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## Rotaxane-based architectures for biological applications

## Architectures à base de rotaxanes en vue d'applications biologiques

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## ABSTRACT

Recently, the development of rotaxane-based architectures for biological applications has started to attract interest. In this short review, we summarize the main advances that have been realized in this burgeoning area of research, including the design of squaraine-rotaxane dyes for optical bioimaging applications, host-rotaxanes as cellular transport agents, enzyme-responsive rotaxanes and mechanized mesoporous silica nanoparticles coated with “nanovalves” as drug delivery systems.

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## R É S U M É

Récemment, le développement de rotaxanes pour des applications biologiques a suscité un intérêt grandissant. Dans cette mise au point, nous résumons les principaux progrès qui ont été réalisés dans ce domaine, en décrivant successivement les rotaxanes encapsulant des squaraines pour l'imagerie biologique, les rotaxanes hôtes comme agents de transport cellulaire, les rotaxanes enzymo-sensibles et les nanoparticules de silice mésoporeuse revêtues de « nanovalves » pour la délivrance de médicaments.

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## 1. Introduction

Since Jean-Pierre Sauvage reported in 1983 the first templated synthesis of a [2]catenane [1], considerable research efforts have been devoted to the development of novel synthetic strategies allowing the efficient preparation of interlocked molecular architectures [2–4]. Forty years of investigations in this field gave birth to a broad collection of structurally diverse rotaxanes, catenanes and knots exhibiting unique chemical properties. More

recently, the functional aspects of such interlocked systems has become the subject of intense research to find practical applications of mechanically bonded molecules [5]. Within this framework, rotaxanes have been widely studied as potential electronic devices, materials, sensors and key components for molecular motors and machines [6–13]. Furthermore, some rotaxane- and pseudorotaxane-based devices have been designed to interact with biological systems, especially for the delivery of bioactive compounds or biomedical imaging. In this short review, we report the advances that have been realized in this burgeoning area of research over the past 15 years. Herein, we will summarize successively the main advances made in the design of

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squaraine-rotaxane dyes for optical bioimaging applications, host-rotaxanes as cellular transport agents, enzyme-responsive rotaxanes and mechanized mesoporous silica nanoparticles coated with “nanovalves” as drug delivery systems.

## 2. Squaraine-rotaxane dyes for optical bioimaging applications

Squaraines are a class of near-IR dyes with promising photophysical properties for optical bioimaging applications [14]. However, their use as fluorescent probes is limited by their inherent chemical instability that results from the attack of biological nucleophiles on the electron-deficient cyclobutene ring. Additionally, squaraines readily form aggregates in water which quench fluorescence. To circumvent these drawbacks, Smith *et al.* proposed to encapsulate the cyclobutene core of the squaraine dye as the thread component inside an interlocked rotaxane structure [15–17]. Thus, using the hydrogen bond directed clipping reaction developed earlier by Leigh *et al.* [18–20], they synthesized a range of squaraine-derived rotaxanes such as **1** (Scheme 1) [21–22].

As expected, the encapsulating macrocycle inhibited aggregation and greatly enhanced the stability of the squaraine dye in various media, preventing nucleophilic attack on the cyclobutene moiety. Therefore, when incubated with bovine serum, rotaxane **1a** was stable for many weeks whereas the corresponding thread was degraded over a few minutes [17].

Soon after, Smith *et al.* published a remarkable extension of this work where they compared the performance advantages of rotaxane **1b** over the commonly used sulfonated cyanine dye Cy-5 [23]. Rotaxane **1b** includes zinc(II)-dipicolyl-amine (Zn-DPA) stoppers that also play the role of targeting ligands since Zn-DPA groups are known to target the anionic surfaces of bacterial cells [24]. The high stability of **1b** permitted real time fluorescence-imaging of *Escherichia coli* bacteria undergoing cell division, which was not possible using probes based on Cy-5. Furthermore, rotaxane **1b** allowed optical imaging of *Staphylococcus aureus* and *E. coli* bacteria in living nude

