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ARTICLE

Multicomponent, Fragment-Based, Synthesis of Polyphenol-containing Peptidomimetics and their Inhibiting Activity on Beta-Amyloid Oligomerization

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A new and concise fragment-based approach towards artificial (but "natural-based") complex polyphenols has been developed, exploiting the Ugi multicomponent reaction of phenol-containing simple substrates. The resulting library of compounds has been tested for the capacity to inhibit β-amyloid protein aggregation, as a possible strategy to develop new chemical entities to be used as a prevention or a therapy for Alzheimer's disease. Some of the members of the library have demonstrated, in Thioflavin assays, a highly promising activity in inhibiting aggregation for two β-amyloid peptides: Aβ1-42 and the truncated AβpE3-42.

Introduction

Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder. The hallmarks of AD are the extracellular plaques, derived from aggregation of β-amyloid peptides, and neurofibrillary tangles composed by hyperphosphorylated protein tau. Inhibition of β-amyloid protein aggregation represents one of the most promising targets in the development of pharmacological treatments for the prevention of Alzheimer's disease.[1-3] Moreover, substances that strongly bind to β-amyloid proteins may be very useful diagnostic tools for an early detection of this disease.[4] Among the various substances that have been found to bind to β-amyloids, natural polyphenols have emerged as a particularly promising class, being able to inhibit β-amyloid aggregation and disrupt preformed amyloid fibrils.[5-11] Hydrogen bonding, hydrophobic interactions, and aromatic stacking are suggested to be the driving forces of the anti-amyloidogenic role of polyphenols. In addition, antioxidant activity may also be involved in the anti-amyloidogenic role.[12] Figure 1 depicts some of the most active natural polyphenols.

However, these natural compounds have often poor pharmacokinetic properties. For example, pharmacokinetic results for curcumin and its metabolites suggested limited or very poor bioavailability; in particular, curcumin was present in very little amount in the cerebrospinal fluid.[13] In addition, several natural polyphenols contain a catechol or a pyrogallol type ring, making them highly susceptible to oxidation, thus strongly reducing their half-life in the body.[12, 14] Finally, chemical modifications of complex natural polyphenols is quite tricky,[15] hampering the systematic synthesis of analogues that might overcome the above quoted limitations and/or be endowed of higher potency.

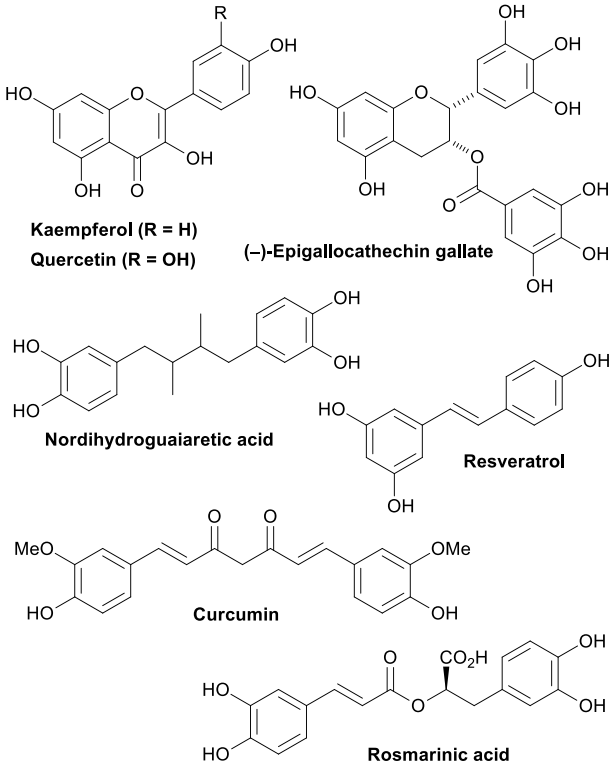

Figure 1 Some natural polyphenols with β-amyloid anti-aggregation properties.

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Therefore, we reasoned that a fragment-based synthesis of natural-derived polyphenols, obtained by joining simple, monocyclic, phenol containing, building blocks, would be a very useful tool to assembly a huge number of molecular entities, allowing: a) optimization of pharmacodynamic properties; b) optimization of pharmacokinetic properties; c) the synthesis of structures that include pharmacophores directed towards alternative AD-related targets, with the aim to develop drugs able to simultaneously interact with different targets (multi-target strategy).[15] If the synthetic sequence is smartly designed, in order to be quite short, and simple building blocks derived from renewable sources are exploited, the final optimized compounds could be easily accessible in an eco-friendly manner, thus making their potential use as nutraceutics definitely feasible.

Multicomponent reactions have emerged in the last 20 years as a powerful tool in drug discovery. They are intrinsically endowed with very high step economy and operational simplicity and are thus perfectly suited for a rapid generation of libraries characterized by several diversity inputs. Among them, the isocyanide-based Ugi reaction (U-MCR)[16] is particularly useful, since it allows the simultaneous joining of 4 diversity inputs, represented by easily accessible compounds, as isocyanides, aldehydes, primary amines and carboxylic acids. Thus, also taking advantage of our previous experience both in the Ugi reaction,[17-20] and in the assembly of natural-based polyphenols,[21] we selected U-MCR at the key step in our fragment-based approach. The classical scaffold obtained by the Ugi reaction is a peptidomimetic structure. This is another added value of our approach, since also peptidomimetics are widely studied as potential inhibitors of β-amyloid aggregation.[22]

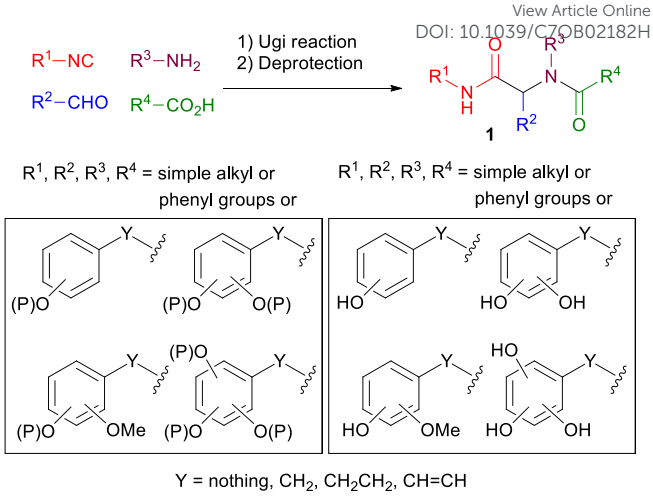
Using this synthetic methodology we were able to prepare a series of complex polyphenols containing 2 to 4 hydroxy-substituted aryl groups, most of them derived from renewable sources, and test them for their ability to inhibit *in vitro* β-amyloid aggregation. In this paper we report our preliminary observations, representing a first "proof of concept" for our approach.

Results and discussion

Synthesis

As depicted in Scheme 1, the Ugi reaction allows us to prepare a peptidomimetic structure **1** with 4 appendages. In our plan, from two to four of these appendages should contain a phenolic aryl group, tethered to the main scaffold through linkers of different lengths. In principle, our target compounds **1** could be accessed in just one step by employing, in the U-MCR, components containing the free phenols. However, preliminary investigation has shown that the presence of free phenols had a negative effect on the yield and cleanliness of the multicomponent reaction. Thus we shifted to a slightly longer (2 steps) sequence, employing suitably protected building blocks.

Many efforts were devoted to the selection of the best protecting group. Initially, because of the high atom economy



Scheme 1 General synthetic strategy

and the easiness of final deblocking, we opted for a simple acetyl group.[21] As shown in Scheme 2, a first Ugi reaction with only two phenol containing components (aniline **3**[23, 24] and aldehyde **4**[25]) worked well, affording compound **2a** in good yields. It was then smoothly deprotected by saponification to the diphenol **1a**. However, the use of the acetyl as protecting group was soon demonstrated to be far from general. For example, simply using the protected phenol containing isocyanide **5**, we failed to isolate any of the expected product **6**. Similarly, all attempted Ugi reaction using diacetyl protected caffeic acid **7** were unsuccessful. We think that the aryl acetates are somehow unstable under the Ugi reaction and that the liberated phenols and acetic acid promote unwanted side reactions. Thus, only with protected hydroxyanilines and reactive isocyanide/carboxylic acids the reaction turned out to be feasible, strongly limiting diversity exploration.

Looking for a more stable protection we shifted to the dimethyl-*tert*-butylsilyl group (TBDMS). In this case the group proved to be fully stable under the Ugi conditions. However, the reactions tend to be rather sluggish. An improvement can be obtained by preforming the imine treating the aldehyde and the amine in CH_2Cl_2 in the presence of dry $MgSO_4$. Anyway, the isolated yield, in the case of compound **11**, was only 25%. Furthermore, the presence of more than two TBDMS groups renders the Ugi products rather insoluble in most solvents making their purification, as well as the assessment of purity by NMR or HPLC, troublesome. In particular, at NMR, broad signals due to slowly converting conformers are observed. Therefore, because of the poor atom economy, the slow reaction kinetics and the unsatisfactory chemico-physical properties, we decided to abandon this protecting group as well.

Our attention was then drawn by the allyl group for its high atom economy (similar to the acetyl), its expected stability under the Ugi conditions, and the possibility to remove it under neutral conditions, thanks to palladium (0) catalysis. The Ugi reaction of substrates containing this group was thoroughly optimized. Scheme 3 shows a representative example. In particular we noticed that benzaldehydes bearing an allyloxy

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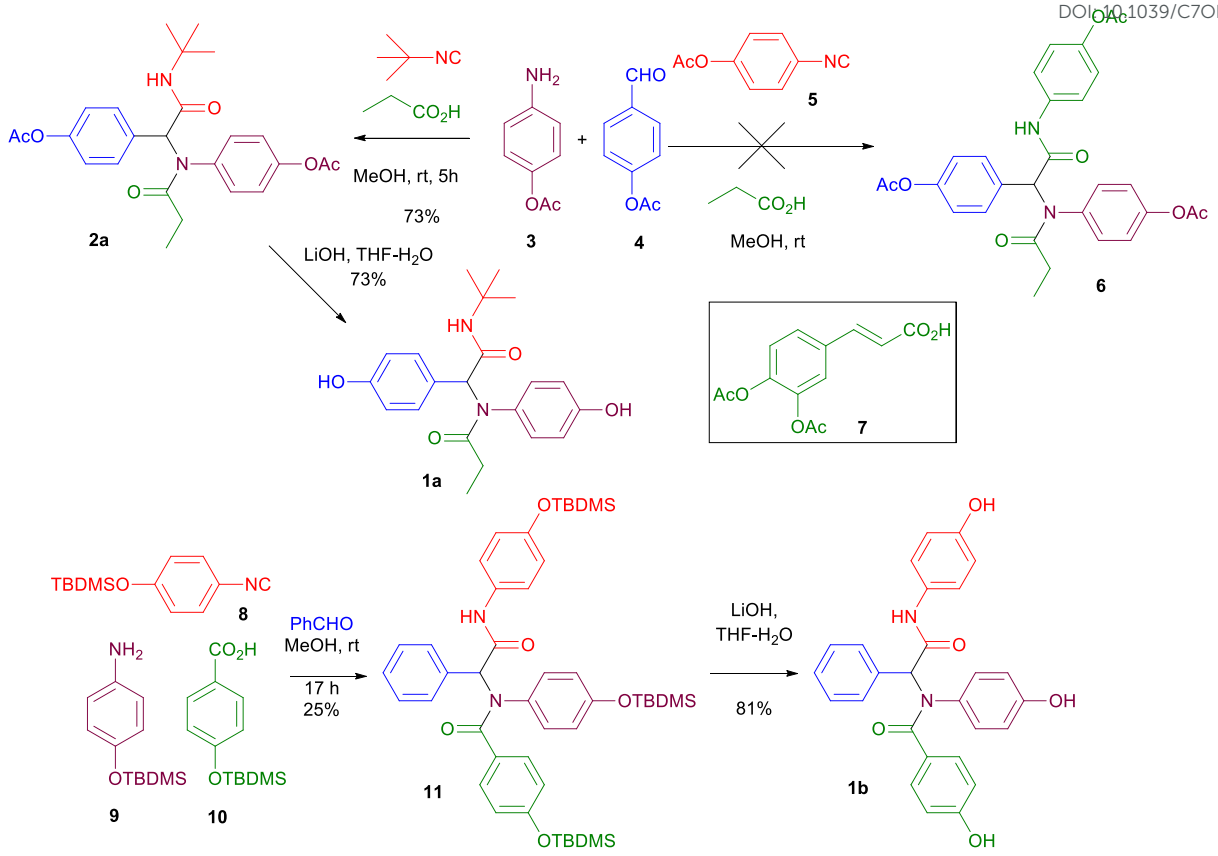

Scheme 2 Synthesis of the first polyphenols using the Ac or TBDMS protecting groups.

group in *para* position resulted less reactive (because of the electron-donating properties of allyloxy) than 4-acetoxybenzaldehyde **4** or benzaldehyde and that substituted cinnamic acids such as protected ferulic and caffeic acids also brought about a slower kinetic. We found that the best solvent, in order to have reasonable reaction times and avoid the formation of Passerini side-products, was a 1:1 mixture of EtOH and trifluoroethanol. Moreover, it was advantageous to preform the imine in this solvent for 5 h, before adding the other reagents. The reactions typically last 48-72 h.

As for the deblocking step, we tried various Pd catalysts and scavengers. Eventually, the reaction was found to be more reproducible using a palladium (II) precursor, $Pd(PPh_3)_2Cl_2$, than with $Pd(PPh_3)_4$. As scavenger, ammonium formate was the best, allowing an easy removal of its excess by a simple extraction under neutral conditions. In the case of compound **1c**, which was initially used as model, chromatographic purification, followed by treatment with active coal, worked fine, affording a very pure product (procedure A). However, in other cases, especially when a catechol or a pyrogallol moiety were present, direct chromatographic purification of the final polyphenol was not fully satisfactory, due to partial degradation. Moreover, we lost some material during the work-up of the deprotection step. To avoid these problems, we decided to react the crude polyphenols with acetic anhydride and purify, store and fully characterize them as the peracetylated derivatives **2**. Removal of the acetyl groups was then carried out only just before biophysical tests, by basic solvolysis, acid resin treatment, and filtration, avoiding extractive or chromatographic treatments, that may be troublesome, because of the polyphenol polarity and/or for the possible partial degradation. This procedure (procedure B) is exemplified in Scheme 3 for the synthesis of compound **1d**. Apart from some products synthesized in the initial part of this research, we later routinely used procedure B. In this case, full characterization was carried out only on the acetylated compounds **2**. The final phenols derived from deacetylation were pure enough for testing, as checked by ^1H NMR and HPLC (HPLC purity ≥ 96% in nearly all cases, except for **1d**, **1l** and **1m** (92%)). Procedure B is also useful in ensuring the complete removal of palladium from our polyphenols. Also when using method A, the residual content of palladium was, after chromatography, negligible. To prove this, in the case of **1c** we have tested two different samples. The first one was simply chromatographed after allyl deblocking. The second one was treated, before chromatography, with a known palladium scavenger, that is Argoresin-MP-TMT. The two samples had the same colour and gave identical results in the biophysical tests.

Scheme 4 depicts all the polyphenols **1a-q** prepared so far, whereas Table 1 reports the procedure used in each case and the yields of various steps (except for compounds **1a,b** prepared as described in Scheme 2).

Concerning the Ugi reactions, we found out that its efficiency depends on the nature of components used. For example, it worked poorer using substituted anilines than with

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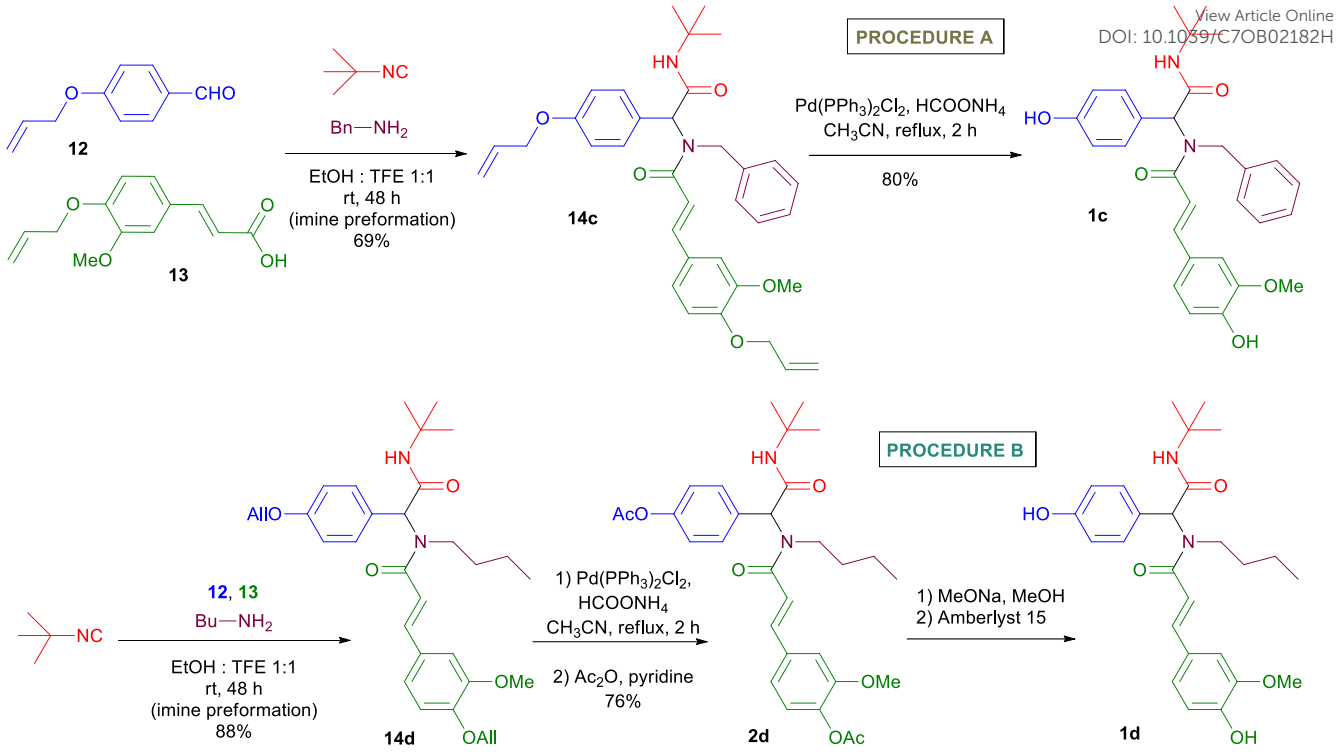

Scheme 3 Representative procedures for the preparation of polyphenols **1** via allyl ethers.

benzylamines or other aliphatic amines. Also protected ferulic and caffeic acids were somehow less reactive than simple acids like propionic acid or benzoic acids. Allyl protected substituted benzaldehydes (*p*-hydroxybenzaldehyde or vanillin) were less reactive than benzaldehyde, probably because of the electron-donating properties of the allyloxy group in *para* position. Finally, aliphatic isocyanides behaved better than the aromatic ones. In particular, during the synthesis of compound **1k**, the combination of 4-allyloxybenzaldehyde, a bulky aromatic isocyanide and an aniline led to a poor yield in the Ugi reaction (18%). In this case, we obtained a moderate improvement using 4-pivaloyloxybenzaldehyde (31%). We then used procedure B and isolated and characterized the mixed pivaloyl-acetyl compound **2k**.

