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Synthesis and Antimicrobial Activity of Some Novel N-Mannich Bases of Imidazole Phenylazetidin-2-one

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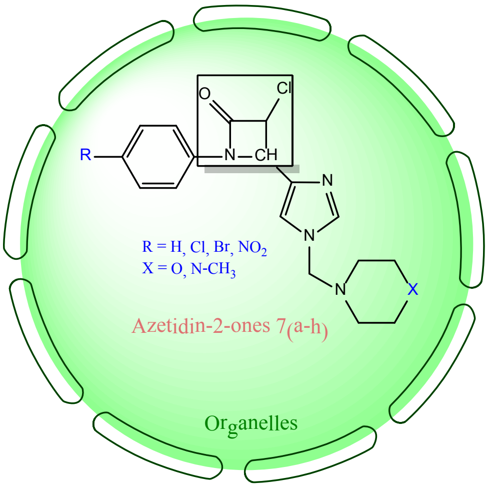
Abstract

The novel derivative of β-lactams of Imidazole phenylazetidin-2-ones 7(a-h) are an important class of heterocycles, having potential biological importance due to their unique features. The process of convert of imine (Schiffs base) to azetidine (β-lactam) through an intermediate of monochloro acetyl chloride is important synthetic method for preparation of azetidine-2-ones.



Keywords: Azetidin-2-one; Imidazole carboxaldehyde; Antimicrobial activity

Introduction

Azetidine-2-one (β-lactam) chemistry is of great importance because of the use of β-lactam derivatives as antibacterial agents. Since the discovery that the structure of penicillin contains a β-lactam function, a vast amount of effort has been devoted to producing other β-lactam antibiotics with a wider spectrum of activity and a greater resistance to enzymic cleavage by β-lactamases. The synthesis of β-lactam antibiotics has occupied an important place in the field of medicinal and research pharmaceutical. The antibiotic activity of Azetidine-2-ones (β-lactam) possessing antiviral, antifungal activities, antithrombotic and cholesterol inhibition [1-4].

The various synthetic approaches to obtain heterocyclic 2-azetidinones have been reported [5-14]. In the present paper, we describe the synthesis of heterocycles comprising Azetidin-2-one of N-Mannich Bases of Imidazole phenylazetidin-2-ones which can be an attractive target to obtain a series of novel compounds with potentially wide range of biological activity such as cholesterol absorption inhibitors, enzyme inhibitors, anticancer, cytotoxic, antitubercular, antitumor and antimicrobial (Scheme 1).

Experimental Section

Instrumentation and chemicals

All the chemicals used in the present investigation were purchased from Sigma-Aldrich Chemicals company, Inc. USA. And used without further purification. Thin Layer Chromatography was performed on aluminium sheet of silica gel 60F254, E-Merk, Germany using iodine as visualizing agent. Melting points were determined in open capillary tubes on Mel-Temp apparatus and are uncorrected. Column chromatography was performed on silica gel with different solvent systems as eluents to afford the pure compound. The IR Spectra were recorded as KBr pellets on Perkin-Elmer 1000 units, instruments. All ^{1}H and ^{13}C-NMR spectra were recorded on a Varian XL-300 spectrometer operating at 400MHz for ^{1}H -NMR and 75 MHz for ^{13}C-NMR. The compounds were dissolved in DMSO-d_6 and Chemical shifts were referenced to TMS (^{1}H and ^{13}C-NMR). Mass spectral data was recorded on FAB-MS instrument at 70ev with direct inlet system. Elemental analysis was recorded on a Carlo Erba 1108 elemental Analyzer, Central Drug Research Institute, Lucknow, India.

Microbial assay (Agar well diffusion method)

Nutrient agar (Bacto-beef extract 3 g; peptone 5 g; NaCl 5 g; and distilled water 1000 mL) was used for bacteria growth and Asthana and

