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Green Synthesis & Biological Evaluation of Novel Benzimidazole Derivatives as Antianxiety Agents

Gollapalli Naga Raju [1a]*, Karumudi Bhavya Sai[1b], Kondeti T Naveen[2b], Rama Rao Nadendla[1a]

[a]Department of Pharmaceutical Chemistry
[b]Depa-rtment of Pharmacy Practice
[1]Chalapathi Institute of Pharmaceutical Sciences, Guntur, India.
[2]Rao's College of Pharmacy, Nellore, India.

*corresponding author: rajaneeraja@gmail.com

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Abstract: Benzimidazole is one of the most important heterocyclic compound, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. In the present study some novel benzimidazole derivatives were synthesized under green synthesis by solvent free conditions by using catalytic amount of silica supported sodium hydrogen sulphate according to the scheme. All the synthesized benzimidazole derivatives have been characterized by using elemental analysis, FT-IR, ^{1}HNMR, ^{13}C NMR spectroscopy and further supported by Mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate and HPLC technique. All the synthesized compounds were tested for their anti anxiety and neurotoxicity activities by elevated plus maze test in mice. Test compounds and diazepam was administered intraperitoneally in antianxiety study at dose of 2 mg/kg. Compounds BZ-6 & BZ-7 showed highest antianxiety activity compared to diazepam and did not show neurotoxicity in rotarod test. All the compounds exhibited moderate to significant antianxiety activity.

INTRODUCTION:

Heterocyclic compound is one which possesses a cyclic structure with at least two different kinds of hetero atoms in the ring. Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways. benzimidazole is a heterocyclic compound, is made from imidazole ring fused with benzene ring, having various biological activities and still of great scientific interest now a days. Benzimidazole compounds and their derivatives were found to numerous pharmacological activities like antitumor (Nofal ZM *et al,* 2011), anticonvulsant (Bhanupriya Bhrigu *et al,* 2012), antimicrobial (Fatmah A. S. Alasmary *et al,* 2015), anthelmintic (Srikanth Lingala *et al,* 2011), anti-tubercular (Zhang HY, *et al,* 2014), schictosomicidal (Ríos N *et al.* 2013), antifungal (S. Khabnadideh *et al,* 2012), anti-inflammatory (Rajasekaran S *et al,* 2014), analgesic (Shobhit Srivastava *et al,* 2010), antioxidant (Subbegowda Rangappa *et al,* 2015) and anti-diabetic activities (Ramanatham Vinodkumar *et al,* 2008). The present research work focuses on the synthesis of newer benzimidazole derivatives under green synthesis by solvent free conditions by using catalytic amount of silica supported sodium hydrogen sulphate with potential activities that are now in development.

EXPERIMENTAL:

Material and Methods:

All the chemicals used were of laboratory grade and procured from E.Merck and S.D. Fine Chemicals (NSP, Guntur).The thin layer chromatography (TLC) was performed either using the Merck precoated TLC plates or on ACME's silica gel with 13% calcium sulphate ($CaSO_4$) as binder and the components were visualized under iodine chamber or by UV exposure or by the potassium permanganate ($KMnO_4$) spray technique. Flash column chromatography was performed using Merck silica gel (100-200 mesh). The chemicals and solvents were purchased from commercial suppliers either from Aldrich, Spectrochem, and Sisco research laboratories (SRL), Mumbai and they were used without purification prior to use. Melting points were determined in digital melting point apparatus and are uncorrected. All compounds were purified by recrystallization with suitable organic solvents. All the microwave experiments were performed using RAGA's microwave synthesizer. IR spectra were recorded on BROOKER-ALPHA FT-IR instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR was determined in $CDCl_3$ solution on a BRUKER Ac 400 MHz spectrometer. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Purity of the synthesized

compounds was checked by HPLC AGILENT. The results are in agreements with the structures assigned. All chemicals were reagent grade and used without further purification, and all solvents were freshly distilled before use.