Apart from the polyphenols listed in Scheme 4, other compounds targeted by us were not obtained in reasonable yields.

Table 1 Yields of polyphenol synthesis using the allyl protecting group

Entry	Polyphenol	Yield of 14	Procedure used[a]	Yield of 2	Yield of 1
1	**1c**	69%	A	-[b]	80%
2	**1d**	57% (91%)[c]	B	76%	-[c]
3	**1e**	72%	A	-[b]	59%
4	**1f**	73%	B	83%	-[d]
5	**1g**	28%	B	59%	-[d]
6	**1h**	22%	A	-[b]	74%
7	**1i**	33%	A	-[b]	68%
8	**1j**	17%	B	64%	-[d]
9	**1k**	31%[e]	B	69%	-[d]
10	**1l**	75%	B	58%	-[d]
11	**1m**	59%	B	78%	-[d]
12	**1n**	63%	B	69%	-[d]
13	**1o**	69%	B	74%	-[d]
14	**1p**	71%	B	60%	-[d]
15	**1q**	72%	B	75%	-[d]

[a] See Scheme 3 and Experimental part. [b] In procedure A, **14** was directly converted to **1**. [c] In brackets the yield calculated taking into account the recovered aldehyde. [d] In procedure B, **2** was converted quantitatively into **1** by hydrolysis of acetates. [e] In this case 4-pivaloyloxybenzaldehyde was used, and Ugi product was not **14a**, but **15** (Scheme 4).

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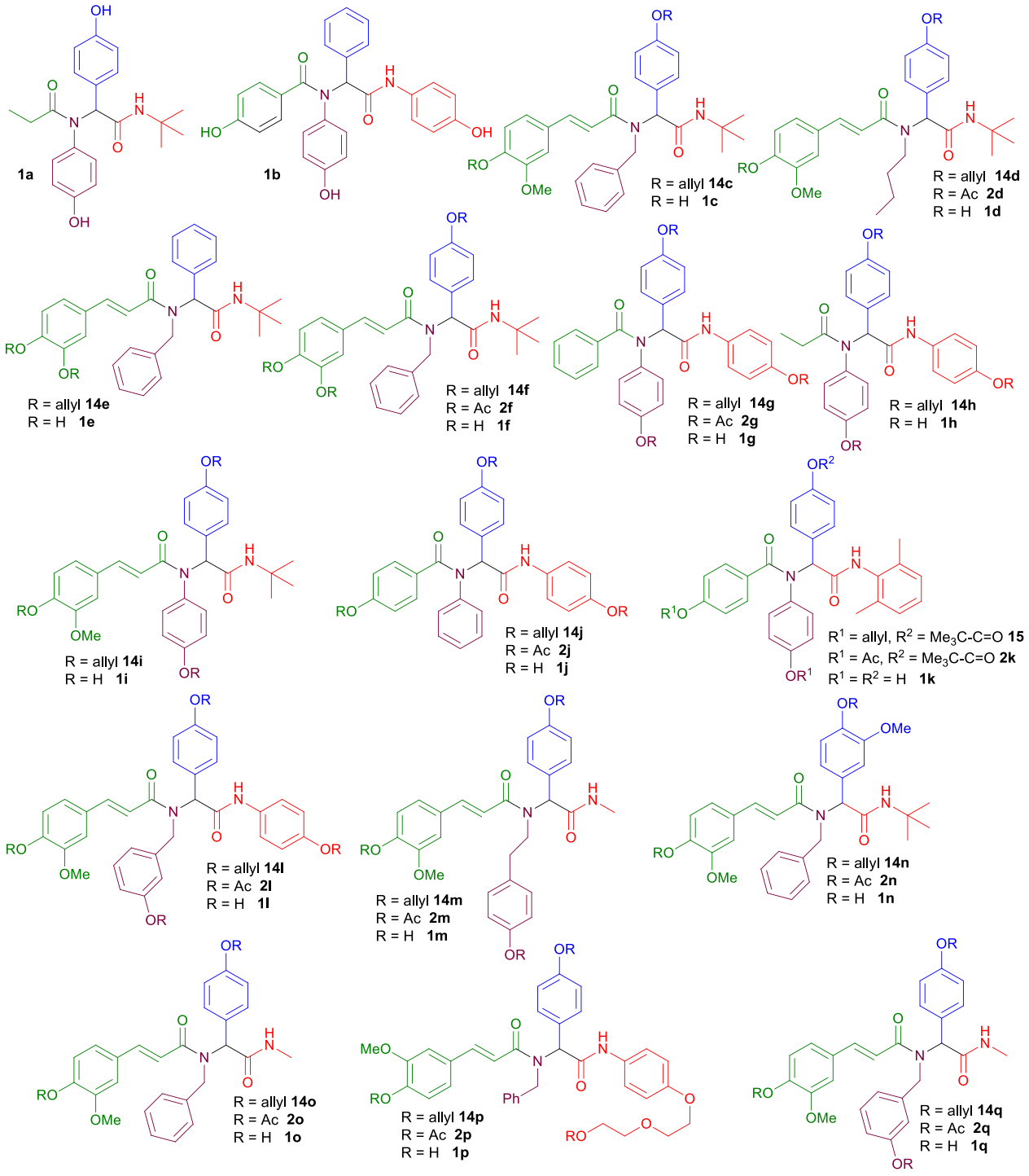

Scheme 4 Polyphenols prepared and their precursors.

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For example, although triallylated gallic acid was a good substrate for the Ugi reaction, all attempts to deprotect it without extensive decomposition were unsuccessful. Similarly, when we saturated the double bond in caffeic acid derived polyacetate **2f**, deblocking of the acetyl group led to decomposition of the final product as well. We attribute this behaviour to the presence of a catechol or pyrogallol moiety, which are prone to oxidation under basic conditions. In the case of caffeic acid adducts, the conjugation with the unsaturated amides makes the catechol less electron-rich and thus more stable to oxidation, but when the double bond is hydrogenated the catechol becomes too reactive.

Biochemical and biophysical assays

The first biophysical analysis performed on the new polyphenols was the solubility in aqueous solution because the working condition is Phosphate Buffer Solution (PBS) at pH 7.4 to mimic the physiological environment. All compounds showed complete solubility at working concentration (25 µM) in PBS containing 1% of DMSO (solubility-related data are reported in the S.I.). This percentage of DMSO does not damage cells and animals for future biological tests, and also does not alter the aggregation of β-amyloids. In any case control blank experiments with samples containing 1% DMSO in the buffer were always performed in parallel.

To investigate their ability to inhibit the amyloid aggregation, kinetics assays monitored by thioflavin-T were used to follow the formation of β-sheet rich structures, visualized then by transmission electron microscopy (TEM).[26, 27]

We explored the interaction of the new complex polyphenols with two particular β-peptides, Aβ1-42 and AβpE3-42. The full-length Aβ1-42 is one of the most abundantly identified in the brain deposits (together with Aβ1-40 and N-terminal truncated Aβ peptides). AβpE3-42 is a peptide N-terminal truncated at residue 3 (Glu) and further modified by cyclization of Glu (E) to pyroglutamic acid (pE). These structural modifications increase AβpE3-42 aggregation propensity, its resistance to degradation of proteases, and display an enhanced cytotoxicity in comparison to Aβ1-42[28, 29] as well as the ability to unfold the full-length into toxic aggregates.[30]

Before aggregation kinetics experiments, we used a natural polyphenol as a positive control to compare the efficacy of the new synthetic polyphenols. From the literature,[31] epigallocatechin gallate (EGCG) was the most potent natural polyphenol in inhibiting (*in vitro*) aggregation of β-amyloid proteins, although it was also reported that *in vivo* has a poor stability.[12] After investigating the lowest concentration at which EGCG strongly inhibited amyloid aggregation, we chose to work at 25 µM and to use this concentration also for our synthetic polyphenols.

We explored the interaction of the new complex polyphenols with Aβ1-42 and AβpE3-42 to verify their ability to inhibit β-amyloid aggregation. β-sheet content and aggregation process at 37 °C in PBS (150 mM, pH 7.4) and 1% DMSO were followed by fluorescence using Thioflavin T (ThT), a probe that detects the presence of β-sheets in the sample. Indeed, the aggregation of β-amyloids starts when they change their secondary

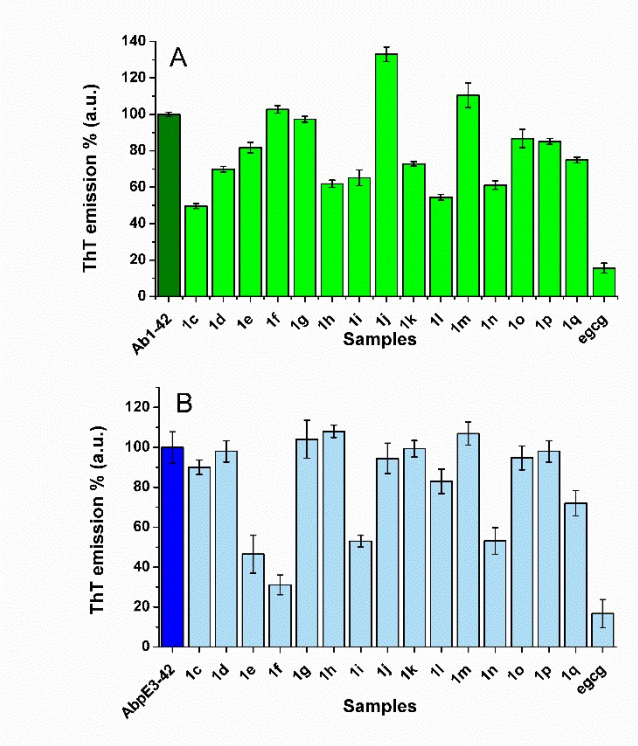

Figure 2 ThT Fluorescence in percentage respect to the control sample, after 24 h of aggregation at 37 °C, the concentration was 5 µM for β-amyloids and 25 µM for polyphenols in PBS + 1% DMSO.

structure from α-helix (in the membrane environment) or coil (in basic environment) to β-sheet conformation.[32] Then the aggregation proceeds forming small aggregates, called oligomers, until reaching larger aggregates such as long fibrils, which will later precipitate.

We used as reference Aβ1-42 and AβpE3-42 alone under the same conditions of the experiments carried out in presence of the new polyphenols. In Figure 2 it is reported, for all samples (except **1a** and **1b**), the ThT emission value after 24 h of aggregation at 37 °C. In the case of **1a** and **1b**, the first polyphenols prepared by us, we carried out the test on Aβ1-42 alone and at higher concentrations. Only **1b** showed moderate activity and we did not repeat the experiments at 25 µM. The relative data are reported in the S.I.

As we can see in panel A, all new polyphenols have some effect on Aβ1-42 aggregation. **1m**, **1f** and especially **1j** even increase the β-sheets content of the peptide, so with these compounds also the fibrils formation grows. On the contrary, the best new polyphenol to inhibit the fibrillation process is **1c**. The degree of inhibition is also quite high for **1h, 1i, 1l** and **1n**, and moderate for **1d**, **1e**, **1k, 1o**, **1p** and **1q**. However, with **1c** also the kinetic of aggregation slows down (see Figure 3).

For AβpE3-42 (Figure 2, panel B) the results were different, the best inhibitor of the aggregation process being indeed **1f**, but also **1e**, **1i** and **1n** showed a good effect. Moderate inhibition was visible for **1l** and **1q**. In both cases, epigallocatechin gallate (ECGC), the most active natural polyphenol, was still more

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effective in preventing amyloid aggregation at the same concentration. It is however worth noting that the presence of two pyrogallol moieties in ECGC make its stability under physiological conditions troublesome, whereas we have obtained a similar, albeit somehow lower, acitivity with much more stable polyphenols derived from ferulic acid[33] (**1c**, **1i**, **1n**), which are much more stable to oxidation and more promising from the pharmacokinetic point of view. Is interesting to note that for Aβ1-42 there are different polyphenols with a good anti-aggregating effect (Inhibition>30%), while for AβpE3-42, which is more prone to aggregation, more resistant to degradation and more toxic in comparison to Aβ1-42, polyphenols with a good anti-aggregating effect are fewer.

To better understand the different inhibition mechanism of the most active molecules, we determined also the aggregation kinetics curve of ThT Fluorescence emission over time for Aβ1-42 and AβpE3-42 in presence of **1c** and **1f** (Figure 3). In the case of Aβ1-42, **1c** slows down the fibril growth phase and reduces the amount of fibrils, while **1f** slows down only the lag phase, but the amount of fibrils is similar to that of Aβ1-42 alone as reported by the plateau value.

On the contrary, in the case of AβpE3-42, **1c** has almost no effect on the aggregation inhibition, while **1f** inhibits the maximum Aβ assembly. AβpE3-42 is very fast to aggregate in the initial stage: in fact, in our conditions, it is never possible to see a lag phase for this peptide. The aggregation pathway is different from that of the full-length peptide and results in the enhancement of the seed production that speeds the aggregation into more fragmented and less structured species.

We think that **1c** and **1f** act at different levels during aggregation, inhibiting the formation of different structural species. **1f** is able to inhibit the formation of oligomers that work as seed for the aggregation. In fact, it extends the lag phase in Aβ1-42 but does not inhibit the fibril formation, whereas is able to strongly reduce the AβpE3-42 aggregation.

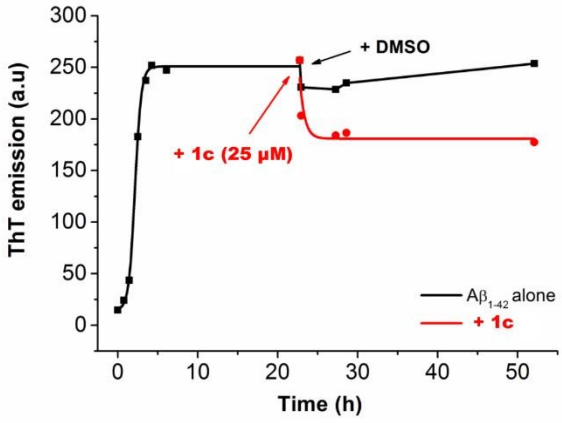

Figure 4 Effect of addition of **1c** to aggregated fibrils (Aβ1-42, monitored by ThT Fluorescence emission).

So **1f** is effective on AβpE3-42 because it inhibits the first phase of aggregation, the one forming the oligomers.

As shown in Figure 4, **1c** is even capable to disrupt fibrils, once they have formed. So, addition of **1c** after 24 h (when the aggregation process in the absence of inhibitors is already complete) provokes a significant decrease of ThT fluorescence emission.

To confirm these data, we studied the morphology of Aβ peptides aggregates in presence of those polyphenols that behaved best from ThT test. They were observed after 24 h of incubation at 37°C at the same ratio of the fluorescence experiments (Figure 5). In Figure 5, panel A, the morphology of Aβ1-42 is reported, showing typical amyloid fibrils that appear as very entangled fibril bundles and also striated ribbons are visible. When **1c** is added to Aβ1-42 (panel B), fibrils bundles decrease and the thinner fibres appear less entangled. Moreover, the fibrils are somehow fragmented, due to the twist

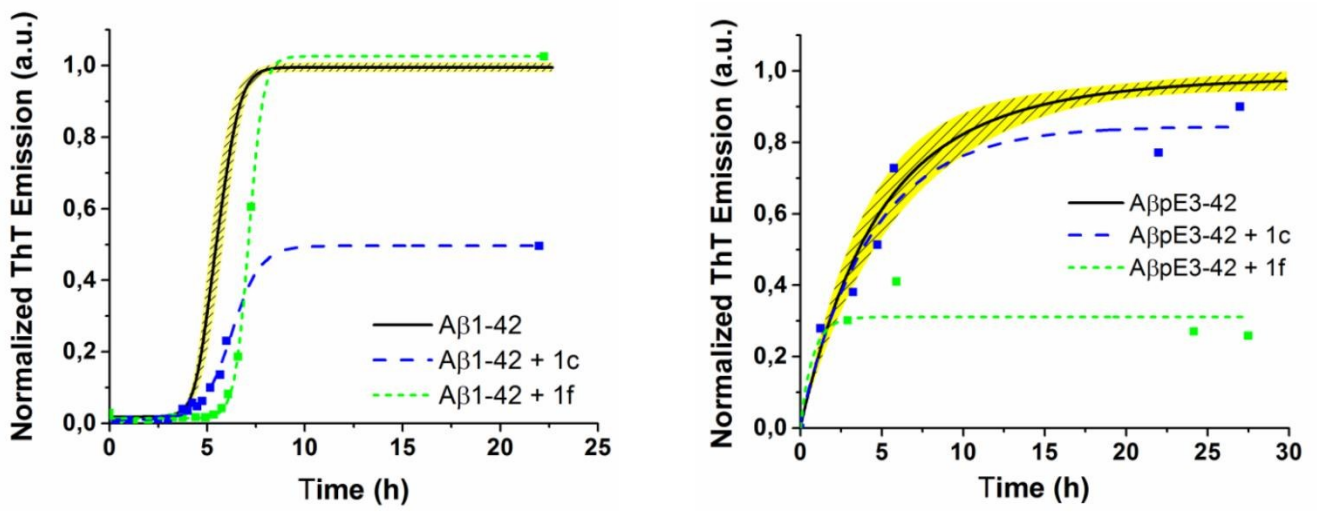

Figure 3 Kinetics of aggregation monitored by ThT Fluorescence emission. A) Kinetics curve for Aβ1-42; B) Kinetics curve for AβpE3-42. The concentration was 5 µM for Aβ peptides and 25 µM for polyphenols in PBS + 1% DMSO, in yellow are reported the standard error for the curves of Aβ alone.

