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Antibacterial activity of some newer 1,2,3 – benzotriazole derivatives synthesized by ultrasonication in solvent – free conditions

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Many of the classical synthetic methodologies have broad scope but generate copious amounts of waste. The chemical and pharmaceutical industries have been subjected to increasing pressure to minimize or, preferably, eliminate this waste. In the present study a series of some newer 1,2,3–benzotriazole derivatives were synthesized under ultrasonicated and solvent–free conditions. Newer "1–(1H–benzo[d][1,2,3]triazole–1–carbonyl) derivatives" (**5A – 5P**) were synthesized from "1H–benzo[d][1,2,3]triazole" (**1**) by optimizing the reaction conditions. The resulting products were isolated and characterized by spectral studies. The anti bacterial activities of these compounds were screened *in vitro* against different strains of bacteria i.e. Gram negative organism (*Pseudonomous aureginosa,* MTCC – 1035) and Gram positive organisms (*Bacillus cereus,* MTCC – 430, *Bacillus subtilis,* MTCC – 441, *Staphylococcus aureus,* MTCC – 737, *Staphylococcus epidermidis,* MTCC – 3086) by paper disc diffusion method. Some of the synthesized compounds showed significant activity against various bacteria.

Key words: Ultrasound irradiation, solvent-free synthesis, 1,2,3 - benzotriazole derivatives, anti bacterial activity.

INTRODUCTION

Heterocyclic compounds containing nitrogen atoms are considered to be one of the most effective antimicrobial drugs used as either single agents or in combination for cancer therapy [1, 2]. Some benzotriazole derivatives have shown anti-inflammatory properties [3]. Touami *et al* [4] reported that the conjugates of benzotriazole derivative photonucleases and DNA minor groove binders exhibit enhanced cleavage efficiency and unique selectivity. It has been proposed that the benzotriazole derivatives have the effect on cancer development [5]. Sparatore and Sparatore reported that 2-(4-(Dialkyl amino alkoxy) phenyl) benzotriazoles and N-oxides works as thromboxane A2 antagonists and as hypocholesterolemic agents, platelet aggregation inhibitors [6], where as benzotriazole carboxylic acid or ester derivatives were found to be effective in the treatment of metabolic related disorders including atherosclerosis, coronary heart disease and type 2 diabetes [7]. Biagi *et al.* [8] reported that 5-(substituted) benzotriazoles and triazolyl benzotriazoles as potential potassium channel activators.

The ultrasound irradiation technique has been increasingly used in organic synthesis for last three decades. A large number of organic reactions have been carried out in higher yield, shorter reaction time and milder condition under ultrasound irradiation [9-12]. It is well known that ultrasonic irradiation to a liquid phase reaction accelerates the chemical reaction and creates a special reaction field for the preparation of various materials [13-16].

There is a growing awareness that the design of synthetic or chemical processes should follow the basic principles of green chemistry to reduce risks to humans and the environment [17-18]. Large-scale use of organic solvents in synthesis causes environmental hazards [19]. There were several advantages of performing syntheses in solvent-free media, such as, short reaction time, increased safety, and low cost [19-21]. Recently, a few papers reported modern synthetic protocols where solvent-less condition have been used [22-24]. Finally, herein we wish to report the anti-bacterial activity of some newer 1,2,3 – benzotriazole derivatives synthesized by ultrasonication in solvent – free conditions.

EXPERIMENTAL

Reagents of analytical grade were used in the synthesis. The reactions under ultrasonic irradiation were carried out at room temperature in a 40 ml glass reactor. An UP 400S ultrasonic processor equipped with a 12 mm wide and 140 mm long

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probe was immersed directly into the reaction mixture. The operating frequency was 24 KHz and the output power was 220 W through manual adjustment. The melting points of synthesized derivatives were determined by using an Electrothermal 9100 digital melting point apparatus and were uncorrected. The structures of synthesized derivatives were elucidated by spectral studies. Spectroscopic data were recorded on the following instruments: Perkin Elmer 1600 series Fourier Transformer – Infrared Spectrophotometer in KBr - Pellet method; 1H NMR, Bruker 400 MHz NMR spectrometer (Bruker Bioscience, Billerica, MA, USA) in MeOD using TMS as internal standard.

