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Synthesis of bioactive quinazolin-4(3*H*)-one derivatives *via* microwave activation tailored by phase-transfer catalysis

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A series of nine new 2,3-disubstituted 4(3*H*)-quinazolin-4-one derivatives was furnished starting from the 2-propyl-4(3*H*)-quinazoline-4-one (**2**). The reinvestigation of the key starting quinazolinone **2** was performed under microwave irradiation (MW) and solvent-free conditions. Combination of MW and phase-transfer catalysis using tetrabutylammonium benzoate (TBAB) as a novel neutral ionic catalyst was used for carrying out *N*-alkylation and condensation reactions of compound **2** as a simple, efficient and eco-friendly technique. The structure of the synthesized compounds was elucidated using different spectral and chemical analyses. *In vitro* antimicrobial activity of the compounds was investigated against four bacterial and two fungal strains; very modest activity was achieved. Some of the synthesized compounds were screened for their antitumor activity against different human tumor cell lines. The screened compounds exhibited a significant antitumor activity on some of the cancer cell lines, melanoma (SK-MEL-2), ovarian cancer (IGROV1), renal cancer (TK-10), prostate cancer (PC-3), breast cancer (MCF7) and colon cancer (HT29). The most active, even more active than the reference 5-fluorouracil, were found to be ethyl 4-[(4-oxo-2-propylquinazolin-3(4*H*)-yl)methyl]benzoate (**3c**), 3-{2-[6-(pyrrolidin-1-yl-sulfonyl)-1,2,3,4-tetrahydroquinoline]-2-oxoethyl}-2-propylquinazolin-4(3*H*)-one (**3e**), *N*′-[(*E*)-(2*H*-1,3-benzodioxo-5-yl)methylidene]-2-(4-oxo-2-propylquinazolin-3(4*H*)-yl)acetohydrazide (**10a**), *N*′-[(*E*)-(4-hydroxyphenyl)methylidene]-2-(4-oxo-2-propylquinazo-lin-3(4*H*)-yl)acetohydrazide (**10b**) and *N*′-[(*E*)-(4-nitrophenyl)methylidene]-2-(4-oxo-2-propylquinazolin-3(4*H*)-yl)acetohydrazide (**10c**).

Keywords: solid-liquid transfer catalysis, microwave-assisted reaction, 2-propylquinazolinone, *N*-alkylation, 2,3-disubstituted quinazolinones, anticancer activity

Quinazolin-4(3*H*)-ones are well-known versatile nitrogen heterocyclic compounds. Their occurrence and properties have been of interest to chemists on the account of their pharmacological and medicinal activities (1–5). The attractive natural and synthetic quinazolin-4(3*H*)-ones include methaqualone (6), piriqualone (7), chrysogine (8) and L-vasicinone (9).

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A multitude of interesting approaches toward the modern methodologies for the rational synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones has been reported during the past years. In particular, Smith and others (10) studied the modifications of the quinazolin--4(3*H*)-ones ring synthesis *via* lithiation. Searching for new synthetic methodologies of 2,3-disubstituted quinazolin-4(3*H*)-ones in order to improve their synthetic medicinal applications are in demand.

Accordingly, uses of ultrasonic, microwaves, solvent-free conditions, as well as ionic catalysts and phase-transfer catalysis are modern attractive synthetic approaches which were successfully applied for heterocycles synthesis, quinazolin-4(3*H*)-ones in particular (11). No one can deny that MW technique is announced as a green approach characterized as clean, simple, efficient and environment-friendly technique.

Majority of the reported 4(3*H*)-quinazolin-4-one derivatives are synthesized following conventional methods of heating (12); reactants are slowly activated by a conventional external heat source. There are very few reports (13) regarding the microwave-assisted synthesis of 4(3*H*)-quinazolinone derivatives. During recent years, MW has been used for carrying out chemical reactions as a useful non-conventional energy source for the 4(3*H*)--quinazolinones synthesis (14).

Due to such observations, much interest has been devoted to the synthesis of novel 2,3-disubstituted quinazolinones **3a-e** and **4a-d** bearing moieties and functional groups affecting their biological activities. Moreover, interesting quinazolinone derivatives **5**–**10** were re-investigated and their biological activities were evaluated.

EXPERIMENTAL

Reagents and instrument

All of the used reagents and solvents were purchased from Merck (Germany). Solvents were dried according to the literature when necessary. The purity of the new compounds was checked with TLC. Büchi (Switzerland) melting point apparatus was used; melting points were uncorrected. MW reactions were performed using a mini-lab microwave catalytic reactor WBFY-205, ZZKD, Henan, China. IR spectra were recorded on FT-IR Nicolet Impact 400D (Spectral lab Scientific Inc. Canada), in KBr pellets (ν in cm^{-1}). ^{1}H- and ^{13}C NMR spectra were obtained on Bruker at 400 and 100 MHz (Bruker AV400 spectrometer, Bruker, USA), resp., in $CDCl_3$ or DMSO-d_6 (δ in ppm relative to Me_4Si as the internal standard, J in Hz). DEPT135-NMR spectroscopy (Bruker AV400 spectrometer, Bruker, USA) was used where appropriate, to aid the assignment of signals in the ^{1}H- and ^{13}C NMR spectra. For HRMS (FAB+) JEOL JMS-SX 102A instrument (Jeol, Japan) was used.

Syntheses

2-Propyl-4*H*-3,1-benzoxazinone (**1**) was prepared according to literature (15).

*2-Propylquinazolin-4(3*H*)-one (**2**).* – A mixture of 2-propyl-4*H*-3,1-benzoxazinone **1** (10 mmol, 1.89 g) and ammonium acetate (40 mmol, 3.08 g) was irradiated in MW bath reactor at 100 W and 120 °C for 2–5 min. The resulting crude was filtered off, washed with cold water and recrystallized from petrol ether to give compound **2**.

*General procedure for the formation of compounds **3a-e**. Method A* (16). – To a solution of quinazolinone **2** (10 mmol, 1.88 g) in DMF (20 mL) K_2CO_3 was added (12 mmol, 1.66 g). The reaction mixture was stirred at 60 °C for 30 min, then KI (5 mmol, 0.88 g) was added and the formed mixture was stirred for another 15 min. Solution of respective alkylating agents (ethyl chloroacetate, chloroacetyl chloride, ethyl 4-(bromomethyl)benzoate, 2-chloro-*N*-phenylpropanamide, 2-chloro-1-[6-(pyrrolidine-1-sulfonyl)-3,4-dihydroquinolin-1(2*H*)-yl] ethan-1-one; 0.5 mL) in DMF (10 mL), was dropped slowly into the mixture. After 4 h at 60 °C, the mixture was allowed to cool down and then was poured into ice-cold water. The solid that formed was scrubbed with water, filtered and crystallized using the suitable solvent to give the respective compounds **3a-e**.

Method B. – A mixture of quinazolinone **2** (40 mmol, 7.52 g), K_2CO_3 (80 mmol, 11.04 g) and tetrabutylammonium benzoate (TBAB, 4 mmol, 14.54 g) was irradiated in an MW bath reactor at 800 W and 120 °C for 2–4 min. Alkylating agent (namely, ethyl chloroacetate, chloroacetyl chloride, ethyl 4-(bromomethyl)benzoate, 2-chloro-*N*-phenylpropanamide, 2-chloro-1-[6-(pyrrolidine-1-sulfonyl)-3,4-dihydroquinolin-1(2*H*)-yl]ethan-1-one) (50 mmol) was added, the mixture was again subjected to MW irradiation for the appropriate time (5–12 min). After finalization of the reaction (followed by TLC), the reaction mixture was cooled down to r.t. and water was added. The formed precipitate was scrubbed and crystallized from a suitable solvent to give **3a**-**e**, resp.

