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Synthesis and Anti-Inflammatory Activity of Some New Schiff's Bases and Azetidinones

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ABSTRACT

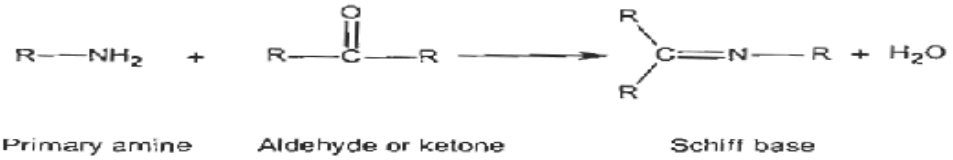
A Schiff's base is nitrogen analog of an aldehyde or ketone in which C=O group is replaced by a C=N—R group. It is usually formed by the condensation of an aldehyde or ketone with a primary amine. 2-Azetidinones, commonly known as β-lactams, are well known heterocyclic compounds among the organic and medicinal chemists. The activity of the known antibiotics such as penicillins, cephalosporins and carbapenems are attributed to the presence of 2-azetidinone ring in them[1-5]. In the present study, we synthesized different Schiff's bases (3a-3h) by treating 2-amino-5-chlorobenzoic acid with different aromatic aldehydes by using glacial acetic acid as a solvent. The Schiff's bases were then treated with chloroacetyl chloride in presence of triethylamine by using 1,4-dioxan as a solvent, it produced different azetidinones (4a-4h). The prepared azetidinones were recrystallized with ethanol[6-8]. The final compounds were then characterized by melting point, TLC, IR and NMR spectral data. These compounds were evaluated for antibacterial, antifungal, anti-inflammatory activities. Some of the newly synthesized compounds showed the significant activity when compared with the standard compounds[9-12].

INTRODUCTION

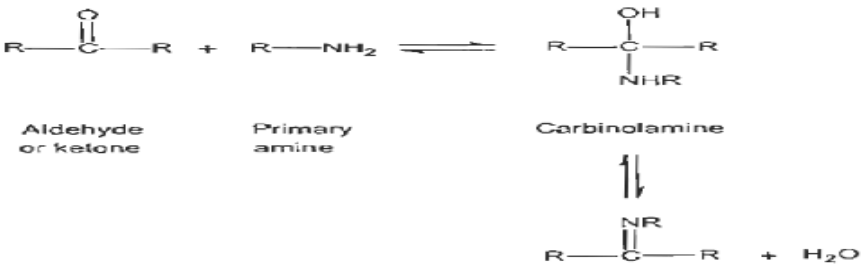
Schiff bases:

Formation of Schiff bases:

A Schiff base is nitrogen analog of an aldehyde or ketone in which the C=O group is replaced by a C=N-R group. It is usually formed by condensation of an aldehyde or ketone with a primary amine according to the following scheme.[13-15]



Where R may be an alkyl or an aryl group. Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable, while those of aromatic aldehydes having effective conjugation are more stable.[17-20]

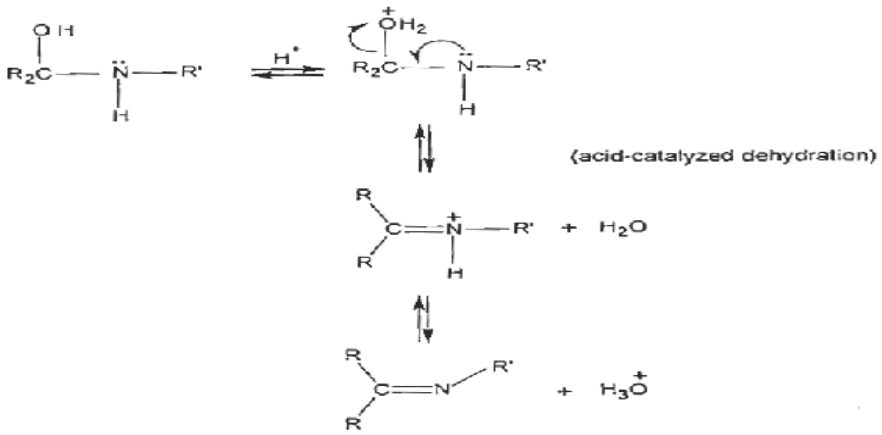


The formation of Schiff base from an aldehyde or ketone is a reversible reaction and generally takes place under acid or base catalyst upon heating.

The formation is generally driven to the completion by separation of the product or removal of water or both. Many Schiff bases can be hydrolyzed back to their aldehydes or ketone and amines by aqueous acid or base.

The mechanism of Schiff base formation is another variation on the theme of nucleophilic addition to the carbonyl group. In this case, the nucleophile is the amine. In the first part of the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine.[21-24]

The carbinolamine loses water by either acid or base catalyzed pathways. Since the carbinolamine is an alcohol it undergoes acid-catalyzed dehydration.



Typically the dehydration of carbinolamine is the rate determining step of Schiff's base formation and this is why the reaction is catalyzed by the acids. Yet the acid concentration cannot be too high because amines are basic compounds. If the amine is protonated and becomes nonnucleophilic, equilibrium is pulled to the left and carbinolamine formation cannot occur. Therefore many Schiff's base syntheses are best carried out at mildly acidic pH. The dehydration of carbinolamines is also catalyzed by a base. This reaction is somewhat analogous to E2 elimination of alkyl halides except that it is not a concerted reaction. It proceeds in 2 steps through an anionic intermediate.[25-26]

Synthetic importance of Schiff's bases:

Acylation of Schiff's bases by acid anhydrides, acid chlorides, and acyl cyanides is initiated by attack at the nitrogen atom and leads to net addition of the acylating agent to the carbon- nitrogen double bond. Reactions of this type have been put to good use in natural product syntheses.

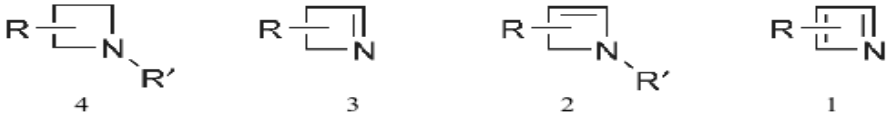
The base catalyzed condensation of acetyl chlorides with aryl aldimines occurs by initial acylation at the nitrogen atom and leads to the beta-lactams of interest in penicillin chemistry.[31-34]

Azetidinones -

The chemistry of ß-lactams has taken an important place in organic chemistry since the discovery of Penicillin by Sir Alexander Fleming in 1928 and shortly thereafter Cephalosporin which was both used as successful antibiotics. Even now the research in this area is stimulated because of the development of bacterial resistance to widely used antibiotics of this type1.There is a need for functionalized ß- lactams or for new active principles in ß- lactam series. Apart from antibiotic activity ß- lactam also possesses cholesterol inhibition, antithrombotic, antiviral and antifungal activities. The 2-azetidinone (ß- lactams) ring is a common structural feature of a number of broad spectrum ß-lactam antibiotics including penicillins, cephalosporins, carbapenems, nocardicin and monobactams which have been widely used as chemotherapeutic agents to treat bacterial infection and microbial diseases. These molecules operate by forming covalent adducts with membrane-bound bacterial transpeptidases which are also known as penicillin-binding proteins (PBPs) involved in the biosynthesis of cell wall. These mechanism based inhibitors prevent the construction of cell wall and eventually lead to cell lysis and death. Moreover due to their ß- lactamase inhibitor action 2-azetidinones based heterocycles represent an attractive target of contemporary organic synthesis. 5 It has been reported that introduction of different substituents to four-

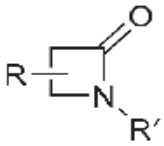
membered ß-lactam nuclei tend to exert profound influence in conferring promising biological activities.[35-36]

There is not much change in scenario with regard to the pace of development on azetidines 1, 1–azetines 2, 2–azetines 3, and azetes 4. While the latter three classes are still underdeveloped, the chemistry of azetidines is growing steadily1.[27]



4 3 2 1

As usual, the chemistry of azetidin–2–ones 5, derivatives of azetidines, has seen an enormous focus because of the biological significance of these substances and their derivatives. Azetidin–2–ones have been again dealt with separately rather than as derivatives of azetidines because of the increasing interest in these β–lactam compounds.



