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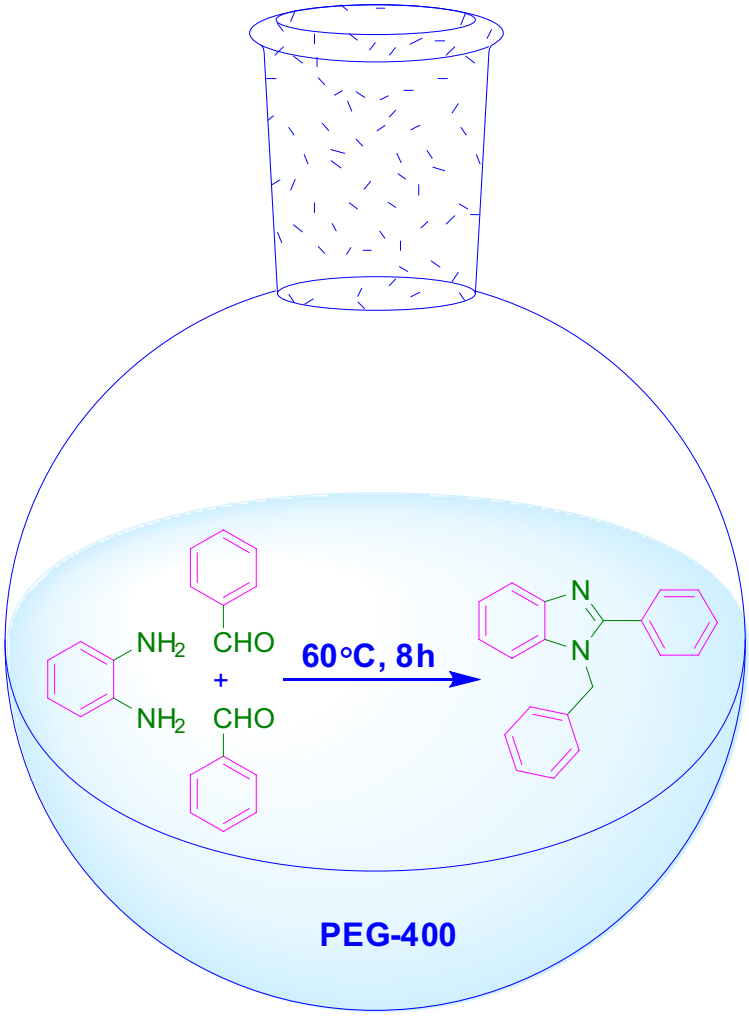

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Polyethylene glycol (PEG-400): An efficient medium for the synthesis of 1,2-disubstituted benzimidazoles

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Abstract: Polyethylene glycol (PEG-400) was found to be an inexpensive, non-toxic, and effective medium for the one-pot synthesis of 1,2-disubstituted benzimidazoles in excellent yields. Eco-friendliness, low cost, high yields, and recyclability of the PEG-400 are the important features of this protocol.

Subjects: Chemistry; Computational and Theoretical Chemistry; Medicinal & Pharmaceutical Chemistry; Organic Chemistry; Physical Sciences

Keywords: benzimidazoles; PEG-400; one-pot reaction; eco-friendly medium

1. Introduction

Benzimidazoles are very useful intermediates for the development of molecules of pharmaceutical and biological interests. Substituted benzimidazole derivatives have found applications in diverse therapeutic areas including antiulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistaminics (Kim et al., 1996; Roth et al., 1997; Spasov, Yozhitsa, Bugaeva, & Anisimova, 1999). In addition, they exhibit significant activity against several viruses, such as HIV, herpes (HSV-1), RNA influenza, and human cytomegalovirus (Migawa et al., 1998; Porcari, Devivar, Kucera, Drach, & Townsend, 1998; Tebbe et al., 1997). They have also commercial applications in veterinary medicine (Spasov et al., 1999), as important intermediates in many organic reactions (Bouwman, Driessen, & Reedijk, 1990; Hasegawa et al., 1999), and as ligands to transition metals for modeling biological systems (Pujar & Bharamgoudar, 1988; Zhu et al., 2008). In addition, the treatment potency of benzimidazoles in diseases such as

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ABOUT THE AUTHORS

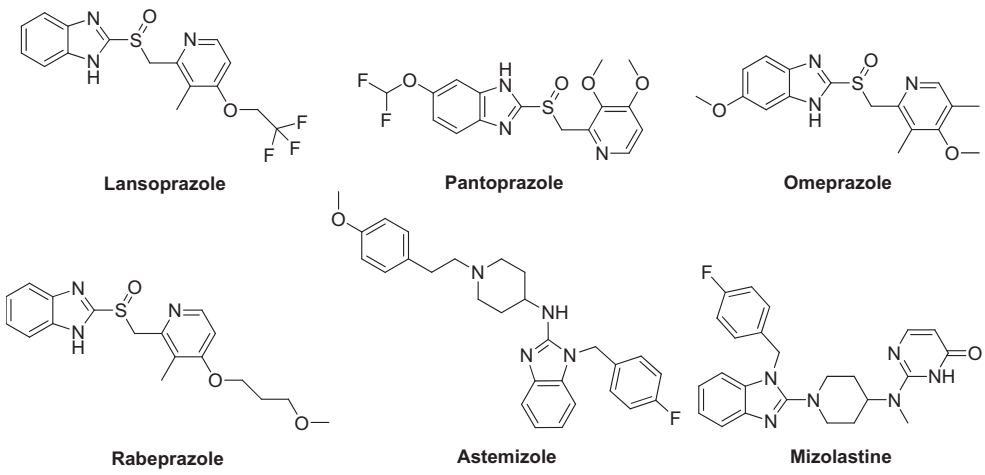
Suresh Reddy Cirandur was born on 1 June 1963 in Nagalapuram village, Chittoor District, Andhra Pradesh, India. He has been awarded PhD degree for the research work in 1990 from Sri Venkateswara University, Tirupati, Andhra Pradesh. He joined as an assistant professor, S V University, Tirupati in 1992. He was honored with "Teacher of Excellence" award in 2009 and in the same year became a professor. He published more than 250 research papers in reputed journals.

