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Synthesis, charecterization and biological activities of some novel thiadiazole derivatives

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Abstract

This work involved the synthesis of some new series of chemical compound which contain Vanillin, 1,3,4 Thiadiazole with Azetidinone or thiazolidinone moieties. In the first step reaction Vanillin and thiosemicarbazide afforded 2-(4-hydroxy-3-methoxybenzylidene) hydrazinecarbo thioamide **(1).** This compound on further cyclized afforded 4-(5-amino-1,3,4-thiadiazol-2-yl)-2- methoxyphenol **(2).** Then we synthesized the various 4-(5-((4-substituted-benzylidene)amino)- 1,3,4-thiadiazol-2-yl)-2-methoxyphenol **(3a-e)** treating with various substitutes aldehydes**.** The synthesized compounds **(3a-e)** treated with chloroacetyl chloride to get 3-chloro-1-(5-(4- hydroxy-3-methoxyphenyl)-1,3,4-thiadiazol-2-yl)-4-(4-substituted-phenyl) azetidin-2-one **(4a-e)**. Further compound **(3a-e)** is reacts with mercaptoacetic acid to afforded 3-(5-(4 hydroxy-3- methoxyphenyl)-1,3,4-thiadiazol-2-yl)-2-(4-substituted- phenyl) thiazolidin-4-one **(5a-e).**

All the synthesized compounds were confirmed by FTIR, ^{1}H NMR and Mass spectral data. Some of the synthesized compounds were screened for biological activity. The compounds showed significant antifungal and antitubercular activity and QSAR studies were carried out for all newly synthesized compounds.

Keywords: Vanillin, Thiosemicarbazide, Antibacterial activity, antifungal activity, Antitubercular activity.

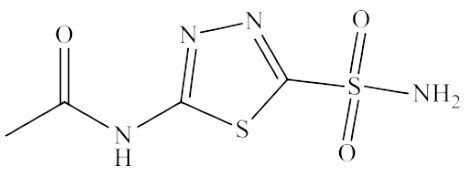
INTRODUCTION

Vanillin is a phenolic aldehyde, which is an organic compound. Vanillin functional groups include aldehyde, hydroxyl, and ether[1]. Similar moiety like Eugenol and Curcumin[2,3]. It exhibits the different biological activity such as antifungal, antibacterial, anticancer and antitubercular[4-7].

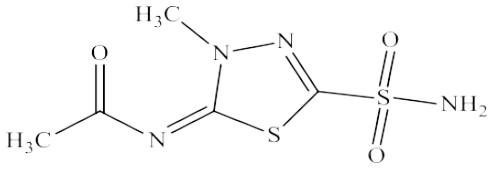
Heterocyclic compounds play an important role among organic compounds with biological activity used as drugs in human and veterinary medicine or as insecticides and pesticides in agriculture[8].

Thiadiazoles belong to the classes of five membered heterocycle ring. It Contains 2- Nitrogen and 1-Sulphur which have extensive application as structural units of biologically active molecules and as useful intermediates in medicinal chemistry[9].

During the past years, substituted 1, 3, 4-thiadiazole derivatives have received significant attention and have been increasingly investigated due to their broad spectrum of pharmacological properties. It is supposed that 1,3, 4-thiadiazole derivatives exhibit various biological activities due to the presence of =N−C−S− moiety[10]. The marketed drugs such as Acetazolamide and Methazolamide proved their therapeutic potential as Glaucoma and Antiepilepsy [11-14].

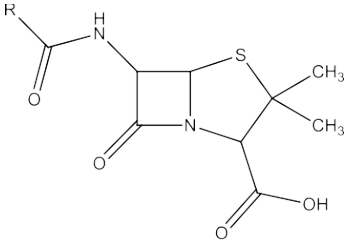


Acetazolamide

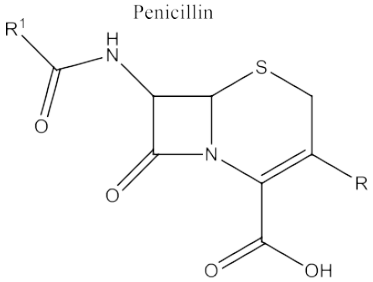


Methazolamide

Azetidinone, commonly known as β-lactams. The activity of the famous antibiotics such as Penicillin and Cephalosporin are attributed to the presence of 2-azetidinone ring in them. Recently, some other types of biological activity besides the antibacterial activity have been reported in compounds containing Azetidinone ring. Such biological activities include antifungal, antitubercular and antitumor [15].