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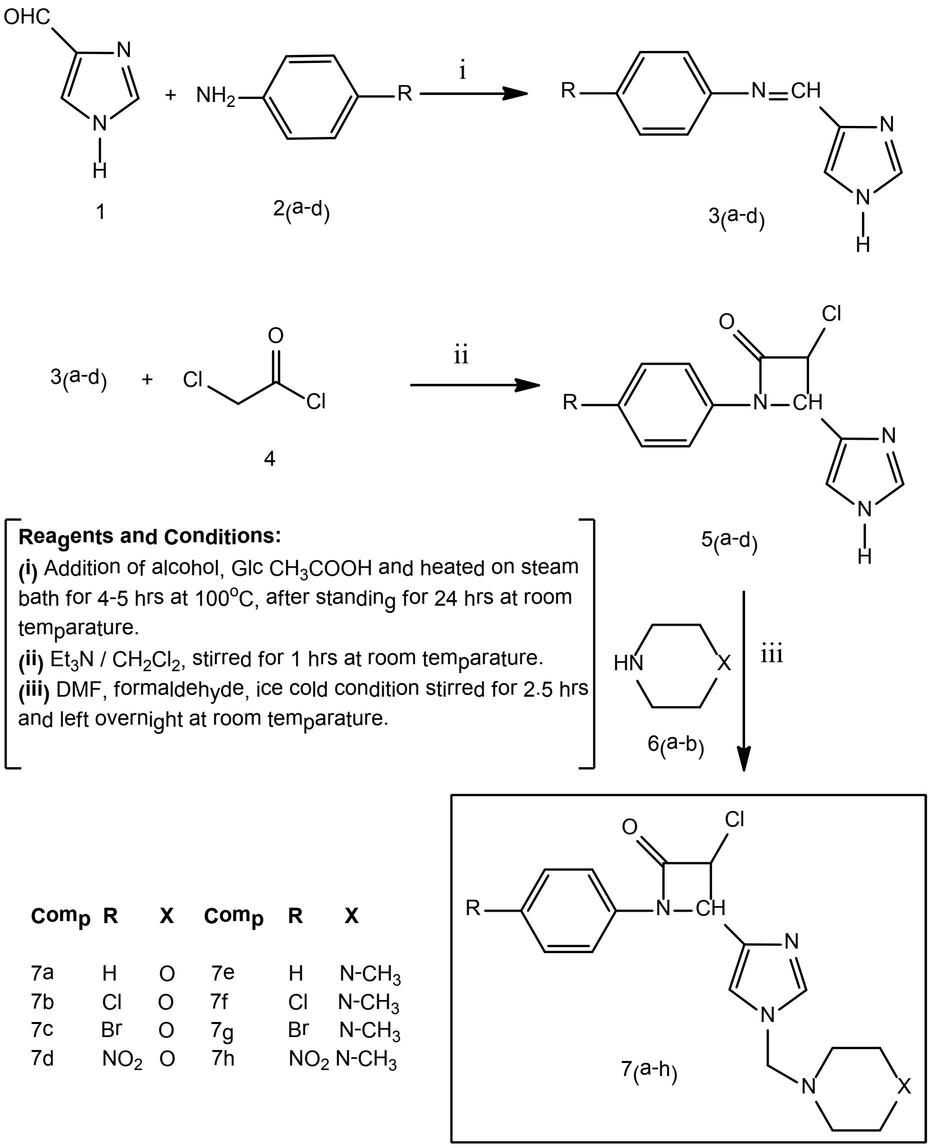

Scheme 1: Synthesis of 3-chloro-4-(1-(morpholinomethyl) / ((4-methylpiperazin-1-yl) methyl)-1H-imidazol-4-yl)-1-(4-substituted phenyl) azetidin-2-one 7(a-h).

Hawker's (Glucose 5 gr; KNO_3 3.5 g; KH_2PO_4 1.75 g; $MgSO_4.7H_2O$ 0.75 g and distilled water 1000 mL) media used for fungi growth. The media chemicals present study purchased from Merck**.** The standard bacterial and fungal strains were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology (IMTECH), and Chandigarh, India. The pure bacterial cultures were maintained on Nutrient Agar Media (NAM) for bacterial and fungal culture on potato dextrose agar (PDA).