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A large number of applications in agrochemistry and in the pharmaceutical field continue to stimulate interest in the chemistry of this class of strained azaheterocycles 2, 3. The discovery of the trinitro azetidines as potentially useful energetic materials and application of many azetidines in asymmetric synthesis has given impetus to studies on this class of compounds 4.

The strain in azetidines influences the tendency for ring formation enormously. Within the homologous series of azaheterocycles, the tendency for cyclization is smallest for the nitrogen–containing four-membered ring (5 > 3 > 6 > 7 ≈ 4). For some other studies on gas-phase proton affinity and ab initio calculations on the azetidin–yl radical, should be consulted 1.[28]

Methodology

Experimental:

Apparatus Techniques:

1. All the melting points are uncorrected and are expressed in degree (°C), in the Department of Chemistry, Mallareddy college of pharmacy melting point apparatus.

2. IR spectra were recorded using perkin Elmer Model 283B and Nicolet 740 FT-IR spectrophotometer in the Indian Institute of Chemical technology, Hyderabad. Only principal absorption bands of interest are reported and expressed in cm^{-1}.

3.^{1}H NMR spectra were recorded using Varian Gemini-200, Varian unity-400 and Avance-300 MHz Bruker UX-NMR instrument in Indian Institute of Chemical technology, Hyderabad. The chemical shift values are expressed as □ (ppm) using tetramethylsilane (TMS) as an internal standard. The coupling constant (J) is given in (Hz). While citing the ^{1}H NMR data the following abbreviations are used: Singlet

(s), Broad single (bs), Doublet (d), triplet (t), quartet (q), Multiplet (m), double doublet (dd), double triplet (br).

4. Mass spectrum was recorded on VG micro mass 7070 H (EI and CI), VG auto spec (FAB) using Cs+ ion gun, m-nitrobenzyl alcohol (MNBA) as a matrix and are given in Mass units(m/z).

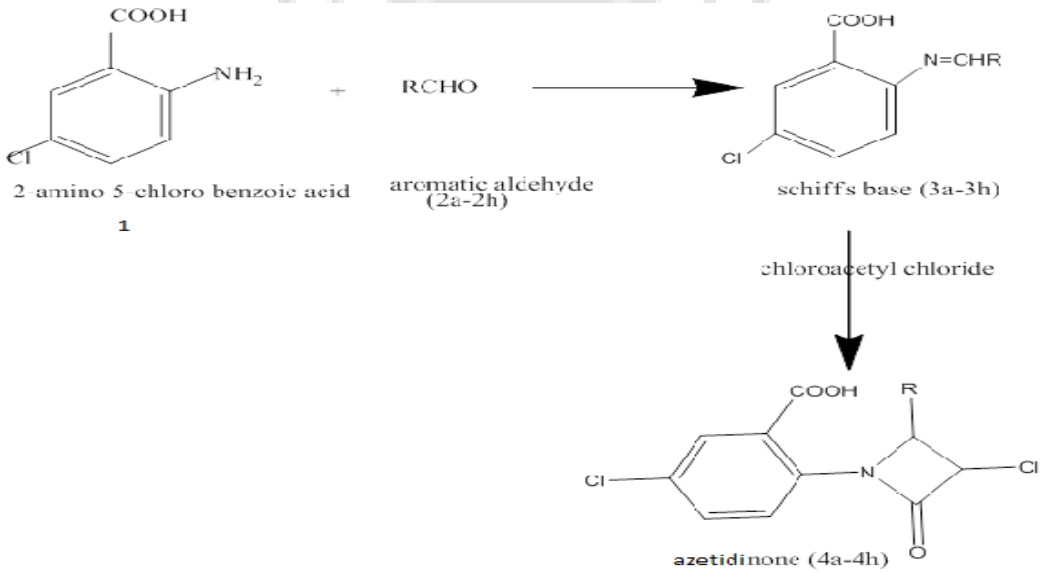
5. Thin layer chromatography (TLC) was performed on precoated silica gel-60 F254 (0.5 mm) aluminum sheets. TLC plates eluted with ethyl acetate: hexane mixtures and the spots were made visible by exposing plates to iodine vapor or UV light.

6. Column chromatography was performed with silica gel (Acme Synthetic Chemicals, 60-120 mesh).

MATERIALS AND METHODS

All solvents were distilled / dried prior to use when this seemed necessary by standard methods. All solvent extracts were dried over anhydrous sodium sulfate unless otherwise specified. 2,4 dichloro benzaldehyde ,4-nitro benzaldehyde, 2,4 dichloro benzaldehyde ,4-nitro benzaldehyde, 3,4-dimethoxy benzaldehyde, p-tolu aldehyde, 4-fluoro benzaldehyde, 4-dimethyl amino benzaldehyde was obtained from Himedia Laboratories, Hyderabad. n-Hexane, Glacial acetic acid, Triethylamine, 1,4 dioxan, Ethyl acetate was obtained from Finar Reagents, Hyderabad. Ethanol obtained from CS chemicals, Hyderabad. Chloro acetyl chloride obtained from INR Chemicals, Hyderabad. Silica gel and Iodine was obtained from Merck, Hyderabad.[29-30]

Scheme



PROCEDURE:

Preparation of Schiff base 3(a-h)

A mixture of an appropriate 2-amino-5-chlorobenzoic acid **(0.01 mole)** and an aromatic aldehyde **(0.015 mole)** in **130 ml** of glacial acetic acid was heated under reflux at (70-80˚C) for 8 hrs .The progress of

the reaction was checked by TLC. After completion on cooling, the solvent was evaporated and the separated solid was filtered, washed with water and then recrystallized from glacial acetic acid.

1. 5-chloro-2-(2,4-dichloro benzylidene amino)benzoic acid 3a

It was prepared by above general procedure from 2-amino-5-chlorobenzoic acid (**0.01 mole, 1.715 g**) and 2,4-dichloro benzaldehyde (**0.015 mole, 2.4 g**)

2. 5-chloro-2-(4-chloro benzylidene amino)benzoic acid 3b

It was prepared by above general procedure from 2-amino-5-chlorobenzoic acid (**0.01 mole, 1.715 g**) and 4-chloro benzaldehyde **(0.015 mole, 2.10855 g**).

3. 5-chloro-2-(4-nitro benzylidene amino)benzoic acid 3c

It was prepared by above general procedure from 2-amino 5-chloro benzoic acid (0.01 **mole, 1.715 g**) and 4-nitro benzaldehyde (**0.015 mole**, **2.2668 g**).

