



Synthesis of some novel benzimidazole derivatives and its biological evaluation

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ABSTRACT

A series of new benzimidazole derivatives have been synthesized by simple condensation reaction between benzimidazole derivatives and phenyl sulphonyl chloride derivatives. All these compounds were characterized by FT-IR, ¹H NMR, MS and elemental analysis. These compounds were screened for antibacterial and antioxidant activities, respectively. The antibacterial activities were compared with the standard drug such as chlorophenicol and antioxidant activities were compared with the ascorbic acid.

1. Introduction

Heterocyclic compounds have occupied a prominent place among various classes of organic compounds by virtue of their diverse biological activities. Hence the design, synthesis and production of new molecules for crop health and human welfare have taken center stage in recent years. Among the wide variety of heterocyclics that have been explored for developing pharmaceutically important role in medicinal chemistry [1].

Benzimidazole and its derivatives are of great importance in medicinal chemistry because of their wide variety of biological and pharmacological applications [1,2]. The literature survey shows several examples of compounds having a benzimidazole ring which exhibit remarkable bioactivity that could make them potentially useful in the treatment of cancer, and cardiovascular diseases [3]. The benzimidazole unit and its derivatives possess anticancer [4], anti-inflammatory [5], antibacterial [6], antifungal [7], antidiabetic [8], and anti-HIV activities [9]. On the basis of this observation we have synthesized benzimidazole derivatives as hitherto unreported analogues.

Literature survey has also revealed the importance of benzimidazoles as antimicrobial and antioxidant agents [10-14]. It has also been reported that certain substituted benzimidazole derivatives have a broad antimicrobial spectrum [11]. Motivated by this above-mentioned facts herein is reported the synthesis and antimicrobial, anti oxidant activities of new benzimidazole series.

2. Experimental

2.1. Instrumentation

All the reagents were purchased from Aldrich Chemicals Co, Loba Chemie. All the solvents and reagents used for the synthesis and analysis were of analytical grade. The progress of

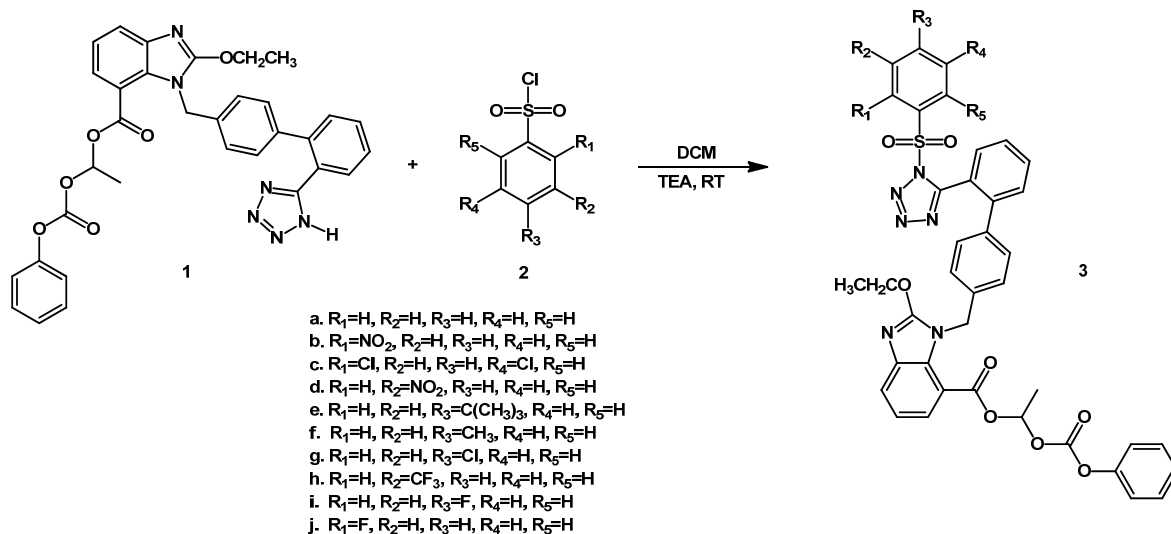
the reaction and the purity of the compounds were checked by thin layer chromatography (TLC). ¹H NMR spectra were recorded on a BRUKER-AV400 spectrometer in CDCl₃ and tetramethylsilane (TMS; δ = 0.00 ppm) served as internal standards. IR spectra were measured using a JASCO FT/IR-4100 spectrometer. Mass spectra were measured with Micromass Q-ToF. CHNS were measured by the Elementar Vario EL III (Germany). Thin-layer chromatography was carried out using SILICA GEL GF₂₅₄. The melting points (uncorrected) were measured on a SALACO apparatus.

