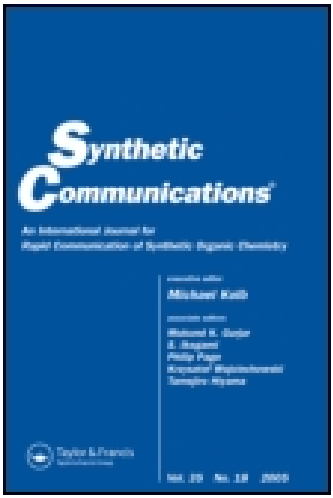

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Microwave-Promoted Synthesis of 2-Amino-4-aryl-4H-pyrans on Soluble Polymeric Support

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Abstract: 2-Amino-4-aryl-4*H*-pyran derivatives could be prepared rapidly and smoothly in good to excellent yields by the microwave-assisted liquid-phase strategy of multicomponent synthesis on polyethylene glycol.

Keywords: Liquid phase, microwave, multicomponent synthesis

The design of multicomponent reactions (MCR) is an important field of research in combinatorial chemistry.[1] Because they are a one-pot reactions, generally MCRs afford good yields and ready operations and are fundamentally different from two-component reactions in several aspects.[2] Therefore, great efforts have been and still are being made to find and develop new multicomponent reactions.[3] Usually, to drive the conversion of MCR, one or two components are excessive and this always leads to the trouble of separating

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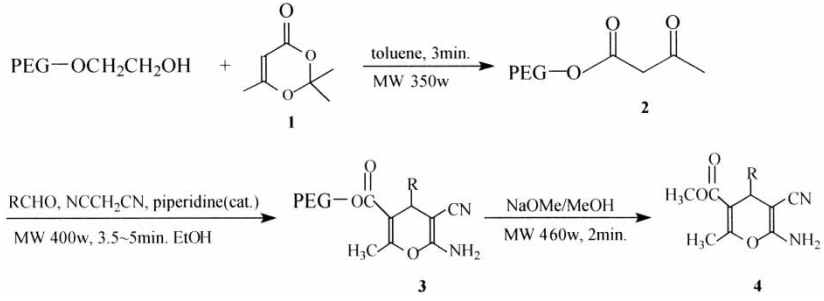
and purifying the target products. In traditional solution-phase systems, it is often the chief drawback of MCRs.

Recently, organic synthesis of small molecular compounds on soluble polymers, that is, liquid-phase chemistry, has increasingly become an attractive research field.[4] It couples the advantages of homogeneous solution-phase chemistry (high reactivity, lack of diffusion phenomena, and ease of analysis without the complicated cleavage-and-check procedure) with those of heterogeneous solid-phase chemistry (use of excessive reagents, ready isolation, and purification of target products). Besides, it is convenient for liquid-phase reactions being grafted from solution-phase systems without apparent kinetic changes. Therefore, they are the optimum choice for MCRs. Among various soluble polymers, polyethylene glycol (PEG) is the most helpful and promising because of its low cost and outstanding chemical stability.

It is well known that many reactions can be dramatically promoted by microwave irradiation[5] and this technology can also be applied to soluble polymer-supported reactions.[6] In this respect, solvent-involved and solvent-free methods are both workable. Currently, 4*H*-pyrans derivatives have been the intriguing focus in the field of medicinal chemistry because of their various bioactivities and pharmaceutical activities.[7–12] In connection with our interests in liquid-phase synthesis on soluble polymeric support,[13] we herein report the efficiently microwave-assisted preparation of 2-amino-4-aryl-4*H*-pyran derivatives on PEG support (Scheme 1).

The PEG 4000–bound acetoacetate **2** was prepared by the microwave-promoted nucleophilic reaction of PEG 4000 with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (TKD). Because of the high toxicity and hazard operation of diketene, TKD has increasingly become an effective alternative to diketen as an acetoacetyl reagent.[14] Classically, the nucleophilic reaction involved with TKD should be carried out at a high temperature for a prolonged time.[15] In our case, however, the acetoacetylation was fulfilled smoothly by microwave irradiation at 350 W within 3 min, affording the quantitative conversion of terminal hydroxyl groups on PEG (determined by ^{1}H NMR).



1 2 3 4

Scheme 1.

