Design, Synthesis and Molecular Docking of some Oxazolidinone Compounds

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A series of oxazolidinone compounds have been obtained and characterized by physico-chemical methods and antimicrobial activity against Staphylococcus Aureus ATCC 6538. For the synthesized compounds have been performed calculations of characteristics and molecular properties, using Spartan 14 Software from Wavefunction, Inc. Irvine, CA. and molecular docking studies using CLC Drug Discovery Workbench 2.4 software, to identify and visualize the most likely interaction ligand (oxazolidinone derivatives) with the receptor protein.

Keywords: linezolid, oxazolidinone, antimicrobial activity, molecular docking

Infectious diseases are the second leading cause of death worldwide [1]. In this context, newer drugs have been developed. Linezolid (Figure 1) is a synthetic drug belonging to oxazolidinone class that was approved by the FDA in 1999. This new drug shows a great activity against gram-positive microorganisms, especially methicilin resistant *St. Aureus* (MRSA), methicilin resistant *St. Epidermis* (MRSE) and Vancomicyn Resistant Enterococci (VRE) [2-7].

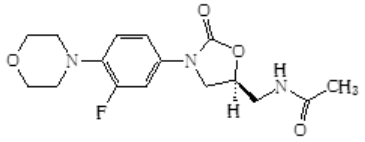

Fig. 1 Linezolid

Experimental part

Melting points were determined in opened capillary on Melting point apparatus OptiMelt and are uncorrected. Progress of the reaction was followed by TLG on Merck silica gel $60F_{254}$ plates eluted with the solvent system: tetrahydrofuran:dioxan: ammoniac (60:20:30) (v:v:v). ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$, DMSO-d_6 and trifluoroacetic acid, on two instruments Varian, Varian Gemini 300 BB (operating at 300 MHz for proton and 75 MHz for carbon) and UNITY 400 Plus(operating at 400 MHz for proton and 100 MHz for carbon).Tetramerthylsilane as internal standard was the reference for the chemical shifts. All chemical shifts are given in the delta scale (ppm *vs* internal TMS). FT IR was recorded on an instrument Bruker Vertex 70 with diamond optic. UV-Vis was recorded on an instrument UV – Vis LAMBDA 12. Elemental analysis was

Synthesis of 1-(2-fluoro-4-nitrophenyl)-3-methyl-piperidine

A solution of 0.03 Mol (5 g) 3,4-difluoronitrobenzene in 50 mL methanol, was treated with 0.075 mol (7.15 g) 3-methyl-piperidine, followed by stirring 5 h at 50^0. The solution was cooled to room temperature and concentrated *in vacuum*. The residue was dissolved in 50 mL ethyl acetate and extracted with 2 x 50 mL water and 50 mL saturated sodium chloride solution followed by drying on sodium sulfate. The solution was concentrated *in vacuum* to afford an brown oil which was chromatographed over 200 g silica gel and eluting with toluene-ethyl acetate : 1:1 (v:v) to yield 6.43 g 1-(2-fluoro-4-nitrophenyl)-3-methyl-piperidine (oil, yield. 90%). ^{1}H-NMR($CDCl_3$, ä ppm, *J* Hz): 7.94(dd, 1H, H-6, J(F-H^6)= 2.2, ^4J(H^5-H^6)=8.8); 7.85(dd, 1H, H-2,^4J(H^2-H^6)=2.5, ^4J(F-H^2)=13.2); 6.90(t, 1H, H-5, J(F-H^5)= ^3J(H^5-H^6)=8.8); 3.27(m, 4H, 2H-7, 2H-11, syst. A_2B_2);1.60. 1.80(m, 6H, 2H-8, 2H-9, 2H-10). ^{13}C-NMR($CDCl_3$, δ ppm): 152.77(d, C-3, J(F-C^3)=248.5 Hz); 146.46(d, C-1, ^3J(F-C^1)=7.4 Hz); 139.56(d, C-4, J(F-C^4)=8.0 Hz); 121.06(d, C-5, ^3J(F-C^5)=2.9 Hz); 116.38(d, C-6, ^4J(F-C^6)=4.3 Hz); 112.32(d, C-2, J(F-C^2)=26.6 Hz); 51.00(d, C-7, C-11, ^4J(F-C^{7,11})=5.2 Hz); 25.81(C-8, C-10); 24.11(C-9).

Synthesis of 1-(2-fluoro-4-nitrophenyl)-4-methyl-piperidine

1-(2-fluoro-4-nitrophenyl)-4-methyl-piperidine: (oil, yield. 85%). ^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.94(dd, 1H, H-6, J(F-H^6)= 2.2, ^4J(H^5-H^6)=8.8); 7.85(dd, 1H, H-2,^4J(H^2-H^6)=2.5, ^4J(F-H^2)=13.2); 6.90(t, 1H, H-5, J(F-H^5)= ^3J(H^5-H^6)=8.8); 3.88(m, 4H, H-7, H-11); 2.87(m, 2H, H-7, H-11); 1.77(m, 2H, H-8, H-10); 1.60(m, 1H, H-9);1.39(m, 2H, H-8, H-10); 1.00(d, 3H, H-12, 6.6). ^{13}C-NMR($CDCl_3$, δ ppm): 152.75(d, C-3, J(F-C^3)=247.8 Hz);146.26(d, C-1, ^3J(F-C^1)=7.9 Hz);139.66(d, C-4, J(F-C^4)=8.9 Hz);121.05(d, C-5, ^3J(F-C^5)=2.9 Hz);117.06(d, C-6, ^4J(F-C^6)=4.5 Hz); 112.50(d, C-2, J(F-C^2)=27.8 Hz); 50.34(d, C-7, C-11, J(F-C^7)=5.1 Hz); 34.02(C-8, C-10); 31.65(C-9); 21.79(C-12).

Synthesis of 1-(2-fluoro-4-nitrophenyl)-piperidine

1-(2-fluoro-4-nitrophenyl)-piperidine: (oil, yield. 93%). ^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.94(dd, 1H, H-6, J(F-H^6)= 2.2, ^4J(H^5-H^6)=8.8); 7.85(dd, 1H, H-2,^4J(H^2-H^6)=2.5, ^4J(F-H^2)=13.2); 6.90(t, 1H, H-5, J(F-H^5)= ^3J(H^5-H^6)=8.8); 3.27(m, 4H, 2H-7, 2H-11, syst. A_2B_2);1.60. 1.80(m, 6H, 2H-8, 2H-9, 2H-10). ^{13}C-NMR($CDCl_3$, δ ppm): 152.77(d, C-3, J(F-C^3)=248.5 Hz); 146.46(d, C-1, ^3J(F-C^1)=7.4 Hz); 139.56(d, C-4, J(F-C^4)=8.0 Hz); 121.06(d, C-5, ^3J(F-C^5)=2.9 Hz); 116.38(d, C-6, ^4J(F-C^6)=4.3 Hz); 112.32(d, C-2, J(F-C^2)=26.6 Hz); 51.00(d, C-7, C-11, ^4J(F-C^{7,11})=5.2 Hz); 25.81(C-8, C-10); 24.11(C-9).

