Tetrahedron 67 (2011) 401–407

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Novel triazolyl derivatives for acidic release of amines

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ARTICLE INFO

Article history:
Received 13 October 2010
Accepted 4 November 2010
Available online 11 November 2010

Keywords:
Huisgen cycloaddition
Triazole
Acidic release
Amine
Carbamate

ABSTRACT

Triazolyl derivatives of amines were prepared using click chemistry and evaluated as releasing systems in mildly acidic environments. Triazolylcarbamates and alkylamines were obtained, depending on the reactivity of the propargylic intermediates used for the Huisgen cycloaddition. A fast hydrolysis of some derivatives in mildly acidic conditions was achieved. The relative rates were correlated to a proposed mechanism highlighting the complementary role of the triazole ring and carbocation reactivity/stability.

1. Introduction

Drug delivery systems have long been developed to offer targeted delivery of bioactive molecules for several diseases, such as cancers. The general idea is to link these biomolecules to a carrier in order to avoid off-target activity, reduce side effects, or improve solubility as well as pharmacodynamic/kinetic properties. The resulting construct must be safe and stable during biological transport, before it can be directed to specific areas, cancer cells for instance. Once the targeted area has been reached, several stimuli can be used to release the biomolecules. One possible approach is to use enzymes overexpressed at the external cellular membrane, leading to extracellular release close to the targeted cells. When small molecules are used, passive diffusion will then promote cellular internalization. In order to improve this approach, the exploitation of cellular endocytosis has been proposed to obtain release of the biomolecules inside cells, avoiding the possible efflux pumps such as the P-glycoprotein efflux. Cellular endocytosis is a natural cell mechanism where external elements like nutriments are internalized. Upon invagination, the cell membrane gives a first vesicle called endosome, with a mild acidic pH of around 6. After maturation as a lysosome, with a more acidic pH of around 4–5, the internalized elements are degraded. In the light of this, acid sensitive derivatives[1] were developed in the context of endocytosis-mediated drug delivery systems,[2] where the acidic biological environment can be exploited to obtain drug release. The first approach relies on the preparation of carriers able to transport the biomolecules in a non-covalent form. The carriers are physically modified upon acidification so that the biomolecules can be released. As an example, aminated carriers were used to obtain materials able to carry complex molecules like DNAs, forming polyplexes stabilized by electronic interactions. These constructs are designed to escape endocytosis at the endosomal stage to avoid degradation by the more acidic lysosomes.[3] Smaller bioactive molecules can be loaded in non-covalent ways in carriers like dendrimers or liposomes. These formulations are safely transported in a biological environment and after physical changes due to pH modifications during endocytosis, the drugs can be released. On the other hand, orthoesters,[4] acetals[5] or polyurethanes[6] were used as vectors that reached the lysosomal stage, before being degraded.

The other strategy for developing acid sensitive drug delivery systems is to covalently link the drug to the vector by means of an acid sensitive linker. These releasing systems exploit protonation of functional groups to produce stabilized positive species, such as carbocations after fragmentation (Scheme 1). The greater the stabilization, the faster the hydrolysis, a result that is typically obtained with trityl groups, the three phenyl rings stabilizing the tertiary carbocation. The presence of an additional electron-donating group on the aromatic ring, such as a methoxy group, can increase this stability and so the hydrolysis rate. Molecular modelling was carried out with several combinations of methyl and methoxy substituted trityl groups. A correlation was observed between the mesomeric

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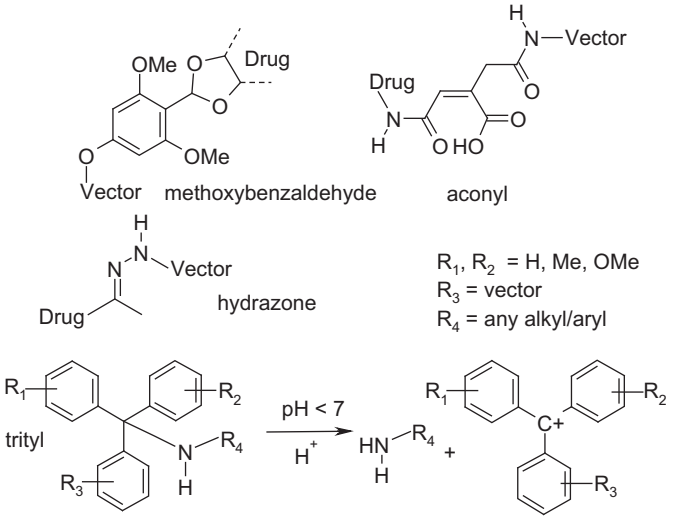
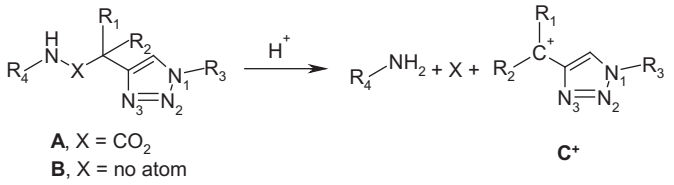
doi:10.1016/j.tet.2010.11.026

effect of the substituent and the stabilization of the resulting carbocation.[9] This acidic sensitivity has long been used for the chemistry of protecting groups, or for the development of solid supported syntheses, as exemplified by the automated peptide synthesis developed by Merrifield. The acidic conditions used to remove these protecting groups or to obtain fragmentation can be adjusted depending on the sensitivity of the starting material. Carbohydrates are commonly protected as 5-*O*-trityl ethers, or the *para*-methoxytrityl derivatives, cleavable at a less acidic pH than the corresponding benzyl or para-methoxybenzyl (PMB) groups. Using this covalent approach for drug delivery strategy requires a pH sensitive group allowing both linking to the vector and to the bioactive cargo. In this respect hydrazones,[7] benzaldehydes,[8] methoxytrityl[9] and aconyl derivatives were developed as pH sensitive linkers (Scheme 1), able to release their cargo in mildly acidic environments (pH below 5) and allowing connection to a carrier. These two parameters necessitated more or less complex syntheses of convenient linkers that are designed for one single application and may not provide high flexibility.



Scheme 1. Examples and principles for designing pH sensitive groups.

