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One-pot four-component synthesis of some novel octahydroquinolindiones using ZnO as an efficient catalyst in water

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ABSTRACT

ZnO has been shown to be an inexpensive, efficient, readily available, and mild catalyst for a one-pot four-component synthesis of some novel octahydroquinolindione-3-carboxylic acid ethyl esters using diethylmalonate, dimedone, ammonium acetate, and appropriate aromatic aldehydes in water at reflux. ZnO acts as a recyclable heterogeneous catalyst to afford the products in excellent yield in short reaction duration.

In recent years, the growing environmental concern in chemistry has turned the spotlight on multicomponent reactions as the new trend in organic chemistry.[1] Multicomponent reactions (MCRs) are very important for the construction of many heterocyclic compounds,[2] using this strategy many biologically active substances and natural products have been synthesized.[3]

The synthesis of nitrogen heterocycles is of great interest because they constitute an important class of natural and synthetic products, many of which exhibit useful biological activity and find application in pharmaceutical preparations.[4–7]

The quinoline ring system is an important structural unit in many naturally occurring alkaloids, therapeutics, and in the synthetic analogues with interesting biological activities.[8] Quinolines are also very important for designing many pharmacologically important compounds,[9] due to their wide spectrum of biological activities such as antimalarial, anti-bacterial, anti-asthmatic, anti-hypertensive, anti-inflammatory, anti-platelet, and tyrokinase PDGF-RTK inhibiting activities.[10–12] Therefore, the development of new and efficient methodologies for the synthesis of quinoline ring system will be interesting in both synthetic organic and medicinal chemistry.[13] Methods for the synthesis of the quinoline ring system have been developed and documented in the literature.[14] However, most of these methods are not completely satisfactory with regard to the yield and reaction conditions. Hence, a simple and an efficient method for the synthesis of the quinolone ring system is still in demand.

Recently, the heterogeneous catalysis has developed considerable interest in the various disciplines of science including organic synthesis due to the prime advantage that, in most of the cases the heterogeneous catalysts can be recovered with only minor change in activity and selectivity so that they can be used in continuous flow reactions.[15] Heterogeneous catalysts have many advantages over their homogeneous counterparts.

In continuation of our efforts to develop new methods for the synthesis of biologically active heterocyclic compounds using readily available, inexpensive, and environment friendly catalysts,[16–22] herein, we wish to report a mild and efficient method for the synthesis[23] of some novel 4-aryl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline-3-carboxylic acid ethyl esters. This method utilizes a one-pot four-component reaction of aromatic aldehydes, diethyl malonate, dimedone/1,3-cyclohexadione, and ammonium acetate in the presence of readily available, inexpensive, mild, recyclable, and common laboratory chemical ZnO as a catalyst (Scheme 1).

An initial study was performed by treating a mixture of anisaldehyde, diethyl malonate, dimedone, and ammonium acetate in water without any catalyst similar to the reaction which was carried out to get N-amino derivative of substituted quinoline-2,5-dione as one of the intermediates in a multistep reaction,[24] and found that, the reaction was possible in water under reflux, and the isolated yield after 8 h was low (45%, Table 2, entry 1). When

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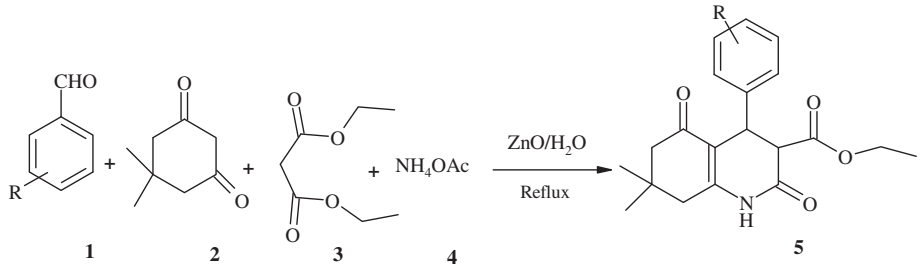

Scheme 1. Synthesis of octahydroquinolindiones.

