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Soluble Polymer-Supported Flow Synthesis: A Green Process for the Preparation of Heterocycles

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PEG-supported aqueous flow synthesis coupled with ultrafiltration as the separation technique has been investigated for the first time. This strategy was applied to the preparation of new 3,4-dihydropyrimidin-2(1*H*)-ones, tetrazoles and tetrahydro-1,3-oxazines from the same PEG-linked aldehyde as case studies. Dihydropyrimidinones were prepared by a copper(II)-catalysed Biginelli reaction whereas a new tetrazole-containing compound was obtained by Baylis–Hillman reaction followed by reduction and 1,3-dipolar cycloaddition. Finally, various new tetrahydro-1,3-oxazines were prepared by a four-step synthesis, that is, Baylis–Hillman reaction, Michael addition of amines, cyclization with formaldehyde and hydrolysis of the linkage to PEG. The use of water during the synthesis and most of the purification steps, as well as the benefits of the flow process in terms of improved safety and heat transfer agree with the principles of green chemistry.

Introduction

The development of more sustainable methodologies in synthesis is a challenge for chemists.[1] In particular, efforts have been made to replace volatile organic solvents with alternative media such as water,[2] supercritical fluids,[3] ionic liquids[4] and, more recently, polyethylene glycols (PEGs)[5] or solventless conditions.[6] Water is a cheap and non-toxic solvent that can be used and stored in large amounts without any associated hazard and its treatment as waste is nowadays an accomplished technology.[7] In many cases, the advantages of using greener media for reactions are counterbalanced by the use of organic solvents during the work-up procedures. Polymer-supported reactions offer the advantage of easy isolation of products by simple filtration, in the case of solid-phase chemistry, or by extraction and precipitation when soluble supports are used.[8] Soluble supports, like PEGs, also offer the possibility of exploiting ultrafiltration techniques to separate molecules on the basis of their molecular weight. Low-molecular-weight molecules pass through the semi-permeable membrane whereas high-molecular-weight species are retained by the membrane with a defined range of pore sizes. This technology has been used in biochemistry but also in synthesis for homogeneous catalyst recycling[9] or to separate PEG-bound polypeptides[10] and oligosaccharides[11] from byproducts and reagents of low molecular weight.[12] In these syntheses, organic solvents were used during the transformations and/or the separation steps. On the other hand, a sustainable methodology should not only improve the chemistry, but also the process by improving its efficiency, energy consumption and safety. In this context, continuous flow micro- or mesofluidic systems represent a good alternative to conventional reaction vessels as their dimensions, typically in the order of less than 1 mm with a high surface area to volume ratio, allow improved control of mass and heat transfer whereas the inherently low reaction volume increases safety making them valuable tools for green chemistry.[13] This technique has been applied to the synthesis of various products,[14] in particular, heterocycles.[14i,14j] Many flow processes are based on the use of polymer-supported reagents, catalysts and/or solid-phase scavengers to facilitate the treatment of reaction mixtures,[14f,14g] but, to the best of our knowledge, reactions of supported substrates under flow conditions have never been explored. With the aim of developing an environmentally benign and efficient process, we have investigated PEG-supported aqueous flow reactions coupled with ultrafiltration as the separation technique for the synthesis of various heterocycles starting from the same PEG-bound aldehyde (Scheme 1). The synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) by a one-step three-component reaction was chosen as proof of concept of the methodology. The process was then applied to the preparation, in a three-step procedure, of a new tetrazole-containing compound. Finally, various new tetrahydro-1,3-oxazines have been prepared in four steps from the same PEG-linked aldehyde.

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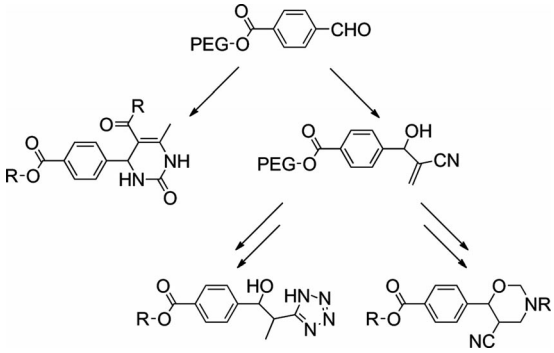
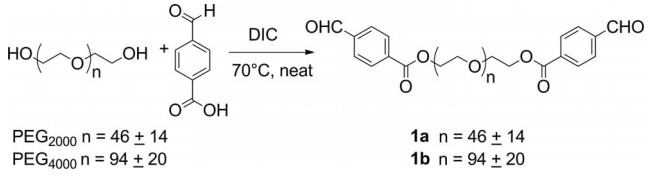


Scheme 1. General strategy for the synthesis of various heterocycles from the same PEG-linked aldehyde.

Results and Discussion

PEG-Bound Aldehyde

The linkage of 4-carboxybenzaldehyde to PEG_{4000} was previously performed in CH_2Cl_2 (8 mL/g of PEG) at room temperature for 24 h in the presence of a stoichiometric amount of dicyclohexylcarbodiimide (DCC) and a catalytic amount of DMAP.[15] We found that the esterification of PEG_{2000} and PEG_{4000} took place at 70 °C (melted PEG) in the presence of diisopropylcarbodiimide (DIC) without additional solvent whereas the use of DCC as coupling agent was unsuccessful, presumably because DCC is poorly soluble in melted PEG (Scheme 2). The conversion was complete after 3.5 h as judged by ^{1}H NMR analysis. Instead of the classical work-up, that is, precipitation of the PEG derivatives from the CH_2Cl_2 solution by addition of *i*PrOH (40 mL/g) and subsequent washing of the solid with Et_2O (≈40 mL/g), we applied the aqueous ultrafiltration technique. Hence, after the addition of water, filtration of insoluble material and ultrafiltration by forcing the aqueous solution through a regenerated cellulose membrane with a molecular-size cut-off of 1000, PEG-bound aldehydes **1a** and **1b** were recovered in 65 and 75% yields, respectively. By using this procedure, only 12 mL of water per gram of PEG was used instead of 88 mL of organic solvents such as CH_2Cl_2 (harmful and suspected human carcinogen), *i*PrOH (flammable) and Et_2O, which is hazardous in terms of flammability, low flash point and explosion risk because of peroxide contamination.

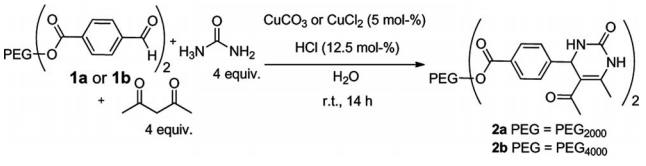


Scheme 2. Solvent-free preparation of PEG-linked aldehydes.

The purity of **1a** and **1b** was established by ^{1}H NMR and MS analyses.[16] In particular, the MALDI-TOF MS spectra showed the characteristic Gaussian-type distribution of isotopic cluster ions with a spacing of m/z = 44.[17]

One-Step Synthesis and Purification of Heterocycles

We first envisaged the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) through the Biginelli reaction.[18] This multicomponent reaction, involving a β-dicarbonylic compound, an aldehyde and a urea (or thiourea), has been extensively studied. Some of the large number of reports on the Biginelli reaction described the search for greener conditions, including the use of water[19] or PEGs[20] as solvents as well as solvent-free conditions using various catalysts with or without microwave activation.[21] Solid- and solution-phase strategies have also been described[22] and, in particular, the use of PEG as a support was explored by Xia and Wang.[22a,22b] They described a reaction carried out in CH_3CN or under solvent-free conditions using microwave activation, however, organic solvents were still used for the separations. First, we performed the reaction in batch by using **1a** and pentane-2,4-dione in water as the solvent. Various catalysts known to be efficient for this kind of transformation in water were tested, including cerium(III) chloride,[23] ammonium carbonate[24] and Brønsted acids.[25] Unfortunately, we never observed a conversion higher than 35% (^{1}H NMR). It is known that metal triflimides such as $Ni(NTf_2)_2$, $Cu(NTf_2)_2$ and $Yb(NTf_2)_3$ in the presence of HCl catalyse the Biginelli reaction in water more efficiently than the corresponding metal triflates.[26] By using $Cu(NTf_2)_2$·HCl, we observed (NMR and MS) that aldehyde **1a** was efficiently converted into dihydropyrimidinone **2** (Scheme 3). Having obtained this good result, we decided to investigate the use of commercially available and inexpensive copper(II) salts such as $CuCO_3$ and $CuCl_2$ as catalysts. We observed that both were efficient in the aqueous Biginelli reaction when associated with HCl.



Scheme 3. Aqueous Biginelli reaction of PEG-linked aldehydes in a batch reaction.

The reaction was then tested under flow conditions by using a commercially available platform, the Vapourtec R2+/R4 combination.[27] Optimization of the reaction parameters, that is, flow-rate, temperature and concentration of aldehyde **1a** as well as the amount of the diketone and urea led us to the best conditions (Table 1). We observed that byproducts were formed at a temperature of 70 °C and above (Table 1, entries 1 and 2). Complete conversion was obtained at 60 °C by using 4 equiv. of urea and diketone at

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a flow rate of 0.06 mL/min at a concentration of **1a** of 0.06 mol/L (Table 1, entry 4). This concentration could be increased to 0.095 mol/L (maximum concentration that gives a reasonable viscosity for pumping) without affecting the conversion. The flow rate could be increased to 0.08 mL/min only if 6 equiv. of urea and diketone were employed (Table 1, entry 8). Finally, we selected conditions using the least amount of excess reagents (Table 1, entry 6). These involved the premixing of the PEG-bound aldehyde **1a** (0.095 M in water) and pentane-2,4-dione (4 equiv.) and the pumping of this mixture (stream A, 0.03 mL/min), which was then mixed through a T-piece with a premixed aqueous solution of urea (4 equiv.), $CuCl_2$ (10%) and HCl (12.5%; stream B, 0.03 mL/min). The mixture was heated to 60 °C through a convection flow coil (CFC, 10 mL internal volume, 1 mm i.d.) to give a residence time of 167 min. On exiting the CFC the flow stream was directly collected over 185 min (11.1 mL) in a stirred 50 mL ultrafiltration cell (SUFC) equipped with a regenerated cellulose membrane (molecular-size cut-off of 1000) filled with water (30 mL; Scheme 4). Ultrafiltration was carried out by applying a pressure of 3.5 bar and the flow from the reactor was collected in a second ultrafiltration cell. Concentration of the retentate afforded **2a** in 72% yield (calculated from the collected volume and the flow rate, see the Exptl. Sect.). PEG_{4000}-linked aldehyde **1b** was also treated in flow conditions with pentanedione and urea in the presence of the same catalyst. Because the aqueous solution of **1b** was quite viscous, a more diluted solution (0.061 M) containing pentanedione (6 equiv.) was mixed with the solution of urea (6 equiv.) and catalyst ($CuCl_2$·HCl). A complete conversion was obtained at 60 °C with a 200 min residence time. PEG_{4000}-linked DHMP **2b** was purified by ultrafiltration to give 79% yield.

Table 1. Optimization of the Biginelli reaction under flow conditions.

	[**1a**] [mol/L]	Urea [equiv.]	Pentanedione [equiv.]	Flow rate [mL/min]	*T* [°C]	Conv. [%][a]
1	0.045	4	4	0.1	80	59[b]
2	0.045	4	4	0.08	70	70[b]
3	0.045	4	4	0.08	60	70
4	0.060	4	4	0.06	60	100
5	0.095	4	4	0.08	60	95
6	0.095	4	4	0.06	60	100
7	0.095	4	4	0.06	40	98
8	0.095	6	6	0.08	60	100

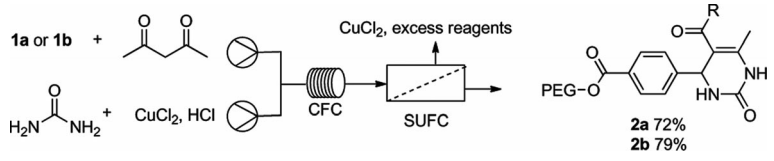
[a] The conversion was determined by ^{1}H NMR spectroscopy. [b] Unidentified byproducts were observed.

Although we chose to use the PEG as a support to carry out the reactions in water, for the sake of comparison we also realized the Biginelli reaction between aldehyde **1a**, pentane-2,4-dione and urea in organic solvents. Because the PEG-supported Biginelli synthesis of DHPM has already been reported in CH_3CN,[22a,22b] we carried out the reaction in this solvent (8.5 mL/g of **1a**) under the same conditions as used in the batch reaction performed in water (see above). Hence, after 14 h at room temp., the $CuCl_2$·HCl-catalysed reaction was treated by removing the solvent under reduced pressure, dissolving the residue in CH_2Cl_2 (8 mL/g) and washing the organic phase with water (8 mL/g). After concentration of the organic phase to one third of its volume, the product was precipitated by the addition of Et_2O (nine volumes of CH_2Cl_2) and washed several times with Et_2O (30 mL/g). ^{1}H NMR analysis of the precipitate indicated an incomplete conversion and the presence of unidentified PEG-linked compounds (Table 2, entry 3). Because the flow conditions could not be tested with CH_3CN because of the poor solubility of urea in this solvent (0.070 M at 25 °C),[28] the reaction was carried out in DMF, a solvent previously used to perform this multicomponent transformation under continuous flow conditions.[29] The reaction was also carried out in batch, as described above. In both cases (batch at room temp. or flow at 60 °C, under the same conditions as used for the aqueous reaction), we also obtained poor conversions and unidentified PEG-linked compounds (Table 2, entries 4 and 5). Thus, under conditions identical to those optimized for water, the Biginelli reaction in organic solvents led to inferior results in terms of yield. Although we cannot exclude that further

Table 2. Comparison of the Biginelli reaction in water and in organic solvents.