Synthesis of 1-(2-fluoro-4-nitrophenyl)-morpholine

1-(2-fluoro-4-nitrophenyl)-morfoline: (m.p. 108-110.9^{0}C, yield 94%). ^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.99(dd, 1H, H-6, ^4J(F-H^6)= 2.2, ^4J(H^5-H^6)=8.8); 7.91(dd, 1H, H-2,^4J(H^2-

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H^6)=2.5, J(F-H^2)=13.2); 6.93(t, 1H, H-5, ^5J(F-H^5)= ^3J(H^5-H^6)=8.8); 3.88(m, 4H, H-8, H-10, syst. A_2B_2); 3.29(m, 4H, H-7, H-11, syst. A_2B_2).^{13}C-NMR($CDCl_3$, δ ppm): 153.12(d, C-3, J(F-C^3)=249.7 Hz);145.49(d, C-1, ^3J(F-C^1)=7.6 Hz);140.86(d, C-4, J(F-C^4)=9.8 Hz);120.99(d, C-5, ^3J(F-C^5)=2.9 Hz);116.88(d, C-6, ^4J(F-C^6)=4.0 Hz); 112.61(d, C-2, J(F-C^2)=26.4 Hz); 66.58(C-8, C-10); 49.89(d, C-7, C-11, J(F-$C^{7,11}$)=5.2 Hz).

Synthesis of 3-fluoro-4-(3-methyl-piperidinyl)-aniline

A solution of 0.03 Mol (7.12 g) 1-(2-fluoro-4-nitrophenyl)-3-methyl-piperidine in 100 mL acetone, was treated with 0.09 mol (5.7 g) ammonium formate (6.53 g) and 0.0712 g Pd/C followed by stirring 6 h at 50^0. The solution was cooled to room temperature and was filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in 50 mL ethyl acetate and extracted with 2 x 50 mL water and 50 mL saturated sodium chloride solution followed by drying on sodium sulfate. The solution was concentrated *in vacuum* to afford an brown oil which was chromatographed over 200 g silica gel and eluting with toluene-ethyl acetate: 3:1 (v:v) to yield 5 g 3-fluoro-4-(3-methyl-piperidinyl)-aniline (oil, yield. 80%). ^{1}H-NMR($CDCl_3$, ä ppm, J Hz): 6.81(t, 1H, H-5, ^4J(F-H^5)= ^3J(H^5-H^6)=8.9); 6.45÷6.35(m, 2H, H-2, H-6); 3.51(bs, 2H, NH_2); 3.18(m, 4H, 2H-7, 2H-11); 2.44(m, 1H, H-8); 2.19(t, 1H, H-9); 1.83÷1.75(m, 3H, H-9, 2H-10);0.92(d, 3H, H-12, 6.5). ^{13}C-NMR($CDCl_3$, δ ppm): 156.72(d, C-3, J(F-C^3)=244.7 Hz);142.21(d, C-1, ^3J(F-C^1)=10.3 Hz);133.10(d, C-4, J(F-C^4)=10.3 Hz);120.58(d, C-5, ^3J(F-C^5)=4.2 Hz);110.56(d, C-6, ^4J(F-C^6)=2.9 Hz);103.87(d, C-2, J(F-C^2)=24.4 Hz); 60.17(d, C-7 or C-11, J(F-C^7)=2.5 Hz); 52.37(d, C-7 or C-11, J(F-C^7)=2.3 Hz); 32.81(C-9 or C-10); 31.43(C-8); 25.87(C-9 or C-10); 19.56(C-12).

Synthesis of 3-fluoro-4-(4-methyl-piperidinyl)-aniline

3-fluoro-4-(4-methyl-piperidinyl)-aniline: (oil, yield. 79%). ^{1}H-NMR($CDCl_3$, δ ppm, J Hz): 6.81(t, 1H, H-5, ^4J(F-H^5)= ^3J(H^5-H^6)=9.1); 6.44÷6.35(m, 2H, H-2, H-6); 3.50(bs, 2H, NH_2, deuterable); 3.23(m, 2H, H-7_{eq}, H-11_{eq} or H-7_{ax}, H-11_{ax}); 2.57(m, 2H, H-7_{eq}, H-11_{eq} or H-7_{ax}, H-11_{ax}); 1.70(m, 2H, H-8_{eq}, H-10_{eq} or H-8_{ax}, H-10_{ax}); 1.38÷1.44(m, 3H, H-8_{eq}, H-10_{eq} or H-8_{ax}, H-10_{ax}, H-9); 0.98(d, 3H, H-12, 5.5). ^{13}C-NMR($CDCl_3$, δ ppm): 156.72(d, C-3, J(F-C^3)=242.6 Hz);142.25(d, C-1, ^3J(F-C^1)=10.5 Hz); 132.99(d, C-4, J(F-C^4)=10.0 Hz);120.52(d, C-5, ^3J(F-C^5)=4.4 Hz); 110.56(d, C-6, ^4J(F-C^6)=2.9 Hz);103.38(d, C-2, J(F-C^2)=22.5 Hz);52.31(d, C-7, C-11, J(F-$C^{7,11}$)=2.0 Hz); 34.61(C-8, C-10); 30.57(C-9); 11.97(C-12).

Synthesis of 3-fluoro-4-piperidinyl-aniline

3-fluoro-4-piperidinyl-aniline: (oil, yield. 92.7%). ^{1}H-NMR($CDCl_3$, δ ppm, J Hz): 6.81(t, 1H, H-5, ^4J(F-H^5)= ^3J(H^5-H^6)=9.2); 6.44÷6.35(m, 2H, H-2, H-6); 3.51(bs, 2H, NH_2, deuterable); 2.89(t, 4H, H-7, H-11, 5.5); 1.71(qv, 4H, H-8, H-10, 5.5); 1.52(m, 2H, H-9). ^{13}C-NMR($CDCl_3$, δ ppm): 156.73(d, C-3, J(F-C^3)=242.5 Hz);142.25(d, C-1, ^3J(F-C^1)=10.2 Hz);133.24(d, C-4, J(F-C^4)=9.5 Hz);120.51(d, C-5, ^3J(F-C^5)=4.5 Hz);110.55(d, C-6, ^4J(F-C^6)=3.4 Hz); 103.86(d, C-2, J(F-C^2)=23.9 Hz); 52.97(d, C-7 and C-11, ^4J(F-$C^{7(11)}$)=2.5 Hz); 26.31(C-8, C-10); 24.18(C-9).

