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# One pot synthesis of 1,3,4-oxadiazoles by Lewis acid catalyst and their study of 2D-QSAR, antimicrobial and anti-tubercular activities

J A Patel[a] & N B Patel[b,]*

[a]Department of Chemistry, Vidhyadeep Institute of Science, Anita, Kim-Olpad Road, Surat 394 110, Gujarat, India
[b]Department of Chemistry, Veer Narmad South Gujarat University, Udhana-Magdalla Road, Surat 395 007, Gujarat, India
*E-mail: drnavinbpatel@gmail.com

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In the present work, Lewis acid catalyzed reactions have been carried out between mefenamic acid, substituted aldehyde and semicarbazide in the presence of $ZnCl_2$ to give the final compounds (*E*)-*N*-(2-(5-((substitutedene)amino)-1,3,4-oxadiazol-2-yl)phenyl)-2,3-dimethylaniline, **A**. The synthesized compounds have been characterized by IR, $^1$H NMR, $^{13}$C NMR, mass spectral studies and biologically screened for the antimicrobial, antitubercular and antimalarial activities. Among the screened molecules, the molecules $A_1$, $A_3$, $A_4$, $A_6$, $A_8$, $A_9$, $A_{10}$ show activity against different antibacterial species. The compounds, active against different antifugal species are $A_3$, $A_7$, $A_8$, $A_9$ against *C. albicans*, compound $A_3$ is active against *A. niger*. Whereas, compound $A_9$ shows good antimycobacterial activity. Compound $A_6$ having 4-hydroxybenzenesubstituent exhibits promising activity against *P. falciparum* antimalerial parasite.

**Keywords:** 1,3,4-oxadiazole, 2D-QSAR study, Antimicrobial activity, Antitubercular activity, Antimalarial activity

1,3,4-Oxadiazoles are effectively reported as intensive toxophoric agents describing significant biological activities vis antibacterial, antifungal, antituberculosis, anti-inflammatory, anticancer, antitumor and antioxidant[1-7]. The ability of 1,3,4-oxadiazole to undergo various chemical reactions as well as its biological potential made them very important for synthetic molecular design. Some biological active 1,3,4-oxadiazole derivatives available as clinical medicines are Raltegravir as antiretroviral, Zibotentan as anticancer, Tiodazosin as antihypertensive and Furamizole as antibiotics. For our interest on mefenamic acid and Schiff base, we have studied their pharmacological activity. Mefenamic acid is a derivative of anthranilic acid, which is very effective against antibacterial, analgesic, antioxidantand antiinflametry activities[8-9]. Schiff base is found to possess pharmacological activitiy such as antifungal, antibacterial, antitubercular, cytotoxicity, antimalarial and anticancer[10-12]. Presence of C=N in the Schiff base results in molecular conjugation which intensively expands the biological activity[13-14]. Molecular conjugation is known for the rational design of new biologically active moieties by fusion of molecules and /or pharmacophoric units derived from known bioactive molecules[15-16]. Because of the effective biological activity of 1,3,4-oxadiazole, Schiff base and mefenamic acid, we decided to generate the mefenamic acid-1,3,4-oxadiazole-Schiff base conjugates.

Here, we were synthesized 1,3,4-oxadiazole derivatives. Different routes have reported for the synthesis of 1,3,4-oxadiazoles[17-20]. But, we have modified one pot synthetic newer path used for 1,3,4-oxadiazole which is promoted by Lewis acid catalyst. From last decades, some researchers have studied bio-response of molecule correlated with physicochemical properties of molecule and study the structure activity relationship (SAR)[21-22]. The correlation between physicochemical properties and molecular structure of compounds are determined by quantitative structure activity relationship (QSAR)[23]. 2D-QSAR studies are performed to determine correlation between the structures and biological activities[24-25]. Our aim is to determine the 2D-QSAR for designed and synthesized biological activenewer 1,3,4-oxadiazoles[26-28]. We performed the 2D-QSAR to determine the structure correlation with antituberculer activity by VLifeMDS software and PLS regression method. 2D-QSAR predicted valuesare compared with actual biological activities.

## Experimental Details

### Materials and methods

All the chemicals were used as of analytical grade. Melting points were determined on a Fisher-Johns

melting point apparatus. A purity of the compounds was checked by TLC on silica gel plates with visualization by UV-light and iodine chamber. FTIR analysis was performed by model FTIR 8400S and frequency obtained in $cm^{-1}$unit. $^{1}$H-NMR spectra were recorded on 400 MHz and $^{13}$C-NMR spectra were recorded on 100 MHz using Bruker Avance II spectrometer instruments, DMSO-$d_6$ as solvent and chemical shifts were recorded in parts per million downfield from TMS. Mass spectra were recorded on LC-MS. Structures and nomenclatures of the compounds were created on Perkin Elmer ChemBioOffice Ultra 14.0.0.117 software. 2D-QSAR parameters were determined by VLife MDS software.

**Chemistry**

***Synthesis of (E)-N-(2-(5-((substitutidene)amino)-1,3,4-oxadiazol-2-yl)phenyl)-2,3-dimethylaniline.- ($A_{1-10}$)***

Mefenamic acid(0.020 mol, 4.82 gm), semicarbazide (0.020 mol, 1.50 g) and substituted aldehydes (0.020 mol, 2.12 g) dissolves in methanol, add acetic acid(1ml) and stirredit around 20-30 min up to 90°C. The reaction mixture followed up by the addition of anhydrous zinc chloride (0.73 mol, 1 g) and stirred up to 90°C around 4-5 h. The completion of the reaction was checked by TLC during each 1.5 h interval. After completion of the reaction the mixture was to room temperature and poured over ice cold water. The product obtained was washed with water, followed by distilled water. Then precipitated was crystallized from methanol to make pure product (**A**) as analytical sample. All the derivatives (**$A_1$-$A_{10}$**) were synthesized by this method and physical data are given in Table 1.

