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σ-Acetylide complexes for biomedical applications: Features, challenges and future directions

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ABSTRACT

Mono-, di- and polynuclear metal alkynyl or σ-acetylide complexes have attracted a great deal of interest due to their multi-dimensional applications. In the past few decades, several small to medium sized neutral and charged metal acetylides have been synthesized and assessed for various biomedical applications. This review explores the progress made in the design and development of rigid-rod type η^1-σ-alkynyl complexes for therapeutic (*viz.* anticancer, antibacterial) and diagnostic (*viz.* enzymes or proteins imaging) purposes. The features that make metal acetylides unique for bio-applications, their diversity as biomaterials, and future potential for clinical usage have been reviewed. Although few challenges exist with this class of materials (which we have identified and discussed in the review), metal acetylides have a bright future in different branches of medical science and hold promise as next generation biomaterials.

Contents

1. Introduction

Metal acetylides or metalla-ynes, in which a transition metal is attached to one or more alkynyl units through σ-linkage, have attracted attention of the new generation researchers [1]. This class of functional materials possesses unique photo-physical, photo- and physico-chemical properties compared to their organic counterparts (oligo-ynes and poly-ynes). This is due to the presence of π-back-bonding or σ-donating auxiliary supported metals along the organic backbone or at the termini. The overall properties and application of metalla-ynes can be fine-tuned by varying the organic core, the transition metal ions, and the auxiliary ligands present [2–8]. For instance, a cationic auxiliary

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gives water solubility while a neutral alkyl chain/arene imparts solubility and processability in organic solvents. Similarly, auxiliary group (phosphines, arsines, NHCs) linked to the metal modulates electronic properties, induces aggregation and so on [1]. Owing to these intriguing features, metal acetylides have found application in optoelectronics (O–Es), catalysis, chemo/bio sensing, memory/magnetic materials, molecular wires and devices [9–15]. While most of the above-mentioned applications were discovered a long time ago, the emergence of metalla-ynes for therapeutic and diagnostic applications is relatively new [16–20]. Interest in biomedical application of metalla-ynes is generated due to diverse bioactivity of acetylenic compounds, intriguing and tunable photo-physical properties of synthetically accessible organic and organometallic systems, environment-sensitive luminescence properties, ability to form aggregates and supramolecular assemblies, tunable lipophilicity, etc. [17] Fascinated by these features, several small to medium sized neutral and charged σ-acetylide complexes have been designed and assessed for biomedical applications such as anticancer, antibacterial, bioimaging, photodynamic therapy, etc. This includes, but is not limited to linear (*trans*), angular (*cis*), and macrocyclic metalla-ynes incorporating one or more transition metal ions (mainly platinum and gold).

In this article, we review the properties, applications and challenges associated with different mono-, di- and polynuclear metal σ-acetylide complexes. The review is divided into four sections: following this section, we highlight the features of metalla-ynes that make them unique. This is followed by a survey of the bio-application of platinum and gold incorporated metalla-ynes in anticancer, bioimaging, antibacterial and others. A comparison has been made in each section according to the structure and activity of the complexes. At the end, we discuss the challenges associated with this class of materials and their future as theranostic agents.

2. Features of metal acetylide

The chemistry of σ-acetylide complexes dates back to 1970s [21]. However, the development of metalla-ynes [(L)n–M–C≡C–Ar], di-ynes [$(L)_n$–M–C≡C–Ar–C≡C–M–$(L)_n$], and poly-ynes [$(-M(L)_n-C\equiv C-Ar-\ C\equiv C-)_\infty$] bearing different transition metal ions started in early 1990s [1,11,22]. In general, σ-acetylide complexes are composed of three main components: (a) an alkynyl core (H/R/Ar–C≡C–) with or without carbocyclic/heterocyclic spacer, (b) one or more transition metal ions in the main chain, and (c) π-back-bonding or σ-donating auxiliaries. Acetylide (H/R/Ar-CC$^-$) is a linear ligand known for its high electronegativity and ability to behave as σ-donor as well as a π-acceptor [23]. It allows the fine-tuning of the frontier orbitals, leading to shift in absorption and emission wavelengths. Depending upon the reaction condition and stoichiometry, an acetylide ligand may interact with transition metal through terminal, bridging or mixed binding modes (Fig. 1a–e). The structure of η^1-σ-alkynyl complexes further depends on the type of transition metal and auxiliary present (structures given in the right panel). One or more metal from group 4–10 determines the geometry (octahedral, square planar), PL, metal-metal and metal-ligand interactions as well as other important properties [1,24–26].

Both bridging and terminal metal alkynyl complexes [27–30] have been assessed for biological applications, but the interest in η^1-σ-alkynyl complexes is a relatively new area of research. As mentioned before, organic core, metal fragment and auxiliary ligand each plays a separate role in the biological applications of η^1-σ-alkynyl complexes. Acetylenic cores are well known for cytotoxicity [1], imaging capability [1,31], supramolecular architecture formation, etc. [32–34] while substituents over the alkynyl ligand control the binding mode and selectivity for bioreceptors such as DNA [34,35]. Metalla-ynes are fluorescent chromophores, can coordinate with the biological targets, show sensitivity towards light and other biogenic conditions such as pH, oxygen level, etc. [36] It has been demonstrated that metal acetylides incorporating cyclometalating ligands such as terpyridine (Tpy) act as excellent intercalator and resist hydrolysis in biological media [37]. Auxiliary functionality endows stability towards photo- and chemical degradation [17].

3. Bioapplication

3.1. Anticancer

3.1.1. Pt(II) arylacetylide complexes

Cancer is a deadly disease affecting millions of people across the globe every year [38]. Among metal based cancer chemotherapeutics, Pt(II) complexes have always been the choice of oncologists [39,40]. Different generations of Pt(II) complexes were developed in the last half century, each with added advantage over the preceding member [40]. However, toxicity, resistance issue, ineffectiveness in the terminal stage, etc. remained as big challenge [41,42]. In order to develop bullet drug to circumvent most, if not all

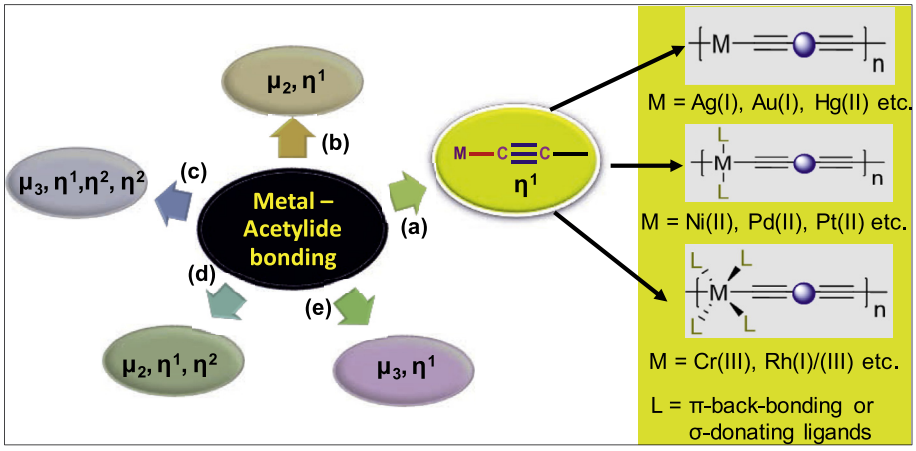

Fig. 1. Binding modes between alkynyl ligand and one or metal ion(s) (a–e). Panel in the right depicts sub-types of σ-alkynyl complexes. Reprinted with permission from A. Haque, R.A. Al-Balushi, I.J. Al-Busaidi, M.S. Khan, P.R. Raithby, Rise of Conjugated Poly-ynes and Poly(Metalla-ynes): From Design Through Synthesis to Structure-Property Relationships and Applications, Chem. Rev. 118(18) (2018) 8474–8597. Copyright (2018) American Chemical Society.

