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Microwave enhanced heterocyclization: A convenient procedure for antimicrobial 1,5-benzothiazepine compounds[§]

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A series of 2,5-dihydro-4-[1′-(*o*-chlorophenyl)-3′-methyl-5′-pyrazolidene azomethine]-2-(substituted phenyl)-1,5 benzothiazepines **7a-j** have been synthesized using environmentally benign procedure and evaluated for their antimicrobial activity. Neat reactants on microwave irradiation (MWI) under solvent-free-condition resulted in enhancement of yields and reaction rates. Structures of the synthesized compounds have been elucidated on the basis of their elemental analyses and spectral data.

Keywords: 1,5-Benzothiazepines, heterocyclization, microwave effect, antimicrobial activity.

Although microwave dielectric heating has been used in areas as divergent as meal preparation and industrial processing[1], the benefits of its use in performing chemical transformations has only emerged within the last 18 years[2,3]. During the last ten years, a number of publications and reviews[4,5] have advocated the use of microwave technology in organic synthesis. They usually describe short reaction times, an increase in the purity of the resulting products and enhancement of chemical yields.

There is an increasing interest in the use of environmentally benign reagents and conditions[6,7] and particularly to solvent-free procedure[8]. Leading to a clean, efficient and economical technology.

Benzothiazepine derivatives are well-known for diverse biological activities and play a key role as antipsychotropic[9], diltiazem[10], antihypertensive[11] and antidepressant[12] compounds. The most straightforward protocol for the synthesis of 1, 5-benzothiazepines **7a-j** involve the one pot condensation of chalcones **5a-j** with 2-aminothiophenol **6** in ethanol under strongly acidic conditions. However, the combination of solvents, strong acid and long reaction time makes this method environmentally hazardous. Thus, a simple, general and efficient procedure for the synthesis of this important heterocyclic system is still required.

Under the framework of "Green Chemistry" we have developed an environmentally benign synthesis of benzothiazepines **7a-j**. Further attractions of this method are that it allows reactions in round bottom flask (thus avoiding the risk of high pressure development) and synthesis on preparative scales[13]. Herein we wish to report a facile microwave synthesis of 1, 5-benzothiazepines **7a-j** from 2-aminothiophenol **6** and various chalcones **5a-j** under MWI using basic alumina as a solid support (**Scheme I**). The yields of the product formed under MWI were higher in comparison to classical thermal method (**Table I**) and time required for completion of these reactions were also less in comparison to classical thermal method. The purity of the compounds was monitored by TLC and the structures of the products were confirmed by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data (**Tables II** and **III**).

Results and Discussion

1-(*o*-Chlorophenyl)-3-methylpyrazoline-5-(*p*-acetylaniline) **3** and substituted aldehyde **4a-j** in ethanol and acidic alumina as solid support afforded chalcones **5a-j**. Formation of chalcones **5a-j** was evidenced by appearance of signal at δ 7.2 due to

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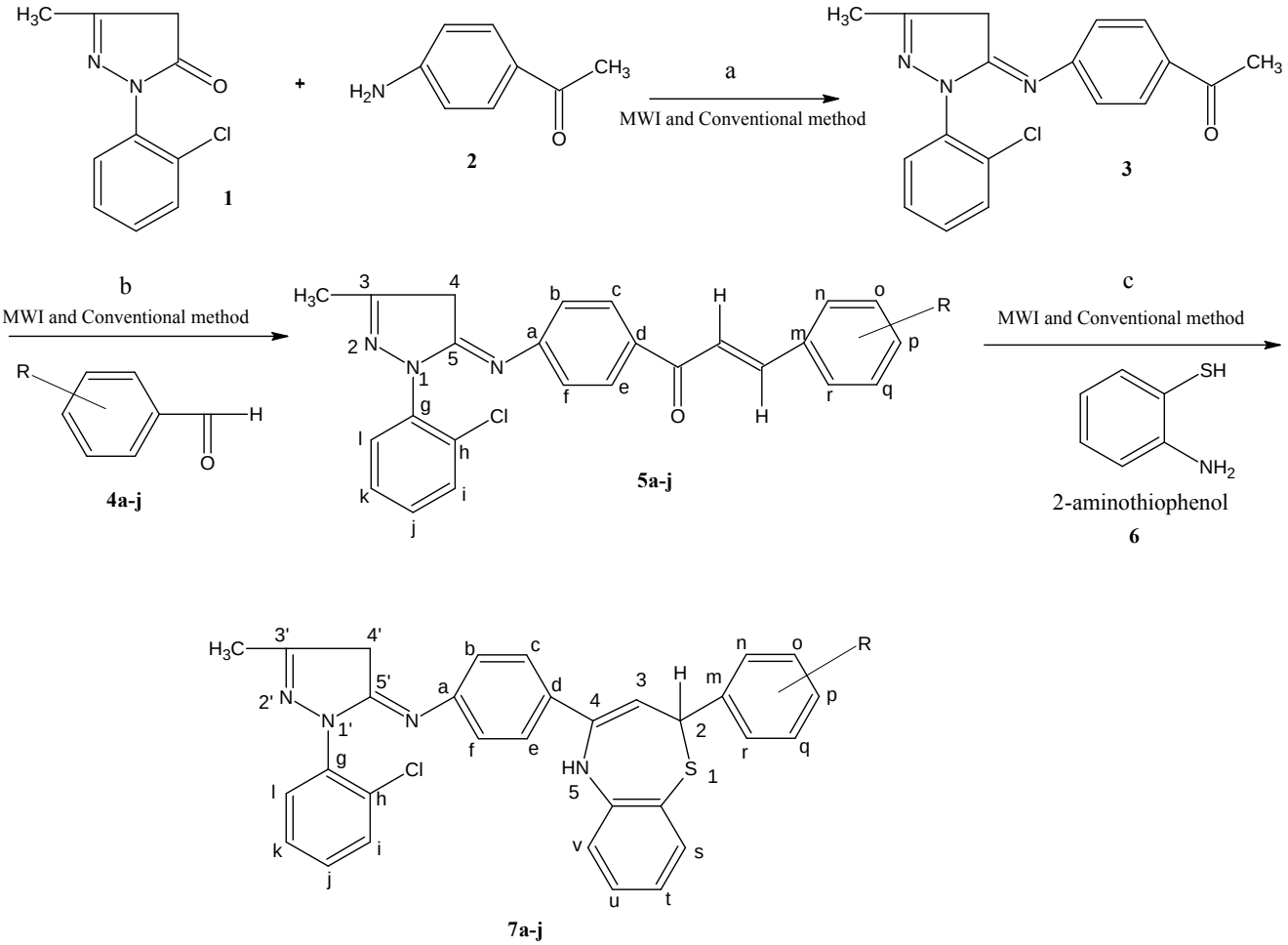
[†] Part of Ph.D. Thesis

