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Microwave-assisted solid phase synthesis of *Imatinib*, a blockbuster anticancer drug

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Abstract—An expeditious, high yield and convenient synthesis of *Imatinib* was carried out on an aldehydic, super acid-sensitive resin, through an efficient, microwave-assisted synthetic protocol. The high versatility of the reaction scheme may enable the straightforward preparation of libraries of potential protein kinase inhibitors endowed with large molecular diversity.
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The emergence of combinatorial library screening strategies to improve the efficiency of drug discovery and development has spurred intense research activity in the field of solid phase organic synthesis (SPOS).[1] The ability to automate SPOS, the use of excess soluble reagents to drive reaction to completion and the ready purification of resin-bound material combine to make SPOS the method of choice for combinatorial library generation.[2] However, this approach is often limited by a narrower choice of reactions, reactants and solvents, and by longer reaction times and higher costs of polymeric resins. Enhancement of SPOS by using microwave irradiation has been recently pursued to obtain shorter reaction times, higher yields and milder experimental conditions to ensure the mechanical and thermal stability of polymeric solid supports.[3]

In the present investigation we combined, therefore, the versatility of SPOS and the performances of microwave heating in the synthesis of *Imatinib* (Gleevec/Glivec™; formerly known as STI571, Chart 1), a potent and selective inhibitor of BCR-ABL and c-kit oncogenic tyrosine kinases, recently approved by the Food and Drug Administration for the chemotherapy of chronic myeloid leukemia and gastrointestinal stromal tumor.[4,5] *Imatinib* has become a paradigm for molecular targeted cancer therapy and acquired soon the status of a blockbuster drug owing to its outstanding therapeutic efficacy and low toxicity profile.[6]

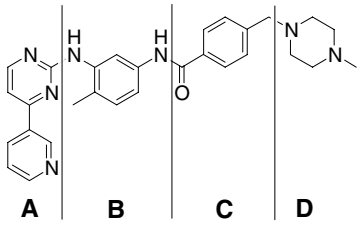

Chart 1. Chemical structure of *Imatinib* (STI571).

Unfortunately, in many patients with advanced diseases a harmful drug resistance frequently develops after an initial positive response to *Imatinib*.[7] Therefore, the development of an efficient synthetic method for the synthesis of *Imatinib* may pave the way to build focused libraries of new, more potent and selective BCR-ABL inhibitors, possibly active against the most common, life-threatening resistant mutants.

Retrosynthetic analysis of *Imatinib* suggests to link four distinct building blocks (Chart 1, **A**–**D**) that are amenable to appropriate structural variation to prepare combinatorial libraries endowed with a large molecular diversity. The presence of an amide bond between building blocks **B** and **C** suggested us to begin the synthesis with the anchoring of an aniline derivative to an appropriate linker on a solid support. Once tethered the first amine building block (**B**) to the resin, the synthesis of *Imatinib* can be accomplished by introducing

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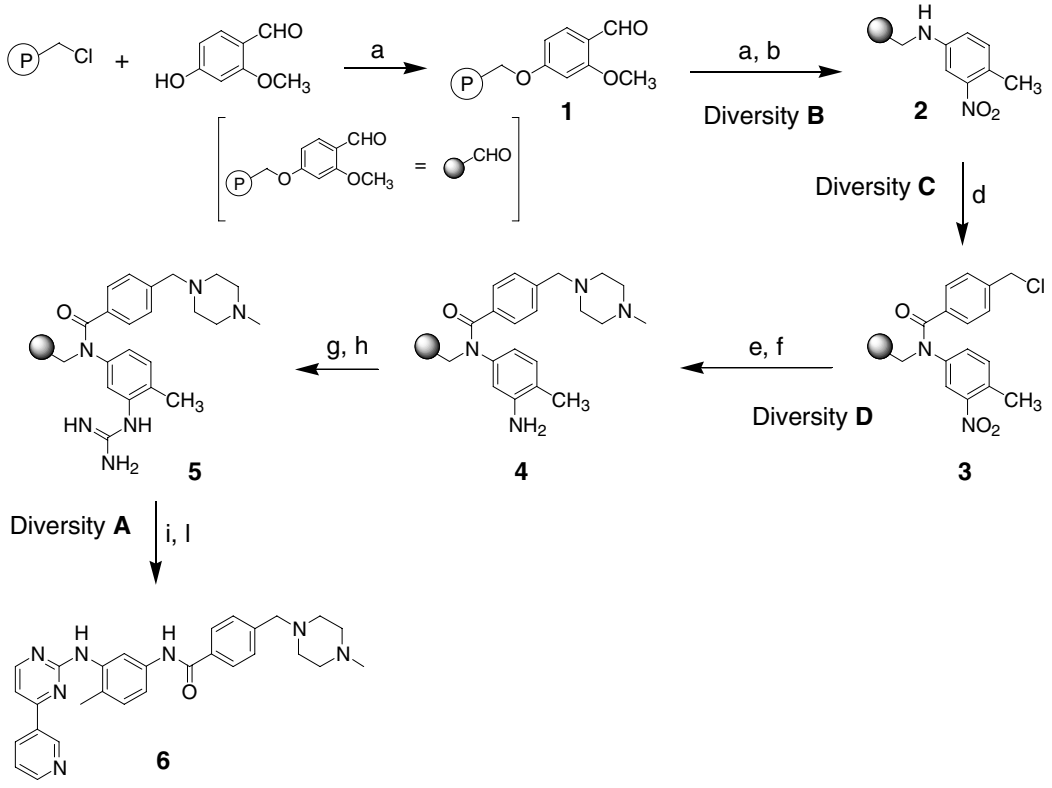
consecutively building blocks **C** and **D**, through simple nucleophilic substitutions, and key pyrimidine building block **A** through cyclization of a guanidine intermediate, obtained in turn from the corresponding aniline.

