

Synthesis, spectral analysis and biological evaluation of sulfamoyl and 1,3,4-oxadiazole derivatives of 3-pipecoline

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Abstract: Heterocyclic chemistry is an important field of organic chemistry due to therapeutic potential. The minor modification in the structure of poly-functional compounds has great effect on therapeutic ability. In the presented research work, substituted 1,3,4-oxadiazole derivatives, 8a-p, have been synthesized by the reaction of 1-(4-bromomethylbenzenesulfonyl)-3-methylpiperidine (7) and 5-substituted-1,3,4-oxadiazole-2-thiol (4a-p). The 5-substituted-1,3,4-oxadiazole-2-thiol were synthesized by converting carboxylic acids correspondingly into esters, hydrazides and oxadiazoles. Secondly the electrophile, 1-(4-Bromomethylbenzenesulfonyl)-3-methylpiperidine (7), was prepared by the reaction of 3-methylpiperidine with 4-bromomethylbenzenesulfonyl chloride in the presence of water and Na₂CO₃ under pH of 9-10. The compounds were structurally corroborated through spectroscopic data analysis of IR, EI-MS and ¹H-NMR. The screening for antibacterial activity revealed the compounds to be moderate to excellent inhibitors against bacteria under study. Anti-enzymatic activity was assessed against urease enzyme and 1-{[4-({[5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl)methyl]phenyl}sulfonyl}-3-methylpiperidine (8d) was the most active one.

Keywords: 1,3,4-Oxadiazole, 3-methylpiperidine, antibacterial activity, anti-urease activity, sulfonamide.

INTRODUCTION

Oxadiazole is a five member heterocyclic compound having four different isomeric forms. Among these forms, 1,3,4-oxadiazole form is found to be the most potent regarding biological behavior (Bostrom *et al.*, 2011; Sanchit and Pandeya, 2011; Nagaraj *et al.*, 2012). Chemistry of this moiety explains weak basic character and also less ease for electrophilic substitution reactions (Sharma and Ahsan, 2014). The 2,5-substituted derivatives of 1,3,4-oxadiazole possess broad range of biological activities like nesapidil have the anticancer activity (Sahin *et al.*, 2002). The presence of oxadiazole moiety had made different organic compounds more effective as antibacterial, antifungal, anti-inflammatory, pesticide, hypoglycemic and anti-parasitic activities along with plant growth regulation (Abbasi *et al.*, 2013; Desai *et al.*, 2014; Raval *et al.*, 2014).

Sulfonamide compounds have at least five different classes of pharmacologically active agents. It contains basic sulfamoyl group (-SO₂N<) (Ordonez *et al.*, 2011). It is structurally similar to *p*-aminobenzoic acid which is a cofactor needed to synthesize the folic acid in bacteria. The antibiotic ability of sulfonamide inhibits the synthesis of purine and DNA by interrupting the conversion of *p*-aminobenzoic acid into folic acid (El-Sayed *et al.*, 2011; Galan *et al.*, 2008). Sulfamoyl moiety is also used as antimicrobial drugs, anti-thyroid agents, antitumor,

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antibiotics and inhibitors of carbonic anhydrase (El-Sayed *et al.*, 2011; Galan *et al.*, 2008 Ordonez *et al.*, 2011; Reddy *et al.*, 2012). This moiety is also known to possess the ability to inhibit the growth of gram positive bacteria, gram negative bacteria, fungi and some protozoa (Zoumpoulakis *et al.*, 2012). The clinical use of this class includes the gastrointestinal and several urinary tract infections along with livestock herbs infections (Aziz-ur-Rehman *et al.*, 2013).

Piperidine also has the pharmaceutical attention due to their biological activities. This moiety has been found to be the part of many pharmacologically important compounds (Ameen *et al.*, 2015; Chou and Huang, 2012). This moiety has been found in natural occurring bioactive compounds like hydrastine and berberine. The local anesthetics such as bupivacaine, ropivacaine and mepivacaine also bear this moiety. The other active features associated with this ring include normalization of insulin, variation in plasma glucose level and curing cocaine abuse (Vitnik and Vitnik, 2015).

Chemists and pharmacists have been working to synthesize novel drugs to immune the human being against the various diseases from the last two decades. Sulfonamide, oxadiazole and piperidine derivatives have been introduced with significant pharmacological activities. The minor modifications in the structure of poly-functional compounds containing oxygen and nitrogen have therapeutic ability (Modi and Modi, 2012).

The growing problem of antibiotic resistance has prompted the interest of chemists in search of different drugs. The therapeutic potential of sulfonamide, oxadiazole and piperidine moieties prompted us to synthesize new compounds bearing these three moieties collectively as single unit. The bioactivity of target molecules has been assessed by screening for antibacterial and enzyme inhibition activities.

MATERIALS AND METHODS

General

Chemicals, 4-Bromomethylbenzenesulfonyl chloride, 3-methylpiperidine and all aryl/aralkyl carboxylic acids were purchased from Alfa Aesar (Germany), Merck and Sigma Aldrich through local suppliers. The analytical grade solvents like methanol and DMF were used for synthesis of new compounds. The reaction mixture was monitored gradually by TLC on pre-coated silica gel plates with mobile phase of *n*-hexane and EtOAc. Detection of spots was made possible by UV₂₅₄ lamp. Gallenkamp apparatus was worked out for melting points in open capillary tubes. Jasco-320-A spectrophotometer was worked out for IR spectra under KBr pellet method. ¹H-NMR spectra were obtained at 400 MHz in CDCl₃ on Bruker spectrophotometer, with 'δ' in ppm and 'J' in hertz (Hz). JEOL JMS-600H instrument was used to get results for mass spectra.

General preparation of ethyl aryl/aralkyl carboxylate (2a-p)

Substituted aryl/aralkylcarboxylic acid (5 g; 1a-p) was homogenized in 99% ethanol (50 mL) in a 250 mL RB flask. Conc. H₂SO₄ (2.5 mL) was added and set to reflux for 3-4 hours (hrs). TLC plates were developed for confirmation of reaction completion. After the reaction completion, 10% aq. Na₂CO₃ solution was added to mixture to adjust pH of 9-10. Excess distilled water was added on shaking. To get the purified ester, neutralized mixture was extracted by using CHCl₃ (25 mL) in parts. CHCl₃ was distilled off to collect the purified ester (2a-p).

General preparation of aryl/aralkyl carbohydrazide (3a-p)

Ethyl ester of aryl/aralkylcarboxylic acid (3 mL, 2a-p) was dissolved in ethanol (15 mL) in a 100 mL RB flask by stirring at the room temperature. Then 80% N₂H₄.H₂O (4.8 mL; 0.096 mol) was added to above mixture. The mixture was set to reflux for 5-6 hrs. Reaction completion was checked by TLC after monitoring by UV lamp. Ice cold dist. H₂O (50 mL) was added and the resulted precipitates were filtered and washed off with dist. H₂O.

General preparation of 5-substituted-1,3,4-Oxadiazol-2-thiol (4a-p)

Aryl/aralkyl carbohydrazide (0.01 mol, 3a-p) was mixed with 20 mL EtOH using 100 mL round bottom flask and then solid KOH (0.02 mol) was homogeneously dissolved

on reflux. The mixture was cooled to room temperature. Then CS₂ (0.04 mol) was added and again set to reflux for 5-6 hrs. Reaction completion was checked by TLC with mobile phase in ratio 60:40 maintained by *n*-hexane and ethyl acetate. When reaction was completed then ice cold dist. H₂O (50 mL) was poured. Dil. HCl was added to adjust pH of 6 and the resulted precipitates were filtered, washed with dist. H₂O and re-crystallized from CH₃OH.

Synthesis of 1-(4-Bromomethylbenzenesulfonyl)-3-methylpiperidine (7)

3-Methylpiperidine (1.5 mL, 0.0126 mol; 6) was dispersed in 15 mL distilled water in a 100 mL iodine flask. A pH of 9-10 was adjusted during the whole reaction by aqueous Na₂CO₃ solution. 4-Bromomethyl benzenesulfonyl chloride (3.389 g, 0.0126 mol; 5) was added in small portions during stirring and further stirred for 4 hrs. Reaction completion was checked by TLC. The mixture was neutralized by dil. HCl and vigorously shaken till precipitation. Precipitates of 1-(4-Bromomethylbenzenesulfonyl)-3-methylpiperidine (7) were filtered, washed with distilled water and dried.

