Synthesis, molecular docking studies, anticancer and antibacterial activities of some novel Dinuclear Nickel (II) Complexes 2, 4-Dihydroxy acetyl-4-Hydroxybenzoic Hydrazone

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INTRODUCTION

The term ligand, concerning silicon chemistry, was first coined by Alfred Stock and Carl Somiesky. A ligand is a co-ordination chemistry ion or molecule or functional group bound to a central metal atom to create a co-ordination compound (Hote and Lokhande, 2014; Rizvi et al., 2012). In general, the bond between metal and ligand requires a formal donation of one or more electron pairs of the ligand (Ventura et al., 2015). The essence of bonding with metal ligands can vary from covalent to ionic. Other orders for metal ligand bonds range from one to two. Ligands are regarded as the pillars of Lewis. In a complex, ligands dictate the central metal atom's reactivity. In several practical fields, including bioinorganic chemistry, medicinal chemistry, homogeneous catalysis and environmental chemistry, the selection of ligand is crucial (Rücker et al., 2015). Ligational behavior of hydrazine ligands towards transition metal ions is expected to be very interesting. The co-ordination chemistry of hydrazine transition metal complexes has been of interest due to different binding modes shown by these ligands (Fang et al., 2014). Metal complexes of pyridyl ligands are found to show excellent DNA binding properties (Kamal et al., 2014; Wasylyk et al., 2008).

Hence, we have selected 2-acetyl pyridine and 2-benzoyl pyridine precursors for the synthesis of hydrazine ligands. A series of hydrazine ligands are prepared by varying the functional groups (Jin et al., 2014).
Hydrazone ligands have been characterized based on analytical data, I.R. spectra, H-NMR and mass spectral analysis (Kumar et al., 2013, 2011).

**MATERIALS AND METHODS**

Melting points have been measured by the open capillary system using the electrical melting point apparatus and are uncorrected. I.R. spectra were registered in KBr on a Shimadzu FTIR 8400S spectrophotometer. On Bruker DPX 400 solvent spectrophotometers, 1H NMR (400 MHz) and 13C NMR (100 MHz) spectra were reported using Internal Standard Tetramethyl silane (TMS), DMSO-d6 and CDCl3 as solvents. HRMS spectra were recorded, and thin-layer chromatography (TLC) was performed on Xevo QT of mass spectrometers to test the purity of compounds under U.V. light and iodine vapour (Dong et al., 2013).

**Synthesis of Ligands and Complexes**

(i) **Synthesis of 2-acetyl pyridine acetoyl hydrazone (APAH)**

2.22 g acetyl pyridine broke down in a 100 ml base carafe in 20 ml of methanol for hot methanol (20 ml) of 2-acetyl pyridine (0.03 mol, 3.36 ml). The response blend was enhanced with frosty acidic corrosive (3-4 drops). These were kept in a water shower for 2 hours, afterwards temperature reduced to normal temperature. After filtration, the crystal synthesized compound created collected, washed a few times with high temp water and vacuum-dried. It was methanol recrystallized (Kamal et al., 2014).

Yield: 85%; M.P: 162-164 °C

(ii) **2-acetyl pyridine benzoyl hydrazone synthesis (APBH)**

A hot methanol (20 ml) solution of 2-acetyl pyridine (0.02 mol, 2.24 ml), in a 100 ml round lower flask was applied to the hot methanol solution (0.02 mol, 2.24 ml). The response blend was enhanced with frosty acidic corrosive (3-4 drops). These were kept in a water shower for 2 hours, afterwards temperature reduced to normal temperature. After filtration, the crystal synthesized compound created collected, washed a few times with high temp water and vacuum-dried. It was methanol recrystallized.

Yield: 80%; M.P: 145-147 °C

(iii) **Synthesis of 2-acetoyl hydrazone benzoyl pyridine (BPAH)**

1.48 g of acetic hydrazide (0.02 mol) dissolved in 20 ml of methanol was applied to the 2-benzoyl pyridine (0.02 mol, 3.66 g) hot methanol solution (20 ml). The response blend was enhanced with frosty acidic corrosive (3-4 drops). These were kept in a water shower for 2 hours, afterwards temperature reduced to normal temperature. After filtration, the crystal synthesized compound created collected, washed a few times with high temp water and vacuum-dried. It was methanol recrystallized (Syam et al., 2012).

