e-ISSN: 2319-9849
p-ISSN: 2322-0082

Research and Reviews: Journal of Chemistry

# Synthesis of Pharmaceutically Important 1,3,4-Thiadiazole Derivatives as Antimicrobials.

Nitin Deshmukh*, Gopkumar P, and Sujit Pillai.

GRY Institute of Pharmacy, Vidya Vihar, Borawan, Khargone, Madhya Pradesh, India.

Research Article

Received: 02/01/2014
Revised: 22/01/2014
Accepted: 27/01/2014

***For Correspondence**

GRY Institute of Pharmacy, Vidya Vihar, Borawan, Khargone, Madhya Pradesh, India.

**Keywords:** Thiadiazole derivatives, synthesis, anti-microbial acivity

## ABSTRACT

Thiosemicarbazide of phenyl hydrazine on cyclization with different aromatic carboxylic acid in POCl3 gives 2-(substituted phenyl)-5-(2-phenylhydrazinyl)-1,3,4-thiadiazole. 1,3,4-thiadiazole constitute a unique class of nitrogen and sulphur containing five member heterocycle. During the last years considerable evidence has also accumulated to demonstrate the efficacy of 1,3,4-thiadiazole including antifungal , anti cancer, anticonvulsant , insecticidal, anti bacterial, anti inflammatory and other biological effects. All the compounds were characterized on the basis of IR and $^1$HNMR spectral data & were screened for antimicrobial activity.
.

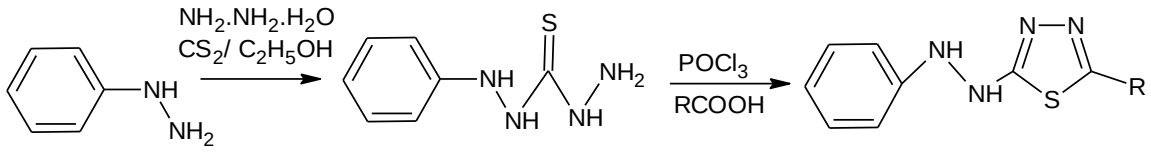
## INTRODUCTION

The progress achieved in the synthesis of heterocyclic compounds with biological potential is due to improvement of the methodological study of tested substances too. It is known that many 1,3,4-thiadiazole derivatives have biological activity, with their antibacterial, antimycobacterial, antimycotic, antifungal, antidepressive and cardiotonic action being notable. Recent research has also established for these heterocycles an antimicrobial activity. Taking these data into account, in the present study, some new 1,3,4-thiadiazole derivatives having a phenylhydrazine moiety have been synthesized and their structure confirmed by elemental and spectral (FT-IR, 1H-NMR, MS) analyses [1-10].

## MATERIAL AND METHODS

### Experimental section

#### Scheme

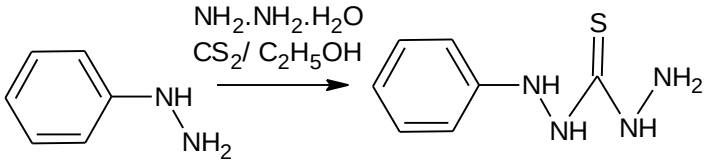



All melting points were determined on a Melt-Temp R apparatus equipped with a digital thermometer and are uncorrected. The IR spectra were measured as potassium bromide pellets on a Digilab Scimitar Series FT-IR Spectrophotometer; the wave numbers are given in cm-1. The 1H-NMR spectra were recorded in DMSO-d6 or $CD_3COCD_3$ solutions on Bruker ARX-300 spectrometer at ambient temperature. Chemical shifts were recorded as δ values in parts per millions (ppm) and were indirectly referenced to tetramethylsilane via residual solvent signal (2.49 for 1H). MS spectra were obtained using an instrument produced by Agilent Technologies, Wilmington, DE, USA. The instrument, Accurate Mass Q-TOF LC/MS 6520 was operated via the manufacture's software, Mass Hunter. Samples were dissolved in acetonitrile/water mixture (95/5 v/v) to obtain a concentration of 10 µg/mL and

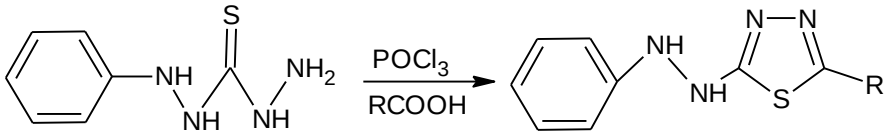
e-ISSN: 2319-9849
p-ISSN: 2322-0082

0.05 mL were directly injected into the electrospray source using the auto sampler at a rate of 0.05 ml/min. The instrument was operated in High resolution mode with an acquisition rate of 4 GHz. The source voltage was set at 4,000 V, the spray gas flow at 5 L/min, heating gas temperature at 325 °C and the fragmentor potential at 215 V. All chemical reagents were obtained from the Aldrich Chemical Company.

