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Short Communication

Synthesis, characterization and analgesic activity of analogues of 1, 3, 4- thiadiazole

Abhay Kumar Verma*, Alex Martin

Department of Pharmaceutical Chemistry, Spectrum Institute of Pharmaceutical Sciences and Research, Greater Noida, India

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ABSTRACT

A new series of novel analogues of 1, 3, 4- thiadiazole were synthesized. These analogues were identified on the basis of melting point range, Rf values, IR, ^{1}H NMR and mass spectral analysis. The analogues were screened for analgesic activity. The analogues exhibited significant to moderate analgesic activity.

Keywords: Thiadiazole**,** analogues, analgesic activity.

INTRODUCTION

Thiadiazole contains five-membered diunsaturated ring structure having molecular structural formula C_2 H_2 N_2S. The ending azole designates a five membered ring system with two or more heteroatoms, one of which is Nitrogen. Thiadiazoles are associated with diverse biological activities probably by virtue of –N=C-S- grouping. Literature reveals that compounds having thiadiazole nucleus have wide spectrum of pharmacological activities such as antimicrobial [1], antitubercular [2], ulcerogenic [3], anti-inflammatory [4], analgesic [5], CNS depressant [6], anticonvulsant [7], anticancer [8], antioxidant [9], antiviral [10] and antiepileptic [11] etc**.** Research in this area is still unexplored, therefore the present study is directed towards the synthesis of newer analogues of 1, 3, 4- thiadiazole with good yield and enhanced analgesic activity.

MATERIALS AND METHODS

All the chemicals procured from Central Drug House (P.) Ltd, New Delhi. The melting points were determined in open glass capillaries and were uncorrected. Thin Layer Chromatography using silica gel G (E. Merck) plates were used to access the reaction and purity of synthesized compounds. The IR spectra were recorded on Perkin-Elmer FTIR/FTFIR system in KBr pellets and noted the absorption levels (cm^{-1}) were listed. ^{1}H NMR spectra were run on Bruker DPX400 in DMSO-d_6 as solvent and TMS as an internal standard. The Mass spectra were recorded on EI ionization mode on a JEOL JMS600H EI mass spectrometer.

