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Synthesis, Characterization and Thermal Analysis of Novel Methylene Bridged Bis-carbazole Based Bis-benzimidazoles

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ABSTRACT

The synthesis of novel bis(3-carbazolyl)methane-linked bis-benzimidazoles is described. The construction of symmetrical bis-benzimidazoles on the bis-carbazolylmethane scaffold was succeeded by condensation reaction of benzene-1,2-diamine derivatives with bis(9-ethyl-9H-carbazole-3-carbaldehyde). The structural analysis of the targeted compounds 4-7 was confirmed by NMR, FT-IR spectroscopy and mass spectrometry. The thermal stability of final products 4-7 was also studied by thermogravimetric analysis (TGA).

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Bis-benzimidazole; Bis-carbazole; Formylation; Thermal stability

INTRODUCTION

By virtue of existing various important biological activities, there has been a growing interest over the past decades for the synthesis of nitrogen containing heterocycles [1-5]. Among these heterocycles, benzimidazole and carbazole platforms are important type of nitrogen possessing building blocks due to their diverse range of biological activity [5-10].

Benzimidazole is benzene and imidazole fused with a bicyclic aromatic compound. The NH functional group in the benzimidazole scaffold is quite weakly primary and relatively strong acidic. Benzimidazoles are also an important class of benzo-fused heterocyclic systems and have several of interesting pharmaceutical activities ranging from antitumor to antimicrobial [11-13]. Benzimidazole based heterocyclic structures display significant activity against various viruses such as HIV, herpes (HSV-1), and RNA influenza [14-16].

Bis-benzimidazole motifs are compounds consisting of two benzimidazole units connected to each by different linkages. Due to having interesting biological properties bis-benzimidazole based compounds are desired target for medicinal chemistry. For example, appropriately substituted benzimidazoles have been discovered to bind helix DNA and used telomerase inhibitors [17-21]. The anticancer and antimicrobial activities of bis-benzimidazoles based compounds have been studied by several groups [22-27].

Carbazoles are also another important class of nitrogen containing electron rich, rigid and fully aromatic heterocycles, and appear in a large number of natural compounds [10, 28]. The carbazole based compounds have been explored in various area of chemosensor, solar cells, and organic-light emitting diodes (OLEDs) [29-32]. In addition carbazole containing compounds have displayed diverse important biological properties such as antimicrobial, antiviral, antitumor and antioxidant activities [33-35]. Facile stability, easy functionalization, good absorption and efficient emissive properties of the carbazole core have made them very popular among chemist. More specifically, one of the most important subclasses of the carbazole ring systems is binary carbazole alkaloids connected through methylene linkages. A range of bis-carbazole compounds have been isolated from the natural sources and displayed interesting biological effects [36-37]. For example, as shown in Figure 1, Chrestifoline-A and Bismurrayafoline-A natural products isolated from Murraya euchrestifolia show moderate antitumor activity [37].

It is well established that the construction of two biologically active heterocyclic units into a single compound represents a strategic approach to potential bioactive systems [38-39]. Therefore due to the wide range of interesting activities and properties of benzimidazole and carbazole based compounds, the synthesis of novel benzimidazole possessing bis-carbazole hybrid compo-

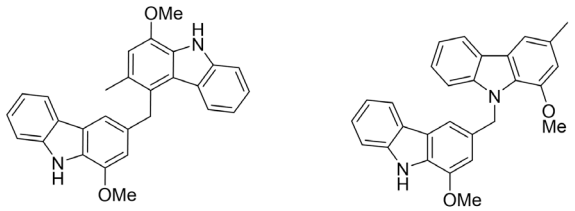

Figure 1. Biologically active methylene bridged bis-carbazole natural products.

unds has been focused and studied in this research.

MATERIAL AND METHODS

All reagents and solvents were purchased from commercial companies and appropriately purified, when necessary [40]. A Varian 500 MHz NMR spectrometer was used to record ^{1}H NMR spectrum at 298 K . The deutero dimethyl sulfoxide, (DMSO-d_6) for NMR spectroscopy was obtained from Merck. A Perkin Elmer Spectrum 100 FT-IR spectrometer was used to record FT-IR spectra. A Bruker Daltonics microTOF was used for MALDI-TOF-MS measurements. Merck silica gel plates, precoated with silica gel 60 F254 (0.2 mm) on aluminium sheets was used for analytical TLC. A Mettler Toledo TGA/SDTA 851TGA was used for TGA measurements by loading compounds as powder into alumina pans and heated at a ramp rate of 10 °C per minute from 25 °C to 700 °C under a nitrogen gas atmosphere. Melting points were measured using a Stuart SMP3 melting point apparatus and are uncorrected.

