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RESEARCH ARTICLE

GREEN SYNTHESISOFSOME HETEROCYCLIC COMPOUNDS DERIVED FROM BENZOAZOLES

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ABSTRACT

A series of 1,2,4-triazole,2-aryllidine hydrazono benzoazole and 3-chloro-2-azetidinone derivatives were synthesized via reactions with different reagents. Reactions were carried out by green synthesis method such as microwave technique andgreen catalysts.The structure of the prepared compounds have been characterized on the basis of their elemental analysis and spectral data.Some of the new compounds were screened for their antimicrobial activity.

INTRODUCTION

Benzoheterocycles such as benzothiazole, benzoxazole and benzoimidazole belong to an important class of heterocyclic compounds (Shirini *et al*., 2014 and Xiang *et al.,* 2012). They are privileged structure unit in various fields such as natural products, pharmaceuticals, and industrial chemistry. (Ingel and Marathe, 2012 and Shuliny *et al*., 2010). In recent years, many synthetic compounds bearing 1,3,4-triazole scaffold possess a wide attention because of their diverse biological significance such asantimicrobial, anti-tumor, anti-nociceptive and anti-inflammatory activities (Sharif *et al*., 2012; Kumbhare *et al*., 2012; Wikel and Paget, 1974 and Naresh *et al*., 2013). 2-Azetidinones are a part of antibiotic structure. The activity of the known antibiotics such as penicillins, cephalosporins, monobactams, and carbapenems are referred to the presence of 2-azetidinone moiety in their structures (Brandi*et al*., 2008 and Sonware *et al*., 2010). A large number of 3-chloro monocyclic β-lactams show a broad spectrum properties of biological and pharmacological activities such as anti-bacterial, antimicrobial, anti-inflammatory, anti-convulsant, and anti-tubercular (Navin and Jaymin, 2011; Sharma *et al*., 1998; and Ameye and Nandini, 2007). The development of effective and eco- friendly methods constitutes an important target in organic synthesis.Microwave irradiationhas become an important tool in a variety of applications including synthetic chemistry, due to certain features particularly mild condition, rate enhancements, excellent yields and shorter reaction times (Lidstrom *et al*., 2001; Bandgar *et al*., 2002; Alexandre *et al.,* 2003; Das *et al*., 2012 and Savita, 2013). Many methods had been reported in the literature for the synthesis of bioactive benzoazolederivatives utilizingvarious catalysts under different techniques (Messri, 2009; Ameta *et al*., 2010; Dua, *et al*., 2010; Kumar *et al*., 2013 and Asrondkar *et al*., 2013). In a continuation of our work on the green synthesis, herein we report the synthesis of some interesting benzoimidazole-1,2,4-triazole derivatives,and3-chloro-azetidinone-benzoazole derivativesunder microwave irradiation and using friendly catalyst.

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MATERIALS AND METHODS

General

All melting points were determined on Gallen Kamp apparatus. The ^{1}HNMR spectra were recorded in $CDCl_3$or DMSO-d_6 on a Junmex-400 FT NMR AM 400 spectrophotometer using TMS as internal reference. IR spectra were recorded in KBr on Perkin-Elmer 380 Spectrometer. The elemental analyses were performed on a Heraus C,H,N analyzer. Mass spectra were record on micro mass 7070 spectrophotometer operating at 70 eV. Microwave irradiation was carried out with microwave oven start SYNTH-Milestone-open vessel. Progress of the reactions was monitored by TLC.

Synthesis of ethyl(benzo(1,3)azol-2-yl thio) acetate (2a,b)

Basic alumina (20 g) was added to the solution of 2-mercaptobenzodiazole 1a,b (1 mmol) and ethyl chloroacetate

(1 mmol) dissolved in dichloromethane (10 cm^3) at room temperature. The reaction mixture was thoroughly mixed and the adsorbed material was air dried (in 100 mL beaker). Placed in an alumina bath and irradiated at (300 W) intermittently30s intervals for specified time. After cooling there action mixture was extracted into chloroform (3×10 mL). The mixture was evaporated under reduced pressure and the residue was recrystallized from ethanol (Table1).