***Spectral characterization of compounds***

**E)-N-(2-(5-((thiophene-2-ylmethylene)amino)-1,3,4-oxadiazol-2-yl)phenyl)-2,3-dimethylaniline ($A_1$)**: IR (KBr) $\nu$ $cm^{-1}$: 3323 (N-H stretching), 3081 (C-H stretching, aromatic), 2988 (C-H stretching, $CH_3$), 2912 (C-H stretching, Schiff base), 1652 (N-N stretching, oxadiazole), 1604 (N-H bending), 1565 (C=C stretching, aromatic), 1508 (N=C stretching), 1437 (C-H bending, aromatic), 1326 (C-H bending, $CH_3$), 1221 (C-O stretching, oxadiazole), 1137 (C-N stretching) 772 (C-S stretching); $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.45 (s, 1H, N-H), 8.79 (s, 1H, N=C-H), 7.86 (d, 1H, $J$ = 3.56 Hz, thiophene), 7.75 (d, 1H, $J$ = 2.36 Hz, Ar-H), 7.67 (d, 1H, $J$ = 5.16 Hz, thiophene), 7.43 (d, 1H, $J$ = 5.06 Hz, Ar-H), 7.30 (d, 1H, $J$ = 4.96 Hz, Ar-H), 7.22 (t, 1H, $J$ = 3.24 Hz, Ar-H), 7.11 (d, 1H, $J$ = 2.32 Hz, Ar-H), 7.08 (t, 1H, $J$ = 6.94 Hz, thiophene), 7.03 (t, 1H, $J$ = 4.12 Hz, Ar-H), 6.96 (t, 1H, $J$ = 6.44 Hz, Ar-H), 2.28, (s, 3H, $CH_3$), 2.14, (s, 3H, $CH_3$).$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm): 170.1 (C-2), 156.4 (C-18), 148.8(C-17), 139.4 (C-4), 138.4 (C-9), 137.6 (C-1), 134.7 (C-11), 133.8 (C-10), 131.6 (C-6), 131.2 (C-14), 128.3 (C-3), 127.9 (C-20), 127.3 (C-21), 126.9 (C-12), 126.2 (C-14), 125.8 (C-5, C-19), 122.1 (C-7), 115.9 (C-8), 112.9 (C-13), 20.3 (C-15), 13.6 (C-16); LC–MS (m/z): 374 $M^+$, 376 $[M+2]^+$.

**(E)-2-(((5-(2-((2,3-dimethylphenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)imino))methyl)phenol ($A_2$):** IR (KBr) $\nu$ $cm^{-1}$: 3430 (O-H stretching), 3310 (N-H stretching), 3016 (C-H stretching, aromatic), 2966 (C-H stretching, $CH_3$), 2926 (C-H stretching, Schiff base), 1646 (N-N stretching, oxadiazole), 1620 (N-H bending), 1588 (C=C stretching, aromatic), 1519 (N=C stretching), 1453 (C-H bending, aromatic), 1332 (C-H bending, $CH_3$), 1263 (C-O stretching, oxadiazole), 1152 (C-N stretching); $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 10.19 (s, 1H, OH), 9.93 (s, 1H, N-H), 9.25 (s, 1H, N=C-H), 7.63 (t, 1H, $J$ = 3.28 Hz, Ar-H), 7.55 (d, 1H, $J$ = 2.54 Hz, Ar-H), 7.46 (t, 1H, $J$ = 2.58 Hz, 2-hydroxybenzene), 7.37 (d, 1H, $J$ = 2.36 Hz, Ar-H), 7.21 (d, 1H, $J$ = 2.20 Hz, 2-hydroxybenzene), 7.13 (t, 1H, $J$ = 7.13 Hz, 2-hydroxybenzene), 7.08 (t, 1H, $J$ = 4.08 Hz, Ar-H), 6.96 (d, 1H, $J$ = 5.20 Hz, Ar-H), 6.83 (t, 1H, $J$ = 7.60 Hz, Ar-H), 6.78 (d, 1H, $J$ = 7.36 Hz, Ar-H),6.69 (d, 1H, $J$ = 5.92 Hz, 2-hydroxybenzene), 2.28, (s, 3H, $CH_3$), 2.11, (s, 3H, $CH_3$);$^{13}$CNMR(100 MHz, DMSO-$d_6$) δ (ppm): 170.2 (C-2), 156.5 (C-18), 155.9 (C-17), 142.0 (C-4), 141.4 (C-9), 138.6 (C-1), 131.2 (C-11), 129.9 (C-10), 128.3 (C-6), 127.9 (C-21, C-22), 127.3 (C-3), 127.0 (C-12, C-23), 125.9 (C-14), 125.2 (C-5, C-19), 120.2 (C-7, C-19), 119.0 (C-8), 115.9 (C-8, C-13), 113.0 (C-13), 20.3 (C-15), 13.6 (C-16); LC–MS(m/z):384 $M^+$.

Table 1 — Physical data table ($A_1$-$A_{10}$)

| Code | R | Yield (%) | M.P. (°C) | M.F. |
|---|---|---|---|---|
| $A_1$ | 3-Thiophenecarboxaldehyde | 63 | 223 | $C_{21}H_{18}ON_4S$ |
| $A_2$ | 2-Hydroxybenzaldehyde | 76 | 251 | $C_{23}H_{20}O_2N_4$ |
| $A_3$ | 4-Fluorobenzldehyde | 78 | 238 | $C_{23}H_{19}ON_4F$ |
| $A_4$ | 3-Pyridinecarboxaldehyde | 73 | 240 | $C_{23}H_{20}ON_4$ |
| $A_5$ | Furfuraldehyde | 84 | 210 | $C_{21}H_{18}O_2N_4$ |
| $A_6$ | 4-Hydroxybenzaldehyde | 74 | 217 | $C_{23}H_{20}O_2N_4$ |
| $A_7$ | 4-Nitrobenzaldehyde | 77 | 257 | $C_{23}H_{19}O_3N_5$ |
| $A_8$ | Cinnamalaldehyde | 83 | 263 | $C_{25}H_{25}ON_4$ |
| $A_9$ | 4-(Diethylamino)salisaldehyde | 81 | 234 | $C_{27}H_{29}O_2N_5$ |
| $A_{10}$ | 2-Pyridinecarboxaldehyde | 73 | 248 | $C_{23}H_{20}ON_5$ |

