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Synthesis of substituted 2-Azetidinones based on 1-N-phenyl-3-phenyl-4-formyl pyrazole (PFP)

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ABSTRACT

Tri ethyl amine (TEA) and chloroacetyl chloride with Schiff base (amino-sulfonamide derivatives) constitute an interesting class of organic compounds with diverse pharmacological applications including antimicrobial activity. (1E)-1-(phenyl)-ethanone-(phenyl)-hydrazone with mixture of Vilsmeir-Haack reagent affords the corresponding 1-N-phenyl-3-phenyl-4-formyl pyrazole (PFP) and further reaction with different amino-sulfonamide derivatives so make a Schiff base and finally new potentially active compound are prepared by condensing these 3-chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-substituted-phenyl benzene sulfonamide-azetidin-2-ones with tri ethyl amine (TEA) and chloro acetyl chloride. 1 H NMR, IR, Mass spectra and elemental analysis, has established the structures of all the newly synthesized compounds.

Key words: Synthesis, 2-Azetidinones, PFP, Chloro acetyl chloride, Schiff base

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INTRODUCTION

2-Azetidinone is a ß-lactam cyclic amide with four atoms in a ring. Traditionally ß-lactam is a part of structure of broad spectrum antibiotic class of drugs – penicillins and ephalosporins.

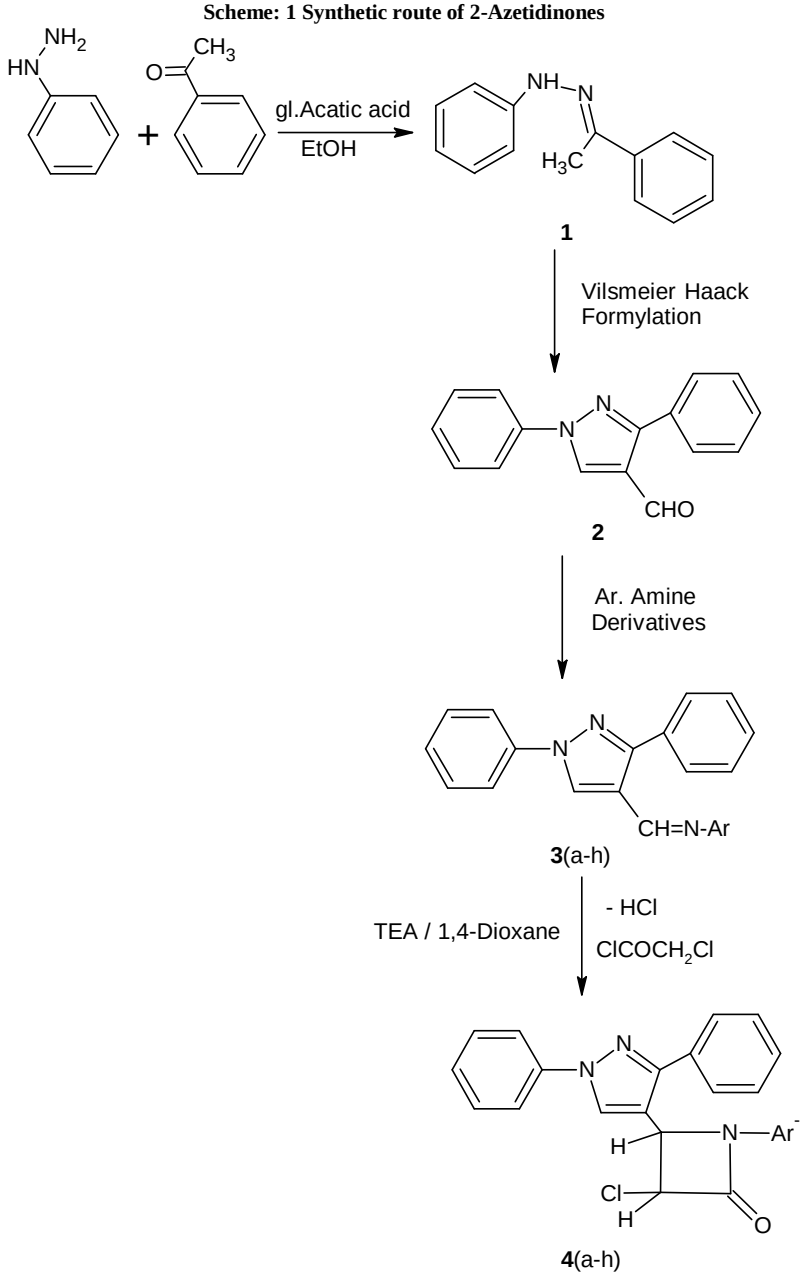
The β-Lactam nucleus is the key to the biological activity of a large class of compounds characterized by the presence of this four-membered ring and differentiated by side chains, unsaturations, hetero atoms, and, in many cases, by the presence of five- or six-membered rings.

