Original Article

Synthesis, Antimicrobial And Antioxidant Potential Of 2-(Substitutedphenyl)-3-(5-(Furan-2-Yl)-1,3,4-Oxadiazol-2-Yl) Thiazolidin-4-One Conjugates

Davinder Kumar[1], Harsh Kumar[1], Aakash Deep[2], Suresh Kumar[3] and Rakesh Kumar Marwaha[1]*

[1]Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, Haryana, India. Email dev.mpharm09@gmail.com
[1]Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, Haryana, India.
Email: goyalpharma86@gmail.com
[2]Department of Pharmaceutical Sciences, Chaudhary Bansi University, Bhiwani-127021, Haryana, India.
E.mail: aakashdeep82@gmail.com
[3]Bharat Institute of Pharmacy, Peladpur, Babain, Kurukshetra, Haryana, India- 136156
E.mail: drsureshkumarbeniwal@gmail.com
[1]Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, Haryana, India.
E.mail: rkmarwaha.mdu@gmail.com
Corresponding Authors:
Dr. Rakesh Kumar Marwaha Associate Professor Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak- 124001, India Email rkmarwaha.mdu@gmail.com

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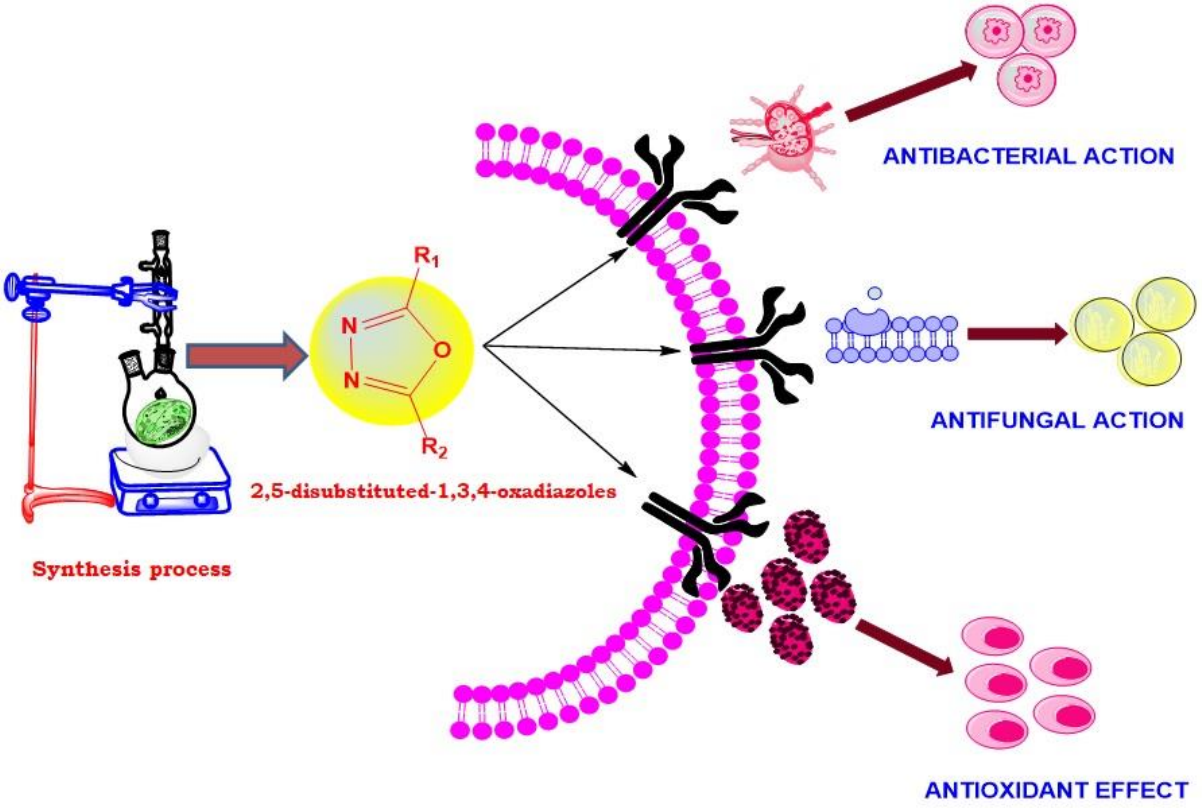
Abstract

Background: A series of novel 5-(furan-2-yl)-1,3,4-oxadiazole analogues was prepared based on the abundant biological potential of the 1,3,4-oxadiazole moiety. A variety of spectral methods (1H-NMR, IR, MS, etc.) were used to confirm the chemical structures of the synthesized analogues. Antioxidant and antimicrobial activities of these synthesized compounds were assessed after they were prepared

Results and discussion: A serial tube dilution method was used to screen against selected strains of fungi and bacteria for antimicrobial activity in comparison with amoxicillin and fluconazole. The antioxidant potential of 5-(furan-2-yl)-1,3,4-oxadiazole compounds was assessed using the stable 2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging method.

Conclusion: The antimicrobial screening results suggested that the synthesized derivatives 2,4,6,8, and 12 possessed moderate to promising potential against the selected species of microbial strains having MIC range 7.96 µM-9.97 µM. Structure activity relationship studies revealed compounds 2, 6 with p-bromo, trifluoro and 8 with p-chloro, substitutions were shown to be the most active among all the derivatives against the selected microbes. Compounds 2,4,6,8,9 and 12 were found to be more potent than the standard drug (ascorbic acid) in antioxidant evaluation assays. Among all the, compound 9 showed the highest antioxidant activity with an IC_{50} of 18.56 µg/mL, compared to 23.22 µg/mL of standard drug.

Keywords: (5-(furan-2-yl)-1,3,4-oxadiazole analogues; Synthesis; anti- free radical scavenging; Antioxidant; Characterization



GRAPHICAL ABSTRACT

INTRODUCTION:

Antimicrobial resistance (AMR) is a major public health challenge and remains a common impediment to effective treatment of serious infections and modern medicine faces the problem of antimicrobial resistance (AMR). Infections poorly treated, over prescription of antibiotics, and improper use of antibiotics by patients have led to some microorganisms becoming resistant to antibiotics. Antibiotics are a precious commodity, and they're running out(1,2). As a result, antibiotics and other antimicrobial drugs no longer work and infections become increasingly difficult to treat. So that worldwide development of antimicrobial resistance has forced scientists to look for new compounds that could replace them(3–5). Researchers are continually developing novel drug molecules against already exploited and unexplored targets because of the emergence of drug-resistant bacteria(6,7). Reactive oxygen species (ROS) are molecules that contain an unpaired electron in their outer shell. The presence of a free radical causes damage to biological macromolecules such as DNA and proteins(8). This damage can lead to cell death or inflammation. Reactive oxygen species play a role in cancer, inflammation and atherosclerosis. They also contribute to neurodegenerative diseases. In addition to preventing oxidative damage to biological substrates, antioxidants also reduce oxidative stress, DNA mutations, and malignant changes, thus preventing cell death(9).

Sulphur and nitrogen containing heterocyclic rings have attracted the interest of medicinal chemists due to their innumerable biological applications. 1,3,4-oxadiazole derivatives are among the most interesting compounds with regard to their pharmacological properties. (10,11). 1,3,4-oxadiazole have been reported to possess anti-inflammatory (12,13) anti-HIV(7,14), (15,16) anticonvulsant activities (17), antimalarial(18,19), herbicidal(20), antianxiety(21), insecticidal (22), antitubercular(23), antiviral(24), antifungal(25), anticancer(26,27) analgesic (28) (**Figure-1).**

