WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 6, 1548-1554. Research Article ISSN 2277– 7105

SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL 1, 3 THIAZOLE DERIVATIVES

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Article Received on
21 March 2019,
Revised on 11 April 2019,
Accepted on 01 May 2019,
DOI: 10.20959/wjpr20196-14881

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ABSTRACT

Aim: Synthesis and biological evaluation of novel 1, 3 thiazole derivatives. **Materials and Methods:** Thin-layer chromatography plates used for final recrystallized product were pre-coated silica gel G plates. Solvent systems were developed using trial and error method by the use of appropriate solvents of different polarity. Fourier transform infrared spectra (FTIR) were recorded using FTIR 8400 F-Shimadzu spectrometer using KBr disc pellet method. ^{1}H nuclear magnetic resonance (NMR) spectra of synthesized compounds were recorded on "BRUKER AVANCE II 400" NMR spectrometer at 400 MHz frequency in dimethyl sulfoxide using tetramethylsilane as internal standard (chemical shift values expressed in delta ppm). Synthesis of ethyl 2-amino-4-methylthiazole- 5-carboxylate, synthesis of ethyl 2-(arylidine amino)-4-methylthiazole-5-carboxylate, and synthesis of ethyl 2-(3- chloro-2-(arylidine)-4 oxazetidine -1-yl)-4-methylthiazole-5-carboxylate. **Results and Discussion:** In the present work, a new series of Schiff bases were synthesized from ethyl 2-amino-4-methyl thiazole5 carboxylate with substituted aromatic aldehydes in the presence of catalytic amount of benzoyl peroxide. The resulted Schiff bases undergoes cyclocondensation reaction with chloroacetyl chloride in the presence of triethylamine under cold conditions will yield the title compounds. **Conclusion:** The new compounds were screened for their antibacterial and antifungal activity. In the antibacterial activity, a compound 3c has shown maximum activity against all the four pathogenic micro-organisms.

KEYWORDS: 1, 3 thiazole, antibacterial and antifungal activity, aryl dine derivatives.

INTRODUCTION

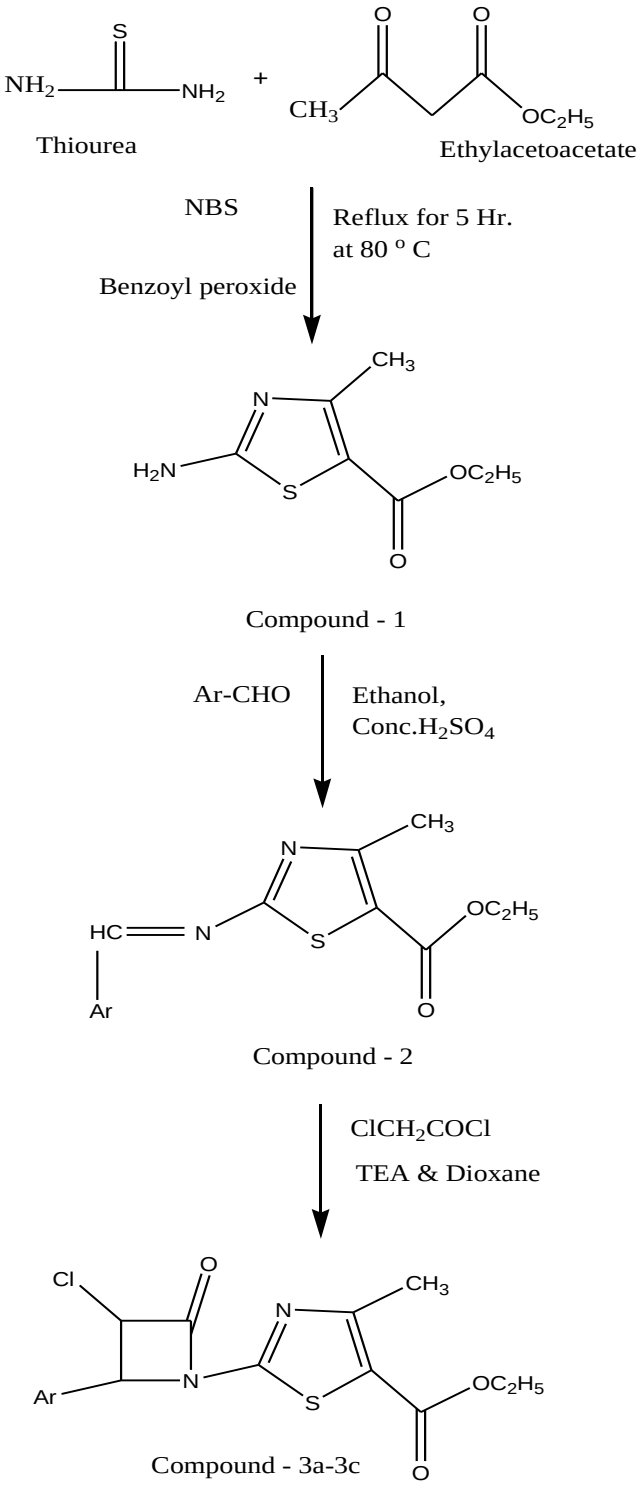
The introduction of a variety of antibacterial agents in multiple unrelated drug classes, resistance continues to emerge. The pharmaceutical researcher must respond to these clinical challenges by bringing forward a stream clinical challenge by bringing forward a stream of new agents with promising antibacterial, antifungal activity against bacteria, fungi. 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 product of the antibacterial market due to their therapeutic efficacy having tolerable side-effects, and thus, challenging the predominance of well-established ß-lactum antibiotics which are becoming more prone to the resistant.[1,2]