4. 5-chloro-2-(3,4-dimethoxy benzylidene amino)benzoic acid 3d

It was prepared by above general procedure from 2-amino-5-chlorobenzoic acid **(0.01 mole, 1.715 g**) and 3,4 dimethoxy benzaldehyde (**0.015 mole**, **2.4927 g**).

5. 5-chloro-2-(4-methyl benzylidene amino)benzoic acid 3e

It was prepared by above general procedure from 2-amino-5-chlorobenzoic acid **(0.01 mole , 1.715 g**) and 3,4 dimethoxy benzaldehyde (**0.015 mole**, **1.80 g**).

6. 5-chloro-2-(4-fluoro benzylidene amino)benzoic acid 3f

It was prepared by above general procedure from 2-amino-5-chlorobenzoic acid (**0.01 mole, 1.715 g**) and 3,4 dimethoxy benzaldehyde (**0.015 mole**, **1.86 g**).

7. 5-chloro-2(4-dimethylamino benzylidene amino)benzoic acid 3g

It was prepared by above general procedure from 2-amino-5-chlorobenzoic acid **(0.01 mole, 1.715 g**) and 4-dimethyl amino benzaldehyde (**0.015 mole**, **2.237 g)**.

8. 5-chloro-2-(4-methoxy benzylidene amino)benzoic acid 3h

It was prepared by above general procedure from 2-amino-5-chlorobenzoic acid **(0.01 mole, 1.715g**) and 3, 4 dimethoxy benzaldehyde (**0.015 mole**, **2.4927 g)**.

Preparation of azetidine-2-one 4(a-h):

General Procedure

The Schiff's base (0.01M) was dissolved in dry 1, 4 dioxan (30ml). To this, triethylamine (0.02M) was added with stirring at 0-5^{0}C. To the reaction mixture, color acetyl chloride (0.01M) was added dropwise

and stirred for 3hrs at room temperature. The reaction mixture was then poured into crushed ice. The solid separated was filtered, washed, dried and recrystallised from ethanol to get the azetidinone.

1. 5-chloro-2-(3-chloro-2-(2,4 dichloro phenyl)-4-oxoazetidin-1-yl)benzoic acid 4a

5-chloro-2-(2,4-dichlorobenzylideneamino)benzoic acid (3a) (0.01M, 3.285g) was dissolved in dry 1,4 dioxan (30ml). To this, triethylamine (0.02M, 0.5g) was added with stirring at 0-5^{0}C. To the reaction mixture chloroacetyl chloride (0.01M, 1.12g) was added dropwise and stirred for 3 hrs at room temperature. The reaction mixture was then poured into crushed ice. The solid separated was filtered, washed, dried and recrystallised from ethanol to get the azetidinone (4a).

2. 5-chloro-2-(3-chloro-2-(4-chloro phenyl)-4-oxoazetidin-1-yl)benzoic acid 4b

5-chloro-2-(4-chlorobenzylideneamino)benzoic acid (3b) (0.01M, 2.94g) was dissolved in dry 1,4 dioxan (30ml). To this, triethylamine (0.02M, 0.5g) was added with stirring at 0-5^{0}C. To the reaction mixture chloroacetyl chloride (0.01M, 1.12g) was added dropwise and stirred for 3 hrs at room temperature. The reaction mixture was then poured into crushed ice. The solid separated was filtered, washed, dried and recrystallised from ethanol to get the azetidinone (4b).

3. 5-chloro-2-(3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)benzoic acid 4c

5-chloro-2-(4-nitrobenzylideneamino)benzoic acid (3c) (0.01M, 3.14g) was dissolved in dry 1,4 dioxan (30ml). To this, triethylamine (0.02M, 0.5g) was added with stirring at 0-5^{0}C. To the reaction mixture chloroacetyl chloride (0.01M, 1.12g) was added dropwise and stirred for 3 hrs at room temperature. The reaction mixture was then poured into crushed ice. The solid separated was filtered, washed, dried and recrystallised from ethanol to get the azetidinone (4c).

4. 5-chloro-2-(3-chloro-2-(3,4 dimethoxy phenyl)-4-oxoazetidin-1-yl)benzoic acid 4d 5-chloro-2-(3,4-dimethoxybenzylideneamino)benzoic acid 3d (0.01M, 3.19 g) was dissolved in dry 1,4 dioxan (30ml). To this, triethylamine (0.02M, 0.5g) was added with stirring at 0-5^{0}C. To the reaction mixture chloroacetyl chloride (0.01M, 1.12g) was added dropwise and stirred for 3 hrs at room temperature. The reaction mixture was then poured into crushed ice. The solid separated was filtered, washed, dried and recrystallised from ethanol to get the azetidinone (4d).

5. 5-chloro-2-(3-chloro-2-(4-methyl)-4-oxoazetidin-1-yl)benzoic acid 4e

5-chloro-2-(4-methylbenzylideneamino)benzoic acid 3e (0.01M, 2.73g) was dissolved in dry 1,4 dioxan (30ml). To this, triethylamine (0.02M, 0.5g) was added with stirring at 0-5^{0}C. To the reaction mixture chloroacetyl chloride (0.01M, 1.12g) was added dropwise and stirred for 3 hrs at room temperature. The reaction mixture was then poured into crushed ice. The solid separated was filtered, washed, dried and recrystallised from ethanol to get the azetidinone (4e).

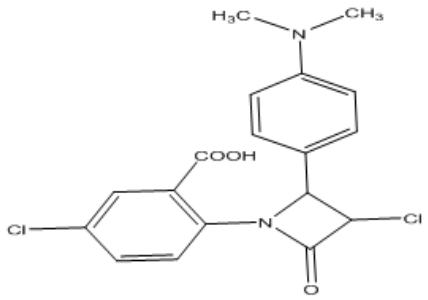
6. 5-chloro-2-(3-chloro-2-(4-fluoro phenyl)-4-oxoazetidin-1-yl)benzoic acid 4f

5-chloro-2-(2,4-dichlorobenzylideneamino)benzoic acid (3a) (0.01M, 2.776g) was dissolved in dry 1,4 dioxan (30ml). To this, triethylamine (0.02M, 0.5g) was added with stirring at 0-5^{0}C. To the reaction mixture chloroacetyl chloride (0.01M,1.12g) was added dropwise and stirred for 3hrs at room

temperature. The reaction mixture was then poured into crushed ice. The solid separated was filtered, washed, dried and recrystallised from ethanol to get the azetidinone (4f).

7. 5-chloro-2-(3-chloro-2-(4-dimethylaminophenyl)-4-oxoazetidin-1-yl)benzoic acid 4g

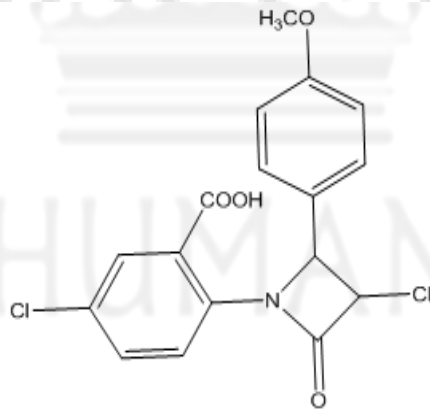
5-chloro-2-(2,4-dichlorobenzylideneamino)benzoic acid (3a) (0.01M, 3.026g) was dissolved in dry 1,4 dioxan (30ml). To this, triethylamine (0.02M, 0.5g) was added with stirring at 0-5^{0}C. To the reaction mixture chloroacetyl chloride (0.01M, 1.12g) was added dropwise and stirred for 3 hrs at room temperature. The reaction mixture was then poured into crushed ice. The solid separated was filtered, washed, dried and recrystallised from ethanol to get the azetidinone (4g).



