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Research paper

Melanoma-targeted delivery system (part 1): Design, synthesis and evaluation of releasable disulfide drug by glutathione

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ABSTRACT

Here we describe the design and synthesis of a prodrug developed for pigmented melanoma therapy, consisting of a Melanin-Targeting Probe (MTP) conjugated to 5-iodo-2′-deoxyuridine (IUdR) with a reduction-sensitive pre-determined breaking point. Compared with the non-cleavable conjugate (**17b**), prodrug (**17a**) bearing a self-immolative disulfide linker achieved complete release of IUdR within 20 min in the presence of reducing agents such as DTT or glutathione. Analytical results also showed that prodrug (**17a**) was more sensitive than parent non-cleavable conjugate (**17b**) for a concentration range of glutathione similar to that found in the intracellular compartment of tumours.

1. Introduction

According to WHO reports for 2012, cancer now causes more deaths than all coronary heart diseases, and more than all strokes. It is estimated that 14.1 million new cancer cases and 8.2 million cancer deaths occurred in 2012 worldwide compared with 12.7 million and 7.6 million, respectively in 2008. Of all cancers combined, malignant melanoma of the skin accounted for 232,000 new cancers (1.6% of new cancers) and 55,000 deaths worldwide (0.7% of cancer deaths) for the year 2012 [1]. Early diagnosis followed by surgical excision of the nevus before metastasis occurs frequently offers an encouraging prognosis [2,3]. However, for a minority of patients, whose melanoma is not diagnosed in the initial stage of the disease, the development and progression of this cancer throughout the body, in the brain, liver, or bones, are very fast. Advanced-stage melanoma (stage IV) is often associated with an overall median survival period of 6–12 months, with only 5% of patients surviving beyond 5 years [4]. Melanoma shows resistance to traditional chemotherapies such as cytotoxic anticancer drugs that prevent cell division. To date, several drugs have been approved by the Food and Drug Administration for malignant metastatic melanoma, e.g. dacarbazine (DNA alkylating agent) [5], interleukin-2 [6], ipilimumab(CTLA-4 blockade) [7], vemurafenib and dabrafenib (anti-BRAF) [8]. Compared with chemotherapy, the potent specific BRAF inhibitors vemurafenib and dabrafenib have significantly improved response rates, along with progression-free and overall survival, in patients with metastatic melanoma with BR AFV600E mutations. However, acquired resistance to BRAF inhibitors frequently develops through reactivation of the mitogen-activated protein kinase (MAPK) pathway, resulting in a median progression-free survival of 6–8 months [9,10]. Although the use of combination therapy with BRAF and MEK inhibitors has provided good responses, only 40% of patients who harbour a BRAFV600 mutation benefit from such an approach [11–13]: dabrafenib plus trametinib, compared with vemurafenib monotherapy, or nivolumab compared with dacarbazine, were associated with significant improvements in overall survival and progression-free survival, among previously untreated patients who had metastatic melanoma without a BRAF mutation. Analysis of these recent data suggests that the treatment of malignant metastatic melanoma should involve simultaneous blockade of more than one cell-signalling pathway [14,15]. Taking into account the difficulties encountered so far and the remaining needs, continued efforts are

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required (i) to explore the entire new range of treatment possibilities and (ii) to develop new entities that, in combination with specific melanoma-targeted drugs, enable effective control of this disease. Among all the different molecular targets investigated, melanins are relevant, as they are detected in more than 90% of primary melanoma cases and in 30–50% of metastatic lesions [16]. The capacity of these amorphous, irregular polymers to bind to many drugs, especially those with coplanar fused aromatic rings and/or polyamine side chains, make it a promising target for a pigmented melanoma-targeting strategy [11,17]. Based on these findings, in the last two decades our research group has developed arylcarboxamide families that have potential applications for PET imaging [18–20] and/or targeting radionuclide therapy [21,22] of melanoma due to their rapid, specific and long-lasting tumour uptake. We are now exploring the use of such Melanin-Targeting Probes (MTPs) [23] to carry an anticancer drug into the melanoma tumour site [24,25]. The MTP-anticancer drug conjugate was to be designed to release the drug after it had reached its intracellular target so as to overcome melanosomal sequestration. This phenomenon was previously observed for cisplatin, which was trapped in these subcellular organelles, inhibiting efficient alkylation of DNA [26].

Accordingly, we planned to use this scavenger effect as a "Trojan horse" to produce a conjugate that would release the known anticancer drug only after reaching the tumour environment and allowing a better and specific tumoral accumulation of the anticancer drug. Thus the use of an appropriate linker between the drug and MTP is crucial for the efficacy of melanoma-targeted therapy. The linker has to be stable during handling, storage and under physiological conditions, while easily cleavable in the tumour intracellular compartment to release the free parent drug [27]. Besides the possibility of conjugating drugs to the carrier through acid-cleavable bonds, which has been previously explored in our laboratory with some success [28], another interesting strategy could involve the use of (i) reductive systems induced by hypoxia [29] (quinines [30], nitro(hetero)aryls [31] and *N*-oxides [32]) or disulfide-bearing linkers by a thiol exchange reaction [33], or (ii) self-immolative linkers activated by tumour-associated enzymes (such as proteases, glucoridinases, carboxylesterases, cathepsin, for example) [34,35]. The concept of specific release of cytotoxic agents in melanocytes from tyrosinase-activated prodrugs, known as Melanocyte-Directed Enzyme Prodrug Therapy (MDEPT), is also attractive [36]. However, for this last strategy, and despite significant efforts, the release of the active substance was unlikely when carbamate, urea or hydrazine linkers were used [37–39]. Among all the above-mentioned linker units, we opted to use the promising disulfide bond function, which is stable in the blood circulation, but efficiently cleaved by intracellular reducing systems present in the tumour cells [33]. Thiols are scarce in the blood circulation, while glutathione (GSH) levels are 1000 times higher in tumour cells than in the blood plasma [39]. This linker is increasingly used to form small molecule drug conjugates. Recently, Santra et al. described a tumour-targeted prodrug (folate-doxorubicin conjugate) that became activated within the cell by GSH-mediated dissociation [40]. Janssen et al. reported a disulfide prodrug conjugate SN38, an active metabolite of irinotecan, linked to the nontoxic B-subunit of the Shiga toxin, a natural ligand of pancreatic cells. The cytotoxic effect of the SN38 conjugate was increased more than 100-fold compared with irinotecan [41]. We can also cite the promising folate-targeted prodrug EC145 bearing a disulfide linker, which is currently being tested in a global phase 3 study in women with platinum-resistant ovarian cancer [42].

Here, we describe the design, synthesis and preliminary evaluation of a melanoma-targeted prodrug based on a melanin-targeting derivative of N-(2-diethylaminoethyl)-6-iodoquinoxaline -2-carboxamide ICF01012 (called MTP) [43] conjugated with a self-immolative disulfide linker to the antimetabolite IUdR, chosen as a model anticancer agent.

2. Results and discussion

We recently modified the **ICF01012** scaffold in order to deliver anticancer agents to pigmented melanoma. Given its favourable clearance and high tumour-melanoma uptake (5.60% ID/g) at 3 h post-injection in melanoma-bearing mice, compound **(1d*)** represents a good building block for the design of new melanoma selective drug delivery systems (Fig. 1) [43]. The synthesis of the disulfide IUdR–SS–MTP-conjugate required first modifying both the IUdR and MTP moieties in order to form the disulfide linkage.

Before synthesising the IUdR–SS–MTP conjugate **(17a)**, carrying a disulfide cleavable linker and its sulfide homolog IUdR-S-MTP **(17b)**, which served as a non-cleavable reference, we investigated the linkage and cleavage of IUdR-(di)thiophenyl conjugate (Fig. 1). To this end, compounds **(11a, b)** were synthesized, and their stability in the presence of (2*S*,3*S*)-dithiothreitol (DTT), known to reduce the disulfide bond, were evaluated. For compounds **(11a, b)**, we planned to develop a synthesis between IUdR and primary alcohols **(2a, b)** obtained from pyridyl disulfide **(1)** (Fig. 2).

As depicted in Scheme 1A, the asymmetrical disulfide **(1)** was easily obtained using a literature procedure by oxidation of the thiol function of 2-mercaptopyridine with sulfuryl chloride in the presence of 2-mercaptoethanol [44]. Using a similar method, compound **(2a)** was obtained in 71% yield from 4-methoxybenzenethiol and 2-mercaptoethanol. S-alkylation of 4-methoxybenzenethiol by 2-chloroethanol gave compound **(2b)** (75%) using the protocol of Fujihara and co-workers, slightly modified [45].

Our synthesis then started by the regioselective monoprotection of IUdR with tert-butyldimethylsilyl chloride to give 5′-protected IUdR **(6)** according to the procedure of Moharram and co-workers (79%) (Scheme 2) [46]. The monoprotected IUdR **(6)** was then converted in the presence of 4-nitrophenylchloroformate into 3′-activated carbonate ester **(7)** with good yield (72%) after silica gel purification. Compound **(8)** was obtained by treatment of IUdR derivative **(7)** with primary alcohol **(1)**. We note that compound **(8)** can be alternatively synthesized from **(6)** with excellent yield (90%) using a one-pot procedure avoiding the carbonate isolation step **(7)**. The condensation of 4-methoxybenzenethiol with derivative **(8)** gave disulfide compound **(10a)** in moderate yield (58%). More conveniently, disulfide **(10a)** can be obtained using a one-pot method from **(6)** and **(2a)** in 74% yield. Final deprotection of the silyl group in the presence of $InCl_3$ in refluxing acetonitrile/water afforded prodrug **(11a)** in 83% yield (34% overall yield from IUdR and **(1)**). Prodrug **(11a)** can also be obtained from **(8)** in 55% overall yield by soft deprotection of the silyl group, yielding compound (**9**), followed by treatment with 4-methoxybenzenethiol. Obviously, in our case, use of the disulfide precursor **(1)** to generate the disulfide **(11a)** was not advantageous. The best procedure was the straightforward formation of the disulfide bond with **(2a),** followed by reaction with activated IUdR **(7)** prepared in situ (49% overall yield from IUdR and **(1)**).

A similar three-step procedure was successfully used for the synthesis of analogue **(11b)** from **(6)** and **(2b)** after a final soft deprotection of compound **(10b)**. Finally, conjugates **(11a, b)** were synthesized from IUdR and **(2a, b)** in four steps, with overall yields of 49 and 39%, respectively.

2.1. Evaluation of IUdR release from *(11a, b)* conjugates

Compounds **(11a, b)** in 0.9 mM PBS (pH = 7.4)/acetonitrile (98/2,

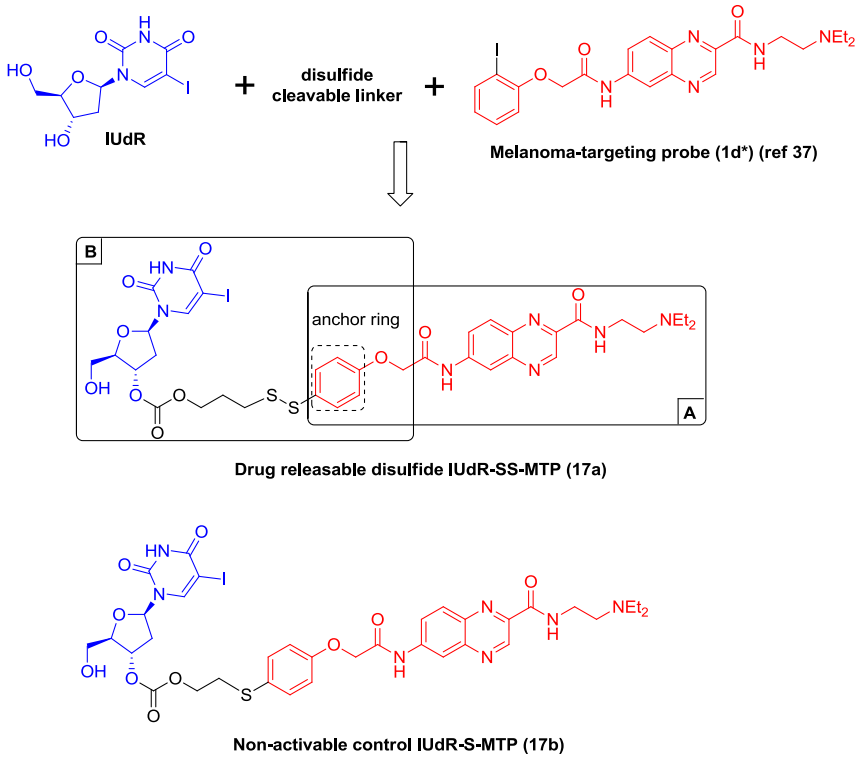


Fig. 1. Rational for the design of releasable disulfide prodrug IUdR–SS–MTP (**17a**) and its non-cleavable derivative IUdR-S-MTP (**17b**).

v/v) solution were treated with one equivalent of DTT at 37 °C, and the advancement of the reaction was monitored by analytical RP-HPLC (see details in Experimental Section).

