

A Simple One-Pot Reaction to the Bis-dibenzo[*b,f*][1,5]diazocines: Useful Precursors of Novel Macrocycles

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Abstract: The title compounds, namely 8,8'-bis-5,6,11,12-tetrahydrodibenzo[*b,f*][1,5]diazocines, have been synthesized in 36–81% yields through a one-pot reaction by treatment of *N,N,N',N'*-tetramethylbiphenyldiamine with the Vilsmeier's reagents derived from substituted *N*-methylformanilides and POCl₃. This was another application of 't-amino effect' in the synthesis of eight-membered ring systems. These products are designed as the precursors of novel macrocycles.

Key words: 8,8'-bis-5,6,11,12-tetrahydrodibenzo[*b,f*][1,5]diazocines, *N,N,N',N'*-tetramethylbiphenyldiamine, *N*-methylformanilides, Vilsmeier's reagent, 't-amino effect'

Several years ago, we established a simple one-pot reaction for the synthesis of 5,6,11,12-tetrahydrodibenzo[*b,f*][1,5]diazocines **4** by treatment of 4-substituted *N,N*-dimethylanilines **3** with the Vilsmeier's reagents that were derived from the *N*-methylformanilides **1** with phosphorus oxychloride or oxalyl chloride^{1,2} (Scheme 1). This methodology was then extended to the synthesis of benzo[2,3]pyrido [6,7-*b*][1,5] diazocine **5**.³ It was reported⁴ that the tetrahydrodibenzo[*b,f*][1,5]diazocines preferred a boat conformation, and consequently we envisaged that larger assemblies of linear fused analogues could be of interest in the synthesis of novel macrocycles such as 'molecular bracelets'. With this aim in mind, we have synthesized the tetracyclic heterocycles, benzo[*b*]naph-

tha[1,2-*f*][1,5]diazocines **6** or benzo[*b*]naphtha[2,1-*f*][1,5]diazocines **7**,⁵ and pentacyclic heterocycles, dibenzo[*b,b'*]benzo[1,2-*f*:4,5-*f'*]bis[1,5]diazocines **8**⁶ (Figure 1). Herein we report our new synthetic approach to the novel heterocycles, bis-dibenzo[*b,f*][1,5]diazocines **9**, which could be the better candidates for macrocycles due to their flexible ring system, as the intramolecular or intermolecular coupling of compound **9** (X = Br) would lead to the formations of bracelets such as **10** with different sizes (Figure 2).

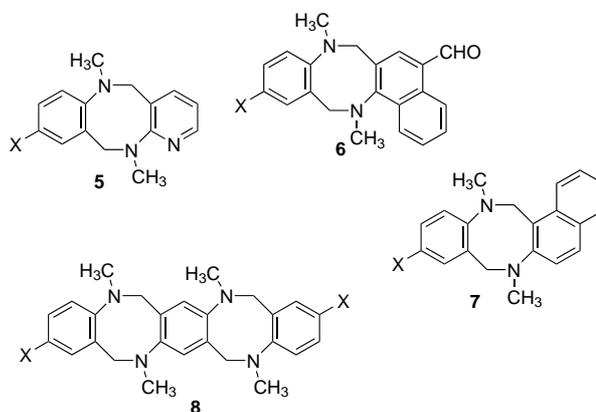
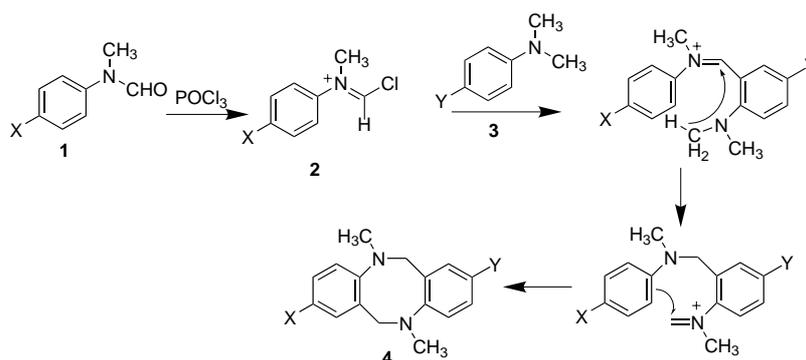


