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# HOCl-triggered amino or carboxyl uncaging platform and its application for imaging and drug design

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**Abstract:** The overproduction of hypochlorous acid (HOCl) is highly correlated with diseases such as atherosclerosis, rheumatoid arthritis and cancer. Whilst acting as a marker of these diseases, HOCl might also be used as an activator of prodrugs or drug delivery systems for the treatment of the corresponding disease, an area that is so far unexplored. In this work, a new platform has been developed that can be used to design and synthesize HOCl probes that integrate detection, imaging and therapeutic functions. The probes derived from this platform can be used to detect HOCl using both NIR emission and the naked eye *in vitro*, with high sensitivity and selectivity at ultralow concentrations (the detection limit is at the nM level). Basal levels of HOCl can be imaged in HL-60 cells without special stimulation. Moreover, the probes provided by this platform can rapidly uncage amino or carboxyl groups from prodrugs during HOCl detection and imaging to realize a therapeutic effect. This platform thus provides new opportunities for the design of multifunctional probes that integrate detection, imaging and therapeutic functions.

Stimuli-responsive 'smart' prodrugs have recently attracted increasing attention because of their ability to improve efficacy and avoid severe side effects.[1] Such prodrugs could be activated by pH and/or redox,[2] ATP,[3] enzyme,[4] reactive oxygen species (ROS),[1c, 5] etc.[1b, 1d] In past few years, we have developed some stimuli-responsive systems[6] and built ROS-identifying fluorescent probes for the detection of biomarkers (e.g. $H_2O_2$ and •OH) in biological systems.[7] Recently, we paid high attention on ROS-triggered prodrugs and found that although most reported ROS-triggered prodrugs or drug release systems could be used to uncage/release drugs *in vitro* or *in vivo*, low reactivity and sensitivity (typically requiring hours or molar levels of ROS to trigger drug release) limited their biological application.[1a, 8]

Among the various ROS, hypochlorous acid (HOCl), generated via peroxidation of chloride ions ($Cl^-$) by hydrogen peroxide ($H_2O_2$) catalyzed by myeloperoxidase (MPO), is an extremely important bactericidal oxidant *in vivo* that plays a protective role in human health.[9] However, overproduction of HOCl has been implicated in an array of pathological disorders, such as atherosclerosis, rheumatoid arthritis and cancer.[10] Whilst acting as a marker for these diseases, HOCl might also be exploited as an activator of prodrugs or drug delivery systems to treat them. However, until now, most chemical tools related to HOCl have focused only on the identification of HOCl *in vitro* or *ex vivo*.[11] Thus a special fluorophore was generally selected as the released model molecule. None of the methods are able to uncaging functional groups such as amino or carboxyl derivatives for activation of prodrugs or drug release systems. It is therefore of vital importance to develop an HOCl stimulus-responsive platform that can be easily used to integrate detection, imaging and therapy of HOCl-related disease.

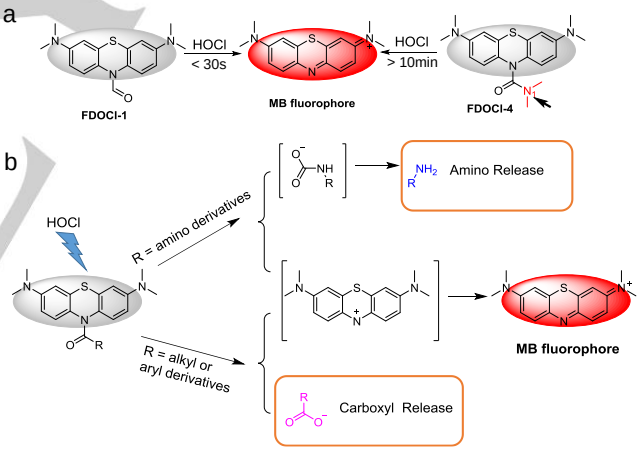


**Figure 1.** (a) Our previous work and (b) the design strategy of this work

We recently reported a new deformylation reaction-based probe by delivering methylene blue (MB) (**FDOCl-1** in **Figure 1**) for rapid detection of HOCl *in vivo*, in which, near infrared fluorescence was switched on when a leucomethylene (LMB) derivative was converted to MB in the presence of HOCl. [12] To further develop this system into a HOCl responsive drug delivery system, we therefore compared the reaction efficiency and products of different derivatives of LMB. We found that the reaction time of dimethylamino carbamide derivative (**FDOCl-4**) with HOCl was > 10 min, much slower than that of **FDOCl-1** (**Figure 1a**), however, when the dimethylamino group of **FDOCl-4** was replaced by $NH_2$ or NHR, or the outer amide group was replaced by alkyl group, the reaction with HOCl became much faster. Inspired by this observation, herein, an HOCl-triggered