of these challenges, researchers are continuously synthesizing and assessing new Pt(II) complexes. In this direction, researchers tested the potential of *cis* and *trans* Pt(II) acetylides and noted some interesting observations [34,43]. For example, acetylide complexes possess extraordinary stability in organic as well as aqueous solvents, high propensity towards biological targets (*viz*. TrxR, ROS, DNA) with diverse activity. In some cases, they surpassed the activity profile of currently used clinical anticancer drugs such as CP and 5-FU. Pt(II) acetylides **1**–**2** (Chart 1) bearing aryl acetylides and diolefin ligands COD in *cis*-configuration exhibit promising activities (in μM range) on HT-29 and MCF-7 cell lines [34]. The replacement of one of the chlorido co-ligands from [(COD)$PtCl_2$] by an alkyl/alkynyl donor significantly improved the activity of the complexes. A further enhancement in the activity was observed upon replacement of the second chlorido co-ligand (Table 1). Interestingly, *cis* Pt(II) complexes bearing one or two alkynyl ligands exhibited cytotoxicity at very low concentration ($IC_{50} = 7.0$ μM against HT-29 and 2.0 μM against MCF-7) (Table 1) [34]. It was suggested that the substituents over the alkynyl and COD moieties induce different level of electronic effects leading to varying kinetic reactivity, bio-distribution, interaction with biological targets and thus the activity. Contrary to CP, which exclusively targets DNA [40], complexes **1**–**2** (Chart 1) were active in targeting DNA as well as TrxR. The same group synthesized and evaluated anti-proliferative activities of Pt(II) complexes decorated with different diolefins and co-ligands [43]. They noted comparatively less impact of varying ligand (especially diolefin) and cationic co-ligands on the cytotoxicity. For example, complex **3** (R = (4-Me) Ph) (Chart 1) bearing two methyl substituents on the COD core showed less activity ($IC_{50} = 1.4 \pm 1.2$ μM against HT-29 and 4.0 ± 0.5 μM against MCF-7) compared to complex **2d** (R = (4-Me) Ph). The exact mechanism of action of this class of complexes remains a mystery.

From the structure property relationships of CP and related analogues, it is known that two labile chlorido ligands hydrolyse under biological environment to yield active species $[Pt(amine)_2]^{2+}$ that covalently binds to the nucleobases to halt the cancer progression [45]. Due to the geometrical constraints and thermodynamic features, *cis* complexes exhibit preferential antitumor activity than the *trans* counterparts [41]. Howevere, attempts have also been made to develop *trans* complexes incorporating different ligands [46,47]. Interestingly, some *trans* complexes outperformed the activity of CP disproving the notion that only complexes adopting *cis*-configuration are active [46]. Das and co-workers [48] reported square planar complexes **4a-c** (Chart 1) with *trans* disposed triethylphosphine (PEt_3) auxiliaries around the Pt(II) connected to pyrazine-triazole through ethynyl linkage. Interestingly, complexes with "Pt–ethynyl" and "1,2,3-triazole" cores showed activity ($IC_{50} = 13.7 \pm 0.5$ μM to 18.0 ± 0.6 against MG-3 and $IC_{50} = 16.6 \pm 1.2$ μM to 22.4 ± 1.2 against MDA-MB-231) better than the standard (CP). It was suggested that complexes showed activity *via* necrosis pathway. Vere recently, Higuchi and co-workers [49] demonstrated that Pt/Fe-based polymers **4d-4e** (Chart 1) possess high affinity towards the calf-thymus DNA (ct-DNA). The reported polymers exerted higher cytotoxicity against A549 in order: **4d** (viability 71%) < **4e** (viability 41%). The higher activity of the latter was attributed to the planar phenyl rings of phosphines, which possibly assisted polymers in intercalative binding with the nucleobases. Besides, cell death mechanistic study showed that apoptosis was the main reason for cytotoxicity. Despite these features, solubility was the major challenge with such constructs.

Cell death *via* necrotic pathway has also been reported for irregular [2 + 2] hexagons (**5** and **6**, Chart 2) [50]. Unlike previous examples of Pt(II) complexes, where the type or planarity of the co-ligands controlled the activity, here the macrocyclic ring size governed the activity (activity order: **6** > **5**). The sensitivity of complex (**6**) was comparable to standard (CP), especially against A549 ($IC_{50} = 25 \pm 0.3$ μM *vs* 20 ± 0.2 μM for **6**) and MCF-7 ($IC_{50} = 20 \pm 0.3$ μM *vs* 05 ± 0.2 μM for **6**) cell lines. This study establishes the fact that metalla-cyclization provides a way of improving bioactivity of the Pt(II) complexes. The same group noted that complexes **7** and **8** (Chart 2) show higher cytotoxicity compared to their non-cyclic Pt(II) alkynyl counterparts [51]. Especially complex **7** exhibited activity in the range of 9.1 ± 0.1 to 19.4 ± 0.5 against HT-29, MCF-7, MDA-MB-231 and RC-124 cell lines (Table 2) [51]. Again, solubility and the lack of tissue selectivity were the main challenges.

Cyclometalated complexes based on bi- (*C^N, N^N)* and polydentate (*C^N^N, N^C^N, C^N^C or N^N^N*) coordinating units are well known for their ability to impart stability to the metals, intense luminescence, metal–metal, and π–π interaction [52,53]. Several examples of complexes based on *N^N^N* cyclometalating cores have been reported as bioprobes, imaging, and photo-cytotoxic agents [54–56]. In such complexes, nature of substituents on the alkynyl ligand plays a crucial role in governing the activity as well as the selectivity [35]. For example, Che and co-workers found that *N^N^N* cyclometalating ligand based cationic Pt(II) complexes bearing glycosylated acetylide and arylacetylide auxiliaries **9a-h** (Chart 3) exhibit excellent anticancer activity against HeLa ($IC_{50} = 0.09–19.2$ μM), HepG2 ($IC_{50} = 0.1–19.6$ μM), SF-268 ($IC_{50} = 0.06–17.1$ μM), NCI–H460 ($IC_{50} = 0.1–28.5$ μM), and MCF-7 ($IC_{50} = 0.08–17.1$ μM) cancer cell lines [37]. All complexes were

Table 1
Anticancer activities of *cis* Pt(II) complexes bearing one or two alkyl/alkynyl ligands[a].

