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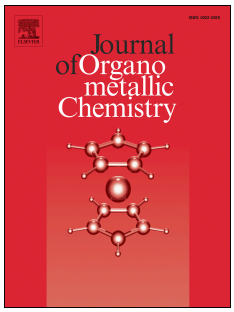

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Synthesis, characterization, *in vitro* antimicrobial and anticancer studies of new platinum *N*-heterocyclic carbene (NHC) complexes and unexpected nickel complexes[1†]

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Abstract

A series of bidendate pyridine-functionalized metal *N*-heterocyclic carbene (NHC) complexes with various wingtip substituents (R = methyl, phenyl and tert-butyl) had been prepared from silver oxide-mediated transmetalation method. The basic backbone of the NHC ligands were prepared in two stepwise reactions: reduction of the commercially available 2-benzoylpyridine, followed by halogenation to yield 2-(chloro(phenyl)methyl)pyridine. Subsequent reactions with different imidazoles gave the desired imidazolium salts (or NHC precursors) with different R groups at the *N* wingtip (R = Me, Ph, t-Bu). Transmetalation of the imidazolium salts into platinum NHC complexes were achieved by using Ag_2O mediated method with $Pt(cod)Cl_2$ as the transmetalating agent. On the other hand, nickel NHC complexes were obtained via one pot synthesis method with nickel chloride as the transmetalating agent and reflux in the presence of a base. Following recrystallisation, the molecular structure of Pt NHC complex **(±)-5a** had been successfully elucidated via single crystal X ray diffraction (XRD) analysis. The six-membered ring of the platinum NHC complexes adopted a boat conformation with the phenyl ring arranged at the axial position. Meanwhile, two unexpected nickel complexes, i.e. a simple nickel coordination complex and a nickelate complex, were obtained and studied using XRD. These Pt NHC complexes and unexpected Ni complexes were evaluated for their *in vitro* antimicrobial and anticancer activities against a panel of pathogenic microorganisms and three selected human cancer cell lines, including breast (MCF7), colon (HCT116) and oral (H103) cancer cells. Generally, the Pt NHC complexes displayed enhanced antimicrobial activities upon coordination to metals, as compared to the corresponding imidazolium salts i.e. NHC precursors, with minimum inhibitory concentration (MIC) values in micromolar (μM) range. A couple of platinum NHC complexes synthesized exhibited antimicrobial activities with MIC as low as 2 μM, which are comparable to silver NHC complexes with renowned antimicrobial profiles. Similarly, upon coordination to the metals, the cytotoxic effects of the platinum NHC complexes increased significantly as compared to the imidazolium salts. Among all, platinum NHC complex (±)-**5c** displayed significant cytotoxicities towards the cancer cells with IC_{50} values that are two to three times lower than that of the anticancer drug cisplatin. In summary, evidences for influence of both wingtip substituents and metals on the biological activities of the complexes have been found.

Keywords

N-heterocyclic carbene • platinum NHC complexes • nickel complexes • cytotoxicity • antimicrobial

[†]*Electronic Supplementary Information (ESI) available: CCDC 1901952, 1901953, and 1901954 contain the crystallographic data (in CIF format) for complex* **(±)-5, 9** and **10**, respectively, and *NMR spectroscopy data of all synthesized compounds.*

Introduction

Current strategy in the development of organometallic drugs has increasingly focused on the use of transition metal complexes containing organic ligands. The effectiveness of metallodrugs is highly associated with the choice of ligands. Ligands are most often, but not limited to, organic compounds that bind metal ions, hence modifying the physical and chemical properties of the compounds. Ligands are important for modifying reactivity and lipophilicity, stabilising special oxidation states and contributing to substitution inertness. Most importantly, with its capability to modify the oral/systemic bioavailability of metal ions, ligands can play an integral role in muting the potential toxicity of a metallodrug to have a positive impact for diagnosis and therapy.

Organometallic drugs with *N*-heterocyclic carbene (NHC) ligands have come into the spotlight over the past decade. There are over multiple hundreds of transition metal NHC complexes being reported as potential antimicrobials and anti-tumour drugs over the past five years. Their therapeutic potential is further highlighted by several patents held by several universities and pharmaceutical companies [1-6]. *N*-heterocyclic carbenes (NHCs) is an interesting class of ligand similar to phosphine ligand. They are generally derived from persistent carbenes, which are stable compounds of divalent carbons. In simpler terms, NHCs are defined as heterocyclic species containing a carbene carbon and at least one nitrogen atom within the ring structures. Today, as an excellent ligand to the transition metals, NHCs have found multiple applications in various field, particularly highlighted in biology, catalysis and supramolecular chemistry [7, 8].

Following the success of platinum based metallodrugs, such as cisplatin, as chemotherapeutic agents, platinum complexes would be a great starting point for the search of novel therapeutic agents. Recently, researchers have shifted the focus towards the synthesis of novel platinum-based drugs by changing the coordinated nitrogen ligand or altering the leaving groups. Platinum NHC complexes have been highlighted as a promising and original platform for building new drugs. One of the most notable highlight of Pt NHC complexes is the patented monometallic *trans*-PtI_2(NHC)(amine) complexes and bimetallic *trans*-[PtI_2(NHC)]$_2$(diamine) complexes developed by Marinetti's group, which exhibited cytotoxic activities with IC_{50} at micromolar range against both cisplatin-sensitive (CEM and H460) and cisplatin-resistant (A2780/DDP, CH1/DDP and SKOV3) cell lines [4, 9, 10]. They even outperformed cisplatin and oxaliplatin, with cytotoxicity that are two- to five-fold higher than the anticancer drugs, under similar experimental condition. While *trans*-configured complexes were previously deemed as inactive in initial anticancer research, they have now been acknowledged for their ability to form different platinum-DNA adducts, less recognized by RNA-repair machinery, and therefore to reduce cross-resistance pertaining to cisplatin [11-13]. Che's group also reported a series of luminescent cyclometalated [Pt(6-phenyl-2,2'-bipyridine)(NHC)] complexes with variable lipophilicity (NHC *N*-substituents) and nuclearity (mono- or bis-), which displayed significant anticancer activities [14-16]. These Pt NHC complexes were about 5 to 300 folds more potent towards HeLa cells compared with cisplatin and displayed high specificity towards cancer cells. Most importantly, *in vivo* study with mice have shown that the Pt NHC complex developed could inhibit tumour growth significantly with no obvious side effects.

Although the study on Ni NHC complexes and their biomedical application is relatively scarce compared to other Group 10 metal NHC complexes, but the apparent potential of nickel complexes in antitumor studies has been reported recently. Ray and co-workers have designed three tetradendate Ni NHC complexes with the intention to use them as agents for developing resistance to nickel toxicity [17]. These Ni NHC complexes have shown less cytotoxicity than $NiCl_2.6H_2O$ against HeLa and MCF7 cell lines under analogous condition. In addition, Ni NHC complex displayed only half the toxicity than that of cisplatin against the non-tumorigenic CHO cell line with minimal cell surface distortion [17]. These observations supported that the drastic reduction

in the cytotoxic activity of nickel was successfully achieved by encapsulation of the metal centre in Ni NHC complexes. This is desirable as the cyclometalated configuration of the Ni NHC complexes can ensure the stability of the complexes during drug delivery.

The impetus for the antimicrobial study came from the knowledge that several elemental metals display antimicrobial properties, for example silver. There is no previous report on the antimicrobial properties of any Group 10 metal NHC complexes. However, numerous transition metal NHC complexes were shown to exhibit significant antimicrobial activities against Gram positive and/or Gram negative bacteria with minimum inhibitory concentration (MIC) below 10 μg/mL, namely Ag, Au, Rh and Ru NHC complexes [1, 3, 18-20]. Although plenty of impressive anticancer properties have been reported for Group 10 metal NHC complexes, the information on their antimicrobial properties are limited. Nonetheless, Haque's group have reported a series of Pd NHC complexes with selective concentration-dependent antimicrobial activity, displaying high effectiveness against Gram positive *S. aureus*, but not the Gram negative *E. coli* [21, 22]. Therefore, we decided to resume the study of these Pt and Ni NHC complexes' antimicrobial activities to explore their potential biomedical applications.

We previously reported a series of pyridine-functionalised bidendate Pd NHC complexes which displayed substantial antimicrobial activities with minimum inhibitory concentration at micromolar range, and they are cytotoxic towards the MCF7 (breast), HCT116 (colon) and H103 (oral) cancer cell lines tested [23]. The promising *in vitro* bioactivity of Pd NHC complexes have prompted us to explore the potential of other Group 10 metal NHC complexes as novel antimicrobial and anticancer agents. The synthesis of the novel Pt and Ni NHC complexes which are analogous to the Pd NHC complexes would be an interesting starting point to study the effect of different metals on the biological activities of these metal NHC complexes. As literature implies, the metal centre plays an important role in interacting with biological targets while lipophilicity is maintained at optimum level by adjusting the side chain in the metal NHC complex [24]. This study focuses on the influence of different *N* wingtip substituents on the structure of respective Group 10 metal NHC complexes on the antimicrobial activities and cytotoxicity against cancer cells.

Results and discussion

Synthesis and characterization of platinum NHC complexes

The synthesis of the targeted complexes followed established synthesis routes with minor modifications (**Scheme 1**) [25, 26]. Firstly, the commercially available 2-benzoylpyridine **1** was reduced to phenyl(pyridine-2-yl)methanol **2**, followed by halogenation to yield 2-(chloro(phenyl)methyl)pyridine **3**. After that, the targeted pyridine-functionalized imidazolium salts **4a**, **4b**, **4c** were attained by reacting with their respective imidazoles (1-methylimidazole, 1-phenylimidazole and 1-*tert*-butylimidazole) under reflux for 48 hours [25, 27]. The racemic Pt NHC complexes **(±)-5** were prepared using silver(I) oxide-mediated transmetalation method from the imidazolium salts **4**. A crude silver NHC complex were generated *in situ*, which was then filtered and immediately subjected to the subsequent reaction to yield Pt NHC complexes **(±)-5**, using dichloro(1,5-cyclooctadine)platinum(II) as the transmetalating agent. On the other hand, Ni NHC complexes **(±)-6** were synthesized via a one pot synthesis method by refluxing the imidazolium salts **4** with $NiCl_2$ and K_2CO_3 for 24 hours, followed by purification to obtain the final product. All synthesized complexes were characterized by ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy as well as mass spectrometry.

As we previously reported, the acidic proton (N*H*CN) signal of compounds **4** in the ^{1}H NMR spectra confirmed the formation of the salts and it resonated in a low field for all salts [23]. For examples, the characteristic imidazolium proton peak was observed at δ 10.39 ppm, 11.30 ppm and 11.19 ppm for compound **4a**, **4b**, **4c**, respectively. Besides that, their identities were also confirmed by the resonance of the different wingtip group on the heterocyclic ring, such as a singlet in the ^{1}H NMR at δ 4.03 ppm for the methyl group in compound **4a** and a singlet at δ 1.70 ppm for the *tert*-butyl group in compound **4c**. For all the salts, the proton at the chiral centre has a downfield shift appearing in the aromatic proton region (^{1}H NMR at δ 6.25 to 7.90) and was indistinguishable from other aromatic protons.

