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Heteromultifunctional oxazolones as versatile linkers for click chemistry reactions

Mathilde Pantin, [a] Julien Caillé, [a] Fabien Boeda, [a] Laurent Fontaine, [a] Morwenna S. M. Pearson-Long,*[a] and Philippe Bertus*[a]

Abstract: New oxazolone-based heteromultifunctional linkers were synthesized using a zinc-mediated double functionalization of nitriles as the key step. The orthogonality of the functional groups displayed by this original scaffold was demonstrated by conducting sequential or simultaneous multi-component reactions with amines (oxazolone ring opening), thiols (thiol-ene radical reaction) and azides (Cu-catalyzed azide-alkyne coupling), in respect to the concept of click chemistry.

Introduction

Heteromultifunctional coupling reagents are molecules of great importance for bioconjugation, diagnosis, therapy and layer functionalization.[1,2] These chemical tools should display different functionalities able to link specific partners orthogonally by a sequential combination of chemoselective ligations.[3,4] Among all these bioorthogonal reactions,[1c] the most widely used is the Sharpless copper-catalyzed azide-alkyne cycloaddition (CuAAC).[5] Nevertheless, the use of copper salts remains a main drawback, especially for bio-related applications.[6] In order to overcome this limitation the Cu-free strain-promoted azide-alkyne cycloaddition was introduced.[7] Several other reactions are also used,[8] such as tetrazine-based inverse-electron demand Diels Alder reactions with strained alkenes,[9] addition to maleimide derivatives,[10] nucleophilic addition of amines onto activated esters (*N*-hydroxysuccinimidyl (NHS), pentafluorophenyl,...),[11] the photocrosslinking involving benzophenone partners,[12] and the transition metal-catalyzed cross coupling reactions (Suzuki,[13] Glaser reactions,[14]...). Among the heterobifunctional linkers reported in the literature, the most popular ones display amine- and thiol-reactive functions particularly useful to directly link biomolecules such as proteins and antibodies.[15]

The introduction of an additional functionality on the linker offers new perspectives of coupling, as reported these last few years with the selected examples of polyfunctional linkers **1-4** presented on figure 1.[16] Nevertheless, the direct orthogonal coupling of several molecules with multifunctional linkers avoiding time-consuming activation and/or deprotection steps and/or the formation of byproducts remains highly desirable.

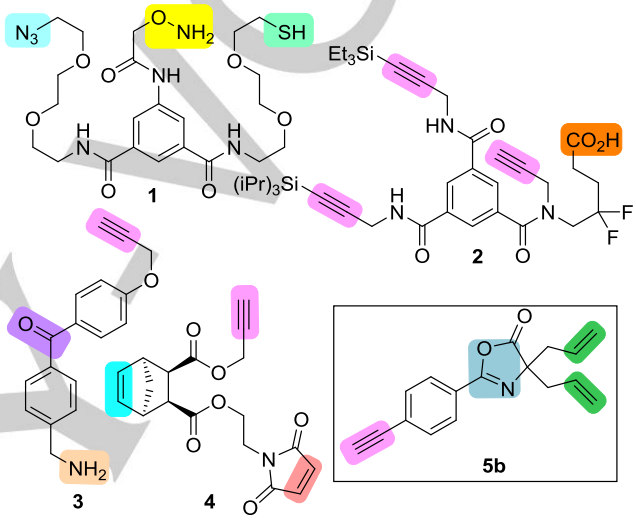

Figure 1. Examples of heteromultifunctional linkers **1**-**4** and the structure of the linker **5b**, subject of this work.

In this context, we were interested in developing new linkers able to react in underexplored coupling reactions, namely the amine-mediated ring opening of 1,3-oxazol-5(4*H*)-ones (also named azlactones),[17] and the thiol-ene radical addition.[18,19] These two reactions present the benefit to directly link amine and thiol moieties respectively, without formation of any byproduct (click chemistry).[20] Indeed, the oxazolone functionality has emerged as a powerful chemical tool due to its high reactivity towards primary and secondary amines without generating byproducts neither requiring any catalyst. This reaction, proceeding with complete atom economy, can be conducted in a broad range of organic solvents as well as in aqueous solution at room temperature. Additionally, the azlactone group is relatively stable to hydrolysis, a substantial advantage compared to NHS ester derivatives.

In this work, we present the elaboration of new linkers displaying both oxazolone and alkene moieties, and possibly a third orthogonal clickable functionality (alkyne), such as in the multifunctional linker **5b** (Fig. 1), with the challenge to increase the functional diversity and multiplicity without affecting the highly reactive oxazolone function.[21] In contrast to succinimidyl 4-(*N*-maleimidomethyl)-cyclohexane-1-carboxylate (SMCC), an amine-to-sulfhydryl linker that contains NHS-ester and maleimide reactive

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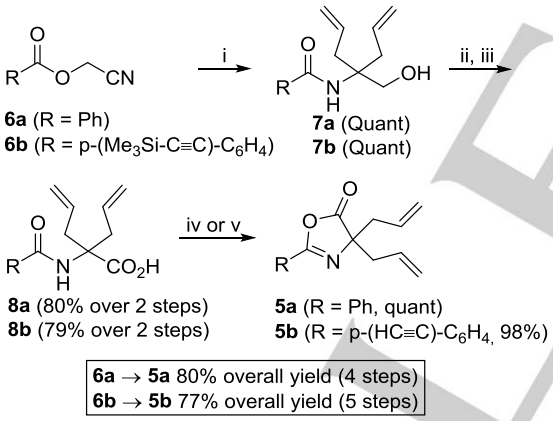
groups frequently used for the preparation of antibody-drug conjugates (ADCs) and other functional conjugates,[22] the reported bis-allyl-functionalized linkers of this work can potentially link two molecules of thiol, thus increasing the loading in active compound of the final bioconjugate. Therefore, these linkers would be able to graft up to four partners without byproduct release, nor activation step. The strategy to access these valuable compounds is based on our recently developed straightforward double functionalization of nitriles.[23]

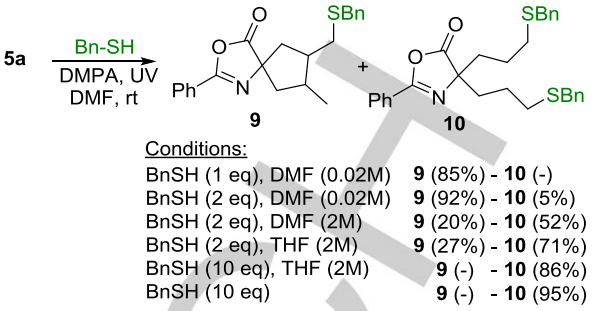
Results and Discussion

As depicted in scheme 1, the reaction of allylzinc reagent on acylcyanohydrins **6a**[23c] and **6b**, easily prepared from the corresponding carboxylic acids, results in the very selective formation of the corresponding hydroxyamides **7**, in quantitative yields. These compounds were efficiently converted into the corresponding acids **8a** and **8b** after a two-step oxidation sequence. The trimethylsilyl group of **8b** was then removed, and the oxazolone heterocycles **5a**-**b** were finally obtained via a cyclization reaction involving ethyl chloroformate reagent. In this procedure, the oxazolones were thus synthesized from the starting nitriles without time-consuming purification of the intermediates, and in excellent overall yields.



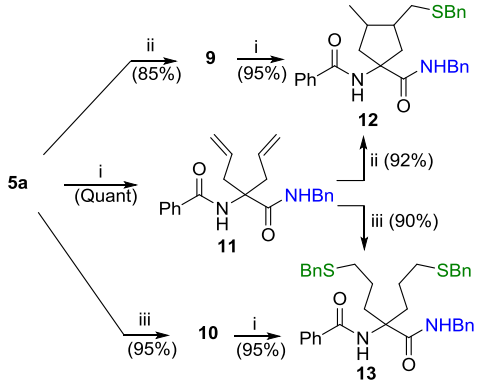
Scheme 1. Synthesis of oxazolones **5a-b**. (i) allyl bromide, activated zinc powder, THF, rt; (ii) IBX, DMSO, 50 °C; (iii) NaH_2PO_4, $NaClO_2$, H_2O_2, MeCN, rt; (iv) For **5a**: ethyl chloroformate, Et_3N, acetone, rt; (v) For **5b**: a) K_2CO_3, MeOH/THF, rt, b) ethyl chloroformate, Et_3N, acetone, rt.

