PLATINUM IN PUMPKIN SHAPED MOLECULES FOR ANTICANCER DRUG DELIVERY

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Abstract:

Despite the synthesis of hundreds of new platinum (II) and platinum (IV)-based complexes each year as potential anticancer drugs, only three have received world-wide approval: cisplatin, carboplatin and oxaliplatin. The next big advance in platinum-based chemotherapy is not likely to come from the development of new drugs, but from the controlled and targeted delivery of already approved drugs or those in late stage clinical trials. Encapsulation of platinum drugs inside macromolecules has already demonstrated promise, and encapsulation within cucurbit[n]urils has shown particular potential. Partial or full encapsulation within cucurbit[n]urils provides steric hindrance to drug degradation by peptides and proteins, and the use of different sized cucurbit[n]urils allows for the tuning of drug release rates, cytotoxicity and toxicity.

Keywords:

Cancer, Drug delivery, Cytotoxicity, Cucurbituril, Platinum, Cisplatin, Oxaliplatin

1. INTRODUCTION:

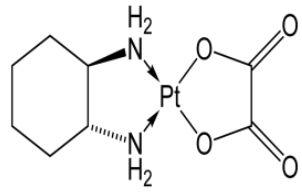
In the 40 years since the discovery of cisplatin[1], hundreds of new platinum (II) - and platinum (IV)-based complexes have been synthesised and tested as anticancer drugs. From these, only carboplatin and oxaliplatin have received world-wide approval. Several new drugs, including satraplatin, picoplatin and multinuclear drugs like BBR3464 are in various stages of clinical trials. All of these drugs have similar structures that are one or more platinum atoms coordinated to amine or amine carrier ligands and chloro, carboxylate, oxalato or acetate leaving groups. Because they share similar structures, their mode of action is the same (i.e. the prevention of DNA transcription

and replication leading to cellular apoptosis), they are all susceptible to the development of drug resistance and all display severe dose-limiting toxicities. Therefore, the biggest advance in platinum-based chemotherapy in the next decade will probably come not from the development of further mono- and multinuclear derivatives, but from the creation of controlled and targeted drug delivery vehicles for already approved drugs, or for those drugs currently undergoing clinical trials. Better delivery can be achieved through drug encapsulation inside a variety of macromolecules and two such strategies for the delivery of oxaliplatin using liposomes and polymers are currently being investigated.

Encapsulation of drugs inside a macromolecule provides two benefits. First, it protects the drugs from degradation by using steric hindrance to prevent the close approach of nucleophiles, particularly glutathione and thiol or thiolate-containing proteins. Secondly, encapsulation can increase the specificity of the drugs for, and uptake into, cancerous cells, through the enhanced permeability and retention effect. Cancerous cells are porous, having cavities that are up to 1000 nm in diameter and which are able to trap and retain large molecules more effectively than normal cells (which have only small cavities). Because the chemical structure of the encapsulated drugs remains unchanged, they can still bind DNA in their normal way and without changing the DNA binding sequence or type of adduct formed. This has been demonstrated by the encapsulation of oxaliplatin using a variety of host molecules. For example, aroplatin is a neodecanato-based liposomal formulation of oxaliplatin that has already been tested on 213 patients in nine clinical trials. The drug recently entered Phase II clinical trials where it demonstrated partial responses in two patients with advanced colorectal cancer. Prolindac is a pH sensitive hydroxypropylmethacrylamide polymer-based formulation of oxaliplatin. From a Phase I clinical trial it demonstrated two partial responses in patients with metastatic melanoma or ovarian cancer. As well as liposomes and polymers, platinum drugs can also be encapsulated by small macrocycles. Cyclodextrins are cyclic oligosaccharides composed of a-D-glucose subunits, and are already used extensively in formulations of organic drugs. Host–guest complexes of carboplatin, an inert dinuclearplatinum complex $[(dien)Pt(l\text{-}NH_2\text{-}(CH2)_n\text{-}NH_2)Pt(dien)]^{4+}$ (where n = 8, 9, 10 or 12 and dien = diethylenetriamine)and various

platinum complexes coordinated to modified b-cyclodextrins have been reported. For the latter complex, in vitro experiments demonstrated that the cyclodextrin–platinum complexes were completely inactive; no other in vitro results have yet been reported.