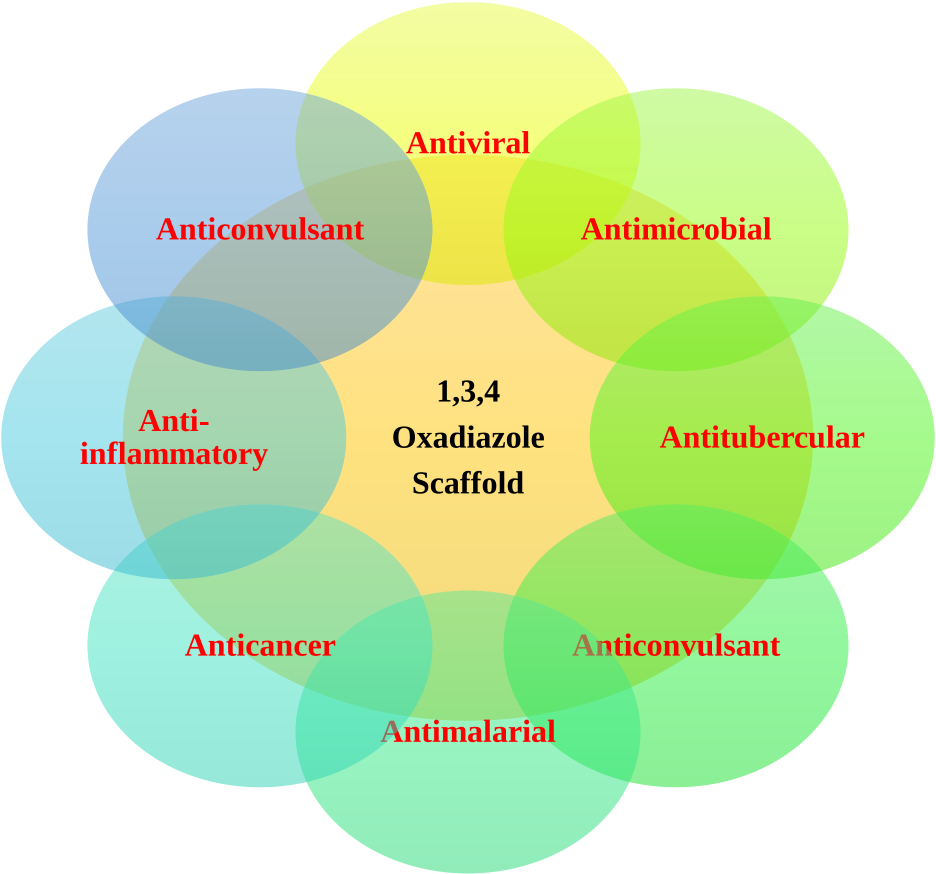


Figure-1 Biological potentials of 1,3,4 Oxadiazoles

Similarly, 1,3,4-oxadiazole ring containing many commercially drugs also available in the market i.e Furamizole having potent antibacterial action, Nesapidil having anti-arrhythmic action, Raltegravir being an antiviral drug, Tiodazosin used as antihypertensive agent and most privileged derivative FDA approved anticancer agent Zibotentan(29–31) (**Figure-2)**

Aiming to explore the pharmacological and structural properties of oxadiazole derivatives in light of the above-mentioned findings. The present study reports the synthesis and characterization of a related series of novel conjugates of 2-(substitutedphenyl)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one with antibacterial, antifungal, and antioxidative properties**.**

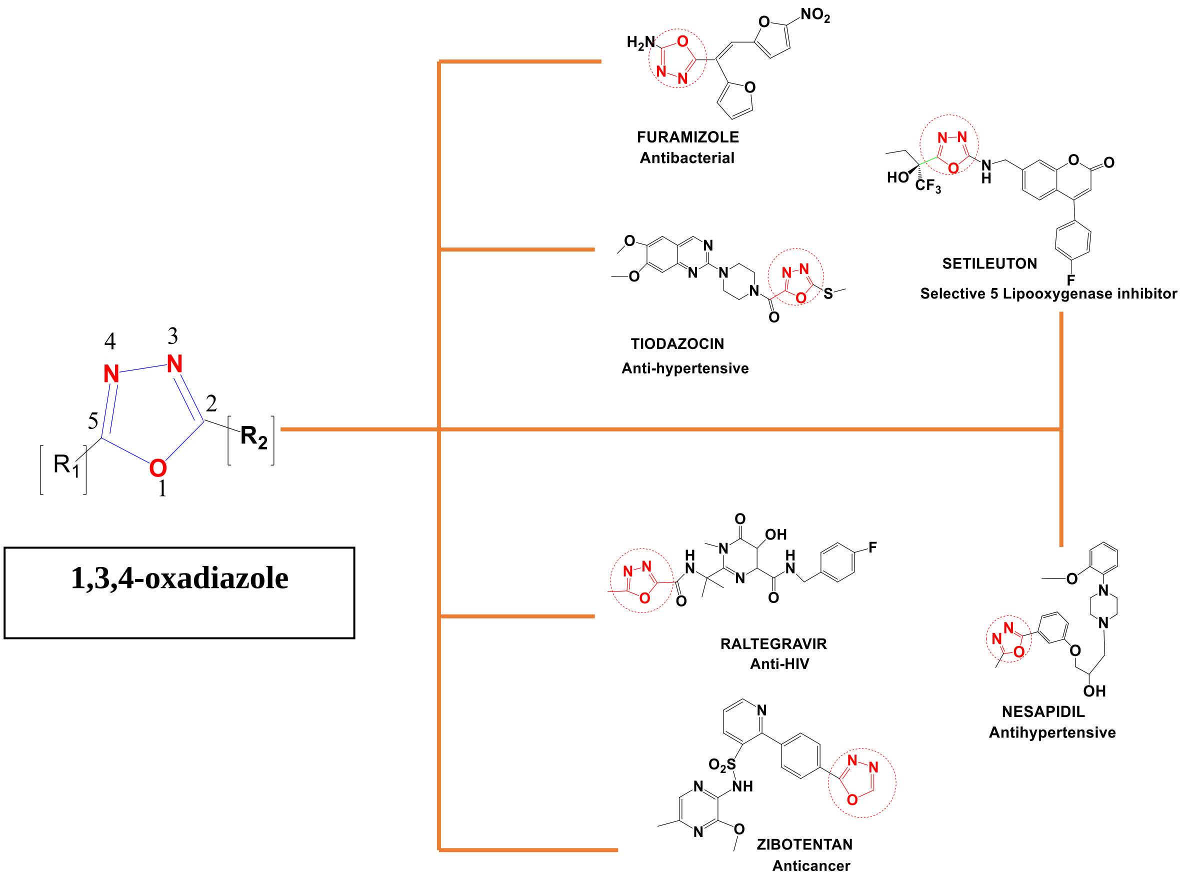
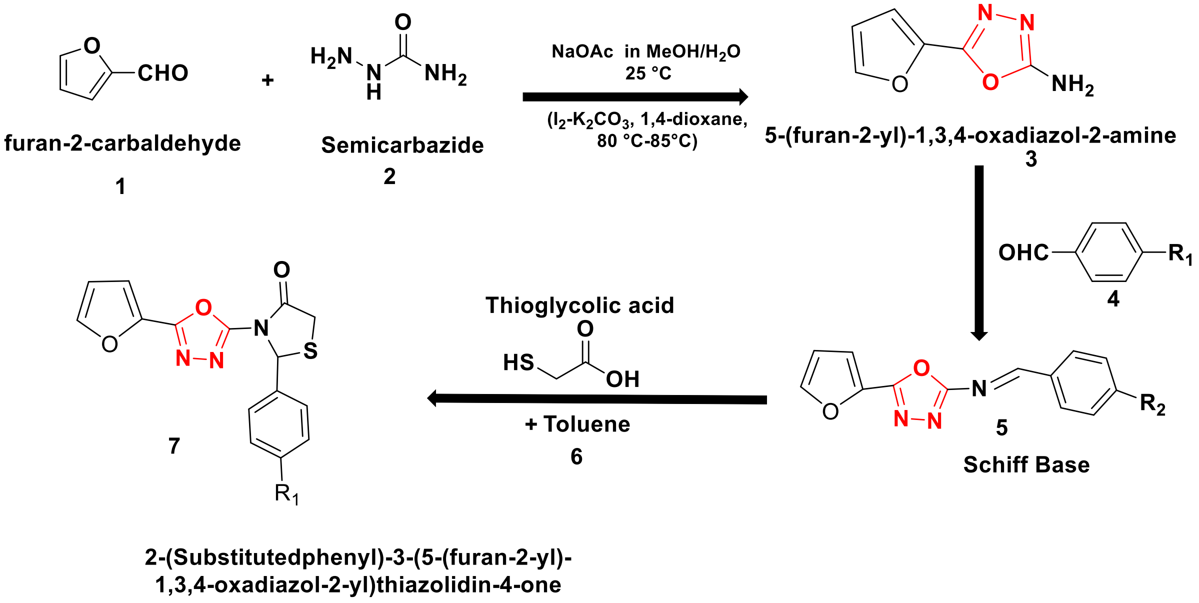


Figure-2-1,3,4-Oxadiazole ring containing commercial drugs

MATERIALS AND METHODS

All oxadiazole derivatives were synthesized by using synthetic method as shown in scheme 1. In the first step a mixture containing semi carbazide hydrochloride (2, 0.5 mmol) and sodium acetate (0.5 mmol) added in the water (15) and stirred well followed by addition of furan-2-carbaldehyde (1) in methanol at room temperature provide intermediate solid residue. The residue redissolved in 1,4-dioxane and string was continued (4-6 Hrs) at 80-85 °C with addition of K_2CO_3 and iodine in sequence to get 2-Amino 1,3,4 oxadiazole derivatives (3). Schiff's bases (intermediate) (5) were obtained by treating different aldehydes (4) with 2-Amino 1,3,4 oxadiazole (3) by taking acetic acid (glacial) as catalyst. At last final compounds (7) were obtained reacting with thioglycolic acid (6) using small quantity of toluene as catalyst.