Traditionally, the preparation of 4-aryl-4*H*-pyrans has taken place in solutions such as benzene, ethanol, acetonitrile, etc. for a long time (6–8 h) under refluxing; β-dicarbonyl compounds, arylaldehydes, and active methylene compounds were needed in this multicomponent synthesis.[16] To our knowledge, however, there has been no literature about the microwave-assisted multicomponent synthesis of 4-aryl-4*H*-pyran derivatives on soluble polymer by liquid-phase methodology.

In ethanol solution, PEG-bound acetoacetate **2**, molononitrile, and corresponding arylaldehyde were mixed in the mole ratio of 1:4:4 with 1–2 drops of piperidine as the catalyst. The resulted mixture was irradiated at 400 W. Because the reaction took place on soluble polymeric support, excessive reagents drove the condensation instead of requiring isolation and purification. When microwave irradiation was over and the mixture was cooled to room temperature, ether was poured to precipitate the PEG-linked intermediate **3**. After simple washing with ether, purified intermediate **3** could be applied to the next step. In this procedure, the advantages of liquid-phase reaction were displayed: one hand, the purity of PEG-bounded intermediate **3** could be conveniently determined by TLC analysis without the complicated cleavage-and-check workup; the other hand, the homogenous reaction afforded intermediate **3** in good to excellent yields (Table 1) in dramatically shorted time (from several hours to several minutes).

During the experiment, we found the presence of a catalytic amount of piperidine was indispensable. Although in our case some kinds of arylaldehydes such as 3-nitrobenzaldehyde could undergo the three-component condensation in moderate yields with the absence of piperidine, the majority of other kinds of arylaldehydes could hardly afford the expected products of 2-amino-4-aryl-3-cyano-4*H*-pyrans without the presence of piperidine. Instead, almost quantitative amount of arylidene malononitriles were isolated.

Table 1. Microwave-promoted liquid-phase synthesis of 4-aryl-4*H*-pyran-5-carboxylates

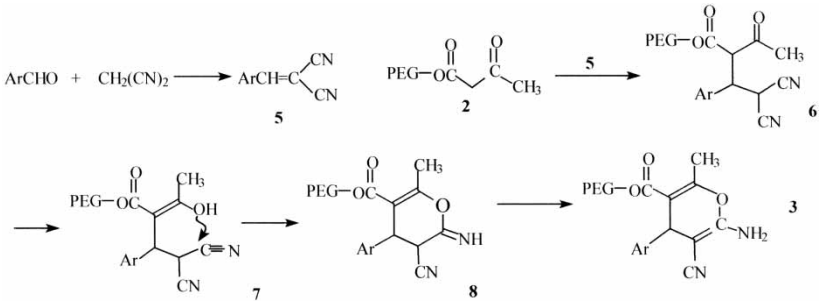
Comp.	Ar	Time (min)[a]	Mp (°C)	Yield (%)[b]
4a	C_6H_5	3.5	187–188	93
4b	2-ClC_6H_4	3.5	161–162	96
4c	3-$O_2NC_6H_4$	3.5	202–204	88
4d	4-$CH_3OC_6H_4$	5.5	134–135	83
4e	4-HOC_6H_4	4.0	181–182	96
4f	4-ClC_6H_4	3.5	160–162	91
4g	2,6-$Cl_2C_6H_3$	5.5	226–228	94
4h	2,4-$Cl_2C_6H_3$	5.0	150–152	89
4i	3,4-$OCH_2OC_6H_3$	4.0	166–167	93
4j	4-FC_6H_4	3.5	153–154	91

[a]Time for condensations.
[b]Isolated yields.

Moreover, it was discovered the formation of arylidene malononitriles was so ready that nearly quantitative conversion could be fulfilled in the absence of piperidine. Apparently, the work of piperidine involved in the catalysis of the nucleophilic addition of PEG-bound acetoacetate to C═C double bonds on arylidene malononitriles. There was reported[17] that 4-(*N,N*-dimethylamino)benzaldehyde could carry out the condensation with malononitrile and 5,5-dimethylcyclohexane-1,3-dione to provide 2-amino-4-(4-*N,N*-dimethylamino-phenyl)-3-cyano-4*H*-pyran in excellent yield. In our case, however, even if in the presence of piperidine, the target product of 4*H*-pyran was not obtained from the microwave-irradiated condensation with malononitrile, arylaldehyde, and PEG-linked acetoacetate **2**. Similarly, almost a quantitative amount of α-cyano-4-(*N,N*-dimethylamino)-cinnamonitrile was separated. We attributed the reason of the phenomena to the weaker electron-withdrawing capacity of ester group on PEG-supported acetoacetate than that of the ketone group on 5,5-dimethylcyclohexane-1,3-dione. Therefore, the methylene on PEG-bound acetoacetate was unable to attack the deactivated C═C double bonds, which were caused from the strong electron-donating capacity of *N, N*-dimethylamino group on α-cyano-4-(*N,N*-dimethylamino)cinnamonitrile. Based on this evidence, we assumed the possible reaction route in this multicomponent protocol might be the following (Scheme 2).