The following compounds were prepared: ethyl (4-oxo-2-propylquinazolin-3(4*H*)-yl) acetate (**3a**), (4-oxo-2-propylquinazolin-3(4*H*)-yl)acetyl chloride (**3b**), ethyl 4-[(4-oxo-2-propylquinazolin-3(4*H*)-yl)methyl]benzoate (**3c**), 2-(4-oxo-2-propylquinazolin-3(4*H*)-yl)-*N*--phenylpropanamide (**3d**) and 3-{2-[6-(pyrrolidin-1-yl-sulfonyl)-1,2,3,4-tetrahydroquinoline]--2-oxoethyl}-2-propylquinazolin-4(3*H*)-one (**3e**).

*General procedure for the synthesis of quinazolinones **4a-d**.* – A suspension of 2-propylquinazolinone (**2**, 5 mmol, 0.94 g), aromatic aldehyde (vetraldehyde, 4-*N*,*N*-dimethylaminobenzaldehyde, piperonal, 4-chlorobenzaldehyde) (5 mmol), TBAB (2.5 mmol, 9.09 g) and K_2CO_3 (2.5 mmol, 3.46 g) in 15 mL of distilled water, was mixed well with the aid of a glass rod and irradiated in MW bath reactor at 600 W and 120 °C for 8–10 min. After cooling, the reaction mixture was acidified with dilute HCl. The crude product was separated by filtration followed by scrubbing with water and crystallization from EtOH and the following respective quinazolinone derivatives were prepared: 2-[(1*E*)-1-(3,4-dimethoxyphenyl)but--1-en-2-yl]quinazolin-4(3*H*)-one (**4a**), 2-{(1*E*)-1-[4-(dimethylamino)phenyl]but-1-en-2-yl} quinazolin-4(3*H*)-one (**4b**), 2-[(1*E*)-1-(2*H*-1,3-benzodioxo-5-yl)but-1-en-2-yl]quinazolin-4(3*H*)-one (**4c**) and 2-[(1*E*)-1-(4-chlorophenyl)but-1-en-2-yl]quinazolin-4(3*H*)-one (**4d**).

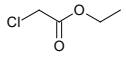
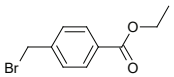
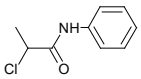
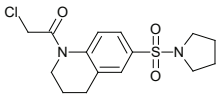
Table I displays reaction conditions and yields under microwave heating and conventional heating procedures of 2-propyl-quinazolinone (**2**) with different alkylating agents.

Compounds **5**–**10a-c** were prepared according to the previous literature with slight modifications (17).

*2-(4-Oxo-2-propylquinazolin-3(4*H*)-yl)acetohydrazide* (**5**). – A suspension of the ester **3a** (10 mmol, 2.74 g) and hydrazine hydrate (15 mmol, 0.75 g) in absolute ethanol (20 mL) was refluxed for 3 h. The reaction mixture was concentrated and then cooled down to r.t. The formed solid was filtered and recrystallized from EtOH to give acetohydrazide **5**.

*3-[(5-Methyl-1,3,4-oxadiazol-2-yl)methyl]-2-propylquinazolin-4(3*H*)-one* (**6**). – A suspension of acetohydrazide **5** (10 mmol, 2.60 g) in 15 mL of acetic acid anhydride was refluxed

*Table I. Reaction of 2-propyl-quinazolinone (**2**) with different alkylating agents*

Compd.	RX	Microwave heating[a]			Conventional heating[b]
		Time (min)	Temp. (°C)	Yield (%)	Yield (%)
3a		5–6	140	87	63
3b		5–6	120	98	67
3c		5–6	120	96	71
3d		10–12	140	85	68
3e		10–12	140	88	59

[a] The reaction proceeds in the presence of K_2CO_3 and TBAB at 800 W.
[b] Conventional thermal heating, K_2CO_3, KI, 60 °C.

for 3 h. The solid that formed after cooling was filtered off and scrubbed with benzene to give quinazolinone derivative **6**.

General procedure for quinazolinones ***7–9***. – A mixture of acetohydrazide **5** (10 mmol, 2.60 g) and acetylacetone, ethyl acetoacetate or 3-nitrophthalic anhydride (10 mmol) in absolute EtOH (30 mL) was heated at 70 °C under reflux for 3 h. The crude solid that precipitated after cooling was filtered off and scrubbed with EtOH and the following quinazolinone derivatives were prepared: 3-[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-oxoethyl]-2-propylquinazolin-4(3*H*)-one (**7**), 3-{[5-(2-oxopropyl)-1,3,4-oxadiazol-2-yl]methyl}-2-propylquinazolin--4(3*H*)-one (**8**) and *N*-(4-nitro-1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-(4-oxo-2-propylquinazolin-3(4*H*)-yl)acetamide (**9**).

General procedure for acetohydrazides ***10a-c***. – An equimolar mixture of acetohydrazide **5** (10 mmol, 2.60 g) and aromatic aldehyde, namely, piperonal, 4-hydroxybenzaldehyde and 4-nitrobenzaldehyde (10 mmol) in 30 mL absolute EtOH was refluxed for 3 h. The reaction mixture was left overnight and the separated solid was filtered off and recrystallized from EtOH and the following acetohydrazides were prepared: *N'*-[(*E*)-(2*H*-1,3-benzodioxo-5-yl) methylidene]-2-(4-oxo-2-propylquinazolin-3(4*H*)-yl)aceto-hydrazide (**10a**), *N'*-[(*E*)-(4-hydroxyphenyl)methylidene]-2-(4-oxo-2-propyl-quinazolin-3(4*H*)-yl)acetohydrazide (**10b**) and *N'*-[(*E*)-(4-nitrophenyl)methylidene]-2-(4-oxo-2-propylquinazolin-3(4*H*)-yl)acetohydrazide (**10c**).

Physicochemical properties and spectral data of the synthesized compounds are presented in Tables II and III.

Table II. Physicochemical data and mass spectra of the prepared compounds **2**, ***3a-e***, ***4a-d*** *and* ***5-10a-c***

