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Note

Microwave assisted rapid and efficient synthesis of nitrogen and sulphur containing heterocyclic compounds and their pharmacological evaluation

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A series of compounds namely, 3-chloro-4-(2″,4″-dichlorophenyl)-4-methyl-1-(substituted-1′,3′-benzothiazol-2′-yl)-azetidin-2-ones **4a-j** and 2-(2″,4″-dichlorophenyl)-2,5-dimethyl-3-(substituted-1′,3′-benzothiazol-2′-yl)-1,3-thiazolidin-4-ones **5a-j** have been prepared by the reaction of schiff base derivatives **3** with chloroacetyl chloride in the presence of triethylamine and thiolactic acid, respectively. The schiff base derivatives **3** have been prepared by the condensation of substituted-2-aminobenzothiazole **1** with 2,4-dichloroacetophenone **2**. The reactions have been carried out by microwave and conventional methods. The microwave assisted reactions are carried out in a "QPro-M modified microwave oven" made in Canada. Both the azetidinones and thiazolidinones are pharmacologically active and screened for their antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Salmonella typhi* and antifungal activity against *Candida albicans*.

Keywords: Azetidinone, thiazolidinone, chloroacetyl chloride, thiolactic acid, 2-aminobenzothiazole, microwave method, antibacterial activity

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Benzothiazole derivatives play a vital role in biological fields such as anti-TB[1] and anti-allergic acvtivity. Schiff base has good antimicrobial[2], fungicidal[3] and pharmacological applications[4] and it can be prepared by the acid catalyzed reaction of amines and ketones or aldehydes[5]. 2-Azetidinone derivatives have been reported to possess anti-inflammatory[6], antidegenerative, fungicidal[7] and antibiotic[8] activities. 4-Thiazolidinones give good pharmacological properties[9]. 4-Thiazolidinones are known to exhibit antitubercular[10], antibacterial, anticonvulsant[11] and antifungal[12] activities.

The application of microwave irradiation is used for carrying out chemical transformations which are pollution free and eco-friendly[13,14]. Commercial microwave oven is used as a convenient source of heat in the laboratory. The microwave assisted organic reactions occur more rapidly, safely and with higher chemical yields[15,16] thus, render the microwave method superior to conventional method.

The starting compounds substituted-2-amino-benzothiazoles **1** have been synthesized from various substituted amines[17]. The condensation of **1** with 2,4-dichloroacetophenone **2** was carried out by both conventional and microwave methods to give compounds N-[1′-(2″,4″-dichlorophenyl)-ethylidene]-substituted-1,3-benzothiazole-2-amine **3**. In conventional method, the reaction was carried out in methanol and it took 5 -6 hr, whereas by microwave irradiation it took only 2-3 min[18].

