Synthesis and Medicinal Applications of N-Heterocyclic Carbene Complexes Based on Caffeine and Other Xanthines

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Abstract: Xanthines are purine derivatives predominantly found in plants. Xanthines include compounds such as caffeine, theophylline, and theobromine and exhibit a variety of pharmacological properties, demonstrating efficacy in treating neurodegenerative disorders, respiratory dysfunctions, and also in cancer. The versatile attributes of these materials render them privileged scaffolds for the development of compounds for various biological applications. Xanthines are N-heterocyclic carbene precursors that combine a pyrimidine and an imidazole ring. Owing to their biological relevance, xanthines have been employed as N-heterocyclic carbenes in the development of metallodrugs for anticancer and antimicrobial purposes. In this conceptual review, we examine key examples of N-heterocyclic carbene complexes derived from caffeine and other xanthines, elucidating their synthetic methods and describing their pertinent medicinal applications.

Introduction

Xanthines are alkaloids that can be produced by plants and animals[1]. These proteins are key components of metabolic processes involving purine nucleobases[2]. Xanthine is often considered the point of convergence for the purine base metabolism of adenine and guanine nucleotides and is involved in the production of uric acid[3]. Xanthines can bear methyl groups at several positions on the ring, and the position and number of N-methyl groups can differ. The most common xanthines are caffeine (1,3,7-trimethylxanthine), theophylline (1,3-dimethylxanthine) and theobromine (3,7-dimethylxanthine). Xanthines are also purines and therefore can be considered nucleobase analogues. Given the similarity between xanthine and the nucleobases guanine and adenine and the metabolic role these compounds can play, they are excellent candidates for developing novel drugs for a variety of pharmacological applications. Indeed, xanthines have been recognized as therapeutically potent compounds for the treatment of various diseases[4] and are effective in the treatment of neurodegenerative and respiratory diseases, diabetes and cancer[5].The most widely known methylxanthine is caffeine, which can be found in coffee, tea, cocoa, cola and other beverages and foods, being the most consumed psychostimulant worldwide[6]. Caffeine is used therapeutically to treat various headache conditions and respiratory depression in neonates, among other conditions[7,8].

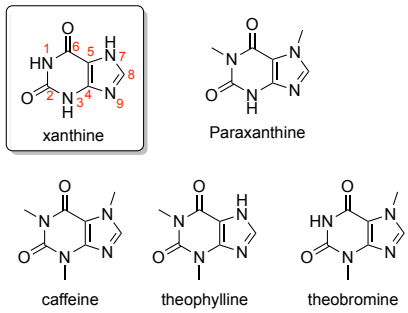


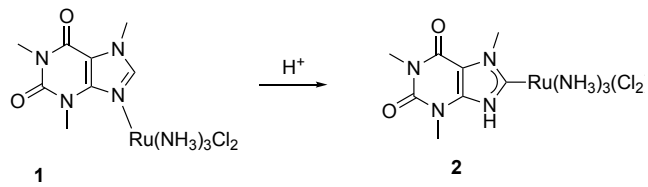
Figure 1. Types of Xanthines

It is well accepted that caffeine is an antagonist of adenosine receptors and can also act as an inhibitor of phosphodiesterases[9]. In addition, caffeine can modulate $GABA_A$ receptors to inhibit acetylcholinesterase, which may be involved in its central nervous system effects[6]. Given the potential for medicinal applications that xanthines have shown thus far[1,10,11], their use as ligands opens a variety of possibilities for drug development. Xanthines are N-heterocyclic carbene precursors (NHCs); therefore, their role as ligands can be explored using this ligand connectivity, in contrast to that of typical N-coordination. In the context of metallodrugs, NHCs are known to impart stability due to the strong donation abilities of this class of compounds[12]. Building NHCs from biologically relevant scaffolds[13] such as xanthines and combining them with a metal centre allows for the development of more biocompatible metallodrugs[13]. Indeed, the stability of metallodrugs in physiological media is often an issue, and in this regard, the stabilization that the NHC ligand can impart to the metal centre undoubtedly makes these ligands privileged candidates for the development of more stable metallodrugs[14]. The application of metal complexes bearing NHCs has been widely explored in catalysis [15]. However, their use in medicinal chemistry has been less explored but is a rapidly growing field [14] [9-12]. A

review focusing on metal complexes based on xanthines and their biological application has been recently published[16], and a short review on xanthine based NHC was published by Morales-Morales in 2018[17]. In this conceptual review, we focus on the development of metal complexes bearing NHCs based on xanthines, particularly caffeine, and on the known medicinal applications of these complexes, discussing key examples for their synthesis and biological applications.