Synthesis of 3-fluoro-4-mopholinyl-aniline

3-fluoro-4-morfolinyl-aniline: (m.p. 120.2-122.2^{0}C, yield 95%). ^{1}H-NMR($CDCl_3$, δ ppm, J Hz): 6.79(t, 1H, H-5, ^4J(F-H^5)= ^3J(H^5-H^6)=9.2); 6.46÷6.38(m, 2H, H-2, H-6); 3.84(m, 4H, H-8, H-10, syst. A_2B_2); 2.95(m, 4H, H-7, H-11, syst. A_2B_2). ^{13}C-NMR($CDCl_3$, δ ppm): 156.70(d, C-3, J(F-C^3)=244.8 Hz);143.20(d, C-1, ^3J(F-C^1)=10.6 Hz);131.32(d, C-4, J(F-C^4)=10.0 Hz); 120.18(d, C-5, ^3J(F-C^5)=4.6 Hz); 110.56(d, C-6, ^4J(F-C^6)=2.8 Hz); 103.73(d, C-2, J(F-C^2)=23.5 Hz);67.08(C-8, C-10); 51.72(d, C-7, C-11, J(F-$C^{7,11}$)=2.0 Hz).

Synthesis of N-Benzyloxycarbonyl-3-fluoro-4-(3-methyl-piperidinyl)-aniline

To a mixture of 0.027 mol (5.32 g) 3-fluoro-4-(3-methyl-piperidinyl)-aniline, 0.065 mol (5.4 g) sodium bicarbonate in 100 mL acetone and 50 mL water cooled at 5^0C was added drop wise for 20-30 min., 0.033 mol (5.63 g) benzyl chloroformate, while maintaining the temperature between 5 and 10^0 C, and then allowed to stir at room temperature 4 h. The mixture was poured over 500 g ice and 100 mL of water. The mixture was filtered, and the solids were washed with water, and then dried to give 8.13 g N-Benzyloxycarbonyl-3-fluoro-4-(3-methyl-piperidinyl)-aniline (109.3-111.6^{0}C; yield 88%). ^{1}H-NMR($CDCl_3$, δ ppm, J Hz): 7.41÷7.33(m, 6H, H-2, H^{15}÷H^{19}); 6.94(dd, 1H, H-6, 2.2, 8.8); 6.88(t, 1H, H-5, ^4J(F-H^5)= ^3J(H^5-H^6)=8.8); 6.58(bs, NH); 3.27(m, 2H, H-7_{ax}, H-11_{ax} or H-7_{eq}, H-11_{eq}); 2.53(m, 1H, H-8); 5.18(s, 2H, H-13); 2.23(m, 2H, H-7_{eq}, H-11_{eq} or H-7_{ax}, H-11_{ax}); 1.85÷1.72(m, 4H, H-9, H-10); 0.92(d, 3H, H-20, 6.4). ^{13}C-NMR($CDCl_3$, δ ppm): 155.72(d, C-3, J(F-C^3)=245.4 Hz); 153.37(C-12); 137.40(d, C-1, ^3J(F-C^1)=9.7 Hz);132.36(d, C-4, J(F-C^4)=10.2 Hz);135.97(C-14); 128.63(C-16, C-18); 28.34(C-17); 128.33(C-15, C-19);119.50(d, C-5, ^3J(F-C^5)=4.4 Hz); 114.38(d, C-6, ^4J(F-C^6)=3.4 Hz); 107.58(d, C-2, J(F-C^2)=22.7 Hz);67.06(C-12); 59.43(C-7 or C-11); 51.79(C-7 or C-11); 32.76(C-9 or C-10); 31.29(C-9 or C-10); 25.68(C-8); 19.89(C-20). Elemental Analyses: Calculated for: $C_{20}H_{23}FN_2O_2$: C: 70.15% H: 6.77% N:8.18%. Found C : 70.22% H: 6.91% N:8.22%.

Synthesis of N-Benzyloxycarbonyl-3-fluoro-4-(4-methyl-piperidinyl)-aniline

N-Benzyloxycarbonyl-3-fluoro-4-(4-methyl-piperidinyl)-aniline: (m.p.121,5-123,4^{0}C; yield 97%). ^{1}H-NMR($CDCl_3$, δ ppm, J Hz): 7.42÷7.34(m, 6H, H-2, H^{15}÷H^{19});6.94(dd, 1H, H-6, 2.2, 8.8);6.88(t, 1H, H-5, ^4J(F-H^5)= ^3J(H^5-H^6)=8.8); 6.61(bs 1H, HN); 5.18(s, 2H, H-13); 3.33(m, 2H, H-7_{eq}, H-11_{eq} or H-7_{ax}, H-11_{ax});2.60(m, 2H, H-7_{eq}, H-11_{eq} or H-7_{ax}, H-11_{ax}); 1.76÷1.36(m, 5H, H-8, H-9, H-10); 0.99(d, 3H, H-20, 5.5).^{13}C-NMR($CDCl_3$, δ ppm): 156.02(d, C-3, J(F-C^3)=244.7 Hz); 154.06(C-12); 137.35(d, C-1, ^3J(F-C^1)=10.1 Hz);132.31(d, C-4, J(F-C^4)=10.4 Hz);135.97(C-14); 128.62(C-16, C-18); 128.38(C-17); 128.33(C-15, C-19);119.43(d, C-5, ^3J(F-C^5)=4.4 Hz); 114.33(d, C-6, ^4J(F-C^6)=3.4 Hz); 107.59(d, C-2, J(F-C^2)=22.7 Hz);67.06(C-13); 51.69(C-7, C-11); 34.44(C-8, C-10);30.58(C-9); 21.94(C-20). Elemental Analyses: Calculated for: $C_{20}H_{23}FN_2O_2$: C: 70.15% H: 6.77% N: 8.18%. Found C: 70.17% H: 6.70% N:8.33%

