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Room temperature ionic liquids promoted three-component coupling reactions: a facile synthesis of *cis*-isoquinolonic acids

J. S. Yadav,* B. V. S. Reddy, K. Saritha Raj and A. R. Prasad

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad-500 007, India

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Abstract—Room temperature ionic liquids are found to catalyze efficiently the three component-coupling reactions of aldehydes, amines and homophthalic anhydride under mild and convenient conditions to afford the corresponding *cis*-isoquinolonic acids in excellent yields with high *cis*-selectivity.

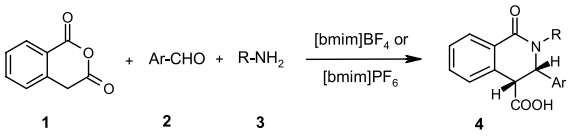
1. Introduction

Tetrahydroquinoline derivatives are an important class of compounds in the field of pharmaceuticals and exhibit a wide spectrum of biological activities[1] including psychotropic, anti-allergenic, anti-inflammatory and estrogenic behaviour. In particular, isoquinolonic acids are found to possess a vast range of pharmacological activities.[2] Particularly, isoquinolonic acids are useful precursors for the total synthesis of naturally occurring phenanthridine alkaloids[3] such as corynoline, oxocorynoline and epicorynoline as well as indenoisoquinolines[4] possessing significant antitumor activity. The cycloaddition of homophthalic anhydride with aldimines provides a useful access to the preparation of isoquinolonic acids.[5] The cycloaddition of homophthalic anhydride with imines has been reported using a base catalysis or no catalyst under thermal conditions,[6,7] which often produce a mixture of *cis*- and *trans*-isomers, favoring *cis*-isomer. Recently, trimethyl orthoformate has also been employed for the synthesis of *trans*-isoquinolonic acids.[8]

Room temperature ionic liquids, especially those based on the 1-*N*-alkyl-3-methylimidazolium cation, have shown great promise as an attractive alternative to conventional solvents. They are non-volatile, recyclable, non-explosive, easy to handle, and thermally robust.[9] In many cases, the products are weakly soluble in the ionic phase so that the products can be easily separated by simple extraction with ether.[10] Because of the great potential of room temperature ionic liquids as novel reaction media for catalytic processes, much attention has been currently focused on organic reactions promoted by ionic liquids.[11]

2. Results and discussion

In view of the emerging importance of the ionic liquids as novel reaction media, we wish to explore the use of ionic liquids as promoters for the synthesis of *cis*-quinolonic acids. Thus treatment of benzaldehyde, aniline and homophthalic anhydride in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) ionic liquid at ambient temperature afforded the corresponding *cis*-isoquinolonic acid derivative **4** in 90% yield (Scheme 1).



Scheme 1.

Similarly, several aryl imines reacted smoothly with homophthalic anhydride to give the corresponding isoquinolonic acids in 75–91% yield. In all reactions, the product was obtained as a *cis*-diastereomer, which was assigned based on the coupling constants of the hydrogens in the ^{1}H NMR spectrum of the product. The stereochemistry of the product was further confirmed by the direct comparison of spectroscopic data with authentic compounds. In all cases, the reactions proceeded efficiently at ambient temperature under mild conditions to afford the corresponding isoquinolonic acids in high yields. However, in the absence of ionic liquids, the reaction did not yield any product even after a long reaction time (10–15 h). The reactions are clean and highly diastereoselective, affording exclusively the corresponding *cis*-isomer in high yields. All the products were characterized by ^{1}H NMR, IR and mass spectroscopy. In this reaction, the efficiency of ionic liquid was strongly influenced by the nature of the anion. The reactions of various aldehydes, amines and homophthalic

Keywords: ionic melts; aldimines; cyclization; *cis*-isoquinolonic acids.