Recently, a family of small macrocycles called cucurbit[n]urils(CB[n]) has shown utility as drug delivery vehicles. In this focused review, the use of CB[n]s as drug delivery vehicles for a variety of platinum (II)-based complexes and the future direction of this technology is discussed.



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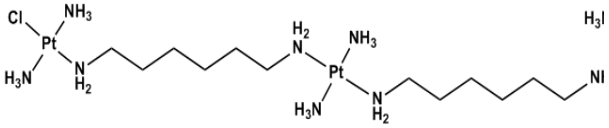

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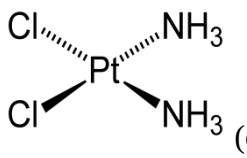

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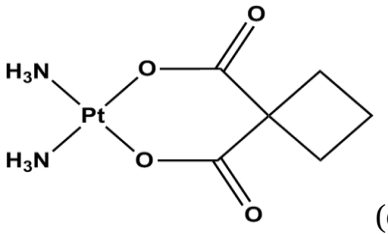

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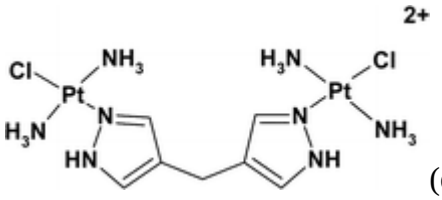

(e)

Figure 1: Chemical structures of the platinum (II)-based anticancer complexes that have been examined with cucurbit[n]urils[3]. (a) Oxaliplatin , (b) BBR3464 ,(c) Cisplatin, (d) Carboplatine,(e)di-Pt(trans-[{PtCl(NH_3)$_2$}2μ-dpzm]$^{2+}$).

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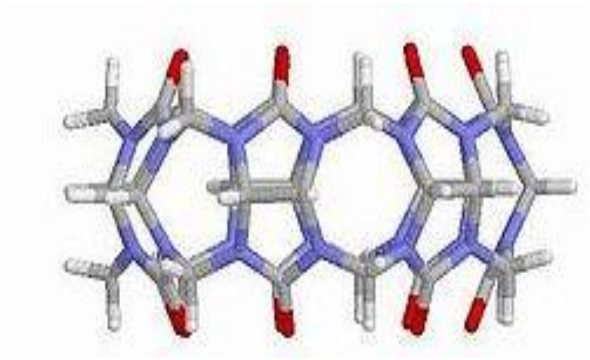
2.CUCURBIT[n]URILS:

Figure 2 a, b: Similarity between pumpkin and cucurbit[n]uril molecule

Cucurbituril (from *cucurbita* = pumpkin) is the fancy name given to the

pumpkin-shaped macrocycle. Cucurbituril is a family of homologues which are most favoured cavitands for host-guest complex formation. CB[6] was first discovered in 1905 by Behrend[2].Their discovery has led to a rapid increase in the interest in, and application of, CB[n] in a variety of fields including nano machines, chromatography, and drug delivery. Effective chemical and physical properties of these complexes with organic molecules and cations as molecular switches and catalysts have been well demonstrated. CB[n] is a pumpkin-shaped molecule, containing a hydrophobic cavity, formed by the acid catalysed condensation of glycoluril and formaldehyde. Figure 3 Cucurbit[n]urils can be synthesised in a variety of sizes (n = 5, 6, 7, 8 and 10), and are capable of encapsulating smaller