Preparation of silica supported sodium hydrogen sulphate:
To a solution of 4.14 gm (0.03 mol) of $NaHSO_4.H_2O$ in 20 ml of water in a 100 ml beaker containing a stir bar was added 10 gm of SiO_2 (column chromatographic grade, 230-400 mesh). The mixture was stirred for 15 min and then gently heated on a hot plate, with intermittent swirling, until a free-flowing white solid was obtained. The catalyst was further dried by placing the beaker in an oven maintained at 120 ^{0}C for at least 48 h prior to use. The synthesized catalyst was characterized by FT-IR spectrum (Raju et al., 2016).

FT-IR spectrum of $NaHSO_4$-SiO_2
The catalyst is solid and its solid state IR spectrum was recorded using the KBr disc technique. For silica (SiO_2), the major peaks are broad antisymmetric Si-O-Si stretching from 1000-1100 cm^{-1} and symmetric Si-O-Si stretching near 798 cm^{-1}, bending modes of Si-O-Si lie around 467 cm^{-1}. The spectrum also shows a broad Si-OH stretching absorption from 3300-3500 cm^{-1}.

General procedure for the synthesis of benzimidazole derivatives (BZ-1 to BZ-10): A mixture of *o*-phenylene diamine (1 m.mol) and aldehyde(1 m.mol) were placed in a sealed vessel containing $NaHSO_4$-SiO_2 (25%/wt) in ethanol (5ml) were placed in 50 ml round bottom flask and stirred at reflux for 8hr. The progress of the reaction was monitored by TLC hexane: ethyl acetate (4:1). After completion of the reaction, the reaction mixture was cooled and diluted with ethylacetate and the catalyst was removed by filtration. The obtained filtrate was evaporated under reduced pressure to get the crude product and purified by column chromatography to give newer benzimidazole derivatives (BZ-1 to BZ-10).

2-Phenyl-1H-benzo[d]imidazole (BZ-1): Yield: 92%, Off white solid; M.P: 289-291 ^{0}C; ^{1}H NMR (DMSO-d_6): δ 13.02 (br s, 1H), 8.20 (d, J=7.6 Hz, 2H), 7.67-7.65 (m, 1H), 7.56-7.49 (m, 4H), 7.22-7.18 (m, 2H); (LC-MS) m/z: 195.08 $[M+H]^+$; IR (KBr, cm^{-1}): 3420, 2920, 2627, 1623, 1410, 1276, 1119, 970, 738. Anal.Calcd. For $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.11; H, 5.01; N, 14.38.

2-*o*-Tolyl-1H-benzo[d]imidazole (BZ-2): Yield: 87%, Colour less solid; M.P: 220-222 ^{0}C; ^{1}H NMR (DMSO-d_6): δ 13.03 (br s, 1H), 7.82-7.79 (m, 3H), 7.60-7.58 (m, 1H), 7.56-7.45 (m, 4H), 2.58 (s, 3H); (LC-MS) m/z: 209.10 $[M+H]^+$; Anal. Calcd. For$C_{14}H_{12}N_2$: C, 82.39; H, 5.39; N, 14.42. Found: C, 82.11; H, 5.31; N, 14.40

2-p-Tolyl-1H-benzo[d]imidazole (BZ-3): Yield: 93%, Colourless solid; M.P: 265-267 ^{0}C; ^{1}H NMR (DMSO-d_6): δ 12.81 (br s, 1H), 8.06 (d, J=8 Hz, 2H), 7.56 (m, 2H), 7.36 (d, J =8 Hz, 2H), 7.19 (m, 2H), 2.38 (s, 3H); (LC-MS) m/z: 209.10 $[M+H]^+$;Anal.Calcd. For $C_{14}H_{12}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.11; H, 5.01; N, 14.38.

2-(2-Methoxyphenyl)-1H-benzo[d]imidazole (BZ-4): Yield: 86%, Colourless solid; M.P: 173-175 ^{0}C; ^{1}H NMR (DMSO-d_6): δ13.5 (br s, 1H), 8.29 (d, J =7.2 Hz, 1H), 7.76-7.74 (m, 2H), 7.63-7.59 (m, 1H), 7.39-7.32 (m, 3H), 7.22-7.18 (m, 1H), 4.06 (s, 3H); (LC-MS) m/z: 225.07 $[M+H]^+$.Anal.Calcd. For $C_{14}H_{12}N_2O$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.11; H, 5.01; N, 14.38.

