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Catalyst-free synthesis of 1,2-disubstituted benzimidazoles in aqueous media using oxygen as the oxidant

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Synthesis of 1, 2-disubstituted benzimidazoles by reaction of *N*-substituted benzene-1,2-diamine with different aldehydes was developed. This greener procedure proceeds with the help of oxygen in water at 60°C. The advantages of proposed method are catalyst-free conditions in water, short reaction time and excellent yields.

1. Introduction

Benzimidazoles are the very important unit in the heterocycles due to their biological as well as pharmaceutical importance. The interest of researchers towards benzimidazole containing heterocycles was increased because 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole is a basic part of vitamin B_{12}.[1] The scaffold like benzimidazole is observed in a number of compounds of pharmaceutical interest.[2] Benzimidazoles exhibit a lot of biological activities like anti-cancer,[3] anti-fungal,[4] anti-bacterial,[5] anti-leishimanial,[6] antiviral,[7,8] anti-inflammatory and antiulcer agents[9] activities. Benzimidazoles are also used as organic ligands,[10] fluorescent whitening agent dyes,[11] and functional materials.[12] Classical methods of benzimidazoles synthesis include the condensation of 1,2-phenylenediamines with either aldehydes[13-16] or carboxylic acids under relatively harsh conditions.[17,18]

Benzimidazoles are formed in one step by coupling of phenylenediamines and carboxylic acids,[19] or their derivatives (nitriles, imidates, or orthoesters),[20] which require acidic conditions, high temperatures or the use of microwave irradiation.[21] Similarly benzimidazoles are formed in two steps i.e. by oxidative cyclodehydrogenation of aniline Schiff's bases. This method requires different oxidative reagents such as nitrobenzene,[22] 1,4-benzoquinone,[23] 2,3-dichloro-5, 6-dicyanobenzoquinone

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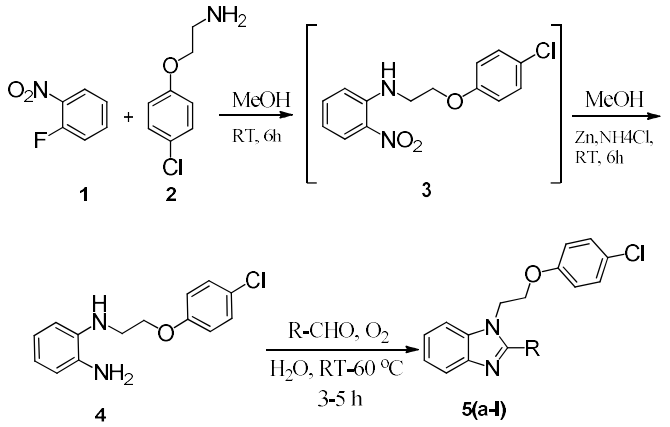
(DDQ),[24] benzofuroxan,[25] MnO_2,[26] $Pb(OAc)_4$,[27] oxone,[28] $NaHSO_3$,[29] $Na_2S_2O_5$,[30] and oxygen.[31] These procedures require work-up and purifications to avoid by-products formation. Therefore, it is important to introduce mild, efficient and catalyst-free environment friendly methods for the synthesis of benzimidazoles. As per literature, imines were formed by the reaction of primary amines with carbonyl compounds in aqueous media.[32] And the same way, benzimidazoles were formed using oxygen as an oxidant,[31,33] and in aqueous media. By using these two conditions, we conclude that oxygen plays an important role in the synthesis of benzimidazoles in water. Here, we are report the preparation of substituted benzimidazoles from *N*-substituted benzene-1,2-diamine and different aldehydes using oxygen as oxidant in water.

2. Results and Discussion

We started our study by designing N^1-(2-(4-chlorophenoxy)ethyl)benzene-1,2-diamine (**4**) as the starting material to generate desired benzimidazole products (**5**). As we have 1-fluoro-2-nitrobenzene (**1**) and 2-(4-chlorophenoxy) ethanamine (**2**) available, synthesis of the starting material was easily performed and then on reduction. We can use any substituted amine for the synthesis instead of 2-(4-chlorophenoxy) ethanamine. The reaction between *N*-substituted-benzene-1,2-diamine and an aldehyde during 3-5 hours in the presence of oxygen in water is fast, clean and high-yielded. The important advantages of this protocol are; (a) no catalyst required; (b) gives excellent yields of products; (c) the method is efficient and environment-friendly.