An arylaldehyde was firstly condensed with malononitrile to afford α-cyanocinnamonitrile derivative **5**, this step could be regarded as a fast Knoevenagel addition without the help of piperidine. The key step took place in the process that active methylene moiety on intermediate **2** reacted with the C═C double bond to provide the intermediate **6**, which was cyclized by nucleophilic attack from the OH group to the cyano moiety. Finally, the expected intermediate **3** was offered by intramolecular tautomerization. Through the deprotection, the target 2-amino-4-aryl-3-cyano-4*H*-pyran-5-carboxylate **4** was obtained.

Usually, it takes several hours or overnight for the cleavage step to be completed in MeONa/MeOH system at room temperature. We had reported[18]



Scheme 2.

that microwave irradiation could be applied to accelerate the release of products from PEG support. Moreover, the time and power of microwave irradiation could be adjusted by simple determination on TLC analysis. Therefore, when the mixture of intermediate **3** in 1N MeONa/MeOH solution was irradiated at 460 W for only 2 min, the target products of 2-amino-4-aryl-3-cyano-4*H*-pyran-5-carboxylates **4** were completely released from the polymer support. In the soluble polymer-supported synthesis, the procedure for the decision on optimum reaction conditions could be largely simplified by the convenient TLC method, avoiding those complicated cleavage-and check workups that are necessary for solid-phase methodology.

In summary, we have demonstrated that soluble polymer-supported acetocetate could be utilized as the versatile precursor for the multicomponent construction of the pharmaceutically interesting 4*H*-pyran derivatives through the use of commercially available building blocks and that the PEG-linked intermediates could tolerate microwave reaction conditions. The soluble polymer supported liquid-phase synthesis overcame the defect of troublesome isolation in this three-component system while microwave irradiation obviously promoted the efficiency of preparation in each step. The coupling of microwave technology and liquid-phase synthesis strategy has constituted a novel and attractive avenue for the rapid generation of structural diverse libraries because of their inherent advantages.

EXPERIMENTAL SECTION

Mps were determined on X_4 mp apparatus and the thermometer was not corrected. ^{1}H NMR spectra were obtained on a Bruker Avance DMX400 MHz instrument. FT-IR spectra were recorded on Perkin-Elmer 298 spectrophotometer. Ms data were recorded on HP 5989B instrument. MW experiments were performed in a 50-mL round-bottomed flask (attached to a reflux condenser) on a Sanle WHL07S-01 microwave instrument at 2450 Hz frequency (0–700 W).

General Procedure for the Preparation of PEG-bound Acetoacetate 2

A mixture of PEG 4000 (1 g, 0.5 mmol) and TKD (1.5 mmol) in anhydrous toluene (10 mL) was irradiated under microwave cavity at 350 W for 3 min. After the completion of the reaction, ether (50 mL) was poured into the cooled mixture to precipitate the PEG-linked acetoacetate **2**, which was washed with ether for several times and then dried over vacuum. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.27$ (s, 3H, CH_3), 3.49 (s, 2H, $COCH_2CO$), 3.53–3.79 (m, PEG backbone, OCH_2CH_2O), 4.30 (t, 2H, J = 5 Hz, PEG-OCH_2CH_2OCO).

General Procedure for the Preparation of 2-Amino-4-aryl-3-cyano-4*H*-pyran-5-carboxylates 4

The mixture of PEG-linked acetoacetate **2** (0.5 g, 0.25 mmol), arylaldehyde (1.0 mmol), malononitrile (1.0 mmol), and piperidine (1–2 drops) in ethanol (20 mL) was heated under microwave irradiation at 400 W for the needed time. Upon the finishing of the reaction, PEG-supported intermediate **3** was separated by precipitation and rinsing from ether (100 mL). It should be further purified by dissolution and precipitation for two or three times.

