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RESEARCH ARTICLE

Tandem reaction for the synthesis of bicyclic *ortho*-aminocarbonitrile derivatives using DMAPA as a cheap and efficient catalyst

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Abstract: To develop a new method for the synthesis of bicyclic *ortho*-aminocarbonitrile derivatives. Reaction of aromatic aldehydes, cycloketones and malononitrile with catalytic amount of 3-(dimethylamino)-1-propylamine (DMAPA) in ethanol via Knoevenagel-Michael cascades. The bicyclic *ortho*-aminocarbonitrile derivatives were obtained with good to excellent yields along with short reaction times. The universality, excellent yields, mild reaction and easy collection through simple filtration indicate the preparation of *ortho*-aminocarbonitriles derivatives is an efficient and suitable protocol, which use one-pot multicomponent reaction of aromatic aldehyde, cycloketone, and 2 equiv. of malononitrile under the catalytic amount of DMAPA in ethanol.

Keywords: *ortho*-Aminocarbonitriles, DMAPA, tandem reaction, one-pot

1 Introduction

As a well-known intermediate in organic synthesis, *ortho*-aminocarbonitrile derivatives have gained much attention due to its multitudinous applications[1,2]. Especially, they have been used extensively in the preparation of diverse heterocyclic compounds[3,4]. Furthermore, *ortho*-aminocarbonitrile derivatives are also useful precursors for the synthesis of their corresponding dicyanoanilines[5–7] because of their optical properties[8].

Due to their fair qualities, the chemical synthesis of the *ortho*-aminocarbonitrile derivatives have attracted the attention of many organic chemists, consequently a number of strategies have been introduced in recent years. Normally, the chemical synthesis of bicyclic *ortho*-aminocarbonitrile derivatives is constructed through the Knoevenagel condensation and Michael addition under various conditions. Basic catalysts are traditionally used for this reaction, organic bases including pyrrolidine[9], piperidine[10], morpholine[11], imidazole[12], 1,4-diazabicyclo[2.2.2]octane[13,14], triethylamine[15,16] and ethanediamine[17] have been reported in the literature, and also different kinds of ionic liquids have also been employed for this condensation[18–22]. In addition, other efficient catalysts[23–30] for the synthesis of these important molecules have been reported in recent years. Although a good deal of strategies showed varying degrees of success, better and more versatile process is still needed because of the multitudinous biological applications of these functionalized molecules. Furthermore, some of the methods existed in the literature suffer from one drawback or another, such as the usage of expensive catalysts or toxic solvents, prolonged reaction times, relatively low yields, harsh conditions and cumbersome procedures.

3-(Dimethylamino)-1-propylamine (DMAPA) as a bulk chemical with low price and safety profile has been widely used in many fields. It can be used as a fuel additive, as a potential absorbent for carbon dioxide (CO_2) capture, for curing epoxy resins, and for the synthesis of betaines in shampoos in chemical industry. DMAPA is also a useful reagent in organic synthesis. As an ucleophile, it has been used for selective anomeric deacylations in carbohydrate chemistry[31] and Pd-catalyzed Buchwald reaction[32].

Considering the safety profile and low price of DMAPA which was compared to the previously reported basic catalysts[9–17], and in continuation of our interest in developing new method in organic synthesis[33–38], herein, we describe an efficient and suitable protocol for the synthesis of bicyclic *ortho*-aminocarbonitriles via one-pot multicomponent reactions of one unit of aromatic aldehyde, one unit of cycloketone and two units of malononitriles catalyzed by DMAPA (Figure 1).

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Table 1. Screening of optimal reaction conditions[a]

Entry	Catalyst(equiv.)	Solvent	T. (°C)	Time(h)	Yield(%)
1		Ethanol	r.t.	6.0	
2		Ethanol	80	6.0	trace
3	DMAPA (0.10)	Ethanol	40	0.5	91
4	DMAPA (0.10)	Methanol	40	0.5	85
5	DMAPA (0.10)	Acetonitrile	40	0.5	74
6	DMAPA (0.10)	Tetrahydrofuran	40	0.5	55
7	DMAPA (0.10)	Dichloromethane	40	0.5	34
8	DMAPA (0.05)	Ethanol	40	0.5	86
9	DMAPA (0.20)	Ethanol	40	0.5	87
10	DMAPA (0.10)	Ethanol	r.t.	0.5	66
11	DMAPA (0.10)	Ethanol	60	0.5	89
12	ethanediamine(0.10)	Ethanol	40	0.5	76
13	triethylamine (0.10)	Ethanol	40	0.5	81
14	pyrrolidine(0.10)	Ethanol	40	0.5	82
15	morpholine(0.10)	Ethanol	40	0.5	89
16	imidazole(0.10)	Ethanol	40	0.5	41

