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Synthesis, Characterization and Antimicrobial Activity of Azetidin-2-One based Phenyl Sulfonyl Pyrazoline Derivatives

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Synthesis, Characterization and Antimicrobial Activity of Azetidin-2-One based Phenyl Sulfonyl Pyrazoline Derivatives

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Abstract- **A new series of 4-(4-Chlorophenyl)-3-chloro-1-{4-[5-(Substituted phenyl)-1-(phenylsulfonyl) -4,5-dihydro-pyrazol-3-yl]phenyl}azetidin-2-one are synthesized by reacting 3-chloro-1-{4-[5-(Substituted phenyl)-4,5-dihydro-pyrazol-3-yl]phenyl}-4-(4-Chlorophenyl)azetidin-2-one with Benzene sulfonyl chloride in presence of pyridine. All these compounds were characterized by means of their IR, 1H NMR, Spectroscopic data and were tested for their antibacterial and antifungal activities by broth dilution method.**

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I. Introduction

Heterocyclic compounds are the well-known class of compounds for its Biological applications. Keeping in view the importance of these Biological activities, it was considered of interest to synthesize some new phenyl sulfonyl derivatives of pyrazoles.

Pyrazolines are heterocyclic compounds which posses wide range of interesting biological activities such as anti-inflammatory [1], insecticidal [2], anti-tubercular [3], antitumor [4], tranquilizing [5], immunosuppressive [6], diuretic [7], anticonvulsant [8], antifungal [9], antidepressant activities [10-11], antibacterial activities [12], molluscidal [13]. In the present communication, we report the reaction of 3-chloro-1-{4-[5-(Substituted phenyl)-4, 5-dihydro-pyrazol-3-yl] phenyl}-4-(4-Chlorophenyl) azetidin-2-one with Benzene sulfonyl chloride in presence of pyridine to form phenyl sulfonyl Pyrazoline (5a-j). The structures of the various synthesized compounds were assigned on the basis of IR, 1H-NMR spectral data and elemental analysis. These compounds were also screened for their antimicrobial activity.

II. Experimental

The IR spectra were recorded on IR affinity-1, DRS-8000A, Shimadzu, Ptc. Ltd., Japan spectrophotometer. The 1H-NMR was recorded in DMSO on Bruker Advance II 400 MHz spectrometer using TMS as an internal standard. Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by TLC-using Silica gel-G (Merck). Column chromatography was performed on silica gel. All the compounds were tested for their antibacterial and antifungal activities by broth dilution method

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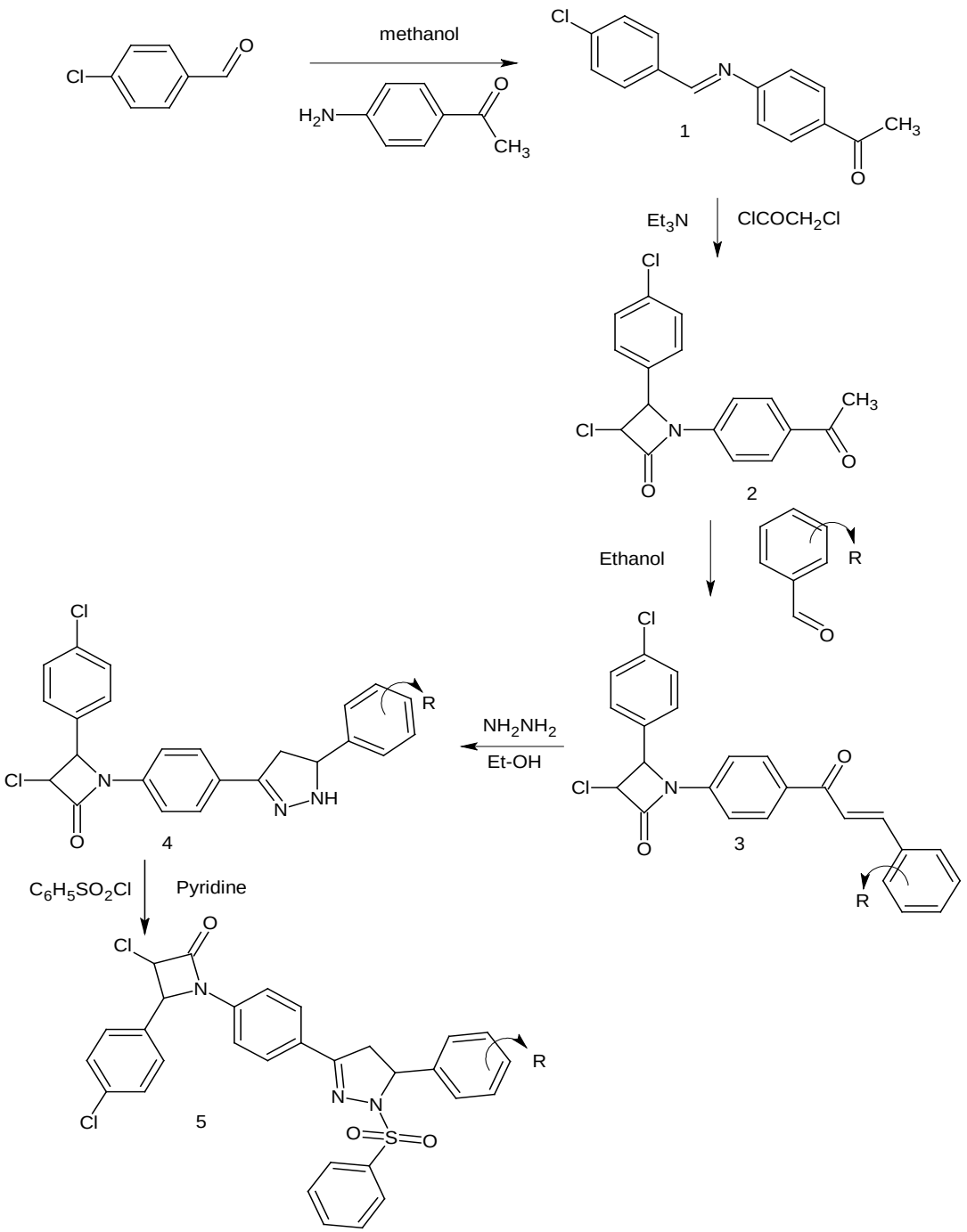
Reaction Scheme



