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One-pot domino reactions for synthesis of heterocyclic[3.3.3] propellanes and spiro[cyclopenta[*b*]pyridine-4,2′-indenes]

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ABSTRACT

An efficient synthetic procedure for the functionalized heterocyclic[3.3.3]propellanes was successfully developed by one-pot domino reaction of ninhydrin, malononitrile with 3-arylamino-2-cyclohexenones and their 5,5-dimethyl derivatives in the presence of triethylamine in ethanol at room temperature. On the other hand the similar one-pot reaction containing 3-arylamino-2-cyclopentenones resulted in the functionalized spiro[cyclopenta[*b*]pyridine-4,2′-indenes] in moderate yields.

1. Introduction

Enaminones (enamino esters) are one kind of readily obtainable and versatile synthetic reagents, in which the nucleophilic enamine and the electrophilic enone (ester) moieties are combined into one molecule.[1,2] These attractive features have made them as important building blocks in current organic synthesis.[3,4] Over the decades, two particular enaminones have been widely used to design multicomponent reactions and domino reactions for the convenient synthesis of a wide variety of heterocyclic compounds. The first kind of widely used enaminones could be readily prepared from the direct condensation of β-dicarbonyl compounds with primary and secondary amines.[5,6] The second commonly used enaminones came from the addition of aliphatic and aromatic amines to the activated alkynes bearing with carbonyl groups.[7,8] We have successfully developed several new domino reactions by using the in situ formed β-enamino esters from the reaction of arylamine with electron-deficient alkynes.[9,10]

Propellane is a special kind of annulated tricyclic system connected by a carbon–carbon single bond[11] and can be found as scaffolds in many non-naturally and naturally occurring products, such as hasubanone, Modhephene, aspidohylline, merrilactone **A** (Fig. 1).[12] Due to their challenging framework and broad spectra of biological and pharmacological activities, propellanes attracted continuous attentions as one of the synthetic targets in organic synthesis.[13] Very recently Alizadeh and his co-workers have successfully reported the efficient synthesis of the interesting heterocyclic[3.3.3]propellanes by the domino four-component reactions of primary amines, acetylenedicarboxylate, ninhydrin and malononitrile.[14] Inspired by these results, we envisaged that the cyclic enaminones derived from the reaction of primary amines with cyclic diketones, such as dimedone could be utilized as readily available building blocks for constructing functionalized cyclic [3.3.3]propellanes with the fused cycloalkyl unit. Here we wish to report the efficient synthesis of heterocyclic[3.3.3]propellanes and spiro[cyclopenta[*b*]pyridine-4,2′-indenes] via the one-pot domino reactions of cyclic enaminones, ninhydrin, and malononitrile.

2. Results and discussions

At first ninhydrin reacted with malononitrile in ethanol at room temperature for about 1 h to give the Knoevenagel adduct according to the previously established reaction conditions.[14a] Then 3-arylamino-5,5-dimethyl-2-cyclohexenone was added and the reaction was finished at room temperature in about 2 h to give the expected heterocyclic[3.3.3]propellanes **1a**–**1h** in satisfactory yields (Table 1, entries 1–8). By using this domino reaction procedure, the reaction was carried out in very convenient manner and the pure products could be easily obtained after filtration of the resulted precipitates without further purification. To demonstrate the practical utility of the current protocol, other kinds of cyclic enaminones, such as 3-arylamino-2-cyclohexenones were also used in the reaction. The reaction also proceeded very smoothly to give the heterocyclic[3.3.3]propellanes **1i**–**1o** in good yields (Table

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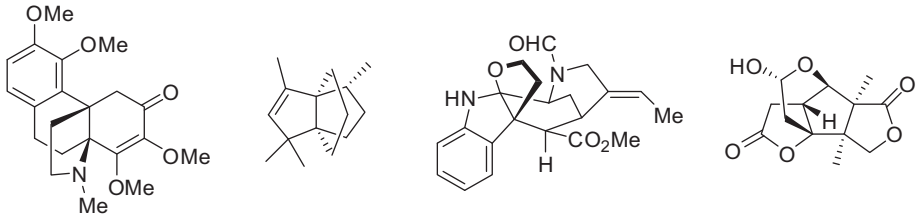
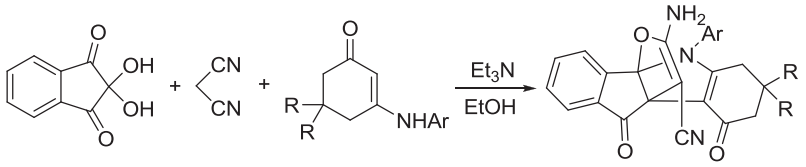


A: hasubanone **B: Modhephene** **C: aspidohylline** **D: merrilactone A**

Fig. 1. Typical natural products containing propellane skeleton.

Table 1
Synthesis of functionalized heterocyclic[3.3.3]propellanes



1a-1o

Entry	Compd	R	Ar	Yield (%)
1	**1a**	CH_3	*p*-$CH_3C_6H_4$	81
2	**1b**	CH_3	*p*-$OCH_3C_6H_4$	73
3	**1c**	CH_3	*o*-$OCH_3C_6H_4$	80
4	**1d**	CH_3	C_6H_5	78
5	**1e**	CH_3	*p*-ClC_6H_4	71
6	**1f**	CH_3	*m*-ClC_6H_4	66
7	**1g**	CH_3	*p*-BrC_6H_4	74
8	**1h**	CH_3	$C_6H_4CH_2$	79
9	**1i**	H	*p*-$CH_3C_6H_4$	72
10	**1j**	H	*p*-$OCH_3C_6H_4$	83
11	**1k**	H	C_6H_5	72
12	**1l**	H	*p*-ClC_6H_4	78
13	**1m**	H	*p*-BrC_6H_4	71
14	**1n**	H	*p*-$NO_2C_6H_4$	65
15	**1o**	H	$C_6H_4CH_2$	78

1, entries 9–15). Totally fifteen new heterocyclic[3.3.3]propellanes were successfully synthesized by the domino reaction. The structures of the above prepared compounds **1a**–**1o** were characterized by ^1H and ^{13}C NMR, HRMS, and IR spectra and were further confirmed by single-crystal X-ray diffraction performed for the two compounds **1a** (Fig. 2) and **1j** (Fig. 3).