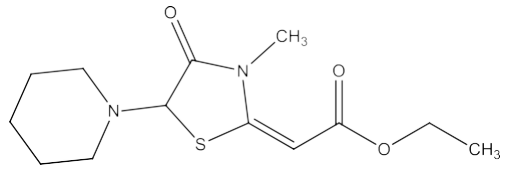


Penicillin

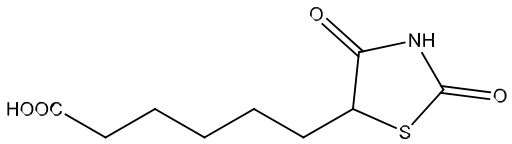


Cephalosporin

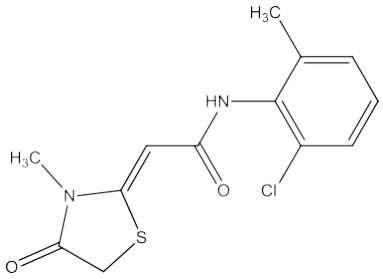
Thiazolidinone and its important class of five membered heterocycles moieties. It is a core structure in various synthetic pharmaceuticals, displaying a broad spectrum of biological activity. Based on this pharmacophore which are already in the market such as Etozoline (antihypertensive), Ralitoline (anticonvulsant), and Thiazolidomycin (activity against Streptomyces species). With this view, we are planning to synthesize vanillin analogue of thiadiazole with Azetidinone and Thiazolidinone ring to evaluate their biological activity[16].



Etozolin



Thiazolidomycin



Ralitoline

By considering above fact on vanillin, thiadiazole, Azetidinone and thiazolidinone, we plan to synthesize the compound containing above moieties. The present work is based upon the Schiff base reaction which involves reaction between vanillin as aromatic aldehyde and Thiosemicarbazide as primary amine in ethanolic media in presence of sodium acetate to get 2- (4-hydroxy-3-methoxybenzylidene) hydrazine carbothioamide **(1)**. This intermediate is reacted with H_2SO_4 to get 4-(5-amino-1,3,4-thiadiazol-2-yl)-2-methoxyphenol **(2).** The compound **2** undergoes Schiff base reaction with different aldehyde **(3a-e)**. Further synthesized compound reacts with 2-chloroacetyl chloride to form different Azetidinone compound **(4a-e).** Similarly the Schiff base **(3a-e)** is reacted with thioglycolic acid in presence of zinc chloride to form thiazolidinone **(5a-e)** derivatives. The series of reaction carried out and it was presenting in **Scheme-01**.

MATERIALS AND METHODS:

The completion of reaction was monitored by TLC and recrystallization was done by a suitable solvent. Determination of melting point was done by open capillary tube. FT-IR spectra of synthesized compounds were recorded in Bruker alpha FT-IR spectrophotometer. ^1H NMR of synthesized compounds was recorded in Bruker Avance II 400 MHz FT-NMR spectrometer. The mass spectra were recorded on quadrupole ion trap LC-MS with ESI source.

Synthesis of 2-(4-hydroxy-3-methoxybenzylidene) hydrazinecarbothioamide (1)

Thiosemicarbazide (0.01 mol) and 5ml ethanol taken in RB Flask, 5-10 ml of ethanol and (0.01 mol) of vanillin was added slowly with continuous stirring. The mixture was refluxed for 5-7hrs. The clear solution obtained shake mixture for few minutes and allowed to stand. Thiosemicarbazone precipitated from the cold solution. Filter off the precipitate and recrystallize with ethanol.

(FTIR) cm^{-1}: (NH_2) 3528cm^{-1}, (OH) 3270cm^{-1}, (NH) 3435cm^{-1}, (CH)2897 cm^{-1} (C=S) 1201cm^{-1}. ^1H NMR (DMSO-*d*6): δ: 11.2 (h, 1H;OH); 9.5 (h, 1H;NH); 8.1 (s, 1H; CH); 7.9 (s, 2H;NH_2); 7.4 (s, 2H;Ar-CH); 7.0 (d, 2H;Ar-CH); 6.7 (d, 2H;Ar-CH); 3.8 (s, 3H;OCH_3).

Elemental analysis. Calculated, (%) for $C_9H_{11}N_3O_2S$: C, 47.99; H, 4.92; N, 18.65; O, 14.20; S, 14.23; Found C, 46.22; H, 4.12; N, 17.05; O, 13.57; S, 13.64; QSAR parameters: C logP-1.08; Drug likeness-004.