The comparison of this method with previous ones shows that the products formed in 3-5 hours in the presence of oxygen in water at 60 °C. This method is advantageous because the products formed in good to excellent yield (70 - 96%) without using any catalyst.

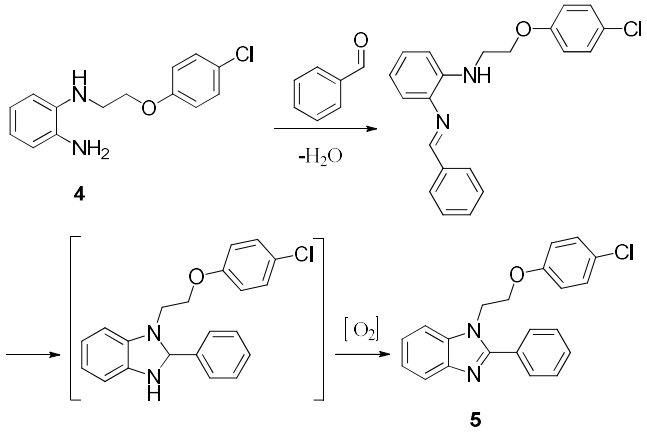


Scheme 1. Synthesis of benzimidazoles in the presence of oxygen in water

The reaction of **(1)** with **(2)** in methanol to produce **(3)** takes six hours. After the confirmation of product formation, zinc and ammonium chloride were added to the same reaction mixture and stirring continued for another six hours at room temperature.[34] Compound **(4)** was reacting with different aldehydes in water in the presence of oxygen to formed respective benzimidazoles. Firstly, N^1-(2-(4-chlorophenoxy)ethyl)benzene-1,2-diamine (**4**) (1 mmol) and benzaldehyde (1 mmol) were taken with water at room temperature and stirred for 10 h to get 10% of the product. The progress of the reaction was monitored by thin layer chromatography. Same reaction was carried out at 60 °C for 5 h to get 50% of desired benzimidazole. However, when the reaction was tried in the presence of oxygen, the reaction precedes fast affording 96% of respective benzimidazole in 3 hours. After optimizing the conditions, the reactions were performed with different aldehydes. The reactions were observed to proceed clean with all the aldehydes **(Table 1).**

Table 1. Synthesis of different benzimidazole derivatives

Entry	Aldehydes	Time, h	Product	Yield, %
1	C_6H_5CHO	3	5a	96
2	4-$OCH_3C_6H_4CHO$	3	5b	94
3	4-OHC_6H_4CHO	5	5c	90
4	4-Cl-2-$NO_2C_6H_3CHO$	3	5d	91
5	4-BrC_6H_4CHO	3	5e	95
6	3,5-$(CF_3)C_6H_3CHO$	4.5	5f	90
7	4-$COOCH_3C_6H_4CHO$	4	5g	92
8	3-F-4-OH-5-$OCH_3C_6H_2CHO$	4	5h	85
9	3,5-Cl-4-CNC_6H_2CHO	3.5	5i	91
10	5,6-ClC_6H_2N-3- CHO	5	5j	88
11	3-BrC_6H_3N-4- CHO	5	5k	89
12	(E)-$C_2H_5OCOCHCHCHO$	4	5l	70



Scheme 2. Proposed mechanism of the reaction of the one-pot synthesis of benzimidazoles.

3. Conclusions

In conclusion, a one pot synthesis of benzimidazoles from *N*^{1}-(2-(4-chlorophenoxy)ethyl)benzene-1,2-diamine and aldehydes in water by using oxygen was successfully developed. This protocol employs the green and readily available oxygen as the oxidant for efficient aromatisation. The whole reaction could be processed in one pot, which greatly simplified operations.

Acknowledgements

We gratefully acknowledge the support of this work by the friends of our department for the help in analysis of the correlation NMR spectra.

