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Newer synthetic approaches of novel benzothiazole derivatives

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ABSTRACT

Benzothiazole is one of the most important heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. In the present study some novel benzothiazole derivatives were synthesized under conventional and parallel synthesizer according to the scheme. All the synthesized benzothiazole derivatives have been characterized by using elemental analysis, FT-IR, ^{1}HNMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate and HPLC technique.

Key words: Parallel synthesizer, Benzothiazole, Antimicrobial, anti-oxidant, anti-tubercular

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INTRODUCTION

Heterocyclic compound is one which possesses a cyclic structure with at least two different kinds of hetero atoms in the ring. Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways. Benzothiazole is a heterocyclic compound, weak base, is made from thiazole ring fused with benzene ring, having various biological activities and still of great scientific interest now a days. Benzothiazole possess interesting biological activities like anti-tumor [1], anti-microbial [2], anti-tubercular [3], anti-convulsant [4], anthelmintic [5], anti-oxidant [6], analgesic [7], anti-inflammatory [8], antifungal [9], antileishmanial [10], antipsychotic [11], anti-ulcer [12], local anesthetic[13], schistosomicidal [14] and diuretic [15] activities. In the 1950s, a number of benzothiazole derivatives were intensively studied, as the benzothiazole scaffold is one of privileged structure in medicinal chemistry.

The conventional synthetic techniques have several drawbacks including usage of bulk amount of solvents, longer duration of time, low yields of products and usage of toxic substances etc. These are insufficient and harmful to environment. Environmental scientists supposed green techniques are micro-wave irradiation, ultra-sonication, phase transfer catalysis, parallel synthesizer and solvent free reactions. In the present work newer benzothiazole derivatives are compared with conventional and parallel synthesis methods and their spectral data also included.

MATERIALS AND METHODS

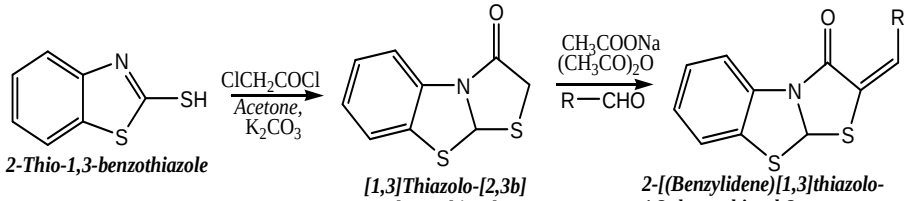
Melting points were determined in Digital melting point apparatus and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. All compounds were purified by recrystallization with suitable organic solvents.. All compounds were also synthesized in CAROUSEL six plus reaction station and as well as by conventional method. IR spectra were recorded on Brooker-ALPHA FT-IR instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR was determined in $CDCl_3$ solution on a Bruker Ac 400 MHz spectrometer. Purity of the synthesized compounds was checked by HPLC Agilent. The results are in agreements with the structures assigned.

STEP (1):

a). Preparation of [1,3]thiazolo[2,3b]1,3-benzothiazole: Equimolar amount of 2-thio-1,3-benzothiazole (0.05 mol) and chloroacetyl chloride (0.05 mol) in acetone (30 ml) was refluxed in the presence of K_2CO_3 (0.05 mol). Excess of solvent was removed in vacuum and the residue was poured in ice cold water (50 ml) and stirred it. The residue was washed with 5% $NaHCO_3$ (30 ml) and subsequently with water (30 ml). The product thus obtained was filtered, washed with water. The crude product was dried and recrystallized with chloroform. Yield 71%, M.W: 209.3, M.P: 125-127^0, IR (KBr): (C-H) 3037, (C=C) 1539, (C=O) 1711, (C-S) 751; Analysis Calculated for$C_9H_7NOS_2$, C, 51.65; H, 3.37; N, 6.69; O, 7.64; S, 30.6%.Found: C, 51.57; H, 3.28; N, 6.52; O, 7.56, S, 30.5%.

b). Preparation of 2-Benzylidene[1,3]thiazolo-1,3-benzothiazol-3-ones (BT-1 to BT-5): A mixture of [1,3]thiazolo-[2,3b]-1,3-benzothiazole (2.0036 mol), different aromatic aldehyde (0.0036 mol) and sodium acetate (0.0036 mol) in the presence of acetic anhydride (10 ml) was refluxed. The reaction mixture was poured in ice cold water (50 ml) and stirred it. The product thus obtained was filtered, washed with water. The crude product was dried and recrystallized with methanol.

