Synthesis of Some New 4-(3H)-quinazoline Analogs as Potential Antioxidant Agents

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في هذا البحث تم تحضير بعض المماثلات الجديدة من الكينازولين-٤-أون كمضادات للأكسدة وتم أثبات البناء الكيماوي للمركبات الجديدة بواسطة التحليل الدقيق للعناصر والأشعة تحت الحمراء والرنين النووي المغناطيسي وكذلك مطياف الكتلة وقد ثبت لبعضها فاعلية كبيرة في إيقاف فاعلية أنزيم الدهيد اوكسيديز بنسبة أكبر من ٩٨%.

A new series of 6-iodo-2-propyl-4(3H)-quinazolinone and its fused heterocyclic were prepared and screened for their antioxidant activity. It was found that compounds **4**, **5**, **7**, **9**, **10**, **20** and **24** inhibit aldehyde oxidase exclusively by more than 98%. This type of inhibition was found to be competitive with Ki value ranging from 50-400 μM with respect to aldehyde oxidase.

INTRODUCTION

Quinazolinones are excellent reservoir of bioactive substances. A number of biological activities[1-9] are associated with quinazolinones especially antioxidant activity.[10-12] The stability of the quinazoline nucleus has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents. In the present study, several acid chloride derivatives and some functional groups such as -OH, -NHCONH-, $-COCH_2Cl$ and $-CH_2CONH_2$ have been incorporated at position -3- of the quinazolinone to result 3-substituted derivatives that likely to have superior antioxidant activity.

RESULTS AND DISCUSSION

Chemistry

Interaction of 5-iodoanthranilic acid with butyryl chloride in pyridine afforded 2-butyrylamino-5-iodobenzoic acid **1**, which was subsequently cyclized to the corresponding benzoxazine derivative **2** by heating with acetic anhydride. Reaction of compound **2** with concentrated ammonia solution afforded 2-(butyrlylamino)-5-iodo-benzamide **3**, which was refluxed in 10% NaOH solution to afford 6-iodo-2-propyl-4-(3*H*)-quinazolinone **4**. The latter compound was prepared directly by refluxing the benzoxazine derivative **2** in large excess formamide.

Compound **2** was reacted with semicarbazide in boiling pyridine to afford N-(6-iodo-2-propyl-4(3*H*)quinazolin-3-yl)urea **5**. The IR spectrum of the latter compound showed strong absorption bands 3390, 3300 (NH/NH_2), 3150 (NH/NH_2), 1695, 1670 (2C=O). Cyclodehydration of compound **5** in glacial acetic acid containing fused sodium acetate afforded 3,4-dihydro-2-oxo-9-iodo-5-propyl-1,2,4-triazolo[1,5-*c*]quinazoline **6**. The

mass spectrum of this compound showed the molecular ion peak at m/z 354. Compound **2** was reacted with hydroxylamine hydrochloride in dry boiling pyridine to afforded 3-hydroxy-6-iodo-2- propyl-4(3*H*)-quinazolinone **7**. IR spectrum showed absorption bands at 3415, 1665 corresponding to OH and C=O groups respectively. Reaction of compound **2** with n-butylamine in boiling pyridine afforded the diamide derivative **8**. The assigned structure **8** was inferred from microanalytical data and IR spectrum which show bands in the region of 3240, 3150 and 1680-1665 cm^{-1} corresponding to NH and C=O (amidic). Interaction of compound **2** with N-aminophthalimide in boiling glacial acetic acid containing fused sodium acetate afforded 6-iodo-2-propyl-3-phthalimido-4-(3*H*)-quinazolinone **9** which was characterized by its spectral data. Thus IR spectrum of this compound gave strong absorption bands at 1800, 1730, 1690 cm^{-1} (3 C=O) while its mass spectrum showed the molecular ion peak 459 (13.96%), 431 (100%), 292 (19.45%).

3-Amino and (3-aminoethyl)-2-propyl-6-iodo-3,4-dihydroquinazolin-4-one **10**, **11** were obtained by reacting compound **2** with large excess of boiling hydrazine hydrate and ethylene diamine respectively. The structures of compounds **10**, **11** were confirmed from their analytical and spectral data. IR spectra of **10** and **11** shows two strong absorption bands at 3495, 3325 and 3400, 3350 cm^{-1} due to the presence of NH_2 group in both compounds respectively. Condensation of **10**, **11** with benzoxazine-4-one **2** afforded the dimeric structures **12** and **13**, respectively. The structures of these compounds were confirmed from its correct elemental analysis and spectral data. The IR spectra showed the lackness of any significant absorption bands in the region characteristic for NH_2 and NH while shows bands due to C=O groups. On the other hand, mass spectrum of **12** showed molecular ion peak at m/z 626. Reaction of compound **2** with benzoic and salicylic acid hydrazides afforded 3-aroylamino-6-iodo-2-propyl-4-(3*H*)quinazoline derivatives **14** and **15**. The IR spectrum of compound **14** showed bands at 3200, 1695, 1670 cm^{-1} corresponding to NH and 2 C=O stretching. Mass spectra of compound **14** showed molecular ion peak at m/z = 433 (2.0%), 416 (8.3%) and 243 (6%), while that of compound **15** showed molecular ion peak at m/z = 449 (3.14%), 421 (10.0%) and 329, 8.86%). Reaction of 3-amino-6-iodo-2-propyl-4(3*H*)-quinazolinone **10** with one mole and two moles of benzoyl chloride in pyridine afforded compound **14** (which was prepared by different routes) and **16** respectively. The structures of these compounds were verified from its correct elemental analysis and also from spectral data. Mass spectrum of compound **16** showed a molecular ion peak at m/z = 537 (1.50%) and its IR spectrum showed the disappearance of any absorption bands for NH_2 and NH while show bands at 1705, 1695, 1685 cm^{-1} due to 3 C=O groups. Compounds **17**-**19** were prepared by the reaction of benzoxasin-4-one **2** with the appropriate aromatic or heterocyclic amines in boiling pyridine for 24 hrs. The IR spectra of compounds **17** and **19** showed no any bands at 3500-3100 cm^{-1} corresponding to NH_2 or NH which exclude the diamide structure. On the other hand, the mass spectrum of compounds **17** and **18** showed molecular ion peak at m/z = 390 and 405 respectively.

Compounds **7** and **10** were reacted with chloroacetyl chloride in DMF to afford chloroacetate ester and 2-chloroacetamide derivatives **20** and **21** which were upon refluxing in glacial acetic acid containing large excess amount of ammonium acetate gave **4** instead of the corresponding tricyclic derivatives **22** and **23**. 3-Hydroxyquinozoline **7** was reacted

with chloracetamide in dimethylformamide to give 2-[6-iodo-2-propyl-4(3*H*)-quinazolinone-3-yloxy)acetamide **24** which upon addition of base and continuous refluxing would undergo cyclodehydration to afford 3,5-dihydro-2-oxo-9-iodo-5-propyl-1,2,4-oxadiazino[2,3-*c*]quinazoline **25**. IR spectrum of the latter compound showed the disappearance of the absorption bands for NH_2 while shows bands due to C=O and C=N.

