

Review on supermolecules as chemical drugs

ZHOU ChengHe^{1†}, GAN LinLing², ZHANG YiYi¹, ZHANG FeiFei¹, WANG GuangZhou¹, JIN Lei² & GENG RongXia¹

¹ School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, China;

² School of Pharmaceutical Sciences, Southwest University, Chongqing 400715, China

Supramolecular medicinal chemistry field has been a quite rapidly developing, increasingly active and newly rising interdisciplinary which is the new expansion of supramolecular chemistry in pharmaceutical sciences, and is gradually becoming a relatively independent scientific area. Supramolecular drugs could be defined as medicinal supermolecules formed by two or more molecules through non-covalent bonds. So far a lot of supermolecules as chemical drugs have been widely used in clinics. Supermolecules as chemical drugs, i.e. supramolecular chemical drugs or supramolecular drugs, which might have the excellences of lower cost, shorter period, higher potential as clinical drugs for their successful research and development, may possess higher bioavailability, better biocompatibility and drug-targeting, fewer multidrug-resistances, lower toxicity, less adverse effect, and better curative effects as well as safety, and therefore exhibit wide potential application. These overwhelming advantages have drawn enormous special attention. This paper gives the definition of supramolecular drugs, proposes the concept of supramolecular chemical drugs, and systematically reviews the recent advances in the research and development of supermolecules, including organic and inorganic complex ones as chemical drugs in the area of antitumor, anti-inflammatory, analgesic, antimalarial, antibacterial, antifungal, antiviral, anti-epileptic, cardiovascular agents and magnetic resonance imaging agents and so on. The perspectives of the foreseeable future and potential application of supermolecules as chemical drugs are also presented.

supramolecular chemistry, cyclodextrin, porphyrin, complex, anticancer, anti-inflammatory, antibacterial, antifungal, antiviral, cardiovascular agent, magnetic resonance imaging agent, supramolecular drug

The emergence of supramolecular chemistry has brought a revolutionary new era for the progress of chemistry^[1,2], and supramolecular chemistry has been growing rapidly at an ever-increasing pace. A great deal of effort has been made directly toward supramolecular chemistry and numerous excellent achievements have been obtained^[2-13]. Supermolecules (or supramolecules) have generally been described as aggregates formed by two or more molecules through non-covalent bonds. According to the concept of supermolecules, to some extent, the inorganic and organic complexes could be relegated to supermolecules. It was generally considered that both inorganic and organic complexes were principally formed through non-covalent bonds. Inorganic (metal) complexes are aggregates mainly formed in general by

the coordination bonds, while organic complexes are aggregates mostly formed by hydrogen bonds, ionic bonds and/or Van der Waals force and so on. The complexes (aggregates) formed by inorganic compounds and inorganic compounds and/or organic compounds could be regarded as inorganic supermolecules. Take the anticancer drug cisplatin for example, this drug was usually considered to be the inorganic metal complex

Received December 8, 2008; accepted December 28, 2008

doi: 10.1007/s11426-009-0103-2

†Corresponding author (email: zhouc@swu.edu.cn)

Supported by the Southwest University (Grant Nos. SWUB2006018 & XSGX0602), the Natural Science Foundation of Chongqing (Grant Nos. 2007BB5369 & 2006BB4341) and the Key Project from the Personnel Department of China (Grant No. 2002-99)

formed by one molecule of inorganic compound PtCl_2 and two NH_3 molecules through coordination bonds, this complex was an aggregate of three molecules formed through non-covalent bonds (here generally considered to be coordination bonds), therefore, cisplatin could be called inorganic (complex) supermolecule. Similarly, the complexes (aggregates) formed by organic compounds and organic compounds could be regarded as organic (complex) supermolecules. Considering the complex of β -cyclodextrin with anticancer drug adriamycin (doxorubicin), it was found that organic molecule β -cyclodextrin with another organic molecule anticancer adriamycin in aqueous solution formed the 1:1 host-guest complex. The drug adriamycin was generally considered to enter into the cavity[0] of macrocyclic compound cyclodextrin, in some cases it was often called (organic) inclusion complex. This complex was an aggregate formed by one molecule of β -cyclodextrin and one molecule of adriamycin mainly through non-covalent bond forces such as hydrophobic interaction, Van der Waals interaction and so on. Therefore, it could be fairly said such complex was organic supermolecule. Supermolecules or polymolecular assembly, formed by the weak interactions of non-covalent bonds via self-process, self-assembly and/or self-organization, showed distinct chemical, physical and biological properties in comparison with the original molecule components. These supramolecular systems exhibited some specific functions, being capable of being used as conductors, magnetic materials, sensors, etc., and thus they possessed wide potential applications in chemistry, physics, materials, information and environmental sciences and so on. Particularly, in materials field, the unprecedented progress has been made, and it has opened up a wholly new and infinite space to create new matters and novel materials.

Supramolecular chemistry was originated from the living biological systems to some extent. Supramolecular systems, formed by weak interactions of non-covalent bonds, exist extensively in numerous vital biological processes. For examples, chlorophylls in plant photosynthesis are magnesium tetrapyrrole complex supermolecules, while Haem in Haemoglobin, playing important roles in uptake and transport of oxygen, are the iron complex supermolecules of porphyrin ring. In the living biological systems, the supramolecular hosts

are various kinds of enzymes, receptors, genes, antibodies of immune system, ionophores, etc., while the guests are substrates, inhibitors, antigens, drugs and so on. The synergistic cooperations between hosts and guests play important roles for biological processes in the living biological systems. Therefore, to some extent, it might be said that living biological system is a huge and particular excellent biological supramolecular system^[14,15]. It was worth mentioning that vitamin B_{12} was the cobalt macrocyclic complex supermolecule, and its discoverers earned the 1964 Nobel Prize in Chemistry^[4]. Organisms just take use of this type of bioactive organization—biological supramolecular system—to participate in the synergistic reactions of various substances in cells, and then perform efficiently and controllably the biological processes of organisms. The utilization of interactions of noncovalent bonds, in attempts to study molecular recognition, regulate and control, model or mimic enzyme catalysis in biological processes, DNA binding, membrane transport, cell-cell recognition, as well as investigate drug interactions, etc., has become the unusually active research area of supramolecular chemistry in life sciences^[2-4,9,10,16-32], which provided a new way available for the research and development of new drugs. The highly interdisciplinary researches in this field were considered to be one of the important sources for new concepts and high-tech. The non-covalent interactions in biological supramolecular system should be highly useful for the development of supramolecular drugs. However, surprisingly, the word “supramolecular drug” has been seldom mentioned up to now^[33].

Along with the extensive expansion of supramolecular chemistry and understanding the concept of supermolecule, it is inevitable to expand into the pharmaceutical sciences. Supramolecular drugs, i.e. supramolecular chemical drugs, can be defined as medicinal supermolecules (or supramolecules) formed by two or more molecules through non-covalent bonds. With the further development of supramolecular chemistry, exploring the application of the supramolecular systems as drugs in pharmaceutical sciences has attracted great interests. Since the discovery of inorganic platinum complex cisplatin with anti-tumor activity, the researches of inorganic metal complex supermolecules in the medicinal field have been paid increasing attention^[34,35]. Inorganic compounds both PtCl_2 and NH_3 are not anticancer drugs, but their cisplatin complex formed through noncovalent

bonds was used widely in clinic as anticancer drug. To some extent, it was fair to say that the anticancer drug cisplatin has opened up a new era for the research and development of new drugs. This led numerous endeavours toward inorganic complex supermolecules as drugs formed by inorganic metal compounds with inorganic compounds such as NH_3 and/or organic compounds (diamines, porphyrins, etc.). In particular, supramolecular inclusion complexes^[36,37], formed by organic macrocyclic compounds cyclodextrins and their derivatives as hosts with guest drugs, not only could improve the water solubility of original drugs, control drug release in the body, help the drug to deliver to the target organ, or even eliminate abnormal flavour of drugs, but also effectively improve the pharmacokinetics properties of drugs, increase the bioavailability and efficacy and so on. These special excellences for drugs encouraged and attracted numerous workers engaging in the research and development of supramolecular drugs. Currently, the researches in supramolecular drugs are quite active and the progresses are unusually rapid, and this area is becoming an emerging highly interdisciplinary field with enormous potential, and gradually becoming a relatively independent scientific area. To date, a large number of supermolecules as chemical drugs have been widely used in clinics. Supermolecules as chemical drugs, i.e. supramolecular chemical drugs or supramolecular drugs, might possess not only less expense, shorter time and larger possibility as clinic drugs for their successful research and development, but also safety, lower toxicity, less adverse effect, higher bioavailability, better biocompatibility and drug-targeting, fewer drug-resistances and better curative effects, and exhibit extensive potential as clinical drugs. These overwhelming advantages have been enormously paid special attention. So far, no work has reported the current whole situation of supermolecules as chemical drugs in medicinal field. In view of this, combining with authors' researches and referring other works from literatures, this work reviewed the recent advances in the research and development of supermolecules as chemical drugs in antitumor, anti-inflammatory, analgesic, antimalarial, antibacterial, antifungal, antiviral, anti-epileptic, cardiovascular agents and magnetic resonance imaging agents and so on. The perspectives of the foreseeable future and potential application of supramolecules as chemical drugs were also presented.

1 Supermolecules as antitumor agents

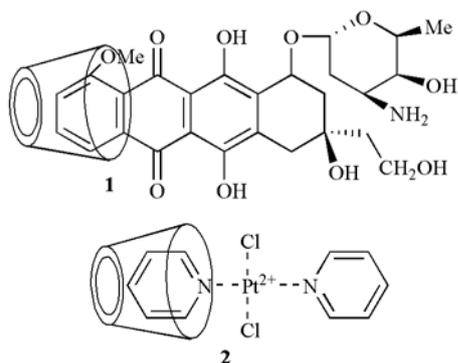
Cancer is currently one of the major diseases with serious threat to human, and its therapy and prevention have been paid great attention. In recent years, various achievements have been obtained in seeking drugs and methods for treating cancers, such as apoptosis antileptics, signal conduction blockade agents, angiogenesis inhibitors, chemotherapy and radiotherapy protectants. Accompanied with the rapid extension of supramolecular chemistry in pharmaceutical sciences, supermolecules as anticancer drugs have become a highlight field of research in recent years, especially the cyclodextrin inclusion compounds, liposomes, nanometer particles and metal complexes like platinum types as representative supramolecular chemical drugs have been playing important roles in treatment of cancers.

1.1 Cyclodextrin-based supermolecules as antitumor agents

Cyclodextrins (CDs), a class of macrocyclic compounds with D-glucopyranose units linked by α -1,4-glycosidic bonds, have a special molecular structure with hydrophilic outside and a hydrophobic cavity. Their cavities with appropriate sizes enable them to form inclusion complex supermolecules with various kinds of hydrophobic drugs, and result in an improvement of the properties of drugs such as solubility, chemical stability, bioavailability, drug-controlled release, or even elimination of drug's abnormal flavour. Therefore the CDs possess good application prospects in oral administration preparation^[2,36-38], and they have also become the important useful functional excipients in modern pharmaceuticals due to the features of CD with easiness to obtain, better biocompatibility, nearly no adverse effects and stable chemical properties as well as clathration simplicity with guest drugs.

Cyclodextrin derivatives with different solubilities can meet the requirements of appropriate drug release rate. At present, the extensively used CDs are mostly β -CD, especially its derivatives such as hydroxypropyl- β -CD (HP- β -CD), hydroxyethyl- β -CD (HE- β -CD) and trimethyl- β -CD (TM- β -CD). The β -CD with appropriate size and shape of cavity could bind efficiently with a series of hydrophobic aromatic guests, and also was widely investigated and applied because of its low price. For instance, anticancer drug doxorubicin and β -CD could form 1:1 inclusion complex (**1**). This supermo-

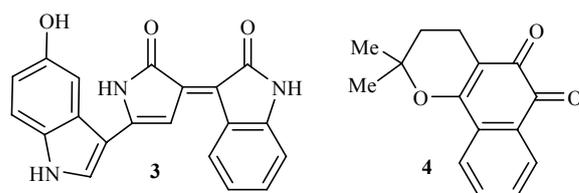
lecule remarkably improved the water solubility of doxorubicin, and enhanced its efficacy as drug. The inclusion complex of *trans*-dichloro(dipyridine) platinum(II) (DDP) with β -CD was a novel class of water-soluble anticancer supermolecule (**2**). Its anticancer activities surpassed significantly that of cisplatin, and the growth inhibition by the prepared CD-DDP complex against CT26 and B16F10 cell lines *in vitro* was found to be 4.6 and 6.1, respectively, times higher than cisplatin^[39].



Violacein **3**, a pigment isolated from *Chromobacterium violaceum*, has significant antitumor effect *in vitro*, but its poor solubility in water results in low biological activity *in vivo*. After forming inclusion complex with β -CD, the stability and solubility of violacein were obviously improved. The formed inclusion complex supermolecule could also provide a sustained release of violacein and effectively kill promyelocytic leukemia cell HL60^[40].

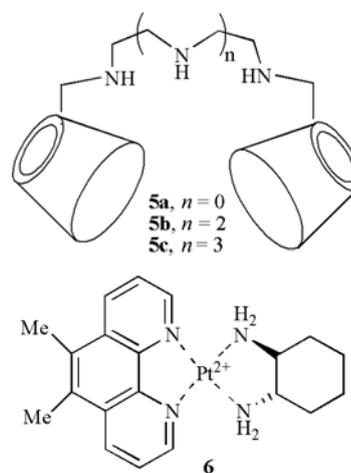
β -Lapachone (β -lap, **4**) was a novel antitumor supermolecule with high anticancer activity against human lung, prostate and breast tumors. Drug β -lap had a distinct mechanism of action, but its low water solubility and bioavailability severely limited its applications. When β -lap and CD formed inclusion complex, its water solubility could be greatly enhanced, and its release rates were available accommodation. The faster release and increased solubility occurred when the β -lap was encapsulated with HP- β -CD, but it could not last too long time. While the supermolecules of β -lap with α -CD or γ -CD may provide a more moderate, sustained release of drug, and this type of supermolecules is hopeful to realize intratumoral delivery of anticancer agents when formed a preparation with poly(D,L-lactide-co-glycolide)^[41].

Recently, it has been highlight to modify the structures of CDs in various ways in order to increase their



drug-loaded capability. Much works by the structural modifications of methylation, hydroxymethylation, sulfonylation and sulfur alkylation are hopeful to improve the water solubility and inclusion capability of β -CD, some good results in enhancement of water solubility and complexation capability of CD have been obtained in different extent. The β -CD dimers^[42] and linear polymers^[33] could serve as potent selective carriers of drugs like anticancer agent busulfan, and improved the physico-chemical properties of drugs. Liu and co-workers^[43] used bis(β -CD)s with paclitaxel to form inclusion complex supermolecules and hoped to improve the water solubility and antineoplastic activity of paclitaxel. Among these supermolecules, complex of **5a** significantly increased the water solubility and thermal stability of paclitaxel, and exhibited antiproliferative activity against human K562 erythroleukemia cell line ($IC_{50} = 0.6 \text{ nmol}\cdot\text{L}^{-1}$), which was even better than that of free paclitaxel ($IC_{50}=0.98 \text{ nmol}\cdot\text{L}^{-1}$). Bridged CD could also greatly increase complexation ability to drugs by the interactions of drug molecule with two adjacent hydrophobic cavities^[44].

Carboxylated- β -CD(c- β -CD) and *p*-sulfonatocalix[4]arene(s-CX[4]) showed that they formed respectively 1:1 and 2:2 inclusion complex supermolecules with platinum complex **6**. Both of them decreased significantly the rate of platinum complex degradation, re-



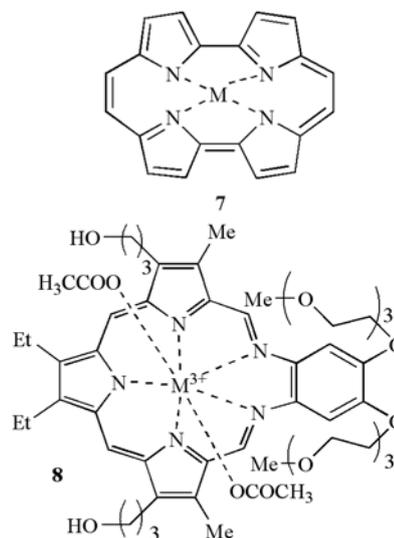
mained the cytotoxicity in the LoVo colorectal cancer cell line effectively, and could be potentially employed as drug delivery carriers. The water solubility of inclusion complexes of α - β -CD was larger than that of γ -CD[4], and this means that α - β -CD complex supermolecules should be better candidates as drug delivery vehicles^[45].

1.2 Porphyrin-based supermolecules as antitumor agents

Porphyrin ring possesses the structural features of both macrocycles and multi-dentates. Porphyrins and their metalloporphyrins may give a lot of distinct physico-chemical properties and functions when changing substituent groups in porphyrin ring, adjusting electron-donor ability of four nitrogen atoms, introducing different center metal ions, or changing different affinity of axial ligands. In recent years, photodynamic therapy (PDT) has become the fourth new and reliable treatment for cancer after operation, radiotherapy and chemotherapy^[46,47]. Porphyrin-based anticancer drugs generally act as photosensitizer to generate photodynamic reactions when light at appropriate wavelength was applied, give highly active singlet oxygens, and then destroy the target cells. Now, the widely used drugs in clinic are hematoporphyrin derivatives, the first generation of photosensitizers with high phototoxicity and dark toxicity. Recently, main researches have been focusing on exploring new photosensitizer with singlet oxygen in high yields, strong absorption at or near infrared region as well as better targeted intelligence carriers^[48].

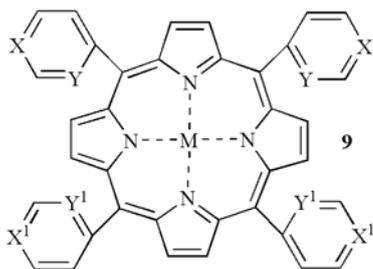
Extended pattern porphyrins were easy to form complexes with diamagnetic metal ions due to the enlargement of ring. Porphyrins **7** and **8** were their main backbone structures for the complexation of metal ions. Compound **7** was an isomer of metalloporphyrin, its maximum absorption wavelength was 630 nm. More researches focused on porphyrin **8**^[49], and compound **8** could form 1:1 complex with trivalence cation of lanthanon. When metal M was lutetium in porphyrin **7**, the formed lutetium complex supermolecule of extended pattern porphyrin could generate singlet oxygen with maximum absorption wavelength 732 nm, then was absorbed quickly by tumor cells and eliminated from tissue. It has tiny skin light sensitivity, and has been approved to put on the market to treat cervical tumor, prostate tumor and pars encephalica tumor, and now it is in the phase II stage of clinical trials for treatment of

recurring breast cancer^[50]. The success of lutetium complex of extended pattern porphyrin highlighted the research in this field, and recently significant achievements in modification of its hydroxy groups and side chains have been obtained.



In PDT, the effects of tumor photoallergy cytotoxicity rely on the absorption wave length of photosensitizer in a great degree, but present photosensitizer could not kill tissue-inner tumor cells. Water-soluble cationic Fe-porphyrin^[51] (**9a** and **9b**) as SOD template showed stronger cytotoxicity to cancer cell lines than to normal cell lines without any phototoxic effect, and Fe-porphyrin **9c** gave higher cytotoxicity than cisplatin^[52]. The SOD, which acts as target enzyme, would cause cell death by activation of **9c**, and supermolecule **9c** was used mainly to inhibit mammary gland and lung adenocarcinoma.

Gold(III) porphyrin (**9d**) was a gold(III) complex supermolecule with selective anticancer activity against a number of human cancer cell lines^[53,54]. The cytotoxic effect of gold(III) porphyrin is not due to its photosensitizing activity, but is closely related to both the porphyrin ligand and the central gold atom. The bind of supermolecule **9d** with DNA was the interaction of noncovalent bond, and this was different from cisplatin. The IC_{50} for **9d** and cisplatin were respectively about 1.3 and 38.0 $\mu\text{mol}\cdot\text{mL}^{-1}$, this clearly indicated that **9d** exhibited higher cytotoxicity than cisplatin under the same conditions.



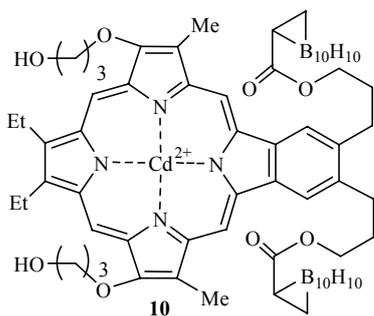
9a, M = Fe²⁺, X = X¹ = N(Me), Y = Y¹ = CH

9b, M = Fe²⁺, X = X¹ = CH, Y = Y¹ = N(Me)

9c, M = Fe²⁺, X = N(Me), X¹ = Y = Y¹ = CH

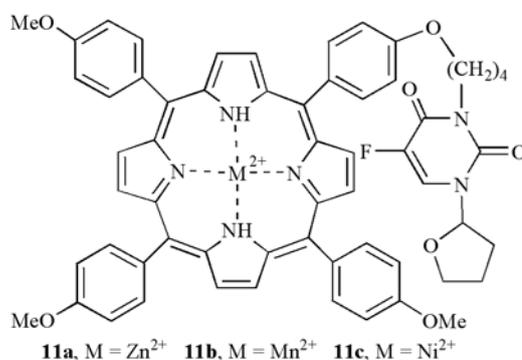
9d, M = Au³⁺, X = X¹ = Y = Y¹ = CH

Boron neutron capture therapy is a modus operandi in radiating tumors for tumor treatment with a small quantity of dosage. Its principle is the interaction of radiationless nucleus ¹⁰B and low-energy neutron to generate cytotoxic ⁴He and ⁷Li. The supermolecule **10** formed by borane and porphyrin through linkage could accumulate in cancer cells, and thus reduce the adverse effects of radiotherapy greatly.

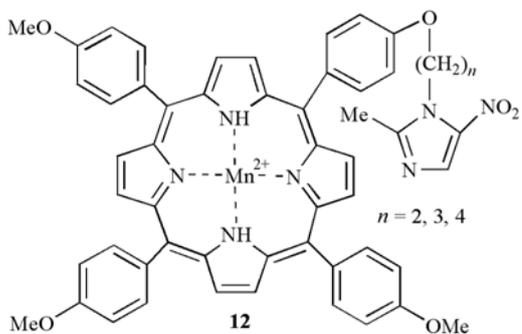


On the basis of the structural features and anticancer activities of both porphyrin and azole compounds^[48,55-63], we designed and synthesized several novel dissymmetric porphyrin compounds, and then linked with clinical anticancer drug tegafur and nitroimidazoles^[63] possessing radiosensitizing effects, to afford tegafur and nitroimidazole porphyrins respectively^[58]. The new porphyrin compounds modified by tegafur gave better anti-tumor activity against liver cancer cell SMCC-7721 and colon cancer Volo *in vitro*. Compared to the anticancer drug tegafur under the same concentration, tegafur-linked porphyrin complex supermolecules (**11**, **12**) also could inhibit the growth of SMCC liver cancer cells to some extent, and their antitumor activi-

ties have been improved significantly. The results suggested that the introduction of metalloporphyrin effectively improve the anti-tumor activity of tegafur. The tumor control rate could reach 36.6% when administration of tegafur to a nude mouse, while supermolecule **11b** resulted in the tumor control rate up to 70.0% *in vivo*. The higher tumor control rate of complex **11b** in comparison with tegafur further revealed that the introduction of metalloporphyrin effectively improve the anti-tumor activity of tegafur. The nitroimidazole-based porphyrin compounds, especially complex **12**, gave better radiosensitization against human cervical cancer cell Helo. Compared to 4-nitroimidazole or 2-methyl-5-nitroimidazole at the same molarity, some of metal complexes in supermolecule **12** showed 95% tumor control rate with six times higher than the free ligand.



11a, M = Zn²⁺ **11b**, M = Mn²⁺ **11c**, M = Ni²⁺



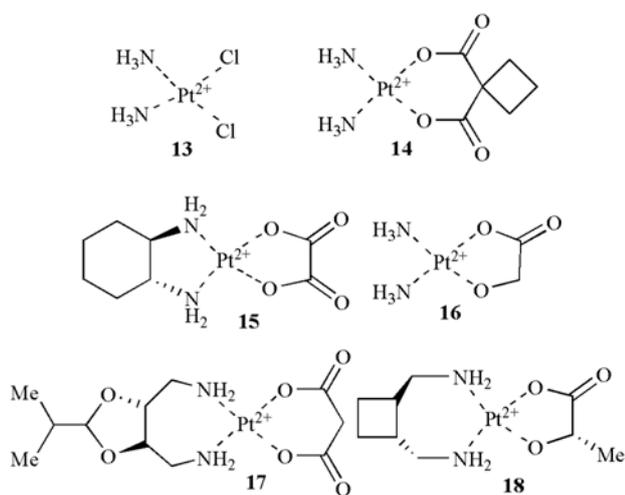
n = 2, 3, 4

1.3 Platinum-based supermolecules as antitumor agents

Metal anticancer complexes are a vigorous field of research. Now, the widely used metal complex supermolecules as anticancer drugs in clinic are platinum complexes. So far no non-platinum metal anti-cancer drugs have been approved for cancer chemotherapy, but some metal complexes of ruthenium, titanium or gallium have already been tested in clinical phase I or II trails^[34,35].

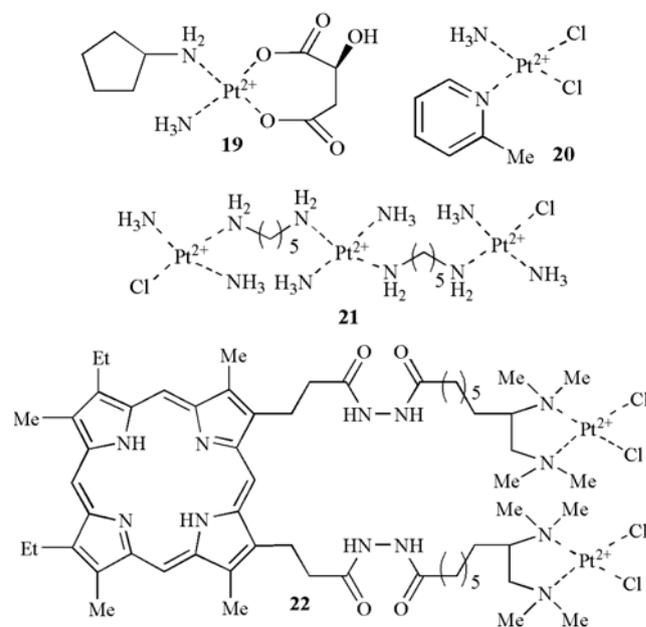
It is well known that a series of platinum complexes

have been investigated extensively since the inorganic coordination complex of platinum, cisplatin, was found to exhibit antitumor activity in 1969^[64,65]. Cisplatin (**13**) as anticancer drug was approved in 1978, and is also widely used to treat many kinds of malignancies, including testicular, ovarian, cervical and bladder types. Due to the distinct anticancer mechanism, widespread anticancer spectrum, and different toxicity spectrum of platinum complexes from many natural and non-natural drugs, more and more researches focused on platinum complexes. After cisplatin, several other platinum complexes such as carboplatin (**14**), nedaplatin (**15**), oxaliplatin (**16**), sunpla (**17**) and lobaplatin (**18**) have been approved for current tumour therapy^[66].



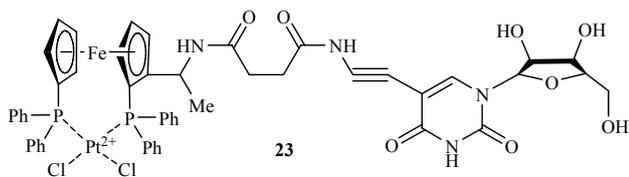
Although cisplatin and carboplatin are the first choice as anticancer drugs, they have the side effects of nephrotoxicity and neurotoxicity, and poor targeting. Therefore, many researches based on the structures of cisplatin and carboplatin, according to the classic structure-activity relationship, designed and synthesized new platinum complexes in order to decrease their toxicity. Complex **19** could inhibit the growth of solid tumor in mouse body, show better anticancer activity than both cisplatin and carboplatin, and also be able to prolong the lifetime of animals suffering from leukemia and liver cancer without any nephrotoxicity. Now it is tested in clinical phase II studies^[67]. ZDO473 (**20**) with stereospecific blockade also had inhibition activity against human ovarian cancer heteroplastied. Currently, complex **20** by the combination with adriamycin was used to treat ovarian cancer with serious drug resistance to paclitaxel and platinum drugs, and was in clinical phase

III studies^[68]. *trans*-Trinuclear platinum complex **21**, containing multi-binding sites, represented an entirely new structural class of anticancer agent, exhibited strong ability to bind with DNA in tumor cells, and showed better anticancer activity. It had no cross resistance to cisplatin^[69], and displayed better cross linkage with DNA than *cis*-platin. Now it is also tested in clinical phase II studies for the treatment of nonsmall-cell lung cancer, stomach cancer and ovarian cancer. It is well known that porphyrin compounds have strong affinity to tumor cells proliferated abnormally. Recently, it is a fresh tendency to link porphyrin with anticancer drug molecules in the research and development of anticancer drugs^[70]. Supermolecule **22**, synthesized by the linkage of porphyrin with anticancer platinum complex, has lethal effect to tumor cells but no side effect to normal cells.