The orthogonal reactivity of the oxazolone and allyl moieties toward aminolysis and radical alkene hydrothiolation was first investigated with the model substrate **5a**. The thiol-ene reaction was performed with benzylmercaptan under conventional conditions (DMPA as photoinitiator, 365 nm UV irradiation, Scheme 2).[24]



Scheme 2. Reactivity of oxazolone **5a** towards thiol-ene reaction. DMPA = 2,2-dimethoxy-2-phenylacetophenone. Yields were calculated after purification of the crude mixture, and separation of **9** and **10**.

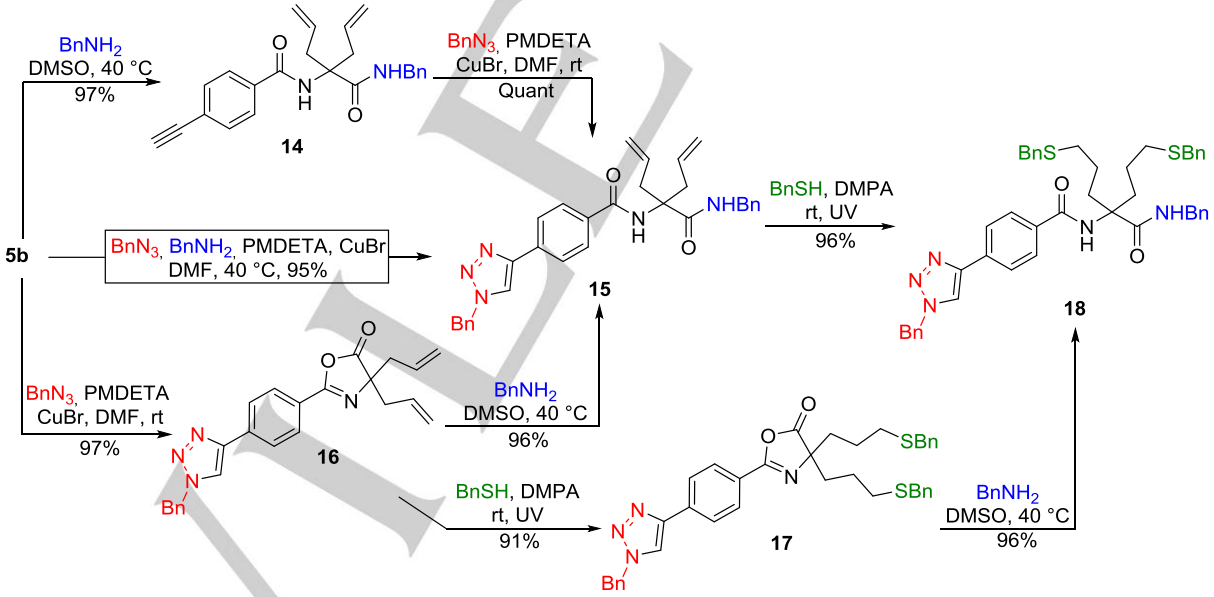
Interestingly, the outcome of the reaction depends on the experimental conditions. When the reaction was carried out in low concentration (0.02 M in DMF), the spirocyclic compound **9** resulting from the incorporation of only one thiol was obtained as the unique or major product, whatever the quantity of mercaptan added. The formation of this compound is easily explained by a first addition of the benzyl thiyl radical onto one double bond, followed by a 5-*exo-trig* subsequent cyclization reaction with the remaining double bond. Performing the reaction with 2 equivalents of thiol in DMF or THF in more concentrated conditions, favors the formation of **10**, and a complete double thiol-ene reaction was observed when 10 equivalents of thiol were added in THF. Finally, the best conditions were found by conducting the reaction in the presence of an excess of the thiol partner and without any solvent, to provide **10** in 95% yield. It should be underlined that under these conditions, the oxazolone moiety remains unaffected. In contrast, as expected, the addition of benzylamine to **5a** occurs selectively and quantitatively in DMSO (40 °C, 24 h), leading to the amide **11** as shown in Scheme 3. Whereas the oxazolone **5a** remains unreactive towards aniline (aromatic amine), the addition was successfully performed with an aminoacid derivative (methyl alaninate).[25] A subsequent thiol-ene reaction under the above optimized conditions afforded **12** or **13**, according to the chosen reaction conditions. These compounds are also accessible by aminolysis of thiol-ene products **9** and **10**, which confirm the orthogonality of the oxazolone and allyl moieties.



Scheme 3. Reactivity of oxazolone **5a** towards thiol-ene and aminolysis reactions. (i) $BnNH_2$, DMSO, 40 °C; (ii) BnSH (1 equiv), DMF (0.02 M), DMPA (10 mol%), UV irradiation (365 nm), rt; (iii) BnSH (10 equiv), DMPA (10 mol%), UV irradiation (365 nm), rt.

The reactivity of oxazolone **5b**, displaying a terminal alkyne function, was then studied in order to propose an additional click transformation, and thus to validate the feasibility of the sequential anchoring of different partners on the linker. First of all, aminolysis and CuAAC reactions have been investigated (Scheme 4). The nucleophilic addition of benzylamine onto oxazolone **5b** proceeded efficiently to provide diamide **14** in 97% yield and the subsequent copper-catalyzed Huisgen cycloaddition with benzyl azide furnished compound **15** quantitatively. Alternatively, the CuAAC reaction involving substrate **5b** and benzyl azide as coupling partner allowed the formation of triazole **16** in 97% yield and the following aminolysis with benzylamine afforded compound **15** in 96% yield. Interestingly, the grafting of the two partners has also been achieved simultaneously on **5b** in a "one-pot" procedure to efficiently provide compound **15** which was isolated in 95% yield. This result clearly highlights the orthogonal chemical reactivity of the alkyne *vs* oxazolone core.

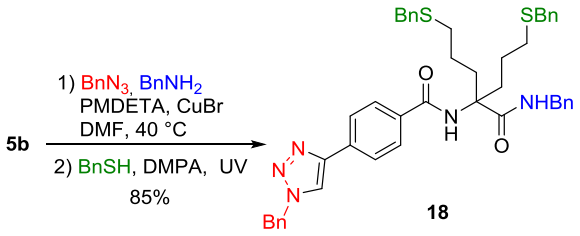
In a second time, aminolysis and hydrothiolation reactions have been investigated. The thiol-ene reaction between benzyl mercaptan and diallyl oxazolone **16** was performed using DMPA as photoinitiator. After one hour of reaction under UV irradiation, *bis*-thioether **17** was isolated in 91% yield. The ring-opening of the oxazolone core was then performed upon nucleophilic addition of benzylamine to furnish compound **18** in 96% yield. The reversed sequence has been also studied. Indeed, after aminolysis of **16** in 96% yield, the product **15** was subjected to hydrothiolation reaction conditions and the expected compound **18** was obtained with a high yield of 96%. Importantly, the CuAAC reaction must be performed before the thiol-ene reaction, otherwise some concomitant hydrothiolation of the alkyne function occurred and a mixture of addition products is formed.



Scheme 4. Reactivity of oxazolone **5b** towards aminolysis and CuAAC reactions.

These results in hand, we focused our attention on a method to anchor three different partners on oxazolone **5b** without any purification step (Scheme 5). For that purpose, alkynyl diallyloxazolone **5b** was mixed with benzyl azide, PMEDTA, copper bromide and benzylamine in DMF. After 16h of reaction at 40 °C, the crude mixture (obtained after addition of water followed by an extraction with AcOEt) was directly treated with DMPA and benzyl mercaptan. After 1h of UV irradiation, the

targeted compound **18** was obtained in 85% yield. This result validates our goal, which was to realize a three-click reactions sequence without byproduct release. It is worth mentioning that a classical "one-pot" methodology did not proceed well since the presence of DMF was detrimental to hydrothiolation reaction.



Scheme 5. Sequential "one-pot" method leading directly to **18**.