He is a principal investigator for four Major Research Projects and UGC-BSR sanctioned him "ONE TIME GRANT". He worked as a post-doctoral research fellow in Taiwan. He guided 11 MPhil and 30 PhD degrees along with 3 post-doctoral young scientists. He was a member for Environment Quality in SEAC of Ministry of Environment & Forest, India. He became an affiliate member in the Royal Society of Chemistry, the UK.

PUBLIC INTEREST STATEMENT

We have chosen polyethylene glycol (PEG-400) as an inexpensive, non-toxic, and effective medium for the one-pot synthesis of 1,2-disubstituted benzimidazoles in excellent yields. The methodology merits the eco-friendliness, cost-effective method, high yields, and recyclability of the PEG-400 as the important features of this protocol. Benzimidazole derivatives were synthesized by the reaction of o-phenylenediamine with aldehydes under uncatalyzed reaction conditions. Operational simplicity and high product yields are the advantages of this new protocol.

Figure 1. Important benzimidazole containing drugs.



ischemia–reperfusion injury (Ogino et al., 2008), hypertension (Shah, Sharma, Bansal, Bansal, & Singh, 2008), obesity (Ghosh & Mandal, 2011), etc. has been recently reported. They also proved to have fungicidal resistance (Delp, 1987, 1988). The important benzimidazole-containing drugs are given in Figure 1.

Owing to their potential biological and other technical interests, a number of synthetic strategies have been developed for their preparation (Dickerson, Reed, & Janda, 2002; Kamal & Reddy, 2005; Suryakiran, Srikanth Reddy, Ashalatha, Laxman, & Venkateswarlu, 2006). Various catalysts such as silica-supported $ZnCl_2$ (Jacob et al., 2009), $LnCl_3$, YCl_3 (Li-Jun, Jing, Yong-Qing, Hua, & Shao-Wu, 2012), SBA-15-Supported Poly(4-styrenesulfonyl (perfluorobutylsulfonyl)imide) (Zhong, Sheng, & Jin, 2012), $(CH_2)_4SO_3HMIM][HSO_4]$, a Bronsted Acid Ionic Liquid (Yahya et al., 2010), Thiamine Hydrochloride (Min, Lei, & Lihong, 2012), and Amberlite IR-120 (Mohamed & Aatika, 2012) were engaged for the facile synthesis of benzimidazoles.

In recent years, PEG emerged as a powerful phase-transfer catalyst that performs many useful organic transformations under mild reaction conditions. Moreover, PEG is inexpensive, easy to handle, thermally stable, non-toxic, and recyclable media. Thus, PEG-400 has emerged as an efficient catalyst for various chemical transformations (Chhanda & Tapaswi, 2008; Nagaraju et al., 2015; Nagarapu, Raghu, & Lingappa, 2010; Upendra et al., 2012; Xiaokang, Tangjun, Yu, & Junmin, 2014). We report the synthesis of biologically active benzimidazole derivatives under catalyst-free conditions using PEG-400 as an eco-friendly and recyclable reaction medium.

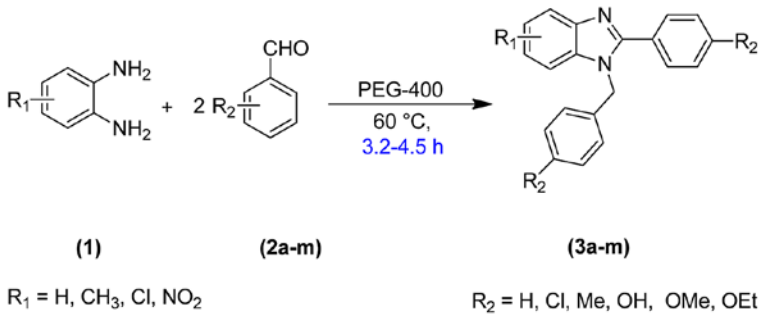
We studied the PEG-400-mediated synthesis of 3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-ones (Raghu, Rajasekhar, Reddy, Reddy, & Reddy, 2013), alkyl phosphonates (Mohan Naidu et al., 2011), α-aminophosphonates (Rao, Jayaprakash, Nayak, & Reddy, 2011), α-aminonitriles (Kumar, Babu, Srinivasulu, Kiran, & Reddy, 2007), and its modified catalytic action in the form of PEG-SO_3H for the synthesis of α-aminophosphonates (Reddy et al., 2012) has driven us to explore its application for the study of some other organic compounds. In this hierarchy, we studied the PEG-400-mediated synthesis of 1,2-disubstituted benzimidazoles and accomplished them with good yields.

