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Green Synthesis and Antihelminthic Activity of 2-Aryl Benzimidazole Derivatives

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ABSTRACT

The green, efficient and practically feasible methods of synthesis were developed for 2-substituted benzimidazole derivatives. The selection and amount of green solvents and green catalyst was optimized to give highest yield at different reaction conditions. From condensation of o-phenylene diamine and different substituted aromatic carboxylic acids and aromatic aldehydes, 10 derivatives of 2-aryl benzimidazole were synthesized. All the compounds were characterized by FTIR spectra and 1H-NMR spectra and evaluated for antihelminthic activity using earthworms *(Pheretima posthuma*). The mean paralysis time and mean death time was recorded and compared using standard Albendazole. Compounds 1b, 1c, 1e, 2b, 2c showed better activity than standard considering the mean paralysis time and mean lethal time. Compounds 1b [2-(3-nitro phenyl) benzimidazole] , 1c [2-(3,5-dinitro 4-hydroxy) benzimidazole], 1e [{2-(N-phenyl carbonyl) glycinyl } benzimidazole] , 2b [2-(4-hydroxy 3-methoxy phenyl) benzimidazole] , 2c [2-(5-nitro 4-hydroxy 3-methoxy phenyl) benzimidazole] showed better activity than standard Albendazole.

INTRODUCTION

The increasing number of developments in drug discovery is leading to increased environmental side effects. These harmful effects are consequently resulting into need of green chemistry. Green chemistry is nothing but environment friendly chemistry which promises to reduce waste and prevent pollution. It helps in sustainable development.[1]

Benzimidazole is a privileged pharmacophore in medicinal chemistry. It shows wide range of biological activities.[12] From the exhaustive review of literature about synthetic approaches to benzimidazole derivatives, 2-substituted benzimidazole derivatives are commonly synthesized from o-phenylene diamines and carboxylic acids, aldehydes and derivatives among all its derivatives. 2-aryl benzimidazole derivatives from aromatic carboxylic acids are synthesized at very high temperature and pressure conditions giving moderate yield. Also, the synthesis of 2-aryl benzimidazole derivatives from aromatic aldehydes are processed by time consuming procedures of synthesis and makes use of harsh catalysts. There is much area for research regarding these syntheses.

The objective of the present research work was to develop the green and efficient methods to synthesize 2-arylbenzimidazole derivatives from aromatic carboxylic acids and aromatic aldehydes, its characterization and antihelminthic evaluation.[15]

MATERIALS AND METHODS

Scheme I

The scheme I was developed for synthesis of 2-aryl benzimidazole derivatives from condensation of o-phenylene diamine and different aromatic carboxylic acids.

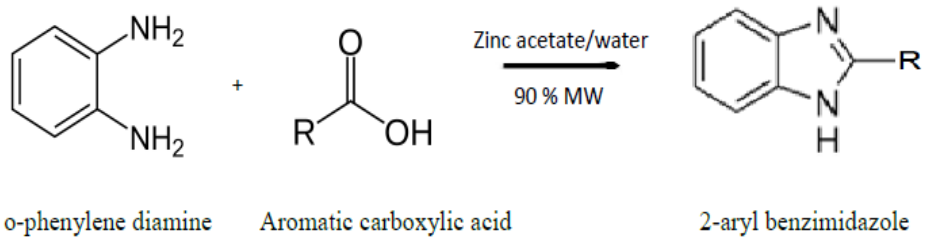


Fig 1: Scheme I (where R= Phenyl, 3-nitro phenyl, Cinnamyl, 3,5-dinitro salicylyl, Hippuryl)

Standardized procedure for Scheme I:

1. o-phenylene diamine (0.01 moles) with aromatic carboxylic acid (0.01 moles), zinc acetate (0.0025 mole) in water (15 ml) were irradiated in microwave at 90 % power (765 W).

2. The reaction was monitored by TLC using mobile phase (ethanol: methanol 8:2).

3. After completion of reaction, the reaction mixture was cooled to room temperature and made just alkaline to litmus by slowly adding 10 % NaOH.

