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DBU-Catalyzed, facile and efficient method for synthesis of spirocyclic 2-oxindole derivatives with incorporated 6-amino-4*H*-pyridazines and fused derivatives via [3+3] atom combination

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ABSTRACT

3-Cyanomethylidene oxindole derivatives were prepared in excellent yields utilizing DBU-promoted Knoevenagel condensation of isatin derivatives with active methylene reagents. The isolated products were then reacted with azaenamines via a DBU-promoted Michael addition to yield spirocyclic 2-oxindole derivatives with incorporated 6-amino-4*H*-pyridazines and their fused derivatives.

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1. Introduction

Spirocyclic systems containing one sp^3 carbon atom common to two rings are structurally interesting.[1] The asymmetric structure of the molecule due to the chiral spiro carbon atom is one of the important criteria of the biological activities.[2,3] The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds.[4] Similarly, functionalized spiro cycloalkyloxindoles are found in a variety of natural products and bioactive molecules.[5,6] Due to the biological activity of pyridazines[7–9] and our interest in the synthesis of heterocyclic compounds,[10–15] herein, we report a simple and efficient method for the preparation of new 4,3′-spiro(pyridazine)-2-oxindole derivatives. To the best of our knowledge, this is the first report on this synthesis.

2. Results and discussion

Many synthetic methodologies have been developed for constructing spirocycles containing 2-oxindole, most of which were based on cycloaddition or condensation reactions.[16–22] Considering these reports, the development of new and simple synthetic methods for the efficient preparation of spiro heterocycles containing pyridazine ring fragments is therefore an interesting challenge. So, in continuation of our interest in azaenamine chemistry[10,23–25] and also of our interest in utilizing green methodologies,[24,26,27] herein, we report an efficient route for the synthesis of spiropyridazines containing 2-oxindole nucleus using DBU as a basic catalyst. Recently, DBU has received considerable attention as an inexpensive and readily available catalyst for Knoevenagel condensations[28] and Michael additions[29] under mild and convenient conditions, affording the corresponding products in excellent yields. Thus, in our initial attempt, 3-cyanomethylidene-2-oxindoles **3a**–**f** were obtained in 80–90% yields by Knoevenagel condensation of isatin derivatives **1a**,**b** with active methylene compounds **2a**–**c**. In the next step, the isolated 3-cyanomethylidene-2-oxindoles **3** were reacted with azaenamine **4**, in the presence of DBU via Michael addition reaction to yield products, which can be formulated as **6** or **8**. Compounds **6** result from Michael addition of CH of azaenamine **4** to the double bond in **3**, followed by cyclization (pathway A), while compounds **8** result from initial addition of NH of compound **4** to the exocyclic double bond in **3**, followed by cyclization (pathway B) (cf. Scheme 1). It is clear that simple spectral tools cannot differentiate between both structures **6** and **8**. So, to establish the structure of the product with certainty, the X-ray crystal structure of product **6f** was determined [30]

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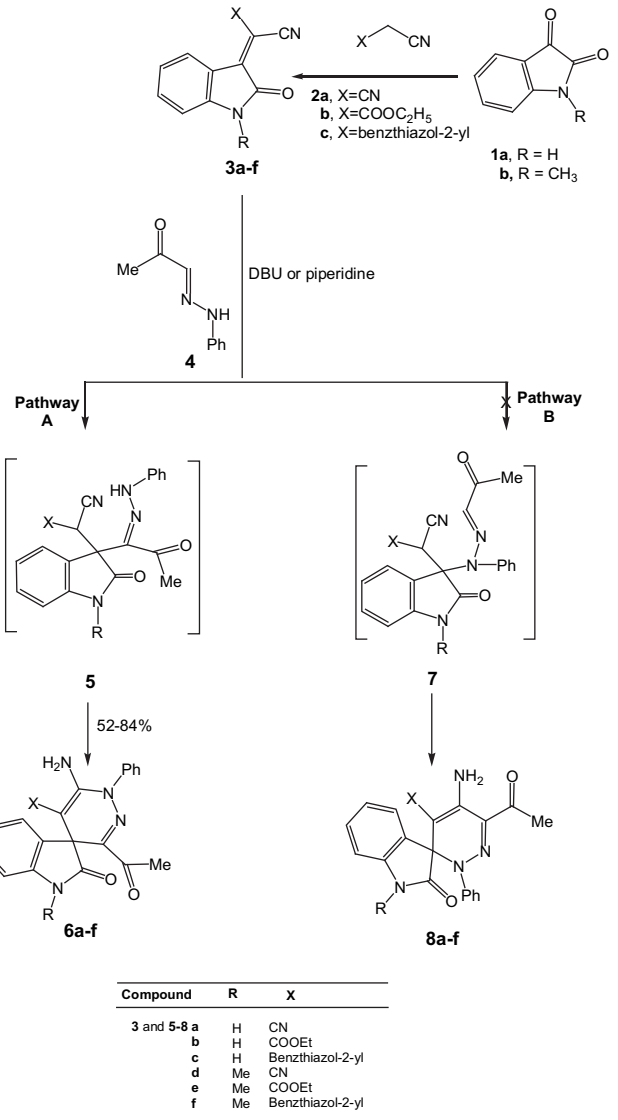


Compound	R	X
3 and 5-8 a	H	CN
b	H	COOEt
c	H	Benzthiazol-2-yl
d	Me	CN
e	Me	COOEt
f	Me	Benzthiazol-2-yl

Scheme 1. Synthesis of compounds **6a**–**f**.

