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Synthesis of a lysosome-targeting aminoferrocene-based prodrug NCure2

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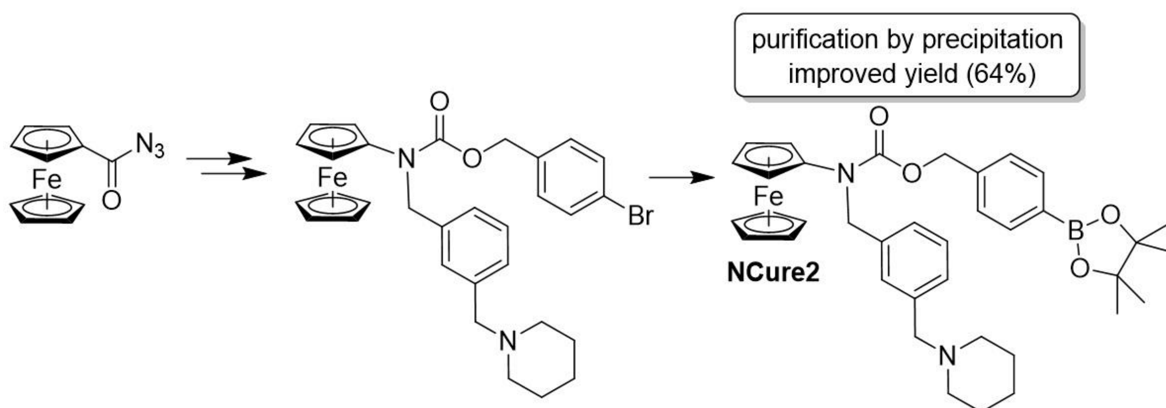
Abstract

Prodrugs can achieve targeting of cancer cells. Therefore, their application can improve the therapy of cancer diseases. The best aminoferrocene-based prodrug developed in the group of Mokhir is 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl (3-(piperidin-1-ylmethyl)benzyl) (ferrocenyl)carbamate, NCure2. It targets lysosomes of cancer cells, where it is activated by H_2O_2. Due to the presence of basic (amine) and Lewis acidic (boronic acid pinacol ester) moieties in NCure2, the previous synthesis is low yielding and purification is laborious. In this work we report on a significantly improved synthetic protocol for preparation of HCl salt of NCure2 by introducing the boronic acid moiety in the last synthetic step *via* Miyaura borylation conditions that allows the facile purification of the final product by its precipitation. This new approach makes NCure2·HCl more synthetically accessible that will facilitate its further pre-clinical and clinical studies.



Keywords: Anticancer prodrug, Aminoferrocene, Synthesis, Scale up, C-B Coupling

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Introduction

One possible approach for precise targeting of cancer cells is based on the prodrug concept. A prodrug is an inactive compound, which can be activated in cancer specific environment with formation of an active drug.[1] Since healthy cells do not possess such an environment, the prodrug remains inactive in these cells. For example, the group of Mokhir, as well as others, have explored differences in the level of H_2O_2 in cancer and healthy cells.[2-6] H_2O_2 is the most abundant intracellular reactive oxygen species (ROS). One of the most successful H_2O_2-responsive prodrugs activated by H_2O_2, which has been developed in the group of Mokhir up to date, is 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl (3-(piperidin-1-ylmethyl)benzyl) (ferrocenyl)carbamate, called NCure2.[7] Its chemical structure is shown in Figure 1.

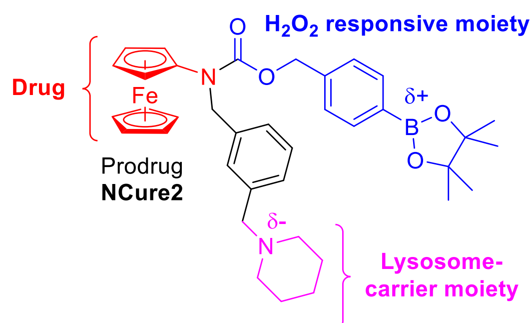

Figure 1. A structure of prodrug NCure2 highlighting with different colors the moieties important for its activity.

NCure2 contains three elements important for its activity. First, a basic piperidine moiety (magenta colored), which is a lysosomal carrier. Second, a Lewis acidic arylboronic acid pinacol ester (blue colored), which is cleaved in the presence of cancer specific levels of H_2O_2 and third, an aminoferrocene drug (red colored), which is released upon the cleavage of the arylboronic acid moiety and induces the oxidative stress in cancer cells leading to their death. NCure2 exhibits excellent antitumor activity *in vitro* in a variety of cancer cell lines derived from blood, ovary, lung and prostate and in some primary cells, e.g., chronic lymphocytic leukemia (CLL) cells. Importantly, it is also active *in vivo* in the Nemeth-Kellner-lymphoma (NK/Ly) model of murine cancer. NCure2 is not toxic towards healthy cell line SBLF9 and primary cells including neutrophils, monocytes, B and T cells at the therapeutically active concentrations.

