Syntheses, Crystal structures, Theoretical studies, and Anticancer properties of an unsymmetrical Schiff base ligand N-2-(6- methylpyridyl)-2-hydroxy-1-naphthaldimine and its Ni(II) complex

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Abstract: In this work, syntheses of Schiff-base ligand, N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine (1) and its hitherto unknown chelate with a Ni(II) salt, bis[N-2-(6-methylpyridyl)-2-oxo-1- naphthaldimnato-k 3N^N^O] nickel(II) (2) have been reported and characterized by spectral techniques (IR, 1H NMR, Mass). Solid state structures and non-covalent interactions persisting in 1 and 2 are studied by Density Functional Theory (DFT) optimizations and Hirshfeld Surface (HS) analysis. X-ray diffraction (XRD) study shows zwitter ionic keto-amine tautomer form of planar Schiff base 1 that exists as dimer formed by C13–H13A···O1i [(i) -x+1, -y, -z+1] hydrogen bonds and distorted octahedral geometry around Ni+2 center in chelate 2, where overall crystal structure stability may be attributed to weak C–H···π, π···π stacking, van der Waals interactions, and C–H···O type intermolecular hydrogen bonds. The HS study and 2D Finger Print (FP) plots corroborate well with XRD data and show prominent O···H/H···O spikes (2.2 Å < de+di < 2.3 Å) and C···H/H···C (2.5 Å < de+di < 2.6 Å) spikes that arise from C–H···O type H-bonds and C–H···π interactions respectively, along with significant C···C interactions (de+di ~ 3.3 Å) due to π···π stacking (2). The anticancer activity has been investigated by using cytotoxicity measure (MTT assay), apoptosis assay, quantitative polymerase chain reaction (qPCR), and colony formation assays. The Ni(II) metal complex demonstrates dose-dependent cytotoxicity in vitro, killing A549 lung cancer cells via an apoptotic pathway.

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Introduction: Schiff bases are referred to as "privileged ligands" as they can form stable compounds with the majority of metals, which made them important in the advancement of coordination chemistry [1]. The ease of their highly modular preparation, which allows control of the type of denticity and chelating capability, along with steric and electronic properties, has sparked an unrelenting interest in the study of Schiff base compounds and related metal organic frameworks. Due to their wide prospective uses in diversified fields and pharmacological activities including antifungal, antibacterial, antioxidant, anti-inflammatory, and anticancer, the design and development of Schiff bases and their corresponding metal chelates have been emphasized over the last decade [1b,2]. Thanks to the presence of an imine or azomethine moiety, Schiff bases and their related metal derivatives have biomimetic capabilities that have the ability to imitate the structural characteristics of active sites, and are thus employed in a variety of domains such as biological regulation and biochemical reactions [3]. The imine nitrogen atoms and other active centers can coordinate to the metal ions of the complexes, resulting in a broad spectrum of pharmacological activities. Furthermore, metal complexes of Schiff bases containing pyridyl moieties have recently sparked interest in the realm of pharmaceutical research and in the development of new therapeutic drugs, owing to their novel electronic properties, in addition to their ability to alter DNA binding and cleaving capabilities [4]. The chemistry of nickel Schiff base complexes is significant in bioinorganic chemistry and redox enzyme systems [5] also. Morrow and colleagues described the plasmid DNA cleavage by a square planar nickel-salen [bis-(salicylidene)ethylenediamine] complex in presence of either magnesium monoperoxypthalic acid (MPPA) or iodosulbenzene [6]. Recently, El-Metwaly and colleagues developed Ni(II) Schiff base compounds, which show promising anticancer activities in vitro against MCF-7 cell line [7]. And many more Schiff base-Ni(II) complexes have been mentioned in literature exhibiting anticancer activity in different cell lines [8, 9]. Non-covalent intermolecular contacts, such as hydrogen bonding, π…π stacking, C–H…π, chalcogen bonding, halogen bonding, and other weak intermolecular contacts, have piqued chemists' interest in the past two decades because they direct and control the supramolecular architecture in crystalline materials [10]. Current research in supramolecular chemistry and crystal engineering arena are focused on attaining more evidence about new weak intermolecular forces. In a Schiff base, the π-system frequently imposes geometrical restrictions resulting alluring supramolecular architecture. As a result, many structural chemists are interested in studying such non-covalent interactions [11]. Following all these observations, and as part of our ongoing research into the coordination chemistry of multidentate ligands [12], we report here the preparation and characterization of an unsymmetrical pyridyl Schiff base ligand, N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine (1) and its Ni(II) complex, bis[N-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato-k 3N^N^O] nickel(II) (2), all possible non-covalent interactions pertaining in the supramolecular array and application as anticancer agents. All the prepared compounds have been characterized by IR, 1H NMR, Mass, and single crystal XRD.