5-chloro-2-(3-chloro-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-yl)benzoic acid

8. 5-chloro-2-(3-chloro-2-(4-methoxy phenyl)-4-oxoazetidin-1-yl)benzoic acid 4h

5-chloro-2-(2,4-dichlorobenzylideneamino)benzoic acid (3a) (0.01M, 2.896g) was dissolved in dry 1,4 dioxan (30ml). To this, triethylamine (0.02M, 0.5g) was added with stirring at 0-5^{0}C. To the reaction mixture chloroacetyl chloride (0.01M, 1.12g) was added dropwise and stirred for 3 hrs at room temperature. The reaction mixture was then poured into crushed ice. The solid separated was filtered, washed, dried and recrystallised from ethanol to get the azetidinone (4h).



5-chloro-2-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)benzoic acid

Antibacterial activity of Schiff's bases (Compounds 3a-3h):

Compound code	Zone of inhibition (in mm)							
	B. subtilis		*S. aureus*		*E. coli*		*P. Vulgaris*	
	0.1%	0.2 %	0.1%	0.2%	0.1%	0.2%	0.1%	0.2%
Standard	28	33	30	32	25	27	28	31
Control	-	-	-	-	-	-	-	-
3a	13	14	16	17	15	17	12	16
3b	11	12	10	14	15	16	12	15
3c	18	18	20	18	18	18	19	18
3d	11	12	15	16	16	15	17	15
3e	12	13	15	15	14	16	15	17
3f	11	12	15	17	13	15	12	16
3g	20	26	24	25	20	22	22	21
3h	17	18	19	18	18	18	19	19

Note: "– ''No zone of inhibition

Antifungal activity of Schiff's bases (compounds 3a -3h):

Compound code	Zone of inhibition (in mm)			
	A. niger		*P. chrysogenum*	
	0.1%	0.2%	0.1%	0.2%
Standard	25	23	22	25
Control	-	-	-	-
3a	11	12	13	15
3b	18	20	18	19
3c	11	11	12	14
3d	14	15	15	14
3e	17	18	17	17
3f	17	17	18	17
3g	12	14	10	15
3h	10	12	12	13

Note: "– " No zone of inhibition

Antibacterial activity of Azetidinones (Compounds 4a – 4h):

Compound code	Zone of inhibition (in mm)							
	B. subtilis		*S. aureus*		*E. coli*		*P. vulgaris*	
	0.1%	0.2%	0.1%	0.2%	0.1%	0.2%	0.1%	0.2%
Standard	28	33	31	32	25	27	28	31
Control	-	-	-	-	-	-	-	-
4a	16	18	13	13	14	16	13	17
4b	13	14	14	15	11	15	11	15
4c	22	25	25	24	20	22	21	25
4d	19	21	18	20	18	19	19	20
4e	10	17	12	14	11	16	12	18
4f	13	12	14	13	13	13	12	14
4g	19	18	18	19	18	20	18	17
4h	12	16	12	14	13	17	12	16

Note: "– " No zone of inhibition

Antifungal activity of Azetidinones (Compounds 4a-4h):

Compound code	Zone of inhibition (in mm)			
	A. niger		*P. chrysogenum*	
	0.1%	0.2%	0.1%	0.2%
Standard	24	28	22	27
Control	-	-	-	-
4a	11	13	14	17
4b	10	13	11	13
4c	13	14	13	14
4d	10	11	10	15
4e	11	13	12	14
4f	10	12	12	17
4g	10	11	11	12
4h	20	21	19	22

RESULTS AND DISCUSSION

Schiff's Bases:

Antibacterial activity:

From the above results, it is evident that compounds 3a to 3h showed significant antibacterial activity at both 100 µg/ml (0.1 ml dose level) and 200 µg/ml (0.2 ml dose level) concentration levels when compared with standard drug Benzyl Penicillin. In particular compounds, 3g showed maximum activity whereas compounds 3c & 3h showed moderate activity. It is interesting to note that the Schiff's bases 3g carrying 4-dimethyl amino showed maximum antibacterial activity, while the other Schiff's bases showed less activity.

Antifungal activity:

Compounds 3a to 3h showed moderate to significant antifungal activity at both 100 µg/ml (0.1 ml dose level) and 200 µg/ml (0.2 ml dose level) concentration levels when compared with standard drug Fluconazole. Compounds 3b, 3e & 3f carrying chlorine at 4-position (3b), methyl at 4-position (3e) & fluorine(3f) at 4-position on the aromatic ring B showed remarkable activity.

Azetidinone:

Antibacterial activity:

From the above results, it is evident that compounds 4a to 4h showed significant antibacterial activity at both 100 µg/ml (0.1 ml dose level) and 200 µg/ml (0.2 ml dose level) concentration levels when compared with standard drug Benzyl Penicillin. It was found that compound 4c showed maximum activity while moderate activity observed in case of compounds 4d & 4g. It is interesting to note that compound 4c is having p-nitro group, while compounds 4d & 4g carrying 3,4-dimethoxy,4-dimethyl amino as pharmacophores respectively.

Antifungal activity:

Compounds 4a to 4h showed significant antifungal activity at both 0.05 ml (50µg) and 0.1 ml (100 µg) concentration levels when compared with standard reference Fluconazole. It is interesting to note that compound 4h possessed maximum activity which may be due to the presence of 4-methoxy phenyl as pharmacophores respectively. The other compounds exhibited less antifungal activity.

Anti-Inflammatory Activity:

Anti–inflammatory activity of Schiff's bases (3a to 3h)

Compound code	% inhibition in paw thickness at various time intervals					
	0.5hr	1hr	2hr	3hr	4hr	6hr
Standard	20.26±0.55	23.95±0.66	58.08±1.75	67.93±1.65	97.09±1.95	98.98±1.92
3a	13.41±0.97	17.71±0.83	41.16±1.07	63.75±1.97	83.10±4.82***	84.64±1.73
3b	13.41±0.97	17.71±0.83	41.16±1.07	63.75±1.97	83.10±4.82***	84.64±1.73
3c	14.47±0.70	27.99±4.54***	36.67±1.26	64.11±1.84	78.33±1.54	86.24±4.14**
3d	23.59±1.34	22.69±1.71	56.46±1.28	72.02±1.86	86.43±4.03	87.66±1.55
3e	19.79±0.62	31.07±2.84*	51.30±3.52	74.05±2.77**	86.19±1.26	92.16±1.55
3f	13.33±0.55	21.34±2.80	53.28±2.41	65.49±2.05	80.66±3.20	86.71±1.27
3g	11.36±1.30	19.97±5.37***	53.62±2.16	77.32±4.27**	83.75±2.07*	88.01±1.47
3h	21.79±1.95	22.71±1.54	51.88±1.96	70.73±1.27	86.29±0.56	90.53±1.54

Values are expressed as mean ± SEM (n=5). *p<0.05; **p<0.01; ***p<0.001 compared to controls. Student's *t*-test

Anti–inflammatory activity of azetidinones (4a to 4h)

