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"Synthesis and Characterization of Some Novel Isoxazoles containing Azetidinone as Antibacterial agents"

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Abstract:

Isoxazole is an azole with an oxygen atom next to the nitrogen. Isoxazoles and their derivatives extracted from natural sources are limited in numbers. The isoxazole compounds and their derivatives have many importance in pharmaceutical industries like work as anti-tumor, anti-cancer, anti-bacterial, antifungal and antimicrobial agents. Therefore, this research work was focused to design the isoxazoles and their derivatives which have strong medicinal and pharmaceutical activities. The calculated result reveals that our designed molecules have better pharmaceutical activities and can be use as anti-bacterial, antifungal and antimicrobial agents. The title compounds were characterized by element analysis, IR and NMR spectral data. All the compounds were tested for their antibacterial and antifungal activities by broth dilution method.

Index Terms: Isoxazole, Azetidinone, MTCC, broth dilution method

1. Introduction:

Isoxazoles are an important class of heterocycles, which are largely employed in the area of pharmaceuticals and therapeutics such as insecticidal, antibacterial, antibiotic, antitumour, antifungal, antituberculosis, anticancer and ulcerogenic [1]. Isoxazole and their derivatives, on the other hand, have received comparable attention to the Azetidinone containing moieties. This is due to their diverse biological activities, which include, but are not limited to, their role as antiplatelet agents [2], antiviral and anti-HIV [3,4], anti-diabetic [5], anti-Alzheimer, anti-cancer and anti-inflammatory agents [6,7].

2. Experimental:

All reagents were of analytical reagent grade and were used without further purification, All the product was synthesized and characterized by their spectral analysis. Melting points were taken in open capillary tube. The IR spectra were recorded on Bruker Model; Alpha, Laser Class1, made in Germany and Brooker instrument used for NMR Spectroscopy was 400 MHz and tetramethyl silane used as internal standard. Solvent used were 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.

2.1 Preparation of 3-chloro-4-(2-chlorophenyl)-1-{4-[3-(substitutedphenyl)prop-2-enoyl] phenyl} azetidin-2-one (1a-1j)

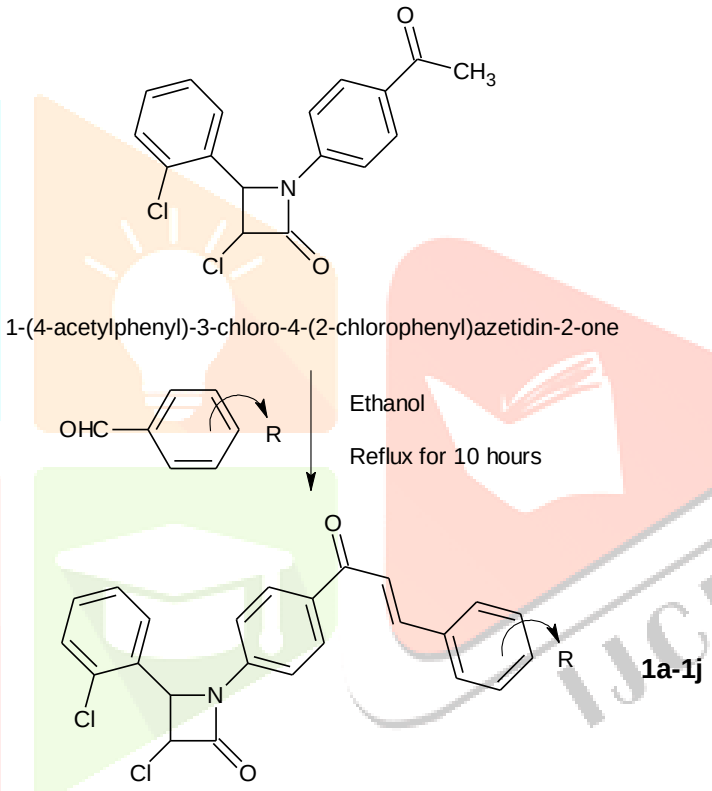
To the solution of 1-(4-acetylphenyl)-3-chloro-4-(2-chlorophenyl)azetidin-2-one (0.01M) in absolute ethanol (50 ml), substituted benzaldehyde (0.01M) and 2% NaOH (10 ml) were added and refluxed for 10 hours. After refluxing the reaction mixture was concentrated, cooled, filtered and neutralized with dil. HCl. The solid residue thus obtained was crystallized by absolute ethanol. IR, cm^{-1}: (1e) 3040 (=C-H), 2933 (-C-H stretching), 1725 (>C=O stretching), 1583 (>C=C< Aromatic), 1335