The antimicrobial activity of these newly synthesized 3-chloro-4-(1-(morpholinomethyl) / ((4-methylpiperazin-1-yl) methyl)-1H-imidazol-4-yl)-1-(4-substituted phenyl) azetidin-2-one 7(a-h) performed according to Agar well diffusion method is preferred to be used in this study since it was found to be better than the disc diffusion method suggested by Parekh et al. [15] and also recommended by the National Committee for Clinical Laboratory. The synthesized compounds were used at the concentration of 2 mg/mL DMSO as a solvent [16]. A standardized 1 to 2 x 10^7 cfu/mL 0.5 MC Farland standard was introduced onto the surface of a sterile agar plate and evenly distributed inoculums by using a sterile glass spreader. Simultaneously, 6 mm wells were cut from the plate using a sterile cork borer. 50μl solution at a concentration of 2mg/mL of the compounds was introduced into well and incubated at 37°C for 24 hrs, the inhibition zones were measured with a ruler and compared with the control well containing only 1mg/mL in DMSO of streptomycin as the standard. The antifungal assay of the compounds was carried out by agar well diffusion method as described by Magaldi et al. [17] 6 mm diameter open wells punched with a sterile cork borer on cultured plates with test organisms before incubated. The wells were filled with 50 μl solution at a concentration of 2 mg/mL of the compounds at 30°C. After 72 hours, the zones of inhibition were measured and compared with those of the control DMSO and the standard Fluconazole at a concentration of 1 mg/mL.

Antibacterial assay

The antibacterial activity of 3-chloro-4-(1-(morpholinomethyl) / ((4-methylpiperazin-1-yl) methyl)-1H-imidazol-4-yl)-1-(4-substituted phenyl) azetidin-2-one 7(a-h) were screened against the *Staphylococcus* *aureus* (MTCC-3160) and *Bacillus subtilis* (MTCC-441) (gram +ve) and *Escherichia coli* (MTCC-1652) and *Pseudomonas aeruginosa* (MTCC-467) (gram -ve) organisms. Here Streptomycin is tested as reference compound to compare the activity.

Antifungal assay

Antifungal activity of 3-chloro-4-(1-(morpholinomethyl) / ((4-methylpiperazin-1-yl) methyl)-1H-imidazol-4-yl)-1-(4-substituted phenyl) azetidin-2-one 7(a-h) were screened against *Aspergillus niger* (MTCC-282) and *Penicillium rubrum,* our isolate. Here Fluconazole is tested as reference compound to compare the activity. The anti-bcterial and anti-fungal activity of 7(a-h) were shown in the Table 1.

Synthesis of N-((1H-imidazol-4-yl) methylene) 4-substituted aniline 3(a-d): The aniline (0.93g, 0.01 mol) (2a) and 4-imidazole carboxaldehyde (0.67g, 0.007 mol) (1) were dissolved in absolute alcohol, to this three drops of glacial acetic acid is added then heated on a steam bath for 4-5 hours at 100°C. After standing for 24 hours at room temperature. The organic layer the solution was dried over anhydrous sodium sulfate. After the evaporation of the solvent, the residue was purified by column chromatography (60-120 mesh silica gel, eluent: 10% EtoAc pet ether). Finally, the product compound N-((1H-imidazol-4-yl) methylene) aniline (3a) which was recrystallized from warm absolute alcohol. Yield 72% with 0.85g, m p 154-156°C.

The similar procedure was adopted to synthesize 3(b-d) (3b-1.02g with 72%, 3c-1.25g with 68% and 3d-1.08g with 66%) by condensing 2-imidazole carboxaldehyde (0.67g, 0.007 mol) (1) with 4-chloro aniline (2b-0.93g, 0.01mol), 4-bromo aniline (2c-1.27g, 0.01 mol) and 4-nitro aniline (2d-1.38g, 0.01 mol) respectively.

Synthesis of 3-chloro-4-(1H-imidazol-4-yl)-1-(4-substituted phenyl) azetidin-2-one 5(a-d): The imine (Schiff's base) (0.51g, 0.003 mol) (3a) was placed in 50 mL round bottom flask equipped with a magnetic pallet at nitrogen atmosphere, followed by addition of monochloro acetyl chloride (0.67g, 0.006 mol) (4) and triethyl amine (5droups, 0.2 mL) in CH_2Cl_2 (25 mL) at room temperature. The mixture was stirred for 1hours and left at room temperature for 72 hours. The progress of reaction was monitored by Thin Layer Chromatography using cyclohexane and ethyl acetate (7:3) solvent mixture as a mobile phase. The mixture was poured on crushed ice. The product 3-chloro-4-(1H-imidazol-4-yl)-1-phenylazetidin-2-one (5a) thus formed was filtered and washed with sodiumbicarbonate solution. The solution was dried over anhydrous sodium sulfate. After the evaporation of the solvent, the residue was purified by column chromatography (60-120 mesh silica gel,eluent: 10% EtoAc pet ether). The dried product recrystallised with absolute alcohol, mp 148-150 °C and yield (0.52g) 70%.

