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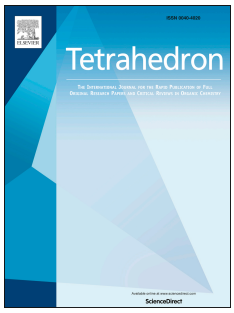

A one-pot access to pyridine/benzo fused cyclododecanes via multi-component tandem reactions

Sundaravel Vivek Kumar, Mani Anusha Rani, Abdulrahman I. Almansour, Raju Suresh Kumar, S. Athimoolam, Raju Ranjith Kumar

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Graphical Abstract

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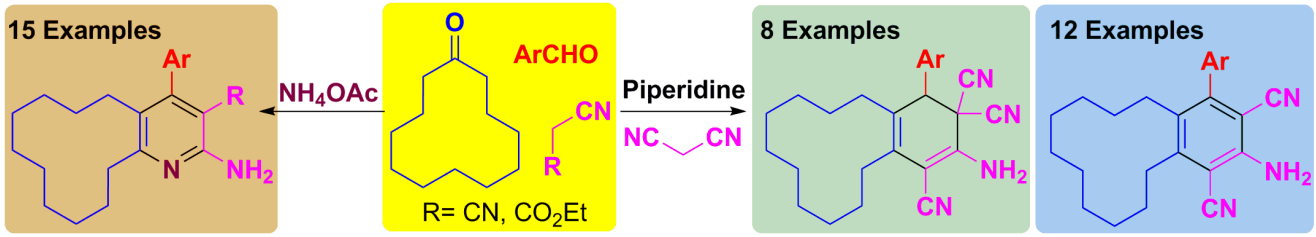

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A one-pot access to pyridine/benzo fused cyclododecanes via multi-component tandem reactions

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ABSTRACT

A facile syntheses of novel poly-substituted pyridine/benzo fused cyclododecane hybrid heterocycles have been achieved through one-pot multi-component tandem strategy employing cyclododecanone, aromatic aldehydes and malononitrile.

1. Introduction

Recent years have witnessed an upsurge of interest in the syntheses of heterocycles with biological or materials applications employing eco-friendly protocols such as multi-component tandem reactions (MTR). MTR's possess several advantages like one-pot process, evade the isolation and purification of intermediates, and shorten the reaction time, cost effective, synthetic efficiency and selectivity.[1] These advantages make MTR's as greener protocols.[2]

On the other hand, heterocycle/benzo fused cycloalkanes have gained immense interest owing to their unique structural features and existence in biologically active natural and unnatural compounds.[3] It is pertinent to note that the ring size of the fused cycloalkanes play crucial role in the nature of biological activities.[4] The macrocycle fused heterocycles such as rosphellin,[5] ingenanes[6] and eryngiolide A[7] are naturally occurring biologically active compounds. In particular, the cyclododecane fused derivatives have been reported as fungicides,[8] herbicides,[9] and possess antimalarial[10] and antiviral[11] activities apart from inhibiting jak kinase[12] and cytochrom P450[13] (**Figure 1**). The cyclododecanone has been employed as key starting material for the synthesis of the above compounds as well as muscone, (*S*)-muscolides, (*R*)-12-methyltridecanolide and hydroxyambran.[14]

Incidentally the macrocycle fused heterocycles like muscopyridine[15] (**Figure 1**) and Lignoxan®[16] are being used in perfume industries. In spite of the significance, studies on the syntheses of heterocycle/benzo fused cyclododecanones have received less attention. For example, the Diels-Alder reaction of 1,2,3-triazines/5-nitropyrimidine and enamines of cyclododecanone,[17] condensation of 3-aminoacrolein and cyclododecanone in the presence of mixture of triethylamine and piperidinium acetate and via a three step reaction starting from cyclododecanone.[18] Similarly, only few reports are available for synthesis of benzo fused cyclododecanes which include benzoannelation of 2-(hydroxymethylene)-cyclododecanone[19] and β-phenol annulation of cyclododecanone.[20] Moreover the above routes have one or more disadvantages like multi-step sequence, low yield and limited diversity.

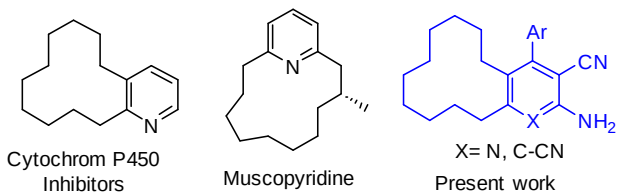

Figure 1. Macrocycle fused pyridines and the present work

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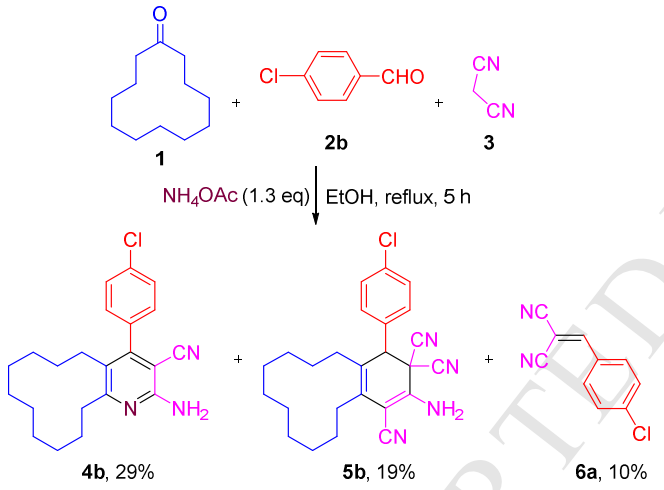
In this context, herein we report a facile one-pot green protocol for the synthesis of pyridine/benzo fused cyclododecanes *via* multi-component tandem reactions. This work stems from our continuous effort to synthesize novel heterocycle/benzo fused cycloalkanes employing multi-component tandem/domino reactions.[21] The synthesis of 2-aminopyridine-3-carbonitrile derivatives through the four-component reaction of cyclic/acyclic active methylene ketones, malonitrile, aldehydes and ammonium acetate is well documented in the literature and offers an efficient platform for achieving these biologically relevant heterocycles.[22]

2. Results and Discussion

Our studies commenced with a pilot experiment of cyclododecanone **1**, *p*-chlorobenzaldehyde **2b** and malononitrile **3** in the presence of ammonium acetate (1.3 equiv.) under reflux in ethanol for 5h which led to the formation of 2-amino-4-(4-chlorophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca-[*b*]pyridine-3-carbonitrile **4b**, 2-amino-4-(4-chlorophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3,3(4*H*)-tricarbonitrile **5b** and the intermediate 2-(4-chlorobenzylidene)-malononitrile **6a** in 29, 19 and 10 % yields, respectively (**Scheme 1**). The structure of **4b** and **5b** was confirmed from NMR analyses.



Scheme 1. Attempted synthesis of cyclododeca[*b*]pyridine-3-carbonitrile **4b**

Gratified, by this preliminary result, we started to optimize the ideal reaction condition for the synthesis of **4b** and **5b** exclusively. The above model reaction was initially performed in solvents such as EtOH, MeOH, *i*-PrOH, THF, toluene, acetic acid, DCE, 1,3-dioxane and solvent free conditions (**Table 1**). Among these solvents, undoubtedly toluene emerged as the best choice affording exclusively the cyclododeca[*b*]pyridine-3-carbonitrile **4b** in 85% yield after 6h of reflux (Table 1, entry 6).

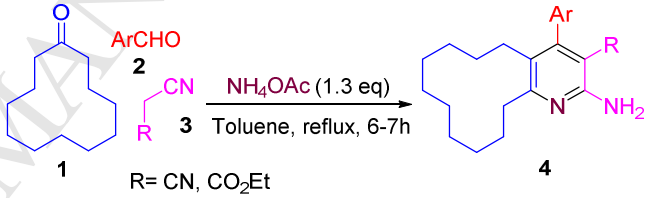
Having established the ideal reaction condition, we explored the substrate scope of the reaction with various aromatic aldehydes to create library. From the data in Table 2, it is obvious that under the optimized conditions this multi-component tandem reaction works well with all the substrates and the presence of electron withdrawing or donating substituents in the aromatic aldehydes posed little effect on the yield of the cyclododeca[*b*]pyridine-3-carbonitriles **4a–l** (79–86%, **Table 2**). The structure of all these compounds **4** was elucidated with the help of NMR spectroscopy as detailed for **4b** as representative example (vide ESI). In the cases of **4d**, the structure was further confirmed from single crystal X-ray studies (**Figure 2**).[23]

Table 1. Optimization of reaction conditions for synthesizing **4b**

Entry	Solvent	Time	Yield (%)[a]	
			4b	5b
1	EtOH	8h	29	19
2	MeOH	8h	27	14
3	*i*-PrOH	5h	25	-
4	CH_3CN	4h	32	-
5	THF	4h	47	-
6	**Toluene**	**6h**	**85**	-
7	AcOH	3h	26	-
8	DCE	3h	12	-
9	1,3-dioxane	3h	trace	-
10	-	4h	56	-

[a]Isolated yield

Table 2. Synthesis of cyclododeca[*b*]pyridines **4**



Entry	Comp	Ar	R	Yield (%)[a]	mp (°C)
1	**4a**	4-FC_6H_4	CN	86	139–140
2	**4b**	4-ClC_6H_4	CN	85	120–122
3	**4c**	4-BrC_6H_4	CN	83	160–161
4	**4d**	C_6H_5	CN	84	169–170
5	**4e**	4-MeC_6H_4	CN	79	190–191
6	**4f**	4-$^iPrC_6H_4$	CN	84	210–211
7	**4g**	4-$^tBuC_6H_4$	CN	81	192–193
8	**4h**	4-$MeOC_6H_4$	CN	80	122–123
9	**4i**	3-FC_6H_4	CN	82	231–233
10	**4j**	3-BrC_6H_4	CN	84	151–153
11	**4k**	3-$NO_2C_6H_4$	CN	81	98–99
12	**4l**	3-Cl,4,5-$(MeO)_2C_6H_2$	CN	85	186–187
13	**4m**	4-ClC_6H_4	CO_2Et	76	145-146
14	**4n**	C_6H_5	CO_2Et	70	123-124
15	**4o**	4-MeC_6H_4	CO_2Et	64	137-138

[a]Yield of isolated product

Further, we extended the scope of this reaction to ethyl cycanoacetate **3b** and dimethyl malonate **3c**. Under our optimized reaction condition, **3b** afforded the cyclododeca[*b*]pyridines **4m-o** in 64-76% yields. However, the reaction was not successful in the case of dimethyl malonate **3c** wherein only the intermediate *viz*. dimethyl 2-(arylidene)malonates were obtained.

