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Synthesis, Characterization and Antimicrobial evaluation of some Thiazolyl Azetidinones

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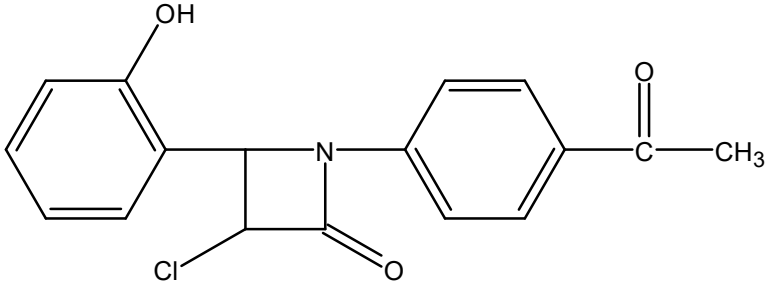
Abstract:
The four membered β-lactum (2-Azetidinone) ring possesses very good biological activities, like antibacterial, antifungal, anticancer, anti- HIV and antimalarial etc. Thiazole nucleous is prone for their multiple biological activities. Based on these observations 2- amino -4- phenyl thiazole was thought to derivaties its β-lactum ring via sequential steps of chemical reactions. The targeted molecule that is 2-Azetidinone was subjected to its characterization and biological activities against various panels of bacterial and fungal strains. The characterization was carried out through IR and NMR spectral studies and elemental analysis. The dyeing properties of the final compounds were also carried out on polyester fibre. Their exhaustion, fixation and various fastness studies have been carried out through various parameters.

Keywords: *Thiazolyl azetidinones, synthesis, characterization, antimicrobial activity, heterocyclic compounds, β-lactam derivatives*

1. Introduction

Thiazole derivatives are known to exhibit biological activities such as anaesthetic, antinflammatory[1,] antithrombotic, antihypertensive, sedative[2] , bacteriostatic, fungistic and antitubercular[3]. Compounds belonging to the thiazole ring system have shown considerable activity in the various fields of medicinal chemistry. Synthetic research among the derivatives of thiazole ring system gave rise to the discovery of many important drugs. Important developments are Thiabendazole, Tetramizole, Niridazole Aminitrazole (antiparasitic agent), Fenclosic acid (anti-inflammatory agent), Penicillin (antibiotic), sluphathiazole (antibacterial agent) which all contain thiazole ring in some form. 2-Amino thiazole derivative acquires a special place in the heterocyclic field because of their diversified activities such as antimicrobial[4,5], antitubercular[6,] antiinflammatory[7]. The four membered β-lactum (2-azetidinone) ring possesses very good pharmacological and biological activity. A large number of antibiotics contain β-lactum heterocyclic moiety[8,9]. β-lactum drugs are still the most widely prescribed antibiotics used in medicine [10].

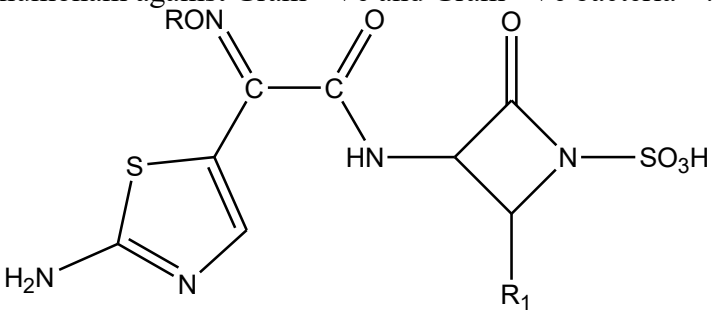
A series of substituted B-lactum (I) were derived from N- arylidene-4-amino acetophenone. These compounds were found to possess antibacterial as well as antifungal activity[11].



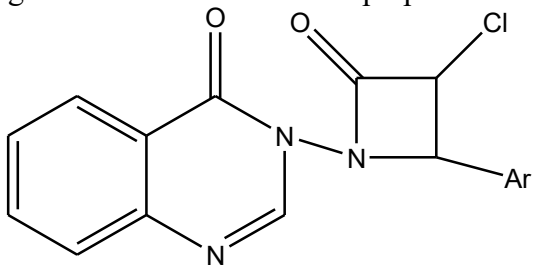
1-(4-Acetyl-phenyl)-3-chloro-4-(2-hydroxy-phenyl)-azetidin-2-one

A large number of 3-Chloro monocyclic β-lactums have been prepared by cycloaddition of β, β-disubstituted enamines with aryl isocynate which possess [owerful antibacterial activity [12].

