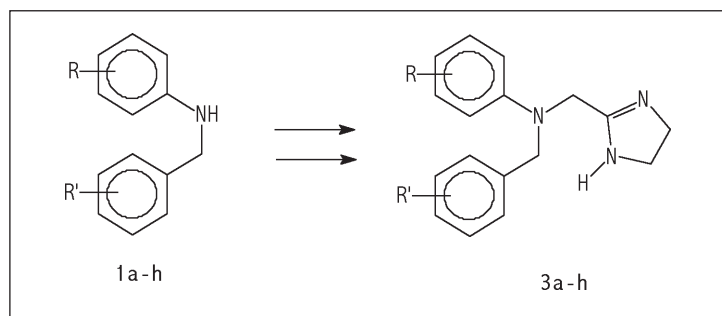


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Different *N*-benzyl anilines were *N*-alkylated with chloroacetonitrile to give the corresponding nitriles, which were subsequently condensed with ethylenediamine in the presence of thioacetamide to afford the corresponding title antazoline derivatives.

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Imidazoline derivatives exhibit significant biological and pharmacological activities including antihypertensive [1,2], antihyperglycemic [3-7], antidepressive [8], antihypercholesterolemic [9] and anti-inflammatory activities [10]. Due to these practical applications, we have expended considerable effort in the preparation of new imidazoline derivatives. Recently we have reported the synthesis 2-imidazoline analogs of phentolamine by the alkylation of diphenylamines with chloroacetonitrile and subsequent cyclisation of aminonitriles with ethylenediamine in presence of thioacetamide [11]. Antazoline is a well-known drug of the imidazoline family having antihistaminic activity [12-13], ambecidal activity [14] and antiarrhythmic activity [15]. Earlier synthesis of antazoline starts the cyanomethylation of the *N*-benzylaniline with NaCN and formaldehyde requiring a closed vessel and long reaction period [16]. In this article we wish to report the synthesis of some novel antazoline derivatives using alkylation of *N*-benzylanilines with chloroacetonitrile as a key step.

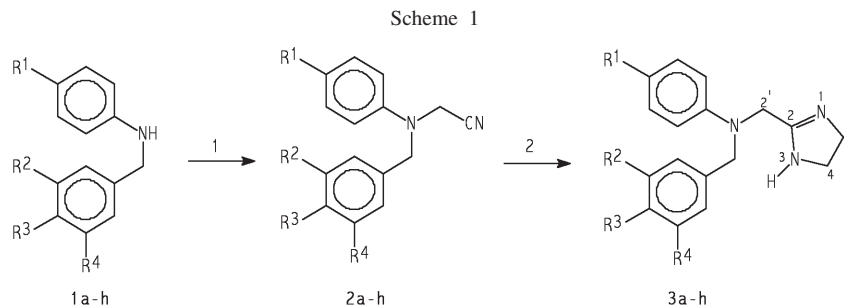
Towards this end the alkylation of *N*-benzylaniline **1a** with chloroacetonitrile was undertaken. All our attempts to carry out the reaction in CH₃CN, DMF, DMSO and THF as reaction solvents using different bases such as K₂CO₃, KF, DMAP and Et(ⁱPr)₂N proved unsuccessful. Although the alkylation of **1a** with ClCH₂CN and NaI in presence of KF, DMAP, Et(ⁱPr)₂N in HMPA at 100 °C afforded the corresponding nitrile **2a**, K₂CO₃ in HMPA in presence of NaI proved to be the most effective reaction condition and **2a** was obtained in 84% yield after the column chromatographic purification (Table 1). This was unlike our earlier observation [11] wherein the *N*-alkylation of diphenyl amine with chloroacetonitrile in the last condition (K₂CO₃/NaI/HMPA) failed to give any *N*-alkylated product. Seebach *et al.* [17]

Table 1

Tested alkylation conditions for the reaction of *N*-benzylaniline (**1a**) with ClCH₂CN.