Similar to our previously reported Pd NHC complexes, we synthesized the Pt NHC complexes via transmetalation through the corresponding Ag(I) NHC complexes which act as a transfer agent. This method is highly established and very attractive compared to other procedures, which often require inert or harsher conditions. In this scenario, silver oxide plays the roles of a base as well as a metalation agent. The ease of the Ag-carbene bond formation is highly desirable because of the great affinity of the electron exchange between carbene C and Ag centre. The NHC species are good electronic donors whereby Ag acts as an excellent acceptor of electron density. The overall electronic exchange is the best example of a σ donation from carbene C to the Ag centre and a π back-donation from Ag to carbene C [24].

In general, the ^{1}H-NMR spectra of Pt NHC complexes **(±)-5** in DMSO-d_6 confirm the successful deprotonation of imidazolium moieties indicating coordination of the ligand to the platinum centre. A crucial observation was the disappearance of the characteristic N*H*CN proton signal of imidazolium salts **4** in the ^{1}H NMR spectra upon coordination of Pt in complex **(±)-5.** Similarly, the proton at the chiral centre shifted downfield and fell within the aromatic region, thus unidentifiable from other aromatic protons. The chemical shift values obtained lay within the range reported in our previous study of the analogous Pd NHC complexes [23]. No N*C*N resonance was observable in the ^{13}C NMR spectrum of the synthesized Pt NHC complexes in DMSO-d_6. This is expected as metal NHC complexes with similar behaviour were previously reported. The rationale behind the absence of carbene signals is still unclear, however a fast dynamic behaviour together with the poor relaxation of quaternary N*C*N could be responsible for it [28].

Due to the poor solubility of complex **(±)-5a** in a wide array of solvents but DMSO, a few drops of DMSO was added to the MeOH solution of **(±)-5a** to solubilize it completely. X-ray crystallography grade single-crystal of **(±)-5a** was obtained upon slow addition of diethyl ether into a methanol/DMSO solution of **(±)-5a**. An X-ray diffraction study was performed to elucidate the molecular structure of complex **(±)-5a**. As illustrated in **Figure 1**, the X-ray diffraction study of complex **(±)-5a** revealed that the six-membered ring is in the boat conformation, with the phenyl ring in the axial position. The platinum centre adopts a square planar geometry with the tetrahedral distortion angle θ = 5.7° between the planes of [Cl(1)-Pt(1)-Cl(2)] and [C(13)-Pt(1)-N(1)]. Besides that, the Pt(1)-Cl(2) bond is 0.058 Å longer than the Pt(1)-Cl(1) bond. This may be due to the trans effect as Cl(2) is trans to a strong trans directing ligand NHC as compared to the Cl(1). In addition, the electron density of the double bond is equally shared among the two nitrogen atoms next to the carbene atom in the imidazole ring. This is observed through the similar bond length of N(2)-C(13) and N(3)-C(13), which both are approximately equal to 1.36 Å (an average of a C–N bond of 1.465 Å and a C=N bond of 1.279 Å).

Hereby we observed the similar interesting characteristics of complex **(±)-5a**, which was similar to its analogous Pd NHC complex [29]. Firstly, instead of the chair conformation, the six-membered ring preferably adopted a boat conformation. This is because in chair conformation, the angles in the pyridine and imidazole ring will be highly tensed owing to the presence of many sp^2 hybridized carbons in the six-membered ring as

well as the planar pyridine and imidazole ring. Secondly, the bulkier phenyl ring is in the axial position rather than the usual equatorial position. In axial position, the phenyl group experienced minimal steric interaction with the pyridine and imidazole ring, which is highly favourable. Besides that, the square planar geometry in the platinum centre reduced the flagpole interaction experienced by the bulky phenyl group as the chlorine atoms will be pointing away from the phenyl group, thereby avoiding unfavourable steric interactions.

As for the complex **(±)-5b**, the recrystallisation attempt to obtain crystals which are suitable for single crystal X-ray diffraction analysis to determine the absolute configuration of **(±)-5b** is still on-going. We also face difficulties in obtaining crystallography grade crystals from recrystallization of racemic complex **(±)-5c**. Attempts to change the ancillary ligand from dichloro to dibromo and diiodo were performed. Dibromo complex **(±)-7** and diiodo complex **(±)-8** would have a poorer solubility as compared to dichloro complex, which may ease recrystallization. The identities of complexes **(±)-7** and **(±)-8** (**Scheme 2**) were verified with NMR and MS analyses, which both resembled the spectral data of complex **(±)-5c**.

Synthesis and characterization of nickel NHC complexes

Unlike the analogous Pd and Pt NHC complexes, transmetalation method was attempted using $NiCl_2$, adapted from Ray et al. for synthesis of Ni NHC complexes [17]. The imidazolium salts **4**, $NiCl_2$ and K_2CO_3 were stirred and refluxed for 24 hours in this one-pot synthesis method to obtain the crude Ni NHC complexes **(±)-6**, which were then subjected to purification using column chromatography method. Generally, it was observed that by using the $NiCl_2$ one-pot synthesis method, we were able to obtain the racemic Ni NHC complexes **(±)-6** after purification with column chromatography, which were preliminarily confirmed by the ^{1}H NMR before recrystallisation. However, unexpected products were obtained after recrystallisation attempts: a nickel coordination complex **9** yielded from the mother liquor of **(±)-6a** and a nickelate complex **10** yielded from the mother liquor of **(±)-6c** (**Scheme 3**).

Light green crystals were obtained from slow diffusion of diethyl ether into a methanol solution of racemic complex **(±)-6a**. Characterisation of the crystals using single crystal XRD analysis confirmed it to be an unexpected nickel coordination complex **9** with molecular formula of $C_{10}H_{20}Cl_2N_4O_2Ni$. The molecular ion peak for $[M\text{-}Cl]^+$ can be found at 322.1890 (calcd. 322.0707) in MS. **Figure 2** displays its molecular structure and **Table 2** lists the selected bond lengths and bond angles. The nickel atom was coordinated to three different ligands including methanol, methylimidazole and chloride. The nickel centre adopted a typical octahedral molecular geometry with six bonding atoms positioned at approximately 90 ° to each other. The incorporation of solvent molecule into a chemical structure as observed in complex **9** was not surprising. Zhang *et al*. had reported nickel NHC complexes that have solvent molecules incorporated into the structure apart of the NHC ring, where the solvent molecule is always located at the equatorial plane and arranged *trans* to a NHC ring [30].

Proton NMR was unable to resolve the peaks of complex **9**, regardless of whether DMSO-d_6 or $CDCl_3$ was used. Essentially, the unexpected complex **9** obtained was a high spin paramagnetic species (d^8 octahedral), which makes NMR spectroscopic characterisation difficult. Hence their structures were only determined by X-ray diffraction studies. In the proton NMR spectra obtained for complex **9**, the signals are broad and poorly resolved due to the different sets of ligand signals which indicate the different magnetically inequivalent ligands coordinated to the nickel centre. This will be further accentuated if there are coordinating solvents, for example DMSO, that will coordinate to the metal centre and induce octahedral broadening. The analysis of NMR spectrum is further complicated by the effect of the paramagnetic nickel centre on chemical shifts.

Our observation on C-N cleavage and isolation of complex **9** was not surprising. Previous literature reported different nickel NHC complexes with C-N bond cleavage which resulted in different Ni complexes as well as cleavage of a pyridine ligand around the metal centre [31, 32]. Zhong et al. proposed that a complex reaction took place during transmetalation, especially in methanol or other alcohol in the presence of a base, which resulted in the cleavage of the C-N bond at the adjacent bridge to the imidazolium ring. However, the exact mechanism is yet to be elucidated [31].

Previously Winston et al. reported a series of Ni NHC complexes with varying coordination geometries, where they encountered the problems in obtaining pure crystals from Ni NHC complexes reaction mixture due to formation of co-crystals [33]. This is similar to our observation on the selective isolation of complex **9** from complex **(±)-6a**. It is characteristic of nickel(II) complexes that complicated equilibria, which are generally temperature dependent and sometimes concentration dependent. It exist between various structural types. Nevertheless, the formation of co-crystals can be rationalised by postulating the establishment of an equilibrium involving mono- and di-substituted Ni containing species. The equilibrium proposed below is thereby plausible and has been suggested for other Ni(II)/bidendate ligand system [33, 34].

$NiCl_2(MeOH) \rightleftharpoons NiCl_2(NHC) \rightleftharpoons NiCl_2(NHC)_2$

$NiCl_2(MeOH) + NiCl_2(NHC)_2 \rightleftharpoons Cl_2Ni(NHC)_2(MeOH)_2 \rightleftharpoons Ni_2Cl_4(NHC)_2 + MeOH$

Blue green crystals were obtained from slow diffusion of diethyl ether into a methanol solution of racemic complex **(±)-6c**. Characterisation of the crystals using single crystal XRD analysis confirmed it to be an unexpected nickelate complex **10** with molecular formula of $(C_{19}H_{22}N_3)_2NiCl_4$ (**Figure 3**). The molecular ion peak for $[M\text{-}NiCl_4]^+$ can be found at 291.1700 (calcd. 292.1814) in MS. **Table 3** presents the selected bond lengths and angles. The X-ray diffraction study showed the crystal was made up of two units of positively-charged pyridine-functionalised imidazole ring with *tert*-butyl at the *N* wing-tip, and a negatively-charged $NiCl_4^{2-}$ ion respectively. The negatively-charged $NiCl_4^{2-}$ ion was in an expected tetrahedral coordination geometry with an average angle of 109.5°. From the bond length of N(3)-C(13), N(2)-C(13) and C(15)-C(14), also corresponded to N(5)-C(32), N(6)-C(32) and C(33)-C(34), which are all approximately 1.33 Å, it is evident that the positive charge delocalised over the entire five-membered imidazole ring, thereby offering the cationic ligand additional stability.

Zhang et al. had suggested that it is impossible to host two ligands around nickel ions due to large steric hindrance, hence the failure in incorporation of large and bulky group to create Ni NHC complexes [30]. In addition to that, weaker M-C bonds are being formed in Ni case as compared to Pd and Pt. Therefore, it is speculated that the separation of the bulky phenyl group and pyridine group from the overall structure of complex **(±)-6c**, which yielded complex **10** upon recrystallization, could be due to their large steric repulsion pressure that force the complex to restructure. It was previously reported in literature that reprotonation of the carbene moieties had occurred upon transmetalation, instead of transfer to nickel, with formation of a mixed tetrachloronickelate/chloride imidazolium salt [35, 36]. It was reasoned that the formation of stable $[NiCl_4]^{2-}$ was more kinetically favoured as compared to transmetalation to Ni, thus preventing transmetalation.