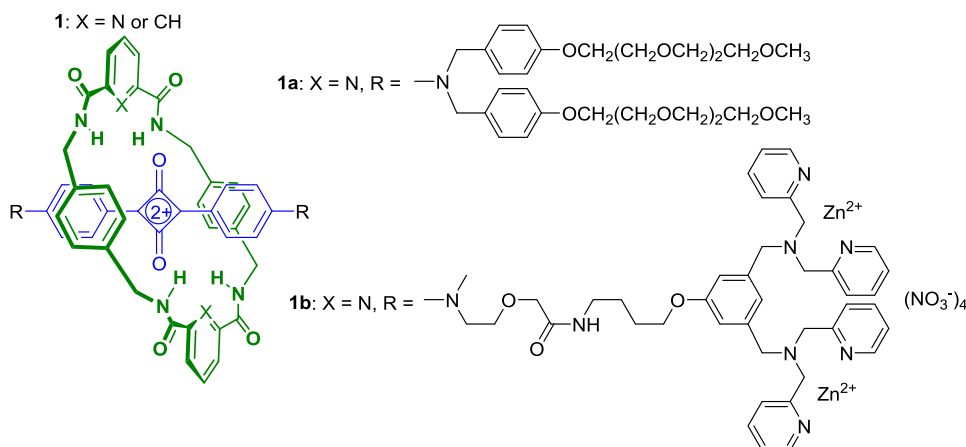
mice showing the great potential of squaraine-rotaxane dyes as bioimaging agents.

The same group developed the highly innovative interlocked system **2** that may be suitable for many types of molecular imaging and biotechnology applications (Scheme 2) [25].

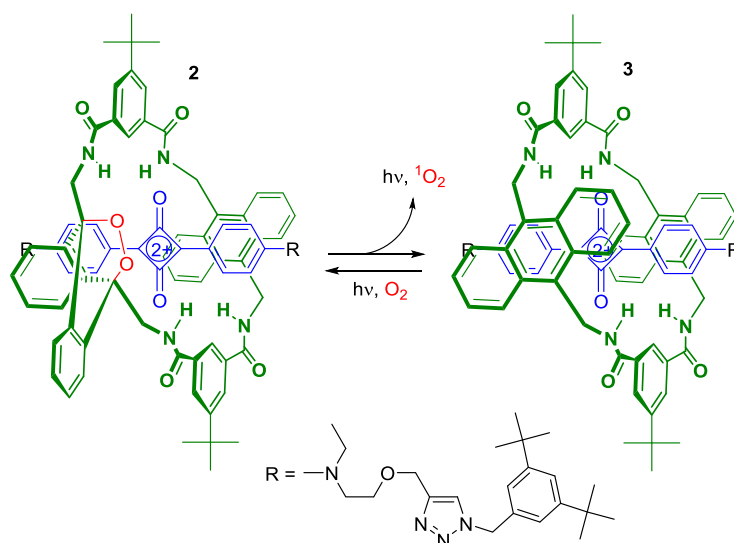
Rotaxane **2** that features an endoperoxide macrocycle was easily prepared from **3** by oxidation of one anthracene unit in the presence of air under irradiation with red light. The synthesis of precursor **3** was achieved using the “Clicked Capping” method reported earlier by Smith *et al.* [26,27]. With this design, interlocked system **2** was very stable and can be stored at  $-20\text{ }^{\circ}\text{C}$  during extremely long periods without any degradation. However, upon warming at  $37\text{ }^{\circ}\text{C}$ , compound **2** underwent a unimolecular cycloreversion reaction leading to the release of singlet oxygen together with the emission of near-IR light. Thus, such a thermally activated rotaxane-based dye possesses both chemiluminescence and fluorescence properties making this interlocked molecular system particularly interesting for optical imaging. The validity of this concept was evaluated in living mouse with **2**-labelled microparticles [25]. The results obtained in this study demonstrated that squaraine rotaxanes including an endoperoxide macrocycle can be used *in vivo* as dual-modality molecular imaging probes.

## 3. Host-rotaxanes as cellular transport agents

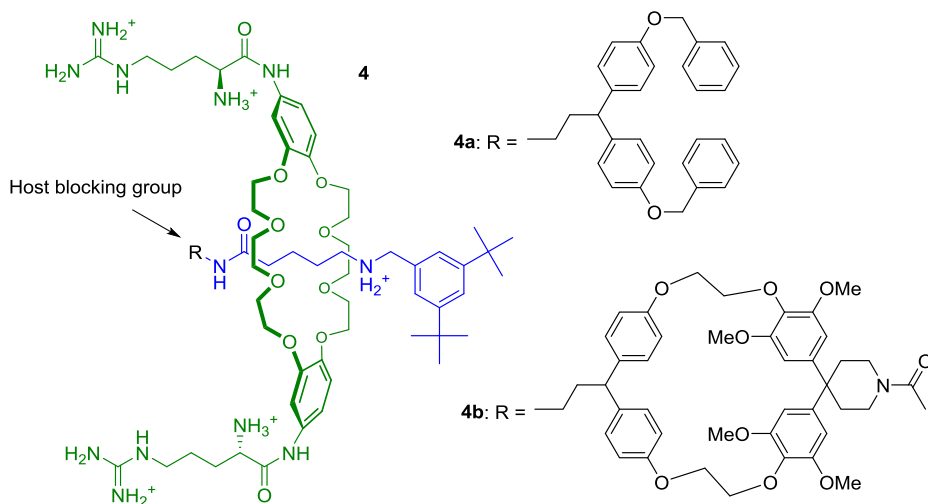
In 2003, Smithrud *et al.* proposed the use of host-[2]rotaxanes with the aim to create synthetic compounds that mimic proteins ensuring the functions of cellular transport agents [28]. For this purpose, they designed a series of [2]rotaxanes **4** containing an arginine-derivatized dibenzyl-24-crown-8 (DB24C8) and a number of host blocking groups, allowing the encapsulation of various guest molecules (Scheme 3) [29]. With this design, the wheel can freely slide along the thread, therefore adjusting its position to form the most stable conformation for the recognition of a given guest [30]. Also, the nature of the host blocking group can be easily modulated by the DCC-rotaxane method developed by the same group [31].



