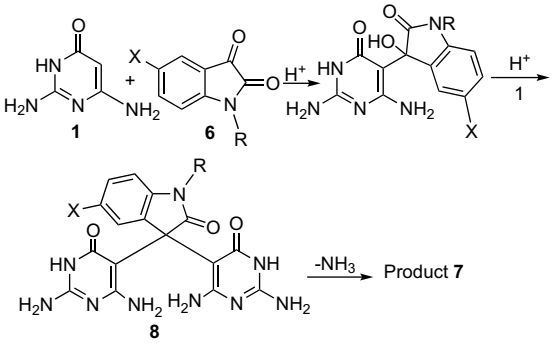
Compounds **3a**–**d** and **7a**–**g** are stable solids whose structures are fully supported by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis.

3. Conclusion

In conclusion, we have described an efficient and simple method for the preparation of spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine] and spiro[indoline-pyrido[2,3-*d*:6,5-*d*′]dipyrimidine] derivatives via a cyclocondensation reaction of 2,6-diaminopyrimidin-4(3*H*)-one and isatins in refluxing ethanol.

Table 2
Synthesis of spiro[indoline-pyrido[2,3-*d*:6,5-*d*′]dipyrimidine] **7**

Entry	Isatin **2**	Product **7**	Yield (%)
1	 **6a**	 **7a**	81
2	 **6b**	 **7b**	80
3	 **6c**	 **7c**	78
4	 **6d**	 **7d**	87
5	 **6e**	 **7e**	86
6	 **6f**	 **7f**	88
7	 **6g**	 **7g**	83



Scheme 5.

4. Experimental

4.1. Typical procedure for the preparation of 2,2′-diamino-3*H*-spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine] 4,4′,6′(3′*H*,7′*H*,10*H*)-trione (3a)

A mixture of 2,6-diaminopyrimidin-4(3*H*)-one (2 mmol), isatin (1 mmol) and *p*-TSA (0.5 mmol) in refluxing EtOH (5 mL) was stirred for 8 h (TLC). After completion of reaction, the reaction mixture was filtered and the precipitate washed with water and then with EtOH to afford the pure product **3a** as a white powder (0.31 g, 85%). Mp>320 °C. IR (KBr) (ν_{max}/cm^{-1}): 3393, 3152, 1681, 1658, 1637. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 6.26 (2H, br s, NH_2), 6.65–7.04 (6H, m, NH_2 and H–Ar), 9.21 (1H, s, NH), 10.07 (1H, s, NH), 10.18 (1H, s, NH), 10.43 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 50.5, 56.5, 85.4, 101.7, 115.5, 121.7, 122.3, 126.3, 127.7, 137.9, 154.4, 155.7, 157.3, 160.9, 163.4, 182.7. MS, *m*/*z* (%): 364 (M^+, 15), 323 (23), 236 (50), 149 (100). Anal. Calcd for $C_{16}H_{12}N_8O_3$: C, 52.75; H, 3.32; N, 30.76%. Found: C, 52.69; H, 3.37; N, 30.69%.

4.2. 2,2′-Diamino-7-nitro-3*H*-spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine]-4,4′,6′(3′*H*,7′*H*,10*H*)-trione (3b)

White powder (0.37 g, 90%); mp>300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3363, 3152, 1733, 1699, 1658. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 6.42 (2H, s, NH_2), 6.72 (2H, s, NH_2), 7.07 (1H, d, $^3J_{HH}$=9.0 Hz, H–Ar), 7.47 (1H, s, H–Ar), 7.97 (1H, d, $^3J_{HH}$=9.0 Hz, H–Ar), 10.05 (1H, s, NH), 10.26 (1H, s, NH), 10.35 (1H, s, NH), 10.66 (1H, s, NH). MS, *m*/*z* (%): 409 (M^+, 10), 236 (52), 149 (100). Anal. Calcd for $C_{16}H_{11}N_9O_5$: C, 46.95; H, 2.71; N, 30.80%. Found: C, 46.89; H, 2.76; N, 30.87%.

Due to very low solubility of products **3b** and **3c**, we can′t report the ^{13}C NMR data for these products.

