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Synthesis Of Pyrazoline Series By Mno_2 Assisted Oxidative Cyclization Of Imidazole Phenyl Hydrazone With Olefins Via Nitrile Imine Intermediate

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Abstract: MnO_2 assisted one pot synthesis of imidazole pyrazolines by oxidative cyclization of imidazole phenyl hydrazone with olefins via nitrile imine intermediate. ^{1}H NMR, ^{13}C NMR, IR and elemental analyses characterized the newly synthesized compounds. All the synthesized compounds were evaluated for their antimicrobial activity and were compared with the standard drugs. All the compounds demonstrated moderate antimicrobial activity.

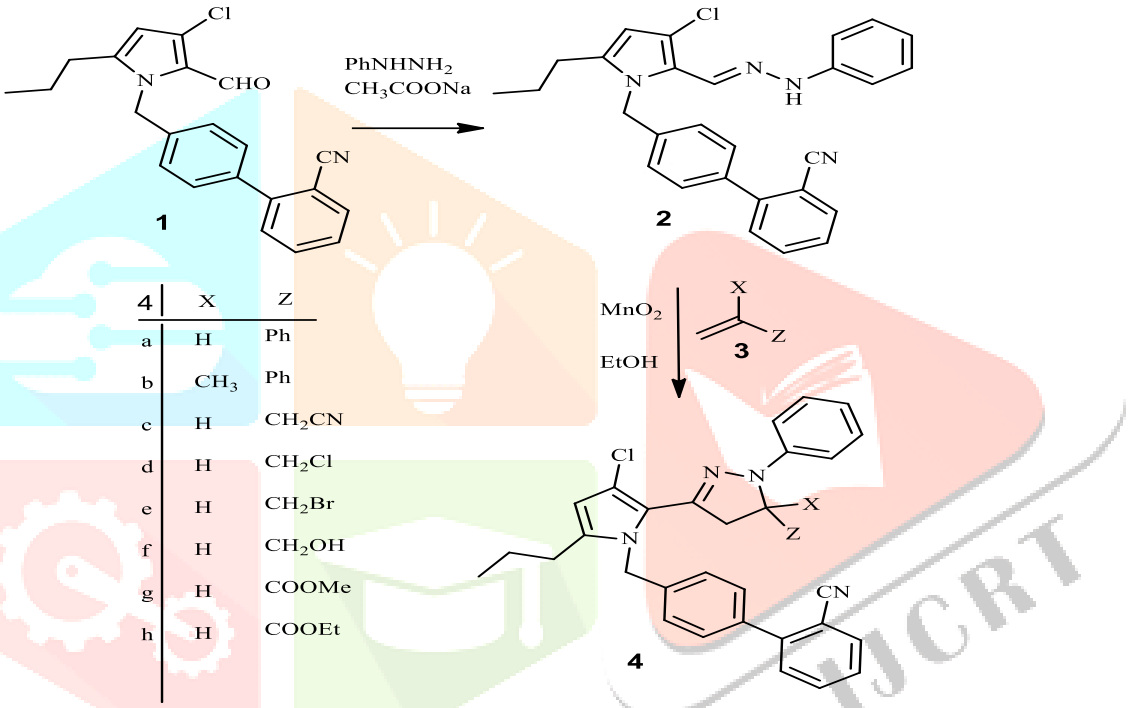
Keywords: Imidazole pyrazolines; Antimicrobial activity; Manganese (IV) oxide (MnO_2).

I. INTRODUCTION

Investigation of simple, facile and efficient reagents for the synthesis of five membered heterocycles is one of the major challenges in organic synthesis. Among all the five membered heterocycles**,** pyrazoline and imidazole are represents a class of compounds of great importance in biological chemistry. For instance, pyrazoline derivatives possess the biological activities like, antidepressant[1], anticonvulsant[2] antimicrobial[3], analgesic[4] and antitumour[5] activities and also serves as human acyl-CoA: cholesterol acyltransferase inhibitors.[6] In fact, celecoxib a pyrazole derivative is now widely used in the market as anti-inflammatory drug.[7] Imidazole derivatives are gaining synthetic interest in recent years due to their broad spectrum of biological activities like anti-inflammatory[8], analgesic[9], antibacterial[10], antifungal[11], antituberculosis[12], anticonvolusant[13] and potential anticytokine agents[14]. 2-*n*-Butyl-4-chloro-5-farmyl-imidazole is a key intermediate for the synthesis of Losartan a nonpeptide angiotensin antagonist, which is an orally active antihypertensive drug[15]. Literature studies reveals that pyrazoline[16,17] were synthesized *via* 1,3-dipolar cycloaddition of aldehyde hydrazone.