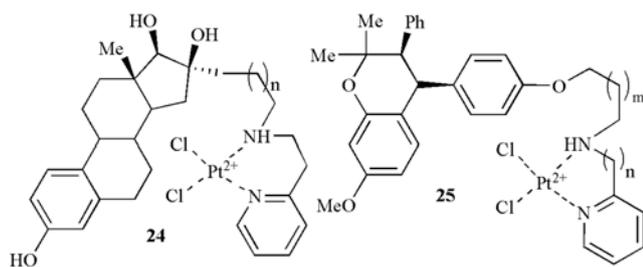


Cisplatin-type complex containing ferrocenylphosphine moiety was linked with a nucleoside through linker to give the new derivative **23**. This supermolecule could improve significantly the physico-chemical property of complexes^[71]. Compared to cisplatin, the complex **23** had better water solubility, longer half life and was easier to bind with DNA.

A unique class of estradiol-Pt(II) hybrid complex **24**, which binds DNA indirectly through hydrogen bonds, showed good potential *in vitro* and *in vivo* for the treatment of hormone dependent cancers^[72], in particular for breast cancer without any apparent side effects^[73-76].

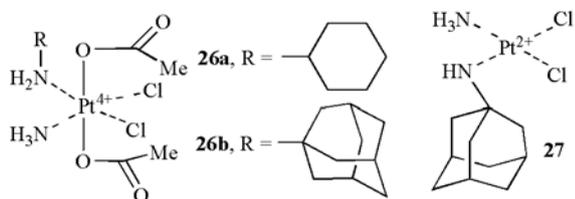


When n was 4, complex **24** was more effective against several types of cancers than cisplatin^[77]. Supermolecule **25** showed significant cytotoxic activity against estrogen receptor-dependent and -independent cancer cell lines, and exhibited significant chemotherapeutic potential.



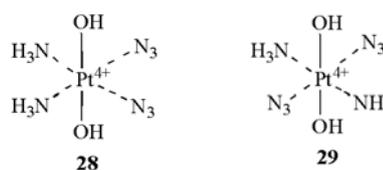
Platinum(IV) complexes possessed the octahedral geometry. The introduction of two extra ligands, compared to Pt(II) complexes, enhanced their lipophilicity, and offered the opportunity to overcome some problems of platinum(II) drugs^[78].

Satraplatin(JM216) (**26a**) was a lipophilic supermolecule administered orally. It is the only platinum(IV) complex currently undergoing clinical trials^[79]. Complex **26a** has been in clinical phase III studies, and shown no nephrotoxicity, neurotoxicity, and ototoxicity in comparison with other platinum drugs in clinic. The high lipophilic complex **26b** is the substituted product of **26a** by changing cyclohexane into adamantane. Supermolecule **26b** showed the comparable activity to **26a**, higher activity than **27** in susceptibility and cancer resistance, and has no cross resistance to cisplatin *in vitro*.

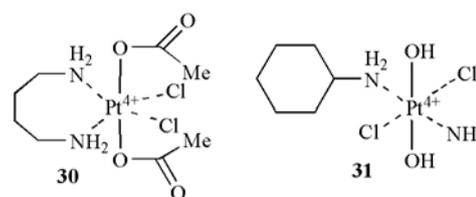


Recently, Sadler et al.^[80,81] have designed and synthesized platinum(IV) complexes **28** and **29** by taking advantage of the photochemical features of azides. The

inert dihydroxy platinum(IV) complexes were nontoxic in the dark, but upon irradiation with UV light they demonstrated good cytotoxicity against human bladder cancer cell lines. Indeed, the complex **29** was as cytotoxic as cisplatin, and was not cross-resistant with the cisplatin-resistant cell lines. These complex supermolecules almost immediately coordinated with calf thymus DNA upon irradiation *in vitro*, and then resulted in DNA lesions. Further, the photoactivation of complexes **28** and **29** did not rely on the presence of oxygen unlike current photodynamic therapy, and thus these supermolecules were suitable for the treatment of microenvironmental tumor hypoxia^[82].



Complexes **30** and **31** are also platinum(IV) complex supermolecules. Preclinical screening showed good activity for supermolecule **30** and its fluoroacetate analogue against colorectal and breast cancer cell lines *in vitro* and *in vivo*^[83]. The assays in mice demonstrated that **30** had activity against colorectal in twice as that of cisplatin with diminished toxicity. Platinum(IV) complex **31** also gave good activity against a range of cisplatin-resistant cell lines.



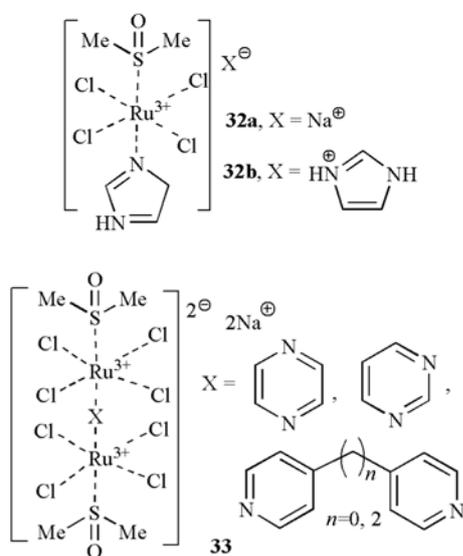
1.4 Ruthenium-based supermolecules as antitumor agents

The successful exploitation and wide use of platinum supermolecules as anticancer drugs attracted researchers' great interests to investigate other transition metals instead of platinum. Ruthenium complexes have become one of promising anticancer drugs because of their hypotoxicity and easier absorption by tumor tissue. At present, most of synthesized complexes were monocationic, including ammonia (imine), multi-pyridine, ethylene diamine tetraacetic acid and dimethyl sulfoxide

ones. Complex **32a**^[84], the first generation of ruthenium antitumor complex and the first antitumor metastasis which entered into the clinical trails in 1999, was tested in clinical phase II studies. It was water-soluble, available for intravenous injection, and showed significant activity toward metastasis of lung and breast cancer, but exhibited poor ability to kill primary tumor cells and no activity *in vitro*. Dicationic Ru(III) dimethyl sulfoxide complex **33**, as the second generation of ruthenium antitumor agents, had 3.5 times higher activity than the first generation^[85].

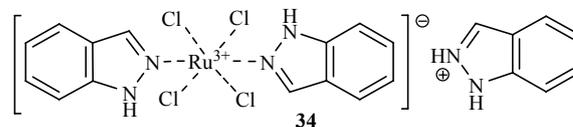
Generally, the cytotoxicity of ruthenium complexes is related to DNA binding. The anticancer mechanism was that the complexes bind with DNA (covalent bond of guanine residue N7) by cross-linking adjacent Gua once entering into the cation, and then inhibit the replication of DNA^[86]. But there were some exceptions, such as the compound **32b**, which didn't bind with DNA but decreased tumor cell extension^[87].

Supermolecule **32b** was octahedral complex, displayed significant inhibition of solid tumor metastasis, and no activity at the reduction of primary tumor^[88]. However, complex **32b** could induce apoptosis on var human epithelium ECV304^[89].

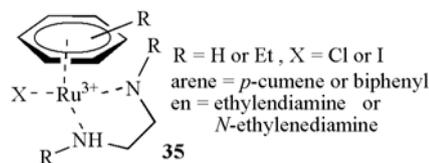


Indazole complex **34** also possessed the octahedral geometry and could inhibit the growth of cancer cells. It was efficiently taken up into cells, induced apoptosis predominantly by the intrinsic mitochondrial pathway, caused DNA damage, and it was bound tightly to serum albumin and transferrin, and showed high pH stability.

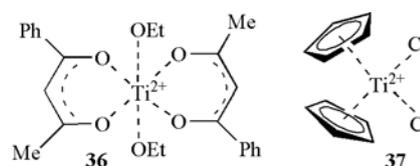
The clinical phase I studies showed good potential in clinic. It inhibited solid tumor and showed high activity in colon cancer. Like **32b**, complex **34** also gave weak side effect in clinical phase I studies.



Since the initial discovery that $[\text{Ru}(\eta^6\text{-C}_6\text{H}_6)(\text{DMSO})\text{Cl}_2]$ could inhibit topoisomerase II, three types of derivatives have been prepared by replacing the DMSO ligand with 3-aminopyridine, *p*-aminobenzoic acid or aminoguanidine. These analogs enhanced efficacy of topoisomerase II inhibition and showed higher cytotoxicity against breast and colon carcinoma cells^[90]. Other aromatic Ru(II) complexes with the formula $[\text{Ru}(\text{II})(\eta^6\text{-arene})(\text{en})\text{X}]$ (**35**) also gave good activity against human ovarian cancer cells, and showed similar activity to that of carboplatin and no cross-resistance to cisplatin^[91].

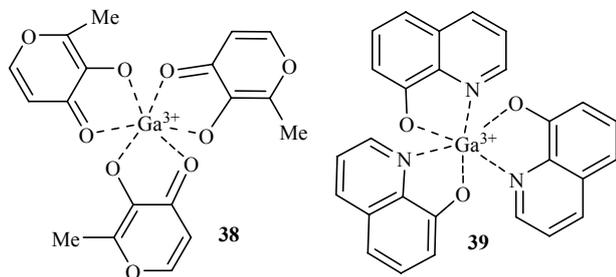


Furthermore, titanium and gallium complex supermolecules have also been paid much attention and some have entered into clinical trails. For instance, budotitan **36** was first discovered by Keppler in 1982 and had completed clinical phase II studies. It showed good activity against ascites cancer and solid tumor, and better activity against colon cancer than 5-fluorouracil. Titanocene dichloride (**37**) has also entered into clinical phase II studies, although displayed some activity to bladder cancer, adenocarcinoma and non-small-cell lung cancer, it had some nephrotoxicity^[92]. Complex **37** could aggregate surrounding the cationic chromatin, and bind with DNA, inhibit DNA synthesis and thereby induce apoptosis.



tosis. Titanocene dichloride could also inhibit topoisomerase and exhibited bioactivity.

Most of gallium anticancer compounds in clinical phase I and II studies were inorganic salts of gallium such as gallium nitrate, gallium chloridate and so on. These compounds have better anticancer activity accompanied with stronger toxic side effects. In order to diminish their toxicity, many organic gallium complex supermolecules were prepared. Complexes **38** and **39** are now tested in clinical phase I studies, and the results showed that supermolecule **38** could inhibit prostate cancer and multiple myeloma^[93]. Complex **39** was found to prevent *in vivo* the proliferation of cancer cells and exerted the cytotoxicity effects and antihypercalcemic properties. Because of its weak aqueous solubility, supermolecule **39** was orally administrated, typically in the form of tablets^[94]. The phase I clinical studies showed that 1/4 and 2/4 patients suffered from renal cell cancer had improved, this revealed that complex **39** could significantly inhibit this tumor^[95]. When linked with platinum complex, complex **39** exhibited higher anticancer activity than inorganic gallium salt *in vitro*, and better effect than gallium chloridate by orally administration.



1.5 Polymer-based supermolecules as antitumor agents

The solubility, stability, targeting or safety of some anticancer drugs seriously influenced the therapeutic efficacy. These problems could be solved by the help of new drug delivery systems. Among these, the most extensive investigation was to use polymers as drug carriers. Drugs were encapsulated into the carrier to form various kinds of supramolecular drugs, like liposomes and nanoparticles ones, etc.^[96]. The delivery systems of liposomes and nanoparticles have merits of increasing solubility, prolonging retention time *in vivo*, enhancing drug-targeting, decreasing toxicity and overcoming

anticancer multidrug resistance. So far many of these supramolecular preparations like liposomes or nanoparticles have been used in clinic. They effectively diminished the side effects, made prophylaxis of cancer and relieved pain caused by cancer deterioration and chemotherapy^[97], and made it possible to adopt original and better chemotherapy method upon present drugs.

It has been an important research area in worldwide for a long time that the antitumor agents would be developed as liposomal drugs. Many antitumor liposomes have been developed, such as platinum liposomes like paclitaxel magnetism liposomes, cisplatin invisible liposomes SPI-077 and oxaliplatin liposomes Lipoxal, doxorubicin temperature sensitive liposomes and doxorubicin long-circulation liposomes DOXILR and so on. The research showed that encapsulation of doxorubicin in polyethylene glycol-coated liposomes could enhance the safety and efficacy of conventional doxorubicin. In preclinical models, liposomal-doxorubicin could relieve and treat many types of cancers including tumors of the breast, lung, ovaries, prostate, colon, bladder, and pancreas, as well as lymphoma, sarcoma, and myeloma. It was also effective as adjuvant therapy. In addition, it was found to penetrate into the blood-brain barrier and inhibit the growth of tumors in the central nervous system. The combination of liposomes with vincristine or trastuzumab resulted in synergistic effects and better efficacy. Liposomes appeared to overcome multidrug resistance, possibly as the result of increased intracellular concentrations and an interaction between the liposome and P-glycoprotein, and showed favorable applications to treat a variety of cancers^[98]. Therefore, it is an important trend to improve anticancer drugs by developing liposomes as long-circulation preparation, and exploiting a variety of liposomes which are new and aggregated in local tumor in high concentration.

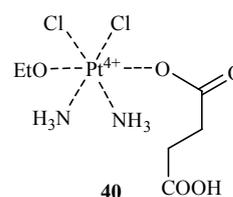
Nanoparticles are submicron-sized polymeric colloidal particles^[99]. Recent years, the clinical values of nanomaterials have been becoming more and more important, and nanoparticles were paid more attention to act as anticancer drugs carriers^[100]. Nanotherapy enhanced the drug accumulation in tumor tissue and stepped down the growth of tumor. Some anticancer nanoparticles have been approved by FDA to use in clinic. At present, much work focused on nanoparticles of paclitaxel, mitomycin, 5-fluorouracil, doxorubicin and platinum drugs. Some nanotechniques were also

employed to improve the therapeutic efficacy of PDT. Researches revealed that paclitaxel nanoparticles prepared by the nanoprecipitation method have shown comparable activity to traditional formulations, like the introduction of solubilizing agent or preparation of cyclodextrins inclusions, with much faster drug release rate and the prolonged action time^[101]. Cellular studies showed up to a 70% loss of viability in NCI-H69 human small cell lung cancer cells at levels of 0.025 $\mu\text{g}\cdot\text{mL}^{-1}$ ^[102].

The anticancer drug doxorubicin is working by inhibiting the synthesis of nucleic acids within cancer cells^[103]. Various researches of doxorubicin encapsulated in nanoparticles focused on the doxorubicin-targeting delivery to cancer tissues and the decrease of its side effects. Both dextran and doxorubicin were encapsulated in chitosan nanoparticles, and then were injected intravenously into mice, it was found a decrease in the tumor volume, and better efficacy in comparison with both dextran and doxorubicin^[104]. Some nanoparticles, formed by the self-assembly of block copolymers with hydrophilic and hydrophobic domains, have the unitary caryo-crust structures. Hydrophobic domains could be used as carrier for hydrophobicity drugs, while hydrophilic domains make particles stable in aqueous solution^[105–107]. These nanoparticles could enhance the solubility of drugs and prolong effective action time, but they could not target toward tumor cells with high efficacy. Therefore, a novel dual targeting strategy was developed and could maximize drug delivery efficacy to tumor cells. For example, folate-PEG-PCL has been developed to encapsulate superparamagnetic Fe_3O_4 and to deliver an anticancer drug, doxorubicin, to tumor cells. The dual targeting strategy opened up several opportunities for enhancing drug delivery efficiency and cancer specificity during chemotherapy^[108].

Platinum supermolecules are one of the most extensively used anticancer drugs in clinic, and developing their nanoparticles as delivery system of tumor cells becomes very important^[109]. This can not only enhance the stability and prevent fast decomposition, but also control effectively drug release and improve the anticancer activity. Cisplatin encapsulated in PDEA-PEG nanoparticles had higher cytotoxicity than the free drug on SKOV-3 cells. The research on intraperitoneally ovarian tumors of mice indicated that the apoptosis activity induced by cisplatin/PDEA-PEG nanoparticles was about

twice that of by the free cisplatin. The platinum(IV) complex **40**, which was nearly nontoxic to testicular cancer cells, displayed a significantly enhanced cytotoxicity profile when attached to the surface of the single-walled carbon nanotubes (SWNTs)^[110]. The important reason is that the soluble nanotubes internalized the platinum(IV) complex through endocytosis, providing six times the concentration that the untethered complex is able to achieve on its own. Then the acidic environment facilitates release of platinum as its core complex by reduction and concomitant loss of the axial ligands and exhibits cytotoxicity.



2 Supermolecules as anti-inflammatory and analgesic agents

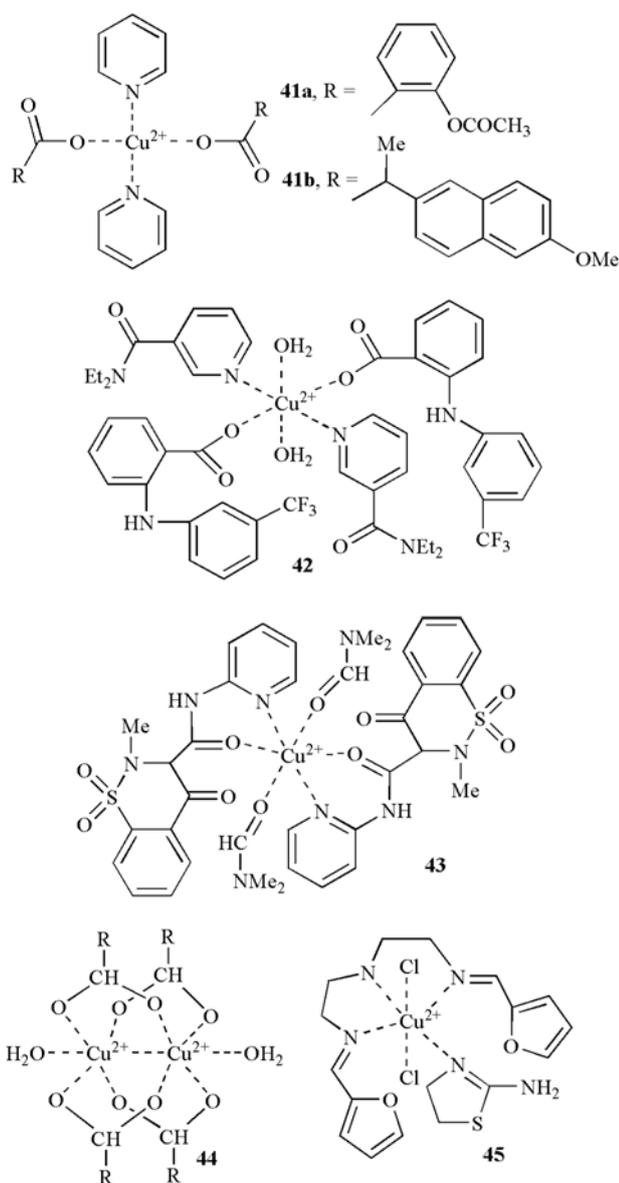
Inflammation is now recognized as a type of nonspecific immune response to destructive stimulus, and is a basic way to prevent the body from infection, irritation or other injuries. Its clinical appearance includes redness, warmth, swelling and pain as well as functional disturbance. Anti-inflammatory and analgesic drugs are a class of drugs against fever and pain, inflammation and rheumatism. Due to its exceptive anti-inflammatory activity, this class of drugs was called non-steroidal anti-inflammatory drugs (NSAIDs) in 1974 international conference at Milan in Italy. Aspirin is the representative of this type of drugs^[111].

Aspirin, the first NSAIDs used in clinic, was a milestone for the use of synthetic drugs to treat inflammation. After this, the NSAIDs expanded to more than one hundred species, and became the first choice to treat osteoarthritis and arthritis pauperum. However, the high gastro-intestinal side effect confined their applications. The complexation of NSAIDs with metal ions could significantly reduce gastric toxicity and some even enhance analgesia and anti-inflammatory activities.

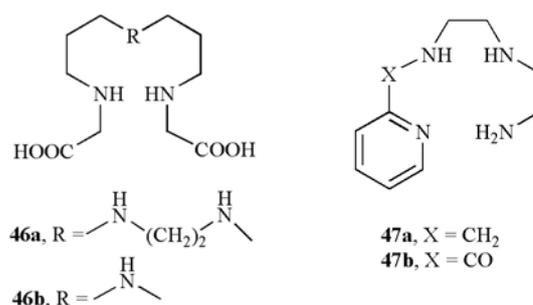
Among numerous NSAIDs metal complexes, copper-NSAIDs complexes were extensively investigated very well^[112]. The earlier research of copper complexes started in 1976. Sorenson et al. found that the anti-

inflammatory activities of Cu-NSAIDs complexes in animal models were better than that of the parent NSAIDs. For example, the anti-inflammatory activity of Cu(II) complex of aspirin displayed 30 times higher than that of the free drug aspirin. So far more than 140 NSAIDs copper complexes including mononuclear and dinuclear copper ones have been reported. Supermolecules **41**–**43**^[113] were mononuclear copper complexes, while **44** represented a series of dinuclear copper complexes formed with ibuprofen, naproxen, diclofenac or indometacin as ligand separately^[114–116].

In view of the notable anti-inflammatory activities of NSAIDs copper complexes, other copper complex supermolecules were also developed. As an example,

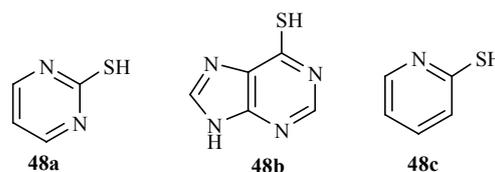


copper complex **45** gave a little lower anti-inflammatory activity than indomethacin^[117]. Jackson group designed and synthesized various types of copper complexes by the use of different polyamine ligands, and found that Cu(II) complexes of compounds **46** and **47** as ligands separately gave longer biological half life and higher bioavailability, and they were also promising to become antiarthritic drugs^[118].



In addition, other NSAIDs metal complexes, such as Zn(II), Pd(II), Sn(IV) and Ru(II,III) ones, also decreased toxicity and enhanced the activities of parent compounds.

The supermolecule wuyisa, a zinc complex formed with aspirin or niacinamide, not only could ameliorate the irritation of aspirin in gastrointestinal tract, but also enhance significantly anti-inflammatory activity. The zinc complexes of indomethacin or aspirin were found to show significantly lower gastro-intestinal damage than the parent drugs^[119,120]. The analgesic behavior of Zn(II)-baclofen complex was better than that of the parent drug^[121]. Recently, a series of Pd(II) complexes of compounds **48(a–c)** as ligands respectively^[122] have been reported, and their anti-inflammatory activity was 10%–15% stronger than that of the standard drug diclofenac. Furthermore, some Sn(IV)/Ru(II,III)-NSAIDs complexes have also been prepared and characterized^[123,124], but few studies were involved in their anti-inflammatory activity. Organotin(IV) complexes of 2-maleimidoacetic acid displayed stronger analgesic activity than its parent, while phthalimido-4-methyl pentanoate(PMPA) organotin(IV) esters showed less



activity than the ligand^[125,126].

Not only the NSAIDs metal complexes could reduce the gastro-intestinal damage of NSAIDs, but also the organic complex supramolecules formed by CD and their derivatives with NSAIDs, could improve their pharmacodynamics and pharmacokinetics properties. Indomethacin-CD inclusion complex had no anabrosis side effect. Naproxen- β -CD significantly increased the water solubility, raised dissolution rate, facilitated absorption, degraded gastro-intestinal damage of naproxen and also possessed lower phototoxicity after complexation with β -CD^[127]. In addition, ibuprofen- β -CD complex also increased the aqueous solubility, absorption rate and bioavailability of ibuprofen. Coating with pH sensitive CD derivatives is a method of drug delivery to the site of action, for example, the anti-inflammatory effect of the Prednisolone succinate/ α -CD (PDsuc/ α -CD) inclusion complex was comparable to that of prednisolone (PD) alone, while its systemic side effect was much lower than that of PD alone when administered orally, this might be related to the specific degradation of the inclusion complex in the large intestine^[128].

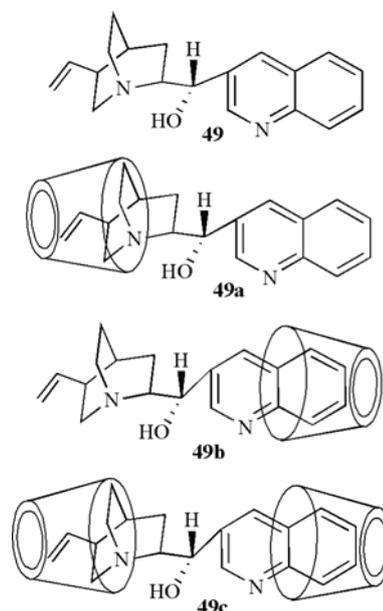
Superoxide dismutase (SOD), a new-type anti-inflammatory agent, is an important oxygen free radical scavenger and is mainly used as the treatment of in inflammatory patients. However, SOD in application aspects has some disadvantages with short half-life, easy inactivation by protease hydrolysis, larger molecular weight and difficult permeation through cell membrane. In order to overcome these problems, modification of the enzyme with aqueous polymers such as polyethylene glycol (PEG), dextran and starch has been reported as useful accessory materials^[129]. Recently, a bienzymatic supramolecular assembly of CAT and SOD has been reported for the first time, its anti-inflammatory activity increased 4.5-fold after associating with the modified CAT form. This SOD modification by supermolecules was still at the initial stage with favorable perspectives^[130].

3 Supermolecules as antimalarial agents

Nowadays, malaria has become one of the challenging public health problems all over the world, and is the most popular and hazardous parasitic disease throughout the world. In recent years, the rapid expansion of multidrug-resistant parasites weakened therapeutic efficacy of antimalarial agents seriously. Thus, it is quite urgent

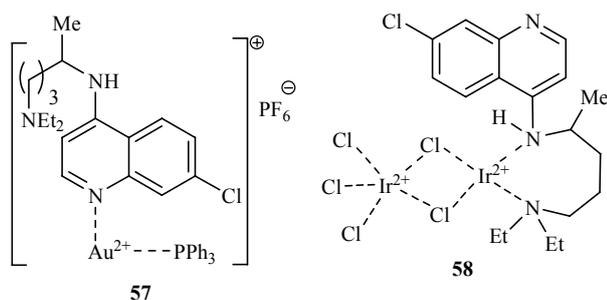
for clinical use to need new antimalarial agents with different structures and mechanisms. Exploring novel antimalarial agents is of importance to control malaria.

Cinchonine **49** is the earlier drug to treat malaria. In order to improve its water solubility, Liu et al.^[131] employed CDs to form inclusion complexes with cinchonine which might give three types of complex supermolecules **49(a-c)**, and these complex supermolecules improved its solubility significantly. Artemisinin is one of the most widely used antimalarial drugs. However, its low aqueous solubility and shorter half life resulted in poor and erratic absorption upon oral administration. After encapsulated with CDs, its solubility and oral bioavailability were enhanced greatly^[132].



Organic metal complexes as a novel class of antimalarial supermolecules were paid close attention. Ferrocene, due to its distinct features of sandwich structure and electrochemical behavior, was widely employed in biological research and drug design. Ferroquine **50** is an earlier antimalaria complex containing ferrocene structure. The survival rate of mice by the treatment of ferroquine was far higher than that of current standard drugs, and also displayed long-term stable antimalaria activity in biosystem. Ferroquine now is an antimalaria candidate which has unique metallocene structure, and phase I clinical trials have been completed. As recommended by the WHO, phase II clinical trials will begin with the examination of efficacy of artemisi-

promising supermolecules as antimalarial agents. With the further development, it would become one of the most important antimalarial agents after the ferrocene complexes. Moreover, other metal complexes also possess excellent antimalarial activities. For example, the Aurum or Iridium complexes **57** and **58** with chloroquine showed higher activity than parent chloroquine^[142,143], and could be used for the treatment of chloroquine-resistant plasmodium.



