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Parallel synthesis of amino bis-benzimidazoles by multistep microwave irradiation

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Abstract—A multistep liquid phase synthesis of specifically functionalized bis-benzimidazoles is presented by the application of single-mode microwave irradiation technique. The sustained solubilizing power and stability of the PEG-ester derived from the commercially available 4-fluoro-3-nitrobenzoic acid has been successfully carried through 10 steps involving *ipso*-S_NAr reaction, neutral reduction and acid cyclization. All the steps in this synthetic sequence were assisted by microwave (MW) irradiation. The polymer support was cleaved to release the final head to tail bisbenzimidazoles in an efficient process.

There has been an unlimited expansion of molecular diversity in synthetic organic compounds by the application of combinatorial methodology.[1] Combinatorial organic synthesis on polymer support integrated with microwave technology has emerged as a powerful technique to generate a large number of aromatic and heterocyclic compounds with a variety of structural features having a high potential to act as lead molecules in drug discovery.[2] Introduction of a soluble polymer support in this field has resulted in functionalized polymer–organic conjugates, possessing a wide range of solubilizing power, which leave the reactivity of the molecules unaltered, thereby facilitating the usual functional group interconversions (FGI) in a multistep organic synthesis and remaining stable to the surrounding molecular events.[3] This has given rise to novel protocols for the generation of molecular libraries of pharmacologically active structural motifs viz. peptides, sulfonamides, azetidinones, tetrahydropyrimidines, triazoles and tetrahydro β-carbolines.[4–9] This technique still retains the classical organic analytical methods such as TLC, IR and NMR to monitor reaction progress without cleavage of support.

The chemotherapeutic potential of head to tail bis-benzimidazoles **4** (Fig. 1) was realized in early 1980's when enviroxime **1** and enviradene **2** underwent clinical trials for their anti-rhinovirus activity.[10] Renewed interest of structure–activity relationship (SAR) studies in their acetylinic analogues[11] and 1-benzyl-5,6-dichloro-1*H*-benzo[*d*]imidazol-2-amine **3**[12] has been recognized as a potent inhibitor of viral RNA synthesis. Mechanistic studies on transcriptional induction of cytochrome P450 1A1 in rat cells has shown that

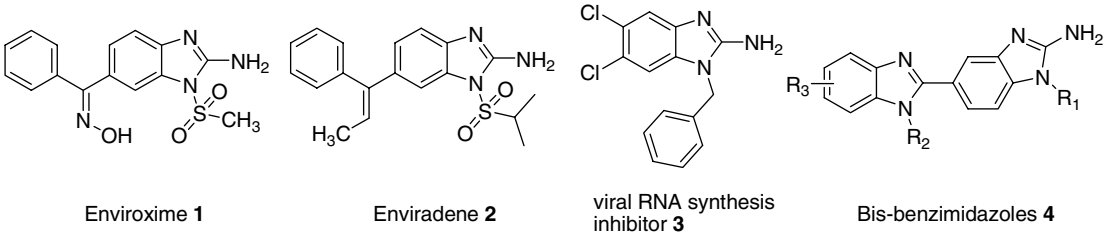

Figure 1. Biologically active amino benzimidazoles.

