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# SYNTHESIS, CHARACTERIZATION, & ANTIMICROBIAL SCREENING OF N-THIADIAZOLYL THIAZOLIDINONE DERIVATIVES

**Vijay V. Dabholkar* and Dinesh Udawant [#], Rahul Jaiswar[#]**

*Organic Research Laboratory, Department of Chemistry,*
**Jai Hind College, Church gate, Mumbai-400 020,*
*[#] K.C. College, Church gate, Mumbai-400 020, INDIA.*
*E-mail: vijaydabholkar@gmail.com*
*dins1323@gmail.com*

**ABSTRACT:**
A new series of 2-(5-(substitutedbenzyl)-1,3,4-thiadiazol-2-yl)-(substitutedphenyl)-thiazolidin-4-one (5) have been synthesized by the reaction of Schiff base of 2-amino-5-(substituted)-benzyl-1,3,4-thiadiazole (3) with α-mercaptoalkanoic acid (4) in glacial acetic acid. The structures of the compounds have been confirmed by IR, NMR and Mass spectroscopy. Representative compounds were screened for their anti-microbial activity against gram-negative bacteria, E coli and P.aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method. Some of these compounds have been found to exhibit excellent antibacterial activity.

**KEYWORDS**: 1,3,4-Thiadiazole, Thiazolidinone, Schiff base, and Antimicrobial activity.

## INTRODUCTION:

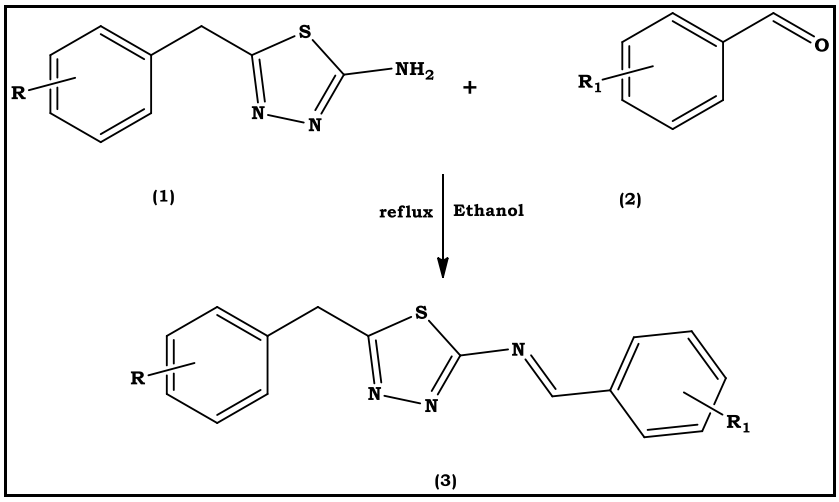
Recently, the chemistry of 1,3,4-thiadiazole derivatives is highlighted due to their wide spectrum of biological activities including antimicrobial [i-iii], anti-inflammatory [iv, v], antioxidant [vi, vii], anti-tumour [viii], anti-cancer [ix] and have other pharmacological activities [x, xi]. Moreover, this ring system is valuable building block for the synthesis of other fused heterocyclic systems. The broad and potent activity of thiadiazole and their derivatives has established them as pharmacologically significant scaffolds. Thiazolidinones are versatile scaffold due to their well-known biological activities including antioxidant [xii], antitumor [xiii], anti-inflammatory [xiv, xv], antimicrobial [xvi], anti-HIV [xvii, xviii], antiviral [xix], anticonvulsant [xx], and antihypertensive [xxi] activities. Therefore, studies of the synthesis and pharmacology of thiazolidinone derivatives have attracted more interest in recent years [xii].