Scheme: 1



R_1

1. 4-CN 2. 4-Br 3. $4\text{-}NH_2$ 4. $4\text{-}NO_2$ 5. $4\text{-}OCH_3$ 6. $4\text{-}CF_3$ 7. 4-CH3
8. 4-Cl 9. 4-I 10. H 11. 3,5 $(CH_3)_2$ 12. 3,5 $(Cl)_2$

Scheme 1: Synthesis of 2-(substitutedphenyl)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one derivatives

Synthesized derivatives are summarized in terms of their physicochemical properties **(Table 1).** The molecular structures of the synthesized conjugates (Ox 1-12) were confirm using a variety of spectral techniques viz. FT-IR (KBr, cm− 1), 1H-NMR (DMSO-d6, 400 MHz, δ ppm), Mass spectra and elemental analysis **(Table 2).** The ^{1}H-NMR spectra designated that the presence of multiplet signals between 7.15 and 7.78 δ ppm reflected the presence of aromatic protons in synthesized molecules. The presence of singlet(s) between 3.62-4.10 δ ppm, 6.05 -6.12 δ ppm indicated the presence of -CH=, -CH=N groups, respectively.

Table 1. Physiochemical properties of 2-(substituted)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one conjugates

S. No	**Molecular Formula**	**M.wt**	**Colour**	**% Yield**	**Melting point**	**R_f Value**
1.	**$C_{16}H_{10}N_4O_3S$**	**338**	**Orange**	**51%**	**145-147°**	**0.7****
2.	**$C_{15}H_{10}BrN_3O_3S$**	**392**	**White**	**53%**	**151-153°**	**0.7**
3.	**$C_{15}H_{12}N_4O_3S$**	**328**	**White**	**36%**	**160-162°**	**0.6**
4.	**$C_{15}H_{10}N_4O_5S$**	**358**	**Green**	**47%**	**155-157°**	**0.6**
5.	**$C_{16}H_{13}N_3O_4S$**	**343**	**Orange**	**51%**	**160-162°**	**0.7**
6.	**$C_{16}H_{10}F_3N_3O_3S$**	**381**	**Brown**	**41%**	**174-176°**	**0.6**
7.	**$C_{16}H_{13}N_3O_3S$**	**327**	**Reddish**	**51%**	**159-161°**	**0.7****
8.	**$C_{15}H_{10}ClN_3O_3S$**	**348**	**Brown**	**54%**	**181-183°**	**0.5**

9.	**$C_{15}H_{10}IN_3O^3S$**	**439**	**Reddish**	**39%**	**146-148°**	**0.7**
10.	**$C_{15}H_{11}N_3O_3S$**	**313**	**Cream**	**67%**	**201-203°**	**0.7**
11.	**$C_{17}H_{15}N_3O_3S$**	**341**	**White**	**69%**	**178-180°**	**0.6****
12.	**$C_{15}H_9Cl_2N_3O_3S$**	**382**	**Pale Yellowish**	**35%**	**207-209°**	**0.6**

TLC mobile phase= Ethyl acetate: Petroleum ether (3:1), Chloroform : Methanol : (7:3)**

The compound 3 exhibited singlet (s) at 3.72 δ ppm due to the existence of H of -NH_2 group. The appearance of singlet (s) at 3.75 δ in compound 5 revealed the existence of CH_3 of Ar-OCH_3. In the compounds 1,2,4,7 and 10 displayed multiplet (s) at 6.71-6.89 δ displayed CH_2 adjacent in the benzene ring. The compound 8 showed doublet signal at 7.03 δ ppm of -CH of ring at 3rd position, triplet signal at 6.71 δ ppm of -CH of furan ring at 4th position and doublet signal at 7.81 δ ppm of -CH of furan ring adjacent to O due to the existence of furfuryl group. In case of IR spectrum, the presence of bands at 3470-3266 cm^{-1}, 3048-2838 cm^{-1}, 3210-3058 cm^{-1}, 1600-1506 cm^{-1}, 1550-1427 cm^{-1}, 1702-1610 cm^{-1}, 1735-1600 cm^{-1}, and 633-585 cm^{-1} displayed the presence of N-H, C-H (aliphatic), C-H (aromatic), C=C (methylene), C=C (aromatic), C=N, C=O and C-S groups respectively in the synthesized analogues. The absorption bands around 1338-1224 cm^{-1} and 1165-1152 cm^{-1} corresponded to C-N and C-C stretching of compounds, respectively. Compounds 8 and 12 displayed absorption bands of C-Cl around 764-698 cm^{-1}. Mass of the synthesized compounds exhibited $M^{+}+1$, M^{+} and $M^{+}-1$ peaks. All spectral analysis has shown in table 2:

Table 2. Spectral analysis of 2-(substituted)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one conjugates

OX-Der.	IUPAC Name of synthesized compounds	Spectral charcterization
1.	4-(3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-4-oxothiazolidin-2-yl) benzonitrile	IR (KBr pellets) cm^{-1}:1699.11 (C=N str., imine group), 1455.1 (C=C str., aromatic ring), 1602.13 (C=C str., methylene group), 3068.05 (C-H str., aromatic ring), 2965.32 (C-H str., aliphatic), 1333.98 (C-N str., thiazolidine ring), 671.10 (C-S bend., thiazolidine ring); ^{1}H-NMR (δ, DMSO): 3.69-4.10 (d, 2H, CH_2- of thiazolidine ring), 6.06 (s, 1H, CH- of thiazolidine ring),), 6.71 (D, 2H, CH_2- of Furan ring)-7.17 (m, 2H -CH_2 of Benzene), 7.85 (m, 2H -CH_2 of Benzene), 7.81 (s, 2H -CH of Furan Ring). m/z: 338 (M^+) Elemental analysis (CHN) Theoretical calc: C, 56.80; H, 2.98; N, 16.56 Found: C, 56.25; H, 2.90; N, 16.79
2.	2-(4-bromophenyl)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one	IR (KBr pellets) cm^{-1}:1616.03 (C=N str., imine group), 1462.45 (C=C str., aromatic ring), 1562.80 (C=C str., methylene group), 1724.42 (C=O str., thiazolidine ring), 2924.38 (C-H str., aliphatic), 1381.62 (C-N str., thiazolidine ring), 748.97 (C-S bend., thiazolidine ring); ^{1}H-NMR (δ, DMSO): 3.69-4.1 (d, 2H, CH_2- of thiazolidine ring), 6.06 (s, 1H, CH- of thiazolidine ring),), 6.71 (D, 2H, CH_2- of Furan ring)-7.30 (m, 2H -CH_2 of Benzene), 7.58 (m, 2H -CH_2 of Benzene), 7.81 (s, 2H -CH of Furan Ring).m/z: 391 (M^+) Elemental analysis (CHN) Theoretical calc: C, 45.93; H, 2.57; N, 10.71; Found: C, 45.80; H, 2.46; N, 10.67;

3.	2-(4-aminophenyl)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one	IR (KBr pellets) cm^{-1}:1673.24 (C=N str., imine group), 1445.94 (C=C str., aromatic ring), 1543.82 (C=C str., methylene group), 17.08.18 (C=O str., thiazolidine ring), 29.32.47 (C-H str., aliphatic), 1346.96 (C-N str., thiazolidine ring), 688.78 (C-S bend., thiazolidine ring); ^{1}H-NMR (δ, DMSO): 3.70-4.09 (d, 2H, CH$_2$- of thiazolidine ring), 6.13 (s, 1H, CH- of thiazolidine ring),), 6.71-6.85 (m, 4H, CH$_2$- of benzene ring)-7.71 (s, 1H -CH of furan ring), 7.03 (s, 1H -CH$_2$ of furan ring), 7.81 (s, 1H -CH-O-CH-of Furan Ring). m/z: 328 (M$^+$), Elemental analysis (CHN) Theoretical calc: C, 54.87; H, 3.68; N, 17.06; Found: C, 54.57; H, 3.48; N, 17.16;
4.	3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-2-(4-nitrophenyl) thiazolidin-4-one	IR (KBr pellets) cm^{-1}:1634.88 (C=N str., imine group), 1465.90 (C=C str., aromatic ring), 1500.47 (C=C str., methylene group), 1688.37 (C=O str., thiazolidine ring), 2963.61 (C-H str., aliphatic), 1366.19 (C-N str., thiazolidine ring), 706.28 (C-S bend., thiazolidine ring); ^{1}H-NMR (δ, DMSO): 3.68-4.09 (d, 2H, CH$_2$- of thiazolidine ring), 6.07 (s, 1H, CH- of thiazolidine ring),), 6.71-7.03 (m, 2H, CH=C-CH= of benzene ring)-7.742(s, 1H -CH of benzene ring), 8.08 (d, 2H, CH=C=CH- of benzene ring), 7.81 (s, 1H =CH-O-CH=of Furan Ring). m/z: 358 (M$^+$), Elemental analysis (CHN) Theoretical calc: C, 50.28; H, 2.81; N, 15.64; Found: C, 50.34; H, 2.75; N, 15.81;
5.	3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-2-(4-methoxyphenyl) thiazolidin-4-one	IR (KBr pellets) cm^{-1}:1604.56 (C=N str., imine group), 1428.57 (C=C str., aromatic ring), 1514.68 (C=C str., methylene group), 1685.05 (C=O str., thiazolidine ring), 2982.40 (C-H str., aliphatic), 1302.63 (C-N str., thiazolidine ring), 771.73 (C-S bend., thiazolidine ring); ^{1}H-NMR (δ, DMSO): 3.68 (S, 1H, -CO-CH- of thiazolidine ring), 3.75 (triplet, 3H, CH- of methoxy ring), 4.09 (s, 1H, -S-CH- of thiazolidine ring), 6.12 (s, 1H, CH- of thiazolidine ring),), 6.89 (d, 2H, CH=C-CH= of benzene ring)-7.25(d, 2H of benzene ring),7.81 (s, 1H =CH-O-CH=of Furan Ring)., m/z: 343 (M$^+$), Elemental analysis (CHN) Theoretical calc: C, 55.97; H, 3.82; N, 12.24; Found: C, 55.81; H, 3.78; N, 12.19;
6.	3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-2-(4-trifluoromethyl) phenyl)thiazolidin-4-one	IR (KBr pellets) cm^{-1}:1607.87 (C=N str., imine group), 1450.31 (C=C str., aromatic ring), 1511.95 (C=C str., methylene group), 1735.50 (C=O str., thiazolidine ring), 2979.96 (C-H str., aliphatic), 1377.09 (C-N str., thiazolidine ring), 761.56 (C-S bend., thiazolidine ring); ^{1}H-NMR (δ, DMSO): 3.68 (S, 1H, -CO-CH- of thiazolidine ring), 4.09 (s, 1H, -S-CH- of thiazolidine ring), 6.05 (s, 1H, CH- of thiazolidine ring),), 6.66-6.79 (m, 4H, -CH-of benzene ring)-6.71-7.03 (d, 2H of Furan Ring),7.80 (s, 1H =CH-O-CH=of Furan Ring)., m/z: 381 (M$^+$), Elemental analysis (CHN) Theoretical calc: C, 50.40; H, 2.64; N, 11.02; Found: C, 50.28; H, 2.51; N, 11.11;
7.	3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-2-(p-tolyl)thiazolidin-4-one	IR (KBr pellets) cm^{-1}:1581.58 (C=N str., imine group), 1421.34 (C=C str., aromatic ring), 1516.65 (C=C str., methylene group), 1696.22 (C=O str., thiazolidine ring), 2984.16 (C-H str., aliphatic), 1346.41 (C-N str., thiazolidine ring), 764.72 (C-S bend., thiazolidine ring);