molecules within their cavities. Cucurbit[n]urils contain two hydrophilic carbonyl lined portals, capping a central hydrophobic cavity. The different sizes of the portals and cavities means they are able to bind a variety of organic and inorganic molecules. A variety of organic drugs and biologically relevant molecules have been encapsulated in CB[n] including: ranitidine, proflavine, cucurmin, amino anthracene, anthraquinones, amino acids, DNA bases and anticancer titanocene and molybdocene compounds. Of most use in platinum drug delivery are CB[6], CB[7] and CB[8]. The portal of CB[5] is too small to allow the entry of coordinated platinum atoms and many organic ligands, and the cavity of CB[10] is generally too large to strongly hold a platinum complex when dissolved at biological concentrations (kb > lM). Cucurbit[n]urils are sparingly soluble in water, but become more soluble upon encapsulation of some platinum complexes, particularly cationic and/or multinuclear complexes. The solubility of CB[n]s in water also varies depending on the method used to synthesise and purify them; many CB[n]s precipitate from solution with co-crystallised acid molecules, which can be difficult to remove. Alkali earth metal salts also increase the solubility of CB[n]s, particularly saline[3, 4]. In the latter case, the cations are strongly bound at the portals and can help stabilise the binding of small guests inside the cavity. Chiral CB[n]s that are capable of recognising and binding

chiral guest shape been synthesised which have an application in the delivery of chiral drugs (e.g. the platinum drug oxaliplatin). CB[n] shape also has been found to form monolayers on gold surfaces, which has applications in cancer diagnostics.

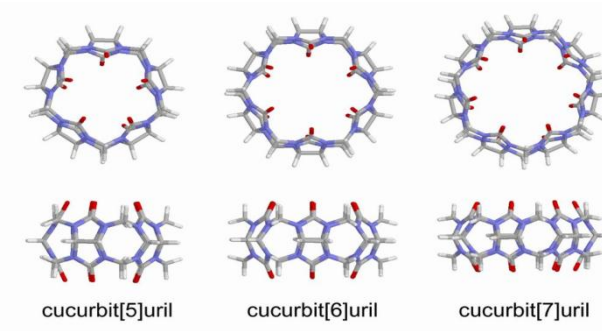


Figure 3: Different types of CB[n]

3. SYNTHESIS:

Cucurbiturils are aminals and synthesized from urea 1 and a diketone (e.g. glyoxal 2) via a nucleophilic reaction to give the intermediate glycoluril 3. This intermediate is condensed with formaldehyde to give hexamer cucurbit [6]uril above 110 °C. Figure 4 Ordinarily, multifunctional monomers such as 3 would undergo a step-growth polymerization that would give a distribution of products, but due to favourable strain and an abundance of hydrogen bonding, the hexamer is the only reaction product isolated after precipitation. Decreasing the temperature of the reaction to between 75 and 90 °C can be used to access other sizes of cucurbiturils including CB [5], CB [7], CB [8], CB [9], and CB [10]. CB [6] is still the major product; the other ring sizes are formed in smaller yields. The isolation of sizes other than CB[6] requires fractional crystallization and dissolution[5,9,10].

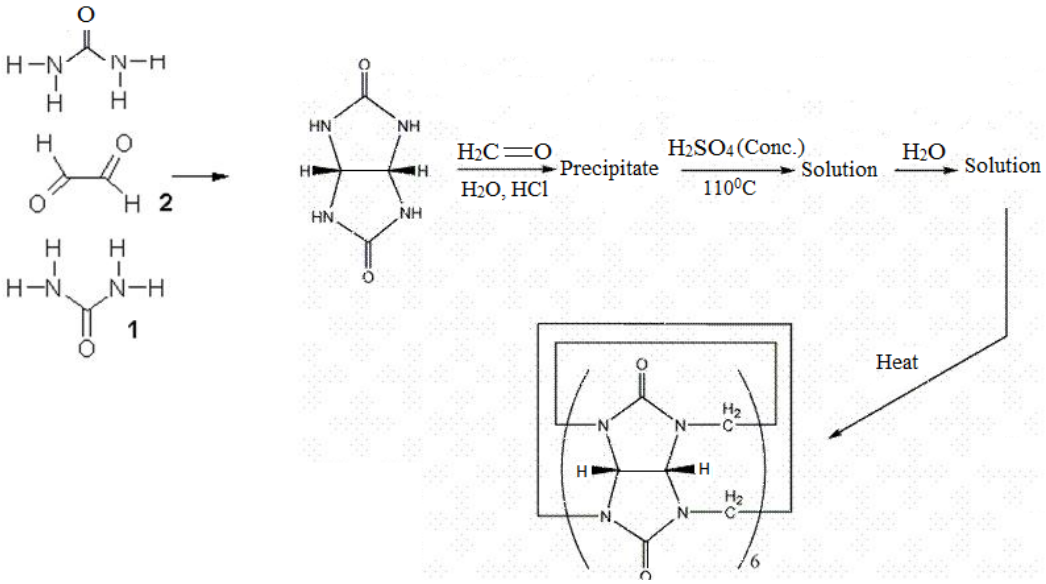
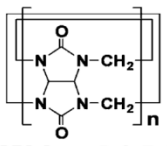