4 Supermolecules as antibacterial agents

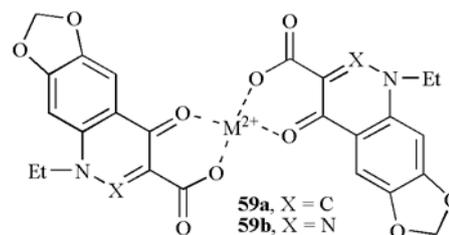
In the past two decades the frequencies and types of life-threatening infections have increased, especially in recent years the high incidence of multidrug-resistant (MDR), they have broken out the last line of defense of vancomycin as antibacterial drug of last resort for the treatment of MDR. The synthetic antibacterial agents being used extensively in clinic, such as quinolones and sulfonamides, and antibiotics such as β -Lactam antibiotics and aminoglycoside antibiotics could not inhibit effectively these bacterial strains, even the oxazolidinon with new mode of action, emerging in the past ten years, can not meet clinical needs. It is quite urgent to develop novel antibacterial agents with new mechanism of action and effectively decrease drug-resistant strains^[144].

In recent years, many investigations have proved that the complexes of antibiotics or potent antibacterial agents with various kinds of metal ions enhanced its activity and in some cases, the complexes possessed even more healing properties than the parent drugs. Therefore, to develop and screen new therapeutic antibacterial agents from these active supermolecules will be extensively investigated. According to the structures of the ligands, the supermolecules as antibacterial agents can be divided into the following parts: quinolones, sulfanilamides, schiff bases, thiosemicarbazides and macrocycles.

4.1 Quinolone-based supermolecules as antibacterial agents

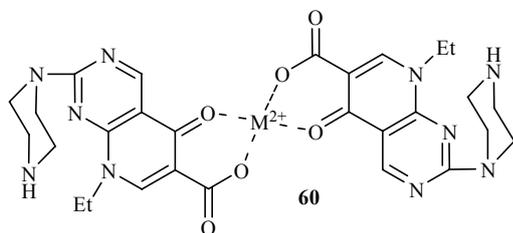
Quinolones are an important class of synthetic antibacterial agents. Since the introduction of nalidixic acid into clinical practice in 1962, quinolones have been developed from the first-generation to the fourth-generation and used to treat various kinds of infections. Many researchers have reviewed on the mode of action, structure-activity relationship and activity of these quinolones^[145,146]. It is found that quinolones can bind with DNA mediated by transition metal. Therefore, it is important to study on the coordination chemistry of quinolone antimicrobial agents with metal ions and their antibacterial activities in biology and pharmacy.

Oxolinic acid, OXO, a first-generation quinolone antimicrobial drug, is used for the treatment of urinary tract infections. The complex of oxolinic acid **59a**, $\text{Cu}(\text{OXO})_2(\text{H}_2\text{O})$, $\text{MoO}_2(\text{OXO})_2$ and $\text{UO}_2(\text{OXO})_2$, showed a decreased biological activities in comparison to the free oxolinic acid^[147,148]. Copper(II) complexes of oxolinic acid did not affect the inhibition of the growth of microorganisms significantly when other ligands were introduced, such as 1,10-phenanthroline, 2,2'-bipyridine, 2,2'-dipyridylamine. The complex of cadmium as soft acid and toxic metal ion **59b** showed similar activities against many Gram-negative bacteria and *P. aeruginosa* to that of cinoxacin.

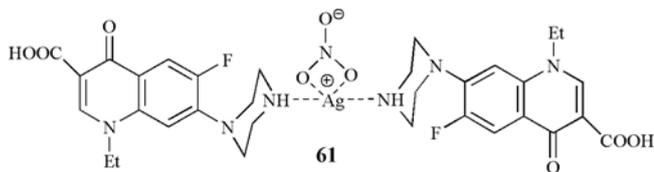


Pipemidic acid, HPPA, a second-generation quinolone antimicrobial drug, is used to treat gram-negative urinary tract infections and severely damages DNA in the absence of an exogenous metabolizing system. The literature reported the complexes of pipemidic acid with $\text{Ca}(\text{II})$, $\text{Sr}(\text{II})$, $\text{Ba}(\text{II})$, $\text{Sn}(\text{IV})$ and with the lanthanides $\text{La}(\text{III})$, $\text{Ce}(\text{III})$, $\text{Pr}(\text{III})$, $\text{Nd}(\text{III})$, $\text{Sm}(\text{III})$, $\text{Tb}(\text{III})$, $\text{Dy}(\text{III})$ and $\text{Y}(\text{III})$ as well as $\text{Cu}(\text{II})$ and $\text{Mn}(\text{II})$ metal ions. The reported results suggest that metal ion coordination play roles in the antibacterial activity of HPPA. Recently, it was found that among a series of complexes of pi-

peptic acid with VO(II), Mn(II), Fe(III), Co(II), Ni(II), Zn(II), MoO₂(II), Cd(II) and UO₂(II) (**60**), the best inhibition is provided by UO₂(PPA)₂ (MIC = 8 μg·mL⁻¹) against the *E. Coli*, *P. aeruginosa* and *S. aureus*^[149].



Norfloxacin is a widely used broad-spectrum antibacterial drug in clinic. Many works reported the biological activities of the metal complex of norfloxacin, such as silver, tungsten, copper and auric complexes as well as ternary complexes of copper(II) with norfloxacin. In these complexes, the norfloxacin is coordinated to Ag(I) and Au(III) ions. Silver complex of norfloxacin **61** was reported to prevent bacterial infection for humans during burn treatment, and its antibacterial property in topical applications is superior to those of silver and zinc sulfadiazine^[150]. In particular, the above complexes have better antibacterial activities against *P. aeruginosa* than the free ligand norfloxacin, but lower against *B. Subtilis*^[151].

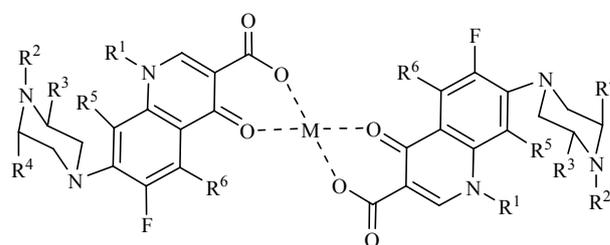


N-propyl-norfloxacin (pr-norf) is the *N*-propyl protected form of norfloxacin, and it has the same antibacterial spectrum as norfloxacin. The complex supermolecule **62a** showed good antibacterial activities, especially, the complex UO₂(pr-norf)₂ showed better inhibition than the free pr-norf with the MIC value of 4 μg·mL⁻¹ against *S. aureus*, and VO(pr-norf)₂(H₂O) and MoO₂(pr-norf)₂ showed comparable activity to that of the ligand against *S. aureus*, *colibacillus*, *P. aeruginosa*, while other complexes showed slightly weaker activity than the ligand^[152]. The ternary complexes of copper(II) with norfloxacin with nitrogen donor heterocyclic

ligands had better antibacterial activities than the free pr-norf, especially when the nitrogen donor heterocyclic ligand is 1,10-phenanthroline^[153], such as Cu(pr-norf)(phen)Cl, this complex supermolecule exhibited best antibacterial activity against *P. aeruginosa* with the MIC of 0.25 μg·mL⁻¹^[154].

The antibacterial activities of the free ligands both ciprofloxacin and enrofloxacin and their corresponding metal complexes **62b** and **62c** were the same as that of the above complexes. It is worth noticing that bis-muth(III)-ciprofloxacin (cf) complex was potential to be used in the treatment of ulcer caused by *H. Pylori*^[155]. The antibacterial activities of its copper complexes depend on the growth rate of the tested bacteria, which can be more lethal at low growth rate^[156]. In general, copper complexes of quinolones have better activities than their ligands. The copper complex of enrofloxacin Cu(ern)₂(H₂O) showed the excellent inhibition against *E. coli* and *P. aeruginosa* (MIC = 0.125 μg·mL⁻¹)^[157]. The same observation results also exist in the copper complex of norfloxacin.

Sparfloxacin (Hsf) is the third-generation quinolone antibacterial drug, mainly used for the treatment of acute exacerbations of chronic bronchitis and community-acquired pneumonia. It has good bioavailability with once-daily dosing. The research in metal complexes of sparfloxacin was seldom reported. Due to the good antibacterial activities of copper complexes of quinolones, the major research focused on the metal complex of sparfloxacin **62d**. The complex Cu(sf)₂ exhibited the same activity against *P. aeruginosa* (MIC = 0.25 μg·mL⁻¹) as the free sparfloxacin, better activity against *E. Coli* than sparfloxacin. The copper complexes containing other nitrogen donors also showed excellent activities, such as Cu(sf)(phen)Cl^[158].

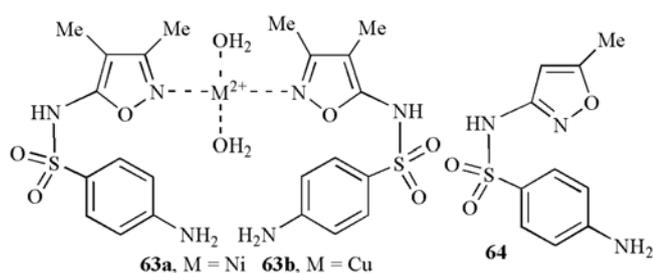


- 62a**, R¹ = CH₂CH₃, R² = CH₂CH₂CH₃, R³ = R⁴ = R⁵ = R⁶ = H
62b, R¹ = cyclopropyl, R² = R³ = R⁴ = R⁵ = R⁶ = H
62c, R¹ = cyclopropyl, R² = CH₂CH₃, R³ = R⁴ = R⁵ = R⁶ = H
62d, R¹ = cyclopropyl, R² = H, R³ = R⁴ = CH₃, R⁵ = F, R⁶ = NH₂

4.2 Sulfanilamide-based supermolecules as antibacterial agents

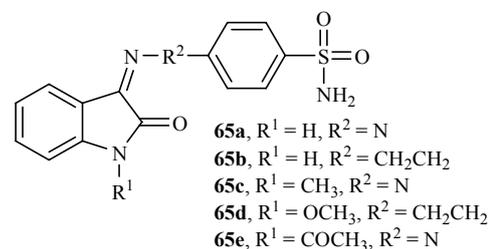
Sulfonamides and their derivatives are first synthetic antibacterial agents used in clinic as therapeutic agents against various bacterial infections. In recent years, some metal sulfonamides have attracted much attention due to the fact that complexes showed more activity than both free ligands and the corresponding metallic salts. In particular, Ag-sulfadiazine has been proved to be an effective topical antimicrobial agent, of significance in burn therapy, better than the free ligand or than AgNO₃. Moreover, some metal complexes of heterocyclic sulfonamides, such as sulfisoxazole, sulfapyridine, sulfadiazine, sulfathiazole and so on, have been extensively investigated^[159].

The metal sulfisoxazole complex **63** presented effective antibacterial activity against *S. aureus*, *E. coli* and *M. tuberculosis*. The complex **63a** presented the same activity against *S. aureus* and *E. coli* as sulfisoxazole, while the structurally similar complex **63b** was more active against the above bacteria than the free ligand and had no activity against *M. tuberculosis*. Probably, the good antimicrobial result is the reason that copper complex **63b** is easy to penetration into a less lipophilic cell wall and ionize into the active compounds inside the cell. New gold(I) and silver(I) complexes of sulfamethoxazole **64** showed better activities against *E. coli*, *P. aeruginosa* and *S. aureus* than their ligands^[160]. This suggested that metal sulfonamide complexes provide new possibility for the development of new antibacterial drugs.

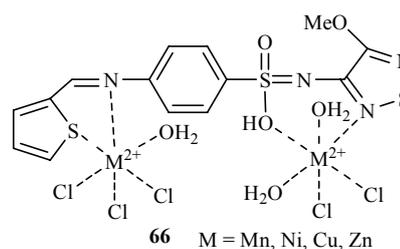


Isatin (2,3-indolinone) compounds have been often employed as valuable synthons in the preparation of biologically active compounds. The introduction of isatin into sulfonamides gave the target compounds **65**, its corresponding cobalt(II), copper(II), nickel(II) and zinc(II) metal complexes showed moderate to significant antibacterial activity against *B. cereus*, *C. diphthe-*

riae, *E. coli*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, *S. typhi*, *S. dysenteriae* and *S. aureus* and also showed significant antifungal activity against *T. schoenleinii*, *C. glabrata*, *P. boydii*, *C. albicans*, *A. niger*, *M. canis* and *T. mentagrophytes*^[161].



The schiff base derived from thiadiazolyl sulfanilamide and thiophene showed broad-spectrum antibacterial and antifungal activities, which were similar to chloramphenicol as standards, and their Mn(II), Co(II), Ni(II), Cu(II), Zn(II) or Cd(II) complex **66** has better activity^[162].

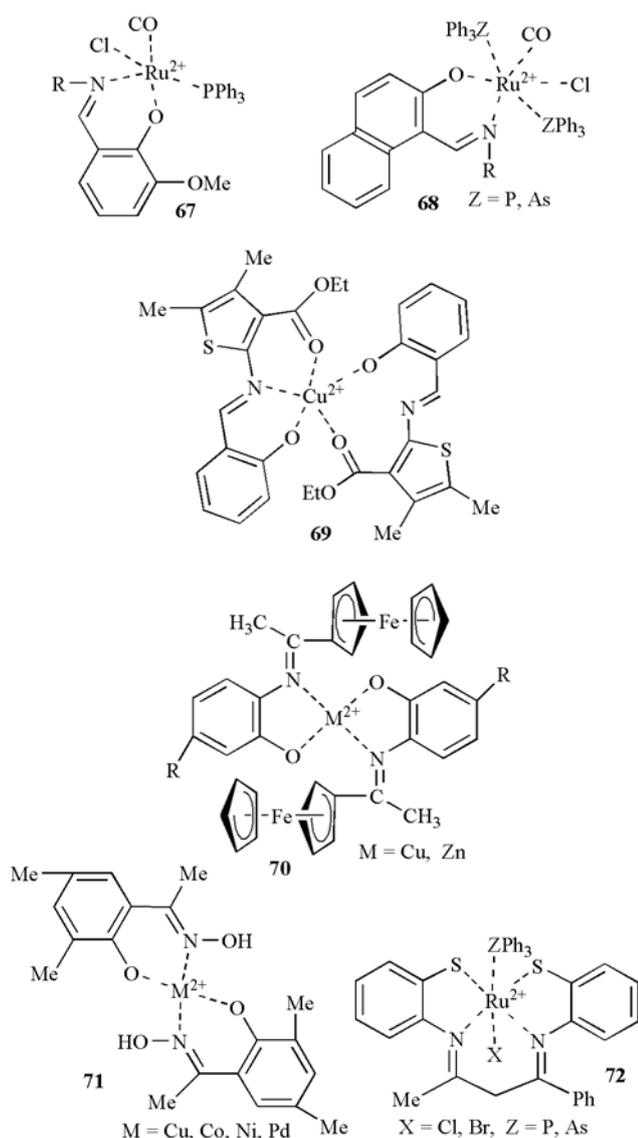


4.3 Schiff base-based supermolecules as antibacterial agents

The metal complexes containing oxygen and nitrogen donor schiff bases possess unusual configuration and structural lability, and they are sensitive to molecular environment. The environment around the metal center, for example, coordination geometry, number of coordinated ligands and their donor groups, is the key factor for metalloprotein to carry out specific physiological functions. The schiff base, containing phenolic hydroxyl group or aromatic heterocycle with three nitrogen atoms, phosphoric acid and phosphonate ester as well as their corresponding metal complexes showed significant antibacterial activities which received considerable attention. Among these complexes, copper complexes were the most important class with good antibacterial activity, and the related work has been reviewed in details^[163].

The oxygen and nitrogen donor atoms in schiff bases containing phenolic hydroxyl group could chelate with

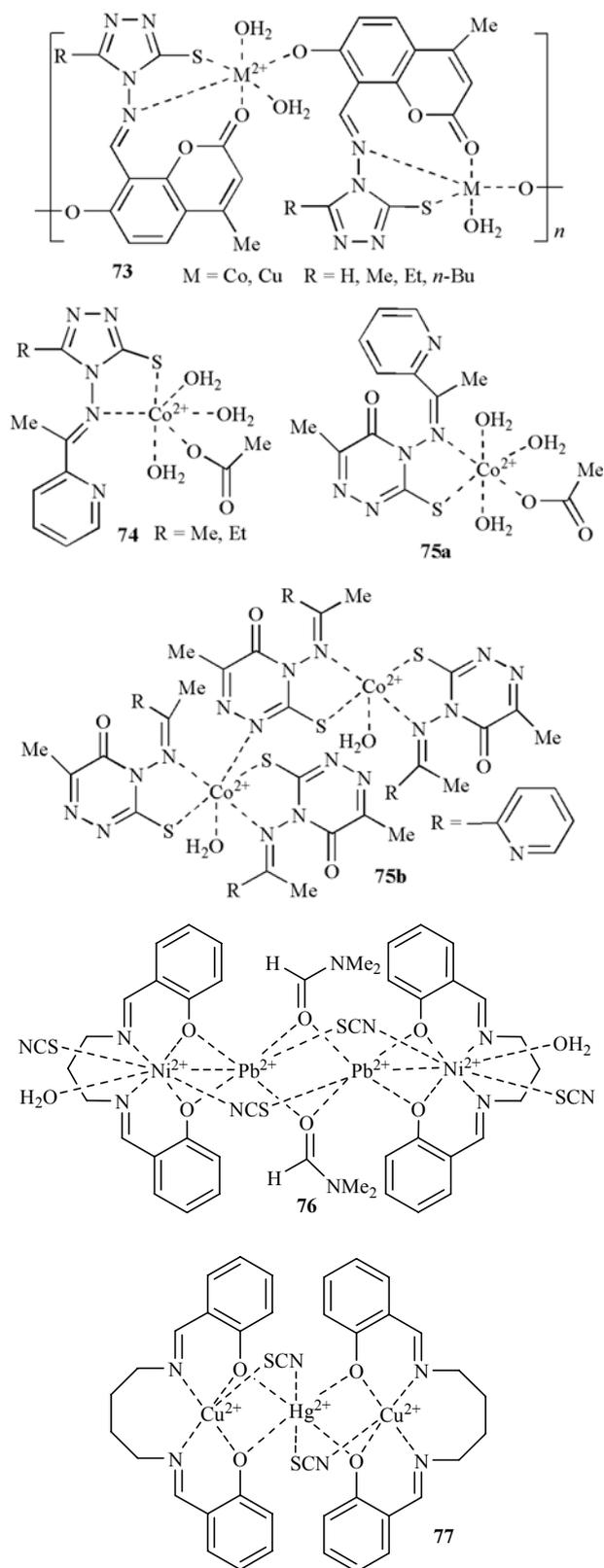
many transition metals, and show their biological activity. For example, the Ru(II)-complex of schiff base derived from vanillin **67** showed significant activity against *S. aureus* and *E. coli*, and its antibacterial efficacy was higher than that of corresponding ligands^[164]. Structural similar ligand naphthylideneimine derivatives exhibited little biological activity, but their Ru(II)-complex **68** showed moderate activity against *S. aureus* and *E. coli*^[165]. Schiff base, formed by condensation of amino thiophene with salicylaldehyde, exhibited moderate antibacterial activity against *S. aureus* and *S. hemolyticus*, and their metal complexes showed higher activity, especially the copper complex **69** with the activity similar to streptomycin^[166]. The copper(II) or zinc(II) complex with ferrocenyl schiff base containing a phenol moiety **70** showed significant antimicrobial activity



against *E. coli*, *B. subtilis*, and *C. albicans*. The good antibacterial activity was related to the chelation with metal ions, and was not due to the contribution of ligand itself^[167]. Acetophenones oximes were employed widely as ligands with important biological activity, the complex with metal Cu(II), Co(II), Ni(II) or Pd(II) ion **71** showed better activity than the corresponding ligands, and the Cu(II) complex was the best one^[168]. Moreover, metal complexes containing phenyl hydrosulfuryl Schiff base, like ruthenium(III) complex **72**, also showed good biological activity^[169].

Aromatic heterocycle with three nitrogen atoms such as triazole and triazine exhibited extensive biological activity, such as antituberculosis, antibacterial and antifungal and so on. Introduction of these structures into Schiff bases can enhance effectively their biological activity. The Co(II) or Cu(II) complex of 1,2,4-triazole Schiff base **73** showed good antibacterial activity against *E. coli*, *S. aureus*, *S. pyogenes*, *P. aeruginosa* and *S. typhi* as well as antifungal activities against *A. niger*, *A. flavus* and *Cladosporium*. The biological activity of the ligands exhibited a marked enhancement on coordination with the metal ions against all bacterial and fungal strains, and the antifungal activity is nearly close to the fluconazole as standard^[170]. The Co(II)-complex of triazole derivative **74** also showed good antimicrobial activity, at the concentration of 10 μg·mL⁻¹, it was found to exhibit better antibacterial activity against *B. Subtilis*, *E. Coli* and *P. aeruginosa* than the ciprofloxacin, chloramphenicol and streptomycin^[171]. The 1:2 metal complex of cobalt(II) **75b** with triazine derivative containing N and S chelate ligands, gave the MIC value 8, 8 and 4 μg·mL⁻¹ respectively against *S. aureus*, *S. epidermidis* and *B. Subtilis*, while 1:1 metal complexes of cobalt(II) **75a** was also found to be inhibitory at concentrations 8 and 4 μg·mL⁻¹ against *S. typhi* and *E. coli*. This enhancement in activity may be due to an efficient diffusion of the metal complexes into the bacterial cell and/or interaction with the bacterial cell^[172].

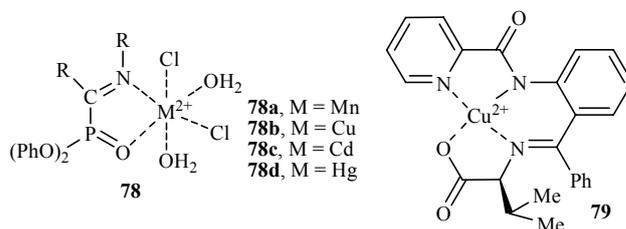
Hetero-polynuclear complexes also had good biological activity. The Ni or Pb complex of tetradentate containing phenolic hydroxyl group **76** exhibited effective broad spectrum antibacterial activity against *E. coli*, and *S. aureus* with MIC values of 15.6 μg·mL⁻¹. This complex gave positive results against *P. aeruginosa*, *E. aerogenes* and good antifungal activity against *A. ni-*



ger^[173]. Heterotrimeric thiocyanato bridged Cu(II)-Hg(II)-Cu(II) complex **77** also showed significant antibacterial activity, and presented higher antifungal ac-

tivity than the standard ketoconazole^[174].

The transition metal complex of phosphonate ester **78** showed excellent antimicrobial activity, and the complex HgLCl₂ (**78d**) was found to be the most active one, and superior to the standard drugs cefobid, sulperazon and erythromycin against *S. aureus*. Copper(II) complex of valine-derived schiff base **79** showed a significant inhibition of the growth of 4 gram-positive bacteria (*S. aureus*, methicillin-resistant *S. aureus*, *B. subtilis*, *M. luteus*), and 6 pathogenic fungi (*Candida spp.*, *C. neoformans*, *R. glutinis*, *S. cerevisia*, *Aspergillus spp.*, *R. nigricans*) and a moderate activity against 4 Gram-negative bacteria (*E. coli*, *P. aeruginosa*, *P. vulgaris* and *E. aerogenes*)^[175].



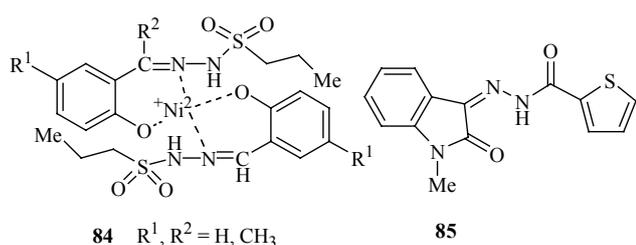
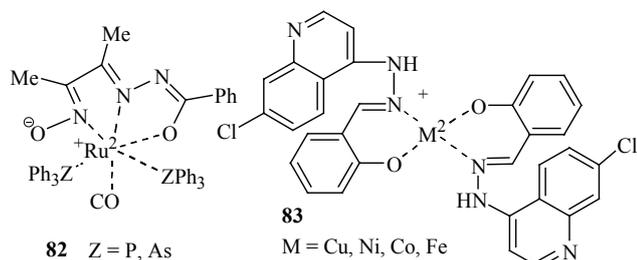
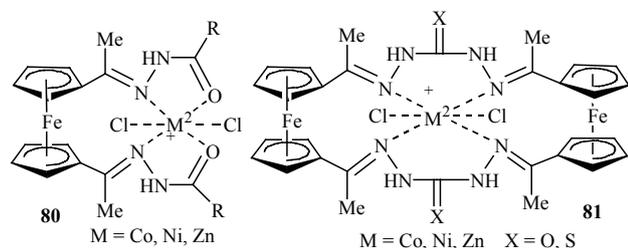
4.4 Hydrazone-based supermolecules as antibacterial agents

The β -nitrogen atom in carbohydrazones coordinated to the metal atom has an interesting stereochemistry, whereas the α -nitrogen remains uncoordinated. Complex supermolecule of carbohydrazones showed significant antibacterial, antifungal and antiproliferative activities, their research and application suggest enormous potential in medicinal area.

The complexes of ferrocenyl carbohydrazone or thio-carbohydrazone **80** and **81** had moderate antibacterial and antifungal activities, and their activities increased significantly compared with their ligands^[176,177]. Ruthenium complexes had been applied in many research areas. Novel Ru(II) oximato complex **82** showed good inhibition of the growth of *E. coli*, *S. sonnei*, *S. aureus*, *S. epidermidis* and *K. pneumoniae*^[178]. The complex of schiff base hydrazone containing quinolines **83** showed more effective antibacterial activity^[179]. Transition metal complexes of hydrazides and sulfonamides also were found to be used as chemotherapy. Nickel(II) complex of new sulfonyl hydrazone **84** exhibited moderate activities against gram-positive bacteria including *S. aureus*, *B. subtilis*, *B. magaterium* and gram-negative bacteria: *S. enteritidis* and *E. coli*^[180].

The cobalt(II), nickel(II), copper(II) or zinc(II)

complex of isatin derivatives **85** exhibited a strong inhibition of the growth of *H. influenzae* with MIC values of 0.15–1.50 $\mu\text{g}\cdot\text{mL}^{-1}$, and good antibacterial properties towards *B. subtilis* with MIC values of 3–25 $\mu\text{g}\cdot\text{mL}^{-1}$. These supermolecules also showed good activities against the dermatophyte mould *E. floccosum*^[181].

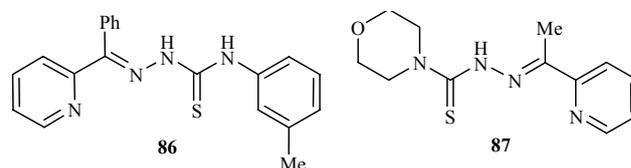


4.5 Thiosemicarbazone-based supermolecules as antibacterial agents

Thiosemicarbazones were considered to be good chelating ligands. Since the activity of metal complexes of 2-formyl and 2-acetylpyridine thiosemicarbazones has been demonstrated in clinical isolates of bacteria in 1990s. Many researches showed that thiosemicarbazones had antimicrobial activity, and exhibited significant inhibitory activity to gram positive bacilli while poor activity to gram negative bacilli.

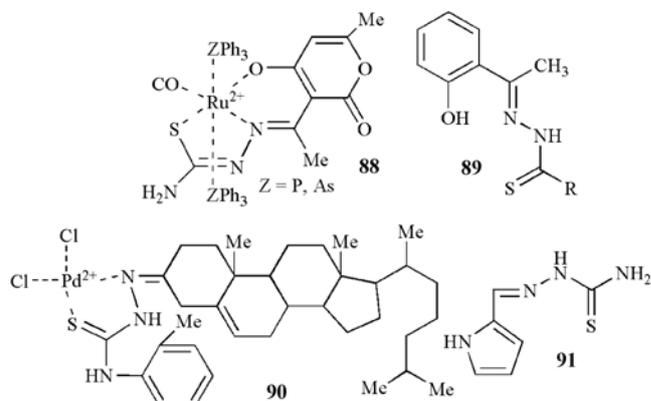
Some researches found that the copper complexes of thiosemicarbazones could be used as novel antimicrobial agents to treat the infectious diseases caused by drug-resistant fungi and bacteria. The copper complexes of pyridine-derived thiosemicarbazones were found to exhibit broad spectrum antibacterial and antifungal activities. Copper complex of compound **86** gave a MIC value of 5 $\mu\text{mol}\cdot\text{L}^{-1}$ against the growth of *S. typhi-*

murium and 0.5 $\mu\text{mol}\cdot\text{L}^{-1}$ against the growth of *C. albicans*^[182]. The bismuth(III) complexes of morpholine-substituted compound **87** showed highly selective inhibition of growth of Gram-positive bacteria *S. aureus* and *B. subtilis*^[183].