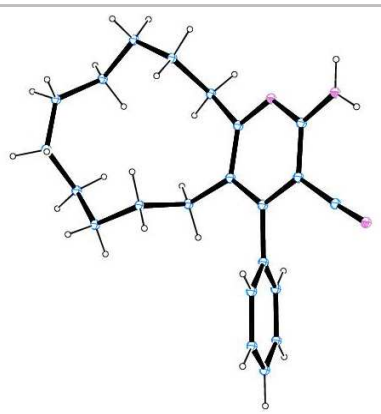
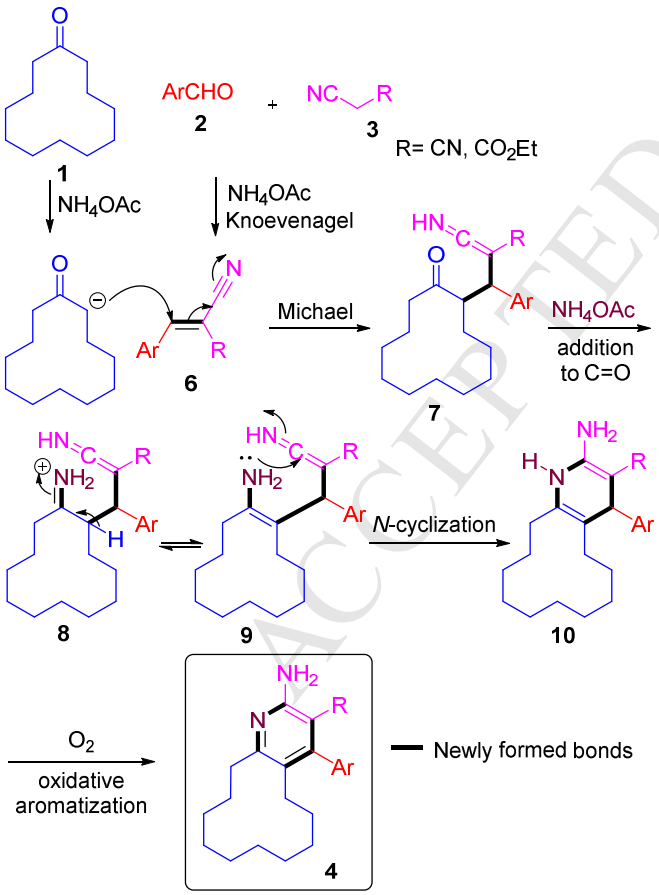


Figure 2. ORTEP diagram of **4d**

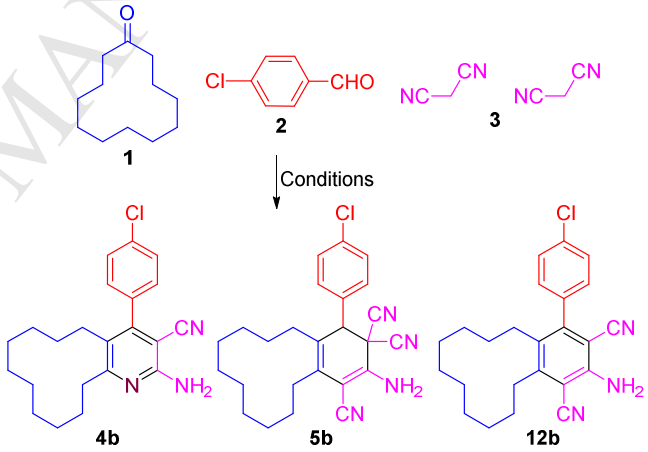
The tentative mechanism for the formation of cyclododeca[*b*]-pyridine-3-carbonitriles **4** can be rationalized through a tandem sequence as depicted in Scheme 2. Initially the base mediated Knoevenagel condensation of **2** and **3** affords 2-arylidenemalononitrile **6**, which upon Michael addition with **1** forms the intermediate **7**. The nucleophilic addition of ammonia to the carbonyl of **7** forms **8**, which undergoes tautomerization to yield **9**. The intermediate **9** undergoes intramolecular *N*-cyclization involving the primary amino group and the imine carbon to afford **10** followed by oxidative aromatization by molecular oxygen as the sole oxidant to form the cyclododeca[*b*]pyridine-3-carbonitriles **4**.



Scheme 2. Plausible mechanism for the formation of cyclododeca[*b*]pyridine-3-carbonitriles **4**

After establishing selective method to prepare cyclododeca[*b*]pyridine-3-carbonitriles **4**, we turned towards synthesizing benzo[12]annulene-1,3,3(4*H*)-tricarbonitrile **5b** exclusively (**Scheme 1**). Accordingly we performed a model reaction of **1**, **2b** and two equiv. of **3** in solvents like EtOH, MeOH and CH_3CN and in solvent-free condition in the presence of bases such as NH_4OAc, KOAc and piperidine (**Table 3**). Albeit two equiv. of **3** was used, the reaction afforded mixture of **4b** and **5b** in the presence of ammonium acetate in ethanol (Table 3, entry 1). When the reaction was carried out in ethanol or methanol in the presence of piperidine **5b** was obtained in moderate yields (Table 3, entries 2 and 3). To our surprise we isolated the aromatized product **12b** in 47–83% yield when the model reaction was performed in refluxing acetonitrile or EtOH in the presence of piperidine or KOAc (Table 3, entries 4–6). Similarly, the reaction under solvent-free condition with piperidine or KOAc as base gave **12b** in 72 or 65 % yields, respectively. To our delight, **5b** was obtained exclusively when the reaction was performed at room temperature for 3h. Hence the reaction in acetonitrile in the presence of piperidine under reflux emerged as the good choice for synthesis of **12b**, whereas the same reaction under room temperature was found to be optimal for synthesizing **5b**.

Table 3. Optimization of reaction conditions for synthesizing **5b** and **12b**



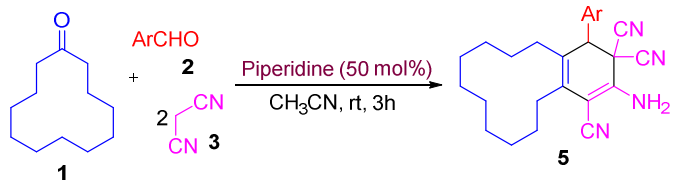
Entry	Solvent	Base (50 mol%)	Time	Yield (%)[a]		
				4b	5b	12b
1	EtOH	NH_4OAc	4h	12	47	-
2	EtOH	Piperidine	4h	-	55	-
3	MeOH	Piperidine	4h	-	45	-
4	**CH_3CN**	**Piperidine**	**4h**	**-**	**-**	**83**
5	EtOH	KOAc	4h	-	trace	47
6	CH_3CN	KOAc	5h	-	-	64
7	-	Piperidine	4h	-	-	72
8	-	KOAc	4h	-	-	65
9[b]	**CH_3CN**	**Piperidine**	**3h**	**-**	**70**	**-**

[a]Isolated yield; [b]Reaction carried out in room temperature

With the optimized conditions in hand, we subsequently explored the substrate scope using various aromatic aldehydes, cyclododecanone and malanonitrile in the presence of piperidine

under reflux or room temperature. The syntheses of a library of benzo[12]annulene-1,3,3(4*H*)-tricarbonitrile **5** and benzo[12] annulene-1,3-dicarbonitrile **12** have been achieved (**Tables 4** and **5**). The structure of the product **5** was unequivocally determined by NMR and in the case of **5b** single crystal X-ray diffraction analysis was performed (**Figure 3**).[23]

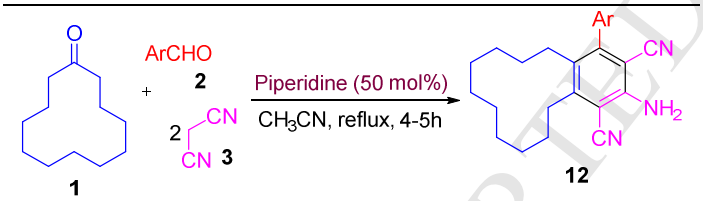
Table 4. Synthesis of benzo[12]annulene-1,3,3(4*H*)-tricarbonitriles **5**



Entry	Comp	Ar	Yield (%)[a]	mp (°C)
1	**5a**	4-FC_6H_4	67	220–221
2	**5b**	4-ClC_6H_4	70	229–230
3	**5c**	C_6H_5	73	194–195
4	**5d**	4-MeC_6H_4	75	218–219
5	**5e**	4-$^iPrC_6H_4$	70	190–191
6	**5f**	4-$^tBuC_6H_4$	73	202–203
7	**5g**	4-$MeOC_6H_4$	68	201–202
8	**5h**	3-FC_6H_4	74	196–197