Synthetic Approaches

Given the parallelism between xanthine rings and imidazoles, strategies for the synthesis of N-heterocyclic carbene complexes employ similar strategies to those used to prepare imidazolium salts [13,14]. However, the preparation of xanthine salts can present some drawbacks depending on the type of xanthine. For example, several reports in the literature point to the difficulty of functionalizing caffeine beyond methylation or benzylation [13-16]. This difference has been attributed to the lower nucleophilicity of N9 of caffeine, which requires harsh reaction conditions to achieve quaternization and is limited by the presence of methyl or benzyl substituents. To circumvent this, functionalization is generally performed starting from theophylline, for which quaternization is more facile since it can take place at N7. For this reason, many reports on NHC complexes, referred to as caffeine NHCs, concern compounds containing substituents at N7 other than a methyl group. The difference in the nucleophilicity of the methylxanthines can also be reflected in their direct reactivity with metal complexes. In 1974, Taube reported the formation of N-bound and C-bound complexes of ruthenium based on xanthines under acidic conditions (Scheme 1). [18]



Scheme 1. N- to C- tautomerization of ruthenium caffeine adducts catalysed by acid

Differences in the methylation sites of xanthines have direct effects on the type of coordination to ruthenium. Caffeine and theobromine form only C8-bound complexes, theophylline forms both N7- and C8-bound complexes, and 9-alkylated xanthines form almost exclusively N-bound complexes (Fig. 2).

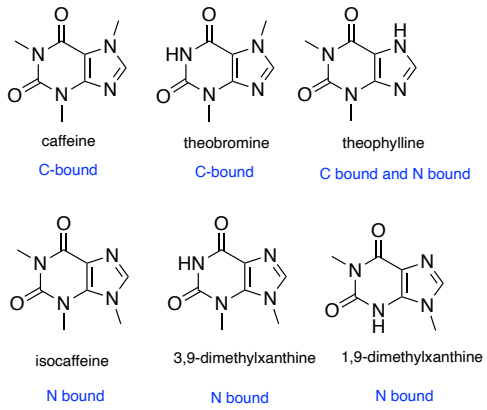
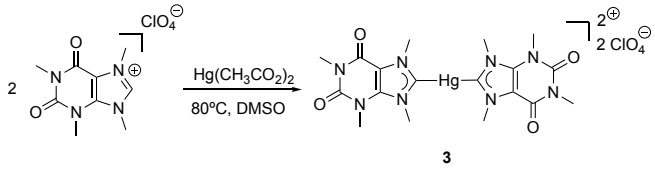


Figure 2. C and N tautomer formation as described by Taube for different xanthines.

Importantly, these studies also demonstrated that the C8 tautomer is thermodynamically favoured, while N7 is kinetically favoured. In line with this, isocaffeine, methylated at N9, only formed the N-bound compounds. Examples of the synthesis of xanthine NHCs by tautomerization are, however, very limited[19].

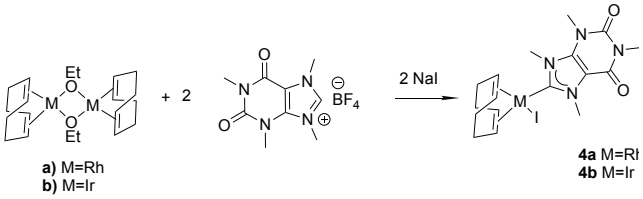
The most common routes[17] for the synthesis of NHC complexes derived from xanthines involve transmetalation and deprotonation. Base-assisted deprotonation can be performed using an external base or a “built-in-base”, i.e., a base already present at the metal precursor. For external bases, two aspects can be considered: one involves the use of a strong base to generate free carbene from the azolium salt, and the other involves the use of a weak base, which does not lead to the free carbene and usually requires milder conditions[20].

