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Solid-phase synthesis of an *N*-(phenylalkyl)cinnamide library via Horner–Wadsworth–Emmons reaction

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Abstract—A readily automated solid-phase approach to the synthesis of diverse *N*-(phenylalkyl)cinnamides, analogues of the NR2B antagonist **2**, is described. The procedure utilizes polymer supported *N*-(phenylalkyl)amines, (diethylphosphono)acetic acid and a wide range of commercially available hydroxybenzaldehydes. The key step, a Horner–Wadsworth–Emmons reaction is achieved under mild conditions and was found to be general for a large number of benzaldehydes. A 225-member focused library was synthesized using a Tecan Combitec synthesizer.

N-methyl-D-aspartate (NMDA) receptors play a fundamental role in an array of physiological processes.[1] The hypothesis that aberrant activation of NMDA receptors underlies a number of neurodegenerative and psychiatric disorders has generated considerable interest in the NMDA receptor as a target for new pharmacotherapies. However, undesired side effects have limited the usefulness of these antagonists in the clinic.[2] NR2B subtype-selective NMDA receptor antagonists may offer one means to limit these side effects.[3]

It was reported by Tamiz et al. that cinnamides **1** and **2** (Fig. 1) are moderate NR2B antagonists.[4] The syntheses of **1**, **2** and their analogues were achieved by that group starting from cinnamoyl chloride or cinnamic acid derivatives and using traditional solution-phase chemistry. Since only a small number of these compounds have been synthesized till now, and it seemed likely that the structure of compound **2** is amenable for automated parallel synthesis, we decided to synthesize a small library of analogues of **2** using this technique.

The synthesis of *N*-(arylalkyl)cinnamides is outlined in Scheme 1. (4-Formyl-3-methoxyphenoxy)benzyl polystyrene resin[5] (**3**) was subjected to reductive amination with (phenylalkyl)amines[6] (**4a–e**) to give the resin bound amines (**5a–e**). This step was achieved by a modified version of the procedure of Bui et al.[7] In order to completely avoid reduction of the formyl group of **3** $NaBH_3CN$ was replaced by $Na(OAc)_3BH$. The conversion proved to be quantitative checked by elemental analysis (N content). The secondary amine intermediate (**5a–e**) was then acylated with (diethylphosphono)acetic acid using a standard acylation procedure[8] to provide the polymer-bound Horner–Wadsworth–Emmons (HWE) reagent[9] (**6a–e**).

To optimize the solid-phase HWE reaction,[10] six benzaldehyde derivatives (**7a–f**) and **6a** were selected as model compounds and their reactions in the presence of three bases, potassium *tert*-butoxide, sodium methoxide and lithium bis(trimethylsilyl)amide (LBTSA) were

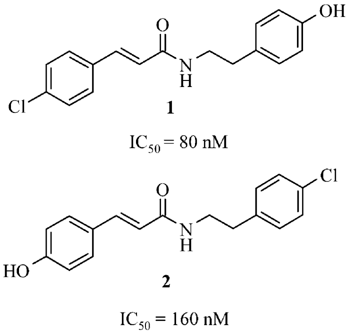

Figure 1. *N*-(Phenylalkyl)cinnamides having NR2B selective NMDA receptor antagonist activity.

Keywords: Solid-phase synthesis; Horner–Wadsworth–Emmons reaction; NMDA; NR2B; Library synthesis.

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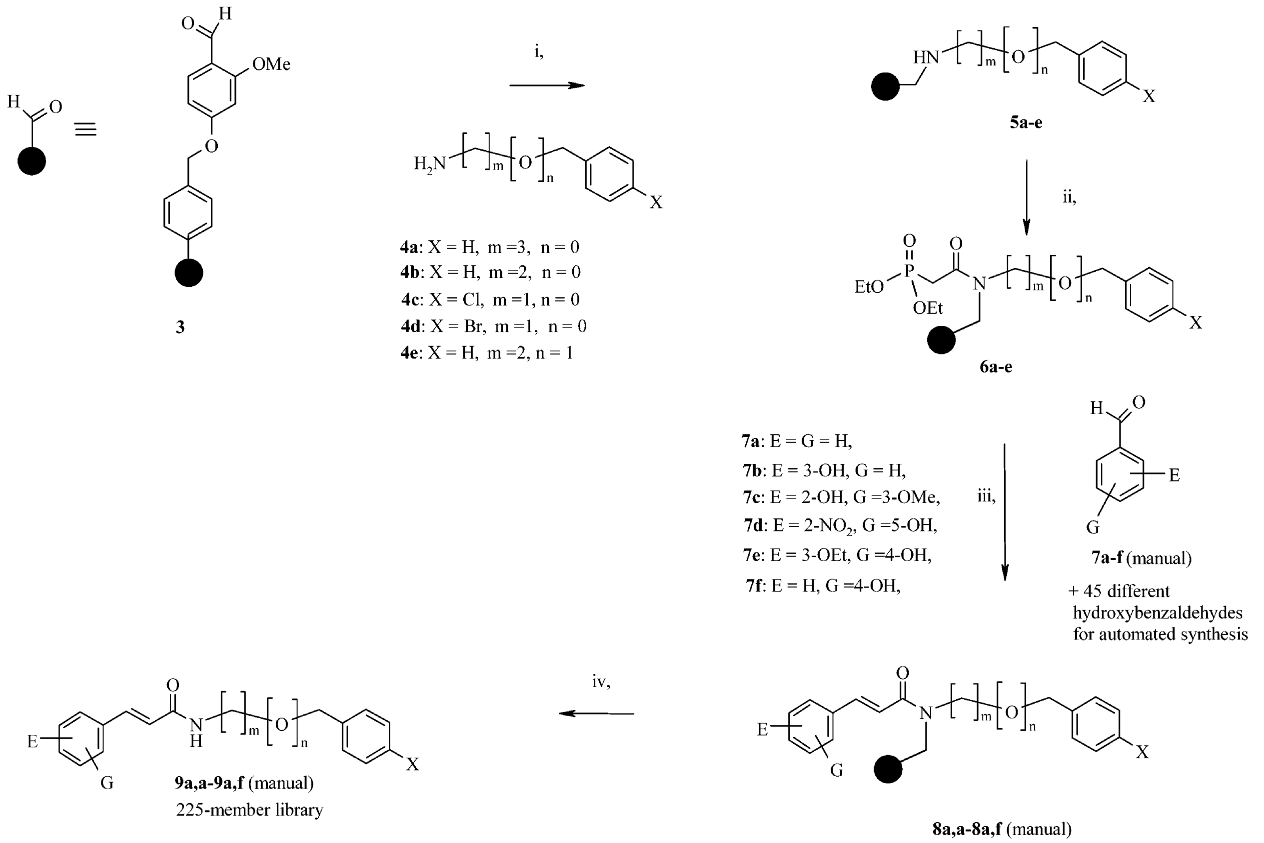