[a]Yield of isolated product

Table 5. Synthesis of benzo[12]annulene-1,3-dicarbonitriles **12**



Entry	Comp	Ar	Yield (%)[a]	mp (°C)
1	**12a**	4-FC_6H_4	85	161–162
2	**12b**	4-ClC_6H_4	83	198–190
3	**12c**	4-BrC_6H_4	86	202–203
4	**12d**	C_6H_5	72	191–193
5	**12e**	4-MeC_6H_4	79	170–171
6	**12f**	4-$^iPrC_6H_4$	81	205–206
7	**12g**	4-$^tBuC_6H_4$	84	187–188
8	**12h**	4-$MeOC_6H_4$	80	194–196
9	**12i**	3-FC_6H_4	83	177–178
10	**12j**	3-BrC_6H_4	82	115–116
11	**12k**	3-$NO_2C_6H_4$	85	208–210
12	**12l**	3-Cl,4,5-$(MeO)_2C_6H_2$	77	179–181

[a]Isolated yield

The plausible mechanism for the formation of benzo[12]annulene-1,3,3(4*H*)-tricarbonitriles **5** and benzo[12] annulene-1,3-dicarbonitriles **12** is given in **Scheme 3**. Initially **2** and one equiv. of **3** undergoes Knoevenagel reaction to form the intermediate **6**. Simultaneously the Knoevenagel reaction of **1** with the second equiv. of **3** affords **13**. The base promoted Michael addition of **6** and **13** leads to the formation of **14**, which undergoes intramolecular cyclization to afford **15**. The subsequent tautomerization of **15** affords the product **5**. Presence of base and reflux temperature, prompts the benzo[12]annulene-1,3,3(4*H*)-tricarbonitrile **5** to undergo further elimination to form the aromatized product **12**.

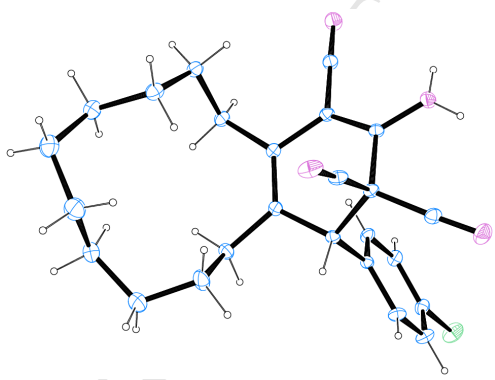
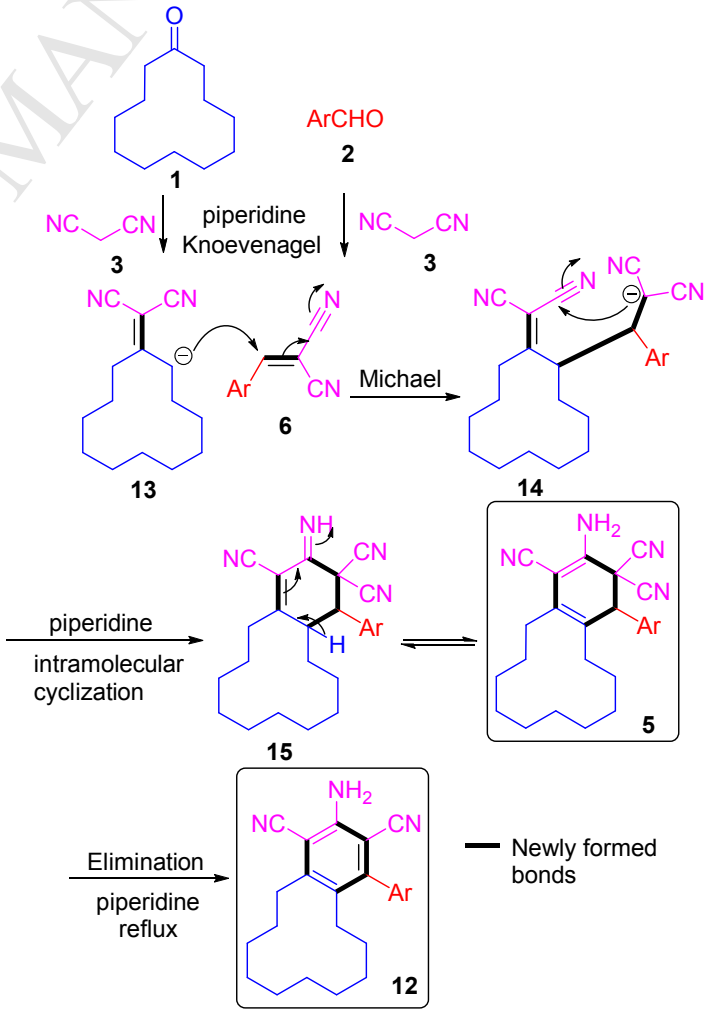


Figure 3. ORTEP diagrams of **5b**



Scheme 3. Plausible mechanism for the formation of **5** and **12**

3. Conclusions

In summary, we have developed multi-component tandem protocol for the selective synthesis of structurally intriguing multi-substituted pyridine or benzo fused cyclododecane derivatives in good yields starting from cyclododecanone, aromatic aldehydes and malononitrile. The cyclododeca[*b*]pyridine-3-carbonitriles/carboxylates were obtained through four-component tandem Knoevenagel condensation–Michael addition–nucleophilic addition–*N*-cyclization–oxidative aromatization sequence of reactions involving the formation of two C–N and two C–C bonds in a single transformation. The benzo[12]annulene-1,3,3(4*H*)-tricarbonitriles and benzo[12]annulene-1,3-dicarbonitriles were obtained as a result of pseudo four-component tandem Knoevenagel condensations–Michael addition–intramolecular cyclization–tautomerization/elimination sequence of reactions with the formation of four C–C bonds in a single transformation.

4. Experimental section

4.1 General information

Melting point of the products was measured on Sigma melting point apparatus, Sl. No. 71281, watts-250, volts-230 AC. Open capillary tubes were used for the measurements and are uncorrected. The ^{1}H,^{13}C, DEPT, H,H-COSY, C,H-COSY and HMBC spectra were recorded on Bruker (Avance) 300/600 MHz NMR instrument using TMS as internal standard and $CDCl_3$ and/or DMSO-d_6 as a solvents. Standard Bruker software was used throughout the spectral analysis. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Electro Spray Ionization Mass Spectrometry (ESI-MS) analyses were recorded in LCQ Fleet, Thermo Fisher Instrument in negative or positive ion mode. The collision voltage and ionization voltage were -70 V and -4.5 kV, respectively, using nitrogen as atomization and desolvation gas. The desolvation temperature was set at 300 ºC. The scan range of mass spectrum was 50–1100 m/z. The relative amount of each component was determined from the LC-MS chromatogram, using the area normalization method. Q-Tof ESI-MS instrument (model HAB 273) was used for recording HRMS data. Infrared spectra were recorded on Shimadzu FT-IR-8400S instrument using neat samples. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 ºC) and ethyl acetate as the eluent. All the chemicals were purchased from Sigma-Aldrich, Alfa-Aesar or Merck and used without further purification. The single crystal X-ray data set was collected on Bruker AXS KAPPA APEX-2 diffractometer equipped with graphite monochromator. The structure was solved by direct methods and refined by full-matrix least squares calculations using SHELXL-2014.

4.2 General procedure for the synthesis of 2-amino-4-phenyl-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carbonitriles/carboxylates **4**

A mixture of cyclododecanone (**1**, 1 mmol), aromatic aldehydes (**2**, 1 mmol), malononitrile/ethyl cyanoacetate (**3**, 1 mmol) and ammonium acetate (1.3 equiv.) in toluene (5 mL) was refluxed for 6-7h and the reaction progress was monitored by TLC analysis. After completion of the reaction the solvent was removed under vacuum. The crude product was purified by column chromatography using 4:1 (v/v) petroleum ether-ethyl acetate mixture to obtain pure **4**.

4.2.1. 2-Amino-4-(4-fluorophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carbonitrile ***(4a)***

White solid; Yield: 86%, mp: 139–140 ºC; IR ν_{max}: 3465, 3304, 3162, 2918, 2209, 1634, 1554, 1508, 1445, 1222 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.24–1.29 (m, 6H) , 1.42–1.52 (m, 4H), 1.67–1.73 (m, 4H), 1.84–1.86 (m, 2H), 2.39–2.48 (m, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 5.04 (s, 2H), 7.13–7.28 (m, 4H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.8, 23.2, 26.2, 26.3, 26.4, 26.9, 27.3, 27.7, 28.7, 33.0, 90.4, 115.7 ($^{2}J_{C,F}$ = 21.6 Hz), 116.4, 124.8, 130.0 ($^{3}J_{C,F}$ = 8.1 Hz), 133.10, 133.15, 153.9, 157.0, 162.8 ($^{1}J_{C,F}$ = 246.7 Hz), 165.5; ESI-MS: m/z. Calcd: 351.21; Found: 352.22 [M+1]$^{+}$; Anal. calcd for $C_{22}H_{26}FN_3$: C, 75.18; H, 7.46; N, 11.96; Found: C, 75.10; H, 7.41; N, 11.89

4.2.2. 2-Amino-4-(4-chlorophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carbonitrile ***(4b)***

White solid; Yield: 85%, mp: 120–122 ºC; IR ν_{max}: 3395, 3320, 3174, 2926, 2851, 2214, 1646, 1552, 1506, 1221 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.23–1.86 (m, 16H), 2.41 (t, *J* = 7.0 Hz, 2H), 2.73 (t, *J* = 8.4 Hz, 2H), 5.06 (s, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.9, 23.2, 26.2, 26.3, 26.4, 27.0, 27.3, 27.7, 28.8, 33.1, 90.2, 116.4, 124.7, 128.9, 129.6, 134.8, 135.6, 153.7, 157.0, 165.6; ESI-MS: m/z. Calcd: 367.18; found: 368.26 [M+1]$^{+}$; Anal. calcd for $C_{22}H_{26}ClN_3$: C, 71.82; H, 7.12; N, 11.42; Found: C, 71.86; H, 7.07; N, 11.48.

