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# EFFICIENT AND GREEN METHOD FOR THE SYNTHESIS OF HIGHLY SUBSTITUTED CYCLOHEXADIENE DERIVATIVES IN AQUEOUS MEDIA

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***Three-component reaction of aromatic aldehyde, malononitrile, and 2-(1-(3-chlorophenyl)propylidene)malononitrile in aqueous media catalyzed by tetraethylbenzylammonium chloride (TEBAC) at 90°C gave 2-amino-6-(3-chlorophenyl)-5-methyl-4-arylcyclohexa-1,5-diene-1,3,3-tricarbonitrile derivatives. The structure of* 4e *was further confirmed by x-ray diffraction. This three-component reaction had the advantages of green solvent, good yield, and operational simplicity.***

***Keywords***: Aqueous media; cyclohexadiene; malononitrile; TEBAC

## INTRODUCTION

Multicomponent reactions (MCRs), defined as one-pot reactions in which at least three functional groups join through covalent bonds, have been steadily gaining importance in synthetic organic chemistry.[1] The reagents employed may be different molecules or different functional groups of the same reagent. Speed, diversity, efficiency, and environmental friendliness are some of the key features of this class of reactions. Up to seven starting components have been used, and MCRs have often produced better yields than classical chemistry.[2] They provide a powerful tool for the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles.[3]

The organic reactions in water without harmful organic solvents have been a current focus, especially in the ecologically conscious environment of today, since Breslow and Rideout,[4] who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic chemistry in 1980s. Water has recently attracted considerable interest as a solvent for a large number of organic transformations[5] because it is abundant, nontoxic, and environmentally friendly. As part of our ongoing program to

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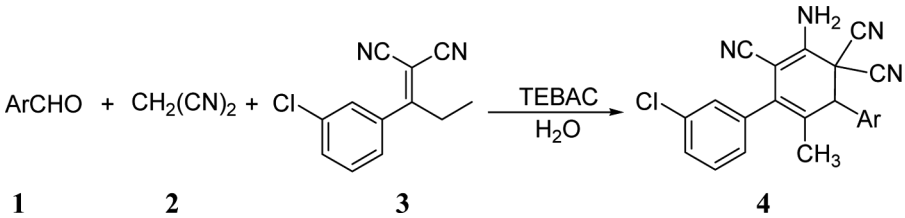
synthesize organic compounds in an environmentally friendly media,[6] herein we report a green synthesis of a series of 2-amino-6-(3-chlorophenyl)-5-methyl-4-arylcyclohexa-1,5-diene-1,3,3-tricarbonitrile derivatives in aqueous media catalyzed by tetraethylbenzylammonium chloride (TEBAC).

## RESULTS AND DISCUSSION

The treatment of aromatic aldehyde **1**, malononitrile **2**, and 2-(1-(3-chlorophenyl)propylidene)malononitrile **3** in water in the presence of 10 mol% TEBAC at 90 °C afforded 2-amino-6-(3-chlorophenyl)-5-methyl-4-arylcyclohexa-1,5-diene-1,3,3-tricarbonitrile derivatives **4** in good yields (Scheme 1).

Subsequently, the reaction of 3-bromobenzaldehyde, malononitrile, and 2-(1-(3-chlorophenyl)propylidene)malononitrile was used as a model reaction to optimize the conditions. The reaction was first carried out in water in the absence of TEBAC. No reaction took place at room temperature (Table 1, entry 1), and only a trace of **4a** was observed by thin-layer chromatography (TLC) when the reaction temperature was raised to 90 °C (Table 1, entry 2). Similar reactions were then attempted in the presence of TEBAC with 1, 5, 10, and 20 mol% (Table 1, entries 5–8); just 10 mol% TEBAC at 90 °C in water gave the best yield. More catalyst did not improve the yield. To find the optimum reaction temperature, the reaction