(cf. Fig. 1 and Table 1) (R=CH_3 and X=benzthiazol-2-yl) that indicates that the reaction proceeds through pathway A not B. The structure of the formed products was also supported based on the elemental analysis and spectral data. IR spectra of compounds **6a**–**f** revealed broad absorption bands at $\nu \sim 3168$–$3496\ cm^{-1}$ assigned to the NH_2 group. It also indicated the absence of CN bands in case of **6b**, **c**, **e**, and **f**. ^1H NMR spectra indicated the presence of NH_2 by a signal at $\delta \sim 6.14$–6.91 ppm. The structure was also supported by the ^{13}C NMR spectrum, which indicated the absence of CN for compounds **6b**, **c**, **e**, and **f**. In addition it featured a signal at $\delta \sim 50$ ppm assigned for the spiro carbon atom. The other carbon atoms appeared at their expected positions (as shown in Experimental part).

These syntheses have been also conducted using a dioxane solution containing piperidine as the catalyst and the yields in every case are compared in Table 2.

In an extension of the program to confirm the proposed pathway we carried out the reaction using azaenamine **9**[31] containing carboxylic ester on thiophene ring, where only further cyclization occurred if the reaction followed pathway A, while in case of pathway B no further cyclization would be occurred (Scheme 2).

Thus, reacting **9** with 3-cyanomethylidene-2-oxindoles **3** has resulted in formation of compounds **10** that then directly cyclized into **11** under the reaction conditions. The chemical structures of

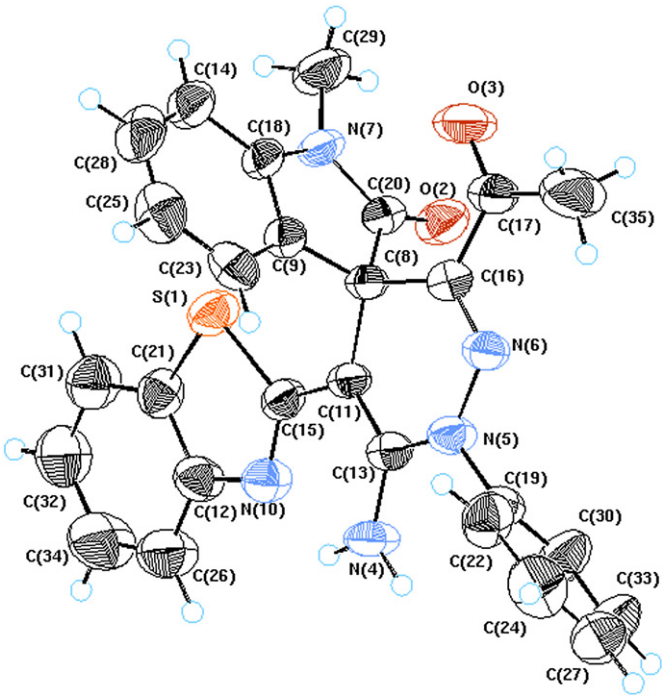


Figure 1. X-ray crystal structure of compound **6f**.

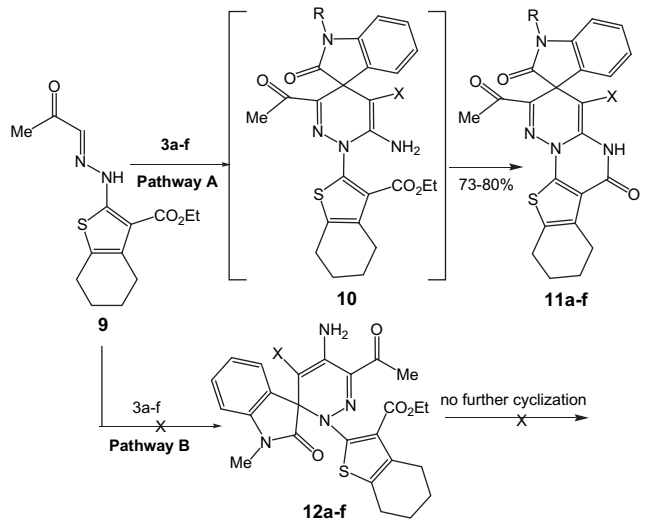
Table 1
Selected bond angles and bond lengths of compound **6f**

Bond lengths (Å)		Bond angles (degrees)	
Atoms	Found	Atoms	Found
N4—C13	1.337	C9—C8—C16	111.2
N5—C13	1.382	C9—C8—C20	100.8
C8—C11	1.535	C11—C8—C16	109.1
C8—C16	1.517	C9—C8—C11	113.8
C8—C9	1.526	C16—C8—C20	108.3
C11—C13	1.382	C8—C11—C15	120.7
		C13—C11—C15	119.4
		N5—C13—C11	120.8