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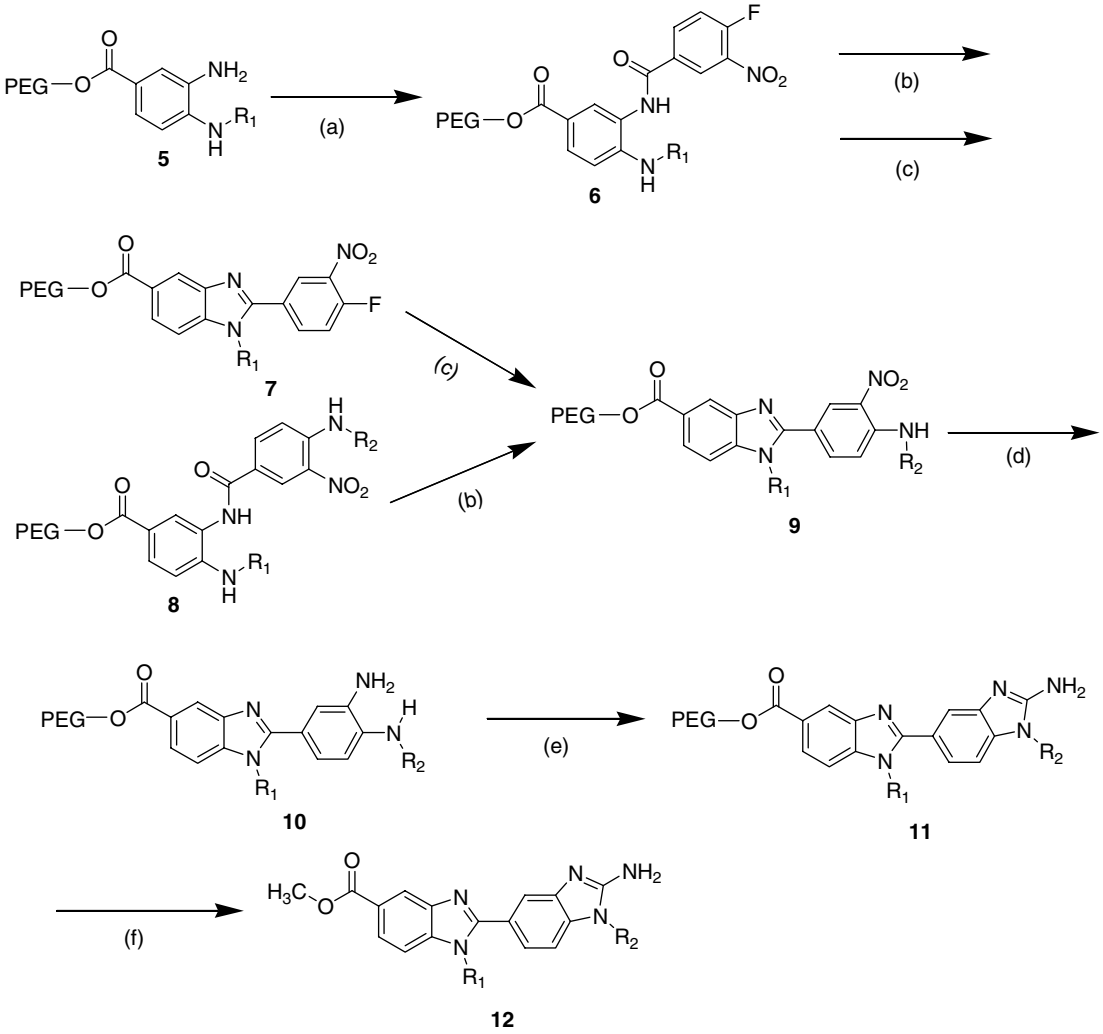
2-amino-benzimidazole favoured the induction, thereby revealing the importance of a nucleophilic amino group at C-2 in benzimidazole.[13] The generation of 2-amino group in the bio-transformation of the broad spectrum anthelmintic drug mebendazole[14] has further strengthened the need for the synthesis of benzimidazole molecular libraries with amino group at C-2 position.[15]

Bis-benzimidazoles are an established class of small molecules having an unusual property of selectively recognizing the minor groove of DNA,[16–19] which makes them potential candidates for the synthetic regulation of gene expression. This site directed specificity has been linked to their promising DNA-topoisomerase I inhibiting[20–24] and anti-tumour properties.[25,26] Recently new insights have been found in sequential binding of bis-benzimidazoles by incorporating an amidine moiety.[27] Therefore rapid synthesis of structurally diverse bis-benzimidazoles[28] is of vital importance to have a better understanding of structure–activity relationship. This is the first report on bis-benzimidazoles with a nucleophilic amino group at C-2 which can function as a masked amidine, thereby retaining the configurational flexibility for the selective recognition of DNA.[27]

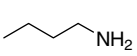
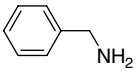
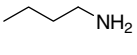
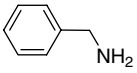
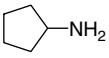
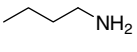
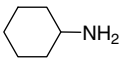
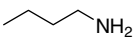
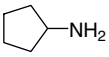
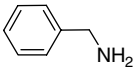
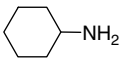
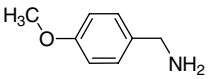
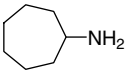
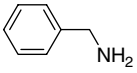
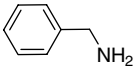
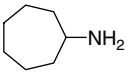
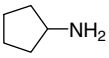
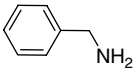
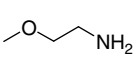
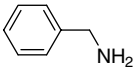
Synthesis of the target molecules (Scheme 1) was achieved by the initial formation of the PEG ester conjugate with 4-fluoro-3-nitrobenzoic acid and S_NAr reaction of primary amines followed by reduction leading to the PEG bound anilines **5**.[6] To construct the second benzimidazole ring, coupling of the polymer immobilized *o*-phenylenediamine **5** with 4-fluoro-3-nitrobenzoic acid again was achieved by using DCC/DMAP activation in 20 min under microwave irradiation with higher yields of benzamides **6**. Regioselectivity in this step lies in the sterically less congested primary amino group compared to the secondary amino group, the nucleophilicity of which is reduced by the electron withdrawing ester group in the *para* position.

