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Conventional and Greener Approach for the Synthesis of Some Novel Substituted -4-Oxothiazolidine and Their 5-Arylidene Derivatives of 2-Methyl-benzimidazole: Antimicrobial Activities

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Abstract

The aim of this work was to investigate the efficiency of N^1–(2-Benzylidene-imino-5'-methylene)-1',3',4'-thiadiazole]-2-methyl-benzimidazoles, **4(a-n)**; N'^1-[2'-{2-Substituted-Phenyl-1,3-thiazolidin-4-one}-5'-methylene-1',3',4'-thiadiazole]-2-methyl-benzimidazoles, **(a-n)** and N^1-[2'-{2-substituted-phenyl-5-substituted-benzylidene-1,3-thiazolidine-4-one}-5'-methylene-1',3',4'-thiadiazole] -2-methyl-benzimidazoles, **6(a-n)** for the synthesis by conventional and greenar approach methods in terms of yield and reaction time along with antimicrobial activity against *Bacillus subtilis*, *Escherichia coli. Klebsiella pneumoniae* and *Streptococcus aureus* bacteria and *Aspergillus niger*, *Aspergillus flavus*, *Fusarium oxisporium* and *Trichoderma viride* fungi *in vitro* at 50 and 100 ppm concentrations. Some of the compounds displayed pronounced biological activity. The structures of all the new compounds were established on the basis of elemental analysis and spectral data (IR, 1HNMR and mass).

Keywords: 2-Methyl benzimidazole, Thiadiazole, Arylidene, 4-Oxothiazolidine, Antimicrobial activity.

Introduction

An important contribution of microwave techniques to organic synthesis has been observed in recent years. Microwave assisted organic synthesis allows not only for the improvement of reaction yield but also decreases reaction time, and simplifies product purification. Last but not least, it offers us an environmentally friendly way of practicing and teaching chemistry. However, classical text books for organic chemistry laboratory only rarely provide

experimental procedures that make use of this established techniques [1] in dry media, reactions occur rapidly and the method avoids hazards associated with solvents especially in sealed vessels. The absence of solvent reduces reaction time and always improves yield. Using microwaves with proper control of power and reaction temperature are more efficient than conventional heating [2]. The benzimidazole ring is an important pharmacophore in modern drug discovery. A variety of benzimidazole are in use, like thiabendazole and flubendazole (anthelmintic), omeprazole and lansoprazole (antiulcerative) and astemizole (antihistaminic). The chemistry and pharmacology of benzimidazoles have been of great interest to medicinal chemistry [3] because its derivatives possessed various biological activities such as antioxidant, [4] antimicrobial, [5,6] antihelmintic, [7] anticancer, [8] antihypertensive, [9] anti-inflammatory, [10] analgesic, [11] and antiprotozoal activities [12]. 4-Oxo-thiazolidines and their 5- arylidene derivatives also possess a variety of therapeutic activities such as analgesic,antiinflammatory, antipyretic [13] anticonvulsant,[14] anti HIV,[15] antidiabetic, [16] antitubercular, [17] anticancer, [18] antibacterial,[19]antifungal [20] etc. The present paper reports the synthesis of compouds **4(a-n)**, **5(a-n)** and **6(a-n)** by conventional as well as microwave assisted synthesis for comparison purpose particularly the reaction time and yields (Scheme-1). In view of the fact thiadiazolo-thiazolidinones were synthesised in our laboratory and were found to possess significant antibacterial activity against *Bacillus subtilis, Escherichia coli. Klebsiella pneumoniae* and *Streptococcus aureus* bacteria and antifungal activity against *Aspergillus niger, Aspergillus flavus, Fusarium oxisporium* and *Trichoderma viride* fungi respectively.