Compound code	% inhibition in paw thickness at various time interval					
	0.5hr	1hr	2hr	3hr	4hr	6hr
Standard	20.26±0.64	23.95±0.66	58.08±1.84	67.93±1.65	97.09±1.95	98.98±1.98
4a	20.06±1.01	25.95±1.21	42.33±1.56	62.67±1.82	82.27±2.20	85.54±1.90
4b	20.79±1.86	32.61±3.27*	61.34±3.96**	79.21±3.27	88.29±3.28**	95.53±1.54
4c	20.89±2.27	34.97±2.20	59.30±1.50	80.37±1.88	85.75±2.07	95.83±1.47
4d	26.23±1.41	25.34±2.27*	59.23±1.42	78.33±2.37	88.43±2.03*	88.72±1.02
4e	20.32±1.04	27.95±0.66	44.27±1.08	63.62±1.86	83.24 ±2.27*	86.27±2.18
4f	17.43±1.67	25.33±2.87*	56.23±2.51	68.72±2.04	86.32±2.14*	88.63±1.05
4g	20.25±0.63	25.71±2.30	56.66±1.66	66.01±1.65	85.76±1.88	86.22±1.05
4h	18.43±1.32	26.83±1.86	57.87±3.17*	78.15±3.89**	89.26±3.01	93.12±1.96

Schiff's Bases:

Anti-inflammatory activity:

The results of anti-inflammatory activity revealed that the compounds (3a-3h) exhibited moderate to considerable activity when compared with reference standard aceclofenac. It was found that compound 3c showed maximum activity and this may be due to the presence of nitro group at 4-position on aromatic ring. Moreover, it was observed that the compounds 3g possessed moderate activity which may be due to the presence of 4-dimethyl amino (3g) aromatic ring B of Schiff's base.

Azetidinones:

Anti-inflammatory activity:

The results of anti-inflammatory activity revealed that the compounds (4a-4h) exhibited moderate to considerable activity when compared with reference standard aceclofenac. Compounds 4b & 4h having 4-chloro and 4-methoxy substituents are found to exhibit good activity respectively whereas other azetidinones showed considerable activity.

Figures:

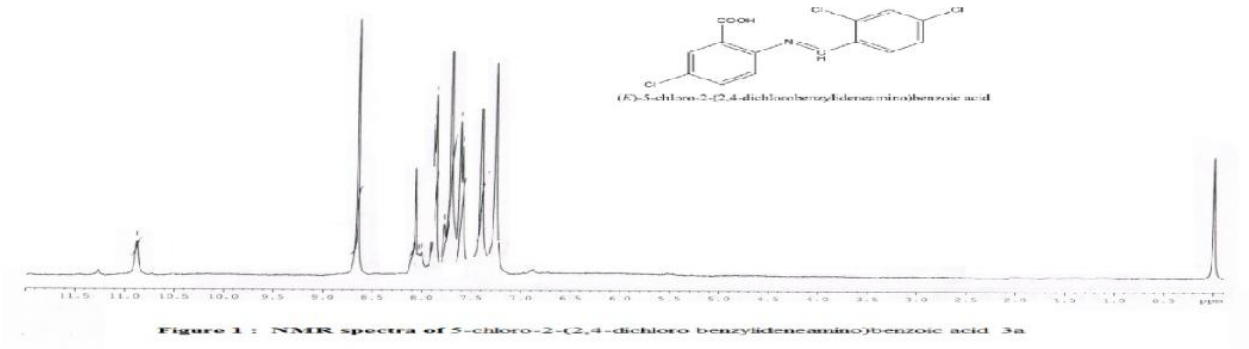


Figure 1 : NMR spectra of 5-chloro-2-(2,4-dichloro benzylideneamino)benzoic acid 3a