Synthesis of 2-(benzo (1,3) azole-2-yl thio) acetohydrazide (3a,b)

Method A

Basic alumina (20 g) was added to the solution of Compound **2a,b** (1 mmol), hydrazine hydrate (0.015 mmol),dissolved in dichloromethane (10 cm^3) at room temperature. The reaction mixture was thoroughly mixed and the adsorbed material was air dried (in 100 mL beaker). Placed in an alumina bath and irradiated at (300 W) intermittently 30s intervals for specified time . After cooling the reaction mixture was extracted into chloroform (3×10 mL).The mixture was evaporated under reduced pressure and the residue was recrystallized from ethanol(Table1).

Method B: One pot synthesis of (3a,b)

Basic alumina (20 g) was added to the solution of 2-mercapto -1,3-benzoazole **1a,b** (0.1 mmol) and ethyl chloroacetate (0.1 mmol), hydrazine hydrate (0.15 mmol),dissolved in dichloromethane (10 cm^3) at room temperaturestirred for 5 min, The reaction mixture was thoroughly mixed and the adsorbed material was air dried (in 100 mL beaker). Placed in an alumina bath and irradiated at (300 W) intermittently 30s intervals for specified time. The workup was carried out as described for synthesis of method A (Table1).

Synthesis of 3-[(benzoimidazole-2-yl thio) methy]4-phenyl-1,2,4-triazol-5-ol (4)or 5-thiol (5)

A mixture of compound **2b** (1 mmol),semicarbazide (1mmol) or thiosemicarbazide (1 mmol) in ethanol (10 mL) was stirred for 10 min. Solution of NaOH (10%) (25 mL) was gradually added dropwise. The mixture was irradiated with microwave at (300 W) for 10 min. The cooled reaction mixture was treated with crushed ice, stirred for 30 min. The solid obtained was filtered, dried and recrystallized from the proper solvents (Table1).

Table 1. Physical data of compounds 2-10

Compd. No.	m.p. °C	Time (min.)	Mol. Formula(Mol. Wt.)	% Analysis (calculated/Found)		
	(Solvent)	(Yield %)		C	H	N
2a	58-60[a]	5	$C_{11}H_{11}NO_2S_2$	52.17	4.34	5.53
	(EtOH)	(85)	253	52.21	4.38	5.54
2b	98-100[a]	4	$C_{11}H_{12}N_2O_2S$	55.93	5.08	11.86
	(EtOH)	(84)	236	55.96	5.04	11.83
3a	192-193[a]	4	$C_9H_9N_3OS_2$	45.18	3.76	17.57
	(EtOH)	(87)	239	45.20	3.78	17.53
3b	231-233[a]	4	$C_9H_{10}N_4OS$	48.64	4.50	25.22
	(EtOH)	(84)	222	48.65	4.59	25.30
4	170-172[a]	10	$C_{16}H_{13}N_5OS$	59.44	4.02	21.67
	(AcOH-H_2O)	(88)	323	59.42	4.10	21.65
5	185-187 [a]	10	$C_{16}H_{13}N_5S_2$	56.63	3.83	20.64
	(EtOH)	(87)	339	56.66	3.85	20.69
7	306-308[a]	8	$C_{10}H_{10}N_6S$	43.16	3.59	30.21
	(EtOH)	(85)	278	43.15	3.56	30.24
8a	197-199	6	$C_7H_7N_3S$	50.63	4.21	19.28
	(EtOH)	(86)	165	50.66	4.40	19.40
8b	223-225	6	$C_7H_8N_4$	56.75	5.40	37.83
	(EtOH)	(92)	148	56.78	5.40	37.83
9a	233-234	4	$C_{13}H_{10}N_4S$	61.40	3.96	22.04
	(EtOH)	(83)	254.3	61.48	3.94	22.11
9b	237-239	4	$C_{13}H_{10}N_4S$	61.11	3.91	22.04
	(EtOH)	(80)	245.3	61.50	3.40	22.08
9c	125-127	3	$C_{14}H_{11}N_3OS$	62. 45	4.08	15.61
	(AcOH)	(78)	269	62.49	4.12	15.56
9d	250-251	3	$C_{16}H_{15}N_3O_2S$	61.31	4.83	13.41
	(EtOH)	(83)	313	61.38	4.88	13.45
9e	235-237	4	$C_{14}H_{10}N_4O_2S$	56.63	3.38	18.78
	(EtOH)	(81)	298.	56.60	3.35	18.77
9f	165-167	3.5	$C_{14}H_{11}ClN_4$	62.10	4.06	20.70
	(EtOH)	(85)	270.5	62.15	4.03	20.65
9g	185-187	3	$C_{14}H_{11}N_5O_2$	59.78	3.91	24.91
	(AcOH)	(77)	281	59.82	3.97	24.88
10a	180-182	10	$C_{15}H_{11}N_4OClS$	54.46	3.32	16.94
	(EtOH)	(86)	330.5	54.45	3.30	16.99
10b	120-123	10	$C_{16}H_{12}N_5O_3Cl$	53.70	3.35	19.58
	(EtOH)	(80)	357.5	53.77	3.38	19.50

