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SYNTHESIS, SPECTRAL AND MICROBIOLOGICAL EVOLUTION OF 3-CHLORO-4-[1-N-PHENYL-3-PHENYL-PYRAZOLE]-1-N-ARYL-AZETIDIN-2-ONE DERIVATIVES

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ABSTRACT

The present work of 3 - chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-aryl-azetidin-2-one derivatives have been synthesized by the reaction of Schiff bases formation of 1-N-phenyl-3-phenyl-4-formyl pyrazole (PFP) (2a-h) and Arylidine-[1-N-phenyl-3-phenyl-pyrazole] (3a-h) gives (4a-h) 3-chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-(3,4-diethoxyphenyl)-azetidin-2-one derivatives. The structure of synthesized compounds elucidate by spectroscopic methods like IR, ^{1}HNMR, Mass and elemental analysis. The efficient novel product (4a-h) with different active substituent was screened against antimicrobial activity and it showed notable efficacy against tested microbes.

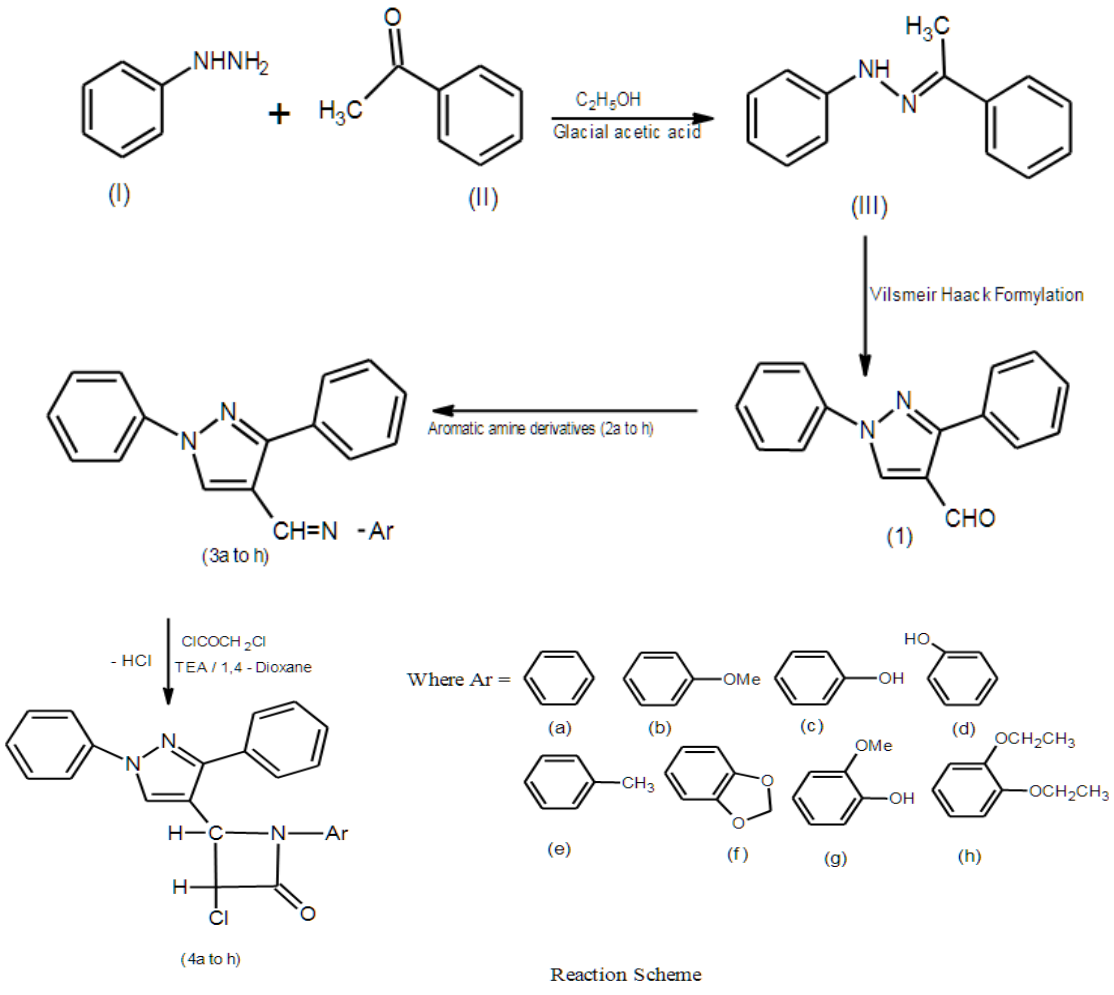
KEYWORDS: Phenyl-pyrazole, azetidin-2-one derivatives, Arylidine, antimicrobial activity.