* Corresponding author. Tel.: +91-40-7160512; fax: +91-40-27160512; e-mail: yadav@iict.ap.nic.in

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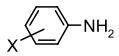
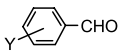
Table 1. Ionic liquids-promoted synthesis of *cis*-isoquinolonic acids

Entry	Amine	Aldehyde	Product	[bmim]BF_4		[bmim]PF_6	
				Time (h)	Yield (%)[a]	Time (h)	Yield (%)[a]
							
a	X=H	Y=4-MeO	**4a**	2.0	89	3.5	83
b	X=4-Me	Y=H	**4b**	2.5	87	3.0	85
c	X=H	Y=H	**4c**	3.0	90	4.0	87
d	X=4-Cl	Y=2-Me	**4d**	3.5	85	4.5	81
e	X=4-Br	Y=H	**4e**	4.0	87	5.0	83
f	X=4-MeO	Y=2-Me	**4f**	3.0	91	4.0	85
g	X=H	Y=4-$N(Me)_2$	**4g**	4.0	90	5.5	82
h	X=3,4,5-$(MeO)_3$	Y=H	**4h**	3.5	85	5.0	81
I	X=4-Me	Y=4-MeO	**4i**	3.0	90	4.0	85
j	X=4-Cl	Y=H	**4j**	3.0	87	4.5	83
k	X=H	Y=2-NO_2	**4k**	6.5	75	8.0	72
l	X=H	Y=4-CN	**4l**	5.5	80	6.0	78
m	Benzyl amine	Y=4-MeO	**4m**	3.5	89	4.5	80
n	2-Phenylethylamine	Y=4-MeO	**4n**	3.5	78	4.5	75
o	X=H	2-Naphthaldehyde	**4o**	5.0	80	6.5	78
p	X=H	Thiophene-2-carboxaldehyde	**4p**	2.5	85[b]	3.5	81[b]

[a] Isolated and unoptimized yields after column chromatography.
[b] 10% *trans*-isomer was also obtained.

anhydride were studied in hydrophilic [bmim]BF_4 and hydrophobic [bmim]PF_6 ionic liquids. Among these ionic liquids, [bmim]BF_4 was found to be superior in terms of yields and reaction rates (Table 1). The advantage of the use of ionic liquids as novel reaction media for this transformation is that these ionic liquids can be easily recovered and recycled in subsequent reactions. Since the products were weakly soluble in the ionic phase, they were easily separated by simple extraction with ether. The rest of the viscous ionic liquid was thoroughly washed with ether and reused in subsequent reactions without further purification. However, the products were obtained of the same purity as in the first run, the yields gradually decreased in runs carried out using recycled ionic liquid. For example, the reaction of benzaldehyde, aniline and homophthalic anhydride afforded the corresponding *cis*-isoquinolonic acid in 90, 87, 85, and 82% yields over four cycles. However, the activity of ionic liquid was consistent in runs and no decrease in yield was obtained when the recycled ionic liquid was activated at 80°C under vacuum in each cycle. Compared to conventional methods, this method avoids the preparation and isolation of unstable imines prior to the reactions. Most of the conventional Lewis acids such as $BF_3.OEt_2$, $TiCl_4$ and $SnCl_4$ were decomposed or deactivated by amines and water that exist during imine formation. However, ionic liquids are stable with amines and water and also effectively activate the imines (formed in situ from aldehydes and amines) to undergo cyclization. To know the role of ionic liquid in this transformation, the reaction was carried out in dichloromethane both in the presence of 10 mol% [bmim]BF_4 ionic liquid and in the absence of ionic liquid. High conversions were obtained in a short reaction time in the combined solvent system i.e. [bmim]BF_4 ionic liquid in dichloromethane. Other polar organic solvents such as methanol and acetonitrile were also used to study the role of ionic liquids in this transformation. In these solvents, the reactions proceeded only at high temperature (70–80°C) and also took longer reaction times (8–15 h). Moreover, the products were obtained in low to moderate yields (45–60%). In further reactions, the efficiency of various quaternary ammonium salts was studied. The three-component condensation was not successful in other molten salts such as *n*-tetrabutyl ammonium chloride (*n*-Bu_4NCl) or in 1-*n*-butyl-3-methylimidazolium chloride ([bmim]Cl. These results indicate that both cation and anion play an important role as the reaction media. The scope and