a) Preparation of 1-(4-{[(4-Chlorophenyl) methylene] amino} phenyl) ethanone (1)

A mixture of 4-Chloro Benzaldehyde (0.01M), 1-(4-aminophenyl) ethanone (0.01M) and methanol (30ml) was heated for about 5 min. in a beaker (250 ml) to get a clear solution. The solution was kept overnight at room temperature to get the respective crude solid which was recrystallized from ethanol to obtain the pure crystals of 1-(4-{[(4-chlorophenyl) methylene] amino} phenyl) ethanone respectively. The yield of the product was 75% and the product melts at 1200C. Found: C(69.88%) H(4.65%) N(5.41%) , Calcd. for C15H12ClNO: C(69.91%) H(4.69%) N(5.43%). IR, cm-1: 3084(=C-H), 2922(-C-H), 1678(>C=O), 1628(>C=N-), 1595 (>C=C<), 1408(-CH3, bend), 1301(-C-N<), 1240(-C-CO-C-), 738(-C-Cl). 1H-NMR (DMSO, d, ppm): 2.5785 (3H, s, COCH3), 6.5144-7.7992 (8H, m, Ar-H), 8.803 (1H, s, -CH=N-).

b) Preparation of 1-(4-acetylphenyl)-3-chloro-4-(4-Chlorophenyl) azetidin-2-one (2)

In a 100ml Round bottom flask 1-(4-{[(4-Chloro phenyl) methylene] amino} phenyl) ethanone (0.01M) in

70ml benzene was taken. Chloro acetyl chloride (0.01M) was added at room temperature with constant stirring and triethylamine 1ml was added and the reaction mixture was refluxed for 7 hours. After the completion of reaction, solvent was removed by vacuum distillation. The solid was filtered, dried and recrystallized from toluene. The yield of the product was 60% and the product melts at 1080C. Found: C(61.07%) H(3.88%) N(4.17%), Calcd. for C17H13Cl2NO2: C(61.10%) H(3.92%) N(4.19%). IR, cm-1: 3041(=C-H), 2921(-C-H), 1712(>C=O), 1548(>C=C<), 1365(-CH3, bend), 1292(-C-N<), 1197(-C-CO-C-), 642(-C-Cl). 1H-NMR (DMSO, d, ppm): 2.5550 (3H, s, COCH3), 4.8102 (1H, d, >CH-Ar), 5.4594 (1H, d, >CH-Cl), 7.3170-8.0618 (8H, m, Ar-H).

c) *Preparation of 3-chloro-1-{4-[3-(Substituted phenyl) prop-2-enoyl] phenyl}-4-(4-Chlorophenyl) azetidin-2-one (3a-j)*

To the solution of 1-(4-acetylphenyl)-3-chloro-4-(4-Chloro phenyl) azetidin-2-one (0.01M) in absolute ethanol (50 ml), substituted Benzaldehyde (0.01M) and 2% NaOH were added and refluxed for 10 hours. After refluxing the reaction mixture was concentrated, cooled, filtered and neutralized with dil. HCl. The solid residue thus obtained was crystallized by absolute ethanol. IR(3d), cm-1: 3043(=C-H), 1722(>C=O), 1624 (>C=C<), 1451(-N=O), 1286(-C-N<), 1232 (-C-O-), 684(-C-Cl). 1H-NMR (3g-DMSO, d, ppm): 4.8757 (1H, d, >CH-Ar), 5.4224 (1H, d, >CH-Cl), 6.3621-8.5674 (12H, m, Ar-H), 7.9978 (2H, d, -CH=CH-), 9.9660 (1H, s, Ar-OH).

