Solid-Phase Synthesis of A Novel Series of 2,3,4,5-Tetrahydro-1,4-benzodiazepin-2,5-Dione Libraries

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An efficient solid-phase synthetic method for 2,3,4,5-Tetrahydro-1,4-benzodiazepin-2,5-diones, having amine derivatives on the benzene ring, was developed. This method has been successfully applied to the synthesis of several spatially separated drug-like and information-rich small-molecule libraries composed of 400 compounds using ACT-496 automatic synthesizer and the IRORI radio frequency-encoded split-mix synthesis technology.

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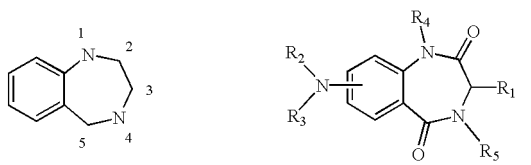
Introduction.

Combinatorial chemistry has become fully integrated into the drug discovery process [1]. Much of the early work on combinatorial chemistry relied upon direct conversion of known solution phase chemistry to the solid phase. As a result of these successes, most pharmaceutical research in this area is now shifted to the construction of designed in-house drug-like compound libraries.

2,3,4,5-Tetrahydro-1,4-benzodiazepin (**I**) is an attractive class of privileged template for the development of pharmacologically active compounds. Especially, the derivatives of 2,3,4,5-tetrahydro-1,4-benzodiazepin-2,5-diones (**II**), which are considered as peptide and/or β-turn mimetic, are reported to possess a wide range of pharmacological activities [2]. They are also attractive targets for solid- and solution-phase combinatorial library synthesis for displaying different functionality on templates [3]. Upon closer inspection of these reported compounds, they are mainly derived from the substitution (R_4 and R_5) of nitrogen atoms of the two amide bonds.



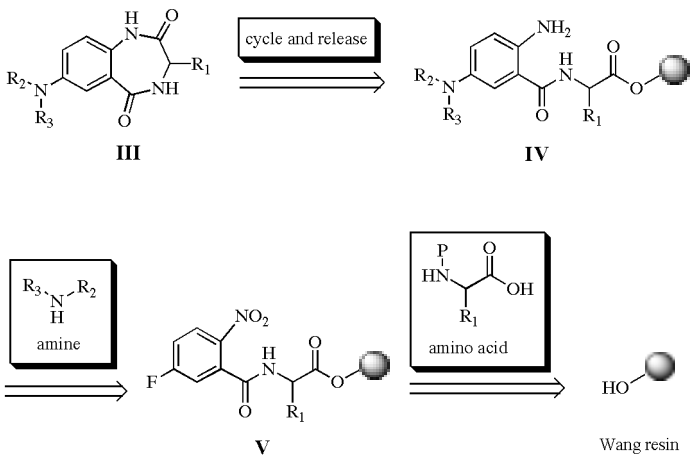
I **II**

Figure 1. 2,3,4,5-Tetrahydro-1,4-benzodiazepin (**I**) and 2,3,4,5-Tetrahydro-1,4-benzodiazepin-2,5-diones (**II**)

On the other hand, there are not so many examples of the introduction of amine derivatives (NR_2R_3) to the benzene ring of the 2,3,4,5-tetrahydro-1,4-benzodiazepin-2,5-dione nucleus in the literatures. Amine and its derivatives (amide, sulfoamide, *etc*.) are privileged pharmacophore for increasing the possibility to find a biologically active compound. This led us to study the synthesis of a library composed of a novel series of 2,3,4,5-tetrahydro-1,4-benzodiazepin-2,5-diones (**II**).

Our synthetic strategy based on solid phase chemistry was shown in Scheme I. The final intramolecular cyclization reaction on bead, so-called cycle and release or traceless linker concept [4], takes advantage of the solid-phase reaction. Attacking the primary amine in **IV** to the carbonyl group in the ester moiety could lead the formation of the benzodiazepine ring and compound **III**. The solid

Scheme I



III **IV** **V**

Solid phase synthetic strategy for 2,3,4,5-tetrahydro-1,4-benzodiazepin-2,5-diones.

support acts as a leaving group during final cyclization of the resin-bound precursor. The easy purification of the final product is another advantage; the undesired compounds, which did not form the cyclization product (**IV**), remain on the resin. Therefore, the purity of a final crude product is expected to be high. The amine was introduced by SNAr reaction; the flurorine atom, which is activated by the nitro group, could be displaced by an amine under mild conditions [5].

