# One-pot synthesis of 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-1-benzopyran-3-carbonitriles in aqueous media

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The reaction of aromatic aldehyde, malononitrile and 1,3-cyclohexanediones in water in the presence of triethylbenzylammonium chloride (TEBA) provides an efficient access to 3-cyano-substituted 2-amino-4-aryl-4,6,7,8-tetrahydro-5*H*-1-benzopyran-5-ones.

**Keywords:** dimedone, 1-benzopyrans, reactions in water, green chemistry

The selective manipulation of one functional group in the presence of other(s) using nontoxic chemicals in economically viable and environmentally benign conditions is a formidable task for synthetic organic chemists.[1] There is a growing interest in carrying out synthetic transformations in aqueous media.[2]

Water possesses many advantages over traditional organic solvents: simple operation, safety, low cost, the minimisation of tedious protection and deprotection, *etc*. Many organic reactions have been successfully carried out in aqueous media, such as Diels–Alder, Barbier and aldol reactions and Claisen rearrangements.[3]

In recent years, the synthesis of benzopyran derivatives has attracted great interest. Since the discovery of cromakalim as a typical ATP-sensitive potassium channel opener (PCO), a large number of benzopyran derivatives have been synthesised and demonstrated to possess potent relaxant activity on blood vessels, cardiac muscle, and other smooth muscles.[4] These agents may find use in the treatment of a variety of diseases such as hypertension, asthma, ischemia, and urinary incontinence.

The pyran pharmacophore is an important core structure of many natural products showing antibacterial, antitumor, antiallergic, antibiotic, hypolipidemic and immunomodulating activities.[5,6] When the hydrogen atom of pyran ring is substituted by amino or cyano, they become synthons[7] of some natural products.

Generally, the conventional synthesis of benzopyran derivatives involves acid as well as base (*e.g*. piperidine or triethylamine) catalysed condensation of appropriate active methylene carbonyl compounds with aldehydes refluxing in organic solvents (*e.g*. ethanol or DMF) and are plagued by the limitation of prolonged reaction times, poor yields, and side reactions of the aldehydes, and additionally by lack of convincing structural proofs and environmental unfriendliness.[8,9]

In the course of our search for new methods for the construction of benzopyran nuclei, we became interested in the preparation of substituted 2-amino-3-cyanotetrahydro-1-benzopyrans with various aryl group substituents. In addition, we also wanted to study the one-pot synthesis of 2-amino-4-aryl-3-cyano-4,6,7,8-tetrahydro-5*H*-1-benzopyran-5-one derivatives by three-component reaction in aqueous media.

When aromatic aldehydes (**1**), malononitrile (**2**), and the 1,3-dicarbonyl compounds cyclohexane-1,3-dione (**3**, R = H) or dimedone (**3**, R = Me) were stirred for 4-10 h at 90 °C in aqueous suspension in the presence of benzyltriethylammonium chloride, 2-amino-3-cyano-4-aryl-4,6,7,8-tetrahydro-5*H*-1-benzopyran-5-ones (**4**) were obtained in excellent yields. (Scheme 1) The results are shown in Table 1.

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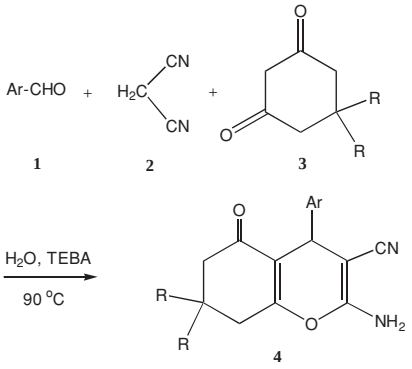


