Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3455–3458

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

Francesco Leonetti, Carmelida Capaldi and Angelo Carotti*

Dipartimento Farmaco-Chimico, University of Bari, via Orabona 4, I-70125 Bari, Italy

Received 8 February 2007; revised 27 February 2007; accepted 6 March 2007
Available online 12 March 2007

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.

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]

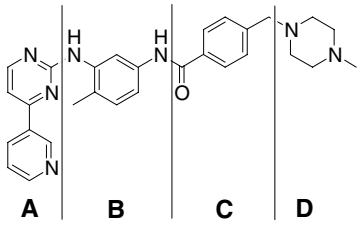


Chart 1. Chemical structure of *Imatinib* (STI571).

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

Keywords: Solid phase synthesis; Microwave heating; *Imatinib*; Gleevec; Chronic myeloid leukaemia.
* Corresponding author. Tel.: +39 080 544 2782; fax: +39 080 544 2230; e-mail: carotti@farmchim.uniba.it

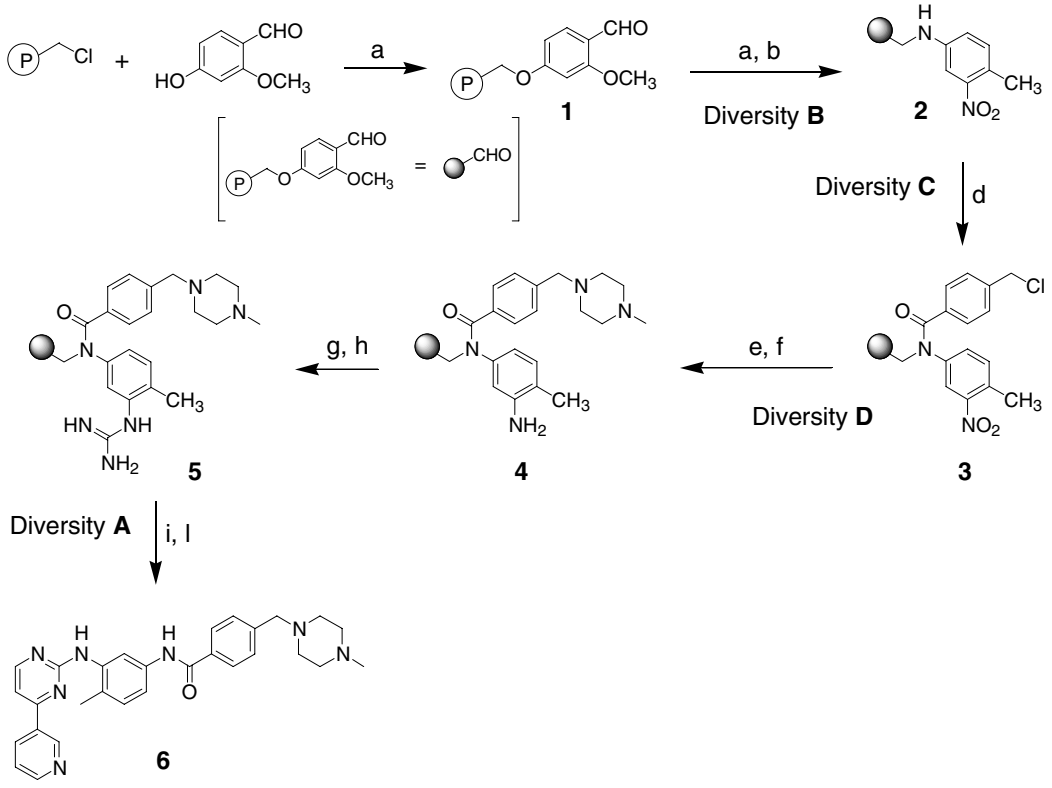
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.03.033

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-



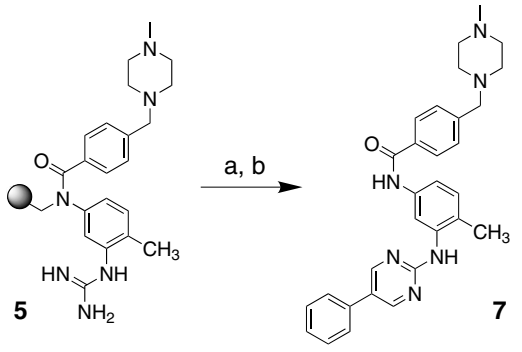
Scheme 1. Solid phase synthesis of *Imatinib*. Reagents and conditions: (a) NaH, DMF, MW, 120 °C, 5 min; (b) 4-methyl-3-nitroaniline, $Ti(O\text{-}iPr)_4$, TEA, THF, overnight; (c) $NaBH(OCOCH_3)_3$, CH_2Cl_2, 4 h; (d) 4-(chloromethyl)benzoyl chloride, DIPEA, DMF, 3 h; (e) *N*-methylpiperazine, DMF, 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.

