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Metal-free synthesis of benzimidazo[2,1-*a*]ellipticines via tandem inter and intramolecular cyclization

T. Krishna Chaitanya, K.S. Prakash, Rajagopal Nagarajan *

School of Chemistry, University of Hyderabad, Hyderabad 500046, Andhra Pradesh, India

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ABSTRACT

Synthesis of the new benzimidazo[2,1-*a*]ellipticine derivatives via tandem inter and intramolecular, 5-*endo*,6-*endo* cyclization of various 9-ethyl-2-(alkynyl)carbazole-3-carbaldehydes with different 1,2-aryldiamines is reported under metal free condition in good yields.

1. Introduction

Ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole; Fig. 1) is a natural plant alkaloid, which was isolated from *Ochrosia elliptica* of the Apocynaceae family that has been found to be a potent antitumour agent.[1] Many of its derivatives, which have different DNA-binding affinities show antitumour and cytotoxic effects and exhibit promising results in the treatment of breast-cancer metastases, brain tumours, kidney sarcomas and myeloblastic leukaemia have gained significant synthetic interest.[1,2] Other pyrido[4,3-*b*]carbazole alkaloids like Olivacine, Calothrixin B etc. (Fig. 1) are also of significant synthetic interest[3] due to their potential biological applications.

Compounds containing benzimidazole core systems and their fused heterocyclic variants have attracted considerable attention from medicinal and synthetic organic chemists because of their wide range of biological activities, such as anxiolytic, antibacterial/antifungal, antineoplastic, anticancer, DNA intercalator etc.[4] Brana et al. and Hranjec et al. reported cyano- and amidino-substituted derivatives of styryl-2-benzimidazoles, benzimidazo[1,2-*a*]quinolines, benzimidazo[1,2-*c*]quinazolines and showed that these compounds have excellent DNA intercalation properties.[5] Considering the importance of benzimidazole fused heterocyclic moieties, synthesis of benzimidazo[2,1-*a*]ellipticine derivatives is desirable.

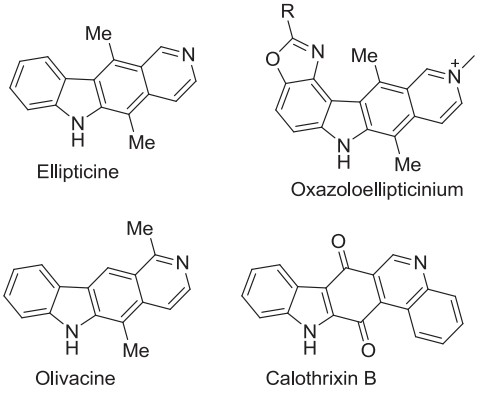

Fig. 1. Pyrido[4,3-*b*]carbazoles.

Tandem cyclization using metal catalysts has become one of the most powerful tools for the synthesis of molecules containing ring systems.[6] One of the most efficient methodologies involves direct formation of the benzimidazole ring from 2-alkynylarylaldehyde derivatives.[7,8]

Recently, our group has reported the synthesis of highly functionalized isomeric ellipticine derivatives from the corresponding 3-aminocarbazoles.[9,10] In continuation of our interest, herein we report a high-yielding, catalyst free synthesis of benzimidazo[2,1-*a*]ellipticine derivatives from corresponding 9-ethyl-2-(phenylethynyl)-9*H*-carbazole-3-carbaldehydes and 1,2-aryldiamines via

* Corresponding author. Tel.: +91 40 23134831; fax: +91 40 23012460; e-mail address: rnsc@uohyd.ernet.in (R. Nagarajan).

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tandem cyclization. The requisite 2-alkynylcarbaldehyde precursors **1a**–**g** (Fig. 2) are readily synthesized from the corresponding 2-bromocarbazoles.