Table 2
Comparison of the % yields of **6a**–**f** in cases of piperidine and DBU catalysts

Entry	R	X	% Yield	
			Piperidine	DBU
6a	H	CN	77	80
6b	H	$COOC_2H_5$	48	52
6c	H	Benzthiazol-2-yl	79	83
6d	CH_3	CN	75	79
6e	CH_3	$COOC_2H_5$	78	81
6f	CH_3	Benzthiazol-2-yl	80	84

compounds **11** are well established based on mass and NMR spectral tools, which indicated the absence of the OEt group attached to thiophene ring. Thus, ^1H NMR spectra of **11a**–**f** compounds revealed characteristic set of multiplets at $\delta \sim 1.76$–2.275 ppm for cyclohexene ring. It also indicated singlet signals at $\delta \sim 2.30$ for (CH_3CO). In addition it indicated singlet signals at 3.12–3.15 for the methyl attached to indole ring in compounds **11d**–**f**. It also featured aromatic protons at 6.8–7.5 ppm, a broad singlet at $\delta \sim 11$–13.8 ppm for NH. The corresponding non-alkylated compounds **11a**–**c** (R=H) also revealed a proton singlet from the NH group of the 2-oxindole ring in a higher field at 10.4–11 ppm. Furthermore, full assignment of the ^{13}C NMR data confirmed the structures **11**, where the key signal at δ 167–168 ppm was assigned to the 2-oxindolic carbonyl group; at 174–177 ppm was assigned for



Scheme 2. Synthesis of compounds **11a–f**.

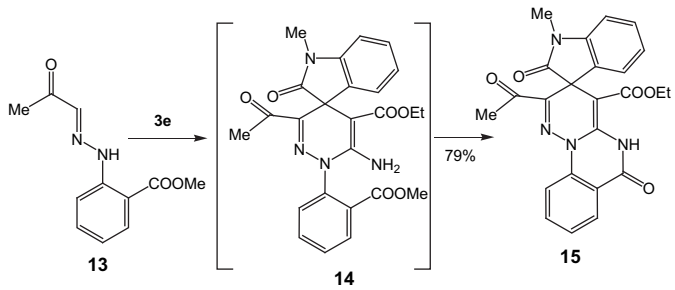
CONH; at δ 50–55 ppm was assigned to the quaternary sp^3 carbon (spiro carbon); at δ 80–145 ppm was assigned to the sp^2 and aromatic carbons. The signal at δ 118 ppm was assigned to the nitrile carbon in the pyridazine ring for compounds **11a**,**d**. Full spectral data for all new compounds are presented in Experimental section.

Also, the reactions were carried out in both conditions of DBU and piperidine catalysts and the % yields were compared each time (Table 3).

Table 3
Comparison of the % yields of **11a–f** in case of piperidine and DBU catalysts

Entry	R	X	% Yield	
			Piperidine	DBU
11a	H	CN	74	78
11b	H	$COOC_2H_5$	73	76
11c	H	Benzthiazol-2-yl	76	80
11d	CH_3	CN	74	78
11e	CH_3	$COOC_2H_5$	69	75
11f	CH_3	Benzthiazol-2-yl	77	79

Similarly azaenamine **13** reacted with 3-cyanomethylidene-2-oxindole **3e** to yield the spiro compound **15** through the intermediate **14**. The structure of this compound was also established based on elemental analysis and spectral data that indicated the absence of OMe (Scheme 3).



Scheme 3. Synthesis of compound **15**.

3. Conclusion

In the present article we could manage to report a new simple and efficient route to new spirocyclic 2-oxindole derivatives of 6-amino-4*H*-pyridazine and fused derivatives via the first reported [3+3] atom combination reaction of azaenamines with 2-methylidene oxindole derivatives.

4. Experimental

4.1. General

Melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using a Bruker–vector 22 spectrophotometer FTIR. The ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 as solvent at 300 MHz and 75 MHz, respectively on Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GMSS-QP-1000 EX mass spectrometer at 70 eV. The crystal structure was determined by the X-ray unit at the National Research Center, Dokki, Cairo.

4.2. General method for preparation of compounds 3a–f

4.2.1. General procedure. A mixture of isatin or *N*-methylisatin **1a** or **b** (10 mmol) and active methylenes **2a–c** (10 mmol) was dissolved in absolute ethanol (10 ml) in presence of piperidine (0.2 ml) or DBU (0.2 ml). The reaction mixture was heated in water bath for about 15 min to ensure complete reaction. The precipitate formed was filtered. The crude products are pure enough to be directly used in the next step without need to further crystallization. However, they may be crystallized from ethanol or ethanol/dioxan.