Antimicrobial study

In this study, broth microdilution assay was conducted to determine the antimicrobial activities of the synthesized complexes against a panel of microorganisms including nine strains of Gram positive bacteria, four strains of Gram negative bacteria, and a *Candida albicans* (yeast). The complexes tested include the pyridine-functionalized imidazolium salts **4a-c,** racemic Pt NHC complexes **(±)-5a-c**, the racemic dibromo and diiodo Pt NHC complexes **(±)-7** and **(±)-8**, the unexpected nickel coordination complex **9** and nickelate complex **10**. Their antimicrobial activities were quantitatively expressed in terms of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). MIC is the minimum concentration of a compound to inhibit the growth of the microorganisms, whereas MBC is referring to the minimum concentration of a compound to kill the microorganisms tested. An antibiotic, chloramphenicol, was used as the reference drug in the antimicrobial assay. Chloramphenicol is a type of broad spectrum antibiotic that exerts antimicrobial effect through protein synthesis inhibition by binding to the 50S ribosomal subunit. **Table 4** shows the compounds tested and their respective MIC and MBC values.

In general, only a lower micromolar concentrations of the synthesized complexes were required to inhibit the growth of the Gram positive bacterial strains, while Gram negative bacterial strain often required a higher concentration. The different susceptibility of Gram positive and Gram negative bacteria can be attributed to their morphological differences. The outer peptidoglycan layer of Gram positive bacteria is not an effective permeability layer. In contrast, the outer membrane of Gram negative bacteria contained structural lipopolysaccharide components, thus making the cell wall impermeable to lipophilic solutes whereby porins, a membrane transport proteins, constitute a selective barrier to the hydrophilic solutes. The metal NHC complexes synthesized were not soluble in a wide array of solvents but DMSO, and they were made up of several conjugated rings, which give rise their hydrophobicity (i.e. lipophilicity). Therefore, the lack of efficacy against gram-negative bacteria was not surprising.

In this study, we have tested multiple strains of the same bacteria. For examples, the *Staphylococcus aureus* strains which are sensitive to methicillin (MSSA) and those which are resistant to methicillin (MRSA), as well as *Enterococcus faecalis* and its antibiotic-resistant strain (vancomycin-resistant Enterococci, VRE). This is because certain compounds may have different degree of antimicrobial activities against different strains of bacteria, especially against the antibiotic-resistant strains. The strain variation effect would render the antimicrobial compound to be effective against some strains but not the other, which in turn would make the antimicrobial compounds less viable to be used as an antimicrobial drug. Notably, the antimicrobial activities of the metal NHC complexes against *S. aureus* was observed to be strain dependent. For instance, there was an eight-fold difference in the MIC values of the **(±)-5b** against MSSA ATCC 6538P and MRSA ATCC 700699 (**Table 4**). CLSI (2012) had proposed that two treatments with MIC values within two-fold difference is not significantly different from each other. The strain dependent activity observed could be due to differences in the cell wall compositions, such as presence of membrane-bound penicillin-binding proteins in MRSA [37, 38]. Majority of the antimicrobial studies of metal NHC complexes focused only on a single strain of each bacterial species and concluded that they are effective against the bacterial species [20-22, 39-42]. However, our results suggested otherwise, which implies the importance of testing the complexes against several strains of a same bacterium.

Imidazolium salts or NHC precursors **4** have showed antimicrobial activities at 5 mM or below against the microorganisms tested. The results are in agreement with other imidazolium-based salts that displayed antimicrobial properties as reported by literature [43-47]. Yet, the activities were not comparable to some imidazolium salts which have MIC values in μM range [45]. This could be due to the structure of the synthesized imidazolium salts **4** were lacking effectively long alkyl chain. Literature have suggested that the antimicrobial activity is often dependent on the chain length of the *N*-substituted imidazolium salts, in which the lowest MIC were achieved by compounds with long alkyl chains (C_8 to C_{16}) while alkyl chains of less than six carbons are generally not active [44, 46]. Longer alkyl chain is thought to be associated with disruption of bacterial membrane, probably due to the integration of the long hydrocarbon chain with the lipid bilayer of the cell membrane, leading to leakage of the cell content [48]. Nonetheless, the optimum antimicrobial activities of an imidazolium salts can be postulated to several factors including hydrophobicity, adsorption, critical micellar concentrations, aqueous solubility and transport in the assay medium, with solubility in the assay medium being the limiting factor for transport.

Notably, the antimicrobial activities increased remarkably upon coordination to platinum (**(±)-5a**). Surprisingly, these Pt NHC complexes **(±)-5** exhibited significant antimicrobial activities surpassed that of their analogous Pd NHC complexes we reported before [23]. The **(±)-5b** and **(±)-5c** complexes, which bear the aromatic phenyl ring and the bulky *tert*-butyl group at the *N* tip of the imidazole ring respectively, were more capable of inhibiting the growth of microorganisms at a lower concentration as compared to the **(±)-5a** complex which bears the aliphatic CH_3 group. The **(±)-5b** and **(±)-5c** complexes displayed similar pattern of antimicrobial activities against the microorganisms tested, with MIC at the micromolar range being reported. The most substantial antimicrobial activities were observed against Gram positive bacteria with MIC below 10 μM (or below 5 μg/mL).

The difference in the antimicrobial activities for **(±)-5a-c** could be due to the overall lipophilicity of the entire structure. The complex **(±)-5a** only made up of a single carbon unit alkyl chain while longer chain length would be expected for better antimicrobial activities. Whereas the respective aromatic phenyl group and bulky *tert*-butyl group in Pt NHC complex **(±)-5b** and **(±)-5c** would give the intrinsic lipophilicity to the structures resulting in better antimicrobial activities of those two complexes. Although there is no available literature reported on the antimicrobial activities of Pt NHC complexes, the antimicrobial activities of **(±)-5** complexes were comparable to those Ag and Au NHC complexes which are widely known for their antimicrobial properties. For examples, Young's group reported a series of Ag NHC complexes with MIC lower than 10 μg/mL [3, 49]. Ray *et al.* also reported two antimicrobial gold and silver NHC complexes with MIC values at 15 μM and 25 μM, respectively [20]. Notably, it is observed that the complexes **(±)-5c**, **(±)-7** and **(±)-8**, which have different ancillary ligands (chloride, bromide and iodide, respectively), exhibited similar antimicrobial activities. This suggested that the change of ancillary ligands does not have significant effect on the complexes' antimicrobial activities in this case.

In general, the findings suggested that the antimicrobial activity arises from a synergy between the metal and the ligand. Based on Tweedy's chelation theory, the ion polarity of the metal centre is reduced by overlapping of the ligand orbitals and the exchange of the partial positive charge of the metal ion to the donor atoms of the ligands; thereby the delocation of π-electrons on the chelate ring increase and improve the lipophilicity of the complexes [50]. The increased lipophilicity allows the complex to penetrate the lipid membrane and block the metal binding sites on the enzymes, which might result in the disturbance of cellular respiration and protein synthesis, thereby inhibiting the growth. Generally, the nucleic acids, especially the deoxyribonucleic acid (DNA), is commonly considered to be the main target of Group 10 metallodrugs through the formation of intra-

and inter-strand adducts, while metal-bonding to sulphur-containing groups in proteins and interference with mitochondria functions were also reported [51].

Lastly, the unexpected nickel coordination complex **9** and nickelate complex **10** did not display antimicrobial activities at the highest concentration tested (0.5 mM). However, nickelate complexes were known to have antimicrobial activities towards both Gram positive and Gram negative bacteria though comparison cannot be made in this case as the antimicrobial activities were reported in terms of zone of inhibition obtained from disk diffusion assay and well diffusion assay [51-53]. It is speculated that the lack of antimicrobial activities of the nickelate complex **10** was due to the low final concentration tested. Therefore, antimicrobial activities are expected in case of increment of the final concentration tested of this nickelate complex **10**.

Cytotoxicity study

As mentioned earlier, numerous Pt NHC complexes have shown outstanding antiproliferative activities against cancer cells. In present study, MTT cell viability assay was performed to determine cell cytotoxicity of the synthesized complexes on selected carcinoma cell lines, including H103 (oral carcinoma), HCT116 (colon carcinoma) and MCF7 (breast carcinoma). In this assay, cisplatin was utilised as a positive control as it is a clinically used antitumor drug. Cisplatin was known to exert its antitumor action via binding of cisplatin to DNA and non-DNA targets, which further induce cell death through apoptosis, necrosis or both within the heterogenous population of cells that forms a tumoral mass. It is a great reference drug for comparing the cell cytotoxicity of the synthesized metal NHC complexes to reflect the possible effectiveness and applicability of these metal NHC complexes as novel anticancer drugs in this preliminary screening stage.

In general, the results showed that the compounds tested had an inhibitory effect in a dose-dependent manner against the cancer cells tested (**Table 5**). This is expected as different cell lines would have different growth rates, drug sensitivities, oncogene expressions and other factors that might possibly cause the variations in the cells [54, 55]. Literatures have also demonstrated that those reported IC_{50} values of metal NHC complexes may vary between different cell lines evaluated, therefore it is plausible that these metal NHC complexes would have different magnitudes of potency in other cell types.

Remarkably, no cell cytotoxicity effect was observed for the imidazolium salts **4** up to 40 μM against the three carcinoma cell lines tested. Therefore, the cytotoxic effects observed in the racemic palladium and platinum complexes **(±)-5** is speculated to be mainly due to the metal-ligand interaction with cellular components. The cell cytotoxic effects of these active complexes were comparable to those of other reported organic anticancer agents, including noscapine (IC_{50} of 20-35 μM) and estramustine (IC_{50} of 0.5-17 μM) [56, 57]. Also, the IC_{50} values of metal NHC complexes were previously reported to vary within different cell lines, hence it is conceivable that these metal NHC complexes could show greater potency in other cell types.

In general, the metal NHC complex **(±)-5b (**with aromatic phenyl *N*-tip) and **(±)-5c** (with bulky tert-butyl *N*-tip), regardless of palladium or platinum, have shown better cytotoxic effect compared to their analogue **(±)-5a** (with aliphatic methyl *N*-tip) against the tested carcinoma cell lines as evidenced by the low IC_{50} values recorded. This structure-activity relationship may be attributed to the central metal atom as explained by Tweedy's chelation theory and overall lipophilicity of the compounds [58]. In addition, it was known that the steric factors (bulk, size and shape) of drug can affect how easily it can approach and interact with a binding site. Bulky substituents may act like a steric shield and hinder the ideal interaction between a compound and its binding site,

alternatively, it may help to orientate the compound properly for maximum binding and increase activity [59, 60].

Comparison between different metal centres of the metal NHC complexes have revealed that there are variations in their cytotoxicities against the cancer cells tested. The **(±)-5** complexes displayed higher cytotoxicities against the carcinoma cell line tested as compared to the analogous Pd NHC complexes (IC_{50} range of 13.90 to 38.74 μM) with IC_{50} ranging from 5.52 to 28.34 μM [23]. Among all, **(±)-5c** with the bulky *tert*-butyl *N* substituent was the most potent among all the metal NHC complexes tested, with IC_{50} that are two to three times lower than that of the anticancer drug cisplatin. These results are not surprising as platinum NHC complexes were well known for their anticancer properties, as evident by the widespread applications of platinum-based drugs as chemotherapeutics. Literature have reported a series of Pt NHC complexes with varying IC_{50} compared to cisplatin, ranging from as low as 0.01 μM to more than 100 μM [9, 15, 61]. Therefore, the Pt NHC complexes **(±)-5** were moderately cytotoxic towards the cancer cells tested, among others.