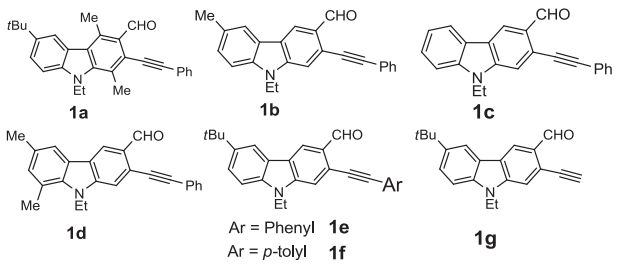
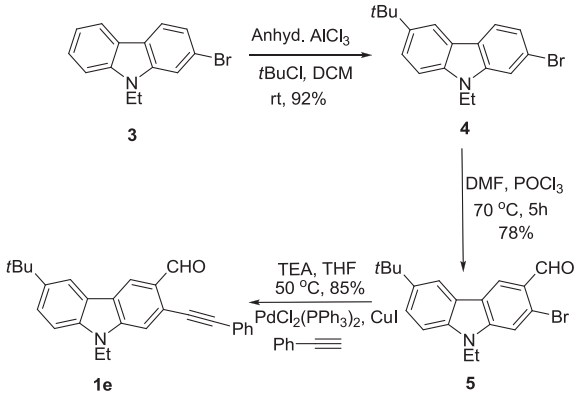


Fig. 2. 2-Alkynyl-3-formylcarbazole precursors.

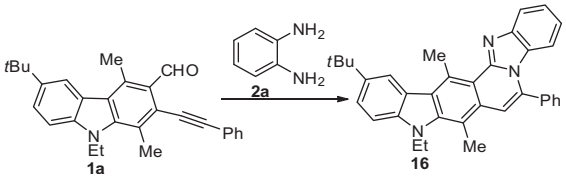
9-Ethyl-2-bromocarbazole **3** was selectively alkylated at sixth position using *tert*-butyl chloride and anhyd aluminium chloride in dichloromethane to give **4** in 92% yield (Scheme 1). Compound **4** on Vilsmeier–Haack formylation furnished the 3-formyl derivative **5** in 78% yield. Compound **5** was coupled with phenylacetylene under Sonogashira conditions to provide the corresponding precursor **1e** in excellent yield. Compounds **1f** and **1g** were also prepared in similar manner. Precursors **1a**–**d** were prepared according to the methods developed in our laboratory (Fig. 2).[10] In the process of synthesizing ellipticine derivatives from 2-alkynyl-3-formylcarbaldimines by reacting with various amines, when we carried out the reaction with phenylenediamine in DMF using AgOTf, to our surprise we observed the formation of benzimidazoellipticine instead of the anticipated ellipticinium derivative. This interesting observation prompted us to investigate this tandem process.



Scheme 1. Preparation of precursor **1c**.

Upon heating the mixture of compounds **1a** and **2a** in nitrobenzene at 140 °C for 48 h,[7] we were able to obtain the desired product **16** but in poor yield; The prolonged reaction time and poor yield prompted us to optimize the reaction conditions (Table 1). When the reaction was carried out in water, a complex mixture of spots was observed in TLC and the desired product was not observed. Upon heating the reactants at 150 °C without solvent, no reaction was observed and starting materials were intact. When we employed comparatively low boiling solvents like tetrahydrofuran and dioxane, we observed less conversion of starting materials with yields ranging from 25 to 40%, but when toluene was employed, we got 70% isolated yield of the product. From Table 1, we concluded that DMF is the optimal choice for this tandem cyclization. A mixture of DMF and water has resulted in a complex mixture of products with 15% yield of product being isolated.

Table 1
Optimization chart of benzimidazo[2,1-*a*]ellipticines



Run	Solvent	T°C	Time in hrs	Yield %
1	$PhNO_2$	140	24	56
2	DMSO	140	8	60
3	DMF	120	2	84
4	DMF+H_2O(1:1)	100	6	15
5	H_2O	Reflux	8	—
6	THF	Reflux	8	25
7	Dioxane	Reflux	8	40
8	Toluene	Reflux	4	70
9	Neat	150	2	—

Equimolar quantities of reactants were taken, 1 mL of solvent was employed for 0.1 mmol of compound. Isolated yields of compound.

Having optimized the conditions, we carried out the reaction with different kinds of aryldiamines like phenyl, naphthyl, pyridyl, 5-bromopyridyl etc. All seven precursors (**1a**–**g**) on reacting with various aryldiamines (**2a**–**d**) under optimized conditions, provided the corresponding benzimidazo[2,1-*a*]ellipticine derivatives in excellent yields (Table 2). Reaction with diamine **2e** has yielded no product indicating that the formation of six membered pyrimidine intermediate after the 5-*endo* cyclization may not be favoured. The electron withdrawing substituents on diamines have negatively affected the formation of products probably because of the decreased nucleophilicity of amino groups. So, we didn't observe any products in case of aryldiamines **2f** and **2g** (Table 2).

Surprisingly when diaminopyridines **2b** and **2d** were employed, we obtained exclusively one regioisomer. The regioisomer was characterized by careful observation of ^{1}H NMR spectra.