Scheme 1. Squaraine-rotaxane dyes for optical bioimaging applications.



**Scheme 2.** A squaraine-rotaxane dye for in vivo dual-modality molecular imaging.



**Scheme 3.** Host-rotaxanes as cellular transport agents.

Rotaxanes **4a** and **4b**, including an aromatic cleft and a cyclophane pocket, respectively, were studied for the delivery of peptides into cells (Scheme 3) [32,33]. Indeed, while many bioactive peptides hold great promise as therapeutic agents, their use *in vivo* is hampered by poor bioavailability mainly due to their inability to pass through cellular membranes. Investigations conducted with **4a** confirmed the importance of conformational flexibility in the ability of host-[2]rotaxanes to bind guests and transport peptides into cells. Thus, Smithrud *et al.* demonstrated that pre-incubation of rotaxane **4a** with COS-7 cells significantly increased the uptake of a fluoresceinated pentapeptide (AVWAL). Furthermore, since cellular uptake was largely temperature- and ATP-independent, it was suggested that the rotaxane-peptide non-covalent complex passed through the cell membrane *via* a passive

mechanism. More recently, the same authors developed an analogue of **4a** containing an oligo(ethylene glycol) chain on the axle, thereby increasing the length of the latter [34]. Interestingly, this new host-[2]rotaxane delivered more efficiently a range of fluoresceinated peptides into ovarian tumour cells than **4a** which possesses a shorter axle.

In a comparative study, Smithrud *et al.* showed that the ability of cyclophane-[2]rotaxane **4b** to transport fluorescein into COS-7 cells was substantially better than that of the cleft-[2]rotaxane **4a** [28]. Additionally, **4b** transported fluorescein to a greater extent into the nucleus, whereas **4a** delivered the fluorescent probe more uniformly throughout a cell. As the cyclophane pocket appeared to be beneficial for cell transport, rotaxane **4b** was tested for the intracellular delivery of peptides possessing a wide range of side chains (displaying apolar and polar groups either

negatively or positively charged). These experiments demonstrated the utility of rotaxane **4b** for the transport of peptides of all polarity across cell membranes, highlighting the versatility of this concept.

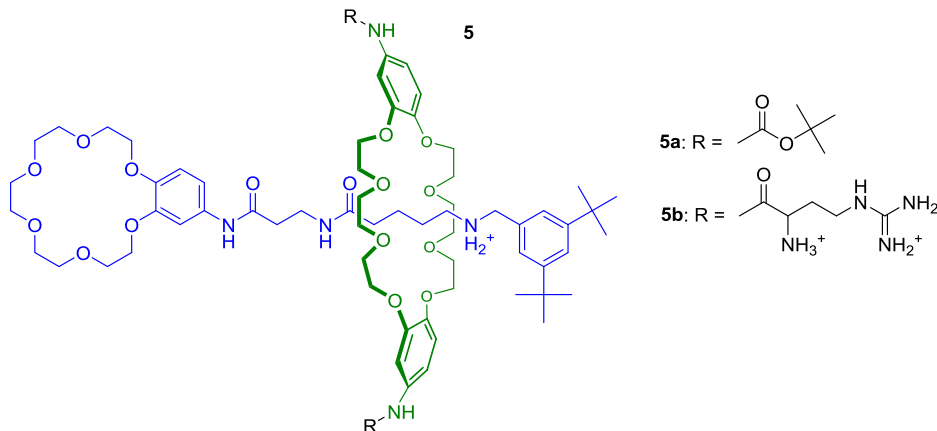
More recently, Smithrud *et al.* studied host-[2]rotaxanes enabling the transfer of alkali and alkaline cations from aqueous solutions into chloroform [35]. In this context, they proposed the use of the crown ether host-rotaxanes **5** as novel bacterial ionophores (Scheme 4) [36]. The authors hypothesized that rotaxanes **5** would increase the intracellular concentration of metal ions such as  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ , thereby inducing cell death through apoptosis. When incubated with SKOV-3 ovarian cancer cells, host-rotaxanes **5a** and **5b** were cytotoxic in the low micromolar range. The cytotoxicity of rotaxanes increased with the concentration of either  $\text{Ca}^{2+}$  or  $\text{Mg}^{2+}$  confirming that **5a** and **5b** operated as expected by enhancing the intracellular concentration of these ions.