Yield: 78%; M.P: 140-145° C

(iv) **2-benzoyl pyridine benzoyl hydrazone synthesis (BPBH)**

In a hot methane solution (20 ml) of 2-benzoyl pyridine (3.66 g, 0.02 mol) in a 100 ml round bottom flask, a solution of benzhydrazide (2.72 g, 0.02 mol) has been added in 20 ml of methanol. A few drops of glacial acetic acid have been added. The response blend was enhanced with frosty acidic corrosive (3-4 drops). These were kept in a water shower for 2 hours, afterwards temperature reduced to normal temperature. After filtration, the crystal synthesized compound created collected, washed a few times with high temp water and vacuum-dried. It was methanol recrystallized (Liang et al., 1998).

Yield: 72%; M.P: 135-137° C
Table 1: Physico-chemical and analytical data of ligands.

| Ligand   | Molecular Formula | Molecular Weight | Color (Yield) | Melting Point | Elemental analysis* |
|----------|------------------|------------------|---------------|---------------|-------------------|
| APAH     | C₉H₁₁N₃O        | 177              | Colourless (85%) | 162-164°C     | C 61.32 (61.0)   |
|          |                  |                  |               |               | H 6.50 (6.25)     |
|          |                  |                  |               |               | N 24.01 (23.71)   |
| APBH     | C₁₄H₁₃N₃O       | 239              | Pale white (80%) | 145-147°C     | C 70.89 (70.27)  |
|          |                  |                  |               |               | H 5.50 (5.47)     |
|          |                  |                  |               |               | N 17.12 (17.56)   |
| BPAH     | C₁₄H₁₃N₃O       | 239              | Yellow (83%)   | 87-90°C       | C 71.2 (70.27)  |
|          |                  |                  |               |               | H 5.70 (5.47)     |
|          |                  |                  |               |               | N 17.96 (17.56)   |
| BPBH     | C₁₉H₁₅N₃O       | 301              | Pale yellow (72%) | 135-137°C     | C 75.89 (75.72)  |
|          |                  |                  |               |               | H 5.23 (5.01)     |
|          |                  |                  |               |               | N 14.02 (13.94)   |

*Calculated values are given in the parenthesis.

Table 2: I.R. spectra and their tentative assignments.

| Ligand   | ν(N-H) | ν(C=O) | ν(C=N) |
|----------|--------|--------|--------|
| APAH     | 3185   | 1678   | 1620   |
| APBH     | 3177   | 1654   | 1616   |
| BPAH     | 3454   | 1666   | 1586   |
| BPBH     | 3453   | 1685   | 1598   |

Metal Complexes Synthesis

[Ni(APAH)Cl]Cl₂ synthesis

APAH (0.88g, 5mmol) and NiCl₂.6H₂O (1.18g, 5 mmol) were mixed with methanol (20ml) and refluxed over 2 hours in a clean 100ml round bottom flask. The response blend was enhanced with frosty acidic corrosive (3-4 drops). These were kept in a water shower for 2 hours, afterwards temperature reduced to normal temperature. After filtration, the crystal synthesized compound created collected, washed a few times with high temp water and vacuum-dried. It was methanol recrystallized. Yield: 63%; M.P: 291-293 °C

[Ni(APBH)Cl]Cl₂ synthesis

The APBH methanol solution (0.95 g and 4 mmol) added the methanol NiCl₂.6H₂O solution (0.94 g) (20 ml) and heated the reflux reaction mixture for 2 hours. The response blend was enhanced with frosty acidic corrosive (3-4 drops). These were kept in a water shower for 2 hours, afterwards temperature reduced to normal temperature. After filtration, the crystal synthesized compound created collected, washed a few times with high temp water and vacuum-dried. It was methanol recrystallized. Yield: 47%; M.P: > 300 °C (D)

[Ni(BPAH)Cl]Cl₂ synthesis

The BPAH methanol solution (0.95 g and 4 mmol) added the methanol NiCl₂.6H₂O solution (0.94 g) (20 ml) of APAH (0.95 g, 4 mmol) and NiCl₂.6H₂O (0.94 g, 4 mmol) dissolved in methanol (20 ml) in a 1:1 ratio and the contents were refluxed in a water bath for 2 hr. The response blend was enhanced with frosty acidic corrosive (3-4 drops). These were kept in a water shower for 2 hours, afterwards temperature reduced to normal temperature. After filtration, the crystal synthesized compound created collected, washed a few times with high temp water and vacuum-dried. It was methanol recrystallized. Yield: 52%; M.P: 285-287 °C