General preparation of 1-[(4-([5-substituted-1,3,4-oxadiazol-2-yl]sulfonyl)methyl)phenyl] sulfonyl-3-methylpiperidine (8a-p)

5-Substituted-1,3,4-oxadiazol-2-thiol (0.1 g; 4a-p) was homogenized in DMF (5 mL) in a 50 mL round bottom flask preceded by LiH (0.02 g, 0.002 mol). The mixture was set to stir for 0.5 hr. The electrophile 1-(4-bromomethylbenzenesulfonyl)-3-methylpiperidine (0.1 g, 0.0003 mol; 7) was poured into homogeneous solution. The mixture was further stirred for 4-6 hrs. Reaction completion was checked by TLC. When the reaction was completed, ice cold dist. water (20 mL) was introduced into reaction contents along with aq. NaOH drop wise to adjust the pH 9-10. Gentle shaking was continued for half an hour till precipitation and the formed precipitates were filtered, washed with dist. H₂O and dried.

Biological activity assays

Antibacterial activity assay

The performance of antibacterial screening was in sterile 96-wells micro plates under aseptic environments. The method was based on the principle that microbial cell number increases as the microbial growth proceeds in a log phase of growth which results in increased absorbance of broth medium (Kaspady *et al.*, 2009). Ciprofloxacin was used as reference standard. All the obtained results were listed as mean of three independent experiments. Minimum inhibitory concentration (MIC) was computed after diluting properly (5-30 µg/well) and estimated by using EZ-Fit Perrella Scientific Inc. Amherst USA software.

Urease enzyme inhibition assay

The performance of urease inhibition followed the method mentioned in literature (Mobley *et al.*, 1988). The

% inhibition and IC₅₀ (Inhibitory Concentration for 50% inhibition) values were measured likewise as in case of antibacterial activity assay.

Spectral characterization of synthesized compounds

1-[[4-([5-(2-Naphthylmethyl)-1,3,4-oxadiazol-2-yl]sulfanyl)methyl]phenyl]sulfonyl]-3-methylpiperidine (8a)

Light brown amorphous solid; M.P: 74-76°C; Yield: 86%; M.F: C₂₆H₂₇N₃O₃S₂; M.W: 493.62; IR (KBr, $\nu_{\max}$, cm⁻¹): 3075 (Ar C-H), 1669 (C=O), 1563 (Ar C=C), 1667 (C=N), 1329 (-SO₂), 1279, 1058 (C-O-C), 631 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.07 (d, J =8.4 Hz, 1H, H-4'), 7.87 (d, J =6.8 Hz, 1H, H-8'), 7.82 (d, J =6.8 Hz, 1H, H-5'), 7.58 (d, J =8.4 Hz, 2H, H-2", H-6"), 7.51 (d, J =7.6 Hz, 1H, H-3'), 7.49 (t, J =8.0 Hz, 1H, H-6'), 7.45 (t, J =7.2 Hz, 1H, H-7'), 7.42 (s, 1H, H-1'), 7.38 (d, J =8.4 Hz, 2H, H-3", H-5"), 4.59 (s, 2H, CH₂-7"), 4.34 (s, 2H, CH₂-11'), 3.59 (t, J =11.2 Hz, 2H, H-6""), 2.18 (d, J =9.6 Hz, 1H, H_{eq}-2""), 1.87 (d, J =10.8 Hz, 1H, H_{ax}-2""), 1.71-1.63 (m, 2H, CH₂-5""), 1.60-1.58 (m, 2H, CH₂-3""), 0.92-0.88 (m, 2H, CH₂-4""), 0.85 (d, J =6.4 Hz, 3H, CH₃-7"""); EIMS: m/z : 493 [M]⁺ (3%), 332 (60.3%), 242 (6.4%), 241 (16.8%), 183 (3.2%), 167 (100%), 162 (5.1%), 141 (67.6%), 98 (87.3%).

1-[[4-([5-Phenyl]-1,3,4-oxadiazol-2-yl]sulfanyl)methyl]phenyl]sulfonyl]-3-methylpiperidine (8b)

Light brown amorphous solid; M.P: 77-79°C; Yield: 78%; M.F: C₂₁H₂₃N₃O₃S₂; M.W: 429.56; IR (KBr, $\nu_{\max}$, cm⁻¹): 3077 (Ar C-H), 1671 (C=O), 1566 (Ar C=C), 1669 (C=N), 1331 (-SO₂), 1280, 1061 (C-O-C), 633 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.93 (d, J =7.2 Hz, 2H, H-2', H-6'), 7.70 (d, J =7.8 Hz, 2H, H-2", H-6"), 7.60 (d, J =7.6 Hz, 2H, H-3", H-5"), 7.50-7.46 (m, 3H, H-3', H-4', H-5'), 4.54 (s, 2H, CH₂-7"), 3.60 (t, J =12.0 Hz, 2H, H-6""), 2.20 (d, J =10.4 Hz, 1H, H_{eq}-2""), 1.88 (d, J =11.2 Hz, 1H, H_{ax}-2""), 1.69-1.65 (m, 2H, CH₂-5""), 1.60-1.53 (m, 2H, CH₂-3""), 0.94-0.90 (m, 2H, CH₂-4""), 0.84 (d, J =6.0 Hz, 3H, CH₃-7"""); EIMS: m/z : 429 [M]⁺ (3%), 267 (60%), 251 (88%), 177 (17%), 119 (3%), 103 (100%), 98 (87%), 77 (68%).

1-[[4-([5-(4-Nitrophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl)methyl]phenyl]sulfonyl]-3-methylpiperidine (8c)

Light yellow powder; M.P: 138-140°C; Yield: 84%; M.F: C₂₁H₂₂N₄O₅S₂; M.W: 474.56; IR (KBr, $\nu_{\max}$, cm⁻¹): 3074 (Ar C-H), 1667 (C=O), 1561 (Ar C=C), 1665 (C=N), 1327 (-SO₂), 1277, 1056 (C-O-C), 629 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.34 (d, J =8.4 Hz, 2H, H-3', H-5'), 8.16 (d, J =8.8 Hz, 2H, H-2', H-6'), 7.71 (d, J =8.0 Hz, 2H, H-2", H-6"), 7.62 (d, J =8.0 Hz, 2H, H-3", H-5"), 4.58 (s, 2H, CH₂-7"), 3.61 (t, J =11.6 Hz, 2H, H-6""), 2.22 (d, J =9.2 Hz, 1H, H_{eq}-2""), 1.88 (d, J =8.8 Hz, 1H, H_{ax}-2""), 1.69-1.66 (m, 2H, CH₂-5""), 1.65-1.60 (m, 2H, CH₂-3""),

0.92-0.87 (m, 2H, CH₂-4""), 0.85 (d, J =8.8 Hz, 3H, CH₃-7"""); EIMS: m/z : 474 [M]⁺ (3%), 312 (60%), 251 (88%), 222 (17%), 164 (3%), 148 (100%), 122 (68%), 98 (87%).