2. Results and discussion

An efficient and environmentally benign approach was developed for the synthesis of benzimidazole derivatives **(3a–m)** by reaction of two mol of aldehydes with one mole of substituted benzene 1,2-diamines using PEG-400 as a reaction medium under catalyst-free conditions at 60°C (Scheme 1).

In order to establish the standard operating conditions, the reaction between benzaldehyde with benzene 1,2-diamine was selected as a model reaction. The model reaction is carried out using

Scheme 1. Synthesis of 1,2-disubstituted benzimidazoles.



(1) **(2a-m)** **(3a-m)**

R_1 = H, CH_3, Cl, NO_2

R_2 = H, Cl, Me, OH, OMe, OEt

PEG-400 as a catalyst at room temperature or 30°C, but there is no sufficient quantity formation of the corresponding benzimidazole derivatives (Table 1, entry 7). Increasing the reaction temperature from 30 to 60°C led to the formation of benzimidazole derivatives up to 86% yield (Table 1, entry 10). Further increase of temperature did not show any improvement in the yields (Table 1, entry 11, 12). In order to compare the rate of the reaction in PEG-400, we carried out the reaction in different solvents (Table 1). It was observed that among the tested solvents, the reaction in PEG-400 was more facile and proceeded to give good yield (86%) when the reaction mixture was stirred at 60°C for 4 h (Table 1, entry 10). Examination of the recyclability of the PEG-400 showed that it can be reused three times without loss of activity (Table 1, entry 10). Moreover, there are many potential advantages of replacing these volatile or toxic organic solvents with PEG-400. Thus, it was established that the reaction carried out in PEG-400 at 60°C was effective for the completion of this reaction, with the above-mentioned parameters being the optimized conditions.

After optimization of the experimental conditions, we extended our studies to various aromatic aldehydes with substituted benzene 1,2-diamines under optimized conditions. In all the cases, reactions were completed within 4.5 h and afforded good to excellent yields (Table 2). Orthophenyldiamine, bearing electron-withdrawing groups (Cl and NO_2) at the *para* position, afforded the desired products in quantitatively high yields. Aromatic aldehydes having both electron-withdrawing and electron-donating groups have no significant effect. Aromatic aldehydes having donating groups require less reaction time when compared to those electron-withdrawing substrates. Results show that the substituents did not play a significant role in governing the overall reaction's reactivity of the substrates and product yields.

Table 1. Optimization of reaction conditions for synthesis of 3a

Entry	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	MeOH	60	24	47
2	EtOH	60	24	44
3	Toluene	80	24	38
4	THF	60	24	41
5	DMF	100	24	33
6	Water	80	24	–
7	PEG-400	rt/30	6	54
8	PEG-400	40	6	70
9	PEG-400	50	4	77
10	PEG-400[b]	60	4	86, 86, 85
11	PEG-400	70	4	86
12	PEG-400	80	4	85

Note: rt denotes room temperature.

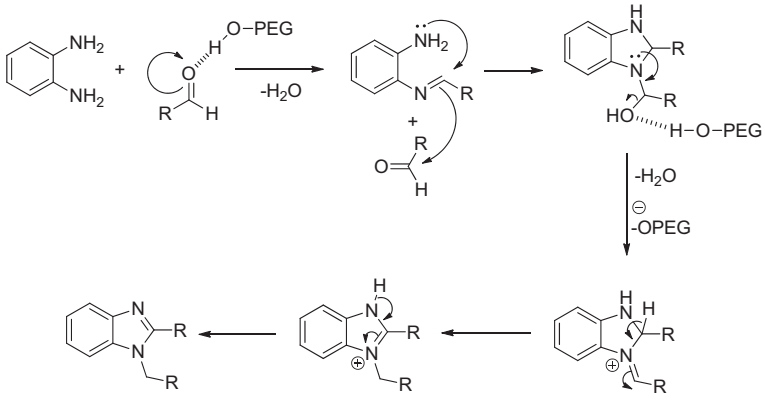
[a]Isolated yields.

[b]Yields with recyclized catalyst.

Table 2. Synthesis of 1,2-disubstituted benzimidazoles

Entry	R_1	R_2	Time (h)	Yield (%)	mp (°C)
3a	H	H	4.0	86	135–137
3b	H	4-OC_2H_5	4.2	85	157–159
3c	H	2-OH	4.2	83	144–146
3d	H	4-CH_3	4.3	82	131–133
3e	3-CH_3	H	3.5	86	159–161
3f	4-Cl	4-CH_3	3.5	85	138–140
3g	4-Cl	4-OCH_3	3.5	87	169–171
3h	4-Cl	H	3.5	86	148–150
3i	4-Cl	4-Cl	3.8	85	133–135
3j	4-NO_2	H	3.6	86	175–177
3k	4-NO_2	4-OC_2H_5	3.5	86	158–160
3l	4-NO_2	4-Cl	3.2	88	187–189
3m	4-NO_2	4-CH_3	3.5	85	129–131

Scheme 2. Mechanism for the PEG-mediated synthesis of benzimidazoles.



The chemical structures of all the products were characterized by their analytical and spectral (IR, ^{1}H NMR, ^{13}C NMR, ESIMS, and HRMS) data.