Conclusions

In summary, we developed the preparation of functionalized oxazolones relying on a high yielding four- or five-step synthetic sequence. One of these new heteromultifunctional linkers (**5b**), displaying three functional groups able to undergo orthogonal modifications, was successfully subjected to the crosslinking of various model partners, with the only requirement to perform the CuAAC reaction previous to the thiol-ene reaction. Ultimately, a sequential "one-pot" method to anchor selectively these three model molecules (azide, amine and thiol) has been performed. These encouraging results pave the way for further studies dealing with the use of our platform in bioconjugation or surface functionalization challenges.

Experimental Section

Experiments involving organometallic reagents and thiol-ene reactions were carried out under N_2 atmosphere. THF and CH_2Cl_2 were purified by passing through neutral alumina columns under nitrogen. DMSO and DMF were distilled under nitrogen before use. The zinc source consists in an activated zinc powder prepared as followed: to an aqueous 1M solution of HCl (100 mL) was added zinc dust (5 g). The resulting suspension was stirred for 30 minutes at rt then filtered and washed successively with water (twice), EtOH and Et_2O. The activated zinc powder was dried under vacuum over at least 10 h. A shining grey appearance of the metal should be observed during this last stage. The activated zinc powder could be stored under argon for several months at rt. IBX was prepared according to the protocol described by the group of B. Schmidt.[21] Analytical TLC were performed on Alugram SIL G/UV254 silica gel sheets (Macherey-Nagel) by using UV revelation or potassium permanganate solution ($KMnO_4$). Column chromatography was carried out using silica gel 60 (0.040-0.063 mm) from Merck. Melting points were determined with a Büchi B-540 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-200 or Bruker AC-400 spectrometer. Chemical shifts (δ) are expressed in ppm units, relative to the residual solvent peak. Coupling constants are given in Hz. The multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quadruplet (q), pentuplet (p), appearing pentuplet (app p), multiplet (m), and broad signal (br s). IR spectra were obtained on a Perkin Elmer Spectrum One spectrometer on a single-reflection diamond ATR unit. High resolution mass spectra were recorded on a Waters Micromass GCT Premier spectrometer.

***N*-(4-(Hydroxymethyl)hepta-1,6-dien-4-yl)benzamide (7a):**[23a] To a suspension of zinc powder (12.2 g, 186.3 mmol) in THF (200 mL) was added allylbromide (16.1 mL, 186.3 mmol). The mixture was refluxed for 2 minutes, and cooled down to rt. The organozinc bromide solution was then added dropwise over 5 minutes, to a solution of the cyanomethyl benzoate **6a** (10.0 g, 62.1 mmol) in THF (100 mL) cooled to 0 °C. The mixture was stirred 5 minutes at 0 °C then a 1M aqueous HCl solution (150 mL) was added. The aqueous layer was extracted with EtOAc (2 x 100 mL) then the combined organic layers were successively washed with a 2M aqueous NaOH solution and brine, dried over anhydrous $MgSO_4$ and filtrated. The solvents were removed *in vacuo* to afford the hydroxyamide **7a** (15.2 g, quantitative yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.73-7.65 (m, 2H, H_{Ar}), 7.55-7.40 (m, 3H, H_{Ar}), 6.38 (br s, 1H, NH), 5.92 (m, 2H, C*H*=CH_2), 5.31-5.21 (m, 4H, CH=C*H*$_2$), 5.08 (t, *J* = 6.5 Hz, 1H, OH), 3.78 (d, *J* = 6.5 Hz, 2H, CH_2OH), 2.66 (ddt, *J* = 13.9, 6.6, 1.2 Hz, 2H, CH_2), 2.38 (ddt, *J* = 13.9, 8.4, 1.0 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 168.4 (C=O), 134.8 (C_{Ar}), 133.1 (2 *C*H=CH_2), 131.9 (C_{Ar}), 128.9 (2 C_{Ar}), 127.0 (2 C_{Ar}), 120.1 (2 CH=CH_2), 68.3 (CH_2OH), 60.4 (C), 39.1 (2 CH_2).

2-Benzamido-2-allylpent-4-enoic acid (8a): IBX (18.26 g, 65.2 mmol) was added to a solution of amino alcohol **7a** (8.0 g, 32.6 mmol) in DMSO (60 mL) at rt. The reaction mixture was then stirred at 50 °C for 16 h. EtOAc was added and the crude mixture was filtered through a pad of Celite®. The filtrate was washed with brine and dried over anhydrous Na_2SO_4. Concentration *in vacuo* afforded *N*-(4-formylhept-1,6-dien-4-yl)benzamide as a yellow oil (7.93 g, quantitative yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.46 (s, 1H, CHO), 7.78-7.76 (m, 2H, H_{Ar}), 7.55-7.50 (m, 1H, H_{Ar}), 7.47-7.43 (m, 2H, H_{Ar}), 6.78 (br s, 1H, NH), 5.65 (dddd, *J* = 17.0, 10.1, 7.4, 7.2 Hz, 2H, C*H*=CH_2), 5.18-5.12 (m, 4H, CH=C*H*$_2$), 3.10 (dd, *J* = 14.3, 7.2 Hz, 2H, CH_2), 2.66 (dd, *J* = 14.3, 7.4 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 199.9 (CHO), 166.8 (C=O), 134.2 (C_{Ar}), 131.8 (C_{Ar}), 131.3 (2 *C*H=CH_2), 128.7 (2 C_{Ar}), 126.9 (2 C_{Ar}), 120.1 (2 CH=*C*H$_2$), 65.8 (C), 37.1 (2 CH_2). IR (neat): ν = 3075, 2926, 1721, 1639, 1525, 1276 cm^{-1}. HRMS (ESI+): *m/z* (M+Na$^+$) calcd for $C_{15}H_{17}NO_2Na$: 266.1152, found: 266.1151.

To a solution of the aldehyde (32.6 mmol) in MeCN (250 mL) cooled to 0 °C were successively added sodium phosphate monobasic dihydrate (10.2 g, 65.2 mmol) in water (100 mL), H_2O_2 (30% w/w in H_2O, 18.5 mL, 163 mmol) and sodium chlorite (4.42 g, 48.9 mmol). The reaction mixture was stirred at rt and the progress of the reaction was monitored by TLC. Sodium thiosulfate (5.15 g, 32.6 mmol) was then added and the reaction mixture was stirred for 1 h. The solvent was removed *in vacuo*, then EtOAc (200 mL) and sat. aq. $NaHCO_3$ (200 mL) were added to the residue. The layers were separated and the organic phase was washed with sat. aq. $NaHCO_3$ (2 x 100 mL). The combined aqueous layers were acidified by adding conc. HCl and extracted with EtOAc (3 x 100 mL). After drying over $MgSO_4$, the combined organic layers were concentrated *in vacuo* to provide the pure *N*-benzoyl-protected amino acid **8a** (6.55 g, 80% yield) as a pale yellow solid; mp = 134-136 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.95 (bs, COOH), 7.78-7.72 (m, 2H, H_{Ar}), 7.59-7.38 (m, 3H, H_{Ar}), 7.11 (br s, 1H, NH), 5.69 (dddd, *J* = 17.1, 10.2, 7.7, 7.2 Hz, 2H, C*H*=CH_2), 5.20-5.05 (m, 4H, CH=C*H*$_2$), 3.31 (dd, *J* = 14.0, 7.7 Hz, 2H, CH_2), 2.70 (dd, *J* = 14.0, 7.2 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 176.2 (COOH), 167.5 (C=O), 134.5 (C_{Ar}), 132.0 (2 *C*H=CH_2), 131.8 (C_{Ar}), 128.7 (2 C_{Ar}), 127.0 (2 C_{Ar}), 119.7 (2 CH=*C*H$_2$), 64.4 (C), 39.1 (2 CH_2). IR (neat): ν = 3342, 3075, 2982, 2926, 2251, 1727, 1639, 1522, 1276 cm^{-1}. HRMS (ESI+): *m/z* (M+Na$^+$) calcd for $C_{15}H_{17}NO_3Na$: 282.1101, found: 282.1097.