As depicted in Fig. 3A, free IUdR (retention time: 2.98 min) was released after 30 min of treatment, but the reaction was incomplete. Over the next 30 min, compound **(11a)** was completely converted into free IUdR. By contrast, compound **(11a)** was found to remain stable in the PBS/acetonitrile mixture for more than 24 h in the absence of DTT (Fig. 3A, retention time: 17.98 min).

When the same method was applied to compound **(11b)**, which has no disulfide bond, no degradation or cleavage was observed over 60 min (Fig. 3B, retention time: 14.65 min). These results also highlight the excellent stability of the carbonate function in PBS/acetonitrile solution with or without DTT. We therefore assume that the IUdR release observed for **(11b)** was mainly due to the reduction of the disulfide bond in the presence of DTT, followed by self-immolative elimination of the thioethyl carbonate residue.

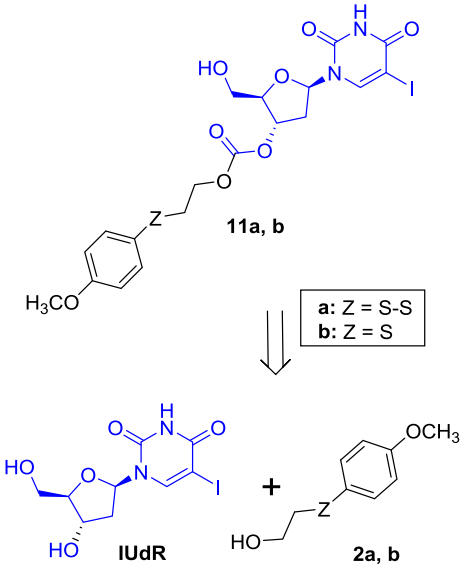
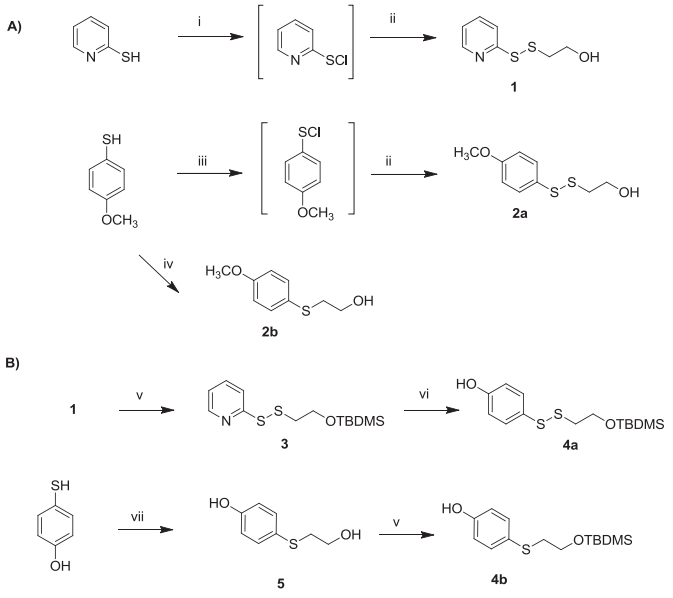
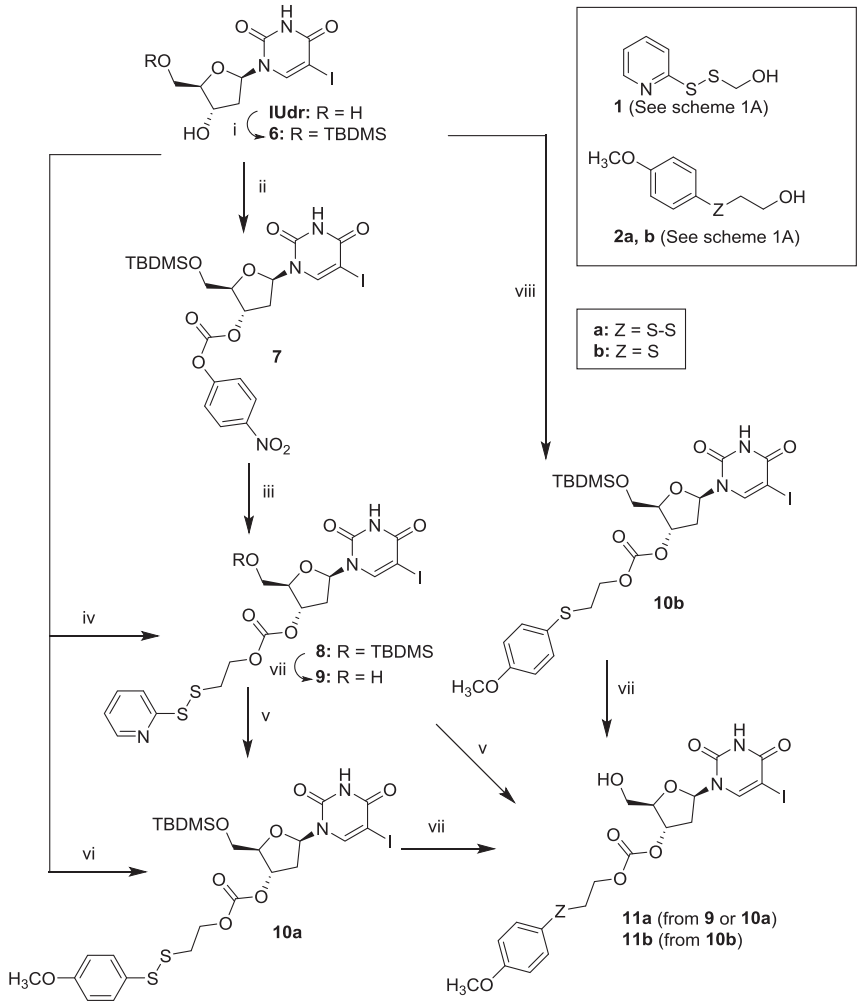


Fig. 2. Rational for the synthesis of releasable disulfide prodrug IUdR–SS–MTP (**11a**, Z = SS) and its non-cleavable derivative (**11b**).



Scheme 1. Synthesis of alcohols (**1**, **2a, b**) and their protected derivatives (**4a, b**). [a]Reagents and conditions: i) DCM, sulfuryl chloride, rt; ii) 2-mercaptoethanol; DCM, rt; iii) NCS; DCM, rt; iv) 2-chloroethanol, Na_2CO_3, DMF, rt; v) TBDMSCl, imidazole, DMAP, DMF, rt; vi) 4-thiophenol, DCM, rt; vii) 2-bromoethanol, Na_2CO_3, DMF, rt.



Scheme 2. Synthesis of IUdR–SS–MTP **(11a)** and IUdR-S-MTP **(11b)**. [a]Reagents and conditions: i) TBDMSCl, imidazole, DMAP, DMF, rt; ii) 4-nitrophenylchloroformate, DMAP, THF, rt; iii) **(1)**, DMAP, THF, rt; iv) a) 4-nitrophenylchloroformate, DMAP, THF, rt; b) **(1)**, DMAP, THF, rt; v) 4-methoxybenzenethiol, THF; rt; vi) a) 4-nitrophenylchloroformate, DMAP, THF, rt; b) **(2a)**, DMAP, THF; rt; vii) $InCl_3$, CH_3CN/H_2O (1/1, v/v), reflux; viii) a) 4-nitrophenylchloroformate, DMAP, THF, rt; b) **(2b)**, DMAP, THF, rt.

We then determined the effective half-life time of prodrug **(11a)** in the presence of DTT. We studied the kinetics of IUdR release from prodrug **(11a)** using compound **(11b)** as an internal standard. At different times (1, 2, 6, 10, 15, 20, 25, 30 and 60 min), aliquots were withdrawn and analyzed by RP-HPLC and the amount of released IUdR was determined from a standard curve (see Experimental Section for details). Using DTT, the half-life of compound **(11a)** was 2.3 min and the IUdR was completely released within 20 min (Fig. 3C).

Taken together, these preliminary results are evidence that disulfide IUdR prodrugs may enable drug release in the reductive conditions found in tumour cells, and encouraged us to develop melanoma-targeted drug **(17a, b)** (Fig. 1).

2.2. Synthesis of conjugates *(17a, b)*

Synthesis of compounds **(17a, b)** was based on the same procedure used for derivatives **(11a, b)**, i.e a condensation of IUdR carbonate **(7)** with the alcohols **(15a, b)**, obtained from 6-aminoquinoxaline **(12)** and (di)sulfides **(4a, b)** (Fig. 4) [47].

Asymmetrical disulfide **(4a)** was obtained by silylation of **(1)** followed by a thiol-disulfide exchange using 4-thiophenol (overall yield 88%) (Scheme 1B). Compound **(4b)** was prepared by S-alkylation of 4-mercaptophenol with 2-bromoethanol, under basic conditions, yielding compound **(5)** (78%), followed by a regioselective TBDMS protection of the aliphatic alcohol to give phenol derivative **(4b)** (88%) (Scheme 1B).

Scheme 3 depicts the synthesis in five steps of IUdR-MTP conjugates **(17a, b)**. The key intermediate **(13)** was obtained by *N*-acylation of compound **(12)** [41] in the presence of 2-bromoacetyl chloride in DMF. Compound **(13)** was then converted into benzyl ethers **(14a, b)** by condensation of the corresponding phenol derivatives **(4a, b)**. After deprotection of the silyl groups under mild conditions, alcohols **(15a, b)** were treated with IUdR carbonate **(7)** to afford **(16a, b)** with 78 and 76% yields, respectively. Finally, TBDMS deprotection in the presence of $InCl_3$ gave IUdR-MTP conjugates **(17a, b)** in 68 and 43% yields, respectively.

2.3. Evaluation of IUdR release from conjugates *(17a, b)*

Using the internal standard method, compounds **(17a, b)** were treated by DTT to evaluate both their half-life and their ability to release IUdR under reductive conditions at 37 °C. After DTT treatment, fast degradation of compound **(17a)** associated with a strong release of IUdR were observed (Fig. 5A), while compound **(17b)** remained stable over 24 h (Fig. 5B). Also, compounds **(17a, b)** were found to remain stable for at least 24 h in the PBS/acetonitrile solution. In the presence of DDT, the half-life of compound **(17a)** was

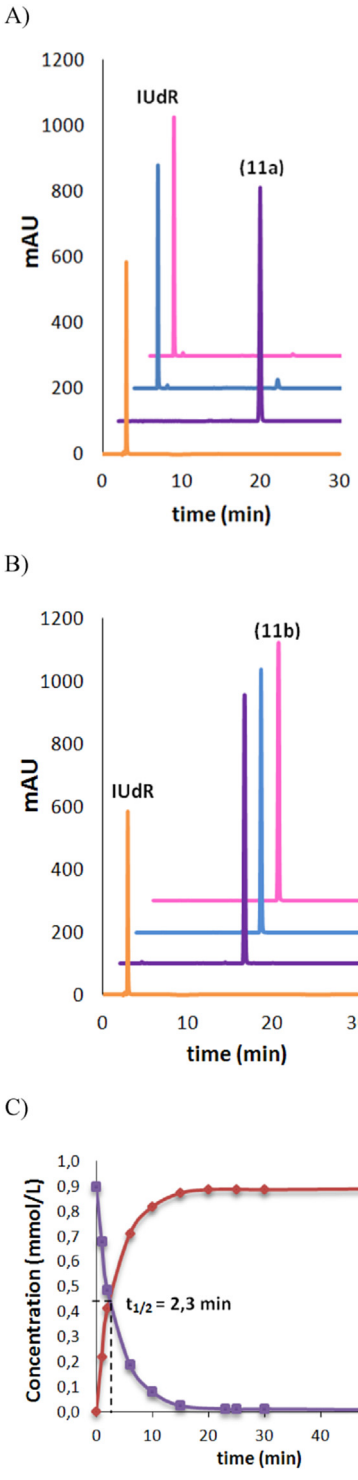


Fig. 3. Evaluation of IUdR release after treatment of disulfide conjugates IUdR–SS–MTP **(11a)** (A) and IUdR-S-MTP **(11b)** (B) by DTT. A) orange: IUdR (retention time 2.98 min); purple: **(11a)** in PBS/acetonitrile (98/2, v/v) (retention time 17.98 min); blue: **(11a)** treated with one equivalent of DTT during 30 min; pink: **(11a)** treated with one equivalent of DTT during 60 min; B) orange: IUdR (retention time 2.98 min); purple: **(11b)** in PBS/acetonitrile (98/2, v/v) (retention time 14.65 min); blue: **(11b)** treated with one equivalent of DTT during 30 min; pink: **(11b)** treated with one equivalent of DTT during 60 min; C) Kinetic rate of cleavage for compound **(11a)** with DTT (1 eq.) and determination of its half-life; red: released IUdR; purple: **(11a)**. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