Synthesis of Bis-carbazolemethane Based Bis-benzimidazole Compounds (4-7)

General Procedure: A reaction flask was charged with compound 3 (1.0 mol equiv) and benzene-1,2-diamine derivatives (2.1 mol equiv) in DMSO (5 mL). The reaction mixture was stirred at 120 °C for 17-21 h. The reaction progress was monitored by TLC using eluent EtOAc:hexane (50:50). The reaction was completed and worked-up once none of the starting material 3 was observed by TLC analysis. The resulting reaction mixture was diluted with EtOAc and brine solution. The organic phase was then separated, washed with water several times and dried under vacuum to give desired products 4-7.

Synthesis of bis(6-(1H-benzo[d]imidazol-2-yl)-9-ethyl-9H-carbazol-3-yl)methane (4)

Compound 3 (0.12 g, 0. 27 mmol) and benzene-1,2-diamine (62 mg, 0.57 mmol) was stirred in DMSO (4.5 mL) at 120 °C for 17 h. By following the general procedure work-up protocol, the desired compound 4 (0.17 g, 99% yield) was obtained as orange colour solid. mp 294-298 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.19 (br.s, 2H), 8.44 (d, ^{3}JHH = 8.4 Hz, 2H), 8.10 (s, 2H), 7.78 (d, ^{3}JHH = 8.6 Hz, 2H), 7.70 – 7.63 (m, 4H), 7.59 (d, ^{3}JHH = 8.4 Hz, 3H), 7.47 (d, ^{3}JHH = 8.1 Hz, 2H), 7.36 – 7.25 (m, 5H), 4.44 (q, ^{3}JHH = 6.9 Hz, 4H), 4.32 (s, 2H), 1.29 (t, ^{3}JHH = 6.9 Hz, 6H) ppm; ^{13}C NMR could not be taken due to low solubility of the compound 4; FT-IR: υ_{max} 3337 (N-H, benzimidazole), 3059 (C-H, aromatic), 2974 (C-H, alkyl), 2915, 1627, 1601 (C=C, aromatic), 1483 (C-H, alkyl), 1377, 1346, 1309, 1233, 1153, 1026, 889, 806, 745 cm^{-1}; MALDI-TOF; calc for $C_{43}H_{34}N_6$ $[M]^+$: 634.787; found $[M - H]^+$:633.254.

Synthesis of bis(6-(6-chloro-1H-benzo[d] imidazol-2-yl)-9-ethyl-9H-carbazol-3-yl)methane (5)

Compound 3 (75 mg, 0. 16 mmol) and 4-chlorobenzene-1,2-diamine (50 mg, 0.34 mmol) was stirred in DMSO (2.5 mL) at 120 °C for 17 h. By following the general procedure work-up protocol, the desired compound 5 (0.10 g, 91% yield) was obtained as brown colour solid. mp 259-261 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.93 (br.s, 2H), 8.31 – 8.21 (m, 3H), 8.13 (s, 1H), 7.79 (d, ^{3}JHH = 8.6 Hz, 2H), 7.71 – 7.64 (m, 4H), 7.65 – 7.59 (m, 4H), 7.53 (d, ^{3}JHH = 7.6 Hz, 2H), 7.31 – 7.24 (m, 2H), 4.47 (q, 3JHH = 6.9 Hz, 4H), 4.36 (s, 2H), 1.33 (t, 3JHH = 6.1 Hz, 6H) ppm; ^{13}C NMR could not be taken due to low solubility of the compound 5; FT-IR: υ_{max} 3392 (N-H, benzimidazole), 3159, 3056 (C-H, aromatic), 2975 (C-H, alkyl), 2159, 1629, 1603 (C=C, aromatic), 1483 (C-H, alkyl), 1400, 1347, 1234, 1159, 1044, 925 cm^{-1}; MALDI-TOF; calc for $C_{43}H_{32}Cl_2N_6$ $[M]^+$: 703.671; found $[M]^+$: 703.185.