**(E)-N-(2-(5-((4-fluorobenzylidene)amino)-1,3,4-oxadiazol-2-yl)phenyl)-2,3-dimethylaniline($A_3$)**: IR (KBr) $\nu$ $cm^{-1}$: 3341 (N-H stretching), 3064 (C-H stretching, aromatic) , 2988 (C-H stretching, $CH_3$), 2911 (C-H stretching, Schiff base), 1655 (N-N stretching, oxadiazole), 1600 (N-H bending), 1573 (C=C stretching, aromatic), 1503 (N=C stretching), 1437 (C-H bending, aromatic), 1337 (C-H bending, $CH_3$), 1255 (C-O stretching, oxadiazole), 1159 (C-N stretching), 824 (C-Fstretching);$^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.67 (s, 1H, N-H), 8.39 (s, 1H, N=C-H),8.02 (d, 2H, $J$ = 2.89 Hz, fluorobenzene), 7.77 (d, 1H, $J$ = 2.45 Hz, Ar-H), 7.58 (t, 1H, $J$ = 3.21 Hz, Ar-H), 7.39 (d, 1H, $J$ = 4.78 Hz, Ar-H), 7.29 (d, 2H, $J$ = 2.84 Hz, fluorobenzene), 7.23 d, 1H, $J$ = 5.32 Hz, Ar-H), 7.15 (t, 1H, $J$ = 3.98 Hz, Ar-H), 7.06 (d, 1H, $J$ = 7.23 Hz, Ar-H), 6.98 (t, 1H, $J$ = 6.78 Hz, Ar-H), 2.28, (s, 3H, $CH_3$), 2.14, (s, 3H, $CH_3$);$^{13}$C NMR(100 MHz, DMSO-$d_6$) δ (ppm): 165.2 (C-2), 160.0 (C-21), 153.5 (C-17), 142.0 (C-4), 138.6 (C-9), 137.1 (C-1), 131.2 (C-11), 129.9 (C-10), 128.3 (C-6), 127.9 (C-18), 127.00 (C-3), 126.3 (C-14), 125.2 (C-12), 124.3 (C-19, C-23), 123.2 (C-5), 119.3 (C-7), 117.3 (C-8), 116.2 (C-13), 20.22 (C-15), 13.6 (C-16); LC–MS (m/z):386 $M^+$ .

**(E)-2,3-dimethyl-N-(2-(5-((pyridin-3-ylmethylene)-amino)-1,3,4-oxadiazol-2-yl)phenyl)aniline ($A_4$):** IR (KBr) $\nu$ $cm^{-1}$: 3311 (N-H stretching), 3015 (C-H stretching, aromatic) , 2976 (C-H stretching, $CH_3$), 2910, (C-Hstretching, $CH_3$), 1653 (N-N stretching, oxadiazole), 1596 (N-H bending), 1576 (C=C stretching, aromatic), 1510 (C-H stretching, Schiff base), 1443 (C-H bending, aromatic), 1329 (C-H bending, $CH_3$), 1259 (C-O stretching, oxadiazole), 1161 (C-N stretching); $^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.76 (s, 1H, N-H), 9.15 (s, 1H, N=C-H),8.29 (d, 1H, $J$ = 4.23 Hz, pyridine), 7.92 (d, 1H, $J$ = 3.17 Hz, pyridine), 7.85 (t, 1H, $J$ = 2.36 Hz, pyridine), 7.68 (d, 1H, $J$ = 2.36 Hz, Ar-H), 7.52 (t, 1H, $J$ = 2.20 Hz, Ar-H), 7.43 (d, 1H, $J$ = 2.29 Hz, Ar-H), 7.39 (t, 1H, $J$ = 2.46 Hz, pyridine), 7.26 (d, 1H, $J$ = 5.28 Hz, Ar-H), 7.17 (t, 1H, $J$ = 4.10 Hz, Ar-H), 6.93 (d, 1H, $J$ = 7.52 Hz, Ar-H), 6.71 (t, 1H, $J$ = 6.93 Hz, Ar-H), 2.27, (s, 3H, $CH_3$), 2.12, (s, 3H, $CH_3$);$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm): 165.2 (C-2), 153.5 (C-17), 149.0 (C-19), 147.5 (C-1), 137.1 (C-20), 136.2 (C-18), 135.9 (C-22), 135.5 (C-21), 131.1 (C-11), 130.3 (C-4), 129.1 (C-10), 128.2 (C-6), 127.9 (C-14), 127.2 (C-3), 126.3(C-12), 125.2 (C-5), 120.5 (C-7), 118.8 (C-8), 116.1 (C-13), 20.4 (C-15), 13.8 (C-16); LC–MS (m/z):368 $M^+$.

**(E)-N-(2-(5-((furan-2-ylmethylene)amino)-1,3,4-oxadiazol-2-yl)phenyl)-2,3-dimethylaniline($A_5$):** IR (KBr) $\nu$ $cm^{-1}$: 3368 (N-H stretching), 3079 (C-H stretching, aromatic), 2965 (C-H stretching, $CH_3$), 2914 (C-H stretching, Schiff base), 1656 (N-N stretching, oxadiazole), 1624 (N-H bending), 1595 (C=C stretching), 1568 (C=N stretching), 1443 (C-H bending, aromatic), 1346 (C-H bending, $CH_3$), 1147 (C-O stretching), 1078 (C-N stretching); $^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.96 (s, 1H, N-H), 8.14 (s, 1H, N=C-H),7.87 (d, 1H, $J$ = 3.47 Hz, furfural), 7.78 (d, 1H, $J$ = 2.32 Hz, Ar-H), 7.48 (d, 1H, $J$ = 4.95 Hz, Ar-H), 7.34 (d, 1H, $J$ = 5.02 Hz, Ar-H), 7.21 (t, 1H, $J$ = 3.11 Hz, Ar-H), 7.13 (d, 1H, $J$ = 2.32 Hz, Ar-H), 6.97 (t, 1H, $J$ = 3.98 Hz, Ar-H), 6.93 (t, 1H, $J$ = 6.57 Hz, Ar-H),6.90 (d, 1H, $J$ = 6.74 Hz, furfural) 6.63 (d, 1H, $J$ = 4.25 Hz, furfural), 2.29, (s, 3H, $CH_3$), 2.08, (s, 3H, $CH_3$).$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm): 166.3 (C-2), 153.3 (C-18), 149.00(C-17), 140.4 (C-4), 138.2 (C-9), 136.5 (C-1), 135.0 (C-11), 133.7 (C-10), 131.0 (C-6), 130.7 (C-14), 128.3 (C-3), 127.6 (C-20), 126.9 (C-21), 126.3 (C-12), 126.1 (C-14), 125.2 (C-5, C-19), 119.4 (C-7), 118.1 (C-8), 113.3 (C-13), 20.4 (C-15), 13.4 (C-16);LC–MS (m/z):357 $M^+$.

