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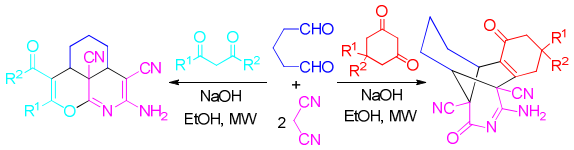

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Two series of novel polyfunctionalized hydroisoquinoline derivatives have been synthesized via the three-component domino reaction of glutaraldehyde, malononitrile and 1,3-dicarbonyl compounds under microwave irradiation conditions in the presence of a catalytic amount of NaOH (10 mol%). Notably, this one-pot transformation allowed for the formation of six or seven new bonds and three new rings depending on the 1,3-dicarbonyl compound. Furthermore, this new multicomponent reaction proceeded rapidly, with the reaction reaching completion within 10 min.

Introduction

Nitrogen-containing polyheterocyclic skeletons are present in a broad range of natural products and synthetic molecules with important biological activities.[1] Among them, hydroisoquinoline scaffolds are interesting synthetic targets because of their potent biological properties, including their insecticidal, anti-bacterial, anti-inflammatory, anti-cancer, and anti-malarial activities.[2] Derivatives of these compounds can be found in a wide range of natural alkaloids, including reserpine[3] and youhimbine[4] (Figure 1). Although several methods have been reported in the literature for the synthesis of these molecules,[5] these methods invariably require long multistep processes and provide low yields of the desired product. For this reason, there is therefore an urgent need for the discovery of new and efficient methods for the construction of these complex molecules, as well as providing a synthetic platform for the exploration of a broad range of complex scaffolds with potentially enhanced bioactivities.

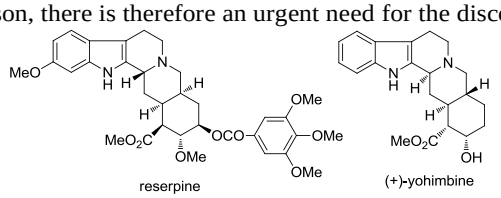

Figure 1. Several hydroisoquinoline scaffolds occurring in natural products

The creation of diverse and complex molecules from readily available starting materials is a challenging theme in modern synthetic organic chemistry.[6] Multicomponent reactions (MCRs) have been widely used in synthetic chemistry as a powerful strategy for the rapid construction of complex structures, including natural products and important organic molecules. Compared with conventional synthetic approaches, MCRs provide facile access to enhanced levels of product diversity, structural complexity, and atom economy. MCRs also allow for a reduction in the number of reaction steps, and therefore avoid some of the issues associated with the separation and purification of intermediates and products.[7] Microwave-assisted organic synthesis has received much attention because of its faster chemistry and formation of cleaner products compared with conventional heating. This technology has recently been used in MCRs.[8] We recently reported the development of new MCRs that provided rapid access to a variety of nitrogen-containing heterocyclic skeletons of chemical and pharmaceutical interest, including pyrrole, 3-pyrrolyl coumarin, 1,8-naphthyridine, and dispiropyrrolidine skeletons.[9] Herein, we describe the development of a novel three-component reaction for the facile synthesis of novel polyfunctionalized hydroisoquinolines from glutaraldehyde, malononitrile and 1,3-dicarbonyl compounds under microwave irradiation conditions in the presence of a catalytic amount of NaOH (10 mol%).

Results and discussion

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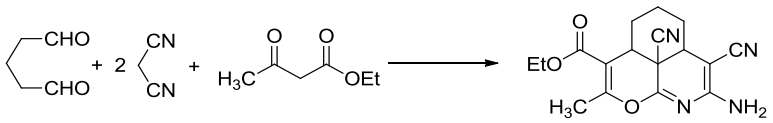
The three-component reaction of glutaraldehyde (**1**), malononitrile (**2**) and ethyl 3-oxobutanoate (**3a**) was initially selected as a model reaction to optimize the reaction conditions. The reaction, which consisted of a 1:2:1 (mol/mol/mol) mixture of **1**, **2**, and **3a**, was conducted under a variety of different conditions (Table 1). The desired product **4a** was obtained in 45% yield when the reaction was carried out in ethanol under microwave irradiation and catalyst-free conditions (Table 1, entry 1). Various solvents were evaluated to determine the impact of the solvent on the outcome of the reaction (Table 1, entries 1–6). The results of these screening experiments revealed that ethanol provided the best results of all of the solvents tested, including DMF, water, acetonitrile, methanol and ethane-1,2-diol, in terms of the yield of the product. Several bases were also evaluated, including pyridine, triethylamine, piperidine, sodium and cesium carbonates and sodium hydroxide (NaOH). A catalyst (10 mol%) was added to all of the reactions, which were carried out in ethanol at 100 ℃ under microwave irradiation conditions. The results of these screening experiments revealed that NaOH provided superior catalytic efficiency compared with all of the other bases tested (Table 1, entries 7–12).

Having identified NaOH as the best catalyst for this transformation, we proceeded to evaluate the amount of NaOH required by the reaction to achieve optimum conversion. The results of these screening experiments showed that a 10 mol% charge of NaOH was sufficient for promoting the current reaction (Table 1, entries 12–15). The reaction was then conducted at a variety of different temperatures, including 60, 70, 80, 90, 100 and 110 ℃, to determine the optimum temperature for the transformation. All of these experiments were conducted under microwave irradiation in ethanol in the presence of a catalytic amount of NaOH (10 mol%), with the desired product **4a** being formed in yields of 40, 65, 68, 75, and 60%, respectively (Table 1, entries 12 and 16–19). Based on all of these experiments, the optimum reaction conditions were determined to be 10 mol% NaOH in ethanol at 100 ℃ under microwave irradiation.