Reaction of 3-amino derivative **10** with aromatic aldehydes in glacial acetic acid afforded 3-arylidene derivatives **26-28**. IR spectra of 3-iminoderivatives showed the disappearance of the absorption bands for NH_2 and NH while shows bands due to C=O and CH=N groups at 1695, 1670 cm^{-1}. Subjecting compounds **26-28** to the action of thioglycolic acid afforded the thiazolidene-4-one derivatives **29-31**. This reaction assumed to proceed by addition followed by cyclodehydration. The structures of **29-31** were established from analytical and spectral data. IR spectra revealed absorption bands at 1710, 1695 cm^{-1} due to C=O group.

EXPERIMENTAL

Melting points were determined on a Mettler FP80 melting point apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 elemental analyzer, all of the new compounds were analyzed for C, H, and N and agreed with the proposed structures within ±0.4% of the theoretical values. ^{1}H NMR spectra were recorded on a Varian XL 400 MHz FT spectrometer, chemical shifts are expressed in δ ppm with reference to TMS. Mass spectral data were obtained on a Shimadzu GC/MS QP 5000 apparatus. Infrared (IR) spectra were recorded on a Pye Unicam SP 1000 IR Spectrometer. Thin layer chromatography was performed on Merck 5×10 cm precoated (0.25 mm) silica gel GF_{254} plates (E. Merck, Germany); compounds were detected with a 254-nm UV lamp. Silica gel (60-320 mesh) was employed for routine column chromatography separations.

N-Butyrylamino-5-iodobenzoic acid (1)

Butyroyl chloride (5.33 g, 0.05 mol) was added dropwise to a stirred solution of 5-iodoanthranilic acid (13.15 g, 0.05 mol) in pyridine (60 ml), the reaction mixture was stirred at room temperature for 2 hours. The separated solid was filtered, washed with water, dried and crystallized from ethanol (Table 1).

2-Propyl-6-iodo-4H-3,1-benzoxazine-4-one (2)

A mixture of compound **1** (13.32 g, 0.04 mol) and acetic anhydride (170 ml) was heated under reflux for 4 hours. The solvent was evaporated under reduced pressure. The solid mass was filtered and washed with petroleum ether and dried (Table 1).

2-(Butyrylamino)-5-iodobenzamide (3)

A compound **2** (0.63 g, 0.002 mol) was stirred with concentrated ammonia solution (20 ml) at room temperature for 5 hours, the solvent was evaporated under reduced pressure, the solid was filtered, washed with water, dried and crystallized from ethanol (Table 1).

6-Iodo-2-propyl-4-(3*H*)-quinazolinone (4)

The compound **2** (0.63 g, 0.002 mol) was refluxed with formamide (30 ml) for 2 hours. The reaction mixture was cooled, solid was filtered, dried and crystallized from ethanol (Table 1).

N-(6-iodo-2-propyl-4(3*H*)-quinazolinon-3-yl)urea (5)

A mixture of compound **2** (0.63 g, 0.002 mol) and semicarbazide (0.33 g, 0.003 mol) was refluxed in dry pyridine (30 ml) for 6 hours. The reaction mixture was allowed to cooled, treated with ice-cold hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from ethanol (Table 1).

2-Oxo-5-propyl-9-iodo-1,2,4-triazolo[1,5-*c*]-quinazoline (6)

A compound **5** (0.37 g, 0.001 mol) was heated in glacial acetic acid (30 ml) and fused sodium acetate (0.5 gm) for 5 hours, the reaction mixture was cooled. The solid obtained was filtered, dried and recrystallized from dioxane (Table 1).

6-Iodo-2-propyl-3-substituted-4-(3*H*)-quinazolinone (7, 8, 9, 17, 18, 19)

A mixture of compound **2** (0.63 g, 0.002 mol) and appropriate amine (0.003 mol) was refluxed in dry pyridine (30 ml) for 6~12 hours. The reaction mixture was allowed to cooled, treated with ice-cold hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from appropriate solvent (Table 1).

3-Amino-6-iodo-3-propyl-4(3*H*)-quinazolinone (10)

A compound **2** (0.63 g, 0.002 mol) was heated with hydrazine hydrate (20 ml) for one hour, the reaction mixture was cooled, the separated mass was filtered, dried and recrystallized from ethanol (Table 1).

3-Aminoethyl-6-iodo-2-propyl-4(3*H*)-quinazolinone (11)

A compound **2** (0.63 g, 0.002 mol) was refluxed with ethylenediamine (0.3 g, 0.005 mol) in absolute ethanol (30 ml) for 2 hours. The reaction mixture was cooled, the solid obtained was filtered, dried and recrystallized from ethanol (Table 1).

3-(3-Quinazolinyl) -6-iodo-2-propyl-4(3*H*)-quinazolinone (13) and
3-(3-Quinazolinylethyl)-6-iodo-2-propyl-4(3*H*)-quinazolinone (14)

A mixture of compound **2** (0.63 g, 0.002 mol) and **10** or **11** (0.002 mol) was refluxed in glacial acetic acid (30 ml) containing fused sodium acetate (1 g) for 18 hours. The reaction mixture was cooled, the solid obtained was filtered, dried and recrystallized from acetic acid (Table 1).

3-(N-Benzoylamino)-6-iodo-2-propyl-4(3*H*)-quinazolinone (14) and
3-[N-(2-Hydroxybenzoyl)amino]-6-iodo-2-propyl-4(3*H*)-quinazolinone (15)

Method A

A mixture of compound **2** (0.63 g, 0.002 mol) and the appropriate acid hydrazide (0.003 mol) was refluxed in dry pyridine (40 ml) for 10 hours. The reaction mixture was cooled, treated with ice-hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from ethanol (Table 1).

Method B

A mixture of compound **10** (0.66 g, 0.002 mol) and benzoyl chloride (0.28, 0.002 mol) was refluxed in pyridine (40 ml) for 2 hr. The reaction mixture as cooled, treated with cold ice-cold hydrochloric acid. The separated solid was filtered washed with water, dried and crystallized from ethanol to afford compound **14**.

3-(N,N-Benzoylamino)-6-iodo—2-propyl-4(3*H*)-quinazolinone (16)

A mixture of compound **10** (0.66 g, 0.002 mol) and benzoyl chloride (0.56 g, 0.004 mol) or (0.004 mol) was refluxed in pyridine (30 ml) for 7 hours. The reaction mixture was

cooled, treated with ice hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from ethanol (Table 1).

2-[6-Iodo-2-propyl-4(3*H*)-quinazolinon-3-yl]chloroacetate (20)

A mixture of compound **7** (0.66 g, 0.002 mol) and chloroacetyl chloride (0.34 g, 0.003 mol) was refluxed in DMF (30 ml) for 6 hours. The reaction mixture was cooled, treated with ice-cold water, the solid obtained was filtered, washed with water, dried and crystallized from ethanol (Table 1).

