SYNTHESIS OF ANTIBACTERIAL ACTIVE SUBSTANCES 1-METHYL-2-PHENYL/O-TOLYL-6-SUBSTITUTEDPHENYL 1H-BENZO[d]-IMIDAZOLE DERIVATIVES

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ABSTRACT

A novel series of 1-methyl-2,6-diphenylbenzoimidazole and 1-methyl-phenyl(o-tolyl)benzo[d]imidazole derivatives were synthesized from 4-bromobenzene-1,2-diamine and benzoic acid using palladium (II) acetate. The synthesized compounds were evaluated for their anti-bacterial activity against Gram-positive *S. aureus* and Gram-negative *E. coli* bacteria by using broth-dilution method.

Keywords: Synthesis, Characterization, Suzuki coupling, Biology, Antibacterial Activity.

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INTRODUCTION

The formation of new carbon-carbon bond is of central importance in organic chemistry and is pre-requisite for all life on earth.¹ Heterocyclic nucleus, such as the pyrrole, indole, imidazole, pyrimidine, pyridine, quinazoline, quinoline carbazole, are most ubiquitous structural motifs which have consistently proven to be the valuable privileged scaffolds for drug discovery and developmental efforts in pharmaceutical industries.^{2,3} The palladium catalyzed Carbon-Carbon bond forming reactions which the aryl boronic acids (or esters) undergo through Suzuki-Miyaura coupling (1979) with triflates, alkenyl and aryl halides have emerged as the reaction of a widespread application in organic synthesis. Its attraction lies in the fact that in this process the competitive homo coupling of the aryl halide is usually minimal. Over the years the Suzuki cross coupling reaction has established into a very powerful and simple method for the formation of carbon-carbon bonds.^{4,5} In last few decades, the imidazole moiety has attracted the researchers and scientist around the globe, due to its high potential biological and chemical properties.^{6,7} Imidazoles are interesting group of heterocyclic compound having diverse biological activities such as antimicrobial,^{8,9} antibacterial,^{10,11} anticancer,¹²⁻¹⁵ analgesic and anti-inflammatory,¹⁶⁻¹⁷ antiviral,¹⁸ anti-HIV,¹⁹ anticonvulsant,²⁰ antiulcer,²¹ anti antifungal activity²² etc. A new research has revealed that several natural products,^{23,24} contains this imidazolium nucleus in their structures in the form the of essential amino-acid histidine or in alkaloids exhibiting anti-cancer (dacarbazine), anti-parasitic (metronidazole) anti-tumoral, antihypertensive (losartan), anti-bacterial and antihistaminic (cimetidine), activities.²⁵⁻²⁷

EXPERIMENTAL

Material and Methods

Melting points of synthesized materials were estimated using manual POLMON electro thermal apparatus (Range 0–300°C) and glass capillary tubes. IR spectra were captured using Perkin- Elmer FT IR. Bruker-400 MHz spectrometer was employed to record ¹H and ¹³C NMR spectra. NMR results were correlated with TMS as internal reference. Moreover, reactions performed in the experiment were monitored by thin layer chromatography. Pre-coated silica gel plates, UV lamp, iodine vapors or KMnO₄ spray as developing agents are ingredient parts of thin layer chromatography. Synthesized products were purified by column chromatography (obtained from Merck) with a suitable eluting system with various polarity mobile phase ratio's, e.g. hexane:ethylacetate, hexane:chloroform, DCM: methanol.

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Scheme-1: Synthesis of 1-methyl-diphenyl-benzoimidazole derivatives from 4-bromobenzene-1,2-diamine and benzoic Acid

Scheme-2: Synthesis of 1-methyl-6-phenyl-(*o*-tolyl)-benzo[d]imidazole

General Procedure for 6-bromo-phenyl-benzo-imidazole (3 and 8)

In a 250 ml round RBF a mixture of 4-bromobenzene-1,2-diamine (1.0 mmol), benzoic acid or 2-methylbenzoic acid (1.1 mmol), and polyphosphoric acid (PPA) was taken at RT. The temperature was raised slowly to 180 °C and the reaction mass was stirred for 4-5 hours, after completion of reaction, the reaction mass was cooled to room temperature then quenched with 5 volumes of water and pH was adjusted with sodium carbonate. The resulting off-white solid material was filtered and dried to afford compound **3** and **8** in good yields (70-90%).

