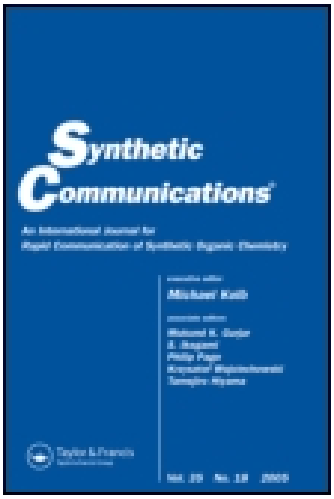

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DABCO-CATALYZED MULTICOMPONENT REACTION FOR SYNTHESIS OF BENZO[*a*]CARBAZOLES

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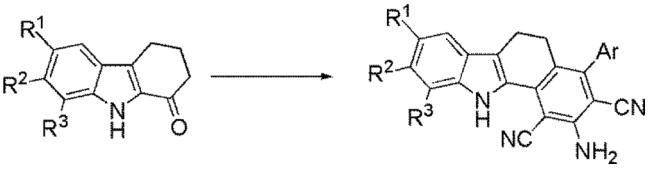
GRAPHICAL ABSTRACT



Abstract *DABCO (1,4-diazabicyclo[2.2.2]octane) catalyzed a multicomponent reaction using the starting precursor 2,3,4,9-tetrahydro-1*H*-carbazol-1-one, malononitrile, and aromatic/heteroaromatic aldehyde.*

Keywords Aromatic/heteroaromatic aldehydes; crystal structure; DABCO; malononitrile; 2,3,4,9-tetrahydro-1*H*-carbazol-1-one

INTRODUCTION

Benzo-annulated carbazole ring systems are found rarely in natural products. Benzo[*a*]carbazole ring systems are of considerable interest because they can exhibit antifungal and pronounced antitumor activity against leukemia, renal tumor, colon cancer, and malignant melanoma tumor cell lines[1–5] and demonstrate kinase inhibitory activities.[6–9] The benzo[*a*]carbazoles, which contain an aromatic ring fused to the *a* face of the carbazole nucleus, are potential candidates for cancer treatment as a result of DNA intercelative binding properties.[10] A series of simple benzo[*a*]-carbazoles have been shown to bind to estrogen receptors and inhibit the growth of mammary tumors of rats.[11] Benzo[*a*]carbazole derivatives have also found extensive application as photographic materials.[12] Very recently, several benzocarbazole

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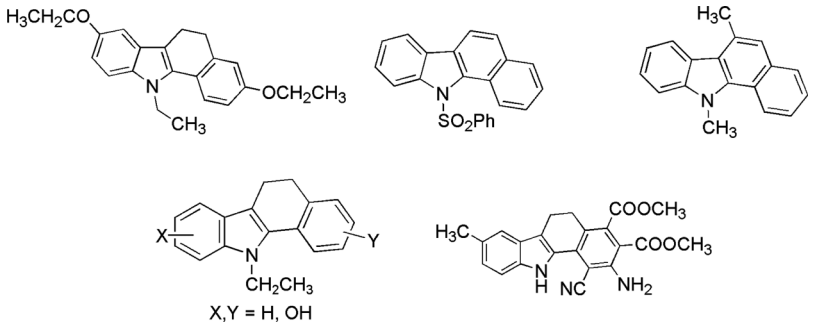


Figure 1. Bioactive compounds with a benzo[*a*]carbazole core structure.

analogs have also been explored as functional building blocks in the construction of organic materials for optoelectronic devices.[13,14] Examples of bioactive benzo[*a*]-carbazoles are shown in Fig. 1.

Numerous synthetic methodologies for the construction of benzo[*a*]carbazoles have been developed in past decades including thermal and photochemical cyclization, Fisher indolization, and pericyclic reaction.[15] In addition to these more classical synthetic strategies, various transition-metal-mediated reactions have been applied as well.[16,17] Most of these procedures have involved several steps, and the overall yields were, in general, not very good. The most serious drawbacks of the established methods, however, are a lack of flexibility and tolerance of functional groups, and regiochemical ambiguities originating from orienting effects of the substituents. There is thus still a considerable need for the development of more versatile and regioselective synthetic routes towards highly substituted benzocarbazoles, especially with respect to tolerance of a wider variety of functional groups. One simple, efficient, and reliable synthetic method for this class of compounds in a direct and atom-economical manner is strongly required. We adopted the method for the construcution of benzo[*a*]carbazoles by multicomponent reaction using precursor 2,3,4,9-tetrahydro-1*H*-carbazol-1-one, malononitrile, and aromatic/heteroaromatic aldehyde using bases. There are few reports for the synthesis of dicyanoanilines using various bases by solvent-free conditions,[17] microwave irradiation,[18] and various other methods.[19] Construction of novel benzo[*a*]carbazole ring systems would also lead to the development of promising templates for drug discovery.