In view of the versatile biological activities and the benefits of novel thiazolidinone derivatives and as a continuation of the efforts to synthesis isolated and fused heterocyclic compounds, herein is reported a facile and convenient route of synthesis of a series of new compounds containing the 1,3,4-thiadiazole and thiazolidin-4-one

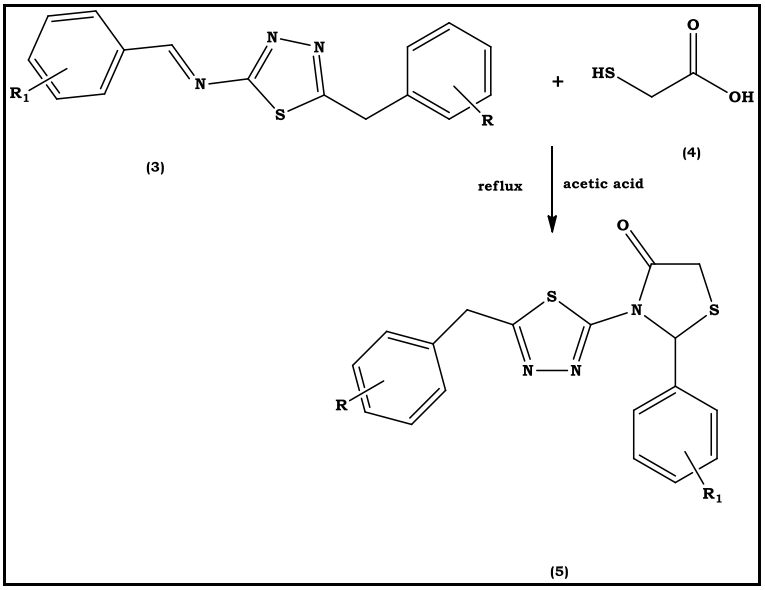
## RESULTS AND DISCUSSION

The molecules 2-amino-5-(substituted)-benzyl-1,3,4-thiadiazole, were synthesized by reported procedure [xxiii] to get 1,3,4-thiadiazole moiety (1). Further these compound were treated with substituted benzaldehydes (2) to get Schiff bases (3) **(Scheme I).** The reaction of Schiff base of 2-amino-5-(substituted)-benzyl-1,3,4-thiadiazole (3) with α-mercaptoalkanoic acid (4) in glacial acetic acid yields in target molecules 2-(5-(substitutedbenzyl)-1,3,4-thiadiazol-2-yl)-(substitutedphenyl)- thiazolidin-4-one (5) **(Scheme II)** .The structures of the compounds have been confirmed by IR and NMR. Representative compounds were screened for their anti-microbial activity against gram-negative bacteria. The result shows these compounds exhibit excellent antibacterial activity.

**Scheme I**




**Scheme II:**




## EXPERIMENTAL

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV

light as visualizing agent. $^{1}$H NMR and $^{13}$C NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

**Synthesis of Schiff base 2-amino-5-(substituted)-benzyl-1,3,4-thiadiazole (3):**
**General Procedure**.

2-Amino-5-(substituted)-benzyl)-1,3,4-thiadiazole (1) (0.01 mol) and substituted benzaldehydes (2) (0.025 mol) in ethanol (50 ml) was refluxed for about 7-8 hrs. The progress of reaction was monitored on TLC. Upon completion, the reaction mixture was quenched onto crushed ice. The product precipitated out was filtered, washed with water and purified by recrystallization from chloroform to yield (3)

The spectral analysis of representative compounds will be as follows:

*5-(4-methoxybenzyl)-N-(4-methylbenzylidene)-1,3,4-thiadiazol-2-amine* (**3a)**:

Light brown solid, yield 58%; **m.p.** (°C): 160-164 ; **IR** (KBr, cm-1): 2989-3061 ( Ar. C-H), 1679 (N=C), 1430 ( C=N) **$^{1}$H NMR** (500 MHz, DMSO, δ ppm): 2.51 (s, 3H, $CH_3$), 3.81 (s, 3H, $OCH_3$), 4.21(s, 2H, $CH_2$), 8.91 ( s, 1H, N=CH), 6.77-7.65 (m, 8H, Ar-H) ppm, **$^{13}$C NMR** (500 MHz, DMSO, δ ppm): 23.1 ($CH_3$), 41.3 ($CH_2$), 58.5 ($OCH_3$), 116.16-134.52 (C=C & Ar-C), 157.2 (C=N), 162.69 (C=N), 165.53(N=CH).