[§]This paper is dedicated to Prof. K R Desai in recognition of his outstanding contributions to "*Green Chemistry*"



4, 5, 7	R	4, 5, 7	R
a	H	**f**	4-$N(CH_3)_2$
b	2-OH	**g**	4-OCH_3; 3-OH
c	3-NO_2	**h**	3,4,5-$(OCH_3)_3$
d	2-Cl	**i**	3-OC_6H_5
e	4-Cl	**j**	4-OCH_3

Scheme I — Reagents and reaction conditions: (a) 2-3 drops piperidine as a catalyst, silica gel as solid support; (b) 2-3 drops piperidine as a catalyst, acidic alumina; (c) 5 mL of gl. AcOH, basic alumina.

-CH=CH- of chalcones **5a-j** in ^{1}H NMR spectra and IR spectra bands due to 1682 cm^{-1} (chalcone). In ^{13}C NMR spectra, the signal at δ 217 was observed due to O=C< in chalcones **5a-j**. Treatment of **5a-j** with 2-aminothiophenol **6** in the presence of gl. AcOH and basic alumina in tetrahydrofuran afforded 2,5-dihydro-4-[1′-(*o*-chlorophenyl)-3′-methyl-5′-pyrazolidene azomethine]-2-(substituted phenyl)-1,5-benzothiazepines **7a-j**. In ^{1}H NMR spectra of 1,5-benzothiazepines **7a-j**, the signal at δ 3.76 was observed due to –NH-, 6.0 due to C_2–H and at 7.35 due to C_3-H and in IR spectra of 1,5-benzothiazepines **7a-j**, the bands at 3070 (-N-H-) and 614 cm^{-1} (-C-S-) also confirmed the formation of 1, 5 benzothiazepines **7a-j**. In ^{13}C NMR spectra of 1, 5 benzothiazepines **7a-j**, the signal at δ 65 was observed due to >CH-S- and 70 (≥C-S-benzothiazepine ring). In mass spectra of chalcones **5a**, the molecular ion peak 413 (41.82) [M^+] also confirmed the formation of chalcone and in 1, 5 benzothiazepines **7a**, the molecular ion peak 520 (100) [M^+] also confirmed the formation of benzothiazepine ring.

All the reactions under MWI were completed within 4-10 min, whereas similar reactions under

Table I — Comparative study in terms of yield and reaction period (Conventional and MWI method), physical data and elemental analysis of compounds **5a-j** and **7a-j**

