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Research Article

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Synthesis and antimicrobial evaluation of N-aryl substituted-1,3,4-thiadiazolidin 2-amines

[1*]Mahendrasinh M. Raj, [2]Hemul V. Patel, [3]Lata M. Raj and [4]Naynika K. Patel

[1]Institute of Science & Technology for Advanced Studies & Research (ISTAR),Vallabh Vidyanagar, Gujarat, India
[2]Ashok and Rita Patel Institute of Integrated study and Research in Biotechnology and Allied Sciences (ARIBAS), New Vallabh Vidyanagar, Gujarat, India
[3]C. N. P. F. Arts and D. N. Science College, Dabhoi, Gujarat, India
[4]Department of Biosciences, Sardar Patel University, Vallabh Vidyanagar, Gujarat, India

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ABSTRACT

A series of variousN-aryl substituted-1,3,4-Thiadiazolidin 2-amines were synthesized bythe reaction All the compounds werecharacterizedby their melting point, solubility against organic solvents, TLC, IR, and1H NMR spectral. All the synthesized compounds were tested forantimicrobial and anti fungal activity.(Staphylococcus aureus (MTCC96), Escherichia coli (MTCC 443)Aspergillusniger (ATCC16404) and Candida albicans (ATCC10231).

Keywords: Thiadiazolidin, Synthesis, antimicrobial activity, IR, NMR,

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INTRODUCTION

1,3,4-Thiadiazole derivatives are of great interestclass of heterocyclic compounds having an important wide range of pharmacological properties[1]. Thiazole is an important scaffold in heterocyclic chemistry and [2,3]-thiazole ring is present in manypharmacological active substances. Thiazole derivatives have attracted a great deal of interest owing to their antimicrobial [3], anti-inflammatory [4,5], CNS depresent [6], antitubercular [7], antitumor [8], anthelmintic[9], sedative[10] antiretroviral properties[11], antineoplastic[12] activities.Drug resistance is steadily increasing process that is reaching alarming level in the treatment of infectious diseases caused by pathogenic bacteria, fungi, parasites and viruses. Over the past few decade, steadily increasing drug resistance in the treatment of infectious disease pose a serious problem in antimicrobial therapy and necessitates continuing research into novel classes of antimicrobials. A number of researchers have reported antimicrobial activities in 2,5-disubstituted-1,3,4-thiazoles[13]. Keeping the above facts in view we considered it of interest to synthesize some novel 2,5-disubstituted-1,3,4-thiadiazole derivatives for their antimicrobial properties.

The resistance towards available drugs I rapidly becoming a major worldwideproblem. The need to design new compound to deal with this resistance has become one of the most important areas of research today. Several five membered aromatic systems having three hetro atoms at symmetrical position have been studied because of their interesting physiological properties. It is also well established that various derivatives of 1,2,4-triazole, 1,3,4-thiadiazole exhibit broad spectrum of pharmacological properties such as antimicrobial and antifungal activities[14-25].The available therapeutically important medicines are terconazole, fluconazole, cefazoline and ribavirin etc. are some of the examples which contain one of these heterocyclic nucleus.

Derivatives of 1,3,4-oxadiazole and 1,3,4-thiadiazole have been found to possess a wide spectrum of pharmacological, medical and biological activities. Schiff bases have also been widely reported to be biologically

versatile compounds having antifungal, herbicidal and plant growth regulating properties. Moreover derivatives of 1,2,4-triazole are known to exhibit anti-inflammatory, antiviral, analgesic, antimicrobial, anticonvulsant and antidepressant activities. A series of 1,2,4-triazole derivatives have been patented and extensively employed in agriculture. We now report on the synthesis of compounds derived from benzothiophene containing oxadiazole, thiadiazole and triazolemoieties, with the purpose of investigating in the future their possible antibacterial and antifungal activities.

EXPERIMENTAL SECTION

All chemicals used in this study were purchase from Aldrich Chemicals and were used without further purification. All melting points are uncorrected were determined using Gallenkamp thermal point apparatus. FTIR spectra were recorded with Perkin Elmerspectrophotometer.The ^{1}HNMR spectra were determined with Brucker400 MHz FTNMR spectrometer.