4.2.1.1. 2-(2-Oxo-1,2-dihydro-indol-3-ylidene)-malononitrile ***3a***. Yield: (84% piperidine, 88% DBU), Mp: 236–238 °C (reported: 143–145 °C).[32]

4.2.1.2. Ethyl cyano-(2-oxo-1,2-dihydro-indol-3-ylidene)-acetate ***3b***. Yield: (82% piperidine, 83% DBU), Mp: 180–182 °C (reported: 173–175 °C).[32]

4.2.1.3. Benzothiazol-2-yl-(2-oxo-1,2-dihydro-indol-3-ylidene)-acetonitrile ***3c***. Yield: (86% piperidine, 89% DBU), Mp: 204–206 °C; IR (KBr): ν 3233 (NH), 2195 (CN), 1617 (CO) cm^{-1}; MS (EI)=303. Anal. Calcd for $C_{17}H_9N_3OS$ (303.34): C, 67.31; H, 2.99; N, 13.85; S, 10.57. Found: C, 67.19; H, 2.78; N, 13.66; S, 10.43.

4.2.1.4. 2-(1-Methyl-2-oxo-1,2-dihydro-indol-3-ylidene)-malononitrile ***3d***. Yield: (83% piperidine, 87% DBU), Mp: 234–236 °C (reported: 148–150 °C).[32]

4.2.1.5. Ethyl cyano-(1-methyl-2-oxo-1,2-dihydro-indol-3-ylidene)-acetate ***3e***. Yield: (81% piperidine, 85% DBU), Mp: 156–158 °C (reported: 190–193 °C).[32]

4.2.1.6. Benzothiazol-2-yl-(1-methyl-2-oxo-1,2-dihydro-indol-3-ylidene)-acetonitrile ***3f***. Yield: (83% piperidine, 88% DBU), Mp: 184–186 °C; IR (KBr): ν 2207 (CN), 1606 (CO) cm^{-1}; MS (EI)=317. Anal. Calcd for $C_{18}H_{11}N_3OS$ (317.36): C, 68.12; H, 3.49; N, 13.24; S, 10.10. Found: C, 68.06; H, 3.22; N, 13.31; S, 10.18.

4.3. General method for preparation of compounds 6a–f

4.3.1. General procedure. A mixture of azaenamine **4** (10 mmol) and cyanomethylidine oxindoles **3a–f** (10 mmol) was refluxed in dioxan (20 ml) in the presence of piperidine (0.2 ml) or DBU (0.2 ml) for 3–5 h. The solvent was evaporated under vacuum and the crude product was crystallized from ethanol/dioxan.

4.3.1.1. 4,3′-Spiro(3-acetyl-6-amino-1-phenyl-1,4-dihydropyridazine-5-carbonitrile)-2′-oxindole ***6a***. Yield: (77% piperidine, 80% DBU), Mp: 262–264 °C; IR (KBr): ν 3444, 3359, 3220 (NH_2 and NH), 2190 (CN), 1724, 1623 (2 CO) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6):

δ=2.18 (s, 3H, CH_3CO), 6.14 (br s, 2H, NH_2), 6.83–7.58 (m, 9H, Ar *H*), 10.57 (br s, 1H, indole N*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ=24.7 (CH_3), 48.5 (spiro C), 59.7 (CCN), 109.5, 118.0 (CN), 122.1, 123.8, 126.6, 128.7, 129.0, 129.7, 134.4, 139.9, 140.6 (Ar CH), 141.3 ($CCOCH_3$), 149.7 (CNH_2), 177 ($CONH_2$), 194.8 (CO); MS (EI): *m*/*z* (%)=357. Anal. Calcd for $C_{20}H_{15}N_5O_2$ (357.12): C, 67.22; H, 4.23; N, 19.60. Found: C, 67.48; H, 4.37; N, 19.78.

4.3.1.2. 4,3′-Spiro(ethyl 3-acetyl-6-amino-1-phenyl-1,4-dihydropyridazine-5-carboxylate)-2′-oxindole ***6b***. Yield: (48% piperidine, 52% DBU), Mp: 244–246 °C; IR (KBr): ν 3496, 3428, 3237 (NH_2 and NH), 1720, 1644, 1608 (3 CO) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ=0.87 (t, 3H, CH_3, *J*=7.2 Hz), 2.11 (s, 3H, CH_3CO), 4.2 (q, 2H, CH_2, *J*=7.2 Hz), 6.71 (br s, 2H, NH_2), 6.86–7.89 (m, 9H, Ar *H*), 10.31 (br s, 1H, indole N*H*); ^{13}C NMR (100 MHz, DMSO-d_6): δ=13.2 (CH_3), 25.4 (NCH_3), 48.6 (CH_2), 56.9 (spiro C), 76.5 (CCOOEt), 108.5, 119.3, 126.9, 128.7, 129.9, 132.8, 136.9, 141.1, 142.9, 143.1 (Ar CH), 144.5 ($CCOCH_3$), 149.4 (CNH_2), 167.9 (CONH), 179.1 (COOEt), 194.8 (CO); MS (EI)=404 (M^+). Anal. Calcd for $C_{22}H_{20}N_4O_4$ (404.15): C, 65.34; H, 4.98; N, 13.85. Found: C, 65.22; H, 4.79; N, 13.68.