This reaction is facilitated by the nucleophilic attack of the phenylenediamine on the carbonyl carbon in which the electrophilicity of the carbonyl carbon has been enhanced in the PEG-400 medium rather than the other solvents, and hence accelerates the reaction by removing the liberated water, which is soluble in the PEG-400 and enables its conversion to the corresponding benzimidazole (Scheme 2).

3. Conclusion

In conclusion, we have developed an efficient and facile eco-friendly method for the synthesis of benzimidazole derivatives by the reaction of *o*-phenylenediamine with aldehydes using PEG-400 as a recyclable reaction medium without the addition of any catalyst or organic co-solvent. The mild reaction conditions, less expensive and recyclable reaction medium, operational simplicity, and high product yields are the advantages of this new protocol.

4. Experimental

All the chemicals were purchased from Aldrich and used without further purification. IR spectra were recorded on a Perkin-Elmer 683 Spectrophotometer using KBr optics. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker AMX 300 MHz NMR spectrometer in DMSO-d_6 using TMS as an internal

standard. ESI mass spectra were recorded on a Micromass Quattro LC instrument. Elemental analyses of the synthesized compounds were performed using EA 1112 Thermo Finnigan, France, instrument at University of Hyderabad, Hyderabad, India.

4.1. General procedure for the synthesis of benzimidazole derivative (3a)

A mixture of *o*-phenylenediamine and benzaldehyde in 1:2 M ratio was taken in 5 ml of polyethylene glycol (PEG-400) and stirred at 60°C for appropriate time. After completion of reaction (TLC), the reaction mixture was cooled and poured in ice cold water. The obtained solid product was filtered and washed with water and recrystallized by ethanol to give pure product **3a**. PEG-400 was recovered from water by direct distillation and reused for second run by charging the same substrates (Table 1, entry 10). The above procedure was adopted for the synthesis of the remaining title compounds (**3b–m**). All the synthesized compounds were obtained in yellow color.

4.2. Spectral data

4.2.1. 1-benzyl-2-phenyl-1H-benzo[d]imidazole (3a)

^{1}H NMR (300 MHz, DMSO-d_6): δ 5.43 (s, 2H), 7.08 (d, 2H Ar), 7.12–7.48 (m, 6H), 7.64 (d, 2H), 7.88 (d, 2H), 8.09 (d, 2H): ^{13}C NMR (75 MHz, DMSO-d_6): 47.4, 110.5, 114.9, 119.1, 121.5, 122.5, 123.4,123.8, 127.5, 127.9, 128.2, 128.8, 130.2, 130.8, 136.5, 136.9, 142.2, 154.2, 158.5, 160.8; IR (KBr): 3230, 3058, 2923, 1895, 1671, 1599, 1445, 1393, 1360, 1322, 1280, 1168, 1116, 1070, 1026, 994, 928, 738, 773; MS (ESI): m/e 285 $(M + H)^+$. HRMS m/z calc for $C_{20}H_{17}N_2$ 285.1388; found 285.1391.

4.2.2. 1-(4-ethoxybenzyl)-2-(4-ethoxyphenyl)-1H- benzo[d]imidazole (3b)

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.10–1.54 (m, 6H), 3.99–4.49 (m, 4H), 6.89–6.94 (m, 4H), 7.24–7.34 (m, 4H), 7.56–7.59 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): 14.2, 14.5, 47.8, 63.5, 114.8, 115.2, 119.5, 121.4, 122.6, 123.5, 123.9, 127.1, 128.2, 128.8, 129.1, 129.8, 130.2, 136.5, 143.8, 147.5, 151.6, 153.8, 158.8, 160.7; IR (KBr): 3429, 2922, 2853, 2854, 1672, 1615, 1585, 1548, 1498, 1428, 1396, 1368, 1314, 1270, 1222, 1180, 1112, 1015, 960, 871, 818, 741; MS (ESI): m/e 373 $(M + H)^+$. HRMS m/z calc for $C_{24}H_{25}N_2O_2$ 373.1931; found 373.1916.

4.2.3. 2-(1-(2-hydroxybenzyl)-1H-benzo[d]imidazol-2-yl)phenol (3c)

^{1}H NMR (300 MHz, DMSO-d_6): δ 5.69 (s, 2H), 7.24–7.34(m, 6H), 7.54–7.58, (m, 8H); ^{13}C NMR (75 MHz, DMSO-d_6): 43.8, 114.5, 115.4, 119.5, 121.1, 122.5, 123.6, 123.9, 127.1, 128.5, 128.9, 129.1, 129.8, 130.2, 136.3, 143.4, 147.8, 151.7, 153.8, 158.5; IR (KBr): 3328, 2821, 2753, 2754, 1688,1678,1565, 1545, 1466, 1445, 1378, 1366, 1333, 1265, 1232, 1187, 1176, 1012, 965, 861, 824, 745; MS (ESI): m/e 317 $(M + H)^+$, HRMS m/z calc for $C_{20}H_{17}N_2O_2$ 317.1293; found 317.1290.