**N''-phenylthiocarbonohydrazide:** phenylhydrazine (0.1 mol) was dissolve in ethanol (95%, 50ml) and ammonia solution 20 ml then $CS_2$ (20 ml) was added slowly within 15 min with shaking and solution allow to stand for 1 hr. to it sodium chloroacetate (0.10 mol) and 50% hydrazine hydrate (20 ml)was added. The reaction mixture was warmed gently, filtered and evaporated to half of its volume and kept overnight. The solid thus obtained was filtered and purified by recrystallization from ethanol.




**2-(substituted phenyl)-5-(2-phenylhydrazinyl)-1,3,4-thiadiazole:** a mixture of N''-phenylthiocarbonohydrazide (0.10 mol), an aromatic acid and phosphorous oxychloride (25 ml) was refluxed for 18-22 hr. after cooling to RT the reaction mixture was poured into the crushed ice and kept overnight. The solid thus separated was filtered, washed with water, dried and purified by recrystallization from methanol.




## RESULT AND DISCUSSION

### Spectral Studies

**1a** IR (KBr):3360 (NH), 3030 $cm^{-1}$ (CH), $^1$HNMR (DMSO-$d_6$) : δ 7.35-7.90 (m, 10H, ArH) 8.32 (s, 2H, NH), MS m/z 268.077718 Da (M+), 269.085543 Da([M+1]+), 270.09 Da ([M+2]).**1b** IR (KBr):3340 (NH), 3036 (CH),750 $cm^{-1}$ (C-Cl), $^1$HNMR (DMSO-$d_6$) : δ 7.25-7.70 (m, 9H, ArH) 8.26 (s, 2H, NH), MS m/z: 302.038745 Da($M^+$),303.046571 Da(M+1), 304.04 Da(M+2). **1c** IR (KBr): 3380 (NH), 3050 (CH), 755 $cm^{-1}$ (C-Cl), $^1$HNMR (DMSO-$d_6$) : δ 7.30-7.65 (m, 9H, ArH) 8.24 (s, 2H, NH), MS m/z: 335.999773 Da (M+),337.007598 Da (M+1), 338.04544 Da(M+2),**1d** IR (KBr): 3386 (NH), 3035 (CH), 1526 $cm^{-1}$ (C-$NO_2$), ), $^1$HNMR (DMSO-$d_6$) : δ 7.54-7.70 (m, 9H, ArH) 8.36 (s, 2H, NH), MS m/z: 313.062796 Da (M+),314.070621 Da (M+1), 315.0346 Da(M+2), **1e** IR (KBr): 3358 (NH), 3020 (CH), 1555 $cm^{-1}$ (C-$NH_2$), $^1$HNMR (DMSO-$d_6$) : δ 7.48-7.56 (m, 9H, ArH) 8.36 (s, 2H, NH), MS m/z: 283.088617 Da (M+),283.089714 Da (M+1), 284.9824 Da(M+2),

| Comp. | R | % Yield | M.P/B.P. | Mol. formula | Composition | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | N | H | Cl | S |
| 1a | phenyl | 76.43 | 178-180 | $C_{14}H_{12}N_4S$ | 62.66 | 20.88 | 4.51 | ------- | 11.95 |
| 1b | 4-chlorophenyl | 81.22 | 155-158 | $C_{14}H_{11}ClN_4S$ | 55.53 | 18.50 | 3.66 | 11.71 | 10.59 |
| 1c | 2,4-dichloro phenyl | 64.31 | 201-203 | $C_{14}H_{10}Cl_2N_4S$ | 49.86 | 16.61 | 2.99 | 21.03 | 9.51 |
| 1d | 4-nitrophenyl | 66.03 | 86-90 | $C_{14}H_{11}N_5O_2S$ | 53.66 | 22.35 | 3.54 | ---- | 10.23 |
| 1e | 4-aminophenyl | 78.3 | 112-114 | $C_{14}H_{13}N_5S$ | 59.34 | 24.72 | 4.62 | ---- | 11.32 |

### Biological evaluation

All the compounds have been screened for antibacterial and antifungal properties using cup plate agar diffusion method by measuring zone of inhibition in mm. oflaxacin (50µg/ml) is used as a standard drug for antibacterial activity and ketoconazole (50µg/ml) as standard drug for antifungal activity. The compounds were screened for antibacterial activity against E.Coli, Staphylococcus aureus, Pseudomonas aerugenosa in nutrient agar medium and for antifungal activity against A. niger and C. albicans sabourauds dextrose agar medium. These sterilized agar media is poured in to the Petri dish and allow to solidify. On the surface of the media microbial suspension were spread with the help of sterilized triangular loop. A stainless steel cylinder of 8 mm diameter (presterlized) was used to bore cavities. All the synthesized compounds (50µg/ml) were placed serially in the cavities with the help of micropipette and allow to diffuse for 1 hr. DMF was used as a solvent for all the compounds and as a control. These plates were incubated at 37 $^0$c for 34 hr. and 28$^0$c for 48 hr for antibacterial

and antifungal activities. The zone of inhibition observed around the cups after respective incubation was measured and percentage inhibition of the compounds was calculated. The results are presented in table II and III.