Figure 1



Scheme 1

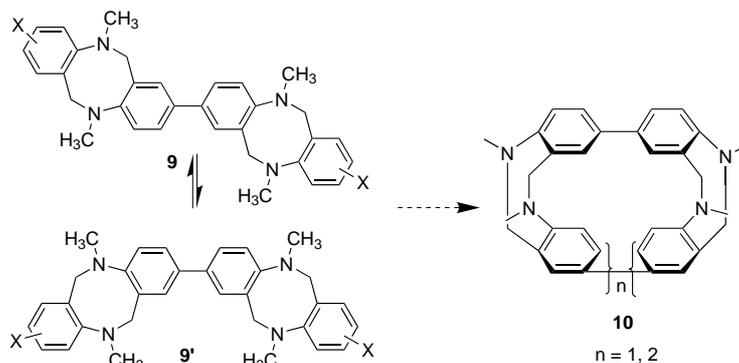


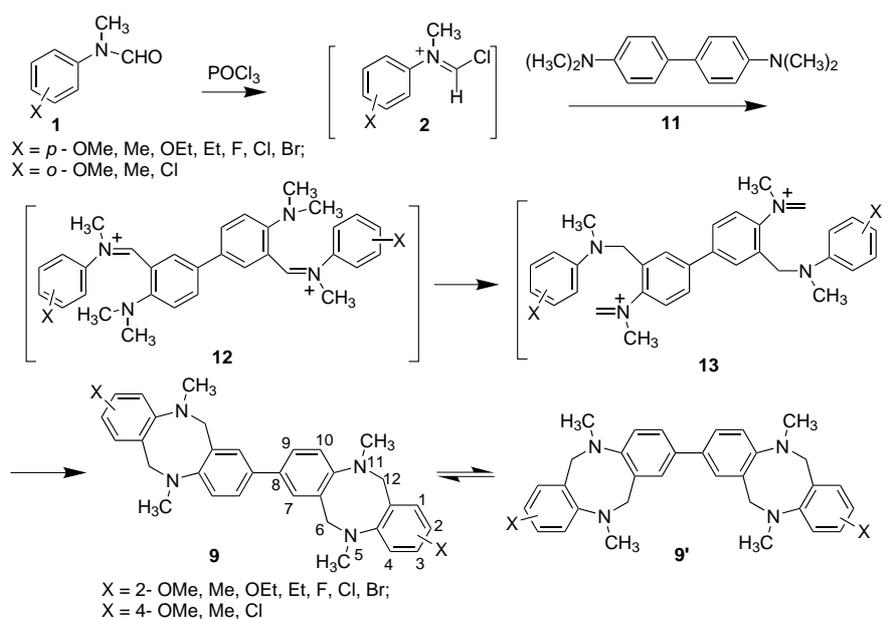
Figure 2

One of the starting materials, *N,N,N',N'*-tetramethylbiphenyldiamine **11**, was prepared from methylation of biphenyl diamine with trimethyl phosphate and followed by alkaline hydrolysis. The expected product precipitated in high yield from the basic aqueous solution. However, an attempted purification of crude products using silica gel column chromatography resulted in a great loss of chemical yield, because the basic tetramethylbiphenyldiamine could not be totally eluted out from the column even via using a huge amount of solvent. Fortunately, the TLC analysis indicated that the crude products were of almost identical composition. Therefore, tetramethylbiphenyldiamine was used in the next step reaction without further purification.

To synthesize the bis-dibenzodiazocines **9**, we initially prepared the Vilsmeier's reagent by treatment of the methylformanilide **1** with oxalyl chloride, and then allowed it to react with diamine in CHCl_3 solution. After refluxing for a period of time, the reaction mixture was basified and worked-up. Under these reaction conditions, however, the product **9** was obtained in only very low yield along with

a large amount of starting materials. We then tried the reaction using phosphorus oxychloride (POCl_3) both as the reactant and the solvent.