The mode of action of platinum NHC complexes is generally due to covalent bonding at the minor groove of DNA causing crosslinking of the bases (especially with guanine), and the square planar configuration at the metal centre enabled intercalation of the compounds with the DNA involving a π–π stacking. There were also reports on the Pt NHC complexes accumulated in the nucleus, mitochondria or cytoplasm and play an important role in triggering cell apoptosis [15, 62]. Apart from the usual DNA target, platinum NHC complexes were recently shown to be interacting with G-quadruplex (G4) structures from telomeric sequence involved in oncogene promotors and thereby causing cell death [63].

Last of all, it was observed that the unexpected nickel coordination complex **9** did not display cytotoxicity against the cancer cells at the highest concentration tested (40 μM). While the unexpected nickelate complex **10** was not cytotoxic towards HCT116 and MCF7 at 40 μM, it was cytotoxic towards the oral cancer cells (H103) with IC_{50} value of 32.71 μM. There was a previous report on a sodium tris(aspartato)nickelate(II) complex which displayed LC_{50} (the concentration of a given compound which is lethal to 50% of the cell) values of 4.187-8.044 μg/mL in an *in vivo* brine shrimp lethality bioassay [64]. This thereby suggesting that nickelate complex could be a cytotoxic agent towards living cells. Nonetheless, the low cytotoxicity of the nickelate complex **10** against cancer cells observed could be attributed the low final concentration used in the assay, and the cytotoxicity is expected to enhance with increment of the final concentration tested of this nickelate complex **10**.

Selectivity index study

Despite that the cytotoxic effects of the tested complexes **(±)-5** towards the selected cancer cells are promising, these metal NHC complexes should not harm the normal cells. Therefore, a selectivity index study was conducted to compare the cytotoxic effects of these metal complexes against both cancer cells and normal cells. First and foremost, the synthesized complexes that were effective against the cancer cells were also tested against a panel of normal human cells including OKF6 (human oral epithelial cells), HACAT (human skin keratinocytes) and BEAS2B (human lung epithelial cells). The selection of these three human cell lines was to explore the prospect of possible drug delivery methods for future applications, i.e. oral administration of drug, dermal or transdermal drug delivery *via* skin, as well as pulmonary delivery *via* lung. **Table 6** shows their respective cytotoxicities against OKF6, HACAT and BEAS2B. Likewise, a dose-dependent pattern was

observed for the same compound against the normal cell lines tested. Besides, the IC_{50} values obtained were neither significantly higher nor lower than that of against the cancer cells.

The selectivity index (SI) indicates the cytotoxic selectivity of the compound against cancer cells and its safety towards normal cells. It was determined from the ratio of the IC_{50} value obtained from the cell viability test on normal cells versus the IC_{50} value obtained for the cancer cells. The compound with selectivity index value higher than 3 is suggested to have high selectivity towards a particular cell line while value above 1 indicates greater inhibition of cancer cells survival than normal cells [65-68]. In this case, selectivity index was computed based on the IC_{50} values of three cancer cell lines and a normal cell at a time. **Table 7** displays the selectivity index of the active complexes for OKF6 (oral epithelial cells), HACAT (skin keratinocytes) and BEAS2B (lung epithelial cells).

Overall, it was observed that the Pt NHC complexes **(±)-5**, **(±)-7** and **(±)-**were not selective against the cancer cells as the SI value obtained were below 2 and lay between the range of 0.22 to 1.88. Although some of the tested complexes have the SI values that are comparable or even surpassed that of cisplatin, the selectivity towards the cancer cells was unsatisfactory as it is less than three. Cisplatin is renowned for its high effectiveness in the treatment for ovarian and testicular cancers and is also widely employed for treatment of cervical, bladder, head and neck, oesophageal and small cell lung cancers. Cisplatin is traditionally administered through the vein intravenously as an infusion. Therefore, the low selectivity index of cisplatin calculated was not surprising as the cell lines utilised are oral, colon and breast cells. On top of that, the low selectivity of cisplatin towards the normal cells explained the toxicities of cisplatin towards the cancer patients, which are reflected by the side effects after cisplatin treatment.

However, these low selectivity index obtained could be due to the fast doubling time of the normal oral epithelial cells (OKF6), normal skin keratinocytes (HACAT) and normal lung epithelial cells (BEAS2B), which are similar to that of the cancer cell lines. As a result, these fast-growing normal cells were also susceptible to the metal complexes at low concentration of compounds, as observed from their IC_{50} values. Otherwise, literature have suggested that higher concentration of drug is required to inhibit slow-growing cells in relations with its higher doubling time in culture, and this would make the cell resistant to the cytotoxic agents tested [65, 69]. Therefore, it is anticipated that the cytotoxicity of these synthesized complexes would reduce when it is tested against a slow-growing cell line, such as CCD841CON (a colorectal epithelial cell line), which resembled the growth rate of typical normal cells, thereby increase the selectivity index in such cases.

Conclusions

This study presented a new series of platinum NHC complexes derived from pyridine-functionalized imidazolium salts. All NHC precursors, imidazolium salts (or NHC precursors), metal NHC complexes and the unexpected nickel complexes were characterized by analytical and spectroscopic techniques. The molecular structure of Pt NHC complex **(±)-5a** were elucidated by the means of single crystal X ray diffraction technique. Besides, the recrystallization attempts of the Ni NHC complexes **(±)-6** have yielded an unexpected nickel coordination complex **9** and a nickelate complex **10**, which both have been structurally determined through X ray crystallography study. While the imidazolium salts (or NHC precursors) **4** exhibited insubstantial antimicrobial activities than those reported by the literatures, the Pt NHC complexes **(±)-5** have shown improved antimicrobial activities upon coordination to metals. Remarkably, complexes **(±)-5b** and **(±)-5c** exhibited significant antimicrobial activities with MIC as low as 2 μM, which are comparable to silver NHC

complexes with renowned antimicrobial profiles. Likewise, the cytotoxic effects of complexes **(±)-5** increased significantly upon coordination to platinum (as compared to the imidazolium salts **4**). Most notably, complex **(±)-5** displayed outstanding cytotoxicities towards the cancer cells with IC_{50} values that are two to three times lower than that of the anticancer benchmark cisplatin. However, selectivity index study's results indicate that the tested complexes and cisplatin demonstrated similar selectivity towards the tested cancer cells. Essentially, evidences for the influence of metals and *N* wingtip substituents on the NHC ring on the antimicrobial and anticancer activities of these metal NHC complexes have been found. Although the mechanism of action for the reported biological activities is not known at present, it is apparent from this work that these Pt NHC complexes could be some potential drug candidates in the future.

Experimental

General procedures

All the commercially available chemicals and solvents were used without prior drying or purification. Dichloro(1, 5-cyclooctadiene)platinum(II) Pt(cod)Cl_2, 1-phenylimidazole and 1-*tert*-butylimidazole were prepared according to literature methods with some modifications [70-72]. Melting point determination was carried out using Stuart Digital Melting Point Apparatus SMP10 with 1 °C resolution. Mass spectra were recorded on Agilent 1290 Infinity LC system coupled to Agilent 6520 Accurate-Mass Q-TOF mass spectrometer with dual ESI source. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on a Bruker Advance 300 NMR spectrometer. The number of protons (n) for a given resonance is indicated by n H. Coupling constants are reported as a *J* value in Hz. Proton nuclear magnetic resonance spectra ^{1}H NMR are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.00). Carbon nuclear magnetic resonance spectra ^{13}C NMR are reported as δ in units of parts per million (ppm) relative to the signal of chloroform-*d* (δ 77.16 ppm, triplet) and DMSO-d_6 (δ 39.52 ppm, septet). All chemical shifts reported are referenced to the chemical shifts of their respective residual solvent resonances. Unless stated otherwise, all NMR experiments are carried out at 300 K. The single crystal X ray diffraction studies were performed by X ray crystallography facilities in University Malaya (UM) and Universiti Kebangsaan Malaysia (UKM), Malaysia.

Synthesis of phenyl(pyridin-2-yl)methanol, 2

The method for reduction of 2-benzoylpyridine into phenyl(pyridin-2-yl)methanol was modified from literature [27]. Sodium borohydride (2.04 g, 54 mmol) in 50 mL 95 % ethanol was added dropwise into a solution of 2-benzoylpyridine (5 g, 27 mmol) in 50 mL 95% ethanol on an ice bath. The reaction mixture was stirred continuously for 1 hour until reaction is completed. Then, 100 mL of water was added to the reaction mixture and the solution was heated at 90 °C for 15 minutes. Then, the solution was extracted with ethyl acetate thrice and the solvent was evaporated under reduced pressure to obtain a pale green oil. Slow evaporation of a solution in ethanol at room temperature yielded the clear crystal solid, 5.01 g, 96.4 %. M.p. = 88 – 90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.29 (d, 1 H, $J_{H,H}$ = 4.5 Hz, OH), 5.75 (d, 1 H, $J_{H,H}$ = 4.5 Hz, *H*C-OH), 7.13-7.39 (m, 7 H, arom.), 7.60-7.61 (m, 1 H, arom.) and 8.55 (ddd, 1 H, $J_{H,H}$ = 5.1 Hz, $J_{H,H}$ = 1.2 Hz, $J_{H,H}$ = 0.9 Hz, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 75.00 (H*C*-OH), 121.35, 122.42, 127.07, 127.82, 128.56, 136.83, 143.23, 147.83 and 160.91 ppm. MS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{12}NO$ 186.0919, found 186.0912.

Synthesis of 2-(chloro(phenyl)methyl)pyridine, 3

Phenyl(pyridin-2-yl)methanol **2** (1.85 g, 10.5 mmol) and triethylamine (3.4 mL, 24.4 mmol) in 32 mL of CH_2Cl_2 was stirred in an ice bath. Methanesulfonyl chloride (1.2 mL, 15.8 mmol) was added dropwise into the stirring solution. The reaction mixture was left to warm up slowly to room temperature. The reaction mixture was allowed to stir overnight and then poured into a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with chloroform thrice. The combined organic layers were washed with H_2O, dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give a red liquid. The resultant red liquid was subjected to column chromatography (ethyl acetate/hexane 1:4 v/v) give yellow oil, 1.52 g, 74.3 %. The spectral data for this compound are consistent with those reported in the literature [25]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.16 (s, 1 H, ClC*H*), 7.20 (ddd, 1 H, $J_{H,H}$ = 7.5 Hz, $J_{H,H}$ = 4.8 Hz, $J_{H,H}$ = 1.2 Hz, arom.), 7.25-7.37 (m, 3 H, arom.), 7.45-7.56 (m, 3 H, arom.), 7.67-7.73 (m, 1 H, arom.) and 8.57 (ddd, 1 H, $J_{H,H}$ = 4.8, $J_{H,H}$ = 1.8, $J_{H,H}$ = 0.9 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.54 (Cl*C*H), 122.09, 122.81, 127.78, 128.28, 128.64 and 137.05, 139.96, 149.19 and 159.75 ppm. MS (ESI) *m/z*: $[M\text{-}Cl]^+$ calcd. for $C_{12}H_{10}N$ 168.0813, found 168.0804.

