Synthesis and Evaluation of Novel Thiazole Derivatives

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Abstract

A vast array of thiazole derivatives having excellent broad spectrum activity forms an invaluable part of the present armory of the clinicians. The synthesis and antibacterial activity of several new ethyl 2-amino-4-methylthiazole-5-carboxylate(1)[5]derivatives substituted at 2nd position by aryl aldehydes of the thiazole moiety have shown some to increase the antibacterial activity of thiazole. In this study we thought to synthesize thiazole system incorporating substituted aryl aldehydes. The most active compound was 4-methyl-5-hydrazine hydrate-2-(4-methoxy-3-hydroxy benzene) methyleneamino thiazole-5-carboxylate (3c) equipotent to Ciprofloxacin.C_2 position of thiazole ring requires large hydrophilic, electronegative functional moieties like substituted phenyl ring etc for enhanced antibacterial activity of thiazole. In our compounds alkyl (methyl) group is present, still most of the compounds show good antibacterial activity.C_5 position of thiazole ring requires small hydrophobic, electronegative functional moieties like amino, hydrazine hydrate attach with ester for antibacterial activity of thiazole in general.

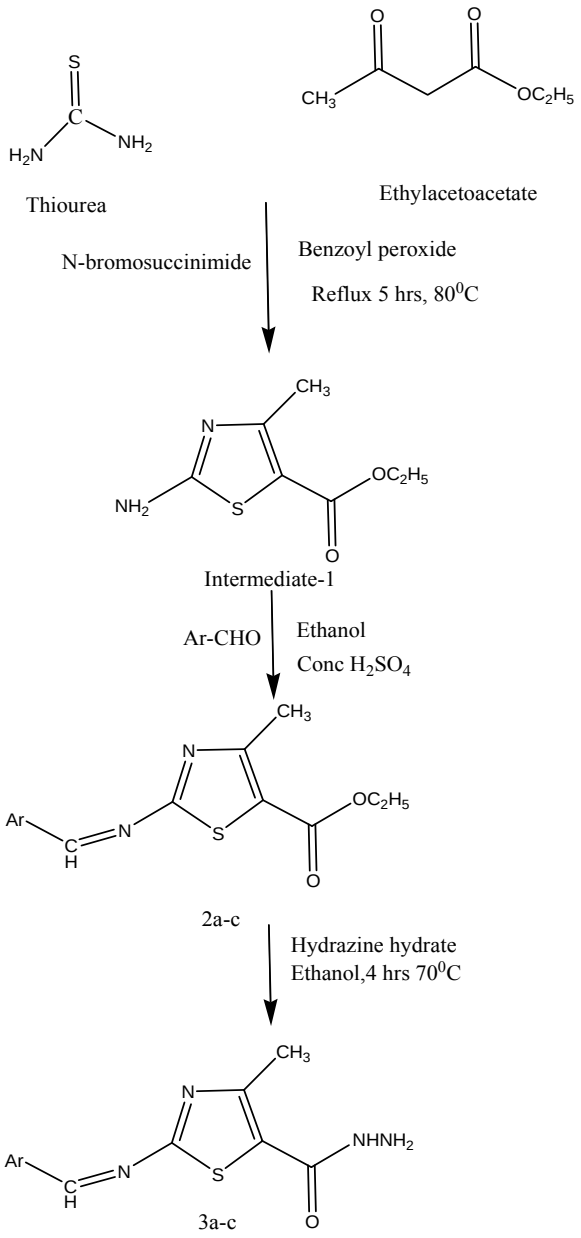
Keywords: Thiazole, Aryl aldehydes, 3c, Antibacterial activity.