While heating in POCl_3 at 75–80 °C, the *N*-methylformanilides **1** were readily converted into the Vilsmeier's reagents **2**, which underwent a smooth reaction with the *N,N,N',N'*-tetramethylbiphenyldiamine (**11**) in POCl_3 at 80 °C for 15–16 hours to give the desired products **9** in 36–81% isolated yields (Table 1). It should be noted that the purification of the crude products with column chromatography proved inefficient, because the products precipitated from the silica gel. The pure products (in powder form) were finally obtained by dissolving the precipitate in CHCl_3 and precipitating again with EtOH. The mechanism of the formation of compounds **9** is similar to that of **4**. The biphenyldiamine **11** was double-formylated by the Vilsmeier's reagent to form a bis-iminium salt **12**, which transformed into the intermediate **13** through the hydride migration via the '*t*-amino effect' rearrangement.⁷ The intramolecular cyclization of **13** led to the formation of bis-dibenzodiazocines **9** (Scheme 2).



Scheme 2

Table 1 The Isolated Yields of Products **9**

1	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j
X	<i>p</i> -MeO	<i>p</i> -Me	<i>p</i> -EtO	<i>p</i> -Et	<i>p</i> -F	<i>p</i> -Cl	<i>p</i> -Br	<i>o</i> -MeO	<i>o</i> -Me	<i>o</i> -Cl
9	9a	9b	9c	9d	9e	9f	9g	9h	9i	9j
X	2-MeO	2-Me	2-EtO	2-Et	2-F	2-Cl	2-Br	4-MeO	4-Me	4-Cl
Yield (%)	65	42	39	38	53	81	79	36	69	53

The structure of products **9** was assigned on the basis of IR, ^1H NMR, ^{13}C NMR and MS spectroscopic data. A characteristic of the compounds **9** in ^1H NMR spectrum is that the methylene protons of the diazocine ring appeared as very broad peaks around 4.5 ppm at 25 °C, which indicated a slow conformational flexion of the eight-membered ring. These broad peaks sharpened to a singlet while the probe temperature was increased to 40 °C. Some products, especially the compound **9e**, did not give all quaternary carbon signals in the ^{13}C NMR spectra due to their very low solubility in CHCl_3 . All of these products **9** are insoluble in water and almost insoluble in most organic solvents such as EtOAc, acetone, EtOH and DMSO. They are only slightly soluble in CHCl_3 and form a yellow solution. The alkyl or alkoxy substituted products show the better solubility in CHCl_3 as compared to their halogen substituted analogs, and the 4-substituted one is more soluble than its 2-substituted analogs. Since the products were isolated through precipitation from EtOH, their isolated yields not only depended on the electronic and steric effects of substituents, but also on their solubility in EtOH. Although those powdery products have been purified by dissolving in CHCl_3 and then precipitating with EtOH for several times, they still did not give satisfactory elemental analysis. It should also be pointed out that the compounds **9** always gave a middle to strong absorption band around 3430 cm^{-1} in their IR spectra. This absorption became weaker but did not disappear totally, even after heating for long under vacuum indicating a strong complexation with water molecules. The composition of compounds **9** was finally confirmed by HRMS.

In conclusion, we have provided a very simple and one-pot reaction for the synthesis of novel heterocycles, 8,8'-bis-5,6,11,12-tetrahydrodibenzo[*b,f*][1,5]diazocines, generally in good yields. We envisage that the intramolecular or intermolecular coupling within one or two molecules of these new heterocycles would lead to the construction of novel supramolecular systems, and this study is under progress.

Melting points are uncorrected. ^1H NMR and ^{13}C NMR were obtained on a Bruker Avance 500 spectrometer. IR spectra were recorded using an AVATAR 360 FT-IR spectrometer. Mass spectra were recorded on a Trace MS instrument (EI-MS) or Bruker APEX-2 (HRMS). The two starting materials, *p*-substituted *N*-methylformanilide⁸ and *N,N,N',N'*-tetramethylbiphenyldiamine,⁹ were prepared according to the literature methods.