Synthesis of pyridine-functionalized imidazolium salts 4

Liquid 1-methylimidazole (**a**) or 1-phenylimidazole (**b**) or 1-tert-butylimidazole (**c**) (1 mol equiv.) was added to a stirring solution of compound **3** (1 mol equiv.) in 50 mL of CH_3CN. The reaction mixture was heated at refluxing temperature for 48 hours. Then, the reaction mixture was reduced in vacuo and the resulting oil was stirred in diethyl ether. The diethyl ether layer was decanted away to give ligand **4a**, **4b** and **4c**. The spectral data for these compounds are consistent with those reported in the literature [25, 26, 29].

Synthesis of 1-methyl-3-[phenyl(pyridin-2-yl)methyl]-1*H*-imidazolium chloride, 4a

Hygroscopic off white solid, 45.8 %. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.03 (s, 3 H, C*H*$_3$), 7.26-7.37 (m, 4 H, arom.) 7.41-7.46 (m, 3 H, arom.), 7.63-7.76 (m, 4 H, arom.), 8.57-8.60 (m, 1 H, arom.) and 10.39 (s, 1 H, carbenic proton) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.63 (*C*H$_3$), 65.98 (N*C*Ph), 122.48, 122.58, 123.78, 124.36, 128.84, 129.24, 129.34, 136.43, 137.61, 137.85, 149.52 and 155.09 ppm. MS (ESI) *m/z*: $[M\text{-}H]^+$ calcd. for $C_{16}H_{15}N_3Cl$ 284.0954, found 284.2074.

Synthesis of 1-phenyl-3-[phenyl(pyridin-2-yl)methyl]-1*H*-imidazolium chloride, 4b

Brown oil, 2.71 g, 28.8 %.^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34-7.39 (m, 3 H, arom.), 7.49-7.61 (m, 5 H, arom.), 7.67-7.79 (m, 5 H, arom.), 7.96 (t, 1 H, $J_{H,H}$ = 1.8 Hz, arom.), 8.23 (s, 1H, arom.), 8.60 (ddd, 1 H, $J_{H,H}$ = 0.9 Hz, $J_{H,H}$ = 1.8 Hz, $J_{H,H}$ = 4.8 Hz, arom.) and 11.30 (s, 1 H, carbenic proton) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.82 (N*C*Ph), 119.47, 121.71, 123.44, 123.80, 124.81, 129.10, 129.25, 129.41, 130.19, 130.56, 134.54, 136.28, 136.42, 137.71, 149.34, and 155.02 ppm. MS (ESI) m/z: $[M\text{-}Cl]^+$ calcd. for $C_{21}H_{18}N_3$ 312.1501, found 312.1508.

Synthesis of 1-tert-butyl-3-[phenyl(pyridin-2-yl)methyl]-1H-imidazolium chloride, 4c

Brown solid, 8.24 g, 54.0 %. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 (s, 9 H, CC*H*$_3$), 7.27-7.37 (m, 5 H, arom.), 7.50-7.55 (m, 2H, arom.), 7.69-7.75 (m, 1 H, arom.), 7.81-7.83 (m, 1 H, arom.), 8.14 (s, 1 H, arom.), 8.59 (ddd, 1 H, $J_{H,H}$ = 0.9 Hz, $J_{H,H}$ = 1.8 Hz, $J_{H,H}$ = 4.8 Hz) and 11.19 (s, 1 H, carbenic proton) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.05 (C*C*H$_3$), 60.13 (N*C*CH3), 65.26 (N*C*Ph), 117.97, 122.50, 123.60, 124.87, 128.91, 129.07, 136.53 and 136.96, 137.55, 149.30 and 155.44 ppm. MS (ESI) *m/z*: $[M\text{-}Cl]^+$ calcd. for $C_{19}H_{22}N_3$ 292.1814, found 292.3259.

Synthesis of pyridine functionalized Pt NHC complexes (±)-5

To a solution of pyridine-functionalized NHC precursors **4a**, **4b**, **4c** (1 mol equiv.) in 30 mL of CH_2Cl_2, Ag_2O (0.5 mol equiv.) was added in the dark. The reaction mixture was stirred at room temperature for 12 hours and was filtered through a short plug of celite. The $Pt(cod)Cl_2$ (1 mol equiv.) was added to the orange filtrate in the dark. The reaction mixture was then allowed to stir at room temperature for two weeks and was filtered through celite. The filtrate was then reduced *in vacuo* to yield the racemic Pt NHC complexes **(±)-5**.

Synthesis of racemic Pt NHC complex (±)-5a

Off white solid 0.760 g, 35.0 %. M.p. = 236 – 238 °C (decomposed). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.90 (s, 3 H, C*H*$_3$), 7.05 (s, 1 H, arom.), 7.26-7.45 (m, 6 H, arom.), 7.54-7.60 (m, 1 H, arom.), 7.75 (d, 1 H, $J_{H,H}$ = 2.1 Hz, arom.), 7.97-7.99 (m, 1 H, arom.), 8.20-8.26 (m, 1 H, arom.) and 9.31 (dd, 1 H, $J_{H,H}$ = 1.5 Hz, $J_{H,H}$ = 6.0 Hz, arom.) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 37.60 (*C*H$_3$), 66.95 (N*C*Ph), 122.09, 123.90, 126.32, 127.22, 128.49, 129.07, 129.48, 138.15, 139.84, 140.29, 154.57, 155.57 ppm. MS (ESI) *m/z*: $[M]^+$ calcd. for $C_{16}H_{15}Cl_2N_3Pt$ 514.0291, found 514.0169. Light yellow crystals were obtained from slow diffusion of diethyl ether into a methanol/DMSO solution of **(±)-5a**.

Synthesis of racemic Pt NHC complex (±)-5b

Orange solid 1.37 g, 44.5 %. M.p. = 241 – 243 °C (decomposed). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.42 (s, 1 H. arom.), 7.47-7.51 (m, 4 H, arom.), 7.55-7.61 (m, 4 H, arom.), 7.72-7.74 (m, 1 H, arom.), 7.86-7.92 (m, 3 H, arom.), 8.14-8.19 (m, 2 H, arom.), 8.30-8.31 (m, 1 H, arom), 9.41 (dd, 1 H, $J_{H,H}$ = 1.2 Hz, 5.7 Hz, arom.) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 67.53 (N*C*Ph), 121.83, 125.37, 127.03, 127.45, 128.89, 129.12, 129.49, 129.82, 130.32, 139.04, 139.37, 140.76, 155.07 and 155.58 ppm. MS (ESI) *m/z*: $[MH\text{-}Cl]^+$ calcd. for $C_{21}H_{18}ClN_3Pt$ 542.0837, found 542.0283.

Synthesis of racemic Pt NHC complex (±)-5c

Brown solid, 1.71g, 51.0%. M.p. = 227 – 228 °C (decomposed). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.61 (s, 9 H, CC*H*$_3$), 7.21 (s, 1 H, arom.), 7.34-7.48 (m, 6 H, arom.), 7.77-7.90 (m, 2 H, arom.), 7.94-7.96 (m, 1 H, arom.), 8.07 (t, 1 H, $J_{H,H}$ = 2.1 Hz, arom.) and 8.64-8.66 (m, 1 H, arom.) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 30.88 (C*C*H$_3$), 60.38 (N*C*CH$_3$), 66.45 (N*C*Ph), 120.90, 123.02, 123.89, 124.34, 128.37, 128.96, 129.56, 135.42,

137.43, 138.23, 150.09 and 155.88 ppm. MS (ESI) *m/z*: $[M-H]^+$ calcd. for $C_{19}H_{20}Cl_2N_3Pt$ 555.0682, found 555.0453.

Preparation of racemic dibromide Pt NHC complex (±)-7

The solution of racemic complex **(±)-5c** (1.64 g, 2.94 mmol) in 50.0 mL dichloromethane was added to potassium bromide (3.53 g, 29.7 mmol) in acetone (50.0 mL) and water (10.0 mL). The mixture was then stirred vigorously for 15 minutes. The solvents were removed *in vacuo* and the residue was extracted with dichloromethane and water. Then, the organic layer was dried by using anhydrous magnesium sulphate. Removal of solvent gave **(±)-7** as a brown solid, 1.04 g, 54.7 %. M.p. = 205 – 207 °C (decomposed). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.61 (s, 9 H, CCH_3), 7.18 (s, 1 H, arom.), 7.41-7.49 (m, 5 H, arom.), 7.65-7.70 (m, 1 H, arom.), 7.88-7.96 (m, 3 H, arom.), 8.07 (t, 1 H, $J_{H,H}$ = 1.8 Hz, arom.) and 8.65 (ddd, 1 H, $J_{H,H}$ = 0.9 Hz, $J_{H,H}$ = 1.8 Hz, $J_{H,H}$ = 4.8 Hz, arom.) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 30.36 (CCH_3), 59.64 (N*C*CH3), 65.70 (N*C*Ph), 120.12, 122.26, 123.10, 123.59, 127.92, 128.18, 128.79, 134.56, 136.61, 137.47, 149.32 and 155.06 ppm. MS (ESI) *m/z*: $[M]^+$ calcd. for $C_{19}H_{21}Br_2N_3Pt$ 643.9750, found 644.0705.

Preparation of racemic diiodo Pt NHC complex (±)-8

The solution of racemic complex **(±)-Pt-5c** (1.01 g, 1.81 mmol) in 100 mL dichloromethane was mixed with sodium iodide (2.00 g, 13.3 mmol) in acetone (100 mL). The mixture was then stirred vigorously for 15 minutes. The solvents were removed *in vacuo* and the residue was extracted with dichloromethane. Then, the solvent was removed under reduced pressure and diethyl ether was added to obtain **(±)-8** as a brown solid, 1.05 g, 78.4 %. M.p. = 213 – 216 °C (decomposed). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.61 (s, 9 H, CCH_3), 7.16 (s, 1 H, arom.), 7.34-7.48 (m, 5 H, arom.), 7.88-7.95 (m, 3 H, arom.), 8.07 (t, 1 H, $J_{H,H}$ = 2.1 Hz, arom.) and 8.65 (ddd, 1 H, $J_{H,H}$ = 0.9 Hz, $J_{H,H}$ = 1.8 Hz, $J_{H,H}$ = 4.8 Hz, arom.) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 31.07 (CCH_3), 59.92 (N*C*CH_3), 66.06 (N*C*Ph), 120.38, 122.54, 123.35, 123.86, 128.44, 129.06, 129.71, 134.77, 136.82, 137.74, 149.58 and 155.30 ppm. MS (ESI) *m/z*: $[M]^+$ calcd. for $C_{19}H_{21}I_2N_3Pt$ 739.9437, found 740.1476.