4.2.3. 2-Amino-4-(4-bromophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carbonitrile ***(4c)***

White solid; Yield: 83%, mp: 160–161 ºC; IR ν_{max}: 3461, 3308, 3173, 2920, 2860, 2210, 1632, 1550, 1443, 1010 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.23–1.51 (m, 14H) , 1.71–1.86 (m, 2H), 2.41 (t, *J* = 6.0 Hz, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 5.08 (s, 2H), 7.13 (t, *J* = 9.0 Hz, 2H), 7.61 (t, *J* = 9.0 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 23.1, 23.5, 26.6, 26.7, 26.9, 27.4, 27.8, 28.2, 29.2, 33.4, 90.4, 116.9, 123.4, 124.9, 130.2, 132.3, 136.5, 154.2, 157.5, 166.0; HRMS (ESI) calcd for [$C_{22}H_{26}BrN_3$+H]$^{+}$ 412.1388, found 412.1389; Anal. calcd for $C_{22}H_{26}BrN_3$: C, 64.08; H, 6.36; N, 10.19; Found: C, 63.99; H, 6.30; N, 10.15.

4.2.4. 2-Amino-4-phenyl-5,6,7,8,9,10,11,12,13,14-decahydro-cyclododeca[b]pyridine-3-carbonitrile ***(4d)***

White solid; Yield: 84%, mp: 169–170 ºC; IR ν_{max}: 3426, 3319, 3239, 3105, 2921, 2850, 2200, 1634, 1553, 1464 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.24–1.52 (m, 14H), 1.88 (m, 2H), 2.44 (t, *J* = 7.6 Hz, 2H), 2.74 (t, *J* = 7.9 Hz, 2H), 5.04 (s, 2H), 7.23–7.26 (m, 2H), 7.45–7.49 (m, 3H) ; ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.8, 23.2, 26.3, 26.4, 26.6, 27.1, 27.5, 27.9, 28.8, 33.1, 90.5, 116.7, 124.8, 128.1, 128.6, 128.7, 137.3, 155.2, 157.0, 165.3; Anal. calcd for $C_{22}H_{27}N_3$: C, 79.24; H, 8.16; N, 12.60; Found: C, 79.30; H, 7.8.24; N, 12.51.

4.2.5. 2-Amino-4-(p-tolyl)-5,6,7,8,9,10,11,12,13,14-decahydro-cyclododeca[b]pyridine-3-carbonitrile ***(4e)***

White solid; Yield: 82%, mp: 190–191 ºC; IR ν_{max}: 3447, 3310, 3174, 2945, 2921, 2851, 2206, 1633, 1553, 1513, 1468 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.24–1.29 (m, 4H), 1.42–1.87 (m, 13H), 2.41–2.47 (m, 4H), 2.74 (t, *J* = 7.5 Hz, 2H), 5.01 (s, 2H), 7.13 (d, *J* = 9.0 Hz, 2H), 7.25–7.26 (m, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 21.8, 23.1, 23.5, 26.6, 26.7, 26.9, 27.4, 27.8, 28.2, 29.2, 33.4, 91.0, 117.3, 125.3, 128.4, 129.6, 134.6, 138.8, 155.7, 157.3, 165.5; HRMS (ESI) calcd for [$C_{23}H_{29}N_3$+H]$^{+}$ 348.2440, found 348.2450; Anal. calcd for $C_{23}H_{29}N_3$: C, 79.50; H, 8.41; N, 12.09; Found: C, 79.53; H, 8.36; N, 12.01.

4.2.6. 2-Amino-4-(4-isopropylphenyl)-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carbonitrile ***(4f)***

White solid; Yield: 84%, mp: 210–211 ºC; IR ν_{max}: 3322, 3186, 2925, 2214, 1650, 1556, 1273 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.26–1.88 (m, 22H) , 2.44 (t, *J* = 7.3 Hz, 2H), 2.74 (t, *J* = 8.1 Hz, 2H), 2.96 (sep, *J* = 6.8 Hz, 1H), 5.14 (s, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.8, 23.2, 24.0, 26.4, 26.5, 26.7, 27.1, 27.5, 27.9, 28.9, 32.9, 33.4, 90.8, 116.8, 124.9, 126.6, 128.1, 134.5, 149.2, 155.6, 157.2, 165.0; HRMS (ESI) calcd for $[C_{25}H_{33}N_3+H]^+$ 376.2753, found 376.2759; Anal. calcd for $C_{25}H_{33}N_3$: C, 79.95; H, 8.86; N, 11.19; Found: C, 80.05; H, 8.91; N, 11.25.

4.2.7. 2-Amino-4-(4-(tert-butyl)phenyl)-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carbonitrile ***(4g)***

White solid; Yield: 81%, mp: 192–193 ºC; IR ν_{max}: 3426, 3325, 3236, 3113, 2924, 2853, 2201, 1638, 1556, 1458 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.15–1.51 (m, 23H) , 1.88 (m, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.74 (t, *J* = 6.0 Hz, 2H), 5.06 (s, 2H), 7.16 (d, *J* = 9.0 Hz, 2H), 7.45 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 23.1, 23.6, 26.6, 27.4, 27.8, 28.1, 29.3, 31.7, 33.3, 35.1, 91.0, 117.1, 125.3, 125.7, 128.2, 134.5, 151.8, 155.8, 157.4, 165.5; ESI-MS: m/z. Calcd: 389.28; Found: 390.33 $[M+1]^+$; Anal. calcd for $C_{26}H_{35}N_3$: C, 80.16; H, 9.06; N, 10.79; Found: C, 80.18; H, 9.14; N, 10.83.

4.2.8. 2-Amino-4-(4-methoxyphenyl)-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carbonitrile ***(4h)***

White solid; Yield: 80%, mp: 122–123 ºC; IR ν_{max}: 3423, 3364, 3322, 3220, 2924, 2846, 2212, 1607, 1553, 1243 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.24–1.28 (m, 2H), 1.42–1.52 (m, 10H), 1.69–1.87 (m, 4H), 2.46 (t, *J* = 7.5 Hz, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 3.86 (s, 3H), 5.01 (s, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.18 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.9, 23.2, 26.3, 26.4, 26.5, 27.0, 27.4, 27.8, 28.7, 33.1, 55.2, 90.8, 114.0, 116.8, 125.1, 126.9, 129.4, 154.9, 157.0, 159.7, 165.1; ESI-MS: m/z. Calcd: 363.23; found: 364.26 $[M+1]^+$; Anal. calcd for $C_{23}H_{29}N_3O$: C, 76.00; H, 8.04; N, 11.56; Found: C, 75.94; H, 8.11; N, 11.51.

4.2.9. 2-Amino-4-(3-fluorophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carbonitrile ***(4i)***

White solid; Yield: 82%, mp: 231–233ºC; IR ν_{max}: 3456, 3391, 3311, 3154, 2920, 2850, 2217, 1644, 1557, 1445 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.25–1.51 (m, 14H),1.87 (m, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 2.74 (t, *J* = 7.9 Hz, 2H), 5.06 (s, 2H), 6.97 (d, *J* = 9.0 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 7.15 (td, *J* = 8.5, 2.3 Hz, 1H), 7.45 (dd, *J* = 13.8, 7.9 Hz, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 26.6, 26.7, 26.9, 27.3, 27.8, 28.1, 29.2, 33.4, 90.4, 115.7, 116.1 ($^2J_{C,F}$ = 20.7 Hz), 116.8, 124.5 ($^4J_{C,F}$ = 2.9 Hz), 124.9, 130.8 ($^3J_{C,F}$ = 8.3 Hz), 139.5 ($^3J_{C,F}$ = 7.6 Hz), 153.9, 157.3, 162.9 ($^1J_{C,F}$ = 246.6 Hz), 166.0; HRMS (ESI) calcd for $[C_{22}H_{26}FN_3+H]^+$ 352.2189, found 352.2189; Anal. calcd for $C_{22}H_{26}FN_3$: C, 75.18; H, 7.46; N, 11.96; Found: C, 75.25; H, 7.41; N, 11.88.

4.2.10. 2-Amino-4-(3-bromophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carbonitrile ***(4j)***

White solid; Yield: 84%, mp: 151–153 ºC; IR ν_{max}: 3393, 3324, 3158, 2923, 2850, 2216, 1655, 1548, 1467 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.26–1.87 (m, 16H) , 2.42 (t, *J* = 7.5 Hz, 2H), 2.69–2.78 (m, 2H), 5.06 (s, 2H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.40–7.41 (m, 1H), 7.59 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.8, 23.2, 26.3, 26.4, 26.6, 27.0, 27.5, 27.8, 28.9, 33.1, 90.1, 116.5, 122.7, 124.7, 127.0, 130.3, 131.1, 131.9, 139.2, 153.3, 157.0, 165.8; HRMS (ESI) calcd for $[C_{22}H_{26}BrN_3+H]^+$ 412.1388, found 412.1395; Anal. calcd for $C_{22}H_{26}BrN_3$: C, 64.08; H, 6.36; N, 10.19; Found: C, 63.99; H, 6.40; N, 10.13.