When we compared the ^{1}H NMR spectra of both phenyl and pyridyl diamines derived products, we observed that the up field aromatic proton peak around δ 6.5–6.2 in phenylenediamine cases is absent in pyridyldiamine spectra. This peak may correspond to the proton of phenylenediamine group that faces the phenyl substituent of alkynyl group. As shown in Fig. 3, probably, because of the spatial electronic clouding of phenyl group (A), the proton signal is moved to up field. The perpendicular conformation of the phenyl ring (Fig. 4) is the reason for this anisotropic effect. Where as in case of pyridyl, the regioisomer formed was the one with nitrogen facing the phenyl group (B); so the corresponding proton signal was absent. This observation was further confirmed by X-ray crystallographic analysis in case of compound **7**.

The formation of single regioisomer in case of diaminopyridines led us to draw some logical conclusions about how this tandem process may be happening (Scheme 2). In case of pyridyl, the benzimidazole intermediate **I** is the exclusive regioisomer that will form after 5-*endo* cyclization[11] and then the nitrogen lone pair attack on the triple bond results in the formation of product **II**. This observation is a clear evidence for the sequence of reactions in this tandem process; 5-*endo* cyclization, oxidative aromatization followed by 6-*endo* cyclization.

Absence of aldehydic proton peak at δ 10–11 and excess aromatic protons for corresponding diamine in ^{1}H NMR spectra indicate the formation of oxidized products. Compounds **7** and **8** were also confirmed by X-ray crystallographic analysis.[12] The ORTEP diagrams are shown in Fig. 4.

In summary, we report here an efficient, metal-free synthesis of benzimidazo[2,1-*a*]ellipticine derivatives via a tandem inter- and intramolecular cyclization; 5-*endo* cyclization, oxidative

Table 2
Benzimidazo[2,1-*a*]ellipticine derivatives

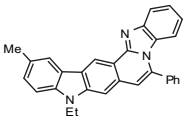
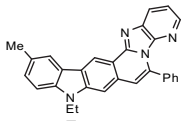
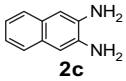
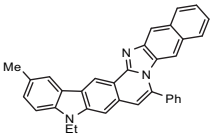
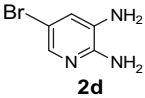
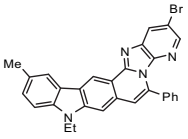
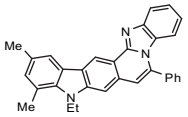
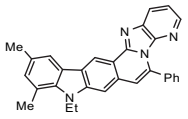
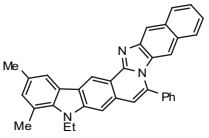
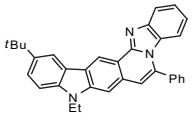
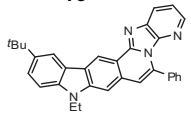
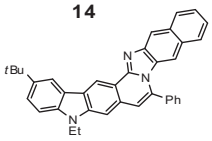
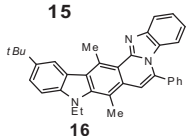
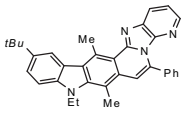
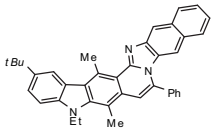
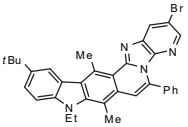
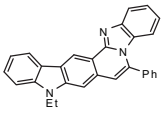
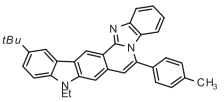
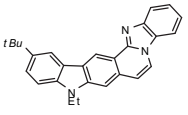
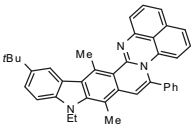
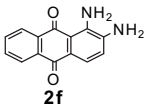
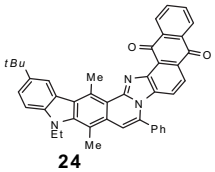
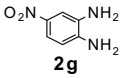
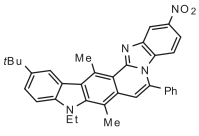
Entry	Precursor	Diamine	Yield (%)	Product
1	**1b**	 **2a**	82	 **6**
2	**1b**	 **2b**	73	 **7**
3	**1b**	 **2c**	78	 **8**
4	**1b**	 **2d**	84	 **9**
5	**1d**	**2a**	81	 **10**
6	**1d**	**2b**	74	 **11**
7	**1d**	**2c**	80	 **12**
8	**1e**	**2a**	81	 **13**
9	**1e**	**2b**	76	 **14**
10	**1e**	**2c**	78	 **15**
11	**1a**	**2a**	84	 **16**