In 1976, Beck reported the synthesis of a mercury biscaffeine complex[21]. The reaction of 1,3,7,9-tetramethylxanthinium perchlorate (methylcaffeine) with Hg(II) acetate affords the C-8 mercurated complex. Acetate acts as a “built-in” base able to deprotonate the caffeinium salt, yielding complex **3** (Scheme 2).



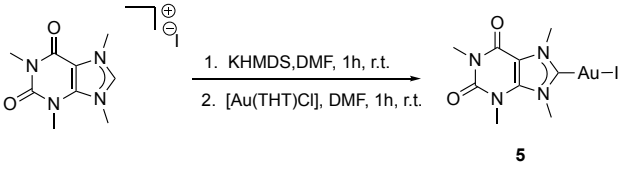
Scheme 2. Synthesis of mercury biscaffeine complex **3**.

Herrman employed a similar methodology for the synthesis of caffeine complexes based on rhodium and iridium (I) [22] and, subsequently, palladium [23]. Reaction of the metal precursors. containing ethoxide with methyl caffeine leads to the formation of complex **4** (Scheme 3). Depending on the reaction conditions, when 4 equivalents of methylcaffeine were used and for prolonged times, biscarbene complexes are formed instead.



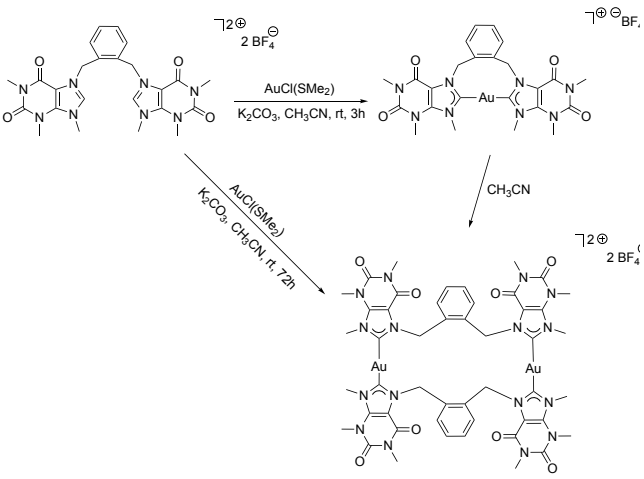
Scheme 3. Synthesis of Rh(I) and Ir(I) NHC complexes **4**.

Another key example was described by Casini in 2014, who employed the free carbene route for the synthesis of a gold compound based on methyl caffeine[24]. The compound was synthesized using KHMDS, a strong base, to generate free carbene from the caffeinium salt, which subsequently reacted with Au(tht)Cl to yield compound **5** (Scheme 4).



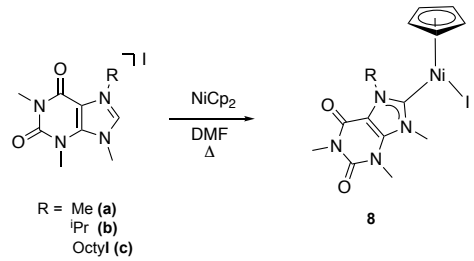
Scheme 4. Synthesis of Gold(I) complex **5** using the free carbene route

More recently, Tubaro, Visentin and Biffis described the synthesis of mononuclear and dinuclear gold complexes based on caffeine by employing K_2CO_3[25] (Scheme 5). The bisxantinium ligand was reacted with the gold(I) precursor in the presence of K_2CO_3, a mild base, in acetonitrile. When the mixture was reacted for 3 h, a monoclear complex was formed with the chelating dicarbene, the kinetic product. When the mixture was reacted for 72 h, a dinuclear gold(I) complex with two bridging dicarbene ligands was formed instead. The mononuclear compound spontaneously transforms into a dinuclear complex, the thermodynamically more stable species.