4.2.11. 2-Amino-4-(3-nitrophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carbonitrile ***(4k)***

White solid; Yield: 81%, mp: 98–99 ºC; IR ν_{max}: 3475, 3298, 3085, 2918, 2847, 2208, 1639, 1557, 1473, 1429, 1270, 1050 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.22–1.88 (m, 16H), 2.41(t, *J* = 7.3 Hz, 2H), 2.72–2.79 (m, 2H), 5.18 (s, 2H), 7.61–7.64 (m, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 8.16–8.17 (m, 1H), 8.32–8.36 (m, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.7, 23.1, 26.2, 26.4, 26.9, 27.4, 27.8, 28.8, 33.1, 89.7, 116.2, 123.4, 123.8, 124.4, 130.0, 134.5, 138.8, 148.2, 152.2, 166.3; HRMS (ESI) calcd for $[C_{22}H_{26}N_4O_2+H]^+$ 379.2134, found 379.2147; Anal. calcd for $C_{22}H_{26}N_4O_2$: C, 69.82; H, 6.92; N, 14.80; Found: C, 69.88; H, 6.90; N, 14.71.

4.2.12. 2-Amino-4-(3-chloro-4,5-dimethoxyphenyl)-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carbonitrile ***(4l)***

White solid; Yield: 85%, mp: 186–187 ºC; IR ν_{max}: 3478, 3370, 2931, 2846, 2215, 1624, 1553, 1492, 1049 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.25–1.51 (m, 12H) , 1.66–1.69 (m, 2H), 1.84–1.87 (m, 2H), 2.44 (t, *J* = 6.0 Hz, 2H), 2.73 (t, *J* = 6.0 Hz, 2H), 3.87 (s, 3H), 3.94 (s, 3H), 5.04 (s, 2H), 6.69 (s, 1H), 6.87 (s, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 23.0, 23.4, 26.4, 26.7, 27.2, 27.5, 27.9, 29.2, 33.2, 56.5, 61.0, 90.3, 111.6, 116.5, 121.9, 124.9, 128.7, 133.4, 145.9, 153.5, 153.9, 157.1, 165.8; ESI-MS: m/z. Calcd: 427.20; Found: 428.20 $[M+1]^+$; Anal. calcd for $C_{24}H_{30}ClN_3O_2$: C, 67.36; H, 7.07; N, 9.82; Found: C, 67.40; H, 7.15; N, 8.96.

4.2.13. Ethyl 2-amino-4-(4-chlorophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carboxylate ***(4m)***

White solid; Yield: 76%, mp: 145–146 ºC; IR ν_{max}: 3421, 3261, 2924, 2847, 1672, 1611, 1489, 1474, 1085 cm^{-1}; ^1H NMR: (600 MHz, $CDCl_3$) δ_H 0.75 (t, *J* = 7.1 Hz, 3H), 1.19–1.25 (m, 5H), 1.40–1.45 (m, 6H), 1.50–1.55 (m, 2H), 1.70 (m, 1H), 1.85–1.89 (m, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.71 (t, *J* = 8.2 Hz, 2H), 3.84 (q, *J* = 7.1 Hz, 2H), 5.76 (s, 2H), 7.06–7.08 (m, 2H), (7.33–7.34 (m, 2H); ^{13}C NMR: (151 MHz, $CDCl_3$) δ_C 13.4, 22.7, 23.2, 26.7, 26.8, 26.9, 27.4, 27.8, 28.1, 29.0, 33.1, 60.6, 106.7, 124.6, 127.9, 129.8, 133.0, 139.1, 151.3, 156.2, 164.0, 168.4; HRMS (ESI): m/z. Calcd for $[C_{24}H_{31}ClN_2O_2+H]^+$: 415.2152, found 415.2185; Anal. calcd for $C_{24}H_{31}ClN_2O_2$: C, 69.47; H, 7.53; N, 6.75; Found: C, 69.55; H, 7.50; N, 6.80.

4.2.14. Ethyl 2-amino-4-phenyl-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carboxylate ***(4n)***

White solid; Yield: 70%, mp: 123–124 ºC; IR ν_{max}: 3496, 3303, 2928, 2864, 1670, 1625, 1552, 1494, 1276, 1088 cm^{-1}; ^1H NMR: (600 MHz, $CDCl_3$) δ_H 0.66 (t, *J* = 7.1 Hz, 3H), 1.16–1.19 (m, 2H), 1.22–1.25 (m, 2H), 1.38–1.45 (m, 6H), 1.49–1.54 (m, 4H), 1.85–1.88 (m, 2H), 2.34 (t, *J* = 7.8 Hz, 2H), 2.71 (t, *J* = 8.2 Hz, 2H), 3.78 (q, *J* = 7.1 Hz, 2H), 5.69 (s, 2H), 7.11–7.12 (m, 2H), 7.30–7.34 (m, 3H); ^{13}C NMR: (151 MHz, $CDCl_3$) δ_C 13.3, 22.7, 23.2, 26.7, 26.8, 26.9, 27.4, 27.7, 28.1, 29.0, 33.1, 60.4, 107.3, 124.7, 127.0, 127.6, 128.3, 140.5, 152.5, 155.9, 163.5, 168.8; HRMS (ESI): m/z. Calcd for $[C_{24}H_{32}N_2O_2+H]^+$: 381.2537, found 381.2501 $[M+1]^+$; Anal. calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36; Found: C, 75.81; H, 8.55; N, 7.34.

4.2.15. Ethyl 2-amino-4-(p-tolyl)-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[b]pyridine-3-carboxylate ***(4o)***

White solid; Yield: 64%, mp: 137–138 ºC; IR ν_{max}: 3437, 3051, 2927, 2865, 1680, 1634, 1550, 1277, 1105, 1022 cm^{-1}; ^1H NMR: (600 MHz, $CDCl_3$) δ_H 0.70 (t, J = 7.1 Hz, 3H), 1.18–1.21 (m, 2H), 1.24–1.27 (m, 2H) 1.41–1.45 (m, 7H), 1.50–1.55 (m, 2H, overlapped with water peak), 1.85–1.88 (m, 2H), 2.10 (s, 1H), 2.36 (t, J = 8.1 Hz, 2H), 2.39 (s, 3H), 2.72 (t, J = 8.2 Hz, 2H), 3.81 (q, J = 7.1 Hz, 2H), 5.90 (s, 2H), 7.00 (d, J = 7.8 Hz, 2H), 7.14 (d, J = 7.7 Hz, 2H); ^{13}C NMR: (151 MHz, $CDCl_3$) δ_C 13.3, 21.4, 22.7, 23.1, 26.8, 27.0, 27.5, 27.8, 28.1, 29.0, 32.7, 60.6, 108.0, 124.8, 128.1, 128.3, 136.7, 137.2, 153.0, 155.7, 162.8, 168.7; ESI: Calcd: 395.27; found: 395.26 $[M+1]^+$; Anal. calcd for $C_{25}H_{34}N_2O_2$: C, 75.91; H, 8.92; N, 7.08; Found: C, 75.87; H, 9.01; N, 7.13.

4.3. General procedure for the synthesis of 2-amino-4-aryl-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3,3(4H)-tricarbonitrile **5**

A mixture of cyclododecanone (**1**, 1 mmol), aromatic aldehydes (**2**, 1 mmol), malononitrile (**3**, 2 mmol) and piperidine (50 mol%) was taken in acetonitrile and stirred in room temperature for 3h with intermittent monitoring by TLC. After completion of the reaction the solvent was removed under vacuum. The crude product was purified by column chromatography using 4:1 (v/v) petroleum ether-ethyl acetate mixture to obtain pure **5**.

4.3.1. 2-Amino-4-(4-fluorophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3,3(4H)-tricarbonitrile ***(5a)***

White solid; Yield: 67%, mp: 220–221 ºC; IR ν_{max}: 3436, 3317, 3212, 2927, 2858, 2212, 1650, 1588, 1505, 1227 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.24–1.82 (m, 17H), 2.22–2.29 (m, 1H), 2.55–2.60 (m, 1H), 2.68–2.75 (m, 1H), 3.94 (s, 1H), 5.16 (s, 2H), 7.03–7.09 (m, 2H), 7.22–7.25 (m, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.1, 22.6, 24.1, 24.8, 24.5, 25.1, 26.0, 26.6, 26.9, 27.2, 42.4, 49.7, 85.6, 111.4, 112.7, 116.3 ($^2J_{C,F}$ = 21.7 Hz), 116.4, 126.3, 126.5 ($^4J_{C,F}$ = 3.0 Hz), 129.3, 131. 6 ($^3J_{C,F}$ = 8.2 Hz), 141.4, 163.5 ($^1J_{C,F}$ = 248.2 Hz); ESI-MS: m/z. Calcd: 402.22; Found: 401.43 $[M–1]^-$; Anal. calcd for $C_{25}H_{27}FN_4$: C, 74.60; H, 6.76; N, 13.92; Found: C, 74.58; H, 6.84; N, 13.88.

4.3.2. 2-Amino-4-(4-chlorophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3,3(4H)-tricarbonitrile ***(5b)***

White solid; Yield: 70%, mp: 230–231 ºC; IR ν_{max}: 3445, 3314, 3208, 2931, 2862, 2211, 1651, 1588 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.24–1.80 (m, 17H), 2.22–2.23 (m, 1H), 2.55–2.60 (m, 1H), 2.68–2.78 (m, 1H), 3.93 (s, 1H), 5.14 (s, 2H), 7.17 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 9.0 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.1, 22.6, 24.2, 24.8, 24.9, 25.1, 26.1, 26.6, 26.9, 27.3, 42.2, 49.8, 83.6, 111.3, 112.6, 126.0. 129.3, 129.52, 129.55, 131.0, 136.0, 141.4; HRMS (ESI) calcd for $[C_{25}H_{27}ClN_4–H]^-$ 417.1851, found 417.1862; Anal. calcd for $C_{25}H_{27}ClN_4$: C, 71.67; H, 6.50; N, 13.37; Found: C, 71.79; H, 6.54; N, 13.42.