**(E)-4-(((5-(2-((2,3-dimethylphenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)imino))methyl)phenol ($A_6$)**: IR (KBr) $\nu$ $cm^{-1}$: 3428 (O-H stretching), 3325 (N-H stretching), 3014 (C-H stretching, aromatic), 2941 (C-H stretching, $CH_3$), 2924 (C-H stretching, Schiff base), 1648 (N-N stretching, oxadiazole), 1606 (N-H bending), 1583 (C=C stretching, aromatic), 1512 (N=C stretching), 1453 (C-H bending, aromatic), 1321 (C-H bending, $CH_3$), 1255 (C-O stretching), 1136 (C-N stretching);$^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 10.28 (s, 1H, OH), 9.93 (s, 1H, N-H), 9.25 (s, 1H, N=C-H), 7.85 (d, 2H, $J$ = 2.83 Hz, 4-hydroxybenzene), 7.68 (d, 1H, $J$ = 2.47 Hz, Ar-H), 7.53 (t, 1H, $J$ = 3.29 Hz, Ar-H), 7.34 (d, 1H, $J$ = 4.63 Hz, Ar-H), 7.27 (d, 2H, $J$ = 2.91 Hz, 4-hydroxybenzene), 7.20 (d, 1H, $J$ = 5.41 Hz, Ar-H), 7.11 (t, 1H, $J$ = 4.06 Hz, Ar-H), 6.91 (d, 1H, $J$ = 7.46 Hz, Ar-H), 6.78 (t, 1H, $J$ = 6.85 Hz, Ar-H), 2.28, (s, 3H, $CH_3$), 2.11, (s, 3H, $CH_3$);$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm): 169.8 (C-2), 156.4 (C-18), 152.8 (C-17), 142.6 (C-4), 141.1 (C-9), 139.2 (C-1), 131.6 (C-11), 130.2 (C-10), 129.1 (C-6), 127.6(C-21, C-22), 127.1 (C-3), 126.8 (C-12, C-23), 126.2 (C-14), 125.7 (C-5, C-19), 121.2 (C-7, C-19), 119.6 (C-8), 116.0 (C-8, C-13), 113.3 (C-13), 20.5 (C-15), 13.4 (C-16); LC–MS (m/z):384 $M^+$.

**(E)-2,3-dimethyl-N-(2-(5-((4-nitrobenzylidene) amino)-1,3,4-oxadiazol-2-yl)phenyl)aniline($A_7$)**: IR (KBr) $\nu$ $cm^{-1}$: 3321 (N-H stretching), 3037 (C-H stretching, aromatic), 2963 (C-H stretching, $CH_3$), 2913, (C-H Stretching, Schiff base), 1658 (N-N stretching, oxadiazole), 1614 (N-H bending), (1578 (C=C stretching, aromatic), 1543 (N=O stretching), 1514 (N=C stretching), 1429 (C-H bending, aromatic), 1337 (C-H bending, $CH_3$), 1257 (C-O stretching), 1113 (C-N stretching); $^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.56 (s, 1H, N-H), 9.08 (s, 1H, N=C-H), 8.32 (d, 2H, $J$ = 3.11 Hz, nitrobenzene),8.20 (d, 2H, $J$ = 2.89 Hz, nitrobenzene), 7.71 (d, 1H, $J$ = 2.43 Hz, Ar-H), 7.56 (t, 1H, $J$ = 3.18 Hz, Ar-H), 7.43 (d, 1H, $J$ = 4.73 Hz, Ar-H),7.28 (d, 1H, $J$ = 5.37 Hz, Ar-H), 7.19 (t, 1H, $J$ = 3.96 Hz, Ar-H), 7.04 (d, 1H, $J$ = 7.19 Hz, Ar-H), 6.91 (t, 1H, $J$ = 6.81 Hz, Ar-H),2.23, (s, 3H, $CH_3$), 2.12, (s, 3H, $CH_3$);$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm): 168.2 (C-2), 162.1 (C-21), 152.4 (C-17), 140.8 (C-4), 138.3 (C-9), 137.3 (C-1), 131.5 (C-11), 130.1 (C-10), 129.2 (C-6), 128.3 (C-18), 127.4 (C-3), 126.2 (C-14), 125.8 (C-12), 124.5 (C-19, C-23), 123.0 (C-5), 120.1 (C-7), 116.8 (C-8), 115.3 (C-13), 20.1 (C-15), 13.3 (C-16); LC–MS (m/z):413 $M^+$.

**2,3-Dimethyl-N-(2-(5-(((1E,2E)-3-phenylidene) amino)-1,3,4-oxadiazol-2-yl)phenyl)aniline($A_8$):** IR (KBr) $\nu$ $cm^{-1}$: 3338 (N-H stretching), 3022 (C-H stretching, aromatic), 2976 (C-H stretching, $CH_3$), 2907 (C-H stretching), 1658 (N-N stretching, oxadiazole), 1620 (N-H bending), 1586 (C=C stretching, aromatic), 1521 (N=C stretching), 1453 (C-H bending, aromatic), 1343 (C-H bending, $CH_3$), 1267 (C-O stretching), 1121 (C-N stretching); $^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.41 (s, 1H, N-H), 7.92 (d, 1H, $J$ = 2.68 Hz, N=C-H), 7.73 (d, 1H, $J$ = 2.51 Hz, Ar-H), 7.51 (t, 1H, $J$ = 3.34 Hz, Ar-H), 7.47 (d, 2H, $J$ = 3.41 Hz, Ar-H), 7.40 (t, 2H, $J$ = 6.15 Hz, Ar-H), 7.35 (t, 1H, $J$ = 6.64 Hz, Ar-H), 7.31 (d, 1H, $J$ = 4.59 Hz, Ar-H), 7.26 (d, 1H, $J$ = 3.79 Hz, HC=C-H), 7.18 (d, 1H, $J$ = 5.38 Hz, Ar-H), 7.09 (t, 1H, $J$ = 3.95 Hz, Ar-H), 6.98 (d, 1H, $J$ = 7.46 Hz, Ar-H), 6.91 (t, 1H, $J$ = 6.83 Hz, Ar-H), 6.79 (t, 1H, $J$ = 7.24 Hz, H-C=CH), 2.15 (s, 3H, $CH_3$), 1.96 (s, 3H, $CH_3$);$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm): 167.2 (C-2), 161.6 (C-1), 153.2 (C-17), 142.2 (C-4), 138.6 (C-9), 131.1 (C-11), 130.2 (C-10), 128.5 (C-6), 127.7 (C-19), 127.1 (C-18), 126.8 (C-3), 126.3 (C-14), 125.1 (C-12), 124.1 (C-21, C-25), 124.6 (C-22, C-24), 123.1 (C-5), 120.1 (C-7), 117.3 (C-8), 115.7 (C-13), 20.6 (C-15), 13.2 (C-16);LC–MS (m/z):395 $M^+$.