Synthesis of N-Benzyloxycarbonyl-3-fluoro-4-piperidinyl-aniline

N-Benzyloxycarbonyl-3-fluoro-4-piperidinyl-aniline: (m.p. 116.4-118.5^{0}C; yield 68.2%). ^{1}H-NMR($CDCl_3$, δ ppm, J Hz): 7.40÷7.32(m, 6H, H-2, H^{15}÷H^{19}); 6.95(dd, 1H, H-6, 2.1, 8.8); 6.87(t, 1H, H-5, ^4J(F-H^5)= ^3J(H^5-H^6)=8.8); 6.63(bs, 1H, NH); 5.18(s, 2H, H-13); 2.95(t, 4H, H-7, H-11, 5.4); 1.72(qv, 4H, H-8, H-10, 5.4); 1.56(m, 2H, H-9).^{13}C-NMR($CDCl_3$, δ ppm): 155.70(d, C-3, J(F-C^3)=244.6 Hz); 153.33(C-12); 137.42(d, C-1, ^3J(F-C^1)=9.3 Hz);132.34(d, C-4, J(F-C^4)=10.8 Hz);135.97(C-14); 128.62(C-16, C-18); 128.37(C-17); 128.32(C-15, C-19);119.39(d, C-5, ^3J(F-C^5)=4.4 Hz); 114.41(d, C-6, ^4J(F-C^6)=3.4 Hz); 107.55(d, C-2, J(F-C^2)=22.7 Hz); 67.05(C-12); 52.34(C-7, C-11); 26.16(C08, C-10); 14.17(C-9). Elemental Analyses: Calculated for: $C_{19}H_{21}FN_2O_2$: C: 69.49% H: 6.45% N: 8.53%. Found C: 70.17% H: 6.70% N: 8.33%

Synthesis of N-Benzyloxycarbonyl-3-fluoro-4-morpholinyl -aniline

N-Benzyloxycarbonyl-3-fluoro-4-mofolinyl-aniline: (m.p. 123-123.7^{0}C; yield 96.6%). ^{1}H-NMR($CDCl_3$, δ ppm, J Hz): 7.40÷7.32(m, 6H, H-2, H^{15}÷H^{19}); 6.95(dd, 1H, H-6, 2.1, 8.8);

6.87(t, 1H, H-5, ^4J(F-H^5)= ^3J(H^5-H^6)=8.8); 6.63(bs, 1H, NH); 5.18(s, 2H, H-13); 2.95(t, 4H, H-7, H-11, 5.4); 1.72(qv, 4H, H-8, H-10, 5.4); 1.56(m, 2H, H-9). ^{13}C-NMR($CDCl_3$, δ ppm): 155.70(d, C-3, J(F-C^3)=244.6 Hz); 153.33(C-12); 137.42(d, C-1, ^3J(F-C^1)=9.3 Hz);132.34(d, C-4, J(F-C^4)=10.8 Hz);135.97(C-14); 128.62(C-16, C-18); 128.37(C-17); 128.32(C-15, C-19);119.39(d, C-5, ^3J(F-C^5)=4.4 Hz); 114.41(d, C-6, ^4J(F-C^6)=3.4 Hz); 107.55(d, C-2, J(F-C^2)=22.7 Hz); 67.05(C-12); 52.34(C-7, C-11); 26.16(C08, C-10); 14.17(C-9). Elemental Analyses: Calculated for: $C_{18}H_{19}FN_2O_3$: C: 65.44% H: 5.80% N: 8.48%. Found C: C : 65.51% H: 5.90% N:8.51%

Synthesis of (R)-[N-3-(3-fluoro-4-(3-methyl-piperidinyl-phenyl)-2-oxo-5-oxazolidinyl]methanol (Alcohol 4)

To a mixture of 0.0207 mol (7.08 g) of N-Benzyloxy-carbonyl-3-fluoro-4-(3-methyl-piperidinyl)-aniline in 100 mL tetrahydrofuran anh. at -78^0 C, under argon was added 0.207 mol (8.4 mL) 2.5M nBuLi – hexane drop wise over 20-30 min. After 35 min. 0.021 mol (3.05 g) of *(R)*-glycidyl butyrate was added and the mixture allowed to stir at -78^0 C for 40 min. and then at room temperature for 24 h. Saturated aqueous ammonium chloride (30 mL) was added followed by 60 mL ethyl acetate and 20 mL water. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give after recrystallized from ethyl acetate-hexane 5.0 g *(R)*-[N-3-(3-fluoro-4-(3-methyl-piperidinyl-phenyl)-2-oxo-5-oxazolidinyl]methanol (m.p. 98.6-101.3^{0}C, yield 78%). ^{1}H-NMR($CDCl_3$, δ ppm, J Hz): 7.38(dd, 1H, H-2, ^4J(H^6-H^2)= 2.1, ^4J(F-H^2)=14.4);7.10(dd, 1H, H-6, ^5J(F-H^6)= 2.1, ^4J(H^5-H^6)=9.1);6.93(t, 1H, H-5,^3J(H^5-H^6)=9.1, J(F-H^5)=9.1); 4.72(m, 1H, H-13);4.00(d, 1H, H-15A, 8.7); 3.94(dd, 1H, H-15B, 8.7, 6.8); 3.96(d, 1H, H-14A, 12.6); 3.74(dd, 1H, H-14B, 12.6, 4.2);3.30(m, 2H, H-11); 2.70(bs, 1H, OH); 2.55(m, 1H, H-7); 2.26(m, H-7); 1.97(m, 5H, H-8, 2H-9, 2H-10); 0.93(d, 3H, H-8', 5.9). ^{13}C-NMR($CDCl_3$, δ ppm): 155.46(d, C-3, J(F-C^3)=243.2 Hz);154.64(C-12);137.81(d, C-4, J(F-C^4)=9.3 Hz); 132.89(d, C-1, J(F-C^4)=10.3 Hz); 119.25(d, C-5, J(F-C^5)=3.8 Hz); 113.87(d, C-6, J(F-C^6)=3.7 Hz); 107.32(d, C-2, J(F-C^2)=26.3 Hz); 72.83(C-13); 62.75(C-15);46.49(C-14);59.28(C-11); 51.65(d, C-7, C-11, J(F-C^{7,11})=3.2 Hz); 32.77(C-10); 31.26(C-8); 25.64(C-9); 19.48(C-8'). Elemental Analyses: Calculated for $C_{16}H_{21}FN_2O_3$: C: 62.32% H: 6.86% N: 9.09%. Found C : 62.19% H: 7.00% N: 9.27%

