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ORIGINAL ARTICLE

1st Heterocyclic Update

Microwave-induced and conventional heterocyclic synthesis: An antimicrobial entites of newer quinazolinyl-Δ^2-pyrazolines☆

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Abstract Heterocyclic compounds containing pyrazolines were reported to possess significant biological activity. Synthesis of 2-(ω-chloroacetonyl)-3-*p*-fluorophenyl-6-bromoquinazoline-4(3*H*)-ones (**2**), 2-(ω-hydrazinoacetonyl)-3-*p*-fluorophenyl-6-bromoquinazoline-4(3*H*)-ones (**3**) and 1′-[3*H*-3-*p*-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(substituted phenyl)-Δ^2-pyrazolines (**4a–j**) have been described. Some of the new compounds were tested against bacteria (Gram –ve and Gram + ve) and fungi.

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1. Introduction

The increasing environmental consciousness throughout the world has put a pressing need to develop an alternate synthesis approach for biologically and synthetically important compounds. The present day industrialization has led to immense environment deterioration. One of the advances in the field of green chemistry (Xie et al., 1999; Desai and Desai, 2006a,b; Desai et al., 2006a,b) where substantial progress has been made is microwave-assisted synthesis (Verma, 1999; Desai and Desai, 2006b,c, 2007).

The chemistry and pharmacology of quinazolinone have been of great interest to medicinal chemistry because quinazolinone derivatives possessed various biological activities, such as antibacterial (Ghorab and Abdel-Hamide, 1995; Reddy et al., 1999), CVS (Kumar et al., 1998) and anticonvulsant (Wolf et al., 1990). Several pyrazolines are of great importance as antimicrobial agents (Kumar and Sinha, 1990; Srivastava and Srivastava, 1999).

Compounds bearing the quinazolinone moiety are endowed with various types of biological activities (Amine, 1998; Holla et al., 1998; Kumar et al., 1985) especially anti-inflammatory activity (Sarvanan et al., 1998; Khilil et al., 1994; Bhalla et al., 1993). It is also reported that substitution of halo group at 6-position in this nucleus enhances its anti-inflammatory action. A large number of pyrazolines are reported to possess potent antifungal and antibacterial activity (Kym et al., 1990; Udupi et al., 1998a,b). This prompted us to synthesize a newer series of quinazolinone derivatives by incorporating the pyrazoline moiety at 2nd position of the quinazolinone nucleus. We report herein the synthesis of 2-(ω-chloroacetonyl)-3-*p*-fluorophenyl-6-bromoquinazoline-4(3*H*)-ones (**2**), 2-(ω-hydrazino acetonyl)-3-*p*-fluorophenyl-6-bromoquinazoline-4(3*H*)-ones (**3**) and 1′-[3*H*-3-*p*-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(substituted phenyl)-Δ^2-pyrazolines (**4a–j**). This starting compound 2-methyl-3-*p*-fluorophenyl-6-bromoquinazoline-4(3*H*)-ones (**1**) was prepared according to the reported method (Mishra et al., 1997).

2. Results and discussion

Conventional methodology sometimes has lower yields than microwave protocols. Microwave irradiation facilitates the polarization of the molecule under irradiation causing rapid reaction to occur. All the compounds synthesised were adequately characterized by their elemental analysis and spectral features.