		^{1}H-NMR (δ, DMSO): 2.26 (triplet, 3H, methyl of benzene ring), 3.68 (S, 1H, -CO-CH- of thiazolidine ring), 4.09 (s, 1H, -S-CH- of thiazolidine ring), 6.093 (s, 1H, CH- of thiazolidine ring),), 6.79 (d, 2H, -CH-of benzene ring)-7.21 (d, 2H, -CH-of benzene ring),7.21 (d, 2H =CH-C-CH=of benzene ring)., m/z: 327 (M$^+$),Elemental analysis (CHN) Theoretical calc: C, 58.71; H, 4.00; N, 12.84; Found: C, 58.49; H, 3.81; N, 12.62;
8.	2-(4-chlorophenyl)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)thiazolidin-4-one	IR (KBr pellets) cm^{-1}:1523.45 (C=N str., imine group), 1425.36 (C=C str., aromatic ring), 1589.85 (C=C str., methylene group), 2959.12 (C-H str., aliphatic), 1375.01 (C-N str., thiazolidine ring), 765.52 (C-S bend., thiazolidine ring); ^{1}H-NMR (δ, DMSO): 3.68 (s, 1H, -CO-CH- of thiazolidine ring), 4.099 (s, 1H, -S-CH- of thiazolidine ring), 6.05 (s, 1H, CH- of thiazolidine ring),), 6.75-7.031(d, 2H, -CH-of furan ring)-7.54-7.65 (m, 4H, -CH-of benzene ring., m/z: 347 (M$^+$),Elemental analysis (CHN) Theoretical calc: C, 51.81; H, 2.90; N, 12.08; Found: C, 51.65; H, 2.72; N, 12.00;
9.	3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-2-(4-iodophenyl)thiazolidin-4-one	IR (KBr pellets) cm^{-1}:1600.53 (C=N str., imine group), 1575.47 (C=C str., aromatic ring), 1506.65 (C=C str., methylene group), 1736.81 (C=O str., thiazolidine ring),2928.77 (C-H str., aliphatic), 1312.36 (C-N str., thiazolidine ring), 767.05 (C-S bend., thiazolidine ring); ^{1}H-NMR (δ, DMSO): 3.66 (s, 1H, -CO-CH- of thiazolidine ring), 4. 10 (s, 1H, -S-CH- of thiazolidine ring), 6.06 (s, 1H, CH- of thiazolidine ring),), 6.71-7.03 (d, 2H, -CH-of furan ring)-7.31-7.32 (m, 4H, -CH-of benzene ring, 7.81 (s, 1H =CH-O-CH=of Furan Ring)., m/z: 439 (M$^+$),Elemental analysis (CHN) Theoretical calc: C, 41.02; H, 2.29; N, 9.57 Found: C, 40.82; H, 2.17; N, 9.39
10.	3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-2-phenylthiazolidin-4-one	IR (KBr pellets) cm^{-1}: 1674.79 (C=C str., aromatic ring), 1524.39 (C=C str., methylene group), 1747.20 (C=O str., thiazolidine ring), 2941.10 (C-H str., aliphatic), 1328.38 (C-N str., thiazolidine ring), 754.18 (C-S bend., thiazolidine ring); ^{1}H-NMR (δ, DMSO): 3.68 (s, 1H, -CO-CH- of thiazolidine ring), 4. 09 (s, 1H, -S-CH- of thiazolidine ring), 6.04 (s, 1H, CH- of thiazolidine ring),), 6.71-7.03 (d, 2H, -CH-of furan ring)-7.33-7.47 (m, 5H, -CH-of benzene ring., m/z: 313 (M$^+$),Elemental analysis (CHN) Theoretical calc: C, 57.50; H, 3.54; N, 13.41; Found: C, 57.39; H, 3.47; N, 13.19;
11.	2-(3,5-dimethylphenyl)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)thiazolidin-4-one	IR (KBr pellets) cm^{-1}:1596.52 (C=N str., imine group), 1501.27 (C=C str., aromatic ring), 1550.63 (C=C str., methylene group), 1705.57 (C=O str., thiazolidine ring),2979.96 (C-H str., aliphatic), 1370.97 (C-N str., thiazolidine ring), 769.30 (C-S bend., thiazolidine ring); ^{1}H-NMR (δ, DMSO): 3.31 (s, 6H, methyl of benzene ring), 3.66 (s, 1H, -CO-CH- of thiazolidine ring), 4. 10 (s, 1H, -S-CH- of thiazolidine ring), 6.00 (s, 1H, CH- of thiazolidine ring),), 6.71 (s, 1H, -CH-of furan ring), 7.03 (s, 1H, -CH-of furan ring)-, 6.94 (d, 2H, -CH-of benzene ring)., m/z: 341 (M$^+$),Elemental analysis (CHN) Theoretical calc: C, 59.81; H, 4.43; N, 12.31; Found: C, 59.65; H, 4.23; N, 12.23;

12.	2-(3,5-dichlorophenyl)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)thiazolidin-4-one	IR (KBr pellets) cm^{-1}:1508.69 (C=N str., imine group), 1429.39 (C=C str., aromatic ring), 1602.93 (C=C str., methylene group), 3185.00 (C-H str., aromatic ring), 2952.30 (C-H str., aliphatic), 1398.39 (C-N str., thiazolidine ring), 717.25 (C-S bend., thiazolidine ring); ^{1}H-NMR (δ, DMSO): 3.68 (s, 1H, -CO-CH- of thiazolidine ring), 4. 10 (s, 1H, -S-CH- of thiazolidine ring), 6.10 (s, 1H, CH- of thiazolidine ring),), 6.71 (s, 1H, -CH-of furan ring), 7.03 (s, 1H, -CH-of furan ring)-, 6.94 (d, 2H, -CH-of benzene ring), 7.20 (s, 1H, -CH-of benzene ring)., m/z: 381 (M^+),Elemental analysis (CHN) Theoretical calc: C, 47.14; H, 2.37; N, 10.99; Found: C, 47.02; H, 2.13; N, 10.86;

Antioxidant evaluation

The antioxidant efficacy of the newly synthesized derivatives was assessed by applying 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method (32)using ascorbic acid as standard. 2, 2-diphenyl-1-picrylhydrazyl radical is a stable free radical which become a stable diamagnetic molecule by accepting an electron or hydrogen radical. A strong absorption band at 517 nm is observed by methanolic solution of DPPH due to its odd electron. DPPH radical reacts with appropriate reducing agent (Synthesized derivatives) to produce new bond, which leads to change in the color of the solution. As concentration of antioxidant increases in the solution, more electrons are taken up by the DPPH radical from the antioxidant molecules leading to loss of color of the solution. Such reactivity has been used to test the ability of compounds that can act as free radical scavengers. Reduction of the DPPH radicals has been monitored at 517 nm absorbance spectrophotometrically indicated by decrease in the intensity of color (Purple color) (33). (**Figure-3).**