posed herein for the guanylation of aniline **4** in the solid phase presented advantages in terms of yield, purity and rapidity compared to other reported procedures.[12] To optimize the cyclization reaction between intermediate **5** and 3-dimethylamino-1-pyridin-3-yl-propenone,[13] several bases (DBU, KHMDS, DIPEA, KOH, BEMP and KO*t*Bu) were tested in a series of parallel reactions carried out in DMF at 80 °C overnight. Among the test bases, KO*t*Bu gave the best results in terms of high yield and clean reaction. The yield was further improved by adding a 15% of HMPA and increasing the temperature to 100 °C.

Analytical checks carried out by HPLC, ESI-MS, and ^{1}H NMR of the sample recovered after cleavage from the resin, highlighted contrasting results of the synthetic protocol. Indeed every step proved complete with very high yield whereas, by contrast, the cyclization reaction was accomplished with moderate yield and low purity likely due to the harsh experimental conditions used which resulted incompatible with the resin stability. To ensure resin stability and reduce reaction time, the final cyclization was performed by means of microwave irradiation. As desired, the time necessary to transform intermediate **5** into final compound **6** was dramatically reduced (from 20 h to 50 min) and the reaction yield was quite high (98%). *Imatinib* **6** was isolated in high overall yields (nearly 65%) and purity (>90%), without any trace of by-products from the resin.[14]

Notably, the microwave-assisted cyclization protocol enabled the use of 3-dimethylamino-2-phenyl-propenal[15] to access the 5-substituted-2-phenylaminopyrimidine derivative **7** (Scheme 2) which was impossible to attain under the previous experimental conditions.

In conclusion, the synthesis of *Imatinib* demonstrated the synergic effect of two important synthetic methodologies—SPOS and microwave heating—for accelerating the process of lead discovery and optimization. SPOS permitted the expedite preparation of all the designed compounds, avoiding the time-consuming steps of purification and isolation of intermediates.[16] On the other hand, the microwave methodology considerably reduced the time required to carry out some energy demanding steps in the reaction scheme and contributed to expand the scope of the synthetic protocol as demonstrated by the synthesis of 5-substituted-2-phenylaminopyrimidine derivative (i.e., **7**).



Scheme 2. Solid phase synthesis of 5-substituted-2-phenylaminopyrimidine derivative **7**. Reagents and conditions: (a) 3-Dimethylamino-2-phenyl-propenal, DBU, nitrobenzene, MW, 120 °C, 50 min; (b) TFA/CH_2Cl_2, (1/9) 1 h.

The microwave-assisted methods used for the preparation of linker **1**, the reduction of nitro group, the formation of guanidine from a slightly hindered aniline, and the cyclization of guanidines to 4- and 5-substituted pyrimidines presented undoubted advantages compared to competing methods reported in the literature.[12,17] Finally, the proposed synthetic pathway shows potential for introducing molecular diversity at the four different steps **A**–**D** shown in Scheme 1, enabling the preparation of large libraries of BCR-ABL kinase inhibitors.

Work is in progress in our laboratories to apply the synthetic approach outlined herein to generate large arrays of potent and selective tyrosine kinase inhibitors using combinatorial methods.

Acknowledgment

We gratefully thank MIUR, Rome (Italy), for financial support.

Supplementary data

Full experimental details of the reactions outlined in Schemes 1 and 2 and not described in the Refs. 11 and 14, are reported. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.033.

References and notes

1. (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555–600; (b) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 17–42; (c) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449–472; (d) Bunin, B. A.; Dener, J. M.; Livingston, D. A. *Ann. Rep. Med. Chem.* **1999**, *34*, 267–286; (e) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969; (f) Dolle, R. E. *J. Comb. Chem.* **2002**, *4*, 369–418.
2. (a) *Solid-Phase Synthesis: A Practical Guide*; Kate, S. A., Albericio, F., Eds.; Marcel Dekker, 2000; (b) Nicolaou, K. C.; Hanko, R.; Hartwig, W. *Handbook of Combinatorial Chemistry*; Wiley-VCH: Weinheim, 2002.
3. (a) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005; (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6285; (c) Lew, A.; Krutznik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95–105; (d) Mavanadadi, F.; Lidström, P. *Curr. Topics Med. Chem.* **2004**, *4*, 773–792.
4. Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. *Nat. Rev. Drug Discov.* **2002**, *1*, 493–502.
5. Arora, A.; Scholar, E. M. *J. Pharmacol. Exp. Ther.* **2005**, *315*, 971–979.
6. Melnikova, I.; Golden, J. *Nat. Rev. Drug Discov.* **2004**, *3*, 993–994.
7. Hochhaus, A.; Hughes, T. *Hematol. Oncol. Clin. North America* **2004**, *18*, 641–656.