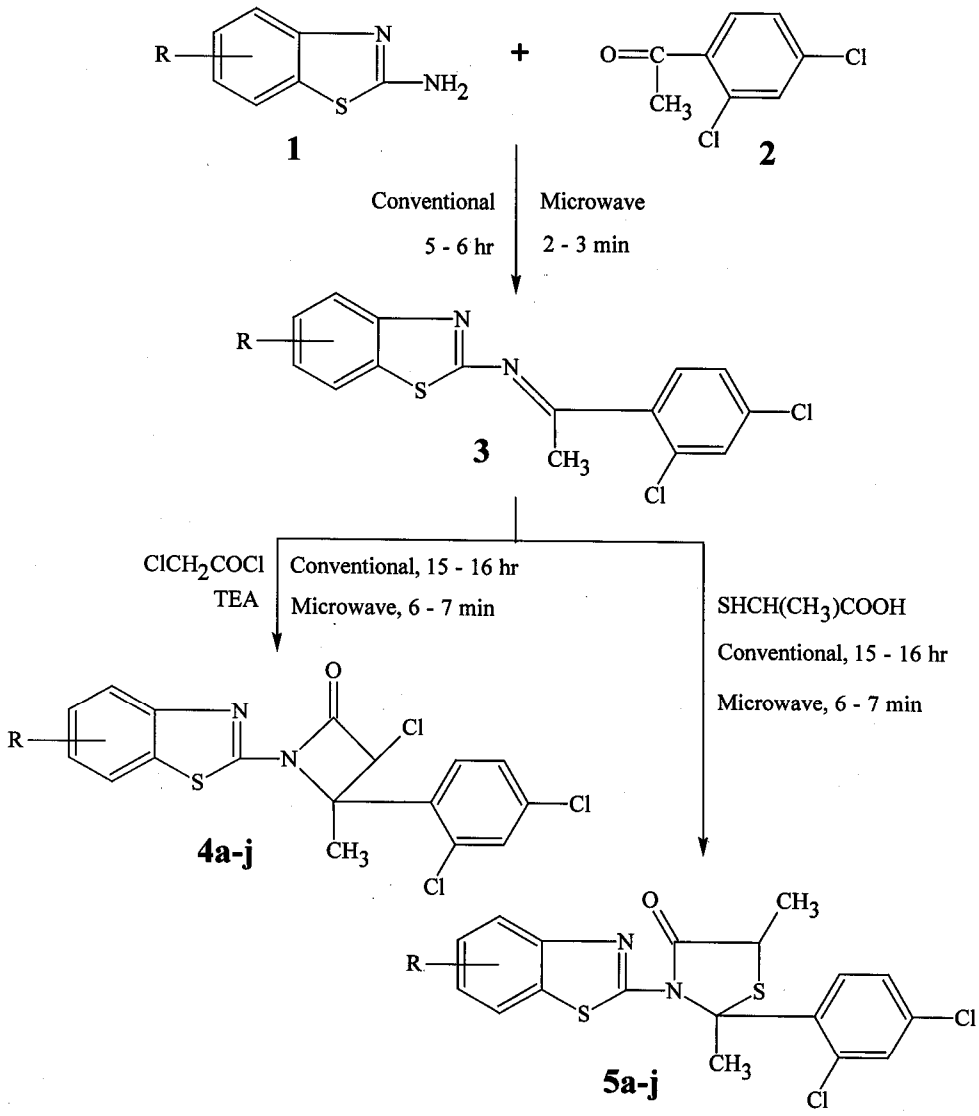
In conventional method treatment of the schiff base **3** with chloroacetyl chloride in the presence of triethylamine and thiolactic acid using benzene as a solvent yielded compounds 3-chloro-4-(2″,4″-dichlorophenyl)-4-methyl-1-(substituted-1′,3′-benzothiazol-2′-yl)-azetidin-2-ones **4a-j** and 2-(2″,4″-dichlorophenyl)-2,5-dimethyl-3-(substituted-1′,3′-benzothiazol-2′-yl)-1,3-thiazolidin-4-ones **5a-j**, respectively (**Scheme I**). It took about 15 - 16 hr in conventional method, while under microwave irradiation using DMF as a solvent the reaction was complete in 6-7 min.

A comparative study in terms of yield and reaction period is shown in **Tables I** and **II**.

Experimental Section

All the melting points were determined on a PMP-DM scientific melting point apparatus and are uncorrected. The purity of compounds was checked by TLC on silica gel 'G' coated glass plates. IR spectra were recorded in KBr on a Shimadzu FT-IR 8300 spectrophotometer, ^{1}H NMR spectra on a Brucker DRX - 300 in $CDCl_3$ at 200 MHz using TMS as an internal standard (chemical shifts in δ, ppm). Microwave assisted reactions were carried out in a "QPro-M modified microwave oven" made in Canada at 300 watt and 2450 MHz frequency. Elemental analysis was carried out on Carlo Erba-1108 analyzer.

Synthesis of 3-chloro-4-(2″,4″-dichlorophenyl)-4-methyl-1-(substituted-1′,3′-benzothiazol-2′-yl)-aze



4,5	R	4,5	R
a	6-NO_2	**f**	6-OCH_3
b	6-SO_3H	**g**	6-CH_3
c	6-OH	**h**	4-OCH_3
d	4-NO_2	**i**	4,6-$(NO_2)_2$
e	6-Cl	**j**	6-$NHCOCH_3$

Scheme I

tidin-2-ones 4a-j (Conventional method). A mixture of Schiff base **3** (0.01 mole) in benzene was taken in a round bottom flask. Then chloroacetyl chloride (0.01 mole) and triethylamine (0.01 mole) in benzene were added slowly. It was refluxed for 15-16 hr. The triethylamine hydrochloride formed during the reaction, was removed and the benzene was distilled off to get the product. The crude product obtained was recrystallised from ethanol.

