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A green approach for the heterocyclization of 2-substituted benzimidazoles: Synthesis, characterisation and pharmacological evaluation

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ABSTRACT

*Several 2-[5-(3-Methyl-1H-1,2,4-triazolyl) substituted benzylidenanilin-2-yl] benzimidazole (**3a-f**),2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(2-substitutedphenylthiazolidinon-3-yl)}phenyl] benzimidazole (**4a-f**) and 2-[{4-(3-Methyl-1H-1,2,4-triazolyl) substituted piperazinyl phenyl}]benzimidazole (**5a-c**) have been synthesised by conventional synthesis and microwave methodology. The synthesized derivatives were characterized by IR, ^{1}H-NMR, Mass and elemental analysis (C, H, N). Furthermore the synthesized benzimidazoles (**3a-f**), (**4a-f**) and (**5a-c**) were screened for antimicrobial, insecticidal and anthelmintic activities. The compound **4e** displayed significant biological activities among the all synthesised derivatives and screened for the acute toxicity.*

Keywords: Insecticidal, Anthelmintic, Acute toxicity, Antimicrobial, Thiazolidinones, Benzimidazoles.

INTRODUCTION

Conventional chemical transformations are found to take several hours to days to complete the organic reactions but with microwave assisted organic synthesis (MAOS) [1] it takes few minutes. On the other hand, MAOS has emerged as frontier in synthetic chemical research as it offers solvent-free conditions, reduced pollution, effective costing with simplicity in processing and handling. MAOS is found quiet helpful in achieving GREEN chemistry approach and creating revolution in organic synthesis. Microwave irradiation is well known to promote the synthesis by selective absorption of microwave energy by polar molecules. Benzimidazole is the heterocyclic aromatic organic compound which is found in large number of natural products [2]. Benzimidazole is a bicyclic compound consists of the fusion of benzene and imidazole. This bicyclic compound explored versatile biological profile such as antifungal [3], antimicrobial [4], anthelmintic [5,6], antiviral [7,8], topoisomerase inhibition [9] and anticancer activities [10]. Currently many benzimidazole nucleus bearing drugs are used clinically to treat many pathogenic infections. This category includes carbendazim as antifungal drug [11], mebendazole and thiabendazole as anthelmintic drug [12], pimozide as antipsychotic drug [13] and omeprazole as antiulcer agent [14]. Furthermore 1, 2, 4-triazoles and substituted thiazolidinones are found the block materials for the various biologically active moieties [15-31]. In the present study we have tried to highlight a comparative study between conventional and MAOS by synthesising various substituted thiazolidinone bearing derivatives of benzimidazole.

MATEIALS AND METHODS

All the chemicals used for the preparation of desired derivatives, were obtained from Sisco Research Laboratories (SRL), Mumbai, India; Qualigen Fine Chemicals, Mumbai, India. The melting points of the compounds were determined in open glass capillaries with the help of thermonic melting points apparatus and are uncorrected. The

homogeneity of all the newly synthesized compounds was routinely checked by TLC on silica gel G plates and spots were located by using iodine chamber. Elemental analysis was performed in Heraeus CHN rapid analyser. The results were found within the ±0.4% of theoretical values. Infrared spectra were recorded on KBr pellets on a Perkin Elmer system 2000 FT-IR spectrometer and ^{1}H NMR spectra on Bruker DPX 200 using TMS as internal standard.

Antimicrobial Tests

All the newly synthesized compounds were screened for their antibacterial and antifungal activity against the clinically isolated and identified microbial strains. The pathogens were obtained from the Department of Pathology, L.L.R.M. Medical College, India. Preliminary antimicrobial susceptibility test for the newly synthesized compounds 3a-f, 4a-f and 5a-b were screened for their antibacterial and antifungal activity. Disk diffusion method [32-33] was used for determination of the preliminary antibacterial activity. While on the other hand, the newly prepared compounds were screened for their in vitro antifungal activity by the serial plate dilution method [34-35]. Ampicillin trihydrate and fluconazole were used as standard drugs. The inhibitory values of the tested compounds against the tested bacterial and fungal strains were recorded in mm (**Table-1**).

Insecticidal study

Periplaneta americana was taken for insecticidal study and 1 and 2% acetone solutions of the synthesized 2-substituted benzimidazole derivatives **3a-f**, **4a-f** and **5a-b** were injected in between 4th and 5th abdominal segment on the ventral side of the body of *P. americana* with the help of micro syringe. The time of cockroach's death was recorded as knock down (KD) value. Cypermethrin was used as standard drug. At the time of death the antennae of *P. americana* became motionless, the appendages shrunk and folded towards the ventral side and cockroach lay dorsally [36] (**Table-2**).

Anthelmintic activity

Indian adult earthworms (*Pheretima posthuma*) were collected from moist soil and washed with normal saline to remove all faecal matter and used for the anthelmintic activity. All the synthesized 2-substituted benzimidazole derivatives **3a-f**, **4a-f** and **5a-b** were dissolved in minimum amount of DMF and the volume adjusted to 10 ml with saline water. All solutions of synthesized derivatives and drugs solutions were freshly prepared. Groups of six earthworms were released into desired formulations and the paralytic and lethal time noted. Albendazole was used as standard drug. Observations were made for the time taken for paralysis and death of individual worms. Paralysis was said to occur when the worms did not receive even in normal saline. Death was concluded when the worms lost their motility followed by fading away of their body colour [37-40] (**Table-3**).