Synthesis of pyridine functionalized Ni NHC complexes (±)-6

The pyridine-functionalized NHC precursors **4a**, **4b**, **4c** (1 mol equiv.), $NiCl_2$ (1.5 mol equiv.) and K_2CO_3 (3 mol equiv.) were taken in 50.0 mL of acetonitrile. The reaction mixture was refluxed for 24 hours, filtered and the solvent was removed. The residue was extracted in CH_2Cl_2, which was filtered and evaporated under vacuum to obtain the oil. The crude oil was subjected to purification using column chromatography with CH_2Cl_2/MeOH (50:50 v/v) as the mobile phase to yield the racemic Ni NHC complexes **(±)-6**.

Synthesis of racemic Ni NHC complex (±)-6a

Hygroscopic greenish brown solid, 3.30 g, 39.2 %. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.05 (s, 3 H, CH_3), 7.21 (s, 1 H, arom.), 7.27-7.37 (m, 5 H, arom.), 7.45-7.48 (m, 3 H, arom.), 7.70-7.76 (m, 2 H, arom.) and 8.59 (d, 1 H, $J_{H,H}$ = 4.5 Hz, arom.) ppm. Light green crystals were obtained from slow diffusion of diethyl ether into

a methanol solution of **(±)-Ni-5a**. Characterisation of the crystals using single crystal XRD analysis confirmed it to be an unexpected nickel coordination complex **9** with molecular formula of $C_{10}H_{20}Cl_2N_4O_2Ni$. MS (ESI) *m/z*: $[MH\text{-}Cl]^+$ calcd. for $C_{10}H_{21}ClN_4O_2Ni$ 322.0707, found 322.1890. M.p. = 130 – 131 °C.

Synthesis of racemic Ni NHC complex (±)-6b

Hygroscopic brown solid, 0.590 g, 25.7%. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.25-7.90 (m, 11 H, arom.), 7.87-7.93 (m, 1 H, arom.), 8.03-8.06 (m, 2 H, arom.), 8.08 (t, 1 H, $J_{H,H}$ = 11.5 Hz, arom.) and 8.72-8.73 (m, 1 H, arom.) ppm.

Synthesis of racemic Ni NHC complex (±)-6c

Hygroscopic green solid, 1.53 g, 72.7 %. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.80 (s, 9 H, CCH_3), 7.24 (s, 1 H, arom.), 7.31-7.33 (m, 1 H, arom.), 7.44-7.49 (m, 1 H, arom.), 7.52-7.57 (m, 2 H, arom.), 8.12-8.22 (m, 4 H, arom.) and 8.33-8.45 (m, 1 H, arom.) ppm. Blue green crystals were obtained from slow diffusion of diethyl ether into a methanol solution of **(±)-Ni-5c**. Characterisation of the crystals using single crystal XRD analysis confirmed it to be an unexpected nickelate complex **10** with molecular formula of $(C_{19}H_{22}N_3)_2NiCl_4$. MS (ESI) *m/z*: $[M\text{-}NiCl_4]^+$ calcd. for $C_{19}H_{22}N_3$ 292.1814, found 292.1700. M.p. = 145 – 146 °C.

Evaluation of Antimicrobial Activity

The broth microdilution assay was conducted on 96-well microtiter plates according to protocol stated by Clinical and Laboratory Standards Institute with some amendments [73]. The compounds tested were prepared in 10% DMSO in PBS solution. Positive controls utilised in this assay were chloramphenicol (0.250 mg/mL) for bacteria and cyclohexamine (1.00 mg/mL) for *Candida sp.*. Two negative controls were prepared: with MHB broth only, and with 10.0 % DMSO in PBS. Overnight bacteria culture in Mueller-Hinton broth (MHB) was adjusted to match 0.5 McFarland standard and diluted 1:100 in MHB. Into each well of the 96-well microtiter plate, the compounds of interest were serially diluted two-fold with MHB to obtain final working concentrations range between 0.500 mM and 0.391 µM (for metal complexes) or 5.00 mM and 3.91 µM (for compounds other than metal complexes) in 100 µL broth. Then, 100 µL of 1:100 diluted bacterial suspensions were added into each well prior to incubation at 37 ºC for 24 hours. The well with the lowest concentration of compounds that has no observed growth was determined as the minimum inhibitory concentration (MIC). The content of clear wells was streaked on Mueller-Hinton agar (MHA) and incubated overnight. The minimum bactericidal concentration (MBC) was determined as the lowest concentration of compound in which the inoculum did not gave bacterial broth on the MHA. The experiment was performed in triplicates.

Evaluation of Cytotoxicity

Cytotoxicity studies were carried out using the human colorectal carcinoma cell line HCT116, the human oral carcinoma cell line H103, and the breast adenocarcinoma cell line MCF7. Besides that, complexes with significant cytotoxicity against cancer cells were tested against three non-cancerous human cell lines for

possible application routes including OKF6 (oral epithelial cells), HACAT (skin keratinocytes) and BEAS2B (lung epithelial cells). All cell lines were obtained from American Type Culture Collection (ATCC). MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) cell viability assay was performed to evaluate the cell cytotoxic effects of the synthesized compounds [74]. The compounds tested were prepared in 2% DMSO in PBS solution. Positive control utilised in this assay was cisplatin (prepared in 0.9% NaCl solution). The cells were seeded in 96-well microtiter plate at a density of 5000 cells/well in 100µL cell culture medium and incubated at 37 ºC (5 % CO_2) for 24 hours. After 18 hours of seeding, the medium was removed and then the cells were incubated at 37 ºC for 48 hours in CO_2 incubator with absence and/or presence of various concentrations of compounds of interest ranging from 10, 20, 25, 30, 35 and 40 µM. Given that the compound's treatments containing 0.2 % of final DMSO concentration, 0.2 % DMSO in PBS solution was used as the negative control. After incubation, 10 µL of MTT solution (5 mg/mL in PBS) was added into each well. These plates were incubated again for 4 hours in CO_2 incubator at 37 ºC. After that, the medium-MTT solutions are removed and the purple formazan crystals formed were dissolved in 200 µL dimethyl sulfoxide. The resulting MTT-products were determined by measuring the absorbance at 570 nm, with reference wavelength at 620 nm. The experiment was carried out in quadruplicate for each compound/complex, and the medium not containing the complexes served as the control. The cell viability was determined by using the formula: Cell viability % = (optical density of sample / optical density of control) × 100 (solvent controls set to 100% viable cells). IC_{50} value were defined as the concentrations that show 50% inhibition of proliferation on any tested cell line.

Conflicts of interest

The authors declare no conflict of interest.

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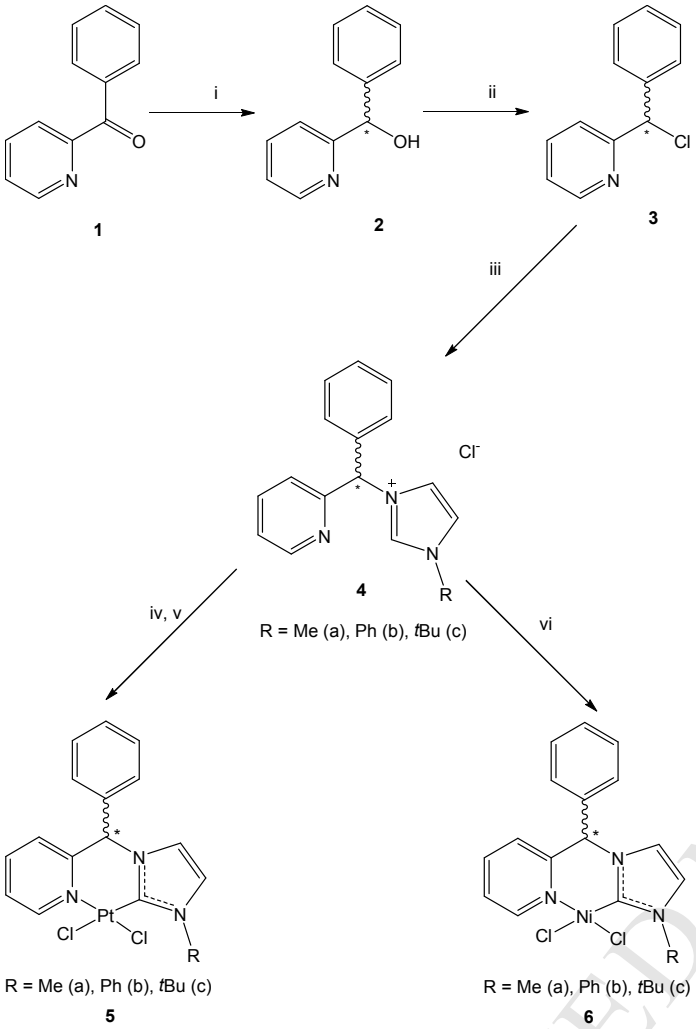
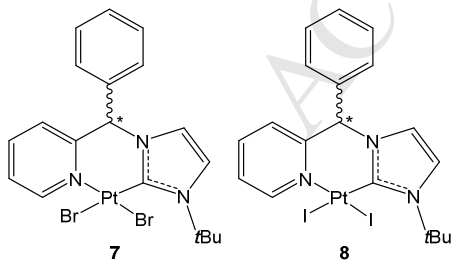
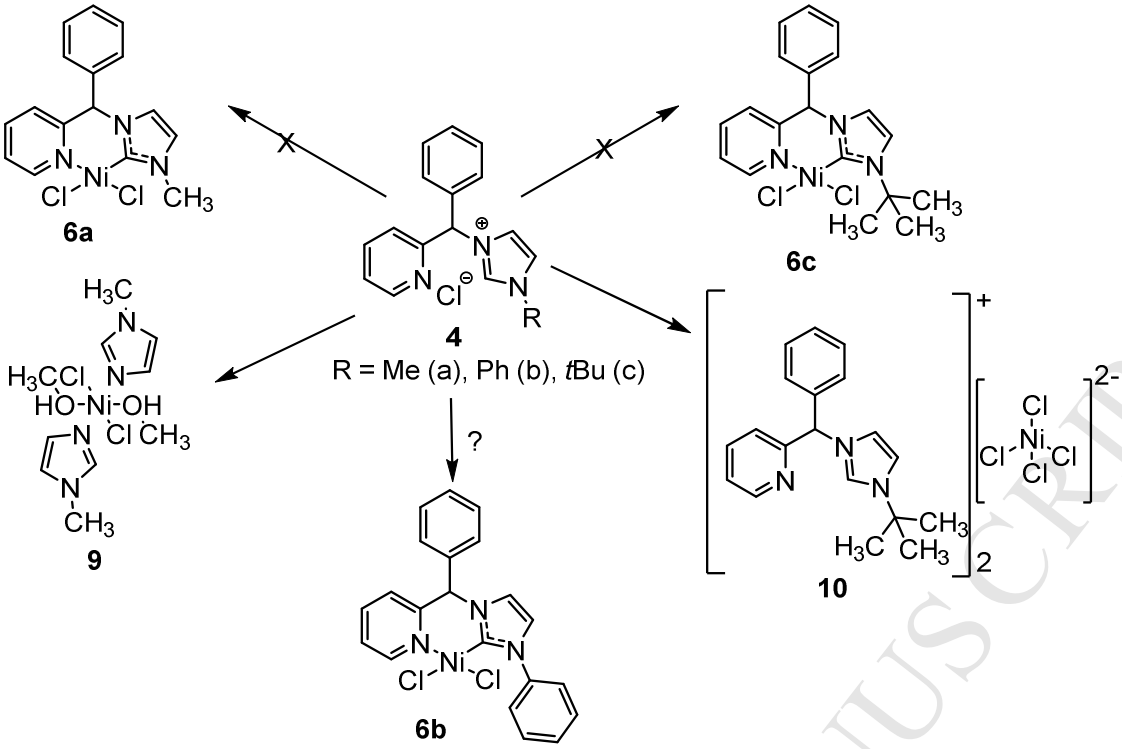
List of Schemes



Scheme 1. Synthesis pathway of racemic Pt and Ni NHC complexes. Reagents and conditions: (i) $NaBH_4$, EtOH, 1hr, 90°C, 15 mins, 1:1 EtOAc/H_2O; (ii) methanesulfonyl chloride, Et_3N, DCM, overnight, rt, 1:4 EtOAc/hexane; (iii) 1-methylimidazole (a)/ 1-phenylimidazole (b)/ 1-tert-butylimidazole (c), CH_3CN, reflux, 48 hrs; (iv) Ag_2O, CH_2Cl_2, rt, overnight, in dark; (v) Pt(cod)Cl_2, rt, 2 weeks, in dark (vi) $NiCl_2$, K_2CO_3, CH_3CN, reflux, 24hr, 1:1 CH_2Cl_2/MeOH.