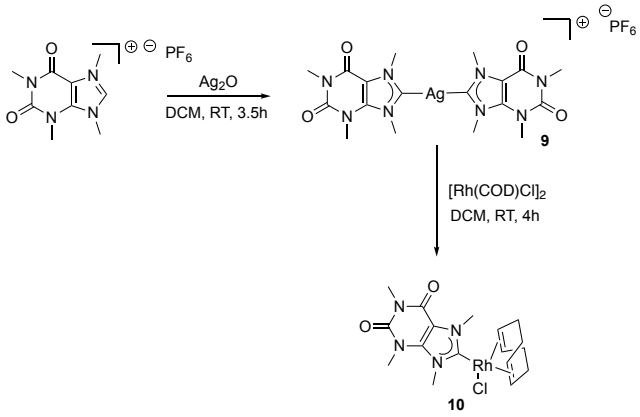
Scheme 5. Synthesis of mono- and dinuclear gold(I) complexes **6** and **7**.

We [26] and Szostak's group[27] reported the synthesis of NHCs based on caffeine by reacting the corresponding caffeinium salts with nickelocene (Scheme 6). The Cp anion acts as an internal base, and cyclopentadiene is released. In the case of methylcaffeine, the formation of a biscarbene was also observed, as had already been reported for analogous imidazolylidene and triazolylidene complexes[28,29].



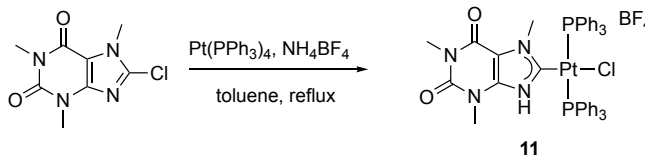
Scheme 6. Synthesis of Nickel NHC complexes **8**.

Transmetalation is perhaps the most prevalent method employed. Young's group reported the synthesis of silver complexes based on caffeine and theobromine [14,26,27]. The corresponding salts were reacted with Ag_2O to yield the corresponding biscarbenes. For example, caffenium salt was reacted with silver oxide to form the silver biscarbene **9**, which was subsequently transmetallated to form rhodium, yielding compound **10**.



Scheme 7. Synthesis of the Rh(I) NHC complex **10** via transmetalation.

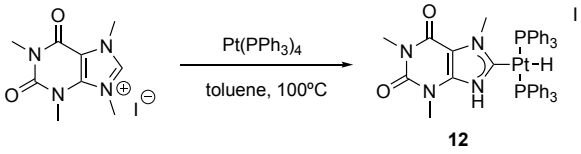
A less explored route was described by Hanh's group, who reported the regioselective C8 metalation of purine bases via the oxidative addition of C8-halogenated caffeine to Pt(0)[30]. 8-Chlorocaffeine reacts with $[Pt(PPh_3)_4]$ to yield the protic NHC compound **11**. This methodology was successfully extended to theophylline and theobromine[31,32]. Compound **11** can be obtained directly from 8-chlorocaffeine if a proton source is added to the initial reaction mixture or by performing the oxidative addition first, followed by protonation of the isolated compound.



Scheme 8. Regioselective C8-Metalation of Caffeine

Notably, in the absence of a proton source, the formation of dinuclear species, typical of other azoles for the same type of compounds, does not occur. This is also a point of contrast in xanthine reactivity compared to that of other azoles. This difference is probably due to the reduced electron density within the five-membered heterocycle due to the electron-withdrawing nature of the annelated ring system[31].

More recently, our group reported the direct C-H oxidative addition of methyl caffeine to form platinum(II) N-heterocyclic carbenes[33]. This reactivity also contrasts with that previously described by Cavell for imidazole derivatives[34]. Indeed, for imidazolium salts, oxidative addition is also possible, but reductive elimination is possible and limits the overall yield of the reaction. For the caffeinium salt, this is not the case, and the compound can be formed easily and isolated in good yields.



Scheme 9. Synthesis of compound 12 by C-H oxidative addition

In summary, the different synthetic methodologies described above highlight the possibilities available for the synthesis of NHCs based on caffeine and other xanthines. While most methodologies are similar to those of imidazolium salts, in some cases, the reactivity of xanthine and xanthinium salts shows some differences, namely, on direct C-H oxidative addition or the formation of dimeric species following C-X oxidative addition.