**(E)-2(((5-(2-((2,3-dimethylphenyl)amino)phenyl)-1,3,4-oxadiazol-2-yl)imino)methyl)-5-(dipropylamino )phenol ($A_9$)**: IR (KBr) $\nu$ $cm^{-1}$:3456 (O-H stretching), 3353 (N-H stretching), 3089 (C-H stretching, aromatic), 2968 (C-H stretching, $CH_3$), 2913 (C-H stretching, Schiff base), 2856 (C-H stretching, $CH_2$), 1665 (N-N stretching, oxadiazole), 1598 (N-H bending), 1566 (C=C stretching, aromatic), 1511 (N=C stretching), 1439 (C-H bending, aromatic), 1328 (C-H bending, aliphatic), 1236 (C-O stretching), 1132 (C-N stretching); $^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 11.23 (s,1H, OH),9.93 (s, 1H, NH), 9.12 (s, 1H, N=C-H), 7.73 (t, 1H, $J$ = 3.33 Hz, Ar-H), 7.48 (d, 1H, $J$ = 2.59 Hz, Ar-H), 7.36 (d, 1H, $J$ = 2.39 Hz, Ar-H), 7.18 (d, 1H, $J$ = 2.28 Hz, N-N-diethyl-2-hydroxybenzene), 7.12 (d, 1H, $J$ = 7.27 Hz, N-N-diethyl-2-hydroxybenzene), 7.06 (t, 1H, $J$ = 4.01 Hz, Ar-H), 6.97 (d, 1H, $J$ = 5.16 Hz, Ar-H), 6.88 (t, 1H, $J$ = 7.60 Hz, Ar-H), 6.79 (d, 1H, $J$ = 7.31 Hz, Ar-H), 6.71 (d, 1H, $J$ = 5.97 Hz, N-N-diethyl-2-hydroxybenzene), 3.78 (t, 4H, $CH_2$) 2.28, (s, 3H, $CH_3$), 2.13, (s, 3H, $CH_3$) 1.57 (m, 4H, $J$ = 8.87 Hz, $CH_2$), 0.87 (t, 6H, $J$ = 5.93 Hz, $CH_3$);$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm):170.1 (C-2), 156.9 (C-18), 153.2 (C-17), 142.2 (C-4), 141.3 (C-9), 138.1 (C-1), 133.5 (C-11), 130.2 (C-10), 128.3 (C-6), 127.9 (C-21, C-22), 127.1 (C-3), 126.3 (C-12, C-23), 125.2 (C-14), 124.8 (C-5, C-19), 120.2 (C-7, C-19), 120.1 (C-8), 116.3 (C-8, C-13), 113.2 (C-13), 57.0 (C-24, C-26), 21.4 (C-25, C-27), 20.5 (C-15), 13.9 (C-16); LC–MS (m/z):356 $M^+$.

**(E)-2,3-dimethyl-N-(2-(5-((pyridin-2-ylmethylene) amino)-1,3,4-oxadiazol-2-yl)phenyl)aniline ($A_{10}$):** IR (KBr) $\nu$ $cm^{-1}$: 3325 (N-H stretching), 3036 (C-H stretching, aromatic), 2991 (C-H stretching, $CH_3$), 2924, (C-H stretching), 1648 (N-N stretching, oxadiazole), 1610 (N-H bending), 1565 (C=C stretching), 1514 (N=C stretching), 1430 (C-H bending, aromatic), 1332 (C-H bending, $CH_3$), 1256 (C-O stretching), 1154 (C-N stretching);$^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.66 (s, 1H, N-H), 9.18 (s, 1H, N=C-H),8.92 (d, 1H, $J$ = 4.31 Hz, 2-pyridine), 8.05 (d, 1H, $J$ = 3.31 Hz, 2-pyridine), 7.88 (t, 1H, $J$ = 2.35 Hz, 2-pyridine), 7.75 (d, 1H, $J$ = 2.39 Hz, Ar-H), 7.56 (t, 1H, $J$ = 2.14 Hz, Ar-H), 7.46 (d, 1H, $J$ = 2.27 Hz, Ar-H), 7.37 (t, 1H, $J$ = 2.55 Hz, 2-pyridine), 7.28 (d, 1H, $J$ = 5.31 Hz, Ar-H), 7.19 (t, 1H, $J$ = 4.14 Hz, Ar-H), 6.99 (d, 1H, $J$ = 7.36 Hz, Ar-H), 6.78 (t, 1H, $J$ = 6.89 Hz, Ar-H), 2.26, (s, 3H, $CH_3$), 2.12, (s, 3H, $CH_3$);$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm): 167.1 (C-2), 153.3 (C-17), 149.5 (C-19), 146.3 (C-1), 138.4 (C-20), 137.1 (C-18), 136.2 (C-20), 135.2 (C-21),

132.2 (C-11), 130.0 (C-4), 129.2 (C-10), 128.1 (C-6), 127.3 (C-14), 127.1 (C-3), 126.3 C-12), 124.8 (C-5), 121.3 (C-7), 119.2 (C-8), 115.2 (C-13), 20.2 (C-15), 13.5 (C-16); LC–MS (m/z):368 $M^+$.

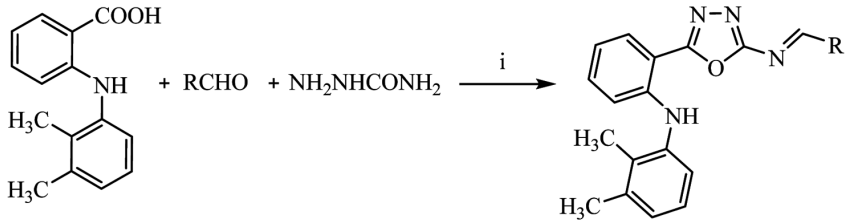
## Results and Discussion

### Chemistry

We had modify the route to generate 1,3,4-oxadiazoles using zinc chloride as catalyst to give higher yield in a one step process. General process for the synthesis of (*E*)-*N*-(2-(5-((substitutidene)amino)-1,3,4-oxadiazol-2-yl)phenyl)-2,3-dimethylaniline is given in Scheme 1 and the reaction mechanism is shown in Scheme 2.