	Solvent (volume [mL/g])[a]	Solvent(s) treatment [mL/g][a]	**1a**[b] [%]	**2a**[b] [%]	Unidentified PEG-linked compounds[b] [%]
1	H_2O[c] (8.5)	H_2O (85)	0	100	0
2	H_2O[d] (8.5)	H_2O (85)	0	100	0
3	CH_3CN[c] (8.5)	H_2O (8) CH_2Cl_2 (8) Et_2O (64)	5	30	65
4	DMF[c] (8.5)	H_2O (8) CH_2Cl_2 (8) Et_2O (64)	50	5	45
5	DMF[d] (8.5)	H_2O (8) CH_2Cl_2 (8) Et_2O (64)	40	20	40

[a] Volume of solvent per g of the starting PEG-linked aldehyde **1a**. [b] Determined by ^{1}H NMR analysis. [c] Batch. [d] Flow.



Scheme 4. $CuCl_2$·HCl-catalysed aqueous Biginelli reaction under flow conditions.

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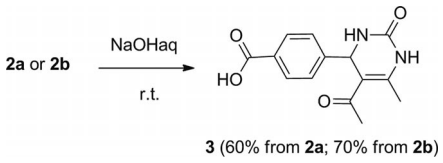
optimization could give results similar to those obtained in aqueous medium, the use of water as solvent gave quantitative yields of product under very mild and safe conditions. Note also that similar volumes of solvents were required for both treatments, that is, ultrafiltration or extraction/precipitation (Table 2).

DHMP **3** was released from the PEG support by basic hydrolysis (1 M aqueous NaOH) of the ester linkage (Scheme 5). Acidification of the reaction mixture gave solid **6** contaminated by less than 5% of PEG (^{1}H NMR). Most of the remaining PEG could be removed by ultrafiltration of an aqueous basic (pH 8) solution. Indeed, upon acidification of the filtrate, compound **3** was isolated by filtration (purity >98%, NMR) in 60% yield from **1a** and 70% from **1b**. We also checked (NMR) that released PEG was pure enough to be reused. In fact, when the recovered PEG was reused to prepare **1a** or **1b**, similar yields and purities were obtained.



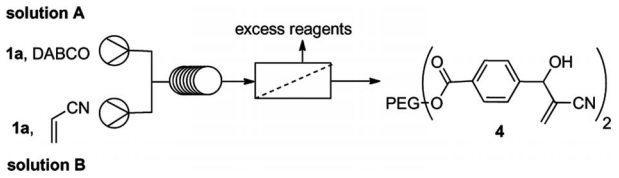
Scheme 5. Hydrolysis of the PEG linkage.

These experiments showed that water is the solvent of choice for the PEG-supported reactions and that purification by ultrafiltration would avoid the use of potentially dangerous and/or toxic solvents. The slightly lower isolated yields obtained by ultrafiltration using the smaller PEG as the support were compensated by the higher loading capacity of PEG_{2000} (1 mmol/g) compared with that of PEG_{4000} (0.5 mmol/g). Furthermore, the higher viscosity of PEG_{4000} derivatives could be problematic during the pumping operation; therefore we decided to test the process for the multistep synthesis of heterocycles (Scheme 1) using PEG_{2000} as the support.

Multistep Syntheses and Purification of Heterocycles

Due to presence of various functional groups, Baylis–Hillman adducts can be used for the synthesis of a broad range of compounds.[30] Although numerous cases of the Baylis–Hillman reaction in the presence of water have been reported,[31] few examples of the reaction in water as solvent have been described.[32] Quite recently, Acke and Stevens reported on the study of this reaction in water/dioxane under continuous flow conditions.[33] They found, in particular, that the reaction was faster under flow conditions than under batch conditions and that the stopped-flow technique as well as a high concentration of the reagents were required to achieve complete conversion.

The reaction between **1a** and acrylonitrile was carried out in the presence of DABCO. Because the viscosity of the PEG-bound aldehyde aqueous solution decreased in the presence of acrylonitrile, to maintain an elevated concentration of the substrate we decided to start with two storage solutions (A and B), both containing **1a** (Scheme 6).



Scheme 6. Aqueous Baylis–Hillman reaction of PEG_{2000}-linked aldehyde under flow conditions.

The initial concentration of **1a** in these solutions, the quantity of DABCO and acrylonitrile, as well as the residence time and the temperature of the CFC, were optimized (Table 3). First, the experiments were performed by setting the concentrations of **1a** in solutions A and B at 0.08 M with 0.25 equiv. of DABCO and 3 equiv. of acrylonitrile. At a total flow rate of 0.2 mL/min and 65 °C, a 47% conversion was observed (Table 1, entry 1). No significant improvement was found by increasing the concentration of **1a** (Table 3, entry 2) whereas a higher temperature (100 °C) gave rise to the formation of byproducts and hydrolysis of the ester linkage (Table 3, entry 3). To facilitate the pumping of the PEG-supported substrate solution by lowering its viscosity, the concentration of **1a** in the solution containing acrylonitrile (solution B) was increased, maintaining the final concentration in the reaction cell. Under these experimental conditions, a repeatable constant flow rate of 0.3 mL/min could be tested and we observed that an increase in flow rate and quantity of DABCO resulted in an enhancement of the conversion up to 80% (Table 3, entry 4), although hydrolysis of the ester linkage still occurred (≈30%). This side-reaction could be limited to 10% by lowering the temperature (Table 3, entries 5–8). Optimal conditions allowing a complete conversion of **1a** were found (Table 3, entry 7) and applied to the preparation of 12 g of **4** (84% yield), purified by ultrafiltration of the resulting aqueous solution.[34]

Table 3. Optimization of the Baylis–Hillman reaction under flow conditions.

	[**1a**] [mol/L], sol. A	[**1a**] [mol/L], sol. B	DABCO [equiv.]	Acrylonitrile [equiv.]	Flow rate [mL/min]	*T* [°C]	Conv. [%][a]
1	0.08	0.08	0.25	3	0.2	65	47
2	0.21	0.21	0.25	3	0.2	65	50
3	0.085	0.085	0.25	3	0.2	100	50[b]
4	0.043	0.13	0.5	3	0.3	100	80[b]
5	0.043	0.13	0.5	3	0.3	80	90[c]
6	0.032	0.097	0.5	4	0.3	60	98[c]
7	0.032	0.097	0.5	5	0.3	60	100[c]
8	0.032	0.097	0.5	5	0.4	60	98[c]

[a] The conversion was determined by ^{1}H NMR spectroscopy. [b] Unidentified byproducts and ca. 30% hydrolysis were observed. [c] <10% hydrolysis was observed.

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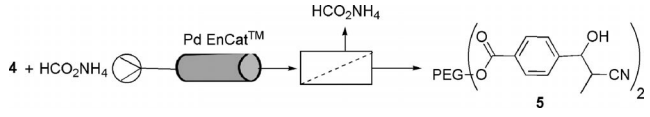
In the next step, the double bond of the PEG-supported Baylis–Hillman adduct **4** was reduced. The reaction, carried out in batch by using H_2 and 10% Pd/C as catalyst, was complete after 2 h at room temp. To perform the reduction under flow conditions, we investigated the use of Pd EnCat™ as catalyst and ammonium formate as hydrogen source. Hence, an aqueous solution of **4** and ammonium formate was passed through an Omnifit cartridge containing the catalyst (Scheme 7). The optimal flow rate and temperature, determined to be 0.111 mL/min and 50 °C, led to **5** as a 60:40 diastereoisomeric mixture (^{1}H NMR) in a residence time of 3 min.[34] PEG-linked compound **5** was separated from the ammonium formate by ultrafiltration and isolated in 90% yield.



Scheme 7. Reduction of PEG-linked Baylis–Hillman adduct in flow condition.

PEG-linked nitrile **5** was then treated with sodium azide to prepare the 1*H*-tetrazole derivative **7**. This reaction is generally carried out in DMF in the presence of ammonium salts[35] but also in water with zinc salt as promoter as demonstrated by Sharpless and co-workers.[36] Hence, we investigated the use of ammonium chloride and $ZnBr_2$ as promoters and water and DMF as solvents at various temperatures (Table 4). PEG-linked tetrazole **6** was obtained in DMF at 140 °C in the presence of NH_4Cl (12 equiv.) in 12 h (Table 4, entry 1) whereas the reaction was effective at 170 °C in water in the presence of $ZnBr_2$ (1.5 equiv.) also in 12 h. Concomitant hydrolysis of the ester linkage afforded the 1*H*-tetrazole derivative **7** (Table 4, entry 6).

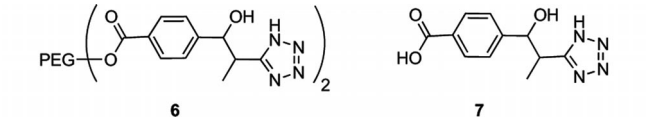


Table 4. Optimisation of tetrazole formation in batch.

	Solvent	*T* [°C]	Promoter	Conv. [%][a]	Hydrolysis [%][a]
1	H_2O	140	NH_4Cl	0	0
2	DMF	140	NH_4Cl	100	0
3	H_2O	75	$ZnBr_2$	0	15
4	H_2O	100	$ZnBr_2$	15	26
5	H_2O	140	$ZnBr_2$	40	100
6	H_2O	170	$ZnBr_2$	100	100

[a] Determined by ^{1}H NMR analysis.

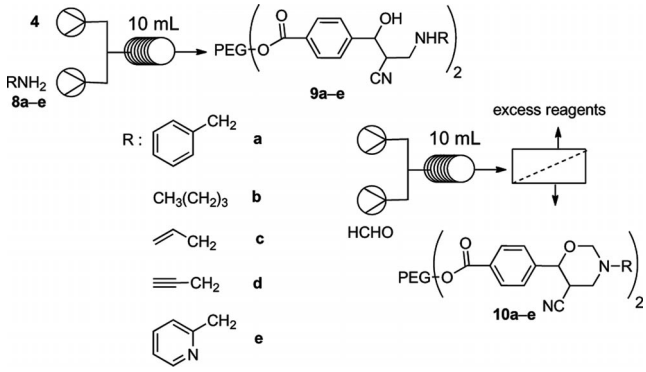
The advantage of using the microreactor approach in such an energy-demanding transformation has recently been demonstrated.[37] Kappe and co-workers obtained good results by using NMP/H_2O/AcOH as solvent under high-temperature conditions[37a] (220 °C, 34 bar back-pressure regulator), whereas Palde and Jamison described a non-catalysed flow process in NMP/H_2O at 190 °C (17 bar back-pressure regulator).[37b] Our preliminary tests under batch conditions showed that a temperature of 170 °C was necessary to obtain compound **7**. As our equipment does not function at temperatures above 150 °C, we optimized the flow conditions (Table 5) and were able to obtain complete conversion by using 2.5 equiv. of $ZnBr_2$ at 150 °C with a residence time of 166 min. The crude aqueous reaction medium containing compound **7**, PEG and excess reactants in this case too was submitted to ultrafiltration. This treatment allowed recovery of the PEG and, at the same time, a solution containing **7** that could be isolated almost pure upon extraction with ethyl acetate after acidification (60% yield).

Table 5. Optimization of the tetrazole synthesis under flow conditions.

	$ZnBr_2$ [equiv.]	Flow rate [mL/min]	Conv. [%][a]
1	1.5	0.166	50
2	1.5	0.111	70
3	1.5	0.08	80
4	2.5	0.08	83
5	2.5	0.06	100

[a] Conversions determined by ^{1}H NMR spectroscopy.

Then we envisaged using the same process to prepare new tetrahydro-1,3-oxazines from PEG-linked aldehyde **1a** through a four-step synthesis, that is, Baylis–Hillman reaction, Michael addition of a range of amines, cyclization with formaldehyde and hydrolysis of the linkage to PEG. Various catalysts are known to be efficient in the aqueous aza-Michael addition reaction[38] but the reaction is also known to proceed without any catalyst.[39] Hence, aqueous solutions of amines **8a**–**e** were added to the PEG-linked Baylis–Hillman adduct **5** without additives. Complete conversions were observed in a residence time of 30 min at 30 °C with benzylamine, butylamine and allylamine, and at 45 °C in a residence time of 45 min with propargylamine and 2-aminopyridine. The β-aminopropionitriles **9a**–**e** were obtained as approximately 70:30 diastereoisomeric mixtures (^{1}H NMR[40]). The aqueous solutions obtained under flow conditions were directly pumped and mixed through a T-piece with a formaldehyde aqueous solution (Scheme 8) to form the tetrahydro-1,3-isoxazine **10a**–**e**, which was purified by ultrafiltration (Table 6).[41]



Scheme 8. Two-step preparation of tetrahydro-1,3-isoxazine under flow conditions.

