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DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION NEW SERIES OF AZETIDINONE BASED PYRIMIDIN-2-ONE DERIVATIVES

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ABSTRACT

Heterocyclic Compounds have so far been synthesized mainly due to the wide range of biological activities. Azetidinone plays an important role in biological field. From these reviews we synthesized a new series of 3-chloro-4-(3,4-dimethoxyphenyl)-1-{4-[6-(2-hydroxyphenyl) -2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl]phenyl}azetidin-2-one derived from 3-chloro-4-(3,4-dimethoxyphenyl)-1-{4-[3-(substitutedphenyl) prop-2-enoyl]phenyl}-azetidin -2-one and urea using ethanol as a solvent. The title compounds were characterized by element analysis, and NMR spectral data. All the compounds were tested for their IR antibacterial and antifungal activities by broth dilution method.

KEYWORDS: Azetidinone, IR, NMR, MTCC, broth dilution method.

INTRODUCTION

2-Azetidines have been extensively investigated by the organic chemists due to their close association with various types of biological activities.[1] It is a four-membered cyclic lactam (ß-lactam) skeleton has been recognized as a useful building block for the synthesis of large number of organic molecules by exploiting the strain energy associated with it. The Staudinger reaction ([2+2] ketene-imine cycloaddition reaction) is regarded as one of the most fundamental and versatile methods for the synthesis of structurally diverse 2-azetidinone derivatives. Azetidine-2-ones also have great importance because of the use of β-lactam derivatives as antibacterial agents recently, some other types of biological activity

beside the antibacterial activity have been reported in compounds containing 2- azetidinone ring. Such biological activities include antimicrobial, anti tubercular, anti inflammatory.[2]

Heterocyclic compounds containing a pyrimidine fragment can be natural or synthetic analogues of nucleosides and nucleotides. They are of considerable interest due to a variety of their biological activities. The pyrimidine structural moiety is responsible for many kinds of biological activity, and is found in the molecules of natural compounds (guanidine, folic acid, etc.) as well as synthetic drugs (antitumor, antiviral, antibacterial drugs, etc.).[3-10]

In the market, there are some approved, effective, well-known medicines containing pyrimidine moieties, such as antimicrobial agent Trimethoprim[11], antiparkinsonian agent Piribedil[12], and antiviral medication Aciclovir (Zovirax)[13], etc. Currently, the interest in pyrimidin-containing biologically active compounds is still significant.[14-16]

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.

Preparation of 1-(4-acetylphenyl)-3-chloro-4-(3,4-dimethoxyphenyl)azetidin-2-one (1)

In a 100ml Round bottom flask 1-(4-{[(3,4-dimethoxyphenyl)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 68 % and the product melts at 105 ^{0}C. Found: C(63.40%) H(5.01%) N(3.86%), Calcd. for $C_{19}H_{18}ClNO_4$: C(63.42%) H(5.04%) N(3.89%). IR, cm^{-1}: (1) 3038 (=C-H), 2936 (-C-H stretching), 1730 (>C=O stretching), 1520 (>C=C< Aromatic), 1415 (-CH_3), 1290 (C-N), 1258 (C-O-C), 775 (C-Cl). ^{1}H-NMR (1- DMSO, δ, ppm): 2.516 (3H, s, -$COCH_3$), 3.343 (6H, s, -OCH_3), 4.820 (1H, s, >CH-Ar Azetidine), 5.485 (1H, s, >CH-Cl Azetidine), 6.610-7.898 (7H, m, Ar-H).

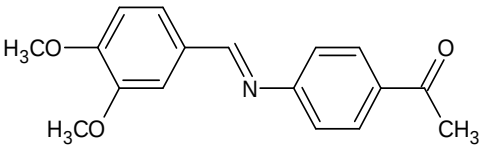
Preparation of 3-chloro-4-(3,4-dimethoxyphenyl)-1-{4-[3-(substitutedphenyl)prop-2-enoyl] phenyl}-azetidin-2-one (2a-2j)

To the solution of 1-(4-acetylphenyl)-3-chloro-4-(3,4-dimethoxyphenyl)azetidin-2-one (0.01M) in absolute ethanol (50 ml), aromatic aldehydes (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}:(2i) 3069 (=C-H), 2904 (-C-H stretching), 1702 (>C=O stretching), 1514 (>C=C< Aromatic), 1421 ($-CH_3$), 1314 (C-N), 1256 (C-O-C), 755 (C-Cl). ^{1}H-NMR (2g- $C_{27}H_{24}ClNO_6$ -DMSO, δ, ppm): 3.353 (9H, s, $-OCH_3$), 4.815 (1H, s, >CH-Ar Azetidine), 5.482 (1H, s, >CH-Cl Azetidine), 7.660 (2H, d, -CH=CH- Chalcone), 9.118 (1H, s, -OH), 6.968-7.729 (10H, m, Ar-H).