Acute toxicity

Lethal doses (LD_{50}) of compound were determined in albino mice. After 24 h of drug administration, mortality in each group was observed and from the data obtained LD_{50} was calculated by the method of Carrol [41]. Data revealed that compound **4e** does not show any toxicity up to dose of 10.2 mg/kg body weight in mice

Synthesis

Synthesis of 2-Amino-4-(3-methyl-1H-1,2,4-triazol-1-yl)benzoic acid (1)

Microwave Irradiation Method

3-Methyl-1*H*-1,2,4-triazole (0.01 mol) and 2-amino-4-bromobenzoic acid (0.01 mol) were taken in ethanol followed by the drop wise addition of triethylamine (0.01 mol) over the period of 20 minutes. After the reaction mixture was placed in microwave oven and refluxed at level-2 (210watt) for 5 min. Progress of reaction was regularly monitored by TLC. On completion of reaction, the reaction mixture was poured over the crushed ice. The resulting crystals are filtered. The crude was recrystallized from ethanol-water to give compound **1**. Yield: 85%.

Conventional Method

An ethanolic mixture of 3-Methyl-1*H*-1,2,4-triazole (0.01 mol) and 2-amino-4-bromobenzoic acid (0.01 mol) was prepared which was followed by the dropwise addition of triethylamine (0.01 mol) over a period of 20 minutes. Thus obtained reaction mixture refluxed for 2 hr. Progress of reaction was regularly monitored by TLC. On completion of the reaction, excess amount of solvent was distilled and obtained residue poured over the crushed ice. The resulting solid washed, filtered, dried and recrystallized from ethanol-water to yield compound **1**. Yield: 72%. M.p.: 108-110 ^{0}C. R_f: 0.76. IR (KBr, ν, cm^{-1}): 3420, 3025, 2942, 1695, 1622. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 2.19 (s, 3H, CH_3), 6.20 (bs, 2H, NH_2-Ph), 7.80-6.96 (m, 3H, ArH), 9.10 (s, 1H, -N=CH-N), 11.50 (s, 1H, HOOC-Ph). MS (m/z, %): 218.08. Anal. calcd. for $C_{10}H_{10}N_4O_2$: C,55.04; H, 4.62; N, 25.68%. Found: C, 55.40; H, 4.58; N, 25.62%.

Synthesis of 2-[5-(3-Methyl-1H-1, 2, 4-triazolyl) aniline-2-yl]benzimidazole (2)
Microwave Irradiation Method
o-Phenylenediamine (0.01 mol) and compound **1** (0.01 mol) were taken in ethanol followed by the addition of a pinch of potassium carbonate. The resulting mixture was placed in microwave oven and refluxed at level-2 (210 watt) for 6 min. Progress of reaction was regularly monitored by TLC. On completion of reaction, the reaction mixture was poured over the crushed ice. The resulted mixture made alkaline by adding 10% NaOH to get the solid product. The product was filtered, washed, dried and recrystallised from ethanol to get compound **2**. Yield: 82%.

Conventional Method
An ethanolic mixture o-phenylenediamine (0.01 mol) and compound **1** (0.01 mol) was refluxed for 4 hr. in presence of pinch of potassium carbonate. After completion of the reaction, ethanol was removed by distillation and the residue was poured into crushed ice. Then it was made alkaline by using 10% NaOH to get the solid product. The product was filtered, washed, dried and recrystallised from ethanol to furnish compound **2**. Yield: 64%. M.p.: 135-137 ^{0}C. R_f: 0.69. IR (KBr, cm^{-1}): 3425, 3022, 2937, 1691, 1620. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 2.10 (s, 3H, CH_3), 3.65 (s, 1H, CH=N), 4.85 (bs, 1H, NH), 6.13 (bs, 2H, NH_2-Ph), 6.82-7.90(m, 7H, ArH). MS (m/z, %): 290.13. Anal. calcd. for $C_{16}H_{14}N_6$: C,66.19; H, 4.86; N,28.95%. Found: C, 66.15; H, 4.85; N, 29.03%.

General preparation of 2-[5-(3-Methyl-1H-1,2,4-triazolyl) substituted benzyliden anilin-2-yl] benzimidazole (3a-f)
Microwave Irradiation Method
A reaction mixture of compound **2** (0.01 mol) with various aromatic aldehydes (0.01 mol) in ethanol was placed in microwave oven and refluxed at power level-2 (210 watt) for 8-12 min. and excess of solvent was removed by distillation. The residue poured on crushed ice and acidified with dil. hydrochloric acid. The appeared solid was filtered, dried and recrystallised from appropriate solvents to obtain compounds **3a-f** .

***2-[5-(3-Methyl-1H-1,2,4-triazolyl)benzylidenanilin-2-yl]benzimidazole* 3a:** Yield: 84%.
***2-[5-(3-Methyl-1H-1,2,4-triazolyl)(2`-chlorobenzyliden)anilin-2-yl]benzimidazole 3b*:** Yield: 81%.
***2-[5-(3-Methyl-1H-1,2,4-triazolyl)(4`-chlorobenzyliden)anilin-2-yl]benzimidazole 3c*:** Yield: 82%.
***2-[5-(3-Methyl-1H-1,2,4-triazolyl)(2`-bromobenzyliden)anilin-2-yl]benzimidazole 3d*:** Yield: 85%.
***2-[5-(3-Methyl-1H-1,2,4-triazolyl)(4`-fluorobenzyliden)anilin-2-yl]benzimidazole 3e*:** Yield: 80%.
***2-[5-(3-Methyl-1H-1,2,4-triazolyl)(4`-bromobenzyliden)anilin-2-yl]benzimidazole 3f*:** Yield: 78%.