Complex	Substituents		IC_{50} (μM)		Ref.
	R_1	R_2	HT-29	MCF-7	
1a	Benzyl	(4-Me)Ph	1.3 ± 0.0	2.1 ± 0.9	[34]
1b	Neopentyl	(4-Me)Ph	13.5 ± 2.2	13.2 ± 0.5	[34]
1c	Methyl	Ph	9.0 ± 1.7	10.5 ± 7.9	[44]
1d	Methyl	(3-Me)Ph	3.2 ± 1.5	5.0 ± 0.8	[34]
1e	Methyl	(4-Me)Ph	0.2 ± 0.1	0.3 ± 0.1	[44]
1f	Methyl	(4-F)Ph	4.6 ± 0.2	4.6 ± 0.5	[34]
1g	Methyl	(2-NO_2)Ph	15.6 ± 5.2	9.1 ± 3.9	[34]
1h	Methyl	(3-NO_2)Ph	2.9 ± 1.2	1.6 ± 0.3	[34]
1i	Methyl	(4-NO_2)Ph	2.3 ± 0.7	1.9 ± 0.6	[34]
1j	Methyl	(4-OMe)Ph	10.8 ± 3.1	6.8 ± 1.1	[34]
1k	Methyl	2-pyridine	29 ± 7.2	17.6 ± 8.2	[34]
2a	(Ph)	(Ph)	0.5 ± 0.3	0.4 ± 0.2	[34]
2b	(2-Me)Ph	(2-Me)Ph	0.5 ± 0.1	0.4 ± 0.1	[34]
2c	(3-Me)Ph	(3-Me)Ph	0.1 ± 0.0	0.1 ± 0.0	[34]
2d	(4-Me)Ph	(4-Me)Ph	0.4 ± 0.1	0.3 ± 0.0	[34]
2e	(2-NO_2)Ph	(2-NO_2)Ph	0.6 ± 0.1	0.3 ± 0.1	[34]
2f	(3-NO_2)Ph	(3-NO_2)Ph	0.4 ± 0.1	0.2 ± 0.1	[34]
2g	(4-OMe)Ph	(4-OMe)Ph	0.6 ± 0.2	0.3 ± 0.2	[34]
2h	(4-F)Ph	(4-F)Ph	0.4 ± 0.1	<0.3	[34]
2i	2-pyridine	2-pyridine	0.3 ± 0.1	0.2 ± 0.1	[34]

[a] Reprinted with permission from A. Lüning, J. Schur, L. Hamel, I. Ott, A. Klein, Strong cytotoxicity of organometallic platinum complexes with alkynyl ligands, Organometallics 32(13) (2013) 3662–3672. Copyright (2013) American Chemical Society.

Table 2
Anticancer activities of macrocyclic Pt(II) complexes.

Complex	IC_{50} (μM)				Ref.
	HT-29	MCF-7	MDA-MB-231	RC-124	
5	–	17.0 ± 0.3	–	–	[50]
6	–	5.0 ± 0.2	–	–	[50]
7	19.4 ± 0.5	9.1 ± 0.1	9.6 ± 0.9	10.4 ± 0.2	[51]
8	>20	16.1 ± 0.2	>20	8.7 ± 1.4	[51]

found to be ~100-times more potent than CP along with very low toxicity (IC_{50} = 0.3–50.3 μM *vs* > 100 μM for CP on normal cell line). Using different analytical techniques, they suggested DNA (K_b ~10^5 M^{-1}) as one of the possible targets of such complexes. Similar range of K_b values has been recently noted by Shi and co-workers [57]. Overall, anticancer activity, water solubility, cellular uptake, binding mode are significantly governed by the ligand attached to alkynyl fragment (such as glucose). This observation was in line with the results of Ou and co-workers [35,58]. They noticed that the cationic complexes **9i-k** (Chart 3) shows high affinity (K_a > 10^7 M^{-1}) and reasonable selectivity for telomeric and c-myc G-quadruplexes over duplex DNA. Their results suggest that complexes **9i-k** associate with telomeric and c-myc G-quadruplexes *via* groove binding, and electrostatic interactions [58]. It was demonstrated that under molecular crowding conditions (40 wt% PEG 200), complexes **9i-j** show weak affinity for c-myc, while **9k** displays high affinity and selectivity for c-myc. On the other hand, complexes **9i-k** act as efficient and selective ligand for telomeric quadruplex DNA under molecular crowding conditions. Large binding constant of **9j-k** than **9a-h** could be attributed to less steric hindrance offered by the former as the latter have glucose units attached to the alkynyl fragment. Unlike **9a-h**, complexes **9j-k** showed activity 25-35-fold higher than that of CP. Interestingly, a minor modification (*N*-methylation or ethylation) has a marked effect on the biological properties. For instance, complex **9j** exhibited IC_{50} = 2.02 μM against A549 cancer cell lines after 24 h of treatment while **9k** showed IC_{50} = 1.10 μM. These values reduced further post 48 h treatment (0.62 and 0.42 μM, respectively).

3.1.2. Au(I) arylacetylide complexes

In the quest of new acetylide complexes with diverse anticancer activity, metals other than platinum have been investigated. Among those, complexes based on gold (Au) metal sit at the top [58,59]. In fact, Au(I/III)-based compounds have a long-standing role in medicinal (chrysotherapy) and biological chemistry [55,60–64]. Several monomeric and dimeric Au(I) aryl acetylide complexes bearing phosphine/NHC at one end and different substituents on other have been reported with interesting biological activities [65–68]. In fact, there are more reports on biological studies of Au(I) aryl acetylide complexes compared to Pt(II) aryl acetylides. Like Pt(II) aryl acetylide complexes, they possess intense emission, metallophilic interaction, form supramolecular aggregates, induce high level of activity, etc. [69] An added advantage of Au(I) complexes lies in their synthesis as they can be obtained in high purity in a single step, which is very important and a prime requirement for biological and pharmacological studies. In a landmark study, Ott and co-workers [68] demonstrated that alkynyl phosphine Au(I) complexes (**10a-f**, Chart 4) are potential candidates for targeting TrxR, inducing anti-proliferative activity, and inhibiting blood vascular formation (i.e. anti-angiogenic). Whereas alkynes exhibited no activity (>100 μM against HT-29 and MCF-7), Au(I) alkynyl complexes display anti-proliferation profile similar to or better (>1.6–12 μM against HT-29 and 0.8–2.2 against MCF-7) than CP and 5-FU (IC_{50} = 0.8–12.0 μM). As expected, cellular uptake was controlled by the size of the ligand (larger the ligand size, slower the cellular uptake).

Recently, the same group [66] carried out an extensive structure activity relationship (SAR) study to find out the role of phosphines on anti-proliferative and TrxR inhibition activity. They replaced triphenylphosphine in complex **10a** [68] by ($P(2\text{-furyl})_3$ (**11a**), $P(DAPTA)_3$ (**11b**), $P(PTA)_3$ (**11c**), $P(Et)_3$ (**11d**), $P(Me)_3$ (**11e**). Despite the differences in auxiliaries, no major difference in the activity was observed as all complexes caused strong antiproliferative effects (Fig. 2). Contrarily, structure-dependent TrxR inhibition was observed. For instance, complexes bearing no heteroatom were more effective in inhibiting TrxR compared to those having N/O atoms. Since solubility is one of the common obstacles with such complexes, they prepared nano-formulation using **10a** (only this complex showed clear effects on cellular signalling in cancer cells) to study its applicability in the animal model. Although nano-formulation (2.5 mg/kg) was insufficient to control the tumour growth, it was well tolerated in the animal model.