Pertinent to this fact, benzo[*a*]carbazole was constructed in the present study by an efficient and versatile method. 1,4-Diazabicyclo[2.2.2]octane (DABCO)–catalyzed multicomponent reaction using the starting precursor 2,3,4,9-tetrahydro-1*H*-carbazol-1-one, malononitrile, and aromatic/heteroaromatic aldehyde was carried out.

RESULTS AND DISCUSSION

Synthesis of Benzo[*a*]carbazoles

2,3,4,9-Tetrahydro-1*H*-carbazol-1-one[20] (**1**) was reacted with malononitrile (**2**) and aromatic/heteroaromatic aldehydes (**3**) in ethanol medium. The reaction condition was optimized using various bases shown in Table 1. When NaOH and

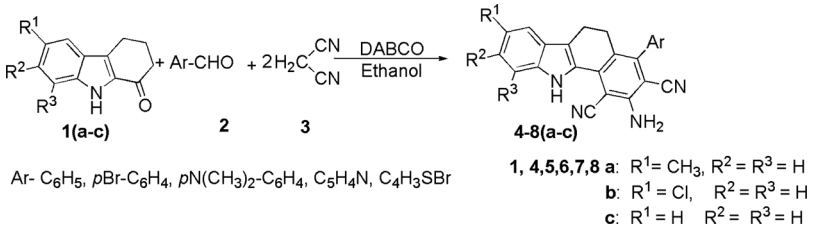
Table 1. Optimization of catalyst

Entry	Solvent	Base	Time (h)	T (°C)	Yield (%)
1	EtOH	—	6	80	25
2	EtOH	NaOH	6	80	40
3	EtOH	KOH	6	80	40
4	EtOH	K_2CO_3	5	80	50
5	EtOH	Et_3N	5	80	62
6	EtOH	Piperidine	5	80	60
7	EtOH	DABCO (10 mol%)	3	80	78
8	EtOH	DBACO (15 mol%)	3	80	75
9	EtOH	DABCO (20 mol%)	2	80	80
10	EtOH	DABCO (25 mol%)	1	80	82

KOH were used as bases, the reaction times were longer and the yields were less than 40%. Using potassium carbonate as the base, the product was obtained in poor yield and the reaction time was longer. With piperidine and triethyl amine as base, a moderate yield of around 60% was achieved. The best yield of the target was obtained using DABCO as base under refluxing condition.

With DABCO as the catalyst the reaction proceeded smoothly in an even shorter reaction time with similar good yields, thus indicating DABCO as the most efficient catalyst of those tested (Table 1). To optimize the reaction condition we evaluated the most appropriate catalyst loading, using 10, 15, 20, and 25 mol% of DABCO at 80 °C. The yield steadily increased with loading until it reached a maximum of >82% at 25 mol% of the catalyst.

6-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1a**) was reacted with benzaldehyde (**2**), malononitrile (**3**), and DABCO in dry ethanol for 1 h (Scheme 1) which afforded compound **4a**. Its IR spectrum showed absorption bands at 3462 cm^{-1} (asym, NH_2), 3321 cm^{-1} (sym, NH_2), and 2221 cm^{-1} (C≡N). In its ^1H NMR spectrum a singlet at δ 5.14 was due to amino protons. The indole NH proton appeared as a broad singlet at δ 8.92. The C_7, C_9, and C_{10} protons appeared as a multiplet between δ 7.56 and 7.51. The five aromatic protons appeared as a multiplet between δ 7.37–7.33 for C_2', C_3', C_4', C_5', and C_6' protons. The four aliphatic protons of C_5 and C_6 appeared as a multiplet between δ 2.88 and 2.82. Methyl protons appeared as a singlet at δ 2.52. The total number of protons matched perfectly with its structure. The ^{13}C NMR spectrum revealed the presence of 25 carbons. The molecular ion peak in the mass spectrum at m/z 374 and the elemental analysis agree well with



Scheme 1. Synthesis of benzo[*a*]carbazoles.