N-(6-Iodo-2-propyl-4(3*H*)-quinazolinon-3-yl)-2-chloracetamide (21)

A mixture of compound **10** (0.66 g, 0.002 mol) and chloroacetyl chloride (0.34 g, 0.003 mol) was reacted in DMF (30 ml) for 5 hours. The reaction mixture was cooled, treated with ice-cold water, the solid obtained was filtered, washed with water, dried and crystallized from ethanol (Table 1).

2-(6-Iodo-2-propyl-4-(3*H*)-quinazolinon-3-yloxy)-acetamide (24)

A mixture of compound **7** (0.66 g, 0.002 mol) and chloroacetamide (0.275 g, 0.003 mol) was refluxed in DMF (30 ml) for 6 hours. The reaction mixture was cooled, treated with ice-cold water, the solid obtained was filtered, washed with water, dried and crystallized from ethanol (Table 1).

3,5-Dihydro-2-oxo-9-iodo-5-propyl[2,3-*c*]quinazoline (25)

A mixture of compound **24** (0.58 g, 0.0015 mol) was refluxed in DMF (30 ml) containing (0.08 g, 0.002 mol) NaOH for 16 hours. The reaction mixture was cooled, treated with ice-cold water, the solid obtained was filtered, washed with water, dried and crystallized from ethanol (Table 1).

3-(Arylideneamino)-6-iodo-2-propyl-4(3*H*)-quinazolinone (26-28)

A mixture of compound **10** (0.66 g, 0.002 mol) and the appropriate aldehyde (0.002 mol) was refluxed in glacial acetic acid (30 ml) for 9 hours. The reaction mixture was cooled, the solid obtained was dried and recrystallized from appropriate solvent (Table 1).

2-Propyl-3-[2-(4-substituted phenyl)-4-oxo-1,3-thiazolidine-3-yl]-6-iodo-4(3*H*)-quinazolinone (29-31)

A mixture of appropriate arylidine (0.001 mol) and thioglycolic acid (0.002 mol) was refluxed in dry benzene (30 ml) for 12 hours. The reaction mixture was cooled, the solvent was evaporated under reduced pressure, the solid was neutralized with 10% Na_2CO_3 solution. The solid obtained was filtered, dried and crystallized from ethanol (Table 1).

Antioxidant Activity

Aldehyde oxidase was partially purified from liver homogenate of mature male/female Dunkin-Hartly guinea pigs following a published methodology.[13] The relative inhibition activities of iodoquinazoline derivatives have been determined by spectrophotometric technique using phthalazine (100 μM) as substrate. The initial oxidation rates of the aldehyde oxidase has been calculated as μmol/min/mg protein in the presence of iodoquinazoline, following for up to 5 min and compared with control.[14]

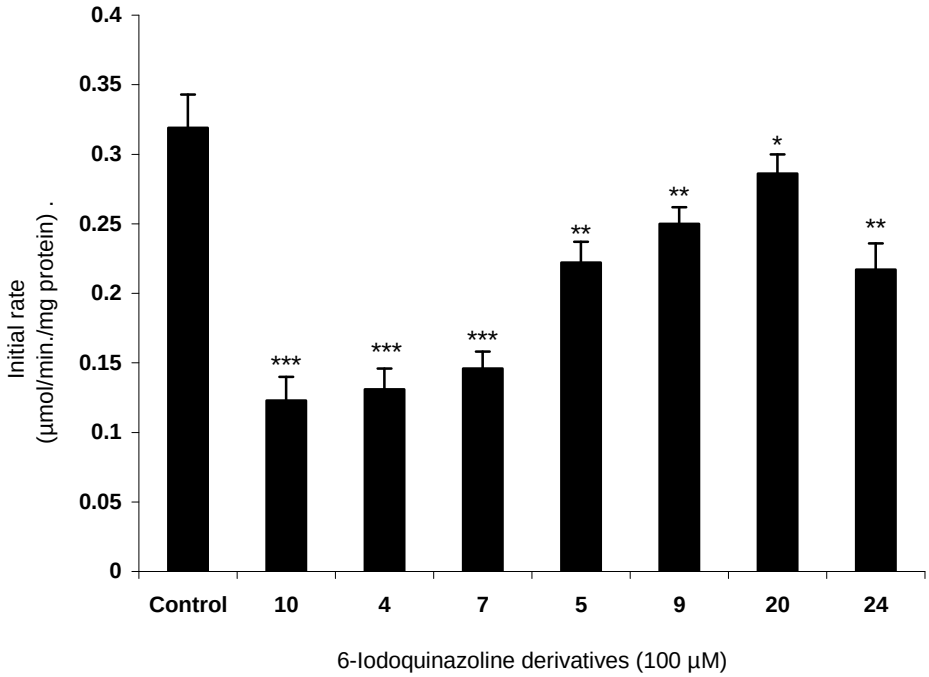
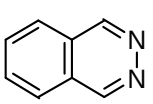


Figure 1: The relative inhibition of phthalazine (100 µM) oxidation by aldehyde oxidase in the presence of 100 µM of iodoquinazoline derivatives (n = 3 ± SD, *P<0.05, **P<0.01, ***P<0.005 *vs* control).

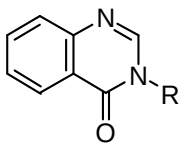
All of newly synthesized quinazoline derivatives were tested as inhibitor for aldehyde oxidase. The effect of iodoquinazolines on substrate oxidation has been compared with traditional aldehyde oxidase inhibitor chlorpromazine. It was found that compounds inhibit aldehyde oxidase exclusively by more 98%. By using 1-tailed student t-test, it has been shown that 100 µM iodoquinazoline derivatives caused a remarkable inhibition (P<0.005 with 4, 10 and 7, P<0.01 with 5, 9 and 24, and P<0.05 with 20) (Figure 1). The type of inhibition was found to be a competitive with Ki value ranging from 50-400 µM with respect to aldehyde oxidase.

There is no clear relationship between lipophilicity and inhibitor constant of aldehyde oxidase. However, the most lipophilic compound **16** gave the highest Ki value with aldehyde oxidase 580 µM. Compounds 12 and 13 are dimmers of iodoquinazoline that have higher Ki value which in part due to their bulky size rather than due to lipophilicity.

In summary, these compounds were capable to interact with aldehyde oxidase as inhibitors (due to there structural similarities with phthalazine) but not as substrate. It was found that the tricyclic fused quinazoline derivatives 6 and 25 failed to give any inhibition to the aldehyde oxidase enzyme.