4.2.4. 1-(4-methylbenzyl)-2-p-tolyl-1H-benzo[d]imidazole (3d)

^{1}H NMR (300 MHz, DMSO-d_6): δ 2.13 (s, 6H), 5.38 (s, 2H), 6.96–6.95 (d, 2H) 7.06–7.30 (m, 4H), 7.82 (d, 2H), 7.89 (d, 2H),7.96 (d, 2H); ^{13}C NMR (75 MHz, DMSO-d_6); 20.2, 20.5, 51.8, 113.4, 125.6, 125.8, 126.8, 126.7, 127.2, 127.4, 128.7, 128.9, 129.5, 129.8, 130.5, 131.2, 131.7, 138.5, 139.9, 148.2, 149.5, 151.5; IR (KBr): 3429, 2922, 2853, 2854, 1672, 1615, 1585, 1548, 1498, 1428, 1396, 1368, 1314, 1270, 1222, 1180, 1112, 1015, 960, 871, 818, 741; MS (ESI): m/e 313 $(M + H)^+$. HRMS m/z calc for $C_{22}H_{21}N_2$ 313.1263; found 313.1268.

4.2.5. 1-benzyl-4-methyl-2-phenyl-1H-benzo[d]imidazole (3e)

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.99(s, 3H), 5.35 (s, 2H), 7.29–7.31 (m, 6H), 7.59–5.61 (m, 7H); ^{13}C NMR (75 MHz, DMSO-d_6): 16.5, 51.5, 108.4, 122.2, 122.7, 123.2, 123.8, 124.1, 125.5, 126.7, 127.7, 128.2, 128.5, 137.1, 137.5, 138.2, 138.7, 139.5, 139.8, 140.5, 151.6; IR (KBr): 3416, 3028, 2923, 2856, 1965, 1599, 1527, 1449, 1393, 1365, 1324, 1276, 1170, 1118, 1068, 1028, 850, 804, 773; MS (ESI): m/e 299 $(M + H)^+$. HRMS m/z calc for $C_{21}H_{19}N_2$ 299.1263; found 299.1268.

4.2.6. 6-chloro-1-(4-methylbenzyl)-2-p-tolyl-1H-benzo[d]imidazole **(3f)**
^{1}H NMR (300 MHz, DMSO-d_6): δ 2.43 (s, 6H), 5.69 (s, 2H), 7.86–7.94 (m, 3H), 7.97–7.99 (m, 4H), 8.20–8.35 (m, 2H), 8.45–8.52 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 20.4, 20.9, 51.2, 11305,114.2, 114.4, 114.8, 115.5, 115.9, 116.2, 117.4, 125.2, 125.8, 126.2, 126.6, 127.4, 127.8, 128.5, 128.6, 138.8, 139.4, 151.7; IR (KBr): 3317, 3055, 2954, 2756, 1944, 1588, 1533, 1453, 1387, 1365, 1324, 1277, 1199, 1108, 1089, 1044, 850, 804, 775; MS (ESI): m/e 347 (M + H)$^+$. HRMS m/z calc for $C_{22}H_{21}N_2$ 347.1263; found 347.1268.

4.2.7. 6-chloro-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-1H benzo[d] imidazole **(3g)**
^{1}H NMR (300 MHz, DMSO-d_6): δ 3.82 (s, 6H), 5.35 (s, 2H), 6.79–6.84 (d, 2H), 6.91–7.00 (m, 4H), 7.25–7.35 (d, 2H), 7.45–7.49 (d, 2H), 8.10 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): 48.5, 56.3, 114.1, 114.5, 115.3, 115.8, 122.1, 122.4, 127.5, 127.8, 128.2, 128.6, 129.4, 129.7, 130.1, 130.5, 135.2, 135.4, 140.5, 153.6, 158.7, 161.1; IR (KBr): 3466, 3033, 2883, 2856, 1945, 1545, 1534, 1457, 1387, 1375, 1334, 1276, 1160, 1112, 1048, 1028, 855, 805, 763; MS (ESI): m/e 379 (M + H)$^+$. HRMS m/z calc for $C_{22}H_{20}ClN_2O_2$ 379.1568; found 379.1598.

4.2.8. 1-benzyl-6-chloro-2-phenyl-1H-benzo[d]imidazole **(3h)**
^{1}H NMR (300 MHz, DMSO-d_6): δ 5.49 (s, 2H), 6.98–7.10 (d, 2H), 7.11–7.60 (m, 6H), 7.61–7.75 (d, 2H), 7.87 (s, 1H), 7.93–8.01 (d, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 48.2, 113.2, 115.1, 116.7, 124.5, 124.9, 125.1, 125.5, 126.2, 127.5, 127.9, 128.1, 128.5, 129.2, 129.8, 138.2, 138.8, 139.4, 139.9, 151.4; IR (KBr): 3315, 3068, 2933, 2922, 1988, 1593, 1555, 1465, 1355, 1323, 1311, 1276, 1160, 1166, 1067, 1045, 855, 824, 763; MS (ESI): m/e 319 (M + H)$^+$. HRMS m/z calc for $C_{20}H_{15}ClN_2$ 319.1353; found 313.1366.

4.2.9. 6-chloro-1-(4-chlorobenzyl)-2-(4-chlorophenyl)-1H-benzo[d] imidazole **(3i)**
^{1}H NMR (300 MHz, DMSO-d_6): δ 5.74 (s, 2H), 7.13–7.15 (d, 4H), 7.35–7.36 (d, 3H), 7.58–7.59 (d, 2H), 8.12–8.14 (d, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 50.1, 115.5, 116.9, 124.7, 125.4, 126.5, 127.2, 127.5, 128.2, 128.5, 129.1, 129.6, 130.1, 130.5, 131.3, 131.8, 134.5, 134.8, 141.7, 151.8; IR (KBr): 3336, 3055, 2966, 2866, 1975, 1569, 1522, 1453, 1376, 1335, 1324, 1276, 1130, 1154, 1066, 1018, 854, 802, 753; MS (ESI): m/e 388 (M + H)$^+$. HRMS m/z calc for $C_{20}H_{13}Cl_3N_2$ 388.1546; found 388.1548.