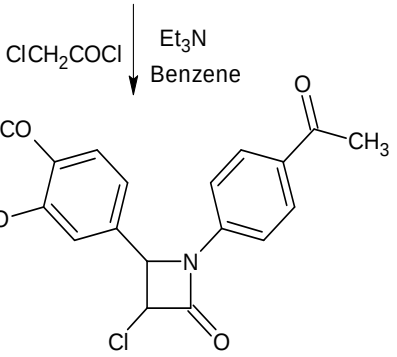
Preparation of 3-chloro-4-(3,4-dimethoxyphenyl)-1-{4-[6-(substitutedphenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl]phenyl}azetidin-2-one (3a-3j)

A mixture of 3-chloro-4-(3,4-dimethoxyphenyl)-1-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-azetidin-2-one (0.01M), urea (0.01M) and 1gm. of potassium hydroxide (KOH) in 30 ml of ethanol was refluxed for 3 hours. After standing overnight the solid formed was collected and crystallized from acetone. IR, cm^{-1}:(3a) 3370 (>NH-), 3265 (-OH), 3078 (=C-H), 2971 (-C-H stretching), 1720 (>C=O stretching), 1596 (>C=N stretching), 1513 (>C=C< Aromatic), 1459 ($-CH_2$ bending), 1370 ($-CH_3$), 1336 (C-N), 1254 (C-O-C), 755 (C-Cl). ^{1}H-NMR (3d- $C_{27}H_{24}ClN_3O_5$ -DMSO, δ, ppm): 1.903 (2H, d, $-CH_2$-Pyrimidine), 3.345 (6H, s, $-OCH_3$), 3.764 (1H, t, -CH< Pyrimidine), 4.871 (1H, s, >CH-Ar Azetidine), 5.448 (1H, s, >CH-Cl Azetidine), 8.584 (1H, s, -NH- Pyrimidine), 9.854 (1H, s, -OH), 6.628-7.927 (11H, m, Ar-H).