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release platform was developed. In the presence of HOCl, this platform can not only produce NIR emissive MB fluorophore for detecting HOCl level, but also release amino or carboxyl group with high release efficiency (**Figure 1**). Since amino and carboxyl groups are functional sites in many anticancer or antiphlogistic drugs, this platform can be developed as an HOCl-triggered drug uncaging system that integrates imaging and therapeutic functions. As proof of concept, a model molecule was designed to illustrate the synergistic effect of imaging, delivery and therapeutic functions in this system.

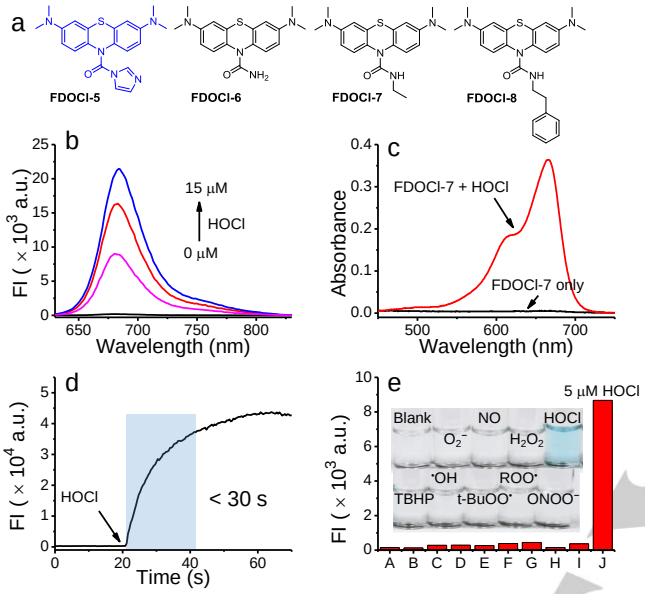


**Figure 2.** (a) Chemical structure of the compounds in **series-I**. (b) Fluorescent spectra of **FDOCI-7** (5 μM) before/after addition of different concentration of HOCl (0, 5, 10 and 15 μM). (c) Absorption spectra of **FDOCI-7** (5 μM) before/after addition of 15 μM HOCl. (d) Time-dependent changes in fluorescent intensity of **FDOCI-7** (5 μM) at 686 nm after adding HOCl (15 μM). (e) Fluorescent intensity of **FDOCI-7** (5 μM) at 686 nm after adding different ROS/RNS (20 μM) (from A to J: Blank, $O_2^-$, NO, $H_2O_2$, t-BuOOH, •OH, t-BuOO•, ROO•, $ONOO^-$ and HOCl); inset in e is the color changes of **FDOCI-7** (5 μM) after adding HOCl (15 μM) and other different ROS/RNS (20 μM). Time range 0–70 s; $\lambda_{ex}$ = 620 nm. The data was recorded in PBS (10 mM, 0.5% EtOH)