2-(4-Methoxyphenyl)-1H-benzo[d]imidazole (BZ-5): Yield: 91%, Colourless solid; M.P: 218-220^{0}C; 1H NMR (DMSO-d_6): δ12.90 (br s, 1H), 8.21 (d, J=8.4 Hz, 2H), 7.70-7.68 (m, 2H), 7.38-7.36 (m, 2H), 7.21 (d, J=8.8 Hz, 2H), 3.88 (s, 3H); (LC-MS) m/z: 225.07 $[M+H]^+$. Anal.Calcd. For $C_{14}H_{12}N_2O$: C, 81.39; H, 5.15; N, 14.32. Found: C, 80.11; H, 5.10; N, 14.36.

2-(2-Chlorophenyl)-1H-benzo[d]imidazole (BZ-6): Yield: 88%, Light pink red solid; M.P: 231-233 ^{0}C; ^{1}H NMR (DMSO-d_6): δ12.80 (br s, 1H), 7.91-.89 (m, 1H), 7.67-7.62 (m, 3H), 7.57-7.52 (m, 2H), 7.25-7.23 (m, 2H); (LCMS) m/z: 229.04 $[M+H]^+$.Anal.Calcd. For$C_{13}H_9ClN_2$;C, 82.30; H, 5.25; N, 14.30. Found: C, 82.21; H, 5.15; N, 14.32.

2-(3-Chlorophenyl)-1H-benzo[d]imidazole (BZ-7): Yield: 87%, Colourless solid; M.P: 234-236 ^{0}C; ^{1}H NMR (DMSO-d_6): δ13.06 (br s, 1H), 8.40 (s, 1H), 8.27 (d, J= 6.8 Hz, 1H), 7.81-7.72 (m, 4H), 7.49-7.47 (m, 2H); (LCMS) m/z: 229.04 $[M+H]^+$. Anal.Calcd. For$C_{13}H_9ClN_2$;C, 81.30; H, 5.25; N, 14.30. Found: C, 81.21; H, 5.20; N, 14.28.

2-Benzyl-1H-benzo[d]imidazole (BZ-8): Yield: 90%, Off white solid, M.P: 177-179 ^{0}C; ^{1}H NMR (DMSO-d_6): δ13.0 (br s, 1H), 7.52-7.50 (m, 2H), 7.34-7.16 (m, 7H), 4.21 (s, 2H); (LC-MS) m/z: 209.10 $[M+H]^+$. Anal.Calcd. For $C_{14}H_{12}N_2$; C, 82.39; H, 5.39; N, 14.42. Found: C, 82.11; H, 5.31; N, 14.40

2-Heptyl-1H-benzo[d]imidazole (BZ-9): Yield: 89%, Off white solid; M.P: 146-147 ^{0}C; ^{1}H NMR (DMSO-d_6): δ12.11 (br s, 1H), 7.49 (d, J=8 Hz, 1H), 7.38 (d, J= 6.4 Hz, 1H), 7.09-7.12 (m, 2H), 2.78 (t, J= 7.6 Hz, 2H), 1.77-1.73 (m, 2H), 1.31-1.25 (m, 8H), 0.85 (t, J=6.4 Hz, 3H); ^{13}C NMR

(DMSO-d_6): δ13.90, 22.06, 27.57, 28.40, 28.52, 28.64, 31.15, 110.50, 117.78, 120.97, 143.15, 155.12; (LC-MS) m/z: 217.21 [M+H]+; IR (KBr, cm-1): 3467, 2926, 2738,1624, 1451, 1272, 1028, 750. Anal.Calcd. For $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.70; H, 9.28; N, 12.86.

2-Heptyl-5-methyl-1H-benzo[d]imidazole (BZ-10): Yield: 88%, Light brown colour solid; M.P: 88-89 ^{0}C; ^{1}H NMR (DMSO-d_6): δ11.98 (br s, 1H), 7.36-7.18 (m, 2H), 6.93-6.89 (m, 1H), 2.74 (t, J=7.6 Hz, 2H), 2.37 (s, 3H), 1.78-1.70 (m, 2H), 1.30-1.21 (m, 8H), 0.85 (t, J=6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 13.88, 21.19, 22.05, 27.61, 28.40, 28.53, 28.64, 31.15, 113.87, 122.28, 129.92, 154.75; (LC-MS) m/z: 231.18 $[M+H]^+$; IR (KBr, cm^{-1}): 2946, 2763, 1861, 1448, 1281, 1030, 803. Anal.Calcd. For $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.19; H, 9.58; N, 12.15.