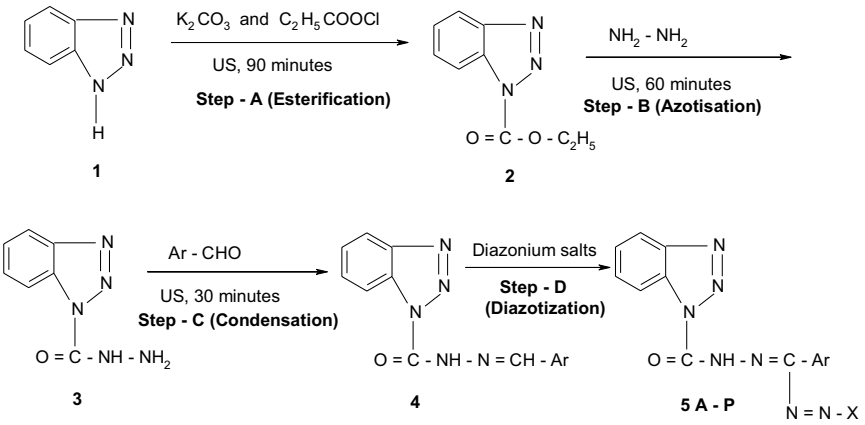
Scheme for the synthesis of the compounds: After suitable modifications to the classical synthesis carried out by other workers [25-27], sixteen new benzotriazole derivatives were synthesized under green conditions (viz., ultrasonication and solvent free conditions) by the addition of diazotization step (as shown in the scheme). *Anti – bacterial activity by Disc Diffusion Method and MIC for Bacteria:* All the synthesized compounds of present study were screened for *in-vitro* anti bacterial activity against five different strains of bacteria i.e. Gram negative organism (*Pseudonomous aureginosa* MTCC – 1035) and Gram positive organisms (*Bacillus cereus* MTCC – 430*, Bacillus subtilis* MTCC – 441*, Staphylococcus aureus* MTCC – 737 *and Staphylococcus epidermidis* MTCC – 3086) by paper disc diffusion method [28]. Cotrimoxazole and Cephotaxime were used as reference drugs for bacteria. An additional control disc without any sample but impregnated with an equivalent amount of solvent (DMSO) was also used. The Minimum Inhibitory Concentration (MIC) study was carried out at different concentrations of the synthesized compounds such as 15.625, 31.25, 62.5 µg/ml.

RESULTS AND DISCUSSION

Antibacterial activity can be enhanced by addition of aromatic rings / moieties / substituents to the basic structures. Hydrophobic molecules with rigid, planar structures such as aromatic rings have been shown to have the ability to insert into membranes of microbes and induce localized permeability changes leading to leakage out of the membrane leading to their death [29]. Earlier reports revealed that para substituted phenyl compounds containing electron withdrawing groups were found to be more active against microbes [30, 31]. The introduction of the schiff's base moiety enhanced the antibacterial activity of aromatic compounds [32]. Hence, newer 1,2,3-benzotriazole derivatives containing schiff's base with electron withdrawing substituted phenyls at para position were synthesized by ultrasound activation in solvent – free condition (with moderate to good yields in the range of 71 – 82%) and tested for their antibacterial activity.

Characterization of newer 1,2,3 – benzotriazole derivatives: The synthesized derivatives were characterized by following methods.

A. Melting Point: Melting points of the synthesized derivatives were determined by an open-end capillary tube method and were uncorrected. Molecular formulae, molecular weights, melting points and yields of the synthesized derivatives were given in Table 1.



Scheme of Synthesis

5A – D: Ar = C_6H_5 ; 5E – H: Ar = C_4H_3O ; 5 I – L: Ar = $C_6H_4NO_2$ and 5M – P: Ar = C_6H_4Cl

5A, E, I, M: X = C_6H_5 ; 5B, F, J, N: X = $C_6H_4NO_2$; 5C, G, K, O: X = C_6H_4Cl and 5D, H, L, P: X = C_6H_4Br

Note: US = Ultrasonication

Table – 1. Physical data of synthesized 1,2,3 – benzotriazole derivatives.

