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Synthesis and evaluation of arylquinones as BACE1 inhibitors, β-amyloid peptide aggregation inhibitors, and destabilizers of preformed β-amyloid fibrils

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ABSTRACT

BACE1 activity, inhibition of Aβ aggregation, and disaggregation of preformed Aβ fibrils constitute the three major targets in the development of small-molecule lipophilic new drugs for the treatment of Alzheimer's disease (AD). Quinones are widely distributed among natural products and possess relevant and varied biological activities including antitumor and antibiotic, inhibition of HIV-1 reverse transcriptase, antidiabetic, or COX-inhibition, among others. We report herein the interaction of several arylquinones and their derivatives with the amyloidogenic pathway of the amyloid precursor protein processing. Our studies put forward that these compounds are promising candidates in the development of new drugs which are effective simultaneously towards the three major targets of AD.

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder of the brain which affects 20–30 million individuals worldwide and is recognized as the leading cause of dementia.[1] Currently, there is no treatment available for AD and medical therapies are usually limited to acetylcholinesterase inhibitors and NMDA antagonists.[2] The pathology of this neurodegenerative disorder uniquely manifests itself with the presence of extraneuronal aggregation of plaques.[3] The β-amyloid peptide (Aβ) is the major constituent of these senile plaques found in the brain of patients with AD. Although the cause of AD remains unknown, a large body of evidence is beginning to accumulate that highlights the central role of Aβ in the pathogenesis of the disease.[4] Two aspartic proteases, β-secretase (BACE1) and γ-secretase, are the key enzymes that generate Aβ from amyloid precursor protein (APP). In particular, the cleavage of the β-site of APP by BACE1 is the rate-limiting initial step in Aβ formation.

It is widely believed that halting the production of Aβ peptide by inhibition of BACE1 is an attractive therapeutic modality for the treatment of AD.[5] BACE1 is an aspartyl protease, and there is significant effort in the pharmaceutical community to apply traditional design methods to the development of active site-directed inhibitors of this enzyme. Despite their high degree of biological validation as drug targets, the aspartyl proteases have generally proven to be difficult to inhibit with low-molecular weight, pharmacologically tractable molecules. Most of the aspartyl protease inhibitors in current clinical use today are peptidomimetics that target the catalytic active site of the enzyme. These drugs have demonstrated meager ability to cross the blood–brain barrier, which may prove to be an obstacle to the use of such compounds for treating diseases of the central nervous system, such as AD.[6] In addition to the active site, BACE1 contains additional binding pockets that engage the substrate protein at locations distal to the site of hydrolytic chemistry and can act as allosteric regulators of enzyme activity through conformational changes, to the active site to effect augmentation or diminution of the enzyme's catalytic reactivity. These allosteric sites could represent an alternative target for small molecules and open new opportunities for the identification and development of potential inhibitors of BACE1.[7]

Since AD is a complex neurodegenerative disorder resulting from multiple molecular abnormalities, strategies to develop drugs that simultaneously affect multiple biological targets are being proposed.[8] Inhibiting Aβ aggregation and destabilizing preformed Aβ fibrils constitutes another useful therapeutic approach for AD.[9]

As current therapies for AD are only palliative, the introduction of disease-modifying small-molecule drugs would be a major therapeutic breakthrough towards the treatment of this disease. Therefore, the design and synthesis of new agents which simultaneously

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inhibit BACE1, inhibit the aggregation of Aβ, and disaggregate preformed Aβ fibrils could be highly welcome.

