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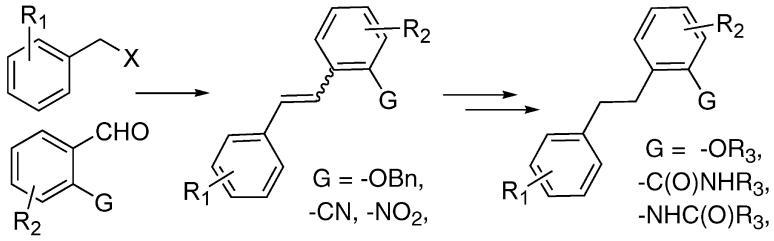

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Solution-Phase Parallel Wittig Olefination: Synthesis of Substituted 1,2-Diarylethanes

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An efficient strategy for solution-phase parallel synthesis of substituted 1,2-diarylethanes is described. A stilbene library was initially generated by Wittig olefination utilizing amino-labeled phosphines. The stilbene analogues were obtained in high yields and excellent purities after solid-phase extraction. Subsequent reduction of the stilbene libraries simultaneously unmasked functional groups by deprotection, facilitating orthogonal synthesis and further diversification into sublibraries. The libraries from libraries were obtained in good yields and purities using parallel solution-phase alkylation and acylation methodologies. Screening of the sublibraries revealed selective 5-HT_{2A} inverse agonists with IC-50 values between 10 and 100 nM.

Introduction

Recently, the role of the serotonin (5-HT) receptors, as targets for antipsychotic drugs, has received increasing attention.[1] Following extensive in vitro profiling, we recently discovered that almost all potent atypical antipsychotics share potent inverse agonism at the 5-HT_{2A} receptor as a common feature.[2] These findings have led us to revisit a number of known compounds with interesting pharmacological profiles. Sarpogrelate (Figure 1) is a selective, although weak, 5-HT_{2A} antagonist that has received some attention.[3] Fujimoto et al.[3] have reported the synthesis of a series of analogues with dual dopamine (D_2)/serotonin activity. A decreasing 5-HT_2 selectivity is observed for analogues with more than two methylene groups between the two aromatic components. Varying the position and nature of the substituents on the ω-phenyl also influenced the 5-HT_2 activities, but not the D_2 activity. Finally, the removal of the secondary alcohol improved both the 5-HT_2 and D_2 activities. The interesting biological activities of molecules belonging to this compound class,[4] and the profile of Sarpogrelate in particular, prompted us to readdress the general motif (Figure 1).

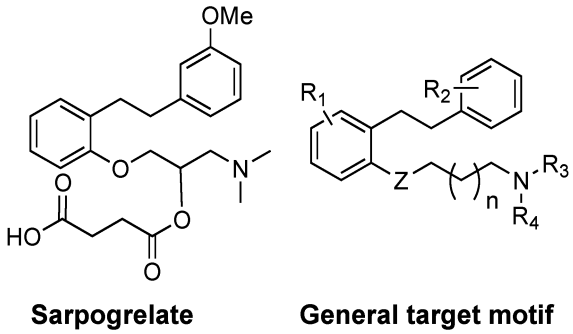

Figure 1.

In this paper, we report the development of a solution-phase strategy for parallel synthesis of substituted 1,2-diarylethanes, generating libraries from libraries.[5] The scope and limitations of the involved chemistry are discussed. The stilbene core of the target structure was assembled by parallel Wittig olefination using a triphenylphosphine analogue containing an amino substituent on one of the phenyl groups. The chosen compound has previously been used for Mitsunobu reactions[6] and Wittig olefinations.[7] However, none of these cases involved parallel synthesis or purification by solid-phase extraction, which is demonstrated in this paper. Solid-supported triphenylphosphine has previously been used with success in parallel synthesis, including Mitsunobu reactions[8] and Wittig olefination.[9] The Wittig reaction is an excellent way to generate stilbene analogues, because a large unmber of starting materials (benzyl halides and aryl aldehydes) are commercially available.

