

# Niementowski reaction: microwave induced and conventional synthesis of quinazolinones and 3-methyl-1*H*-5-pyrazolones and their antimicrobial activity

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## Abstract

The Niementowski reaction has been extended to synthesize 3-substituted/2,3-disubstituted-4(3H) quinazolinones instead of the 2-substituted derivatives. The methodology is environmentally benign and completely eliminates the need of solvent for the reaction. Neat reactants were cyclocondensed under microwaves to afford, in good yield, the desired product in less irradiation time as compared to the classical technique. The compared results of microwave and conventional techniques have been discussed. 3-Methyl-1*H*-pyrazolones were synthesized from substituted hydrazides using various solid supports under microwave irradiation (MWI). The results obtained highlight the versatility of the solid supports. All synthesized compounds were screened for their antibacterial activity against gram positive and gram negative bacteria and showed good to significant activity, as well as demonstrated significant antifungal activity against *Candida albicans* ATCC 10231 and *C. krusei* GO3.

**Keywords:** Niementowski reaction, microwave, pyrazolone, quinazolinone

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## Introduction

The present day industrialization has led to immense environmental deterioration. The increasing environmental consciousness throughout the world has put a pressing need to develop an alternate synthetic approach for biologically and synthetically important compounds. This requires a new approach, which will reduce the material and energy intensity of chemical processes and products, minimize or eliminate the dispersion of harmful chemicals in the environment in a way that enhances the industrially benign approach and meets the challenges of green chemistry.<sup>1</sup> One of the advances in this area where substantial progress has been made is the microwave-assisted solid-support synthesis.<sup>2</sup> Aluminas can be selected as acidic or basic or neutral catalyst depending on the type of organic reaction. The dream of green chemistry has

thus come true with the help of the “neat reaction” technology. “Neat reaction” is an alternative solvent-free approach in which a mixture of reactants in the absence of solvent is irradiated under microwaves. The striking features are improved yield, shorter reaction time and easier work-up. This justifies the definition of “no solvent” because it completely eliminates the need of a solvent. However, absorption of the conventional heating procedures in the absence of solvent may lead to charring.

Quinazolinone derivatives attract a widespread interest due to the diverse biological activities<sup>3</sup> associated with them. They are pharmaceutically important as antituberculars<sup>4</sup>, antibacterial<sup>5</sup>, antiparkinsons<sup>6</sup>, antihelmintics<sup>6</sup>, and they also show blood platelet anti-aggregating activity.<sup>7</sup> Formation of 2-alkyl-4(3H)-quinazolinones by condensation of anthranilic acid or substituted anthranilic acid and amides is designated as the Niementowski reaction.<sup>8</sup> Pyrazolones are associated with broad spectrum of biological activities including antifungal, antibacterial, anti-inflammatory properties.<sup>9-11</sup> Hydrazone derivatives have been extensively used as a good precursor for the synthesis of these derivatives.<sup>12-13</sup>

Keeping in view the biological importance of the above mentioned heterocyclic compounds and in continuation to our endeavor towards environmentally benign synthesis,<sup>14</sup> we report herein the synthesis of 6-substituted-2-(methyl/phenyl)-3-[-2-(methyl-5-oxo-2,5-dihydro-1H-pyrazol-1-yl)-2-oxo(ethyl/phenyl)]-quinazolin-4(3H)-ones **3(a-l)** from 6-substituted-2-(methyl/phenyl)-4-oxoquinazolin-3(4H)-yl-(aceto/benzo) hydrazone **2(a-l)** using different solid supports under MWI as well as with the conventional techniques (Table 1). These derivatives were screened for their antifungal and antibacterial activity against *Candida albicans* and *E.coli* as well as *S. aureus* respectively by the cup-plate method<sup>15</sup> (Table 2).

