A three-component synthesis of *N*-substituted quinoline- 3-carbonitrile derivatives catalysed by L-proline

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A series of new *N*-substituted quinoline-3-carbonitrile derivatives were synthesised by the three-component reaction of *N*-substituted 5,5-dimethyl-3-aminocyclohex-2-enone, an arylaldehyde, and malononitrile catalysed by L-proline in ethanol at 80 °C.

Keywords: *N*-substituted quinoline-3-carbonitrile, L-proline catalysis, multi-component reaction

Quinolines are important as the scaffolds of bioactive substances. The ring structure is one of the most popular N-heteroaromatic moieties incorporated into the structures of pharmaceuticals. Many quinoline-containing compounds exhibit a wide range of pharmacological activities, such as antiplasmodial,[1] intrinsic,[2] cytotoxic,[3] functional,[4] antibacterial,[5] antiproliferative,[6] antimalarial[7] and anticancer activities.[8] Therefore, the synthesis of quinolines has become an attractive research field.

Multi-component reactions (MCRs) play an increasingly important role in organic and medicinal chemistry for their high degree of atom economy, convergence, productivity, easy execution, excellent yields and broad applications in combinatorial chemistry.[9]

Recently, many small organic molecules, for instance cinchona alkaloids and L-proline and its derivatives have been used in various organic reactions to give excellent yields. Amongst these enamine-based direct catalytic asymmetric aldol,[10,11] Mannich,[12,13] Michael,[14,15] Diels–Alder,[16,17] α-amination reactions, and Knoevenagel type reactions[16,17,18] using L-proline as catalyst have been reported. More recently, L-proline and its derivatives have been used in multi-component unsymmetric Biginelli[19,20] and Hantzsch reactions.[21] We have reported the synthesis of furo[3',4':5,6] pyrido[2,3-*c*]pyrazole derivatives catalysed by organo-catalysts.[22] Therefore, we are interested in investigating the novel three-component syntheses of *N*-substituted quinoline-3-carbonitrile derivatives catalysed by L-proline.

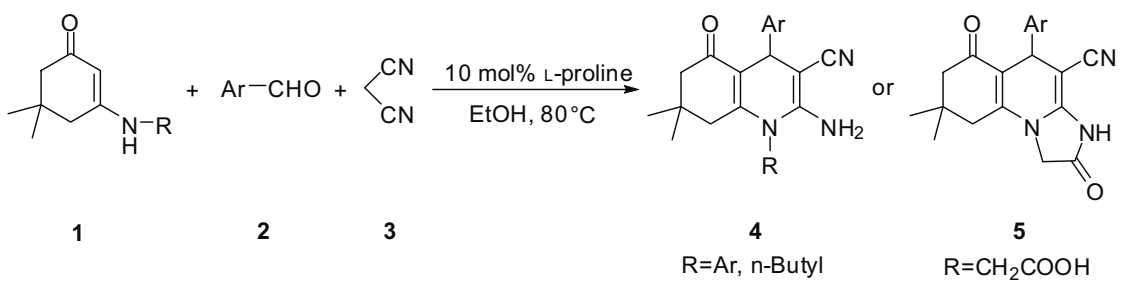
In a preliminary study, the syntheses of **4d** was chosen as a research template (see Scheme 1). Firstly, the reaction without any catalyst was tested in ethanol at 80 °C, and after 2 h only 42% of the target compound **4d** was obtained. Encouraged by this result, effects of different catalysts (glycine, lactamine, and L-proline) to the reaction were studied, and the results are shown in Table 1. It can be seen that glycine and lactamine have some efficiency, but that of L-proline is better. So L-proline was chosen to catalyse this reaction.