Synthesis of bis(9-ethyl-6-(6-methyl-1H-benzo[d] imidazol-2-yl)-9H-carbazol-3-yl)methane (6)

Compound 3 (0.10 g, 0. 22 mmol) and 4-methylbenzene-1,2-diamine (56 mg, 0.46 mmol) was stirred in DMSO (3 mL) at 120 °C for 17 h. By following the general procedure work-up protocol, the desired compound 6 (0.14 g, 95% yield) was obtained as brown colour solid. mp >300 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.14 (br.s, 2H), 8.40 (d, ^{3}JHH = 8.2 Hz, 2H), 8.14 (s, 2H), 7.99 – 7.86 (m, 1H), 7.80 (d, ^{3}JHH = 8.6 Hz, 2H), 7.62 (d, ^{3}JHH = 8.3 Hz, 2H), 7.57 (d, ^{3}JHH = 8.1 Hz, 2H), 7.52 (d, ^{3}JHH = 8.3 Hz, 3H), 7.47 (s, 2H), 7.16 (d, ^{3}JHH = 7.9 Hz, 2H), 4.47 (q, ^{3}JHH = 6.5 Hz, 4H), 4.36 (s, 2H), 2.54 (s, 6H), 1.32 (t, ^{3}JHH = 6.7 Hz, 6H) ppm; ^{13}C NMR could not be taken due to low solubility of the compound 6; FT-IR: υ_{max} 3385 (N-H, benzimidazole), 3056 (C-H, aromatic), 2975 (C-H, alkyl), 2917, 1630, 1600 (C=C, aromatic), 1444 (C-H, alkyl), 1346, 1233, 1023, 949 cm^{-1}; MALDI-TOF; calc for $C_{45}H_{38}N_6$ $[M]^+$: 662.841; found $[M]^+$: 662.272.

Synthesis of bis(9-ethyl-6-(6-nitro-1H-benzo[d] imidazol-2-yl)-9H-carbazol-3-yl)methane (7)

Compound 3 (0.10 g, 0. 22 mmol) and 4-nitrobenzene-1,2-diamine (70 mg, 0.46 mmol) was stirred in DMSO (3 mL) at 120 °C for 21 h. By following the general procedure work-up protocol, the desired compound 7 (0.13 g, 85% yield) was obtained as brown colour solid. mp 202-204 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.00 (s, 1H), 8.94 (s, 1H), 8.45 – 8.34 (m, 1H), 8.32 – 8.25 (m, 2H), 8.23 (d, ^{3}JHH = 7.2 Hz, 1H), 8.14 (s, 1H), 8.12 – 8.04 (m, 3H), 7.80 (d, ^{3}JHH = 8.3 Hz, 1H), 7.76 (d, ^{3}JHH = 8.3 Hz, 1H), 7.76 – 7.67 (m, 2H), 7.65 (d, ^{3}JHH = 8.3 Hz, 1H), 7.60 (d, ^{3}JHH = 7.8 Hz, 2H), 7.53 – 7.46 (m, 2H), 7.27 (t, ^{3}JHH = 7.2 Hz, 1H), 4.52 – 4.41 (m, 4H), 4.34 (s, 2H), 1.31 (t, ^{3}JHH = 7.1 Hz, 6H) ppm; ^{13}C NMR could not be taken due to low solubility of the compound 7; FT-IR: υmax 3333 (N-H, benzimidazole), 3185, 3067 (C-H, aromatic), 2954 (C-H, alkyl), 1876, 1629, 1599 (C=C, aromatic), 1472 (C-H, alkyl), 1426, 1330 (Ar-NO_2), 1292, 1235, 1127, 1023, 947 cm^{-1}; MALDI-TOF; calc for $C_{43}H_{32}N_8O_4$ $[M]^+$: 724.781; found $[M]^+$: 724.148.

RESULTS AND DISCUSSION

The most reactive positions of the carbazole core 1 with respect to electrophilic substitution are the C3 and C6 positions. It is noteworthy that the carbazole-3-carbaldehyde is capable of undergoing further functionalization at the C6 position and thus may serve as precursors for novel compounds. Aldehyde functional groups are suitable precursor to benzimidazole through the condensation reaction with benzene-1,2-diamine derivative.

It proved that formaldehyde is reactive under acidic conditions in the presence of carbazole [41-43]. Following the literature method, the suitable carbazole mono-aldehyde building block 2 was prepared from the reaction of N-ethyl carbazole 1 with phosphoryl chloride and dimethyl formamide via the Vismeier-Haack reaction which is well established method for the formylation of various aromatic compounds, since heteroaromatic compounds undergo formylation at the electron rich positions when treated with Vilsmeier-Haack reagents (Figure 2) [44]. In the event that C3 position of the carbazole is blocked by aldehyde functionality, C6 position becomes the only active site for a further reaction through the aromatic system.