4.2.10. 1-benzyl-6-nitro-2-phenyl-1H-benzo[d]imidazole **(3j)**
^{1}H NMR (300 MHz, DMSO-d_6): δ 5.78 (s, 2H), 7.24–7.34 (m, 6H), 7.65–7.68 (d, 2H) 8.24–8.26 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6): 51.4, 107.5, 118.7, 125.1, 125.5, 126.5, 127.8, 128.8, 129.1, 130.5, 131.0, 135.5, 135.9, 136.4, 137.6, 137.9, 141.2, 144.0, 147.1, 151.5; IR (KBr): 3376, 3053, 2955, 2845, 1999, 1555, 1534, 1465, 1376, 1345, 1323, 1266, 1178, 1108, 1008, 859, 806, 772; MS (ESI): m/e 330 (M + H)$^+$. HRMS m/z calc for $C_{20}H_{15}N_3O_2$ 330.1266; found 330.1268.

4.2.11. 1-(4-ethoxybenzyl)-2-(4-ethoxyphenyl)-6-nitro-1H-benzo[d] imidazole **(3k)**
^{1}H NMR (300 MHz, DMSO-d_6): δ 1.30–1.34 (t, 6H), 3.99–4.49 (q, 4H), 5.78 (s, 2H), 6.89–6.94 (d, 4H), 7.24–7.34 (m, 4H), 7.97–7.98 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): 15.4, 52.2, 112.7, 112.9, 114.1, 115.2, 116.5, 118.5, 118.1, 122.7, 128.6, 128.9, 129.1, 129.5, 135.2, 135.4, 136.5, 136.7, 137.2, 144.5, 148.6, 149.0, 151.2, 152.5; IR (KBr): 3386, 3074, 2863, 2813, 1905, 1569, 1545, 1443, 1354, 1334, 1313, 1246, 1198, 1168, 1045, 1009, 845, 823, 715; MS (ESI): m/e 418 (M + H)$^+$. HRMS m/z calc for $C_{24}H_{23}N_3O_3$ 418.1366; found 418.1368.

4.2.12. 1-(4-chlorobenzyl)-2-(4-chlorophenyl)-6-nitro-1H-benzo[d] imidazole **(3l)**
^{1}H NMR (300 MHz, DMSO-d_6): δ 5.60 (s, 2H), 7.15–7.18 (d, 2H), 7.25–7.28 (d, 2H), 7.38–7.55(d, 2H), 7.77–8.01(m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6): 51.2, 107.5, 115.6, 116.3, 116.7, 118.2, 128.1, 128.5, 129.2, 129.6, 131.1, 131.2, 135.3, 135.5, 144.5, 145.6, 146.8, 148.2, 148.5, 151.2; IR (KBr): 3485, 3376, 2921, 1599, 1490, 1341, 1151, 1093, 976, 896, 871, 819; MS (ESI): m/e 398 (M + H)$^+$. HRMS m/z calc for $C_{20}H_{13}Cl_2N_3O_2$ 398.1553; found 398.1588.

4.2.13. 1-(4-methylbenzyl)-6-nitro-2-p-tolyl-1H-benzo[d]imidazole **(3m)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 2.36 (s, 6H), 5.78 (s, 2H), 7.15–7.18 (d, 4H), 7.28–7.30 (d, 2H), 7.66–7.69 (d, 2H), 7.99–8.12 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): 14.4, 17.1, 21.2, 106.5, 125.3, 126.7, 123.5, 127.5, 127.7, 129.5, 137.2, 137.6, 138.4, 139.8, 140.4, 140.8, 141.2, 142.5, 142.7, 145.5, 152.6, 156.2; IR (KBr): 3324, 2923, 1621, 1550, 1501, 1446, 1183, 1120, 1062, 882, 819, 736; MS (ESI): m/e 358 $(M + H)^+$. HRMS m/z calc for $C_{22}H_{20}N_3O_2$ 358.1463; found 358.1468.

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Note

Working on the synthesis of Organophosphorus Chemistry since 1990 as a successor scientist of Dr. C. Devendranath Reddy, who paved the way for Organophosphorus Chemistry research in the Department of Chemistry, Sri Venkateswara University, Tirupati, India.

References

Bouwman, E., Driessen, W. L., & Reedijk, J. (1990). Model systems for type I copper proteins: Structures of copper coordination compounds with thioether and azole-containing ligands. *Coordination Chemistry Reviews, 104*, 143–172. http://dx.doi.org/10.1016/0010-8545(90)80042-R

Chhanda, M., & Tapaswi, P. K. (2008). PEG-mediated catalyst-free expeditious synthesis of 2-substitutedbenzimidazoles and bis-benzimidazoles under solvent-less conditions. *Tetrahedron Letters, 49*, 6237–6240.

Delp, C. J. (1987). Benzimidazole and related fungicides. In H. Lyr (Ed.), *Modern selective fungicides*. (2nd ed., pp. 291–303). Jena: Gustav Fisher Verlag.