Currently known methods of synthesis of this interesting prodrug are outlined in Scheme 1. The first method is based on *N*-alkylation of 4-(ferrocenylaminocarbonyloxymethyl)phenylboronic acid pinacol ester (**1**) with 1,3-bis(chloromethyl)benzene (**2**) in the presence of Cs_2CO_3, followed by amination of the resulting product **3** by using piperidine. These reactions can be conducted either one after another with isolation of the intermediate **3** or sequentially in one pot. In both cases the conversion of **1** to NCure2 is less than 5%. The isolation is tedious and leads to only traces of the desired product due to the presence of the large number of unidentified side products in the reaction mixture. We improved the initial protocol by coupling of pre-synthesized *N*-(3-(chloromethyl)benzyl)piperidine **4** to the starting material **1**. The conversion of **1** to NCure2 is 49% under these optimized conditions. Unfortunately, overalkylated (**5**), hydrolyzed NCure2 (**6**) as well as other unidentified products are also formed. Some of these side products are difficult to separate from NCure2 which reduces the yield of the isolated product to 24%. The latter optimized protocol was used extensively by our group for the preparation of 10 – 100 mg of NCure2 in one run that was sufficient for the majority of *in vitro* and preliminary *in vivo* studies. However, for further pre-clinical evaluation of this prodrug, e.g. *in vivo* studies in different cancer

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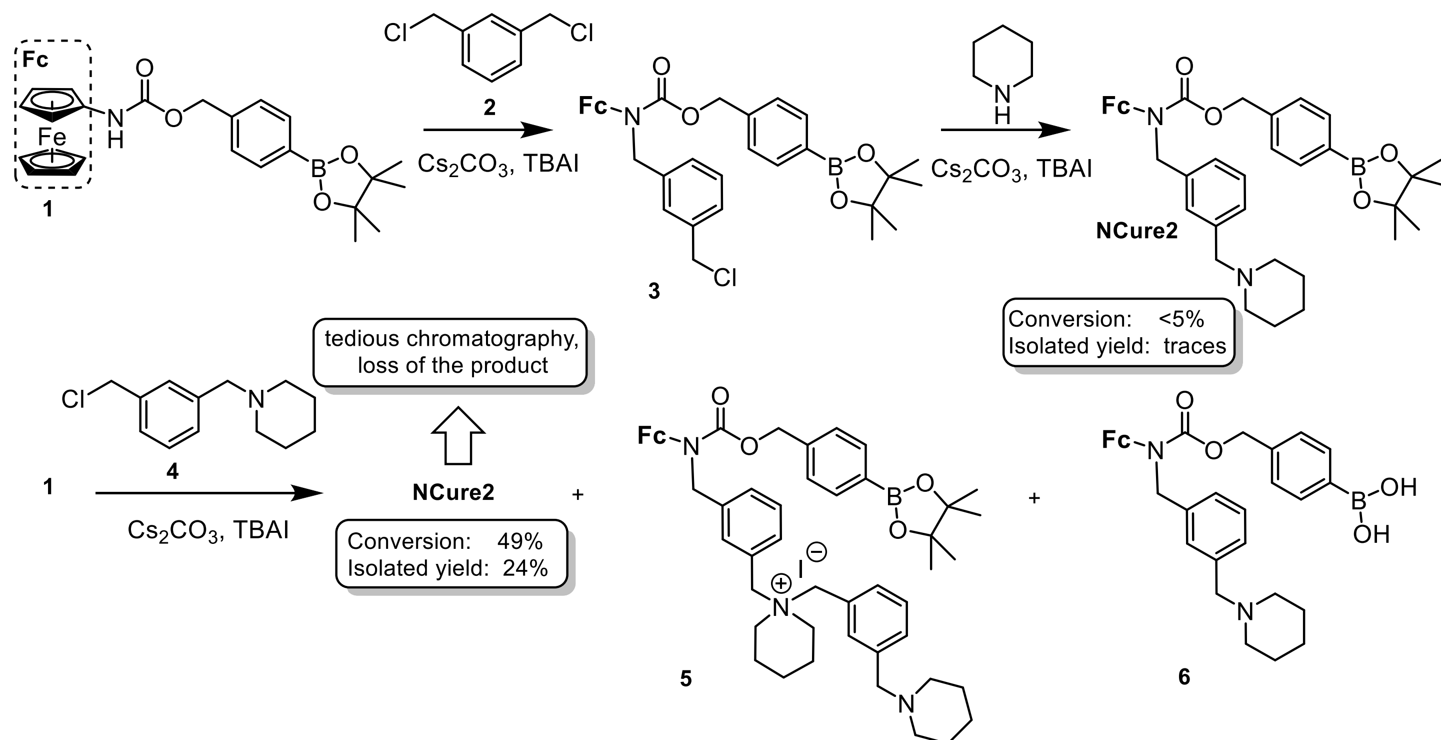
models in mice and rats, larger quantities (>100 mg) are required. The current work addresses this need by reporting an improved protocol that should enable facile larger scale synthesis of NCure2. The key advancement is the introduction of the boronic acid pinacol ester moiety during the last synthetic step, which occurs with almost quantitative conversion thereby eliminating the need for the extensive purification of the prodrug.