2.1. Chemistry

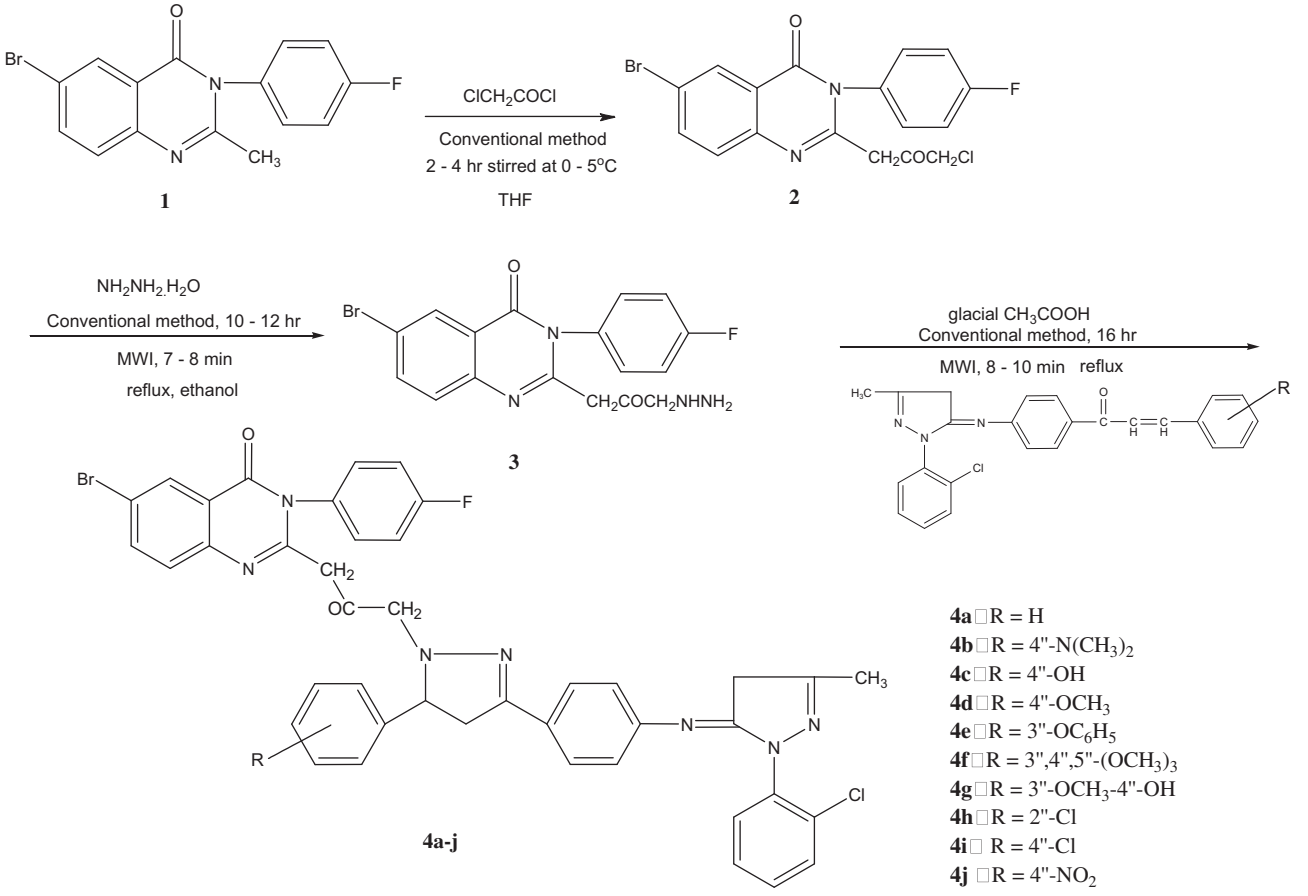
2-(ω-Chloroacetonyl)-3-*p*-fluorophenyl-6-bromoquinazoline-4(3*H*)-one (**2**) was prepared by the reaction of 2-methyl-3-*p*-fluorophenyl-6-bromoquinazoline-4(3*H*)-one (**1**) with $ClCH_2COCl$ in dry tetrahydrofuran by only conventional method. 2-(ω-Hydrazinoacetonyl)-3-*p*-fluorophenyl-6-bromoquinazoline-4(3*H*)-one (**3**) was prepared by the reaction of 2-(ω-chloroacetonyl)-3-*p*-fluorophenyl-6-bromoquinazoline-4(3*H*)-one (**2**) with $NH_2NH_2.H_2O$ in absolute ethanol by both conventional and microwave method. 1′-[3*H*-3-*p*-Fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(phenyl)-Δ^2-pyrazolines (**4a–j**) were prepared by the reaction of 2-(ω-hydrazinoacetonyl)-3-*p*-fluorophenyl-6-bromoquinazoline-4(3*H*)-one (**3**) with 1-(o-chlorophenyl)-3-methylpyrazolideneazomethine-5-chalcones (Desai and Desai, 2007; Khalafalla and Hassan, 1986) in glacial acetic acid by conventional method and in DMF by microwave method respectively. 1-(o-Chlorophenyl)-3-methylpyrazolideneazomethine-5-chalcones was prepared by following the method reported in the literature (Desai and Desai, 2007; Khalafalla and Hassan, 1986).

Compound (**1**) on reaction with chloroacetylchloride yielded 2-(ω-chloroacetonyl)-3-*p*-fluorophenyl-6-bromoquinazoline-4(3*H*)-one (**2**). Among the significant features of ^{1}H NMR data of (**1**), the disappearance of singlet at δ 2.50 (CH_3) and appearance of two singlets at δ 2.30 and δ 2.50 due to the chloroacetyl group confirmed the structure. Furthermore, compound (**2**) on treatment with hydrazine hydrate gave their corresponding 2-ω-hydrazinoacetonyl-3-*p*-fluorophenyl-6-haloquinazoline-4(3*H*)-one (**3**). The appearance of bands at 3380 and 3440 cm^{-1} for NH and NH_2, respectively in the IR spectra, and two broad signals at δ 4.55 and δ 5.56 in ^{1}H NMR spectra clearly showed the presence of hydrazino group in compound (**3**). Further, compound (**3**) on refluxing with different 1-(o-chlorophenyl)-3-methylpyrazolideneazomethine-
5-chalcones in the presence of glacial acetic acid yielded the corresponding 1′-[3*H*-3-*p*-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-

Table 1 Comparative study in terms of yield and reaction period for microwave and conventional techniques (compounds **4a–j**).