STEP 1: Synthesis of N-phenyl thiosemi carbazide

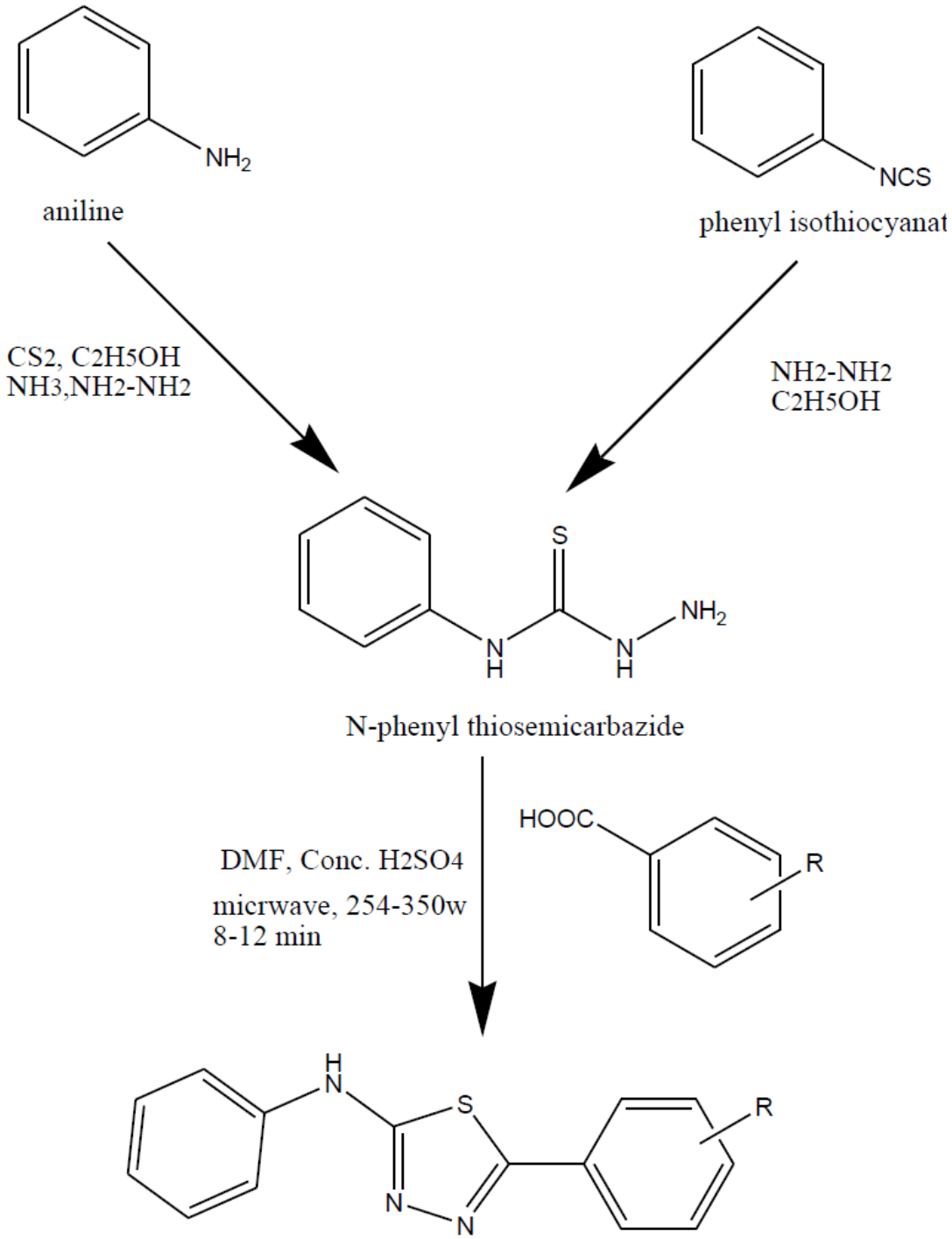
From aromatic amines: Aniline (0.01mol) was dissolved in ethanol and ammonia (25ml). Carbon disulfide (0.01mol) was added drop wise and stirred for 30 minutes. To this mixture, hydrazine hydrate (0.01mol) was added, Reaction mixture was refluxed on water bath for 9-12 hrs. Completion of reaction was checked by TLC. After reaction, reaction mixture was allowed to cool to room temperature, kept overnight in freezing condition to get solid product. Separated solid product was filtered and dried. Recrystalized from ethanol-water mixture (4:1 ratio) to yield white shining crystals. Yield: 62.33% W/W.

From phenylisothiocyanate: Phenylisothiocya nate (0.01mol), hydrazine hydrate (0.01mol) in ethyl alcohol (25ml) were taken and subjected to microwave irradiation for 6-12 minutes at 245-350W power. In between, the completion of reaction was checked by TLC. After that reaction mixture was slowly poured into crushed ice and kept overnight. Separated solid was filtered, washed with water and dried. Solid was then purified by recrystallisation from ethanol-water mixture (4:1 ratio) to yield desired compound.

STEP 2: Synthesis of 5-aryl-N-phenyl-1,3,4-thiadiazole-2-amine: N-phenyl thiosemicarbazide (0.01mol), aromatic acid (0.01mol) and sulfuric

***Corresponding Author Address:** Abhay Kumar Verma, Department of Pharmaceutical Chemistry, Spectrum Institute of Pharmaceutical Sciences and Research, Greater Noida, India; E-mail: abhayverma72@gmail.com*

acid in DMF (25ml) were taken and subjected to microwave irradiation for 6-12 minutes at 245-350W power. In between, the completion of reaction was checked by TLC. After that reaction, mixture was slowly poured into crushed ice and kept overnight. Separated solid was filtered, washed with water and dried. Solid was then purified by recrystallisation from ethanol-water mixture (4:1 ratio) to yield desired compounds [TD1-TD8]respectively.



