Open access Journal International Journal of Emerging Trends in Science and Technology

Impact Factor: 2.838 DOI: http://dx.doi.org/10.18535/ijetst/v3i05.18

Synthesis and Antimicrobial Studies of Some New Thiadiazepine Derivatives

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ABSTRACT

A new series of thiadiazepine derivatives 4a-k were synthesized from aldehyde and triazoles. They were characterized by advanced techniques like IR, ^{1}HNMR and mass spectroscopy and their antimicrobial studies were carried out.

Key words: *Thiadiazepine, antimicrobial, spectral analysis, 1, 2, 4-triazoles and heterocyclization.*

INTRODUCTION

Currently, there is wide range and spectrum of effective antimicrobials is essential for the future.1, 2, 4-triazole,a five member heterocyclic with three nitrogen atoms in the ring which are by far the best known class of triazoles, Comprises wide variety of medicinal activities like antifungal, antimicrobial, anticonvulsant [1-8]. 1,2,4-triazole is an important emerging moietyin pharmaceutical study and a lot of work can be carried out on this molecule for obtaining better therapeutic activity. The synthesis of compounds belonging to thiadiazepine series constitute an important area due to their interesting diverse biological activities such as antibacterial, antifungal, analgesic, anti HIV and antidepressant properties [9-16]

MATERIALS AND METHOD

3-substituted-4-amino-5-mercapto-1,2,4triazoles 2a-b were synthesis through multistep sequential reaction from different phenols[17].The reaction between triazoles1 a-b and 1-phenyl-chloro pyrazole gave the twelve new thiadiazepine 4a-k(Scheme1)

Characterization Data

Compd. No.	R	Mol. Formula Mol. Wt.	Yield (%) m.p.^{0}C	Colour and crystal nature	% Analysis Found (Calculated)		
					C	H	N
4a	H	$C_{13}H_{11}N_6ClS$ 318	72 140-43	Yellow crystals	49.07 (49.05)	3.49 (3.45)	26.46 (26.41)
4b	CH_3	$C_{14}H_{13}N_6ClS$ 332	68 208-10	White crystals	50.64 (50.60)	3.96 (3.91)	25.38 (25.30)
4c	C_2H_5	$C_{15}H_{15}N_6ClS$ 346	85 140 - 45	Yellow crystals	43.38 (43.35)	4.39 (4.33)	24.21 (24.27)
4d	C_3H_7	$C_{16}H_{17}N_6ClS$ 360	76 179-81	White crystals	53.35 (53.33)	4.77 (4.72)	23.36 (23.33)
4c	C_6H_5	$C_{19}H_{15}N_6ClS$ 394	65 247-48	Pale Yellow crystals	57.81 (57.86)	3.86 (3.80)	21.34 (21.31)
4f	4-ClC_6H_4	$C_{19}H_{14}N_6Cl_2S$ 429	71 212-14	Yellow crystals	53.22 (53.27)	3.24 (3.27)	19.66 (19.62)
4g	4-$CH_3C_6H_4$	$C_{20}H_{17}N_6ClS$ 418	88 134-36	Yellow crystals	58.88 (58.82)	4.12 (4.16)	20.54 (20.58)
4h	4-$OCH_3C_6H_4$	$C_{20}H_{17}N_6OClS$ 424	73 132-35	Pale Yellow crystals	56.68 (56.60)	4.06 (4.01)	33.09 (33.01)
4i	4-BrC_6H_4	$G_9H_{14}N_6ClSBr$ 473	64 110-12	Brown crystals	48.36 (48.30)	2.98 (2.96)	17.71 (17.79)

4j	4-$NO_2C_6H_4$	$C_{19}H_{14}N_7O_2ClS$ 439	66 225- 28	Dark Yellow crystals	51.98 (51.93)	3.12 (3.18)	22.36 (22.32)
4k	2-OHC_6H_4	$C_{19}H_{15}N_6OSCl$ 420	74 156–58	White crystals	55.59 (55.60)	3.66 (3.65)	20.47 (20.48)

Solvent for crystallization :Ethanol

Antimicrobial studies (Antibacterial and antifungal activities)

The antibacterial activity of the newly synthesized compounds were carried out against four different pathogenic organisms, two each of Gram-negative and Gram-positive, they are

i) *Staphylococcus aureus* : (Gram-positive)
ii) *Bacillus subtilis* : (Gram-positive)
iii) *Escherichia coli* : (Gram-negative)
iv) *Pseudomonas aeruginosa* : (Gram-negative)

The fungus is

i) Candida albicans

The antibacterial activity and antifungal activity of the newly synthesized compounds in the present investigation has been assessed by minimum inhibitory concentration (MIC) by serial dilution method.