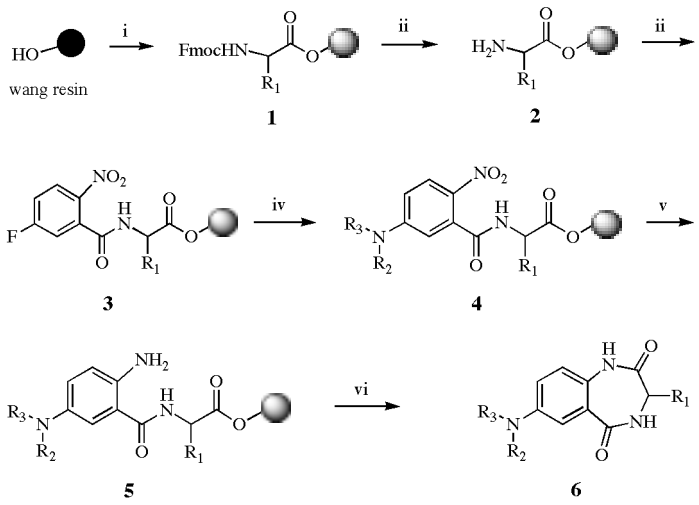
The number of reactions for the introduction of diversity during the construction of the target molecule, and the availability of the building block, are important factors for the construction of the large library. The origins of diversity of our target molecules are easily available aminoacids and amines.

After establishment of the solid-phase synthetic method for 2,3,4,5-tetrahydro-1,4-benzodiazepins, ACT-496 automatic synthesizer and IRORI radio frequency-encoded split-mix synthesis technology were used for the construction of libraries.

Chemistry.

9-Fluorenylmethoxycarbonyl (Fmoc) aminoacid attached on Wang resin (**1**) was synthesized by a standard ester-condensation method [6] (Scheme 2). After deprotection of **1** by treating twice with 20% piperidine in DMF, 2-fluoro-5-nitrobenzoic acid was condensed in the presence of Water soluble carbodiimide® (WSC), *N*-Hydroxybenzotriazole (HOBT), and 4-Dimethylaminopridine (DMAP) for 16 hr at

Scheme 2



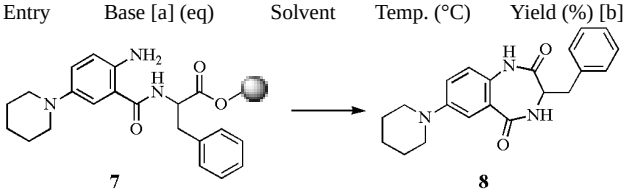
(i) FMOC-aminoacid, DCC, DMAP, CH_2Cl_2. (ii) 20% piperidine in DMF. (iii) 3-fluoro-6-nitrobenzoic acid, WSC, HOBT, DMAP, CH_2Cl_2. (iv) amine, DMSO. (v) $SnCl_2$-$2H_2O$, DMF. (iv) 2eq. LiO^{t}Bu, THF.

room temperature to give **3**. Displacement of an aryl fluoride activated by the nitro group with secondary amine proceeded smoothly in DMSO at room temperature to give the desired compound **4**. The reaction with primary or bulkier amines was incomplete even when elevating the reaction temperature up to 80 °C. Reduction of the nitro group of **4** with $SnCl_2$ in DMF for 16 hr furnished the a small amount of water is essential for this reducing condition.

A number of organic bases for the intramolecular cyclization were evaluated (Table 1). Among them, LiOtBu was found to be the optimal base. LiOtBu is soluble in organic solvents; 1 *M* hexane solution is commercially available. Therefore, it is easy to dispense the exact amount of base in organic solvent to a large number of reaction wells either by manual or auto mechanical dispenser. NaOtBu was also found to be an effective base for the cyclization reaction [7], however, it is very difficult to weigh out an exact amount; NaOtBu did show low solubility in organic solvent. As expected, the purity of crude reaction product was found to be very high. In order to remove inorganic wastes, the organic layer was washed with water and then passed through a solid phase extraction column (Extrelut®). Partial racemization occurred during the cyclization reaction, which was determined using a chiral HPLC: 48% enantiomeric excess was observed in the case of compound **8**.