Solvent	Base	Additive	Temp (°C)	Time (h)	Yield (%)
HMPA	K ₂ CO ₃	NaI	100	0.75	84
		NaI	100	5	51
		DMAP	100	6	19
		Et(ⁱ Pr) ₂ N	100	6	24
DMPU	K ₂ CO ₃	NaI	100	3	64

have used DMPU as a good and safe alternative for HMPA for the *N*-alkylation of less reactive amines. Hence we thought to investigate the influence of DMPU for the *N*-alkylation **1a** with chloroacetonitrile. Heating *N*-benzylaniline **1a** with chloroacetonitrile and NaI in the presence of K₂CO₃ in DMPU at 100 °C for 3 h gave **2a** in 64% yield after the column chromatographic purification. The structure of **2a** was ascertained from its elemental analysis and spectroscopic data. The IR spectrum of **2a** displayed C-N stretching at 2255 cm⁻¹ for the CN group and ¹H-NMR spectrum displayed two 2H singlets for CH₂-CN and CH₂-Ar at δ_H 4.53 and δ_H 4.11 respectively thus confirming the alkylation of **1a** with chloroacetonitrile. These two reaction conditions (K₂CO₃, NaI, HMPA and K₂CO₃, NaI, DMPU) were then utilized for the *N*-alkylation of other *N*-benzylanilines with chloroacetonitrile to give the corresponding aminoacetonitriles **2b-h** in 80-88% and 61-72% yields respectively (Scheme 1, Table 2). The aminoacetonitriles **2a-h** thus obtained were condensed by refluxing with ethylenediamine in the presence of a catalytic amount of thioacetamide for 3 h to afford the corresponding analytically pure title compounds **3a-h** in 75-80% yields (Scheme 1, Table 2). The structures of **3a-h** were ascertained from their elemental



Reagents and conditions: 1) Chloroacetonitrile, K_2CO_3 , NaI, HMPA/DMPU, 100 $^\circ$ C. 2) ethylenediamine, thioacetamide, reflux.

Synthesis of antazoline derivatives.

Table 2
Synthesized aminoacetonitriles and antazoline derivatives.

Compound	R ¹	R ²	R ³	R ⁴	Yield ^a / %
2a	H	H	H	H	84 ^b (64) ^c
2b	OCH ₃	H	H	H	87 ^b (71) ^c
2c	CH ₃	H	H	H	81 ^b (61) ^c
2d	H	H	OCH ₃	H	85 ^b (67) ^c
2e	H	OCH ₃	OCH ₃	H	88 ^b (72) ^c
2f	H	OCH ₃	OCH ₃	OCH ₃	84 ^b (68) ^c
2g	CH ₃	H	OCH ₃	H	82 ^b (66) ^c
2h	Cl	H	OCH ₃	H	80 ^b (65) ^c
3a	H	H	H	H	77
3b	OCH ₃	H	H	H	79
3c	CH ₃	H	H	H	75
3d	H	H	OCH ₃	H	77
3e	H	OCH ₃	OCH ₃	H	80
3f	H	OCH ₃	OCH ₃	OCH ₃	76
3g	CH ₃	H	OCH ₃	H	79
3h	Cl	H	OCH ₃	H	78

^a Yield refers to purified product; ^b Yield obtained with K_2CO_3 , NaI, HMPA; Yield obtained with K_2CO_3 , NaI, DMPU.

analysis and spectroscopic data. The ¹H-NMR spectrum of **3e** displayed a 4H singlet at δ_H 3.56 for N-CH₂-CH₂-N, two 3H singlets at δ_H 3.81 and δ_H 3.86 for two OCH₃ and two 2H singlets for CH₂-C=N and CH₂-Ar at δ_H 4.53 and δ_H 4.15 respectively. The ¹³C-NMR spectrum of **3e** displayed a signal at δ_C 166.6 for C=N and MS showed molecular ion peak at m/z = 325. In the ¹H-¹³C gHSQC spectrum of **3e** a signal at δ_C 50.2 showed correlation with δ_H 4.53 as well as δ_H 3.56 and a signal at δ_C 55.5 showed correlation with δ_H 4.15. Based on this, a signal at δ_C 50.2 was assigned for C-4 and C-5 of imidazoline ring and C-2' and a signal at δ_C 55.5 was assigned for Ar-CH₂. Use of CS₂ [18] and P₂S₅ [19] instead of thioacetamide as H₂S source gives impure compound, which requires complicated purification. The yields of the compounds synthesized are listed in Table 2.

In conclusion, *N*-benzyl anilines were *N*-alkylated with chloroacetonitrile in presence of K_2CO_3 and NaI in HMPA to give the corresponding nitriles **1a-h**. Carcinogenic

HMPA was also replaced by DMPU, though the yields obtained in HMPA were slightly better. Nitriles **2a-h** were subsequently condensed with ethylenediamine in the presence of thioacetamide to afford the corresponding title compounds **3a-h** in good yields.

EXPERIMENTAL

General Procedure for the Synthesis of Aminoacetonitrile **2a-h**.