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change along the fibre. When Aβ1-42 and **1f** are mixed (panel C), fibril bundles and little spheroidal aggregates appear even if the fibrils have smaller diameters than Aβ1-42 alone. The quantity of β-sheet in this sample is not different from that of full-length alone (as showed in the ThT assay). This alternative morphology depends on amyloid multi-step assembly pathways that is altered from the slowdown of the lag phase by **1f**. Looking at panel D, the morphology of AβpE3-42 is shown with few bundles and short fibrils. The addition of **1c** (panel E), results in the decrease in the amount of fibrils but the morphology is very similar to that of the AβpE3-42 alone. As a matter of fact this polyphenol is not very effective in inhibiting the assembly of the pyroglutamate β-amyloid. Finally, in the presence of **1f** (panel F), in agreement with the ThT assay, the number of fibrils and their length strongly decrease and many dispersed small spheroidal aggregates appears. Moreover, globular aggregates attached along the fibrils are visible. Also the morphology confirms the structural changes induced by the addition of the best new polyphenols.

applied. One of these was the creation of short synthetic peptides capable of binding Aβ but unable to become part of a β-sheet structure (β-sheet breaker peptides) that destabilize the amyloidogenic Aβ conformer and hence preclude amyloid formation.[36] These β-sheet breaker peptides act by the binding of the central hydrophobic region of Aβ protein (amino acids 17-21: LVFFA). Another approach was the use of polyphenolic compounds as β-sheet inhibitors. The possible mechanisms by which polyphenols destabilize β-amyloid aggregation still remain unclear, but several mechanisms have been proposed to date and structural similarities between various highly efficient inhibitors have been identified. It has become evident that the presence of phenolic rings with a few linkers and at least two hydroxy groups could favour effective non-covalent interactions with the fibril β-sheet structures and interfere with their elongation and/or assembly.[33] Both the number of hydroxy groups and the positioning of these groups on the polyphenolic structure is important, however there is no clear understanding of the link between phenol positional

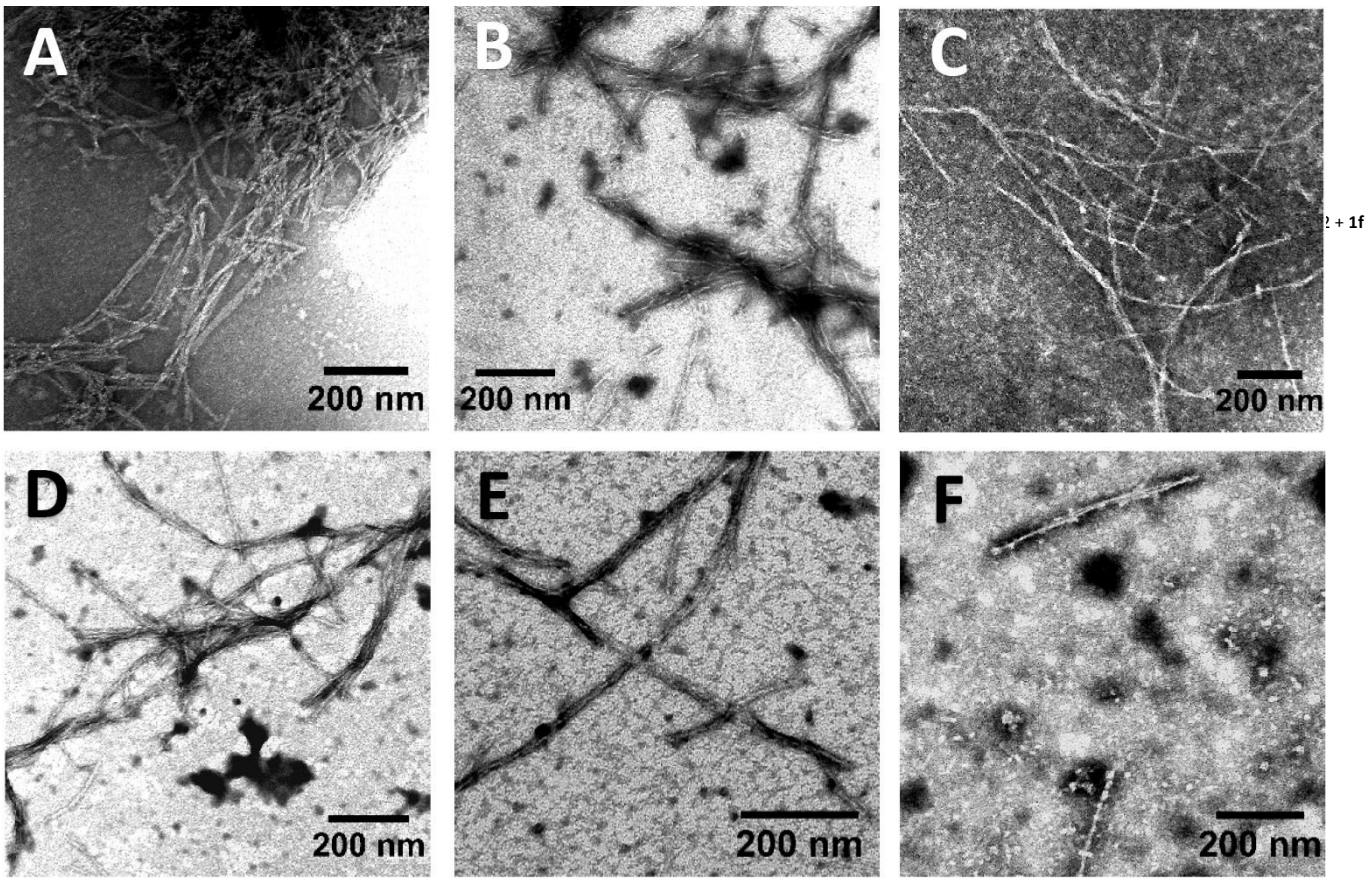

Figure 5 Morphology of the species by TEM. A) Aβ1-42 alone; B) Aβ1-42 + **1c**; C) Aβ1-42 + **1f**; D) AβpE3-42 alone; E) AβpE3-42 + **1c**; F) AβpE3-42 + **1f**

Several studies have indicated that hydrophobic forces, aromatic stacking, and electrostatic interactions stabilize the Aβ structure.[34] It was found that short fragments of Aβ (QKLVFF) self-assemble and also bind specifically to full-length peptides, supporting the hypothesis that π-π interactions may play a central role in the molecular recognition and Aβ self-assembly process.[35] In the last years, various approaches to inhibit and reverse misfolding and aggregation of β-amyloid have been

substitution and corresponding anti-aggregation activity. Moreover, the planarity of the inhibitor is essential for increasing surface contact with Aβ peptides.[5]

All of our polyphenols have a peptidomimetic structure, more than two aromatic rings essential for π–π stacking interactions with hydrophobic amino acid residues of Aβ and at least two hydroxyl groups to form hydrogen bonds with hydrophilic amino acid residues of Aβ. The resonance structure of

polyphenols provides enough planarity to penetrate the Aβ fibril hydrophobic grove, thus disturbing the fibril structure.[37]

On the basis of the results collected till now, we can try to correlate the observed activity with the various pharmacophores. As far as it concerns the groups derived from the isocyanide, it is noteworthy that the most active compounds so far have a *tert*-butyl group as the isocyanide derived one, suggesting that the presence of an aromatic ring in this position is not essential.

On the contrary, the structure of the residues derived from the carboxylic acid and the amine seems more important. Regarding the first one, best results have been obtained with cinnamic acid derivatives (caffeic and ferulic acid). For the pyroglutamate β-amyloid, we noted that polyphenols synthesized from caffeic acid (**1e** and **1f**) are able to strong inhibit aggregation, whereas among polyphenols derived from ferulic acid, only **1i** and **1n** show good activity. On the other hand, for the full-length peptide we noticed in most cases (except for **1m**) a good inhibitory effect when the starting carboxylic acid is ferulic acid. The effect is good for **1c**, **1i**, **1l**, **1n** and moderate for **1d**, **1o**, **1p** and **1q**. On the other hand, polyphenols where carboxylic acid is a benzoic acid (**1g**, **1j** an **1k**) have no or little inhibitory effect on both peptides. A propionyl group (**1h**) resulted in no effect on the truncated peptide, but in a moderate activity on the full-length one. We can conclude that ferulic acid is best for Aβ1-42, whereas as caffeic acid is the best for AβpE3-42, although, as shown by **1i** and **1n**, also ferulic acid derivatives may inhibit this peptide.

The nature of the group derived from the amine component in the Ugi seems important for both peptides. Best results have been obtained with benzylamines or anilines, whereas a drop of activity was observed in the case of **1m**, having just one more carbon atom, or for **1d**, where the benzyl/aryl group is replaced by a simple butyl. The benzyl groups seem better than the aryl ones (the most promising compounds, **1c** and **1f** have indeed a simple benzyl group), although it is remarkable that 4-hydroxyphenyl containing **1i** is more active than **1c** for the truncated peptide.

Finally, the group derived from the aldehyde has been so far less explored by us. However, in particular for the pyroglutamate β-amyloid peptide, we have noticed a remarkable influence of an additional methoxy group (compare compound **1c**, containing the 4-hydroxyphenyl group, and **1n**, containing the 4-hydroxy-3-methoxyphenyl group).

It is interesting to note that only **1n** and **1i** are able to inhibit the aggregation of both Aβ1-42 and AβpE3-42. This great variation of substituent effects on the two β-amyloid peptides likely depends on their intrinsic differences. Probably our polyphenols bind in different region of the chain by interacting with diverse residues and/or at distinct levels in the assembly mechanism that brings to the aggregation.

Conclusions

To the best of our knowledge, this paper represents one of the first report on the combinatorial synthesis of complex artificial (but "natural-based") polyphenols using a fragment-based approach and on the demonstration that some of these compounds are indeed able to inhibit or even disrupt β-amyloid aggregation. In fact, we tested the anti-aggregation activity on two different β-amyloid peptides (Aβ1-42 and AβpE3-42), normally present in AD brains, that have a different assembly pathway. For this reason, some polyphenols are more prone to inhibit the aggregation process of Aβ1-42 than that of AβpE3-42 and vice versa. This approach could allow the formulation of mixtures of active polyphenols to inhibit simultaneously the aggregation of both peptides and avoid the formation of more neurotoxic co-aggregates.

Clearly more insight into the mechanism by which our systems inhibit β-amyloid protein aggregation is needed, for example by using NMR spectroscopy or computational models. However, notwithstanding the still limited number of molecules tested, the results depicted in Figure 3 indicates that subtle variation in the structure of the appendages may have a strong impact on activity. Thus, the smart synthetic approach (based on Ugi MCR), that allows to assemble these polyphenols in 2 steps, by varying up to 4 diversity inputs, will strongly facilitate the fine tuning of the pharmacophores in order to increase potency and/or selectively target different sub-species of β-amyloid proteins. The incorporation of fragments with known anti-oxidant activity, such as ferulic acid, may have other kind of beneficial effects on AD patients, as pointed out in a recent paper.[38] Compared to the most active natural compounds (e.g. epigallocatechin gallate), our systems are expected to be metabolically much more stable (especially those, like **1c**, not containing a catechol system), thus overcoming the main drawback of some natural polyphenols and making them better suited for *in vivo* experiments, that will soon be carried out.

Experimental

NMR spectra were taken at r.t. in $CDCl_3$ or in d_6-DMSO at 300 MHz (^1H), and 75 MHz (^{13}C), using, as internal standard, TMS (^1H NMR in $CDCl_3$; 0.000 ppm) or the central peak of DMSO (^1H NMR in d_6-DMSO; 2.506 ppm) or the central peak of $CDCl_3$ (^{13}C in $CDCl_3$; 77.02 ppm), or the central peak of DMSO (^{13}C in d_6-DMSO; 39.43 ppm). Chemical shifts are reported in ppm (δ scale). Peak assignments were made with the aid of gCOSY and gHSQC experiments. In ABX system, the proton A is considered upfield and B downfield. $[\alpha]_D$values are given in 10^{-1}deg cm^2 g^{-1}. IR spectra were recorded as solid, oil, or foamy samples, with the ATR (attenuated total reflectance) technique. TLC analyses were carried out on silica gel plates and viewed at UV (λ=254 nm or 360 nm) and developed with Hanessian stain (dipping into a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL) and warming). R_f values were measured after an elution of 7–9 cm. GC-MS analysis were recorded on HP-5890 series II HEWLETT PACKARD equipped with a HP-1 column (12 m, Ø = 0.2 mm) using He as carrier gas. MS were recorded on an electronic impact (EI, 70 eV) HP-5971A detector. Chromatography condition: flow 1.0 mL/min, injector temperature 250 °C, method 1 (initial temperature 100 °C, initial time 2 min, rate 20 °C/min, final temperature 290 °C); method 2 (initial temperature 70 °C, initial time 2 min, rate 20

°C/min, final temperature 260 °C). The data are reported as follow: retention time (Rt, min), m/z values and the abundance relative. Only m/z > 5 are reported. HRMS: samples were analysed with a Synapt G2 QToF mass spectrometer. MS signals were acquired from 50 to 1200 m/z in either ESI positive or negative ionization mode. Column chromatography was done with the "flash" methodology by using 220–400 mesh silica. Petroleum ether (40–60 °C) is abbreviated as PE. All reactions employing dry solvents were carried out under nitrogen. Extractions were always repeated three times and organic extracts were always dried over Na_2SO_4 and filtered before evaporation to dryness.

Compounds **3**,[23, 24] **4**,[25] **5**,[39] **10**,[40] **12**,[41, 42] 4-allyloxybenzoic acid,[43] 4-allyloxy-3-methoxybenzaldehyde,[44] *E*-3,4-*bis*(allyloxy)phenylpropenoic acid,[45] and 4-pivaloyloxybenzaldehyde[46] were prepared by the reported methods.

Due to a tendency to partially degrade, the peptidomimetics were in most cases fully characterized and stored in the acetylated form **2** and then deprotected shortly before use through procedure B, checking the purity by ^{1}H NMR and HPLC.

4-((*tert*-Butyldimethylsilyl)oxy)aniline 9. A solution of *p*-aminophenol (1.00 g, 9.16 mmol) in dry CH_2Cl_2 (30 mL) was treated with imidazole (1.25 g, 18.3 mmol) and *tert*-butyldimethylsilyl chloride (2.07 g, 13.7 mmol). After stirring for 3 h at r.t. a purple suspension was obtained. It was treated with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. After evaporation and chromatography (PE / AcOEt 8:2), pure **9** (1.880 g, 92%) was obtained as a colorless liquid. δ_H(300 MHz, $CDCl_3$, 25 °C): 6.68-6.54 (AA'XX' system, 4 H); 3.41 (br s, 2 H), 0.97 (s, 9 H), 0.15 (s, 6 H). The other spectroscopic and analytical data were in agreement with those reported.[47]

4-((*tert*-Butyldimethylsilyl)oxy)phenyl isocyanide 8. A solution of 4-((*tert*-butyldimethylsilyl)oxy)aniline **9** (1.00 g, 4.48 mmol) in dry CH_2Cl_2 (45 mL) was treated with formic acid (203 µL, 5.38 mmol), 4-dimethylaminopyridine (DMAP) (101 mg, 0.90 mmol) and, finally, dicyclohexylcarbodiimide (DCC) (1.017 g, 4.93 mmol). After 3.5 h at r.t., the resulting suspension was treated with additional formic acid (51 µL, 1.34 mmol) and DCC (185 mg, 0.90 mmol). After further 1.5 h, the suspension was filtered through a celite cake washing with CH_2Cl_2. After evaporation and chromatography (CH_2Cl_2 / acetone 95:5), *N*-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)formamide[48] was obtained (83%). 172 mg (0.65 mmol) of this formamide was dissolved in dry CH_2Cl_2 (2.5 mL), cooled to −15 °C, and treated with Et_3N (272 µL, 1.95 mmol) and trichloromethyl chloroformate (diphosgene) (46 µL, 0.39 mmol). The temperature was allowed to reach 0°C during 1 h and the mixture further stirred for 30 min. Then, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were washed with saturated brine, evaporated and chromatographed (PE / CH_2Cl_2 70:30) to give pure **8** as a pearlaceous oil (152 mg, 95% from formamide). δ_H(300 MHz, $CDCl_3$, 25 °C): 7.25 (d, J 8.7, 2 H,); 6.81 (d, 2 H, J 8.7); 0.98 (s, 9 H), 0.21 (s, 3 H). The other spectroscopic and analytical data were in agreement with those reported.[48]

(*E*)-3-(4-(allyloxy)-3-methoxyphenyl)acrylic acid 13. A solution of *trans*-ferulic acid (6.00 g, 30.9 mmol) in dry MeCN (100 mL) was treated with K_2CO_3 (10.3 g, 74.16 mmol) and allylbromide (8.8 mL, 102 mmol). After stirring for 18 h at 70 °C, the resulting suspension was filtered through a celite cake washing with MeCN. After evaporation, the obtained allyl (*E*)-3-(4-(allyloxy)-3-methoxyphenyl)acrylate was directly dissolved in MeOH (150 mL) and treated with 1 N KOH aqueous solution (62 mL, 61.8 mmol). After stirring for 24 h at 60 °C and evaporation to reduced volume, the crude was treated with 1 N NaOH aqueous solution and extracted with AcOEt. The aqueous phase was acidified with 12 N HCl (final pH = 3) and extracted with AcOEt. The organic extracts were washed with saturated brine and evaporated. The resulting crude was triturated with Et_2O to give pure (*E*)-3-(4-(allyloxy)-3-methoxyphenyl)acrylic acid as white solid (6.65 g, 96%). The other spectroscopic and analytical data were in agreement with those reported.[45]

4-allyloxyaniline. A solution of 4-nitrophenol (5.00 g, 35.9 mmol) in dry MeCN (70 mL) was treated with K_2CO_3 (12.4 g, 89.7 mmol) and allylbromide (4.7 mL, 53.9 mmol). After stirring for 18 h at 70 °C, the resulting suspension was filtered through a celite cake washing with MeOH. After evaporation, the crude was treated with saturated aqueous NH_4Cl and extracted with Et_2O in order to completely remove the salts. The organic extracts were washed with saturated brine and evaporated. The obtained 1-(allyloxy)-4-nitrobenzene was directly dissolved in EtOH (70 mL) and treated with Fe powder (16.0 g, 287.2 mmol) and a solution of NH_4Cl (7.68 g, 143.6 mmol) in deionized H_2O (28 mL). After stirring for 18 h at 75 °C, the resulting black suspension was filtered through a celite cake washing with MeOH. After evaporation, the crude was treated with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic extracts were washed with saturated brine and evaporated. The resulting crude 4-allyloxyaniline (light brown oil) was used in the next step without further purification. δ_H(300 MHz, d6-DMSO, 25 °C): 12.23 (s, 1 H, OH); 7.52 (d, J 15.9, 1 H, ArC*H*=CH); 7.33 (d, J 2.1, 1 H, 1 H, H *ortho* to OMe); 7.18 (dd, J 8.4, 1.8, 1 H, H *para* to OMe); 6.98 (d, J 8.4, 1 H, H *meta* to OMe); 6.45 (d, J 15.9, 1 H, ArCH=C*H*); 6.04 (ddt, J 17.2, 10.6, 5.4, 1 H, C*H*=CH_2); 5.40 (dq, J 17.3, 1.6, 1 H, CH=C*H*H); 5.27 (dq, J 10.6, 1.5, 1 H, CH=C*H*H); 4.60 (dt, J 5.4, 1.5, 2 H, CH_2O); 3.82 (s, 3 H, OCH_3). The spectroscopic and analytical data were in agreement with those reported.[47]

