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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF SOME SUBSTITUTED AZETIDINONE DERIVATIVES

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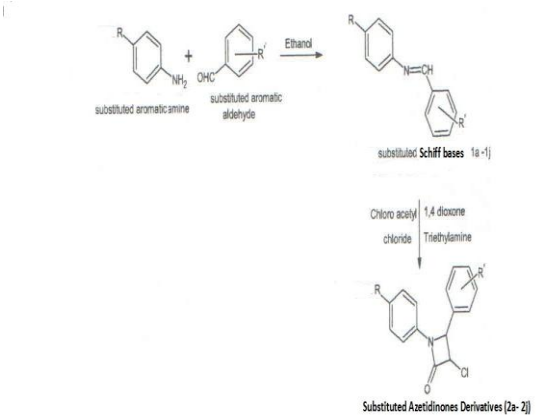
ABSTRACT
A noble series of substutied azitidinone derivatives can be synthesized by the cyclocondensation of different Schiff bases with chloro acetyl chloride. Different Schiff bases can be synthesized by the condation of Substituted aromatic aldehyde with substituted anilene. the newly synthesized compound were characterized by IR, ^{1}HNMR spectroscopy and tested for their promising biological activity i.e. anti-inflammatory activity, anticonvulsant activity.

KEYWORDS: Azitidinone, Schiff bases, substituted aromatic aldehyde, Anti-inflammatory activity.

INTRODUCTION
Heterocyclic compounds are abundant in nature and are of great significant tolife because their structural unit exit in many natural product such as vitamin, hormones, antibiotics etc. a practical method for synthesis of such compound is of a great interest in synthetic organic chemistry. Sulfar conating hetercyclic compounds show their pharmacological importance.[1-3]

Azetidinones which are part of antibiotics structure are known to exhibit interesting biological activities. A large number of 3-chloro2- azetidinones possesses powerful antimicrobial, anti-inflammatory, analgesic, anticonvulsant, antitubercular, antioxidant.[4-14]

An attment has been done to synthesize various azetidonone derivative by following scheme



MATERIAL AND METHODS
Melting points were determined in an open capillary tube method and are uncorrected. IR spectra were recorded (in KBr) on Shimadzu FT-IR spectrometer. ^{1}H-NMR spectra was recorded on Bruker DRX-300 (300 MHz FT-NMR) using DMSO as solvent and TMS as Internal standard. TLC using silica gel- G checked the purity of the compounds. The spots were developed in iodine chamber and visualized under ultraviolet lamp.

General Procedure
1) Synthesis of SubstitutedSchiff Bases (1a-1j)
Anilene (0.014mol, 2gm) was dissolved in 10 ml ethanol. The appropriate aromatic aldehyde (0.014mol, 1.48gm) was added to the reaction mixture. It was refluxed for 6-7 hours, cooled to R.T. and then poured into crushed ice. The solid obtained was filtered, washed with water and recrystallized with ethanol. Mobile phase for TLC Benzene: Acetone (4.5:0.5).

2) Synthesis of substituted 3-Chloro-2-Azetidinones Derivatives (2a-j)
To a stirred solution of synthesized substituted schiff bases (1a-j) (0.01mol), in 1,4 dioxan (25ml), triethylamine (0.01mol,) and chloroacetylchloride (0.01mol) were added drop wise with constant stirring at 0-200C. The reaction mixture was kept for 30 min and then refluxed for 7-8 hours. Excess of solvent distilled off and the residue was poured into ice-cold water. A solid obtained was filtered and which was recrystallized from ethanol. Mobile phase for TLC Benzene: Ethanol (7:3).

Synthesis of N- (4-chloro phenyl) 3-chloro 4-phenyl Azetidinone
Yield 37.81%, mp 210-212^{0}C, IR (KBr) cm -1; 3246.77cm-1 (-OH), 3123.18cm-1 (Ar C-H). 1719.95cm-1 (C=O ß-lactum), 1680.16cm(C=O), 1547.67 cm-1 (Ar C=C), 1346.46cm-1 (C-N), 778.52cm-1 (C- Cl), NMR(DMSO) d; 10 (S,1H –COOH),7.6 -8 (m,9H, phenyl), 6.4(d,1H,3-CH of ß-lactum), 6.2(d,1H,4-CH of ß-lactum).

