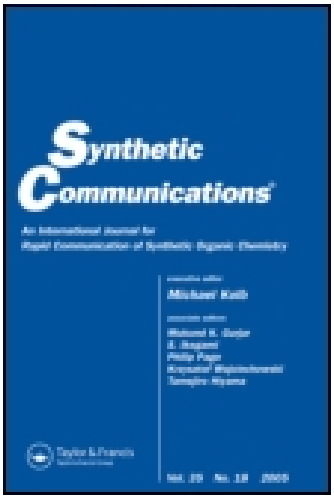

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Ultrasound-Assisted, One-Pot, Four-Component Synthesis of 1,4,6,8-Tetrahydroquinolines in Aqueous Medium

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ULTRASOUND-ASSISTED, ONE-POT, FOUR-COMPONENT SYNTHESIS OF 1,4,6,8-TETRAHYDROQUINOLINES IN AQUEOUS MEDIUM

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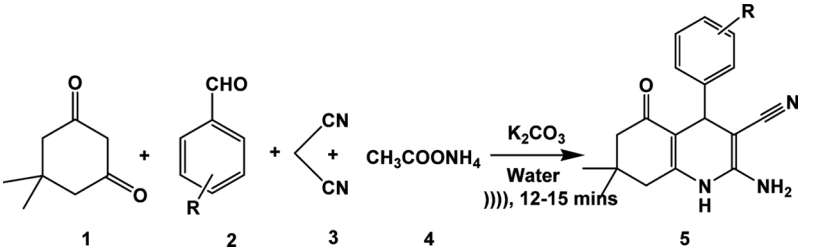
GRAPHICAL ABSTRACT



Abstract *A series of 2-amino-3-cyano-4-aryl-5-oxo-7,7-dimethyl-1,4,6,8-tetrahydroquinolines were prepared by a one-pot, four-component condensation of aromatic aldehydes, dimedone, malononitrile, and ammonium acetate using K_2CO_3 as a catalyst in aqueous medium under sonic conditions. This protocol, being a single-step reaction, has the advantages of operational simplicity and minimal environmental impact. The synthesized compounds were confirmed through spectral characterization using infrared, ^1H NMR, ^{13}C NMR, and CHN analysis.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords 2-Amino-3-cyano-4-aryl-5-oxo-7,7-dimethyl-1,4,6,8-tetrahydroquinolines; aromatic aldehydes; malononitrile; potassium carbonate; ultrasonication; water

INTRODUCTION

Multicomponent reactions (MCRs) have attracted considerable attention for their ease of execution and generation of good yields of the products.[1–3] MCRs

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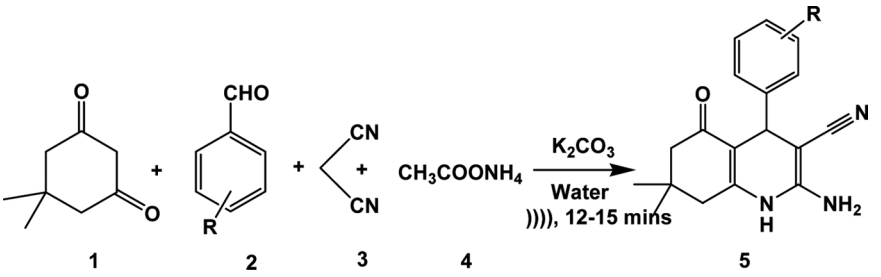
are used in designing highly functionalized, biologically active, heterocyclic compounds from readily available starting materials in a single step, without the isolation and purification of intermediates.[4] In the past few years, there has been a huge development in the synthesis of various heterocyclic compounds using effective MCRs.[5] Further, use of water as solvent makes the MCRs comply with the principles of green chemistry; water is abundant and environmentally benign, offers the benefits of easy workup, and purification of the products can be achieved by simple filtration. MCRs are suggested to have a negative activation volume,[6] and these reactions are reported to occur faster in water than in organic solvents.[7] A few high-yielding, mild, fast, and selective one-pot ultrasound-assisted MCRs have been reported earlier in water as a solvent.[8] Acceleration of the rates of the sonochemical reactions has been attributed to the acoustic cavitation phenomenon.[9,10] In the recent past, ultrasonochemistry has emerged as a ecofriendly synthetic methodology owing to its rate accelerating capacity, by-product minimization, and enhancement of yields of products.