General procedure for 6-bromo-methyl-phenyl-benzo[d]imidazole (4 and 9)

Compound **3** or **8** (1.0 mol) was added in to a mixture of DMS (1.0 mol), potassium carbonate (3.0 mol) in acetone (8 volumes) and heated to reflux for 8 hours. The reaction mass was cooled to room temperature once reaction was completed, and the potassium carbonate filtered off. The mother liquor was distilled to remove acetone and the resulting residue was extracted with isopropyl alcohol to afford compound **4** or **9** in fair yields (60-70%).

General Procedure for 1-methyl-2-phenyl-6-substituted phenyl 1H-benzo[d]imidazole derivatives 6 and 10 (Ha-Ho)

In 500 ml round bottom flask compound **4** or **9** (1.0 mol) was added in to a mixture of potassium carbonate (1.8 mol), substituted phenyl boronic acid (1.2 mol), Pd(OAc)₂ (0.6 mol) and water (0.5 vol.) in isopropyl alcohol (10 volumes) and heated to reflux for 4 to 5 hours. After confirmation of completion of reaction,

solvent stripped off completely under vacuum from the reaction mass and then sufficient quantity of methylene chloride and water added to the reaction mass. After stirring the reaction mass for some time, separated the organic layer as well as aqueous layer and organic layer was distilled off under vacuum to get crude desired product, which was further triturated with solvent hexane to achieve free flowing pure compound **6** and **10** in good yields (65-80%).

RESULTS AND DISCUSSION

Bromo-phenyl-benzo-imidazole (**3** and **8**) were formed by the reaction of 4-bromobenzene-1,2-diamine (**1**) and benzoic acid (**2** and **7**) in the presence of PPA, respectively (Scheme-1 and 2). Formation of bromo-phenyl-benzo-imidazole (**3** and **8**) were confirmed by their ^1H NMR spectra, which showed downfield at δ 5.56 for one proton of imidazole N-H and one sharp singlet of CH_3 group attached with benzene ring. bromo-methyl-phenyl-benzo-imidazole (**4** and **9**) were formed by the reaction of bromo-phenyl-benzo-imidazole (**3** and **8**) with dimethyl sulfide, respectively. The formation of **4** and **9** were established on the basis of one sharp singlet at δ 3.21 for three proton of CH_3 in imidazole ring. The cycloaddition of bromo-methyl-phenyl-benzo-imidazole **4** and **9** with substituted phenyl boronic acid by using palladium acetate catalyst induced a series of C-C cross-coupling to afford methyl-diphenyl-benzo-imidazole derivatives (**6** and **10**), in moderate to good yields respectively, as shown in Scheme-1 and 2. The palladium catalyst was used to increase the yield of the product. A peak at 1675 cm^{-1} in the IR spectrum of compound **6** and **10** indicated $\text{C}=\text{N}$ of imidazole ring. Multiplet signal in ^1H NMR spectrum confirms the presence of phenyl ring. Similarly, the derivatives of compound **6** and **10** was confirmed (Table-1).

Table-1 Spectral Characterization of Synthesized Compounds

S. No.	Chemical Name	Code	Chemical Structure	Mol. Wt.	Spectral Characterization
1	1-methyl-2,6-diphenyl-1H-benzo[d]imidazole	Ha		284.35	^1H NMR (DMSO- D_6): δ 7.85 (d, 2H), δ 8.56 (s, 1H), δ 7.45 (m, 2H), δ 7.50 (t, 3H), δ 6.68 (d, 2H), δ 7.37 (t, 1H), δ 7.30 (t, 1H), δ 7.09 (d, 2H), δ 4.22 (d, 2H), δ 6.18 (t, 1H), ^{13}C NMR: 153.3, 152.8, 150.7, 147.4, 139.4, 138.8, 132.8, 131.8, 129.9, 127.9, 126.1, 122.6, 119.6, 118.5, 113.6, 38.1 MASS: 359.85 (m^+), 358.29 ($\text{m-H})^+$
2	6-(4-fluorophenyl)-methyl-phenyl-benzo-imidazole	Hb		302.34	^1H NMR (DMSO- D_6): δ 8.06 (d, 2H), δ 7.93 (d, 1H), δ 8.13 (s, 1H), δ 7.86 (m, 2H), δ 7.88 (t, 2H), δ 7.58 (m, 2H), δ 7.76 (d, 1H), δ 7.28 (t, 2H), δ 4.06 (m, 3H), δ 6.51 (s, 1H), MASS: 303.1 (m^+)
3	6-(3-methoxyphenyl)-1-methyl-2-phenyl-1H-benzo[d]imidazole	Hc		314.38	^1H NMR (DMSO- D_6): δ 7.93 (d, 1H), δ 8.01 (s, 1H), δ 7.71 (d, 1H), δ 7.88 (d, 1H), δ 7.33 (m, 3H), δ 7.57 (m, 3H), δ 6.93 (m, 1H), δ 7.23 (t, 1H), 3.95 (d, 2H), δ 7.03 (t, 1H), δ 3.73 (d, 2H), δ 6.29 (m, 1H), δ 3.84 (d, 2H), MASS: 315.1 (m^+)

