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One pot synthesis of substituted 2-(phenoxymethyl)-1-phenyl-1H-benzo(d)imidazoles and their bioactivity evaluations

P.Lavanya, M.Suresh, C.Venkata Rao*

Department of Chemistry, Sri Venkateswara University, Tirupati - 517 502, (INDIA)

E-mail : cvrsvu@gmail.com

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ABSTRACT

A Series of 2-(Phenoxymethyl)-1-phenyl-1H-benzo(d)imidazole, with different substituent's at the phenoxymethyl ring have been synthesized in good yields by the condensation of N^1-phenylbenzene-1,2-diaminedihydrochloride and substituted henoxyacetic acids in presence of water as solvent under reflux condition. All the synthesized compounds were evaluated for their bioactivity studies like antioxidants, antibacterial, antifungal.

KEYWORDS

Benzimidazole derivatives;
N^1-phenylbenzene-1,2-diaminedihydrochloride;
Substituted phenoxyacetic acids;
Water;
Bioactivity studies.

INTRODUCTION

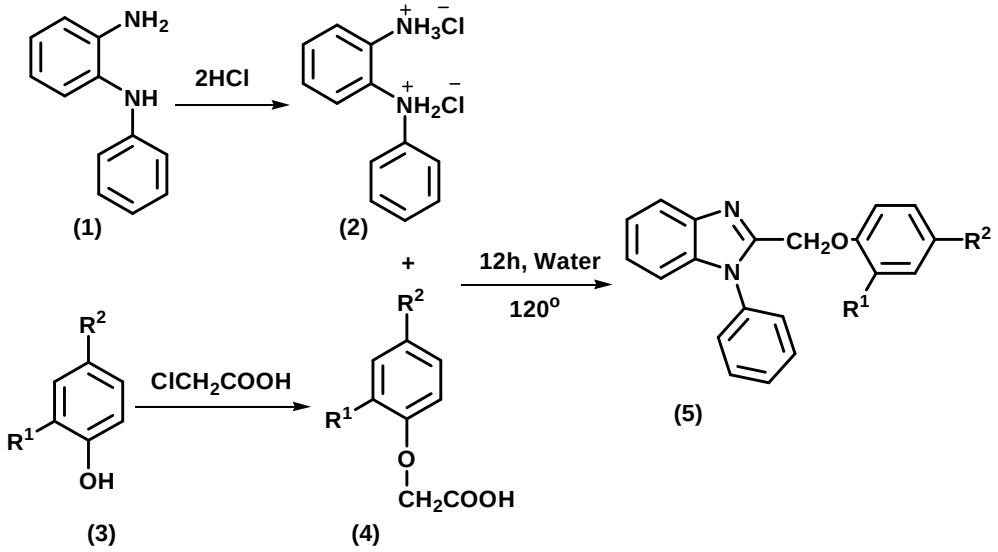
The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine and nucleic acid. There fore, the bulk of imidazole produced is used in the preparation of biologically active compounds. Benzimidazoles and their derivatives are important constituents of biological active compounds like albendazole, mebendazole etc. They exhibit several biological activities such as antibacterial[1], antiviral[2], antitumoral[3,4], antiinflammatery[5], antifungal[6], antihelmintic[7], antiHIV[8], antihistaminic[9-11], antiulcer[12,13], cardiotonic[14], antihypertensive[15,16], and neuroleptic[17] activities. There fore we have synthesized the title compounds and their derivatives by the condensation of N1-phenylbenzene-1,2-diaminedihydrochloride with substituted phenoxyacetic acids in reflux condition and screened for antioxidants, antibacterial, antifungal activity studies.

EXPERIMENTAL

Melting points were determined over Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on Bio-Rad win FTIR and Perkin Elmer 283 double beam spectrophotometer as KBr pellets. 1H-NMR spectra were recorded at 500 MHz with a Bruker Avance Dpx 300 instrument in $CDCl_3$ unless otherwise specified. Mass spectra were recorded, under ESI-Mass with a LC-Trap-SL instrument and presented as m/z (% rel. int). TLC was used to monitor the progress of the reactions and purity of the synthesized compounds.