2- Azetidinones of type (II) were prepared to improve the antibacterial activity of sulphazecines, out of which derivatives in which R = C $(CH_3)_2$ COOH and R= $CONH_2$ showed potent antibacterial activity comparable to that of canumonam against Gram +Ve and Gram –Ve bacteria [13].

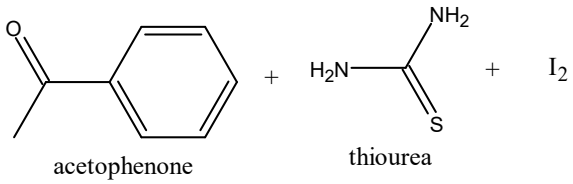


The four membered β-lactum (2- azetidinone) ring possess very good pharmacologicl and biological activity. Azetidinone (III) [14] was synthesized and tested for their antiparkinsonian activity against tremor, rigidity, ptosis, hypokinesia and catatonia. It was also studied further for their mode of action on dopamine receptor binding using rat brain strait membrane preparation.



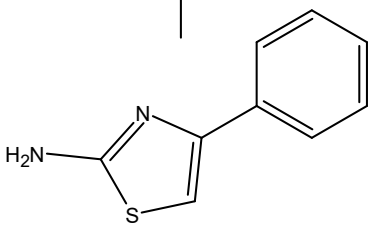
2. Methodology: Series -1

Step-I



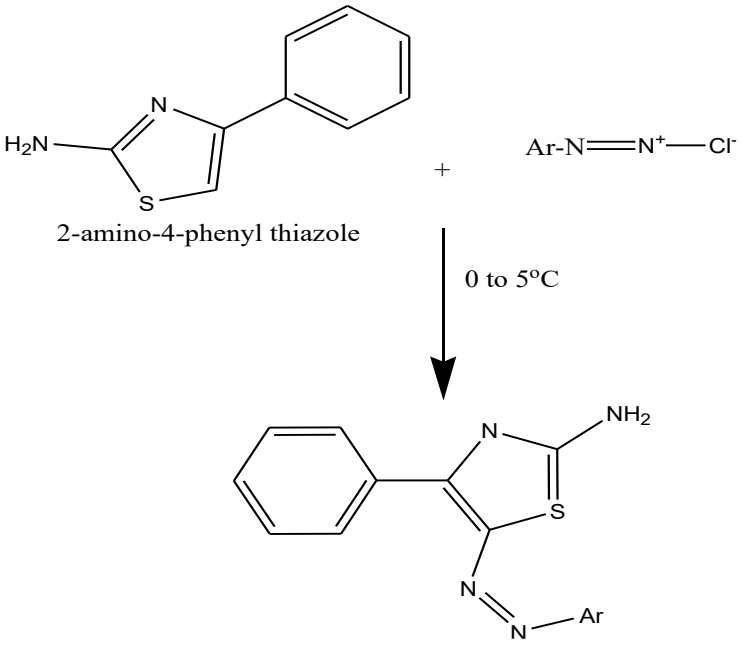
acetophenone thiourea

Reflux

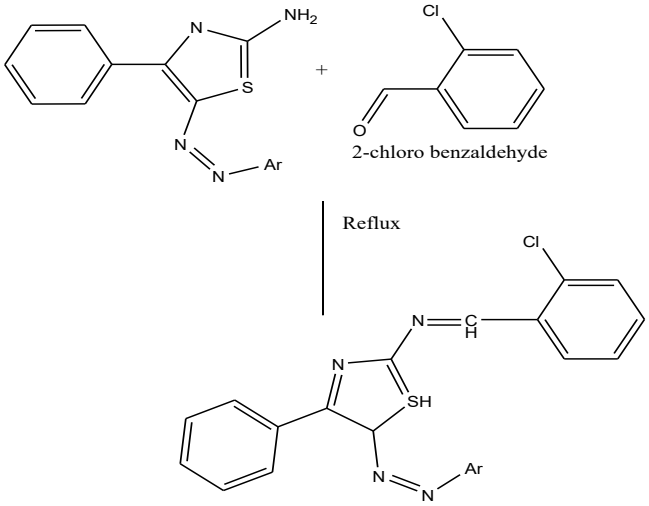


2-amino-4-phenyl thiazole

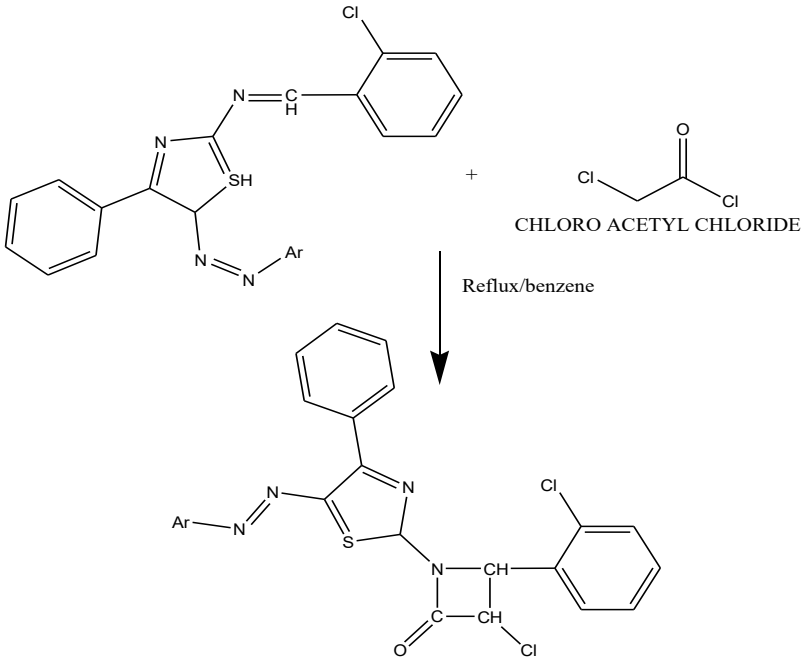
Step-II



STEP-III



Step-IV



3. Experimental

Step –I

Preparation of 2-Amino- 4- phenyl thiazole [A]

Iodine (5.18g, 0.02 mole) was added to a slurry consisting of acetophenone (4.8g, 0.02 mole) and thiourea (3.04g, 0.02mole). The mixture was heated for 15 hours. It was cooled and the contents were washed with water. The residue left was dissolved in boiling water and filtered. The filtrate was made alkaline by adding liq. NH_3. The solid thus obtained was filtered, dried and crystallised from absolute alcohol. M. P.: 152^{0}C Yield: 70 %

