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CONVENTIONAL AND MICROWAVE ASSISTED SYNTHESIS OF 4-OXO-2-SUBSTITUTED ARYL-1,3-THIAZOLIDINE DERIVATIVES OF BENZOTRIAZOLE: A NEW CLASS OF BIOLOGICAL COMPOUNDS

Adesh Dubey *, S.K. Srivastava and S.D. Srivastava

abstract: Some new kinds of thiazolidine derivatives of benzotriazole 5a-e were prepared. The reaction was carried out by both conventional and microwave methods. The structures of all the synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and FAB-Mass spectral and microanalytical data. All the synthesized compounds of series 5a-e were screened for their antimicrobial activity against some selected microorganism. Unexpectedly, some thiazolidine derivatives of benzotriazole showed better activity.

key words: Antimicrobial; Benzotriazole; Thiazolidine; Conventional and microwave irradiation.

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Introduction

Small ring heterocycles containing nitrogen, sulphur and oxygen have been under investigation for a long time because of their medicinal properties. In past several decades benzotriazole and its derivatives have captured the imagination of organic chemists for more than a century. A large number of compounds containing 1,2,3-benzotriazole system have been investigated because of their broad spectrum of biological activities which include antimicrobial [1], antiviral [2], anti-inflammatory, anticonvaulsant [3], DNA cleavage [4], herbicidal [5], antitubercular [6], antimicrobial [7] etc. The thiazolidinone and its derivatives have also taken a considerable pharmacological importance. 4-Thiazolidinones substituted at the 2-position and their derivatives exhibit high *in vitro* antitubercular activity [8]. Thiazolidine and its derivatives are important compounds due to their broad range of biological activities such as antibacterial [9,10], antifungal [11], anti-inflammatory [12], anticancer [13] and antitubercular [14]. Microwave assisted organic synthesis under solvent free conditions are attractive offering reduced pollution, simple reaction conditions, low cost and offer high yields together with simplicity in processing and handling. These features render the microwave method superior to the conventional one.

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The biological significances of these class of heterocycles and important features of microwave assisted synthesis impelled us to synthesize some new thiazolidinone derivatives having benzotriazole moiety by conventional and microwave irradiation. In this study we report the synthesis and antimicrobial screening of 4-oxo-2-substituted aryl-1,3-thiazolidine derivatives of benzotriazole.

Materials and methods

Experimental Section

All the melting points were determined by open capillary method. All reagents were obtained from Sigma-Aldrich chemicals Pvt. Ltd. Solvents were commercially obtained as laboratory grade. All chemicals were used after further purification (recrystallization or distillation). The progress of reactions and the purity of the compounds were controlled by thin layer chromatography (TLC). TLC was carried out on silica gel G coated glass plates. The purification of the compounds was carried out by column chromatography using 100-200 mesh Silica gel. ^{1}H-NMR spectra were recorded on a Bruker DRX 300 instrument at 300 MHz in $CDCl_3$ on δ scale in ppm using TMS as a reference. ^{13}C-NMR spectra were recorded on a Varian AMX 400 spectrophotometer at 50 MHz using $CDCl_3$. The FTIR spectra were recorded on a Perkin-Elmer IR spectrophotometer using KBr disc of the sample in cm^{-1}. Mass spectra of the synthesized compounds have been recorded on a JEOL SX 102/DA-6000 spectrometer.

General Procedure of the synthesis

Synthetic Protocol for the synthesis of N-(chloropropyl) -benzotriazole (2)