Methylene bridged bis-carbazole 3 was previously reported by Sengul et al [43]. In this protocol from the Vilsmeier-Haack reaction of N-ethyl carbazole 1 bis-carbazole 3 was isolated as a by-product in 4% yield. This low yielding formation of the compound is unfortunately not useful for the synthetic modifications. In the same study, an alternative approach for preparation of methylene bridge containing bis-carbazole was likely described in high yield [43]. Therefore following the high yield product production protocol which involves treatment of formyl carbazole 2 with formaldehyde (CHCO) in the presence of catalytic amount of acetic acid at 100 °C, the compound 3 was obtained almost in quantitative yield (Figure 2).

Once the two aldehyde functional group containing methylene bridged bis-carbazole 3 in hand, condensation reaction was attempted to form benzimidazole rings on both C3 and C3' positions of the bis-carbazole. Several protocols have been used for the synthesis of benzimidazoles, and therefore one of the most common protocols for synthesis of benzimidazoles is surely the condensation of benzene-1,2-diamine derivative with carbaldehydes [45-47].

In this study, the synthesis of various benzimidazole derivatives of methylene bridges bis-carbazoles was achieved in high yield with condensation reaction in dimethylsulfoxide. Reaction between compound 3 and 4-substitue benzene-1,2-diamine derivatives (R = H, Cl, Me, NO_2) in DMSO at 120 °C produced the corresponding benzimidazole compounds 4-7 in 85-99% yield (Figure 2).

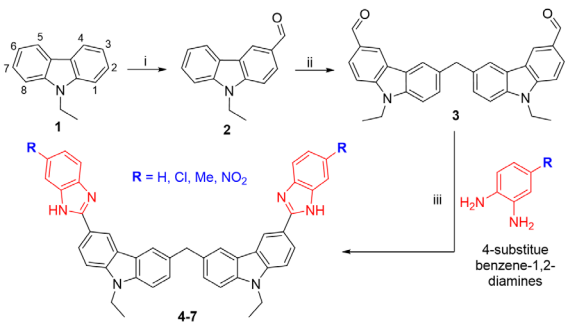

Figure 2. Reagent and conditions: i) DMF, $POCl_3$, reflux; ii) HCOH, CH_3COOH, 100 °C; iii) 4-substitue benzene-1,2-diamine derivative (R = H, Cl, Me, NO_2), DMSO, 120 °C.

The characterization of the new compounds 4-7 was determined using NMR and FTIR spectroscopy along with mass spectrometry. The spectroscopic data of the compound 4 is characteristic for the other remaining derivatives. The successful construction of the new benzimidazole heterocyclic units in the main platform was clearly identified by ^{1}H NMR analysis of the starting material and its corresponding product. The ^{1}H NMR spectrum of starting material 3 has a singlet at δ 10.04 ppm assigned to carbonyl aldehyde (CHO) proton. The examination of the ^{1}H NMR spectrum of target compound 4 indicated that disappearing of carbonyl CHO proton signals and displaying a new broad singlet signal at δ 9.19 ppm belong to NH proton of the newly formed benzimidazole rings as shown in Figure 3. Thus, ^{1}H NMR spectrum indicated that construction of the new heterocyclic unit in the main platform had successfully

occurred. In addition, two protons signal belongs to CH_2 signal at δ 4.32 ppm indicates the methylene bridge in the main structure, four protons quarted signals at δ 4.44 ppm and a six protons triplet signals at δ 1.29 ppm are also show the N-ethyl moiety of the carbazoles. Due to low solubility of the final compounds 4-7, their ^{13}C NMR spectra could not be performed.

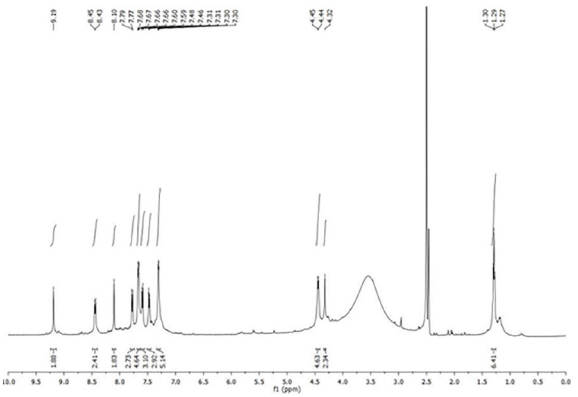

Figure 3. ^{1}H NMR spectrum of compound 4.