Scheme 1. Previous synthetic routes to NCure2.[7]

Results and Discussion

NCure2 is a polar compound due to the presence of a basic moiety (*N*-alkylated piperidine) and a Lewis acidic moiety (arylboronic acid pinacol ester). It is challenging to purify this compound even from simple mixtures by using flash chromatography, because it diffuses on the column to a broad band under all neutral, basic or acidic conditions, presumably owing to on column hydrolysis followed by strong absorption of the boronic acid product of the solid phase. Furthermore, purification of NCure2 on silica often leads to the on-column hydrolysis followed by strong, partially irreversible absorption of the boronic acid product **6** (Scheme 1) that contributes to the product loss. The latter property has been also described for other arylboronic acid esters.[8-10] To address these challenges, we planned the synthesis of NCure2 in a way that the last step is high yielding and produces side products which can be removed by non-chromatographic methods. The synthetic approach is outlined in Scheme 2. In contrast to the previous methods (Scheme 1), where the boronic acid pinacol ester was present from the very beginning (starting material **1**), the latter fragment is introduced in the last step in the new synthesis (Scheme 2). We selected for this critical step the Miyaura borylation, since its mild conditions are compatible with other functional groups present in NCure2. In particular, we started with Curtius rearrangement including the conversion of ferrocenecarboxylic azide (**7**) to ferrocenylisocyanate **8** in refluxing toluene, followed by trapping of the latter compound with 4-bromobenzyl alcohol (**9**) in the presence of Cs_2CO_3 with formation of