S. No.	Compound Code	Molecular Formula	Molecular Weight	Melting Point (^{0}C)	Yield (%)
1.	5 A	$C_{20}H_{15}N_7O$	369.4	99	82
2.	5 B	$C_{20}H_{14}N_8O_3$	414.4	96	79
3.	5 C	$C_{20}H_{14}ClN_7O$	403.8	99	81
4.	5 D	$C_{20}H_{14}BrN_7O$	448.3	98	82
5.	5 E	$C_{18}H_{13}N_7O_2$	359.3	88	79
6.	5 F	$C_{18}H_{12}N_8O_4$	404.3	93	72
7.	5 G	$C_{18}H_{12}ClN_7O_2$	393.8	95	73
8.	5 H	$C_{18}H_{12}BrN_7O_2$	438.2	97	72
9.	5 I	$C_{20}H_{14}N_8O_3$	414.4	101	71
10.	5 J	$C_{20}H_{13}N_9O_5$	459.4	102	79
11.	5 K	$C_{20}H_{13}ClN_8O_3$	448.8	99	75
12.	5 L	$C_{20}H_{13}BrN_8O_3$	493.3	103	77
13.	5 M	$C_{20}H_{14}ClN_7O$	403.8	80	72
14.	5 N	$C_{20}H_{13}ClN_8O_3$	448.8	82	77
15.	5 O	$C_{20}H_{13}Cl_2N_7O$	438.3	100	82
16.	5 P	$C_{20}H_{13}BrClN_7O$	482.7	95	81

B. Infra – Red and ^{1}H NMR spectral analysis: The synthesized derivatives were characterized by FTIR and ^{1}H NMR values measured in cm^{-1} and δ (ppm) respectively. The data was interpreted with reference to standard values [33, 34] and given below for some of the synthesized compounds.

❖ *1-(1H-benzo[d][1,2,3]triazole-1-carbonyl)-3,5-diphenylformazan (5A):*

IR (KBr, cm^{-1}): 1696.66 (Ar C = C, stretch); 1603.37 (N = N, stretch), 1542.28 (N – H, stretch), 1256.37 (Aryl C – N, stretch), 1007.57 (Aniline C – N, stretch) and 737.28 (CHO – deformation); ^{1}H NMR (400 MHz) (MeOD) δ (ppm): 3.33 (1H, s, N-H), 7.06 (1H, d, C-H), 7.33 (2H, d, C-H), 7.40 (2H, d, C-H), 7.45 – 7.48 (2H, m, C-H), 7.56 – 7.59 (3H, m, C-H), 7.83 (2H, d, C-H) and 7.96 (2H, d, C-H).

❖ *1-(1H-benzo[d][1,2,3]triazole-1-carbonyl)-5-(4-nitrophenyl)-3-phenyl formazan (5B):* IR (KBr, cm^{-1}): 1698.47 (Ar C = C, stretch); 1593.99 (N = N, stretch), 1495.50 (Ar – NO_2, stretch), 1301.09 (Aryl C – N, stretch), 1206.78 (Aniline C – N, stretch), 843.07 (p – disubstitution, stretch) and 739.50 (CHO – deformation); ^{1}H NMR (400 MHz) (MeOD) δ (ppm): 3.20 (1H, s, N-H), 7.18 (2H, d, C-H), 7.40 (2H, d, C-H), 7.52 – 7.59 (3H, m, C-H), 7.83 (2H, d, C-H), 7.96 (2H, d, C-H) and 8.10 (2H, d, C-H).

❖ *1-(1H-benzo[d][1,2,3]triazole-1-carbonyl)-5-(4-chlorophenyl)-3-(furan-2-yl) formazan (5G):* IR (KBr, cm^{-1}): 3649.31 (Amide – CONH, stretch), 1594.63 (N = N, stretch), 1485.68 (Furan Ring, C = C, stretch), 1206.43 (Aniline C – N, stretch), 1007.96 (C – O – C, stretch), 820.27 (p – disubstitution, stretch), 740.62 (CHO deformation, stretch) and 539.68 (C – Cl); ^{1}H NMR (400 MHz) (MeOD) δ (ppm): 3.33 (1H, s, N-H), 6.52 (1H, m, Furan C-H), 6.54 (1H, d, Furan C-H), 7.0 (1H, s, N-H), 7.27 (2H, d, C-H), 7.40 (2H, d, C-H), 7.49 (2H, d, C-H), 7.75 (1H, d, Furan C-H) and 7.96 (2H, d, C-H).