**Mass:** EI MS m/z: 324.10 $[M+1]^+$

*5-(2-methylbenzyl)-N-(4-methylbenzylidene)-1,3,4-thiadiazol-2-amine* (**3b)**:

Brown solid, yield 62%; **m.p.** (°C): 168-171; **IR** (KBr, cm-1): 2995-3081 ( Ar. C-H), 1681 (N=C), 1445 ( C=N) **$^{1}$H NMR** (500 MHz, DMSO, δ ppm): 2.67 (s, 6H, $2CH_3$), 4.45(s, 2H, $CH_2$), 8.77 ( s, 1H, N=CH), 6.79-7.59 (m, 8H, Ar-H) ppm, **$^{13}$C NMR** (500 MHz, DMSO, δ ppm): 21.2 ($CH_3$), 24.1 ($CH_3$), 39.3 ($CH_2$), 122.1-136.24 (C=C & Ar-C), 159.2 (C=N),161.79 (C=N), 163.23(N=CH).

**Mass:** EI MS m/z: 308.10 $[M+1]^+$

The physical characterization of synthesized compound **(3a-o)** was given in **Table I**.

**Table-I**

**Physical data of Schiff base 2-amino-5-(substituted)-benzyl-1,3,4-thiadiazole (3)**

| Compounds | R | $R_1$ | M.P. (°C) | Yield (%) |
|---|---|---|---|---|
| **3a** | 4-$OCH_3$ | 4-$CH_3$ | 160-164 | 58 |
| **3b** | 2-$CH_3$ | 4-$CH_3$ | 168-171 | 62 |
| **3c** | 4-Cl | 4-$CH_3$ | 165-169 | 59 |
| **3d** | 2,4-dichloro | 4-$CH_3$ | 186-190 | 65 |
| **3e** | H | 4-$CH_3$ | 178-182 | 61 |
| **3f** | 4-$OCH_3$ | 4-Cl | 169-174 | 63 |
| **3g** | 2-$CH_3$ | 4-Cl | 162-166 | 68 |
| **3h** | 4-Cl | 4-Cl | 179-183 | 62 |
| **3i** | 2,4-dichloro | 4-Cl | 168-172 | 69 |
| **3j** | H | 4-Cl | 159-163 | 65 |
| **3k** | 4-$OCH_3$ | 2-$CH_3$ | 171-174 | 57 |
| **3l** | 2-$CH_3$ | 2-$CH_3$ | 169-173 | 59 |
| **3m** | 4-Cl | 2-$CH_3$ | 163-167 | 61 |
| **3n** | 2,4-dichloro | 2-$CH_3$ | 179-183 | 63 |
| **3o** | H | 2-$CH_3$ | 189-193 | 64 |

**Synthesis of 2-(5-(substitutedbenzyl)-1,3,4-thiadiazol-2-yl)-(substitutedphenyl)-thiazolidin-4-one, (5a-o)**

**General Procedure**.

An equimolar mixture of compound (3) (0.01 0mol) and thioglycolic acid (4) (0.01 mol,) in acetic acid (25ml) as solvent, was refluxed for about 10-12 hrs. The progress of reaction was monitored on TLC. Upon completion, the reaction mixture was cooled to room temperature and neutralized with 10% sodium carbonate solution. The product obtained was filtered, washed with cold water and purified by recrystallization from ethanol to yield desired product (5).