Conversion of aldehyde functional group to the corresponding benzimidazole was also confirmed through comparison of the FT-IR analysis of the target product 4 and its starting material 3. In the FT-IR spectrum of the compound 4 a new broad peak observed between 3500-2900 cm^{-1} belongs to benzimidazole N–H stretching (Figure 4). In addition, the disappearing of aldehyde carbonyl (C=O) bond stretching peak at 1672 cm^{-1} was proved the successful condensation reaction was carried out.

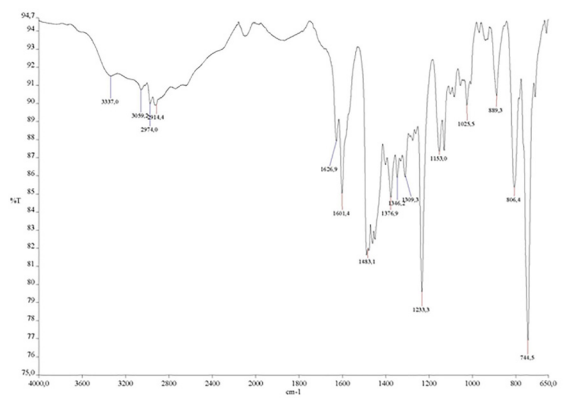

Figure 4. FT-IR spectrum of compound 4.

Final confirmation of the structure of the targeted bis-benzimidazole 4 was provided through MALDI-TOF mass spectrometry. The mass spectrometry of compound 4 showed molecular ions at 633 ([M-H]$^{+}$) (Figure 5).

Thermal Analysis of Bis-benzimidazoles 4-7

The thermal stability of compounds 4-7 were investigated by thermogravimetric analysis (TGA) via progressing the weight loss of a sample upon linearly increasing the temperature (heating rate of 10 °C per minute up to 700 °C) under nitrogen gas flow. Bis-benzimidazoles 4-7 were found stable in air at room temperature and showed high thermal stability. As shown in Figure 6, the thermal stability of 4 was the highest due to 62% of the compound remained intact up to 543 °C. The compound 6 and 5 showed good thermal stability by remaining 49% of 6 and 30% of 5 intact up to 561 °C and 545 °C, respectively (Table 1). While decomposition of compounds 4 and 5 showed one step TGA curve, compound 6 displayed two steps. Between 381°C and 458 °C, bis-benzimidazole 6 lost 12% of its weight. This was followed by further 21% of weight loss at the second step. As compound 6, the nitro substituted bis-imidazole 7 presented different decomposition pattern by showing three steps TGA curves. An initial weight loss of 9% was observed at 173 °C, the second one was detected at 314 °C with a weight loss of 12%, and at the final step at 553 °C with a weight loss of 11% observed and overall 64% of compound 7 remained. Once the temperature reached to 700°C, it can clearly seen that the most stable bis-benzimidazole derivative is compound 7 due to loosing only 36% of weight loss whereas compound 5 is the least stable one by weight loss of almost 70%. It is noteworthy that these compounds represent outstanding thermal stability. In addition it was observed that both of the compounds 4 and 7 lost their weight less than both 5 and 6, because initial mass of both bis-benzimidazoles 4 and 7 retained over 62% and 64%, respectively, even at 700 °C.

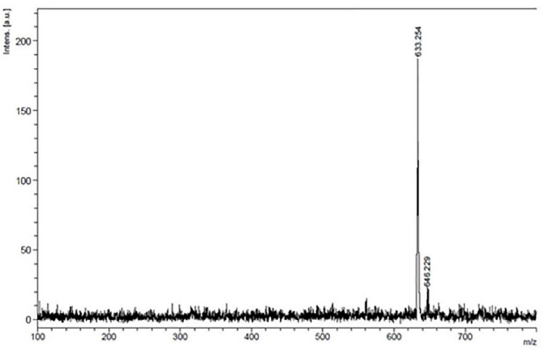

Figure 5. MALDI-TOF spectrum of compound 4.