Table 1 Study on the catalytic efficiency of different catalysts in the synthesis of **4d**[a]

Entry	Catalyst	Time/h	Yield/%
1	None	4	42
2	Glycine,	3	80
3	Lactamine	3	78
4	L-Proline	2	90

[a]Reaction conditions: 5,5-dimethyl-3-(3-(trifluoromethyl) phenylamino)cyclohex-2-enone (1 mmol), 4-nitrobenzaldehyde (1 mmol) and malononitrile (1 mmol), catalyst 0.1 mmol, EtOH, 80 °C.

When *N*-substituted 5,5-dimethyl-3-aminocyclohex-2-enone (**1**), an arylaldehyde (**2**), and malononitrile (**3**) were stirred at 80 °C for 1–3 h in ethanol catalysed by L-proline, some new *N*-substituted quinoline-3-carbonitrile derivatives (**4**) were obtained in excellent yields (Scheme 1). The results shown in Table 2 indicate that *N*-substituted groups can be not only aromatic or aliphatic, but also carboxymethyl in this reaction. In all cases, products can be obtained with good yield in a short reaction time. When the *N*-substituted group of 5,5-dimethyl-3-aminocyclohex-2-enone is carboxymethyl the product is cyclised. All the products were fully characterised by IR, ^{1}H NMR and HRMS. The structure of **4i** was further confirmed by X-ray diffraction analysis. Crystallographic data are presented in Table 3. An ORTEP plot and atom numbering is given in Fig. 1. In compound **4i**, the 1,4-dihydropyridine ring (N1–C1–C2–C3–C4–C9) is a new ring. X-ray structure analysis of 4i showed that the 1,4-dihydropyridine ring in the structure has a boat conformation with C3 and N1 being –0.321(6) Å and –0.128(6) Å, respectively, from the plane



Scheme 1

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Table 2 Synthesis of *N*-substituted quinoline-3-carbonitrile derivatives catalysed by 10 mol% L-proline

Product	R	Ar	Time /h	Yield/%
4a	3-Cl-4-$CH_3C_6H_3$	4-$CH_3C_6H_4$	2	88
4b	3-$CF_3C_6H_4$	3,4,5-$(CH_3O)_3C_6H_2$	1	90
4c	3-$CF_3C_6H_4$	3,4-$Cl_2C_6H_3$	2	93
4d	3-$CF_3C_6H_4$	4-$NO_2C_6H_4$	2	91
4e	3-$CF_3C_6H_4$	3-ClC_6H_4	2.5	95
4f	4-FC_6H_4	4-BrC_6H_4	2.5	92
4g	4-$CH_3C_6H_4$	4-ClC_6H_4	2	90
4h	*n*-Butyl	4-FC_6H_4	2.5	89
4i	*n*-Butyl	3,4-$Cl_2C_6H_3$	3	91
4j	*n*-Butyl	2-ClC_6H_4	2	91
5a	CH_2COOH	4-ClC_6H_4	2.5	90
5b	CH_2COOH	Pyridin-2-yl	1	90
5c	CH_2COOH	5-Cl-2-$NO_2C_6H_3$	2	87
5d	CH_2COOH	2,4-$Cl_2C_6H_3$	2	92

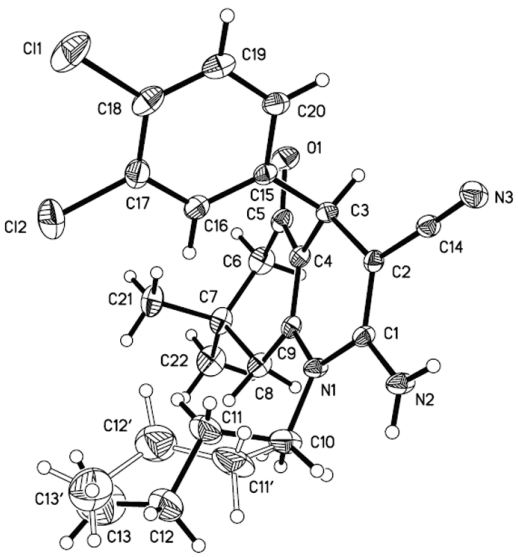

Fig. 1 ORTEP diagram of **4i**.