Materials and Methods

Experimental

General

Melting points were taken in open capillaries. Purity of compounds was monitored on silica gel "G" coated TLC plates. All instrumental analysis was performed at the Central Drugs Research Institute, Lucknow (India). IR spectra were recorded in KBr disc on a Schimadzu 8201 PC, FTIR spectrophotometer (ν_{max} in cm^{-1}) and ^{1}HNMR spectra were measured on a Brucker DRX-300 spectrometer in $CDCl_3$ at 300 MHz using TMS as an internal standard. All chemical shifts were reported as δ (ppm) values. The FAB mass spectra were recorded on a Jeol SX–102 mass spectrometer. Elemental analyses were performed on a Carlo Erba–1108 analyzer. The analytical data of all the synthesized compounds were highly satisfactory. For chromatographic purification Merck silica Gel 60 (230-400 Mesh) was used. Microwave assisted reaction were carried out in a Qpro-M-modified microwave oven. The reagent grade chemicals were purchased Merck and Aldrich Chemical Co. Ltd. were used. Anhydrous silica gel 60 (0.063-0.2 mm) was used as solid support after dehydration under microwave irradiation for 4 minutes.

General procedure for the synthesis of compounds

Preparation of N^1-Ethylacetate-2-methyl-benzimidazole (1):

Conventional Method: A mixture of 2-methyl-benzimidazole (0.30 mole, 39.60 g) and ethyl-chloroacetate (0.30 mole, 36.74 g) with K_2CO_3 (6.168 g) in methanol (250 ml) was kept overnight at room temperature. The reaction mixture was refluxed on a steam bath for about 3 hr. It was cooled filtered and solvent was distilled off under reduced pressure and the solid thus obtained was passed through a column of silica gel using chloroform: methanol (5:5 v/v) mixture as eluant. The eluate (250 ml) was concentrated to give a product which was recrystallised with ethanol to furnish colourless needles of compound **1**. Yield 83%, m.p. 94-

96ºC. Anal. Calcd for $C_{12}H_{14}N_2O_2S$: C, 66.05, H, 6.42, N, 12.84%; found C, 65.97, H, 6.38, N, 12.79%; IR: 2866, 1470, 1270 (-NCH_2), 2912, 2875, 1427, 710 (-CH_2 and -CH_3), 1720 (>C=O of ester), 1050 (C-O-C), 3012, 2842, 1598, 1392, 744 (benzimidazole ring) , 2816 (-CH_3) ; ^{1}HNMR : 1.90 (t, 3H, J=7.0 Hz, -$COOCH_2\underline{CH_3}$), 4.19 (q, 2H, J= 7.0 Hz, -$\underline{CH_2}CH_3$), 2.64 (s,1H, -CH_3), 7.30 – 7.65 (m, 4H, ArH), 3.63 (s, 2H, -NCH_2); MS : 218(M^+).

Microwave Method: A mixture of 2-methyl-benzimidazole (0.30 mole, 39.60 g) and ethyl-chloroacetate (0.30 mole, 36.74 g) with K_2CO_3 (6.168g) was added and mixed thoroughly. The mixture was air dried and subjected to microwave irradiation for 3 minutes (completion of reaction as indicated by TLC). The reaction mixture was cooled to room temperature and the separated solid was extracted with ethanol. On standing the filtrate afforded colourless crystalline solid. The product was purified by column chromatography and recrystallised from ethanol, yield 94%. Spectral and analytical data were found to similar as reported for conventional method.

Preparation of N^1-Acetylthiosemicarbazide-2-methyl-benzimidazole (2):

Conventional Method: The compound **1** (0.15 mole, 32.70 g) and thiosemicarbazide (0.15 mole, 30.67g) in methanol (200 ml) was refluxed on a steam bath for about 8 hrs. It was then cooled, filtered and excess of solvent was removed which gave a product. It was purified over the column of silica gel using acetone: methanol 6:4 (v/v) mixture as an eluant. The eluate (200 ml) was concentrated and product was recrystallised with ethanol to give compound **2**. Yield 73%, m.p. 146 - 48ºC. Anal. Calcd for $C_{11}H_{13}N_5OS$: C, 50.19, H, 4.91, N, 26.61% ; found C, 49.97, H, 4.91, N, 26.56%; IR : 3400, 3275 (-NH_2), 3352 (-NH), 1128 (>C=S), 2864, 1471, 1274 (-NCH_2), 1668 (>CO), 2822 (-CH_3), 3018,2844, 1601,1408,742 (benzimidazole ring); ^{1}HNMR : 8.12 - 8.35 (m, 4H, -$NHNHCSNH_2$), 2.65 (s,1H, -CH_3), 3.68(s, 2H, -NCH_2) 7.28-7.64 (m, 4H, Ar-H); Mass(FAB): 262(M^+).