The Huisgen[10] cycloaddition of terminal alkyne and azide catalyzed by copper salts, leading to the major 1,4-triazole adduct, has recently been popularized in the concept of click chemistry.[11] Many examples using this strategy are now available in the literature and a selective [1,5] cycloadduct formation was also proposed.[12] This reaction has been used in carbohydrates chemistry,[13] polyamides[14] or new materials.[15] This reaction is most of the time only intended to obtain simple connections. However, the resulting triazole ring has sometimes been exploited to produce fluorophore,[16] to obtain proton transport[17] or for the design of alternative polyplexes.[13b] We proposed to use triazole rings obtained by click chemistry for the development of new pH sensitive systems **A** (Scheme 2) allowing at the same time the ligation to any vectors (R_4).[18] A carbamic ester was selected in this study due to the classical use of carbamates for the design of prodrugs,[19] particularly of phenolic drugs, that however can be cleaved at mildly basic pH.[20] In the case of the more nucleophilic

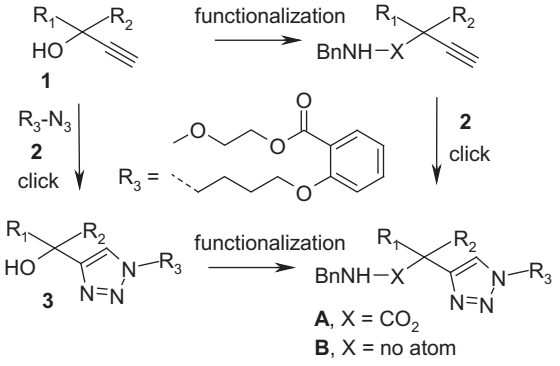


Scheme 2. Acidic release of amines from triazolyl derivatives.

aliphatic alkoxide, the equilibrated reaction is in favour of the carbamate formation.[21] The other parameter is the substitution of the amine, as N-monosubstituted carbamates are more easily cleaved by E_{1CB} mechanisms than disubstituted ones, which may be degraded slowly by other pathways, such as *N*-alkyl oxidations.[22] As a result, carbamic acid esters of aliphatic alcohols may be prone to acidic hydrolysis like the *tert*-butoxycarbonyl protecting groups.[23] Other cascade systems were also developed with carbamates based on enzymatic cleavage. In our initial work, the mild acidic hydrolysis of carbamates was validated with a *N*-benzylcarbamate bearing a dimethyltriazolylmethyl group (Scheme 2, R_1=R_2=Me, R_3=Bn, X=CO_2). An interesting sensitivity to mildly acidic conditions was observed with a fast hydrolysis obtained at pH=1 and a $t_{1/2}$=22 h was found at pH=4. This result was attributed to the presence of the two electron donating methyl groups having I^+ inductive effect of the aromatic triazole[24] group, which probably stabilizes the resulting carbocation $\mathbf{C}^+$ (Scheme 2). Although a half-life of 22 h was thought interesting for a possible application as a new protecting group for amines, this time is too long when compared to the requirement of endocytosis-mediated release, a process that is accomplished in less than 1 h. The key parameter for faster fragmentation to the intermediate carbocation $\mathbf{C}^+$ is the possibility to have better stabilizing groups for R_1 and R_2 than methyl groups. On the other hand, acid sensitive derivatives of aromatic amines were also proposed in the form of *N*-trityl protected nucleosides that may not be hydrolyzed in mildly basic conditions.[9] According to these observations it was postulated that introducing two phenyl rings (Scheme 2, R_1=R_2=Ph) instead of the two methyl groups should give a system equivalent to the trityl group used by Patel et al. An increase in hydrolysis rate should be also possible with additional electron-donating groups on the aromatic rings if necessary. Beside carbamates (Scheme 2, **A**, X=CO_2), it should be possible to prepare alkylamines (**B**, X=no atom as in scheme 2). The resulting structure may solve in an efficient way the connection to the vectors by means of click chemistry and the required mild acidic sensitivity. The other parameter for such biological applications is the stability at physiological pH (7.4) that should be validated. We report herein our results regarding the synthesis and hydrolysis rates of various dialkyltriazolyl derivatives of benzylamine (Scheme 2, R_4=Bn) as acid sensitive systems. A theoretical study is also performed by means of molecular DFT calculations in order to gain structural and mechanistic insights into acidic release of amines from these triazolyl compounds.

2. Results and discussion

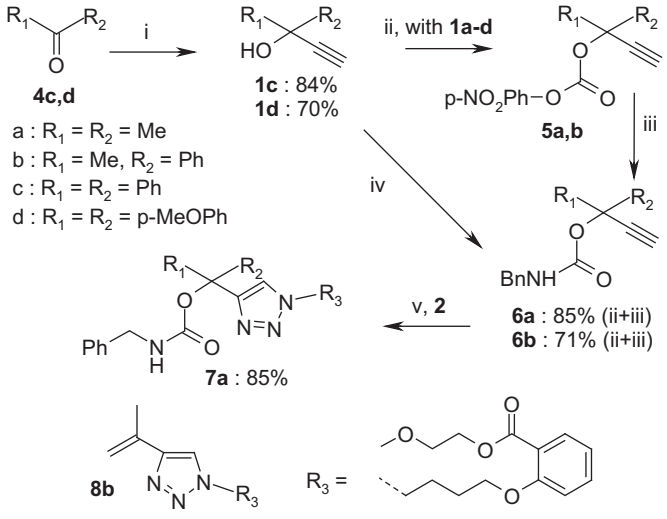
A convergent synthetic strategy (Scheme 3) was implemented for the preparation of both carbamates **A** and alkylamines **B** versions (Scheme 3, X=CO_2 or no atom as in scheme 2). Triazoles **A** were planned to be prepared by click chemistry, via access to convenient propargylic alcohols **1**. The already described vector



Scheme 3. Synthetic strategy.

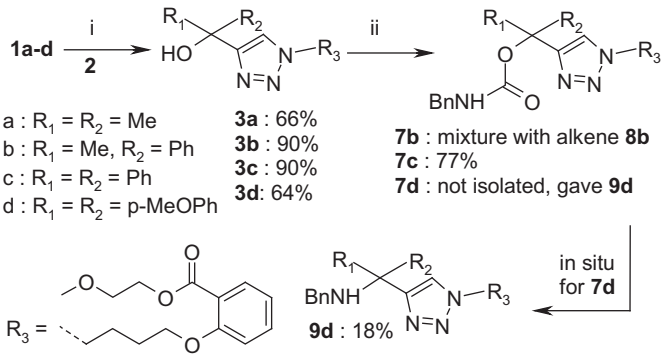
model azide **2** was used in this work for the cycloaddition.[18] Thus, according to Scheme 3, two possible paths can be investigated, with first functionalization of the propargylic alcohols **1** and then the cycloaddition, or first the cycloaddition to triazolyl alcohols **3** and then functionalization.