INTRODUCTION

Azetidinones, commonly known as β-lactams, β-lactams ring is a four member cyclic amide. It is named as such, because the nitrogen atom is attached to the β-carbon relative to the carbonyl. The skeleton of azetidinone, has been recognized as a useful molecule in the synthesis of biologically important compounds. Azetindin-2-one derivatives display interesting biological activities such as antifungal, antimicrobial,[1,2,3,4] antitubercular,[5,6] analgesic, anti-inflammatory,[7,8] chymase inhibitory,[9] antitumoral,[10,11,12] antiviral,

antidiabetic and cholesterol absorption inhibitory properties.[13] The efficacy of famous antibiotic classes such as the penicillins, cephalosporins, carumonam, aztreonam, thienamicine, nocardicins and carbapenems are give significations to the presence of an azetidinone-2-one ring. This has led to the discovery of a wide variety of compounds that are of high interest from the point of view antibacterial, anti-inflammatory, antihyperlipidemic, CNS activity, anticancer, antimicrobial, pesticidal, cytotoxic, antidiabetic, antitumor, antifungal, antitubercular activities. The work presented here was to synthesize azetidinone-2-one derivatives using arylidine-[1-n-phenyl-3-phenyl-pyrazole] as parent motif. Preparation of those molecules plays a really important role in their organic synthesis. The purpose of the present work is to synthesize a series of new 1-N-phenyl-3-phenyl-4-formyl pyrazole (PFP) (2a-h) and Arylidine-[1-N-phenyl-3-phenyl-pyrazole] (3a-h) gives (4a-h) 3-chloro -4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-(3,4-diethoxyphenyl)-azetidin-2-one derivatives derivatives to investigate their anti microbiological activity.

RESULT AND DISCUSSION



Reaction Scheme

MATERIAL AND METHOD

(1) Synthesis of 1-(phenyl)-ethanone-(phenyl)-hydrazone: A mixture of phenyl hydrazine (0.01 mole) and acetophenone (0.01 mole) in absolute ethanol was refluxed in water bath for 2 hrs, in presence of 1 ml glacial acetic acid, the crude product was isolated and crystallized from absolute alcohol. Yield was about 94%.

(2) Synthesis of 1-N-phenyl-3-phenyl 4-formyl pyrazole (PFP):1-(phenyl)-ethanone-(phenyl)-hydrazone (0.01 mole) was added in mixture of Vilsmeir-Haack reagent (prepared by drop wise addition of 3 ml of $POCl_3$ in ice cooled 25 ml di-methylformamide [DMF]) and refluxed for 5 hrs. The reaction mixture was poured into ice followed by neutralization using sodium bicarbonate. Crude product was isolated and crystalized from ethanol. Yield was about 82%.

(3) Synthesis of derivatives (4a-h) 3-chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-(3,4-diethoxyphenyl)-azetidin-2-one: Using schiff bases formation of 1-N-phenyl-3-phenyl-4-formyl pyrazole (PFP)(2a-h) and synthesis of Arylidine-[1-N-phenyl-3-phenyl-pyrazole] (3a-h). A mixture of equimolar amount of 1-N-phenyl-3-phenyl-4-formyl pyrazole (PFP) (0.01 mole) and various aromatic amines (0.01 mole) (2a-h) in mention above 50 ml acetic acid was refluxed for about 10-12 hrs. on oil bath with TLC monitoring. The reaction mixture was cooled and it was poured into ice water and extracted with ethyl acetate and water and finally dried over anhydrous sodium sulfate. The solvent was evaporated to give the solid product. It was crystallized from ethyl acetate and hexane using decolorizing charcoal to give amines.

Spectroscopy analysis and analytical data of 1-N-phenyl-3-phenyl-4-formyl pyrazole (PFP): M.P.142-44^{0}C, Yield 82%, IRcm^{-1}1630 (C=O of CHO), 3030, 1500, 1600 (Aromatic C-H str.), 1250 (α, β unsaturated aldehydes), 1500 (C=N), 1590 (C-N). ^{1}H NMR δHppm 6.4-8.86 (multipletAr-H of pyrazole), 2.09 (1H, singlet, -CHO), ^{13}CMRδHppm120-129 Benzene, 162, 150, 113 pyrazole, 162 CHO. Mol. For. $C_{16}H_{12}N_2O$, Mol.Wt. 248 gm/mole, Anal.data. (Cal/Found) C% 77.4/77.2, H% 4.8/4.7, N% 11.2/11.0.