Microwave method. A mixture of Schiff base **3** (0.01 mole) in DMF was taken in a round bottom flask, and to it chloroacetyl chloride (0.01 mole) and triethylamine (0.01 mole) were added slowly. The mixture was irradiated in a QPro-M modified microwave oven for about 6-7 min. It was then diluted with ice-cold water. The solid product thus formed was filtered, dried and recrystallised from ethanol.

Table I — Characterization data of compounds **4a-j**

Compd	Mol. formula (Mol. wt.)	Yield (%) Conven. method (period/hr)	Yield (%) M. W. method (period/min)	m.p. °C	Required (Found) % C	H	N
4a	$C_{17}H_{10}N_3O_3SCl_3$ (442.70)	68 (15.0)	80 (6.5)	169	46.12 (46.11	2.28 2.25	9.49 9.46)
4b	$C_{17}H_{11}N_2O_4S_2Cl_3$ (477.77)	64 (15.0)	82 (7.0)	158	42.74 (42.72	2.32 2.34	5.86 5.84)
4c	$C_{17}H_{11}N_2O_2SCl_3$ (413.70)	64 (16.0)	80 (7.0)	155	49.35 (49.39	2.68 2.65	6.77 6.79)
4d	$C_{17}H_{10}N_3O_3SCl_3$ (442.70)	60 (16.0)	75 (7.0)	145	46.12 (46.13	2.28 2.29	9.49 9.48)
4e	$C_{17}H_{10}N_2OSCl_4$ (432.15)	65 (16.0)	78 (7.0)	165	47.25 (47.24	2.33 2.37	6.48 6.47)
4f	$C_{18}H_{13}N_2O_2SCl_3$ (427.73)	68 (16.0)	75 (6.5)	139	50.54 (50.56	3.06 3.04	6.55 6.52)
4g	$C_{18}H_{13}N_2OSCl_3$ (411.73)	65 (15.0)	78 (6.5)	129	52.51 (52.50	3.18 3.19	6.80 6.82)
4h	$C_{18}H_{13}N_2O_2SCl_3$ (427.73)	68 (15.0)	80 (7.0)	132	50.54 (50.53	3.06 3.02	6.55 6.59)
4i	$C_{17}H_9N_4O_5SCl_3$ (487.70)	70 (16.0)	80 (6.5)	140	41.87 (41.85	1.86 1.87	11.49 11.45)
4j	$C_{19}H_{14}N_3O_2SCl_3$ (454.75)	60 (16.0)	75 (6.5)	162	50.18 (50.19	3.10 3.12	9.24 9.22)

4a: ^{1}H NMR: δ 6.98 - 7.78 (6H, m, Ar-H), 4.0 (1H, s, -CHCl), 1.1 (3H, s, -CH_3); MS (M^+): 441
4b: ^{1}H NMR: δ 7.15 - 7.83 (6H, m, Ar-H), 4.15 (1H, s, -CHCl), 1.33 (3H, s, -CH_3), 3.5 (1H, s, -SO_3H); MS (M^+): 476
4c: ^{1}H NMR: δ 6.87 - 7.62 (6H, m, Ar-H), 4.3 (1H, s, -CHCl), 1.37 (3H, s, -CH_3), 5.0 (1H, s, -OH); MS (M^+): 412
4f: ^{1}H NMR: δ 6.78 - 7.69 (6H, m, Ar-H), 4.4 (1H, s, -CHCl), 1.5 (3H, s, -CH_3), 2.82 (3H, s, -OCH_3); MS (M+): 427
4j: ^{1}H NMR: δ 7.12 - 7.71 (6H, m, Ar-H), 4.2 (1H, s, -CHCl), 1.42 (3H, s, -CH_3), 7.85 (1H, s, -CONH), 0.13 (3H, d, -$NHCOCH_3$); MS (M+): 453