a:Messri, 2009

Synthesis of 3-(benzoimidazole-2-yl thio) methyl)-4mino-1,2,4-triazole-5-thiol (7)

Step 1: Synthesis of Potassium salt: potassium 3-[(benzoimidazole-2-yl thio) methyl] dithiocarbazate (6)

A mixture of compound **2b** (1 mmol), CS_2 (1mmol) in (10 mL) ethanol, KOH (0.5 g) were stirred for 12 h.The resulting solid was collected by filtration, washed with ether and dried to give the potassium salt **6:** 78%, m.p ›300 C^0, IR (cm^{-1}) : 3360,3230 (NH) ,1685(C=O) , 1220 (C=S).

Step 2:potassium salt of phenyl carboxy –hydrazide**6**(1 mmol), hydrazine hydrate (1.5 mmol), LiBr (10 mol%) was placed in a conical flask and stirred for 5 min. The reaction mixture then irradiated with microwave at (350 W) for 8 min. The formed solid was filtered, washed several times with water, dried and recrystallized from ethanol (Table1).

Synthesis of 2-hydrazinobenzo(1,3)azole (8a,b)

A mixture of **1a,b** (1 mmol), hydrazine hydrate (1.2 mmol) in ethanol (10 mL) was subjected to microwave irradiation at (60 W) for 6. min. After cooling, the reaction mixture was poured into ice-cooled water, the formed solid was collected by filtration, dried and crystallized from the proper solvent (Table1).

Synthesis of 2-(Aryl methylene)-hydrazono benzo(1,3)azoles (9a-f)

To a mixture of **1a,b** (1 mmol), aromatic aldehyde (1 mmol), cetyl trimethyl ammonium bromide (CTAB) (0.05 mmol, 5 mol%) in water (5 mL), was subjected to micro wave irradiation at (300 W) for 3-4 min. The cooled reaction mixture was poured into ice-cooled water, stirred for 10 min., the formed solid was collected, dried and recrystallized (Table1).

Synthesis of 2-(4-phenyl-3-chloro-2-oxo-azetidine)-2-imino-benzo(1,3)azoles (10a,b)

Compound **8a,b** (1mmol), chloroacetyl chloride (1 mmol) and triethyl amine (TEA) (1mmol) in methanol (10 mL) was subjected to microwave irradiation at (100 W) for 10 min. Initial and final samples temperature were increased. The sample cooled and the irradiation repeated 5 times. The cooled reaction mixture was poured into ice-cooled water. The solid was filtered, dried and crystallized from the proper solvent (Table 1).