4.3.3. 2-Amino-4-phenyl-5,6,7,8,9,10,11,12,13,14-decahydro benzo[12]annulene-1,3,3(4H)-tricarbonitrile ***(5c)***

White solid; Yield: 73%, mp: 194–195 ºC; IR ν_{max}: 3427, 3308, 3200, 2928, 2863, 2209, 1647, 1585, 1468 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.39–1.83 (m, 17H), 2.23–2.28 (m, 1H), 2.55–2.56 (m, 1H), 2.69–2.76 (m, 1H), 3.95 (s, 1H), 5.09 (s, 2H), 7.24–2.26 (m, 2H), 7.36–7.38 (m, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.2, 22.6, 24.3, 24.8, 25.0, 25.1, 26.1, 26.5, 26.9, 27.2, 42.3, 50.6, 84.2, 111.4, 112.8, 126.6, 129.1, 129.5, 129.8, 130.9, 141.2; ESI-MS: m/z. Calcd: 384.23; Found: 383.38 $[M–1]^-$; Anal. calcd for $C_{25}H_{28}N_4$: C, 78.09; H, 7.34; N, 14.57 Found: C, 78.04; H, 7.41; N, 14.53.

4.3.4. 2-Amino-4-(p-tolyl)-5,6,7,8,9,10,11,12,13,14-decahydro benzo[12]annulene-1,3,3(4H)-tricarbonitrile ***(5d)***

White solid; Yield: 75%, mp: 218–219 ºC; IR ν_{max}: 3438, 3314, 3207, 2930, 2847, 2211, 1651, 1588, 1466 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.39–1.80 (m, 17H), 2.20–2.35 (m, 1H), 2.35 (s, 3H), 2.54–2.59 (m, 1H), 2.69–2.78 (m, 1H), 3.92 (s, 1H), 5.05 (s, 2H), 7.11 (d, J = 6.0 Hz, 2H), 7.16 (d, J = 9.0 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 21.3, 22.1, 22.6, 24.2, 24.8, 25.1, 26.1, 26.6, 26.9, 42.5, 50.3, 83.8, 111.6, 112.9, 126.7, 127.7, 128.9, 129.5, 129.9, 139.9, 141.4; HRMS (ESI) calcd for $[C_{26}H_{30}N_4–H]^-$ 397.2398, found 397.2395; Anal. calcd for $C_{26}H_{30}N_4$: C, 78.35; H, 7.59; N, 14.06; Found: C, 78.43; H, 7.52; N, 14.10.

4.3.5. 2-Amino-4-(4-isopropylphenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3,3(4H)-tricarbonitrile ***(5e)***

White solid; Yield: 70%, mp: 190–191 ºC; IR ν_{max}: 3443, 3320, 3214, 2932, 2864, 2209, 1651, 1589, 1468 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.23 (d, J = 6.9 Hz, 6H), 1.32–1.61 (m, 18H), 2.22–2.28 (m, 1H), 2.55–2.59 (m, 1H), 2.72–2.59 (m, 1H), 2.72–2.91 (m, 1H), 5.02 (s, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.2, 22.6, 23.8, 23.9, 24.9, 25.1, 26.1, 26.7, 26.9, 27.2, 33.9, 42.5, 50.3, 84.0, 115.6, 112.9, 116.5, 126.8, 127.3, 127.9, 128.9, 129.6, 141.4, 150.7; HRMS (ESI) calcd for $[C_{28}H_{34}N_4–H]^-$ 425.2711, found 425.2707; Anal. calcd for $C_{28}H_{34}N_4$: C, 78.83; H, 8.03; N, 13.13; Found: C, 78.89; H, 8.07; N, 13.04.

4.3.6. 2-Amino-4-(4-(tert-butyl)phenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3,3(4H)-tricarbonitrile ***(5f)***

White solid; Yield: 73%, mp: 202–203 ºC; IR ν_{max}: 3439, 3320, 3211, 2929, 2862, 2211, 1650, 1588 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.30 (s, 9H), 1.39–1.63 (m, 17H), 2.21–2.28 (m, 1H), 2.57–2.59 (m, 1H), 2.69–2.76 (m, 1H), 3.94 (s, 1H), 5.07 (s, 2H), 7.14 (d, J = 9.0 Hz, 2H), 7.35 (d, J = 9.0 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.1, 22.6, 24.2, 24.9, 25.1, 26.1, 26.7, 26.9, 27.2, 31.3, 34.8, 42.5, 50.1, 83.9, 111.6, 112.9, 126.2, 126.8, 127.5, 128.9, 129.3, 141.4, 152.9; HRMS (ESI) calcd for $[C_{29}H_{36}N_4–H]^-$ 439.2867, found 439.2853; Anal. calcd for $C_{29}H_{36}N_4$: C, 79.05; H, 8.24; N, 12.72; Found: C, 79.08; H, 8.18; N, 12.79.

4.3.7. 2-Amino-4-(4-methoxyphenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3,3(4H)-tricarbonitrile ***(5g)***

White solid; Yield: 68%, mp: 201–202 ºC; IR ν_{max}: 3433, 3313, 3205, 2932, 2863, 2209, 1644, 1586 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.22–1.82 (m, 17H), 2.19–2.29 (m, 1H), 2.54–2.58 (m, 1H), 2.68–2.78 (m, 1H), 3.80 (s, 3H), 3.92 (s, 1H), 5.07 (s, 2H), 6.87 (d, J = 9.0 Hz, 2H), 7.15 (d, J = 9.0 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.1, 22.6, 24.9, 25.1, 26.1, 26.7, 26.9, 42.5, 50.0, 55.4, 83.6, 111.6, 112.9, 114.5, 122.4, 126.8, 128.9, 130.9, 141.5, 160.6; HRMS (ESI) calcd for $[C_{26}H_{30}N_4O–H]^-$ 413.2347, found 413.2317; Anal. calcd for $C_{26}H_{30}N_4O$: C, 75.33; H, 7.29; N, 13.52; Found: C, 75.28; H, 7.36; N, 13.48.

4.3.8. 2-Amino-4-(3-fluorophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3,3(4H)-tricarbonitrile ***(5h)***

White solid; Yield: 76%, mp: 196–197 ºC; IR ν_{max}: 3382, 3328, 2928, 2857, 2206, 1656, 1580, 1485 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$) δ_H 1.39–1.82 (m, 17H), 2.24–2.31 (m, 1H), 2.59–2.61 (m, 1H), 2.69–2.76 (m, 1H), 3.95 (s, 1H), 5.10 (s, 2H), 6.93 (d, J = 9.5 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 7.11 (dd, J = 8.7, 2.1 Hz, 1H), 7.36 (dd, J = 13.9, 7.9 Hz, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.1, 22.6, 24.2, 24.8, 24.9, 25.1, 26.1, 26.6, 27.0, 27.3, 42.2, 50.0, 83.9, 111.3, 112.6, 116.4 ($^2J_{C,F}$ = 22.4 Hz), 117.1

($^2J_{C,F}$ = 20.9 Hz), 125.7, 126.1, 130.9 ($^3J_{C,F}$ = 8.1 Hz), 133.4 ($^3J_{C,F}$ = 7.0 Hz), 141.2, 163.0 ($^1J_{C,F}$ = 246.6 Hz), 165.5; HRMS (ESI) calcd for $[C_{25}H_{27}FN_4–H]^-$ 401.2147, found 401.2121; Anal. calcd for $C_{25}H_{27}FN_4$: C, 74.60; H, 6.76; N, 13.92; Found: C, 74.68; H, 6.71; N, 14.01.

4.4. General procedure for the synthesis of 2-amino-4-phenyl-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3-dicarbonitrile **12**

A mixture of cyclododecanone (**1**, 1 mmol), aromatic aldehydes (**2**, 1 mmol), malononitrile (**3**, 2 mmol) and piperidine (50 mol%) was refluxed in acetonitrile for 4–5h and the reaction progress was monitored by TLC. After completion of the reaction the solvent was removed under vacuum. The crude product was purified by column chromatography using 4:1 (v/v) petroleum ether-ethyl acetate mixture to obtain pure **12**.

4.4.1. 2-Amino-4-(4-fluorophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3-dicarbonitrile ***(12a)***

White solid; Yield: 85%, mp: 161–162 ºC; IR ν_{max}: 3470, 3363, 3235, 2924, 2866, 2223, 1632, 1563, 1511, 1446 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.25–1.85 (m, 16H), 2.39 (t, *J* = 7.5 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 5.04 (s, 2H), 7.14–7.21 (m, 4H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.5, 22.7, 27.3, 27.5, 27.8, 28.11, 28.15, 28.3, 28.6, 31.2, 97.2, 98.0, 115.4, 115.7 ($^2J_{C,F}$ = 21.5 Hz), 115.8, 130.2 ($^3J_{C,F}$ = 8.2 Hz), 133. 9 ($^4J_{C,F}$ = 3.3 Hz), 149.7, 149.8, 151.4, 162.8 ($^1J_{C,F}$ = 247.1 Hz); HRMS (ESI) calcd for $[C_{24}H_{26}FN_3+NH_4]^+$ 393.2449, found 393.2451; Anal. calcd for $C_{24}H_{26}FN_3$: C, 76.77; H, 6.98; N, 11.19 ; Found: C, 76.83; H, 6.90; N, 11.10.