Quinoline and its derivatives are an important class of pharmaceutical compounds which occur predominately in natural products, exhibit a broad spectrum of biological activities, and act as antivirals,[11,12] antiherpetics,[13] antidepressants,[14] antiasthamatics, antimalarials, antibacterials, tyrosine kinase inhibiting agents,[15] antioxidants,[16] and antiinflammatory,[17] antiproliferation,[18] and anticancer[19] agents. Quinolines are not only known as pharmaceuticals but, due to their excellent mechanical properties, also find use in polymer chemistry, electronics, and optoelectronics.[20] Copolymers of quinoline derivatives undergo hierarchical self-assembly into nano- and meso-structures having electronic and photonic functions.[21]

Hexahydroquinolines have been found to show antioxidant activity[22] and are considered to be the prime candidates in the construction of bacterial topoisomerase inhibitors[23] and as potential cytotoxic agents.[24] Because of their various applications in the pharmaceutical industry, a few synthetic methods have been developed for the construction of these quinoline rings.

A literature survey reveals the synthesis of 2-amino-3-cyano-4-aryl-5-oxo-7, 7-dimethyl-1,4,6,8-tetrahydroquinolines by a two-step reaction of *N*-unsubstituted-3-aminocyclohex-2-en-1-one with 2-benzylidenemalononitrile in the presence of a base.[25] Two reports on the four-component reaction of an aldehyde, dimedone, malononitrile, and ammonium acetate using nano–ZnO[26] and by grinding[27] are available in the literature. While nano–ZnO has to be prepared under very special conditions and should be characterized using instruments such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), and x-ray differaction, (XRD) the reaction by grinding the reactants in an open atmosphere is not safe, and hence, is discouraged in recent years. Further, only two products have been prepared by these two methods. In continuation of our research work on the use of K_2CO_3 in the multicomponent reactions in aqueous medium,[28] and development of new green synthetic routes for the preparation of heterocyclic compounds[29–31] using readily available catalysts by ultrasonic irradiation,[32,33] we herein report a simple, efficient, and novel method of the synthesis of some novel 2-amino-3-cyano-4-aryl-5-oxo-7,7-dimethyl1,4,6,8-tetrahydroquinolines using readily available, inexpensive K_2CO_3 as a catalyst in water as shown in Scheme 1.



Scheme 1. Synthesis of 2-amino-3-cyano-4-aryl-5-oxo-7,7-dimethyl-1,4,6,8-tetrahydroquinolines.

RESULTS AND DISCUSSION

To evaluate the feasibility of the reaction, initially a mixture of anisaldehyde (2 mmol), dimedone (2 mmol), malononitrile (2 mmol), ammonium acetate (4 mmol), and K_2CO_3 (10 mol%) was taken in water (10 mL) and subjected to ultrasonic irradiation (35 kHz) at 26°C to get the product in 92% within 15 min (Table 1, entry 5); the reaction was also carried out at reflux to get 85% of the product in 60 min (entry 6). As the reaction was four-fold faster under sonic condition, we planned to vary the amount of catalyst; the reaction was carried out without any catalyst but did not proceed in the absence of the catalyst (Table 1, entry 7). To choose a suitable catalyst, the reaction was carried out in the presence of 10 mol% each of basic catalysts such as piperidine, imidazole, ZnO (bulk), MgO (bulk), and K_2CO_3, and it was found that K_2CO_3 is the best in terms of yield and time of the reaction (entry 5). As K_2CO_3 has been shown earlier to catalyze many organic reactions efficiently,[34] we decided to study all the further reactions with catalytic K_2CO_3.

To optimize the amount of the catalyst, the reaction was carried out in water (10 mL), with different amounts of K_2CO_3 (10, 7.5, 5, and 2.5 mol%) under sonic condition and found that 5 mol% gives the best results (Table 2, entry 3).

To verify the possibility of further improvement of the yield of the product, the model reaction was carried out in different solvents such as water (10 mL), ethanol (10 mL), and a water–ethanol mixture (1:1, 10 mL); water was found to be optimal as it gave the product in maximum yield (92%, Table 3, entry 3) in 15 min.

