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SYNTHESIS, CHARACTERIZATION AND ANALGESIC EVALUATION OF NOVEL SCHIFF BASES OF ARYL AMINES BASED 2-AZETIDINONES AND 4-THIAZOLIDINONES

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ABSTRACT
The present study deals with the synthesis of series of aryl amines based 4-thiazolidinone and 2-azetidinone derivatives from Schiff bases obtained from the condensation of 2-chloro-3-formylquinoline and 2-(4-aminophenyl) benzimidazole. The newly synthesized compounds are illustrated in scheme. Schiff bases of aryl amines based 4-thiazolidinone and 2-azetidinone derivatives have been prepared by the reaction of various substituted Schiff base with thioglycholic acid and chloroacetyl chloride respectively. The intermediate Schiff bases were synthesized by the condensation of different quinoline aldehydes with aminophenyl benzimidazole. The starting compound *i.e* aldehyde was synthesized through Vilsmeier reaction from respective acetanilides. The synthesized compounds were characterized by their physical and spectral data, and were screened for their analgesic activity by Tail flick method. Results obtained established compounds 14a, 14c, 15a and 15b to have highly significant analgesic activity with reference to the standard aspirin and consequently further exploration of these 2-Azetidinones and 4-Thiazolidinones derivatives should make these molecules accessible for widespread use as potent analgesic agents.

KEYWORDS: Schiff base, Azetidinone, Thiazolidinone, Analgesic activity, Tail flick method.

INTRODUCTION
The 2-azetidinone (□-lactam) ring system is the common structural feature of a number of broad spectrum □-lactam antibiotics, which have been widely used as chemotherapeutic agents to treat bacterial infections and microbial diseases.[1-2] The biological activity of the □-lactam skeleton is generally believed to be associated with the chemical reactivity of their □-lactam ring and on the substituent's especially at nitrogen of the 2-azetidinone ring. The wide range of pharmacological profile shown by 2-azetidinone includes antimicrobial, antifungal, antitubercular, cholesterol absorption inhibitor, tryptase and chymase inhibitor, thrombin inhibitor, human leukocyte elastase inhibitor, human cytomegalovirus inhibitor, cysteine protease cathepsin K inhibitor, antidiabetic, anti-inflammatory and analgesic activity, anticancer, and vasopressin VIa antagonist activities.[3-6]

Thiazolidinone is an important scaffold known to be associated with several biological activities, 1,3-Thiazolidin-4-ones are heterocycles that have an atom of sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 4. Substituents in the 2-3-, and 5-position may be varied, numerous methods for the synthesis of thiazolidinones and also their diverse reactions offer enormous scope in the field of medicinal chemistr.[7-9] The wide range of pharmacological profile shown by 4-Thiazolidinone includes antiretroviral, antimicrobial, antimalarial, antidiarrhoeal, anti-yellow fever virus, antiarrhythmic, anticonvulsant and anti-inflammatory activities.[10-13]

Schiff bases have also been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties. Imine or azomethine groups are present in various natural, natural-derived, and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities.[14-17]

MATERIALS AND METHODS
All the reagents used for synthesis were analytical grade commercial products and used without further purification. The melting points of the synthesized

compounds were determined using an electric melting point apparatus by open capillary method (expressed in degree Celsius) and are uncorrected. The progress of reactions and purity of synthesized compounds were checked on silica gel- G TLC plates using various solvent combinations of different polarity. The spots were detected with iodine vapors as visualizing agent. The FT-IR spectra of the synthesized compounds were recorded on a FT-IR perkin Elmer Spectrum RX-I spectrometer using KBr disc in the range of 4000-400 cm^{-1}. The proton NMR (^{1}H NMR) spectra were recorded in Bruker AC-F 400 FT-NMR spectrometer at a frequency of 400 MHz. Spectra were obtained in deuterated acetone (acetone-d6) using TMS (δ 0.00 ppm) as an internal standard at room temperature. Chemical shift (δ) values are expressed in ppm relative to internal standard.

