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Solid-phase synthesis of quinol fatty alcohols, design of N/O-substituted quinol fatty alcohols and comparative activities on axonal growth

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Abstract—Following the promising activity of Q_2FA15 on axonal growth, two new series of N/O-substituted QFAs were synthesized, based on a S_N2-type reaction. O-alkylated QFA bearing 14 carbon atoms on the side chain ($n = 14$) shows a very potent activity on axonal growth though lowered when compared to Q_2FA15. While O-alkylation allows good retention of the biological activity, N-alkylation abolishes it nonetheless. A solid-phase-supported synthesis of Q_2FA15 allowing the conception of new hybrid compounds is also described.

Regeneration of the CNS after injury is very limited due to the presence in the lesion site of many inhibitory factors such as myelin-associated proteins (MAG, OMGp and NOGO),[1] Sema3A[2] or chondroitin sulfate proteoglycan.[3,4] In a prior publication, we have shown that quinol fatty alcohols have the ability to promote axonal growth especially on inhibitory substrates present within the CNS.[5] Specifically, Q_2FA15 is able to promote axonal growth at 181% relative to control conditions, while allowing proper axonal growth on myelin proteins and Sema3A substrates.

Ω-Alkanol derivatives have proven in recent years to be very active towards various targets in the CNS.[6–8] The need of a synthetic strategy applicable to differently substituted ω-alkanols is nowadays a crucial aspect of our research. To address that, a synthetic strategy using solid-phase organic synthesis was designed in order to obtain Q_2FA15, based on the Sonogashira cross-coupling reaction between an arylbromide and a resin-supported terminal alkyne derivative.

Though Q_2FA15 is a very active compound, its chemical synthesis is rather tiresome. Based on a convergent synthetic route, four steps are needed for the synthesis of the side terminal alkyne chain, while an additional three steps are required for obtaining the final compound. In addition, the coupling reaction between the quinol and the alkyne moieties is based on Sonogashira cross-coupling[9,10] therefore using palladium catalysts.[11]

Palladium is known to interact with organic compounds and common purification procedures are often not sufficient to eliminate the excess metal catalyst.[12] In order to circumvent that problem, pharmaceutical industries are using techniques such as distillation, adsorption,[13] crystallization[14] and extraction[15] thus reducing palladium levels to acceptable amounts.

In this paper, we thereby describe the design of two new series of O-alkylated and N-alkylated quinol fatty alcohols where the carbon–carbon bond between the quinol and the ω-alkanol moieties was replaced by a C–O and C–N bond, respectively. O/N-alkylated QFAs were tested on a cellular model of axonal growth in order to compare their activity to lead compound Q_2FA15, while their free radical scavenging activity was also evaluated.

Solid-phase Sonogashira cross-coupling reactions are usually accomplished between a supported arylhalide/

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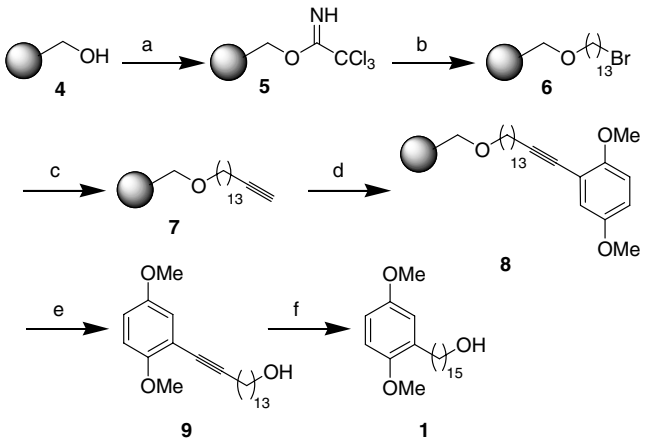
triflate and soluble terminal alkynes.[16] In our case, supported terminal alkynes were needed in order to be coupled to a variety of arylhalides/triflates. To do so, we used a trichloroacetamidate[17] Wang resin **5** which was subsequently substituted by 13-bromotridecan-1-ol in a mixture of methylene chloride and cyclohexane in acidic conditions to give resin **6**. Terminal alkyne **7** was obtained with lithium acetylide in DMSO.[18] The Sonogashira cross-coupling reaction was followed by a cleavage of our compound from the Wang resin with 10% TFA in methylene chloride and water. A final catalytic hydrogenation gave Q_2FA15 **1** (Scheme 1).

