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SYNTHESIS AND *IN-VITRO* ANTIMICROBIAL EVALUATION OF SOME 1, 3, 4-OXADIAZOLES INCORPORATED WITH 5-(5-(5-(BENZOFURAN-2-YL)-1-PHENYL-1*H*-PYRAZOL-3-YL)-1, 3, 4-OXADIAZOL-2-YLTHIO) METHYL MOIETY

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ABSTRACT

In the present article a series of novel 2, 3, 5-trisubstituted 1, 3, 4-Oxadiazole (9a-i) derivatives possessing 5-(5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) methyl moiety were synthesised by cyclization cum acetylation of 8a-i with acetic anhydride. Reaction of 2-(5-(5-(benzofuran-2-yl)-1-methyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) acetohydrazide (7) with different aryl aldehydes (2a-i) in ethanol was carried out to gain 8a-i derivatives. The reaction of 5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazole-2(3*H*)-thione (5) with ethyl 2-chloroacetate afforded ethyl 2-(5-(5-(benzofuran-2-yl)-1-methyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-yl-thio) acetate (6) which upon reaction with hydrazine hydrate yielded starting compound (7). The structures of newly synthesized compounds were corroborated through elemental and spectral studies like IR, ^{1}H NMR, C^{13} NMR and Mass spectra. All the synthesised compounds were screened for their *in vitro* antibacterial activity against panel of pathogenic microorganism including *S. aureus* as Gram positive bacterial strain and *E. coli, P. vulgaris, S. typhi* as Gram negative strains. The result of bioassay was compared with Chloramphenicol as standard reference drug.

KEYWORDS

1, 3, 4-Oxadiazole, Benzofuran pyrazole-3-carbohydrazide and Acetohydrazide.

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INTRODUCTON

Research in the field of pharmaceutics has its most important task in the enhancement of new and superior drugs and their prosperous introduction into clinical practice. Treatment of infectious diseases is an important and challenging problem but in recent years misuse and overuse of antibiotic against human pathogenic microorganisms has developed antibiotic resistant resulting in potential global health crisis. To overcome the development of resistance it is crucial to synthesize a new class

of antibiotics possessing promising biological and pharmacological activities. Heterocyclic molecules belongs to the most attractive group and valuable synthetic templates owing to their broad spectrum of antimicrobial activities. These held core stage in the development of molecules to enhance quality of human life. Perhaps, more than seventy per cent of drugs used today are heterocyclic compounds. Consequently over the year oxadiazole related drugs have attracted the attention of the scientific community to synthesize a large number of 1, 3, 4-oxadiazole derivatives as novel chemotherapeutic medicines. Oxadiazole nucleus is fertile source of bioactivity in the area of drug discovery and its derivatives had been reported to exhibit numerous activities like, antibacterial[1-5], anti-tubercular[6-8], antiviral[9], anti-inflammatory[10-12], anticancer[13,14], anti-allergic[15], lipoxygenase inhibitors[16], tubulin inhibitors[17], antitumor[18], anticonvulsant[19], analgesic[20], and many more biological activities[21-25]. They are also useful as HIV integrated inhibitors[26], insecticidal[27] and used as dye pigments[28]. Oxadiazole nucleus containing drugs are commercially available in the market like Furamizole as Tiodazosin[29] and Nesapidil[30], antibiotic[31] as an anti-hypertensive agents.

The extensive literature survey revealed that the presence of heterocyclic rings at the 2nd and 5th position of the oxadiazole ring increases the biological profile of these compounds to a greater extent. In the view of above observation an attempt has been made in present study to design and react 2-(5-(5-(benzofuran-2-yl)-1-methyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) acetohydrazides with various aryl aldehydes to obtain acid hydrazones which can be further reacted with acetic anhydride to yield some novel 2, 3, 5-trisubstituted 1, 3, 4-Oxadiazole derivatives. Simultaneously, it was thought to evaluate these synthesized compounds for their *in-vitro* antimicrobial activity.

MATERIAL AND METHODS

All the chemicals used for the synthesis were of AR grade of Merck, S.D. Fine and Aldrich. The reactions were monitored by E. Merck TLC aluminium sheet silica gel60F254 and visualizing the spot in UV cabinet and iodine chamber. IR spectra were recorded on a Shimadzu IR Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra are recorded on a Bruker AM 400 instrument (400 MHz) using tetramethylsilane (TMS) as an internal reference and DMSO-d_6 and $CDCl_3$ as solvent. Waters Micro mass Q–TOF Micro, Mass Spectrophotometer was used to record the ESI-MS mass spectra. Elemental analysis (CHN) was done using Thermo Scientific (Flash-2000). The compounds were analyzed for carbon, hydrogen, nitrogen and the results obtained are in good conformity with the calculated values. The melting points were recorded in open capillary in paraffin bath and are uncorrected. All the obtained products were screened for their antimicrobial activities.