Quinones are widely distributed among natural products[10] and possess relevant and varied biological activities including antitumor and antibiotic,[11] inhibition of HIV-1 reverse transcriptase,[12] antidiabetic,[13] or COX-inhibition,[14] among others. The basic knowledge on quinone studies has been used to design new anticancer drugs, improving selectivity and providing a more rational therapeutic application of them. The 1,4-naphthoquinone scaffold has been identified as a new class of Hsp90 inhibitors which could be useful for the treatment of cancer and numerous neurodegenerative disorders, including AD and Parkinson's disease, in which protein aggregation is a common etiology.[15] Memoquin, a 2,5-bis(diamino)-1,4-benzoquinone derivative, affects several mechanisms relevant to AD: the formation of reactive oxygen species, the processing and aggregation of Aβ, acetylcholinesterase activity and BACE1 activity. In animal models, it causes a remarkable decrease in the formation of AD neurodegenerative hallmarks and a significant reversal of behavioral deficits. Based on this unique pharmacological profile, memoquin is a promising drug candidate for the treatment of AD.[16] Also, it has been demonstrated that the protective action of 1,4-benzoquinone against amylin fibril-induced toxicity was most likely due to the binding interaction between 1,4-benzoquinone and amylin aggregated/fibrillar species.[17] Moreover, 1,4-benzoquinone has been reported to effectively attenuate fibrillogenesis and neurotoxic effect of Aβ.[18] It has been shown that 1,4-benzoquinone was able to suppress the aggregation process of α-synuclein.[19] Idebenone, (2-(10-hydroxydecyl)-5,6-dimethoxy-3-methyl-cyclohexa-2,5-diene-1,4-dione), a synthetic analog of coenzyme Q_{10}, blocks the oxidative stress and causes a depletion of ATP levels induced by Aβ. Moreover, pretreatment of rats with idebenone prevents the adverse behavioral learning and memory effects induced by intracerebroventricular infusion of Aβ.[20]

Based on these features, it was our interest to find out whether several aryl-1,4-napththoquinones could interact with the amyloidogenic pathway of the APP processing, particularly targeting at BACE1 as well as at Aβ aggregation and destabilizing preformed Aβ fibrils.[21] In the search for new quinones with enhanced activities towards the three targets, we have considered herein the structurally related 2,5-diaryl- or 2,6-diaryl-1,4-benzoquinones (Fig. 1).

Depending on the substitution pattern, arylated quinones have been obtained only by a few general methods.[22,23] Meerwein reactions with aryldiazonium salts and oxidation of the corresponding aromatics are among the most popular. Other methods such as the Pummerer arylation and direct arylation protocols have also been used for the installment of electron rich aryls or heteroaromatics. When these reactions are carried out on mono-substituted 1, 4-benzoquinones, an issue of regioselectivity arises, as the arylation can lead to a 2,5- or to a 2,6-disubstituted 1,4-benzoquinone. Most of these procedures take place with low regioselectivities and give poor yields with electron-deficient aryl groups. In this respect, transition-metal mediated cross-couplings are wider in scope than other procedures.[24] However, their application requires the previous selective functionalization of the starting quinone with a halogen or a triflate group suitable for coupling. Thus, the development of new synthetic methods leading to diarylated quinones in a regioselective fashion, suitable for the installment of both electron-rich and electron-poor aromatics, is worthy.

Quinones are well known for their Michael acceptor properties. In connection with arylation methods by conjugate addition reactions, the readily available non-toxic arylboronic acids are known to react with a wide variety of electron-deficient systems under transition-metal catalysis, mainly with Rh(I) species. Some scattered reports of the Rh(I)-catalyzed addition of boronic acids to quinones and their derivatives have been reported.[25–27] More recently, it has been shown that the addition of arylboronic acids to some electron-deficient alkenes can also be catalyzed by dicationic Pd(II) species, which are cheaper than Rh(I)-catalysts.[28] This method has been applied to the regioselective arylation of the 2- and 3-positions of naphtho- and anthraquinones.[29]