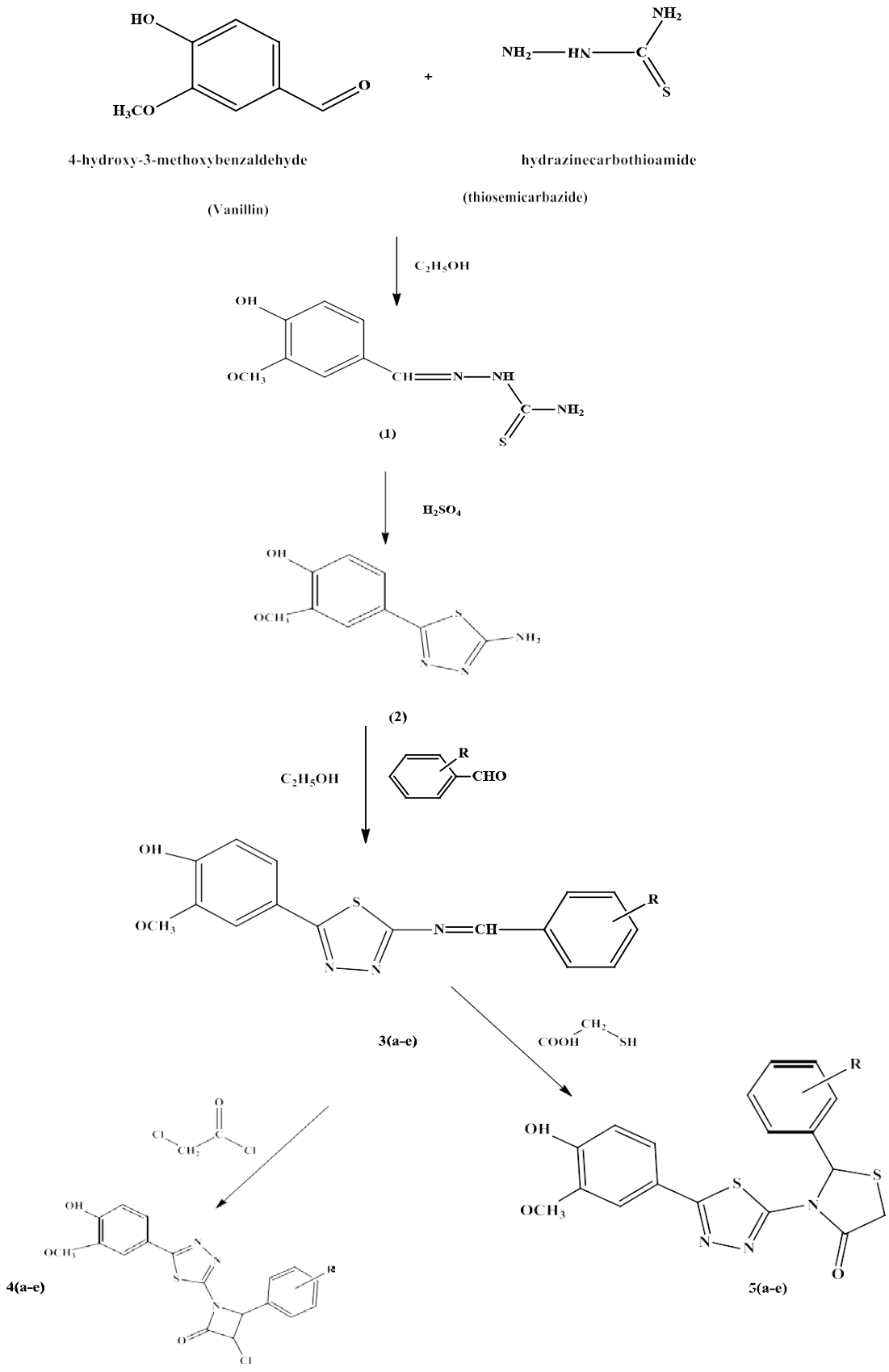
Synthesis of 4-(5-amino-1,3,4-thiadiazol-2-yl)-2-methoxyphenol (2)

Then, this intermediate **2**. (0.002 mol) was dissolved in 2 mL conc. H_2SO_4. This solution was stirred at room temperature and left overnight. It was then poured into crushed ice. The resulting suspension was kept in ammonical water for 2 hrs, filtered and recrystallized from ethanol.

(FTIR) cm^{-1}: (OH) 3122 cm^{-1}, (NH_2) 1589 cm^{-1}, (C-S) 636cm^{-1}; ^1H NMR (DMSO-*d6*):δ: 11.2 (h, 1H;OH); 7.9 (s, 2H; NH_2); 7.4 (s, 1H;Ar-CH); 7 (d, 2H;Ar-CH); 6.7 (d, 2H;Ar-CH);3.8 (s, 3H, OCH_3); Elemental analysis. Calculated, (%) for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82; O, 14.33; S, 14.36; Found C, 47.66; H, 3.35; N, 17.05; O, 13.57; S, 13.26; QSAR parameters C logP–1.09; Drug likeness- (-)0.34.

Synthesis of 4-(5-((4-(substituted)benzylidene)amino)-1,3,4-thiadiazol-2-yl)-2-methoxy phenol (3a-e)

A solution of 3a (0.001 mol) was prepared in 10 ml alcohol in a round bottom flask. Required aldehyde (0.001 mol) was dissolved in 10 ml alcohol, then added to it. The mixture was refluxed for 5-6 hr. The volume of alcohol was reduced to half by distillation under reduced pressure. The resulting solution was poured on crushed ice. The precipitate which got separated was dried and recrystallized from ethanol.