General procedure

The title compounds, 2-(Phenoxymethyl)-1-phenyl-1H-benzo(d)imidazole were synthesized according to the reactions shown in Scheme 1. First phenoxyacetic acids **(4)** were prepared by base mediated condensation of corresponding phenols with chloroacetic acid. The desired N1-phenylbenzene-1,2-diaminedihydrochloride **(2)** was prepared from commercially available N1-phenylbenzene-1,2-diamine. Compounds **(5a-5i)** were obtained in the final step by conventional refluxion of compounds **(2)** and **(4)** in water. The resulting reaction mixture is cooled and it is made distinctly basic by



Scheme 1

TABLE 1: 2-(Phenoxymethyl)-1-phenyl-1*H*-benzo(d)imidazole (5a-5i)

Compound	R^1	R^2	Yield(%)	melting point°C
5a	H	H	80	200-202
5b	CH_3	H	83	110-112
5c	H	CH_3	86	68-70
5d	Cl	H	86.5	138-140
5e	H	Cl	81	82-84
5f	H	Br	80	120-121
5g	Cl	NO_2	82	158-159
5h	NO_2	CH_3	84	189-190
5i	CH_3	Cl	85	105-106

TABLE 2: Antioxidant oxidant

Compound	I^C 50 μM
Vitamic C	852
Vitamin-E	726
BHA	966
BHT	381
5a	150
5b	250
5c	280
5d	320
5e	350
5f	330
5g	310
5h	350
5i	340

the gradual addition of concentrated ammonia solution. The resulting solid was filtered, dried and purified by recrystallization.

2-(Phenoxymethyl)-1-phenyl-1*H*-benzo(d)imidazole (5a)

IR(KBr) ν cm^{-1}: 3048, 2942, 1605, 1590, 1505, 1454, 1402, 1365, 1334, 1292, 1236, 1182, 1012, 932, 884, 815, 754. ^{1}H-NMR (δ ppm): 7.85 (1H, d, H-5), 7.43-7.53 (5H, m, Ar-H″), 7.31 (1H, d, H-4), 7.28 (1H, d, H-3), 7.21 (1H, d, H-2), 6.82-6.98 (5H, m, N-Ar-H′), 5.14 (2H, s, CH_2). LC-MS (ESI, positive ion mode): m/z 301$(M+H)^+$.

2-((o-tolyloxy)methyl)-1-phenyl-1H-benzo(d)imidazole 5b

IR(KBr) ν cm^{-1}: 3068, 2920, 1610, 1589, 1490, 1445, 1420, 1290, 1245, 818, 752. ^{1}H-NMR (δ ppm): 7.84 (1H, d, H-5), 7.40-7.50 (5H, m, N-Ar-H′), 7.28 (1H, d, H-4), 7.18 (1H, d, H-3), 7.08 (1H, d, H-2), 7.32 (1H, dd, H-3″), 7.12 (1H, d, H-4″), 6.88 (1H, d, H-5″), 6.76 (1H, dd, H-6″), 5.16 (2H, s, CH_2), 2.26 (3H, s, CH_3). LC-MS: (ESI, positive ion mode): m/z 315 $(M+H)^+$.

2-((p-tolyloxy)methyl)-1-phenyl-1H-benzo(d)imidazole (5c)

IR(KBr) ν cm^{-1}: 3052, 2943, 1610, 1588, 1505, 1452, 1401, 1363, 1290, 1235, 1182, 1010, 930, 880, 812, 752. ^{1}H-NMR (δ ppm): 7.86 (1H, d, H-5) 7.45-7.55 (5H, m, N-Ar-H′), 7.32-7.35 (1H, d, H-4), 7.29 (1H, d, H-3), 7.20 (1H, d, H-2), 7.03 (2H, d, H-3″,5″), 6.79 (2H, d, H-2″, 6″), 5.18 (2H, s, CH_2), 2.25 (3H, s, CH_3). LC-MS: (ESI, positive ion mode): m/z 315 $(M+H)^+$.