4. The product was filtered and washed with cold water, recrystallized with absolute ethanol.

5. The five derivatives were synthesized using different aromatic carboxylic acids. (Table 1)

Table 1: 2-arylbenzimidazolederivatives synthesized by using Scheme I

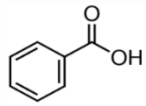
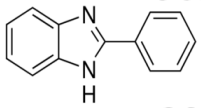
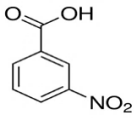
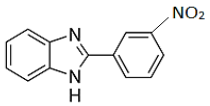
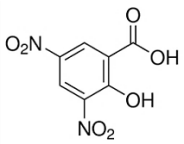
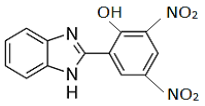
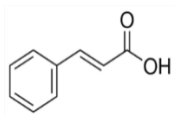
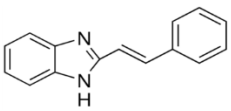
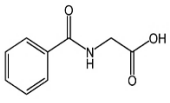
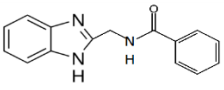
Sr. No	Aromatic carboxylic acid	Structure	Time (Minutes)	Yield	M.P.	Appearance
1a			5	96 %	275-278°C	Light brown crystals
1b			4.5	92.8 %	105-108°C	Light brown amorphous
1c			3	89 %	237-240°C	White amorphous
1d			3.5	91.2 %	180-183°C	Light brown amorphous
1e			2.5	91.3 %	271-274°C	Off white amorphous

Table 2: Comparison between conventional heating and green method of synthesis of scheme I (reaction between o-pheneylene diamine and benzoic acid)

Sr. No.	Parameters	Conventional heating (Reflux on water bath)	Green method (Microwave Irradiation)
1.	Reaction time	2 hours	5 minutes
2.	Amount of solvent	More	Less
3.	Yield	94.5%	96%

Scheme II

Scheme II was developed for synthesis of 2-aryl benzimidazole derivatives from condensation of o-phenylene diamine and different aromatic aldehydes.

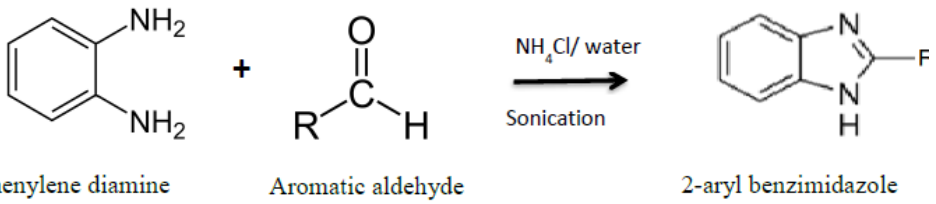


Fig 2: Scheme II (where 4-methoxy phenyl, 4-hydroxy 3-methoxy phenyl, 5-nitro 4-hydroxy 3-methoxy phenyl, furfuryl, 4-isopropyl phenyl)

Standardized procedure of scheme II**:**

1. o-phenylene diamine (0.01 mole), aromatic aldehyde (0.01mole) solubilized in minimum quantity of ethanol(10 ml) and aqueous solution(10ml) of 0.5 g ammonium chloride(0.01 mole) was sonicated till the spot for product formed can be seen on TLC using mobile phase hexane : ethyl acetate (3:7).

2. The reaction mixture was cooled to room temperature and made just alkaline to litmus by slowly adding 10 % NaOH.

3. The product was filtered and washed with cold water, recrystallized with absolute ethanol.

4. The five derivatives were synthesized using different aromatic aldehydes. (Table 3)

Table 3: 2-aryl benzimidazole derivatives synthesized using scheme II

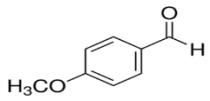
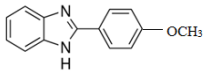
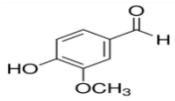
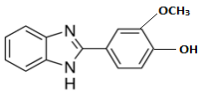
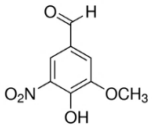
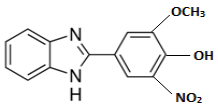
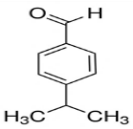
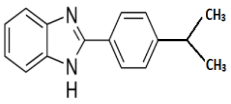
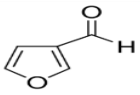
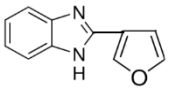
Sr. No	Aromatic aldehyde	Structure	Time (Minutes)	Yield	M.P.	Appearance
2a			15	93.5%	231-234°C	Pale yellow crystals
2b			10.5	91.8%	245-248°C	Off white amorphous
2c			12	90.5%	108-111°C	Orange amorphous
2d			20	88.5%	215-218°C	White amorphous
2e			15.5	89.7%	208-211°C	Light yellow amorphous