The replacement of anisole in **10a** (Chart 4) by 4-pyridine supported by triphenylphosphine-3,3′,3”-trisulfonic acid yielded charged and lipophilic Au(I) complex **12a** (Chart 5) [70]. High cellular gold accumulation was observed for **12a** compared to other coumarin analogues based complexes, leading to the conclusion that ethynyl pyridinyl unit has high cell membrane permeability. Despite the favourable physico-chemical properties, **12a** showed very poor cell growth inhibitory effects (due to aggregation effects that hampered the biological assays). Complex **12b** bearing lipophilic adamantane moiety was found to induce apoptosis in Caco-

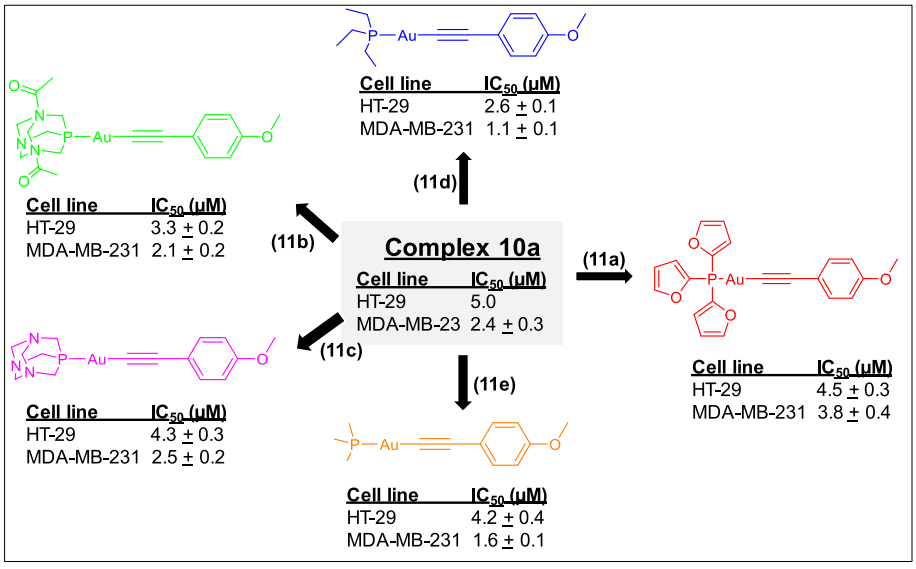

Fig. 2. Structure and activity of different phosphine supported Au(I) complexes.

2 cells [71]. Complex **12b** (Chart 5) showed antiproliferative activity *via* multiple pathways (targeting TrxR 1, increasing ROS levels, reducing cell viability and proliferation and inducing mitochondrial apoptotic pathway, pro-apoptotic and anti-apoptotic protein imbalance, loss of mitochondrial membrane potential, cytochrome-c release and activation of caspases 9 and 3). The authors concluded that such Au(I) based complexes are safer as they did not target the DNA, thereby reducing the risk of side mutation. Motivated by these features, the same group [72] replaced phenylethynyl by 2-pyridinylethynyl and noted that complex **12c** disrupts function of mitochondria, leading to an increase in ROS production and necroptosis induction. This was the first example of an Au(I) acetylide complex able to induce necroptosis in cancer cells. Necroptosis induction has been found dependent on TNF-α (Tumor necrosis factor α) and TNFR1 (Tumor necrosis factor receptor 1) binding, RIP1 (Receptor-Interacting Protein 1) activation and NF-κB (Nuclear Factor Kappa-Light-Chain Enhancer of Activated B Cells) signalling. The complex neither affected normal enterocytes, nor targeted nucleic acids. Therefore, it holds promise as a chemotherapeutic agent for colorectal carcinoma and apoptosis resistance cancers.

To gain a better insight into the role of Au(I) nuclearity, ligand rigidity, and solubility on the biological activity, Rodríguez and co-workers prepared a range of mono (**13a-e**) and bimetallic (**14a-c**) complexes bearing mono- and diphosphane auxiliaries (Chart 5) [67,73]. They noted that except **14a** with rigid phosphane, all dinuclear complexes exhibited higher cytotoxicity against HCT116 cells as well as A2780 compared to the mononuclear complexes **13a-e** [73]. This observation was in line with the previous study in which dinuclear complexes bearing flexible phosphine linkers showed higher activity against MCF-7 and HT-29 cell lines [67]. Therefore, the ligand rigidity has a direct impact on the bioactivity. Mononuclear complex bearing napthyl phosphine showed excellent selectivity for ovarian cancer cell line with negligible cytotoxicity against normal cell. Mechanistically, it was suggested that complexes caused apoptosis (not TrxR) dependent ROS level enhancement. Prior to this work, Wong and co-workers [74] have also had the same observation, i.e. bimetallic Au(I) complexes **15a-b** (Chart 5) show significantly high activity against cancer cell lines Hep3B, MDA-MB-231 and SKHep-1 and generate ROS on Hep3B hepatocellular carcinoma cells. Among the reported compounds, complex **15a** (2.5 mg/kg dosage) significantly reduced the tumour volume *in-vivo* without any adverse effects on vital organs including liver and kidney. They concluded that the carbonyl group of the central ligand was responsible for ROS generation. Some Au(I) complexes showed excellent TrxR inhibition activity but low anticancer activity, primarily due to the lower bioavailability and high Au–P bond dissociation [65,70]. To circumvent this challenge, incorporation of a second organometallic framework (viz. metallocenes) has been found useful. For example, bimetallic cobaltocenium ethynyl Au(I) complexes **16a** & **16b** (Chart 5) with partial cobaltocenium unit exerted anticancer effect with strong TrxR inhibition [75].