Note: [a]Unless otherwise stated, all reactions were carried out with **1a** (2 mmol), **2h**(2 mmol), **3** (4 mmol) and solvent (10 ml)

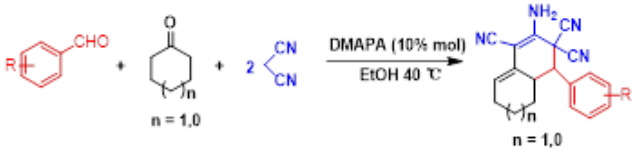


Figure 1. The synthesis of *ortho*-aminocarbonitriles

2 Results and discussion

In order to optimize the reaction conditions, cyclohexanone **1a** (2 mmol), 4-chlorobenzaldehyde **2h** (2 mmol)and malononitrile **3** (4 mmol) were chosen as the model reaction at the outset (Figure 2). A systematic study was considered by varying reaction parameters such as solvent, temperature, catalyst type, amount of catalyst and the results are summarized in Table 1.

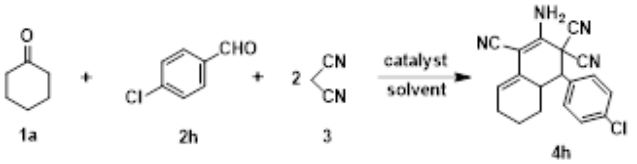
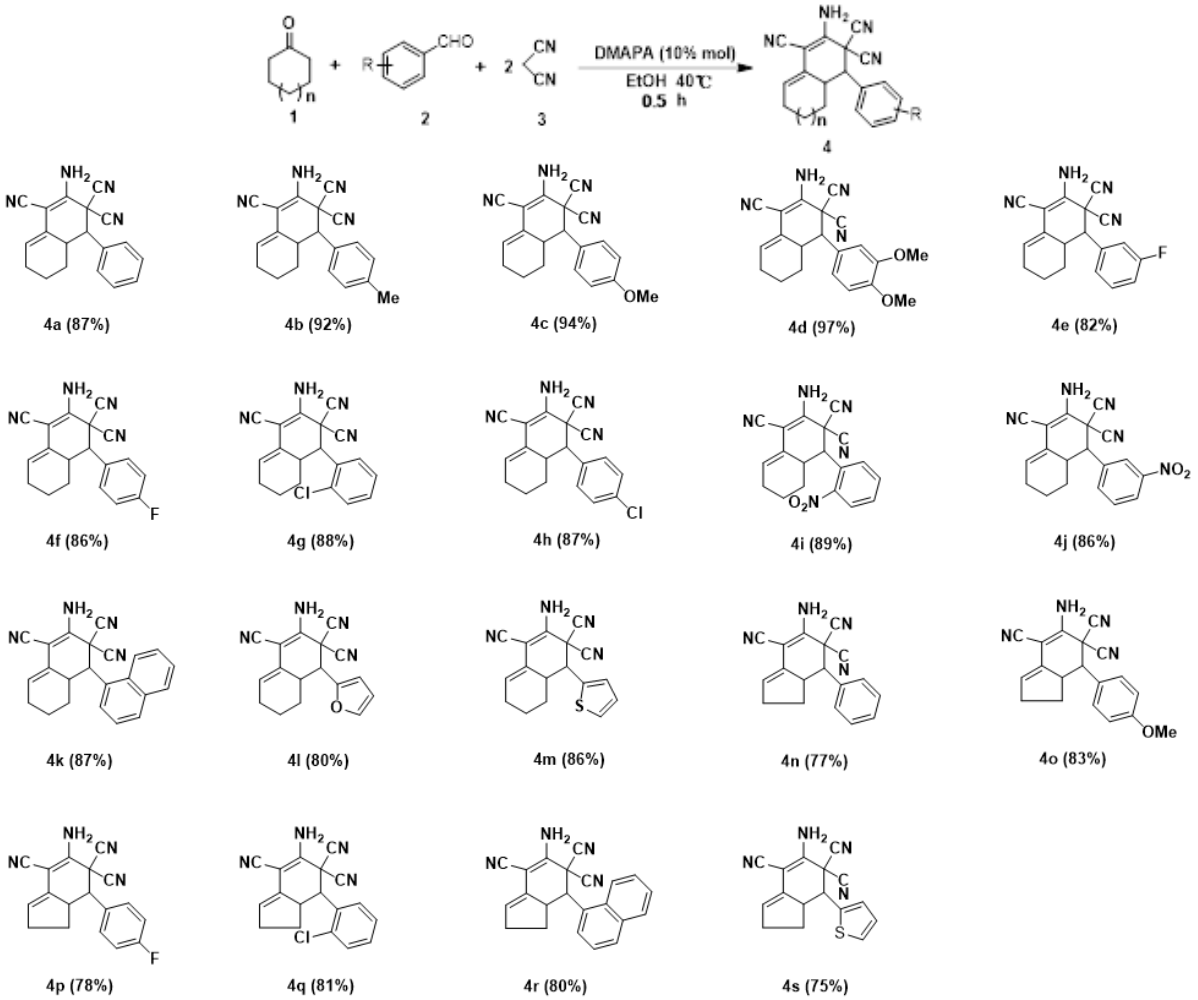