Table 4: Comparison between conventional method and green method of synthesis of scheme II (reaction between o-phenylene diamine and 4-anisaldehyde)

Sr. No.	Parameters	Conventional method (Mechanical stirring)	Green method (Sonication)
1.	Reaction time	1.5 hours	15 minutes
2.	Amount of solvent	More	Less
3.	Yield	91.8%	93.5%

Spectroscopic evaluation data:

Compound 1a: 3415.2, 3212.0 (N=H), 1547.0, 1465.5(C=C), 1611.4(C=N); 7.2(m, 2H), 7.4(m, 2H), 7.6(d, 1H), J=8.6, 7.67(m, 2H), 8.17(d, 2H), J=8.6, 8.54(s, 1H)

Compound 1b: 3405.9,3210.7 (N-H), 1679.8 (C=N),1464.5,1401.7 (C=C), 1547.2,1336.4 (N=O); 7.29(m,2H), 7.5(d,1H), J=7.3, 7.7(d,1H), J=7.8, 7.85(dd,1H),J=7.9, 8.32(dd,1H),J=2 8.61(d,1H),J=7.9, 9.01(dd,1H),J=2, 13.30(s,1H) N-H

Compound 1c: 3552.4 (O-H), 1547.8 (N=O), 1610.4 (C=N), 1400.2, 1464.5 (C=C); 3416.4,3211.4 (N-H), 7.3(m, 2H), 7.9(dd, 1H) J=7.7, J=7.7, 8.30(dd, 1H)J=2.1, J=7.7, 8.71(d, 1H)J=8, 9.01(dd, 1H)J=2, J=2, 13.5(s, 1H) N-H, 5.4(s, 1H) O-H

Compound 2a: 3416.4,3219.8 (N-H), 1402.3,1464.5 (C=C), 1610.8 (C=N); 3.84(s,3H) O-CH3, 6.9(d,2H),J=8.8 , 7.2(dd,2H),J=3.2,J=6, 7.6 (dd,2H),J=3.2,J=6

8.0(d, 2H), J=8.8, 12.3(s, 1H) N-H

Compound 2b: 3551.5 O-H, 3416.2, 3213.2 N-H, 1611.4 C=N, 2878.0 C-H; 3.8(d, 3H) O-CH3,

5.4(s, 1H) O-H, 7.4(m, 1H), 7.67(m, 2H), 8.17(d, 2H), J=8.21, 8.53(s, 1H) N-H

Compound 2c: 1545.1, 1336.4 N=O, 1612.0 C=N, 3550.8 O-H, 3430.1, 3230.5 N-H

3.8(d, 3H) O-CH3; 5.4(s, 1H) O-H, 7.2(m, H), 7.6(d, 2H), J=8.5, 7.67(m, 1H), 8.17(d, 2H), J=8.5, 8.54(s, 1H) N-H

Antihelminthic evaluation of the synthesized compounds:

Model organism: *Pheretima posthuma* (earth worms)

Description: 6+/- 1 cm

Groups: 4 groups of 6 worms each

Standard: Albendazole

Control: Normal saline

Concentrations: 0.1, 0.2, 0.5 and 1 % (*m/V*) of each compound

Procedure:

1. The animals were acclimatized to laboratory environment by washing them with normal saline water (0.9 % NaCl).

2. The 25ml of each concentration of each compound and standard was put in petri plate.

3. Six earthworms were transferred to each petri plate and observed for the following parameters.

4. The time taken for complete paralysis and death was recorded. The mean paralysis time and mean lethal time were calculated for each compound (each reading was taken in triplicate).