Compound 3a Benzylidine- [1-N-phenyl-3-phenyl-pyrazole]: M.P.167-69^{0}C, Yield 87%, IRcm^{-1}1040 (-N-N), 3030, 3080, 1500, 1600 (Aromatic -C-H str.), 1630 (-CH=N), 1095 (-C-N). ^{1}H NMR δHppm 6.4-8.86(multipletAr +CH of -CH=N protons + H of pyrazole).^{13}CMRδHppm130-150 pyrazole, 115-123 Benzene, 153 CH=N. Mol. For.

$C_{22}H_{17}N_3$, Mol.Wt. 323 gm/mole, Anal. data. (Cal/Found) C%81.7/81.5, H% 5.2/4.9, N% 13.0/12.8.

Compound 3b 4-Methoxy benzylidine- [1-N-phenyl-3-phenyl-pyrazole]: M.P.252-54^{0}C, Yield 82%, IRcm^{-1}1040 (-N-N), 3030,1500, 1600 (Aromatic -C-H str.), 1625 (-CH=N), 1095 (-C-N), 1200 (Ar - O – alkyl).^{1}H NMR δHppm 6.14-8.58(multipletAr+CH of CH=N protons + H of pyrazole), 3.85 (3H singlet, -OCH_3). ^{13}CMRδHppm136-150 pyrazole, 114-129 Benzene, 153 CH=N, 113 C-O, 56 CH_3. Mol. For. $C_{23}H_{19}N_3O$, Mol.Wt. 353 gm/mole, Anal. data. (Cal/Found) C%78.2/78.0, H% 5.3/5.2, N% 11.8/11.8.

Compound 3c 4-Hydroxy benzylidine- [1-N-phenyl-3-phenyl-pyrazole]: M.P.233-34^{0}C, Yield 85%, IRcm^{-1}3370 (-OH), 1040 (-N-N), 3030, 1500, 1600 (Aromatic -C-H str.), 1627 (-CH=N), 1095 (-C-N). ^{1}H NMR δHppm 6.3-8.1(multipletAr +CH of CH=N protons + H of pyrazole), 3.85 (3H singlet, -OCH_3). ^{13}CMRδHppm130-150 pyrazole, 114-129 Benzene, 153 CH=N, 114 C-O. Mol. For. $C_{22}H_{17}N_3O$, Mol.Wt. 339 gm/mole, Anal. data. (Cal/Found) C% 77.8/77.5, H% 5.0/4.9, N% 12.3/12.2.

Compound 3d 2-Hydroxy benzylidine- [1-N-phenyl-3-phenyl-pyrazole]: M.P.236-37^{0}C, Yield 87%, IRcm^{-1}3370 (-OH), 1040 (-N-N), 3030, 1500, 1600 (Aromatic -C-H str.), 1627 (-CH=N), 1095 (-C-N). ^{1}H NMR δHppm 6.2-8.1 (multipletAr +CH of CH=N protons + H of pyrazole), 3.85 (3H singlet, -OCH_3). ^{13}CMRδHppm136-150 pyrazole, 114-129 Benzene, 153 CH=N, 113 C-O. Mol. For. $C_{22}H_{17}N_3O$, Mol.Wt. 339 gm/mole, Anal. data. (Cal/Found) C% 77.8/77.5, H% 5.0/4.9, N% 12.3/12.2.

Compound 3e 4-Methoxy benzylidine- [1-N-phenyl-3-phenyl-pyrazole]: M.P.240-41^{0}C, Yield 86%, IRcm^{-1}2950, 1370 (-CH_3), 1040 (-N-N), 3030, 1500, 1600 (Aromatic -C-H str.), 1625 (-CH=N), 1095 (-C-N). ^{1}H NMR δHppm 6.2-8.1 (multipletAr +-CH of -CH=N protons + H of pyrazole),2.5 (3H singlet, -CH_3). ^{13}CMRδHppm20.9 -CH_3,136-150 pyrazole, 114-129 Benzene, 150 CH=N. Mol. For. $C_{22}H_{17}N_3O$, Mol.Wt. 339 gm/mole, Anal. data. (Cal/Found) C%81.8/81.5, H% 5.6/5.5, N% 12.4/12.3.