4. Experimental

4.1. Materials and Methods

All chemicals were purchased from Aldrich and Merck companies. Thin layer chromatography was carried out on silica gel 60 F254 pre-coated plates and visualized with UV light. ^{1}H NMR spectra were recorded on Bruker 400-MHz Ultrashield Advance II 400 instrument using TMS as internal standard. LCMS data was obtained to confirmed molar mass and purity of products.

4.2. General procedure for the synthesis of 1,2-disubstituted benzimidazoles

The aldehydes (1 mmol) were added to the suspension of N^1-(2-(4-chlorophenoxy)ethyl)benzene-1,2-diamine (4) (1 mmol) in water (10 mL) and the mixture was stirred at room temperature for 1 hour to get imine having different type of suspension. Then, the reaction mixture was heated to 60^0C for 3-5 hours in the presence of oxygen. As soon as the reaction proceeds, the reaction mixture became clear. The progress of reaction was monitored by TLC in ethyl acetate. After completion of the reaction, the reaction mixture was cooled to room temperature to obtained solids. Solid product was filtered and washed by ice water. The crude solid product was further washed with ice cooled diethyl ether to remove traces of water to afford the pure product 5a-l. The structures of desired products were analyzed using ^{1}H NMR and LCMS spectra.

4.3 Physical and Spectral Data

1-(2-(4-chlorophenoxy)ethyl)-2-phenyl-1H-imidazole (5a):

Light brown solid, M.P.-1880C, Rf:0.6; 1H NMR (400 MHz, DMSO-d6): δ (ppm) 7.82-7.83 (m, 2H, ArH), 7.76 (d, J=8.0 Hz, 1H, ArH), 7.68 (d, J=7.6 Hz, 1H, ArH), 7.56-7.57 (m, 3H, ArH), 7.25-7.32 (m, 2H, ArH), 7.23 (d, J=8.8 Hz, 2H, ArH), 6.75 (d, J=8.8 Hz, 2H, ArH), 4.68 (t, J=4.8 Hz, 2H, CH), 4.28 (t, J=4.8 Hz, 2H, CH); LCMS (ESI) m/z=349.00 [M+H]+; Anal. Calcd. for C21H17ClN2O: C, 72.31; H, 4.91; Cl, 10.16; N, 8.03; O, 4.59; Found: C, 72.25; H, 4.91; Cl, 10.14; N, 8.08; O, 4.62.

1-(2-(4-chlorophenoxy)ethyl)-2-(4-methoxyphenyl)-1H-benzo[d]imidazole (5b):

Off white solid, M.P.-1920C, Rf:0.7; 1H NMR (400 MHz, DMSO-d6): δ (ppm) 7.76 (d, J=8.8 Hz, 2H, ArH), 7.72 (d, J=7.2 Hz, 1H, ArH), 7.64 (d, J=7.2 Hz, 1H, ArH), 7.22-7.27 (m, 4H, ArH), 7.10 (d, J=8.8 Hz, 2H, ArH), 6.78 (d, J=8.8 Hz, 2H, ArH), 4.66 (t, J=5.2 Hz, 2H, CH), 4.30 (t, J=4.8 Hz, 2H, CH), 3.85 (s, 3H, CH); LCMS (ESI) m/z=379.02 [M+H]+; Anal. Calcd. for C22H19ClN2O2: C, 69.75; H, 5.05; Cl, 9.36; N, 7.39; O, 8.43; Found: C, 69.62; H, 5.00; Cl, 9.40; N, 7.49; O, 8.49.

1-(2-(4-chlorophenoxy)ethyl)-2-(4-hydroxyphenyl)-1H-benzo[d]imidazole (5c):

White solid, M.P.-1980C, Rf:0.4; 1H NMR (400 MHz, DMSO-d6): δ (ppm) 9.93 (s, 1H, OH), 7.71 (d, J=7.6 Hz, 1H, ArH), 7.61-7.66 (m, 3H, ArH), 7.21-7.25 (m, 4H, ArH), 6.93 (d, J=8.8 Hz, 2H, ArH), 6.79 (d, J=8.8 Hz, 2H, ArH), 4.64 (t, J=5.2 Hz, 2H, N), 4.29 (t, J=4.8 Hz, 2H, CH); LCMS (ESI) m/z=363.10 [M-H]+; Anal. Calcd. for C21H17ClN2O2: C, 69.14; H, 4.70; Cl, 9.72; N, 7.68; O, 8.77; Found: C, 68.85; H, 4.69; Cl, 9.84; N, 7.78; O, 8.84.