Conventional Method
An ethanolic mixture of compound **2** (0.01 mol) and various aromatic aldehydes (0.01 mol) in ethanol heated to reflux in presence of acetic acid for 3-5 hr. On completion the reaction, the excess of solvent was removed by distillation. The residue poured on crushed ice and acidified with dil. hydrochloric acid. The appeared solid was filtered, dried and recrystallised from appropriate solvents to furnish compounds **3a-f**.

***2-[5-(3-Methyl-1H-1,2,4-triazolyl)benzylidenanilin-2-yl]benzimidazole* 3a:** Yield: 56%. M.p.: 159-161 ^{0}C. R_f: 0.60. IR (KBr, cm^{-1}): 3025, 2942, 1622, 1552, 1312. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 2.10 (s, 3H, CH_3), 5.00 (bs, 1H, -NH), 7.10-7.85 (m, 12H, ArH), 8.50 (s, 1H,-CH=N), 9.25 (s, 1H, -N=CH-N). MS (m/z, %): 378.43. Anal. calcd. for $C_{23}H_{18}N_6$: C,73.00; H, 4.79; N,22.21%. Found: C, 72.88; H, 4.82; N, 22.30%.

***2-[5-(3-Methyl-1H-1,2,4-triazolyl)(2`-chlorobenzyliden)anilin-2-yl]benzimidazole 3b*:** Yield: 62%. M.p.: 126-128 ^{0}C. R_f: 0.67. IR (KBr, cm^{-1}): 3020, 2946, 1627, 1547, 1320. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 2.00 (s, 3H, CH_3), 5.08 (bs, 1H, -NH), 6.96-7.65 (m, 11H, ArH), 8.40 (s, 1H,-CH=N), 9.27(s, 1H, -N=CH-N). MS (m/z, %): 412.87. Anal. calcd. for $C_{23}H_{17}N_6Cl$: C,66.90; H, 4.15; N,20.35%. Found: C, 66.85; H, 4.11; N, 22.30%.

***2-[5-(3-Methyl-1H-1,2,4-triazolyl)(4`-chlorobenzyliden)anilin-2-yl]benzimidazole 3c*:** Yield: 60%. M.p.: 163-165 ^{0}C. R_f: 0.71. IR (KBr, cm^{-1}): 3023, 2940, 1620, 1556, 1316. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 2.05 (s, 3H, CH_3), 4.96 (bs, 1H, -NH), 6.90-7.62 (m, 11H, ArH), 8.38 (s, 1H,-CH=N), 9.16(s, 1H, -N=CH-N). MS (m/z, %): 412.87. Anal. calcd. for $C_{23}H_{17}N_6Cl$: C,66.90; H, 4.15; N,20.35%. Found: C, 67.00; H, 4.08; N, 22.25%.

***2-[5-(3-Methyl-1H-1,2,4-triazolyl)(2`-bromobenzyliden)anilin-2-yl]benzimidazole 3d*:** Yield: 55%. M.p.: 138-140 ^{0}C. R_f: 0.78. IR (KBr, cm^{-1}): 3017, 2942, 1630, 1541, 1323. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 1.94 (s, 3H, CH_3), 5.10 (bs, 1H, -NH), 6.77-7.45 (m, 11H, ArH), 8.51 (s, 1H,-CH=N), 9.10(s, 1H, -N=CH-N). MS (m/z, %): 457.33. Anal. calcd. for $C_{23}H_{17}N_6Br$: C,60.40; H, 3.75; N,18.38%. Found: C, 60.21; H, 3.71; N, 18.32%.

***2-[5-(3-Methyl-1H-1,2,4-triazolyl)(4`-fluorobenzyliden)anilin-2-yl]benzimidazole 3e*:** Yield: 58%. M.p.: 165-167 ^{0}C. R_f: 0.74. IR (KBr, cm^{-1}): 3022, 2945, 1629, 1553, 1314. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 2.02 (s, 3H, CH_3),

4.82 (bs, 1H, -NH), 6.81-7.66 (m, 11H, ArH), 8.33 (s, 1H,-CH=N), 9.15(s, 1H, -N=CH-N). MS (m/z, %): 396.42. Anal. calcd. for $C_{23}H_{17}FN_6$: C,69.69; H, 4.32; N,21.20%. Found: C, 69.44; H, 4.27; N, 21.26%.

***2-[5-(3-Methyl-1H-1,2,4-triazolyl)(4`-bromobenzyliden)anilin-2-yl]benzimidazole 3f*:** Yield: 50%. M.p.: 150-152 ^{0}C. R_f: 0.70. IR (KBr, cm^{-1}): 3025, 2937, 1635, 1550, 1325. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 2.11 (s, 3H, CH_3), 4.90 (bs, 1H, -NH), 6.70-7.49 (m, 11H, ArH), 8.46 (s, 1H,-CH=N), 9.21(s, 1H, -N=CH-N). MS (m/z, %): 457.33. Anal. calcd. for $C_{23}H_{17}N_6Br$: C,60.40; H, 3.75; N,18.38%. Found: C, 60.25; H, 3.68; N, 18.36%.

2.5.4. General preparation of 2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(2-substitutedphenyl thiazolidinon-3-yl)}phenyl]benzimidazole (4a-f)

Microwave Irradiation Method

A reaction mixture of compound **3a-f** (0.01 mol) and thioglycolic acid (0.01 mol) in DMF with a catalytic amount of zinc chloride was placed in a round-bottomed flask inside a microwave oven and refluxed at power level-2 for 8-12 min. and the excess of DMF was removed by distillation. The residue poured on crushed ice and acidified with dilute hydrochloric acid. The appeared solid was filtered, dried and recrystallised with appropriate solvents to obtain compounds **4a-f**.