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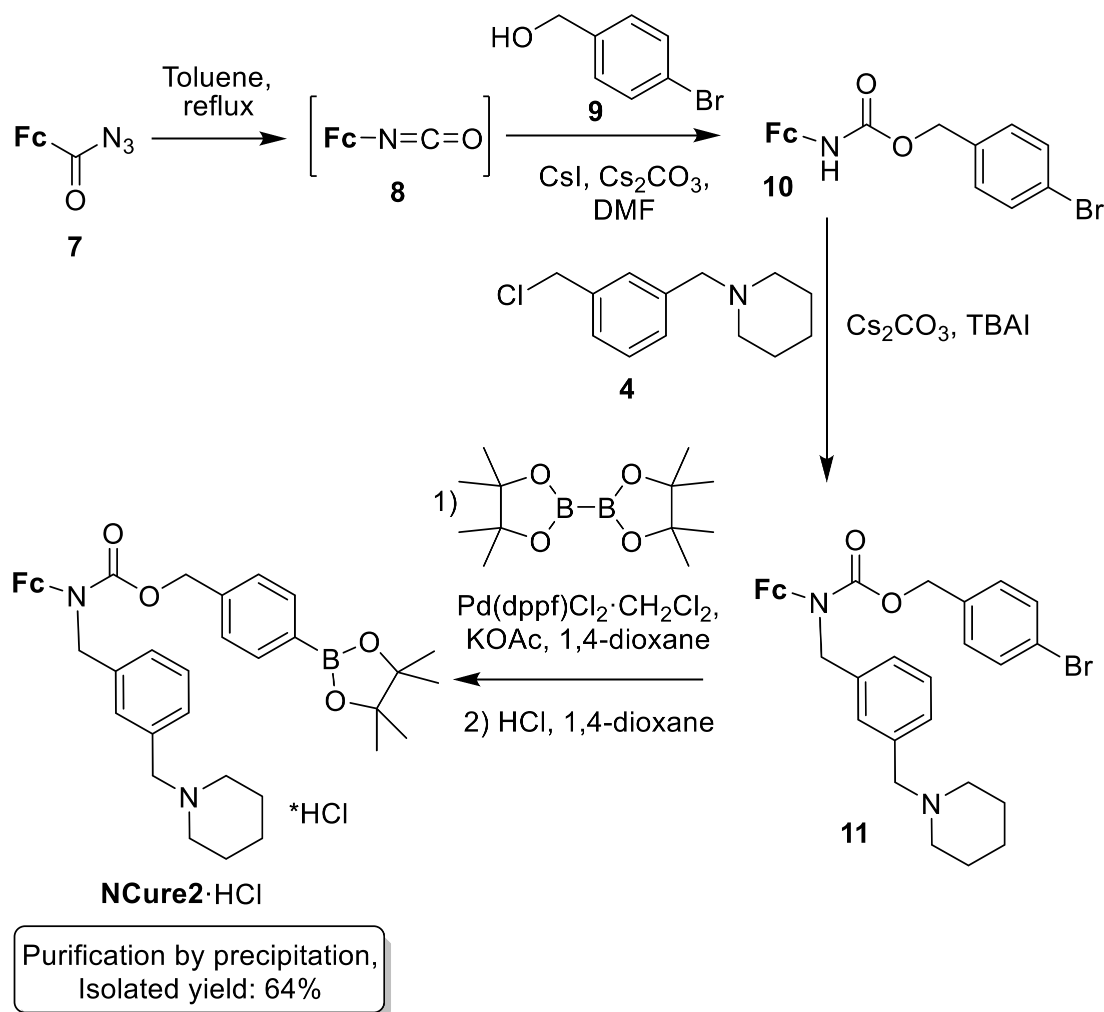
4-bromobenzyl (ferrocenyl)carbamate(**10**) with the excellent yield of 87%. Curtius reactions with azide **7** are well known and have been previously applied to a vast variety of alcohols.[11-13] Next, intermediate **10** was reacted with known *N*-(3-(chloromethyl)benzyl)piperidine (**4**)[7] to obtain precursor **11**. This compound was purified by silica column chromatography using the trimethylamine-containing eluent mixture to keep the aliphatic amine moiety in the deprotonated state to minimize strong absorption and diffusion of the band. The purification under these conditions was efficient and yielded 65% of **11**. In the final step, the boronate ester was introduced *via* Miyaura borylation using Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ as catalyst in 1,4-dioxane together with $(BPin)_2$ and KOAc. The mixture was degassed with N_2, sealed in a microwave tube and heated to 80 °C for 19 h. The product mixture was filtered through Celite® with charcoal topping, which removes palladium residues. Afterwards, the product NCure2 was transformed to its HCl salt by addition of a HCl solution in 1,4-dioxane. The solution was filtered once more to remove remaining Pd nanoparticles. Then, isopropanol was added, leading to precipitation of NCure2·HCl, which was filtered, washed and dried. Through precipitation, 64% yield of NCure2·HCl were obtained. Byproducts of the reaction remained in the mother liquor. The obtained product was unambiguously identified by high resolution, atmospheric pressure photoionization mass spectrometry (HRMS APPI) as well as ^{1}H and ^{13}C NMR spectroscopy (Figures S5 & S6, supporting information (*SI*)) and elemental analysis. The purity of the product was confirmed by thin layer chromatography in three different eluents.



Scheme 2. An improved method of synthesis of the prodrug NCure2·HCl.

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The new method gives rise to NCure2·HCl and the conventional method gives rise to NCure2 (Scheme 1). To compare qualities of the products obtained *via* these approaches, we converted the NCure2 obtained with the conventional route to its salt by adding HCl in 1,4-dioxane, followed by the precipitation of NCure2·HCl with isopropanol. According to ^{1}H NMR spectroscopy, both samples were found to be practically identical (Figure 2).