To explore the generality and scope of this domino reaction, other enaminones, such as 3-arylamino-2-cyclopentenones were also employed in the reaction and the results are summarized in Table 2. In the presence of triethylamine the domino reaction of ninhydrin, malononitrile, and 3-arylamino-2-cyclopentenones in ethanol did not give the expected heterocyclic[3.3.3]propellanes, but afforded the functionalized spiro[cyclopenta[*b*]pyridine-4,2′-indenes] **2a**–**2f** in moderate yields. Their structures were established by spectroscopic methods and X-ray diffraction determination of single-crystal of spiro compound **2a** (Fig. 4).

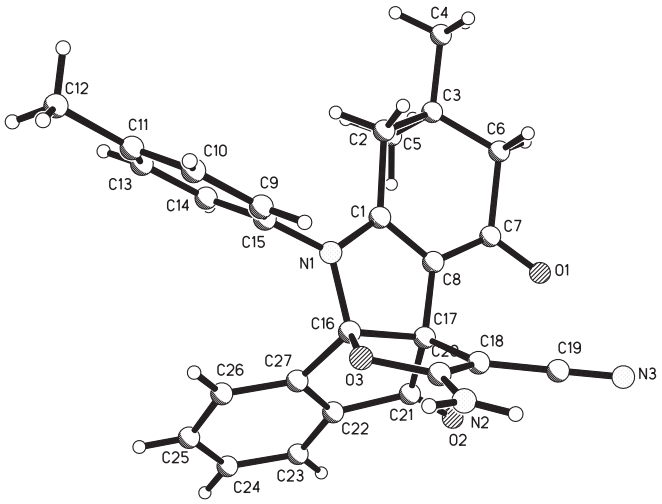


Fig. 2. Molecular structure of compound **1a**.

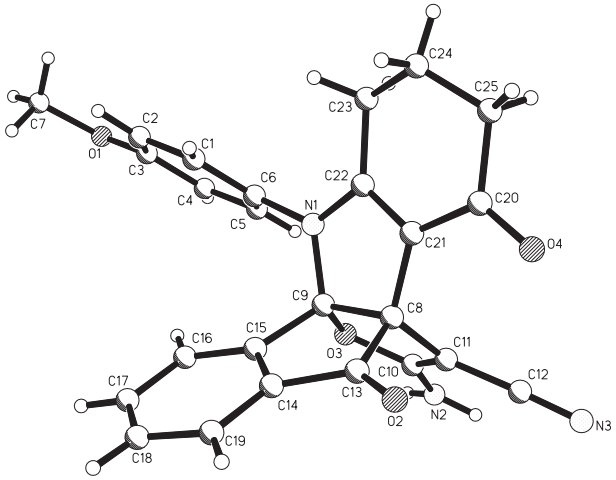
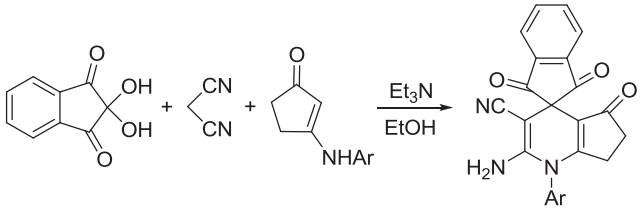


Fig. 3. Molecular structure of compound **1j**.

Table 2
Synthesis of spiro[cyclopenta[*b*]pyridine-4,2′-indenes] **2a**–**2f**



2a-2f

Entry	Compd	Ar	Yield (%)
1	**2a**	*p*-$CH_3C_6H_4$	73
2	**2b**	*p*-$OCH_3C_6H_4$	64
3	**2c**	*o*-$OCH_3C_6H_4$	78
4	**2d**	*p*-ClC_6H_4	61
5	**2e**	*m*-ClC_6H_4	66
6	**2f**	*p*-BrC_6H_4	63

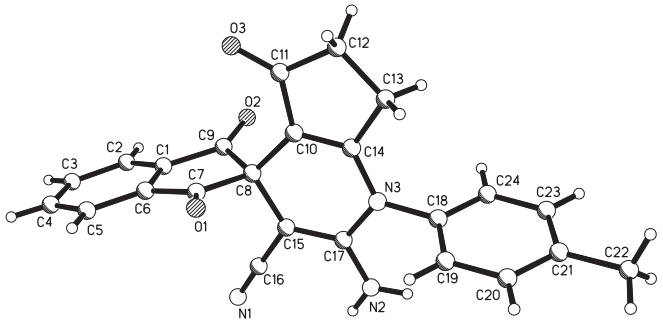
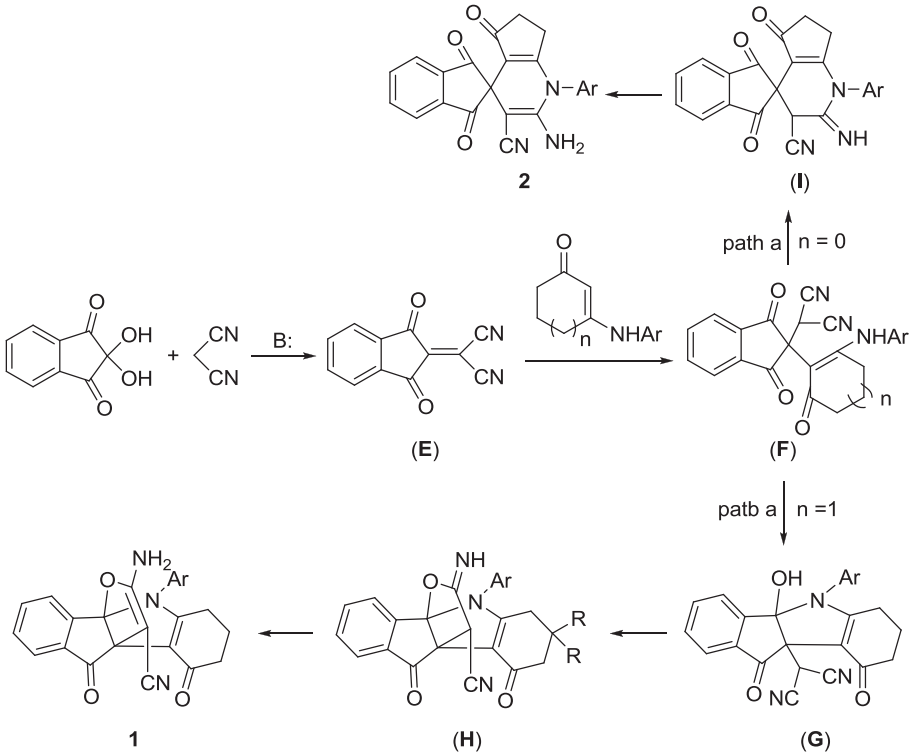


Fig. 4. Molecular structure of compound **2a**.