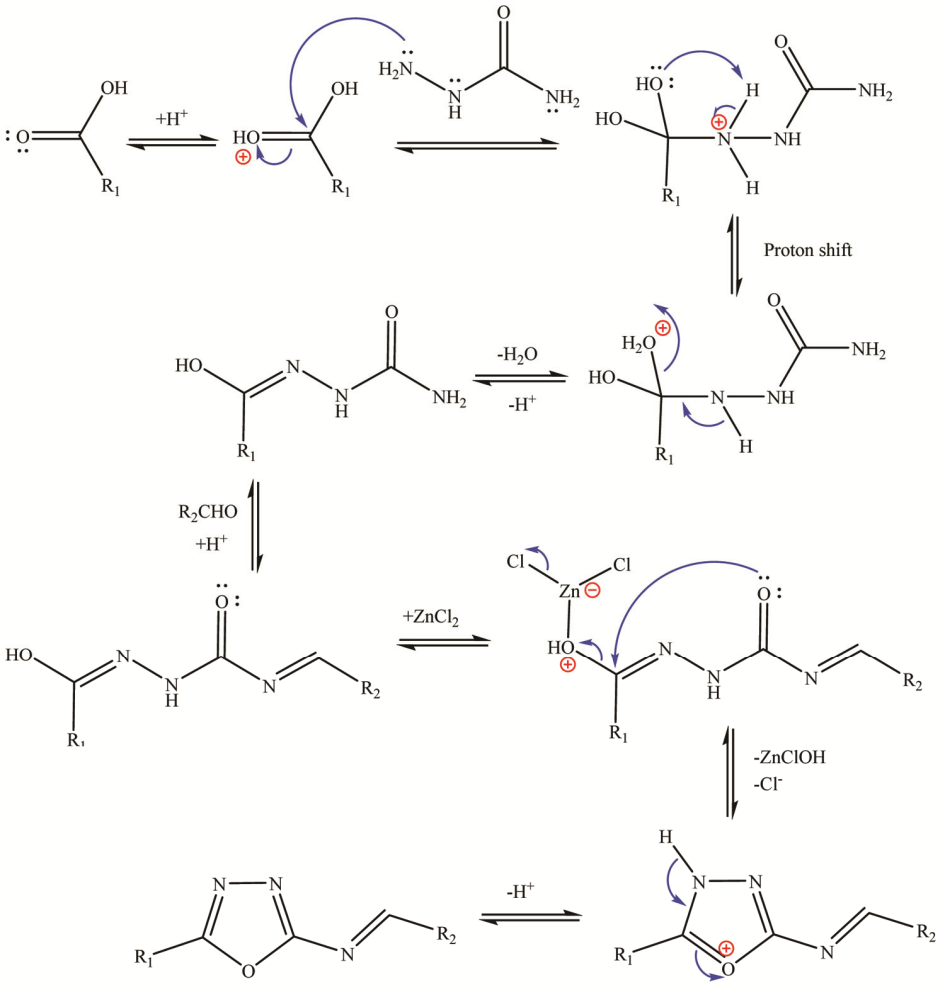
### Antimicrobial activity

Synthesized molecules were evaluated for their antibacterial activity against two Gram-positive




Reagents and conditions: (i) 2-3 drops $CH_3COOH$, methanol, anh $ZnCl_2$, heating with sturring for 4-5 h

Scheme 1 — Synthesis of (*E*)-*N*-(2-(5-(substitutideneamino)-1,3,4-oxadiazol-2-yl)phenyl)-2,3-dimethylaniline




Scheme 2 — Synthetic mechanism of 1,3,4-oxadiazole

Table 2 — Antimicrobial activity of compounds ($A_1$-$A_{10}$)

| Code | Minimal bactericidal concentration (μg/mL) | | | | Minimal fungicidal concentration (μg/mL) | | |
|---|---|---|---|---|---|---|---|
| | *E. coli* MTCC 443 | *P. aeruginosa* MTCC 1688 | *S. aureus* MTCC 96 | *S. pyogenus* MTCC 442 | *C. albicans* MTCC 227 | *A. niger* MTCC 228 | *A. clavatus* MTCC 1323 |
| $A_1$ | 500 | 250 | 125 | 500 | 500 | >1000 | >1000 |
| $A_2$ | 125 | 500 | 250 | 250 | 500 | 500 | >1000 |
| $A_3$ | 100 | 125 | 250 | 125 | 250 | 100 | 200 |
| $A_4$ | 25 | 62.5 | 100 | 125 | 500 | 250 | >1000 |
| $A_5$ | 500 | 250 | 500 | 500 | >1000 | >1000 | >1000 |
| $A_6$ | 100 | 250 | 500 | 250 | 500 | >1000 | >1000 |
| $A_7$ | 125 | 250 | 250 | 250 | 250 | 500 | 1000 |
| $A_8$ | 100 | 50 | 62.5 | 25 | 250 | 500 | 500 |
| $A_9$ | 125 | 100 | 25 | 100 | 100 | 500 | 500 |
| $A_{10}$ | 125 | 100 | 50 | 125 | 500 | 1000 | 1000 |
| Drug | Micromolar (μg/mL) | | | | | | |
| Ampicillin | 100 | - | 250 | 100 | - | - | - |
| Chloramphenicol | 50 | 50 | 50 | 50 | - | - | - |
| Nystatin | - | - | - | - | 100 | 100 | 100 |
| Greseofulvin | - | - | - | - | 500 | 100 | 100 |

All the values are presented as mean of six experiments. Antimicrobial activity is zero for 2% DMSO which was used as control and diluent.

organisms viz, *S. aureus (MTCC-96)*, *S. payogenus (MTCC-442)* as well as two Gram-negative organisms viz, *E. coli (MTCC-443), P.aeruginosa (MTCC-1688)* and antifungal activity against three fungal species *C. albicans (MTCC 227)*, *A. niger (MTCC228),* and *A. clavatus (MTCC1323)*. Microbial strains used were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology (IMTECH), Chandigarh. Antimicrobial activities were determined by the broth dilution method[29-30]. Chloramphenicol and ampicillin were used as standard antibacterial drugs. Nystatin and greseofulvin were used as standard antifungal drugs. The results depicted in Table 2 reveal that the tested compounds showed variable inhibitory effects on the growth of Gram-positive and Gram negative bacterial strains. Amongst the evaluated compounds, the compounds active against different antibacterial species are $A_6$, $A_8$ against *E. coli*. $A_4$, $A_8$, $A_9$, $A_{10}$ against *A. aeruginosa*, $A_1$, $A_4$ against *S. aureus* and $A_3$, $A_4$, $A_8$ against *S. pyogenus*. From which compounds $A_3$, $A_4$, $A_6$, $A_8$, $A_9$ and $A_{10}$ are having electron withdrawing groups. The antifungal screening data are displayed in Table 2 gives the variable inhibitory effects against fungal species. The compounds found active against different fungal species are $A_3$, $A_7$, $A_8$, $A_9$ against *C. albicans*, $A_3$ active against *A.niger*. The compounds having an electron withdrawing substitution displayed promising antimicrobial activity.

Table 3 — Antimalarial activity of compounds ($A_1$-$A_{10}$)

| Compounds | Mean IC50 values (μg/mL) |
|---|---|
| $A_1$ | 2.13 |
| $A_2$ | 1.55 |
| $A_3$ | 1.40 |
| $A_4$ | 1.15 |
| $A_5$ | 1.19 |
| $A_6$ | 0.75 |
| $A_7$ | 1.32 |
| $A_8$ | 1.47 |
| $A_9$ | 0.98 |
| $A_{10}$ | 1.80 |
| Drugs | Micromolar (μg/mL) |
| Chloroquine | 0.020 |
| Quinine | 0.268 |

A stock solution of 5 μg/mL of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. All the values of IC50 presented as mean of six experiments.