They exhibit a variety of activity from antimicrobial to antitumor activity. N-substituted triazolyl derivatives have found to possess anticonvulsant property, whereas 4-thiazolidone derivatives have shown a very good antifungal activity.[3,4] Thus, thiazole has been a subject of investigations. As part of interest in heterocycles have been studied extensively because of their ready accessibility, diverse chemical reactivity, and broad spectrum of biological activity.

EXPERIMENTAL METHODS

All the chemicals for the synthesis were purchased from approved vendors of different make Such as Aldrich, Loba, and Spectrochem, and all chemicals were of laboratory grade. Completion of reaction was 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 thin-layer chromatography (TLC) wherein single spots (1 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 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 the use of appropriate solvents of different polarity. Fourier transform infrared (FTIR) spectra were recorded using FTIR 8400 F-Shimadzu spectrometer using KBr disc

pellet method. ^{1}H nuclear magnetic resonance (NMR) spectraof synthesized compounds were recorded on "BRUKER AVANCE II 400" NMR spectrometer at 400 MHz frequency in Dimethyl sulfoxide (DMSO) using tetramethylsilane as internal standard (chemical shift values expressed in delta ppm) [Scheme 1].



Scheme 1: synthesis of thiazole derivatives.

MATERIALS AND METHODS

Synthesis of Ethyl 2-amino-4-methylthiazole-5-carboxylate (1)

Condensation of thiourea with ethyl acetoacetate in the presence of N-bromosuccinimide using benzoyl peroxide as a catalyst to yield (1).

Synthesis of Ethyl 2-(arylidineamino) -4-methylthiazole-5-carboxylate (2a-c)

Compound (1) reacted with different substituted aryl aldehydes (3,4,5-trimethoxy benzene, m-phenoxybenzene, 4-methoxy-3-hydroxy benzene) in the presence of ethanol and concentrated sulphuric acid to obtain compounds (2a-c).

Synthesis of Ethyl 2-(3-chloro-2-(arylidine)-4 oxazetidine-1-yl)-4-methylthiazole-5-carboxylate (3a-c)

A mixture of Schiff bases (0.01 mol) and triethylamine (0.02 mol) was dissolved in dioxane (50 ml) and stirred. To this well stirred solution chloroacetylchloride (0.04 mol) was added drop by drop for a period of 30 min at low temperature. The reaction was further stirred for 6-12 h (as monitored from TLC). The reaction mixture is poured into crushed ice and the resultant product was filtered and washed with water, dried and recrystallized from ethanol. The physical data of the compounds (3a-c) is given in Table 1.

Table 1: Physical data of compound (3a-3c).

Compound	Ar-CHO	% Yield	Melting Point (^{0}C)	R_f Value
3a	3,4,5 $(OCH_3)_2$	58	192-194	0.68
3b	OC_6H_5	54	222-224	0.62
3c	4- OCH_3,3-OH	61	228-230	0.64

Spectral Data

For compound (3a) ethyl 2-(3-chloro-2oxo-4-(3, 4,5trimethoyphenyl) azetidine-1-yl)-4-methylthiazole-5-carboxylate

IR (KBr) cm^{-1} 3035 (C-H Ar), 1649 (CN), 1758 (C=O), 1576 (C=C), 760 (CH), C-Cl (748), ^{1}H-NMR (CDCl) d ppm: 4.9-5.1 (s, 1H of CH of -CH-N), 6.4-6.56 (s, 2H of CH of phenyl ring), 3.62-3.80 (s, 9H of -OCH3), 2.30-2.55 (s, 3H -CH_3 on thiazole ring). 5.4 (d, 1H, C-CH-Cl) 1.10-1.29(s, 5H of -OC_2H_5).

For compound (3b) ethyl 2-(3- chloro-2oxo-4- (phenoxyphenyl) azetidine -1-yl)-4-methylthiazole-5-carboxylate

IR (KBr) cm^{-1} 3015 (CH Ar), 1622 (CN), C-Cl (750), 2815(CH_3-O), 799 (C-H out of plane),

1236 (N tertiary); 1758 (C=O), 1600 (C=C), ^{1}H NMR ($CDCl_3$) deltappm 5.1(s, 1H of CH of -CH-N), 7.12-7.41 (s, 9H of CH of phenyl ring), 2.20-2.65 (s, 3H -CH_3 on thiazole ring). 5.4 (d, 1H, C-CH-Cl) 1.29-4.2(s, 5H of -OC_2H_5).

