

Click-and-Release Formation of Urea Bonds in Living Cells Enabled by Micelle Nanoreactors

Léa Madegard,^{[a]†} Melissa Girard,^{[b]†} Estelle Blochouse,^[b] Benjamin Riss Yaw,^[b] Alberto Palazzolo,^[a] Mélanie Laquembe,^[a] Davide Audisio,^[a] Pauline Pointot,^[b] Sébastien Papot^{[b]*} and Frédéric Taran^{[a]*}

Abstract: The development of innovative strategies enabling chemical reactions in living systems is of great interest for exploring and manipulating biological processes. Herein, we present a pioneering approach based on both bioorthogonal and confined chemistry for intracellular drug synthesis. Exploiting a click-to-release reaction, we engineered nanoparticles capable of synthesizing drugs within cellular environments through bioorthogonal reactions with cyclooctynes. Proof of concept experiments showed that this new approach could be successfully applied to the synthesis of the FDA-approved Sorafenib within cancer cells. The integration of bioorthogonal and confined chemistry not only offers exciting prospects for advancing therapeutic strategies but also opens up new avenues for exploring non-natural reactions within living systems. This innovative approach represents a fundamental extension of the bioorthogonal chemistry concept and holds great promise for pioneering developments in therapeutic applications.

Bioorthogonal chemistry,^[1] which refers to chemical transformations that proceed in biological media without interfering with endogenous functional groups, emerged as a powerful tool to develop new therapeutic strategies.^[2] By operating independently of biochemical processes, bioorthogonal chemistry can precisely trigger biological activities via the formation and/or the breaking of chemical bonds with high spatiotemporal resolution. Within this framework, cleavage^[3] and click-to-release^[4] reactions have been designed for the selective release of drugs upon bioorthogonal activation of the corresponding prodrugs.^[2b,c] Besides, metal-catalyzed ligation^[5] reactions were investigated to construct drugs from non-toxic precursors. So far, this approach has been mainly explored using the copper-catalyzed azide-alkyne cycloaddition (CuAAC)^[6] to produce bioactive triazoles in living systems. In 2016, the Bradley's team was the first to report the formation of an anticancer agent within tumor cells by coupling an azide and an alkyne in the presence of a heterogenous Cu(I) catalyst.^[7] Based on the same principle, Zhang and Sun developed mesoporous organosilicon nanoparticles encapsulating stabilized Cu(I) that catalyzed the synthesis of a triazole-

containing antibacterial agent both *in vitro* and *in vivo*.^[8] Ren and Qu also used the CuAAC to produce a cytotoxic compound in tumors implanted in mice with a high level of selectivity by the mean of a DNA-based nanocatalyst designed to recognize specifically cancer cells.^[9] Alongside the CuAAC, the Suzuki-Miyaura cross-coupling chemistry demonstrated as well its potential for the intracellular synthesis of a cytotoxic kinase inhibitor using a Pd catalyst previously targeted inside glioblastoma cells.^[10] Gold and ruthenium-promoted intramolecular cyclization were also studied to construct heterocycle-containing fluorophores in living cells.^[11] Although not yet used for drug synthesis, such bimolecular reactions offer advantages for producing bioactive compounds under the dilute conditions prevailing in complex biological medium.

Herein, we propose a new paradigm for the synthesis of drugs in living systems based on the development of stimuli-responsive micelles (Figure 1). After bioorthogonal activation, these nanoreactors produce a chemical species that can then react with a compound previously encapsulated inside the micelles. Inspired by Nature that performs simultaneously a multitude of different transformations in confined environments (such as organelles in cells) and by recent developments in nanozymes design,^[12] this approach enables carrying out chemical reactions independently of biological processes. In this manner, molecular precursors containing functional groups found in living systems can be employed to construct drugs via non-bioorthogonal ligation.

- [a] Dr. L. Madegard, Dr. D. Audisio, Dr. A. Palazzolo, M. Laquembe, Dr. F. Taran. Université Paris Saclay, CEA, INRAE, Département Médicaments et Technologies pour la Santé (DMTS), 91191 Gif-sur-Yvette, France.
E-mail: frederic.taran@cea.fr
- [b] Dr. M. Girard, E. Blochouse, Dr. B. Riss Yaw, Dr.P. Pointot, Prof. S. Papot. Equipe labellisée Ligue contre le cancer, Université de Poitiers, UMR CNRS 7285, Institut de Chimie des Milieux et Matériaux de Poitiers (IC2MP), 4 rue Michel-Brunet, TSA 51106, 86073 Poitiers cedex 9, France.
E-mail: sebastien.papot@univ-poitiers.fr

† These authors contributed equally to this work

Supporting information for this article is given via a link at the end of the document.

