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# Synthesis, Characterization, DFT Study, Molecular Modelling and Biological Evaluation of Novel 5-Aryl-3-(pyridine-3-yl)isoxazole Hybrids as Potent Anticancer Agents with Inhibitory Effect on Skin Cancer

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A novel series of pyridinyl isoxazole derivatives was synthesized and characterized by IR, $^{1}$H and $^{13}$C NMR and high-resolution mass spectrometry. Geometrical and electronic properties of pyridinyl isoxazole derivative was investigated by using B3LYP/6-31G (d,p) basis sets. The HOMO and LUMO analysis was used to determine the charge transfer within the molecule. The pyridinyl isoxazole derivatives exhibited good docking scores against liver cancer 4MMH. The results revealed clearly compound **2b** exhibited better radical scavenging ability. Among the synthesized pyridinyl isoxazole derivatives, compound **2b** was highly active on the SKMEL cell line (human skin cancer).

**Keywords: 3-Acetylpyridine, Isoxazoles, DFT, Antioxidant, Anticancer, Docking.**

## INTRODUCTION

Cancer is a second serious leading cause of death and health problems in the worldwide and one of the leading cause of deaths in developed countries. Awareness and advances in treatment of the disease have led to reduce the cancer deaths, but the new novel number of new diagnoses continues [1]. Isoxazoles belong to an important class of five-membered aromatic heterocycles containing two electronegative heteroatoms, nitrogen and oxygen in the ring [2,3]. Owing to their good chemotherapeutic activity, isoxazole placed a dominant position in the medicinal and industrial chemistry [4].

Pyridine derivatives are the versatile building blocks for drug design and development due to their roles in biological processes, their diverse biological activities and their coordinating abilities [5,6]. Many anticancer drugs have these privileged structures [7]. These anticancer drugs act on various drug targets have been designed and developed. Cytotoxic agents such as naphthoquinone derivatives [8], coumarins [9] as well as fused pyridines/pyrimidines have been developed in recent years [10]. Skin cancer is one of the major causes of cancer-related deaths in the world. Isoxazole derivatives were used as antimalarial, anti-inflammatory, anti-hypolipidemic and antitumor activity [11,12].

Hence, the aim of present study attempt to investigate the synthesize, antioxidant, molecular modelling and anticancer study of pyridinyl isoxazole compounds. Computational results predict relatively accurate molecular vibrations and molecular structure of pyridinyl isoxazole derivatives.

## EXPERIMENTAL

The reagents and solvents used were of AR grade. All chemicals were purchased from Merck Specialties Pvt. Ltd and Sigma-Aldrich, USA. The spectra were recorded on Bruker Avance III, 400 MHz NMR spectrometer (400 MHz for $^{1}$H and 400 MHz for $^{13}$C NMR spectra), Waters UPLC-TQD mass spectrometer (ESI-MS and APCI-MS) for ESI mass spectra and Nicolet 400D FTIR spectrometer. Melting points were uncorrected. Elemental analysis was done at the Central Drug Research Institute, Lucknow, India. The computational study was carried out using Gaussian 09 program. The optimized geometry and electronic parameters of the compounds was performed using B3LYP/6-31G basis set. The molecular modelling

was done by using the Hex8.0 docking software and visualized by Discovery studio 3.5. Anticancer study done by MTT method.

**Synthesis of 5-aryl-3-(pyridine-3-yl)isoxazole (2a-e):** 3-Acetyl pyridine (**1**) was treated with commercially available aromatic aldehyde to form 5-aryl-3-(pyridine-3-yl)-2-propen-1-one (**2**). The compound 5-aryl-3-(pyridine-3-yl)-2-propen-1-one (0.01 mol), hydroxylamine hydrochloride (0.01) in the presence of sodium acetate and exactly 50 mL of ethanol with glacial acetic acid was added and refluxed for 6-10 h to afford the main compound **3** (**Scheme-I**). The obtained product was filtered, dried and recrystallized from ethanol (**Scheme-I**).