Disubstituted propargylalcohols **1a**,**b** (Scheme 4) are commercially available while alcohols **1c**,**d** were prepared from ketone **4c**,**d** according to a known procedure.[25] Activation of alcohol **1a** as the isolable paranitrophenylformiate **5a** and subsequent displacement by benzylamine to give carbamate **6a** has already been described. Applied to alcohol **1b** for the preparation of carbamate **6b**, this activation does not allow isolation of the formiate **5b**, that should be reacted in situ with benzylamine to give **6b** in good yield. Preparation of carbamates **6c**,**d** from alcohols **1c**,**d** with this method were unsuccessful. Alcohols **1c**,**d** being less nucleophilic than alcohols **1a**,**b**, initial deprotonation was evaluated to activate these two alcohols (NaH, THF). Alternative procedures for preparing carbamates from alcohols are known, using isocyanates[26] or by prior treatment of amines with triphosgene. Finally, the formiate and isocyanate methods were found to be equivalent for the preparation of carbamates **6a** and **6b** in similar yields, but were ineffective in our hand for the preparation of carbamate **6c**,**d**. It should be noted that only one example of *N*-alkyl-diarylpropargylcarbamate was described in the literature, with a moderate 30% yield.[27] Carbamates **6a**,**b** were then submitted to the Huisgen cycloaddition (Scheme 4) with azide **2** in pyridine and CuI as the catalyst.[18] Compound **7a** was obtained as previously described, while **6b** led to the prevalence of the elimination product **8b** due to the resulting alkene conjugation. At this stage, only triazolylcarbamate **7a** was obtained.



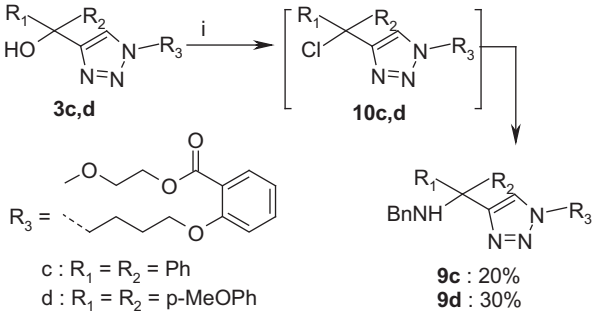
Scheme 4. Synthesis of propargyl carbamates **6**. (a) Conditions: (i) THF, Li–C≡C–TMS, −60 to −0 °C overnight; (ii) *p*-NO_2PhCOCl, NEt_3, CH_2Cl_2; (iii) Benzylamine, Pyridine, 20 °C, 24 h; (iv) $PhCH_2$–N=C=O, heptane, NEt_3 cat., reflux, 30 min; (v) CuI, pyridine, 24 h, 20 °C.

The difficulties faced for obtaining the other compounds prompted us to investigate the second path, involving prior cycloaddition between alcohols **1** and azide **2** to give alcohols **3** and subsequent functionalization (Scheme 5). Although some carbamates had already been obtained, all alcohols **3a**–**d** were prepared as references for hydrolysis experiments. The Huisgen's cycloaddition between alcohols **1** and azide **2** gave the corresponding triazolyl alcohols **3a**–**d** in good to excellent yields. Several copper catalysts have been described for this kind of reaction. The usual Sharpless conditions with $CuSO_4 \cdot 5H_2O$ and sodium ascorbate could have been used, but CuI was preferred for consistency with the other cycloadditions investigated during the course of this work. The use of tetrahydrofuran as a solvent for this reaction instead of *tert*-butanol was found more suitable for a better solubility of the reacting compounds and products.[18] Access to the missing triazolylcarbamates **7** from alcohols **3** was then evaluated. The isocyanate method gave additional compound **7c** in satisfactory yields while a mixture with alkene **8b** was again observed for **7b**. In the case of **3d**, the projected intermediate **7d** unexpectedly gave the rearranged alkylbenzylamine **9d** in moderate yield. This type of rearrangement had previously been observed during the cycloaddition of carbamate **6a** with **2** under Sharpless conditions to give **9a**.[18] The cycloadducted **7a** being stable in the Sharpless conditions, we proposed that the rearrangement should intervene during the cycloaddition. In the present reaction of compound **3d** to give **7d**, the observed rearrangement to **9d** appeared to be a new reaction, independent from the cycloaddition, and probably occurred from the heating conditions necessary for the reaction to take place, thus indicating a thermal instability of carbamate **7d**.



Scheme 5. Synthesis of carbamates **7** via alcohols **3**. (a) Conditions: (i) $CuSO_4 \cdot 5H_2O$, *t*BuOH/H_2O 1/1, 24 h, 20 °C (**3a**) or CuI, THF/H_2O 1/1, 24 h, 20 °C (**3a**–**d**); (ii) Ph–CH_2–N=C=O, heptane, NEt_3 cat., reflux, 30 min.

This work was then extended to the preparation of alkylamines **9** (Scheme 6). In this part of the synthesis, it was thought more efficient to try to directly convert alcohols **3** to amines **9**, a method that has been developed with trityl alcohols to prepare the corresponding tritylamines, and applicable to our case. The preparation of alkylamine derivatives **9** should also confirm the rearrangement of **7d** to **9d**. The already-known compound **9a** was used for hydrolysis and was not prepared in this work. Conversion of the alcohols **3c**,**d** into the never-isolated halogenated intermediates **10** was accomplished with various methods, depending on the substituents (R_1, R_2). Treatment with anhydrous HCl in ether solution was found more effective for the preparation of triazolylalkylamines **9**, alternative solutions with $SOCl_2$ being also possible. The preparation of compound **9d** from **3d** confirmed the rearrangement of **7d** to **9d**. The moderate isolated yields obtained should be considered in light of the crude ^{1}H NMR analysis of the reactions, where a 50% conversion of alcohols **3** to amines **9** was observed. The loss of compound is attributed to the separation step, these compounds having similar elution times.



Scheme 6. Synthesis of triazolylalkylamines. (a) Conditions: (i) HCl, DCM, reflux then amine, NEt_3, reflux.

Overall, this synthetic work interestingly demonstrated that the preparation of our targeted compounds was not as obvious as it first appeared. The triazolylcarbamates were prepared more easily by reaction of the corresponding isocyanates with the alcohols **3**. Low to moderate yields were obtained, that should be in part due to the reaction conditions, when heating is necessary for the reaction, while the carbamates, particularly the diphenyltriazolyl carbamates, may be sensitive and be decomposed or rearranged. The presence of a methyl and phenyl group at the same time (R_1, R_2) always led to prevalent elimination products, or at least mixtures. Triazolylalkylamines of the **9c**,**d** series were prepared from alcohols **3**, and for **9d** as a result of a rearrangement via carbamate **7d**.