Scheme 2. Structure of dibromo complex **(±)-7** and diiodo complex **(±)-8**.



Scheme 3. Overall schematic representation for synthesis and characterisation of Ni NHC complexes in this study.

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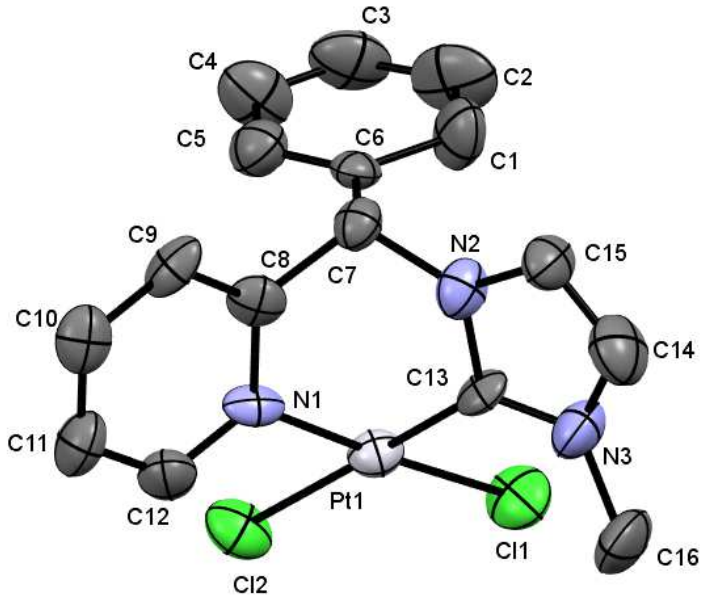

Figure 1. Molecular structure of racemic Pt NHC complex **(±)-5a** with thermal ellipsoids at 50% probability. Hydrogen atoms are omitted for clarity.

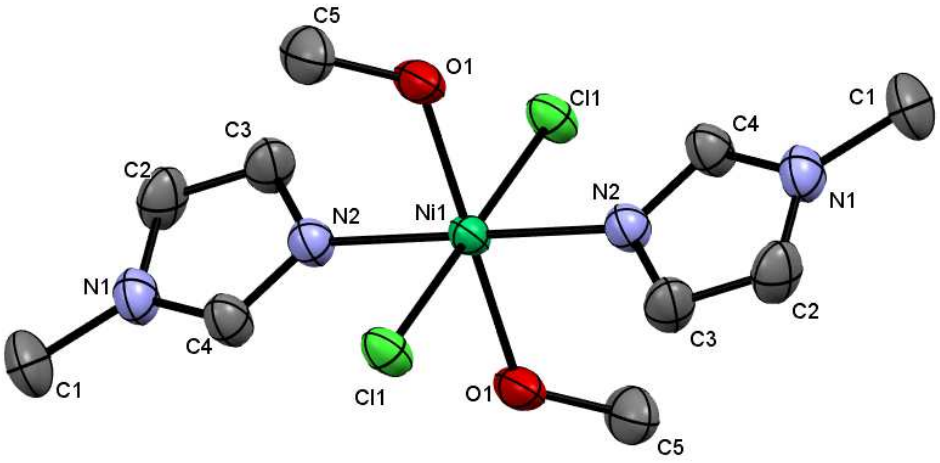

Figure 2. Molecular structure of unexpected nickel complex **9** with thermal ellipsoids at 50% probability. Hydrogen atoms are omitted for clarity.

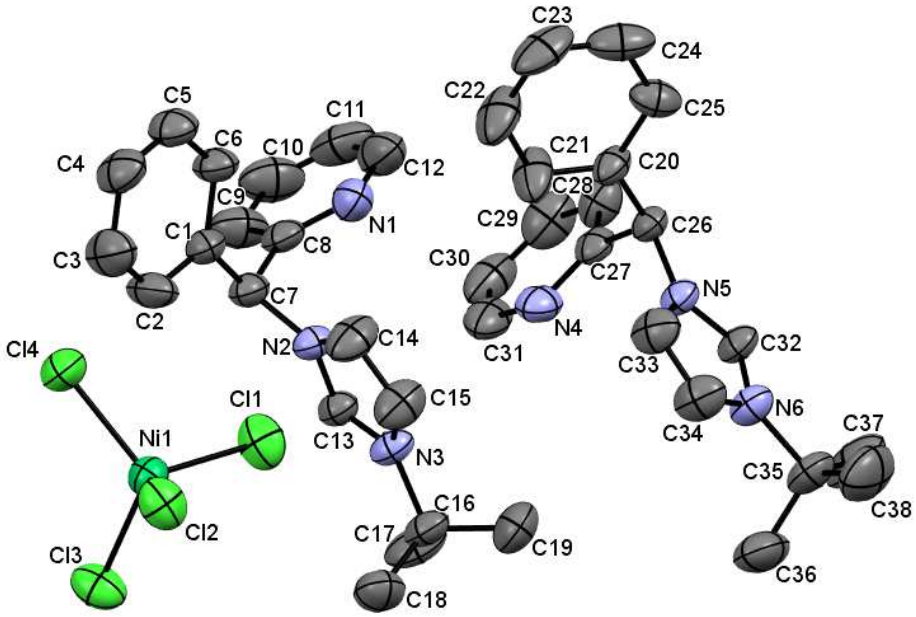

Figure 3. Molecular structure of unexpected nickelate complex **10** with thermal ellipsoids at 50% probability. Hydrogen atoms are omitted for clarity.

List of Tables

Table 1. Selected bond lengths (Å) and angles (°) for racemic Pt NHC complex **(±)-5a**.

Bond length (Å)	Pt(1)-Cl(1)	2.301(4)	N(2)-C(7)	1.47(2)
	Pt(1)-Cl(2)	2.359(4)	N(2)-C(13)	1.37(2)
	Pt(1)-N(1)	2.02(1)	N(2)-C(15)	1.41(2)
	Pt(1)-C(13)	1.95(1)	N(3)-C(13)	1.35(2)
	N(1)-C(8)	1.36(2)	N(3)-C(14)	1.40(2)
	N(1)-C(12)	1.33(2)	N(3)-C(16)	1.44(2)
Bond angle (°)	Cl(1)-Pt(1)-Cl(2)	91.2(1)	Cl(2)-Pt(1)-C(13)	176.1(4)
	Cl(1)-Pt(1)-C(13)	92.4(4)	Cl(1)-Pt(1)-N(1)	176.8(3)
	Cl(2)-Pt(1)-N(1)	90.8(3)	Pt(1)-C(13)-N(2)	119.9(9)
	C(13)-Pt(1)-N(1)	85.8(5)	Pt(1)-N(1)-C(8)	120.1(9)
	Pt(1)-C(13)-N(3)	136(1)	Pt(1)-N(1)-C(12)	120.0(9)

Table 2. Selected bond lengths (Å) and angles (°) for unexpected nickel complex **9.**

Bond length (Å)	Ni(1)-Cl(1)	2.4502	Ni(1)-Cl(1)	2.4502
	Ni(1)-O(1)	2.1	Ni(1)-O(1)	2.1
	Ni(1)-N(2)	2.076	Ni(1)-N(2)	2.076
	O(1)-H(1)	0.85(2)	O(1)-H(1)	0.85(2)
	O(1)-C(5)	1.418(3)	O(1)-C(5)	1.418(3)
	N(2)-C(4)	1.315(4)	N(2)-C(4)	1.315(4)
	N(2)-C(3)	1.373(3)	N(2)-C(3)	1.373(3)
	N(1)-C(4)	1.344(3)	N(1)-C(4)	1.344(3)
	N(1)-C(2)	1.359(4)	N(1)-C(2)	1.359(4)
	N(1)-C(1)	1.467(5)	N(1)-C(1)	1.467(5)
	C(3)-C(2)	1.350(4)	C(3)-C(2)	1.350(4)
Bond angle (°)	N(2)-Ni(1)-Cl(1)	90.72	Cl(5)-Ni(1)-O(1)	89.59
	N(2)-Ni(1)-O(1)	90.79	Cl(4)-Ni(1)-O(1)	90.41
	N(2)-Ni(1)-Cl(1)	89.28	Cl(5)-Ni(1)-O(1)	89.59
	N(2)-Ni(1)-O(1)	89.21	Cl(4)-Ni(1)-O(1)	90.41
	O(7)-Ni(1)-N(1)	90.79	Cl(1)-Ni(1)-Cl(1)	180
	O(2)-Ni(1)-N(1)	89.21	O(1)-Ni(1)-O(1)	180
	Cl(2)-Ni(1)-N(1)	89.28	N(1)-Ni(1)-N(1)	180
	N(7)-Ni(1)-Cl(1)	90.72		

Table 3. Selected bond lengths (Å) and angles (°) for unexpected nickelate complex **10.**

Bond length (Å)	Ni(1)-Cl(2)	2.268(2)	Ni(1)-Cl(3)	2.238(2)
	Ni(1)-Cl(1)	2.253(2)	Ni(1)-Cl(4)	2.253(2)
	N(3)-C(13)	1.342(8)	N(2)-C(13)	1.323(6)
	N(3)-C(15)	1.359(8)	N(2)-C(7)	1.488(7)
	N(3)-C(16)	1.496(6)	N(2)-C(14)	1.365(9)
	N(1)-C(8)	1.315(7)	N(1)-C(12)	1.34(1)
	C(1)-C(6)	1.382(7)	C(16)-C(17)	1.52(1)
	C(1)-C(7)	1.517(6)	C(16)-C(18)	1.53(1)
	C(1)-C(2)	1.39(1)	C(16)-C(19)	1.52(1)
	C(8)-C(7)	1.508(9)	C(9)-C(10)	1.38(2)
	C(8)-C(9)	1.41(1)	C(5)-C(4)	1.37(1)
	C(6)-C(5)	1.380(7)	C(2)-C(3)	1.375(9)
	C(15)-C(14)	1.35(1)	C(10)-C(11)	1.33(1)
	C(12)-C(11)	1.37(2)	C(4)-C(3)	1.38(1)
Bond angle (°)	Cl(1)-Ni(1)-Cl(2)	116.54(7)	Cl(1)-Ni(1)-Cl(2)	105.02(7)
	Cl(1)-Ni(1)-Cl(3)	106.88(7)	Cl(1)-Ni(1)-Cl(3)	112.82(7)
	Cl(1)-Ni(1)-Cl(4)	107.64(7)	Cl(1)-Ni(1)-Cl(2)	108.12(7)