Table II — Characterization data of compounds **5a-j**

Compd	Mol. formula (Mol. wt.)	Yield (%) Conven. method (period/hr)	Yield (%) M. W. method (period/min)	m.p. ºC	Required (Found) % C	H	N
5a	$C_{18}H_{13}N_3O_3S_2Cl_2$ (454.35)	60 (16.0)	72 (7.0)	158	47.58 (47.59	2.88 2.89	9.25 9.28)
5b	$C_{18}H_{14}N_2O_4S_3Cl_2$ (489.41)	62 (16.0)	75 (7.0)	188	44.17 (44.16	2.88 2.87	5.72 5.74)
5c	$C_{18}H_{14}N_2O_2S_2Cl_2$ (425.35)	62 (16.0)	75 (7.5)	146	50.83 (50.82	3.32 3.31	6.59 6.58)
5d	$C_{18}H_{13}N_3O_3S_2Cl_2$ (454.35)	65 (16.0)	75 (7.5)	157	47.58 (47.59	2.88 2.87	9.25 9.28)
5e	$C_{18}H_{13}N_2OS_2Cl_3$ (443.79)	62 (15.0)	78 (7.5)	141	48.71 (48.74	2.95 2.94	6.31 6.34)
5f	$C_{19}H_{16}N_2O_2S_2Cl_2$ (439.38)	70 (16.0)	78 (7.5)	152	51.94 (51.90	3.67 3.68	6.38 6.35)
5g	$C_{19}H_{16}N_2OS_2Cl_2$ (423.38)	65 (16.0)	75 (7.0)	129	53.90 (53.93	3.81 3.84	6.62 6.61)

—Contd

Table II — Characterization data of compounds **5a-j**—*Contd*

Compd	Mol. formula (Mol. wt.)	Yield (%)		m.p. ºC	Required (Found) %		
		Conven. method (period/hr)	M. W. method (period/min)		C	H	N
5a	$C_{18}H_{13}N_3O_3S_2Cl_2$ (454.35)	60 (16.0)	72 (7.0)	158	47.58 (47.59	2.88 2.89	9.25 9.28)
5b	$C_{18}H_{14}N_2O_4S_3Cl_2$ (489.41)	62 (16.0)	75 (7.0)	188	44.17 (44.16	2.88 2.87	5.72 5.74)
5c	$C_{18}H_{14}N_2O_2S_2Cl_2$ (425.35)	62 (16.0)	75 (7.5)	146	50.83 (50.82	3.32 3.31	6.59 6.58)
5d	$C_{18}H_{13}N_3O_3S_2Cl_2$ (454.35)	65 (16.0)	75 (7.5)	157	47.58 (47.59	2.88 2.87	9.25 9.28)
5e	$C_{18}H_{13}N_2OS_2Cl_3$ (443.79)	62 (15.0)	78 (7.5)	141	48.71 (48.74	2.95 2.94	6.31 6.34)
5f	$C_{19}H_{16}N_2O_2S_2Cl_2$ (439.38)	70 (16.0)	78 (7.5)	152	51.94 (51.90	3.67 3.68	6.38 6.35)
5g	$C_{19}H_{16}N_2OS_2Cl_2$ (423.38)	65 (16.0)	75 (7.0)	129	53.90 (53.93	3.81 3.84	6.62 6.61)
5h	$C_{19}H_{16}N_2O_2S_2Cl_2$ (439.38)	70 (16.0)	78 (7.0)	162	51.94 (51.92	3.67 3.69	6.38 6.35)
5i	$C_{18}H_{12}N_4O_5S_2Cl_2$ (499.34)	68 (15.0)	80 (7.5)	171	43.29 (43.25	2.42 2.45	11.22 11.20)
5j	$C_{20}H_{17}N_3O_2S_2Cl_2$ (466.40)	65 (15.0)	82 (7.5)	177	51.50 (51.51	3.67 3.69	9.01 9.02)