The domino reactions of different cyclic enaminones could give heterocyclic[3.3.3]propellanes and spiro[cyclopenta[*b*]pyridine-4,2′-indenes] under similar reaction conditions. Though the exact mechanism is not investigated in detail, a possible reaction mechanism for the formation of two kinds of products was proposed in Scheme 1, which was on the basis of the Alizadeh's recently published works[14] and the similar multicomponent reactions of malononitirile.[15] At first a base catalyzed condensation of ninhydrin with malononitrile produced the adduct (**E**). Secondly Michael addition of cyclic enaminone to adduct (**E**) afforded the intermediate (**F**). Then the reaction could proceed further according to two paths. On the path a, the intramolecular addition of arylamino group of 3-arylamino-2-cyclohexenones and their 5,5-dimethyl derivatives to one of carbonyl group of ninhydrin unit to give the hydroxyl intermediate (**G**) with formation of nitrogen-containing five-member ring. In the presence of triethylamine, the deprotonated anion of intermediate (**G**) attacked the cyano group to give an imine intermediate (**H**) with formation of oxygen-containing five-member ring. At last the tautomerization of imino group to amino group resulted in the heterocyclic[3.3.3]propellane **1**. On the path b, arylamino group of 3-arylamino-2-cyclopentanones did not firstly attack the carbonyl group, while added to cyano group to form a cyclic imine intermediate (**I**), which in turn transferred to spiro compound **2** though the imino–amino tautomerization. The reasons for 3-arylamino-2-cyclopentanones and 3-arylamino-2-cyclohexanones showing different reactivities might be due to the steric effects of cyclopentyl and cyclohexyl units.

In conclusion, an efficient synthetic procedure for the functionalized heterocyclic[3.3.3]propellanes as well as spiro[cyclopenta[*b*]pyridine-4,2′-indenes] was successfully developed by one-pot domino reaction of ninhydrin, malononitrile with cyclic enaminones. The scope and limitation of this domino reaction was established and the reaction mechanism was briefly discussed. This protocol has advantages of mild reaction conditions, easily accessible starting material, and easy purification of the products, which makes it a useful and attractive method for the synthesis of the



Scheme 1. The proposed formation mechanism of compounds **1** and **2**.

complex propellanes in synthetic medicinal chemistry. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.

3. Experimental section

3.1. Reagents and apparatus

All reagents and solvents were commercial available with analytical grade and used as received. Cyclic enaminones were prepared by the condensation of cyclic diketones with arylamines according to the published methods.[16] Evaporation removal of organic solvents was carried out with a rotary evaporator in conjunction with a water aspirator. Melting points were taken on a hotplate microscope apparatus and without calibrating. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-600 instrument. IR spectra were obtained on a Bruker Tensor 27 spectrometer (KBr disc). HRMS were measured at Bruker UHR-TOF maXis spectrometer. X-ray data were collected on a Bruker Smart APEX-2 diffractometer.

3.2. General procedure for the preparation of heterocyclic [3.3.3]propellanes (1a–1o) from one-pot domino reaction of ninhydrin, malononitrile, and cyclic enaminones

In a round bottom flask a mixture of ninhydrin (1.0 mmol), malononitrile (1.0 mmol), and triethylamine (0.1 mmol) in 5.0 mL ethanol was stirred at room temperature for about 1 h. Then cyclic enaminone (1.0 mmol) was added to it. The solution was stirred at room temperature for additional 2 h. The resulting yellow precipitates were collected by filtration and washed with cold alcohol to give the pure product.

*3.2.1. Heterocyclic[3.3.3]propellanes (**1a**).* Yellow solid, 81%, mp 216–218 °C; IR (KBr) υ: 3080, 2958, 2875, 2193, 1712, 1595, 1540, 1513, 1462, 1427, 1404, 1325, 1275, 1234, 1205, 1181, 1145, 1089, 1011, 953, 921, 867, 810, 762, 675, 617 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.83 (s, 1H, ArH), 7.88 (d, J=7.8 Hz, 1H, ArH), 7.75 (t, J=7.2 Hz, 1H, ArH), 7.65 (t, J=7.8 Hz, 1H, ArH), 7.36 (d, J=7.2 Hz, 2H, ArH), 7.17 (s, 2H, NH_2), 6.88 (d, J=7.8 Hz, 1H, ArH), 5.94 (s, 1H, ArH), 2.50 (d, J=16.8 Hz, 1H, CH_2), 2.41 (s, 3H, CH_3), 2.28 (d, J=15.6 Hz, 1H, CH_2), 1.91 (d, J=15.6 Hz, 1H, CH_2), 1.74 (d, J=17.4 Hz, 1H, CH_2), 0.98 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 194.1, 189.7, 164.3, 148.0, 138.4, 135.7, 134.1, 132.0, 131.0, 129.8, 129.2, 125.3, 123.9, 112.8, 112.7, 99.1, 98.0, 63.7, 50.6, 36.8, 34.0, 29.7, 25.9, 21.8, 20.8; MS (m/z): HRMS (ESI) calcd for $C_{27}H_{23}NaN_3O_3$ ([M+Na]$^+$): 460.1632, found: 460.1634.