2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(2- phenylthiazolidinon-3-yl)}phenyl]benzimidazole 4a: Yield: 79%.
2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(2`-chlorophenylthiazolidinon-3-yl)}phenyl]benzimidazole 4b: Yield: 81%.
2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(4`-chlorophenylthiazolidinon-3-yl)}phenyl]benzimidazole 4c: Yield: 77%.
2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(2`-bromophenylthiazolidinon-3-yl)}phenyl]benzimidazole 4d: Yield: 84%.
2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(4`-fluorophenylthiazolidinon-3-yl)}phenyl]benzimidazole 4e: Yield: 81%.
2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(4`-bromophenylthiazolidinon-3-yl)}phenyl]benzimidazole 4f: Yield: 76%.

Conventional Method

Compound **3a-f** (0.01 mol) and thioglycolic acid (0.01 mol) was taken in DMF followed and refluxed with a catalytic amount of zinc chloride over an oil bath for about 3-6 hr. The solvent was distilled and residue poured in ice water, filtered, washed, dried, recrystallised from appropriate solvents mixture to yield compound **4a-f**.

2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(2-phenylthiazolidinon-3-yl)}phenyl]benzimidazole 4a: Yield: 66%. M.p.: 128-130 ^{0}C. R_f: 0.66. IR (KBr, cm^{-1}): 3024, 2946, 1707, 1620, 1557, 1310, 674. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 1.88 (s, 3H, CH_3), 3.90 (s, 2H, -CH_2-S-), 5.08 (bs, 1H, -NH), 6.45 (s, 1H,-CH of thialactam), 7.01-7.85 (m, 12H, ArH), 9.20 (s, 1H, -N=CH-N). MS (m/z, %): 452.53. Anal. calcd. for $C_{25}H_{20}N_6SO$: C, 66.35; H, 4.45; N, 18.57%. Found: C, 66.29; H, 4.40; N, 18.55%.

2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(2`-chlorophenylthiazolidinon-3-yl)}phenyl]benzimidazole 4b: Yield: 50%. M.p.: 149-151 ^{0}C. R_f: 0.60. IR (KBr, cm^{-1}): 3026, 2940, 1710, 1622, 1560, 1312, 670. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 1.92 (s, 3H, CH_3), 3.99 (s, 2H, -CH_2-S-), 5.00 (bs, 1H, -NH), 6.30 (s, 1H,-CH of thialactam), 6.96-7.75 (m, 11H, ArH), 9.30 (s, 1H, -N=CH-N). MS (m/z, %): 486.98. Anal. calcd. for $C_{25}H_{19}N_6SOCl$: C, 61.66; H, 3.93; N, 17.26%. Found: C, 61.60; H, 3.92; N, 17.22%.

2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(4`-chlorophenylthiazolidinon-3-yl)}phenyl]benzimidazole 4c: Yield: 59%. M.p.: 132-135 ^{0}C. R_f: 0.67. IR (KBr, cm^{-1}): 3020, 2943, 1705, 1625, 1562, 1315, 675. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 1.80 (s, 3H, CH_3), 3.82 (s, 2H, -CH_2-S-), 5.15 (bs, 1H, -NH), 6.39 (s, 1H,-CH of thialactam), 6.78-7.56 (m, 11H, ArH), 9.18 (s, 1H, -N=CH-N). MS (m/z, %): 486.98. Anal. calcd. for $C_{25}H_{19}N_6SOCl$: C,61.66; H, 3.93; N,17.26%. Found: C, 61.57; H, 3.88; N, 17.12%.

2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(2`-bromophenylthiazolidinon-3-yl)}phenyl]benzimidazole 4d: Yield: 49%. M.p.: 166-168 ^{0}C. R_f: 0.72. IR (KBr, cm^{-1}): 3027, 2938, 1709, 1620, 1567, 1320, 677. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 1.94 (s, 3H, CH_3), 3.80 (s, 2H, -CH_2-S-), 5.21 (bs, 1H, -NH), 6.42 (s, 1H,-CH of thialactam), 6.72-7.53 (m, 11H, ArH), 9.13 (s, 1H, -N=CH-N). MS (m/z, %): 531.43. Anal. calcd. For $C_{25}H_{19}N_6SOBr$: C, 56.50; H, 3.60; N, 15.81%. Found: C, 56.21; H, 3.67; N, 16.02%.

2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(4`-fluorophenylthiazolidinon-3-yl)}phenyl]benzimidazole 4e: Yield: 58%. M.p.: 169-171 ^{0}C. R_f: 0.71. IR (KBr, cm^{-1}): 3023, 2945, 1711, 1621, 1558, 1311, 672. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 1.96 (s, 3H, CH_3), 3.87 (s, 2H, -CH_2-S-), 5.20 (bs, 1H, -NH), 6.35 (s, 1H,-CH of thialactam), 6.80-7.60 (m, 11H, ArH), 9.15 (s, 1H, -N=CH-N). MS (m/z, %): 470.52. Anal. calcd. for $C_{25}H_{19}N_6SOF$: C, 63.82; H, 4.07; N,17.86%. Found: C, 64.00; H, 4.12; N, 18.02%.

