A facile synthesis of some 3-(benzimidazol-2-yl)- and 3,6-di(benzimidazol-2-yl)-9-ethyl-9H-carbazoles

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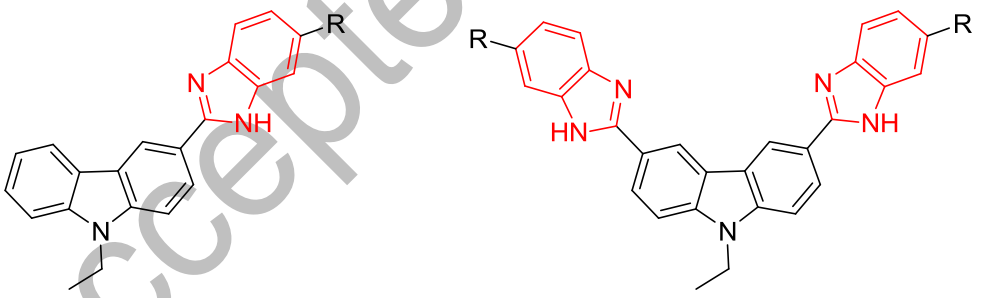
Abstract

A simple and efficient synthesis of novel 3-(benzimidazol-2-yl)- and 3,6-di(benzimidazol-2-yl)-9-ethyl-9H-carbazoles is described. The synthetic approach for the preparation of 2-substituted benzimidazoles **4-8** and bis-benzimidazoles **9-12** was achieved by the condensation of carbazole-3-carbaldehyde **2** and carbazole-3,6-dicarbaldehyde **3** with *o*-phenyldiamines in dimethylformamide or dimethylsulfoxide in moderate to excellent yield. The identities of synthesized compounds were confirmed using ^{1}H NMR, ^{13}C NMR, IR and high resolution mass spectrometry.



KEYWORDS: Benzimidazole, bis-benzimidazole, carbazole, Vilsmeier-Haack method

INTRODUCTION

Nitrogen containing heterocycles have been the subject of intense study and considerable effort has been devoted to the synthesis of these heterocyclic systems as they are found in a wide range of biologically active molecules and alkaloids.[1,2] Among these, benzimidazole and carbazole derivatives are of significant synthetic interest due to their diverse range of biological activity.

Benzimidazole and its derivatives are an important class of nitrogen containing aromatic heterocyclic compounds, having long attracted attention from researchers due to their valuable properties.[3] They have a multitude of interesting biological activities, including antimicrobial, anti-inflammatory, antitumor, antiviral and antihypertensive activity.[4-8] In recent years, they have also attracted particular interest due to their anticancer activities.[9-10] In particular, benzimidazole compounds have been explored as topoisomerase I, PARP-1, kinase Chk2, metallo and serine protease inhibitors.[11] Furthermore, compounds possessing benzimidazole express significant activity against several viruses such as HIV, herpes (HSV-1) and RNA influenza.[12-14]

More complex benzimdazoles, such as bis-benzimidazoles, are also very important biologically active scaffold that are found in many pharmacologically active alkaloids. For example, Hoechst 33258 (also known as Pibenzimol) is an A/T base pair selective compound that binds in the minor groove of DNA.[15]

Carbazole and its derivatives are rigid heterocyclic systems that have been a source of great interest for chemists due to their reactivity to electrophilic substitutions and wide spectrum of biological properties.[16] The preferred site of electrophilic substitution for carbazole is the C3 position. The blocking of this position directs the electrophilic substitution to the C6 position. This gives the opportunity for the realization of further substitutions on the C6 position.

Also, diaryl or heteroaryl carbazoles have been associated with cytotoxic and antiplatelet activitiy, and are attractive molecules for the potential development of anti-tumor agents.[17-18] Furthermore, carbazole derivatives are widely used as building blocks for new organic materials and play a very important role in electroactive and photoactive materials.[19] Currently, there is a strong interest in the synthesis of novel heteroarylcarbazole derivatives having their important structural features and promising biological activities.[20] Although most heteroarylcarbazoles reported in the literature contain a common heterocyclic ring moiety fused with a carbazole such as pyridocarbazoles, thienocarbazole, quino and chromecarbazoles, pyranocarbazoles, pyrrolo carbazoles, indolocarbazoles and their synthetic analogues, to the best of our knowledge, there are very few reports where the heteroaryl moiety is substituted with a carbazole unit.[21-26] Consequently, the synthesis of such compounds is desirable. In this regard, we previously reported the synthesis of some di-(2-indolyl)heteroarenes in which the linker between two indoles is a carbazole.[27-28]

Recently, carbazole based benzimidazoles have been reported to show significant biological activities including telomerase inhibition and anti-cancer activities.[29-31] Considering the importance of benzimidazole and carbazole derivatives, we are interested in the synthesis of mono- and bis-benzimidazoles linked by the structurally rigid carbazole ring system. The synthesis of mono-benzimidazoles is also important due to having a reactive C6 position for further substitutions.