4.4.2. 2-Amino-4-(4-chlorophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3-dicarbonitrile ***(12b)***

White solid; Yield: 83%, mp: 198–190 ºC; IR ν_{max}: 3465, 3355, 3235, 2987, 2924, 2864, 2848, 2220, 1633, 1561, 1445 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.26–1.84 (m, 16H), 2.39 (m, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 5.04 (s, 2H), 7.18 (d, *J* = 6.0 Hz, 2H), 7.46 (d, *J* = 6.0 Hz, 2H);^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.5, 22.7, 27.4, 27.7, 27.9, 28.2, 28.3, 28.4, 29.0, 31.2, 96.9, 98.4, 115.5, 116.0, 129.1, 129.8, 130.1, 134.9, 136.4, 149.5, 149.9, 151.6; HRMS (ESI) calcd for $[C_{24}H_{26}ClN_3+NH_4]^+$ 409.2154, found 409.2160; Anal. calcd for $C_{24}H_{26}ClN_3$: C, 73.55; H, 6.69; N, 10.72; Found: C, 73.48; H, 6.74; N, 10.78.

4.4.3. 2-Amino-4-(4-bromophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3-dicarbonitrile ***(12c)***

White solid; Yield: 86%, mp: 202–203 ºC; IR ν_{max}: 3475, 3359, 3233, 2923, 2863, 2213, 1629, 1557, 1440 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.26–1.85 (m, 16H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 5.04 (s, 2H), 7.12 (d, *J* = 9.0 Hz, 2H), 7.62 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.5, 22.7, 27.4, 27.7, 27.9, 28.2, 28.3, 28.4, 29.0, 31.2, 96.9, 98.5, 115.6, 115.9, 123.2, 130.09, 130.1, 132.0, 136.9, 149.5, 149.9, 151.6; HRMS (ESI) calcd for $[C_{24}H_{26}BrN_3+NH_4]^+$ 453.1648, found 453.1648; Anal. calcd for $C_{24}H_{26}BrN_3$: C, 66.06; H, 6.01; N, 9.63; Found: C, 66.03; H, 6.09; N, 9.59.

4.4.4. 2-Amino-4-phenyl-5,6,7,8,9,10,11,12,13,14-decahydro benzo[12]annulene-1,3-dicarbonitrile ***(12d)***

White solid; Yield: 72%, mp: 191–193 ºC; IR ν_{max}: 3460, 3344, 3239, 2928, 2862, 2223, 2209, 1635, 1562, 1445 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.18–1.78 (m, 16H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.83 (t, *J* = 9.0 Hz, 2H), 4.97 (s, 2H), 7.14–7.19 (m, 2H), 7.38–7.43 (m, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.7, 22.8, 27.4, 27.7, 27.9, 28.3, 28.4, 29.0, 31.3, 97.3, 98.2, 115.7, 116.0, 128.4, 128.6, 128.8, 130.1, 149.9, 151.0, 151.3; HRMS (ESI) calcd for $[C_{24}H_{27}N_3+NH_4]^+$ 375.2543, found 375.2543; Anal. calcd for $C_{24}H_{27}N_3$: C, 80.63; H, 7.61; N, 11.75; Found: C, 80.69; H, 7.54; N, 11.80.

4.4.5. 2-Amino-4-(p-tolyl)-5,6,7,8,9,10,11,12,13,14-decahydro benzo[12]annulene-1,3-dicarbonitrile ***(12e)***

White solid; Yield: 79%, mp: 170–171 ºC; IR ν_{max}: 3463, 3352, 3236, 2987, 2924, 2865, 2220, 1634, 1561, 1445 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 0.88–1.85 (m, 16H), 2.42 (m, 5H, methyl peak overlapped), 2.89 (t, *J* = 9.0 Hz, 2H), 5.01 (s, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 7.27 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 21.4, 21.5, 22.5, 22.7, 27.4, 27.7, 27.8, 28.3, 28.4, 29.0, 31.2, 97.3, 97.9, 116.0, 116.1, 128.2, 129.3, 130.3, 135.6, 149.8, 151.2; HRMS (ESI) calcd for $[C_{25}H_{29}N_3+NH_4]^+$ 389.2700, found 389.2700; Anal. calcd for $C_{25}H_{29}N_3$: C, 80.82; H, 7.87; N, 11.31; Found: C, 80.75; H, 7.92; N, 11.23.

4.4.6. 2-Amino-4-(4-isopropylphenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3-dicarbonitrile ***(12f)***

White solid; Yield: 81%, mp: 205–206 ºC; IR ν_{max}: 3471, 3350, 3237, 2923, 2865, 2215, 1632, 1556, 1441 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.25–1.83 (m, 22H), 2.41–2.49 (m, 2H), 2.86–3.01 (m, 3H), 5.02 (s, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.7, 24.0, 27.4, 27.8, 27.9, 28.3, 29.1, 31.3, 34.0, 97.5, 98.0, 116.1, 116.2, 126.7, 128.3, 128.4, 130.5, 135.4, 149.4, 149.9, 151.2; HRMS (ESI) calcd for $[C_{27}H_{33}N_3+NH_4]^+$ 417.3013, found 417.3015; Anal. calcd for $C_{27}H_{33}N_3$: C, 81.16; H, 8.32; N, 10.52; Found: C, 81.25; H, 8.28; N, 10.46.

4.4.7. 2-Amino-4-(4-(tert-butyl)phenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3-dicarbonitrile ***(12g)***

White solid; Yield: 84%, mp: 187–188 ºC; IR ν_{max}: 3477, 3364, 3232, 2930, 2863, 2213, 1629, 1556, 1440 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.26–1.86 (m, 25H), 2.38–2.41 (m, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 5.02 (s, 2H), 7.15 (d, *J* = 6.0 Hz, 2H), 7.47 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.8, 22.9, 27.4, 27.8, 28.0, 29.1, 31.3, 31.5, 34.9, 97.5, 98.0, 115.8, 116.1, 125.5, 128.1, 130.5, 135.1, 149.9, 151.2, 151.8; HRMS (ESI) calcd for $[C_{28}H_{35}N_3+NH_4]^+$ 431.3169, found 431.3172; Anal. calcd for $C_{28}H_{35}N_3$: C, 81.31; H, 8.53; N, 10.16; Found: C, 81.26; H, 8.55; N, 10.26.

4.4.8. 2-Amino-4-(4-methoxyphenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3-dicarbonitrile ***(12h)***

White solid; Yield: 80%, mp: 194–196 ºC; IR ν_{max}: 3471, 3352, 3236, 2920, 2846, 2215, 1632, 1560, 1480 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.18–1.76 (m, 16H), 2.35 (m, 2H), 2.82–2.84 (m, 2H), 3.79 (s, 3H), 4.97 (s, 2H), 6.91 (d, *J* = 6.0 Hz, 2H), 7.14 (d, *J* = 9.0 Hz, 2H);^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.5, 22.7, 27.4, 27.7, 27.8, 28.3, 28.9, 31.2, 55.4, 97.5, 97.8, 106.0, 114.1, 115.9, 116.2, 129.6, 130.2, 130.6, 149.9, 151.2, 159.8; HRMS (ESI) calcd for $[C_{25}H_{29}N_3O+NH_4]^+$ 405.2649, found 405.2653; Anal. calcd for $C_{25}H_{29}N_3O$: C, 77.48; H, 7.54; N, 10.84; Found: C, 77.44; H, 7.46; N, 10.80.

4.4.9. 2-Amino-4-(3-fluorophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3-dicarbonitrile ***(12i)***

White solid; Yield: 83%, mp: 177–178 ºC; IR ν_{max}: 3463, 3333, 3239, 2927, 2860, 2210, 1636, 1581, 1444 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.26–1.85 (m, 16H), 2.40 (t, *J* = 6.9 Hz, 2H), 2.90 (t, *J* = 8.5 Hz, 2H), 5.05 (s, 2H), 6.93–6.99 (m, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 7.16 (td, *J* = 8.5, 1.7 Hz, 1H), 7.42–7.49 (m, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 21.9, 22.1, 26.8,

27.1, 27.3, 27.6, 27.7, 27.8, 28.5, 30.7, 96.3, 97.9, 114.9, 115.1, 115.3, 115.4 ($^2J_{C,F}$ = 20.6 Hz), 123.8 ($^4J_{C,F}$ = 3.0 Hz), 129.4, 129.9, 130.0 ($^3J_{C,F}$ = 8.6 Hz), 139.3, 148.7, 149.3, 151.1, 162.0 ($^1J_{C,F}$ = 246.5 Hz); HRMS (ESI) calcd for $[C_{24}H_{26}FN_3+NH_4]^+$ 393.2449, found 393.2457; Anal. calcd for $C_{24}H_{26}FN_3$: C, 76.77; H, 6.98; N, 11.19 ; Found: C, 76.69; H, 6.93; N, 11.12.

4.4.10. 2-Amino-4-(3-bromophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3-dicarbonitrile ***(12j)***

White solid; Yield: 82%, mp: 115–116 ºC; IR ν_{max}: 3393, 3324, 3156, 2923, 2846, 2215, 1653, 1548, 1468 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.26–1.51 (m, 15H), 1.84–1.86 (m, 2H), 2.39–2.44 (m, 1H), 2.69–2.80 (m, 2H), 5.05 (s, 2H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.40 (s, 1H), 7.58 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 21.7, 23.1, 27.7, 27.9, 28.2, 28.5, 28.6, 28.7, 29.3, 31.6, 94.32, 94.35, 116.0, 116.1, 120.6, 127.4, 130.5, 130.7, 131.6, 132.3, 132.9, 139.8, 151.9, 152.8; HRMS (ESI) calcd for $[C_{24}H_{26}BrN_3+NH_4]^+$ 453.1648, found 453.1645; Anal. calcd for $C_{24}H_{26}BrN_3$: C, 66.06; H, 6.01; N, 9.63; Found: C, 66.02; H, 6.06; N, 9.69.