The IC_{50} value in µg/mL was calculated for all the synthesized compounds. The antioxidant assay revealed all the synthesized compounds 6,8,9 and12 to be more potent than the standard drug. Further, amongst all the compound 9 was found to be most active antioxidant compound. The percentage of inhibition at different concentration and IC_{50} value (s) results are displayed in Table 3 and **Figure**. 4

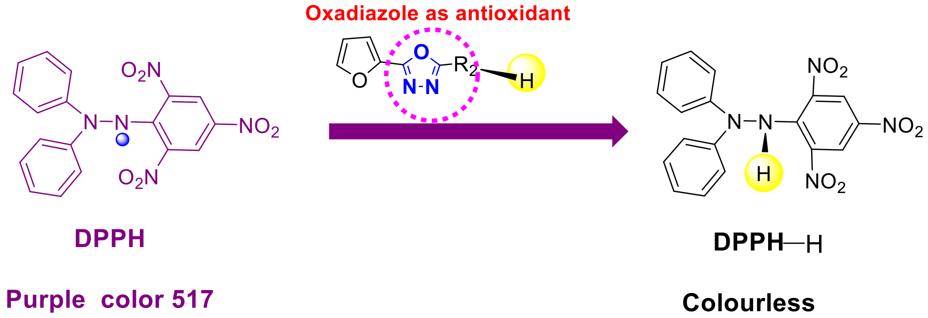


Figure:3 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging

Table 3. Antioxidant screening of 2-(substituted)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one conjugates

Antioxidant evaluation					
Compounds	**Inhibition% of synthesised derivatives**				**IC_{50}**
	25%	**50%**	**75%**	**100%**	
OX-1	26.12	38.12	52.04	62.08	25.55

OX-2	16.57	29.47	43.28	56.32	20.35
OX-3	34.74	46.18	59.03	72.65	29.47
OX-4	26.12	41.38	57.12	74.18	25.55
OX-5	40.26	52.18	68.18	81.04	31.72
OX-6	16.18	26.06	38.17	49.03	20.11
OX-7	37.41	47.01	61.04	76.26	30.58
OX-8	14.24	26.08	38.11	49.03	18.86
OX-9	13.78	24.78	42.07	52.74	18.56
OX-10	36.18	52.15	68.56	86.04	30.07
OX-11	29.02	41.08	55.34	69.67	26.93
OX-12	19.18	31.45	44.14	57.46	21.89
Standard drug (Ascorbic acid)	21.57	32.09	46.27	58.14	23.22

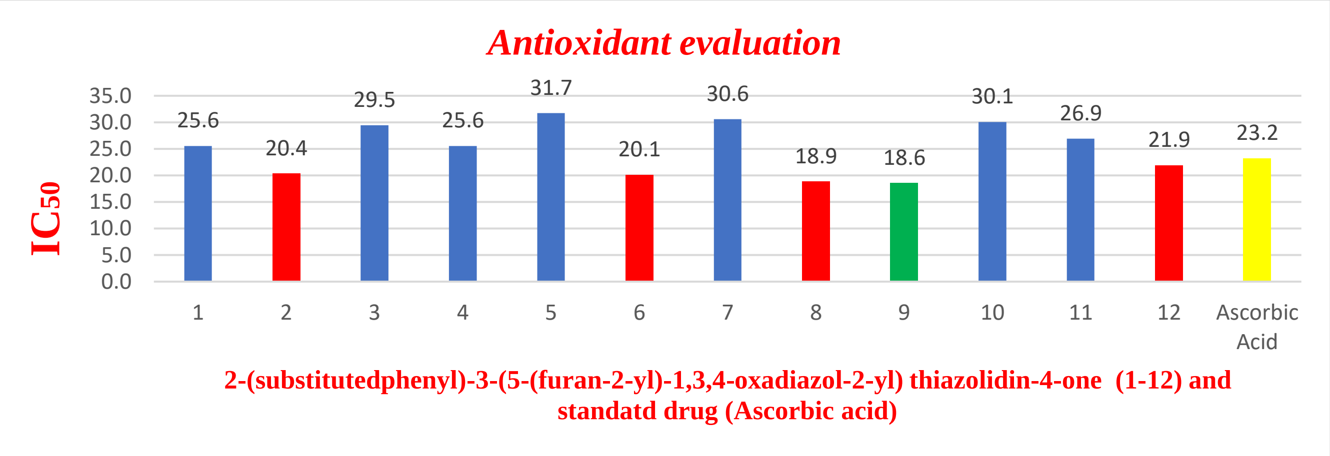


Figure:4 Antioxidant evaluation of 2-(substituted)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one conjugates

IN VITRO ANTIMICROBIAL EVALUATION

The in vitro antimicrobial screening studies of the synthesized oxadiazole derivatives was evaluated by serial tube dilution procedure (Table 4, **Figure 5 and 6**). The antibacterial screening outcomes revealed that compounds 4 and 12 were moderately active against Pseudomonas aeruginosa with MIC_{pa} value of 8.72 µM and 8.17 µM, respectively. Further screening revealed that compound 6 were moderately active against Enterococcus faecalis and Escherichia coli with $MIC_{ef/ec}$ value of 8.19 µM respectively. Compound 2 (MIC_{sa} = 7.96 µM, MIC_{ef} = 7.96 µM and MIC_{pa}=7.96 µM) was found to be effective against Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa. Compound 8 and 12 (MIC_{kp} = 8.97 µM and 8.17 µM) was found to be effective against K. pneumoniae. The antifungal screening results revealed that the compounds 6, 8 and 11 with MIC_{th} = 8.19 µM, 8.97 µM and 9.15 µM respectively were found to be effective against Trichoderma harzianum and 10 (MIC_{an}= 9.97 µM) had good activity against A. niger. The antibacterial screening results were found to be comparable with the standard drug (Amoxicillin), whereas antifungal results of synthesized molecules exhibited mild to moderate activity against both the fungal strains i.e. Trichoderma harzianum and A. niger comparison to the standard drug (fluconazole). So, these synthesized compounds can be taken as lead structures and may further be optimized to yield new antimicrobial agents with better activity.

Table 4. Antimicrobial screening of 2-(substituted)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one conjugates

Antimicrobial screening (MIC = µM)							
S. No	Antibacterial Screening					Antifungal Screening	
	Gram +ve			Gram -ve			
	SA	EF	PA	EC	KP	TH	AN
OX-1	36.98	36.98	18.49	18.49	18.49	18.49	18.49
OX-2	7.96	7.96	7.96	15.94	7.96	15.94	31.89
OX-3	38.11	38.11	38.11	38.11	38.11	19.05	38.11
OX-4	34.92	34.92	8.72	8.72	34.92	17.46	17.46
OX-5	72.89	36.44	36.44	72.89	18.22	36.44	18.22
OX-6	16.40	8.19	16.40	8.19	16.40	8.19	16.40
OX-7	19.11	19.11	19.11	19.11	19.11	19.11	38.23
OX-8	17.96	71.84	17.96	35.92	8.97	8.97	71.84
OX-9	28.47	56.95	28.47	28.47	28.47	28.47	28.47
OX-10	79.87	19.97	19.97	39.94	39.94	39.94	9.97
OX-11	73.31	36.66	36.66	36.66	36.66	9.15	36.66
OX-12	16.36	16.36	8.17	16.36	8.17	32.72	16.36
Amoxicilli	4.29	4.29	4.29	4.29	4.29		
Fluconazole						5.10	5.10

SA: Staphylococcus aureus, EF: Enterococcus faecalis, PA Pseudomonas aeruginosa EC: Escherichia coli, KP: Klebsiella pneumoniae, TH Trichoderma harzianum AN: Aspergillus Niger

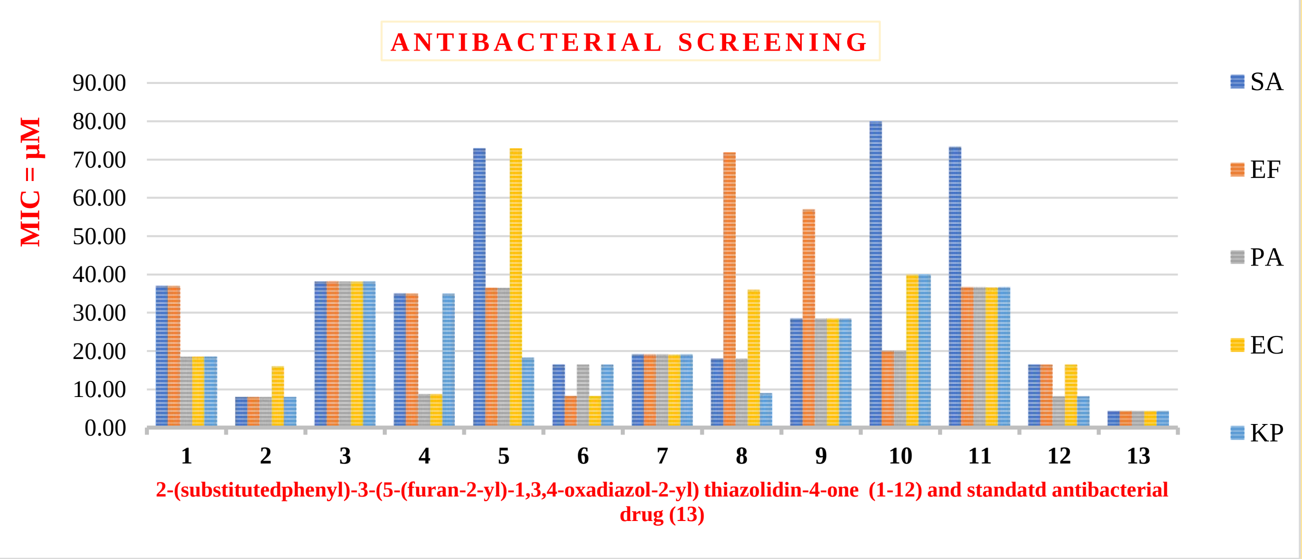


Figure:5 Antibacterial Screening of 2-(substituted)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one conjugates