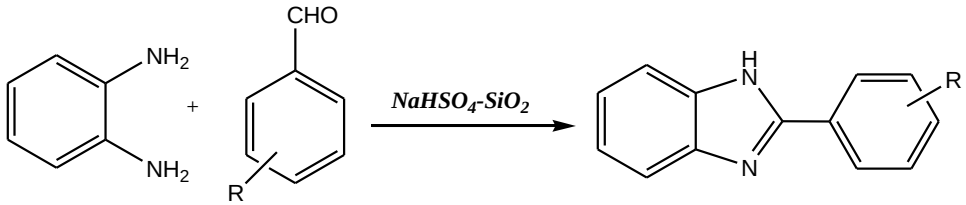
BIOLOGICAL EVALUATION:

ANTIANXIETY ACTIVITY (Elevated plus maze test in mice):

Swiss albino mice, weighing 20–24 g each, were selected from the stock colony maintained in our animal facility with free access to food and water. Animals were maintained in an air-conditioned room. The room was maintained at 25 ± 2 ^{0}C with natural day time. Concentration of each compound (10 mg/kg) was used in the form of freshly prepared suspensions in 1% tween 80. All solutions were prepared freshly on test days and given intraperitoneally (ip) in a volume of 2 ml/kg body weight of mice. The experimental animals were treated with Diazepam (2 mg/ kg, n = 6), or the test compounds (10 mg/kg) 60 min before evaluation in the maze. The control group was given saline with 1% tween 80. Plus maze for mice consisted of two open (16 × 5 cm^2) and two closed arms (16 × 5 × 12 cm^3) facing each other with an open roof. The entire maze is elevated a height of 25 cm. In the test, mice were individually examined in 5 min sessions in this apparatus. Each mouse was placed in the central platform facing one open arm. The numbers of entries into open and closed arms and the time spent in the respective arms were recorded during a 5-min period. The percentage of time spent in the open arms [(open/open + closed) × 100] was calculated for each mice. The results of EPM have been summarized in Table 2.

NEUROTOXICITY:

The rotarod test was used to evaluate neurotoxicity. The mice were trained to stay on a 1 inch diameter knurled wooden rod rotating at 6 rpm for 1 min. The animal was placed on rotating at 6 rpm. The trained animals were injected intraperitoneally with the test compounds BT-6 at doses of 50 mg/kg, 30 min prior to the test session. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rotating rod and results are reported as duration for which the animal is able to balance on the moving rod (i.e. till the animal falls) is noted as coordination time (mean±S.E.M). Results of *in vitro* inhibition activity and neurotoxicity shown in given Table 3.



Scheme 1: Synthesis of benzimidazole derivatives (BZ-1 to BZ-10)

Table 1: Physical data of benzothiazole derivatives (BT-1 to BT-10)

Comp	Name	M.F	M.W	M.P (^{0}C)	Yield (%)
BZ-1	2-Phenyl-1H-benzo[d]imidazole	$C_{13}H_{10}N_2$	194.23	289-290	92
BZ-2	2-o-Tolyl-1H-benzo[d]imidazole	$C_{14}H_{12}N_2$	208.26	220-221	87
BZ-3	2-p-Tolyl-1H-benzo[d]imidazole	$C_{14}H_{12}N_2$	208.26	265-266	93
BZ-4	2-(2-Methoxyphenyl)-1H-benzo[d]imidazole	$C_{14}H_{12}N_2O$	224.26	173-175	86
BZ-5	2-(4-Methoxyphenyl)-1H-benzo[d]imidazole	$C_{14}H_{12}N_2O$	224.26	218-220	91
BZ-6	2-(2-Chlorophenyl)-1H-benzo[d]imidazole	$C_{13}H_9ClN_2$	228.68	231-232	88
BZ-7	2-(3-Chlorophenyl)-1H-benzo[d]imidazole	$C_{13}H_9ClN_2$	228.68	234-236	87
BZ-8	2-Benzyl-1H-benzo[d]imidazole	$C_{14}H_{12}N_2$	208.26	177-179	90
BZ-9	2-Heptyl-1H-benzo[d]imidazole	$C_{14}H_{20}N_2$	216.32	146-147	89
BZ-10	2-Heptyl-5-methyl-1H-benzo[d]imidazole	$C_{15}H_{22}N_2$	230.35	88-89	88