Table 2 (*continued*)

Entry	Precursor	Diamine	Yield (%)	Product
12	**1a**	**2b**	72	 **17**
13	**1a**	**2c**	81	 **18**
14	**1a**	**2d**	85	 **19**
15	**1c**	**2a**	82	 **20**
16	**1f**	**2a**	79	 **21**
17	**1g**	**2a**	77	 **22**
18	**1a**	 **2e**	0	 **23**
19	**1a**	 **2f**	0	 **24**
20	**1a**	 **2g**	Trace	 **25**

Unless otherwise noted, all reactions were carried out in 0.5 mmol scale in 5 mL of DMF at 100 °C for 2 h. Isolated yields after column chromatography.

aromatization followed by 6-*endo* cyclization in good yields. We successfully characterized and analyzed the formation of a single regioisomer in case of diaminopyridines. DNA-binding studies of these molecules are under progress. This report may also provide an evidence for the order of reactions in this tandem process. This process is noteworthy because of its catalyst free nature and short reaction time.

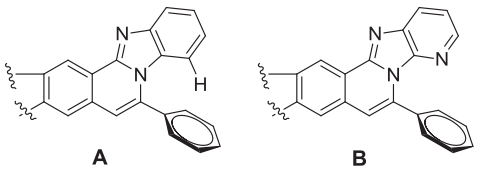


Fig. 3. Electronic interactions between the proton and phenyl ring (A). In pyridine case it is absent (B).

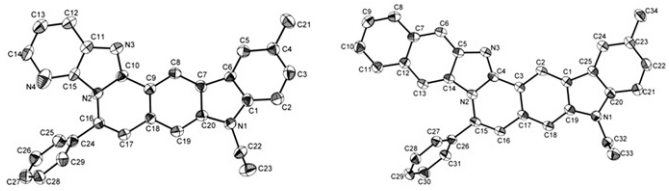
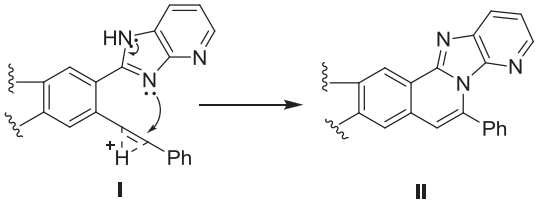


Fig. 4. ORTEP diagrams of **7** and **8**. Hydrogen atoms are omitted for clarity.



Scheme 2. Possible mechanism.

2. Experimental section

2.1. General information

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in parts per million downfield to TMS (δ=0) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ=77.0) and DMSO-d_6 (δ=39.51) for ^{13}C NMR. The coupling constants *J* are given in hertz. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112-CHN analyzer. The X-ray diffraction measurements were carried out at 298 K on an automated diffractometer using graphite monochromated, Mo Kα (λ=0.71073 Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K equipped with a graphite monochromator and a Mo Kα fine-focus sealed tube (λ=0.71073 Å). Melting points were measured in open capillary tubes and are uncorrected. All reaction solvents used are of GR grade and used without drying unless mentioned. Triethylphosphite, *N*-methylformanilide, palladium acetate, $Pd(PPh_3)_2Cl_2$, are purchased and used directly. Phenylacetylene, phosphoryl chloride, ethyl bromide and hydrazine hydrate were purchased.

*2.1.1. 2-Bromo-6-tert-butyl-9-ethyl-9H-carbazole (**4**).* An oven dried 100 mL round bottom flask equipped with a Teflon coated magnetic stirring bar is charged with 2 g (6.6 mmol) of 2-bromocarbazole, 40 mL of dichloromethane and 0.9 g (6.6 mmol) of anhydrous aluminium chloride under stirring. To it, 2 mL of *tert*-butyl chloride is added slowly and the reaction mixture is stirred at room temperature for 6 h, after which time TLC (98:02 hexane/ethyl acetate) indicated complete conversion. Reaction mass is poured into crushed ice slowly, neutralized with a solution of aq 5% sodium bicarbonate and extracted with ethyl acetate. The organic layer is washed with water and brine, dried over anhydrous sodium sulfate and solvent is removed under reduced pressure to give **4** as a white solid in 94% yield. Mp: 78–80 °C; IR (KBr): 2955, 1652, 1634, 1475, 1341, 1310, 1257, 1229, 929, 798, 642 cm^{-1}; 100% hexanes; R_f=0.32; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.12 (1H, s), 8.01 (1H, d, *J*=8.0 Hz), 7.61 (1H, *J*=8.5 Hz), 7.57 (1H, s), 7.37 (2H, d, *J*=8.5 Hz), 4.32 (2H, q, *J*=7.0 Hz), 1.50 (9H, s), 1.45 (3H, t, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 142.5, 141.1, 138.3, 124.1, 122.2, 121.7, 121.4, 120.0, 116.5, 111.5, 108.2, 105.0 (aromatic C), 37.7, 34.7, 32.0, 13.8 (aliphatic C); *m*/*z*=331, 333 (M+2), positive mode; Anal. Calcd for $C_{18}H_{20}BrN$: C, 65.46; H, 6.10; N, 4.24%; found: C, 65.36; H, 6.21; N, 4.32%.