**Table 1.** Observed Yield and Reaction time of compounds 3 (a-l)

Comp. No.	Y	R	X	mp/°C	Microwave Irradiation <sup>(a)</sup> (neat Conditions)				Yield% <sup>(b)</sup>	
					<i>t</i> <sub>1</sub> /min	<i>p</i> <sub>1</sub> /w	<i>t</i> <sub>2</sub> /min	<i>p</i> <sub>2</sub> /w	A	B
3a	Br	CH <sub>3</sub>	4-C <sub>6</sub> H <sub>4</sub>	175-178	5.0	400	4.0	500	26	90
3b	H	CH <sub>3</sub>	4-C <sub>6</sub> H <sub>4</sub>	182-185	4.0	320	5.0	450	80	92
3c	Br	C <sub>6</sub> H <sub>5</sub>	4-C <sub>6</sub> H <sub>4</sub>	252-256	5.0	450	3.5	450	72	85
3d	H	C <sub>6</sub> H <sub>5</sub>	4-C <sub>6</sub> H <sub>4</sub>	196-198	4.0	400	5.0	400	78	90
3e	Br	CH <sub>3</sub>	CH <sub>2</sub>	225-229	5.0	450	4.0	500	80	92
3f	H	CH <sub>3</sub>	CH <sub>2</sub>	187-191	5.0	320	4.0	450	78	90
3g	Br	C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub>	180-182	4.5	400	3.5	500	82	95
3h	H	C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub>	174-177	5.0	320	4.5	450	74	88
3i	Br	CH <sub>3</sub>	3-C <sub>6</sub> H <sub>4</sub>	126-128	4.0	450	4.0	500	72	85
3j	H	CH <sub>3</sub>	3-C <sub>6</sub> H <sub>4</sub>	195-197	4.0	420	5.0	350	70	89

**Table 1.** Continued

3k	Br	C <sub>6</sub> H <sub>5</sub>	3-C <sub>6</sub> H <sub>4</sub>	275-278	4.5	400	3.5	450	77	90
3l	H	C <sub>6</sub> H <sub>5</sub>	3-C <sub>6</sub> H <sub>4</sub>	248-250	5.0	400	4.0	350	75	92

<sup>(a)</sup> Microwave irradiations were carried out in a Kenstar microwave oven, model No. OM9925E (2560 MHz, 750 Watts). <sup>(b)</sup> A: Conventional heating; B: Microwave heating.

**Table 2.** Antibacterial and Antifungal activity screening data of compounds 3(a-l)

Compound No.	Antibacterial in (µg/ml)				Antifungal in (µg/ml)	
	Gram positive		Gram negative		Candida	C.krusei
	S.a <sup>a</sup>	B.s <sup>b</sup>	E.c <sup>c</sup>	P.a <sup>d</sup>	ATCC 10231	G03
3a	12	14	15	14	11	10
3b	11	10	13	12	21h	22
3c	16	17	11	10	20	18h
3d	08	09	09	07	08	05
3e	13	12	11	10	20	22
3f	06	08	04	09	18h	24
3g	11	09	17	16	07	09
3h	09	08	18	16	10	11
3i	16	14	11	10	17	20h
3j	05	06	06	07	05	08
3k	07	09	07	06	07	09
3l	17	19	08	11	15h	18
	Zone of inhibition of standard drugs (µg/ml)					
Ampicillin	17	19	18	20	-	-
Amoxicillin	19	22	21	23	-	-
Penicillin	20	21	18	17	-	-
Flucanazole	-	-	-	-	25	28