INTRODUCTION

Research over the past 50 years has been focused on meeting medical needs to treat infectious disease caused by life threatening pathogens. In spite of the introduction of a variety of antibacterial agents in multiple unrelated drug classes, resistance continues to emerge. The pharmaceutical field (including academic) must respond to these clinical challenges by bringing forward a stream of new agents with promising antibacterial activity against bacteria, Advantages of these agents include their higher predictability for success, well-defined biomarkers, shorter clinical trials, and shorter duration of therapy leading to fewer long-term safety concerns[24]. Due to the rapid development of bacterial resistance to antibacterial agents, it is vital to discover novels scaffold for the design and synthesis of the new antibacterial agents to help in the battle against pathogenic microorganisms. Much research has been carried out with the aim to discover the therapeutic values of thiazole derivatives. . A number of these compounds are today's blockbusters of the antibacterial market due to their therapeutic efficacy having tolerable side-effects and thus, challenging the predominance of well established β-lactum antibiotics which are becoming more prone to the resistant pathogenic bacteria[29]. Thiazoles are thus important molecules. They exhibit a variety of activity from antimicrobial to antitumour activity. N_4-substituted triazolyl derivatives[1] have found to posses anticonvulsant property whereas 4- thiazolidone derivatives have show a very good antifungal activity. (1, 3 benzothiazol-2yl) amino 9-(10H) acridinone derivatives[22] have found to posses antileshmanial activity. 4-Substituted Methoxybenzoyl-aryl-thiazole[5] has been found to possess a very good anticancer activity. Thus thiazole has been a subject of investigations. As part of interest in heterocycles that have been explored for developing pharmaceutically important molecules, aryl aldehyde derivatives have played an important role in medicinal chemistry. Moreover they have been studied extensively because of their ready accessibility, diverse chemical reactivity and broad spectrum of biological activity. Hence it was thought interesting to study such type of moieties shown in scheme-1.Current investigations have found that aryl aldehyde derivatives posses a very good antibacterial activity with its novel mechanism of action thought to be involving inhibition of 50s subunit of the ribosomal protein at a very early stage and are found to

be very effective against gram negative bacteria[31]. The first product is synthesized by condensation of thiourea with ethyl acetoacetate in presence of N-bromosuccinimide using benzoyl peroxide as a catalyst.

SCHEME-I[12, 13]



CHEMISTRY

The synthesis of compound (3a-c) is as outlined in scheme (I) and described previously by

condensation of thiourea with ethyl acetoacetate in presence of N-bromosuccinimide using benzoyl peroxide as a catalyst to yield (1) to which different substituted aryl aldehydes (3,4,5-trimethoxy benzene, m-phenoxybenzene, 4-methoxy-3-hydroxy benzene) were added to obtain compounds (2a-c).

To the products obtained by the above reactions was added hydrazine hydrate. The mixture was then refluxed for 10 minutes. Alcohol was then added to the mixture to yield the final product (3a-c).Cyclocondensation of thiourea with ethylacetoacatae in the presence of N-bromosuccinimide by refluxing with benzene and a pinch of benzoyl peroxide as the catalyst yielded (1).Further to this product were added different substituted aryl aldehydes (3, 4, 5-trimethoxy benzene, m-phenoxybenzene, 4-methoxy-3-hydroxy benzene) to obtain derivatives of ethyl 4-methyl-2-(aryl derivatives of methyleneamino) thiazole-5-carboxylate (2a-c).To each of the above obtained products was added an equimolar amount of hydrazine hydrate. The mixture was then refluxed for 10 minutes. Alcohol was then added to the mixture till both the layers were miscible and the mixture was further refluxed for 4 hours. The excess of alcohol and hydrazine hydrate were distilled out and the solid obtained was recrystallized to obtain the final products

4-methyl-5-hydrazine hydrate-2-(aryl aldehyde derivatives of methyleneamino) thiazole-5-carboxylate (3a-c).

RESULTS AND DISCUSSION

Reviewing of the antibacterial activities of compounds (3a-c), with the exception of activity of the compounds (3a) and (3b) against *E.coli, compound* (3c) was found to be equipotent to Ciprofloxacin. In case of antibacterial activity against *S.aureus* compound (3c) was found to be more active than ciprofloxacin whereas compounds (3a) and (3b) were found to be moderately active to that of ciprofloxacin. When evaluation of the compounds against *P.aeruginosa* was done it was found compound (3c) was more active than ciprofloxacin and compounds (3a) and (3b) were found to be moderately active. Antibacterial activity against *B. subtilis* compounds (3a) and (3b) were found to be moderately active whereas (3c) was found to be more potent to that of Ciprofloxacin.