#### 4. Enzyme-responsive rotaxanes

Besides their poor ability to cross cell membranes, many bioactive peptides suffer from *in vivo* instability as a result of rapid enzymatic degradation. For instance, Met-enkephalin is a pentapeptide (YGGFM) with interesting antiproliferative activities against several cancer cell lines [37–39]. However, this compound cannot be used as an anticancer drug since it is degraded in less than 5 min in human plasma. With the aim to circumvent this drawback, our group, in collaboration with those of Leigh and Aucagne, proposed the concept of enzyme-responsive rotaxane-based propeptides [40]. Within this framework, a pilot study was conducted with the glycorotaxane [41–44] **6** programmed for the selective delivery of Met-enkephalin at the tumour site (Scheme 5). This mechanically interlocked system was composed of a galactoside trigger, a self-immolative stopper [45,46], a pentapeptide-based axle and a benzylic amide macrocycle [18,47,48]. With this design, we hypothesized that the macrocycle should play the role of a temporary molecular shield protecting the peptidic bonds of Met-enkephalin from degradation by plasmatic peptidases. Thus, when incubated in

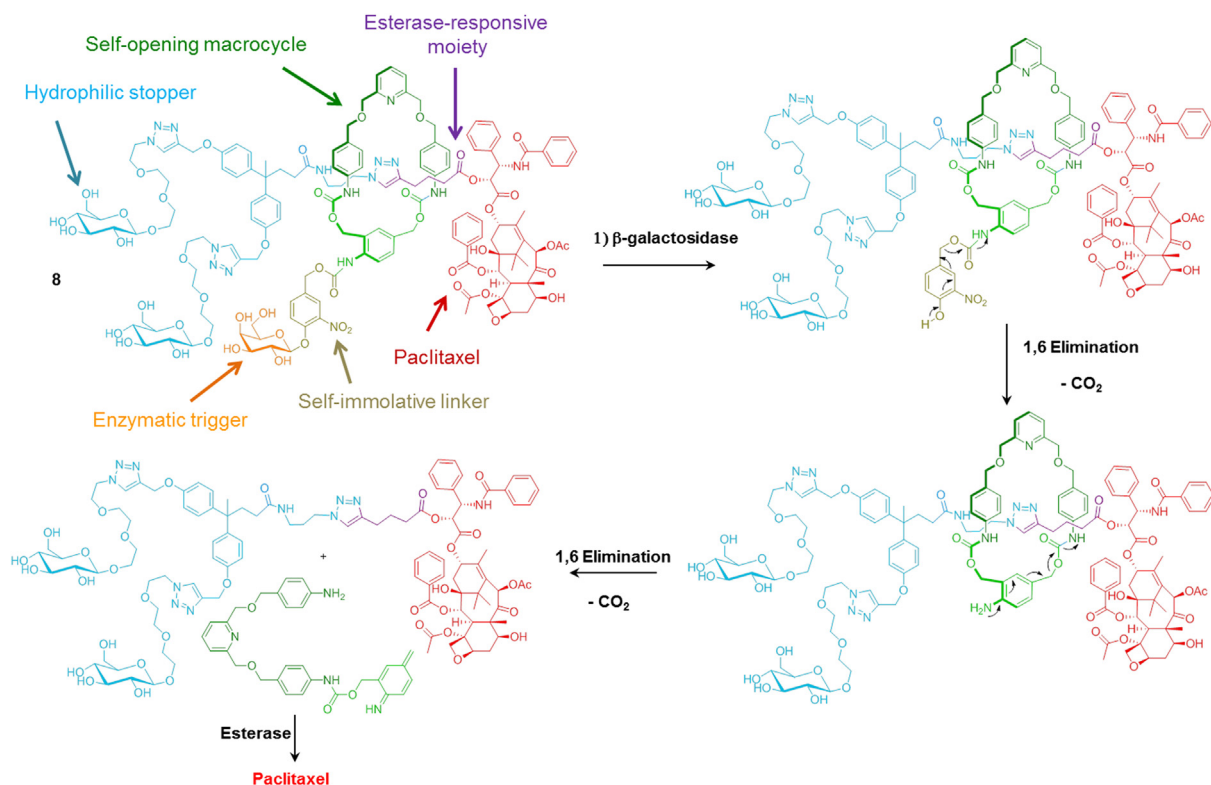
human plasma containing peptidases responsible of Met-enkephalin degradation, rotaxane **6** was perfectly stable over several days. In contrast, the corresponding thread was degraded with a half-life of 5 h under the same conditions, therefore demonstrating that encapsulation of the pentapeptide within the rotaxane structure **6** prevented its peptidase-mediated hydrolysis in plasma. We also showed that the active peptide can be readily released in the presence of  $\beta$ -galactosidase, an enzyme that has been successfully targeted [49] in tumour tissues *via* antibody-directed enzyme prodrug therapy strategies (ADEPT [50,51]). As illustrated in Scheme 5, activation of the galactoside trigger led to the formation of an unstable phenolate intermediate that underwent a 1,6-elimination followed by a spontaneous decarboxylation, enabling the disassembly of the mechanically interlocked components and the subsequent liberation of the free bioactive pentapeptide.