R= a – 4-Chloro, b - 4-Hydroxy, c - 4-Hydroxy-3-Methoxy, d - 3-Hydroxy and e – 4- Dimethylamine

Scheme 1

Table-01
Physical data of the newly synthesized compounds

Sl. No	Compounds	M.F	M. Wt.	M.P (˚C)	% yield
1.	1	$C_9H_{11}N_3O_2S$	225	204	63
2.	2	$C_9H_9N_3O_2S$	223	130	58
3.	3a	$C_{16}H_{12}ClN_3O_2S$	345	150	32
4.	3b	$C_{16}H_{13}N_3O_3S$	327	150	32
5.	3c	$C_{17}H_{15}N_3O_4S$	357	195	48
6.	3d	$C_{16}H_{13}N_3O_3S$	327	180	40
7.	3e	$C_{18}H_{18}N_4O_2S$	354	190	38
8.	4a	$C_{18}H_{13}Cl_2N_3O_3S$	422	250	35
9.	4b	$C_{18}H_{14}ClN_3O_4S$	403	240	38
10.	4c	$C_{19}H_{16}ClN_3O_5S$	433	210	39
11.	4d	$C_{18}H_{14}ClN_3O_4S$	403	230	36
12.	4e	$C_{20}H_{19}ClN_4O_3S$	430	230	36
13.	5a	$C_{18}H_{14}ClN_3O_3S_2$	419	140	36
14.	5b	$C_{18}H_{14}N_3O_4S_2$	401	210	36
15.	5c	$C_{19}H_{17}N_3O_5S_2$	431	175	36
16.	5d	$C_{18}H_{14}N_3O_4S_2$	401	210	36
17.	5e	$C_{20}H_{20}N_4O_3S_2$	428	210	32

4-(5-((4-chlorobenzylidene)amino)-1,3,4-thiadiazol-2-yl)-2-methoxyphenol (3a)

(FTIR) cm^{-1}: (OH) 3268 cm^{-1}, (C-H) 2898 cm^{-1}, (C-S) 696 cm^{-1}, (C-Cl) 776 cm^{-1},. ^1H NMR (DMSO-*d6*): δ: 11.4 (h, 1H;OH); 8.2 (s, 1H;CH); 8.0(s, 2H;Ar-CH); 7.9 (d, 2H;Ar-CH); 7.8 (d, 2H;Ar-CH); 7.4 (d, 2H;Ar-CH); 3.8 (s, 3H, OCH_3); Elemental analysis: Calculate (%) for $C_{16}H_{12}ClN_3O_2S$: C, 55057; H, 3.50; Cl, 10.25; N, 12.15; O, 9.25; S, 9.27; Found: C, 54.40; H,2.75; Cl, 9.53; N, 11.35; O, 8.57; S, 8.58; QSAR parameter : C log P- 3.20; Drug likeness: -0.08, M^+ peak 345m/z.

4-(5-((4-hydroxybenzylidene)amino)-1,3,4-thiadiazol-2-yl)-2-methoxyphenol (3b)

(FTIR) cm^{-1}: (OH) 3428 cm^{-1}, (C-H) 2970 cm^{-1}, (C-S) 687cm^{-1}; Elemental analysis. Calculated, (%) for $C_{16}H_{13}N_3O_3S$: C, 58.70; H, 4.0; N, 12.84; O, 14.66; S, 9.80; Found C, 57.60;
H, 3.35; N, 11.35; O, 13.57; S, 8.26; QSAR parameters: C logP–2.72; Drug likeness-(-)0.21,.

4-(5-((4-hydroxy-3-methoxybenzylidene)amino)-1,3,4-thiadiazol-2-yl)-2-methoxyphenol (3c)

(FTIR) cm^{-1}: (OH) 3278 cm^{-1}, (C-H) 2970cm^{-1}; Elemental analysis. Calculated, (%) for $C_{17}H_{15}N_3O_4S$: C, 57.13; H, 4.23; N, 11.76; O, 17.91; S, 8.97; Found C, 56.60; H, 3.75; N, 10.55;
O, 16.57; S, 7.26; QSAR parameters: C logP–2.58;Drug likeness-(-)028,.

4-(5-((3-hydroxybenzylidene)amino)-1,3,4-thiadiazol-2-yl)-2-methoxyphenol (3d)

(FTIR) cm^{-1}: (OH) 3260 cm^{-1}, (C-H) 2971 cm^{-1}, (C-S) 689cm^{-1}; Elemental analysis. Calculated, (%) for $C_{16}H_{13}N_3O_4S$: C, 58.70; H, 4.0; N, 12.84; O, 14.66; S, 9.80; Found C, 57.60;
H, 3.35; N, 11.35; O, 13.57; S, 8.26; QSAR parameters: C logP–2.72; Drug likeness-0.03,.

4-(5-((4-(dimethylamino)benzylidene)amino)-1,3,4-thiadiazol-2-yl)-2-methoxyphenol (3e)

(FTIR) cm^{-1}: (OH) 3253 cm^{-1}, (C-H) 2925 cm^{-1}; Elemental analysis. Calculated, (%) for $C_{16}H_{13}N_3O_4S$: C, 58.70; H, 4.0; N, 12.84; O, 14.66; S, 9.80; Found C, 57.60; H, 3.35; N, 11.35;
O, 13.57; S, 8.26; QSAR parameters: C logP–3.17; Drug likeness-(-)0.48,.