Synthetic Scheme

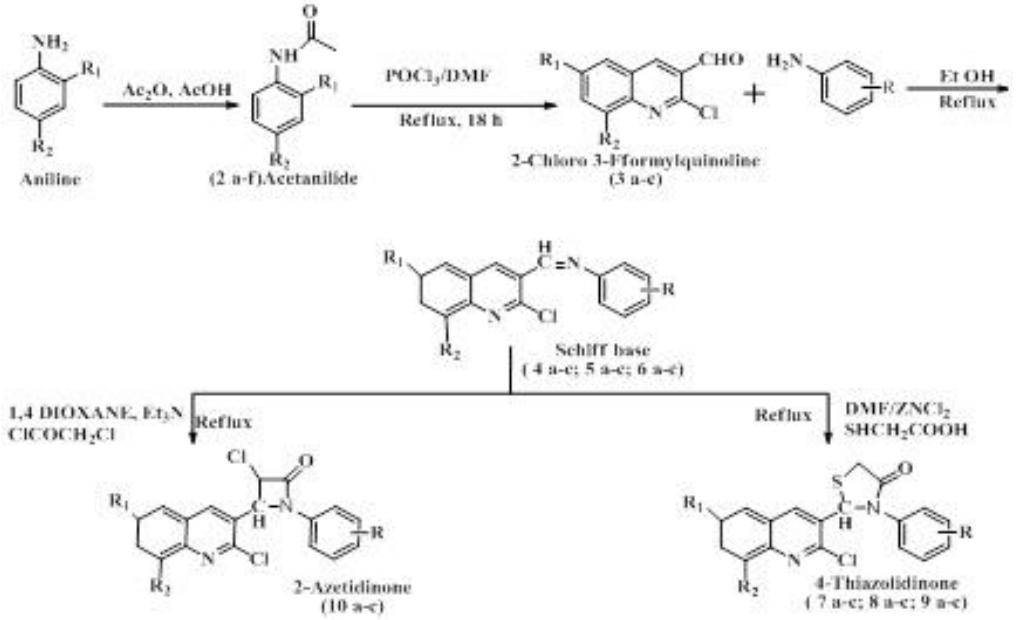

Figure No. 1: Synthetic Scheme for Schiff bases of aryl amines based 2-Azetidinones and 4-Thiazolidinones.

General method for Synthesis of novel aryl amines based 2-azetidinones and 4-thiazolidinones

Procedure for synthesis of Acetanilide (Step I): Anilines [0.01mol] were dissolved in 15 ml of glacial acetic acid and treated with 10 ml of acetic anhydride. This reaction mixture was poured into ice to obtain respective acetanilide as solid products (2a-f).

Procedure for synthesis of 2-Chloro-3-formylquinoline (Step II): Charged 500ml 3N RBF with 0.12mol of DMF at 0°C, 0.35 mol of $POCl_3$ for a period of an hour at 0°C. It was allowed to stir at 0°C for an hour. 0.05mol of acetanilides was added portion wise for a period of 30 min at 0°C; the reaction mixture refluxed at 85 °C for 16 hours and was monitored by TLC. After completion of reaction, the reaction mixture was quenched with 300 gm of ice and stirred at 0°C for 30 min. It was then extracted with ethyl acetate and this layer was evaporated to obtain solid substances. The compounds were obtained as solids (3a-c).

Procedure for synthesis of 4-(1H-benzoimidazol-2-yl) aniline (Step III): Phenylenediamine (0.01mol), and Para amino benzoic acid (0.01mol) were taken into 500ml RBF, to this 10ml of poly phosphoric acid was added and heated on sand bath at 200ºC for 2 h.

Procedure for synthesis of Schiff's base (Step IV): In a 100 ml 3N RBF, 0.01mol 2, 6-dichloro-3-formylquinoline derivatives and 0.01mol of 2-(4-aminophenyl) benzimidazole were dissolved in ethanol and catalytic amount of sulphuric acid was added into it. It was then allowed to reflux for 4 hours and was monitored by TLC. After completion of reaction the reaction mixture was poured into ice, solid mass separated out was filtered, washed several times with water, dried, and recrystallized with ethanol to obtain desired products. The compounds were obtained as solids (4a-c), (5a-c), (6a-c).

Procedure for synthesis of 2-Azetidinone derivatives (Step V): A mixture of Schiff's bases [0.001mol] and triethyl amine [0.002mol] was dissolved in 1-4-dioxane. To this well stirred mixture, a cooled solution of chloroacetyl chloride [0.002mol] was added. Then this reaction mixture was refluxed with stirring for about 12 hours and was monitored by TLC. After the completion of reaction the triethyl amine hydrochloride salt formed was filtered off and the reaction mixture was poured into crushed ice. The precipitate obtain was filtered washed several times with water, dried, and recrystallized from ethanol to get desired compound (10a-c)**.**