4-allyloxyphenethylamine. A solution of tyramine (1.50 g, 11.00 mmol) in dioxane / H_2O (22 mL, 3:1) was treated at r.t. with triethylamine (1.53 mL, 11.00 mmol) and di-*tert*-butyl dicarbonate (2.40 g, 11.00 mmol). After 2 h the solution was concentrated under vacuum, and the residue was poured into a mixture of 5% aq $(NH_4)H_2PO_4$ and 1 M HCl and extracted with CH_2Cl_2. The organic extracts were washed with saturated brine and evaporated. The resulting *N*-Boc-tyramine was diluted in dry DMF (26 mL) and treated with Cs_2CO_3 (4.70 g, 14.4 mmol) and allylbromide (1.3 mL, 14.1 mmol). After stirring for 4 h at 50 °C, the mixture was poured in saturated aqueous NH_4Cl and extracted with Et_2O. The organic extracts were washed with saturated brine and evaporated. Then, the crude was dissolved in dry CH_2Cl_2 (10 mL) at 0 °C and treated with trifluoroacetic acid

(5 mL). After stirring for 3 h at r.t., the solution was evaporated to dryness, taken up with 1 M aqueous NaOH and extracted with CH_2Cl_2 to give pure 4-allyloxyphenethylamine as yellow oil (1.72 g, 88% from tyramine). R_f = 0.33 (CH_2Cl_2 /MeOH 15:1 + 1% of Et_3N). δ_H(300 MHz, $CDCl_3$, 25 °C): 7.10 (d, J 8.4, 2 H, H *meta* to OAll); 6.86 (d, J 8.4, 2 H H *ortho* to OAll); 6.05 (ddt, J 17.0, 10.6, 5.3, 1 H, C*H*=CH_2); 5.40 (dq, J 17.0, 1.5, 1 H, CH=C*H*H); 5.27 (dq, J 10.6, 1.2, 1 H, CH=C*H*H); 4.51 (dt, J 5.4, 1.2, 2 H, CH_2O); 2.92 (t, J 6.8, 2 H, CH_2N); 2.68 (t, J 6.8, 2 H, ArCH_2). δ_C(75 MHz, $CDCl_3$, 25 °C): 156.8, 133.1, 131.4, 129.4 (x2), 117.1, 114.4 (x2), 68.5, 49.3, 43.1, 38.4. IR: ν_{max}/cm^{-1} 3373, 3029, 2926, 2857, 1715, 1648, 1610, 1582, 1509, 1457, 1424, 1382, 1362, 1297, 1237, 1221, 1177, 1154, 1111, 1069, 1021, 996, 924, 818, 752, 644, 617. GC-MS (method 1) t_R 7.17 min, *m/z* (%) 148 ([M-CH_2NH_2]$^+$, 7.4), 107 (17), 91 (7.2), 79 (6.4), 78 (7.4), 77 (13), 55 (7.6), 52 (7.5), 51 (9.7), 42 (5.0), 41 (100), 39 (35). The other spectroscopic and analytical data were in agreement with those reported.[49]

3-allyloxybenzylamine. A solution of 3-allyloxybenzyl alcohol[50] (2.66 g, 16.1 mmol) in dry CH_2Cl_2 (55 mL) was cooled at −15 °C and treated with Et_3N (2.9 mL, 20.9 mmol) and mesyl chloride (1.5 mL, 19.3 mmol). After stirring for 4 h at −15 °C, the solvent was evaporated and the obtained mesylate was directly dissolved in dry DMF (23 mL) and treated NaN_3 (2.30 g, 33.8 mmol). After stirring for 3 days at r.t., the mixture was poured in H_2O and extracted with Et_2O. The organic extracts were washed with saturated brine (× 5) and evaporated. The crude was purified by chromatography (PE / CH_2Cl_2 from 8:2 to 7:3) to give pure 3-allyloxybenzyl azide as pale yellow oil (2.63 g, 86% from 3-allyloxybenzyl alcohol). R_f = 0.29 (PE / CH_2Cl_2 8:2). δ_H(300 MHz, $CDCl_3$, 25 °C): 7.29 (mc) (1 H, m, Ar*CH*); 6.93-6.86 (3 H, m, Ar*CH*); 6.06 (1 H, ddt, J 10.5, 17.2, 5.3 (t), C*H*=CH_2); 5.42 (1 H, dq, J 17.2(d), 1.5 (q), CH=C*H*H); 5.30 (1 H, dq, J 10.5 (d), 1.5 (q), CH=C*H*H); 4.55 (2 H, dt, J 5.3 (d), 1.5 (t), CH_2CH=CH_2); 4.30 (2 H, s, CH_2N_3). δ_C (75 MHz, $CDCl_3$, 25 °C): 158.9, 136.9 (arom. quat.), 133.1 (*C*H=CH_2), 129.9, 120.6, 114.6, 114.5 (Ar*C*H), 117.8 (CH=*C*H_2), 68.8 (*C*H_2O), 54.7 (*C*H_2N). IR: ν_{max}/cm^{-1} 3064, 2925, 2870, 2094, 1649, 1599, 1586, 1489, 1448, 1424, 1342, 1263, 1157, 1098, 1027, 994, 927, 878, 854, 783, 762, 695, 650. GC-MS (method 1) t_R 5.02 min, *m/z* (%) 189 (1.2) [M]$^+$, 120 (5.5), 92 (6.2), 91 (6.7), 79 (5.5), 78 (9.2), 77 (8.1), 65 (20), 64 (6.8), 63 (10), 51 (9.5), 50 (6.2), 41 (100), 39 (46), 38 (7.0). A solution of this azide (2.63 g, 13.9 mmol) in dry DMF (40 mL) cooled to 0 °C was treated with PMe_3 (1 M in toluene, 15.3 mL, 15.3 mmol). When the gas evolution ceased, the mixture was warmed up to r.t. and stirred for 2 h. Then H_2O (1 mL, 55.6 mmol) was added and the reaction was further stirred for 2 h at r.t. After evaporation, the mixture was treated with saturated aqueous Na_2CO_3 and extracted with AcOEt. The organic extracts were washed with saturated brine and evaporated to give crude 3-allyloxybenzylamine, that was not purified, but used as such for the Ugi reaction. It was just controlled at ^{1}H NMR, that showed a purity > 95%. δ_H(300 MHz, $CDCl_3$, 25 °C): 7.24 (1 H, t, J 8.1); 6.92-6.87 (2 H, m); 6.85-6.77 (1 H, m); 6.06 (1 H, ddt, J 10.5, 17.3 (d), 5.3 (t), C*H*=CH_2); 5.45 (1 H, dq, J 17.3 (d), 1.5 (q), CH=C*H*H); 5.28 (1 H, dq, J 10.5 (d), 1.5 (q), CH=C*H*H); 4.55 (2 H, dt, J 5.3 (d), 1.5 (t), CH_2CH=CH_2); 3.84 (2 H, s, CH_2NH_2).

***N*-(4-allyloxyphenyl)formamide.** A solution of 4-allyloxyaniline[51] (499 mg, 3.35 mmol) in dry CH_2Cl_2 (17 mL) at 0 °C was treated with formic acid (152 µL, 4.02 mmol), 4-dimethylaminopyridine (DMAP) (82 mg, 0.67 mmol) and, finally, dicyclohexylcarbodiimide (DCC) (760 mg, 3.69 mmol). After 2 h at r.t., the resulting suspension was filtered through a celite cake washing with Et_2O + 2% of CH_2Cl_2. After evaporation and chromatography (CH_2Cl_2 / AcOEt 7:1), *N*-(4-allyloxyphenyl)formamide was obtained (564 mg, 95%) as yellow solid. M.p.: 50.9−52.1 °C (CH_2Cl_2). R_f = 0.45 (PE / AcOEt 1:1). δ_H(300 MHz, $CDCl_3$, 25 °C)(two conformers in about 1:1 ratio are visible): 8.50 (0.5 H, d, J 11.6, C*H*O of 1 conformer); 8.34 (0.5 H, d, J 1.8, 0.5 H, C*H*O of 1 conformer); 7.59 (0.5 H, broad s, N*H* of 1 conformer); 7.44 (1 H, d, J 9.0, Ar*CH* of 1 conformer); 7.12 (0.5 H, broad s, N*H* of 1 conformer); 7.03 (1 H, d, J 9.0, Ar*CH* of 1 conformer); 6.91 (1 H, d, J 9.0, Ar*CH* of 1 conformer); 6.89 (1 H, d, J 9.0, Ar*CH* of 1 conformer); 6.05 (1 H, ddt, J 10.5 17.2 (d), 5.3 (t), C*H*=CH_2); 5.46-5.36 (1 H, m, CH=C*H*H); 5.33-5.26 (1 H, m, CH=C*H*H); 4.55-4.50 (2 H, m, CH_2CH=CH_2). δ_C (75 MHz, $CDCl_3$, 25 °C): 163.3, 159.3 (C=O), 156.4, 155.5, 130.2, 129.8 (arom. quat.), 133.0, 132.9 (*C*H=CH_2), 121.7, 121.2, 115.6, 114.9 (Ar*C*H), 117.8, 117.6 (CH=*C*H_2), 69.0, 68.9 (*C*H_2O). IR: ν_{max}/cm^{-1} 3297, 3269, 3208, 3144, 3106, 3084, 3020, 2977, 2941, 2925, 2869, 2803, 2771, 1657, 1644, 1612, 1547, 1507, 1465, 1426, 1409, 1391, 1370, 1340, 1327, 1303, 1254, 1229, 1177, 1151, 1123, 1111, 1062, 1013, 1002, 940, 931, 873, 839, 822, 749, 737, 709, 648, 633. GC-MS (method 2) t_R 7.88 min, *m/z* (%) 177 (43) [M]$^+$, 137 (8.5), 136 (100), 109 (11), 108 (99), 81 (6.4), 80 (50), 65 (8.6), 63 (5.2), 54 (5.5), 53 (26), 52 (16), 41 (37), 39 (27). *m/z* (ESI+) 178.0867 (M + H$^+$). $C_{10}H_{12}O_2N$ requires 178.0868.

4-allyloxyphenyl isocyanide. A solution of *N*-(4-allyloxyphenyl)formamide (130 mg, 0.734 mmol) in dry CH_2Cl_2 (7 mL) was treated with Et_3N (470 µL, 3.37 mmol) and cooled at −30 °C. Then $POCl_3$ (103 µL, 1.10 mmol) was added dropwise. After stirring for 1 h at −30 °C, the cold mixture was poured in saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic extracts were washed with saturated brine and evaporated. The crude was purified by chromatography (PE / Et_2O 15:1) to give pure 4-allyloxyphenyl isocyanide as green oil (107 mg, 91%). R_f = 0.30 (PE / Et_2O 15:1). δ_H(300 MHz, $CDCl_3$, 25 °C): 7.30 (2 H, d, J 8.9, ArCH); 6.88 (2 H, d, J 8.9, ArCH); 6.03 (1 H, ddt, J 10.5, 17.3 (d), 5.3 (t), C*H*=CH_2); 5.41 (1 H, dq, J 17.3 (d), 1.5 (q), CH=C*H*H); 5.32 (1 H, dq, J 10.5 (d), 1.5 (q), CH=C*H*H); 4.55 (2 H, dt, J 5.3 (d), 1.5 (t), CH_2CH=CH_2). δ_C(75 MHz, $CDCl_3$, 25 °C): 162.5 (N*C*), 158.8, 119.6 (broad) (arom. quat.), 132.3 (*C*H=CH_2), 127.7, 115.3 (Ar*C*H), 118.3 (CH=*C*H_2), 69.0 (*C*H_2O). IR: ν_{max}/cm^{-1} 3675, 3082, 2986, 2901, 2123, 1735, 1648, 1605, 1584, 1502, 1456, 1423, 1409, 1383, 1298, 1247, 1230, 1192, 1164, 1109, 1067, 1048, 1015, 995, 928, 830, 739, 700, 647, 618. GC-MS (method 2) t_R 5.67 min, *m/z* (%) 159 (92) [M]$^+$, 158 (19), 144 (19), 132 (7.0), 131 (8.0), 130 (19), 119 (29), 103 (5.9), 102 (11), 91 (11), 90 (12), 76 (7.7), 75 (8.6), 64 (19), 63 (13), 41 (100), 39 (19). *m/z* (ESI+) 160.0769 (M + H$^+$). $C_{10}H_{10}ON$ requires 160.0762.

***N*-(4-(2-(2-(allyloxy)ethoxy)ethoxy)phenyl)formamide.** Known 1-(2-(2-(allyloxy)ethoxy)ethoxy)-4-nitrobenzene was prepared according to literature procedures.[52, 53] This compound (760

mg, 2.84 mmol) was dissolved in EtOH (33 mL) and treated with Fe powder (1.27 g, 22.7 mmol) and a solution of NH_4Cl (607 mg, 11.4 mmol) in deionized H_2O (6 mL). After stirring for 2 h at 75 °C, the resulting black suspension was filtered through a celite cake washing with MeOH. After evaporation, the crude was treated with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic extracts were washed with saturated brine and evaporated. The resulting crude 3-(2-(2-(allyloxy)ethoxy)ethoxy)aniline was directly treated with ethyl formate (4 mL) and stirred at 60 °C for 6 days. After evaporation, the crude was purified by chromatography (PE / AcOEt 1:1) to give pure *N*-(4-(2-(2-(allyloxy)ethoxy)ethoxy)phenyl)formamide as brown oil (506 mg, 67% from 1-(2-(2-(allyloxy)ethoxy)ethoxy)-4-nitrobenzene). R_f = 0.24 (PE / AcOEt 1:1). δ_H(300 MHz, $CDCl_3$, 25 °C)(two conformers in about 1:1 ratio are visible): 8.50 (0.5 H, d, J 11.6, C*H*O of 1 conformer); 8.33 (0.5 H, d, J 1.8, C*H*O of 1 conformer); 7.46 (0.5 H, broad s, N*H* of 1 conformer); 7.43 (1 H, d, J 9.0, ArC*H* of 1 conformer); 7.12 (0.5 H, broad s, N*H* of 1 conformer); 7.01 (1 H, d, J 9.0, ArC*H* of 1 conformer); 6.91 (1 H, d, J 9.0, ArC*H* of 1 conformer); 6.89 (1 H, d, J 9.0, ArC*H* of 1 conformer); 5.92 (1 H, ddt, J 10.4, 17.2 (d), 5.7 (t), C*H*=CH_2); 5.28 (1 H, dq, J 17.2 (d), 1.5 (q), CH=C*H*H); 5.19 (1 H, dq, J 10.5 (d), 1.5 (q), CH=C*H*H); 4.15-4.09 (2 H, m, CH_2O); 4.04 (2 H, dt, J 5.7(d), 1.5 (t), OCH_2CH=CH_2); 3.89-3.83 (2 H, m, CH_2O); 3.76-3.69 (2 H, m, CH_2O); 3.67-3.60 (m, 2 H, CH_2O). δ_C(75 MHz, $CDCl_3$, 25 °C): δ = 163.1, 159.3 (*C*=O), 156.4, 155.4, 130.4, 129.9 (arom. quat.), 134.3 (*C*H=CH_2), 121.5, 121.1, 115.4, 114.6 (Ar*C*H), 117.2 (CH=*C*H_2), 72.0, 70.6, 69.5, 69.2, 67.5, 67.4 (*C*H_2O). IR: ν_{max}/cm^{-1} 3676, 3274, 3130, 3071, 2871, 1669, 1602, 1536, 1509, 1455, 1412, 1351, 1290, 1234, 1176, 1127, 1090, 1062, 994, 923, 872, 827, 726, 643, 633. GC-MS (method 1) t_R 9.19 min, *m/z* (%) 163 ([M–$OCH_2CH_2OAllyl]^+$, 1.0) 108 (8.7), 87 (8.8), 85 (9.2), 80 (8.1), 65 (9.7), 53 (7.0), 45 (9.5), 44 (5.4), 43 (21), 41 (100), 39 (10). *m/z* (ESI+): 266.1392 ($M + H^+$). $C_{14}H_{20}O_4N$ requires 266.1392.

***N*-(4-(2-(2-(allyloxy)ethoxy)ethoxy)phenyl) isocyanide.** A solution of *N*-(4-(2-(2-(allyloxy)ethoxy)ethoxy)phenyl)formamide (374 mg, 1.41 mmol) in dry CH_2Cl_2 (7 mL) was treated with Et_3N (590 µL, 4.23 mmol) and cooled at 0 °C. Then diphosgene (103 µL, 0.85 mmol) was added dropwise. After stirring for 1 h at 0 °C, the cold mixture was poured in saturated aqueous $NaHCO_3$ and extracted with Et_2O. The organic extracts were washed with saturated brine and evaporated. The crude was purified by chromatography (PE / AcOEt 8:2) to give pure *N*-(4-(2-(2-(allyloxy)ethoxy)ethoxy)phenyl) isocyanide as yellow oil (307 mg, 88%). R_f = 0.34 (PE / AcOEt 8:2). δ_H(300 MHz, $CDCl_3$, 25 °C): 7.30 (2 H, d, J 9.0, ArC*H*); 6.89 (2 H, d, J 9.0, ArC*H*); 5.92 (1 H, ddt, J 10.4, 17.2 (d), 5.7 (q), C*H*=CH_2); 5.28 (1 H, dq, J 17.2 (d), 1.6 (q), CH=C*H*H); 5.19 (1 H, dq, J 10.5 (d), 1.2 (q), CH=C*H*H); 4.17-4.11 (2 H, m, CH_2O); 4.03 (2 H, dt, J 5.7 (d), 1.3 (t), OCH_2CH=CH_2); 3.89-3.85 (2 H, m, CH_2O); 3.75-3.69 (2 H, m, CH_2O); 3.66-3.60 (2 H, m, CH_2O). δ_C(75 MHz, $CDCl_3$, 25 °C): 162.5 (N*C*), 159.1, 119.3 (broad) (arom. quat.), 134.6 (*C*H=CH_2), 127.6, 155.2 (Ar*C*H), 117.1 (CH=*C*H_2), 72.2, 70.8, 69.5, 69.3, 67.7 (*C*H_2O). IR: ν_{max}/cm^{-1} 3676, 3078, 2871, 2122, 1741, 1646, 1605, 1585, 1504, 1453, 1423, 1394, 1352, 1298, 1252, 1194, 1164, 1127, 1108, 1058, 995, 923, 883, 832, 724, 681, 641. GC-MS (method 1) t_R 7.50 min, *m/z* (%) 159 (1.1), 102 (6.9), 85 (7.1), 73 (6.0), 71 (5.2), 45 (11), 43 (18), 41 (100), 39 (13). *m/z* (ESI+): 248.1288 ($M + H^+$). $C_{14}H_{18}O_3N$ requires 248.1287.

