"SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF SUBSTITUTED THIADIAZOLE DERIVATIVES"

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Abstract

Thiadiazole and its derivatives have been widely studied due to their broad range of biological effects. Medicines that are antimicrobial, antifungal, anticancer, anti-inflammatory, and anti-malarial have been found to be efficacious. The substituted-1,3,4-thiadiazole nucleus is quite common, and it may be found in a variety of commercially marketed medications.

The synthesis of 1,3,4-thiadiazole derivatives has sparked a lot of attention due to their diverse biological effects, such as antibacterial, anticancer, antiviral, and anti-inflammatory. Certain 1,3,4-thiadiazole derivatives were synthesised as a consequence. They are thought to have better antibacterial characteristics. Under acidic conditions, cyclization of identical thiosemicarbazides gave 1,3,4-thiadiazoles with isomeric pyridyl. Based on the screening results, the final compounds EEE1, EEE2, EEE3, and EEE4 have been identified. A excellent zone of inhibition against gramme positive and gramme negative bacteria using conventional antibiotics.

Key Words: Antibacterial, Thiadiazoles, Antimicrobial.
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INTRODUCTION

Thiadiazoles are five-member hetero compounds, mostly nitrogen and sulphurheterocycles, that have been tested for a range of diseases. They have gained substantial relevance in healthcare and biopharmaceutical science, and this is due to more than simply their extensive potential applications.

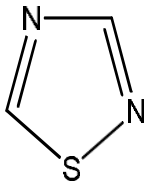
Basic five-membered heterocyclic compounds with one oxygen atom and two nitrogen atoms are thiadiazoles and their variations. Oxadiazoles come in a variety of stereoisomers, including 1,2,4-, 1,2,5-, 1,2,3-, and 1,3,4-thiadiazoles.

Some of the most crucial chemicals that make life worth living are heterocyclic compounds. For a long time, the chemical compound heterocyclic molecules has been an intriguing study topic. A key category of compounds for innovative pharmaceutical development is the 1,3,4-thiadiazole with a heteroatoms core. The synthesis of novel thiadiazole compounds, as well as the research of their physical and biological activities, has become more relevant in recent generations. In recent years, there has been a lot of study into various types of thiadiazole compounds, and most of them offer a lot of medicinal promise.

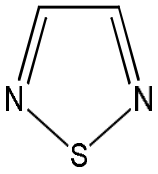
Chemopreventive action, in vitro suppression of cox 1 and 2 and 5-lipoxygenase characteristics, mollusk inhibiting capabilities, and molluscicidal activity are all known features of such compounds having these qualities.

Thiadiazoles are a heteroatomic compound with several applications in chemical processes, pharmacology, and biology. Their applications include antioxidant

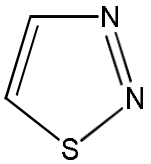
inhibitors, cyano pigments, metallic chelators, and anti-corrosion chemicals. Because of its vast variety of applications, scientists from all over the world are interested in this moiety, which has assisted in the expansion of thiadiazole synthesis. Recent advances, innovative methodology, chemical approaches, methodologies employed in the manufacture of thiadiazoles& their varied pharmacological activities, structure-activity connections among the most potent chemicals, as well as physical characteristics, are all included in this review study. The findings will aid chemical and pharmaceutical researchers in developing new thiadiazole-based medications that may be more successful.



1,2,4-Thiadiazole



1,2,5-Thiadiazole



1,2,3-Thiadiazole

MATERIALS AND METHODS

The melting temperatures of the objects were calculated using an open tubes model. The IR spectra (KBr) were re-recorded at 4000-400 cm-1 in an FTIR spectrophotometer (SHIMADZU). The electrospinning spectral data was collected using a THERMO LCQ advantages maximum ion trap mass spectrometer. The findings of nonlinear absorption in parts per million were acquired in CDCL3 using a Bruker DRX-300 MHz spectrometer with TMS as an internal standard and a 1H resonance frequency of 300 MHz.