With the optimal reaction conditions in hand, we proceeded to evaluate the substrate scope of the transformation using a variety of different 1,3-dicarbonyl compounds (Table 2). The results of these experiments revealed that the newly developed protocol performed well with a variety of acyclic 1,3-dicarbonyl compounds, including1,3-diketones and *β*-ketoesters. Interestingly, the use of the cyclic 1,3-diketone 5,5-dimethyl-1,3-cyclohexandione (dimedone) (**5a**) did not result in the formation of the desired product **4**. HPLC analysis of the product mixture, however, indicated that all of the starting materials had been consumed by the reaction with the formation of a new product, which was subsequently identified as decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno) benzo [8]annulene (**6a**) (Scheme 1). One of the key features of these new MCR is that they allow for the formation of up to seven new bonds, and three new rings (i.e., tricyclic 6–6–6 skeletons, consisting of cyclohexane, cyclohexene, and pyridine rings). Furthermore, both of these new MCRs were fast, with all of the reactions reaching completion within 10 min. Water was formed as the major by-product of these reactions, indicating that these reactions are both atom economical and environmentally friendly. Several other cyclic 1,3-diketones bearing aliphatic groups (such as methyl, propyl, and isopropyl groups) or an aryl group (such as phenyl, 4-methoxyphenyl and 4-bromophenyl) at C-5 of 1,3-cyclohexandione reacted smoothly under the optimized reaction conditions to give the desired products (**6**) in satisfactory yields (Table 3). The reaction pathways could therefore been controlled by varying

Table 1. Optimization of the reaction conditions



1 **2** **3a** **4a**

Entry	Solvent	Catalyst (mol%)	Temp (^{o}C)	Time (min)	Yield (%)[a]
1	EtOH	No	100	10	45
2	DMF	No	100	10	30
3	H_2O	No	100	20	15
4	CH_3CN	No	100	15	40
5	CH_3OH	No	90	15	42
6	$HOCH_2CH_2OH$	No	100	10	34
7	EtOH	Pyridine (10)	100	10	50
8	EtOH	Triethylamine (10)	100	10	55
9	EtOH	Piperidine (10)	100	10	59
10	EtOH	Na_2CO_3 (10)	100	10	60

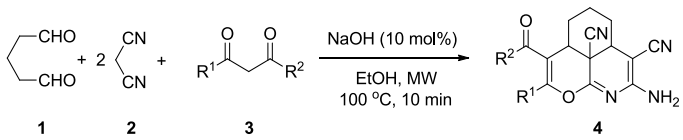
11	EtOH	Cs_2CO_3 (10)	100	10	62
12	EtOH	NaOH (10)	100	10	75
13	EtOH	NaOH (5)	100	10	68
14	EtOH	NaOH (15)	100	10	60
15	EtOH	NaOH (20)	100	10	56
16	EtOH	NaOH (10)	70	20	40
17	EtOH	NaOH (10)	80	15	65
18	EtOH	NaOH (10)	90	10	68
19	EtOH	NaOH (10)	110	10	60

[a] yield was determined by HPLC-MS

the structures of the 1,3-dicarbonyl compound to give a series of novel hydroisoquinoline derivatives and decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8]annulene derivatives selectively.

Compounds **4** and **6** were fully characterized by IR, ^{1}H and ^{13}C NMR and HRMS. Furthermore, the structures of compounds **4a** and **6a** were unambiguously confirmed by single-crystal X-ray crystallography[10] (Figure 2).

Table 2. The Synthesis of hydroisoquinoline derivatives **4**



1 2 3 4

Entry	Product	R^1	R^2	Isolated Yield (%)
1	**4a**	Me	EtO	75
2	**4b**	Me	MeO	70
3	**4c**	Me	Me	72
4	**4d**	Ph	EtO	80
5	**4e**	Ph	Ph	51
6	**4f**	Et	EtO	68
7	**4g**	*n*-Pr	EtO	66
8	**4h**	*i*-Pr	MeO	69
9	**4i**	Me	CH_2=CH-CH_2O	70
10	**4j**	4-ClC_6H_4	EtO	65
11	**4k**	4-BrC_6H_4	EtO	68
12	**4l**	4-$CH_3C_6H_4$	EtO	76

Based on our experimental observations, we have proposed a mechanism for this new multicomponent domino reaction (Scheme 2). The initial Knoevenagel condensation of glutaraldehyde (**1**) with two molecules of malononitrile (**2**) would give intermediate **A**. Intermediate **A** then undergo a Michael addition with compound **3** or **5** catalyzed by base to give the intermediate **B**, which would undergo H shift and cyclization to give intermediate **D**. For acyclic 1,3-dicarbonyl compounds, intermediate **D** would undergo an intramolecular cyclization and tautomerization to give the products **4**. For cyclic 1,3-dicarbonyl compounds, intermediate **D** would undergo the Michael addition catalyzed by base to give intermediate **G**, which then undergo a ring-opening reaction in the presence of base to give intermediate **H**. Intermediate **H** then undergo an intramolecular cyclization reactions to give intermediate **I**. Intermediate **I** would then tautomerize to give the product **6**.

The key reaction is the ring-opening reaction of intermediate **G**. A similar ring-opening reactions have been reported by Wu[11] and our group[9a]. To evaluate the likelihood that this transformation occurred in our system, we carried out density functional theory calculations of the possible configurations of intermediates **D**, **G** and **H** at the B3LYP/6-31G level of theory. First, we optimized the geometries of three possible configurations and then calaulated the lowest-energy minima of those configurations (Figure 3). We found that the most stable configuration of intermediate **H** was 69.02 and 80.82 kJ/mol lower in energy than the most stable configuration of intermediate **G** and **D**, respectively. This result suggests that intermediate **D** could be easily transformed to more stable intermediate **H**.

Conclusion

In summary, we have developed an efficient protocol for the construction of a broad range polyfunctionalized hydroisoquinoline and decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo [8]annulene of mild reaction conditions, atom economy, convenient operation, short reaction times, and high chemoselectivity.