Entry	Substituents R	Microwave method				Conventional method	
		Time (min)	Power (W)	Constant temperature (°C)	Yield[a] (%)	Time (h)	Yield[a] (%)
4a	H	10.0	400	116	88	16.0	65
4b	4″-$N(CH_3)_2$	9.0	500	120	82	15.5	55
4c	4″-OH	9.5	450	118	80	16.5	60
4d	4″-OCH_3	9.5	450	118	83	15.0	71
4e	3″-OC_6H_5	9.0	500	120	79	17.0	59
4f	3″,4″,5″-$(OCH_3)_3$	10.0	400	116	86	15.5	49
4g	3″-OCH_3-4″-OH	9.5	450	118	94	16.0	68
4h	2″-Cl	10.0	400	116	90	16.5	73
4i	4″-Cl	10.5	350	114	82	15.0	54
4j	4″-NO_2	10.0	400	118	89	15.5	63

[a] Yield of isolated products.



Scheme 1

2-pyrazolidene]-5′-(substituted phenyl)-Δ^2-pyrazolines (**4a–j**). A comparative study in terms of yield and reaction period is shown in Table 1. The synthetic route of above mentioned compounds is shown in Scheme 1.

2.2. Microwave irradiation technique

All the reactions that used microwave irradiation (MWI) were completed within 9–10 min, whereas similar reactions under conventional heating (oil bath) at similar temperatures (110–120 °C) gave poor yields with comparatively longer reaction time period (Table 1), 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 (Loupy et al., 2001). The effectiveness of microwave irradiation and conventional heating for the synthesis of compound (**4a–j**) has been compared (Table 1). Under microwave irradiation conditions, the yields of (**4a–j**) are high (94–79%). Whereas using conventional heating the yields are only 49–73%.

3. Antimicrobial activity

The compounds (**4a–j**) were screened for their antibacterial activity against *Bacillus substilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538), *Escherichia coli* (ATCC 8739) and *Pseudomonas aeruginosa* (ATCC 1539) and antifungal activity against *Candida albicans* (ATCC 10231) and *Candida krusei* (G03) by filter paper disc technique (Desai and Desai, 2005a,b, 2006d,e). Standard antibacterial and antifungal drugs Ampicillin, Amoxicillin, Penicillin and Flucanozole were also tested under similar conditions for comparison. Results are presented in Table 2. By visualizing the antimicrobial data it could be observed that some of the compounds possess significant activity.

3.1. Conclusion of activity

Zone of inhibition was measured in millimetre. The antifungal activities were compared to the standard drug flucanozole (30–35 mm) with DMF as solvent. Ampicillin (30–35 mm), amoxicillin (23–38 mm) and penicillin (30–38 mm) were used as standard drugs for antibacterial activity. Compounds (**2**), (**4a**), (**4f**), (**4h**) and (**4i**) showed significant antibacterial activity. Compounds (**2**), (**3**), (**4a**), (**4e**), (**4f**) and (**4g**) showed moderate to good antifungal activity (Table 2).

4. Experimental

4.1. General

All the melting points were determined in PMP-DM scientific melting point apparatus and were uncorrected. The purity of compounds was checked routinely by TLC (0.5 mm thickness)

Table 2 Antimicrobial activity data of compounds **4a–j**.

Compound	Antibacterial (mm)				Antifungal (mm)	
	Gram positive (+ve)		Gram negative (−ve)		*C. a* [e]	*C. k* [f]
	S. a [a] ATCC 6538	*B. s* [b] ATCC 6633	*E. c* [c] ATCC 8739	*P. a* [d] ATCC 1539	ATCC 10231	G03
2	–	22	9	25	10	25
3	15	0.9	8	18	18	22
4a	9	11	22	16	–	20
4b	8	0.8	9	1.1	12	0.8
4c	13	–	16	11	17	9
4d	7	10	13	13	–	12
4e	6	17	0.9	1.8	20	–
4f	11	21	–	19	0.9	20
4g	13	1.1	0.9	–	10	17
4h	15	20	12	12	17	8
4i	–	16	–	17	10	0.7
4j	9	10	12	9	7	0.8
Zone of inhibition of standard drugs (mm)						
Ampicillin	30	35	30	30	–	–
Amoxicillin	25	34	38	35	–	–
Penicillin	30	38	32	38	–	–
Flucanozole	–	–	–	–	30	35