2.2. Synthesis

2.2.1. General procedure for the synthesis of 1-(phenoxy carbonyloxy)ethyl 2-ethoxy-1-((2'-(1-(phenylsulfonyl)-1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate derivatives

The compound 1-(phenoxy carbonyloxy)ethyl 1-((2'-(1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate was purchased from Pure Chem. Scientific Limited, USA. Mixture of 1-(phenoxy carbonyloxy)ethyl 1-((2'-(1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate (0.2 g, 0.33 mmol), substituted phenyl sulfonyl chloride (0.36 mmol) and triethyl amine (0.66 mmol) in 10 mL of dichloromethane was stirred for 2 h at room temperature. After the completion of the reaction, 5 mL water was poured; the organic layer was extracted and distilled off completely to get product in good yield (Scheme 1).

1-(Phenoxy carbonyloxy)ethyl-2-ethoxy-1-((2'-(1-(phenyl sulfonyl)-1H-tetrazol-5-yl) biphenyl-4-yl) methyl)-1H-benzo[d]imidazole-7-carboxylate (**3a**): Color: White. Yield: 80% (0.2 g). M.p.: 78-80 °C. FT-IR (KBr, cm⁻¹): 1690 (ketone CO stretch.), 1700 (ester CO stretch.), 3030 (aromatic CH stretch.). ¹H NMR (400 MHz, CDCl₃, δ, ppm): 1.25-1.32 (t, 3H, CH₃), 1.43-1.45 (d,



Scheme 1

3H, CH₃), 2.9-3.0 (q, 2H, OCH₂), 4.66 (s, 2H, NCH₂), 5.59-5.67 (m, 1H, CH), 6.81-7.10 (m, $J = 7.5$ Hz, 2H, ArH), 7.12-7.46 (m, 9H, ArH), 7.58-7.88 (m, $J = 8$ Hz, 10H, ArH). Anal. calcd. for C₃₉H₃₂N₆O₈S: C, 62.89; H, 4.33; N, 11.28; S, 4.31. Found: C, 62.80; H, 4.29; N, 11.26; S, 4.30%. MS (m/z): (M+1) 745.79.

1-(Phenoxy-carboxyloxy)ethyl 2-ethoxy-1-((2'-(1-(2-nitrophenylsulfonyl)-1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate (**3b**): Color: Yellow. Yield: 70% (0.18 g). M.p.: 132-134 °C. FT-IR (KBr, cm⁻¹): 1450 (NO₂ stretch.), 1695 (ketone CO stretch.), 1710 (ester CO stretch.), 3040 (aromatic CH stretch.). ¹H NMR (400 MHz, CDCl₃, δ , ppm): 1.21-1.23 (t, 3H, CH₃), 1.7-2.0 (d, 3H, CH₃), 3.18-3.21 (q, 2H, OCH₂), 4.63 (s, 2H, NCH₂), 5.29-5.47 (m, 1H, CH), 6.89-7.10 (m, $J = 7.2$ Hz, 3H, ArH), 7.14-7.48 (m, 12H, ArH), 8.28-8.32 (m, 5H, ArH). Anal. calcd. for C₃₉H₃₁N₇O₁₀S: C, 59.31; H, 3.96; N, 12.41; S, 4.06. Found: C, 59.29; H, 3.98; N, 12.38; S, 4.01%. MS (m/z): (M+1) 790.91.

1-(Phenoxy-carboxyloxy)ethyl 1-((2'-(1-(2,5-dichlorophenylsulfonyl)-1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate (**3c**): Color: White. Yield: 76% (0.20 g). M.p.: 92-94 °C. FT-IR (KBr, cm⁻¹): 1710 (ketone CO stretch.), 1729 (ester CO stretch.), 3039 (aromatic CH stretch.). ¹H NMR (400 MHz, CDCl₃, δ , ppm): 1.23-1.24 (t, 3H, CH₃), 1.72-2.02 (d, 3H, CH₃), 3.17-3.19 (q, 2H, OCH₂), 4.66 (s, 2H, NCH₂), 5.27-5.31 (m, 1H, CH), 7.01-7.12 (m, $J = 7.2$ Hz, 3H, ArH), 8.01-8.11 (m, 7H, ArH), 8.18-8.29 (m, 9H, ArH). Anal. calcd. for C₃₉H₃₀Cl₂N₆O₈S: C, 57.57; H, 3.72; N, 10.33; S, 3.94. Found: C, 56.99; H, 3.70; N, 10.29; S, 3.89%. MS (m/z): (M+1) 814.22.