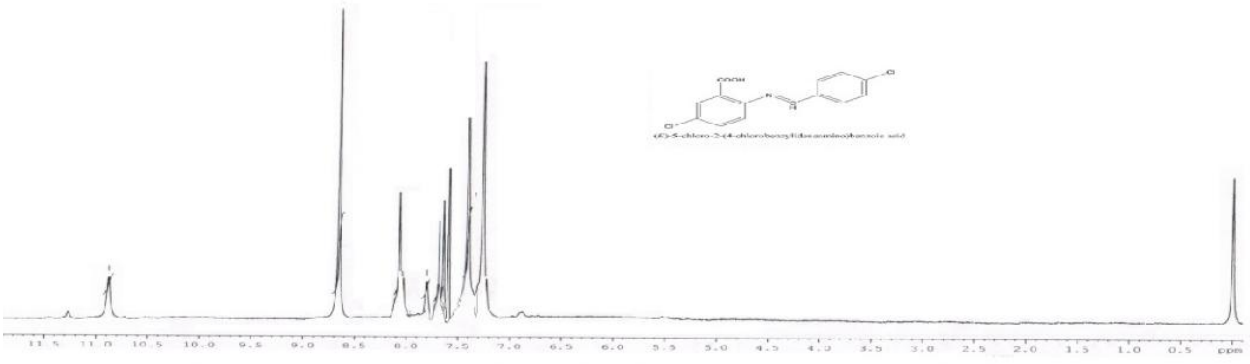


Figure 2 : NMR spectra of 5-chloro-2-(4-chloro benzylideneamino)benzoic acid 3b

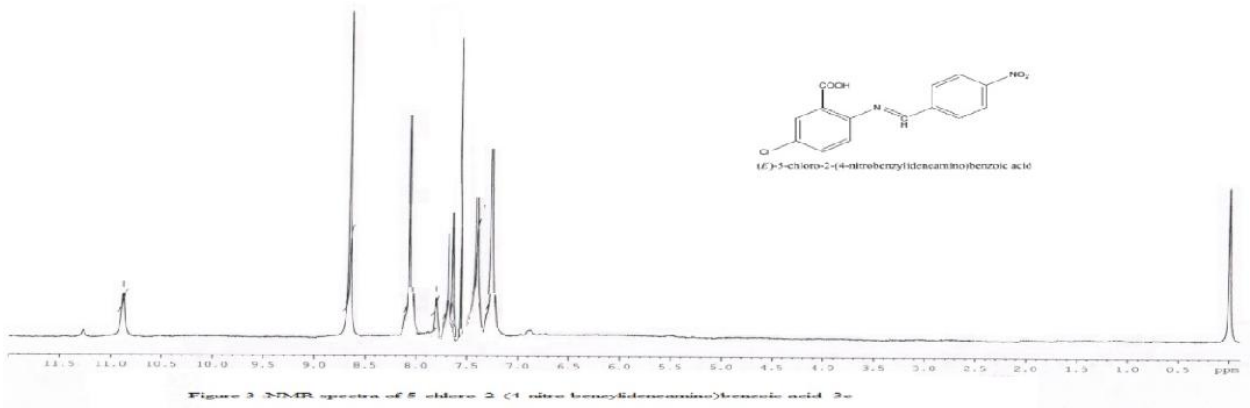


Figure 3 NMR spectra of 5-chloro-2-(4-nitro benzylideneamino)benzoic acid 3c

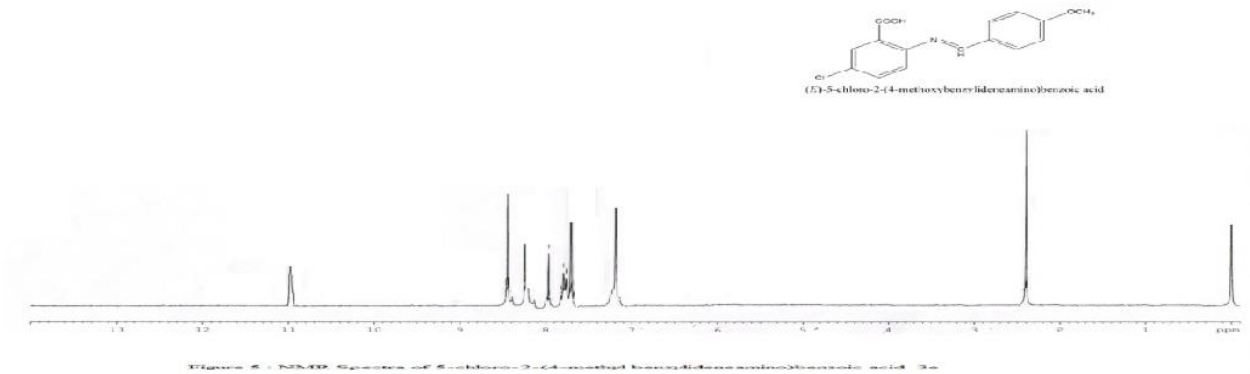


Figure 4 : NMR Spectra of 5-chloro-2-(4-methyl benzylideneamino)benzoic acid 3c

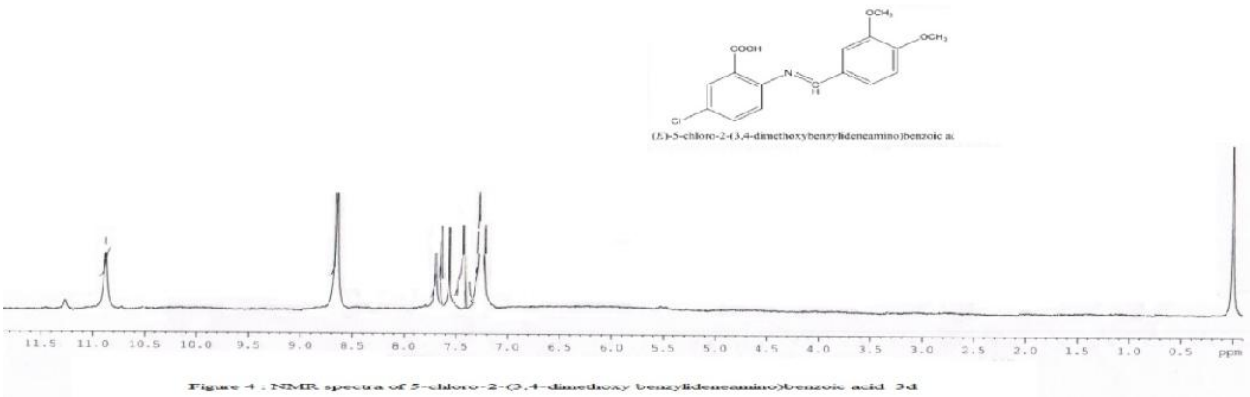


Figure 4 : NMR spectra of 5-chloro-2-(3,4-dimethoxy benzylideneamino)benzoic acid 3d

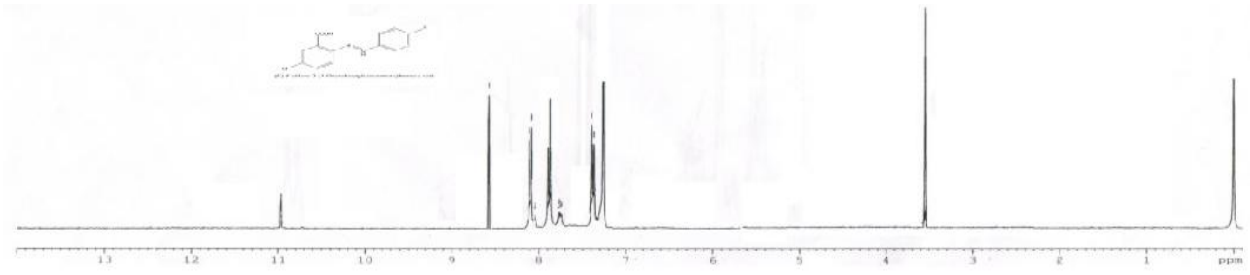


Figure 6 : NMR Spectra of 5-chloro-2-(4-fluoro benzylideneamino)benzoic acid 3f

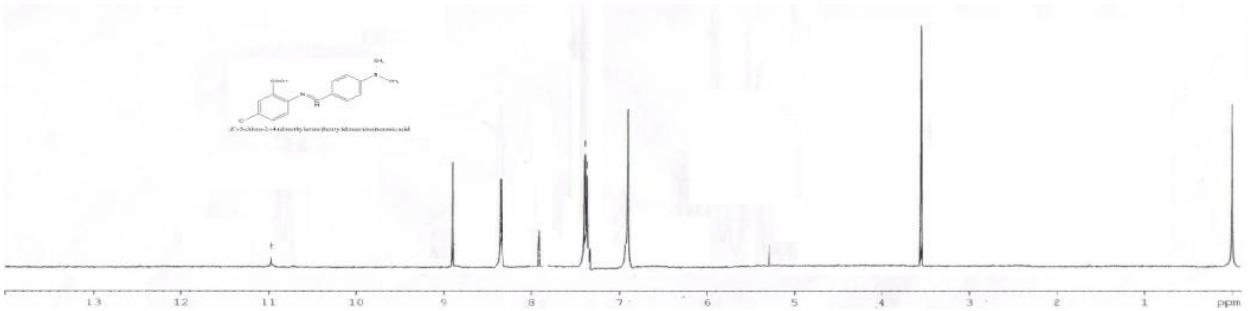


Figure 7 : NMR Spectra of 5-chloro-2(4-dimethylamino benzylideneamino)benzoicacid 3g