Compound 3f 3,4-Methylenedioxybenzylidine - [1-N-phenyl-3-phenyl-pyrazole]: M.P. 237-38^{0}C, Yield 87%, IRcm^{-1}2920, 2850, 1450 -(CH_2), 1040 (-N-N), 3030, 1500, 1600

(Aromatic -C-H str.), 1640 (-CH=N), 1095 (-C-N). ^{1}H NMR δHppm 6.1-8.1 (multipletAr +CH of CH=N protons + H of pyrazole),5.9(2H singlet, -O-CH_2-O). ^{13}CMRδHppm91.3 -O-CH_2-O-, 136-150 pyrazole, 114-129 Benzene, 153-CH=N. Mol. For. $C_{23}H_{17}N_3O_2$, Mol.Wt. 367 gm/mole, Anal. data. (Cal/Found) C%75.2/74.9, H% 4.7/4.6, N% 11.4/11.3.

Compound 3g 4-Hydroxy-3-methoxy benzylidine- [1-N-phenyl-3-phenyl-pyrazole]: M.P.243-44^{0}C, Yield 78%, IRcm^{-1}3370 (-OH), 1040 (-N-N),2950, 1370, (-CH_3), 3030, 1500, 1600 (Aromatic -C-H str.), 1640 (-CH=N), 1095 (-C-N). ^{1}H NMR δHppm 6.2-8.1 (multipletAr + CH of CH=N protons + H of pyrazole), 3.36 (3H, singlet, -OCH_3), 3.85 (1H, singlet, -OCH_3).^{13}CMRδHppm56.3 OCH_3, 113 -C-O, 136-150 pyrazole, 114-129 Benzene, 153 CH=N. Mol. For. $C_{23}H_{17}N_3O_2$, Mol.Wt. 367 gm/mole, Anal. data. (Cal/Found) C% 74.7/74.5, H% 5.1/4.9, N% 11.3/11.2.

Compound 3h 3, 4-Diethoxy benzylidine- [1-N-phenyl-3-phenyl-pyrazole]: M.P.239-41^{0}C, Yield 90%, IRcm^{-1}2950, 2820, 1450 (-CH_2), 1040 (-N-N), 3030, 1500, 1600 (Aromatic C-H str.), 1640 (-CH=N), 1095 (-C-N). ^{1}H NMR δHppm 6.1-8.1 (multipletAr + CH of CH=N protons + H of pyrazole),4.0(4H,quartet, 2CH_2), 1.33 (6H, triplet 2CH_2).^{13}CMRδHppm65.4 CH_2, 14.3 CH_3, 113 C-O, 136-150 pyrazole, 114-129 Benzene, 153 CH=N. Mol. For. $C_{26}H_{25}N_3O_2$, Mol.Wt. 411 gm/mole, Anal. data. (Cal/Found) C% 75.2/74.9, H% 4.7/4.6, N% 11.4/11.3.

Synthesis of 3 - chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-aryl-azetidin-2-ones.: A mixture of Schiff base (3 a-h) (0.002 mole) and triethyl amine (TEA) (0.004 mole) was dissolved in 1,4 dioxane (50 ml), cooled, and stirred. To this well-stirred cooled solution chloroacetyl chloride (0.004 mole) was added drop wise within a period of 30 minutes. The reaction mixture was then stirred for an additional 3 hrs, and left at room temperature for 48 hrs. the resultant mixture was concentrated, cooled, poured into ice-cold water, and then air dried. The product thus obtained was purified by column chromatography over silica gel using 30% ethyl acetate: 70% benzene as eluent. Recrystallization from ether/n-hexane gave 2-azetidinone, which were obtained 55-70% yield.

4a Synthesis of 3 - chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-phenyl-azetidin-2-one.: M.P.180-82^{0}C, Yield 90%, IRcm^{-1}2950, 2820, 1450 (-CH_2), 1040 (-N-N), 3030, 1500, 1600

(Aromatic C-H str.), 1697 (-C=O), 1095 (-C-N). ^{1}H NMR δHppm 6.14-7.88(multipletAr + C_4H of + H of pyrazole),10.8 (1H, C_3H). ^{13}CMRδHppm136-145 pyrazole, 169 C=O, 114-130 Benzene, 143,148,156 β-lactum. Mol. For. $C_{24}H_{18}N_3OCl$, Mol.Wt. 399.5 gm/mole, Anal. data. (Cal/Found) C% 72.0/71.8, H% 4.5/4.4, N% 10.5/10.4.