❖ *1-(1H-benzo[d][1,2,3]triazole-1-carbonyl)-5-(4-bromophenyl)-3-(furan-2-yl)formazan (5H):* IR (KBr, cm^{-1}): 3652.10 (Amide – CONH, stretch), 1722.17 (Furan Ring, stretch), 1622.31 (N = N, stretch), 1511.18 (Ar C = C, stretch), 1457.07 (Furan Ring C = C, stretch), 1202.93 (Aniline C – N, stretch), 1005.36 (C – O – C, stretch), 875.16 (p – disubstitution, stretch), 773.52 (CHO deformation, stretch) and 515.35 (C – Br, stretch); ^{1}H NMR (400 MHz) (MeOD) δ (ppm): 3.20 (1H, s, N-H), 6.52 (1H, m, Furan C-H), 6.54 (1H, d, Furan C-H), 7.0 (1H, s, N-H), 7.22 (2H, d, C-H), 7.40 (2H, d, C-H), 7.75 (1H, d, Furan C-H), 7.76 (2H, d, C-H) and 7.96 (2H, d, C-H).

❖ **1**-*(1H-benzo[d][1,2,3]triazole-1-carbonyl)-3-(4-chlorophenyl)-5-phenyl form--azan (5M):* IR (KBr, cm^{-1}): 3650.62 (Amide – CONH), 1706.94 (Ar, C = C, stretch), 1593.76 (N = N, stretch), 1513.71 (N – H, stretch), 1264.35 (Aryl C – N, stretch), 1204.85 (Aniline C – N, stretch), 820.56 (p – disubstitution, stretch), 772.75 (CHO – deformation, stretch) and 605.30 (C – Cl, stretch); ^{1}H NMR (400 MHz) (MeOD) δ (ppm): 3.3 (1H, s, N-H), 7.06 (1H, d, C-H), 7.33 (2H, d, C-H), 7.40 (2H, d, C-H), 7.45 (2H, d, C-H), 7.52 (2H, d, C-H), 7.77 (2H, d, C-H) and 7.96 (2H, d, C-H).

❖ *1-(1H-benzo[d][1,2,3]triazole-1-carbonyl)-3,5-bis(4-chloro- phenyl) formazan (5O):* IR (KBr, cm^{-1}): 1710.45 (Ar, C = C, stretch), 1593.50 (N = N, stretch), 1486.45 (N – H, stretch), 1256.86 (Aryl C – N, stretch), 1143.95 (Aniline C – N, stretch), 827.70 (p – disubstitution, stretch), 773.01 (CHO – deformation, stretch) and 620.81 (C – Cl, stretch);

Table 2. Anti – bacterial activity of 1,2,3 – benzotrtiazole derivatives.

S.No.	Compound Code	Anti – bacterial activity (in mm)* For disks soaked in 100µg/ml solutions of compounds				
		Pseudonomous aureginosa MTCC – 1035	*Bacillus cereus* MTCC – 430	*Bacillus subtilis* MTCC – 441	*Staphylococcus aureus* MTCC – 737	*Staphylococcus epidermidis* MTCC – 3086
1.	5 A	10.9	9.0	7.0	--	--
2.	5 B	14.6	10.0	7.0	9.5	--
3.	5 C	8.2	11.0	9.0	11.9	--
4.	5 D	7.4	10.0	8.0	--	10.7
5.	5 E	6.0	10.0	--	--	9.2
6.	5 F	6.8	9.6	15.0	17.1	9.7
7.	5 G	7.0	7.3	7.0	--	8.0
8.	5 H	--	8.0	9.5	--	11.9
9.	5 I	--	19.9	10	9.6	15.1
10.	5 J	8.7	9.0	25	10.4	12.6
11.	5 K	--	11.4	18	--	8.7
12.	5 L	8.1	10.4	8.0	--	--
13.	5 M	7.8	9.5	7.0	7.1	--
14.	5 N	--	12.7	8.0	--	--
15.	5 O	7.5	17.5	9.0	8.5	--
16.	5P	6.7	12.4	--	12.1	8.4
	Cotrimoxazole,	--	10.7	3.3	18	21.8
	Cephotaxime	22	--	--	--	--
	Control (10%DMSO In Methanol)	--	--	--	--	--