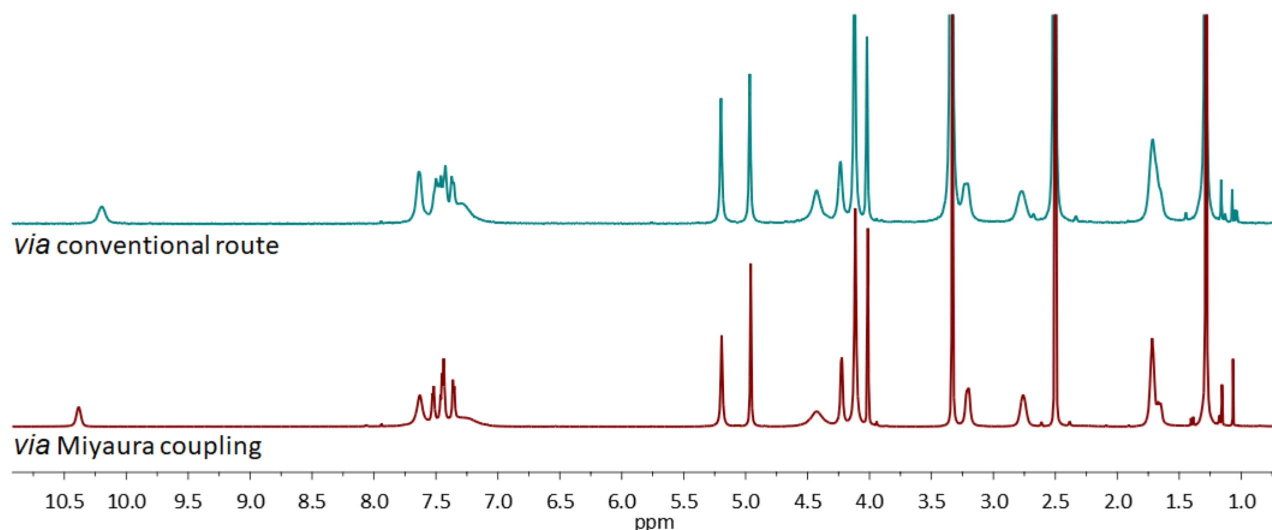

Figure 2. ^{1}H NMR spectra of NCure2·HCl synthesized by the conventional route[7] (upper trace) and Miyaura borylation (lower trace).

We obtained 453 mg of analytically pure NCure2·HCl in a single run without the need for tedious chromatographic purification in the last step. This protocol was repeated three times giving rise to similar yields of NCure2·HCl.

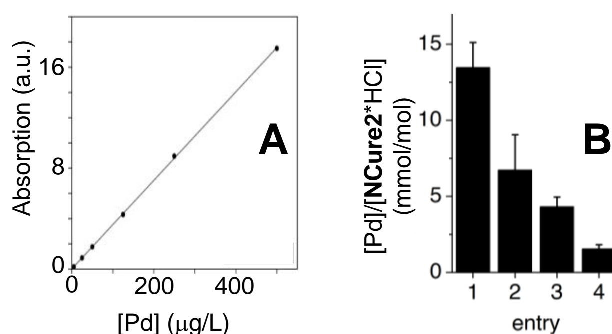

Figure 3. Atomic emission spectroscopy (AES) data. **A**: A calibration plot of the AES response (OY axis: absorbance, expressed in arbitrary units, a.u.) *versus* the concentration of $Pd(NO_3)_2$ solution in HNO_3 (OX axis: [Pd]). **B**: Content of Pd in samples of NCure2·HCl prepared by the new method described in this paper (entries 1-3). Entry 4: a negative control. Conventionally synthesized NCure2·HCl (Scheme 1) was used as a negative control, since no palladium-containing reagents were used during its synthesis.

Since palladium, palladium nanoparticles and ions can exhibit toxicity towards cells,[14-16] we tested the content of Pd in the samples of NCure2·HCl obtained from three independent syntheses, conducted by two different researchers. We used atomic emission spectroscopy (AES), since it is a highly sensitive method. Under

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our experimental settings, AES allowed the accurate detection of as little as 25 μg/L Pd in solution (235 nM) as it is apparent from the calibration of the AES signal intensity *versus* the concentration of Pd(II) (Figure 3A).

The data on the Pd content in the NCure2·HCl samples are provided in Figure 3B. We observed that the palladium concentration is increased statistically significantly in the samples of NCure2·HCl prepared by the new method when compared to the sample of the prodrug prepared by the conventional method (a negative control, entry 4): Student's t test, entry 1: $p<0.001$; entry 3: $p<0.05$; entry 3: $p<0.01$. The absolute palladium amount is 0.04 – 0.19% Pd in the samples of the prodrug.

To exclude that the Pd traces will have some effect on the biological activity of the NCure2·HCl, we investigated its cytotoxicity towards human ovarian cancer (A2780) cells. We used (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide probe (MTT) to determine the number of viable A2780 cells. Conventionally synthesized NCure2·HCl (Scheme 1) was used as a control lacking Pd traces (Figure 4). We found that there is no difference in the anticancer effect of NCure2·HCl prodrugs prepared by the different methods: inhibitory concentrations (IC_{50}'s) for the NCure2·HCl obtained by the new method (from 5.10 ± 0.02 μM to 5.62 ± 0.50 μM, entries 1-3) are the same as the IC_{50} for the NCure2·HCl obtained by the conventional method (4.97 ± 1.13 μM, entry 4; Student's t test, $p>0.05$ for all pairs). These data confirm that the Pd traces present in the samples obtained by the new method do not modulate their anticancer activity.