Synthesis of 3-chloro-1-(5-(4-(substituted)3-methoxyphenyl)-1,3,4-thiadiazol-2-yl)-4-(4-hydroxyphenyl)azetidin-2-one (4a-e)

To a mixture of compound 3 (0.001mol) and triethylamine (0.2ml) in dioxane (1ml), Chloroacetyl chloride (0.1ml) was added drop-wise at 5-10^{0}C. the reaction mixture was stirred for 6hr. After the completion of reaction, the reaction mixture was poured into crushed ice to get solid, which was filtered and dried.

3-chloro-4-(4-chlorophenyl)-1-(5-(4-hydroxy-3-methoxyphenyl)-1,3,4-thiadiazol-2- yl)azetidin-2-one (4a)

(FTIR) cm^{-1}: (OH) 3345 cm^{-1}, (C-H) 2971 cm^{-1}, (C=O) 1702cm^{-1}; Elemental analysis.
Calculated, (%) for $C_{18}H_{13}Cl_2N_3O_3S$: C, 51.20; H, 3.10; Cl, 16.79; N, 9.95; O, 11.37; S, 7.59;
Found C, 50.60; H, 2.52; Cl, 15.85; N, 9.05; O, 10.67; S, 6.78; QSAR parameter; C logP–3.69;

Drug likeness-0.40, M^+ peak 422m/z.

3-chloro-1-(5-(4-hydroxy-3-methoxyphenyl)-1,3,4-thiadiazol-2-yl)-4-(4-hydroxyphenyl) azetidin-2-one (4b)

(FTIR) cm^{-1}: (OH) 3301 cm^{-1}, (C-H) 2972 cm^{-1}, (C-S) 670 cm^{-1}, (C=O) 1706cm^{-1},. ^1H NMR (DMSO-*d6*): δ 11.2 (h, 1H;OH); 9.5 (d, H;CH); 8.1 (d, H;CH); 7.9 (s, 1H, Ar-CH); 7.4 (d,2H, Ar-CH); 7.0 (d, 2H, Ar-CH); 6.7 (d, 2H;Ar-CH); 3.8 (s, 3H, OCH_3); Elemental analysis. Calculated, (%) for $C_{18}H_{14}ClN_3O_4S$: C, 53.53; H, 3.49; Cl, 8.78; N, 10.41; O, 15.85; S, 7.94.
Found C, 52.60; H, 2.52; Cl, 7.85; N, 9.25; O, 14.67; S, 6.78; QSAR parameters: C logP–2.3;Drug likeness-0.09;

3-chloro-4-(4-hydroxy-3-methoxyphenyl)-1-(5-(4-hydroxy-3-methoxyphenyl)-1,3,4- thiadiazol-2-yl)azetidin-2-one (4c)

(FTIR) cm^{-1}: (OH) 3228 cm^{-1}, (C-H) 2969 cm^{-1}, (C=O) 1766cm^{-1}; Elemental analysis. Calculated, (%) for $C_{19}H_{16}ClN_3O_5S$: C, 52.60; H, 3.72; Cl, 8.17; N, 9.69; O, 18.44; S, 7.39;
Found C, 51.82; H, 2.52; Cl, 7.85; N, 9.25; O, 17.67; S, 6.78; QSAR parameters: C logP–2.16;
Drug likeness-0.01.

3-chloro-1-(5-(4-hydroxy-3-methoxyphenyl)-1,3,4-thiadiazol-2-yl)-4-(3-hydroxyphenyl) azetidin-2-one (4d)

(FTIR) cm^{-1}: (OH) 3319 cm^{-1}, (C-H) 2937 cm^{-1}, (C-S) 681 cm^{-1}, (C=O) 1699cm^{-1};
Elemental analysis. Calculated, (%) for $C_{18}H_{14}ClN_3O_4S$: C, 53.53; H, 3.49; Cl, 8.78; N, 10.41; O, 15.85; S, 7.94; Found C, 52.60; H, 2.52; Cl, 7.85; N, 9.25; O, 14.67; S, 6.78; QSAR parameters:
C logP–2.31; Drug likeness-0.27;

3-chloro-4-(4-(dimethylamino)phenyl)-1-(5-(4-hydroxy-3-methoxyphenyl)-1,3,4-thiadiazol- 2-yl)azetidin-2-one (4e)

(FTIR) cm^{-1}:(OH) 3219 cm^{-1}, (C-H) 2922 cm^{-1}, (C=O) 1761cm^{-1}; Elemental analysis. Calculated, (%) for $C_{20}H_{19}ClN_4O_3S$: C, 55.75; H, 4.44; Cl, 8.23; N, 13.0; O, 11.14; S, 7.44;
Found C, 54.66; H, 3.70; Cl, 7.85; N, 12.65; O, 10.52; S, 6.55; QSAR parameters: C logP-3.15;
Drug likeness-(-)0.13;

Synthesis of 3-(5-(4-hydroxy-3-methoxyphenyl)-1,3,4-thiadiazol-2-yl)-2-(4(substituted) phenyl)thiazolidin-4-one (5a-e)

A solution of **3 (**0.001 mol) in DMF and mercaptoacetic acid (0.0012 mol) was refluxed with a pinch of anhydrous $ZnCl_2$ for 10-14 hr. on a water bath. After completion of reaction, excess of DMF was distilled off. The resulting product was treated with 5% $NaHCO_3$ solution to remove unreacted mercaptoacetic acid. The separated product was washed with water, dried and recrystallized from DMF.