Scheme 1. The three-component reaction of glutaraldehyde, malononitrile and dimedone

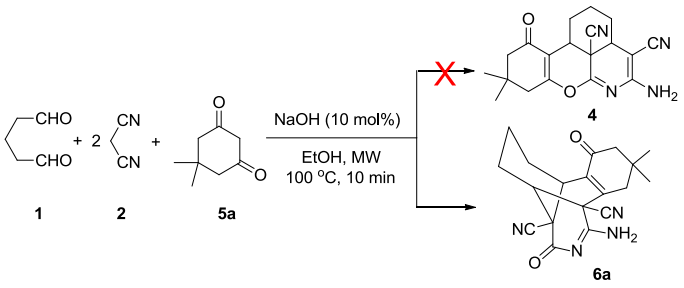
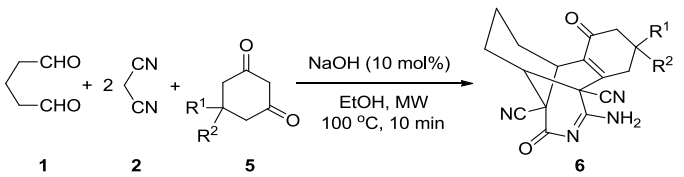


Table 3. The synthesis of benzo[8]annulene derivatives **6**



Entry	Product	R^1	R^2	Isolated Yield (%)
1	**6a**	CH_3	CH_3	70
2	**6b**	H	H	60
3	**6c**	CH_3	H	68
4	**6d**	*n*-Pr	H	65
5	**6e**	*i*-Pr	H	70
6	**6f**	C_6H_5	H	65
7	**6g**	4-$CH_3OC_6H_4$	H	66
8	**6h**	4-BrC_6H_4	H	61

Experimental section

Melting points were determined using an XT-5 melting point apparatus and are uncorrected. IR spectra were recorded (cm^{-1}) with a Varian F-1000 spectrometer, using KBr. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Varian Inova-400 MHz spectrometer, in DMSO-d_6 solution. J values are in hertz. Chemical shifts are expressed in parts million downfield from TMS as an internal standard. HRMS of all the compounds were obtained using a Bruker MicrOTOF-QII mass spectrometer with an ESI resource. General Methods. Microwave irradiation experiments were conducted in an Initiator 2.5 Microwave system (Biotage, Uppsala, Sweden). The reaction temperatures were measured using an infrared detector during the microwave heating stages. All chemicals and solvents were used without further purification, unless otherwise stated.

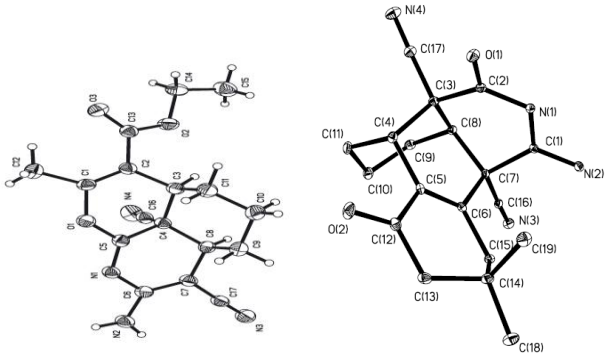


Figure 2. The crystal structures of **4a** (left) and **6a** (right). Carbon, oxygen, and nitrogen atoms are depicted with thermal ellipsoids set at the 30% probability level.

General procedure for the synthesis of compounds 4

Glutaraldehyde (**1**, 50% solution, 0.200g, 1 mmol), malononitrile (**2**, 0.132 g, 2 mmol) and acyclic 1,3-dicarbonyl compounds (**3**, 1 mmol) were placed in a 10 mL Initiator reactor vial, followed by NaOH (0.004 g, 0.1 mmol) and EtOH (2 mL). The reaction vial was then sealed and prestirred for 10 s before being irradiated in the microwave (time, 10 min; temperature, 100 ℃; absorption level, high; fixed hold time) until TLC (3:1 mixture of petroleum ether and acetone) revealed the complete consumption of the starting materials. The reaction mixture was then cooled to room temperature and diluted with cold water (20 mL) to give a precipitate, which was collected by Büchner filtration. The solid material was then purified by recrystallization from 95% EtOH to afford the desired product. The products were further identified using FTIR and NMR spectroscopies, and HRMS.

Ethyl 8-amino-3a^1,7-dicyano-2-methyl-3a,3a^1,4,5,6,6a-hexahydropyrano[4,3,2-*ij*]isoquinoline-3- carboxylate (4a)

Yellow solid, 0.245 g, yield 75%; mp 188–190 ℃. IR (KBr): 3389, 2964, 2167, 1650, 1638, 1560, 1543, 1323, 1320, 1230, 1175, 1000, 878, 746 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.95 (s, 2H, NH_2), 4.30–4.17 (m, 2H, CH_2O), 3.22–3.16 (m, 1H, CH), 2.98–2.94 (m, 1H, CH), 2.38 (s, 3H, CH_3), 1.91–1.82 (m, 2H, 2 × CH), 1.49–1.46 (m, 1H, CH), 1.28–1.25 (m, 4H, CH_3 and CH), 1.04–0.98 (m, 2H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 196.8, 159.4, 159.1, 156.5, 120.5, 120.4, 117.7, 59.9, 37.8, 35.6, 30.5, 29.6, 28.6, 20.5, 19.4; HRMS (ESI): *m/z* calcd for $C_{17}H_{19}N_4O_3$ [$(M+H)^+$], 327.1457; found, 327.1460.