Synthesis of (R)-[N-3-(3-fluoro-4-(4-methyl-piperidinyl-phenyl)-2-oxo-5-oxazolidinyl]methanol (Alcohol 5)

(R)-[N-3-(3-fluoro-4-(3-methyl-piperidinyl-phenyl)-2-oxo-5-oxazolidinyl]methanol (m.p. 121.5-123.4^{0}C, yield 75%). ^{1}H-NMR($CDCl_3$, δ ppm, J, Hz): 7.38(dd, 1H, H-2, ^4J(H^6-H^2)= 1.9, ^4J(F-H^2)=14.4);7.08(dd, 1H, H-6, ^5J(F-H^6)= 1.9, ^4J(H^5-H^6)=9.1);6.93(t, 1H, H-5,^3J(H^5-H^6)=8.7, J(F-H^5)=9.1);4.70(m, 1H, H-13); 3.99(m, 1H, H-15A, J(A-B)=16.9, J(H^{15A}-H^{13})=8.7); 3.93(m, 1H, H-15B, J(A-B)=16.9, J(H^{15B}-H^{13}=8.7); 3.92(m, 1H, H-14A); 3.72(dd, 1H, H-14B, J(A-B)=12.6, J(H^{13}-H^{14B})=3.9); 3.35(m, 2H, H-7eq, H-11eq or H-7ax, H-11ax); 3.13(bs, 1H, OH); 2.62(m, 2H, H-7eq, H-11eq or H-7ax, H-11ax); 1.73(m, 2H, H-8eq, H-10eq or H-8ax, H-10ax); 1.32÷1.48(m, 3H, H-13, H-8eq, H-10eq or H-8ax, H-10ax); 0.98(d, 3H, H-9', 5.8). 4.01÷3.89(m, 3H, H-14A, H-15A, H-15B);^{13}C-NMR($CDCl_3$, δ ppm): 155.42(d, C-3, J(F-C^3)=245.1 Hz);154.73(C-12);137.56(d, C-4, J(F-C^4)=8.8 Hz); 132.46(d, C-1, J(F-C^4)=10.3 Hz);119.25(d, C-5, J(F-C^5)=4.5 Hz);113.86(d, C-6, J(F-C^6)=3.3 Hz); 107.31(d, C-2, J(F-C^2)=26.1 Hz); 72.92(C-13); 62.66(C-15); 51.57(C-7, C-11); 46.51(C-14); 34.41(C-8, C-10); 30.59(C-9); 21.93(C-9'). Elemental Analyses: Calculated for $C_{16}H_{21}FN_2O_3$: C: 62.32% H: 6.86% N: 9.09%. Found C: 62.37% H: 6.80% N:9.23%.

Synthesis of (R)-[N-3-(3-fluoro-4-(piperidinyl-phenyl)-2-oxo-5-oxazolidinyl]methanol (Alchool 3)

(R)-[N-3-(3-fluoro-4-(piperidinyl-phenyl)-2-oxo-5-oxazolidinyl]methanol: (m.p. 116.4-118.5^{0}C, yield 77%).

p.t.116,4-118,5^{0}C. ^{1}H-NMR($CDCl_3$, δ ppm, J Hz): 7.38(dd, 1H, H-2, ^4J(F-H^2)= 2.1, ^4J(H^6-H^2)=14.4) ;7.10(dd, 1H, H-6, ^5J(F-H^6)= 2.1, ^4J(H^5-H^6)=9.1);6.93(t, 1H, H-5,^3J(H^5-H^6)=9.1, J(F-H^5)=9.1); 4.72(m, 1H, H-13); 4.00(d, 1H, H-15A, 8.7); 3.92(dd, 1H, H-15B, 8.7, 6.8); 3.96(d, 1H, H-14A, 12.6); 3.74(dd, 1H, H-14B, 12.6, 4.2); 2.98(m, 4H, H-7, H-11); 2.70(bs, 1H, OH); 1.70(qv, 4H, H-8, H-10, 5.6); 1.58(m, 2H, H-9). ^{13}C-NMR($CDCl_3$, δ ppm): 155.46(d, C-3, J(F-C^3)=243.2 Hz);154.64(C-12);137.81(d, C-4, J(F-C^4)=9.3 Hz); 132.89(d, C-1, J(F-C^4)=10.3 Hz); 119.22(d, C-5, J(F-C^5)=3.8 Hz); 113.86(d, C-6, J(F-C^6)=3.7 Hz); 107.32(d, C-2, J(F-C^2)=26.3 Hz); 72.83(C-13); 62.75(C-15); 52.22(d, C-7, C-11, J(F-C^{7,11})=3.2 Hz);46.48(C-14); 26.14(C-8, C-10); 24.19(C-9).Elemental Analyses: Calculated for $C_{15}H_{19}FN_2O_3$: C: 61.21% H: 6.51% N: 9.52%. Found: C : 61.02% H: 6.70% N: 9.50%

Synthesis of (R)-[N-3-(3-fluoro-4-(morpholinyl-fenil)-2-oxo-5-oxazolidinyl]methanol (Alcohol 1)

(R)-[N-3-(3-fluoro-4-(morpholinyl-phenyl)-2-oxo-5-oxazolidinyl]methanol: (m.p. 111.7-112.5^{0}C, yield 75%). ^{1}H-NMR($CDCl_3$, δ ppm, J Hz): 7.43(dd, 1H, H-2, ^4J(F-H^2)= 1.9, ^4J(H^6-H^2)=14.4);7.10(dd, 1H, H-6, ^5J(F-H^6)= 1.9, ^4J(H^5-H^6)=9.1); 6.91(t, 1H, H-5,^3J(H^5-H^6)=8.7, J(F-H^5)=8.7); 3.86(m, 4H, H-8, H-10, syst. A_2B_2); 3.14(bs, 1H, HO); 3.04(m, 4H, H-7, H-11, syst. A_2B_2);4.73(m, 1H, H-13); 3.99(d, 1H, H-15A, syst. AB, 8.6); 3.94(dd, 1H, H-15B, syst AB, 8.6, J(H^{15B}-H^{13})=6.8 Hz); 3.97(bd, 1H. H-14A, 11.4); 3.73(bd, 1H, H-14B, syst. AB, 11.4).^{13}C-NMR($CDCl_3$, δ ppm): 155.34(d, C-3, J(F-C^3)=244.4 Hz);154.71(C-12); 136.25(d, C-4, J(F-C^4)=9.1 Hz); 133.11(d, C-1, J(F-C^4)=10.5 Hz); 118.73(d, C-5, J(F-C^5)=4.1 Hz); 113.86(d, C-6, J(F-C^6)=3.7 Hz); 107.40(d, C-2, J(F-C^2)=26.1 Hz);72.95(C-13); 62.60(C-15); 46.39(C-14); 66.91(C-8, C-10); 50.97(d, C-7, C-11, J(F-C^{7,11})=2.9 Hz). Elemental Analyses: Calculated for $C_{15}H_{19}FN_2O_3$: C: 61.21% H: 6.51% N: 9.52%. Found: C : C : 61.02% H: 6.70% N: 9.50%.