Medicinal applications

The utilization of xanthines in the clinic discussed earlier makes these compounds privileged candidates for use as ligands in the development of metallodrugs. While metals provide a wide array of coordination numbers and redox states, the introduction of biologically relevant ligands such as xanthines can impart [important] additional properties, for example, to achieve higher selectivity. Thus far, relevant results have been described for antimicrobial and anticancer activities.

Antimicrobial Activity

In 2006, Youngs and coworkers reported the antimicrobial activity of methylated caffeine and its silver complex **13** against bacterial and fungal strains[31-33] (Fig. 3). This work focused on developing complexes for the treatment of lung infections that develop in cystic fibrosis patients. Cystic fibrosis leads to an increase in mucus viscosity in the lungs, creating a prone environment for bacterial growth. Compound **13** was tested against pathogens relevant to cystic fibrosis-related infections. Specifically, the test organisms included *Escherichia coli* and *Pseudomonas aeruginosa* as representative gram-negative bacteria and *Staphylococcus aureus* as a gram-positive bacterium. *Candida albicans, Aspergillus niger* and *Saccharomyces cerevisiae* were used as representative fungal strains. Compound **13** was found to be highly active against *C. albicans*, *S. cerevisiae* and *A. niger*. Among the bacteria, **13** were very active against an array of bacterial strains, including strains isolated from patients with cystic fibrosis (CF). In vivo studies with rat models showed that **13** has very low toxicity. To examine the role of silver, the pMG101 plasmid, which is known to confer resistance to silver, was also examined. The MIC for the *E. coli* J53 strain lacking this plasmid was lower than that for the other strains, which confirmed that the silver centre is the main site responsible for the antimicrobial activity.

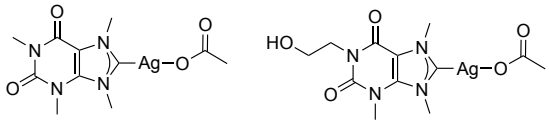


Figure 3. Structures of silver complexes **13** and **14**.

Compound **14** (Fig.3) was also synthesized and found to be more soluble than **13** by approximately 10-fold due to the presence of the hydroxyethyl group. Compound **14** was subsequently tested and found to be active against several virulent and multidrug-resistant pathogens obtained from patients with cystic fibrosis. Like **13**, for **14,** the role of silver is key for antimicrobial activity. In vivo tests in a mouse pneumonia model were performed. *P. aeruginosa*-infected mice were treated with various doses of aerosolized compounds, and both **13** and **14** improved survival rates. Animals treated with **13** and **14** had significantly less dissemination of bacteria than did the control animals, demonstrating their potential to treat MDR pulmonary infections associated with cystic fibrosis.

Our group examined the antifungal activity of half-sandwich nickel complexes bearing caffeine-based NHCs **15** and **16** (Fig. 4). The nickel complexes **15** were active against *C. albicans* and *C. glabrata*. Monocarbenes **15a** and **15b** were similarly active against both yeasts, while **15c** and **16** were more effective against *C. glabrata*. All the nickel NHC complexes had greater antifungal activity than did their ligand precursors, which were generally not active.

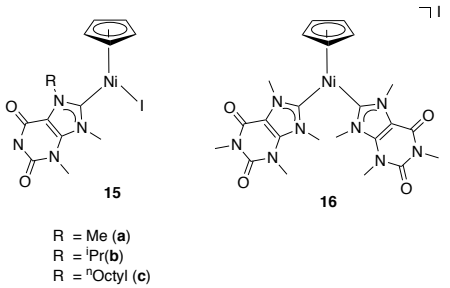


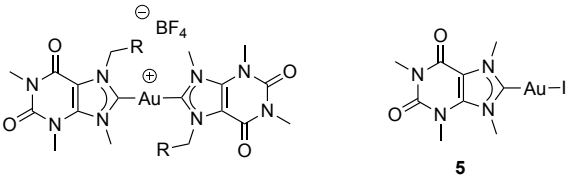
Figure 4. Half sandwich Nickel caffeine complexes **15** and **16**.

Interestingly, biscarbene **16** was strongly active against *C. glabrata,* while for *C. albicans* was only slightly active or not active after 24 and 48 h, respectively. Seemingly, the presence of more than one NHC ligand and/or the influence of the overall charge of the nickel cation yields a selective antifungal compound for *C. glabrata*, suggesting different mechanistic performances for different *Candida sp*. strains.