(*R*,*S*)-*N*-(4-Acetoxyphenyl)-*N*-(1-(4-acetoxyphenyl)-2-(tert-butylamino)-2-oxoethyl)propionamide 2a. A solution of aldehyde **4**[25] (228 mg, 2.0 mmol) in dry methanol (6.7 mL) was treated with amine **3**[23, 24] (302 mg, 2.0 mmol), propionic acid (150 µL, 2.0 mmol), and *tert*-butyl isocyanide (225 µL, 2.0 mmol). The solution was stirred at r.t. for 5 h. Then the solvent was evaporated and the crude purified by chromatography (PE / AcOEt 1:1) to give pure **2a** as a slightly brown solid (665 mg, 73%). M.p. = 144.6-146.8 °C. R_f = 0.29 (PE / AcOEt 40:60). δ_H(300 MHz, $CDCl_3$, 25 °C): 7.13 (2 H, d, J 8.5, ArC*H* from aldehyde); 6.92 (2 H, d, J 8.5, ArC*H* from aldehyde); 7.05-6.85 (2 H, broad m, ArC*H* from amine) (NOTE: the other 2 ArC*H* from amine give a very broad signal from 7.50 to 7.00), 5.99 (1H, 1 H, C*H*), 5.72 (1H, s, N*H*), 2.25 (6H, s, CH_3CO), 2.12-2.00 (2H, m, CH_2CH_3), 1.34 (9H, s, (CH_3)$_3$)C), 1.04 (3 H, t, J= 7.4, CH_2CH_3). δ_C(75 MHz, $CDCl_3$, 25 °C): 174.3 (*C*=O), 169.0 (*C*=O), 168.8 (*C*=O), 168.7 (*C*=O), 150.5, 150.0, 137.2, 132.3 (quat.), 131.5, 131.3, 121.8, 121.4 (Ar*C*H), 64.3 (*C*H), 51.5 (*C*(CH_3)$_3$), 28.5 (C(*C*H_3)$_3$), 28.3 (*C*H_2CH_3), 21.0 (*C*H_3CO), 9.3 (CH_2*C*H_3). IR: ν_{max}/cm^{-1} 3339, 3234, 3078, 2976, 1759, 1681,1636, 1551, 1504, 1459, 1418, 1390, 1366, 1305, 1270, 1251, 1209, 1186, 1166, 1160, 1105, 1099, 1044, 1012, 958, 941, 910, 859, 848, 813, 784, 775, 744, 735, 722, 656, 632. *m/z* (ESI+): 455.2180 ($M + H^+$). $C_{25}H_{31}O_6N_2$ requires 455.2182.

(*R*,*S*)-*N*-(4-Hydroxyphenyl)-*N*-(2-(tert-butylamino)-1-(4-hydroxyphenyl)-2-oxoethyl)propionamide 1a. A solution of compound **2a** (137 mg, 0.30 mmol) in tetrahydrofuran (2.25 mL) was treated, at r.t., with 1 M acqueous LiOH (0.78 µL, 0.78 mmol). The solution became yellow. After 20 h, the reaction not being yet complete, other 0.39 µL of LiOH solution were added. After other 20 h, the reaction was worked out with a 1 M NaH_2PO_4 solution and extracted with AcOEt. After evaporation of the organic phase, two consecutive chromatographies (first PE / AcOEt 3:7; then CH_2Cl_2 / MeOH 93:7) afforded pure **1a** as a white solid (85 mg, 76%). M.p. = 203.4-204.1 °C. R_f = 0.24 (PE / AcOEt 30:70). δ_H(300 MHz, DMSO-*d6*, 50 °C): 9.22 (1 H, br s, O*H*), 9.16 (1 H, br s, O*H*); 7.28 (1 H, s, N*H*); 6.81 (2 H, d, J 8.5, ArC*H* from aldehyde); 6.49 (2 H, d, J 8.5, ArC*H* from aldehyde); 6.70-6.45 (2 H, broad m, ArC*H* from amine) (NOTE: the other 2 ArC*H* from amine give a very broad signal from 7.30 to 6.80), 5.87 (1H, s, C*H*), 2.01-1.81 (2H, m, CH_2CH_3), 1.23 (9H, s, (CH_3)$_3$)C), 0.89 (3 H, t, J= 7.4, CH_2CH_3). δ_C(75 MHz, DMSO-*d6*, 50 °C): 172.6 (*C*=O), 169.5 (*C*=O), 156.1, 155.8, 131.5, 131.1 (quat.), 130.9, 126.1, 114.5, 114.2 (Ar*C*H), 63.0 (*C*H), 49.9 (*C*(CH_3)$_3$), 28.3 (C(*C*H_3)$_3$), 27.3 (*C*H_2CH_3), 9.2 (CH_2*C*H_3). IR: ν_{max}/cm^{-1} 3274, 3234, 2969, 1661, 1614, 1593, 1511, 1452, 1393, 1365, 1258, 1221, 1174, 1096, 1044, 1023, 960, 845, 816, 780, 740, 633. *m/z* (ESI+): 371.1976 ($M + H^+$). $C_{21}H_{27}O_4N_2$ requires 371.1971. HPLC (see supplementary information) showed a purity of 99.5%.

(*R*,*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-*N*-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-*N*-(2-((4-((*tert*-butyldimethylsilyl)oxy)phenyl)amino)-2-oxo-1-phenylethyl)benzamide 11. A solution of amine **9** (224 mg, 1.00

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mmol) in dry CH_2Cl_2 (10.0 mL) was treated at r.t. with benzaldehyde (102 µL, 1.00 mmol) and anhydrous $MgSO_4$ (100 mg) and stirred overnight. After filtration of $MgSO_4$ and evaporation, the residue was taken up in MeOH (5.0 mL), added with freshly activated powdered 3 Å molecular sieves (50 mg), and finally treated with acid **10** (252 mg, 1.00 mmol) and isocyanide **8** (234 mg, 1.00 mmol). After 17 h, the mixture was filtered, evaporated to dryness and chromatographed (PE / AcOEt 60:40) to give pure **11** as a yellow-brown solid (200 mg, 25%). M.p: = 156.7-157.3 °C. R_f = 0.58 (PE / AcOEt 6:4). δ_H(300 MHz, $CDCl_3$, 25 °C): δ 8.19 (1 H, s, N*H*), 7.35 (2 H, d, J 9.0, Ar*H*), 7.32-7.18 (7 H, m), 6.85 (2 H, broad d, J= 7.7 Hz, Ar*H*), 6.74 (2 H, d, J= 8.8 Hz, Ar*H*), 6.56 (2 H, d, J= 8.7 Hz, Ar*H*), 6.50 (2 H, d, J= 8.9 Hz, Ar*H*), 6.34 (1 H, s, C*H*), 0.96, 0.92, 0.91 (3 x 9 H, 3 s, $(CH_3)_3$C); 0.16, 0.11, 0.08 (3 x 6 H, 3 s, (CH_3Si). δ_C(75 MHz, $CDCl_3$, 25 °C, TMS): 171.1, 168.1 (*C*=O), 156.9, 154.6, 152.3, 135.0, 134.5, 131.50, 131.2 (quat.), 131.4 (x2), 130.8 (x2), 130.2 (x2), 128.6, 128.5 (x2), 121.7 (x2), 120.2 (x2), 120.0 (x2), 119.1 (x2) (Ar*C*H), 67.4 (*C*H), 25.69, 25.64, 25.56 (C(CH_3)$_3$), 18.38 ($C(CH_3)_3$), 18.24, 18.19, 18.14 (quat. C *t*-Bu), −4.48 (x2), −4.54 (CH_3Si). IR: ν_{max}/cm^{-1} 3260, 3201, 3075, 2957, 2930, 2896, 2858, 1689, 1617, 1604, 1551, 1505, 1472, 1462, 1410, 1389, 1362, 1341, 1253, 1201, 1166, 1103, 1080, 1052, 1006, 966, 908, 831, 803, 777, 764, 735, 716, 698, 666, 638, 623. *m/z* (ESI+): 797.4187 (M + H$^+$). $C_{45}H_{65}O_5N_2Si_3$ requires 797.4201.

(*R*,*S*)-4-Hydroxy-*N*-(4-hydroxyphenyl)-*N*-(2-((4-hydroxyphenyl)amino)-2-oxo-1-phenylethyl)benzamide 1b. A solution of compound **2a** (117 mg, 0.15 mmol) in tetrahydrofuran (1.2 mL) was treated, at r.t., with 1 M acqueous LiOH (0.59 µL, 0.59 mmol). The solution became orange. After 22 h the solution was evaporated, taken up with MeOH, and treated with previously washed Amberlyst 15 acid resin until pH = 7. The resin was filtered off and the solution evaporated to dryness and chromatographed (PE / AcOEt 4:6 + 2% EtOH) to give pure **1b** as a white solid (54 mg, 81%). M.p. = 177.7-178.2 °C °C. R_f = 0.34 (PE / AcOEt 40:60 + 2% EtOH). δ_H(300 MHz, DMSO-*d6*, 25 °C): δ 9.98, 9.68, 9.24 (3 x 1 H, 3 s, O*H*), 7.40 (2 H, d, J= 9.0, Ar*H*), 7.24–7.10 (5 H, m, Ar*H*+N*H*), 7.07 (2 H, d, J= 9.3, Ar*H*), 6.69 (2 H, d, J= 9.0, Ar*H*), 6.51 (2 H, d, J= 8.7, Ar*H*), 6.33 (2 H, broad d, J= 8.4, Ar*H*), 6.26 (1H, s, C*H*). δ_C(75 MHz, DMSO-*d6*, 25 °C): 169.8, 168.2 (*C*=O), 158.1, 155.4, 153.1, 135.2, 132.0, 131.9, 130.8 (quat.), 130.2 (x4), 127.8 (x 2), 127.7, 127.0 (x2), 120.6 (x2), 115.0 (x2), 114.2 (x2), 114.0 (x2) (Ar*C*H) 64.9 (*C*H). IR: ν_{max}/cm^{-1} 3275, 3234, 1665, 1607, 1509, 1440, 1365, 1223, 1167, 1103, 1081, 831, 761, 729, 698, 626. *m/z* (ESI+): 455.1604 (M + H$^+$). $C_{27}H_{23}O_5N_2$ requires 455.1607. HPLC (see supplementary information) showed a purity of 96%.

General procedure for the preparation of polyphenols 1c,e,hi through allylated derivatives 14c,e,h,i (Method A). A solution of the appropriate aldehyde (1 equiv) in dry EtOH and trifluoroethanol in 1:1 ratio (0.26 M) was treated with the amine (1.1 equiv) and molecular sieves (3 Å, 50 mg/mmol). After 5 h, the acid (1.1 equiv), and the isocyanide (1.1 equiv) were added. The reaction mixture was stirred at r.t. for 2-4 days, then filtered with celite on a sintered funnel, washed with AcOEt, concentrated and purified by chromatography. A 0.1 M solution of the Ugi product in MeCN under nitrogen atmosphere, was treated with $PdCl_2(PPh_3)_2$ (0.025 equiv for allyl group) and ammonium formate (2.2 equiv for allyl group) at 80 °C for 2 h in a sealed flask. Then, the crude was diluted with AcOEt, washed with saturated aqueous $NaHCO_3$. After evaporation, the residue was eluted from a column of silica gel with the suitable eluent.

(*R*,*S*)-(*E*)-*N*-Benzyl-*N*-(2-(*tert*-butylamino)-1-(4-hydroxyphenyl)-2-oxoethyl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide 1c. Following the general procedure A, a mixture of aldehyde **12** (113 mg, 0.70 mmol), benzylamine (80 µL, 0.77 mmol), acid **13** (180 mg, 0.77 mmol), *t*-butyl isocyanide (87 µL, 1.19 mmol) and 3 Å molecular sieves (32 mg) was stirred for 3 days at r.t. After work-up and purification (PE / AcOEt 50:50) compound **14c** was obtained pure as white foam (275 mg, 69%). Then a mixture of **14c** (255 mg, 0.45 mmol), $PdCl_2(PPh_3)_2$ (16 mg, 0.023 mmol) and ammonium formate (124 mg, 1.98 mmol) was stirred for 2 h at 80 °C. After work-up and purification (chromatography with PE / AcOEt 3:4, followed by treatment with active coal) compound **1c** was obtained pure as white solid (177 mg, 80%). M.p. = 125 °C with decomposition. R_f = 0.19 (PE / AcOEt 50:50). δ_H(300 MHz, DMSO-*d6*, 90 °C): δ 9.06 (2 H, s, O*H*), 7.43 (1 H, broad s, N*H*), 7.41 (1 H, d, J= 15.0, ArC*H*=CH), 7.20-6.87 (9 H, m, Ar*H*, ArCH=C*H*), 6.80-6.60 (1 H, broad signal, ArCH=C*H*), 6.76 (1 H, d, J 8.1, *H* meta to OMe), 6.67 (2 H, d, J 8.7, *H* ortho to OH), 6.00 (1 H, broad s, C*H*N), 4.87 (1 H, d, J 16.7, C*H*HPh), 4.55 (1 H, d, J 16.7, C*H*HPh), 3.78 (3 H, s, OCH_3), 1.26 (9 H, s, C(CH_3)$_3$). δ_C(75 MHz, DMSO-*d6*, 25 °C) (note: at this temperature, 2 conformers are visible and thus most signals are doubled): 169.6, 169.2, 167.1, 166.9 (*C*=O), 156.9, 156.8, 148.4, 147.7, 147.6, 140.1, 139.4, 130.0 (quat.), 141.7 (Ar*C*H=CH), 130.4, 127.8, 127.4, 126.8, 126.4, 126.2, 126.1, 122.3, 121.9, 116.3, 114.9, 110.6 (Ar*C*H), 115.4 (ArCH=*C*H), 62.8, 60.2 (*C*HN), 55.5, 55.4 (OCH_3), 50.2 ($C(CH_3)_3$), 48.0 (CH_2Ph), 28.3, 28.1 (C(CH_3)$_3$). IR: ν_{max}/cm^{-1} 3283, 2967, 1641, 1589, 1511, 1452, 1429, 1364, 1265, 1203, 1171, 1123, 1080, 1030, 976, 947, 891, 865, 837, 814, 726, 696. *m/z* (ESI+): 489.2396 (M + H$^+$). $C_{29}H_{33}O_5N_2$ requires 489.2389. HPLC (see supplementary information) showed a purity of 99%.

(*R*,*S*)-(*E*)-*N*-Benzyl-*N*-(2-(*tert*-butylamino)-1-phenyl-2-oxoethyl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide 1e. Following the general procedure A, a mixture of benzaldehyde (67 mg, 0.63 mmol), benzylamine (76 µL, 0.69 mmol), (*E*)-3-(3,4-bis(allyloxy)phenyl)acrylic acid (179 mg, 0.69 mmol), *t*-butyl isocyanide (78 µL, 0.69 mmol) and 3 Å molecular sieves (28 mg) was stirred for 3 days at r.t. After work-up and purification (PE / AcOEt 75:25) compound **14e** was obtained pure as white foam (208 mg, 72%). Then a mixture of **14e** (200 mg, 0.37 mmol), $PdCl_2(PPh_3)_2$ (12 mg, 0.017 mmol) and ammonium formate (95 mg, 1.50 mmol) was stirred for 2 h at 80 °C. After work-up and purification (two consecutive chromatograhies with PE / AcOEt from 60:40 to 50:50 and a filtration with celite on a sintered funnel) compound **1e** was obtained pure as pale yellow solid (101 mg, 59%). M.p. = 120.0 – 121.0 °C (MeOH). R_f = 0.40 (PE / AcOEt 50:50). δ_H(300 MHz, DMSO-*d6*, 80 °C) (note: the O*H* protons give a very broad signal around 9 ppm): 7.61 (1 H, broad s, 1 H, N*H*), 7.38 (1 H, d, J= 15.2, ArC*H*=CH), 7.30-7.03 (10 H, m, Ar*H*), 6.87 (1 H, s, *H* ortho to OH and CH=CH), 6.79, 6.72 (2 H, AB syst., J 8.3, *H* para to OH and meta to CH=CH), 6.65 (1 H, broad

d, J 15.2, ArCH=C*H*), 6.12 (1 H, broad s, C*H*N), 4.91, 4.65 (2 H, AB syst., J 17.0, CH_2Ph), 1.24 (9 H, s, C(CH_3)$_3$). δ_C(75 MHz, DMSO-*d6*, 25 °C) (note: at this temperature, 2 conformers are visible and thus most signals are doubled, although one conformer is prevailing, only the peaks of major conformer are reported): 168.9, 167.1 (*C*=O), 147.6, 145.3, 139.5, 136.9, 128.2 (quat.), 142.5 (Ar*C*H=CH), 128.9 (x2), 128.1 (x2), 127.8 (x2), 127.4, 126.2, 125.8 (x2), 120.7, 115.4, 114.1 (Ar*C*H), 115.1 (ArCH=*C*H), 60.6 (*C*HN), 54.8 (O*C*H_3), 50.3 (*C*(CH_3)$_3$), 48.1 (*C*H_2Ph), 28.2 (C(*C*H_3)$_3$). IR (ATR): ν = 3276, 3064, 2969, 1640, 1578, 1513, 1451, 1413, 1363, 1278, 1192, 1112, 1080, 1032, 975, 948, 893, 845, 810, 753, 730, 696, 617 cm^{-1}. *m/z* (ESI-): 457.2143 (M - H$^+$). $C_{28}H_{29}O_4N_2$ requires 457.2127. HPLC (see supplementary information) showed a purity of 100%.