4,4-Diallyl-2-phenyloxazol-5(4*H*)-one (5a):[27] Et_3N (2.75 mL, 20.4 mmol) and ethyl chloroformate (1.29 mL, 13.6 mmol) were added to a solution of acid **8a** (3.52 g, 13.6 mmol) in acetone (100 mL) at 0 °C. After stirring at rt for 3 h, the reaction mixture was filtered through a pad of silicagel then concentrated *in vacuo* to afford the oxazolone **5a** (3.28 g, quantitative yield) as a orange oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.02-7.98 (m, 2H, H_{Ar}), 7.60-7.52 (m, 1H, H_{Ar}), 7.51-7.42 (m, 2H, H_{Ar}), 5.66 (dddd, *J* = 17.0, 10.0, 8.0, 6.8 Hz, 2H, C*H*=CH_2), 5.23-5.06 (m, 4H, CH=CH_2), 2.68 (dd, *J* = 13.8, 6.8 Hz, 2H, CH_2), 2.58 (dd, *J* = 13.8, 8.0 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 179.2 (C=O), 160.1 (C=N), 132.8 (C_{Ar}), 130.8 (2 C_{Ar}), 128.8 (2 C_{Ar}), 128.0 (2 *C*H=CH_2), 125.9 (C_{Ar}), 120.6 (2 CH=*C*H_2), 73.8 (C), 41.1 (2 CH_2). HRMS (ESI+): *m/z* ($M+Na^+$) calcd for $C_{15}H_{15}NO_2Na$: 264.0995, found: 264.1002.

Cyanomethyl 4-((trimethylsilyl)ethynyl)benzoate (6b): To a solution of 4-iodobenzoic acid (2.48 g, 10 mmol) in dry triethylamine (20 mL) and THF (40 mL) under argon were successively added $Pd(PPh_3)Cl_2$ (421 mg, 0.6 mmol), CuI (191 mg, 1 mmol) and trimethylsilylacetylene (2.40 mL, 17 mmol). Stirring was maintained for 18 h at rt and the reaction mixture was filtered through a pad of Celite®. The organic filtrate was successively washed with 1M aq. HCl solution (3 x 100 mL), water (150 mL) and brine (2 x 100 mL). After drying over $MgSO_4$, the organic fraction was filtered and concentrated *in vacuo* to give the crude 4-((trimethylsilyl)ethynyl)benzoic acid, which was directly dissolved in CH_2Cl_2 (20 mL). Triethylamine (2.7 mL, 20 mmol) and chloroacetonitrile (1.0 mL, 15 mmol) were added and the resulting mixture was stirred for 48 h at rt. The reaction mixture was concentrated *in vacuo* and the residue was taken up with water (10 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography on silicagel (Cyclohexane/EtOAc 98:2, then 9:1) provided the acylcyanohydrin **6b** (1.93g, 75% yield) as an orange solid; mp = 50-52 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.98 (m, 2H, H_{Ar}), 7.55 (m, 2H, H_{Ar}), 4.96 (s, 2H, CH_2), 0.27 (s, 9H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 164.6 (C=O), 132.3 (C_{Ar}), 130.0 (2 C_{Ar}), 129.4 (2 C_{Ar}), 127.5 (C_{Ar}), 114.6 (CN), 103.8 (*C*≡C), 99.2 (*C*≡C), 49.2 (CH_2), 0.0 (3 CH_3). IR (neat): ν = 3097, 2959, 2903, 2113, 1737, 1603, 1410, 1253, 1097 cm^{-1}. HRMS (ESI+): *m/z* ($M+Na^+$) calcd for $C_{14}H_{15}NO_2SiNa$: 280.0770, found: 280.0766.

***N*-4-((Hydroxymethyl)hepta-1,6-dien-4-yl)-4-((trimethylsilyl)ethynyl)-benzamide (7b):** Same procedure as for **7a**. A pale yellow solid is obtained starting from **6b** (1.5 g, 5.80 mmol), no purification was required (2.0 g, quantitative yield); mp = 88-90 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.63 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.50 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 6.35 (br s, 1H, NH), 5.90 (dddd, *J* = 16.3, 11.0, 8.6, 6.7 Hz, 2H, C*H*=CH_2), 5.25-5.18 (m, 4H, CH=CH_2), 4.92 (br s, 1H, OH), 3.76 (s, 2H, CH_2OH), 2.64 (dd, *J* = 13.9, 6.7 Hz, 2H, CH_2), 2.37 (dd, *J* = 13.9, 8.6 Hz, 2H, CH_2), 0.25 (s, 9H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 167.6 (C=O), 134.3 (C_{Ar}), 133.0 (2 *C*H=CH_2), 132.3 (2 C_{Ar}), 126.9 (C_{Ar}), 126.8 (2 C_{Ar}), 120.1 (2 CH=*C*H_2), 104.0 (*C*≡C), 97.5 (C≡*C*), 68.1 (CH_2OH), 60.4 (C), 39.1 (2 CH_2), -0.02 (3 CH_3). IR (neat): ν = 3294, 3082, 2959, 2925, 2903, 2873, 2162, 1726, 1637, 1547, 1465, 1439, 1328, 1253, 1074 cm^{-1}. HRMS (CI+, NH_3/CH_4): *m/z* ($M+H^+$) calcd for $C_{20}H_{28}NO_2Si$: 342.1889, found: 342.1889.

2-Allyl-2-(4-((trimethylsilyl)ethynyl)benzamido)pent-4-en-oic acid (8b): Same procedure as for **8a**. An orange oil is obtained starting from **7b** (1.44 g, 4.23 mmol), no purification was required (1.19 g, 79% yield over the 2 steps). *N*-(4-Formylhepta-1,6-dien-4-yl)-4-((trimethylsilyl)-ethynyl) benzamide: ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.43 (s, 1H, CHO), 7.71-7.67 (m, 2H, H_{Ar}), 7.52-7.48 (m, 2H, H_{Ar}), 6.81 (s, 1H, NH), 5.62 (ddt, *J* = 17.1, 10.0, 7.3 Hz, 2H, C*H*=CH_2), 5.17-5.07 (m, 4H, CH=CH_2), 3.07 (dd, *J* = 14.4, 7.4 Hz, 2H, CH_2), 2.64 (dd, *J* = 14.4, 7.4 Hz, 2H, CH_2), 0.25 (s, 9H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 199.9 (CHO), 166.2 (C=O), 133.7 (C_{Ar}), 132.3 (2 C_{Ar}), 131.2 (2 *C*H=CH_2), 126.9 (C_{Ar}), 126.9 (2 C_{Ar}), 120.2 (2 CH=*C*H_2), 104.0 (*C*≡C), 97.4 (C≡*C*), 66.0 (C), 37.1 (2 CH_2), 0.0 (3 CH_3). IR (neat): ν = 3295, 2164, 1733, 1629, 1525 cm^{-1}. HRMS (ESI+): *m/z* ($M+Na^+$) calcd for $C_{20}H_{35}NNaO_2Si$: 362.1547, found: 362.1539. 2-Allyl-2-(4-((trimethylsilyl)ethynyl)benzamido)-pent-4-enoic acid (**8b**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.67 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.50 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.00 (s, 1H, NH), 5.68 (dddd, *J* = 17.1, 9.9, 7.3, 7.3 Hz, 2H, C*H*=CH_2), 5.21-5.06 (m, 4H, CH=CH_2), 3.29 (dd, *J* = 13.9, 7.6 Hz, 2H, CH_2), 2.69 (dd, *J* = 14.0, 7.2 Hz, 2H, CH_2), 0.25 (s, 9H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 177.6 (COOH), 166.5 (C=O), 134.2 (C_{Ar}), 132.3 (2 C_{Ar}), 131.9 (2 *C*H=CH_2), 126.9 (3 C_{Ar}), 119.9 (2 CH=*C*H_2), 104.1 (*C*≡C), 97.3 (C≡*C*), 64.6 (C), 39.2 (2 CH_2), 0.0 (3 CH_3). IR (neat): ν = 2959, 2162, 1709, 1639, 1525, 1493, 1251 cm^{-1}. HRMS (ESI+): *m/z* ($M+Na^+$) calcd for $C_{20}H_{25}NNaO_3Si$: 378.1496, found: 378.1492.