Given that primary, secondary and tertiary amines may have different steric hindrance or electrical properties, compounds **FDOCI-5**–**FDOCI-7** were synthesized by changing the substituent attached to the N1 atom of the urea bond of **FDOCI-4** to enhance HOCl sensitivity (**Figure 2a**). The ability of these three compounds to detect HOCl was then evaluated by spectroscopy under simulated physiological conditions (sodium phosphate buffer (PBS), 10 mM, pH 7.2, 0.5% EtOH). As shown in **Figures S1** and **2**, the fluorescence intensities of **FDOCI-6** and **FDOCI-7** at 686 nm both increased > 100-fold after treatment with HOCl (15 μM, 3.0 equiv), combined with increased absorption at 664 nm, indicating the production of MB (further confirmed by HRMS as shown in **Figure S2**). Further selectivity studies of **FDOCI-6** and **FDOCI-7** for HOCl found that similar ROS/RNS, including $H_2O_2$, $O_2^-$, t-BuOOH, NO, ROO•, $ONOO^-$, •OH and t-BuOO•, did not induce noticeable enhancement of the fluorescence intensity or absorption (**Figures S1e**, **S1f**, **2e** and **S3b**). Notably, only HOCl induced a blue color change that could be clearly observed by the naked eye (**Figures 2e** and **S1g**). However, the reaction of **FDOCI-5** with HOCl was so slow that equilibrium was not reached even after two hours (**Figure S4**). These results showed that the sensitivity of these compounds towards HOCl was clearly increased when the outer amide of the urea bond not fully substituted (**series-I**).

To confirm the amino uncaging capability of the series, a further four analogues containing different functional groups on the outer amide were designed and synthesized (**FDOCI-8**–**FDOCI-11**, **Figure 2a** and **S5,** crystallographic data for **FDOCI-11** was shown in **Table S1**). All of these compounds reacted rapidly with HOCl (typically < 60 s) with high sensitivity (typically > 100-fold increase of fluorescence intensity after treatment with 3.0 equiv of HOCl; **Figures S6**–**S9**) and selectivity. Moreover, both MB and phenylethylamine were observed in the reaction of **FDOCI-8** with HOCl, which was demonstrated by HRMS analysis (**Figure S10**). This demonstrated that **series-I** could uncage amino derivatives after reaction with HOCl.

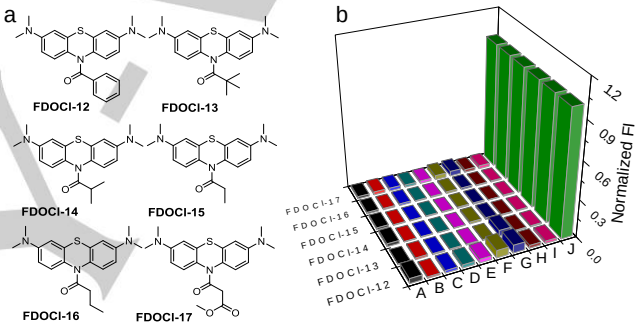


**Figure 3.** (a) Chemical structure of the compounds in **series-II**. (b) Fluorescence intensity of different probes (**FDOCI-12** ~ **FDOCI-17**, 5 μM) at 686 nm after adding various ROS/RNS. From A to J: Blank, $O_2^-$, NO, $H_2O_2$, t-BuOOH, •OH, t-BuOO•, ROO•, $ONOO^-$ and HOCl (5 μM HOCl were used for **FDOCI-13** and 1 μM HOCl were used for other probes; other ROS/RNS were 20 μM). The data was recorded in PBS (10 mM, 0.5% EtOH), $\lambda_{ex}$ = 620 nm.

In addition to changing the type of amino group in **series I**, we also tried to replace the urea bond with other functional groups to scale the HOCl responsive platform. **FDOCI-12**–**FDOCI-17**, replacing the urea group with amide group of different outer alkyl or aryl derivatives were therefore designed and synthesized (**series-II, Figure 3a,** crystallographic data for **FDOCI-16** was shown in **Table S1**). All of these compounds reacted rapidly with HOCl (typically < 60 s, **Figures S11**–**S16**). Further studies showed that changing the length of the carbon chain (e.g. **FDOCI-16**) or steric hindrance (e.g. **FDOCI-13** and **FDOCI-17**) had little influence on the reaction sensitivity even though the selectivity for HOCl slightly decreased when the position ortho to the carbonyl was saturated (**FDOCI-12** and **FDOCI-13**) (**Figure 3b**). However, even with high steric hindrance, the fluorescence intensity increase of **FDOCI-13** caused by 1 μM HOCl was 22.6–fold higher than that produced by 20 μM $ONOO^-$ (**Figure S12**). These data showed that the **series-II** compounds could react rapidly with HOCl with high sensitivity and selectivity. In addition to MB, reaction of **FDOCI-12** with HOCl also generated the carboxyl compound, benzoic acid, which was confirmed by HPLC (**Figure**

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**S17**). Moreover, further quantitative analysis by HPLC found that the release efficiency of **FDOCl-12** was over 70%.