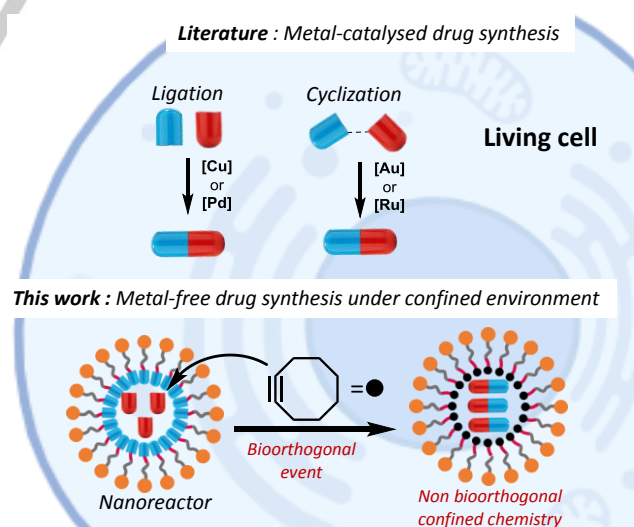


Figure 1. Strategies for constructing drugs inside living cells.

Such nanoreactors are constituted of sydnonimine-based amphiphiles assembled in the form of micelles,^[13] encapsulating an amine-containing building block (Figure 2). Sydnonimines are mesoionic compounds reported by our group to release

isocyanates upon bioorthogonal reaction with cyclooctynes, a reaction called Strain-Promoted Sydnonimine-Cycloalkyne

cycloaddition reaction (SPSIC).

[14]