Compds	Substituted groups -R	m. p. (°C)	Conventional method		[g] Microwave method (MWI)		Mol. formula	Found (%)(Calcd)		
			Time (hr)	[d]Yield (%)	Time (min)	[k]Yield (%)				
5a	H	200	5.0	78	4.5	82	$C_{25}H_{20}ON_3Cl$	72.55 (72.53	4.83 4.80	10.15 10.16)
5b	2-OH	172	5.5	74	4.0	84	$C_{25}H_{21}O_2N_3Cl$	69.76 (69.80	4.88 4.85	9.76 9.73)
5c	3-NO_2	175	5.0	76	4.5	80	$C_{25}H_{19}O_3N_4Cl$	65.35 (65.30	4.13 4.15	12.20 12.25)
5d	2-Cl	167	5.0	75	4.0	86	$C_{25}H_{19}O_2N_3Cl_2$	66.81 (66.83	4.23 4.20	9.35 9.38)
5e	4-Cl	190	6.0	72	5.0	83	$C_{25}H_{19}O_2N_3Cl_2$	66.83 (66.80	4.25 4.21	9.40 9.38)
5f	4-$N(CH_3)_2$	180	5.0	68	4.5	80	$C_{27}H_{25}ON_4Cl$	70.89 (70.92	5.47 5.50	12.25 12.23)
5g	4-OCH_3; 3-OH	163	5.0	71	4.5	85	$C_{26}H_{22}O_3N_3Cl$	67.82 (67.89	4.78 4.80	9.13 9.15)
5h	3,4,5-$(OCH_3)_3$	203	6.0	75	5.0	82	$C_{28}H_{26}O_4N_3Cl$	66.55 (66.53	5.14 5.15	8.31 8.27)
5i	3-OC_6H_5	156	6.0	81	4.5	81	$C_{28}H_{26}O_4N_3Cl$	73.51 (73.54	4.73 4.78	8.30 8.27)
5j	4-OCH_3	197	6.0	80	4.5	88	$C_{28}H_{22}O_2N_3Cl$	75.67 (75.70	4.95 4.99	9.45 10.47)
7a	H	205	8.5	66	9.5	76	$C_{31}H_{25}N_4SCl$	71.46 (71.48	4.80 4.85	10.75 10.70)
7b	2-OH	147	9.0	68	9.5	78	$C_{31}H_{26}ON_4SCl$	69.27 (69.30	4.84 4.85	10.42 10.47)
7c	3-NO_2	154	10.0	65	9.0	78	$C_{31}H_{24}O_2N_5SCl$	65.72 (65.74	4.24 4.27	12.36 12.40)
7d	2-Cl	194	9.5	63	9.5	81	$C_{31}H_{24}ON_4SCl_2$	66.90 (66.93	4.31 4.33	10.05 10.07)
7e	4-Cl	165	9.5	65	9.5	89	$C_{31}H_{24}ON_4SCl_2$	66.95 (66.98	4.28 4.29	10.08 10.06)
7f	4-$N(CH_3)_2$	207	9.0	68	10.0	84	$C_{33}H_{30}N_5SCl$	70.21 (70.25	5.31 5.33	12.41 12.44)
7g	4-OCH_3; 3-OH	135	9.0	62	9.5	78	$C_{32}H_{27}O_2N_4SCl$	67.72 (67.75	4.76 4.80	9.87 9.85)
7h	3,4,5-$(OCH_3)_3$	214	10.0	60	10.0	77	$C_{34}H_{31}O_3N_5SCl$	66.55 (66.58	5.05 5.08	11.41 11.35)
7i	3-OC_6H_5	136	10.0	65	9.5	85	$C_{37}H_{29}ON_4SCl$	73.87 (73.90	4.82 4.85	9.31 9.33)
7j	4-OCH_3	214	10.0	68	10.0	80	$C_{34}H_{27}ON_4SCl$	74.04 (74.00	4.90 4.88	10.16 10.20)

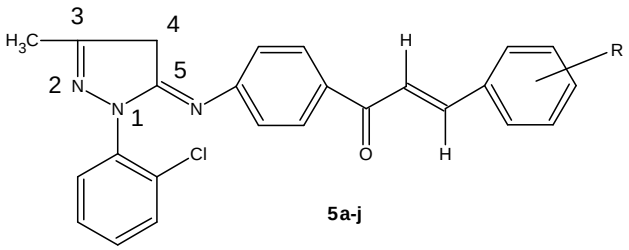
[k]Yield of isolated products from microwave method; [d]Yield of isolated products from conventional method.

[g] Microwave irradiations were carried out in a QPro-M Microwave Synthesis System manufactured by Questron Technologies Corporation, Mississauga, Ontario L4Z 2E9, Canada has been used, In this unit, microwaves are generated by magnetron at a frequency of 2450 MHz having an output energy range of 100 to 500 W and individual sensor for temperature control (fibre optic is used as a individual sensor for temperature control). There is an attachment of reflux condenser with constant stirring, avoiding the risk of high pressure development and permitting synthesis on preparative scales.