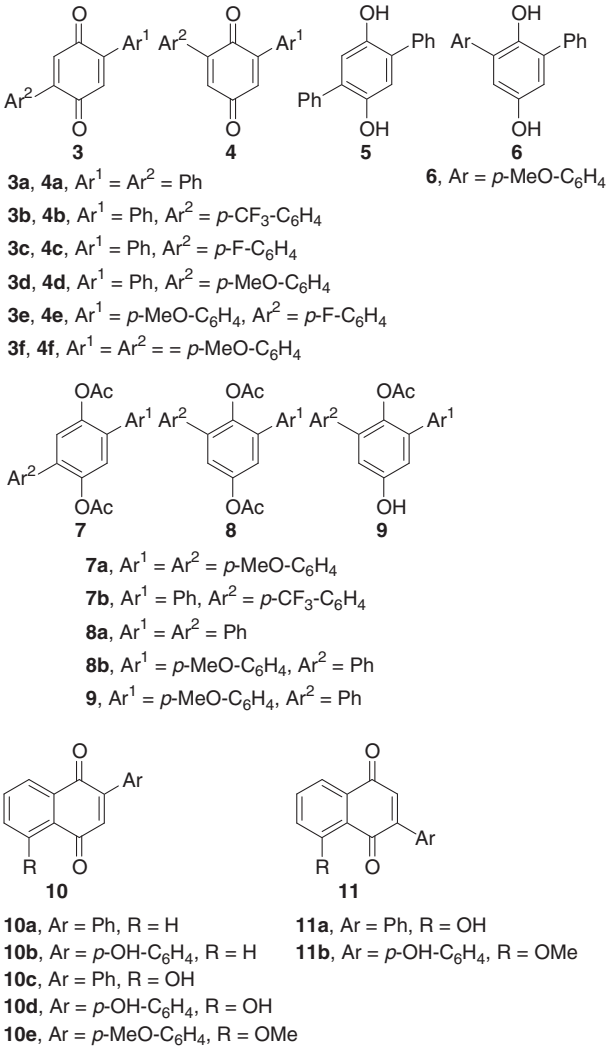
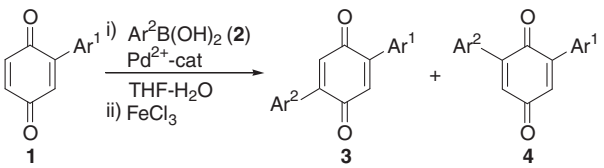


Figure 1. Compounds considered in this Letter.

Based on these results, in this paper we have developed a new mild method for the direct arylation of 2-aryl-1,4-benzoquinones (**1**) which permits the addition of either electron-rich or electron-poor arylboronic acids (**2**) under dicationic Pd(II)-catalysis leading to 2,5-diaryl-1,4-benzoquinones (**3**) and to 2,6-diaryl-1,4-benzoquinones (**4**) (Scheme 1). Good regioselectivities have been achieved in some cases (Table 1).

Optimization of the palladium precursor, phosphine ligands, protic or Lewis acidic additives and solvent–H_2O combination was carried out initially using 2-phenyl-1,4-benzoquinone **1a** and



Scheme 1. Synthesis of compounds **3** and **4**.

Table 1
Synthesis of compounds **3** and **4**

Entry	1	2	Method[a]	3:4 ratio[b], yield[c] (%)
1	**1a**	**2a**	A	**3a**:**4a** = 85:15 (90)
2	**1a**	**2b**	A	**3b**:**4b** = 70:30 (70)
3	**1a**	**2c**	A	**3c**:**4c** = 65:35 (85)
4	**1a**	**2d**	A	**3d**:**4d** = 50:50 (60)
5	**1a**	**2a**	B	**3a**:**4a** = 20:80 (90)
6	**1a**	**2b**	B	**3b**:**4b** = 35:65 (70)
7	**1a**	**2c**	B	**3c**:**4c** = 30:70 (60)
8	**1a**	**2d**	B	**3d**:**4d** = 40:60 (60)
9	**1b**	**2a**	A	**3d**:**4d** = 70:30 (70)
10	**1b**	**2c**	A	**3e**:**4e** = 70: 30 (70)
11	**1b**	**2d**	A	**3f**: **4f** = 50:50 (60)
12	**1b**	**2a**	B	**3d**:**4d** = 40:60 (70)
13	**1b**	**2c**	B	**3e**:**4e** = 30:70 (65)
14	**1b**	**2d**	B	**3f**:**4f** = 40:60 (60)

[a] Method A: (i) **1** (1.0 equiv), **2** (3.0 equiv), $Pd(OCOCF_3)_2$ (5 mol %), dppben (5.5 mol %), HBF_4 (1.0 equiv), THF–H_2O 8:2; (ii) $FeCl_3$, CH_2Cl_2, rt, 1 h. Method B: (i) **1** (1.0 equiv), **2** (3.0 equiv), $Pd(OCOCF_3)_2$ (5 mol %), AgOTf (1.0 equiv), THF–H_2O 10:1; (ii) $FeCl_3$, CH_2Cl_2, rt, 1 h.