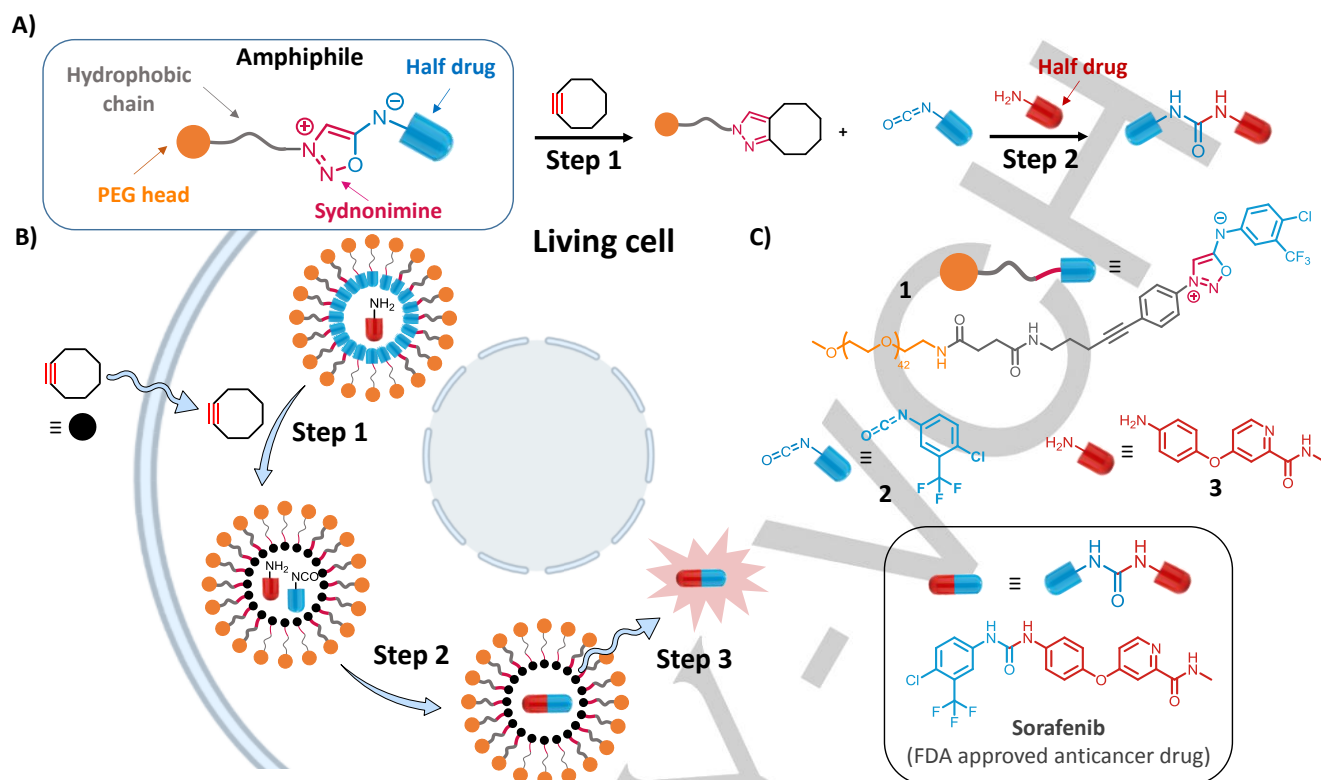


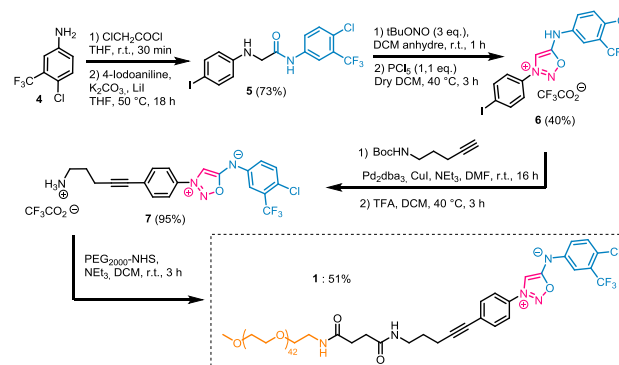
Figure 2. Design and operation of stimuli-responsive nanoreactors for the *in situ* synthesis of the FDA approved anticancer drug Sorafenib. A) General structure of sydnimine-based amphiphiles that react with a cyclooctyne via the SPSIC reaction (Step 1) to produce a pyrazole derivative and an isocyanate, which leads then to the formation of an urea by reacting with an amine (Step 2); B) Operation of stimuli-responsive micelles inside living cells. Step 1: SPSIC-mediated micelle activation inside living cells; Step 2: Formation of urea-containing drug in confined environment; Step 3: Drug diffusion outside the micelles to trigger biological activities; C) Chemical structures of amphiphile **1**, isocyanate **2**, aniline **3** and Sorafenib.

With this design, bioorthogonal activation of the nanoreactor through the **SPSIC** reaction will produce a reactive isocyanate within the micelle core (step 1). This later will then react with the encapsulated amine to generate a bioactive urea derivative (step 2) that will diffuse subsequently outside of the micelle to exert its biological activity (step 3).

As proof of principle, we designed a nanoreactor resulting from the assembly of the amphiphile **1** and encapsulating the amine **3** (Figure 2c). In the presence of a cyclooctyne, the **SPSIC** reaction triggered the production of the isocyanate **2** that reacted inside the micelles with **3** for generating the Sorafenib, an urea-containing FDA approved anticancer drug. We demonstrated that such process occurred within living cancer cells, leading to biological effects identical to those induced by native Sorafenib.

Amphiphile **1** was prepared in 7 steps starting from the aniline **4** (scheme 1). The key step of the synthesis was the cyclization of the nitrosylated aniline **5** with PCl_5 to provide the sydnimine **6** according to our previous described methodology.^{13b} Sonogashira coupling and further amide coupling using standard conditions afforded amphiphile **1** in reasonable yields. Physicochemical characterizations proved that **1** self-assembles in aqueous solutions into micelles **M1** of ~ 9 nm size according to DLS analysis. Surface tension measurements showed a critical micellar concentration (CMC) of less than 10 μM (Figure

3, S1 and S2). Control experiments indicated complete stability of these micelles for more than one week in PBS buffer at pH 7.4.



Scheme 1. Synthesis of amphiphile **1**.

As expected, addition of **DBCO** in solutions containing micelles **M1** provoked very fast click-to-release **SPSIC** reaction, forming a new amphiphile **8** and releasing the isocyanate **2** inside the micelle core, with a second-order rate constant k of almost $650 \text{ M}^{-1} \cdot \text{sec}^{-1}$ (Figure 3). Interestingly, the integrity of the

micellar assembly was conserved after the **SPSIC** reaction, the newly formed micelle **M2** presenting similar size than **M1** (Figure S2).

These results in hand, we hypothesized that the isocyanate-generated bioorthogonally could react with nucleophiles encapsulated inside the micelles to produce bioactive derivatives. Furthermore, we hypothesized that these coupling reactions could proceed efficiently within complex biological environments by being confined within the nanoassembly, thereby minimizing interference from endogenous nucleophiles.

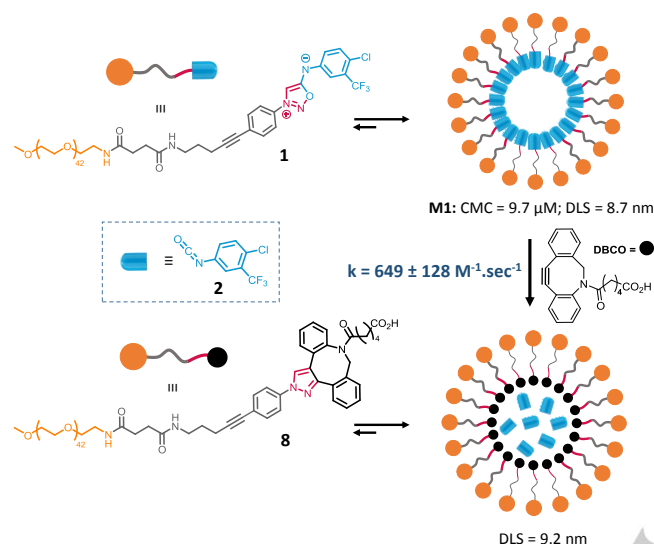


Figure 3. Formation, characterization of micelles **M1** and reactivity towards DBCO. CMC and size were determined using surface tension and DLS respectively.