Step: II

Preparation of 2-Amino-4- phenyl -5- phenyl azo thiazole [B]:

Aniline (0.93g, 0.01 mole) was dissolved in Con. HCl (0.03g, 0.03 mole) and cooled to 0^{0}c. A Previously cooled solution of $NaNO_2$ (0.8G 0.012 mole) in water was added to it with stirring. It was further stirred until the positive test of nitrous acid on starch iodide paper was obtained. The excess of nitrous acid was neutralized with sulphamic acid. The resultant diazonium salt solution was poured with stirring into a previously cooled solution of (A) (1.76g, 0.01 mole) and sodium acetate in ethanol. It was further stirred for 4 hours and filtered. The solid thus obtained was dried and crystallised from absolute alcohol to give the title compound. M. P.: 194 ^{0}C. Yield: 94 % Similarly intermediates B1 to B16 were prepared from intermediate (A) and corresponding aryl diazonium chlorides.

Step-II

Preparation of 2- (2- Chlorobenzylideneamino)- 4- phenyl-5- phenyl azo thiazole

A mixture of B1 (2.8g, 0.01 mole) and 2-chlorobenzaldehyde (1.4g, 0.01mole) in methanol with 1-2 drops of piperidine was refluxed for 3 hours. The refluxed content was treated with crushed ice to give the solid product. It was filtered, dried and crystallised from absolute alcohol to give the compound. M. P.: 156 Yield: 72 % Similarly compounds were prepared from corresponding intremediates (B) and 2-chlorobenzaldehyde. They were purified by crystallization from absolute alcohol.