[b] Determined by integration of the ^1H NMR ($CDCl_3$, 300 MHz) of the reaction crudes.

[c] Combined isolated yields. Compounds **3** and **4** were separated by column chromatography (hexane/DCM = 20: 80).

phenylboronic acid **2a**. This led to optimum conditions for the regioselective synthesis of compounds **3** or **4**, which were obtained as mixtures with variable amounts of the corresponding hydroquinones **5**, **6**. Without any separation, the reaction crudes were oxidized to afford compounds **3** and **4**.

The synthesis of the 2,5-diaryl-1,4-benzoquinones **3a**–**3c** was favored by treatment of quinones **1** with the arylboronic acids **2** (3.0 equiv) in the presence of $Pd(OCOCF_3)_2$ (5 mol %), 1, 2-bis(diphenylphosphino)benzene (dppben, 5.5 mol %) and HBF_4 (1.0 equiv) as the optimum reagent combination for generating the catalytically active dicationic Pd(II)-species at room temperature in THF–H_2O (8:2) as solvent (Table 1, entries 1–3). However, low regioselectivity was observed for the reaction with the electron-rich boronic acid **3d** (Table 1, entry 4).

On the other hand, the synthesis of the 2,6-diaryl-1,4-benzoquinones **4a–d** was favored under ligandless (no phosphine) conditions. Thus, reaction of quinones **1** with the arylboronic acids **2** (3.0 equiv) in the presence of $Pd(OCOCF_3)_2$ (5 mol %), and AgOTf (1.0 mol %) at room temperature in THF–H_2O (10:1) allowed the regioselective synthesis of the 2,6-diaryl-1,4-benzoquinones **4** after oxidation of the crude reaction mixtures (Table 1, entries 5–8).

Similar trends were observed when the reactions were carried out on quinone **1b** by either method (Table 1, entries 9–14).

Reduction of compounds **3a** or **4d** ($NaBH_4$, MeOH, rt, 1 h) gave compounds **5** and **6,** respectively. Compounds **7a**, **7b**, **8a**, and **8b** were prepared respectively by reductive acetylation of **3f**, **3b**, 4a and **4d** (Zn, Ac_2O, NaOAc, Δ, 90 min). Compound **9** was prepared by selective hydrolysis of the less hindered acetyl group of **8b** (K_2CO_3, MeOH, 0 °C, 5 h).

The mitochondrial-dependent reduction of MTT to formazan (described in Supplementary data) was used to exclude a cytotoxic effect of the 1,4-benzoquinones (1,4-BQ) in SH-SY5Y neuroblastoma cells. Non-cytotoxic concentrations of these compounds for brain cells must be tested since they would be eventually administered to organisms if active. For that purpose, these 1,4-benzoquinones were previously tested for cell viability in the SH-SY5Y cell line which is widely used for studies of neuroprotection and neurotoxicity. We found that several 1,4-benzoquinones (**4b**, **3c**, **3d**, 3e and **4e**) showed cytotoxicity up to 20 μM, therefore, they were discarded for the in vitro assays accomplished in the present work. Percentages of cell death at 20 μM for those compounds are shown in the Table 2. For aggregation inhibition experiments, Aβ (25–35) peptide was dissolved at 1 mM in PBS and 10 μM of the solution was mixed with the quinone and incubated at 37 °C for 4 days. For disaggregating experiments, 10 μM Aβ (25–35) peptide was incubated at 37 °C for 4 days to generate fibrils. Preformed fibrils were mixed with the quinones for 4 additional days at 37 °C. The degree of Aβ aggregation and disaggregation was determined using thioflavin-T (Thio-T) fluorescence analyses. Excitation and emission wavelengths were 448 and 483 nm, respectively. Sample fluorescence was determined by subtracting the fluorescence of a Thio-T blank. The assay for BACE1 activity was based on the secretase-dependent cleavage of a specific fluorogenic substrate (H-RE(EDANS)EVNLDAEFK(DABCYL)R-OH), which results in the release of a fluorescent signal. The level of secretase enzymatic activity was proportional to the fluorimetric reaction. BACE1 assay was carried out at 37 °C using 0.24 U of human recombinant BACE1 enzyme and 10 μM substrate in 20 mM sodium acetate buffer (pH 4.5) in a final volume of 100 μl. Wavelengths of excitation and emission were 360 and 528 nm, respectively. The enzyme activity assay was performed in the absence (control reaction), and in the presence of the quinone. Before the addition of the substrate the human recombinant BACE1 enzyme and the quinone were preincubated at 37 °C for 1 h. The inhibition ratio of BACE1 activity was calculated from the percentage of control after 1 h of incubation once the substrate was added. Data were expressed as the fifty percent inhibitory concentration (IC_{50}).