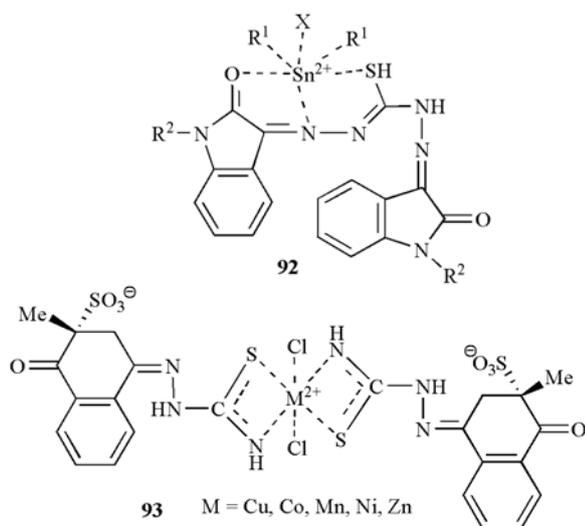


The interaction of small molecules such as CO and O₂ with transition metal complexes particularly those containing a ruthenium metal centre coordinated to nitrogen and oxygen donor ligands has attracted a great deal interest in recent years. New complex **88** showed good activity against *S. aureus*, *E. coli*, *C. albicans* and *A. fumigatus*^[184]. The derivative of 2-hydroxyacetophenone *N*(4)-substituted thiosemicarbazone **89** and its copper complex showed significant growth inhibitory activity against bacteria *E. coli*, *S. aureus*, and fungi *C. albicans* and *A. flavus*^[185]. Steroidal thiosemicarbazone and its palladium complex **90** were the same antibacterial activity as amoxicillin against *E. coli*, *P. streptococcus* and *S. aureus*^[186]. The copper complex of pyrrole-2-carbaldehyde thiosemicarbazone **91** was confirmed to be broad-spectrum antibacterial agent, and gave a MIC value of 12 $\mu\text{g}\cdot\text{mL}^{-1}$ against *B. Subtilis* and *S. aureus*. Interestingly, it could effectively inhibit the growth of both penicillin-susceptible and resistant *Staphylococcus* strains, acted as 25 $\mu\text{g}\cdot\text{mL}^{-1}$ towards *S. cerevisiae*, and 50 $\mu\text{g}\cdot\text{mL}^{-1}$ towards *C. tropicalis* and *A. fumigatus*^[187].

Organotin(IV) complex of isatin and *N*-alkylisatin bithiocarbonohydrazone **92** exhibit good antibacterial activity, and was the most sensitive to gram positive

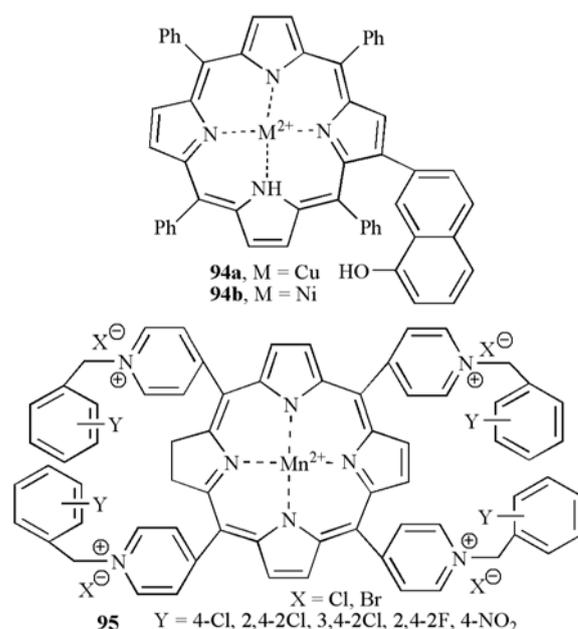


bacteria^[188]. Vitamin K₁₃ plays important roles in human life, its transition metal complexes of thiosemicarbazone derivatives were hopeful to result in better bioactive supermolecules. Complex **93** had strong inhibitory actions against G(+) *S. aureus* and G(+) *H. bacillus* similar to that of penicillin. These complexes gave good antibacterial activities against *E. coli*, they were superior to streptomycin, especially its Cu(II) complex gave the best efficacy^[189].

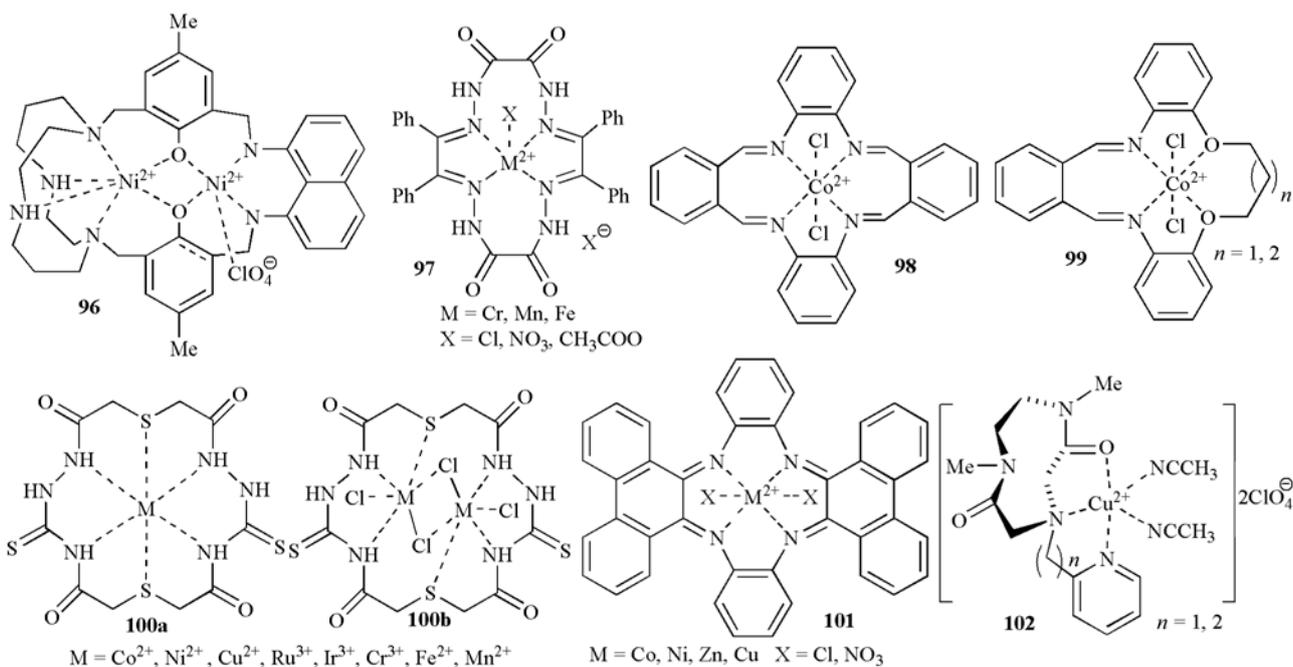


4.6 Macrocycle-based supermolecules as antibacterial agents

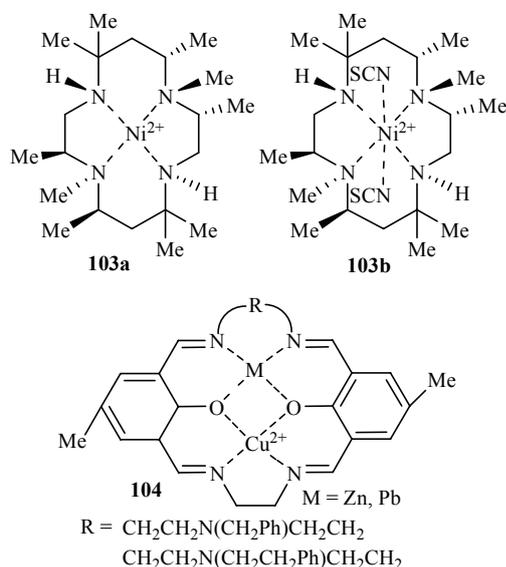
Macrocyclic complexes have attracted great attention because of their pharmacological properties against bacterial and fungal growth. Porphyrins were a class of good photodynamic photosensitizer, can be used for the research of the inhibition of bacteria and treatment of various kinds of bacterial infections, and can be also used as sterilizing agent and antiseptics in hospitals. The bactericidal activity against *S. aureus* has been tested with 2-(1-hydroxynaphthyl)-5,10,15,20-tetraphenylporphyrinato metal complex **94**. It is shown that the Ni(II) complex **94b** has photodynamic antibacterial activity. The clonal formation unit was only 18 at concentration of 320 $\mu\text{mol}\cdot\text{L}^{-1}$ under light. This result suggested that **94b** could be a good photosensitizer, which produced singlet oxygen to inhibit the growth of *S. aureus*^[190]. Our group designed and synthesized a new series of Mn(II) complexes of porphyrin **95**, all the metal complexes showed good photodynamic antibacterial activity while the corresponding ligands gave weak activity. These complexes also gave good photodynamic antifungal activity against *C. albicans*.



Unsymmetrical macrocyclic binuclear nickel(II) complex **96** showed excellent antibacterial activities against *S. aureus*, *P. aeruginosa*, *K. pneumonia* and *B. cearus*, and also gave good antifungal inhibition of the growth of *C. albicans*^[191]. The macrocyclic complex **97** derived from benzil and oxalyldihydrazide was found to exhibit remarkable antibacterial activities against *S. typhi*, *S. aureus* and *E. coli*, and some complexes were equal to standard antibiotic linezolid against the same bacterial strains^[192]. Novel macrocyclic Co(II) compounds derived from *o*-phthalaldehyde showed remarkable antibacterial activity, for example, the complexes **98** and **99** were more active against *S. aureus*, *E. coli* and *P. aeruginosa*, compared to streptomycin and ampicillin, and also showed very good efficacy on clinically resistant strains^[193]. Nickel(II) complexes of macrocyclic ligand derived from semicarbazide and thiodiglycolic acid **100a** and **100b** displayed that the percentage inhibition of bacterial growth of *S. aureus* was 90% at the concentration of 0.5 $\text{mg}\cdot\text{mL}^{-1}$, and showed good antifungal activity against *A. fumigatus*^[194]. The Ni(II), Cu(II), Co(II) or Zn(II) complexes of aromatic tetraazamacrocycle **101** exhibited potential activity against *S. typhimurium* and *E. coli* and fungal *C. albicans* and *C. neoformans*^[195]. The copper complexes of aliphatic macrocycle **102** exhibited obvious activity against most of the tested strains, they also gave the same inhibitory characteristics against clinically isolated resistant strains as gentamycin^[196].



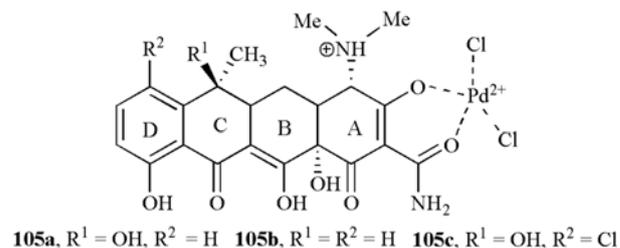
Nickel(II) complexes of polyaza macrocycle **103** were found to decrease their antibacterial activities upon coordination in all cases^[197]. However, the macrocyclic dinuclear complexes **104** gave selective antibacterial activity with moderate inhibition of the growth of *S. aureus*^[198].



4.7 Other supermolecules as antibacterial agents

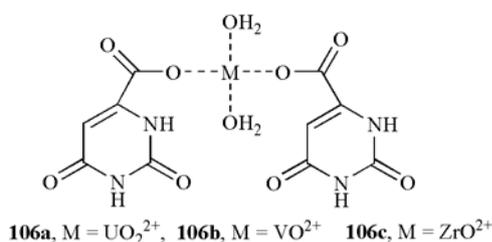
Besides these supermolecules discussed above as antimicrobial agents, there are other complexes formed with other structures including the drug ligands such as tetracycline and vitamin, and others such as chalcone and phenanthroline.

Tetracyclines (TC) are broad-spectrum agents with effective activity against both gram-positive and gram-negative bacteria, chlamydia, mycoplasmas, rickettsia, and protozoan parasites. Other antibiotics of this TC family doxycycline and chlortetracycline (Chl) showed the same antibacterial activity. Compared to the tetracycline compounds, their corresponding Pd(II) complex **105** resulted in a significant change of biological activity against *E. coli*. Practically, complex **105a** showed 16 times in inhibiting the growth of *E. coli* strains, while complex **105b** increased its activity in the resistant strain by a factor of 2 times. Curiously, the complex **105c** did not improve its activity against the *E. coli* strain^[199].

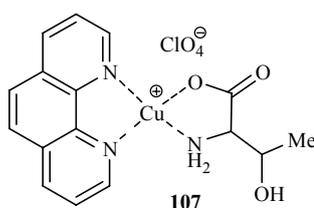


Vitamin B₁₃ belonged to pyrimidine bases in nucleic acid, is important for the regenerated cell of aged person, especially the liver and gastrointestinal tract cell, and is also valuable to be used as anticancer drugs. It is of importance that vitamin B₁₃ and its derivatives could coordinate with many metals to form biological active complexes. The biological assay showed that the

synthesized complex **106** has an enhanced activity compared to vitamin B₁₃. The biological activities of metal complexes increase in the order **106a** > **106b** > **106c**^[200].

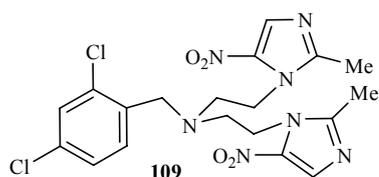
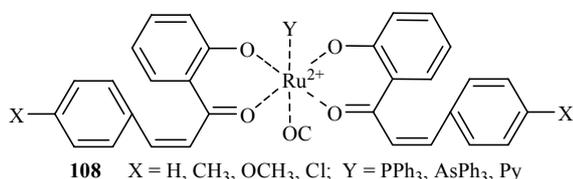


Metal complexes of phenanthroline and its derivatives possess extensive biological activities such as anti-*candida*, anti-*mycobacterium*, antibacterial activities and so on. Complex **107** showed stronger activity against 4 fungi and bacteria than the standard ciprofloxacin and clotrimazole^[201].



It was well known that chalcones and their analogues have bactericidal, fungicidal and carcinogenic activity. Ruthenium complexes of chalconate derivatives **108** also gave good biological activities, and their activities were better than that of corresponding ligands^[202]. Not all the complexes showed better antibacterial activity than their ligands, such as copper and nickel complexes of bis-nitroimidazole **109** with weaker activity.

Other complexes of imidazole and picolinamide have also been extensively investigated. Among these re-



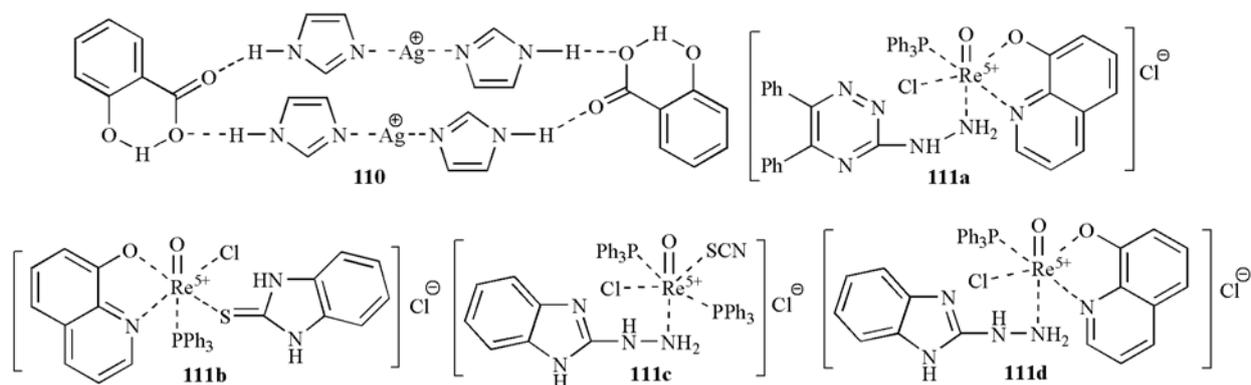
searches, the most reports were about copper complexes with stronger biological activity. Most of them gave broad spectrum antibacterial and antifungal activities, and were superior to other metal complexes and their corresponding ligands in most cases. This might be these reasons that: (1) the copper complexes had proper lipid-water partition coefficient which enable these compounds easier to penetrate into the cell and the release of the active matters; (2) the activated oxygen on copper surface can inhibit the bacterial growth. With rapid progress of the supramolecular chemistry, it would certainly be able to develop supramolecular antibacterial agents with high efficacy, low toxicity, broad spectrum and novel mode of action, to overcome the problem of microbial resistance to current antimicrobial drugs.

5 Supermolecules as antifungal agents

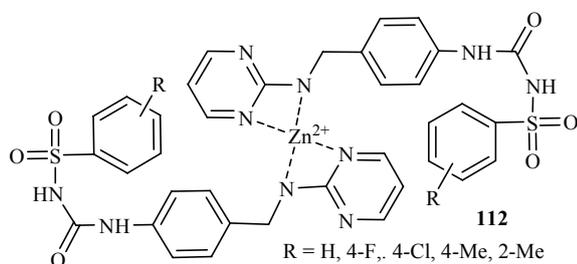
Fungal infections were one of the leading causes of death of immunocompromised patients. Azole drugs such as ketoconazole and fluconazole are currently prescribed to treat fungal infections caused by the pathogenic yeast *C. albicans*. However, many antimicrobial agents were toxic, and their extensive therapeutic uses were often accompanied by problems of drug resistance, unwanted side effects and so on. It is quite urgent to develop new and highly effective antifungal agents.

Aliphatic and aromatic thiourea, triazole and thiazine compounds are considered to be antimicrobial agents being able to control different microorganisms. In 2005, one work reviewed thiourea derivatives, triazines and their metal complexes as antifungal agents^[203]. Azole compounds were safe and effective therapeutic agents for the treatment of fungal infections^[204]. The Ag(I) complex of imidazole **110** was reported to be better antifungal agent against the fungus *C. albicans*, and it was 47 times more potent than the marketed drug ketoconazole^[205]. Regrettably, the Ag(I) complex of (*Z*)-3-(1-imidazolyl)-2-phenylpropenenitrile did not inhibit the growth of the pathogenic yeast *C. albicans in vitro* due to its low water solubility^[206]. Much effort has been expended to study the coordination chemistry of rhenium, the oxorhenium(V) complexes of mixed ligands **111(a-d)** showed excellent antifungal activities against *A. alternata* and *A. niger* and better efficacy than some well known antibiotics Dalacin C and Flumox^[207].

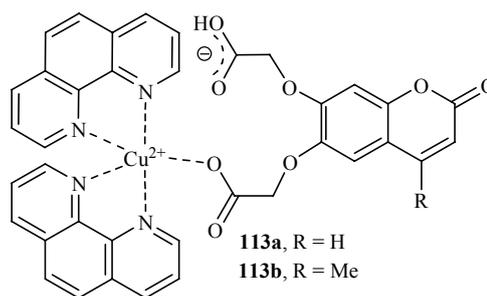
Besides well-known antibacterial activity, silver sulfadiazine was reported to possess strong antifungal



properties. Their mechanism of antifungal action seemed to be different from that of the azole antifungal drugs. By the inhibition of phosphomannose isomerase, they were to inhibit the biosynthesis of yeast cell walls and gave antifungal properties. It was known that the zinc enzyme has a specific binding site for silver ions, and this is important for its inhibition by the sulfanilamide complexes. Using silver sulfadiazine as lead molecule, the new zinc complex of sulfacarbamide **112** was synthesized, and proved to act as effective antifungal agents against several *A. flavus*, *A. fumigatus* and *Candida spp.*, but slightly weaker activities than standard ketoconazole^[208]. The cobalt complexes of sulfathiazolate (ST), $[\text{Co}(\text{ST})_2(\text{H}_2\text{O})_4]$, showed better antifungal activity against *A. flavus* and *A. fumigatus* than ST^[209].

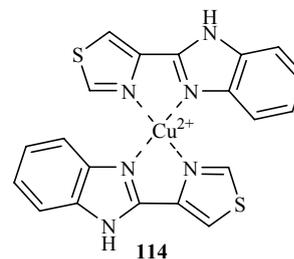


Supramolecular antifungal agents might facilitate to overcome the problem of drug resistance due to their possibly different mechanism of antifungal action. The carboxylic ester containing transition metal or the carboxylic ester complex **113** could inhibit the growth of *C. albicans in vitro*. However, when phenanthroline was substituted by bipyridine, the antifungal activity would disappear. The copper, manganese or silver complexes of phenanthroline showed fungicidal activity at concentration of $10 \mu\text{g}\cdot\text{mL}^{-1}$, and the anti-*Candida* activity of complex **113a** ($\text{MIC}_{80} = 22 \mu\text{mol}\cdot\text{mL}^{-1}$) seemed to be



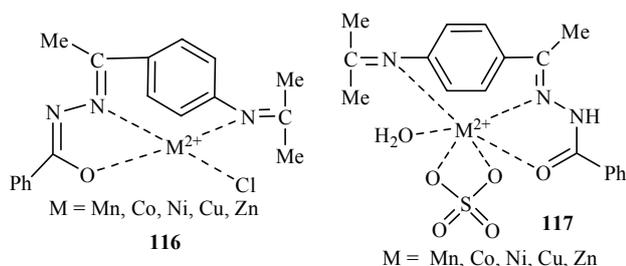
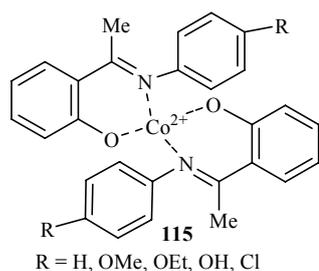
superior to that of ketoconazole ($\text{MIC}_{80} = 25 \mu\text{mol}\cdot\text{mL}^{-1}$)^[210]. Dithiocarbamate and its substituted compounds coordinated with many metals could form biological active supermolecules, and among them the copper complexes possessed best antifungal activity^[211].

Thiabendazole, with structural similarity to the chelating agents 1,10-phenanthroline and 2,2'-bipyridine, is a well-known anthelmintic agent and fungicide in agriculture with poor anti-*Candida* activity. However, its copper complex **114** was an activity-strong supermolecule with effective inhibition in growth of *C. candida* strains^[212].



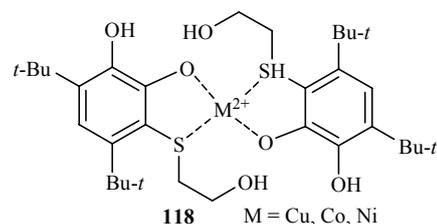
The substituents in the aromatic rings have effect on antifungal activity. It has also been found that in general the complexation of schiff bases with iron, copper, zinc and other metals also influences their antifungal activity. Makkar et al. found that cobalt complex of ethylidene-

aniline **115** gave moderate antifungal activity against *A. alternata*, *F. oxysporum* and *M. roridum*^[213]. Acylhydrazones constitute an interesting class of chelating agents, their metal complexes may have potential use in the biological fields. The metal(II) complexes of benzoylhydrazone **116** and **117** showed a significant antifungal activity against *Rizoctonia sp.*, *Aspergillus sp.* and *Penicillium sp.*^[214]. Among them, the most extensively investigation was heterocyclic thiosemicarbazones and their metal complexes. The nickel(II) complexes of 5-methyl-2-furfural thiosemi-carbazone were found to exhibit moderate antifungal activity against human pathogenic fungi, *A. fumigatus* and *C. albicans*. Although their activities were weaker than their similar copper complexes, lower toxicity was observed^[215]. The copper complex formed with 6-methyl-2-formylpyridine-*N*-dimethyl thiosemicarbazone is fungitoxic against the phytopathogenic fungi, *A. alternata*, *F. equiseti* and *M. phaseolina*, but it was less active than the free ligand^[216].



Besides the above complexes with effective antifungal activities, copper(II) complexes of sterically hindered catechol derivatives exert pronounced antifungal properties against *A. niger*, *Fusarium sp.*, *P. lividum*, *Mucor sp.* and *B. cinerea*^[217]. The antifungal activities of Cu(II), Co(II) and Ni(II) complexes of (2-hydroxyethyl)thiobenzene-1,2-diol **118** against 8 fungi showed that the copper complex was the most active supermolecule^[218]. The marketed antifungal agents such as amphotericin B and viroconazole were changed to

form liposome or nanoparticle supermolecules, they can not only improve the drug targeting and but also reduce the times of administration.

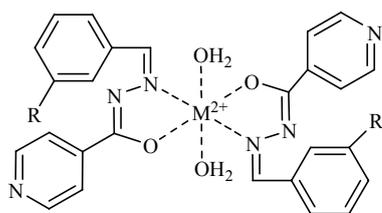


6 Supermolecules as anti-tuberculosis agents

Tuberculosis (TB) is considered to be the highly dangerous infective diseases to cause death with the high mortality throughout the world. The traditional anti-TB drugs, which have been used in clinic for several decades, displayed multidrug-resistance to some extent and affected clinical therapeutic efficacy. The long treatment cycle of tuberculosis increased drug resistance, and decreased the effectiveness of most available antitubercular agents. This resulted in reemergence of tuberculosis to threaten human. It is quite urgent to develop new anti-TB drugs.

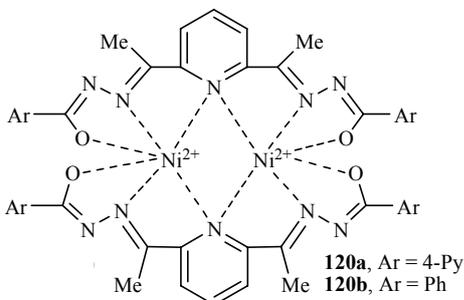
Isoniazid (INH) is still one of the important anti-TB drugs in clinic because of its distinct antitubercule bacillus activity, and its combination with rifampicin is often used to treat TB in short-course chemotherapy. INH is a good metal ion chelator, and can be coordinated with Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Pb(II) and rare earth metal ions to form stable complexes and thus ameliorate their liposolubility. Vigorita et al.^[219,220] prepared the Cu(II), Ni(II) and Co(II) complexes of INH, and found that complex **119** exhibited higher *Mycobacterium tuberculosis* H₃₇Rv growth inhibition than the parent drug. After that, this group reported Ni(II) complex of isoniazid **120**^[221], and the complex **120b** displayed 10-fold higher activity against *Mycobacterium tuberculosis* H₃₇Rv (MIC = 0.025 μg·mL⁻¹) than rifampin and equal to isoniazid.

N¹-Benzylidene-pyridine derivatives exhibited moderate anti-TB activities. In order to improve their anti-TB efficacy, Padhye et al.^[222] prepared their Cu(II) and Fe(III) complexes **121(a–b)**, and found that the antitubercular activities for these metal complexes was 32–64-fold enhancement in comparison with their



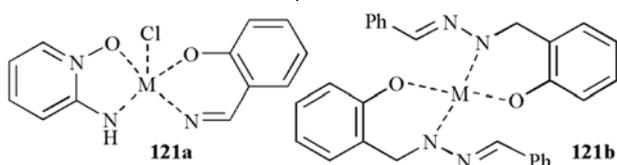
119a, M = Co, R = CF₃

119b, M = Cu, R = F



120a, Ar = 4-Py

120b, Ar = Ph



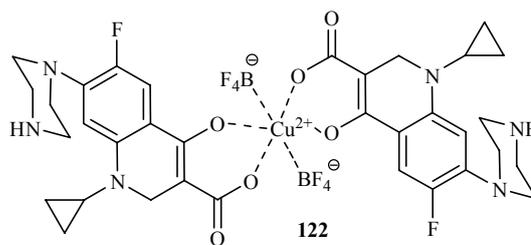
121a

121b

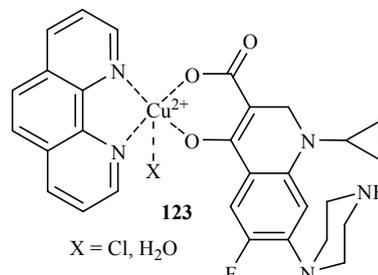
parent drugs.

Ciprofloxacin (cf) is often used as anti-TB drug in clinic. Its application was limited to some extent because of rapid emergence of drug-resistant strains. Lately, its metal complexes were found to enhance remarkably the anti-TB activities, such as copper(II) complex of ciprofloxacin (cf) **122**. Possibly, the formation of organometal complexes increased its liposolubility, made it easier to penetrate into the bacterial cell, and at the same time, Cu(II) ion was reduced to give copper(I) species intracellularly resulting ultimately in oxygen activation which is detrimental to the *Mycobacteria*. This result revealed that metal complexes with reducibility should be valuably helpful for the design of highly active anti-tubercular drugs^[223]. On the basis of this, Padhye et al.^[224] again reported a mixed-ligand Cu(II) complex containing ciprofloxacin and phenanthroline **123**, but this mixed-ligand Cu(II) complex did not enhance the antitubercular activity, this might be related to phenanthridine to stabilize the cupric species and degrade reduction activity of cupric species.