In a preliminary experimental approach SPOS of *Imatinib* began with the loading of the first building block **B** (i.e., 4-methyl-3-nitroaniline) on a brominated, super acid-sensitive *o*-methoxyphenyl-substituted Wang resin (SASRIN). Low loading yield and high cost of resin prompted us to look for a cheaper polymeric support, different linkers and loading reactions. AMEBA[8] linker **1** was selected and obtained by us in high yield and very short reaction time (5 min) by reacting the inexpensive Merrifield resin with 4-hydroxy-2-methoxy-benzaldehyde and NaH in DMF under microwave exposure (Scheme 1). To the best of our knowledge, this expedite microwave-assisted procedure has never been used for the preparation of linker **1**. The loading of the first building block, that is, 4-methyl-3-nitroaniline, was then accomplished through reductive amination employing an efficient method,[9] adapted to solid phase in our laboratory for the synthesis of some antiparkinson's agents.[10] The reaction was successfully carried out in two sequential steps in an overall 80% yield using $Ti(O\text{-}iPr)_4$ and TEA for the formation of aldimine intermediate, and $NaBH(OCOCH_3)_3$ for the reduction of the imine bond.

Standard acylation with 4-chloromethylbenzoylchloride, followed by chloride nucleophilic displacement by *N*-methylpiperazine and reduction of the nitro group by $SnCl_2$ afforded the pivotal *ortho*-methyl aniline **4** in very good yield. Remarkably, the last two chemical steps can also be successfully accomplished under microwave irradiation at 100 °C in 5 min. The most critical steps of our synthetic strategy were the formation of guanidine intermediate **5** and the final cyclization reaction leading to the pyrimidine ring of *Imatinib* **6**. Poor results were obtained in the guanylation of aniline **4** with a series of common reagents, such as guanylpyrazole and sodium cyanamide, whereas the bis-alloc protected methylthiopseudourea gave satisfactory results. The reaction was carried out using $HgCl_2$ and TEA in DMF (from 0 °C to rt, 15 h total), whereas deprotection was performed with $Pd(PPh_3)_4$ and $PhSiH_3$ in CH_2Cl_2. Using this protocol aniline intermediate **4** was transformed into guanidine derivative **5** in a fairly high yield. To considerably reduce the reaction time, the synthesis was repeated in the same solvent by first adding $HgCl_2$ and TEA at 0 °C and then heating by microwave irradiation at 80 °C for 5 min.

Following deprotection and cleavage from the resin, HPLC and ^1H NMR analyses indicated a high reaction yield and good purity of guanidine derivative **5**.[11] It is worth noting that the microwave-assisted method pro-



Scheme 1. Solid phase synthesis of *Imatinib*. Reagents and conditions: (a) NaH, DMF, MW, 120 °C, 5 min; (b) 4-methyl-3-nitroaniline, $Ti(O\text{-}iPr)_4$, TEA, THF, overnight; (c) $NaBH(OCOCH_3)_3$, CH_2Cl_2, 4 h; (d) 4-(chloromethyl)benzoyl chloride, DIPEA, DMF, 3 h; (e) *N*-methylpiperazine, DMF, DIPEA, MW, 100 °C, 5 min; (f) $SnCl_2$, DMF, MW, 100 °C, 5 min; (g) bis-(*N*-alloc)-methylthiopseudourea, $HgCl_2$, TEA, DMF, 0 °C, 10 min, then MW, 80 °C, 5 min. (h) $Pd(PPh_3)_4$, $PhSiH_3$, CH_2Cl_2, 1 h; (i) 3-dimethylamino-1-pyridin-3-yl-propenone, nitrobenzene, BEMP (or DBU), MW, 120 °C, 50 min; (l) TFA/CH_2Cl_2, (1/9) 1 h.

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