Experimental Materials and physical measurements: All chemicals were of reagent grade, obtained from commercial sources, and were used without purification. The solvents were purified by standard procedures. Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer with KBr pellets in the range of 4000–500 cm−1 . NMR spectra were recorded on a Bruker Advance II (400MHz) spectrometer using the residual protic solvent resonance as the internal standard and chemical shifts were expressed in ppm. Mass spectra of 1 and 2 were recorded on inkarp instruments (Expression-S). Elemental analysis was carried out in PerkinElmer 2500 series II elemental analyzer. Synthesis of pyridyl Schiff base ligand (1) and its Ni(II) metal complex (2):
Synthesis of pyridyl Schiff base ligand, N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine (1) (LH):

The pyridyl Schiff base ligand 1 was synthesized according to earlier published method with slight modification [13]. 2-Hydroxy-1-napthaldehyde (1g, 5.81mmol) was dissolved in 20 mL of HPLC grade methanol with continuous stirring for 15 min. After that, 2-3 drops of conc. acetic acid was added and stirred for 10 min. An equimolar amount of 2-amino-6-methyl pyridine (0.628g, 5.81mmol) was added to the reaction mixture. The resulting solution was then refluxed for 8 h and colour changed to yellow. The solvent was evaporated to 50% in vacuo, and the solution left to crystallize by gradual evaporation at room temperature. The crystals were filtered off and washed with methanol three times. The yellow crystals were then dried in air for 24 h. Pyridyl Schiff base ligand 1: Yield: 84%, 1H NMR (400 MHz, CDCl3, δ in ppm): 15.43 (d, 1H, - OH), 9.95 (d, 1H, -CH=N-), 8.14 (d, 1H, Ar-H), 7.74 (d, 1H, Ar-H), 7.63 (m, 2H, Ar-H), 7.53 (m, 1H, Ar-H), 7.32 (m, 1H, Ar-H), 7.03 (d, 1H, Ar-H), 6.97 (d, 1H, Ar-H), 6.91 (d, 1H, Ar-H), 2.62 (s, 3H, -CH3). FT IR (ν cm-1 , KBr): 3437 (νO-H), 3053 (νC-H), 1624 (νC=N), 1566 (νC=C), and 1304-1134 (νC-O). ESI-MS m/z = 261.3 [M - H +], 262.3 [M+]; Anal. Calc. for C17H14N2O: C, 48.92; H, 5.05; N, 14.63%. Found: C, 48.88; H, 5.03; N, 14.60%. Synthesis of Bis[N-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato-k 3N^N^O] nickel(II) (2) Two equivalents of the pyridyl Schiff base ligand 1, (0.13g, 0.5mmol) and one equivalent of NiCl2.6H2O (0.06g, 0.252mmol) were dissolved in 10 mL and 5 mL of HPLC grade methanol respectively and both the solutions were placed in main arm of a branched tube. An extra amount of methanol was cautiously added to fill up the arms. The tube was sealed and placed in an oil bath at 60 ºC, while the branched arm was left at room temperature. After 2 days, light brown crystals of the nickel complex formed in cooler arm. The solvent was evaporated and the crystals were collected. Complex 2: Yield: 79%, 1H NMR (400 MHz, CDCl3, δ in ppm): 11.41 (t, 1H, -CH=N-), 9.42 (s, 1H, Ar-H), 9.23 (s, 1H, Ar-H), 7.78 (m, 3H, Ar-H), 7.59 (m, 1H, Ar-H), 6.99 (m, 1H, Ar-H), 6.60 (d, 1H, Ar-H), 5.95 (s, 1H, Ar-H), 2.62 (s, 3H, -CH3). FT IR (ν cm-1 , KBr): 3337-3272 IR(KBr cm-1`): 3060, 3031, 2920 (νC-H), 1614 (νC=N), 1591, 1566 (νC=C), 1254-1089 (νC-O), 655 (νNi-O), and 490 (νNi-N). ESI-MS m/z = 579.7 [M - 2H+]; Anal. Calc. for C34H26N4NiO2: C, 56.98; H, 4.85; N, 12.74%. Found: C, 56.94; H, 4.82; N, 12.70%. Crystallographic data collection and refinement Single-crystal XRD data for 1 were collected using a Rigaku XtaLAB Mini II diffractometer equipped with a fine-focus sealed X-ray tube using MoKα radiation (λ=0.71073 Å) operating at 296(2) K. Data for 2 were recorded using ω scans CuKα radiation (λ=1.54184 Å) on a Rigaku Diffraction Synergy spectrometer fitted with a micro-source tube at 100(2) K. The Olex2 software [14] was used extensively for producing asymmetric unit and other materials for publication. The structure was solved, refined, and molecular graphics managed using SHELXT [15], SHELXL [16], and Bruker SHELXTL [17] program packages respectively. An empirical absorption correction was done by using multiscan method (SADABS) [18]. All the available non-hydrogen atoms were refined anisotropically. The amine N-H was located in the difference density map and refined isotropically. The positions of hydrogen atoms were calculated geometrically and riding model was use for refinement. All e.s.d.s were estimated using the full covariance matrix. The crystallographic data and structure refinement details are given in Table 1. Bond lengths, bond angles, and torsion angles are listed in Table S1–S3. Hirshfeld Surface Analysis Non-covalent interactions in 1 and 2 were investigated by generating 3D Hirshfeld surfaces (HS) and the associated 2D fingerprint (FP) plots [19-22] using Crystal Explorer 17.5 [23]. The Hirshfeld surfaces were generated based on dnorm, shape index (S) and curvedness (C) [20]. The surface parameter dnorm [21] is defined as ( ) ( ) vdW vdW i i e e norm vdW vdW i e d r d r d r r $-\,-\,=+$ Where di, de and r vdW provide information about the distance between surface point to closest interior atom, surface point to closest exterior atom and van der Waals radii of atoms respectively. Shorter contacts, longer contacts and contacts in or beyond the range of van der Waals separation are observed as red, white, and blue depressions on dnorm mapped HSs, respectively. Cell Culture Cells and cell culture To assess the anticancer activity of pyridyl Schiff base ligand (1) and its Ni(II) metal complex (2), three distinct cancer cell lines were used: hepatocellular carcinoma cell line (HUH7), colon carcinoma