4,4-Diallyl-2-(4-ethynylphenyl)oxazol-5(4*H*)-one (5b): To a solution of acid **8b** (1.0 g, 2.81 mmol) in a 2:1 mixture of MeOH and THF (15 mL) was added K_2CO_3 (777 mg, 5.62 mmol). The mixture was stirred at rt for 2 h, and then concentrated *in vacuo.* The residue was taken up in water (20 mL) and EtOAc (20 mL) and the pH was adjusted to pH 1 by adding conc. HCl. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford the pure corresponding 4-(ethynyl)benzamido-2-allylpent-4-enoic acid (795 mg, quantitative yield, yellow oil) without any further purification. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 12.59 (br s, 1H, COO*H*), 8.22 (br s, 1H, N*H*), 7.81 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 7.57 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 5.70 (dddd, *J* = 16.2, 11.0, 7.4, 7.2 Hz, 2H, C*H*=CH_2), 5.09-5.05 (m, 4H, CH_2=CH), 4.36 (C≡C*H*), 2.73 (dd, *J* = 14.1, 7.2 Hz, 2H, CH_2), 2.61 (dd, *J* = 14.1, 7.4 Hz, CH_2). ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 173.3 (COOH), 165.0 (C=O), 134.4 (C_{Ar}), 132.8 (2 *C*H=CH_2), 131.6 (2 C_{Ar}), 127.6 (2 C_{Ar}), 124.5 (C_{Ar}), 118.7 (2 CH=*C*H_2), 82.9 and 82.8 (*C*≡CH and C≡*C*H), 61.4 (C), 37.5 (2 CH_2). HRMS (ESI+): *m/z* ($M+Na^+$) calcd for $C_{17}H_{17}NO_3Na$: 306.1106, found: 306.1105.

The crude acid was then dissolved in acetone (10 mL) and the solution was cooled to 0 °C. Et_3N (0.57 mL, 4.22 mmol) and ethyl chloroformate (0.27 mL, 2.81 mmol) were added and the mixture was stirred at rt for 3 h. The reaction mixture was filtered through a pad of silicagel then concentrated *in vacuo* to afford the oxazolone **5b** (731 mg, 98% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.98-7.91 (m, 2H, H_{Ar}), 7.62-7.56 (m, 2H, H_{Ar}), 5.63 (dddd, *J* = 17.0, 9.9, 7.7, 6.9 Hz, 2H, C*H*=CH_2), 5.22-5.08 (m, 4H, CH=CH_2), 3.25 (s, 1H, C≡CH), 2.67 (dd, *J* = 13.7, 6.9 Hz, 2H, CH_2), 2.58 (dd, *J* = 13.7, 7.7 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 179.0 (C=O), 159.6 (C=N), 132.5 (2 C_{Ar}), 130.6 (2 *C*H=CH_2), 127.9 (2 C_{Ar}), 126.7 (C_{Ar}), 125.9 (C_{Ar}), 120.7 (2 CH=*C*H_2), 82.8 (*C*≡CH), 80.5 (C≡*C*H), 73.9 (C), 41.1 (2 CH_2). IR (neat): ν = 3290, 2925, 1820, 1722, 1644, 1525, 1495, 1220 cm^{-1}. HRMS (ESI+): *m/z* ($M+Na^+$) calcd for $C_{17}H_{15}NNaO_2$: 288.0995, found: 288.0987.

7-((Benzylthio)methyl)-8-methyl-2-phenyl-3-oxa-1-aza-spiro[4.4]non-1-en-4-one (9): DMPA (8.8 mg, 33 µmol) and benzylmercaptan (40 µL, 0.33 mmol) were added to a solution of **5a** (80 mg, 0.33 mmol) in degassed DMF (17 mL) at rt. The reaction mixture was stirred at rt under UV irradiation (365 nm) for 1 h then diluted with EtOAc and brine. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (Cyclohexane/Et_2O 95:5) provided the spiro compound **9** (102 mg, 85% yield) as a 70:30 mixture of diastereoisomers, which were separated by flash chromatography and isolated as colorless

oils (minor diastereoisomer **9a**: 8 mg, 7% yield; major diastereoisomer **9b**: 79 mg, 66% yield). **9a:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.00-7.93 (m, 2H, H_{Ar}), 7.55 (m, 1H, H_{Ar}), 7.50-7.43 (m, 2H, H_{Ar}), 7.37-7.22 (m, 5H, H_{Ar}), 3.74 (s, 2H, CH_2), 2.62-2.43 (m, 4H, CH_2, 2 CH), 2.32 (dd, 1H, *J* = 13.6, 7.1 Hz, 1H, CH_2), 2.25 (dd, 1H, *J* = 13.9, 6.2 Hz, 1H, CH_2), 2.04 (dd, 1H, *J* = 13.7, 7.1 Hz, 1H, CH_2), 1.81 (dd, 1H, *J* = 13.6, 4.8 Hz, 1H, CH_2), 1.04 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 182.9 (C=O), 159.7 (C=N), 138.6 (C_{Ar}), 132.6 (C_{Ar}), 129.0 (2 C_{Ar}), 128.9 (2 C_{Ar}), 128.7 (2 C_{Ar}), 128.0 (2 C_{Ar}), 127.1 (C_{Ar}), 126.2 (C_{Ar}), 75.5 (C), 45.3 (CH_2), 43.1 (CH), 42.1 (CH_2), 37.1 (CH), 36.7 (CH_2), 31.9 (CH_2), 14.8 (CH_3). **9b:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.01-7.94 (m, 2H, H_{Ar}), 7.62-7.53 (m, 1H, H_{Ar}), 7.50-7.43 (m, 2H, H_{Ar}), 7.37-7.21 (m, 5H, H_{Ar}), 3.74 (d, *J* = 0.9 Hz, 2H, CH_2), 2.69-2.54 (m, 3H, CH_2, 2 CH), 2.50-2.42 (m, 1H, CH_2), 2.19 (dd, 1H, *J* = 13.7, 6.9 Hz, 1H, CH_2), 2.14-2.09 (m, 2H, CH_2), 1.91 (dd, 1H, *J* = 13.7, 5.8 Hz, 1H, CH_2), 1.00 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 182.0 (C=O), 159.8 (C=N), 138.5 (C_{Ar}), 132.7 (C_{Ar}), 129.0 (2 C_{Ar}2), 128.9 (2 C_{Ar}), 128.6 (2 C_{Ar}), 128.0 (2 C_{Ar}), 127.1 (C_{Ar}), 126.2 (C_{Ar}), 74.0 (C), 45.7 (CH_2), 43.0 (CH_2), 42.5 (CH), 37.8 (CH_2), 36.5 (CH), 32.1 (CH_2), 15.0 (CH_3). IR (neat): ν = 2924, 1812, 1650, 1452, 1324, 1290 cm^{-1}. HRMS (ESI+): *m/z* ($M+Na^+$) calcd for $C_{22}H_{23}NNaO_2S$: 388.1342, found: 388.1343.

4,4-Bis(3-(benzylthio)propyl)-2-phenyloxazol-5(4*H*)-one (10): DMPA (26 mg, 0.10 mmol) was added to a solution of **5a** (241 mg, 1.0 mmol) in benzylmercaptan (1.2 mL, 10.0 mmol). The reaction mixture was stirred at rt under UV irradiation (365 nm) for 1 h then diluted with EtOAc and brine. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (Cyclohexane/Et_2O 98:2, then 95:5) afforded compound **10** (465 mg, 95% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.06-8.00 (m, 2H, H_{Ar}), 7.66-7.59 (m, 1H, H_{Ar}), 7.58-7.50 (m, 2H, H_{Ar}), 7.34-7.26 (m, 8H, H_{Ar}), 7.26-7.20 (m, 2H, H_{Ar}), 3.68 (s, 4H, SCH_2), 2.41 (t, *J* = 7.1 Hz, 4H, CH_2), 2.03-1.89 (m, 4H, CH_2), 1.61-1.39 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 180.1 (C=O), 160.2 (C=N), 138.3 (2 C_{Ar}), 132.9 (C_{Ar}), 128.9 (2 C_{Ar}), 128.8 (4 C_{Ar}), 128.5 (4 C_{Ar}), 128.0 (2 C_{Ar}), 127.0 (2 C_{Ar}), 125.7 (C_{Ar}), 73.0 (C), 36.3 (2 CH_2), 36.1 (2 CH_2), 30.9 (2 CH_2), 23.5 (2 CH_2). IR (neat): ν = 3289, 2916, 1816, 1652, 1495, 1452, 1290, 1073, 1004 cm^{-1}. HRMS (ESI+): *m/z* ($M+Na^+$) calcd for $C_{29}H_{31}NNaO_2S_2$: 512.1688, found: 512.1687.