Figure 2. Model reaction

Initially, we performed a blank experiment in ethanol as solvent, no reaction occurred in the absence of catalyst (Table 1, entry 1), while only the Knoevenagel condensation product of 4-chloroaldehyde and malononitrile was formed under reflux conditions (Table 1, entry 2). To our delight, the corresponding product was isolated in 91% yield when DMAPA was used as catalyst (Table 1, entry 3). Encouraged by these results, the other solvents such as methanol, acetonitrile, tetrahydrofuran and dichloromethane were also tested, it was found that ethanol was the best solvent (Table 1, entries 4-7). Furthermore, the amount of catalyst was also examined, the yield decreased slightly as the concentration of the catalyst was reduced from 10 mol% to 5 mol% (Table 1, entry 8). The increase of catalyst concentration did not achieve any improvement (Table 1, entry 9). At last, other previously literature reported organic base catalysts such as ethanediamine, triethylamine, pyrrolidine, morpholine, and imidazole were examined, and their catalytic activities were compared with DMAPA (Table 1, entries 12-16). Hence, the best results were obtained using10 mol% of DMAPA as catalyst at 40°C in ethanol.

In order to explore the generality of our protocol, the scope of the substrates was evaluated with a variety of substituted aromatic aldehydes, cyclic ketones and malononitrile under the optimal conditions, and the results are summarized in Figure 3. In all cases, the desired product precipitated in the reaction mixtures spontaneously after cooling down to the room temperature. This allowed easy purification of the products by a simple filtration while time consuming was avoided. The structure of the products was confirmed according to their spectral properties.

Structurally diverse benzaldehydes bearing substituents such as Me, OMe, F, Cl and NO_2were examined under the optimized reaction conditions. In general, benzaldehydes bearing electron-donating or electron-withdrawing functional groups at different positions generated the corresponding *ortho*-aminocarbonitrile derivatives with no regular and obviousin fluence on the yield .In all cases, the corresponding products were obtained in good to excellent yields (4b-4j). Besides substituted benzaldehyde, our strategy was also suitable for aromatic heterocyclic aldehydes, affording the desired *ortho*-aminocarbonitrile derivatives also in high yields (4k-4m). Furthermore, cyclopentanone was also found to be suitable for this reaction and the desired products can be formed in moderate to high yields (4o-4s). The corresponding compounds crystallized directly from the solvent and isolated through simple filtration.



Note: reaction conditons: **1** (2 mmol), **2** (2mmol), **3** (4mmol), ethanol (10 mL), DMAPA (0.2 mmol) at 40°C

Figure 3. Synthesis of **4** under optimum conditions

3 Conclusion

In summary, an efficient and suitable protocol for the preparation of *ortho*-aminocarbonitriles derivatives via one-pot multicomponent reaction of aromatic aldehyde, cycloketone, and 2 equiv. of malononitrile under the catalytic amount of DMAPA in ethanol has been developed. The corresponding products have been obtained with good to excellent yields in most cases under mild reaction conditions. More important, the desired products could be easily collected through simple filtration, which avoided the time-consuming column chromatographic separation.

4 Experimental section

All reagents were purchased from Adamas (China), and were used as received without further purification. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel plates (60F-254) using UV light. Yields refer to pure compounds. Melting points were measured on an electrothermal 9100 apparatus. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 500MHz spectrometer as indicated in the data list.

The abbreviations s, d, dd, t, q, br, and m stand for the resonance multiplicity singlet, doublet, doublet of doublets, triplet, quartet, broad and multiplet, respectively.

General procedure for the synthesis of bicyclic *ortho*-aminocarbonitrilederivatives:

A mixture of cyclic ketone (2 mmol), aromatic aldehyde (2 mmol), malononitrile (4mmol), DMAPA (0.2 mmol), and ethanol (10 mL) was stirred at 40°C. The progress of the reaction was monitored by TLC. On completion of the reaction, cooled down to the room temperature the solid product was collected by simple filtration and washed with ethanol and dried. The solid was further recrystallized with 95% EtOH/DMF (1/4, v/v) to provide the pure desired product.