4.4.11. 2-Amino-4-(3-nitrophenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3-dicarbonitrile ***(12k)***

White solid; Yield: 85%, mp: 208–210 ºC; IR ν_{max}: 3497, 3393, 2923, 2211, 1615, 1518, 1445, 1342 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.24–1.86 (m, 16H), 2.35–2.38 (m, 2H), 2.91 (t, *J* = 8.2 Hz, 2H), 5.10 (s, 2H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.70 (t, *J* = 7.9 Hz, 1H), 8.15 (s, 1H), 8.35 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.6, 27.4, 27.6, 27.9, 28.1, 28.3, 28.4, 29.0, 31.3, 96.6, 99.1, 115.3, 115.7, 123.7, 123.9, 130.0, 134.7, 139.5, 147.8, 148.2, 150.0, 152.2; HRMS (ESI) calcd for $[C_{24}H_{26}N_4O_2+NH_4]^+$ 420.2394, found 420.2394; Anal. calcd for $C_{24}H_{26}N_4O_2$: C, 71.62; H, 6.51; N, 13.92; Found: C, 71.56; H, 6.43; N, 14.01.

4.4.12. 2-Amino-4-(3-chloro-4,5-dimethoxyphenyl)-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3-dicarbonitrile ***(12l)***

White solid; Yield: 77%, mp: 179–181 ºC; IR ν_{max}: 3431, 3354, 3250, 2928, 2212, 1741, 1560, 1453 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ_H 1.30–1.85 (m, 16H), 2.42 (t, *J* = 6.0 Hz, 2H), 2.89 (t, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 3.95 (s, 3H), 5.04 (s, 2H), 6.67 (s, 1H), 6.86 (s, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ_C 22.3, 22.5, 27.3, 27.6, 27.8, 28.1, 28.1, 28.2, 29.1, 31.1, 56.2, 60.9, 96.8, 98.3, 111.3, 115.4, 115.8, 121.8, 128.5, 130.1, 134.0, 145.6, 149.0, 149.7, 151.5, 153.7; Anal. calcd for $C_{26}H_{30}ClN_3O_2$: C, 69.09; H, 6.69; N, 9.30; Found: C, 69.12; H, 6.65; N, 9.36.

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at http://

References and notes

1. (a) Ho, T-L, *Tandem Organic Reactions*; John Wiley & Sons, 1992; (b) Ugi, I, Dömling, A, Hörl, W, *Endeavour* 1994; 18:115; (c) Zhu, J, Bienaymé, H, *Multicomponent Reaction*; Wiley-VCH: Weinheim, 2005; (d) Armstrong, RM, Combs, AP, Tempest, PA, Brown, SD, Keating, TA, *Acc. Chem. Res.* 1996; 29:123; (e) Dçmling, A, *Chem. Rev.* 2006;106:17; (f) Ruijter, E, Scheffelaar, R, Orru, RVA, *Angew. Chem. Int. Ed.* 2011;50:6234; (f) Dçmling, A, Wang, W, Wang, K, *Chem. Rev.* 2012;112:3083.
2. (a) Anastas, PT, Warner, JC, *Green Chemistry, Theory and Practice*; Oxford University Press: Oxford, UK, 2000; p. 135; (b) Matlack, AS, *Introduction to Green Chemistry*; Marcel Dekker: New York, NY, USA, 2001; p. 570.
3. (a) EIgemeie, GEH, Attia, AME, Hussain, BAW, *Nucleos Nucleot Nucl*, 1998;17:855; (b) Egea, J, de los Rios, C, *Curr. Top. Med. Chem.* 2011;11:2807; (c) Gill, RK, Kaur, R, Kumar, V, Gupta, V, Singh, G, Bariwal, J, 2016;7:1966; (d) Taylor, EC, Berrier, JV, Cocuzza, AJ, Kobylecki, R, McCormack, JJ, *J. Med. Chem.* 1977; 20:1215; (e) Poutiainen, PK, Oravilahti, T, Perakyla, M, Palvimo, JJ, Ihalainen, JA, Laatikainen, R, Pulkkinen, JT, *J. Med. Chem.* 2012;55:6316; (f) Yoshizumi,T, Takahashi, H, Miyazoe, H, Sugimoto, Y, Tsujita, T, Kato, T, Ito, H, Kawamoto, H, Hirayama, M, Ichikawa, D, Azuma-Kanoh, T, Ozaki, S, Shibata, Y, Tani, T, Chiba, M, Ishii, Y, Okuda, S, Tadano, K, Fukuroda, T, Okamoto, O, Ohta, H, *J. Med. Chem.* 2008;51:4021.
4. (a) Naydenova, E, Pencheva, N, Popova, J, Stoyanov, N, Lazarova, M, Aleksiev, B, *II Farmaco* 2002;57:189; (b) Kim, HS, Nagai, Y, Ono, K, Begum, K, Wataya, Y, Hamada, Y, Tsuchiya, K, Masuyama, A, Nojima, M, McCullough, KJ, *J. Med. Chem.* 2001;44:2357; (c) Taylor, EC, Berrier, JV, Cocuzza, AJ, Kobylecki, R, McCormack, JJ, J. Med. Chem. 1977; 20:1215;
5. (a) Hayakawa, Y, Kawakami, K, Seto, H, *Tetrahedron Lett.* 1992;33:2701; (b) Boger, DL, Hong, J, *J. Am. Chem. Soc.* 2001;123:8515.
6. (a) Harmata, M, Elahmad, S, Barnes, CL, *Tetrahedron Lett.* 1995;36:1397; (b) Harmata, M, *Tetrahedron* 1997;53:6235.
7. Wang, S-J, Li, Y-X, Bao, L, Han, J-J, Yang, X-L, Li, H-R, Wang, Y-Q, Li, S-J, Liu, H-W, *Org. Lett.* 2012;14:3672.
8. Odile C, *Fungicides*; InTech, 2010; p.497; (b) Zhu, W-J, Wu, P, Liang, X-M, Dong, Y-H, Zhang, J-J, Yuan, H-Z, Qi, S-H, Meng, X-Q, Wu, J-P, Chen, F-H, Wang, D-Q, *J. Agric. Food Chem.* 2008;56:6547; (c) Li, X-H, Yang, X-L, Ling, Y, Fan, Z-J, Liang, X-M, Wang, D-Q, Chen,F-H, Li, Z-M, *J. Agric. Food Chem.* 2005;53:2202
9. Zhang, Y, Li, X.-W, Li, X.-H, Wang Y.-Zi , Qi, Z.-Q, Ji, M.-S, Gu, Z.-M, Wei, S.-H, Chin. Patent CN 102633697 A, 2012.
10. Hamada, Y, Tokuhara, H, Masuyama, A, Nojima, M, Kim, H-S, Ono, K, Ogura, N, Wataya, Y. *J. Med. Chem.* 2002;45:1374.
11. Kim, S.H. U.S. Patent, US4814335 A, 1989.
12. Pericle, F, Ross, J. A. U.S. Patent, US9371265 B2, 2016.
13. Schilling, B, Woggon, W.D, Chougnet, A, Granier, T, Frater, G, Hanhort, A. WO 2008/116339 A2, 2008.
14. (a) Scafato, P, Larocca, A, Rosini, C, *Tetrahedron: Asymmetry* 2006;17:2511; (b) Shi, Z, Qiang, J, Li, Z, *Chin. Sci. Bull.* 2001; 46:393; (c) Bollbuck, B, Kraft, P, Tochtermann, W, *Tetrahedron* 1996;52:4581; (d) Dowd, P, Choi, S-C, Tetrahedron 1992;48:4773; (e) Nowicki, J, *Molecules* 2000;5:1033; (f) Hafner, W, Gebauer, H, Markel, E, Regiert, M. U.S. Patent 4 948 780, 1990;
15. Biemann, K, Buchi, G, Walke, BH, *J. Am. Chem. Soc.* 1957;70: 5558.
16. Munro, D, Sell, C.S, U.S. Patent, US6444637 B1, 2002.
17. Okatani,T, Koyama, J, Tagahara, K, *Heterocycles* 1989;29:1809.
18. Shkil', GP, Sagitnllin, RS, *Chem. Heterocycl. Compd.* 1998;34:507.(references cited there in)
19. Tius, MA, Ali, S, J. Org. Chem. 1982;47:3163.
20. Barun, O, Nandi, S, Panda, K, Ila, H, Junjappa, H, *J. Org. Chem* 2002;67:5398.
21. Maharani, S, Almansour, AI, Suresh Kumar, R, Arumugam, N, Ranjith Kumar, R, *Tetrahedron* 2016;72:4582; (b) Maharani, S, Ranjith Kumar, R, *Tetrahedron Lett.* 2015;56:179; (c) Maharani, S, Ranjith Kumar, R, *Tetrahedron Lett.* 2013;54:4800.
22. For examples of synthesis of pyridines see: (a) Tang, J, Wang, L, Yao, Y, Zhang, L, Wang, W, *Tetrahedron Lett.* 2011;52:509; (b) Pagadala, R, Maddila, S, Moodley, V, van Zyl, WE, Jonnalagadda, SB, *Tetrahedron Lett.* 2014;55:4006; (c) Kankala, S, Pagadala, R, Maddila, S, Vasam CS, Jonnalagadda, SB, *RSC*

Adv. 2015;5:105446; (d) Maleki, A, Jafari, AA, Yousefia, S, Eskandarpoura, V, *Comptes Rendus Chimie* 2015;18:1307; (e) Wang, J, Li, Z, Wang, X, Zhou, Y, Guo, C, *Heterocycles* 2015;91:49.

23. Crystallographic data (excluding structure factors) for compounds **4d** and **5b** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 1840402 and 1840401, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 762911 or e-mail: deposit@ccdc.cam.ac.uk].

Highlights

One-pot multi-component approach to pyridine/benzo fused cyclododecanes

Tandem Knoevenagel–Michael–intramolecular cyclization–air oxidation/elimination steps

Formation of two C–N and two C–C/four C–C bonds in a single transformation

Structure elucidated unambiguously by NMR and single crystal X-ray