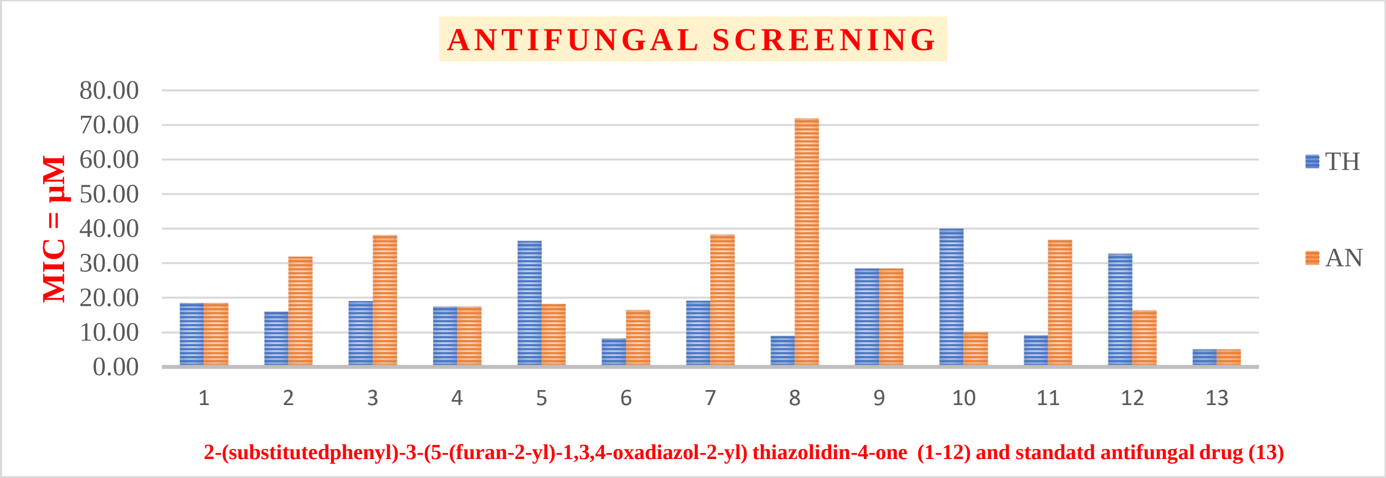


Figure:6 Antifungal Screening of 2-(substituted)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one conjugates

Structure activity relationship:

From the antimicrobial and antioxidant evaluation studies following structure activity relationship can be drawn (**Figure**. 7):

- The different R_1 substitution used to synthesize the final derivatives of 2-(substitutedphenyl)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one played an important role in improving the antimicrobial and antioxidant activities. Substitution of electron releasing group methyl ($-NH_2$ and CH_3) at para position in the synthesized compound 4 and 7, increased the antibacterial and antifungal potential against P. aeruginosa, E coli and T. harzianum.
- Presence of Electron withdrawing group (Br,-Cl, CF_3-) at para position in the synthesized compound 2, 6 and 8 showed potent broad spectrum antibacterial activity against Both Gram +ve (S. aureus, E. faecalis, P. aeruginosa) and Gram -ve (E.coli and K. pneumoniae) bacterial strains.
- 1,3,4 oxadiazole ring overall increasing antimicrobial as well antioxidant activity
- electron withdrawing group $-(CH_3)_2$ at para position of the synthesized compound 11, enhanced the antifungal potential against A. Niger whereas substitution of -Cl, in the derived compound 8, shown most potent antioxidant potential. These molecules may further be used as lead compounds to derive more potent and less toxic novel antioxidant and antimicrobial agents.
- Electron withdrawing group I at para position in compound 9 showed most potent antioxidant potential
- Presence of Presence of furfuryl group also helps to enhanced antioxidant activity.

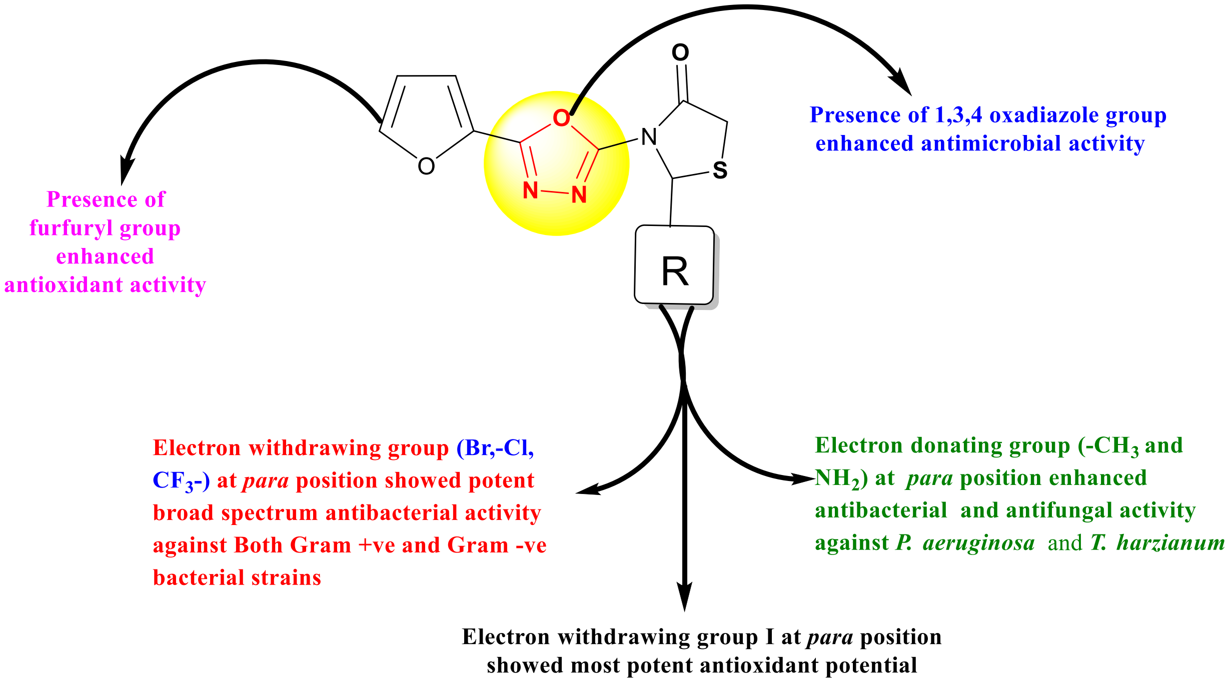


Figure:7 Structure activity relationship of synthesized conjugates

Experimental part:

Synthesis of derivatives was conducted using commercially available analytical grade chemicals without purification. The melting point (MP) was determined using open glass capillaries on melting point apparatus. Every synthetic step was monitored by TLC glass plates containing silica gel G. A Shimadzu Fourier transform infrared spectroscopy (FTIR) was used to measure infrared (IR, KBr, cm-1) reflected from KBr pellets. As an internal standard, tetramethylsilane has been used as a deuterated solvent and a Bruker Advance III 400 NMR spectrometer was used to determine ^{1}H spectra in appropriate deuterated solvents. Agilent mass spectrometers were used to obtain mass spectra. An elemental analysis was performed on a CHN analyzer.

General procedure of Scheme 1:

Step 1: Synthesis of 5-(furan-2-yl)-1,3,4-oxadiazol-2-amine (03):

A mixture containing semi carbazide hydrochloride (0.5 mol) (02) and sodium acetate (0.5 mol) was added to water (10 ml) and stirred well, then furan-2-carbaldehyde (01) were added to methanol at room temperature. The string was continued with reduced pressure until the solvent had not evaporated completely. Afterward, 1,4-dioxane was added to the residue and the reaction was carried out at 80 -85 °C for 4-6 hours with addition of K_2CO_3 (1.5 mol) and iodine (0.5 mol). TLC analysis was used to monitor and check the whole reaction step by step. It was cooled to room temperature, then treated with 5% Na2S2O3 (30 mL), followed by extraction with a 5:1 mixture of CH_2Cl_2/MeOH. Anhydrous sodium sulfate was used to dry and concentrate the combined organic layer. By recrystallizing the residue, 2-amino-1,3,4-oxadiazoles (03) were obtained in 80-90% yield (1-12 derivatives)(34).