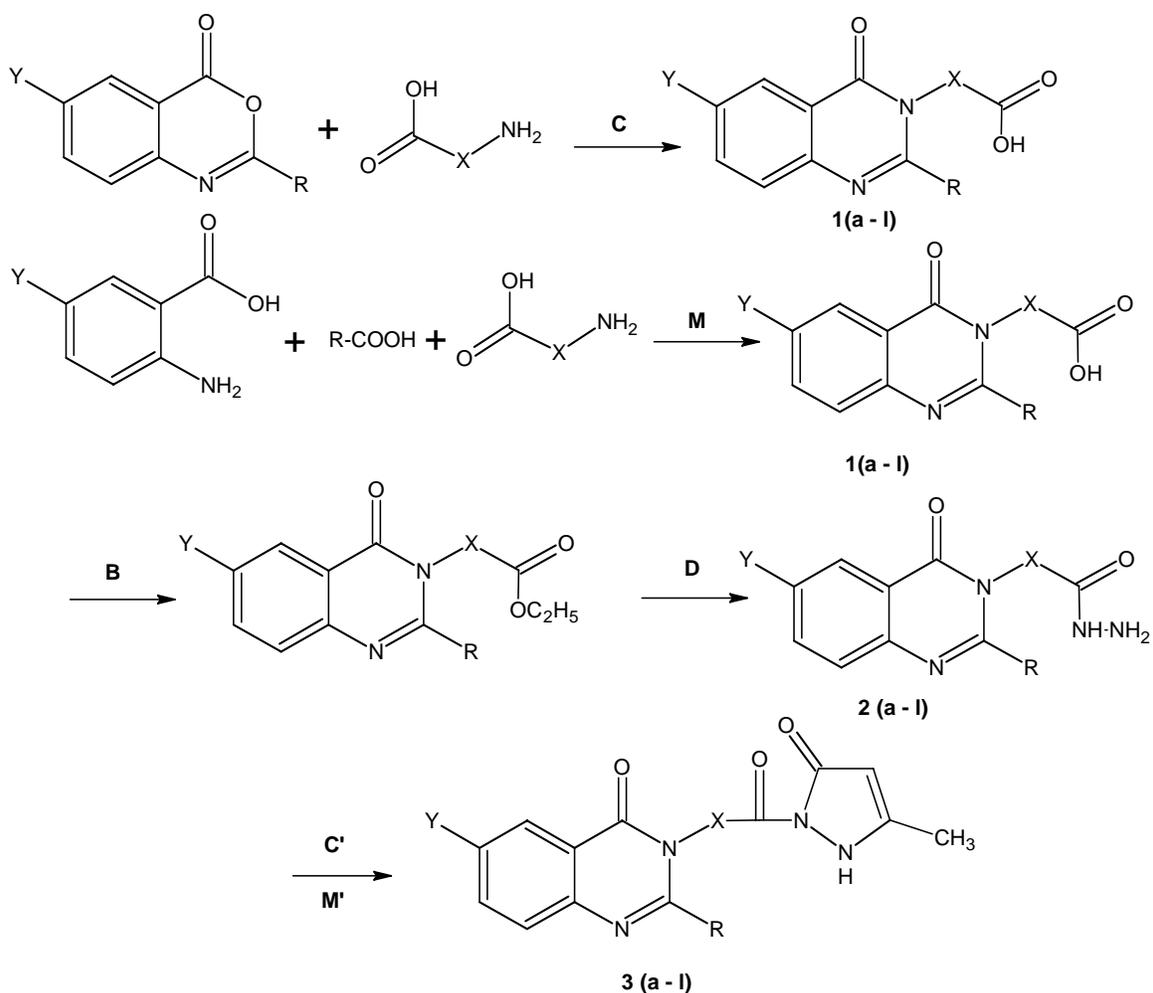
Where <sup>a</sup> S.aureus. <sup>b</sup> B.subtilis. <sup>c</sup> E.coli. <sup>d</sup> P.aeruginosa 'h' denotes hazy zone.

## Results and Discussion

The amides or amidines generally used in the Niementowski reaction were replaced by formic acid and primary aromatic or heteroaromatic amines, which afforded 3-substituted-4(3H) quinazolinones instead of the corresponding 2-substituted derivative. In continuation of our earlier work on microwave synthesis<sup>16</sup> and with respect to the advantage of coupling, solvent free conditions<sup>17</sup> with microwave irradiation (MWI), equimolar amounts of neat reactants were

mixed and irradiated under microwaves. This proved to be a high-yielding protocol (Table 1). Inspired by the high yields obtained using formic acid, a further study of 4(3H) quinazolinones synthesis, as a possible Niementowski reaction, was carried out using different aromatic and heteroaromatic carboxylic acid, amine and carboxylic acid were mixed and irradiated under microwaves to yield 2,3-disubstituted-4(3H) quinazolinones **1(a-l)**. Good yields were obtained in less irradiation time (Table 1) compared to the conventional procedure<sup>17</sup> requiring 5-substituted anthranilic acid, acetyl chloride, pyridine and amino acids and long refluxing time. The hydrazide **2(a-l)** from the corresponding acid was prepared by hydrazine hydrate. Novel route towards synthesis of 6-bromo-2-methyl-3-[-4-[3-methyl-5-oxo-2,5-dihydro-1H-pyrazol-1-yl]carbonyl]phenyl}quinazoline-4(3H)-one **3(a)** from 4-(6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl) benzohydrazide **2(a)** using different solid supports as neutral alumina and by conventional technique using ethyl acetoacetate in ethanol solvent. It gave new 3-methyl-1H 5-pyrazolone in good yield.

The structures of **3(a-l)** were confirmed on the basis of spectral and analytical data. IR spectra showed disappearance of bands at 1710-1720  $\text{cm}^{-1}$  to C=O of carboxylic group and 3400-3300  $\text{cm}^{-1}$  due to NH of amine and appearance of the band at 1685-1699  $\text{cm}^{-1}$  (C=O) and 1590-1615  $\text{cm}^{-1}$  (C=N). In  $^1\text{H}$  NMR, appearance of the signal at  $\delta$  10.5-12 ppm due to carboxylic proton of amino carboxylic acid and a broad signal at  $\delta$  3-4 ppm due to amine confirmed the formation of products **3(a-l)**. The final structures were established by the appearance of band at 1595  $\text{cm}^{-1}$  and disappearance of band at 1730  $\text{cm}^{-1}$  of carboxylic acid. The disappearance of band at 1720  $\text{cm}^{-1}$  (C=O) of ester and appearance of band at 1660  $\text{cm}^{-1}$  due to the pyrazolone ring.  $^1\text{H}$  NMR signal at  $\delta$  5.5 due to H-4 proton and at  $\delta$  2.3 due to the methyl group protons was present. Elemental analysis is furnished in the experimental section. The reaction pathways are depicted in Scheme 1.