***N*-(4-(Benzylcarbamoyl)hepta-1,6-dien-4-yl)benzamide (11):** Benzylamine (0.14 mL, 1.24 mmol) was added to a solution of oxazolone **5a** (300 mg, 1.24 mmol) in DMSO (6 mL) at rt. The reaction mixture was stirred at 40 °C for 16 h then diluted with EtOAc and brine. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (Cyclohexane/Et_2O 6:4) afforded compound **11** (431 mg, quantitative yield) as a white solid; mp = 154-156 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.75-7.70 (m, 2H, H_{Ar}), 7.50-7.45 (m, 1H, H_{Ar}), 7.42-7.36 (m, 2H, H_{Ar}), 7.32-7.22 (m, 6H, H_{Ar}, NH), 6.92 (t, *J* = 5.8 Hz, 1H, NH), 5.69 (dddd, *J* = 16.1, 11.0, 7.9, 6.7 Hz, 2H, C*H*=CH_2), 5.14-5.04 (m, 4H, CH=C*H*$_2$), 4.46 (d, *J* = 5.8 Hz, 2H, CH_2N), 3.14 (ddt, *J* = 14.2, 7.9, 1.1 Hz, 2H, CH_2), 2.70 (ddt, *J* = 14.2, 6.7, 1.3 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.5 (C=O), 167.1 (C=O), 138.0 (C_{Ar}), 135.0 (C_{Ar}), 132.4 (2 *C*H=CH_2), 131.8 (C_{Ar}), 128.8 (2 C_{Ar}), 128.8 2 (C_{Ar}), 127.9 (2 C_{Ar}), 127.7 (C_{Ar}), 127.0 (2 C_{Ar}), 119.9 (2 CH=*C*H$_2$), 63.4 (C), 44.2 (CH_2), 39.9 (CH_2). IR (neat): ν = 3245, 2925, 1745, 1666, 1640, 1599, 1525, 1495, 1313, 1249, 1127 cm^{-1}. HRMS (ESI+): *m/z* ($M+H^+$) calcd for $C_{22}H_{25}N_2O_2$: 349.1911, found: 349.1903.

***N*-(1-(Benzylcarbamoyl)-3-((benzylthio)methyl)-4-methylcyclo-pentyl)-benzamide (12): From 9**: Benzylamine (27 µL, 0.25 mmol) was added to a solution of **9** (90 mg, 0.25 mmol, 30:70 mixture of diastereoisomers) in DMSO (2 mL) at rt. The reaction mixture was stirred at 40 °C for 16 h then diluted with EtOAc and brine. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (Cyclohexane/Et_2O 6:4, then 5:5) afforded compound **12** as a 30:70 mixture of two inseparable diastereoisomers (110 mg, 95%, white solid); mp = 154-156 °C. **From 11:** DMPA (2.9 mg, 12 µmol) and benzylmercaptan (13.5 µL, 115 µmol) were added to a solution of **11** (40 mg, 115 µmol) in degassed DMF (6 mL) at rt. The reaction mixture was stirred at rt under UV irradiation (365 nm) for 1 h then diluted with EtOAc and brine. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (Cyclohexane/Et_2O 6:4, then 5:5) provided the spiro compound **12** as a 70:30 mixture of diastereoisomers (50 mg, 92% yield, white solid). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.72-7.70 (m, 2H, H_{Ar}), 7.50-7.40 (m, 2H, H_{Ar}), 7.39-7.33 (m, 2H, H_{Ar}), 7.30-7.15 (m, 11H, H_{Ar}, NH), 7.05 (s, 0.3H, NH), 6.37 (s, 0.7H, NH), 4.36-4.30 (m, 2H, NCH_2), 3.68 (d, *J* = 12.0 Hz, 1H, SCH_2), 3.63 (d, *J* = 12.0 Hz, 1H, SCH_2), 2.81 (dd, *J* = 14.0, 7.1 Hz, 0.3H, CH_2), 2.74 (dd, *J* = 13.7, 6.3 Hz, 0.3H, CH_2), 2.50-2.42 (m, 0.7H, CH_2), 2.37-2.17 (m, 5.4H, CH_2, CH), 2.12-2.06 (m, 0.7H, CH_2), 1.86 (dd, *J* = 13.7, 6.6 Hz, 0.3H, CH_2), 1.69 (dd, *J* = 14.0, 6.1 Hz, 0.3H, CH_2), 0.88 (d, *J* = 6.5 Hz, 0.9H, CH), 0.84 (d, *J* = 6.0 Hz, 2.1H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 174.3 (0.3 C=O), 173.6 (0.7 C=O), 168.1 (0.7 C=O), 167.6 (0.3 C=O), 138.7 (0.3 C_{Ar}), 138.7 (0.7 C_{Ar}), 138.6 (0.7 C_{Ar}), 138.3 (0.3 C_{Ar}), 134.2 (0.7 C_{Ar}), 133.9 (0.3 C_{Ar}), 132.0 (0.3 C_{Ar}), 132.0 (0.7 C_{Ar}), 128.9 (0.3 C_{Ar}), 128.8 (0.7 C_{Ar}), 128.7 (0.3 C_{Ar}), 128.7 (0.7 C_{Ar}), 128.6 (0.3 C_{Ar}), 128.6 (0.3 C_{Ar}), 128.6 (0.7 C_{Ar}), 128.5 (0.7 C_{Ar}), 127.4 (0.7 C_{Ar}), 127.3 (0.3 C_{Ar}), 127.2 (0.7 C_{Ar}), 127.2 (0.3 C_{Ar}), 127.2 (0.3 C_{Ar}), 127.2 (0.7 C_{Ar}), 127.1 (0.3 C_{Ar}), 127.0 (0.7 C_{Ar}), 67.0 (0.7 C), 66.3 (0.3 C), 45.0 (0.3 CH_2), 44.5 (0.7 CH_2), 43.7 (NCH_2), 42.6 (0.3 CH_2), 41.3 (0.7 CH_2), 41.2 (0.3 CH), 40.6 (0.7 CH), 37.1 (0.7 SCH_2), 36.5 (0.3 SCH_2), 35.9 (0.3 CH), 34.3 (0.7 CH), 32.7 (0.7 CH_2), 32.2 (0.3 CH_2), 15.2 (0.7 CH_3), 15.1 (0.3 CH_3). IR (neat): ν = 3289, 2916, 1654, 1525, 1492, 1313, 1074, 1030 cm^{-1}. HRMS (ESI+): *m/z* ($M+Na^+$) calcd for $C_{29}H_{32}N_2NaO_2Si$: 495.2077, found: 495.2072.