The BACE1 inhibitory activity of the quinones and their effect of Aβ aggregation are given in Table 2.

We found[21] that several 2-aryl and 3-aryl-1,4-naphthoquinones (**10a**–**10d**, **11a**) were selective for BACE1 inhibition, with no effect on Aβ aggregation or disaggregation. On the other hand, quinone **10e** showed BACE1 inhibition and also inhibited Aβ aggregation, but had no effect on disaggregation of preformed Aβ fibrils. Compound **11b** was active on the three targets.

Concerning benzoquinones and their reduced derivatives, since no neurotoxicity of compounds **3b**, **3f**, **4a**, **4d**, **5**, **6**, **7a**, **7b**, **8a**, 8b and **9** was found up to 20 μM, initial screening of compounds for inhibition of Aβ aggregation and disaggregation of Aβ aggregates was performed at concentration of 20 μM. Those compounds exhibiting inhibitory or disaggregating activity at least of a 50% were further analyzed to determine their IC_{50} values.

For the analysis of the data from inhibition of amyloid aggregation, we began by considering the 2,6-diarylbenzoquinones **4a** and **4d** which differed only by a *p*-methoxy group on one of the phenyl rings. We observed that both displayed a similar activity. Then, we compared the activity of **4d** with that of its reduced form, the hydroquinone **6**. This showed a decreased inhibitory activity, displaying the highest IC_{50} value among all the 1,4-benzoquinones tested. The inhibitory activity was completely lost upon mono- or diacetylation (compounds **9** and **8b**, respectively). Comparison of **4a** with **8a** showed a similar effect. Therefore, acetylation of the hydroxyl groups of the hydroquinone molecule was definitely detrimental for the inhibitory activity since it could involve a loss of hydrogen bond donors. Indeed, many studies indicate that hydrogen bonds are crucial in the interactions between polyphenols and proteins.[30] Next, switching to the 2,5-diaryl series, we observed that, opposite to 2,6-diphenyl-1,4-benzoquinone (**4a**), 2,5-diphenyl-1,4-benzoquinone (**3a**) was toxic to SH-SY5Y neuroblastoma cells at 20 μM. However, toxicity was reduced either by making both aryl rings electron-rich (**3f**) or by making one of the aryl rings electron-poor (**3b**). Compound **3f** exhibited the lowest IC_{50} value of all compounds studied, while **3b** showed a considerably higher IC_{50} value than **3f**. This puts forward that trifluoromethylation of one of the aryls reduces the protective activity against aggregation. As previously observed for the 2,6-diarylated compounds, the diacetylated 2,5-diarylhydroquinones **7a** and **7b**

Table 2
BACE1 inhibitory activity, inhibition of Aβ aggregation and disaggregation of Aβ fibrils