TABLE : 3 Antibacterial activity

S.No	compound	Zone of inhibition (mm)		
		Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*
1	5a	10	8	8
2	5b	12	10	10
3	5c	12	10	10
4	5d	14	12	14
5	5e	14	12	14
6	5f	15	14	10
7	5g	13	12	12
8	5h	14	13	14
9	5i	13	14	13
10	Chloramphenicol	18	16	18

TABLE 4 : Antifungal activity

S.No.	Compound	Concentration µL	Zone of inhibition (mm)	
			A.niger	P.chrysogenium
1	5a	10	2	2
		20	2	2
2	5b	10	2	2
		20	3	3
3	5c	10	2	3
		20	3	4
4	5d	10	2	2
		20	2	4
5	5e	10	2	2
		20	2	4
6	5f	10	2	3
		20	3	3
7	5g	10	3	4
		20	3	3
8	5h	10	2	4
		20	3	4
9	5i	10	3	3
		20	4	4
10	Fluconazole	10	8	8
		20	10	10

2-((2-chlorophenoxy)methyl)-1-phenyl-1H-benzo-(d)imidazole (5d)

IR(KBr) ν cm^{-1}: 3070, 2919, 1605, 1588, 1488, 1450, 1421, 1291, 1241, 816, 754. ^{1}H-NMR (δ ppm): 7.85 (1H, d, H-5) 7.44-7.53 (5H, m, N-Ar-H′), 7.40 (1H, dd, H-3′′), 7.32 (1H, d, H-4), 7.26 (1H, d, H-3), 7.22 (1H, d, H-4′′), 7.18 (1H, d, H-2), 6.99 (1H, d, H-5′′), 6.89 (1H, dd, H-6′′),5.12 (2H, s, CH_2) . LC-MS: (ESI, positive ion mode): m/z 335.5 $(M+H)^+$.

2-((4-chlorophenoxy)methyl)-1-phenyl-1H-benzo-(d)imidazole (5e)

IR(KBr) ν cm^{-1}: 3051, 2941, 1605, 1590, 1500, 1455, 1400, 1365, 1285, 1230, 1180, 1015, 935, 875, 812, 755. ^{1}H-NMR (δ ppm): 7.80 (1H, d, H-5) 7.40-7.51 (5H, m, N-Ar-H′), 7.32 (1H, d, H-4), 7.25 (1H, d, H-3), 7.01 (1H, d, H-2), 6.99 (2H, d, H-3′′, 5′′), 6.75 (2H, d, H-2′′, 6′′), 5.12 (2H, s, CH_2). LC-MS: (ESI, positive ion mode): m/z 335.5 $(M+H)^+$.

2-((4-bromophenoxy)methyl)-1-phenyl-1H-benzo-(d)imidazole (5f)

IR(KBr) ν cm^{-1}: 3052, 2941, 1610, 1595, 1500, 1455, 1400, 1365, 1285, 1230, 1170, 1015, 920, 875, 812, 745. ^{1}H-NMR (δ ppm): 7.80 (1H, d, H-5) 7.40-7.50 (5H, m, N-Ar-H′), 7.30 (1H, d, H-4), 7.24 (1H, d, H-3), 7.0 (1H, d, H-2), 6.89 (2H, d, H-3′′, 5′′), 6.70 (2H, d, H-2′′, 6′′), 5.10 (2H, s, CH_2). LC-MS: (ESI, positive ion mode): m/z 380 $(M+H)^+$.