4.3.1.3. 4,3′-Spiro(3-acetyl-6-amino-5-benzthiazol-2-yl-1-phenyl-1,4-dihydropyridazine)-2′-oxindole ***6c***. Yield: (79% piperidine, 83% DBU), Mp: 244–246 °C; IR (KBr): ν 3455, 3558, 3168 (NH_2 and NH), 1700, 1617 (2 CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.16 (s, 3H, CH_3CO), 6.90–7.75 (m, 13H, Ar *H*), 8.05 (br s, 2H, NH_2), 10.8 (br s, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ=25.5 (CH_3), 50.9 (spiro C), 81.8 (*C*-benzthiazol-2-yl), 109.6, 119.6, 120.6, 122.0, 123.1, 124.3, 125.8, 126.7, 128.5, 129.4, 129.7, 131.7, 131.8, 140.3, 140.9, 143.6 (Ar CH), 144.0 (C–NH_2), 150.9 (C–$COCH_3$), 166.4 (benzthiazole C-2), 176.7 (CONH), 194.6 (CO); MS (EI)=465 (M^+). Anal. Calcd for $C_{26}H_{19}N_5O_2S$ (465.53): C, 67.08; H, 4.11; N, 15.04; S, 6.89. Found: C, 66.98; H, 4.03; N, 14.96; S, 6.77.

4.3.1.4. 4,3′-Spiro(3-acetyl-6-amino-1-phenyl-1,4-dihydropyridazine-5-carbonitrile)-1′-methyl-2′-oxindole ***6d***. Yield: (75% piperidine, 79% DBU), Mp: 248–250 °C; IR (KBr): ν 3469, 3335 (NH_2), 2190 (CN), 1725, 1684 (2 CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.17 (s, 3H, CH_3CO), 3.20 (s, 3H, NCH_3), 6.18 (br s, 2H, NH_2), 7.02–7.59 (m, 9H, Ar *H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ=25.1 (CH_3), 27.3 (CH_3), 48.6 (spiro C), 58.7 (CCN), 109.2, 118.3 (CN), 123.3, 124.1, 127.3, 129.1, 129.6, 130.2, 130.9, 140.3, 140.8 (Ar CH), 143.2 ($CCOCH_3$), 149.2 (CNH_2), 175.9 ($CONH_2$), 195.2 (CO); MS (EI): *m*/*z* (%)=371 (M^+, 0.8), 328 (67.9), 345.2 (0.7). Anal. Calcd for $C_{21}H_{17}N_5O_2$ (371.39): C, 67.91; H, 4.61; N, 18.86. Found: C, 67.45; H, 4.22; N, 18.50.

4.3.1.5. 4,3′-Spiro(ethyl 3-acetyl-6-amino-1-phenyl-1,4-dihydropyridazine-5-carboxylate)-1′-methyl-2′-oxindole ***6e***. Yield: (78% piperidine, 81% DBU), Mp: 198–200 °C; IR (KBr): ν 3402, 3281 (NH_2), 1715 ($COOC_5H_5$), 1654, 1613 (2 CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.79 (t, 3H, CH_3, *J*=7.2 Hz), 2.11 (s, 3H, CH_3CO), 3.18 (s, 3H, NCH_3), 3.73 (q, 2H, CH_2, J=7.2 Hz), 6.91–7.65 (m, 11H, Ar *H* and NH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ=14.0 (CH_3), 25.8 (CH_3CO), 26.7 (NCH_3), 56 (spiro C), 59.2 (CH_2), 76.7 (CCN), 107.7, 122.3, 123.6, 127.4, 128.9, 130.3, 134.7, 140.2, 143.0, 144.7 (Ar CH), 149.9 ($CCOCH_3$), 149.9 (CNH_2), 168.2 (CONH), 177.8 (COOEt), 195.2 (CO); MS (EI): *m*/*z* (%)=418 (M^+, 1.6), 375 (29.3), 345 (31.3). Anal. Calcd for $C_{23}H_{22}N_4O_4$ (418.45): C, 66.02; H, 5.30; N, 13.39. Found: C, 65.99; H, 5.44; N, 13.11.

4.3.1.6. 4,3′-Spiro(3-acetyl-6-amino-5-benzthiazol-2-yl-1-phenyl-1,4-dihydropyridazine)-1′-methyl-2′-oxindole ***6f***. Yield: (80% piperidine, 84% DBU), Mp: 270–272 °C; IR (KBr): ν 3409, 3296 (NH_2), 1709 (CH_3CO), 1610 (CO oxindole) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.11 (CH_3CO), 2.17 (NCH_3), 7.01–7.80 (m, 13H, Ar *H*), 8.20 (br s, 2H, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ=25.9 (CH_3CO), 27.1 (NCH_3), 50.9 (spiro C), 81.9 (*C*-benzthiazol-2-yl), 108.8, 120.5, 121.3, 123.3, 123.7, 124.5, 126.5, 127.3, 129.2, 130.0, 130.3, 131.3, 132.0, 140.6, 140.9, 144.6 (Ar CH), 145.0 (C–NH_2), 151.5 (C–$COCH_3$), 166.6 (benzthiazole C-2), 175.8 (CONH), 195.2 (CO); MS (EI): *m*/*z* (%)=481 (M^++2, 6.9), 480 (M^++1, 5.9), 478 (M^+–1, 6.9), 436 (28.7), 345 (54.5). Anal. Calcd for $C_{27}H_{21}N_5O_2S$ (479.55): C, 67.62; H, 4.41; N, 14.60; S, 6.69. Found: C, 67.42; H, 4.18; N, 14.25; S, 6.51.