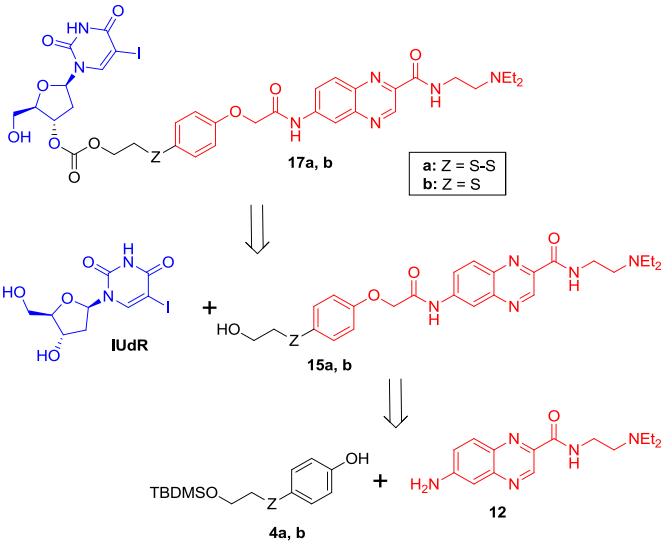
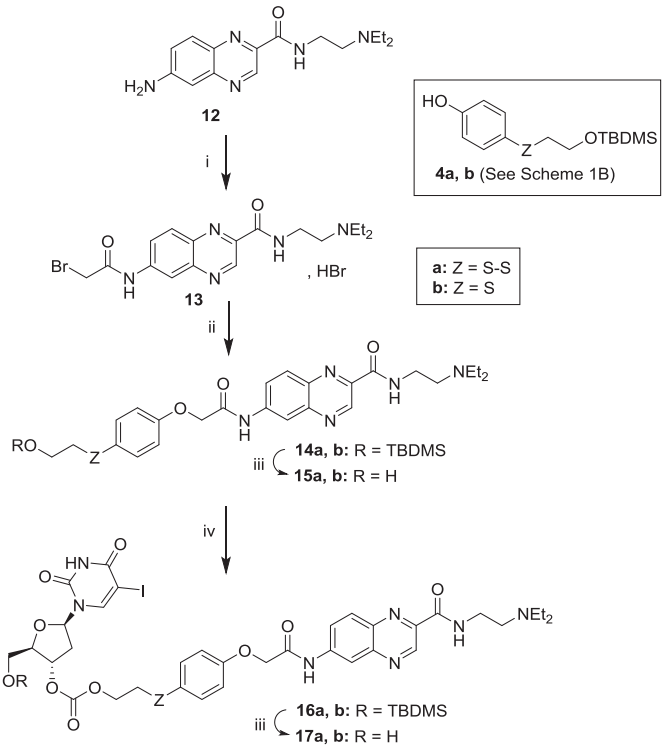


Fig. 4. Rational for the synthesis of releasable disulfide prodrug IUDR–SS–MTP (**17a**) and its non-cleavable derivative IUdR-S-MTP (**17b**).

3.1 min and the IUdR was completely released after 12 min (Fig. 5C).

From these results, we decided to evaluate the release of IUdR from compound **(17a)** in the presence of glutathione (GSH) at 37 °C. The cytoplasmic concentration of this thiol-containing tripeptide is in the millimolar range (1–10 mM), whereas it is present in the micromolar range in the blood (1–10 μM) [48]. In order to assess the influence of intracellular and extracellular glutathione concentrations on the parent drug release, prodrug **(17a)** was incubated with two different concentrations of GSH (5 mM and 5 μM,



Scheme 3. Synthesis of IUdR–SS–MTP **(11a)** and IUdR-S-MTP **(11b)**. [a]Reagents and conditions: i) 2-bromoacetyl chloride, DMF, rt; ii) **(4a)** or **(4b)**, NaH, THF, rt; iii) $InCl_3$, CH_3CN/H_2O (1/1, v/v), reflux; iv) **(7)**, DMAP, THF, rt.

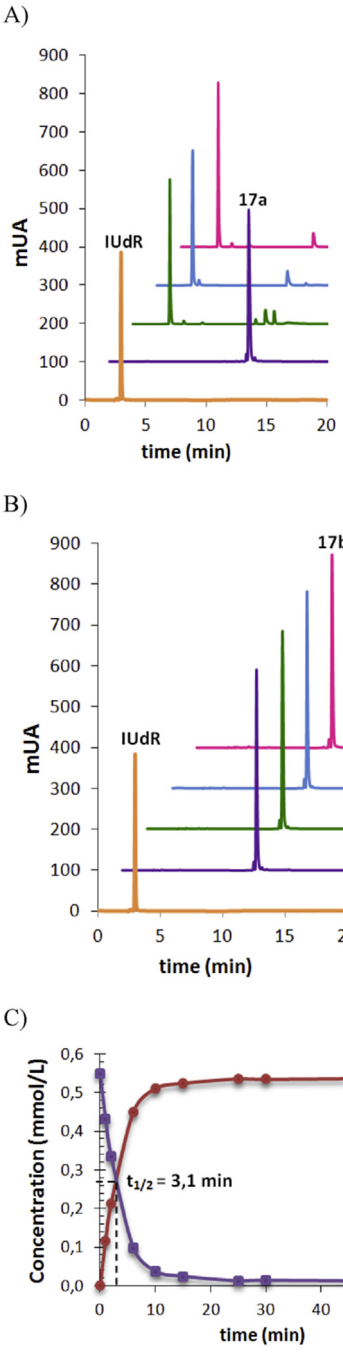


Fig. 5. Evaluation of IUdR release after treatment of disulfide prodrug IUdR–SS–MTP (**17a**) (A) and IUdR-S-MTP (**17b**) (B) by DTT. A) orange: IUdR (retention time 3.02 min); purple: **(17a)** in PBS/acetonitrile (retention time 11.63 min); blue: **(17a)** treated with one equivalent of DTT during 30 min; pink: **(17a)** treated with one equivalent of DTT during 60 min; B) orange: IUdR (retention time 3.02 min); purple: **(17b)** in PBS/acetonitrile (retention time 10.68 min); blue: **(17b)** treated with one equivalent of DTT during 30 min; pink: **(17b)** treated with one equivalent of DTT during 60 min; C) Kinetic of cleavage of **(17a)** with DTT (1 eq.) and determination of its half-life; red: released IUdR; purple: **(17a)**. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

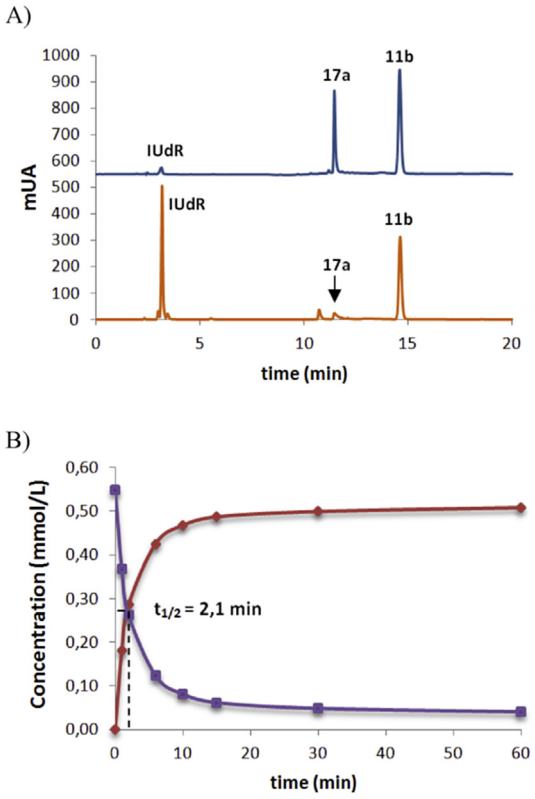


Fig. 6. Evaluation of IUdR release after treatment of disulfide prodrug IUdR–SS–MTP (**17a**) by GSH. A) orange: **(17a)** treated with GSH (5 mM) during 60 min; blue: **(17a)** treated with GSH (5 μM) during 60 min; B) Kinetic of cleavage of **(17a)** with GSH (5 mM) and determination of its half-life; red: released IUdR; purple: **(17a)**. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

respectively). This study was monitored by analytical RP-HPLC to follow the IUdR release. Compound **(11b)** served as an internal standard. As shown in Fig. 6A, the release of the parent drug from prodrug **(17a)** was only observed for the GSH concentration of 5 mM (Fig. 6A). Conversely, no degradation was detected when compound **(17a)** was treated with a 5 μM GSH solution. On the basis of these data and similar protocol described by Santra et al., these results further indicate the stability of the prodrug in the bloodstream and its activation only in the presence of intracellular GSH [40].

We went on to study the kinetics of IUdR release from prodrug **(17a)** treated with a GSH intracellular concentration of 5 mM using compound (**11b**) as an internal standard. At different times (1, 2, 6, 10, 15, 20, 25, 30 and 60 min), aliquots were withdrawn and analyzed by RP-HPLC, and the amount of IUdR released was determined from the standard curve. The half-life of compound **(17a)** was 2.1 min, while the IUdR release reached a plateau within 20 min (Fig. 6B). We assume that after cleavage of disulfide linker by GSH, the resultant thiol would then undergo cyclization leading to the release: i) of alkylcarbamate IUdR derivative, then free IUdR (Fig. S1, Path A) or ii) free IUdR by attack of the resulting thiol on carbonyl function of carbamate group as described in the literature (Fig. S1, Path B) [49].

3. Conclusion

Our approach to improving the efficiency of melanoma-targeted therapies was based on the use of a cytotoxic drug connected to an MTP via a self-immolative linker. In this study, we successively synthesized four IUdR conjugates **(11a, b)** and **(17a, b)**. We demonstrate that only compounds **(11a)** and **(17a)**, bearing a self-immolative disulfide linker, were able to release IUdR efficiently under disulfide reductive conditions. Also, GSH treatment of **(17a)** suggests a potential activation in the intracellular tumour

compartment. We consider that the resulting anticancer agent-MTP prodrug holds the promise of tumour-specific delivery of the cytotoxic drug (targeted therapy), thus avoiding the dose-limiting toxicity of standard chemotherapies. Our next objective will be to study our activatable IUdR–SS–MTP prodrug in melanoma-bearing mice.

4. Experimental section

4.1. Materials for chemical syntheses

Unless otherwise mentioned, all manipulations were performed under argon; all reagents were purchased from the following commercial suppliers: Sigma–Aldrich, Acros Organics, Carlo Erba, TCI Europa. Anhydrous DMF and anhydrous triethylamine were purchased from Acros Organics. THF was distilled over benzophenone and sodium. Dichloromethane was distilled over calcium hydride. Nuclear magnetic resonance (NMR) spectra were acquired on a Bruker AC-200 operating at 200 and 50 MHz for ^{1}H NMR and ^{13}C NMR, respectively. All ^{1}H NMR spectra are reported in δ units, parts per million (ppm) and the coupling constants are indicated in hertz (Hz). The following abbreviations are used for spin multiplicity: s singlet, d doublet, t triplet, q quadruplet, m multiplet, and br broad. Electrospray ionization mass spectra (ESI-MS) were recorded on an Esquire (Bruker Daltonics, Wissenbourg, France) spectrometer. High resolution mass spectra (HRMS) were recorded on an Alliance 2695 (Waters) liquid chromatography coupled with a Q-ToF micro (Waters/Micromass) spectrometer. Tyrosyl tyrosine, an internal mass standard, is used to correct mass values. TLC was performed on aluminum backed silica gel sheets (60F254 plates) and visualized under UV light (254 nm). Column chromatography was performed using silica gel normal phase (Merck or SDS) (35–70 μm). Uncorrected melting points (Mp) were recorded on a Wagner & Munz Heizbank-Koffler apparatus or an Electrothermal IA9300. Infrared spectra (IR) were recorded on a Bruker FT Vector 22.