2-((2-chloro-4-nitrophenoxy)methyl)-1-phenyl-1H-benzo(d)imidazole (5g)

IR(KBr) ν cm^{-1}: 3070, 2919, 1605, 1588, 1488, 1450, 1421, 1291, 1241, 816, 754. ^{1}H-NMR (δ ppm): 7.85 (1H, d, H-5) 7.40-7.50 (5H, m, N-Ar-H′), 7.45 (1H, dd, H-3′′), 7.30 (1H, d, H-4), 7.25 (1H, d, H-3), 7.12 (1H, d, H-2), 6.90 (1H, d, H-5′′), 6.81 (1H, dd, H-6′′) 5.1 (2H, s, CH_2) LC-MS: (ESI, positive ion mode): m/z 380 $(M+H)^+$.

2-((4-methyl-2-nitrophenoxy)methyl)-1-phenyl-1H-benzo(d)imidazole (5h)

IR(KBr) ν cm^{-1} : 3052, 2943, 1610, 1588, 1505, 1452, 1401, 1363, 1290, 1235, 1182, 1010, 930, 880, 812, 752. ^{1}H-NMR (δ ppm): 7.84 (1H, d, H-5) 7.40-7.51 (5H, m, N-Ar-H), 7.30-7.32 (1H, d, H-4), 7.22 (1H, d, H-3), 7.20 (1H, d, H-2), 7.03 (2H, d, H-3′′, 5′′), 6.72 (2H, d, H-6′′), 5.16 (2H, s, CH_2), 2.20 (3H, s, CH_3). LC-MS : (ESI, positive ion mode): m/z 360 $(M+H)^+$.

2-((4-chloro-2-methylphenoxy)methyl)-1-phenyl-1H-benzo(d)imidazole (5i)

IR(KBr) ν cm^{-1} : 3052, 2943, 1610, 1588, 1505, 1452, 1401, 1363, 1290, 1235, 1182, 1010, 930, 880, 812, 752. ^{1}H-NMR (δ ppm): 7.82 (1H, d, H-5) 7.42-7.48 (5H, m, N-Ar-H′), 7.22(1H, d, H-4), 7.16(1H,

d, H-3), 7.08 (1H, d, H-2), 7.03 (1H, dd, H-3′′), 6.79 (1H, d, H-5′′), 6.7(1H, dd, H-6′′), 5.18 (2H, s, CH_2), 2.25 (3H, s, CH_3). LC-MS : (ESI, positive ion mode) : m/z 349 $(M+H)^+$.

RESULTS AND DISCUSSION

2-(Phenoxymethyl)-1-phenyl-1*H*-benzo(d)imidazole **(5a)** was synthesized by the condensation of N^1-phenylbenzene-1,2-diaminedihydro- chloride **(2)** and phenoxy acetic acid **(4)** in presence of water as solvent under reflux condition at 120°. The structure of the compounds **(5a)** to **(5i)** is established by IR, NMR, Mass spectra. The IR spectrum of **(5a)** showed peaks at 3048, 2945, 1590-1454, 1605-1590 due to aromatic, aliphatic, C = N and aromatic groups respectively. Its LCMS spectrum at m/z 301 for $(M+H)^+$ and the elemental analysis indicated the MF of the compound to be $C_{20}H_{16}N_{20}$. The ^{1}HNMR of **(5a)** showed characteristic peaks at 7.432-7.53 (5H, m, Ar-H′′), 6.82-6.98 (5H, m, N-Ar-H′), 5.14 (2H, s, CH_2) indicating the structure to be 2-phenoxymethyl-1-phenyl-1H-benzo(d)imidazole. The other derivatives like **(5b-5i)** were synthesized using different substituted phenoxy acetic acids. (TABLE 1, Scheme 1).