Table 1. Selection of a suitable catalyst for the synthesis of **5a**

Entry	Catalyst[a]	Time (min)	Yield[b] (%)
1	Piperidine	60	55
2	Imidazole	65	45
3	MgO	30	55
4	ZnO	30	60
5	K_2CO_3	15	92
6	K_2CO_3[c]	60	85
7	No catalyst	60	ND

[a]10 mol%. Ultrasound (at 26 °C).
[b]Isolated yields.
[c]Reflux in water. ND, not detected.

Table 2. Optimization of amount of catalyst for the synthesis of **5a** in water under sonic conditions

Entry	Amount of K_2CO_3 (mol%)	Time (min)	Yield[a] (%)
1	10	15	90
2	7.5	15	92
3	5	15	92
4	2.5	60	65

[a]Isolated yields.

The reaction was carried out with different aromatic aldehydes as shown in Table 4 to establish the generality. It was found that the reaction is effective for all aromatic aldehydes used and not much difference has been found between electron-withdrawing and electron-donating substituents in terms of yield. However, aliphatic aldehydes (entries 8–10) and the α,β-unsaturated aldehydes such as cinnamaldehyde and crotonaldehyde (entries 11 and 12) did not give any product even after the reaction was carried out for longer duration as shown in Table 4.

Table 3. Optimization of solvent for the synthesis of **5a**[a]

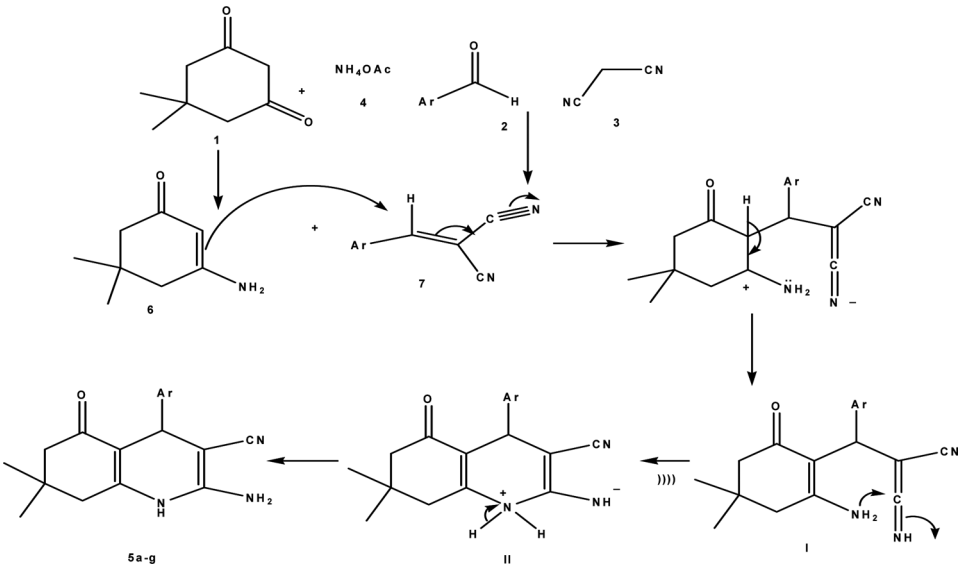
Entry	Solvent[b]	Time (min)	Yield[c] (%)
1	EtOH	60	55
2	Water–ethanol (1:1)	45	50
3	H_2O	30	92

[a]K_2CO_3 (5 mol%).
[b]Ultrasound (at 26 °C).
[c]Isolated yields.

Table 4. Synthesis of 2-amino-3-cyano-4-aryl-5-oxo-7,7-dimethyl-1,4,6,8-tetrahydroquinolines (**5a–g**) from various aldehydes, malononitrile, dimedone, and K_2CO_3 (5 mol%) under sonic condition