*3.2.2. Heterocyclic[3.3.3]propellanes (**1b**).* Yellow solid, 73%, mp 184–186 °C; IR (KBr) υ: 3029, 2962, 2878, 2776, 2551, 2258, 2190, 2029, 1719, 1600, 1512, 1461, 1284, 1249, 1155, 1082, 1011, 967, 926, 819, 774, 680 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.74 (s, 1H, ArH), 7.87 (d, J=7.2 Hz, 1H, ArH), 7.76 (t, J=7.2 Hz, 1H, ArH), 7.65 (t, J=7.2 Hz, 1H, ArH), 7.19 (s, 1H, NH_2), 7.09 (d, J=7.8 Hz, 2H, ArH), 6.92 (d, J=7.8 Hz, 1H, ArH), 5.91 (s, 1H, ArH), 3.84 (s, 3H, OCH_3), 2.46 (d, J=17.4 Hz, 1H, CH_2), 2.27 (d, J=15.6 Hz, 1H, CH_2), 1.91 (d, J=15.6 Hz, 1H, CH_2), 1.74 (d, J=17.4 Hz, 1H, CH_2), 0.98 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 194.1, 189.7, 164.6, 159.3, 148.0, 135.7, 134.1, 130.9, 130.7, 127.0, 125.3, 123.9, 114.9, 114.4, 112.8, 98.9, 97.9, 63.6, 55.4, 50.6, 36.7, 33.9, 29.7, 25.9, 21.8; MS (m/z): HRMS (ESI) calcd for $C_{27}H_{23}NaN_3O_4$ ([M+Na]$^+$): 476.1581, found: 476.1585.

*3.2.3. Heterocyclic[3.3.3]propellanes (**1c**).* Yellow solid, 80%, mp 186–188 °C; IR (KBr) υ: 2963, 2872, 2644, 2536, 2362, 2255, 2193, 2026, 1722, 1598, 1546, 1499, 1463, 1403, 1327, 1283, 1247, 1205, 1183, 1145, 1089, 1066, 1042, 1019, 993, 961, 920, 885, 868, 830, 779, 758, 718 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.63 (s, 1H, ArH), 7.85 (d, J=7.8 Hz, 1H, ArH), 7.68 (t, J=7.8 Hz, 1H, ArH), 7.62–7.58 (m, 2H, NH_2), 7.53 (t, J=7.2 Hz, 1H, ArH), 7.18 (t, J=7.8 Hz, 1H, ArH), 7.10 (d, J=8.4 Hz, 1H, ArH), 6.74 (d, J=7.8 Hz, 1H, ArH), 5.95 (s, 1H, ArH), 3.23 (s, 3H, OCH_3), 2.26 (d, J=16.2 Hz, 1H, CH_2), 2.11 (d, J=17.4 Hz, 1H, CH_2), 1.98 (d, J=16.2 Hz, 1H, CH_2), 1.85 (d, J=16.8 Hz, 1H, CH_2), 0.98 (s, 3H, CH_3), 0.88 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 194.4, 189.6, 165.5, 155.9, 148.3, 135.2, 134.1, 131.2, 130.9, 130.6, 124.9, 123.7, 122.7, 120.8, 112.8, 112.7, 112.2, 99.0, 97.7, 63.5, 55.2, 50.6, 36.1, 33.8, 28.9, 26.7, 21.9; MS (m/z): HRMS (ESI) calcd for $C_{27}H_{23}NaN_3O_4$ ([M+Na]$^+$): 476.1581, found: 476.1587.

*3.2.4. Heterocyclic[3.3.3]propellanes (**1d**).* Yellow solid, 78%, mp 208–210 °C; IR (KBr) υ: 2960, 2936, 2878, 2335, 2257, 2194, 2026, 1713, 1599, 1542, 1496, 1462, 1425, 1407, 1387, 1325, 1276, 1234, 1203, 1182, 1139, 1088, 1010, 968, 922, 886, 867, 825, 780, 765, 728, 701 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.84 (s, 1H, ArH), 7.88 (d, J=7.8 Hz, 1H, ArH), 7.73 (t, J=7.8 Hz, 1H, ArH), 7.65 (t, J=7.8 Hz, 1H, ArH), 7.56–7.53 (m, 3H, ArH), 7.30 (s, 2H, NH_2), 6.82 (d, J=7.8 Hz, 1H, ArH), 5.94 (s, 1H, ArH), 2.53 (d, J=16.8 Hz, 1H, CH_2), 2.29 (d, J=15.6 Hz, 1H, CH_2), 1.92 (d, J=15.6 Hz, 1H, CH_2), 1.75 (d, J=16.8 Hz, 1H, CH_2), 0.98 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 194.0, 189.9, 164.2, 147.9, 135.7, 134.7, 134.1, 131.0, 129.4, 129.3, 128.8, 125.2, 124.0, 112.8, 99.4, 98.1, 63.7, 50.6, 36.9, 34.1, 29.8, 25.9, 21.9; MS (m/z): HRMS (ESI) calcd for $C_{26}H_{21}NaN_3O_3$ ([M+Na]$^+$): 446.1475, found: 446.1481.

*3.2.5. Heterocyclic[3.3.3]propellanes (**1e**).* Yellow solid, 72%, mp 222–224 °C; IR (KBr) υ: 2961, 2933, 2878, 2771, 2194, 2026, 1714, 1643, 1600, 1542, 1495, 1459, 1425, 1403, 1325, 1276, 1234, 1182, 1142, 1089, 1013, 971, 952, 921, 868, 813, 768, 750, 707 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.93 (s, 1H, ArH), 7.88 (d, J=7.8 Hz, 1H, ArH), 7.77 (t, J=7.2 Hz, 1H, ArH), 7.67–7.63 (m, 3H, ArH), 7.33 (s, 2H, NH_2), 6.88 (d, J=7.8 Hz, 1H, ArH), 5.93 (s, 1H, ArH), 2.53 (d, J=17.4 Hz, 1H, CH_2), 2.28 (d, J=15.6 Hz, 1H, CH_2), 1.93 (d, J=15.6 Hz, 1H, CH_2), 1.78 (d, J=16.8 Hz, 1H, CH_2), 0.98 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 193.9, 190.0, 164.0, 147.8, 135.9, 134.0, 133.7, 133.5, 131.1, 129.4, 125.1, 124.1, 112.7, 99.8, 98.1, 63.7, 50.6, 36.7, 34.1, 29.8, 25.8, 21.9; MS (m/z): HRMS (ESI) calcd for $C_{26}H_{20}ClNaN_3O_3$ ([M+Na]$^+$): 480.1085, found: 480.1091.