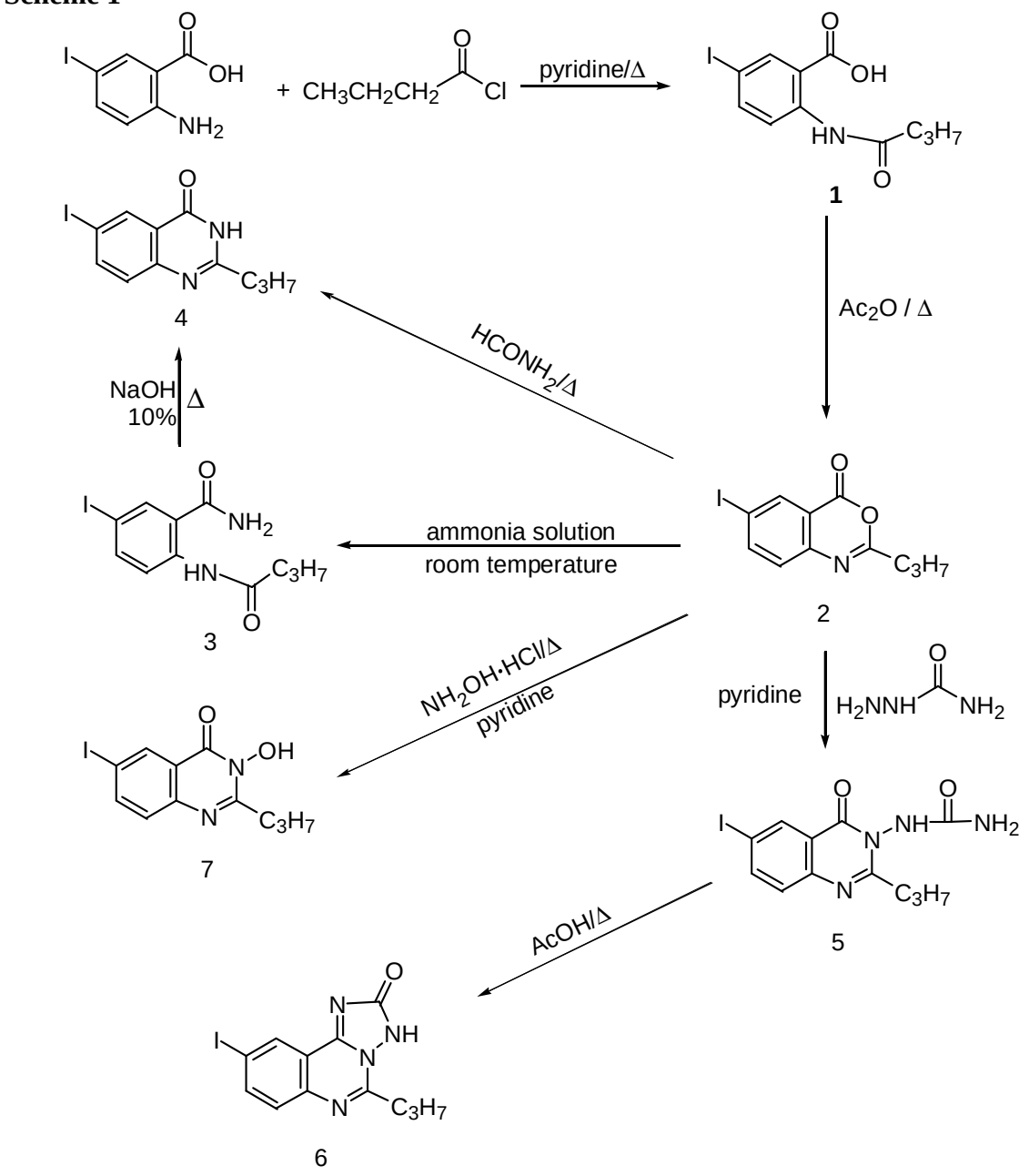


Phthalazine

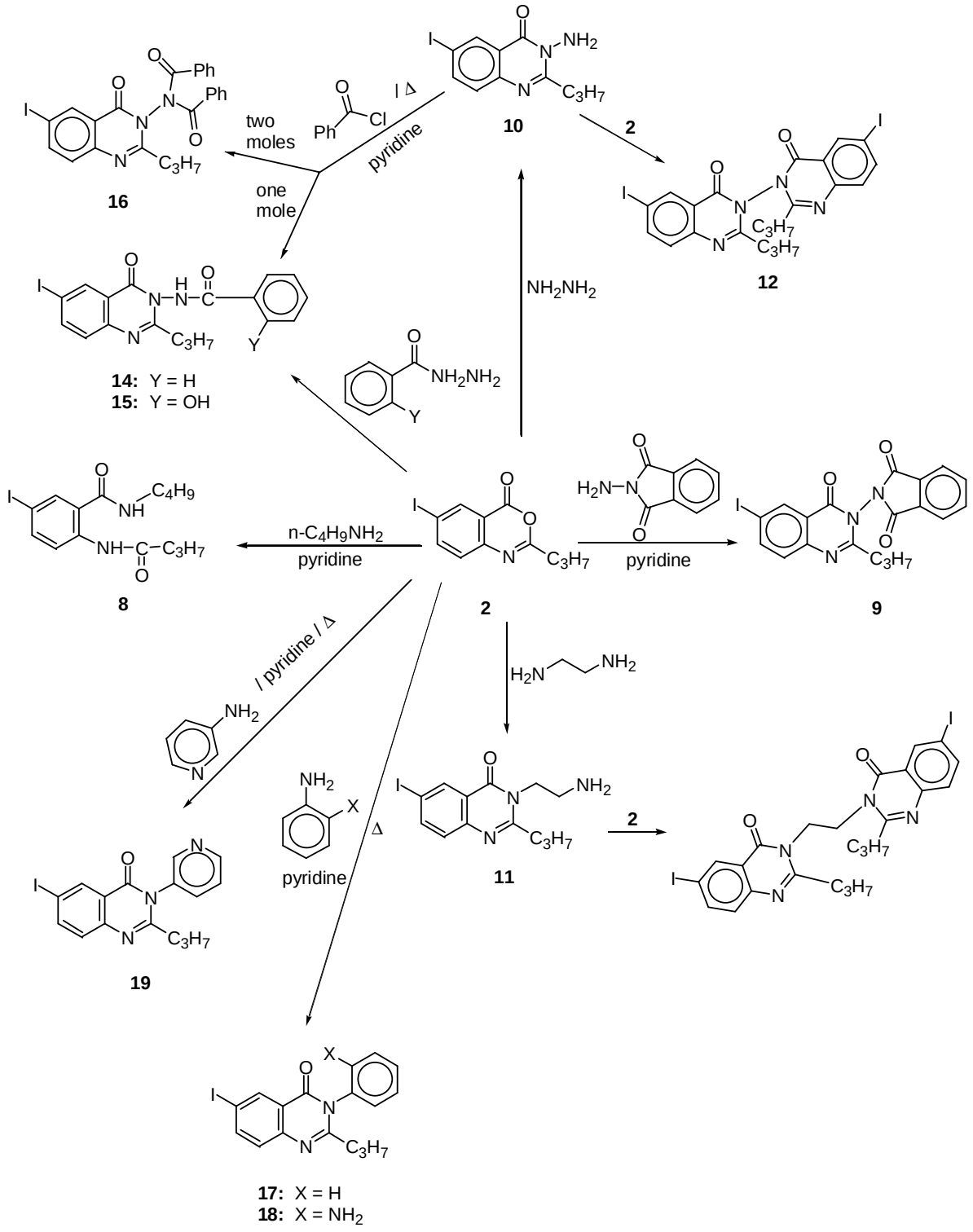


Quinazolinone

Scheme 1


pyridine/Δ
1
Ac2O / Δ
2
pyridine
H2NNH
NH2
5
AcOH/Δ
6
NH2OH·HCl/Δ
pyridine
7
ammonia solution
room temperature
3
NaOH
10%
Δ
HCONH2/Δ
4