1-(phenoxy-carboxyloxy)ethyl 2-ethoxy-1-((2'-(1-(3-nitrophenylsulfonyl)-1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate (**3d**): Color: White. Yield: 72% (0.19 g). M.p.: 98-100 °C. FT-IR (KBr, cm⁻¹): 1445 (NO₂ stretch.), 1690 (ketone CO stretch.), 1700 (ester CO stretch.), 3039 (aromatic CH stretch.). ¹H NMR (400 MHz, CDCl₃, δ , ppm): 1.18-1.20 (t, 3H, CH₃), 1.91-2.01 (d, 3H, CH₃), 3.13-3.15 (q, 2H, OCH₂), 4.78 (s, 2H, NCH₂), 5.27-5.29 (m, 1H, CH), 7.11-7.12 (m, 3H, ArH), 8.11-8.17 (m, 7H, ArH), 8.17-8.28 (m, 10H, ArH). Anal. calcd. for C₃₉H₃₁N₇O₁₀S: C, 59.31; H, 3.96; N, 12.41; S, 4.06. Found: C, 59.22; H, 3.89; N, 12.39; S, 3.99%. MS (m/z): (M+1) 790.19.

1-(Phenoxy-carboxyloxy)ethyl 1-((2'-(1-(4-tert-butylphenylsulfonyl)-1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate (**3e**): Color: White. Yield: 86% (0.22 g). M.p.: 72-74 °C. FT-IR (KBr, cm⁻¹): 1700 (ketone CO stretch.), 1729 (ester CO stretch.), 3050 (aromatic CH stretch.).

¹H NMR (400 MHz, CDCl₃, δ , ppm): 1.13-1.18 (s, 9H, 3CH₃), 1.19-1.20 (t, 3H, CH₃), 1.90-2.01 (d, 3H, CH₃), 3.14-3.15 (q, 2H, OCH₂), 4.79 (s, 2H, NCH₂), 5.18-5.20 (m, 1H, CH), 7.10-7.12 (m, $J = 7.4$ Hz, 3H, ArH), 8.15-8.20 (m, 8H, ArH), 8.20-8.27 (m, 9H, ArH). Anal. calcd. for C₄₃H₄₀N₆O₈S: C, 64.49; H, 5.03; N, 10.49; S, 4.00. Found: C, 64.19; H, 4.99; N, 10.29; S, 3.87%. MS (m/z): (M+1) 801.73.

1-(Phenoxy-carboxyloxy)ethyl 2-ethoxy-1-((2'-(1-(tosyl-1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate (**3f**): Color: Yellow. Yield: 78% (0.19 g). m.p. 87-89 °C. FT-IR (KBr, cm⁻¹): 1690 (ketone CO stretch.), 1710 (ester CO stretch.), 3041 (aromatic CH stretch.). ¹H NMR (400 MHz, CDCl₃, δ , ppm): 1.18-1.20 (t, 3H, CH₃), 1.88-1.91 (d, 3H, CH₃), 2.10 (s, 3H, ArCH₃), 3.14-3.15 (q, 2H, OCH₂), 4.79 (s, 2H, NCH₂), 5.17-5.18 (m, 1H, CH), 7.11-7.12 (m, $J = 8.0$ Hz, 3H, ArH), 8.11-8.16 (m, 8H, ArH), 8.20-8.25 (m, 9H, ArH). Anal. calcd. for C₄₀H₃₄N₆O₈S: C, 63.31; H, 4.52; N, 11.08; S, 4.23. Found: C, 63.11; H, 4.22; N, 10.87; S, 3.98%. MS (m/z): (M+1) 759.80.