*3.2.6. Heterocyclic[3.3.3]propellanes (**1f**).* Yellow solid, 66%, mp >250 °C; IR (KBr) υ: 2954, 2895, 2756, 2543, 2365, 2195, 2026, 1732, 1586, 1544, 1483, 1459, 1436, 1409, 1328, 1286, 1248, 1229, 1184, 1150, 1090, 1003, 924, 864, 821, 779, 755 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.98 (s, 1H, ArH), 7.89 (d, J=7.8 Hz, 1H, ArH), 7.77 (t, J=7.2 Hz, 1H, ArH), 7.68–7.62 (m, 2H, ArH), 7.58 (t, J=7.8 Hz, 1H, ArH), 7.46 (s, 1H, NH_2), 7.24 (s, 1H, NH_2), 6.85 (d, J=7.8 Hz, 1H, ArH), 5.94 (s, 1H, ArH), 2.60 (d, J=17.4 Hz, 1H, CH_2), 2.29 (d, J=15.6 Hz, 1H, CH_2), 1.93 (d, J=15.6 Hz, 1H, CH_2), 1.80 (d, J=17.4 Hz, 1H, CH_2), 0.99 (s, 3H, CH_3), 0.95 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 193.9, 190.2, 163.9, 147.8, 136.2, 135.8, 134.1, 133.4, 131.1, 130.9, 129.0, 128.8, 128.1, 125.0, 124.1, 112.7, 112.6, 100.1, 98.3, 63.7, 50.7, 36.7, 34.2, 29.8, 25.8, 22.0; MS (m/z): HRMS (ESI) calcd for $C_{26}H_{20}ClNaN_3O_3$ ([M+Na]$^+$): 480.1085, found: 480.1080.

*3.2.7. Heterocyclic[3.3.3]propellanes (**1g**).* Yellow solid, 74%, mp 228–230 °C; IR (KBr) υ: 2961, 2933, 2877, 2351, 2194, 2026, 1714, 1633, 1599, 1541, 1493, 1456, 1426, 1405, 1325, 1279, 1234, 1183, 1143, 1089, 1012, 922, 813, 780, 748 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.93 (s, 1H, ArH), 7.88 (d, J=7.8 Hz, 1H, ArH), 7.73 (t, J=7.2 Hz, 3H, ArH), 7.66 (t, J=7.8 Hz, 1H, ArH), 7.26 (s, 2H, NH_2), 6.88 (d, J=7.8 Hz, 1H, ArH), 5.93 (s, 1H, ArH), 2.53 (d, J=17.4 Hz, 1H, CH_2), 2.29 (d, J=15.6 Hz, 1H, CH_2), 1.92 (d, J=15.6 Hz, 1H, CH_2), 1.79 (d, J=17.4 Hz, 1H, CH_2), 0.98 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C NMR

(150 MHz, DMSO-d_6) δ: 193.9, 190.0, 164.0, 147.8, 135.9, 134.1, 134.0, 132.4, 131.4, 131.1, 125.1, 124.1, 122.0, 112.7, 99.8, 98.1, 63.7, 50.6, 36.8, 34.1, 29.8, 25.8, 21.9; MS (m/z): HRMS (ESI) calcd for $C_{26}H_{21}BrN_3O_3$ ($[M+H]^+$): 502.0761, found: 502.0755.

*3.2.8. Heterocyclic[3.3.3]propellanes (**1h**).* Yellow solid, 79%, mp 196–198 °C; IR (KBr) υ: 2961, 2868, 2370, 2191, 2027, 1724, 1588, 1536, 1497, 1432, 1406, 1355, 1331, 1271, 1246, 1181, 1147, 1089, 1039, 945, 866, 833, 773, 745 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.85 (s, 1H, ArH), 8.04 (d, J=7.8 Hz, 1H, ArH), 7.90–7.86 (m, 2H, ArH), 7.69 (t, J=7.2 Hz, 1H, ArH), 7.34 (d, J=7.8 Hz, 2H, NH_2), 7.30 (d, J=7.2 Hz, 2H, ArH), 7.26 (t, J=7.2 Hz, 1H, ArH), 5.94 (s, 1H, ArH), 5.22 (d, J=16.8 Hz, 1H, CH_2), 4.77 (d, J=17.4 Hz, 1H, CH_2), 2.23 (d, J=17.4 Hz, 1H, CH_2), 2.13 (d, J=15.6 Hz, 1H, CH_2), 1.93 (d, J=17.4 Hz, 1H, CH_2), 1.88 (d, J=16.2 Hz, 1H, CH_2), 0.81 (s, 3H, CH_3), 0.79 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 194.0, 188.7, 164.9, 148.8, 137.8, 136.4, 134.1, 131.0, 128.3, 127.1, 126.7, 125.0, 124.1, 113.1, 112.7, 98.1, 97.3, 63.7, 50.3, 44.9, 35.9, 33.6, 28.9, 26.7, 21.7; MS (m/z): HRMS (ESI) calcd for $C_{27}H_{24}N_3O_3$ ($[M+H]^+$): 438.1812, found: 438.1811.

*3.2.9. Heterocyclic[3.3.3]propellanes (**1i**).* Yellow solid, 72%, mp 222–224 °C; IR (KBr) υ: 2949, 2875, 2770, 2026, 1716, 1635, 1596, 1543, 1511, 1461, 1410, 1324, 1296, 1239, 1195, 1148, 1089, 1047, 994, 923, 854, 800, 767 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.75 (s, 1H, ArH), 7.87 (d, J=7.2 Hz, 1H, ArH), 7.75 (d, J=6.6 Hz, 1H, ArH), 7.65 (t, J=6.6 Hz, 1H, ArH), 7.35 (d, J=6.6 Hz, 2H, ArH), 7.19 (s, 2H, NH_2), 6.92 (d, J=7.2 Hz, 1H, ArH), 5.92 (s, 1H, ArH), 2.41 (s, 3H, CH_3), 2.24–2.13 (m, 3H, CH_2), 2.00 (d, J=17.4 Hz, 1H, CH_2), 1.83–1.78 (m, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 194.2, 190.3, 165.8, 148.0, 138.4, 135.7, 134.2, 132.0, 130.9, 130.1, 129.8, 129.3, 128.0, 125.3, 123.9, 112.8, 112.4, 100.5, 97.8, 63.8, 36.5, 23.4, 22.0, 21.8, 20.8; MS (m/z): HRMS (ESI) calcd for $C_{25}H_{20}N_3O_3$($[M+H]^+$): 410.1499, found: 410.1499.