1,3-Dipolar cycloaddition reactions are useful tools for constructing biologically potent five membered heterocycles[18]. Apart from the various dipolar reagents known, nitrile imines are used in numerous 1,3-dipolar cycloaddition reactions leading to pyrazoles, pyrazolines, pyrazolidines and other heterocyclic compounds[19]. Huisgen and co-workers[20] first reported the authentic *in situ* generation of nitrile imines by the thermolysis of 2,5-diphenyl tetrazole in the presence of ethyl phenylpropionate and obtained

2,3,5-triphenyl carbethoxypyrazole. Nitrile imines can be generated by photolysis of sydnones[21] and oxidation of aryl aldehyde hydrazones with lead tetraacetate[22], chloramine-T[23] *etc*. Keigel[23] *et al* used MnO_2 for the generation of nitrile oxide. In our laboratory we search for the reagents to generate nitrile oxide and nitrile imine from aldoxime and aldehyde hydrazones. Hence it is considered worthwhile to prepare *imidazole pyrazolines* using 2-*n*-butyl-4-chloro-(*N*-substituted)–imidazole substituted phenyl hydrazone with different olefins via 1,3-dipolar cycloaddition reaction of nitrile imine which was generated *insitu* by Manganese(IV) oxide and screen them for antimicrobial activity. The present communication deals with the synthesis of a series *imidazole pyrazolines* and studies their antimicrobial activity. In conclusion 4, 5-dihydro -3- (substituted - imidazole) – 5 - substituted-1-phenyl-1H-pyrazoline derivatives were synthesized and their antimicrobial activity have been evaluated. Compounds **4d** and **4e** shows significant inhibition, remaining compounds demonstrated potent to moderate antimicrobial activity.



4	X	Z
a	H	Ph
b	CH_3	Ph
c	H	CH_2CN
d	H	CH_2Cl
e	H	CH_2Br
f	H	CH_2OH
g	H	COOMe
h	H	COOEt

Scheme

II Experimental

^{1}H NMR spectra were recorded on a Bruker AM 300 MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were measured on Jeol 400 (100MHz) instrument. The chemical shifts are expressed in δ and following abbreviations were used: s = singlet, d = doublet, t = triplet and m = multiplet. Infrared (IR) spectra were measured on Shimadzu 8300 spectrometer. Elemental analyses were obtained on a Vaio-EL intrument. Thinlayer chromatography (TLC) was done with pre-coated silica gel G plates using benzene-ethylacetrate as eluent.

Antimicrobial activity

All the synthesized compounds were evaluated for antimicrobial activity by the disc diffusion method[26] and microdilution method[27]. Five bacteria and five fungal species were used as the antimicrobial test strains namely: *Bacillus substilis, Escherichia coli, Pseudomonas fluorescens, Xanthomonas campestris pvs, Xanthomonas oryzae, Aspergillusniger, Aspergillus flavus, Fusarium oxysporium, Trichoderma species*

and Fusarium monaliforme. Streptomycin and *tetracycline* were used as standard drugs against bacteria and *nystatin* was used against fungi. In all the determinations tests were performed in triplicate and the results were taken as a mean of at least three determinations.

***Synthesis of 4,5-dihydro-3-(substituted-imidazole)-1,5-diphenyl-1H-pyrazoline* (4a)**

A mixture of **2** (1.0 g, 2.13 mmol), **3a** (0.23 g, 2.2 mmol) and MnO_2 (0.2g, 2.3 mmol) in ethanol (20 mL) was warmed on a water bath for 2-3 h. TLC monitored the progress of the reaction. After completion of the reaction the solvent was evaporated in vacuum. The residual mass was extracted into ether (25 mL), washed successively with water (2 x 20 mL), brine solution (2 x 15 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent afforded crude oily substance, which was purified by column chromatography using benzene-ethylacetate (8:1) as eluent to give the product as thick oil (0.68 g, 57%).

4,5-dihydro-3-(substituted-imidazole)-5-methyl-1,5-diphenyl-1H-pyrazoline **(4b):** Obtained from **2** (1.0 g, 2.13 mmol), **3b** (0.25 g, 2.12 mmol) and MnO_2 (0.2 g, 2.3 mmol) as thick oil (0.88 g, 70%).