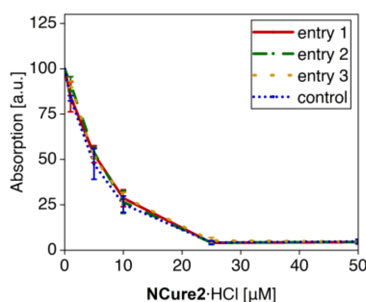

Figure 4. Effect of NCure2·HCl prodrugs obtained by different methods of the viability of A2780 cells.

Conclusions

We developed an alternative synthetic route to lysosome-targeting anticancer prodrug NCure2·HCl. By employing high-yielding Miyaura borylation in the final step to introduce the ROS-sensitive boronic acid pinacol ester, chromatographic purification was avoided during product isolation, minimizing losses. Atomic emission spectroscopy confirmed residual amounts of palladium (<0.19%), which, as shown by MTT assays on human ovarian cancer A2780 cells, did not affect the prodrug's cytotoxicity. This improved synthesis enhances the accessibility of NCure2·HCl, facilitating its preclinical and eventual clinical studies. Moreover, it offers a more scalable approach. However, further optimization is required to eliminate chromatography in the first two steps and develop a more effective protocol for palladium removal.

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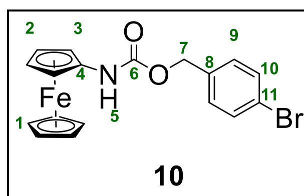
Experimental Section

General. Chemicals were used as received, if not stated otherwise. Dichloromethane (DCM) and EtOAc were distilled from K_2CO_3 before usage. Hexanes were distilled before usage. Thin Layer Chromatography (TLC) was performed on Merck silica gel 60 F254. Compounds on TLCs were visualized under ultraviolet-light lamp (254 nm or 366 nm). Column chromatography was performed on deactivated Macherey-Nagel silica gel 60 M (230 - 400 mesh, 0.04 - 0.063 mm). Given solvent ratios used for TLCs refer to volumes. Nuclear Magnetic Resonance (NMR) spectroscopy experiments were performed on Bruker Avance Neo 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz), Bruker Avance Neo 500 (^{1}H: 500 MHz, ^{13}C: 126 MHz) or Bruker Avance Neo 600 Cryo Probe DCH (^{1}H: 600 MHz, ^{13}C: 150 MHz). All NMR experiments were carried out at 22 °C. Chemical shifts (δ's) are referenced to residual proton impurities of stated solvents or to deuterated solvents itself.[1] The shortcut 'ps' refers to pseudo singlets and 'pt' refers to pseudo triplets. NMR data were processed using MestReNova 6.0.2. High resolution mass spectrometry (HRMS) was performed on a Bruker maXis 4G UHR MS/MS spectrometer or a Bruker micrOTOF II focus TOF MS spectrometer. Elemental analysis (EA) was performed in the microanalytical laboratory of the chemical institutes of the Friedrich-Alexander-University of Erlangen-Nürnberg, Erlangen, Germany. Atomic emission spectroscopy (AES) was carried out with an Agilent 4200 MP-AES instrument for the detection of Pd using an ICP standard from Bernd Kraft (1 M solution of $Pd(NO_3)_2$ in HNO_3). Human ovarian cancer cell line A2780 was purchased from Sigma Aldrich and cultivated in Roswell Park Memorial Institute (RPMI) 1640 medium supplemented with 10% fetal bovine serum (FBS), 1% Gibco GlutaMAX and 1% penicillin/streptomycin to a confluency of 80% at 37 °C in a chamber with 5% CO_2. The cells were harvested using trypsin/ethylenediamine-*N,N,N',N'*-tetraacetic acid (EDTA, 0.025%/0.01%, w/v) diluted in phosphate-buffered saline (PBS).