F: Synthesis of 5–(4-nitro phenyl –1, 3, 4 thiadiazolidin– 2- amine
A mixture of thiosemicarbazide (0.1 mole), 4 – nitrobenzoic acid (0.1) mole and concentrated sulphuric acid (5 m) in50 ml ethanol was refluxed for 1 hour. After that the resultant mixture was poured on to crushed ice.The solid separated out was filtered. On filtration and washing with cold H_2O several times, and was recrystallized from ethanol to give product. M.P. 147^{o}C

FA: Synthesis of N-benzylidene-5 (4-nitrophenyl)-1,3,4 thiadiazolidin-2-amine
(0.01 M) product of step -1, (0.01 M) benzaldehyde and (2 ml) glacial acetic acid were refluxed in 50 ml methanol for 8 hours. Solvent was distilled of and product recrystallized from mixture of benzene and chloroform (1:6 v/v). Yield obtained was 70%.

FB: N- (4- chlorobenzylidene)-5(4-nitrophenyl) 1,3,4 thiadiazolidin-2-amine.
(0.01M) product of step 1, (0.01M)2- chlorobenzaldehyde and (2ml) glacial acetic acid were refluxed in 50 ml methanol for 8 hours. Solvent was distilled off and product recrystallised from mixture of benzene and chloroform (1:6 v/v). Yield obtained was 71%.

FC: Z-N (4-methoxybenzylidene)-5-(4-nitrophenyl)-1, 3, 4 thiadiazoline-2-amine
(0.01M) product of step 1, (0.01M) Anisaldehyde and (2ml) glacial acetic acid were refluxed in 50 ml methanol for 8 hours. Solvent was distilled off and product recrystallised from mixture of benzene and chloroform (1:6 v/v). Yield obtained was 69%.

FD: N (furan-2-yl methyllidene)-5-(4-nitrophenyl)-1, 3, 4 thiadiazoline-2-amine
(0.01M) product of step 1, (0.01M) Furfural and (2ml) glacial acetic acid were refluxed in 50 ml methanol for 8 hours. Solvent was distilled off and product recrystallised from mixture of benzene and chloroform (1:6 v/v). Yield obtained was 67%.

FE: 5(4-nitrophenyl) N-(1Z, 2E)-3 phenylprop-1en-1-ylidene)-1,3,4 thiadiazoline-2-amine
(0.01M) product of step 1, (0.01M) Cinnamaldehyde and (2ml) glacial acetic acid were refluxed in 50 ml methanol for 8 hours. Solvent was distilled off and product recrystallised from mixture of benzene and chloroform (1:6 v/v). Yield obtained was 68%.

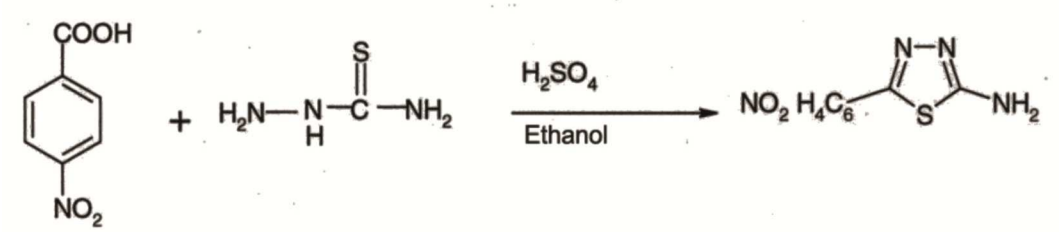
FF: 3 methoxy-5{[5-(4-nitrophenyl)-1,3,4thiadiazolidin 2-yl] imino}methyl)phenol
(0.01M) product of step 1, (0.01M) Vaniline and (2ml) glacial acetic acid were refluxed in 50 ml methanol for 8 hours. Solvent was distilled off and product recrystallised from mixture of benzene and chloroform (1:6 v/v). Yield obtained was 66%.

FG: N-ethyllidene-5-(4-nitrophenyl)-1,3,4 thiadiazolidin-2 amine
(0.01M) product of step 1, (0.01M) Acetaldehyde and (2ml) glacial acetic acid were refluxed in 50 ml methanol for 8 hours. Solvent was distilled off and product recrystalized from mixture of benzene and chloroform (1:6 v/v). Yield obtained was 65%.