[a] *S. a – Staphylococcus aureus.*
[b] *B. s – Bacills substilis.*
[c] *E. c – Escherchia coli.*
[d] *P. a – Pseudomonas aeruginosa.*
[e] *C. a – Candida albicans.*
[f] *C. k – Candida krusei.*

using silica gel-G coated Al plates (Merck) and spots were visualized by exposing the dry plates in iodine vapours. The IR spectra (υ_{max} in cm^{-1}) were recorded on a shimadzu FT-IR 8300 spectrophotometer using KBr or Nujol technique, UV spectra (λ_{max} in nm) were recorded on a shimadzu UV – 160 A (200–400 nm) on using DMF as solvent, ^{1}H NMR spectra 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, ppm); ^{13}C NMR on a Varian AMX 400 (100 MHz) spectrometer as solutions in $CDCl_3$ and Mass spectra on a Jeol JMS D-300 spectrometer. The elemental analysis (C, H, N) of compounds was performed on Carlo Erba-1108 elemental analyzer. The microwave assisted reactions are carried out in a ''QPro-M Microwave Synthesis System'' manufactured by Questron Technologies Corporation, Mississauga, Ontario L4Z 2E9 has been used (Made in Canada). In this unit, microwaves are generated by magnetron at a frequency of 2450 MHz having an output energy range of 100–500 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.

In the present work we used a new kind of QPro-M Microwave Synthesis System apparatus that is well suited for stringent reaction conditions [anhydrous atmosphere, controlled temperature (fibre optic is used as an individual sensor for temperature control) and attachment of reflux condenser with constant stirring]. This high-intensity microwave generator is equipped with magnetron. The frequency can be tuned at 2450 MHz.

4.2. Synthesis

4.2.1. Synthesis of 2-methyl-3-p-fluorophenyl-6-bromoquinazoline-4(3H)-one ***1***

These compounds were synthesized according to the method (Mishra et al., 1997).

4.2.2. Conventional synthesis of 2-(ω-chloroacetonyl)-3-p-fluorophenyl-6-bromoquinazoline-4(3H)-ones ***2***

To the solution of 2-Methyl-3-*p*-fluorophenyl-6-bromoquinazoline-4(3*H*)-one (**1**) (3.33 g, 0.01 mol) in dry THF (20 mL), a solution of $ClCH_2COCl$ (2.26 mL, 0.02 mol) in dry THF (10 mL) was added at 0 °C drop wise with constant stirring for 2 h. The reaction mixtures were further stirred for 2–4 h at room temperature, and then excess of solvents distilled off. The reaction mixtures were cooled and poured onto ice-cold water. The solids that separated in each case were filtered and recrystallised from ethanol as a white solid, mp 166 °C, yield (3.14 g, 77%). IR υ_{max}: 173 (C═O), 1590 (C═N), 3060 (aromatic C–H), 780 (C–Br), 740 (C–Cl), 1111 (C–F), 2570 (CH_2) cm^{-1}; ^{1}H NMR: δ 8.75–8.30 (m, 7H, Ar-H), 2.30 (s, 2H, CH_2CO), 2.50 (s, 2H, $COCH_2Cl$) ppm; MS: *m/z* 415 [M^+]; *Anal*. Calcd. For $C_{17}H_{11}O_2N_2Cl$ Br F: C, 49.81; H, 2.68; N, 6.83. Found: C, 49.83; H, 2.70; N, 6.83%.

4.2.3. Conventional synthesis of 2-(ω-hydrazinoacetonyl)-3-p-fluorophenyl-6-bromo quinazoline-4(3H)-one ***3***

A solution of compound (**2**) and $NH_2NH_2.H_2O$ (99%) in absolute ethanol (15 mL) was refluxed for 10–12 h in a 250 mL round bottom flask. The excess solvent was then

removed by distillation under reduced pressure and the residue was poured into ice-cold water. The products that separated were recrystallised from ethanol as a pinkish white powder, mp 196 °C, yield (2.01 g, 61%). IR υ_{max}: 1710 (C═O), 1580 (C═N), 3080 (aromatic C–H), 750 (C–Br), 1113 (C–F), 2570 (CH_2), 3440 (NH_2), 3380 (NH) cm^{-1}; ^1H NMR: δ 8.70–8.20 (m, 7H, Ar-H), 2.35 (s, 2H, CH_2CO), 5.56 (br, 1H, NH, exchangeable), 4.55 (hump, 2H, NH_2, exchangeable), 2.45 (d, 2H, CH_2NH) ppm; MS: *m*/*z* 411 [M^+]; *Anal*. Calcd. For $C_{17}H_{14}O_2N_4BrF$: C, 50.37; H, 3.45; N, 13.82. Found: C, 50.34; H, 3.47; N, 13.84%.

