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Solid-Phase Synthesis of Small Molecule Libraries using Double Combinatorial Chemistry

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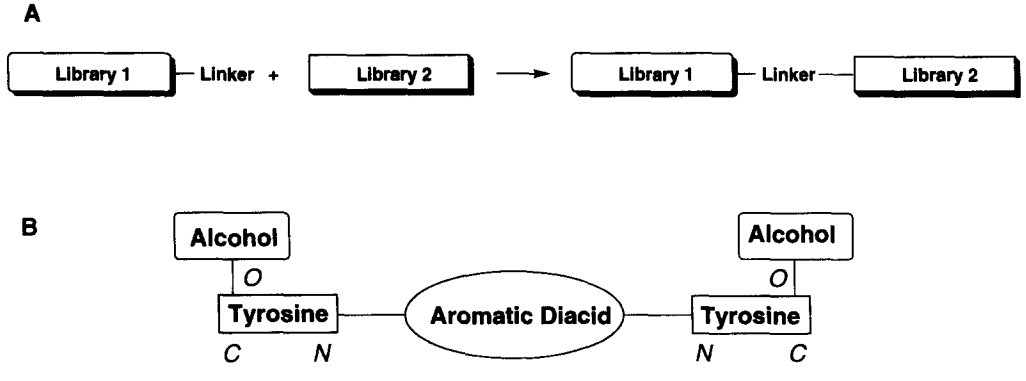
Abstract: The first synthesis of a combinatorial library using *double combinatorial chemistry* is presented. Coupling of unprotected Fmoc-tyrosine to the solid support was followed by Mitsunobu O-alkylation. Introduction of a diacid linker yields a system in which the double combinatorial step can be demonstrated. The resulting library of model compounds was verified by LC-MS analysis.

The application of solid-phase synthesis and combinatorial chemistry for drug discovery, lead generation and lead optimization is now well-established.[1] This paper describes the first implementation of what we have termed*double combinatorial chemistry*. This double combinatorial technique or combinatorialization "at two centers" has been exemplified by the synthesis of a small [6+3]-member model library.



(A) The basic principle of double combinatorial chemistry is the chemical ligation of one library with another library (or the same library) to yield a resulting library with an exponentially increase in library members.
(B) The design of the actual model library was based on Mitsunobu-alkylated tyrosine linked together with an aromatic diacid.

Scheme 1

Double combinatorial chemistry is a new strategy in synthesis of combinatorial libraries which affords the possibility of simple, few-step syntheses of combinatorial libraries containing a very large number of molecules. Likewise, this technique enables convergent solid-phase synthesis of some structurally highly complicated natural products and analogues thereof or generally structures showing a high degree of symmetry. In fact, the concept of double combinatorial chemistry was recently introduced in our laboratory during the solid-phase synthesis of a structural analogue of actinomycin D, implying the possibility of combining two libraries of respectively n and m members to a third library of n x m members (Scheme 1A).[2] Recently, the term double combinatorial chemistry was used also by Pavia *et. al.* but in a conceptually different scheme for the synthesis of substituted biphenyl libraries.[3]

To prove the concept, we designed an appropriate scaffold resulting in the model compound shown (a Mitsunobu-alkylated tyrosine dimer, Scheme 1B) as a starting point for the implementation of chemical synthesis of libraries using the double combinatorial technique. Basically, this model links two hydroxy-alkylated tyrosine units using an aromatic diacid. Thus, Fmoc-tyrosine was coupled to deprotected Rink Amide resin using a modified 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) coupling protocol which minimized the amount of dimer byproduct formation resulting from the acylation of the 4-hydroxy function of tyrosine.[4] The synthesis of the aryl ether part of the model was carried out using Mitsunobu-conditions[5] [diethylazodicarboxylate (DEAD)/triphenylphosphine (TPP)] following a modification of the method described by Rano.[6] During the initial investigations of the Mitsunobu reaction, substantial loss of the Fmoc-protecting group was observed. It was possible to prove that this loss of Fmoc group lowered the yields during the subsequent *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)-mediated coupling with 1,4-benzenedicarboxylic acid monoallyl ester. The reasons for this behavior are not yet totally clear but will be investigated further. However, through careful control of the reaction conditions, it was possible to avoid the cleavage of the Fmoc-group. Using DEAD/TPP in THF:DCM (1:1), three aryl ethers were synthesized in a one-pot reaction on the solid-phase, yielding approximately 90% of an equimolar mixture of compounds **2-4**, (Scheme 2). The remaining 10% was shown by HPLC to be unreacted starting material (data not shown).

Successful coupling of the diacid to the tyrosine residue required the diacid to be monoprotected, and the allylester function was chosen as protecting group due to its facile and selective removal by $(PPh_3)_4Pd(0)$.[7] The synthesis of monoallyl esters of aromatic diacids has been reported using cesium carbonate, which through a stepwise addition gave the desired monoester in moderate yield.[2]

Subsequently, the resin was split into two portions (1:2), and the coupling of 1,4-benzenedicarboxylic acid monoallyl ester was performed on the larger portion of resin, leaving 1/3 behind to be used in the double combinatorial step. The actual coupling of the 1,4-benzenedicarboxylic acid monoallylester to resin-bound, ether-functionalized Fmoc-tyrosine was done by removal of the Fmoc-group using 20% piperidine/DMF, and subsequent HATU-mediated coupling in DMF.[8] This reaction was for all practical purposes quantitative, as found by HPLC-analysis (data not shown).

Using $(PPh_3)_4Pd(0)$/5% AcOH/2,5% N-methylmorpholine (NMM)/$CHCl_3$, selective and quantitative allyl ester cleavage was obtained, and subsequent cleavage of the library from the resin with 50% TFA/DCM yielded upon evaporation, an oily residue consisting primarily of products **6-8**.

These reactions provide the conditions required to perform the double combinatorial step. Removal of the Fmoc-group from the remaining 1/3 of the ether-functionalized tyrosine library allowed HATU-coupling of the