Experimental Procedure

Procedure for the synthesis of 2-(5-(5-(benzofuran-2-yl)-1-methyl-1H-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) acetohydrazide (7)

The synthesis of acetohydrazide **(7)** was carried out by two step procedure:

Step-I

Procedure for the synthesis of ethyl 2-(5-(5-(benzofuran-2-yl)-1-methyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) acetate (6). Ethyl 2-chloroacetate (3.22mL, 30mmol) and potassium carbonate (4.14g, 30 mmol) were added to 5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazole-2(3*H*)-thione[32] **(**5, 3.60g, 10mmol) in DMF(30mL) and reaction mixture was refluxed for 6h, it was then concentrated and poured in ice-cold water, solid separated out was filtered and recrystallize from ethanol to get white amorphous solid (6) (yield 78%); m.p.142-145°C; M.F. $C_{23}H_{18}N_4O_4S$; IR(KBr, υ_{max} in cm^{-1}): 1736(C=O, ester), 1609(C=N), 1496, 1457,1375 (C=C), 3062, 3035(C-H str. Ar-H), 2984, 2938 (C-H str. -CH_3); 1199,1170(C-O-Csym. str.), 1021, 1005 (C-O-C asym. str.) 1304 (-C-N str. in pyrazole),^{1}H NMR δ ppm (DMSO-d_6): 1.19 -1.20 (t, 3H, -CH_3), 4.16 -4.19 (q, 2H, -O$\underline{CH_2}$-) 6.66 (s, 1H, of pyrazole –CH), 7.24-7.50 (m, 10H, Ar-H), 4.31(s,1H, -OH keto-enol), 4.95 (s,1H, -C(OH)=$\underline{CH}$-), 7.24-7.50 (m,10H,Ar-H); ^{13}C NMR δ ppm (DMSO-d_6): 13.98, 33.92, 107.04, 109.60, 111.16, 121.82, 123.60,

125.91, 127.44, 129.82, 135.68, 137.18, 138.98, 139.09, 142.73, 144.15 153.94, 160.27, 163.13, 167.52 Elemental Anal. Calcd. For $C_{24}H_{23}N_4O_4S$, calculated: C, 61.87; H, 4.06; N, 12.55; O, 14.33; S, 7.18 Found: C, 61.17; H, 4.30; N, 12.63; S, 6.95.

Step-II

Synthesis of 2-(5-(5-(benzofuran-2-yl)-1-methyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) acetohydrazide (7). Hydrazine hydrate (100%, 1.7mL) was added to a mixture of ethyl 2-(5-(5-(benzofuran-2-yl)-1-methyl-1*H*-pyrazol-3-yl)-2, 3-dihydro-1, 3, 4-oxadiazol-2-yl thio) acetate (6, 4.32g, 10mmol) in absolute ethanol and stirred for 8h, then it was poured in ice-cold water. Solid separated out was filtered and recrystallized from ethanol to get white amorphous solid (7) (yield 70%); m.p.180°C; M.F. $C_{21}H_{16}N_6O_3S$; IR (KBr, υ_{max} in cm^{-1}): 3329, 3200 (N-H str., $-NH_2$), 3058(C-H str., Ar-H), 1681 (C=O str. in CONH-), 1623(C=N str. in pyrazole), 1595, 1623, 1499, 1448 (C=C str. in aromatic ring), 1087, 1000(C-H i.p. def.), 810 (C-H o.o.p. def), 1250, 1290, 1370(C-N str. in pyrazole), 1256 (C-O-C sym. str.), 1087 (C-O-C asym. str.), 751, 697 (C-S-C str.), 697(C-S str.); ^{1}H NMR δ ppm (DMSO-d_6): 3.39 (s, 2H, $-NH_2$),4.25 (s,2H,-SC<u>H</u>$_2$CO-), 10.57 (s,1H,-NH-), 6.13(s,1H,-CH-C_4 of pyrazole ring), 6.49-7.60 (m,10H,ArH); ^{13}C NMR δ ppm (DMSO-d_6): 40.61(S-<u>C</u>H$_2$-), 160 (C=O in amide), 135, 139 (-C=N- C_3 in pyrazole), 121 (C_4 of benzofuran), 111 (C_7 of benzofuran), 108 (C=N in pyrazole), 106 (C_3 of benzofuran), 153, 149, 144, 145, 143, 137, 134, 129, 127, 125, 123. ESI-MS (*m/z*): 432 M^+, 433 $[M+1]^+$, 455 $[M+Na]^+$, 456 $[M+Na+H]^+$. Elemental Anal. Calcd. For $C_{21}H_{16}N_6O_3S$ calculated C, 58.32; H, 3.73; N, 19.43; S, 7.41 Found: C, 57.40; H, 4.23; N, 20.43.

Procedure for the synthesis of *N′*-(4-methoxybenzylidene)-2-(5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) acetohydrazide (8a)

2-(5-(5-(benzofuran -2-yl)-1-methyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) acetohydrazide (7, 4.34g, 10mmol), and 4-methoxy benzaldehyde (1.2mL, 10mmol) were taken in absolute ethanol (25mL), 2-3 drops of acetic acid was added as a catalyst, the reaction mixture was refluxed for 2h. Resulting mass was allow to cool, filtered and the product was recrystallized from absolute ethanol to get 8a (Scheme No.2).

Similarly, 8b-i was synthesized by reaction of 7 and 2b-i, adopting the same procedure as described for synthesis of 8a and all were recrystallized from absolute ethanol.

***N′*-(4-methoxybenzylidene)-2-(5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) acetohydrazide (8a)**

White amorphous solid m.p., 198°C; yield, 72%; M.F.$C_{29}H_{22}N_6O_4S$; IR(KBr, υ_{max} in cm^{-1}): 3187, 3493(N-H str.), 3070(C-H, str., aromatic), 2996, 2936 (C-H asym. str., aliphatic), 2836 (C-H sym. str., aliphatic), 1501,1483 (C=C str., aromatic), 1107, 1102 (C-H i.p. def., aromatic), 835 (C-H o.o.p. def., aromatic), 1678 (C=O str. ,CONH), 1605 (C=N str.), 1254 (C-O-C sym. str.), 1031 (C-O-C asym.str.), 1461 (C-H asym. def. ,CH_2 and CH_3), 1372 (C-H sym. def. , CH_2 and CH_3), 744, 776, 697 (C-S-C str.), 640 (C-S str.). ^{1}H NMR δ ppm (DMSO-d_6): 3.77 (s,3H, -OCH_3 attached to aromatic ring), 4.65(s, 2H, hetero aryl, -S-<u>CH</u>$_2$CONHN=CH-Ar), 11.69 (s, 1H, -NHCO-), 8.15(s,1H,-CH=N-), 6.67 (s,1H, at C_4-carbon of pyrazole), 6.69-7.98 (m,14H, aromatic + heteroaryl).