The prepared carbamates **7a**,**c** and alkylamines **9a**,**c**,**d** were then submitted to mild acidic hydrolysis using a citrate buffer (pH=4) to simulate the pH of endocytosis and a TRISMA buffer (pH 7.4) to check the stability at physiological pH. Initial aqueous treatment showed incomplete starting material solubility, particularly for the phenyl derivatives, supposed to be more hydrophobic than the methyl ones. A co-solvent was used to solve this problem and acetonitrile was found better than methanol or DME (1,2-dimethoxyethane) in our case. A 20/80 ratio in CH_3CN/citrate buffer pH 4 co-system was found convenient, leading to a global buffered pH of 4.3. For the CH_3CN/TRISMA co-system the pH was 7.38. Initial measurements with ^1H NMR were possible, based on typical triazole hydrogen atom signals, clearly identified in the initial compounds and the resulting alcohols,[18] and this technique has previously been used in a similar case. However, partial precipitation occurred during hydrolysis, particularly for aromatic derivatives, and the measurements based only on solution samples were not expected to be reliable. Despite this, even in these unfavourable cases, the hydrolysis was taking place. As the hydrolysis should occur in biological medium, the high concentrations used for NMR experiments were questioned in order to avoid precipitation. The concentration of hydrolyzed products in solution was found to be around 0.1 mg/mL and HPLC provides better methods for hydrolysis rate determination. Reacting mixture were thus prepared directly in an HPLC sample vial used as reacting vessel. In order to check the retention time deviation due to buffer addition, co-injection was performed with the starting material when the hydrolysis was almost complete or higher than 50%. The time required to hydrolyze 50% of the starting material ($t_{1/2}$) is reported for each tested carbamates **7** and alkylamines **9** (Table 1). In the case of carbamate **7a** (Table 1, entry 1), hydrolysis was previously measured in a different system, with a half-life of 22 h. Using the CH_3CN/citrate buffer system, a shorter 11-h (660 min) half-life was found, showing that this different solvent system gave the same range of hydrolysis rate. The diphenylcarbamate **7c** (Table 1, entry 2) was rapidly hydrolyzed in time suited to our targeted application, highlighting the impact of the carbocation stabilization induced by the two phenyl rings.

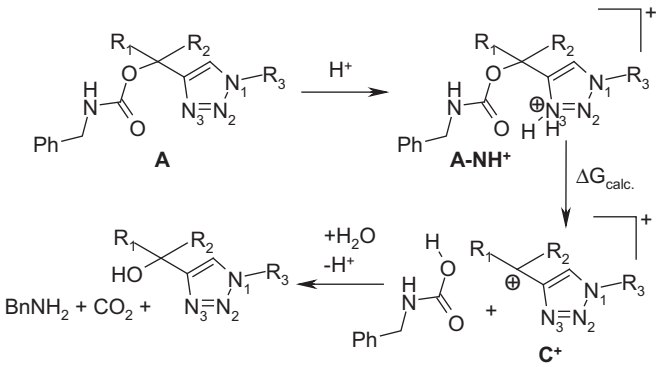
Table 1
Observed $t_{1/2}$ for available carbamates **7** and alkylamines **9**

	Compounds	R_1	R_2	$t_{1/2}$ (min)	
				pH 4.3	pH 7.4
1	**7a**	Me	Me	660	Stable
2	**7c**	Ph	Ph	4.92	Stable
3	**9a**	Me	Me	Stable	Stable
4	**9c**	Ph	Ph	9000[a]	Stable
5	**9d**	An	An	1.31	360

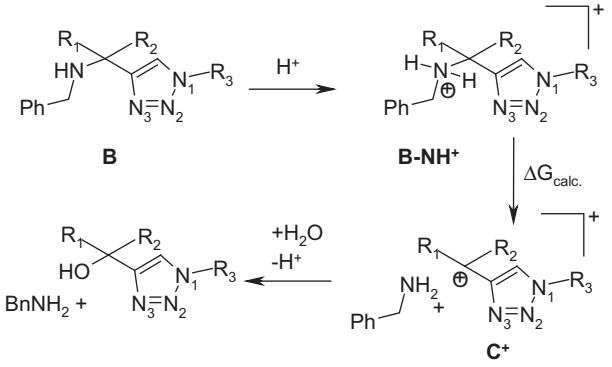
[a] Extrapolated from 11% hydrolysis at 33 h.

As regards the amines **9**, the hydrolysis rate is also dependent on the two substituents with derivative **9a** being stable, as expected (Table 1, entry 3). Aromatic derivatives with increasing stabilization gave faster hydrolysis with **9d** hydrolyzed within minutes. At physiological pH, all compounds were stable, except the amine **9d**, less stable than expected at pH=7.4. This should be related to the high stability of the dianisyltriazolyl carbocation **Cd**$^+$, where nucleophilic substitution by water (or hydroxide) can be facilitated under such conditions.

In order to rationalize these experimental kinetic data and to enlighten the hydrolysis mechanism, we have performed molecular DFT B3LYP calculations both in gas and aqueous phases (See Experimental section). Interestingly, this B3LYP-based method was validated in studies of carbamate stability,[28] triazoles protonation[29] and in the modelling of reactions with similar mechanisms.[30] Several couples of substituents R_1 and R_2 were investigated for both triazolylcarbamates and triazolylbenzylamines series, although some of the calculated compounds were not obtained (Table 1). The R_4 vector was not expected to modify the kinetics of the hydrolysis reactions and was replaced with a methyl group in our molecular models in order to reduce the computational effort. The proposed triazolylcarbamates and triazolylalkylamines hydrolysis mechanisms are depicted in Schemes 7 and 8, respectively.



Scheme 7. Proposed hydrolysis mechanism for triazolylcarbamates **A**.



Scheme 8. Proposed hydrolysis mechanism for triazolylalkylamines **B**.

The hydrolysis of **A** or **B** being expected to be mild in acidic medium, the protonation sites of **A** and **B** were first determined in order to characterize the most stable **AH**$^+$ and **BH**$^+$ compounds. Calculations were performed on all compounds of a given series (**A** and **B**) but as similar protonation energies trends were observed, only the results for R_1=R_2=Me are given for illustration in Fig. 1. Let us first start our discussion with carbamates **A**. When solvent effects were included using the SMD continuum model, similar results were obtained, so only gas phase protonation free energies are discussed. The basic nitrogen atoms N_1, N_2 and N_3 of the triazole ring, the nitrogen atom of the amine to be released and the carbonyle function of the carbamate group were possible protonation sites.