Figure 4: Synthesis of CB[n].

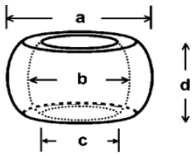
3. PROPERTIES:

Cucurbit[n]urils contain two hydrophilic carbonyl lined portals, capping a central hydrophobic cavity. The different sizes of the portals and cavities figure 5means they are able to bind a variety of organic and inorganic molecules. Cucurbit[n]urils are sparingly soluble in water, but become more soluble upon encapsulation of some platinum complexes, particularly cationic and/or multinuclear complexes. The solubility of CB[n]s in water also varies depending on the method used to synthesise and purify them; many CB[n]s precipitate from solution with co-crystallised acid molecules, which can be difficult to remove. Alkali earth metal salts also increase the solubility of CB[n]s,

particularly saline. In the latter case, the cations are strongly bound at the portals and can help stabilise the binding of small guests inside the cavity.



CB[*n*]: *n* = 5, 6, 7, 8



		CB[5]	CB[6]	CB[7]
outer diameter (Å)	a	13.1	14.4	16.0
cavity (Å)	b	4.4	5.8	7.3
	c	2.4	3.9	5.4
height (Å)	d	9.1	9.1	9.1

Figure 5: Dimensions of CB[2][n].

4. DRUG ENCAPSULATION BY CB[n]:

The encapsulated platinum complexes are obtained by either direct crystallisation or by titration of the metal complex into a cucurbituril solution. Equimolar, or in some cases a two- or three-fold excess of cucurbituril, amounts of the platinum complex and cucurbituril were dissolved in hot water containing 20 mM NaCl. Slow evaporation of the solution resulted in crystals of cucurbituril-encapsulated metal complexes. Aliquots of the platinum complex dissolved in D_2O (approx. 2 mM) were directly titrated into a 5 to 10 mL solution of the appropriate cucurbituril (2–4 mM) in D_2O to give the desired molar ratio. Aliquots of the solution were then taken for analysis by NMR spectroscopy[4, 14, 15].

Full or partial encapsulation of platinum complexes is stabilised through hydrophobic interactions within the CB[n] cavity and through ion–dipole and dipole–dipole interactions at the portals. The mode of binding can be examined through a range of spectroscopic techniques, most importantly using nuclear magnetic resonance (NMR) [16].

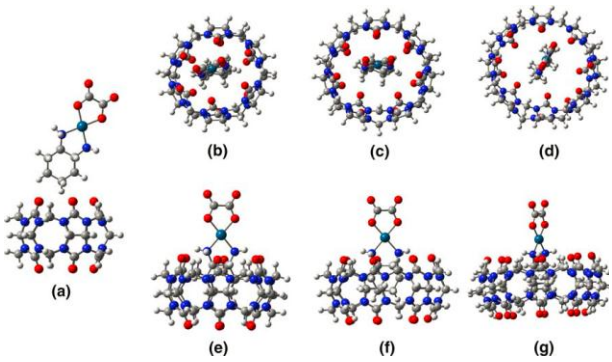


Figure 6[13]: Optimized structures of (a) CB[5]-oxaliplatin, (b) birds eye-view of CB[6]-oxaliplatin, (c) birds eye-view of CB[7]-oxaliplatin, (d) birds eye-view of CB[8]-oxaliplatin, (e) side view of CB[6]-oxaliplatin, (f) CB[7]-oxaliplatin, (g) CB[8]-oxaliplatin complexes.