Table 2. Synthesis of benzo[*a*]carbazoles using aromatic/heteroaromatic aldehydes

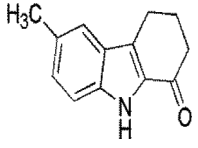
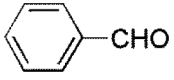
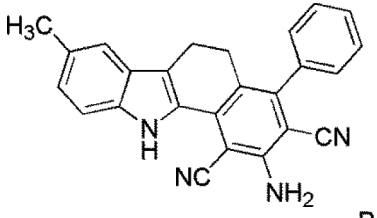
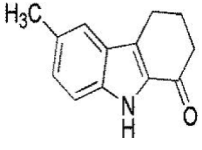
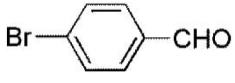
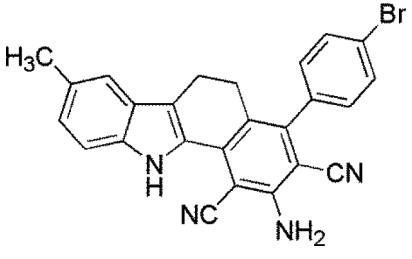
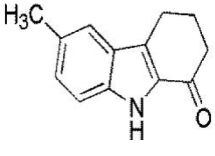
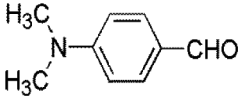
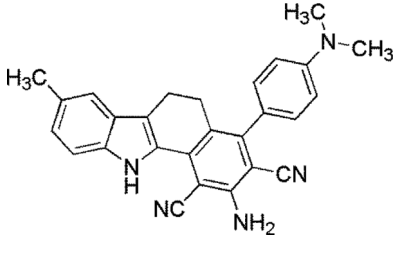
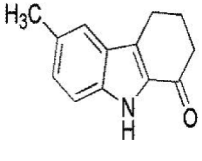
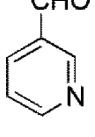
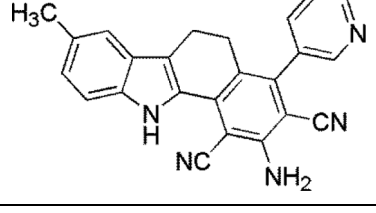
Compound	Precursor	Aldehyde	Product	Yield (%)
4a				82
5a				81
6a				80
7a				82

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Table 2. Continued

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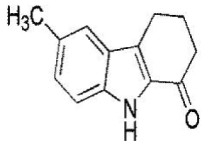
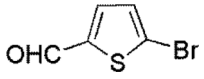
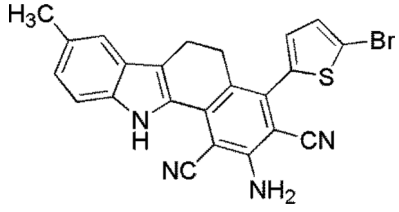
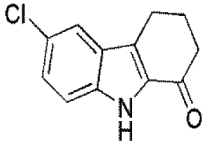
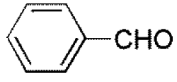
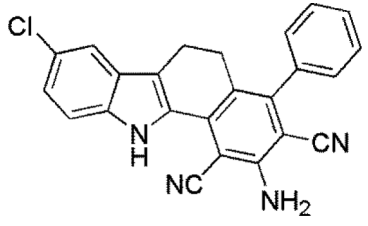
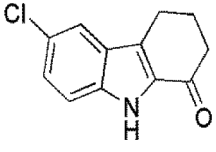
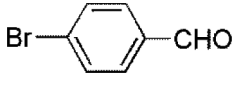
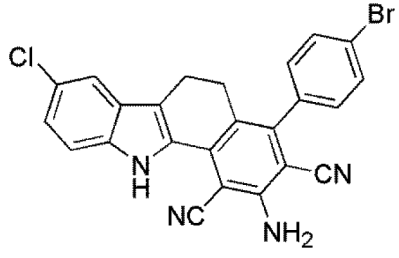
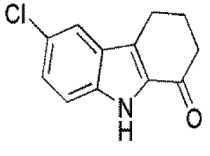
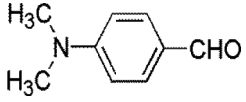
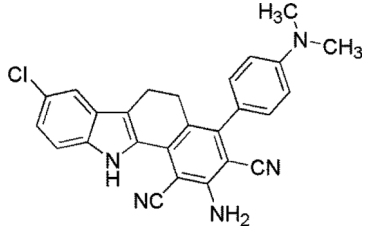
8a				80
4b				80
5b				80
6b				80