Conventional method: Benzotriazole **1** (50g, 0.42mol) was dissolved in methanol (100 mL) and 1-bromo-3-chloropropane (67.06g, 0.42mol) was added. The mixture was refluxed for about 5.5 hrs, filtered and the solvent was evaporated to dryness in vacuo. The crude product was readily purified by passing it through a chromatographic column packed with silica gel using chloroform: methanol (7:3 v/v) as eluant to obtain pure derivative. The resulting purified product was recrystallized by chloroform to give compounds **2**. M.P. 84-85ºC; IR: 3080 (C-H), 1316 (N-CH_2), 734 (C-Cl). ^{1}H-NMR: 8.01-7.30 (m, 4H, Ar.), 3.10 (t, 2H, J=7.03, $\underline{CH_2}CH_2CH_2$), 2.57 (t, 2H, J=7.03, $CH_2CH_2\underline{CH_2}$), 1.65 (m, 2H, J=7.03, $CH_2\underline{CH_2}CH_2$). ^{13}C-NMR: 114.81-146.12 (Ar.), 42.40 ($\underline{CH_2}CH_2CH_2$), 36.29 ($CH_2CH_2\underline{CH_2}$), 31.19 ($CH_2\underline{CH_2}CH_2$). MS, m/z: 196 $(M)^+$, 160, 146, 132, 118. Anal. calcd. for $C_9H_{10}N_3Cl$:C, 55.25; H, 5.15; N,21.47. Found: C, 55.23; H, 5.11; N,21.44.

Microwave irradiation method: An equimolar mixture of benzotriazole **1** (50g, 0.42mol) and 1-bromo-3-chloropropane (67.06g, 0.42mol) was subjected to microwave irradiation for 2.5 minutes. The crude product was readily purified by passing it through a chromatographic column packed with silica gel using chloroform: methanol (7:3 v/v) as eluant to obtain pure derivative. The resulting purified product was recrystallized by chloroform to give compounds 2.

Synthesis of N-(hydrazino propyl)-benzotriazole (3)

Conventional method: Compound **2** (14g, 0.072 mol) was dissolved in acetone (35 mL) and hydrazine hydrate (3.6g, 0.072 mol) was added. The well stirred (2hrs) mixture was

refluxed for 7 hrs. After cooling and filtration the solvent was evaporated under in vacuo to obtain a solid crude product. This resulting crude product was purified by passing it through a chromatographic column packed with silica gel using acetone: methanol (6:4 v/v) as eluant to obtain pure derivative. The resulting purified product was recrystallized by ethanol to give compound **3**. M.P. 98-99ºC; IR: 3361 (-NH_2), 3316 (-NH), 3072 (C-H), 1318 (N-CH_2). ^{1}H-NMR: 8.76 (s, 1H, NH), 8.05-7.29 (m, 4H, Ar.), 4.23 (s, 1H, NH_2), 3.14 (t, 2H, J-7.05, $\underline{CH_2}CH_2CH_2$), 2.62 (t, 2H, J= 7.05, CH_2 CH_2 $\underline{CH_2}$), 1.59 (m, 2H, J= 7.05, CH_2 $\underline{CH_2}$ CH_2). ^{13}C-NMR: 113.42-148.16 (Ar.), 42.24 ($\underline{CH_2}CH_2CH_2$), 36.92 ($CH_2CH_2\underline{CH_2}$), 32.32 ($CH_2\underline{CH_2}CH_2$). MS, m/z: 191$(M)^+$, 175, 160, 146, 132, 118. Anal. Calcd. for $C_9H_{13}N_5$:C,56.52; H, 6.85; N, 36.62. Found: C, 56.48; H, 6.80; N, 36.58.

Microwave irradiation method: An equimolar mixture of compound **2** (14g, 0.072mol) and hydrazine hydrate (3.6g, 0.072mol) was placed in a microwave oven for 3.0 minutes. The crude product was readily purified by passing it through a chromatographic column packed with silica gel using acetone: methanol (6:4 v/v) as eluant to obtain pure derivative. The resulting purified product was recrystallized by ethanol to give compounds **3**.