Synthesis of [Ni(BPBH)Cl]Cl₂

It was prepared by mixing, in a clean 100 ml round bottom flask, hot methanol solution (20 ml) of BPBH (1.2 g, 4 mmol) and NiCl₂.6H₂O (0.94 g, 4 mmol) dissolved in methanol (20 ml) in a 1:1 ratio and the contents were refluxed in a water bath for 2 hr. The response blend was enhanced with frosty acidic corrosive (3-4 drops). These were kept in a water shower for 2 hours, afterwards temperature reduced to normal temperature. After filtration, the crystal synthesized compound created collected, washed a few times with high temp water and vacuum-dried. It was methanol recrystallized. Yield: 55%; M.P: > 300 °C (D)

[Ni(APAH)CH₃COO]Cl₂ syntheses

Hot methanol (20ml) solution APAH (1.77g, 10 mmol) and methanolic (20 ml) solution Ni(CH₃COO)₂.4H₂O (1.24 g, 5 mmol) were mixed and refluxed for 2 hr in a clean 100 ml round bottom flask.
flask. The response blend was enhanced with frosty acidic corrosive (3-4 drops). These were kept in a water shower for 2 hours, afterwards temperature reduced to normal temperature. After filtration, the crystal synthesized compound created collected, washed a few times with high temp water and vacuum-dried. It was methanol recrystallized 45% yield; M.P: 276-278 0C (D)

\[\text{Ni(ABPH)}\text{CH}_2\text{COO}\] \_synthesis

The complex was prepared by mixing in a clean 100 ml round bottom flask hot methanol solution (20 ml) of APBH (1.91 g, 8 mmol) and Ni(CH\_3COO)\_2\cdot4H\_2O (0.99 g, 4 mmol) dissolved in methanol (20 ml) in a 2:1 ratio and the contents were refluxed in a water bath for 3 hr. The response blend was enhanced with frosty acidic corrosive (3-4 drops). These were kept in a water shower for 2 hours, afterwards temperature reduced to normal temperature. After filtration, the crystal synthesized compound created collected, washed a few times with high temp water and vacuum-dried. It was methanol recrystallized.

Yield: 42%; M.P: 298-300 0C (D)

\[\text{Ni(BPAH)}\text{CH}_2\text{COO}\] \_Synthesis

A methanolic solution (20 ml) of Ni(CH\_3COO)\_2\cdot4H\_2O (0.99 g, 4 mmol) was applied to the methanolic solution (20 ml) of BPAH (1.91 g, 8 mmol) and the reaction mixture was heated under reflux for 3 hr. The response blend was enhanced with frosty acidic corrosive (3-4 drops). These were kept in a water shower for 2 hours, afterwards temperature reduced to normal temperature. After filtration, the crystal synthesized compound created collected, washed a few times with high temp water and vacuum-dried. It was methanol recrystallized.

Yield: 63%; M.P: 285-287 0C (D)

\[\text{Ni(BPBH)}\text{CH}_2\text{COO}\] \_Synthesis:

A methanolic solution (20 ml) of Ni(CH\_3COO)\_2\cdot4H\_2O (0.99 g, 4 mmol) was applied to a methanolic solution (20 ml) of BPBH (2.4 g, 8 mmol) and the reaction mixture was heated under reflux for 3 hours. The response blend was enhanced with frosty acidic corrosive (3-4 drops). These were kept in a water shower for 2 hours, afterwards temperature reduced to normal temperature. After filtration, the crystal synthesized compound created collected, washed a few times with high temp water and vacuum-dried. It was methanol recrystallized 55 percent yield; M.P: 300-302 0C (D). The general structure of ligands is depicted in Figure 1.

Where \(R_1\) \(R_2\) Name of the Ligand

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{A general structure of ligands.}
\end{figure}

CH\_3 C\_2 H\_5 2-acetyl pyridine acetoxy hydrazone
CH\_3 C\_6 H\_5 2-acetyl pyridine benzoyl hydrazone
C\_6 H\_5 C\_2 H\_5 2-benzoyl pyridine acetoxy hydrazone
C\_6 H\_5 C\_2 H\_5 2-benzoyl pyridine benzoyl hydrazone