8,8'-Bis-5,6,11,12-tetrahydrodibenzo[*b,f*][1,5]diazocines **9**:

General Procedure

Under a N_2 atmosphere, the mixture of substituted *N*-methylformanilide **1** (10 mmol) in POCl_3 (10 mL) was heated at 75–80 °C for 30 min to form a red solution. The powder of *N,N,N',N'*-tetramethylbiphenyldiamine (**11**) was added portionwise to the red solution of the Vilsmeier's reagent in POCl_3 after it cooled to r.t. The mixture was then heated at 80 °C for about 16 h and then quenched to ice-cold water (100 mL). The aq solution was basified to pH 9 with 10% NaOH and extracted efficiently with a large amount of CHCl_3 ($5 \times 100\text{ mL}$). After drying over MgSO_4 and removal of the solvent, the crude product was precipitated by refluxing the residue in EtOH. The crude products were further purified by dissolving in CHCl_3 , filtering off the insoluble materials and precipitating again with EtOH.

8,8'-Bis-5,11-dimethyl-5,6,11,12-tetrahydro-2-methoxydibenzo[*b,f*][1,5]diazocine (**9a**)

Yield: 65%; mp 241–242 °C.

IR (KBr): 1608, 1504 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.57 (d, J = 6.4 Hz, 1 H), 7.50 (s, 1 H), 7.10 (br s, 2 H), 6.94 (d, J = 7.1 Hz, 1 H), 6.90 (s, 1 H), 4.52 (s, 2 H), 4.46 (s, 2 H), 3.95 (s, 3 H), 3.07 (s, 3 H), 3.00 (s, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 152.5, 149.8, 145.5, 131.3, 129.9, 129.4, 126.8, 126.2, 117.7, 117.6, 116.1, 113.2, 59.0, 58.7, 56.2, 40.0, 39.7.

MS (EI): m/z (%) = 162 (35), 503 (37), 534 (100) [M^+], 535 (35).

HRMS (FT-MS): m/z calcd for $\text{C}_{34}\text{H}_{38}\text{N}_4\text{O}_2$: 534.2989; found: 534.2992.

8,8'-Bis-5,6,11,12-tetrahydro-2,5,11-trimethyldibenzo[*b,f*][1,5]diazocine (**9b**)

Yield: 42%; mp 264–265 °C.

IR (KBr): 1610, 1509 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.45 (dd, J = 8.3, 2.0 Hz, 1 H), 7.37 (s, 1 H), 7.05 (d, J = 7.9 Hz, 1 H), 6.98 (s, 1 H), 6.95 (d, J = 8.3 Hz, 1 H), 6.84 (d, J = 8.1 Hz, 1 H), 4.38 (s, 2 H), 4.34 (s, 2 H), 2.91 (s, 3 H), 2.87 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 149.8, 149.0, 132.4, 131.2, 129.9, 128.9, 127.9, 127.5, 126.2, 116.2, 116.1, 59.3, 59.0, 39.6, 39.5, 20.6.

MS (EI): m/z (%) = 146 (55), 471 (47), 502(100) [M^+], 503 (45).

HRMS (FT-MS): m/z calcd for $\text{C}_{34}\text{H}_{38}\text{N}_4$: 502.3091; found: 502.3092.

8,8'-Bis-5,11-dimethyl-5,6,11,12-tetrahydro-2-ethoxydibenzo[*b,f*][1,5]diazocine (**9c**)

Yield: 39%; mp 257–259 °C.

IR (KBr): 1608, 1504 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.44 (dd, J = 8.3, 1.8 Hz, 1 H), 7.36 (s, 1 H), 6.96 (d, J = 8.3 Hz, 1 H), 6.88 (d, J = 8.5 Hz, 1 H),

6.81 (dd, $J = 8.6, 2.6$ Hz, 1 H), 6.78 (d, $J = 2.4$ Hz, 1 H), 4.36 (s, 2 H), 4.31 (s, 2 H), 4.05 (q, $J = 7.0$ Hz, 2 H), 2.92 (s, 3 H), 2.84 (s, 3 H), 1.43 (t, $J = 7.0$ Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 152.1, 149.9, 145.6, 131.5, 129.9, 129.5, 128.3, 126.1, 118.6, 117.8, 116.4, 114.2, 64.5, 59.5, 59.1, 40.1, 39.6, 15.4$.

MS (EI): m/z (%) = 531 (45), 562 (100) [M^+], 563 (40).

HRMS (FT-MS): m/z calcd for $\text{C}_{36}\text{H}_{42}\text{N}_4\text{O}_2$: 562.3302; found: 562.3271.