Microwave Method: A mixture compound **1** (0.15 mole, 32.70 g) and thiosemicarbazide (0.15 mole, 30.67g) was ground in a mortar using a pestle for uniform mixing. The mixture was kept inside a microwave oven operating at 160w for 5 min. The completion of the reaction was checked by TLC. The product was purified by column chromatography and recrystallised from ethanol. Spectral and analytical data were found to similar as reported for conventional method.

Preparation of N^1–(2'-amino-5'-methylene) - 1', 3', 4'-thiadiazole-2—methyl-benzimidazole (3):

Conventional Method: Equimolar solution of compound **2** (0.10 mole, 26.30 g) and concentrated H_2SO_4 (0.10mole, 9.80 g, AR grade) in methanol (150 ml) was kept overnight at room temperature. It was then refluxed on a steam bath for about 10 hr. After cooling the solution was neutralized with concentrated liq. ammonia and filtered. The solvent was removed *in vacvo* and the solid thus obtained was dried and purified over the column of silica gel using chloroform: methanol (5:5 v/v) mixture as eluant. The eluate (180 ml) was concentrated to give a product which was recrystallised from ethanol to give compound **3**. Yield, 68%, m.p. 126-28ºC. Anal. Calcd. for $C_{11}H_{11}N_5S$: C, 53.87, H, 4.48, N, 28.57%, found : C, 53.79, H, 4.43, N, 28.51%; IR : 3396 (-NH_2), 2829, 1463, 1279 (-NCH_2), 1630, 1196, 1132, 1068, 624 (thiadiazole),3016, 2846, 1603, 1408,740 (benzimidazole ring) 2820 (-CH_3) ; ^{1}HNMR : 4.81 (s, 1H, -NH_2), 2.64(s,1H,-CH_3), 7.25-7.69(m, 4H, Ar-H). MS: 245(M^+).

Microwave Method: The compound **2** (0.10 mole, 26.30g) dissolved in chloroform and concentrated H_2SO_4 (0.10 mole, 9.80g) was added at room temperature. Anhydrous transparent inorganic solid support silica gel was added and the solvent was removed under

vacuum. The adsorbed reaction mixture was introduced in an open quartz tube which was subjected to microwave irradiation in the resonance cavity of the microwave power system for 1.30 minutes. The initial and the final sample temperature was measured. The sample was cooled in an ice bath and the irradiation was repeated several times. TLC was used to monitor the reaction progress. The reaction product was extracted with ethanol and filtered. After filtration of the solution, it was neutralized with concentrated liq.ammonia and solvent was removed *in vacuo*. The product was purified by column of silica gel and recrystallised from ethanol to give compound **3** yield 91%. Spectral and analytical data were found to similar as reported for conventional method.

Preparation of N^1–(2-Benzylidene-imino-5'-methylene)-1', 3', 4'-thiadiazole]-2-methyl-benzimidazole (4a):

Conventional Method : The equimolar solution of compound **3** (0.0085 mole, 2.08 g) and benzaldehyde (0.0085 mole, 0.902 g) in methanol (50 ml) with 4-5 drops of glacial acetic acid was refluxed on a water bath for about 3 hr. The solvent was distilled off under reduced pressure. The solid thus obtained was purified over the column of silica gel using chloroform: methanol (6:4 v/v) mixture as eluant. The eluate (60 ml) was concentrated and the product was recrystallised with ethanol to give compound **4a**. Yield 74%, m.p. 172-74ºC. Anal. Calcd. for $C_{18}H_{15}N_5S$:C, 64.86, H, 4.50, N, 21.02%,found: C,64.83, H, 4.47, N,20.96%;IR:1546(-N=CH),2824(-CH_3),2861,1467,1276(-NCH_2),1632,1191,1139,1070,634(thiadiazole ring), 3018, 2842, 1610, 1411,739 (benzimidazole ring); ^{1}HNMR : 7.20-7.68 (m, 9H, Ar-H), 2.66 (s, 1H, -CH_3) 3.65(-NCH_2),, 4.91(s, 1H, -N=CH); MS: 333(M^+).