RESULTS AND DISCUSSION

Many synthetic approaches have been reported for the synthesis of benzimidazole ring systems.[32] Traditionally, benzimidazoles have most commonly been prepared from the condensation of *o*-phenylenediamines with carbonyl compounds such as aldehydes or carboxylic acids and their derivatives, which often require strongly acid conditions, sometimes combined with very high temperatures or microwave irradiation.[32] In this current study, the construction of benzimidazole-carbazole hybrid molecules was successfully achieved *via* the condensation of *o*-phenylenediamines with carbazolecarbaldehydes in dimethysulfoxide or dimethlyformamide.

The synthesis of carbazole-linked mono- and bis-benzimidazoles began with the formylation of *N*-ethylcarbazole **1** using $POCl_3$/DMF *via* the Vilsmeier-Haack method, which gave mono- and diformylcarbazoles **2** and **3** in 70% and 90% yields, respectively (Scheme 1).[33] With the carbazole-3-carbaldehyde **2** and carbazole-3,6-dicarbaldehyde **3** in hand, it was of interest to use a monomeric model for the preparation of mono-benzimidazoles **4-8** before extending the chemistry to bis-benzimidazoles. Initially,

carbazolecarbaldehyde **2** was treated with *o*-phenylenediamine in a variety of solvents, such as ethanol, isopropanol, nitrobenzene and dimethylformamide, to optimize the reaction and to obtain the maximum yields and highest purity of the products. It was found that when the reaction was conducted in dimethylformamide at 100 °C, 94% yield of benzimidazole **4** was obtained. In contrast, the use of other solvents resulted in a mixture of products, which could not be separated by column chromatography. Similarly, treatment of carbazolecarbaldehyde **2** with other *o*-phenylenediamine derivatives in DMF afforded the corresponding benzimidazole derivatives **5-8** in good yields (Table-1). It is worth noting here that compound **4** was reported as a neuropeptide Y5 receptor.[34] Also, the antimicrobial activity of compound **4** against *Bacillus subtilis* and *Escherichia coli* was previously investigated.[35]

Compounds **5-8** are novel and their structures were established with the help of spectroscopic data. The ^{1}H NMR and ^{13}C NMR spectra of compound **5** were characteristic for compounds **5-8**. The ^{1}H NMR spectrum (DMSO) of **5** showed the appearance of a new singlet at 12.6 ppm correlating to the NH proton of the benzimidazole ring. The disappearance of the CHO proton for the spectrum indicated that benzimidazole cyclisation had taken place. Further structural verification was obtained *via* mass spectroscopy, with MALDI mass spectra revealing (M+1) peaks at *m/z* 312, 326, 346, 342 and 357, consistent for compounds **4-8** respectively.

Having successfully used this method to prepare monomeric carbazole linked benzimidazoles, preparation of related bis-benzimidazole systems was next examined. It

is worth noting here that bis-benzimidazole **9** was previously synthesized *via* a three steps process from the reaction between *N*-ethylcarbazole-3,6-dicarboxylic acid and *o*-phenylenediamine in the presence of polyphosphoric acid.[36] Herein, we report the successful preparation of carbazole linked bis-benzimidazoles **9-12** with a convenient three-step process, as shown in Scheme 1.

The reaction between **3** and *o*-phenylenediamine derivatives was first performed in DMF, however, a clean product was not obtained after column chromatography. Therefore, dicarbaldehyde **3** was condensed with *o*-phenylenediamine in dimethylsulfoxide and the carbazole linked bis-benzimidazole **9** was successfully produced in 63% yield. Similarly, treatment of carbazole-3,6-dicarbaldehyde **3** with other *o*-phenylenediamine derivatives gave the corresponding bis-benzimidazoles **10-12** in moderate yields (Table 1). Unfortunately, the reaction of compound **3** with 4-nitro-*o*-phenylenediamine produced a mixture of products which could not be separated by flash column chromatography.