3.2. Bio-labelling and photocytotoxic agent

The fact that metal acetylides are often emissive and capable of self-assembling into nano architectures over physiological pH, this class of complexes offers promise in the area of bio-labelling [24,25,52,76,77]. Metals with d^6, d^8 and d^{10} configurations are commonly used for imaging and detection of pH sensitive organelles. Yam and co-workers [24,26] found that *N,N,N* ligand based cyclometalated Pt(II) aryl acetylide complexes undergo pH dependent assembly-disassembly phenomena. The functionality over the ligand greatly determined the emission switching at different pHs. At lower pH, complexes formed aggregate and emitted in the near infrared (NIR) region (^{3}MMLCT NIR emission through metal–metal and/or π–π interactions). For instance, complex **17** (Chart 6) [26] having phenolic core (pKa* = 6.27) attached via alkynyl unit displays potential as an NIR luminescent probe ($\lambda_{em.} = 795$ at pH 3, and 788 nm at pH 7 in aqueous solution). Although the emission was very weak (~118-fold) at 20 μM (concentration used in fixed cell studies), this concentration was sufficient to perform imaging studies without producing any significant damage to the normal cells. An increase in pH above their pKa* values (pH > 7.6) resulted in deprotonation of the phenolic protons of the alkynyl ligands, leading to an increase in the hydrophilicity of the complexes and hence de-aggregation. Due to the de-aggregation coupled with the PET, the NIR emission of complex **17** was completely "*turned-off*". On the other hand, complex **18** ($\lambda_{em.} = 613$ in 1: 1 CH_3CN–MeOH) (Chart 6) [24] exhibited two-step changes in the ^{3}MMLCT emission intensity in the NIR region over two different pHs (Fig. 3a). This was due to the presence of two acid sensitive groups (–COOH and $-CH_2NHMe_2$ with pKa 3.26 and 8.53, respectively). Fig. 3b–e depicts emission in the NIR region from different cellular component. The strongest emission was noted for complex **18** when it was present in vesicular region (Fig. 3b). This observation clearly

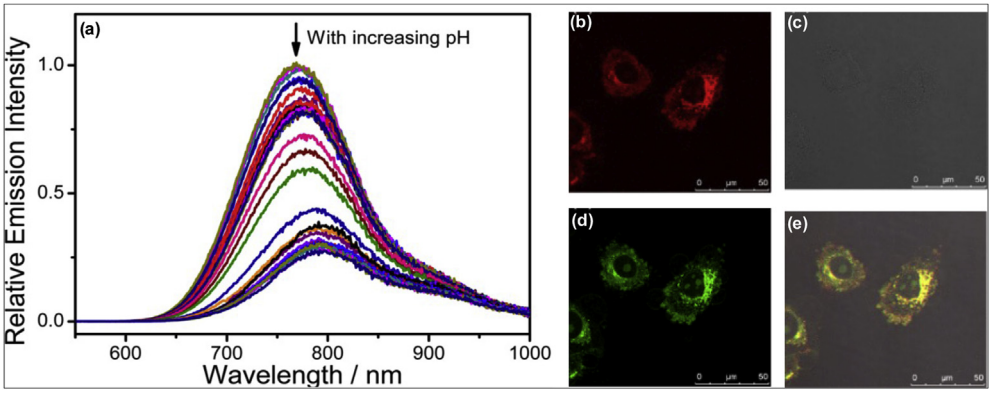

Fig. 3. (a) Emission spectra of complex **18** (200 μM) in an aqueous solution (50 mM NaCl) at different pHs. Confocal microscopy images of live HeLa cells incubated with complex **18** (16 μM) for 1 h, followed by incubation with DND189 (1 μM) in serum- and phenol-red-free DMEM for 15 min $\lambda ex = 488$ nm. (b) Luminescence image at $\lambda_{em} = 750 \pm 50$ nm, (c) brightfield image, (d) luminescence image at $\lambda_{em} = 525 \pm 25$ nm from the costained DND-189, and (e) the merged image of the emissions at $\lambda_{em} = 750 \pm 50$ and 525 ± 25 nm are shown in the corresponding figures. Reprinted with permission from (C.Y.-S. Chung, S.P.-Y. Li, K.K.-W. Lo, V.W.-W. Yam, Synthesis and Electrochemical, Photophysical, and Self-Assembly Studies on Water-Soluble pH-Responsive Alkynylplatinum (II) Terpyridine Complexes, Inorg. Chem. 55(9) (2016) 4650–4663. Copyright (2016) American Chemical Society. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Pt(II) acetylide complexes bearing cyclometalating ligands for the detection of analyte/organelle under physiological condition.

Complex	Analyte/organelle detection	Ref.
19	Trypsin, acetylcholinesterase (AChE)	[25,82]
20	Heparin, Lysosyme, thrombin	[83,84]
21	Glucose and a-glucosidase activity	[85]
21 (in combination of sulfonated poly(phenylene ethnylene)	Proteins (glucose oxidase (GOx), phospholipase D (PLD2), bovine serum albumin (BSA), human serum albumin (HSA), hexokinase (HX3), peptidase (PEP), myoglobin (MB), horseradish peroxidase (HRP), avidin, and protease (PRT)	[86]
22	Human serum albumin	[77]
23	Hg^{2+} detection in live cell	[87]
24	Lysosome	[88]

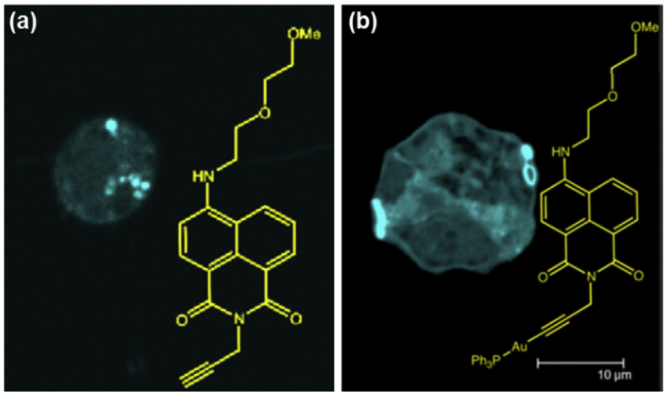

Fig. 4. Fluorescence microscopy of HEK cells imaged with (a) alkynyl ligands ($\lambda_{ex} = 405$ nm; $\lambda_{em} = 535$ nm) showing relatively weak uptake and fluorescent signals, (b) complex **25b** ($\lambda_{ex} = 488$ nm; $\lambda_{em} = 535$ nm). Cells incubated with 100 μg mL^{-1} of the lumophore. Reprinted with permission from (E.E. Langdon-Jones, D. Lloyd, A.J. Hayes, S.D. Wainwright, H.J. Mottram, S.J. Coles, P.N. Horton, S.J. Pope, Alkynyl-naphthalimide Fluorophores: Gold Coordination Chemistry and Cellular Imaging Applications, Inorg. Chem. 54(13) (2015) 6606–15 (2015) American Chemical Society. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

indicated that the complex has high affinity for organelles with low pH (such as lysosome) and is thus an excellent candidate for the NIR imaging.

Similar features (pH sensitive assembly-disassembly leading to the NIR emission switching) have also been investigated by other researchers for sensitive and selective detection of human serum albumin (HSA) [76], human telomere [78], etc. under physiological condition. Table 3 and Chart 6 show some representative examples of Pt(II) acetylide complexes bearing cyclometalating ligands that have been exploited for the detection of analyte/organelle under physiological condition. These complexes showed variation in the absorption/emission properties (appearance/disappearance) upon the addition of analyte. In addition, square planar Pt(II) acetylides also have a tendency to form nanofibers and nanospheres [79–81] in which emission undergoes *switch on/off*. However, drawback of low emission intensity often haunts the researchers. To circumvent this issue, Shi et al. [17] prepared benzothiadiazole-functionalized dinuclear Pt(II) acetylide bolaamphiphile incorporating D-A fragments. The complex formed nano-sphere in aqueous as well as alcoholic environment. Hydrophobicity induced self-assembly in water while in alcohol it was induced by H-bonding. The fact that bolaamphiphile displayed intense orange-red fluorescent signals following cellular internalization with acceptable biocompatibility, it offers unique opportunity to image cells.