***N*-(4-(Benzylcarbamoyl)-1,7-bis(benzylthio)heptan-4-yl)benzamide (13): From 10:** Benzylamine (9 µL, 82 µmol) was added to a solution of **10** (40 mg, 82 µmol) in DMSO (1 mL) at rt. The reaction mixture was stirred at 40 °C for 16 h then diluted with EtOAc and brine. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (Cyclohexane/EtOAc 7:3) afforded compound **13** (45 mg, 95% yield) as a colorless oil. **From 11:** DMPA (13 mg, 0.10 mmol) was added to a solution of **11** (174 mg, 0.51 mmol) in benzylmercaptan (0.6 mL, 5.10 mmol). The reaction mixture was stirred at rt under UV irradiation (365 nm) for 1 h then diluted with EtOAc and brine. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (Cyclohexane/Et_2O 8:2) afforded compound **13** (271 mg, 90% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.86-7.81 (m, 2H, H_{Ar}), 7.78 (s, 1H, NH), 7.55-7.48 (m, 1H, H_{Ar}), 7.45-7.41 (m, 2H, H_{Ar}), 7.38-7.16 (m, 15H, H_{Ar}), 6.21 (t, *J* = 5.6 Hz, 1H, N*H*CH_2), 4.49 (d, *J* = 5.6 Hz, 2H, NHC*H*$_2$), 3.58 (d, *J* = 12.0 Hz, 2H, SCH_2), 3.54 (d, *J* = 12.0 Hz, 2H, SCH_2), 2.84-2.71 (m, 2H, CH_2), 2.40 (ddd, *J* = 13.0, 7.1, 5.5 Hz, 2H, CH_2), 2.26 (ddd, *J* = 13.0, 6.6, 5.4 Hz, 2H, CH_2), 1.71-1.54 (m, 4H, CH_2), 1.35-1.22 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.1 (C=O), 166.0 (C=O), 138.4 (2 C_{Ar}), 137.7 (C_{Ar}), 134.9 (C_{Ar}), 131.7 (C_{Ar}), 129.1 (2 C_{Ar}), 128.9 (4 C_{Ar}), 128.8 (2 C_{Ar}), 128.6 (4 C_{Ar}), 128.1 (2 C_{Ar}),

128.1 (C_{Ar}), 127.1 (C_{Ar}), 127.06 (2 C_{Ar}), 64.0 (C), 44.5 (CH_2), 36.2 (2 SCH_2), 35.4 (2 CH_2), 31.0 (2 CH_2), 23.6 (2 CH_2). IR (neat): v = 3341, 2918, 1639, 1510, 1480, 1266 cm^{-1}. HRMS (ESI+): *m/z* ($M+Na^+$) calcd for $C_{36}H_{40}N_2NaO_2S_2$: 619.2423, found: 619.2439.

***N*-(4-(Benzylcarbamoyl)hepta-1,6-dien-4-yl)-4-ethynyl-benzamide (14):** Benzylamine (21 µL, 0.19 mmol) was added to a solution of oxazolone **5b** (50 mg, 0.19 mmol) in DMSO (1 mL) at rt. The reaction mixture was stirred at 40 °C for 16 h then diluted with EtOAc and brine. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 1 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Cyclohexane/EtOAc 85:15) afforded compound **14** (69 mg, 97% yield) as a white solid; mp = 107-109°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.71-7.67 (m, 2H, H_{Ar}), 7.54-7.49 (m, 2H, H_{Ar}), 7.40 (bs, 1H, NH), 7.35-7.24 (m, 5H, H_{Ar}), 6.95 (t, *J* = 5.7 Hz, 1H, N*H*CH_2), 5.68 (m, 2H, C*H*=CH_2), 5.13-5.06 (m, 4H, CH=C*H*$_2$), 4.47 (d, *J* = 5.7 Hz, 2H, NHC*H*$_2$), 3.23 (ddt, *J* = 14.2, 7.9, 1.2 Hz, 2H, CH_2), 3.20 (s, 1H, C≡CH), 2.67 (ddt, *J* = 14.2, 6.7, 1.2 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.3 (C=O), 166.1 (C=O), 137.9 (C_{Ar}), 135.0 (C_{Ar}), 132.4 (2 C_{Ar}), 132.2 (2 *C*H=CH_2), 128.8 (C_{Ar}), 127.9 (C_{Ar}), 127.7 (C_{Ar}), 126.9 (C_{Ar}), 125.6 (C_{Ar}), 119.9 (2 CH=*C*H$_2$), 82.8 (*C*≡CH), 79.7 (C≡*C*H), 63.5 (C), 44.2 (NCH_2), 39.8 (2 CH_2). IR (neat): v = 3279, 3086, 2952, 1644, 1629, 1540, 1499, 1313, 1279, 1238 cm^{-1}. HRMS (ESI+): *m/z* ($M+Na^+$) calcd for $C_{24}H_{24}N_2NaO_2$: 395.1730, found: 395.1720.

4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*-(4-(benzyl-carbamoyl)hepta-1,6-dien-4-yl)benzamide (15): From 14: CuBr (4.6 mg, 32 µmol), benzyl azide (13 µL, 0.107 mmol) and PMDETA (27 µL, 0.129 mmol) were successively added to a solution of **14** (40 mg, 0.107 mmol) in degassed DMF (0.6 mL). After stirring at rt for 16 h, the reaction mixture was diluted with EtOAc and brine. The aqueous phase was extracted with EtOAc (2 x 2 mL) and the combined organic layers were washed with brine (3 x 3 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Filtration through a pad of silicagel afforded triazole **15** (54 mg, quantitative yield) as a white solid. **From 5b:** CuBr (8.2 mg, 57 µmol), benzyl azide (24 µL, 0.188 mmol), PMDETA (47 µL, 0.226 mmol) and benzylamine (21 µL, 0.188 mmol) were successively added to a solution of **5b** (50 mg, 0.188 mmol) in degassed DMF (1 mL). After stirring at 40 °C for 16 h, the reaction mixture was diluted with EtOAc and brine. The aqueous phase was extracted with EtOAc (2 x 2 mL) and the combined organic layers were washed with brine (3 x 3 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Cyclohexane/EtOAc 7:3) afforded compound **15** (90 mg, 95% yield) as a white solid. **From 16:** Benzylamine (7 µL, 68 µmol) was added to a solution of oxazolone **16** (27 mg, 68 µmol) in DMSO (0.5 mL) at rt. The reaction mixture was stirred at 40 °C for 16 h then diluted with EtOAc and brine. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 2 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Cyclohexane/EtOAc 7:3) afforded compound **15** (33 mg, 96% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.87-7.81 (m, 2H, H_{Ar}), 7.80-7.76 (m, 2H, H_{Ar}), 7.73 (s, 1H, C=CH), 7.43-7.36 (m, 3H, H_{Ar}, NH), 7.42-7.24 (m, 10H, H_{Ar}), 6.99 (t, *J* = 5.7 Hz, 1H, N*H*CH_2), 5.72 (dddd, *J* = 16.3, 10.8, 7.8, 6.8 Hz, 2H, C*H*=CH_2), 5.57 (s, 2H, NCH_2), 5.16-5.05 (m, 4H, CH=C*H*$_2$), 4.49 (d, *J* = 5.7 Hz, 2H, NHC*H*$_2$), 3.20 (ddt, *J* = 14.3, 7.8, 1.1 Hz, 2H, CH_2), 2.72 (ddt, *J* = 14.3, 6.8, 1.3 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 172.4 (C=O), 166.5 (C=O), 147.3 (*C*=CH), 138.0 (C_{Ar}), 134.5 (C_{Ar}), 134.3 (C_{Ar}), 133.8 (C_{Ar}), 132.4 (2 *C*H=CH_2), 129.3 (2 C_{Ar}), 129.0 (C_{Ar}), 128.8 (2 C_{Ar}), 128.2 (2 C_{Ar}), 127.9 (2 C_{Ar}), 127.7 (C_{Ar}), 127.6 (2 C_{Ar}), 125.8 (2 C_{Ar}), 120.3 (C=*C*H), 119.8 (2 CH=*C*H$_2$), 63.5 (C), 54.5 (NCH_2), 44.1 ($NHCH_2$), 39.9 (2 CH_2). IR (neat): v = 3346, 3070, 1644, 1514, 1488, 1458, 1235 cm^{-1}. HRMS (ESI+): *m/z* ($M+Na^+$) calcd for $C_{31}H_{31}N_5NaO_2$: 528.2370, found: 528.2373.