4,5-dihydro-3-(substituted-imidazole)-1-phenyl-1H-pyrazoline-5-carbonitrile **(4c):** Obtained from **2** (1.0 g, 2.13 mmol), **3c** (0.12 g, 2.20 mmol) and MnO_2 (0.2 g, 2.3 mmol) as thick oil (0.7 g, 63%).

5-(Chloromethyl)-4,5-dihydro-3-(substituted-imidazole)-1-phenyl-1H-pyrazoline **(4d):** Obtained from **2** (1.0 g, 2.13 mmol), **3d** (0.17 g, 2.23 mmol) and MnO_2 (0.2 g, 2.3 mmol) as thick oil (0.73 g, 63%).

5-(bromomethyl)-4,5-dihydro-3-(substituted-imidazole)-1-phenyl-1H-pyrazoline **(4e):** Obtained from **2** (1.0 g, 2.13 mmol), **3e** (0.26 g, 2.14 mmol) and MnO_2 (0.2 g, 2.3 mmol) as thick oil (0.70 g, 61%).

4,5-dihydro-3-(substituted-imidazole)-1-phenyl-1H-pyrazol-yl)methanol **(4f):** Obtained from **2** (1.0 g, 2.13 mmol), **3f** (0.125 g, 2.15 mmol) and MnO_2 (0.2 g, 2.3 mmol) as thick oil (0.65 g, 56%).

4,5-dihydro-3-(substituted-imidazole)-1-phenyl-1H-pyrazol-5-yl acetate **(4g):** Obtained from **2** (1.0 g, 2.13 mmol), **3g** (0.185 g, 2.15 mmol) and MnO_2 (0.2 g, 2.3 mmol) as thick oil (0.65 g, 60%).

4,5-dihydro-3-(substituted-imidazole)-1-phenyl-1H-pyrazol-5-yl propionate **(4h):** Obtained from **2** (1.0 g, 2.13 mmol), **3h** (0.215 g, 2.15 mmol) and MnO_2 (0.2 g, 2.3 mmol) as thick oil (0.73 g, 64%).

III Results and Discussion

The general synthetic pathway discussed hereafter is depicted in the Scheme. farmyl function Compound **1** was converted into the phenylhydrazone **2**. When oxidative dehydrogenation of **2** by MnO_2 afforded nitrile imine, which was *in situ* trapped by the different olefins **3 (a-h)** under refluxing condition in ethanol. Thus produced compound was identified by NMR spectroscopy and elemental analyses as 4,5-dihydro-3-(substituted imidazole)-5-substituted-1-phenyl-1*H*-pyrazoline **4(a-h)** in good quality and yield. The starting substrate 2-n-butyl-4-chloro-(N-substituted)–imidazole-5-carbaldehyde **1** was prepared according to literature procedure[24]. Imidazole aldehyde phenylhydrazone was prepared by known procedure[25].

Antimicrobial activity

Antimicrobial activity of all the compounds was shown in **Table 1** and **2.** Among the series of synthesized compounds, **4d** and **4e** shown better inhibition. Remaining compounds shown moderate inhibition. The better inhibition shown by **4d** and **4e** may be due to the presence of chloro and bromo group in the compound.

Table 1. Minimal inhibitory concentration in µg mL^{-1} and Inhibitory zone in (diameter) mm of the synthesized compounds against tested bacterial strains by micro dilution method and disk diffusion method respectively

Compound	*Bacillus substilis*		*Escherichia coli*		*Pseudomonas fluorescens*		*Xanthomonas campestris pvs*		*Xanthomonas oryzae*	
4a	22µg	8mm	25µg	13mm	23µg	16mm	24µg	11mm	23µg	12mm
4b	23µg	10mm	22µg	12mm	25µg	14mm	21µg	11mm	24µg	10mm
4c	20µg	13mm	18µg	13mm	21µg	17mm	18µg	14mm	23µg	12mm
4d	18µg	15mm	12µg	14mm	14µg	15mm	24µg	10mm	11µg	10mm
4e	18µg	12mm	14µg	14mm	13µg	16mm	12µg	11mm	14µg	12mm
4f	23µg	8mm	22µg	14mm	28µg	13mm	26µg	12mm	23µg	10mm
4g	23µg	8mm	22µg	14mm	26µg	13mm	22µg	10mm	23µg	12mm
4h	23µg	8mm	21µg	14mm	29µg	13mm	24µg	11mm	22µg	11mm
Streptomycin	19µg	8mm	13µg	14mm	12µg	13mm	-	-	-	-
Tetracycline	-	-	-	-	-	-	9µg	12mm	13µg	12mm