Step – IV

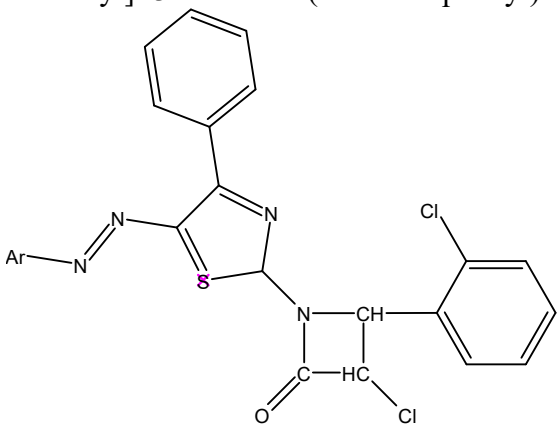
Preparation of 1- [5- Aryl azo)-4- phenyl thiazol -2- yl] -3- chloro-4-(2- chloro phenyl)-2-azetidinone

To a solution of C1 (0.874g, 0.002 mole) in dioxane (10 ml), chloro acetyl chloride (0. 27g, 0.0024 mole) was added dropwise at room temperature with constant stirring. Then triethyl amine (o.0396g, 0.004 mole) was added and reaction mixture was refluxed for 12 hours. After the completion of reaction it was filtered, dried and crystallised from absolute alcohol. M. P.: 120^{0}C Yield: 65 %

4. Characterisation

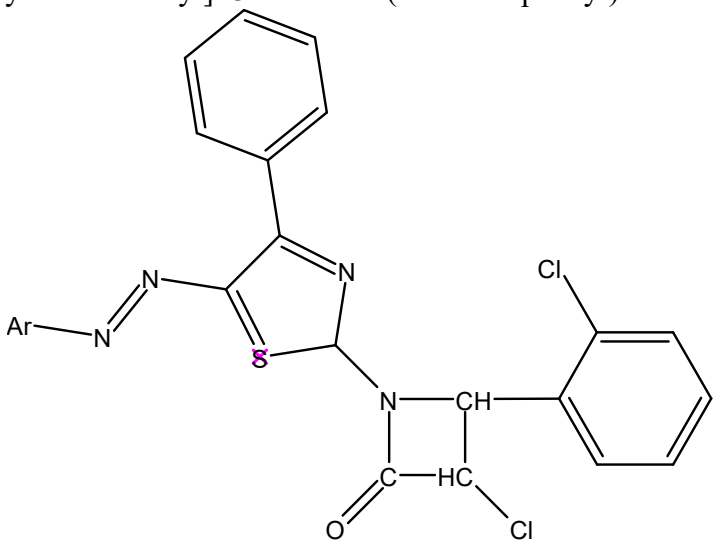
LP-7 (Ar = 4-Cl C_6H_4)

1- [5- Aryl azo)-4- phenyl thiazol -2- yl] -3- chloro-4-(2- chloro phenyl)-2-azetidinone



IR (KBr):
1086 cm^{-1} (=C-S- stretching in thiazole)
1478 cm^{-1} (=C=N- ring stretching in thiazole
1533 cm^{-1} (-N=N-- stretching in diazo comp.)
1690 cm^{-1} (=C=O stretching in β-lactum)
831 cm^{-1} (=C-Cl stretching in aryl chloride)
780 cm^{-1} (o- disubstituted benzene)
693 cm^{-1} (mono substitution benzene)
1385 cm^{-1} (-N- stretching in 3^{0} amine β-lactum I)

NMR (Acetone- D6):
LP-9 (2- CH_3)
1- [5- Aryl azo)-4- phenyl thiazol -2- yl] -3- chloro-4-(2- chloro phenyl)-2-azetidinone



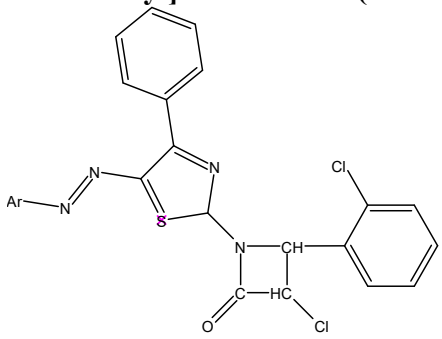
2.4 (s, 3H, Ar-CH_3)
3.9 (S, 2H, -(-CH_2 -)
4.3 (S, 1H, -CH-)
7.2 – 7.7 (m, 13 H, Ar-H)