Table I

Effect of Base on Cyclization Reaction



Entry	Base [a] (eq)	Solvent	Temp. (°C)	Yield (%) [b]
1	NaO^{t}Bu (2)	THF	50	16
2	NaO^{t}Bu (5)	THF	50	9
3	NaO^{t}Bu (2)	tBuOH	50	<1
4	KO^{t}Bu (2)	THF	50	0
5	KHMDS (2)	THF	rt	<1
6	KHMDS (2)	THF	50	1
7	NHMDS (2)	THF	rt	<1
8	LHMDS (2)	THF	rt	<1
9	TEA (2)	THF	50	0
10	LiO^{t}Bu (2)	THF	rt	0
11	LiO^{t}Bu (2)	THF	50	21 [c]
12	LiO^{t}Bu (2)	toluene	50	0

[a] KHMDS, NHMDS, LHMDS are 0.5 *M* THF solution and LiO^{t}Bu is 1.0 *M* hexane solution; [b] Yields are calculated based on the loading amount of Fmoc aminoacid wang resin (**1**); [c] The purity was 98% (HPLC).

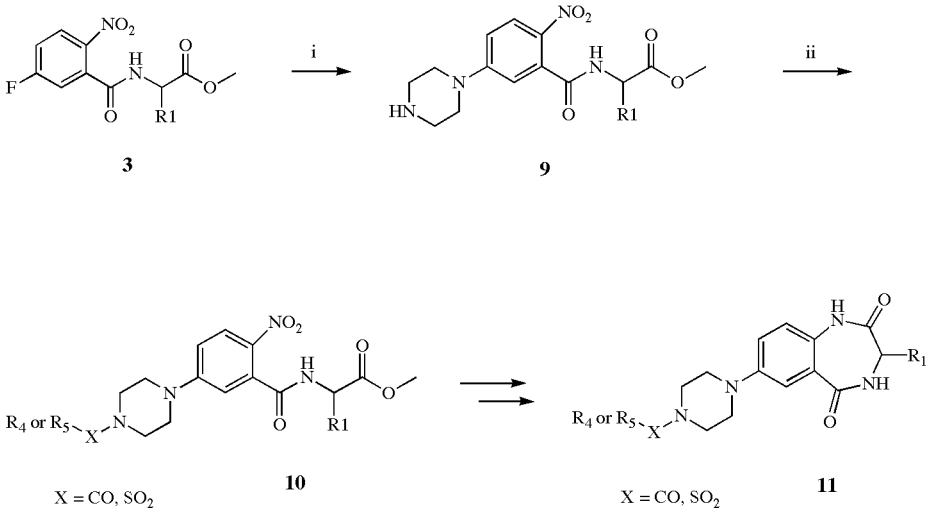
In order to expand diversity, we planned to form an amide or a sulfonamide bond with terminal nitrogen atom in the piperazine moiety of **9** (Scheme 3). Taking advantage of solid-phase reaction, a large excess piperazine was reacted with **3** to afford **9** without the concomitant formation of dimer-type piperazine derivative. Amidation or sulfonamidation was carried out using acid chloride or sulfonyl chloride to give desired compound (**10**) under standard conditions [8]. Other diamines ($C_{2\text{-}4}$, Figure 2) also underwent successful reactions to give the desired compounds. In the cases of reaction of 4-aminopiperidine and 3-aminopyrrolidine with **3**, the fluorine atom was replaced selectively by secondary nitrogen atoms of these diamines. Compounds **10** were converted to final 2,3,4,5-tetrahydro-1,4-benzodiazepin-2,5-diones (**11**) by the same procedures as those for **6**.

In these validated studies for the solid-phase synthesis of 2,3,4,5-tetrahydro-1,4-benzodiazepin-2,5-diones, each reaction was monitored using analytical constructs (^{1}H-NMR, IR, MS, and TLC).

Library Synthesis.