1-(Phenoxy-carboxyloxy)ethyl 1-((2'-(1-(4-chlorophenylsulfonyl)-1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate (**3g**): Color: White. Yield: 78% (0.16 g). M.p.: 138-140 °C. FT-IR (KBr, cm⁻¹): 1690 (ketone CO stretch.), 1710 (ester CO stretch.), 3041 (aromatic CH stretch.). ¹H NMR (400 MHz, CDCl₃, δ , ppm): 1.21-1.23 (t, 3H, CH₃), 1.78-1.79 (d, 3H, CH₃), 3.78-3.80 (q, 2H, OCH₂), 4.82 (s, 2H, NCH₂), 5.16-5.17 (m, 1H, CH), 7.10-7.12 (m, $J = 8.0$ Hz, 3H, ArH), 8.11-8.15 (m, 7H, ArH), 8.20-8.25 (m, 10H, ArH). Anal. calcd. for C₃₉H₃₁ClN₆O₈S: C, 60.11; H, 4.01; N, 10.79; S, 4.12. Found: C, 60.07; H, 3.71; N, 10.29; S, 3.82%. MS (m/z): (M+1) 780.18.

1-(Phenoxy-carboxyloxy)ethyl 2-ethoxy-1-((2'-(1-(3-(trifluoromethyl)phenylsulfonyl)-1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate (**3h**): Color: White. Yield: 78% (0.15 g). M.p.: 63-65 °C. FT-IR (KBr, cm⁻¹): 1695 (ketone CO stretch.), 1725 (ester CO stretch.), 3052 (aromatic CH stretch.). ¹H NMR (400 MHz, CDCl₃, δ , ppm): 1.22-1.23 (t, 3H, CH₃), 1.69-1.71 (d, 3H, CH₃), 3.79-3.81 (q, 2H, OCH₂), 4.79 (s, 2H, NCH₂), 5.28-5.29 (m, 1H, CH), 7.16-7.18 (m, $J = 6.9$ Hz, 3H, ArH), 8.16-8.18 (m, 7H, ArH), 8.19-8.22 (m, 10H, ArH). Anal. calcd. for C₄₀H₃₁F₃N₆O₈S: C, 59.11; H, 3.84; N, 10.34; S, 3.95%. Found: C, 58.91; H, 3.69; N, 10.31; S, 3.43. MS (m/z): (M+1) 813.15.

1-(Phenoxy-carboxyloxy)ethyl 2-ethoxy-1-((2'-(1-(4-fluorophenylsulfonyl)-1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate (**3i**): Color: White. Yield: 78% (0.19 g). M.p.: 80-82 °C.

Table 1. Antibacterial activity of synthesized compounds*.

Compound	<i>Bacillus subtilis</i>		<i>Klebsiellapneumoniae</i>		<i>Xanthomonasvesicatoria</i>		<i>Bacillus cereus</i>		<i>Shigella flexneri</i>		<i>Salmonella Typhi</i>	
	5 mg	10 mg	5 mg	10 mg	5 mg	10 mg	5 mg	10 mg	5 mg	10 mg	5 mg	10 mg
3a	-	-	11	10	-	-	10	-	14	-	-	-
3b	10	-	14	10	12	-	-	-	15	14	-	-
3c	-	-	10	-	-	10	11	12	10	-	-	-
3d	12	-	-	-	10	10	16	-	17	-	-	-
3e	18	-	10	-	18	-	-	-	-	-	-	-
3f	10	-	22	-	19	-	10	-	-	-	-	-
3g	10	-	16	11	10	-	-	-	10	-	-	-
3h	-	-	10	10	-	-	17	-	19	-	-	-
3i	-	-	11	10	-	-	10	-	-	-	-	-
3j	-	-	10	14	-	-	-	-	-	-	-	-
Chloramphenicol	31	-	37	36	30	-	37	33	36	-	-	-

* Positive control zone is 30 to 40 mm; Standard drug: Chloramphenicol; '-' = Not active.

FT-IR (KBr, cm⁻¹): 1692 (ketone CO stretch.), 1723 (ester CO stretch.), 3049 (aromatic CH stretch.). ¹H NMR (400 MHz, CDCl₃, δ, ppm): 1.26-1.28 (t, 3H, CH₃), 1.68-1.70 (d, 3H, CH₃), 3.77-3.78 (q, 2H, OCH₂), 4.88 (s, 2H, NCH₂), 5.27-5.28 (m, 1H, CH), 6.98-7.10 (m, 3H, ArH), 8.00-8.31 (m, 7H, ArH), 8.42-8.51 (m, 10H, ArH). Anal. calcd. for C₃₉H₃₁FN₆O₈S: C, 61.41; H, 4.10; N, 11.02; S, 4.20. Found: C, 61.11; H, 3.91; N, 10.78; S, 4.10%. MS (*m/z*): (M+1) 763.67.