**5-Phenyl-3-(pyridine-3-yl)isoxazole (2a):** Yellow crystalline solid. Yield: 68%; m.p.: 158 ºC. Elemental analysis of $C_{14}H_{10}N_2O$ calcd. (found) %: C, 75.60 (75.66), H, 4.50 (4.54), N, 12.55 (12.60). FTIR (KBr, $cm^{-1}$): 3191 ν(C-H), 1583 ν(C=N), 1233 ν(C-N). $^1$H NMR: (400 MHz, DMSO-$d_6$) δ ppm: 8.511 (s, 1H,), 8.455 (d, 1H), 8.194-8.205 (m, 2H), 7.232 (d, 2H), δ 7.345-7.389 (m, 3H), δ 6.876 (s, 1H, isoxazole).

**5-(4-Chlorophenyl)-3-(pyridine-3-yl)isoxazole (2b):** Yellow crystalline solid. Yield: 64%; m.p.: 165 ºC. Elemental analysis of $C_{14}H_9N_2OCl$ calcd. (found) %: C, 65.59 (65.51); H, 3.59 (3.53); N, 10.98 (10.91). FTIR (KBr, $cm^{-1}$): 3147 ν(C-H), 1586 ν(C=N), 1230 ν(C-N). $^1$H NMR: (400 MHz, DMSO-$d_6$) δ ppm: 8.505 (s, 1H,), 8.468 (d, 1H), 7.433-7.454 (m, 3H), 7.968 (d, 1H), δ 6.808 (s, 1H, isoxazole), 7.341 (d, 2H).

**5-(4-Methylphenyl)-3-(pyridine-3-yl)isoxazole (2c):** Yellow crystalline solid. Yield: 50%; m.p.: 170 ºC. Elemental analysis of $C_{15}H_{12}N_2O$ calcd. (found) %: C, 76.33 (76.25); H, 5.20 (5.12); N, 11.80 (11.86). FTIR (KBr, $cm^{-1}$): 3141 ν(C-H), 1591 ν(C=N), 1257 ν(C-N). $^1$H NMR: (400 MHz, DMSO-$d_6$) δ ppm: 8.673 (s, 1H,), 8.489 (d, 1H), 7.393-7.491 (m, 3H), 6.703 (s, 1H, isoxazole), 7.912 (d, 1H), 7.124 (d, 2H), 3.405 (s, 3H). $^{13}$C NMR (400 MHz, DMSO-$d_6$) δ ppm: 153.03, 149.23, 148.72, 148.47, 147.97, 137.03, 134.20, 133.10, 129.25, 129.13, 126.75, 126.32, 123.68, 115.97, 20.88. ESI MS: $MH^+$ (237.5).

**5-(4-Methoxyphenyl)-3-(pyridine-3-yl)isoxazole (2d):** Yellow crystalline solid. Yield: 47%; m.p.: 156 ºC. Elemental analysis of $C_{15}H_{12}N_2O_2$ calcd. (found) %: C, 71.49 (71.42); H, 4.88 (4.79); N, 11.20 (11.10). FTIR (KBr, $cm^{-1}$): 3190 ν(C-H), 1583 ν(C=N), 1339 ν(C-N). $^1$H NMR: (400 MHz, DMSO-$d_6$) 8.512 (s, 1H,), 8.461 (d, 1H), 7.467-7.470 (m, 3H), 6.524 (s, 1H, isoxazole), 7.479 (d, 1H), 6.954 (d, 2H), 3.759 (s, 3H).

**5-(2-Phenylethenyl)-3-(pyridine-3-yl)isoxazole (2e):** Yellow crystalline solid. Yield: 55%; m.p.: 178 ºC. Elemental analysis of $C_{16}H_{12}N_2O$ calcd. (found) %: C, 77.60 (77.40); H, 4.90 (4.87); N, 11.30 (11.28). FTIR (KBr, $cm^{-1}$): 3025 ν(C-H), 1584 ν(C=N), 1333 ν(C-N). $^1$H NMR: (400 MHz, DMSO-$d_6$) 8.531 (s, 1H,), 8.519 (d, 1H), 7.712-7.868 (m, 2H), 7.339 (d, 2H), 7.118-7.181 (m, 3H), 6.562 (s, 1H, isoxazole), 6.986 (d, 2H).