***N′*-(2-chlorobenzylidene)-2-(5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) acetohydrazide (8b)**

White amorphous solid m.p. 207°C; yield, 74%; M.F.$C_{28}H_{19}ClN_6O_3S$; IR (KBr, υ_{max} in cm^{-1}): 3100, 3485 (N-H str.), 3050 (C-H str., aromatic), 2975, 2930 (C-H asym. str., aliphatic), 2830 (C-H sym. str., aliphatic), 1521, 1453 (C=C str., aromatic), 1100, 1120 (C-H i.p. def, aromatic), 845 (-C-H o.o.p. def, aromatic, 1680 (C=O str. ,CONH), 1630 (C=N str.), 1260 (C-O-C sym. str.), 1050 (C-O-C asym. str.), 1458 (C-H asym.def ,CH_2 and CH_3), 1362 (C-H sym. def. , CH_2 and CH_3), 750, 770, 690 (C-S-C str.), 640 (C-S str.).

***N'*-(2-fluorobenzylidene)-2-(5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) acetohydrazide (8c)**

White amorphous solid; m.p., 205°C; yield, 76% ; M.F.$C_{28}H_{19}FN_6O_3S$; IR (KBr, υ_{max} in cm^{-1}): 3105, 3495 (N-H str.), 3050 (C-H str., aromatic), 2985, 2940 (C-H asym. str. aliphatic), 2830 (C-H sym. str., aliphatic), 1500, 1463 (C=C str., aromatic), 1115, 1125 (C-H i.p. def., aromatic), 860 (C-H o.o.p. def., aromatic), 1688 (C=O str. ,CONH), 1632 (C=N str.), 1263 (C-O-C sym. str.), 1050 (C-O-C asym.str.), 1460 (C-H asym.def ,CH_2 and CH_3),1362 (C-H sym. def. , CH_2 and CH_3), 751, 770, 680 (C-S-C str.),652 (C-S str.).

N'-(4-(benzyloxy)benzylidene)-2-(5-(5-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) acetohydrazide (8d)

White amorphous solid mp, 203°C; yield, 70%; M.F ; $C_{35}H_{26}N_6O_4S$; IR (KBr, υ_{max} in cm^{-1}): 3100, 3485 (N-H str.), 3050 (C-H str., aromatic), 2975, 2930 (C-H asym. str. aliphatic), 2830 (C-H sym. str., aliphatic),1521,1453 (C=C str., aromatic), 1100,1120 (C-H i.p.def, aromatic), 855 (C-H o.o.p.def, aromatic), 1680 (C=O str. ,CONH), 1630 (C=N str.), 1260 (C-O-C sym. str.), 1052(C-O-C asym.str.), 1459 (C-H asym.def, CH_2 and CH_3), 1364 (C-H sym. def., CH_2 and CH_3), 750, 770, 690 (C-S-C str.), 640(C-S str.).

2-(5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio)-*N'*-(3-phenylallylidene) acetohydrazide (8e)

White amorphous solid; m.p. 209°C; yield, 65%; M.F.$C_{30}H_{22}N_6O_3S$; IR (KBr, υ_{max} in cm^{-1}): 3010, 3382 (N-H str.), 3063 (C-H str., aromatic), 2972, 2935 (C-H asym. str. aliphatic), 2833 (C-H sym. str., aliphatic), 1523, 1463 (C=C str., aromatic), 1123, 1140 (C-H i.p. def, aromatic), 832 (C-H o.o.p. def., aromatic), 1682 (C=O str., CONH), 1625 (C=N str.), 1256 (C-O-C sym. str.), 1057 (C-O-C asym.str.), 1417 (C-H asym.def ,CH_2 and CH_3), 1372 (C-H sym. def., CH_2 and CH_3), 752, 776, 693 (C-S-C str.), 641 (C-S str.).

2-(5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio)-*N'*-((furan-2-yl) methylene) acetohydrazide (8f)

White amorphous solid; m.p. 214°C; yield, 75%; (from absolute ethanol); M.F. $C_{26}H_{18}N_6O_4S$.IR (KBr, υ_{max} in cm^{-1}): 3140, 3485 (N-H str.), 3050 (C-H str., aromatic), 2975, 2930 (C-H asym. str. aliphatic), 2830 (C-H sym. str., aliphatic), 1521, 1453 (C=C str., aromatic), 1100, 1122 (C-H i.p. def., aromatic), 8345 (C-H o.o.p. def., aromatic), 1681 (C=O str., CONH), 1620 (C=N str.), 1262 (C-O-C sym. str.), 1041 (C-O-C asym.str.), 1455 (C-H asym. def., CH_2 and CH_3), 13762 (C-H sym. def., CH_2 and CH_3), 754, 770, 691 (C-S-C str.), 642 (C-S str.).