Synthesis of N- (4-chloro phenyl) 3-chloro 4-[3-chloro phenyl] Azetidinone: Yield 62.01%, mp 128-130^{0}C, IR(KBr) cm -1; 3196.77cm-1(-OH), 3143.18cm-1 (Ar C-H). 1730.95cm-1 (C=O ß-lactum), 1695.16 cm-1(C=O), 1556.67 cm-1 (Ar C=C), 1346.46cm-1 (C-N), 775.52cm-1 (C-Cl). NMR(DMSO) d; 10.2 (S,1H –COOH), 8.2-8.4(m,4H,chlorophenyl), 7.7-8 (m,4H, phenyl), 6.6(d,1H,3-CH of ß-lactum), 6.4(d,1H,4-CH of ß-lactum).

Synthesis of N- (4-chloro phenyl) 3-chloro 4-[4-methoxy phenyl] Azetidinone: Yield 51.04%, mp 180-182^{0}C,IR (KBr) cm -1: 3150cm-1 (-OH), 3080cm-1 (Ar C-H), 1710.12cm-1(C=O ß-lactum), 1687.77cm-1 (C=O), 1574.93 cm-1 (Ar C=C), 1453.41cm-1 (C-N), 1261.49cm-1 (-C-O), 772.52cm-1 (C-Cl), NMR(DMSO) d; 10.2 (S,1H –COOH), 8.28.4(m,4H,methoxyphenyl), 7.6-7.9 (m,4H, phenyl), 6.4(d,1H,3-CH of ß-lactum), 6.2(d,1H,4-CH of ß-lactum), 1.3(s,3H,CH3).

Synthesis of N- (4-chloro phenyl) 3-chloro 4-[4-hydroxy phenyl] Azetidinone: Yield 43.72%, mp 160-162^{0}C,IR (KBr) cm -1: 3200cm-1 (-OH), 3135cm-1 (Ar C-H), 1715.12cm-1(C=O ß-lactum), 1681.02cm-1 (C=O),1570.11 cm-1 (Ar C=C),1420.62cm-1 (C-N), 1286.56cm-1 (-C-O), 772.52cm-1 (C-Cl), NMR(DMSO) d; 10.3 (S,1H –COOH), 7.457.86(m,4H,hydroxyphenyl), 7.2-7.5 (m,4H, phenyl), 6.4(d,1H,3-CH of ß-lactum), 5.9(d,1H,4-CH of ß-lactum), 3.15(s,1H,Ar-OH).

Synthesis of N- (4-chloro phenyl) 3-chloro 4-[2-hydroxy phenyl] Azetidinone: Yield 53.23%, mp 210-212^{0}C,IR (KBr) cm -1: 3200cm-1 (-OH), 3135cm-1 (Ar C-H), 1715.12cm-1(C=O ß-lactum), 1681.02cm-1 (C=O),1570.11 cm-1 (Ar C=C),1420.62cm-1 (C-N), 1286.56cm-1 (-C-O), 772.52cm-1 (C-Cl), NMR(DMSO) d; 10.3 (S,1H –COOH), 7.457.86(m,4H,hydroxyphenyl), 7.2-7.5 (m,4H, phenyl), 6.4(d,1H,3-CH of ß-lactum), 5.9(d,1H,4-CH of ß-lactum), 3.15(s,1H,Ar-OH).

Synthesis of N- (4-chloro phenyl) 3-chloro 4-[3-nitro phenyl] Azetidinone: Yield 67.96%, mp 160-162^{0}C,IR (KBr) cm-1: 3260cm-1 (-OH), 3114.18cm-1 (Ar C-H), 1710.12cm-1(C=O ß-lactum), 1677.16cm-1 (C=O), 1527.67 cm-1 (Ar C=C), 1503.67 cm-1 (NO2),1343.46cm-1 (CN), 772.52cm-1 (C-Cl), NMR(DMSO) d; 10.3 (S,1H –COOH), 8.68.9(m,4H, nitrophenyl), 7.6-8 (m,4H, phenyl), 6.45(d,1H,3-CH of ßlactum), 6.2(d,1H,4-CH of ß-lactum).