CONCLUSION

In this study, a range of carbazole linked bis-benzimidazole was prepared and characterized. In addition, the thermogravimetric analysis (TGA) results of the final bis-benzimidazoles 4-7 displayed outstanding thermal stability. These kind of frameworks can be potentially used in variety of areas ranging from organic devices

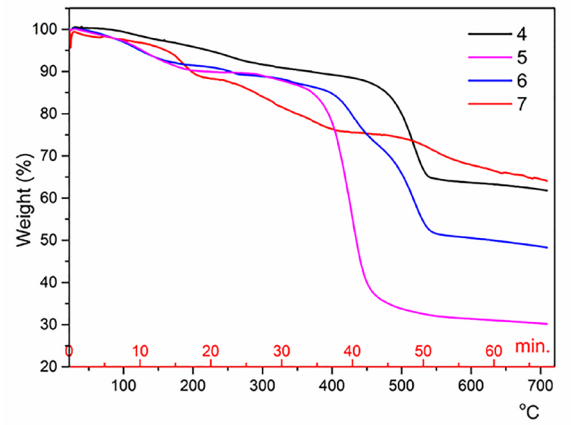

Figure 6. TGA curves of bis-benzimidazoles 4-7.

Table 1. The results of TGA analysis.

Compound	Stages	Range (°C)	Peak (°C)	Weight loss (%)	Residue at 700 °C (%)
4	1st	424 - 543	518	25	62
5	1st	350 – 545	425	57	30
6	1st	381 - 458	429	12	49
	2nd	465 - 561	512	21	
7	1st	58 - 209	173	9	64
	2nd	220 - 410	314	12	
	3rd	440 - 680	553	11	

to biologically active molecules.

CONFLICT OF INTEREST

The author deny any conflict of interest.

References

1. Eftekhari-Sis B, Zirak M, Akbari A. Arylglyoxals in synthesis of heterocyclic compounds. Chemical Reviews 113 (2013) 2958–3043.
2. Ju Y.Varma RS. Aqueous N-heterocyclization of primary amines and hydrazines with dihalides: microwave-assisted syntheses of N-azacycloalkanes, isoindole, pyrazole, pyrazolidine, and phthalazinederivatives. Journal of Organic Chemistry 71 (2006) 135–141.
3. Kerru N, Gummidi L, Maddila S, Gangu KK, Jonnalagadda SB. A review on recent advances in nitrogen-containing molecules and their biological applications. Molecules 25 (2020) 1909-1951.
4. Bingul M, Şenkuytu E, Saglam MF, Boga M, Kandemir H, Sengul IF. Synthesis, photophysical and antioxidant properties of carbazole based bis thiosemicarbazones. Research on Chemical Intermediates 45 (2019) 4487-4499.
5. Saglam MF, Gündogdu A, Hora M, Kandemir H, Sengul IF.Synthesis of Pyrrolo[3,2-c]carbazole-2-carbohydrazide and Pyrrolo[3,2-c]carbazol-2-yl-1,3,4-oxadiazole and Their in vitro Antibacterial Evaluation. Synthetic Communications 51 (2021) 3164-3174.
6. Sengul IF, Bingul M, Kandemir H, Kumar N, Black DStC. Synthesis, Reactivity and Biological Properties of Methoxy-Activated Indoles. in: Attanasi OA, Gabriele B, Merino P, Spinelli D (Eds.). Targets in Heterocyclic Systems. Società Chimica Italiana, Italy, pp. 162-212, 2021.
7. Pathare B, Bansode T. Review- biological active benzimidazole derivatives. Results in Chemistry 3 (2021) 100200.
8. Negi DS, Kumar G, SinghM, Singh N. Antibacterial Activity of Benzimidazole Derivatives: A Mini Review. Research & Reviews: Journal of Chemistry 6 (2017) 18-28.
9. Bashir M, Bano A, Ijaz AS, Chaudhary BA. Recent Developments and Biological Activities of N-Substituted Carbazole Derivatives: A Review. Molecules 20 (2015)13496-13517.
10. Knölker HJ, Reddy KR. Isolation and Synthesis of Biologically Active Carbazole Alkaloids. Chemical Reviews 102 (2002) 4303−4427.
11. Son DS, Lee ES, Adunyah SA. The Antitumor Potentials of Benzimidazole Anthelmintics as Repurposing Drugs. Immune Network 20 (2020) 1–20.