4.2. Access to compounds (1), (2a, b) (3), (4a, b) and (5)

4.2.1. 2-(Pyridin-2-yldisulfanyl)ethanol (1)

To a solution of 2-mercaptopyridine (2.0 g, 17.22 mmol, 1 eq.) in anhydrous dichloromethane (50 mL), cooled at −5 °C, sulfuryl chloride (1.8 mL, 22.23 mmol, 1.3 eq.) was added dropwise. The reaction mixture was stirred at room temperature for 2 h, then concentrated under reduced pressure. To this crude product taken up in anhydrous dichloromethane (40 mL) and cooled at −5 °C, was added a solution of 2-mercaptoethanol (1.51 mL, 22.23 mmol, 1.3 eq.) dissolved in anhydrous dichloromethane (2 mL). The resulting mixture was stirred at room temperature for 6 h. After cooling to −5 °C, the obtained precipitate was filtered, taken up in dichloromethane (20 mL) and DMAP (1.89 g, 15.47 mmol, 0.9 eq.) was added. After stirring at room temperature for 10 min, the reaction solvent was concentrated under reduced pressure. The crude product was purified on silica gel eluted with dichloromethane/methanol (95/5, v/v) to afford **(1)** (2.17 g, 11.58 mmol). Yield: 67%; IR (KBr) ν (cm^{-1}) 3344, 2866, 1576, 1561, 1448, 1417, 1117; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 8.26 (m, 1H, H-5), 7.42 (m, 1H, H-7), 7.32 (m, 1H, H-8), 6.95 (m, 1H, H-6), 5.46 (brs, 1H, OH), 3.64 (t, ^{3}J = 5.3 Hz, 2H, H-1), 2.77 (t, ^{3}J = 5.3 Hz, 2H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 159.2 (C-3), 149.5 (C-5), 137.0 (C-7), 121.3 (C-6, C-8), 58.6 (C-1), 42.3 (C-2); ESI-MS: *m*/*z* 187.94 $[M + H^+]^+$.

4.2.2. 2-((4-Methoxyphenyl)disulfanyl)ethanol (2a)

To a suspension of *N*-chlorosuccinimide (952.5 mg, 7.13 mmol, 1 eq.) in anhydrous dichloromethane (40 mL), a solution of 4-methoxythiophenol (1.0 g, 7.13 mmol, 1 eq.) dissolved in anhydrous dichloromethane (4 mL) was added. After stirring at room temperature for 45 min, a solution of 2-mercaptoethanol (602 μL, 8.55 mmol, 1.2 eq.) dissolved in anhydrous dichloromethane (3 mL) was added dropwise. The reaction mixture was stirred at room temperature for 48 h, then washed with brine (2 × 25 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with a gradient ethyl acetate/cyclohexane (20/80 to 30/70, v/v) to afford compound **(2a)** (1.1 g, 5.09 mmol). Yield: 71%; IR (KBr) ν (cm^{-1}) 3373, 2937, 2835, 1590, 1571, 1491, 1461, 1288, 1247, 1172; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 7.45 (d, ^{3}J = 8.9 Hz, 2H, H-4), 6.83 (d, ^{3}J = 8.9 Hz, 2H, H-5), 3.81 (t, ^{3}J = 6.0 Hz, 2H, H-1), 3.75 (s, 3H, H-7), 2.84 (t, ^{3}J = 6.0 Hz, 2H, H-2), 2.69 (brs, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 159.9 (C-6), 132.1 (C-4), 127.9 (C-3), 114.9 (C-5), 60.2 (C-1), 55.6 (C-7), 40.9 (C-2); HRMS *m*/*z* for $[M + H^+]^+$: calc: 217.0357; found: 217.0351.

4.2.3. 2-((4-Methoxyphenyl)thio)ethanol (2b)

To a solution of 4-methoxythiophenol (1.0 g, 7.13 mmol, 1 eq.) dissolved in anhydrous DMF (5 mL) cooled to 0 °C, sodium carbonate (3.1 g, 22.38 mmol, 3.1 eq.) and 2-chloroethanol (472 μL, 7.05 mmol, 1.05 eq.) were added, successively. The resulting mixture was stirred at 0 °C for 15 min, then at room temperature for 1 h 15 min. Water (25 mL) was added and the reaction mixture was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (2 × 25 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with a gradient ethyl acetate/cyclohexane (25/75 to 30/70, v/v) to afford compound **(2b)** (980 mg, 5.32 mmol). Yield: 75%; IR (KBr) ν (cm^{-1}) 3296, 2953, 2833, 1632, 1596, 1495, 1285, 1247, 1178; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 7.37 (d, ^{3}J = 8.8 Hz, 2H, H-4), 6.83 (d, ^{3}J = 8.8 Hz, 2H, H-5), 3.79 (s, 3H, H-7), 3.66 (t, ^{3}J = 5.9 Hz, 2H, H-1), 2.98 (t, ^{3}J = 5.9 Hz, 2H, H-2), 2.03 (brs, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 159.4 (C-6), 134.1 (C-4), 124.6 (C-3), 114.7 (C-5), 60.0 (C-1), 55.3 (C-7), 39.3 (C-2). HRMS *m*/*z* for $[M + H^+]^+$: calc:185.0636; found: 185.0639.

4.2.4. 2-((2-((tert-Butyldimethylsilyl)oxy)ethyl)disulfanyl)pyridine (3)

To a solution of **(1)** (3.2 g, 17.24 mmol, 1 eq.) dissolved in anhydrous DMF (30 mL), cooled at −5 °C, imidazole (56.89 mmol, 3.3 eq.) and DMAP (2.24 mmol, 0.13 eq.) were added, followed by a solution of *tert*-butyldimethylsilane chloride (1.1 eq.) dissolved in anhydrous DMF (15 mL). The reaction mixture was stirred at −5 °C for 30 min and then at room temperature for 2 h 30 min. An aqueous saturated ammonium chloride solution (60 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (40 mL), brine (2 × 30 mL), dried over sulfate magnesium, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted by ethyl acetate/cyclohexane (10/90, v/v) to afford compound **(3)** (4.5 g, 14.92 mmol). Yield: 87%; IR (KBr) ν (cm^{-1}) 2954, 2856, 1574, 1446, 1417, 1255, 1112; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 8.46 (m, 1H, H-6), 7.78 (m, 1H, H-3), 7.65 (m, 1H, H-4), 7.09 (m, 1H, H-5), 3.87 (t, ^{3}J = 6.5 Hz, 2H, H-8), 2.93 (t, ^{3}J = 6.5 Hz, 2H, H-7), 0.90 (s, 9H, H-11), 0.06 (s, 6H, H-9); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 160.5 (C-2), 149.5 (C-6), 137.0 (C-4), 120.5 (C-5), 119.6 (C-3), 61.3 (C-8), 41.5 (C-7), 25.9 (C-11), 17.9 (C-10), -5.3 (C-9). HRMS *m*/*z* for $[MH^+\text{-}C_6H_{15}Si + H]^+$ calc: 188.0204; found: 188.0204.

4.2.5. 4-((2-((tert-Butyldimethylsilyl)oxy)ethyl)disulfanyl)phenol (4a)

To a solution of **(3)** (3.0 g, 9.94 mmol, 1 eq.) dissolved in dichloromethane (60 mL), a solution of 4-mercaptophenol (1.5 g,

11.92 mmol, 1.2 eq.) dissolved in dichloromethane (5 mL) was added. The resulting mixture was stirred at room temperature for 16 h. The reaction solvent was evaporated under reduced pressure and the crude product was purified on silica gel eluted with ethyl acetate/cyclohexane (10/90, v/v) to afford compound **(4a)** (3.1 g, 9.79 mmol). Yield: 98%; IR (KBr) ν (cm^{-1}) 3328, 2929, 2857, 1598, 1583, 1493, 1471, 1257, 1089; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 7.35 (d, ^3J = 8.6 Hz, 2H, H-3), 6.71 (d, ^3J = 8.6 Hz, 2H, H-2), 5.99 (brs, 1H, OH), 3.83 (t, ^3J = 7.0 Hz, 2H, H-6), 2.81 (t, ^3J = 7.0 Hz, 2H, H-5), 0.85 (s, 9H, H-9), 0.03 (s, 6H, H-7); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 155.9 (C-1), 132.1 (C-3), 128.3 (C-4), 116.2 (C-2), 61.9 (C-6), 40.8 (C-5), 30.0 (C-9), 18.4 (C-8), -5.2 (C-7); HRMS *m/z* for $[M + Na^+]^+$: calc: 339.0885; found: 339.0887.

4.2.6. 4-((2-Hydroxyethyl)thio)phenol (5)

To a solution of 4-mercaptophenol (1.6 g, 12.52 mmol, 1 eq.) dissolved in anhydrous DMF(10 mL), cooled to −5 °C, potassium carbonate (1.9 g, 13.74 mmol, 1.1 eq.) and 2-bromoethanol (932 μL, 13.14 mmol, 1.05 eq.) were added, successively. The resulting mixture was stirred at −5 °C for 30 min, then at room temperature for 1 h 30 min. Ethyl acetate (25 mL) was added and the organic layer was washed with water (2 × 20 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with a gradient cyclohexane/ethyl acetate (100/0 to 60/40, v/v) to afford compound **(5)** (1.66 g, 9.75 mmol). Yield: 78%; IR (KBr) ν (cm^{-1}) 3328, 2931, 2877, 2487, 1598, 1584, 1494, 1262; ^{1}H NMR (200 MHz, MeOD) δ_{ppm} 7.30 (d, ^3J = 8.7 Hz, 2H, H-3), 6.76 (d, ^3J = 8.7 Hz, 2H, H-2), 3.61 (t, ^3J = 6.9 Hz, 2H, H-6), 2.89 (t, ^3J = 6.9 Hz, 2H, H-5); ^{13}C NMR (50 MHz, MeOD) δ_{ppm} 158.3 (C-1), 135.1 (C-3), 125.4 (C-4), 117.0 (C-2), 61.7 (C-6), 39.2 (C-5).

4.2.7. 4-((2-((tert-Butyldimethylsilyl)oxy)ethyl)thio)phenol (4b)

Compound **(4b)** was synthesized from **(5)** (684.3 mg, 4.02 mmol) according to the previously method described for the synthesis of compound **(3)**. The crude product was purified on silica gel eluted with ethyl acetate/cyclohexane (15/85, v/v) to afford compound **(4b)** (1.0 g, 3.52 mmol). Yield: 88%; IR (KBr) ν (cm^{-1}) 3329, 2955, 2857, 1600, 1583, 1495, 1471, 1258; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 7.27 (d, ^3J = 8.7 Hz, 2H, H-3), 6.74 (d, ^3J = 8.7 Hz, 2H, H-2), 6.67 (brs, 1H, OH), 3.78 (t, ^3J = 7.6 Hz, 2H, H-6), 2.96 (t, ^3J = 7.6 Hz, 2H, H-5), 0.90 (s, 9H, H-9), 0.07 (s, 6H, H-7); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 155.2 (C-1), 133.5 (C-3), 125.8 (C-4), 116.1 (C-2), 62.6 (C-6), 37.7 (C-5), 25.9 (C-9), 18.4 (C-8), -5.2 (C-7). HRMS *m/z* $[M + Na^+]^+$: calc: 307.1164; found: 307.1163.