4.2.4. Microwave mediated synthesis of 2-(ω-hydrazinoaceto nyl)-3-p-fluorophenyl-6-bromo quinazoline-4(3H)-one ***3***

The mixture of compound (**2**) and $NH_2NH_2{\cdot}H_2O$ (99%) in absolute ethanol (15 mL) was taken in round bottom flask placed in a microwave oven and irradiated for about 7–8 min (300 W, 68 °C). The excess solvent was then removed by distillation under reduced pressure and the residue was poured into ice-cold water. The products that separated were recrystallised from ethanol as a pinkish white crystal, yield (2.03 g, 83%).

4.2.5. Conventional synthesis of 1′-[3H-3-p-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(phenyl)-Δ^2-pyrazoline ***4a***

A solution of compound (**3**) (4.05 g, 0.01 mol) in glacial acetic acid (20 mL) and 1-(o-chlorophenyl)-3-methylpyrazolidene azomethine-5-chalcones (4.13 g, 0.01 mol) was refluxed for 16 h. The excess solvent was then removed by distillation under reduced pressure and the residue was poured into ice-cold water. The products that separated were recrystallised from ethanol as a dark pinkish solid, mp 230 °C, yield (5.14 g, 65%).

4.2.6. Microwave mediated synthesis of 1′-[3H-3-p-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(phenyl)-Δ^2-pyrazoline ***4a***

A mixture of compound (**3**) (4.05 g, 0.01 mol) in glacial acetic acid (20 mL) and 1-(o-chlorophenyl)-3-methylpyrazolideneazomethine-5-chalcones (4.13 g, 0.01 mol) was taken in 250 mL round bottom flask placed in a microwave oven and irradiated for about 8–10 min. The excess solvent was then removed by distillation under reduced pressure and the residue was poured into ice-cold water. The products that separated were recrystallised from ethanol as a dark pinkish powder, yield (5.15 g, 88%). Likewise other compounds (**4b–j**) were prepared by treating (**3**) with various substituted chalcones.

5. Spectral data of 1′-[3*H*-3-*p*-fluoro phenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chloro phenyl-3-methyl-5-azo methine-2-pyrazolidene]-5′-(substituted phenyl)-D^2-pyrazolines (4a–j)

5.1. 1′-[3H-3-p-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(phenyl)-Δ^2-pyrazoline ***4a***

Dark pinkish powder, UV λ_{max}: 313 nm; IR υ_{max}: 1725 (C═O), 1590 (C═N), 3060 (aromatic C–H), 745 (C–Cl), 770 (C–Br), 1118 (C–F), 2480 (CH_2), 2480, 2960 (aliphatic C–H), 1314 (C–CH_3) cm^{-1}; ^1H NMR: δ 8.60–7.20 (m, 20H, Ar–H), 2.40 (s, 3H, CH_3 attached to pyrazolidene nucleus), 5.80 (d, 2H, 2×CH_2 of pyrazoline ring), 3.95 (t, 1H, CH of pyrazoline ring), 2.26 (s, 2H, 2×CH_2–CO) ppm; ^{13}C NMR: 115–135 (aromatic > C═C <), 40 (CH_3), 49 (2×CH_2 of pyrazoline ring), 38 (–CH_2–), 189 (> C═O), 172 (aliphatic > C═O), 110–140 (heteroaromatics > C═N–) ppm; MS: *m*/*z* 800 [M^+]; *Anal*. Calcd. For $C_{42}H_{32}O_2N_7ClBrF$: C, 62.96; H, 3.99; N, 12.24. Found: C, 62.98; H, 3.97; N, 12.26%.

5.2. 1′-[3H-3-p-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(4″-dimethylaminophenyl)-Δ^2-pyrazoline ***4b***

Yellowish brown solid, mp 237 °C; UV λ_{max}: 291 nm; IR υ_{max}: 1728 (C═O), 1598 (C═N), 3052 (aromatic C–H), 748 (C–Cl), 767 (C–Br), 1115 (C–F), 2479 (CH_2), 2485, 2957 (aliphatic C–H), 1318 (C–CH_3), 1315 [C–N(CH_3)$_2$] cm^{-1}; ^1H NMR: δ 7.00–7.95 (m, 19H, Ar-H), 2.38 (s, 3H, CH_3 attached to pyrazolidene nucleus), 5.85 (d, 2H, 2×CH_2 of pyrazoline ring), 3.97 (t, 1H, CH of pyrazoline ring), 2.23 (s, 2H, 2×CH_2–CO), 2.9 (m, 6H, –N(CH_3)$_2$) ppm; ^{13}C NMR: 113–133 (aromatic > C═C <), 42 (CH_3), 50 (2×CH_2 of pyrazoline ring), 40 (–CH_2–), 192 (> C═O), 170 (aliphatic > C═O), 113–143 (heteroaromatics > C═N–) ppm; MS (*m*/*z*): 852 [M^+]; *Anal*. Calcd. for $C_{44}H_{37}O_2N_8ClBrF$: C, 62.00; H, 4.34; N, 13.15. Found: C, 62.03; H, 4.37; N, 13.12%.