RESULTS AND DISCUSSION

In the present work,, a various series of some new 1,2,4-triazoles and 2- azetidinone derivatives were accomplished from 2-mercaptobenzo(1,3)azoles under microwave irradiation, the synthetic route used isshown in

Table 2. IR, ^{1}H NMR and mass spectral data of compounds 2-10

Compd. No.	IR (cm^{-1})	^{1}H NMR (δ ppm)(A,B)	*m/z* (%)
2a	11720 (C=O of ester) 1610(C=N) 1223,1045(C-O-C)	(A) 1.34 (t, 3H, *J* = 7.0 Hz, $-CH_3$),4.13 (q, 2H, *J* = 7.0 Hz, O-CH_2),4.46 (s, 2H, S–CH_2),7.00-7.88 (m, 4H, Ar–H).	253 [M^+]
2b	1730 (C=O of ester), 1610(C=N) 1225,1040(C-O-C)	(A) 1.24 (t, 3H, *J* = 7.0 Hz, CH_3),4.18 (q, 2H, *J* = 7.0 Hz, O-CH_2),4.40 (s, 2H, S–CH_2),6.88-7.89 (m, 4H, Ar–H),8.50 (s, 1H, NH, benzoimidazole–H)	236 [M^+]
3a	3310, 3300 (-$NHNH_2$) , 1640(›C=O of amide)	(B) 4.31 (br.s, 2H, NH_2), 4.60 (s, 2H, S–CH_2),6.96-7.88 (m, 4H, Ar-H), 8.50 (s, 1H, NH).	239[M^+]
3b	br. 3300(-$NHNH_2$), 1635(›C=O of amide)	(A) 4.40 (br.s, 2H, NH_2), 3.80 (s, 2H, S–CH_2),4.10 (s, 1H, SH), 7.00-7.99 (m, 4H, Ar–H), 8.60 (br.s, 1H, NH)..	222[M^+]
4	br. 3390(-NH&-OH),	(B) 4.60 (s, 2H, S–CH_2), 6.99-7.87 (m, 9H, Ar–H), 8.50 (br.s, 1H, NH, benzoimidazole–H), 9.10 (.s, 1H, OH).	323 [M^+]
5	3280(-NH),2565(-SH)	(A) 4.23 (s, 2H, S–CH_2),7.01-8.11 (m,9H, Ar–H), 8.44 (br.s, 1H, NH, benzoimidazole-H),8. 71. (s, 1H, SH).	339 [M^+]
7	3360 , 3310(-NH&- NH_2),1240(-C=S)	(A) 4.43 (s, 2H,S–CH_2),4.98 (br.s, 2H, NH_2), 7.00-7.80(m,4H,Ar–H),8.50(br.s,1H,NH,benzoimidazole-H),8.15 (s, 1H, SH).	278[M^+]
8a	3385,3340(-$NHNH_2$)	(B) 4.80 (br.s, 2H, NH_2), 6.90-7.80 (m ,4H, Ar–H), 8.65 (s, 1H, NH).	165[M^+]
8b	3350,3290(-$NHNH_2$)	(A) 4.78 (br.s, 2H, NH_2), 7.00-7.90 (m ,4H, Ar–H), 8.66(s, 1H, NH), 8.80(br.s,1H,NH).	148[M^+]
9a	3350 (-NH)	(A) 4.80 (s, 1H, N=CH), 7.00-7.90 (m, 8H, Ar–H),8.50 (s, 1H, NH,).	254 [M^+]
9b	3200(-NH)	(A) 4.60 (s, 1H, N=CH), 7.10-8.18 (m, 8H, Ar–H δpy–H), 8.7.00 (br. s, 1H, NH)	245[M^+]
9c	3310(-NH),	(A) 4.41 (s, 1H, N=CH), 7.10-7.90 (m, 8H, Ar–H), 8.50 (br. s, 1H, NH), 12.30 (s, 1H, OH) .	269[M^+]
9d	3310(-NH)	(B) 1.40 (s, 3H, CH_3), 1.60 (s, 3H, CH_3),4.40 (s, 1H, N=CH), 6.80-7.93 (m, 7H, Ar–H), 8.61 (s, 1H, NH).	313[M^+]
9e	3265(-NH)	(A) 4.50 (s, 1H, N=CH), 7.10-8.20 (m, 8H, Ar–H), 8.61 (s, 1H, NH)	298[M^+]
9f	3315(-NH)	(A) 4.43 (s, 1H, N=CH), 6.89-7.98 (m, 8H, Ar–H),8.50 (s, 1H, NH), 8.80 (br.s, 1H, bnzoimidazole-H)	270.5[M^+]
9g	3320(-NH)	(A) 4.40 (s, 1H, N=CH), 6.90-7.88 (m, 8H, Ar–H),8.45 (br.s, 1H, NNH), 8.75 (br.s, 1H,bnzoimidazole-H)	281[M^+]
10a	3330(-NH),1718 C=O)	(B) 4.18 (d, 1H, *J* = 6.80 Hz, N–CH), 5.20 (d, 1H, *J* = 7.00 Hz, CHCl), 7.00-8.20 (m, 8H, Ar–H), 8.50 (br. s, 1H, NH).	330.5[M^+]
10b	3315(-NH),1725 (C=O)	(B) 4.48 (d, 1H, *J* = 7.00 Hz, N–CH–Ar), 5.30 (d, 1H, *J* = 7.00 Hz, CHCl), 7.11-8.15 (m,9H, Ar–H), 8.30 (br. s, 1H, NH), 8.80 (br.s, 1H, bnzoimidazole-H)	357.5[M^+]