The results of the antimicrobial studies are shown in Table 4.2.

Results

Among the compounds tested for antibacterial and antifungal activity compounds 4b and 4h showed very good activity, which may be due to the presence of chlorine atom in the molecule. Most of other compounds also showed significant activity comparable with that of the standard and in many cases, the activity was much higher.

Table 4.2: Antibacterial and antifungal activity data of compounds 4a-j

Compd. No.	Antibacterial activity (MIC in µg/ mL)				Antifungal activity (MIC in µg/ mL)
	S. aureus	*E.coli*	*P.aeruaginosa*	*B. subtilis*	*C. albicans*
4a	0.25	0.25	0.25	0.25	0.25
4b	0.125	0.125	0.125	0.125	0.125
4c	0.25	0.25	0.25	0.25	0.25
4d	0.25	0.25	0.25	0.25	0.25
4e	0.25	0.25	0.25	0.25	0.25
4f	0.25	0.25	0.25	0.25	0.25
4g	0.25	0.25	0.25	0.25	0.25
4h	0.125	0.125	0.125	0.125	0.125
4i	0.25	0.25	0.25	0.25	0.25
4j	0.25	0.25	0.25	0.25	0.25
Standard Furacin	0.5	0.5	0.5	0.5	-
Standard Flucanazol	-	-	-	-	0.25

RESULTS AND DISCUSSION

δ 0.93(t, 3H, methyl proton of propyl group), 1.67(m, 2H, methylene protons of propyl group), 2.48(s, 3H, methyl protons of pyrazole group), 2.68(t, 2H, methylene protons of propyl group), 7.51-7.63 (m, 5H, phenyl protons), 10.14 (s, 1H, -N=CH proton).

Further the structure has been confirmed by recording the mass spectra of some selected compounds.

The mass spectra of compound 4b and 4d showed (M^++1) peak at m/z 333/335 and 361/363 respectively consistent with the molecular formula $C_{14}H_{13}N_6ClS$ and $C_{16}H_{17}N_6ClS$.

Similarly the structural elucidation of novel triazolothiadiazepines was performed by elemental analysis, IR, ^{1}H-NMR and mass spectral IR spetra were recorded in a Schimadzu FTIR 8400s spectrophotometer using KBr pellets. H^1 – NMR spetra were recorded in deuterated dimethyl sulphoxide in an AV500 NMR spectrometer with

tetramethylsilane as internal standard. The mass spectra were recorded in a Schimadzu GC MS-Q P5050 mass spectrometer. The elemental analysis of all the compounds done in Flash thermo1112 series CHN analyser gave the values within the permissible limit of 0.4%.Melting point were determined by open capillary and are uncorrected.

The IR, ^{1}H-NMR and MS were consistent with the assigned structures. IR spectra of condensed thiadiazepines displayed disappearance of band at1665cm^{-1} due to C=O str. And 2750cm^{-1} due to SH str.of 5-substituted -4-amino -3-mercapto-1,2,4-triazoles.