Compd.	Yield (%)	M. p. (°C)	Molecular formula (M_r)	Elemental analysis (%)		HR-FAB-MS (pos.)
				Calcd.	Found	
2	96	200–202	$C_{11}H_{12}N_2O$ (188.23)	C: 70.19 H: 6.43	C: 70.28 H: 3.37	188.0942 (M^+, $C_{11}H_{12}N_2O^+$; calc. 188.0950)
3a	63, 87	165–166	$C_{15}H_{18}N_2O_3$ (274.32)	C: 65.68 H: 6.61	C: 65.60 H: 6.49	274.1309 (M^+, $C_{15}H_{18}N_2O_3^+$; calc. 274.1317)
3b	67, 98	285–287	$C_{13}H_{13}ClN_2O_2$ (264.71)	C: 58.99 H: 4.95	C: 58.78 H: 4.87	265.0739 ($[M+H]^+$, $C_{13}H_{14}N_2O_2^+$; calc. 265.0744)
3c	71, 96	179–180	$C_{21}H_{22}N_2O_3$ (350.41)	C: 71.98 H: 6.33	C: 72.18 H: 3.26	351.1704 ($[M+H]^+$, $C_{21}H_{23}N_2O_3^+$; calc. 351.1709)
3d	68, 85	271–272	$C_{20}H_{21}N_3O_2$ (335.40)	C: 71.62 H: 6.31	C: 71.75 H: 6.24	336.1708 ($[M+H]^+$, $C_{20}H_{22}N_3O_2^+$; calc. 336.1712)
3e	59, 88	> 300	$C_{26}H_{30}N_4O_4S$ (494.61)	C: 63.14 H: 6.11	C: 63.23 H: 6.03	494.1991 (M^+, $C_{26}H_{30}N_4O_4S^+$; calc. 494.1988)
4a	82	260–261	$C_{20}H_{20}N_2O_3$ (336.39)	C: 71.41 H: 5.99	C: 71.53 H: 6.07	337.1547 ($[M+H]^+$, $C_{20}H_{21}N_2O_3^+$; calc. 337.1552)
4b	79	253–255	$C_{20}H_{21}N_3O$ (319.40)	C: 75.21 H: 6.63	C: 75.36 H: 6.58	320.1760 ($[M+H]^+$, $C_{20}H_{22}N_3O^+$; calc. 320.1763)
4c	91	244–246	$C_{19}H_{16}N_2O_3$ (320.34)	C: 71.24 H: 5.03	C: 71.35 H: 4.94	320.1168 (M^+, $C_{19}H_{16}N_2O_3^+$; calc. 320.1161)

Compd.	Yield (%)	M. p. (°C)	Molecular formula (M_r)	Elemental analysis (%)		HR-FAB-MS (pos.)
				Calcd.	Found	
4d	84	251–253	$C_{18}H_{15}ClN_2O$ (310.78)	C: 69.57 H: 4.86	C: 69.74 H: 4.90	311.0947 ([M+H]$^+$, $C_{18}H_{16}N_2OCl^+$; calc. 311.0951)
5	75	166–167	$C_{13}H_{16}N_4O_2$ (260.29)	C: 59.99 H: 6.20	C: 59.83 H: 6.29	260.1267 (M$^+$, $C_{13}H_{16}N_4O_2^+$; calc. 260.1273)
6	63	145–146	$C_{15}H_{16}N_4O_2$ (284.31)	C: 63.37 H: 5.67	C: 63.42 H: 5.61	285.1347 ([M+H]$^+$, $C_{15}H_{17}N_4O_2^+$; calc. 285.1352)
7	72	193–195	$C_{18}H_{20}N_4O_2$ (324.38)	C: 66.65 H: 6.21	C: 66.78 H: 6.33	324.1593 (M$^+$, $C_{18}H_{20}N_4O_2^+$; calc. 324.1586)
8	69	266–267	$C_{17}H_{18}N_4O_3$ (326.35)	C: 62.57 H: 5.56	C: 62.75 H: 5.47	327.1453 ([M+H]$^+$, $C_{17}H_{19}N_4O_3^+$; calc. 327.1457)
9	56	246–248	$C_{21}H_{17}N_5O_6$ (435.39)	C: 57.93 H: 3.94	C: 58.15 H: 3.80	435.1171 (M$^+$, $C_{21}H_{17}N_5O_6^+$; calc. 435.1197)
10a	81	193–195	$C_{21}H_{20}N_4O_4$ (392.41)	C: 64.28 H: 5.14	C: 64.37 H: 5.23	392.1477 (M$^+$, $C_{21}H_{20}N_4O_4^+$; calc. 392.1485)
10b	74	174–175	$C_{20}H_{20}N_4O_3$ (364.40)	C: 65.92 H: 5.53	C: 66.13 H: 5.44	364.1528 (M$^+$, $C_{20}H_{20}N_4O_3^+$; calc. 364.1535)
10c	71	260–261	$C_{20}H_{19}N_5O_4$ (393.40)	C: 61.06 H: 4.87	C: 61.14 H: 4.72	393.1511 ([M+H]$^+$, $C_{20}H_{20}N_5O_4^+$; calc. 393.1515)

Table III. IR, ^{1}H NMR, ^{13}C NMR and DEPT 135 spectra

Compd.	IR (ν, cm^{-1})	^{1}H NMR (400 MHz, δ ppm)	^{13}C NMR (100 MHz, δ ppm)
2	3215 (NH), 1675 (C=O), 1597 (C=N)	($CDCl_3$): 1.10 (t, J = 7.0 Hz, 3H, CH_3), 1.92 (h, J = 7.0 Hz, 2H, CH_2), 2.78 (t, J = 7.0 Hz, 2H, CH_2), 7.49 (d, J = 8.0 Hz, 1H, Ar-H), 7.72-7.93 (m, 3H, Ar-H), 12.27 (brs, 1H, D_2O-exchangeable, NH)	($CDCl_3$): 13.8 (CH_3), 16.3, 29.9 ($2CH_2$), 121.8 (C), 122.9, 125.2, 126.3, 134.3 (4CH), 146.3, 149.2, 161.7 (3C)
3a	1735, 1676 (C=O), 1607 (C=N), 1234 (C-O)	($CDCl_3$): 1.10 (t, J = 7.0 Hz, 3H, CH_3), 1.32 (t, J = 7.5 Hz, 3H, CH_3), 1.92 (h, J = 7.0 Hz, 2H, CH_2), 2.76 (t, J = 7.0 Hz, 2H, CH_2), 4.16 (q, J = 7.5 Hz, 2H, CH_2), 4.67 (s, 2H, CH_2),7.49 (d, J = 8.0 Hz, 1H, Ar-H), 7.75-7.91 (m, 3H, Ar-H)	($CDCl_3$): 13.8 (CH_3), 16.3, 29.9, 41.4, 57.1 ($4CH_2$), 121.8 (C), 123.0, 125.8, 126.3, 134.2 (4CH), 149.2, 157.4, 162.9, 165.2 (4C)
3b	1710, 1668 (C=O), 1607 (C=N)	(DMSO-d_6): 1.10 (t, J = 7.0 Hz, 3H, CH_3), 1.92 (h, J = 7.0 Hz, 2H, CH_2), 2.73 (t, J = 7.0 Hz, 2H, CH_2), 4.75 (s, 2H, CH_2), 7.44 (d, J = 8.0 Hz, 1H, Ar-H), 7.75-7.84 (m, 2H, Ar-H), 8.16 (d, J = 8.0 Hz, 1H, Ar-H)	(DMSO-d_6): 13.8 (CH_3), 16.3, 29.9, 41.0 ($3CH_2$), 120.7 (C), 122.6, 125.1, 126.3, 134.2 (4CH), 149.2, 157.4, 162.9, 166.4 (4C)
3c	1734, 1677 (C=O), 1598 (C=N), 1234 (C-O)	($CDCl_3$): 1.13 (t, J = 7.0 Hz, 3H, CH_3), 1.34 (t, J = 7.4 Hz, 3H, CH_3), 1.89 (h, J = 7.0 Hz, 2H, CH_2), 2.78 (t, J = 7.0 Hz, 2H, CH_2), 4.56 (t, J = 7.4 Hz, 2H, CH_2), 5.31 (s, 2H, CH_2), 7.28-7.43 (m, 3H, Ar-H), 7.72-8.17 (m, 5H, Ar-H)	($CDCl_3$): 13.8, 14.1 ($2CH_3$), 16.3, 29.8, 42.9, 53.5 ($4CH_2$), 120.6 (C), 123.1, 124.2, 125.9, 126.4, 130.0 (7CH), 131.6, 138.4 (2C), 134.2 (CH), 149.2, 157.4, 161.9, 166.2 (4C)
3d	3178 (NH), 1679, 1675 (C=O), 1600 (C=N)	(DMSO-d_6): 1.12 (t, J = 7.0 Hz, 3H, CH_3), 1.34 (t, J = 6.8 Hz, 3H, CH_3), 1.94 (h, J = 7.0 Hz, 2H, CH_2), 2.68 (t, J = 7.0 Hz, 2H, CH_2), 4.90 (q, J = 6.8 Hz, 1H, CH), 7.34-7.56 (m, 5H, Ar-H), 7.68 (d, J = 8.0 Hz, 2H, Ar-H), 7.95 (brs, 1H, D_2O-exchangeable, NH), 8.14 (d, J = 7.2 Hz, 2H, Ar-H)	(DMSO-d_6): 13.8, 17.1 ($2CH_3$), 16.3, 29.5($2CH_2$), 49.7 (CH), 120.9 (C), 121.2, 122.8, 124.7, 125.1, 126.7, 127.9, 134.2 (9CH), 136.4, 149.2, 157.4, 160.1, 162.9 (5C)
3e	1700, 1675 (C=O), 1607 (C=N)	(DMSO-d_6): 1.12 (t, J = 7.0 Hz, 3H, CH_3), 1.68-1.92 (m, 6H, $3CH_2$), 1.96-2.05 (m, 2H, CH_2), 2.69 (t, J = 7.0 Hz, 2H, CH_2), 2.98 (t, J = 6.2 Hz, 2H, CH_2), 3.07-3.16 (m, 4H, $2CH_2$), 3.62-3.74 (m, 2H, CH_2), 4.56 (s, 2H, CH_2), 7.42 (d, J = 7.2 Hz, 1H, Ar-H), 7.56 (d, J = 8.0 Hz, 1H, Ar-H), 7.65 (d, J = 8.0 Hz, 1H, Ar-H), 7.78 (d, J = 8.0 Hz, 1H, Ar-H), 7.96 (d, J = 8.0 Hz, 1H, Ar-H), 8.12 (d, J = 7.2 Hz, 1H, Ar-H), 8.41 (s, 1H, Ar-H)	(DMSO-d_6): 13.8 (CH_3), 16.3, 23.6, 24.9, 27.4, 29.9, 33.6, 42.3, 49.0 ($10CH_2$), 120.7 (C), 121.5, 122.9, 124.1, 124.9, 126.8, 130.9, 134.2 (7CH), 134.8, 135.6, 145.7, 149.2, 157.5, 162.9, 166.3 (7C)