Table 2. Minimal inhibitory concentration in µg mL^{-1} and Inhibitory zone in (diameter) mm of the synthesized compounds against tested fungal strains by micro dilution method and disk diffusion method respectively

Compound	*Aspergillus niger*		*Aspergillus flavus*		*Fusarium oxysporium*		*Trichoderma species*		*Fusarium monalifome*	
4a	18µg	8mm	18µg	9mm	15µg	10mm	24µg	12mm	13µg	11mm
4b	19µg	7mm	18µg	7mm	17µg	11mm	21µg	13mm	14µg	09mm
4c	16µg	8mm	18µg	10mm	12µg	14mm	18µg	14mm	11µg	12mm
4d	15µg	9mm	13µg	12mm	10µg	14mm	24µg	10mm	11µg	12mm
4e	16µg	9mm	14µg	11mm	10µg	15mm	12µg	11mm	14µg	12mm
4f	20µg	8mm	20µg	7mm	16µg	16mm	26µg	16mm	13µg	10mm
4g	20µg	7mm	22µg	8mm	22µg	22mm	22µg	10mm	23µg	12mm
4h	22µg	8mm	19µg	10mm	24µg	20mm	24µg	12mm	22µg	11mm
Nystatin	15µg	8mm	13µg	8mm	14µg	11mm	11µg	15mm	10µg	12mm

Spectral analysis of compounds

Compound 4a: ^{1}H NMR $CDCl_3$: δ 0.94 (t, 3H, CH_3), 1.34 (m, 2H, CH_2), 1,66 (m, 2H, CH_2), 2.57 (t, 2H, CH_2), 3.34 (dd, *J*=6.2, 1H, 4-H), 3.42 (dd, 1H, *J*=6.2, 4-H), 5.17 (dd, 1H, *J*=2.0, 5-H), 5.02 (s, 2H, CH_2), 6.62-7.10 (m, 5H, ArH), 7.18-7.37 (m, 4H, ArH), 7.42-7.65 (m, 4H, ArH), ^{13}C NMR $CDCl_3$: δ 14.1 (C), 23.1 (C), 26.7 (C), 33.2 (C), 39.5 (C), 53.2 (C), 104.7 (C), 113.5 (2C), 115.9 (C), 117.7 (C), 122.2 (C), 126.3 (C), 126.8 (C), 127.2 (2C), 127.8 (2C), 128.4 (C), 128.7 (4C), 129.7 (4C), 132.9 (C), 133.8 (2C), 135.4 (C), 142.7 (C), 143.4 (C), 143.8 (C), 148.6 (C), 156.1 (C). Anal.Calcd. For $C_{36}H_{32}ClN_5$; C, 75.84; H, 5.66; N, 12.28; Found: C, 75.85, H, 5.67, N, 12.28%.

Compound 4b: ^{1}H NMR $CDCl_3$: δ 0.96 (t, 3H, CH_3), 1.36 (m, 2H, CH_2), 1.62 (s, 3H, CH_3), 1.65 (m, 2H, CH_2), 2.58 (t, 2H, CH_2), 3.32 (s, 2H, 4-CH_2), 5.10 (s, 2H, CH_2), 6.64-7.06 (m, 6H, ArH), 7.13-7.19 (m, 6H, ArH), 7.38-7.68 (m, 6H, ArH). ^{13}C NMR $CDCl_3$: _ 14.2 (C), 23.2 (C), 26.8 (C), 30.1 (C), 33.4 (C), 41.4 (C), 47.3 (C), 56.2 (C), 104.6 (C), 113.5 (2C), 115.9 (C), 117.8 (C), 122.2 (C), 126.2 (C), 126.2 (C), 126.6 (2C), 127.7 (2C), 128.4 (3C), 128.7 (C), 129.9 (4C), 132.9 (C), 133.4 (C), 133.8 (C), 135.4 (C), 142.7 (C), 143.8 (C), 144.4 (C), 148.3 (C), 156.3 (C). Anal.Calcd. For $C_{37}H_{34}ClN_5$; C, 76.08; H, 5.87; N, 11.99; Found: C, 76.10, H, 5.86, N, 11.98%.