O-alkylated QFAs **2a–d** were obtained by a S_N2-type reaction between 2,5-dimethoxyphenol **14** and bromoalcohols **11a–d** with potassium carbonate in acetone.[19] 2,5-dimethoxyphenol **14** was obtained through a Baeyer–Villiger oxidation of 2,5-dimethoxycarboxaldehyde **13**.[20]



Scheme 1. Reagents and conditions: (a) CCl_3CN, DBU, 0 °C, 67%; (b) $BF_3 \cdot OEt_2$, 13-bromotridecan-1-ol, cyclohexane, CH_2Cl_2, 90%; (c) lithium acetylide (ethylene diamine complex), 0 °C to rt, 95%; (d) 1-bromo-2,5-dimethoxyphenol, $Pd(PPh_3)_4$, piperidine, 80 °C, 90%; (e) TFA 10%, CH_2Cl_2, H_2O, rt, 80%; (f) H_2, Pd/C 10%, EtOH, 90%.

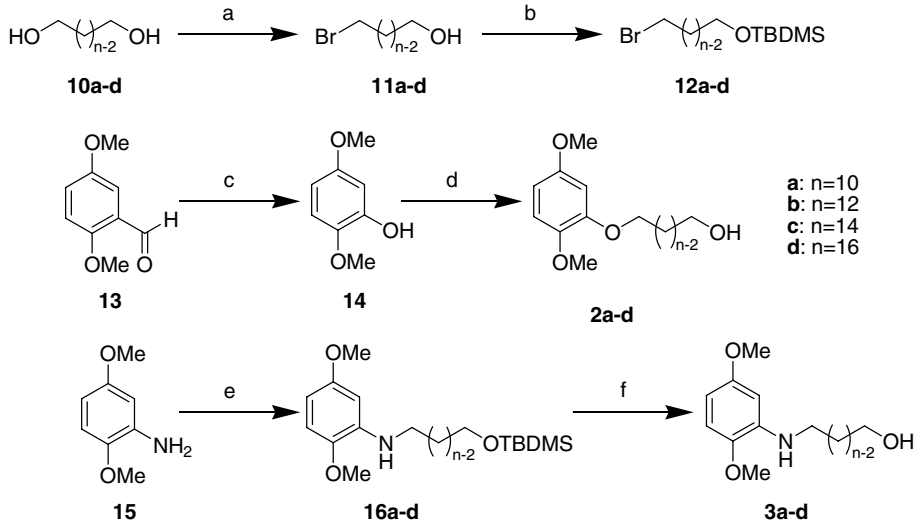
N-alkylated QFAs **3a–d** were obtained by a S_N2-type reaction between commercial 2,5-dimethoxyaniline **15** and protected bromoalcohols **12a–d** with *n*-BuLi in THF,[21] followed by deprotection with TBAF[22] (Scheme 2).

The C10 and C12 diols were commercially available. Diol C14 was obtained by reduction of the corresponding diacid with lithium aluminium hydride. Diol C16 is obtained by reduction of the corresponding lactone with the same reducing agent.[6] Bromoalcohols **11a–d** were obtained by monobromination of the corresponding diols in a mixture of HBr–cyclohexane.[6] The use of *tert*-butyldimethylsilyl chloride in methylene chloride[23] gave silylated bromoalkanols **12a–d**.

In an attempt to study the biological activity of our heteroatom-alkylated QFAs, we analyzed the ability of each compound to promote axonal growth on mouse cortical neurons (Table 1). The experimental protocol has been described in a prior publication.[24] Briefly, mice embryos at the 15th day of gestation were dissected and cortical extracts were dissociated with trypsin. The neurons obtained were plated in 6-well plates and cultured on poly-L-lysine coverslips for 24 h at 37 °C, 5% CO_2. On day 2, neurons were incubated with the test compound and grown for 24 h at 37 °C, 5% CO_2.

On day 3, neurons were fixed and immunostained with a primary anti-phosphoneurofilament antibody (SMi312, Sternberger) and a secondary Alexa488-coupled antibody. Coverslips were then mounted on plates with aqua-polymount.

A complete screening of all compounds at 10^{-9} M showed that O-alkylated compound (*O*-QFA14) with a 14-carbon side chain was the most effective, while its N-alkylated homologue had no apparent biological activity (Fig. 1).



Scheme 2. Reagents and conditions: (a) HBr 47%, cyclohexane, reflux, 6 h, 79–89%; (b) TBDMS-Cl, Imid., CH_2Cl_2, rt, 4 h, 89–95%; (c) i—mCPBA, CH_2Cl_2, 0 °C to rt, ii—NaOH 10%, MeOH, 95%; (d) K_2CO_3, **11a–d**, acetone, reflux, 6 h, 62–70%; (e) i—*n*-BuLi, THF, 0 °C, ii—**12a–d**, THF, 60 °C, iii—dioxane, 60 °C, 14 h, 54–65%; (f) TBAF, THF, rt, 4 h, 93–95%.