**Scheme 1.** The reaction of aromatic aldehyde, malononitrile, and **3** in water.

**Table 1.** Synthesis of **4a** in water under different reaction conditions[a]

| Entry | Temp. (°C) | Cat. (mol%) | Catalyst | Yield[b] (%) |
|---|---|---|---|---|
| 1 | rt | 0 | — | 0 |
| 2 | 90 | 0 | — | Trace |
| 3 | rt | 10 | TEBAC | Trace |
| 4 | 50 | 10 | TEBAC | 72 |
| 5 | 90 | 10 | TEBAC | 88 |
| 6 | 90 | 20 | TEBAC | 85 |
| 7 | 90 | 5 | TEBAC | 82 |
| 8 | 90 | 1 | TEBAC | 78 |
| 9 | 90 | 10 | $CH_3(CH_2)_{15}NMe_3Br$ | 83 |
| 10 | 90 | 10 | $CH_3(CH_2)_{11}SO_3Na$ | 82 |

[a]Reagents and conditions: **1** (0.370 g, 2 mmol), malononitrile **2** (0.145 g, 2.2 mmol), **3** (0.432 g, 2 mmol), TEBAC (0.091 g, 0.2 mmol), $H_2O$ (10 mL).
[b]Isolated yields.

**Table 2.** Reactions of aromatic aldehyde, malononitrile, and 2-(1-(3-chlorophenyl)propylidene)malononitrile in water[a]

| Entry | Ar | Products | Time (h) | Yields (%)[b] |
|---|---|---|---|---|
| 1 | 3-$BrC_6H_4$ | **4a** | 12 | 88 |
| 2 | 4-$NO_2C_6H_4$ | **4b** | 10 | 90 |
| 3 | 4-$CH_3OC_6H_4$ | **4c** | 18 | 83 |
| 4 | 3,4-$(CH_3O)_2C_6H_3$ | **4d** | 20 | 84 |
| 5 | 2-$ClC_6H_4$ | **4e** | 14 | 87 |
| 6 | 4-$CH_3C_6H_4$ | **4f** | 16 | 85 |
| 7 | 3-$ClC_6H_4$ | **4g** | 14 | 85 |
| 8 | 3,4-$Cl_2C_6H_3$ | **4h** | 16 | 83 |
| 9 | 4-$ClC_6H_4$ | **4i** | 15 | 84 |
| 10 | 4-$BrC_6H_4$ | **4j** | 17 | 82 |
| 11 | 2,4-$Cl_2C_6H_3$ | **4k** | 14 | 80 |
| 12 | 3,4-$(CH_3)_2C_6H_3$ | **4l** | 18 | 87 |

[a]Reagents and conditions: **1** (2 mmol), malononitrile **2** (0.145 g, 2.2 mmol), **3** (0.432 g, 2 mmol), TEBAC (0.091 g, 0.2 mmol), and $H_2O$ (10 mL).
[b]Isolated yields.

was carried out in the presence of TEBAC with 10 mol% at room temperature, 50, and 90 °C, resulting in the isolation of **4a** in trace, 72%, and 88% yield (Table 1, entries 3–5), respectively. Thus, 10 mol% TEBAC and a reaction temperature of 90 °C were chosen. In addition, $CH_3(CH_2)_{15}NMe_3Br$ and $CH_3(CH_2)_{11}SO_3Na$ (Table 1, entries 9 and 10) were also tested as catalysts. In these cases, product **4a** was formed in slightly lower yields. The TEBAC catalyst could be reused for the synthesis of **4a** without significant loss of activity; even in the fourth round, **4a** could be obtained in good yield (82%).