The similar procedure was adopted to synthesize 5(b-d) (5b-0.57 g with 68%, 5c-0.60 g with 65% and 5d-0.59 g with 68%) by condensing Schiffs bases 3(b-d) (3b-0.61 g, 3c-0.70 g and 3d-0.60 g) with monochloro acetyl chloride (0.67 g, 0.006 mol) (4) respectively.

Synthesis of 3-chloro-4-(1-(morpholinomethyl) methyl)-1H-imidazol-4-yl)-1-(4-substituted phenyl) azetidin-2-one 7(a-h): A mixture of (0.49 g, 0.002 mol) 3 -chloro - 4 - (1H - imidazol - 4 - yl) - 1 -phenylazetidin - 2 - one (5a), morpholine (6a) (0.5 g, 0.006 mol) and water 20 mL was stirred to obtained a clear solution. To this solution, Farmaldehide (0.05 mol, 15 mL) and DMF (10ml) were added in ice cold condition and stirred for 2 hours in an ice bath and left over night at room temperature. The progress of the reaction was monitored by Thin Layer Chromatography using cyclohexane and ethylacetate (7:3) solvent mixture as a mobile phase. At the end of the reaction dichloromethane (30ml) was added to the mixture followed by neutralization with 50 ml of 1N NaOH solution, after neutralization the mixture was extracted with CH_2Cl_2 (3x25 mL). The combined extract was dried on anhydrous Na_2SO_4. After filtration, the solvent was removed with rota evaporator. The residue was purified by column chromatography, using 60-120 mesh silica and $CHCl_3$ solvent was used as an elutent. Finally the product 3-chloro-4-(1-(morpholinomethyl)-1H-imidazol-4-yl)-1-phenylazetidin-2-one (7a) was purified from aqueous dimethyl formamide. Yield 70% with 0.47g, m p 162-164°C.

The similar procedure was adopted to synthesize 7(b-d) by condensing 5(b-d) (5b-0.56 g, 5c-0.65 g and 5d-0.58 g) with morpholine (0.5 g, 0.006 mol) (6a) respectively.

The structure of these newly synthesized compounds of 7(a-d) were established by IR, ^{1}H-NMR, ^{13}C-NMR, mass data and elemental analysis.

3-chloro-4-(1-(morpholinomethyl)-1H-imidazol-4-yl)-1-phenylazetidin-2-one (7a) The product was synthesized according to general procedure **5.3** to afford the target compound as a white solid with 0.47g (68%) and m p 162-164°C.

IR (KBr 4000-400 cm^{-1}): 3062 (stretching of Ar-H), 2940 and 2895 (CH_2 of aliphatic-CH), 1690 (C=O of azetidinone), 1560 (C-N), 1478-

Entry	COMP	R	X	Zone of inhibition (mm) 50 µL for well					
				[1]Anti-bacterial activity				[2]Anti-fungal activity	
				S.a	B.s	E.c	P.a	A.n	P.r
1	7a	H	O	12	14	10	09	07	05
2	7b	*Cl	O	16	18	13	12	09	12
3	7c	*Br	O	18	16	15	11	14	10
4	7d	*NO_2	O	15	13	10	16	13	12
5	7e	H	NCH_3	11	07	09	10	04	06
6	7f	*Cl	NCH_3	17	12	15	18	11	13
7	7g	*Br	NCH_3	19	16	12	14	09	08
8	7h	*NO_2	NCH_3	17	13	11	14	12	14
Std		Streptomycin		25	20	20	23	-	-
Std		Fluconazole		-	-	-	-	18	15

[1]S.a - *Staphylococcus aureus*, B.s - *Bacillus subtilis*, E.c - *Escherichia coli*, P.a - *Pseudomonas aeruginosa*
[2]A.n - *Aspergillus niger* P.r - *Penicillium rubrum*
*Indicates more activity

Table 1: Anti-bcterial and anti-fungal activity of 3-chloro-4-(1-(morpholinomethyl) / ((4- methylpiperazin-1-yl) methyl)-1H-imidazol-4-yl)-1-(4-substituted phenyl) azetidin-2-one 7(a-h).