4.3. Access to compounds (6), (7), (8), (9), (10a, b) and (11a, b)

4.3.1. 5-Iodo-5′-O-tert-butyldimethylsilyl-2′-deoxyuridine (6)

Compound **(6)** was synthesized from 5-iodo-2′-deoxyuridine (4.5 g, 12.70 mmol) according to the previous described protocol to synthesize compound **(3)**. The crude product was purified on silica gel eluted with a gradient of dichloromethane/ethyl acetate (60/40 to 50/50, v/v) to afford product **(6)** (4.68 g, 9.99 mmol). Yield: 79%; Mp: 223 ± 1 °C; IR (KBr) ν (cm^{-1}) 3568, 3173, 2953, 2852, 1733 (CO), 1676 (CO), 1608, 1261, 1119; ^{1}H NMR (200 MHz, acetone-d_6) δ_{ppm} 10.37 (brs, 1H, NH), 8.13 (s, 1H, H-6), 6.23 (dd, ^3J = 9.1 Hz, ^3J = 5.2 Hz, 1H, H-1′), 4.43 (m, 1H, H-3′), 4.01 (m, 1H, H-4′), 3.90 (m, 2H, H-5′), 2.27 (m, 2H, H-2′), 0.95 (s, 9H, H-9), 0.17 (s, 3H, H-7 or H-7′), 0.16 (s, 3H, H-7 or H-7′). ^{13}C NMR (50 MHz, acetone-d_6) δ_{ppm} 161.4 (C_4O), 151.5 (C_2O), 145.9 (C-6), 89.4 (C-4′), 87.0 (C-1′), 73.1 (C-3′), 69.4 (C-5), 65.1 (C-5′), 42.5 (C-2′), 27.2 (C-9), 19.7 (C-8), -4.3 and −4.4 (C-7, C-7′).

4.3.2. 3′-O-((4-Nitrophenyloxy)carbonyl)-5-iodo-5′-O-tert-butyldimethylsilyl-2′-deoxyuridine (7)

To a solution of **(6)** (1.1 g, 2.42 mmol, 1.05 eq.) and 4-nitrophenyl chloroformate (465.1 mg, 2.31 mmol, 1 eq.) dissolved in anhydrous THF (15 mL), a solution of DMAP (422.8 mg, 3.46 mmol, 1.5 eq.) dissolved in anhydrous THF (5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 3 h 30 min. The reaction mixture was quenched by an aqueous saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (40 mL) and brine (40 mL), dried over sulfate magnesium, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with a gradient of ethyl acetate/cyclohexane (20/80 to 40/60, v/v) to afford product **(7)** (1.05 g, 1.66 mmol). Yield: 72%; Mp: 95 ± 1 °C; IR (KBr) ν (cm^{-1}) 2929, 2856, 1765 (CO), 1689 (CO), 1524, 1251, 1191, 1082; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 8.29 (d, ^3J = 9.2 Hz, 2H, H-13), 8.12 (s, 1H, H-6), 7.40 (d, ^3J = 9.2 Hz, 2H, H-12), 6.37 (dd, ^3J = 9.1 Hz, ^3J = 5.2 Hz, 1H, H-1′), 5.29 (m, 1H, H-3′), 4.36 (m, 1H, H-4′), 3.96 (m, 2H, H-5′), 2.70 (dd, ^2J = 14.1 Hz, ^3J 5.2 Hz, 1H, H-2′), 2.20 (m, 1H, H-2′), 0.94 (s, 9H, H-9), 0.18 (s, 3H, H-7 or H-7′), 0.16 (s, 3H, H-7 or H-7′). ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 160.6 (C-4), 155.8 (C-10), 152.8 (C-2), 150.8 (C-11), 146.3 (C-14), 144.5 (C-6), 126.1 (C-13), 122.4 (C-12), 86.1 (C-1′, C-4′), 81.2 (C-3′), 69.8 (C-5), 64.3 (C-5′), 39.4 (C-2′), 26.9 (C-9), 19.1 (C-8), −4.4 and −4.6 (C-7, C-7′). ESI-MS: *m/z* 631.97 $[M\text{-}H^+]^-$.

4.3.3. 2-(((tert-Butyldimethylsilyl)oxy)methyl)-5-(5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl (2-(pyridin-2-yldisulfanyl)ethyl) carbonate (8)

4.3.3.1. Method A. To a solution of **(7)** (540 mg, 0.85 mmol, 1 eq.) dissolved in anhydrous THF (10 mL), DMAP (270.1 mg, 2.22 mmol, 2.6 eq.) and a solution of **(1)** (286.4 mg, 1.28 mmol, 1.5 eq.) dissolved in anhydrous THF (10 mL) were added, successively. After stirring at room temperature for 16 h, the reaction solvent was evaporated under reduced pressure and the crude product was dissolved in ethyl acetate (15 mL). The organic layer was washed with water (2 × 30 mL) and brine (2 × 20 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted by ethyl acetate/cyclohexane (40/60, v/v) to afford compound **(8)** (390 mg, 0.57 mmol). Yield: 67%.

4.3.3.2. Method B. To a solution of **(6)** (1.0 g, 2.13 mmol, 1 eq.) and 4-nitrophenyl chloroformate (430.3 mg, 2.13 mmol, 1 eq.) dissolved in anhydrous THF (25 mL), a solution of DMAP (416.4 mg, 3.41 mmol, 1.6 eq.) dissolved in anhydrous THF (6 mL) was added dropwise. After stirring at room temperature for 3 h 30 min, DMAP (169.1 mg, 1.38 mmol, 0.65 eq.) then a solution of **(1)** (478.7 mg, 2.56 mmol, 1.2 eq.) dissolved in anhydrous THF (5 mL) were added. After stirring at room temperature for 16 h, the solvent reaction was evaporated under reduced pressure. The crude product was taken up in dichloromethane (40 mL) then washed with water (30 mL) and brine (2 × 30 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with a gradient ethyl acetate/cyclohexane (30/70 to 60/40, v/v) to afford compound **(8)** (1.31 g, 1.92 mmol). Yield: 90%. IR (KBr) ν (cm^{-1}) 2953, 2856, 1746 (CO), 1689 (CO), 1447, 1418, 1259, 1197, 1124; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 9.89 (brs, 1H, NH), 8.45 (m, 1H, H-15), 8.06 (s, 1H, H-6), 7.63 (m, 2H, H-17, H-18), 7.08 (m, 1H, H-16), 6.25 (dd, ^3J = 9.1 Hz, ^3J = 5.2 Hz, 1H, H-1′), 5.08 (d, ^3J = 5.6 Hz, 1H, H-3′), 4.37 (t, ^3J = 6.5 Hz, 2H, H-11), 4.18 (m, 1H, H-4′), 3.87 (m, 2H, H-5′), 3.07 (t, ^3J = 6.5 Hz, 2H, H-12), 2.54 (dd, ^2J = 13.9 Hz, ^3J = 5.2 Hz, 1H, H-2′), 2.06 (m, 1H, H-2′), 0.89 (s, 9H, H-9), 0.13 (s, 3H, H-7 ou H-7′), 0.11 (s, 3H, H-7′ ou H-7); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 161.7 (C-4), 160.8 (C-10), 155.7 (C-2), 151.6 (C-13), 151.3 (C-15), 145.4 (C-6), 138.7 (C-

17), 122.5 (C-16), 121.5 (C-18), 87.0 (C-1′, C-4′), 80.6 (C-3′), 70.6 (C-5), 67.3 (C-11), 65.1 (C-5′), 40.2 (C-2′), 38.4 (C-12), 27.7 (C-9), 19.9 (C-8), -3.5 and −3.8 (C-7, C-7′). ESI-MS: *m/z* 680.03 [M-H$^+$]$^-$.

4.3.4. 2-(Hydroxymethyl)-5-(5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl (2-(pyridin-2-yldisulfanyl)ethyl) carbonate (9)

To a solution of compound **(8)** (200 mg, 0.29 mmol, 1 eq.) dissolved in acetonitrile/eau (40 mL, 1/1, v/v), indium chloride (1 eq.) was added. The resulting mixture was heated at reflux for 7 h. After cooling to room temperature, acetonitrile was evaporated under reduced pressure. The resulting aqueous solution was extracted with acetate (3 × 20 mL). The combined organic layers were washed with brine (2 × 15 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with a gradient ethyl acetate/cyclohexane (40/60 to 60/40, v/v) to afford compound **(9)** (110 mg, 0.19 mmol). Yield: 66%; IR (KBr) ν (cm^{-1}) 3450, 1745 (CO), 1685 (CO), 1448, 1418, 1263, 1101; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 8.51 (m, 1H, H-12), 8.43 (brs, 1H, NH), 8.31 (s, 1H, H-6), 7.69 (m, 2H, H-14, H-15), 7.14 (m, 1H, H-13), 6.23 (dd, ^{3}J = 9.2 Hz, ^{3}J = 5.2 Hz, 1H, H-1′), 5.27 (m, 1H, H-3′), 4.44 (t, ^{3}J = 6.4 Hz, 2H, H-8), 4.23 (m, 1H, H-4′), 3.98 (m, 2H, H-5′), 3.09 (t, ^{3}J = 6.4 Hz, 2H, H-9), 2.50 (m, 2H, H-2′); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 160.9 (C-4), 160.5 (C-7), 155.6 (C-2), 151.1 (C-12, C-10), 151.3 (C-15), 146.8 (C-6), 138.7 (C-14), 122.5 (C-13), 121.4 (C-15), 87.8 (C-1′), 86.4 (C-4′), 78.6 (C-3′), 69.7 (C-5), 67.4 (C-8), 63.7 (C-5′), 39.3 (C-2′), 38.1 (C-9). ESI-MS: *m/z* 565.95 [M-H$^+$]$^-$.

4.3.5. 2-(((tert-Butyldimethylsilyl)oxy)methyl)-5-(5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl(2-((4-methoxyphenyl)disulfanyl)ethyl) carbonate (10a)

4.3.5.1. Method A. To a solution of **(9)** (200 mg, 0.29 mmol, 1 eq.) dissolved in anhydrous THF (4 mL) cooled at 0 °C, a solution of 4-methoxythiophenol (45.1 mg, 0.32 mmol, 1.1 eq.) dissolved in anhydrous THF (3 mL) was added. The resulting mixture was stirred for 1 h at 0 °C, then 3 h at room temperature. The solvent reaction was evaporated under reduced pressure and the crude product was dissolved in dichloromethane (20 mL). The resulting solution was washed with brine (2 × 20 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with a gradient ethyl acetate/cyclohexane (10/90 to 30/70, v/v) to afford compound **(10a)** (120 mg, 0.17 mmol). Yield: 58%.

4.3.5.2. Method B. To a solution of **(6)** (500 mg, 1.07 mmol, 1 eq.) and 4-nitrophenyl chloroformate (215.1 mg, 1.07 mmol, 1 eq.) dissolved in anhydrous THF (15 mL), a solution of DMAP (208.6 mg, 1.70 mmol, 1.6 eq.) dissolved in anhydrous THF(3 mL) was added dropwise. After stirring at room temperature for 3 h 30 min, DMAP (85.0 mg, 0.70 mmol, 0.65 eq.) and a solution of (**2a**) (277.0 mg, 1.28 mmol, 1.2 eq.) dissolved in anhydrous THF (3 mL) were added. The reaction mixture was stirred at room temperature for 16 h. The reaction solvent was evaporated under reduced pressure. The crude product was dissolved in dichloromethane (20 mL) and the resulting solution was washed with water (25 mL) and brine (2 × 20 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with a gradient ethyl acetate/cyclohexane (10/90 to 30/70, v/v) to afford compound **(10a)** (560 mg, 0.79 mmol). Yield: 74%.

IR (KBr) ν (cm^{-1}) 2927, 2855, 1756 (CO), 1686 (CO), 1590, 1491, 1257, 1196, 1125; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 9.60 (brs, 1H, NH), 8.09 (s, 1H, H-6), 7.46 (d, ^{3}J = 8.9 Hz, 2H, H-14), 6.85 (d, ^{3}J = 8.9 Hz, 2H, H-15), 6.27 (dd, ^{3}J = 9.2 Hz, ^{3}J = 5.3 Hz, 1H, H-1′), 5.13 (d, ^{3}J = 5.7 Hz, 1H, H-3′), 4.38 (t, ^{3}J = 6.7 Hz, 2H, H-11), 4.21 (m, 1H, H-4′), 3.90 (m, 2H, H-5′), 3.78 (s, 3H, H-17), 2.94 (t, ^{3}J = 6.7 Hz, 2H, H-12), 2.56 (dd, ^{2}J = 14.0 Hz, ^{3}J = 5.3 Hz, 1H, H-2′), 2.10 (m, 1H, H-2′), 0.93 (s, 9H, H-9), 0.16 (s, 3H, H-7 or H-7′), 0.15 (s, 3H, H-7′ or H-7); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 160.1 (C-4), 159.9 (C-16), 154.2 (C-10), 150.1 (C-2), 143.9 (C-6), 132.4 (C-14), 127.4 (C-13), 114.8 (C-15), 85.6 (C-1, C-4′), 79.1 (C-3′), 68.9 (C-5), 65.8 (C-11), 63.6 (C-5′), 55.5 (C-17), 38.7 (C-2′), 36.2 (C-12), 26.2 (C-9), 18.5 (C-8), −5.0 and −5.3 (C-7, C-7′). HRMS *m/z* [M + H$^+$]$^+$:calc: 711.0727; found: 711.0724.