Entry	Aldehyde (**1**)	Product	Time (min)	Yield[a] (%)	MP (°C)	
					Found	Reported
1	4-$MeOC_6H_4CHO$	**5a**	12	92	284–286	289–293[26]
2	4-ClC_6H_4CHO	**5b**	15	85	282–284	287–288[26]
3	3-MeO,4-HOC_6H_3CHO	**5c**	15	92	253–255[b]	—
4	3-$NO_2C_6H_4CHO$	**5d**	12	90	305–306[b]	—
5	4-HOC_6H_4CHO	**5e**	12	85	269–271[b]	—
6	4-$NO_2C_6H_4CHO$	**5f**	12	90	260–262[b]	—
7	3,4,5-$(MeO)_3C_6H_2CHO$	**5g**	15	90	270–274[b]	—
8	HCHO	**5h**	60	ND	—	—
9	CH_3CHO	**5i**	60	ND	—	—
10	$CH_3CH_2CH_2CHO$	**5j**	60	ND	—	—
11	$C_6H_5CH{=}CHCHO$	**5k**	120	ND	—	—
12	$CH_3CH{=}CHCHO$	**5l**	120	ND	—	—

[a]Isolated yields.
[b]Novel compounds.
ND, not detected.



Scheme 2. Plausible mechanism for the formation of 2-amino-3-cyano-4-aryl-5-oxo-7,7-dimethyl-1,4,6,8-tetrahydroquinolines.

The formation of the product **5** is expected to involve the formation of an enaminone **6** (Scheme 2) by the condensation of **1** with **4**; formation of Knoevenagel adduct **7** by the reaction of **2** with **3**; followed by the Michael addition between **6** and **7** to give the intermediate **I**, which may undergo cyclization under sonication to give a bicyclic intermediate **II**, which in the last step may undergo a 1,3-proton shift to give the final products **5a–g** as shown in Scheme 2.

CONCLUSION

In conclusion, a series of novel and known 2-amino-3-cyano-4-aryl-5-oxo-7,7-dimethyl-1,4,6,8-tetrahydroquinolines were synthesized by a novel one-pot, four-component reaction of different aromatic aldehydes, malononitrile, dimedone, and ammonium acetate in water under ultrasonic irradiation using K_2CO_3 as catalyst in very good yields. The advantages of this protocol are use of a readily available catalyst, good yield of the products, short reaction times, use of water as a reaction medium, use of an energy-efficient technique, and operational simplicity.

EXPERIMENTAL

Chemicals and Instruments

All chemicals used were commercial; all reactions were carried out in water at 26 °C under ultrasonic irradiation. The progress of the reaction was monitored by thin-layer chromatography (TLC) (eluent; 2:8 ethyl acetate–petroleum ether). Ultrasonication was performed using SIDILU, Indian-make sonic bath working at a constant frequency of 35 kHz and an output power of 70 W at 26 °C (maintained

by circulating water). Melting points were determined on a RAAGA, Indian-make melting-point apparatus. The infrared (IR) spectra were recorded in the solid phase on a Bruker Optics Alpha-P Fourier transform (FT)–IR spectrophotometer with an attenuated total reflectance (ATR) module. ^{1}H NMR and ^{13}C NMR spectra of the products were recorded on Bruker AMX 400-MHz and 100-MHz instruments respectively in dimethylsulfoxide (DMSO-d_6) as solvent. Elemental analysis was carried out using a Vario MICRO CHN analyser.

General Procedure for the Synthesis of 2-Amino-3-cyano-4-aryl-5-oxo-7,7-dimethyl-1,4,6,8-tetrahydroquinolines (5a–g)

A mixture of aldehyde (2 mmol), dimedone (2 mmol), malononitrile (2 mmol), ammonium acetate (4 mmol), and K_2CO_3 (5 mol%) taken in water (10 mL) was sonicated for 12–15 min. The crude product thus obtained was filtered, washed with water, and recrystallized from ethanol to get a nearly pure product. All the prepared products were subjected directly without further purification by chromatography for characterization by FT-IR, ^{1}H NMR, ^{13}C NMR and CHN analyses.