1366 (bending vibrations of imidazole ring), 1140 (C-O) and 725 cm^{-1} (C-Cl).

^{1}H-NMR (400 MHz, DMSO-d_6): δ_{PPM} 2.50 (t, 4H, $(CH_2)_2$ of morpholine ring J = 7.1Hz), 3.65 (t, 4H, $(CH_2)_2$ of morpholine ring J = 7.1Hz), 3.93 (m, 1H, CH of azetidine ring), 4.69 (d, 1H, CH of azetidine ring J = 7.1Hz), 4.80 (s, 2H of CH_2), 5.38 (d, 1H, CH of azetidine ring J = 7.1Hz), 6.88 (s, 1H, CH of imidazole ring), 7.27-7.40 (m, 5H of phenyl ring) and 7.83 (s, 1H of imidazole ring).

^{13}C-NMR (75 MHz, DMSO-d_6): δ_{PPM}. 137.2, 118.8, 137.8, 40.9, 68.5, 199.4, 54.3, 139.2, 128.1, 128.8, 126.0, 128.8, 128.1, 76.1, 53.6, 66.4, 53.6 and 66.4 corresponding to C_1 to C_{18} respectively. MS 345.12 for $C_{18}H_{20}ClN_3O_2$. Anal. Found (Calcd) C, 62.52 (61.72); H, 5.83 (5.53); N, 12.15 (11.55).

3-chloro-1-(4-chlorophenyl)-4-(1-(morpholinomethyl)-1H-imidazol-4-yl) azetidin-2-one (7b) The product was synthesized according to general procedure **5.3** to afford the target compound as a yellow solid with 0.51g (68%) and m p 154-156^{O}C.

IR (KBr 4000-400 cm^{-1}): 3052 (stretching of Ar-H), 2940 and 2895 (CH_2 of aliphatic-CH), 1690 (C=O of azetidinone), 1556 (C-N), 1475-1360 (bending vibrations of imidazole ring), 1100 (C-O) and 720 cm^{-1} (C-Cl).

^{1}H-NMR (400 MHz, DMSO-d_6): δ_{PPM} 2.50 (t, 4H, $(CH_2)_2$ of morpholine ring J = 7.1Hz), 3.65 (t, 4H, $(CH_2)_2$ of morpholine ring J = 7.1Hz), 3.93 (m, 1H, CH of azetidine ring), 4.69 (d, 1H, CH of azetidine ring J = 7.1Hz), 4.80 (s, 2H of CH_2), 5.38 (d, 1H, CH of azetidine ring J = 7.1Hz), 6.88 (s, 1H, CH of imidazole ring), 7.42-7.45 (m, 4H of chloro phenyl ring) and 7.83 (s, 1H of imidazole ring).

^{13}C-NMR (75 MHz, DMSO-d_6): δ_{PPM}. 137.2, 118.8, 137.8, 40.9, 68.5, 199.4, 54.3, 137.3, 129.5, 128.9, 131.6, 128.9, 129.5, 76.1, 53.6, 66.4, 53.6 and 66.4 corresponding to C_1 to C_{18} respectively.MS 379.09 for $C_{18}H_{19}Cl_2N_3O_2$. Anal. Found (Calcd) C, 56.85 (56.05); H, 5.04 (4.54); N, 11.05 (10.45).

1-(4-bromophenyl)-3-chloro-4-(1-(morpholinomethyl)-1H-imidazol-4-yl) azetidin-2-one (7c) The product was synthesized according to general procedure **5.3** to afford the target compound as a yellow solid with 0.55g (65%) and m p 142-144^{O}C.

IR (KBr 4000-400 cm^{-1}): 3055 (stretching of Ar-H), 2940 and 2895 (CH_2 of aliphatic-CH), 1685 (C=O of azetidinone), 1550 (C-N), 1478-1371 (bending vibrations of imidazole ring), 1112 (C-O) and 718 cm^{-1} (C-Cl).