We decided to explore a novel strategy for the installation of the aminoalkyl chain that would allow us a high degree of flexibility to introduce a diverse set of functionalities. We deemed this important because both the nature of the chain, as well as the chain length, have a significant influence on the biological activity. A combination of stilbene reduction and deprotection of functional groups would efficiently facilitate orthogonal synthesis of sublibraries.

Results and Discussion

Parallel Wittig Olefination. The commercially available (*p*-(dimethylamino)-phenyl)diphenylphosphine (Scheme 1) was chosen for the Wittig reaction. The phosphonium salts

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Scheme 1. Solution-Phase Parallel Wittig Olefination and Evaluated Building Blocks

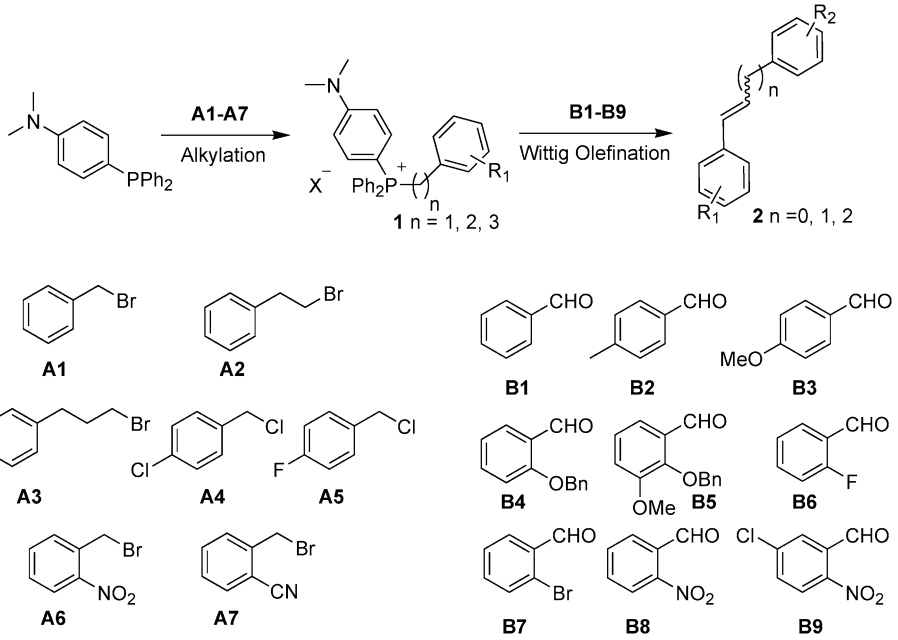


Table 1. Analytical Data for Selected Compounds

compd	yield (%)	purity (UV)	compd	yield (%)	purity (UV)	compd	yield (%)	purity (UV)
1-A1	79	95	**2-A6B2**	91	95	**3-A6B2**	85	88
1-A2	97	99	**2-A6B3**	97	93	**3-A6B3**	90	100
1-A3	99	97	**2-A6B6**	98	100	**3-A6B6**	77	100
1-A4	99	98	**2-A6B7**	99	100	**3-A7B1**	98	100
1-A5	78	97	**2-A7B1**	99	100	**3-A7B2**	96	93
1-A6	99	95	**2-A7B2**	93	100	**3-A7B6**	83	100
1-A7	83	97	**2-A7B3**	95	100	**4-A4B4C1**	99	100
2-A1B4	94	100	**2-A7B6**	96	98	**4-A4B4C2**	88	95
2-A1B5	96	100	**2-A7B7**	90	100	**4-A4B4C3**	58	100
2-A1B8	99	100	**3-A1B4**	85	100	**4-A4B5C1**	66	90
2-A1B9	94	100	**3-A1B5**	70	94	**4-A4B5C2**	69	90
2-A4B1	79	100	**3-A1B8**	63	96	**4-A5B4C1**	81	90
2-A4B4	99	100	**3-A4B4**	67	100	**4-A5B4C2**	92	95
2-A4B5	94	100	**3-A4B5**	42	100	**4-A5B4C3**	40	98
2-A4B8	91	100	**3-A4B8**	87	94	**5-A1B8C7**	65	77
2-A4B9	99	100	**3-A5B1**	69	100	**5-A1B8C8**	71	77
2-A5B4	91	93	**3-A5B4**	99	100	**6-A7B1C4**	99	73
2-A5B5	99	100	**3-A5B5**	79	100	**6-A7B1C5**	99	64
2-A5B8	90	100	**3-A5B8**	93	100	**6-A7B1C6**	96	73
2-A5B9	93	100						