4	6-(4-chlorophenyl)-1-methyl-2-phenyl-1 <i>H</i> -benzo[<i>d</i>]imidazole	Hd		318.8	¹ H NMR (DMSO-D ₆): δ 7.82 (d, 2H), δ 8.45 (s, 1H), δ 7.49 (t, 3H), δ 7.94 (d, 1H), δ 3.77 (s, 2H), δ 7.25 (m, 5H), 2.83 (t, 2H), δ 2.92 (t, 2H), MASS: 398.46 (m ⁺), 397.2(m-H) ⁺
5	1-methyl-2-phenyl-6- <i>p</i> -tolyl-1 <i>H</i> -benzo[<i>d</i>]imidazole	He		298.38	¹ H NMR (DMSO-D ₆): δ 7.66 (m, 1H), δ 7.56 (m, 2H), δ 7.27 (m, 3H), δ 7.85 (m, 2H), δ 6.92 (d, 1H), δ 7.13 (d, 1H), δ 3.31 (m, 2H), δ 6.63 (d, 1H), δ 1.50 (m, 2H), δ 2.35 (m, 2H), δ 0.86 (m, 3H), δ 1.22 (m, 1H), δ 6.92 (d, 1H), δ 7.13 (d, 1H), MASS: 299.1 (m ⁺)
6	6-(4-(trifluoromethyl)phenyl)-methyl-phenyl-benzo-imidazole	Hf		352.35	¹ H NMR (DMSO-D ₆): δ 7.64 (m, 4H), δ 7.89 (m, 2H), δ 0.86 (m, 3H), δ 7.50 (m, 1H), δ 7.21 (t, 1H), δ 7.30 (t, 1H), MASS: 353.0 (m ⁺)
7	1-methyl-6-(naphthalenyl)-phenyl-benzo-imidazole	Hg		334.41	¹ H NMR (DMSO-D ₆): δ 7.65 (t, 1H), δ 7.20 (d, 1H), δ 8.04(t, 2H), δ 7.33(t, 1H), δ 7.49 (m, 2H), MASS: 335.1
8	1-methyl-6-phenyl-2- <i>o</i> -tolyl-1 <i>H</i> -benzo[<i>d</i>]imidazole	Hh		298.38	¹ H NMR (DMSO-D ₆): δ 2.22 (s, 3H), δ 8.00 (s, 1H), δ 3.66(t, 3H), δ 7.93 (d, 1H), δ 6.51(s, 1H), δ 7.75 (m, 2H), δ 7.71 (d, 1H), δ 7.37 (m, 1H), δ 7.66(d, 1H), δ 7.56(m, 1H), δ 7.14 (t, 1H), δ 6.74(d, 1H), δ 7.46(m, 1H), MASS: 299.1 (m ⁺)
9	6-(4-fluorophenyl)-1-methyl- <i>o</i> -tolyl-benzoimidazole	Hi		316.37	¹ H NMR (DMSO-D ₆): δ 7.18 (t, 2H), δ 8.22 (t, 2H), MASS: 317.1 (m ⁺)
10	6-(4-chlorophenyl)-1-methyl- <i>o</i> -tolyl-benz-imidazole	Hj		332.83	¹ H NMR (DMSO-D ₆): δ 7.37(m, 1H), δ 8.65 (s, 1H), δ 7.53(m, 3H), δ 7.44 (d, 1H), δ 7.66 (d, 1H), δ 7.84 (m, 1H), δ 2.05(s, 6H), δ 6.78(d, 4H), δ 4.45 (s, 2H), δ 6.40 (t, 2H), , MASS: 353.19 (m ⁺), 352.3 (m-H) ⁺
11	6-(3-methoxyphenyl)-methyl- <i>o</i> -tolyl-benzo-imidazole	Hk		328.41	¹ H NMR (DMSO-D ₆): δ 1.25(s, 3H), δ 8.02 (s, 1H), δ 3.75 (s, 3H), δ 7.84 (d, 1H), δ 6.40 (t, 2H), δ 7.71 (d, 1H), δ 6.91 (t, 2H), δ 7.58 (m, 3H), δ 7.25(m, 1H), δ 3.89 (t, 3H), δ