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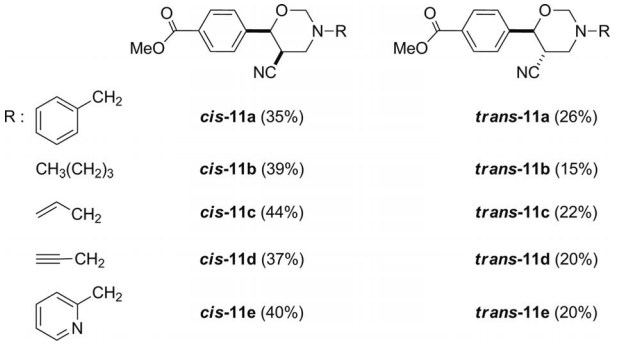
Table 6. Optimization of preparation of tetrahydro-1,3-isoxazine in flow condition.

	RNH_2 [equiv.]	T [°C][a]	Residence time [min][a]	HCHO [equiv.]	Product	Yield [%][b]
1	**8a** (1.3)	30	30	3	**10a**	80
2	**8b** (1.3)	30	30	3	**10b**	76
3	**8c** (1.5)	30	30	3	**10c**	64
4	**8d** (4)	45	45	4	**10d**	75
5	**8e** (3)	45	45	4	**10e**	85

[a] For both steps. [b] Products purified by ultrafiltration through a regenerated cellulose membrane (molecular size cut-off of 1,000) at a pressure of 3.5 bar.

Finally, the tetrahydro-1,3-isoxazines **11a**–**e** were released from the PEG by treatment with sodium methoxide to obtain the corresponding methyl ester derivatives. The diastereoisomers were separated by flash chromatography, the only non-aqueous separation of the sequence, and characterized by NMR analysis.



In all cases, the *cis*-disubstituted compound was obtained as the major compound (*cis*/*trans* ca. 2:1). The relationship between the substituents at C-5 and C-6 was established by examining the ^{1}H NMR coupling pattern of the isoxazine protons. Irrespective of the substituent on the nitrogen atom, the heterocycles adopt a chair conformation in which the phenyl moiety is in an equatorial position, as shown by the NOE observed between 2-H and 4-H and 6-H as well as a W coupling constant between 2-H and 4-H [$J_{2eq,4eq}$ = 1.5 or 2.0 Hz] for compounds **11a**–**e**. The *cis* relative orientation at C-5 and C-6 was deduced from the small (2.5 or 3.0 Hz) coupling constant between 6_{ax}-H and 5-H, whereas a large coupling constant was observed (10.0 or 11.0 Hz) in the *trans* compounds.

Conclusions

We have shown that a PEG-supported multistep synthesis could be achieved in aqueous media under continuous flow conditions. PEG_{2000} offers a good compromise between charge capacity and recovery rate by ultrafiltration. The coupling of flow synthesis in water with ultrafiltration reduces the use of organic solvents in both the synthetic and purification steps, and allows safer working conditions. We also demonstrated in the study of the Biginelli reaction that the volume of wastewater generated by this process is similar to that produced in the synthesis and work-up performed in organic solvents. Of course, the wastewater must be treated like all chemical waste, but various methodologies, including membrane techniques[7a–7d] and microchannel reactors,[42] have been proven to be effective for removing hazardous pollutants.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded at room temperature with Bruker spectrometers (250, 300 or 360 MHz). Chemical shifts are reported in parts per million (ppm) relative to Me_4Si for ^{1}H NMR spectroscopy. Signals were assigned on the basis of the results of ^{1}H–^{1}H COSY and gradient-HMQC experiments. MALDI-TOF MS spectra were performed at the Service de Spectrométrie de Masse IMAGIF/ICSN, CNRS (Gif-sur-Yvette, France) with a Perseptive Voyager DE STR MALDI-TOF mass spectrometer (Perseptive Biosystems) by using 2,5-dihydroxybenzoic acid as the matrix. The spectra of the compounds were compared with commercial PEG_{2000} [calcd. for $C_{94}H_{190}NaO_{48}$ [M + Na]$^+$ (n = 46) 2110.23; found 2110.31 (batch A); calcd. for $C_{86}H_{174}NaO_{44}$ [M + Na]$^+$ (n = 42) 1935.13; found 1935.15 (batch B)] or commercial PEG_{4000} [calcd. for $C_{190}H_{382}NaO_{96}$ [M + Na]$^+$ (n = 94) 4223.49; found 4223.53]. HRMS were recorded in positive mode with a Microtof-QII spectrometer (Bruker) using electrospray ionization. The yields of the continuous flow process were calculated from the collected volume and the flow rate.

General Procedure for Ultrafiltration: Ultrafiltration of the aqueous solutions was performed in an Amicon 8050 or 8200 stirred cell fitted with Amicon Ultracell PL Membrane Disk with a molecular weight cut-off of 1000 under a pressure of 3.8 bar. The ultrafiltration retentate was concentrated under reduced pressure to afford the product.

PEG-Bound Aldehyde 1a: A mixture of PEG_{2000} (10.0 g, 4.8 mmol), 4-formylbenzoic acid (5.8 g, 38.4 mmol) and *N*,*N*′-diisopropylcarbodiimide (8.6 mL, 55.2 mmol) was heated at 70 °C for 3.5 h and cooled to room temp. The product was diluted with water (40 mL), filtered through a PVDF membrane (47 mm, 0.45 μm) and subjected to ultrafiltration. After the first ultrafiltration, the retentate (10 mL) was diluted with water (40 mL) and the solution was subjected to ultrafiltration again. The operation was repeated once to afford 7.3 g of **1a** as a white powder (65%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.45–3.90 (m, ca. 180 H, PEG backbone), 4.53 (t, J = 5.0 Hz, 4 H, PEG-CH_2OCO), 7.98 (d, J = 8.0 Hz, 4 H, 4-H), 8.24 (d, J = 8.0 Hz, 4 H, 3-H), 10.13 (s, 2 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 64.1 (*C*H_2OCO), 68.5 (*C*H_2CH$_2$OCO), 70.0 (PEG), 128.9 (C-4), 129.7 (C-3), 134.5 (C-2), 138.6 (C-5), 164.9 (*C*OO-PEG), 191.1 (CHO) ppm. IR (KBr): $\tilde{\nu}$ = 1112 (C–O), 1650 (C=C Ar), 1698 (C=O), 2628 (CO–H) 1967 (Ar), 2880 (C–H) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{110}H_{198}NaO_{52}$ [M + Na]$^+$ (n = 46) 2374.27; found 2374.39.

PEG-Bound Aldehyde 1b: PEG_{4000} (8.0 g, 1.9 mmol) was treated with 4-formylbenzoic acid (2.3 g, 15.3 mmol) and *N*,*N*′-diisopropylcarbodiimide (3.6 mL, 23 mmol) as described for the preparation of **1a** to afford, after ultrafiltration, 6.4 g of **1b** as a white powder (75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.45–3.88 (m, 380 H, PEG backbone), 4.53 (t, J = 5.0 Hz, 4 H, PEG-CH_2OCO), 7.97 (d, J = 8.0 Hz, 4 H, 4-H), 8.23 (d, J = 8.0 Hz, 4 H, 3-H) 10.12 (s, 2 H, CHO) ppm. ^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 64.5 (*C*H_2OCO), 68.8 (*C*H_2CH$_2$OCO), 70.4 (PEG), 129.3 (C-4), 130.1 (C-3), 134.8 (C-2), 139.1 (C-5), 165.2 (C-1), 191.5 (CHO) ppm. IR (KBr): $\tilde{\nu}$ = 1112 (C–O), 1650 (C=C Ar), 1698 (C=O), 2628 (CO–

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H) 1967 (Ar), 2880 (C–H) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{206}H_{390}NaO_{100}$ $[M + Na]^+$ (n = 94) 4487.53; found 4487.52.

PEG-Bound DHPM 2a, Batch Procedure: An aqueous 1 M solution of HCl (30 μL) was added to a solution of **1a** (588 mg, 0.25 mmol), pentane-2,4-dione (200 μL, 2 mmol), urea (120 mg, 2 mmol) and $CuCl_2·2H_2O$ (4.3 mg, 0.025 mmol) in water (5 mL). The reaction mixture was then stirred at room temperature overnight, diluted with water (20 mL) and subjected to ultrafiltration. The retentate (10 mL) was diluted with water (15 mL) and the solution was subjected to ultrafiltration again. The operation was repeated to afford **2a** as a white powder (465 mg, 72%).

Flow Procedure: An aqueous solution of **1a** (0.095 M, 8.4 mL) containing pentane-2,4-dione (660 μL, 6.4 mmol; stream A) and an aqueous solution of urea (0.76 M, 8.4 mL) containing $CuCl_2·2H_2O$ (27 mg, 0.16 mmol) and aqueous HCl (1 M, 0.2 mL; stream B) were filtered with a PTFE syringe filter (13 mm, 20 μm). Streams were mixed together at the same flow rate (0.03 mL/min) in a T-mixer at room temperature and the resulting stream (0.06 mL/min) was passed through the Vapourtec R4® reactor (10 mL heated volume, 167 min residence time) at 60 °C. Two 8 bar back-pressure regulators were employed. The leading (ca. 1.0 mL) and trailing ends of the plug were rejected to ensure that only the steady-state reaction mixture was purified. The aqueous solution was collected for 185 min (11.1 mL) in an Amicon 8050 stirred cell containing water (40 mL) and subjected to ultrafiltration. The retentate (10 mL) was diluted with water (35 mL) and the solution was again subjected to ultrafiltration. The operation was repeated to afford **2a** as a white powder (990 mg, 72%). ^{1}H NMR (250 MHz, MeOD): δ = 2.23 (s, 4.8 H, 12-H), 2.41 (s, 4.6 H, 14-H), 3.48–3.95 (m, 200 H, PEG backbone), 4.47 (t, J = 4.0 Hz, 4 H, CH_2OCO), 5.52 (s, 1.6 H, 6-H), 7.47 (d, J = 8 Hz, 3.2 H, 4-H), 8.04 (d, J = 8 Hz, 3.3 H, 3-H) ppm. ^{13}C NMR (75.47 MHz, DMSO): δ = 19.2 (C-12), 30.6 (C-14), 53.7 (C-6), 64.2 (*C*H_2OCO), 68.6 (*C*H_2CH$_2$OCO), 70.0 (PEG), 109.6 (C-11), 126.9 (C-4), 128.9 (C-5), 129.5 (C-3), 148.8 (C-10), 149.7 (C-2), 152.2 (C-8), 165.6 (C-1), 194.2 (C-13) ppm. IR (KBr): $\tilde{\nu}$ = 1107 (C–O), 1654 (C=C Ar), 1717 (C=O), 1967 (Ar), 2879 (C–H), 3567 (N–H) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{122}H_{214}N_4NaO_{54}$ $[M + Na]^+$ (n = 46) 2622.40; found 2622.41.

PEG-Bound DHPM 2b, Batch Procedure: PEG-bound aldehyde **1b** (1.12 g, 0.25 mmol) was treated with pentane-2,4-dione (200 μL, 2 mmol), urea (120 mg, 2 mmol), $CuCl_2·2H_2O$ (4.3 mg, 0.025 mmol) and 1 M aqueous HCl (30 μL) as described for the preparation of **2a** to afford, after ultrafiltration, **2b** as a white solid (946 mg, 87%).

Flow Procedure: An aqueous solution of **1b** (0.061 M, 4.1 mL) containing pentane-2,4-dione (310 μL, 3 mmol; stream A) and an aqueous solution of urea (0.73 M, 4.1 mL) containing $CuCl_2·2H_2O$ (8.5 mg, 0.05 mmol) and 1 M aqueous HCl (65 μL; stream B) were filtered through a PTFE syringe filter (13 mm, 20 μm). Streams were mixed together at the same flow rate (0.025 mL/min) in a T-mixer at room temperature and the resulting stream (0.05 mL/min) was passed through the Vapourtec R4® reactor (10 mL heated volume, 200 min residence time) at 60 °C. Two 8 bar back-pressure regulators were employed. The leading (ca. 1.0 mL) and trailing ends of the plug were rejected to ensure that only the steady-state reaction mixture was purified. The aqueous solution was collected for 100 min (5 mL) in an Amicon 8050 stirred cell containing water (20 mL) and subjected to ultrafiltration. The retentate (10 mL) was diluted with water (15 mL) and the solution was subjected to ultrafiltration again. The operation was repeated to afford **2b** as a white powder (567 mg, 79%). ^{1}H NMR (300 MHz, DMSO): δ = 2.13 (s, 6 H, CH_3), 2.29 (s, 6 H, CH_3CO), 3.41–3.73 (m, ca. 380 H, PEG backbone), 4.37 (t, J = 4.0 Hz, 4 H, CH_2OCO), 5.32 (d, J = 3.0 Hz, 2 H, 4-H), 7.38 (d, J = 8.0 Hz, 4 H, 3′-H, 5′-H), 7.91 (d, J = 8.0 Hz, 6 H, 2′-H, 6′-H, 1-H), 9.25 (s, 2 H, 3-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 19.32 (CH_3), 30.21 (*C*H_3CO), 54.68 (C-4), 63.72 (*C*H_2OCO), 68.71 (*C*H_2CH$_2$OCO), 70.1 (PEG), 110.27 (C-5), 126.2 (C-2′, C-6′), 129.31 (C-1′), 129.9 (C-3′, C-5′), 146.34 (C-6), 147.68 (C-4′), 152.68 (C-2), 165.56 (*C*OO), 194.24 (CH$_3$*C*O) ppm. MS (MALDI-TOF): calcd. for $C_{218}H_{406}N_4NaO_{102}$ $[M + Na]^+$ (n = 94) 4735.66; found 4735.43.