1-(2-(4-chlorophenoxy)ethyl)-2-(4-chloro-2-nitrophenyl)-1H-benzo[d]imidazole (5d):

Light brown solid, M.P.-1820C, Rf:0.8; 1H NMR (400 MHz, DMSO-d6): δ (ppm) 8.37 (s, 1H, ArH), 8.03 (d, J=8.0 Hz, 1H, ArH), 7.96 (d, J=8.0 Hz, 1H, ArH), 7.81 (d, J=8.0 Hz, 1H, ArH), 7.65 (d, J=7.6 Hz, 1H, ArH), 7.34-7.37 (m, 1H, ArH), 7.27-7.29 (m, 1H, ArH), 7.24 (d, J=8.8 Hz, 2H, ArH), 6.78 (d, J=8.8 Hz, 2H, ArH), 4.54-4.55 (m, 2H, CH), 4.24-4.25 (m, 2H, CH); LCMS (ESI) m/z=428.05 [M+H]+; Anal. Calcd. for C21H15Cl2N3O3: C, 58.89; H, 3.53; Cl, 16.56; N, 9.81; O, 11.21; Found: C, 59.09; H, 3.58; Cl, 16.47; N, 9.71; O, 11.15.

1-(2-(4-chlorophenoxy)ethyl)-2-(4-bromophenyl)-1H-benzo[d]imidazole (5e):

White solid, M.P.-1910C, Rf:0.7; 1H NMR (400 MHz, DMSO-d6): δ (ppm) 7.76-7.79 (m, 5H, ArH), 7.68 (d, J=8.0 Hz, 1H, ArH), 7.26-7.33 (m, 2H, ArH), 7.22 (d, J=9.2 Hz, 2H, ArH), 6.74 (d, J=9.2 Hz, 2H, ArH), 4.67-4.68 (m, 2H, CH), 4.27-4.29 (m, 2H, CH); LCMS (ESI) m/z=428.05 [M+H]+; Anal.

Calcd. for C21H16BrClN2O: C, 58.97; H, 3.77; Br, 18.68; Cl, 8.29; N, 6.55; O, 3.74; Found: C, 59.10; H, 3.79; Br, 18.60; Cl, 8.30; N, 6.50; O, 3.71.

1-(2-(4-chlorophenoxy)ethyl)-2-(3,5-bis(trifluoromethyl)phenyl)-1H-benzo[d]imidazole (5f).
White solid, M.P.-1900C, Rf:0.7; 1H NMR (400 MHz, DMSO-d6): δ (ppm) 8.53 (s, 2H, ArH), 8.28 (s, 1H, ArH), 7.84 (d, J=8.0 Hz, 1H, ArH), 7.75 (d, J=8.0 Hz, 1H, ArH), 7.30-7.39 (m, 2H, ArH), 7.19 (d, J=8.8 Hz, 2H, ArH), 6.69 (d, J=8.8 Hz, 2H, ArH), 4.75 (s, 2H, CH), 4.36 (s, 2H, CH); LCMS (ESI) m/z=485.40 [M+H]+; Anal. Calcd. for C23H15ClF6N2O: C, 56.98; H, 3.12; Cl, 7.31; F, 23.51; N, 5.78; O, 3.30; Found: C, 56.90; H, 3.00; Cl, 7.30; F, 23.57; N, 5.88; O, 3.35.