defined by C1, C2, C4 and C9 (plane 1). The six-membered ring fused on to the 1,4-dihydropyridine ring adopts a skew-boat conformation: atoms C8, C9, C4 and C5 (plane 2) are coplanar, while atoms C6 and C7 deviate from the plane by 0.196(8) Å and –0.494(8) Å, respectively. The dihedral angle between the plane 1 and plane 2 is 10.68(3)°, and the dihedral angle between the plane 2 and phenyl ring is 85.31(8)°. The structure exhibits intermolecular hydrogen bonds: N2-H…N3 ($-x + 1, -y + 2, -z + 1$) and N2-H…O1 ($x, -y + 1, z + 1/2$), which help in stabilising the crystal structure.

In conclusion a novel method for the synthesis of *N*-substituted quinoline-3-carbonitrile derivatives, by the three component reaction of *N*-substituted 5,5-dimethyl-3-aminocyclohex-2-enone, arylaldehyde and malononitrile has been found. The advantages of this procedure are mild reaction conditions, high yields, operational simplicity and new products.

Experiental

Melting points are uncorrected. IR spectra were recorded on a VARIAN 1000 FT-IR spectrometer in KBr with absorption in cm^{-1}. ^1H NMR spectra were recorded on a VARIAN INVOA-400 spectrometer in DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in δ downfield from internal tetramethylsilane. HRMS were obtained using TOF–MS instrument. X-ray crystallographic analysis was performed with a Smart-1000 CCD diffractometer.

Typical procedure for the synthesis of compound **4** *and* **5**
A mixture of 3-arylamino-5,5-dimethylcyclohex-2-enone **1** (1 mmol), aldehyde **2** (1 mmol), malononitrile **3** (1 mmol), L-proline (10 mol%) and EtOH (2 ml) in a 50 ml round bottom flask was stirred at 80 °C for 1–3 h. At the end of the reaction, the mixture was cooled to room temperature. The precipitate was collected by filtration and purified by recrystallisation from EtOH and DMF to give products **4** or **5**.

2-Amino-1-(3-chloro-4-methylphenyl)-7,7-dimethyl-5-oxo-4-p-tolyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4a**): M.p. 266–267 °C; ^1H NMR (DMSO-d_6, δ, ppm): 0.76 (3H, s, CH_3), 0.91 (3H, s, CH_3), 1.76 (1H, d, J = 17.2 Hz, CH_2), 2.00 (1H, d, J = 16.0 Hz, CH_2), 2.16–2.21 (2H, m, CH_2), 2.26 (3H, s, CH_3), 2.42 (3H, s, CH_3), 4.41 (1H, s, CH), 5.39 (2H, s, NH_2), 7.14 (4H, dd, J_1 = 8.0 Hz, J_2 = 15.2 Hz, ArH), 7.26 (1H, d, J = 8.4 Hz, ArH), 7.51 (1H, s, ArH), 7.55 (1H, d, J = 8.0 Hz, ArH); IR (KBr, ν, cm^{-1}): 3457, 3330, 2958, 2182, 1657, 1371, 1257; HRMS [Found: *m/z* 431.1755 (M^+), Calc.. for $C_{26}H_{26}N_3O^{35}Cl$: M, 431.1764].