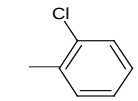
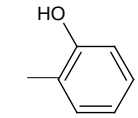
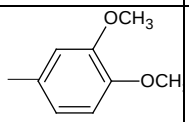
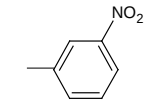
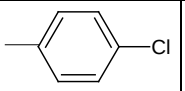
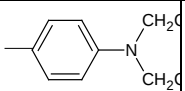
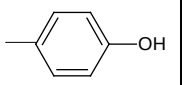
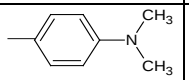
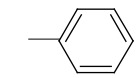
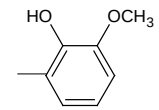
d) *Preparation3-chloro-1-{4-[5-(Substituted phenyl)-4,5-dihydro-pyrazol-3-yl]phenyl}-4-(4-Chlorophenyl)azetidin-2-one.(4a-j)*

A mixture of 3-chloro-1-{4-[3-(Substituted phenyl) prop-2-enoyl] phenyl}-4-(4-Chlorophenyl) azetidin-2-one (0.01M) and 99% hydrazine hydrate (0.015M) in ethanol (50ml) refluxed gently for 3 hours. Then the mixture was concentrated and allowed to cool. The resulting solid was filtered, washed with ethanol and recrystallized from ethanol to give a pale brown solid. IR(4e), cm-1: 3041 (=C-H), 2931(-C-H), 1728(>C=O), 1643(>C=N-), 1552 (>C=C<), 1452(-CH2, bend), 1313(-C-N<),1290 (-N-N), 663 (-C-Cl-),. 1H-NMR (4b-DMSO, δ, ppm): 3.61 (2H, d, CH2-of Pyrazol), 4.33 (1H, t, >CH-Ar of Pyrazol), 4.80 (1H, d, >CH-Ar of Azetidine), 5.32 (1H, d, >CH-Cl of Azetidine), 6.56-7.92 (13H, m, Ar-H), 9.65 (1H, s, Ar-OH).

e) *Preparation of 4-(4-Chlorophenyl)-3-chloro-1-{4-[5-(Substituted phenyl)-1-(phenyl sulfonyl)-4, 5 -dihydro-pyrazol-3-yl] phenyl} azetidin-2-one (5a-j)*

A solution of 3-chloro-1-{4-[5-(Substituted phenyl)-4, 5-dihydro-pyrazol-3-yl] phenyl}-4-(4-Chlorophenyl) azetidin-2-one (0.001M) in dry pyridine (25ml) cooled in an ice-bath and to it benzene sulfonyl chloride (0.0011M) was added. The mixture was stirred for 1 hour at room temperature and was then treated with cold dilute HCl (2N). The resulting solid was filtered, washed with water, and recrystallized from absolute ethanol IR(5f), cm-1: 3040(=C-H), 1730(>C=O), 1631(>C=N-), 1529 (>C=C<), 1452(-CH2,bend), 1375 (CH3,bend), 1313 (-C-N-), 1230(-N-N), 696 (-C-Cl-), 1133 (>S=O). 1H-NMR (5e-DMSO, δ, ppm): 3.9 (2H, d, CH2- of Pyrazol), 4.3 (1H, t, >CH-Ar of Pyrazol), 4.8 (1H, d, >CH-Ar of Azetidine), 5.6 (1H, d, >CH-Cl of Azetidine), 6.9-8.0 (17H, m, Ar-H).

Table 1 : Physical constant of 4-(4-Chlorophenyl)-3-chloro-1-{4-[5-(Substituted phenyl)-1-(phenyl sulfonyl)-4, 5 -dihydro-pyrazol-3-yl] phenyl} azetidin-2- one