Table 2. $InCl_3$-Catalyzed synthesis of *cis*-isoquinolonic acids

Entry	X–Ar NH_2	Y–ArCHO	Product[a]	5% $InCl_3$–[bmim]BF_4		5% $InCl_3$–CH_2Cl_2	
				Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
a	X=H	Y=4-MeO	**4a**	1.0	92	2.0	81
b	X=4-Me	Y=H	**4b**	1.0	90	1.5	85
c	X=H	Y=H	**4c**	0.5	95	1.0	87
d	X=4-Cl	Y=2-Me	**4d**	1.5	91	2.0	83
e	X=4-Br	Y=H	**4e**	1.0	89	2.5	80
f	X=4-MeO	Y=2-Me	**4f**	1.5	92	2.0	82
g	X=H	Y=4-$N(Me)_2$	**4g**	2.5	87	3.5	75
h	X=3,4,5-$(MeO)_3$	Y=H	**4h**	2.0	89	3.0	78
i	X=4-Me	Y=4-MeO	**4i**	1.5	91	2.5	82

[a] All products were obtained as *cis*-isomers in both solvents at room temperature.
[b] Yields refer to after purification.

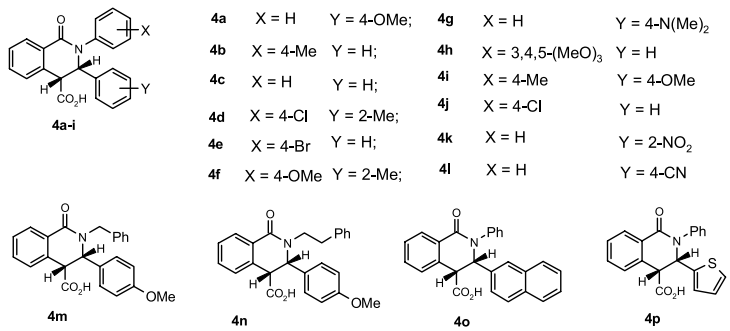


Figure 1. Structures of products **4(a–p)**.

generality of this process is illustrated with respect to various aldehydes, amines and homophthalic anhydride in ionic liquids and the results are presented in the Table 1. We have also performed these three-component coupling reactions using indium trichloride in ionic liquids as well as in dichloromethane to compare the efficiency of ionic liquids and the results are presented in Table 2. Although, these cyclization reactions proceeded smoothly in the presence of 5 mol% indium trichloride in both solvents, the recovery and reuse of indium trichloride is especially simple in ionic liquids. In contrast to organic solvents, enhanced reaction rates, improved yields and high selectivity are the features obtained in ionic liquids. For example, the treatment of benzaldehyde and aniline with homophthalic anhydride in [bmim]BF_4 ionic liquid for 3.0 h afforded the corresponding *cis*-isoquinolonic acid in 90% yield whereas the same reaction in refluxing methanol after 8.0 h gave the product in 60% yield as a mixture of *cis*- and *trans*-isomers in 3:1 ratio. In most cases, the reactions gave mixtures of *cis*- and *trans*-products along with homophthalic amides under refluxing conditions. The use of ionic liquids as reaction media for this transformation avoids the use of moisture sensitive reagents or high temperature reaction conditions to promote the reaction. This clearly indicates the efficiency of ionic liquids for this transformation.

3. Conclusion

The paper describes a novel and efficient method for the synthesis of tetrahydroisoquinolonic acids involving three component-coupling reactions of aldehydes, amines and homophthalic anhydride using ionic liquids as reaction media as well as promoters. The notable features of this procedure are mild reaction conditions, greater *cis*-selectivity, improved yields, cleaner reaction profiles, enhanced rates, ease of recovery and reuse of this novel reaction medium, which make it a simple and convenient method for the synthesis of isoquinoline derivatives of biological importance.

4. Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. ^1H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. CHN analyses were recorded on a Vario EL analyzer. [Bmim]BF_4 and [bmim]PF_6 ionic liquids were prepared according to the procedures reported in the literature.[12]

4.1. General procedure

Method A. A mixture of aldehyde (2 mmol), amine (2 mmol), and homophthalic anhydride (2 mmol) in 1-butyl-3-methylimidazolium tetrafluoroborate or 1-butyl-3-methylimidazolium hexafluorophosphate (2 mL) was stirred at ambient temperature for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3×10 mL). The combined ether extracts were concentrated in vacuo and the resulting product was directly charged on small silica gel column and eluted with a mixture of ethyl acetate: *n*-hexane (2:8) to afford pure isoquinolonic acid. On the other hand, the combined ether layers were concentrated in vacuo and the resulting product was recrystallized in a mixture of ether and pentane solvent system to afford the pure product. The rest of the viscous ionic liquid was further washed with ether and dried at 80°C under reduced pressure to retain its activity in subsequent runs.