**Antioxidant study:** Radical scavenging activity of the test sample against stable 2,2′-diphenyl 2-picrylhydrazyl hydrate (DPPH) was determined [13] with slight modification. For DPPH assay, the ascorbic acid was used as reference standard. The ascorbic acid stock solution was prepared in distilled water (1 mg/mL; w/v). A 60 µM solution of DPPH in methanol was freshly prepared and a 200 vL of this solution was mixed with 50 µL of test sample at various concentrations (1.56, 3.12, 6.25, 12.5, 25, 50 µg/mL). The tubes were kept in the dark for 15 min at room temperature and the decrease in absorbance was measured at 515 nm. Control was prepared with DPPH solution only, without any extract or ascorbic acid and 95% methanol was used as blank. Radical scavenging activity was calculated by the following formula:

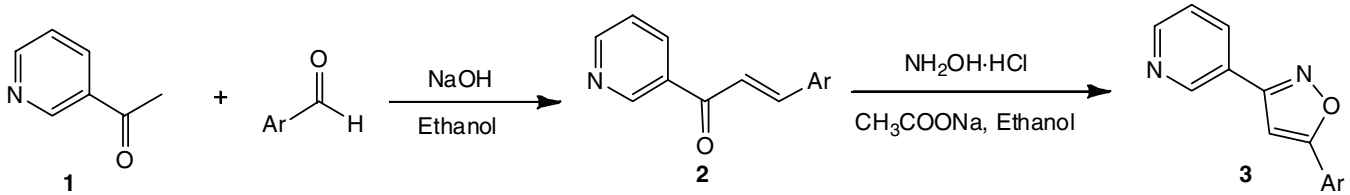
$$\text{Inhibition (\%)} = \frac{\text{Abs. of control at 0 min} - \text{Abs. of test}}{\text{Abs. of control at 15 min}} \times 100$$

## RESULTS AND DISCUSSION

The synthetic approach shows that the targeted compound can be obtained from 5-aryl-3-(pyridine-3-yl)-2-propen-1-ones and hydroxylamine hydrochloride. This reaction mechanism shows that the nucleophilc attack of hydroxylamine hydrochloride at the β-carbon of α,β-unsaturated carbonyl system leads ultimately to isoxazole. The homogeneity of compounds was noticed and purified by column chromatography (silica gel 60, 150 mesh) using chloroform as the eluent to obtain pure yellow crystals of compounds.

**Antioxidant study:** The DPPH assay was used to evaluate the free radical scavenging activities of pyridinyl isoxazole derivatives. The antioxidant activity of the synthesized compounds were also determined. Compound **2b** exhibited good radical scavenging activity because compound having substitution with electron withdrawing groups enhanced antioxidant activity against DPPH free radicals and their $IC_{50}$ values were found to be 110 µM. Moreover, compounds **2a**, **2c**, **2d** and **2e** showed moderate scavenging activity with $IC_{50}$ values 280, 203, 376 and 350 µM (Table-1).

**Anticancer study:** The high antioxidant potentiality of the synthesized compounds (**2a-e**) were examined for their anticancer activity against SKMEL cell line *in vitro* by MTT assay method. The *in vitro* cell viability test was conducted on the SKMEL cell line (human skin cancer) to determine the anticancer activity by MTT method. The results (Table-2) shows that the 5-(4-chlorophenyl)-3-(pyridine-3-yl)isoxazole (**2b**) has the highest anticancer potential ($IC_{50}$ 68.29 µg/mL).




**2a**:Ar = phenyl; **2b**: Ar = chlorophenyl; **2c**: Ar = methylphenyl; **2d**: Ar = methoxyphenyl; **2e**: Ar = phenylethenyl

**Scheme-I:** Retro synthetic approach of some new novel pyridine containing isoxazole derivatives

TABLE-1
ANTIOXIDANT STUDY OF 5-ARYL-3-(PYRIDINE-3-YL)ISOXAZOLE

| Compounds | $IC_{50}$ value (μM) |
|---|---|
| **2a** | 280 |
| **2b** | 110 |
| **2c** | 203 |
| **2d** | 376 |
| **2e** | 350 |
| Ascorbic acid (Std.) | 662 |

TABLE-2
ANTICANCER POTENTIAL OF5-(4-CHLOROPHENYL)-3-(PYRIDINE-3-YL)ISOXAZOLE (**2b**)

| Concentration (μg/mL) | Viability (%) | $IC_{50}$ value (μg/mL) |
|---|---|---|
| 6.25 | 82.40 | 68.29 |
| 12.5 | 71.87 | |
| 25 | 61.80 | |
| 50 | 51.18 | |
| 100 | 41.24 | |

**Geometrical optimization study:** The optimized geometry and the structural features of all the five synthesized compounds was investigated and optimized with the help of B3LYP/6-31G(d,p) level of DFT method using Gaussian 09 software program package [14]. The geometrical parameters like bond length, bond angles, dihedral angles are given in Table-3. Structural optimization of compound **2a** with numbering of the atoms is shown in Fig. 1. The components of atomic orbital like HOMO and LUMO and the distribution pattern of pyridinyl isoxazole derivatives **2a** are shown in Fig. 2.