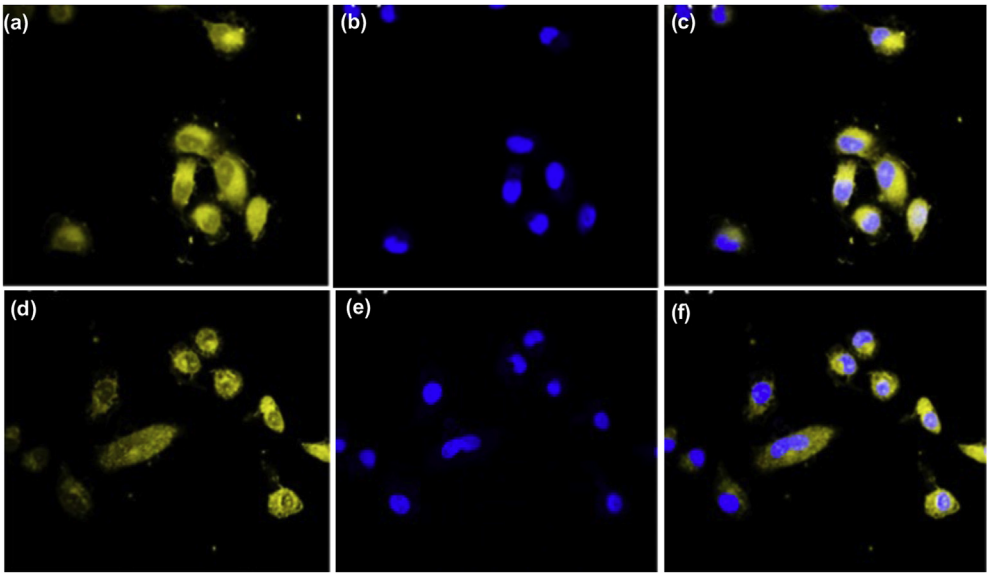

Fig. 5. Images of complexes **28a** (a–c) and **28b** (d-f) incubated with A549 cells and Draq5 at 37 °C for 4h. (a & d) after irradiation at 405 nm, (b & e) after irradiation at 647 nm, and (c & f) superimposed image. Reprinted with permission from A. Luengo, V. Fernández-Moreira, I. Marzo, M.C. Gimeno, Bioactive Heterobimetallic Re(I)/Au(I) Complexes Containing Bidentate N-Heterocyclic Carbenes, Organometallics 37(21) (2018) 3993–4001. Copyright (2018).

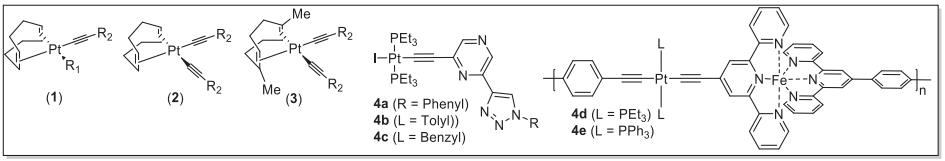

Chart 1. Some recent examples of *cis* and *trans*-Pt(II) acetylide complexes.

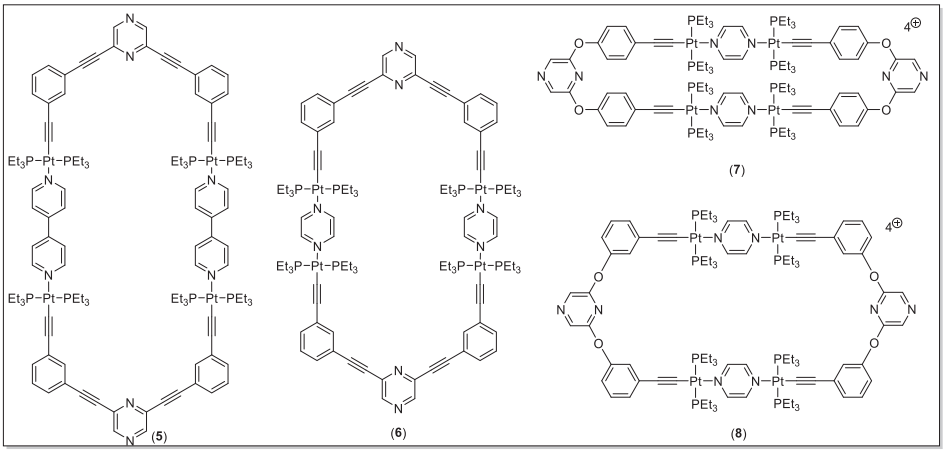

Chart 2. Examples of macrocyclic Pt(II) complexes which showed improved activity compared to their precursor ligands and non-cyclic complexes.

Metalla-ynes based on d^{10} metal such as Au(I) bearing an ancillary phosphine (with varying alkyl/aryl groups) and fluorophoric ligand (such as naphthalene, NHCs) have also been explored for cellular component imaging. Pope and co-workers [8] assessed the imaging capabilities of alkynyl-naphthalimide ligands and their corresponding Au(I) complexes **25a-f** (Chart 7) on HEK cells and *Spironucleus vortens*. Interestingly, the ligands showed appreciable absorption and emission properties ($\lambda_{max} = 353–430$ nm, $\lambda_{em} = 392–535$ nm, $\tau = 0.6–10.4$ ns in MeCN) which were retained in the Au(I) complexes ($\lambda_{max} = 353–428$ nm, $\lambda_{em} = 391–530$ nm, $\tau = 1.2–10.1$ ns in MeCN). Both the ligands and the complexes showed moderate to high cytotoxicity against LOVO, PC3, and MCF7 cancer cell lines with low toxicity against HEK cell line. In all cases, complexes performed better than the corresponding ligands. Expectedly, ligands and complexes with biocompatible fragment (glycol) showed more uptake, intracellular (mitochondria) localization and strong emission than others (Fig. 4). In contrast to this work, Poyatos and co-workers [89] prepared pyrene tetraalkynyl ligand and its corresponding tetraalkynyl Au(I) complexes with NHCs auxiliaries. Compared to mono-substituted naphthalimide-based alkynyl systems **26a-b** (Chart 7), tetraalkynyl complexes possess excellent quantum yield values in solution. Preliminary studies on healthy cheek cells show that one of the complexes was efficiently and rapidly taken up into the cell.

