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DESIGN, SYNTHESIS, AND PHARMACOLOGICAL EVALUATION OF NEW AZITIDIN 2-ONE DERIVATIVES.

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ABSTRACT

A new series of 3-chloro-4-{4-[2-{5-(4-chlorophenyl)-3-(4-methoxy phenyl)-4,5-dihydro-pyrazol-1-yl}-2-oxoethoxy]phenyl}-1-(substitutedphenyl)azetidin-2-one derivatives has been synthesized and subjected to evaluate their antimicrobial activity. All the synthesized compounds of the series elicit remarkable activity in comparison to standard drug. Structures of the synthesized compounds have been elucidated on the basis of their elemental analyses and spectral data.

KEYWORDS: azetidinones, β-lactams, antimicrobial, DMSO.

1. INTRODUCTION

A large number of azetidinones containing β-lactam rings[1-5] are known to exhibit various biological activities like antibacterial, antifungal[6] and antibiotic[7] activities. More particularly and recently these types of compounds have been found in the treatment of T.B. and other chemotherapeutic diseases. Some azetidinons can also be prepared from hydazide derivaties, play medicinal activity like antibacterial, antifungicidal, analgesic, anti-inflammatory activity.[8-22] More particularly and recently these types of compounds have been found in the treatment of T.B. and other chemotherapeutic diseases. Hence, it was thought of interest in merging of both azetidinone and phthalimide moieties may enhance the drug activity of compounds up to some extent or might posses some of the above mentioned biological activities. The β-lactams also serve as synthons for many biologically important classes of organic compounds. Due to this, the investigation of chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic chemists.[23-25] The present work is undertaken to explore more possibilities of

finding a suitable derivatives, which would exceed its activity more than the already known drugs containing β-lactam.

2. EXPERIMENTAL

Melting points were taken in open capillary tube and were uncorrected. IR spectra were recorded on I.R. Spectrophotometer of Buck scientific Model No. 500 and instrument used for NMR Spectroscopy was Bruker Advance II 400 and DMSO used as internal standard. Solvent used were $CDCl_3$ and DMSO. Purity of the compounds was checked by TLC on silica- G plates. All the compounds were tested for their antibacterial and antifungal activities by broth dilution method.

3. MATERIALS AND METHODS

3.1 Preparation of *N*-[{4-[2-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-pyrazol -1-yl)-2-oxoethoxy]phenyl}methylene]substitutedaniline (1a-j)

A mixture of 2-(4-{[(substitutedphenyl)imino]methyl}phenoxy)acetohydrazide (0.1M), ethanol (25ml) and 3-(4-chlorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (0.1M) with piperidine (1ml) was refluxed for 16 hours. The resulting mixture was concentrated, cooled and poured into cold water containing 6 to 8 drops of HCl, when orange coloured product separated. It was filtered, washed with water and crystallized from methanol-petroleum ether mixture.

IR ; 1-d (cm^{-1})**:** 3011(=CH-), 2933 (-CH-), 1710 (>C=O) ,1665 (C=N-), 1606(>C=C<), 1449 ($-CH_2-$), 1392($-CH_3-$), 1258 (C-N) 1223 (-N-N-), 1167(-C-O-), 1107(-C-O-C), 624(-C-Cl).

^{1}H NMR (DMSO);1-e: 2.5675, doudlet (2H) (CH_2 -cyclic), 3.8489, singlet (3H) ($-OCH_3-$), 4.5719, singlate (2H) ($-CH_2-$),5.0906 triplet (1H) (-CH<) 8.5267, singlet (1H) (Ar-CH=N-), 6.6093-8.0824 multiplate (16H) (Ar-H)

3.2 Prepration 3-chloro-4-{4-[2-{5-(4-chlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-pyrazol-1-yl}-2-oxoethoxy]phenyl}-1-(substitutedphenyl)azetidin-2-one (2a-2j)

In a 100 ml Round bottom flask N-[{4-[2-{5-(4-chlorophenyl)-3-(4-methoxy phenyl)-4,5-dihydro-pyrazol-1-yl}-2-oxoethoxy]phenyl}methylene]substitutedaniline (0.01M) in 70 ml benzene was taken Chlororo acetry chlororide (0.01M) was added at room temperature with constant stirring and triethyle amine 1ml was added and the reaction mixture was refluxed

for 7 hours. After the completion of reaction, solvent was removed by vacuum distillation. The soild was filtered, dried and recrystallized from toluene.

IR ; 2-e (cm^{-1})**:** 3010(=CH-), 2692 (-CH-stretch), 1720 (>C=O) ,1655 (C=N-str), 1603(>C=C<) aromatic, 1512 (N=O),1439 ($-CH_2$-bend), 1339($-CH_3$-bend), 1255 (C-N) 1223 (-N-N-), 1169(-C-O), 1110(-C-O-C), 605(-C-Cl).