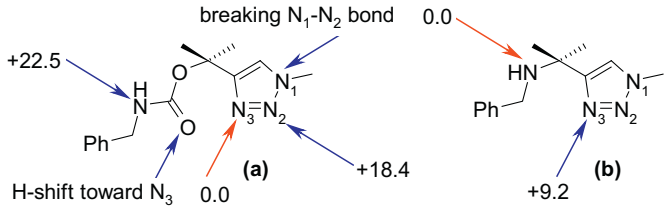


Fig. 1. Relative free energies of protonation sites (kcal/mol) at the B3LYP/6-31G(d,p) level for (a) carbamate **7a** and (b) alkylkamine **9a** models.

In these calculations, the N_3 atom of the triazole is clearly protonated first by more than 18 kcal/mol compared to the second side. This protonated species is referred to as **A-NH**$^+$. This result is in agreement with application of triazoles in proton transport[17] and reported theoretical calculations on triazole protonation.[29] Attempts to protonate the carbonyle first led to a proton migration towards the more nucleophilic N_3 atom. Thus, in an acidic medium (pH=4), the protonated carbamates have structures analogous to the one displayed in Fig. 2a (structural parameters are given in Supplementary data). It is worthwhile to note the very short distance of 1.57 Å between the N_3-proton and the oxygen atom of the carbonyle, the oxygen lone-pair and the steric effect induced by the two methyl groups favouring this short contact and structural orientation, respectively.[28] In the triazolylamines series **B**, the initial protonation of the nitrogen atom of the benzylamine can be proposed as the initial step to give an ammonium **B-NH**$^+$. To validate this proposition based on well-known alkylamines pK_a values, several protonation sites were studied in order to characterize local minima (stationary structures on the potential energy surface) and the most stable one is in all cases the secondary ammonium $-NH_2^+-$ site. To illustrate these findings, the ammonium site in **9a** is more stable by as much as 9.2 kcal/mol than the triazolyl N_3 one (Fig. 1b). Regarding the structural parameters, it must be noted that an ammonium hydrogen atom is pointing towards the nucleophilic N_3 site of the triazolyl group (See Fig. 2b). The second step of our proposed hydrolysis mechanism consists in the decomposition of the protonated species to a carbocation **C**$^+$ (see Fig. 2c). This carbocation **C**$^+$ is probably a short-lived intermediate in the aqueous medium.

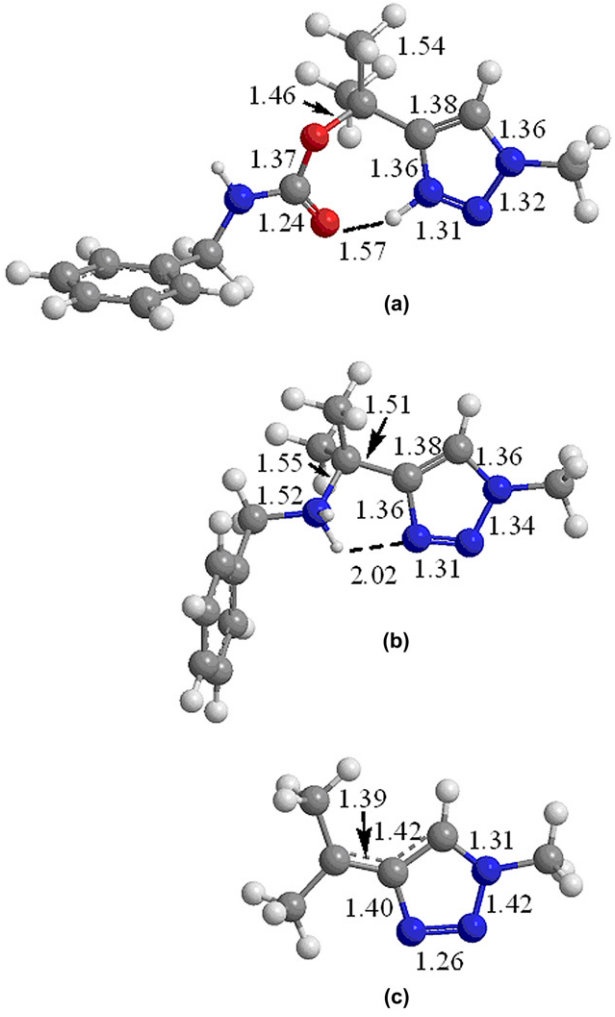


Fig. 2. Selected distances (in angstroms) for (a) Protonated carbamate **A-NH**$^+$ (**7a** model), (b) alkylamine **B-NH**$^+$ (**9a** model) and (c) triazolyl carbocation **C**$^+$ (R_1=R_2=Me) optimized structures at the B3LYP/6-31G(d,p) level.

In the carbamates series, starting from **A-NH**$^+$, a proton migration to the carbonyl group causes a carbon–ether oxygen elongation in the transition state leading to the carbocation **C**$^+$ and an unstable carbamic acid $PhCH_2NH-COOH$. In the alkylamines series, an N–C bond cleavage leads to the **C**$^+$ carbocation and the amine release. The decomposition of the intermediate **A-NH**$^+$ or **B-NH**$^+$ to carbocation **C**$^+$ and $Ph-CH_2-NH-X-H$ (X=none, CO_2) was supposed to be the rate-limiting step of the hydrolysis. The corresponding free energies ΔGs of reaction were calculated at the B3LYP/6-31G(d,p) level using the following Eq. (1):

$$\mathbf{A/B}-\mathbf{NH}^+ \rightarrow \mathrm{Bn{-}NH{-}X{-}H} + \mathbf{C}^+ \quad \Delta G_{\mathrm{water}}(\mathrm{X}=\mathrm{none},\mathrm{CO_2}) \qquad (1)$$

$$\text{with } \Delta G_{\mathrm{water}} = G(\mathrm{Bn{-}NH{-}X{-}H})_{\mathrm{water}} + G(\mathbf{C}^+)_{\mathrm{water}} - G(\mathbf{A/B}\text{-}\mathbf{NH}^+)_{\mathrm{water}}$$

To account for the medium-sensitivity of these reactions, solvent effects were included in these calculations.[25] Water solution free energies results, $\Delta G_{\mathrm{water}}$, are reported in Table 2.