2-(5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio)-*N'*-((thiophen-2-yl) methylene) acetohydrazide (8g)

White amorphous solid; m.p. 208°C; yield, 73% ; M.F. $C_{26}H_{18}N_6O_3S_2$; IR (KBr, υ_{max} in cm^{-1}): 3164, 3470 (N-H str.), 3040 (C-Hstr., aromatic), 2965, 2922 (C-H asym. str. aliphatic), 2825 (C-H sym. str., aliphatic), 1514, 1487 (C=C str., aromatic), 1130, 1130 (C-H i.p. def., aromatic), 830 (C-H o.o.p. def., aromatic), 1681 (C=O str., CONH), 1626 (C=N str.), 1257 (C-O-C sym. str.), 1056 (C-O-C asym.str.), 1450 (C-H asym.def., CH_2 and CH_3), 1364 (C-H sym. def., CH_2 and CH_3), 753, 771, 690 (C-S-C str.), 641 (C-S str.).

2-(5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio)-*N'*-((naphthalen-1-yl) methylene) acetohydrazide (8h)

White amorphous solid; m.p.195°C; yield, 70%; M.F. $C_{32}H_{22}N_6O_3S$; IR (KBr, υ_{max} in cm^{-1}): 3182, 3488 (N-H str.), 3060 (C-H str., aromatic), 2972, 2925 (C-H asym. str. aliphatic), 2846 (C-H sym. str., aliphatic), 1523, 1473 (C=C str., aromatic), 1128, 1110 (C-H i.p. def., aromatic), 836 (C-H o.o.p. def, aromatic), 1672 (C=O str., CONH), 1610 (C=N str.), 1259 (C-O-C sym. str.), 1045 (C-O-C asym.str.), 1458 (C-H asym. def. ,CH_2 and CH_3), 1368 (C-H sym. def., CH_2 and CH_3),754, 770, 691 (C-S-C str.), 643 (C-S str.).

2-(5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio)-*N'*-benzylidene acetohydrazide (8i)

White amorphous solid; m.p. 210°C; yield, 72%; M.F. $C_{28}H_{20}N_6O_3S$; IR (KBr, υ_{max} in cm^{-1}): 3182, 3489(N-H str.), 3063 (C-H str., aromatic), 2990, 2931 (C-H asym. str. aliphatic), 2838 (C-H sym. str., aliphatic), 1511, 1482 (C=C str., aromatic), 1103, 1108 (C-H i.p. def., aromatic), 838 (C-H o.o.p. def., aromatic), 1688 (C=O str., CONH), 1612 (C=N str.), 1258 (C-O-C sym. str.), 1042 (C-O-C asym.str.), 1452 (C-H asym.def., CH_2 and CH_3), 1368 (C-H sym. def., CH_2 and CH_3), 746, 782, 692 (C-S-C str.), 642 (C-S str.).

Procedure for the synthesis of 1-(5-((5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) methyl)-2-(4-methoxyphenyl)-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone (9a)

N'-(4-methoxybenzylidene)-2-(5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-2, 3-dihydro-1, 3, 4-oxadiazol-2-ylthio) acetohydrazide (8a, 2.76g, 0.005 moles) was taken in acetic anhydride (30mL). The reaction mixture was refluxed for 6h, allowed to cool and poured on crushed ice, reaction content kept overnight, product obtained was filtered, washed, dried and recrystallized from ethanol to get white crystalline solid (9a). (Scheme No.3).

Similarly, 9b-i was synthesized from 8b-i by following the same procedure as for the synthesis of 9a and all were recrystallized from absolute ethanol.

1-(5-((5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) methyl)-2-(4-methoxyphenyl)-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone (9a)

White amorphous solid; m.p. 170°C; yield, 70 % ; R*f*, 0.74; M.F. $C_{31}H_{24}N_6O_5S$; IR (KBr, υ_{max} in cm^{-1}); 3062, 3034 (C-H str., aromatic), 2983, 2938 (C-H asym. str. aliphatic), 2905 (C-H sym. str., aliphatic), 1373 (C-H sym. def., CH_2 and CH_3), 1486,1409 (C=C str., aromatic), 1092 (C-H i.p. def., aromatic), 896, 799 (C-H o.o.p. def, aromatic), 1609 (C=N str. pyrazole and oxadiazole ring), 1305 (C-N str.), 1259 (C-O-C sym. str.), 1022 (C-O-C asym. str.), 1022, 979 (N-N str., oxadiazole), 1737 (C=O str., -$COCH_3$),^{1}HNMR δ ppm (DMSO-*d6*): 2.50 (s, 3H,-$COCH_3$), 3.34 (s, 3H, -OCH_3), 4.30 (s, 2H, hetero aryl -S$\underline{CH_2}$- hetero aryl), 6.68 (s,1H, one proton at C_4 of pyrazole ring), 7.27-7.65 (m,15H, aromatic, hetero aryl and fused hetero aryl ring).

1-(5-((5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) methyl)-2-(2-chlorophenyl)-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone (9b)

White amorphous solid; m.p.185°C ; yield, 72% ; R*f*, 0.63; M.F. $C_{30}H_{21}ClN_6O_4S$; IR (KBr, υ_{max} in cm^{-1}): 3069, 3030 (C-H str., aromatic), 2985, 2940 (C-H asym. str. aliphatic), 2900 (C-H sym. str., aliphatic), 1367 (C-H sym. def., CH_2 and CH_3), 1482, 1410 (C=C str., aromatic), 1089 (C-H i.p. def, aromatic), 896, 799 (C-H o.o.p. def, aromatic), 1609 (C=N str., pyrazole and oxadiazole ring), 1305 (C-N str.), 1256 (C-O-C sym. str.), 1027 (C-O-C asym. str.), 1024, 975 (N-N str., oxadiazole), 1732 (C=O str., -$COCH_3$).