(*R*,*S*)-*N*-(4-hydroxyphenyl)-*N*-(1-(4-hydroxyphenyl)-2-((4-hydroxyphenyl)amino)-2-oxoethyl)- propanamide 1h. Following the general procedure A, a mixture of aldehyde **12** (170 mg, 1.05 mmol), 4-allyloxyaniline (173 mg, 1.16 mmol), propionic acid (87 µL, 1.16 mmol), 4-allyloxyphenyl isocyanide (185 mg, 1.16 mmol) and 3 Å molecular sieves (50 mg) was stirred for 5 days at r.t. After usual work-up, the crude was diluted with AcOEt, washed with HCl 1 N to remove the excess of amine. Then, the crude was purified (PE / Et_2O 1:2) obtaining compound **14h** as white foam (121 mg, 22%). Then a mixture of **14h** (102 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) and ammonium formate (83 mg, 1.32 mmol) was stirred for 2 h at 80 °C. After work-up and purification (from CH_2Cl_2 / AcOEt 3:4 to AcOEt with 1% MeOH) compound **1h** was obtained as red solid (60 mg, 74%). A final treatment with active coal gave **1h** as a pale yellow solid. M.p. = 158.0 – 160.0 °C (MeOH). R_f = 0.35 (CH_2Cl_2 / AcOEt 3:4). δ_H(300 MHz, DMSO-*d6*, 90 °C) (Note: the 3 phenolic OH exchange with H_2O contained in the solvent giving a broad signal around 4.90 ppm): 9.38 (1 H, s, N*H*), 9.30 (1 H, s, O*H*), 7.32 (2 H, d, J 8.8, *H* ortho to CH), 7.0-6.80 (2 H, broad signal, *H* ortho to N), 6.86 (2 H, d, J 8.4, *H* ortho to NH), 6.67 (2 H, d, J 8.8, *H* meta to CH), 6.50 (4 H, d, J 8.4, *H* meta to N and to NH), 6.03 (2 H, s, C*H*), 1.97 (2 H, q, J 7.4, CH_2CH$_3$), 0.92 (3 H, t, J 7.5, CH$_2$CH_3). δ_C(75 MHz, DMSO-*d6*, 25 °C): 173.1, 168.8 (*C*=O), 157.5, 157.0, 153.3, 130.7, 130.2, 124.5 (quat.), 131.7 (x2), 131.2 (x2), 120.15 (x2), 115.0 (x2), 114.8 (x4) (Ar*C*H), 63.6 (*C*HN), 27.6 (*C*H$_2$), 9.4 (*C*H$_3$). IR: ν_{max}/cm^{-1} 3268, 3202, 3005, 1650, 1602, 1584, 1533, 1471, 1379, 1360, 1260, 1205, 1173, 1099, 1043, 1001, 965, 845, 815, 631. *m/z* (ESI+): 407.1605 (M + H$^+$). $C_{23}H_{23}O_5N_2$ requires 407.1607. HPLC (see supplementary information) showed a purity of 98%.

(*R*,*S*)-(*E*)-*N*-(2-(*tert*-butylamino)-1-(4-hydroxyphenyl)-2-oxoethyl)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(4-hydroxyphenyl)acrylamide 1i. Following the general procedure A, a mixture of aldehyde **12** (94 mg, 0.58 mmol), 4-allyloxyaniline (95 mg, 0.64 mmol), acid **13** (150 mg, 0.64 mmol), *t*-butyl isocyanide (72 µL, 0.64 mmol) and 3 Å molecular sieves (29 mg) was stirred for 3 days at r.t. After work-up and purification (PE / AcOEt 3:2) compound **14i** was obtained pure as yellow foam (117 mg, 33%). Then a mixture of **14i** (88 mg, 0.15 mmol), $PdCl_2(PPh_3)_2$ (8 mg, 0.011 mmol) and ammonium formate (63 mg, 1.00 mmol) was stirred for 2 h at 80 °C. After work-up and purification (the crude was triturated with PE/AcOEt) compound **1i** was obtained pure as white solid (50 mg, 68%). M.p. = 150 °C with decomposition. R_f = 0.10 (PE / AcOEt 50:50). δ_H(300 MHz, DMSO-*d6*, 25 °C): 9.42 (2 H, s, O*H*), 9.30 (1 H, s, O*H*), 7.56 (1 H, s, N*H*), 7.38 (1 H, d, J 15.3, Ar*C*H=CH), 6.88 (1 H, s, *H* ortho to OMe), 6.83 (2 H, d, J 8.4, *H* meta to OH), 6.76-6.67 (2 H, m, *H* meta and para to OMe), 6.70-6.40 (2 H, very broad signal, *H* meta to OH), 6.50 (4 H, d, J 8.4, *H* ortho to OH), 5.98 (1 H, s, C*H*N), 5.95 (1 H, d, J 15.3, ArCH=C*H*), 3.70 (3 H, s, OCH_3), 1.24 (9 H, s, (CH_3)$_3$C). δ_H(75 MHz, DMSO-*d6*, 25 °C): 169.7, 165.4 (*C*=O), 156.3, 156.0, 148.3, 147.5, 132.0, 130.7, 126.2 (quat.), 140.6 (Ar*C*H=CH), 132.0 (x2), 131.2 (x2), 126.1, 120.2, 114.5 (x4), 112.2 (Ar*C*H), 116.6 (ArCH=*C*H), 63.3 (*C*HN), 55.5 (OCH_3), 50.1 (*C*(CH_3)$_3$), 28.4 (C(CH_3)$_3$). IR: ν_{max}/cm^{-1} 3269, 2966, 2930, 1662, 1640, 1592, 1511, 1450, 1388, 1366, 1258, 1216, 1161, 1121, 1030, 1009, 976, 936, 885, 840, 814, 791, 742, 723, 693, 645, 610. *m/z* (ESI+): 491.2187 (M + H$^+$). $C_{28}H_{31}O_6N_2$ requires 491.2182. HPLC (see supplementary information) showed a purity of 98.5%.

General procedure for the preparation of acetylated polyphenols 2d,f,g,,j,l,m,n,o,p,q and 15 (Method B). A solution of the appropriate aldehyde (1 equiv) in dry EtOH and trifluoroethanol in 1:1 ratio (0.26 M) was treated with the amine (1.1 equiv) and molecular sieves (3 Å, 50 mg/mmol). After 5 h, the acid (1.1 equiv), and the isocyanide (1.1 equiv) were added. The reaction mixture was stirred at r.t. for 2-4 days, then filtered with celite on a sintered funnel, washed with AcOEt and concentrated. The residue was treated with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic extracts were washed with saturated brine and evaporated. The crude was purified by chromatography. A 0.1 M solution of the Ugi product in MeCN under nitrogen atmosphere, was treated with $PdCl_2(PPh_3)_2$ (0.025 equiv for allyl group) and ammonium formate (2.2 equiv for allyl group) at 80 °C in a sealed flask (2-5 h). Then, the crude was diluted with AcOEt, washed with saturated aqueous $NaHCO_3$. After evaporation, the residue was directly dissolved in 1:1 pyridine / acetic anhydride (0.1 M) and stirred for 18 h at r.t. Then, the mixture was poured in 2 N HCl (final pH = 2) and extracted with CH_2Cl_2. The organic extracts were washed with saturated brine and evaporated, then the crude was purified by chromatography.

(*R*,*S*)-(*E*)-3-(4-Acetoxy-3-methoxyphenyl)-*N*-(1-(4-acetoxyphenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-butylacrylamide 2d. Following the general procedure B, a mixture of aldehyde **12** (176 mg, 1.08 mmol), *n*-butylamine (120 µL, 1.19 mmol), acid **13** (280 mg, 1.19 mmol), *t*-butyl isocyanide (135 µL, 1.19 mmol) and 3 Å molecular sieves (50 mg) was stirred for 3 days at r.t. After work-up and purification (PE / AcOEt 75:25 + 1% EtOH) compound **14d** was obtained pure as yellow oil (330 mg, 57%, 91% based on the recovery of unreacted aldehyde). Then a mixture of **14d** (270 mg, 0.50 mmol), $PdCl_2(PPh_3)_2$ (18 mg, 0.0025 mmol) and ammonium formate (140 mg, 2.22 mmol) was stirred for 5 h at 80 °C. After work-up, the crude was treated with 1:1 pyridine / acetic anhydride (3.7 mL) and stirred for 18 h at r.t. After work-up and purification (PE / AcOEt 7:3 + 3% EtOH) compound **2d** was obtained pure as white foam (226 mg, 76%). R_f = 0.28 (PE / AcOEt 7:3 + 3% EtOH). δ_H(300 MHz, $CDCl_3$, 25 °C): δ 7.72 (1 H, d,

J 15.3, ArC*H*=CH), 7.47 (2 H, d, J 8.4), 7.15-7.01 (5 H, m), 6.78 (1 H, d, J 15.3, ArCH=C*H*), 6.04 (1 H, s, C*H*), 5.87 (1 H, s, N*H*), 3.85 (3 H, s, OCH_3), 3.57-3.32 (mc = 3.46) (2 H, m, CH_2N), 2.32, 2.31 (2 x 3 H, 2 s, CH_3CO), 1.55-1.39 (1 H, m, C*H*H), 1.37 (9 H, s, (CH_3)$_3$C), 1.22-0.95 (3 H, m, CH_2 and C*H*H), 0.79 (3 H, t, J 7.2, CH_3CH$_2$). δ_H(75 MHz, $CDCl_3$, 25 °C): 169.3, 168.9 (x2), 166.9 (*C*=O), 151.3, 150.6, 140.9, 134.3, 133.4 (quat.), 142.8 (Ar*C*H=CH), 130.5 (x2), 123.2, 121.9 (x2), 120.4, 111.6 (Ar*C*H), 118.0 (ArCH=*C*H), 61.5 (*C*H), 58.8 (O*C*H$_3$), 51.7 (*C*(CH$_3$)$_3$), 46.1 (NCH$_2$), 32.6 (NCH$_2$*C*H$_2$), 28.6 (C(*C*H$_3$)$_3$), 21.1, 20.7 (*C*H$_3$CO), 20.0 (*C*H$_2$CH$_3$), 13.5 (CH$_2$*C*H$_3$). IR: ν_{max}/cm^{-1} 3676, 3295, 3056, 2965, 2930, 2877, 2856, 1768, 1742, 1684, 1640, 1608, 1582, 1542, 1508, 1486, 1473, 1454, 1431, 1407, 1392, 1364, 1349, 1311, 1302, 1288, 1268, 1259, 1246, 1208, 1194, 1166, 1123, 1066, 1045, 1032, 1012, 979, 951, 937, 918, 906, 889, 865, 842, 815, 801, 792, 753, 737, 731, 709, 688, 633, 620. *m/z* (ESI+): 539.2758 (M + H$^+$). $C_{30}H_{39}O_7N_2$ requires 539.2757.

(*R*,*S*)-(*E*)-*N*-(1-(4-Acetoxyphenyl)-2-(*tert*-butylamino)-2-oxoethyl)-3-(3,4-diacetoxyphenyl)-*N*-benzylacrylamide 2f. Following the general procedure B, a mixture of aldehyde **12** (596 mg, 3.70 mmol), benzylamine (445 µL, 4.07 mmol), (*E*)-3-(3,4-bis(allyloxy)phenyl)acrylic acid (1.06 g, 4.07 mmol), *t*-butyl isocyanide (460 µL, 4.07 mmol) and 3 Å molecular sieves (200 mg) was stirred for 3 days at r.t. After work-up and purification (PE / AcOEt 2:1) compound **14f** was obtained pure as white foam (1.59 g, 73%). Then a mixture of **14f** (710 mg, 1.20 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol) and ammonium formate (500 mg, 7.90 mmol) was stirred for 2 h at 80 °C. After work-up, the crude was treated with 1:1 pyridine / acetic anhydride (8 mL) and stirred for 18 h at r.t. After work-up and purification (the crude was triturated with AcOEt and the mother liquor was purified by chromatography PE / Et_2O 1:2 + 2% EtOH) pure compound **2f** was obtained as white solid (602 mg, 83%). M.p. = 189.0 – 190.0 °C (CH_2Cl_2). R_f = 0.70 (CH_2Cl_2 / MeOH 15:1). δ_H(300 MHz, $CDCl_3$, 25 °C): δ 7.70 (1 H, d, J 15.4, ArC*H*=CH), 7.38 (2 H, d, J 8.4), 7.25-7.10 (6 H, m), 7.02-6.92 (4 H, m), 6.66 (1 H. d, J 15.4, ArCH=C*H*), 6.06 (1 H, s, C*H*), 5.67 (1 H, s, N*H*), 4.90 (1 H, d, J 17.5, C*H*Ph), 4.66 (1 H, d, J 17.5, C*H*Ph), 2.27 (3 H, s, CH_3CO), 2.26 (6 H, s, CH_3CO), 1.35 (9 H, s, (CH_3)$_3$C). δ_C(75 MHz, $CDCl_3$, 25 °C): 169.1, 168.6, 168.0 (x2), 167.6 (*C*=O), 150.6, 143.0, 142.2, 137.9, 134.0, 132.6 (quat.), 141.9 (Ar*C*H=CH), 130.8 (x2), 128.5 (x2), 127.0, 126.1 (x3), 123.7, 122.6, 121.7 (x2) (Ar*C*H), 119.2 (ArCH=*C*H), 62.0 (*C*H), 51.7 (*C*(CH$_3$)$_3$), 49.6 (NCH$_2$), 28.6 (C(*C*H$_3$)$_3$), 21.1, 20.6, 20.5 (*C*H$_3$CO). IR: ν_{max}/cm^{-1} 3295, 3071, 2939, 1758, 1694, 1646, 1602, 1546, 1505, 1451, 1408, 1368, 1302, 1258, 1185, 1162, 1122, 1013, 979, 953, 909, 832, 793, 730, 692, 638. *m/z* (ESI-): 599.2381 (M - H$^+$). $C_{34}H_{35}O_8N_2$ requires 599.2393.

(*R*,*S*)-*N*-(4-Acetoxyphenyl)-*N*-(1-(4-Acetoxyphenyl)-2-((4-acetoxyphenyl)amino)-2-oxoethyl)benzamide 2g. Following the general procedure B, a mixture of aldehyde **12** (122 mg, 0.75 mmol), 4-allyloxyaniline (114 µL, 0.82 mmol), benzoic acid (100 mg, 0.82 mmol), 4-allyloxyphenyl isocyanide (130 mg, 0.82 mmol) and 3 Å molecular sieves (70 mg) was stirred for 3 days at r.t. After usual work-up, the crude was diluted with AcOEt, washed with HCl 1 N to remove the excess of amine. Then, the crude was purified (PE / AcOEt 3:2) obtaining compound **14g** as brown foam (119 mg, 28%). Then a mixture of **14g** (94 mg, 0.16 mmol), $PdCl_2(PPh_3)_2$ (9 mg, 0.01 mmol) and ammonium formate (67 mg, 1.06 mmol) was stirred for 4 h at 80 °C. After work-up, the crude was treated with 1:1 pyridine / acetic anhydride (3 mL) and stirred for 18 h at r.t. After work-up and purification (PE / AcOEt 1:1) pure compound **2g** was obtained as white foam (55 mg, 59%). R_f = 0.72 (PE / AcOEt 3:7). δ_H(300 MHz, $CDCl_3$, 25 °C): 8.43 (1 H, s, N*H*), 7.48 (2 H, d, J 8.8), 7.28 (4 H, d, J 8.1), 7.25-7.10 (3 H, m), 7.02-6.93 (6 H, m), 6.78 (2 H, d, J 8.5), 6.42 (1 H, s, C*H*), 2.26 (6 H, s, CH_3CO), 2.19 (3 H, s, CH_3CO). δ_H(75 MHz, $CDCl_3$, 25 °C): δ 171.6, 169.5, 169.1, 168.7, 167.9 (*C*=O), 150.9, 149.5, 146.9, 138.0, 135.4, 135.3, 129.9 (quat.), 131.51 (x2), 131.43 (x2), 131.37, 128.6 (x2), 127.8 (x2), 121.9 (x4), 121.5 (x2), 120.9 (x2) (Ar*C*H), 66.2 (*C*H), 21.1 (*C*H$_3$CO). IR: ν_{max}/cm^{-1} 3275, 3054, 2980, 1743, 1691, 1615, 1594, 1533, 1551, 1488, 1463, 1401, 1333, 1301, 1198, 1133, 1101, 1045, 1007, 965, 841, 761, 732, 679, 630, 603. *m/z* (ESI+): 581.1914 (M + H$^+$). $C_{33}H_{29}O_8N_2$ requires 581.19244.

(*R*,*S*)-4-Acetoxy-*N*-(1-(4-Acetoxyphenyl)-2-((4-acetoxyphenyl)amino)-2-oxoethyl)-*N*-phenylbenzamide 2j. Following the general procedure B, a mixture of aldehyde **12** (122 mg, 0.75 mmol), aniline (74 µL, 0.82 mmol), 4-(allyloxy)benzoic acid (146 mg, 0.82 mmol), 4-allyloxyphenyl isocyanide (130 mg, 0.82 mmol) and 3 Å molecular sieves (70 mg) was stirred for 3 days at r.t. After usual work-up, the crude was diluted with AcOEt, washed with HCl 1 N to remove the excess of amine. Then, the crude was purified (PE / AcOEt 7:3) obtaining compound **14j** as yellow oil (74 mg, 17%). Then a mixture of **14j** (74 mg, 0.13 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) and ammonium formate (54 mg, 0.86 mmol) was stirred for 3 h at 80 °C. After work-up, the crude was treated with 1:1 pyridine / acetic anhydride (3 mL) and stirred for 18 h at r.t. After work-up and purification (PE / AcOEt from 3:2 to 1:1) pure compound **2j** was obtained as white foam (48 mg, 64%). R_f = 0.50 (PE / AcOEt 3:7). δ_H(300 MHz, $CDCl_3$, 25 °C): 8.05 (1 H, s, N*H*), 7.55 (2 H, d, J 8.9), 7.36 (2 H, d, J 8.7), 7.35 (2 H, d, J 8.4), 7.12-6.96 (9 H, m), 6.89 (2 H, d, J 8.7), 6.28 (1 H, s, C*H*), 2.28 (6 H, s, CH_3CO), 2.22 (3 H, s, CH_3CO). δ_C(75 MHz, $CDCl_3$, 25 °C): 170.5, 169.5, 169.1, 168.7, 167.8 (*C*=O), 151.5, 150.8, 146.8, 140.6, 135.5, 132.9, 131.4 (quat.), 131.3 (x2), 130.4 (x2), 130.2 (x2), 128.6 (x2), 127.6, 121.9 (x2), 121.7 (x2), 120.9 (x2), 120.8 (x2) (Ar*C*H), 66.6 (*C*H), 21.1 (*C*H$_3$CO). IR: ν_{max}/cm^{-1} 3282, 3070, 2988, 1756, 1697, 1621, 1595, 1546, 1505, 1494, 1453, 1409, 1367, 1310, 1187, 1163, 1106, 1075, 1046, 1014, 966, 909, 846, 757, 737, 700, 675, 634, 611. *m/z* (ESI+): 581.1929 (M + H$^+$). $C_{33}H_{29}O_8N_2$ requires 581.1924.