Different compounds from the two series were chosen to study the detection limits of this platform for HOCl (**Table S2**). As shown in **Figures S18** and **S19**, the detection limit of all those compounds could reach to nM level (1.46 ~ 14.23 nM), confirming the high sensitivity of these two series derived from the HOCl detecting platform. Meanwhile, as shown in **Figures S18**, **S20** and **S21**, both series were stable in the pH range of 3–10 in the absence of HOCl, and remarkable fluorescence intensity enhancement was observed after addition of HOCl. Notably, the **series-II** probes maintained remarkable selectivity even under acidic (pH = 4.52) and alkaline (pH = 9.00) conditions (**Figures S18** and **S21**). Moreover, some cellular reductants such as formaldehyde and glucose, had very little impact on the reaction of the two series towards HOCl (**Figures S22**–**S25**). Meanwhile, even in the presence of 10 equiv of sulfhydryl compounds (50 μM), such as glutathione (GSH) and N-acetyl cysteine (NAC), HOCl (3.0 equiv) induced increased fluorescence intensity of these **FDOCl-n** probes. It should be noted that the ability of the probes to overcome interference decreased as steric hindrance increased in **series-II**. All these data illustrate that both of the two series could be used in complex cellular media.

By comparing the reaction efficiencies and products, we propose that reaction of compounds from both series with HOCl occurs via nucleophilic oxidation, as shown in **Figure S26**. The first step could be nucleophilic attack by HOCl on the electron-deficient carbon atom in amide carbonyl, followed by oxidation to cleave the amide. This would generate MB and release either a carboxyl derivative or an unstable carbamic acid that would rapidly hydrolyze in aqueous solution to form the amino derivative. This reaction mechanism is consistent with the observation that greater steric hindrance resulted in slower reaction, since nucleophilic attack by HOCl would be more difficult.

Since compounds from both series were remarkably effective *in vitro*, we then studied the application of the two series for HOCl detection in living cells and *in vivo*. The above **FDOCl** series compounds are not fluorescent until reaction with HOCl, so to enable visualization of cellular membrane transport of the probe, **FDOCl-18**, containing an additional green emissive naphthalene fluorophore to determine the distribution of the probe, was designed and synthesized (**Figure 4a**). After reaction with HOCl, both the absorption and fluorescence of MB were activated (**Figures 4b** and **4c**), while the fluorescence signal of the naphthalene was unchanged (**Figure 4c**).

Human promyelocytic leukemia (HL-60) cells, blood cancer cells that contain an abundance of MPO for endogenic generation of HOCl, were chosen as the cell model in this study.[13] As shown in **Figure 4d1**, HL-60 cells incubated in cell medium displayed no fluorescence, while those incubated with **FDOCl-18** showed remarkable fluorescence in both the green (**Figure 4e1**) and red channels (**Figure 4e3**). The fluorescence in the green channel indicates that the probe has good cell membrane permeability. To confirm the fluorescence in the red channel coming from intracellular basal HOCl, 4-aminobenzoic acid hydrazide (ABAH), an MPO inhibitor that should decrease the level of HOCl, was also added (**Figure 4f1-4f3**). As expected, the fluorescence intensity in the red channel in the presence of ABAH was clearly decreased, confirming that the red fluorescence in the cells was induced by HOCl. Cells with low MPO expression, such as HeLa cells, were also used to study the performance of **FDOCl-18**. As shown in **Figure S27**, although the probe was able to penetrate the cell (the fluorescence in the green channel), no significant fluorescence enhancement was observed in the red channel until treatment with HOCl. However, there was a remarkable increase in red fluorescence intensity after treatment with HOCl. The results demonstrated that the probe was able to distinguish cells with high and low expression of HOCl. To confirm the universality of this platform, a further two compounds, **FDOCl-8** (**series-I**, **Figure S28**) and **FDOCl-12** (**series-II**, **Figure S29**), were also studied in live cells. As expected, both compounds were able to detect basal HOCl in HL-60 cells. These data illustrated that both series have good sensitivity to HOCl in cells.