The solution of PEG-bound intermediate **3** (0.25 g) in 1N MeONa/MeOH (10 mL) was irradiated at 460 W for 2 min. After cooling, water (15 mL) was poured and then CH_2Cl_2 (10 mL) was added to extract the product, which could be further purified by column chromatography using EtOAc/hexane (1:3) as the eluent.

2-Amino-4-phenyl-3-cyano-4*H*-pyran-5-carboxylates (4a): White, crystalline solid (recrystallized from 95% ethanol); mp 187–188°C; Anal. $C_{15}H_{14}N_2O_3$ calcd.: C, 66.67; H, 5.18; N, 10.37. Found: C, 66.56; H, 5.09; N, 10.31. FT-IR (KBr): 3412, 3330, 3226, 3203, 2195, 1701, 1680, 1608, 1408, 1334, 1264, 1178, 1122, 1062, 696 cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 2.36$ (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 4.43 (s, 1H, CH), 4.49 (s, 2H, NH_2), 7.18–7.31 (m, 5H, ArH); MS: m/z (%) = 270 (M^+, 18.04), 255 (9.37), 238 (6.69), 223 (2.02), 211 (11.71), 193 (100.00), 176 (11.71), 161 (32.16), 133 (8.84), 105 (7.13), 77 (10.95), 67 (10.09), 43 (31.43).

2-Amino-4-(2-chlorophenyl)-3-cyano-4*H*-pyran-5-carboxylates (4b): White, crystalline solid (recrystallized from 95% ethanol); mp 161–162°C; Anal. $C_{15}H_{13}ClN_2O_3$ calcd.: C, 59.21; H, 4.27; N, 9.21. Found: C, 59.11; H, 4.19; N, 9.14. FT-IR (KBr): 3424, 3333, 3221, 3198, 2949, 2196, 1702, 1679, 1647, 1603, 1409, 1345, 1264, 1063, 746; ^1H NMR (DMSO-d_6): 2.39 (s, 3H, CH_3), 3.56 (s, 3H, OCH_3), 4.50 (br, s, 2H, NH_2), 5.04 (s, 1H, CH), 7.14–7.16 (m, 2H, ArH), 7.21 (d, 1H, J = 6.4 Hz, ArH), 7.34 (d, 1H, J = 8 Hz, ArH); MS: m/z (%) = 304 (M^+,5.49), 289 (5.33), 269 (22.21), 245 (6.13), 193 (100.00), 176 (11.20), 161 (26.84), 133 (7.07), 105 (4.83), 67 (17.77), 43 (43.42).

2-Amino-4-(3-nitrophenyl)-3-cyano-4*H*-pyran-5-carboxylates (4c): Pale red, crystalline solid (recrystallized from 95% ethanol); mp 202–204°C; Anal. $C_{15}H_{13}N_3O_5$ calcd.: C, 57.14; H, 4.12; N, 13.33. Found: C, 57.03; H, 4.05; N, 13.31. FT-IR (KBr): 3400, 3330, 3266, 3223, 2192, 1699, 1675, 1607, 1530, 1416, 1345, 1270, 1115, 1064, 791; ^1H NMR (DMSO-d_6): $\delta = 2.42$ (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 4.58 (s, 1H, CH), 4.67 (s, 2H, NH_2), 7.49 (t, J = 8 Hz, 1H, ArH), 7.57 (d, J = 8 Hz, 1H, ArH), 8.04 (s, 1H, ArH), 8.13 (d, J = 8 Hz, 1H, ArH); MS: m/z (%) = 316 ($[M + 1]^+$, 21.08), 298 (35.69), 284 (9.27), 268 (5.38), 256 (2.81), 210 (1.91), 193 (100.00), 176 (9.14), 161 (23.00), 133 (7.13), 105 (4.54), 76 (6.87), 67 (7.66), 43 (14.99).