Table 1
Influence of various catalysts on the synthesis of octahydroquinolindiones

Entry	Catalyst[a]	Time (h)	Yield[b](%)
1	AmberliteIR120 H[c]	13	20
2	$CeCl_3$	12	30
3	$ZnCl_2$	10	35
4	K_2CO_3	6	40
5	$Ba(OH)_2$	6	70
6	ZnO	2	90

[a] 30 mol %.
[b] Isolated yield.
[c] 0.1 g.

the reaction was carried out with ammonium acetate (3 mmol), the yield was again 45% (isolated yield) after 15 h (Table 2, entry 2). As the reaction requires a catalyst, we performed the reaction using Amberlite IR-120H (0.1 g), 30 mol % acidic ($CeCl_3$, $ZnCl_2$,) and basic catalysts (K_2CO_3, $Ba(OH)_2$, ZnO). We found that, ZnO is best in terms of yield and duration of reaction (Table 1, entry 6). ZnO has earlier been shown to be a mild base and finds application in organic synthesis.[25]

Further, studies were carried out to optimize the amount of catalyst by using different amounts of ZnO (3, 5, 6, 7.5, 10, 15, and 30 mol %) and the results are presented in Table 2; we found that, 7.5 mol % of ZnO affords the product in 90% isolated yield. Increasing the amount of catalyst did not improve the yield (Table 2).

It was noticed that, the reaction is also possible by ZnO in refluxing EtOH, MeOH, and CH_3CN; among the solvents used H_2O was found to be the best solvent as shown in Table 3.

To demonstrate the generality of this method, we performed all further reactions using ZnO (7.5 mol %) in water at reflux, and found that, ZnO can efficiently catalyze the reaction between dimedone, diethyl malonate, ammonium acetate, and different aromatic aldehydes to afford excellent yield of the desired products within 2–2.5 h. When we carried out the reaction using aliphatic aldehydes, there was no product formation even after 15 h (Table 4, entries 7,8). We also examined the use of 1,3-cyclohexandione instead of dimedone (Table 4, entry 9) and found that, the reaction works but the isolated yield after 10 h is only 40%. From Table 4, it is clear that, the method is equally effective for both electron withdrawing and electron donating aromatic aldehydes.

Table 2
Optimization of the amount of ZnO

Entry	ZnO mol %	Amount of H_2O (ml)	Amount of NH_4OAc (mmol)	Time (h)	Yield[a] (%)
1	0	10	2	8	45
2	0	10	3	15	45
3	3	10	2	15	60
4	3	10	2	3	50
5	5	10	2	3	60
6	6	10	2	2	75
7	7.5	10	2	2	90
8	10	10	2	2	90
9	15	10	2	2	90
10	30	10	2	2	89

[a] Isolated yield.

Table 3
Effect of solvent on the synthesis of octahydroquinolindiones

Entry	Solvent (reflux)	Time(h)	Yield[a] (%)
1	EtOH	4	65
2	MeOH	5	70
3	CH_3CN	6	55
4	H_2O	2	90

[a] Isolated yield.

Table 4
Synthesis of octahydroquinolindiones catalyzed by ZnO in water

Entry	Aldehydes	Product[a]	Time (h)	Yield[b] (%)	Mp °C
1	4-$MeOC_6H_4CHO$	**5a**	2	90	145–147
2	3,4-$(MeO)_2C_6H_3CHO$	**5b**	2.5	85	160–163
3	2-HOC_6H_4CHO	**5c**	2.5	87	230–232
4	3-$NO_2C_6H_4CHO$	**5d**	2	90	168–170
5	2-$NO_2C_6H_4CHO$	**5e**	2	88	173–175
6	4-ClC_6H_4CHO	**5f**	2.5	86	238–240
7	HCHO	**5g**	15	ND	—
8	CH_3CHO	**5h**	15	ND	—
9	3-$NO_2C_6H_4CHO$	**5i**[c]	10	40	186–189

[a] All isolated products are new and were characterized by IR, ^1H NMR, ^{13}C NMR spectral and CHN analyses.
[b] Isolated yields.
[c] 1,3-cyclohexandione (0.1 mmol) was used instead of dimedone.