Methyl 8-amino-3a^1,7-dicyano-2-methyl-3a,3a^1,4,5,6,6a-hexahydropyrano[4,3,2-*ij*]isoquinoline-3- carboxylate (4b)

Yellow solid, 0.219 g, yield 70%; mp 228–230 ℃. IR (KBr): 3394, 2958, 2189, 1655, 1584, 1443, 1368, 1320, 1258, 1134, 1103, 885, 781 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.96 (s, 2H, NH_2), 3.76 (s, 3H, CH_3O), 3.24–3.20 (m, 1H, CH), 2.98–2.93 (m, 1H, CH), 2.38 (s, 3H, CH_3), 1.92–1.82 (m, 2H, 2 × CH), 1.48–1.45 (m, 1H, CH), 1.32–1.23 (m, 1H, CH), 1.07–0.95 (m, 2H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.5, 160.4, 159.2, 156.4, 120.4, 117.7, 111.7, 60.0, 52.7, 39.3, 37.6, 35.6, 29.6, 28.6, 20.3, 18.8; HRMS (ESI): *m/z* calcd for $C_{16}H_{17}N_4O_3$ [$(M+H)^+$], 313.1301; found, 313.1298.

3-Acetyl-8-amino-2-methyl-3a,3a^1,4,5,6,6a-

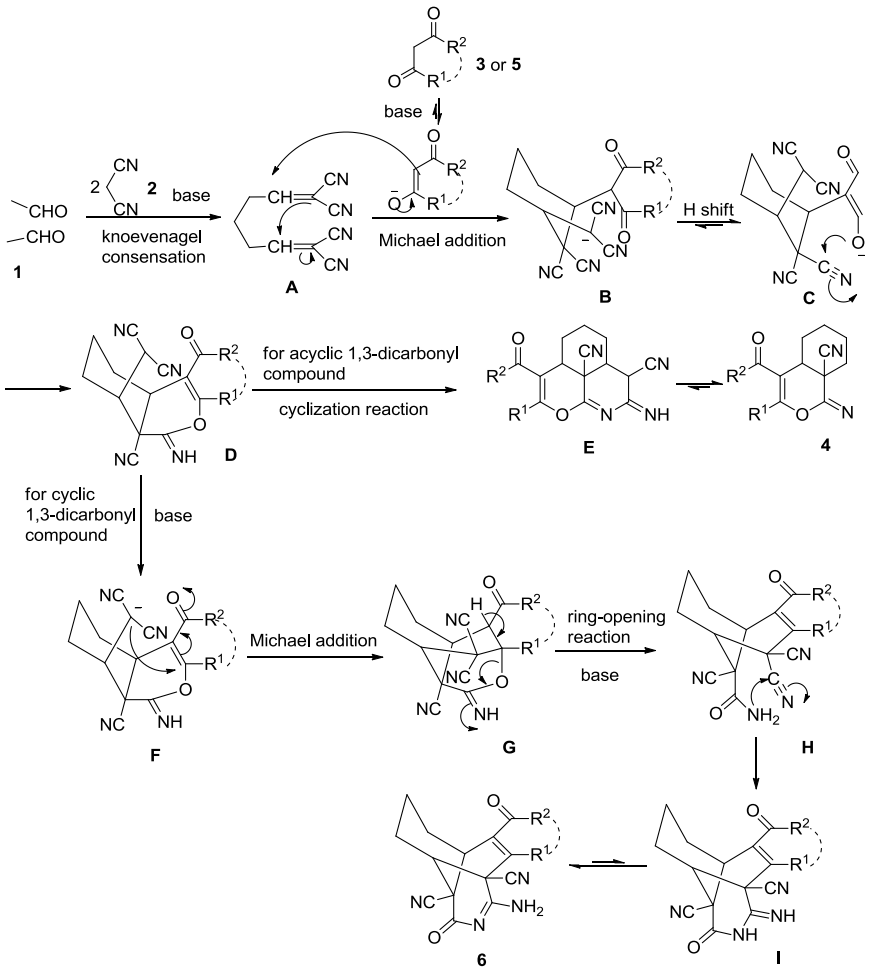
hexahydropyrano[4,3,2-*ij*]isoquinoline-3a[1],7-dicarbonitrile (4c)
Yellow solid, 0.213 g, yield 72%; mp 258–260 ℃. IR (KBr): 3356, 2964, 2177, 1642, 1669, 1559, 1551, 1332, 1326, 1238, 1115, 1004, 876, 740 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.93 (s, 2H, NH_2), 3.31–3.28 (m,2.39 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 1.95–1.78 (m, 2H, 2 × CH), 1.49–1.46 (m, 1H, CH), 1.34–1.24 (m, 1H, CH), 1.05–0.96 (m, 2H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.1, 160.2, 159.2, 156.4, 120.4, 117.8, 111.8, 61.52, 60.0, 39.3, 37.6, 35.7, 29.7, 28.7, 20.3, 18.9, 14.5; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{17}N_4O_2$ [$(M+H)^+$], 297.1352; found, 297.1327.

Ethyl 8-amino-3a[1],7-dicyano-2-phenyl-3a,3a[1],4,5,6,6a-hexahydro pyrano[4,3,2-*ij*]isoquinoline-3- carboxylate (4d)
Yellow solid, 0.311 g, yield 80%; mp 228–230 ℃. IR (KBr): 3356, 2956, 2167, 1652, 1649, 1579, 1571, 1392, 1326, 1249, 1123, 1000, 879, 745 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 7.53–7.34 (m, 5H, ArH), 7.01 (s, 2H, NH_2), 4.01 (q, *J* = 6.8 Hz, 2H, CH_2O), 3.34–3.23 (m, 1H, CH), 3.02 (d, *J* = 8.4 Hz, 1H, CH), 2.09 (d, *J* = 11.4 Hz, 1H, CH), 1.88 (d, *J* = 11.8 Hz, 1H, CH), 1.55–1.52 (m, 1H, CH), 1.36–1.19 (m, 2H, 2 × CH), 1.12–1.03 (m, 1H, CH), 0.91 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.5, 159.4 , 157.3, 156.36 , 132.3, 131.1, 129.0, 128.7, 120.4, 117.7, 113.4, 61.5, 60.1, 39.5, 37.6, 36.8, 29.6, 28.7, 20.3, 13.8; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{21}N_4O_3$ [$(M+H)^+$], 389.1614; found, 389.1609.