5-Acetyl-4-(4-carboxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3): A solution of **2a** (570 mg) or **2b** (1.04 g) in 1 M NaOH (5 mL) was stirred at room temperature for 24 h. A 0.5 M HCl solution was added until pH 2, the resulting suspension was stirred for 1 h at 0 °C and the precipitate was filtered. The solid (contaminated by ca. 5% PEG) was suspended in water (40 mL), the pH was adjusted to 8 with 1 M NaOH and the resulting solution was subjected to ultrafiltration. The filtrate was concentrated to 10 mL, 0.5 M HCl was then added until pH 2 and the resulting suspension was stirred for 1 h at 0 °C. The precipitate was filtered and washed with water (20 mL) to afford **3** contaminated by less than 2% PEG (72 mg, 60% from **2a**, 84 mg, 70% from **2b**). ^{1}H NMR (360 MHz, DMSO): δ = 2.12 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3CO), 5.30 (d, J = 3.0 Hz, 1 H, 4-H) 7.29 (d, J = 8.0 Hz, 2 H, 3′-H, 5′-H), 7.85 (m, 3 H, 2′-H, 6′-H, NH), 9.18 (s, 1 H, NH) ppm. ^{13}C NMR (75.47 MHz, DMSO): δ = 194.61 (*C*OCH_3), 168.19 (*C*OOH), 152.54 (C-2), 148.81 (C-4′), 148.01 (C-6), 133.39 (C-1′), 129.95 (C-2′, C-6′), 126.63 (C-3′, C-5′), 109.99 (C-5), 54.08 (C-4), 30.86 (*C*H_3CO), 19.43 (CH_3) ppm. HRMS (ESI-TOF): calcd. for $C_{14}H_{13}N_2O_4$ $[M – H]^–$ 273.0875; found 273.0883.

PEG-Bound BH Adduct 4: An aqueous solution (stream A, 55 mL) of **1a** (12.5 g, 5.33 mmol) and acrylonitrile (4.6 mL, 70 mmol), and an aqueous solution (55 mL; stream B) of **1a** (4.1 g, 1.76 mmol) and DABCO (795 mg, 7.1 mmol) were filtered through a PTFE syringe filter (25 mm, 20 μm) before flow processing. Streams were mixed together at the same flow rate (0.150 mL/min) in a T-mixer at room temperature and the resulting stream (0.300 mL/min) was passed through the Vapourtec R4® reactor (10 mL heated volume, 33 min residence time) at 60 °C. Two 8 bar back-pressure regulators were employed. The leading sample (ca. 6.6 mL) was rejected, and the aqueous solution was collected for 150 min (45 mL) in an Amicon 8200 stirred cell containing water (150 mL) and subjected to ultrafiltration and the output of the reactor was collected for 150 min (45 mL) in a second Amicon 8200 stirred cell also containing water (150 mL). The retentate (40 mL) was diluted with water (150 mL) and the solution was again subjected to ultrafiltration. The operation was repeated. The ultrafiltration retentates were concentrated under reduced pressure to afford 12 g (84%) of **4**. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 3.40–3.71 (m, 180 H, PEG backbone), 4.48 (t, J = 4.5 Hz, 4 H, CH_2OCO), 5.40 (s, 2 H, 6-H), 6.04 (s, 2 H, 8a-H), 6.15 (s, 2 H, 8b-H), 7.50 (d, $J_{3\text{-}4}$ = 8.0 Hz, 4 H, 4-H), 8.07 (d, 4 H, 3-H) ppm. ^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 64.2 (CH_2OCO), 69.2 (*C*H_2CH$_2$OCO), 70.6 (PEG), 73.2 (C-6), 117.0 (C-9), 126.6 (C-4), 126.7 (C-8), 129.9 (C-7), 130.1 (C-3), 130.1 (C-5), 145.2 (C-2), 166.1 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 1108 (C–O), 1637 (C=C Ar), 1717 (C=O), 1968 (Ar), 2224 (CN), 2874 (C–H), 3433 (O–H) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{116}H_{204}N_2NaO_{52}$ $[M + Na]^+$ (n = 46) 2480.22; found 2480.30.

Compound 5, Batch Procedure: Pd/C (10%, 22 mg, 0.021 mmol) was added to a solution of **4** (250 mg, 0.105 mmol) in water (2.5 mL). The reaction mixture was stirred at 25 °C under H_2 for 2 h, diluted with water (30 mL), filtered through a short pad of Celite and subjected to ultrafiltration. The retentate (10 mL) was

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diluted with water (25 mL) and the solution was subjected to ultrafiltration again. The operation was repeated to afford **5** (225 mg, 90%) as a solid.

Flow Procedure: An aqueous solution of **4** (0.041 M, 10 mL) and ammonium formate (1.4 g, 22.6 mmol) was filtered through a PTFE syringe filter (25 mm, 20 μm) before flow processing. A column reactor (6.6 mm id) was charged with Pd EnCat (490 mg). A stream (0.111 mL/min) was passed through the column reactor (3 min residence time) at 50 °C. Two 8 bar back-pressure regulators were employed. The leading (ca. 0.5 mL) and trailing ends of the plug were rejected so that only the steady-state reaction product was used for establishing product yield and purity. The product was collected for 80 min (8.9 mL) in an Amicon 8050 stirred cell containing water (25 mL) and subjected to ultrafiltration. The retentate (10 mL) was diluted with water (25 mL) and the solution was subjected to ultrafiltration again. The operation was repeated to afford **5** (802 mg, 90%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.28 (d, $J_{8\text{-}7}$ = 7.5 Hz, 6 H, 8-H), 2.95 (dq, $J_{7\text{-}6}$ = 5.5 Hz), 3.54–3.91 (m, 230 H, PEG backbone), 4.49 (t, J = 4.5 Hz, 4 H, CH_2OCO), 4.80 (d, 0.8 H, 6-H minor), 4.88 (d, 1 H, 6-H major), 7.46 (d, $J_{3\text{-}4}$ = 8.5 Hz, 1.5 H, 4-H minor), 7.48 (d, $J_{3\text{-}4}$ = 8.5 Hz, 2.5 H, 4-H major), 8.07 (d, 4 H, 3-H) ppm. ^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 13.4 (C-8 minor), 14.5 (C-8 major), 33.9 (C-7 major), 34.4 (C-7 minor), 61.6 (CH_2OH), 64.2 (CH_2OCO), 69.1 (CH_2CH_2OCO), 70.6 (PEG), 72.5 (C-6 major), 73.5 (C-6 minor), 120.7 (C-9 minor), 120.9 (C-9 major), 126.4 (C-4 minor), 128.5 (C-4 major), 129.7 (C-3 major), 129.8 (C-3 minor), 130.1 (C-5), 145.7 (C-2 major), 146.0 (C-2 minor), 166.1 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 1108 (C–O), 1637 (C=C Ar), 1717 (C=O), 1967 (Ar), 2241 (CN), 2872 (C–H), 3466 (O–H) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{116}H_{208}N_2O_{52}Na$ [M + Na]$^+$ (n = 46) 2484.37; found 2484.31.

Compound 6: NaN_3 (624 mg, 9.6 mmol) and NH_4Cl (513 mg, 9.6 mmol) were added to a solution of **5** (1 g, 0.4 mmol) in DMF (10 mL). The reaction mixture was stirred at 140 °C in a screw-locked tube overnight, diluted with H_2O and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4, filtered, and concentrated to around 2 mL under reduced pressure. Et_2O (ca. 20 mL) was added, under vigorous stirring, at 0 °C to precipitate the solid, which was filtered, washed with Et_2O (ca. 40 mL) and dried under vacuum to give 727 mg of **6** (72%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.21 (d, $J_{8\text{-}7}$ = 7.5 Hz, 1.7 H, 8-H major), 1.25 (d, $J_{8\text{-}7}$ = 7.5 Hz, 1.4 H, 8-H minor), 3.31–3.91 (m, 237 H, PEG, 7-H), 4.44 (t, J = 4.0 Hz, CH_2OCO), 4.81 (d, $J_{6\text{-}7}$ = 7.0 Hz, 0.7 H, 6-H minor), 5.20 (m, 6-H major), 7.41 (d, $J_{4\text{-}3}$ = 8.0 Hz, 2.5 H, 4-H), 7.94 (d, 2.6 H, 3-H) ppm. ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 12.3 (C-8 major), 16.3 (C-8 minor), 37.4 (C-7 major), 38.0 (C-7 minor), 61.6 (PEG-CH_2OH), 64.15 (CH_2OCO), 70.6 (PEG), 73.7 (C-6), 126.2 (C-4 major), 126.8 (C-4 minor), 129.1 (C-3 minor), 129.6 (C-3 major), 129.8 (C-5), 147.3 (C-2), 159.4 (C-9), 166.4 (C-1) ppm.

4-[1-Hydroxy-2-(1*H*-tetrazol-5-yl)propyl]benzoic Acid (7), Batch Procedure: NaN_3 (312 mg, 4.8 mmol) and $ZnBr_2$ (135 mg, 0.6 mmol) were added to a solution of **5** (500 mg, 0.2 mmol) in water (3 mL). The reaction mixture was stirred at 170 °C in a screw-locked tube for 12 h, diluted with water (10 mL), filtered through a short pad of Celite and subjected to ultrafiltration twice (Amicon 8050 stirred cell). The ultrafiltration filtrate (40 mL) was concentrated (5 mL) and acidified to pH 2 with 1 M HCl and extracted with AcOEt (3 × 5 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated to afford compound **7** (62 mg, 62%).

Flow Procedure: An aqueous solution of **5** (0.0529 M, 7 mL), NaN_3 (577 mg, 8.88 mmol) and $ZnBr_2$ (417, mg, 1.85 mmol) was filtered through a PTFE syringe filter (25 mm, 20 μm) before flow processing. A stream (0.06 mL/min) was passed through the Vapourtec R4® reactor (10 mL heated volume, 166 min residence time) at 150 °C. Two 8 bar back-pressure regulators were employed. The leading sample (ca. 0.5 mL) of the plug was rejected and the solution was then collected for 108 min (6.5 mL) in an Amicon 8050 stirred cell containing water (25 mL) and subjected to ultrafiltration. The retentate (10 mL) was diluted with water (25 mL) and the solution was subjected to ultrafiltration again. The operation was repeated and the ultrafiltration filtrate (71.5 mL) was treated as described before to give compound **7** contaminated by around 2% PEG (95 mg, 56%). ^{1}H NMR (360 MHz, MeOD): δ = 1.30 (d, $J_{8\text{-}7}$ = 7.5 Hz, 1.3 H, 8-H minor), 1.36 (d, $J_{8\text{-}7}$ = 7.5 Hz, 1.7 H, 8-H major), 3.52–3.63 (m, 1 H, 7-H), 4.88 (d, $J_{6\text{-}7}$ = 7.0 Hz, 0.4 H, 6-H minor), 5.03 (d, $J_{6\text{-}7}$ = 5.5 Hz, 0.6 H, 6-H major), 7.33 (d, $J_{4\text{–}3}$ = 8.5 Hz, 1.2 H, 4-H major), 7.38 (d, $J_{4\text{–}3}$ = 8.5 Hz, 0.8 H, 4-H minor), 7.94 (d, 1.2 H, 3-H major), 7.97 (d, 0.8 H, 3-H minor) ppm. ^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 13.7 (C-8 major), 16.5 (C-8 minor), 38.9 (C-7 major), 39.3 (C-7 minor), 76.2 (C-6 major), 76.9 (C-6 minor), 127.5 (C-4 major), 127.7 (C-4 minor), 130.7 (C-3 major), 130.9 (C-3 minor), 131.2 (C-5 major), 131.5 (C-5 minor), 148.7 (C-2 major), 149.2 (C-2 minor), 159.2 (C-9 minor), 159.5 (C-9 major), 169.7 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 1611 (C=C Ar), 1685 (C=O), 1943 (Ar), 2924 (C–H), 3446 (N–H, O–H) cm^{-1}. HRMS (ESI): calcd. for $[C_{11}H_{11}N_4O_3 - H]^-$ 247.0837; found 247.0855.