Scheme 2


two moles
one mole
pyridine
NH2NH2
n-C4H9NH2
pyridine
pyridine
I pyridine / Δ
Δ
pyridine
16
10
12
14: Y = H
15: Y = OH
8
2
9
19
11
17: X = H
18: X = NH2

Scheme 3

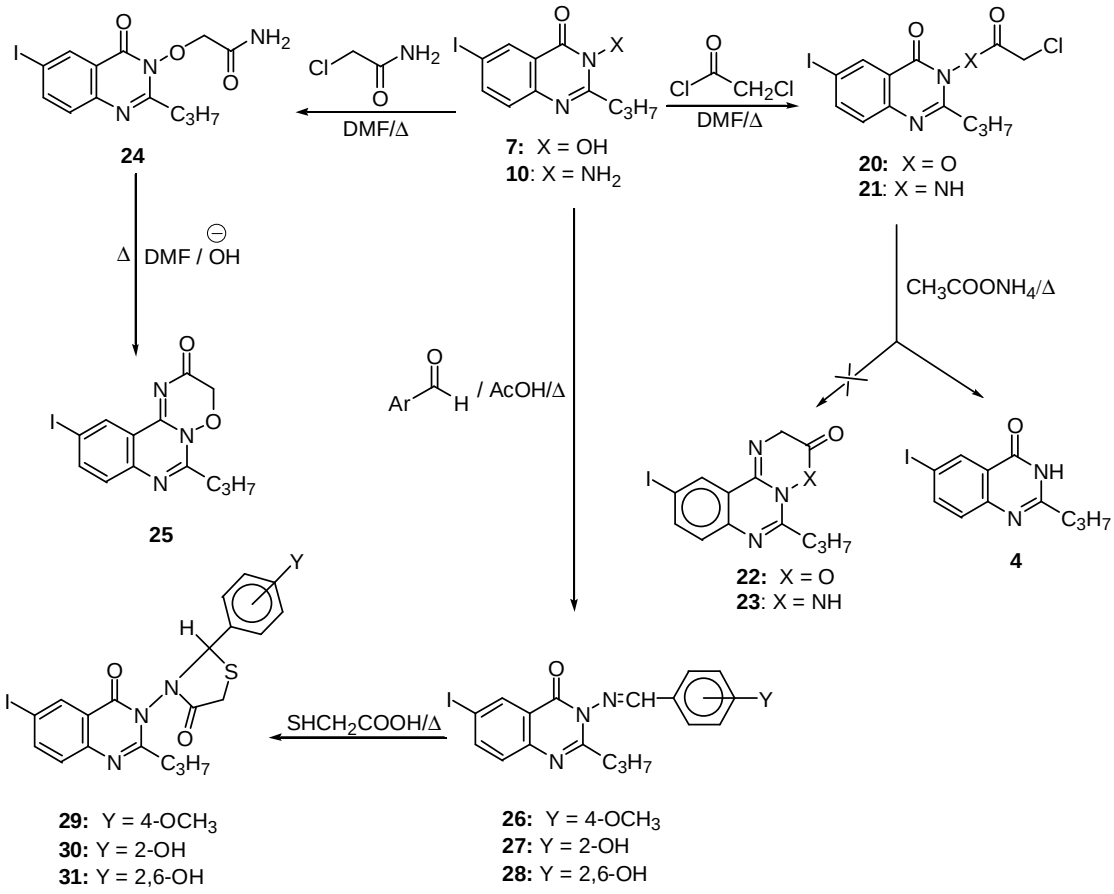

24
DMF/Δ
7: X = OH
10: X = NH2
DMF/Δ
20: X = O
21: X = NH
Δ DMF / ⊖OH
CH3COONH4/Δ
25
Ar H / AcOH/Δ
22: X = O
23: X = NH
4
SHCH2COOH/Δ
29: Y = 4-OCH3
30: Y = 2-OH
31: Y = 2,6-OH
26: Y = 4-OCH3
27: Y = 2-OH
28: Y = 2,6-OH

Table 1: Physical and analytical data of newly synthesized compounds.

Compd	Formula (Mol. Wt.)	M.P.	Yield %	Solvent	Analysis		
					C	H	N
1	$C_{11}H_{12}NO_3I$ (333)	195-07	80	Ethanol	39.63 40.02	3.6 3.44	4.2 4.36
2	$C_{11}H_{10}N_1O_2I$ (315)	85-87	75	Dioxane	41.90 41.53	3.17 3.06	4.44 4.21
3	$C_{11}H_{13}N_2O_2I$ (332)	260-262	85	Ethanol	39.76 39.42	3.91 4.11	8.43 8.67
4	$C_{11}H_{11}N_2OI$ (314)	265-267	70	Ethanol	42.03 41.83	3.50 3.68	8.91 9.13
5	$C_{12}H_{13}N_4O_2I$ (372)	250-252	85	Ethanol	38.70 39.11	3.49 3.78	15.05 14.88
6	$C_{12}H_{11}N_4OI$ (354)	165-167	65	Dioxane	40.67 40.89	3.10 3.46	15.82 16.05
7	$C_{11}H_{11}N_2O_2I$ (330)	175-177	77	Ethanol	40.00 39.79	3.33 3.00	8.48 8.15
8	$C_{15}H_{21}N_2O_2I$ (388)	95-97	84	Ethanol	46.39 46.12	5.41 5.61	7.21 7.44
9	$C_{19}H_{14}N_3O_3I$ (459)	213-215	72	Ethanol	49.67 50.02	3.05 3.26	9.15 9.19
10	$C_{11}H_{12}N_3OI$ (329)	170-172	77	Ethanol	40.12 39.94	3.64 3.66	12.76 12.89
11	$C_{13}H_{16}N_3OI$ (357)	193-195	45	Ethanol	43.70 44.12	4.48 8.66	11.76 11.54
12	$C_{22}H_{20}N_4O_2I_2$ (626)	218-220	63	Ethanol	42.17 42.20	3.19 3.31	8.94 8.96
13	$C_{24}H_{24}N_4O_2I_2$ (654)	<300	56	AcOH	44.03 43.72	3.67 3.56	8.56 8.29
14	$C_{18}H_{16}N_3O_2I$ (433)	178-180	73	AcOH	49.88 50.20	3.69 3.39	9.70 9.85
15	$C_{18}H_{16}N_3O_3I$ (449)	185-187	71	Ethanol	48.10 47.75	3.56 3.93	9.35 9.47
16	$C_{25}H_{20}N_3O_3I$ (537)	298-300	81	Ethanol	55.86 55.49	3.72 3.97	7.82 7.53
17	$C_{17}H_{15}N_2OI$ (390)	210-212	76	Ethanol	52.30 52.19	3.84 3.89	7.18 7.29
18	$C_{17}H_{16}N_3OI$ (405)	190-192	80	Dioxane	50.37 49.94	3.95 4.16	10.37 10.14
19	$C_{16}H_{14}N_3OI$ (391)	115-117	83	Ethanol	49.10 48.82	3.58 3.22	10.74 11.09
20	$C_{13}H_{12}N_2O_3ClI$ (406.5)	225-227	80	AcOH	38.37 38.06	2.95 3.13	6.88 6.56
21	$C_{13}H_{13}N_3O_2ClI$ (405.5)	260-262	71	Ethanol	38.47 38.21	3.20 3.47	10.35 9.86
24	$C_{13}H_{14}N_3O_3I$ (387)	265-267	88	Ethanol	40.31 39.96	3.61 3.83	10.85 11.06
25	$C_{13}H_{12}N_3O_2I$ (369)	255-257	71	Dioxane	42.27 41.84	3.25 3.47	11.38 11.17
26	$C_{19}H_{18}N_3O_2I$ (447)	185-187	79	AcOH	51.00 50.69	4.02 3.62	9.39 9.79