Synthesis of N-[(benzylidene hydrazino)-propyl]- benzotriazole (4a)

Conventional method: A mixture of compound **3** (2g, 0.01 mol) and benzaldehyde (1.11g, 0.01 mol) in methanol (20 mL) in the presence of a catalytic amount of glacial acetic acid was refluxed for 5.3 hrs. The solvent was removed under reduced pressure to and the resulting crude product was purified by passing it through a chromatographic column packed with silica gel using chloroform: methanol (8:2 v/v) as eluant. Resulting purified product was recrystallized by chloroform to give compounds, **4a**. M.P. 113-114ºC: IR: 3358 (N-H), 3081 (C-H), 1581 (CH=N, azomet.), 1319 (N-CH_2). ^{1}H-NMR: 8.74 (s,1H, N=CH, azomet.), 8.32 (s,1H, N-H), 8.06-7.22 (m, 9H, Ar.), 3.12 (t, 2H, J=708, $\underline{CH_2}CH_2CH_2$), 2.59 (t, 2H, J=7.08, $CH_2CH_2\underline{CH_2}$), 1.58 (m, 2H,J=7.08, $CH_2\underline{CH_2}CH_2$). ^{13}C-NMR: 114.20-149.16 (Ar.), 132.13 (N=CH, azomet.), 42.16 ($\underline{CH_2}CH_2CH_2$), 36.92 ($CH_2CH_2\underline{CH_2}$), 32.46 ($CH_2\underline{CH_2}CH_2$). M/S, m/z: 279$(M)^+$, 175, 160, 146, 132, 118, 104, 77. Anal. Calcd. for $C_{16}H_{17}N_5$:C, 68.81; H, 6.13; N, 25.08. Found : C, 68.78; H, 6.11; N, 25.04.

Microwave irradiation method: An equimolar mixture of compound **3** (2g, 0.01 mol) and benzaldehyde (1.11g, 0.01 mol) in the presence of a catalytic amount of glacial acetic acid was placed in a microwave oven for for 3.0 minutes. The resulting crude product was purified by passing it through a chromatographic column packed with silica gel using chloroform: methanol (8:2 v/v) as eluant. Resulting purified product was recrystallized by chloroform to give compounds, **4a**.

Other compounds **4b-e** was synthesized in the similar manner by treating compound **3** with selected aromatic aldehydes (Scheme 1).

Synthesis of N-[(4-oxo-2-phenyl-1,3-thiazolidineimino)-propyl]-benzotriazole (5a).

Conventional Method: A mixture of compound **4a** (1g, 0.003 mol) and $SHCH_2COOH$ (0.331g 0.003 mol) in methanol (20 mL) containing a pinch of anhy. $ZnCl_2$ was first stirred for about 2 hours followed by refluxing on a steam bath for about 6 hrs. The recation mixture was cooled and excess of solvent was evaporated under reduced pressure. The solid crude product was purified by passing it through a chromatographic column packed with silica gel using chloroform: methonal (8:2 v/v) as eluant and again purified by recrystallisation from ethanol to give compound **5a.** M.P. 99-100ºC: IR: 3368 (N-H), 3069

(C-H), 1731 (C=O), 1316 (N-CH_2), 731 (C-S-C). ^{1}H-NMR: 8.52 (s, 1H, N-H), 5.52 (s,1H, N-CH-S), 3.31 (s, 2H, CO$\underline{CH_2}$S), 3.21 (t, 2H, J=7.10, C$\underline{H_2}CH_2CH_2$), 2.60 (t, 2H, J=7.10, $CH_2CH_2\underline{CH_2}$), 1.51 (m, 2H, $CH_2\underline{CH_2}CH_2$). ^{13}C-NMR: 169.22 (C=O), 113.78-156.19 (Ar.), 47.57 (N-CH-Ar), 34.28 (COCH$_2$S) 42.67 ($\underline{CH_2}$ CH_2CH_2), 37.69 ($CH_2CH_2\underline{CH_2}$), 32.43 ($CH_2\underline{CH_2}CH_2$). MS, m/z: 353(M)$^+$, 178, 175, 160, 150, 146, 136, 132, 118, 77, 59. Anal. Calcd. for $C_{18}H_{19}N_5OS_1$: C, 61.17; H, 5.41; N,19.81. Found: C, 61.14; H, 5.37; N, 19.77.