4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*-(4-(benzyl-carbamoyl)hepta-1,6-dien-4-yl)benzamide (16): CuBr (8.2 mg, 57 µmol), benzyl azide (24 µL, 188 µmol) and PMDETA (47 µL, 226 µmol) were successively added to a solution of **5b** (50 mg, 188 µmol) in degassed DMF (1 mL). After stirring at rt for 16 h, the reaction mixture was diluted with EtOAc and brine. The aqueous phase was extracted with EtOAc (2 x 2 mL) and the combined organic layers were washed with brine (3 x 3 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Cyclohexane/EtOAc 4:1) afforded triazole **16** (45 mg, 59% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.03-7.98 (m, 2H, H_{Ar}), 7.94-7.89 (m, 2H, H_{Ar}), 7.78 (s, 1H, C=CH), 7.42-7.30 (m, 5H, H_{Ar}), 5.65 (dddd, *J* = 17.1, 10.1, 7.8, 6.8 Hz, 2H, C*H*=CH_2), 5.58 (s, 2H, NCH_2), 5.17 (m, 2H, CH=C*H*$_2$), 5.10 (m, 2H, CH=C*H*$_2$), 2.67 (ddt, *J* = 13.7, 6.8, 1.2 Hz, 2H, CH_2), 2.58 (ddt, *J* = 13.7, 7.8, 1.0 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 179.2 (C=O), 159.8 (C=N), 147.1 (*C*=CH), 134.8 (C_{Ar}), 134.5 (C_{Ar}), 130.7 (2 *C*H=CH_2), 129.3 (2 C_{Ar}), 129.0 (C_{Ar}), 128.6 (2 C_{Ar}), 128.2 (2 C_{Ar}), 125.9 (2 C_{Ar}), 125.2 (C_{Ar}), 120.6 (2 CH=*C*H$_2$), 120.5 (C=*C*H), 73.8 (C), 54.5 (NCH_2), 41.1 (2 CH_2). IR (neat): v = 3100, 2900, 1815, 1652, 1294, 1048 cm^{-1}. HRMS (ESI+): *m/z* ($M+Na^+$) calcd for $C_{24}H_{22}N_4NaO_2$: 421.1635, found: 421.1620.

2-(4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)phenyl)-4,4-bis(3-(benzylthio)-propyl)oxazol-5(4*H*)-one (17): DMPA (4.6 mg, 18 µmol) was added to a solution of **16** (70 mg, 176 µmol) in benzylmercaptan (0.21 mL, 1.76 mmol). The reaction mixture was stirred at rt under UV irradiation (365 nm) for 1 h then diluted with EtOAc and brine. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (neat CH_2Cl_2) afforded compound **17** (104 mg, 91% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.03-7.98 (m, 2H, H_{Ar}), 7.96-7.92 (m, 2H, H_{Ar}), 7.76 (s, 1H, C=CH), 7.45-7.32 (m, 5H, H_{Ar}), 7.30-7.15 (m, 10H, H_{Ar}), 5.61 (s, 2H, NCH_2), 3.66 (d, *J* = 12.0 Hz, 2H, SC*H*$_2$), 3.62 (d, *J* = 12.0 Hz, 2H, SC*H*$_2$), 2.37 (t, *J* = 7.2 Hz, 4H, CH_2), 1.98-1.84 (m, 4H, CH_2), 1.55-1.35 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 180.1 (C=O), 160.1 (C=N), 147.2 (*C*=CH), 138.4 (2 C_{Ar}), 135.0 (C_{Ar}), 134.5 (C_{Ar}), 129.4 (2 C_{Ar}), 129.1 (C_{Ar}), 128.9 (4 C_{Ar}), 128.7 (2 C_{Ar}), 128.6 (4 C_{Ar}), 128.4 (2 C_{Ar}), 127.1 (2 C_{Ar}), 126.0 (2 C_{Ar}), 125.1 (C_{Ar}), 120.5 (C=*C*H), 73.1 (C), 54.6 (NCH_2), 36.5 (2 CH_2), 36.2 (2 SCH_2), 31.0 (2 SCH_2), 23.6 (2 CH_2). IR (neat): v = 2925, 1722, 1659, 1495, 1458, 1238 cm^{-1}.

4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*-(4-(benzyl-carbamoyl)-1,7-bis-(benzylthio)heptan-4-yl)benzamide (18): From 15: DMPA (2.0 mg, 12 µmol) was added to a solution of **15** (60 mg, 0.12 mmol) in benzylmercaptan (0.14 mL, 1.20 mmol). The reaction mixture was stirred at rt under UV irradiation (365 nm) for 1 h then diluted with EtOAc and brine. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (Cyclohexane/EtOAc 95:5 to 1:1) afforded compound **18** (86 mg, 96% yield) as a colorless oil. **From 17:** Benzylamine (10 µL, 93 µmol) was added to a solution of oxazolone **17** (60 mg, 93 µmol) in DMSO (2 mL) at rt. The reaction mixture was stirred at 40 °C for 16 h then diluted with EtOAc and brine. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 5 mL).The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Filtration on a pad of silicagel (Cyclohexane/EtOAc 7:3) afforded compound **18** (67 mg, 96% yield) as a colorless oil. **Sequential "one pot" from 5b:** CuBr (8.2 mg, 57 µmol), benzyl azide (24 µL, 188 µmol), PMDETA (47 µL, 226 µmol) and benzylamine (21 µL, 188 µmol) were successively added to a solution of **5b** (50 mg, 188 µmol) in degassed DMF (1 mL). After stirring at 40 °C for 16 h, the reaction mixture was diluted with EtOAc and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.

Benzylmercaptan (0.22 mL, 1.90 mmol) and DMPA (3.0 mg, 19 µmol) were added and the reaction mixture was stirred at rt under UV irradiation (365 nm) for 1 h. EtOAc and brine were added. The phases were separated and the aqueous fraction was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Cyclohexane/EtOAc 95:5 to 1:1) afforded compound **18** (120 mg, 85% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.88-7.82 (m, 4H, H_{Ar}), 7.80 (bs, 1H, NH), 7.72 (s, 1H, C=CH), 7.43-7.14 (m, 20H, H_{Ar}), 6.39 (t, *J* = 5.7 Hz, 1H, N*H*CH_2), 5.57 (s, 2H, NCH_2), 4.49 (d, *J* = 5.7 Hz, 1H, NHC*H*$_2$), 3.57 (d, *J* = 12.0 Hz, 2H, SC*H*$_2$), 3.53 (d, *J* = 12.0 Hz, 2H, SC*H*$_2$), 2.76 (m, 2H, CH_2), 2.39 (ddd, *J* = 12.6, 6.5, 5.7 Hz, 2H, CH_2), 2.26 (dt, *J* = 12.7, 7.2 Hz, 2H, CH_2), 1.72-1.52 (m, 4H, CH_2), 1.35-1.25 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.1 (C=O), 165.4 (C=O), 147.3 (*C*=CH), 138.4 (C_{Ar}), 137.7 (C_{Ar}), 134.5 (2 C_{Ar}), 134.3 (2 C_{Ar}), 133.7 (C_{Ar}), 129.3 (2 C_{Ar}), 129.0 (2 C_{Ar}), 128.9 (4 C_{Ar}), 128.6 (4 C_{Ar}), 128.2 (2 C_{Ar}), 128.0 (2 C_{Ar}), 128.0 (2 C_{Ar}), 127.6 (2 C_{Ar}), 127.0 (2 C_{Ar}), 125.8 (2 C_{Ar}), 120.3 (C=C*H*), 64.1 (C), 54.4 (NCH_2), 44.4 ($NHCH_2$), 36.1 (2 SCH_2), 35.3 (2 CH_2), 31.0 (2 CH_2), 23.6 (2 CH_2). IR (neat): ν = 3353, 2921, 1644, 1484, 1458, 1231 cm^{-1}. HRMS (ESI+): *m/z* ($M+H^+$) calcd for $C_{45}H_{48}N_5O_2S_2$: 754.3244, found: 754.3253.

Supporting information (see footnote on the first page of this article): experimental procedure and characterization data for the reaction of oxazolone **5a** with methyl alaninate, and ^{1}H and ^{13}C NMR spectra of new compounds.

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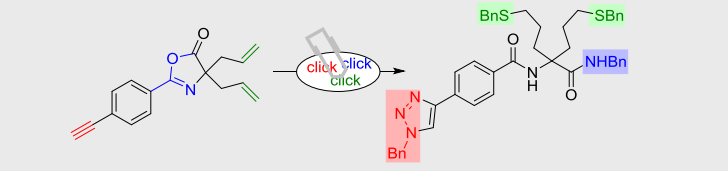

New oxazolone-based heteromultifunctional linkers were synthesized using a zinc-mediated double functionalization of nitriles as the key step. The orthogonality of the functional groups was demonstrated by conducting sequential or simultaneous multi-component reactions with amines, thiols and azides, in respect to the concept of click chemistry.

Linkers, click chemistry

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Heteromultifunctional oxazolones as versatile linkers for click chemistry reactions