Analgesic activity [12,13]: Eddy's hot plate method was used for screening of analgesic activity. Male Swiss albino mice weight between 25-30g were used for the experiment. In this method heat is used as a source of pain. Animals were individually placed on a hot plate maintained at constant temperature (55 ^{0}C) and the reaction of animals such as paw licking or jump response (whichever appears first) was taken as end point. A cut off time of 20 seconds were taken as maximum analgesic response to avoid injury to the paws. The animals were divided into 4 groups of 1 animal each. Test compounds at a dose of 100 and 200 mg/kg body weight and Aspirin (standard) in 0.1% suspension in Sodium Carboxy Methyl Cellulose (CMC Sodium) was given as suspension orally to animals and observed the reaction time of animals on the hot plate at 30, 60 and 90 minutes after the compounds administration.

Percentage analgesic activity was calculated by using the formula,

% analgesic activity = [(Rt/Rc)-1]100

Rt = Reaction time of test

Rc = Reaction time of control

The result was expressed as percentage analgesic activity (Table)

RESULTS AND DISCUSSION

The melting points of all synthesized compounds were found in open capillary tubes and readings were uncorrected. The structures of the synthesized compounds were supported by physical data and following spectral analysis.

N-phenyl thiosemicarbazide: MF: $C_7H_9N_3S$, MW: 167.23 AMU, m.p: 120-123 ^{0}C, Rf: 0.77 (ethanol : ethyl acetate ;9:1), IR(υ cm^{-1}) : 3414.32 (NH-NH2), 3051.37 (aromatic C-H str),1648.11(primary amino N-H str), 1591.27 (N-H bend), 1490.97, 1425.40 (aromatic C=C ring str), 1233.87 (C=S), 755.38 (C_6H_5), LC-MS: *m/z* 167 (M^+).

5-(4-chlorophenyl)-N-phenyl-1,3,4-thiadiazole-2-amine [TD1]: MF: $C_{14}H_{10}ClN_3S$, MW: 287.77 AMU, m.p: 233-235 ^{0}C, Rf: 0.86 (ethyl acetate:n Hexane; 1:1), IR(υ cm^{-1}) : 3051.39 (aromatic C-H str), 1573.91 (N-H bend), 1490.97 (C6H5), 1425.40 (aromatic C=C ring str), 1321.24 (secondary aromatic C-N str), 1111.00 (N-N=C), 1091.71(C-Cl str), 1014.56 (N-N str), 852.54(C_6H_4), 761.88 (C_6H_5), 682.80 (C-S-C), ^{1}H NMR(DMSO- *d6*) δ: 13.201- singlet, -NH (1H)7.563-7.953- m, Ar (9H), LC-MS: *m/z* 287.66 (M^+).

5-(4-nitrophenyl)-N-phenyl-1,3,4-thiadiazole-2-amine [TD2]: MF: $C_{14}H_{10}N_4O_2S$, MW: 298.327 AMU, m.p: 230-232 ^{0}C, Rf: 0.87 (ethyl acetate: n Hexane; 1:1), IR(υ cm^{-1}) : 3035.71 (aromatic C-H str), 1686.41(asymmetric aromatic NO2 str),1604.99 (N-H bend, 1426.19 (aromatic C=C ring str), 1349.58(symmetric aromatic NO2 str), 1310.55 (secondary aromatic C-N str), 1109.23 (N-N=C), 1014.04 (N-N str),887.97(aromatic nitro C-N str), 800.45(C_6H_4), 715.31 (C_6H_5), 671.45 (C-S-C), ^{1}H NMR(DMSO- *d6*) δ: 13.692- singlet, -NH (1H)8.163-8.342- m, Ar (9H), LC-MS: *m/z* 298.3 (M^+).

4(5-(phenylamino)-1,3,4-thiadiazole-2-yl) phenol [TD3]: MF: $C_{14}H_{11}N_3OS$, MW: 269.329 AMU, m.p: 168-171 ^{0}C, Rf: 0.75 (ethyl acetate: n Hexane; 1:1), IR(υ cm^{-1}) : 3380.88 (O-H str), 3085.72 (aromatic C-H str), 1600.57(N-H bend),1574.46, 1487.82,1455.51, 1418.21 (aromatic C-C ring str), 1298.57 (secondary aromatic C-N str), 1200.14(phenolic C-O str), 1181.76 (N-N=C), 1032.53 (N-N str), 771.51(C_6H_4), 746.84 (C_6H_5), 686.08 (C-S-C), 606.83(O-H out of plane bend), LC-MS: *m/z* 269.3 (M^+).