Synthetic procedures



Intermediate **10.** A stirred mixture of ferrocenecarboxylic azide 7 (513 mg, 2.01 mmol, 1 eq), 4 bromobenzyl alcohol (**9**, 453 mg, 2.42 mmol, 1.2 eq), and toluene (HPLC grade, 1.5 mL) was heated at reflux for 3 h. The solvent was evaporated and the desired product **10** (713 mg, 1.72 mmol, 87%) was obtained pure after silica gel column chromatography (DCM = 1, Ø 6.5 cm x 7 cm) as an orange crystalline solid. ^{1}H NMR (acetone-d6, 400 MHz): δ [ppm] = 8.09 (s, 1H, 5); 7.58 - 7.56 (m, 2H, 10); 7.39 - 7.37 (m, 2H, 9); 5.12 (s, 2H, 7); 4.55 (ps, 2H, 3); 4.09 (s, 5H, 1); 3.93 (ps, 2H, 2). ^{13}C{^{1}H} NMR (acetone-d6, 400 MHz) δ [ppm] = 154.5 (6); 137.6 (8); 132.3 (10); 130.7 (9); 122.1 (11); 97.4 (4); 69.6 (1); 65.8 (7); 64.6 (2); 61.0 (3). HRMS APPI (DCM) for $C_{18}H_{16}BrFeNO_2$, calculated: 412.9708 *m/z*, found: 412.9709, err [ppm] = 0.4. Elemental analysis (EA): for $C_{18}H_{16}BrFeNO_2$, calculated: C(52.2); H(3.9); N(3.4), found: C(52.3); H(3.8); N(3.5). TLC: R_f (DCM) = 0.42 – 0.51.

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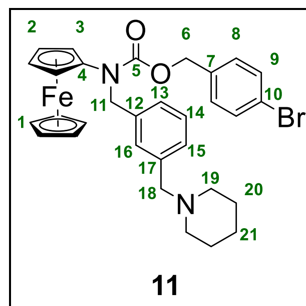
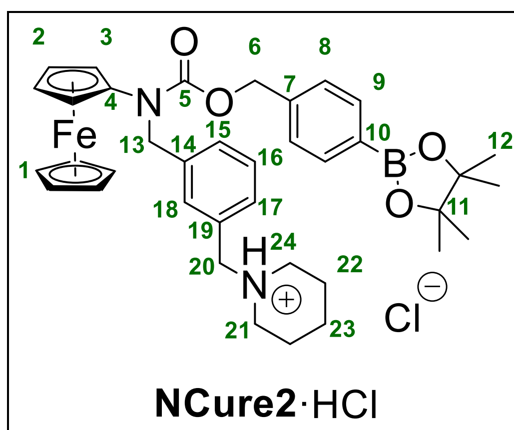


Intermediate **11**. A mixture of intermediate **10** (99 mg, 239 µmol, 1 eq), Cs_2CO_3 (241 mg, 740 µmol, 3.06 eq), CsI (73 mg, 281 µmol, 1.17 eq), and DMF (dry, 2.2 mL) was stirred for 30 min at 22 °C under N_2-atmosphere resulting in an orange suspension. *N*-((3-chloromethyl)benzyl)piperidinium chloride (**4**, 71 mg, 273 µmol, 1.14 eq) was added and the mixture was stirred at 22 °C under N_2-atmosphere for a further 69 h. Solids were filtered off and the filtrate was evaporated. Pure product **11** (94 mg, 156 µmol, 65%) was obtained after silica gel column chromatography (DCM/NEt_3 = 100/1, Ø 4 cm x 7 cm) as an orange oil. ^{1}H NMR (acetone-d6, 400 MHz, rt): *δ* [ppm] = 7.50 – 7.17 (m, 8H, 8+9+13-16); 5.18 (s, 2H, 6); 4.97 (s, 2H, 11); 4.44 (ps, 2H, 3); 4.11 (s, 5H, 1); 3.97 (ps, 2H, 2); 3.40 (s, 2H, 18); 2.32 (ps, 4H, 19); 1.54 – 1.48 (m, 4H, 20); 1.41 (ps, 2H, 21). ^{13}C{^{1}H} NMR (acetone-d6, 150 MHz, rt) *δ* [ppm] = 155.1 (5); 140.3 (17); 139.6 (12); 137.1 (7); 132.2; 130.8; 129.0; 128.2; 127.5; 125.7; 122.2 (10); 102.3 (4); 69.7 (1); 67.0 (6); 65.0 (2); 64.1 (19); 63.2 (3); 55.1 (11); 54.2 (18); 26.7 (20); 25.1 (21). HRMS APPI (DCM) for $C_{31}H_{34}BrFeN_2O_2$, calculated: 601.1148, found: 601.1148, err [ppm] = 0.3. EA for $C_{31}H_{33}BrFeN_2O_2$, calculated: C(61.9); H(5.5); N(4.7), found: C(61.7); H(5.5); N(4.6). **TLC:** R_f (DCM/NEt_3 = 100/1) = 0.22 – 0.31.