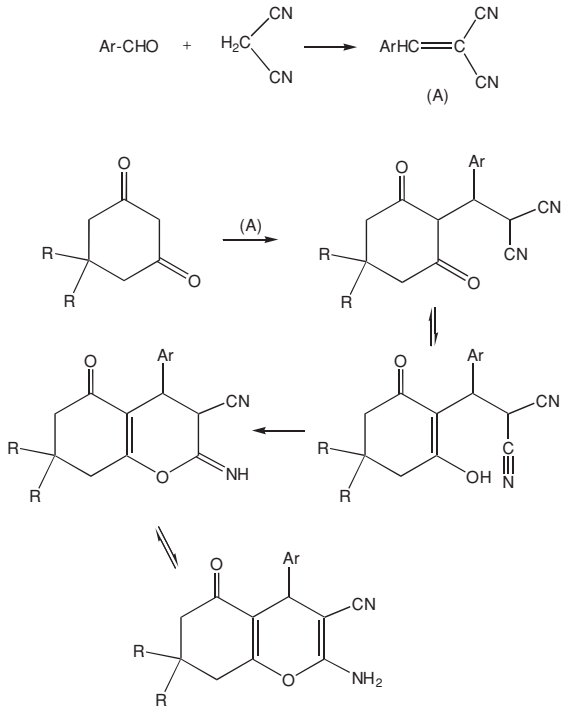

**Scheme 1**

Table 1 shows the results using a series of aldehydes that undergo the reaction to give excellent yields (79–99 %) of the products. This procedure does not require the use of any organic solvent. In fact the target compounds **4** were isolated in a practically pure form by simple Buchner filtration of the final aqueous mixture. The reactions are complete in a short time.

All the products were characterised by IR and $^1$H NMR analysis. The IR spectra of compound **4** show the NH stretching in the region 3500–3200, the CN group at around 2200 and the C=O group at 1700-1661 cm$^{-1}$. The $^1$H NMR spectra of compound **4** show the NH proton absorption as a broad singlet at δ 7.0 ppm. The one proton on C–4 gives a singlet at 4.1–4.7 ppm. The two methyl groups on C-7 of **4a**–**k** appear as two sharp singlets at 0.95 and 1.0 ppm, indicating that these two protons are not equivalent.

**Table 1** 2-Amino-4-aryl-3-cyano-4,6,7,8-tetrahydro-5*H*-1-benzopyran-5-ones (**4**)

| Entry | Ar | R | Time /h | Isolated yield /% |
|---|---|---|---|---|
| **4a** | $C_6H_5$ | $CH_3$ | 4 | 95 |
| **4b** | 4-$ClC_6H_4$ | $CH_3$ | 7 | 94 |
| **4c** | 4-$FC_6H_4$ | $CH_3$ | 5 | 96 |
| **4d** | 4-$CH_3C_6H_4$ | $CH_3$ | 5 | 88 |
| **4e** | 4-$CH_3OC_6H_4$ | $CH_3$ | 6 | 96 |
| **4f** | 2-$ClC_6H_4$ | $CH_3$ | 10 | 97 |
| **4g** | 3,4-$OCH_2OC_6H_3$ | $CH_3$ | 5 | 96 |
| **4h** | 2,4-$(CH_3O)_2C_6H_3$ | $CH_3$ | 6 | 88 |
| **4i** | 3-$NO_2C_6H_4$ | $CH_3$ | 7 | 90 |
| **4j** | 4-$NO_2C_6H_4$ | $CH_3$ | 10 | 99 |
| **4k** | 2-$NO_2C_6H_4$ | $CH_3$ | 6 | 79 |
| **4l** | 4-$ClC_6H_4$ | H | 6 | 94 |
| **4m** | 2-$ClC_6H_4$ | H | 6 | 82 |
| **4n** | 2,4-$Cl_2C_6H_3$ | H | 6 | 90 |
| **4o** | 4-$CH_3OC_6H_4$ | H | 5 | 95 |
| **4p** | 3,4-$OCH_2OC_6H_3$ | H | 5 | 82 |
| **4q** | 3,4-$(CH_3O)_2C_6H_3$ | H | 6 | 97 |
| **4r** | 4-$NO_2C_6H_4$ | H | 6 | 99 |
| **4s** | 3-$NO_2C_6H_4$ | H | 6 | 98 |



**Scheme 2**

As earlier proposed,[10] we consider the reaction to proceed via condensation, addition, enolisation, cyclodehydration and tautomerisation. (Scheme 2)

In conclusion: we have developed a facile and effective procedure for carrying out the synthesis of 2-amino-4-aryl-3-cyano-4,6,7,8-tetrahydro-5*H*-1-benzopyran-5-ones from aromatic aldehydes, 1,3-dicarbonyl compounds and malononitrile in water in the presence of TEBA. Compared to the classical synthetic method, this method has the advantages of excellent yields, inexpensive operation and environmental friendliness.