5.3. 1′-[3H-3-p-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(4″-hydroxyphenyl)-Δ^2-pyrazoline ***4c***

Dark pink powder, mp 217 °C; UV λ_{max}: 298 nm; IR υ_{max}: 1721 (C═O), 1589 (C═N), 3065 (aromatic C–H), 741 (C–Cl), 772 (C–Br), 1111 (C–F), 2484 (CH_2), 2478, 2964 (aliphatic C–H), 1315 (C–CH_3), 3572 (C–OH) cm^{-1}; ^1H NMR: δ 6.98–7.93 (m, 19H, Ar-H), 2.42 (s, 3H, CH_3 attached to pyrazolidene nucleus), 5.78 (d, 2H, 2×CH_2 of pyrazoline ring), 3.89 (t, 1H, CH of pyrazoline ring), 2.36 (s, 2H, 2×CH_2–CO), 3.58 (s, 1H, -OH) ppm; ^{13}C NMR: 114–131 (aromatic > C═C <), 43 (CH_3), 53 (2×CH_2 of pyrazoline ring), 37 (–CH_2–), 197 (> C═O), 174 (aliphatic > C═O), 112–141 (heteroaromatics > C═N–) ppm; MS (*m*/*z*): 813 [M^+]; *Anal*. Calcd. for $C_{42}H_{33}O_2N_7ClBrF$: C, 61.70; H, 4.04; N, 12.00. Found: C, 61.72; H, 4.06; N, 12.03%.

5.4. 1′-[3H-3-p-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(4″-methoxyphenyl)-Δ^2-pyrazoline ***4d***

Brown powder, mp 247∼250 °C; UV λ_{max}: 320 nm; IR υ_{max}: 1730 (C═O), 1578 (C═N), 3050 (aromatic C–H), 744 (C–Cl), 780 (C–Br), 1128 (C–F), 2475 (CH_2), 2485, 2965 (aliphatic C–H), 1317 (C–CH_3), 2831 (C–OCH_3) cm^{-1}; ^1H NMR: δ 7.20–7.90 (m, 19H, Ar-H), 2.31 (s, 3H, CH_3 attached to pyrazolidene nucleus), 5.72 (d, 2H, 2×CH_2 of pyrazoline ring), 3.99 (t, 1H, CH of pyrazoline ring), 2.28 (s, 2H, 2×CH_2–CO), 3.89 (s, 3H, –OCH_3) ppm; ^{13}C NMR: 115–135 (aromatic > C═C <), 44 (CH_3), 51 (2×CH_2 of pyrazoline ring), 39 (–CH_2–), 199 (> C═O), 171 (aliphatic > C═O), 35.7 (OCH_3), 112–145 (heteroaromatics > C═N–) ppm; MS (*m*/*z*): 832 [M^+]; *Anal*. Calcd. for $C_{43}H_{34}O_3N_7ClBrF$: C, 62.13; H, 4.09; N, 11.80. Found: C, 62.10; H, 4.11; N, 11.83%.

5.5. 1′-[3H-3-p-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(3″-phenoxyphenyl)-Δ^2-pyrazoline ***4e***

Violet powder, mp 199 °C; UV λ_{max}: 300 nm; IR υ_{max}: 1721 (C═O), 1593 (C═N), 3061 (aromatic C–H), 748 (C–Cl), 771 (C–Br), 1113 (C–F), 2473 (CH_2), 2467, 2964 (aliphatic C–H), 1310 (C–CH_3) cm^{-1}; ^{1}H NMR: δ 6.85–7.65 (m, 24H, Ar-H), 2.34 (s, 3H, CH_3 attached to pyrazolidene nucleus), 5.86 (d, 4H, 2×CH_2 of pyrazoline ring), 3.91 (t, 1H, CH of pyrazoline ring), 2.37 (s, 2H, 2×CH_2–CO), 6.79–7.77 (m, 5H, –OC_6H_5) ppm; ^{13}C NMR: 111–132 (aromatic > C═C <), 42 (CH_3), 50 (2×CH_2 of pyrazoline ring), 39 (–CH_2–), 194 (> C═O), 170 (aliphatic > C═O), 115–148 (heteroaromatics > C═N–) ppm; MS (*m*/*z*): 890 [M^+]; Anal. Calcd. for $C_{48}H_{36}O_3N_7ClBrF$: C, 64.53; H, 4.03; N, 10.98. Found: C, 64.56; H, 4.06; N, 10.95% .