12. Satija G, Sharma B, Madan A, Iqubal A, Shaquiquzzaman M, Akhter M, Parvez S, Khan MA, Alam MM. Benzimidazole based derivatives as anticancer agents: Structure activity relationship analysis for various targets. Journal of Heterocyclic Chemistry 59 (2022) 22−66.
13. Dokla EME, Abutaleb NS, Milik SN, Li D, El-Baz K, Shalaby MAW, Al-Karaki R, Nasr M, Klein CD, Abouzid KAM, Seleem MN. Development of benzimidazole-based derivatives as antimicrobial agents and their synergistic effect with colistin against gram-negative bacteria. European Journal of Medicinal Chemistry 186 (2020) 111850.
14. Porcari AR, Devivar RV, Kucera LS, Drach JC, Townsend LB. Design, Synthesis, and Antiviral Evaluations of 1-(Substituted benzyl)-2-substituted-5,6-dichlorobenzimidazoles as Nonnucleoside Analogues of 2,5,6-Trichloro-1-(β-d-ribofuranosyl)benzimidazole. Journal of Medicinal Chemistry 41 (1998) 1252-1262.
15. Migawa MT, Girardet JL, Walker JA, Koszalka GW, Chamberlain SD, Drach JC, Townsend LB. Design, Synthesis, and Antiviral Activity of α-Nucleosides: d- and l-Isomers of Lyxofuranosyl- and (5-Deoxylyxofuranosyl)benzimidazoles. Journal of Medicinal Chemistry 41 (1998) 1242-1251.
16. Tamm I, Folkers K, Shunk CH, Horsfall FL, Jr MD. Inhibition of Influenza Virus Multiplication by N-Glycosides of Benzimidazoles. Journal of Experimental Medicine 99 (1954) 227-250.
17. Alpan AS, Zencir S, Zupkó I, Coban G, Réthy B, Gunes HS, Topcu Z. Biological activity of bis-benzimidazole derivatives on DNA topoisomerase I and HeLa, MCF7 and A431 cells. Journal of Enzyme Inhibition and Medicinal Chemistry 24 (2009) 844-849.
18. Maji B, Kumar K, Kaulage M, Muniyappa K, Bhattacharya S. Design and Synthesis of New Benzimidazole−Carbazole Conjugates for the Stabilization of Human Telomeric DNA, Telomerase Inhibition, and Their Selective Action on Cancer Cells. Journal of Medicinal Chemistry 57 (2014) 6973-6988.
19. Neidle S, Mann J, Rayner EL, Baron A, Opoku-Boahen Y, Simpson IJ, Smith NJ, Fox KR, Hartleyd JA, Kellande LR. Symmetric bis-benzimidazoles: new sequence-selective DNA-binding molecules. Chemical Communications (1999) 929–930.
20. Chaudhuri P, Ganguly B, Bhattacharya S. An Experimental and Computational Analysis on the Differential Role of the Positional Isomers of Symmetric Bis-2-(pyridyl)-1H-benzimidazoles as DNA Binding Agents. Journal of Organic Chemistry 72 (2007) 1912-1923.
21. Bhattacharya S, Chaudhuri P, Jain AK, Paul A. Symmetrical Bisbenzimidazoles with Benzenediyl Spacer: The Role of the Shape of the Ligand on the Stabilization and Structural Alterations in Telomeric G-Quadruplex DNA and Telomerase Inhibition. Bioconjugate Chemistry 21 (2010) 1148-1159.
22. Soderlind KJ, Gorodetsky B, Singh AK, Bachur NR, Miller GG,