2-Amino-7,7-dimethyl-5-oxo-1-(3-(trifluoromethyl)phenyl)-4-(3,4,5-trimethoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4b**): M.p. 245–246 °C; ^1H NMR (DMSO-d_6, δ, ppm): 0.83 (3H, s, CH_3), 0.92 (3H, s, CH_3), 1.71 (1H, d, J = 17.6 Hz, CH_2), 2.08 (1H, d, J = 16.0 Hz, CH_2), 2.21–2.31 (2H, m, CH_2), 3.66 (3H, s, OCH_3), 3.78 (6H, s, 2 × OCH_3), 4.45 (1H, s, CH), 5.54 (2H, s, NH_2), 6.53 (2H, s, ArH), 7.67 (2H, d, J = 8.4 Hz, ArH), 7.83 (1H, t, J = 8.0 Hz, ArH), 7.93 (1H, d, J = 8.0 Hz, ArH); IR (KBr, ν, cm^{-1}): 3423, 3340, 2953, 2175, 1658, 1374, 1254; HRMS [Found: *m/z* 527.2019 (M^+), Calc. for $C_{28}H_{28}N_3O_4F_3$: M, 527.2032].

2-Amino-4-(3,4-dichlorophenyl)-7,7-dimethyl-5-oxo-1-(3-(trifluoromethyl)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4c**): M.p. 266–268 °C; ^1H NMR (DMSO-d_6, δ, ppm): 0.76 (3H, s, CH_3), 0.89 (3H, s, CH_3), 1.71 (1H, d, J = 17.2 Hz, CH_2), 2.04 (1H, d, J = 16.4 Hz, CH_2), 2.16–2.21 (2H, m, CH_2), 4.53 (1H, s, CH), 5.64 (2H, s, NH_2), 7.34 (1H, d, J = 8.4 Hz, ArH), 7.48 (1H, s,

Table 3 Crystal data and structure refinement

Empirical formula	$C_{22}H_{25}Cl_2N_3O$
Formula weight	418.35
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 29.635(3) Å α = 90° b = 9.0495(10) Å β = 95.124(2)° c = 16.0456(19) Å γ = 90°
Volume	4285.9(8) $Å^3$
Z	8
Density (calculated)	1.297 mg/m^3
Absorption coefficient	0.320 mm^{-1}
F(000)	1760
Crystal size	0.43 × 0.40 × 0.18 mm
Theta range for data collection	1.38 to 25.01°
Index ranges	$-35 \le h \le 30, -8 \le k \le 10, -18 \le l \le 19$
Reflections collected	10414
Independent reflections	3780 [R(int) = 0.0482]
Completeness to theta = 25.01	99.8%
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3780/0/281
Goodness-of-fit on F^2	1.030
Final R indices [I>2σ(I)]	R^1 = 0.0614, wR^2 = 0.1481
R indices (all data)	R^1 = 0.1373, wR^2 = 0.2039
Largest diff. peak and hole	0.354 and –0.398 e. $Å^{-3}$

7.61 (1H, d, J = 8.4 Hz, ArH), 7.73 (1H, d, J = 7.2 Hz, ArH), 7.80–7.84 (2H, m, ArH), 7.94 (1H, d, J = 8.0 Hz, ArH); IR (KBr, ν, cm^{-1}): 3468, 3336, 2959, 2180, 1652, 1372, 1266; HRMS [Found: m/z 505.0940 (M$^+$), Calc. for $C_{25}H_{20}N_3OF_3{}^{35}Cl_2$: M, 505.0936].

2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-1-(3-(trifluoromethyl) phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4d**): M.p. 276–278 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.75 (3H, s, CH_3), 0.90 (3H, s, CH_3), 1.69 (1H, d, J = 17.2 Hz, CH_2), 2.02 (1H, d, J = 16.0 Hz, CH_2), 2.18–2.23 (2H, m, CH_2), 4.63 (1H, s, CH), 5.68 (2H, s, NH_2), 7.60 (2H, d, J = 8.8 Hz, ArH), 7.77–7.84 (2H, m, ArH), 7.91–7.95 (2H, m, ArH), 8.22 (2H, d, J = 8.4 Hz, ArH); IR (KBr, ν, cm^{-1}): 3446, 3324, 2967, 2187, 1656, 1373, 1259; HRMS [Found: *m/z* 482.1564 (M$^+$), Calc. for $C_{25}H_{21}N_4O_3F_3$: M, 482.1566].