2-amino-4-phenyl-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (**4a**): white solid.Yield 87%; MP 248.7 – 252.5°C; IR (KBr) 3420, 3339, 3254, 3231, 2936, 2210, 1649, 1601, 1454, 1393, 714 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ7.61 - 7.59 (m, 1H), 7.50 - 7.43 (m, 4H), 7.36 (s, 2H), 5.75 - 5.71 (m, 1H), 3.54 (d, *J* = 12.5 Hz, 1H), 2.81 (t, *J* = 11.5 Hz, 1H), 2.19 (d, *J* = 18.9 Hz, 1H), 2.11 - 1.99 (m, 1H), 1.68 (dd, *J* = 11.3, 3.8 Hz, 1H), 1.52 - 1.37 (m, 2H), 0.85 (dt, *J* = 13.5, 6.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ144.04, 135.11, 132.86, 129.40, 129.33, 129.07, 127.41, 120.80, 116.64, 113.03, 112.82, 82.01, 51.00, 43.34, 34.31, 27.47, 25.33, 21.46; HRMS (ESI) m/z: calc. for $C_{19}H_{17}N_4$ $[M+H]^+$ 301.1448 found 301.1453.

2-amino-4-(4-methphenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (**4b**): white solid.Yield 92%; MP 256.5– 260.1°C; IR (KBr)3423, 3337, 3251, 2948, 2362, 2213, 1647, 1600, 1391, 830 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.47 (d, *J* = 6.6 Hz, 1H), 7.35 (s, 2H), 7.26 (m, 3H), 5.75 – 5.69 (m, 1H), 3.47 (d, *J* = 12.5 Hz, 1H), 2.77 (t, *J* = 11.5 Hz, 1H), 2.34 (s, 3H), 2.22 – 2.13 (m, 1H), 2.11 – 2.00 (m, 1H), 1.67 (dd, *J* = 9.6, 5.3 Hz, 1H), 1.51 – 1.39 (m, 2H), 0.89 – 0.78 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ144.07, 138.79, 132.74, 132.06, 129.74, 129.56, 129.40, 127.220, 120.70, 116.650, 113.070, 112.89, 82.00, 50.78, 43.46, 34.37, 27.48, 25.34, 21.48, 21.21; HRMS (ESI) m/z: calc. for $C_{20}H_{19}N_4$ $[M+H]^+$ 315.1604 found 315.1600.

2-amino-4-(4-methoxyphenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (**4c**): white solid. Yield 94%; MP 239.2– 247.2°C; IR (KBr)3421, 3340, 3252, 2947, 2213, 1647, 1599, 1516, 1256, 1181, 1028, 839 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.50 (d, *J* = 8.0 Hz, 1H), 7.34 (s, 3H), 7.02 (dd, *J* = 40.6, 7.7 Hz, 2H), 5.75 – 5.68 (m, 1H), 3.79 (s, 3H), 3.47 (d, *J* = 12.5 Hz, 1H), 2.76 (t, *J* = 11.5 Hz, 1H), 2.18 (d, *J* = 18.7 Hz, 1H), 2.12 – 1.99 (m, 1H), 1.68 (dd, *J* = 9.8, 5.2 Hz, 1H), 1.54 – 1.39 (m, 2H), 0.90 – 0.79 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ160.01, 144.08, 134.06, 129.45, 128.53, 126.84, 120.68, 116.67, 114.80, 114.06, 113.12, 112.97, 81.99, 55.60, 50.47, 43.63, 34.49, 27.50, 25.35, 21.50; HRMS (ESI) m/z: calc. for $C_{20}H_{18}N_4Na$ $[M+Na]^+$ 353.1373 found 353.1370.

2-amino-4-(3,4-dimethoxyphenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (**4d**): white solid. Yield 97%; MP 223.9– 228.9°C; IR (KBr)3432, 3335, 3253, 3229, 2938, 2211, 1649, 1600, 1519, 1264, 1144, 1021 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.36 (s, 2H), 7.15 – 7.07 (m, 2H), 6.97 (s, 1H), 5.72 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.44 (dd, *J* = 15.5, 12.9 Hz, 1H), 2.78 (d, *J* = 44.0 Hz, 1H), 2.19 (d, *J* = 18.6 Hz, 1H), 2.05 (s, 1H), 1.67 (s, 1H), 1.52 (m, 2H), 0.88 – 0.85 (m, 1H);^{13}C NMR (125 MHz, DMSO-d_6) δ149.75, 149.38, 149.19, 148.53, 144.19, 144.05, 129.46, 127.34, 127.07, 125.13, 120.65, 119.71, 116.80, 116.71, 113.45, 113.14, 113.02, 112.96, 112.31, 111.68, 110.70, 81.88, 56.06, 55.90, 51.17, 50.74, 43.70, 43.53, 34.66, 34.35, 27.44, 25.35, 21.48, 19.04; HRMS (ESI) m/z: calc. for $C_{21}H_{20}N_4O_2Na$ $[M+Na]^+$ 383.1484 found 383.1479.