Compd.	IR (ν, cm^{-1})	^{1}H NMR (400 MHz, δ ppm)	^{13}C NMR (100 MHz, δ ppm)
4a	3217 (NH), 1674 (C=O), 1605 (C=N), 1251 (C-O)	(DMSO-d_6): 1.15 (t, J = 7.3 Hz, 3H, CH_3), 2.43 (q, J = 7.3 Hz, 2H, CH_2), 3.86 (s, 6H, $2CH_3$), 6.72 (s, 1H, =CH), 6.89 (d, J = 8.3 Hz, 1H, Ar-H), 7.21 (d, J = 8.3 Hz, 1H, Ar-H), 7.34 (d, J = 8.3 Hz, 1H, Ar-H), 7.49-7.88 (m, 4H, Ar-H), 12.74 (brs, 1H, D_2O-exchangeable, NH)	(DMSO-d_6): 14.4 (CH_3), 21.7 (CH_2), 53.1, 55.6 ($2CH_3$), 109.3, 111.5 (2CH), 120.7 (C), 121.0, 125.2, 125.7 (3CH), 125.9 (C), 126.2 (CH), 130.0 (C), 134.0, 138.4 (2CH), 148.8, 149.0, 150.3, 156.9, 162.3 (5C)
4b	3210 (NH), 1671 (C=O), 1606 (C=N)	(DMSO-d_6): 1.13 (t, J = 7.3 Hz, 3H, CH_3), 2.43 (q, J = 7.3 Hz, 2H, CH_2), 3.08 (s, 6H, $2CH_3$), 6.51 (d, J = 8.9 Hz, 2H, Ar-H), 6.81 (s, 1H, =CH), 7.43-7.65 (m, 4H, Ar-H), 7.82-8.04 (m, 2H, Ar-H), 12.73 (brs, 1H, D_2O-exchangeable, NH)	(DMSO-d_6): 14.4 (CH_3), 21.6 (CH_2), 37.4 ($2CH_3$), 111.6 (2CH), 120.8 (C), 122.9, 124.1 (2CH), 124.7, 126.3 (2CH), 126.5 (C), 130.1, 134.0, 136.9 (4CH), 148.7, 149.9, 156.2, 162.8 (4C)
4c	3212 (NH), 1675 (C=O), 1605 (C=N), 1238 (C-O)	(DMSO-d_6): 1.14 (t, J = 7.3 Hz, 3H, CH_3), 2.41 (q, J = 7.3 Hz, 2H, CH_2), 5.87 (s, 2H, CH_2), 6.72 (s, 1H, =CH), 6.92 (d, J = 8.4 Hz, 1H, Ar-H), 7.24 (d, J = 8.4 Hz, 1H, Ar-H), 7.36-7.78 (m, 4H, Ar-H), 8.04 (d, J = 8.4 Hz, 1H, Ar-H), 12.71 (brs, 1H, D_2O-exchangeable, NH)	(DMSO-d_6): 14.3 (CH_3), 21.8, 100.6 ($2CH_2$), 103.5, 107.9, 119.6 (3CH), 120.7 (C), 122.9, 124.7, 126.3 (3CH), 126.6, 127.0, 129.8 (3C), 134.1, 138.4 (2CH), 148.2, 149.0, 157.1, 162.8 (4C)
4d	3215 (NH), 1673 (C=O), 1606 (C=N)	(DMSO-d_6): 1.16 (t, J = 7.3 Hz, 3H, CH_3), 2.43 (q, J = 7.3 Hz, 2H, CH_2), 6.79 (s, 1H, =CH), 7.06 (d, J = 8.1 Hz, 2H, Ar-H), 7.18 (d, J = 8.1 Hz, 2H, Ar-H), 7.48 (d, J = 8.1 Hz, 1H, Ar-H), 7.60 (d, J = 8.1 Hz, 1H, Ar-H), 7.84-8.03 (m, 2H, Ar-H), 12.69 (brs, 1H, D_2O-exchangeable, NH)	(DMSO-d_6): 14.4 (CH_3), 21.7 (CH_2), 120.7 (C), 122.9, 124.7, 126.3 (3CH), 126.5 (C), 127.9, 129.2 (4CH), 133.5 (C), 134.1, 137.9 (2CH), 138.4, 149.0, 157.2, 162.7 (4C)
5	3314, 3270 (NH_2), 3162 (NH), 1686, 1675 (C=O), 1605 (C=N)	(DMSO-d_6): 1.11 (t, J = 7.0 Hz, 3H, CH_3), 1.89 (t, J = 7.0 Hz, 2H, CH_2), 2.74 (t, J = 7.0 Hz, 2H, CH_2), 4.62 (s, 2H, CH_2), 4.86 (brs, 3H, D_2O-exchangeable, 3NH), 7.42 (t, J = 7.2 Hz, 1H, Ar-H), 7.62 (d, J = 8.1 Hz, 1H, Ar-H), 7.78 (t, J = 8.1 Hz, 1H, Ar-H), 8.13 (d, J = 7.2 Hz, 1H, Ar-H)	(DMSO-d_6): 13.8 (CH_3), 16.3, 29.9, 43.5 ($3CH_2$), 120.9 (C), 122.9, 124.7, 126.8, 134.2 (4CH), 149.2, 157.5, 162.6, 165.1 (4C)
6	1675 (C=O), 1605, 1597 (C=N)	(DMSO-d_6): 1.12 (t, J = 7.0 Hz, 3H, CH_3), 1.91 (h, J = 7.0 Hz, 2H, CH_2), 2.69 (t, J = 7.0 Hz, 2H, CH_2), 2.43 (s, 3H, CH_3), 4.92 (s, 2H, CH_2), 7.49 (t, J = 8.1 Hz, 1H, Ar-H), 7.64-7.87 (m, 2H, Ar-H), 8.09 (d, J = 8.1 Hz, 1H, Ar-H)	(DMSO-d_6): 10.7, 13.8 ($2CH_3$), 16.3, 29.9, 38.4 ($3CH_2$), 120.9 (C), 122.9, 126.1, 126.8, 133.9 (4CH), 149.2, 155.6, 157.5, 161.8, 164.4 (5C)