2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(4`-bromophenylthiazolidinon-3-yl)}phenyl]benzimidazole 4f: Yield: 54%. M.p.: 147-149 ^{0}C. R_f: 0.79. IR (KBr, cm^{-1}): 3020, 2940, 1705, 1622, 1560, 1318, 679. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 1.79 (s, 3H, CH_3), 3.72 (s, 2H, -CH_2-S-), 5.25 (bs, 1H, -NH), 6.49 (s, 1H,-CH of thialactam), 6.63-7.50 (m, 11H, ArH), 9.10 (s, 1H, -N=CH-N). MS (m/z, %): 531.43. Anal. calcd. for $C_{25}H_{19}N_6SOBr$: C,56.50; H, 3.60; N,15.81%. Found: C, 56.40; H, 3.62; N, 15.92%.

General preparation of 2-[{4-(3-Methyl-1H-1,2,4-triazolyl)substitutedpiperazinylphenyl}] benzimidazole (5a-c)
Microwave Irradiation Method
Compound **2** (0.01mol) and substituted morpholines (0.01mol) were taken in DMF, stirred for 15 minutes at room temperature. After, resulting reaction mixture was placed in a round-bottomed flask inside a microwave oven and refluxed at power level-2 (210watt) for 6-8 min. and the excess of DMF was removed by distillation. The residue dumped on ice water, filtered, washed, dried, triturated with petroleum ether and recrystallised with appropriate solvents to obtain compound **5a-c**.

2-[4-{(3-Methyl-1H-1,2,4-triazol-1-yl)-2-(piperazine-1-yl)phenyl}]benzimidazole 5a: Yield: 76%.
2-[2-{4-(2-bromoethyl)piperazin-1-yl)-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl}]benzimidazole 5b: Yield: 70%.
2-[2-{4-(2-bromopropyl)piperazin-1-yl)-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl}]benzimidazole 5c: Yield: 81%.

Conventional Method
A reaction mixture of compound **2** (0.01 mol) and substituted morpholines (0.01mol) was prepared in DMF and allowed to stir for 15 minutes at room temperature. After, resulting reaction mixture refluxed over an oil bath for about 1-2 hr. On completion of reaction, excess solvent was distilled and residue dumped in ice water, filtered, washed, dried, triturated with petroleum ether and recrystallised with appropriate solvents to yield compound **5a-c**.

2-[4-{(3-Methyl-1H-1,2,4-triazol-1-yl)-2-(piperazine-1-yl)phenyl}]benzimidazole 5a: Yield: 56%. M.p.: 128-130 ^{0}C. R_f: 0.70. IR (KBr, cm^{-1}): 3020, 2933, 1629, 1552, 1316. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 1.05-1.30 (s, 8H, 4XCH_2), 1.76 (bs, 1H, NH), 2.28 (s, 3H, CH_3), 3.82 (s, 1H, CH=N), 5.55 (bs, 1H, NH), 6.74-7.57 (m, 7H, ArH). MS (m/z, %): 359.43. Anal. calcd. for $C_{20}H_{21}N_7$: C,66.83; H, 5.89; N,27.28%. Found: C, 67.05; H, 5.83; N, 27.20%.

2-[2-{4-(2-bromoethyl)piperazin-1-yl)-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl}]benzimidazole 5b: Yield: 48%. M.p.: 139-141 ^{0}C. R_f: 0.76. IR (KBr, cm^{-1}): 3026, 2937, 1633, 1545, 1307. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 1.07-1.28 (s, 8H, 4XCH_2), 2.15 (s, 3H, CH_3), 2.70(t, 2H, CH_2-), 3.50 (t, 2H, CH_2-), 3.97 (s, 1H, CH=N), 5.55 (bs, 1H, NH), 6.74-7.57 (m, 7H, ArH). MS (m/z, %): 466.38. Anal. calcd. for $C_{22}H_{24}N_7Br$: C,56.66; H, 5.19; N,21.02%. Found: C, 56.50; H, 5.10; N, 20.90%.

2-[2-{4-(2-bromopropyl)piperazin-1-yl)-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl}]benzimidazole 5c: Yield: 63%. M.p.: 144-146 ^{0}C. R_f: 0.69. IR (KBr, cm^{-1}): 3023, 2934, 1636, 1548, 1311. ^{1}H-NMR (200 MHz, $CDCl_3$, δ, ppm): 1.12-1.33 (s, 8H, 4XCH_2), 2.04 (s, 3H, CH_3), 2.68-3.59 (m, 6H,-$(CH_2)_3$-), 4.10 (s, 1H, CH=N), 5.51 (bs, 1H, NH), 6.70-7.52 (m, 7H, ArH). MS (m/z, %): 480.40. Anal. calcd. for $C_{23}H_{26}N_7Br$: C,57.50; H, 5.46; N,20.41%. Found: C, 57.66; H, 5.50; N, 20.62%.

RESULTS AND DISCUSSION

Chemistry
The synthetic route for the synthesis is outlined in **Scheme-1** & **2**. Reaction of 2-amino-4-bromo benzoic acid with 3-methyl-1*H*-1,2,4-triazole yielded compound **1**, which on further refluxing with o-phenylene diamine furnished compound **2**. A sub-route also designed by the reaction of compound 2 with 4-substituted morpholines to furnish compound **5a-c (Scheme-2)**. The condensation reaction of compound **2** and substituted aryl aldehydes resulted into the Schiff bases (**3a-f**). Schiff bases (**3a-f**) were refluxed with thioglycolic acid in presence of a pinch of anhydrous zinc chloride to furnish 2-[{4-(3-methyl-1*H*-1,2,4-triazolyl)}{2-(2-substituted phenyl-4-thiazolidinon-3-yl)} phenyl] benzimidazole (**4a-f**) (***Scheme-1***). The synthesised benzimidazoles were evaluated for antimicrobial, insecticidal and anthelmintic activities (**Table 1**, **2** & **3**).