5. The time taken for worms to become motionless was noted as paralysis time.

6. To ascertain death (lethal time), each worm was frequently subjected to external stimuli that stimulate and induce movement in earth worms, if alive.[17]

Table 5: Antihelminthic evaluation data for the synthesized compounds

	Paralysis time (minutes)				Death time (minutes)			
	Concentration %				Concentration %			
Compound	**0.1**	**0.2**	**0.5**	**1**	**0.1**	**0.2**	**0.5**	**1**
1a	4.70± 0.1	3.10± 0.2	2.36 ±0.1	1.53± 0.1	13.30 ±0.2	11.83± 0.1	9.80± 0.3	9.86±0 0.2
1b	2.40± 0.3	1.60± 0.1	1.34 ±0.1	0.74± 0.04	8.67± 0.02	5.13±0. 1	4.2±0 .06	2.67±0. 2
1c	2.24± 0.1	1.77± 0.2	1.34 ±0.1	0.73± 0.04	8.20± 0.2	7.33±0. 03	6.63± 0.1	5.67±0. 01
1d	5.20± 0.2	4.34± 0.1	3.27 ±0.3	2.20± 0.1	8.20± 0.01	5.37±0. 1	4.24± 0.2	3.17±0. 01
1e	1.34± 0.1	1.34± 0.1	0.4± 0.06	0.20± 0.1	7.47± 0.1	6.20±0. 02	4.34± 0.1	3.03±0. 1
2a	3.40± 0.1	2.30± 0.2	1.27 ±0.1	1.40± 0.02	7.30± 0.2	5.44±0. 1	3.40± 0.3	2.37±0. 2
2b	1.36± 0.1	1.27± 0.3	0.67 ±0.1	0.50± 0.1	3.23± 0.1	2.40±0. 04	2.36± 0.1	1.50±0. 1
2c	2.67± 0.1	2.14± 0.2	1.57 ±0.2	1.27± 0.2	6.46± 0.1	4.27±0. 1	3.27± 0.1	2.54±0. 01
2d	3.20± 0.2	2.54± 0.1	2.27 ±0.1	1.64± 0.2	7.27± 0.1	5.17±0. 1	4.27± 0.2	2.34±0. 3
2e	3.20± 0.1	2.64± 0.1	2.27 ±0.2	1.27± 0.1	8.20± 0.1	5.43±0. 2	4.30± 0.1	2.37±0. 3
Negative control (DMSO)	31.1± 0.1	31.5± 0.1	30.2 ±0.1	30.03 ±0.1	38.40 ±0.2	37.14± 0.1	34.9± 0.2	34.50± 0.2
Standard (Albendazole)	2.27± 0.1	2.67± 0.1	2.30 ±0.2	2.34± 0.03	4.27± 0.2	4.43±0. 1	4.1±0 .02	3.60±0. 1

RESULTS AND DISCUSSION

- Microwave assisted synthesis resulted in drastic reduction in reaction time from 2-3 hours to 3-5 minutes and the subsequent increase in the yield of all the compounds by 2-3 % as compared to the conventional method. The decrease in reaction time is due to the phenomenon 'core heating' which allows achieving target temperature in short time.

- Sonochemical synthesis resulted in reduction in reaction time from 1-2 hours to 15-20 minutes and the subsequent increase in yield of all the compounds by 2-3 % as compared to the conventional method. It is due to mechanical activation in sonochemistry which is called as acoustic cavitation.

- Water as a solvent and zinc acetate as a catalyst proved to be good reaction medium for microwave assisted green synthesis of 2-aryl benzimidazole derivatives. Microwave irradiation increases the temperature by several folds which increase the solubility and amount of solvent required is less subsequently.

- Ethanol as a solvent and ammonium chloride as a catalyst proved to be good reaction medium for sonication assisted green synthesis of 2-aryl benzimidazole derivatives. Sonication aids the solubility. Hence, the amount of solvent required was less.

- Compounds 1b [2-(3-nitro phenyl) benzimidazole], 1c [2-(3,5-dinitro 4-hydroxy) benzimidazole], 1e [{2-(N-phenyl carbonyl) glycinyl} benzimidazole], 2b [2-(4-hydroxy 3-methoxy phenyl) benzimidazole], 2c [2-(5-nitro 4-hydroxy 3-methoxy phenyl) benzimidazole] showed better activity than standard Albendazole.

- Electron withdrawing nitro group at 3 and 5 positions of phenyl ring showed increased activity.

- Electron donating methoxy group at position 4 of phenyl ring seem to show improved activity.

- Electron donating hydroxy group at carbon 4 of phenyl ring seem to be responsible for higher activity.

CONCLUSION

The methods used were time and energy efficient. The reactions are carried out in reduced time period and by using green solvents and catalysts.

The 2-aryl benzimidazole derivatives with nitro group at 3 and position, methoxy group at 4 positions, hydroxyl group at 4 position of phenyl ring can be further explored to show better antihelminthic activity.

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