5d: ^{1}H NMR: δ 6.82 - 7.83 (6H, m, Ar-H), 1.11 (3H, s, -C-CH_3), 1.5 (3H, d, -CH-CH_3), 4.2 (1H, s, -CH); MS (M^+): 453
5e: ^{1}H NMR: δ 6.78 - 7.67 (6H, m, Ar-H), 1.2 (3H, s, -C-CH_3), 1.43 (3H, d, -CH-CH_3), 4.23 (1H, s, -CH); MS (M^+): 443
5g: ^{1}H NMR: δ 7.08 - 7.72 (6H, m, Ar-H), 1.25 (6H, s, -C-CH_3), 1.52 (3H, d, -CH-CH_3), 4.3 (1H, s, -CH); MS (M^+): 422
5h: ^{1}H NMR: δ 7.13 - 7.84 (6H, m, Ar-H), 1.18 (3H, s, -C-CH_3), 1.58 (3H, d, -CH-CH_3), 2.87 (3H, s, -OCH_3), 4.1 (1H, s, -CH); MS (M+): 438
5i: ^{1}H NMR: δ 7.17 - 7.81 (5H, m, Ar-H), 1.15 (3H, s, -C-CH_3), 1.6 (3H, d, -CH-CH_3), 4.11 (1H, s, -CH); MS (M+): 498

Following the same procedure, the compounds **4a-j** were prepared. Their characterization data are recorded in **Table I**.

Synthesis of 2-(2″,4″-dichlorophenyl)-2,5-dimethyl-3-(substituted-1′,3′-benzothiazol-2′-yl)-1,3-thiazolidin-4-ones 5a-j (Conventional method). A mixture of schiff base **3** (0.01 mole) in benzene was taken in a round bottom flask. Then thiolactic acid (0.01 mole) in benzene was added slowly. It was refluxed for 15 - 16 hr. The benzene was distilled off to get the crude product, which was recrystallised from ethanol.

Microwave method. A mixture of schiff base **3** (0.01 mole) in DMF was taken in a round bottom flask, and thiolactic acid (0.01 mole) was added slowly. The mixture was irradiated in a QPro-M modified microwave oven for about 6 - 7 min. It was then diluted with ice-cold water. The solid product thus formed was filtered, dried and recrystallised from ethanol.

Following the same procedure, the compounds **5a-j** were prepared. Their characterization data are recorded in **Table II**.

Antimicrobial activity

The synthesized compounds were tested for their antibacterial activity by measuring the zone of inhibition on agar plates (diffusimetric method)[19] with *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Salmonella typhi* and antifungal activity against *Candida albicans* as test organisms **(Table III)**. The MIC of the compound

Table III — Zone of inhibition (mm) of compounds **4a-j** and **5a-j**

Compd	R	Antibacterial				Antifungal
		S.aureus	*B.subtilis*	*E.coli*	*S.typhi*	*C.albicans*
4a	6-NO_2	9	7	8	7	13
4b	6-SO_3H	13	10	12	8	11
4c	6-OH	12	11	13	13	8
4d	4-NO_2	11	9	12	8	13
4e	6-Cl	7	10	14	9	7
4f	6-OCH_3	7	13	7	10	14
4g	6-CH_3	12	7	10	14	9
4h	4-OCH_3	9	14	12	11	12
4i	4,6-$(NO_2)_2$	9	8	8	11	11
4j	6-$NHCOCH_3$	14	9	13	7	12
5a	6-NO_2	8	13	14	8	8
5b	6-SO_3H	12	12	12	12	9
5c	6-OH	12	9	8	9	12
5d	4-NO_2	7	13	9	12	7
5e	6-Cl	14	9	10	11	12
5f	6-OCH_3	10	14	8	11	7
5g	6-CH_3	8	14	12	14	14
5h	4-OCH_3	8	7	7	7	13
5i	4,6-$(NO_2)_2$	11	8	14	13	14
5j	6-$NHCOCH_3$	10	9	7	12	8
Penicillin	-	16	18	16	19	-
Tetracycline	-	18	19	20	18	-

was defined as the lowest concentration at which there was 80 % inhibition of growth compared with the growth for a drug-free control. By visualizing the antibacterial data, it could be observed that compounds of the series showed moderate to good activity at 100 µg/mL.

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