8. Fivush, A. M.; Wilson, T. M. *Tetrahedron Lett.* **1997**, *38*, 7151–7154.
9. Bhattacharyya, S.; Fan, L.; Vo, L.; Labadie, J. *Comb. Chem. High Throughput Scr.* **2000**, *3*, 117–124.
10. Leonetti, F.; Salvati, P.; Caccia, C.; Ferappi, M.; Carotti, A. In *Proceedings of the 17th Convegno Nazionale Divisione di Chimica Farmaceutica*, Pisa, Italy, September 6–10, **2004**, p 97, 163.
11. *SPOS of guanidine intermediate* **5**. After swelling in DMF, polymer-bound aniline intermediate **4** (0.77 mmol, 1.5 g) was reacted with bis-alloc protected methylthiopseudourea (3.9 mmol, 0.8 g), $HgCl_2$ (3.9 mmol, 1.0 g), TEA (3.9 mmol, 0.5 mL) in DMF (25 mL) for 10 min at 0 °C, and then heated under microwave exposure (80 °C) for 5 min. The alloc protecting group was removed treating the resin with $Pd(PPh_3)_4$ (0.5 mmol, 0.6 g), $PhSiH_3$ (40 equiv, 1.30 mL) in CH_2Cl_2 (36 mL) for 1 h. The solution was filtered off and the resin washed with CH_2Cl_2 (3×10 mL) and DMF (3×10 mL). Deprotection was repeated to assure a high yield removal of the protecting group (98% yield).
12. (a) Bonnat, M.; Bradley, M.; Kilburn, J. D. *Tetrahedron Lett.* **1996**, *37*, 5409–5412; (b) Kearney, P. C.; Fernandez, M.; Flygare, J. A. *Tetrahedron Lett.* **1998**, *39*, 2663–2666; (c) Dodd, D. S.; Fallace, O. B. *Tetrahedron Lett.* **1998**, *39*, 5701–5704; (d) Paladino, A.; Mugnaini, C.; Botta, M.; Corelli, F. *Org. Lett.* **2005**, *7*, 565–568.
13. Szakács, Z.; Béni, S.; Varga, Z.; Örfi, L.; Kéri, G.; Noszál, B. *J. Med. Chem.* **2005**, *48*, 249–255.
14. *SPOS of Imatinib* **6** *from guanidine intermediate* **5**. A solution of 3-dimethylamino-1-pyridin-3-yl-propenone (7.7 mmol, 1.4 g), BEMP (3.9 mmol, 1.1 mL), and nitrobenzene (15 mL) was added to the support-bound guanidine **5** (0.77 mmol, 1.6 g). The reaction mixture was kept under stirring for 50 min under microwave exposure (120 °C). The resin was filtered, washed with nitrobenzene (3×10 mL), DMF (3×10 mL), THF (3×10 mL), CH_2Cl_2 (3×10 mL) and finally treated for 1 h with a 10% solution of TFA in CH_2Cl_2 (20 mL). The cleaved solution was filtered and the resin washed with the same solvent mixture (3×10 mL). The solvent mixtures were combined and immediately concentrated with rotary evaporation. Toluene (2 mL) was added twice during the concentration step in order to remove the remaining TFA (98% yield).
15. Haefliger, W.; Hauser, D. *Synthesis* **1980**, *3*, 236–238.
16. Zimmermann, J.; Buchdunger, E.; Mett, H.; Meyer, T.; Lydon, N. B. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 187–192.
17. (a) Scheuerman, R. A.; Tumelty, D. *Tetrahedron Lett.* **2000**, *41*, 6531–6535; (b) Yongping, Y.; Ostresh, J. M.; Houghten, R. A. *J. Org. Chem.* **2002**, *67*, 5831–5834; (c) Bimbisar, D.; kappe, C. O. *J. Comb. Chem.* **2005**, *7*, 641–643; (d) Wong-Jin, C.; Wen-Ben, Y.; Chung-Ming, S. *Synlett* **2003**, 1688–1692.