PEG-Bound Tetrahydro-1,3-oxazines 10a–e: An aqueous solution of **4** (0.1 M, 7.9 mL) was mixed with an aqueous solution of amine **8** (7.9 mL; 0.26 M **8a** or **8b**, 0.3 M **8c**, 0.8 M **8d** or 0.6 M for **8e**) at the same flow rate (0.167 mL/min for **8a**, **8b** or **8c** or 0.111 mL/min for **8d** or **8e**) in a T-mixer at room temperature and the resulting stream (0.333 or 0.222 mL/min) was passed through the Vapourtec R4® reactor (10 mL heated volume, 30 or 45 min residence time, respectively) at 45 °C. Two 8 bar back-pressure regulators were employed. The leading sample (ca. 0.4 mL) of the plug was rejected and 15.4 mL of the aqueous solutions of **9a**–**e** were collected (for analytical purposes, some experiments were carried out in which solutions of **9a**–**e** were subjected to ultrafiltration, see below) and mixed with aqueous formaldehyde (15.4 mL; 0.3 M for **9a**–**c**, 0.4 M for **9d**–**e**) in a T-mixer at room temperature at the same flow rate (0.167 mL/min for **9a**–**c** or 0.111 mL/min for **9d** and **9e**) The resulting stream (0.333 or 0.222 mL/min) was passed through the Vapourtec R4® reactor (10 mL heated volume) at 30 °C. Two 8 bar back-pressure regulators were employed. The leading sample (ca. 1.8 mL) of the plug was rejected and the aqueous solution (29 mL) was collected in an Amicon 8050 stirred cell containing water (20 mL) and subjected to ultrafiltration. The retentate (10 mL) was diluted with water (40 mL) and the solution was subjected to ultrafiltration again. The operation was repeated. The ultrafiltration retentate was concentrated under reduced pressure to afford compounds **10a**–**e**.

9a: ^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.85–2.92 (m, 2 H, 7-H), 2.95 (dd, $J_{9b\text{-}7}$ = 4.5, $J_{9a\text{-}9b}$ = 12.5 Hz, 2 H, 9b-H), 3.13 (dd, $J_{9a\text{-}7}$ = 4.5 Hz, 2 H, 9a-H), 3.35–3.77 (m, 240 H, PEG backbone), 3.77 (d, $J_{10a\text{-}10b}$ = 13.0 Hz, 10a-H), 3.84 (d, 2 H, 10b-H), 4.40 (t, J = 4.5 Hz, 4 H, CH_2OCO), 5.00–5.02 (m, 1.5 H, 6-H), 7.16–7.32 (m, 10 H, 11-H, 12-H, 13-H, 14-H), 7.37 (d, $J_{4\text{-}3}$ = 8.5 Hz, 1.3 H, 4-H minor), 7.42 (d, $J_{4\text{-}3}$ = 8.5 Hz, 2.3 H, 4-H major), 7.96 (d, 3-H minor), 7.98 (d, 4 H, 3-H major) ppm. ^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 39.1 (C-7 minor), 40.5 (C-7 major), 48.2 (C-9 minor), 49.2 (C-9 major), 53.7 (C-10 minor), 53.8 (C-10 major), 61.8 (CH_2OH), 64.3 (CH_2OCO), 69.3 (CH_2CH_2OCO), 70.7 (PEG), 73.7 (C-6 major), 74.4 (C-6 minor), 118.3 (C-8 major), 118.9 (C-8 minor), 126.0 (C-4 major), 126.4 (C-4 minor), 127.7 (C-14), 128.3 (C-13 major),

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128.4 (C-13 minor), 128.6 (C-12 minor), 128.8 (C-12 major), 130.0 (C-3), 130.2 (C-5), 138.5 (C-11 minor), 138.6 (C-11 major), 145.8 (C-2), 166.2 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 1108 (C–O), 1653 (C=C Ar), 1717 (C=O), 1968 (Ar), 2240 (CN), 2873 (C–H), 3434 (O–H) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{130}H_{223}N_4O_{52}$ $[M + H]^+$ (n = 46) 2672.48; found 2672.47.

9b: ^1H NMR (360 MHz, $CDCl_3$): δ = 0.96 (t, $J_{13\text{-}12}$ = 7.5 Hz, 6 H, 13-H), 1.34–1.46 (m, 4 H, 12-H), 1.49–1.56 (m, 4 H, 11-H), 2.66–2.73 (m, 2.5 H, 10-H major), 2.77–2.84 (m, 1.5 H, 10-H minor), 2.88–2.93 (m, 0.6 H, 7-H minor), 2.99–3.02 (m, 1.4 H, 7-H major), 3.04–3.09 (m, 2 H, 9b major, 9b minor), 3.16 (dd, $J_{9a\text{-}9b}$ = 12.5, $J_{9a\text{-}7}$ = 8.0 Hz, 0.7 H, 9a-H minor), 3.33 (dd, $J_{9a\text{-}9b}$ = 12.5, $J_{9a\text{-}7}$ = 4.5 Hz, 1.4 H, 9a-H major), 3.44–3.86 (m, 249 H, PEG backbone), 4.49 (t, J = 4.5 Hz, 4 H, CH_2OCO), 5.14–5.16 (m, 1.8 H, 6-H), 7.52 (d, $J_{4\text{-}3}$ = 8.5 Hz, 1.5 H, 4-H minor), 7.55 (d, $J_{4\text{-}3}$ = 8.5 Hz, 2.5 H, 4-H major), 8.09 (d, 4 H, 3-H) ppm. ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 13.7 (C-13), 20.1 (C-12), 31.7 (C-11 major), 31.9 (C-11 minor), 38.5 (C-7 minor), 39.9 (C-7 major), 49.1 (C-10), 49.3 (C-9 major), 49.7 (C-9 minor), 61.4 (CH_2OH), 64.0 (CH_2OCO), 69.0 (CH_2CH_2OCO), 70.4 (PEG), 73.5 (C-6 major), 74.3 (C-6 minor), 118.1 (C-8 major), 118.7 (C-8 minor), 125.8 (C-4 major), 126.2 (C-4 minor), 129.7 (C-3), 129.9 (C-5), 145.8 (C-2 major), 145.9 (C-2 minor), 165.9 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 1094 (C–O), 1611 (C=C Ar), 1716 (C=O), 1957 (Ar), 2242 (CN), 2868 (C–H), 3253 (O–H) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{116}H_{221}N_4O_{48}$ $[M + H]^+$ (n = 42) 2428.41; found 2428.37.

9c: ^1H NMR (360 MHz, $CDCl_3$): δ = 2.91–3.09 (m, 4 H, 7-H, 9a-H), 3.23 (dd, $J_{9b\text{-}9a}$ = 12.5, $J_{9b\text{-}7}$ = 4.5 Hz, 2 H, 9b-H), 3.30 (dd, $J_{10a\text{-}10b}$ = 14.0, $J_{10a\text{-}11}$ = 6.5 Hz, 2 H, 10a-H), 3.38 (dd, $J_{10b\text{-}11}$ = 6.5 Hz, 2 H, 10b-H), 3.42–3.85 (m, 235 H, PEG backbone), 4.45 (t, J = 4.5 Hz, 4 H, CH_2OCO), 5.08–5.12 (m, 1.7 H, 6-H), 5.14–5.24 (m, 4 H, 12-H), 5.80–5.91 (m, 2 H, 11-H), 7.49 (d, $J_{4\text{-}3}$ = 8.5 Hz, 1 H, 4-H minor), 7.51 (d, $J_{4\text{-}3}$ = 8.5 Hz, 3 H, 4-H major), 8.06 (d, 3-H) ppm. ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 39.0 (C-7 minor), 40.3 (C-7 major), 48.0 (C-9 minor), 48.8 (C-9 major), 51.7 (C-10 minor), 51.9 (C-10 major), 61.5 (CH_2OH), 64.2 (CH_2OCO), 69.1 (CH_2CH_2OCO), 70.5 (PEG), 72.5 (C-6 major), 73.3 (C-6 minor), 117.3 (C-12), 118.3 (C-8 major), 118.8 (C-8 minor), 125.9 (C-4 major), 126.3 (C-4 minor), 129.8 (C-3, C-5), 135.3 (C-11), 145.9 (C-2), 166.1 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 1109 (C–O), 1647–1654 (C=C Ar), 1718 (C=O), 1957 (Ar), 2242 (CN), 2877 (C–H), 3447 (O–H) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{114}H_{203}N_4O_{48}$ $[M + H]^+$ (n = 42) 2396.35; found 2396.34.

9d: ^1H NMR (360 MHz, $CDCl_3$): δ = 2.31 (t, $J_{12\text{-}10}$ = 2.0 Hz, 0.5 H, 12-H minor), 2.32 (t, $J_{12\text{-}10}$ = 2 Hz, 1.1 H, 12-H major), 3.00–3.06 (m, 1.6 H, 7-H), 3.08 (dd, $J_{9a\text{-}9b}$ = 12.0, $J_{9a\text{-}7}$ = 4.5 Hz, 1.6 H, 9a-H), 3.37 (dd, $J_{9b\text{-}7}$ = 4.5 Hz, 1.6 H, 9b-H), 3.44–3.86 (m, 249 H, PEG backbone, 10-H), 4.49 (t, J = 4.5 Hz, 4 H, CH_2OCO), 5.13–5.16 (m, 1.6 H, 6-H), 7.53 (d, $J_{4\text{-}3}$ = 8.0 Hz, 1.3 H, 4-H minor), 7.55 (d, $J_{4\text{-}3}$ = 8.0 Hz, 2.4 H, 4-H major), 8.10 (d, 4 H, 3-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 37.9 (C-10 minor), 38.1 (C-10 major), 39.4 (C-7 minor), 40.5 (C-7 major), 47.3 (C-9 minor), 48.2 (C-9 major), 61.6 (CH_2OH), 64.2 (CH_2OCO), 69.2 (CH_2CH_2OCO), 70.6 (PEG), 72.5 (C-12), 72.8 (C-6 major), 73.4 (C-6 minor), 80.7 (C-11), 118.3 (C-8 major), 118.9 (C-8 minor), 126.0 (C-4 major), 126.4 (C-4 minor), 129.9 (C-3), 130.2 (C-5), 145.9 (C-2), 166.1 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 1111 (C–O), 1638 (C=C Ar), 1716 (C=O), 1952 (Ar), 2242 (CN), 2880 (C–H), 3449 (OH, C≡C–H) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{114}H_{199}N_4O_{48}$ $[M + H]^+$ (n = 42) 2392.35; found 2392.28.

9e: ^1H NMR (360 MHz, $CDCl_3$): δ = 2.89–2.94 (m, 0.5 H, 7-H minor), 2.99–3.03 (m, 1.5, 7-H major), 3.16 (dd, $J_{9a\text{-}9b}$ = 12.5, $J_{9b\text{-}7}$ = 4.0 Hz, 1.5 H, 9b-H major), 3.19 (m, 1 H, 9a-H minor, 9b-H minor), 3.30 (dd, $J_{9a\text{-}7}$ = 5.5 Hz, 1.5 H, 9a-H major), 3.44–3.94 (m, 224 H, PEG backbone), 3.99 (d, $J_{10a\text{-}10b}$ = 15.5 Hz, 10a-H), 4.04 (d, 2 H, 10b-H), 4.45 (t, J = 4.5 Hz, 4 H, CH_2OCO), 5.21–5.23 (m, 1.5 H, 6-H), 7.22–7.30 (m, 4 H, 12-H, 14-H), 7.50 (d, $J_{4\text{-}3}$ = 8.0 Hz, 1 H, 4-H minor), 7.52 (d, $J_{4\text{-}3}$ = 8.0 Hz, 3 H, 4-H major), 7.65 (ddd, $J_{12\text{-}13}$ = 7.5, $J_{13\text{-}14}$ = 7.5, $J_{13\text{-}15}$ = 1.5 Hz, 2 H, 13-H), 8.09 (d, 4 H, 3-H), 8.57–8.60 (m, 2 H, 15-H) ppm. ^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 39.7 (C-7 minor), 40.5 (C-7 major), 47.9 (C-9 minor), 48.9 (C-9 major), 53.7 (C-10 minor), 54.2 (C-10 major), 61.5 (CH_2OH), 64.0 (CH_2OCO), 69.1 (CH_2CH_2OCO), 70.7 (PEG), 72.5 (C-6 major), 73.1 (C-6 minor), 118.4 (C-8 major), 119.1 (C-8 minor), 122.2 (C-12, C-14), 125.9 (C-4 major), 126.3 (C-4 minor), 129.8 (C-3, C-5), 136.7 (C-13), 146.0 (C-2), 149.0 (C-15 minor), 149.2 (C-15 major), 146.0 (C-11), 166.0 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 1113 (C–O), 1613 (C=C Ar), 1715 (C=O), 1965 (Ar), 2241 (CN), 2883 (C–H), 3500 (O–H) cm^{-1}. MS (MALDI-TOF): calcd. for $C_{120}H_{205}N_6O_{48}$ $[M + H]^+$ (n = 42) 2498.37; found 2498.32.