Procedure for synthesis of 4-Thiazolidinone derivatives (Step VI): A mixture of Schiff base [0.001mol] and catalytic amount of zinc chloride in DMF was taken in dean stark apparatus and to it. Thioglyclic acid [0.002mol] in DMF was added to this. Then this reaction mixture was refluxed with stirring for about 12 hours and was monitored by TLC. After the completion of reaction, the reaction mixture was poured into crushed ice and was extracted with ethyl acetate. This ethyl acetate layer was distilled off to obtain the desired products; the obtained compounds were dried, and recrystallized from ethanol to get desired compounds (7a-c), (8a-c), (9a-c)**.**

Analgesic Activity

Albino mice of either sex as experimental models were maintained at VJs College of Pharmacy, Rajahmundry. The animals were maintained in an animal house under standard environmental conditions. The acute oral toxicity of the synthesized compounds was performed as per OECD guidelines (OECD guideline 423). Animals were observed individually after dosing at least once during the first 30 min; periodically during the first 24 hr with special attention given during the first 4 hr and daily thereafter, for a total of 14 days. As no mortality was observed with the administered dose, a dose of 200 mg/Kg body weight was selected for the pharmacological screening. Aspirin at the dose of 10 mg/kg was administered as standard drug for comparison. The test compounds were administered by the oral routes using an animal feeding needle at the dose level of 100 mg/kg body weight. The control group received appropriate volume of vehicle (distilled water, oral). The analgesic activity was tested using analgesiometer.[18] The instrument is fitted with hot-plate maintained at constant temperature (adjustable with front panel controls both coarse and fine). The temperature to be maintained is 55° C and the acrylic box is fitted to place the mice on hot-plate. This box is fitted with hinge arrangement and consists of lid over it. Analgesiometer operates at 220-230 Volts, 50 Hz. The reaction time (in seconds) of animals to radiant heat was recorded by taking the tail flick from the radiant heat source as end point for every 0, 30, 60 and 90 min time intervals. A cut-off point of 15 sec was imposed to avoid the tail damage.

RESULTS AND DISCUSSON

The results revealed that novel aryl amines based 2-azetidinones and 4-thiazolidinones derivatives were synthesized in satisfactory yields and pharmacologically evaluated for their analgesic activity.

Table No. 1: Physical data of synthesized compounds of Acetanilides (2a-e).

Compound	R1	R2	R3	Yield (%)	Melting Point (^{0}C)	R
2a	H	H	Cl	90	180-182	0.90
2b	H	H	H	88	154-156	0.88
2c	H	CH_3	H	92	212-214	0.86
2d	H	H	CH_3	85	150-152	0.92
2e	H	H	OCH_3	86	157-159	0.87

Table No. 2: Physical data of synthesized compounds of 2-Chloro-3-formylquinoline (3a-e).

Compound	R1	R2	Yield (%)	Melting Point (^{0}C)	R
3a	Cl	H	65	162-164	0.92
3b	H	H	60	156-158	0.90
3c	H	CH_3	64	166-168	0.88
3d	CH_3	H	62	152-154	0.94
3e	OCH_3	H	58	160-162	0.86

Table No. 3: Physical data of synthesized compounds of 4-(1H-benzoimidazol-2-yl) aniline (4a-b).

Compound	R	Yield (%)	Melting Point (^{0}C)	R
4a	H	85	162-164	0.85
4b	Cl	88	165-167	0.88

Table No. 4: Physical and Spectral data of synthesized compounds of Schiff's base (13a-h).

Compound Code	R_1	R_2	R	Nature	Melting point (^{0}C)	% Yield	Rf values	$_1$H NMR (300 MHz, CDCl3)	FTIR (KBr) cm-1
13a	H	H	H	Brick red Solid	320	74	0.85	δ 9.20 (1H, s), 7.74-7.80 (2H, s), 7.53-8.05(4H, dd, *J* = 2.35, 9.2Hz), 8.05(1H, s), 2.80 (3H, s).	758 (C-Cl), 1680(C=O), 1658(C=N)
13b	OCH_3	H	H	Pink Solid	340	76	0.80	δ 9.24 (1H, s), 7.51-7.66(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.92(1H, s), 2.50 (3H, s).	755 (C-F), 1689(C=O), 1668(C=N)