1-(5-((5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) methyl)-2-(2-fluorophenyl)-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone (9c)

White amorphous solid; m.p. 173°C ; yield, 70%; R*f*, 0.70 ; M.F. $C_{30}H_{21}FN_6O_4S$; IR (KBr,υ_{max}incm^{-1}); 3072, 3035 (C-H str., aromatic), 2973, 2937 (C-H asym. str. aliphatic), 2903 (C-H sym. str., aliphatic), 1372 (C-H sym. def., CH_2 and CH_3), 1478, 1409 (C=C str., aromatic), 1079 (C-H i.p. def., aromatic), 890, 789 (C-H, o.o.p. def, aromatic), 1620 (C=N str., pyrazole and oxadiazole ring), 1312 (C-N str.), 1256 (C-O-C sym. str.), 1035 (C-O-C asym. str.), 1022, 983 (N-N str., oxadiazole), 1725 (C=O str., -$COCH_3$).

1-(5-((5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) methyl)-2-(4-(benzyloxy) phenyl)-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone (9d)

White amorphous solid; m.p.,178°C; yield, 75% ; R*f*, 0.73; M.F.$C_{37}H_{28}N_6O_5S$**;** IR (KBr, υ_{max} in cm^{-1}); 3074, 3041 (C-H str., aromatic), 2979, 2948 (C-H asym. str., aliphatic), 2885 (C-H sym. str., aliphatic), 1373 (C-H sym. def., CH_2 and CH_3), 1475, 1429 (C=C str., aromatic), 1070 (C-H i.p. def., aromatic), 875, 789 (C-H o.o.p. def, aromatic), 1623 (C=N str., pyrazole and oxadiazole ring), 1318

(C-N str.), 1245 (C-O-C sym. str.), 1038 (C-O-C asym. str.), 1022, 983 (N-N str., oxadiazole), 1701 (C=O str., -$COCH_3$).

1-(5-((5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) methyl)-2-styryl-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone (9e)

White amorphous solid; m.p. 172°C; yield, 75 % ; R*f*, 0.71; M.F. $C_{32}H_{24}N_6O_4S$; IR (KBr, υ_{max} in cm^{-1}): 3062, 3034 (C-H str., aromatic), 2978, 2938 (C-H asym. str., aliphatic), 2900 (C-H sym. str., aliphatic), 1364 (C-H sym. def., CH_2 and CH_3), 1490, 1400 (C=C str., aromatic), 1092 (C-H i.p. def, aromatic), 896, 799 (C-H o.o.p. def, aromatic), 1609 (C=N str. pyrazole and oxadiazole ring), 1316 (C-N str.), 1264 (C-O-C sym. str.), 1022 (C-O-C asym. str.), 1028, 976 (N-N str., oxadiazole), 1730 (C=O str., -$COCH_3$).

1-(5-((5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) methyl)-2-(furan-2-yl)-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone (9f)

White amorphous solid; m.p. 173°C; yield, 67%; R*f*, 0.69; M.F. $C_{28}H_{20}N_6O_5S$; IR (KBr, υ_{max} in cm^{-1}); 3085, 3034 (C-H str., aromatic), 2983, 2938 (C-H asym. str. aliphatic), 2905 (C-H sym. str., aliphatic), 1373 (C-H sym. def. , CH_2 and CH_3), 1486, 1409 (C=C str., aromatic), 1092 (C-H i.p.def, aromatic), 890, 795 (C-H, o.o.p. def, aromatic), 1600 (C=N str. pyrazole and oxadiazole ring), 1298 (C-N str.), 1259 (C-O-C sym. str.), 1022 (C-O-C asym. str.), 1018, 978 (N-N str., oxadiazole),1732 (C=O str., -$COCH_3$).

1-(5-((5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) methyl)-2-(thiophen-2-yl)-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone (9g)

White amorphous solid; m.p. 174°C; yield, 75% ; R*f*, 0.70; M.F. $C_{28}H_{20}N_6O_4S_2$; IR (KBr, υ_{max} in cm^{-1}): 3062, 3034 (C-H str., aromatic), 2985, 2938 (C-H asym. str. aliphatic), 2900 (C-H sym. str., aliphatic), 1375 (C-H sym. def., CH_2 and CH_3), 1482, 1405 (C=C str., aromatic), 1096 (C-H i.p. def., aromatic), 896, 795 (C-H o.o.p..def., aromatic), 1615 (C=N str. pyrazole and oxadiazole ring), 1275 (C-N str.), 1259 (C-O-C sym. str.), 1022 (C-O-C asym. str.), 1018, 978 (N-N str., oxadiazole), 1732 (C=O str., -$COCH_3$).

1-(5-((5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) methyl)-2-(naphthalen-3-yl)-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone (9h)

White amorphous solid; m.p. 176°C; yield, 75% ; R*f*, 0.71; M.F. $C_{34}H_{24}N_6O_4S$; IR (KBr, υ_{max} in cm^{-1}): 3058, 3036 (C-H str., aromatic), 2980, 2935 (C-H asym. str. aliphatic), 2900 (C-H sym. str., aliphatic), 1375 (C-H sym. def., CH_2 and CH_3), 1482, 1409 (C=C str., aromatic), 1096 (C-H i.p. def., aromatic), 898, 800 (C-H, o.o.p. def., aromatic), 1612 (C=N str. pyrazole and oxadiazole ring), 1308 (C-N str.), 1255 (C-O-C sym.).