Combinatorial library design based on the best selection of pharmacophoric substituents maximizes the chance of

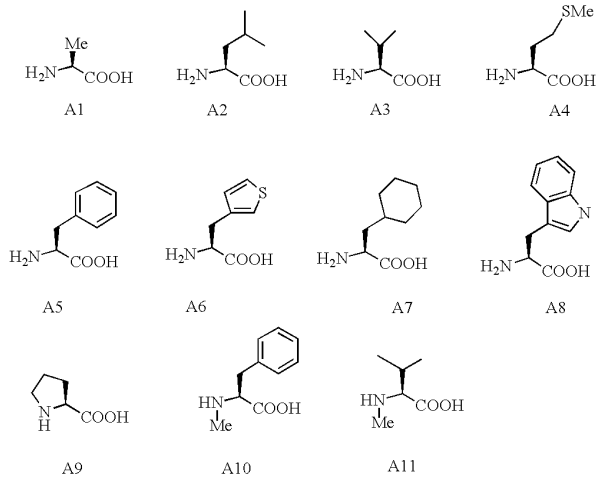
Scheme 3



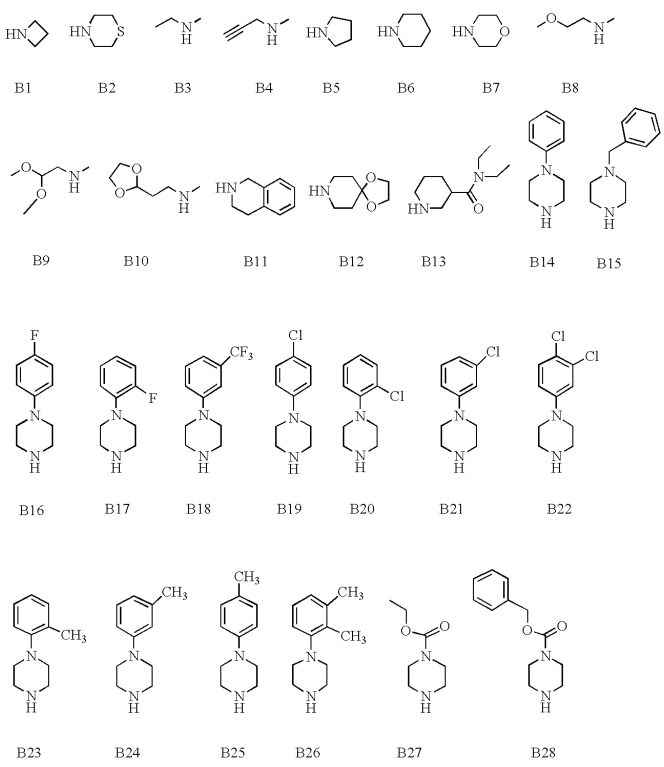
(i) piperazine, THF. (ii) R_4-X-Cl, iPr_2NEt, CH_2Cl_2 or R_5COOH, WSC, DMAP, CH_2Cl_2

finding pharmacologically active compounds. Identification of the candidate pool of reagents began with commercially available reagents in the database of available chemicals directory (ACD). Subsequently, these collected reagents were filtered by evaluating their diversity and chemical reactivity by creating a virtual library using Project Library [9]. The final list of selected reagents are shown in Figure 2. Combinatorial library synthesis of a series of amine-type compounds was run in an ACT-496 automatic synthesizer with 40-well reactor block. The IRORI radio frequency-encoded split-mix synthesis technology was used for the production of libraries of amide-type compounds and sulfonamide-type compounds. A total of 400 compounds were synthesized. All the compounds showed over 90% purity with correct molecular weights determined by LC-MS.

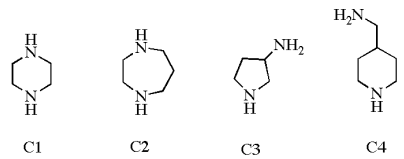
Amino acids attached on bead (A1-11)



Amines (NR_2R_3, B1-28)



Diamines (C1-4)