Microwave Method : Equimolar solution of compound 3 (0.0085 mole, 2.08g) and benzaldehyde (0.0085 mole, 0.902g) in methanol (20 ml) with 4-5 drops of glacial acetic acid was kept at room temperature. Anhydrous microwave transparent solid support silica gel was added and the solvent was removed under vacuum. The adsorbed reaction mixture was introduced in an open quartz tube which was then subjected to microwave irradiation in the resonance cavity of the microwave power system for 1.30 minutes. The sample was cooled in an ice bath and TLC was used to monitor the reaction progress. The reaction product was extracted with methanol, filtered and dried over anhydrous sodium sulphate and then the solvent was removed. The product was purified by column of silica gel and recrystallised with ethanol gave compound **4a**. Yield 89%.

Other compounds **4(b-n)** were synthesized in the similar manner using compound **3** and various aromatic aldehydes. Characterization data are presented in **Table -1**.

Preparation of N'-[2'-{2-phenyl-1, 3-thiazolidin-4-one}-5'-methylene-1',3',4'-thiadiazole]-2-methyl-benzimidazole (5a):

Conventional Method : The equimolar solution of compounds **4a** (0.005 mole, 1.66g) and mercaptoacetic acid (0.005 mole, 0.36g) with a pinch of anhydrous $ZnCl_2$ in methanol (30ml) was first stirred for about 6 hr. followed by refluxing on a steam bath for about 4hr. The solvent was distilled off under reduced pressure and the solid thus obtained was purified over the column of silica gel using chloroform: methanol 8:2 (v/v) mixture as an eluant. The eluate (60 ml) was concentrated and product was recrystallized with ethanol to give compound **5a**. Yield 76%, m.p. 112-14%. Anal. calcd. for $C_{20}H_{17}N_5OS_2$: C, 58.96, H, 4.17, N, 17.19 % found: C, 58.93, H, 4.15, N, 17.16%; IR, 1712 (cyclic, >C=O), 2994 (-NCH_2S), 2810 (-CH_3), 2874, 1460, 1268 (-NCH_2), 1631, 1192, 1143, 1078, 643 (thiadiazole ring), 3015, 2849, 1610, 1420, 746 (benzimidazole ring); ^{1}HNMR: 3.68 (s, 2H, -CH_2S), 4.86 (s, 1H,-NCH), 2.64 (s, 1H, -CH_3), 7.23-7.68 (m, 9H, Ar-H); MS : 407 (M+).

Microwave Method : The equimolar solution of compounds 4a (0.005 mole, 1.60g) and mercaptoacetic acid (0.005 mole, 0.36g) with a pinch of anhydrous $ZnCl_2$ in methanol (30ml) was introduced in an open quartz tube which was then subjected to microwave irradiation for about 8 minutes. Initial and final sample temperature was measured. The sample was cooled in an ice bath. The reaction product was extracted with chloroform, filtered and passed through a column of silica gel and recrystallised with ethanol to give compound **5a**. Yield 89%.

Other compounds **5(b-n)** were synthesized in the similar manner using compounds **4(b-n)**. Characterization data are presented in **Table -1**

Preparation of N^1-[2'-{2-Phenyl-5-benzylidene-1, 3-thiazolidin-4-one}-5'-methylene -1', 3', 4'-thiadiazole]-2-methyl-1, 3-benzimidazole (6a):