1-(Phenoxy carbonyloxy)ethyl 2-ethoxy-1-((2'-((1-(2-fluoro phenylsulfonyl)-1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate (**3j**): Color: White. Yield: 72% (0.18 g). M.p.: 118-120 °C. FT-IR (KBr, cm⁻¹): 1691 (ketone CO stretch.), 1719 (ester CO stretch.), 3039 (aromatic CH stretch.). ¹H NMR (400 MHz, CDCl₃, δ, ppm): 1.19-1.21 (t, 3H, CH₃), 1.44-1.46 (d, 3H, CH₃), 3.1-3.2 (q, 2H, OCH₂), 4.78 (s, 2H, NCH₂), 5.55-5.59 (m, 1H, CH), 7.11-7.13 (m, 2H, ArH), 7.12-7.38 (m, 8H, ArH), 8.98-9.16 (m, 10H, ArH). Anal. calcd. for C₃₉H₃₁FN₆O₈S: C, 61.41; H, 4.10; N, 11.02; S, 4.20. Found: C, 61.11; H, 3.97; N, 10.80; S, 4.11%. MS (*m/z*): (M+1) 763.28.

2.3. Biological evaluation - antibacterial and antioxidant activity studies

2.3.1. Antibacterial activity

Antibacterial tests were carried out by disc diffusion method using 100 μL of suspension containing 10⁶ cells/mL of bacteria. The discs (6 mm diameter) were impregnated with 5 mg and 10 mg/mL of each compound and placed on the inoculated nutrient agar. Then, the inoculated plates were incubated at 37±0.1 °C at 24 h. One antibacterial drug, chloramphenicol, also is used as positive control. Antibacterial activity was evaluated by measuring the zone of inhibition against the test organisms.

2.3.2. Antioxidant activity

The DPPH assay was done by using solution of each compound made in methanol was added to 95 μL of DPPH solution (0.2 mM/mL methanol) and mixed vigorously. The mixture was incubated in dark at room temperature for 30 min. Absorbance was measured at 517 nm using an Elisa reader. Ascorbic acid was used as positive control.

The level of percentage inhibition of DPPH• by each compound was calculated according to the Equation 1.

$$\% \text{ Radical scavenging} = [(A_c - A)/A_c] \times 100 \quad (1)$$

where A_c is the absorbance of the control and A is the absorbance of sample. Percentage scavenging was also evaluated in ascorbic acid equivalence.

3. Results and discussion

We have synthesized a series of 1-(phenoxy carbonyloxy)ethyl 2-ethoxy-1-((2'-((1-(phenylsulfonyl)-1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate derivatives using a known procedure and obtained products with good yield.

The structures of all the synthesized compounds were characterized by spectroscopic data, and allowed these molecules for study of antibacterial and antioxidant activities (Table 1 and 2). Benzimidazole derivatives shows a very good anti bacterial activities [10-14], we are comparing the synthesized new benzimidazole derivatives to the marketed chlorophenicol [15] which shows very good anti bacterial activity, here we are synthesizing the newly substituted benzimidazole derivatives for the studies of antibacterial activities by comparison with the drug molecule. In this studies compound **3f** shows good bacterial activity, in which the tertiary butyl group is the electron releasing group, which is attached to the *para* position. The compound **3i** shows least antibacterial activity, in which the fluoro group is attached to the *para* position, which is the electron withdrawing group. The remaining molecules showing the moderate activity.

The synthesized compounds were tested for anti oxidant activities by evaluation with ascorbic acid [16,17]. In antioxidant studies the compound **3h** shows the good antioxidant activity, in which the trifluoro methyl group is attached to the meta position which is highly electron withdrawing. Compound **3a** shows the least antioxidant activity, which does not having any substitution.

Table 2. Antioxidant activity of synthesized compounds.

Sample	Antioxidant percentage, 5 mg/mL
3a	14
3b	22
3c	21
3d	16
3e	16
3f	16
3g	31
3h	55
3i	24
3j	18
Ascorbic acid	90

4. Conclusion

The structure proposed of the synthesized compound is well supported by spectroscopic data. From the data of antibacterial activity and antioxidant activity, it may be concluded that all the synthesized compounds possess good to moderate activity.

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