The structures of compounds **9-12** were supported by ^{1}H NMR and ^{13}C NMR spectroscopic data. The ^{1}H NMR spectrum of the compound **10** in DMSO, as a typical example of the carbazole linked bis-benzimidazoles **9-12**, displayed a broad singlet at 12.9 ppm corresponding to the benzimidazole ring NH proton, and the carbazole CH_2 and CH_3 protons appeared as a quartet and triplet at 1.44 ppm and 4.55 ppm respectively. The ^{13}C NMR spectrum displayed the carbazole CH_2 and CH_3 peaks at 14.3 and 37.9 ppm respectively.

CONCLUSION

In the present study, a series of mono- (**4-9**) and bis-benzimidazoles (**10-12**) connecting benzimidazoles to *N*-ethylcarbazole units were synthesized and characterized. While mono-benzimidazoles were produced in DMF, DMSO was needed for a clean synthesis of bis-benzimidazoles.

EXPERIMENTAL

All reagents and solvents were obtained from commercial sources and appropriately purified, if necessary. The deuterated solvent (DMSO) for NMR spectroscopy was obtained from Merck. Following chemicals were obtained from Sigma Aldrich Melting points were measured using a Mel-Temp melting point apparatus and are uncorrected. Measurements IR spectra were recorded between 4000 and 650 cm^{-1} using a Perkin Elmer Spectrum 100 FT-IR spectrometer ^{1}H and ^{13}C NMR spectra were recorded in DMSO solution on a Varian 500 MHz spectrophotometer. Matrix-assisted laser desorption/ionization time-of- flight mass spectrometry (MALDI-TOF-MS) measurements were performed on a Bruker Daltonics microTOF. High resolution mass spectra (HRMS) reported to 4 decimal places were recorded on a Agilent G6530B Accurate-Mass Q-TOF LC/MS.

General Procedure for the preparation of mono-benzimidazoles (**4-8**). A mixture of 3-carbaldehyde **2** and *o*-phenyldiamine derivatives (1:1 eq) was heated at 100 °C in DMF (4 mL) for 8 h. The reaction mixture was poured into ice-water and the resulting precipitate was filtered, washed with water and dried. The crude product was purified by

flash column chromatography using dichloromethane/ethyl acetate (9:1) as eluent to afford the mono-benzimidazoles.

3-(1H-benzo[d]imidazol-2-yl)-9-ethyl-9H-carbazole (**4**). This compound was obtained as a white solid; yield: 94%; m.p: 255-257 ^{o}C; IR (KBr): υ_{max} 3648, 3049, 2977, 1628, 1599, 1488, 1470, 1439, 1403, 1374, 1346, 1328, 1150, 744 cm^{-1} ; ^{1}H NMR (500 MHz, DMSO): δ 1.54 (s, 3H, CH_3), 4.68 (s, 2H, CH_2), 7.38 (s, 2H, aryl H), 7.47 (s, H, aryl H), 7.71 and 7.97 (m, 5H, aryl H), 8.43 (s, H, aryl H), 8.50 (s, H, aryl H), 9.18 (s, H aryl H), 13.05 (s, H, benzimidazole NH); ^{13}C NMR (DMSO): δ 13.8 (CH_3), 37.3 (CH_2), 119.0, 119.1, 120.0, 121.1, 121.9, 121.9, 122, 124.7, 126.4, 140.3, 140.6, 152.8 (aryl C and CH); Maldi (TOF); *m/z* 312 $[M]^+$; HRMS (ESI): Found *m/z* 312.1501 $[M]^+$; calculated for $C_{21}H_{17}N_3$ 312.1510.

General Procedure For The Preparation Of Bis-Benzimidazoles (9-12)

A mixture of 3,6-dicarbaldehyde **3** (1 eq) and *o*-phenylenediamine derivative (2 eq) was heated at 120 °C in DMSO (5 mL) for 24 h. The reaction mixture was poured into ice-water and the resulting precipitate was filtered, washed with water and dried. The crude product was purified by flash column chromatography using dichloromethane/ethyl acetate (5:5) as eluent to afford the bis-benzimidazoles.