Conventional Method : The equimolar solution of compounds **5a** (0.004 mole, 1.62g) and benzaldehyde (0.004 mole, 0.40g) in methanol (30 ml) in the presence of sodium ethoxide were refluxed on a steam bath for about 2 hr. The solvent was distilled off under reduced pressure. The solid thus obtained was purified over the column of silica gel using acetone: methanol 5: 5 (v/v) mixture as an eluant. The eluate (50 ml) was concentrated and the product was recrystallized from ethanol to give compounds **6a**. Yield 61% m.p. 139-141^{o}C Anal. cold for $C_{27}H_{27}N_5OS_2$: C, 65.45, H, 4.24, N, 14.14% found: C, 65.42, H, 4.23, N, 14.12 %; IR: 1638(-C=CHAr), 2989(-NCHS), 1714 (cyclic>C=O), 2810 (-CH_3), 2830, 1471, 1263(-NCH_2), 1631, 1192,1142, 1079, 646 (thiadiazole ring), 3025, 3016, 2848, 16015, 1418, 743 (benzimidazole with aromatic ring); ^{1}HNMR: 5.26 (s, 1H, -C=CHAr), 3.65 (s, 2H,-NCH_2), 2.63 (s, 1H, -CH_3), 7.13-7.72 (m, 14H, Ar-H); MS: 495 (M+).

Microwave Method : The equimolar solution of compound 5a (0.004 mole, 1.62g) and benzaldehyde (0.004 mole, 0.40g) in methanol (10 ml) in the presence of sodium ethoxide were ground in a mortar using a pestle for uniform mixing. This mixture was taken in a 50 ml beaker. The beaker was kept inside a microwave oven operating at 300w for about 5 min. The completion of the reaction was checked by TLC. The product was poured to crushed ice. The solid obtained was filtered, dried and recrystallised from a mixture of chloroform: ethanol (6:4 v/v) to give compound **6a.**Yield 96%.

Other compounds **6(b-**n) were synthesized in the similar manner using compounds **5(b-n**). Characterization data are presented in **Table-1**.

Antimicrobial activity

Antibacterial activity: All the synthesized compounds were evaluated *in vitro* for antibacterial activity by using filter paper disc method [21-23] against different strains of bacteria viz. *B. substilis, E. coli, S. aureus* and *K. pneumoniae.* All the compounds along with standard antibacterial Streptomycin were used at 50 and 100 ppm concentrations.

Procedure: Solution of known concentration (50 and 100 ppm) of the test sample were made by dissolving in DMSO. Dried and sterilized filter paper discs (6mm in diameter) soaked with known amount of test agents were placed on the nutrient agar media solidified in petridishes (120 mm diameter) and inoculated with the test organisms. These plates were then kept at low temperature (4ºC) for 24 hours to allow maximum growth of the organisms. The antibacterial activity was determined by measuring the diameter of zone of inhibition in mm.

Table-1: Characterization data of the compounds 4(b-n), 5(b-n) and 6(b-n)