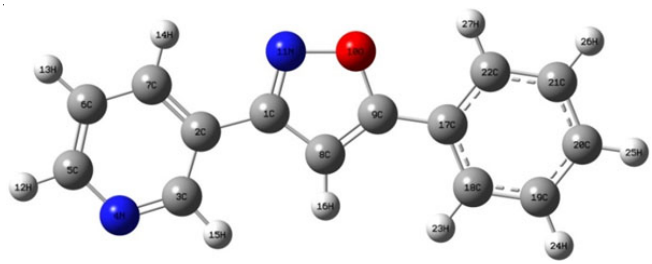


Fig. 1. Optimized structure of 5-phenyl-3-(pyridine-3-yl)isoxazole (**2a**)

The frontier molecular orbitals (FMOs) of compound **2a** shows that the transferring of electrons from the phenyl ring towards isoxazole ring due to HOMO-LUMO excitation. Then we compared the frontier molecular orbitals of pyridinyl isoxazole derivatives at the ground state, the HOMO is delocalized over the phenyl moiety whereas the LUMO is placed over the isox-azole moiety. HOMO and LUMO analysis of compounds like ionization potential, electronegativity, softness, hardness

TABLE-3
OPTIMIZED GEOMETRICAL PROPERTIES OF 5-PHENYL-3-(PYRIDINE-3-YL)ISOXAZOLE AT THE B3LYP-6-31G BASIS SET (**2a**)

| Parameters | Bond length (Å) | Parameter | Bond angle (°) | Parameter | Dihedral angle (°) |
|---|---|---|---|---|---|
| C1-C2 | 1.468 | C1-C2-C3 | 121.246 | C1-C2-C3-N4 | -179.992 |
| C2-C3 | 1.404 | C2-C3-N4 | 123.465 | C5-N4-C3-H15 | 179.995 |
| C3-N4 | 1.348 | C3-N4-C5 | 118.081 | C3-N4-C5-H12 | 180.000 |
| N4-C5 | 1.351 | N4-C5-C6 | 122.625 | N4-C5-C6-H13 | -179.998 |
| C5-C6 | 1.399 | C5-C6-C7 | 118.967 | C5-C6-C7-H14 | 179.990 |
| C6-C7 | 1.394 | C6-C7-C2 | 119.204 | C3-C2-C7-H14 | -179.994 |
| C7-C2 | 1.408 | C1-C8-C9 | 105.855 | C7-C2-C3-H15 | -179.995 |
| C1-C8 | 1.431 | C8-C9-O10 | 108.597 | C2-C1-N11-O10 | -179.995 |
| C8-C9 | 1.371 | C9-O10-N11 | 108.915 | C2-C1-C8-C9 | 179.996 |
| C9-O10 | 1.386 | O10-N11-C1 | 104.741 | H16-C8-C9-O10 | 179.998 |
| O10-N11 | 1.446 | C2-C3-H15 | 121.010 | C8-C9-C17-C22 | -179.993 |
| N11-C1 | 1.337 | N4-C3-H15 | 115.523 | C17-C18-C19-H24 | 179.998 |
| C3-H15 | 1.084 | N4-C5-H12 | 116.138 | H23-C18-C19-C20 | -179.999 |
| C5-H12 | 1.084 | C5-C6-H13 | 120.271 | C18-C19-C20-H25 | -179.997 |
| C6-H13 | 1.084 | C6-C7-H14 | 121.291 | C19-C20-C21-H26 | 179.996 |
| C7-H14 | 1.083 | C1-C8-H16 | 127.019 | C21-C20-C19-H24 | -179.998 |
| C8-H16 | 1.076 | C9-C17-C18 | 120.339 | C20-C21-C22-H27 | -179.999 |
| C9-C17 | 1.457 | C17-C18-C19 | 120.356 | C18-C17-C22-H27 | 180.000 |
| C17-C18 | 1.408 | C18-C19-C20 | 120.191 | C9-C17-C22-C21 | -179.998 |