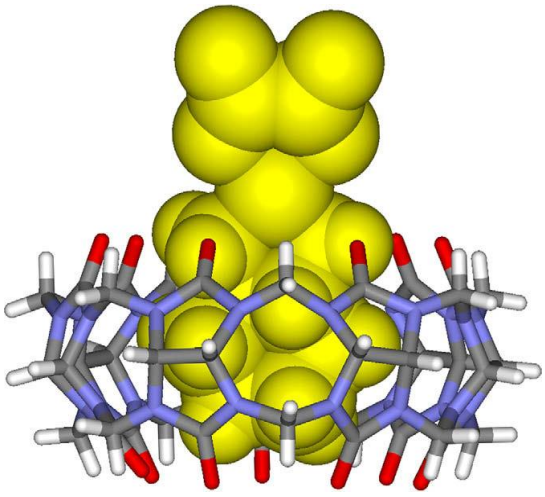


Figure 7: The encapsulation complex of oxaliplatin (yellow) within CB[7] based on the X-ray crystal structure data of Jeon et al[8].

Complex of oxaliplatin with different CB[n] is of interest. The formation of inclusion complexes of CB[n]-oxaliplatin are facile in CB[n] n = 6–8, while for the cucurbit[5]uril, the oxaliplatin is expelled out of the cavity. In the complexes, the cyclohexyl group is found to be deep inside the cavity, with the formation of a hydrogen bonding between the portal oxygen atoms and the amine nitrogen of the oxaliplatin guest. The formation energy increases with the increase in the size of CB[n] and the energetically favoured complex was CB[7]–oxaliplatin. NBO analysis shows the transfer of charge from the metal centre to the CB[7] unit and the existence of hydrogen bonding between the oxygen portal and amine nitrogen. The strength of the interaction determined here reflects the ability of cucurbit[n]urils to act as a host for suitably oxaliplatin guests, even in aqueous solution[6,7].

5. DRUG PROTECTION:

Degradation of platinum-based complexes is a problem in their in vivo delivery[17]. Platinum atoms are readily bound by nucleophiles, particularly soft nucleophiles, and form bonds to guanosine and adenosine bases in DNA, cysteine and methionine residues in peptides and proteins , and various anions found in the human body, including: phosphates,

sulphates and carbamates[18, 19]. The utility of CB[n] as a drug delivery vehicle primarily stems from its ability to protect platinum drugs from degradation, either through hydrolysis (as is the case for oxaliplatin) or through sulphur attack from thiol peptides and proteins. Oxaliplatin is also susceptible to light activated degradation, but upon encapsulation within CB[7], oxaliplatin is stable for over 1 year. Partial encapsulation of oxaliplatin by CB[7] also decreased significantly the drug's reactivity towards guanosine and L-methionine. The bound drug was 2–3-fold slower to react with guanosine at 37 ^{o}C and 15-fold slower to react with methionine, compared with the free drug. Partial encapsulation multinuclear complexes within CB[7] and CB[8] was shown to reduce their rates of reaction with guanine, L-cysteine and glutathione. Encapsulation of di-Pt within CB[7] reduces its rate of reaction with guanine 3-fold at 60 ^{o}C, whilst the dinuclear platinum complex trans-[{PtCl(NH_3)$_2$}2l-H_2N-(CH_2)$_8$- NH_2]$^{2+}$ (12), when encapsulated by either CB[7] and CB[8], was significantly less reactive towards L-cysteine and glutathione. It was found that CB[8] was better able to protect the metal complex compared with CB[7] due to the substantial folding of the diamino octane linker inside the cavity, which positioned the platinum atoms much closer to the CB[8] portals compared with CB[7]. The degradation of platinum (II)-based DNA intercalator complexes by reduced L-glutathione has recently been reported. The complexes have degradation half-lives of between 20 and 68 h which are inversely proportional to their activity[20]. When the platinum intercalators are partially encapsulated by CB[6], CB[7] or CB[8], however, no degradation is observed at time periods upto 7 days, under the same conditions.