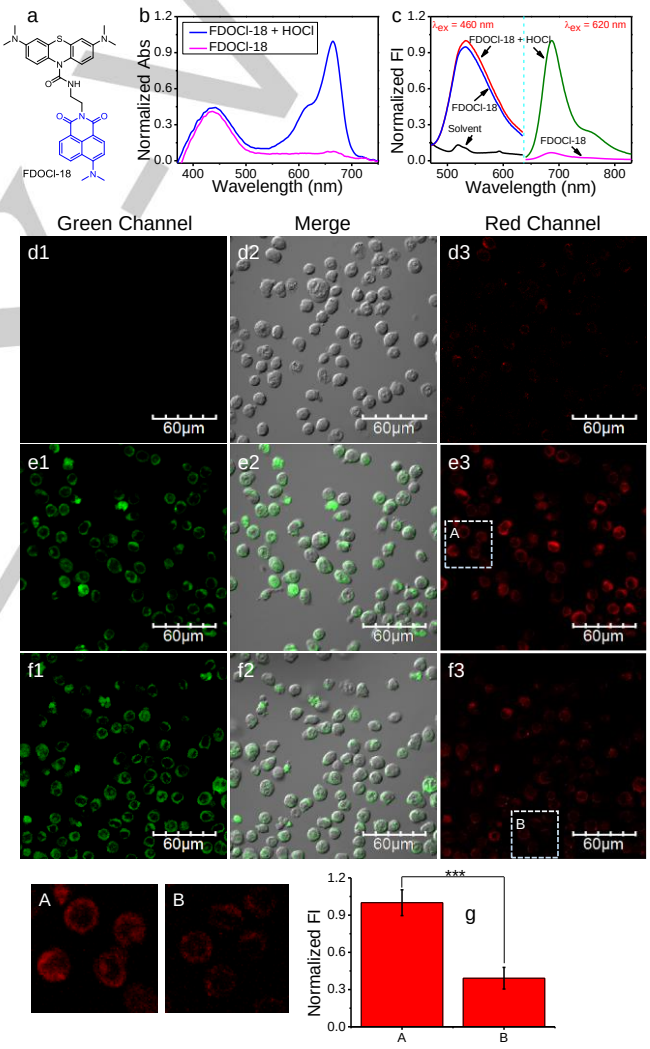


**Figure 4.** (a) Chemical structure of **FDOCl-18**. (b) Fluorescent spectra and (c) absorption spectra of **FDOCl-18** (5 μM in THF-PBS solution (1/1, v/v, 10 mM, pH = 7.2)) before/after addition of 15 μM HOCl. CLSM images of HL-60 cells (d1, d2, d3) without any treatment; (e1, e2, e3) incubated with **FDOCl-18** (10 μM) for 12 h; (f1, f2, f3) preincubated with ABAH (200 μM) for 1 h then incubated with ABAH (200 μM) and **FDOCl-18** (10 μM) for 12 h. (h) The fluorescence intensity within square A and B in e3 and f3, respectively. Red channel: 700 ± 50 nm, λex = 633 nm; Green channel: 535 ± 25 nm, $\lambda_{ex}$ = 488 nm, ***$P$ < 0.001.

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*In vivo* studies were then carried on using mouse model of arthritis generated according to our reported method (details in supporting information).[12] The three typical probes **FDOCl-12** (**series II**), **FDOCl-6** and **FDOCl-8** (**series I**) were selected for the *in vivo* detection. As shown in **Figure S32**, after injected with the same amount of probes (100 μL, 1 mM), only the arthritic paw area displayed remarkable fluorescent signal (**Figure S32**). In the control paws, without λ-carrageenan-induced arthritis, no fluorescent signal was observed (**Figures S33** and **S34**). These data illustrated that all the two series could be used to identify HOCl *in vivo*.