4.3.6. ((4-Methoxyphenyl)disulfanyl)ethyl) carbonate (11a)

4.3.6.1. Method A. Compound **(11a)** was synthesized from **(10a)** (100 mg, 0.14 mmol) according to the method previously described for the synthesis of compound **(9)** (reaction time: 4 h). The crude product was purified on silica gel eluted with a gradient ethyl acetate/cyclohexane (10/90 to 35/65, v/v) to afford compound **(11a)** (72 mg, 0.12 mmol). Yield: 83%.

4.3.6.2. Method B. To a solution of **(9)** (100 mg, 0.18 mmol, 1 eq.) dissolved in anhydrous THF (5 mL), cooled at 0 °C, a solution of 4-methoxythiophenol (27.2 mg, 0.19 mmol, 1.1 eq.) dissolved in anhydrous THF (3 mL) was added. The resulting mixture was stirred at 0 °C for 1 h 30 min, then at room temperature for 4 h. The reaction solvent was evaporated under reduced pressure and the crude product was purified on silica gel eluted with a gradient ethyl acetate/cyclohexane (10/90 to 40/60, v/v) to afford compound **(11a)** (89 mg, 0.15 mmol). Yield: 83%.

IR (KBr) ν (cm^{-1}) 3465, 3055, 1743 (CO), 1685 (CO), 1589, 1491, 1448, 1247, 1099; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 9.75 (brs, 1H, NH), 8.29 (s, 1H, H-6), 7.45 (d, ^{3}J = 8.8 Hz, 2H, H-11), 6.83 (d, ^{3}J = 8.8 Hz, 2H, H-12), 6.20 (t, ^{3}J = 6.1 Hz, 1H, H-1′), 5.24 (m, 1H, H-3′), 4.36 (t, ^{3}J = 6.6 Hz, 2H, H-8), 4.17 (m, 1H, H-4′), 4.03 (m, 2H, H-5′), 3.77 (s, 3H, H-14), 2.92 (t, ^{3}J = 6.6 Hz, 2H, H-9), 2.46 (m, 2H, H-2′). ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 160.4 (C-4), 159.9 (C-13), 154.3 (C-7), 150.1 (C-2), 145.7 (C-6), 132.4 (C-11), 127.5 (C-10), 114.9 (C-12), 86.5 (C-1′), 85.2 (C-4′), 78.4 (C-3′), 68.7 (C-5), 65.9 (C-8), 62.5 (C-5′), 55.5 (C-14), 38.0 (C-2′), 36.3 (C-9). HRMS *m/z* for [M + H$^+$]$^+$: calc: 596.9862; found: 596.9838.

4.3.7. 2-(((tert-Butyldimethylsilyl)oxy)methyl)-5-(5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl (2-((4-methoxyphenyl)thio)ethyl) carbonate (10b)

To a solution of **(6)** (500 mg, 1.07 mmol, 1 eq.) and 4-nitrophenyl chloroformate (215.1 mg, 1.07 mmol, 1 eq.) dissolved in anhydrous THF (15 mL), a solution of DMAP (208.6 mg, 1.70 mmol, 1.6 eq.) dissolved in anhydrous THF (3 mL) was added. The resulting mixture was stirred at room temperature for 3 h 30 min. DMAP (85 mg, 0.70 mmol, 0.65 eq.) was added, followed by a solution of **(2b)** (236 mg, 1.28 mmol, 1.2 eq.) dissolved in anhydrous THF (3 mL). The reaction mixture was stirred at room temperature for 16 h. After evaporation of THF under reduced pressure, the crude product was dissolved in dichloromethane (20 mL), washed with water (25 mL) and brine (2 × 20 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with a gradient ethyl acetate/cyclohexane (10/90 to 35/65, v/v) to afford compound **(10b)** (430 mg, 0.63 mmol). Yield: 59%; IR (KBr) ν (cm^{-1}) 1745 (CO), 1713 (CO), 1420, 1362, 1269, 1222; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 9.26 (brs, 1H, NH), 8.09 (s, 1H, H-6), 7.37 (d, ^{3}J = 8.9 Hz, 2H, H-14), 6.83 (d, ^{3}J = 8.9 Hz, 2H, H-15), 6.26 (dd, ^{3}J = 9.1, ^{3}J = 5.2 Hz, 1H, H-1′), 5.10 (d, ^{3}J = 5.9 Hz, 1H, H-3′), 4.23 (t, ^{3}J = 7.0 Hz, 2H, H-11), 4.19 (m, 1H, H-4′), 3.89 (m, 2H, H-5′), 3.77 (s, 3H, H-17), 3.03 (t, ^{3}J = 7.0 Hz, 2H, H-12), 2.54 (dd, ^{2}J = 13.9 Hz, ^{3}J = 5.2 Hz, 1H, H-2′), 2.08 (m, 1H, H-2′), 0.92 (s, 9H, H-9), 0.15 (s, 3H, H-7 or H-7′), 0.14 (s, 3H, H-7′ or H-7); ^{13}C NMR (50 MHz, $CDCl_3$): δ_{ppm} 160.1 (C-4), 159.5 (C-16), 154.3

(C-10), 150.0 (C-2), 144.0 (C-6), 132.2 (C-14), 124.6 (C-13), 114.8 (C-15), 85.6 (C-1, C-4′), 79.0 (C-3′), 68.8 (C-5), 66.7 (C-11), 63.6 (C-5′), 55.4 (C-17), 38.7 (C-2′), 34.2 (C-12), 26.2 (C-9), 18.4 (C-8), -5.1 and −5.3 (C-7, C-7′). HRMS *m/z* for $[M + H^+]^+$: calc: 679.1006 found: 679.0992.

4.3.8. 2-(Hydroxymethyl)-5-(5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl (2-((4-methoxyphenyl)thio)ethyl) carbonate (11b)

Compound **(11b)** was synthesized from **(10b)** (290 mg, 0.43 mmol) according to the method previously described for the synthesis of compound **(9)** (reaction time: 4 h). The crude product was purified on silica gel eluted with a gradient ethyl acetate/cyclohexane (20/80 to 55/45, v/v) to afford compound **(11b)** (200 mg, 0.36 mmol). Yield: 83%; IR (KBr) ν (cm^{-1}) 3456, 2926, 1751 (CO), 1687 (CO), 1494, 1449, 1264, 1099; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 8.87 (brs, 1H, NH), 8.27 (s, 1H, H-6), 7.41 (d, ^{3}J = 8.9 Hz, 2H, H-11), 6.88 (d, ^{3}J = 8.9 Hz, 2H, H-12), 6.23 (dd, ^{3}J = 9.2, ^{3}J = 5.2 Hz, 1H, H-1′), 5.26 (m, 1H, H-3′), 4.23 (m, 3H, H-8, H-4′), 3.97 (m, 2H, H-5′), 3.81 (s, 3H, H-14), 3.07 (t, ^{3}J = 6.9 Hz, 2H, H-9), 2.45 (m, 2H, H-2′). ^{13}C NMR (50 MHz, Acetone-d_6) δ_{ppm} 159.9 (C-4), 159.7 (C-13), 154.3 (C-7), 150.2 (C-2), 145.3 (C-6), 133.7 (C-11), 125.1 (C-10), 114.8 (C-12), 85.4 (C-1′, C-4′), 79.0 (C-3′), 68.1 (C-5), 66.4 (C-8), 62.0 (C-5′), 54.9 (C-14), 37.9 (C-2′), 33.8 (C-9). HRMS *m/z* for $[M + H^+]^+$ calc: 565.0142; found: 565.0137.

4.4. Access to compounds (13), (14a, b), (15a, b), (16a, b) and (17a, b)

4.4.1. 6-(2-Bromoacetamido)-N-(2-(diethylamino)ethyl) quinoxaline-2-carboxamide hydrobromide (13)

To a solution of **(12)** [42] (1.2 g, 4.03 mmol, 1 eq.) dissolved in anhydrous dichloromethane (15 mL), 2-bromoacetoyle bromide (459 μL, 5.25 mmol, 1.3 eq.) was added dropwise. The resulting mixture was stirred at room temperature for 16 h. The precipitate was filtered, then dried under reduced pressure to afford compound **(13)** (2.05 g). Yield: quant; Mp: 212 ± 1 °C; IR (KBr) ν (cm^{-1}) 2947, 2655, 1704 (CO), 1671 (CO), 1624, 1560, 1529, 1486, 1420, 1211; ^{1}H NMR (200 MHz, MeOD) δ_{ppm} 9.45 (s, 1H, H-3), 8.62 (d, ^{4}J = 2.2 Hz, 1H, H-5), 8.17 (d, ^{3}J = 9.2 Hz, 1H, H-8), 8.02 (dd, ^{3}J = 9.2 Hz, ^{4}J = 2.2 Hz, 1H, H-7), 4.10 (s, 2H, H-e), 3.90 (t, ^{3}J = 6.2 Hz, 2H, H-a), 3.40 (m, 6H, H-b, H-c), 1.39 (t, ^{3}J = 7.3 Hz, 6H, H-d); ^{13}C NMR (50 MHz, DMSO-d_6) δ_{ppm} 166.4 (C-x), 164.4 (C-y), 144.5 (C-3), 144.3 (C-4a), 142.9 (C-2), 141.9 (C-6), 137.2 (C-8a), 130.6 (C-8), 125.2 (C-7), 115.9 (C-5), 49.9 (C-b), 47.2 (C—c), 34.6 (C-a), 30.7 (C-e), 8.9 (C-d). ESI-MS: *m/z* 408.08 $[M + H^+]^+$

4.4.2. 6-(2-(4-((2-((tert-Butyldimethylsilyl)oxy)ethyl)disulfanyl) phenoxy)acetamido)-N-(2-(diethylamino)ethyl)quinoxaline-2-carboxamide (14a)

To a solution of **(4a)** (358.7 mg, 1.13 mmol, 1.1 eq.) dissolved in anhydrous THF (8 mL), sodium hydride (63%, in oil) (118 mg, 3.10 mmol, 3 eq.) was added. After 15 min, a solution of **(13)** (500 mg, 1.03 mmol, 1 eq.) and triethylamine (171 μL, 1.23 mmol, 1.2 eq.) dissolved in anhydrous THF (20 mL) was added. The resulting mixture was stirred at room temperature for 1 h. The reaction solvent was evaporated under reduced pressure and the crude product was taken up in dichloromethane (50 mL). The mixture was washed with brine (3 × 10 mL), dried over magnesium sulfate, filtered, then evaporated under reduced pressure. The crude product was purified on silica gel eluted with a gradient dichloromethane/methanol (95/5 to 90/10, v/v) to afford compound **(14a)** (330 mg, 0.51 mmol). Yield: 50%; IR (KBr) ν (cm^{-1}) 3343, 2927, 2855, 1682 (CO), 1655 (CO), 1517, 1491, 1238, 1090; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 9.64 (s, 1H, H-3), 8.66 (brs, 1H, NH-v), 8.46 (m, 2H, NH-w, H-5), 8.12 (m, 2H, H-7, H-8), 7.56 (d, ^{3}J = 8.9 Hz, 2H, H-3′), 7.01 (d, ^{3}J = 8.9 Hz, 2H, H-2′), 4.70 (s, 2H, H-e), 3.84 (t, ^{3}J = 6.7 Hz, 2H, H-10), 3.63 (q, ^{3}J = 5.9 Hz, 2H, H-a), 2.87 (t, ^{3}J = 6.7 Hz, 2H, H-9), 2.81 (t, ^{3}J = 5.9 Hz, 2H, H-b), 2.68 (q, ^{3}J = 7.1 Hz, 4H, H-c), 1.13 (t, ^{3}J = 7.1 Hz, 6H, H-d), 0.89 (s, 9H, H-13), 0.06 (s, 6H, H-11); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 165.5 (C-x), 162.5 (C-y), 155.4 (C-1′), 143.7 (C-3), 143.6 (C-4a), 142.0 (C-2), 138.4 (C-6), 136.9 (C-8a), 130.3 (C-4′), 130.0 (C-3′), 129.8 (C-8), 123.5 (C-7), 116.4 (C-5), 114.7 (C-2′), 66.9 (C-e), 60.6 (C-10), 50.7 (C-b), 46.3 (C—c), 40.4 (C-9), 36.3 (C-a), 25.0 (C-13), 17.4 (C-12), 10.9 (C-d), −6.3 (C-11). HRMS *m/z* for $[M + H^+]^+$calc: 644.2761; found: 644.2778.