2-(4-chlorophenyl)-3-(5-(4-hydroxy-3-methoxyphenyl)-1,3,4-thiadiazol-2-yl)thiazolidin-4- one (5a)

(FTIR) cm^{-1}: (OH) 3331 cm^{-1}, (C-H) 2922 cm^{-1}, (C=O) 1787cm^{-1}, (C-S) 788 cm^{-1};
Elemental analysis. Calculated, (%) for $Cz_{18}H_{14}ClN_3O_3S_2$: C, 51.49; H, 3.36; Cl, 8.44; N, 10.01; O, 11.43; S, 15.27; Found C, 50.52; H, 2.44; Cl, 7.49; N, 9.65; O, 10.52; S, 14.55; QSAR parameters: C logP–1.08; Drug likeness-0.39; M^+ peak 419

3-(5-(4-hydroxy-3-methoxyphenyl)-1,3,4-thiadiazol-2-yl)-2-(4-hydroxyphenyl) thiazolidine- 4-one (5b)

(FTIR) cm^{-1}: (OH) 3252 cm^{-1}, (C=O) 1690cm^{-1}, (C-S) 721 cm^{-1},. ^1H NMR (DMSO-*d6*): δ: 8.9 (s, 1H; OH); 3.4 (s, 2H, CH_2); 6.6 (d, 2H;Ar-CH); 6.8 (d, 2H;Ar-CH); 6.9 (d, 2H;Ar-CH); 7.1 (d, 2H;Ar-CH); 7.2 (d, 2H;Ar-CH); 3.8 (s, 3H, OCH_3);
Elemental analysis. Calculated, (%) for $C_{18}H_{15}N_3O_4S_2$: C, 53.85; H, 3.77; N, 10.47; O, 15.94; S, 15.97; Found C, 52.52; H, 2.44; N, 9.65; O, 14.52; S, 14.55; QSAR parameters: C logP–1.71; Drug likeness-0.06;

2-(4-hydroxy-3-methoxyphenyl)-3-(5-(4-hydroxy-3-methoxyphenyl)-1,3,4-thiadiazol-2- yl)thiazolidin-4-one (5c)

(FTIR) cm^{-1}: (OH) 3244 cm^{-1}, (C=O) 1817cm^{-1};
Elemental analysis. Calculated, (%) for $C_{19}H_{17}N_3O_5S_2$: C, 52.89; H, 3.97; N, 9.74; O, 18.54; S, 14.86; Found C, 51.25; H, 2.35; N, 8.45;O, 17.72; S, 14.55 QSAR parameters: C logP–1.56; Drug likeness-(-)0.02;

3-(5-(4-hydroxy-3-methoxyphenyl)-1,3,4-thiadiazol-2-yl)-2-(3-hydroxyphenyl) thiazolidine- 4-one (5d)

(FTIR) cm^{-1}: (OH) 3314 cm^{-1}, (C-H) 2930 cm^{-1}, (C=O) 1694cm^{-1}, (C-S) 660 cm^{-1};
Elemental analysis. Calculated, (%) for $C_{18}H_{15}N_3O_4S_2$: C, 53.85; H, 3.77; N, 10.47; O, 15.94; S, 15.97; Found C, 52.52; H, 2.44; N, 9.65; O, 14.52; S, 14.55; QSAR parameters: C logP–1.71;Drug likeness-0.25;

2-(4-(dimethylamino)phenyl)-3-(5-(4-hydroxy-3-methoxyphenyl)-1,3,4-thiadiazol-2- yl)thiazolidin-4-one (5e)

(FTIR) cm^{-1}: (OH) 3261 cm^{-1}, (C=O) 1688cm^{-1}, (C-S) 681 cm^{-1}; Elemental analysis. Calculated, (%) for $C_{20}H_{20}N_4O_3S_2$: C, 56.06; H, 4.70; N, 13.07; O, 11.20; S, 14.97; Found C,56.52; H, 3.44; N, 12.35; O, 10.72; S, 14.55; QSAR parameters:C logP–2.55; Drug likeness-(-) 0.15;

BIOLOGICAL EVALUATION

***In vitro* Antibacterial activity**

Cup plate method using Hi-Media agar medium has been employed to study the antibacterial activity of compounds **1, 2, 3e, 4e** and **5e** against *S. aureus, S. typhi, E. coli* and *K. pneumoniae.* Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was done as per the standard procedure. Each test compound was dissolved in Dimethylformamide, making a concentration of 100µg/ml and 50µg/ml. These were used as sample solution. Sample size for all the compounds was fixed as 0.1ml. The cups are made by scooping out agar medium with sterilized cork borer in a petri dish, which was previously inoculated with the microorganisms. The solution of each test compound (0.1ml) was added in the cups and petri dishes were subsequently incubated at 37^{o}C for 48hrs. Benzyl Penicillin and Streptomycin were used as standard drugs and Dimethylformamide as a control. Zones of inhibition produced by each compound, was measured in mm, as shown in **Table 02.** Compound **3c** exhibits moderate antibacterial activity compared with standard drugs Benzyl penicillin and Streptomycin.