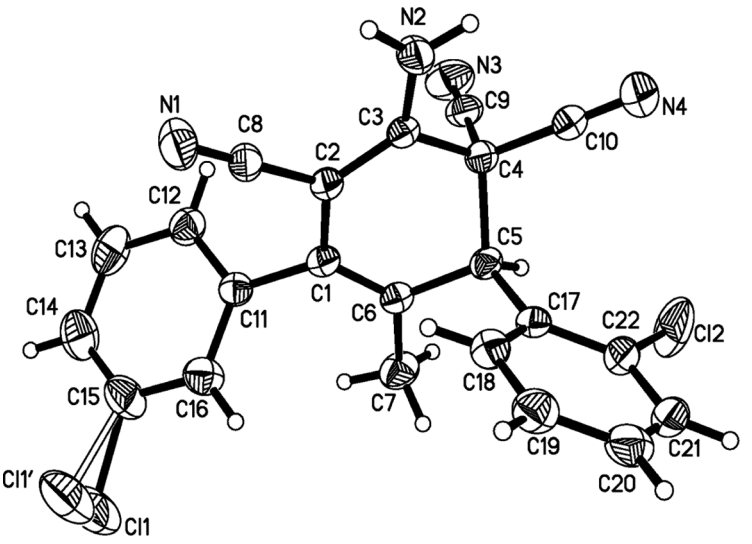
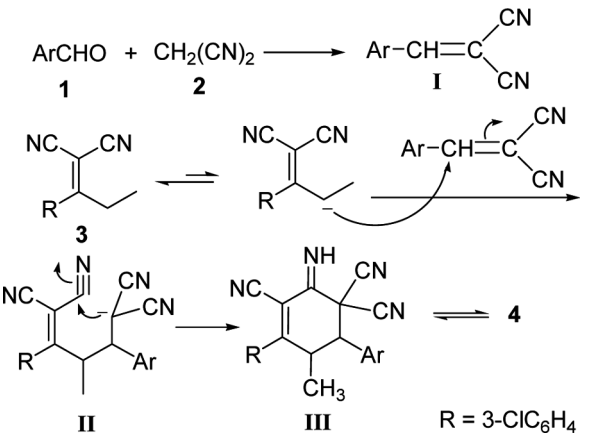



**Figure 1.** Crystal structure of the product **4e** with the solvent $H_2O$ deleted for clarity.




**Scheme 2.** The possible mechanism for the formation of products **4**.

To extend the reaction (Scheme 1) to a library system, various kinds of aromatic aldehydes **1** were reacted with malononitrile and 2-(1-(3-chlorophenyl) propylidene)malononitrile, giving the corresponding 2-amino-6-(3-chlorophenyl)-5-methyl-4-arylcyclohexa-1,5-diene-1,3,3-tricarbonitrile derivatives **4** successfully (Table 2). All of **1** gave expected products in good yields, either bearing electron-withdrawing groups (such as halide or nitro) or electron-donating groups (such as alkyl or alkoxyl) under the same reaction condition (Table 2). The structure of **4e** was confirmed by x-ray diffraction analysis, shown in Fig. 1.

Although the detailed mechanism of this reaction has not been clarified, the formation of 2-amino-6-(3-chlorophenyl)-5-methyl-4-arylcyclohexa-1,5-diene-1,3,3-tricarbonitrile derivatives **4** could be explained by a possible mechanism as presented in Scheme 2. The Knoevenagel condensation of aromatic aldehydes and malononitrile may occur to generate α,β-unsaturated dinitriles **I** first, then Michael addition reaction takes place between the reactant **3** and **I** to give **II**, and the anion in **II** then attacks one of the cyano groups to afford **III**, which then isomerizes to yield the final product **4**.

## CONCLUSION

In conclusion, we found a simple and green method for the synthesis of 2-amino-6-(3-chlorophenyl)-5-methyl-4-arylcyclohexa-1,5-diene-1,3,3-tricarbonitrile derivatives by three-component reaction of aromatic aldehyde, malononitrile, and 2-(1-(3-chlorophenyl)propylidene)malononitrile in aqueous media catalyzed by TEBAC at 90 °C. This three-component reaction had advantages of green solvent, good yields, and operational simplicity.

## EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Infrared (IR) spectra were recorded on a Tensor 27 spectrometer in KBr pellets. $^1$H NMR

spectra were obtained from solution in dimethylsulfoxide (DMSO-$d_6$) with $Me_4Si$ as internal standard using a Bruker-400 spectrometer. High-resolution mass spectrometry (HRMS) analyses were carried out using a Bruker micro-TOF-Q-MS analyzer.

### General Procedure for the Syntheses of 2-Amino-6-(3-chlorophenyl)-5-methyl-4-aryl-cyclohexa-1,5-diene-1,3,3-tricarbonitrile Derivatives

A 50-mL flask was charged with aromatic aldehyde (2.0 mmol), malononitrile (2.2 mmol, 0.145 g), 2-(1-(3-chlorophenyl)propylidene)malononitrile (2.0 mmol, 0.432 g), TEBAC (0.2 mmol, 0.091 g), and water (10 mL). The reaction mixture was stirred at 90 °C for 10–20 h; the solid was isolated by filtration. The filtrate together with TEBAC could be used again directly for the same reaction. The crude products were washed with water, purified by recrystallization from dimethylformamide (DMF) and water, and dried at 80 °C for several hours in a vacuum to give **4**.