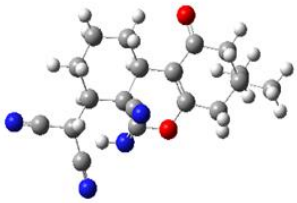
8-Amino-3-benzoyl-2-phenyl-2,3,3a,3a[1],4,5,6,6a-octahydro pyrano[4,3,2-*ij*]isoquinoline-3a[1],7-dicarbonitrile (4e)
Yellow solid, 0.215 g, yield 51%; mp 238–240 ℃. IR (KBr): 3359, 2952, 2166, 1663, 1638, 1587, 1564, 1383, 1333, 1247, 1124, 1004, 875, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 7.66–7.64 (m, 2H, ArH), 7.39–7.36 (m, 1H, ArH), 7.28–7.18 (m, 7H, ArH), 7.04 (s, 2H, NH_2), 3.32–3.29 (m, 1H, CH), 3.04–3.00 (m, 1H, CH), 2.25–2.23 (m, 1H, CH), 1.92–1.89 (m, 1H, CH), 1.57–1.55 (m, 1H, CH), 1.46–1.31 (m, 2H, 2 × CH), 1.16–1.07 (m, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 195.5, 193.3, 165.0, 151.6, 136.9, 136.8, 129.8, 129.5, 129.4, 128.4, 120.1, 118.2, 58.3, 56.8, 39.9, 39.7, 39.5, 39.3, 39.1, 28.8, 25.10, 24.9; HRMS (ESI): *m*/*z* calcd for $C_{26}H_{23}N_4O_2$ [$(M+H)^+$], 423.1821; found, 423.1834.

Ethyl 8-amino-3a[1],7-dicyano-2-ethyl-3a,3a[1],4,5,6,6a-hexahydro pyrano[4,3,2-ij]isoquinoline-3-carboxylate (4f)
Yellow solid, 0.231 g, yield 68%; mp 148–150 ℃. IR (KBr): 3344, 2967, 2168, 1666, 1649, 1569, 1541, 1392, 1346, 1258, 1135, 989, 877, 742 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.96 (s, 2H, NH_2), 4.24–4.21 (m, 2H, CH_2O), 3.22–3.17 (m, 1H, CH), 2.98–2.93 (m, 1H, CH), 2.87–2.82 (m, 1H, CH), 2.69–2.64 (m, 1H, CH), 1.92–1.82 (m, 2H, CH_2), 1.49–1.45 (m, 1H, CH), 1.29–1.23 (m, 4H, CH_3 and CH), 1.11 (t, *J* = 7.4 Hz, 3H, CH_3), 1.05–0.96 (m, 2H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 164.9, 164.3, 159.6, 156.4,

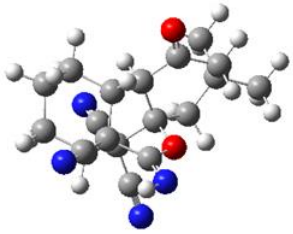
Scheme 2. Proposed mechanism for the formation of compounds **4** and **6**



120.4, 117.7, 111.4, 61.6, 60.0, 39.3, 37.5, 35.60, 29.7, 28.7, 25.2, 20.4, 14.4, 11.8; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{21}N_4O_3$ [(M+H)$^+$], 341.1614; found, 341.1592.



Intermediate D: E = -1104.715646 hartree



Intermediate G: E = -1104.720138 hartree

Intermediate H: E = -1104.746429 hartree

Figure 3. Lowest energy minimum of intermediates **D**, **G** and **H**

Ethyl 8-amino-3a^1,7-dicyano-2-propyl-3a,3a^1,4,5,6,6a-hexahydro pyrano[4,3,2-ij]isoquinoline-3-carboxylate (4g)

Yellow solid, 0.234 g, yield 66%; mp 143–145 ℃. IR (KBr): 3339, 2956, 2164, 1655, 1645, 1556, 1575, 1333, 1216, 1148, 1025, 1000, 876, 744 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.94 (s, 2H, NH_2), 4.25–4.19 (m, 2H, CH_2O), 3.24–3.18 (m, 1H, CH), 2.97–2.87 (m, 2H, CH_2), 2.67–2.60 (m, 1H, CH), 1.93–1.82 (m, 2H, CH_2), 1.62–1.46 (m, 3H, CH_3), 1.28–1.23 (m, 4H, 2 × CH_2), 1.10–0.95 (m, 2H, CH_2), 0.91 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.0, 163.0, 159.5, 156.4, 120.4, 117.8, 112.6, 61.6, 60.0, 39.3, 37.5, 35.8, 33.0, 29.7, 28.7, 20.4, 14.4, 13.4; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{23}N_4O_3$ [(M+H)$^+$], 355.1770; found, 355.1750.

Methyl 8-amino-3a^1,7-dicyano-2-isopropyl-3a,3a^1,4,5,6,6a-hexa hydropyrano[4,3,2-*ij*]isoquinoline-3-carboxylate (4h)

Yellow solid, 0.235 g, yield 69%; mp 238–240 ℃. IR (KBr): 3356, 2944, 2157, 1762, 1539, 1489, 1361, 1282, 1136, 1247, 1126, 1004, 889, 732 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.00 (s, 2H, NH_2), 3.85–3.79 (m, 1H, CH), 3.77 (s, 3H, CH_3O), 3.21–3.18 (m, 1H, CH), 2.97–2.92(m, 1H, CH), 1.94–1.82 (m, 2H, 2 × CH), 1.49–1.45 (m, 1H, CH), 1.29–1.23 (m, 1H, CH), 1.12–1.08 (m, 6H, 2 × CH_3), 1.03–0.97 (m, 2H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 166.5, 165.6, 160.2, 156.5, 120.5, 117.7, 110.7, 60.1, 52.9, 39.3, 37.4, 35.6, 29.6, 29.3, 28.4, 20.3, 19.4, 19.1; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{21}N_4O_3$ [(M+H)$^+$], 341.1614; found, 341.1604.