4.3. 2,2′-Diamino-7-bromo-3*H*-spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine]-4,4′,6′(3′*H*,7′*H*,10*H*)-trione (3c)

White powder (0.39 g, 88%); mp>300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3342, 3168, 1660, 1658. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 6.28 (2H, s, NH_2), 6.66 (2H, s, NH_2), 6.68–7.21 (3H, m, H–Ar), 9.37 (1H, s, NH), 10.11 (1H, s, NH), 10.22 (1H, s, NH), 10.49 (1H, s, NH). MS, *m*/*z* (%): 444 (M^+, 12), 442 (M^+, 12), 236 (100), 149 (97). Anal. Calcd for $C_{16}H_{11}BrN_8O_3$: C, 43.36; H, 2.50; N, 25.28%. Found: C, 43.42; H, 2.44; N, 25.36%.

4.4. 2,2′-Diamino-7-methyl-3*H*-spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine]-4,4′,6′(3′*H*,7′*H*,10*H*)-trione (3d)

White powder (0.32 g, 85%); mp>320 °C. IR (KBr) (ν_{max}/cm^{-1}): 3360, 3193, 1714, 1653. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 2.09 (3H, s, CH_3), 6.19 (2H, s, NH_2), 6.45 (1H, s, H–Ar), 6.59 (2H, s, NH_2), 6.79–6.82 (2H, m, H–Ar), 9.10 (1H, s, NH), 9.98 (1H, s, NH), 10.15 (1H, s, NH), 10.38(1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 20.8, 50.5, 85.2, 101.6, 115.4, 122.1, 126.3, 128.4, 130.2, 135.6, 154.3, 155.8, 157.2, 160.9, 163.4, 182.8. MS, *m*/*z* (%): 378 (M$^+$, 8), 368 (100), 313 (42), 236 (57), 149 (78). Anal. Calcd for $C_{17}H_{14}N_8O_3$: C, 53.97; H, 3.73; N, 29.62%. Found: C, 53.92; H, 3.69; N, 29.69%.

4.5. 2′,8′-Diamino-spiro[1-methylindoline-3,5′-pyrido[2,3-*d*:6,5-*d*′]dipyrimidine]-2,4′,6′(3′*H*,7′*H*,10′*H*)-trione (7a)

White powder (0.31 g, 81%); mp>300 °C; IR (KBr) (ν_{max}/cm^{-1}): 3358, 3173, 1653, 1607. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.05 (3H, s, CH_3), 6.62 (4H, br s, $2NH_2$), 6.75–7.11 (4H, m, H–Ar), 9.48 (1H, s, NH), 10.26 (2H, s, 2NH). MS, *m*/*z* (%): 378 (M$^+$, 5), 368 (100), 236 (50). Anal. Calcd for $C_{17}H_{14}N_8O_3$: C, 53.97; H, 3.73; N, 29.62%. Found: C, 53.91; H, 3.78; N, 29.54%.

Due to very low solubility of products **7a–d** and **7g**, we can't report the ^{13}C NMR data for these products.

4.6. 2′,8′-Diamino-spiro[1-ethylindoline-3,5′-pyrido[2,3-*d*:6,5-*d*′]dipyrimidine]-2,4′,6′(3′*H*,7′*H*,10′*H*)-trione (7b)

White powder (0.31 g, 80%); mp>320 °C; IR (KBr) (ν_{max}/cm^{-1}): 3440, 3168, 1702, 1643. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.18 (3H, t, $^3J_{HH}$=6.2 Hz, CH_3), 3.63 (2H, q, $^3J_{HH}$=6.3 Hz, CH_2), 6.72 (4H, br s, $2NH_2$), 6.75–710 (4H, m, H–Ar), 9.54 (1H, s, NH), 10.33 (2H, s, 2NH). MS, *m*/*z* (%): 392 (M$^+$, 8), 264 (25), 236 (50), 149 (100). Anal. Calcd for $C_{18}H_{16}N_8O_3$: C, 55.10; H, 4.11; N, 28.56%. Found: C, 55.04; H, 4.06; N, 28.64%.

4.7. 2′,8′-Diamino-spiro[1-benzylindoline-3,5′-pyrido[2,3-*d*:6,5-*d*′]dipyrimidine]-2,4′,6′(3′*H*,7′*H*,10′*H*)-trione (7c)

White powder (0.35 g, 78%); mp>320 °C; IR (KBr) (ν_{max}/cm^{-1}): 3342, 3203, 1719, 1659. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 4.82 (2H, s, CH_2), 6.75 (4H, br s, $2NH_2$), 6.35–768 (9H, m, H–Ar), 9.61 (1H, s, NH), 10.54 (2H, s, 2NH). MS, *m*/*z* (%): 454 (M$^+$, 10), 264 (45), 149 (100). Anal. Calcd for $C_{23}H_{18}N_8O_3$: C, 60.79; H, 3.99; N, 24.66%. Found: C, 60.75; H, 3.94; N, 24.60%.