1-(5-((5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) methyl)-2-phenyl-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone (9i)

White amorphous solid; m.p. 172°C; .yield, 78%; R*f*, 0.73; M.F. $C_{30}H_{22}N_6O_4S$; IR (KBr, υ_{max} in cm^{-1}): 3060, 3032 (C-H str., aromatic), 2982, 2938 (C-H asym. str. aliphatic), 2906 (C-H sym. str., aliphatic), 1376 (C-H sym. def. , CH_2 and CH_3), 1485, 1406 (C=C str., aromatic), 1098 (C-H i.p. def, aromatic), 893, 805 (C-H o.o.p. def, aromatic), 1615 (C=N str. pyrazole and oxadiazole ring), 1310 (C-N str.), 1252 (C-O-C sym.).

Antibacterial activity

The novel synthesized heterocyclic compounds (9a-i) were screened for their *in-vitro* antimicrobial activity using disc-diffusion method against panel of pathogenic microorganism including *S. aureus* as Gram positive and *E. coli, P. vulgaris, S. typhi* as Gram negative bacterial strains and their activities were compared with well-known commercial antibiotic Chloramphenicol.

Procedure of disc-diffusion method

Test solution was prepared by dissolving known weight of each compound (9a-i) in dimethyl sulphoxide (DMSO) as solvent and diluted suitably to give the resultant concentration of 31-1000µg/mL. Petri plates were prepared by pouring 10mL of Mueller Hinton Agar for bacteria containing microbial culture was allowed to solidify. Microorganism strains were maintained in nutrient agar medium at 37°C**,** the culture were

inoculated in 10mL fresh nutrient broth to yield an initial suspension. The bacterial suspension were diluted 10 times with distilled water.0.1 mL of diluted culture was spread over nutrient agar in plate. Whatmann No.1 sterile paper discs (6 mm) were impregnated with solution and allowed to dry at room temperature. The discs were then applied and the plates were incubated at 37°C for 24h (bacteria) and the inhibition zone was measured in mm in four directions and expressed as mean.

RESULTS AND DISCUSSION

In the undertaken research we have synthesized novel 2, 3, 5-trisubstituted 1, 3, 4-oxadiazoles (9a-i) derivatives. The synthetic protocol has been outlined in Schemes 1, 2, and 3. The synthesis of starting compound acetohydrazide (7) was carried out in two step procedure, in the first step the synthesis of compound (6) was carried out by reacting 5 with Ethyl 2-chloroacetate and potassium carbonate in DMF. IR spectrum of 6 showed absorption bands due to C=O, stretch in ester at 1736 cm^{-1} and -CH_3 stretch at 2984, 2938 which supported the structure of this derivative. ^{1}H NMR of 6 revealed a triplet signal in between 1.19-1.20 ppm due to three protons of -$CH_2\underline{CH_3}$ and a quartet signal in the range of 4.16 - 4.19 ppm due to two protons of -$O\underline{CH_2}$-, which showed the presence of –OCH_2CH_3 group. ^{13}C NMR data revealed a signal at δ 13.98 ppm due to -CH_3 while a signal at δ 167.52 ppm is due to carbon atom of ester group; similarly, a signal at δ 33.92 ppm was observed due to carbon of -S-$\underline{C}H_2$-O- linkage.

In the second step synthesis of acetohydrazide (7) was carried out by reaction of (6) with hydrazine hydrate in alcohol. IR spectrum of 7 indicated disappearance of bands obtained due to ester group and appearance of characteristic absorption bands predominantly at 3329 cm^{-1} and 3200 cm^{-1} due to -NH- stretch of -NH_2, and absorption band at 1681cm^{-1} assigned due to C=O str. in CONH, confirms its formation. Its ^{1}H NMR spectra showed a singlet at 3.39 ppm due to two protons of NH_2 group and another singlet appeared at 10.57 ppm due to one proton of -NH- of CON$\underline{H}NH_2$. A singlet was observed at δ 6.13 ppm due to one aromatic proton of pyrazole ring located at fourth position. ^{13}C NMR spectra showed a singlet at 160 ppm due to the carbon atom of $\underline{C}ONHNH_2$. The mass spectrum of this compound indicated *m/z* values peak at 432 M^+, and 433 $[M+1]^+$, confirming its molecular formula to be $C_{21}H_{16}N_6O_3S$. Percentage of elements as determined by elemental analysis i.e. C, 57.40%, H, 4.23% and N, 20.43% is also in good agreement with calculated value. All of the above spectral data confirms the formation of 2-(5-(5-(benzofuran-2-yl)-1-methyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) acetohydrazide (7).

Similarly, compounds 8a-i was also synthesized by reacting acetohydrazide (7) with aryl aldehydes 2a-i in alcohol in good yield. The IR spectrum of 8a showed principal absorption bands at 3187 cm^{-1} and 3493 cm^{-1} due to -NH- stretch, while bands at 1605 cm^{-1} and 1678 cm^{-1} were observed due to C=N and C=O stretch in CONH respectively. ^{1}H NMR of 8a showed a singlet at 3.77 ppm, due to three protons of OCH_3 group attached to aromatic ring, another singlet at 11.69 ppm is due to one proton of NHCO group, yet another singlet 8.15 ppm was observed due to one azomethine proton. Synthesis of 1, 3, 4-oxadiazol derivatives (9a-i) were carried out by reacting 8a-i with acetic anhydride. IR spectrum of 9a revealed that the absorption bands observed in 8a due to NH stretching has been disappeared in 9a, but appearance of peak at 1737 cm^{-1} assigned due to C=O stretch of $COCH_3$ group confirms its cyclization cum acetylation. A singlet appeared in ^{1}H NMR spectrum at 2.50 ppm due to three protons of $COCH_3$ group, another singlet appeared at 3.34 ppm due to three protons of OCH_3 attached to the aromatic ring. Similarly, a singlet is also observed at 4.30 ppm due to two protons of CH_2 group and other signals related to aromatic protons were observed in the expected region.