**Antibacterial activity test**

Escherichia coli (MTCC 2692), Pseudomonas aeruginosa (MTCC 2453), Staphylococcus aureus (MTCC 902) and Bacillus subtilis (MTCC 441) were analyzed for in vitro antibacterial activity of the compounds by the cup plate method using literature protocol (Daddam et al., 2020a). The stock solution of the antibiotic was prepared as 1000\(\mu\)g/1ml (1mg/1ml). Prepared dilutions of the antibiotic of known concentration of the standard and the test antibiotic to be examined, sterilized the Muller-Hinton agar medium in an autoclave at 121\(^0\)C at 15 lbs pressure for 15 minutes. Added 1ml suspension of standard test organism to Muller Hinton medium and mixed thoroughly while maintaining the temperature at 50\(^0\)C. Poured the above mixture into a petri dish to form a layer of about 3mm thickness, allowed the medium to solidify and cut the reservoirs/cup with a sharp tool such as cork borer and removed the cylindrical plugs with a scalpel or sharp forceps.

Marked the cups as per dilutions and added in each cup the respective dilutions of the antibiotic, kept the plate carefully in the refrigerator for the diffusion of antibiotic for 20 minutes. The condensed water was wiped carefully from the lid of the Petri dish, with the sterile cotton plugs and incubated the Petri dish at 37\(^0\)C for 18-24 hrs. Recorded the size of the zone of inhibition against each cavity and the size is measured in mm with the help of antibiotic zone reader. The antibacterial activity of the samples is measured with the various sample concentrations low, medium and large.

**Anti-cancer activity test**

Human lung carcinoma cell lines (A549) were obtained from NCCS Pune. They have been preserved with 10% Fetal Bovine Serum in the medium RPMI 1640. In a humidified atmosphere CO2 incubator and 5% CO2, the cells converged at 37\(^0\)C. Sow
Table 3: $^1$H-NMR Spectral data of ligands.

| Ligand | Chemical Shift (δ) | Multiplicity | No. of Protons | Assignment                                      |
|--------|-------------------|--------------|----------------|-----------------------------------------------|
| APAH   | 2.45              | Singlet      | 3              | -CH$_3$ Group                                 |
|        | 2.45              | Singlet      | 3              | -CH$_3$ Group                                 |
|        | 7.25              | Singlet      | 1              | -N.H. Group                                   |
|        | 7.75-7.85         | Multiplet    | 4              | Pyridine                                      |
| APBH   | 2.51              | Singlet      | 3              | -CH$_3$ Group                                 |
|        | 7.25              | Singlet      | 1              | -N.H. Group                                   |
|        | 7.75-7.85         | Multiplet    | 9              | The aromatic ring (Pyridine, Phenyl)          |
| BPAH   | 1.82              | Singlet      | 3              | -CH$_3$ Group                                 |
|        | 7.45              | Singlet      | 1              | -N.H. Group                                   |
|        | 7.42-8.84         | Multiplet    | 9              | The aromatic ring (Pyridine, Phenyl)          |
| BPBH   | 7.22              | Singlet      | 1              | -N.H. Group                                   |
|        | 7.32-8.84         | Multiplet    | 13             | Aromatic ring (2 Phenyl, pyridine)            |

Table 4: Antibacterial activity of compounds.