A: DMSO-d_6
B: $CDCl_3$

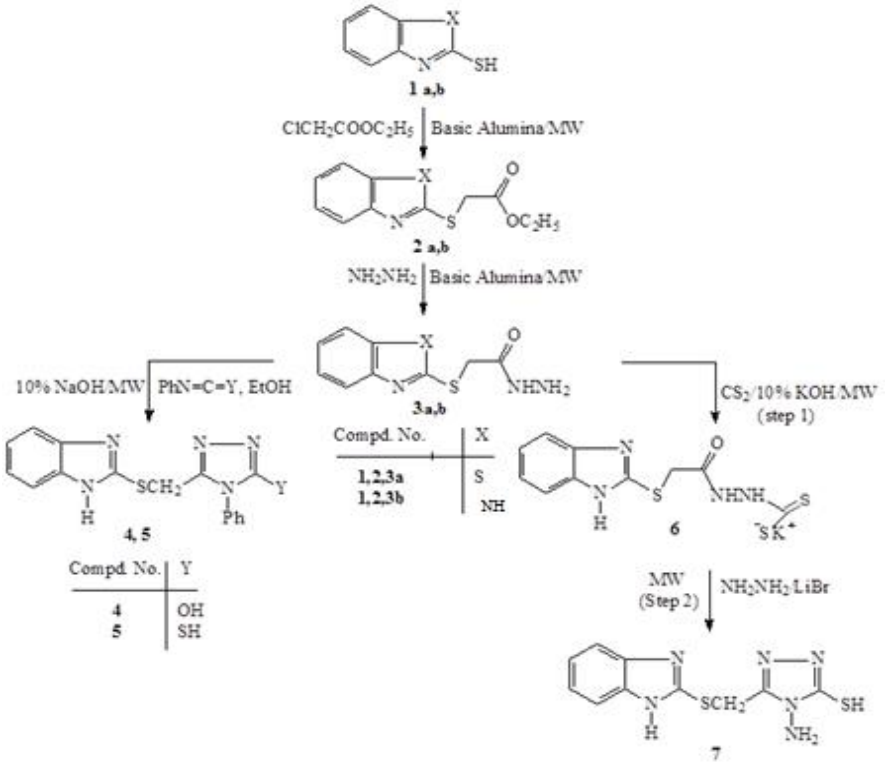
(Schemes 1 & 2). Ethyl(benzo(1,3)azol-2-lthio) acetate derivatives **2a,b** were prepared by condensing 2 –thio -1,3-benzo (1,3) zoles with ethylchloro acetate under microwave irradiation over basic alumina. The structure of synthesized compounds **2a,b** were confirmed from spectral and analytical data (Table 1&2). IR spectrum of compound **2a** showed an C=O (of ester) peak at 1720. The ^{1}HNMR illustrated a triplet at 1.34 due to methyl group,quartet at 4.13 due to O-CH_2 and singlet at 4.46 due to S-CH_2 besides aromatic protons(Table2).