In recent years, Raman spectroscopy has been proved to be a valuable tool in the investigation of structure of complex molecules of biological interest.[26] Recently, we have reported the vibrational studies on 6-amino-4-(4′-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole.[27]

To determine the configuration of C15 (C4) and C16 (C3) in 4-(2′-nitrophenyl)-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline-3-carboxylic acid ethyl ester (**5e**), the vibrational frequencies were calculated and the scaled values were compared with experimental FT-IR and FT-Raman spectral values for both *cis*- and *trans*- isomers to find the structure of **5e**. It is found that, the observed and the calculated frequencies of *e,e′-trans*- isomer are found to be in good agreement for the important functional groups as shown in Table 5. These frequency calculations were carried out on the optimized structure of **5e** using the program available in the GAUSSIAN software.[28–30]

The optimized geometry of **5e** and the numbering system is given in Figure 1. From the density functional theory (DFT) calculations we found that, the configuration of C15 (C4) and C16 (C3) in **5e** is *ee′-trans*.

The possibility of recycling the catalyst was then examined. After completion of the reaction (2–2.5 h), the contents were filtered and dichloromethane (10 ml) was added to the residue,

Table 5
Comparison of some important computed and experimental vibrational frequencies of *cis*- and *trans*-**5e**

Serial no.	Functional group	Calculated frequency ν cm^{-1} *trans*	Exptl. FT-IR[a] ν cm^{-1}	Exptl. FT-Raman[a] ν cm^{-1}	Calculated frequency ν cm^{-1} *cis*
1	C=O(pyridine)	1618	1617	1616	1715
2	C=O (Ester)	1718	1721	1723	1697
3	C15-H19 (str)	2921	2922	2916	2949
4	C16-H50 (str)	2973	2961	2952	3018

[a] (FT-IR and FT-Raman spectra are available as supplementary data).

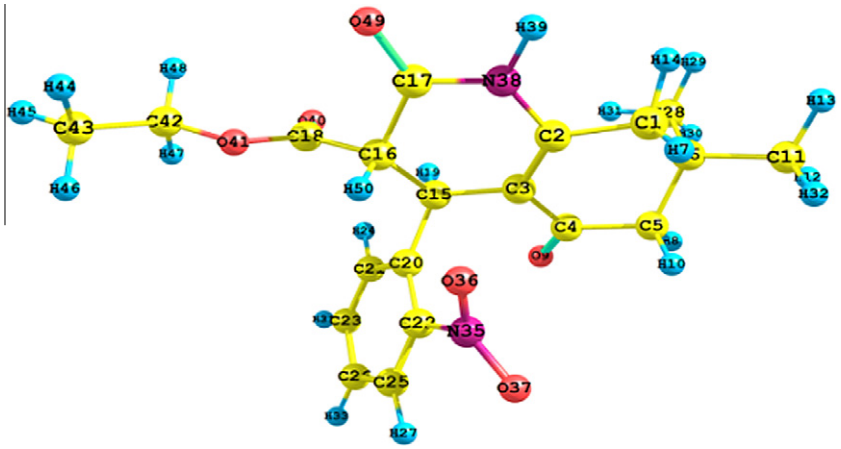

Figure 1. Optimized structure of **5e**.

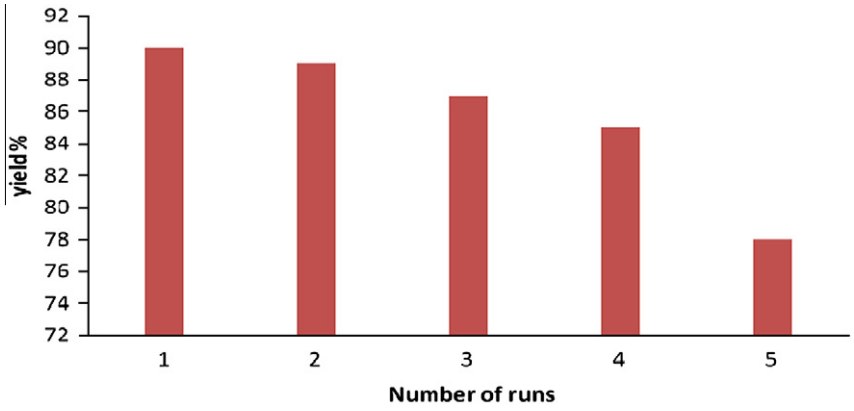

Figure 2. Reusability of ZnO in the synthesis of octahydroquinolindiones.

the catalyst was filtered and washed with dichloromethane and recycled five times. From the Figure 2, it can be seen that, in the first four runs the activity was more or less maintained but after the fourth run it starts decreasing, which is due to loss of the catalyst during recovery and the recovered amount of catalyst is 0.025, 0.024, 0.023, 0.022, and 0.020 g and the respective isolated yields for the five runs is found to be 90%, 89%, 87%, 85%, and 78%.