Table II — IR, ^{1}H NMR, ^{13}C NMR and mass data of compounds **5a-j**

Compd	IR (KBr) υ_{max} in cm^{-1}	^{1}H NMR ($CDCl_3$ - DMSO-d_6) δ in ppm	^{13}C NMR ($CDCl_3$ – DMSO-d_6) δ in ppm	MS (EI) [K] *m/z* (%)
5b	1615 (>C=N str.), 1685 (chalcone), 2931, 1311 (Ar-CH_3), 738 (C-Cl), 3571 (Ar-OH).	2.5 (s, 3H, -CH_3), 3.58 (s, 1H, Ar-OH), 5.83 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 7.8 (s, 2H, α, β unsaturated ketone), 6.85-7.97 (m, 12H, Ar-H).	28 (C-3), 38 (-CH_3), 45 (CH_2 of pyrazoline ring), 68 (C-5), 115-142 (aromatic), 211 (O=C<, chalcone).	429 (100) [M^+].
5c	1618 (>C=N str.), 1671 (chalcone), 2940, 1301 (Ar-CH_3), 740 (C-Cl), 1340 (Ar-NO_2).	2.7 (s, 3H, -CH_3), 5.78 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 7.4 (s, 2H, α, β unsaturated ketone), 6.98-7.77 (m, 12H, Ar-H).	25 (C-3), 36 (-CH_3), 48 (CH_2 of pyrazoline ring), 74 (C-5), 118-133 (aromatic), 214 (O=C<, chalcone).	458 (61.52) [M^+], 459 (89.35) [$M+H^+$].
5d	1620 (>C=N str.), 1667 (chalcone), 2933, 1308 (Ar-CH_3), 734 (C-Cl).	2.5 (s, 3H, -CH_3), 5.71 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 6.9 (s, 2H, α, β unsaturated ketone), 7.77-7.97 (m, 12H, Ar-H).	22 (C-3), 39 (-CH_3), 51 (CH_2 of pyrazoline ring), 77 (C-5), 121-130 (aromatic), 217 (O=C<, chalcone).	448 (49.42) [M^+], 449 (95.35) [$M+H^+$].
5e	1616 (>C=N str.), 1657 (chalcone), 2943, 1300 (Ar-CH_3), 724 (C-Cl).	2.1 (s, 3H, -CH_3), 5.69 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 7.3 (s, 2H, α, β unsaturated ketone), 7.87-7.97 (m, 12H, Ar-H).	20 (C-3), 39 (-CH_3), 49 (CH_2 of pyrazoline ring), 75 (C-5), 119-132 (aromatic), 215 (O=C<, chalcone).	448 (52.42) [M^+], 449 (100) [$M+H^+$].
5f	1605 (>C=N str.), 1682 (chalcone), 2937, 1309 (Ar-CH_3), 731 (C-Cl), 1315 (Ar-$N(CH_3)_2$).	2.2 (s, 3H, -CH_3), 2.8 (m, 6H, Ar-$N(CH_3)_2$), 5.80 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 7.2 (s, 2H, α, β unsaturated ketone), 7.25-7.95 (m, 12H, Ar-H).	22 (C-3), 35 (-CH_3), 41 (-$N(CH_3)_2$), 42 (CH_2 of pyrazoline ring), 70 (C-5), 112-138 (aromatic), 210 (O=C<, chalcone).	456 (35.38) [M^+], 457 (96.88) [$M+H^+$].
5g	1605 (>C=N str.), 1682 (chalcone), 2937, 1309 (Ar-CH_3), 731 (C-Cl), 2831 (Ar-OCH_3), 3572 (Ar-OH).	2.2 (s, 3H, -CH_3), 3.49 (s, 1H, Ar-OH), 3.89 (s, 3H, Ar-OCH_3), 5.80 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 7.2 (s, 2H, α, β unsaturated ketone), 7.25-7.95 (m, 11H, Ar-H).	22 (C-3), 35 (-CH_3), 35.4 (-OCH_3), 42 (CH_2 of pyrazoline ring), 70 (C-5), 112-138 (aromatic), 210 (O=C<, chalcone).	459 (55.79) [M^+], 460 (100) [$M+H^+$].
5h	1605 (>C=N str.), 1682 (chalcone), 2937, 1309 (Ar-CH_3), 731 (C-Cl), 2840 (Ar-OCH_3).	2.2 (s, 3H, -CH_3), 3.95 (s, 9H, 3×Ar-OCH_3), 5.80 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 7.2 (s, 2H, α, β unsaturated ketone), 7.25-7.95 (m, 10H, Ar-H).	22 (C-3), 35 (-CH_3), 35.7 (3×-OCH_3), 42 (CH_2 of pyrazoline ring), 70 (C-5), 112-138 (aromatic), 210 (O=C<, chalcone).	505 (89.99) [M^+].
5i	1605 (>C=N str.), 1682 (chalcone), 2937, 1309 (Ar-CH_3), 731 (C-Cl).	2.2 (s, 3H, -CH_3), 5.80 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 7.2 (s, 2H, α, β unsaturated ketone), 7.25-7.95 (m, 17H, Ar-H).	22 (C-3), 35 (-CH_3), 42 (CH_2 of pyrazoline ring), 70 (C-5), 112-138 (aromatic), 210 (O=C<, chalcone).	506 (100) [M^+].
5j	1605 (>C=N str.), 1682 (chalcone), 2937, 1309 (Ar-CH_3), 731 (C-Cl), 2847 (Ar-OCH_3).	2.2 (s, 3H, -CH_3), 3.88 (s, 3H, Ar-OCH_3), 5.80 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 7.2 (s, 2H, α, β unsaturated ketone), 7.25-7.95 (m, 12H, Ar-H).	22 (C-3), 35 (-CH_3), 36.1 (-OCH_3), 42 (CH_2 of pyrazoline ring), 70 (C-5), 112-138 (aromatic), 210 (O=C<, chalcone).	443 (66.81) [M^+], 444 (100) [$M+H^+$].

[K] Source temperature - 250º C; Sample temperature - 190º C; Reservoir – 75 ev.