4.8. 2′,8′-Diamino-5-nitro-spiro[1-methylindoline-3,5′-pyrido[2,3-*d*:6,5-*d*′]dipyrimidine]-2,4′,6′(3′*H*,7′*H*,10′*H*)-trione (7d)

White powder (0.37 g, 87%); mp>320 °C; IR (KBr) (ν_{max}/cm^{-1}): 3373, 3163, 1716, 1668. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.04 (3H, s, CH_3), 6.75 (4H, br s, $2NH_2$), 6.76–7.26 (3H, m, H–Ar), 9.61 (1H, s, NH), 10.37 (2H, s, 2NH). MS, *m*/*z* (%): 423 (M$^+$, 5), 264 (35), 236 (100), 149 (90). Anal. Calcd for $C_{17}H_{13}N_9O_5$: C, 48.23; H, 3.10; N, 29.78%. Found: C, 48.29; H, 3.16; N, 29.86%.

4.9. 2′,8′-Diamino-5-nitro-spiro[1-ethylindoline-3,5′-pyrido[2,3-*d*:6,5-*d*′]dipyrimidine]-2,4′,6′(3′*H*,7′*H*,10′*H*)-trione (7e)

White powder (0.38 g, 86%); mp>320 °C; IR (KBr) (ν_{max}/cm^{-1}): 3360, 3166, 1714, 1661. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.20 (3H, t, $^3J_{HH}$=6.5 Hz, CH_3), 3.75 (2H, q, $^3J_{HH}$=6.5 Hz, CH_2), 6.79 (4H, br s, $2NH_2$), 7.08 (1H, d, $^3J_{HH}$=8.5 Hz, H–Ar), 7.71 (1H, s, H–Ar), 8.11 (1H, d, $^3J_{HH}$=8.5 Hz, H–Ar), 9.71 (1H, s, NH), 10.46 (2H, s, 2NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm): 12.3, 30.5, 48.4, 89.3, 106.9, 118.0, 125.2, 137.8, 142.2, 150.8, 155.1, 155.6, 160.6, 179.6. MS, *m*/*z* (%): 437 (M$^+$, 4), 368 (22), 313 (31), 264 (15), 236 (40), 149 (100). Anal. Calcd for $C_{18}H_{15}N_9O_5$: C, 49.43; H, 3.46; N, 28.82%. Found: C, 49.49; H, 3.40; N, 28.76%.

4.10. 2′,8′-Diamino-5-bromo-spiro[1-methylindoline-3,5′-pyrido[2,3-*d*:6,5-*d*′]dipyrimidine]-2,4′,6′(3′*H*,7′*H*,10′*H*)-trione (7f)

White powder (0.40 g, 88%); mp>320 °C; IR (KBr) (ν_{max}/cm^{-1}): 3361, 3164, 1656, 1606. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.05 (3H, s, CH_3), 6.76 (4H, br s, $2NH_2$), 6.78–6.99 (3H, m, H–Ar), 9.62 (1H, s, NH), 10.39 (2H, s, 2NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 26.7, 48.5, 89.8, 108.9, 113.2, 125.5, 129.9, 138.9, 144.7, 154.9, 155.2, 160.2, 179.4. MS, *m*/*z* (%): 458 (M$^+$, 8), 456 (M$^+$, 8), 236 (50), 149 (100). Anal. Calcd for $C_{17}H_{13}BrN_8O_3$: C, 44.66; H, 2.87; N, 24.51%. Found: C, 44.70; H, 2.84; N, 24.56%.

4.11. 2′,8′-Diamino-5-bromo-spiro[1-ethylindoline-3,5′-pyrido[2,3-*d*:6,5-*d*′]dipyrimidine]-2,4′,6′(3′*H*,7′*H*,10′*H*)-trione (7g)

White powder (0.39 g, 83%); mp>320 °C; IR (KBr) (ν_{max}/cm^{-1}): 3363, 3162, 1652, 1604. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 1.15 (3H, br s, CH_3), 3.62 (2H, br s, CH_2), 6.75 (4H, br s, $2NH_2$), 6.97–7.46 (3H, m, H–Ar), 9.56 (1H, s, NH), 10.36 (2H, s, 2NH). MS, *m*/*z* (%): 472 (M$^+$, 10), 470 (M$^+$, 10), 236 (100), 149 (100). Anal. Calcd for $C_{18}H_{15}BrN_8O_3$: C, 45.87; H, 3.21; N, 23.78%. Found: C, 45.82; H, 3.25; N, 23.73%.

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