Scheme 1

Where: **C** Conventional Method: - Pyridine, Reflux 6-8 hrs.

**M** Microwave Method: -  $\mu\nu$  ( $t_1 = 5$  min and  $t_2 = 4$  min) for ( $p_1 = 400$  w and  $p_2 = 500$  w).

**B** SOCl<sub>2</sub>, reflux 1-2 hrs, C<sub>2</sub>H<sub>5</sub>OH reflux 5-6 hrs.

**D** Hydrazine hydrate 99%, reflux 6 hrs in ethanol as solvent.

**C'** Reflux 6-8 hrs, CH<sub>3</sub>COCH=CHCO<sub>2</sub>Et in ethanol as solvent.

**M'** Microwave Method: - MWI 5-7 min, Neutral Alumina CH<sub>3</sub>COCH=CHCO<sub>2</sub>Et in ethanol as solvent and dried in air.

CodeNo.	Y	R	X	CodeNo.	Y	R	X
3a	Br	CH <sub>3</sub>	4-C <sub>6</sub> H <sub>4</sub>	3g	Br	C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub>
3b	H	CH <sub>3</sub>	4-C <sub>6</sub> H <sub>4</sub>	3h	H	C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub>
3c	Br	C <sub>6</sub> H <sub>5</sub>	4-C <sub>6</sub> H <sub>4</sub>	3i	Br	CH <sub>3</sub>	3-C <sub>6</sub> H <sub>4</sub>
3d	H	C <sub>6</sub> H <sub>5</sub>	4-C <sub>6</sub> H <sub>4</sub>	3j	H	CH <sub>3</sub>	3-C <sub>6</sub> H <sub>4</sub>
3e	Br	CH <sub>3</sub>	CH <sub>2</sub>	3k	Br	C <sub>6</sub> H <sub>5</sub>	3-C <sub>6</sub> H <sub>4</sub>
3f	H	CH <sub>3</sub>	CH <sub>2</sub>	3l	H	C <sub>6</sub> H <sub>5</sub>	3-C <sub>6</sub> H <sub>4</sub>

## Experimental Section

**General Procedures.** All microwave reactions were carried out in a Kenstar microwave oven, model no. OM9925E (2560 MHz, 750 Watts). Melting points were determined in PMP-DM scientific melting point apparatus and were uncorrected. The IR spectra were recorded in KBr on a "Perkin-Elmer RX 1 FT-IR" spectrophotometer (serial No. 51448) and  $^1\text{H}$  NMR spectra were recorded on a Bruker A/C 300 F spectrophotometer and chemical shifts ( $\delta$ ) are in ppm relative to internal tetramethylsilane. The mass spectra were run on a Varian model MAT MS-311 spectrometer at 70 eV. Purity of the compounds in addition to elemental analysis was checked by TLC.

### General synthesis of 6-Bromo-2-methyl-4-oxoquinazolin-3(4H)-yl benzoic acid 1(a)

#### (a) By conventional heating

In a 250 ml beaker, 5-bromoanthranilic acid (2.16g, 0.01mol) in presence of pyridine (0.79 g, 0.01mol) was taken. Acetyl chloride (0.78 g, 0.01 mol) at 0-5 °C was added dropwise to afford cyclization to give 2-methyl-6-bromo-4H-3,1-benzoxazin-4-one. The 6-bromobenzoxazine and p-aminobenzoic acid (1.37g, 0.01 mol) were dissolved in pyridine and refluxed for 6 hrs. Excess of solvent was distilled off. The resulting mixture was cooled and poured over crushed ice. The solid was filtered, washed with cold water, and recrystallised from glacial acetic acid. The % yield is 75%, m.p 175°C. Similarly 6-bromo-2-phenyl-3-[4-(carboxyphenyl)]-4-(3H)-quinazolinones were also synthesized by using benzoyl chloride in place of acetyl chloride. The different 6-substituted compounds have been synthesized by using various amino carboxylic acids by above method.