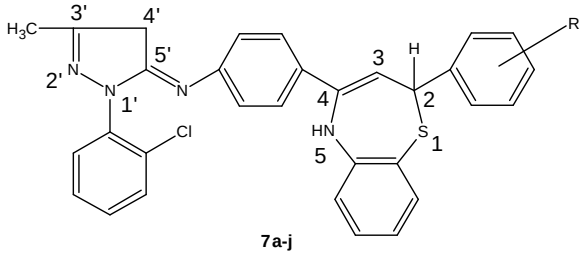


5a-j

Table III — IR, ^{1}H NMR, ^{13}C NMR and mass data of compounds **7a-j**

Compd	IR (KBr) υ_{max} in cm^{-1}	^{1}H NMR ($CDCl_3$ – DMSO-d_6) δ in ppm	^{13}C NMR ($CDCl_3$ – DMSO-d_6) δ in ppm	MS (EI) [K] *m/z* (%)
7b	1615 (>C=N str.), 2931, 1311 (Ar-CH_3), 738 (C-Cl), 3571 (Ar-OH), 3094 (N-H), 615 (C-S).	2.5 (s, 3H, -CH_3), 3.58 (s, 1H, Ar-OH), 3.78 (s, 1H, NH), 5.83 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring) 6.30 (d, 1H, *J* = 7.2 MHz, C_2-H), 7.34 (d, 1H, *J* = 7.2 MHz, C_3-H), 6.85-7.97 (m, 16H, Ar-H).	25 (C-3'), 35 (-CH_3), 44 (CH_2 of pyrazoline ring), 65 (C-2), 70 (C-5'), 70 (C-7), 114-138 (aromatic).	536 (42.61) [M^+], 537 (98.35) [M+H^+].
7c	1618 (>C=N str.), 2940, 1301 (Ar-CH_3), 740 (C-Cl), 1340 (Ar-NO_2), 3060 (N-H), 618 (C-S).	2.7 (s, 3H, -CH_3), 3.78 (s, 1H, NH), 5.78 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 6.30 (d, 1H, *J* = 7.2 MHz, C_2-H), 7.34 (d, 1H, *J* = 7.2 MHz, C_3-H), 6.98-7.77 (m, 16H, Ar-H).	30 (C-3'), 33 (-CH_3), 47 (CH_2 of pyrazoline ring), 66 (C-2), 69 (C-7), 73 (C-5'), 116-136 (aromatic).	565 (62.61) [M^+], 566 (100) [M+H^+].
7d	1620 (>C=N str.), 2933, 1308 (Ar-CH_3), 734 (C-Cl), 3065 (N-H), 618 (C-S).	2.5 (s, 3H, -CH_3), 3.75 (s, 1H, NH), 5.71 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 5.98 (d, 1H, *J* = 7.2 MHz, C_2-H), 7.24 (d, 1H, *J* = 7.2 MHz, C_3-H), 7.77-7.97 (m, 16H, Ar-H).	31 (-CH_3), 32 (C-3'), 46 (CH_2 of pyrazoline ring), 68 (C-2), 71 (C-5'), 73 (C-7), 113-133 (aromatic).	555 (59.52) [M^+], 556 (98.25) [M+H^+].
7e	1616 (>C=N str.), 2943, 1300 (Ar-CH_3), 724 (C-Cl), 3075 (N-H), 612 (C-S).	2.1 (s, 3H, -CH_3), 3.73 (s, 1H, NH), 5.69 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 6.04 (d, 1H, *J* = 7.2 MHz, C_2-H), 7.28 (d, 1H, *J* = 7.2 MHz, C_3-H), 7.87-7.97 (m, 16H, Ar-H).	34 (-CH_3), 36 (C-3'), 43 (CH_2 of pyrazoline ring), 64 (C-2), 75 (C-7), 76 (C-5'), 117-137 (aromatic).	555 (52.42) [M^+], 556 (100) [M+H^+].
7f	1618 (>C=N str.), 2939, 1311 (Ar-CH_3), 728 (C-Cl), 3071 (N-H), 615 (C-S), 1313 (Ar-N[CH_3]$_2$).	2.5 (s, 3H, -CH_3), 2.9 (m, 6H, -N(CH_3)$_2$), 3.71 (s, 1H, NH), 5.70 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 6.06 (d, 1H, *J* = 7.2 MHz, C_2-H), 7.30 (d, 1H, *J* = 7.2 MHz, C_3-H), 6.87-7.97 (m, 17H, Ar-H).	32 (-CH_3), 38 (C-3'), 41 (CH_2 of pyrazoline ring), 43 (-N(CH_3)$_2$), 68 (C-2), 76 (C-5'), 77 (C-7), 119-139 (aromatic).	563 (48.34) [M^+], 564 (100) [M+H^+].
7g	1615 (>C=N str.), 2931, 1318 (Ar-CH_3), 738 (C-Cl), 3571 (Ar-OH), 3094 (N-H), 615 (C-S), 2835 (Ar-OCH_3).	2.5 (s, 3H, -CH_3), 3.58 (s, 1H, Ar-OH), 3.78 (s, 1H, NH), 3.85 (s, 3H, -OCH_3), 5.83 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 6.30 (d, 1H, *J* = 7.2 MHz, C_2-H), 7.34 (d, 1H, *J* = 7.2 MHz, C_3-H), 6.85-7.97 (m, 15H, Ar-H).	25 (C-3'), 35 (-CH_3), 35.4 (-OCH_3), 44 (CH_2 of pyrazoline ring), 65 (C-2), 70 (C-5'), 70 (C-7), 114-138 (aromatic).	566 (42.61) [M^+], 567 (98.35) [M+H^+].
7h	1605 (>C=N str.), 2937, 1309 (Ar-CH_3), 731 (C-Cl), 3070 (N-H), 614 (C-S), 2832 (Ar-OCH_3).	2.2 (s, 3H, -CH_3), 3.76 (s, 1H, NH), 3.95 (s, 9H, 3×-OCH_3), 5.80 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 6.0 (d, 1H, *J* = 7.2 MHz, C_2-H), 7.35 (d, 1H, *J* = 7.2 MHz, C_3-H), 7.25-7.95 (m, 14H, Ar-H).	20 (C-3'), 35.1 (3×-OCH_3), 40 (-CH_3), 49 (CH_2 of pyrazoline ring), 60 (C-2), 72 (C-7), 75 (C-5'), 119-132 (aromatic).	613 (100) [M^+].
7i	1611 (>C=N str.), 2923, 1318 (Ar-CH_3), 738 (C-Cl), 3054 (N-H), 625 (C-S).	2.8 (s, 3H, -CH_3), 3.67 (s, 1H, NH), 5.74 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 6.8 (d, 1H, *J* = 7.2 MHz, C_2-H), 7.44 (d, 1H, *J* = 7.2 MHz, C_3-H), 7.25-8.91 (m, 21H, Ar-H).	24 (C-3'), 45 (-CH_3), 53 (CH_2 of pyrazoline ring), 62 (C-2), 74 (C-7), 76 (C-5'), 116-136 (aromatic).	601 (100) [M^+].
7j	1608 (>C=N str.), 2931, 1310 (Ar-CH_3), 727 (C-Cl), 3068 (N-H), 618 (C-S), 2838 (Ar-OCH_3).	2.5 (s, 3H, -CH_3), 3.79 (s, 1H, NH), 3.89 (s, 3H, -OCH_3), 5.78 (d, 2H, *J* = 4.5, CH_2 of pyrazoline ring), 6.3 (d, 1H, *J* = 7.2 MHz, C_2-H), 7.31 (d, 1H, *J* = 7.2 MHz, C_3-H), 6.25-7.91 (m, 16H, Ar-H).	22 (C-3'), 35.4 (-OCH_3), 41 (-CH_3), 51 (CH_2 of pyrazoline ring), 63 (C-2), 71 (C-7), 72 (C-5'), 120-138 (aromatic).	551 (100) [M^+].