Pharmacology
All the prepared derivatives 2-[5-(3-Methyl-1H-1,2,4-triazolyl) substituted benzylidenanilin-2-yl] benzimidazole (**3a-f**), 2-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(2-substitutedphenylthiazolidinon-3-yl)}phenyl] benzimidazole (**4a-f**) and 2-[{4-(3-Methyl-1H-1,2,4-triazolyl) substituted piperazinyl phenyl}]benzimidazole (**5a-c**) were tested for antibacterial, antifunagal, insecticidal and anthelmintic activities. *Staphylococcus aureus, Klabsiella pneumoniae, Aspergillus fumigatus* (plant isolate), *Candida glabrata* pathogens were used for antimicrobial activity. Insecticidal activity performed against *Periplaneta Americana*. *Pheretima posthuma* were used for the anthelmintic activity.

During antimicrobial screening, results revealed that compound **4e** showed remarkable antimicrobial spectrum. Compounds **3a-f** displayed milder inhibitory action. Compound **3c** and **3e** showed broader antimicrobial activity but comparatively better inhibition was demonstrated by compound **3e**. Among the thiazolidinone bearing benzimidazoles **4a-f**, compound **4d** and **4e** illustrated significant antimicrobial spectrum. But compound **4e** claimed better inhibition against the used pathogens. Piperazinyl bearing benzimidazoles **5a-c** displayed very poor inhibitory action. Compound **5b** and **5c** showed poor inhibition against *A. fumigatus* only.

Insecticidal activity results cleared that among the tested compounds **3a-f**, **4a-f** and **5a-c**. Compound **3e** and **4e** gave better KD values at two different doses- 1% and 2% against *P. americana*. Compound **4e** displayed considerable insecticidal potential in comparison to used standard cypermethrin. During anthelmintic activity, resulta were collected as paralytic and lethal time in minutes. Compounds **3a-f**, **4a-f** and **5a-c** tested against *P. posthuma*. Data cleared that compound **5a-f** showed no insecticidal activity. Compounds **3a-f** and **4a-f** displayed mild to moderate insecticidal activity. Compound **3b**, **4a** and **4e** showed better potential than the remaining derivatives. Compound **3b** and **4a** claimed same potentials but it was **4e** who elicited significant insecticidal activity among the all tested series of compounds.

Table 1. Antimicrobial test of 2-substituted benzimidazoles

Comp.	R	R'	Antibacterial activity (mm)		Antifungal activity	
			S. aureus	*K. pneumoniae*	*A. fumigatus*	*C. glabrata*
3a.	H		-	6	-	-
3b.	2-Cl		10	8	6	-
3c.	4-Cl		8	10	8	8
3d.	2-Br		-	10	10	-
3e.	4-F		10	15	12	8
3f.	4-Br		8	10	8	-
4a.	H		8	6	10	-
4b.	2-Cl		12	10	10	6
4c.	4-Cl		15	10	8	10
4d.	2-Br		12	12	12	8
4e.	4-F		18	18	16	10
4f.	4-Br		6	10	10	10
5a.		4-$(CH_2)_2$Br	-	-	6	-
5b.		4-$(CH_2)_3$Br	-	-	8	-
5c.		H				
Ampicillin trihydrate			16	20	-	-
Fluconazole			-	-	20	15
DMF (control)			-	-	-	-

- means no activity.

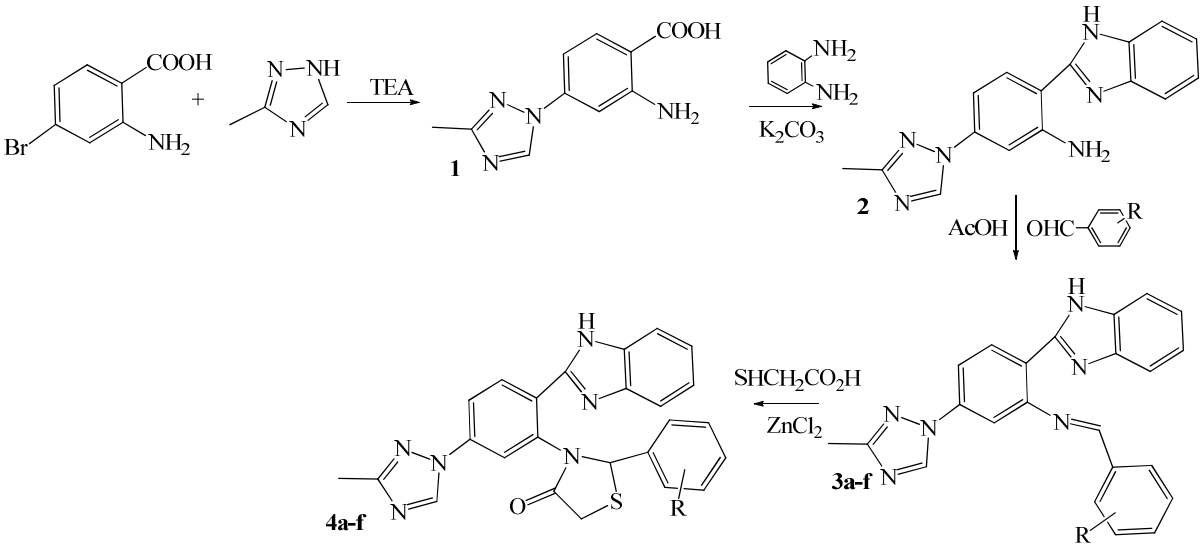
Table 2. Insecticidal activity of 2-substituted benzimidazoles at two different concentrations (KD value in min.)