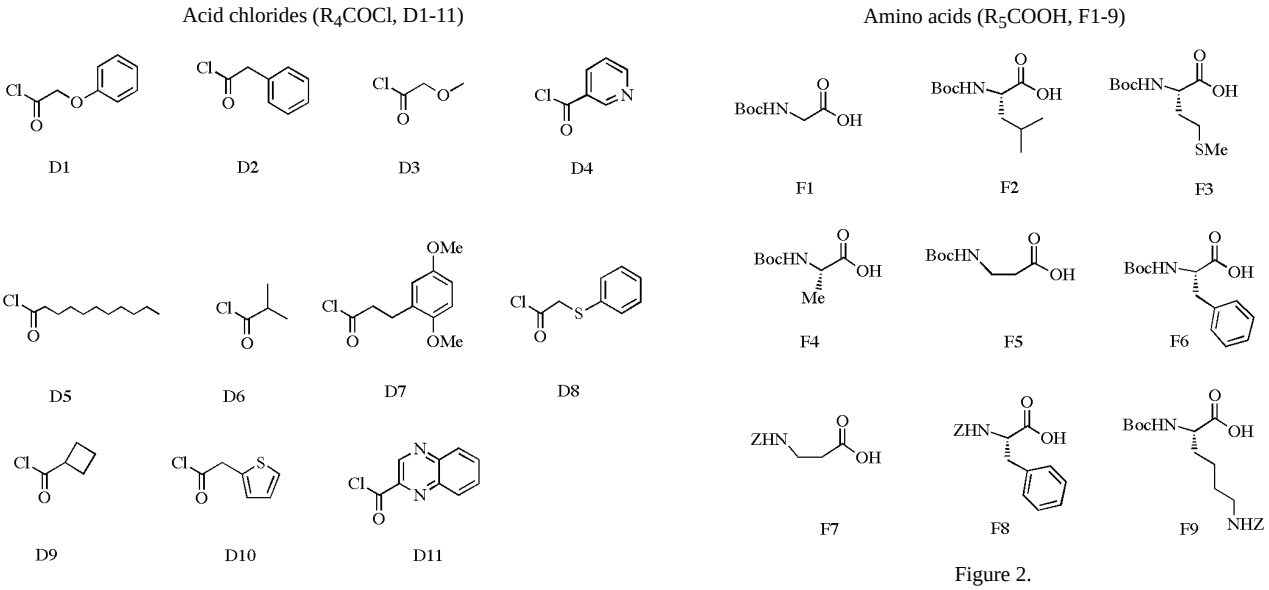
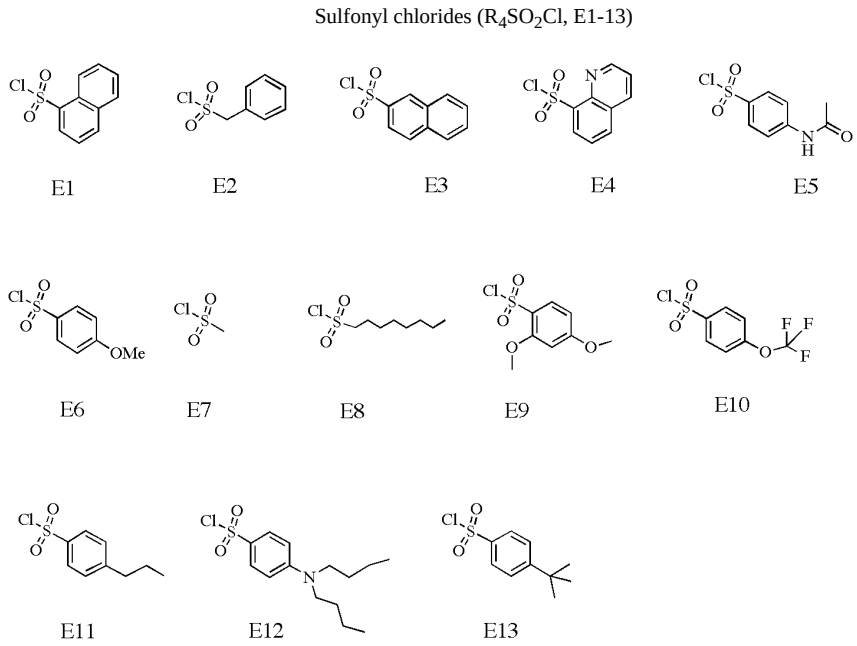


Figure 2.



Conclusion.

We have developed an efficient solid-phase synthetic method for 2,3,4,5-tetrahydro-1,4-benzodiazepin-2,5-diones which have amine derivatives on the benzene ring. This method has been successfully applied to the synthesis of several spatially separated drug-like small-molecule libraries composed of 400 compounds using ACT-496 automatic synthesizer and the IRORI radio frequency-encoded split-mix synthesis technology. This is well adapted for creating larger drug-like libraries as well as for incorporation of another set of reagents. The "information-rich" library (in a sense) would make it possible to gain much SAR information around any interesting hits, from other compounds in the library.

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