Antioxidant activity

All the synthesized compounds were screened for their antioxidant activity by superoxide free radical scavenging activity[22,23]. The reaction mixture contained EDTA (6.6mM), NaCN (3μg) riboflavin (2μm), NBT (50μm), various concentrations of the test drug in ethanol and a phosphate buffer (58mM, PH 7.8) in a final volume of 3ml. Optical density was measured at 560nm. The test tubes were uniformly illuminated with an incandescent lamp for 15 min, after which the optical density was measured again at 560nm. The percent inhibition of superoxide radical generation was measured by comparing mean absorbance values of the control and those of the test substances. IC_{50} values were obtained from the plot drawn of concentration in μg verses percentage inhibition and were converted into μM. All the tests were run in triplicate and averaged. Vitamin C, Vitamin E, BHA, and BHT were used as reference standards to determine the sensitivity of antioxidant activity. Based on the results (TABLE 2) it is concluded that compounds **(5a-5i)** showed moderate antioxidant property.

Antibacterial activity

All the synthesized compounds were screened for their antibacterial activity by paper disc diffusion method[18,19]. *Staphylococcus aureus, Bacillus subtilis* and *Escherichia coli* were used as test organism. The discs (6mm in diameter) impregnated with 10νL of the test compounds (500μg/disc) at the concentration of 50mg/mL were placed on the inoculated agar. DMF was employed as the solvent to dissolve the test compound and negative control. Chloramphenicol (5μg/disc) was used as positive reference standards to determine the sensitivity of each microbial species tested. The inoculated plates were incubated at 37°C for 24h. Antimicrobial activity was evaluated by measuring the diameter of zone of inhibition against test organisms. Based on the results (TABLE 3) it is concluded that compounds **(5a-5i)** showed moderate activity against *Staphylococcus aureus, Bacillus subtilis* and *Escherichia coli*.

Antifungal activity

All the newly synthesized compounds were screened invitro for their antifungal activity by Agar cup method[20,21] and *Aspergillus niger, Pencillium chrysogenium* were used as test organisms. Potato dextrose agar was used as basal medium on sterile glass Petri dishes. The saboroudes broth medium was prepared by taking peptone (1.0g) and dextrose (4.0g) in warm distilled water (100mL). The selected fungal culture, single colony was inoculated in to broth medium and kept for incubation for overnight at 25°C. The saboroudes agar medium was prepared by taking peptone (1.0g), dextrose (4.0g) and agar (2.0g) in warm distilled water (100mL) and plated into petri dishes, allowed to solidification. The fungal culture was spread evenly over the surface and left for few minutes to percolate the culture. Wells were created using a sterile borer into the solidified agar medium and the compounds were added to each well 10-20μL at peripheral and the reference compound fluconazole was added at the centre. The plates were incubated at about 25°C for 3 days. After incubation period the plates were collected and record the inhibition zone in mm from the margin of the well.

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Dimethyl sulphoxide (DMSO) was used as solvent to prepare the stock solutions (5mg in 0.5mL) of the compounds initially and also to maintain proper control. A control well was also placed on the test plates to compare the effect of the test samples and to nullify the effect of solvent (DMSO) respectively. Based on the results (TABLE 4) it is concluded that compounds **(5a-5i)** exhibited less antifungal activities against *Aspergillus niger* and *Pencillium chrysogenium*.

CONCLUSION

The significance of present finding also relates to reducing use of organic solvents and potentially toxic hazardous materials, as well as its simplicity and inherent lower costs. Many reports have revealed that the influence of the substitution at the 1,2 and 5 positions of the benzimidazole ring is very important for various types of biological activities such as antibacterial, antiviral, antitumor and anti-inflammatory have been reported 2-(Phenoxymethyl)-1-phenyl-1H-benzo(d)imidazole **(5a-5i)** were synthesized and evaluated for their bioactivity studies. All the compounds were found to possess moderate antibacterial activity less antifungal activity and moderate antioxidant when compared to standard.

REFERENCES

[1] R.A.Coburn, M.T.Clark, R.T.Evans, R.J.Genco; J.Med.Chem., **30**, 205 **(1987)**.