2-Amino-4-(3-chlorophenyl)-7,7-dimethyl-5-oxo-1-(3-(trifluoromethyl)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4e**): M.p. 232–234 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.75 (3H, s, CH_3), 0.90 (3H, s, CH_3), 1.70 (1H, d, J = 17.2 Hz, CH_2), 2.04 (1H, d, J = 16.4 Hz, CH_2), 2.20 (2H, d, J = 18.0 Hz, CH_2), 4.51 (1H, s, CH), 5.61 (2H, s, NH_2), 7.29 (3H, t, J = 8.0 Hz, ArH), 7.39 (1H, t, J = 7.6 Hz, ArH), 7.71 (1H, d, J = 8.0 Hz, ArH), 7.80–7.84 (2H, m, ArH), 7.95 (1H, d, J = 7.6 Hz, ArH); IR (KBr, ν, cm^{-1}): 3469, 3344, 2959, 2179, 1655, 1373, 1259; HRMS [Found: *m/z* 471.1315 (M$^+$), Calc. for $C_{25}H_{21}N_3OF_3{}^{35}Cl$: M, 471.1325].

2-Amino-4-(4-bromophenyl)-1-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4f**): M.p. >300 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.74 (3H, s, CH_3), 0.90 (3H, s, CH_3), 1.73 (1H, d, J = 17.6 Hz, CH_2), 2.01 (1H, d, J = 16.0 Hz, CH_2), 2.17–2.22 (2H, m, CH_2), 4.46 (1H, s, CH), 5.47 (2H, s, NH_2), 7.25 (2H, d, J = 8.0 Hz, ArH), 7.41 (2H, t, J = 8.4 Hz, ArH), 7.46–7.49 (2H, m, ArH), 7.52 (2H, d, J = 8.4 Hz, ArH); IR (KBr, ν, cm^{-1}): 3465, 3326, 2962, 2179, 1652, 1373, 1259; HRMS [Found: *m/z* 465.0849 (M$^+$), Calc. for $C_{24}H_{21}N_3OF^{79}Br$: M, 465.0852].

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1-p-tolyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4g**): M.p. 258–260 °C (Lit.[23] 260–262 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 0.74 (3H, s, CH_3), 0.89 (3H, s, CH_3), 1.75 (1H, d, J = 17.6 Hz, CH_2), 2.01 (1H, d, J = 16.4 Hz, CH_2), 2.19 (2H, d, J = 16.4 Hz, CH_2), 2.42 (3H, s, CH_3), 4.48 (1H, s, CH), 5.30 (2H, s, NH_2), 7.27–7.31 (4H, m, ArH), 7.38–7.41 (4H, m, ArH); IR (KBr, ν, cm^{-1}): 3463, 3322, 2951, 2180, 1654, 1372, 1258; HRMS [Found: *m/z* 417.1588 (M$^+$), Calc. for $C_{25}H_{24}N_3O^{35}Cl$: M, 417.1608].

2-Amino-1-butyl-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4h**): M.p. 230–232 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.85 (3H, t, J = 7.2 Hz, CH_3), 0.95 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.16–1.25 (2H, m, CH_2), 1.41–1.50 (2H, m, CH_2), 2.12–2.21(2H, m, CH_2), 2.44 (1H, d, J = 16.8 Hz, CH_2), 2.65 (1H, d, J = 17.2 Hz, CH_2), 3.55–3.63(1H, m, CH_2), 3.78–3.85 (1H, m, CH_2), 4.42 (1H, s, CH), 6.08 (2H, s, NH_2), 7.07–7.12 (4H, m, ArH); IR (KBr, ν, cm^{-1}): 3384, 3236, 2961, 2173, 1662, 1505, 1373, 1230; HRMS [Found: *m/z* 367.2076 (M$^+$), Calc. for $C_{22}H_{26}N_3OF$: M, 367.2060].