5.6. 1′-[3H-3-p-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(3″,4″,5″-trimethoxyphenyl)-Δ^2-pyrazoline ***4f***

Dark brown crystal, mp 202 °C; UV λ_{max}: 275 nm; IR υ_{max}: 1725 (C═O), 1591 (C═N), 3062 (aromatic C–H), 743 (C–Cl), 771 (C–Br), 1112 (C–F), 2483 (CH_2), 2481, 2962 (aliphatic C–H), 1313 (C–CH_3), 2828 [C–$(OCH_3)_3$] cm^{-1}; ^{1}H NMR: δ 6.99–7.80 (m, 17H, Ar–H), 2.45 (s, 3H, CH_3 attached to pyrazolidene nucleus), 5.89 (d, 2H, 2×CH_2 of pyrazoline ring), 3.87 (t, 1H, CH of pyrazoline ring), 2.31 (s, 2H, 2×CH_2- CO), 3.92 (s, 3H, –OCH_3) ppm; ^{13}C NMR: 110–135 (aromatic > C═C <), 37 (CH_3), 50 (2×CH_2 of pyrazoline ring), 38.7 (–CH_2–), 189 (> C═O), 171 (aliphatic > C═O), 37.5 (3×OCH_3), 110–140 (heteroaromatics > C═N–) ppm; MS (*m*/*z*): 893 [M^+]; *Anal.* Calcd. for $C_{45}H_{40}O_5N_7ClBrF$: C, 60.64; H, 4.49; N, 11.00. Found: C, 60.66; H, 4.51; N, 11.04%.

5.7. 1′-[3H-3-p-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(3″-methoxy-4″-hydroxyphenyl)-Δ^2-pyrazoline ***4g***

Light brown powder, mp 250∼255 °C; UV λ_{max}: 277 nm; IR υ_{max}: 1728 (C═O), 1590 (C═N), 3060 (aromatic C–H), 745 (C–Cl), 770 (C–Br), 1118 (C–F), 2480 (CH_2), 2480, 2960 (aliphatic C–H), 1312 (C–CH_3), 3566 (C–OH), 2825 (C– OCH_3) cm^{-1}; ^{1}H NMR: δ 6.78–7.86 (m, 18H, Ar-H), 2.48 (s, 3H, CH_3 attached to pyrazolidene nucleus), 5.79 (d, 2H, 2×CH_2 of pyrazoline ring), 3.82 (t, 1H, CH of pyrazoline ring), 2.27 (s, 2H, 2×CH_2–CO), 3.79 (s, 3H, - OCH_3), 3.50 (s, 1H, -OH) ppm; ^{13}C NMR: 112–134 (aromatic > C═C <), 44 (CH_3), 48 (2×CH_2 of pyrazoline ring), 35 (–CH_2–), 193 (> C═O), 169 (aliphatic > C═O), 113–148 (heteroaromatics > C═N–) ppm; MS (*m*/*z*): 847 [M^+]; *Anal.* Calcd. for $C_{43}H_{35}O_4N_7ClBrF$: C, 60.95; H, 4.13; N, 11.57. Found: C, 60.93; H, 4.16; N, 11.60%.

5.8. 1′-[3H-3-p-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(2″-chlorophenyl)-Δ^2-pyrazoline ***4h***

Yellow powder, mp 241 °C; UV λ_{max}: 335 nm; IR υ_{max}: 1726 (C═O), 1592 (C═N), 3063 (aromatic C–H), 749 (C–Cl), 775 (C–Br), 1120 (C–F), 2482 (CH_2), 2488, 2966 (aliphatic C–H), 1315 (C–CH_3) cm^{-1}; ^{1}H NMR: δ 6.65–7.77 (m, 17H, Ar-H), 2.42 (s, 3H, CH_3 attached to pyrazolidene nucleus), 5.88 (d, 2H, 2×CH_2 of pyrazoline ring), 3.96 (t, 1H, CH of pyrazoline ring), 2.22 (s, 2H, 2×CH_2–CO) ppm; ^{13}C NMR: 114–131 (aromatic > C═C <), 41 (CH_3), 55 (2×CH_2 of pyrazoline ring), 38 (–CH_2–), 188 (> C═O), 175 (aliphatic > C═O), 118–150 (heteroaromatics > C═N–) ppm; MS (*m*/*z*): 835 [M^+]; *Anal.* Calcd. for $C_{42}H_{31}O_2N_7Cl_2BrF$: C, 60.35; H, 3.71; N, 11.73. Found: C, 60.37; H, 3.73; N, 11.74%.