[2] T.Roth, M.L.Morningstar, P.L.Boyer, S.H.Hughes, R.W.Buckheit, C.J.Michejda; J.Med.Chem., **40**, 4199 **(1997)**.

[3] A.Y.Chem, C.Yu, A.Bodley, L.F.Peng, L.F.Liu; Cancer Research, **53**, 1332 **(1993)**.

[4] W.A.Denny, G.W.Rewcastle, B.C.Baguley; J.Med. Chem., **33**, 814 **(1990)**.

[5] D.Evams, T.A.Hicks, W.R.N.Williamson, W.Dawson, S.C.R.Meacock, E.A.Kitchen; Eur. J.Med. Chem., **31**, 635 **(1996)**.

[6] D.Berg, K.H.Buchel, M.Plempel, A.Zywietz; Mykosen., **29**, 221 **(1986)**.

[7] A.G.Saimot, A.C.Cremieux, J.M.Hay, A.Meulemans, M.D.Giovanangeli, B.B.Delaitre, F.P.Couloud; Lancet, **17**, 652 **(1983)**.

[8] A.Chimirri, S.Gravo, A.M.Monforte, P.Monforte, M.Zappala; I.Farmaco., **46**, 925 **(1991)**.

[9] C.J.E.Niemegeers, F.Awouters, P.A.J.Janssen; Agents and Actions, **18**, 141 **(1986)**.

[10] R.Iemura, M.Hori, H.Ohatoka; Chem.Pharm.Bull., **37**, 962 **(1989)**.

[11] J.Benavides, H.Schoemaker, C.Dana, Y.Claustre, M.Delahaye, M.Prouteau, P.Manoury, J.V.Allon, B.Scatton, S.Z.Langer, S.Arbilla; Arzneim-Forsch., **45**, 551 **(1995)**.

[12] K.Ishihara, T.Ichikawa, Y.Komuro, S.Ohara, K.Hotta; Arzneim-Forsch., **44**, 827 **(1994)**.

[13] D.Y.Graham, A.Mccullough, M.Sklar, J.S.Sontag, W.M.Roufail, R.Stone, R.H.Bishop, N.Gitlin, A.J.Cagliola, R.S.Berman, T.Humphries; Digestive Disease and Sciences, **35**, 66 **(1990)**.

[14] G.Piazzesi, L.Morano, J.C.Ruegg; Arzneim-Forsch., **37**, 1141 **(1987)**.

[15] I.Wiedemann, H.Peil, H.Justus, H.Adamus, V.Brantl, H.Lohmann; Arzneim-Forsch., **35**, 964 **(1985)**.

[16] K.Kubo, Y.Kohara, E.Imamiya, Y.Sugiura, Y.Indana, Y.Farukawa, N.Nishikawa, T.Naka; J.Med.Chem., **36**, 2182 **(1993)**.

[17] P.A.J.Janssen, F.T.N.Allewijin; Arzneim-Forsch., **18**, 279 **(1968)**.

[18] B.Esterhuizen, K.J.D.V.Merve; Mycologia, **69**, 975 **(1977)**.

[19] A.W.Bauer, M.M.W.Kirby, C.V.Sherris, M.Turk; Am.J.Clin.Path., **45**, 493 **(1999)**.

[20] F.D.Spooner, G.Sykes; 'Methods in Microbiology', E.Norris, D.N.Ribbon, Eds., London: Academic Press, **(1972)**.

[21] D.Greenwood, R.C.B.Slack, J.F.Peutherer; 'Medical Microbiology', 14th Edn., ELBS, London, **1**, **(1992)**.

[22] J.M.MC Cord, I.Fridroch; J.Biol.Chem., **244**, 6049 **(1969)**.

[23] S.Venkateswarlu, M.S.S.Raju, G.V.Subbaraju; Biosci.Biotechnol.Biochem., **66**, 2236 **(2002)**.