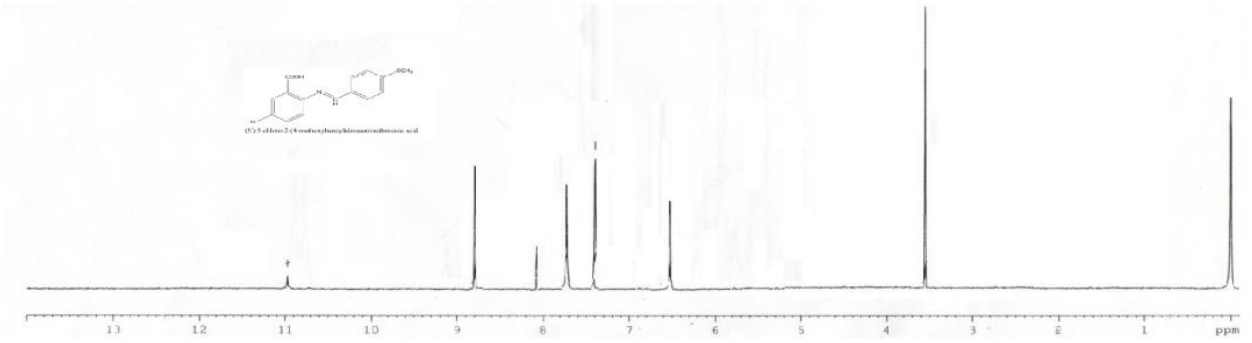


Figure 8 : NMR Spectra of 5-chloro-2-(4-methoxy benzylideneamino)benzoic acid 3h

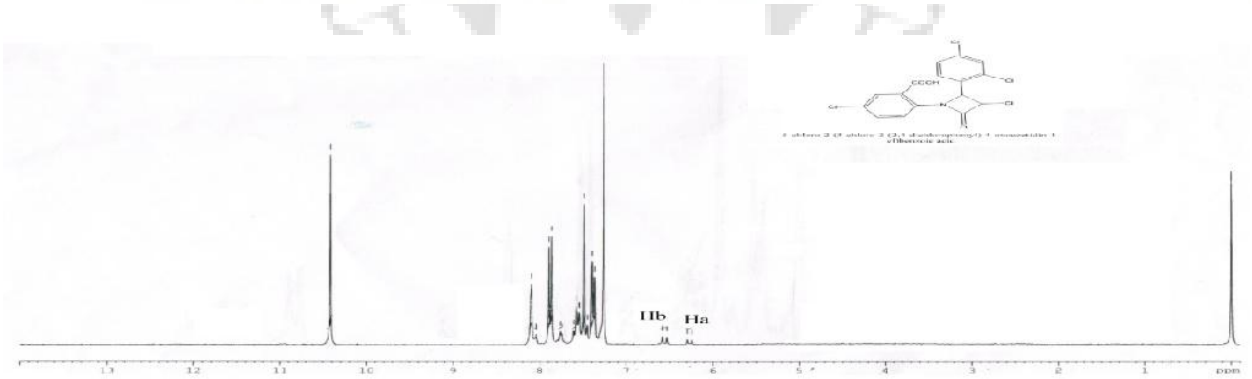


Figure 9 : NMR Spectra of 5-chloro-2-(3-chloro-2-(2,4 dichloro phenyl)-4-oxoazetidin-1-yl)benzoic acid 4a

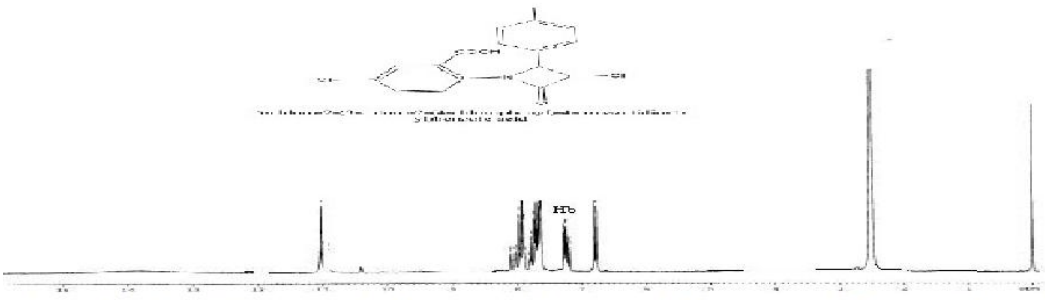
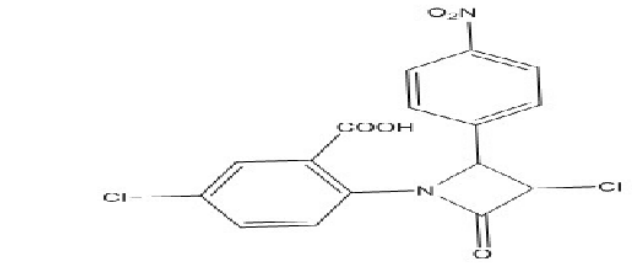


Figure 10 : NMR Spectra of 5-chloro-2-(3-chloro-2-(4-chloro phenyl)-4-oxoazetidin-1-yl)benzoic acid 4b



5-chloro-2-(3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)benzoic acid

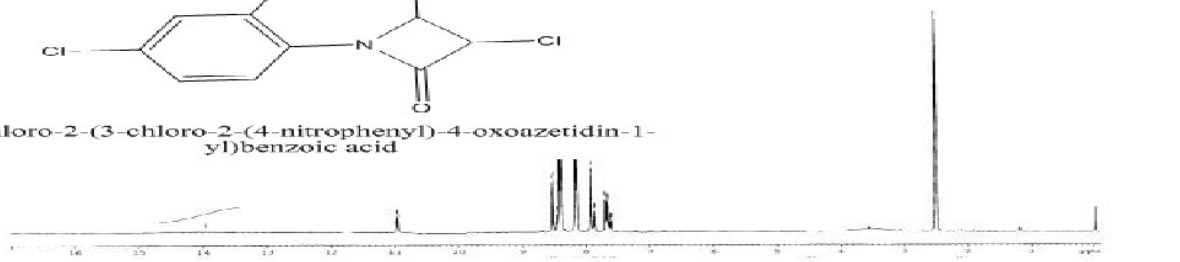


Figure 11:NMR spectra of 5-chloro-2-(3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)benzoic acid 4c

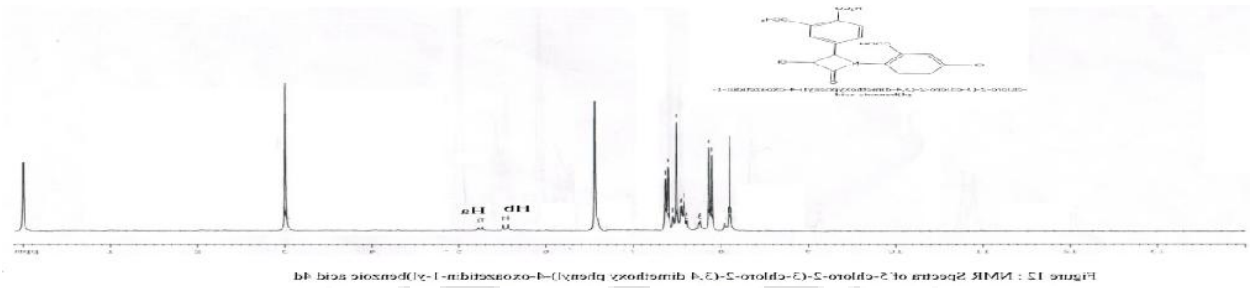


Figure 12 : NMR Spectra of 5-chloro-2-(3-chloro-2-(3,4 dimethoxy phenyl)-4-oxoazetidin-1-yl)benzoic acid 4d

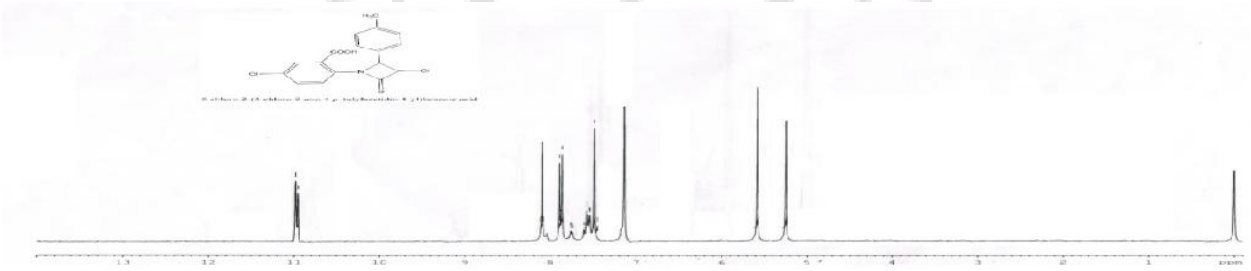


Figure 13 : NMR Spectra of 5-chloro-2-(3-chloro-2-(4-methyl)-4-oxoazetidin-1-yl)benzoic acid 4e