***In Vitro* Antifungal activity**

The antifungal activity of compounds **1, 2, 3e, 4e and 5e** were tested using potato dextrose agar medium, against two different fungi such as *C. albicans*, and *A. niger* by filter paper disc technique. The concentration of test compounds was 100µg/ml and 50µg/ml. After 48hrs of treatment, zones of inhibition produced by all compound, were measured in mm, and is shown in **Table 03.** Fluconazole was used as the standard antifungal agent and Dimethylformamide as a control. All the tested compounds showed significant antifungal activity.

***In Vitro* Antitubercular activity**

Compounds **1, 2, 3e, 4e** and **5e** were screened against Mycobacterium tuberculosis *H37 RV* & middlebrook 7H – 9 broths following the standard procedure. The compounds were screened at the Concentrations of 100-0.1µg/ml. The compound **2** showed promising activity at 6.25µg/ml in comparison with standard drugs streptomycin.

Table-02
Antibacterial activity of synthesized compounds

Compounds	Zone of inhibition (in mm)							
	S. aureus		*S. typhi*		*E. coli*		*K. pneumoniae*	
	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
1	15	17	14	16	18	20	17	19
2	12	14	14	17	15	17	12	15
3e	16	19	15	17	17	21	13	15
4e	12	15	11	15	15	17	12	16
5e	16	20	14	17	17	20	14	19

Table-03
Antifungal activity of synthesized compounds

compound	Zone of inhibition (in mm)			
	C. albicans		*A. niger*	
	50µg/ml	100µg/ml	50µg/ml	100µg/ml
1	R	10	18	20
2	13	15	15	18
3e	15	17	18	20
4e	15	18	20	23
5e	10	12	15	18
Standard: Fluconazole	20	27	18	20
Control: DMF	--	--	--	--

Table-04
Antitubercular activity of synthesized compound

Sl No	Compounds	100 µg/ ml	50 µg/ ml	25 µg/ ml	12.5 µg/ ml	6.25 µg/ ml	3.12 µg/ ml	1.6 µg/ ml	0.8 µg/ ml	0.4 µg/ ml	0.2 µg/ ml	0.1 µg/ ml
1	**1**	S	R	R	R	R	R	R	R	R	R	R
2	**2**	S	S	S	S	S	R	R	R	R	R	R
3	**3e**	S	S	R	R	R	R	R	R	R	R	R
4	**4e**	R	R	R	R	R	R	R	R	R	R	R
5	**5e**	S	R	R	R	R	R	R	R	R	R	R
6	**Std drug INH**	S	S	S	S	S	S	S	S	R	R	R
7	**Streptomycin**	S	S	S	S	R	R	R	R	R	R	R

RESULT AND DISCUSSION:

The synthesized compound which contain Thiadiazole pharmacophore by using thiosemicarbazide. Two components were subjected to conventional and microwave method cyclization is done by using concentrated H_2SO_4, which comply with our requirement of synthesizing compounds containing Thiadiazole moieties. In this method Vanillin and Thiosemicarbazide is reacted in presence of ethanol **(1).** The compound confirmed by FTIR data in which the exhibit peaks at 3528cm^{-1}, 3270cm^{-1} 3435cm^{-1}, 2897 cm^{-1} and 1275cm^{-1} due to NH_2, OH, NH, CH and C=S respectively. ^1H NMR spectrum of the compound exhibited **7** peaks corresponding to **11** hydrogen. This intermediate was reacted with H_2SO_4 to get cyclized product **(2).** The compound confirmed by FTIR data in which the peak exhibit 1275cm^{-1} (C=S) is replaced by 636cm^{-1} (C-S) and ^1H NMR spectrum of the compound exhibited **5** peaks corresponding to **9** hydrogen.

In the third step the above intermediate **2** undergoes Schiff base reaction with different aldehyde **(3a-e)** in presence of ethanol. The compound confirmed by FTIR data in which peaks exhibits 776cm^{-1}(C-Cl) showed the formation Schiff base product. ^1H NMR spectrum of the compound exhibited **7** peaks corresponding to **12** hydrogen. M^+ peak 345m/z.

Further synthesized compound reacts with 2-chloroacetyl chloride to form different Azetidinone compound **(4a-e)** in presence of triethylamine and 1,4 dioxane**.** The compound confirmed by FTIR data in which the exhibit peaks 1706cm^{-1}(C=O) it shows the presence of beta lactam ring in compound **4b**. ^1H NMR spectrum of the compound exhibited **8** peaks corresponding to **14** hydrogen. M^+ peak 422m/z.