A mixture of *N*-benzylaniline (10 mmol) **1a-h**, chloroacetonitrile (15 mmol), anhyd. K_2CO_3 (10 mmol) and NaI (10 mmol) in dry HMPA (**caution!**)/DMPU (7 cm³) was heated at 100 $^\circ$ C for 45 min/3 h. The reaction mixture was diluted with water and extracted with EtOAc (4 \times 50 cm³). The combined EtOAc extracts were washed with water (3 \times 50 cm³) and then dried (anhydrous Na₂SO₄). Evaporation of the solvent gave a brown residue which was purified by column chromatography [silica gel, Hexane:CHCl₃ (50:50)] to afford the corresponding aminoacetonitrile **2a-h**.

[Benzyl(phenyl)amino]acetonitrile (**2a**).

Pale yellow oil; IR (oil film): ν 2255 (CN) cm⁻¹; ¹H-NMR (CDCl₃, 60 MHz) δ 4.11 (2H, s, Ar-CH₂), 4.53 (2H, s, CH₂-CN), 6.54-7.47 (10H, m, Ar-H).

Anal. Calcd. for C₁₅H₁₄N₂: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.96; H, 6.39; N, 12.65.

[Benzyl(4-methoxyphenyl)amino]acetonitrile (**2b**).

Pale yellow oil; IR (oil film) ν 2252 (CN) cm⁻¹; ¹H-NMR (CDCl₃, 60 MHz) δ 3.69 (3H, s, OCH₃), 4.01 (2H, s, Ar-CH₂), 4.42 (2H, s, CH₂-CN), 6.66-7.42 (9H, m, Ar-H); MS (EI) m/z (relative intensity): 252 (M⁺, 10%), 107 (18), 91(100).

Anal. Calcd. for C₁₆H₁₆N₂O: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.07; H, 6.44; N, 11.14.

[Benzyl(4-methylphenyl)amino]acetonitrile (**2c**).

Pale yellow oil; IR (oil film) ν 2257 (CN) cm⁻¹; ¹H-NMR (CDCl₃, 60 MHz) δ 2.25 (3H, s, CH₃), 4.13 (2H, s, Ar-CH₂), 4.49 (2H, s, CH₂-CN), 6.50-7.45 (9H, m, Ar-H); MS (EI) m/z (relative intensity): 236 (M⁺, 9%), 91 (100).

Anal. Calcd. for C₁₆H₁₆N₂: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.41; H, 6.78; N, 11.80.

[[4-Methoxybenzyl)(phenyl)amino]acetonitrile (**2d**).

Colourless solid; mp 84 °C; IR (KBr) ν 2251 (CN) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 3.80 (3H, s, OCH_3), 4.02 (2H, s, Ar-CH_2), 4.42 (2H, s, $\text{CH}_2\text{-CN}$), 6.88 (2H, d, $J = 8.7$, H-3 & H-5 of Bn group), 6.92-6.98 (3H, m, H-2, H-6 & H-4 of Ph group), 7.23 (2H, d, $J = 8.7$, H-2 & H-6 of Bn group), 7.30 (2H, dd, $J = 7.4$ & 7.1, H-3 & H-5 of Ph group).

Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.26; H, 6.35; N, 11.06.

[[3,4-Dimethoxybenzyl)(phenyl)amino]acetonitrile (**2e**).

Colourless solid; mp 75-77 °C; IR (KBr) ν 2260 (CN) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ 3.71 (6H, combined singlet, OCH_3), 4.05 (2H, s, Ar-CH_2), 4.50 (2H, s, $\text{CH}_2\text{-CN}$), 6.53-7.44 (8H, m, Ar-H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.23; H, 6.45; N, 9.96.

[Phenyl(3,4,5-trimethoxybenzyl)amino]acetonitrile (**2f**).

Colourless solid; mp 88 °C; IR (KBr) ν 2256 (CN) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ 3.69 (9H, combined singlet, OCH_3), 4.00 (2H, s, Ar-CH_2), 4.41 (2H, s, $\text{CH}_2\text{-CN}$), 6.65-7.40 (7H, m, Ar-H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.29; H, 6.41; N, 8.95.

[[4-Methoxybenzyl)(4-methylphenyl)amino]acetonitrile (**2g**).

Colourless solid; mp 94; IR (KBr) ν 2260 (CN) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ 2.23 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 4.12 (2H, s, Ar-CH_2), 4.50 (2H, s, $\text{CH}_2\text{-CN}$), 6.52-7.30 (8H, m, Ar-H); MS (EI) m/z (relative intensity): 266 (M^+ , 4%), 121 (100), 91 (10).