Table 2
Computed water solution free energies ($\Delta G_{\mathrm{water}}$ in kcal/mol) for protonated triazolylcarbamates **A-NH**$^+$ and triazolylalkylamines **B-NH**$^+$ decomposition reactions[a]

R_1	R_2	Carbamates **A-NH**$^+$ (**7**)	Alkylamines **B-NH**$^+$ (**9**)
Me	Me	+1.4	+15.5
Me	Ph	−3.0	+10.6
Ph	Ph	−10.0	+1.3
Tol	Tol	−13.7	−2.5
An	An	−16.0	−5.9

[a] An=Anisyl=4-MeOPh; Tol=4-MePh.

In a series (carbamates **7** and alkylamines **9**), the more $\Delta G_{\mathrm{water}}$ decreases, the more stable the carbocation **C**$^+$ is. These calculations allow an evaluation of the substituent effects. As expected, the more π-donating the substituent is, the more stable the carbocation **C**$^+$ is and the more exergonic the decomposition of **A/B-NH**$^+$ is. These effects can approximately be quantified as follows: the replacement of a Me with a Ph gives a −4 to −7 kcal/mol stabilization. Then the replacement of a Ph with a tolyl and of a tolyl with a methoxyphenyl gives a −4 and a −2 to −3 kcal/mol stabilization, respectively. The calculated free energies can be satisfactorily correlated to the experimental $t_{1/2}$ hydrolysis rates in both **7** carbamates and **9** alkylamines series (see Table 1). A direct comparison may be done between the **7** and **9** series. Going from **7** to **9** series, the calculated $\Delta G_{\mathrm{water}}$ increases by 10–14 kcal/mol (+11.3 for R_2=R_3=Ph). These theoretical results corroborate the experimental kinetics ones and illustrate the better ability for carbamates **7** compared to alkylamines **9** to decompose under acidic conditions. Our proposed hydrolysis mechanisms of triazolyl derivatives are

validated. In carbamates, the triazolyl group is protonated first, followed by the concerted proton migration to carbonyl group and carbon–oxygen cleavage leading to the carbocation $\mathbf{C}^+$ and amine release. In amines, a direct amine group protonation leads to a carbon–nitrogen activation and then the release of the corresponding amines. The final formation of the alcohol from $\mathbf{C}^+$ can be the result of a E1cb or SN_2 mechanism.[31]

3. Conclusion

The synthesis of triazolyl derivatives of benzylamine has been achieved for several systems, while others have been found difficult to synthesize. Different reactivities of the intermediate substituted propargylic alcohols were outlined for the preparation of these carbamates. Two synthetic paths were investigated, one being more adapted to aliphatic propargylic alcohols and their subsequent use in click chemistry, while the second, involving click chemistry first, followed by carbamate preparation, was more convenient for general purposes. During the course of this work, a new rearrangement was discovered, confirmed by alternative synthesis as a possible preparation of amines from their corresponding isocyanates. The carbamate **7c** was found a good candidate for further development of our concept applied to nucleophilic amines like benzylamine, with a half-life of around 5 min at mildly acidic pH and a good stability at physiological pH. Interestingly, the amine **9d** was also rapidly hydrolyzed at low pH but was less stable than expected at pH=7.4. For carbamates **7**, theoretical investigations demonstrated a proton transfer from the triazol ring to the carbonyl of the carbamate group as the initial step towards hydrolysis. A balance between the carbocation stability/reactivity and the nucleophilic character of the amine explained the results observed during hydrolysis. Work is ongoing to apply these results to the release of amines in biological environments.

4. Experimental section

4.1. General

Compounds **7a** and **9a** were obtained according to previous procedures.

*4.1.1. 2-{4-[4-(1-Hydroxy-1-phenyl-ethyl)-[1,2,3]triazol-1-yl]-butoxy}-benzoic acid 2-methoxy-ethyl ester (**3b**).* To a solution of alkynol **1b** (2.41 g, 2.83 mmol) and azide **2** (1 equiv) in THF/H_2O (1/1, 80 mL) were added sodium ascorbate (95.5 mg, 0.48 mmol) and $CuSO_4 \cdot 5H_2O$ (60.5 mg, 0.24 mmol). After stirring overnight at ambient temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified (flash chromatography, silica gel, 20–50% gradient EA/PE) to provide 1.11 g (92%) of alcohol **3b** as solid (mp 60–63 °C). ^{1}H NMR (400 MHz, DMSO): δ ppm: 7.85 (s, 1H), 7.63 (dd, 1H, J=7.6, 1.6 Hz), 7.52 (ddd, 1H, J=8.0, 7.6, 2 Hz), 7.45 (m, 2H), 7.28 (m, 2H), 7.20 (m, 1H), 7.11 (d, 1H, J=8.0 Hz), 7.01 (td, 1H, J=7.6, 0.8 Hz), 5.82 (s, 1H), 4.39 (t, 2H, J=7.2 Hz), 4.30 (m, 2H), 4.04 (t, 2H, J=6.0 Hz), 3.57 (m, 2H), 3,.24 (s, 3H), 2.01 (m, 2H), 1.80 (s, 3H), 1.69 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ ppm: 165.8, 157.5, 155.0, 148.4, 133.5, 130.7, 127.1, 126.1, 125.1, 121.4, 120.15, 120.05, 113.4, 70.9, 69.7, 67.5, 63.4, 58.0, 48.9, 30.8, 26.5, 25.6; HRMS (TOF MS ES+) calcd for $[M+Na]^+$ $C_{29}H_{32}N_3O_5Na$: 462.2005, found 462.2000.