While our study confirmed the potential of this approach for the transport and delivery of peptides with antitumour activity, rotaxane **6** exhibited poor aqueous solubility. We then decided to pursue our investigations in this field with the galactosidase-responsive rotaxane propeptides **7** composed of a novel self-immolative linker and a triglycyl peptide encapsulated by a macrocycle bearing two hydrophilic moieties (Scheme 6) [52]. The compounds **7a** and **7b** were easily prepared *via* post-functionalisation of the same *bis*-azido rotaxane **7c** using the well-known CuAAC ‘click’ reaction. Under such circumstances, the clickable precursor **7c** appeared as a useful platform for accessing a wide range of propeptides decorated for specific biological applications. As expected both rotaxanes **7a** and **7b** were more soluble in aqueous media than the undecorated rotaxane analogue **7d**. Interestingly, the introduction of the two glucosylated tetra(ethylene glycol) substituents (rotaxane **7b**) afforded an excellent aqueous solubility that was 50,000-fold higher than that of rotaxane **7d**. Moreover, the presence of the bulky hydrophilic groups on the macrocycle did not alter the recognition of the galactoside trigger, as the activation of the rotaxane propeptide **7b** with  $\beta$ -galactosidase efficiently released the parent tripeptide.



Scheme 4. Host-rotaxanes as bacterial ionophores.