13c	OCH_3	H	Cl	Brown Solid	375	75	0.83	δ 9.24 (1H, s), 7.51-7.66(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.92(1H, s), 2.50 (3H, s), 2.34 (3H, s).	752 (C-H), 1691(C=O), 1659(C=N)
13d	H	CH_3	H	Yellow Solid	355	81	0.85	δ 9.27 (1H, s), 7.78-8.06(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.60-7.98(2H, s), 7.92(1H, s), 2.50 (3H, s), 2.39 (3H, s).	768 (C-CH_3), 1651 (C=N), 1680(C=O)
13e	H	CH_3	Cl	Brick red Solid	380	70	0.82	δ 9.20 (1H, s), 7.17-7.31(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.79(1H, s), 2.50 (3H, s), 3.83 (3H, s).	750 (C-H), 1669 (C=N), 1670(C=O)
13f	H	H	Cl	Brown Solid	300	70	0.80	δ 9.26 (1H, s), 7.50-7.68(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.70(1H, s), 2.50 (3H, s), 3.83 (3H, s).	750 (C-OCH_3), 1695 (C=O), 1659(C=N)
13g	Cl	H	H	Violet Solid	290	72	0.86	δ 9.20 (1H, s), 7.55-7.68(2H, s), 7.53-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.80(1H, s), 2.60 (3H, s), 3.93 (3H, s).	750 (C-H), 1660 (C=N), 1680(C=O)
13h	Cl	H	Cl	Light Pink solid	310	74	0.84	δ 9.22 (1H, s), 7.60-7.88(2H, s), 7.53-8.00(4H, dd, *J* = 2.35, 9.2Hz), 7.90(1H, s), 2.70 (3H, s), 3.63 (3H, s).	750 (C-H), 1670 (C=N), 1690(C=O)

Physical and spectral data of synthesized compounds of 2-Azetidinones (14a-d)

Compound 14a: R_1=H, R_2=H, Red solid, MP: 352^{0}C, Yield: 74, Rf: 0.85.

$_1$H NMR (300 MHz, CDCl3): δ 9.27 (1H, s), 7.64-7.82(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 8.11(1H, s), 2.50 (3H, s).

FTIR (KBr) cm-1: 759 (C-Cl), 1680(C=O), 1658(C=N)

Compound 14b: R_1=OCH_3, R_2=H, Brown solid, MP: 380^{0}C, Yield: 76, Rf: 0.80.

$_1$H NMR (300 MHz, CDCl3): δ 9.24 (1H, s), 7.51-7.66(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.92(1H, s), 2.50 (3H, s).

FTIR (KBr) cm-1: 755 (C-F), 1689(C=O), 1668(C=N)

Compound 14c: R_1=CH_3, R_2=Cl, Brown solid, MP: 355^{0}C, Yield: 75, Rf: 0.83.

$_1$H NMR (300 MHz, CDCl3): δ 9.24 (1H, s), 7.51-7.66(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.92(1H, s), 2.50 (3H, s), 2.34 (3H, s).

FTIR (KBr) cm-1: 752 (C-H), 1691(C=O), 1659(C=N).

Compound 14d: R_1=CH_3, R_2=H, Yellow solid, MP: 325^{0}C, Yield: 81, Rf: 0.85.

$_1$H NMR (300 MHz, CDCl3): δ 9.27 (1H, s), 7.78-8.06(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.60-7.98(2H, s), 7.92(1H, s), 2.50 (3H, s), 2.39 (3H, s).

FTIR (KBr) cm-1: 768 (C-CH_3), 1651 (C=N), 1680(C=O).

Physical and spectral data of synthesized compounds of 4 –Thiazolidinone (15a-g)

Compound 15a: R_1=H, R_2=H, Red solid, MP: 350^{0}C, Yield: 76, Rf: 0.88.

$_1$H NMR (300 MHz, CDCl3): δ 9.27 (1H, s), 7.64-7.82(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 8.11(1H, s), 2.50 (3H, s).

FTIR (KBr) cm-1: 759 (C-Cl), 1680(C=O), 1658(C=N)

Compound 15b: R_1=OCH_3, R_2=H, Brown solid, MP: 380^{0}C, Yield: 76, Rf: 0.80.

$_1$H NMR (300 MHz, CDCl3): δ 9.24 (1H, s), 7.51-7.66(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.92(1H, s), 2.50 (3H, s).

FTIR (KBr) cm-1: 755 (C-H), 1689(C=O), 1668(C=N).

Compound 15c: R_1=CH_3, R_2=Cl, Brown solid, MP: 355^{0}C, Yield: 75, Rf: 0.83.

$_1$H NMR (300 MHz, CDCl3): δ 9.24 (1H, s), 7.51-7.66(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.92(1H, s), 2.50 (3H, s), 2.34 (3H, s).