In order to demonstrate that micelles **M1** can operate as nanoreactors inside living cells, we investigated the **SPSIC**-mediated urea formation using the fluorogenic aniline **BODIPY-NH₂** (Figure 4). Indeed, this compound displays fluorescence enhancement when the amine function is less delocalized into the BODIPY system.^[15] Control experiments confirmed that the formation of **BODIPY-urea**, resulting from the reaction of isocyanate **2** with **BODIPY-NH₂**, led to a significant increase in the fluorescence (Figure S7), facilitating the monitoring of the reaction in biological media. We then investigated the synthesis of **BODIPY-urea** inside micelles **M1** previously loaded with **BODIPY-NH₂** (**M1@BODIPY-NH₂**) by adding **DBCO** in the reaction medium. As shown in Figure 4A, the **SPSIC** reaction triggered a quick fluorescence increase that reached a plateau after 5 min indicating the complete formation of the **BODIPY-urea**. Following these promising results, we pursued our study by exploring the possibility to carry out such a synthetic process inside living cells. For this purpose, HepG2 tumor cells (human liver carcinoma) were incubated for 2 hours with micelles **M1@BODIPY-NH₂**, thereby allowing their cellular internalization. The cells were then washed to remove non-internalized micelles and the fluorescence within the cells of either **BODIPY-NH₂** or **BODIPY-urea** was monitored by confocal microscopy imaging (Figures 4B and 4C). When **BODIPY-NH₂** and **BODIPY-urea** were incubated at 50 μM, a significant green fluorescence was observed inside cancer cells (entries 3 and 4) in comparison to control experiments (entries 1 and 2). As expected, the

fluorescence recorded in cells treated with **BODIPY-urea** was higher than in those that received **BODIPY-NH₂**. Incubation of **M1@BODIPY-NH₂** (50 μM equivalent **BODIPY-NH₂**) with the cells also led to the appearance of intracellular green fluorescent dots confirming micelles internalization (entry 5). However, addition of **DBCO** in the culture medium produced a significant fluorescence enhancement, hence highlighting the formation of **BODIPY-urea** inside living cancer cells (entry 6). Confocal microscopy revealed green spherical spots within the cytoplasm of the cells (Figure S14), suggesting the preservation of the spherical nanostructure of micelles following the **SPSIC** reaction. This result indicated that the coupling between an exogenous amine and an isocyanate, produced in situ through the **SPSIC** reaction, can proceed efficiently within complex biological medium. In fact, using our nanoreactors, the urea formation occurred in a confined environment, isolated from the numerous nucleophiles naturally present inside cells, thereby favoring the expected coupling reaction.

We next considered using such bioorthogonal-responsive nanoreactors for the in situ synthesis of urea-containing drugs. Within this framework, we turned our attention to Sorafenib (**SOR**, Figure 5), a FDA approved multikinase inhibitor currently employed for the treatment of several malignancies including kidney and liver cancers.^[16] Thus, we investigated the formation of the urea **SOR** inside micelles **M1** loaded with the aniline **3** (**M1@3**, Figure 5A). In the first experiment conducted in aqueous solution, we encapsulated 1.3 equiv. of **3** compared to amphiphile **1** and triggered the **SPSIC**-mediated release of isocyanate **2** by adding 1.5 equiv. of **DBCO** in the reaction medium. After 5 min under these conditions, the crude mixture was analyzed by HPLC and showed complete conversion of amphiphile **1** into **8** as well as the formation of **SOR** (Figures 5B and S9).

Interestingly, despite the sensitivity of the isocyanate **2** toward hydrolysis, no trace of the corresponding amine was detected by HPLC proving that **SOR** was formed in the confined environment of the micelle core. In contrast, when the same experiment was performed in a MeOH / H₂O mixture, avoiding the formation of micelles **M1**, only small amount of **SOR** was observed due to massive hydrolysis of isocyanate **2**.

The nanoreactor was then investigated for its ability to produce **SOR** inside HepG2 tumor cells following bioorthogonal activation. In this case, cancer cells were treated for 2 hours with **M1@3** (50 μM equivalent of **3**) and washed twice with fresh culture medium to withdraw non-internalized micelles. **DBCO** (75 μM) was next incubated with the cells and treatment effects were assessed on cell proliferation, apoptosis and both ERK (Extracellular signal-Regulated Kinase) and JNK (c-Jun NH₂-terminal Kinase) signaling pathways that are known to be targeted by **SOR** (Figure 6).^[17-19] Thus, the antiproliferative activity of **M1@3** was evaluated using Ki-67 assay and compared to that of **SOR** at 50 μM (Figure 6A). Control experiments showed that neither aniline **3** nor empty micelles **M1** exhibited substantial cellular toxicity, when incubated alone or in the presence of **DBCO**. Similarly, treatment of HepG2 cells with **M1@3** in the absence of **DBCO** did not result in a significant reduction of cell proliferation. However, addition of **DBCO** in the culture medium of cells previously treated with **M1@3** triggered a strong antiproliferative activity, which was comparable to that observed with **SOR**.