(*R*,*S*)-4-Acetoxy-*N*-(4-acetoxyphenyl)-*N*-(1-(4-(pivaloyloxy)phenyl)-2-((4-acetoxyphenyl)amino)-2-oxoethyl)benzamide 2k. Following the general procedure B, a mixture of 4-pivaloyloxybenzaldehyde (203 mg, 1.00 mmol), 4-allyloxyaniline (153 µL, 1.11 mmol), 4-allyloxybenzoic acid (200 mg, 1.11 mmol), and 2,6-dimethylphenyl isocyanide (144 mg, 1.11 mmol) and 3 Å molecular sieves (50 mg) was stirred for 3 days at r.t. After work-up and purification (PE / AcOEt 7:3) compound **15** was obtained pure as off-white foam (198 mg, 31%). Then a mixture of **15** (168 mg, 0.26 mmol), $PdCl_2(PPh_3)_2$ (9 mg, 0.013 mmol) and ammonium formate (72 mg, 1.14

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mmol) was stirred for 5 h at 80 °C. After work-up, the crude was treated with 1:1 pyridine / acetic anhydride (2.6 mL) and stirred for 18 h at r.t. After work-up and purification (PE / Et_2O 1:3 + 1% EtOH) compound **2d** was obtained pure as white foam (117 mg, 69%). R_f = 0.15 (PE / Et_2O 1:3 + 1% EtOH). δ_H(300 MHz, $CDCl_3$, 25 °C): δ 7.42 (2 H, d, J 8.2), 7.42 (2 H, d, J 8.4), 7.26 (1 H, s, N*H*), 7.20-6.98 (7 H, m), 6.90 (2 H, d, J 8.3), 6.82 (2 H, d, J 8.5), 6.28 (1 H, s, C*H*), 2.23 (12 H, s, CH_3CO and CH_3Ar), 1.35 (9 H, s, $C(CH_3)_3$). δ_H(75 MHz, $CDCl_3$, 25 °C): 176.8, 170.3, 168.7 (x2), 167.9 (*C*=O), 151.5 (x2), 149.6, 138.4, 135.5 (x2), 133.4, 133.0, 131.6 (quat.), 131.4 (x4), 130.0 (x2), 128.2 (x2), 127.4, 121.9 (x2), 121.6 (x2), 120.9 (x2) (Ar*C*H), 66.3 (*C*H), 39.1 ($C(CH_3)_3$), 27.1 (ArCH_3), 21.1, 18.6 (CH_3CO). IR: ν_{max}/cm^{-1} 3269, 3046, 2970, 2874, 1752, 1643, 1603, 1503, 1479, 1418, 1367, 1279, 1263, 1189, 1164, 1107, 1015, 945, 910, 850, 803, 765, 703, 678, 626. *m/z* (ESI+): 651.2713 (M + H^+). $C_{38}H_{39}O_8N_2$ requires 651.2706.

(*R*,*S*)-(*E*)-*N*-(3-Acetoxybenzyl)-*N*-(1-(4-acetoxyphenyl)-2-((4-acetoxyphenyl)amino)-2-oxoethyl)-3-(4-acetoxy-3-methoxyphenyl)acrylamide 2l. Following the general procedure B, a mixture of aldehyde **12** (404 mg, 2.49 mmol), 3-allyloxybenzylamine (406 mg, 2.49 mmol), acid **13** (530 mg, 2.26 mmol), 4-allyloxyphenyl isocyanide (397 mg, 2.49 mmol) and 3 Å molecular sieves (250 mg) was stirred for 3 days at r.t. After work-up and purification (PE / AcOEt from 2:1 to 1:1) compound **14l** was obtained as yellow foam (1.19 g, 75%). Then a mixture of **14l** (200 mg, 0.29 mmol), $PdCl_2(PPh_3)_2$ (16 mg, 0.02 mmol) and ammonium formate (161 mg, 2.56 mmol) was stirred for 4 h at 80 °C. After work-up, the crude was treated with 1:1 pyridine / acetic anhydride (4 mL) and stirred for 18 h at r.t. After work-up and purification (PE / AcOEt 3:4) compound **2l** was obtained pure as white foam (118 mg, 58%). R_f = 0.80 (PE / AcOEt 1:6). δ_H(300 MHz, $CDCl_3$, 25 °C): 8.50 (1 H, s, N*H*), 7.67 (1 H, d, J 15.3, Ar*CH*=CH), 7.48 (2 H, d, J 8.7), 7.42 (2 H, d, J 8.4), 7.20 (1 H, t, J 7.9), 7.03-6.80 (10 H, m), 6.67 (1 H, d, J 15.3, ArCH=C*H*), 6.30 (1 H, s, C*H*), 4.93 and 4.69 (2 H, AB syst., J 17.9, CH_2Ar), 3.76 (3 H, s, OCH_3), 2.30, 2.26, 2.24 (4 x 3 H, 4 s, CH_3CO). δ_C(75 MHz, $CDCl_3$, 25 °C): 169.5, 169.2, 169.1, 168.8, 168.3, 167.9 (*C*=O), 151.2, 150.9 (x2), 146.9, 141.1, 139.5, 135.4, 133.7, 131.5, 144.2 (Ar*C*H=CH), 131.0 (x2), 129.6, 123.6, 123.1, 122.0 (x2), 121.9 (x2), 120.9 (x3), 120.4, 119.6, 111.5 (Ar*C*H), 117.6 (ArCH=*C*H), 63.0 (*C*H), 55.9 (OCH_3), 49.6 (ArCH_2), 21.10 (x2), 21.08, 20.6 (CH_3CO). IR: ν_{max}/cm^{-1} 3285, 3072, 2940, 1758, 1694, 1647, 1602, 1545, 1505, 1452, 1408, 1368, 1302, 1258, 1185, 1161, 1122, 1013, 978, 955, 908, 831, 792, 730, 691, 637. *m/z* (ESI+): 709.2405 (M + H^+). $C_{39}H_{37}O_{11}N_2$ requires 709.2397.

(*R*,*S*)-(*E*)-*N*-(2-(4-Acetoxyphenyl)ethyl)-*N*-(1-(4-acetoxyphenyl)-2-(methylamino)-2-oxoethyl)-3-(4-acetoxy-3-methoxyphenyl)acrylamide 2m. Following the general procedure B, a mixture of aldehyde **12** (135 mg, 0.83 mmol), 4-allyloxyphenethylamine (148 mg, 0.83 mmol), acid **13** (176 mg, 0.75 mmol), methyl isocyanide (74 µL, 1.23 mmol) and 3 Å molecular sieves (50 mg) was stirred for 3 days at r.t. After work-up and purification (PE / AcOEt 1:2) compound **14m** was obtained as yellow foam (263 mg, 59%). Then a mixture of **14m** (237 mg, 0.40 mmol), $PdCl_2(PPh_3)_2$ (23 mg, 0.03 mmol) and ammonium formate (170 mg, 2.70 mmol) was stirred for 4 h at 80 °C. After work-up, the crude was treated with 1:1 pyridine / acetic anhydride (9 mL) and stirred for 18 h at r.t. After work-up and purification (PE / AcOEt from 1:3 to 1:4) compound **2m** was obtained pure as white foam (188 mg, 78%). R_f = 0.32 (PE / AcOEt 1:6). δ_H(300 MHz, $CDCl_3$, 50 °C): 7.68 (1 H, d, J 15.3, Ar*CH*=CH), 7.56-7.45 (2 H, m), 7.13 (2 H, d, J 8.4), 7.11-6.89 (7 H, m), 6.74 (1 H, d, J 15.3, ArCH=C*H*), 6.21 (1 H, broad d, J 4.8, N*H*), 6.12 (1 H, s, C*H*), 3.84 (3 H, s, OCH_3), 3.80-3.55 (2 H, broad m, CH_2N), 2.87-2.73 (1 H, m, Ar*CH*H), 2.83 (3 H, d, J 4.8, CH_3NH), 2.45-2.17 (1 H, m, ArCH_2), 2.30, 2.29, 2.24 (3 x 3 H, 3 s, CH_3CO). δ_H(75 MHz, $CDCl_3$, 25 °C): 170.0, 169.2, 169.0, 168.6, 167.2 (*C*=O), 151.5, 151.0, 149.5, 141.3, 135.8, 134.1, 132.9 (quat.), 143.1 (Ar*C*H=CH), 130.7 (x2), 129.5 (x2), 123.3, 122.1 (x2), 121.7 (x2), 120.6, 111.8 (Ar*C*H), 117.8 (ArCH=*C*H), 61.6 (*C*H), 56.0 (OCH_3), 48.0 (NCH_2), 36.4 (ArCH_2), 26.4 (CH_3NH), 21.0 (x2), 20.5 (CH_3CO). IR: ν_{max}/cm^{-1} 3311, 2941, 2249, 1759, 1674, 1647, 1601, 1506, 1466, 1450, 1416, 1369, 1262, 1190, 1153, 1121, 1032, 1013, 979, 908, 829, 726, 646, 623. *m/z* (ESI+): 603.2352 (M + H^+). $C_{33}H_{35}O_9N_2$ requires 603.2343.

(*R*,*S*)-(*E*)-3-(4-Acetoxy-3-methoxyphenyl)-*N*-(1-(4-acetoxy-3-methoxyphenyl)-2-(*tert*-butylamino)-2-oxoethyl)-*N*-benzylacrylamide 2n. Following the general procedure B, a mixture of 4-allyloxy-3-methoxybenzaldehyde (140 mg, 0.70 mmol), benzylamine (84 µL, 0.77 mmol), acid **13** (180 mg, 0.77 mmol), *t*-butyl isocyanide (87 µL, 0.77 mmol) and 3 Å molecular sieves (35 mg) was stirred for 3 days at r.t. After work-up and purification (PE / AcOEt 6:4) compound **14n** was obtained pure as pale yellow foam (249 mg, 63%). Then a mixture of **14n** (249 mg, 0.42 mmol), $PdCl_2(PPh_3)_2$ (15 mg, 0.021 mmol) and ammonium formate (117 mg, 1.85 mmol) was stirred for 5 h at 80 °C. After work-up, the crude was treated with 1:1 pyridine / acetic anhydride (4.2 mL) and stirred for 18 h at r.t. After work-up and purification (PE / AcOEt 6:4 + 3% EtOH) compound **2n** was obtained pure as white foam (144 mg, 36%). R_f = 0.26 (PE / AcOEt 6:4 + 3% EtOH). δ_H(300 MHz, $CDCl_3$, 25 °C): 7.71 (1 H, d, J 15.3, Ar*CH*=CH), 7.45-7.10 (4 H, m), 7.10-6.90 (6 H, m), 6.83 (1 H, s), 6.65 (1 H, d, J 15.3, ArCH=C*H*), 6.12 (1 H, s, C*H*), 5.76 (1 H, s, N*H*), 4.92, 4.68 (2 H, AB syst., J 17.9, CH_2Ph), 3.74, 3.67 (2 x 3 H, 2 s, OCH_3), 2.29, 2.28 (2 x 3 H, 2 s, CH_3CO), 1.37 (9 H, s, $C(CH_3)_3$). δ_C(75 MHz, $CDCl_3$, 25 °C): δ 168.8 (x2), 168.0 (x2) (*C*=O), 151.1, 151.0, 140.9, 139.8, 138.4, 134.1, 133.9 (quat.), 143.0 (Ar*C*H=CH), 128.5 (x2), 127.0, 126.2 (x2), 123.0, 122.8, 122.0, 120.8, 114.1, 111.3 (Ar*C*H), 118.6 (ArCH=*C*H), 62.2 (*C*H), 55.8 (OCH_3), 51.8 ($C(CH_3)_3$), 49.6 (NCH_2), 28.6 ($C(CH_3)_3$), 20.6 (CH_3CO). IR: ν_{max}/cm^{-1} 3279, 3064, 2939, 1761, 1735, 1688, 1646, 1601, 1547, 1507, 1454, 1414, 1368, 1298, 1213, 1191, 1156, 1121, 1031, 1012, 976, 953, 909, 829, 723, 696, 635, 603. *m/z* (ESI+): 603.2697 (M + H^+). $C_{34}H_{39}O_8N_2$ requires 603.2706.

(*R*,*S*)-(*E*)-3-(4-Acetoxy-3-methoxyphenyl)-*N*-(1-(4-acetoxyphenyl)-2-(methylamino)-2-oxoethyl)-*N*-benzylacrylamide 2o. Following the general procedure B, a mixture of 4-allyloxybenzaldehyde (150 mg, 0.93 mmol), benzylamine (111 µL, 1.02 mmol), acid **13** (238 mg, 1.02 mmol), methyl isocyanide (61 µL, 1.02 mmol) and 3 Å molecular sieves (47 mg) was stirred for 3 days at r.t. After work-up and purification (PE / AcOEt 4:6) compound **14o** was obtained pure as pale yellow foam (246 mg, 51%). Then a mixture of **14o** (229 mg, 0.43 mmol), $PdCl_2(PPh_3)_2$ (15 mg, 0.022 mmol) and

ammonium formate (120 mg, 1.91 mmol) was stirred for 5 h at 80 °C. After work-up, the crude was treated with 1:1 pyridine / acetic anhydride (4.3 mL) and stirred for 18 h at r.t. After work-up and purification (PE / AcOEt 4:6 + 3% EtOH) compound **2o** was obtained pure as white foam (168 mg, 74%). R_f = 0.40 (PE / AcOEt 4:6 + 3% EtOH). δ_H(300 MHz, $CDCl_3$, 25 °C): 7.70 (1 H, d, J 15.3, ArC*H*=CH), 7.43 (2 H, d, J 8.4), 7.27-7.13 (3 H, m), 7.09 (2 H, broad d, J 7.2), 7.05-6.93 (4 H, m), 6.84 (1 H, s), 6.63 (1 H, d, J 15.3, ArCH=C*H*), 5.99 (1 H, s, C*H*), 5.94 (1 H, s, N*H*), 4.89, 4.66 (2 H, AB syst., J 17.8, CH_2Ph), 3.75 (3 H, s, OCH_3), 2.84 (3 H, d, J 4.8, CH_3NH), 2.29, 2.28 (2 x 3 H, 2 s, CH_3CO). δ_C(75 MHz, $CDCl_3$, 25 °C): 169.9, 169.2, 168.8, 168.0 (*C*=O), 151.2, 150.7, 141.0, 137.7, 134.0, 132.5 (quat.), 143.3 (Ar*C*H=CH), 130.9 (x2), 128.6 (x2), 127.2, 126.2 (x2), 123.1, 121.9 (x2), 120.8, 111.3 (Ar*C*H), 118.3 (ArCH=*C*H), 62.5 (*C*H), 55.8 (OCH_3), 50.2 (NCH_2), 26.5 (NCH_3), 21.1, 20.6 (CH_3CO). IR: ν_{max}/cm^{-1} 3302, 3065, 2940, 1760, 1674, 1647, 1601, 1506, 1453, 1407, 1368, 1300, 1257, 1189, 1155, 1121, 1080, 1030, 1012, 976, 957, 907, 844, 829, 724, 697, 676, 635. *m/z* (ESI+): 531.2137 (M + H$^+$). $C_{30}H_{31}O_7N_2$ requires 531.2131.

(*R*,*S*)-(*E*)- *N*-(2-((4-(2-(2-Acetoxyethoxy)ethoxy)phenyl)amino)-1-(4-acetoxyphenyl)-2-oxoethyl)-3-(4-acetoxy-3-methoxyphenyl)-*N*-benzylacrylamide 2p. Following the general procedure B, a mixture of 4-allyloxybenzaldehyde (146 mg, 0.90 mmol), benzylamine (106 µL, 0.99 mmol), acid **13** (231 mg, 0.99 mmol), *N*-(4-(2-(2-(allyloxy)ethoxy)ethoxy)phenyl) isocyanide (244 mg, 0.99 mmol) and 3 Å molecular sieves (45 mg) was stirred for 3 days at r.t. After work-up and purification (PE / AcOEt 1:1) compound **14p** was obtained pure as pale yellow foam (449 mg, 71%). Then a mixture of **14p** (449 mg, 0.61 mmol), $PdCl_2(PPh_3)_2$ (32 mg, 0.046 mmol) and ammonium formate (254 mg, 4.03 mmol) was stirred for 5 h at 80 °C. After work-up, the crude was treated with 1:1 pyridine / acetic anhydride (6.1 mL) and stirred for 18 h at r.t. After work-up and purification (PE / AcOEt 1:1 + 3% EtOH) compound **2p** was obtained pure as white foam (271 mg, 60%). R_f = 0.40 (PE / AcOEt 4:6 + 3% EtOH). δ_H(300 MHz, $CDCl_3$, 25 °C): δ 7.90 (1 H, s, N*H*), 7.71 (1 H, d, J 15.2, ArC*H*=CH), 7.49 (2 H, d, J 8.2), 7.39 (2 H, d, J 8.7), 7.30-7.07 (5 H, m), 7.03 (2 H, d, J 8.3), 6.96 (2 H, s), 6.90-6.81 (3 H, m), 6.67 (1 H, d, J 15.3, ArCH=C*H*), 6.19 (1 H, s, C*H*), 4.92, 4.72 (2 H, AB syst., J 17.6, CH_2Ph), 4.25 (2 H, dd, J 4.5, 5.0, OCH_2), 4.10 (2 H, broad t, J 4.5, CH_2O), 3.83 (2 H, broad t, J 4.5, CH_2O), 3.76 (2 H, dd, J 4.5, 5.0, OCH_2), 3.75 (3 H, s, OCH_3), 2.29, 2.28, 2.07 (3 x 3 H, 3 s, CH_3CO). δ_C(75 MHz, $CDCl_3$, 25 °C): δ 171.1, 169.1, 168.3, 167.6 (*C*=O), 155.6, 151.2, 150.8, 141.0, 137.7, 133.9, 135.5, 132.0 (quat.), 143.6 (Ar*C*H=CH), 130.8 (x2), 128.7 (x2), 127.3, 126.3 (x2), 123.1, 122.0 (x2), 121.8 (x2), 120.8, 114.9 (x2), 111.4 (Ar*C*H), 118.1 (ArCH=*C*H), 69.7, 69.3, 67.7, 63.6 (*C*H_2O), 63.0 (*C*H), 55.8 (OCH_3), 50.2 (NCH_2), 21.1, 21.0, 20.6 (*C*H_3CO). IR: ν_{max}/cm^{-1} 3278, 3065, 2940, 1760, 1735, 1688, 1647, 1601, 1546, 1507, 1454, 1414, 1368, 1299, 1191, 1157, 1121, 1031, 1012, 975, 953, 909, 829, 723, 697, 636, 604. *m/z* (ESI+): 739.2875 (M + H$^+$). $C_{41}H_{43}O_{11}N_2$ requires 739.2867.