2-amino-4-(3-fluorophenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (**4e**): white solid. Yield 82%; MP 242.8– 244.0°C; IR (KBr)3421, 3342, 3258, 3233, 2213, 1648, 1604, 1591, 1491, 1393, 744 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.60 – 7.43 (m, 2H), 7.39 (s, 2H), 7.35 – 7.25 (m, 2H), 5.75 – 5.72 (m, 1H), 3.65 (t, *J* = 13.3 Hz, 1H), 2.83 (d, *J* = 8.8 Hz, 1H), 2.23 – 2.14 (m, 1H), 2.11 – 1.98 (m, 1H), 1.68 (d, *J* = 7.5 Hz, 1H), 1.47 (m, 2H), 0.88 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ143.87, 137.85, 131.19, 129.08, 128.90, 123.67, 120.98, 119.61, 116.57, 116.24, 114.49, 112.87, 112.68, 82.06, 50.38, 43.05, 34.15, 27.37, 25.31, 21.37; HRMS (ESI) m/z: calc. for $C_{19}H_{15}FN_4Na$ $[M+Na]^+$ 341.1173 found 341.1177.

2-amino-4-(4-fluorophenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (**4f**): white solid. Yield 86%; MP 262.0– 265.0°C; IR (KBr)3420, 3341, 3255, 2950, 2212, 1647, 1605, 1511, 1391, 1230, 1165, 845, 808 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.64 (s, 1H), 7.49 (s, 1H), 7.40 – 7.32 (m, 3H), 7.28 (t, *J* = 8.0 Hz, 1H), 5.76 – 5.69 (m, 1H), 3.62 (d, *J* = 12.5 Hz, 1H), 2.80 (t, *J* = 11.4 Hz, 1H), 2.24 – 2.13 (m, 1H), 2.11 – 1.99 (m, 1H), 1.72 – 1.63 (m, 1H), 1.52 – 1.40 (m, 2H), 0.85 (q, *J* = 11.3 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ163.78, 161.83, 143.88, 134.91, 131.35, 129.59, 129.22, 120.86, 116.60, 116.27, 116.10, 115.92, 115.75, 112.86, 82.04, 50.11, 43.34, 34.31, 27.43, 25.32, 21.43; HRMS (ESI) m/z: calc. for $C_{19}H_{15}FN_4Na$ $[M+Na]^+$ 341.1173 found 341.1174.

2-amino-4-(2-chlorophenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (**4g**): white solid. Yield 88%; MP 251.4– 259.2°C; IR (KBr)3447, 3357, 2949, 2217, 1632, 1618, 1595, 1391, 1270, 748 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.77 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.62 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.51 (m, 2H), 7.43 (s, 2H), 5.77 - 5.74 (m, 1H), 3.88 (d, *J* = 12.4 Hz, 1H), 2.86 (t, *J* = 12.1 Hz, 1H), 2.23 – 2.13 (m, 1H), 2.13 – 2.04 (m, 1H), 1.72 – 1.62 (m, 1H), 1.44 (ddd, *J* = 13.4, 10.6, 6.8 Hz, 1H), 1.40 – 1.32 (m, 1H), 0.81 (td, *J* = 13.4, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ143.93, 135.58, 132.28, 131.14, 130.65, 129.70, 128.87, 128.38, 121.35, 116.45, 112.72, 112.04, 81.93, 46.94, 42.11, 34.96, 27.21, 25.22, 21.27; HRMS (ESI) m/z: calc. for $C_{19}H_{15}ClN_4Na$ $[M+Na]^+$ 357.0877 found 357.0869.