1-[[4-([5-(3-Nitrophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl)methyl]phenyl]sulfonyl]-3-methylpiperidine (8d)

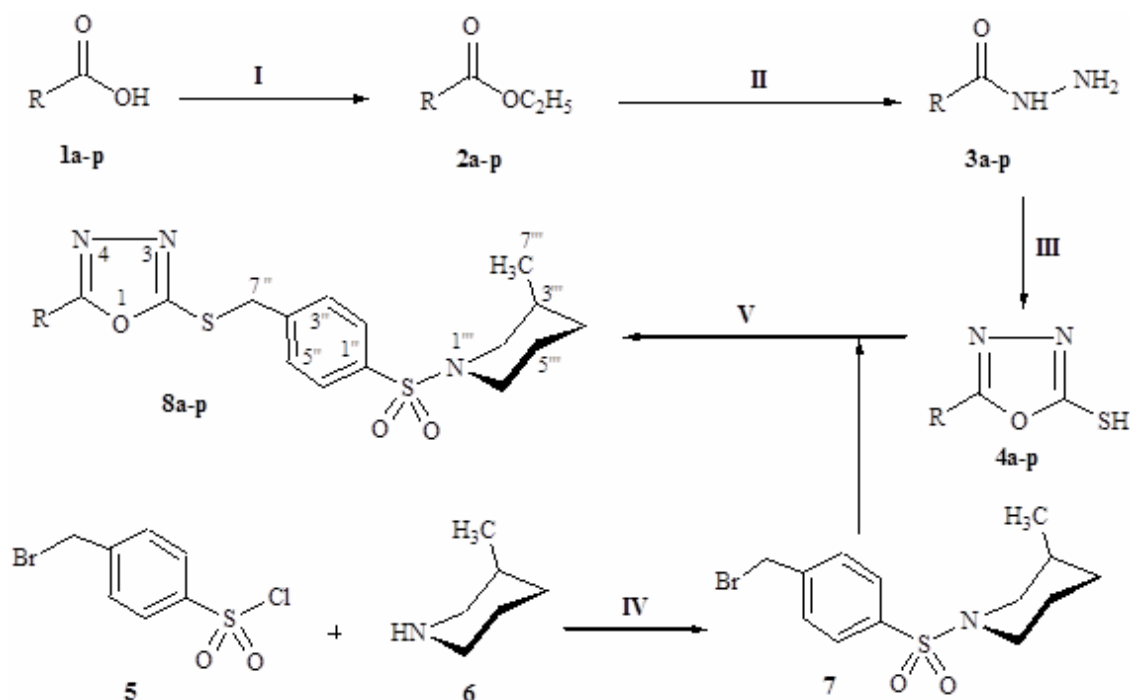
Yellow powder; M.P: 81-83°C; Yield: 88%; M.F: C₂₁H₂₂N₄O₅S₂; M.W: 474.56; IR (KBr, $\nu_{\max}$, cm⁻¹): 3075 (Ar C-H), 1669 (C=O), 1563 (Ar C=C), 1667 (C=N), 1329 (-SO₂), 1279, 1058 (C-O-C), 631 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.34 (d, J =8.8 Hz, 1H, H-4'), 8.16 (d, J =8.8 Hz, 1H, H-6'), 7.94 (t, J =8.0 Hz, 1H, H-5'), 7.81 (s, 1H, H-2'), 7.71 (d, J =8.0 Hz, 2H, H-2", H-6"), 7.62 (d, J =8.0 Hz, 2H, H-3", H-5"), 4.55 (s, 2H, CH₂-7"), 3.61 (t, J =10.8 Hz, 2H, H-6""), 2.24 (d, J =11.6 Hz, 1H, H_{eq}-2""), 1.91 (d, J =10.8 Hz, 1H, H_{ax}-2""), 1.70-1.65 (m, 2H, CH₂-5""), 1.63-1.58 (m, 2H, CH₂-3""), 1.03-0.90 (m, 2H, CH₂-4""), 0.85 (d, J =8.8 Hz, 3H, CH₃-7"""); EIMS: m/z : 474 [M]⁺ (3%), 312 (60.3%), 251 (87.9%), 222 (16.8%), 164 (3.2%), 148 (100%), 98 (87.3%), 122 (67.6%).

1-[[4-([5-(2-Nitrophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl)methyl]phenyl]sulfonyl]-3-methylpiperidine (8e)

Black sticky solid; Yield: 90%; M.F: C₂₁H₂₂N₄O₅S₂; M.W: 474.56; IR (KBr, $\nu_{\max}$, cm⁻¹): 3074 (Ar C-H), 1668 (C=O), 1562 (Ar C=C), 1666 (C=N), 1328 (-SO₂), 1277, 1057 (C-O-C), 630 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.02 (d, J =7.6 Hz, 1H, H-3'), 7.91 (d, J =6.8 Hz, 1H, H-6'), 7.81 (br.s, 1H, H-4'), 7.76 (t, J =6.4 Hz, 1H, H-5'), 7.71 (d, J =8.0 Hz, 2H, H-2", H-6"), 7.59 (d, J =8.0 Hz, 2H, H-3", H-5"), 4.51 (s, 2H, CH₂-7"), 3.61 (t, J =12.0 Hz, 2H, H-6""), 2.24 (d, J =11.2 Hz, 1H, H_{eq}-2""), 1.91 (d, J =10.4 Hz, 1H, H_{ax}-2""), 1.70-1.65 (m, 2H, CH₂-5""), 1.60-1.56 (m, 2H, CH₂-3""), 0.92-0.85 (m, 2H, CH₂-4""), 0.85 (d, J =6.4 Hz, 3H, CH₃-7"""); EIMS: m/z : 474 [M]⁺ (3%), 312 (60.3%), 251 (87.9%), 222 (16.8%), 164 (3.2%), 148 (100%), 122 (67.6%), 98 (87.3%).

1-[[4-([5-(3,5-Dinitrophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl)methyl]phenyl]sulfonyl]-3-methylpiperidine (8f)

Brown sticky solid; Yield: 84%; M.F: C₂₁H₂₁N₅O₇S₂; M.W: 519.55; IR (KBr, $\nu_{\max}$, cm⁻¹): 3077 (Ar C-H), 1671 (C=O), 1566 (Ar C=C), 1669 (C=N), 1331 (-SO₂), 1280, 1061 (C-O-C), 633 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 9.15 (s, 2H, H-2', H-6'), 9.11 (s, 1H, H-4'), 7.72 (d, J =8.0 Hz, 2H, H-2", H-6"), 7.63 (d, J =8.0 Hz, 2H, H-3", H-5"), 4.61 (s, 2H, CH₂-7"), 3.62 (br.s, 2H, H-6""), 2.25 (d, J =10.8 Hz, 1H, H_{eq}-2""), 1.91 (d, J =10.8 Hz, 1H, H_{ax}-2""), 1.72-1.68 (m, 2H, CH₂-5""), 1.62-1.56 (m, 2H, CH₂-3""), 1.03-0.90 (m, 2H, CH₂-4""), 0.85 (d, J =7.2 Hz, 3H, CH₃-7"""); EIMS: m/z : 519 [M]⁺ (3%), 357 (60.3%), 267 (16.8%), 251 (87.9%), 209 (16.8%), 193 (3.2%), 167 (100%), 98 (87.3%).



Scheme 1: Outline for the synthesis of 1-[[4-({[5-substituted-1,3,4-oxadiazol-2-yl]sulfanyl}methyl)phenyl]sulfonyl]-3-methylpiperidine. Reagents & conditions: (I) $\text{H}_2\text{SO}_4/\text{EtOH}/\text{refluxing}$ for 3-4 hours (II) $\text{N}_2\text{H}_4/\text{EtOH}/\text{refluxing}$ for 5-6 hours (III) $\text{CS}_2/\text{KOH}/\text{EtOH}/\text{refluxing}$ for 5-6 hours (IV) $\text{H}_2\text{O}/5\% \text{Na}_2\text{CO}_3 \text{ soln.}/\text{stirring}$ for 4 hours (V) $\text{DMF}/\text{LiH}/\text{stirring}$ for 4-6 hours.