4b Synthesis of 3 - chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-(4-methoxy phenyl-azetidin-2-one.: M.P.192-93^{0}C, Yield 64%, IRcm^{-1}3030, 1500, 1600 (Aromatic C-H stretching), 1040 (-N-N), 3400, 3030, 1500, 1600 (Aromatic C-H str.), 1697 (-C=O), 1095 (-C-N), 1200 Aryl-alkyl ether.^{1}H NMR δHppm 6.12-7.85(multipletAr + C_4H of + H of pyrazole), 10.4 (1H, C_3H), 4.3 (3H $CH_3$of OCH_3).^{13}CMRδHppm136-145 pyrazole, 169 C=O, 114-130 Benzene, 144,148,156 β-lactum, 46 OCH_3.Mol. For. $C_{25}H_{20}N_3O_2Cl$, Mol.Wt. 429.5 gm/mole, Anal. data. (Cal/Found) C% 69.8/69.8, H% 4.6/4.4, N% 9.7/9.4, Cl 8.2/8.5.

4c Synthesis of 3 - chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-(4-hydroxy phenyl-azetidin-2-one.: M.P.187-88^{0}C, Yield 55%, IRcm^{-1}3370, 3030, 1500, 1600 (Aromatic C-H str.),3030, 1500, 1600 (Aromatic C-H stretching),1697 (-C=O), 3200-2600 -OH phenolic, 1095 (-C-N). ^{1}H NMR δHppm 6.2-7.9(multipletAr + C_4H of + H of pyrazole), 10.8 (1H, C_3H), 3.6 (H of OH). ^{13}CMRδHppm136-145 pyrazole, 166 C of CO, 119-130 Benzene, 144,148,156 β-lactum, 119-C-O-H.Mol. For. $C_{24}H_{18}N_3O_2Cl$, Mol.Wt. 415.5 gm/mole, Anal. data. (Cal/Found) C% 69.3/69.1, H% 4.3/4.2, N% 10.1/10.0, Cl 8.5/8.4.

4d Synthesis of 3 - chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-(2-hydroxy phenyl-azetidin-2-one.: M.P.189-90^{0}C, Yield 57%, IRcm^{-1}2950, 2820, 1450 (-CH_2), 1040 (-N-N), 3030, 1500, 1600 (Aromatic C-H str.), 1690 (-C=O of β-lactum), 3200-2600 -OH phenolic, 1095 (-C-N).^{1}H NMR δHppm 6.2-7.9 (multipletAr + C_4H of + H of pyrazole), 10.4 (1H, C_3H of β-lactum), 3.9 (H of OH). ^{13}CMRδHppm136-145 pyrazole, 165 C of CO, 114-130 Benzene, 144,148,156 β-lactum, 135 C-OH.Mol. For. $C_{24}H_{18}N_3O_2Cl$, Mol.Wt. 415.5 gm/mole, Anal. data. (Cal/Found) C% 69.3/69.2, H% 4.3/4.2, N% 10.1/10.0, Cl 8.5/8.4.

4e Synthesis of 3 - chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-(4-methyl phenyl-azetidin-2-one.: M.P.174-75^{0}C, Yield 64%, IRcm^{-1}2950, 2820, 1370 (-CH_3), 1040 (-N-N), 3030, 1500, 1600 (Aromatic C-H str.), 1690 (-C=O of β-lactum), 3200-2600 -OH phenolic,

1095 (-C-N), ^{1}H NMR δHppm 6.2-7.9 (multipletAr + C_4H of + H of pyrazole),2.1 (3H of CH_3). ^{13}CMRδHppm136-148pyrazole, 114-130 Benzene, 143,148,156 β-lactum, 24.65 CH_3.Mol. For. $C_{25}H_{20}N_3OCl$, Mol.Wt. 413.5 gm/mole, Anal. data. (Cal/Found) C% 72.5/72.3, H% 4.8/4.7, N% 10.1/10.0, Cl 8.4/8.3.