***A*llyl 8-amino-3a^1,7-dicyano-2-methyl-3a,3a^1,4,5,6,6a-hexahydro pyrano[4,3,2-*ij*]isoquinoline-3-carboxylate (4i)**

Yellow solid, 0.237 g, yield 70%; mp 248–250 ℃. IR (KBr): 3396, 2934, 2147, 1652, 1629, 1549, 1501, 1342, 1306, 1233, 1105, 1004, 875, 741 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.94 (s, 2H, NH_2), 6.02–5.91 (m, 1H, CH), 5.36–5.24 (m, 2H, 2 × CH), 4.71 (d, *J* = 5.2 Hz, 2H, CH_2O), 3.26–3.20 (m, 1H, CH), 2.99–2.93 (m, 1H, CH), 2.38 (s, 3H, CH_3), 1.92–1.81 (m, 2H, 2 × CH), 1.50–1.47 (m, 1H, CH), 1.33–1.22 (m, 1H, CH), 1.09–0.97 (m, 2H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 166.5, 165.5, 160.0, 156.5, 120.4, 117.7, 110.7, 60.0, 52.9, 37.4, 35.6, 29.6, 29.30, 28.5, 20.3, 19.5, 19.1; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}N_4O_3$ [(M+H)$^+$], 339.1457; found, 339.1485.

Ethyl 8-amino-2-(4-chlorophenyl)-3a^1,7-dicyano-3a,3a^1,4,5,6,6a-hexahydropyrano[4,3,2-*ij*]isoquino line-3-carboxylate (4j)

Yellow solid, 0.275 g, yield 65%; mp 120–122 ℃. IR (KBr): 2925, 2851, 2764, 2380, 2174, 1690, 1656, 1491, 1383, 1270, 1192, 1093, 1016, 844, 782, 730 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.56–7.54 (m, 2H, ArH), 7.49–7.47 (m, 2H, ArH), 7.02 (s, 2H, NH_2), 4.04 (q, *J* = 6.8 Hz, 2H, CH_2O), 3.02 (dd, J_1 = 4.4, J_2 = 4.4 Hz, 1H, CH), 2.07 (d, *J* = 12.4 Hz, 1H, CH), 1.87 (d, *J* = 11.2 Hz, 1H, CH), 1.53 (d, *J* = 12.8 Hz, 1H, CH), 1.363–1.05 (m, 4H, 4 × CH), 0.95 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.1, 159.2, 156.3, 156.2, 135.8, 131.2, 131.1, 128.8, 120.3, 117.7, 113.8, 61.6, 60.0, 37.6, 36.7, 29.6, 28.6, 20.2, 13.9; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{19}ClNaN_4O_3$ [(M+Na)$^+$], 445.1043; found, 445.1049.

Ethyl 8-amino-2-(4-bromophenyl)-3a^1,7-dicyano-3a,3a^1,4,5,6,6a-hexahydropyrano[4,3,2-*ij*]isoquino line-3-carboxylate (4k)

Yellow solid, 0.318 g, yield 68%; mp 216–218 ℃. IR (KBr): 2988, 2941, 2860, 2358, 2173, 1687, 1656, 1575, 1440, 1371, 1410, 1368, 1329, 1210, 1086, 834, 786, 722 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.71–7.67 (m, 2H, ArH), 7.42–7.39 (m, 2H, ArH), 7.02 (s, 2H, NH_2), 4.04 (q, *J* = 7.2 Hz, 2H, CH_2O), 3.02 (dd, J_1 = 4.8, J_2 = 4.8 Hz, 1H, CH), 2.07 (d, *J* = 11.2 Hz, 1H, CH), 1.87 (d, *J* = 11.2 Hz, 1H, CH), 1.53 (d, *J* = 13.2 Hz, 1H, CH), 1.39–0.94 (m, 4H, 4 × CH), 0.95 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.0, 159.1, 156.3, 156.2, 131.7, 131.5, 131.2, 124.6, 120.3, 117.6, 113.8, 61.6, 60.0, 37.6, 36.7, 29.6, 28.6, 20.2, 13.8; HRMS (ESI): *m*/*z* calcd for $C_{22}H_{19}BrNaN_4O_3$ [(M+Na)$^+$], 489.0538; found, 489.0520.

Ethyl 8-amino-3a^1,7-dicyano-2-(*p*-tolyl)-3a,3a^1,4,5,6,6a-hexa hydropyrano[4,3,2-*ij*]isoquinoline-3- carboxylate (4l)

Yellow solid, 0.306 g, yield 76%; mp 120–122 ℃. IR (KBr): 3336, 2985, 2935, 2864, 2362, 2175, 1692, 1658, 1578, 1446, 1373, 1411, 1373, 1331, 1219, 1088, 1015, 837, 824, 781, 721 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.33–7.27 (m, 4H, ArH), 7.00 (s, 2H, NH_2), 4.03 (q, *J* = 7.2 Hz, 2H, CH_2O), 3.01 (dd, J_1 = 4.0, J_2 = 4.4 Hz, 1H, CH), 2,37 (s, 3H, CH_3), 2.08 (d, *J* = 11.6 Hz, 1H, CH), 1.87 (d, *J* = 11.6 Hz, 1H, CH), 1.53 (d, *J* = 12.8 Hz, 1H, CH), 1.39–1.02 (m, 4H, 4 × CH), 0.95 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.6, 159.5, 157.3, 156.4, 141.1, 129.4, 129.2,

129.0, 120.4, 117.8, 112.9, 61.4, 60.0, 37.6, 36.9, 29.6, 28.7, 21.5, 20.3, 13.9; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{22}NaN_4O_3$ [(M+Na)$^+$], 425.1590; found, 425.1599.