The spectral analysis of representative compounds will be as follows:

*3-(5-(4-methoxybenzyl)-1,3,4-thiadiazol-2-yl)-2-(p-tolyl)thiazolidin-4-one* (**5a)**:

Light brown solid, yield 71%; **m.p.** (°C): 216-220; **IR** (KBr, cm-1): 3069-3100 ( Ar. C-H), 1555-1575 (C=N), 1780 (C=O), 644 (C-S-C) **$^1$H NMR** (500 MHz, DMSO, δ ppm): 2.43 (s, 3H, $CH_3$), 3.45 (s, 2H, $CH_2$), 3.87 (s, 3H, $OCH_3$), 4.5(s, 2H, $CH_2$), 5.85 (s, 1H, CH), 6.87-7.24 (m, 8H, Ar-H) ppm, **$^{13}$C NMR** (500 MHz, DMSO, δ ppm): 22.1 ($CH_3$), 34.5 ($CH_2$), 39.3 ($CH_2$), 59.5 ($OCH_3$), 71.4(CH), 119.16-139.52 (C=C & Ar-C), 158.2 (C=N), 162.69 (C=N), 175.53(C=O),

**Mass:** EI MS m/z: 398.10 $[M+1]^+$

*3-(5-(2-methylbenzyl)-1,3,4-thiadiazol-2-yl)-2-(p-tolyl)thiazolidin-4-one* (**5b)**:

Brown solid, yield 68%; **m.p.** (°C): 206-210; **IR** (KBr, cm-1): 3061-3105 ( Ar. C-H), 1545-1567 (C=N), 1776 (C=O), 654 (C-S-C) **$^1$H NMR** (500 MHz, DMSO, δ ppm): 2.43 (s, 6H, $2CH_3$), 3.49 (s, 2H, $CH_2$), 4.45(s, 2H, $CH_2$), 6.15 (s, 1H, CH), 6.89-7.29 (m, 8H, Ar-H) ppm, **$^{13}$C NMR** (500 MHz, DMSO, δ ppm): 20.2 ($CH_3$), 22.1 ($CH_3$), 34.5 ($CH_2$), 36.3 ($CH_2$), 72.4(CH), 119.16-139.52 (C=C & Ar-C), 158.2 (C=N), 163.4 (C=N), 172.53(C=O),

**Mass:** EI MS m/z: 382.10 $[M+1]^+$

*3-(5-benzyl-1,3,4-thiadiazol-2-yl)-2-(p-tolyl)thiazolidin-4-one* (**5e)**:

Beige color solid, yield 73 %; **m.p.** (°C): 187-190; **IR** (KBr, cm-1): 3087-3119 ( Ar. C-H), 1549-1573 (C=N), 1783 (C=O), 646 (C-S-C)**$^1$H NMR** (500 MHz, DMSO, δ ppm): 2.39 (s, 3H, $CH_3$), 3.69 (s, 2H, $CH_2$), 4.15(s, 2H, $CH_2$), 5.95 (s, 1H, CH), 6.81-7.29 (m, 9H, Ar-H) ppm, **$^{13}$C NMR** (500 MHz, DMSO, δ ppm): 21.6 ($CH_3$), 34.5 ($CH_2$), 37.3 ($CH_2$), 71.4(CH), 121.16-139.52 (C=C & Ar-C), 159.2 (C=N), 161.4 (C=N), 171.53(C=O),

**Mass:** EI MS m/z: 368.10 $[M+1]^+$

*2-(4-chlorophenyl)-3-(5-(2-methylbenzyl)-1,3,4-thiadiazol-2-yl)thiazolidin-4-one* (**5g)**:

Light brown solid, yield 67 %; **m.p.** (°C): 179-182; **IR** (KBr, cm-1): 3067-3109 ( Ar. C-H), 1545-1570 (C=N), 1785 (C=O), 650 (C-S-C) **$^1$H NMR** (500 MHz, DMSO, δ ppm): 2.45 (s, 3H, $CH_3$), 3.89 (s, 2H, $CH_2$), 4.25(s, 2H, $CH_2$), 5.88 (s, 1H, CH), 6.95-7.37 (m, 8H, Ar-H) ppm, **$^{13}$C NMR** (500 MHz, DMSO, δ ppm): 20.6 ($CH_3$), 32.5 ($CH_2$), 36.3 ($CH_2$), 75.4(CH), 120.16-135.52 (C=C & Ar-C), 160.2 (C=N), 162.4 (C=N), 175.53(C=O),