### 2-Amino-4-(3-bromophenyl)-6-(3-chlorophenyl)-5-methylcyclohexa-1,5-diene-1,3,3-tricarbonitrile (4a)

Mp 187 – 189 °C. IR (KBr): 3411, 3322, 3054, 2201, 1644, 1591, 1567, 1474, 1427, 1406, 1216, 1180, 1095, 1078, 998, 879, 795, 783 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): 1.55 (s, 3H, $CH_3$), 4.73 (s, 1H, CH), 7.19 (d, $J = 7.2$ Hz, 1H, ArH), 7.28 (s, 1H, ArH), 7.43–7.52 (m, 4H, ArH), 7.64–7.68 (m, 4H, ArH + $NH_2$). HRMS (ESI, $m/z$): calcd. for $C_{22}H_{14}BrClN_4Na$ (M + $Na^+$) 470.9988; found 470.9988.

### 2-Amino-6-(3-chlorophenyl)-5-methyl-4-(4-nitrophenyl)cyclohexa-1,5-diene-1,3,3-tri carbonitrile (4b)

Mp 209 – 210 °C. IR (KBr): 3426, 3328, 2199, 1713, 1637, 1590, 1567, 1523, 1478, 1396, 1348, 1218, 1108, 863, 826, 793, 751 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): 1.54 (s, 3H, $CH_3$), 4.95 (s, 1H, CH), 7.22 (d, $J = 6.8$ Hz, 1H, ArH), 7.48 (s, 1H, ArH), 7.49–7.54 (m, 2H, ArH), 7.70 (s, 2H, $NH_2$), 7.78 (d, $J = 8.8$ Hz, 2H, ArH), 8.32 (d, $J = 8.8$ Hz, 2H, ArH). HRMS (ESI, $m/z$): calcd. for $C_{22}H_{14}ClN_5O_2Na$ (M + $Na^+$) 483.0734; found 438.0732.

### 2-Amino-6-(3-chlorophenyl)-4-(methoxyphenyl)-5-methylcyclohexa-1,5-diene-1,3,3-tricarbonitrile (4c)

Mp 202 – 204 °C. IR (KBr): 3439, 3315, 3009, 2976, 2215, 1646, 1594, 1566, 1511, 1464, 1418, 1390, 1303, 1253, 1214, 1177, 1025, 840, 802, 757 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): 1.53 (s, 3H, $CH_3$), 3.77 (s, 3H, $CH_3O$), 4.59 (s, 1H, CH), 7.00 (d, $J = 8.4$ Hz, 2H, ArH), 7.18 (d, $J = 6.8$ Hz, 1H, ArH), 7.25 (s, 1H, ArH), 7.38 (d, $J = 8.4$ Hz, 2H, ArH), 7.48–7.51 (m, 2H, ArH), 7.57 (s, 2H, $NH_2$). HRMS (ESI, $m/z$): calcd. for $C_{23}H_{17}ClN_4ONa$ (M + $Na^+$) 423.0989; found 423.0985.

### 2-Amino-6-(3-chlorophenyl)-4-(3,4-dimethoxyphenyl)-5-methylcyclohexa-1,5-diene-1,3,3-tricarbonitrile (4d)

Mp 168 – 171 °C. IR (KBr): 3432, 3310, 3056, 3005, 2971, 2933, 2213, 1649, 1586, 1567, 1515, 1444, 1420, 1275, 1214, 1159, 1142, 1024, 852, 795, 772 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): 1.56 (s, 3H, $CH_3$), 3.76 (s, 3H, $CH_3O$), 3.78 (s, 3H, $CH_3O$), 4.57 (s, 1H, CH), 7.00–7.04 (m, 2H, ArH), 7.08 (d, $J = 2.4$ Hz, 1H, ArH), 7.21 (d, $J = 6.8$ Hz, 1H, ArH), 7.24 (s, 1H, ArH), 7.49–7.51 (m, 2H, ArH), 7.61 (s, 2H, $NH_2$). HRMS (ESI, $m/z$): calcd. for $C_{24}H_{19}ClN_4O_2Na$ (M $+Na^+$) 453.1094; found 453.1080.