Scheme 1: Synthesis of 2-Benzylidene[1,3]thiazolo-1,3-benzothiazol-3-ones (BT-1 to BT-5)



2-Thio-1,3-benzothiazole *[1,3]Thiazolo-[2,3b] 1,3-benzothiazole* *2-[(Benzylidene)[1,3]thiazolo-1,3- benzothiazol-3-one*

Table 1: Physical constants of 2-Benzylidene[1,3]thiazolo-1,3-benzothiazol-3-ones(BT-1 to BT-5)

Compd	R	M.F	M.W	Yield (%)		M.P (^{0}C)	R_f	Time	
				C.M	P.S			C.M	P.S
BT-1	C_6H_5	$C_{16}H_{11}NOS_2$	297.4	60	68	187-189	0.59	6hrs	2hrs
BT-2	*p*-ClC_6H_4	$C_{16}H_{10}ClNOS_2$	331.8	64	72	147-149	0.81	6hrs	2hrs
BT-3	*m*-$NO_2C_6H_4$	$C_{16}H_{10}N_2O_3S_2$	342.4	59	65	177-179	0.67	6hrs	2hrs
BT-4	*p*-OHC_6H_4	$C_{16}H_{11}NO_2S_2$	313.3	66	78	136-138	0.58	6hrs	2hrs
BT-5	*p*-$OCH_3C_6H_4$	$C_{17}H_{13}NO_3S_2$	327.4	70	82	220-222	0.66	6hrs	2hrs

Table-2: I.R Spectral data of 2-Benzylidene[1,3]thiazolo-1,3-benzothiazol-3-ones(BT-1 to BT-5)

Compd	Substitution (R)	IR ν_{max} (cm^{-1})
BT-1	C_6H_5	(C=O) 1711, (C-H) 2961, (C-N) 1144
BT-2	*p*-ClC_6H_4	(C=O) 1718, (C-S) 761, (C-Cl) 726
BT-3	*m*-$NO_2C_6H_4$	(C=O) 1715, (NO_2) 1520 sym, 1374 asym (C-S) 752
BT-4	*p*-OHC_6H_4	(C=O) 1711, (O-H) 3425.6, (C-S) 752
BT-5	*p*-$OCH_3C_6H_4$	(C=O) 1716,

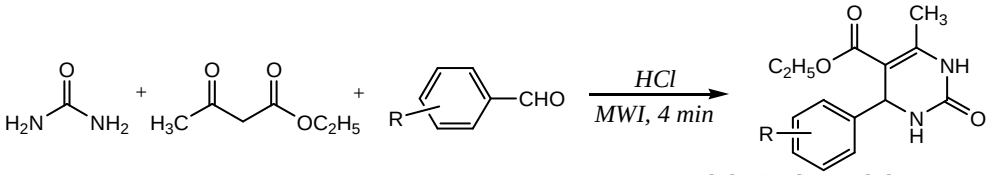
STEP (2):

a). Preparation of 2-Amino-6-chloro-1,3-benzothiazole: To take a 20 ml of glacial acetic acid pre-cooled to -5^{0}C were added 8 g potassium thiocyanate and 0.01mol of 4-chloroaniline. The mixture was placed in freezing mixture of ice and was magnetically stirred, while 1.6 ml of bromine in 6ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature never rise beyond 0^{0}C, after all bromine was added in the reaction mixture was stirred additionally at 0^{0}C and 25-30^{0}C respectively. The mixture was then allowed to stand overnight and add 50 ml of water quickly; slurry was heated to about 85^{0}C on a steam bath and filtered. The combined filtrates were cool and neutralized with concentrated ammonia solution to PH 6.The separated dark yellow colored precipitate was filtered, washed with water, dried and recrystallized from methanol. Yield 76%, M.W: 184.64, M.P: 200-202^0.