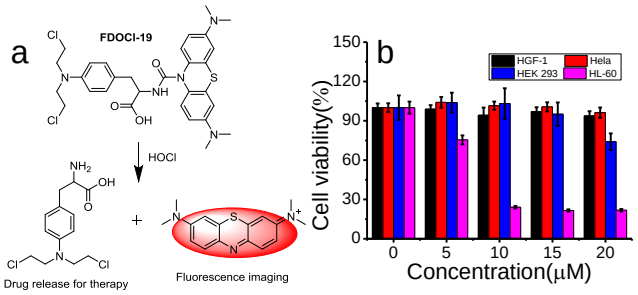


**Figure 5.** (a) Chemical structure of **FDOCl-19**. (b) The cell viability of **FDOCl-19** at different concentrations (0, 5, 10, 15 and 20 μM) in different cell lines for 12 h. The toxicity of the compounds was measured by CCK-8 assay.

Compared with other HOCl probes, the most obvious advantage of this platform is the uncaging of amino or carboxyl groups when imaging HOCl. Considering that amino and carboxyl groups are present in many organic compounds and medicines, this platform may enable construction of multifunctional probes that integrate imaging and therapeutic functions.[14] To exemplify the concept, an HOCl-triggered prodrug (**FDOCl-19**) was synthesized using a marketed drug melphalan (a kind of anticancer drug for treating multiple myeloma) as the parent drug since the amide derivatives of melphalan are generally less cytotoxic than the parent drug (**Figure 5**).[15] When treated with HOCl, both the fluorescence intensity and absorbance of **FDOCl-19** increased a lot coupled with the release of melphalan with high release efficiency (> 70%) (**Figures S35** and **S36**). The bioactivity studies in cells shown that **FDOCl-19** was highly cytotoxic toward HL-60 cells, reducing cell viability to < 30% after incubation with 10 μM **FDOCl-19** for 12 h (**Figure 5b**). Meanwhile, the prodrug was found to be non-toxic toward cell lines that had low MPO expression, such as human gingival fibroblasts (HGF-1), HeLa and human embryonic kidney (HEK 293) cell lines. CLSM studies shown that only HL-60 cells treated with **FDOCl-19** shown remarkable fluorescence in the red channel, indicating that only HL-60 cells could active the prodrug and uncage the toxic drug melphalan when imaging (**Figures S37** and **S38**). The toxicity of the uncaged drug caused the morphology of fluorescent HL-60 cells quite different from those with low or none fluorescence (**Figure S37b**).

In conclusion, we have developed a new HOCl-responsive platform for the design and synthesis of probes that can integrate detection, imaging and therapeutic functions. The probes derived from this platform can be used to detect HOCl using both NIR emission and the naked eye *in vitro*, with high sensitivity and selectivity at ultralow concentrations (the detection limit is at the nM level) and image basal levels of HOCl in HL-60 cells without special stimulation. Moreover, the probes in this platform can release amino or carboxyl groups, which are ubiquitously present in drugs, both *in vitro* and during cell imaging in the presence of HOCl. This may enable the design of multifunctional probes that integrate imaging and therapeutic functions. This utility was confirmed using a ROS-related prodrug as an example to treat HL-60 cancer cells expressing high levels of HOCl. Further *in vivo* exploration of probes derived from this platform is ongoing.

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**Keywords:** hypochlorous acid • methylene blue • amino and carboxyl uncaging• bioimaging • therapy

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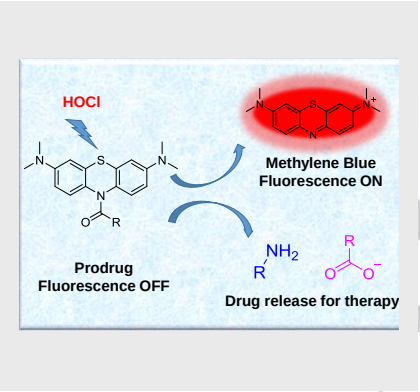
Layout 1:

## COMMUNICATION

An HOCl responsive platform has been developed that can integrate detection, imaging and therapeutic functions. The probes derived from this platform can not only detect HOCl by using NIR emission *in vitro* and *in vivo*, with high sensitivity and selectivity, but also rapidly uncage amino or carboxyl groups from prodrugs during HOCl detection and imaging to realize a therapeutic effect




*Peng Wei, Lingyan Liu, Ying Wen Guilong Zhao, Fengfeng Xue, Wei Yuan, Ruohan Li, Yaping Zhong, Mengfan Zhang and Tao Yi**

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**HOCl-triggered amino or carboxyl uncaging platform and its application for imaging and drug design**

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