### 2-Amino-6-(3-chlorophenyl)-4-(2-chlorophenyl)-5-methylcyclohexa-1,5-diene-1,3,3-tricarbonitrile (4e)

Mp 196 – 198 °C. IR (KBr): 3434, 3311, 2973, 2215, 1650, 1594, 1565, 1471, 1441, 1416, 1392, 1216, 1165, 1080, 1057, 1040, 896, 796, 757, 702 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): 1.51 (s, 3H, $CH_3$), 4.84 (s, 1H, CH), 7.20 (d, $J = 6.4$ Hz, 1H, ArH), 7.31 (s, 1H, ArH), 7.47–7.55 (m, 5H, ArH), 7.62–7.64 (m, 1H, ArH), 7.77 (s, 2H, $NH_2$). HRMS (ESI, $m/z$): calcd. for $C_{22}H_{14}Cl_2N_4Na$ (M $+Na^+$) 427.0493; found 427.0499.

### 2-Amino-6-(3-chlorophenyl)-5-methyl-4-(4-methylphenyl)cyclohexa-1,5-diene-1,3,3-tricarbonitrile (4f)

Mp 242 – 245 °C. IR (KBr): 3434, 3311, 3028, 2214, 1651, 1588, 1564, 1509, 1473, 1456, 1417, 1395, 1217, 1190, 1078, 888, 805, 788, 758 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): 1.53 (s, 3H, $CH_3$), 2.32 (s, 3H, $CH_3$), 4.59 (s, 1H, CH), 7.18 (d, $J = 7.2$ Hz, 1H, ArH), 7.24 (d, $J = 8.0$ Hz, 2H, ArH), 7.25 (s, 1H, ArH), 7.34 (d, $J = 8.0$ Hz, 2H, ArH), 7.48–7.51 (m, 2H, ArH), 7.58 (s, 2H, $NH_2$). HRMS (ESI, $m/z$): calcd. for $C_{23}H_{17}ClN_4Na$ (M $+Na^+$) 407.1039; found 407.1056.

### 2-Amino-4,6-di(3-chlorophenyl)-5-methylcyclohexa-1,5-diene-1,3,3-tricarbonitrile (4g)

Mp 178 – 181 °C. IR (KBr): 3413, 3323, 3065, 2995, 2200, 1644, 1592, 1570, 1476, 1430, 1406, 1216, 1184, 1096, 1081, 879, 785, 764, 713 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): 1.55 (s, 3H, $CH_3$), 4.74 (s, 1H, CH), 7.19 (d, $J = 6.8$ Hz, 1H, ArH), 7.27 (s, 1H, ArH), 7.42–7.43 (m, 1H, ArH), 7.47–7.53 (m, 5H, ArH), 7.68 (s, 2H, $NH_2$). HRMS (ESI, $m/z$): calcd. for $C_{22}H_{14}Cl_2N_4Na$ (M $+Na^+$) 427.0493; found 427.0499.

### 2-Amino-6-(3-chlorophenyl)-4-(3,4-dichlorophenyl)-5-methylcyclohexa-1,5-diene-1,3,3-tricarbonitrile (4h)

Mp 211 – 213 °C. IR (KBr): 3410, 3323, 2994, 2904, 2200, 1643, 1590, 1564, 1474, 1404, 1330, 1215, 1185, 1095, 1079, 1033, 961, 880, 807, 792, 767 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): 1.54 (s, 3H, $CH_3$), 4.78 (s, 1H, CH), 7.19 (d, $J = 6.8$ Hz, 1H, ArH), 7.30 (s, 1H, ArH), 7.43 (dd, $J = 8.4$ Hz, $J' = 2.0$ Hz, 1H,

ArH), 7.48–7.51 (m, 2H, ArH), 7.71–7.76 (m, 4H, ArH + $NH_2$). HRMS (ESI, $m/z$): calcd. for $C_{22}H_{13}Cl_3N_4Na$ (M +$Na^+$) 461.0103; found 461.0105.