Method B. A mixture of aldehyde (2 mmol), amine (2 mmol), homophthalic anhydride (2 mmol) and $InCl_3$ (5 mol%) in [bmim]BF_4 ionic liquid (2 mL) or dichloromethane (5 mL) was stirred at ambient temperature for 0.5–1.5 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and the resulting solid was separated by filtration. The crude product was recrystallized in a mixture of ether and pentane solvent system to afford pure *cis*-isoquinolonic acids in 80–90% yields (Fig. 1).

4.1.1. 3-(4-Methoxyphenyl)-1-oxo-2-phenyl-1,2,3,4-tetrahydro-4-isoquinoline-carboxylic acid (4a). White solid, m.p. 110°C; ^1H NMR ($CDCl_3$) δ: 3.70 (s, 3H), 4.80 (d, 1H, J=6.0 Hz), 5.38 (d, 1H, J=6.0 Hz), 6.63 (d, 2H, J=8.4 Hz), 6.97 (d, 2H, J=8.4 Hz), 7.18 (d, 2H, J=8.3 Hz), 7.20–7.37 (m, 3H), 7.40–7.58 (m, 2H), 7.65 (d, 1H, J=8.2 Hz), 8.18 (dd, 1H, J=2.1, 8.2 Hz). IR (KBr) ν: 2925, 1733, 1603, 1508, 1252, 1171, 1025, 784 cm^{-1}. EIMS: *m/z*: 373[M^+], 258, 181, 166, 143, 95, 70, 42. Anal. Calcd for $C_{23}H_{19}NO_4$ (373.40): C, 73.98; H, 5.13; N, 3.75. Found: C, 74.07; H, 5.18; N, 3.737.

4.1.2. 2-(4-Methylphenyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydro-4-isoquinoline-carboxylic acid (4b). Pale yellow solid, m.p. 178°C; ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 3H), 4.85 (d, 1H, J=6.0 Hz), 5.40 (d, 1H, J=6.0 Hz), 7.05–7.35 (m, 7H), 7.40–7.60 (m, 3H), 7.70 (d, 2H, J=8.0 Hz), 8.20 (dd, 1H, J=2.0, 8.0 Hz). IR (KBr) ν: 2927, 1736, 1625, 1510, 1435, 1175, 698 cm^{-1}. EIMS: m/z: 357[M$^+$], 350, 308, 278, 252, 208, 191, 174, 133, 106, 79, 42. Anal. Calcd for $C_{23}H_{19}NO_3$ (357.40): C, 77.29; H, 5.36; N, 3.92. Found: C, 77.31; H, 5.34; N, 3.95.

4.1.3. 1-Oxo-2,3-diphenyl-1,2,3,4-tetrahydro-4-isoquinoline-carboxylic acid (4c). White solid, m.p. 198°C; ^{1}H NMR ($CDCl_3$) δ: 4.85 (d, 1H, J=6.0 Hz), 5.40 (d, 1H, J=6.0 Hz), 7.05 (m, 8H), 7.40 (m, 3H), 7.70 (d, 1H, J=8.0 Hz), 8.20 (dd, 1H, J=2.1, 8.0 Hz). IR (KBr) ν: 3033, 1724, 1633, 1494, 1222, 1023, 770, 696 cm^{-1}. EIMS: m/z: 343[M$^+$], 182, 134, 106, 89, 78.Anal. Calcd for $C_{22}H_{17}NO_3$ (343.38): C, 76.95; H, 4.99; N, 4.08. Found: C, 76.97; H, 4.97; N, 4.10.

4.1.4. 2-(4-Chlorophenyl)-3-(2-methylphenyl)-1-oxo-1,2,3,4-tetrahydro-4-isoquinoline carboxylic acid (4d). Pale yellow solid, m.p. 186°C; ^{1}H NMR ($CDCl_3$) δ: 2.25 (s, 3H), 4.80 (d, 1H, J=6.0 Hz), 5.38 (d, 1H, J=8.0 Hz), 7.10–7.35 (m, 5H), 7.40–7.55 (m, 5H), 7.65 (d, 1H, J=8.0 Hz), 8.20 (dd, 1H, J=2.1, 8.0 Hz). IR (KBr) ν: 2927, 1736, 1625, 1510, 1435, 1175, 698 cm^{-1}. EIMS: m/z: 391[M$^+$], 229, 127, 84, 66, 46. Anal. Calcd for $C_{23}H_{18}ClNO_3$ (391.85): C, 70.50; H, 4.63; Cl, 9.05; N, 3.57. Found: C, 70.53; H, 4.67; Cl, 9.10; N, 3.59.