8,8'-Bis-5,11-dimethyl-5,6,11,12-tetrahydro-2-ethylidibenzo- $[b,f]$ [1,5]diazocine (9d)

Yield: 38%; mp 273–274 °C.

IR (KBr): 1610, 1509 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 7.45$ (dd, $J = 8.3, 2.0$ Hz, 1 H), 7.37 (d, $J = 1.7$ Hz, 1 H), 7.07 (d, $J = 8.1$ Hz, 1 H), 7.00 (s, 1 H), 6.95 (d, $J = 8.3$ Hz, 1 H), 6.86 (d, $J = 8.1$ Hz, 1 H), 4.39 (s, 2 H), 4.36 (s, 2 H), 2.91 (s, 3 H), 2.88 (s, 3 H), 2.63 (q, $J = 7.6$ Hz, 2 H), 1.28 (t, $J = 7.6$ Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 149.7, 149.1, 137.0, 134.1, 131.2, 129.8, 127.8, 127.6, 127.4, 126.2, 116.1, 116.0, 59.3, 59.1, 39.5, 39.0, 28.2, 16.0$.

MS (EI): m/z (%) = 160 (25), 234 (26), 499 (35), 530 (100) [M^+], 531 (35).

HRMS (FT-MS): m/z calcd for $\text{C}_{36}\text{H}_{42}\text{N}_4$: 530.3404; found: 530.3398.

8,8'-Bis-5,11-dimethyl-5,6,11,12-tetrahydro-2-fluorodibenzo- $[b,f]$ [1,5]diazocine (9e)

Yield: 53%, mp 274–276 °C.

IR (KBr): 1608, 1505 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 7.57$ (br s, 1 H), 7.49 (s, 1 H), 7.10 (d, $J = 6.6$ Hz, 1 H), 7.02–7.04 (m, 3 H), 4.50 (s, 2 H), 4.45 (s, 2 H), 3.05 (s, 3 H), 2.99 (s, 3 H).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 131.3, 129.9, 127.6, 126.3, 118.1, 117.9, 116.8, 116.1, 114.6, 114.4, 59.2, 58.7, 39.9, 39.6$.

MS (EI): m/z (%) = 150 (40), 479 (35), 510 (100) [M^+], 511 (30).

HRMS (FT-MS): m/z calcd for $\text{C}_{32}\text{H}_{32}\text{N}_4\text{F}_2$: 510.2589; found: 510.2577.

8,8'-Bis-5,11-dimethyl-5,6,11,12-tetrahydro-2-chlorodibenzo- $[b,f]$ [1,5]diazocine (9f)

Yield: 81%; mp 279–281 °C.

IR (KBr): 1608, 1500 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 7.57$ (d, $J = 7.9$ Hz, 1 H), 7.48 (s, 1 H), 7.29 (d, $J = 8.2$ Hz, 1 H), 7.26 (s, 1 H), 7.10 (d, $J = 8.0$ Hz, 1 H), 6.96 (d, $J = 8.4$ Hz, 1 H), 4.51 (s, 2 H), 4.46 (s, 2 H), 3.03 (s, 3 H), 3.00 (s, 3 H).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 149.4, 131.4, 131.3, 130.0, 128.5, 128.2, 128.2, 127.0, 126.4, 122.6, 116.6, 116.1, 58.9, 58.5, 39.6, 39.5$.

MS (EI): m/z (%) = 166 (40), 511 (35), 542 (100) [M^+], 544 (65), 546 (18).

HRMS (FT-MS): m/z calcd for $\text{C}_{32}\text{H}_{32}\text{N}_4\text{Cl}_2$: 542.1998; found: 542.1986.

8,8'-Bis-5,11-dimethyl-5,6,11,12-tetrahydro-2-bromodibenzo- $[b,f]$ [1,5]diazocine (9g)

Yield: 79%; mp 286–288 °C.