Lown JW. Bis-benzimidazole anticancer agents: targeting human tumour helicases. Anti-Cancer Drug Design 14(1999) 19-36.
23. Huang ST, Hseib IJ, Chen C. Synthesis and anticancer evaluation of bis(benzimidazoles), bis(benzoxazoles), and benzothiazoles. Bioorganic & Medicinal Chemistry 14 (2006) 6106–6119.
24. Hebishy AMS, Abdelfattah MS, Elmorsy A, Elwahy AHM. Synthesis of novel bis- and poly(benzimidazoles) as well as bis- and poly(benzothiazoles) as anticancer agents. Journal of Heterocyclic Chemistry 57 (2020) 2256– 2270.
25. Küçükbay H, Yılmaz Ü, Şireci N, Güvenç AN. Synthesis and antimicrobial activities of some bridged bis-benzimidazole derivatives. Turkish Journal of Chemistry 35 (2011) 561 – 571.
26. Moreira JB, Mann J, Neidle S, McHugh TD, Taylor PW. Antibacterial activity of head-to-head bis-benzimidazoles. International Journal of Antimicrobial Agents 42 (2013) 361-366.
27. Smaili, A. Jebbari, S. Rifai, L.A, Faize L, Koussa T, Sir HA, Makroum K, Belfaiza M, Kihel A, Ahbala M, Venisse JS, Faize M. Synthesis and in planta antibacterial activity of head-to-head bis-benzimidazole and bis-benzoxazole derivatives. Phytoparasitica 47 (2019) 733–741.
28. Rahman, M. M. and Gray A. I. A benzoisofuranone derivative and carbazole alkaloids from Murraya koenigii and their antimicrobial activity. Phytochemistry 66 (2005) 1601-1606.
29. David CI, Prabakaran G, Karuppasamy A, Veetil JC, Kumar RS, Almansour AI, Perumal, Ramalingan KC, Nandhakumar R. A single carbazole based chemosensor for multiple targets: Sensing of Fe^{3+} and arginine by fluorimetry and its applications, Journal of Photochemistry and Photobiology A: Chemistry 425 (2022) 113693.
30. Feng XJ, Tian PZ, Xu Z, Chen SF, Wong MS. Fluorescence-Enhanced Chemosensor for Metal Cation Detection Based on Pyridine and Carbazole. The Journal of Organic Chemistry 78 (2013) 11318-11325.
31. Sathiyan G, Sivakumar EKT, Ganesamoorthy R, Thangamuthu R, P Sakthivel P. Review of carbazole based conjugated molecules for highly efficient organic solar cell application. Tetrahedron Letters 57 (2016) 243-252.
32. Ledwon P. Recent advances of donor-acceptor type carbazole-based molecules for light emitting applications. Organic Electronics 75 (2019) 105422.
33. Xue YJ, Li MY, Jin XJ, Zheng CJ, Piao HR. Design, synthesis and evaluation of carbazole derivatives as potential antimicrobial agents. Journal of Enzyme Inhibition and Medicinal Chemistry 36 (2021) 296-307.
34. Caruso A, Ceramella J, Iacopetta D, Saturnino C, Mauro MV, Bruno R, Aquaro S, Sinicropi MS. Carbazole Derivatives as Antiviral Agents: An Overview. Molecules. 24 (2019) 1912.
35. Liu LX, Wang XQ, Zhou B, Yang LJ, Li Y, Zhang HB, Yang XD. Synthesis and antitumor activity of novel N-substituted carbazole imidazolium salt derivatives. Scientific Reports 5(2015) 13101.
36. Bringmann G. Tasler S. Synthesis of methylene-bridged binary carbazole alkaloids and a related tricarbazole. Tetrahedron 57 (2001) 2337-2343.
37. Börger C, Schmid WA, Knölker H. First total syntheses of chrestifoline-B and (±)-chrestifoline-C, and improved synthetic routes to bismurrayafoline-A, bismurrayafolinol and chrestifoline-D. Journal of Organic and Biomolecular Chemistry 12 (2014) 3831-3835.
38. Horton DA, Bourne GT, Smythe ML. The Combinatorial Synthesis of Bicyclic Privileged Structures or Privileged Substructures. Chemical Reviews 103 (2003) 893-930.
39. Gil C, Brase S. Solid-Phase Synthesis of Biologically Active Benzoannelated Nitrogen Heterocycles: An Update. Journal of Combinatorial Chemistry 11 (2009) 175-97.
40. Armarego WLF, Chai CLL. Purification of Laboratory Chemicals, seventh ed. Elsevier, Oxford, 2013.
41. Sengul IF, Wood K, Bowyer PK, Bhadbhade, Chen R, Kumar N, Black DStC. Synthesis of new di-(3-indolyl)arenes. Tetrahedron 68 (2012) 7429-7434.
42. Kandemir H, Sengul IF, Kumar N, Black, DStC. Synthesis of Imine and Amine-Linked Macrocycles Containing Tris-Indoles. Australian Journal Chemistry 70 (2017) 1196-1201.
43. Kandemir H, Saglam MF, Sengul IF. Synthesis of Methylene Bridged Bis-pyrrolo[3,2-c] Carbazoles via an Unusual Vilsmeier-Haack Product of N-ethylcarbazole. Polycyclic Aromatic Compounds 40 (2020) 516-523.
44. Sengul IF, Astarci E, Kandemir H. Synthesis of novel pyrrolo[3,2-c] carbazole and dipyrrolo[3,2-c:2',3'-g]carbazole derivatives. Synlett 27 (2016) 1277-1281.
45. Wright JB. The Chemistry of the Benzimidazoles. Chemical Reviews 48 (1951) 397-541.
46. Faheem M, Rathaur A, Pandey A, Singh VK, Tiwari AK. A Review on the Modern Synthetic Approach of Benzimidazole Candidate. Chemistry Select 5 (2020) 3981-3994.
47. Alaqeel SI. Synthetic approaches to benzimidazoles from o-phenylenediamine: A literature review. Journal of Saudi Chemical Society 21 (2017) 229-237.