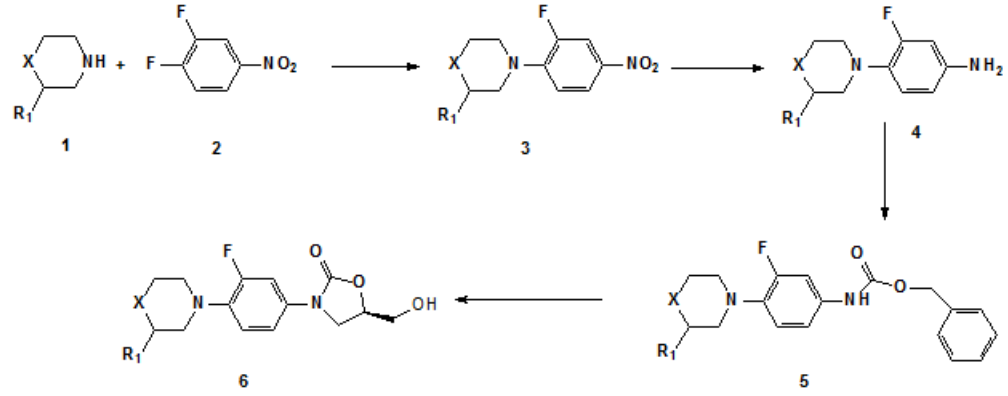
Biological Assays: The oxazolidinone derivatives were evaluated for *in vitro* activity by determining minimum inhibitory concentration against *S. aureus* ATCC6538 by agar dilution method [8].

Molecular mechanics calculations: Molecular, topological, conformational characteristics on 3D oxazolidinone derivatives optimized structure were calculated using Spartan 14 Software [10]

Docking studies: Molecular docking approach**,** using CLC Drug Discovery Workbench Software was conducted in order to achieve accurate predictions on optimized conformation for both, the oxazolidinone compounds (as ligand) and their target receptor protein (*Staphylococcus Aureus* ribosomal subunit, PDB ID: 4WFA) to form a stable complex.

Results and discussions

It were obtained some oxazolidinone compounds (Scheme 1). 3,4-Dfluoro-nitrobenzene with excess piperidine or morpholine selectively gave the p-substituted nitrobenzene (**3**). Reduction of (**3**) compounds was followed by attachment of a carbobenzoxy activating group to the arylamines (**4**). Carbamate (**5**) was deprotonated with *n*-Bu-Li and then *(R)*-glycidyl butyrate was added to give the alchools (**6**).The oxazolidinone compounds was characterized structurally and



Scheme 1. Synthesis of oxazolidinone compounds

pharmacologically. All compounds exhibit moderate activity from *Staphylococcus aureus*, MIC > 64μg/mL.

Ligand preparation: The ligands have been prepared using SPARTAN'14 software package [10]. In this study, the DFT/B3LYP/6-31 G* level of basis set has been used for the computation of molecular structure, vibrational frequencies and energies of optimized structures (fig. 2-5). In order to perform structure-activity relationship (SAR) studies, some electronic properties (table 1), such as HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) energy values, HOMO and LUMO orbital coefficients distribution,

Compounds	Molecular properties									
	Dipole moment [debye]	E HOMO [eV]	E LUMO [eV]	HOMO-LUMO GAP	Polarizability [10^{-30} m^3]	PSA[Å²]	Ovality	Log P	HBA count	HBD count
Alcohol 1	2.82	-5.44	-0.28	5.72	62.87	50.368	1.44	1.03	5	1
Alcohol 3	3.21	-5.29	-0.16	5.45	63.61	42.451	1.45	2.16	4	1
Alcohol 4	3.15	-5.27	-0.14	5.41	65.08	42.482	1.48	2.56	4	1
Alcohol 5	3.18	-5.29	-0.16	5.45	65.08	42.472	1.48	2.49	4	1

Table 1
MOLECULAR PROPERTIES FOR CPK MODEL COMPUTATIONS FOR OXAZOLIDINONE COMPOUNDS USING SPARTAN 14 V1.1.4 SOFTWARE.

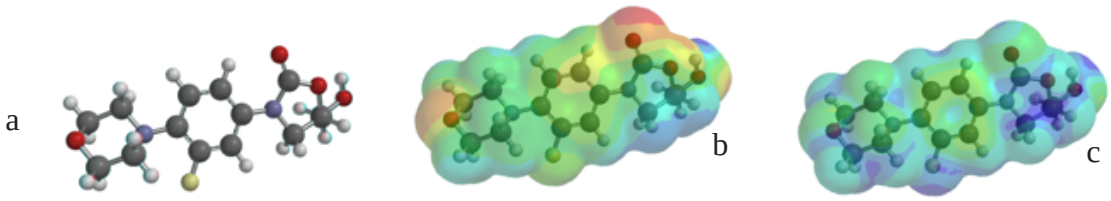


Fig. 2. The optimized geometry (2a), electrostatic potential pattern of the surface of Alcohol 1 (red- negative, high electron density, blue- positive area, low electron density) (2b) and local ionization potential map (2c)

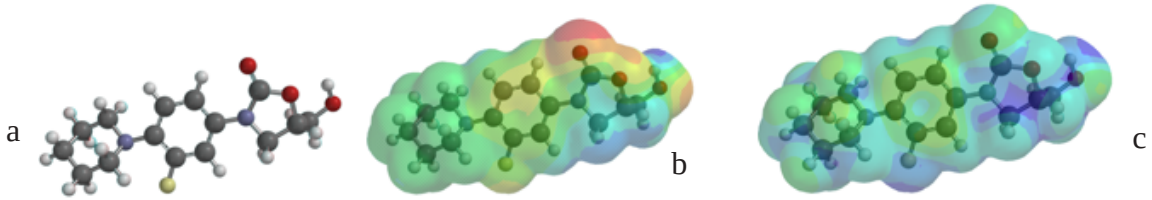


Fig. 3. The optimized geometry (3a), electrostatic potential pattern of the surface of Alcohol 3 (red- negative, high electron density, blue- positive area, low electron density) (3b) and local ionization potential map (3c)