4f Synthesis of 3 - chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-(3,4-methylenedioxy phenyl)-azetidin-2-one.: M.P.172-73^{0}C, Yield 64%, IRcm^{-1}2920, 2850, 1450 (-CH_2), 1040 (-N-N), 3030, 1500, 1600 (Aromatic C-H str.), 1690 (-C=O of β-lactum), 3200-2600 -OH phenolic, 1095 (-C-N), 1200 Aryl-alkyl ether.^{1}H NMR δHppm 6.2-7.9 (multipletAr + C_4H of + H of pyrazole),10.4 (1H, C_3H of β-lactum),5.8 (2H of O-CH_2-O). ^{13}CMRδHppm136-148pyrazole, 114-130 Benzene, 143,148,156 β-lactum, 135 C-OH, 165 C of CO, 91 O-CH_2-O.Mol. For. $C_{25}H_{18}N_3O_3Cl$, Mol.Wt. 443.5 gm/mole, Anal. data. (Cal/Found) C% 67.6/67.4, H% 4.0/4.0, N% 9.4/9.4, Cl 8.0/8.0.

4g Synthesis of 3 - chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-(4-hydroxy-3-methoxy phenyl)-azetidin-2-one.: M.P.178-79^{0}C, Yield55%, IRcm^{-1}2950, 2820, 1370 (-CH_3), 1040 (-N-N), 3030, 1500, 1600 (Aromatic C-H str.), 1690 (-C=O of β-lactum), 3200-2600 -OH phenolic, 1095 (-C-N), 1200 Aryl-alkyl ether.^{1}H NMR δHppm 6.1-7.9 (multipletAr + C_4H of + H of pyrazole), 10.4 (1H, C_3H of β-lactum), 3.36 (1H of OH), 4.3 (3H, s,OCH_3). ^{13}CMRδHppm136-148pyrazole, 114-130 Benzene, 143,148,156 β-lactum, 135 C-OH, 165 C of CO, 56O-CH_3, 135 C-OH.Mol. For. $C_{25}H_{20}N_3O_3Cl$, Mol.Wt. 445.5 gm/mole, Anal. data. (Cal/Found) C% 67.3/67.0, H% 4.4/4.4, N% 9.4/9.4, Cl 7.9/7.7.

4h Synthesis of 3 - chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-(3,4-diethoxyphenyl)-azetidin-2-one.: M.P.170-71^{0}C, Yield 58%, IRcm^{-1}2950, 2820, 1370 (-CH_3), 2920, 2850, 1450 (-CH_2), 1040 (-N-N), 3030, 1500, 1600 (Aromatic C-H str.), 1690 (-C=O of β-lactum), 1095 (-C-N).^{1}H NMR δHppm 6.1-7.9 (multipletAr + C_4H of + H of pyrazole), 10.4 (1H, C_3H of β-lactum), 3.36 (1H of OH), 4.3 (3H, s, OCH_3). ^{13}CMRδHppm136-148pyrazole, 114-130 Benzene, 143,148,156 β-lactum, 135 C-OH, 165 C of CO, 56 O-CH_3, 135 C-OH.Mol. For. $C_{28}H_{26}N_3O_3Cl$, Mol.Wt. 487.5 gm/mole, Anal. data. (Cal/Found) C% 68.9/68.8, H% 5.3/5.2, N% 8.6/8.4, Cl 7.2/7.0.

RESULT AND DISCUSSION

All the synthesized compounds **4a** to **4h** were tested against microorganism species at 1000 ppm concentration. The observed results of antibacterial screening reported in above table indicate that derivatives of 3 - chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-aryl-azetidin-2-ones **4c, 4f, 4g** and **4h** are shows good activity against bacterial spices *B.substilis*, *S.aureus*, *E.coil* and *Ps. Aeruginosa*. Compounds show significant efficacy against the conventional antibiotics Ampicillin, Tetracyclin, Gentamycin, Chloremphenicol.

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Table 1: Antimicrobial activity of 3 - chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-aryl-azetidin-2-ones (4a-h).

Compound Name	Inhibition Zone (in mm)			
	B. Substilis	***S. Aureus***	***E. Coli***	***Ps. Aeruginosa***
4a	08	13	10	10
4b	15	11	11	08
4c	19	19	17	18
4d	13	11	19	15
4e	18	13	14	09
4f	19	18	16	21
4g	15	15	15	13
4h	14	16	17	21
DMF	5	5	5	5
Ampicillin	18	15	20	20
Tetracyclin	30	25	30	19
Gentamycin	21	22	15	22
Chloremphenicol	20	23	18	23

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