IR (KBr): NH(3330), 3036(Ar=CH), 1602(C=N),1470(C-N), 1262(C-S), 920,730(Ar-H bending vibration), 785(C-Cl), ^{1}HNMR(δ-ppm):3.62(s, 2H, NH_2), 6.78 (dd, 1H, Ar-ortho-H to Cl J= 4.9Hz), 7.19(t, 1H, ortho to chlorine atom, ortho, meta hydrogen coupling), 7.36(m, Ar-H ortho to chlorine and adjacent to sulphur).

b). Preparation of Ethyl 4-(aryl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (PD-1 TO PD-5):A mixture of ethyl acetoacetate (2.58ml, 0.02mol), urea (1.52g, 0.02mol), different aromatic benzaldehydes (2.8g, 0.02mol) treated in the presence of absolute ethanol(30ml) with catalytic amount of Conc. HCl and continue the heating. Then, the mixture was poured in crushed ice to form the precipitate; it was collected by filtration after washing with ice cold water. Further, it was purified by recrystallization with alcohol.

Scheme 2: Synthesis of Ethyl 4-(aryl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (PD-1 TO PD-5)



Ethyl 4-(Aryl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylates

Table 2: Physical constants of Ethyl 4-(aryl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (PD-1 TO PD-5)

Compd	R	M.F	M.W	Yield (%)		M.P (^{0}C)	R_f	Time	
				C.M	P.S			C.M	P.S
PD-1	*p*-ClC_6H_4	$C_{14}H_{15}ClN_2O_3$	294.7	75	86	211-213	0.74	30min	5min
PD-2	*m*-OHC_6H_4	$C_{14}H_{16}N_2O_4$	276.2	59	71	192-194	0.65	30min	5min
PD-3	*p*-OHC_6H_4	$C_{14}H_{16}N_2O_4$	276.2	70	80	170-172	0.71	30min	5min
PD-4	*p*-$CH_3C_6H_4$	$C_{15}H_{18}N_2O_4$	290.3	68	79	190-192	0.54	30min	5min
PD-5	*p*-$N(CH_3)_2C_6H_4$	$C_{16}H_{21}N_3O_3$	330.3	70	82	202-204	0.68	30min	5min

STEP (3):

Preparation of N-(6-Chlorobenzothiazol-2-yl)-4-(aryl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (BTZ-1 TO BTZ-5): Equimolar amount of 2-amino-6-chloro-1,3-benzothiazole (0.01 mol) and ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0.01mol) was reflux in the presence of glacial acetic acid and add a few drop of Conc. HCl in water bath. The residue was cooled and poured in ice cold water and stirred it. The product thus obtained was filtered and washed with water. The crude product was dried and recrystallized with methanol.

Scheme 3: N-(6-Chlorobenzothiazol-2-yl)-4-(aryl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (BTZ-1 TO BTZ-5)

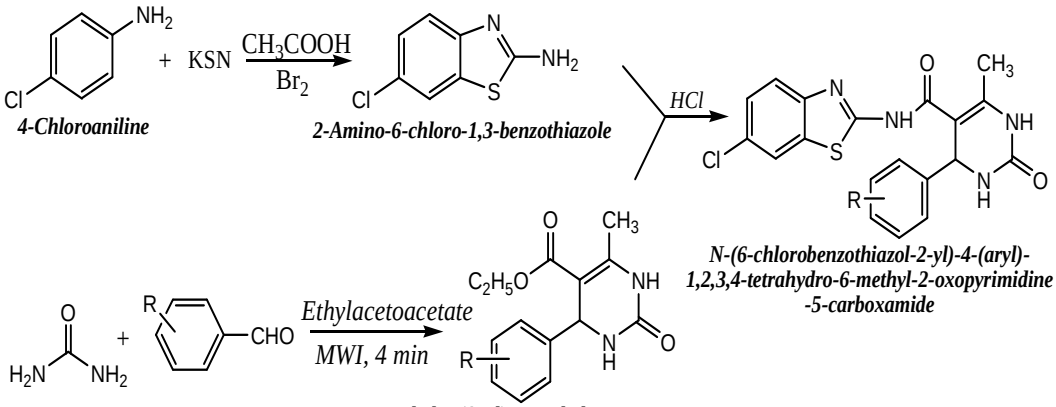


Table 3: Physical constants of N-(6-Chlorobenzothiazol-2-yl)-4-(aryl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (BTZ-1 TO BTZ-5)