cell line (HCT116), and non-small cell lung carcinoma cell line (A549). Additionally to determine the cytotoxic activity the Beas-2B normal lung cell line was used as a control. BG İzmir provided HUH7 and HCT116, while the University of Gaziantep provided A549 and Beas-2B. All cell lines were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS) (HyClone Cat. No: SV30160.03) and 1% antibiotics (HyClone Cat. No: SV30079.01) in a CO2 incubator (Thermo Sci.) at a CO2 concentration of 5% CO2 and 21% O2. Cells were harvested with Trypsin (HyClone Cat. No. SH30042.01) and washed with PBS 1X (HyClone Cat. No. SH30256.01) when necessary. The compounds were dissolved in DMSO at a stock concentration of 10 mM and diluted further in the cell culture media during the experiments. Cytotoxicity assay The cytotoxicity of compounds 1 and 2 dissolved in DMSO was determined using the 3- (4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide method (MTT) against HUH7, HCT116, and A549 cells [24]. In brief, 1.0 x 104 cells per well were cultured overnight at 37 °C in 5% CO2 in RPMI medium containing 10% FBS and 1% antibiotics in a 96-well plate. After 24 hours, the old medium was removed and the cells were incubated for 24 hours with compounds at increasing concentrations (0, 0.3, 1, 3, 10, 30, 100, and 300 µM). Under the same conditions, cells treated with 0.1 percent DMSO (vehicle control) were incubated. At the conclusion of the incubation time, the MTT solution was added to each well at a final concentration of 0.5 mg mL– 1 , and the cells were further incubated for 4 hours to allow viable cells to metabolize the MTT. After removing the supernatant, 50 L of 96 percent ethanol was added to each well to dissolve the purple crystals, which are a byproduct of living cells' metabolism. The absorbance at 570 nm was determined using a microplate reader (Biochrom EZ Read 400). Apoptosis assay Annexin-V/propidium iodide (PI) fluorescein isothiocyanate (FITC) staining was performed according to the protocol of the Biolegend apoptosis detection kit [25]. For quantitative analysis, approximately IC50 concentrations of the compounds were tested on HUH7, HCT116, and A549 cells. A cancer cell (105 cells per 1 mL) suspension in a serum-free medium was incubated with the respective compound in 6-well plates in a CO2 incubator. After treatment with compounds for 48 h, the cancer cells were harvested and incubated with APC-Annexin V and propidium iodide (PI). The fluorescence emission of APC-Annexin-V stained cells was measured at 633 nm (red laser) in a flow cytometer (Beckman Coulter/CytoFLEX, United States). Dots represent cells as follows: bottom left quadrant – living cells (APC−/PI−); bottom right quadrant – early apoptotic cells (APC+/PI−); top left quadrant – necrotic cells (APC−/PI+); top right quadrant – late apoptotic cells (APC+/PI+). Quantitative polymerase chain reaction (qPCR) Total RNA was extracted from HCT116 and A549 cells incubated for 1 and 2 to 6 hours at concentrations half the IC50 doses using RNA assay kit (Macherey-Nagel) and reverse transcribed using cDNA reverse transcription kit (Thermo Fisher) according to manufacturer's protocols. Quantitative PCR was done on an Eppendorf Mastercycler using SYBR Green mix (Sigma Aldrich). Reactions were performed in triplicate in a 96-well plate (Bio-rad i Cycler). Gene expressions were normalized to 18S rRNA, and fold differences were calculated using the comparative CT method: 2-(ΔΔCT), where ΔΔCT refers to (normalized control sample) − (normalized treated sample). Primer pairs were as follows; 18S rRNA: sense: 5'- cttagagggacaagtggcg-3', antisense: 5'-acgctgagccagtcagtgta-3'; p21: sense: 5'- cgaggcacaagggtacaaga -3', antisense: 5'-cccgtgagccatggact-3'; p53: sense: 5'- cctggttagtacggtgaagtg -3', antisense: 5'-agggatgtttgggagatgtaag -3'. Colony forming assay: Colony forming assay was performed in a 6-well plate. The cells were seeded at a density of 200 cells per well for HCT116 and HUH7 in a 3 mL complete culture medium. Two different concentrations of 1 and 2 were applied to the cells. After 24 h. the old medium was removed and a new fresh medium was added to the cells. The medium was changed with a new one twice per week. After two weeks, the colonies formed were dyed with methylene blue solution included 50% methanol, 50% distilled water and 0.4 g methylene blue. The colonies were counted using the ImageJ 1.53a software (NIH, USA). Differences between the groups were analyzed with Prism V8 (GraphPad Software, Inc, CA, USA). Result and discussion: FT-IR and NMR spectral