Methyl-4-(1-(2-(4-chlorophenoxy)ethyl)-1H-benzo[d]imidazole-2-yl)benzoate (5g):
White solid, M.P.-1930C, Rf:0.8; 1H NMR (400 MHz, DMSO-d6): δ (ppm) 8.11 (d, J=7.6 Hz, 2H, ArH), 7.98 (d, J=8.0 Hz, 2H, ArH), 7.79 (d, J=8.0 Hz, 1H, ArH), 7.70 (d, J=7.6 Hz, 1H, ArH), 7.26-7.35 (m, 2H, ArH), 7.20 (d, J=8.4 Hz, 2H, ArH), 6.72 (d, J=8.4 Hz, 2H, ArH), 4.73 (s, 2H, CH), 4.28 (s, 2H, CH), 3.91 (s, 3H, CH); LCMS (ESI) m/z=407.04 [M+H]+; Anal. Calcd. for C23H19ClN2O3: C, C, 67.90; H, 4.71; Cl, 8.71; N, 6.89; O, 11.80; Found: C, 67.80; H, 4.61; Cl, 8.79; N, 6.95; O, 11.85.

4-(1-(2-(4-Chlorophenoxy)ethyl)-1H-benzo[d]imidazol-2-yl)-2-fluoro-6-methoxyphenol (5h):
Off white solid, M.P.-2010C, Rf:0.5; 1H NMR (400 MHz, DMSO-d6): δ (ppm) 9.75 (s, 1H, OH), 7.73 (d, J=7.6 Hz, 1H, ArH), 7.65 (d, J=8.0 Hz, 1H, ArH), 7.28-7.32 (m, 4H, ArH), 7.24 (d, J=7.6 Hz, 2H, ArH), 6.79 (d, J=8.8 Hz, 2H, ArH), 4.69-4.70 (m, 2H, CH), 4.33 (t, J=4.4 Hz, 2H, CH), 3.87 (s, 3H, CH)); LCMS (ESI) m/z=413.10 [M+H]+; Anal. Calcd. for C22H18ClFN2O3: C, 64.00; H, 4.39; Cl, 8.59; F, 4.60; N, 6.79; O, 11.63; Found: C, 64.21; H, 4.40; Cl, 8.63; F, 4.48; N, 6.69; O, 11.59.

2,6-Dichloro-4-(1-(2-(4-Chlorophenoxy)ethyl)-1H-benzo[d]imidazol-2-yl)benzonitrile (5i):
Light yellow solid, M.P.-1990C, Rf:0.5; 1H NMR (400 MHz, DMSO-d6): δ (ppm) 8.16 (s, 2H, ArH), 7.84 (d, J=8.0 Hz, 1H, ArH), 7.74 (d, J=7.6 Hz, 1H, ArH), 7.3.-7.40 (m, 2H, ArH), 7.21 (d, J=8.8 Hz, 2H, ArH), 6.72 (d, J=8.8 Hz, 2H, ArH), 4.77 (t, J=4.8 Hz, 2H, CH), 4.32 (t, J=4.4 Hz, 2H, CH); LCMS (ESI) m/z=442.17 [M+H]+; Anal. Calcd. for C22H14Cl3N3O: C, 59.68; H, 3.19; Cl, 24.02; N, 9.49; O, 3.61; Found: C, 59.71; H, 3.22; Cl, 24.12; N, 9.39; O, 3.56.

1-(2-(4-Chlorophenoxy)ethyl)-2-(5,6-dichloropyridin-3-yl)-1H-benzo[d]imidazole (5j):
White solid, M.P.-2020C, Rf:0.3; 1H NMR (400 MHz, DMSO-d6): δ (ppm) 8.82 (s, 1H, ArH), 8.59 (s, 1H, ArH), 7.82 (d, J=8.0 Hz, 1H, ArH), 7.73 (d, J=8.0 Hz, 1H, ArH), 7.29.-7.39 (m, 2H, ArH), 7.22 (d, J=8.4 Hz, 2H, ArH), 6.72 (d, J=8.8 Hz, 2H, ArH), 4.75 (s, 2H, CH), 4.31 (s, 2H, CH); LCMS (ESI) m/z=418.02 [M+H]+; Anal. Calcd. for C20H14Cl3N3O: C, 57.37; H, 3.37; Cl, 25.40; N, 10.04; O, 3.82; Found: C, 57.47; H, 3.40; Cl, 25.42; N, 10.10; O, 3.61.