[K] Source temperature - 250º C; Sample temperature - 190º C; Reservoir – 75 ev.



7a-j

conventional heating (steam-bath) at similar temperature (80-100°C) gave poor yields with comparatively longer reaction time periods (**Table II**), demonstrating that the effect of microwave irradiation is not purely thermal. Microwave irradiation facilitates the polarization of the molecules under irradiation causing rapid reaction to occur. This is consistent with the reaction mechanism, which involves a polar transition state[14].

Antimicrobial activity

The compounds **7a-j** were screened for their antibacterial activity against *Escherichia coli (Gram -ve)* (ATCC-8739) and *Staphylococcus aureus (Gram +ve)* (ATCC-6538) and antifungal activity against *Candida albicans* (ATCC-64550) and *Candida krusei* (ATCC-14243) by filter paper disc technique[15]. Standard antibacterial streptomycin and antifungal griseofulvin were also tested under similar conditions for comparison. Results are presented in **Table IV**.

It is evident from the screening data (**Table I**) that compounds **5c**, **5e**, **5h**, **5j**, **7b**, **7d**, **7e**, **7g**, **7i** and **7j** exhibited the highest degree of inhibition against all the tested organisms, while compounds **5a**, **5c**, **5e**, **5h**, **5j**, **7b**, **7d**, **7e**, **7h**, **7i** and **7j** showed highest degree of inhibition only against all the bacterial species and compounds **5d**, **5h**, **7d**, **7e**, **7g** and **7j** showed activity against all the fungal species. In case of compound **5h** and **7d** showed significant activity against *Candida albicans* (ATCC-64550) and *Candida krusei* (ATCC-14243) species. In case of compounds **5a**, **5c**, **5e**, **5h**, **5j**, **7b**, **7d**, **7e**, **7f** and **7i** showed significant activity against *Escherichia coli (Gram –ve)* (ATCC-8739) species. Compounds **5h** and **7d** showed lowest degree of inhibition against *Candida albicans* (ATCC-64550) and *Candida krusei* (ATCC-14243) respectively.