*4.1.2. 2-{4-[4-(Hydroxy-diphenyl-methyl)-[1,2,3]triazol-1-yl]-butoxy}-benzoic acid 2-methoxy-ethyl ester (**3c**).* To a solution of alkynol **1c** (2.41 g, 2.83 mmol) and azide **2** (1 equiv) in THF/H_2O (1/1, 80 mL) were added sodium ascorbate (95.5 mg, 0.48 mmol) and $CuSO_4 \cdot 5H_2O$ (60.5 mg, 0.24 mmol). After being stirring overnight at ambient temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified (flash chromatography, silica gel, 20–50% gradient EA/PE) to provide 1.11 g (92%) of alcohol **3c** as solid (mp 104–105 °C). CCM: PE/EA: 50/50 R_f=0.26; CH_2Cl_2/MeOH: 95/5 R_f=0.54; HPLC: MeOH/H_2O 70/30% (0.1% TFA), rt=4.54 min. ^{1}H NMR (400 MHz, DMSO): δ ppm: 7.85 (s, 1H), 7.64 (dd, 1H, J=7.5, 1.7 Hz), 7.51 (ddd, 1H, J=8.3, 7.5, 1.7 Hz), 7.21–7.38 (m, 10H), 7.11 (d, 1H, J=8.3 Hz), 7.01 (t, 1H, J=7.5 Hz), 6.54 (s, 1H), 4.44 (t, 2H, J=7.0 Hz), 4.30 (t, 2H, J=4.6 Hz), 4.05 (t, 2H, J=6.0 Hz), 3.57 (t, 2H, J=4.6 Hz), 3.24 (s, 3H), 2.03 (m, 2H), 1.70 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ ppm: 165.7, 157.4, 153.7, 147.0, 133.5, 130.7, 127.4, 126.9, 126.5, 123.1, 120.1, 120.0, 113.4, 75.6, 69.7, 68.5, 63.4, 57.9, 48.9, 26.5, 25.5; HRMS (TOF MS ES+) calcd for $[M+H]^+$ $C_{29}H_{32}N_3O_5$: 502.2342, found 502.2335; IR: ν cm^{-1}: 3209, 1719, 1448, 1649, 1091, 1020, 755, 702.

*4.1.3. 2-(4-{4-[Hydroxy-bis-(4-methoxy-phenyl)-methyl]-[1,2,3]triazol-1-yl}-butoxy)-benzoic acid 2-methoxy-ethyl ester (**3d**).* To a solution of alkynol **1d** (760 mg, 2.83 mmol) and azide **2** (831 mg, 2.83 mmol) in THF/H_2O (1/1, 80 mL) were added sodium ascorbate (113 mg, 0.56 mmol) and $CuSO_4 \cdot 5H_2O$ (70.8 mg, 0.28 mmol). After being stirring overnight at ambient temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified (flash chromatography, silica gel, 20–50% gradient EA/PE) to provide 1.36 g (85.5%) of **3d** as a gum. CCM: PE/EA: 50/50 R_f=0.14; CH_2Cl_2/MeOH: 95/5 R_f=0.41. ^{1}H NMR (400 MHz, DMSO): δ ppm: 7.80 (s, 1H), 7.64 (dd, 1H, J=7.4, 1.8 Hz), 7.51 (ddd, 1H, J=8.9, 7.4, 1.8 Hz), 7.23 (d, 4H, J=8.9 Hz), 7.11 (d, 1H, J=8.4 Hz), 7.00 (t, 1H, J=7.4 Hz), 6.83 (d, 4H, J=8.9 Hz), 6.31 (s, 1H), 4.43 (t, 2H, J=7.0 Hz), 4.30 (m, 2H), 4.04 (t, 2H, J=3.0 Hz), 3.57 (m, 2H), 3,.24 (s, 3H), 2.01 (m, 2H), 1.70 (m, 2H); ^{13}C NMR (100 MHz, DMSO): δ ppm: 165.7, 157.8, 157.5, 154.4, 139.6, 133.5, 130.7, 128.1, 122.8, 120.15, 120.05, 113.4, 112.7, 75.1, 69.7, 67.5, 63.4, 58.0, 54.9, 48.9, 26.5, 25.6; HRMS (TOF MS ES+) calcd for $[M+H]^+$ $C_{31}H_{36}N_3O_7$: 562.2553, found 562.2535.

*4.1.4. Benzyl-carbamic acid 1-methyl-1-phenyl-prop-2-ynyl ester (**5b**).* To a solution of 2-phenylbut-3-yn-2-ol (1 g, 6.84 mmol, 1 equiv) in 25 mL DCM were added at 0 °C 0.61 mL (7.52 mmol, 1.1 equiv) of pyridine and 1.52 g (7.52 mmol, 1.1 equiv) of *para*-nitrophenylchloroformate. The formation of a white precipitate was observed which disappeared after a few hours. After 24 h, triethylamine (2.86 mL, 20.52 mmol, 3 equiv) and benzylamine (1.49 mL, 13.68 mmol, 2 equiv) were added at 0 °C to the solution. The solution was stirred for 3 h and then diluted in diethyl ether. The solution was washed twice with $KHSO_4$ 1 M, Na_2CO_3 satd and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography using a solvent gradient from pure petroleum ether to PE/EA 4/1. The resulting carbamate was obtained in 71% yield (1.35 g) as a slightly yellowish solid. R_f (PE/EA 4/1): 0.50. ^{1}H NMR ($CDCl_3$, 400 MHz) δ=7.61 (d, 2H, J=7.7 Hz), 7.32 (m, 8H), 5.06 (t, 1H, J=6.1 Hz), 4.32 (d, 2H, J=6.4 Hz), 2.84 (s, 1H), 1.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ=176.5, 154.1, 142.5, 138.3, 128.6, 128.3, 127.8, 127.6, 127.4, 124.7, 83.5, 75.3, 44.8, 32.3; HRMS (ESI): $[M+Na]^+$ ($C_{18}H_{17}NO_2Na$) calculated: 302.11570, found: 302.1156 (0 ppm).

*4.1.5. 2-{4-[4-(Benzylcarbamoyloxy-diphenyl-methyl)-[1,2,3]triazol-1-yl]-butoxy}-benzoic acid 2-methoxy-ethyl ester (**7c**).* To a solution of alcohol **1c** (0.2 g, 0.40 mmol, 1 equiv) in heptane/THF (10/10 mL) under nitrogen atmosphere was added Et_3N (0.011 mL, 8 mg, 0.08 mmol, 0.2 equiv). The solution was heated until refluxing and benzylisocyanate was added slowly (0.074 mL, 80 mg, 0.60 mmol,

1.5 equiv). After 2 h reflux, the solution was cooled down and the solvent was removed under vacuum. The crude product was purified (flash chromatography, silica gel, PE/EA/Et_3N 95/4/1 to 30/69/1) affording the carbamate **7c** as a colourless viscous oil with traces of the starting alcohol **3c** (195 mg, 0.31 mmol, 77%). ^1H NMR (acetone-d_6, 400 MHz): δ=8.01 (s, 1H), 7.73 (dd, 1H, J=1.8, 7.7 Hz), 7.48 (m, 5H), 7.24 (m, 11H), 7.08 (d, 1H, J=8.4 Hz), 7.00 (dt, 1H, J=0.8, 7.6 Hz), 4.51 (t, 2H, J=7.1 Hz), 4.35 (m, 2H), 4.24 (d, 2H, J=6.1 Hz), 4.07 (t, 2H, J=6.1 Hz), 3.62 (m, 2H), 3.29 (s, 3H), 2.15 (m, 2H), 1.82 (m, 2H); ^{13}C NMR (acetone-d_6, 100 MHz): δ=166.8, 159.1, 155.4, 150.5, 145.7, 140.6, 134.2, 131.9, 129.1, 128.4, 128.3, 128.1, 127.9, 127.7, 125.7, 121.7, 120.9, 114.3, 83.6, 71.1, 68.7, 64.4, 58.8, 50.2, 44.9, 27.9, 26.8; HRMS (ESI): $[M+Na]^+$ ($C_{37}H_{38}N_4O_6Na$) calculated: 657.26836, found: 657.2687 (0 ppm).