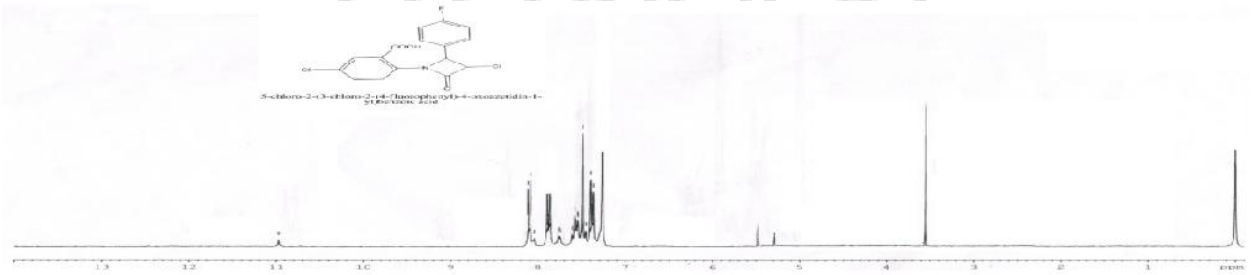


Figure 14 : NMR Spectra of 5-chloro-2-(3-chloro-2-(4-fluoro phenyl)-4-oxoazetidin-1-yl)benzoic acid 4f

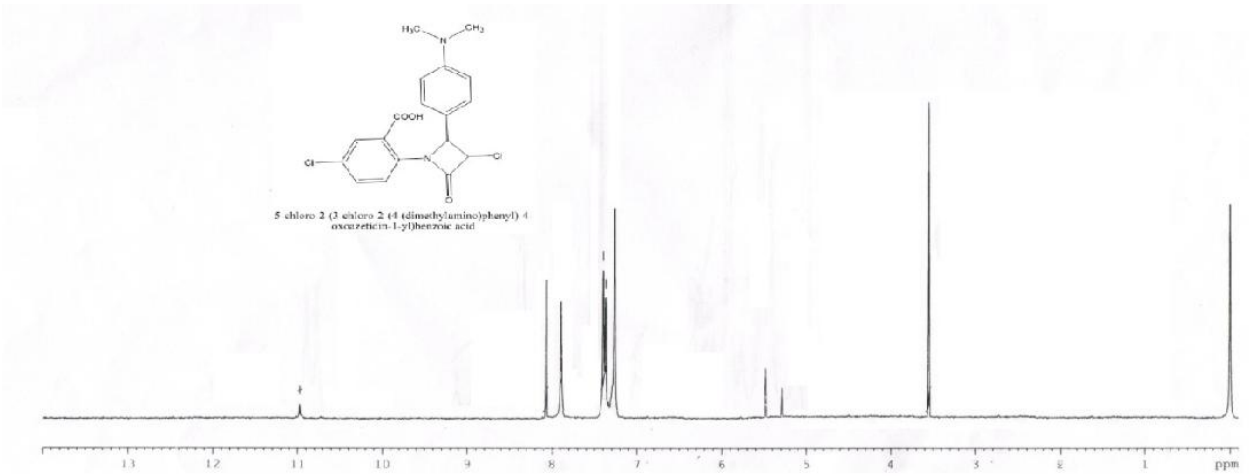


Figure 15 : NMR Spectra of 5-chloro-2-(3-chloro-2-(4-dimethylaminophenyl)-4-oxoazetidin-1-yl)benzoic acid 4g

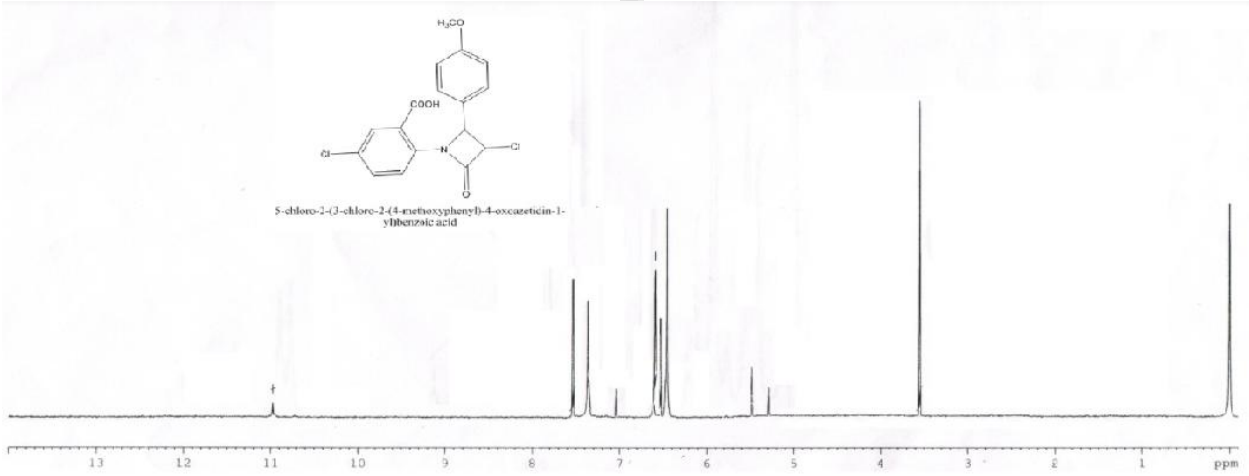


Figure 16 : NMR Spectra of 5-chloro-2-(3-chloro-2-(4-methoxy phenyl)-4-oxoazetidin-1-yl)benzoic acid 4h

CONCLUSION

The title demonstrates **"Synthesis and Anti-inflammatory Activity of Some New Schiff's bases and Azetidinones"** through the synthesis of Schiff's bases with 5-chloro anthranilic acid in glacial acetic acid and different aromatic aldehydes followed by the synthesis of Azetidinones by treating Schiff's bases with chloroacetyl chloride and triethylamine in presence of 1, 4 dioxan.

The proposed compounds were synthesized successfully and characterized by ^{1}H NMR, IR spectroscopy.

All the synthesized compounds were subjected to anti-inflammatory, antibacterial, antifungal activity.

Anti-inflammatory activity of Schiff's bases and Azetidinones has been evaluated by using carrageenan-induced rat paw edema method. The results of the evaluation have been viewed by taking aceclofenac as the standard drug. From the results, it is concluded that compounds with nitro, dimethylamino substitution on aromatic ring-B at 4-position of Schiff's base found to be moderate activity. Azetidinone compounds with chloro and methoxy substitutions at 4th position show good activity.

The Schiff's bases and Azetidinone derivatives evaluated for antibacterial activity were effective against *B. subtilis, S. aureus* (gram +ve) and *E. coli, P. vulgaris* (gram -ve) at both the concentration levels when compared with penicillin-G as a standard reference.

It is interesting to note from the result of antifungal evaluation of Schiff's bases and Azetidinone derivatives are effective against *A. niger* when compared with fluconazole as reference standard. From the above results, it is interesting to note that the Schiff's bases and Azetidinones, which are having electron-releasing substituents like dimethylamino, nitro, dimethoxy at the C-4 position of aromatic ring showed moderate to considerable antibacterial and antifungal activities when compared to that of standards.

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