Compd	R	M.F.	Yield %	M.P. °C	Elemental Analysis		
					% C Found (Calcd)	% N Found (Calcd)	% H Found (Calcd)
5a		$C_{30}H_{22}Cl_3N_3O_3S$	66	65	58.93 (58.98)	6.84 (6.88)	3.61 (3.63)
5b		$C_{30}H_{23}Cl_2N_3O_4S$	65	82	60.76 (60.81)	7.03 (7.09)	3.88 (3.91)
5c		$C_{32}H_{27}Cl_2N_3O_5S$	63	79	60.33 (60.38)	6.56 (6.60)	4.22 (4.28)
5d		$C_{30}H_{22}Cl_2N_4O_5S$	67	100	57.93 (57.98)	8.98 (9.01)	3.54 (3.57)
5e		$C_{30}H_{22}Cl_3N_3O_3S$	62	78	58.92 (58.98)	6.84 (6.88)	3.59 (3.63)
5f		$C_{34}H_{32}Cl_2N_4O_3S$	68	80	63.02 (63.06)	8.61 (8.65)	4.92 (4.98)
5g		$C_{30}H_{23}Cl_2N_3O_4S$	70	108	60.78 (60.81)	7.04 (7.09)	3.88 (3.91)
5h		$C_{32}H_{28}Cl_2N_4O_3S$	64	145	62.00 (62.03)	9.01 (9.04)	4.51 (4.56)
5i		$C_{30}H_{23}Cl_2N_3O_3S$	71	138	62.46 (62.50)	7.25 (7.29)	3.98 (4.02)
5j		$C_{31}H_{25}Cl_2N_3O_5S$	69	75	59.78 (59.81)	6.71 (6.75)	4.01 (4.05)

III. Results and Discussion

a) Antimicrobial activity

The MICs of synthesized compounds were carried out by broth micro dilution method as described by Rattan (2000). It is one of the non automated in vitro bacterial susceptibility tests. This classic method yields a quantitative result for the amount of antimicrobial agents that is needed to inhibit growth of specific microorganisms.

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 4-(4-Chlorophenyl)-3-chloro-1-{4-[5-(Substituted phenyl)-1-(phenyl sulfonyl)-4, 5 -dihydro-pyrazol-3-yl] phenyl} azetidin-2-one

SR. NO.	COMP. NO.	R	ANTIBACTERIAL ACTIVITY MINIMAL INHIBITION CONCENTRATION				ANTIFUNGAL ACTIVITY MINIMAL INHIBITION CONCENTRATION		
			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	5a	-2-Cl	200	250	200	62.5	1000	>1000	>1000
2	5b	-2-OH	200	250	125	250	1000	1000	1000
3	5c	-3-OCH_3, -4-OCH_3	175	225	200	125	800	800	800
4	5d	-3-NO_2	200	200	225	200	1000	1000	**>1000**
5	5e	-4-Cl	100	125	100	250	>1000	>1000	>1000
6	5f	-4-$N(C_2H_5)_2$	125	200	62.5	100	1000	1000	1000
7	5g	-4-OH	200	200	175	250	800	1000	800
8	5h	-4-$N(CH_3)_2$	225	225	150	200	>1000	800	700
9	5i	-H	175	225	200	150	1000	1000	1000
10	5j	-3-OCH_3, -4-OH	100	125	100	250	500	>1000	1000

Table 3 : Antibacterial Activity: Minimal Inhibition Concentration (The Standard Drugs)

DRUG	E.COLI	P.AERUGINOSA	S.AUREUS	S.PYOGENUS
-	MTCC 443	MTCC 1688	MTCC 96	MTCC 442
(MICROGRAMME/ML)				
GENTAMYCIN	0.05	1	0.25	0.5
AMPICILLIN	100	--	250	100
CHLORAMPHENICOL	50	50	50	50
CIPROFLOXACIN	25	25	50	50
NORFLOXACIN	10	10	10	10

Table 4 : Antifungal Activity: Minimal Inhibition Concentration (The Standard Drugs)

DRUG	C.ALBICANS	A.NIGER	A.CLAVATUS
-	MTCC 227	MTCC 282	MTCC 1323
(MICROGRAMME/ML)			
NYSTATIN	100	100	100
GRESEOFULVIN	500	100	100

Biological screening result of activities 4-(4-Chlorophenyl)-3-chloro-1-{4-[5-(Substituted phenyl)-1-(phenyl sulfonyl)-4, 5 -dihydro-pyrazol-3-yl] phenyl} azetidin-2-one based derivatives shows that compound 5e & 5j have shown better activity against E. coli. Compound 5f show good to very good activity against S. pyogenus, while rest of all compound possessed good activity against S.aureus in the range of 62.5-225 μg/ml. Compound 5j is found to be good antifungal activity against C. albicans, against standard drugs Greseofulvin. While rest of all derivatives are poor against A. Niger, and A.clavatus.

IV. Conclusion

The Main focus of this research work was to synthesize, characterize and evaluate antimicrobial activities of the newly synthesized phenyl sulfonyl Pyrazoline 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 some new 4-(4-Chlorophenyl)-3-chloro-1-{4-[5-(Substituted phenyl)-1-(phenyl sulfonyl) -4, 5 -dihydro-pyrazol-3-yl] phenyl} azetidin-2-one MIC values revealed that amongst newly synthesized

compound having Methoxy-Hydroxide type linkage has shown good activity against the bacterial strains.

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