^{1}H NMR (DMSO); 2-i: 2.5828, doudlet (2H) (CH_2 -cyclic), 3.1236, doublet (1H) (-CH-C), 3.8512(3H)singlet (OCH_3-), 4.7946, singlate (2H) ($-CH_2$-), 4.9112 triplet (1H) (-CH<), 5.1034, doublet (1H) (-CH<), 6.7284-8.0801 multiplate (16H) (Ar-H).

Reaction Scheme

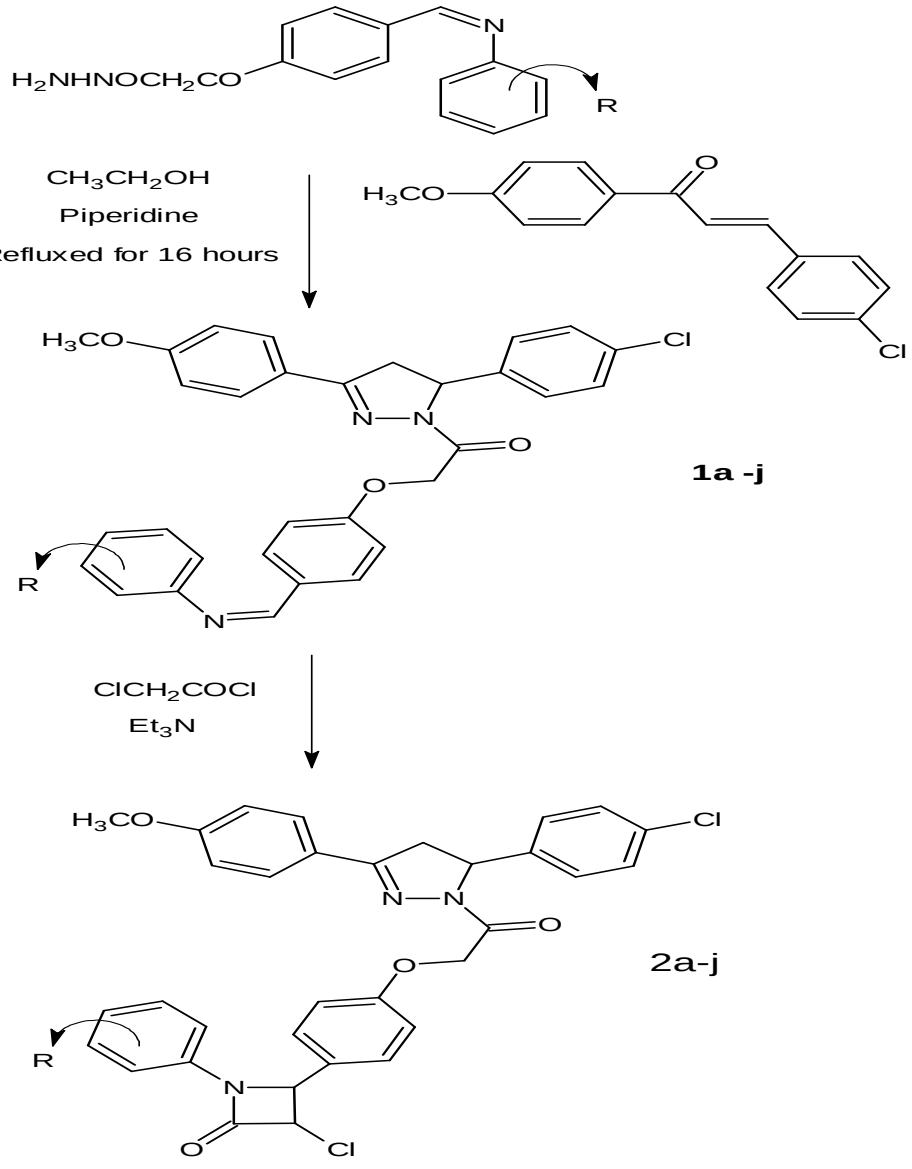

Table-1: Physical constant of 3-chloro-4-{4-[2-{5-(4-chlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-pyrazol-1-yl}-2-oxoethoxy]phenyl}-1-(substitutedphenyl) azetidin-2-one