**Mass:** EI MS m/z: 402.9 $[M+1]^+$

*3-(5-(4-methoxybenzyl)-1,3,4-thiadiazol-2-yl)-2-(o-tolyl)thiazolidin-4-one* (**5k)**:

Light brown solid, yield 61 %; **m.p.** (°C): 183-187; **IR** (KBr, cm-1): 3077-3103 ( Ar. C-H), 1543-1574 (C=N), 1781 (C=O), 649 (C-S-C) **$^1$H NMR** (500 MHz, DMSO, δ ppm): 2.41 (s, 3H, $CH_3$), 3.69 (s, 2H, $CH_2$), 3.87 (s, 3H, $OCH_3$), 4.32 (s, 2H, $CH_2$), 5.92 (s, 1H, CH), 6.88-7.29 (m, 8H, Ar-H) ppm, **$^{13}$C NMR** (500 MHz, DMSO, δ ppm): 19.6 ($CH_3$), 33.5 ($CH_2$), 37.3

($CH_2$), 58.5 ($OCH_3$), 74.4(CH), 119.6-138.52 (C=C & Ar-C), 157.2 (C=N), 160.4 (C=N), 173.3(C=O),
**Mass:** EI MS m/z: 398.10 $[M+1]^+$

*3-(5-(2-methylbenzyl)-1,3,4-thiadiazol-2-yl)-2-(o-tolyl)thiazolidin-4-one* (**5l**):
Brown solid, yield 71 %; **m.p.** (°C): 193-197; **IR** (KBr, cm-1): 3067-3110 ( Ar. C-H), 1541-1570 (C=N), 1785 (C=O), 652 (C-S-C) **$^1$H NMR** (500 MHz, DMSO, δ ppm): 2.48 (s, 6H, $2CH_3$), 3.89 (s, 2H, $CH_2$), 4.21 (s, 2H, $CH_2$), 6.14 (s, 1H, CH), 6.78-7.17 (m, 8H, Ar-H) ppm, **$^{13}$C NMR** (500 MHz, DMSO, δ ppm): 19.6 ($CH_3$), 21.5 ($CH_3$), 38.5 ($CH_2$), 41.3 ($CH_2$), 76.4(CH), 122.6-136.52 (C=C & Ar-C), 158.2 (C=N), 161.4 (C=N), 176.3(C=O),
Mass: EI MS m/z: 382.10 $[M+1]^+$

## ANTIMICROBIAL ACTIVITIES

Representative compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method [xxiv, xxv]. The zone of inhibition was measured in mm and the activity was compared with standard drug. The antimicrobial data was given in **Table II**.

**TABLE II: Antibacterial Activity of compound 5**

| **Antibacterial Activity of compound 5** | | | | |
|---|---|---|---|---|
| **Comp.** | **Zone of inhibition (in mm)** | | | |
| | **Gram Positive** | | **Gram negative** | |
| | **S.aureus** | **C.diphtheria** | **P.aeruginosa** | **E.coli** |
| **5a** | 21 | 22 | 20 | 23 |
| **5b** | 23 | 24 | 21 | 26 |
| **5e** | 18 | 20 | 19 | 20 |
| **5h** | 22 | 23 | 23 | 19 |
| **5i** | 20 | 19 | 26 | 21 |
| **5k** | 14 | 17 | 22 | 17 |
| **5l** | 12 | 14 | 21 | 24 |
| **5o** | 23 | 24 | 20 | 22 |
| **Ampicillin trihydrate** | 26 | 28 | 24 | 21 |
| **DMSO** | 0 | 0 | 0 | 0 |

* Diameter of the disc was 6mm;
Concentration of the compounds taken was about 100 µg/mL.

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