SYNTHESIS OF TITLE COMPOUNDS IN GENERAL:

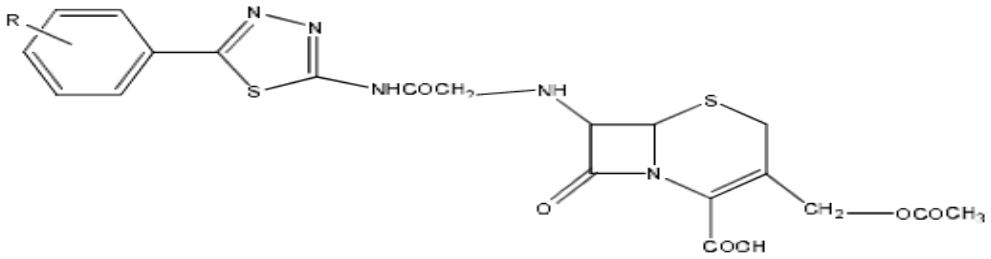
Step-1:

A solution containing 40 mmol of different substituted benzeldehyde, equimolar quantities of thiosemicarbazide and phosphorous oxychloride (30 ml), and an equal molar quantity of CH5N3S thiosemicarbazide and phosphorus oxychloride was refluxed for 2-4 hours. The beaker was filled with ice cubes when the fluid had cooled down (100ml). Before being filtered, the solution is chilled for about 4 hours.

The solution was stirred with an ammonia solution. The ppt of ethanol and water was collected, filtered, washed with distilled water, dried, and recrystallized. The concentration of the products was determined by TLC, with the mobile phase consisting of benzene and acetone (9:1).

Step: 2

3-[(acetyloxy)methyl]-7-[(2-amino-2-oxoethyl)amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carbo



Chloroacetylchloride (20 mmol) into 20mL containing dried benzene is slowly mixed with continuous stirring to a solution of properly modified substance 2.3(2.3.1-2.3.12) (10 millimoles) in 20ml of dried benzene & 2 mL of dried pyridine. This reaction mixture was incubated approximately 6–8 hours upon complete addition before being dumped into ice cubes. To get drug 2.3, the precipitate was filter, separated, rinsed from water, dried and purified by re-crystalization from dioxane water (2.3.1-2.3.12). TLC was used to determine the concentrations of the substances, with benzene and acetone (9:1) for the mobile phase.

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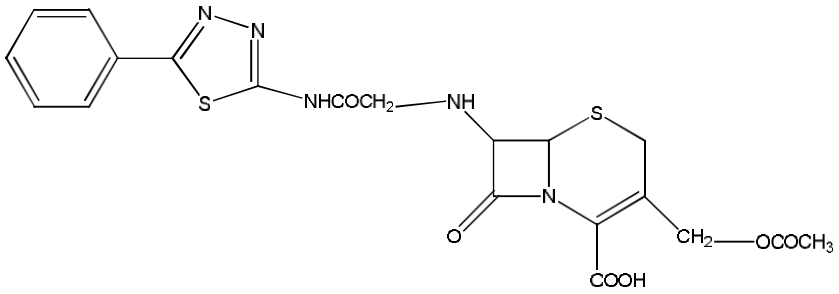
Compounds	R
EEE_1	H
EEE_2	Cl
EEE_3	Br
EEE_4	NO_2

Physicochemical Data for Step-3 (FigureEEE1-EEE4)

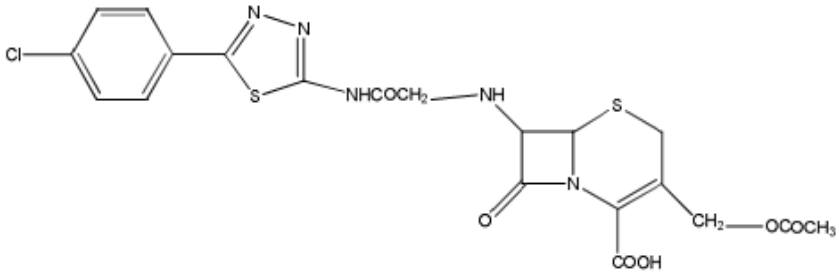
Sr.No.	MolecularFormula	% Yield	M.P.	Molecularweight	TLC(Rf)
1.	$C_{20}H_{19}N_5O_6S_2$	51%	176-180^{0}C	489.08	0.19
2.	$C_{20}H_{18}ClN_5O_6S_2$	49%	142-144^{0}C	523.04	0.23
3.	$C_{20}H_{18}BrN_5O_6S_2$	48%	133-140^{0}C	566.99	0.41
4.	$C_{20}H_{18}N_6O_8S_2$	41%	148-152^{0}C	534.06	0.22



3-[(acetyloxy)methyl]-7-[(2-(5-(benzylideneamino)-1,3,4-thiadiazol-2- ylthio)amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid(EEE1)

Molecular Weight: 489.52
m/z: 489.08 (100.0%), 490.08 (23.7%), 491.07 (9.1%), 491.08 (4.2%), 492.08 (2.1%), 490.07 (1.8%)
Elemental Analysis: C, 49.07; H, 3.91; N, 14.31; O, 19.61; S, 13.10
Figure - EEE1