10a: Yield 80%. ^1H NMR (360 MHz, $CDCl_3$): δ = 2.83 (m, 1.5 H, 5_{eq}-H major), 2.95 (ddd, $J_{5ax\text{-}4ax}$ = 11.0, $J_{5ax\text{-}6ax}$ = 11.0, $J_{5ax\text{-}4eq}$ = 5.0 Hz, 0.5 H, 5_{ax}-H minor), 3.16 (dd, $J_{4ax\text{-}4eq}$ = 13.5, $J_{4ax\text{-}5eq}$ = 3.0 Hz, 1.5 H, 4_{ax}-H major), 3.25–3.91 (m, 270 H, PEG backbone, 4_{eq}-H minor, 4_{ax}-H minor, 4_{eq}-H major, 1′a-H minor), 4.03 (d, $J_{1'a\text{-}1'b}$ = 13.5 Hz, 0.5 H, 1′b-H minor), 4.04 (d, $J_{1'a\text{-}1'b}$ = 13.5 Hz, 1.5 H, 1′a-H major), 4.18 (d, 1.5 H, 1′b-H major), 4.38 (d, $J_{2ax\text{-}2eq}$ = 10.0 Hz, 1.5 H, 2_{ax}-H major), 4.45 (t, J = 4.5 Hz, 4 H, CH_2OCO), 4.51 (d, $J_{2ax\text{-}2eq}$ = 10.5 Hz, 0.5 H, 2_{ax}-H minor), 4.60 (d, 0.5 H, 2_{eq}-H minor), 4.64 (d, 0.5 H, 6_{ax}-H minor), 4.73 (d, $J_{6ax\text{-}5eq}$ = 2.5 Hz, 1.5 H, 6_{ax}-H major), 4.79 (dd, $J_{2eq\text{-}4eq(W)}$ = 1.5 Hz, 1.5 H, 2_{eq}-H major), 7.23–7.40 (m, 10 H, 2′-H, 3′-H, 4′-H, 5′-H), 7.49 (d, $J_{2''\text{-}3''}$ = 8.0 Hz, 3 H, 2′′-H major), 7.52 (d, $J_{2''\text{-}3''}$ = 8.0 Hz, 1 H, 2′′-H minor), 8.08 (d, 4 H, 3′′-H minor, 3′′-H major) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 30.2 (C-5 minor), 32.0 (C-5 major), 51.1 (C-4 major), 51.8 (C-4 minor), 55.5 (C-1′ minor), 56.5 (C-1′ major), 61.7 (CH_2OH), 64.3 (CH_2OCO), 69.3 (CH_2CH_2OCO), 70.6 (PEG), 78.2 (C-6 major), 80.2 (C-6 minor), 84.0 (C-2 minor), 85.1 (C-2 major), 117.8 (CN minor), 119,1 (CN major), 125.6 (C-2′′ major), 126.5 (C-5′ major), 127.8 (C-5′ minor), 128.6 (C-4′ major), 128.7 (C-4′ minor), 128.9 (C-3′′ major), 130.2 (C-3′′ minor), 130.2 (C-1′′), 137.1 (C-2′ minor), 137.5 (C-2′ major), 143.1 (C-4′′ minor), 143.3 (C-4′′ major), 166.1 (COO minor), 166.2 (COO major) ppm. IR (KBr): $\tilde{\nu}$ = 1112 (C–O), 1647 (C=C Ar), 1718 (C=O), 1968 (Ar), 2240 (CN), 2882 (C–H) cm^{-1}.

10b: Yield 76%. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, $J_{4'\text{-}3'}$ = 7.0 Hz), 1.29–1.39 (m, 4 H, 3′-H), 1.40–1.51 (m, 4 H, 2′-H), 2.79 (m, 2 H, 5-H), 2.82–2.94 (m, 4 H, 1′-H), 3.12 (dd, $J_{4ax\text{-}4eq}$ = 13.5, $J_{4ax\text{-}5eq}$ = 3.5 Hz, 1.4 H, 4_{ax}-H major), 3.22–3.85 (m, 256 H, PEG backbone, 4_{eq}-H minor, 4_{ax}-H minor, 4_{eq}-H major), 4.26 (d, $J_{2ax\text{-}2eq}$ = 9.5 Hz, 1.3 H, 2_{ax}-H major), 4.42 (t, J = 4.5 Hz, 4 H, CH_2OCO), 4.53 (d, $J_{2ax\text{-}2eq}$ = 10.5 Hz, 0.6 H, 2_{ax}-H minor), 4.62 (d, 0.6 H, 2_{eq}-H minor), 4.66 (d, $J_{6ax\text{-}5eq}$ = 2.0 Hz, 1.3 H, 6_{ax}-H major), 4.75 (d, 1.3 H, 2_{eq}-H major), 7.43 (d, $J_{2''\text{-}3''}$ = 8.0 Hz, 3 H, 2′′-H major), 7.46 (d, $J_{2''\text{-}3''}$ = 8.0 Hz, 1 H, 2′′-H minor), 8.04 (d, 4 H, 3′′-H minor, 3′′-H major) ppm. ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 13.9 (C-4′), 20.2 (C-3′), 30.1 (C-2′), 33.0 (C-5), 50.7 (C-4 minor), 51.9 (C-4 major), 52.0 (C-1′ major), 52.6 (C-1′ minor), 61.7 (CH_2OH), 64.2 (CH_2OCO), 69.2 (CH_2CH_2OCO), 70.6 (PEG), 78.1 (C-6 major), 80.1 (C-6 minor), 84.1 (C-2 minor), 85.0 (C-2 major), 117.8 (CN minor), 118.9 (CN major), 125.5 (C-2′′ major), 126.4 (C-2′′ minor), 130.0 (C-3′′), 130.1 (C-1′′ major), 130.7 (C-1′′ minor), 143.2 (C-4′′ minor), 143.4 (C-4′′ major), 166.0 (COO minor), 166.1 (COO major) ppm. IR (KBr): $\tilde{\nu}$ = 1114 (C–

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O), 1653 (C=C Ar), 1718 (C=O), 1967 (Ar), 2240 (CN), 2885 (C–H) cm^{-1}.

10c: Yield 64%. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.84 (m, 1.2 H, 5_{eq}-H major), 2.91 (ddd, $J_{5ax-4ax}$ = 10.0, $J_{5ax-6ax}$ = 10.0, $J_{5ax-4eq}$ = 3.5 Hz, 0.8 H, 5_{ax}-H minor), 3.19 (dd, $J_{4ax-4eq}$ = 13.5, $J_{4ax-5eq}$ = 3.5 Hz, 1.5 H, 4_{ax}-H major), 3.35–3.89 (m, 256 H, PEG backbone, 4_{eq}-H minor, 4_{ax}-H minor, 4_{eq}-H major, 1′-H), 4.36 (d, $J_{2ax-2eq}$ = 10.0 Hz, 1.3 H, 2_{ax}-H major), 4.48 (t, J = 4.5 Hz, 4 H, CH_2OCO), 4.60 (d, $J_{2ax-2eq}$ = 9.5 Hz, 0.7 H, 2_{ax}-H minor), 4.69 (dd, $J_{2eq-4eq(W)}$ = 1.5 Hz, 0.7 H, 2_{eq}-H minor), 4.73 (d, $J_{6ax-5eq}$ = 2.5 Hz, 1.3 H, 6_{ax}-H major), 4.82 (dd, $J_{2eq-4eq(W)}$ = 1.5 Hz, 1.3 H, 2_{eq}-H major), 5.25 (dd, $J_{3'e-2'}$ = 9.5, $J_{3'e-3'z}$ = 1.0 Hz, 2 H, 3′e-H), 5.35 (dd, $J_{3'z-2'}$ = 15 Hz, 2 H, 3′z-H), 5.77–5.90 (m, 2 H, 2′-H), 7.49 (d, $J_{2''-3''}$ = 8.0 Hz, 2.5 H, 2′′-H major), 7.52 (d, $J_{2''-3''}$ = 8.0 Hz, 1.5 H, 2′′-H minor), 8.09 (d, 4 H, 3′′-H minor, 3′′-H major) ppm. ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 30.2 (C-5 minor), 32.9 (C-5 major), 51.3 (C-4 major), 51.8 (C-4 minor), 54.4 (C-1′ minor), 55.4 (C-1′ major), 61.7 (CH_2OH), 64.3 (CH_2OCO), 69.2 (CH_2CH_2OCO), 70.6 (PEG), 78.1 (C-6 major), 80.0 (C-6 minor), 83.9 (C-2 minor), 84.7 (C-2 major), 118.8 (CN), 119.0 (C-3′), 125.6 (C-2′′ major), 126.5 (C-2′′ minor), 130.1 (C-3′′), 130.2 (C-1′′), 134.5 (C-2), 143.1 (C-4′′ minor), 143.3 (C-4′′ major), 166.1 (COO) ppm. IR (KBr): $\tilde{\nu}$ = 1113 (C–O), 1614 (C=C Ar), 1718 (C=O), 1969 (Ar), 2233 (CN), 2881 (C–H) cm^{-1}.

10d: Yield 75%. ^1H NMR (360 MHz, $CDCl_3$): δ = 2.35 (t, $J_{3'-1'}$ = 2.5 Hz, 1 H, 3′-H major), 2.39 (t, $J_{3'-1'}$ = 2.5 Hz, 0.5 H, 3′-H minor), 2.95 (m, 1.3 H, 5_{eq}-H major), 3.04 (ddd, $J_{5ax-4ax}$ = 11.5, $J_{5ax-6ax}$ = 10.5, $J_{5ax-4eq}$ = 4.5 Hz, 0.7 H, 5_{ax}-H minor), 3.31 (dd, $J_{4ax-4eq}$ = 13.0, $J_{4ax-5eq}$ = 3.5 Hz, 1.6 H, 4_{ax}-H major), 3.37–3.88 (m, 261 H, PEG backbone, 4_{eq}-H minor, 4_{ax}-H minor, 4_{eq}-H major, 1′-H), 4.40 (d, $J_{2ax-2eq}$ = 10.0 Hz, 1.3 H, 2_{ax}-H major), 4.49 (t, J = 4.5 Hz, 4 H, CH_2OCO), 4.53 (d, $J_{2ax-2eq}$ = 10.5 Hz, 0.7 H, 2_{ax}-H minor), 4.61 (d, 0.5 H, 6_{ax}-H minor), 4.71 (d, $J_{6ax-5eq}$ = 2.5 Hz, 1.3 H, 6_{ax}-H major), 4.77 (dd, $J_{2eq-4eq(W)}$ = 2.0 Hz, 0.6 H, 2_{eq}-H minor), 4.87 (dd, $J_{2eq-4eq(W)}$ = 1.5 Hz, 1.3 H, 2_{eq}-H major), 7.50 (d, $J_{2''-3''}$ = 8.5 Hz, 2.5 H, 2′′-H major), 7.53 (d, $J_{2''-3''}$ = 8.5 Hz, 1.5 H, 2′′-H minor), 8.11 (d, 4 H, 3′′-H minor, 3′′-H major) ppm. ^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 30.6 (C-5 minor), 33.5 (C-5 major), 40.9 (C-1′ minor), 41.8 (C-1′ major), 51.1 (C-4 major), 51.4 (C-4 minor), 61.6 (CH_2OH), 64.2 (CH_2OCO), 69.1 (CH_2CH_2OCO), 70.5 (PEG), 73.9 (C-3′ major), 74.0 (C-3′ minor), 77.7 (C-2′), 78.0 (C-6 major), 79.8 (C-6 minor), 83.7 (C-2 minor), 84.2 (C-2 major), 117.3 (CN minor), 118.5 (CN major), 125.5 (C-2′′ major), 126.4 (C-2′′ minor), 129.9 (C-3′′ major), 130.0 (C-3′′ minor), 130.2 (C-1′′), 142.7 (C-4′′ minor), 142.8 (C-4′′ major), 165.9 (COO) ppm. IR (KBr): $\tilde{\nu}$ = 1108 (C–O), 1613 (C=C Ar), 1719 (C=O), 1957 (Ar), 2242 (CN), 2870 (C–H), 3511 (C≡C–H) cm^{-1}.