Table 1: (*Continued …)*
Physical and analytical data of newly synthesized compounds.

Compd	Formula (Mol. Wt.)	M.P.	Yield %	Solvent	Analysis		
					C	H	N
27	$C_{18}H_{167}N_3O_2I$ (433)	180-182	83	AcOH	49.88 50.22	3.69 3.61	9.70 9.75
28	$C_{18}H_{16}N_3O_3I$ (449)	175-177	70	Ethanol	48.10 48.41	3.56 3.67	9.35 9.66
29	$C_{21}H_{20}N_3O_3SI$ (521)	165-167	60	Ethanol	48.36 48.31	3.83 3.50	8.06 7.72
30	$C_{20}H_{18}N_3O_3SI$ (507)	190-192	55	Ethanol	47.33 46.89	3.55 3.16	8.28 8.47
31	$C_{20}H_{18}N_3O_4SI$ (523)	170-172	51	Ethanol	45.89 46.27	3.44 3.86	8.03 7.72

Table 2: Spectral data for the prepared compounds.

Compd	IR (V_{max}/cm^{-1}	^1H NMR (δ, ppm)	MS (relative intensity %)
1	3300-2500 (COOH), 1700, 1685 (2C=O)	0.91 (t, *J*=7.5 Hz, 3H, NHCOCH$_2$CH$_2$CH$_3$), 1.58-1.65 (m, 2H, -NHCOCH$_2$CH$_2$CH$_3$), 2.34 (t, *J*=7.5 Hz, 2H, NHCOCH$_2$CH$_2$CH$_3$), 7.77-7.84 (dd, *J*=8.5, 2.5 Hz, 1H, Ar-H$_4$), 8.18 (d, *J*=2.5 Hz, 1H, Ar-H$_6$), 8.30 (d, *J*=8.5 Hz, 1H, Ar-H$_6$), 11.04 (s, 1H,COOH) and 12.4 (s, 1H, PhNHCO).	m/z 333 (M^+, 7.25%).
2	3060 (CH-Ar), 2980 (CH, aliph.), 1740 (C=O).	0.91-0.98 (t, *J*=7.5 Hz, 3H, -CH$_2$CH$_2$CH$_3$), 1.7-1.77 (m, 2H, -CH$_2$CH$_2$CH$_3$), 2.62 (t, *J*=7.5 Hz, 2H, -CH$_2$-CH$_2$-CH$_3$), 7.34 (d, *J*=8.5 Hz, 1H, Ar-H$_8$), 8.16-8.19 (dd, *J*=8.5, 2.5 Hz, 1H, Ar-H$_7$) and 8.30 (d, *J*=2.5 Hz, 1H, Ar-H$_5$).	
3	3360, 3200 (NH_2), 3150 (NH), 1680, 1665 (2C=O)	0.97 (t, *J*=7.5 Hz, 3H, NHCOCH$_2$CH$_2$CH$_3$), 1.58-1.65 (m, 2H, -NHCOCH$_2$CH$_2$CH$_3$), 2.62 (t, *J*=7.5 Hz, 2H, -CH$_2$CH$_2$CH$_3$), 7.78-7.85 (dd, *J*=8.5, 2.5 Hz, 1H, Ar-H$_4$), 8.18 (d, *J*=2.5 Hz, 1H, Ar-H$_6$), 8.30 (d, *J*=8.5 Hz, 1H, Ar-H$_3$), 11.2 (s, 2H, CONH$_2$) and 12.3 (s, 1H, PhNHCO).	m/z 332 (M^+, 3.35%), 286 (100%), 262 (16.28).
4	3150 (NH), 3040 (CH-Ar), 2980 (CH-aliph.), 1685 (C=O).	0.91-0.94 (t, *J*=7.5 Hz, 3H, -CH$_2$CH$_2$CH$_3$), 1.69-1.76 (m, 2H, CH$_2$-CH$_2$-CH$_3$), 2.56 (t, *J*=7.5 Hz, 2H, -CH$_2$CH$_2$CH$_3$), 7.38 (d, *J*=8.5 Hz, 1H, quinazoline-H$_8$), 8.02-8.07 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H$_7$), 8.33 (d, *J*=2.5 Hz, 1H, quinazoine-H$_5$), 12.12 (s, 1H, NH-CO).	
5	3390, 3300 (NH_2), 3150 (NH), 1695 1670 (2C=O), 1620 (C=N).	0.91 (t, *J*=7.5 Hz, -CH$_2$CH$_2$CH$_3$), 1.70-1.77 (m, 2H, -CH$_2$CH$_2$CH$_3$), 2.61 (t, *J*=7.5 Hz, 2H, -CH$_2$CH$_2$CH$_3$), 7.39 (d, *J*=8.5 Hz, 1H, quinazoline-H$_8$), 7.96-8.04 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H$_7$), 8.31 (d, *J*=2.5 Hz, 1H, quinazoline-H$_5$), 10.5 (bs, 2H, CONH$_2$), 12.2 (s, 1H, N-NHCO).	
6	3150 (NH), 3050 (CH'-Ar), 2970 (CH-aliph.), 1665 (C=O).	0.91 (t, *J*=7.5 Hz, -CH$_2$CH$_2$CH$_3$), 1.69-1.76 (m, 2H, -CH$_2$-CH$_2$CH$_3$), 2.58 (t, *J*=7.5 Hz, -CH$_2$CH$_2$CH$_3$), 7.38 (d, *J*=8.5 Hz, 1H, quinazoline-H$_8$), 8.01-8.06 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H$_7$), 8.33 (d, *J*=2.5 Hz, 1H, quinazoline-H$_5$) and 11.9 (s, 1H, NHCO).	m/z 354 (M^+, 20.12%), 263 (24.91).
7	3415 (OH), 3070 (CH-Ar), 2960 (CH-aliph.), 1665 (C=O).	0.91 (t, *J*=7.5 Hz, 3H, CH$_2$CH$_2$CH$_3$), 1.70-1.77 (m, 2H, -CH$_2$CH$_2$CH$_3$), 2.60 (t, *J*=7.5 Hz, 2H, -CH$_2$CH$_2$CH$_3$), 5.1 (s, 1H, OH, D$_2$O disappeared), 7.39 (d, *J*=8.5 Hz, 1H, quinazoline-H$_8$), 8.01-8.06 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H$_7$), 8.32 (d, *J*=2.5 Hz, 1H, quinazoline-H$_5$).	