General procedure for the synthesis of compounds 6

Glutaraldehyde (**1**, 50% solution, 0.200g,1 mmol), malononitrile (**2**, 0.132 g, 2 mmol) and cyclic 1,3-dicarbonyl compounds (**5**, 1 mmol) were placed in a 10-mL Initiator reactor vial, followed by NaOH (0.004 g, 0.1 mmol) and and EtOH (2 mL) The reaction vial was then sealed and prestirred for 10 s before being irradiated in the microwave (time, 10 min; temperature, 100 ℃; absorption level, high; fixed hold time) until TLC (petroleum ether/ acetone 3/1) revealed the complete consumption of the starting materials. The reaction mixture was then cooled to room temperature and diluted with cold water (20 mL) to give a precipitate, which was collected by Büchner filtration. The solid material was then purified by recrystallization from 95% EtOH to afford the desired product. The products were further identified using FTIR and NMR spectroscopies, and HRMS.

11-Amino-2,2-dimethyl-4,13-dioxo-1,2,3,4,5,6,7,8,9,10-deca hydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8] annulene-10,14-dicarbonitrile (6a)

White solid, 0.235 g, yield 70%; mp > 300 ℃. IR (KBr) 3416, 2174, 1675, 1642, 1536, 1448, 1382, 1290, 1129, 1051, 1038 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.44 (s, 1H, NH), 8.90 (s, 1H, NH), 3.20 (s, 2H, 2 × CH), 2.77–2.73 (m, 1H, CH), 2.46 (s, 1H, CH), 2.23–2.19 (m, 2H, 2 × CH), 2.08–2.04 (m, 1H, CH), 1.90–1.86 (m, 2H, 2 × CH), 1.52–1.49 (m, 2H, 2 × CH), 1.33–1.29 (s, 1H, CH), 1.04 (s, 3H, CH_3), 0.75 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 196.0, 146.5, 133.0, 119.2, 115.2, 56.5, 50.3, 49.3, 46.6, 37.9, 34.6, 33.49, 29.2, 26.0, 25.5, 24.8, 19.0, 16.0; HRMS (ESI): *m*/*z* calcd for $C_{19}H_{20}N_4O_2$ [(M)$^+$], 336.1586; found, 336.1581.

11-Amino-4,13-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8]annulene-10,14-dicarbonitrile (6b)

White solid, 0.185 g, yield 60%; mp 238–240 ℃. IR (KBr): 3410, 2175, 1670, 1630, 1538, 1420, 1380, 1280, 1123, 1042, 1036 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.42 (s, 1H, NH), 8.94 (s, 1H, NH), 3.13–3.19 (m, 2H, 2 × CH), 2.74–2.79 (m, 1H, CH), 2.34–2.47 (m, 3H, 3 × CH), 2.03–2.06 (m, 2H, 2 × CH), 1.83–1.92 (m, 3H, 3 × CH), 1.51–1.54 (m, 2H, 2 × CH), 1.30–1.37 (m, 1H, CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 195.7, 148.9, 133.9, 119.2, 115.4, 56.5, 49.1, 46.7, 37.9, 37.2, 34.6, 26.9, 26.0, 24.8, 22.3, 19.0, 15.8; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}N_4O_2$ [(M)$^+$], 308.1273; found, 308.1272.

11-Amino-2-methyl-4,13-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8]annulene-10,14-dicarbonitrile (6c)

White solid, 0.219 g, yield 68%; mp 170–172 ℃. IR (KBr): 3417, 2173, 1681, 1637, 1617, 1533, 1384, 1294, 1123, 1041 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.40 (s, 1H, NH), 8.93 (s, 1H, NH), 3.19–3.16 (m, 2H, 2 × CH), 2.85–2.81 (m, 1H, CH), 2.54 (s, 1H, CH), 2.36–2.31 (m, 1H, CH), 2.22–2.03 (m, 2H, 2 × CH), 1.93–1.81 (m, 2H, 2 × CH), 1.52–1.50 (m, 2H, 2 × CH), 1.33–1.30 (m, 1H, CH), 1.03–1.01 (m, 1H, CH), 0.90 (d, *J* = 6.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 195.8, 147.3, 133.5, 119.2, 115.5, 46.7, 45.0, 44.6, 38.1, 34.5, 31.2, 30.1, 28.7, 26.0, 24.8, 21.1, 19.7, 15.8; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{18}N_4O_2$ [(M)$^+$], 322.1430; found, 322.1418.

11-Amino-4,13-dioxo-2-propyl-1,2,3,4,5,6,7,8,9,10-decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8]annulene-10,14-dicarbonitrile (6d)

White solid, 0.228 g, yield 65%; mp 162–164 ℃. IR (KBr) 3413, 2172, 1675, 1542, 1444, 1297, 1290, 1134, 1002 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.44 (s, 1H, NH), 8.94 (s, 1H, NH), 3.18–3.13 (m, 2H, 2 × CH), 2.87–2.84 (m, 1H, CH), 2.56–2.53 (m, 1H, CH), 2.42–2.13 (m, 3H, 3 × CH), 2.07–2.03 (m, 1H, CH), 1.89–1.79 (m, 2H, CH_2), 1.52–1.49 (m, 2H, CH_2), 1.31–1.19 (m, 5H, 5 × CH), 0.85 (t, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 195.7, 147.3, 133.7, 119.2, 115.5, 46.6, 43.4, 43.2, 38.1, 37.3, 35.9, 34.5, 33.3, 32.5, 26.0, 24.8, 19.7, 19.4, 15.8, 14.3; HRMS (ESI): *m*/*z* calcd for $C_{20}H_{22}N_4O_2$ [(M)$^+$], 350.1743; found, 350.1736.

11-Amino-2-isopropyl-4,13-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8]annulene-10,14-dicarbonitrile (6e)

White solid, 0.245 g, yield 70%; mp 170–172 ℃. IR (KBr): 3418, 2174, 1680, 1547, 1450, 1382, 1257, 1134, 1033 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.39 (s, 1H, NH), 8.96 (s, 1H, NH), 3.18–3.16 (m, 2H, 2 × CH), 2.84–2.80 (m, 1H, CH), 2.38–2.19 (m, 2H, 2 × CH), 2.07–2.04 (m, 1H, CH), 1.90–1.80 (m, 3H, 3 × CH), 1.58–1.45 (m, 3H, 3 × CH), 1.35–1.28 (m, 1H, CH), 0.91–0.84 (m, 7H, 3 × CH_3 and CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 196.0, 147.8, 133.8, 119.3, 115.6, 46.6, 41.4, 41.1, 38.2, 34.5, 31.6, 30.8, 25.9, 24.8, 20.2, 19.9, 19.69, 19.6, 15.8; HRMS (ESI): *m*/*z* calcd for $C_{20}H_{22}N_4O_2$ [(M)$^+$], 350.1743; found, 350.1742.