4.4. General method for preparation of compounds 11a–f

4.4.1. General procedure. A mixture of azaenamine **9** (10 mmol) and cyanomethylidine oxindoles **3a–f** (10 mmol) was refluxed in dioxan (20 ml) in the presence of piperidine (0.2 ml) or DBU (0.2 ml) for 3–5 h. The solvent was evaporated under vacuum and the crude product was crystallized from ethanol/dioxan.

4.4.1.1. 3,3′-Spiro(2-acetyl-6-oxo-3,5,6,7,10-pentahydro-11-thia-1,5,11b-triaza-benzo[a]fluorene-4-carbonitrile)-2′-oxindole ***11a***. Yield: (74% piperidine, 78% DBU), Mp: 256–258 °C; IR (KBr): ν 3446 (NH), 3283 (NH), 2204 (CN), 1730, 1690, 1641 (3 CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.76 (m, 4H, cyclohexene *H*), 2.30 (s, 3H, CH_3CO), 2.69 (m, 2H, cyclohexene *H*), 2.75 (m, 2H, cyclohexene *H*), 6.86–7.36 (m, 4H, Ar *H*), 10.70 (s, 1H, CON*H*), 11.41 (s, 1H, oxindole N*H*); MS (EI): *m*/*z* (%)=443 (M^+, 6.1), 417 (0.9), 400 (100), 374 (27.1). Anal. Calcd for $C_{23}H_{17}N_5O_3S$ (443.48): C, 62.29; H, 3.86; N, 15.79; S, 7.23. Found: C, 62.11; H, 3.57; N, 15.57; S, 7.11.

4.4.1.2. 3,3′-Spiro(ethyl 2-acetyl-6-oxo-3,5,6,7,10-pentahydro-11-thia-1,5,11b-triaza-benzo[a]fluorene-4-carboxylate)-2′-oxindole ***11b***. Yield: (73% piperidine, 76% DBU), Mp: 290–294 °C; IR (KBr): ν 1711 ($COOC_2H_5$), 1663, 1621, 1562 (3 CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.85 (t, 3H, CH_3, *J*=7.2), 1.79 (m, 4H, cyclohexene *H*), 2.27 (s, 3H, CH_3CO), 2.71 (m, 2H, cyclohexene *H*), 2.79 (m, 2H, cyclohexene *H*), 3.85 (q, 2H, CH_2, *J*=7.2), 6.76–7.30 (m, 4H, Ar *H*), 10.44 (s, 1H, CON*H*), 11.70 (s, 1H, oxindole N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ=12.7, 21.3, 22.2, 23.7, 24.6, 25.4, 48.8, 60.0, 66.2, 78.6, 108.6, 113.0, 120.6, 121.2, 124.0, 128.7, 132.0, 134.3, 141.2, 146.3, 149.8, 154.7, 166.9, 177.1, 193.6; MS (EI): *m*/*z* (%)=491 (M^++1, 5.6), 490 (M^+, 15.3), 447 (72.9), 417 (100). Anal. Calcd for $C_{25}H_{22}N_4O_5S$ (490.53): C, 61.21; H, 4.52; N, 11.42; S, 6.54. Found: C, 61.05; H, 4.14; N, 11.25; S, 6.44.

4.4.1.3. 3,3′-Spiro(2-acetyl-6-oxo-4-benzthiazol-2-yl-3,5,6,7,10-pentahydro-11-thia-1,5,11b-triaza-benzo[a]fluorene)-2′-oxindole ***11c***. Yield: (76% piperidine, 80% DBU), Mp: 280–282 °C; IR (KBr): ν 3444 (NH), 3194 (NH oxindole), 1711, 1681, 1619 (3 CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.76 (m, 4H, cyclohexene *H*), 2.66 (s, 3H, CH_3CO), 2.65 (m, 2H, cyclohexene *H*), 2.79 (m, 2H, cyclohexene *H*), 6.97–7.81 (m, 8H, Ar *H*), 11.07 (s, 1H, CON*H*), 13.85 (s, 1H, oxindole N*H*); MS (EI): *m*/*z* (%)=552 (M^++1, 5.2), 551 (M^+, 16.9), 508 (100), 417 (53.5). Anal. Calcd for $C_{29}H_{21}N_5O_3S_2$ (551.64): C, 63.14; H, 3.84; N, 12.70; S, 11.63. Found: C, 63.02; H, 3.45; N, 12.38; S, 11.44.