Anticancer Activity

The utilization of N-heterocyclic carbenes for the development of novel anticancer agents has grown considerably in recent years. In this regard, the use of bioactive compounds such as xanthines as NHC precursors is very appealing owing to their low toxicity and high versatility in terms of tunability in terms of steric and electronic properties.

Gold NHC compounds have been shown to be active antiproliferative compounds able to inhibit the selenoenzyme thioredoxin reductase (TrxR), which is important for redox homeostasis in cells. Casini and coworkers subsequently reported a series of caffeine-based gold compounds with potent anticancer properties[24] (Fig. 5). Compound **17** is a theophylline derivative with different substituents at N7, while **5** is a monocarbene gold compound with a methyl caffeine-2-yliene substituent.

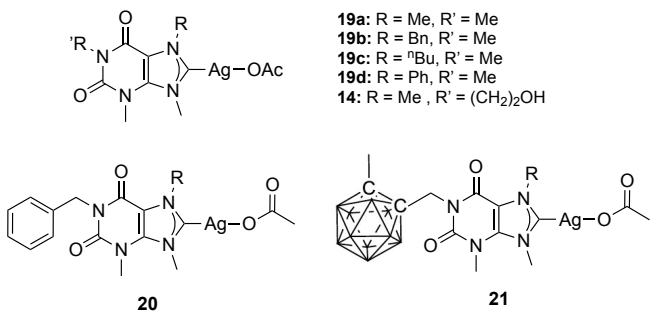


17a R= H
17b R= vinyl
17c R= *E*-propenyl
17d R= Ph
17e R= *p*-$C_6H_4NO_2$
17f R= *p*-$C_6H_4CO_2Me$
17g R= *p*-$C_6H_4CF_3$

Figure 5. Mono and Biscarbene gold(I) complexes **5** and **17**.

The compounds were evaluated against different human cancer cell lines (i.e., A2780, A2780/R, SKOV3, and A549) and noncancerous cells (HEK-293T). All the compounds exhibited moderate antiproliferative activity against the tested cancerous cell lines, with IC50 values in the micromolar range. The compounds showed some degree of selectivity and were not toxic to HEK-293T or A459 cells. Complex **17a** is the most promising compound but is less active than cis-platin in A2780 cells, while it is 2-fold more potent in A2780/R cells. The interactions of the compounds with quadruplex and duplex DNAs were also screened. Previous studies on the development of G-quadruplex ligands revealed that the ideal ligand for G-quadruplex binding should mimic the naturally occurring self-assembly of G-quartets, the origin of quadruplex stability. This work identified complex **17a** as an effective G-quadruplex ligand. Next, complex 17a was evaluated for interactions with G-quadruplexes by FRET. These results parallel those found for antiproliferative activity. Complex **17a** exhibited high affinity and selectivity for quadruplex DNA. Overall, these findings suggest that the use of caffeine as a guanine mimic is an excellent option for the construction of ligands that can bind G-quadruplex DNA. The compounds were examined ex vivo in precision cut tissue slices (PCTS) of the liver, kidney, and colon, and the results obtained via PCTS were in line with those observed in nontumorous cells regarding toxicity. These compounds were also evaluated for their interaction with the zinc-finger protein PARP-1 since these proteins are involved in cancer resistance to chemotherapies. Compound **17a** is also a modest PARP1 inhibitor and can impair the DNA damage response.

The Willans group reported the anticancer activity of a series of silver(I)–N-heterocyclic carbene complexes based on caffeine, theophylline and theobromine (Fig 6.). The in vitro cytotoxicities of compounds **19** and **14** were tested against A375 (malignant melanoma), HCT116 (colorectal carcinoma), HT-29 (colorectal adenocarcinoma), LN229 (glioblastoma), Panc-1 (pancreatic carcinoma), SiHa (grade II, squamous cell carcinoma cervix), U-87 MG (glioblastoma) and U-251 (glioblastoma) cells.



19a: R = Me, R' = Me
19b: R = Bn, R' = Me
19c: R = nBu, R' = Me
19d: R = Ph, R' = Me
14: R = Me , R' = $(CH_2)_2OH$

Figure 6. Synthesis of silver NHC complexes **19-21**.