Synthesis of N- (4-chloro phenyl) 3-chloro 4-[N,N'dimethyl amino phenyl] Azetidinone: Yield 60.54%, mp 182-184^{0}C,IR (KBr) cm -1: 3245cm-1 (-OH), 3123.28cm-1 (Ar C-H), 1714.12cm-1(C=O ß-lactum), 1684.36cm-1 (C=O), 1532.60 cm-1 (Ar C=C), 1343.46cm-1 (C-N), 772.52cm-1 (C-Cl), NMR(DMSO) d; 10.3(S,1H –COOH), 8.5-8.9 (m,4H, dimethylamino phenyl), 7.6-8 (m,4H, phenyl), 6.6(d,1H,3-CH of ß-lactum), 6.3(d,1H,4-CH of ß-lactum),1.45(s,6H,CH3). HOOC + NH2 OHC.

Synthesis of N- (4-chloro phenyl) 3-chloro 4-[2-vinyl phenyl] Azetidinone: Yield 67.87%, mp 120-122^{0}C,IR (KBr) cm-1: 3245.77cm-1 (-OH), 3145cm-1 (Ar C-H), 1709.95cm-1(C=O ß-lactum), 1677.16cm-1 (C=O), 1527.67 cm-1 (Ar C=C), 1343.46cm-1 (C-N), 772.52cm-1 (C-Cl), NMR(DMSO) d; 10.3 (S,1H –COOH), 7.6-8 (m,9H, phenyl), 6.45(d,1H,3-CH of ß-lactum), 6.2(d,1H,4-CH of ß-lactum), 6(t,1H,CH).

Synthesis of N- (4-chloro phenyl) 3-chloro 4-[4-Nitro phenyl] Azetidinone: Yield 69.53%, mp 178-180^{0}C,IR (KBr) cm -1: 3260cm-1 (-OH), 3114.18cm-1 (Ar C-H), 1709.95cm-1(C=O ß-lactum), 1677.16cm-1 (C=O), 1527.67 cm-1 (Ar C=C), 1503.56 cm-1 (NO2),1343.46cm-1 (CN), 772.52cm-1 (C-Cl), NMR(DMSO) d; 10.3 (S,1H –COOH), 8.68.9(m,4H, nitrophenyl), 7.6-8 (m,4H, phenyl), 6.45(d,1H,3-CH of ßlactum), 6.2(d,1H,4-CH of ß-lactum).

Synthesis of N- (4-chloro phenyl) 3-chloro 4-[3,4,5-methoxy phenyl] Azetidinone: Yield 71.77%, mp 180-182^{0}C,IR (KBr) cm-1: 3246.77cm-1 (-OH), 3124.18cm-1 (Ar C-H), 1719.95cm-1(C=O ß-lactum), 1687.16cm-1 (C=O), 1530.67 cm-1 (Ar C=C),1343.46cm-1 (C-N), 1261.49cm-1 (-CO), 772.52cm-1 (C-Cl). NMR(DMSO) d; 10.4 (S,1H –COOH), 8.68.9(m,4H, nitrophenyl), 7.6-7.9 (m,4H, phenyl), 6.5(d,1H,3-CH of ßlactum), 6.25(d,1H,4-CH of ß-lactum), 1.5(s,9H,CH3). HOOC Ethanol CH N R N-substituted benzylidine -1a -1j p-amino benzoic acid.

Table 1: Physical constants of different synthesised Azetidinone derivatives (2a-2j)

Compound No.	R	R'	Mol. Formula	Mol. Wt.	M.P.^{0}C	$R_{f\ Value}$	% Yield
2a	Cl	-C_6H_5	$C_{15}H_{11}ONCl_2$	292	211	0.75	37.80
2b	Cl	4-Cl C_6H_5	$C_{15}H_{10}ONCl_3$	326.5	128	0.81	65
2c	Cl	4-OCH_3-C_6H_5	$C_{15}H_{13}O_2NCl_2$	310	182	0.87	54
2d	Cl	4-OH- C_6H_5	$C_{15}H_{11}O_2NCl_2$	308	161.5	0.89	52
2e	Cl	2-OH-C_6H_5	$C_{15}H_{11}O_2NCl_2$	308	211	0.82	65

2f	Cl	3-NO_2 C_6H_5	$C_{15}H_{10}O_3N_2Cl_2$	337	162	0.74	58
2g	Cl	4-N(CH_3) C_6H_5	$C_{16}H_{13}ON_2Cl_2$	320	184	0.67	61
2h	Cl	4-CH=CH- C_6H_5	$C_{18}H_{12}ONCl_2$	317	122	0.74	70
2i	Cl	4-NO_2 C_6H_5	$C_{15}H_{10}O_3N_2Cl_2$	337	180	0.85	71
2j	Cl	4-[3,4,5-tri methoxy] C_6H_5	$C_{18}H_{19}O_4NCl_2$	384	182	0.81	73

RESULT AND DISCUSSION

The newly synthesized compounds were tested for their promising biological activity i.e. anti-inflammatory and anticonvulsant activity. Some of newly synthesized compound show their promising activity.