5-(3-aminophenyl)-N-phenyl-1,3,4-thiadiazole-2-amine [TD4]: MF: $C_{14}H_{12}N_4S$, MW: 268.34 AMU, m.p: 165-167 ^{0}C, Rf: 0.79 (ethyl acetate: n Hexane; 1:1), IR(υ cm^{-1}) : 3030.31 (aromatic C-H str), 1598.29(N-H bend), 1545.71,1477.21,1442.96 (aromatic C=C ring str), 1310.49 (secondary aromatic C-N str), 1252.29(primary aromatic C-N str) 1100.88 (N-N=C), 1011.31 (N-N str), 825.13(C_6H_4), 745.00 (C_6H_5), 692.84 (C-S-C), LC-MS: *m/z* 268.34 (M^+).

3(5-(phenylamino)-1,3,4-thiadiazole-2-yl) phenol [TD5]: MF: $C_{14}H_{11}N_3OS$, MW: 269.329 AMU, m.p: 163-165 ^{0}C, Rf: 0.73 (ethyl acetate: n Hexane; 1:1), IR(υ cm^{-1}) : 3186.16(O-H str), 3030.85 (aromatic C-H str), 1598.17 (N-H bend), 1546.99 (C6H5), 1470.98,1442.65 (aromatic C=C ring str), 1310.00 (secondary aromatic C-N str), 1251.65, 1170.15(phenolic C-O str), 1189.39 (N-N=C),1024.77 (N-N str), 833.26(C_6H_4), 743.88 (C_6H_5), 692.53 (C-S-C), 603.93(out of plane O-H bend), LC-MS: *m/z* 269.32 (M^+).

N-phenyl-5-ptolyl-1,3,4-thiadiazole-2-amine [TD6]: MF: $C_{15}H_{13}N_3S$, MW: 267.357 AMU, m.p: 143-145 ^{0}C, Rf: 0.76 (ethyl acetate: n Hexane; 1:1), IR(υ cm^{-1}) : 2970.43 (aliphatic C-H str), 1601.49 (N-H bend), 1501.35 (C6H5), 1455.72, 1417.97 (aromatic C=C ring str), 1280.17 (secondary aromatic C-N str), 1115.69 (N-N=C), 771.92(C_6H_4), 747.50 (C_6H_5), 686.95 (C-S-C) ^{1} H NMR(DMSO- *d6*) δ: 12.794- singlet, -NH

(1H)6.981-7.846- m, Ar (9H)2.371- s, -CH3(3H), LC-MS: *m/z* 267.35 (M^+).

5-(5-(phenylamino)-1,3,4-thiadiazole-2-yl) benzene 1,2,3 triol [TD7]: MF: $C_{14}H_{11}N_3O_3S$, MW: 301.328 AMU, m.p: 167-169 ^{0}C, Rf: 0.78 (ethyl acetate: n Hexane; 1:1), IR(υ cm^{-1}) : 3393.43 (secondary aromatic N-H str) 3030.51 (aromatic C-H str), 3242.74(O-H str), 1601.11 (N-H bend), 1496.41, 1455.68, 1422.31(aromatic C=C ring str), 1299.00 (secondary aromatic C-N str), 1200.42(phenolic C-O str), 1082.15(N-N=C), 1058.84 (N-N str), 893.34(C_6H_3), 745.58 (C_6H_5), 687.88 (C-S-C), 606.94 (O-H out of plane bend), LC-MS: *m/z* 301.3 (M^+).