2-Amino-1-butyl-4-(3,4-dichlorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4i**): M.p. 263–265 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.86 (3H, t, J = 7.2 Hz, CH_3), 0.95 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.16–1.25 (2H, m, CH_2), 1.41–1.50 (2H, m, CH_2), 2.18(2H, s, CH_2), 2.44 (1H, d, J = 16.8 Hz, CH_2), 2.68 (1H, d, J = 17.2 Hz, CH_2), 3.57–3.65(1H, m, CH_2), 3.80–3.88 (1H, m, CH_2), 4.44 (1H, s, CH), 6.22 (2H, s, NH_2), 7.12 (1H, d, J = 8.0 Hz, ArH), 7.50 (1H, d, J = 1.6 Hz, ArH), 7.54 (1H, d, J = 8.0 Hz, ArH); IR (KBr, ν, cm^{-1}): 3383, 3235, 2959, 2172, 1665, 1557, 1367, 1278; HRMS [Found: *m/z* 417.1389 (M$^+$), Calc. for $C_{22}H_{25}N_3O^{35}Cl_2$: M, 417.1375].

2-Amino-1-butyl-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4j**): M.p. 259–261 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.94 (3H, t, J = 7.2 Hz, CH_3), 1.00 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.31–1.40 (2H, m, CH_2), 1.50–1.59 (2H, m, CH_2), 2.07 (1H, d, J = 15.6 Hz, CH_2), 2.17 (1H, d, J = 16.0 Hz, CH_2), 2.53 (1H, d, J = 16.4 Hz, CH_2), 2.73 (1H, d, J = 16.8 Hz, CH_2), 3.61–3.69 (1H, m, CH_2), 3.77–3.84 (1H, m, CH_2), 4.93 (1H, s, CH), 5.97 (2H, s, NH_2), 7.05 (1H, d, J = 7.6 Hz, ArH), 7.13–7.17 (1H, m, ArH), 7.21 (1H, t, J = 7.2 Hz, ArH), 7.34 (1H, d, J = 8.0 Hz, ArH); IR (KBr, ν, cm^{-1}): 3371, 3202, 2965, 2180, 1661, 1614, 1369, 1272; HRMS [Found: *m/z* 383.1748 (M$^+$), Calc. for $C_{22}H_{26}N_3O^{35}Cl$: M, 383.1764].

1,2,3,5,6,7,8,9-Octahydro-5-(4-chlorophenyl)-8,8-dimethyl-2,6-dioxoimidazo[1,2-a]quinoline-4-carbonitrile (**5a**): M.p. >300 °C (Lit.[24] >300 °C); ^{1}H NMR (DMSO-d_6, δ, ppm): 0.89 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.02 (1H, d, J = 16.0 Hz, CH_2), 2.19 (1H, d, J = 16.0 Hz, CH_2), 2.43 (1H, d, J = 17.6 Hz, CH_2), 2.55 (1H, d, J = 17.6 Hz, CH_2), 4.40 (2H, s, CH_2-N), 4.53 (1H, s, CH), 7.29 (2H, d, J = 8.4 Hz, ArH), 7.35 (2H, d, J = 8.4 Hz, ArH), 11.95 (1H, s, NH); IR (KBr, ν, cm^{-1}): 3137, 3061, 2962, 2206, 1764, 1686, 1415, 1261; HRMS [Found: *m/z* 367.1100 (M$^+$), Calc. for $C_{20}H_{18}N_3O_2{}^{35}Cl$: M, 367.1088].