2-amino-4-(4-chlorophenyl)-4a,5,6,7-tetrahydronaph-

thalene-1,3,3(4H)-tricarbonitrile (**4h**): white solid. Yield 87%; MP 267.2– 269.8°C; IR (KBr)3421, 3343, 2932, 2947, 2213, 1645, 1602, 1391, 1095, 1015, 838 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.61 (dd, *J* = 24.2, 8.1 Hz, 2H), 7.50 (dd, *J* = 30.3, 7.8 Hz, 2H), 7.40 (s, 2H), 5.74 – 5.73 (m, 1H), 3.65 (d, *J* = 12.5 Hz, 1H), 2.80 (t, *J* = 11.3 Hz, 1H), 2.19 (d, *J* = 19.1 Hz, 1H), 2.11 – 1.99 (m, 1H), 1.68 (d, *J* = 7.8 Hz, 1H), 1.56 – 1.37 (m, 2H), 0.86 (q, *J* = 11.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ143.40, 134.20, 133.83, 133.70, 129.02, 128.79, 128.69, 120.48, 116.18, 112.44, 112.30, 81.55, 49.66, 42.71, 33.71, 26.97, 24.88, 20.99; HRMS (ESI) m/z: calc. for $C_{19}H_{15}ClN_4Na$ $[M+Na]^+$ 357.0877 found 357.0869.

2-amino-4-(2-nitrophenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (**4i**): white solid. Yield 89%; MP 249.7 – 250.9°C; IR (KBr)3446, 3358, 2949, 2216, 1631, 1618, 1528, 1357, 1271, 779 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ8.11–8.07 (m, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.92 (t, *J* = 7.6 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.43 (s, 2H), 5.84 – 5.72 (m, 1H), 4.07 (d, *J* = 12.2 Hz, 1H), 3.01 (t, *J* = 11.1 Hz, 1H), 2.25 – 2.06 (m, 2H), 1.70 (d, *J* = 8.4 Hz, 1H), 1.54 – 1.42 (m, 2H), 1.08 – 0.98 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ151.37, 143.61, 134.06, 131.11, 130.15, 128.59, 128.25, 125.92, 121.67, 116.38, 112.47, 112.44, 81.94, 45.38, 42.55, 34.67, 27.07, 25.24, 21.27; HRMS (ESI) m/z: calc. for $C_{19}H_{15}O_2N_5Na$ $[M+Na]^+$ 368.1118 found 368.1117.

2-amino-4-(3-nitrophenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (**4j**): white solid. Yield 86%;MP 194.0–196.4°C; IR (KBr)3424, 3331, 3227, 2957, 2214, 1649, 1600, 1528, 1351, 723 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ8.41 (s, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 8.02 (dd, *J* = 93.5, 7.5 Hz, 1H), 7.81 (dt, *J* = 31.0, 7.9 Hz, 1H), 7.43 (s, 2H), 5.76 (s, 1H), 3.93 (dd, *J* = 24.9, 12.5 Hz, 1H), 2.92 (s, 1H), 2.20 (d, *J* = 18.8 Hz, 1H), 2.07 (d, *J* = 7.8 Hz, 1H), 1.67 (s, 1H), 1.45 (dd, *J* = 23.4, 11.8 Hz, 2H), 0.90 (dd, *J* = 24.6, 12.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ148.67, 148.04, 143.54, 139.32, 137.36, 134.71, 130.84, 128.85, 127.21, 124.49, 122.41, 121.15, 116.54, 112.63, 82.07, 49.94, 42.93, 33.98, 27.40, 25.28, 21.35; HRMS (ESI) m/z: calc. for $C_{19}H_{15}O_2N_5Na$ $[M+Na]^+$ 368.1118 found 368.1110.

2-amino-4-(1-naphthyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (**4k**): white solid. Yield 87%; MP 223.9– 233.6°C; IR (KBr)3424, 3335, 3248, 3225, 2212, 1644, 1598, 1392, 783 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ8.56 - 8.48 (m, 1H), 8.05 - 7.96 (m, 2H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.59 - 7.50 (m, 2H), 7.32 (s, 2H), 5.79 - 5.74 (m, 1H), 4.57 (d, *J* = 12.2 Hz, 1H), 2.95 (t, *J* = 11.4 Hz, 1H), 2.19 (d, *J* = 18.9 Hz, 1H), 2.12 - 1.99 (m, 1H), 1.64 - 1.55 (m, 1H), 1.50 - 1.34 (m, 2H), 0.78 (td, *J* = 13.2, 2.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ144.48, 134.05, 133.23, 131.76, 129.71, 129.70, 129.14, 126.96, 126.49, 126.35, 125.65, 124.30, 120.66, 116.89, 113.49, 112.71, 82.30, 43.75, 43.18, 35.85, 26.96, 25.36, 21.48; HRMS (ESI) m/z: calc. for $C_{23}H_{18}N_4Na$ $[M+Na]^+$ 373.1424 found 373.1419.