4.1.5. 2-(4-Bromophenyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydro-4-isoquinoline-carboxylic acid (4e). Yellow solid, m.p. 180°C; ^{1}H NMR ($CDCl_3$) δ: 4.80 (d, 1H, J=6.0 Hz), 5.40 (d, 1H, J=6.0 Hz), 7.05–7.20 (m, 6H), 7.30–7.45 (m, 5H), 7.65 (d, 1H, J=8.0 Hz), 8.18 (d, 1H, J=8.0 Hz). IR (KBr) ν: 3034, 1727, 1634, 1575, 1487, 1384, 1227, 1164, 1010, 811, 724 cm^{-1}. EIMS: m/z: 421[M$^+$], 343, 178, 140, 117, 77, 65. Anal. Calcd for $C_{22}H_{16}BrNO_3$ (422.27): C, 62.58; H, 3.82; Br, 18.92; N, 3.32. Found: C, 62.60; H, 3.85; Br, 18.90; N, 3.35.

4.1.6. 2-(4-Methoxyphenyl)-3-(2-methylphenyl)-1-oxo-1,2,3,4-tetrahydro-4-isoquinoline carboxylic acid (4f). White solid, m.p. 150°C; ^{1}H NMR ($CDCl_3$) δ: 2.23 (s, 3H), 3.85 (s, 3H), 4.80 (d, 1H, J=6.0 Hz), 5.28 (d, 1H, J=6.0 Hz), 6.70–6.83 (m, 3H), 6.98–7.05 (m, 2H), 7.40–7.55 (m, 5H, J=2.4 Hz), 7.65 (d, 1H, J=8.0 Hz), 8.20 (d, 1H, J=8.0 Hz). IR (KBr) ν: 3027, 1728, 1682, 1512, 1415, 1275, 1171, 1033, 821, 717 cm^{-1}. EIMS: m/z: 387[M$^+$], 285, 225, 123, 108, 90, 63. Anal. Calcd for $C_{24}H_{21}NO_4$ (387.43): C, 74.40; H, 5.46; N, 3.62. Found: C, 74.43; H, 5.48; N, 3.65.

4.1.7. 3-(4-Dimethylaminophenyl)-1-oxo-2-phenyl-1,2,3,4-tetrahydro-4-isoquinoline carboxylic acid (4g). Yellow solid, m.p. 152°C; ^{1}H NMR ($CDCl_3$) δ: 2.80 (s, 6H), 4.80 (d, 1H, J=6.0 Hz), 5.25 (d, 1H, J=6.0 Hz), 6.40 (d, 1H, J=8.2 Hz), 6.80 (d, 1H, J=8.2 Hz), 6.98 (t, 1H, J=8.0 Hz), 7.15–7.25 (m, 5H), 7.38–7.45 (m, 3H), 7.65 (d, 1H, J=8.0 Hz), 8.18 (d, 1H, J=8.0 Hz). IR (KBr) ν: 3421, 3324, 1701, 1664, 1539, 1440, 1351, 1265, 754, 695 cm^{-1}. EIMS: m/z: 384[M$^+$], 372, 356, 237, 165, 135, 93, 77, 65. Anal. Calcd for $C_{24}H_{22}N_2O_3$ (384.44): C, 74.59; H, 5.74; N, 7.25. Found: C, 74.60; H, 5.76; N, 7.23.

4.1.8. 1-Oxo-3-phenyl-2-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-4-isoquinoline carboxylic acid (4h). White solid, m.p. 192°C; ^{1}H NMR ($CDCl_3$) δ: 3.60 (s, 6H), 3.75 (s, 3H), 4.85 (d, 2H, J=6.0 Hz), 5.30 (d, 1H, J=6.0 Hz), 6.28 (s, 2H), 7.15–7.05 (m, 5H), 7.40–7.58 (m, 2H), 7.68 (d, 1H, J=8.0 Hz), 8.20 (d, 1H, J=8.0 Hz). IR (KBr) ν: 3438, 2967, 1736, 1648, 1519, 1428, 1260, 1172, 1042, 813, 759 cm^{-1}. EIMS: m/z: 433[M$^+$], 414, 271, 256, 141, 105, 91, 69. Anal. Calcd for $C_{25}H_{23}NO_6$ (433.45): C, 69.27; H, 5.35; N, 3.23. Found: C, 69.30; H, 5.37; N, 3.25.