Compd	R	M.F	M.W	Yield (%)		M.P (^{0}C)	R_f	Time	
				C.M	P.S			C.M	P.S
BTZ-1	*p*-ClC_6H_4	$C_{19}H_{14}Cl_2N_4O_2S$	433.3	65	74	205-207	0.78	26Hr	8Hr
BTZ-2	*m*-OHC_6H_4	$C_{19}H_{15}ClN_4O_3S$	414.8	71	81	185-187	0.73	26Hr	8Hr
BTZ-3	*p*-OHC_6H_4	$C_{19}H_{15}ClN_4O_3S$	414.8	68	79	227-229	0.65	26Hr	8Hr
BTZ-4	*p*-$CH_3C_6H_4$	$C_{20}H_{17}ClN_4O_3S$	428.9	59	65	197-199	0.59	26Hr	8Hr
BTZ-5	*p*-$N(CH_3)_2C_6H_4$	$C_{21}H_{20}ClN_5O_2S$	441.9	71	80	178-180	0.62	26Hr	8Hr

Table 4: I.R Spectral data of Ethyl 4-(aryl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (PD-1 TO PD-5) and N-(6-Chlorobenzothiazol-2-yl)-4-(aryl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (BTZ-1 TO BTZ-5)

Compd	Substitution (R)	IR ν_{max} (cm^{-1})
PD-1	*p*-ClC_6H_4	(N-H) 3243, (C=O) 1274, (C-Cl) 782
PD-2	*m*-OHC_6H_4	(O-H) 3352, (C=O) 1706, (N-H) 3226
BTZ-1	*p*-ClC_6H_4	(N-H) 3232, (C=O) 1701, (C-Cl) 785
BTZ-3	*p*-OHC_6H_4	(O-H) 3380, (C=O) 1667, (N-H) 3302
BTZ-4	*p*-$CH_3C_6H_4$	(N-H) 3302, (C=O) 1666, (C-O-C) 1278
BTZ-5	*p*-$N(CH_3)_2C_6H_4$	(N-H) 3264, (C=O) 1690,

Table 5:^{1}H NMR Spectral data

Compd	R	δ value
BT	H	4.1(S, 2H, CH_2); 7.1 (S, 1H , CH); 7.3-7.8 (m, 4H, Ar-H)
BT-3	*m*-$NO_2C_6H_4$	7.13 (S, 1H, CH); 7.22-7.9 (m, 8H, Ar-H); 11.5 (S, 1H, CH)
BTZ-1	*p*-ClC_6H_4	2.2 (s, 3H, CH_3); 2.5 (s, 1H, NH); 5.1 (s, 1H, CH); 6.5 (d, 2H, Ar-H); 7.2 (d, 2H, Ar-H); 7.3 (d, 2H, Ar-H); 7.7 (s, 1H, Ar-H); 7.9 (d, 1H, Ar-H); 8.1 (s, 1H, NH); 9.1 (s, 1H, NH).
BTZ-3	*p*-OHC_6H_4	2.2 (s, 3H, CH_3); 2.4 (s, 3H, NH); 5.4 (s, 3H, CH); 7.1 (m, 7H, Ar-H); 8.0 (s, 1H, NH); 9.2 (s, 1H, NH); 12.4 (s, 1H, OH).

Table 6: Mass Spectral data Mass Spectral data newer benzothiazole derivatives

Compd	R	δ value		Compd	R	δ value
BT-1	*p*-ClC_6H_4	298(M^+)		BTZ-1	*m*-OHC_6H_4	414(M^+)
BT-2	*m*-$NO_2C_6H_4$	332(M^+)		BTZ-2	*p*-OHC_6H_4	414(M^+)
BT-3	*p*-OHC_6H_4	343(M^+)		BTZ-3	*p*-$CH_3C_6H_4$	412(M^+)
BT-4	*p*-$OCH_3C_6H_4$	314(M^+)		BTZ-4	*p*-$N(CH_3)_2C_6H_4$	441(M^+)
BT-5	*p*-ClC_6H_4	327(M^+)		BTZ-5	C_6H_5	398(M^+)

RESULTS AND DISCUSSION

Comparing with conventional synthesis and parallel synthesizer a considerable increase in the reaction rate has been observed and that too with better yields is more beneficial because it has solid-liquid interactions, pollution free and environmentally acceptable, high degree of stereo selectivity in products and shorter reaction time with simple work.

CONCLUSION

Finally newer benzothiazole derivatives synthesized by using parallel synthesizer with noteworthy advantages viz., shorter reaction times, moderate reaction conditions, simple workup procedure, easy preparation and handling, operational simplicity, simple work-up, easy to handle and eco-friendly nature. This methodology may find wide applications in organic synthesis for preparation of newer benzothiazole derivatives.

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