Microwave irradiation method: An equimolar mixture of compound **4a** (1g, 0.003 mol) and $SHCH_2COOH$ (0.331g 0.003 mol) with a pinch of anhy. $ZnCl_2$ was subjected to microwave irradiation for 3 minutes. The solid crude product was purified by passing it through a chromatographic column packed with silica- gel using chloroform; methanol (6:4 v/v) as eluant and again purified by recrystalisation from ethanol to give compounds **5a.**

Other compounds **5b-e** was synthesized in the similar manner using compounds **4b-e**. Characterisation data are presented in table II.

N-[{4-oxo-2-(2-chlorophenyl)-1,3-thiazolidineimino}-propyl]-benzotriazole **(5b)**. M.P. 108-109ºC: IR: 3365 (N-H), 3074 (C-H), 1733 (C=O), 1321 (N-CH_2), 729 (C-S-C), 748 (Ar-Cl). ^{1}H-NMR: 8.53 (s, 1H, N-H), 5.69 (s, 1H, N-CH-S), 3.36 (s, 2H, CO$\underline{CH_2}$S), 3.09 (t, 2H, J=7.13, C$\underline{H_2}CH_2CH_2$), 2.63 (t, 2H, J=7.13, $CH_2CH_2\underline{CH_2}$), 1.61 (m, 2H, $CH_2\underline{CH_2}CH_2$). ^{13}C-NMR: 168.85 (C=O), 114.45-153.23 (Ar.), 47.57 (N-CH-Ar), 34.23 (COCH$_2$S), 43.37 ($\underline{CH_2}CH_2CH_2$), 37.88 ($CH_2CH_2\underline{CH_2}$), 31.82 ($CH_2\underline{CH_2}CH_2$). MS, m/z: 388(M)$^+$, 213, 185, 175, 171, 160, 146, 132, 118, 112, 59. Anal. Calcd. for $C_{18}H_{18}N_5OSCl$: C, 55.73; H, 4.67; N,18.05. Found : C, 55.69; H, 4.64; N,18.03.

N-[{4-oxo-2-(2-bromophenyl)-1,3-thiazolidineimino}-propyl]-benzotriazole **(5c)**. M.P.- 98-99ºC: IR: 3366 (N-H), 3091 (C-H), 1735 (C=O), 1334 (N-CH_2), 734 (C-S-C), 641 (Ar-Br). ^{1}H-NMR: 8.46 (s, 1H, NH), 5.64 (s, 1H, N-CH-S), 3.36 (s, 2H, CO$\underline{CH_2}$S), 3.03 (t, 2H, J=7.20, C$\underline{H_2}CH_2CH_2$), 2.61 (t, 2H, J=7.20, $CH_2CH_2\underline{CH_2}$), 1.59 (m, 2H, $CH_2\underline{CH_2}CH_2$). ^{13}C-NMR: 168.55 (C=O), 113.89-154.38 (Ar.), 46.16 (N-CH-Ar), 34.16 (COCH$_2$S), 43.53 ($\underline{CH_2}CH_2CH_2$), 37.64 ($CH_2CH_2\underline{CH_2}$), 32.62 ($CH_2\underline{CH_2}CH_2$). MS, m/z: 432(M)$^+$, 257, 229, 215, 175, 160, 156, 146, 132, 118, 59. Anal. Calcd. for $C_{18}H_{18}N_5OSBr$: C, 50.00; H, 4.19; N,16.19. Found : C, 49.94; H, 4.14; N,16.16.

N-[{4-oxo-2-(2-nitrophenyl)-1,3-thiazolidineimino}-propyl]-benzotriazole **(5d)**. M.P.- 111-112ºC: IR: 3385 (N-H), 3086 (C-H), 1742 (C=O), 1338 (N-CH_2), 738 (C-S-C), 1359 (Ar-NO_2). ^{1}H-NMR: 8.54 (s, 1H, N-H), 5.69 (s, 1H, N-CH-S), 3.43 (s, 2H, CO$\underline{CH_2}$S), 3.16 (t, 2H, J=7.30, C$\underline{H_2}CH_2CH_2$), 2.65 (t, 2H, J=7.30, $CH_2CH_2\underline{CH_2}$), 1.73 (m, 2H, $CH_2\underline{CH_2}CH_2$). ^{13}C-NMR: 166.83 (C=O), 111.83-154.76 (Ar.), 46.85 (N-CH-Ar), 35.85 (COCH$_2$S), 44.42 ($\underline{CH_2}CH_2CH_2$), 38.21 ($CH_2CH_2\underline{CH_2}$), 32.33 ($CH_2\underline{CH_2}CH_2$). MS, m/z: 399(M)$^+$, 223, 195, 181, 175, 160, 146, 132, 122, 118, 59. Anal. Calcd. for $C_{18}H_{18}N_6O_3S$: C, 54.26; H, 4.55; N, 21.09. Found: C, 54.22; H, 4.51; N, 21.04.