					7.21(s, 2H), δ 7.09(t, 1H), MASS: 329.1 (m^+)
12	1-methyl- <i>o</i> -tolyl-6- <i>p</i> -tolyl-benzo-imidazole	Hi		312.41	^1H NMR (DMSO-D6): δ 0.85 (m, 3H), δ 7.49 (d, 2H), δ 1.27 (s, 10H), δ 7.27 (t, 2H), δ 6.40 (t, 2H), δ 7.37 (m, 1H), δ 2.40 (s, 3H), δ 6.78 (d, 4H), MASS: 313.1 (m^+)
13	6-(4-(trifluoromethyl)phenyl)-1-methyl-2- <i>o</i> -tolyl-benzo[d]imidazole	Hm		366.38	^1H NMR (DMSO-D6): δ 1.25 (s, 3H), δ 8.03 (s, 1H), δ 7.85 (t, 3H), δ 7.92 (s, 1H), δ 7.88 (t, 3H), δ 7.91 (s, 1H), δ 2.29 (t, 3H), δ 7.82 (d, 2H), δ 3.67 (s, 1H), δ 63.69 (t, 3H), MASS: 367.1 (m^+)
14	1-methyl-6-(naphthalen-3-yl)-2- <i>o</i> -tolyl-1H-benzo[d]imidazole	Hn		348.44	^1H NMR (DMSO-D6): δ 2.05 (s, 8H), δ 7.94 (d, 1H), δ 2.35 (s, 6H), δ 2.28 (s, 4H), δ 7.92 (m, 3H), δ 4.21 (m, 3H), δ 7.73 (m, 2H), δ 7.54 (m, 6H), δ 4.23 (m, 4H), δ 7.53 (m, 4H), δ 3.66 (d, 4H), δ 7.37 (m, 2H), δ 7.35 (d, 4H), MASS: 349.1 (m^+)
15	6-(4-methoxyphenyl)-1-methyl-2- <i>o</i> -tolyl-benzo[d]imidazole	Ho		328.41	^1H NMR (DMSO-D6): δ 1.25 (s, 3H), δ 7.98 (s, 1H), δ 2.28 (s, 3H), δ 7.85 (d, 1H), δ 3.65 (d, 3H), δ 7.62 (m, 2H), δ 7.07 (d, 1H), δ 7.60 (m, 2H), δ 7.25 (s, 1H), δ 7.53 (t, 1H), δ 7.52 (m, 2H), MASS: 329.1 (m^+)

Fig.-1: Zone of Inhibition of Test Compounds against Bacteria (a) *E. coli* and (b) *S. aureus***Anti-bacterial Activity Assay**

The anti-bacterial activity was studied by selecting Gram-positive *S. aureus* and Gram-negative *E. coli* bacteria by using agar well diffusion method. The anti-bacterial study of the synthesized compounds shows good to excellent activity against tested Gram-positive and Gram negative bacteria. Among these

compound Hg, and Hk were the most effective against *E. coli* and *S. aureus* bacteria of all the tested compounds (Fig.-1).

CONCLUSION

A novel series of 1-methyl-2,6-diphenyl-benzo-imidazole and 1-methyl-6-phenyl-(o-tolyl)-benzo-imidazole derivatives have been synthesized from 4-bromobenzene-1,2-diamine and benzoic acid using palladium (II) acetate. The synthesized compounds evaluated for their anti-bacterial activity against Gram-positive *S. aureus* and Gram-negative *E. coli* bacteria by using broth-dilution method. Among these compound **Hg**, and **Hk** were the most effective against *S. aureus* and *E. coli* bacteria of all the tested compounds.

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