Ferrocenyl diamine complexes also possess potential antitubercular activity^[225], the MIC values of complexes **124a** and **124b** against *Mycobacterium tuberculosis* H₃₇Rv were 8 μg·mL⁻¹, lower activity than standard drug ethambutol (MIC = 2 μg·mL⁻¹). The replacement



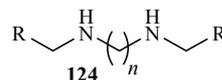
122



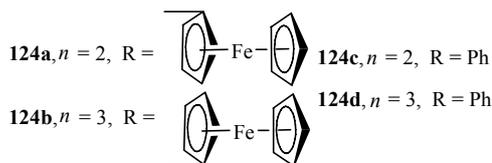
123

X = Cl, H₂O

of the ferrocenyl moiety with the phenyl group (**124c** and **124d**) resulted in complete loss of anti-tubercular activity. Some silver complexes of hydroxyl acids have potent and broad-spectrum antimicrobial activity^[226]. Cavicchioli et al.^[227] synthesized Ag(I)-complexes **125** and **126** coordinated with aspartame and cyclamate separately. The anti-mycobacterium activities showed that the Ag(I)-aspartame complex **125** gave better efficacy against *M. kansasII* (MIC = 9.75 μmol·mL⁻¹), while Ag(I)-cyclamate complex **126** has a better activity (MIC = 15.7 μmol·mL⁻¹) against *M. tuberculosis* and was promising as a new candidate for treatment of tuberculosis.



124

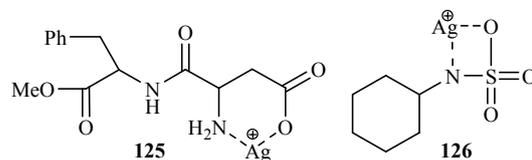


124a, n = 2, R =

124c, n = 2, R = Ph

124b, n = 3, R =

124d, n = 3, R = Ph



125

126

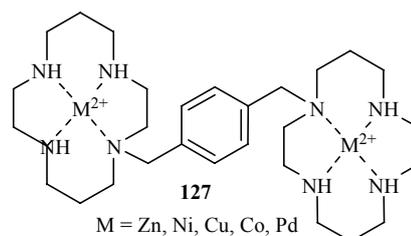
7 Supermolecules as antiviral agents

Viral infections often result in serious diseases such as hepatitis, AIDS and SARS to threaten human health and life. In spite of this, viral enormous harm to human did not result in rapid progress of antiviral drugs. This is

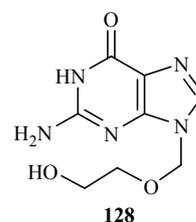
because viruses replication has close relation to human normal cells and would damage normal cells when inhibit viruses. Like other anti-infection drugs, antiviral drugs in long-term use easily lead to drug resistance, cut down curative effect and result in relapse. They have become quite urgent problems for clinical therapy and drug development to resolve.

Disoxaril is an anti-rhinovirus agent with good activity, it was withdrawn from clinical studies due to the appearance of asymptomatic crystalluria with large dosage, and the concentration of the drug acting on nasal mucosa was very low. In order to improve the water solubility of disoxaril, Ventura et al.^[228] employed 2,6-di-*O*-methyl- β -cyclodextrin (DM- β -CD) to encapsulate the anti-rhinovirus drug disoxaril, and formed the 1:1 inclusion complex. It was found that DM- β -CD was able to increase significantly water solubility of disoxaril, from 123 to 471.42 $\mu\text{g}\cdot\text{mL}^{-1}$ and improve efficiently the stability of drugs. The bovine nasal mucosa trail revealed that the formation of inclusion complexes could control efficiently the disoxaril release rate, and resulted in a lag time of 2 h and enhanced the bioavailability of drugs.

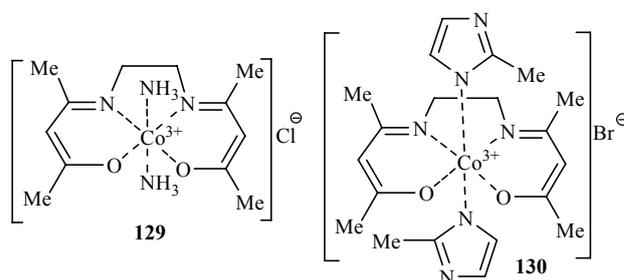
The CD4 cell surface molecules were the first target of HIV infection, thus inhibiting the entry of HIV into the cells through receptor CD4 antagonism became a dramatic method to prevent HIV infection. The entry of HIV into the cells requires the sequential interaction of the virus with a co-receptor CXCR4, therefore CXCR4 can serve as a target for the research of new drugs, and this is a new breakthrough for anti-HIV therapy. Bicyclams AMD3100 is a favorable CXCR4 antagonist, it can inhibit replication of both X₄ and X₄/R₅ types of HIV^[229]. Compound AMD3100 displayed significant activity against HIV virus, unfortunately, it was found to have significant side effect to heart leading to its withdrawal from further development as an anti-HIV agent in phase II studies. In order to improve anti-HIV activity of AMD3100, the complexation of AMD3100 with metal Zn(II), Ni(II), Cu(II), Co(II) or Pd(II) ion produced 1:2 complex **127**, and it was found that the Zn(II) complex (AMD3479) and Ni(II) complex (AMD3462) were slightly more active than the parent ligand AMD3100. The Cu(II) (AMD3469) and Co(III) (AMD3461) complexes were less active than AMD3100, while Pd(II) complex (AMD3158) was virtually inactive.



Acyclovir (**128**) is an efficient nucleobase guanosine antiviral agent, and can be transformed into diphosphate in body. It could inhibit the replication of HSV by interfering with DNA synthesis, and has become the first choice against herpesvirus infection. In order to improve the antiviral activity of acyclovir, many metal complexes of acyclovir with Cd(II), Co(II), Cu(II), Ni(II), Zn(II) and Hg(II) ions have been prepared and characterized^[230-233], however, so far their antiviral properties have not been reported.



Research showed that some Co(III) organic chelates also exhibited favorable antiviral activity. CTC-23 (**129**) was the first reported Co(III) organic complex with antiviral activity, and displayed moderate activity against HSV-1^[234]. Its analogue CTC-96 (**130**) exhibited least toxicity and best activity among these series of complex supermolecules against HSV-1 and HSV-2. CTC-96 accelerated herpetic dendritic keratitis recovery better than trifluorothymidine as reference drug^[235].



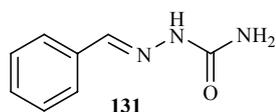
In addition to above complexes with antiviral activity, cobalt(III) hexammine complex also exhibited significant antiviral activity. The IC₅₀ value against Sindbis virus-infected cells is 0.13±0.04 mmol·mL⁻¹^[236]. Ruthenium(II) complex [H₄Ru₄(η^6 -*p*-benzene)₄]²⁺ was active

against the Polio virus without inhibiting the growth of human cells^[237].

8 Supermolecules as anti-epileptic agents

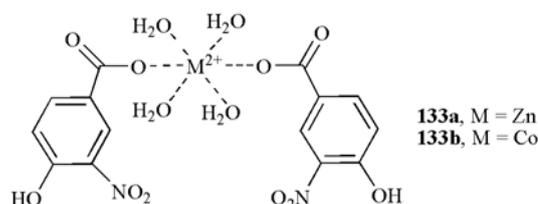
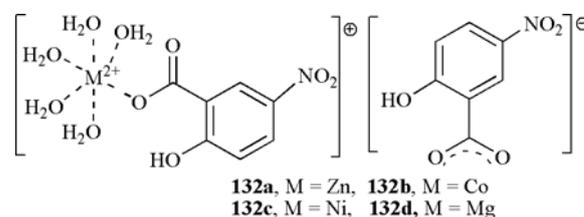
A large number of experiments revealed that metabolic defects and glutamic acid anomaly may intensify or induce excitotoxicity, and thus result in some neurogenic diseases. Epilepsy is a common neurological disorder, characterized by myoclonus, absence of psychomotor, loss of consciousness, paraesthesia, disorder of sentiment and psychomotor. The serious patients may suddenly lose the consciousness, tonic-clonic (grand mal) with symptom such as screaming, vultus cyanoderma, regurgitating foam and pupil diffusion, if the seizure lasts in a long time, it may make a threat to life.

Carbamazepine (CBZ), a widely used anticonvulsant drug, was absorbed slow and gave low bioavailability *in vivo* due to poor water solubility and unstable metabolism. The 1:1 inclusion complex of carbamazepine, formed with β -CD, increased its aqueous solubility, and could reach enough concentration in minidose through controlling release rate^[238]. Aryl semicarbazones encapsulated with CD or CD derivatives also can improve their aqueous solubility and bioavailability. For example, the inclusion complex of benzaldehyde semicarbazone (BS, **131**) with HP- β -CD^[239], its minimum dose necessary to produce activity decreased from 100 mg·kg⁻¹ for the free semicarbazone to 35 mg·kg⁻¹, indicating that this inclusion complex increased significantly the water solubility, decreased release rate, and then improved its bioavailability.



Some metal-NSAIDs complexes possessed not only the anti-inflammatory and analgesic activities, but also anticonvulsant potential. Many researches in anticonvulsant agents focused on the copper and zinc supra-molecular complexes of NSAIDs, especially the Cu₂-(aspirinate)₄ complexes^[240]. The [Cu₂(aspirinate)₄-(DMF)₂] complex was more effective in inhibiting MES-induced seizures than other binuclear or mono-nuclear copper chelates of aspirin, but had no activity in the scMET model of seizure. [Cu₂(niflumate)₄] com-

plexes, formed by cupric salt and niflumic acid^[241], showed some activity in inhibiting Grand Mal and Psychomotor type seizures, and this was consistent with inhibition of electroshock-mediated brain inflammation. However, no activity was found for the prevention of Petit Mal type seizures. Some Zn-NSAIDs complexes have also been proved to possess anticonvulsant activities^[242]. Complexes [Zn(aspirinate)₂(H₂O)₂] and [Zn-(salicylate)₂(phen)] were found to have excellent rivalry activity without Rotorod toxicity against psychomotor seizures, while complexes [Zn(3,5-DIPS)₂-(DMSO)₂], [Zn(aspirinate)₂(H₂O)₂] and [Zn(salicylate)₂-(phen)] exhibited particular useful efficacy in protecting against MES and scMET seizures. In view of the good potential of salicylato-metal complexes in anti-inflammatory and anticonvulsant activities, a series of metal Zn(II), Co(II), Ni(II) and Mg(II) complexes with 5-nitrosalicylate were prepared^[243]. Only **132b** was found to exhibit activity against MES-induced seizures, and all of the complexes had activity in protecting against the less intense minimal clonic seizure. Their activity order was **132c**>**133b**, **133a**>**132a**, **132b**, **132d**. Complexes **132a** and **133** showed moderate activity against the MET-induced seizure and the relative order of effectiveness was **133a**>**133b**>**132a**.



9 Supermolecules as cardiovascular agents

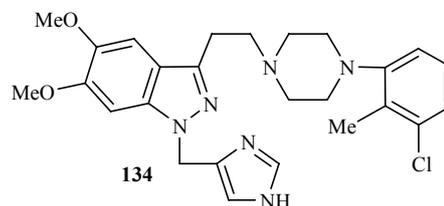
Cardiovascular disease is one of the major causes of death in developed countries over the world, and also has gradually become the life-threatening first killer in some developing countries. The cardiovascular drugs have high requirements in drug release, some require

quick drug release, while some demand sustained drug release to decrease the times of administration. The inclusion complexation of CD or its derivatives with the available cardiovascular drugs can meet these requirements.

The inclusion complexes of CDs with dihydropyridines calcium antagonist could overcome the problems of low dissolvability and easy oxygenolysis under light. The inclusion complexes of β -CD or HP- β -CD with the drug nifedipine, nitrendipine, captopril, nicardipine and nimodipine separately were confirmed to improve effectively the stability, bioavailability and solubility of these drugs, and the double-layer tablets of nifedipine encapsulated by 2-HP- β -CD and hydroxypropyl cellulose could satisfy with the need of different release rate by changing their component ratio^[244]. Uekama et al. prepared the binary system formed by captopril with HP- β -CD or TB- β -CD and the ternary system of captopril/TB- β -CD/HP- β -CD in different molar ratios, and investigated their release behavior in dogs^[245]. It was found that the release rate of captopril from the binary HP- β -CD system was rather fast, whereas that from the binary TB- β -CD system was comparatively slower, the retarding effect being dependent on the amounts of TB- β -CD. The release rate from the ternary captopril/TB- β -CD/HP- β -CD system was slowed down by the addition of small amounts of HP- β -CD, whereas the rate became faster as the molar ratio of HP- β -CD further increased (>0.25 molar ratio). The oral administration of the ternary captopril/TB- β -CD/HP- β -CD system (molar ratio of 1:0.5:0.5) in dogs gave a plasma profile comparable to that of a commercially available sustained release preparation. Some works investigated comparably the solubility-enhancing efficacy of Nimodipine by the use of several CDs including HP- β -CD and their derivatives, and found that HP- β -CD resulted in better solubilizing efficiency than methyl- β -CD, which may be acceptable for the injectable preparation of parenteral nimodipine solutions^[246]. Fernandes et al.^[247] prepared the inclusion complex of triacetyl- β -cyclodextrin (TA- β -CD) with nicardipine hydrochloride (NC), and carried out dissolution investigation in simulated gastric and intestinal fluids *in vitro*. The result showed that release rate of the inclusion complex was consistent with zero order kinetics, and it was concluded that TA- β -CD can be used as sustained release preparation excipient.

DY-9760e (**134**) was a novel cytoprotection agent for the treatment of acute ischemic stroke. Compared to

neutral HP- β -CD, the electronegative SBE7- β -CD formed more stable inclusion complex with **134**, and resulted in the significant enhancement of water solubility and light stability for drug **134**^[248], and also decreased the DY-9760e-induced cytotoxicity toward HUVECs and vascular damage in rabbits^[249].



10 Supermolecules as MRI agents

Magnetic resonance imaging (MRI) is a special imaging technique with multiparameter and polynucleation. Its physical principles are involved in the use of special frequency of electromagnetic waves to irradiate the human tissues placed in the magnetic field and then result in the nuclear magnetic resonance of hydrogen atoms in different tissues. The electromagnetic waves were absorbed and then emitted so-called nuclear magnetic resonance (NMR) signal^[250]. This NMR signal revealed the internal structural information of matter, and the later was measured and analyzed to be able to give the corresponding physical and chemical information. Thus this technique exhibits important application values in physics, chemistry, biology, medicine, etc.^[251].

Since Lauterbur first used MRI in 1973, the MRI technique has been widely used in various biomedical domains as clinical diagnosis with no traumatic occlusion and multi-contrast. No matter in clinical diagnosis or fundamental researches, MRI has currently become an indispensable tool^[252]. Its distinct feature is that the images are very clear for soft tissue. Up to now, none of any diagnostic imaging can be compared with MRI^[253].

Metal ions, such as Gd(III), Dy(III), Fe(III) and Mn(II) with large magnetic moment, could form stable chelates by chelation with appropriate ligands. These complex supermolecules may decrease toxicity and increase molecular volume, and have become the chief objects in the research of MRI contrast agents^[254]. Free Gd(III) with hydration water and most of its corresponding complexes were not compatible to venous blood, easy to precipitate, and exhibited strong toxicity. Therefore, it was of importance to choose a series of Gd

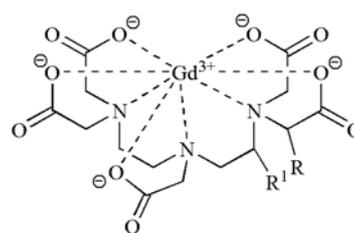
complexes which were stable in blood or humor^[255]. The first magnetic resonance contrast medium Gd-DTPA, Gd(III) complex of diethylene triaminepentaacetic acid (DTPA), was developed by Bayer Schering Pharma, Germany, and was used in clinic in 1988. To date, nine Gd(III) complexes have been used as MRI contrast agents in clinic, they are Magnevist (**135a**), MultiHance (**135b**), Primovist (**135c**), Vasovist (**135d**), Omniscan (**135e**), OptiMARK (**135f**), Dotarem (**136a**), ProHance (**136b**) and Gadovist (**136c**). Besides Gd(III) complexes, Mn-DPDP complex Teslascan (**137**) has also entered into the clinical practice^[256].

Recently, the development and application researches of contrast agents mostly focused on the improvement of the ligands, and Gd(III) was generally chosen as metal ion. The ligands included both linear and macrocyclic compounds. The current design has been majorly oriented on modifications of the structural motifs of DOTA and DTPA to improve their selectivity and biocompatibility^[257]. In recent years, much effort in the development and application of contrast agents has been mainly expended two following aspects.

First is to modify the ligands to reduce their toxicities and increase the stability and selectivity.

The introduction of some functional groups in the modification of the ligand backbone of the contrast agents could ameliorate their hydrophobicity to obtain the tissue- or organ-specific contrast agents. Currently, major research fields were involved in three types of targeting contrast agents including liver-targeting agents, tumor-targeting agents and blood pool agents. Some hydrophobic groups, such as long chain bisamide, aliphatic moiety and phenyl ring, have been incorporated into the backbone of these complexes to increase their hydrophobicity, facilitate them to be absorbed selectively by hepatic cell, and therefore possessed great potential as liver imaging contrast agents. The contrast agents Gd(BOPTA) and Gd(EOB-DTPA) have been in the stage of clinic trials.

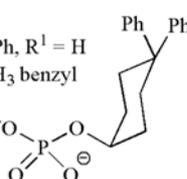
Supramolecular complex Gd-DTPA is a MRI contrast agent being used extensively in clinic. It belongs to ionic contrast agent with high osmotic pressure and short detention time *in vivo*, and is easy to excret from kidney metabolism, as well as has no tissue or organ specificity. Complex Gd-DTPA was modified to form electroneutral molecules, and thus exhibited much lower osmolality

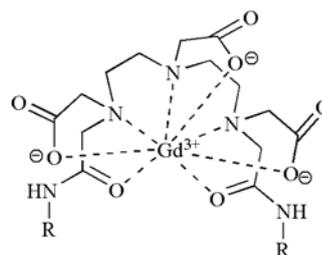


135a (Magnevist), R = H, R¹ = H

135b (MultiHance), R = CH₂(CH₂)₂Ph, R¹ = H

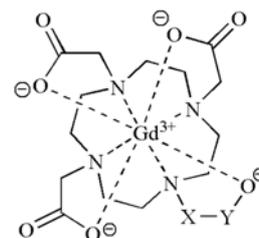
135c (Primovist), R = H, R¹ = 3-OCH₃ benzyl

135d (Vasovist), R = H, R¹ = 



135e (Omniscan), R = Me

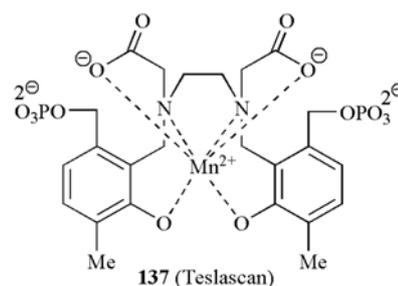
135f (OptiMARK), R = CH₂(CH₂)₂OMe



136a (Dotarem), X = CH₂, Y = CO

136b (ProHance), X = CH(CH₃), Y = CH₂

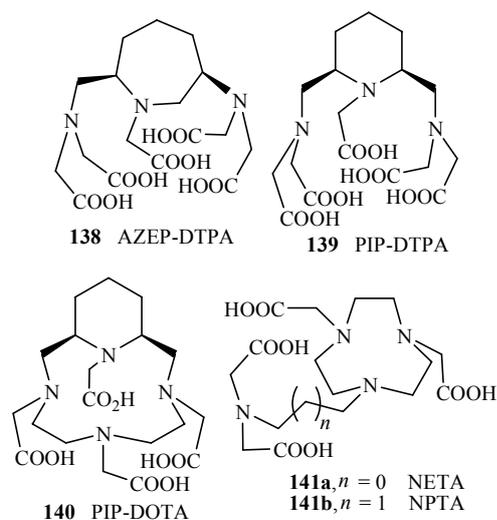
136c (Gadovist), X = Y = CH(CH₂OH)



137 (Teslascan)

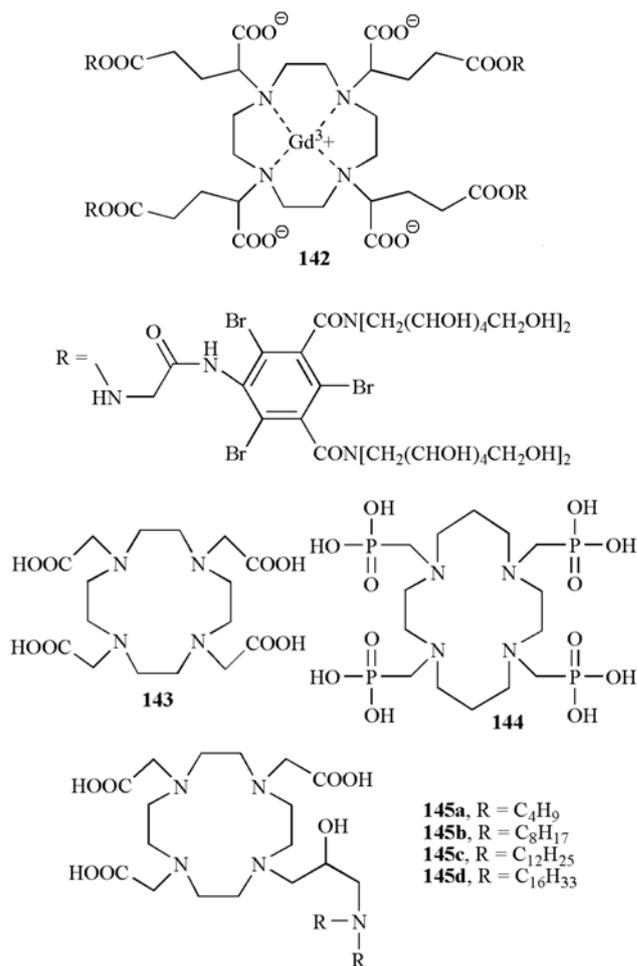
and toxicity in animals. The reaction of Gd-DTPA with bis-amides produced bisamido non-ion ligands such as Gd(DTPA-BDMA), Gd(DTPA-BDEA), Gd(DTPA-BIN) and Gd(cyclic-DTPA-1,2-pn)^[258]. The animal experiments and MRI evaluation showed that four neutral Gd-DTPA bisamide derivatives gave good relaxation in bovine serum albumin, and possessed features of liver targeting, better water solubility, hypotoxicity, and long detention time *in vivo*. The Gd-DTPA derivative MS-325 (Vasovist, **135d**)^[259] showed favorable binding ability

with human serum albumin (HSA) by using a bulky hydrophobic residue consisting of two phenyl rings attached to a cyclohexyl moiety linked, and reduced filtration of glomerulus monomer, which resulted in low renal excretion rate and prolonged half-life time in blood vessel. Complex **135d** is also the first Gd(III)-based contrast agent for angiographic applications to proceed to human trials. Chong et al. also prepared a series of DOTA derivatives **138–141**^[260] with liver targeting, these supramolecular complexes displayed higher relaxivity than standard Gd(DTPA) and Gd(DOTA). The Gd(III) complexes of the piperidine backbone PIP-DOTA and PIP-DTPA displayed reduced kidney accumulation, compared with the nonspecific Gd(DOTA). The strategy to increase lipophilicity and rigidity of the chelate system and thus enhance hepatobiliary clearance and complex stability by incorporating either a piperidine or an azepane ring into the DTPA system appears desirable for the design of liver specific MRI contrast agents. Gd(III) complexes **138–141** are promising to act as MRI liver agents or nonspecific agents in clinic.

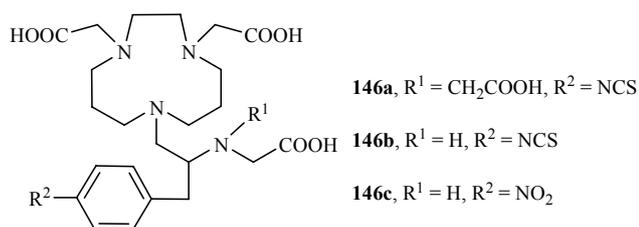


Recently, many researches focused on Gd-DOTA derivatives. The complex P760 (**142**), a gadolinium macrocycle based on a DOTA structure that is substituted by hydrophilic bulky groups, had higher relaxivity and good biocompatibility^[261]. In rabbits, 5 minutes after the injection of **142**, the blood concentration of $1036 \pm 105 \mu\text{mol} \cdot \text{kg}^{-1}$ was equivalent to the blood concentration of Gd-DOTA 1 minute after injection. Furthermore, the slow permeability process, increased the sensitivity of **142** for revealing permeability abnormalities, especially

for tumor detection, and it displayed potential application. The complexes **143** and **144** were another two DOTA derivatives^[262], and lanthanide radionuclide chelates of **143** and **144**, when linked to appropriate biomolecules such as monoclonal antibodies or small peptides, were promising radiopharmaceuticals for MRI imaging. The Gd(III) complex supermolecule of amphiphilic macrocyclic polyamine **145** could have been used as pH responsive MRI contrast agents *in vitro*^[263,264]. The T_1 -relaxivity (r_1) of Gd(III)-HADO-DO3A (**145a**) increased 142% on changing the pH from 6 to 8. The pH dependence was thought to arise from the formation of supramolecular structures caused by deprotonation of the amphiphilic complex at alkaline pH. These complexes are able to form supramolecular systems such as micelles and mixed micelles in aqueous solutions, in the presence or absence of surfactants. The formation of these supramolecular systems increased the efficacy of the contrast agent due to an increase in the rotational correlation time (τ_R) of the Gd(III) complex.



The novel bifunctional ligand **146** contains both acyclic and macrocyclic moieties^[265], and the compound **146c** was fortuitously discovered during the preparation of **146b**. The Gd(III) complexes of **146(a–c)** were prepared and indicated that Gd(III) complexes of ligand **146** possessed higher relaxivity than Gd(C-DOTA). The supermolecules formed by the complexation of ligand **146** with radiolabeled atoms ¹⁷⁷Lu, ⁹⁰Y, ^{205/6}Bi and ¹⁵³Gd exhibited good stability with retention time of 11 days in serum. The ligand **146** may be further modified by conjugating to the monoclonal antibody trastuzumab and then be used as antitumor agents.



Another aspect in the exploitation and application of contrast agents is to couple with macromolecule covalently, resulting in the enhanced relaxation efficiency and targeting property.

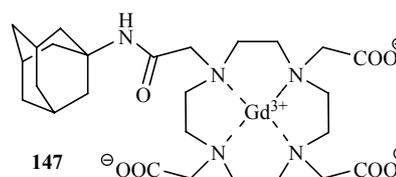
The DTPA and DOTA were introduced by polyester or polyamide into the backbone of polymer, or coupled covalently with natural or artificial synthetic polymer to be capable of forming macromolecular MRI contrast agents. They could decrease molecular spin rate, increase relaxivity, maintain stable concentration in prolonged time in blood vessel, and further profit angiography, as a result these compounds were called blood pool contrast agent. In addition, when an organ- or tissue-targeting group was attached to this macromolecular metal complex, it could be endowed with organ- or tissue-targeting property.

The Gd chelates of DTPA derivatives coupled with deoxycholic acid moiety had a higher relaxivity and longer half-life in human blood^[266]. Preliminary clinical tests showed that T_1 decurtated to about 100 ms when injected 50 mmol·kg⁻¹, and had good visualize effective toward aetia coronaria in 30 min.

The Gd-DTPA derivatives in covalent conjugation with the surface of polyamidoamine dendrimer separately to form dendritic chelates exhibited higher relaxivities than Gd-DTPA. The macrocyclic Gd(III) complexes formed by the conjugates of polyamidoamine

(PAMAM) backbone with macrocyclic polyamine Gd(III) complexes^[267] could decrease the internal mobility of the MRI photographic developer, enhance its relaxivity efficacy, and could be used as pH-responsive MRI contrast agent *in vivo*.

The supramolecular assembly, resulting from the self-association of a hydrophobic modified dextran (MD), a polymer of β -CD (p β -CD) and a Gd(III) chelate **147**^[268], led to homogeneous stable nanoparticles with diameter of about 200 nm. This system possessed larger loading capacity, and exhibited a great relaxivity enhancement (r_1 48.4 m·MS⁻¹, at 20 MHz and 37°C), while for the Gd(III) chelate itself the r_1 value was 5.2 m·MS⁻¹. The MD/p β -CD nanoparticles appeared to be a good candidate for the delivery of contrast agents that could be further improved in terms of relaxivity by using Gd complexes endowed with a shorter exchange lifetime. It could also be improved in terms of stability by using a multifunctionalized Gd(III) chelate of higher affinity and through the modification of the nanoparticle surface with hydrophilic polymers.