*4.1.6. 2-{4-[4-(Benzylamino-diphenyl-methyl)-[1,2,3]triazol-1-yl]-butoxy}-benzoic acid 2-methoxy-ethyl ester (**9c**).* To a solution of alcohol **1c** (0.2 g, 0.40 mmol, 1 equiv) in dry DCM (10 mL) at 0 °C under nitrogen atmosphere was added a 2 M solution of HCl in Et_2O (0.239 mL, 0.48 mmol, 1.2 equiv). The solution was stirred for 1 h and Et_3N (0.122 mL, 0.089 g, 0.88 mmol, 2.2 equiv) and benzylamine (0.057 mL, 0.056 g, 0.52 mmol, 1.3 equiv) were added. After 2 h reflux, the solvent was evaporated under vacuum and the crude product was purified (flash chromatography, silica gel, PE/EA/Et_3N 80/19/1 to 30/69/1) affording the amine **9c** as a colourless viscous oil (47 mg, 0.0795 mmol, 20%). ^1H NMR (acetone-d_6, 400 MHz): δ=7.77 (s, 1H), 7.70 (dd, 1H, J=1.8, 7.7 Hz), 7.58 (m, 4H), 7.46 (ddd, 1H, J=1.8, 7.4, 8.4 Hz), 7.39 (m, 2H), 7.30 (m, 6H), 7.21 (m, 3H), 7.08 (dd, 1H, J=1.1, 8.4 Hz), 6.98 (dt, 1H, J=1.0, 7.6 Hz), 4.54 (t, 2H, J=7.1 Hz), 4.30 (m, 2H), 4.09 (t, 2H, J=6.0 Hz), 3.61 (m, 2H), 3.50 (d, 2H, J=7.2 Hz), 3.29 (s, 3H), 2.76 (br t, 1H), 2.19 (m, 2H), 1.84 (m, 2H); ^{13}C NMR (acetone-d_6, 100 MHz): δ=166.8, 159.1, 153.5, 147.0, 142.15, 134.2, 132.0, 129.1, 129.0, 128.8, 128.6, 127.5, 127.4, 124.6, 121.8, 120.9, 114.3, 71.1, 68.7, 67.0, 64.4, 58.8, 50.3, 48.8, 27.9, 26.9; HRMS (ESI): $[M+Na]^+$ ($C_{36}H_{38}N_4O_4Na$) calculated: 613.27853, found: 613.2788 (0 ppm).

*4.1.7. 2-(4-{4-[Benzylamino-bis-(4-methoxy-phenyl)-methyl]-[1,2,3]triazol-1-yl}-butoxy)-benzoic acid 2-methoxy-ethyl ester (**9d**).* To a two-neck flask solution of alcohol **1d** (0.050 g, 0.089 mmol, 1 equiv) in 2 mL dry DCM under nitrogen atmosphere was added 89 μL HCl/Et_2O 2 M (0.178 mmol, 2 equiv). The solution was refluxed for 2 h and then 37 μL Et_3N (0.267 mmol, 3 equiv) and 11 μL $BnNH_2$ (0.098 mmol, 1.1 equiv) were added. The solution was refluxed overnight. The solution was then cooled down and the solvent was evaporated under reduced pressure. The crude residue was separated by preparative chromatography on silica gel plates by slow elution with a mixture of PE/EA/Et_3N (59/39/2) affording 16 mg of the desired compound as a colourless viscous oil (0.025 mmol, 30% yield). ^1H NMR (acetone-d_6, 400 MHz): δ=7.71 (m, 2H), 7.46 (m, 5H), 7.38 (d, 2H, J=7.4 Hz), 7.28 (t, 2H, J=7.4 Hz), 7.20 (m, 1H), 7.07 (d, 1H, J=8.4 Hz), 6.98 (dt, 1H, J=0.9, 7.6 Hz), 6.84 (m, 4H), 4.53 (t, 2H, J=7.1 Hz), 4.30 (m, 2H), 4.09 (t, 2H, J=6.0 Hz), 3.76 (s, 6H), 3.61 (m, 2H), 3.51 (br s, 2H), 3.29 (s, 3H), 2.68 (br s, 1H), 2.18 (m, 2H), 1.83 (m, 2H); ^{13}C NMR (acetone-d_6, 100 MHz): δ=166.8, 159.2, 159.1, 154.2, 142.3, 139.2, 134.2, 132.1, 130.2, 129.1, 128.9, 127.4, 124.3, 121.8, 120.9, 114.3, 113.9, 71.1, 68.8, 66.0, 64.4, 58.8, 55.5, 50.3, 48.8, 27.9, 26.9; HRMS (ESI): $[M+Na]^+$ ($C_{38}H_{42}N_4O_6Na$) calculated: 673.29966, found: 673.3000 (0 ppm).

All structures were studied using the B3LYP method[32] of the density functional theory. The structures were fully optimized using the 6-31G(d,p) basis sets (B3LYP/6-31G(d,p)). In the gas phase, free energies were computed at 298.15 K without scaling vibrational frequencies. Solvent effects were calculated using the Polarizable Continuum SMD model[33] (solvent=water) as single point energy calculations at the B3LYP/6-31G(d) level on the gas phase optimized structures. All calculations were performed with the Gaussian 09 package (see Molecular modelling in Supplementary data).

Acknowledgements

We thank CNRS, ANR and Université de Poitiers for financial support and ANR (Contract to R.D.).

Supplementary data

Additional experimental procedure for compounds **1** and analytical data for all synthesized compounds, HPLC method and analysis, graphical $t_{1/2}$ determination of acidic hydrolysis of available compounds **7** and **9**, details for calculations performed with the Gaussian 09 package (energies, cartesian coordinates) and additional references. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.11.026.

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