Compound	Cell death at 20 μM (%)	BACE1 inhibitory activity IC_{50} (μM)	Effect on Aβ aggregation, IC_{50} (μM)	
			Inhibition of Aβ aggregation	Disaggregation of Aβ fibrils
10a	Non-toxic	9.33	Non-active	Non-active
10b	Non-toxic	8.22	Non-active	Non-active
10c	Non-toxic	12.56	Non-active	Non-active
10d	Non-toxic	16.09	Non-active	Non-active
10e	Non-toxic	11.21	22.55	Non-active
11a	Non-toxic	8.98	Non-active	Non-active
11b	Non-toxic	10.31	16.59	5.05
3b	Non-toxic	6.52	14.19	12.31
3c	78.08	Non-tested	Non-tested	Non-tested
3d	56.29	Non-tested	Non-tested	Non-tested
3e	66.22	Non-tested	Non-tested	Non-tested
3f	Non-toxic	23.26	6.37	7.15
4a	Non-toxic	11.43	9.28	9.00
4b	100	Non-tested	Non-tested	Non-tested
4d	Non-toxic	13.41	9.56	7.87
4e	62.50	Non-tested	Non-tested	Non-tested
5	Non-toxic	15.96	>50	14.28
6	Non-toxic	9.10	17.83	8.24
7a	Non-toxic	23.92	Non-active	>50
7b	Non-toxic	12.12	>50	>50
8a	Non-toxic	20.01	Non-active	Non-active
8b	Non-toxic	11.15	Non-active	Non-active
9	Non-toxic	11.29	Non-active	Non-active

showed no inhibitory activity. However, 2,5-diphenylhydroquinone (**5**) showed no inhibitory activity, in contrast to the 2,6-diaryl series (**6**). As for disaggregation activity of Aβ aggregates (or fibrils), we observed that in the 2,6-series reduction of the quinone preserved the activity, as observed when comparing **4d** with **6**, while in the 2,5-series quinone **3f** was considerably more active than hydroquinone **5**. However, trifluoromethylation of the benzoquinone molecule on a phenyl ring, as shown in **3b**, led to the loss of activity, probably due to steric hindrance in the process of binding to amyloid protein. No activity was found for the acetylated derivatives in any case.

With respect to BACE1 inhibition, all compounds tested were active towards BACE1 inhibition at μM range. Comparison of the 2,6-diarylbenzoquinones **4a** and **4d**, whose IC_{50} values are 11.43 and 13.41 μM, respectively, indicated that introduction of a *p*-methoxy group was slightly detrimental for the activity. This effect was also observed in the 2,5-series, with compound **3f** displaying the highest IC_{50} value among all the quinones tested. Opposite to the effect on Aβ aggregation, trifluoromethylation of the benzoquinone molecule on a phenyl ring (**3b**) provided the highest inhibitory activity, with an IC_{50} value of 6.52 μM. Acetylation of the reduced form of **3b** was not favorable for the activity, since **7b** approximately displayed an IC_{50} value which doubled that of **3b**. However, as shown by the pairs **3f** & **7a**, 4a & **8a**, 4d & **8b** and **4d** & **9**, acetylation did not affect significantly the activity in the rest of cases. Last, hydroquinone **6** was slightly more active than the parent quinone (**4d**), while **5** was considerable less active than **6**.

Our studies revealed that, together with the 3-aryl-1,4-naphthoquinone **11b**, the 2,6-diaryl-1,4-benzoquinones **4a** and **4d** were the most effective compounds among those studied in altering simultaneously an important effect in the AD neurotoxic cascade: inhibition of amyloid aggregation and disaggregation of preformed Aβ fibrils. These 1,4-benzoquinones (**4a** and **4d**) were particularly effective in the inhibition of Aβ aggregation in comparison with **11b**, while the latter was more effective on disaggregation of preformed Aβ fibrils. In addition, the 2,5-diaryl-1,4-benzoquinone **3b**, which was also active against the three targets, showed the best activity towards BACE1 inhibition, although it was less effective both in the inhibition of Aβ aggregation and the disaggregation of preformed Aβ fibrils than compounds **4a** and **4d**.

In conclusion, our studies put forward that 2,6-diaryl-1,4-benzoquinones are promising candidates in the development of small-molecule lipophilic new drugs for the treatment of neurodegenerative diseases targeting simultaneously BACE1 activity, inhibition of Aβ aggregation, and disaggregation of preformed Aβ fibrils.

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Supplementary data

Supplementary data (experimental protocols for the synthesis of compounds **3**–**9**, pharmacological assays, and characterization of new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.03.023.

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