The thiadiazole derivative **1c** having 2,4-dichlorophenyl group showed potent activity against S. aureus (87.50%) where as compound 1c & 1d showed maximum inhibition against E.coli when compared with standard drug ofloxacin.the compound 1c having 2,4-dichlorophenyl group showed significant antibacterial activity (88.23, 87.50, 81.25 % inhibition.) against E.Coli, Staphylococcus aureus, Pseudomonas aerugenosa respectively.

The thiadiazole derivative **1c** having 2,4-dichlorophenyl group showed potent activity against S. aureus (87.50%) where as compound 1c & 1d showed maximum inhibition against E.coli when compared with standard drug ofloxacin.the compound 1c having 2,4-dichlorophenyl group showed significant antibacterial activity (88.23, 87.50, 81.25 % inhibition.) against E.Coli, Staphylococcus aureus, Pseudomonas aerugenosa respectively.

The patern of the result of antifungal activity of test compounds was quite different from their antibacterial activity. The 1,3,4-thiadiazole derivative **1e** having 4-aminophenyl group showed maximum inhibition (91.66%) against A.Niger whereas 1c having 2,4-dichlorophenyl group showed maximum inhibition (72.72%) against C.albicans.thus it is concluded that 1,3,4-thiadiazole derivative were most effective against all microorganism at the concentration of 50µg/ml.

**Table II: Antibacterial activity of 1,3,4-thiadiazole derivatives**

| Comp | Staphylococcus aureus | | E. coli | | Pseudomonas aerugenosa | |
|---|---|---|---|---|---|---|
| | Zone of inhibition | % inhibition | Zone of inhibition | % inhibition | Zone of inhibition | % inhibition |
| 1a | 11 | 68.75 | 11 | 64.70 | 12 | 75.00 |
| 1b | 13 | 81.25 | 12 | 70.58 | 11 | 68.75 |
| 1c | 14 | 87.50 | 15 | 88.23 | 13 | 81.25 |
| 1d | 12 | 75.00 | 15 | 88.23 | 11 | 68.75 |
| 1e | 13 | 81.25 | 12 | 70.58 | 12 | 75.00 |
| Ofloxacin | 16 | 100 | 17 | 100 | 16 | 100 |

**Table III: Antifungal activity of 1,3,4-thiadiazole derivatives**

| Comp | Aspergillus niger | | Candida albicans | |
|---|---|---|---|---|
| | Zone of inhibition | % inhibition | Zone of inhibition | % inhibition |
| 1a | 14 | 58.33 | 12 | 54.54 |
| 1b | 16 | 66.66 | 13 | 59.09 |
| 1c | 14 | 58.33 | 16 | 72.72 |
| 1d | 12 | 50.0 | 12 | 54.54 |
| 1e | 22 | 91.66 | 12 | 54.54 |
| Ketoconazole | 24 | 100 | 22 | 100 |

## CONCLUSION

Anti-microbial and antifungal study of newly synthesized compounds was performed using cup-plate method. The patern of the result of antifungal activity of test compounds was quite different from their antibacterial activity. The 1,3,4-thiadiazole derivative **1e** having 4-aminophenyl group showed maximum inhibition (91.66%) against A.Niger whereas 1c having 2,4-dichlorophenyl group showed maximum inhibition (72.72%) against C.albicans. Thus it is concluded that 1,3,4-thiadiazole derivative were most effective against all microorganism at the concentration of 50µg/ml.

## .ACKNOWLEDGEMENT

The authors would like to thank GRY institute of Pharmacy Borawan, and JNCET Borawan, Kahargone M.P.for providing the necessary research facilities.

e-ISSN: 2319-9849
p-ISSN: 2322-0082

## REFERENCES

1. Moise M, Sunel V , Profire L , Popa M , Desbrieres J and Peptu C. Molecule 2009;2621-31.
2. Raj MM, Patel HV, Raj LM and. Patel NK. International Journal Of Pharmaceutical, Chemical And Biological Sciences 2013;3(3):814-19.
3. Farghaly TA, Abdallah MA and Abdel Aziz MR. Molecules 2012;17:4625-636.
4. Vasoya SL, Paghdar DJ, Chovatia PT, Joshi HS. Journal of Sciences, Islamic Republic of Iran 2005;16(1): 33-36.
5. Solak N ,Rollas S. ARKIVOC 2006;xii:173-81.
6. Jalhan S, Jindal A,Gupta A. Asian Journal of Pharmaceutical and Clinical Research 2012;5(3):199-208.
7. Aly Aa , Sayed Rl. Chem. Pap. 2006;60(1):56—60.
8. Gupta JK, Dudhey R, Sharma PK. Medichemonline 2010;1: 1001.
9. Purohit DH, Dodiya BL, Ghetiya RM, Vekariya PB , Josh HS. Acta Chim. Slov. 2011; 53:53–59.
10. Khan SA, Mo. Amir, kumar A. Indian journal of chemistry. 2009;(48B): 1288-93