^{1}H-NMR (400 MHz, DMSO-d_6): δ_{PPM} 2.50 (t, 4H, $(CH_2)_2$ of morpholine ring J = 7.1Hz), 3.65 (t, 4H, $(CH_2)_2$ of morpholine ring J = 7.1Hz), 3.93 (m, 1H, CH of azetidine ring), 4.69 (d, 1H, CH of azetidine ring J = 7.1Hz), 4.80 (s, 2H of CH_2), 5.38 (d, 1H, CH of azetidine ring J = 7.1Hz), 6.88 (s, 1H, CH of imidazole ring), 7.18-7.82 (m, 4H of bromo phenyl ring) and 7.83 (s, 1H of imidazole ring).

^{13}C-NMR (75 MHz, DMSO-d_6): δ_{PPM}. 137.2, 118.8, 137.8, 40.9, 68.5, 199.4, 54.3, 138.2, 130.3, 131.7, 120.4, 131.7, 130.3, 76.1, 53.6, 66.4, 53.6 and 66.4 corresponding to C_1 to C_{18}respectively.MS 423.03 for $C_{18}H_{19}BrClN_3O_2$. Anal. Found (Calcd) C, 50.90 (50.50); H, 4.51 (4.01); N, 9.89 (9.39).

3 - chloro - 4 - (1 -(morpholinomethyl) -1H- imidazol - 4 - yl) -1-(4 - nitrophenyl) azetidin - 2 - one (7d) The product was synthesized according to general procedure **5.3** to afford the target compound as a yellow solid with 0.54g (70%) and m p 154-156^{O}C.

IR (KBr 4000-400 cm^{-1}): 3068 (stretching of Ar-H), 2940 and 2895 (CH_2 of aliphatic-CH), 1675 (C=O of azetidinone), 1560 (C-N), 1550-1330 (C-NO_2), 1476-1365 (bending vibrations of imidazole ring), 1116 (C-O) and 715 cm^{-1} (C-Cl).

^{1}H-NMR (400 MHz, DMSO-d_6): δ_{PPM} 2.50 (t, 4H, $(CH_2)_2$ of morpholine ring J = 7.1Hz), 3.65 (t, 4H, $(CH_2)_2$ of morpholine ring J = 7.1Hz), 3.93 (m, 1H, CH of azetidine ring), 4.69 (d, 1H, CH of azetidine ring J = 7.1Hz), 4.80 (s, 2H of CH_2), 5.39 (d, 1H, CH of azetidine ring J = 7.1Hz), 6.88 (s, 1H, CH of imidazole ring), 7.83 (s, 1H of imidazole ring) and 7.55-8.21 (m, 4H of chloro phenyl ring).

^{13}C-NMR (75 MHz, DMSO-d_6): δ_{PPM}. 137.2, 118.8, 137.8, 40.9, 68.5, 199.4, 54.3, 145.3, 129.0, 124.0, 145.2, 124.0, 129.0, 76.1, 53.6, 66.4, 53.6 and 66.4 corresponding to C_1 to C_{18} respectively. MS 390.11 for $C_{18}H_{19}ClN_4O_4$. Anal. Found (Calcd) C, 55.32 (54.82); H, 4.90 (4.50); N, 14.34 (13.74).

2.4. Synthesis of 3 – chloro - 4-(1-((4-methylpiperazin-1-yl) methyl) -1H- imidazol-4-yl) - 1 - (4-substituted phenyl) azetidin-2-one 7(e-h):

A mixture of (0.49 g, 0.002 mol) 3 - chloro - 4 - (1H - imidazol - 4 - yl) - 1 -phenylazetidin - 2 - one **(5a)**, N-methylpiperazine (0.6 g, 0.006 mol) **(6b)** and water 20 mL was stirred to obtain a clear solution. To this solution, Farmaldehide (0.05 mol, 15 mL) and DMF (10ml) were added in ice cold condition and stirred for 2 hours in an ice bath and left over night at room temperature. The progress of the reaction was monitored by Thin Layer Chromatography using cyclohexane and ethylacetate (7:3) solvent mixture as a mobile phase. At the end of the reaction dichloromethane (30ml) was added to the mixture followed by neutralization with 50ml of 1N NaOH solution, after neutralization the mixture was extracted with CH_2Cl_2 (3x25 mL). The combined extract was dried on anhydrous Na_2SO_4. After filtration, the solvent was removed with rota evaporator. The residue was purified by column chromatography, using 60-120 mesh silica and $CHCl_3$ solvent was used as an elutent. Finally the product 3-chloro-4-(1-((4-methylpiperazin-1-yl) methyl) – 1H – imidazol – 4 - yl) – 1 -phenylazetidin-2-one **(7e)** was purified from aqueous dimethyl formamide. Yield 68% with 0.48g, m p 142-144^{o}C.