*2.1.2. 2-Bromo-6-tert-butyl-9-ethyl-9H-carbazole-3-carbaldehyde (**5**).* An oven dried 50 mL round bottom flask equipped with a Teflon coated magnetic stirring bar is charged with 2 g (0.006 mol) of 6-*tert*-butyl-2-bromo-9-ethylcarbazole and 15 mL of dimethylformamide under stirring and cooled to 0 °C. 2 mL (0.021 mol) of phosphoryl chloride is added dropwise for 5 min. Reaction is allowed to room temperature and heated at 70 °C for 5 h, after which time TLC (95:5 hexane/ethyl acetate) indicated complete conversion. Reaction is allowed to room temperature and quenched with ice. The reaction mass is poured into crushed ice slowly, neutralized with 5% aq sodium hydroxide and extracted with ethyl acetate. The organic layer is washed with water and brine, dried over anhydrous sodium sulfate and solvent is removed under reduced pressure; purified by column chromatography (96:4 hexane/ethyl acetate) to give **5** as a white solid in 72% yield. Mp: 150–152 °C; IR (KBr): 2951, 2858, 1672, 1628, 1483, 1344, 1300, 1255, 1236, 926, 833, 800, 638 cm^{-1}; hexane/EtOAc (4:1); R_f=0.34; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 10.45 (1H, s), 8.72 (1H, s), 8.16 (1H, d, *J*=3.0 Hz), 7.64 (1H, dd, *J*=8.5, 3.0 Hz), 7.56 (1H, s), 7.38 (1H, d, *J*=8.5 Hz), 4.31 (2H, q, *J*=7 Hz), 1.47 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 191.8, 144.2, 144.1, 139.0, 125.2, 124.7, 123.9, 123.1, 122.7, 122.5, 117.3, 112.6, 108.8 (aromatic C), 38.1, 34.8, 31.9, 13.8 (aliphatic C); *m*/*z*=359, 361 (M+2), positive mode; Anal. Calcd for $C_{19}H_{20}BrNO$: C, 63.70; H, 5.63; N, 3.91%; found: C, 63.85; H, 5.68; N, 3.85%.

*2.1.3. 6-tert-Butyl-9-ethyl-2-(phenylethynyl)-9H-carbazole-3-carbaldehyde (**1e**).* An oven dried 50 mL Schlenk tube equipped with a Teflon coated magnetic stirring bar is charged with 1 g (3 mmol) of **5**, 1 g of molecular sieves and 0.42 mL (3.8 mmol) of phenylacetylene. The tube is evacuated and filled with nitrogen. To it, 10 mL of dry THF and 5 mL of freshly distilled triethylamine are added under nitrogen and the reaction is stirred for 10 min at room temperature. $Pd(PPh_3)_2Cl_2$ (42 mg, 2 mol %) and 6 mg of CuI (1 mol %) are added under nitrogen and the Schlenk tube is heated at 60 °C for 4 h, after which time TLC (85:15 hexane/ethyl acetate) indicated complete conversion. Reaction is allowed to room temperature and filtered. The filtrate is poured into crushed ice slowly and extracted with ethyl acetate. The organic layer is washed with water and brine, dried over anhydrous sodium sulfate and solvent is removed under reduced pressure. Crude material is purified by column chromatography (eluent: 8–15% ethyl acetate in hexane). The product is eluted in 12% eluent as a pale yellow solid. Yield: 85%. Mp: 104–106 °C; IR (KBr): 3061, 2961, 1668, 1626, 1587, 1485, 1367, 1304, 848, 794, 686 cm^{-1}; hexane/EtOAc (4:1); R_f=0.42; ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 10.74 (1H, s), 8.77 (1H, s), 8.18 (1H, s), 7.59–7.62 (4H, m), 7.39 (4H, m), 4.37 (2H, s), 1.46 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 191.5, 143.9, 143.0, 139.6, 131.6, 128.8, 128.5, 127.8, 125.3, 123.7, 123.6, 123.0, 122.8, 120.6, 117.4, 112.4, 108.7 (aromatic C), 95.1, 86.7 (alkyne C), 38.0, 34.8, 31.9, 13.9 (aliphatic C); *m*/*z*=380, positive mode; Anal. Calcd for $C_{27}H_{25}NO$: C, 85.45; H, 6.64; N, 3.69%; found: C, 85.31; H, 6.58; N, 3.75%.