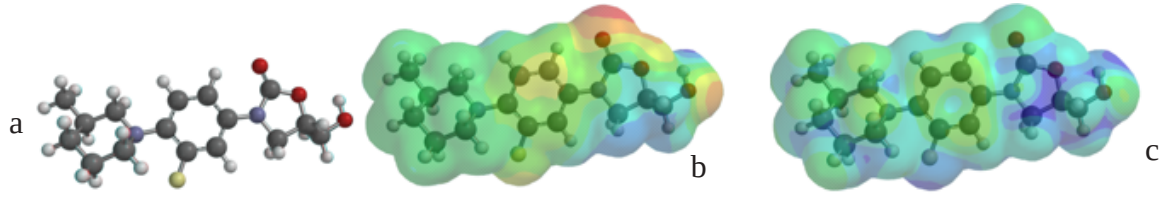


Fig. 4. The optimized geometry (4a), electrostatic potential pattern of the surface of Alcohol 4 (red- negative, high electron density, blue- positive area, low electron density) (4b) and local ionization potential map (4c)

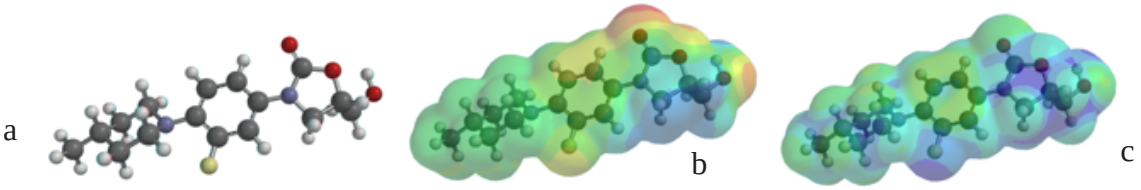


Fig. 5. The optimized geometry (5a), electrostatic potential pattern of the surface of Alcohol 5 (red- negative, high electron density, blue- positive area, low electron density) (5b) and local ionization potential map (5c)

Table 2

THE LIST OF INTERMOLECULAR INTERACTIONS BETWEEN THE LIGAND OXAZOLIDINONES DOCKED WITH 4WFA

Comp.	Score/ RMSD	Interacting group	Hydrogen bond	Length bond
LZD co-crystallized	-32.73/ 1.88	ARG 33:I, GLY 34:I, HIS 35:I, LYS 36:I, GLY 37:I, GLN 38:I, LYS 39:I, ARG 41:I, ALA 40:I, SER 42:I	N sp²(N4)-O sp²din GLN 38:I	2.989 A
Alcohol 1	-35.52/ 0.08	LYS 39:I, ALA 40:I, GLN 38:I, HIS 35:I, LYS 36:I, SER 42:I, ARG 41:I	O sp² (O3)- N sp² din AlA 40:I O sp² (O3)-N sp² din LYS 39:I	2.585 A 3.085 A
Alcohol 3	-32.74/ 0.53	LYS 39:I, ALA 40:I, GLN 38:I, HIS 35:I, LYS 36:I, SER 42:I, ARG 41:I, GLY 34:I	O sp² (O3)- N sp² din AlA 40:I O sp² (O3)-N sp² din LYS 39:I	2.578 A 3.028 A
Alcohol 4	-37.86/ 0.08	LYS 39:I, ALA 40:I, GLN 38:I, HIS 35:I, LYS 36:I, SER 42:I, ARG 41:I, GLY 34:I	O sp³ (O74- N sp² din LYS 39:I	2.948 A
Alcohol 5	-38.11/ 0.06	LYS 39:I, ALA 40:I, GLN 38:I, HIS 35:I, LYS 36:I, SER 42:I, ARG 41:I.	O sp² (O3)- N sp² din AlA 40:I O sp² (O3)-N sp² din LYS 39:I	2.635 A 3.105 A

molecular dipole moment, polar surface area (PSA), the ovality, polarizability, the octanol water partition coefficient (logP), the number of hydrogen-bond donors (HBDs) and acceptors (HBAs). The polarizability is useful to predict the interactions between non-polar atoms or groups and other electrically charged species, such as ions and polar molecules having a strong dipole moment.

Compounds molecular properties

Molecular Docking :The steps to go through to explore protein-ligand interaction using docking, are: setup the binding site in a Molecule Project, dock ligands imported to a Molecule Table, inspect the docking results.The docking studies have been carried out using CLC Drug Discovery Workbench Software. The score and hydrogen bonds formed with the amino acids from group interaction atoms are used to predict the binding modes, the binding affinities and the orientation of the docked compounds (fig. 6) in the active site of the protein-receptor (table 2). It was realized molecular docking studies in order to to identify and visualize the most likely interaction, the binding affinities and the orientation of the docked ligands at the active site of *Staphylococcus aureus* ribosomal subunit (PDB ID: 4WFA) [11].

Docking method validation

The ensure that the ligand orientations and position obtained from the molecular docking studies are valid and reasonable potential binding modes of ligands, the docking methods and parameters used have been validated by redocking (fig. 7).

Calculate molecular properties

Using the Calculate Molecular Properties tool it have been calculated commonly used properties of small molecules, such as Lipinski's rule of five [12]: number of hydrogen bond donors less than 5 (the total number of nitrogen-hydrogen and oxygen-hydrogen bonds), number of hydrogen bond acceptors less than 10 (the total number of nitrogen and oxygen atoms), the molecular weight less than 500 Daltons; Log P (octanol-water partition coefficient) less than 5. The calculation of the log P is based on the XLOGP3-AA method [13].The number of violations of the Lipinski rules gives an indication of how *drug-like* for a molecule is. In general, orally active drugs have fewer than two violations. These properties can be useful for identifying potential drug-like molecules, or for removing non drug-like molecules from a compound library before starting a large virtual screening experiment (table 3).