The successful application of β-lactam antibiotics in the treatment of infectious diseases has been well documented for many years [1]. Azetidinones are of great biological interest, especially as anti-tubercular [2], antibacterial [3],[4],[5],[6] The important and structural diversity of biologically active β -lactam antibiotics led to the development of many novel methods for the construction of appropriately substituted azetidine with attendant control of functional group and stereochemistry. Azetidinone derivatives are reported to show a variety of antimicrobial [7],[8], anticonvulsant [9], anti-inflammatory [10] and cardiovascular activities [11], antimycobacterial activity[12], antibacterial activity [13], antihypertensive activity [14].

MATERIALS AND METHODS

These β -lactam derivatives were characterized by elemental analysis, infrared spectral data and ^{1}H and ^{13}C magnetic resonance spectral data.

Scheme: 1 Synthetic route of 2-Azetidinones



Preparation of (1E)-1-(phenyl)-ethanone-(phenyl)-hydrazone (1)

A mixture of phenyl hydrazine (I) (0.01 mol) and acetophenone (II) (0.01 mol) 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%.

Preparation of 1-N-phenyl-3-phenyl-4-formyl pyrazole (PFP) (2)

(1E)-1-(phenyl)-ethanone-(phenyl)-hydrazone (III) (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 crystallized from ethanol. Yield was about 82%.

Preparation 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 mol) (1) and various aromatic amino sulfonamides (0.01 mol) in 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-hexane using decolorizing charcoal to give various anils.

Preparation of 3-chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-substituted phenyl- benzene sulfonamide-azetidin-2-ones (4a-h)

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 mol) was added drop wise within a period of 30 minutes. The reaction mixture was then stirred for an additional 3 hours and left at room temperature for 48 hours. 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 (4a-h), which were obtained in 55-70% yield.

Table: 1 Physical constant of 3-chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-substituted phenyl- benzene sulfonamide-azetidin-2-ones (4a-h)

Compd	R	Mol. Formula (Mol. Wt)	m.p. (°C)	Yield %	% of C,H,N Calcd./Found				
					C	H	N	S	Cl
4a	$C_{12}H_{12}N_2O_2S$-	$C_{30}H_{23}N_4O_3SCl$ 554.5	180°C	64%	64.9	4.1	10.0	5.7	6.4
					64.8	4.0	10.0	5.6	6.4
4b	$C_{12}H_{11}N_2O_2SCl$-	$C_{30}H_{22}N_4O_3SCl_2$ 589	183°C	61%	61.1	3.7	9.5	5.4	12.1
					61.0	3.6	9.3	5.3	12.0
4c	$C_{12}H_{11}N_2O_2SBr$-	$C_{30}H_{22}N_4O_3SClBr$ 633.5	178°C	57%	56.8	3.5	8.8	5.1	5.6
					56.7	3.4	8.7	5.0	5.5
4d	$C_{12}H_{11}N_3O_4S$-	$C_{30}H_{22}N_5O_5SCl$ 599.5	180°C	54%	60.0	3.6	11.6	5.3	5.9
					60.0	3.5	11.5	5.2	5.8
4e	$C_{13}H_{14}N_2O_2S$-	$C_{31}H_{25}N_4O_3SCl$ 568.5	172°C	62%	65.4	4.4	9.8	5.6	6.2
					65.4	4.2	9.8	5.5	6.1
4f	$C_{12}H_9N_3O_4SCl_2$-	$C_{30}H_{20}N_5O_5SCl_3$ 668.5	181°C	58%	53.8	3.0	10.4	4.8	15.9
					53.6	2.8	10.2	4.7	15.8
4g	$C_8H_{10}N_2O_3S$-	$C_{26}H_{21}N_4O_4SCl$ 520.5	186°C	55%	59.9	4.0	10.7	6.1	6.8
					59.8	3.7	10.6	6.0	6.8
4h	$C_{10}H_{10}N_4O_2S$-	$C_{28}H_{21}N_6O_3SCl$ 556.5	176°C	63%	604	3.7	15.0	5.7	6.4
					60.2	3.5	15.0	5.6	6.4

RESULTS AND DISCUSSION

1-N-phenyl-3-phenyl-4-formyl pyrazole (PFP), IR (cm^{-1}): 3030(Ar-C-H str.), 2855 (C-H str.), 1630 (C=O str.), 1250 (-CHO), 1600-1500 (C=C Ar-C-H str.), 1590 (C-N); **NMR** (δ,ppm): 9.62 (1H singlet -CHO); **CMR** (δ,ppm)**:** 120-129 (Benzene), 162, 150, 113 (pyrazole), 162 (- CHO).