The excellent efficacy of MRI contrast agents enables them to be an important assistant method in daily application. The first liver-targeting contrast agent has been in market, lymph and blood pool contrast agents will also be in market soon. In the near future, diseased region or organ targeting contrast agents with wide application will become a basic tool in medical diagnosis image. With the development of new MRI techniques, such as MR angiography (MRA), perfusion MRI and diffusion-weighted MRI and their extensive use in clinical diagnosis, the research and development of MRI contrast agents will be faced with greater challenges. The major trends in the research and development of MRI contrast agents will focus on the tissue- or organ-targeting materials with high relaxivity and specificity, high contrast enhancement with low doses, low toxicity and side effects, and minimal expense. Along with the progress of biocoordination chemistry, NMR spectroscopy and medicine, it is no doubt that more and more novel, highly effective and low toxic contrast agents will

be used in clinic and bring more benefits to human.

11 Supramolecules as other pharmaceutical agents

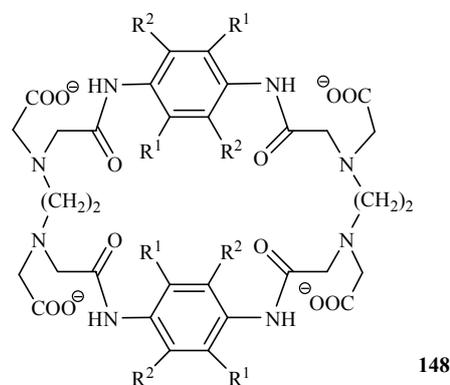
Insulin is the most effective and the first choice in the treatment of advanced-stage diabetes. However, polypeptide drugs like nidas insulin can aggregate by the interaction of internal hydrophobic residues and are often accompanied by drastic reduction of biological potency. The application of CD complexation represents a unique and effective strategy for improving drug solubility and activity by stabilizing them against aggregation^[269]. Sa-jeech et al. prepared HP- β -CD-insulin complex encapsulated mucoadhesive nanoparticles, which could protect the insulin from proteolytic degradation, resulting in the good oral insulin delivery systems^[270]. Hirayama et al. prepared polypseudorotaxanes of pegylated insulin with CDs as supramolecular system. It was found that the release rate of the insulin in the γ -CD polypseudorotaxane was lower than that of insulin alone, and the γ -CD polypseudorotaxane could prolong hypoglycemic effect of insulin in rats. The results indicated that the pegylated insulin/CD polypseudorotaxanes could work as a sustained drug release system^[271]. Tolbutamide (TBM) was used clinically in tablet form as an oral hypoglycemic agent, and the inclusion complex of TBM with β -CD or HP- β -CD increased its aqueous solubility, dissolution rate and oral absorption rate^[272]. Metal vanadium was a trace metal ion in higher animals and was well known to be essential to some organisms^[273], and the vanadium complex VO-Hglu of D-gluconic acid as anti-hyperglycemic agent showed good efficacy and necessity to further develop as potential drug.

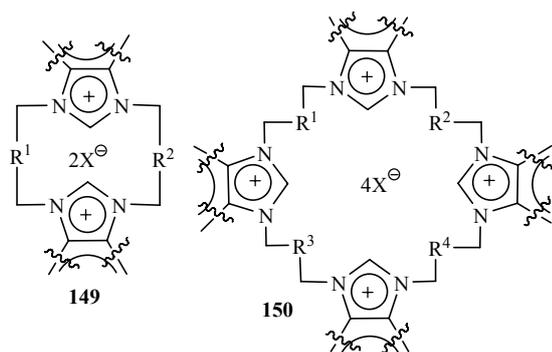
The inclusion research of tacrolimus showed that complex of β -CD with tacrolimus gave the highest stability constant among natural α -, β - and γ -CDs, this indicated that the cavity of β -CD matched with tacrolimus well^[274]. Rocuronium bromide is frequently used as neuromuscular block agent in surgery. But a reversal agent, for example, neostigmine as inhibitor of acetylcholinesterase (AChE) was often administered in order to facilitate rapid neuromuscular recovery after surgery and to prevent residual blockade. However, the reversal agent would cause side effects like bradycardia, nausea and vomiting. Zhang et al.^[275] prepared γ -CD-rocuronium bromide inclusion complex, and X-ray crystallography data showed that their complex was stable in

the cavity of γ -CDs, which blocked the pharmaco-activity of rocuronium indirectly. The γ -CD derivative rapidly reversed the neuromuscular block effect of rocuronium bromide *in vitro* (mouse hemi-diaphragm) and *in vivo* (anaesthetized monkeys), and appeared to be superior to neostigmine without any toxic side effects, now has entered into clinical trial stage.

Dopamine plays an important role in maintaining physiological functions of human body, and numerous efforts have been devoted to the development of dopamine for medicine. The macrocyclic compound **148** could easily include aromatic amine guests such as dopamine, tyramine and phenyl ethylamine^[276]. In order to improve its selectivity, considering the hydrophobicity of cavity and steric conformational restriction, the substituent groups R¹ and R² of **148** were changed to afford their corresponding derivatives with better selectivity to dopamine. This provided a new research approach for dopaminergics drugs. In the researches of macrocyclic compound cyclophanes, imidazolium or benzimidazolium cyclophanes became the highlight. For example, bis-imidazolium **149** and tetraimidazolium **150** have gained large success in host-guest researches and mimicking enzyme catalysis^[24–26, 277–280], and the onium cations in macrocycles as the host molecules of supramolecular drugs inevitably play important roles in the research and development of supramolecular drugs.

Buserelin acetate, an artificial synthetic nonapeptide, could form inclusion complex with DM- β -CD. Ultra-violet absorption and circular dichroism (CD) spectroscopies indicated that the aromatic rings in side chain residues of L-tryptophan and L-tyrosine and butyl group in serine were incorporated into the hydrophobic cavity of DM- β -CD, and resulted in space conformational





change of peptide chain, prevented unstable sites from being attacked by prolyase, and thereby enhanced the stability of buserelin^[36]. Flutamide (FLT) is a non-steroidal antiandrogen, and the formed FLT-HP- β -CD complex could improve oral bioavailability relative to FLT suspension. Intravenous pharmacokinetic profiles for both FLT and FLT-HP- β -CD were identical^[281]. Bary et al.^[282] investigated the effect of HP- β -CD on bioavailability of hydrocortisone (HC) as ophthalmology administration in the rabbit from New Zealand, and found that HP- β -CD increased the bioavailability of HC in the cornea by 75% and enhanced permeability of cornea greatly.

12 Conclusions and outlooks

As was mentioned above, supermolecules as chemical drugs formed by two or more molecules through the weak interactions of non-covalent bonds have been a quite rapidly developing, increasingly active and newly rising interdisciplinary highlight. Supramolecular drugs have been playing positive roles in many medicinal aspects such as antitumor, anti-inflammatory, analgesic, antimalarial, antibacterial, antifungal, antiviral, anti-epileptic, cardiovascular agents and magnetic resonance imaging agents and so on. In particular, a lot of supramolecular drugs as anti-tumor, anti-inflammatory and magnetic resonance imaging agents etc. have been extensively used in clinic, and brought benefits to mankind. The supramolecular drugs might enhance effectively the stability and safety, decrease the toxicity, eliminate abnormal flavour, overcome multidrug resistance and reduce adverse effects, improve the drug-targeting, the biocompatibility and bioavailability and so on. All of these properties could improve greatly the therapeutic efficacy of drugs. More importance is that numerous supermolecules as clinical drugs' candidates are in actively ongoing research and development,

and have shown that supermolecules as chemical drugs possess enormous potential. In addition, supramolecular drugs might spend less expense, take shorter time and have larger possibility as clinic drugs for their successful research and development, these virtues have been powerfully encouraging numerous researchers to engage in the research and development of novel supramolecular drugs. As predicting, it is inevitable that the research and development of supermolecules as chemical drugs will become increasingly active in near future.

Currently, much important progress has been made in the research of supermolecules as chemical drugs. The hosts of supramolecular drugs were involved in cyclodextrins, porphyrins, polymers and some other structural compounds, and the guests themselves were drugs or non-drug molecules, but major researches in this field focused on the cyclodextrin, porphyrin and metal complexes. Thus it should be fairly said that the research of supramolecular drugs was still in their initial stage. With the further expansion of supramolecular chemistry and the deep investigation of the supramolecular drugs, the research and development of supermolecules as chemical drugs will be consequentially further extended. The key topic area to research in the future might mainly include the following eight aspects:

- (1) Continuing using drugs themselves as guests to prepare supramolecular drugs, inevitably, further extension to employ some non-drug guests and/or non-drug hosts;
- (2) Continuing using CDs and their derivatives as hosts, meanwhile, future highlight probably in more and more efforts toward exploring other traditional macrocyclic compounds as hosts, such as cyclophanes, crown ethers, calixarenes, porphyrins, phthalocyanines, cyclopeptides, cucurbiturils and so on;
- (3) Researches of metal complexes becoming more active, increasingly important field maybe in the design and synthesis of novel organometallic ligands as drugs;
- (4) Design and synthesis of highly selective hosts and their researches as novel types of drug-delivery systems to facilitate the drugs to reach easily and safely the target organs;
- (5) Design and synthesis of highly drug-loaded hosts being able to load more drugs and the researches of these hosts as drug carriers;
- (6) Researches in the solubility, stability, drug dissolution, selectivity as well as safety of supramo-

lecular drugs themselves;

(7) Exploring the action mechanism of supramolecular drugs;

(8) Studies in structure-activity relationships of supramolecular drugs.

With the further expansion of supramolecular chemistry and its extensive extension in pharmaceutical sciences, as well as the ongoing progress of cell biology,

molecular biology, pharmaceuticals, materials science, medicine and other disciplines, it is inevitable that more and more workers will engage in the research and development of supramolecules as chemical drugs. More and more supramolecular drugs with good efficacy, low toxicity and good pharmacokinetics properties will be used in clinic and make remarkable contributions for the protection of human health.

- 1 Lehn J M. *Supramolecular Chemistry—Concepts and Perspectives*. Weinheim: VCH, 1995; Translated by Shen X H. *Supramolecular Chemistry—Concepts and Perspectives (in Chinese)*. Beijing: Peking University Press, 2002
- 2 Lehn J M, Atwood J L, Davies L E D, MacNicol D D, Vögtle F. *Comprehensive Supramolecular Chemistry*. Vol. 1—11. New York: Pergamon, 1996
- 3 Liu Y, You C C, Zhang H Y. *Supramolecular Chemistry—Molecular Recognition and Assembly of Synthesized Receptors (in Chinese)*. Tianjin: Nankai University Press, 2001
- 4 Steed J W, Atwood J L. *Supramolecular Chemistry*. Chichester: John Wiley & Sons, 2000; Translated by Zhao Y P, Sun Z. *Supramolecular Chemistry (in Chinese)*. Beijing: Chemical Industry Press, 2006
- 5 Dodziuk H. *Introduction to Supramolecular Chemistry*. Dordrecht: Kluwer Academic Publishers, 2002
- 6 Translated by Zhang X, Lin Z H, Gao Q (Vögtle F ed). *Supramolecular Chemistry (in Chinese)*. Jilin: Jilin University Press, 1995
- 7 Tong L H, Shen B J. *Physical Methods in Supramolecular Chemistry (in Chinese)*. Beijing: Science Press, 2004
- 8 Sun X Q, Meng Q, Yan H B. *Introduction of Supramolecular Chemistry (in Chinese)*. Beijing: China Petrochemical Press, 2000
- 9 Bianchi A, Bowman-James K, Garcia-Espana E. *Supramolecular Chemistry of Anions*. New York: John Wiley & Sons, 1997
- 10 Yui N. *Supramolecular Design for Biological Applications*. Boca Raton: CRC Press, 2002
- 11 Jones W, Rao C N R. *Supramolecular Organization and Materials Design*. Cambridge: Cambridge University Press, 2002
- 12 Schneider H J, Yatsimirsky A K. *Principles and Methods in Supramolecular Chemistry*. Chichester: John Wiley & Sons, 2000
- 13 Shen J C, Sun J Q. Research development of supramolecular science. *Bull Chin Aca Sci (in Chinese)*, 2004, 19(6): 420—424
- 14 Bertini I, Sigel A, Sigel H. *Handbook of Metalloproteins*. New York: Marcel Dekker, 2001
- 15 Li W. *Biological Supramolecular Systems (in Chinese)*. Beijing: Chemical Industry Press, 2003
- 16 Penadés S. *Host-Guest Chemistry—Mimetic Approaches to Study Carbohydrate Recognition*. Berlin: Springer, 2002
- 17 Cho S K. *Synthetic Multivalent Molecules—Concepts and Biomedical Applications*. New Jersey: John Wiley & Sons, 2004
- 18 Wu C T. *Crown Ether Chemistry (in Chinese)*. Beijing: Science Press, 1992
- 19 Gloe K. *Macrocyclic Chemistry—Current Trends and Future Perspectives*. Berlin: Springer, 2005
- 20 Simons C. *Nucleoside Mimetics—Their Chemistry and Biological Properties*. Australia: Gordon and Breach Science Publishers, 2001
- 21 Yang M. *Molecular Recognition in the Drug Research (in Chinese)*. Beijing: Beijing Medical University-Peking Union Medical College Union Press, 1999
- 22 Li R X, Yang J J. *Molecular Bionics and Their Application (in Chinese)*. Beijing: Chemical Industry Press, 2003
- 23 Yan J M, Zhou C H, Xie R G. Advance in the artificial receptors and enzymes of cyclophane. *Chin J Org Chem (in Chinese)*, 1995, 15(6): 577—586
- 24 Luo M M, Guo J S, Zhou C H, Xie R G. Design and synthesis of imidazolium cyclophane. *Heterocycles*, 1995, 41(7): 1421—1424
- 25 Zhou C H, Xie R G, Zhao H M. Convenient and efficient synthesis of imidazolium cyclophanes. *Org Prep Proc Int*, 1996, 28(3): 345—347
- 26 Liu Z C, Zhou C H, Su X Y, Xie R G. First synthesis of estrogen-imidazolium cyclophanes. *Synth Commun*, 1999, 29(17): 2979—2983
- 27 Jiang H Y, Zhou C H, Luo K, Chen H, Lan J B, Xie R G. Chiral imidazole metalloenzyme models: Synthesis and enantioselective hydrolysis for α -amino acid esters. *J Mol Catal A: Chem*, 2006, 260(1-2): 288—294
- 28 Wei X, Liu J, Zhang G L, Jiang Z L, Zhou C H, Luo K, Xie R G. An effective methodology to novel larger imidazolium cyclophanes. *Lett Org Chem*, 2005, 2: 507—511
- 29 Gao G, Xiao R, Yuan Y, Zhou C H, Xie R G. Efficient imidazolium catalysts for benzoin condensation. *J Chem Res*, 2002, 6: 262—263
- 30 Wu J, Mi J L, Zhou C H. Advance in histamine H₃ receptor ligands. *Chin Pharm J (in Chinese)*, 2007, 46(6): 404—409
- 31 Song C Z, Zhou C H, Yuan Y. Advance in sulfonamides as carbonic anhydrase inhibitors. *Chin J New Drugs (in Chinese)*, 2007, 16(18): 1438—1444
- 32 Meng J P, Lu Y H, Yibulayin H, Zhou C H. Advances in the research of benzimidazole compounds as enzyme inhibitors. *Chin J Biochem Pharm (in Chinese)*, 2008, 29 (6): 422—425
- 33 Yu K G, Zhou C H, Li D H. Advances in the macrocyclic drugs. *Chin Pharm J (in Chinese)*, 2008, 43(7): 481—488
- 34 Clarke M J, Zhu F C, Frasca D R. Non-platinum chemotherapeutic metallopharmaceuticals. *Chem Rev*, 1999, 99(9): 2511—2533
- 35 Ott I, Gust R. Non platinum metal complexes as anti-cancer drugs. *Arch Pharm Chem Life Sci*, 2007, 340(3): 117—126
- 36 Dai G F, Wang M W. Progress in pharmaceutical applications of cyclodextrin and its derivatives. *Chin J New Drugs (in Chinese)*, 2005,

- 14(11): 1261–1264
- 37 Deng S M. Study on the drug—Cyclodextrin supramolecular system. Dissertation for the Doctoral Degree (in Chinese). Guangzhou: South China University of Technology, 1998
- 38 Beni S, Szakacs Z, Cserniak O, Barcza L, Noszal B. Cyclodextrin/imatinib complexation: Binding mode and charge dependent stabilities. *Eur J Pharm Sci*, 2007, 30(2): 167–174
- 39 Horvath G, Premkumar T, Boztas A, Lee E, Jon S, Geckeler K E. Supramolecular nanoencapsulation as a tool: Solubilization of the anticancer drug *trans*-dichloro(dipyridine)platinum(II) by complexation with β -cyclodextrin. *Mol Pharm*, 2008, 5(2): 358–363
- 40 Melo P S, Justo G Z, Azevedo M B M, Duran N, Haun M. Violacein and its β -cyclodextrin complexes induce apoptosis and differentiation in HL60 cells. *Toxicology*, 2003, 186(3): 217–225
- 41 Wang F J, Blanco E, Ai H, Boothman D A, Gao J M. Modulating β -lapachone release from polymer millirods through cyclodextrin complexation. *J Pharm Sci*, 2006, 95(10): 2309–2319
- 42 Manuel S, Joly J P, Courcot B, Elysee J, Ghermani N E, Marsura A. Synthesis and inclusion ability of a bis- β -cyclodextrin pseudo-cryptand towards busulfan anticancer agent. *Tetrahedron*, 2007, 63(7): 1706–1714
- 43 Liu Y, Chen G S, Chen Y, Cao D X, Ge Z Q, Yuan Y J. Inclusion complexes of paclitaxel and oligo (ethylenediamino) bridged bis(β -cyclodextrins): Solubilization and antitumor activity. *Bioorg Med Chem*, 2004, 12(22): 5767–5775
- 44 Jong M R, Knegtel R M A, Grootenhuis P D J, Huskens J, Reinhoudt D N. A method to identify and screen libraries of guests that complex to a synthetic host. *Angew Chem Int Ed*, 2002, 41(6): 1004–1008
- 45 Krause-Heuer A M, Wheate N J, Tilby M J, Pearson D G, Ottley C J, Aldrich-Wright J R. Substituted β -cyclodextrin and calix[4]arene as encapsulatory vehicles for platinum(II)-based DNA intercalators. *Inorg Chem*, 2008, 47(15): 6880–6888
- 46 Comuzzi C, Cogoi S, Overhand M, Marel G A V, Overkleeft H S, Xodo L E. Synthesis and biological evaluation of new pentaphyrin macrocycles for photodynamic therapy. *J Med Chem*, 2006, 49(1): 196–204
- 47 Desroches M C, Bautista-Sanchez A, Lamotte C, Labeque B, Auchère D, Farinotti R, Maillard P, Grierson D S, Prognon P, Kasselouri A. Pharmacokinetics of a tri-glucoconjugated 5,10,15-(meta)-trihydroxyphenyl-20-phenyl porphyrin photosensitizer for PDT. A single dose study in the rat. *J Photochem Photobiol B: Biol*, 2006, 85(1): 56–64
- 48 Yu K G, Zhou C H, Li D H. Recent progress of porphyrin-based anticancer drugs. *Chem Res Appl (in Chinese)*, 2007, 19(12): 1296–1303
- 49 Nyman E S, Hynninen P H. Research advances in the use of tetrapyrrolic photosensitizers for photodynamic therapy. *J Photochem Photobiol B: Biol*, 2004, 73(1-2): 1–28
- 50 Ma J S. Development of second generational porphyrin-based photosensitizers. *Photogra Sci Photochem (in Chinese)*, 2002, 20(2): 131–148
- 51 Hirakaa K, Kanehisaa M, Tamaia M, Asayamaa S, Nagaokaa S, Oyaizuc K, Yuasab M, Kawakami H. Preparation of pH-sensitive liposomes retaining SOD mimic and their anticancer effect. *Colloids Surf B: Biointerfaces*, 2008, 67(1): 54–58
- 52 Asayama S, Kasugai N, Kubota S, Nagaoka S, Kawakami H. Superoxide dismutase as a target enzyme for Fe-porphyrin-induced cell death. *J Inorg Biochem*, 2007, 101(2): 261–266
- 53 Wang Y, He Q Y, Che C M, Tsao S W, Sun R W Y, Chiu J F. Modulation of gold(III) porphyrin 1a-induced apoptosis by mitogen-activated protein kinase signaling pathways. *Biochem Pharm*, 2008, 75(6): 1282–1291
- 54 Wang Y, He Q Y, Raymond Sun W Y, Che C M, Chiu J F. Cellular pharmacological properties of gold(III) porphyrin 1a, a potential anticancer drug lead. *Eur J Pharmacol*, 2007, 554(2-3): 113–122
- 55 Li DH, Diao J L, Yu K G, Zhou C H. Synthesis and anticancer activities of porphyrin induced anticancer drugs. *Chin Chem Lett*, 2007, 18(11): 1331–1334
- 56 Zhuang Y Y, Zhou C H, Wang Y F, Li D H. Advances of nitrogen mustard compounds in antitumor agents. *Chin Pharm J (in Chinese)*, 2008, 44(17): 1281–1287
- 57 Cai J L, Li S, Zhou C H, Gan L L. Advances in imidazoles as anti-tumor agents. *Chin J New Drugs (in Chinese)*, 2009, 18(7): in press
- 58 Yu K G, Liu J C, Zhou C H, Diao J L, Xu T, Li D H. Study on synthesis of porphyrin-nitroimidazole derivatives and their radiosensitization. *Chin J Med Chem (in Chinese)*, 2008, 18(6): 414–419
- 59 Meng J P, Geng R X, Zhou C H, Gan L L. Advances in the research of benzimidazole compounds. *Chin J New Drugs (in Chinese)*, 2009, 18(8): in press
- 60 Mi J L, Wu J, Zhou C H. Advances in the triazoles as anticancer drugs. *West China J Pharm Sci (in Chinese)*, 2008, 23(1): 84–86
- 61 Bai X, Zhou C H, Mi J L. Research and application of triazoles. *Chem Res Appl (in Chinese)*, 2007, 19(7): 721–729
- 62 Zhou C H, Hassner A. Synthesis and anticancer activity of novel chiral glucose derived bis-imidazoles and their analogs. *Carbohydrates Res*, 2001, 333(4): 313–326
- 63 Huang J, Zhou C H. Progress in nitroimidazoles as medicinal agents. *Chin Clin J Traditional Chin West Med (in Chinese)*, 2007, 7(7): 538–542
- 64 Jamieson E R, Lippard S J. Structure, recognition, and processing of cisplatin-DNA adducts. *Chem Rev*, 1999, 99(9): 2467–2498
- 65 Qu P, He H, Liu X H. Antitumor activity and mechanism of rhodium complexes. *Prog Chem (in Chinese)*, 2006, 18(12): 1646–1651
- 66 Liu W P, Zhang Y L, Sun R L. Future development of platinum anticancer drugs. *Precious Met (in Chinese)*, 2005, 26(1): 47–52
- 67 Bagrova S G. Results of phase I clinical trials of cycloplatin in refractory solid tumors. *Vopr Onkol*, 2001, 47(6): 752–756
- 68 Raynaud F I, Boxall F E, Goddard P M, Valenti M, Jones M, Murrer B A, Abrams M, Kelland L R. *cis*-Amminedichloro(2-methylpyridine) platinum(II) (AMD473), a novel sterically hindered platinum complex: *In vivo* activity, toxicology, and pharmacokinetics in mice. *Clin Cancer Res*, 1997, 3(11): 2063–2074
- 69 Brabec V, Kašpárková J, Vrána O, Nováková O, Cox J W, Qu Y, Farrell N. DNA modification by a novel bifunctional trinuclear platinum antitumor agent. *Biochem*, 1999, 38(21): 6781–6790
- 70 Ulrich S, Milod S. DE Patent, 19 824 653, 1999-08-26
- 71 Bjelosevic H, Spéjel C, Snygg Å S, Gorton L, Elmroth S K C,

- Persson T. Synthesis and structural characterisation of novel platinum-based drug candidates with extended functionality by incorporation of bis(diphenylphosphino)ferrocene units as metal chelators. *Tetrahedron*, 2006, 62(18): 4519–4527
- 72 Gupta A, Mandal S K, Leblanc V, Descocaux C, Asselin É, Bérubé G. Synthesis and cytotoxic activity of benzopyran-based platinum(II) complexes. *Bioorg Med Chem Lett*, 2008, 18(14): 3982–3987
- 73 Descôteaux C, Provencher-Mandeville J, Mathieu I, Perron V, Mandal S K, Asselin É, Bérubé G. Synthesis of 17 β -estradiol platinum(II) complexes: biological evaluation on breast cancer cell lines. *Bioorg Med Chem Lett*, 2003, 13(22): 3927–3931
- 74 Gagnon V, St-Germain M É, Descôteaux C, Provencher-Mandeville J, Parent S, Mandal S K, Asselin E, Bérubé G. Biological evaluation of novel estrogen-platinum(II) hybrid molecules on uterine and ovarian cancers—Molecular modeling studies. *Bioorg Med Chem Lett*, 2004, 14(23): 5919–5924
- 75 Perron V, Rabouin D, Asselin É, Parent S, Gaudreault R C, Bérubé G. Synthesis of 17 β -estradiol-linked platinum(II) complexes and their cytotoxic activity on estrogen-dependent and -independent breast tumor cells. *Bioorg Chem*, 2005, 33(1): 1–15
- 76 Berube G. US Patent, 7 153 844, 2004-01-08
- 77 N'soukpoé-Kossi C N, Descocaux C, Asselin E, Tajmir-Riahi H A, Bérubé G. DNA Interaction with novel antitumor estradiol-platinum(II) hybrid molecule: A comparative study with cisplatin drug. *DNA Cell Biol*, 2008, 27(2): 101–107
- 78 Hall M D, Mellor H R, Callaghan R, Hambley T W. Basis for design and development of platinum(IV) anticancer complexes. *J Med Chem*, 2007, 50(15): 3403–3411
- 79 Kašpárková J, Nováková O, Vrána O, Intini F, Natile G, Brabec V. Molecular aspects of antitumor effects of a new platinum(IV) drug. *Mol Pharmacol*, 2006, 70(50): 1708–1719
- 80 Bednarski P J, Grünert R, Zielzki M, Wellner A, Mackay F S, Sadler P J. Light-activated destruction of cancer cell nuclei by platinum diazide complexes. *Chem Biol*, 2006, 13(1): 61–67
- 81 Mackay F S, Woods J A, Moseley H, Ferguson J, Dawson A, Parsons S, Sadler P J. A photoactivated trans-diammine platinum complex as cytotoxic as cisplatin. *Chemistry*, 2006, 12(11): 3155–3161
- 82 Chen Q, Huang Z, Chen H, Shapiro H, Beckers J, Hetzel F W. Improvement of tumor response by manipulation of tumor oxygenation during photodynamic therapy. *Photochem Photobiol*, 2002, 76(2): 197–203
- 83 Kwon Y E, Whang K J, Park Y J, Kim K H. Synthesis, characterization and antitumor activity of novel octahedral Pt(IV) complexes. *Bioorg Med Chem*, 2003, 11(8): 1669–1676
- 84 Zhang C X, Lippard S J. New metal complexes as potential therapeutics. *Curr Opin Chem Biol*, 2003, 7(4): 481–489
- 85 Enzo A, Angela B, Elisabetta I. International conference on DNA conformation, modification and recognition in biomedicine. Brno Czech Republic, 2000, 1: 72–73
- 86 Chai X H, Wang F L, Huang J, Zhang J. Progress in investigation of metallodrugs. *Chem Agen (in Chinese)*, 2008, 30(2): 99–104
- 87 Clarke M J. Ruthenium metallopharmaceuticals. *Coord Chem Rev*, 2003, 236(1-2): 209–233
- 88 Vargiu A V, Robertazzi A, Magistrato A, Ruggerone P, Carloni P. The hydrolysis mechanism of the anticancer ruthenium drugs NAMI-A and ICR investigated by DFT-PCM calculations. *J Phys Chem B*, 2008, 112(14): 4401–4409
- 89 Sanna B, Debidda M, Pintus G, Tadolini B, Posadino A M, Bennardini F, Sava G, Ventura C. The anti-metastatic agent imidazolium trans-imidazoledimethylsulfoxidetetrachlororuthenate induces endothelial cell apoptosis by inhibiting the mitogen-activated protein kinase/extracellular signal-regulated kinase signaling pathway. *Arch Biochem Biophys*, 2002, 403(2): 209–218
- 90 Gopal Y N V, Konuru N, Kondapi A K. Topoisomerase II antagonism and anticancer activity of coordinated derivatives of [RuCl₂(C₆H₆)(dms)]. *Arch Biochem Biophys*, 2002, 401(1): 53–62
- 91 Cebrián-Losantos B, Reisner E, Kowol C R, Roller A, Shova S, Arion V B, Keppler B K. Synthesis and reactivity of the aquation product of the antitumor complex trans-[Ru^{III}Cl₂(indazole)₂]⁻. *Inorg Chem*, 2008, 47(14): 6513–6523
- 92 Korfel A, Scheulen M E, Schmoll H J, Gründel O, Harstrick A, Knoche M, Fels L M, Skorzec M, Bach F, Baumgart J, Safi G, Seeber S, Thiel E, Berdel W E. Phase I clinical and pharmacokinetic study of titanocene dichloride in adults with advanced solid tumors. *Clin Cancer Res*, 1998, 4(11): 2701–2708
- 93 Lum B L, Srivanas S, Beck J T, Vesole D, Largey M, Valone F H, Sayre P H. Phase I trial of oral gallium maltolate in refractory malignancies. *Proc. Am Soc Clin Oncol*, 2003, 22: 943
- 94 Foteeva L S, Stolyarova N V, Timerbaev A R, Keppler B K. Capillary electrophoretic assay for the stability of tris(8-quinolinolato) gallium(III) in tablet formulations. *J Pharm Biomed Anal*, 2008, 48(1): 218–222
- 95 Heffeter P, Jungwirth U, Jakupec M, Hartinger C, Galanski M, Elbling L, Micksche M, Keppler B, Berger W. Resistance against novel anticancer metal compounds: Difference and similarities. *Drug Resistance Updates*, 2008, 11(1-2): 1–16
- 96 Rieter W J, Pott K M, Taylor K M L, Lin W. Nanoscale coordination polymers for platinum-based anticancer drug delivery. *J Am Chem Soc*, 2008, 130(35): 11584–11585
- 97 Moses M A, Brem H, Langer R. Advancing the field of drug delivery: taking aim at cancer. *Cancer Cell*, 2003, 4(5): 337–341
- 98 Vail D M, Amantea M A, Colbern G T, Martin F J, Hilger R A, Working P K. Pegylated liposomal doxorubicin: proof of principle using preclinical animal models and pharmacokinetic studies. *Semin Oncol*, 2004, 31(13): 16–35
- 99 Panyam J, Labhasetwar V. Biodegradable nanoparticles for drug and gene delivery to cells and tissue. *Adv Drug Delivery Rev*, 2003, 55(3): 329–347
- 100 Ferrari, M. Cancer nanotechnology: opportunities and challenges. *Nat Rev Cancer*, 2005, 5(3): 161–171
- 101 Fonseca C, Simões S, Gaspar R. Paclitaxel-loaded PLGA nanoparticles: Preparation, physicochemical characterization and *in vitro* antitumoral activity. *J Controlled Release*, 2002, 83(2): 273–286
- 102 Brannon-Peppas L, Blanchette J O. Nanoparticle and targeted systems for cancer therapy. *Adv Drug Delivery Rev*, 2004, 56(11): 1649–1659
- 103 Yoo H S, Park T G. *In vitro* and *in vivo* anti-tumor activities of nanoparticles based on doxorubicin-PLGA conjugates. *J Controlled*