5. Biological Activity

5.1 Antibacterial Activity

The results of antibacterial screenin g are mentioned in Table-1, These results revealed that against different organisms. Azetidinone exhibiting maximum activity in terms of zone of inhibition are (E. Coli, LP-16, 12 mm), (S. Aureus, LP—16, 14 mm), (S. Paratyphi B, LP-3, 12 mm), (P, Vulgaris, LP-9, 6 mm) and (Enterobactor, LP-5, LP-11, 12 mm)

Table: 1 [5- Aryl azo)-4- phenyl thiazol -2- yl] -3- chloro-4-(2- chloro phenyl)-2-azetidinone

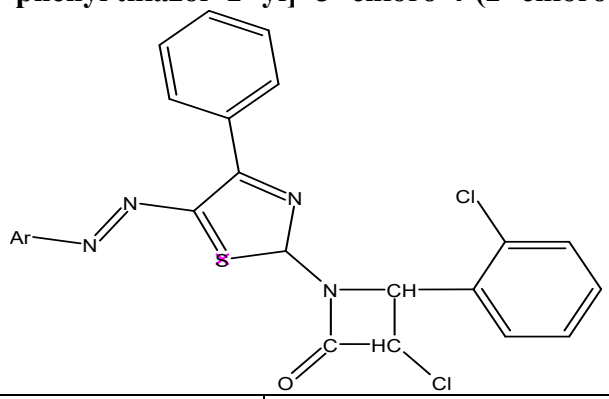


Sr. No.	Ar	Antibacteria Activity (Zone of inhibition) in mm at 50 µg/ml concentration				
		E. Coli	S. Aureus	S. Paratyphi	P. Vulgaris	Enterobactor
LP-1	C_6H_5	10	-	-	-	8
LP-2	2- $O_2NC_6H_4$	-	-	-	4	10
LP-3	3- $O_2NC_6H_4$	11	12	12	-	-
LP-4	4- $O_2NC_6H_4$	-	-	-	-	-
LP-5	2-ClC_6H_4	-	12	-	-	12
LP-6	3-ClC_6H_4	-	-	8	-	-
LP-7	4-ClC_6H_4	-	-	10	-	8
LP-8	2- $H_3CC_6H_4$	11	10	10	-	-
LP-9	3- $H_3CC_6H_4$	-	-	-	6	-
LP-10	4- $H_3CC_6H_4$	10	8	8	-	-
LP-11	2- $H_3COC_6H_4$	8	8	-	4	12
LP-12	4- $H_3COC_6H_4$	-	10	8	-	10
LP-13	4- Br C_6H_4	10	-	--	-	-
LP-14	1-$C_{10}H_7$	10	-	-	-	10
LP-15	2-$C_{10}H_7$	-	12	10	-	-
LP-16	3- Cl-4-F- C_6H_3	12	14	-	-	8

6. Antitubercular Activity

The results of antitubercular screening of some of azetidinones are mentioned in Table – II. These results revealed that against H_{37} Rv strain of M. Tuberculosis, azetidinones (LP-7) was found active at 50 µg/ml concentration (MIC)

Table: 2 1- [5- Aryl azo)-4- phenyl thiazol -2- yl] -3- chloro-4-(2- chloro phenyl)-2-azetidinone