The transformation of benzamides **6** to the mono-benzimidazole conjugates **9**, with the introduction of the second point of diversity was achieved by two pathways. In the first path various aliphatic and benzyl amines



Scheme 1. Reagents and conditions: (a) 4-fluoro-3-nitrobenzoic acid, DCC/cat. DMAP, CH_2Cl_2, MW (300 W), 20 min; (b) TFA, $CHCl_3$, MW (300 W), 15 min; (c) R_2NH_2, CH_2Cl_2, MW (300 W), 10 min; (d) Zn/NH_4Cl, CH_3OH, MW (300 W), 30 min; (e) CNBr, CH_2Cl_2, MW (300 W), 20 min; (f) CH_3ONa/CH_3OH, MW (300 W), 10 min.

Table 1. Novel head to tail bis-benzimidazoles **12** synthesized by multistep microwave irradiation on the support

Compound	R_1–NH_2	R_2–NH_2	Mass (FAB^+)	Isolated yield (%)
12a			454	84
12b			406	81
12c			440	78
12d			432	82
12e			446	82
12f			480	82
12g			510	78
12h			494	77
12i			454	81
12j			460	86
12k			466	80
12l			384	85

were reacted to obtain the polymer bound intermediates **8**. The construction of the first benzimidazole ring was visualized in terms of an intramolecular N–C bond formation followed by dehydration. This ring closure was brought about by using trifluoroacetic acid (TFA) and chloroform under MW heating for 15 min, leading to the 2-aryl benzimidazole conjugates **9**, which required 48 h in classical refluxing conditions. This was also arrived by the reverse sequence of reactions, that is, by the initial cyclization to obtain the 2-*o*-fluoronitro benzimidazoles **7** and then the S_NAr reaction with primary amines.

Reduction of the nitro group in mono-benzimidazole **9** was accomplished under MW conditions to obtain diamines **10**. The amino group at C-2 was generated by the [4+1] approach with cyanogen bromide under microwave irradiation for 20 min to obtain the target compounds **11** on the support. The microwave induced cleavage of the polymer support achieved in methanolic sodium methoxide to obtain the final 2-amino bis-benzimidazoles **12** in good yields (Table 1).

All the steps in this synthetic sequence have been accomplished under focused microwave irradiation resulting in reduced reaction times and enhanced yields.[29] It should be noted that polymer-supported intermediates and polymer itself are stable during the MW irradiation.

In conclusion, it is a rare sequence of reactions in which each step is powered by microwave irradiation in addition to the chemical methods leading to the synthesis of flexible bis-benzimidazoles functionalized for potential DNA minor groove recognition study.

Acknowledgements

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References and notes

1. (a) Dolle, R. E. *Mol. Divers.* **1996**, *2*, 223–236; (b) Dolle, R. E.; Nelson, K. H. *J. Comb. Chem.* **1999**, *1*, 235–282; (c)