Step 2: General procedure for synthesis of Schiff bases (5):

In ethanolic solution, 2-amino-1,3,4-oxadiazole (0.5 mol) was refluxed with different aromatic aldehydes (4) (0.5 mol). In order to complete the reaction, a small amount of glacial acetic acid (2-3 mL) (dehydrating agent) was added to the whole reaction mixture and the mixture was refluxed for 7-8 hours, or until the reaction was complete. Completion of reactions were checked by TLC. The excess ethanol as a solvent was distilled away after confirmation of the reaction, and the resulting residue was stirred for 20 minutes on ice. After filtering, filtration, washing with ice cold water, drying, and recrystallization from alcohol, precipitates were obtained.

Step 3: General procedure for synthesis 2-(substitutedphenyl)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one (7)

The Schiff bases (5, 1 mol) was dissolved in 60 mL of toluene and added to 0.7 mL of thioglycolic acid (6). Dean stark traps were used to reflux the solution. Monitoring the reaction progress with TLC was carried out. An 3% $NaHCO_3$ solution and brine were used to wash the mixture. Organic layers were dried over Na_2SO_4 then concentrated under vacuum. Ethanol was used to re-crystallize the products(35).

IN VITRO ANTIOXIDANT ASSAY

2-(substitutedphenyl)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-ones were evaluated for their antioxidant properties using a 2-diphenyl-1-picrylhydrazil (DPPH) free radical scavenging model. Synthesized compounds were diluted in methanol to 25 mg/mL, 50 mg/mL, 75 mg/mL, and 100 mg/mL concentrations, and then a solution of DPPH was added to each, followed by vigorous shaking. An UV-visible double beam spectrophotometer was used to measure the absorbance of the above solution spectrophotometrically at 517 nm after being kept in the dark for 30 minutes. The % Inhibition of synthesised derivatives was calculated by following equation. (Eq. 1)

$$\text{Inhibition\%} = \frac{A_c - A_{ox}}{A_c} \times 100 \qquad \text{Eq. 1}$$

where A_{ox} is the absorbance in the presence of synthesised Oxadiazole derivatives, A_C is the absorbance of the control and AB is the absorbance of blank reading. The mean of at least three observations was taken as mean IC_{50} value in the data presented (Table 5). The IC_{50} value in μg/mL was calculated for all the synthesized compounds by using following equation (Eq. 2). (36)

$$Y = \text{Min} + \frac{\text{Max} - \text{Min}}{1(\frac{x}{IC_{50}})\text{Hill Cofficient}} \qquad \text{Eq. 2}$$

IN VITRO ANTIMICROBIAL ASSAY

The antimicrobial potential of the synthesized compounds was evaluated by serial tube dilution method (37)using fluconazole (antifungal) and cefadroxil (antibacterial) as standard drugs. Both Gram +ve {MTCC-3160 (S. aureus), MTCC-441 (E. faecalis), MTCC-1034 (P. aeruginosa)} and Gram -ve MTCC-443 (E. coli) MTCC-9024, (K. pneumoniae)} bacterial species were used in the study. The antifungal potential was evaluated against MTCC-3683 (T. harzianum) and MTCC-281 (A. niger) strains. Nutrient broth double strength I.P. (for bacteria) or sabouraud dextrose broth I.P. (for fungi) nutrient media were used for antimicrobial potential. Stock solutions of the test and reference compounds were prepared in dimethyl sulfoxide. A control set was also used at the same dilutions with the test medium supplemented with dimethyl sulfoxide. Results were recorded in MIC after incubating the samples at 25 ± 1 °C (7 days) for A. niger, at 37 ± 1 °C (24 h) for bacteria and at 37 ± 1 °C (48 h) for C. albicans, respectively. MIC was recorded for the tested compound as lowest concentration that showed no observable growth of microorganisms in the test tube(38). The antimicrobial potential screening value was calculated in 1 Micromolar [μM] for all the synthesized compounds by using following equation (Eq. 3).

$$\text{Micromolar } [\mu M] = \frac{MIC}{MW} \text{ X } 1000 \qquad \text{Eq. 3}$$

CONCLUSION:

A series of 2-(substitutedphenyl)-3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl) thiazolidin-4-one was synthesized and then screened for its antimicrobial and antioxidant potential. The antimicrobial screening results suggested that the synthesized derivatives 2,4,6,8, and 12 possessed moderate to promising potential against the selected species of microbial strains having MIC range 7.96 μM-9.97 μM. Structure activity relationship studies revealed compounds 2, 6 with p-bromo, trifluoro and 8 with p-chloro, substitutions were shown to be the most active among all the derivatives against the selected microbes. Compounds 6,8,9 and 12 were found to be more potent than the standard drug (ascorbic acid) in antioxidant evaluation assays. Among all the compounds, compound 9, [(3-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-2-(4-iodophenyl) thiazolidin-4-one)] showed the highest antioxidant activity with an IC_{50} of 18.56 µg/mL, compared standard drug with to 23.22 µg/mL. Further modifications or optimization can be done to the derivatives to produce more potent antimicrobial and antioxidant molecules with the least amount of toxicity.

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Author's declaration:

Conflict of interest:

The authors have no conflict of interest.

Ethics approval and consent to participate- Not applicable

REFERENCES

1. Sass P. Antibiotics: Precious Goods in Changing Times. Methods Mol Biol [Internet]. 2017 [cited 2022 Nov 5];1520:3–22. Available from: https://pubmed.ncbi.nlm.nih.gov/27873243/

2. Glomb T, Świątek P. Antimicrobial Activity of 1,3,4-Oxadiazole Derivatives. Int J Mol Sci [Internet]. 2021 Jul 1 [cited 2022 Nov 18];22(13). Available from: https://pubmed.ncbi.nlm.nih.gov/34209520/

3. Ventola CL. The Antibiotic Resistance Crisis: Part 1: Causes and Threats. Pharmacy and Therapeutics [Internet]. 2015 [cited 2022 Nov 5];40(4):277. Available from: /pmc/articles/PMC4378521/

4. Kumar D, Narang R, Judge V, Kumar D, Narasimhan B. Antimicrobial evaluation of 4-methylsulfanyl benzylidene/3-hydroxy benzylidene hydrazides and QSAR studies. Medicinal Chemistry Research. 2012 Mar;21(3):382–94.

5. Kumar D, Judge V, Narang R, Sangwan S, de Clercq E, Balzarini J, et al. Benzylidene/2-chlorobenzylidene hydrazides: Synthesis, antimicrobial activity, QSAR studies and antiviral evaluation. Eur J Med Chem. 2010 Jul;45(7):2806–16.

6. Fair RJ, Tor Y. Antibiotics and Bacterial Resistance in the 21st Century. Perspect Medicin Chem [Internet]. 2014 Jun 24 [cited 2022 Nov 5];6(6):25. Available from: /pmc/articles/PMC4159373/

7. Kumar D, Kumar V, Marwaha R, Singh G. Oxadiazole-An Important Bioactive Scaffold for Drug Discovery and Development Process Against HIV and Cancer- A Review. Curr Bioact Compd. 2017 Oct 19;15(3):271–9.

8. Phaniendra A, Jestadi DB, Periyasamy L. Free Radicals: Properties, Sources, Targets, and Their Implication in Various Diseases. Indian Journal of Clinical Biochemistry [Internet]. 2015 Jan 1 [cited 2022 Nov 5];30(1):11. Available from: /pmc/articles/PMC4310837/

9. Sharifi-Rad M, Anil Kumar N v., Zucca P, Varoni EM, Dini L, Panzarini E, et al. Lifestyle, Oxidative Stress, and Antioxidants: Back and Forth in the Pathophysiology of Chronic Diseases. Front Physiol. 2020 Jul 2;11:694.

10. K R, None S, JK S. Significance of 1,3,4-Oxadiazole Containing Compounds in New Drug Development. Curr Drug Res Rev [Internet]. 2021 Dec 22 [cited 2022 Nov 5];13(2):90–100. Available from: https://pubmed.ncbi.nlm.nih.gov/33349230/

11. Kumar D, Kumar V, Kumar H, Deep A, Kumar Marwaha R. ,3,4-Oxadiazole as an emerging telomerase inhibitor-a promising anticancer motif Corresponding to. Cancer Advances. 2022;5.