Table IV — Antimicrobial activity data of the compounds **5a-j** and **7a-j**

Compds	Antibacterial activity in (μg/mL)		Antifungal activity in (μg/mL)	
	E. c (Gram –ve) [a] (ATCC-8739)	*S. a (Gram +ve) [b] (ATCC-6538)*	*C. a [c] (ATCC-64550)*	*C. k [d] (ATCC-14243)*
5a	+ + +	+ + +	–	–
5b	–	+	+	+
5c	+ + +	+ + +	+ +	+
5d	+	–	+ + +	+ +
5e	+ + +	+ + +	+ + +	–
5f	+ + +	+ +	–	+
5g	–	+	–	–
5h	+ + +	+ + +	+ + +	+ + +
5i	+ +	+ +	+	–
5j	+ + +	+ + +	+ +	+ +
7a	–	–	+ + +	–
7b	+ + +	+ +	+ +	+ +
7c	+ +	+ +	–	+ + +
7d	+ + +	+ +	+ + +	+ + +
7e	+ + +	+ +	+ + +	+ +
7f	+ + +	–	+ +	+
7g	+ +	+ +	+ + +	+ +
7h	+ +	+ + +	–	+ + +
7i	+ + +	+ +	+ +	+ +
7j	+ +	+ + +	+ + +	+ +
Zone of inhibition of standard drugs (μg/mL)				
Streptomycin	+ + + +	+ + + +	-	-
Griscofulvin	-	-	+ + + +	+ + + +

Zone of inhibition: (-) 6 mm; (+) 6-15 mm; (+ +) 15-20 mm; (+ + +) 20-25 mm; (+ + + +) 25-30 mm.

[a] *E. c - Escherchia coli*; [b] *S. a - Staphylococcus aureus*; [c] *C. a - Candida albicans*; [d] *C. k - Candida krusei*.

However, the activities of tested compounds are less than that of standard agent used.

Experimental Section

All the melting points were determined in PMP-DM scientific melting point apparatus and are uncorrected. The purity of compounds was checked routinely by TLC (0.5 mm thickness) using silica gel-G coated Al-plates (Merck) and spots were visualized by exposing the dry plates in iodine vapours. IR spectra (cm^{-1}) were recorded on a Shimadzu FT-IR 8300 spectrophotometer using KBr or Nujol technique; ^1H NMR spectra were recorded on a Bruker WM 400FT MHz NMR instrument using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal reference (chemical shifts in δ); ^{13}C NMR were recorded on a Varian AMX 400 (100 MHz) spectrometer as solutions in $CDCl_3$ and mass spectra were recorded on a Jeol JMS D-300 spectrometer operating at 75 eV. The elemental analysis (C, H, N) of compounds was performed on a Carlo Erba-1108 elemental analyzer. Microwave irradiations were carried out in a QPro-M Microwave Synthesis System manufactured by Questron Technologies Corporation, Ontario L4Z 2E9, Canada has been used, wherein microwaves are generated by magnetron at a frequency of 2450 MHz having an output energy range of 100 to 500 W and individual sensor for temperature control.

General procedure. 1-(*o*-Chlorophenyl)-3-methyl pyrazoline-5-(*p*-acetyl aniline) 3. **Microwave method**. 1-(*o*-Chlorophenyl)-3-methyl pyrazoline-5-one **1** (2.08 g, 0.01 mole) and *p*-amino acetophenone **2** (1.35 g, 0.01 mole) were dissolved in ethanol (15 mL) and silica gel (5 g) was added and 2-3 drops piperidine used as a catalyst. Reaction mixture was stirred well and dried in air and subjected to microwave irradiation (500 W, 90-95°C, ref.16) for 7-10 min. After the completion of reaction, the product was extracted with ethanol. The solvent was removed under reduced pressure to yield the product which was recrystalized from ethanol. Yield 2.73 g (83.8 %).

Conventional method. 1-(*o*-Chlorophenyl)-3-methyl pyrazoline-5-one **1** (2.08 g, 0.01 mole) and *p*-amino acetophenone **2** (1.35 g, 0.01 mole) in equimolar ratio were dissolved in absolute ethanol (15 mL) and few drops of piperidine as a catalyst added, and the mixture was refluxed for 10 hr. The reaction mixture was then evaporated under vaccum, and the resulting precipitate was filtered off, washed with alcohol and recrystalized from absolute alcohol. Yield 2.11 g (65%). Spectral data of compound **3**: m.p. 145ºC. IR (KBr): 1605 (>C=N str.), 2937, 1309 (Ar-CH_3), 731 (C-Cl) cm^{-1}; ^1H NMR ($CDCl_3$-DMSO-d_6): δ 2.1 (s, 3H, -CH_3), 2.13 (s, 3H, -$COCH_3$), 5.83 (d, 2H, *J*= 4.5 MHz, CH_2 of pyrazoline ring), 7.00-7.85 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ 21 (C-3), 35 (-CH_3), 41 (CH_2 of pyrazoline ring), 75 (C-5), 126.43 (C-k), 126.88 (C-b, C-f), 128.16 (C-c, C-e), 128.63 (C-g, C-i), 129.72 (C-j, C-l), 130.91 (C-d), 133.30 (C-a), 134.33 (C-h), 165.88 (>C=O).

Anal. Calcd. for $C_{18}H_{16}ON_3Cl$: C, 66.33; H, 4.91; N, 12.92. Found: C, 66.35; H, 4.87; N, 12.95%.

1-(*o*-Chlorophenyl)-3-methyl pyrazolidene azo-methine-5-chalcone 5a. **Microwave method**. A mixture of compound **3** (3.25 g, 0.01 mole) and benzaldehyde **4a** (1.06 g, 0.01 mole) were dissolved in ethanol (15 mL) and acidic alumina (7 g) was added and 2-3 drops of piperidine was used as a catalyst. Reaction mixture was stirred well and dried in air and subjected to microwave irradiation (450 W, 100-105°C, ref.16) for 4.5 min. After the completion of reaction, the product was extracted with ethanol. The solvent was removed under reduced pressure to yield the product which was recrystalized from ethanol. Yield 3.38 g (82 %).