| Compound | Microorganism | Ampicillin (Conc.) | Zone of inhibition (mm) |
|----------|---------------|--------------------|-------------------------|
|          |               | 10 μl  | 20 μl  | 30 μl  | 10 μl  | 20 μl  | 30 μl  |
| Standard | *E.Coli*      | 2.0    | 2.2    | 2.4    | 2.0    | 2.2    | 2.5    |
|          | *Pseudomonas* | 1.6    | 2.1    | 2.4    | 2.0    | 2.1    | 2.2    |
|          | *S.aureus*    | 1.7    | 1.8    | 2.2    | 2.1    | 2.2    | 2.4    |
|          | *Bacillus*    | 2.4    | 2.6    | 2.7    | 2.1    | 2.5    | 2.7    |
| APAH     | *E.Coli*      | 1.6    | 2.1    | 2.4    | 3.0    | 3.1    | 3.2    |
|          | *Pseudomonas* | 2.0    | 2.2    | 2.4    | 2.0    | 2.2    | 2.5    |
|          | *S.aureus*    | 1.7    | 1.8    | 2.2    | 2.1    | 2.2    | 2.4    |
|          | *Bacillus*    | 2.0    | 2.2    | 2.4    | 2.0    | 2.2    | 2.5    |
| APBH     | *E.Coli*      | 3.0    | 3.2    | 3.4    | 3.0    | 3.2    | 3.5    |
|          | *Pseudomonas* | 1.0    | 1.2    | 1.4    | 1.0    | 1.2    | 1.5    |
|          | *S.aureus*    | 1.0    | 1.2    | 1.4    | 1.0    | 1.2    | 1.5    |
|          | *Bacillus*    | 3.0    | 3.3    | 3.5    | 3.0    | 3.3    | 3.5    |
| BPAH     | *E.Coli*      | 2.0    | 2.2    | 2.4    | 2.0    | 2.2    | 2.5    |
|          | *Pseudomonas* | 2.0    | 2.2    | 2.4    | 2.0    | 2.2    | 2.5    |
|          | *S.aureus*    | 2.0    | 2.2    | 2.4    | 3.0    | 3.2    | 3.5    |
|          | *Bacillus*    | 2.0    | 2.2    | 2.4    | 2.0    | 2.2    | 2.5    |
| BPBH     | *E.Coli*      | 2.2    | 2.5    | 2.7    | 2.6    | 3.2    | 3.5    |
|          | *Pseudomonas* | 3.0    | 3.2    | 3.4    | 3.0    | 2.8    | 3.0    |
|          | *S.aureus*    | 2.5    | 2.7    | 3.1    | 1.8    | 2.2    | 2.7    |
|          | *Bacillus*    | 2.0    | 2.2    | 2.4    | 2.0    | 2.2    | 2.5    |
Table 5: Cytotoxic activity of 2, 4-Dihydroxy acetyl-4-Hydroxybenzoic Hydrazone complexes.

| Compound | (IC50 μg/mL) |
|----------|-------------|
| APAH     | 40.0± 0.01  |
| APBH     | 42.33 ± 0.02|
| BPAH     | 43.94 ± 0.01|
| BPBH     | 44.35 ± 0.02|
| A549 (SD)| 34.36 ± 0.02|

200μl of cell suspension on a 96-well plate at the target cell density (20,000 cells per well), without the test material. Enable cells to extend for approximately 12 hours. Test samples were separately applied to the grown-up cells in a concentration of 25μg, 50μg, 75μg, 100μg, 125μg/mL of the compound and 40μg/mL of medication, while the plate was incubated 24 hours at 37 °C in a 5 per cent CO2 atmosphere. After the incubation time, the plates were removed from the incubator, and the spent media were removed.

The MTT reagent (Camptothecin) was applied to the final concentration of 0.5 mg/mL, and the plates were placed in the incubator and incubated for 3 hours. A linear regression equation was used to obtain the IC50 value (Kurjogi et al., 2018).

i.e. Y=Mx+C.

Here, Y = 50, M and C values were derived from the viability graph.

**Molecular Docking method**

Homo sapiens BCL2 structure was extracted from the PDB database. Hydrogen has been added to the protein and used to identify an active site after SPDBV software removed from unwanted chains and hetero-atoms. BCL2 Active sites were found with the CASTp server. A new CASTp programme focuses on accurate calculation methods, including alpha-shaped methods and theory of discrete flow, for the automated position and measurement of protein pockets and cavities. CASTp identifies and checks openings of pockets and pocket mouths and cavities. The software describes the lining pockets of the atoms, pocket openings and buried cavities, the amount and area of pockets and cavities, and the area of openings in the mouth (Daddam et al., 2020b).

Docking was done with the software GOLD (Genetic Optimization of Ligand Docking) based on genetic algorithms (G.A.). This technology enables partial protein flexibility and maximum ligand flexibility. The compounds are bound to the active site of the BCL2 (Hussein et al., 2017). The interaction of these compounds with the active site residues will be extensively investigated using molecular mechanics equations.

The parameters used for G.A. were population size (100), selection pressure (1.1), number of operations (10,000), island number (1) and niche size (2). Operator parameters for crossover, mutation and migration have been set at 100, 100 and 10, respectively. The default cutoff values for the vander Waals were 3.0 Å (dH-X) and 6.0 Å hydrogen bonds. During docking, the default algorithm speed was chosen, and the BCL2 ligand binding position was specified as GLN111’s C.E. atom within a radius of 10°C with the centroid.
The number of positions was set at 100 for each inhibitor, and the early termination was allowed if the top three ligand conformance were less than 1.5Å RMSD. When docked, each ligand’s binding poses were observed, and its interactions with the protein were analyzed.