Compound 4c: ^{1}H NMR $CDCl_3$: δ 0.94 (t, 3H, CH_3), 1.33 (m, 2H, CH_2), 1,64 (m, 2H, CH_2), 2.55 (t, 2H, CH_2), 3.37 (dd, 1H, *J*=6.0, 4-H), 3.40 (dd, 1H, *J*=6.0, 4-H), 5.19 (dd, 1H, *J*=3.6, 5-H), 5.00 (s, 2H, CH_2), 6.60-7.08 (m, 5H, ArH), 7.16-7.32 (m, 4H, ArH), 7.40-7.65 (m, 4H, ArH), ^{13}C NMR $CDCl_3$: δ 14.2 (C), 23.0 (C), 25.7 (C), 32.6 (C), 33.5 (C), 40.8 (C), 41.1 (C), 104.7 (C), 113.7 (2C), 115.9 (C), 116.6 (C), 117.8 (C), 122.3 (C), 126.3 (C), 127.9 (2C), 128.5 (C), 128.8(C), 129.7 (4C), 132.8 (C) 133.6 (2C), 135.4 (C), 142.7 (C), 144.0 (C), 148.5 (C), 156.7 (C). Anal.Calcd. For $C_{31}H_{27}ClN_6$; C, 71.73; H, 5.24; N, 16.19. Found: C, 71.73; H, 5.23; N, 16.19 %.

Compound 4d: ^{1}H NMR $CDCl_3$: δ 0.98 (t, 3H, CH_3), 1.35 (m, 2H, CH_2), 1,66 (m, 2H, CH_2), 2.57 (t, 2H, CH_2), 3.32 (dd, 1H, *J*=6.4, 4-H), 3.37 (dd, 1H, *J*=6.4, 4-H), 3.46 (dd, 1H, *J*=4.0, CH_2Cl), 3.70 (dd, 1H, *J*=4.0, CH_2Cl), 4.98 (s, 2H, CH_2), 5.10 (m, 1H, 5-H), 6.58-7.08 (m, 5H, ArH), 7.16-7.38 (m, 4H, ArH), 7.42-7.65 (m, 4H, ArH), ^{13}C NMR $CDCl_3$: δ 14.2 (C), 22.8 (C), 26.0 (C), 33.2 (C), 34.6 (C), 40.7 (C), 52.4 (C), 53.4 (C), 104.7 (C), 113.6 (2C), 116.0 (C), 117.5 (C), 122.2 (C), 126.3 (C), 127.8 (2C), 128.4 (C), 128.8 (C), 129.7 (4C), 132.4 (C), 133.5 (2C), 135.4 (C), 142.5 (C), 144.0 (C), 148.4 (C), 156.4 (C). Anal.Calcd. For $C_{31}H_{29}Cl_2N_5$; C, 68.63; H, 5.39; N, 12.91. Found: C, 68.64; H, 5.38; N, 12.93 %.

Compound 4e: ^{1}H NMR $CDCl_3$: δ 0.95 (t, 3H, CH_3), 1.32 (m, 2H, CH_2), 1,63 (m, 2H, CH_2), 2.54 (t, 2H, CH_2), 3.30 (dd, 1H, *J*=6.6, 4-H), 3.35 (dd, 1H, *J*=6.6, 4-H), 3.42 (dd, 1H, *J*=3.2, CH_2Br), 3.68 (dd, 1H, *J*=3.2, CH_2Br), 5.16 (m, 1H, 5-H), 4.98 (s, 2H, CH_2), 6.50-7.08 (m, 5H, ArH), 7.12-7.36 (m, 4H, ArH), 7.42-7.65 (m, 4H, ArH), ^{13}C NMR $CDCl_3$: δ 14.2 (C), 22.6 (C), 26.0 (C), 33.2 (C), 35.9 (C), 36.6 (C), 39.2 (C), 40.5 (C), 54.4 (C), 104.7 (C), 113.6 (2C), 116.0 (C), 117.4 (C), 122.0 (C), 126.2 (C), 127.8 (2C), 128.4 (C), 128.7 (C), 129.7 (4C), 132.5 (C), 133.5 (C), 135.4 (C), 142.6 (C), 143.8 (C), 148.2 (C), 155.4 (C). Anal.Calcd. For $C_{31}H_{29}BrClN_5$; C, 63.43; H, 4.98; N, 11.93. Found: C, 63.45, H, 4.98, N, 11.91 %.