As was anticipated it was found out that

C_2 position: C_2 position of thiazole ring requires large hydrophilic, electronegative functional moieties like substituted phenyl ring etc for enhanced antibacterial activity of thiazole in general. **C_4 position:** In the literature different groups like alkyl,-$COOC_2H_5$ or ketone etc. are reported for antibacterial activity, in our compounds alkyl (methyl) groups is present, still most of the compounds show good antibacterial activity.

C_5 position: C_5 position of thiazole ring requires small hydrophobic, electronegative functional moieties like amino, hydrazine hydrate attach with ester for antibacterial activity of thiazole.

The most active compound in the series was found out to be (3c) with the exception of activity equipotent to Ciprofloxacin against *E.coli.* The activity was found to be more as compared to ciprofloxacin against all tested organisms particularly, *S.aureus, P.aeruginosa*, *B.subtilis*. Compounds (3b) and (3c) showed moderate activity as compared to ciprofloxacin. The compounds in the series were active against both gram negative and gram positive bacteria.

EXPERIMENTAL

All the chemicals for the synthesis were purchased from approved vendors of different make like Aldrich, Loba, Spectrochem and all chemicals were of laboratory grade. Completion of reaction were confirmed using physical constant determination (Sharp or narrow melting ranges, physical constants were not matching any of the reactants/starting material/s).Melting points were determined using Labin Melting Point Apparatus in open capillaries and are uncorrected. Further the compounds synthesized were proceeded for TLC wherein single spots (1^{st} TLC run) were observed, indicating completion of reaction. After work-up was completed, (unreacted starting materials were removed), the products were subjected to purification by recrystallization process. Again TLC was run to find out exact R_f value. TLC plates used for final recrystallized product were pre-coated silica gel G plates. Solvent systems were developed using trial and error method by use of appropriate solvents of different polarity .FT-IR spectra were recorded using JASCO FT-IR V-430+ spectrophotometer.1H-NMR spectra were recorded on Varian mercury NMR spectrometer at 200MHz using CDCl3 as the solvent and TMS as the internal standard(chemical shift values expressed in delta ppm)Elemental values were determined using Hwreuscarlo Erba 1108 CHN analyzer and the molecular formulae were characterized using the data obtained from different physicochemical studies stated above.

Compound 3a [4-methyl-5-hydrazine hydrate-2-(3,4,5 trimethoxy benzyl methyleneamino) thiazole-5-carboxylate]

For compound (3a), yield 70 % M.P-1980C, IR(KBr) cm-1 3015 (CH Ar),1622 (CN),

3365(NH primary), 2815 (CH3-O), 799 (C-H out of plane), 3222 9N-H secondary), 2967 (C-H Al), 1236 (N tertiary); 1H NMR(CDCl3) deltappm 8.15-8.35(s, 1H of CHof -CH=N),

6.7-6.8 (s, 2H of CH of phenyl ring), 4.78-4.90(s, 3H of -OCH3),3.95-4.15 (t, 2H of N-H of -NHNH2), 3.6-3.75 (d 3H OF N-H of NH2), 1.2-1.3 (s 3H -CH3 on thiazole ring)

Elemental Analysis (%): C 49.12, H 4.52, N 15.57 calculated for C 49.17, H 4.52, N 15.29.

Compound 3b [4-methyl-5-hydrazine hydrate-2-(m-phenoxy benzyl methyleneamino) thiazole-5- Carboxylate]

For compound (3b), yield 74.23 % M.P-204^{0}C, IR(KBr) cm-1 3035(C-H Ar), 1649(CN), 3239(NH primary), 1758(C=O),1239(C-O stretching of ester);2945(C-H stretch Ar),760(CH); 1H NMR(CDCl3) deltappm: 8.25-8.40 (s, 1H of CH of -CH=N),7.15-7.80(s, 9H of aromatic ring),3.95-4.15(t, 2H of N-H of -N-H-N-H2),3.6-3.75(d,3H of N-H-NH2),1.2-1.3(s, 3H -CH3 on thiazole ring).