The best and most energetically favorable conformation of each ligand was selected (Kumar et al., 2017). Gold Score plays a force-based scoring role and consists of four components: 1. Protein-ligand hydrogen bond energy (external H-bond); 2. Protein-ligand energy of waals (external vdw); 3. ligand inner vander of waals (internal vdw); 4. ligand intramolecular bond of hydrogen (internal-h-bond).

The external VDW score is multiplied by a factor of 1.375 when the overall fitness score is determined. This is an empirical correction to facilitate hydrophobic co-ordination between protein and the ligand. The exercise function has been optimized to predict ligand binding positions.

RESULTS AND DISCUSSION

(i) Elemental analysis
The results obtained in the elemental analysis are in agreement with their molecular formulae of respective ligands. The ligands are sparingly soluble in water, soluble in methanol but readily soluble in DMF, DMSO and CH₃CN. Physicochemical and analytical data of ligands are presented in Table 1.

(ii) Infrared spectral analysis
The infrared spectra of all ligands were reported in the medium KBr region 4000-450 cm\(^{-1}\). Table 2 offers significant I.R. spectral bands and their temporary assignments. Figure 2 displays a standard FT-IR APBH spectrum. For \(\tilde{\delta}(\text{N-H})\) stretching vibrations, large bands observed in area 3177-3454 cm\(^{-1}\) are assigned. In the 1654-1685 cm\(^{-1}\) area, vibration bands indicate a \(\tilde{\delta}(\text{C = O})\) stretching vibration. These two findings indicate that amido ligands are in stable condition. Azomethinic (C = N) linking formed from the reaction between the keto group of carbonyl compound and corresponding hydrazide is assigned to prominent bands in 1586-1620 cm\(^{-1}\) area.

Antibacterial activity
Complexes (1-4) were screened for their antibacterial activity (inhibition zone) against Escherichia coli (MTCC 2692), Pseudomonas aeruginosa (MTCC 2453) as gram-negative and Staphylococcus aureus (MTCC 902) and Bacillus subtilis (MTCC 441) as gram-positive bacterial strains using the literature-protocol cup plate method.

Based on the results of the test, it is apparent that APAH compounds showed lower activity against gram-negative E.Coli bacteria and all other compounds showed no activity compared to standard ampicillin compounds. The BPAH compound showed strong activity against E.Coli, S.aureus and
bacillus bacterial strains, showed no activity against Pseudomonas, and the BPH compound showed moderate activity compared to the standard drug Streptomycin against all bacterial strains Table 4.

**Anti-cancer activity**

Compounds have been tested using the MTT assay for their cytotoxic ability against the human lung carcinoma (A549) cell line, and the IC50 values obtained are shown in Table 5. APAH demonstrated potent activities among all the compounds, becoming the most potent compound at micro molar concentration among all the synthesized compounds compared to the standard drug. While other compounds showed moderate operations, as seen from the table, compound BPH was the least active. It is clear from the results of the cytotoxic activity that, relative to the regular drug, the compounds containing 2,4-Dihydroxacycetyl-4-Hydroxybenzoic Hydrazone complexes exhibited anti-cancer activity Figure 5.

**Docking studies**

Figure 6 shows the final stable structure of the BCL2 (PDB ID: 4HJO) obtained Figure 7. It was identified from the CASTp results that BCL2 proteins contain amino acid residues of GLN27, GLN111, GLY41, LYS42, GLU154, PRO155, ALA415, GLN408, ILE94 in the active site region Figure 8. In the binding pocket, common H-bonding interactions were formed between all docked compounds and LYS347, LYS356 and GLU354., to explain the binding of these compounds, the H-bonding interactions with the other surrounding residues in the hydrophobic binding pocket were also investigated. In Figure 8, strong H-bonding interactions between the methoxyl oxygen (O23) of compound APAH with the hydrogen atom of LYS356, carbonyl oxygen (O2) with hydrogen atoms of LYS356 and LYS347 and benzopyrone hydrogen with the hydrogen atom of LYS347. In Figure 2, benzopyrone oxygen of compound 6a interacts with hydrogen atoms of GLU354 and oxygen (O23) with LYS347 Figure 9.

**CONCLUSIONS**

In conclusion, several novel 2, 4-dihydroxy acetyl-4-hydroxy benzoic complexes with nickel have been synthesized and evaluated for antibacterial activity by well-to-excellent condensation. Some of the compounds demonstrate antibacterial activity among the synthesized compounds. The operation against cancer confirmed the effective regulation of A549 cell lines in the complex APAH.

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**Conflict of Interest**

The authors declare that they have no conflict of interest for this study.

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