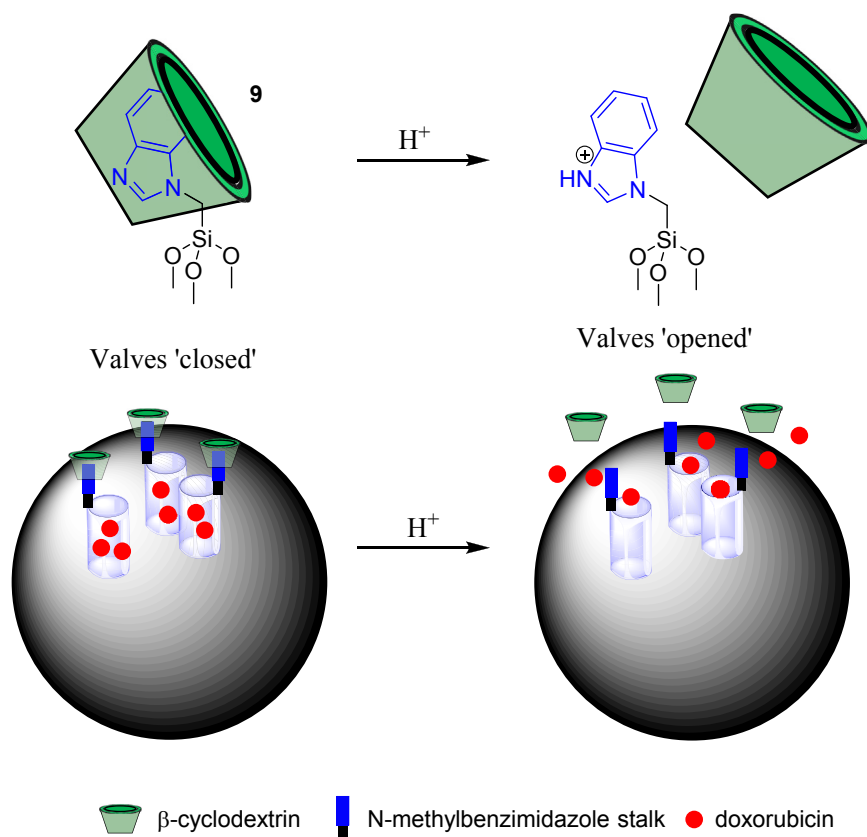


**Scheme 7.** An enzyme-responsive rotaxane with a self-opening macrocycle.

nanoparticles (MSNPs) possess the ability to encapsulate a wide variety of organic molecules and can accumulate passively in solid tumours (the enhanced permeability and retention of macromolecules in solid tumours is known as the EPR effect [55]). As a result, MSNPs have been considered as potential carriers for the delivery of therapeutic and diagnostic agents [56,57]. By attaching either rotaxane or pseudorotaxane architectures to the silica matrix, Stoddart and Zink aimed to release host molecules in a stringently controlled fashion using a mobile macrocycle as a valve. In this approach, when the macrocycle is close to the surface of the particle (valves ‘closed’), the guest molecules remain trapped within the pores of silica. On the other hand, in response to a specific stimulus, the macrocycle can move away from the surface (valves ‘opened’), thereby allowing the liberation of cargo molecules. Based on this principle, several types of ‘nanovalves’ have been studied in order to control the nanopore opening using various stimuli such as light, oxidation/reduction, changes in pH, and enzymes [51,58–66]. Until now, most of these functional systems have been designed to operate exclusively under abiotic conditions. However, a few remarkable examples of MSNPs functionalized with ‘nanovalves’, capable of delivering potent anticancer drugs autonomously within living tumour cells *in vitro* and *in vivo*, have been recently reported in the literature [67,68]. In this context, the first example is the pH-sensitive supramolecular ‘nanovalve’ **9** composed of an *N*-methylbenzimidazole stalk attached covalently to the nanopore opening and encircled by a  $\beta$ -cyclodextrin (Scheme 8) [69]. At pH 7.0, the resulting

pseudorotaxane was highly stable and no cargo leakage was observed, showing that the ‘nanovalves’ remained closed under these conditions. In contrast, upon decreasing the pH at 5.0, protonation of the benzimidazole induced the disassembly of the interlocked components leading to the liberation of doxorubicin. These results indicated that such MSNPs should be stable in plasma (pH 7.2), while releasing the active drug once inside acidic cellular compartments. To verify this hypothesis, the MSNPs loaded with doxorubicin were incubated with squamous carcinoma KB-31 cell lines. These experiments revealed that MSNPs were efficiently taken up into the endosomal compartment where doxorubicin was released under acidic conditions provoking cell death.

Very recently, Zhao *et al.* studied a range of redox-responsive ‘nanovalves’ comprising a disulfide bond linkage that can be reduced in the presence of intracellular reductive agents such as glutathione (GSH) (Scheme 9) [70–72]. These ‘nanovalves’ were equipped with various targeting ligands allowing the selective recognition of the corresponding membrane receptors overexpressed at the surface of cancer cells. In this approach, following receptor–ligand interactions, the MSNPs are internalized *via* receptor-mediated endocytosis [73]. Once inside the target cancer cell, the GSH-triggered disulfide cleavage induces the opening of the valves and the subsequent drug release. Based on this principle, Zhao *et al.* designed MSNPs loaded with doxorubicin and decorated with the pseudorotaxane **10** [71]. This latter included an adamantyl stalk and a lactobionic acid-grafted- $\beta$ -cyclodextrin serving as an end-