Scheme 1. Solid-phase synthesis of an *N*-(phenylalkyl)cinnamide library. Reagents and conditions: (i) 4 equiv Na(OAc)$_3$BH, 4 equiv primary amine, 10% AcOH/DCM, rt, 24 h; (ii) 5 equiv (EtO)$_2$OPCH$_2$COOH, 5 equiv HBTU, 5 equiv NEt$_3$, DMF, rt, 24 h; (iii) 5 equiv (manual) or 5 + 5 equiv (automated) benzaldehyde, 10 equiv (manual) or 10 + 10 equiv (automated) KO*t*Bu, NaOMe or LiN(SiMe$_3$)$_2$, 24 h (manual) or 16 + 16 h (automated), rt; (iv) 20% TFA/DCM, rt, 1.5 h.

studied. In some cases after addition of the base the phenol salts precipitated from the solution. Though there was no clear relationship between precipitate formation and conversion, we assume that the inactivity of **7e** toward **6a** (Table 1 entry 5) was due to the fact that the potassium salt of **7e** has very poor solubility in the THF/*t*-BuOH mixture. The cleavage of the polymer-bound cinnamides (**8a**,**a**–**8a**,**f**) from the resin was carried out with the mixture of TFA/DCM. The products (**9a**,**a**–**9a**,**f**) obtained in moderate yield and high purity. Since the molar extinction coefficients of the product and the starting (diethylphosphono)acetic amide are very different, the starting material content of the product was determined by the external standard method. The purity and the assumed *trans* geometry of **9a**,**a** were confirmed by ^{1}H NMR.[11] Based on the results summarized in Table 1 the method seemed suitable for library construction.

Table 1. Purity of cinnamides (**9a**,**a**–**9a**,**f**) prepared manually in different solvents using different bases

Entry	Cinnamides	Purity[a] (%)		
		KO*t*Bu/ *t*-BuOH, THF	NaOMe/MeOH THF THF	Li(SiMe$_3$)$_2$/ THF
1	**9a,a**	98	98	98
2	**9a,b**	98	93	92
3	**9a,c**	87	84	94
4	**9a,d**	96	97	93
5	**9a,e**	0	97	96
6	**9a,f**	93	95	97

[a] The purities and MW-s of the crude products were determined by LC-MS.

The feasibility of the HWE reaction for automated solid-phase synthesis was first demonstrated by Salvino et al.[12] Their procedure is based on generation of the resin-bound phosphonate anion in THF at 0 °C by addition of an excess of LBTSA. This procedure differed from earlier reported solid-phase HWE reactions because the excess of base was removed before addition of the aldehyde.

The first step in the optimization of the automated synthesis was the selection of a suitable base for each aldehyde. Based on the results obtained from the experiments carried out manually (Table 1) LBTSA was used first. The reactions of 51 different, commercially available hydroxybenzaldehydes with **6a** in the presence of LBTSA were investigated. In the case of aldehydes that did not furnish the desired product in at least 85% purity, sodium methoxide was tried next. In order to validate the results we obtained manually and to make this step robuster, in both cases after 16 h the resin was filtered off, washed and this was followed by addition of a second amount of aldehyde and base. The potassium *tert*-butoxide/*tert*-butanol system did not prove to be suitable for automated synthesis, because of the problems with the addition in the desired concentration range. It was observed that in the case of di- and trihydroxybenzaldehydes the conversions were low in spite of using two- or three-fold amount of base relative to aldehyde. 2,6-Disubstituted hydroxybenzaldehydes also gave products with low purity.

Aldehydes which did not give product in at least 85% purity using either one of the bases were removed from the building block library.

The library was characterized by LC-MS. The purities of the individual compounds were determined by LC integration without calibration. As a result, 58% of the library showed purity greater than 90%, 19% had purity between 80–90%, while 23% of the compounds did not reach the purity of 80%.

The functional NMDA antagonist potency of all members of the library was assessed according to the procedure described in the literature.[13] Every compound showed lower activity than both Co 101526 (**1**) and **2**. **9a**,**f** (Scheme 1) proved to be the most active member of the library (IC_{50} = 225 nM). This compound contains the same monosubstituted 4-hydroxycinnamoyl moiety as **2**, but has a butyl linker and no Cl at the 4′ position.

In summary, a new solid-phase method for the preparation of 2-(arylalkyl)cinnamides has been developed and the feasibility for automated library synthesis has been demonstrated.

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