2-(2-Bromopyridin-4-yl)-1-(2-(4-Chlorophenoxy)ethyl)-1H-benzo[d]imidazole (5k):
White solid, M.P.-1980C, Rf:0.3; 1H NMR (400 MHz, DMSO-d6): δ (ppm) 8.57 (d, J=4.8 Hz, 1H, ArH), 8.12 (s, 1H, ArH), 7.92 (d, J=4.4 Hz, 1H, ArH), 7.83 (d, J=7.6 Hz, 1H, ArH), 7.74 (d, J=8.0 Hz, 1H, ArH), 7.29-7.39 (m, 2H, ArH), 7.23 (d, J=8.8 Hz, 2H, ArH), 6.73 (d, J=8.4 Hz, 2H, ArH), 4.78 (s, 2H, CH), 4.31 (s, 2H, CH); LCMS (ESI) m/z=427.95 [M+H]+; Anal. Calcd. for C20H15BrClN3O: C, 56.03; H, 3.53; Br, 18.64; Cl, 8.27; N, 9.80; O, 3.73; Found: C, 55.90; H, 3.50; Br, 18.60; Cl, 8.37; N, 9.86; O, 3.77.

(E)-ethyl-3-(1-(2-(4-Chlorophenoxy)ethyl)-1H-benzo[d]imidazol-2-yl)acrylate (5l):
Brown solid, M.P.-1750C, Rf:0.8; 1H NMR (400 MHz, DMSO-d6): δ (ppm) 7.90 (d, J=15.2 Hz, 1H, ArH), 7.7 (dd, J=7.6 Hz, J=8.0 Hz, 2H, ArH), 7.30-7.34 (m, 2H, ArH), 7.26 (d, J=8.4 Hz, 2H, ArH), 6.96 (d, J=15.6 Hz, 1H, ArH), 6.80 (d, J=8.8 Hz, 2H, CH), 4.85 (s, 2H, CH), 4.22-4.27 (m, 4H, CH), 1.28 (t, J=7.2 Hz, 3H, CH); LCMS (ESI) m/z=371.11 [M+H]+; Anal. Calcd. for C20H19ClN2O3: C,

64.78; H, 5.16; Cl, 9.56; N, 7.55; O, 12.94; N, 9.80; O, 3.73; Found: C, 64.60; H, 5.14; Cl, 9.66; N, 7.61; O, 12.99.