(*R*,*S*)-(*E*)-*N*-(3-acetoxybenzyl)-3-(4-acetoxy-3-methoxyphenyl)-*N*-(1-(4-acetoxyphenyl)-2-(methylamino)-2-oxoethyl)-acrylamide 2q. Following the general procedure B, a mixture of aldehyde **12** (135 mg, 0.83 mmol), 3-allyloxybenzylamine (135 mg, 0.83 mmol), acid **13** (176 mg, 0.75 mmol), methyl isocyanide (49 µL, 0.83 mmol) and 3 Å molecular sieves (50 mg) was stirred for 3 days at r.t. After work-up and purification (PE / AcOEt 3:7) compound **14q** was obtained as white foam (313 mg, 72%). Then a mixture of **14q** (97 mg, 0.17 mmol), $PdCl_2(PPh_3)_2$ (10 mg, 0.014 mmol) and ammonium formate (71 mg, 1.12 mmol) was stirred for 3 h at 80 °C. After work-up, the crude was treated with 1:1 pyridine / acetic anhydride (2.5 mL) and stirred for 18 h at r.t. After work-up and purification (PE / AcOEt 1:6) compound **2q** was obtained pure as white foam (73 mg, 75%). R_f = 0.49 (PE / AcOEt 1:6). δ_H(300 MHz, $CDCl_3$, 25 °C): 7.72 (1 H, d, J 15.3, ArC*H*=CH), 7.40 (2 H, d, J 8.1), 7.21 (1 H, t, J 7.8), 7.03-6.82 (8 H, m), 6.63 (1 H, d, J 15.3, ArCH=C*H*), 5.97 (1 H, s, C*H*), 5.94 (1 H, broad s, N*H*), 4.89, 4.65 (2 H, AB syst., J 17.9, CH_2Ar), 3.77 (3 H, s, OCH_3), 2.83 (3 H, d, J 4.6, CH_3N), 2.29, 2.27, 2.26 (3 x 3 H, 3 s, CH_3CO). δ_C(75 MHz, $CDCl_3$, 25 °C): 169.9, 169.21, 169.16, 168.8, 168.0 (*C*=O), 151.2, 150.9, 150.8, 141.0, 139.6, 133.9, 132.2 (quat.), 143.8 (Ar*C*H=CH), 131.0 (x2), 129.6, 123.6, 123.1, 121.9 (x2), 120.9, 120.4, 119.6, 111.4 (Ar*C*H), 117.9 (ArCH=*C*H), 62.5 (*C*H), 55.9 (O*C*H_3), 49.7 (N*C*H_2), 26.4 (*C*H_3N), 21.1 (x2), 20.6 (*C*H_3CO). IR: ν_{max}/cm^{-1} 3302, 3072, 2967, 2940, 1760, 1676, 1648, 1602, 1506, 1438, 1414, 1368, 1302, 1258, 1190, 1156, 1120, 1014, 975, 909, 829, 794, 751, 722, 694, 635. *m/z* (ESI+): 589.2200 (M + H$^+$). $C_{32}H_{33}O_9N_2$ requires 589.2186.

General procedure for the preparation of polyphenols 1d,f,g,h,j,k,l,m,n,o,p,q from the corresponding acetylated derivatives 2. The peracylated Ugi product was treated with 0.2 M MeONa in MeOH (freshly prepared by adding Na to dry MeOH) under N_2 atmosphere. After stirring for 1 h (18 h for compound **15**) at r.t., the mixture was treated with previously washed Amberlyst 15 acid resin until pH = 4. The resin was filtered off and the solution evaporated to dryness (with exception of compound **1n**). The resulting polyphenols were not fully characterized, but only examined at ^{1}H NMR and HPLC in order to establish their degree of purity.

(*R*,*S*)-(*E*)-*N*-Butyl-*N*-(2-(*tert*-butylamino)-1-(4-hydroxyphenyl)-2-oxoethyl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide 1d. δ_H(300 MHz, DMSO-*d6*, 90 °C) (Note: the 2 phenolic OH exchange with H_2O contained in the solvent giving a broad signal around 9 ppm): 7.42 (1 H, d, J 15.2, ArC*H*=CH), 7.35 (1 H, s, N*H*), 7.17 (1 H, d, J 1.8), 7.14 (2 H, d, J 8.7), 7.06 (1 H, dd, J 8.2, 1.8), 6.82 (1 H, d, J 15.2, ArCH=C*H*), 6.81 (1 H, d, J 8.2), 6.79 (2 H, d, J 8.7), 5.87 (1 H, s, C*H*), 3.83 (3 H, s, OCH_3), 3.50-3.25 (mc = 3.38) (2 H, m, CH_2N), 1.50-1.30 (1 H, m, C*H*H), 1.29 (9 H, s, (CH_3)$_3$C), 1.20-0.95 (3 H, m, CH_2 and C*H*H), 0.74 (3 H, t, J 7.2, CH_3CH$_2$). HPLC (see supplementary information) showed a purity of 92%.

(*R*,*S*)-(*E*)-*N*-Benzyl-*N*-(2-(*tert*-butylamino)-1-(4-hydroxyphenyl)-2-oxoethyl)-3-(3,4-dihydroxyphenyl)acrylamide 1f. δ_H(300 MHz, DMSO-*d6*, 70 °C) (Note: the 2 phenolic OH exchange with H_2O contained in the solvent giving a very broad signal around 9 ppm): 7.53 (1 H, s, N*H*), 7.35 (1 H, d, J 15.2, ArC*H*=CH), 7.20-7.00 (6 H, m, Ar*CH*), 6.95-6.75 (2 H, m, Ar*CH*), 6.73-6.62 (4 H, m, ArCH=C*H* and Ar*CH*), 6.01 (1 H, s, C*H*), 4.85 (1 H, d, J 16.9, C*H*HPh), 4.55 (1 H, d, J 16.9,

C*H*HPh), 1.24 (9 H, s, (C*H*$_3$)$_3$C). HPLC (see supplementary information) showed a purity of 97%.

(*R*,*S*)-*N*-(4-Hydroxyphenyl)-*N*-(1-(4-hydroxyphenyl)-2-((4-hydroxyphenyl)amino)-2-oxoethyl)benzamide 1g. δ_H(300 MHz, DMSO-*d6*, 70 °C) (Note: the 3 phenolic OH exchange with H_2O contained in the solvent giving a very broad signal not visible in the spectrum): 9.69 (1 H, s, N*H*), 7.39 (2 H, d, J 8.8), 7.25-7.12 (5 H, m), 6.96 (2 H, d, J 8.5), 6.81 (2 H, broad d, J 7.2), 6.70 (2 H, d, J 9.0), 6.57 (2 H, d, J 8.7), 6.33 (2 H, d, J 8.9), 6.21 (1 H, s, C*H*). HPLC (see supplementary information) showed a purity of 99%.

(*R*,*S*)-4-Hydroxy-*N*-(1-(4-hydroxyphenyl)-2-((4-hydroxyphenyl)amino)-2-oxoethyl)-*N*-phenylbenzamide 1j. δ_H(300 MHz, DMSO-*d6*, 30 °C) (Note: the 3 phenolic OH exchange with H_2O contained in the solvent giving a very broad signal not visible in the spectrum): δ 9.91 (1 H, s, NH), 7.40 (2 H, d, J 8.9), 7.04 (2 H, d, J 8.7), 6.99 (5 H, broad s), 6.93 (2 H, d, J 8.4), 6.69 (2 H, d, J 8.9), 6.53 (2 H, d, J 8.4), 6.49 (2 H, d, J 8.7), 6.22 (1 H, s, C*H*). HPLC (see supplementary information) showed a purity of 100%.

(*R*,*S*)-4-Hydroxy-*N*-(4-hydroxyphenyl)-*N*-(1-(4-(hydroxy)phenyl)-2-((4-hydroxyphenyl)amino)-2-oxoethyl)benzamide 1k. δ_H(300 MHz, DMSO-*d6*, 70 °C): δ 9.39, 9.14, 9.03 (3 x 1 H, 3 broad s, O*H*), 9.21 (1 H, s, N*H*), 7.08 (2 H, d, J 8.7), 7.03 (2 H, d, J 8.4), 7.03 (3 H, s), 6.77 (2 H, d, J 8.2), 6.59 (2 H, d, J 8.5), 6.52 (2 H, d, J 8.6), 6.36 (2 H, d, J 8.8), 6.23 (1 H, s, C*H*), 2.12 (6 H, s, C*H*$_3$Ar), 1.35 (9 H, s, C(C*H*$_3$)$_3$). HPLC (see supplementary information) showed a purity of 100%.

(*R*,*S*)-(*E*)-*N*-(3-Hydroxybenzyl)-*N*-(1-(4-hydroxyphenyl)-2-((4-hydroxyphenyl)amino)-2-oxoethyl)-3-(4-hydroxyoxy-3-methoxyphenyl)acrylamide 1l. δ_H(300 MHz, DMSO-*d6*, 90 °C) (Note: the 4 phenolic OH exchange with H_2O contained in the solvent giving a very broad signal at around 9 ppm): 9.63 (1 H, s, N*H*), 7.41 (1 H, d, J 15.3, ArC*H*=CH), 7.33 (2 H, d, J 8.7), 7.17 (2 H, d, J 8.5), 7.00-6.85 (3 H, m), 6.75 (2 H, d, J 8.1), 6.73-6.63 (4 H, m), 6.58 (1 H, s), 6.55-6.48 (2 H, m), 6.17 (1 H, s, C*H*), 4.79 and 4.53 (2 H, AB syst., J 17.1, C*H*$_2$Ar), 3.76 (3 H, s, OC*H*$_3$). HPLC (see supplementary information) showed a purity of 92%.

(*R*,*S*)-(*E*)-*N*-(2-(4-hydroxyphenyl)ethyl)-*N*-(1-(4-hydroxyphenyl)-2-(methylamino)-2-oxoethyl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide 1m. δ_H(300 MHz, DMSO-*d6*, 90 °C) (Note: the 4 phenolic OH exchange with H_2O contained in the solvent giving a very broad signal at around 6 ppm): 7.73 (1 H, broad s, N*H*), 7.44 (1 H, d, J 15.3, ArC*H*=CH), 7.21-7.14 (3 H, m), 7.05 (1 H, dd, J 8.2, 1.9), 6.87-6.74 (6 H, m), 6.63 (2 H, d, J 8.4), 6.01 (1 H, s, C*H*), 3.85 (3 H, s, OC*H*$_3$), 3.64-3.40 (2 H, m, C*H*$_2$N), 2.66 (3 H, d, J 4.5, C*H*$_3$NH), 2.63-2.48 (1 H, m, ArC*H*H), 2.18-2.03 (1 H, m, ArC*H*$_2$). HPLC (see supplementary information) showed a purity of 92%.

(*R*,*S*)-(*E*)-*N*-benzyl-3-(4-hydroxy-3-methoxyphenyl)-*N*-(2-(*tert*-butylamino)-1-(4-hydroxy-3-methoxyphenyl)-2-oxoethyl)acrylamide 1n. After the treatment with the resin and evaporation, in this case the residue was further purified by chromatography (PE / AcOEt 6:4). δ_H(300 MHz, DMSO-*d6*, 90 °C): 9.00 (1 H, s, O*H*), 8.57 (1 H, s, O*H*), 7.45 (1 H, broad s, N*H*), 7.42 (1 H, d, J 15.3, ArC*H*=CH), 7.21-6.99 (6 H, m), 6.94 (1 H, d, J 8.0), 6.84-6.66 (4 H, m), 6.70 (1 H, d, J 15.3, ArCH=C*H*), 5.97 (1 H, s, C*H*), 4.87, 4.55 (2 H, AB syst., J 16.7, PhC*H*$_2$), 3.78 (3 H, s, OC*H*$_3$), 3.63 (3 H, s, OC*H*$_3$), 1.27 (9 H, s, (C*H*$_3$)$_3$C). HPLC (see supplementary information) showed a purity of 99%.

(*R*,*S*)-(*E*)-*N*-Benzyl-3-(4-hydroxy-3-methoxyphenyl)-*N*-(1-(4-hydroxyphenyl)-2-(methylamino)-2-oxoethyl)-acrylamide 1o. δ_H(300 MHz, DMSO-*d6*, 90 °C): 9.09, 9.00 (2 x 1 H, 2 broad s, O*H*), 7.73 (1 H, s, N*H*), 7.40 (1 H, d, J 15.3, ArC*H*=CH$_2$), 7.21-7.02 (6 H, m), 6.96 (1 H, s), 6.90 (1 H, d, J 8.1), 6.75 (2 H, d, J 8.4), 6.67 (2 H, d, J 8.7), 6.66 (1 H, broad signal, ArCH=C*H*), 6.04 (1 H, s, CH), 4.85, 4.62 (2 H, AB syst., J 17.1, C*H*$_2$Ph), 3.77 (3 H, s, OC*H*$_3$), 2.63 (3 H, d, J 4.6, C*H*$_3$NH). HPLC (see supplementary information) showed a purity of 96%.

(*R*,*S*)-(*E*)-*N*-Benzyl-*N*-(2-((4-(2-(2-hydroxyethoxy)ethoxy)phenyl)amino)-1-(4-hydroxyphenyl)-2-oxoethyl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide 1p. δ_H(300 MHz, DMSO-*d6*, 90 °C): 9.80 (1 H, s, N*H*), 9.15, 9.01 (2 x 1 H, 2 broad s, O*H*), 7.46 (2 H, d, J 9.0), 7.43 (1 H, d, J 15.0, ArC*H*=CH), 7.22-7.06 (4 H, m), 6.94 (1 H, broad d, J 15.0, ArCH=C*H*), 6.88 (2 H, d, J 9.0), 6.75 (1 H, d, J 8.1), 6.69 (2 H, d, J 8.4), 6.21 (1 H, s, C*H*), 4.90, 4.63 (2 H, AB syst., J 17.1, C*H*$_2$Ph), 4.08 (2 H, t, J 5.0, OC*H*$_2$), 3.75 (2 H, t, J 4.8, C*H*$_2$O), 3.75 (3 H, s, OC*H*$_3$), 3.58-3.48 (4 H, m, C*H*$_2$O). HPLC (see supplementary information) showed a purity of 97.5%.

(*R*,*S*)-(*E*)-*N*-(3-hydroxybenzyl)-3-(4-hydroxy-3-methoxyphenyl)-*N*-(1-(4-hydroxyphenyl)-2-(methylamino)-2-oxoethyl)acrylamide 1q. δ_H(300 MHz, DMSO-*d6*, 90 °C) (Note: the 4 phenolic OH exchange with H_2O contained in the solvent giving a very broad signal at around 9 ppm): 7.71 (1 H, s, N*H*), 7.39 (1 H, d, J 15.3, ArC*H*=CH), 7.11 (2 H, d, J 8.1), 7.00-6.87 (3 H, m), 6.75 (1 H, d, J 8.1), 6.68 (2 H, d, J 8.7), 6.67-6.46 (4 H, m), 6.02 (1 H, s, CH), 4.76, 4.53 (2 H, AB syst., J 17.1, C*H*$_2$Ar), 3.77 (3 H, s, OC*H*$_3$), 2.63 (3 H, d, J 4.5, C*H*$_3$N). HPLC (see supplementary information) showed a purity of 99%.

Biophysical and Biochemical tests

UV Spectroscopy

Synthetic polyphenols stock solutions were obtained by dissolving the compounds in 100% dimethyl sulfoxide (DMSO; Sigma) at given concentration (1.25 – 50 mM). Work solutions were prepared diluting the appropriate stock solution in PBS (150 mM, pH 7.4) at 12.5 – 500 μM, in such a manner that each tube contained 1% of stock solution in DMSO. Solubility and turbidity of polyphenols in function of the concentration was determined by spectrophotometric measures using Shimadzu UV-2700 Spectrophotometer and reading the absorbance respectively at characteristic wavelength of each polyphenols and at λ = 405 nm.

Aβ sample preparation

One milliliter of DMSO was added to 1 mg of lyophilized synthetic peptide (Aβ1-42, AβpE3-42 AnaSpec), reaching a final concentration of 1 mg/mL. Aliquots of 75 μL were lyophilized and stored at −20°C until used. For all experiments, stock peptides were reconstituted as reported.[54] The concentration of the peptide in the stock solution was estimated using a molar extinction coefficient at 214 nm, by Shimadzu UV-2700 Spectrophotometer.[55]

For the preparation of the working samples, stock solution of each peptide was divided in two or more aliquots. One was diluted to 5 µM in PBS containing 1% (v/v) DMSO to have a reference sample, the others were diluted in PBS containing the appropriate quantity of polyphenols stock solution in DMSO in such a manner that each samples contains 1% of DMSO. Final pH was measured and eventually corrected at 7.4 with few µL of 1M HCl.

Thioflavine T Fluorescence Spectroscopy

Aβ peptides (5 µM) were incubated at 37 °C in presence /absence of polyphenols as previous described and analyzed in parallel. ThT fluorescence was followed in time during aggregation. For this purpose, 47.5 µl of Aβ with and without test compounds, were mixed with 2.5 µL ThT (400 µM) in a 3 mm path length fluorescence cuvette. ThT fluorescence was measured by Luminescence Spectrometer Perkin Elmer LS50B at excitation and emission wavelengths of 440 nm (slit width=5 nm) and 482 nm (slit width = 10 nm), respectively.

Transmission electron microscopy (TEM)

Aβ peptides (10 µM) were separately co-incubated with single polyphenol at molar ratio 1:5 (Aβ:polyphenol) in sterile microtubes. To evaluate the morphology and the sizes of the species in the different samples, 5 µL of each one were adsorbed for 5 min onto carbon coated 300-mesh copper grids. The aggregates species were negatively stained for 1 min with 5 µL of 1% Uranyl Acetate. All air-dried specimens were examined with a Zeiss LEO 900 electron microscope (Zeiss, Stuttgart, Germany) operating at 80 kV. Images flattening and analysis was performed by ImageJ software.

Conflicts of interest

There are no conflicts to declare

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