#### (b) By microwave heating

Equimolar amounts of 6-bromo-anthranilic acid (2.16 g, 0.01 mol), p-amino benzoic acid (1.37 g, 0.01 mol), and acetic acid (0.60 g, 0.01 mol) were put in an Erlenmeyer flask and irradiated under microwaves in two stages ( $t_1 = 5$  min and  $t_2 = 4$  min) at two different power levels ( $p_1 = 400$  w and  $p_2 = 500$  w) (Table 1) respectively. Reactions progress was monitored by TLC. Upon completion of reaction, the reaction mixture was worked up with an excess of 10%  $\text{NaHCO}_3$  solution and recrystallised from ethanol. The % yield is 90%, m.p 175°C. Similarly 6-bromo-2-phenyl-4-oxoquinazolin-3(4H)-yl benzoic acid 1(b) was also synthesized by using benzoic acid in place of acetic acid. The different 6-substituted compounds have been synthesized by using various amino carboxylic acids by above method.

**6-Bromo-2-methyl-4-oxoquinazolin-3(4H)-yl benzoic acid.** Reagents: For **A** 6-bromo anthranilic acid (216 mg), pyridine (79 mg), acetyl chloride (78 mg), p-amino benzoic acid (137 mg). Yield: 75%; For **B** 6-bromo anthranilic acid (216 mg), p-amino benzoic acid (137 mg), acetic acid (60 mg). Yield: 90%; mp 175°C. IR (KBr): 1699 (C=O), 1600 (C=N) quinazoline; 1680, 1685 (C=O), 3060 (aromatic C-H), 1310 (N-C-N), 2890 (COOH), 565 (C-Br).  $^1\text{H}$ -NMR:

1.2 (s, 3H, Me), 7.1-8.1 (m, 7H, Ph & H-5, H-7, H-8), 9.5-10.2 (s, 1H, COOH). MS: m/z 359 [M]<sup>+</sup>. Anal. calcd. for C<sub>16</sub>H<sub>11</sub>BrN<sub>2</sub>O<sub>3</sub>: C, 53.50; H, 3.04; N, 7.80; Found: C, 53.52; H, 3.01; N, 7.78.

### Synthesis of 4-(6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl) benzoyl chloride

#### (a) By conventional heating

In a 250 ml round bottom flask 6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl benzoic acid **1(a)** (3.59g, 0.01 mol) and thionyl chloride (1.785g, 0.015mol) were added and refluxed for 1-2 hrs. Excess of thionyl chloride was then distilled off and then the reaction mixture was cooled in an ice bath. The solid was separated and immediately used for the next reaction.

### Synthesis of 4-(6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl) benzohydrazide **2(a)**

#### (a) By conventional heating

In a 250 ml round bottom flask 4-(6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl) benzoyl chloride (3.775g, 0.01 mol) in ethanol (40 ml) was taken, hydrazine hydrate (95% 1.00g, 0.02 mol) was added slowly with constant stirring and the reaction mixture was kept under reflux condition for 6 hrs. The solvent was then removed by distillation under reduced pressure and the residue was poured into ice-cold water, and recrystallised by using ethanol.

**4-(6-Bromo-2-methyl-4-oxoquinazolin-3(4H)-yl) benzohydrazide.** Yield: 76%; mp 180°C. IR (KBr): 3410 (NH<sub>2</sub>), 3280 (NH), 1695 (C=O), 1599 (C=N) quinazoline; 1675, 1690 (C=O), 3040 (aromatic C-H), 1530 (C---C of aromatic ring), 1312 (N-C-N), 568 (C-Br). <sup>1</sup>H-NMR (CDCl<sub>3</sub>+DMSO-d<sub>6</sub>): 6.1 (t, 1H, -NHNH<sub>2</sub>, exchangeable with D<sub>2</sub>O), 5.96 (d, 2H, NHNH<sub>2</sub>, exchangeable with D<sub>2</sub>O) 1.4 (s, 3H, Me), 7.2-8.15 (m, 7H, Ph & H-5, H-7, H-8). MS: m/z 373 [M]<sup>+</sup>. Anal. calcd. for C<sub>16</sub>H<sub>11</sub>BrN<sub>2</sub>O<sub>3</sub>: C, 55.02; H, 3.04; N, 16.88; Found: C, 55.04; H, 3.01; N, 16.92.

### General synthesis of 6-bromo-2-methyl-3-{4-[(3-methyl-5-oxo-2,5-dihydro-1H-pyrazol-1-yl)carbonyl] phenyl}quinazolin-4(3H)-one **3(a)**

#### (a) By conventional heating

In a round bottom flask a solution of 4-(6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl) benzohydrazide **2(a)** (3.732g, 0.01mol) in ethanol (30 ml) was taken. Ethyl acetoacetate (1.30ml, 0.01mol) was added and it was refluxed on a water bath for 6 hrs. Excess of solvent was then distilled off. The resulting solid was crystallized from ethanol to give above product.