In conclusion, we have developed a new, rapid, and efficient method for the synthesis of 4-aryl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline-3-carboxylic acid ethyl esters by a one-pot four component reaction of aromatic aldehydes, diethyl malonate, dimedone/1,3-cyclohexadione, and ammonium acetate using ZnO as an efficient, mild, and heterogeneous catalyst which could be reused for at least five times. The reaction is facile, simple, and environment-friendly.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012. 09.053.

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23. *General procedure*: A mixture of aldehyde (1 mmol), diethyl malonate (1 mmol), ZnO (0.025 g, 7.5 mol %) and water (10 ml) was refluxed for 30 min; dimedone/I,3-cyclohehadione (1 mmol) and ammonium acetate (2 mmol) were then added to the reaction mixture and refluxed for the remaining time (Table 4). The crude product thus separated was filtered and washed with water, The dried solid residue was treated with dichloromethane and filtered to get ZnO which could be reused. The filtrate was then evaporated to get the desired solid 4-aryl-7,7-dimethyl-2,5dioxo-1,2,3,4,5,6,7,8-octahydroquinoline-3-carboxylic acid ethyl ester which was subjected to silica gel column chromatography [silica gel G, 100–200 mesh] to get the pure product.

    The yields and Mps of all the products are presented in Table 4, and the structures were confirmed by ^{1}H NMR, ^{13}C NMR spectral and CHN analyses.

    Spectral data:

    5a: Mp 145–147 °C; IR (KBr): *ν* 3384 (br), 2958 (s), 1734 (s), 1704 (s), 1668 (s), 1615 (vs), 1508 (s), 1448 (s), 1375 (vs), 1245 (vs), 1173 (vs), 1033 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 6H, 2Me), 1.23 (t, J = 5.2 Hz, 3H, Me), 2.55 (s,2H, CH_2), 2.67 (s, 2H, CH_2), 3.53 (s, 3H, CH_3), 3.98 (q, J = 6.0 Hz, 2H, CH_2), 4.15 (d, J = 7.2 Hz,1H, CH), 5.82 (d, J = 7.2 Hz,1H, CH), 7.00–7.02 (m, 2H, Ph), 7.21–7.23 (m, 2H, Ph), 10.87 (br, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9 (C=O), 181.8 (NC=O), 158.0 (OC=O), 139.2 (NC=C), 130.2, 128.2, 127.2, 116.2, 114.1, 112.2 (all Ar**C**), 112.2 (OC–**C**=C), 55.6 (O–**C**H$_2$), 52.8 (O–**C**H$_3$), 47.5 (O=C–**C**H–C=O), 46.9 (CH_2), 41.2 (CH_2), 32.4 (C=C–**C**H), 31.8 (>**C**<), 30.2, 27.8 (**C**H$_3$), 18.8 (**C**H$_3$); Anal. Calcd for $C_{21}H_{25}N_1O_5$: C, 67.91; H, 6.78; N, 3.77%. Found: C, 67.91; H, 6.782; N, 3.77%.

    5b: Mp 160-163 °C; IR (KBr): *ν* 3398 (br), 2962 (s), 1733(s), 1705 (s), 1668 (s), 1615 (vs), 1514 (s), 1448 (s), 1375 (vs), 1240 (vs), 1147 (vs), 1027 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 6H, 2Me), 1.23 (t, J = 5.2 Hz, 3H, Me), 2.35 (s,2H, CH_2), 2.40 (s, 2H, CH_2), 3.76 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 3.98 (q, J = 5.2 Hz, 2H, CH_2), 4.15 (d, J = 7.2 Hz,1H, CH), 5.48 (d, J = 7.2 Hz,1H, CH), 6.61 (s, 1H, Ph), 6.62 (d, J = 8.0 Hz, 1H, Ph), 6.76 (d, J = 8.0 Hz, 1H, Ph), 10.99 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9 (C=O), 179.8 (NC=O), 160.0 (OC=O), 147.4 (NC=C), 130.8, 122.8, 119.3, 116.2, 111.2, 110.8 (all Ar**C**), 110.8 (OC–**C**=C), 61.8 (O–**C**H$_2$), 56.2 (O–**C**H$_3$), 56.1 (O–**C**H$_3$), 47.5 (O=C–**C**H–C=O), 47.5 (CH_2), 46.8 (CH_2), 32.7 (C=C–**C**H), 31.7 (>**C**<), 30.4, 27.5 (**C**H$_3$), 17.8 (**C**H$_3$); Anal. Calcd for $C_{22}H_{27}N_1O_6$: C, 65.82; H, 6.78; N, 3.49%. Found: C, 65.82; H, 6.782; N, 3.49%.