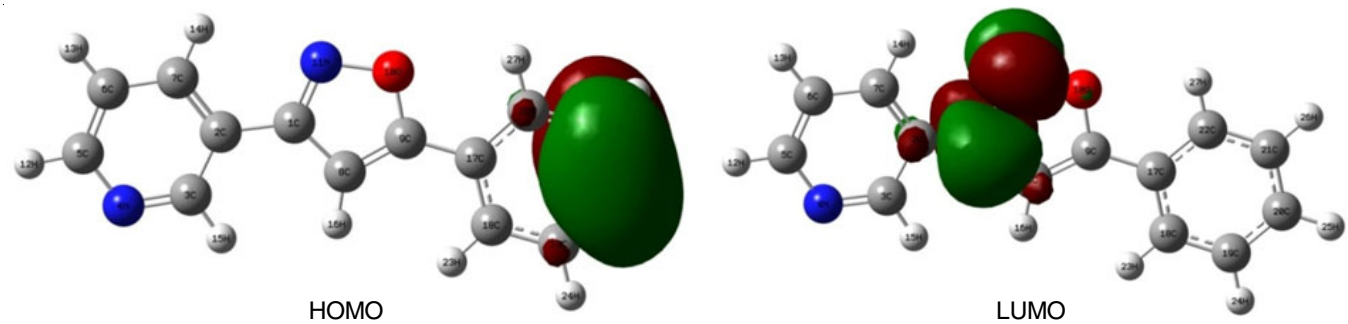



Fig. 2. Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of 5-phenyl-3-(pyridine-3-yl)isoxazole (**2a**)

TABLE-4
ELECTRONIC PROPERTIES OF 5-ARYL-3-(PYRIDINE-3-YL)-1*H*-PYRAZOLES (**2a-e**)

| Parameters (a.u) | B3LYP/6-31G | | | | |
|---|---|---|---|---|---|
| | **2a** | **2b** | **2c** | **2d** | **2e** |
| $E_{HOMO}$ | -0.2569 | -0.2693 | -0.2511 | -0.2588 | -0.2509 |
| $E_{LUMO}$ | -0.0185 | -0.0241 | -0.0162 | -0.0072 | -0.0167 |
| ΔE | 0.2384 | 0.2452 | 0.2349 | 0.2516 | 0.2342 |
| Ionization potential | -0.2569 | -0.2693 | -0.2511 | -0.2588 | -0.2509 |
| Electron affinity (A) | -0.0185 | -0.0241 | -0.0162 | -0.0072 | -0.0167 |
| Electronegativity (χ) | 0.1377 | 0.1467 | 0.1336 | 0.1330 | 0.1338 |
| Hardness (η) | 0.1192 | 0.1226 | 0.1174 | 0.1258 | 0.1171 |
| Softness (S) | 4.1946 | 4.0783 | 4.2589 | 3.9745 | 4.2698 |

(**2a-e**) along with their energy gaps and the reactivity analysis of the synthesized compounds (**2a-e**) were calculated and are listed in Table-4. Among all the five compounds, compound **2d** showed the highest HOMO-LUMO energy gap, *i.e.* 0.2516 eV, while compound **2e** showed the smallest energy gap *i.e.* 0.2342 eV.

The Mulliken atomic charge values were obtained from the Mulliken population analysis. The charge distribution structure of compound **2a** is shown in Fig. 3. The corresponding characteristics of the atomic charge population of the constituent atoms are presented in Table-5. All the hydrogen atoms having positive Mulliken atomic charge. Nitrogen and oxygen atoms possess negative Mulliken atomic charge. Carbon atoms having positive or negative charge depending upon the neighbouring atoms. The proton transfer of pyridinyl isoxazole compounds has been investigated here using reactivity indices. From the electronic properties results, it is clear that among all the compounds, compound **2d** has the highest value of hardness (0.1258 eV) whereas compound **2e** has the lowest value of hardness (η) *i.e.* 0.1171 eV. Compound **2b** has the lowest chemical potential value (-0.2693 eV), while compound **2e** has the highest ionization potential (I) value (-0.2509 eV). The results clearly indicate that compound **2b** has the highest value of electron affinity (A) 0.1467eV whereas the compound **2d** has the lowest electron affinity (A) value 0.1330 eV. In addition, among the five synthesized compounds, compound **2d** has the lowest value of electronegativity (0.1330 eV) and the compound **2b** has the highest electronegativity (χ) value (0.1467 eV. Among all the synthesized compounds, compound **2e** (4.2698 eV) has the highest value of softness and compound **2d** (3.9745 eV) having lowest value of softness (Table-4).