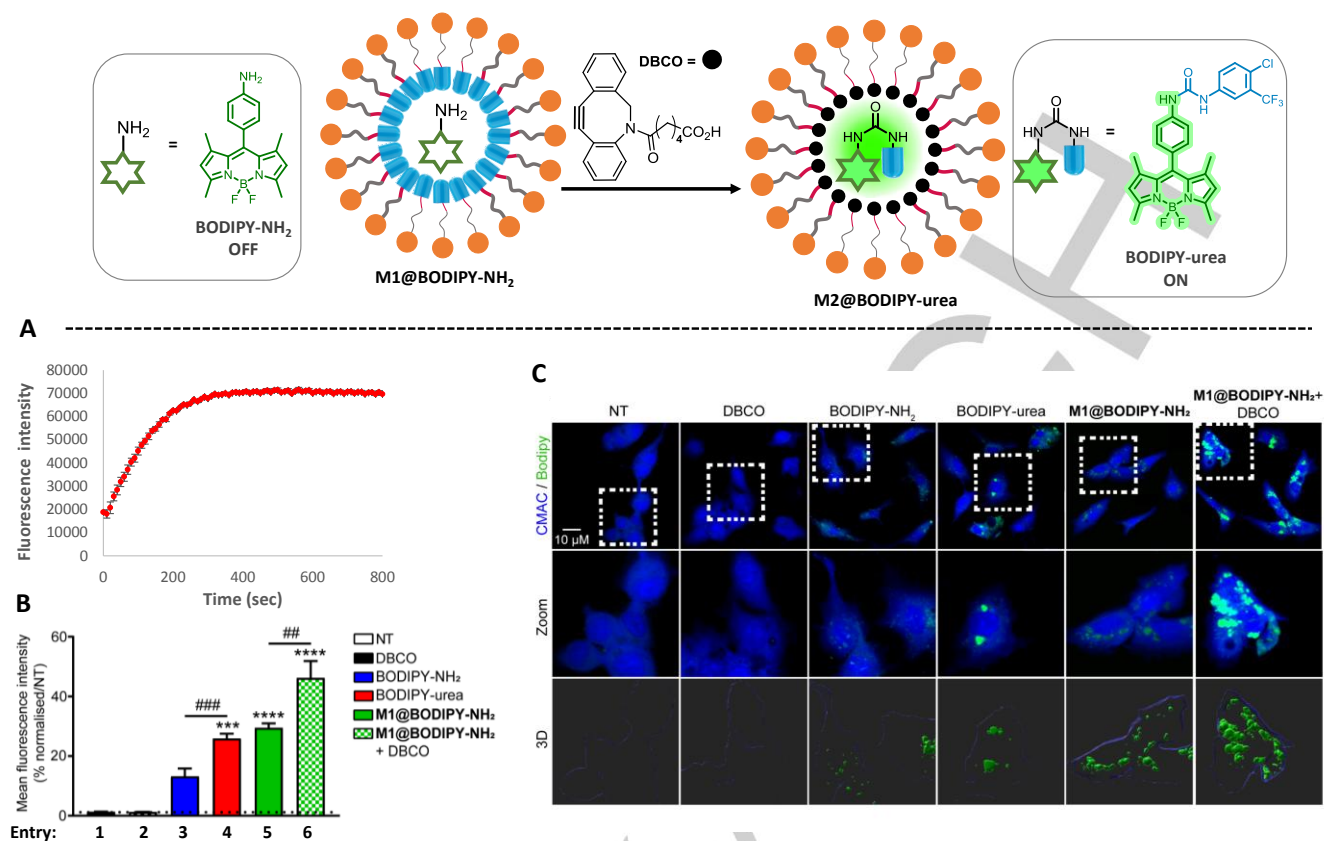


Figure 4 Synthesis of ureas inside living cancer cells through the SPSIC-mediated activation of nanoreactors. A) Fluorescence over the time of micelles **M1@BODIPY-NH₂** (100 μ M) when placed in the presence of **DBCO** (150 μ M) in water. Fluorescence enhancement is consistent with the formation of micelles **M2@BODIPY-urea** triggered by the SPSIC reaction; B) Quantification of the mean fluorescence intensity inside HepG2 tumor cells treated with **M1@BODIPY-NH₂** (50 μ M) and **DBCO** (70 μ M) for 30 min. Values represent the mean \pm SEM from three independent experiments. Statistical significance was determined by a One-Way ANOVA test with multiple comparisons followed by Tukey posttest (**: $p < 0,001$; ****: $p < 0,0001$ = NT vs **BODIPY-urea**, **M1@BODIPY-NH₂**, **M1@BODIPY-NH₂ + DBCO** and #: $p < 0,01$ = **M1@BODIPY-NH₂** vs **M1@BODIPY-NH₂ + DBCO**; ###: $p < 0,001$ = **BODIPY-NH₂** vs **BODIPY-urea**); C) Representative confocal microscopy pictures showing green BODIPY signal inside HepG2 tumor cells (blue) treated as indicated.