#### B) By microwave heating

To the ethanolic solution (20ml) of **2a** (0.01 mol) and ethyl acetoacetate (1.30 ml, 0.01mol) in 100 ml beaker, neutral alumina (20 g) was added. The reaction mixture was stirred well and dried in air. It was placed in an alumina bath and subjected to MWI intermittently at an interval of 30s for specified time (Table I). On completion of the reaction, as monitored by TLC examination (at an interval of 30s), the product was extracted with ethanol (3x10 mL). Removal

of solvent under reduced pressure gave the desired product (Table 2) which was recrystallised from ethanol.

**6-Bromo-2-methyl-3-{4-[(3-methyl-5-oxo-2,5-dihydro-1H-pyrazol-1-yl)carbonyl]phenyl}quinazolin-4(3H)-one (3a).** For **A** Yield: 75%; For **B** Yield: 90% mp 219-220°C. IR (KBr): 1699 (C=O), 1600 (C=N) Quinazoline; 1680, 1685, (C=O), 1310 (C-CH<sub>3</sub>) Pyrazolone, 3060 (aromatic C-H), 1529 (C---C of aromatic ring) 1317 (N-C-N), 547 (C-Br). <sup>1</sup>H-NMR (CDCl<sub>3</sub>+DMSO-d<sub>6</sub>): 1.2 (s, 3H, Me), 7.1-8.1 (m, 7H, Ph & H-5, H-7, H-8), 2.3 (s, 3H, Me), 5.5 (s, 1H, CH), 8.4 (br, 1H, NH) Pyrazolone. MS: m/z [439]<sup>+</sup>. Anal. calcd. for C<sub>20</sub>H<sub>15</sub>BrN<sub>4</sub>O<sub>3</sub>: C, 54.69; H, 3.44; N, 12.75; Found: C, 54.67; H, 3.42; N, 12.77.

**2-Methyl-3-{4-[(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)carbonyl]phenyl}quinazolin-4(3H)-one (3b).** For **A** Yield: 80%; For **B** Yield: 92% mp 182-185°C. IR (KBr): 1678 (C=O), 1605 (C=N) Quinazoline; 1698, 1710, (C=O), 1308 (C-CH<sub>3</sub>) Pyrazolone, 3065 (aromatic C-H), 1521 (C---C of aromatic ring) 1318 (N-C-N), <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.3 (s, 3H, Me), 7.3-8.4 (m, 8H, Ph & H-5 to H-8), 2.4 (s, 3H, Me), 5.7 (s, 1H, CH), 8.3 (br, 1H, NH) Pyrazolone. MS: m/z [360]<sup>+</sup>. Anal. calcd. for C<sub>20</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>: C, 66.66; H, 4.48; N, 15.55; Found: C, 66.68; H, 4.46; N, 15.56.

**6-Bromo-3-{4-[(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)carbonyl]phenyl}-2-phenylquinazolin-4(3H)-one (3c).** For **A** Yield: 72%; For **B** Yield: 85% mp 252°C. IR (KBr): 1672 (C=O), 1611 (C=N) Quinazoline; 1685, 1692, (C=O), 1312 (C-CH<sub>3</sub>) Pyrazolone, 3045 (aromatic C-H), 1538 (C---C of aromatic ring) 1320 (N-C-N), 560 (C-Br). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 7.3-8.4 (m, 12H, 2 x Ph & H-5, H-7, H-8), 2.4 (s, 3H, Me), 5.6 (s, 1H, CH), 8.4 (br, 1H, NH) Pyrazolone. MS: m/z [501]<sup>+</sup>. Anal. calcd. for C<sub>25</sub>H<sub>17</sub>BrN<sub>4</sub>O<sub>3</sub>: C, 59.89; H, 3.42; N, 11.18; Found: C, 59.91; H, 3.41; N, 11.16.

**3-{4-[(3-Methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)carbonyl] phenyl}-2-phenyl quinazolin-4(3H)-one (3d).** For **A** Yield: 78%; For **B** Yield: 90% mp 196-198°C. IR (KBr): 1685 (C=O), 1598 (C=N) Quinazoline; 1705, 1715, (C=O), 1307 (C-CH<sub>3</sub>) Pyrazolone, 3049 (aromatic C-H), 1530 (C---C of aromatic ring) 1311 (N-C-N). <sup>1</sup>H-NMR (CDCl<sub>3</sub>+DMSO-d<sub>6</sub>): 7.2-8.0 (m, 13H, 2 x Ph & H-5 to H-8), 2.4 (s, 3H, Me), 5.4 (s, 1H, CH), 8.7 (br, 1H, NH) Pyrazolone. MS: m/z [422]<sup>+</sup>. Anal. calcd. for C<sub>25</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>: C, 71.08; H, 4.29; N, 13.26; Found: C, 71.10; H, 4.27; N, 13.29.