The similar procedure was adopted to synthesize **7(f-h)** by condensing **5(b-d)** (**5b**-0.56 g, **5c**-0.65 g and **5d**-0.58 g) with N-methylpiperazine (0.6 g, 0.006 mol) **(6b)** respectively.

The structure of these newly synthesized compounds of **7(e-h)** were established by IR, ^{1}H-NMR, ^{13}C-NMR, mass data and elemental analysis.

3-chloro-4-(1-((4-methylpiperazin-1-yl) methyl) – 1H – imidazol – 4 - yl) – 1 -phenylazetidin-2-one (7e) The product was synthesized according to general procedure **5.3** to afford the target compound as a white 0.48g (68%) and m p 142-144^{O}C.

IR (KBr 4000-400 cm^{-1}): 3051 (stretching of Ar-H), 2940 and 2895 (CH_2 of aliphatic-CH), 1678 (C=O of azetidinone), 1562 (C-N), 1478-1360 (bending vibrations of imidazole ring), 1120 (C-O) and 725 cm^{-1} (C-Cl).

^{1}H-NMR (400 MHz, DMSO-d_6): δ_{PPM} 2.26 (s, 3H, N-CH_3), 2.35 (m, 8H of methylpiperazin ring), 3.93 (m, 1H, CH of azetidine ring), 4.69 (d, 1H, CH of azetidine ring J = 7.1Hz), 4.80 (s, 2H of CH_2), 5.39 (d, 1H, CH of azetidine ring J = 7.1Hz), 6.88 (s, 1H, CH of imidazole ring), 7.27-7.40 (m, 5H of phenyl ring) and 7.83 (s, 1H of imidazole ring).

^{13}C-NMR (75 MHz, DMSO-d_6): δ_{PPM}. 137.2, 118.8, 137.8, 40.9, 68.5, 199.4, 54.3, 139.2, 128.1, 128.8, 126.0, 128.8, 128.1, 75.8, 52.6, 57.3, 52.6, 57.3 and 46.6 corresponding to C_1 to C_{19} respectively. MS 358.16 for $C_{19}H_{23}ClN_4O$. Anal. Found (Calcd) C, 63.59 (62.79); H, 6.46 (5.96); N, 15.61 (15.01).

3-chloro-1-(4-chlorophenyl)-4-(1-((4-methylpiperazin-1-yl) methyl)-1H-imidazol-4-yl) azetidin-2-one (7f) The product was synthesized according to general procedure **5.3** to afford the target compound as a yellow solid with 0.51g (66%) and m p 147-149°C.

IR (KBr 4000-400 cm^{-1}): 3055 (stretching of Ar-H), 2940 and 2895 (CH_2 of aliphatic-CH), 1690 (C=O of azetidinone), 1558 (C-N), 1475-1366 (bending vibrations of imidazole ring), 1100 (C-O) and 728 cm^{-1} (C-Cl).

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ_{PPM} 2.26 (s, 3H, N-CH_3), 2.35 (m, 8H of methylpiperazin ring), 3.93 (m, 1H, CH of azetidine ring), 4.69 (d, 1H, CH of azetidine ring J = 7.1Hz), 4.80 (s, 2H of CH_2), 5.39 (d, 1H, CH of azetidine ring J = 7.1Hz), 6.88 (s, 1H, CH of imidazole ring), 7.42-7.45 (m, 4H of chloro phenyl ring) and 7.83 (s, 1H of imidazole ring).

^{13}C-NMR (75 MHz, DMSO-d$_6$): δ_{PPM}. 137.2, 118.8, 137.8, 40.9, 68.5, 199.4, 54.3, 137.3, 129.5, 128.9, 131.6, 128.9, 129.5, 75.8, 52.6, 57.3, 52.6, 57.3 and 46.6 corresponding to C_1 to C_{19} respectively. MS 392.12 for $C_{19}H_{22}Cl_2N_4O$. Anal. Found (Calcd) C, 58.02 (57.22); H, 5.64 (5.14); N, 14.24 (13.64).