2.2. General procedure for the preparation of benzimidazo [2,1-*a*]ellipticine derivatives

An oven dried 10 mL round bottom flask equipped with a Teflon coated magnetic stirring bar is charged with 0.5 mmol of 3-formyl-

2-phenylethynylcarbazole (**1a**–**g**), 1,2-aryldiamine (0.5 mmol) (**2a**–**2f**) and 5 mL of dimethylformamide. The reaction mixture was heated at 120 °C for 2 h under stirring until complete consumption of starting material as monitored by TLC. After the reaction was completed, the reaction mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, and evaporated in vacuum. The residue was adsorbed on silica gel and purified by column chromatography using silica gel (94:6 hexane/ethyl acetate) to afford the desired product.

*2.2.1. Compound (**6**).* Mp: 198–200 °C; IR (KBr): 1635, 1610, 1529, 1467, 1302, 1230, 734, 700 cm^{-1}; hexane/EtOAc (4:1); R_f=0.40; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 9.62 (1H, s), 8.12 (1H, s), 8.04 (1H, s), 7.34–7.64 (5H, s), 7.32–7.34 (4H, m), 6.52 (2H, s), 6.50 (1H, s), 4.41 (2H, s), 2.62 (3H, s), 1.48 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ: 149.7, 144.3, 141.9, 139.9, 136.3, 135.0, 131.0, 130.0, 129.7, 129.5, 129.2, 129.0, 128.3, 124.6, 123.8, 123.1, 121.4, 120.6, 119.1, 117.4, 115.2, 113.8, 113.4, 108.3, 103.8 (aromatic C), 37.8, 21.5, 13.6 (aliphatic C); m/z=426, positive mode; Anal. Calcd for $C_{30}H_{23}N_3$: C, 84.68; H, 5.45; N, 9.87%; found: C, 84.51; H, 5.41; N, 9.93%.

*2.2.2. Compound (**7**).* Mp: 197–199 °C; IR (KBr): 1628, 1610, 1529, 1467, 1230, 1014, 869, 792, 734, 700, 576 cm^{-1}; hexane/EtOAc (4:1); R_f=0.43; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 9.61 (1H, s), 8.25 (1H, d, J=8.0 Hz), 8.19 (1H, d, J=3.6 Hz), 8.14 (1H, s), 7.74 (2H, d, J=6.0 Hz), 7.56–7.62 (4H, m), 7.35–7.41 (3H, m), 7.12 (1H, s), 4.60 (2H, q, J=8.0 Hz), 2.61 (3H, s), 1.51 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 150.3, 145.0, 142.3, 141.5, 140.0, 136.4, 136.3, 134.7, 130.6, 129.7, 129.4, 129.0, 128.5, 127.7, 126.0, 124.8, 123.0, 121.5, 119.7, 117.2, 115.2, 114.9, 108.4, 104.1 (aromatic C), 37.9, 21.5, 13.6 (aliphatic C); m/z=427, positive mode; Anal. Calcd for $C_{29}H_{22}N_4$: C, 81.66; H, 5.20; N, 13.14%; found: C, 81.52; H, 5.23; N, 13.07%.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.076.

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12. (a) The CCDC deposition number of **7** is 814066; Molecular formula: $C_{29}H_{22}N_4$, unit cell parameters: a 9.3186(15) b 18.272(2) c 13.1361(18) beta 99.788(12) space group $P21/n$. (b) The CCDC deposition number of **8** is 814065; molecular formula: $C_{34}H_{27}N_3O_1$, unit cell parameters: a 18.3228(9) c 26.723(3) gamma 120.00 space group P-3c1.