5.9. 1′-[3H-3-p-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(4″-chlorophenyl)-Δ^2-pyrazolines ***4i***

Pale yellow crystalline powder, mp 250 °C; UV λ_{max}: 298 nm; IR υ_{max}: 1730 (C═O), 1588 (C═N), 3058 (aromatic C–H), 735 (C–Cl), 773 (C–Br), 1120 (C–F), 2481 (CH_2), 2482, 2961 (aliphatic C–H), 1314 (C–CH_3) cm^{-1}; ^{1}H NMR: δ 6.72–7.82 (m, 17H, Ar-H), 2.44 (s, 3H, CH_3 attached to pyrazolidene nucleus), 5.90 (d, 2H, 2×CH_2 of pyrazoline ring), 3.92 (t, 1H, CH of pyrazoline ring), 2.33 (s, 2H, 2×CH_2–CO) ppm; ^{13}C NMR: 114–134 (aromatic > C═C <), 41 (CH_3), 49 (2×CH_2 of pyrazoline ring), 36 (–CH_2–), 196 (> C═O), 170 (aliphatic > C═O), 116–142 (heteroaromatics > C═N–) ppm; MS (*m*/*z*): 837 [M^+]; *Anal.* Calcd. for $C_{42}H_{31}O_2N_7Cl_2BrF$: C, 60.35; H, 3.71; N, 11.73. Found: C, 60.33; H, 3.72; N, 3.72%.

5.10. 1′-[3H-3-p-fluorophenyl-4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(4″-nitrophenyl)-Δ^2-pyrazoline ***4j***

Pink powder, mp 262 °C; UV λ_{max}: 288 nm; IR υ_{max}: 1728 (C═O), 1596 (C═N), 3061 (aromatic C–H), 748 (C–Cl), 771 (C–Br), 1118 (C–F), 2481 (CH_2), 2487, 2967 (aliphatic C–H), 1315 (C–CH_3), 1340 (C–NO_2) cm^{-1}; ^{1}H NMR: δ 7.15–7.92 (m, 19H, Ar-H), 2.36 (s, 3H, CH_3 attached to pyrazolidene nucleus), 5.76 (d, 2H, 2×CH_2 of pyrazoline ring), 3.88 (t, 1H, CH of pyrazoline ring), 2.36 (s, 2H, 2×CH_2–CO) ppm; ^{13}C NMR: 113–133 (aromatic > C═C <), 43 (CH_3), 50 (2×CH_2 of pyrazoline ring), 37 (–CH_2–), 185 (> C═O), 172 (aliphatic > C═O), 114–146 (heteroaromatics > C═N–) ppm; MS (*m*/*z*): 847 [M^+]; *Anal.* Calcd. for $C_{42}H_{31}O_4N_8ClBrF$: C, 59.60; H, 3.66; N, 13.24. Found: C, 59.61; H, 3.68; N, 13.21%.

6. Conclusion

In conclusion, this new method for the synthesis of quinazolinyl-Δ^2-pyrazolines in glacial acetic acid under microwave irradiation offers significant improvements over existing procedures and thus helps facile entry into a variety of quinazolinyl-Δ^2-pyrazolines of potentially high synthetic utility. Also, this simple and reproducible technique affords various quinazolinyl-Δ^2-pyrazolines with short reaction times, excellent yields, and without formation of undesirable by-products.

A series of quinazolinyl-Δ^2-pyrazolines derivatives were prepared and tested for their in vitro antibacterial activity against the four strains of bacteria (gram + ve, gram –ve) and antifungal activities against the two strains of human pathogenic fungi. Five compounds of the obtained series showed high in vitro antimicrobial activity. 2-(ω-chloroacetonyl)-3-*p*-fluorophenyl-6-bromoquinazoline-4(3*H*)-ones (**2**) showed excellent activity against *B. substilis* and *P. aeruginosa*, 1′-[3*H*-3-*p*-fluorophenyl-

4-oxo-6-bromoquinazoline-2-acetonyl]-3′-[1-o-chlorophenyl-3-methyl-5-azomethine-2-pyrazolidene]-5′-(phenyl)-Δ^2-pyrazoline (**4a**) showed excellent activity against *E. coli* indicated in vitro antibacterial activity comparable to or slightly lower than that of Ampicillin, Amoxicillin and Penicillin. Compound (**2**) and 2-(ω-hydrazinoacetonyl)-3-*p*-fluorophenyl-6-bromo quinazoline-4(3*H*)-one (**3**) showed excellent activity against *C. krusei* indicated in vitro antifungal activity comparable to or slightly lower than that of flucanozole. The substitution in the $C_{(4)}$ position of the phenyl ring by methoxy, chloro and phenoxy groups seems to be very important for antifungal effect, as well as the presence and the position of the $-CH_2COCH_2-$ group in the connecting linker between the quinazoline and pyrazoline ring and quinazolinyl-Δ^2-pyrazolines derivatives seems to be very important for anti bacterial effect.

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