Table 1: Different aryl/aralkyl groups

Comp.	R	Comp.	R	Comp.	R
8a		8g		8m	
8b		8h		8n	
8c		8i		8o	
8d		8j		8p	
8e		8k			
8f		8l			

Table 2: % Inhibition for antibacterial activity of synthesized compounds

Compounds	% Inhibition				
	<i>S. typhi</i> (-)	<i>E. coli</i> (-)	<i>P. aeruginosa</i> (-)	<i>B. subtilis</i> (+)	<i>S. aureus</i> (+)
8a	57.71±1.45	59.33±1.20	77.79±1.07	77.40±1.00	64.56±1.04
8b	78.14±0.20	55.22±0.50	72.57±0.20	78.70±0.50	69.07±0.58
8c	73.86±1.55	77.67±0.50	65.36±0.35	75.85±0.53	64.64±1.00
8d	63.00±0.85	72.78±0.95	72.64±0.07	78.10±0.10	73.57±0.89
8e	56.43±1.45	82.33±1.80	78.36±1.35	75.14±1.90	64.14±0.65
8f	39.00±0.85	61.11±0.14	76.21±1.00	74.30±0.20	66.07±0.95
8g	67.29±0.15	78.11±1.59	48.00±1.65	53.50±0.70	24.57±0.00
8h	79.29±0.25	83.44±0.17	20.71±0.05	51.65±1.85	26.43±1.15
8i	43.29±0.8	80.11±1.27	50.21±0.30	65.80±0.60	52.64±1.00
8j	76.57±0.65	71.78±1.27	65.93±0.60	76.55±1.25	67.29±0.44
8k	50.57±0.80	62.22±1.86	69.29±0.65	76.45±0.95	66.79±0.93
8l	60.57±0.95	72.13±1.14	60.57±0.43	70.55±0.95	67.15±0.95
8m	56.43±2.65	56.56±1.27	70.79±0.79	74.80±0.90	70.36±0.63
8n	58.71±0.35	74.67±0.20	68.21±0.86	78.70±1.20	64.86±0.05
8o	79.86±0.25	76.89±0.48	70.29±0.80	77.15±1.95	66.29±0.28
8p	47.29±0.9	81.78±0.20	73.50±0.20	75.50±0.81	68.00±0.53
Ciprofloxacin	92.87±0.91	92.27±0.64	92.34±0.35	91.63±0.05	90.57±0.35

Table 3: MIC for antibacterial activity of synthesized compounds

Compounds	MIC				
	<i>S. typhi</i> (-)	<i>E. coli</i> (-)	<i>P. aeruginosa</i> (-)	<i>B. subtilis</i> (+)	<i>S. aureus</i> (+)
8a	18.24±1.45	15.39±0.53	9.53±0.47	9.93±0.92	11.76±0.50
8b	9.21±0.44	16.48±0.39	9.76±0.51	9.69±0.74	10.86±0.18
8c	9.98±0.72	9.42±0.87	10.38±0.92	9.79±0.65	12.53±0.59
8d	12.87±0.90	9.80±0.17	9.97±0.52	8.97±0.50	9.59±0.52
8e	17.97±0.54	8.88±0.10	8.97±0.63	9.36±0.17	12.96±0.10
8f	-	12.98±0.77	9.10±0.78	10.13±0.54	10.13±0.94
8g	10.32±0.50	9.12±0.54	-	17.65±0.69	-
8h	9.11±0.76	8.79±0.49	-	19.78±0.76	-
8i	-	9.86±0.27	19.93±0.59	11.60±0.40	18.43±1.56
8j	9.31±0.69	9.92±0.58	10.73±0.18	9.76±0.99	10.72±0.52
8k	-	-	10.29±0.19	9.73±0.53	10.16±0.15
8l	14.87±0.23	10.97±0.67	14.90±0.12	11.42±0.89	10.56±0.28
8m	17.96±0.78	17.44±0.52	10.39±0.69	10.12±0.38	10.64±0.15
8n	17.34±0.65	9.65±0.19	10.27±0.83	9.59±0.87	11.87±0.32
8o	9.43±0.75	9.57±0.90	10.54±0.80	9.24±0.67	10.39±0.70
8p	-	8.97±0.71	9.45±1.08	9.28±0.81	10.43±0.89
Ciprofloxacin	7.83±0.78	8.01±0.12	7.98±0.89	7.22±0.67	7.00±1.54

1-[[4-([5-(2-Chloro-3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl)sulfanyl)methyl]phenyl]sulfonyl]-3-methylpiperidine (8g)

Brown sticky solid; Yield: 78%; M.F: C₂₁H₂₀ClN₅O₇S₂; M.W: 554.58; IR (KBr, $\nu_{\max}$, cm⁻¹): 3076 (Ar C-H), 1670 (C=O), 1564 (Ar C=C), 1668 (C=N), 1330 (-SO₂), 1279, 1059 (C-O-C), 632 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 8.84 (s, 1H, H-6'), 8.62 (s, 2H, H-4'), 7.71 (d, *J*=8.4 Hz, 2H, H-2", H-6"), 7.62 (d, *J*=8.0 Hz, 2H, H-3", H-5"), 4.58 (s, 2H, CH₂-7"), 3.63 (t, *J*=12.4 Hz, 2H, H-6""), 2.24 (d, *J*=10.8 Hz, 1H, H_{eq}-2""), 1.91 (d, *J*=11.2 Hz, 1H, H_{ax}-2""), 1.71-1.66 (m, 2H, CH₂-5""), 1.61-1.56 (m, 2H,

CH₂-3""), 0.96-0.88 (m, 2H, CH₂-4""), 0.86 (d, *J*=6.4 Hz, 3H, CH₃-7""); EIMS: *m/z*: 554 [M⁺] (3%), 392 (60.3%), 302 (16.8%), 251 (87.9%), 244 (16.8%), 228 (3.2%), 202 (100%), 98 (87.3%).

1-[[4-([5-(2-Methyl-3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl)sulfanyl)methyl]phenyl]sulfonyl]-3-methylpiperidine (8h)

Orange powder; M.P: 89-91°C; Yield: 88%; M.F: C₂₂H₂₃N₅O₇S₂; M.W: 533.58; IR (KBr, $\nu_{\max}$, cm⁻¹): 3075 (Ar C-H), 1669 (C=O), 1563 (Ar C=C), 1667 (C=N), 1329 (-SO₂), 1279, 1058 (C-O-C), 631 (C-S); ¹H-NMR

(400 MHz, CDCl₃): δ (ppm) 8.85 (s, 1H, H-6'), 8.61 (s, 2H, H-4'), 7.73 (d, $J=8.4$ Hz, 2H, H-2'', H-6''), 7.64 (d, $J=8.0$ Hz, 2H, H-3'', H-5''), 4.60 (s, 2H, CH₂-7''), 3.62 (t, $J=12.4$ Hz, 2H, H-6'''), 2.91 (s, 3H, CH₃-7'), 2.23 (d, $J=11.2$ Hz, 1H, H_{eq}-2'''), 1.94 (d, $J=10.8$ Hz, 1H, H_{ax}-2'''), 1.76-1.65 (m, 2H, CH₂-5'''), 1.63-1.55 (m, 2H, CH₂-3'''), 0.93-0.88 (m, 2H, CH₂-4'''), 0.85 (d, $J=8.0$ Hz, 3H, CH₃-7'''); EIMS: m/z : 533[M⁺] (3%), 371 (60.3%), 281 (16.8%), 251 (87.9%), 223 (16.8%), 207 (3.2%), 181 (100%), 98 (87.3%).

1-[[4-[[5-(2-Chlorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl]methyl]phenyl]sulfonyl]-3-methylpiperidine (8i)

Brown sticky solid; Yield: 86%; M.F: C₂₁H₂₂ClN₃O₃S₂; M.W: 464.00; IR (KBr, $\nu_{\max}$, cm⁻¹): 3074 (Ar C-H), 1668 (C=O), 1562 (Ar C=C), 1666 (C=N), 1328 (-SO₂), 1277, 1057 (C-O-C), 630 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.89 (dd, $J=8.0, 1.2$ Hz, 1H, H-6'), 7.69 (d, $J=8.4$ Hz, 2H, H-2'', H-6''), 7.61 (d, $J=8.4$ Hz, 2H, H-3'', H-5''), 7.51 (dd, $J=8.0, 0.4$ Hz, 1H, H-3'), 7.44 (t, $J=7.6$ Hz, 1H, H-5'), 7.37 (t, $J=6.8$ Hz, 1H, H-4'), 4.54 (s, 2H, CH₂-7''), 3.60 (t, $J=9.6$ Hz, 2H, H-6'''), 2.22 (d, $J=8.0$ Hz, 1H, H_{eq}-2'''), 1.88 (d, $J=10.8$ Hz, 1H, H_{ax}-2'''), 1.70-1.65 (m, 2H, CH₂-5'''), 1.59-1.56 (m, 2H, CH₂-3'''), 0.90-0.86 (m, 2H, CH₂-4'''), 0.85 (d, $J=7.6$ Hz, 3H, CH₃-7'''); EIMS: m/z : 464 [M⁺] (3%), 302 (60.3%), 251 (87.9%), 212 (16.8%), 153 (16.8%), 137 (3.2%), 116 (100%), 98 (87.3%).