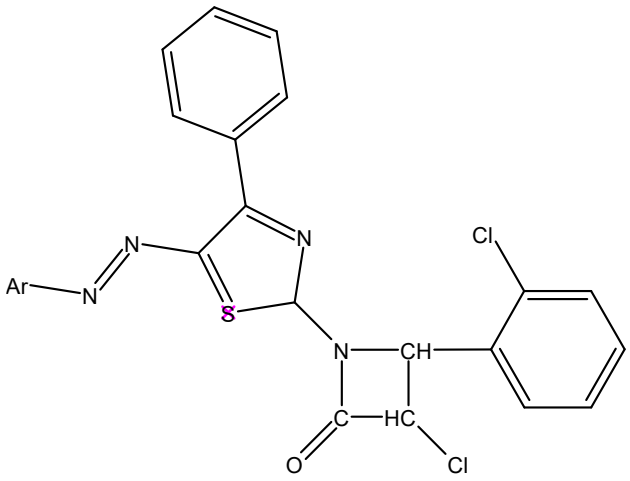


Sr. No.	Ar	Antitubercular Activity $H_{37}R_V$ stain of M. Tuberculosis (µg/ml)
LP-2	2- $O_2NC_6H_4$	-
LP-4	4- $O_2NC_6H_4$	200
LP-5	2-ClC_6H_4	100
LP-6	3-ClC_6H_4	-
LP-7	4-ClC_6H_4	50
LP-10	4- $H_3CC_6H_4$	
LP-12	4- $H_3COC_6H_4$	100
LP-13	4- Br C_6H_4	200
LP-14	1-$C_{10}H_7$	200
LP-16	3- Cl-4-F- C_6H_3	100

7. Antifungal Activity

The results of antifungal screening of some of azetidinones are mentioned in Table – III. These results revealed that against fungus C. Albicans. Azetidinones (LP-6, LP-7 and LP-16) were found active at 50 µg/ml concentration (MIC)

Table: 31- [5- Aryl azo)-4- phenyl thiazol -2- yl] -3- chloro-4-(2- chloro phenyl)-2-azetidinone

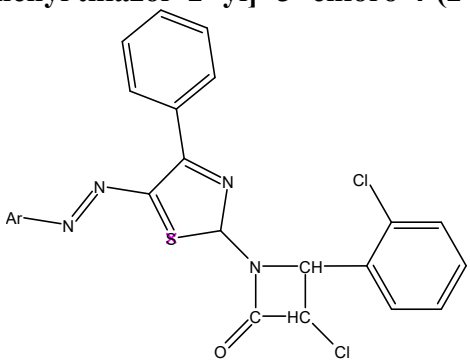


Sr. No.	Ar	Antifungal Activity C. Albicans (µg/ml)
LP-2	2- $O_2NC_6H_4$	100
LP-4	4- $H_3COC_6H_4$	-
LP-5	2-ClC_6H_4	100
LP-6	3-ClC_6H_4	50
LP-7	4-ClC_6H_4	50
LP-10	4- $H_3CC_6H_4$	-
LP-12	4- $H_3COC_6H_4$	200
LP-13	4- Br C_6H_4	100
LP-14	1-$C_{10}H_7$	-
LP-16	3- Cl-4-F- C_6H_3	50

8. Dyeing Properties

The results of exhaustion- fixation and fastness properties of some of the dyes applied on nylon are shown in Table – IV.

Table: 4 1- [5- Aryl azo)-4- phenyl thiazol -2- yl] -3- chloro-4-(2- chloro phenyl)-2-azetidinone



Sr. No.	Ar	λ max	% Exhaution	% Fixation
LP-1	C_6H_5	440	46	58
LP-2	2- $O_2NC_6H_4$	430	48	59
LP-3	3- $O_2NC_6H_4$	430	44	51
LP-4	4- $O_2NC_6H_4$	440	56	49
LP-5	2-ClC_6H_4	430	51	52
LP-6	3-ClC_6H_4	440	48	52
LP-7	4-ClC_6H_4	460	39	67
LP-8	2- $H_3CC_6H_4$	450	48	60
LP-9	3- $H_3CC_6H_4$	440	48	58
LP-10	4- $H_3CC_6H_4$	440	47	68
LP-11	2- $H_3COC_6H_4$	440	45	65
LP-12	4- $H_3COC_6H_4$	450	47	67
LP-13	4- Br C_6H_4	440	52	59
LP-14	1-$C_{10}H_7$	450	44	61
LP-15	2-$C_{10}H_7$	440	56	62
LP-16	3- Cl-4-F- C_6H_3	450	48	65

9. Conclusion

In the derivatives of Scheme-1 the presence of nitro group at position-3 and methoxy group at position-2 to the azo linkage showed good activity while other did not show any significant activity, whereas chloro group at position 4 to azo linkage proved beneficial for anti -mycobacterium and antifungal activity.

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