Table 4. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) (in mM) of the synthesized complexes against selected microorganisms. [a]

Compound	**4a**	**4b**	**4c**	**(±)-5a**	**(±)-5b**	**(±)-5c**	**(±)-7**	**(±)-8**	**9**	**10**	**CHL** [c]
Microorganisms tested	Minimum inhibitory concentration (MIC), mM										
Bacillus cereus ATCC 8188	5.000	2.500	5.000	0.500	0.002	0.002	0.008	0.002	> 0.500	> 0.500	0.006
Bacillus subtilis ATCC 14579	5.000	2.500	5.000	0.500	0.004	0.002	0.016	0.002	> 0.500	> 0.500	0.006
Staphylococcus aureus ATCC 29213	2.500	1.250	2.500	0.500	0.002	0.004	0.008	0.004	> 0.500	> 0.500	0.025
Staphylococcus aureus ATCC 6538P	2.500	1.250	2.500	0.500	0.008	0.004	0.031	0.004	> 0.500	> 0.500	0.025
Staphylococcus aureus ATCC 700699[b]	5.000	1.250	5.000	0.500	0.001	0.004	0.004	0.002	> 0.500	> 0.500	0.025
Staphylococcus aureus ATCC 43300[b]	5.000	1.250	2.500	0.500	0.001	0.002	0.004	0.002	> 0.500	> 0.500	0.025
Staphylococcus aureus ATCC 33591[b]	5.000	1.250	5.000	0.500	0.004	0.004	0.016	0.004	> 0.500	> 0.500	0.025
Enterococcus faecalis ATCC 29212	> 5.000	5.000	> 5.000	0.500	0.031	0.031	0.125	0.031	> 0.500	> 0.500	0.050
Enterococcus faecalis ATCC 700802[c]	> 5.000	> 5.000	> 5.000	0.500	0.063	0.031	0.125	0.031	> 0.500	> 0.500	0.050
Escherichia coli ATCC 25922	> 5.000	5.000	> 5.000	0.500	0.125	0.063	0.500	0.125	> 0.500	> 0.500	0.025
Klebsiella. pneumoniae ATCC 10031	> 5.000	2.500	> 5.000	0.500	0.125	0.016	0.250	0.031	> 0.500	> 0.500	0.003
Pseudomonas aeruginosa ATCC 10145	> 5.000	> 5.000	> 5.000	0.500	0.063	0.013	0.250	0.500	> 0.500	> 0.500	> 0.050
Shigella flexneri ATCC 12022	5.000	1.250	5.000	0.500	0.063	0.625	0.250	0.063	> 0.500	> 0.500	0.006
Candida albicans IMR	2.500	1.250	5.000	0.500	0.063	0.008	0.063	0.008	> 0.500	> 0.500	> 0.050
Microorganisms tested	Minimum bactericidal concentration (MBC), mM										
Bacillus cereus ATCC 8188	5.000	2.500	5.000	> 0.500	0.250	0.125	0.125	0.125	> 0.500	> 0.500	> 0.050
Bacillus subtilis ATCC 14579	> 5.000	2.500	> 5.000	> 0.500	0.125	0.016	0.031	0.002	> 0.500	> 0.500	> 0.050
Staphylococcus aureus ATCC 29213	5.000	5.000	5.000	> 0.500	0.125	0.031	0.250	0.500	> 0.500	> 0.500	> 0.050
Staphylococcus aureus ATCC 6538P	5.000	5.000	5.000	> 0.500	0.125	0.063	0.031	0.125	> 0.500	> 0.500	> 0.050
Staphylococcus aureus ATCC 700699[b]	> 5.000	5.000	> 5.000	> 0.500	0.125	0.063	0.063	0.125	> 0.500	> 0.500	> 0.050
Staphylococcus aureus ATCC 43300[b]	5.000	2.500	5.000	> 0.500	0.031	0.031	0.063	0.063	> 0.500	> 0.500	> 0.050
Staphylococcus aureus ATCC 33591[b]	> 5.000	> 5.000	> 5.000	> 0.500	0.063	0.008	0.063	0.063	> 0.500	> 0.500	> 0.050
Enterococcus faecalis ATCC 29212	> 5.000	> 5.000	> 5.000	> 0.500	0.250	0.250	0.250	0.250	> 0.500	> 0.500	> 0.050
Enterococcus faecalis ATCC 700802[c]	> 5.000	> 5.000	> 5.000	> 0.500	0.250	0.125	0.250	0.063	> 0.500	> 0.500	> 0.050
Escherichia coli ATCC 25922	> 5.000	5.000	> 5.000	> 0.500	0.250	0.125	> 0.500	0.500	> 0.500	> 0.500	> 0.050
Klebsiella. pneumoniae ATCC 10031	> 5.000	5.000	> 5.000	> 0.500	0.250	0.031	0.250	0.250	> 0.500	> 0.500	0.003
Pseudomonas aeruginosa ATCC 10145	> 5.000	> 5.000	> 5.000	> 0.500	0.500	0.500	0.500	> 0.500	> 0.500	> 0.500	> 0.050
Shigella flexneri ATCC 12022	5.000	5.000	> 5.000	> 0.500	0.250	0.250	0.250	0.250	> 0.500	> 0.500	0.050
Candida albicans IMR	5.000	2.500	5.000	> 0.500	0.250	0.063	0.125	0.031	> 0.500	> 0.500	> 0.050

[a] The antimicrobial assay was performed in triplicates. The compounds with no antimicrobial activity were reported as more than the maximum working concentration tested in mM.
[b] Methicillin-resistant *S. aureus*; [c] Vancomycin-resistant *Enterococci*.
[c] CHL Chloramphenicol, an antibiotic and positive control in this study.

Table 5. Cell viability (half inhibitory concentration) IC_{50} values (in μM) of screened imidazolium salts, Pd NHC complexes and cisplatin against human breast MCF7, human colon HCT116 and human oral H103 tumour cells incubated for 48 hours.

Complex	Half inhibitory concentration, IC_{50} (μM)*		
	H103	HCT116	MCF7
4a	> 40.00	> 40.00	> 40.00
4b	> 40.00	> 40.00	> 40.00
4c	> 40.00	> 40.00	> 40.00
(±)-5a	> 40.00	> 40.00	> 40.00
(±)-5b	21.93 ± 0.50 [b]	15.19 ± 0.14 [b]	28.34 ± 0.26 [b]
(±)-5c	6.18 ± 0.19 [a]	5.52 ± 0.03 [c]	7.33 ± 0.13 [c]
(±)-7	16.90 ± 1.07 [c]	11.96 ± 0.65 [d]	25.98 ± 0.33 [d]
(±)-8	11.28 ± 0.87 [d]	6.04 ± 0.07 [e]	15.91 ± 0.19 [e]
9	> 40.00	> 40.00	> 40.00
10	32.71 ± 1.12 [e]	> 40.00	> 40.00
Cisplatin	6.16 ± 0.04 [a]	10.78 ± 0.21[a]	19.78 ± 0.21 [a]

*Cells were exposed to different concentrations of complexes for 48 hours and cell viability was assessed using MTT assay. The IC_{50} tabulated represents the average of four independent experiments ± SEM. Different letters (a-e) represent significant differences between different compounds tested for the cell line.

Table 6. Cell viability (half inhibitory concentration) IC_{50} values (in μM) of of selected compounds against selected human normal cell lines: OKF6 oral epithelial cells, HACAT skin keratinocytes and BEAS2B lung epithelial cells after incubation of 48 hours.

Complex	Half inhibitory concentration, IC_{50} (μM)*		
	OKF6	HACAT	BEAS2B
(±)-5b	8.08 ± 0.03 [a]	24.26 ± 0.51 [c]	10.71 ± 0.24 [c]
(±)-5c	5.20 ± 0.01 [b]	5.89 ± 0.07 [d]	5.46 ± 0.02 [d]
(±)-7	8.45 ± 0.28 [c]	15.04 ± 0.78 [b]	6.40 ± 0.18 [e]
(±)-8	5.98 ± 0.03 [d]	11.38 ± 0.49 [e]	5.50 ± 0.06 [d]
10	18.75 ± 1.61 [e]	> 40.00	32.91 ± 1.13 [b]
Cisplatin	ND	7.59 ± 0.62 [a]	9.64 ± 0.21 [a]

* Cells were exposed to different concentrations of complexes for 48 hours and cell viability was assessed using MTT assay. The IC_{50} values were calculated from a graph of mean ± SEM, which are experiments performed in quadruplicates, and tabulated. * The IC_{50} tabulated represents the average of four independent experiments ± SEM. Different letters (a-e) represent significant differences between different compounds tested for the cell line.

Table 7. Selectivity index (SI) of selected compounds for normal cell lines against oral cancer (H103), colon cancer (HCT116), and breast cancer (MCF7) cells.

Normal cell lines	**Cancer cell lines**	Selectivity Index *					
		(±)-5b	**(±)-5c**	**(±)-7**	**(±)-8**	**10**	Cisplatin
OKF6	Oral	0.37	0.84	0.50	0.53	0.57	ND
	Colon	0.53	0.94	0.71	0.99	ND	ND
	Breast	0.29	0.71	0.22	0.38	ND	ND
HACAT	Oral	1.11	0.95	0.89	1.01	ND	1.23
	Colon	1.60	1.07	1.26	1.88	ND	0.70
	Breast	0.86	0.80	0.58	0.72	ND	0.38
BEAS2B	Oral	0.49	0.88	0.38	0.49	1.01	1.57
	Colon	0.71	0.99	0.54	0.91	ND	0.89
	Breast	0.38	0.75	0.25	0.35	ND	0.49

* Selectivity index (SI) was determined from the ratio of the IC_{50} obtained from the test against normal cells versus the IC_{50} for cancer cells. Abbreviation: ND, not determined.

Synthesis, characterization, *in vitro* antimicrobial and anticancer studies of new platinum *N*-heterocyclic carbene (NHC) complexes and unexpected nickel complexes

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Highlights

- A series of new Pt and Ni NHC complexes had been synthesized and characterised.
- Two unexpected crystal structures of Ni complexes were obtained upon recrystallisation.
- The Pt NHC complexes exhibited enhanced bioactivities upon coordination to Pt.
- A couple of Pt NHC complexes displayed biological activities comparable to benchmark drugs.
- Results suggested that both wingtip substituents and metals influence their bioactivities.