1-[[4-[[5-(3-Chlorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl]methyl]phenyl]sulfonyl]-3-methylpiperidine (8j)

Off white amorphous solid; M.P: 82-84°C; Yield: 80%; M.F: C₂₁H₂₂ClN₃O₃S₂; M.W: 464.00; IR (KBr, $\nu_{\max}$, cm⁻¹): 3074 (Ar C-H), 1668 (C=O), 1562 (Ar C=C), 1666 (C=N), 1328 (-SO₂), 1277, 1057 (C-O-C), 630 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.86 (d, $J=7.0$ Hz, 1H, H-6'), 7.70 (d, $J=8.0$ Hz, 2H, H-2'', H-6''), 7.61 (d, $J=8.4$ Hz, 2H, H-3'', H-5''), 7.47 (t, $J=7.2$ Hz, 1H, H-5'), 7.42 (d, $J=8.0$ Hz, 1H, H-4'), 7.24 (s, 1H, H-2'), 4.54 (s, 2H, CH₂-7''), 3.61 (t, $J=12.0$ Hz, 2H, H-6'''), 2.21 (d, $J=11.2$ Hz, 1H, H_{eq}-2'''), 1.89 (d, $J=10.4$ Hz, 1H, H_{ax}-2'''), 1.72-1.65 (m, 2H, CH₂-5'''), 1.64-1.55 (m, 2H, CH₂-3'''), 0.92-0.88 (m, 2H, CH₂-4'''), 0.87 (d, $J=8.8$ Hz, 3H, CH₃-7'''); EIMS: m/z : 464[M⁺] (3%), 302 (60.3%), 251 (87.9%), 212 (16.8%), 153 (16.8%), 137 (3.2%), 116 (100%), 98 (87.3%).

1-[[4-[[5-(2,4-Dichlorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl]methyl]phenyl]sulfonyl]-3-methylpiperidine (8k)

Light brown amorphous solid; M.P: 92-94°C; Yield: 80%; M.F: C₂₁H₂₁Cl₂N₃O₃S₂; M.W: 498.44; IR (KBr, $\nu_{\max}$, cm⁻¹): 3074 (Ar C-H), 1667 (C=O), 1561 (Ar C=C), 1665 (C=N), 1327 (-SO₂), 1277, 1056 (C-O-C), 629 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.85 (d, $J=8.4$ Hz, 1H, H-6'), 7.70 (d, $J=7.2$ Hz, 2H, H-2'', H-6''), 7.61 (d, $J=7.6$ Hz, 2H, H-3'', H-5''), 7.54 (s, 1H, H-3'), 7.36 (d, $J=8.0$ Hz, 1H, H-5'), 4.54 (s, 2H, CH₂-7''), 3.60 (br.s, 2H, H-6'''),

2.22 (br.s, 1H, H_{eq}-2'''), 1.87 (d, $J=10.4$ Hz, 1H, H_{ax}-2'''), 1.70-1.65 (m, 2H, CH₂-5'''), 1.63-1.59 (m, 2H, CH₂-3'''), 0.99-0.90 (m, 2H, CH₂-4'''), 0.87 (br.s, 3H, CH₃-7'''); EIMS: m/z : 464 [M⁺] (3%), 302 (60.3%), 251 (87.9%), 212 (16.8%), 153.5 (16.8%), 137.5 (3.2%), 116 (100%), 98 (87.3%).

1-[[4-[[5-(4-Methylphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl]methyl]phenyl]sulfonyl]-3-methylpiperidine (8l)

Brown sticky solid; Yield: 74%; M.F: C₂₂H₂₅N₃O₃S₂; M.W: 443.58; IR (KBr, $\nu_{\max}$, cm⁻¹): 3074 (Ar C-H), 1667 (C=O), 1561 (Ar C=C), 1665 (C=N), 1327 (-SO₂), 1277, 1056 (C-O-C), 629 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.84 (d, $J=8.0$ Hz, 2H, H-2'', H-6''), 7.69 (d, $J=8.4$ Hz, 2H, H-2'', H-6''), 7.61 (d, $J=8.0$ Hz, 2H, H-3'', H-5''), 7.27 (d, $J=8.0$ Hz, 2H, H-3'', H-5''), 4.52 (s, 2H, CH₂-7''), 3.61 (t, $J=11.6$ Hz, 2H, H-6'''), 2.39 (s, 3H, CH₃-7'), 2.22 (d, $J=12.0$ Hz, 1H, H_{eq}-2'''), 1.90 (d, $J=11.2$ Hz, 1H, H_{ax}-2'''), 1.70-1.64 (m, 2H, CH₂-5'''), 1.63-1.58 (m, 2H, CH₂-3'''), 0.92-0.86 (m, 2H, CH₂-4'''), 0.84 (d, $J=6.8$ Hz, 3H, CH₃-7'''); EIMS: m/z : 443.6 [M⁺] (3%), 281 (60.3%), 251 (87.9%), 191 (16.8%), 133 (3.2%), 117 (100%), 91 (67.6%), 98 (87.3%).

1-[[4-[[5-(Benzyl)-1,3,4-oxadiazol-2-yl]sulfanyl]methyl]phenyl]sulfonyl]-3-methylpiperidine (8m)

Brown sticky solid; Yield: 76%; M.F: C₂₂H₂₅N₃O₃S₂; M.W: 443.58; IR (KBr, $\nu_{\max}$, cm⁻¹): 3076 (Ar C-H), 1670 (C=O), 1564 (Ar C=C), 1668 (C=N), 1330 (-SO₂), 1279, 1059 (C-O-C), 632 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.64 (d, $J=8.0$ Hz, 2H, H-2'', H-6''), 7.50 (d, $J=8.0$ Hz, 2H, H-3'', H-5''), 7.32 (d, $J=7.2$ Hz, 2H, H-2', H-6'), 7.25-7.20 (m, 3H, H-3', H-4', H-5'), 4.42 (s, 2H, CH₂-7''), 4.32 (t, $J=7.2$ Hz, 2H, H-6'''), 4.13 (s, 2H, CH₂-7'), 2.25 (d, $J=8.0$ Hz, 1H, H_{eq}-2'''), 1.87 (d, $J=10.8$ Hz, 1H, H_{ax}-2'''), 1.70-1.65 (m, 2H, CH₂-5'''), 1.61-1.56 (m, 2H, CH₂-3'''), 0.92-0.86 (m, 2H, CH₂-4'''), 0.85 (d, $J=6.4$ Hz, 3H, CH₃-7'''); EIMS: m/z : 443 [M⁺] (3%), 281 (60.3%), 251 (87.9%), 191 (16.8%), 133 (3.2%), 117 (100%), 91 (67.6%), 98 (87.3%).

1-[[4-[[5-(4-Hydroxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl]methyl]phenyl]sulfonyl]-3-methylpiperidine (8n)

Light brown powder; M.P: 68-70°C; Yield: 76%; M.F: C₂₁H₂₃N₃O₄S₂; M.W: 445.56; IR (KBr, $\nu_{\max}$, cm⁻¹): 3074 (Ar C-H), 1668 (C=O), 1562 (Ar C=C), 1666 (C=N), 1328 (-SO₂), 1277, 1057 (C-O-C), 630 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.85 (d, $J=6.8$ Hz, 2H, H-2'', H-6''), 7.70 (d, $J=7.6$ Hz, 2H, H-2'', H-6''), 7.61 (d, $J=7.6$ Hz, 2H, H-3'', H-5''), 7.44 (d, $J=8.8$ Hz, 2H, H-3', H-5'), 4.53 (s, 2H, CH₂-7''), 3.62 (t, $J=11.6$ Hz, 2H, H-6'''), 2.23 (d, $J=11.2$ Hz, 1H, H_{eq}-2'''), 1.92 (d, $J=11.2$ Hz, 1H, H_{ax}-2''), 1.70-1.67 (m, 2H, CH₂-5'''), 1.55-1.65 (m, 2H, CH₂-3'''), 1.00-0.92 (m, 2H, CH₂-4'''), 0.85 (d, $J=8.0$ Hz, 3H,

Table 4: % Inhibition and IC₅₀ for anti-urease activity of synthesized compounds

Compound	Inhibition (%) at 0.5mM	IC ₅₀ (μM)
8a	61.76±0.42	156.98±0.18
8b	58.61±0.21	231.86±0.07
8c	43.78±0.23	-
8d	76.12±0.42	52.45±0.11
8e	45.78±0.92	187.53±0.27
8f	54.14±0.91	398.65±0.48
8g	49.52±0.44	-
8h	65.30±0.72	173.23±0.28
8i	34.92±0.36	-
8j	42.85±0.98	-
8k	38.58±0.56	-
8l	39.47±0.31	-
8m	44.89±0.63	-
8n	49.65±0.45	-
8o	46.92±0.45	-
8p	47.97±0.64	-
Thiourea	98.45±0.87	21.25±0.15

CH₃-7'''); EIMS: *m/z*: 445 [M]⁺ (3%), 283 (60%), 251 (88%), 193 (17%), 135 (3%), 119 (100%), 98 (87%), 93 (68%).