- Release, 2000, 68(3): 419–431
- 104 Mitra S, Gaur U, Ghosh P C, Maitra A N. Tumour targeted delivery of encapsulated dextran-doxorubicin conjugate using chitosan nanoparticles as carrier. *J Controlled Release*, 2001, 74(1-3): 317–323
- 105 Savić R, Luo L, Eisenberg A, Maysinger D. Micell nanocontainers distribute to defined cytoplasmic organelles. *Science*, 2003, 300(5619): 615–618
- 106 Hu Y Q, Kim M S, Kim B S, Lee D S. Synthesis and pH-dependent micellization of 2-(diisopropylamino)ethyl methacrylate based amphiphilic diblock copolymers via RAFT polymerization. *Polymer*, 2007, 48(12): 3437–3443
- 107 Sutton D, Nasongkla N, Blanco E, Gao J. Functionalized micellar systems for cancer targeted drug delivery. *Pharm Res*, 2007, 24(6): 1029–1046
- 108 Yang X Q, Chen Y H, Yuan R X, Chen G H, Blanco E, Gao J M, Shuai X T. Folate-encoded and Fe₃O₄-loaded polymeric micelles for dual targeting of cancer cells. *Polymer*, 2008, 49(16): 3477–3485
- 109 Xu P S, Kirk E A V, Murdoch W J, Zhan Y H, Isaak D D, Radosz M, Shen Y Q. Anticancer efficacies of cisplatin releasing pH-responsive nanoparticles. *Biomacromolecules*, 2006, 7(3): 829–835
- 110 Feazell R P, Nakayama-Ratchford N, Dai H J, Lippard S J. Soluble single-walled carbon nanotubes as longboat delivery systems for platinum(IV) anticancer drug design. *J Am Chem Soc*, 2007, 129(27): 8438–8439
- 111 Shi G Y. Progress in the study of non-steroidal anti-inflammatory drugs. *Chin J New Drugs (in Chinese)*, 1999, 8(9): 699–701
- 112 Weder J E, Dillon C T, Hambley T W, Kennedy B J, Lay P A, Biffin J R, Regtop H L, Davies N M. Copper complexes of non-steroidal anti-inflammatory drugs: an opportunity yet to be realized. *Coord Chem Rev*, 2002, 232(1-2): 95–126
- 113 Moya-Hernández M R, Mederos A, Domínguez S, Orlandini A, Ghilardi C A, Ceconi F, González-Vergara E, Rojas-Hernández A. Speciation study of the anti-inflammatory drug tenoxicam (Htenox) with Cu(II): X-ray crystal structure of [Cu(tenox)₂(py)₂·EtOH]. *J Inorg Biochem*, 2003, 95(2-3): 131–140
- 114 Morgan Y R, Turner P, Kennedy B J, Hambley T W, Lay P A, Biffin J R, Regtop H L, Warwick B. Preparation and characterization of dinuclear copper-indomethacin anti-inflammatory drugs. *Inorg Chim Acta*, 2001, 324(1-2): 150–161
- 115 Trinchero A, Bonora S, Tinti A, Fini G. Spectroscopic behavior of copper complexes of nonsteroidal anti-inflammatory drugs. *Biopolymers*, 2004, 74(1-2): 120–124
- 116 Weder J E, Hambley T W, Kennedy B J, Lay P A, MacLachlan D, Bramley R, Delfs C D, Murray K S, Moubaraki B, Warwick B, Biffin J R, Regtop H L. Anti-inflammatory dinuclear copper(II) complexes with indomethacin. Synthesis, magnetism and EPR spectroscopy. crystal structure of the *N,N*-dimethylformamide adduct. *Inorg Chem*, 1999, 38(8): 1736–1744
- 117 Chaviara A T, Christidis P C, Papageorgiou A, Chrysogelou E, Hadjipavlou-Litina D J, Bolos C A. *In vivo* anticancer, anti-inflammatory, and toxicity studies of mixed-ligand Cu(II) complexes of dien and its Schiff dibases with heterocyclic aldehydes and 2-amino-2-thiazoline. crystal structure of [Cu(dien)(Br)(2a-2tzn)] (Br)(H₂O). *J Inorg Biochem*, 2005, 99(11): 2102–2109
- 118 Zvimba J N, Jackson G E. Copper chelating anti-inflammatory agents; *N*¹-(2-aminoethyl)-*N*²-(pyridin-2-ylmethyl)-ethane-1,2-diamine and *N*-(2-(2-aminoethylamino)ethyl)picolinamide: An *in vitro* and *in vivo* study. *J Inorg Biochem*, 2007, 101(1): 148–158
- 119 Zhou Q D, Hambley T W, Kennedy B J, Lay P A, Turner P, Warwick B, Biffin J R, Regtop H L. Syntheses and characterization of anti-inflammatory dinuclear and mononuclear zinc indomethacin complexes. crystal structures of [Zn₂(Indomethacin)₄(L)₂] (L = *N,N*-dimethylacetamide, pyridine, 1-methyl-2-pyrrolidinone) and [Zn(Indomethacin)₂(L₁)₂] (L₁ = ethanol, methanol). *Inorg Chem*, 2000, 39(17): 3742–3748
- 120 Zhou Q D, Hambley T W, Kennedy B J, Lay P A. XAFS studies of anti-inflammatory dinuclear and mononuclear Zn(II) complexes of indomethacin. *Inorg Chem*, 2003, 42(25): 8557–8566
- 121 Jain S, Jain N K, Pitre K S. Electrochemical analysis and analgesic behavior of Zn(II)-baclofen complex. *J Pharm Biomed Anal*, 2003, 31(5): 1035–1039
- 122 Shaheen F, Badshah A, Gielen M, Gieck C, Jamil M, Vos D D. Synthesis, characterization, *in vitro* cytotoxicity and anti-inflammatory activity of palladium(II) complexes with tertiary phosphines and heterocyclic thiolates: Crystal structure of [PdC₂₈H₁₉N₈PS₂]. *J Inorg Biochem*, 2008, 693(6): 1117–1126
- 123 Kovala-Demertzi D. Recent advances on non-steroidal anti-inflammatory drugs, NSAIDs: Organotin complexes of NSAIDs. *J Organomet Chem*, 2006, 691(8): 1767–1774
- 124 Ribeiro G, Benadiba M, Colquhoun A, Silva D D O. Diruthenium(II, III) complexes of ibuprofen, aspirin, naproxen and indomethacin non-steroidal anti-inflammatory drugs: Synthesis, characterization and their effects on tumor-cell proliferation. *Polyhedron*, 2008, 27(3): 1131–1137
- 125 Ashfaq M, Khan M I, Baloch M K, Malik A. Biologically potent organotin(IV) complexes of 2-maleimidoacetic acid. *J Organomet Chem*, 2004, 689(1): 238–245
- 126 Ashfaq M. Synthesis of novel bioactive phthalimido-4-methyl pentanoateorganotin(IV) esters with spectroscopic investigation. *J Organomet Chem*, 2006, 691(8): 1803–1808
- 127 Partyka M, Au B, Evans C. Cyclodextrins as phototoxicity inhibitors in drug formulations: studies on model systems involving naproxen and beta-cyclodextrin. *J Photoch Photobio A*, 2001, 140(1): 67–74
- 128 Yano H, Hirayama F, Kamada M, Arima H, Uekama K. Colon-specific delivery of prednisolone-appended α -cyclodextrin conjugate: Alleviation of systemic side effect after oral administration. *J Controlled Release*, 2002, 79(1-3): 103–112
- 129 Zhang Y, Wang J Z, Wu Y J. Progress of pharmaceutical studies on superoxide dismutase. *Acta Pharm Sinica (in Chinese)*, 2003, 38(1): 71–74
- 130 Valdivia A, Pérez Y, Cao R, Baños M, García A, Villalonga R. Bionzymatic supramolecular complex of catalase modified with cyclodextrin-branched carboxymethylcellulose and superoxide dismutase: Stability and anti-inflammatory properties. *Macromol Biosci*, 2007, 7(1): 70–75
- 131 Wen X H, Liu Z Y, Zhu T Q, Zhu M Q, Jiang K Z, Huang Q Q. Evidence for the 2:1 molecular recognition and inclusion behaviour between β - and γ -cyclodextrins and cinchonine. *Bioorg Chem*, 2004,

- 32(4): 223–233
- 132 Wong J W, Yuen K H. Improved oral bioavailability of artemisinin through inclusion complexation with β - and γ -cyclodextrins. *Int J Pharm*, 2001, 227(1-2): 177–185
- 133 Dive D, Biot C. Ferrocene conjugates of chloroquine and other antimalarials: The development of ferroquine, a new antimalarial. *Chem Med Chem*, 2008, 3(3): 383–391
- 134 Chibale K, Moss J R, Blackie M, Schalkwyk D V, Smith P J. New amine and urea analogs of ferrochloroquine: synthesis, antimalarial activity *in vitro* and electrochemical studies. *Tetrahedron Lett*, 2000, 41(32): 6231–6235
- 135 Biot C, Dessolin J, Ricard I, Dive D. Easily synthesized antimalarial ferrocene triazacyclononane quinoline conjugates. *J Organomet Chem*, 2004, 689(25): 4678–4682
- 136 Biot C, Delhaes L, Maciejewski L A, Mortuaire M, Camus D, Dive D, Brocard J S. Synthetic ferrocenic mefloquine and quinine analogues as potential antimalarial agents. *Eur J Med Chem*, 2000, 35(7-8): 707–714
- 137 Biot C, Pradines B, Sergeant M H, Gut J, Rosenthal P J, Chibale K. Design, synthesis, and antimalarial activity of structural chimeras of thiosemicarbazone and ferroquine analogues. *Bioorg Med Chem Lett*, 2007, 17(23): 6434–6438
- 138 Guillo J, Moreau S, Mouray E, Sinou V, Forfar I, Fabre S B, Desplat V, Millet P, Parzy D, Jarry C, Grellier P. New ferrocenic pyrrolo[1,2-a]quinoxaline derivatives: Synthesis, and *in vitro* antimalarial activity. *Bioorg Med Chem*, 2008, 16(20): 9133–9144
- 139 Gokhale N H, Padhye S B, Billington D C, Rathbone D L, Croft S L, Kendrick H D, Anson C E, Powell A K. Synthesis and characterization of copper(II) complexes of pyridine-2-carboxamido-drazones as potent antimalarial agents. *Inorg Chim Acta*, 2003, 349: 23–29
- 140 Gokhale N H, Padhye S B, Croft S L, Kendrick H D, Davies W, Anson C E, Powell A K. Transition metal complexes of buparvaquone as potent new antimalarial agents I. Synthesis, X-ray crystal-structures, electrochemistry and antimalarial activity against *Plasmodium falciparum*. *J Inorg Biochem*, 2003, 95(4): 249–258
- 141 Gokhale N H, Shirisha K, Padhye S B, Croft S L, Kendrick H D, Mckee V. Metalloantimalarials: Synthesis, X-ray crystal structure of potent antimalarial copper(II) complex of arylazo-4-hydroxy-1,2-naphthoquinone. *Bioorg Med Chem Lett*, 2006, 16(2): 430–432
- 142 Dadachova E. Preparation of $^{198}\text{Au}(\text{I})$ -labelled gold-chloroquine complex $[\text{}^{198}\text{Au}(\text{PPh}_3)(\text{CQ})]\text{PF}_6$ as a potential antimalarial agent. *J Labelled Cpd Radiopharm*, 1999, 42(3): 287–292
- 143 Navarro M, Pekarar S, Pérez H A. Synthesis, characterization and antimalarial activity of new iridium-chloroquine complexes. *Polyhedron*, 2007, 26(12): 2420–2424
- 144 Yuan Y, Zhou C H, Liu Q, Song C Z. New synthetic antibacterial agents. *Chin J New Drugs (in Chinese)*, 2007, 16(5): 343–350
- 145 Zhang Y. Progress in research of quinolone antibacterials. *Chin J New Drugs*, 2006, 15(16): 1344–1356
- 146 Mitscher L A. Bacterial topoisomerase inhibitors: Quinolone and pyridone antibacterial. *Chem Rev*, 2005, 105(2): 559–592
- 147 Psomas G, Tarushi A, Efthimiadou E K, Sanakis Y, Raptopoulou C P, Katsaros N. Synthesis, structure and biological activity of copper(II) complexes with oxolinic acid. *J Inorg Biochem*, 2006, 100(11): 1764–1773
- 148 Tarushi A, Efthimiadou E K, Christofis P, Psomas G. Neutral mononuclear dioxomolybdenum(VI) and dioxouranium(VI) complexes of oxolinic acid: Characterization and biological evaluation. *Inorg Chim Acta*, 2007, 360(14): 3978–3986
- 149 Efthimiadou E K, Sanakis Y, Katsaros N, Karaliota A, Psomas G. Transition metal complexes with the quinolone antibacterial agent pipemidic acid: Synthesis, characterization and biological activity. *Polyhedron*, 2007, 26(5): 1148–1158
- 150 Li Y X, Chen Z F, Xiong R G, Xue Z, Ju H X, You X Z. A mononuclear complex of norfloxacin with silver(I) and its properties. *Inorg Chem Commun*, 2003, 6(7): 819–822
- 151 Refat M S. Synthesis and characterization of norfloxacin-transition metal complexes (group 11, IB): spectroscopic, thermal, kinetic measurements and biological activity. *Spectrochim Acta Part A*, 2007, 68(5): 1393–1405
- 152 Efthimiadou E K, Psomas G, Sanakis Y, Katsaros N, Karaliota A. Metal complexes with the quinolone antibacterial agent *N*-propyl-norfloxacin: Synthesis, structure and bioactivity. *J Inorg Biochem*, 2007, 101(3): 525–535
- 153 Efthimiadou E K, Thomadaki H, Sanakis Y, Raptopoulou C P, Katsaros N, Scorilas A, Karaliota A, Psomas G. Structure and biological properties of the copper(II) complex with the quinolone antibacterial drug *N*-propyl-norfloxacin and 2,20-bipyridine. *J Inorg Biochem*, 2007, 101(1): 64–73
- 154 Efthimiadou E K, Katsaros N, Karaliota A, Psomas G. Mononuclear copper(II) complexes with quinolones and nitrogen-donor heterocyclic ligands: synthesis, characterization, biological activity and interaction with DNA. *Inorg Chim Acta*, 2007, 360(15): 4093–4102
- 155 Turel I, Golič L, Bukovec P, Gubina M. Antibacterial tests of Bismuth(III)-quinolone (ciprofloxacin, cf) compounds against *Helicobacter pylori* and some other bacteria. Crystal structure of $(\text{cfH}_2)_2[\text{Bi}_2\text{Cl}_{10}]\cdot 4\text{H}_2\text{O}$. *J Inorg Biochem*, 1998, 71(1): 53–60
- 156 López-Gresa M P, Ortiz R, Perelló L, Latorre J, Liu-González M, García-granda S, Pérez-Priede M, Cantón E. Interactions of metal ions with two quinolone antimicrobial agents (cinoxacin and ciprofloxacin) spectroscopic and X-ray structural characterization. *Antibacterial studies*. *J Inorg Biochem*, 2002, 92(1): 65–74
- 157 Efthimiadou E K, Sanakis Y, Katsaros M, Raptopoulou C P, Karaliota A, Katsaros N, Psomas G. Neutral and cationic mononuclear copper(II) complexes with enrofloxacin: structure and biological activity. *J Inorg Biochem*, 2006, 100(8): 1378–1388
- 158 Efthimiadou E K, Katsaros M E, Karaliota A, Psomas G. Copper(II) complexes with sparfloxacin and nitrogen-donor heterocyclic ligands: Structure-activity relationship. *J Inorg Biochem*, 2008, 102(4): 910–920
- 159 Mondelli M, Bruné V, Borthagaray G, Ellena J, Nascimento O R, Leite C Q, Batista A A, Torre M H. New Ni(II)-sulfonamide complexes: synthesis, structural characterization and antibacterial properties. X-ray diffraction of $[\text{Ni}(\text{sulfisoxazole})_2(\text{H}_2\text{O})_4]\cdot 2\text{H}_2\text{O}$ and $[\text{Ni}(\text{sulfapyridine})_2]$. *J Inorg Biochem*, 2008, 102(2): 285–292
- 160 Marques L L, Oliveira G M, Lang E S, Campos M M A, Gris L R S. New gold(I) and silver(I) complexes of sulfamethoxazole: synthesis, X-ray structural characterization and microbiological activities

- of triphenylphosphine(sulfamethoxazolato-N2)gold(I) and (sulfamethoxazolato)silver(I). *Inorg Chem Commun*, 2007, 10(9): 1083–1087
- 161 Chohan Z H, Shaikh A U, Naseer M M. Metal-based isatin-bearing sulfonamides: Their synthesis, characterization and biological properties. *Appl Organometal Chem*, 2006, 20(11): 729–739
- 162 Sharaby C M. Synthesis, spectroscopic, thermal and antimicrobial studies of some novel metal complexes of Schiff base derived from [N1-(4-methoxy-1,2,5-thiadiazol-3-yl)sulfanilamide] and 2-thiophene carboxaldehyde. *Spectrochim Acta Part A*, 2007, 66(4-5): 1271–1278
- 163 Huang J, Cui Z N, Li Y, Yang X L. Bioactivities of copper complexes with schiff bases. *Chin J Org Chem (in Chinese)*, 2008, 28(4): 598–604
- 164 Kumar K N, Ramesh R. Synthesis, characterization, redox property and biological activity of Ru(II) carbonyl complexes containing O,N-donor ligands and heterocyclic bases. *Spectrochim Acta Part A*, 2004, 60(12): 2913–2918
- 165 Venkatachalam G, Ramesh R. Catalytic and biological activities of Ru(III) mixed ligand complexes containing N, O donor of 2-hydroxy-1-naphthylideneimines. *Spectrochim Acta Part A*, 2005, 61(9): 2081–2087
- 166 Daniel V P, Murukan B, Kumari B S, Mohanan K. Synthesis, spectroscopic characterization, electrochemical behaviour, reactivity and antibacterial activity of some transition metal complexes with 2-(N-salicylideneamino)-3-carboxyethyl-4,5-dimethylthiophene. *Spectrochim Acta Part A*, 2008, 70(2): 403–410
- 167 Abd-Elzaher M M. Synthesis, characterization, and antimicrobial activity of cobalt(II), nickel(II), copper(II) and zinc(II) complexes with ferrocenyl Schiff bases containing a phenol moiety. *Appl Organometal Chem*, 2004, 18(4): 149–155
- 168 Singh B K, Jetley U K, Sharma R K, Garg B S. Synthesis, characterization and biological activity of complexes of 2-hydroxy-3,5-dimethylaceto-phenoneoxime(HDMAOX) with copper(II), cobalt(II), nickel(II) and palladium(II). *Spectrochim Acta Part A*, 2007, 68(1): 63–73
- 169 Prabhakaran R, Geetha A, Thilagavathi M, Karvembu R, Krishnan V, Bertagnolli H, Natarajan K. Synthesis, characterization, EXAFS investigation and antibacterial activities of new ruthenium(III) complexes containing tetradentate Schiff base. *J Inorg Biochem*, 2004, 98(12): 2131–2140
- 170 Bagihalli G B, Avaji P G, Patil S A, Badami P S. Synthesis, spectral characterization, in vitro antibacterial, antifungal and cytotoxic activities of Co(II), Ni(II) and Cu(II) complexes with 1,2,4-triazole Schiff bases. *Eur J Med Chem*, 2008, 43(12): 2639–2649
- 171 Singh K, Barwa M S, Tyagi P. Synthesis, characterization and biological studies of Co(II), Ni(II), Cu(II) and Zn(II) complexes with bidentate Schiff bases derived by heterocyclic ketone. *Eur J Med Chem*, 2006, 41(1): 147–153
- 172 Singh K, Barwa M S, Tyagi P. Synthesis and characterization of cobalt(II), nickel(II), copper(II) and zinc(II) complexes with Schiff base derived from 4-amino-3-mercapto-6-methyl-5-oxo-1,2,4-triazine. *Eur J Med Chem*, 2007, 42(3): 394–402
- 173 Kurtaran R, Yildirim L T, Azaz A D, Namli H, Atakol O. Synthesis, characterization, crystal structure and biological activity of a novel heterotetranuclear complex: $[\text{NiLPb}(\text{SCN})_2(\text{DMF})(\text{H}_2\text{O})]_2$, bis- $\{[\mu\text{-N, N'}$ -bis(salicylidene)-1,3-propanediaminato-aqua-nickel(II)](thiocyanato) (l-thiocyanato) (l-N,N-dimethylformamide)lead(II)] $\}$. *J Inorg Biochem*, 2005, 99(10): 1937–1944
- 174 Yildirim L T, Kurtaran R, Namli H, Azaz A D, Atakol O. Synthesis, crystal structure and biological activity of two new heterotrinnuclear thiocyanato bridged Cu(II)-Hg(II)-Cu(II) complexes. *Polyhedron*, 2007, 26(15): 4187–4194
- 175 Lv J, Liu T T, Cai S L, Wang X, Liu L, Wang Y M. Synthesis, structure and biological activity of cobalt(II) and copper(II) complexes of valine-derived schiff bases. *J Inorg Biochem*, 2006, 100(11): 1888–1896
- 176 Chohan Z H, Supuran C T. Organometallic compounds with biologically active molecules: in vitro antibacterial and antifungal activity of some 1,1'-(dicarbohydrazone) ferrocenes and their cobalt(II), copper(II), nickel(II) and zinc(II) complexes. *Appl Organometal Chem*, 2005, 19(12): 1207–1214
- 177 Chohan Z H, Khan K M, Supuran C T. Synthesis of antibacterial and antifungal cobalt(II), copper(II), nickel(II) and zinc(II) complexes with bis-(1,1'-disubstituted ferrocenyl)thiocarbohydrazone and bis-(1,1'-disubstituted ferrocenyl)carbohydrazone. *Appl Organometal Chem*, 2004, 18(7): 305–310
- 178 Chitrapriya N, Mahalingam V, Channels L C, Zeller M, Fronczek F R, Natarajan K. Novel Ru(II) oximate complexes with silent oxygen atom: synthesis, chemistry and biological activities. *Inorg Chim Acta*, 2008, 361(9-10): 2841–2850
- 179 El-Behery M, El-Twigry H. Synthesis, magnetic, spectral, and antimicrobial studies of Cu(II), Ni(II) Co(II), Fe(III), and $\text{UO}_2(\text{II})$ complexes of a new Schiff base hydrazone derived from 7-chloro-4-hydrazinoquinoline. *Spectrochimica Acta Part A*, 2007, 66(1): 28–36
- 180 Özmen Ö Ü, Olgun G. Synthesis, characterization and antibacterial activity of new sulfonyl hydrazone derivatives and their nickel(II) complexes. *Spectrochim Acta Part A*, 2008, 70(3): 641–645
- 181 Rodríguez-Argüelles M C, Mosquera-Vázquez S, Tourón-Touceda P, Sanmartín-Matalobos J, Garca-Deibe A M, Belicchi-Ferrari M, Pelosi G, Pelizzi C, Zani F. Complexes of 2-thiophenecarbonyl and isonicotinoyl hydrazones of 3-(N-methyl)isatin. A study of their antimicrobial activity. *J Inorg Biochem*, 2007, 101(1): 138–147
- 182 Mendes I C, Moreira J P, Mangrich A S, Balena S P, Rodrigues B L, Beraldo H. Coordination to copper(II) strongly enhances the *in vitro* antimicrobial activity of pyridine-derived N(4)-tolyl thiosemicarbazones. *Polyhedron*, 2007, 26(13): 3263–3270
- 183 Nomiya K, Sekino K, Ishikawa M, Honda A, Yokoyama M, Kasuga N C, Yokoyama H, Nakano S, Onodera K. Syntheses, crystal structures and antimicrobial activities of monomeric 8-coordinate, and dimeric and monomeric 7-coordinate bismuth(III) complexes with tridentate and pentadentate thiosemicarbazones and pentadentate semicarbazone ligands. *J Inorg Biochem*, 2004, 98(4): 601–615
- 184 Kannan S, Sivagamasundari M, Ramesh R, Liu Y. Ruthenium(II) carbonyl complexes of dehydroacetic acid thiosemicarbazone: synthesis, structure, light emission and biological activity. *J Organomet Chem*, 2008, 693(13): 2251–2257