*3.2.10. Heterocyclic[3.3.3]propellanes (**1j**).* Yellow solid, 83%, mp 224–226 °C; IR (KBr) υ: 2973, 2875, 2776, 2554, 2368, 2194, 2026, 1720, 1611, 1535, 1511, 1462, 1429, 1410, 1326, 1299, 1252, 1196, 1151, 1089, 1031, 997, 940, 923, 855, 801, 774 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.70 (s, 1H, ArH), 7.87 (d, J=7.8 Hz, 1H, ArH), 7.77 (t, J=7.8 Hz, 1H, ArH), 7.66 (t, J=7.2 Hz, 1H, ArH), 7.21 (s, 2H, NH_2), 7.09 (d, J=8.4 Hz, 2H, ArH), 6.96 (d, J=7.8 Hz, 1H, ArH), 5.91 (s, 1H, ArH), 3.84 (s, 3H, OCH_3), 2.42–2.36 (m, 1H, CH_2), 2.26–2.21 (m, 1H, CH_2), 2.17–2.12 (m, 1H, CH_2), 2.03–1.98 (m, 1H, CH_2), 1.86–1.76 (m, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 194.3, 190.2, 166.0, 159.4, 140.1, 135.7, 134.2, 130.9, 130.8, 126.9, 125.3, 123.9, 114.4, 112.8, 112.4, 100.3, 97.6, 63.7, 55.4, 36.5, 23.3, 22.0, 21.7; MS (m/z): HRMS (ESI) calcd for $C_{25}H_{20}N_3O_4$ ($[M+H]^+$): 426.1448, found: 426.1447.

*3.2.11. Heterocyclic[3.3.3]propellanes (**1k**).* Yellow solid, 72%, mp 218–220 °C; IR (KBr) υ: 2948, 2879, 2759, 2546, 2357, 2342, 2256, 2193, 2026, 1718, 1598, 1545, 1496, 1463, 1410, 1347, 1323, 1297, 1270, 1240, 1196, 1145, 1089, 1047, 990, 972, 926, 854, 792, 773, 754, 735 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.80 (s, 1H, ArH), 7.88 (d, J=7.2 Hz, 1H, ArH), 7.74 (t, J=7.8 Hz, 1H, ArH), 7.66 (t, J=7.2 Hz, 1H, ArH), 7.55 (d, J=3.6 Hz, 3H, ArH), 7.32 (s, 2H, NH_2), 6.88 (d, J=7.8 Hz, 1H, ArH), 5.93 (s, 1H, ArH), 2.48–2.43 (m, 1H, CH_2), 2.28–2.23 (m, 1H, CH_2), 2.18–2.13 (m, 1H, CH_2), 2.04–1.99 (m, 1H, CH_2), 1.88–1.76 (m, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 194.2, 190.4, 165.7, 148.0, 135.7, 134.7, 134.2, 131.0, 129.5, 129.3, 128.9, 128.2, 125.2, 124.0, 112.8, 112.4, 100.8, 97.9, 63.8, 36.6, 23.4, 22.1, 21.8; MS (m/z): HRMS (ESI) calcd for $C_{24}H_{18}N_3O_3$ ($[M+H]^+$): 396.1343, found: 396.1343.

*3.2.12. Heterocyclic[3.3.3]propellanes (**1l**).* Yellow solid, 78%, mp 236–238 °C; IR (KBr) υ: 2948, 2880, 2771, 2552, 2194, 2026, 1717, 1560, 1543, 1494, 1459, 1409, 1323, 1296, 1267, 1239, 1196, 1148, 1090, 1048, 1014, 994, 974, 946, 923, 855, 799, 769, 710 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.88 (s, 1H, ArH), 7.88 (d, J=7.8 Hz, 1H, ArH), 7.77 (t, J=7.2 Hz, 1H, ArH), 7.67 (t, J=7.2 Hz, 1H, ArH), 7.63 (d, J=8.4 Hz, 2H, ArH), 7.35 (d, J=7.2 Hz, 2H, NH_2), 6.92 (d, J=7.8 Hz, 1H, ArH), 5.92 (s, 1H, ArH), 2.49–2.43 (m, 1H, CH_2), 2.28–2.22 (m, 1H, CH_2), 2.18–2.14 (m, 1H, CH_2), 2.06–2.02 (m, 1H, CH_2), 1.88–1.76 (m, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 194.1, 190.5, 165.5, 147.8, 135.9, 134.2, 133.6, 133.5, 131.3, 131.1, 129.4, 125.2, 124.0, 112.7, 112.4, 101.2, 97.9, 63.8, 36.6, 23.3, 22.1, 21.8; MS (m/z): HRMS (ESI) calcd for $C_{24}H_{16}ClNaN_3O_3$ ($[M+Na]^+$): 452.0772, found: 452.0778.