FTIR (KBr) cm-1: 752 (C-CH_3), 1691(C=O), 1659(C=N).

Compound 15d: R_1=Cl, R_2=H, Yellow solid, MP: 325^{0}C, Yield: 81, Rf: 0.85.

$_1$H NMR (300 MHz, CDCl3): δ 9.27 (1H, s), 7.78-8.06(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.60-7.98(2H, s), 7.92(1H, s), 2.50 (3H, s), 2.39 (3H, s).

FTIR (KBr) cm-1: 768 (C-H), 1651 (C=N), 1680(C=O).

Compound 15e: R_1=H, R_2=Cl, Light Pink solid, MP: 332^{0}C, Yield: 84, Rf: 0.85.

$_1$H NMR (300 MHz, CDCl3): δ 9.29 (1H, s), 7.51-7.66(2H, s), 7.33-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.92(1H, s), 2.50 (3H, s), 2.34 (3H, s).

FTIR (KBr) cm-1: 752 (C-Cl), 1691(C=O), 1659(C=N).

Compound 15f: R_1=CH_3, R_2=H, Violet solid, MP: 360^{0}C, Yield: 78, Rf: 0.80.

$_1$H NMR (300 MHz, CDCl3): δ 9.34 (1H, s), 7.61-7.68(2H, s), 7.53-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.92(1H, s), 2.50 (3H, s).
FTIR (KBr) cm-1: 755 (C-F), 1689(C=O), 1668(C=N).
Compound 15g: R_1=Cl, R_2=Cl, Brown solid, MP: 342^{0}C, Yield: 80, Rf: 0.85.
$_1$H NMR (300 MHz, CDCl3): δ 9.30 (1H, s), 7.78-8.06(2H, s), 7.63-8.05(4H, dd, *J* = 2.35, 9.2Hz), 7.80-7.98(2H, s), 7.92(1H, s), 2.50 (3H, s), 2.40 (3H, s).
FTIR (KBr) cm-1: 768 (C-H), 1651 (C=N), 1680(C=O).

Analgesic activity data of the synthesized compounds

Analgesic screening of the synthesized compounds show 14a, 14c, 15a and 15b exhibiting marked analgesic activity in comparison to standard aspirin whereas compound 14b too showed good analgesic activity. Compound 15c showed the least activity amongst the series. The results are statistically expressed in terms of Mean ± SEM as depicted in Table.5. P < 0.05 was considered significant.

Table No. 5: Analgesic activity of synthesized compounds.

Compound	Dose (in mg/kg body weight)	Tail Flick Method Reaction time (in seconds)			
Control	1 ml	0 min	30 min	60 min	90 min
Standard (Aspirin)	10	3.52 ± 0.12	3.78 ± 0.10	3.64 ± 0.14	3.64 ± 0.14
14a	200	3.56 ± 0.17	6.38 ± 0.28	11.56 ± 0.17	10.20 ± 0.17
14b	200	3.53 ± 0.42	7.28 ± 0.20	3.53 ± 0.42	7.53 ± 0.42
14c	200	3.60 ± 0.15	6.29 ± 0.20	7.60 ± 0.15	4.60 ± 0.15
15a	200	3.65 ± 0.30	6.65 ± 0.30	10.65 ± 0.30	10.65 ± 0.30
15b	200	3.64 ± 0.08	6.98 ± 0.08	6.64 ± 0.08	6.64 ± 0.08
15c	200	3.30 ± 0.25	3.30 ± 0.25	4.40 ± 0.25	4.30 ± 0.25

Reaction time expressed statistically in terms of Mean ± SEM

CONCLUSION

The Schiff's bases of aryl amines based their azetidinone; thaizolidinone derivatives have been synthesized to screen the potential analgesic agent. The synthesis of various substituted Schiff's bases of aryl amines based their azetidinone, thaizolidinone derivatives have been prepared using reported synthetic procedures, and the melting point, ^{1}H-NMR, and IR spectrophotometric studies were used in characterized the compounds. The synthesized compounds were tested for their potential biological activity as analgesic agent. Results obtained established compounds 14a, 14c, 15a and 15b to have highly significant analgesic activity with reference to the standard aspirin and consequently further exploration of these 2-Azetidinones and 4-Thiazolidinones derivatives should make these molecules accessible for widespread use as potent analgesic agents.