## Experimental

Infrared spectra were recorded on an FT IR-8101 spectrometer in KBr with absorptions in $cm^{-1}$. $^1H$ NMR spectra were determined on a Bruker-400 spectrometer as DMSO-$d_6$ solutions. Chemical shifts (δ) are expressed in ppm downfield from internal tetramethylsilane.

*Typical procedure for the preparation of tetrahydrobenzopyran-5-ones* **4**: To a solution of 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione **3** (5 mmol) in water (15 ml) were added the aromatic aldehyde **1** (5 mmol), malononitrile **2** (5 mmol) and TEBA (0.2 g). The resulting mixture was vigorously stirred at 90 °C for 4–10 h, and then cooled to room temperature to obtain a crystalline product. Suction filtration and recrystallisation from 95 % ethanol gave pure products **4**.

*2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4a**): m.p. 232–234 °C. (Lit.[11] 233–234 °C).

*2-Amino-7,7-dimethyl-5-oxo-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4b**): m.p. 239–241 °C (Lit.[11] 240-242 °C).

*2-Amino-7,7-dimethyl-5-oxo-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4c**): m.p. 192–194 °C. IR: ν/$cm^{-1}$ 3367, 3179, 2960, 2190, 1675, 1628, 1593, 1506, 1406, 1367, 1253, 1216, 1156, 1131, 1033, 975, 859, 838, 775, 706. $^1H$ NMR: δ 0.94 (s, 3H, $CH_3$), 1.03 (s, 3H, $CH_3$), 2.10 (d, J = 16.0 Hz, 1H, $C^8$-H), 2.24 (d, J = 16.0 Hz, 1H, $C^8$-H'), 2.45-2.57 (m, 2H, $C^6$-$H_2$), 4.19 (s, 1H, $C^4$-H), 7.02 (s, 2H, $NH_2$), 7.07-7.19 (m, 4H, ArH); Anal. calcd for $C_{18}H_{17}FN_2O_2$: C 69.22, H 5.49, N 8.97; found C 69.35, H 5.32, N 8.75 % .

*2-Amino-7,7-dimethyl-5-oxo-4-(4-methylphenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4d**): m.p. 220–222 °C. IR: ν/$cm^{-1}$ 3426, 3331, 2957, 2192, 1676, 1640, 1601, 1510, 1459, 1404, 1369, 1318, 1242, 1205, 1157, 1136, 1033, 971, 909, 842, 765. $^1H$ NMR: δ 0.95 (s, 3H, $CH_3$), 1.04 (s, 3H, $CH_3$), 2.09 (d, *J* = 16.0 Hz, 1H, $C^8$-H), 2.24 (d, *J* = 16.0 Hz, 1H, $C^8$-H'), 2.25 (s, 3H, $CH_3$), 2.45-2.56 (m, 2H, $C^6$-H), 4.12 (s, 1H, $C^4$-H), 6.96 (s, 2H, $NH_2$), 7.02 (d, *J* = 8.0 Hz, 2H, ArH), 7.08 (d, *J* = 8.0 Hz, 2H, ArH); Anal. calcd for $C_{19}H_{20}N_2O_2$: C 74.00, H 6.54, N 9.08; found C 74.30, H 6.77, N 9.31 %.

*2-Amino-7,7-dimethyl-5-oxo-4-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4e**): m.p. 196-198 °C (Lit.[11] 192-194 °C).