Delp, C. J. (1988). Resistance management strategies for benzimidazoles. In C. J. Delp (Ed.), *Fungicide resistance in North America* (pp. 41–43). St. Paul, MN: American Phytopathological Society.

Dickerson, T. J., Reed, N. N., & Janda, K. D. (2002). Soluble polymers as scaffolds for recoverable catalysts and reagents. *Chemical Reviews, 102*, 3325–3344. http://dx.doi.org/10.1021/cr010335e

Ghosh, P., & Mandal, A. (2011). Catalytic role of sodium dodecyl sulfate: Selective synthesis of 1, 2-disubstituted benzimidazoles in water. *Catalysis Communications, 12*, 744–747. http://dx.doi.org/10.1016/j.catcom.2011.01.005

Hasegawa, E., Yoneoka, A., Suzuki, K., Kato, T., Kitazume, T., & Yanagi, K. (1999). Reductive transformation of α,β-epoxy ketones and other compounds promoted through photoinduced electron transfer processes with 1,3-dimethyl-2-phenylbenzimidazoline (DMPBI). *Tetrahedron, 55*, 12957–12968. http://dx.doi.org/10.1016/S0040-4020(99)00804-2

Jacob, R. G., Dutra, L. G., Radatz, C. S., Mendes, S. R., Perin, G., & Lenardão, E. J. (2009). Synthesis of 1,2-disubstitued benzimidazoles using SiO2/ZnCl2. *Tetrahedron Letters, 50*, 1495–1497. http://dx.doi.org/10.1016/j.tetlet.2009.01.076

Kamal, A., & Reddy, D. R. (2005). A simple and green procedure for the conjugate addition of thiols to conjugated alkenes employing polyethylene glycol (PEG) as an efficient recyclable medium. *Tetrahedron Letters, 46*, 7951–7953. http://dx.doi.org/10.1016/j.tetlet.2005.09.082

Kim, J. S., Gatto, B., Yu, C., Liu, A., Liu, L. F., & LaVoie, E. J. (1996). Substituted 2,5′-Bi-1 *H*-benzimidazoles: Topoisomerase I inhibition and cytotoxicity. *Journal of Medicinal Chemistry, 39*, 992–998. http://dx.doi.org/10.1021/jm950412w

Kumar, M. A., Babu, M. F. S., Srinivasulu, K., Kiran, Y. B., & Reddy, C. S. (2007). Polyethylene glycol in water: A simple and environment friendly media for Strecker reaction. *Journal of Molecular Catalysis A: Chemical, 265*, 268–271.

Li-Jun, Z., Jing, X., Yong-Qing, Z., Hua, W., & Shao-Wu, W. (2012). Rare-earth metal chlorides as efficient catalysts for the simple and green synthesis of 1,2-disubstituted benzimidazoles and 2-substituted benzothiazoles under ultrasound irradiation*Synthetic Communications, 42*, 328–336.

Migawa, M. T., Girardet, J. L., Walker, J. A., Koszalka, G. W., Chamberlain, S. D., Drach, J. C., & Townsend, L. B. (1998). Design, synthesis, and antiviral activity of α-nucleosides: D- and L-isomers of Lyxofuranosyl- and (5-Deoxylyxofuranosyl) benzimidazoles. *Journal of Medicinal Chemistry, 41*, 1242–1251. http://dx.doi.org/10.1021/jm970545c

Min, L., Lei, M., & Lihong, H. (2012). One pot synthesis of 1H-benzamidazole derivatives using thiamine hydrochloride as a reusable organocatalyst. *Synthetic Communications, 42*, 2981–2993.

Mohamed, A. P., & Aatika, N. (2012). Amberlite IR-120 catalyzed, microwave-assisted rapid synthesis of 2-aryl-benzimidazoles. *Journal of Saudi Chemical Society, 16*, 237–240.

Mohan Naidu, K. R., Dadapeer, E., Reddy, C. B., Rao, A. J., Reddy, C. S., & Raju, C. N. (2011). Polyethylene glycol–promoted dialkyl, aryl/heteroaryl phosphonates. *Synthetic Communications, 41*, 3462–3468. http://dx.doi.org/10.1080/00397911.2010.518279

Nagaraju, A., Ramulu, B. J., Shukla, G., Srivastava, A., Verma, G. K., Raghuvanshi, K., & Singh, M. S. (2015). Catalyst-free one-pot four-component domino reactions in water–PEG-400: Highly efficient and convergent approach to thiazoloquinoline scaffolds. *Green Chemistry, 17*, 950–958. http://dx.doi.org/10.1039/C4GC01431F

Nagarapu, L., Raghu, M., & Lingappa, Y. (2010). Polyethylene glycol (PEG-400) mediated synthesis of quinoxalines. *European Journal of Chemistry, 1*, 228–231. http://dx.doi.org/10.5155/eurjchem.1.3.228-231.172

Ogino, Y., Ohtake, N., Nagae, Y., Matsuda, K., Moriya, M., Suga, T., … Fukami, T. (2008). Design, syntheses, and structure–activity relationships of novel NPY Y5 receptor antagonists: 2-{3-Oxospiro[isobenzofuran-1(3H),4′-piperidin]-1′-yl}benzimidazole derivatives. *Bioorganic & Medicinal Chemistry Letters, 18*, 5010–5014. http://dx.doi.org/10.1016/j.bmcl.2008.08.018