References

1. Spasov A. A., Yozhitsa I. N. (**1999**) Benzimidazole derivatives: Spectrum of pharmacological activity and toxicological properties. *J. Pharma. Chem*., 33 (6) 232-243.
2. Horton D. A., Bourne G. T., Smythe M. L. (**2003**) The Combinatorial Synthesis of Bicyclic Privileged Structures or Privileged Substructures. *Chem. Rev.,* 103 (3) 893-930.
3. Alkahtani H. M., Abbas A. Y., Wang S. D. (**2012**) Synthesis and biological evaluation of benzo[d]imidazole derivatives as potential anti-cancer agents. *Biorg. Med. Chem. Lett.,* 22 (3) 1317-1321.
4. Fang B., Zhou, C. H., Rao X. C. (**2010**) Synthesis and biological activities of novel amine-derived bis-azoles as potential antibacterial and antifungal agents. *Eur. J. Med. Chem*., 45 (10) 4388-4389.
5. Braun S., Botzki A., Salmen S., Textor C., Bernhardt G., Dove S., Buschauer A. (**2011**) Design of benzimidazole- and benzoxazole-2-thione derivatives as inhibitors of bacterial hyaluronanlyase. *Eur. J. Med. Chem*., 46 (9) 4419-4429.
6. Tipparaju S. K., Joyasawal S., Pieroni M., Kaiser M., Brun R., Kozikowski A. P. (**2008**) In Pursuit of Natural Product Leads: Synthesis and Biological Evaluation of 2-[3-hydroxy-2-[(3-hydroxypyridine-2-carbonyl)amino]phenyl]benzoxazole-4-carboxylic acid (A-33853) and Its Analogues: Discovery of N-(2-Benzoxazol-2-ylphenyl)benzamides as Novel Antileishmanial Chemotypes. *J. Med. Chem*., 51 (23) 7344-7347.
7. Moore T. W., Sana K., Yan D., Krumm S. A., Thepchatri P., Snyder J. P., Marengo J., Arrendale R. F., Prussia A. J., Natchus M. G., Liotta D. C., Plemper R. K., Sun A. (**2013**) Synthesis and Metabolic Studies of Host-Directed Inhibitors for Antiviral Therapy. *ACS Med. Chem. Lett*., 4 (8) 762-767.
8. Rida S. M., Ashour F. A., El-Hawash S. A. M., Elsemary M. M., Badr M. H., Shalaby M. A. (**2005**) Synthesis of some novel benzoxazole derivatives as anticancer, anti-HIV-1 and antimicrobial agentsSynthesis, Antiinflammatory and Antibacterial Activities of Substituted Phenyl Benzimidazoles. *Eur. J. Med. Chem*., 40 (9) 949-959.
9. Leonard J T., Rajesh O. S., Jeyaseeli L., Murugesh K., Sivakumar R., Gunasekaran V. (**2007**) Synthesis, Antiinflammatory and Antibacterial Activities of Substituted Phenyl Benzimidazoles. *Asian J. Chem.,* 19 (1) 116-120.
10 Pal S., Hwang W. –S., Lin I. J. B., Lee C. –S. (**2007**) Benzene benzimidazole containing Pd(II) metallacycle: Synthesis, X-ray crystallographic characterization and its use as an efficient Suzuki coupling catalyst. *J. Mol. Catal. A.: Chem*., 269 (1-2) 197-203.
11 Rajadhyaksha D. D., Rangnekar D. W. (**1986**) Synthesis of pyrazolo[4′,3′:5,6]pyrido[1,2-a]benzimidazole derivatives and study of their fluorescence properties. *J. Chem. Technol. Biotechnol*., 36 (7) 300-304.
12 Asensio J. A., Gomez-Romero P. (**2005**) Recent Developments on Proton Conduc-ting Poly(2,5-benzimidazole) (ABPBI) Membranes for High Temperature Poly-mer Electrolyte Membrane Fuel Cell. *Fuel Cells*, 5 (3) 336-343.
13 Das B., Holla H., Srinivas Y. (**2007**) Efficient (bromodimethyl)sulfonium bromide mediated synthesis of benzimidazoles. *Tetrahedron Lett*., 48 (6) 61-64.
14 Chang J. B., Zhao K., Pan S. (**2002**) Synthesis of 2-arylbenzoxazoles via DDQ promoted oxidative cyclization of phenolic Schiff bases—a solution-phase strategy for library synthesis. *Tetrahedron Lett*., 43 (6) 951-954.
15 Liu M. R., Li H. L. (**2012**) TEMPO-mediated oxidation of unbleached bagasse pulp. *Advanced Materials Research*, 496, 71-74.
16 Chen Y. X., Qian L. F., Zhang W., Han B. (**2008**) Efficient Aerobic Oxidative Synthesis of 2-Substituted Benzoxazoles, Benzothiazoles, and Benzimidazoles Catalyzed by 4-Methoxy-TEMPO. *Angew. Chem. Int. Ed*., 47 (48) 9330-9333.

17 Hein D. W., Alheim R. J., Leavitt J. J. (**1957**) The Use of Polyphosphoric Acid in the Synthesis of 2-Aryl- and 2-Alkyl-substituted Benzimidazoles, Benzoxazoles and Benzothiazoles. *J. Am. Chem. Soc*., 79 (2) 427-429.

18 Terashima M., Ishii M., Kanaoka Y. (**1982**) A facile synthesis of 2-substituted benzoxazoles. *Synthesis,* 484-485.

19 Wright J. B. (**1951**) The chemistry of the benzimidazoles. *Chem. Rev.,* 48 (3) 397–541.

20 (a) Tidwell R. R., Geratz J. D., Dann O., Volz G., Zeh D., Loewe H. (**1978**) Diarylamidine derivatives with one or both of the aryl moieties consisting of an indole or indole-like ring. Inhibitors of arginine-specific esteroproteases. *J. Med. Chem*., 21 (7) 613–623; (b) Fairley T. A., Tidwell R. R., Donkor I., Naiman, N. A., Ohemeng K. A., Lombardy R. J., Bentley J. A., Cory B. M. (**1993**) Structure, DNA minor groove binding, and base pair specificity of alkyl- and aryl-linked bis(amidinobenzimidazoles) and bis(amidinoindoles). *Med. Chem*., 36 (12) 1746–1753.