1,2,3,5,6,7,8,9-Octahydro-5-(pyridin-2-yl)-8,8-dimethyl-2,6-dioxoimidazo[1,2-a]quinoline-4-carbonitrile (**5b**): M.p. 258–260 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.89 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.03 (1H, d, J = 16.0 Hz, CH_2), 2.21 (1H, d, J = 16.4 Hz, CH_2), 2.44 (1H, d, J = 17.6 Hz, CH_2), 2.56 (1H, d, J = 17.6 Hz, CH_2), 4.41 (2H, s, CH_2-N), 4.57 (1H, s, CH), 7.33 (1H, dd, J_1 = 4.8 Hz, J_2 = 7.6 Hz, ArH), 7.68 (1H, d, J = 8.0 Hz, ArH), 8.41 (1H, d, J = 4.8 Hz, ArH), 8.51 (1H, s, ArH), 11.97 (1H, s, NH); IR (KBr, ν, cm^{-1}): 3586, 3461, 2964, 2193, 1762, 1687, 1422, 1265; HRMS [Found: *m/z* 334.1427 (M$^+$), Calc. for $C_{19}H_{18}N_4O_2$: M, 334.1430].

1,2,3,5,6,7,8,9-Octahydro-5-(5-chloro-2-nitrophenyl)-8,8-dimethyl-2,6-dioxoimidazo[1,2-a]quinoline-4-carbonitrile (**5c**): M.p. 276–278 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.86 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.95 (1H, d, J = 16.0 Hz, CH_2), 2.13 (1H, d, J = 16.4 Hz, CH_2), 2.43 (1H, d, J = 18.0 Hz, CH_2), 2.51 (1H, d, J = 16.8 Hz, CH_2), 4.40 (2H, d, J = 7.2 Hz, CH_2-N), 5.27 (1H, s, CH), 7.51 (1H, d, J = 7.2 Hz, ArH), 7.75 (1H, s, ArH), 7.86 (1H, d, J = 9.2 Hz, ArH), 12.03 (1H, s, NH); IR (KBr, ν, cm^{-1}): 3274, 3068, 2960, 2199, 1761, 1679, 1532, 1385, 1265; HRMS [Found: *m/z* 412.0929 (M$^+$), Calc. for $C_{20}H_{17}N_4O_4{}^{35}Cl$: M, 412.0938].

1,2,3,5,6,7,8,9-Octahydro-5-(2,4-dichlorophenyl)-8,8-dimethyl-2,6-dioxoimidazo[1,2-a]quinoline-4-carbonitrile (**5d**): M.p. >300 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 0.95 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.00 (1H, d, J = 16.0 Hz, CH_2), 2.19 (1H, d, J = 16.4 Hz, CH_2), 2.45 (1H, d, J = 17.6 Hz, CH_2), 2.55 (1H, d, J = 17.6 Hz, CH_2), 4.43 (2H, d, J = 7.2 Hz, CH_2-N), 5.04 (1H, s, CH), 7.36 (1H, d, J = 8.4 Hz, ArH), 7.40 (1H, d, J = 8.4 Hz, ArH), 7.52 (1H, s, ArH), 11.94 (1H, s, NH); IR (KBr, ν, cm^{-1}): 3135, 3066, 2958, 2175, 1763, 1686, 1383, 1262; HRMS [Found: *m/z* 401.0672 (M$^+$), Calc. for $C_{20}H_{17}N_3O_2{}^{35}Cl_2$: M, 401.0698].

X-ray crystal analysis of **4i**

X-ray diffraction data were collected on a Bruker Smart 1000 CCD detector with graphite-monochromatised *MoK*α radiation (λ = 0.71073 Å) for compound **4i**. The structures have been solved by direct methods using the program SHELXL 97[25] and Fourier difference techniques. Refinement has been by full-matrix least-squares method on F^2 using SHELXL 97.[26] CCDC 693968 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request.cif.

We are grateful to the Foundation of Key Laboratory of Organic Synthesis of Jiangsu Province and Key Laboratory of Biotechnology on Medical Plants of Jiangsu Province.

Received 28 April 2008; accepted 14 July 2008
Paper 08/5244 *doi: 10.3184/030823408X347567*
Published online: 8 September 2008

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