Following these results, we pursued the biological evaluations of micelles **M1@3** by analysing their effects on cancer cell apoptosis using Annexin V assays (Figure 6B). In these experiments, a significant increase in apoptosis was observed only when HepG2 cells were treated with **SOR** or the **M1@3 / DBCO** combination. Once again, biological consequences of both treatments were similar, therefore suggesting that the SPSIC-mediated micelles activation led to the efficient production of **SOR** inside tumor cells. In order to verify this hypothesis, we examined the impact of micelles **M1@3** on ERK and JNK phosphorylation (Figure 6C-D). Thus, when **M1@3** were incubated in the culture medium with **DBCO**, the amount of phosphorylated ERK (p-ERK) was reduced of approximately 40 % compared to untreated HepG2 cells. Such a decrease was not observed upon treatments with **3**, empty micelles **M1** or **M1@3** alone. In contrast, treatment of cells with **SOR** led to a nearly identical effect.

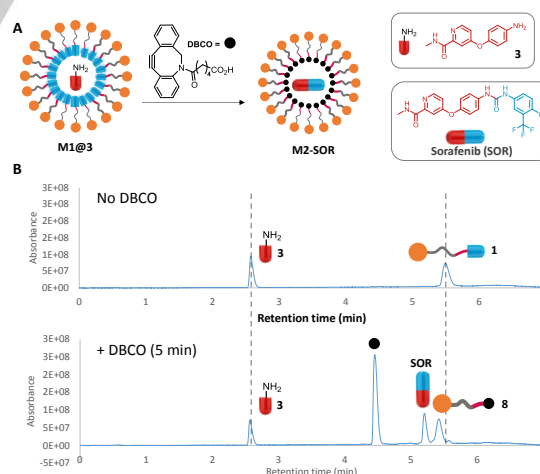


Figure 5 A) Principle of Sorafenib formation inside micelles **M1@3** through the SPSIC reaction; B) Synthesis of Sorafenib in aqueous medium monitored by HPLC after 5 minutes incubation of micelles **M1@3** (200 μ M) with **DBCO** (300 μ M).

At the same time, consistent results were obtained for JNK phosphorylation. Indeed, similar increase in phosphorylated JNK

(p-JNK) amount was recorded with either **SOR** or the **M1@3** / **DBCO** combination while no significant variation in p-JNK expression was noticed when cells were incubated with **3**, empty micelles **M1** or **M1@3** alone. Thus, these whole results demonstrated unambiguously the production of **SOR** inside living cancer cells.

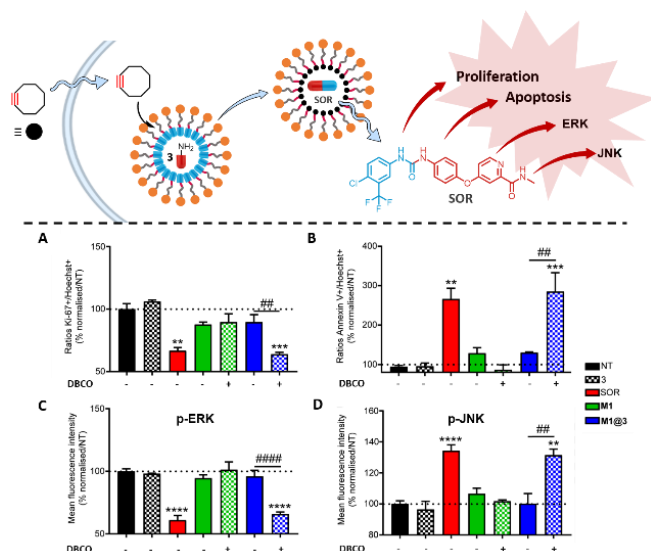


Figure 6. Biological evaluation of nanoreactors **M1@3**. A) Cell proliferation. Quantification of the ratio Ki-67 positive HepG2 cells / total HepG2 cells. B) Cell apoptosis. Quantification of the ratio Annexin V positive HepG2 cells / total HepG2 cells; C) p-ERK immunodetection assays; D) p-JNK immunodetection assays. Values represent the mean \pm SEM from three independent experiments. Statistical significance was determined by a Two-Way ANOVA test with multiple comparisons followed by Tukey posttest (** : $p < 0,01$; *** : $p < 0,001$; **** : $p < 0,0001$ = NT vs other treatments; ## : $p < 0,01$; #### : $p < 0,0001$ = **M1@3** with or without **DBCO**).