Scheme-1

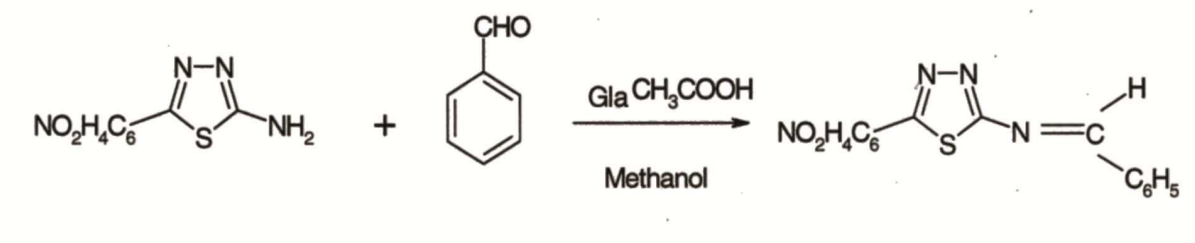
(Step-1)

F: Synthesis of 5–(4-nitro phenyl –1, 3, 4 thiadiazolidin– 2- amine

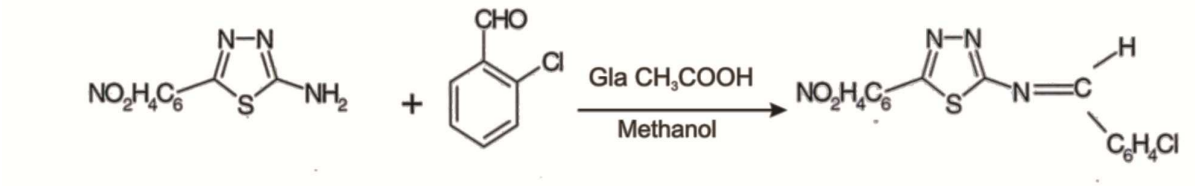


(Step-2)

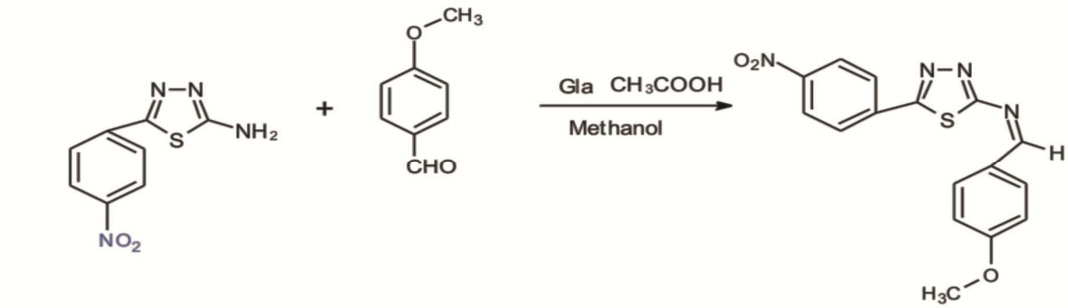
FA: Synthesis of N-benzylidene-5 (4-nitrophenyl)-1,3,4 thiadiazolidin-2-amine



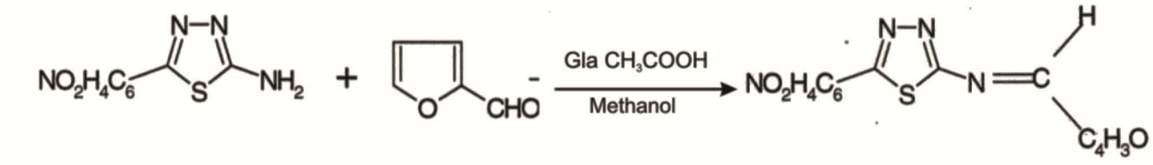
FB: N- (4- chlorobenzylidene)-5(4-nitrophenyl) 1,3,4 thiadiazolidin-2-amine.



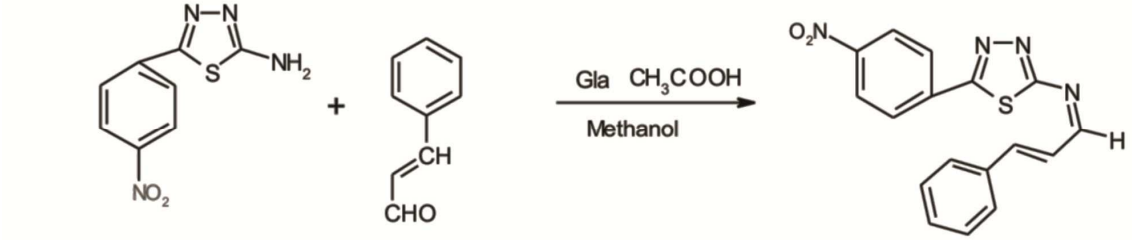
FC: Z-N (4-methoxybenzylidene)-5-(4-nitrophenyl)-1, 3, 4 thiadiazoline-2-amine