3,6-di(1H-benzo[d]imidazol-2-yl)-9-ethyl-9H-carbazole (**9**). This compound was obtained as a brown solid; yield: 63%; m.p: >320 ^{o}C (lit.[33] m.p: >300 ^{o}C); IR (KBr): υ_{max} 3638, 3052, 2971, 2925, 1602, 1485, 1437, 1400, 1364, 1276, 1230, 1147, 804, 734

cm^{-1} ; ^{1}H NMR (500 MHz, DMSO): δ 1.41 (t, 3H, *J*=7.10 Hz, CH_3), 4.55 (q, 2H, *J*=7.03 Hz, CH_2), 7.21 (s, 4H, aryl H), 7.62(s, 4H, aryl H), 7.83 (d, 2H, *J*=8.54 Hz, aryl H), 8.37 (d, 2H, *J*=8.36 Hz, aryl H), 9.14 (s, 2H, aryl H), 12.9 (s, 2H, 2x benzimidazole H); ^{13}C NMR (DMSO): δ 14.3 (CH_3), 37.9 (CH_2), 110.4, 119.3, 122.1, 122.2, 122.9, 125.2, 141.4, 152.8 (aryl C and CH); Maldi (TOF); *m/z* 428 $[M]^+$; HRMS (ESI): Found *m/z* 428.1878 $[M]^+$; calculated for $C_{28}H_{21}N_5$ 428.1875.

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SUPPLEMENTAL MATERIAL

Detailed experimental procedures and spectral characterizasion data for this article can be accessed on the publisher's website.

REFERENCES

1. Rodriguez, S. L.; Zaballos, G. E.; Gonzalez, R. E.; Testa, M. L.; Sepulveda, A. J.; Jones, R. A. *Tetrahedron* **2000**, *56*, 4511-4514.

2. Hudkins, R. L.; Johnson, N. W.; Angeles, T. S.; Gessner, G. W.; Mallamo, J. P. *J. Med. Chem.* **2007**, *50*, 433-441.

3. Dawood, K. M; Bakr A. W. *Arkivoc* **2010**, *1*, 333-389.

4. Tong, Y. S.; Bouska, J. J.; Ellis, P. A.; Johnson, E. F.; Leverson, J.; Liu, X. S.; Marcotte, P. A.; Olson, A. M.; Sterling, D. J.; Przytulinska, M.; Rodriguez, L. E.; Shi, Y.; Soni, N.; Stavropoulos, J.; Thomas, S.; Donawho, C. K.; Frost, D. J.; Luo, Y.; Giranda, V.L.; Penning, T. D. *J. Med. Chem*. **2009**, *52*, 6803-6813.

5. Li, Y. F.; Wang, G. F.; He, P. L.; Huang, W. G.; Zhu, F. H.; Gao, H. Y.; Tang, W.; Luo, Y.; Feng, C. L.; Shi, L. P.; Ren, Y. D.; Lu, W.; Zuo, J. P. *J. Med. Chem*. **2006**, *49*, 4790-4794.

6. Achar, K. C. S.; Hosamani, K. M.; Seetharamareddy, H. R. *Eur. J. Med. Chem.* **2010**, *45*, 2048-2054.

7. Le, S. C.; Baron, A.; Mann, J.; Van den Berg, H.; Gunaratnam, M.; Neidle, S. *Org. Biomol. Chem*. **2006**, *7*, 1305-1312.

8. Kálai, T.; Balog, M.; Szabó, A.; Gulyás, G.; Jek , J.; S megi, B.; Hideg, K. *J. Med. Chem.* **2009**, *5*, 1619-1629.

9. Husain, A.; Rashid, M.; Mishra, R.; Parveen, S.; Shin, D. S.; Kumar, D. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5438-5344.

10. El Rashedy, A.; Aboul-Enein, H. *Mini-Rew. Med. Chem.* **2013**, *13*, 399-407.

11. Li, Y.; Tan, C.; Gao, C.; Zhang, C.; Luan, X.; Chen, X.; Jiang, Y. *Biorg. Med. Chem.* **2011**, *19*, 4529-4535.

12. Porcari, A. R.; Devivar, R. V.; Kucera, L. S.; Drach, J. C.; Townsend, L. B. *J Med Chem* **1998**, *41*, 1252-1262.

13. Migawa, M. T.; Girardet, J. L.; Walker, J. A.; Koszalka, G. W.; Chamberlain, S. D.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1998**, *41*, 1242-1252.