Table 2: (*Continued…*)
Spectral data for the prepared compounds.

Compd	IR (V_{max}/cm^{-1}	^{1}H NMR (δ, ppm)	MS (relative intensity %)
8	3240, 3150 (2NH) 3060 (CH-Ar), 2980 (CH-aliph.), 1685, 1665 (2C=O).	0.89-0.92 (t, *J*=7.5 Hz, 6H, -CONHCH$_2$CH$_2$CH$_3$ and NHCO-CH$_2$CH$_2$.CH$_3$), 1.35 (m, 2H, CONH-CH$_2$CH$_2$CH$_2$CH$_3$), 1.52 (m, 2H, CONHCH$_2$CH$_2$CH$_2$CH$_3$), 1.61 (m, 2H, NHCOCH$_2$CH$_2$CH$_2$CH$_3$), 2.30 (t, *J*=7.5 Hz, 2H, NHCOCH$_2$CH$_2$CH$_3$), 3.25 (q, *J*=7.5 Hz, 2H, CONHCH$_2$CH$_2$CH$_2$CH$_3$), 7.77-7.83 (dd, *J*=8.5, 2.5 Hz, 1H, Ar-H), 8.01 (d, *J*=2.5 Hz, 1H, Ar-H), 8.23 (d, *J*=8.5 Hz, 1H, Ar-H), 8.8 (s, 1H, CONH-CH$_2$-), and 11.22 (s, 1H, PhNHCO).	
9	3040 (CH-Ar), 2980 (CH-aliph.), 1800, 1730, 1690 (3C=O).	0.92-0.96 (t, *J*=7.5 Hz, 3H, -CH$_2$CH$_2$CH$_3$), 1.71-1.77 (m, 2H, CH$_2$CH$_2$CH$_3$), 2.59 (t, *J*=7.5 Hz, 2H, -CH$_2$CH$_2$CH$_3$), 7.36 (d, *J*=8.5 Hz, 1H, quinazoline-H$_8$), 7.91-7.95 (m, 4H, phthalimido-H), 8.03-8.03 (dd, *J*=8.5 Hz, 2.5 Hz, 1H, quinazoline-H$_7$) and 8.34 (d, *J*=2.5 Hz, 1H, quinazoline-H$_5$).	m/z 459 (M^+, 13.96%), 431 (100%), 292 (19.45%)
10	3495, 3325 (NH_2), 3043 (CH-Ar), 2980 (CH-aliph.), 1670 (C=O).	0.91-0.96 (t, *J*=7.5 Hz, 3H, -CH$_2$CH$_2$CH$_3$), 1.73-1.78 (m, 2H, -CH$_2$CH$_2$CH$_3$), 2.65 (t, *J*=7.5 Hz, 2H, -CH$_2$CH$_2$CH$_3$), 5.3-5.4 (bs, 2H, NH_2, D_2O disappeared), 7.34 (d, *J*=8.5 Hz, 1H, quinazoline-H$_8$), 8.16-8.19 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H$_7$) and 8.30 (d, *J*=2.5 Hz, 1H, quinazoline-H$_5$).	
11	3400, 3350 (NH_2), 3060 (CH-Ar), 2962 (CH-aliph.), 1662 (C=O).	0.96 (t, *J*=7.5 Hz, 3H, -CH$_2$CH$_2$CH$_3$), 1.69-1.75 (m, 2H, -CH$_2$CH$_2$CH$_3$), 2.56 (t, *J*=7.5 Hz, 2H, -CH$_2$CH$_2$CH$_3$), 2.95 (m, 2H, N-CH$_2$CH$_2$NH$_2$), 3.46 (t, *J*=10 Hz, 2H, N-CH$_2$CH$_2$NH$_2$), 7.33 (d, *J*=8.5 Hz, 1H, quinazoline-H$_8$), 8.09-8.13 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H$_7$), 8.30 (d, *J*=2.5 Hz, 1H, quinazoline-H$_5$), 9.1 (brs, 2H, NH_2, D_2O disappeared).	
12	3040 (CH-Ar), 2970 (CH-aliph.), 1690 (C=O).	0.93 (t, *J*=7.5 Hz, 6H, CH$_2$CH$_2$CH$_3$), 1.70-1.76 (m, 4H, CH$_2$CH$_2$CH$_3$), 2.60 (t, *J*=7.5 Hz, 4H, -CH$_2$CH$_2$CH$_3$), 7.34 (d, *J*=8.5 Hz, 2H, quinazoline-H$_8$), 8.02-8.08 (dd, *J*=8.5, 2.5 Hz, 2H, quinazoline-H$_7$) and 8.33 (d, *J*=2.5 Hz, 2H, quinazoline-H$_5$).	m/z 626 (M^+, 1.2%), 343 (8.75%), 181 (15.36%).
13		0.96 (t, *J*=7.5 Hz, 6H, -CH$_2$CH$_2$CH$_3$), 1.71-1.77 (m, 4H, -CH$_2$CH$_2$CH$_3$), 2.64 (t, *J*=7.5 Hz, 4H, -CH$_2$CH$_2$CH$_3$), 2.8 (t, *J*=10 Hz, 2H, CH$_2$-CH$_2$), 2.9 (t, *J*=10 Hz, 2H, CH$_2$CH$_2$), 7.34 (d, *J*=8.5 Hz, 2H, quinazoline-H$_8$), 8.04-8.09 (dd, *J*=8.5, 2.5 Hz, 2H, quinazoline-H$_7$) and 8.28 (d, *J*=25 Hz, 2H, quinazoline-H$_5$).	

Table 2: (*Continued…*)
Spectral data for the prepared compounds.