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.56; H, 6.85; N, 10.55.

[[4-Chlorophenyl)(4-methoxybenzyl)amino]acetonitrile (**2h**).

Colourless solid; mp 65 °C; IR (KBr) ν 2258 (CN) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 3.81 (3H, s, OCH_3), 4.01 (2H, s, Ar-CH_2), 4.40 (2H, s, $\text{CH}_2\text{-CN}$), 6.88 (2H, d, $J = 9.0$, H-3 & H-5 of Bn group), 6.91 (2H, d, $J = 8.9$, H-2 & H-6 of Ph group), 7.23 (2H, d, $J = 9.0$, H-2 & H-6 of Bn group), 7.27 (2H, d, $J = 8.9$, H-3 & H-5 of Ph group).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}$: C, 67.02; H, 5.27; Cl, 12.36; N, 9.77. Found: C, 67.13; H, 5.23; Cl, 12.33; N, 9.74.

General Procedure for the Synthesis of Antazoline Derivatives **3a-h**.

A mixture of aminoacetonitrile **2a-h** (10 mmol), thioacetamide (1 mmol) in ethylenediamine (7 cm^3) was refluxed with stirring for 3 h. The reaction mixture was diluted with water and extracted with CHCl_3 (4 \times 50 cm^3). The combined CHCl_3 extracts were washed with water (3 \times 50 cm^3) and then dried (anhydrous Na_2SO_4). Evaporation of the solvent followed by trituration of the residue obtained with petroleum ether (60:80) afforded the corresponding analytically pure antazoline derivatives **3a-h** which were then further purified by recrystallization with CHCl_3 and hexane.

Benzyl(4,5-dihydro-1H-imidazol-2-ylmethyl)phenylamine (**3a**).

Colourless solid; mp 120 °C (Lit. [16] mp 120 °C); IR (KBr) ν 3215 (N-H str.) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ 3.52 (4H, s), 4.00 (2H, s, Ar-CH_2), 4.55 (2H, s, $\text{CH}_2\text{-C=N}$), 6.95-7.43 (10H, m, Ar-H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{N}_3$: C, 76.95; H, 7.22; N, 15.84. Found: C, 76.88; H, 7.25; N, 15.80.

Benzyl(4,5-dihydro-1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amine (**3b**).

Colourless solid; mp 107 °C; IR (KBr) ν 3210 (N-H str.) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 3.55 (4H, s), 3.73 (3H, s, OCH_3), 4.10 (2H, s, Ar-CH_2), 4.56 (2H, s, $\text{CH}_2\text{-C=N}$), 6.78-7.00 (4H, m, Ar-H), 7.22-7.32 (5H, m, Ar-H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.28; H, 7.13; N, 14.20.

Benzyl(4,5-dihydro-1H-imidazol-2-ylmethyl)(4-methylphenyl)amine (**3c**).

Colourless solid; mp 93 °C; IR (KBr) ν 3220 (N-H str.) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 2.24 (3H, s, CH_3), 3.54 (4H, s), 4.13 (2H, s, Ar-CH_2), 4.54 (2H, s, $\text{CH}_2\text{-C=N}$), 6.71 (2H, d, $J = 8.2$, H-2 & H-6 of Ph group), 7.1 (2H, d, $J = 8.2$, H-3 & H-5 of Ph group), 7.20-7.31 (5H, m, Ar-H of Bn group); MS (EI) m/z (relative intensity): 279 (M^+ , 6%), 91 (61), 84 (100).

Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_3$: C, 77.38; H, 7.58; N, 15.04; found: C, 77.30; H, 7.61; N, 15.09.

(4,5-Dihydro-1H-imidazol-2-ylmethyl)(4-methoxybenzyl)phenylamine (**3d**).

Colourless solid; mp 116 °C; IR (KBr) ν 3250 (N-H str.) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 3.55 (4H, s), 3.79 (3H, s, OCH_3), 4.14 (2H, s, Ar-CH_2), 4.53 (2H, s, $\text{CH}_2\text{-C=N}$), 6.78 (1H, t, $J = 7.5$, H-4 of Ph group), 6.84-6.96 (4H, m, Ar-H), 7.16 (2H, d, $J = 7.8$, H-2 & H-6 of Bn group), 7.23 (2H, t, $J = 7.5$, H-3 & H-5 of Ph group).