Spectral and Analytical Data

Compound 5a. Mp 284–286 °C; IR (ATR-neat): ν 3374, 3309, 3171, 2969, 2190, 1687, 1655, 1510, 1374, 1249, 1034 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.94 (s, 3H, Me), 1.02 (s, 3H, Me), 2.06 (d, 2H, $J = 16$ Hz, CH_2) 2.22 (d, 2H, $J = 16$ Hz, CH_2), 3.33 (s, 2H, NH_2), 3.70 (s, 3H, OCH_3), 4.11 (s, 1H, CH), 6.82–6.84 (m, 2H, Ph), 7.03–7.05 (m, 2H, Ph), 8.18 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.9 (C=O), 164.0 (=**C**-NH_2), 159.2 (C=**C**-NH), 147.1, 146.1, 136.7, 120.6, 120.2, 113.8 (all Ar**C**s), 116.2 (C-**C**N), 112.2 (C=**C**-CO), 60.8 (=**C**-CN), 59.2 (**C**H_2-CO), 56.6 (O**C**H_3), 50.8 (**C**H_2-C=C), 36.5 (CH), 32.6 (**C**<), 29.5 (**C**H_3), 27.4 (**C**H_3). Anal. calcd. for $C_{19}H_{21}N_3O_2$(%): C, 65.95; H, 5.53; N, 12.82. Found: C, 70.57; H, 6.55; N, 12.98.

Compound 5b. Mp 282–284 °C; IR (ATR-neat): ν 3381, 3165, 2963, 2184, 1674, 1635, 1491, 1367, 1216 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.94 (s, 3H, Me), 1.03 (s, 3H, Me), 2.07 (d, 2H, $J = 16$ Hz, CH_2), 2.22 (d, 2H, $J = 16$ Hz, CH_2), 3.33 (s, 2H, NH_2), 3.70 (s, 3H, OCH_3), 4.18 (s, 1H, CH), 7.15–7.35 (m, 4H, Ph), 8.10 (s, 1H, NH); ^{13}CNMR (100 MHz, DMSO-d_6): δ 197.9 (C=O), 163.7 (=**C**-NH_2), 159.1 (C=**C**-NH), 141.1, 137.0, 130.0, 125.0, 120.6 (all Ar**C**), 114.1 (C-**C**N), 109.9 (C=**C**-CO), 60.8 (=**C**-CN), 59.1 (**C**H_2-CO), 50.8 (**C**H_2-C=C), 36.4 (CH), 32.6 (**C**<), 29.4 (**C**H_3), 28.1 (**C**H_3). Anal. calcd. for $C_{18}H_{18}ClN_3O$ (%): C, 65.95; H, 5.53; N, 12.82. Found: C, 65.96; H, 5.54; N, 12.83.

Compound 5c. Mp 253–255 °C; IR (ATR-neat): ν 3493, 3401, 3316, 3193, 2963, 2361, 2198, 1655, 1602, 1517, 1452, 1354, 1276, 1145, 870 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.96 (s, 3H, Me), 1.03 (s, 3H, Me), 2.08 (d, 2H, $J = 16$ Hz, CH_2) 2.23 (d, 2H, $J = 16$ Hz, CH_2), 3.34 (s, 2H, NH_2), 3.70 (s, 3H, OCH_3), 4.07 (s, 1H, CH), 5.1 (s, 1H, OH), 6.50–6.68 (m, 3H, Ph), 8.83 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.6 (C=O), 163.0 (=**C**-NH_2), 159.2 (C=**C**-NH), 148.1, 146.1, 136.7, 120.8, 120.2, 113.9 (all Ar**C**s), 116.2 (C-**C**N), 112.2 (C=**C**-CO), 60.8

(=**C**-CN), 59.5 (**C**H_2-CO), 56.4 (O**C**H_3), 50.9 (**C**H_2-C=C), 35.8 (CH), 32.6 (**C**<), 29.4 (**C**H_3), 27.5 (**C**H_3). Anal. calcd. for $C_{19}H_{21}N_3O_3$(%): C, 67.24; H, 6.24; N, 12.38. Found: C, 67.24; H, 6.24; N, 12.39.

Compound 5d. Mp 305–306 °C; IR (ATR-neat): ν 3434, 3323, 3204, 2956, 2184, 1661, 1524, 1413, 1347, 1145, 1034, 903 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.95 (s, 3H, Me), 1.04 (s, 3H, Me), 2.09 (d, 2H, $J = 16$ Hz, CH_2) 2.24 (d, 2H, $J = 16$ Hz, CH_2), 3.33 (s, 2H, NH_2), 4.41 (s, 1H, CH), 7.19–7.67 (m, 2H, Ph), 7.96–8.09 (m, 2H, Ph), 8.40 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.7 (C=O), 164.0 (=**C**-NH_2), 159.5 (C=**C**-NH), 147.1, 146.1, 136.7, 120.6, 120.2, 116.2 (all Ar**C**s), 120.3 (C-**C**N), 112.6 (C=**C**-CO), 64.5 (=**C**-CN), 58.0 (**C**H_2-CO), 50.8 (**C**H_2-C=C), 36.3 (CH), 32.7 (**C**<), 29.2 (**C**H_3), 27.6 (**C**H_3). Anal. calcd. for $C_{18}H_{18}N_4O_3$(%): C, 63.89; H, 5.36; N, 16.56. Found: C, 63.90; H, 5.36; N, 16.57.