14. Tamm, I. *Science* **1957**, *126*, 1235.

15. Pedersen, H.; Brauner-Osborne, H.; Ball, R. G.; Frydenvang, K.; Meier, E.; Bogeso, K. P.; Krogsgaard-Larsen, P. *Bioorg. Med. Chem.* **1999**, *7*, 795-809.

16. Zhang, F. F.; Gan, L. L.; Zhou, C. H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1881-1884.

17. Wang, T. C.; Chen, I. *Helv. Chim. Acta* **2004**, *87*, 983-990.

18. Chang, C. C.; Kuo, I. C.; Lin, J. J.; Lu, Y. C.; Chen, C. T.; Back, H. T.; Chang, T. C. *Chemistry Biodiversity* **2004**, *9*, 1377-1384.

19. Li, Y.; Gao, W. *Beilstein J. Org. Chem.* **2010**, *6*, 966-972.

20. Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saá, C. *Tetrahedron* **2008**, *64*, 3674-3686.

21. Barbieri, V.; Ferlin, M. G. *Tetrahedron Lett.* **2006**, *47*, 8289-8292.

22. Ferreira, I. C. F. R.; Queiroz, M. J. R. P.; Kirsch, G. *Tetrahedron Lett.* **2003**, *44*, 4327-4329.

23. Meesala, R.; Nagarajan, R. *Tetrahedron* **2009**, *65*, 6050-6056.

24. Laronze, M.; Boisbrun, M.; Léonce, S.; Pfeiffer, B.; Renard, P.; Lozach, O.; Meijer, L.; Lansiaux, A.; Bailly, C.; Sapi, J.; Laronze, J. Y. *Bioorg. Med. Chem.* **2005**, *13*, 2263-2283.

25. Janosik, T.; Wahlström, N.; Bergman, J. *Tetrahedron* **2008**, *64*, 9159-9180.

26. Bakthadoss, M.; Selvakumar, R.; Srinivasan, J. *Tet. Lett*. **2014**, *55*, 5808-5812.

27. Sengul, I. F.; Wood, K.; Kumar, N.; Black, D. StC. *Tetrahedron* **2012**, 68, 9050-9055.

28. Sengul, I. F.; Samphol, K.; Kandemir, H.; Kumar, N.; Black, D. StC. *Tetrahedron* **2014**, 70, 9601-9614.

29. Maji, B.; Kumar, K.; Kaulage, M.; Muniyappa, K.; Bhattacharya, S. *J. Med. Chem.* **2014**, *57*, 6973-6988.

30. Maji, B.; Kumar, K.; Muniyappa, K.; Bhattacharya, S. *Org. Biomol. Chem*. **2015**, *13*, 8335-8348.

31. Bashir, M.; Bano, A.; Ijaz, A. S.; Chaudhary, B. A. *Molecules*, **2015**, *20*, 13496-13517.

32. Panda, S.; Malik, R.; Jain, S. *Curr. Org. Chem.* **2012**, *16*, 1905-1919.

33. Yu, L.; Li, L.; Fei, X. *J. Lumin.* **2014**, *149*, 28-34.

34. Block, M. H.; Donald, C. S.; Foote, K. M.; Schofield, P.; Marsham, P. R. *PCT Int Appl* **2001**.

35. Berghot, M. A.; Badawy, D. S.; Moawad, E. B. *Revue Roumaine de Chimie* **1995**, *40*, 377-386.

36. Shi, H. P.; Cheng, Y.; Jing, W. J.; Chao, J. B.; Fang, L.; Dong, X.; Dong, C. *Spectrochimica Acta Part A: Mol. and Biomol. Spect*. **2010**, *75*, 525-532.

Table 1. Synthesis of mono-benzimidazoles (**4-8**) and bis-benzimidazoles (**9-12**).