1-(4-bromophenyl)-3-chloro-4-(1-((4-methylpiperazin-1-yl) methyl)-1H-imidazol-4-yl) azetidin-2-one (7g) The product was synthesized according to general procedure **5.3** to afford the target compound as a yellow solid with 0.56g (65%) and m p 141-142^{O}C.

IR (KBr 4000-400 cm^{-1}): 3050 (stretching of Ar-H), 2940 and 2895 (CH_2 of aliphatic-CH), 1678 (C=O of azetidinone), 1558 (C-N), 1470-1360 (bending vibrations of imidazole ring), 1120 (C-O) and 714 cm^{-1}(C-Cl).

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ_{PPM} 2.26 (s, 3H, N-CH_3), 2.35 (m, 8H of methylpiperazin ring), 3.93 (m, 1H, CH of azetidine ring), 4.69 (d, 1H, CH of azetidine ring J = 7.1Hz), 4.80 (s, 2H of CH_2), 5.39 (d, 1H, CH of azetidine ring J = 7.1Hz), 6.88 (s, 1H, CH of imidazole ring), 7.18-7.82 (m, 4H of bromo phenyl ring) and 7.83 (s, 1H of imidazole ring).

^{13}C-NMR (75 MHz, DMSO-d$_6$): δ_{PPM}. 137.2, 118.8, 137.8, 40.9, 68.5, 199.4, 54.3, 138.2, 130.3, 131.7, 120.4, 131.7, 130.3, 75.8, 52.6, 57.3, 52.6, 57.3 and 46.6 corresponding to C_1 to C_{19} respectively. MS 436.07 for $C_{19}H_{22}BrClN_4O$. Anal. Found (Calcd) C, 52.13(51.33); H, 5.07 (5.57); N, 12.80 (12.00).

3 – chloro - 4-(1-((4-methylpiperazin-1-yl) methyl) -1H-imidazol-4-yl) - 1 - (4-nitrophenyl) azetidin-2-one (7h) The product was synthesized according to general procedure **5.3** to afford the target compound as a yellow solid with 0.54g (68%) and m p 155-157^{o}C.

IR (KBr 4000-400 cm^{-1}): 3068 (stretching of Ar-H), 2940 and 2895 (CH_2 of aliphatic-CH), 1692 (C=O of azetidinone), 1558 (C-N), 1550-1330 (C-NO_2), 1480-1369 (bending vibrations of imidazole ring), 1116 (C-O) and 726 cm^{-1} (C-Cl).

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ_{PPM} 2.26 (s, 3H, N-CH_3), 2.35 (m, 8H of methylpiperazin ring), 3.93 (m, 1H, CH of azetidine ring), 4.69 (d, 1H, CH of azetidine ring J = 7.1Hz), 4.80 (s, 2H of CH_2), 5.39 (d, 1H, CH of azetidine ring J = 7.1Hz), 6.88 (s, 1H, CH of imidazole ring), 7.83 (s, 1H of imidazole ring) and 7.55-8.21 (m, 4H of chloro phenyl ring).

^{13}C-NMR (75 MHz, DMSO-d$_6$): δ_{PPM}. 137.2, 118.8, 137.8, 40.9, 68.5, 199.4, 54.3, 145.3, 129.0, 124.0, 145.2, 124.0, 129.0, 75.8, 52.6, 57.3, 52.6, 57.3 and 46.6 corresponding to C_1 to C_{19} respectively. MS 403.14 for $C_{19}H_{22}ClN_5O_3$. Anal. Found (Calcd) C, 56.51 (55.71); H, 5.49 (4.99); N, 17.34 (16.74).

Result and Discussion

The anti-bacterial and anti-fungal activity of **7(a-h)** were shown in the Table 1**.** The compounds 7(a-h) were tested for antimicrobial activity. Amongst all the tested compounds, 7b-d and 7f-h exhibited higher activity than other which may be due to the presence of electron withdrawing substituents increases the activity when compared with electron donating substituents.

Conclusion

In conclusion, we have demonstrated the synthesis of a series of novel N-Mannich Bases of Imidazole phenylazetidin-2-ones derivatives with different substituents. Some of the compounds were found to have good antimicrobial activity.

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