**6-Bromo-2-methyl-3-[2-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl]quinazolin-4(3H)-one (3e).** For **A** Yield: 80%; For **B** Yield: 92% mp 225°C. IR (KBr): 1695 (C=O), 1590 (C=N) Quinazoline; 1686, 1699, (C=O), 1315 (C-CH<sub>3</sub>) Pyrazolone, 3055 (aromatic C-H), 1542 (C---C of aromatic ring) 1310 (N-C-N), 552 (C-Br). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 1.2 (s, 3H, Me), 7.1-8.5 (m, 3H, H-5, H-7, H-8), 1.1 (s, 2H, CH<sub>2</sub>) 2.3 (s, 3H, Me), 5.5 (s, 1H, CH), 8.4 (br, 1H, NH) Pyrazolone. MS: m/z [455]<sup>+</sup>. Anal. calcd. for C<sub>21</sub>H<sub>19</sub>BrN<sub>4</sub>O<sub>3</sub>: C, 55.40; H, 4.21; N, 12.31; Found: C, 55.42; H, 4.23; N, 12.29.

**2-Methyl-3-[2-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl]quinazolin-4(3H)-one (3f).** For **A** Yield: 78%; For **B** Yield: 90% mp 187°C. IR (KBr): 1705 (C=O), 1605 (C=N)

Quinazoline; 1682, 1685, (C=O), 1307 (C-CH<sub>3</sub>) Pyrazolone, 3080 (aromatic C-H), 1540 (C---C of aromatic ring) 1321 (N-C-N). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 1.2 (s, 3H, Me), 7.3-7.9 (m, 4H, H-5 to H-8), 1.2 (s, 2H, CH<sub>2</sub>) 2.5 (s, 3H, Me), 5.3 (s, 1H, CH), 8.2 (br, 1H, NH) Pyrazolone. MS: m/z [376]<sup>+</sup>. Anal. calcd. for C<sub>20</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub>: C, 67.01; H, 5.36; N, 14.88; Found: C, 67.04; H, 5.34; N, 14.85.

**6-Bromo-3-[2-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl]-2-phenylquinazolin-4(3H)-one (3g).** For **A** Yield: 82%; For **B** Yield: 95% mp 180°C. IR (KBr): 1699 (C=O), 1597 (C=N) Quinazoline; 1710, 1686, (C=O), 1318 (C-CH<sub>3</sub>) Pyrazolone, 3045 (aromatic C-H), 1538 (C---C of aromatic ring) 1325 (N-C-N), 560 (C-Br). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.2-7.8 (m, 8H, Ph, H-5, H-7, H-8), 1.3 (s, 2H, CH<sub>2</sub>) 2.3 (s, 3H, Me), 5.5 (s, 1H, CH), 8.4 (br, 1H, NH) Pyrazolone. MS: m/z [439]<sup>+</sup>. Anal. calcd. for C<sub>20</sub>H<sub>15</sub>BrN<sub>4</sub>O<sub>3</sub>: C, 54.59; H, 3.40; N, 12.85; Found: C, 54.62; H, 3.38; N, 12.84.

**3-[2-(3-Methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl]-2-phenylquinazolin-4(3H)-one (3h).** For **A** Yield: 74%; For **B** Yield: 88% mp 174°C. IR (KBr): 1685 (C=O), 1599 (C=N) Quinazoline; 1698, 1705, (C=O), 1310 (C-CH<sub>3</sub>) Pyrazolone, 3058 (aromatic C-H), 1535 (C---C of aromatic ring) 1320 (N-C-N). <sup>1</sup>H-NMR (CDCl<sub>3</sub>+DMSO-d<sub>6</sub>): 7.1-8.5 (m, 9H, Ph, H-5 to H-8), 1.2 (s, 2H, CH<sub>2</sub>) 2.3 (s, 3H, Me), 5.5 (s, 1H, CH), 8.4 (br, 1H, NH) Pyrazolone. MS: m/z [360]<sup>+</sup>. Anal. calcd. for C<sub>20</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>: C, 66.75; H, 4.48; N, 15.55; Found: C, 66.78; H, 4.50; N, 15.53.