10e: Yield 85%. ^1H NMR (360 MHz, $CDCl_3$): δ = 2.90 (m, 1.5 H, 5_{eq}-H major), 3.07 (ddd, $J_{5ax-4ax}$ = 10.0, $J_{5ax-6ax}$ = 10.0, $J_{5ax-4eq}$ = 5.5 Hz, 0.5 H, 5_{ax}-H minor), 3.27 (dd, $J_{4ax-4eq}$ = 13.5, $J_{4ax-5eq}$ = 3.5 Hz, 1.5 H, 4_{ax}-H major), 3.37–3.44 (m, 2 H, 4_{ax}-H minor, 4_{eq}-H minor), 3.49 (dm, 1.5 H, 4_{eq}-H major), 3.53–3.87 (m, 237 H, PEG backbone), 4.08 (d, $J_{1'a-1'b}$ = 14.0 Hz, 0.5 H, 1′a-H minor), 4.19 (d, 0.5 H, 1′b-H minor), 4.20 (d, $J_{1'a-1'b}$ = 14.0 Hz, 1.5 H, 1′a-H major), 4.26 (d, 1.5 H, 1′b-H major), 4.43 (d, $J_{2ax-2eq}$ = 9.5 Hz, 1.5 H, 2_{ax}-H major), 4.45 (t, J = 4.5 Hz, 4 H, CH_2OCO), 4.60 (d, $J_{2ax-2eq}$ = 10.5 Hz, 0.5 H, 2_{ax}-H minor), 4.62 (d, 0.5 H, 6_{ax}-H minor), 4.71 (dd, $J_{2eq-4eq(W)}$ = 1.0 Hz, 0.5 H, 2_{eq}-H minor), 4.74 (d, $J_{6ax-5eq}$ = 3.0 Hz, 1.5 H, 6_{ax}-H major), 4.86 (dd, $J_{2eq-4eq(W)}$ = 1.5 Hz, 1.5 H, 2_{eq}-H major), 7.18–7.23 (m, 2 H, 5′-H major, 5′-H minor), 7.40 (d, $J_{3'-4'}$ = 8.0 Hz, 0.5 H, 3′-H minor), 7.50 (d, $J_{2''-3''}$ = 8.5 Hz, 3 H, 2′′-H major), 7.52 (d, $J_{2''-3''}$ = 8.5 Hz, 1 H, 2′′-H minor), 7.52 (d, $J_{3'-4'}$ = 7.5 Hz, 1.5 H, 3′-H major), 7.67–7.72 (m, 2 H, 4′-H major, 4′-H minor), 8.09 (d, 1 H, 3′′-H minor), 8.10 (d, 3 H, 3′′-H major), 8.57–8.59 (m, 2 H, 6′-H minor, 6′-H major) ppm. ^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 29.8 (C-5 minor), 31.1 (C-5 major), 51.6 (C-4 minor), 51.7 (C-4 major), 57.0 (C-1′ minor), 57.8 (C-1′ major), 61.3 (CH_2OH), 64.0 (CH_2OCO), 68.9 (CH_2CH_2OCO), 70.3 (PEG), 77.7 (C-6 major), 79.8 (C-6 minor), 84.3 (C-2 minor), 84.9 (C-2 major), 117.4 (CN minor), 118.7 (CN major), 122.3 (C-5′ major), 122.5 (C-5′ minor), 122.8 (C-3′ minor), 122.9 (C-3′ major), 125.4 (C-2′′ major), 126.3 (C-2′′ minor), 129.8 (C-3′′ major), 129.9 (C-3′′ minor), 129.9 (C-1′′ major), 130.5 (C-1′′ minor), 136.6 (C-4′ major), 136.7 (C-4′ minor), 142.8 (C-4′′ minor), 143.0 (C-4′′ major), 149.3 (C-6′), 157.3 (C-2′), 165.7 (COO) ppm. IR (KBr): $\tilde{\nu}$ = 1108 (C–O), 1653 (C=C Ar), 1717 (C=O), 2240 (CN), 2876 (C–H) cm^{-1}.

General Procedure for the Synthesis of Tetrahydro-1,3-oxazines 11a–e: Compound **10** (0.68 mmol) was added to a 0.1 M solution of MeONa in MeOH (2 mL). The reaction mixture was stirred at room temperature for 3 h and a 0.1 M solution of CH_3COOH in MeOH (2 mL) was added and the mixture was stirred at room temperature for 10 min. Et_2O (25 mL) was added, under vigorous stirring, at room temperature to precipitate the PEG, which was filtered and washed with Et_2O. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography.

3-Benzyl-5-cyano-6-(4-methoxycarbonylphenyl)-tetrahydro-2*H*-1,3-oxazine (11a): Flash chromatography of the residue (AcOEt/petroleum ether, 2:8) afforded first *cis*-**11a** (160 mg, 35%) as a white solid (m.p. 144–147 °C). ^1H NMR (360 MHz, $CDCl_3$): δ = 2.84 (m, 1 H, 5-H), 3.21 (dd, $J_{4ax-4eq}$ = 12, $J_{4ax-5eq}$ = 3.0 Hz, 1 H, 4_{ax}-H), 3.52 (dm, 1 H, 4_{eq}-H), 3.94 (s, 3 H, CH_3), 4.10 (d, $J_{1'a-1'b}$ = 13.0 Hz, 1 H, 1′a-H), 4.23 (d, 1 H, 1′b-H), 4.43 (d, $J_{2ax-2eq}$ = 9.0 Hz, 1 H, 2_{ax}-H), 4.75 (d, $J_{6ax-5eq}$ = 2.5 Hz, 1 H, 6_{ax}-H), 4.84 (dd, $J_{2eq-4eq(W)}$ = 1.5 Hz, 1 H, 2_{eq}-H), 7.29–7.45 (m, 5 H, Ar′), 7.54 (d, $J_{2''-3''}$ = 8.5 Hz, 2 H, 2′′-H), 8.12 (d, 2 H, 3′′-H) ppm. ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 32.9 (C-5), 51.1 (C-4), 52.1 (CH_3), 56.4 (C-1′), 78.2 (C-6), 85.1 (C-2), 119.0 (CN), 125.5 (C-2′′), 127.5 (C-5′), 128.5 (C-4′), 128.8 (C-3′), 130.0 (C-3′′), 130.3 (C-1′′), 137.5 (C-2′), 143.1 (C-4′′), 166.7 (*C*OOMe) ppm. IR (KBr): $\tilde{\nu}$ = 1614 (C=C Ar), 1719 (C=O), 2076 (Ar), 2234 (CN), 2864 (C–H) cm^{-1}. HRMS (ESI): calcd. for $[C_{20}H_{20}N_2O_3 + Na]^+$ 359.1372; found 359.1352.

Eluted second was *trans*-**11a** (119 mg, 26%) as a colourless oil. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.97 (ddd, $J_{5ax-4ax}$ = 11.0, $J_{5ax-6ax}$ = 11.0, $J_{5ax-4eq}$ = 5.5 Hz, 1 H, 5_{ax}-H), 3.31 (dd, $J_{4ax-4eq}$ = 14.0 Hz, 1 H, 4_{ax}-H), 3.41 (ddd, $J_{4eq-2eq}$ = 1.5 Hz, 1 H, 4_{eq}-H), 3.90 (d, $J_{1'a-1'b}$ = 13.5 Hz, 1 H, 1′a-H), 3.92 (s, 3 H, CH_3), 4.04 (d, 1 H, 1′b-H), 4.52 (d, $J_{2ax-2eq}$ = 10.5 Hz, 1 H, 2_{ax}-H), 4.61 (d, 1 H, 6_{ax}-H), 4.66 (dd, 1 H, 2_{eq}-H), 7.27–7.39 (m, 5 H, Ar′), 7.53 (d, $J_{2''-3''}$ = 8.5 Hz, 2 H, 2′′-H), 8.08 (d, 2 H, 3′′-H) ppm. ^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 30.3 (C-5), 52.1 (C-4), 52.4 (CH_3), 55.7 (C-1′), 80.4 (C-6), 84.3 (C-2), 117.9 (CN), 126.7 (C-2′′), 128.0 (C-5′), 128.9 (C-4′), 129.0 (C-3′), 130.3 (C-3′′), 131.0 (C-1′′), 137.3 (C-2′), 143.2 (C-4′′), 166.7 (*C*OOMe) ppm. IR (KBr): $\tilde{\nu}$ = 1614 (C=C Ar), 1719 (C=O), 2076 (Ar), 2234 (CN), 2864 (C–H) cm^{-1}. HRMS (ESI): calcd. for $[C_{20}H_{20}N_2O_3 + H]^+$ 337.1547; found 337.1541.

3-Butyl-5-cyano-6-(4-methoxycarbonylphenyl)tetrahydro-2*H*-1,3-oxazine (11b): Flash chromatography of the residue (Et_2O/petroleum ether, 2:3 then 7:3) afforded first *cis*-**11b** (162 mg, 39%) as a white solid (m.p. 105–107 °C). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.94 (t,

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$J_{4'\text{-}3'}$ = 7.0 Hz, 3 H, 4′-H), 1.34–1.45 (m, 2 H, 3′-H), 1.46–1.58 (m, 2 H, 2′-H), 2.83 (m, 1 H, 5-H), 2.86–3.02 (m, 2 H, 1′-H), 3.18 (dd, $J_{4ax\text{-}4eq}$ = 13.0, $J_{4ax\text{-}5eq}$ = 3.5 Hz, 1 H, 4_{ax}-H), 3.53 (dm, 1 H, 4_{eq}-H), 3.92 (s, 3 H, CH_3), 4.31 (d, $J_{2ax\text{-}2eq}$ = 10.0 Hz, 1 H, 2_{ax}-H), 4.71 (d, $J_{6ax\text{-}5eq}$ = 3.0 Hz, 1 H, 6_{ax}-H), 4.82 (dd, $J_{2eq\text{-}4eq(W)}$ = 1.5 Hz, 1 H, 2_{eq}-H), 7.50 (d, $J_{2''\text{-}3''}$ = 8.5 Hz, 2 H, 2′′-H), 8.09 (d, 2 H, 3′′-H) ppm. ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 13.9 (C-4′), 20.2 (C-3′), 30.1 (C-2′), 33.1 (C-5), 52.0 (C-4, C-1′, CH_3), 78.2 (C-6), 85.0 (C-2), 118.8 (CN), 125.5 (C-2′′), 129.9 (C-3′′), 130.2 (C-1′′), 143.2 (C-4′′), 166.7 (*C*OOMe) ppm. IR (KBr): $\tilde{\nu}$ = 1613 (C=C Ar), 1716 (C=O), 1967 (Ar), 2244 (CN), 2868 (C–H) cm^{-1}. HRMS (ESI): calcd. for $[C_{17}H_{22}N_2O_3 + H]^+$ 303.1709; found 303.1703.

Eluted second was *trans*-**11b** (63 mg, 15%) as a colourless oil. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.97 (t, $J_{4'\text{-}3'}$ = 7.5 Hz, 3 H, 4′-H), 1.34–1.44 (m, 2 H, 3′-H), 1.48–1.56 (m, 2 H, 2′-H), 2.67–2.74 (m, 1 H, 1′a-H), 2.87–2.97 (m, 2 H, 5-H, 1′b-H), 3.33 (dd, $J_{4ax\text{-}4eq}$ = 13.5, $J_{4ax\text{-}5}$ = 11.5 Hz, 1 H, 4_{ax}-H), 3.47 (ddd, $J_{4eq\text{-}5}$ = 4.0, $J_{4eq\text{-}2eq(W)}$ = 1.5 Hz, 1 H, 4_{eq}-H), 3.94 (s, 3 H, CH_3), 4.48 (d, $J_{2ax\text{-}2eq}$ = 10.5 Hz, 1 H, 2_{ax}-H), 4.60 (d, $J_{6ax\text{-}5}$ = 10.0 Hz, 1 H, 6_{ax}-H), 4.69 (dd, 1 H, 2_{eq}-H), 7.53 (d, $J_{2''\text{-}3''}$ = 8.0 Hz, 2 H, 2′′-H), 8.09 (d, 2 H, 3′′-H) ppm. ^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 14.1 (C-4′), 20.4 (C-3′), 30.3 (C-2′, C-5), 50.9 (C-1′), 52.4 (CH_3), 52.8 (C-4), 80.3 (C-6), 84.3 (C-2), 118.0 (CN), 126.7 (C-2′′), 130.2 (C-3′′), 130.9 (C-1′′), 143.3 (C-4′′), 166.8 (*C*OOMe) ppm. IR (KBr): $\tilde{\nu}$ = 1613 (C=C Ar), 1716 (C=O), 1967 (Ar), 2244 (CN), 2868 (C–H) cm^{-1}. HRMS (ESI): calcd. for $[C_{17}H_{22}N_2O_3 + H]^+$ 303.1703; found 303.1697.