    5c: Mp 230–232 °C; IR (KBr): *ν* 3433 (br), 3232 (br), 2954 (s), 1734 (s), 1705 (s), 1668 (s), 1615 (vs), 1517 (s), 1448 (s), 1375 (vs), 1244 (s), 1135 (vs), 1037 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 6H, 2Me), 1.23 (t, J = 5.2 Hz, 3H, Me), 2.35 (s,2H, CH_2), 2.40 (s, 2H, CH_2), 3.93 (q, J = 7.2 Hz, 2H, CH_2), 4.07 (d, J = 7.2 Hz,1H, CH), 4.57 (s, 1H, OH), 5.28 (d, J = 7.2 Hz, 1H, CH), 6.99 (d, J = 5.6 Hz, 1H, Ph), 7.13 (d, J = 5.6 Hz, 1H, Ph),7.37 (d, J = 7.6 Hz, 1H, Ph), 7.41 (d, J = J = 7.6 Hz, 1H, Ph), 10.49 (br, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5 (C=O), 187.1 (NC=O), 169.1 (OC=O), 151.5 (NC=C), 128.4, 128.0, 125.0, 124.7, 118.7, 116.2 (all Ar**C**), 111.4 (OC–**C**=C), 50.3 (O–**C**H$_2$), 43.6 (O=C–**C**H–C=O), 42.0 (CH_2), 31.4 (CH_2), 30.4 (C=C–**C**H), 29.6 (>**C**<), 28.2, 26.8 (**C**H$_3$), 17.1 (**C**H$_3$); Anal. Calcd for $C_{20}H_{23}N_1O_5$: C, 67.21; H, 6.49; N, 3.92%. Found: C, 67.20; H, 6.461; N, 3.91%.

    5d: Mp 168–170 °C; IR (KBr): *ν* 3433 (br), 2960 (s),1737(s), 1705 (s), 1668 (s), 1615 (vs), 1527 (s), 1448 (s), 1377 (vs), 1336 (vs)1253 (s), 1166 (s), 1022 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 6H, 2Me), 1.23 (t, J = 5.2 Hz, 3H, Me), 2.35 (s,2H, CH_2), 2.40 (s, 2H, CH_2), 4.09 (q, J = 6.0 Hz, 2H, CH_2), 4.38 (d, J = 6 Hz,1H, CH), 5.54 (d, J = 7.2 Hz,1H, CH), 7.40–7.44 (m, 2H, Ph), 8.00–8.04 (m, 2H, Ph), 10.96 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3 (C=O), 180.9 (NC=O), 159.1 (OC=O), 137.5 (NC=C), 137.5, 132.5, 131.8, 130.0, 127.8, 124.6 (all Ar**C**), 115.1 (OC–**C**=C), 57.8 (O–**C**H$_2$), 47.3 (O=C–**C**H–C=O), 46.7 (CH_2), 32.3 (CH_2), 30.5 (C=C–**C**H), 29.0 (>**C**<), 28.6, 26.0 (**C**H$_3$), 15.1 (**C**H$_3$); Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.17; H, 5.74; N, 7.25%. Found: C, 62.17; H, 5.741; N, 7.25%.