2-Amino-4-(4-methoxylphenyl)-3-cyano-4*H*-pyran-5-carboxylates (4d): White, crystalline solid (recrystallized from 95% ethanol); mp 134–135°C; Anal. $C_{16}H_{16}N_2O_4$ calcd.: C, 64.00; H, 5.33; N, 9.33. Found: C, 63.88; H, 5.27; N, 9.39. FT-IR (KBr): 3406, 3333, 3205, 2194, 1701, 1676, 1649, 1607, 1511, 1402, 1342, 1265, 1176, 1123, 1060; ^{1}H NMR (DMSO-d_6): $\delta = 2.04$ (s, 3H, CH_3), 3.59 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.39 (s, 1H, CH), 4.42 (br, s, 2H, NH_2), 6.83 (d, 2H, J = 8 Hz, ArH), 7.12 (d, 2H, J = 8 Hz, ArH); MS: m/z (%) = 300 (M^+, 22.37), 285 (7.31), 268 (11.50), 241 (11.73), 225 (6.59), 193 (55.43), 184 (25.77), 176 (4.20), 161 (15.23), 133 (9.02), 114 (17.42), 105 (4.67), 67 (11.54), 63 (19.49), 43 (100.00).

2-Amino-4-(4-hydroxylphenyl)-3-cyano-4*H*-pyran-5-carboxylates (4e): White, crystalline solid (recrystallized from 95% ethanol); mp 181–182°C; Anal. $C_{15}H_{14}N_2O_4$ calcd.: C, 62.94; H, 4.90; N, 9.80. Found: C, 63.08; H, 4.96; N, 9.71. FT-IR (KBr): 3440, 3317, 3026, 2958, 2193, 1710, 1672, 1594, 1513, 1410, 1338, 1247, 1068, 821; ^{1}H NMR (DMSO-d_6): $\delta = 2.26$ (s, 3H, CH_3), 3.53 (s, 3H. OCH_3), 4.17 (s, 1H, CH), 6.66 (d, J = 8.2 Hz, 2H, ArH), 6.82 (s, 2H, NH_2), 6.92 (d, J = 8.2 Hz, 2H, ArH), 9.28 (s, 1H, OH); MS: m/z (%) = 286 (M^+, 28.87), 271 (16.84), 254 (15.15), 239 (6.42), 227 (25.78), 21 (15.55), 193 (100.00), 176 (14.27), 161 (40.97), 133 (13.89), 105 (10.54), 89 (12.47), 77 (11.78), 67 (21.45), 43 (70.50).

2-Amino-4-(4-chlorophenyl)-3-cyano-4*H*-pyran-5-carboxylates (4f): White, crystalline solid (recrystallized from 95% ethanol); mp 160–162°C; Anal. $C_{15}H_{13}ClN_2O_3$ calcd.: C, 59.21; H, 4.27; N, 9.21. Found: C, 59.33; H, 4.32; N, 9.16. FT-IR (KBr): 3410, 3332, 3227, 3204, 2193, 1700, 1676, 1647, 1607, 1409, 1342, 1267, 1064, 838, 764; ^{1}H NMR (DMSO-d_6): $\delta = 2.31$ (s, 3H, CH_3), 3.52 (s, 3H. OCH_3), 4.30 (s, 1H, CH), 6.97 (s, 2H, NH_2), 7.15 (d, J = 8.4 Hz, 2H, ArH), 7.38 (d, J = 8.4 Hz, 2H, ArH); MS: m/z (%) = 304 (M^+, 15.32), 289 (10.42), 269 (4.80), 245 (13.56), 193 (100.00), 176 (12.77), 161 (31.97), 149 (20.12), 133 (8.72), 105 (7.06), 67 (11.19), 43 (80.43).

2-Amino-4-(2,6-dichlorophenyl)-3-cyano-4*H*-pyran-5-carboxylates (4g): Yellow, crystalline solid (recrystallized from 95% ethanol); mp 226–228°C; Anal. $C_{15}H_{12}Cl_2N_2O_3$ calcd.: C, 53.10; H, 3.54; N, 8.26. Found: C, 53.01; H, 3.49; N, 8.31. FT-IR (KBr): 3457, 3400, 3332, 3262, 3205, 2195, 1709, 1671, 1608, 1434, 1403, 1372, 1267, 1227, 1125, 1083, 772, 734; ^{1}H NMR (DMSO-d_6): $\delta = 2.26$ (s, 3H, CH_3), 3.46 (s, 3H, OCH_3), 5.36 (s, 1H, CH), 7.00 (s, 2H, NH_2), 7.27 (t, 1H, J = 8 Hz, ArH), 7.33 (d, 1H, J = 8 Hz, ArH), 7.38 (d, 1H, J = 8 Hz, ArH); MS: m/z (%) = 338 ($[M\text{-}1]^+$, 14.84), 323 (14.90), 279 (10.37), 193 (100.00), 176 (10.90), 161 (29.34), 133 (8.94), 67 (13.34), 43 (42.91).