4.4.3. 6-(2-(4-((2-((tert-Butyldimethylsilyl)oxy)ethyl)thio) phenoxy)acetamido)-N-(2-(diethylamino)ethyl)quinoxaline-2-carboxamide (14b)

Compound **(14b)** was synthesized from **(4b)** (540 mg, 1.90 mmol) and **(13)** (837.2 mg, 1.72 mmol) according to the method previously described for the synthesis of compound **(14a)** (reaction time: 1 h). The crude product was purified on silica gel eluted with a gradient of dichloromethane/methanol (95/5 to 90/10, v/v) to afford compound **(14b)** (520 mg, 0.85 mmol). Yield: 50%; IR (KBr) ν (cm^{-1}) 2955, 1662(CO), 1631 (CO), 1526, 1492, 1235; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 9.40 (s, 1H, H-3), 9.36 (brs, 1H, NH-v), 8.78 (t, ^{3}J = 5.5 Hz, 1H, NH-w), 8.44 (m, 1H, H-5), 7.98 (m, 1H, H-7), 7.86 (d, ^{3}J = 9.0 Hz, 1H, H-8), 7.27 (d, ^{3}J = 8.6 Hz, 2H, H-3′), 6.87 (d, ^{3}J = 8.6 Hz, 2H, H-2′), 4.66 (s, 2H, H-e), 3.82 (m, 2H, H-a), 3.67 (t, ^{3}J = 7.2 Hz, 2H, H-10), 3.12 (t, ^{3}J = 5.6 Hz, 2H, H-b), 3.00 (q, ^{3}J = 7.1 Hz, 4H, H-c), 2.89 (t, ^{3}J = 7.2 Hz, 2H, H-9), 1.26 (t, ^{3}J = 7.1 Hz, 6H, H-d), 0.79 (s, 9H, H-13), 0.04 (s, 6H, H-11); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 166.8 (C-x), 163.9 (C-y), 156.0 (C-1′), 144.4 (C-4a), 144.2 (C-3), 142.3 (C-2), 139.9 (C-6), 137.6 (C-8a), 132.5 (C-3′), 130.6 (C-8), 129.1 (C-4′), 124.7 (C-7), 117.1 (C-5), 115.5 (C-2′), 67.7 (C-e), 62.3 (C-10), 51.6 (C-b), 47.4 (C—c), 37.4 (C-9), 36.3 (C-a), 25.9 (C-13), 18.3 (C-12), 10.6 (C-d), -5.3 (C-11). HRMS *m/z* for $[M + H^+]^+$calc: 612.3040; found: 612.3026.

4.4.4. N-(2-(Diethylamino)ethyl)-6-(2-(4-((2-hydroxyethyl) disulfanyl)phenoxy)acetamido)quinoxaline-2-carboxamide (15a)

Compound **(15a)** was synthesized from **(14a)** (890 mg, 1.38 mmol) according to the method previously described for the synthesis of compound **(9)** (reaction time: 2 h 30 min). The crude product was purified on silica gel eluted with a gradient dichloromethane/methanol (95/5 to 85/15, v/v) to afford compound **(15a)** (700 mg, 1.32 mmol). Yield: 96%; IR (KBr) ν (cm^{-1}) 3313, 2963, 1720 (CO), 1645, 1531, 1489, 1449, 1246, 1208; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 9.51 (s, 1H, H-3), 9.11 (brs, 1H, NH-v), 8.48 (m, 2H, NH-w, H-5), 8.10 (dd, ^{3}J = 9.1 Hz, ^{4}J = 1.9 Hz, 1H, H-7), 8.00 (d, ^{3}J = 9.1 Hz, 1H, H-8), 7.42 (d, ^{3}J = 8.7 Hz, 2H, H-3′), 6.89 (d, ^{3}J = 8.7 Hz, 2H, H-2′), 4.64 (s, 2H, H-e), 3.83 (t, ^{3}J = 6.1 Hz, 2H, H-10), 3.62 (m, 3H, H-a, OH), 2.87 (t, ^{3}J = 6.1 Hz, 2H, H-9), 2.80 (t, ^{3}J = 6.1 Hz, 2H, H-b), 2.67 (q, ^{3}J = 7.1 Hz, 4H, H-c), 1.09 (t, ^{3}J = 7.1 Hz, 6H, H-d); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 166.8(C-x), 163.5 (C-y), 156.7 (C-1′), 144.3 (C-3), 144.2 (C-4a), 142.7 (C-2), 139.8 (C-6), 137.7 (C-8a), 131.2 (C-3′), 130.6 (C-8), 130.4 (C-4′), 124.8 (C-7), 117.2 (C-5), 115.6 (C-2′), 67.7 (C-e), 60.0 (C-10), 51.6 (C-b), 47.2 (C—c), 41.3 (C-9), 37.1 (C-a), 11.5 (C-d). HRMS *m/z* for $[M + H^+]^+$ calc: 530.1896; found: 530.1872.

4.4.5. N-(2-(Diethylamino)ethyl)-6-(2-(4-((2-hydroxyethyl)thio) phenoxy)acetamido)quinoxaline-2-carboxamide (15b)

Compound **(15b)** was synthesized from **(14b)** (440 mg, 0.72 mmol) according to the method previously described for the synthesis of compound **(9)** (reaction time: 5 h). The crude product was purified on silica gel eluted with a gradient of dichloromethane/methanol (95/5 to 85/15, v/v) to afford compound **(15b)** (330 mg, 0.66 mmol). Yield: 92%; IR (KBr) ν (cm^{-1}) 3281, 2966, 1713

(CO), 1656 (CO), 1525, 1491, 1352, 1222; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 9.59 (s, 1H, H-3), 8.80 (brs, 1H, NH-v), 8.55 (t, ^3J = 4.9 Hz, 1H, NH-w), 8.45 (m, 1H, H-5), 8.10 (m, 2H, H-7, H-8), 7.41 (d, ^3J = 8.8 Hz, 2H, H-3′), 6.94 (d, ^3J = 8.8 Hz, 2H, H-2′), 4.68 (s, 2H, H-e), 3.70 (m, 4H, H-10, H-a), 3.05 (t, ^3J = 6.0 Hz, 2H, H-9), 2.84 (t, ^3J = 6.0 Hz, 2H, H-b), 2.73 (q, ^3J = 7.0 Hz, 4H, H-c), 1.15 (t, ^3J = 7.0 Hz, 6H, H-d); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 166.5 (C-x), 163.6 (C-y), 156.2 (C-1′), 144.5 (C-3), 144.4 (C-4a), 142.8 (C-2), 139.5 (C-6), 137.8 (C-8a), 133.4 (C-3′), 130.7 (C-8), 128.0 (C-4′), 124.6 (C-7), 117.3 (C-5), 115.6 (C-2′), 67.7 (C-e), 60.3 (C-10), 51.7 (C-b), 47.3 (C—c), 38.5 (C-9), 37.0 (C-a), 11.4 (C-d). HRMS *m*/*z* for $[M + H^+]^+$ calc: 498.2159; found: 498.2159.

4.4.6. 2-(((tert-Butyldimethylsilyl)oxy)methyl)-5-(5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl(2-((4-(2-((2-((2-(diethylamino)ethyl)carbamoyl)quinoxalin-6-yl)amino)-2-oxoethoxy)phenyl)disulfanyl)ethyl) carbonate (16a)

To a solution of **(15a)** (300 mg, 0.57 mmol, 1 eq.) dissolved in anhydrous THF (5 mL), DMAP (83 mg, 0.68 mmol, 1.2 eq.) and **(7)** (448.5 mg, 0.71 mmol, 1.3 eq.) were added, successively. After stirring for 16 h at room temperature, the reaction solvent was evaporated under reduced pressure and the crude product was taken up in dichloromethane (15 mL). The organic layer was washed with an aqueous saturated sodium bicarbonate solution (10 mL) and brine (2 × 5 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified on silica gel eluted with a gradient dichloromethane/methanol (95/5 to 85/15, v/v) to afford compound **(16a)** (456 mg, 0.446 mmol). Yield: 78%; IR (KBr) ν (cm^{-1}) 2928, 1747 (CO), 1685 (CO), 1605, 1523, 1489, 1256; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 9.63 (s, 1H, H-15), 8.88 (brs, 1H, NH-v), 8.43 (m, 3H, NH-w, NH-3, H-17), 8.24 (dd, ^3J = 9.1 Hz, ^4J = 2.3 Hz, 1H, H-19), 8.07 (d, ^3J = 9.1 Hz, 1H, H-20), 8.05 (s, 1H, H-6), 7.55 (d, ^3J = 8.8 Hz, 2H, H-2″), 7.01 (d, ^3J = 8.8 Hz, 2H, H-3″), 6.29 (dd, ^3J = 9.1 Hz, ^3J = 5.2 Hz, 1H, H-1′), 5.13 (d, ^3J = 5.5 Hz, 1H, H-3′), 4.70 (s, 2H, H-e), 4.37 (t, ^3J = 6.4 Hz, 2H, H-11), 4.20 (m, 1H, H-4′), 3.92 (m, 2H, H-5′), 3.63 (m, 2H, H-a), 3.00 (t, ^3J = 6.4 Hz, 2H, H-12), 2.74 (t, ^3J = 6.1 Hz, 2H, H-b), 2.68 (q, ^3J = 7.1 Hz, 4H, H-c), 2.53 (dd, ^3J = 14.1 Hz, ^3J = 5.2 Hz, 1H, H-2′), 2.07 (m,1H, H-2′), 1.10 (t, ^3J = 7.1 Hz, 6H, H-d), 0.93 (s, 9H, H-9), 0.17 (s, 3H, H-7 or H-7′), 0.15 (s, 3H, H-7 or H-7′); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 166.5 (C-x), 163.4 (C-y), 160.3 (C_4O), 156.7 (C-4″), 154.2 ($C_{10}O$), 150.3 (C_2O), 144.5 (C-15), 144.2 (C-16a), 143.6 (C-6), 143.0 (C-14), 139.7 (C-18), 137.8 (C-20a), 131.3 (C-2″), 130.7 (C-20), 130.1 (C-1″), 124.5 (C-19), 117.2 (C-17), 115.7 (C-3″), 85.5 (C-1′), 85.4 (C-4′), 79.2 (C-3′), 69.4 (C-5), 67.7 (C-e), 65.6 (C-11), 63.6 (C-5′), 51.5 (C-b), 47.0 (C—c), 38.7 (C-2′), 37.2 (C-a), 36.9 (C-12), 26.2 (C-9), 18.4 (C-8), 11.6 (C-d), −5.1 and −5.3 (C-7, C-7′). HRMS *m*/*z* for $[M + H^+]^+$ calc: 1024.2266; found: 1024.2224.