Conventional method. A mixture of compound **3** (3.25 g, 0.01 mole) and benzaldehyde **4a** (1.06 g, 0.01 mole) in equimolar ratio were dissolved in absolute ethanol (15 mL) and few drops of piperidine used as a catalyst was added, and refluxed for 5 hr. The reaction mixture was then evaporated under vaccum, and the resulting precipitate filtered off, washed with alcohol and recrystalized from absolute alcohol. Yield 3.21 g (78 %). Spectral data of compound **5a**: m.p. 200ºC. IR (KBr): 1605 (>C=N str.), 1682 (chalcone), 2937, 1309 (Ar-CH_3), 731 (C-Cl) cm^{-1}; ^1H NMR ($CDCl_3$-DMSO-d_6): δ 2.2 (s, 3H, -CH_3), 5.80 (d, 2H, *J*= 4.5, CH_2 of pyrazoline ring), 7.2 (s, 2H, α, β unsaturated ketone), 7.25-7.95 (m, 13H, Ar-H); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ 22 (C-3), 35 (-CH_3), 42 (CH_2 of pyrazoline ring), 70 (C-5'), 125.38 (C-p), 126.25 (C-k), 127.0 (C-b, C-f), 128.0 (C-g, C-i), 128.28 (C-o, C-q), 128.95 (C-c, C-e), 129.09 (C-n, C-r), 129.55 (C-d), 130.0 (C-j, C-l), 132.85 (C-a), 135.20 (C-h), 137.83 (C-m), 210 (O=C<, chalcone); MS (EI): *m/z* (%) = 413 (41.82) [M^+], 414 (100) [$M+H^+$].

Anal. Calcd. for $C_{25}H_{20}ON_3Cl$: C, 72.55; H, 4.83; N, 10.15. Found: C, 72.53; H, 4.80; N, 10.16%.

Likewise other compounds **5b-j** were prepared by treating compound **3** with various aromatic aldehydes **4b-j**.

2, 5-Di hydro-4-[1′-(*o*-chlorophenyl) - 3′-methyl-5′-pyrazolidene azomethine]-2-(phenyl)-1,5 benzothiazepines 7a. **Microwave method**. A mixture of compound **5a** (4.13 g, 0.01 mole), 2-aminothiophenol (1.25 g, 0.01 mole) and gl. acetic acid (5 mL) in tetrahydrofuran (15 mL) and basic alumina (7 g) was added. Reaction mixture was stirred well and dried in air and subjected to microwave irradiation (450W, 100-105°C, ref.16) for 9.5 min. After the completion of reaction, the product was extracted with tetrahydrofuran. The solvent was removed under reduced pressure to yield the product which was recrystalized from ethanol-acetone mixture. Yield 3.95 g (76 %).

Conventional method. A mixture of compound **5a** (4.13 g, 0.01 mole), 2-aminothiophenol (1.25 g, 0.01 mole) and gl. acetic acid (5 mL) in tetrahydrofuran (15 mL) was refluxed for 8.5 hr. After the completion of reaction, the solvent was removed under reduced pressure to yield the product which was recrystalized from ethanol-acetone mixture. Yield 3.43 g (66 %). Spectral data of compound **7a**: m.p. 205ºC. IR (KBr): 1605 (>C=N str.), 2937,1309 (Ar-CH_3), 731 (C-Cl), 3070 (N-H), 614 (C-S) cm^{-1}; ^1H NMR ($CDCl_3$-DMSO-d_6): δ 2.2 (s, 3H, -CH_3), 3.76 (s, 1H, NH), 5.80 (d, 2H, J = 4.5, CH_2 of pyrazoline ring), 6.0 (d, 1H, J = 7.2 MHz, C_2-H), 7.35 (d, 1H, J = 7.2 MHz, C_3-H), 7.25-7.95 (m, 17H, Ar-H); ^{13}C NMR ($CDCl_3$-DMSO-d_6): δ 20 (C-3'), 40 (-CH_3), 49 (CH_2 of pyrazoline ring), 60 (C-2), 75 (C-5'), 121.76 (C-s), 123.52 (C-v), 125.22 (C-p), 125.38 (C-t), 125.98 (C-k), 126.04 (C-u), 127.09 (C-b, C-f), 128.18 (C-g, C-i), 128.52 (C-o, C-q), 128.80 (C-c, C-e), 129.0 (C-n, C-r), 129.25 (C-d), 130.11 (C-j, C-l), 132.89 (C-a), 135.29 (C-h), 137.75 (C-m); MS (EI): *m/z* (%) = 520 (100) [M^+]. Anal. Calcd. for $C_{31}H_{25}N_4SCl$: C, 71.46; H, 4.80; N, 10.75. Found: C, 71.48; H, 4.85; N, 10.70%.

Likewise other compounds **7b-j** were prepared by treating compound **6** with various compounds **5b-j**.

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