IR (KBr): 1607, 1589, 1499 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 7.45$ (dd, $J = 8.2, 1.5$ Hz, 1 H), 7.35 (s, 1 H), 7.27–7.32 (m, 2 H), 6.96 (d, $J = 8.3$ Hz, 1 H), 6.77 (d, $J = 8.6$ Hz, 1 H), 4.38 (s, 2 H), 4.33 (s, 2 H), 2.90 (s, 3 H), 2.87 (s, 3 H).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 149.9, 149.4, 134.2, 131.4, 129.9, 129.1, 127.1, 126.5, 117.3, 116.4, 110.1, 58.9, 58.5, 39.5, 39.4$.

MS (EI): m/z (%) = 131 (40), 601 (35), 630 (55) [M^+], 632 (100), 634 (50).

HRMS (FT-MS): m/z calcd for $\text{C}_{32}\text{H}_{33}\text{N}_4\text{Br}_2$: 631.1066; found: 631.1059.

8,8'-Bis-5,11-dimethyl-5,6,11,12-tetrahydro-4-methoxydibenzo- $[b,f]$ [1,5]diazocine (9h)

Yield: 36%; mp 262–264 °C.

IR (KBr): 1607, 1498 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 7.46$ (d, $J = 8.1$ Hz, 1 H), 7.40 (s, 1 H), 6.93 (d, $J = 7.6$ Hz, 2 H), 6.88 (d, $J = 7.8$ Hz, 1 H), 6.84 (d, $J = 7.1$ Hz, 1 H), 4.55 (s, 2 H), 4.27 (s, 2 H), 3.92 (s, 3 H), 2.92 (s, 3 H), 2.61 (s, 3 H).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 154.5, 148.9, 140.7, 134.1, 131.7, 130.7, 126.9, 126.2, 123.5, 121.8, 115.0, 111.9, 58.9, 58.6, 56.2, 39.0, 38.7$.

MS (EI): m/z (%) = 162 (35), 503 (30), 534 (100) [M^+], 535 (35).

HRMS (FT-MS): m/z calcd for $\text{C}_{34}\text{H}_{38}\text{N}_4\text{O}_2$: 534.2989; found: 534.2990.

8,8'-Bis-5,6,11,12-tetrahydro-4,5,11-trimethyldibenzo- $[b,f]$ -[1,5]diazocine (9i)

Yield: 69%; mp 220–222 °C.

IR (KBr): 1607, 1499, 1477 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 7.45$ (dd, $J = 8.3, 1.9$ Hz, 1 H), 7.41 (s, 1 H), 7.16 (d, $J = 7.3$ Hz, 1 H), 7.05 (br s, 1 H), 6.92–6.97 (m, 2 H), 4.54 (s, 2 H), 4.26 (s, 2 H), 2.96 (s, 3 H), 2.54 (s, 3 H), 2.39 (s, 3 H).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 150.6, 149.1, 134.5, 131.0, 130.5, 130.1, 129.0, 128.5, 126.1, 122.2, 114.9, 113.4, 58.9, 58.6, 39.2, 39.1, 19.5$.

MS (EI): m/z (%) = 146 (37), 502 (100) [M^+], 503 (35).

HRMS (FT-MS): m/z calcd for $\text{C}_{34}\text{H}_{38}\text{N}_4$: 502.3091; found: 502.3088.

8,8'-Bis-5,11-dimethyl-5,6,11,12-tetrahydro-4-chlorodibenzo- $[b,f]$ [1,5]diazocine (9j)

Yield: 53%; mp 199–201 °C.

IR (KBr): 1609, 1497 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 7.47$ (dd, $J = 8.2, 2.0$ Hz, 1 H), 7.42 (s, 1 H), 7.36 (d, $J = 7.9$ Hz, 1 H), 7.10 (d, $J = 7.6$ Hz, 1 H), 6.90–6.97 (m, 2 H), 4.53 (s, 2 H), 4.25 (s, 2 H), 2.93 (s, 3 H), 2.64 (s, 3 H).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 148.5, 143.1, 135.9, 131.3, 130.3, 129.7, 126.3, 122.7, 120.3, 115.3, 112.2, 58.8, 58.3, 39.1, 39.0$.

MS (EI): m/z (%) = 166 (40), 542 (100) [M^+], 544 (75), 546 (20).

HRMS (FT-MS): m/z calcd for $\text{C}_{32}\text{H}_{32}\text{N}_4\text{Cl}_2$: 542.1998; found: 542.1988.

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