Arylidine-[1-N-phenyl-3-phenyl-pyrazole] (3a-h): IR (cm^{-1}): 3250-3330 (-NH of -SO_2NH), 3030-3080(Ar-C-H str.), 1600-1500 (C=C Ar-C-H str), 1630(-C=N), 1315-1365 (-SO_2), 1095 (C-N); **NMR** (δ,ppm): 6.14-7.88 (H of SO_2NH and Pyrazole); **CMR** (δ,ppm)**:** 130-150 (pyrazole), 115-129 (Benzene), 153(CH=N).

3-chloro-4-[1-N-phenyl-3-phenyl-pyrazole]-1-N-substituted phenyl- benzene sulfonamide-azetidin-2-ones (4a-h): IR (cm^{-1}): 3030(Ar-C-H str.), 2855 (C-H str.), 1697 (C=O str. β-lactam), 1500 (C=C Ar-C-H str), 1590 (C-N); **NMR** (δ,ppm): 6.14-7.88 (H of SO_2NH and Pyrazole); **CMR** (δ,ppm)**:** 136-145 (pyrazole), 114-130 (Benzene), 143,148,156 (β-lactam), 169 (-C=O), 136,145 (C_3).

Their structures were confirmed by analytical and spectral data. The infrared spectra show the band in the region 1680-1710cm^{-1} for carbonyl (>C=O) group, which is the characteristic band for the cyclic β-lactam ring.

The proton magnetic resonance spectra of the prepared compounds (4a-h) shows two doublets, one around 10.4 δ for CH proton at position-3 in the 2-azetidinone ring and other at 7.9 δ for CH proton at position-4 in the ring. All other signals are at their respective positions in the PMR spectrum.

The ^{13}C NMR spectra of all the compounds 4a-h show the signal for unsubstituted carbons of pyridine and phenyl rings. The β-lactam carbons are appeared at 156, 135 and 48 ppm.

Antibacterial susceptibility testing

The study has been conducted according to the method adopted by Cruickshank et al [12]. Nutrient agar broth was melted in a water bath and cooked to 45^{O}C with gentle shaking to bring about uniform cooling. It was inoculated with 0.5-0.6 ml of 24 hour old culture especially and mixed well by gentle shaking before pouring on the sterilized Petri dish (25 ml each). The poured material was allowed to set (1.5 hour) and there after the “cups” were made by punching into the agar surface with a sterile cork borer and sooping out the punched part of agar. Into this “cups” 0.1

ml of test solution (prepared by dissolving 10gm of sample in 10ml DMF) was added by sterile micropipette. The plates were noted. Ampicillin, Tetracycline, Gentamycin, and Chloramphenicol were used as standard drugs and a solvent control was also run to know the activity of solvent.

Activity of standards and inhibition due to DMF (solvent) are given in Table-2. The results shown by compounds and standards are corrected for DMF. Typical specimens are shown in figures.

Table-2 Antimicrobial activity of Standards and Solvent (DMF)

No.	Name of compound	*Zone of inhibition (in mm)*			
		Gram positive		*Gram negative*	
		B.Subtillis	*S.Aureus*	*E.Coli*	*Ps.Aeruginosa*
1	DMF	7	5	5	5
2	Ampicillin	14	12	21	19
3	Tetracyclin	21	22	15	18
4	Gentamycin	20	19	18	22
5	Chloramphenicol	21	23	17	24

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

Compound (designation)	*Zone of Inhibition (in mm)*			
	Gram positive		*Gram negative*	
	B. Subtillis	*S. Aureus*	*E. Coli*	*Ps. Aeruginosa*
4a	07	12	11	17
4b	14	08	12	08
4c	12	12	08	08
4d	14	10	20	14
4e	19	14	14	09
4f	22	19	17	20
4g	14	16	15	13
4h	15	17	18	20

CONCLUSION

The compounds tested for antimicrobial activity are listed in Table-3.Zone of inhibition of bacterial growth procedure by test compounds for broad range of antimicrobial activity inhibiting growth of Gram-positive bacterial strains *B. Subtillis* and *S. Aureus*, and Gram-negative bacterial strains *E. Coli* and *Ps. Aeruginosa*.

Comparison of antimicrobial activity of produced compounds with that of standard antimicrobial drugs reveals that the produce compounds shows moderate to good activity against all four bacterial strains.

Among all synthesized compounds, compound 4e, 4d and 4f show good antimicrobial activity.

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