4.4.7. 2-(((tert-Butyldimethylsilyl)oxy)methyl)-5-(5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl (2-((4-(2-((2-((2-(diethylamino)ethyl)carbamoyl)quinoxalin-6-yl)amino)-2-oxoethoxy)phenyl)thio)ethyl) carbonate (16b)

Compound **(16b)** was synthesized from **(15b)** (270 mg, 0.54 mmol) and **(7)** (429.2 mg, 0.68 mmol) according to the method previously described for the synthesis of compound **(16a)** (reaction time: 16 h). The crude product was purified on silica gel eluted with a gradient dichloromethane/methanol (95/5 to 85/15, v/v) to afford compound **(16b)** (410 mg, 0.41 mmol). Yield: 76%; IR (KBr) ν (cm^{-1}) 2929, 1721 (CO), 1686 (CO), 1619, 1523, 1491, 1257; ^{1}H NMR (200 MHz, $CDCl_3$) δ_{ppm} 9.56 (s, 1H, H-15), 9.01 (brs, 1H, NH-v), 8.37 (m, 3H, NH-w, NH-3, H-17), 8.18 (dd, ^3J = 9.1 Hz, ^4J = 1.2 Hz, 1H, H-19), 8.00 (m, 2H, H-20, H-6), 7.40 (d, ^3J = 8.0 Hz, 2H, H-2″), 6.94 (d, ^3J = 8.0 Hz, 2H, H-3″), 6.24 (dd, ^3J = 8.9 Hz, ^3J = 5.1 Hz, 1H, H-1′), 5.07 (d, ^3J = 5.5 Hz, 1H, H-3′), 4.67 (s, 2H, H-e), 4.26 (t, ^3J = 6.0 Hz, 2H, H-11), 4.14 (m, 1H, H-4′), 3.88 (m, 2H, H-5′), 3.58 (q, ^3J = 6.0 Hz, 2H, H-a), 3.06 (t, ^3J = 6.0 Hz, 2H, H-12), 2.75 (t, ^3J = 6.0 Hz, 2H, H-b), 2.64 (q, ^3J = 7.1 Hz, 4H, H-c), 2.47 (dd, ^3J = 14.0 Hz, ^3J = 5.1 Hz, 1H, H-2′), 2.08 (m, 1H, H-2′), 1.06 (t, ^3J = 7.1 Hz, 6H, H-d), 0.90 (s, 9H, H-9), 0.14 (s, 3H, H-7 or H-7′), 0.13 (s, 3H, H-7 or H-7′); ^{13}C NMR (50 MHz, $CDCl_3$) δ_{ppm} 166.6 (C-x), 163.4 (C-y), 160.4 (C-4), 156.6 (C-4″), 154.2 (C-10), 150.4 (C_2O), 144.4 (C-15), 144.2 (C-16a), 143.6 (C-6), 142.9 (C-14), 139.7 (C-18), 137.7 (C-20a), 134.1 (C-2″), 130.7 (C-20), 127.6 (C-1″), 124.5 (C-19), 117.2 (C-17), 115.7 (C-3″), 85.4 (C-1′), 85.3 (C-4′), 79.1 (C-3′), 69.5 (C-5), 67.7 (C-e), 67.2 (C-11), 63.6 (C-5′), 51.4 (C-b), 46.9 (C—c), 38.6 (C-2′), 37.2 (C-a), 34.1 (C-12), 26.2 (C-9), 18.4 (C-8), 11.6 (C-d), -5.1 and −5.3 (C-7, C-7′). HRMS *m*/*z* for $[M + H^+]^+$calc: 992.2545; found: 992.2508.

4.4.8. 2-((4-(2-((2-((2-(Diethylamino)ethyl)carbamoyl)quinoxalin-6-yl)amino)-2-oxoethoxy)phenyl)disulfanyl)ethyl (2-(hydroxymethyl)-5-(5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl) carbonate (17a)

Compound **(17a)** was synthesized from **(16a)** (280 mg, 0.27 mmol) according to the briefly modified method described for the synthesis of compound **(9)** (reaction time: 16 h). After evaporation of the reaction solvent, the crude product was dissolved in methanol (40 mL) then filtered. The filtrate was concentrated under reduced pressure and was purified on silica gel with a gradient of dichloromethane/methanol (95/5 to 90/10, v/v) to afford compound **(17a)** (170 mg, 0.184 mmol). Yield: 68%; IR (KBr) ν (cm^{-1}) 3368, 2926, 1712 (CO), 1677 (CO), 1618, 1525, 1489, 1261; ^{1}H NMR (200 MHz, MeOD) δ_{ppm} 9.44 (s, 1H, H-12), 8.61 (m, 1H, H-14), 8.42 (s, 1H, H-6), 8.12 (m, 2H, H-16, H-17), 7.54 (d, ^3J = 8.9 Hz, 2H, H-2″), 7.09 (d, ^3J = 8.9 Hz, 2H, H-3″), 6.19 (dd, ^3J = 8.3 Hz, ^3J = 5.9 Hz, 1H, H-1′), 5.15 (d, ^3J = 5.7 Hz, 1H, H-3′), 4.80 (s, 2H, H-e), 4.34 (t, ^3J = 6.2 Hz, 2H, H-8), 4.10 (m, 1H, H-4′), 3.89 (t, ^3J = 6.1 Hz, 2H, H-a), 3.80 (m, 2H, H-5′), 3.47 (t, ^3J = 6.1 Hz, 2H, H-b), 3.37 (q, ^3J = 7.2 Hz, 4H, H-c), 3.03 (t, ^3J = 6.2 Hz, 2H, H-9), 2.36 (m, 2H, H-2′), 1.38 (t, ^3J = 7.2 Hz, 6H, H-d); ^{13}C NMR (50 MHz, MeOD) δ_{ppm} 168.4 (C-x), 165.5 (C-y), 161.3 (C-4), 158.0 (C-4″), 154.3 (C-7), 150.6 (C-2), 145.6 (C-6), 144.2 (C-13a), 143.7 (C-12), 142.3 (C-11), 141.3 (C-15), 137.8 (C-17a), 131.4 (C-2″), 130.2 (C-1″), 129.5 (C-17), 125.3 (C-16), 116.5 (C-14), 115.6 (C-3″), 85.6 (C-1′), 85.4 (C-4′), 78.9 (C-3′), 67.7 (C-5), 67.4 (C-e), 65.4 (C-8), 61.6 (C-5′), 51.2 (C-b), 37.7 (C-2′), 36.9 (C-9), 34.5 (C-a), 7.9 (C-d). HRMS *m*/*z* for $[M + H^+]^+$calc: 910.1401; found: 910.1403.

4.4.9. 2-((4-(2-((2-((2-(Diethylamino)ethyl)carbamoyl)quinoxalin-6-yl)amino)-2-oxoethoxy)phenyl)thio)ethyl(2-(hydroxymethyl)-5-(5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl) carbonate (17b)

Compound **(17b)** was synthesized from **(16b)** (130 mg, 0.13 mmol) according to the briefly modified method described for the synthesis of compound **(9)** (time: 16 h). The reaction solvent was evaporated under reduced pressure and the crude product was dissolved in methanol (30 mL), then filtered. The filtrate was concentrated under reduced pressure and purified on silica gel eluted with a gradient dichloromethane/methanol (95/5 to 90/10, v/v) to afford compound **(17b)** (49 mg, 0.056 mmol). Yield: 43%; IR (KBr) ν (cm^{-1}) 3338, 1713 (CO), 1678 (CO), 1618, 1525, 1491, 1263; ^{1}H NMR (200 MHz, MeOD) δ_{ppm} 9.45 (s, 1H, H-12), 8.63 (m, 1H, H-14), 8.42 (s, 1H, H-6), 8.13 (m, 2H, H-16, H-17), 7.49 (d, ^3J = 8.8 Hz, 2H, H-2″), 7.07 (d, ^3J = 8.8 Hz, 2H, H-3″), 6.15 (dd, ^3J = 8.2 Hz, ^3J = 5.8 Hz, 1H, H-1′), 5.12 (d, ^3J = 5.7 Hz, 1H, H-3′), 4.79 (s, 2H, H-e), 4.29 (m, 2H, H-8), 4.04 (m, 1H, H-4′), 3.88 (t, ^3J = 5.9 Hz, 2H, H-a), 3.80 (m, 2H, H-5′), 3.33 (m, 6H, H-b, H-c), 3.13 (t, ^3J = 6.1 Hz, 2H, H-9), 2.29 (m, 2H, H-2′), 1.37 (t, ^3J = 7.1 Hz, 6H, H-d); ^{13}C NMR (50 MHz, MeOD) δ_{ppm} 168.4 (C-x), 165.4 (C-y), 161.2 (C-4), 157.4 (C-4″), 154.2 (C-7), 150.5 (C-2), 145.4 (C-6), 144.1 (C-13a), 143.5 (C-12), 141.2 (C-11),

140.2 (C-15), 137.6 (C-17a), 133.5 (C-2″), 130.1 (C-17), 127.1 (C-1″), 125.2 (C-16), 116.4 (C-14), 115.3 (C-3″), 85.5 (C-1′), 85.2 (C-4′), 78.7 (C-3′), 67.5 (C-e), 67.2 (C-5, C-8), 61.5 (C-5′), 51.1 (C-b), 47.5 (C–c), 37.5 (C-2′), 34.5 (C-a), 33.6 (C-9), 7.9 (C-d). HRMS *m*/*z* for $[M + H^+]^+$calc: 878.1680; found: 878.1640.

4.5. Material for analytical experiments

4.5.1. HPLC material and conditions

The analytical reversed phase-high pressure liquid chromatography (RP-HPLC) measurements were performed on a system consisting of HP1100 (Hewlett Packard, Les Ulis, France). The separation was carried out on a C_{18} column (Agilent Zorbax, 80 Å, 4.6 mm × 150 mm, 5 μM) using the following conditions:

- For standard curve preparation and conjugates **(11a,b)** cleavage and stability studies: gradient time = 30 min, flow rate = 0.5 mL/min, eluent A (ammonium formate buffer, pH 4), eluent B (acetonitrile); gradient: 75/25 (A/B, v/v) for 0–3.5 min, 75/25 → 50/50 (A/B, v/v) for 3.5–7 min, 50/50 (A/B, v/v) for 7–15 min, 50/50 → 75/25 (A/B, v/v) for 15–20 min, 75/25 (A/B, v/v) for 20–30 min, λ = 285 nm (Conditions A).
- For conjugates **(17a,b)** cleavage and stability studies: gradient time = 20 min, flow rate = 0.5 mL/min, eluent A (ammonium formate buffer, pH 4), eluent B (acetonitrile); gradient: 75/25 (A/B, v/v) for 0–3.5 min, 75/25 → 50/50 (A/B, v/v) for 3.5–7 min, 50/50 (A/B, v/v) for 7–18 min, 50/50 → 75/25 (A/B, v/v) for 18–20 min, λ = 285 nm (Conditions B).

4.5.2. Standard curve preparation

Five solutions with one known concentration of internal standard **(11b)** (0.5 mM) and increasing concentrations of IUdR (0.35–2.12 mM) were prepared and analyzed by RP-HPLC (see ***Conditions A***). The corresponding peak areas were determined using Chemstation software. The ratio of two areas obtained, for a given concentration, has set a standard curve (Fig. 7).

4.5.3. IUdR dosage

For each aliquot withdrawn from the reaction mixture and analyzed by RP-HPLC (see Conditions A and B), the ratio of peak areas corresponding to IUdR and (**11b**) was calculated. The concentration of IUdR released from prodrug **(11a and 17a)** in the presence of reducing agent (DTT, glutathione) was determined by projecting the found value on the standard curve.

4.5.4. Half-life determination

Kinetic rate of IUdR release from prodrug **(11a and 17a)** was studied. A solution of the prodrug and the internal standard (**11b**) (0.5 mM) was treated with one equivalent of DTT (or with a glutathione solution 5 mM). At different times (1, 2, 6, 10, 15, 20, 25, 30 and 60 min) aliquots was withdrawn and analyzed by RP-HPLC (see conditions A and B) and the amount of released IUdR was determined from the standard curve.

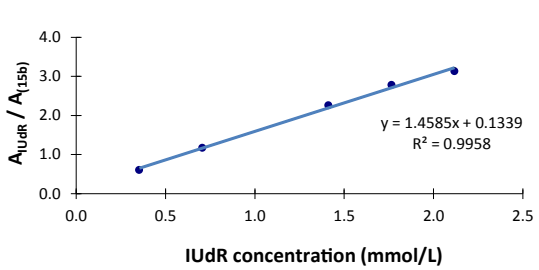


Fig. 7. Standard curve for cleavage studies.

Difference between the initial concentration of the prodrug and the concentration of released IUdR give access to the effective concentration of the prodrug (= sum of concentrations of all species other than IUdR, present in the reaction mixture and resulting from the prodrug cleavage) at each time analysis. These species are noted (**11a*** and **17a***). The intersection of the two curves concentration = f (time) then gave access to the effective half-life time of the prodrug (**11a*** and **17a***), which also corresponds to the half-formation time of IUdR. Note that the half-formation times are the concentrations for which (**11a** or **17a**) and IUdR are equal to half of the initial concentration of the prodrug (**11a** and **17a**).

- initial concentration of **(11a)** = 0.9 mM
- initial concentration of **(17a)** = 0.55 mM

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.06.055.

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