Table 2: Results of anti-anxiety activity of compounds (BZ-1 to BZ-10) by Elevated plus maze test in mice

Comp	% preference to open arm	Open arm	
		No. of entries (mean ± SEM)	Average time spent (mean ± SEM)
BT-1	10.28	5.83±0.16	26.50±2.21**
BT-2	7.61	4.83±0.30	19.16±1.16
BT-3	11.97	6.33±0.33	29.16±1.40**
BT-4	19.61	7.33±0.49*	47.66±2.21**
BT-5	7.14	4.33±0.21	18.00±1.15
BT-6	20.44	7.50±0.22**	48.83±1.99**
BT-7	20.54	7.52±012**	49.91±1.88**
BT-8	6.84	4.83±0.30	18.33±1.16
BT-9	17.81	6.33±0.33	42.50±2.01**
BT-10	10.03	5.33±0.21	25.16±1.74**
Control	6.09	5.16±0.16	16.16±1.42
Diazepam	21.34	8.50±0.34**	54.33±2.60**

*Values represent the mean ±SEM (n = 6); p < 0.05, ** p < 0.01 (Dunnet's test compared to control)*

Table 3: Results of *in vitro* inhibition activity and neurotoxicity study of selected benzothizole derivatives.

S.No	Compound	Neurotoxicity Coordination time in sec.[c] (mean ± SEM)	Monoamine oxidase inhibition[a] (%)
1	BZ-6	56.00 ± 1.06	Not tested
2	BZ-7	58.10 ± 1.00	Not tested
3	BZ-10	Not tested	27.05
4	Tranylcypromine[b]	Not tested	84.50
	Control	58.33 ± 1.70	Not tested

[a] *Each value is the mean from three separate experiments with SE of mean. Compound BZ-10 was used at a final concentration of 5×10^{-4} M.*
[b] *Concentration of tranylcypromine used $5.0\ x10^{-4}$ M.*
[c] *Values represent the mean ±SEM (n = 6)*

RESULTS AND DISCUSSION:

A simple and practical method for the preparation of benzimidazole derivatives through the reaction of *o*-phenylenediamine and aldehydes in the presence of catalytic amount of silica supported sodium hydrogen sulphate ($NaHSO_4$-SiO_2) was developed. In the preliminarily investigation on the model reaction of *o*-phenylenediamine and benzaldehyde, it was found that the reaction could be finished under very simple reaction conditions in the presence of catalytic amount of $NaHSO_4$-SiO_2 in reflux in ethanol solvent, which gave the desired 2-phenyl benzimidazole product in good yield.

A novel protocol for the rapid synthesis of a variety of biologically significant benzimidazoles using a catalytic amount of $NaHSO_4$-SiO_2 under optimized reaction conditions. Different aldehydes and o-phenylenediamine react without any significant difference to give the corresponding benzimidazoles in good yield. When the mole ratio of *o*-phenylenediamine and aldehyde are taken in 1:1 ratio, the product benzimidazoles derivatives were obtained selectively. It indicated that silica supported sodium hydrogen sulphate catalysed reaction has a favourable selectivity for the synthesis of benzimidazoles derivatives.

A mixture of o-phenylenediamine (1 m.mol), aldehyde (1 m.mol) and $NaHSO_4$-SiO_2 (25%/wt) in ethanol (5ml) were placed in 50 ml round bottom flask and stirred at reflux for 8hrs. The progress of the reaction was monitored by TLC hexane: ethyl acetate (4:1). After completion of the reaction, the reaction mixture was cooled and diluted with ethyl acetate and the catalyst was removed by filtration. The obtained filtrate was evaporated under reduced pressure to get the crude product and purified by column chromatography to give newer benzimidazole derivatives.