Anal. Calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.30; H, 7.12; N, 14.20.

(4,5-Dihydro-1H-imidazol-2-ylmethyl)(3,4-dimethoxybenzyl)phenylamine (**3e**).

Colourless solid; mp 115 °C; IR (KBr) ν 3300 (N-H str.) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 3.56 (4H, s), 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.15 (2H, s, Ar-CH_2), 4.53 (2H, s, $\text{CH}_2\text{-C=N}$), 6.76-6.84 (6H, m, Ar-H), 7.24 (2H, t, $J = 7.7$, H-3 & H-5 of Ph group); $^{13}\text{C-NMR}$ (CDCl_3 , 400 MHz): δ 50.2 (C-4, C-5 of imidazoline ring and C-2'), 55.5 (Ar- CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 110.3 (CH), 111.3 (CH), 113.2 (C-2, C-6 of phenyl ring), 130.4 (C), 148.2 (C), 148.7, 149.2 (C), 166.6 (C=N); MS (EI) m/z (relative intensity): 325 (M^+ , 8%), 241 (65), 150 (48), 82 (100).

Anal. Calcd. for $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.03; H, 7.16; N, 12.95.

(4,5-Dihydro-1H-imidazol-2-ylmethyl)phenyl(3,4,5-trimethoxybenzyl)amine (**3f**).

Colourless solid; mp 117 °C; IR (KBr) ν 3220 (N-H str.) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 3.57 (4H, s), 3.78 (6H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.17 (2H, s, Ar-CH_2), 4.51 (2H, s, $\text{CH}_2\text{-C=N}$), 6.45 (2H, s, H-2 & H-6 of Bn group), 6.79 (3H, m, H-2, H-4 & H-6 of Ph group), 7.22 (2H, t, $J = 7.7$, H-3 & H-5 of Ph group).

Anal. Calcd. for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_3$: C, 67.58; H, 7.09; N, 11.82; found: C, 67.67; H, 7.06; N, 11.87.

(4,5-Dihydro-1*H*-imidazol-2-ylmethyl)(4-methoxybenzyl)(4-methylphenyl)amine (**3g**).

Colourless solid: mp 104 °C; IR (KBr) ν 3230 (N-H str.) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 2.25 (3H, s, CH_3), 3.54 (4H, s), 3.78 (3H, s, OCH_3), 4.10 (2H, s, Ar- CH_2), 4.47 (2H, s, $\text{CH}_2\text{-C=N}$), 6.74 (2H, d, $J = 8.2$, H-2 & H-6 of Ph group), 6.84 (2H, d, $J = 8.3$, H-3 & H-5 of Bn group), 7.04 (2H, d, $J = 8.2$, H-3 & H-5 of Ph group), 7.15 (2H, d, $J = 8.3$, H-2 & H-6 of Bn group); MS (EI) m/z (relative intensity): 309 (M^+ , 1%), 121 (40), 84 (100).

Anal. Calcd. for $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}$: C, 73.76; H, 7.49; N, 13.58. Found: C, 73.66; H, 7.46; N, 13.54.

(4-Chlorophenyl)(4,5-dihydro-1*H*-imidazol-2-ylmethyl)(4-methoxybenzyl)amine (**3h**).

Colourless solid: mp 103 °C; IR (KBr) ν 3200 (N-H str.) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 3.56 (4H, s), 3.78 (3H, s, OCH_3), 4.12 (2H, s, Ar- CH_2), 4.49 (2H, s, $\text{CH}_2\text{-C=N}$), 6.71 (2H, d, $J = 8.2$, H-2 & H-6 of Ph group), 6.84 (2H, d, $J = 8.3$, H-3 & H-5 of Bn group), 7.09-7.25 (4H, m, Ar-H); $^{13}\text{C-NMR}$ (CDCl_3 , 400 MHz): $\delta = 50.3$ (C-4, C-5 of imidazoline ring and C-2'), 55.2 (Ar- CH_2), 55.3 (OCH_3), 114.2 (2 CH), 114.4 (2 CH), 122.9 (C), 128.1 (2 CH), 129.1 (2 CH), 129.4 (C), 147.2 (C), 158.9 (C), 167 (C=N).

Anal. Calcd. for $\text{C}_{18}\text{H}_{20}\text{N}_3\text{OCl}$: C, 65.55; H, 6.11; Cl, 10.75; N, 12.74. Found: C, 65.66; H, 6.08; Cl, 10.72; N, 12.70.

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