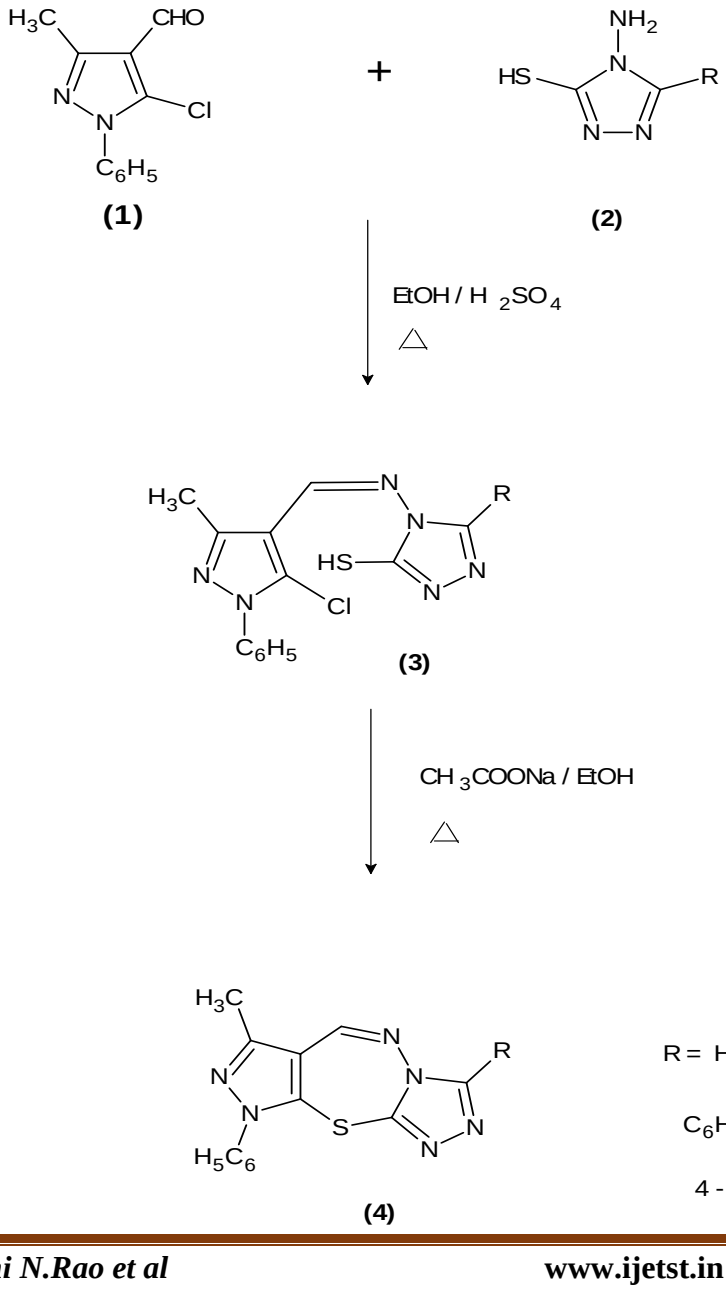
H^{1}-NMR spectra of thiadiazepines showed the C-H proton at 5ppm and-CH proton at 7.5 ppm. The proton attached to nitrogen of thiadiazepine ring was observed at 8.5 ppm.The solvent peak due to DMSO-d_6 was observed at 2.4ppm.

MATERIALS AND METHOD

1- Phenyl -3-methyl-chloro-pyrazole- 4 - aldehyde (1) was obtained by Vilsmeier-Haack formylation of 1-phenyl-3-methyl- pyrazole -4-one

Condensation of 3-substituted-4-amino-5-mercapto-1,2,4- triazoles (2) with 1-phenyl–3-methyl-5-chloro-pyrazole-4- aldehyde (1) in ethanol medium in presence of conc. sulphuric acid as catalyst gave Schiff 's base (3).

Schiff's base (3) when treated with anhydrous sodium acetatein ethanol medium gave novel triazolothiadiazepines(4).



R = H, CH $_3$, C_2H_5, C_3H_7

C_6H_5, 4 -CH $_3C_6H_4$, 4 - OCH $_3C_6H_4$, 4 - Cl C_6H_4

4 -BrC_6H_4, 2 -HOC_6H_4, 4 - NO $_2C_6H_4$

CONCLUSIONS

In the present study,our attention was focused on the synthesis and antimicrobial evaluation of a series of thiadiazepines .Based on the resulting biological evaluation data, all the compound showed mild to moderate antimicrobial potential. Among all the synthesized thiadiazepines, compound 4b and 4h showed broad antimicrobial activity against the all tested microbes.

ACKOWLEDGEMENT

We are thankful for SAIF, Punjab University, India for Spectral and elemental analysis.

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