21 Bourgrin K., Loupy A., Soufiaoui M. (**1998**) Troisnouvellesvoies de synthèse des dérivés 1,3-azoliques sous micro-ondes. *Tetrahedron*, 54 (28) 8055–8064.

22 Harapanhalli R. S., McLaughlin L. W., Howell R. W., Rao D. V., Adelstein S. J., Kassis A. I. (**1996**) [^{125}I/^{127}I]IodoHoechst 33342: Synthesis, DNA Binding, and Biodistribution. *J. Med. Chem*., 39 (24) 4804–4809.

23 Verner E., Katz B. A., Spencer, J. R. Allen D., Hataye J., Hruzewicz, W., Hui, H. C., Kolesnikov A., Li Y., Luong C., Martelli A., Radika K., Rai R., She M., Shrader W., Sprengeler P. A., Trapp S., Wang J., Young W. B., Mackman R. L. (**2001**) Development of serine protease inhibitors displaying a multicentered short (<2.3 Å) hydrogen bond binding mode: inhibitors of urokinase-type plasminogen activator and factor Xa. *J. Med. Chem*., 44 (17) 2753–2771.

24 Vanden Eynde J. J., Delfosse F., Lor P., Van Haverbeke Y. (**1995**) .2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, a mild catalyst for the formation of carbon-nitrogen bonds. *Tetrahedron*, 51 (20) 5813–5818.

25 Patzold F., Zeuner F., Heyer Th., Niclas H.-J. (**1992**) Dehydrogenations using benzofuroxan as oxidant. *Synth. Commun.*, 22 281–284.

26 Bhatnagar I., George M. V. (1968) Oxidation with metal oxides—II : Oxidation of chalconephenylhydrazones, pyrazolines, *o*-aminobenzylidineanils and *o*-hydroxybenzylidineanils with manganese dioxide. *Tetrahedron*, 24 1293–1298.

27 Stephens F. F., Bower J. D. (**1949**) The preparation of benziminazoles and benzoxazoles from Schiff's bases. PartI. *J. Chem. Soc.*, 2971–2972.

28 Beaulieu P. L., Hache B., von Moos E. A. (**2003**) A practical oxone®-mediated, high-throughput, solution-phase synthesis of benzimidazoles from 1,2-phenylenediamines and aldehydes and its application to preparative scale synthesis. *Synthesis*, 11 1683–1692.

29 Austen S. C., Kane J. M. (**2001**) A short synthesis of the parp inhibitor 2-(4-trifluoro-methylphenyl)benzimidazole-4-carboxamide (NU1077). *J. Heterocycl. Chem.*, 38 (4) 979–980.

30 Lombardy R. L., Tanious F. A., Ramachandran K., Tidwell R. R., Wilson W. D. (**1996**) Synthesis and DNA Interactions of BenzimidazoleDications Which Have Activity against Opportunistic Infections. *J. Med. Chem*., 39 (7) 1452–1462.

31 Lin S., Yang L. H. (**2005**) A simple and efficient procedure for the synthesis of benzimidazoles using air as the oxidant. *Tetrahedron Lett*., 46 (25) 4315–4319.

32 Saggiomo V., Lüning U. (2009) On the formation of imines in water—a comparison. *Tetrahedron Lett*., 50 (32) 4663-4665.

33 Sharghi H., Asemani O., Khalifeh R. (**2008**) New one-pot procedure for the synthesis of 2-substituted benzimidazoles. *Synth. Commun.*, 38 (7) 1128-1136.

34 Thakare M. P., Shaikh R., Thakare A. (**2016**) Synthesis, characterization and evaluation of antimicrobial activity of novel chiral benzimidazoles. *Chemistry & Biology Interface*, 6 (5) 327-332.