**Scheme 8.** pH-responsive 'nanovalves'.

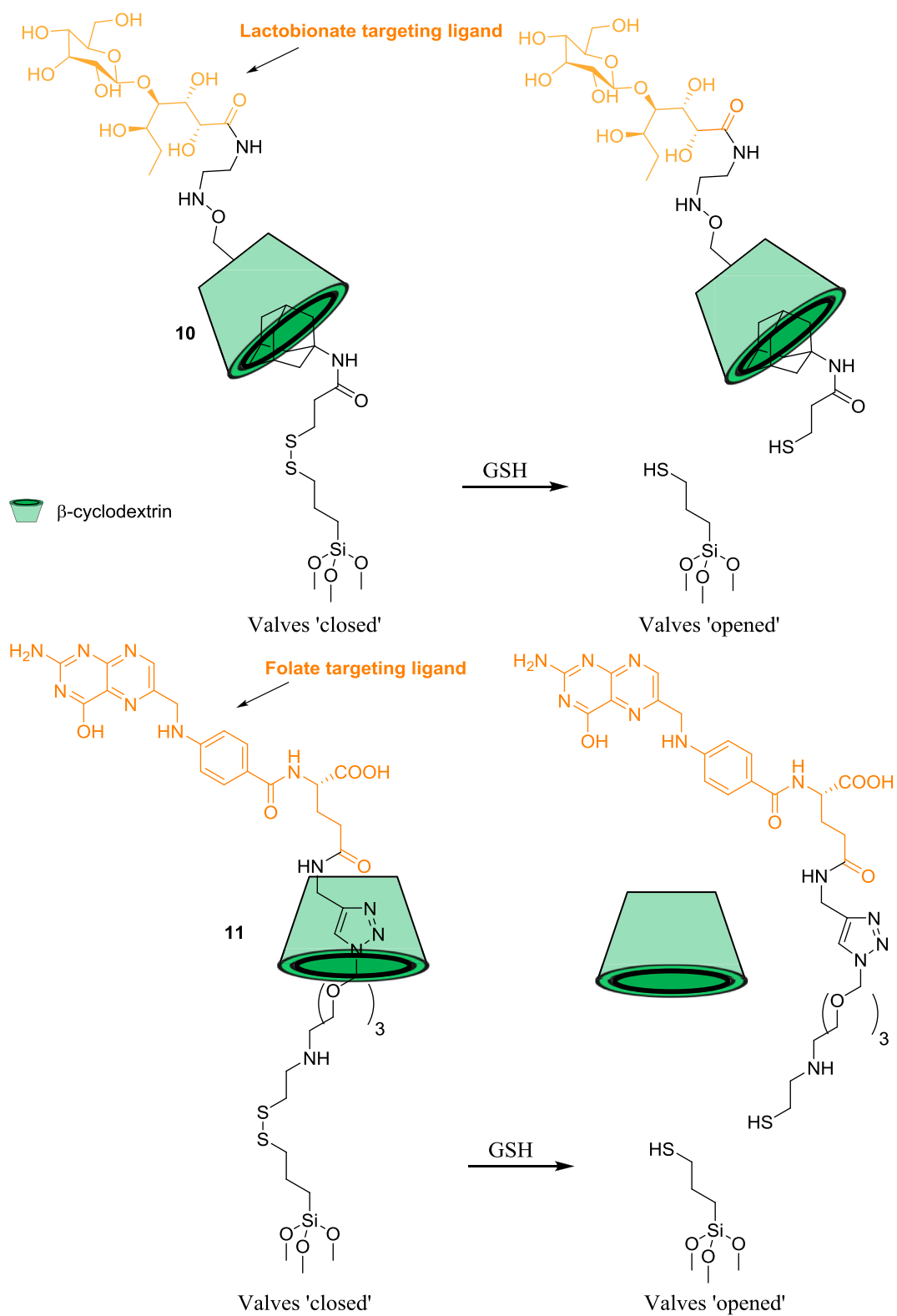
copper to prevent drug leakage. The lactobionic acid moiety was employed as a targeting ligand to enter selectively HepG2 liver cancer cells expressing the asialoglycoprotein receptor (ASGP-R) [74]. The anticancer efficacy of such MSNPs was evaluated on tumour-bearing nude mice *in vivo*. This study demonstrated that doxorubicin was selectively delivered and released within ASGP-R-positive cancer cells thereby inhibiting the tumour growth with minimal side effects.

The same group developed the [2]rotaxane **11** as a redox-responsive 'nanovalve' programmed for the selective delivery of doxorubicin inside cancer cells overexpressing the folate receptor (FR) [72]. With this design the folate groups anchored at the surface of MSNPs act as both the stoppers of the rotaxane **11** and targeting ligands. The FR is indeed overexpressed in several cancer types while it is mainly undetectable in most normal tissues [75]. Thus, the FR represents a target of choice to improve the selectivity of cancer chemotherapies [76–78]. Under physiological conditions, a negligible quantity of doxorubicin leaked from the MSNPs, showing a good capping efficiency of rotaxane **11** on the nanoparticle surface. However, in the presence of GSH, doxorubicin was released from MSNPs with a rate depending on the concentration of the reducing agent, indicating that the 'valves' opening proceeded as illustrated in Scheme 9. The potential of this targeting strategy was confirmed *in vivo* during the treatment of a subcutaneous HeLa

xenograft implanted in nude mice. In these experiments, the therapeutic efficacy of MSNPs coated with rotaxane **11** was superior to that of the free drug, inhibiting the tumour growth without inducing significant side effects.