1 were synthesized in parallel from the alkyl halides (**A1**−**A7**) (Scheme 1) by mixing the phosphine and halide (1:1) in acetonitrile at reflux. Some of the phosphonium salts crystallized by cooling to room temperature, and they were isolated by filtration. The phosphonium salts which did not solidify were simply concentrated. For both cases, the good yields and excellent purities were comparable (Table 1). N-alkylation was not detectable (^{1}H NMR and MS) in any of the cases studied or in a control experiment using methyl iodide as the electrophile.

The stilbene derivatives were synthesized in parallel by mixing an excess of the phosphonium salts (**1-A1**−**1-A7**) with aldehydes (**B1**−**9**) in acetonitrile. The mixtures were heated in sealed vials in the presence of DBU. The reactions went to completion over a period of 15 h. After cooling to ambient temperature, the products were isolated by solid-phase extraction. The amino-labeled phosphine derivatives and DBU were captured on the resin, allowing the products to be collected. In general, products derived from benzylic halides (**A1**, **A4**−**A7**) gave olefins of excellent purities (≥95%) and very high yields (Table 1). The cis/trans ratio varied from 1:1 to 1:10, favoring the trans analogues. However, extending the procedure to phosphonium salts **A2** and **A3** was less unsuccessful. Reactions with the aldehydes (**B1**, **B4**, and **B5**) gave products of low to modest purities (31−70%, data not shown).

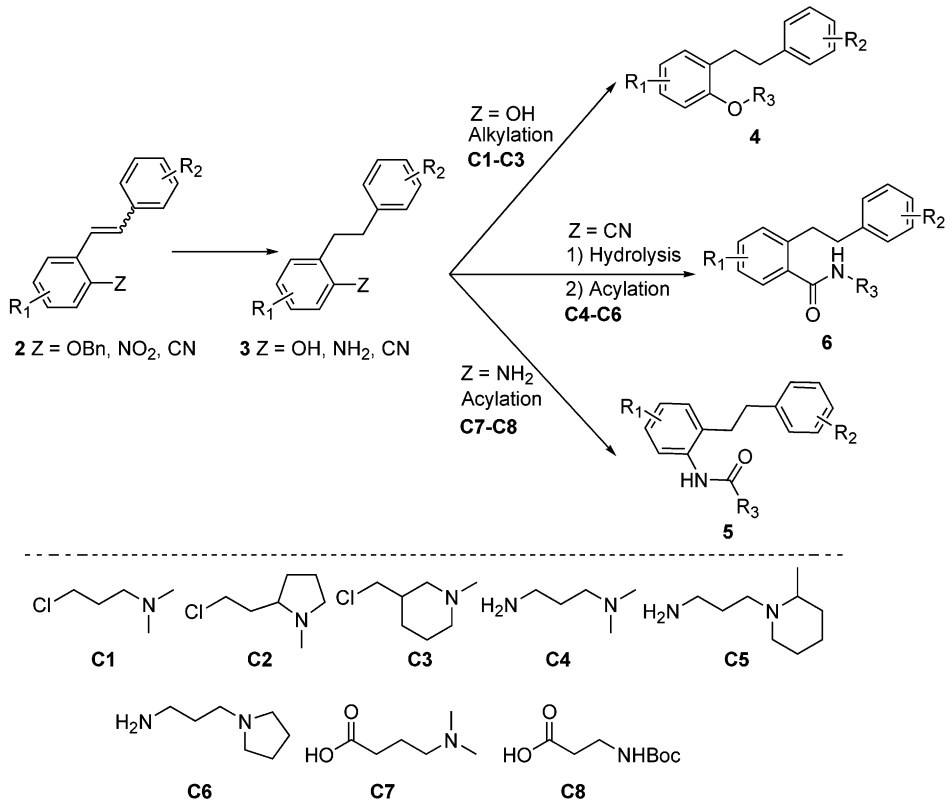
Alternatively, the Wittig olefination was performed in a microwave oven. Under these conditions, the aldehydes were consumed in 10 min. However, both yields and purities were lower than observed for the procedure described above. These findings are in agreement with previously reported microwave-assisted Wittig olefination using solid-supported phosphines.[9a]