### 2-Amino-6-(3-chlorophenyl)-4-(4-chlorophenyl)-5-methylcyclohexa-1,5-diene-1,3,3-tricarbonitrile (4i)

Mp 192 – 194 °C. IR (KBr): 3414, 3325, 2200, 1642, 1591, 1566, 1490, 1478, 1408, 1298, 1216, 1095, 1016, 960, 879, 835, 804, 792, 766 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): 1.53 (s, 3H, $CH_3$), 4.73 (s, 1H, CH), 7.19 (d, $J = 6.8$ Hz, 1H, ArH), 7.29 (s, 1H, ArH), 7.37–7.55 (m, 6H, ArH), 7.63 (s, 2H, $NH_2$). HRMS (ESI, $m/z$): calcd. for $C_{22}H_{14}Cl_2N_4Na$ (M + $Na^+$) 427.0493; found 427.0501.

### 2-Amino-4-(4-bromophenyl)-6-(3-chlorophenyl)-5-methylcyclohexa-1,5-diene-1,3,3-tricarbonitrile (4j)

Mp 191 – 194 °C. IR (KBr): 3413, 3325, 2199, 1642, 1590, 1567, 1486, 1406, 1215, 1077, 1013, 959, 803, 791 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): 1.53 (s, 3H, $CH_3$), 4.71 (s, 1H, CH), 7.19 (d, $J = 6.8$ Hz, 1H, ArH), 7.28 (s, 1H, ArH), 7.42 (d, $J = 8.8$ Hz, 2H, ArH), 7.48–7.53 (m, 2H, ArH), 7.65–7.68 (m, 4H, ArH + $NH_2$). HRMS (ESI, $m/z$): calcd. for $C_{22}H_{14}BrClN_4Na$ (M + $Na^+$) 470.9988; found 470.9976.

### 2-Amino-6-(3-chlorophenyl)-4-(2,4-dichlorophenyl)-5-methylcyclohexa-1,5-diene-1,3,3-tricarbonitrile (4k)

Mp 195 – 196 °C. IR (KBr): 3443, 3309, 2218, 1651, 1594, 1561, 1470, 1415, 1387, 1214, 1187, 1146, 1107, 1081, 1054, 893, 847, 811, 795, 756, 729, 700 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): 1.50 (s, 3H, $CH_3$), 4.82 (s, 1H, CH), 7.19 (d, $J = 6.8$ Hz, 1H, ArH), 7.31 (s, 1H, ArH), 7.48–7.58 (m, 4H, ArH), 7.79 (s, 2H, $NH_2$), 7.81 (d, $J = 8.8$ Hz, 1H, ArH). HRMS (ESI, $m/z$): calcd. for $C_{22}H_{13}Cl_3N_4Na$ (M + $Na^+$) 461.0103; found 461.0110.

### 2-Amino-6-(3-chlorophenyl)-4-(3,4-dimethylphenyl)-5-methylcyclohexa-1,5-diene-1,3,3-tricarbonitrile (4l)

Mp 219 – 221 °C. IR (KBr): 3411, 3324, 2923, 2199, 1643, 1591, 1564, 1502, 1475, 1405, 1215, 1078, 808, 796, 765 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 400 MHz): 1.52 (s, 3H, $CH_3$), 2.227 (s, 3H, $CH_3$), 2.234 (s, 3H, $CH_3$), 4.53 (s, 1H, CH), 7.14–7.23 (m, 5H, ArH), 7.48–7.53 (m, 2H, ArH), 7.57 (s, 2H, $NH_2$). HRMS (ESI, $m/z$): calcd. for $C_{24}H_{19}ClN_4Na$ (M + $Na^+$) 421.1196; found 421.1228.

### X-Ray Crystallography for 4e

Empirical formula $C_{22}H_{14.5}Cl_2N_4O_{0.25}$, $F_W = 409.78$, $T = 294(2)$ K, triclinic, space group P – 1, $a = 7.443(2)$ Å, $b = 11.387(3)$ Å, $c = 13.351(4)$ Å, $\alpha = 79.785(5)°$, $\beta = 84.205(5)°$, $\gamma = 84.219(5)°$, $V = 1103.8(5)$ $Å^3$, $Z = 2$, $Dc = 1.233$ $Mg/m^3$, $\lambda(MoK\alpha) = 0.71073$ Å, $\mu = 0.309$ $mm^{-1}$, $F(000) = 421$. $2.76° < \theta < 25.02°$, $R = 0.0637$, $wR = 0.1539$, $S = 1.087$, largest diff. peak and hole: 0.690 and -0.231 e · $Å^{-3}$.

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