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REFERENCES

1. Viswajanani J, Sattigeri A, Singhal S, Khan S, Pandya M, Bhateja P, Mathur T, Rattan A, Khanna J, Mehta A.: Synthesis and antimicrobial activity of novel thiazolidinones, Arkivoc, 2005; 2: 46-59.
2. Matiychuk VS, Lesyk RB, Obushak MD, Gzella A, Atamanyuk DV, Ostapiuk YV, Kryshchyshyn. AP.: A new domino-Knoevenagel–hetero-Diels–Alder reaction, Tetrahedron Lett., 2008; 49: 4648-4651.
3. Vicini P, Geronikaki A, Anastasia K, Incerti M, Zani F.: Synthesis and antimicrobial activity of novel 2-thiazolylimino-5-arylidene-4-thiazolidinones, Arkivoc, 2005; 19: 46-49.
4. Gouveia FL, Oliveira RMB, Oliveira TB, Silva IM, Nascimento SC, Sena K, Albuquerque.: Synthesis, antimicrobial and cytotoxic activities of some 5-arylidene-4-thioxo-thiazolidine-2-ones., Eur. J. Med. Chem., 2009; 44: 2038-2043.
5. Pandeya D, Nair KB.: Bridged bis(4-thiazolidinones) and related compounds with antibacterial activity, Die Pharmazie, 1993; 48(6): 414-417.
6. Puspak M, Shah M, Patel P.: Zinc (II) chloride catalysed one pot synthesis of some new 4-thiazolidinone derivatives as biologically potent agents, Indian. J. Chem., 2011; 50B: 310-314.
7. Goto J, Sakane K, Nakai Y, Teraji T, Kamiya T.: Studies of 7 beta-[2-(aminoaryl)acetamido]-cephalosporin derivatives. Synthesis and structure-activity relationships in the aminopyridine series, J. Antibiot., 1984; 37(5): 546-56.
8. Pandey Y, Singh A, Sharma P, Kumar N.: Biological Activities of Thiazolidine – A Review, J. Current. Pharm. Res., 2011; 1(2): 192-196.
9. Bhat A, Singh D.: Synthesis of Novel 2-(2-chloro-(substituted) quinolin-3-yl)-3- ((substituted) phenyl) thiazolidin-4-one analogues with antimicrobial activity, Indian J. Pharm. Sci., 1988; 50: 169-171.
10. Sendai M, Hashiguchi S, Tomimoto M, Kishimoto S, Matsuo T, Kondo M, Ochiai M.: Chemical modification of sulfazecin. Synthesis of 4-(substituted methyl)-2-azetidinone-1-sulfonic acid derivatives, Chem. Pharm. Bull., 1985; 38(3): 346-71.
11. Vasoya S L, Patel M R, Dobaria SR, Joshi HS.: Facial Synthesis of some new azetidinone and acetyl oxadiazoles bearing benzo thiaphene nucleus as

potent biological active agent, Indian J. Chem., 2005; 44B: 405-409.
12. Plantan I, Stephan M, Urleb U, Mohar B.: Stereoselective synthesis of (1′*S*, 3*R*, 4*R*)-4-acetoxy-3-(2′-fluoro-1′-trimethylsilyloxyethyl)-2-azetidinone, Tetrahedron Lett., 2009; 50: 2676- 2677.
13. Dua R, Somwane S, Srivastava S.: A Brief Review on Recent Synthesis of 2-Azetidinone Derivatives, World J. Chem., 2010; 5: 52-56.
14. Alhamadsheh M, Waters N, Huddlers D, Deitric M, Florova G, Reynolds K.: Antibacterial Targets in Fatty Acid Biosynthesis, Bioorg. Med. Chem. Lett., 2007; 17: 879–883.
15. Kavita R, Annamalai P, Namrata S, Amit K.: A Systemic Review Of Schiff Bases As An Analgesic, Anti-Inflammatory, Int. J. of Current Pharm. Res., 2012; 4(2): 5-11.
16. Rajasekaran M, Periasamy, Venkatesan S.: Synthesis, characterization and biological activity of some novel azetidinones, J. Dev. Bio. Tissue. Eng., 2010; 2: 5-13.
17. Halve A, Bhadauria D, Dubey R.: N/C-4 substituted azetidin-2-ones: synthesis and preliminary evaluation as new class of antimicrobial agents, Bioorg. Med. Chem. Lett., 2006; 17(2): 341-345.
18. Kulakarni SK, Hand Book of Experimental Pharmacology. 3rd edition. New Delhi:Vallabh Prakashan, 1997; 49.