characterization To better understand the nature of coordination modes of the pyridyl Schiff base ligand 1 to the Ni(II) metal centre, the IR spectra of 1 and 2 were carefully investigated (Figure S1 and S2). In the experimental section, selected vibrational spectroscopy data of 1 and complex 2 are presented. The presence of intense absorption band at 1624 cm-1 , which is due to ν(C=N) of azomethine group (-CH=N-) in the spectra of ligand, confirms the formation of pyridyl Schiff base ligand 1. The intense absorption band at 1614 cm-1 in the spectra of 2 is ascribed to the imine stretching frequency of the azomethine scaffold of the ligand. The shift of the band to lower frequency, compared to free ligand 1 (1624 cm-1), signifies that the coordination interaction persists between imine nitrogen atom to Ni(II) metal centre. This appears to be due to electron density shifting from nitrogen atom to Ni(II), which decreases the stretching frequency and weakens the C=N bond. The ligand stretching frequencies at 3053 cm-1 in the spectra of 1 was ascribed to ν(C-H) of aromatic group. The peaks at 3031 cm-1 and 2920 cm-1 were assigned ν(C-H) of olefinic and aliphatic groups in 2 respectively. Downward shift of ν(C-O) band from 1304 cm-1 -1134 cm-1 in 1 to 1254 cm-1 -1089 cm-1 in 2 corroborates the involvement of deprotonated phenolic oxygen in the coordination with Ni(II) metal centre. The ligand coordination to the nickel ion is also confirmed by appearance of new noticeable bands at 655 cm-1 and 490 cm-1 which can be attributed to ν(Ni-N) and ν(Ni-O) stretching vibrations respectively. In addition to IR data, a comprehensive examination of 1H NMR of 1 and 2 gave additional evidence to support the complex formation (Figure S5 and S6). The Schiff base ligand's phenolic proton (-OH) displays a doublet at most down field δ 15.43 ppm, which is conspicuously absent in 2 that confirms the complex formation. The azomethine proton displays a doublet at δ 9.95 ppm in the free ligand 1, while the same shows a triplet at δ 11.41 ppm in 2. The downfield shift of azomethine proton further corroborates the formation of 2. The other aromatic protons in both free ligand and Ni(II) complex bare found at their suitable positions. Overall, the structure of the synthesized Ni(II) complex in the solution state seems to be similar to that of the solid state, according to FT-IR and 1H NMR data. Description of structures Crystallographic study of pyridyl Schiff base ligands of the class N-2-(R-pyridyl)-2-hydroxy-1-naphthaldimine (R: H, 4-CH3, 6-CH3) and corresponding metal chelates remain unexplored till date with mere twelve examples of free ligands and metal chelates [13, 26-36] reported so far in Cambridge Structural Database (CSD). These pyridyl Schiff base ligands generally remain either as enol-imino tautomer or as keto-amine tautomer (zwitter ions) [26, 29]. The zwitter ionic structure adaptation arises due to para-substitution of electron withdrawing or electron donating moieties [27, 28] at the pyridine ring. The relative energies of keto-enol tautomer forms are further explored by DFT methods in the present study; vide infra. The pyridyl Schiff base ligand architecture generally favours bidentate coordination to metal ions through oxo and imine ends yielding six-membered chelate ring [30-36]. In principle, the pyridyl N-atom could also participate in coordination to metal center rendering the ligand tridentate but no such structures are reported so far in CSD. Thus we intend to investigate the possibility of tridentate coordination mode in N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine towards Ni+2 metal center, which might form new solid chelate with fascinating crystal structure and supramolecular array. In this section, crystal structures of free ligand N-2-(6-methylpyridyl)-2-hydroxy-1- naphthaldimine (1) and its complex with Ni(II) salt, bis[N-2-(6-methylpyridyl)-2-oxo-1- naphthaldimnato-k3N^N^O] nickel(II) (2) are presented. N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine (1) The ligand 1 was previously reported [13], but its crystal structure remains hitherto unexamined. The crystals of 1 are orthorhombic having Pbca space group with a single un-fragmented molecule in the asymmetric unit as shown in Fig. 1. It adopts an E-conformation at the imine double bond and extended π-conjugation favours a planar geometry, which is evident from dihedral angles of 1.41(9)0 between naphthyl and pyridyl rings. The ligand 1 appears as zwitter ion in solid state confirming its keto-amine tautomer form which is further evident from C1–O1 [1.269(4) Å] bond length. In the optimization section, relative energy of