Similarly the Schiff base **(3a-e)** is reacted with thioglycolic acid in DMF solvent in presence of zinc chloride to form thiazolidinone **(5a-e)** derivatives. The compound confirmed by FTIR data in which exhibit peaks at 1700cm^{-1} (C=O) it showed the presence of thiazolidinone ring. ^1H NMR spectrum of the compound exhibited **8** peaks corresponding to **15** hydrogen, M^+ peak 419.

The series of reactions were carried out in present work is depicted in **scheme-1.**

Physical data of all the synthesized compounds are shown in **Table1**.

All the newly synthesized compounds showed good antibacterial activity against *S. aureus, S. typhi, E. coli* and *K. pneumoniae*, significant antifungal activity against *C. albicans* and *A. niger* and promising antitubercular activity against Mycobacterium tuberculosis *H37 RV*. The data of these studies is summarized in **Table 2, Table 3** and **Table 4.**

CONCLUSION

In conclusion, a new class of vanillin encompassing thiadiazole derivatives were synthesized and evaluated as antibacterial agents. The newly synthesized heterocyclic exhibited moderate antibacterial activity against *S. aureus, S. typhi, E. coli* and *K. pneumoniae* and significant antifungal activity against *C. albicans* and *A. niger*. It can be concluded that these classes of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress.

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REFERENCE

1. Kumar R, Sharma P, Mishra P. ChemInform Abstract: Vanillin Derivatives Showing Various Biological Activities. *ChemInform.* 2012;43(28):266-279.
2. Gallage N, Moller B. Vanillin–Bioconversion and Bioengineering of the Most Popular Plant Flavor and Its De Novo Biosynthesis in the Vanilla Orchid. *Mol. Plant.* 2015;8(1):40-57.
3. Shen Y, Han C, Liu B, Lin Z, Zhou X, Wang C et al. Determination of vanillin, ethyl vanillin, and coumarin in infant formula by liquid chromatography-quadrupole linear ion trap mass spectrometry. *J. Dairy Sci*. 2014;97(2):679-686.
4. Cheng Y, Ge C, Lodge J, Santhanam K, Lu L. Evaluation of Natural Plant Powders with Potential Use in Antimicrobial Packaging Applications. *J App Pack Res.* 2014;6(2):29-39.
5. Boonchird C, Flegel T. In vitro antifungal activity of eugenol and vanillin against Candida albicans and Cryptococcus neoformans. *Canadian J Microbiol*. 1982;28(11):1235-1241.
6. Bezerra D, Soares A, de Sousa D. Overview of the Role of Vanillin on Redox Status and Cancer Development. *Oxid Med and Cell Longev*. 2016;2016:1-9.
7. Sharma S, Pal R, Hameed S, Fatima Z. Antimycobacterial mechanism of vanillin involves disruption of cell-surface integrity, virulence attributes, and iron homeostasis. *Int J Mycobacteriol*. 2016;5(4):460-468.
8. Wermuth C, Giethlen B, Bazzini P. comprehensive medicinal chemistry. *Elsevier*.2007;2:649-711.
9. Shrivastava K, Purohit S, Singhal S. Studies On Nitrogen And Sulphur Containing Heterocyclic Compound: 1,3,4 - thiadiazole. *Asian J Biomed Pharma Sci.* 2013;3(21):6-23.
10. Holla B, Poojary K, Rao B, Shivananda M. ChemInform Abstract: New Bis- aminomercaptotriazoles and Bis-Triazolothiadiazoles as Possible Anticancer Agents. *ChemInform.* 2010;33(47).
11. Yousif E, Majeed A, Al-Sammarrae K, Salih N, Salimon J, Abdullah B. Metal complexes of Schiff base: Preparation, characterization and antibacterial activity. *Arab J Chem.* 2017;10:1639-1644.
12. Ghosh S, Malik S, Jain B, Ganesh N. Synthesis, Characterization and Biological Studies of Zn(II) Complexof Schiff Base Derived from 5-Acetazolamido-1,3,4 - Thiadiazole-2- Sulphonamide, A Diuretic Drug. *Asian J Exp Sci*. 2009;23(1):189-192.
13. Supuran C, Scozzafava A. Carbonic anhydrase inhibitors -

Part 94. 1,3,4-Thiadiazole-2- sulfonamide derivatives as antitumor agents. *Eur J Med Chem.* 2000;35(9):867-874.

14. Iizawa Y, Okonogi K, Hayashi R, Iwahi T, Yamazaki T, Imada A. Therapeutic effect of cefozopran (SCE-2787), a new parenteral cephalosporin, against experimental infections in mice. Antimicrobia Agents and Chemotherapy. 1993;37(1):100-105.
15. Singh G, Mbukwa E, Pheko T. Synthesis and antimicrobial activity of new 2-azetidinones from N-(salicylidene)amines and 2-diazo-1,2-diarylethanones. *Arkat*. 2006;2007(9):80-90.
16. Barakat A, Al-Najjar H, Al-Majid A, Soliman S, Mabkhot Y, Al-Agamy M et al. Synthesis, molecular structure investigations and antimicrobial activity of 2-thioxothiazolidin-4-one derivatives. *J Mol Struct*. 2015;1081:519-529.