1-[[4-([5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl)methyl]phenyl]sulfonyl]-3-methylpiperidine (8o)

Light brown sticky solid; Yield: 82%; M.F: C₂₂H₂₅N₃O₄S₂; M.W: 459.54; IR (KBr, *v*_{max}, cm⁻¹): 3075 (Ar C-H), 1669 (C=O), 1563 (Ar C=C), 1667 (C=N), 1329 (-SO₂), 1279, 1058 (C-O-C), 631 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.68 (d, *J*=8.0 Hz, 2H, H-2'', H-6''), 7.61 (d, *J*=8.0 Hz, 2H, H-3'', H-5''), 7.47 (d, *J*= 8.0 Hz, 2H, H-2', H-6'), 7.02 (d, *J*=8.0 Hz, 2H, H-3', H-5'), 4.51 (s, 2H, CH₂-7''), 3.92 (s, 3H, -OCH₃-7''), 3.61 (br.s, 2H, H-6'''), 2.23 (d, *J*=10.8 Hz, 1H, H_{eq}-2'''), 1.88 (d, *J*=10.8 Hz, 1H, H_{ax}-2'''), 1.70-1.65 (m, 2H, CH₂-5'''), 1.63-1.57 (m, 2H, CH₂-3'''), 0.87-0.83 (m, 2H, CH₂-4'''), 0.83 (d, *J*=6.0 Hz, 3H, CH₃-7'''); EIMS: *m/z*: 459 [M]⁺ (3%), 297 (60.3%), 251 (87.9%), 207 (16.8%), 149 (3.2%), 113 (100%), 107 (67.6%), 98 (87.3%).

1-[[4-([5-(3-Aminophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl)methyl]phenyl]sulfonyl]-3-methylpiperidine (8p)

Brown sticky solid; Yield: 82%; M.F: C₂₁H₂₄N₄O₃S₂; M.W: 444.57; IR (KBr, *v*_{max}, cm⁻¹): 3076 (Ar C-H), 1670 (C=O), 1564 (Ar C=C), 1668 (C=N), 1330 (-SO₂), 1279, 1059 (C-O-C), 632 (C-S); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.95 (d, *J*=7.2 Hz, 1H, H-6'), 7.76 (s, 1H, H-2'), 7.69 (d, *J*=8.4 Hz, 2H, H-2'', H-6''), 7.61 (d, *J*=8.0 Hz, 2H, H-3'', H-5''), 7.49 (t, *J*=9.6 Hz, 1H, H-5'), 7.46 (d, *J*=7.6 Hz, 1H, H-4'), 4.54 (s, 2H, CH₂-7''), 3.59 (t, *J*=11.2 Hz, 2H, H-6'''), 2.23 (d, *J*=7.6 Hz, 1H, H_{eq}-2'''), 1.87 (d, *J*=10.8 Hz, 1H, H_{ax}-2'''), 1.702-1.64 (m, 2H, CH₂-5'''), 1.58-1.53 (m, 2H, CH₂-3'''), 0.88-0.85 (m, 2H, CH₂-4'''), 0.82 (d, *J*=6.4 Hz, 3H, CH₃-7'''); EIMS: *m/z*: 444 [M]⁺

(3%), 282 (60%), 251 (88%), 192 (17%), 134 (3%), 118 (100%), 98 (87%), 92 (68%).

RESULT

The different 1,3,4-oxadiazole and 3-pipecoline derivatives, 8a-p, were synthesized by scheme-1 and varying aryl/aralkyl groups are given in table 1. The elaborated synthetic methods are written in experimental section. Spectral data of IR, EIMS and ¹H-NMR was used to corroborate the structures of compounds. The pharmacological evaluation involves antibacterial activity against certain bacterial strains of Gram-positive and Gram-negative bacteria and anti-enzymatic potential against urease enzyme. The antibacterial activity results have been depicted as % inhibition in table 2 and MIC (Minimum Inhibitory Concentration) in table 3. The anti-urease enzyme inhibition results are depicted as % inhibition and IC₅₀ (Inhibitory Concentration for 50% inhibition) in table 4. These synthesized organic molecules have better antibacterial activity and low anti-urease enzyme inhibition activity.

DISCUSSION

Chemistry

For single compound discussion, the molecule 1-[[4-([5-(2-naphthylmethyl)-1,3,4-oxadiazol-2-yl]sulfanyl)methyl]phenyl]sulfonyl]-3-methylpiperidine (8a) is selected. It was synthesized through a series of steps. Firstly naphthalene acetic acid was refluxed for 3 hrs with 99% ethanol and conc. H₂SO₄ in a RB flask (250 mL). After maximum completion, reaction contents were neutralized by aq. Na₂CO₃ and ester was extracted by solvent extraction using CHCl₃ after addition of distilled water. CHCl₃ was distilled off to collect ethyl-2-