keto/enol forms is extensively probed using DFT methods (vide infra). The elongation of N1–C11 [1.323(4) Å] bond as compared to a typical C=N imine (ca. 1.28 Å) highlights the existence of keto-amine form. The strong N1–H1N···O1 intramolecular hydrogen bond characteristics of the class N-2-(R-pyridyl)-2-hydroxy-1-naphthaldimine, exists between ketonic acceptor O1 and amine donor N1–H1N forming a six membered intra of graph-set-motifs S(6) which stabilize the molecular geometry and crystal packing array along with nonspecific, non-directional van der Waals interactions. Crystal structure is further stabilized by intermolecular C13–H13A···O1i [(i) -x+1, - y, -z+1] H-bond (Table 2) resulting in the formation of a dimer where a twelve membered ring of graph-set-motif (Fig. 2 and Fig. S7) is observed. When extended in three dimensions (3D), stacked columns of independent dimers are observed along [010] axis (Fig. 2). Fig. 1. Molecular structure of N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine [Displacement ellipsoids at 50% probability level]. Fig. 2. Partial view of 3D stacked dimeric columns along ac plane (left) and dimer formation by N1–H1N···O1 and C13–H13A···O1i hydrogen bonds (right) [Symmetri code (i) -x+1, -y, -z+1]. Bis[N-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato-k 3N^N^O] nickel(II) (2) The chelate bis[N-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato-k 3N^N^O] nickel(II) (2) has monoclinic crystal system having space group of I2/a; and the asymmetric unit contains half a molecule that is one Ni+2 ion and one N-2-(6-methylpyridyl)-2-oxo-1-naphthaldimine deprotonated ligand (L). The metal center experiences hexa-coordination, NiN4O2. Each deprotonated ligand molecule (L) is coordinated to Ni+2 in a bischelated mode (tridentate) through imine N-atom (N1); pyridyl N-atom (N2) and oxo O-atom (O1) forming a distorted octahedral coordination kernel around metal center bearing N1,N1i ,O1,N2 atoms [(i) -x+½, y, -z+1] occupying corners of equatorial basal plane, axial sites having O1i ,N2i atoms [(i) -x+½, y, -z+1], and Ni+2 resides marginally below the plane by a distance of 0.1683(8) Å [0.3794(7) Å from centroid of basal plane] (Fig 3). The deviation from ideal octahedral geometry apparently observed from trans angles 163.04(10) 0 [N1–Ni1–N1i], 148.20(5) 0 [O1i–Ni1–N2i and O1–Ni1–N2], and chelate bite angles varying in the range of 60.77(6)0 to 106.41(6)0 . The observed deviation of chelate bite angles (axial–metal–equatorial) from 900 [60.77(6) 0 (N1i–Ni1–N2i), 87.64(5)0 (N1i–Ni1–O1i)] is due to the unusual coordination from non-flexible 1 to Ni+2. In fact the two L molecules are almost perpendicular to each other [89.22(4)0], permitting the close proximity of 20 - imine N-atoms (N1,N1i) to metal center, which is evident from shorter Ni–Nimine bonds [1.9746(13) Å (Ni1–N1 and Ni1–N1i)] as compared to Ni–N pyridyl bonds [2.3818(16) Å (Ni1–N2 and Ni1–N2i)] leading to relatively weaker coordination through the later. The factor of longer equatorial Ni1–N2 bonds also influences the octahedral distortion and the equatorial and axial Ni–O bond distances are found to be 2.0033(13) Å [Ni1–O1 and Ni1–O1i] respectively. Mean triangle twist angle of 42.17(6) 0 between trigonal planes [plane N1N2O1i and plane N1iN2iO1, (i) -x+½, y, -z+1)] and 1.14 s/h ratio (s = average length of the sides of the trigonal faces of the polygon, h = distance between the trigonal faces] unambiguously prove the octahedral geometry with distortions in 2, rather than trigonal prism geometry [For ideal octahedron, s/h 1.22 and twist angle 60° (staggered)]. Contrary to 2, the ligand 1 favours tetrahedral geometry in reported Schiff base complexes of Cu(II) and Zn(II) [13,36]. Interestingly, complex 2 is found to be the first ever octahedral Ni+2 based chelate harvested from N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine in CSD. The large Ni....Ni distances [6.2716(2) Å–12.2347(10) Å] between neighboring asymmetric units nullifies the possibility of Ni(II)....Ni(II) metallophilic interaction [37]. In 2, each ligand moiety forms three C–H···O type intermolecular hydrogen bonds with oxo Oatoms of perpendicular L moieties in nearby asymmetric units contribute to supramolecular crystal architecture (Table 2, Fig. 4). These C–H···O hydrogen bonds and other existing interactions (van der Waals) are responsible for imparting stability to crystal structure. Apart from C–H···O type H-bonds, weak interactions arising from C–H···π and π···π stacking also contribute to crystal stability. The weak C–H···π interactions exist between naphthyl C10–H10 of 2 and cg that is naphthyl ring of adjacent 2 with a distance of 2.235(2) Å [H10 to cg centroid distance 3.3885(7) Å]