For compound (3c) ethyl 2-(3- chloro-2- (3-hydroxy-4-methoxyphenyl)-4 oxazetidine -1-yl)-4-methylthiazole-5-carboxylate

IR (KBr) cm^{-1} 3022 (C-H Ar), 1649 (CN), 1240 (N-tertiary), C-Cl (750), 1760 (C=O), 1540 (C=C), 2813 (O-CH_3 stretch);1H NMR ($CDCl_3$) delta ppm 4.9-5.1 (s, 1H of CHof -CH-N), 6.74-6.92 (s, 3H of CH of phenyl ring), 3.72-3.90 (s, 3H of -OCH3), 2.20-2.65 (s, 3H -CH_3 on thiazole ring). 5.4 (d, 1H, C-CH-Cl) 3.71(s, 3H, (OCH_3), 9.4 (s, 1H of CH of OH), 1.10-1.29 (s, 5H of -OC_2H_5).

Antimicrobial Activity

The antimicrobial activity was assayed using the cup-plate agar diffusion method, by measuring the zone of inhibition in mm.[5-7,11] All the compounds were screened in-vitro for their antimicrobial activity against Staphylococcus aureus, Bacillus subtilis, Klebsiella pneumoniae, Escherichia coli, and fungi Aspergillus niger and Saccharomyces cerevisiae. The activities of these compounds were tested at a concentration of 100 µg/ml. Ampicillin and fluconazole were used as standard drugs for the comparison purpose. DMSO was used as a solvent control. The antimicrobial activity data is reported in Table 2.

Table 2: The Antimicrobial and Antifungal data of compound (3a-3c).

Compound	Zone of inhibition (mm) 100 µg/ml (Mean*±SEM)					
	E. coli	K. pneumonia	S. aureus	B. subtillis	A. niger	S. cerevisiae
3a	5.22±0.307	5.25±0.365	5.66±0.33	5.66±0.333	4.52±0.223	4.66±0.223
3b	5.23±0.333	4.26±0.223	6.22±0.516	4.66±0.333	4.84±0.307	5.56±0.307
3c	6.42±0.307	5.50±0.307	6.23±0.477	6.66±0.33	5.78±0.365	5.66±0.33
Ampicillin	8.43±0.47	8.37±0.42	8.17±0.307	8.83±0.47	-	-
fluconazole	-	-	-	-	8.6±0.33	8.7±0.44

SEM: Standard error of mean, S. aureus: Staphylococcus aureus, B. subtillis: Bacillus subtilis, K. pneumonia: Klebsiella pneumonia, E. coli: Escherichia coli, A. Niger: Aspergillus Niger, S. cerevisiae: Saccharomyces cerevisiae.

RESULTS AND DISCUSSION

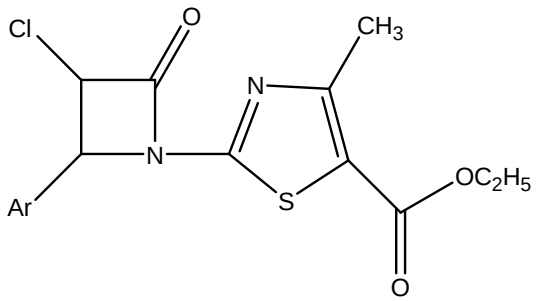
In the present work, a new series of Schiff bases were synthesized from ethyl 2-amino-4-methyl thiazole 5 carboxylate with substituted aromatic aldehydes in the presence of catalytic amount of benzoyl peroxide. The resulted Schiff bases undergoes cyclocondensation reaction

with chloroacetyl chloride in the presence of trietylamine under cold conditions will yield the title compounds. The purity of the compounds is checked by TLC. The final synthesized compounds were established on the basis of spectral data. All the new compounds were screened for their antibacterial and antifungal activity. In the antibacterial activity, a compound 3c has shown maximum activity against all the four pathogenic micro-organisms. However, most of the compounds are moderately active against S. aureus and B. subtilis. In the antifungal study, compounds 3c have shown highest activity against both the fungi. In overall, most of the synthesized compounds have shown moderate activity.

Structure Activity Relationship

The general structural formula of basic compound can be written as:

As was anticipated it was found out that:



C2 position: C2 position of thiazole ring requires large hydrophilic, electronegative functional moieties such as substituted phenyl ring for enhanced antibacterial activity of thiazole in general.

C_4 position: In the literature different groups such as alkyl, - $COOC_2H_5$ or ketone 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.

ACKNOWLEDGMENT

The authors are thankful to Dr. V.K. Deshmukh, Principal, MES's College of Pharmacy, Sonai for providing all laboratory facilities, Jagdamba Education societys SND College of Pharmacy, Yeola for recording FTIR Spectra, H-NMR spectra at SAIF Punjab University, Chandigarh, GC-MS spectra at Savitribai Phule Pune University, Pune for recording spectra.

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