Yield: -51 %, m.p.- 176-180^{o}C, IR spectra (v, cm): 3100 (N-H), 1785 (β-lactum C=O), 1750(C=O), 1660 (amide (C=N), 1595 (C=C aromatic), 1HNMR :- 12.56 (s, 1H, -COOH), 8.36 (s, 1H-N=CH), 8.23 (d, 1H –CO-NH-), 7.52-7.83 (m, 5H, Ar-H),5.56 (d,1H,C7-H), 5.10 (dd, 1H,C6-H), 4.75 (s, 2H,-CH2-O=O), 3.56 (s,2H, -S-CH2-), 3.09-3.16 (m,2H, C4-H), 2.23 (s,3H,-CH3).



Exact Mass: 523.04

Molecular Weight: 523.97
m/z: 523.04 (100.0%), 525.04 (34.0%), 524.04 (25.5%), 526.04 (9.7%), 525.03 (9.1%), 527.03

(3.2%), 525.05 (2.3%), 527.04 (1.7%)
Elemental Analysis: C, 45.85; H, 3.46; Cl, 6.77; N, 13.37; O, 18.32; S, 12.24

Figure - EEE2

3-(Acetoxymethyl)-7-(2-(5-(4-chlorobenzylideneamino)-1,3,4-thiadiazol-2-ylthio)amino)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (EEE2)

Exact Mass: 523.04

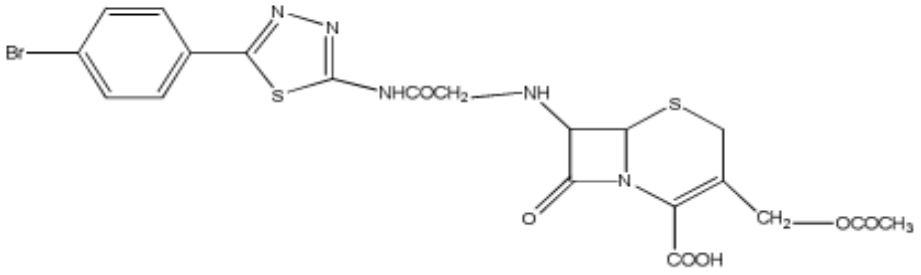
Molecular Weight: 523.97
m/z: 523.04 (100.0%), 525.04 (34.0%), 524.04 (25.5%), 526.04 (9.7%), 525.03 (9.1%), 527.03

(3.2%), 525.05 (2.3%), 527.04 (1.7%)
Elemental Analysis: C, 45.85; H, 3.46; Cl, 6.77; N, 13.37; O, 18.32; S, 12.24

Figure - EEE2

Yield: -49 %, m.p.- 142-144°C, IR spectra (v, cm): 3150 (N-H), 1780 (β-lactum C=O), 1750(C=O), 1730 (amide (C=N),

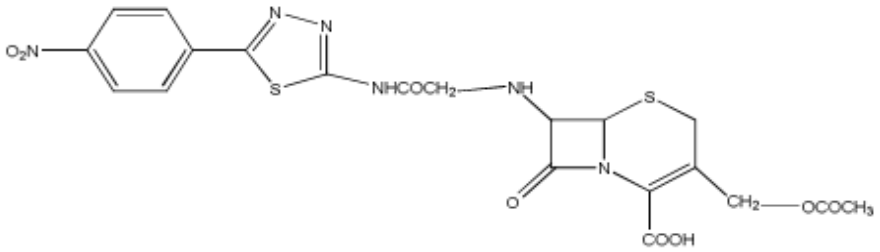
1630 (C=C aromatic) 870(C-Cl), 1HNMR :- 12.56 (s, 1H, -COOH), 8.36 (s, 1H-N=CH), 8.23 (d, 1H –CO-NH-), 7.52-7.83 (m, 5H, Ar-H),5.75 (d,1H,C7-H), 5.10 (dd, 1H,C6-H), 4.75 (s, 2H,-CH2-O=O), 3.56 (s,2H, -S-CH2-), 3.09-3.16 (m,2H, C4-H), 2.23 (s,3H,-CH3).