Libraries from Libraries. The stilbene analogues **2** were reduced by catalytic hydrogenation to give the corresponding 1,2-diaryl-ethane derivatives **3** (Scheme 2). As mentioned above, these conditions also unmasked the functionalities facilitating further library diversity. The *O*-benzyl group and the nitro groups were reduced to give the corresponding phenols and anilines, respectively. As anticipated, not all of the aromatic halides could withstand the reaction conditions. In general, only the fluorides were stable under the conditions employed. The analogues that did survive the reduction were obtained in excellent purities and good yields (Table 1).

To illustrate the utility of our synthetic strategy, analogues of **3**, containing phenols (Z = OH), anilines (Z = NH_2), and nitriles (Z = CN) were further derivatized, using parallel solution-phase techniques. The deprotected phenols **3** (Z = OH) were alkylated in parallel with a set of 3-chloroalkyl-amines (**C1**−**C3**) in 2-propanol/KOH. An excess of phenol was used to ensure consumption of the amine. The products **4** were isolated by solid-phase extraction in excellent purities (Table 1).

The aniline derivatives **3** (Z = NH_2) were acylated in parallel, using a set of carboxylic acids (**C7** and **C8**, Scheme 2). For amino acid **C7**, a procedure using DIC and NHS

Scheme 2. Libraries from Libraries



was employed. This allowed purification by liquid−liquid extraction, and the products were obtained in good yields and purities (Table 1). The only observed impurity was diisopropylcarbamide. For the *N*-Boc-protected amino acid **C8**, a procedure using EDC and HOBt was employed. The products **5** were isolated by simple liquid−liquid extraction. It was anticipated that the *N*-Boc-protected compounds **5** may be further derivatized using previously described parallel solution-phase procedures for reductive amination.[10] This is not demonstrated here.

Finally, the nitriles **3** (Z = CN) were hydrolyzed to the corresponding carboxylic acids and then used in acylation of a set of amines (**C4**−**C6**, Scheme 2). The hydrolyses were best accomplished using aqueous base. The products were isolated by simple liquid−liquid extraction. Without further purification, the carboxylic acids were used in parallel acylation processes. The products **6** were isolated by ion-exchange chromatography in good yields and moderate purities (Table 1). Again, the main impurity was diisopropylcarbamide, which proved to be difficult to wash off the ion-exchange resin columns.

Conclusion

We have developed a practical and efficient solution-phase methodology for parallel Wittig olefination and applied the methodology to parallel synthesis of 2′-substituted 1,2-diarylethanes. In addition, the described protecting group strategy for unmasking functionalities is an efficient way to generate libraries from libraries, which allows for simultaneous exploration of different parts of a pharmacophore. Efficient use of protection groups in parallel synthesis will become more important as the desire to generate increasingly complex libraries rises.

Preliminary in vitro pharmacological characterization of the synthesized sublibraries, using R-SAT revealed 5-HT_{2A}-selective compounds with moderate inhibition constants (IC_{50} 10−100 nM).

Experimental Section

Materials and General Methods. All of the solvents and reagents used were obtained commercially and were used as received unless noted otherwise. All solvents were dried over molecular sieves. NMR spectra were recorded on a Varian 400 MHz Mercury VX spectrometer (^{1}H at 400 MHz and ^{13}C at 100 MHz) or on a Varian 300 MHz Mercury (^{31}P at 121.5 MHz). Chemical shifts are reported in parts per million relative to tetramethylsilane. The coupling constants are reported in Hertz. HPLC/MS data were recorded on an HP1100 LC/MS instrument using DAD/MSD electrospray detection. Eluent: 8 mM ammonium acetate in acetonitrile/water. UV data were recorded at UV_{max}. GC/MS data were recorded on an HP 5890 II combined with a JEOL JMS-HX/HX 110A tandem mass spectrometer. The reaction steps were performed in parallel using a Labmate from Advanced ChemTech or equivalent equipment. A Speedvac SC-210A was used for parallel concentration. The catalytic hydrogenation steps were performed in parallel using a desiccator as the reaction chamber. Ion-exchange chromatography was performed on prepacked Varian Every Bond Elut (SCX, 0.75 meq/g) or on a column packed with Dowex 50 × 8-200. The prepacked columns were washed with methanol (4×) prior to use. A solution of ammonia (10%) in methanol was used to elute amines from the ion-exchange columns. For known compounds, the obtained data were compared to published values.