4.4.1.4. 3,3′-Spiro(2-acetyl-6-oxo-3,5,6,7,10-pentahydro-11-thia-1,5,11b-triaza-benzo[a]fluorene-4-carbonitrile)-1′-methyl-2′-oxindole ***11d***. Yield: (74% piperidine, 78% DBU), Mp: 258–260 °C; IR (KBr): ν 3442 (NH), 2199 (CN), 1729, 1689, 1639 (3 CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.76 (m, 4H, cyclohexene *H*), 2.29 (s, 3H, CH_3CO), 2.70 (m, 2H, cyclohexene *H*), 2.76 (m, 2H, cyclohexene *H*), 3.19 (s, 3H, NCH_3), 7.03–7.46 (m, 4H, Ar *H*), 11.49 (s, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ=21.3, 22.3, 23.8, 24.6, 24.7, 26.4, 62.2, 108.5, 113.6, 114.5, 120.7, 122.9, 124.4, 128.5, 129.7, 132.2, 132.5, 141.2, 142.4, 142.7, 149.4, 155.9, 174.4, 193.7; MS (EI): *m*/*z* (%)=458 (M^++1, 3.8), 457 (M^+, 8.1), 414 (100), 388 (20). Anal. Calcd for $C_{24}H_{19}N_5O_3S$ (457.50): C, 63.01; H, 4.19; N, 15.31; S, 7.01. Found: C, 62.98; H, 4.21; N, 15.18; S, 6.89.

4.4.1.5. 3,3′-Spiro(ethyl 2-acetyl-6-oxo-3,5,6,7,10-pentahydro-11-thia-1,5,11b-triaza-benzo[a]fluorene-4-carboxylate)-1′-methyl-2′-oxindole ***11e***. Yield: (83% piperidine, 79% DBU), Mp: 290–292 °C; IR (KBr): ν 3516 (NH), 1704 ($COOC_2H_5$), 1662, 1604, 1565 (3 CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.78 (t, 3H, C*H*$_3$, *J*=7.2), 1.79 (m, 4H, cyclohexene *H*), 2.27 (s, 3H, C*H*$_3$CO), 2.73 (m, 2H, cyclohexene *H*), 2.80 (s, 2H, cyclohexene *H*), 3.18 (s, 3H, NC*H*$_3$) 3.81 (q, 2H, C*H*$_2$), 6.93–7.38 (m, 4H, Ar *H*), 11.70 (s, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ=13.1, 21.3, 22.2, 23.7, 24.6, 25.3, 26.1, 48.0, 60.0, 78.2, 107.4, 113.2, 122.0, 124.0, 128.8, 129.0, 132.0, 133.3, 141.4, 143.7, 145.8, 149.8, 154.7, 166.7, 175.7, 193.7; MS (EI): *m*/*z* (%)=506 (M^++2, 5.7), 505 (M^++1, 5.2), 504 (M^+, 5.2), 461 (12.3). Anal. Calcd for $C_{26}H_{24}N_4O_5S$ (504.56): C, 61.89; H, 4.79; N, 11.10; S, 6.36. Found: C, 61.66; H, 4.61; N, 10.98; S, 6.19.

4.4.1.6. 3,3′-Spiro(2-acetyl-6-oxo-4-benzthiazol-2-yl-3,5,6,7,10-pentahydro-11-thia-1,5,11b-triaza-benzo[a]fluorene)-1′-methyl-2′-oxindole ***11f***. Yield: (77% piperidine, 79% DBU), Mp: 286–288 °C; IR (KBr): ν 3429 (NH), 1717, 1618, 1586 (3 CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=1.80 (m, 4H, cyclohexene *H*), 2.31 (s, 3H, C*H*$_3$CO), 2.74 (m, 2H, cyclohexene *H*), 2.85 (m, 2H, cyclohexene *H*), 3.2 (s, 3H, NC*H*$_3$), 7.01–7.85 (m, 8H, Ar *H*), 13.85 (s, 1H, N*H*); MS (EI): *m*/*z* (%)=568 (M^++3, 1.5), 567 (M^++2, 4.5), 566 (M^++1, 7.7), 565 (M^+, 22.4), 522 (100), 431 (55.1). Anal. Calcd for $C_{30}H_{23}N_5O_3S_2$ (565.67): C, 63.70; H, 4.10; N, 12.38; S, 11.34. Found: C, 63.62; H, 3.98; N, 12.17; S, 11.39.

4.5. Preparation of compound (15)

A mixture of azaenamine **13** (10 mmol) and cyanomethylidine oxindole **3e** (10 mmol) was refluxed in dioxan (20 ml) in the presence of piperidine (0.2 ml) or DBU (0.2 ml) for 5 h. The solvent was evaporated under vacuum and the crude product was crystallized from ethanol/dioxan.

4.5.1. 2,3′-Spiro(ethyl 3-acetyl-9-oxo-2,9,10-trihydro-4,4a,10-triaza-phenanthrene-1-carboxylate)-1′-methyl-2′-oxindole ***15***. Yield: (77% piperidine, 79% DBU), Mp: 256–258 °C; IR (KBr): ν 3389 (NH), 1702, 1660, 1614, 1598 (4 CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.78 (t, 3H, C*H*$_3$ *J*=7.2), 2.40 (s, 3H, C*H*$_3$CO), 3.19 (s, 3H, NC*H*$_3$), 3.82 (q, 2H, C*H*$_2$, *J*=7.2), 6.94–8.06 (m, 8H, Ar *H*), 12.24 (s, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ=13.1, 25.9, 26.1, 60.1, 79.6, 107.3, 114.6, 115.3, 120.4, 121.9, 123.8, 124.9, 127.0, 128.9, 133.2, 135.6, 140.0, 141.9, 143.9, 145.0, 157.1, 167.2, 175.9, 194.4; MS (EI): *m*/*z* (%)=446 (M^++2, 0.8), 445 (M^++1, 3.7), 444 (M^+, 9.5), 401 (100), 371 (80.2). Anal. Calcd for $C_{24}H_{20}N_4O_5$ (444.44): C, 64.86; H, 4.54; N, 12.61. Found: C, 64.44; H, 4.17; N, 12.44.