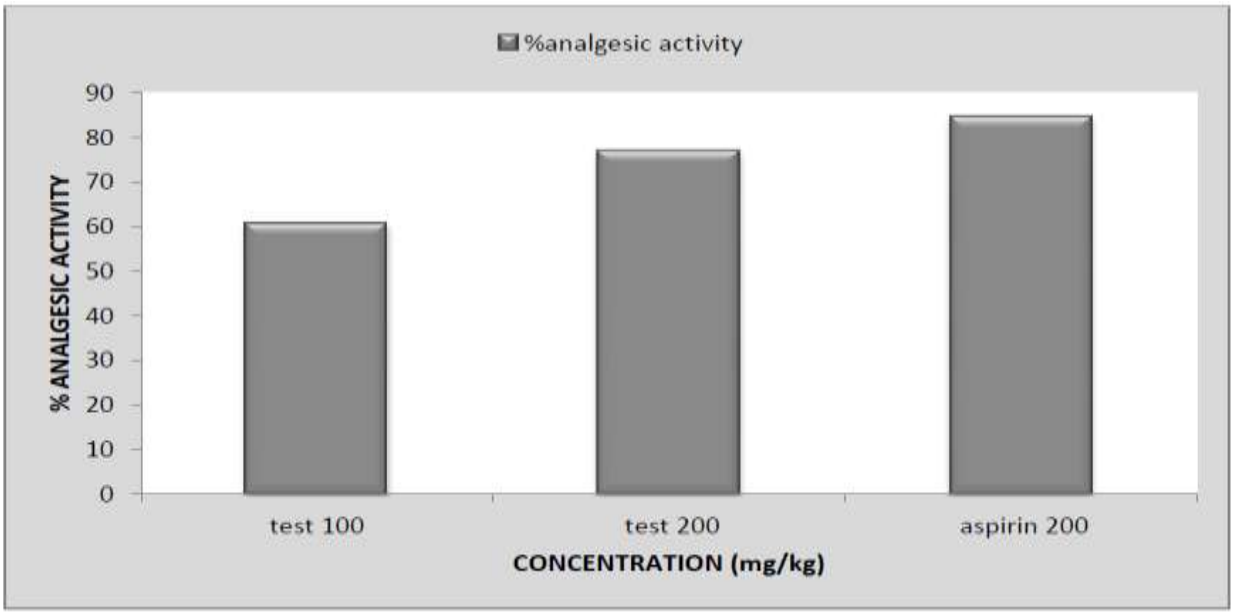
2(5-(phenylamino)-1,3,4-thiadiazole-2-yl) phenol [TD8]: MF: $C_{14}H_{11}N_3OS$, MW: 269.329 AMU, m.p: 231-233 ^{0}C, Rf: 0.8 (ethyl acetate: n Hexane; 1:1), IR(υ cm^{-1}) : 3186.18(O-H str), 3031.01 (aromatic C-H str), 1598.87 (N-H bend), 1548.49,1495.67, 1471.68 (aromatic C=C ring str), 1310.95 (secondary aromatic C-N str), 1252.13(phenolic C-O str), 1189.61 (N-N=C), 1024.73 (N-N str), 743.78(C_6H_4), 692.41 (C-S-C), 603.93(O-H out of plane bend), LC-MS: *m/z* 269.32 (M^+).

Analogue TD1 was selected and evaluated for the analgesic activity at a dose of 100 and 200 mg/kg body weight. Standard drug Aspirin was used at a dose of 200 mg/kg body weight. The test compound TD1 showed comparable activity as compared to Aspirin. The test compound given orally gave good result and therefore it is revealed that the test analogue showed better absorption from GIT. The results observed for analgesic activity by Eddy's hot plate method in *Albino mice* was given in Table.

Analgesic activity screening of analogue TD1

GROUP	DOSE mg/kg	REACTION TIME (sec) 90 MIN	% ANALGESIC ACTIVITY
CONTROL	-	7.34	
TEST 1	100	11.78	60.49
TEST 2	200	12.97	76.70
+ CONTROL (Aspirin)	200	13.53	84.33

Graphical representation of % analgesic activity of analogue TD1



CONCLUSION

The research work was oriented towards the finding of newer analogues of 1, 3, 4- thiadiazole with enhance analgesic activity. The different analogues were synthesized. Synthesized analogue TD1 showed very good analgesic activity against previously reported analogues of 1, 3, 4-thiadiazole.

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