In conclusion, we have developed a new strategy to perform organic synthesis in biological media by designing biocompatible nanoreactors that can be activated on demand in a bioorthogonal manner. Taking advantage of the **SPSIC** reaction, these latter have the ability to generate reactive isocyanates under confined environment that react then with encapsulated amines for producing ureas, in spite of the presence of the surrounding endogenous nucleophiles. This approach is compatible with the *in situ* synthesis of bioactive compounds such as the FDA approved anticancer drug Sorafenib. Thus, this novel synthetic strategy extends the scope of chemical functions that can be formed selectively in living systems, including some of those built into the structure of endogenous molecules such as urea. Since isocyanates react readily with alcohols and thiols, stimuli-responsive nanoreactors could be designed for the synthesis of either carbamate- or thiocarbamate-containing derivatives. The concept described in this article should be easily extended to other types of molecular construction in living systems. In fact, a wide array of chemical functionalities can be released *via* bioorthogonal reactions, and their confinement within nanoreactors could then be exploited to perform a panel of non-bioorthogonal reactions in biological systems.

Acknowledgements

This work was supported by the Agence Nationale pour la Recherche (ANR-19-CE06-0006-01). The authors also thank La

Ligue contre le Cancer for financial support. The authors thank David-Alexandre Buisson and Sabrina Lebrequier for excellent analytical support.

Keywords: Mesoionics • Click chemistry • Nanoreactors • Chemical Biology • Cancer