**6-Bromo-2-methyl-3-{3-[(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)carbonyl]phenyl}quinazolin-4(3H)-one (3i).** For **A** Yield: 72%; For **B** Yield: 85% mp 126°C. IR (KBr): 1695 (C=O), 1590 (C=N) Quinazoline; 1686, 1699, (C=O), 1315 (C-CH<sub>3</sub>) Pyrazolone, 3060 (aromatic C-H), 1540 (C---C of aromatic ring) 1317 (N-C-N), 547 (C-Br). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 1.3 (s, 3H, Me), 7.1-7.9 (m, 7H, Ph & H-5, H-7, H-8), 2.3 (s, 3H, Me), 5.5 (s, 1H, CH), 8.4 (br, 1H, NH) Pyrazolone. MS: m/z [439]<sup>+</sup>. Anal. calcd. for C<sub>20</sub>H<sub>15</sub>BrN<sub>4</sub>O<sub>3</sub>: C, 60.36; H, 4.09; N, 10.38; Found: C, 60.38; H, 4.50; N, 15.53.

**2-Methyl-3-{3-[(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)carbonyl]phenyl}quinazolin-4(3H)-one (3j).** For **A** Yield: 70%; For **B** Yield: 89% mp 195°C. IR (KBr): 1705 (C=O), 1605 (C=N) Quinazoline; 1682, 1685, (C=O), 1307 (C-CH<sub>3</sub>) Pyrazolone, 3048 (aromatic C-H), 1527 (C---C of aromatic ring) 1314 (N-C-N). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 1.5 (s, 3H, Me), 7.3-7.7 (m, 8H, Ph & H-5 to H-8), 2.5 (s, 3H, Me), 5.7 (s, 1H, CH), 8.3 (br, 1H, NH) Pyrazolone. MS: m/z [360]<sup>+</sup>. Anal. calcd. for C<sub>20</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>: C, 71.22; H, 5.06; N, 12.78; Found: C, 71.20; H, 5.10; N, 12.80.

**6-Bromo-3-{3-[(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)carbonyl]phenyl}-2-phenylquinazolin-4(3H)-one (3k).** For **A** Yield: 77%; For **B** Yield: 90% mp 275°C. IR (KBr): 1710 (C=O), 1598 (C=N) Quinazoline; 1705, 1695, (C=O), 1308 (C-CH<sub>3</sub>) Pyrazolone, 3062 (aromatic C-H), 1522 (C---C of aromatic ring) 1312 (N-C-N), 545 (C-Br). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.3-8.2 (m, 12H, 2 x Ph & H-5, H-7, H-8), 2.3 (s, 3H, Me), 5.9 (s, 1H, CH), 8.2 (br, 1H, NH) Pyrazolone. MS: m/z [501]<sup>+</sup>. Anal. calcd. for C<sub>25</sub>H<sub>17</sub>BrN<sub>4</sub>O<sub>3</sub>: C, 59.89; H, 3.42; N, 11.18; Found: C, 59.92; H, 3.45; N, 11.21.

**3-{3-[(3-Methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)carbonyl]phenyl}-2-phenylquinazolin-4(3H)-one (3l).** For **A** Yield: 75%; For **B** Yield: 92% mp 248°C. IR (KBr): 1695 (C=O), 1590 (C=N) Quinazoline; 1686, 1699, (C=O), 1315 (C-CH<sub>3</sub>) Pyrazolone, 3075 (aromatic C-H), 1530 (C---C of aromatic ring) 1318 (N-C-N). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.2-7.7 (m, 13H, 2 x Ph & H-5 to H-8), 2.2 (s, 3H, Me), 5.4 (s, 1H, CH), 8.1 (br, 1H, NH) Pyrazolone. MS: m/z [422]<sup>+</sup>. Anal. calcd. for C<sub>20</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>: C, 71.08; H, 4.29; N, 13.26; Found: C, 71.10 H, 4.27; N, 13.30.

## Conclusions

All compounds were screened for their antifungal against *C.albicans* ATC and *candida krusei* and antibacterial against *B.subtilis*, *S.aureus* as gram positive and *E.coli*, *P.aeruginosa* as gram negative bacteria. Zone of inhibition were measured in millimeters. The antifungal activities of the tested compounds were compared to the standard drug fluconazole (25-28 mm). DMF was used as solvent. All compounds have shown good activity against *candida albicans* Table 2. Ampicillin (18-20mm), Amoxicillin (19-21mm) and penicillin (17-19mm) were used as standard drugs for antibacterial activity. The compounds **3a**, **3b**, **3e**, **3g** and **3h** showed significant activity (11-18 mm) against *E.Coli* and *P. aeruginosa* (gram-ve) at 100 µg/mL concentration. The compounds **3a**, **3c**, **3e**, **3i** and **3l** showed good activity (12-19 mm) against *S.aureus* and *B.subtilis* (gram +ve) at 100 µg/mL concentration. The **3b**, **3c**, **3e**, **3f** and **3i** showed good to significant activity against *C. albicans* ATCC 10231 and *C. Krusei* G03 at 100 µg/mL concentration.

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