Antibacterial activity

All the synthesized compounds have been assayed at different concentrations from 31 to 1000 µg/mL. Antibacterial screening results in term of zone of inhibition is summarised and depicted in Table No.1 and 2 which indicate that most of the synthesized compounds 9a-i exhibited significant antibacterial activity. The entire synthesized compound shows

moderate activity against Gram negative bacteria *S. typhi*.

It is seen from the table that at the conc. of 1000 µg/mL, 9b is found to be excellent active against *S. aureus* as compared to the reference drug. While the compounds 9a, 9d and 9f are found to show good activity against *S. aureus*, *E. coli* and *P. vulgaris w*ith reference to the Chloramphenicol.

Results also indicated that few of the titled compounds exhibited moderate to good activity while some of them were poorly active towards all the selected strains.

Table No.1: Antibacterial activity of the compounds 9a-i

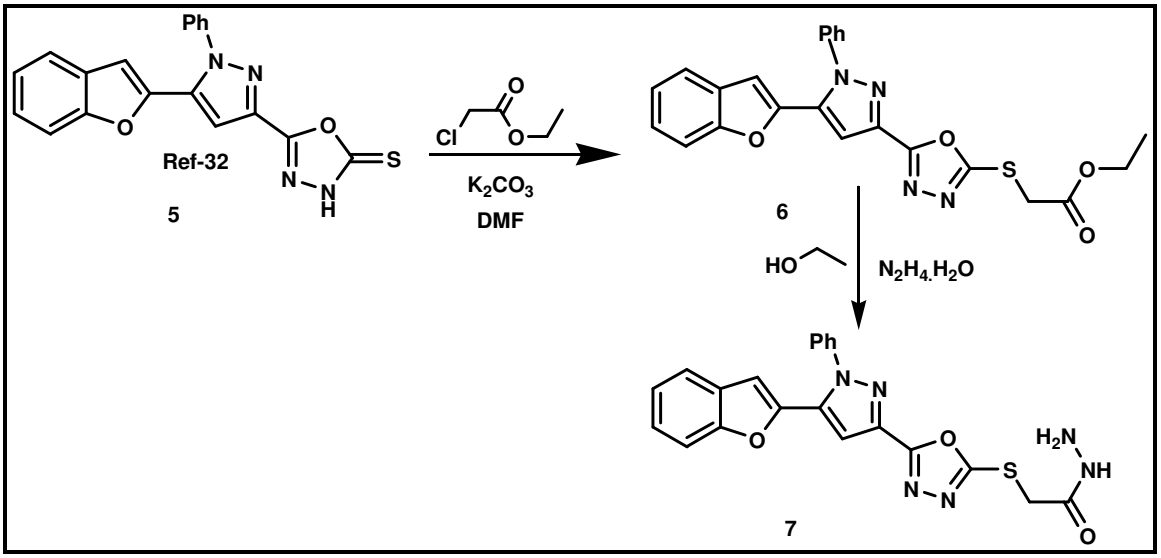
Zone of Inhibition (mm)												
Compd. Code	**Gram +ve**						**Gram –ve**					
	S. aureus						***P.vulgaris***					
	Conc. (µg/mL)						**Conc. (µg/mL)**					
	1000	**500**	**250**	**125**	**63.5**	**31**	**1000**	**500**	**250**	**125**	**63.5**	**31**
9a	24	23	20	20	17	18	28	23	22	18	16	14
9b	25	21	20	19	16	15	25	21	19	15	18	11
9c	23	22	21	20	15	16	26	24	22	18	16	15
9d	25	24	21	18	17	15	27	24	21	19	17	13
9e	21	20	17	15	14	13	24	21	18	15	14	10
9f	25	23	18	17	18	15	26	22	20	19	16	12
9g	22	18	17	15	14	11	25	23	18	15	14	10
9h	23	20	18	17	15	13	21	19	17	16	13	11
9i	20	19	17	15	14	12	20	19	17	15	14	12
DMSO	-	-	-	-	-	-	-	-	-	-	-	-
Std. Drug	24	22	20	19	17	15	28	24	20	17	16	13