**Antitubercular activity**

All the synthesized compounds of the series were evaluated for their antitubercular activity. Determination of MIC of the test compounds against *Mycobacterium tuberculosis H37Rv* were performed by the agar micro dilution method[31-32]. Isoniazid and rifampicin are used as standard drug. The MIC levels of screened compounds ($A_1$-$A_{10}$) against the organisms are given in Table 3. From the table, it is observed that, evaluated compounds displayed variable inhibitory effects on the growth of the tested *M. tuberculosis H37Rv* strains. Among the evaluated compounds, compound $A_9$ containing

electron donating groups showed positive activity against *M. tuberculosis H37Rv*.

**Antimalarial activity**

All the compounds were screened for antimalarial activity. The *in vitro* antimalarial assay was carried out in 96 well microtitre plates according to the micro assay protocol[33] with minor modifications. The cultures of *P. falciparum* strain was maintained in medium RPMI 1640 which was determined by Jaswant Singh Bhattacharya staining to assess the percent parasitemia (rings) and uniformly maintained with 50% RBCs ($O^+$)[34]. The test concentration which inhibited the complete maturation into schizonts was recorded as the MIC. Chloroquine and quinine were used as the reference drug. Out of the tested compounds, $A_6$ was more active than other synthesized compounds against *P. falciparum*. The results are shown in Table 3.

**Structure activity relationship (SAR)**

Structure activity relationship suggests 1,3,4-oxadiazole moieties, especially, 2 and 5 substituted 1,3,4-oxadiazole moieties show important biological activities. It is observed that substituents at position-2 of the 1,3,4-oxadiazole such as SH, C=O, $NH_2$,C=N, $CH_3$ and aryl ring which are electron withdrawing substituents, increase the antimicrobial, antitubercular and antimalarial activities. Moreover, Schiff base at position-2 of the 1,3,4-oxadiazole increases the resonance on 1,3,4-oxadiazole ring that enhance the biological activity of the compounds. The presence of 1,3,4-oxadiazole moiety in compound enhance the biological activity due to presence of C=N in the ring. 1,3,4-oxadiazole enhances the *P. falciparum* antimalarial parasite[35]. Mefenamic acid at position-5 of the 1,3,4-oxadiazole increases the antimicrobial activity, especially, having $CH_3$ at 2 and 3 position increases potency against antimicrobial activity. SAR study revealed that synthesized lead targeted compounds containing substituted phenyl ring attached with Schiff base at position-2 of the 1,3,4-oxadiazole which potent against different biological species are 3-pyridine potent against *E. coli*, 2-hydroxy-4-diethylaminobenzene potent against *S.aureus* and styrene,4-hydroxybenzene potent against *S. pyogenus* antibacterial species. 2-hydroxy-4-diethylaminobenzene substituent of the 1,3,4-oxadiazole derivative showed more effective against antituberculer activity. 4-chlorobenzene and 3-nitrobenzene more substituents of the 1,3,4-oxadiazole derivative showed effective against *P. falciparum* antimalerial parasite. Styrene is exhausting more effective activity due to extending conjugation. The arrangement of the 1,3,4-oxadiazole derivatives having a Schiff base with a substituted phenyl ring at position-2 and mefenamic acid at position-5 enhance the biological activities as shown in Fig. 1.

**2D-QSAR (Two dimensional quantitative structure activity relationships)**

2D-QSAR analysis is used to understand observed biological properties and determines the structural parameter that control biological activity. A large number of molecular descriptors (physico chemical, spatial, electronic and topological parameters) are

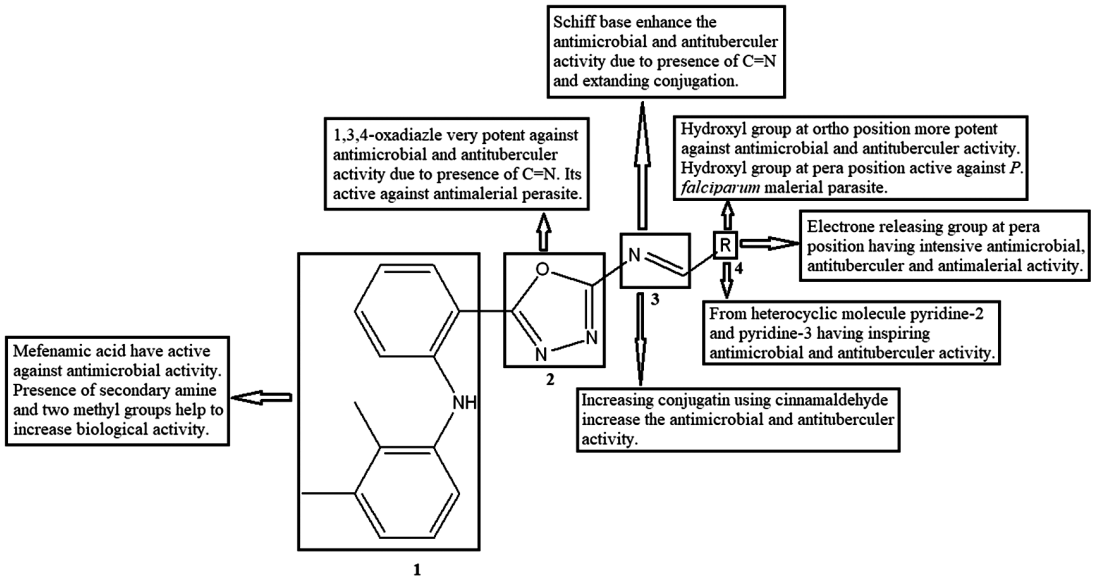



Fig. 1 — SAR (Structure activity relationship)

usually used in the QSAR analysis using Vlife MDS software. The various physico chemical descriptors calculate the free energy change due to drug receptor complex and topological structure descriptors are used for the alignment independent descriptor, these both independent descriptors are considered as independent variables. Spatial parameters give steric features of drug molecules which are required to fit with receptor. Non-covalent bonding between drug molecules and receptors describe electronic descriptor. QSAR analysis regression was performed using pMIC values as dependent variables and calculated parameters as independent variables. Manually selecting and placing molecules in the training and test sets are comprising of 8 and 2 molecules, respectively.

Partial least square analysis method generated significant QSAR model, which considered on the basis of statistical parameters, correlation coefficient (r), squared correlation coefficient ($r^2$), predictive $r^2$ for the external test set (pred $r^2$) for the external validation, and Fischer's value (F). External validation for the activity in the test set was predicted using the model developed by the training set as calculated[36]. The cross-validated coefficient, q2 was calculated[37]. The significance of the models which obtained based on a calculated $Z_{score}$[38].