6. EFFECT OF CB[n] BINDING ON DRUGS' IN VITRO AND IN VIVO EFFICACY:

Encapsulation of platinum complexes within CB[n] has an effect on both the metal complexes' cytotoxicity and toxicity. CB[n] molecules all of sizes appear to have no intrinsic cytotoxicity, with IC_{50} values of >100 µM in many human cancer cell lines. Similarly, CB[n]s also appear to be relatively non-toxic, with in vivo studies in mice indicating that the maximum tolerated dose of CB[7] is around 200 mg/kg. The first metal complex to be studied with CB[n] was di-Pt. As the free complex, di-Pt has IC_{50} values in the murine leukaemia cell lines L1210 and L1210/DDP of 3.8 and 8.8 µM, respectively. When examined as a 1:1 host–guest complex with CB[7], the IC_{50} are 2.6 and 16.5 µM, respectively. In this case, CB[7] had no significant affect on the

cytotoxicity of the metal complex. Similarly, for BBR3571, a dinuclear platinum complex with potent in vitro cytotoxicity in a number of cisplatin sensitive and resistant cancer cell lines, the metal complex has identical IC_{50} values (0.0115 µM) in the L1210 line with and without CB[7]. In the L1210/DDP resistant line only a slight decrease in cytotoxicity is observed, IC_{50} values of 0.0075 and 0.009µM for the free and encapsulated metal complex, respectively. The effect of CB[n] on the cytotoxicity of platinum metal complexes appears to be related, to some extent, to the strength of the binding. For BBR3464, a trinuclear platinum complex that was recently undergoing Phase II clinical trials as an anticancer drug, CB[7], CB[8] and CB[10] all decrease the cytotoxicity of the drug inversely proportionally to the size of the CB[n] molecule. That is, the larger the CB[n], the smaller the effect it has, presumably due to the easier movement of the drug in and out of the CB[n] cavity[21]. The effect of CB[7] on the cytotoxicity of oxaliplatin has been studied in five human cancer cell lines, including lung, ovarian, melanoma and colon cancers. Whilst free oxaliplatin is as active or more active than cisplatin in all the cell lines, encapsulation by CB[7] decreases the cytotoxicity of the drug 6- to 19-fold. For a family of platinum (II)-based DNA intercalators a clear correlation between CB[n] size and cytotoxicity is harder to determine. CB[6] has a positive or only slightly negative effect on the cytotoxicity of $[Pt(5\text{-Cl-phen})(R,R\text{-dach})]^{2+}$ (5CLRR) and 5CLSS but causes the loss of all cytotoxicity for $[Pt(5\text{-Cl-phen})(en)]^{2+}$ (5CLEN; where en = ethylenediamine). In contrast, CB[7] results in the complete loss of cytotoxicity for 5CLSS and 5CLRR ligands but has no effect on 5CLEN. CB[8] results in a slight decrease in cytotoxicity of all three platinum(II) DNA intercalator complexes tested [22]. The observed general decrease in cytotoxicity that many metal complexes experience upon encapsulation by CB[n]s could arise for two different reasons. First, it may be because encapsulation reduces the metal complexes' reactivity towards nucleophiles (similar to the decrease in cytotoxicity of less reactive carboplatin compared with cisplatin) and this result in a slower rate of DNA binding or a reduction in the number of DNA adducts formed. Alternatively, CB[n] may affect the cellular uptake of the metal complexes and thus prevent sufficient concentrations of drug from entering cells and inducing apoptosis.

Regardless of the mechanism causing the general decrease in metal complex cytotoxicity, this effect is manageable provided that the reduction in vitro activity also equates to a reduction in the metal complexes' toxicity and an improvement of

their therapeutic index. In vivo data are also available that demonstrates the utility of CB[n]s as drug delivery vehicles. The effect of CB[7] on the toxicity and efficacy of BBR3571 has been studied using an in vivo nude mouse model and the human ovarian cancer cell line 2008 xenograph . The addition of CB[7] almost doubles the maximum tolerated dose of BBR3571 when administered to tumour bearing nude mice. When free and encapsulated BBR3571 are administered in equivalent metal complexes doses, the encapsulated drug exhibits a similar ability to inhibit cancer tumour growth as the free drug.