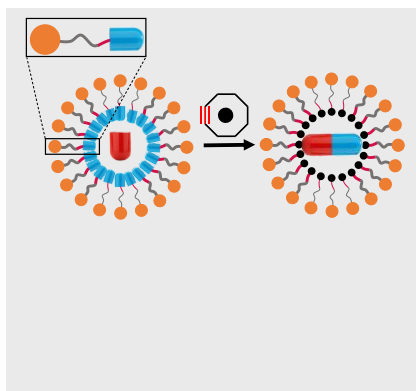
- [1] a) H. C. Hang, C. Yu, D. L. Kato, C.R. Bertozzi *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 14846; b) E. M. Sletten, C. R. Bertozzi *Angew. Chem. Int. Ed.* **2009**, *48*, 6974; c) J. A. Prescher, C. R. Bertozzi, *Nat. Chem. Biol.* **2005**, *1*, 13.
- [2] For recent reviews see: a) D. Schauenburg, T. Weil, *Adv. Sci.* **2024**, *11*, 2303396; b) Q. Fu, S. Shen, P. Sun, Z. Gu, Y. Bai; X. Wang, Z. Liu *Chem. Soc. Rev.* **2023**, *52*, 7737; c) Q. Min, X. Ji *J. Med. Chem.* **2023**, *66*, 16546; d) M. M. A. Mitry, F. Greco, H. M. I. Osborn *Chem. Eur. J.*, **2023**, *29*, e202203942. e) K. Porte, M. Riberaud, R. Châtre, D. Audisio, S. Papot, F. Taran *ChemBioChem* **2021**, *22*, 100.
- [3] J. Lie, P. R. Chen *Nat. Chem. Biol.* **2016**, *12*, 129.
- [4] a) A. H. A. M. van Onzen, R. M. Versteegen, F. J. M. Hoeven, I. A. W. Filot, R. Rossin, T. Zhu, J. Wu, P. J. Hudson, H. M. Janssen, W. ten Hoeve, M. S. Robillard *J. Am. Chem. Soc.* **2020**, *142*, 10955; b) K. Neumann, A. Gambardella, A. Lilienkamp, M. Bradley *Chem. Sci.*, **2018**, *9*, 7198; c) X. Ji, Z. Pan, B. Yu, L. K. De La Cruz, Y. Zheng, B. Ke, B. Wang *Chem. Soc. Rev.* **2019**, *48*, 1077.
- [5] a) J. Miguel-Avila, M. Tomas-Gamasa, J. L. Mascareñas *Trends Chem.* **2023**, *5*, 74; b) P. Destito, C. Vidal, F. Lopez, J. L. Mascareñas *Chem. Eur. J.* **2021**, *27*, 4789.
- [6] a) J. Miguel-Avila, M. Tomas-Gamasa, A. Olmos, P. J. Perez, J. L. Mascareñas, *Chem. Sci.*, **2018**, *9*, 1947; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596; c) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057.
- [7] J. Clavadetscher, S. Hoffmann, A. Lilienkamp, L. Mackay, R. M. Yusop, S. A. Rider, J. J. Mullins, M. Bradley, *Angew. Chem. Int. Ed.* **2016**, *55*, 15662.
- [8] Z. Gao, Y. Li, Z. Liu, Y. Zhang, F. Chen, P. An, W. Lu, J. Hu, C. You, J. Xu, X. Zhang, B. Sun. *Nano Lett.* **2021**, *21*, 3401.
- [9] Y. You, Q. Deng, Y. Wang, Y. Sang, G. Li, F. Pu, J. Ren, X. Qu. *Nat. Commun.* **2022**, *13*, 1459.
- [10] J. Clavadetscher, E. Indrigo, S. V. Chankeshwara, A. Lilienkamp, M. Bradley. *Angew. Chem. Int. Ed.* **2017**, *56*, 6864.
- [11] a) C. Vidal, M. Tomás-Gamasa, P. Destito, F. López, J. L. Mascareñas. *Nat. Commun.* **2018**, *9*, 1913; b) C. D'Avino, S. Gutiérrez, M. J. Feldhaus, M. Tomas-Gamasa, J. L. Mascareñas *J. Am. Chem. Soc.* **2024**, *146*, 2895.
- [12] a) R. Huang, C-M. Hirschbiegel, V. Lehot, L. Liu, Y. A. Cicek, V. M. Rotello. *Adv. Mater.* **2024**, *36*, 2300943; b) W. Wang, X. Zhang, R. Huang, C-M. Hirschbiegel, H. Wang, Y. Ding, V. M. Rotello. *Adv. Drug Deliv. Rev.* **2021**, *176*, 113893; c) P. Destito, A. Sousa-Castillo, J. R. Couceiro, F. Lopez, M. A. Correa-Duarte, J. L. Mascareñas. *Chem. Sci.*, **2019**, *10*, 2598.
- [13] a) K. Porte, B. Renoux, E. Péraudeau, J. Clarhaut, B. Eddhif, P. Point, E. Gravel, E. Doris, A. Wijkhuisen, D. Audisio, S. Papot and F. Taran. *Angew. Chem. Int. Ed.* **2019**, *58*, 6366; b) L. Madegard, M. Girard, B. Riss Yaw, K. Porte, D. Audisio, S. Papot, F. Taran, *Chem. Eur. J.*, **2023**, *29*, e202301359.
- [14] a) S. Bernard, D. Audisio, M. Riomet, S. Bregant, A. Sallustrau, L. Plougastel, E. Decuypere, S. Gabillet, R. A. Kumar, J. Elyan, M. Nguyen Trinh, O. Koniev, A. Wagner, S. Kolodych, F. Taran. *Angew. Chem. Int. Ed.* **2017**, *56*, 15612; b) M. Ribéraud, K. Porte, A. Chevalier, L. Madegard, A. Ratchet, A. Delaunay-Moisan, F. Vinchon, P. Thuéry, G. Chiappetta, P. A. Champagne, G. Pieters, D. Audisio, F. Taran. *J. Am. Chem. Soc.* **2023**, *145*, 4, 2219.
- [15] D. Aydın Tekdaş, G. Viswanathan, S. Zehra Topal, C. Y. Looi, W. F. Wong, G. Min Yi Tan, Y. Zorlu, A. G. Gürek, H. B. Lee et F. Dumoulin, *Org. Biomol. Chem.*, **2016**, *14*, 2665.
- [16] S. Wihelm, C. Carter, M. Lynch, T. Lowinger, J. Dumas, R. A. Smith, B. Schwartz, R. Simantov, S. Kelley, *Nat. Rev. Drug Discov.* **2006**, *5*, 835.

-
- [17] M. Cervello, D. Bachvarov, N. Lampiasi, A. Cusimano, A. Azzolina, J. A. McCubrey, G. Montalto, *Cell Cycle*, **2012**, *11*, 2843.
- [18] L. Liu, Y. Cao, C. Chen, X. Zhang, A. McNabola, D. Wilkie, S. Wilhelm, M. Lynch, C. Carter, *Cancer Res.*, **2006**, *66*, 11851.
- [19] D. Yan, X. Yan, X. Dai, L. Chen, L. Sun, T. Li, F. He, J. Lian, W. Cai, *Oncol. Rep.*, **2019**, *42*, 785.

WILEY-VCH

COMMUNICATION

Behind bioorthogonal chemistry: micelles constructed with amphiphiles bearing bioorthogonal reactants allowed non-bioorthogonal chemistry in a confined environment. Application of this strategy was made with the synthesis of an FDA-approved anticancer drug inside living cells. Apart from this application, this strategy could represent a change of paradigm, allowing an extension of the concept of bioorthogonal chemistry.



Léa Madegard, Melissa Girard, Estelle Blochouse, Benjamin Riss Yaw, Alberto Palazzolo, Mélanie Laquembe, Davide Audisio, Pauline Poinot, Sébastien Papot and Frédéric Taran

Page No. – Page No.

Bioorthogonal Nanoreactors for Abiotic Chemistry in Living Cells