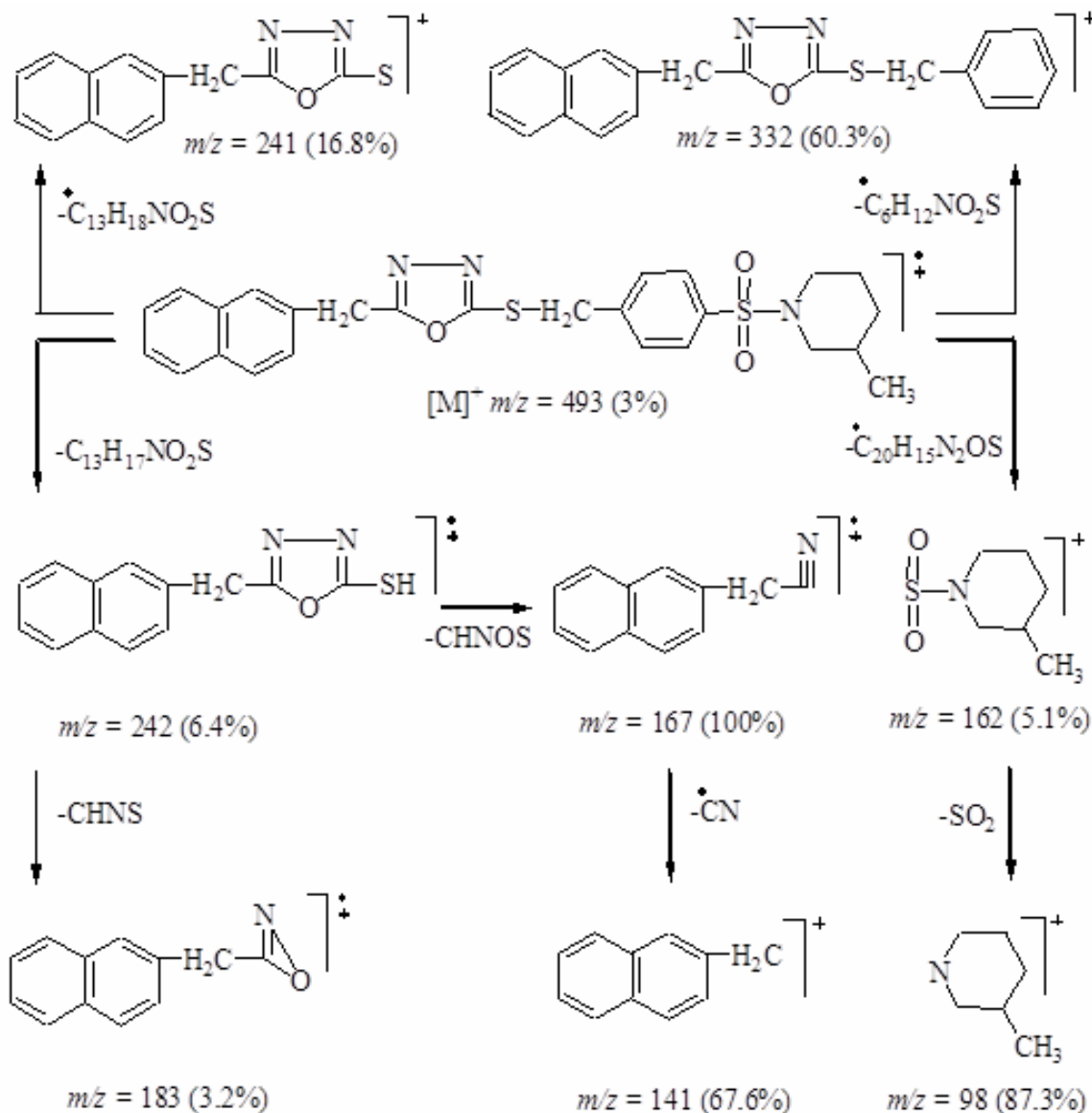


Fig. 1: Proposed Mass fragmentation pattern of compound 8a

naphthylacetate. Secondly ethyl 2-naphthylacetate was refluxed with 80% $N_2H_4 \cdot H_2O$ in ethanol for 6 hrs. The precipitates of 2-naphthylacetohydrazide were acquired after addition of excess dist. H_2O . The precipitates were filtered, washed and dried. Thirdly 2-naphthylacetohydrazide was refluxed with CS_2 and KOH in ethanol for 5 hrs. After final TLC, distilled water was added along with dil. HCl to adjust pH of 3-4 to acquire the precipitates of 5-(naphthalen-2-ylmethyl)-1,3,4-oxadiazol-2-thiol. The addition of acid is crucial to change back the salt form of 5-(naphthalen-2-ylmethyl)-1,3,4-oxadiazol-2-thiol into acidic one but limited amount is used because excess reduces the amount of product. The precipitates were filtered, washed with dist. H_2O and re-crystallized from CH_3OH . Fourthly electrophile was prepared from 3-methylpiperidine and 4-bromomethylbenzenesulfonyl chloride upon stirring in a

basic aqueous medium. The mixture was acidified by dil. HCl to adjust pH of 5-6. Precipitates of 1-(4-bromomethylbenzenesulfonyl)-3-methylpiperidine were filtered, washed with distilled water, dried and used for further reaction. Finally 5-(naphthalen-2-ylmethyl)-1,3,4-oxadiazol-2-thiol was homogenized in DMF in a round bottom flask and then LiH was added along with stirring. 1-(4-Bromomethylbenzenesulfonyl)-3-methylpiperidine was poured into homogeneous solution after half an hour and further stirred for 4-6 hours. Ice cold dist. water was introduced into reaction contents along with aq. NaOH to acquire the precipitates. Precipitates were filtered, washed with dist. H_2O and dried.

The compound 8a was prepared as light brown amorphous solid with 86% yield and melting point of 74-76°C. Its molecular formula was conformed through

EIMS showing a $[M]^+$ ion at m/z 493 stepping to molecular formula, $C_{26}H_{27}N_3O_3S_2$ which was also supported by the integration of protons in its 1H -NMR spectrum. The different mass fragments of 8a have been elaborated in figure-1 for convenience to read out the other EIMS patterns. In 1H -NMR spectrum, the nine protons of 5-(naphthalen-2-ylmethyl)-1,3,4-oxadiazol-2-thiol were assigned as two singlets at δ 7.42 (s, 1H, H-1') and 4.34 (s, 2H, CH_2 -11'); four doublets at δ 8.07 (d, J = 8.4 Hz, 1H, H-4'), 7.87 (d, J = 6.8 Hz, 1H, H-8'), 7.82 (d, J = 6.8 Hz, 1H, H-5') and 7.51 (d, J = 7.6 Hz, 1H, H-3'); and two triplets at δ 7.49 (t, J = 8.0 Hz, 1H, H-6') and 7.45 (t, J = 7.2 Hz, 1H, H-7'). The aromatic four protons of 1-(4-bromomethylbenzenesulfonyl)-3-methylpiperidine were appeared as two doublets at δ 7.58 (d, J = 8.4 Hz, 2H, H-2", H-6") and 7.38 (d, J = 8.4 Hz, 2H, H-3", H-5"); and aliphatic two methylene protons were appeared as a singlet at δ 4.59 (s, 2H, CH_2 -7"). In the aliphatic region, five protons resonating as three doublets with δ 2.18 (d, J = 9.6 Hz, 1H, H_{eq} -2"), 1.87 (d, J = 10.8 Hz, 1H, H_{ax} -2") and 0.85 (d, J = 6.4 Hz, 3H, CH_3 -7"); two protons resonating as one triplet at δ 3.59 (t, J = 11.2 Hz, 2H, H-6"); and six protons giving three multiplets at δ 1.71-1.63 (m, 2H, CH_2 -5"), 1.60-1.58 (m, 2H, CH_2 -3") and 0.92-0.88 (m, 2H, CH_2 -4"). The IR spectrum well supported the molecular structure by showing the absorption bands for the main functional groups present in the molecule at 3075 (Ar C-H), 1669 (C=O), 1563 (Ar C=C), 1667 (C=N), 1329 (-SO₂ str.); 1279, 1058 (C-O-C) and 631 (C-S). All these evidences validated the proposed structure of 8a and named as 1-([4-([5-(2-naphthylmethyl)-1,3,4-oxadiazol-2-yl]sulfonyl)methyl]phenyl)sulfonyl}-3-methylpiperidine. Likewise the other compounds, 8b-p, were structurally corroborated.

Antibacterial activity

For antibacterial activity evaluation, Gram-positive bacteria taken into account include *B. subtilis* & *S. aureus* and Gram-negative bacteria taken into account include *S. typhi*, *E. coli* & *P. aeruginosa*. The antibacterial activity results have been depicted as % inhibition and MIC (Minimum Inhibitory Concentration) in table 2 & 3 and listed with reference of ciprofloxacin. The two compounds, 8j and 8o were the best inhibitors of all the five bacterial strains among all the synthesized compounds.

Against *S. typhi*, the compounds exhibited excellent to moderate activity except a few ones. The most active compounds were 8b, 8c, 8g, 8h, 8j and 8o as indicated by their MIC values given in table 1. The best activity of these compounds might be attributed to the presence of phenyl, 4-nitrophenyl, 2-chloro-3,5-dinitrophenyl, 2-methyl-3,5-dinitrophenyl, 3-chlorophenyl and 4-methoxyphenyl moieties respectively attached to 5th position of 1,3,4-oxadiazole ring. The most active compound was 8h with MIC value of 9.11 ± 0.76 μ M with

respect to 7.83 ± 0.78 μ M, the MIC of the reference standard, ciprofloxacin. The compounds, 8f, 8i, 8k and 8p remained inactive at all against this strain. Against *E. coli*, all the compounds remained active except 8k. The active compounds remained excellent inhibitors and a few ones with moderate activity. The compound 8k remained inactive at all against this strain. The most active compounds were 8e, 8h and 8p owing to the presence of 2-nitrophenyl, 2-methyl-3,5-dinitrophenyl and 3-aminophenyl moieties respectively attached to 5th position of 1,3,4-oxadiazole ring. The most active compound was again 8h with MIC value of 8.79 ± 0.49 μ M with respect to 8.01 ± 0.12 μ M, the MIC of the reference standard, ciprofloxacin. The whole series of compounds remained best inhibitor of this bacterial strain. Against *P. aeruginosa*, the most of the compounds remained efficient inhibitors except 8g and 8h, which were inactive at all. The most active compounds were 8e and 8f owing to the presence of 2-nitrophenyl and 3,5-dinitrophenyl moieties respectively attached to 5th position of 1,3,4-oxadiazole ring. The most active compound was 8e with MIC value of 8.97 ± 0.63 μ M with respect to 7.98 ± 0.89 μ M, the MIC of the reference standard, ciprofloxacin. The whole series of compounds also remained best inhibitor of this bacterial strain. Overall three compounds, 8c, 8j and 8o remained the most efficient against all the three bacterial strains of Gram-negative bacteria taken into account.