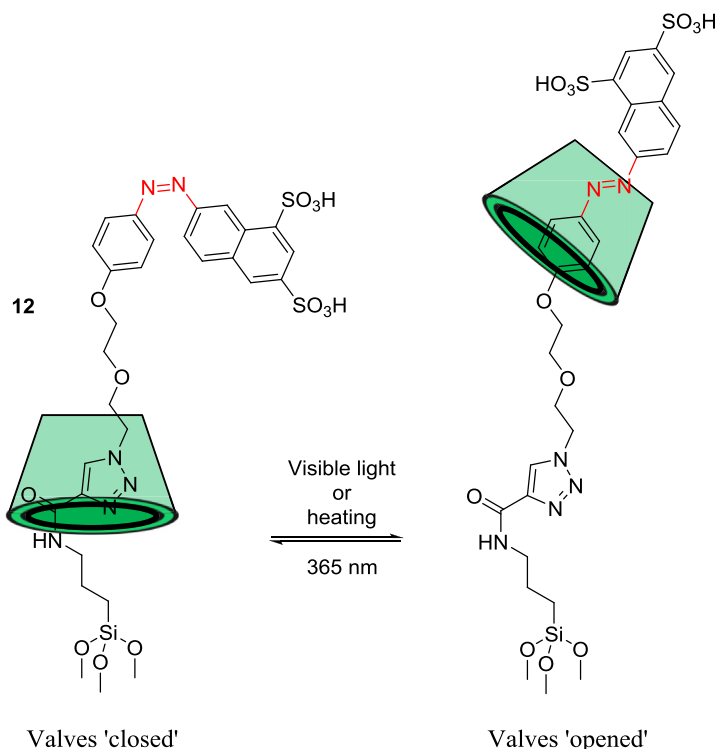
Zhao *et al.* also proposed the use of photothermal-responsive rotaxane-functionalized MSNPs for the controlled release of bioactive compounds *in vivo* [79]. For this purpose, they attached at the surface of MSNPs the rotaxane **12** in which the cyclodextrin ring was threaded with an azobenzene axle ended by a stopper containing two sulfonic groups, enhancing the aqueous solubility of the whole delivery system (Scheme 10).

Upon exposure to visible light or heating, the *cis*-to-*trans* isomerization of the azobenzene unit induces the cyclodextrin to shuttle to the *trans*-azobenzene position, thereby opening the mesopores. On the other hand, irradiation at 365 nm produces the *trans*-to-*cis* photoisomerization of the azobenzene that causes the cyclodextrin to move back to the triazole/ethylene glycol position, resulting in the blockage of the pores of the MSNPs. Thus, the control of the movement of the cyclodextrin along the thread allows both drug storage and release. The validity of this concept was confirmed *in vivo* on zebrafish models with curcumin-loaded MSNPs. Curcumin, a naturally fluorescent polyphenol, was indeed efficiently released when optically transparent zebrafish larvae were treated with either visible light or heat.



**Scheme 9.** Redox-responsive 'nanovalves'.





**Scheme 10.** Photothermal-responsive 'nanovalves'.

## 6. Concluding remarks

The development of functional rotaxanes for biological applications started to attract interest about fifteen years ago. While this field of research has not reached maturity yet, some stimulating advances have been achieved, particularly in the design of new molecular delivery devices and probes. These systems possess unusual chemical properties due to the presence of mechanical bonds within their structures. Thus, by using the macrocycle of rotaxanes as a molecular shield, some labile chemical moieties can be protected from premature degradation in biological environments. This feature of rotaxane architectures has already demonstrated its usefulness in preventing nucleophilic attack on the cyclobutene core of squaraines and the hydrolysis of peptides or ester bonds in plasma. It was also possible to exploit the mobility of the macrocycle along the thread to develop adaptable host systems allowing the transport of various peptides through cell membranes. Moreover, 'nanovalves' and prodrugs, with functionalities based on the controlled disassembly of the mechanically interlocked components, have emerged as innovative drug delivery systems.

Future research directions should focus on the improvement of the biocompatibility of rotaxane-based architectures that usually suffer from poor water solubility. For this purpose, novel versatile synthetic methods allowing the preparation of a wide variety of rotaxanes under aqueous conditions would be extremely useful. Such synthetic advances could lead to the emergence of new families of interlocked systems that could operate in

various biological environments, while until now these types of rotaxane-based molecular machines functioned exclusively under abiotic conditions (*i.e.* artificial muscles and processive enzymes, rotaxane catalysts...). Next generations of functional rotaxanes should also interact more selectively with biological targets in order to compete with non-interlocked molecular systems already developed for similar applications. Within this framework, an important step has been realized very recently by Zhao *et al.* who developed the first MSNPs coated with 'nanovalves' bearing targeting ligands that enabled the selective recognition of malignant cells *in vivo*.

Although numerous advances still remain to be accomplished to evaluate the real potential of rotaxane-based architectures for biological applications, the functional systems presented in this short review highlight the promise offered by these interlocked molecules. Further developments in this area will certainly permit to determine whatever this class of compounds will be of practical use to explore or manipulate biological systems in the near future.

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