along ac plane (Fig. 5). The parallel naphthyl and pyridyl rings in crystal packing array favours the π···π stacking with cg···cg distance of 3.6800(10) Å (Fig. 6). The cg···cg twist angle is 12.00(15) 0 [1.522(3) Å {plane shift angle}, 0.12(6)0 {fold angle}]. These C–H···O connectors create intermolecular seven membered [ring O1iH1C1N1C12C13H13 (i: x-½, -y+1, z)], ten membered ring geometries [ring H10C10C11C2C1N1C12C13H13O1i (i: x-½, -y+1, z)] and infinite chain geometries (chain bearing atoms H1, C1, N1, Ni1, O1) of graph-set-motifs and C(5) respectively (Fig. S8). In 2D these H-bonds are found to link the molecules in the formation of independent parallel infinite chains, and each chain consists of parallel moieties of L flanked by consecutive perpendicular pair of L moieties. Further extension of the connectivity through these C–H···O Hbonds in crystal packing forms a three-dimensional (3D) stacked chain like array along bc plane (Fig. 7). The crystal packing pattern is 3D right handed helix, showing consecutive perpendicular and parallel pairs of L moieties in a chain assuming the imaginary axis passing through Ni+2 ions of each complex molecule (Fig. 7), where parallel naphthyl and pyridyl rings are linked presumably by weak π···π interactions. Table 1. Crystal data and structure refinement for 1 and 2. Parameters 1 2 Empirical formula C17H14N2O C34H26N4NiO2 Formula weight 262.30 581.30 Temperature (K) 296(2) K 100(2) K Crystal system Orthorhombic Monoclinic Space group P b c a I 2/a a (Å) 16.2423(11) 12.2347(1) b (Å) 5.6367(4) 9.4157(1) c (Å) 29.285(2) 23.5556(3) α (0) 90 90 β (0) 90 91.696(1) γ (0) 90 90 V (A3) 2681.2(3) 2712.38(5) Z 8 4 D cal (gcm-3) 1.300 1.423 μ (mm-1) 0.082 1.347 F(000) 1104 1208 θ range for data collection (0) 1.872 to 30.725 3.755 to 71.228 Index ranges -22<=h<=16, -7<=k<=8, -41<=l<=33 -13<=h<=15, -11<=k<=11, -28<=l<=28 Reflections collected 44797 11926 Independent reflections 4050 [R(int) = 0.1316] 2623 [R(int) = 0.0190] Absorption correction Semi-empirical from equivalents Semi-empirical from equivalents Max and min transmission 1.00000 and 0.80969 1.00000 and 0.04306 Data/restraints/parameters 4050/0/186 2623/0/191 Goodness-of-fit on F2 1.013 1.089 Final R indices [I > 2σ(I)] R1 = 0.1002, wR2 = 0.1395 R1 = 0.0361, wR2 = 0.0957 Final R indices [all data] R1 = 0.2952, wR2 = 0.1880 R1 = 0.0390, wR2 = 0.0973 Largest difference in peak and hole (e A3) 0.169 and - 0.132 0.230 and -0.489 Table 2. Summary of intermolecular interactions in 1 and 2. D–H···A d(D–H) (Å) d(H···A) (Å) d(D···A) (Å) < de+di < 2.3 Å, C···H/H···C contacts around 2.5 Å < de+di < 2.6 Å and the C···C contacts (for 2) (π–π interactions) around de+di ~ 3.3 Å. The H···H weak interactions manifested as scattered points that expand up to di = de= 2.4 Å in 1 and di = de= 2.5 Å in 2, which is responsible for crystalline lattice strength. It is found that H···C/C···H interactions [39.1% (1), 27.5% (2)] and H···H interactions [43.8% (1), 52.7% (2)] dominate interaction contribution chart. The O···H/H···O contacts [8.1% (1), 7.4% (2)] and C···C contacts [8.7% (2)] have small contributions but play vital role in supramolecular crystal packing. Some minor weak interactions such as O···N/N···O (0.5%), O···C/C···O (1.3%), N···C/C···N (1.9%), C···C (0.5%) in 1 and N···N (0.2%), N···C/C···N (0.7%) in 2 have also been observed in 2D FP plots. The comparative distributions of all non-covalent interactions are shown as 2D pie diagram in Fig. 13. The HS analysis [45] at the atomic level (nickel center) was performed to observe the coordination impact of N,O-atoms (1) at Ni+2 as minimal changes in coordination direction resulted in abrupt significant depressions on HS so changes in the inherent HS properties like volume, globularity etc. [45] are inevitable as shown in Table 3. Interestingly, asphericity value suggests that HS at Ni+2 center is close to isotropic nature (Ω=0 for isotropic object). The Ni−N coordination bonds appeared as circular bright-red depressions perpendicular to the Ni−N bond direction on HS (dnorm). The strength of Ni−N bonds manifests as rectangular shaped orange spots and green flat patches on HS (S) and HS (C), respectively (Fig. 14). For Ni–O bonds, similar characteristic coloured depressions observed on HS mapped with dnorm, S and C. Due to differences in Ni–N optimized bond lengths [Ni–N1 (1.975 Å), Ni–N2 (2.053 Å)] irregular concave orange depressions appeared, which are surrounded by yellow coloured regions on S mapped HS (Fig. 14). All the Ni–N coordination seems to be through regions that reside outside the orange patches on HS [shape index] and that might be due to deviation of Ni−N bonds. These Ni–

N coordination manifested as a prominent sharp red upper spike at de + di ≈ 1.9 Å in the 2D FP plots (translated range) and similar red spike at de + di ≈ 2 Å observed for Ni–O bonds (Fig. 14). At higher di (2.3 Å), de (1.9 Å) values in 2D FP plot, chunk of blue abrupt dots appears symbolizing weak Ni···H interactions (Fig. S12), which are associated with the edges of the HS. These Ni···H interactions originate from intramolecular Ni···H17A interaction (3.573 Å) and intermolecular Ni···H13 interactions (3.484 Å). This type of weak Ni···H13 interactions link neighbouring asymmetric units of 2 (Fig. 15) and thereby contribute to crystal packing stabilization along with other hydrogen bonds. Overall contributions of Ni–N, Ni–O coordination and Ni···H contacts are in the order of 54.3%, 37.1% and 8.6% respectively in the 2D FP plots. Fig. 10. View of Hirshfeld surfaces mapped over dnorm (left), shape index (middle), and curvedness (right) for 1 and 2. Fig. 11. View of Hirshfeld surfaces mapped on dnorm (left), SI (middle), and C (right) showing C–H···π (top) and π–π interactions (bottom) in 2. Fig. 12. 