- 185 John R P, Sreekanth A, Rajakannan V, Ajith T A, Kurup M R P. New copper(II) complexes of 2-hydroxyacetophenone *N*(4)-substituted thiosemicarbazones and polypyridyl co-ligands: Structural, electrochemical and antimicrobial studies. *Polyhedron*, 2004, 23(16): 2549–2559
- 186 Khan S A, Yusuf M. Synthesis, spectral studies and *in vitro* antibacterial activity of steroidal thiosemicarbazone and their palladium (Pd(II)) complexes. *Eur J Med Chem*, 2009, doi:10.1016/j.ejmech
- 187 Rodríguez-Argüelles M C, López-Silva E C, Sanmartín J, Pelagatti P, Zani F. Copper complexes of imidazole-2-, pyrrole-2- and indol-3-carbaldehyde thiosemicarbazones: Inhibitory activity against fungi and bacteria. *J Inorg Biochem*, 2005, 99(11): 2231–2239
- 188 Bacchi A, Carcelli M, Pelagatti P, Pelizzi G, Rodríguez-Argüelles M C, Rogolino D, Solinas C, Zani F. Antimicrobial and mutagenic properties of organotin(IV) complexes with isatin and *N*-alkylisatin bisthiocarbonohydrazones. *J Inorg Biochem*, 2005, 99(2): 397–408
- 189 Li Q X, Tang H A, Li Y Z, Wang M, Wang L F, Xia C G. Synthesis, characterization, and antibacterial activity of novel Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) complexes with vitamin K3-thiosemicarbazone. *J Inorg Biochem*, 2000, 78(2): 167–174
- 190 Zhang Y, Xiao X, Deng P X, Huang Q M, Pan Z Q, Chen Z P. Synthesis and antibacterial activity of β -substituted metalporphyrins of 1-naphthol. *J Wuhan Inst Tech (in Chinese)*, 2008, 30(4): 8–11
- 191 Sreedaran S, Bharathi K S, Rahiman A K, Rajesh K, Nirmala G, Jagadish L, Kaviyaran V, Narayanan V. Synthesis, electrochemical, catalytic and antimicrobial activities of novel unsymmetrical macrocyclic dicompartmental binuclear nickel(II) complexes. *Polyhedron*, 2008, 27(7): 1867–1874
- 192 Singh D P, Kumar R, Singh J. Synthesis and spectroscopic studies of biologically active compounds derived from oxalylidihydrazide and benzil, and their Cr(III), Fe(III) and Mn(III) complexes. *Eur J Med Chem*, 2009, doi:10.1016/j.ejmech.2008.03.007 (in press)
- 193 Reddy P M, Prasad A V S S, Shanker K, Ravinder V. Synthesis, spectral studies and antibacterial activity of novel macrocyclic Co(II) compounds. *Spectrochim Acta Part A*, 2007, 68(3): 1000–1006
- 194 Chandra S, Sangeetika. Spectroscopic, redox and biological activities of transition metal complexes with one donor macrocyclic ligand derived from semicarbazide and thiodiglycolic acid. *Spectrochim Acta Part A*, 2004, 60(8): 2153–2162
- 195 Shakir M, Azim Y, Chishti H T N, Parveen S. Synthesis, characterization of complexes of Co(II), Ni(II), Cu(II) and Zn(II) with 12-membered Schiff base tetraazamacrocyclic ligand and the study of their antimicrobial and reducing power. *Spectrochim Acta Part A*, 2006, 65(2): 490–496
- 196 Singh A P, Kaushik N K, Verma A K, Hundal G, Gupta R. Synthesis, structure and biological activity of copper(II) complexes of 4-(2-pyridylmethyl)-1,7-dimethyl-1,4,7-triazonane-2,6-dione and 4-(2-pyridylethyl)-1,7-dimethyl-1,4,7-triazonane-2,6-dione. *Eur J Med Chem*, 2009, doi:10.1016/j.ejmech.2008.07.029 (in press)
- 197 Roy T G, Hazari S K S, Dey B K, Miah H A, Olbrich F, Rehder D. Synthesis and antimicrobial activities of isomers of *N*(4), *N*(II)-dimethyl-3,5,7,7,10,12,14,14-octamethyl-1,4,8,11-tetraazacyclo tetra- adecane and their nickel(II) complexes. *Inorg Chem*, 2007, 46(13): 5372–5380
- 198 Khanmohammadi H, Arabahmadi R, Abnosi M H, Khavasi H R. Synthesis, crystal structure, spectral and biological studies of Cu^{II}-M^{II}(M = Zn and Pb)heterodinuclear complexes of new phenol-based macrocyclic ligands. *Polyhedron*, 2007, 26(17): 4963–4970
- 199 Guerra W, Azevedo E A, Monteiro A R S, Bucciarelli-Rodríguez M, Chartone-Souza E, Nascimento A M A, Fontes A P S, Moyec L L, Pereira-Maia E C, Chartone-Souza E. Synthesis, characterization, and antibacterial activity of three palladium(II) complexes of tetracyclines. *J Inorg Biochem*, 2005, 99(12): 2348–2354
- 200 Refat M S. Complexes of uranyl(II), vanadyl(II) and zirconyl(II) with orotic acid “vitamin B₁₃”: Synthesis, spectroscopic, thermal studies and antibacterial activity. *J Mol Struct*, 2007, 842(1-3): 24–37
- 201 Kumar R S, Arunachalam S. DNA binding and antimicrobial studies of some polyethyleneimine-copper(II) complex samples containing 1,10-phenanthroline and L-theronine as co-ligands. *Polyhedron*, 2007, 26(13): 3255–3262
- 202 Muthukumar M, Viswanathamurthi P, Natarajan K. Synthesis and spectral characterization of 2'-hydroxy chalconate complexes of ruthenium(II) and their catalytic and biological applications. *Spectrochimica Acta Part A*, 2008, 70(5): 1222–1226
- 203 Rodríguez-Fernández E, Manzano J L, Benito J J, Hermosa R, Monte E, Criado J J. Thiourea, triazole and thiaziazine compounds and their metal complexes as antifungal agents. *J Inorg Biochem*, 2005, 99(8): 1558–1572
- 204 Mi J L, Zhou C H, Bai X. Advances in triazole antimicrobial agents. *Chin J Antibiotics (in Chinese)*, 2007, 32(10): 587–593
- 205 Rowan R, Tallon T, Sheahan A M, Curran R, McCann M, Kavanagh K, Devereux M, McKee V. ‘Silver bullets’ in antimicrobial chemotherapy: Synthesis, characterisation and biological screening of some new Ag(I)-containing imidazole complexes. *Polyhedron*, 2006, 25(8): 1771–1778
- 206 McCann M, Coyle B, Briody J, Bass F, O’Gorman N, Devereux M, Kavanagh K, McKee V. Synthesis and antimicrobial activity of (Z)-3-(1*H*-imidazol-1-yl)-2-phenylpropenenitrile and its metal complexes: X-ray crystal structures of the Zn(II) and Ag(I) complexes. *Polyhedron*, 2003, 22(12): 1595–1601
- 207 Mashaly M M, El-Shafiy H F, El-Maraghy S B, Habib H A. Synthesis, properties and thermal studies of oxorhenium(V) complexes with 3-hydrazino-5,6-diphenyl-1,2,4-triazine, benzimidazolethione and 2-hydrazinobenzimidazole mixed ligand complexes, pyrolytical products and biological activity. *Spectrochim Acta Part A*, 2005, 61(8): 1853–1869
- 208 Mastrolorenzo A, Scozzafava A, Supuran C T. Antifungal activity of silver and zinc complexes of sulfadrug derivatives incorporating arylsulfonylureido moieties. *Eur J Pharmaceu Sci*, 2000, 11(2): 99–107
- 209 Bellú S, Hure E, Trapé M, Trossero C, Molina G, Drogo C, Williams P A M, Atria A M, Acevedo J C M, Zacchino S, Sortino M, Campagnoli D, Rizzotto M. Synthesis, structure and antifungal properties of Co(II)-sulfathiazolate complexes. *Polyhedron*, 2005, 24(4): 501–509
- 210 Creaven B S, Egan D A, Karcz D, Kavanagh K, McCann M, Mahon

- M, Noble A, Thati B, Walsh M. Synthesis, characterisation and antimicrobial activity of copper(II) and manganese(II) complexes of coumarin-6,7-dioxyacetic acid (cdoaH₂) and 4-methylcoumarin-6,7-dioxyacetic acid (4-MeccdoaH₂): X-ray crystal structures of [Cu(cdoa-phen)₂] \cdot 8.8H₂O and [Cu(4-Meccdoa)(phen)₂] \cdot 13H₂O (phen=1,10-phenanthroline). *J Inorg Biochem*, 2007, 101(8): 1108–1119
- 211 How F N F, Crouse K A, Tahir M I M, Tarafder M T H, Cowley A R. Synthesis, characterization and biological studies of *S*-benzyl- β -*N*-(benzoyl) dithiocarbamate and its metal complexes. *Polyhedron*, 2008, 27(15): 3325–3329
- 212 Devereux M, McCann M, Shea D O, Kelly R, Egan D, Deegan C, Kavanagh K, McKee V, Finn G. Synthesis, antimicrobial activity and chemotherapeutic potential of inorganic derivatives of 2-(4'-thiazolyl) benzimidazole{thiabendazole}: X-ray crystal structures of [Cu(TBZH)₂Cl]Cl \cdot H₂O \cdot EtOH and TBZH₂NO₃ (TBZH = thiabendazole). *J Inorg Biochem*, 2004, 98(6): 1023–1031
- 213 Hothi H S, Makkar A, Sharma J R, Manrao M R. Synthesis and antifungal potential of Co(II) complexes of 1-(2'-hydroxyphenyl) ethylideneanilines. *Eur J Med Chem*, 2006, 41(2): 253–255
- 214 Singh V P, Katiyar A. Synthesis, spectral characterization and antimicrobial activity of some transition metal(II) complexes with acetone *p*-amino acetophenone benzoylhydrazine. *Pesticide Biochem Physiol*, 2008, 92(1): 8–14
- 215 Jouada E M, Larcherb G, Allain M, Riou A, Boueta G M, Khan M A, Thanh X D. Synthesis, structure and biological activity of nickel(II) complexes of 5-methyl-2-furfural thiosemicarbazone. *J Inorg Biochem*, 2001, 86(2): 565–571
- 216 Ali M A, Mirza A H, Hossain A M S, Nazimuddin M. Synthesis, characterization, antifungal properties and X-ray crystal structures of five- and six-coordinate copper(II) complexes of the 6-methyl-2-formylpyridine ⁴N-dimethylthiosemicarbazone. *Polyhedron*, 2001, 20(9-10): 1045–1052
- 217 Loginova N V, Koval'chuk T V, Zheldakova R A, Chernyavskaya A A, Osipovich N P, Glushonok G K, Polozov G I, Povalishev V N, Sorokin V L, Shadyro O I. Synthesis, characterization and antifungal activity of copper(II) complexes of sterically hindered *o*-diphenol derivatives. *Polyhedron*, 2006, 25(18): 3603–3610
- 218 Loginova N V, Koval'chuk T V, Polozov G I, Osipovich N P, Rytik P G, Kucherov I I, Chernyavskaya A A, Sorokin V L, Shadyro O I. Synthesis, characterization, antifungal and anti-HIV activities of metal(II) complexes of 4,6-di-tert-butyl-3-[(2-hydroxyethyl)thio] benzene-1,2-diol. *Eur J Med Chem*, 2008, 43(7): 1536–1542
- 219 Bottari B, Maccari R, Monforte F, Ottanà R, Rotondo E, Vigorita M G. Isoniazid-related copper(II) and nickel(II) complexes with antimycobacterial *in vitro* activity. Part 9. *Bioorg Med Chem Lett*, 2000, 10(7): 657–660
- 220 Maccari R, Ottanà R, Bottari B, Rotondo E, Vigorita M G. In vitro advanced antimycobacterial screening of cobalt(II) and copper(II) complexes of fluorinated isonicotinoylhydrazones. *Bioorg Med Chem Lett*, 2004, 14(23): 5731–5733
- 221 Bottari B, Maccari R, Monforte F, Ottanà R, Vigorita M G, Bruno G, Nicolò F, Rotondo A, Rotondo E. Nickel(II) 2,6-diacetylpyridine bis(isonicotinoylhydrazonate) and bis(benzoylhydrazonate) complexes: Structure and antimycobacterial evaluation. Part XI. *Bioorg Med Chem*, 2001, 9(8): 2203–2211
- 222 Sandbhor U, Padhye S, Billington D, Rathbone D, Franzblau S, Anson C E, Powell A K. Metal complexes of carboxamidrazone analogs as antitubercular agents I. Synthesis, X-ray crystal-structures, spectroscopic properties and antimycobacterial activity against mycobacterium tuberculosis H37Rv. *J Inorg Biochem*, 2002, 90(3-4): 127–136
- 223 Saha D K, Padhye S, Anson C E, Powell A K. Hydrothermal synthesis, crystal structure, spectroscopy, electrochemistry and antimycobacterial evaluation of the copper(II) ciprofloxacin complex: [Cu(cf)₂(BF₄)₂] \cdot 6H₂O. *Inorg Chem Commun*, 2002, 5(12): 1022–1027
- 224 Saha D K, Sandbhor U, Shirisha K, Padhye S, Deobagkar D, Anson C E, Powell A K. A novel mixed-ligand antimycobacterial dimeric copper complex of ciprofloxacin and phenanthroline. *Bioorg Med Chem Lett*, 2004, 14(12): 3027–3032
- 225 Razafimahefa D, Ralambomanana D A, Hammouche L, Pélinski L, Lauvagie S, Bebear C, Brocard J, Maugein J. Synthesis and antimycobacterial activity of ferrocenyl ethambutol analogues and ferrocenyl diamines. *Bioorg Med Chem Lett*, 2005, 15(9): 2301–2303
- 226 Cuin A, Massabni A C, Leite C Q F, Sato D N, Neves A, Szpoganicz B, Silva M S, Bortoluzzi A J. Synthesis, X-ray structure and antimycobacterial activity of silver complexes with α -hydroxycarboxylic acids. *J Inorg Biochem*, 2007, 101(2): 291–296
- 227 Cavicchioli M, Leite C Q F, Sato D N, Massabni A C. Synthesis, characterization and antimycobacterial activity of Ag(I)-aspartame, Ag(I)-saccharin and Ag(I)-cyclamate complexes. *Arch Pharm Chem Life Sci*, 2007, 340(10): 538–542
- 228 Ventura C A, Giannone I, Musumeci T, Pignatello R, Ragni L, Landolfi C, Milanese C, Paolino D, Puglisi G. Physico-chemical characterization of disoxaril-dimethyl- β -cyclodextrin inclusion complex and in vitro permeation studies. *Eur J Med Chem*, 2006, 41(2): 233–240
- 229 Liang X Y, Sadler P J. Cyclam complexes and their applications in medicine. *Chem Soc Rev*, 2004, 33(4): 246–266
- 230 Turel I, Bukovec N, Goodgame M, Williams D J. Synthesis and characterization of copper(II) coordination compounds with acyclovir: crystal structure of triaquabis [9-[(2-hydroxyethoxy)methyl]guanin]copper(II)nitrate(V)hydrate. *Polyhedron*, 1997, 16(10): 1701–1706
- 231 Turel I, Andersen B, Sletten E, White A J P, Williams D J. New studies in the copper(II) acyclovir (acv) system. NMR relaxation studies and the X-ray crystal structure of [Cu(acv)₂(H₂O)₂](NO₃)₂. *Polyhedron*, 1998, 17(23-24): 4195–4201
- 232 García-Raso Á, Fiol J J, Bádenas F, Cons R, Terrón Á, Quirós M. Synthesis and structural characteristics of metal-acyclovir (ACV) complexes: [Ni(or Co)(ACV)₂(H₂O)₄]Cl₂ \cdot 2ACV, [Zn(ACV)Cl₂(H₂O)], [Cd(ACV)Cl₂] \cdot H₂O and [Hg(ACV)Cl₂] \cdot x. Recognition of acyclovir by Ni-ACV. *J Chem Soc Dalton Trans*, 1999, 2: 167–173
- 233 Panagiotopoulou A, Katsaros N, Masi N G D, Natile G. Synthesis and characterisation of platinum(II) complexes with the antiviral agents florafur and furavir. *Inorg Chim Acta*, 2001, 325(1-2): 73–78
- 234 Wooley P H, Whalen J D. The influence of superoxide scavenging compound CTC 23 on type II collagen-induced arthritis in mice. *Agents Actions*, 1992, 35(3-4): 273–279
- 235 Schwartz J A, Lium E K, Verstein S J S. Herpes simplex virus type I entry is inhibited by the cobalt chelate complex CTC-96. *J Virology*,

- 2001, 75(9): 4117–4128
- 236 Delehanty J B, Bongard J E, Thach D C, Knight D A, Hickey T E, Chang E L. Antiviral properties of cobalt(III)-complexes. *Bioorg Med Chem*, 2008, 16(2): 830–837
- 237 Allardyce C S, Dyson P J, Ellis D J, Salter P A, Scopelliti R. Synthesis and characterisation of some water soluble ruthenium(II)-arene complexes and an investigation of their antibiotic and antiviral properties. *J Organomet Chem*, 2003, 668(1-2): 35–42
- 238 Koester L S, Bertuol, J B, Groch K R, Xavier C R, Moellerke R, Mayorga P, Costa T D, Bassani V L. Bioavailability of carbamazepine: β -cyclodextrin complex in beagle dogs from hydroxypropylmethylcellulose matrix tablets. *Eur J Pharm Sci*, 2004, 22(2-3): 201–207
- 239 Beraldo H, Sinisterra R D, Teixeira L R, Vieira R P, Doretto M C. An effective anticonvulsant prepared following a host–guest strategy that uses hydroxypropyl- β -cyclodextrin and benzaldehyde semicarbazone. *Biochem Biophys Res Commun*, 2002, 296(2): 241–246
- 240 Viossat B, Daran J C, Savouret G, Morgant G, Greenaway F T, Dung N H, Pham-Tran V A, Sorenson J R J. Low-temperature (180 K) crystal structure, electron paramagnetic resonance spectroscopy, and propitious anticonvulsant activities of Cu_2^{II} (aspirinate) $_4$ (DMF) $_2$ and other Cu_2^{II} (aspirinate) $_4$ chelates. *J Inorg Biochem*, 2003, 96(2-3): 375–385
- 241 Viossat B, Greenaway F T, Morgant G, Daran J C, Dung N H, Sorenson J R J. Low-temperature (180 K) crystal structures of tetrakis- μ -(niflumato)di(aqua)dicationic copper(II) *N,N*-dimethylformamide and *N,N*-dimethylacetamide solvates, their EPR properties, and anticonvulsant activities of these and other ternary binuclear copper(II) niflumate complexes. *J Inorg Biochem*, 2005, 99(2): 355–367
- 242 Lemoine P, Viossat B, Dung N H, Tomas A, Morgant G, Greenaway F T, Sorenson, J R J. Synthesis, crystal structures, and anti-convulsant activities of ternary $[\text{Zn}^{\text{II}}(3,5\text{-diisopropylsalicylate})_2]$, $[\text{Zn}^{\text{II}}(\text{salicylate})_2]$ and $[\text{Zn}^{\text{II}}(\text{aspirinate})_2]$ complexes. *J Inorg Biochem*, 2004, 98(11): 1734–1749
- 243 d'Angelo J, Morgant G, Ghermani N E, Desmaële D, Fraisse B, Bonhomme F, Dichi E, Sghaier M, Li Y L, Journaux Y, Sorenson J R J. Crystal structures and physico-chemical properties of Zn(II) and Co(II) tetraaqua(3-nitro-4-hydroxybenzoato) complexes: their anticonvulsant activities as well as related (5-nitrosalicylato)-metal complexes. *Polyhedron*, 2008, 27(2): 537–546
- 244 Wang Z, Hirayama F, Uekama K. *In-vivo* and *in-vitro* evaluations of a modified-release oral dosage form of nifedipine by hybridization of hydroxypropyl-beta-cyclodextrin and hydroxypropylcelluloses in dogs. *J Pharm Pharmacol*, 1994, 46(6): 505–507
- 245 Ikeda Y, Kimura K, Hirayama F, Arima H, Uekama K. Controlled release of a water-soluble drug, captopril, by a combination of hydrophilic and hydrophobic cyclodextrin derivatives. *J Controlled Release*, 2000, 66(2-3): 271–280
- 246 Kopecky F, Kopecka B, Kaclik P. Dissolution of nimodipine in an aqueous solution of hydroxyethyl-beta-cyclodextrin and a review of solubility of nimodipine with cyclodextrins. *Ceska Slov Farm*, 2003, 52(1): 33–38
- 247 Fernandes C M, Veiga F J B. Effect of the hydrophobic nature of triacetyl- β -cyclodextrin on the complexation with nicardipine hydrochloride: physicochemical and dissolution properties of the kneaded and spray-dried complexes. *Chem Pharm Bull*, 2002, 50(12): 1597–1602
- 248 Nagase Y, Hirata M, Wada K, Arima H, Hirayama F, Irie T, Kikuchi M, Uekama K. Improvement of some pharmaceutical properties of DY-9760e by sulfobutyl ether β -cyclodextrin. *Int J Pharm*, 2001, 229(1-2): 163–172
- 249 Nagase Y, Arima H, Wada K, Sugawara T, Satoh H, Hirayama F, Uekama K. Inhibitory effect of sulfobutyl ether β -cyclodextrin on DY-9760e-induced cellular damage: *In vitro* and *in vivo* studies. *J Pharm Sci*, 2003, 92(12): 2466–2474
- 250 Judenhofer M S, Wehr H F, Newport D F, Catana C, Siegel S B, Becker M, Thielscher A, Kneilling M, Lichy M P, Eichner M, Klingel K, Reischl G, Widmaier S, Röcken M, Nutt R E, Machulla H J, Uludag K, Cherry S R, Claussen C D, Pichler B J. Simultaneous PET-MRI: A new approach for functional and morphological imaging. *Nat Med*, 2008, 14(4): 459–465
- 251 Caravan P, Ellison J J, McMurry T J, Lauffer R B. Gadolinium(III) chelates as MRI contrast agents: Structure, dynamics, and applications. *Chem Rev*, 1999, 99(9): 2293–2352
- 252 Parker D, Dickins R S, Puschmann H, Crossland C, Howard J A K. Being Excited by lanthanide coordination complexes: Aqua species, chirality, excited-state chemistry, and exchange dynamics. *Chem Rev*, 2002, 102(6): 1977–2010
- 253 Bellin M F. MR contrast agents, the old and the new. *Eur J Radiol*, 2006, 60(3): 314–323
- 254 Aime S, Crich S G, Gianolio E, Giovenzana G B, Tei L, Terreno E. High sensitivity lanthanide(III) based probes for MR-medical imaging. *Coord Chem Rev*, 2006, 250(11-12): 1562–1579
- 255 Lattuada L, Demattio S, Vincenzi V, Cabella C, Visigalli M, Aime S, Crich S G, Gianolio E. Magnetic resonance imaging of tumor cells by targeting the amino acid transport system. *Bioorg Med Chem Lett*, 2006, 16(15): 4111–4114
- 256 Hermann P, Kotek J, Kubiček V, Lukš I. Gadolinium(III) complexes as MRI contrast agents: ligand design and properties of the complexes. *Dalton Trans*, 2008, 23: 3027–3047
- 257 Yan G P, Robinson L, Hogg P. Magnetic resonance imaging contrast agents: Overview and perspectives. *Radiography*, 2007, 13(1): e5–e19
- 258 Feng J H, Sun G Y, Pei F K, Liu M L. Comparison between Gd-DTPA and several bisamide derivatives as potential MRI contrast agents. *Bioorg Med Chem*, 2003, 11(15): 3359–3366
- 259 Caravan P, Cloutier N J, Greenfield M T, McDermid S A, Dunham S U, Bulte J W, Amedio M J C, Looby J R J, Supkowski R M, Horrocks W D, McMurry J T J, Lauffer R B. The interaction of MS-325 with human serum albumin and its effect on proton relaxation rates. *J Am Chem Soc*, 2002, 124(12): 3152–3162
- 260 Chong H S, Garmestani K, Bryant L H, Milenic J D E, Overstreet T, Birch N, Le T, Brady E D, Brechbiel M W. Synthesis and evaluation of novel macrocyclic and acyclic ligands as contrast enhancement agents for magnetic resonance imaging. *J Med Chem*, 2006, 49(6): 2055–2062
- 261 Corot C, Port M, Raynal I, Dencausse A, Schaefer M, Rousseaux O, Simonot C, Devoldere L, Lin J, Foulon M, Bourrinet P, Bonnemain B, Meyer D. Physical, chemical, and biological evaluations of P760: A new gadolinium complex characterized by a low rate of interstitial

- diffusion. *J Magn Reson Imaging*, 2000, 11(2): 182–191
- 262 Delgado R, Félix V, Lima L M P, Price D W. Metal complexes of cyclen and cyclam derivatives useful for medical applications: A discussion based on thermodynamic stability constants and structural data. *Dalton Trans*, 2007, 26: 2734–2745
- 263 Hovland R, Gløgård C, Aasen A J, Klaveness J. Gadolinium DO3A derivatives mimicking phospholipids: preparation and *in vitro* evaluation as pH responsive MRI contrast agents. *J Chem Soc, Perkin Trans*, 2001, 2(6): 929–933
- 264 Xiang Q X, Xia C Q, Yu X Q, Zhang L Q, Xie R G. Recent advances in macrocyclic polyamines and their metal complexes. *Chin J Org Chem (in Chinese)*, 2004, 24(9): 981–986
- 265 Chong H S, Song H A, Ma X, Milenic D E, Brady E D, Lim S Y, Lee H S, Baidoo K E, Cheng D F, Brechbiel M W. Novel bimodal bifunctional ligands for adioimmunotherapy and targeted MRI. *Bioconjugate Chem*. 2008, 19(7): 1439–1447
- 266 Cavagna F M, Lorusso V, Anelli P L, Maggioni F, de-Haën C. Pre-clinical profile and clinical potential of gadocoletic acid trisodium salt (B22956/1), A new intravascular contrast medium for MRI. *Acad Radiol*. 2002, 9(2): 491–494
- 267 Rudovský J, Botta M, Hermann P, Hardcastle K I, Lukeš I, Aime S. PAMAM dendrimeric conjugates with a Gd-DOTA phosphinate derivative and their adducts with polyaminoacids: The interplay of global motion, internal rotation, and fast water exchange. *Bioconjugate Chem*, 2006, 17(4): 975–987
- 268 Battistini E, Gianolio E, Gref R, Couvreur P, Fuzerova S, Othman M, Aime S, Badet B, Durand P. High-relaxivity magnetic resonance imaging (MRI) contrast agent based on supramolecular assembly between a gadolinium chelate, a modified dextran, and poly- β -cyclodextrin. *Chem Eur J*, 2008, 14(15): 4551–4561
- 269 Khafagy E S, Morishita M, Onuki Y, Takayama K. Current challenges in non-invasive insulin delivery systems: A comparative review. *Adv Drug Deliv Rev*, 2007, 59(15): 1521–1546
- 270 Sajeesh S, Sharma C P. Cyclodextrin–insulin complex encapsulated polymethacrylic acid based nanoparticles for oral insulin delivery. *Int J Pharm*, 2006, 325(1-2): 147–154
- 271 Higashi T, Hirayama F, Misumi S, Arima H, Uekama K. Design and evaluation of polypseudorotaxanes of pegylated insulin with cyclodextrins as sustained release system. *Biomaterials*, 2008, 29(28): 3866–3871
- 272 Suihko E, Korhonen O, Järvinen T, Ketolainen J, Jarho P, Laine E, Paronen P. Complexation with tolbutamide modifies the physico-chemical and tableting properties of hydroxypropyl- β -cyclodextrin. *Int J Pharm*, 2001, 215(1-2): 137–145
- 273 Guiotoku M, Silva F R M B, Azzolini J C, Mercê A L R, Mangrich A S, Sala L F, Szpoganicz B. Monosaccharides and the VO(IV) metal ion: equilibrium, thermal studies and hypoglycemic effect. *Polyhedron*, 2007, 26(6): 1269–1276
- 274 Hidetoshi A, Kiyokazu Y, Kouzou M, Tetsumi I, Fumitoshi H, Kaneto U. Comparative studies of the enhancing effects of cyclodextrins on the solubility and oral bioavailability of tacrolimus in rats. *J Pharm Sci*, 2001, 90(6): 690–701
- 275 Bom A, Bradley M, Cameron K, Clark J K., Van E J, Feilden H, Maclean E J, Muir A W, Palin R, Rees D C, Zhang M Q. A novel concept of reversing neuromuscular block: Chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. *Angew Chem Int Ed Engl*, 2002, 41(2): 266–270
- 276 Virués C, Zquez E F V, Inoue M B, Inoue M. NMR studies of host guest complexes of anionic cyclophanes with dopamine and its analogues in aqueous media. *J Inclusion Phenom Macrocyclic Chem*, 2004, 48(3-4): 141–146
- 277 Yoon J, Kim S K, Singh N J, Kim K S. Imidazolium receptors for the recognition of anions. *Chem Soc Rev*, 2006, 35(4): 355–360
- 278 Baker M V, Brown D H, Heath C H, Skelton B W, White A H, Williams C C. Azolium-linked cyclophanes: Effects of structure, solvent, and counteranions on solution conformation behavior. *J Org Chem*, 2008, 73(23): 9340–9352
- 279 Baker M V, Bosnich M J, Brown D H, Byrne L T, Hesler V J, Skelton B W, White A H, Williams C C. Azolium-linked cyclophanes: A comprehensive examination of conformations by ^1H NMR spectroscopy and structural studies. *J Org Chem*, 2004, 69(22): 7640–7652
- 280 Zhou C H. Design and synthesis of imidazolium cyclophanes and their biomimetic chemistry. Dissertation for the Doctoral Degree (in Chinese). Chengdu: Sichuan University, 1996
- 281 Zuo Z, Tam Y K, Diakur J, Wiebe L I. Hydroxypropyl-beta- cyclodextrin-flutamide inclusion complex. II. Oral and intravenous pharmacokinetics of flutamide in the rat. *J Pharm Pharm Sci*, 2002, 5(3): 292–298
- 282 Bary A R, Tucker I G, Davies N M. Considerations in the use of hydroxypropyl-beta-cyclodextrin in the formulation of aqueous ophthalmic solutions of hydrocortisone. *Eur J Pharm Biopharm*, 2000, 50(2): 237–244