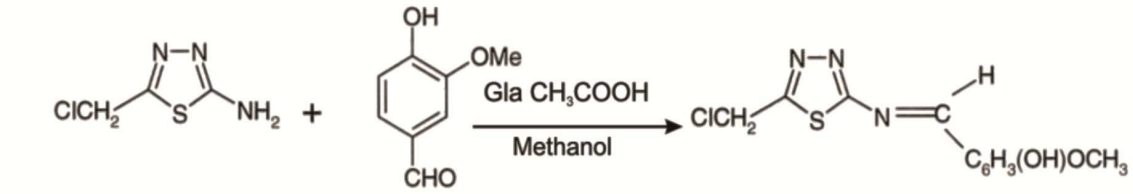
FD: N (furan-2-yl methyllidene)-5-(4-nitrophenyl)-1, 3, 4 thiadiazoline-2-amine



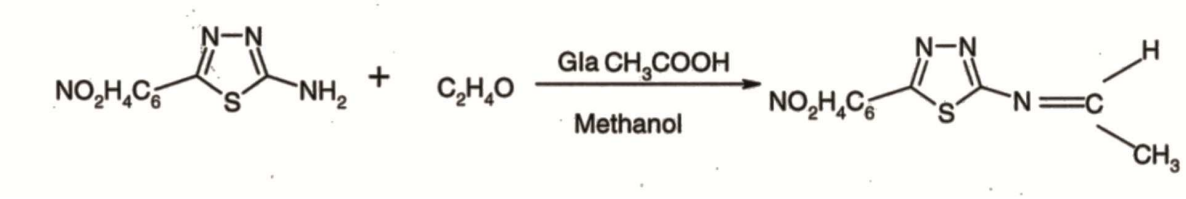
FE: 5(4-nitrophenyl) N-(1Z,2E)-3 phenylprop-1en-1-ylidene)-1,3,4 thiadiazoline-2-amine



FF: 3 methoxy-5{[5-(4-nitrophenyl)-1,3,4thiadiazolidin 2-yl] imino}methyl)phenol



FG: N-ethyllidene-5-(4-nitrophenyl)-1,3,4 thiadiazolidin-2 amine



The data of physical characteristics of synthesized compoundsare shown in table-1. Percentage of nitrogen was estimated byKjeldahl method.All the synthesized compounds were characterized by IR and 1 H NMR. The spectral data of synthesized compoundsare shown in table-2.

Table: 1. Characterization data of synthesized compounds (F – FG)

Compd.	Molecular Formula	Melting Point ° C	Yield (%)	Mol.Wt gm/mole	Nitrogen (%)	
F	$C_8H_{10}N_4O_2S$	146°C	69%	226	Cal	Est
FA	$C_{15}H_{14}N_4O_2S$	144 °C	72%	314	24.76%	21.46%
FB	$C_{15}H_{13}ClN_4O_2S$	147 °C	69%	348	17.82%	15.91%
FC	$C_{16}H_{12}N_4O_3S$	155 °C	67%	340	16.06%	13.92%
FD	$C_{13}H_{12}N_4O_2S$	162 °C	68%	304	16.46%	12.39%
FE	$C_{17}H_{12}N_4O_2S$	167 °C	68%	336	18.41%	16.22%
FF	$C_{16}H_{16}N_4O_4S$	161 °C	65%	360	16.66%	13.32%
FG	$C_{10}H_{12}N_4O_2S$	165 °C	67%	252	15.55%	13.56%