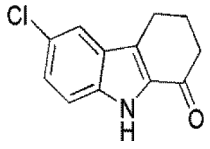
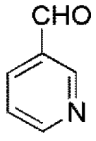
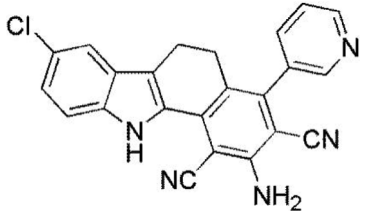
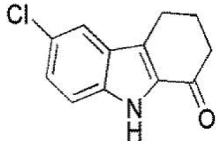
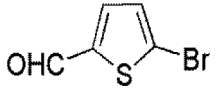
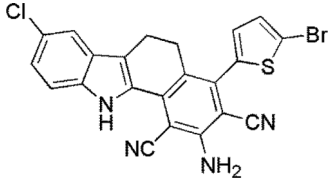
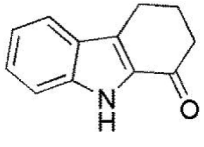
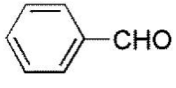
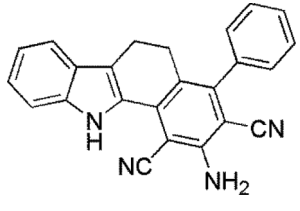
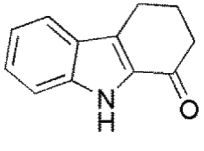
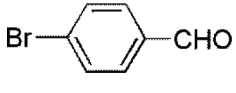
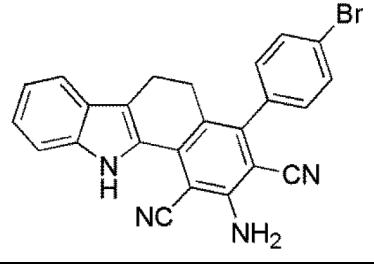
7b				81
8b				82
4c				81
5c				80

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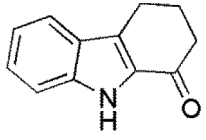
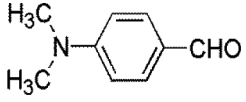
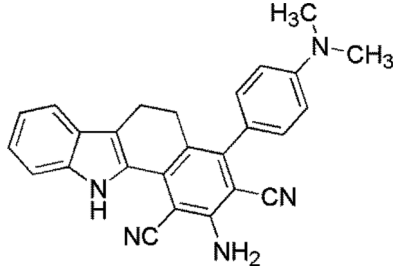
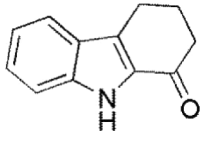
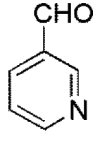
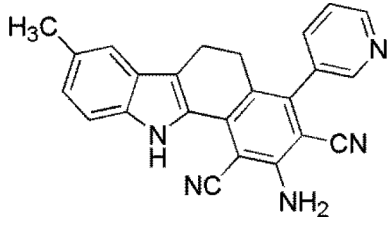
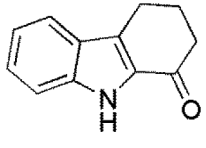
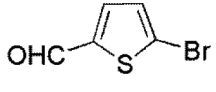
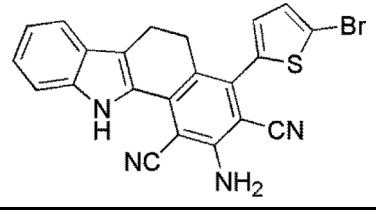
Table 2. Continued

Compound	Precursor	Aldehyde	Product	Yield (%)
6c				81
7c				82
8c				80

the molecular formula $C_{25}H_{18}N_4$. All details attest to the structure of the compound as 2-amino-4-phenyl-8-methyl-5,6-dihydro-11*H*-benzo[*a*]carbazole-1,3-dicarbonitrile (**4a**). The generality of the reaction was tested with various aromatic/heteroaromatic aldehydes to form the corresponding product, which is represented in Table 2.