4.1.9. 3-(4-Methoxyphenyl)-2-(4-methylphenyl)-1-oxo-1,2,3,4-tetrahydro-4-isoquinoline carboxylic acid (4i). White solid, m.p. 180°C; ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 3H), 3.70 (s, 3H), 4.90 (d, 1H, J=5.9 Hz), 5.30 (d, 1H, J=5.9 Hz), 6.65 (d, 2H, J=8.1 Hz), 6.90–7.20 (m, 5H), 7.45–7.60 (m, 4H), 8.30 (d, 1H, J=8.0 Hz). IR (KBr) ν: 2932, 1748, 1610, 1580, 1249, 1182, 1035, 778, 682 cm^{-1}. FAB mass: m/z: 387[M$^+$], 370, 342, 237, 225, 154, 136, 107, 91, 77, 69, 55. Anal. Calcd for $C_{24}H_{21}NO_4$ (387.43): C, 74.40; H, 5.46; N, 3.62. Found: C, 74.43; H, 5.48; N, 3.65.

4.1.10. 2-(4-Chlorophenyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydro-4-isoquinolinecarboxylic acid (4j). Pale yellow solid, m.p. 182°C; ^{1}H NMR ($CDCl_3$) δ: 4.95 (d, 1H, J=6.0 Hz), 5.50 (d, 1H, J=6.0 Hz), 7.15–7.65 (m, 12H), 8.15 (d, 1H, J=8.0 Hz). IR (KBr) ν: 2931, 2815, 1732, 1481, 1389, 1234, 1168, 779 cm^{-1}. FAB mass: m/z: 377[M$^+$], 332, 307, 290, 272, 216, 176, 154, 136, 120, 107, 89, 77, 63. Anal. Calcd for $C_{22}H_{16}ClNO_3$ (377.82): C, 69.94; H, 4.27; Cl, 9.38; N, 3.71. Found: C, 69.96; H, 4.31; Cl, 9.40; N, 3.74.

4.1.11. 3-(2-Nitrophenyl)-1-oxo-2-phenyl-1,2,3,4-tetrahydro-4-isoquinoline carboxylic acid (4k). Yellow solid, m.p. 222°C; ^{1}H NMR ($CDCl_3$) δ: 4.90 (d, 1H, J=5.9 Hz), 5.60 (d, 1H, J=5.9 Hz), 7.15–7.70 (m, 10H), 7.95 (d, 1H, J=2.0 Hz), 8.10 (d, 1H, J=8.0 Hz), 8.25 (dd, 1H, J=8.0, 2.0 Hz). IR (KBr) ν: 3318, 1728, 1659, 1527, 1438, 1273, 1178, 1048, 748, 674 cm^{-1}. FAB mass: m/z: 388[M$^+$], 369, 339, 313, 307, 289, 273, 259, 241, 227, 211, 107, 91, 77. Anal. Calcd for $C_{22}H_{16}N_2O_5$ (388.37): C, 68.04; H, 4.15; N, 7.21. Found: C, 68.02; H, 4.17; N, 7.23.

4.1.12. 3-(4-Cyanophenyl)-1-oxo-2-phenyl-1,2,3,4-tetrahydro-4-isoquinoline carboxylic acid (4l). Pale yellow solid, m.p. 180°C; ^{1}H NMR ($CDCl_3$) δ: 4.85 (d, 1H, J=5.9 Hz), 5.50 (d, 1H, J=5.9 Hz), 7.10–7.65 (m, 12H), 8.20 (d, 1H, J=8.0 Hz). IR (KBr) ν: 3414, 2925, 1703, 1619, 1528, 1267, 755, 615 cm^{-1}. EIMS: m/z: 368 M$^+$, 206, 181, 162, 77, 65. Anal. Calcd for $C_{23}H_{16}N_2O_3$ (368.39): C, 74.99; H, 4.38; N, 7.60. Found: C, 75.01; H, 4.40; N, 7.64.