Compound 5e. Mp 269–271 °C; IR (ATR-neat): ν 3427, 3322, 3198, 2956, 2191, 1662, 1530, 1420, 1375, 1204 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.97 (s, 3H, Me), 1.05 (s, 3H, Me), 2.09 (d, 2H, $J = 16$ Hz, CH_2), 2.23 (d, 2H, $J = 16$ Hz, CH_2), 3.28 (s, 2H, NH_2), 4.07 (s, 1H, CH), 5.20 (s, 1H,OH), 6.50–6.92 (m, 3H, Ph), 8.93 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.7 (C=O), 163.9 (=**C**-NH_2), 150.1 (C=**C**-NH), 158.4, 147.1, 129.3, 124.5, 120.2, 115.2 (all Ar**C**s), 112.2 (C-**C**N), 105.2 (C=**C**-CO), 64.9 (=**C**-CN), 57.8 (**C**H_2-CO), 50.5 (**C**H_2-C=C), 37.1 (CH), 32.7 (**C**<), 29.1 (**C**H_3), 27.8 (**C**H_3). Anal. calcd. for $C_{18}H_{18}N_3O_2$(%): C, 69.88; H, 6.19; N, 13.58. Found: C, 69.89; H, 6.18; N, 13.57.

Compound 5f. Mp 260–262 °C; IR (ATR-neat): ν 3408, 3316, 3178, 2930, 2184, 1664, 1629, 1524, 1347, 1216, 1138, 1027, 857, 733 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.95 (s, 3H, Me), 1.03 (s, 3H, Me), 2.08 (d, 2H, $J = 16$ Hz, CH_2), 2.24 (d, 2H, $J = 16$ Hz, CH_2), 2.53 (s, 2H, NH_2), 4.36 (s, 1H, CH), 7.19 (m, 2H, Ph), 7.43 (m, 2H, Ph), 8.18 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.6 (C=O), 164.0 (=**C**-NH_2), 159.4 (C=**C**-NH), 153.2, 147.1, 129.5, 124.5 (all Ar**C**s), 120.2 (C-**C**N), 112.6 (C=**C**-CO), 65.7 (=**C**-CN), 57.8 (**C**H_2-CO), 50.7 (**C**H_2-C=C), 36.5 (CH), 32.7 (**C**<), 29.1 (**C**H_3), 27.8 (**C**H_3). Anal. calcd. for $C_{18}H_{18}N_4O_3$(%): C, 63.89; H, 5.36; N, 16.56. Found: C, 63.90; H, 5.36; N, 16.57.

Compound 5g. Mp 270–274 °C; IR (ATR-neat): ν 3401, 3302, 3178, 2930, 2190, 1668, 1641, 1589, 1498, 1360, 1125 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02 (s, 3H, Me), 1.05 (s, 3H, Me), 2.12 (d, 2H, $J = 16$ Hz, CH_2), 2.64 (d, 2H, $J = 16$ Hz, CH_2), 3.04 (s, 2H, NH_2), 3.35 (s, 3H, OCH_3), 3.71 (s, 6H, OCH_3), 4.13 (s, 1H, CH), 6.37 (m, 2H, Ph), 8.89 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.6 (C=O), 163.7 (=**C**-NH_2), 159.2 (C=**C**-NH), 153.6, 141.3, 137.0, 120.6 (all Ar**C**s), 113.2 (C-**C**N), 105.0 (C=**C**-CO), 60.8 (=**C**-CN), 59.2 (**C**H_2-CO), 56.6 (O**C**H_3), 50.8 (**C**H_2-C=C), 36.5 (CH), 32.6 (**C**<), 29.5 (**C**H_3), 27.4 (**C**H_3). Anal. calcd. for $C_{18}H_{18}N_3O_4$(%): C, 65.78; H, 6.57; N, 10.96. Found: C, 65.78; H, 6.57; N, 10.50.