Elemental Analysis (%): C 58.51, H 4.58, N 15.86 calculated for C 58.68, H 4.38, N 15.21

Compound 3c [4-methyl-5-hydrazine hydrate-2-(4-hydroxy-3-methoxy benzyl methyleneamino) thiazole-5- carboxylate]

For compound (3c), yield 68.66 %, M.P 1770C, IR(KBr) cm-1 3022(C-H Ar), 1649(CN), 3357(NH primary), 1240 (N- tertiary),2992(C-H Al), 3239(NH secondary),2813(O-CH3 stretch);1H NMR(CDCl3) deltappm 8.20-8.35(s, 1H of CHof -CH=N), 7.4-7.6 (s, 2H of CH of phenyl ring), 6.75-6.90(d, 1H of C-H of phenyl ring), 4.85-4.95(s, 3H of -OCH3),4.05-4.15 (t, 2H of N-H of -NHNH2),3.6-3.75(d,3H of N-H-NH2),1.15-1.35(s, 3H -CH3 on thiazole ring).

Elemental Analysis (%): C 48.39, H 4.79, N 17.58 calculated for C 48.44, H 4.38, N 17.38.

Table No. 1 shows Minimum Inhibitory Concentration of Novel Thiazole Derivatives and Table No.2 Shows antibacterial activity of compounds Cip, 3a,3b,3c against *E. coli* (ATCC 25922), *S. aureus*(ATCC 25923) , *P.aeruginosa* (ATCC 27853), *B.subtilis*(ATCC 6633).

Table No.1: Minimum Inhibitory Concentration (MIC) of Novel Thiazole Derivatives

Sr. No.	Compound Code	Minimum Inhibitory Concentration (MIC) mg/L			
		E. coli **(ATCC 25922)**	***S. aureus*** **(ATCC 25923)**	***P.aeruginosa*** **(ATCC 27853)**	***B.subtilis*** **(ATCC 6633)**
1	**Ciprofloxacin**	**0.4**	**0.8**	**1.56**	**1.56**
2	**3a**	**3.12**	**6.5**	**3.12**	**N.S.**
6	**3b**	**3.12**	**3.12**	**6.5**	**3.12**
8	**3c**	**0.8**	**0.4**	**0.4**	**0.8**

N.S. = Not Sensitive

Cip - Ciprofloxacin.
3a - 4-methyl-5-hydrazine hydrate-2-(3,4,5 trimethoxy benzyl methyleneamino) thiazole-5-carboxylate.
3b - 4-methyl-5-hydrazine hydrate-2-(m-phenoxy benzyl methyleneamino) thiazole-5-carboxylate
3c- 4-methyl-5-hydrazine hydrate-2-(4-hydroxy-3-methoxy benzyl methyleneamino) thiazole-5-carboxylate

Table No. 2: Antibacterial Activity of Novel Thiazole Derivative

Sr. No.	Compound Code	Concentration mg/L	Zone of Inhibition (mm)			
			E. coli **ATCC 25922**	***S. aureus*** **ATCC 25923**	***B.subtilis*** **ATCC 6633**	***P. aeruginosa*** **ATCC 27853**
1	**Cip.**	25	32	29	30	30

		12.5	26	20	26	25
		6.25	22	18	20	20
		3.12	17	15	16	13
		1.56	13.5	10	**10**	**10**
		0.8	10	**7.5**	N.S.	N.S.
		0.4	**7.5**	N.S.	N.S.	N.S.
2	3a	25	19	15	22	N.S.
		12.5	16	10	17	N.S.
		6.5	11	**04**	14	N.S.
		3.12	**7**	N.S.	**10**	N.S.
3	3b.	25	22	15	12	18
		12.5	17	13	09	14
		6.5	13	09	**06**	10
		3.12	**8.5**	**06**	N.S.	**05**
4	3c	25	28	30	34	28
		12.5	23.5	23	25	25
		6.5	16	19	20	19.5
		3.12	13	15.5	15	15
		1.56	10	11	12	12
		0.8	**7.5**	09	09.5	**09**
		0.4	N.S.	**06**	**07**	N.S.

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