Complexes **19** and **14** (previously reported) exhibited moderate cytotoxicity against all the cell lines, with IC_{50}

values in the micromolar range. The most active complex is **19d**, which has an N7-phenyl substituent. The higher activity of **19d** is attributed to the possible stabilizing effect of the phenyl substituent on the silver–NHC bond, which could lead to a decreased silver release rate and enhanced cytotoxic profile. It is also noted that the presence of a hydroxyethyl group in the backbone of xanthine (compound **14**) improved the activity 2-fold, probably due to its higher solubility, as described previously by Youngs. Hence, the combination of both steric effects of the ligand and the solubility of the silver complex contribute to the overall activity against cancer cells. Following on this, the antiproliferative abilities of silver complexes of tethered N-heterocyclic carbene-carboranyl ligands, based on caffeine **20** and **21**, were also examined on colon cancer cell lines HCT116 $p53^{+/+}$ and HCT116 $p53^{-/-}$ (which does not possess the p53 gene). Both silver(I) NHC complexes **20** and **21** were active against both cancer cell lines, and the activity of the complexes is independent of the p53 gene, often mutated in cancer cells.

Ott's group confirmed the importance of the NHC connectivity of xanthine ligands, by evaluation a set of of platinum(II) terpyridine complexes based on caffeine[35] (Fig.7) Thus, complexes **22** and **23** bearing NHCs based on caffeine and complexes **24** and **25** with a N5-coordinated theobromine as ligand were examined for their antiproliferative activity towards the tumour cells MCF-7, MDA- MB-231 and HT-29. Organometallic complexes **22** and **23** exhibited greater activity (IC_{50} values in the submicromolar range) than complexes **24** and **25**. Complexes **22-25** induced neural differentiation-like morphological changes in MCF-7 cells, but complexes **24** and **25** required considerably greater concentrations to achieve these changes. Antiangiogenic behaviour was inferred from the screening of **22-25** via the tube formation assay. Inhibition by complexes **22** and **24** was evaluated as a possible mode of action. Moderate TrxR activity was also confirmed, indicating that this mechanism might be a contributing factor to overall TrxR activity. These results also indicate that the greater charge of **22** and **23** and their organometallic nature, bearing the caffeine NHC ligand, might be responsible for the different biological effects.

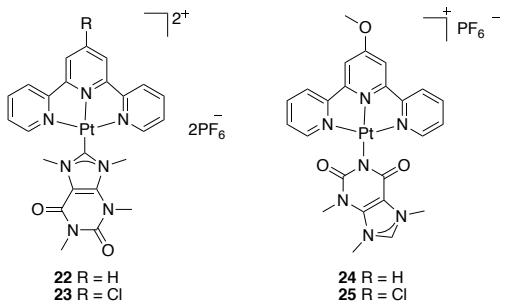
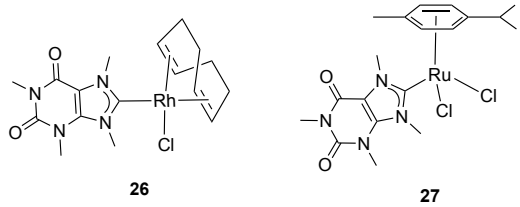


Figure 7. Structure of platinum terpyridine complexes **22-24**.

The same group described the anticancer properties of compounds **26** and **27** based on rhodium(I) and ruthenium(I) (Fig.8), demonstrating, in this case, the specificity of the role of the metal[36]. The compounds were examined against five human cancer cell lines (human hepatoma cell line (HepG2), human breast cancer cell lines (MCF-7 and MDA-MB-231), a human colon carcinoma cell line (HCT-116), human pancreatic cell lines (Panc-1 and JoPaca-1), and a human prostate adenocarcinoma cell line (LNCaP). Complex **26** exhibited a wide spectrum of cytotoxic effects (IC_{50} values ranging from 8.8 to 76.7 μM; 96 h) and was particularly active against HCT-116 cells (IC_{50} values 2–8 times lower than those in the other cancer cell lines). In this cell line, DNA damage and cell cycle arrest were also induced in the sub-G1 fraction, eventually leading to apoptosis. In contrast, compound **27** and its ligand precursor did not exhibit any anticancer activity, which indicates that the presence of rhodium is essential for inducing activity.