SUPPORTING INFORMATION

Full experimental detail, IR, CHN analysis, and ^{1}H and ^{13}C NMR spectra can be found via the Supplementary Content section of this article's Web page.

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REFERENCES

1. Jieping, Z. *J. Eur. Org. Chem.* **2003**, *7*, 1133–1134.
2. Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51–80.
3. Shi, C. L.; Shi, D. Q.; Kim, S. H.; Huang, Z. B.; Ji, S. J.; Ji, S. *Tetrahedron* **2008**, *64*, 2425–2432.
4. (a) Zhu, J.; Bienayme, H. In *Multicomponent Reactions*; J. Zhu, H. Bienayme (Eds.); Wiley-VCH Verlag: Weinheim, Germany, 2005, and references cited therein; (b) Tejedor, D.; Garcia-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484–491; (c) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187–191; For MCR-based heterocyclic libraries, see (d) Lie'by- Muller, F.; Simon, C.; Constantieux, T.; Rodriguez, J. *QSAR Comb. Sci.* **2006**, *25*, 432–438; (e) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980; (f) Evdokimov, N. M.; Kireev, A. S.; Yakovenko, A. A.; Antipin, M. Y.; Magedov, I. V.; Kornienko, A. *J. Org. Chem.* **2007**, *72*, 3443–3453.
5. (a) Domling, A.; Ugi, I. *Angew Chem.* **2000**, *39*, 3168–3210; (b) Bazgir, A.; Khanaposhtani, M. M.; Soorki, A. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5800–5803; (c) Kumar, A.; Maurya, R. A. *Tetrahedron.* **2007**, *63*, 1946–1952.
6. (a) Kljin, J. E.; Engberts, J. B. N. *Nature.* **2005**, *435*, 746–747; (b) Narayan, S.; Fokin, M. G.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279; (c) Kanizsai, I.; Gyónfalvi, S.; Szadonyi, Z.; Sillanpää, R.; Fülöp, F. *Green Chem.* **2007**, *9*, 357–360.
7. (a) Pirrung, M. C.; Das Sarma, K. *Tetrahedron* **2005**, *61*, 11456–11472; (b) Pirrung, M. C.; Das Sarma, K. *J. Am. Chem. Soc.* **2004**, *126*, 444–445; (c) Hailes, H. C. *Org. Process Res. Dev.* **2007**, *11*, 114–120.
8. (a) Shelke, K. F.; Sapkal, S. B.; Shingare, M. S. *Chin. Chem. Lett.* **2009**, *20*, 283–287; (b) Zhang, D.-N.; Li, J.-T.; Song, Y.-L.; Liu, H.-M.; Li, H.-Y. *Ultrason. Sonochem.* **2012**, *19*, 475–478.
9. (a) Mason, T. J.; Peters, D. *Practical Sonochemistry*, 2nd ed.; Ellis Horwood: London, 2002; (b) Luche, J. L. *Synthetic Organic Sonochemistry*; Plenum Press: New York, 1998; (c) Li, J. T.; Wang, S. X.; Chen, G. F.; Li, T. S. *Curr. Org. Synth.* **2005**, *2*, 415–436.
10. (a) Mason, T. J. *Chem. Soc. Rev.* **1997**, *26*, 443–451; (b) Suslick, K. S. *Annu. Rev. Mater. Sci.* **1999**, *29*, 295–326.
11. Wentland, M. P. O. U.S. Patent 4,959,363, *Chem. Abstr*. **1997**, *114*, 122367t.
12. Gester, J. F. Egypt. Pat. Appl. EP 385,630, 1990.
13. Diona, S. G. *Egypt. J. Pharm. Sci.* **1993**, *34*, 529–532.
14. Ukhov, S. V.; Gavrilov, M. Y.; Nikulina, S. N.; Kolla, V. E.; Kanshin, M. E. *Khim. Pharm. Zh.* **1991**, *25*, 20–21.
15. (a) Chen, Y. L.; Fang, K.-C.; Sheu, J.-Y.; Hsu, S.-L.; Tzeng, C.-C. *J. Med. Chem.* **2001**, *44*, 2374–2377; (b) Roma, G.; Braccio, M. D.; Grossi, G.; Chia, M. *Eur. J. Med. Chem.* **2000**, *35*, 1021–1035; (c) Maguire, M. P.; Sheets, K. R.; McVety, K.; Spada, A. P.; Zilberstein, A. *J. Med. Chem.* **1994**, *37*, 2129–2137.
16. Chung, H. S.; Woo, W. S. *J. Nat. Prod.* **2001**, *64*, 1579–1580.