Reaction Scheme

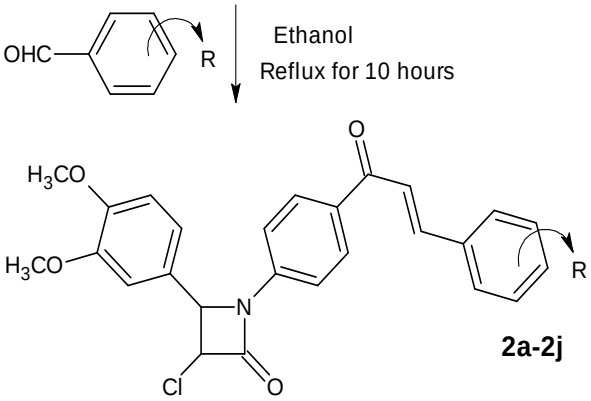


1-(4-{[(3,4-dimethoxyphenyl)methylene]amino}phenyl)ethanone



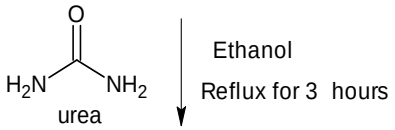
1

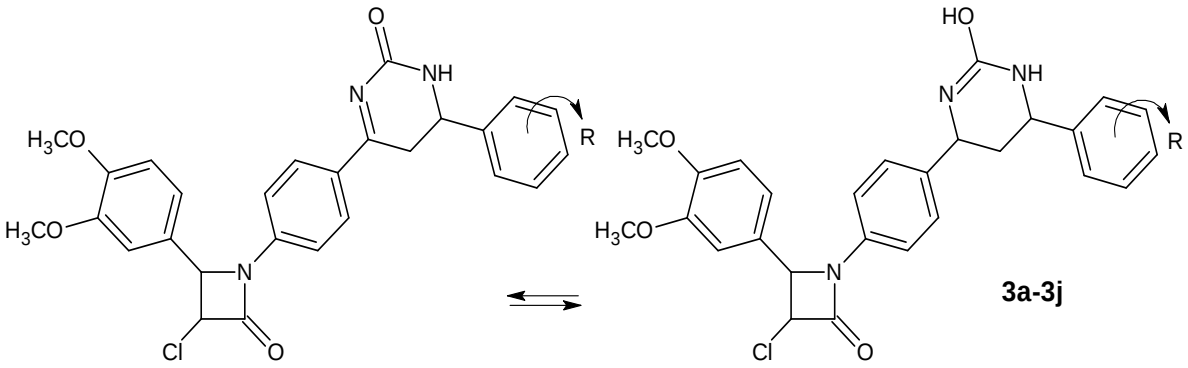
1-(4-acetylphenyl)-3-chloro-4-(3,4-dimethoxyphenyl)azetidin-2-one



2a-2j

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





3a-3j

3-chloro-4-(3,4-dimethoxyphenyl)-1-{4-[6-(substituted phenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl]phenyl} azetidin-2-one

3-chloro-4-(3,4-dimethoxyphenyl)-1-{4-[2-hydroxy-6-(substitutedphenyl)-1,4,5,6-tetrahydropyrimidin-4-yl] phenyl}azetidin-2-one

Table 1: ***Physical constant of 3a-3j.***

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	3a	-2-OH	$C_{27}H_{24}ClN_3O_5$	505.94	77	146	64.07	64.10	4.77	4.78	8.28	8.31
2	3b	-2-Cl	$C_{27}H_{23}Cl_2N_3O_4$	524.39	72	140	61.81	61.84	4.40	4.42	7.95	8.01
3	3c	-4-Cl	$C_{27}H_{23}Cl_2N_3O_4$	524.39	80	156	61.81	61.84	4.40	4.42	7.99	8.01
4	3d	-4-OH	$C_{27}H_{24}ClN_3O_5$	505.94	85	159	64.07	64.10	4.75	4.78	8.30	8.31
5	3e	-H	$C_{27}H_{24}ClN_3O_4$	489.95	73	147	66.16	66.19	4.93	4.94	8.57	8.58
6	3f	-3,4-OCH_3	$C_{29}H_{28}ClN_3O_6$	550.00	78	162	63.32	63.33	5.10	5.13	7.60	7.64
7	3g	-4-OH-3-OCH_3	$C_{28}H_{26}ClN_3O_6$	535.97	81	168	62.74	62.75	4.83	4.89	7.80	7.84
8	3h	-4-$N(CH_3)_2$	$C_{29}H_{29}ClN_4O_4$	533.02	83	153	65.31	65.35	5.46	5.48	10.47	10.51
9	3i	4-OCH_3	$C_{28}H_{26}ClN_3O_5$	519.98	74	158	64.66	64.68	5.01	5.04	8.05	8.08
10	3j	-3-NO_2	$C_{27}H_{23}ClN_4O_6$	534.95	72	148	60.60	60.62	4.31	4.33	10.44	10.47

Table 2: ***Antimicrobial activities of 3a-3j.***

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	3a	-2-OH	500	500	500	250	>1000	500	250
2	3b	-2-Cl	500	500	500	500	1000	100	500
3	3c	-4-Cl	1000	250	250	500	500	500	1000
4	3d	-4-OH	500	500	500	500	250	500	100
5	3e	-H	250	250	500	100	>1000	250	250
6	3f	-3,4-OCH_3	500	500	100	500	500	1000	500
7	3g	-4-OH-3-OCH_3	1000	500	1000	250	500	>1000	500
8	3h	-4-$N(CH_3)_2$	250	1000	500	250	250	>1000	>1000
9	3i	4-OCH_3	100	250	250	100	250	500	250
10	3j	-3-NO_2	500	100	500	250	500	500	250

Table 3: ***The Standard Drugs minimum inhibition concentration.***

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

CONCLUSION

The Main focus of this research work was to synthesize, characterize and evaluate antimicrobial activities of the newly synthesized Azetidinone based Pyrimidin-2-one 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-4-(3,4-dimethoxyphenyl)-1-{4-[6-(substitutedphenyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl]phenyl}azetidin-2-one. MIC values revealed that amongst newly synthesized compound having 2-chlorophenyl and 4-dimethylaminophenyl 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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