2D fingerprint plots for 1 (top) and 2 (bottom). Fig. 13. 2D Pie diagram illustrating the relative distribution (% scale) of non-covalent interactions from HS analysis of 1 (left) and 2 (right). Fig. 14. View of atomic HS study (top) at Ni+2 -center mapped on dnorm (left), SI (middle), C (right) and corresponding 2D FP plots (bottom) showing Ni···N, Ni···O, and Ni···H interactions. Fig. 15. Partial view of atomic Hirshfeld surface (dnorm) showing asymmetric units of 2 linked by weak Ni···H interactions (non-bonded H-atoms omitted for clarity). Table 3: Quantitative data from HS of 1 and 2. Compound VH (Å3) AH (Å2) G Ω 1 328.38 310.33 0.742 0.256 2 667.54 564.90 0.654 0.102 2* 13.81 37.18 0.749 0.023 * Atomic Hirshfeld surface analysis at the Ni+2 metal center of 2. Anticancer activities According to the results of the MTT assay was performed to evaluate the cytotoxic activities of free pyridyl Schiff base ligand (1) and Ni(II) complex (2), 1 showed an IC50 value of 154.7µM in HUH7 cells, 88.32µM in A549 cells, and 47.80µM in HCT116 cells. The IC50 values for 2 were calculated as 86.82 µM in HUH7 cell, 24.85 µM in A549 cells, and 56.02 µM in HCT116 cells. 2 showed toxic effect at high concentrations in Beas-2B cells, while 1 showed almost the same cytotoxic effect (IC50=85.72 µM) as compared to A549 cells (Fig. 16). Therefore, it cannot be said that 1 has a cancer cell specific cytotoxic effect. However, in order for 2 to have a toxic effect on normal lung cells, higher concentrations must be applied, which is promising in terms of specificity for cancer cells. A similar study showed that a Ni(II) complex showed better cytotoxic effect in A549 lung cancer cell with a lower IC50 value than Ag(I) and Pd(II) of the same ligand and compared to Ploxal-S and 5-fluorouracil used as reference drugs revealed in the study [8]. It is seen that 1 and 2 show moderate cytotoxic activity in other cell lines, while 2 shows good cytotoxic effect in A549 cell. It can be said that this new Ni(II) Schiff base complex (2) has a specific effect on A549 cell. The ability of the HUH7 and HCT116 cells to form colonies in two weeks in the presence of 1, 2 and equal concentrations of DMSO as controls were tested. The percentage of colonies formed by HUH7 and HCT116 cells treated with 1 after two weeks was calculated as 32% and 42%, respectively, based on DMSO. The percentage of colonization of HUH7 cell treated with 2 was 3% and HCT116 cell 28%. 2 inhibited colonization in both cells more than 1 (Fig. 17). Both compounds were able to affect the proliferation and growth rate of cells at different doses. Whether 1 and 2 affect the apoptotic pathway was investigated by Flow cytometry. Fig. 18 shows Annexin V/PI diagrams showing the ratio of viable and apoptotic cells. Apoptosis rates of all cells incubated with IC50 concentrations of 1 for 48h did not differ significantly from control (DMSO). Incubation of HCT116 cell with IC50 dose of 2 for 48 hours resulted in 45.73% of apoptotic cells. 2 also resulted in 23.63% apoptotic cells in A549 cell. These results are significantly different from the control (DMSO). 2 did not show apoptotic activity in HUH7 cells. These findings can be supported by different studies proving the effectiveness of Schiff base Ni(II) complexes in the apoptotic pathway [9, 46]. According to the PCR results, 1 and 2 slightly increased p53 expression in A549 cell. This could mean minor DNA damage. However, neither 1 nor 2 increased p21 expression in A549 cells, so cell cycle arrest was not induced. In HCT116 cells, 1 and 2 significantly increased the expressions of both p21 and p53. This shows that 1

and 2 both cause DNA damage and affect the cell cycle in HCT116 cell (Fig. 19). In this study, 2 showed much better efficacy than 1 in terms of cytotoxicity, inducing apoptosis or preventing colonization. Thus it is clear that the anticancer activity of 1, increases with the incorporation of Ni(II). Many anticancer studies with nickel complexes have shown that Ni(II), like other transition elements has the ability to bind to DNA and various oncoproteins, and has the ability to act as an antitumoral agent by affecting cell proliferation, cell cycle steps, and many more processes [47-49]. The 3D structure of the ligand, its electronic properties and ligand-metal interactions are of great importance as well as metal in antitumoral activity. In many studies, it has been shown that there are significant differences in anticancer activity between subclasses of Schiff base compounds (Quinazolines, pyrazole-naphthalene derivatives, azosal, sulfonamides, indoles, porphyrines, and chitosan derivatives, etc.), as well as between Schiff base ligands and