*2-Amino-7,7-dimethyl-5-oxo-4-(2-chlorophenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4f**): m.p. 215–216 °C. IR: ν/$cm^{-1}$ 3332, 3187, 2960, 2200, 1662, 1598, 1468, 1434, 1406, 1364, 1250, 1213, 1156, 1134, 1029, 973, 835, 816, 750, 718, 684; $^1H$ NMR: δ 0.98 (s, 3H, $CH_3$), 1.04 (s, 3H, $CH_3$), 2.08 (d, *J* = 16.0 Hz, 1H, $C^8$-H), 2.24 (d, *J* = 16.0 Hz, 1H, $C^8$-H'), 2.46–2.57 (m, 2H, $C^6$-H), 4.69 (s, 1H, $C^4$-H), 7.02 (s, 2H, $NH_2$), 7.16–7.37 (m, 4H, ArH). Anal. calcd for $C_{18}H_{17}ClN_2O_2$: C 65.75, H 5.21, N 8.52; found C 65.47, H 5.42, N 8.48 %.

*2-Amino-7,7-dimethyl-5-oxo-4-(3,4-methylenedioxyphenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4g**): m.p. 221–223 °C. IR: ν/$cm^{-1}$ 3362, 3193, 2964, 2194, 1654, 1607, 1489, 1429, 1375, 1359, 1249, 1210, 1156, 1125, 1038, 925, 856, 825, 785. $^1H$ NMR: δ 0.96 (s, 3H, $CH_3$), 1.03 (s, 3H, $CH_3$), 2.12 (d, *J* = 16.0 Hz, 1H, $C^8$-H), 2.24 (d, *J* = 16.0 Hz, 1H, $C^8$-H'), 2.46–2.57 (m, 2H, $C^6$-H), 4.11 (s, 1H, $C^4$-H), 5.97 (s, 2H, $OCH_2O$), 6.61 (d, *J* = 8.0 Hz, 1H, ArH), 6.64 (s, 1H, ArH), 6.81 (d, *J* = 8.0 Hz, 1H, ArH), 6.97 (s, 2H, $NH_2$). Anal. calcd for $C_{19}H_{18}N_2O_2$: C 67.44, H 5.36, N 8.28; found C 67.52, H 5.43, N 8.34 %.

*2-Amino-7,7-dimethyl-5-oxo-4-(2,4-dimethoxyphenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4h**): m.p. 181-183 °C. IR: ν/$cm^{-1}$ 3370, 3150, 2970, 2210, 1690, 1657, 1606, 1490, 1413, 1370, 1255, 1210, 1100, 1040, 860, 794, 750. $^1H$ NMR: δ 0.98 (s, 3H, $CH_3$), 1.05 (s, 3H, $CH_3$), 2.11 (d, *J* = 16.0 Hz, 1H, $C^8$-H), 2.26 (d, *J* = 16.0 Hz, 1H, $C^8$-H), 2.15–2.53 (m, 2H, $C^6$-H), 3.71 (s, 3H, $OCH_3$), 3.72 (s, 3H, $OCH_3$), 4.13 (s, 1H, $C^4$-H), 6.64–6.69 (m, 2H, ArH), 6.86 (s, 1H, ArH), 6.95 (s, 2H, $NH_2$). Anal. calcd for $C_{20}H_{22}N_2O_4$: C 67.78, H 6.26, N 7.90; found C 68.03, H 5.97, N 7.72 %.

*2-Amino-7,7-dimethyl-5-oxo-4-(3-nitrophenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4i**): m.p. 213–214 °C (Lit.[11] 210–212 °C).

*2-Amino-7,7-dimethyl-5-oxo-4-(4-nitrophenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4j**): m.p. 176–178 °C (Lit.[11] 174–176 °C).