Compound 4f: ^{1}H NMR $CDCl_3$: δ 0.96 (t, 3H, CH_3), 1.33 (m, 2H, CH_2), 1,63 (m, 2H, CH_2), 2.56 (t, 2H, CH_2), 3.24 (dd, 1H, *J*=6.2, 4-H), 3.30 (dd, 1H, *J*=6.2, 4-H), 3.61-3.86 (m, 2H, CH_2), 5.02 (s, 2H, CH_2), 5.17 (m, 1H, 5-H), 6.52-7.10 (m, 5H, ArH), 7.16-7.37 (m, 4H, ArH), 7.42-7.65 (m, 4H, ArH). ^{13}C NMR $CDCl_3$:

δ 14.3 (C), 23.1 (C), 26.0 (C), 33.2 (C), 33.7 (C), 40.9 (C), 53.1 (C), 66.4 (C), 104.5 (C), 113.5 (2C), 115.8 (C), 117.2 (C), 122.2 (C), 126.7 (C), 127.7 (2C), 128.5 (C), 128.9 (C), 129.7 (4C), 132.8 (C), 133.3 (C), 133.8 (C), 135.4 (C), 142.6 (C), 144.0 (C), 148.4 (C), 156.5 (C). Anal.Calcd. For $C_{31}H_{30}ClN_5O$; C, 71.05; H, 5.77; N, 13.36; Found: C, 69.99, H, 6.13, N, 13.03%.

Compound 4g: ^{1}H NMR $CDCl_3$: δ 0.94 (t, 3H, CH_3), 1.33 (m, 2H, CH_2), 1,66 (m, 2H, CH_2), 2.02 (s, 3H, CH_3), 2.55 (t, 2H, CH_2), 3.37 (dd, 1H, *J*=6.0, 4-H), 3.42 (dd, 1H, *J*=6.0, 4-H), 5.42 (dd, 1H, *J*=4.0, 5-H), 5.04 (s, 2H, CH_2), 6.57-7.06 (m, 5H, ArH), 7.15 (d, 2H), 7.37 (d, 2H, ArH), 7.42-7.67 (m, 4H, ArH), ^{13}C NMR $CDCl_3$: δ 14.3 (C), 20.8 (C), 23.3 (C), 26.7 (C), 33.5 (C), 37.2 (C), 40.6 (C), 78.4 (C), 104.7 (C), 113.6 (2C), 115.9 (C), 117.3 (C), 122.1 (C), 126.6 (C), 127.8 (2C), 128.4 (C), 128.8 (C), 129.6 (4C), 132.7 (C), 133.5 (C), 133.8 (C), 135.4 (C), 142.7 (C), 144.1 (C), 148.3 (C), 155.9 (C), 170.5 (C). Anal.Calcd. For $C_{32}H_{30}ClN_5O_2$ C, 69.62; H, 5.48; N, 12.69; Found: C, 69.62, H, 5.46, N, 12.70 %.

Compound 4h: ^{1}H NMR $CDCl_3$: δ 0.96 (t, 3H, CH_3), 1.14 (t, 3H, CH_3), 1.34 (m, 2H, CH_2), 1,66 (m, 2H, CH_2), 2.32 (q, 2H, CH_2), 2.57 (t, 2H, CH_2), 3.34 (dd, 1H, *J*=6.4, 4-H), 3.42 (dd, 1H, *J*=6.4, 4-H), 5.38 (dd, 1H, *J*=4.0, 5-H), 5.02 (s, 2H, CH_2), 6.52-7.05 (m, 5H, ArH), 7.14-7.37 (m, 4H, ArH), 7.40-7.66 (m, 4H, ArH), ^{13}C NMR $CDCl_3$: δ 10.1 (C), 14.1 (C), 22.9 (C), 25.7 (C), 27.6 (C), 33.7 (C), 37.5 (C), 40.7 (C), 50.1 (C), 78.9 (C), 104.7 (C), 113.6 (2C), 115.8 (C), 117.7 (C), 122.3 (C), 126.7 (C), 127.8 (2C), 128.4 (C), 128.7 (C), 129.7 (4C), 132.8 (C), 133.5 (C), 135.4 (C), 142.7 (C), 144.0 (C), 148.4 (C), 156.8 (C), 173.2 (C). Anal.Calcd. For $C_{33}H_{32}ClN_5O_2$; C, 70.02; H, 5.70; N, 12.37; Found: C, 70.04, H, 5.70, N, 12.38 %.

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