Dolle, R. E. *J. Comb. Chem.* **2000**, *2*, 383–433; (d) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 477–517; (e) Dolle, R. E. *J. Comb. Chem.* **2003**, *5*, 693–753; (f) Dolle, R. E. *J. Comb. Chem.* **2004**, *5*, 623–679.
2. Microwave-assisted combinatorial synthesis: (a) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95–105; (b) Al-Obeidi, F.; Austin, R. E.; Okonya, J. F.; Bond, D. R. S. *Mini Rev. Med. Chem.* **2003**, *3*, 459–470; (c) Blackwell, H. E. *Org. Biomol. Chem.* **2003**, *1*, 1251–1255; (d) Swamy, K. M. K.; Yeh, W. B.; Lin, M. J.; Sun, C. M. *Current Medicinal Chemistry* **2003**, *10*, 2403–2423; (e) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
3. Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489–509.
4. (a) Sun, C. M. Soluble Polymer-Supported Synthesis of Heterocyclic Libraries. In *Combinatorial Chemistry Methods and Protocols, Methods in Molecular Biology Series*; Bellavance, L., Ed.; The Humana Press: New Jersey, 2002; Chapter 10, pp 345–371; (b) Lee, M. J.; Sun, C. M. *Chin. Pharm. J.* **2003**, *55*, 405–452.
5. Shey, J. Y.; Sun, C. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 519–522.
6. Yeh, C. M.; Tung, C. L.; Sun, C. M. *J. Comb. Chem.* **2000**, *2*, 341–348.
7. Yeh, W. B.; Lin, M. J.; Lee, M. J.; Sun, C. M. *Mol. Divers.* **2003**, *7*, 185–198.
8. Yeh, W. B.; Lin, M. J.; Sun, C. M. *Tetrahedron Lett.* **2003**, *44*, 4923–4926.
9. Chung, W. J.; Yeh, W. B.; Sun, C. M. *Synlett* **2003**, *11*, 1688–1692.
10. Wikel, J. H.; Paget, C. J.; Delong, D. C.; Nelson, J. D.; Wu, C. Y. E.; Paschal, J. W.; Dinner, A.; Templeton, R. J.; Chaney, M. O.; Jones, M. D. *J. Med. Chem.* **1980**, *23*, 368–379.
11. Victor, F.; Brown, T. J.; Campanale, K.; Heinz, B. A.; Stripley, L. A.; Su, K. S.; Tang, J.; Vance, L. M.; Spitzer, W. A. *J. Med. Chem.* **1997**, *40*, 1511–1518.
12. Porcari, A. R.; Devivar, R. V.; Kucera, L. S.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1998**, *41*, 1252–1262.
13. Backlund, M.; Weidolf, L.; Sundberg, M. I. *Eur. J. Biochem.* **1999**, *261*, 66–71.
14. Lee, J.; Doucette, A.; Wilson, N. S.; Lord, J. *Tetrahedron Lett.* **2001**, *42*, 2635–2638.
15. Iosifidou, E. G.; Haagasma, N.; Olling, M.; Boon, J. H.; Tanck, M. W. T. *Drug. Metab. Disp.* **1997**, *25*, 317–320.
16. Alexandra, J.; Sun, X. W.; Eric, J.; Christian, B.; John, M.; Stephen, N. *Biochemistry* **2003**, *42*, 5984–5992.
17. Woynarowski, J. M.; McHugh, M.; Sigmund, R. D.; Beerman, T. A. *Mol. Pharmacol.* **1988**, *35*, 177–182.
18. Minehan, T. G.; Gottwald, K.; Dervan, P. B. *Helv. Chim. Acta* **2000**, *83*, 2197–2213.
19. Ji, Y. H.; Bur, D.; Hasler, W.; Schimitt, V. R.; Dorn, A.; Bailly, C.; Waring, M. J.; Hochstrasser, R.; Leupin, W. L. *Bioorg. Med. Chem.* **2001**, *9*, 2905–2919.
20. Goldman, G. H.; Yu, C.; Sanders, M. M.; LaVoie, E. J. *Biochemistry* **1997**, *36*, 6488–6494.
21. Kim, J. S.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem.* **1996**, *39*, 992–998.
22. Alper, S.; Arpaci, O. T.; Aki-Sener, E. S.; Yalcin, Y. *Farmaco* **2003**, *58*, 497–507.
23. Sun, Q.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2871–2876.
24. Jin, S.; Kim, J. S.; Sim, S. P.; Liu, A.; Pilch, D. S.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 719–723.
25. Mann, J.; Baron, A.; Opoku-Boahen, Y.; Johansson, E.; Parkinson, G.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **2001**, *44*, 138–144.
26. Rastogi, K.; Chang, J. Y.; Pan, W. Y.; Chou, C. H.; Chen, T. C.; Su, T. L. *J. Med. Chem.* **2002**, *45*, 4485–4493.
27. Tanious, D.; Hamelberg, D.; Bailly, A.; Czamy, D.; Boykin, W. D.; Wilson, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 143–153.
28. Yeh, W. B.; Lin, M. J.; Sun, C. M. *Comb. Chem. High T Scr.* **2004**, *7*, 251–255.
29. All the microwave assisted polymer-supported reactions described here were performed in a 50 mL round bottom flask (attached to the reflux condenser) with CEM Discover Microwave System at a frequency of 2450 MHz (0–300 W). A detailed reaction procedure for the synthesis polymer bound intermediate **5** by domestic microwave oven can be found: Bendale, P. M.; Sun, C. M. *J. Comb. Chem.* **2002**, *4*, 359–361.
The spectral data for **12a**: ^{1}H NMR (300 MHz, $CDCl_3$) 8.51 (s, 1H), 8.03 (d, $J = 9.0$ Hz, 1H), 7.73 (s, 1H), 7.2–7.5 (m, 8H), 5.22 (s, 2H), 4.23 (t, $J = 7.6$ Hz, 2H), 3.95 (s, 3H), 1.18–1.5 (m, 4H), 1.02 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 168, 157, 155, 143, 142, 139, 136, 135, 129, 128, 126, 124, 123, 122, 121, 120, 117, 109, 108, 71, 52, 46, 43, 42, 32, 20, 13; mass spectrum (FAB) *m/z* 454 (MH^+). Exact mass calcd for $C_{27}H_{27}N_5O_2$: *m/z* 453.2159, found 453.2153.