Comp	Ar_1	Ar_2	% Yield (Reaction time)		M.P. (^oC)	Molecular formula	MS (FAB)
			MW (mins)	Conv. (hrs.)			
4b	2-ClC_6H_4	-	92 (2)	66 (4)	122-24	$C_{18}H_{14}N_5SCl$	367
4c	3-ClC_6H_4	-	89 (2)	54 (4)	118-20	$C_{18}H_{14}N_5SCl$	367
4d	4-ClC_6H_4	-	88 (2)	58 (4)	126-28	$C_{18}H_{14}N_5SCl$	367
4e	2-BrC_6H_4	-	76 (3)	70 (5)	141-43	$C_{18}H_{14}N_5SBr$	412
4f	3-BrC_6H_4	-	75 (3)	65 (5)	149-51	$C_{18}H_{14}N_5SBr$	412
4g	4-BrC_6H_4	-	72 (3)	68 (5)	167-69	$C_{18}H_{14}N_5SBr$	412
4h	2-$OCH_3C_6H_4$	-	86 (5)	61 (6)	76-78	$C_{19}H_{17}N_5OS$	363
4i	3-$OCH_3C_6H_4$	-	85 (5)	60 (6)	80-82	$C_{19}H_{17}N_5OS$	363
4j	4-$OCH_3C_6H_4$	-	87 (5)	59 (6)	95-97	$C_{19}H_{17}N_5OS$	363
4k	2-$NO_2C_6H_4$	-	94 (1)	65 (2)	168-70	$C_{18}H_{14}N_6O_2S$	378
4l	3-$NO_2C_6H_4$	-	93 (1)	86 (2)	176-78	$C_{18}H_{14}N_6O_2S$	378
4m	4-$NO_2C_6H_4$	-	97 (1)	84 (2)	173-75	$C_{18}H_{14}N_6O_2S$	378
4n	4,4'-$(CH_3)_2NC_6H_4$	-	86 (2)	79 (4)	183-85	$C_{20}H_{20}N_6S$	376
5b	2-ClC_6H_4	-	89 (6)	76 (12)	130-32	$C_{20}H_{16}N_5OS_2Cl$	441
5c	3-ClC_6H_4	-	87 (6)	82 (11)	134-36	$C_{20}H_{16}N_5OS_2Cl$	441
5d	4-ClC_6H_4	-	90 (6)	78 (12)	131-33	$C_{20}H_{16}N_5OS_2Cl$	441
5e	2-BrC_6H_4	-	89 (5)	74(9)	148-50	$C_{20}H_{16}N_5OS_2Br$	486
5f	3-BrC_6H_4	-	86(5)	72 (11)	139-41	$C_{20}H_{16}N_5OS_2Br$	486
5g	4-BrC_6H_4	-	90 (5)	75(10)	142-43	$C_{20}H_{16}N_5OS_2Br$	486
5h	2-$OCH_3C_6H_4$	-	98 (7)	81 (12)	108-10	$C_{21}H_{19}N_5O_2S_2$	437
5i	3-$OCH_3C_6H_4$	-	95 (7)	84 (10)	112-15	$C_{21}H_{19}N_5O_2S_2$	437
5j	4-$OCH_3C_6H_4$	-	91(7)	86 (12)	110-12	$C_{21}H_{19}N_5O_2S_2$	437
5k	2-$NO_2C_6H_4$	-	95 (5)	75 (8)	151-63	$C_{20}H_{19}N_6O_3S_2$	452
5l	3-$NO_2C_6H_4$	-	94 (5)	74 (8)	156-58	$C_{20}H_{19}N_6O_3S_2$	452
5m	4-$NO_2C_6H_4$	-	93 (5)	79 (8)	155-60	$C_{20}H_{19}N_6O_3S_2$	452
5n	4,4'-$(CH_3)_2NC_6H_4$	-	81 (6)	74 (10)	168-70	$C_{22}H_{22}N_6OS_2$	450
6b	2-ClC_6H_4	2-ClC_6H_4	79 (4)	68 (2)	112-64	$C_{27}H_{19}N_5S_2Cl_2$	547
6c	3-ClC_6H_4	3-ClC_6H_4	89 (3)	64 (3)	158-60	$C_{27}H_{19}N_5S_2Cl_2$	547
6d	4-ClC_6H_4	4-ClC_6H_4	86 (4)	67 (2)	167-69	$C_{27}H_{19}N_5S_2Cl_2$	547
6e	2-BrC_6H_4	2-BrC_6H_4	87 (4)	71(2)	173-75	$C_{27}H_{19}N_5S_2Br_2$	637
6f	3-BrC_6H_4	3-BrC_6H_4	73 (4)	73 (2)	174-76	$C_{27}H_{19}N_5S_2Br_2$	637
6g	4-BrC_6H_4	4-BrC_6H_4	72 (4)	72 (2)	180-82	$C_{27}H_{19}N_5S_2Br_2$	637
6h	2-$OCH_3C_6H_4$	2-$OCH_3C_6H_4$	84 (3)	77 (2)	119-21	$C_{29}H_{25}N_5O_3S_2$	555
6i	3-$OCH_3C_6H_4$	3-$OCH_3C_6H_4$	86 (3)	78 (1)	120-22	$C_{29}H_{25}N_5O_3S_2$	555
6j	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	82 (3)	75 (1)	140-42	$C_{29}H_{25}N_5O_3S_2$	555
6k	2-$NO_2C_6H_4$	2-$NO_2C_6H_4$	87(4)	62 (2)	188-90	$C_{27}H_{19}N_7O_5S_2$	585
6l	3-$NO_2C_6H_4$	3-$NO_2C_6H_4$	65 (4)	65 (2)	193-95	$C_{27}H_{19}N_7O_5S_2$	585
6m	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	91 (4)	63 (2)	188-90	$C_{27}H_{19}N_7O_5S_2$	585
6n	4,4'-$(CH_3)_2NC_6H_4$	4,4'-$(CH_3)_2NC_6H_4$	93 (4)	69 (4)	176-78	$C_{31}H_{31}N_7OS_2$	581