2-amino-4-(2-furyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (**4l**): white solid. Yield 80%; MP 198.7 – 202.0°C; IR (KBr)3462, 3367, 2944, 2360, 2342, 2205, 1640, 1596, 1392, 1013, 756 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.80 (d, *J* = 1.2 Hz, 1H), 7.38 (s, 2H), 6.63 – 6.51 (m, 2H), 5.73 – 5.65 (m, 1H), 3.82 (d, *J* = 12.4 Hz, 1H), 2.69 (dd, *J* = 15.1, 8.1 Hz, 1H), 2.24 – 2.15 (m, 1H), 2.14 – 1.99 (m, 1H), 1.77 – 1.67 (m, 1H), 1.43 (dddd, *J* = 28.7, 12.5, 6.9, 3.4 Hz, 2H), 1.03 (td, *J* = 13.5, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ148.94, 144.73, 143.74, 128.75, 120.69, 116.52, 112.82, 112.71, 111.93, 111.20, 81.85, 45.91, 41.57, 34.79, 26.97, 25.20, 21.38; HRMS (ESI) m/z: calc. for $C_{17}H_{14}ON_4Na$ $[M+Na]^+$ 313.1060 found 313.1054.

2-amino-4-(2-thenyl)-4a,5,6,7-tetrahydronaphthalene-1,3,3(4H)-tricarbonitrile (**4m**): white solid. Yield 86%; MP 225.6– 229.1°C; IR (KBr)3418, 3340, 3254, 3232, 2932, 2212, 1650, 1602, 1394, 713 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.66 (d, *J* = 5.0 Hz, 1H), 7.37 (s, 2H), 7.29 (d, *J* = 3.3 Hz, 1H), 7.14 (dd, *J* = 5.0, 3.6 Hz, 1H), 5.74 – 5.63 (m, 1H), 4.02 (d, *J* = 12.3 Hz, 1H), 2.61 (t, *J* = 11.7 Hz, 1H), 2.24 – 2.14 (m, 1H), 2.13 – 2.01 (m, 1H), 1.75 – 1.65 (m, 1H), 1.54 – 1.37 (m, 2H), 1.02 – 0.92 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ143.83, 137.32, 129.52, 128.98, 127.76, 127.52, 120.88, 116.57, 113.25, 112.73, 81.95, 47.42, 43.81, 36.78, 27.34, 25.31, 21.45; HRMS (ESI) m/z: calc. for $C_{17}H_{14}N_4SNa$ $[M+Na]^+$ 329.0831 found 329.0824.

5-Amino-1,2,7,7a-tetrahydro-7-phenylindene-4,6,6-tricarbonitrile (**4n**): white solid. Yield 77%; MP 199.5–204.9°C; IR (KBr)3414, 3336, 3245, 3234, 2967, 2360, 2213, 1655, 1590, 1395, 713 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.69 (s, 2H), 7.55 (d, *J* = 6.6 Hz, 2H), 7.51 – 7.40 (m, 3H), 5.50 (d, *J* = 2.1 Hz, 1H), 3.64 (d, *J* = 12.6 Hz, 1H), 3.40 – 3.27 (m, 1H), 2.43 – 2.26 (m, 2H), 1.93 – 1.82 (m, 1H), 1.18 (dq, *J* = 20.1, 9.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ146.59 135.67 135.04, 130.10, 129.53, 129.03, 119.87, 116.40, 112.81, 112.68, 77.59, 51.37, 44.21, 42.96, 31.45, 29.78; HRMS (ESI) m/z: calc. for $C_{18}H_{14}N_4Na$ $[M+Na]^+$ 309.1111 found 309.1107.

5-Amino-1,2,7,7a-tetrahydro-7-(4-methoxyphenyl) indene-4,6,6-tricarbonitrile (**4o**): white solid. Yield 83%; MP 200.0– 204.4°C; IR (KBr)3413, 3334, 3247, 2217, 1652, 1589, 1515, 1257, 1181, 1029, 841 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.66 (s, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 5.48 (d, *J* = 1.6

Hz, 1H), 3.78 (s, 3H), 3.56 (d, *J* = 12.6 Hz, 1H), 3.31 – 3.22 (m, 1H), 2.43 – 2.22 (m, 2H), 1.91 – 1.83 (m, 1H), 1.22 – 1.10 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ160.20, 146.64, 135.79, 131.27, 126.81, 119.76, 116.43, 114.43, 112.96, 112.78, 77.57, 55.62, 50.90, 44.50, 43.13, 31.43, 29.81; HRMS (ESI) m/z: calc. for $C_{19}H_{16}ON_4Na$ $[M+Na]^+$ 339.1216 found 339.1207.