4.1.13. 2-Benzyl-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydro-4-isoquinolinecarboxylic acid (4m). White solid, m.p. 198°C; ^{1}H NMR ($CDCl_3$) δ: 3.60 (d, 1H, J=14.0 Hz), 3.75 (s, 3H), 4.80 (d, 1H, J=6.0 Hz), 5.85 (d, 1H, J=6.0 Hz), 5.70 (d, 1H, J=14.0 Hz), 6.70 (d, 2H, J=8.0 Hz), 6. 90 (d, 2H, J=8.0 Hz), 7.2–7.35 (m, 6H),

7.58–7.60 (m, 2H), 8.25 (dd, 1H, J=2.0, 8.0 Hz). IR (KBr) ν: 3439, 1741, 1617, 1513, 1257, 1168, 1023, 829, 748 cm^{-1}. EIMS: m/z: 387[M^+], 381, 282, 237, 226, 165, 134, 121, 91, 77, 65. Anal. Calcd for $C_{24}H_{21}NO_4$ (387.43): C, 74.40; H, 5.46; N, 3.62. Found: C, 74.43; H, 5.48; N, 3.65.

4.1.14. 3-(4-Methoxyphenyl)-1-oxo-2-phenethyl-1,2,3,4-tetrahydro-4-isoquinoline carboxylic acid (4n). White solid, m.p. 166°C; ^1H NMR ($CDCl_3$) δ: 2.90–3.05 (m, 4H), 3.70 (s, 3H) 4.40 (d, 1H, J=5.7 Hz), 4.78 (d, 1H, J=5.7 Hz), 6.65 (d, 2H, J=8.0 Hz), 6.90 (d, 2H, J=8.0 Hz), 7.25–7.60 (m, 8H), 8.20 (dd, 1H, J=8.0, 1.8 Hz). IR (KBr) ν: 3035, 2928, 1727, 1622, 1513, 1472, 1252, 1173, 1031, 762, 702 cm^{-1}. FAB mass: m/z: 401 M^+, 356, 337, 255, 238, 162, 152, 132, 118, 107, 93, 77, 65, 43. Anal. Calcd for $C_{26}H_{23}NO_4$ (401.45): C, 74.80; H, 5.77; N, 3.49. Found: C, 74.83; H, 5.78; N, 3.50.

4.1.15. 3-(2-Naphthyl)-1-oxo-2-phenyl-1,2,3,4-tetrahydro-4-isoquinoline-carboxylic acid (4o). White Solid, m.p. 164°C; ^1H NMR ($CDCl_3$) δ: 4.85 (d, 1H, J=6.0 Hz), 5.58 (d, 1H, J=6.0 Hz), 7.10–7.30 (m, 6H), 7.38–7.50 (m, 4H), 7.58–7.75 (m, 5H), 8.20 (dd, 1H, J=2.0, 8.0 Hz). IR (KBr) ν: 2981, 1736, 1628, 1431, 1383, 1242, 1176, 1037, 752, 694 cm^{-1}. EIMS: m/z: 393[M^+], 384, 347, 230, 133, 104, 77, 43. Anal. Calcd for $C_{26}H_{19}NO_3$ (393.44): C, 79.37; H, 4.87; N, 3.56. Found: C, 79.40; H, 4.89; N, 3.58.

4.1.16. 1-Oxo-2-phenyl-3-(2-thienyl)-1,2,3,4-tetrahydro-4-isoquinoline carboxylic acid (4p). Pale yellow solid, m.p. 172°C; ^1H NMR ($CDCl_3$) δ: 4.90 (d, 1H, J=5.6 Hz), 5.65 (d, 1H, J=5.6 Hz), 6.80–6.90 (m, 2H), 7.05–7.15 (m, 1H), 7.10–7.65 (m, 10H), 8.20 (d, 1H, J=8.0 Hz). IR (KBr) ν: 3418, 1736, 1651, 1538, 1493, 1339, 1251, 1026, 1007, 824, 762 cm^{-1}. EIMS: m/z: 349 M^+, 278, 154, 136, 77, 68. Anal. Calcd for $C_{22}H_{15}ClN_2O_5$ (348.40): C, 68.75; H, 4.33; N, 4.01; S, 9.18. Found: C, 68.80; H, 4.35; N, 4.05; S, 9.20.

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