*2-Amino-7,7-dimethyl-5-oxo-4-(2-nitrophenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4k**): m.p. 180–182 °C. IR: ν/$cm^{-1}$ 3330, 3260, 2925, 2200, 1690, 1600, 1510, 1450, 1365, 1240, 1140, 1035, 912, 782, 738, 700. $^1H$ NMR: δ 0.89 (s, 3H, $CH_3$), 1.02 (s, 3H, $CH_3$), 2.02 (d, *J* = 16.0 Hz, 1H, $C^8$-H), 2.20 (d, *J* = 16.0 Hz, 1H, $C^8$-H'), 2.48–2.56 (m, 2H, $C^6$-H), 4.94 (s, 1H, $C^4$-H), 7.18 (s, 2H, $NH_2$), 7.35–7.37 (m, 1H, ArH), 7.41-7.45 (m, 1H, ArH), 7.65–7.68 (m, 1H, ArH), 7.81–7.83 (m, 1H, ArH). Anal. calcd for $C_{18}H_{17}N_3O_4$: C 63.71, H 5.05, N 12.38; found C 63.86, H 4.91, N 12.53 %.

*2-Amino-5-oxo-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4l**): m.p. 226–229 °C. IR: ν/$cm^{-1}$ 3415, 3340, 2200, 1685, 1605, 1600, 1494, 1410, 1360, 1260, 1205, 1000, 910, 780, 750. $^1H$ NMR: δ 1.87-2.00 (m, 2H, $C^7$-H), 2.21–2.35 (m, 2H, $C^8$-H), 2.61–2.73 (m, 2H, $C^6$-H), 4.21 (s, 1H, $C^4$-H), 7.04 (s, 2H, $NH_2$), 7.17–7.20 (m, 2H, ArH), 7.33–7.36 (m, 2H, ArH). Anal. calcd for $C_{16}H_{13}ClN_2O_2$: C 63.90, H 4.36, N 9.31; found C 64.06, H 4.15, N 9.47 %.

*2-Amino-5-oxo-4-(2-chlorophenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4m**): m.p. 213–215 °C. IR: ν/$cm^{-1}$ 3310, 3200, 2200, 1700, 1685, 1600, 1510, 1364, 1208, 1000, 750, 710. $^1H$ NMR: δ 1.88–2.01 (m, 2H, $C^7$-H), 2.18–2.34 (m, 2H, $C^8$-H), 2.51–2.67 (m, 2H, $C^6$-H), 4.71 (s, 1H, $C^4$-H), 7.00 (s, 2H, $NH_2$), 7.18–7.28 (m, 3H, ArH), 7.35–7.36 (m, 1H, ArH). Anal. calcd for $C_{16}H_{13}ClN_2O_2$: C 63.90, H 4.36, N 9.31; found C 64.12, H 4.22, N 9.27 %.

*2-Amino-5-oxo-4-(2,4-dichlorophenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4n**): m.p. 225–227 °C. IR: ν/$cm^{-1}$ 3350, 3150, 2210, 1705, 1680, 1650, 1610, 1505, 1468, 1415, 1278, 1005, 810, 770. $^1H$ NMR: δ 1.92–2.00 (m, 2H, $C^7$-H), 2.22–2.34 (m, 2H, $C^8$-H), 2.57–2.66 (m, 2H, $C^6$-H), 4.69 (s, 1H, $C^4$-H), 7.07 (s, 2H, $NH_2$), 7.22–7.24 (m, 1H, ArH), 7.33–7.36 (m, 1H, ArH), 7.51–7.52 (m, 1H, ArH). Anal. calcd for $C_{16}H_{12}Cl_2N_2O_2$: C 57.33, H 3.61, N 8.36; found C 57.46, H 3.42, N 8.53 %.

*2-Amino-5-oxo-4-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4o**): m.p. 193–195 °C. IR: ν/$cm^{-1}$ 3460, 3325, 2220, 1700, 1600, 1510, 1452, 1367, 1244, 1025, 835, 772,

750. $^1$H NMR: δ 1.94–1.96 (m, 2H, C$^7$-H), 2.24–2.30 (m, 2H, C$^8$-H), 2.58–2.60 (m, 2H, C$^6$-H), 3.72 (s, 3H, $OCH_3$), 4.14 (s, 1H, C$^4$-H), 6.83 (d, *J* = 8.0 Hz, 2H, ArH), 6.94 (s, 1H, $NH_2$), 7.06 (d, *J* = 8.0 Hz, 2H, ArH). Anal. calcd for $C_{17}H_{16}N_2O_3$: C 68.91, H 5.44, N 9.45; found C 69.13, H 5.27, N 9.36 %.