3-(Acetoxymethyl)-7-(2-(5-(4-bromobenzylideneamino)-1,3,4-thiadiazol-2- ylthio)amino)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid (EEE3)

Molecular Weight: 568.42
m/z: 568.99 (100.0%), 566.99 (98.5%), 567.99 (25.1%), 569.99 (24.8%), 570.98 (9.0%), 568.98 (8.9%), 570.99 (4.4%), 571.99 (2.3%), 569.98 (2.0%)
Elemental Analysis: C, 42.26; H, 3.19; Br, 14.06; N, 12.32; O, 16.89; S, 11.28
Figure - EEE3

Yield: -48 %, m.p.- 133-140°C, IR spectra (v, cm): 1885 (β-lactum C=O), 1720(amide C=O), 1745(C=N), 1600 (C=C aromatic) 1350 (N-H), 1HNMR :- 12.56 (s, 1H, -COOH), 8.36 (s, 1H-N=CH), 7.95 (d, 1H –CO-NH-), 7.52-7.72 (m, 5H, Ar-H),5.75 (d,1H,C7-H), 5.10 (dd, 1H,C6-H), 4.70 (s, 2H,-CH2-O=O), 3.56 (s,2H, -S-CH2-), 3.09-3.16 (m,2H, C4-H), 2.23 (s,3H,-CH3).



3-(Acetoxymethyl)-7-(2-(5-(4-nitrobenzylideneamino)-1,3,4-thiadiazol-2-ylthio)amino)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid (EEE4)

Molecular Weight: 534.52
m/z: 534.06 (100.0%), 535.07 (22.1%), 536.06 (9.6%), 536.07 (4.3%), 535.06 (3.8%), 537.06 (2.3%)
Elemental Analysis: C, 44.94; H, 3.39; N, 15.72; O, 23.95; S, 12.00
Figure - EEE4

Yield: -41 %, m.p.- 148-152°C, IR spectra (v, cm): 1785 (β-lactum C=O), 1745(carboxylate C=O), 1725(amide C=O), 1630 (C=N), 1528 and 1350 (NO_2),3150 (N-H), 870 (C-NO2), 1HNMR :- 12.56 (s, 1H, -COOH), 8.31 (s, 1H-N=CH), 8.23 (d, 1H –CO-NH-), 8.09-8.33 (m, 4H, Ar-H),5.56 (d,1H,C7-H), 5.10 (dd, 1H,C6-H), 4.75 (s, 2H,-CH2-O=O), 3.56 (s,2H, -S-CH2-), 3.09-3.16 (m,2H, C4-H), 2.23 (s,3H,-CH3).

Antibacterial activity: -

Based on screening results, the final compounds EEE1, EEE2, EEE3, and EEE4 have been proven to have a high level of activity against gram-negative bacteria. Micrococcus luteus and Staphylococcus aureus are resistant to Escherichia coli, Pseudomonas aeruginosa EEE1, EEE2, EEE3, and EEE4. EEE1, EEE2, EEE3, and EEE4 have greater antibacterial action against Escherichia coli than the traditional drug Cephalexin, according to new chemical synthesis. The MIC of EEE1 is 36 g/ml, which is higher than the MIC of Cephalexin, which is 30 g/ml. EEE2 has a higher MIC value of 29g/ml against Staphylococcus aureus than cephalexin, which has a MIC of 25g/ml.

Antimicrobial action

Sr. NO	Code of Compounds	Amount (Conc.) (µg/ml)							
		Z.O.I (1)	Inhibition percentage	Z.O.I (2)	Inhibition percentage	Z.O.I (3)	Inhibition percentage	Z.O.I (4)	Inhibition percentage
a.	Standard (Cephalexin)	19	18.10	13	12.22	17	14.21	16	26.00
b.	EEE1	11	20.33	12	18.34	18	17.00	15	24.33
c.	EEE2	14	23.12	13	12.12	24	20.00	19	26.67
d.	EEE3	20	19.00	15	13.25	20	15.16	21	24.00
e.	EEE4	20	20.00	14	14.65	21	18.95	23	24.58