Comp.	R	R`	Time [min.]	
			1%	2%
3a.	H		19	16
3b.	2-Cl		19	16
3c.	4-Cl		16	10
3d.	2-Br		17	13
3e.	4-F		14	8
3f.	4-Br		19	15
4a.	H		14	8
4b.	2-Cl		12	10
4c.	4-Cl		12	8
4d.	2-Br		10	8
4e.	4-F		7	6
4f.	4-Br		15	10
5a.		H	20	15
5b.		4-$(CH_2)_2$Br	22	16
5c.		4-$(CH_2)_3$Br	22	18
Cypermethrin			7	5

Table 3. Anthelmintic activity of 2-substituted benzimidazoles against *Pheretima posthuma* (paralytic and lethal time in min.)

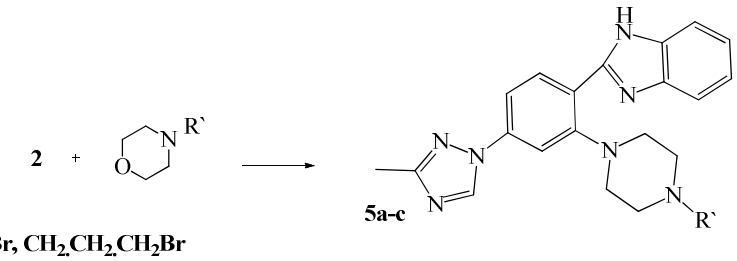
Comp.	R	R'	Paralytic time (min.)	Lethal time (min.)
3a.	H		14	20
3b.	2-Cl		10	13
3c.	4-Cl		13	15
3d.	2-Br		10	16
3e.	4-F		15	20
3f.	4-Br		18	20
4a.	H		10	13
4b.	2-Cl		15	18
4c.	4-Cl		10	16
4d.	2-Br		12	18
4e.	4-F		6	10
4f.	4-Br		10	16
5a.		4-$(CH_2)_2Br$	-	-
5b.		4-$(CH_2)_3Br$	-	-
5c.		H	14	20
Albendazole			5	8

(-) Means no activity.



R = H, 2-Cl, 4-Cl, 2-Br, 4-F, 4-Br

SCHEME-1



R` = H, CH_2CH_2Br, $CH_2CH_2CH_2Br$

SCHEME-2

CONCLUSION

Microwave irradiation offers significant improvements over existing conventional synthetic methodology. Synthesis of 2-substituted thiazolidinonyl benzimdazoles using catalytic amount of zinc chloride in DMF under MAOS helps facile access into of 2-thiazolidinones of potentially high synthetic utility. This simple and reproducible technique affords various *2*-[4-{(3-Methyl-1H-1,2,4-triazolyl)-2-(2-substituted phenylthiazolidinon-3-yl)}phenyl] benzimidazole (**4a-f**) & 2-[{4-(3-Methyl-1H-1,2,4-triazolyl) substituted piperazinylphenyl}] benzimidazole (**5a-c**)

with shorter reaction time spans, excellent yields and without formation of undesirable by-products in comparison to conventional synthetic methodology. The different substitution on the block structure of benzimidazole was incorporated with various substituted aromatic rings bring a significant influence on the biological spectrum of benzimidazoles (**4a-f**) instead of piperazines bearing benzimidazoles (**5a-c**). Among the synthesised substituted benzimidazoles (**3a-f**), (**4a-f**) & (**5a-c**), only thiazolidinone bearing benzimidazole derivatives displayed notable biological activity viz. antifungal, insecticidal and antihelmintic; in compare to used standard drugs.

On the basis of structure activity relationship, it was found that presence of electron-withdrawing group on the aromatic ring in general displayed remarkable pharmacological potential in term of antibacterial, antifungal, insecticidal and antihelmintic activity. Among the biologically screened substituted benzimidazoles (**3a-f**), (**4a-f**) & (**5a-c**), only derivative **4e** educed better biological potency. Based upon the biological screening data, it is cleared that 4-fluro phenyl substitution in 2-substituted benzimidazole derivative i.e. **4e**, will be necessary to modifying the antibacterial, antifungal, insecticidal and antihelmintic activity.