The presence of a second metal often shows synergism and improves the PL properties of metal acetylide complexes. A similar trend has also been found in biological properties. Gimeno and co-workers [90] found that hetero-bimetallic complexes containing Au(I)/Re(I) fragments exert more anti-proliferative effects (10 x) than their mono-metallic Re(I) counterparts. Moreover, different

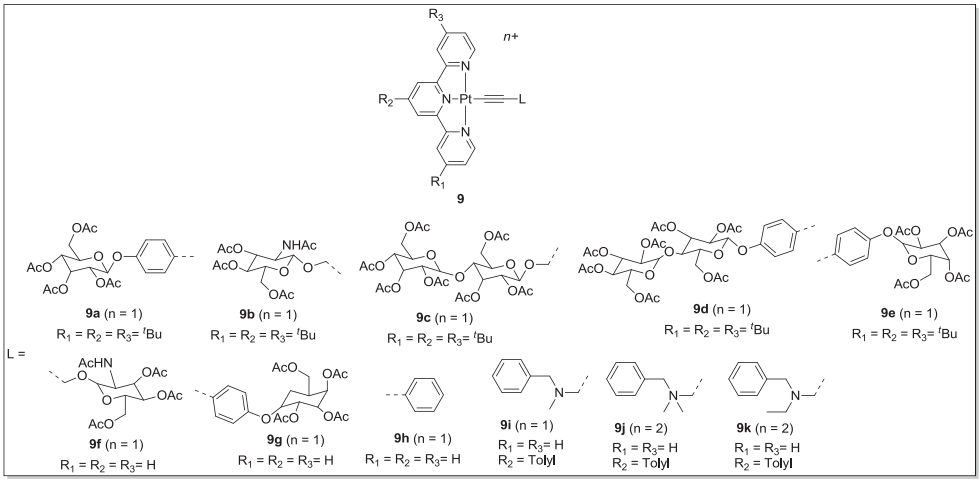

Chart 3. Examples of cyclometalated Pt(II) acetylide complexes as anticancer agents.

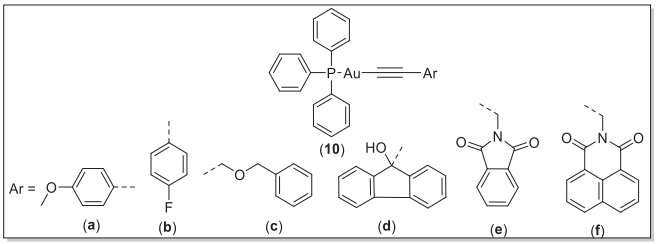

Chart 4. Examples of monometallic Au(I) acetylide complexes as anticancer agents.

bio-distribution behaviour were also reported. Whereas the monometallic Re(I) species **27a-c** (Chart 7) showed cytoplasmatic staining with mitochondrial accumulation, hetero-metallic Re(I)/Au(I) derivatives **27d-f** (Chart 7) localised in nucleus and nucleolus. These features motivated Luengo et al. [91] to synthesize the first example of highly emissive cationic hetero-bimetallic complex of type *fac*-$[Re(CO)_3(NHC)\ (LAuPPh_3)]^+$, (NHC is an imidazole pyridine-based carbene and L is 3-pyridylalkyne, 4-pyridylalkyne, or 5-ethynyl-1-methyl-1H-imidazole ligands) **28a-c** (Chart 7) The emissive properties of such complexes were governed by the NHC-Re(I) fragment while the anticancer activity ($IC_{50} = 10.82–12.65$ μM against A549 cell line) against tumor lung A549 cells was related to the Au(I) counterpart. Interestingly, the effect was increased (x 5 times) after irradiation at 405 nm ($IC_{50} = 2.66–9.97$ μM against A549 cell line). Authors suggested a necrotic process as the cell death mechanism. Complex **28a** and **28b** localized in cytoplasm close to the nucleus with some nucleus permeation (Fig. 5). These findings revealed that bimetallic species can serve as excellent partner in cell imaging and cancer therapy.

3.3. Antimicrobial

Due to increasing drug resistance and decreasing effectiveness of currently employed antibiotics, new antibacterial agents are urgently required. It was against this backdrop that some researchers assessed the effectiveness of metalla-ynes. Younus and co-workers [92] reported the antibacterial properties of sugar-containing Pt(II) acetylide complexes **29**–**30** (Chart 8). Like previously discussed examples [92], here also complexes displayed better activity than the corresponding ligands. For example, complexes **29**–**30** (Chart 8) were resistant to four bacterial strains (*E. coli, P. penneri, K. oxytoca* and *P. aeruginosa*), whereas ethynyl ligand was resistant against *P. aeruginosa* only. The enhanced lipophilic character of the ligand attached to the metal centre was suggested as the main

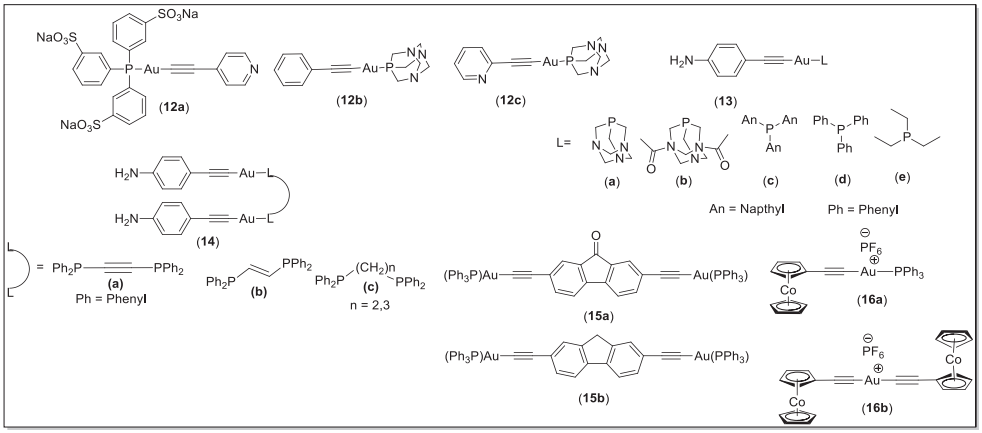

Chart 5. Examples of homo and heterometallic Au(I) acetylide complexes as potential anticancer agents.

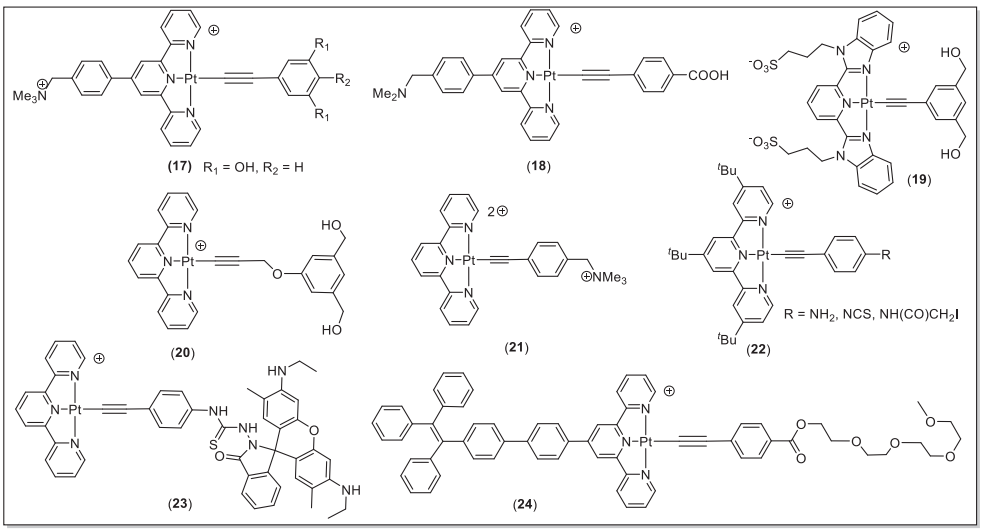

Chart 6. Examples of cyclometalated Pt(II) complexes as imaging probe.