their metal complexes. In addition, it has been proven that all Schiff bases in general have the potential to interact with many proteins and DNA, thanks to their flexible bond structure and unique π–π interactions [50]. Fig. 16. Cytotoxic effects of 1 (blue) and 2 (red) on the HUH7, HCT116, A549 cancer cells and Beas-2B normal lung cells. Cell viability assay was performed via a MTT protocol at concentrations of 0, 0.3, 1, 3, 10, 30, 100, and 300 μM for 24 h. Graphs show the best curve fit of non-linear regression analysis. Calculated IC50 values are given in Table. Fig. 17. Colony formation assay, performed in the HUH7 and HCT116 cells exposed to 1 and 2, and DMSO as a control, at two different concentrations. Cells were allowed to grow for two weeks before staining with methylene blue solution. Fig. 18. Apoptotic cell rates in the HUH7, HCT116, and A549 cells treated with 1, 2 and equal amount of DMSO with 1 and 2 as a control. Apoptosis ratio was measured by flow cytometry. The upper (late) and lower (early) right quadrants show the apoptotic cells of the population. p21 p53 p21 p53 0 1 2 3 4 Fold change 1 HCT116 A549 2 Fig. 19. HCT116 and A549 cells incubated with 1 and 2 for 4 h, and qPCR, performed after mRNA isolation to evaluate expression levels of apoptosis and cell cycle related genes p21 as well as p53. Fold differences of mRNA levels of the compound-treated samples were normalized to DMSO-treated samples. Conclusions The pyridyl Schiff-base ligand, N-2-(6-methylpyridyl)-2-hydroxy-1-naphthaldimine (1) and its Ni(II) complex, bis[N-2-(6-methylpyridyl)-2-oxo-1-naphthaldimnato-k 3N^N^O] nickel(II) (2) have been synthesized and well characterized by IR, 1H NMR, mass, and X-ray diffraction. Xray diffraction study reveals that 1 has zwitter ionic structure due to the prevalence of keto-amine tautomer form and the C13–H13A···O1i [(i) -x+1, -y, -z+1] intermolecular hydrogen bonds succour the existence of dimeric form. In complex 2, the NiN4O2 coordination kernel attains distorted octahedral geometry around Ni+2 center and overall crystal stability is contributed by C–H···O type intermolecular hydrogen bonds, weak C–H···π, π···π stacking and van der Waals interactions. These non-covalent interactions in 1 and 2 are well reflected in HS study at molecular level with the appearance of O···H/H···O and C···H/H···C interactions as coloured depressions on dnorm mapped HS having spikes in 2D FP at 2.2 Å < de+di < 2.3 Å and 2.5 Å < de+di < 2.6 Å respectively where the later invokes for C–H···π interactions and specific C···C interactions (de+di ~ 3.3 Å) in 2 signifies π···π stacking pattern. The effect of ligand coordination on Ni+2 center and related interactions are also evaluated by HS study at the atomic level and surprising revelation is the Ni···H interactions [3.573 Å (Ni···H17A), 3.484 Å (Ni···H13)] that connects the neighbouring asymmetric units of 2. Overall contributions of Ni–N, Ni–O coordination, and Ni···H contacts are in the order of 54.3%, 37.1% and 8.6%, respectively, as apparent in the 2D FP plots. The solid state structures of 1 and 2 are optimized by DFT using basis set CAM-B3LYP/6-311G. The ligand 1 attains the lowest energy conformation (2.4 kJ mol–1) that is keto-amine tautomeric form and the intramolecular hydrogen bond stabilizes 1 by 74.5 kJ mol–1 in the formation of a dimer. The octahedral geometry vis-à-vis tridentate coordination of ligand 1 is less favoured towards Ni+2 center having high energy reference (82.4 kJ mol–1) but still it exists in the present scenario and that might be possible due to requisite energy transfer by crystallization technique in sealed tube at

elevated temperature. MTT assay results direct to the fact that at higher concentration, 2 showed toxic effect in Beas2B cells, while 1 showed almost similar cytotoxic effect (IC50=85.72 µM) as compared to A549 cells. On the A549 lung cancer cell line, the novel Ni(II) complex 2 has a good cytotoxic effect and causes apoptotic cell death. Colony forming assay study reveals that both 1 and 2 affect the proliferation and growth rate of cells at different doses, in fact, 2 inhibited colonization in HUH7 and HCT116 cells more than 1. Flow cytometry shows effectiveness of 2 in the apoptotic pathway by the generation of 45.73% and 23.63% apoptotic cells when incubated with HCT116 cell, IC50 dose, and A549 cell, IC50 dose respectively. The PCR results show 1 and 2 have slightly increased p53 expression in A549 cell and both cause DNA damage. Thus we can conclude that anticancer activity of 2 is higher than 1. Conflicts of interest

The authors declare no competing financial interest. Acknowledgements SA acknowledges support from Govt. Degree College, Dharmanagar, Tripura(N)-799253, India.. Electronic Supplementary Information Electronic Supplementary Information (ESI) available: CCDC 2077047, CCDC 2150126. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or email: deposit@ccdc.cam.ac.uk].

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