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REFERENCES

[1]. R. S. Varma, *Microwaves in Organic Synthesis, A. Loupy, Ed., Wiley-VCH, Weinheim*, **2002**, 6, 181.
[2]. G. Balboni, C. Trapella, Y. Sasaki, *J. Med. Chem.*, **2009**, 52(17), 5556.
[3]. A. W. Maxwell, G. Brody, *Appl. Microb.*, **1971**, 21(5), 944.
[4]. D. Sharma, B. Narasimhan, P. Kumar, A. Jalbout, *Eur. J. Med. Chem.*, **2009**, 44(3), 1119.
[5]. A. A. Farahat, E. Paliakov, A. Kumar , *Bioorg. Med. Chem.*, **2011**, 19(7), 2156.
[6]. D.Valdez-Padilla, S. Rodrguez-Morales, A. Hernandez-Campos, *Bioorg. Med. Chem.*, **2009**, 17(4), 1724.
[7]. Y. F. Li, G. F. Wang, P. L. He, *J. Med. Chem.*, **2006**, 49(15), 4790.
[8]. H. Banie, A. Sinha, R. J. Thomas, C. J. Sircar, L. M. Richards, *J. Med. Chem.*, **2007**, 50(24), 5984.
[9]. P. S. Charifson, A. L. Grillot, T. H. Grossman, *J. Med. Chem.*, **2008**, 51(17), 5243.
[10]. J. Chen, Z. Wang, C. M. Li, *J. Med. Chem.*, **2010**, 53(20), 7414.
[11]. H. Goker, C. Kus¸ D. W. Boykin, S. Yıldız, N. Altanlar, *Bioorg. Med. Chem.*, **2011**, 10(8), 2589.
[12]. G. N. Vazquez, L. Yepez, A. H. Campos, *Bioorg. Med. Chem.*, **2003**, 11(21), 4615.
[13]. K. J. Spivak, Z. Amit, *Physiol. Behav.* **1986**, 36(3), 457.
[14]. P. Lindberg, P. Nordberg, T. Alminger, *J. Med. Chem.*, **1986**, 29(8), 1327.
[15]. B. S. Patil, G. Krishnamurthy, H. B. Naik, P. R. Latthe, M. Ghate, *Eur. J. Med. Chem.*, **2010**, 45(8), 3329.
[16]. H. Bayrak, A. Demirbas, N. Demirbas, S. A. Karaoglu, *Eur. J. Med. Chem.*, **2009**, 44(11), 4362.
[17]. J. Xu, Y. Cao, J. Zhang, S. Yu, Y. Zuo, C. Xiaogyun, Q. Wu, D. Zhang, Y. Jiang, Q. Sun, *Eur. J. Med. Chem.*, **2011**, 46(7), 3142.
[18]. B. Tozkpran, E. Kupeli, E. Yesilada, M. Ertan, *Bioorg. Med. Chem.*, **2007**, 15(4), 1808.
[19]. B. S. Holla, B. Veerandra, M. K. Shivananda, B. Poojary, *Eur. J. Med. Chem.*, **2003**, 38(7-8), 759.
[20]. A. Duran, H. N. Dogan, S. Rollas, *Il Farmaco*, **2002**, 57(7), 559.
[21]. M. T. Abdel-Aal, W. A. El-Sayed, S. M. El-Kosy, E. S. H. El-Ashry, *Arch. Pharm.*, **2008**, 341(5), 307.
[22]. I. Kucukguzel, S. G. Kucukguzel, S. Rollas, M. Kiraz, *Bioorg. Med. Chem. Lett.* **2001**,11(13), 1703.
[23]. A. R. Bhat, S. Shetty, *Ind. J. Pharm. Sci.*,**1987**, 49(5), 194.
[24]. G. Capan, N. Ulusoy, N. Ergenc, M. Kiraz, *Montsch Chem.*, **1999**,130(11), 1399.
[25]. M. Abhinit, M. Ghodke, N. A. Pratima, *Int. J. Pharm. Sci.*, **2009**, 1, 47.
[26]. N. J. Hrib, J. G. Jurcak, J. G. Bregna, *J. Med. Chem.*, **1992**, 35(14), 2712.
[27]. A. Solanki, K. Kishore, *Asian J. Chem.*, **1994**, 6(3), 177.
[28]. N. J. Gaikwad, S. B. Agrawal, *Ind. Drugs*, **1997**, 34(9), 542.
[29]. N. C. Desai, B. R. Parekh, K. A. Thaker, *J. Ind. Chem. Soc.*, **1987**, 64(8), 491.
[30]. T. Kato, T. Ozaki, K. Tamura, Y. Suzuki, M. Akima, N. Ohi, *J. Med. Chem.*, **1999**, 42(16), 3134.
[31]. V. S. Ingle, A. R. Sawale, R. D. Ingle, R. A. Mane, *Ind. J. Chem. B*, **2001**, 40(2), 124.
[32]. R. Cruickshank, J. P. Duguid, B. P. Marion, R. H. A. Swain, *Medicinal Microbiology, 12th ed.; Churchill Livingstone: London, UK*, **1975**, 2, 196.
[33]. A. H. Collins, *Microbiological Methods 2nd ed., Butterworth, London, U.K.*, **1976**, 63.
[34]. Z. K. Khan, *In vitro and vivo screening techniques for bioactivity screening and evaluation in Proceedings of the International Workshop on UNIDO-CDRI*, **1997**, 210.
[35]. R. S. Verma, Z. K. Khan, A. P. Singh, *National Academy of Chemistry and Biology*, **1998**, India, 55.
[36]. R. Kaneko, H. Murayama, K. Seki, H. Shimamura, K. Shimano, H. Yamaguchi, *US Pat.*, **1986**.
[37]. A. S. Nirmal, G. Malwadkar, R. B. Laware, *Son. J. Sci. Tech.* **2007**, 29(3), 755.

[38]. V. D. Tambe, S. A. Nirmal, R. S. Jadhav, P. B. Ghogare, R. D. Bhalke, A. S. Girme, R. S. Bhamber, *Ind. J. Nat. Prod.*, **2006**, 22, 27.
[39]. G. W. Thorn, R. D. Adams, R. G. Petersdrof, *Harrison's Principles of Internal Medicine*, **1977**, 1088.
[40]. Z. Vilgar, *Atlas of Medical Parasitology*, **1984**, 216.
[41]. S. W. Carol, *Biometrics*, **1952**, 249.