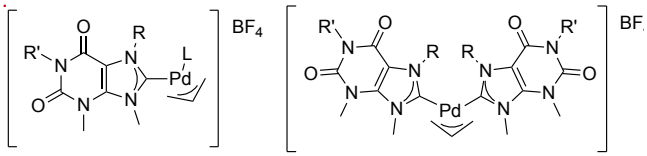


26 **27**

Figure 8. Compounds **26** and **27** bearing a caffeine derived NHC.

Complex **26** can also induce significant accumulation of ROS, which is most likely due to inhibition of TrxR, which was also observed. A decrease in the mitochondrial membrane potential was also observed, leading to apoptosis accompanied by a decrease in the levels of pro-caspase 9 and pro-caspase 3 and in the cleavage of PARP.

Our last example concerns the work developed by Visentin[37] and coworkers on a series of palladium NHC complexes derived from caffeine, theophylline and theobromine with different substitution patterns. These comprise monocarbenes bearing different phosphine ligands, and biscarbene complexes featuring an allyl moiety. These complexes were examined for their cytotoxic activity inhuman ovarian cancer cell lines A2780 (cisplatin-sensitive) and SKOV-3 (cisplatin-resistant). All the complexes, except **31a** displayed good antiproliferative effects on cisplatin-sensitive A2780 cells, although only **28c**, **28d** and **29d** displayed better activity than cisplatin. In the cisplatin-resistant SKOV-3 cells, compounds **28b–d**, **29a**, **30b** and **30d** exhibited greater activity than did cisplatin. Compound **28d** was the most active compound, with an IC_{50} 3.5 times lower than that of cisplatin-



28a-d L = PPh_3,
29a,b,d L = PTA
30a,b,d L = DIC
31a,b,d L = TPPTS

a R = CH_3, R' = CH_3
b R = CH_2Ph, R' = CH_3
c R = H_2C-C°CPh, R' = CH_3
d R = CH_3, R' = Ch_2Ph

32a R = CH_3, R' = CH_3
32b R = CH_2Ph, R' = CH_3
32c R = H_2C-C°CPh, R' = CH_3
32d R = CH_3, R' = Ch_2Ph

Figure 9. Palladium complexes **28**-**32**.

Importantly, representative compounds of the different subclasses were almost inactive against fibroblasts. For example, compound **28d** is the most active compound in the A2780 and SKOV3 cancer cell lines but has an IC_{50} > 100 μM in fibroblasts. Complexes were also evaluated for their apoptotic effects. The complexes that showed the highest pro-apoptotic activity for the A2780 cells, were **28c-d**, **30b-d**, **32b-d,** with **28c** showing the greatest total pro-apoptotic activity. On the cisplatin-resistant SKOV-3 cell line, derivatives **28b-d**, **29d**, **30**, **31** and **32** and complexes to be particularly active, notably **28c**.

This work was later expanded to other palladium complexes[38,39], and in general, complexes bearing NHC derivatives show good antiproliferative activity. The presence of phosphines such as PTA leads to highly soluble compounds and it was also noted that less hindered compounds are more effective cytotoxic agents.

Conclusions

The synthetic approaches described above demonstrate that the development of NHCs derived from xanthines is diverse and easily accessible. While many of these methodologies parallel those used for imidazole-based NHCs, subtle distinctions arise in the reactivity of xanthines, particularly in processes such as direct C-H oxidative addition or the formation of dimeric species subsequent to C-X oxidative addition. Moreover, the medicinal properties of xanthine-based NHC complexes have led to important advances, namely, through their ability to act as antimicrobial agents with a high degree of selectivity for different fungal strains and to be very effective for both gram-positive and gram-negative bacterial strains. The anticancer effects of these compounds, for example, their ability to interact with G-quadruplexes, where the purine core is key, are also highly significant. As mentioned throughout this manuscript, the versatility of xanthines for further functionalization, combined with their low toxicity and pharmacological properties and the potential of NHC complexes for medicinal applications, suggest that the development of these compounds is an emerging field for bioorganometallic medicinal applications.

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