17. El-Sayed, O. A.; Al-Turki, T. M.; Al-Daffiri, H. M.; Al-Bassam, B. A.; Hussein, M. E. *Boll. Chim. Farm.* **2004**, *143*, 227–238.
18. Sedic, M.; Poznic, M.; Gehrig, P.; Scott, M. *Mol. Cancer Ther.* **2008**, *7*, 2121–2132.
19. Gakhar, G.; Ohira, T.; Shi, A.; Hua, D. H.; Nguyen, T. A. *Drug Dev. Res.* **2009**, *69*, 526–534.
20. (a) Jenekhe, S. A.; Lu, L.; Alam, M. M. *Macromolecules* **2001**, *34*, 7315–7324; (b) Agrawal, A. K.; Jenekhe, S. A. *Chem. Mater.* **1993**, *5*, 633–640; (c) Jegou, G.; Jenekhe, S. A. *Macromolecules* **2001**, *34*, 7926–7928.
21. (a) Jenekhe, S. A.; Chen, X. L. *Science* **1998**, *279*, 1903; (b) Jenekhe, S. A.; Chen, X. L. *Science* **1999**, *283*, 372–375.
22. Yang, X.-H.; Zhang, P.-H.; Zhou, Y.-H.; Liu, C.-G.; Lin, X.-Y.; Cui, J.-F. *Arkivoc* **2011**, *10*, 335–345.
23. Mitscher, L. A. *Chem. Rev.* **2005**, *105*, 559–592.
24. Alqasoumi, S. I.; Al-Taweel, A. M.; Alafeefy, A. M.; Hamed, M. M.; Noaman, E.; Ghorab, M. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6939–6942.
25. Lichitsky, B. V.; Dudinov, A. A.; Krayushkin, M. M. *Arkivoc* **2001**, *9*, 73–79.
26. Kassaee, M. Z.; Masrour, H.; Movahedi, F. *Monatsh Chem.* **2010**, *141*, 317–322.
27. Kumar, S.; Sharma, P.; Kapoor, K. K.; Hundal, M. S. *Tetrahedron* **2008**, *64*, 536–542.
28. Sadeq, H. S. A.; Pasha, M. A. *Tetrahedron Lett.* **2012**, *53*, 7056–7059.
29. Siddekha, A.; Nizam, A.; Pasha, M. A. *Spectrochim. Acta A* **2011**, *81*, 431–440.
30. Sadeq, H. S. A.; Siddekha, A.; Nizam, A.; Pasha, M. A. *Chin. J. Catal.* **2012**, *33*, 677–680.
31. (a) Sadeq, H. S. A.; Pasha, M. A. *Tetrahedron Lett.* **2012**, *53*, 6834–6837; (b) Sadeq, H. S. A.; Siddekha, A.; Pasha, M. A. *Tetrahedron Lett.* **2012**, *53*, 6306–6309; (c) Pasha, M. A.; Aatika, N. *Synth. Commun.* **2010**, *40*, 2864–2868.
32. Sudha, S.; Pasha, M. A. *Ultrason. Sonochem.* **2012**, *19*, 994–998.
33. Datta, B.; Pasha, M. A. *Ultrason. Sonochem.* **2012**, *4*, 725–728.
34. (a) Li, J.-T.; Lin, Z.-P.; Han, J.-F.; Li, T.-S. *Synth. Commun.* **2004**, *34*, 2623–2631; (b) Zhang, Z.; Dong, Y.-W.; Wang, G.-W.; Komatsu, K. *Synlett* **2004**, *1*, 61–64; (c) Misra, M.; Sharma, R.; Kant, R.; Maulik, P. R.; Tripathi, R. P. *Tetrahedron Lett.* **2011**, *67*, 740–748; (d) Shen, L.; Cao, S.; Wu, J. *Tetrahedron Lett.* **2010**, *51*, 4866–4869.