Antifungal activity: All the compounds were assayed *in vitro* for antifungal activity against *A. niger, A. flavus, F. oxisporium and T. viride* fungi employing the filter paper disc method [24, 25] by measuring inhibition zone in mm. All the tested compounds along with standard fungicide Griseofulvin were used at 50 and 100 ppm concentrations.

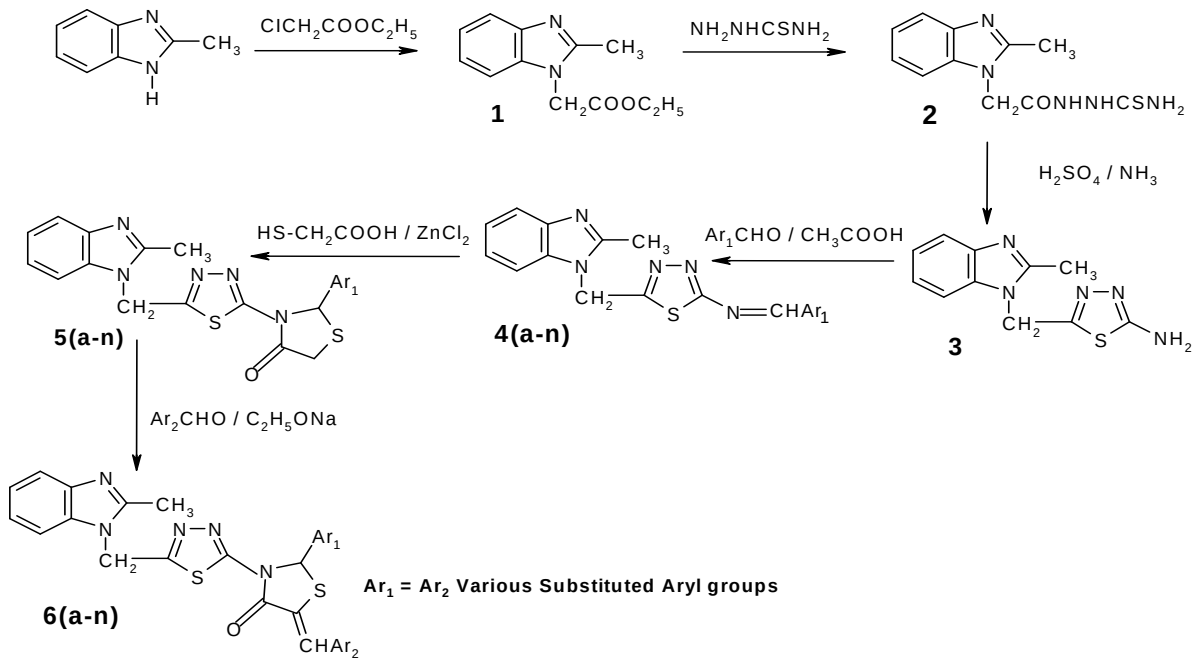
Procedure: The test samples were dissolved in DMSO to make 50 and 100 ppm concentration solutions. Sterilized symmetrical filter paper discs of 6 mm diameter were taken in a blank petridishes sample solution 10 µl/discs were applied on the discs with the help of a micropipette in an aseptic condition. The discs were left for a few minutes in the aseptic condition for complete removal of the solvent. Isolated spore (4-6 similar) of pure

fungus was inoculated in screw capped tube containing equal amount of potato dextrose agar (PDA) media and incubated at 28ºC for 5-7 days for development of new pure culture that was used as inoculum. PDA medium was steamed to dissolve and dispersed 4 ml amount of it into a petridish. It was then autoclaved at 121ºC for 15 minutes. It was allowed to cool to 30ºC until the media became solid. Each petridish was inoculated with different types of inoculums removed from a seven days old culture fungus. Dried and sterile sample discs and standard (Fungal) disc were placed on nutrient agar plates seeded with the test organism. These were then kept at low temperature (4ºC) for 24 hours to allow maximum diffusion. Finally the petridishes were inoculated at 27-28ºC for 5-7 days. The activity was justified by meaning the diameter of zone of inhibition in mm.