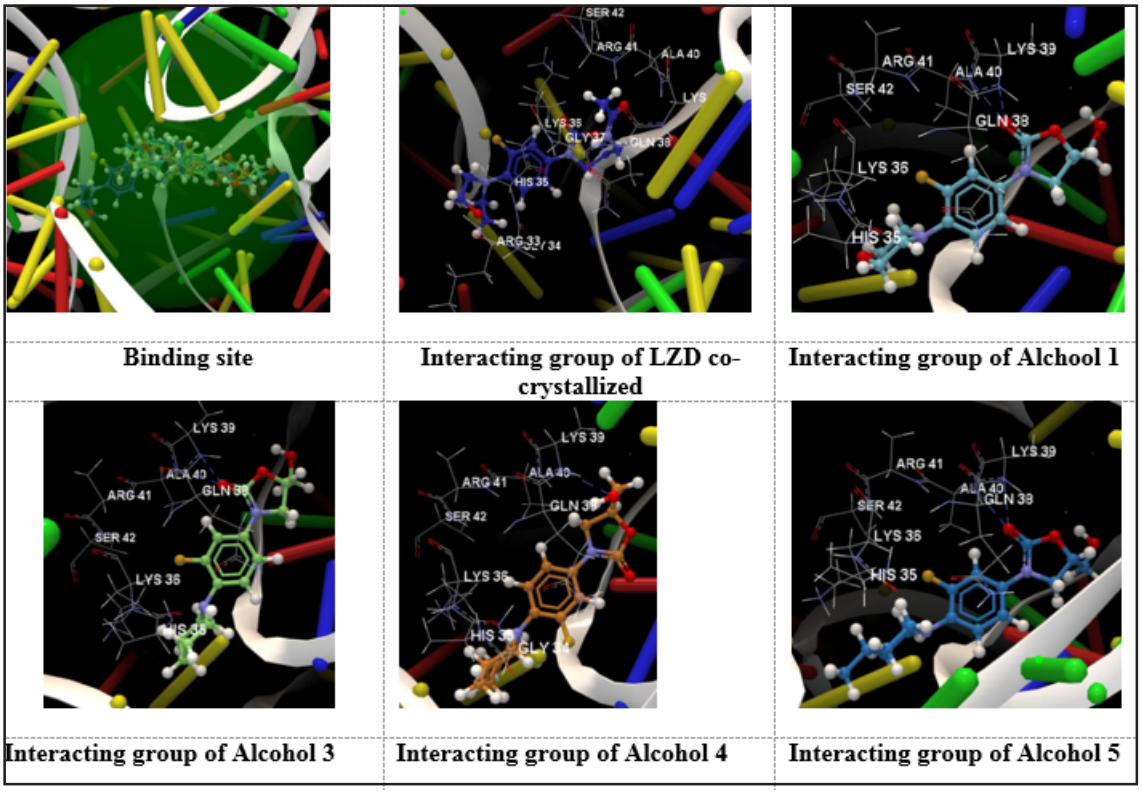


Fig. 6. The binding affinities and the orientation of the docked compound

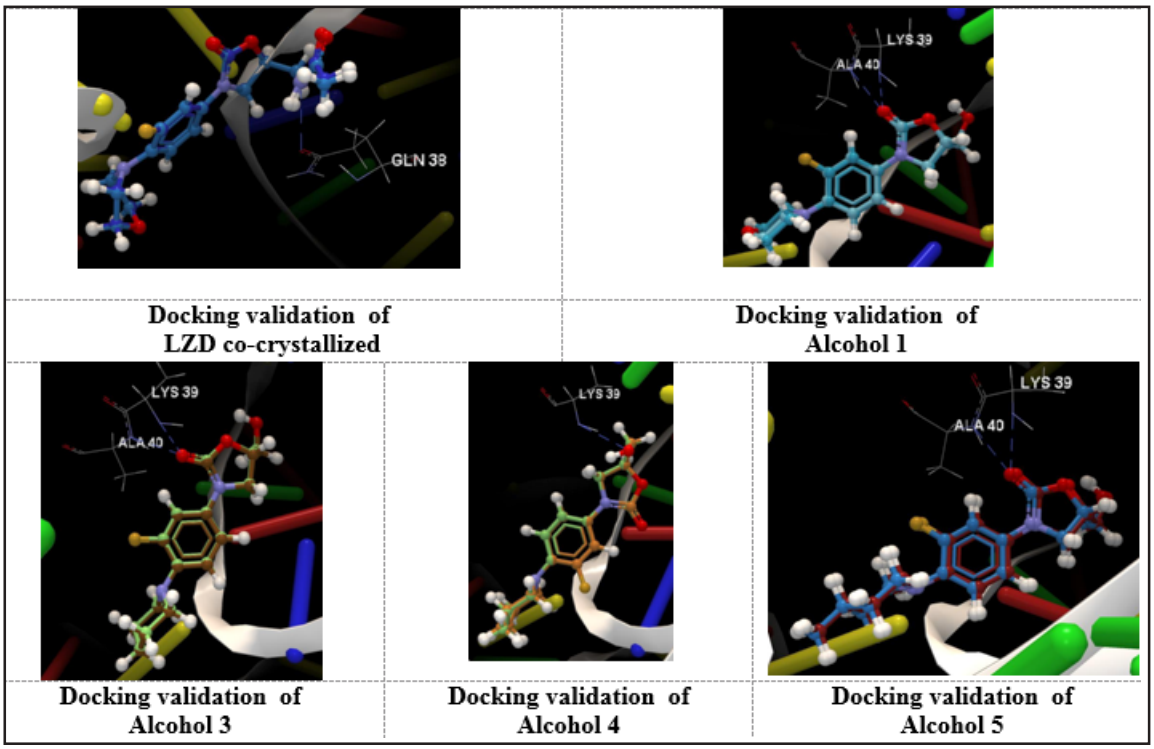


Fig. 7. Molecular docking studies with 4WFA receptor: docking validatio

Compound	Atoms	Weight [Daltons]	Flexible bonds	Lipinski violations	Hydrogen donors	Hydrogen acceptors	LogP
Alcohol 1	38	296.29	3	0	1	6	0.69
Alcohol 3	40	294.32	3	0	1	5	1.91
Alcohol 4	43	308.35	3	0	1	5	2.34
Alcohol 5	43	308.35	3	0	1	5	2.34

Table 3
LIGANDS WITH PROPERTIES

Drug-likeness of the oxazolidinone compounds

According to the data presented in table 3, all oxazolidinone compounds have zero violation of all the parameters involved in Lipinski's rule of five.

Conclusions

We have synthesized somme oxazolidinone compounds and we have investigated their antibacterial activity. For the synthesized oxazolidinone derivatives, a study of the characteristics and molecular properties has been realized. The docking studies revealed that the all compounds showed good docking score. The docking score is a measure of the antimicrobial activity of the studied compounds.

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