Compd.	IR (ν, cm^{-1})	^{1}H NMR (400 MHz, δ ppm)	^{13}C NMR (100 MHz, δ ppm)
7	1675 (C=O), 1605, 1597 (C=N)	(DMSO-d_6): 1.12 (t, J = 7.0 Hz, 3H, CH_3), 1.92 (h, J = 7.0 Hz, 2H, CH_2), 2.23, 2.28 (s, 6H, $2CH_3$), 2.71 (t, J = 7.0 Hz, 2H, CH_2), 5.16 (s, 2H, CH_2), 6.23 (s, 1H, =CH), 7.38 (t, J = 8.0 Hz, 1H, Ar-H), 7.66 (d, J = 8.0 Hz, 1H, Ar-H), 7.82 (t, J = 8.0 Hz, 1H, Ar-H), 8.09 (d, J = 8.0 Hz, 1H, Ar-H);	(DMSO-d_6): 11.5, 13.8, 14.2 ($3CH_3$), 16.3, 29.9, 44.8 ($3CH_2$), 112.8 (CH), 120.9 (C), 122.8, 124.7, 126.8, 134.2 (4CH), 137.1, 149.2, 152.8, 157.5, 162.6, 163.0 (6C)
8	1736, 1675 (C=O), 1607, 1597 (C=N)	(DMSO-d_6): 1.12 (t, J = 7.0 Hz, 3H, CH_3), 1.87 (h, J = 7.0 Hz, 2H, CH_2), 2.27 (s, 3H, CH_3), 2.60 (t, J = 7.0 Hz, 2H, CH_2), 3.64 (s, 2H, CH_2), 4.92 (s, 2H, CH_2), 7.48 (t, J = 7.8 Hz, 1H, Ar-H), 7.79-8.24 (m, 3H, Ar-H)	(DMSO-d_6): 13.7 (CH_3), 16.3, 29.9 ($2CH_2$), 30.4 (CH_3), 39.5, 41.7 ($2CH_2$), 120.9 (C), 122.9, 124.7, 126.8, 134.2 (4CH), 149.2, 154.6, 156.1, 159.4, 161.9, 201.8 (6C)
9	3194 (NH), 1760, 1730, 1680, 1675 (C=O), 1608, 1597 (C=N)	(DMSO-d_6): 1.10 (t, J = 7.0 Hz, 3H, CH_3), 1.92 (h, J = 7.0 Hz, 2H, CH_2), 2.74 (t, J = 7.0 Hz, 2H, CH_2), 4.66 (s, 2H, CH_2), 7.39 (t, J = 8.1 Hz, 1H, Ar-H), 7.73-8.16 (m, 4H, Ar-H), 8.32 (d, J = 7.9 Hz, 1H, Ar-H), 8.48 (d, J = 7.9 Hz, 1H, Ar-H), 12.31 (brs, 1H, D_2O-exchangeable, NH)	(DMSO-d_6): 13.8 (CH_3), 16.3, 29.9, 48.3 ($3CH_2$), 120.8 (C), 122.7, 124.9, 126.0, 127.2, 128.8, (5CH), 130.1, 130.5 (2C), 133.9, 134.1 (2CH), 139.8, 149.1, 157.5, 157.6, 160.7, 160.9, 162.2 (7C)
10a	3200 (NH), 1682, 1673 (C=O), 1605, 1597 (C=N)	(DMSO-d_6): 1.10 (t, J = 7.0 Hz, 3H, CH_3), 1.92 (h, J = 7.0 Hz, 2H, CH_2), 2.73 (t, J = 7.0 Hz, 2H, CH_2), 4.63 (s, 2H, CH_2), 6.17 (s, 2H, CH_2), 6.82 (d, J = 8.1 Hz, 1H, Ar-H), 7.39 (t, J = 8.1 Hz, 3H, Ar-H), 7.72-8.06 (m, 3H, Ar-H), 8.29 (s, 1H, =CH), 12.68 (brs, 1H, D_2O-exchangeable, NH)	(DMSO-d_6): 13.8 (CH_3), 16.3, 29.9, 48.7, 100.2 ($4CH_2$), 107.4, 108.6 (2CH), 120.8 (C), 122.3, 122.9, 124.7, 126.8 (4CH), 127.2 (C), 134.2, 143.6 (2CH), 146.1, 149.2, 149.7, 157.5, 160.7, 163.4 (6C)
10b	3364 (OH), 3219 (NH), 1680, 1676 (C=O), 1606, 1602 (C=N)	(DMSO-d_6): 1.10 (t, J = 7.0 Hz, 3H, CH_3), 1.92 (h, J = 7.0 Hz, 2H, CH_2), 2.76 (t, J = 7.0 Hz, 2H, CH_2), 4.67 (s, 2H, CH_2), 7.08 (d, J = 8.1 Hz, 2H, Ar-H), 7.37 (t, J = 8.1 Hz, 1H, Ar-H), 7.67-7.86 (m, 4H, Ar-H), 8.14 (d, J = 8.1 Hz, 1H, Ar-H), 8.38 (s, 1H, =CH), 12.63 (brs, 1H, D_2O--exchangeable, NH), 13.09 (brs, 1H, D_2O-exchangeable, OH)	(DMSO-d_6): 13.8 (CH_3), 16.3, 29.9, 48.8 ($3CH_2$), 113.7 (2CH), 120.8 (C), 122.9 (CH), 124.0 (C), 124.7, 126.8, 128.9, 134.2, 143.7 (6CH), 149.2, 156.6, 157.5, 162.2, 163.4 (5C)
10c	3211 (NH), 1680, 1677 (C=O), 1606, 1594 (C=N)	(DMSO-d_6): 1.10 (t, J = 7.0 Hz, 3H, CH_3), 1.92 (h, J = 7.0 Hz, 2H, CH_2), 2.74 (t, J = 7.0 Hz, 2H, CH_2), 4.65 (s, 2H, CH_2), 7.40 (t, J = 8.1 Hz, 1H, Ar-H), 7.63 (d, J = 8.1 Hz, 1H, Ar-H), 7.78-7.94 (m, 6H, Ar-H), 8.41 (s, 1H, =CH), 12.73 (brs, 1H, D_2O-exchangeable, NH)	(DMSO-d_6): 13.8 (CH_3), 16.3, 29.9, 48.7 ($3CH_2$), 120.8 (C), 121.7, 122.9, 124.7, 125.3, 126.8, 134.1 (8CH), 135.8 (C), 143.6 (CH), 144.5, 149.2, 157.5, 162.2, 163.1 (5C)