Results and Discussion

Reaction of ethylchloroacetate with 2-methyl-benzimidazole followed by thiosemicarbazide resulted in the formation of N^1-acetylthiosemicarbazide-2-methyl-benzimidazole, **2.** The compound **2** on dehydrative annulation by mineral acid afforded N^1–(2-amino-5'-methylene)-1',3',4'-thiadiazole-2-methyl-benzimidazole **3** which on condensation with various substituted aromatic aldehydes furnished N^1–(2-substituted-benzylidene-imino-5'-methylene)-1',3',4'-thiadiazole]- 2-methyl-benzimidazoles **4(a-n).** The compounds **4(a-n)** on reaction with mercaptoacetic acid underwent dehydrate annulation in the presence of anhydrous $ZnCl_2$ to afford N^1-[2'-{2-substituted-phenyl-1,3-thiazolidin-4-one}-5'-methylene-1',3',4'-thiadiazole]-2-methyl-1,3-benzimidazoles, **5(a-n)**. The compounds **5(a-n)** which on the application of Knoevenagel reaction with various substituted aromatic aldehydes gave N^1-[2'-{2-substituted-phenyl-5-substituted-benzylidene-1,3-thiazolidin-4-one}-5'-methylene-1',3',4'-thiadiazole]-2-methyl-benzimidazoles, **6(a-n)**. The structures of all the synthesized compounds were confirmed by elemental analysis IR, ^{1}HNMR and mass spectral data.

Scheme-1



All the synthesized compounds **4(a-n)** and **5(a-n)** have been screened *in vitro* for their antibacterial activity against *B. subtilis* (Bs), *E. coli* (Ec), *S. aureus* (Sa) and *K. pneumoniae* (Kp) at two concentrations (50 and 100 ppm) and antifungal activity against *A. niger* (An), *A.*

flavus (Af), *F. oxisporium* (Fo) and *T. viride* (Tv) at two concentrations (50 and 100 ppm). Standard antibacterial Streptomycin and fungicide Griseofulvin were also screened under the similar conditions for comparison. The following compounds were found to active against the tested becteria :4d(Ec,Sa), 4f(Bs,Kp), 4g(Ec), 4h(Bs,Ec,Sa), 4i,4j (Kp), 5b, 5c, 5d, 5e ,5f, 5g (Bs, Ec, Kp, Sa), 5i(Ec,Kp,Sa), 5h(Kp), 5k (Ec), 5n(Kp,Sa), 6c, 5d, 6f (Bs, Ec, Kp, Sa), 6i (Ec, Kp), 6h (Ec),6k (Kp), 6n(Kp) and fungi :5f(Af,Tv),5g(An),4n (Fo), 5b(Tv), 5c (Af, Fo), 5d(An), 5e, 5f, 5g(An, Af, Fo,Tv), 5i(Af, Fo), 5j (An,Af), 5h(Fo,Tv), 5k(An,Af), 5l, 3m, 5n(An), 6d (Af, Tv), 6f (An, Af), 6g (Fo. Tv), 4h (Af, An, Tv), 6i, 6j (An, Af, Fo, Tv), 6k, 6l, 6m, 6n (An, Af, Tv). On the basis of structural activity relationship it has been observed that among the substituents present on the phenyl ring, halo derivatives were found to be highly active the series. Further study reveals that bromo derivatives are highly active.

Conclusion

The dynamic microwave power system employed offered an efficient heating of the material, thus reduced chemical reactions times and increased reaction yields were observed in most of the experiments performed.

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