(C-N), 806 (C-Cl). ^{1}H-NMR (1f- $C_{26}H_{21}Cl_2NO_4$ - DMSO, δ, ppm): 3.348 (6H, s, -OCH_3), 4.854 (1H, s, >CH-Ar Azetidine), 5.477 (1H, s, >CH-Cl Azetidine), 7.582 (2H, d, -CH=CH- Chalcone), 7.178-7.950 (11H, m, Ar-H).

2.2 Preparation of 3-chloro-1-{4-[5-(substitutedphenyl)isoxazol-3-yl]phenyl}-4-(2-chloro phenyl) azetidin-2-one (2a-2j)

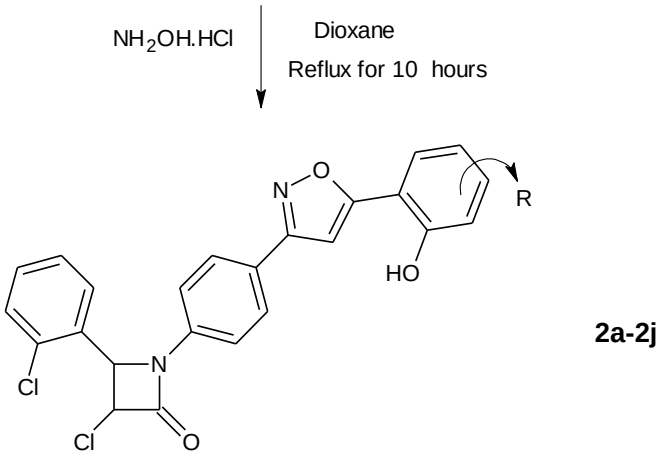
A mixture of 3-chloro-4-(2-chlorophenyl)-1-{4-[3-(substitutedphenyl)prop-2-enoyl] phenyl}azetidin-2-one (0.01M) in 25ml dioxane, hydroxylamine hydrochloride (0.01M) and 40% potassium hydroxide (KOH) was refluxed for 10 hours. Then the reaction mixture was cooled, poured into crushed ice (100g) and neutralized with HCl. The product separated out was filtered, washed with water, dried and recrystallized from alcohol. IR, cm^{-1}:(2g) 3230 (-OH), 3087 (=C-H), 2975 (-C-H stretching), 1699 (>C=O stretching), 1634 (>C=N stretching), 1553 (>C=C< Aromatic), 1384 (-CH_3), 1280 (C-N), 1220 (C-O-C), 763 (C-Cl). ^{1}H-NMR (2h- $C_{26}H_{21}Cl_2N_3O_2$ -DMSO, δ, ppm): 3.046 (6H, s, -$N(CH_3)_2$), 4.841 (1H, s, >CH-Ar Azetidine), 5.434 (1H, s, >CH-Cl Azetidine), 6.609 (1H, s, -CH= Isoxazole), 6.609-7.925 (12H, m, Ar-H).