Porcari, A. R., Devivar, R. V., Kucera, L. S., Drach, J. C., & Townsend, L. B. (1998). Design, synthesis, and antiviral evaluations of 1-(substituted benzyl)-2-substituted-5,6-dichlorobenzimidazoles as nonnucleoside analogues of 2,5,6-trichloro-1-(β-d-ribofuranosyl)benzimidazole. *Journal of Medicinal Chemistry, 41*, 1252–1262. http://dx.doi.org/10.1021/jm970559i

Pujar, M. A., & Bharamgoudar, T. D. (1988). Cobalt(II), nickel(II) and copper(II) complexes of bidentate bibenzimidazoles. *Transition Metal Chemistry, 13*, 423–425. http://dx.doi.org/10.1007/BF01043702

Raghu, M., Rajasekhar, M., Chandra Obula Reddy, B., Suresh Reddy, C., & Subba Reddy, B. V. (2013). Polyethylene glycol (PEG-400): A mild and efficient reaction medium for one-pot synthesis of 3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-ones. *Tetrahedron Letters, 54*, 3503–3506. http://dx.doi.org/10.1016/j.tetlet.2013.04.089

Rao, K. U. M., Jayaprakash, S. H., Nayak, S. K., & Reddy, C. S. (2011). Polyethylene glycol in: A simple and environment friendly medium for C–P bond formation. *Catalysis Science & Technology, 1*, 1665–1670.

Reddy, C. B., Kumar, K. S., Kumar, M. A., Narayana Reddy, M. V., Krishna, B. S., Naveen, M., … Reddy, C. D. (2012). PEG-SO3H catalyzed synthesis and cytotoxicity of α-aminophosphonates. *European Journal of Medicinal Chemistry, 47*, 553–559. http://dx.doi.org/10.1016/j.ejmech.2011.11.026

Roth, T., Morningstar, M. L., Boyer, P. L., Hughes, S. H., Buckheit, Jr., R. W., & Michejda, C. J. (1997). Synthesis and biological activity of novel nonnucleoside inhibitors of HIV-1 reverse transcriptase. 2-Aryl-substituted benzimidazoles. *Journal of Medicinal Chemistry, 40*, 4199–4207. http://dx.doi.org/10.1021/jm970096g

Shah, D. I., Sharma, M., Bansal, Y., Bansal, G., & Singh, M. (2008). Angiotensin II–AT1 receptor antagonists: Design, synthesis and evaluation of substituted carboxamido benzimidazole derivatives. *European Journal of Medicinal Chemistry, 43*, 1808–1812.

Spasov, A. A., Yozhitsa, I. N., Bugaeva, L. I., & Anisimova, V. A. (1999). Benzimidazole derivatives: Spectrum of pharmacological activity and toxicological properties (a review). *Pharmaceutical Chemistry Journal, 33*, 232–243. http://dx.doi.org/10.1007/BF02510042

Suryakiran, N., Srikanth Reddy, T., Ashalatha, K., Laxman, M., & Venkateswarlu, Y. (2006). Facile polyethylene glycol (PEG-400) promoted synthesis of β-ketosulfones. *Tetrahedron Letters, 47*, 3853–3856. http://dx.doi.org/10.1016/j.tetlet.2006.03.181

Tebbe, M. J., Spitzer, W. A., Victor, F., Miller, S. C., Lee, C. C., Sattelberg, T. R., McKinney, E., & Tang, J. C. (1997). Antirhino/enteroviral vinylacetylene benzimidazoles: A study of their activity and oral plasma levels in mice. *Journal of Medicinal Chemistry, 40*, 3937–3946. http://dx.doi.org/10.1021/jm970423k

Upendra, S., Neeraj, K., Praveen, K. V., Vishal, K., & Bikram, S. (2012). Zinc phthalocyanine with PEG-400 as a recyclable catalytic system for selective reduction of aromatic nitro compounds. *Green Chemistry, 14*, 2289–2293.

Xiaokang, L., Tangjun, Y., Yu, Y., & Junmin, C. (2014). Novel copper/PEG-400 catalyst systems for chemoselective S- and N-arylation of 2-mercaptobenzothiazole. *Tetrahedron, 70*, 9652–9660.

Yahya, S. B., Majid, M. H., Mina, S., Narges, K., Masumeh, Z., & Niloofar, T. H. (2010). Efficient and green synthesis of 1,2-disubstituted benzimidazoles and quinoxalines using brønsted acid ionic liquid, $[(CH_2)_4SO_3HMIM][HSO_4]$, in water at room temperature. *Synthetic Communications, 40*, 1216–1223.

Zhong, H. M., Sheng, L., & Jin, N. (2012). Simple and mild protocol for synthesis of 1,2-disubstitued benzimidazoles using SBA15-supported poly(4-styrenesulfonyl(perfluoro butylsulfonyl)imide) catalyst. *Synthetic Communications, 42*, 506–515.

Zhu, G. D., Gandhi, V. B., Gong, J., Thomas, S., Luo, Y., Liu, X., … Penning, T. D. (2008). Synthesis and SAR of novel, potent and orally bioavailable benzimidazole inhibitors of poly(ADP-ribose) polymerase (PARP) with a quaternary methylene-amino substituent. *Bioorganic & Medicinal Chemistry Letters, 18*, 3955–3958. http://dx.doi.org/10.1016/j.bmcl.2008.06.023