Anti inflammatory activity

All newly synthesised compounds were screened for their anti inflammatory activity with the help of following method as compared to standard Indomethacin at 200 µg/ml. Mice of either sex weighing between 15 and 25 gm were divided into groups of 5 each. carrageenin solution (1.0%, 0.025ml) in normal saline was injected in the left planter aponeurosis, after one hour, the oral feeding of drug. one group acted as control and received only the vehicle and another group received, a standard anti-inflammatory compound (Indomethacin). Both the hind limbs of all the groups were cut 4 hours after the carrageenin injection at level of the ankle Joint. Difference between the weight of the left and right limbs gave the amount of edma developed. Difference in the amount of edema developed in each group from the control group in used to calculate the percentage inhabitation.

Some of newly synthesized compound show significant anti-inflammatory activity recorded in table 2.

Table 2 ALD_{50} and Antiinflammatory activity data.

S.No.	Name of Compound	Approximate		Anti inflammatory Activity of inhibition
		ALD_{50} Dose(mg/kg)	Mice P.O.	
1-	2a	>1000	200	74
2-	2b	681	200	79
3-	2c	825	168	77
4-	2d	681	198	79
5-	2e	825	173	62
6-	2f	715	185	64
7-	2g	680	192	76
8-	2h	700	186	52
9-	2i	625	184	66
10-	2j	750	163	72

Pharmacological Evaluation Anticonvulsant activity 465

The title compounds (2a-2j) were evaluated for in vivo anticonvulsant activity against by MES method. The anticonvulsant activity of the compounds was evaluated by maximal electro shock (MES) method using mice where the electroshock is applied through the corneal electrodes. Producing optic stimulation cortical excitation. The MES convulsions are divided into five phases such as (a) Toxic flexion (b) Tonic extension (c) clonic convulsion (d) stupor and (e) Recovery or death. A drug is known to posses anticonvulsant properties. If it reduces or abolishes the extensor phase of MES convulsions, for the evaluation anticonvulsant activity the total 12 groups of animals each containing 6-animals were kept fasting for 10-14 hrs. In that 10 groups were served for testing the synthesized compounds, one as control and one as standard. After that the synthesized compounds were administered to each group at a dose of 25mg/kg of bodyweight, 1% C.M.C. was used as vehicle control and diazepam (5mg/kg of body weight) was used as a standard drug respectively. The activities of each group were measured after the intervals of 60 mins and 120 mins of administration including control and standard.

Results and data are given in table 3.

Table 3: Anticonvulsant activity data of synthesized compounds (2a-2j)

Group	Treatment	Dose(mg/Kg)	Duration of hind limb extensor in sec.	
			60 min.	120 min.
I	control	---	52±0.9661	65±0.610
II	standard	5mg	11.33±0.4944	23±0.5774
III	2a	25mg	27±0.7544**	40.17±0.6009**
IV	2b	25mg	12±0.4551**	21±0.6841**
V	2c	25mg	25±0.5412**	36.22±0.6847**
VI	2d	25mg	15±0.5431**	25.14±0.7923**

VII	2e	25mg	30±0.7412**	50±0.8775**
VIII	2f	25mg	31.15±0.5442**	46.21±0.8021**
IX	2g	25mg	26.8±0.7415**	60.83±0.5442^{ns}
X	2h	25mg	47±0.8841^{ns}	63.2±0.5448^{ns}
XI	2i	25mg	19±0.4775**	26.45±0.6641**
XII	2j	25mg	30±0.6847**	26.16±0.6009**

Data were analyzed by one-way ANOVA followed by Dunnett's test. Values are expressed as mean ± S.E.M. ** P<0.01 when compared to control, ns-non significant.

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