Interaction of esters 2 with hydrazine hydrate under microwave irradiation over basic alumina afforded acetohydrazide derivatives **3a,b** (Ameta *et al*., 2010; Shish *et al*., 2013), Also, compounds **3a,b** could be synthesized by one pot multi-component reaction under microwave irradiation of a mixture of compounds **1a,b**, ethyl chloroacetate and hydrazine hydrate in the presence of anhydrous potassium carbonate in ethanol. The IR spectrum of the compound **3a** showed strong absorption bands 3300-3310 for -$NHNH_2$, the absorption of C=O showed a shift in the band from 1720 cm^{-1} to 1640 cm^{-1} amide I. while its^{1}H NMR showed disappearance of-CH_2CH_3 group (Table 2).

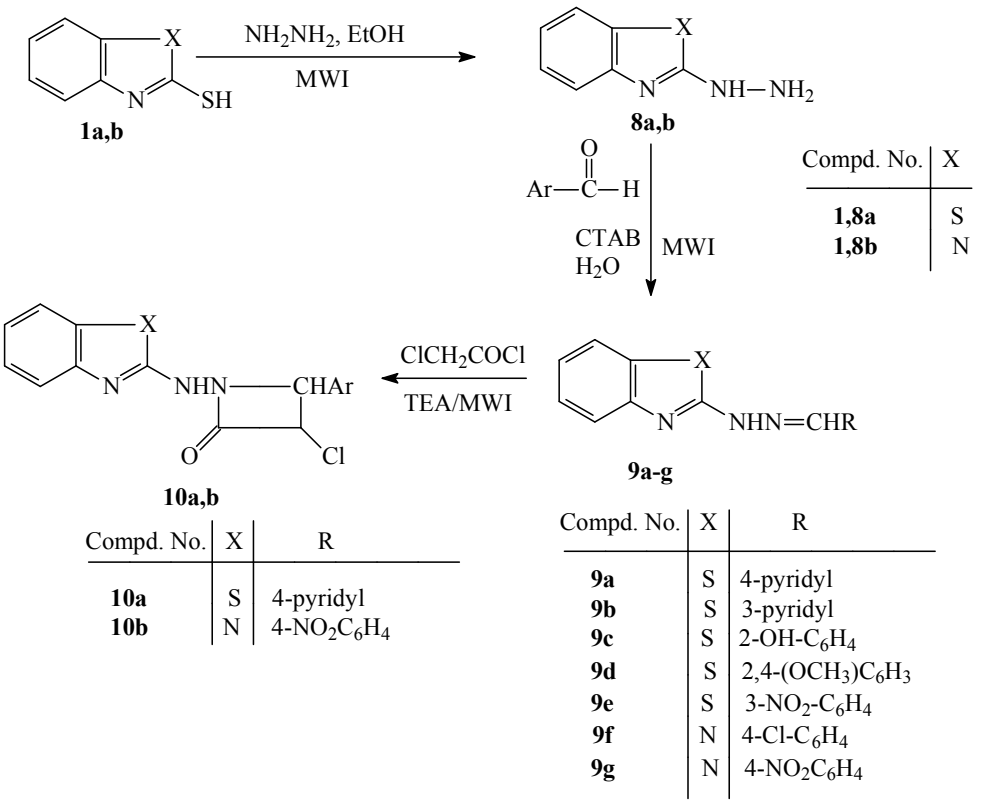
1,2,4-triazol-5-ol derivatives **4** and 1,2,4-triazole-5-thiol derivatives 5 were obtained via intramolecular cyclization by reacting compound **3b** with semicarbazide and thiosemicarbazide respectively in 10% NaOH solution under microwave irradiation at 300 W for 10 min.The structures of compounds **4, 5** were confirmed fromtheir analytical and spectral data. IR spectra of **4** and **5** shows two strong absorption bands at 3390 and 3280 cm-1 respectively due to the presence of OH and NH groups in both compounds respectively. Full analysis of ^{1}HNMR data of **4** and **5** reported in (Table 2), confirmed their structures.