**Molecular modelling:** In present study, the selected receptor docked with different pyridinyl isoxazole derivatives and the energy values were obtained. The synthesized compounds were analyzed for the Lipinski rule of five, which shows

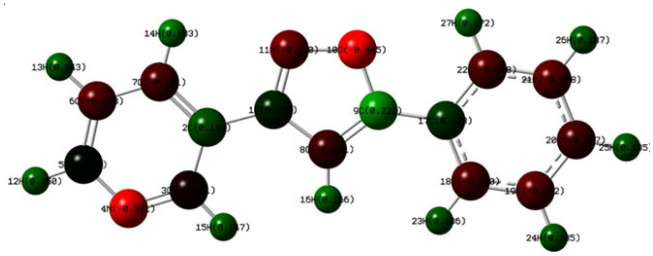


Fig. 3. Mulliken atomic charge distribution of 5-phenyl-3-(pyridine-3-yl)isoxazole (**2a**)

TABLE-5
MULLIKEN ATOMIC CHARGE DISTRIBUTION OF 5-PHENYL-3-(PYRIDINE-3-YL)ISOXAZOLE (**2a**)

| Atom | Mulliken charge | Atom | Mulliken charge |
|---|---|---|---|
| C1 | 0.049 | H15 | 0.147 |
| C2 | 0.119 | H16 | 0.166 |
| C3 | -0.031 | C17 | 0.078 |
| N4 | -0.371 | C18 | -0.120 |
| C5 | 0.011 | C19 | -0.142 |
| C6 | -0.128 | C20 | -0.107 |
| C7 | -0.111 | C21 | -0.138 |
| C8 | -0.091 | C22 | -0.128 |
| C9 | 0.222 | H23 | 0.136 |
| O10 | -0.445 | H24 | 0.135 |
| N11 | -0.170 | H25 | 0.135 |
| H12 | 0.150 | H26 | 0.137 |
| H13 | 0.143 | H27 | 0.172 |
| H14 | 0.183 | | |

whether the chemical compound has certain biological activities or not (Table-6). The synthesized ligand were docked into the active site of the protein heparan sulfate lyase HepC mutant from Pedobacter heparinus (PDB code: 4MMH). Molecular docking between ligands and the protein 4MMH were analyzed and visualized using Hex 8.0 docking software. The 2D pose of the compounds are visualized using the Discovery studio

TABLE-6
LIPINSKI RULE OF 5-ARYL-3-(PYRIDINE-3-YL)ISOXAZOLES (**2a-e**)

| Compound | Molecular weight < 500 Dalton | HB donar < 5 | HB acceptor < 10 | log P < 5 | Molecular refractivity 40-130 |
|---|---|---|---|---|---|
| **2a** | 222 | 0 | 2 | 3.40 | 65.17 |
| **2b** | 256 | 0 | 2 | 4.05 | 70.18 |
| **2c** | 236 | 0 | 2 | 3.71 | 70.13 |
| **2d** | 252 | 0 | 3 | 3.41 | 71.66 |
| **2e** | 248 | 0 | 2 | 3.90 | 75.10 |