Biological activity

Antimicrobial activity. – Antimicrobial activity of all compounds was determined by agar well diffusion method (18). Microbial inocula were uniformly spread using a sterile L-shaped rod on sterile Petri dishes loaded with nutrient agar and potato dextrose agar for antibacterial and antifungal tests, resp. Screened compounds were dissolved in DMSO in order to prepare solutions in the concentration range 10–30 mmol L^{-1}. Reference substances were amphotericin B for fungi, ampicillin and gentamicin for Gram-positive and Gram--negative bacteria, resp.; all were dissolved in DMSO in concentration around 3 mmol L^{-1}.

A hundred mL of screened compounds and/or reference substance solutions were added to 5 wells (6-mm diameter holes scooped out with a sterile cork borer). They were then incubated under aerobic conditions (24 h at 37 °C for bacteria and 48 h at 28 °C for fungi). Inhibition zones were determined; the diameter was expressed in millimeters. Furthermore, minimum inhibitory concentration (*MIC*) for substances with potent antimicrobial activity was determined. Thus, the compounds were dissolved in DMSO in order to prepare a series of different concentrations (150, 275, 325, 425 and 600 mmol L^{-1}). Results are presented in Table IV.

Antitumor activity. – *In vitro* screening of compounds **3c-e** and **10a-c** for its antitumor activity were performed where a single dose (25 μmol L^{-1}) of the test compounds was used against 60 cell lines panel assay (19, 20).

After a drug-free incubation period of 24 h, the test compound was added and incubated for another 48 h, followed by assaying the cell growth using the sulforhodamine B (SRB) protocol (21). The results were presented as percentage growth inhibition (GI_{50}) caused by the tested compounds. The parameters GI_{50} and LC_{50} (median lethal concentration) were calculated for each cell line (Table V).

RESULTS AND DISCUSSION

Chemistry

Synthesis of 2-propyl-4(3*H*)-quinazolin-4-one (**2**) in 96 % yield has been performed using the ammonolysis of 3,1-benzoxazin-4-one (**1**) with ammonium acetate under the action of MW irradiation and solvent-free conditions (see Scheme 1).

In the conventional method, the reaction was carried out *via* the fusion at an elevated temperature for 3 h, and consequently leading to the degradation process and low yield of the isolated product. The main advantages of applying microwave-assisted technology are that the completion of the reaction in few minutes (3–5 min) and the satisfactory yields (96 %) of the product, higher than those achieved by traditional methods (see Scheme 1 and Table I). The structure of the prepared quinazolinone **2** was elucidated using elemental and spectral analysis (Tables II and III).

In the present study, the authors decided to use a catalytic procedure through combining MW and the phase-transfer catalytic (PTC) conditions, as this technique has found great applications in essentially all disciplines of organic synthesis (22). The solid-liquid PTC has been described as an attractive procedure in the heterocyclic synthesis and was

Table IV. Antimicrobial activity of the synthesized compounds using agar well diffusion method

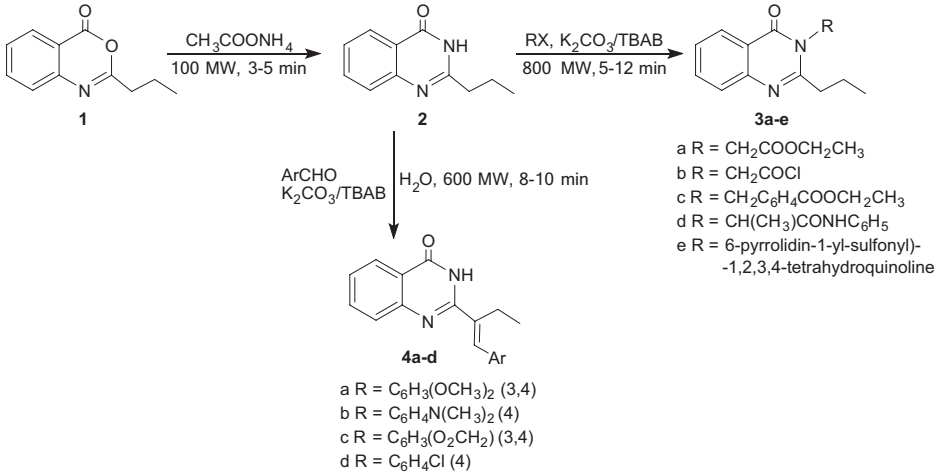
Compd.	Zone of inhibition (mm)[a] (MIC, μmol L^{-1})					
	Gram-positive		Gram-negative		Fungi	
	B. subtilis (ATCC-19635)	*S. aureus* (ATCC-25923)	*E. coli* (ATCC-63059)	*P. aeruginosa* (ATCC-27853)	*A. niger* (ATCC-700608)	*C. albicans* (ATCC- 90028)
2	16 (425)	13 (600)	17 (425)	18 (325)	18 (275)	14 (425)
3a	8 (600)	17 (425)	12 (600)	NA	NA	13 (425)
3b	11 (600)	19 (325)	13 (425)	15 (425)	17 (275)	16 (325)
3c	12 (600)	14 (600)	11 (600)	NA	NA	NA
3d	15 (600)	13 (600)	16 (275)	14 (425)	NA	15 (425)
3e	29 (275)	31 (150)	26 (150)	18 (275)	18 (275)	22 (275)
4a	19 (425)	18 (325)	17 (275)	NA	NA	NA
4b	21 (325)	17 (425)	15 (325)	NA	15 (425)	13 (425)
4c	13 (600)	15 (600)	16 (275)	NA	14 (600)	NA
4d	26 (275)	27 (275)	23 (150)	NA	**21** (275)	NA
5	24 (275)	21 (325)	14 (425)	NA	NA	24 (275)
6	21 (325)	21 (325)	12 (600)	NA	NA	NA
7	23 (275)	16 (425)	16 (275)	NA	23 (150)	26 (150)
8	13 (600)	23 (275)	19 (275)	NA	19 (275)	21 (275)
9	21 (325)	18 (325)	18 (275)	20 (275)	17 (275)	22 (275)
10a	12 (600)	19 (325)	17 (275)	NA	NA	NA
10b	10 (600)	13 (600)	9 (600)	NA	NA	NA
10c	14 (600)	17 (425)	13 (425)	19 (325)	14 (425)	NA
Ampicillin[b]	33 (70)	30 (70)	–	–	–	–
Gentamicin[b]	–	–	20 (60)	24 (60)	–	–
Amphotericin B[b]	–	–	–	–	21 (35)	25 (35)

NA – no activity
[a] Concentration 10–30 mmol L^{-1} for the zone of inhibition testing.
[b] Control drug concentrations (3 mmol L^{-1}), 6.00 mm, (100 μL was tested).