3. Reaction Scheme



1-(4-acetylphenyl)-3-chloro-4-(2-chlorophenyl)azetidin-2-one

3-chloro-4-(2-chlorophenyl)-1-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}azetidin-2-one



3-chloro-1-{4-[5-(substitutedphenyl)isoxazol-3-yl]phenyl}-4-(2-chlorophenyl)azetidin-2-one

4. Physical constant of 2a-2j

Table: 1

Sr. No	Sub. No.	R	M.F.	Mol.Wt (g/m)	Yield %	M.P. °C	% Carbon		% Hydrogen		% Nitrogen	
							Found	Calcd	Found	Calcd	Found	Calcd
1	2a	-2-OH	$C_{24}H_{16}Cl_2N_2O_3$	451.30	80	161	63.83	63.87	3.54	3.57	6.18	6.21
2	2b	-2-Cl	$C_{24}H_{15}Cl_3N_2O_2$	469.75	82	163	61.34	61.36	3.18	3.22	5.92	5.96
3	2c	-4-Cl	$C_{24}H_{15}Cl_3N_2O_2$	469.75	83	179	61.34	61.36	3.20	3.22	5.92	5.96
4	2d	-4-OH	$C_{24}H_{16}Cl_2N_2O_3$	451.30	79	176	63.81	63.87	3.54	3.57	6.18	6.21
5	2e	-H	$C_{24}H_{16}Cl_2N_2O_2$	435.30	75	165	66.18	66.22	3.67	3.70	6.42	6.44
6	2f	-3,4-OCH_3	$C_{26}H_{20}Cl_2N_2O_4$	495.35	84	183	63.00	63.04	4.04	4.07	5.60	5.66
7	2g	-4-OH-3-OCH_3	$C_{25}H_{18}Cl_2N_2O_4$	481.33	85	197	62.37	62.38	3.75	3.77	5.78	5.82
8	2h	-4-$N(CH_3)_2$	$C_{26}H_{21}Cl_2N_3O_2$	478.37	78	179	65.25	65.28	4.37	4.42	8.71	8.76
9	2i	4-OCH_3	$C_{25}H_{18}Cl_2N_2O_3$	465.32	81	162	64.51	64.53	3.86	3.90	5.97	6.02
10	2j	-3-NO_2	$C_{24}H_{15}Cl_2N_3O_4$	480.30	78	163	60.00	60.02	3.12	3.15	8.73	8.75

5. Antimicrobial activities of 2a-2j

Table: 2

Sr. No.	Comp. No.	R	**ANTIBACTERIAL ACTIVITY Minimal Inhibition Concentration**(µg/ml)				**ANTIFUNGAL ACTIVITY** Minimal Inhibition Concentration (µg/ml)		
			Gram - *Ve* bacteria		**Gram + *Ve* 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	-2-OH	1000	500	1000	500	1000	500	500
2	2b	-2-Cl	100	250	250	100	500	250	100
3	2c	-4-Cl	500	500	500	1000	1000	>1000	500
4	2d	-4-OH	500	1000	500	500	250	250	250
5	2e	-H	250	500	500	250	250	500	250
6	2f	-3,4-OCH_3	500	250	100	100	>1000	250	1000
7	2g	-4-OH-3-OCH_3	500	500	500	1000	500	500	500
8	2h	-4-$N(CH_3)_2$	1000	100	1000	500	250	100	>1000
9	2i	4-OCH_3	250	500	100	500	500	>1000	250
10	2j	-3-NO_2	500	250	250	250	500	500	500

5.1 The Standard Drugs minimum inhibition concentration

Table: 3

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

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

6. Conclusion

The Main focus of this research work was to synthesize, characterize and evaluate antimicrobial activities of the newly synthesized Azetidinone based Isoxazole derivatives, structures of synthesized compounds were confirmed and characterized with the help of analytical data's such as IR and ^{1}H-NMR. In summary, we have described the synthesis and antimicrobial activity of novel 3-chloro-1-{4-[5-(substitutedphenyl)isoxazol-3-yl]phenyl}-4-(2-chlorophenyl)azetidin-2-one. Minimum Inhibitory Concentration (MIC) values revealed that amongst newly synthesized compound having 2-hydroxyphenyl and 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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