N-[{4-oxo-2-(2-methoxyphenyl)-1,3-thiazolidineimino}-propyl]-benzotriazole **(5e)**. M.P. 97-98ºC: IR: 3369 (N-H), 3076 (C-H), 1743 (C=O), 1327 (N-CH_2), 1236(Ar-OCH_3), 731 (C-S-C). ^{1}H-NMR: 8.38 (s, 1H, N-H), 5.71 (s, 1H, N-CH-S), 3.74 (s, 1H, -OCH_3), 3.35 (s, 2H, CO$\underline{CH_2}$S), 3.03 (t, 2H, J=7.10, C$\underline{H_2}CH_2CH_2$), 2.66 (t, 2H, J=7.10, $CH_2CH_2\underline{CH_2}$), 1.64 (m, 2H, $CH_2\underline{CH_2}CH_2$). ^{13}C-NMR: 113.92-152.81 (Ar.), 168.48 (C=O), 46.83 (N-CH-Ar), 34.83 (COCH$_2$S), 43.73 ($\underline{CH_2}CH_2CH_2$), 38.28 ($CH_2CH_2\underline{CH_2}$), 31.83 ($CH_2\underline{CH_2}CH_2$), 55.42 (O-CH_3). MS, m/z: 383(M)$^+$, 208, 181, 175, 167, 160, 146, 132, 118, 108, 59. Anal. Calcd. for $C_{19}H_{21}N_5O_2S$: C, 59.51; H, 5.52, N, 18.26. Found : C, 59.48; H, 5.49, N, 18.21.

Results and Discussion

Evaluation of antimicrobial screening

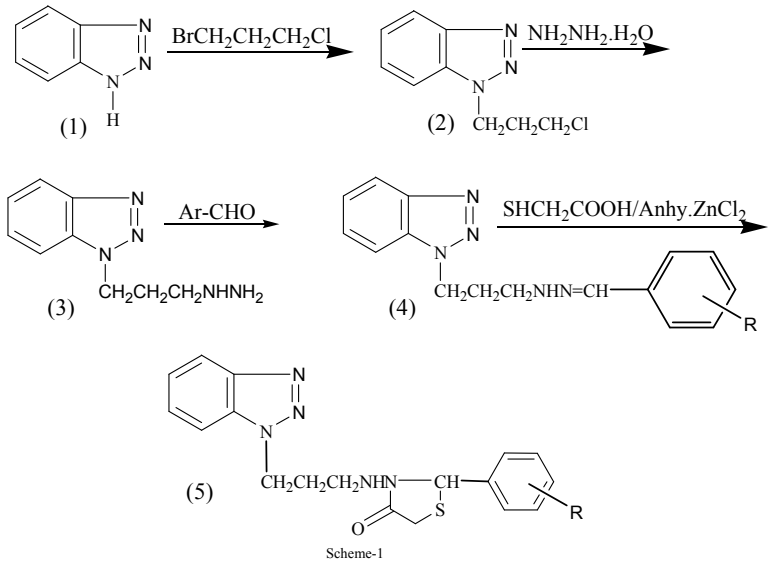
All the synthesized compounds of series **5a-e** were tested for their antimicrobial activity. For antibacterial screening a gram-positive bacterium *S. aureus* and two gram-negative becteria, *E.coli* and *S.pneumoniae* were used. For antifungal activity *C.albicans*, *A. pumigatus* and *A.niger* was taken. Antibacterial and antifungal screenings were performed by dilution method using nutrient agar media. MIC was determined at five concentrations (in µg/mL) ranging from 0.5 µg, 1.0 µg, 5.0 µg, 10.0 µg, 25.0 µg and 50.0 µg of each compounds. Oflaxacin was used as standard drug for antibacterial screening and miconazole was used as standard drug for antifungal screening. The MIC level of some active compounds **5a-e** against these organisms is given in Table 1.