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References and notes

1. Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007.
2. James, D. M.; Kunze, H. B.; Faulkner, D. J. *J. Nat. Prod.* **1991**, *54*, 1137.
3. Kobayashi, J.; Tsuda, M.; Agemi, K.; Shigemiri, H.; Ishibashi, M.; Sasaki, T.; Mikami, Y. *Tetrahedron* **1991**, *47*, 6617.
4. Srivastav, N.; Mittal, A.; Kumar, A. *J. Chem. Soc., Chem. Commun.* **1992**, 493.
5. Williams, R. M.; Cox, R. *J. Acc. Chem. Res.* **2003**, *36*, 127.
6. Da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, 273.
7. Haider, N.; Holzer, W. *Sci. Synthesis* **2004**, *16*, 125–249.
8. Woo, G. H. C.; Snyder, J. K.; Wan, Z.-K. *Prog. Heterocycl. Chem.* **2002**, *14*, 279–309.
9. Cignarella, G.; Barlocco, D. *J. Heterocycl. Chem.* **2002**, *39*, 545–550.
10. Ghozlan, S. A. S.; Mohamed, M. H.; Abdelmoniem, A. M.; Abdelhamid, I. A. *ARKIVOC* **2009**, *x*, 302–311.
11. Abdelhamid, I. A.; Ghozlan, S. A. S.; Kolshorn, H.; Meier, H.; Elnagdi, M. H. *Heterocycles* **2007**, *71*, 2627–2637.
12. Al-Awadi, N. A.; Ibrahim, M. I.; Abdelhamid, I. A.; Elnagdi, M. H. *Tetrahedron* **2008**, *64*, 8202–8205.
13. Ghozlan, S. A. S.; Abdelhamid, I. A.; Gaber, H.; Elnagdi, M. H. *J. Chem. Res.* **2004**, *12*, 789–793.
14. Ghozlan, S. A. S.; Abdelhamid, I. A.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2005**, *42*, 1185–1189.
15. Ghozlan, S. A. S.; Abdelhamid, I. A.; Al-Dib, H. I.; Elnagdi, M. H. *ARKIVOC* **2006**, *xv*, 53–60.
16. Yong, S. R.; Ung, A. T.; Pyne, S. G.; Skelton, B. W.; White, A. H. *Tetrahedron* **2007**, *63*, 1191.
17. Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505.
18. Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *J. Med. Chem.* **1987**, *30*, 824.
19. Yong, S. R.; Williams, M. C.; Pyne, S. G.; Ung, A. T.; Skelton, B. W.; White, A. H.; Turner, P. *Tetrahedron* **2005**, *61*, 8120.
20. Feldman, K. S.; Vidulova, D. B.; Karatjas, A. G. *J. Org. Chem.* **2005**, *70*, 6429.
21. Mao, Z.; Baldwin, S. W. *Org. Lett.* **2004**, *6*, 2425.
22. Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2006**, *8*, 4137.
23. Ghozlan, S. A. S.; Abdelhamid, I. A.; Hassaneen, H. M.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2007**, *44*, 105–108.
24. Abdelhamid, I. A. *Synlett* **2009**, 625.
25. Ghozlan, S. A. S.; Abdelhamid, I. A.; Elnagdi, M. H. *ARKIVOC* **2006**, *xiii*, 147–157.
26. Al-Awadi, N.; Abdelhamid, I. A.; Al-Etaibi, A.; Elnagdi, M. H. *Synlett* **2007**, 2205–2208.
27. Al-Awadi, N. A.; Abdelkhalik, M. M.; Abdelhamid, I. A.; Elnagdi, M. H. *Synlett* **2007**, 2979–2982.
28. Warea, M.; Madjeb, B.; Pokalwara, R.; Kakadea, G.; Shingarea, M. *Bull. Cat. Soc. Ind.* **2007**, *6*, 104–106.
29. Yeom, C.-E.; Kim, M. J.; Kim, B. M. *Tetrahedron* **2007**, *63*, 904–909.
30. Further details of the crystal structure of 8b will be available in the Cambridge Crystallographic Data centre under deposit numbers CCDC 739769.
31. Darwish, E.S.; Abdelhamid, I.A.; Nasra, M.A.; Abdel-Gallil, F.M.; Fleita, D.H., submitted for publication.
32. Redkin, R. G.; Shemchuk, L. A.; Chernykh, V. P.; Shishkin, O. V.; Shishkina, S. V. *Tetrahedron* **2007**, *63*, 11444–11450.