3-Allyl-5-cyano-6-(4-methoxycarbonylphenyl)tetrahydro-2*H*-1,3-oxazine (11c): Flash chromatography of the residue (Et_2O/petroleum ether, 3:7 then 7:3) afforded first *cis*-**11c** (171 mg, 44%) as a white solid (m.p. 121–123 °C). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.84 (m, 1 H, 5-H), 3.21 (dd, $J_{4ax\text{-}4eq}$ = 14.0, $J_{4ax\text{-}5eq}$ = 3.5 Hz, 1 H, 4_{ax}-H), 3.58 (dm, 1 H, 4_{eq}-H), 3.61 (dd, $J_{1'a\text{-}1'b}$ = 13.5, $J_{1'a\text{-}2'}$ = 6.5 Hz, 1 H, 1′a-H), 3.65 (dd, $J_{1'b\text{-}2'}$ = 6.5 Hz, 1 H, 1′b-H), 3.94 (s, 3 H, CH_3), 4.37 (d, $J_{2ax\text{-}2eq}$ = 10.0 Hz, 1 H, 2_{ax}-H), 4.73 (d, $J_{6ax\text{-}5eq}$ = 3.0 Hz, 1 H, 6_{ax}-H), 4.84 (dd, $J_{2eq\text{-}4eq(W)}$ = 2.0 Hz, 1 H, 2_{eq}-H), 5.25 (dd, $J_{3'e\text{-}2'}$ = 10.5, $J_{3'e\text{-}3'z}$ = 1.0 Hz, 1 H, 3′e-H), 5.36 (dd, $J_{3'z\text{-}2'}$ = 17.0 Hz, 1 H, 3′z-H), 5.85 (dddd, 1 H, 2′-H), 7.51 (d, $J_{2''\text{-}3''}$ = 8.0 Hz, 2 H, 2′′-H), 8.10 (d, 2 H, 3′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 33.1 (C-5), 51.5 (C-4), 52.3 (CH_3), 55.6 (C-1′), 78.4 (C-6), 84.9 (C-2), 119.0 (C-3′), 119.1 (CN), 125.7 (C-2′′), 130.2 (C-3′′), 130.5 (C-1′′), 134.6 (C-2′), 143.3 (C-4′′), 166.9 (*C*OOMe) ppm. IR (KBr): $\tilde{\nu}$ = 1645 (C=C Ar), 1715 (C=O), 1955 (Ar), 2236 (CN), 2852 (C–H) cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{18}N_2O_3 + H]^+$ 287.1396; found 287.1389.

Eluted second was *trans*-**11c** (85 mg, 22%) as a colourless oil. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.93 (ddd, $J_{5ax\text{-}4ax}$ = 11.5, $J_{5ax\text{-}6ax}$ = 10.0, $J_{5ax\text{-}4eq}$ = 4.0 Hz, 1 H, 5_{ax}-H), 3.32 (dd, $J_{4ax\text{-}4eq}$ = 13.5 Hz, 1 H, 4_{ax}-H), 3.41 (dd, $J_{1'a\text{-}1'b}$ = 13.5, $J_{1'a\text{-}2'}$ = 6.5 Hz, 1 H, 1′a-H), 3.50 (ddd, $J_{4eq\text{-}2eq(W)}$ = 1.5 Hz, 1 H, 4_{eq}-H), 3.53 (dd, $J_{1'b\text{-}2'}$ = 6.5 Hz, 1 H, 1′b-H), 3.95 (s, 3 H, CH_3), 4.51 (d, $J_{2ax\text{-}2eq}$ = 10.5 Hz, 1 H, 2_{ax}-H), 4.62 (d, 1 H, 6_{ax}-H), 4.71 (dd, 1 H, 2_{eq}-H), 5.27 (dd, $J_{3'e\text{-}2'}$ = 10.0, $J_{3'e\text{-}3'z}$ = 1.0 Hz, 1 H, 3′e-H), 5.32 (dd, $J_{3'z\text{-}2'}$ = 17.0 Hz, 1 H, 3′z-H), 5.85 (dddd, 1 H, 2′-H), 7.54 (d, $J_{2''\text{-}3''}$ = 8.5 Hz, 2 H, 2′′-H), 8.10 (d, 2 H, 3′′-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 30.3 (C-5), 51.9 (C-4), 52.4 (CH_3), 54.5 (C-1′), 80.2 (C-6), 84.0 (C-2), 117.9 (CN), 119.1 (C-3′), 126.7 (C-2′′), 130.2 (C-3′′), 130.9 (C-1′′), 134.5 (C-2′), 143.2 (C-4′′), 166.9 (*C*OOMe) ppm. IR (KBr): $\tilde{\nu}$ = 1645 (C=C Ar), 1715 (C=O), 1955 (Ar), 2236 (CN), 2852 (C–H) cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{18}N_2O_3 + H]^+$ 287.1390; found 287.1392.

5-Cyano-6-(4-methoxycarbonylphenyl)-3-propargyltetrahydro-2*H*-1,3-oxazine (11d): Flash chromatography of the residue (AcOEt/petroleum ether, 7:3) afforded first *cis*-**11d** (143 mg, 37%) as a white solid (m.p. 138–140 °C). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.31 (t, $J_{3'\text{-}1'}$ = 2.5 Hz, 1 H, 3′-H) 2.91 (m, 1 H, 5-H), 3.26 (dd, $J_{4ax\text{-}4eq}$ = 13.0, $J_{4ax\text{-}5eq}$ = 3.5 Hz, 1 H, 4_{ax}-H), 3.49 (dm, 1 H, 4_{eq}-H), 3.71 (dd, $J_{1'a\text{-}1'b}$ = 13.5 Hz, 1 H, 1′a-H), 3.80 (dd, 1 H, 1′b-H), 3.89 (s, 3 H, CH_3), 4.35 (d, $J_{2ax\text{-}2eq}$ = 9.5 Hz, 1 H, 2_{ax}-H), 4.66 (d, $J_{6ax\text{-}5eq}$ = 2.5 Hz, 1 H, 6_{ax}-H), 4.83 (dd, $J_{2eq\text{-}4eq(W)}$ = 1.5 Hz, 1 H, 2_{eq}-H), 7.46 (d, $J_{2''\text{-}3''}$ = 8.5 Hz, 2 H, 2′′-H), 8.05 (d, 2 H, 3′′-H) ppm. ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 33.8 (C-5), 42.1 (C-1′), 51.4 (C-4), 52.3 (CH_3), 73.9 (C-3′), 77.9 (C-6), 78.2 (C-2′), 84.5 (C-2), 118.7 (CN), 125.7 (C-2′′), 130.1 (C-3′′), 130.5 (C-1′′), 142.9 (C-4′′), 166.7 (*C*OOMe) ppm. IR (KBr): $\tilde{\nu}$ = 1613 (C=C Ar), 1710 (C=O), 1949 (Ar), 2240 (CN), 2836 (C–H), 3408 (C≡C–H) cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{16}N_2O_3 + Na]^+$ 307.1053; found = 307.1053.

Eluted second was *trans*-**11d** (77 mg, 20%) as a colourless oil. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.39 (t, $J_{3'\text{-}1'}$ = 2.5 Hz, 1 H, 3′-H), 3.02 (ddd, $J_{5ax\text{-}4ax}$ = 11.5, $J_{5ax\text{-}6ax}$ = 10.0, $J_{5ax\text{-}4eq}$ = 4.5 Hz, 1 H, 5_{ax}-H), 3.34 (dd, $J_{4ax\text{-}4eq}$ = 13.5 Hz, 1 H, 4_{ax}-H), 3.64 (ddd, $J_{4eq\text{-}2eq(W)}$ = 2.0 Hz, 1 H, 4_{eq}-H), 3.65 (dd, $J_{1'a\text{-}1'b}$ = 17.0 Hz, 1 H, 1′a-H), 3.70 (dd, 1 H, 1′b-H), 3.94 (s, 3 H, CH_3), 4.50 (d, $J_{2ax\text{-}2eq}$ = 10.5 Hz, 1 H, 2_{ax}-H), 4.57 (d, 1 H, 6_{ax}-H), 4.74 (dd, 1 H, 2_{eq}-H), 7.50 (d, $J_{2''\text{-}3''}$ = 8.5 Hz, 2 H, 2′′-H), 8.06 (d, 2 H, 3′′-H) ppm. ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 30.9 (C-5), 41.3 (C-1′), 51.7 (C-4), 52.4 (CH_3), 74.1 (C-3′), 79.1 (C-2′), 80.2 (C-6), 84.0 (C-2), 117.6 (CN), 126.7 (C-2′′), 130.2 (C-3′′), 131.0 (C-1′′), 142.8 (C-4′′), 166.7 (*C*OOMe) ppm. IR (KBr): $\tilde{\nu}$ = 1613 (C=C Ar), 1710 (C=O), 1949 (Ar), 2240 (CN), 2836 (C–H), 3408 (C≡C–H) cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{16}N_2O_3 + Na]^+$ 307.1053; found 307.1048.

5-Cyano-6-(4-methoxycarbonylphenyl)-3-(2-pyridylmethyl)tetrahydro-2*H*-1,3-oxazine (11e): Flash chromatography of the residue (AcOEt) afforded first *cis*-**11e** (183 mg, 40%) as a white solid (m.p. 149–151 °C). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.86 (m, 1 H, 5-H), 3.24 (dd, $J_{4ax\text{-}4eq}$ = 13.5, $J_{4ax\text{-}5eq}$ = 3.5 Hz, 1 H, 4_{ax}-H), 3.48 (dm, 1 H, 4_{eq}-H), 3.89 (s, 3 H, CH_3), 4.18 (d, $J_{1'a\text{-}1'b}$ = 14.5 Hz, 1 H, 1′a-H), 4.24 (d, 1 H, 1′b-H), 4.41 (d, $J_{2ax\text{-}2eq}$ = 10.0 Hz, 1 H, 2_{ax}-H), 4.72 (d, $J_{6ax\text{-}5eq}$ = 2.5 Hz, 1 H, 6_{ax}-H), 4.81 (dd, $J_{2eq\text{-}4eq(W)}$ = 1.5 Hz, 1 H, 2_{eq}-H), 7.18 (dd, $J_{5'\text{-}4'}$ = 7.5, $J_{5'\text{-}6'}$ = 5.0 Hz, 1 H, 5′-H), 7.49 (d, $J_{2''\text{-}3''}$ = 8.5 Hz, 2 H, 2′′-H), 7.52 (d, $J_{3'\text{-}4'}$ = 7.5 Hz, 1 H, 3′-H), 7.68 (ddd, $J_{4'\text{-}6'}$ = 1.5 Hz, 1 H, 4′-H), 8.07 (d, 2 H, 3′′-H), 8.57 (dd, 1 H, 6′-H) ppm. ^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 33.6 (C-5), 52.1 (C-4), 52.3 (CH_3), 58.2 (C-1′), 78.3 (C-6), 85.3 (C-2), 119.0 (CN), 122.7 (C-5′), 123.4 (C-3′), 125.7 (C-2′′), 130.2 (C-3′′), 130.5 (C-1′′), 137.0 (C-4′), 143.2 (C-4′′), 149.8 (C-6′), 157.6 (C-2′), 166.8 (*C*OOMe) ppm. IR (KBr): $\tilde{\nu}$ = 1614 (C=C Ar), 1720 (C=O), 1936 (Ar), 2236 (CN), 2884 (C–H) cm^{-1}. HRMS (ESI): calcd. for $[C_{19}H_{20}N_3O_3 + H]^+$ 338.1499; found 338.1495.

Eluted second was *trans*-**11e** (92 mg, 20%) as a colourless oil. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 3.05 (ddd, $J_{5ax\text{-}4ax}$ = 10.0, $J_{5ax\text{-}6ax}$ = 10.0, $J_{5ax\text{-}4eq}$ = 5.5 Hz, 1 H, 5_{ax}-H), 3.34–3.44 (m, 2 H, 4_{ax}-H, 4_{eq}-H), 3.91 (s, 3 H, CH_3), 4.08 (d, $J_{1'a\text{-}1'b}$ = 14.0 Hz, 1 H, 1′a-H), 4.19 (d, 1 H, 1′b-H), 4.60 (d, $J_{2ax\text{-}2eq}$ = 10.5 Hz, 1 H, 2_{ax}-H), 4.62 (d, 1 H, 6_{ax}-H), 4.71 (dd, $J_{2eq\text{-}4eq(W)}$ = 1 Hz, 1 H, 2_{eq}-H), 7.21 (dd, $J_{5'\text{-}4'}$ = 8.0, $J_{5'\text{-}6'}$ = 5.5 Hz, 1 H, 5′-H), 7.40 (d, $J_{3'\text{-}4'}$ = 7.5 Hz, 1 H, 3′-H), 7.52 (d, $J_{2''\text{-}3''}$ = 8.0 Hz, 2 H, 2′′-H), 7.69 (ddd, $J_{4'\text{-}6'}$ = 1.5 Hz, 1 H, 4′-H), 8.07 (d, 2 H, 3′′-H), 8.57 (dd, 1 H, 6′-H) ppm. ^{13}C NMR (90.56 MHz, $CDCl_3$): δ = 30.2 (C-5), 52.0 (C-4), 52.4 (CH_3), 57.5 (C-1′), 80.3 (C-6), 84.7 (C-2), 117.8 (CN), 122.9 (C-5′), 123.1 (C-3′), 126.7 (C-2′′), 130.2 (C-3′′), 130.9 (C-1′′), 137.1 (C-4′), 143.1 (C-4′′), 149.8 (C-6′), 157.6 (C-2′), 166.8 (*C*OOMe) ppm. IR (KBr): $\tilde{\nu}$ = 1614 (C=C Ar), 1720 (C=O), 1936 (Ar), 2236 (CN), 2884 (C–H) cm^{-1}. HRMS (ESI): calcd. for $[C_{19}H_{20}N_3O_3 + H]^+$ 338.1499; found 338.1498.

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Supporting Information (see footnote on the first page of this article): Analytical data of by-products obtained during PEG esterification, ^{1}H NMR, ^{13}C NMR and MALDI-TOF mass spectra of the prepared compounds.

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