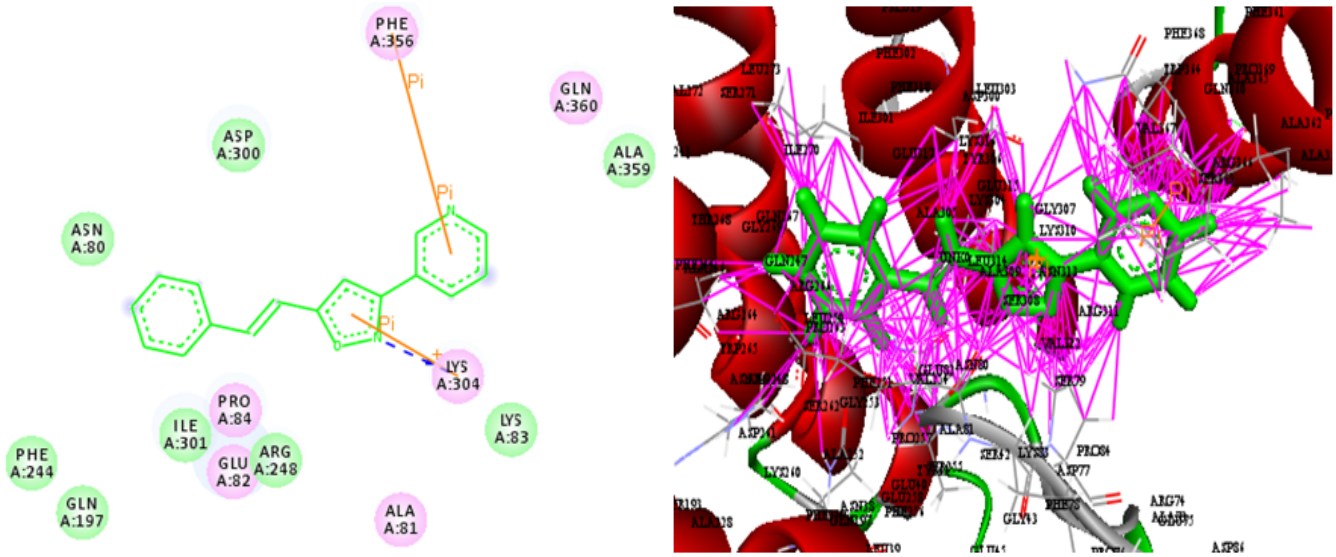



Fig. 4. 2D and 3D representations of the compound **2e** and the receptor (4MMH)

TABLE-7
BINDING ENERGY AND INTERACTION OF THE COMPOUNDS (**2a-e**) WITH THE PROTEIN 4MMH

| Compd. | Binding energy (kJ/mol) | Active sites of interactions | | | | | |
|---|---|---|---|---|---|---|---|
| | | π-σ interactions | π-cation interactions | π-π interaction | Electrostatic | van der Waals | Covalent bond |
| **2a** | -228.63 | – | ARG A:356 | – | ARG A:356, LYS A:304, ILE A:87, SER A:363 | GLN A:360, PRO A:84, SER A:79, ARG A:311, PHE A:78 | – |
| **2b** | -233.11 | – | ARG A:311, ARG A:88, ARG A:366 | – | ARG A:311, ARG A:88, GLU A:75 | ARG A:366, ALA A:85, PRO A:84 | ARG A:311 |
| **2c** | -234.36 | – | LYS A:304 | PHE A:356, LYS A:304 | PHE A:356, LYS A:304, GLU A:82, ALA A:81 | PRO A:84, ASP A:300, ALA A:297 | LYS A:304 |
| **2d** | -235.59 | – | – | PHE A:356 | LYS A:304, GLU A:82, GLN A:360 | PHE A:356, ALA A:359, PRO A:84, SER A:363 | LYS A:304 |
| **2e** | -242.40 | – | LYS A:304 | PHE A:356 | LYS A:304, PHE A:356, PRO A:84, GLN A:360 | ALA A:359, LYS A:83, ASP A:300, ASN A:80 | LYS A:304 |

3.5 visualizer. Among all the compounds, compound **2e** has less binding energy which indicates a greater binding interaction with the receptor protein 4MMH (Fig. 4). The results (Tables 6 & 7) clearly explore the less binding energy of the molecule indicates a greater interaction with the receptor protein. On the basis of docking results, all the five compounds posses good docking score and highly active, so it is concluded that it possess high agreements with the liver cancer cell.

## Conclusion

Some novel compounds 5-aryl-3-(pyridine-3-yl)isoxazoles were successfully synthesized by the reaction between 3-acetylpyridine and different aromatic aldehyde and characterized. All the compounds were evaluated for their antioxidant activity using by DPPH free radical scavenging assay. Among all the synthesized compounds, compound **2b** posess highest antioxidant potential and also proved very good cytotoxic activity against SKMEL cell line. The structural optimization and the parameters were calculated by using B3LYP/6-31G-(d,p) basis set. The HOMO and LUMO analysis clearly indicated that the compounds with lower HOMO-LUMO band gap has higher biological activities.

## ACKNOWLEDGEMENTS

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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