All the compounds remained efficient inhibitors against *B. subtilis* except 8g and 8h which were weak inhibitors of this strain. The most active compound was 8d bearing 3-nitrophenyl moiety. It presented MIC value of 8.97 ± 0.50 μ M with respect to 7.22 ± 0.67 μ M, the MIC of the reference standard, ciprofloxacin. All the series of compounds remained moderate inhibitors of *S. aureus* except 8g and 8h which were inactive at all. The compound 8d also remained best inhibitor of both of the Gram-positive bacterial strains.

Anti-urease enzyme inhibition

All the synthesized compounds were evaluated for enzyme inhibition potential against urease enzyme. The % inhibition and IC₅₀ values of results are listed in table 4. Out of sixteen synthesized molecules, only six molecules, 8a, 8b, 8d, 8e, 8f and 8h were active. Among these six compounds, five were moderately active. The compound 8d was the excellent inhibitor with IC₅₀ value of 52.45 ± 0.11 μ M with respect to 21.25 ± 0.15 μ M, the IC₅₀ value of thiourea taken as reference standard. The better activity of 8d might be attributed to the presence of 3-nitrophenyl group. The activity order of the active compounds was found to be $8d > 8a > 8h > 8e > 8b > 8f$.

CONCLUSION

All the compounds were obtained in notable yields by the methods of preparation employed in this research project.

Initially the synthesis of compounds was intimated by single spot on TLC plate and finally the structures were corroborated through spectral techniques including IR, EIMS and 1D ¹H-NMR. The evaluation against antibacterial activity rendered these compounds excellent to moderate inhibitors of five bacterial strains from Gram-positive and Gram-negative bacteria taken into account. All the results were interpreted as MIC and compared with that of ciprofloxacin. The compound 8h was most active against *S. typhi* and *E. coli*. Against *P. aeruginosa*, the most active compound was 8e; and against *B. subtilis*, the most active compound was 8d. The compound 8d bearing 3-nitrophenyl group, was the most active one among the six active compounds for anti-urease activity. Owing to low MIC values, these molecules can be further subjected to *in vivo* study along with cytotoxicity evaluation. The series of molecules might be used as drug candidates by the pharmacological industries for the drug discovery program.

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REFERENCES

- Abbasi MA, Akhtar A, Aziz-ur-Rehman, Nafeesa K, Siddiqui SZ, Khan KM, Ashraf M and Ejaz SA (2013). Synthesis, structural characterization and enzyme inhibition studies on 5-(2-nitrostyryl)-1,3,4-oxadiazole-2-thiol derivatives. *J. Chil. Chem. Soc.*, **58**: 2186-2196.
- Ameen S, Akhtar MS, Seo HK and Shin HS (2015). An electrochemical sensing platform based on hollow mesoporous ZnO nanoglobules modified glassy carbon electrode: Selective detection of piperidine chemical. *Chem. Eng. J.*, **270**: 564-571.
- Aziz-ur-Rehman, Fatima A, Abbasi MA, Khan KM, Ashraf M, Ahmad I and Ejaz SA (2013). Synthesis, characterization and biological screening of *N*-substituted (5-chloro-2-methoxyphenyl)benzene sulfonamide. *Asian J. Chem.*, **25**: 3735-3740.
- Boström J, Hogner A, Llinàs A, Wellner E and Plowright AT (2011). Oxadiazoles in medicinal chemistry. *J. Med. Chem.*, **55**: 1817-1830.
- Chou SSP and Huang JL (2012). Tandem cross metathesis and intramolecular aza-Michael reaction to synthesize bicyclic piperidines and indolizidine 167E. *Tetrahedron Lett.*, **53**(41): 5552-5554.
- Desai NC, Dodiya AM, Rajpara KM and Rupala YM (2014). Synthesis and antimicrobial screening of 1,3,4-oxadiazole and clubbed thiophene derivatives. *J. Saud. Chem. Soc.*, **18**: 255-261.
- El-Sayed NS, El-Bendary RE, El-Ashry SM and El-Kerdawy MM (2011). Synthesis and antitumor activity of new sulfonamide derivatives of thiadiazolo[3,2-*a*]pyrimidines. *Eur. J. Pharm. Sci.*, **46**: 3714-3720.
- Galan MJG, Cruz MSD and Berceño D (2008). Identification and determination of metabolites and degradation products of sulfonamide antibiotics. *Trends Anal. Chem.*, **27**: 1008-1022.
- Kaspady M, Narayanaswamy VK, Raju M and Rao GK (2009). Synthesis, antibacterial activity of 2, 4-disubstituted oxazoles and thiazoles as bioisosteres. *Lett. Drug Des. Discov.*, **6**: 21-28.
- Mobley HL, Cortesia MJ, Rosenthal LE and Jones BD (1988). Characterization of urease from *Campylobacter pylori*. *J. Clin. Microbiol.*, **26**: 831-836.
- Modi V and Modi P (2012). Oxadiazole: Synthesis, characterization and biological activities. *J. Saud. Chem. Soc.*, **16**: 327-332.
- Nagaraj, Chaluvajuru KC, Niranjan MS and Kiran S (2012). 1,3,4-Oxadiazole: A potent drug candidate with various pharmacological activities. *Int. J. Pharm. Pharm. Sci.*, **3**: 9-16.
- Ordoñez AC, Reyes CM, Santibáñez FO, Hernández SM, García VB and Rivera G (2011). Efficient synthesis of sulfonamide derivatives on solid supports catalyzed using solvent-free and microwave-assisted methods. *J. Quim. Nova.*, **5**: 787-791.
- Raval JP, Akhaja TN, Jaspara DM, Myangar KN and Patel NH (2014). Synthesis and in vitro antibacterial activity of new oxoethylthio-1,3,4-oxadiazole derivatives. *J. Saud. Chem. Soc.*, **18**: 101-106.
- Reddy NS, Rao AS, Chari MA, Kumar VR, Jyothy V and Himabind V (2012). Synthesis and antibacterial activity of sulfonamide derivatives at C-8 alkyl chain of anacardic acid mixture isolated from a natural product cashew nut shell liquid (CNSL). *J. Chem. Sci.*, **3**: 723-730.
- Sahin G, Palaska E, Ekizoglu M and Ozalp M (2002). Synthesis and antimicrobial activity of some 1,3,4-oxadiazole derivatives. *Il. Farmacol.*, **57**: 539-542.
- Sanchit S and Pandeya SN (2011). Various approaches for synthesis of oxadiazole derivatives. *Int. J. Res. Ayurv. Pharm.*, **2**: 459-468.
- Sharma J and Ahsan MJ (2014). 1,3,4-Oxadiazole: A versatile therapeutic heterocycle. *Adv. Biomed. Pharma.*, **1**: 1-10.
- Vitnik VD and Vitnik ZJ (2015). The spectroscopic (FT-IR, FT-Raman, ¹³C, ¹H NMR and UV) and NBO analyses of 4-bromo-1-(ethoxycarbonyl)piperidine-4-carboxylic acid. *Spectrochimica Acta Part A: Mole. Biom. Spec.*, **138**: 1-12.
- Zoumpoulakis P, Camoutsis C, Pairas G, Sokovic M, Glamoclija J, Potamitis C and Pitsas A (2012). Synthesis of novel sulfonamide-1,2,4-triazoles, 1,3,4-thiadiazoles and 1,3,4-oxadiazoles, as potential antibacterial and antifungal agents. Biological evaluation and conformational analysis studies. *J. Bioorg. Med. Chem.*, **20**: 1569-1583.