General Procedure for Parallel Synthesis of Phosphonium Salts. The alkyl halide (**A1**−**A7**) (2.5 mmol) and (4-*N*,*N*-dimethylaminophenyl)diphenylphosphine (2.5 mmol) were mixed in acetonitrile (6 mL). The reaction mixture was kept at reflux temperature for 5 h. After cooling to room temperature, the phosphonium salts **1** were collected by filtration or concentration under reduced pressure.

Microwave-Assisted Parallel Synthesis of Phosphonium Salts. The halide (0.3 mmol) and 4-(*N*,*N*-dimethylaminophenyl)diphenylphosphine (85.2 mg, 0.3 mmol) were mixed in acetonitrile (3 mL). The reaction mixture was heated in a domestic microwave oven (600 W, 10 min). The mixture was cooled to room temperature and concentrated.

General Procedure for Parallel Wittig Olefination. The phosphonium salt **1** (0.5 mmol), DBU (0.5 mmol), and aldehyde (**B1**−**B9**) (0.33 mmol) were mixed in acetonitrile (6 mL). The reaction mixture was heated (100 °C) in a sealed tube for 15 h. After cooling to room temperature, the reaction mixture was purified by solid-phase extraction and concentrated.

General Procedure for Parallel Catalytic Hydrogenation. The olefins **2** were dissolved in 2-propanol, and a catalytic amount of Pd/C was added to each reaction vessel. The reaction vessels were situated in a desiccator, and the vigorously stirred reaction mixtures were kept under H_2 (1 atm) for 24 h at room temperature. The reaction mixtures were filtered and concentrated to give the desired products without further purification.

General Procedure for Parallel Synthesis of Ethers. To a solution of the 2′-hydroxy-1,2-diphenylethane **3** (0.02 mmol) and KOH (0.02 mmol) in 2-propanol (2 mL) was added one of the 3-chloroalkylamines (**C1**−**C3**) (0.014 mmol). The reaction mixture was shaken at reflux temperature. After 16 h, the product **4** was collected and purified by solid-phase extraction.

General Procedures for Parallel Synthesis of Amides from Anilines. (a) A solution of the aniline analogues **3** (0.25 mmol), amino acid **C7** (0.75 mmol), DIC (1.25 mmol), and NHS (1.25 mmol) was shaken at room temperature. After 5 h, the reaction mixture was concentrated. The product **5** was isolated by liquid−liquid extraction, or (b) aniline **3** (1.5 mmol), Boc-protected amino acid **C8** (4.5 mmol), EDC (7.5 mmol), and HOBt (4.5 mmol) were mixed in dichloromethane (30 mL). After 5 h at room temperature, the reaction mixture was concentrated. The product **5** was isolated by liquid−liquid extraction.

General Procedure for Parallel Synthesis of Amides from Nitriles. The 2-styrylbenzonitrile (1.3 mmol) was dissolved in water/methanol 2:5 (7 mL). Base (KOH, 2.8 mmol) was added, and the reaction mixture was stirred at 80 °C in a sealed vial for 48 h. The acid was isolated by liquid−liquid extraction. The crude acid derivative (0.23 mmol), alkylamine (**C4**−**C6**, 0.22 mmol), NHS (0.34 mmol), and DIC (0.34 mmol) were mixed in dichloromethane (5 mL) and shaken for 19 h at room temperature. The product **6** was purified by solid-phase extraction.

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Supporting Information Available. Experimental data are available as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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