5-Amino-1,2,7,7a-tetrahydro-7-(4-fluorophenyl) indene-4,6,6-tricarbonitrile (**4p**): white solid. Yield 78%;MP 175.4–189.6°C; IR (KBr)3418, 3337, 3246, 2851, 2211, 1646, 1590, 1512, 1393, 1231, 1165, 843 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.69 (s, 2H), 7.60 (dd, *J* = 8.4, 5.5 Hz, 2H), 7.32 (t, *J* = 8.8 Hz, 2H), 5.49 (d, *J* = 1.7 Hz, 1H), 3.72 (d, *J* = 12.6 Hz, 1H), 3.46 – 3.22 (m, 1H), 2.43 – 2.24 (m, 2H), 1.94 – 1.81 (m, 1H), 1.23 – 1.10 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ163.94, 161.99, 160.67, 146.44, 135.57, 134.04, 132.27, 131.31, 119.92, 117.51, 117.33, 116.36, 116.07, 115.90, 112.77, 112.60, 77.62, 50.50, 44.20, 43.03, 31.45, 29.70; HRMS (ESI) m/z: calc. for $C_{18}H_{13}FN_4Na$ $[M+Na]^+$ 327.1016 found 327.1007.

5-Amino-1,2,7,7a-tetrahydro-7-(2-chlorophenyl) indene-4,6,6-tricarbonitrile (**4q**): white solid. Yield 81%; MP 219.1– 225.2°C; IR (KBr)3423, 3333, 3248, 3233, 2962, 2217, 1655, 1593, 1395, 1048, 749 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.78 (d, *J* = 6.8 Hz, 1H), 7.74 (s, 2H), 7.65 – 7.59 (m, 1H), 7.57 – 7.45 (m, 2H), 5.53 (d, *J* = 2.1 Hz, 1H), 3.98 (d, *J* = 12.5 Hz, 1H), 3.45 – 3.35 (m, 1H), 2.40 – 2.27 (m, 2H), 1.85 – 1.75 (m, 1H), 1.17 – 1.04 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ146.49, 135.48, 135.39, 132.33, 131.24, 130.56, 129.99, 128.40, 120.44, 116.23, 112.48, 111.98, 77.54, 47.51, 43.93, 42.91, 31.37, 29.80; HRMS (ESI) m/z: calc. for $C_{18}H_{13}ClN_4Na$ $[M+Na]^+$ 343.0721 found 343.0717.

5-Amino-1,2,7,7a-tetrahydro-7-(1-naphthyl)indene-4,6,6-tricarbonitrile (**4r**): white solid.Yield 80%; MP 256.8– 257.9°C; IR (KBr)3404, 3353, 3319, 3213, 2214, 1650, 1586, 1393, 809, 785 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ8.62 – 8.57 (m, 1H), 8.06 – 7.96 (m, 2H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.70 – 7.60 (m, 3H), 7.60 – 7.50 (m, 2H), 5.52 (d, *J* = 2.1 Hz, 1H), 4.69 (d, *J* = 12.2 Hz, 1H), 3.49 (dd, *J* = 17.9, 9.7 Hz, 1H), 2.41 – 2.19 (m, 2H), 1.87 – 1.73 (m, 1H), 1.07 (dq, *J* = 20.1, 9.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ147.16, 136.21, 133.97, 133.15, 131.75, 129.84, 129.03, 126.83, 126.75, 126.50, 125.71, 124.57, 119.64, 116.66, 113.14, 112.70, 77.81, 44.59, 44.42, 44.02, 31.28, 29.78; HRMS (ESI) m/z: calc. for $C_{22}H_{16}N_4Na$ $[M+Na]^+$ 359.1267 found 359.1257.

5-Amino-1,2,7,7a-tetrahydro-7-(2-thenyl)indene-4,6,6-tricarbonitrile (**4s**): white solid. Yield 75%; MP 220.1– 221.0°C; IR (KBr)3403, 3334, 3231, 2214, 1654, 1588, 1394, 718 cm^{-1};^{1}H NMR (500 MHz, DMSO-d_6) δ7.75 – 7.62 (m, 3H), 7.31 (d, *J* = 3.2 Hz, 1H), 7.14 (dd, *J* = 5.0, 3.6 Hz, 1H), 5.50 (d, *J* = 2.1 Hz, 1H), 4.08 (d, *J* = 12.4 Hz, 1H), 3.15 (dd, *J* = 17.8, 10.1 Hz, 1H), 2.43 – 2.24 (m, 2H), 2.01 – 1.89 (m, 1H), 1.30 (dq, *J* = 20.2, 9.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ146.23, 137.30, 135.29, 129.42, 127.92, 127.51, 120.33, 116.34, 112.90, 112.81, 77.57, 47.84, 45.10, 44.78, 31.32, 30.03; HRMS (ESI) m/z: calc. for $C_{16}H_{12}N_4SNa$ $[M+Na]^+$ 315.0675 found 315.0667.

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