11-Amino-4,13-dioxo-2-phenyl-1,2,3,4,5,6,7,8,9,10-decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8]annulene-10,14-dicarbonitrile (6f)

White solid, 0.250 g, yield 65%; mp 278–280 ℃. IR (KBr) 3404, 2173, 1678, 1538, 1448, 1378, 1294, 1145, 1027 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.34 (s, 1H, NH), 8.88 (s, 1H, NH), 7.35–7.27 (m, 5H, ArH), 3.55–3.49 (m, 1H, CH), 3.24–3.18 (m, 2H, 2 × CH), 2.96–2.84 (m, 2H, 2 × CH), 2.66–2.55 (m, 2H, 2 × CH), 2.11–1.83 (m, 3H, 3 × CH), 1.58–1.39 (m, 3H, 3 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 195.4, 147.5, 143.2, 133.9, 129.1, 127.4, 119.3, 115.7, 115.1, 49.5, 46.7, 46.6, 43.8, 43.6, 39.2, 38.2, 34.8, 34.5, 26.0, 24.9, 15.8; HRMS (ESI): *m*/*z* calcd for $C_{23}H_{20}N_4O_2$ [(M)$^+$], 384.1586; found, 384.1585.

11-Amino-2-(4-methoxyphenyl)-4,13-dioxo-1,2,3,4,5,6,7,8,9,10-decahydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8] annulene-10,14-dicarbonitrile (6g)

White solid, 0.273 g, yield 66%; mp > 300 ℃. IR (KBr): 3396, 2174, 1678, 1544, 1448, 1380, 1294, 1138, 1072, 1030 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.31 (s, 1H, NH), 8.87 (s, 1H, NH), 7.26 (s, 2H, ArH), 6.89 (s, 2H, ArH), 3.72 (s, 3H, CH_3O), 3.45 (s, 1H, CH), 3.23–3.17 (m, 2H, 2 × CH), 2.89–2.80 (m, 2H, 2 × CH), 2.61–2.56 (m, 2H, 2 × CH), 2.10–1.86 (m, 3H, 3 × CH), 1.57–1.41 (m, 3H, 3 × CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.5, 158.6, 147.6, 135.2, 133.8, 128.4, 119.3, 115.7, 114.4, 55.5, 46.7, 44.2, 44.0, 38.5, 38.2, 35.1, 34.5, 34.3, 26.0, 24.9, 15.8, 15.5; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}N_4O_3$ [(M)$^+$], 414.1692; found, 414.1695.

11-Amino-2-(4-bromophenyl)-4,13-dioxo-1,2,3,4,5,6,7,8,9,10-deca hydro-5,9,10-(epiethane[1,1,2]triylazenometheno)benzo[8]

annulene-10,14-dicarbonitrile (6h)

White solid, 0.283 g, yield 61%; mp > 300 ℃. IR (KBr): 3416, 2172, 1673, 1604, 1515, 1382, 1292, 1235, 1182, 1114, 1032 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.31 (s, 1H, NH), 8.86 (s, 1H, NH), 7.52 (s, 2H, ArH), 7.33(s, 2H, ArH), 3.54 (s, 1H, CH), 3.23–3.18 (m, 2H, 2 × CH), 2.91–2.87 (m, 2H, 2 × CH), 2.66–2.59 (m, 2H, 2 × CH), 2.10–1.86 (m, 3H, 3 × CH), 1.57–1.43 (m, 3H, 3 × CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 194.3, 146.5, 141.7, 132.97, 131.0, 128.9, 119.5, 118.4, 114.7, 48.6, 45.8, 42.7, 42.4, 37.7, 37.3, 33.6, 33.5, 25.1, 24.0, 14.9, 14.6; HRMS (ESI): *m/z* calcd for $C_{23}H_{19}BrN_4O_2$ [$(M)^+$], 462.0691; found, 462.0691.

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10 Crystallographic data for the structures of **4a** and **6a** has been deposited at the Cambridge Crystallographic Data Centre, deposit numbers are CCDC-1029241 and CCDC-1000128. Copies of available material can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax, +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk). Crystal data for **4a**: empirical formula $C_{17}H_{18}N_4O_3$, colorless, crystal dimension 0.32 × 0.30 × 0.23 mm, triclinic, space group P-1, a = 7.9219(8) Å, b = 10.2365(13) Å, c = 11.9557(14) Å, α = 108.694(2) °, β = 105.2940(10) °, γ = 100.3700(10) °, V = 847.90(17) $Å^3$, Mr = 326.35, Z = 2, D_c = 1.278 Mg/m^3, μ(Mo$K\alpha$) = 0.090 mm^{-1}, F(000) = 344, S = 0.969, R_1 = 0.0549, wR_2 = 0.1125. Crystal data for **6a**: empirical formula $C_{19}H_{20}N_4O_2$, colorless, crystal dimension 0.23 × 0.18 × 0.15 mm, monoclinic,

space group $P2_1/c$, a = 7.7983(8) Å, b = 15.7822(14) Å, c = 14.3700(13) Å, α = 90 °, β = 98.5090(10) °, γ = 90 °, V = 1749.1(3) Å^3, Mr = 336.39, Z = 4, D_c = 1.277 Mg/m^3, μ(Mo$K\alpha$) = 0.086 mm^{-1}, F(000) = 712, S = 1.032, R_1 = 0.0578, wR_2 = 0.0975.

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