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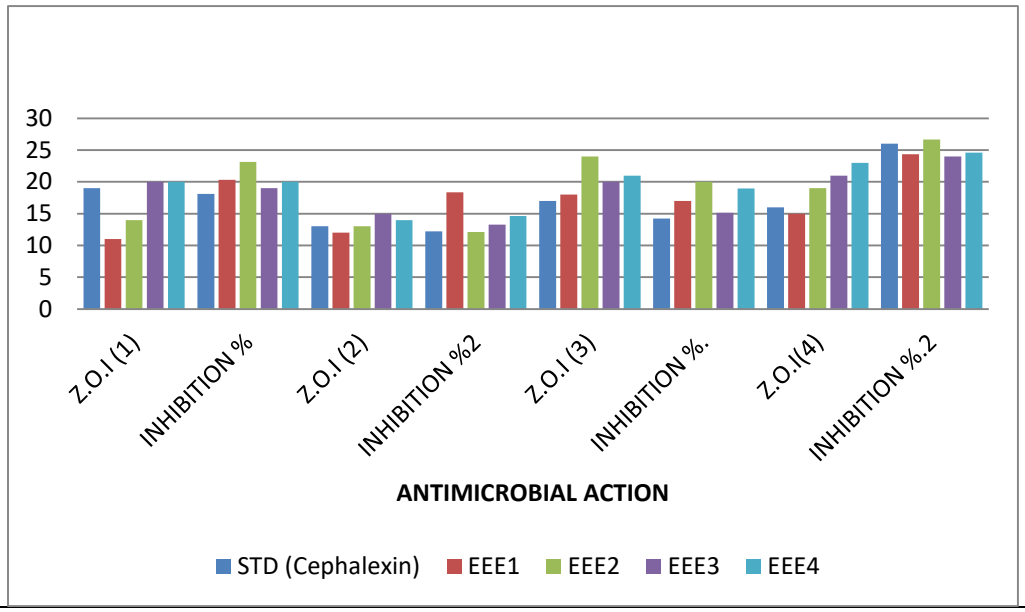
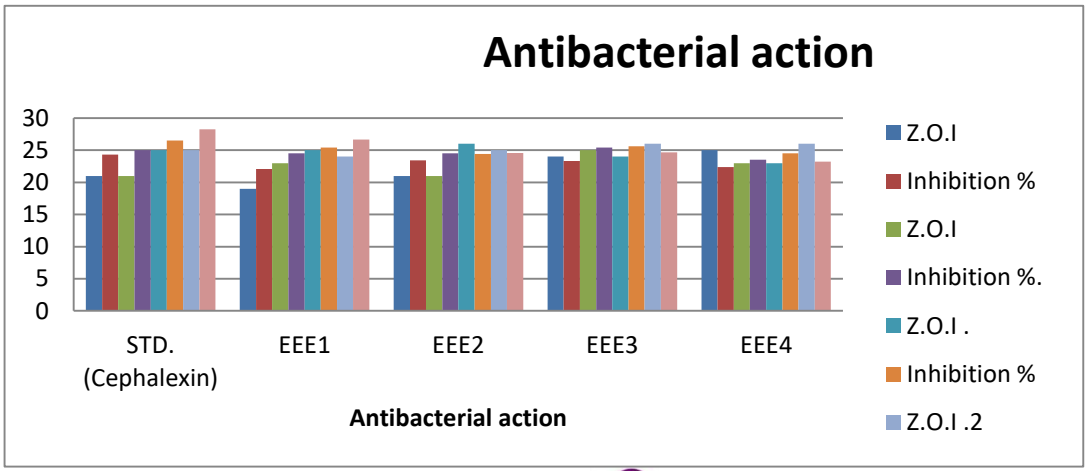


Antibacterial action									
S. No.	Codes of compounds	Concentration(µg/ml)							
		Z.O.I	Inhibition percentage	Z.O.I	Inhibition percentage	Z.O.I	Inhibition percentage	Z.O.I	Inhibition percentage
a.	Std (Cephalexin)	21	24.33	21	25.00	25	26.53	25	28.27
b.	EEE1	19	22.10	23	24.52	25	25.41	24	26.67
c.	EEE2	21	23.45	21	24.53	26	24.43	25	24.56
d.	EEE3	24	23.35	25	25.42	24	25.63	26	24.69
e.	EEE4	25	22.38	23	23.52	23	24.52	26	23.25



Minimum Inhibitory concentration of newly synthesized compounds

Compounds	*Micrococcus Leutus*	*Staphylococcus Aureus*	*Escherichia Coli*	*Pseudomonas Aeruginosa*
EEE1	24	25	36	54
EEE2	22	29	27	45
EEE3	20	23	26	39
EEE4	18	22	25	36
Cephalexin	15	25	30	61

C**ONCLUSION**

Thiadiazole-based heterocyclic compounds have been shown to have promising antibacterial properties. Some have potential and should be further investigated in order to identify better agents. In the future, these chemicals might be employed as lead molecules. Infrared and 1H-NMR examinations were used to confirm the structural properties of the substituted thiadiazoles generated. The compounds EEE1, EEE2, EEE3, and EEE4 have very good antibacterial activity against Gram negative (E. Coli, P. aeruginosa) and Gram positive (bacillus subtillus and Staph. Aureus) bacteria, while the other compounds have moderate to good antibacterial activity against the reference compounds Cephalexin.

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