Sr. No.	Sample No.	R	Molecular Formula	Molecular Weight	Melting Point C	Yield	%C		%H	
							Found	Required	Found	Required
1	2a	1-PHENYL	$C_{33}H_{27}Cl_2N_3O_4$	600.49	93	81	65.97	66	4.51	4.53
2	2b	1-AMINO	$C_{37}H_{29}Cl_2N_3O_5$	650.55	98	77	68.29	68.31	4.45	4.49
3	2c	4-CH_3	$C_{34}H_{29}Cl_2N_3O_6$	614.52	110	72	66.41	66.45	4.72	4.76
4	2d	3-CH_3	$C_{34}H_{29}Cl_2N_3O_7$	614.52	90	85	66.42	66.45	4.73	4.76
5	2e	2-NO_2	$C_{33}H_{26}Cl_2N_4O_6$	645.49	105	70	61.36	61.4	4.01	4.06
6	2f	3-NO_2	$C_{33}H_{26}Cl_2N_4O_6$	645.49	113	79	61.37	61.4	4.02	4.06
7	2g	4-NO_2	$C_{33}H_{26}Cl_2N_4O_6$	645.49	101	82	61.35	61.4	4.03	4.06
8	2h	2-Cl	$C_{33}H_{26}Cl_3N_3O_4$	634.94	120	75	62.39	62.42	4.1	4.13
9	2i	3-Cl	$C_{33}H_{26}Cl_3N_3O_4$	634.94	107	69	62.4	62.42	4.09	4.13
10	2j	4-Cl	$C_{33}H_{26}Cl_3N_3O_4$	634.94	115	80	62.38	62.42	4.11	4.13

4. RESULTS AND DISCUSSION

Antimicrobial activity

The MICs of synthesized compounds were carried out by broth micro dilution method as described by Ratan (2000). The invitro antimicrobial activity of test compounds were assessed against 24 hr cultures of several selected bacteria and fungi. The bacteria used were *E. coli*, *S.aureus*,*P. aeruginosa*, and *S. pyogenus*; the fungi used were *C. albicans*, *A. niger*, *and A.clavatus.* The antimicrobial activity was performed by broth dilution method in DMSO. Gentamycin, Ampicilin, Chloramphenicol, Ciprofloxacin, Norfloxacin, Nystatin and Greseofulvin were used as standard for the evaluation of antibacterial and antifungal activities respectively. The activity was reported by Minimal Inhibition Concentration. The results are summarized in Table-2.

Table -2: Antimicrobial activity of 3-chloro-4-{4-[2-{5-(4-chlorophenyl)-3-(4-methoxy phenyl)-4,5-dihydro-pyrazol-1-yl}-2-oxoethoxy]phenyl}-1-substitutedpheny l) azetidin-2-one

SR. NO.	COMP. NO.	R	ANTIBACTERIAL ACTIVITY Minimal Inhibition Concentration(µg/ml)				ANTIFUNGAL ACTIVITY Minimal Inhibition Concentration (µg/ml)		
			Gram negative bacteria		Gram positive bacteria		Fungus		
			E.COLI	P.AERUGINOSA	S.AUREUS	S.PYOGENUS	C.ALBICANS	A.NIGER	A.CLAVATUS
			MTCC 443	MTCC 1688	MTCC 96	MTCC 442	MTCC 227	MTCC 282	MTCC 1323
1	2a	1-Phenyl	175	100	125	100	700	500	800
2	2b	1- Napthyl	150	150	200	150	600	>1000	500
3	2c	-4-CH_3	200	250	150	125	500	600	700
4	2d	-3-CH_3	200	175	125	200	800	700	600
5	2e	-2-NO_2	125	150	200	225	900	700	>1000
6	2f	-3-NO_2	175	200	275	150	>1000	800	700
7	2g	-4-NO_2	100	100	200	200	500	1000	>1000
8	2h	-2-Cl	200	250	125	150	600	600	500
9	2i	-3-Cl	150	200	175	175	700	500	700
10	2j	-4-Cl	125	150	150	200	500	1000	>1000

Biological screening result of 2-{4-[2-{5-(4-chlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-pyrazol-1-yl}-2-oxoethoxy]phenyl}-3-(substitutedphenyl)-1,3-thiazolidin-4-one based derivatives shows that compound (**2e,2j**) have shown better activity against E. coli, S. aureus, while rest of all compound possessed good activity against S.aureus in the range of 125-250 μg/ml.. Compounds with substitution 4-hydroxy (**2a** and **2c**), shown good antibacterial activity against S. pyogenus , while rest of all derivatives possessed good activity against S. pyogenus in the range of 100-250 μg/ml. Compound **(2c)** and **(2g)** is found to be significant antifungal activity against C. albicans, while rest of all derivatives are poor against A. niger, and A. clavatus.

5. CONCLUSION

The Main focus of this research work was to synthesize, characterize and evaluate antimicrobial activities of the newly synthesized Chalcone derivatives, structures of synthesized compounds were confirmed and characterized with the help of analytical data's such as IR and 1H-NMR. In summary, we have described the synthesis and antimicrobial activity of novel3-chloro-4-{4-[2-{5-(4-chlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-pyrazol-1-yl}-2-oxoethoxy]phenyl}-1-substitutedpheny l) azetidin-2-one Substitutedaniline MIC values revealed that amongst newly synthesized compound having 4-chlorophenyl type linkage has shown good activity against the bacterial strains. Rest of all compounds exhibit moderate improvement in activity against some of the pathogenic strains.

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