Anti-anxiety activity: The antianxiety activity of the synthesized compounds was evaluated by elevated plus maze test in mice The test compounds showed antianxiety activity ranging from 6.84% to 20.44% preference to open arm, whereas diazepam showed 21.34% preference to open arm (Table 3). Among 12 compounds tested, three compounds BZ-4, BZ-6 and BZ-9 showed promising antianxiety activity (17% preference to open arm). Compounds BZ-6 & BZ-7 showed highest antianxiety activity 20.44% & 20.54% preference to open arm. Compound BZ-4 was also found to have a good antianxiety activity 19.61% preference to open arm. Compound BZ-9 exhibited good activity (17.81%). Compound BZ-7, showed moderate antianxiety activity. Other compounds did not show encouraging results. It was interesting to note that compound BZ-6 & BZ-7 possessing excellent antianxiety activity did not show significant antidepressant activity.

MAO inhibition activity: Compound showed very weak MAO inhibition (27.05%) at a final concentration of 5×10^{-4} M compared to standard drug tranylcypromine (84.50%)

CONCLUSION:

$NaHSO_4$-SiO_2 was found to be an efficient catalyst for the formation of benzimidazole derivatives from aldehydes. The use of this inexpensive, easily available and reusable catalyst makes this protocol practical, environment friendly and economically attractive. The simple work-up procedure, high yields of products and nontoxic nature of the catalyst are other advantages of the present method. Compounds BZ-6 & BZ-7 displayed excellent results when studied for antianxiety activity. Compounds BZ-6 & BZ-7 did not show any neurotoxicity in the rotarod test. Therefore, it can be concluded that compounds BZ-6 & BZ-7 would

constitute a useful model for further investigations in the development of antianxiety compounds.

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REFERENCES:

BhanupriyaBhrigu*et al,* Anticonvulsant evaluation of some newer benzimidazole derivatives: design and synthesis; ActaPoloniaePharmaceutica ñ Drug Research, Vol. 69 No. 1 pp. 53ñ62, 2012

Fatmah A. S. Alasmary*et al,* Synthesis and Evaluation of Selected Benzimidazole Derivatives as Potential Antimicrobial Agents; *Molecules* 2015, *20*.

Nofal ZM et al; Novel benzimidazole derivatives as expected anticancer agents; Acta Pol Pharm; 2011 Jul-Aug;68(4):519-34.

Raju, G. N., Prasanna, T. S. K. T., Surekha, M. K. L., Nadendla, R. R. (2016) Synthesis and Biological Screening of Benzothiazole Derivatives with Pyrazole Moiety**.** J. basic appl. Res 2(2): 133-139

Rajasekaran S *et al;* Synthesis, Anti-Inflammatory and Anti-oxidant activity of some substituted Benzimidazole Derivatives.

Ríos N et al; dentification of novel benzimidazole derivatives as anti-Trypanosoma cruzi agents: solid-phase synthesis, structure-activity relationships and molecular docking studies; Future Med Chem; 2013 Oct;5(15):1719-32.

S. Khabnadideh *et al;* Synthesis and antifungal activity of benzimidazole, benzotriazole and aminothiazole derivatives; Res Pharm Sci. 2012 Apr-Jun; 7(2): 65–72

Shobhit Srivastava et al; Synthesis and Analgesic Activity of Novel Derivatives of 1,2-Substituted Benzimidazoles; Journal of Chemistry;Volume 2013 (2013).

Srikanth Lingala et al; Synthesis, antimicrobial and anthelmintic activity of some novel benzimidazole derivatives; Der Pharma Chemica, 2011, 3 (4):344-352

SubbegowdaRangappa *et al,* Synthesis, antibacterial, antioxidant and anti-inflammatory activities of new benzimidazole derivatives; Asian Journal of Biochemical and Pharmaceutical Research Issue 4(Vol. 5) 2015.

Vinodkumar*et al,* Synthesis, anti-bacterial, anti-asthmatic and anti-diabetic activities of novel N-substituted 2-(4-styrylphenyl)-1H-benzimidazole and N- substituted-3[4-(1H-benzimidazole-2-yl)-phenyl]-acrylic acid tert-butyl ester; ARKIVOC 2008 (xiv) 37-49

Zhang HY, *et al*, Design and synthesis of novel benzimidazole derivatives as anti-tuberculosis agents; Yao XueXueBao; 2014 May;49(5):644-5