The QSAR determined for antitubercular activity of ten derivatives. The PLSR methodology was used to predict QSAR of synthesized derivatives against *M. tuberculosis H37Rv*. The training and test set molecules for this group of compounds were selected by the sphere exclusion method and the models were validated by both internal and external validation procedures. Model generated equation as follow.

pMIC = + 232.7641 SaaOcount - 20.8406 T_T_C_1 + 1026.0207

$N_{training}$= 8, $N_{test}$= 2, Degree of freedom = 6, $r^2$ =0.8609, $q^2$ = 0.6125, F test = 37.1428, $r^2$_se = 58.2501, $q^2$_se = 129.5158, pred_$r^2$ = 0.6200, pred_$r^2$se = 138.7283.

The equation explains 86 % ($r^2$ = 0.8609) of the total variance in the training set as well as it was internal ($q^2$) and external (pred_$r^2$) predictive ability of ~61 % and ~62%, respectively. The F test = 37.14 shows the statistical significance of 99.99% of the model which means that the probability of failure of the model is 1 in 10000. The model incorporates two parameters SaaOcount and T_T_C_1 their corresponding values for each molecule in the selected model. The descriptor SaaOcount in the model indices for number of oxygen atom connected with two single bonds. The positive correlation suggests that the antitubercular activity of 1,3,4-oxadiazole derivatives may be dependent on oxygen atom present in the molecules. As a negative contributing descriptor, T_T_C_1 is an alignment-independent descriptor influencing activity variation and itis inversely proportional to the activity. The model is validated by $Z_{Score}$ $R^{\wedge 2}$ = 17.4243,$Z_{Score}$ $Q^{\wedge 2}$ = 2.1623, Best Rand $R^{\wedge 2}$ = 0.1775, Best Rand $Q^{\wedge 2}$ = -0.2662, Alpha Rand $R^{\wedge 2}$ = 0.0000, Alpha Rand $Q^{\wedge 2}$ = 0.0500,$Z_{Score}$Pred $R^{\wedge 2}$ = -1.4158, best Rand Pred $R^{\wedge 2}$ = 0.1999, alpha Rand Pred $R^{\wedge 2}$ = 0.0000. The randomization test suggests that the developed model has a probability less than1% that the model is generated by chance. The observed and predicted pMIC along with residual values are shown in Table 4. Activity distribution graph for Predicted *vs* Actual data shown in Fig. 2.

Table 4 — Antitubercular activity of compounds ($A_1$-$A_{10}$)

| *H37Rv* MIC (μg/mL) | | | | | Discriptors Used | |
|---|---|---|---|---|---|---|
| Code | Actual MIC | Actual pMIC | Predicted pMIC | Residual pMIC | SaaOcount | T_T_C_1 |
| $A_1$ | 250 | -2.39 | -2.39 | 0.00 | 1 | 60.5155 |
| $A_2$ | 100 | -2.00 | -2.01 | 0.01 | 1 | 60.4972 |
| $A_3$ | 100 | -2.00 | -1.98 | -0.02 | 1 | 60.4958 |
| $A_4$ | 125 | -2.09 | -2.08 | -0.01 | 1 | 60.5006 |
| $A_5$ | 500 | -2.69 | -2.69 | 0.00 | 2 | 71.6985 |
| $A_6$ | 100 | -2.00 | -2.00 | 0.00 | 1 | 60.4968 |
| $A_7$ | 125 | -2.09 | -2.10 | 0.01 | 1 | 60.5014 |
| $A_8$ | 50 | -1.69 | -1.68 | -0.01 | 2 | 60.4814 |
| $A_9$ | 25 | -1.39 | -1.39 | 0.00 | 1 | 60.4675 |
| $A_{10}$ | 100 | -2.00 | -1.99 | -0.01 | 1 | 60.4962 |

| Drug | Micromolar (μg/mL) |
|---|---|
| Isoniazid | 0.20 |
| Rifampicin | 40 |

pMIC = (1/log MIC) value used for 2D-QSAR determination. All the values of MIC presented as mean of six experiments. Antitubercular activity is zero for 2% DMSO which was used as control and diluent.

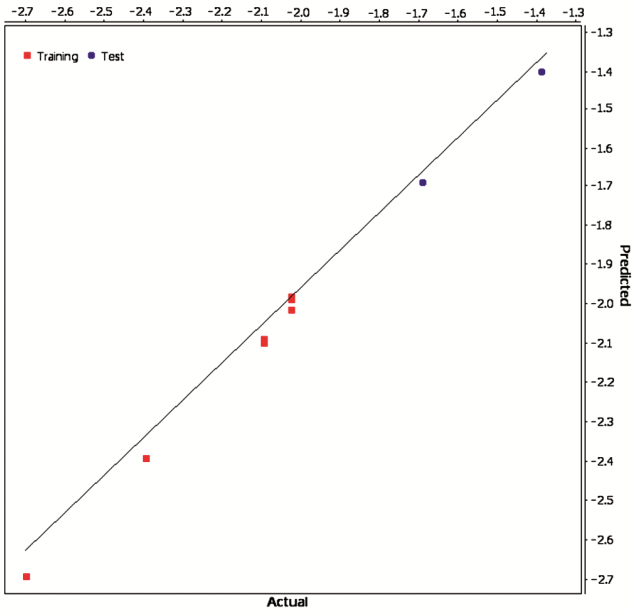



Fig. 2 — Activity distribution graph for Predicted vs Actual data ($A_1$-$A_{10}$)

## Conclusion

Synthesis of biologically active 1,3,4-oxadiazoles of mefenamic acid and Schiff base conjugates was achieved by applying newer modified one pot synthetic process followed by catalyst Lewis acid ($ZnCl_2$). This reaction consumed less time and gave comparatively higher yield. Synthesized compounds were evaluated against antimicrobial species and antitubercular species *M. tuberculosis H37Rv*. On the basis of structural activity relationship study of sythesized compounds, it was observed that mefenamic acid moiety enhanced the antibacterial activity, whereas 1,3,4-oxadiazole and Schiff base showed good antimicrobial and antitubercular activities. The electron releasing groups, 3-pyridine, 4-(diethylamino)salisylicphenyl and styrene having extending conjugation showed antimicrobial and antitubercular activity. Two dimensional structure activity relationship (2D-QSAR) was carried out for *M. tuberculosis H37Rv*by using VLife MDS software, which gave predicted pMIC value using descriptors SaaOcount and T_T_C_1. The Predicted values are nearer to original activities and calculated residual values.

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## Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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