Table 1 Antibacterial and Antifungal activity of Compounds 5a-e (MIC µg/mL).

No.	*S.aures*	*E.coli*	*S.pneumoe*	*C.albicas*	*A.fumigats*	*A.niger*
5a	1.0	1.0	0.5	1.0	0.5	1.0
5b	0.5	0.1	0.5	1.0	0.5	0.5
5c	0.5	0.1	0.5	0.5	0.5	1.0
5d	0.1	0.5	0.5	1.0	0.5	0.5
5e	1.0	0.5	0.5	0.5	0.5	0.1
Oflaxacin	0.1	0.1	0.1			
Miconazole				0.1	0.1	0.1

Table 2 Physical data of the compounds, 2, 3, 4a-e and 5a-e.

Comp. No.	Molecular Formula	R	Conventional		Microwave	
			Yield (%)	Rea.T.(hrs)	Yield (%)	Rea.T.(min.)
2	$C_9H_{10}N_3Cl$	–	72	6.0	84	2.5
3	$C_9H_{13}N_3$	–	65	7.0	86	3.0
4a	$C_{16}H_{17}N_5$	–	68	5.0	86	4.0
4b	$C_{16}H_{16}N_5Cl$	2-Cl	62	4.0	89	3.5
4c	$C_{16}H_{16}N_5Br$	2-Br	65	5.0	90	4.0
4d	$C_{16}H_{16}N_6O_2$	2-NO_2	63	3.5	88	3.0
4e	$C_{17}H_{19}N_5O$	2-OCH_3	65	5.5	90	5.0
5a	$C_{18}H_{19}N_5OS$	-H	68	6.0	91	4.5
5b	$C_{18}H_{18}N_5OSCl$	2-Cl	63	4.5	92	3.5
5c	$C_{18}H_{18}N_5OSBr$	2-Br	72	5.5	87	4.0
5d	$C_{18}H_{18}N_6O_3S$	2-NO_2	68	4.0	86	3.0
5e	$C_{19}H_{21}N_5O_2S$	2-OCH_3	64	5.5	84	4.0



Scheme-1

R= H, 2-Cl, 2-Br, 2-NO_2, 2-CH_3O

Scheme 1 *Route of synthesis of the target compounds.*

Conclusions

Our synthesis strategy was based on to synthesize a highly biologically active heterocycle containing benzotriazole and thiazolidine moieties. As the results, we obtained a mixture of the 1- and 2-substituted isomers of benzotriazole derivatives in all steps by Scheme 1. Generally the compounds bearing the substituent in 1-position were obtained in higher yields. So we were mentioned here only major products (1-substituted). Separation of the compounds was performed by column chromatography. The spectroscopic data supported the formation of the products in end step. Comparative study results obtained by microwave assisted synthesis; versus conventional heating method is that some reactions which required 4-7 h by conventional method, was completed with in 2-5 minutes by the microwave irradiation technique and yields have been improved from 61-74% to 83-93%. The comparison study data in form of yields and reaction time are given in Table 2.

All the synthesized compounds of series **5a-e** were screened against some microorganisms for their antimicrobial activities. Generally compounds possessing electron withdrawing groups showed good antibacterial activity. Some derivatives containing electron withdrawing groups (-Cl, -Br, -NO_2) have shown promising activity against some bacteria. Compounds possessing electron donating groups have shown good antifungal activity. Activity data are given in Table 1. It is thus concluded that new synthesized 4-thiazolidinones are good antimicrobial compounds for therapeutic uses.

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