Compound **7**has been prepared following the reported method (Ameta *et al*., 2010). The reaction of hydrazide **3** with CS_2 in the presence of KOH obtained potassium salt of phenyl carboxy-hydrazide (first step), which, was then cyclized by reacting with 98% hydrazine hydrate in the presence of catalytic amount of LiBr under MWI at 350 W for 8 min. to give 3-[(benzoimidazol-2-yl thio)methyl]-4-amino-1,2,4-triazole- 5-thiol **7** in good yield. The assigned structure **7**was inferred from analytical data and IR spectrum which show bands in the region of 3310, 3360 cm-1 corresponding to NH & NH_2group$_S$ and appearance of a band due to carbonyl group. The ^{1}H NMR showed a singlet of SH at δ 8.15 (Table1). 2-hydrazobenzoazoles **8a,b** were synthesized by nucleophilic substation reactions via the action of hydrazine hydrate on compounds **1a,b** under MWI at60W for 6. min. The structures of **8** were established from analytical and spectral data. Furthermore, Compounds **8** can easily condensed with various aromatic aldehyde in the presence of CTBA in water under a microwave irradiation to yield the corresponding Schiff bases **9a-g** in good to moderate yields (77-85%).The structures of these compounds were confirmed on the basis of their various spectral data.IR spectra showed the disappearance of the NH_2 band in similar of spectra of 2-hydrazobenzoazole **8a**,b, while the^1 HNMR data of **9a-g** firmly assigned their structures (Table 2).

Finally, treatment of compounds **9** with chloroacetyl chloride in the presence of TEA in DMF under microwave irradiation at 100w for 10 min. furnished the target compounds azetidine-2-iminobenzoazole derivatives **10a,b** (Dua, *et al*., 2010; Desai and Desail, 2005). The structures of compounds 10a,b were also confirmed by various spectroscopic techniques. Their IR spectra showed bands in the range 1718-1725 cm^{-1} for C=O in azetidine ring. The ^{1}HNMR spectral data of compounds **10a,b** confirmed their structures (Table 2).



Scheme 1: Synthetic route for compounds 2-7.



Scheme 2: Synthetic route for compounds 8-10

Table 3. Antimicrobial activity of the compounds against bacteria and fungi

Test	Compounds											
Organism	4	5	7	9a	9c	9d	9g	9F	10a	10b	CX	GF
S. aurous	+	+	+++	+	+	-	++	-	++	++	+++	
E.coli	+	++	+	-	-	-	+	+	++	+	++++	
B.cereus	+	++	-	-	++	-	+	+	-	++	+++	
A. niger	-	-	+	+	+	-	-	++	++	++		+++
C. albcans	++	-	+	++	-	-	+	+	+	-		++++

CX= Ciprofloxacin , GF=Flucanazole
The inhibition diameter in mm :
++++ = inhibition zone 24-29mm.
+++ = inhibition zone 16-22 mm.
++ = inhibition zone 10-15 mm.
+ = inhibition zone 7-9 mm.
- =inhibition zone<5

Antimicrobial activity

Some of newly synthesize compounds were evaluated for their antimicrobial activity against Staphylococcus aurous, *Escherichia coli, Bacillus cereus* and antifungal activity *Aspergillus niger*, *Candida albicans* using cup-plate method adopted with some modifications (Abau-Zeid. and Shehata, 1969). Commercial antibacterial ciprofloxacin and antifungal flucanazole were used as standard drugs (Table 3).

Conclusion

In conclusion, a serious of various substituted triazoles derivatives and 3-chloro-2-azetidinone were synthesized in the presence of green catalyst under microwave irradiation is reported in this paper. Microwave irradiation proved to be efficient, eco-friendly method for acceleration rate reaction and also increase the yields. Antibacterial, antifungal activity of some synthesized compounds have been evaluated and some of these compounds shown good antimicrobial effect.

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