    5e: Mp 173–175 °C; IR (KBr): *ν* 3433 (br), 2960 (s),1730 (s), 1705 (s), 1668 (s), 1615 (vs), 1523 (vs), 1448 (s), 1388 (s), 1367(s), 1238 (s), 1135 (vs), 1058 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 6H, 2Me), 1.23 (t, J = 5.2 Hz, 3H, Me), 2.35 (s,2H, CH_2), 2.40 (s, 2H, CH_2), 4.09 (q, J = 6.0 Hz, 2H, CH_2), 4.45 (d, J = 6.8 Hz,1H, CH), 6.05 (d, J = 6.8 Hz, 1H, CH), 7.24 (d, J = 7.6 Hz, 1H, Ph), 7.03 (d, J = 7.6 Hz, 1H, Ph), 7.44 (d, J = 8.0 Hz, 1H, Ph), 7.47 (d, J = 8.0 Hz, 1H, Ph), 10.86 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6 (C=O), 178.1 (NC=O), 161.8 (OC=O), 148.8 (NC=C), 141.1, 133.3, 129.5, 122.7, 121.5, 115.2 (all Ar**C**), 115.2 (OC–**C**=C), 54.8 (O–**C**H$_2$), 47.4 (O=C–**C**H–C=O), 46.8 (CH_2), 32.3 (CH_2), 31.9 (C=C–**C**H), 30.1 (>**C**<), 27.6, 26.1 (**C**H$_3$), 16.2 (**C**H$_3$); Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.17; H, 5.74; N, 7.25%. Found: C, 62.17; H, 5.741; N, 7.24%.

    5f: Mp 238–240 °C; IR (KBr): *ν* 3431 (br), 2956 (s),1734 (s), 1704 (s), 1668 (s), 1615 (vs), 1498 (s), 1396 (s), 1257 (s), 1135 (s), 1020 (s),827 (vs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 6H, 2Me), 1.23 (t, J = 5.2 Hz, 3H, Me), 2.55 (s,2H, CH_2), 2.67 (s, 2H, CH_2), 3.98 (q, J = 6 Hz, 2H, CH_2), 4.16 (d, J = 7.2 Hz, 1H, CH), 5.48 (d, J = 7.2 Hz, 1H, CH), 7.00–7.02 (m, 2H, Ph), 7.21–7.23 (m, 2H, Ph), 10.87 (br, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.4 (C=O), 176.9 (NC=O), 160.9 (OC=O), 148.8 (NC=C), 131.4, 129.9, 128.8, 128.6, 117.8, 110.2 (all Ar**C**), 110.2 (OC–**C**=C), 55.8 (O–**C**H$_2$), 47.5 (O=C–**C**H–C=O), 46.8 (CH_2), 32.8 (CH_2), 31.8(C=C–**C**H), 30.1 (>**C**<), 30.1, 27.8 (**C**H$_3$), 18.8 (**C**H$_3$); Anal. Calcd for $C_{20}H_{22}ClN_1O_4$: C, 63.91; H, 5.90; N, 3.73%. Found: C, 63.91; H, 5.901; N, 3.72%.

    5i: Mp 186–189 °C; IR (KBr): *ν* 3437 (br), 2958 (s),1730 (s), 1705 (s), 1667 (s), 1612 (vs), 1489 (s), 1386 (s), 1267 (s), 1138 (s), 1027 (s),824 (vs) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.24 (t, J = 7.2 Hz, 3H, 1Me), 1.89 (qn, J = 5.2 Hz, 2H, CH_2), 2.19 (t, J = 6.0 Hz, 2H, CH_2), 3.34 (t, J = 8.0 Hz, 2H, CH_2), 3.92 (d, J = 8.0 Hz, 1H, CH), 4.24 (q, J = 6 Hz, 2H, CH_2), 4.99 (d, J = 8.0 Hz, 1H, CH), 5.48 (d, J = 7.2 Hz, 1H, CH), 7.00–7.02 (m, 2H, Ph), 7.21–7.23 (m, 2H, Ph), 10.87 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.7 (C=O), 183.7 (NC=O), 168.7 (OC=O), 148.3 (NC=C), 152.9, 140.2, 135.2, 134.8, 131.6, 126.0 (all Ar**C**), 112.4 (OC–**C**=C), 62.6 (O–**C**H$_2$), 57.0 (O=C–**C**H–C=O), 36.5 (CH_2), 33.7 (**C**H$_2$), 27.2 (C=C–**C**H), 21.6 (**C**H$_2$), 14.8 (**C**H$_3$); Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 60.33; H, 5.06; N, 7.82%. Found: C, 60.33; H, 5.056; N, 7.83%.

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