(--) indicates No zone of inhibition and * indicates average of triplicate

^{1}H NMR (400 MHz) (MeOD) δ (ppm): 3.3 (1H, s, N-H), 7.27 (2H, d, C-H), 7.40 (2H, d, C-H), 7.49 (2H, d, C-H), 7.52 (2H, d, C-H), 7.77 (2H, d, C-H) and 7.96 (2H, d, C-H).

C. Anti bacterial assay of synthesized derivatives: The zones of inhibitions (mm) of tested compounds against bacterial strains were shown in Table 2 and the experimental result indicated variable degree of efficacy of the compounds against different strains of bacteria. Poor activity was shown by 5B, 5A, 5J, 5C and 5L (zone diameters 14.6, 10.9, 8.7, 8.2 and 8.1mm respectively) against Gram positive bacteria (*Pseudonomous aureginosa,* MTCC – 1035) compared to the reference compound – Cephotaxime (zone diameter 22 mm), whereas 5H, 5I, 5K and 5N were completely ineffective.

Exceptionally high antibacterial activity was shown by 5J (zone diameter-25mm, i.e., 7.5 fold activity) against the Gram negative bacteria – *Bacillus subtilis* (MTCC – 441) in comparison to the reference compound Cotrimoxazole (zone diameter-3.3mm), which can be attributed to the nitro substitution on phenyl groups that were attached to cyano and azo groups. The nitro group affects the charge distribution which confers significant improvement in biological effect. The enhanced inhibition observed in the presence of nitro group is then more likely due to its interaction with some intracellular target. The presence of a strong electron-withdrawing group must alter the nature of the compound in such a way as to promote binding to the target(s) [35]. Even in earlier reports, p-nitro substitution on phenyl group displayed high activity against *B. subtilis* in the case of benzotriazole substituted carboxamides [36] and phenyl methanamine [37]. Other compounds (5A, 5B, 5C, 5D, 5F, 5G, 5H, 5I, 5K, 5L, 5M, 5N, 5O) have shown 5.5 to 2.0 fold activity compared to the reference compound Cotrimoxazole, where as 5E and 5P were inactive.

Compounds 5I and 5O have shown 1.8 and 1.6 fold activity respectively against *Bacillus cereus* (MTCC – 430) compared to the reference compound – Cotrimoxazole, where as all other synthesized compounds were as good as Cotrimoxazole. Better activity of compound 5O might be due to the attachment of chloro phenyl to azo and cyano groups. This result suggested that the introduction of halogen substituent increased the hydrophobicity of the synthesized compounds and lead to the increase of the antibacterial activity [38]. Electron withdrawing groups like halogens will increase bactericidal potential. According to Rajendra Prasad *et al* [39], designing the compounds bearing electron withdrawing

Table 3. Minimum Inhibitory Concentrations for Bacteria (μg/ml)

S. No.	Compound Code	*Pseudonomous aureginosa* MTCC – 1035	*Bacillus cereus* MTCC – 430	*Bacillus subtilis* MTCC – 441	*Staphylococcus aureus* MTCC – 737	*Staphylococcus epidermidis* MTCC – 3086
1.	5 A	62.5	31.25	31.25	--	--
2.	5 B	62.5	62.5	62.5	31.25	--
3.	5 C	62.5	62.5	31.25	31.25	--
4.	5 D	31.25	62.5	62.5	--	62.5
5.	5 E	62.5	15.625	--	--	15.625
6.	5 F	62.5	31.25	62.5	62.5	62.5
7.	5 G	62.5	62.5	15.625	--	62.5
8.	5 H	--	62.5	62.5	--	62.5
9.	5 I	--	62.5	62.5	15.625	31.25
10.	5 J	31.25	62.5	31.25	62.5	62.5
11.	5 K	--	62.5	62.5	--	31.25
12.	5 L	31.25	62.5	31.25	--	--
13.	5 M	62.5	62.5	62.5	62.5	--
14.	5 N	--	31.25	62.5	--	--
15.	5 O	62.5	62.5	62.5	62.5	--
16.	5 P	62.5	31.25	--	62.5	62.5

substituents and with high degree of binding linearity with groups those results in high molecular weights increases antibacterial activity.