Table: 2. Infra Red / ^{1}H NHR spectral study of the synthesized compounds

Compound	IR (cm^{-1}),	H – NMR (δ, ppm)
FA	3391 (N-H str.), 2377 (Ar.C-H str.), 1628 (Ar.C-C str.), 1413 (C-N str.), 1567 (N-O str.), 619 (C-S str.)	7.8-8.31 (8H, Ar-CH), 6.87 (1H, NH), 4.72 (1H, NH), 4.50 (2H, CH_2)
FB	3444 (N-H str.), 2223 (Ar.C-H str.), 1566 (Ar.C-C str.), 1427 (C-N str.), 619 (C-S str.)	-
FC	3422 (N-H str.), 2369 (Ar.C-H str.), 1705 (Ar.C-C str.), 1426 (C-N str.), 1535 (N-O str.), 616 (C-S str.)	-
FD	3451 (N-H str.), 2287 (Ar.C-H str.), 1616 (Ar.C-C str.), 1427 (C-N str.), 1527 (N-O str.), 613 (C-S str.)	11.85 (1H, OH), 7.9-8.31 (7H, Ar-CH), 4.85 (2H, CH_2), 4.50 (1H, NH)
FE	3428 (N-H str.), 2294 (Ar.C-H str.), 1621 (Ar.C-C str.), 1448 (C-N str.), 1520 (N-O str.), 615 (C-S str.)	-
FF	3439 (N-H str.), 2366 (Ar.C-H str.), 1621 (Ar.C-C str.), 1440 (C-N str.), 1479 (N-O str.), 617 (C-S str.)	-
FG	3283 (N-H str.), 2364 (Ar.C-H str.), 1620 (Ar.C-C str.), 1383 (C-N str.), 1533 (N-O str.), 615 (C-S str.)	7.3-8.29 (4H, Ar-CH), 4.87 (1H, NH), 4.87 (2H, CH_2)

Antibacterial activity

The in vitro antibacterial screening of all the compoundswere evaluated against selected (Table 1) Gram-positiveorganisms viz. *Staphylococcus aureus* (MTCC96) and Gram-negative organisms viz. *Escherichia coli* (MTCC443). Similarly the antifungal activity was carried out by using *Aspergillus niger* (ATCC16404) and *Candida albicans* (ATCC10231) by broth dilution method recommended by NationalCommittee for Clinical Laboratory (NCCL) standards. The concentration of sample compounds was 100mcg/mL. Norfloxacin and Griseofulvin were used as standard drugs for antibacterial and antifungal activity respectively. Control test with solvents were performed for every assay but showed no inhibition of the microbial growth. The results obtained are reported in Table-3. All bioassay experiments were carried out in duplicate. The zone of inhibition of compound showing antibacterial activity. The potency also determined by zone of inhibition. The zone of inhibition in mm is given in table -3.

Table: 3. *In-vitro* antibacterial and antifungal activity of synthesized compounds

Compound	Zone of inhibition at 100 mcg/mL (in mm)			
	E.coli	***S.aureus***	***A.niger***	***C.albcans***
FA	24	24	25	26
FB	14	16	17	22
FC	25	24	19	20
FD	16	17	18	19
FE	24	23	25	25
FF	16	19	13	16
FG	24	25	25	26
Norfloxacin	24	25		
Griseofulvin	-	-	26	27

RESULTS AND DISCUSSION

In vitro antibacterial activity data of 1, 3, 4-Thiadiazole derivatives **(Table 3)** against tested organisms displayed significantactivity with a wide degree of variation. It is found thatcompound **FA, FC, FE** and **FG** have shown significant antibacterial activity. Rest of thecompounds has exhibited significant to substantialactivity against the same strain. Substantial activity isachieved in case of compounds **FG**against *S. aureus* and the remaining compounds are significantly active against the same species. All the 1,3,4-Thiadiazole derivatives have exhibited significant to moderate activity against Gramnegative bacteria. Derivatives **FA, FE and FG**have exhibited substantial activity against *A.niger*. Remaining 1,3,4-Thiadiazole derivatives in this series, compound**FF** displayed least activity against *A.niger*.. Against *C.albcans* compounds **FA, FE** and **FG** has been found to possess significant activity, comparatively weak activity has been reported by remaining compounds. E. coli was found to be more susceptible than rest of the other strains of bacteria,among them compounds **FA, FC, FE**and **FG**were showingsignificant activity for the same strain. From *in vitro*antifungal activity **(Table 3),** data reveals that all thenewly synthesized compounds displayed moderate tosignificant activity in comparison to standards. Thus, it isobvious from the structure-activity profile of substituted1,3,4-Thiadiazole derivatives; a small structural variation may induce aneffect on antibacterial activity.

CONCLUSION

1,3,4-Thiadiazole derivatives were synthesized and the structures of the compounds were established by means of IR, 1H NMR and elemental analysis. All the compounds were evaluated for antibacterial activity by cup-plate method. Compounds FA, FE and FG haveshown significant activity. Remaining compounds have also shown moderate to weak antibacterial activity.

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