Table No.2: Antibacterial activity of the compounds 9a-i

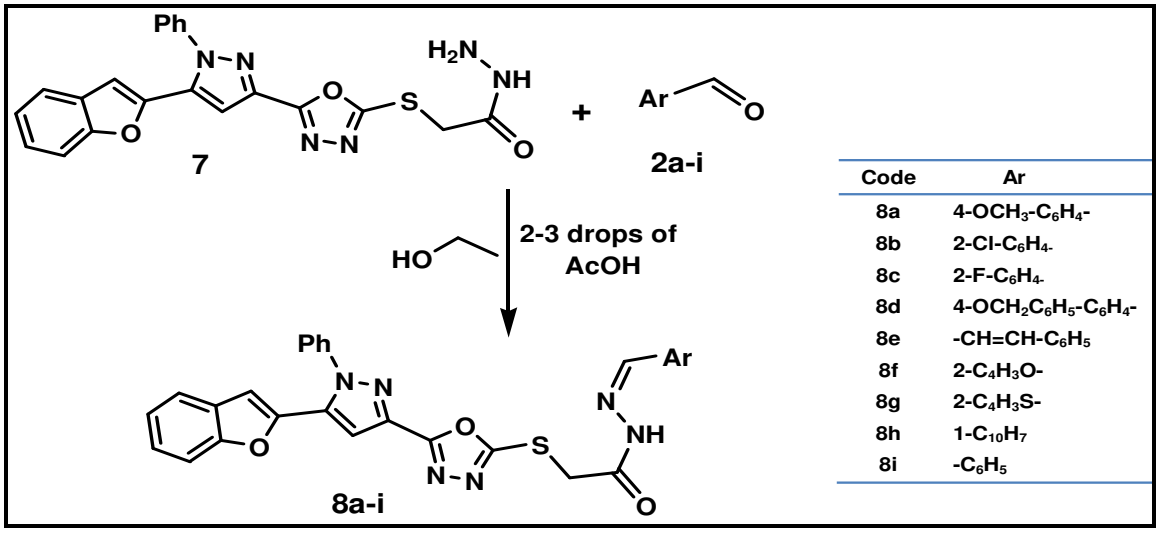
Zone of Inhibition (mm)												
Compd. Code	**Gram –ve**											
	E. coli						***S.typhi***					
	Conc. (µg/mL)						**Conc. (µg/mL)**					
	1000	**500**	**250**	**125**	**63.5**	**31**	**1000**	**500**	**250**	**125**	**63.5**	**31**
9a	26	24	22	21	16	12	18	15	13	11	10	09
9b	24	21	19	18	17	16	16	14	10	09	06	07
9c	25	24	20	17	16	15	17	16	12	10	09	08
9d	26	23	21	20	18	15	14	10	08	08	07	09
9e	23	22	20	18	14	12	16	14	12	11	09	07
9f	25	24	22	20	18	15	17	16	14	12	09	08
9g	21	20	17	16	14	11	15	13	11	10	08	07
9h	22	21	20	18	16	13	14	12	10	08	06	05
9i	20	19	16	15	13	12	16	15	11	09	07	04
DMSO	-	-	-	-	-	-	-	-	-	-	-	-
Std. Drug	26	24	23	21	17	14	17	15	12	11	09	08

Std. Drug: Chloramphenicol

Reaction Scheme No.1

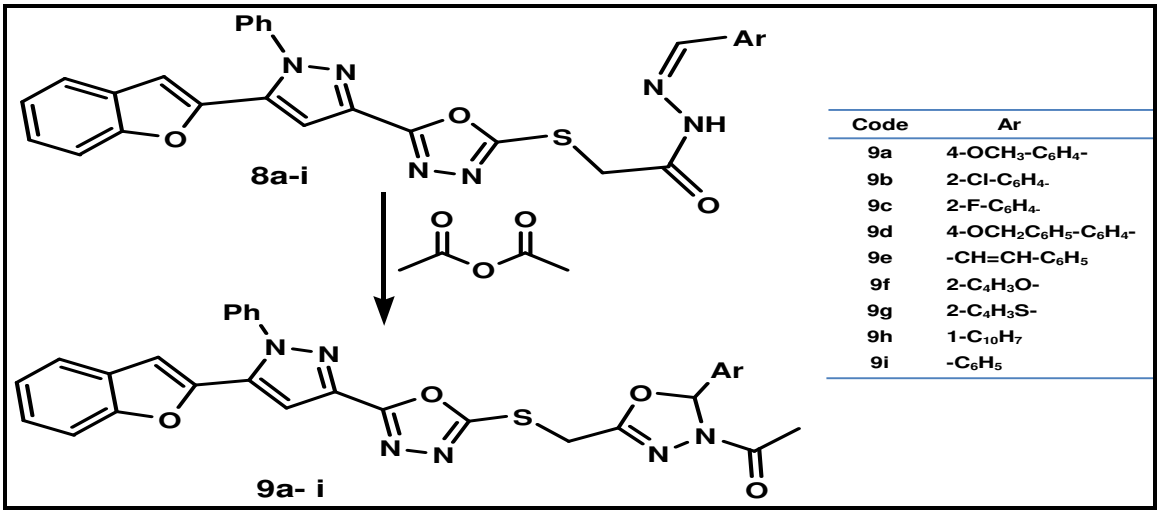


Reaction Scheme No.2



Code	Ar
8a	4-OCH_3-C_6H_4-
8b	2-Cl-C_6H_4-
8c	2-F-C_6H_4-
8d	4-$OCH_2C_6H_5$-C_6H_4-
8e	-CH=CH-C_6H_5
8f	2-C_4H_3O-
8g	2-C_4H_3S-
8h	1-$C_{10}H_7$
8i	-C_6H_5

Reaction Scheme No.3



Code	Ar
9a	4-OCH_3-C_6H_4-
9b	2-Cl-C_6H_4-
9c	2-F-C_6H_4-
9d	4-$OCH_2C_6H_5$-C_6H_4-
9e	-CH=CH-C_6H_5
9f	2-C_4H_3O-
9g	2-C_4H_3S-
9h	1-$C_{10}H_7$
9i	-C_6H_5

CONCLUSION

In summary, we have reported here synthesis of some new compounds 1-(5-((5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio)methyl)-2-(substituted aryl)-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone (9a-i) from *N'*-(substituted aryl)-2-(5-(5-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazol-3-yl)-1, 3, 4-oxadiazol-2-ylthio) acetohydrazide 8a-i. The presented series of compounds was synthesized in good yield. The structure and purity of newly synthesized compound was confirmed by spectroscopic investigation and chemical analysis. Among the synthesized compounds all the compound show good to moderate activity against selected strains *S. aureus*, *P. vulgaris* and *E. coli, S. typhi* at lower concentration.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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