Compounds 5A, 5D, 5E, 5G, 5H, 5K, 5L and 5N were inactive against *Staphylococcus aureus* (MTCC – 737), whereas 5B, 5C, 5F, 5I, 5J, 5M, 5O and 5P have shown approximately half of the activity compared to the reference compound – Cotrimoxazole. 5A, 5B, 5C, 5L, 5M, 5N and 5O were inactive, where as 5D, 5E, 5F, 5G, 5H, 5I, 5J and 5K have shown in the order of half of the activity against *Staphylococcus epidermidis* (MTCC – 3086) compared to the reference compound – Cotrimoxazole.

The Minimum Inhibitory Concentrations (MIC) of the synthesized 1,2,3-benzotriazole derivatives for bacteria were shown in Table 3 and found to be 62.5 μg / ml for most of the synthesized compounds.

CONCLUSIONS

Excellent antibacterial activity was shown by all the synthesized compounds except 5E and 5P, against the Gram negative bacteria – *Bacillus subtilis* (MTCC – 441) compared to the reference compound - Cotrimoxazole. All the synthesized compounds have shown comparable antibacterial activity to the reference compound – Cotrimoxazole against *Bacillus cereus (*MTCC – 430). Against *Staphylococcus aureus* (MTCC – 737) and *Staphylococcus epidermidis* (MTCC – 3086) some of the compounds were inactive and other were feebly active. In the case of Gram positive bacteria (*Pseudonomous aureginosa,* MTCC – 1035), the activity shown by the synthesized compounds was not significant compared to the reference compound – Cephotaxime. The Minimum Inhibitory Concentrations (MIC) of the most of the synthesized 1,2,3-benzotriazole derivatives for these bacteria was found to be 62.5 μg / ml.

Finally in conclusion, 1,2,3 – benzotriazole derivatives synthesized under solvent-free and ultrasound irradiation with noteworthy advantages viz., shorter reaction times, operational simplicity, simple work-up, and eco-friendly nature, have shown anti bacterial activities against selected Gram negative organisms.

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АНТИБАКТЕРИАЛНА АКТИВНОСТ НА НЯКОИ НОВИ ПРОИЗВОДНИ НА 1,2,3 – БЕНЗОТРИАЗОЛА, СИНТЕЗИРАНИ ПРИ УЛТРАЗВУКОВО ВЪЗДЕЙСТВИЕ БЕЗ РАЗТВОРИТЕЛИ

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(Резюме)

Много класически методики за синтези генерират големи количества отпадъци. Химичната и фармацевтичната индустрии са под нарастващия натиск да минимизират и дори да избягват тези отпадъци. В настоящата работа се съобщава за синтезирането на нови производни на 1,2,3–бензотриазола при ултразвуково въдействие и без използването на разтворители. Нови "1–(1H–бензо[d][1,2,3]триазол–1–карбонил)-ови производни (**5A – 5P**) са синтезирани от "1H–бензо[d][1,2,3]триазол" (**1**) оптимизирайки условията на реакцията. Получените продукти са изолирани и охарактеризирани чрез спектрални методи. Антибактериалната активност на тези съединения е изследвана *in vitro* спрямо различни бактериални Грам-отрицателни щамове (*Pseudonomous aureginosa,* MTCC – 1035) and Gram positive organisms (*Bacillus cereus,* MTCC – 430, *Bacillus subtilis,* MTCC – 441, *Staphylococcus aureus,* MTCC – 737, *Staphylococcus epidermidis,* MTCC – 3086). Някои от синтезираните съединения показват значителна активност спрямо различни бактерии.