Table V. In vitro screening expressed as growth inhibition of cancer cell lines for some synthesized compounds and 5-fluorouracil

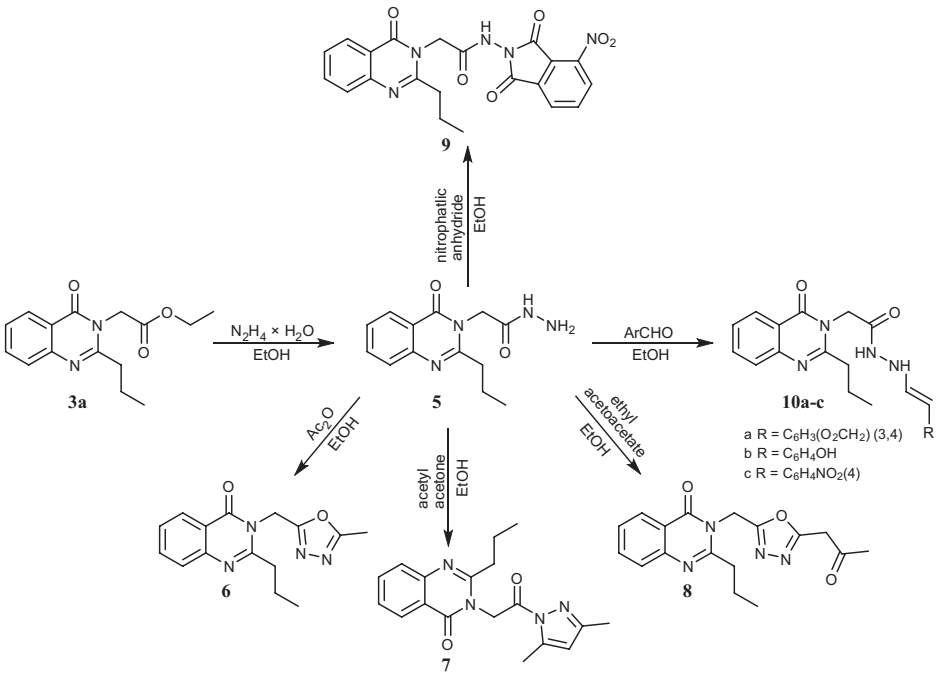
Tumor cell line	Compound GI_{50} (mmol L^{-1})[a] [LC_{50} (mmol L^{-1})[b]]						
	3c	**3d**	**3e**	**10a**	**10b**	**10c**	**5–FU**
Melanoma							
MALME–3M	14.3[c]	17.5 [94.2]	7.61[c]	6.18 [70.4]	–	–	
M14	28.1[c]	22.8[c]	5.18[c]	–	–	–	43.2[c]
SK–MEL–2	22.6[c]	–	3.34[c]	10.4[c]	13.6[c]	–	60.7[c]
SK–MEL–5	–	–	9.42[c]	–	–	–	
Ovarian cancer							
IGROVI	–	–	2.50[c]	–	17.8 [71.2]	–	36.8[c]
OVCAR–3	–	–	7.32[c]	12.7 [22.7]	–	–	
OVCAR–4	11.4[c]	–	22.7 [67.2]	27.9 [19.6]	–	–	
SK–OV–3	–	28.2 [63.5]	16.3[c]	–	–	–	
Renal cancer							
CAKI–1	–	12.6[c]	5.37 [65.8]	–	18.4[c]	13.8[c]	
TK–10	–	–	2.85[c]	6.86[c]	11.3[c]	7.93 [12.6]	45.3[c]
UO–31	–	–	7.66 [17.8]	22.1 [81.7]	–	23.1 [56.8]	
Prostate cancer							
PC–3	10.7 [56.4]	–	4.26[c]	3.48[c]	8.94[c]	15.7 [80.6]	23.4[c]
DU–145	–	–	12.82 [72.9]	–	14.3 [92.4]	–	
Breast cancer							
MCF7	21.4 [70.2]	–	3.05[c]	2.19[c]	30.1 [38.7]	6.92[c]	67.6[c]
MDA–MB–231/TCC	–	15.9[c]	5.69 [84.6]	16.2 [88.5]	–	24.1 [43.8]	
BT–549	–	28.3 [81.6]	–	12.8[c]	–	–	
Colon cancer							
HCC–2998	7.84[c]	12.9 [58.4]	4.43 [56.3]	2.84[c]	8.14[c]	14.3[81.6]	22.5[c]
HT29	–	–	8.12[c]	3.75 [79.3]	–	–	33.9[c]

[a] GI_{50} – concentration causing growth inhibition effect of fifty percent
[b] LC_{50} – median lethal concentration
[c] Compounds showed LC_{50} values > 100 μmol L^{-1}.



Scheme 1

under numerous investigations (23). Formation of *N*-alkylated quinazolinones **3a-e** is presented in Scheme 1. This method is associated with anionic activation, where a catalytic amount of tetrabutylammonium benzoate (TBAB), as a model tetra-alkyl ammonium salt,



Scheme 2

joined the pure reactants blend (24). For the reactions percolate in the liquid organic phase, the electrophilic alkyl halide was chosen as the model constitute which, therefore, acts as the reactant, as well as the liquid organic phase for the reaction. The combination of solid-liquid PTC and MW irradiation was proven to give the best results (25).

Under these circumstances, a simple, efficient and eco-friendly procedure has been developed using TBAB as a novel neutral ionic liquid catalyst for the construction of new 3-substituted-2-propyl-4(3*H*)-quinazolin-4-one derivatives **3a-e**. The rapid *N*-alkylation of 2-propyl-4(3*H*)-quinazolin-4-one (**2**) using different alkylating agents (namely, ethyl chloroacetate, chloroacetyl chloride, ethyl 4-(bromomethyl)benzoate, 2-chloro-*N*-phenyl-propanamide, 2-chloro-1-[6-(pyrrolidine-1-sulfonyl)-3,4-dihydroquinolin-1(2*H*)-yl]ethan--1-one, resp.) was performed under the action of MW irradiation and PTC solvent-free conditions (25). The quinazolinones **3a-e** were obtained in high yields with short reaction times. Yields exceeded 80 %, a dramatic improvement when compared with those from conventional heating. The best yield, for example, was from chloroacetyl chloride in the presence of TBAB as the catalyst at 120 °C (see Scheme 1 and Table I).

Classically, 2-propylquinazolin-4(3*H*)-one (**2**) has been promoted to react with divergent aromatic aldehydes in glacial acetic acid, generating 2-(1-arylbut-1-en-2-yl)quinazolin-4(3*H*)-ones (14, 26). Gupta and Wakhloo (27) studied the well-known Knoevenagel condensation under MW to produce unsaturated acids. They carried out condensation between carbonyl compounds and active methylene compounds using tetrabutylammonium bromide and potassium carbonate in water under MW irradiation.

In the present work, 2-propylquinazolinone **2** was endowed to react with distinctive aromatic aldehydes (namely, vetraldehyde, 4-*N*,*N*-dimethylaminobenzaldehyde, piperonal, 4-chlorobenzaldehyde) under the above-mentioned conditions of Gupta and Wakhloo (27). The mixture of 2-propylquinazolinone **2** and aldehydes was adsorbed on potassium carbonate, then irradiated in MW bath reactor at 600 W for 8–10 min. 2-(1-Arylbut-1-en-2-yl) quinazolinone derivatives **4a-d** were achieved in excellent yields and purity (see Scheme 1, Tables I and II). In such a reaction, water as a solvent was used; this is often intended to exploit the hydrophobic effect (28). Such effect can be explained in terms of the fact that water, at elevated temperature, has a markedly lower dielectric constant (20 at 300 °C); this value seems comparable with the solvents like acetone, at ambient temperature (29). So, one can consider water at an elevated temperature to behave as a pseudo-organic solvent, a good environmentally replacement for the organic solvent.