Table 3: In vivo toxicity and efficacy data for the dinuclear platinum anticancer complex
BBR3571 (10) with and without CB[7] in female balb/c nude mice bearing the human
ovarian cancer cell line 2008[22].

Drug toxicity	BBR3571	BBR3571-CB[7]
MTD (mg/kg)	0.1	0.45
Drug equivalence	1	1.7
Administered dose (mg/kg)	0.1	0.27
Drug equivalence 1 1	1	1
TGIb (%)	48.5	44.9
GDIc	1.6	1.7

1. Tumour growth index (TGI) is defined as 100-(median relative tumour volume of treated group of mice divided by the median relative tumour volume of the control group ×100).
2. Growth delay index (GDI) is defined as the median growth delay of the tumour in treated mice divided by the median growth delay of the tumours in untreated mice.

7. CONCLUSIONS:

Cucurbit[n]urils provide a unique method of protecting mono and multinuclear platinum drugs from degradation by thiol peptides and proteins. Whilst they can sometimes significantly decrease metal complexes cytotoxicity in vitro, they can also lower their toxicity.
The internal cavity is hydrophobic and capable of encapsulating the aliphatic or aromatic linking ligands of multinuclear platinum drugs. Secondly, the oxygen-rimmed portals could stabilise the encapsulation of the metal complexes through electrostatic interactions and hydrogen bonds with the platinum–ammine groups, and could sterically hinder attack by biological nucleophiles. It is hoped that encapsulation of metal complexes within cucurbituril will allow it to be transported through the body, minimising deactivation or degradation by nucleophilic plasma proteins. The

development of water soluble CB[n]s will allow the further development of this technology and the creation of targeted drug delivery vehicles that can specifically recognise and delivery of platinum-based drugs to cancerous cells. They also show promising potentials for encapsulation of other drugs.

8. FUTURE DIRECTION:

The utility of CB[n]s as drug delivery vehicles for platinum anticancer drugs has been demonstrated but requires further research in two specific areas. First, further in vitro and in vivo trials are required to properly determine the structure–activity relationship between CB[n] size and binding and its effect on cytotoxicity. These need to be completed with different types of platinum complexes and with different CB[n]s to find the optimum combination. A systematic examination of the pharmacology of both free CB[n]s and CB[n]-encapsulated metal complexes is also needed, including their effect on metal complex uptake into cells, their mechanism of cell uptake, their metabolism and in vivo metabolomics. Secondly, whilst CB[n] encapsulation of platinum-based drugs addresses the problem of serum and intracellular drug degradation and deactivation by thiols, it is unlikely to increase the specificity of these drugs for cancerous cells in preference to normal cells. Functionalization of CB[n]s with targeting groups would allow drug delivery vehicles to deliver platinum drugs specifically to cancerous cells. Unfortunately CB[n]s are highly stable compounds, resistant to both degradation and functionalization. They are stable against a range of oxidising agents and strong acids and do not decompose at temperatures up to 420°C. The design and development of targeted CB[n] drug delivery vehicles is therefore dependant on the development of a simple and reliable method to synthesise water soluble CB[n]s, preferably with carboxylic acid or amine groups which can be used to conjugate targeting compounds through peptide bonds.

9. ABBREVIATIONS:

BBR3464 - [trans-{$PtCl(NH_3)_2$}$_2$trans-{$Pt(NH_3)_2(\mu\text{-}H_2N\text{-}(CH_2)_6\text{-}NH_2)_2$}]$^{4+}$

BBR3571 - trans-[{$PtCl(NH_3)_2$}$_2\mu$-N^4-spermidine-N^1,N^8]$^{3+}$

CB[n] - Cucurbit[n]uril

di-Pt - trans-[{$PtCl(NH_3)_2$}2μ-dpzm]$^{2+}$

dpzm - 4,4’-dipyrazolylmethane

phen - 1,10-phenanthroline

R, R-dach - 1R, 2R-diaminocyclohexane

S, S-dach - 1S, 2S-diaminocyclohexane

tri-Pt - [trans-{$PtCl(NH_3)_2$}2trans-{$Pt(NH_3)_2(\mu\text{-dpzm})_2$}]$^{4+}$

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