Prodrug NCure2·HCl. A mixture of intermediate **11** (610 mg, 1.01 mmol, 1 eq),$(BPin)_2$ (293 mg, 1.15 mmol, 1.14 eq), KOAc (298 mg, 3.04 mmol, 3 eq), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (97 mg, 119 µmol, 0.12 eq) and 1,4-dixoane (3.4 mL) were degassed with N_2 for 5 min. The tube was sealed and heated to 80 °C in an oil bath for 19 h. The mixture was allowed to cool to 22 °C. The crude was filtered via Celite© plug filtration with charcoal topping (EtOAc = 1, Ø 3 cm x 2 cm) to remove impurities and Pd residues.

HCl salt formation: The product was dissolved in EtOAc (25 mL) and a solution of HCl in 1,4-dioxane (4 M, dry, 10 mL, 40 eq) was added dropwise under stirring. Volatiles were removed and the mixture was dried for 20 min. Then, *iso*-propanol (20 mL) was added and the mixture was stirred vigorously for 45 min, which led to product precipitation after 20 minutes. The product NCure2·HCl (453 mg, 661 µmol, 64%) was obtained pure after filtration and drying for several days under vacuum. ^{1}H NMR (DMSO-d6, 600 MHz, rt): *δ* [ppm] = 10.38 (s, 1H, 24); 7.63 – 7.26 (m, 8H, 8+9+15-18); 5.19 (s, 2H, 6); 4.96 (s, 2H, 13); 4.43 (ps, 2H, 3); 4.22 (d, 2H, ^2J = 4.9 Hz, 20); 4.11 (s, 5H, 1); 4.01 (pt, 2H, ^3J = 1.9 Hz, 2); 3.21 – 3.20 (m, 2H, 21); 2.76 (ps, 2H, 21); 1.72 (ps, 5H, 22+23);

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1,67 – 1.65 (pd, 1H, 23) 1.28 (s, 13H, 23+12). ^{13}C NMR (DMSO-d6, 151 MHz, rt): δ [ppm] = 154.1 (5); 139.7 (7); 139.2 (14); 134.4 (9); 129.9; 129.2; 128.9; 128.0; 127.3; 126.9 (8); 100.8 (4); 83.7 (11); 68.8 (1); 66.8 (6); 64.2 (2); 62.2 (3); 58.7 (20); 52.9 (13); 51.4 (21); 24,6 (12); 22.1 (22); 21.3 (23). HRMS APPI (DCM) for $C_{37}H_{45}BFeN_2O_4$, calculated: 648.2816, found: 648.2824, err [ppm] = -0.1. EA for $C_{37}H_{46}BClFeN_2O_4 \cdot H_2O$, calculated: C(63.2); H(6.9); N(4.0), found: C(63.3); H(6.7); N(3.9). TLC: R_f (CH_2Cl_2/NEt_3 = 100/1) = 0.17 ± 0.02; R_f (EtOAc) = 0.23 ± 0.05; R_f (EtOAc/NEt_3 = 100/1) = 0.72 ± 0.07. Ratios are given in v/v.

Atomic emission spectroscopy (AES)

For AES measurements, a small amount of compound (0.3 mg – 2 mg) was suspended in aqueous HNO_3 (65%, 50 µL) and boiled for 30 min at 95 °C. Then, water (550 µL) was added and the resulting solution (30 µL) was diluted to 1 mL with water. Measurements were carried out with this diluted solution and measured intensities were converted into concentrations via the calibration curve (Figure 3A).

Experiments with A2780 cells

A2780 cells were resuspended in RPMI 1640 medium containing 5% FBS and seeded on a 96 well microtiter plate (250 cells/µL, 100 µL/well). After overnight incubation, investigated compounds dissolved in dimethyl sulfoxide (DMSO) were added (1 µL) to final concentrations of 50 µM, 25 µM, 10 µM, 5 µM and 1 µM. Each condition was tested in triplicates, while DMSO was tested in nine technical replicates. Treated cells were incubated for 48 h, and a solution of MTT (5 mg/mL in PBS, 20 µL/well) was added. After further 3 h of incubation, sodium dodecyl sulfate solution (SDS, 10% in 0.01 M HCl, 90 µL/well) was added. Next day, the absorbance was measured at 690 nm and 590 nm. While 590 nm absorbance was exploited to detect intensity of metabolized MTT, absorbance at 690 nm served as baseline value (A(590 nm) – A(690 nm)). Each experiment was repeated two times. An unpaired Student`s t test was used to compare data pairs. The values were considered statistically significantly different for $p<0.05$.

Acknowledgements

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Supplementary Material

Additional spectra are provided in the supporting Information.

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