Furthermore, the chemical structure of ester **3a** was confirmed chemically *via* its hydrazinolysis using hydrazine hydrate in boiling ethanol to afford 2-(4-oxo-2-propylquinazolin-4(3*H*)-yl)acetohydrazide **5**. Subsequently, the acetohydrazide **5** was functionalized as the key starting material for obtaining some heterocycles with potential biological activity. In this respect, acetohydrazide **5** has been reacted with the acetic acid anhydride, acetylacetone, ethyl acetoacetate, 3-nitrophthalic acid anhydride and the compounds **6**–**9** were afforded, resp. Additionally, its condensation with aromatic aldehydes, namely, piperonal, 4-hydroxy benzaldehyde, and 4-nitrobenzaldehyde in boiling ethanol at 70 °C furnishing the analogous aminoquinazolinones **10a-c** (see Scheme 2, Tables II and III).

Biological activity

Antimicrobial activity. – The compounds were tested against two Gram-positive bacteria (*Bacillus subtilis*, ATCC-19635 and *Streptococcus aureus*, ATCC-25923), two Gram-negative

bacteria (*Escherichia coli*, ATCC-63059 and *Pseudomonas aeruginosa*, ATCC-27853) and two pathogenic fungi (*Aspergillus niger*, ATCC-700608 and *Candida albicans*, ATCC-90028). Table IV revealed that only compounds **3e** and **4d** displayed promising activity against *S. aureus* and *E. coli* (*MIC* = 150 mmol L^{-1}) as compared to the standard control drugs (ampicillin, 70 mmol L^{-1} and gentamicin, 60 mmol L^{-1}). Remaining compounds exhibited lower activity.

Only compound **7** (*MIC* = 150 mmol L^{-1}) exhibited promising activity against the fungal strains studied compared to the standard drug used (amphotericin B, 35 mmol L^{-1}) (Table IV).

Antitumor activity. – Compounds **3c,e** and **10a-c** were evaluated at five different concentrations (0.001, 0.1, 1.0, 10, and 100 mmol L^{-1}) against 60 different human cell line panel assay using the known drug 5-fluorouracil (5-FU) as a positive control (30).

It was envisioned that all screened compounds displayed activities against the tested cell lines with positive cytotoxic effects (PCE). Considering broad-spectrum antitumor activity, insightful examination of the data presented in Table IV showed that compounds **3e** and **10a** are the most active quinazolinone derivatives displaying selectivity towards numerous cell lines.

Compound **3e** (LC_{50} > 100 mmol L^{-1}) exhibited remarkable growth inhibitory activity pattern against SK-MEL-2 & M14 (melanoma cancer) (GI_{50} 3.34 and 5.18 mmol L^{-1}, resp.), IGROVI (ovarian cancer) (GI_{50} 2.50 mmol L^{-1}), TK-10 (renal cancer) (GI_{50} 2.85 mmol L^{-1}), PC-3 (prostate cancer) (GI_{50} 4.26 mmol L^{-1}), MCF7 (breast cancer) (GI_{50} 3.05 mmol L^{-1}) and HT29 (colon) (GI_{50} 8.12 mmol L^{-1}) in comparison to the standard drug 5-FU (60.7, 43.2, 36.8, 45.3, 23.4, 67.6 and 33.9 mmol L^{-1}, resp.) (Table V). Also, compound **10a** (LC_{50} > 100 mmol L^{-1}) exhibited growth inhibitory activity pattern against PC-3 (prostate cancer) (GI_{50} 3.48 mmol L^{-1}), MCF7 (breast cancer) (GI_{50} 2.19 mmol L^{-1}) and HCC-2998 (colon cancer) (GI_{50} 2.84 mmol L^{-1}) in comparison to the standard drug 5-FU (23.4, 67.6 and 22.5 mmol L^{-1}, resp.) (Table V). The rest of the tested compounds (**3c**, **3d**, **10b** and **10c**) showed also high activity against HCC-2998, PC-3 and MCF7, and moderate to low activity against the rest of studied human cell lines. Such results are encouraging the authors with the hope of finding new potential antitumor agents. In addition, Table V also revealed that, according to LC_{50}, these compounds were of low toxicity for the normal human cell lines, which is an inevitable requirement for potential antitumor agents.

Structure-activity relationship

For antitumor activity, it was envisioned that the more hybridity of quinazolinone with a high functionalized 2nd chromophore at the 3-position ([6-(pyrrolidin-1-yl-sulfonyl)--1,2,3,4-tetrahydroquinoline] and (1,3-benzodioxo-5-yl)methylidene, for **3e** and **10a**, resp., as the antitumor activity is excellent. The presence of 6-(pyrrolidin-1-yl-sulfonyl)-1,2,3,4--tetrahydroquinoline moiety in compound **3e** increased the activity against M14, SK-MEL-2, IGROVI, TK-10, PC-3, MCF7 and HT29 cell lines. However, the existence of ethyl 4-(methyl)-benzoate and phenylpropanamide in quinazolinones **3c** and **3d**, resp., decreased the activity towards M14, SK-MEL-2, PC-3 and MCF7 cell lines.

Moreover, the existence of piperonal moiety has an excellent influence on activity against PC-3, MCF7, HCC-2298, TK10 and SK-MEL-2 cell lines. This antitumor activity against the mentioned cell lines of compound **10a** emphasizes that the presence of 1,3-ben-

zodioxole moiety at position-3 is superior in its effect to the electronic effect of either the electron-donating OH-group or the electron-withdrawing NO_2-group existing in quinazolinones **10b** and **10c**, resp.

In the present study, the highest antibacterial activity was exerted by quinazolinones bearing sulfonamide or electron-withdrawing chloro group (**3e** and **4d**), whereas the best antifungal efficiency has been observed with compound **7** bearing dimethyl-pyrazolyl at position-3.

CONCLUSIONS

The authors successfully endeavor to reinvestigate the synthesis of 2-propylquinazolin-4(3*H*)-one (**2**) in excellent yield using microwave-assisted reaction under solvent-free conditions. Comparison between conventional heating and microwave irradiation revealed the powerful and selective microwaves action on producing the *N*-alkylated quinazolinones namely, ethyl (4-oxo-2-propylquinazolin-3(4*H*)-yl)acetate (**3a**), (4-oxo-2-propylquinazolin-3(4*H*)-yl)acetyl chloride (**3b**), ethyl 4-[(4-oxo-2-propylquinazolin-3(4*H*)-yl) methyl]benzoate (**3c**), 2-(4-oxo-2-propylquinazolin-3(4*H*)-yl)-*N*-phenylpropanamide (**3d**) and 3-{2-[6-(pyrrolidin-1-yl-sulfonyl)-1,2,3,4-tetrahydroquinoline]-2-oxoethyl}-2-propylquinazolin-4(3*H*)-one (**3e**). In addition, the combination of phase-transfer catalysis and microwaves resulted in producing the more interesting functionalized heterocycles **4a-d** containing the important 4(3*H*)-quinazolinone core. We hereby highlighted the potential of some of the synthesized heterocycles as potential antitumor agents. Quinazolinone core that endows propyl group at 2-position and substitution at 3rd position (generation the 2nd chromophore at 3-position) was found superior in bioactivity.

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