2-Amino-4-(2,4-dichlorophenyl)-3-cyano-4*H*-pyran-5-carboxylates (4h): White, crystalline solid (recrystallized from 95% ethanol); mp 150–152°C; Anal. $C_{15}H_{12}Cl_2N_2O_3$ calcd.: C, 53.10; H, 3.54; N, 8.26. Found: C,

53.19; H, 3.61; N, 8.21. FT-IR (KBr): 3447, 3324, 3292, 3260, 3197, 2208, 1714, 1683, 1604, 1380, 1254, 1074, 845; ^{1}H NMR (DMSO-d_6): $\delta = 2.33$ (s, 3H, CH_3), 3.49 (s, 3H, OCH_3), 4.84 (s, 1H, CH), 7.01 (s, 2H, NH_2), 7.23 (d, J = 8.2 Hz, 1H, ArH), 7.38–7.40 (dd, J = 8.2 Hz, J = 2.1 Hz, 1H, ArH), 7.55 (d, J = 2.1 Hz, 1H, ArH); MS: m/z (%) = 339 (M^+, 29.97), 323 (8.19), 303 (35.07), 279 (5.96), 243 (3.68), 193 (100.00), 176 (7.09), 161 (18.95), 133 (5.54), 105 (3.47), 67 (11.96), 43 (44.71).

2-Amino-4-(3,4-dimethyleneoxylphenyl)-3-cyano-4*H*-pyran-5-carboxylates (4i): White, crystalline solid (recrystallized from 95% ethanol); mp 166–167°C; Anal. $C_{17}H_{16}N_2O_4$ calcd.: C, 65.38; H, 5.13; N, 8.97. Found: C, 65.49; H, 5.18; N, 8.88. FT-IR (KBr): 3416, 3332, 3209, 2949, 2870, 2195, 1699, 1683, 1609, 1502, 1430, 1344, 1254, 1060, 943, 810, 763; ^{1}H NMR (DMSO-d_6): $\delta = 2.28$ (s, 3H, CH_3), 3.54 (s, 3H, OCH_3), 4.22 (s, 1H, CH), 5.98 (d, J = 1.7 Hz, 2H, OCH_2O), 6.58 (dd, J = 1.7 Hz, J = 8 Hz, 1H, ArH), 6.64 (d, J = 1.7 Hz, 1H, ArH), 6.83 (d, J = 8 Hz, 1H, ArH), 6.88 (s, 2H, NH_2); MS: m/z (%) = 314 (M^+, 43.14), 299 (10.28), 282 (8.98), 254 (16.17), 239 (13.80), 193 (100.00), 176 (12.81), 161 (36.82), 133 (13.25), 105 (10.02), 63 (30.62), 43 (61.73).

2-Amino-4-(4-fluorophenyl)-3-cyano-4*H*-pyran-5-carboxylates (4j): White, crystalline solid (recrystallized from 95% ethanol); mp 153–154°C; Anal. $C_{15}H_{14}FN_2O_3$ calcd.: C, 62.28; H, 4.84; N, 9.68. Found: C, 62.38; H, 4.90; N, 9.59. FT-IR (KBr): 3410, 3332, 3272, 3205, 2197, 1700, 1680, 1649, 1611, 1507, 1408, 1380, 1341, 1269, 1064, 850, 766; ^{1}H NMR (DMSO-d_6): $\delta = 2.36$ (s, 3H, CH_3), 3.59 (s, 3H, OCH_3), 4.43 (s, 1H, CH), 4.48 (br, s, 2H, NH_2), 6.98 (t, 2H, J = 8.4 Hz, ArH), 7.14–7.18 (m, 2H, ArH); MS: m/z (%) = 288 (M^+, 23.59), 273 (17.51), 257 (4.55), 229 (22.33), 213 (8.13), 193 (100.00), 176 (13.57), 161 (37.89), 149 (28.63), 133 (14.39), 105 (7.69), 67 (14.98), 43 (48.07).

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