*3.2.13. Heterocyclic[3.3.3]propellanes (**1m**).* Yellow solid, 71%, mp 228–230 °C; IR (KBr) υ: 2949, 2878, 2775, 2555, 2347, 2194, 2026, 1717, 1632, 1598, 1542, 1492, 1458, 1409, 1323, 1296, 1266, 1240, 1196, 1147, 1089, 1070, 1048, 1011, 996, 975, 946, 922, 855, 798, 769, 709 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.88 (s, 1H, ArH), 7.88 (d, J=7.8 Hz, 1H, ArH), 7.79–7.76 (m, 3H, ArH), 7.67 (t, J=7.2 Hz, 1H, ArH), 7.28 (d, J=7.8 Hz, 2H, NH_2), 6.92 (d, J=7.8 Hz, 1H, ArH), 5.92 (s, 1H, ArH), 2.48–2.43 (m, 1H, CH_2), 2.27–2.22 (m, 1H, CH_2), 2.18–2.14 (m, 1H, CH_2), 2.07–2.02 (m, 1H, CH_2), 1.88–1.77 (m, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 194.1, 190.5, 165.4, 147.8, 135.9, 134.1, 134.0, 132.3, 131.6, 131.1, 125.1, 124.0, 122.1, 112.7, 112.4, 101.2, 97.9, 63.8, 36.6, 23.3, 22.1, 21.8; MS (m/z): HRMS (ESI) calcd for $C_{24}H_{16}BrNaN_3O_3$($[M+Na]^+$): 496.0267, found: 496.0269.

*3.2.14. Heterocyclic[3.3.3]propellanes (**1n**).* Yellow solid, 65%, mp 214–216 °C; IR (KBr) υ: 2950, 2883, 2195, 2026, 1727, 1597, 1558, 1524, 1500, 1436, 1404, 1345, 1328, 1296, 1264, 1249, 1192, 1173, 1146, 1111, 1087, 991, 958, 928, 902, 863, 799, 770, 746 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 9.14 (s, 1H, ArH), 8.40 (d, J=8.4 Hz, 2H, NH_2), 7.89 (t, J=7.8 Hz, 1H, ArH), 7.73 (t, J=7.2 Hz, 1H, ArH), 7.68–7.64 (m, 3H, ArH), 6.86 (d, J=7.8 Hz, 1H, ArH), 5.95 (s, 1H, ArH), 2.63–2.58 (m, 1H, CH_2), 2.33–2.28 (m, 1H, CH_2), 2.21–2.18 (m, 1H, CH_2), 2.11–2.08 (m, 1H, CH_2), 1.93–1.90 (m, 1H, CH_2), 1.83–1.77 (m, 1H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 193.9, 191.1, 164.9, 147.6, 146.8, 141.2, 136.1, 134.1, 131.2, 130.0, 125.0, 124.9, 124.6, 124.1, 118.6, 112.6, 112.3, 102.5, 98.5, 63.9, 36.6, 23.5, 22.2, 22.1; MS (m/z): HRMS (ESI) calcd for $C_{24}H_{16}NaN_4O_5$ ($[M+Na]^+$): 463.1013, found: 463.1014.

*3.2.15. Heterocyclic[3.3.3]propellanes (**1o**).* Yellow solid, 78%, mp 194–196 °C; ^{1}IR (KBr) υ: 2955, 2875, 2192, 2026, 1722, 1639, 1600, 1539, 1498, 1406, 1358, 1325, 1292, 1243, 1194, 1146, 1089, 1013, 948, 852, 800, 776, 747 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.85 (s, 1H, ArH), 8.06 (d, J=7.8 Hz, 1H, ArH), 7.90 (t, J=7.2 Hz, 2H, ArH), 7.70 (t, J=7.8 Hz, 1H, ArH), 7.36 (d, J=7.2 Hz, 2H, NH_2), 7.31 (d, J=7.2 Hz, 2H, ArH), 7.26 (t, J=7.2 Hz, 1H, ArH), 5.96 (s, 1H, ArH), 5.22 (d, J=16.2 Hz, 1H, CH_2), 4.78 (d, J=16.2 Hz, 1H, CH_2), 2.35–2.31 (m, 1H, CH_2), 2.12–2.05 (m, 2H, CH_2), 1.94–1.86 (m, 1H, CH_2), 1.73–1.69 (m, 1H, CH_2), 1.63–1.58 (m, 1H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 194.2, 189.3, 166.2, 148.7, 137.5, 136.5, 134.2, 131.0, 128.4, 127.2, 126.9, 126.3, 125.0, 124.1, 112.7, 99.5, 97.0, 63.9, 45.1, 36.1, 23.0, 21.6, 21.0; MS (m/z): HRMS (ESI) calcd for $C_{25}H_{19}NaN_3O_3$ ($[M+Na]^+$): 432.1319, found: 432.1321.

3.3. General procedure for the preparation of spiro[cyclopenta[*b*]pyridine-4,2′-indenes] 2a–2f from one-pot domino reactions of ninhydrin, malononitrile, and cyclic enaminones

In a round bottom flask a mixture of ninhydrin (1.0 mmol), malononitrile (1.0 mmol), and triethylamine (0.1 mmol) in 5.0 mL ethanol was stirred at room temperature for about 1 h. Then cyclic enaminone (1.0 mmol) was added to it. The solution was stirred at room temperature for additional 2 h. The resulting yellow precipitates were collected by filtration and washed with cold alcohol to give the pure product.

*3.3.1. 2-Amino-1′,3′,5-trioxo-1-(4-methylphenyl)-1,1′,3′,5,6,7-hexahydrospiro[cyclopenta[b]pyridine-4,2′-indene]-3-carbonitrile (**2a**).* Yellow solid, 73%, mp 224–226 °C; IR (KBr) υ: 2924, 2181, 2026, 1745, 1714, 1642, 1555, 1511, 1415, 1383, 1338, 1305, 1189, 1131, 1020, 767, 744 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.06 (d, *J*=6.0 Hz, 4H, ArH), 7.41–7.34 (m, 4H, ArH), 6.20 (s, 2H, NH_2), 2.40 (s, 3H, CH_3), 2.33 (s, 2H, CH_2), 2.20 (s, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 200.3, 200.2, 168.4, 153.9, 140.9, 139.7, 136.9, 131.6, 130.7, 128.9, 123.1, 118.8, 112.6, 56.0, 53.3, 32.7, 26.4, 20.8; MS (*m*/*z*): HRMS (ESI) calcd for $C_{24}H_{18}N_3O_3$ ($[M+H]^+$): 396.1343, found: 396.1338.