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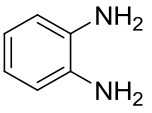
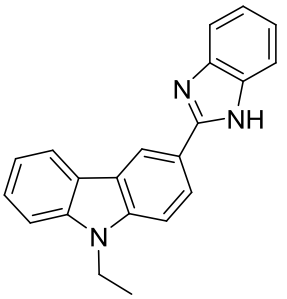
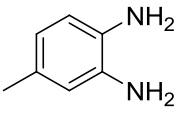
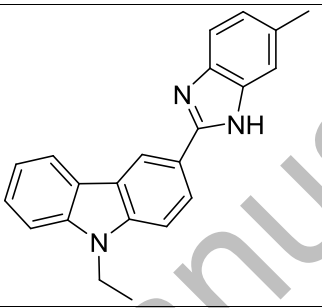
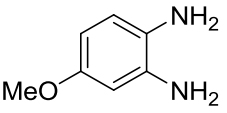
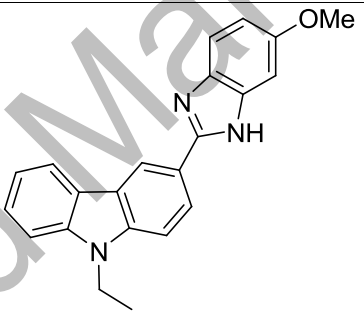
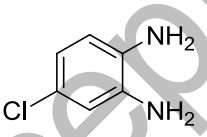
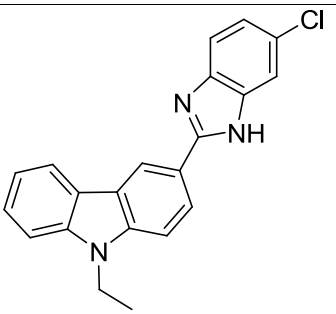
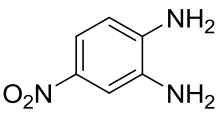
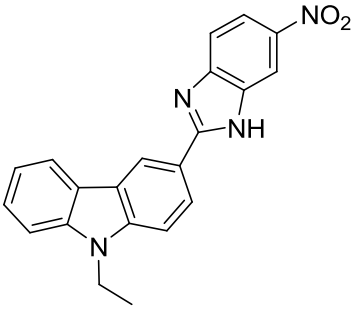
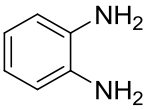
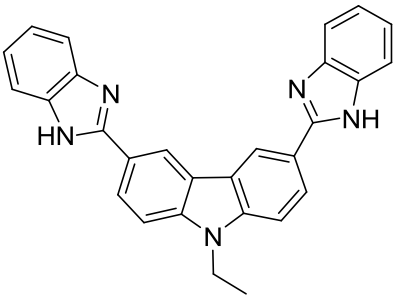
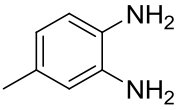
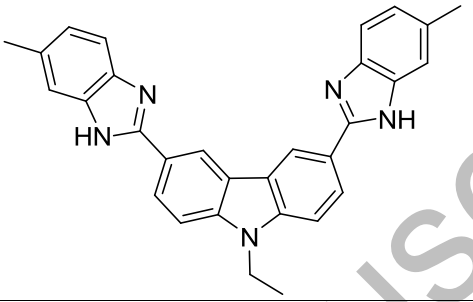
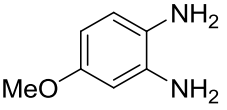
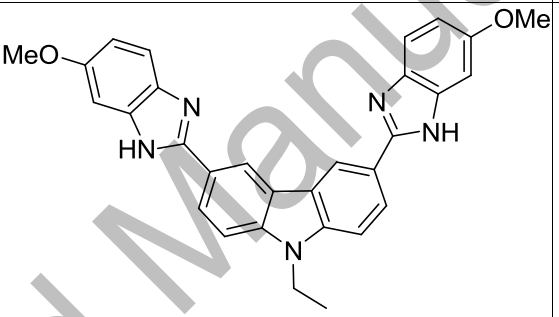
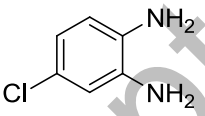
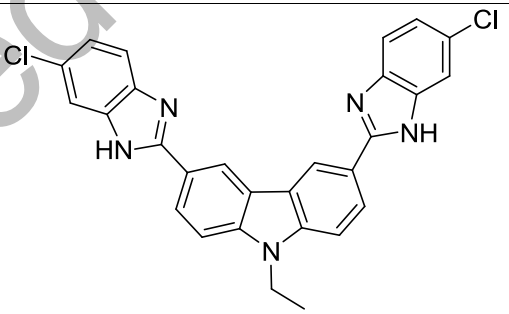
4			94
5			90
6			73
7			89
8			78

9			63
10			51
11			46
12			42

Scheme 1. Reagents and conditions: a) DMF, $POCl_3$, reflux; b) *o*-Phenylenediamine derivatives DMF, 100 ℃, 8h; c) *o*-Phenylenediamine derivatives, DMSO, 120 ℃, 24h.