12. Santosh R, Prabhu A, Selvam MK, Krishna PM, Nagaraja GK, Rekha PD. Design, synthesis, and pharmacology of some oxadiazole and hydroxypyrazoline hybrids bearing thiazoyl scaffold: antiproliferative activity, molecular docking and DNA binding studies. Heliyon [Internet]. 2019 Feb 1 [cited 2022 Nov 5];5(2). Available from: https://pubmed.ncbi.nlm.nih.gov/30886919/

13. Kashid BB, Salunkhe PH, Dongare BB, More KR, Khedkar VM, Ghanwat AA. Synthesis of novel of 2, 5-disubstituted 1, 3, 4- oxadiazole derivatives and their in vitro anti-inflammatory, anti-oxidant evaluation, and molecular docking study. Bioorg Med Chem Lett [Internet]. 2020 Jun 15 [cited 2022 Jul 26];30(12). Available from: https://pubmed.ncbi.nlm.nih.gov/32280025/

14. Davindera K, Virendera K, Rakeshb M, Gajendraa S. Oxadiazole-an important bioactive scaffold for drug discovery and development process against HIV and cancer- a review. Curr Bioact Compd. 2019;15(3).

15. Sindhe MA, Bodke YD, Kenchappa R, Telkar S, Chandrashekar A. Synthesis of a series of novel 2,5-disubstituted-1,3,4-oxadiazole derivatives as potential antioxidant and antibacterial agents. J Chem Biol [Internet]. 2016 Jul 1 [cited 2022 Sep 7];9(3):79. Available from: /pmc/articles/PMC4958064/

16. Sindhe MA, Bodke YD, Kenchappa R, Telkar S, Chandrashekar A. Synthesis of a series of novel 2,5-disubstituted-1,3,4-oxadiazole derivatives as potential antioxidant and antibacterial agents. J Chem Biol [Internet]. 2016 Jul 1 [cited 2022 Jul 26];9(3):79. Available from: /pmc/articles/PMC4958064/

17. Abbas Tabatabai S, Lashkari SB, Zarrindast MR, Gholibeikian M, Shafiee A. Design, Synthesis and Anticonvulsant Activity of 2-(2-Phenoxy) phenyl-1,3,4-oxadiazole Derivatives. Shaheed Beheshti University of Medical Sciences and Health Services Iranian Journal of Pharmaceutical Research. 2013;12:105–11.

18. Thakkar SS, Thakor P, Doshi H, Ray A. 1,2,4-Triazole and 1,3,4-oxadiazole analogues: Synthesis, MO studies, in silico molecular docking studies, antimalarial as DHFR inhibitor and antimicrobial activities. Bioorg Med Chem. 2017 Aug 1;25(15):4064–75.

19. Kumar D, Kumar H, Deep A, Kumar Marwaha R. An updated study of traditional medicines to the era of 1,3,4 oxadiazole derivatives for malaria treatment Corresponding to. Traditional Medicine Research [Internet]. 2023 [cited 2022 Nov 18];8(1):5. Available from: https://creativecommons.org/licenses/by/4.0/

20. Shi HB, Zhai ZW, Min LJ, Han L, Sun NB, Cantrell CL, et al. Synthesis and pesticidal activity of new 1,3,4-oxadiazole thioether compounds containing a trifluoromethylpyrazoyl moiety. Research on Chemical Intermediates [Internet]. 2022 Nov 1 [cited 2022 Nov 5];48(11):4753–67. Available from: https://link.springer.com/article/10.1007/s11164-022-04839-x

21. Singh P, Sharma PK, Sharma JK, Upadhyay A, Kumar N. Synthesis and evaluation of substituted diphenyl-1,3,4-oxadiazole derivatives for central nervous system depressant activity. Org Med Chem Lett [Internet]. 2012 [cited 2022 Nov 5];2(1):8. Available from: /pmc/articles/PMC3306192/

22. Elbarbary AA, Kenawy ER, Hamada EGI, Edries TB, Meshrif WS. Insecticidal activity of some synthesized 1,3,4-oxadiazole derivatives grafted on chitosan and polymethylmethacrylate against the cotton leafworm Spodoptera littoralis. Int J Biol Macromol. 2021 Jun 1;180:539–46.

23. Suresh Kumar G v., Rajendraprasad Y, Mallikarjuna BP, Chandrashekar SM, Kistayya C. Synthesis of some novel 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole and 1,3,4-oxadiazoles as potential antimicrobial and antitubercular agents. Eur J Med Chem [Internet]. 2010 May [cited 2022 Jul 26];45(5):2063–74. Available from: https://pubmed.ncbi.nlm.nih.gov/20149496/

24. Peng F, Liu T, Wang Q, Liu F, Cao X, Yang J, et al. Antibacterial and Antiviral Activities of 1,3,4-Oxadiazole Thioether 4H-Chromen-4-one Derivatives. J Agric Food Chem [Internet]. 2021 Sep 22 [cited 2022 Nov 5];69(37):11085–94. Available from: https://pubs.acs.org/doi/abs/10.1021/acs.jafc.1c03755

25. Capoci IRG, Sakita KM, Faria DR, Rodrigues-Vendramini FAV, Arita GS, de Oliveira AG, et al. Two New 1,3,4-Oxadiazoles With Effective Antifungal Activity Against Candida albicans. Front Microbiol. 2019 Sep 12;10:2130.

26. Pidugu VR, Yarla NS, Pedada SR, Kalle AM, Satya AK. Design and synthesis of novel HDAC8 inhibitory 2,5-disubstituted-1,3,4-oxadiazoles containing glycine and alanine hybrids with anti cancer activity. Bioorg Med Chem [Internet]. 2016 Sep 12 [cited 2022 Jul 27];24(21):5611–7. Available from: https://europepmc.org/article/med/27665180

27. Pidugu VR, Yarla NS, Pedada SR, Kalle AM, Satya AK. Design and synthesis of novel HDAC8 inhibitory 2,5-disubstituted-1,3,4-oxadiazoles containing glycine and alanine hybrids with anti cancer activity. Bioorg Med Chem [Internet]. 2016 Sep 12 [cited 2022 Jul 27];24(21):5611–7. Available from: https://europepmc.org/article/med/27665180

28. Abd-Ellah HS, Abdel-Aziz M, Shoman ME, Beshr EAM, Kaoud TS, Ahmed ASFF. Novel 1,3,4-oxadiazole/oxime hybrids: Synthesis, docking studies and investigation of anti-inflammatory, ulcerogenic liability and analgesic activities. Bioorg Chem [Internet]. 2016 Dec 1 [cited 2022 Jul 26];69:48–63. Available from: https://pubmed.ncbi.nlm.nih.gov/27669120/

29. Siwach A, Verma PK. Therapeutic potential of oxadiazole or furadiazole containing compounds. BMC Chem [Internet]. 2020 Dec 1 [cited 2022 Jul 26];14(1):1–40. Available from: https://bmcchem.biomedcentral.com/articles/10.1186/s13065-020-00721-2

30. Sun J, Makawana J, Zhu HL. 1,3,4-oxadiazole derivatives as potential biological agents. Mini Rev Med Chem [Internet]. 2013 Sep 18 [cited 2022 Jul 26];13(12):1725–43. Available from: https://pubmed.ncbi.nlm.nih.gov/23815585/

31. Kumar D, Kumar V, Mundlia J, Pradhan D, Malik S. Thiazolidin-4-one Derivatives as Central Nervous System Potential Agents.

32. Kumar H, Kumar D, Kumar P, Gupta Marwaha M, Shankar U, Kumar Marwaha R. 5-(4-(3-(substituted aryl/alkyl)-4-oxothiazolidin-2-yl)benzylidene)thiazolidine-2,4-dione molecules: Synthesis, Biological potential and in silico studies. 2022 Jun 6 [cited 2022 Nov 19]; Available from: https://www.researchsquare.com

33. Prevc T, Šegatin N, Poklar Ulrih N, Cigić B. DPPH assay of vegetable oils and model antioxidants in protic and aprotic solvents. Talanta [Internet]. 2013 [cited 2022 Nov 19];109:13–9. Available from: https://pubmed.ncbi.nlm.nih.gov/23618135/

34. Niu P, Kang J, Tian X, Song L, Liu H, Wu J, et al. Synthesis of 2-amino-1,3,4-oxadiazoles and 2-Amino-1,3,4-thiadiazoles via sequential condensation and I2-mediated oxidative C-O/C-S bond formation. Journal of Organic Chemistry [Internet]. 2015 Jan 16 [cited 2022 Nov 19];80(2):1018–24. Available from: https://pubs.acs.org/doi/abs/10.1021/jo502518c

35. Kumar H, Deep A, Marwaha RK. Design, synthesis, in silico studies and biological evaluation of 5-((E)-4-((E)-(substituted aryl/alkyl)methyl)benzylidene)thiazolidine-2,4-dione derivatives. BMC Chem [Internet]. 2020 Mar 31 [cited 2022 Nov 19];14(1). Available from: https://pubmed.ncbi.nlm.nih.gov/32266332/

36. Sebaugh JL. Guidelines for accurate EC50/IC50 estimation. Pharm Stat. 2011 Mar;10(2):128–34.

37. INDIAN PHARMACOPOEIA 2007 Volume 1 THE INDIAN PHARMACOPOEIA COMMISSION GHAZIABAD. 2007 [cited 2022 Nov 19]; Available from: www.ipc.gov.in

38. Microbiology : a laboratory manual | WorldCat.org [Internet]. [cited 2022 Nov 19]. Available from: https://www.worldcat.org/title/microbiology-a-laboratory-manual/oclc/876232639