CRYSTAL STRUCTURE OF COMPOUND 8b

The structure of one of the members of the series **8b** was confirmed by single-crystal x-ray analysis (Fig. 2).

Mechanism for the Formation of Final Compounds 4–8

We proposed the following mechanism for the multicomponent reaction (Scheme 2): DABCO-assisted Knoevenagel condensation of the aldehyde with malononitrile to yield arylidene malononitrile intermediate (**I**). Then the intermediate (**I**) on Michael addition gives the arylidene malononitrile (**II**), which subsequently reacts with another mole of malononitrile to give intermediate **III** and further on cyclization yields the intermediate **IV**. The base abstracts the proton from intermediate **IV** followed by β-elimination, which leads to intermediate **V**. The intermediate **V** on imino-amino tautomerisation afforded the final product.

CONCLUSION

We have designed and synthesized novel benzo[*a*]carbazoles by multicomponent reaction of 2,3,4,9-tetrahydro-1*H*-carbazol-1-ones with malononitrile and aromatic/heteroaromatic aldehydes in ethanol medium, and the reaction condition was optimized using various bases. The best yield of the product was obtained using

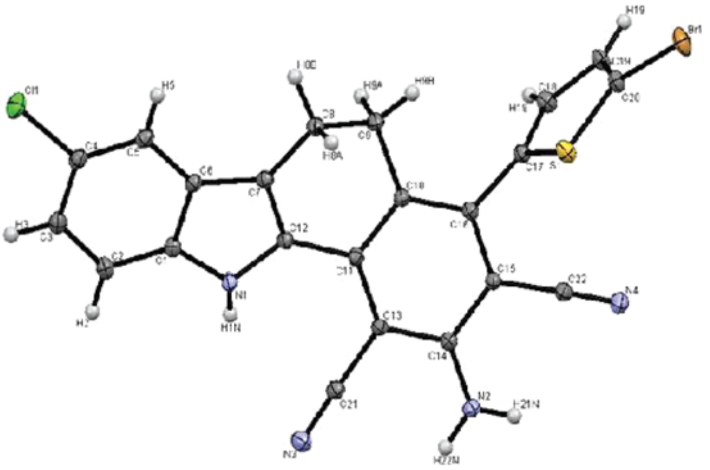
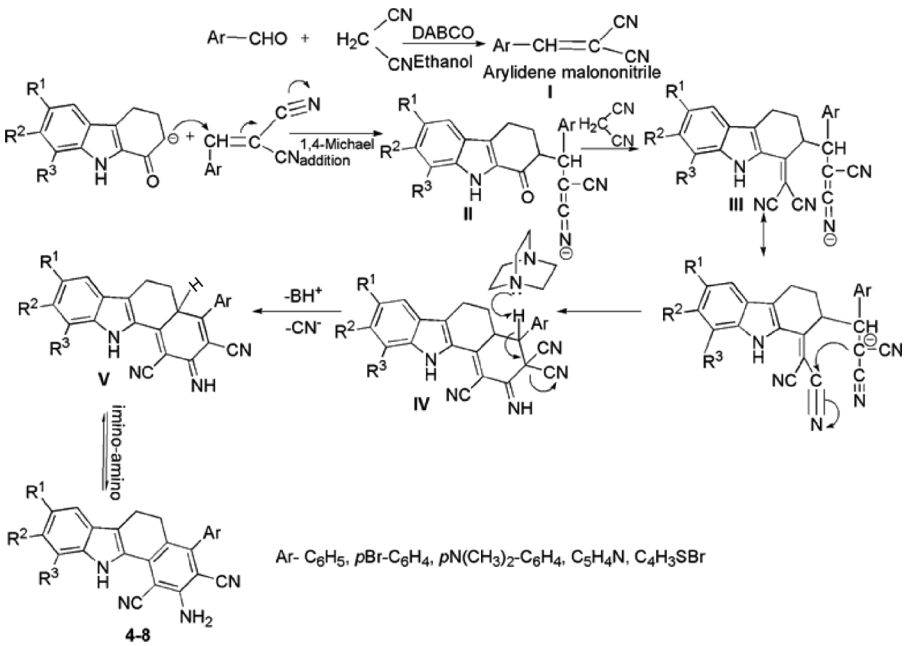


Figure 2. X-ray crystal structure and atom numbering scheme for **8b** as thermal ellipsoids at 50% probability level. Solvent moiety is omitted for clarity.