*3.3.2. 2-Amino-1′,3′,5-trioxo-1-(4-methoxyphenyl)-1,1′,3′,5,6,7-hexahydrospiro[cyclopenta[b]pyridine-4,2′-indene]-3-carbonitrile (**2b**).* Yellow solid, 64%, mp >250 °C; IR (KBr) υ: 3347, 2932, 2835, 2361, 2174, 2026, 1745, 1712, 1640, 1552, 1510, 1461, 1424, 1383, 1338, 1296, 1250, 1171, 1130, 1032, 845, 801, 766, 752 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.06 (d, *J*=6.6 Hz, 4H, ArH), 7.39 (d, *J*=7.8 Hz, 2H, ArH), 7.12 (d, *J*=7.8 Hz, 2H, ArH), 6.26 (s, 2H, NH_2), 3.84 (s, 3H, OCH_3), 2.34 (s, 2H, CH_2), 2.20 (s, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 200.3, 200.2, 168.7, 160.1, 154.1, 140.9, 136.8, 130.4, 126.6, 123.1, 118.8, 115.3, 112.5, 55.9, 55.5, 53.4, 32.7, 26.4; MS (*m*/*z*): HRMS (ESI) calcd for $C_{24}H_{17}NaN_3O_4$ ($[M+Na]^+$): 434.1111, found: 434.1105.

*3.3.3. 2-Amino-1′,3′,5-trioxo-1-(2-methoxyphenyl)-1,1′,3′,5,6,7-hexahydrospiro[cyclopenta[b]pyridine-4,2′-indene]-3-carbonitrile (**2c**).* Yellow solid, 78%, mp >250 °C; IR (KBr) υ: 2927, 2372, 2344, 2182, 2025, 1747, 1718, 1652, 1548, 1497, 1462, 1420, 1385, 1337, 1275, 1233, 1116, 1041, 791, 754 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.06 (s, 4H, ArH), 7.56–7.13 (m, 4H, ArH), 6.24 (s, 2H, NH_2), 3.86 (s, 3H, OCH_3), 2.35–2.17 (m, 4H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 200.5, 200.1, 168.8, 156.0, 154.1, 141.1, 140.8, 136.8, 136.7, 132.0, 130.6, 123.1, 122.2, 121.3, 118.9, 113.3, 112.7, 56.1, 55.8, 32.6, 25.8; MS (*m*/*z*): HRMS (ESI) calcd for $C_{24}H_{17}NaN_3O_4$ ($[M+Na]^+$): 434.1111, found: 434.1102.

*3.3.4. 2-Amino-1′,3′,5-trioxo-1-(4-chlorophenyl)-1,1′,3′,5,6,7-hexahydrospiro[cyclopenta[b]pyridine-4,2′-indene]-3-carbonitrile (**2d**).* Yellow solid, 61%, mp >250 °C; IR (KBr) υ: 2925, 2371, 2346, 2172, 2026, 1708, 1643, 1414, 1383, 1189, 1133, 1015, 816, 754 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.06 (d, *J*=6.0 Hz, 4H, ArH), 7.64 (s, 2H, ArH), 7.51 (s, 2H, ArH), 6.41 (s, 2H, NH_2), 2.36 (s, 2H, CH_2), 2.21 (s, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 200.2, 168.0, 153.8, 140.9, 136.9, 134.7, 133.3, 131.3, 130.2, 123.1, 118.7, 112.8, 56.1, 53.3, 32.7, 26.4; MS (*m*/*z*): HRMS (ESI) calcd for $C_{23}H_{14}ClNaN_3O_3$ ($[M+Na]^+$): 438.0616, found: 438.0612.

*3.3.5. 2-Amino-1′,3′,5-trioxo-1-(3-chlorophenyl)-1,1′,3′,5,6,7-hexahydrospiro[cyclopenta[b]pyridine-4,2′-indene]-3-carbonitrile (**2e**).* Yellow solid, 66%, mp >250 °C; IR (KBr) υ: 3338, 2933, 2375, 2347, 2181, 2026, 1747, 1718, 1644, 1623, 1591, 1554, 1476, 1417, 1380, 1336, 1308, 1256, 1161, 1130, 1097, 1077, 1042, 881, 811, 787, 752, 717 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.07 (s, 4H, ArH), 7.65–7.44 (m, 4H, ArH), 6.47 (s, 2H, NH_2), 2.41 (s, 1H, CH_2), 2.33 (s, 1H, CH_2), 2.21 (s, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 200.2, 168.0, 153.7, 140.9, 140.8, 136.9, 135.7, 134.1, 131.5, 130.3, 129.6, 128.2, 123.1, 118.7, 112.9, 56.2, 53.3, 32.7, 26.4; MS (*m*/*z*): HRMS (ESI) calcd for $C_{23}H_{14}ClNaN_3O_3$ ($[M+Na]^+$): 438.0616, found: 438.0611.

*3.3.6. 2-Amino-1′,3′,5-trioxo-1-(4-bromophenyl)-1,1′,3′,5,6,7-hexahydrospiro[cyclopenta[b]pyridine-4,2′-indene]-3-carbonitrile (**2f**).* Yellow solid, 63%, mp >250 °C; IR (KBr) υ: 3371, 2933, 2373, 2345, 2174, 2026, 1743, 1709, 1666, 1624, 1543, 1486, 1427, 1376, 1346, 1274, 1239, 1132, 1044, 1011, 824, 794, 772, 752 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 8.06 (d, *J*=5.4 Hz, 4H, ArH), 7.78 (d, *J*=7.8 Hz, 2H, ArH), 7.44 (d, *J*=8.4 Hz, 2H, ArH), 6.45 (s, 2H, NH_2), 2.36 (s, 2H, CH_2), 2.21 (s, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 200.2, 168.0, 153.7, 140.9, 136.9, 133.7, 133.2, 131.5, 123.4, 123.1, 118.7, 112.8, 56.1, 53.3, 32.7, 26.4; MS (*m*/*z*): HRMS (ESI) calcd for $C_{23}H_{14}BrNaN_3O_3$ ($[M+Na]^+$): 482.0111, found: 482.0106.

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Supplementary data

Crystallographic data **1a** (CCDC 921960), **1j** (CCDC 921961), and **2a** (CCDC 921962) have been deposited at the Cambridge Crystallographic Database Centre. These data can be obtained free of charge via www.ccdc.ac.ck./data_request/cif. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2013.04.048.

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