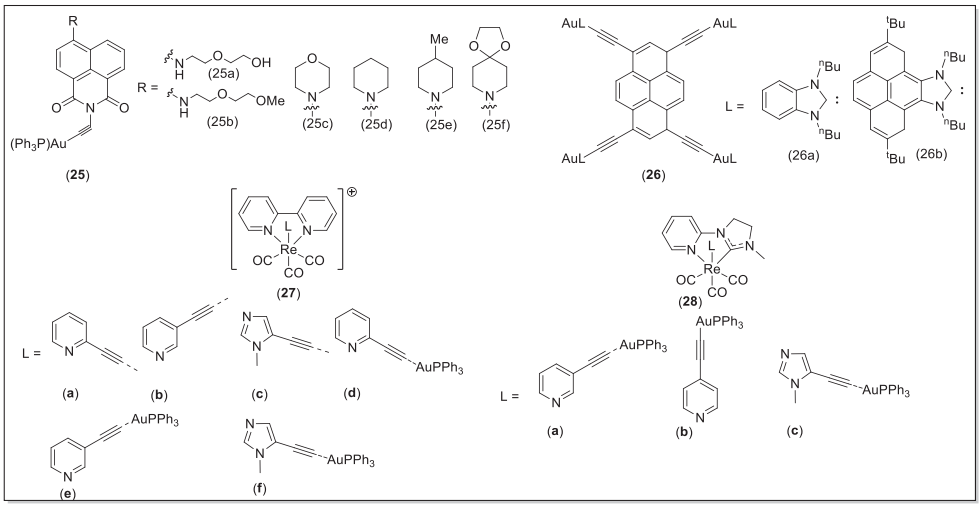

Chart 7. Examples of homo and hetero-metallic Au(I) complexes as luminophores.

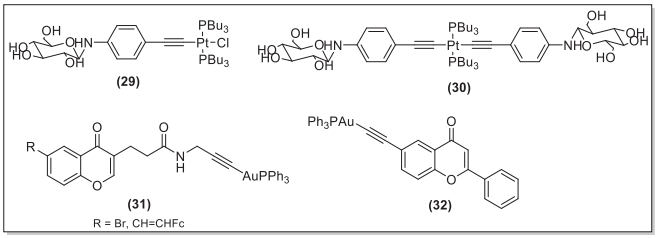

Chart 8. Examples of metalla-ynes with antibacterial properties.

reason behind activity of complexes. Au(I) complexes **31**–**32** (Chart 8) exhibited bactericidal activities against gram-positive methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) bacterial strains [93]. However, no activity against the Gram-negative *E. coli* bacterial strain was reported [93].

4. Challenges and future directions

In this review, we delineated biological applications of metalla-ynes, especially those containing Pt(II), Au(I) and Re(I) metals. We discussed the features and properties of rigid-rod type η^1-σ-alkynyl complexes followed by anticancer, antibacterial and imaging potential of some representative examples. From the above discussion, it is quite clear that mono-, di- and polynuclear metal σ-acetylide complexes possess unique properties and are attractive candidates for biomedical applications. They are not only emerging as potential candidates to combat diseases (cancer, bacterial infection, etc.), but also offer a unique platform for tagging diseased sites (i.e. as imaging probes). Some of the above discussed complexes have shown remarkable *in-vitro* activity. For instance, glycosylated Pt(II) metalla-ynes have been found to target DNA with high propensity (K_b ~10^5 M^{-1}) and exert superb cytotoxicity (~100-times higher than the clinically used drug CP) [37]. Similarly, [Au(C≡CPh)(PTA)] exhibits high activity without causing genomic mutation. Due to the presence of heavy metal centres (Pt(II)/Au(I), such complexes possess luminescence and lifetime suitable for live cell tracking. Furthermore, fine tuning of ligands allows selective localization/delivery of the probes. Some cyclometalated Pt(II) acetylide complexes produce light-induced singlet oxygen ($^1O_2$) *in-vitro*, offering opportunity to image diseased sites [94]. In addition, we also demonstrated how the size/topology of a metalla-cycle controls the activity of the complexes and how desired emission and cellular localization can be tuned by varying biomolecule or fluorophore to the metal centre.

Despite these features, issues such as biocompatibility, selectivity, and lack of *in-vivo* results are considered as barriers ahead with this class of materials. Another challenge often faced by researchers during imaging is the contamination (monomeric-polymeric) of spectral background which limits their usages [36]. Similarly, some complexes demonstrate activity via multiple pathways, which is not always welcomed by the researchers. Lacking a particular mode of action restricts the use of a drug for specific treatment. Based on the handful of available results, it is too early to predict the exact clinical fate of this class of materials as pharmacophores often display excellent *in-vitro* and *in-vivo* profiles but fail in clinical trials.

Future research should consider a detailed bioassay of well-defined small to large functional architectures (i.e. η^1-σ-alkynyl metal complexes). In particular, Ruthenium, Iridium, Osmium etc. metals-based σ-alkynyl complexes decorated with recognizable unit (such as pyridine) are yet to be studied. To gain a better understanding at supramolecular level, detailed computational study (drug-likeness, molecular docking, MD simulation, QSAR etc.) is also desirable. Earlier studies indicated relationship between the energy of frontier orbitals and the activity in organic pharmacophores [95]. This aspect needs to be considered and delineated for metal acetylides.

5. Conclusion

In this article, we reviewed the therapeutic (*viz.* anticancer, antibacterial) and diagnostic (*viz.* enzymes or proteins imaging) application of several small to medium sized neutral and charged η^1-σ-alkynyl complexes. Attempts have been made to understand the SAR of Pt(II) and Au(I) containing arylacetylide complexes. Moreover, drawbacks and suggestions have also been delineated. Considering the pros and cons, we strongly feel that metal acetylides have a bright future and hold promise as next generation biomaterials.

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List of abbreviations

5-FU	5-flurouracil
A2780	Ovarian cancer cell line
A549	Lung cancer cell line
COD	Cycloocta-1,5-diene
CP	Cisplatin
DAPTA	3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1] nonane
DNA	deoxyribose nucleic acids
HEK	Embryonic kidney cancer cell line
HeLa	Cervical cancer cells
Hep3B	Hepatoma cancer cell line
HepG2	Liver cancer cell line
HT-29	Colon carcinoma cancer cell line
LOVO	Colon adenocarcinoma
MCF-7	Breast adenocarcinoma
MDA-MB-231	Breast cancer cell line
MG-3	Osteosarcoma cell line
NCI–H460	Lung cancer cell line
NHCs	N-heterocyclic carbenes
PC3	Prostate adenocarcinoma
PTA	1,3,5-triaza-7-phosphaadamantane
QSAR	Quantitative structure activity relationship
RC-124	Kidney (adult) primary cell line
ROS	Reactive oxygen species
SF-268	Glioblastoma line
SKHep-1	Hepatic adenocarcinoma cell line
TrxR	Thioredoxin reductase

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