Scheme 2. Mechanism for the formation of compounds **4–8**.

DABCO as base under refluxing condition. All the synthesized compounds were characterized by infrared (IR), ^{1}H NMR, ^{13}C NMR, and mass spectroscopic techniques. One of the synthesized compounds, 2-amino-4-(5′-bromothiophen-2′-yl)-8-chloro-5,6-dihydro-11*H*-benzo[*a*]carbazole-1,3-dicarbonitrile (**8b**), was solved by x-ray crystallography.

EXPERIMENTAL

Melting points (mp) were determined on a Mettler FP 51 apparatus (Mettler Instruments, Switzerland) and are uncorrected. They are expressed in degrees centigrade (°C). A Nicolet Avatar model FT-IR spectrophotometer was used to record the IR spectra (4000–400 cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AV 500 (500 MHz, ^{1}H, and 125 MHz, ^{13}C) spectrometer using tetramethylsilane (TMS) as an internal reference. The chemical shifts are expressed in parts per million (ppm). Mass spectra (MS) were recorded on an Auto Spec EI + Shimadzu QP 2010 Plus gas chromatography–mass spectrometry (GC-MS) instrument. Microanalyses were performed on a Vario EL III model CHNS analyzer (Vario, Germany) at the Department of Chemistry, Bharathiar University. X-ray diffraction measurements were performed on a Bruker Kappa Apex-II diffractometer equipped with an Oxford Cryostream chiller and graphite monochromatized CuK alpha radiation. The purity of the products was tested by thin-layer chromatography (TLC) with plates coated with silica gel G; petroleum ether and ethyl acetate were used as developing solvents.

General Procedure for the Synthesis of 2-Amino-5,6-dihydro-11H-benzo[*a*]carbazole-1,3-dicarbonitrile 4–8

A mixture of 2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1**, 0.001 mol), aromatic/hetero aromatic aldehyde (**2**, 0.01 mol), malononitrile (**3**, 0.002 mol), and DABCO (25 mol%) in dry ethanol (15 mL) was heated under reflux for 1 h. After completion of the reaction, the excess solvent was evaporated. The residue was poured in ice water and extracted with ethyl acetate. Combined organic layers were dried over anhydrous sodium sulfate. It was then purified on a silica-gel column (eluent: petroleum ether/ethyl acetate, 95:5). The pure product was recrystallized from ethanol.

2-Amino-4-phenyl-8-methyl-5,6-dihydro-11H-benzo[*a*]carbazole-1,3-dicarbonitrile (4a)

Yellow solid; yield: 82%; mp 220–222 °C; IR (KBr, cm^{-1}) ν_{max}: 3462 (asym, NH_2), 3321 (sym, NH_2), 2221 (C≡N); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 8.92 (b s, 1H, N_{11}-H), 7.56–7.51 (m, 3H, C_7, C_9 & C_{10}-H), 7.37–7.33 (m, 5H, C_2', C_3', C_4', C_5' & C_6'-H), 5.14 (s, 2H, NH_2), 2.88–2.82 (m, 4H, C_5-2H & C_6-2H), 2.52 (s, 3H, C_8-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 159.5 (C_2), 147.9 (C_{11b}), 143.4 (C_4), 136.2 (C_{10a}), 130.0 (C_1'), 129.2 (C_3' & C_5'), 128.0 (C_{4a}), 127.2 (C_8), 126.9 (C_2' & C_6'), 126.4 (C_4'), 125.5 (C_{6b}), 122.8 (C_{11a}), 120.0 (C_9), 119.1 (C_7), 116.4 (C_{6a}), 115.4 (C≡N), 114.3 (C≡N), 110.2 (C_{10}), 95.0 (C_3), 93.3 (C_1), 29.7 (C_5), 24.2 (C_6), 21.7 (C_8-CH_3); MS: m/z (%) 374 (M^+ 100). Anal. calcd. for $C_{25}H_{18}N_4$: C, 80.19; H, 4.85; N, 19.6. Found: C, 80.21; H, 4.88; N, 19.3%.

The supplementary data includes the experimental details of all the newly synthesized compounds and x-ray single-crystal structure details of compound **8b**. The IR spectrum of compound **4a** and ^{1}H NMR and ^{13} C NMR spectra of **4a**–**8a, 4b**–**8b**, and **4c**–**8c** have also been provided. The crystallographic data of **8b** is given in Table 3.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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