*2-Amino-5-oxo-4-(3,4-methylenedioxyphenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4p**): m.p. 211–214 °C. IR: ν/cm$^{-1}$ 3410, 3340, 2200, 1706, 1658, 1604, 1600, 1496, 1450, 1365, 1250, 1210, 1040, 1000, 920, 790, 750. $^1$H NMR: δ 1.88–1.98 (m, 2H, C$^7$-H), 2.26–2.31 (m, 2H, C$^8$-H), 2.57–2.63 (m, 2H, C$^6$-H), 4.13 (s, 1H, C$^4$-H), 5.97 (s, 2H, $OCH_2O$), 6.62–6.67 (m, 2H, ArH), 6.80 (s, 1H, ArH), 6.96 (s, 2H, $NH_2$). Anal. calcd for $C_{17}H_{14}N_2O_4$: C 65.80, H 4.55, N 9.03; found C 65.93, H 4.36, N 8.90 %.

*2-Amino-5-oxo-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4q**): m.p. 228–231 °C. IR: ν/cm$^{-1}$ 3415, 3320, 2210, 1692, 1595, 1515, 1455, 1350, 1210, 1075, 1005, 810, 728. $^1$H NMR: δ 1.96–2.00 (m, 2H, C$^7$-H), 2.27–2.30 (m, 2H, C$^8$-H), 2.60–2.62 (m, 2H, C$^6$-H), 3.71 (s, 3H, $OCH_3$), 3.72 (s, 3H, $OCH_3$), 4.15 (s, 1H, C$^4$-H), 6.64–6.66 (m, 1H, ArH), 6.72 (m, 1H, ArH), 6.85 (s, 1H, ArH), 6.94 (s, 2H, $NH_2$). Anal. calcd for $C_{18}H_{18}N_2O_4$: C 66.25, H 5.56, N 8.58; found C 66.42, H 5.37, N 8.74 %.

*2-Amino-5-oxo-4-(4-nitrophenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4r**): m.p. 234–235 °C. IR: ν/cm$^{-1}$ 3408, 3340, 2200, 1704, 1688, 1590, 1510, 1435, 1350, 1210, 1005, 820, 790, 735. $^1$H NMR: δ 1.93–1.98 (m, 2H, C$^7$-H), 2.26–2.32 (m, 2H, C$^8$-H), 2.64–2.65 (m, 2H, C$^6$-H), 4.37 (s, 1H, C$^4$–H), 7.16 (s, 2H, $NH_2$), 7.45 (d, *J* = 8.0 Hz, 2H, ArH), 8.15 (d, *J* = 8.0 Hz, 2H, ArH). Anal. calcd for $C_{16}H_{13}N_3O_4$: C 61.73, H 4.21, N 13.50; found C 62.01, H 3.95, N 13.63 %.

*2-Amino-5-oxo-4-(3-nitrophenyl)-5,6,7,8-tetrahydro-4H-1-benzopyran-3-carbonitrile* (**4s**): m.p. 198–200 °C. IR: ν/cm$^{-1}$ 3360, 3310, 2200, 1685, 1645, 1600, 1508, 1450, 1368, 1260, 1140, 1000, 850, 780, 750. $^1$H NMR: δ 1.86–2.00 (m, 2H, C$^7$-H), 2.21–2.37 (m, 2H, C$^8$-H), 2.62–2.70 (m, 2H, C$^6$-H), 4.42 (s, 1H, C$^4$-H), 7.17 (s, 2H, $NH_2$), 7.60–7.69 (m, 2H, ArH), 7.99 (s, 1H, ArH), 8.07–8.09 (m, 1H, ArH). Anal. calcd for $C_{16}H_{13}N_3O_4$: C 61.73, H 4.21, N 13.50; found C 61.98, H 4.06, N 13.37 %.

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