Compd	IR (V_{max}/cm^{-1}	^{1}H NMR (δ, ppm)	MS (relative intensity %)
14	3150 (NH), 3040 (CH-Ar), 2970 (CH-aliph.), 1690, 1670 (2C=O).	0.95 (t, *J*=7.5 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.70-1.76 (m, 2H, $CH_2\underline{CH_2}CH_3$), 2.61 (t, *J*=7.5 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 7.33 (d, *J*=8.5 Hz, 1H, Ar-H_8), 7.44-7.95 (m, 6H, Ar-H), 8.09-8.13 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7), 8.32 (d, *J*=2.5 Hz, 1H, quinazoline-H_5), and 9.8 (s, 1H, N−NHCO).	m/z 433 (M^+, 1.1%), 416 (8.30%), 243 (5.7%).
15	3250 (OH), 3150, (NH), 3050 (CH-Ar), 2980 (CH, aliph.), 1690, 1660 (2C=O).	0.95 (t, *J*=7.5 Hz, 3H, -CH2CH2$\underline{CH_3}$), 1.70-1.76 (m, 2H, $CH_2\underline{CH_2}CH_3$), 2.59 (t, *J*=7.5 Hz, $\underline{CH_2}CH_2CH_3$), 6.91-7.78 (m, 5H, 4Ar-H and quinazoline-H_8), 8.04-8.09 (dd, *J*=8.5, 2.5 Hz, quinazoline-H_7), 8.34 (d, *J*=2.5 Hz, 1H, quinazoline-H_5) and 9.8 (s, 1H, N−NHCO).	m/z 449 (M^+, 3.14%), 421 (10%), 329 (8.86%).
16	3059 (CH-Ar), 2980 (CH, aliph.), 1690, 1765, 1665 (3C=O)	0.97 (t, *J*=7.5 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.72-1.78 (m, 2H, $CH_2\underline{CH_2}CH_3$), 2.61 (t, *J*=7.5 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 7.32 (d, *J*=8.5 Hz, 1H, Ar-H_8), 7.44-7.95 (m, 11H, Ar-H), 8.04-8.09 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7) and 8.34 (d, *J*=2.5 Hz, 1H, quinazoline-H_5).	m/z 537 (M^+, 1.5%).
17	3040 (CH-Ar), 2880 (CH, aliph.), 1685 (C=O	0.91 (t, *J*=7.5 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.70-176 (m, 2H, -$CH_2\underline{CH_2}$-CH_3), 2.59 (t, *J*=7.5 Hz, 2H, -$\underline{CH_2}CH_2CH_3$), 7.00-7.64 (m, 6H, Ar-H), 7.91-8.02 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7) and 8.32 (d, *J*=2.5 Hz, 1H, quinazoline-H_5).	m/z 390 (M^+, 6.66%), 316 (44.74), 246 (41.59%).
18	3390, 3310 (NH_2), 3050 (CH-Ar), 2980 (CH, aliph.), 1690 (C=O).	0.93 (t, *J*=7.5 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.72-1.77 (m, 2H, $CH_2\underline{CH_2}CH_3$), 2.61 (t, *J*=7.5, 2H, -$\underline{CH_2}CH_2CH_3$), 4.5 (s, 2H, $\underline{NH_2}$, D_2O disappeared), 6.40-7.39 (m, 5H, Ar-H), 8.01-8.07 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7) and 8.34 (d, *J*=2.5 Hz, 1H, quinazoline-H_5).	m/z 405 (M^+, 3.11%), 263 (110%), 245 (82.85%).
19	3050 (CH-Ar), 2940 (CH, aliph.), 1690 (C=O).	0.94 (t, *J*=7.5 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.68-1.73 (m, 2H, $CH_2\underline{CH_2}CH_2$), 2.59 (t, *J*=7.5 Hz, $\underline{CH_2}$-CH_2-CH_3), 7.26-8.53 (m, 7H, Ar-H).	
20	3040 (CH-Ar), 2940 (CH, aliph.), 1750, 1690 (2C=O)	0.92 (t, *J*=7.5 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.66-1.71 (m, 2H, $CH_2\underline{CH_2}CH_3$), 2.59 (t, *J*=7.5 Hz, $\underline{CH_2}$-CH_2-CH_3), 4.27 (s, 2H, O-CO-$\underline{CH_2}$Cl), 7.33 (d, *J*=8.5 Hz, 1H, quinazoline-H_8), 7.99-8.03 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7) and 8.32 (d, *J*=2.5 Hz, 1H, quinazoline-H_5).	m/z 406 (M^+, 11.1%), 408 (M^{+2}, 3.9%), 313 (10.31%), 284 (7.1%).

Table 2: (*Continued…*)
Spectral data for the prepared compounds.

Compd	IR (V_{max}/cm^{-1}	^{1}H NMR (δ, ppm)	MS (relative intensity %)
21	3150 (NH), 3050 (CH-Ar), 2950 (CH, aliph.), 1690, 1665 (2C=O).	0.90 (t, *J*=7.5 Hz, 3H, -$CH_2CH_2\underline{CH_3}$), 1.70-1.76 (m, 2H, -$CH_2\underline{CH_2}CH_3$), 2.61 (t, *J*=7.5 Hz, 2H, -$\underline{CH_2}CH_2CH_3$), 4.21 (s, 2H, -NHCO$\underline{CH_2}$Cl), 7.34 (d, *J*=8.5 Hz, 1H, quinazoline-H_8), 8.03-8.07 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7), 8.32 (d, *J*=2.5 Hz, 1H, quinazoline-H_5), 8.9 (s, 1H, ).	
24	3400, 3320 (NH_2), 3040 (CH-Ar), 2960 (CH, aliph.), 1690, 1665 (2C=O).	0.90 (t, *J*=7.5 Hz, 3H, -$CH_2CH_2\underline{CH_3}$), 1.70-1.76 (m, 2H, -$CH_2\underline{CH_2}CH_3$), 2.51 (t, *J*=7.5 Hz, 2H, -$\underline{CH_2}CH_2CH_3$), 4.22 (s, 2H, O-$\underline{CH_2}CONH_2$), 7.33 (d, *J*=8.5 Hz, 1H, Ar-H_8), 8.02-8.07 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7), 8.32 (d, *J*=2.5 Hz, 1H, quinazoline-H_3) and 9.1 (s, 2H, CO$\underline{NH_2}$).	
25	3040 (CH-Ar), 2890 (CH, aliph.), 1695 (C=O).	0.9 (t, *J*=7.5 Hz, 3H, -$CH_2CH_2\underline{CH_3}$), 1.70-1.76 (m, 2H, -$CH_2\underline{CH_2}CH_3$), 2.61 (t, *J*=7.5 Hz, 2H, -$\underline{CH_2}CH_2CH_3$), 4.44 (s, 2H, CO$\underline{CH_2}$O), 4.64 (s, 2H, $COCH_2O$), 7.32 (d, *J*=8.5 Hz, 1H, quinazoline-H_8), 8.01-8.06 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7) and 8.32 (d, *J*=2.5 Hz, 1H, quinazoline-H_5).	
26	3050 (CH-Ar), 2890 (CH, aliph.), 1695 (C=O), 1630 (C=N).	0.9 (t, *J*=7.5 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.70-1.76 (m, 2H, -$CH_2\underline{CH_2}CH_3$), 2.6 (t, *J*=7.5 Hz, 2H, -$\underline{CH_2}CH_2CH_3$), 3.73 (s, 3H, OCH_3), 6.8-7.5 (dd, *J*=5.0 Hz, 4H, Ar-H), 7.34 (d, *J*=8.5 Hz, 1H, quinazoline-H_8), 8.01-8.06 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7), 8.15 (s, 1H, $\underline{CH}$=N), 8.30 (d, *J*=2.5 Hz, 1H, quinazoline-H_5).	
27	3300 (OH), 3050 (CH-Ar), 2980 (CH, aliph.), 1690 (C=O).	0.9 (t, *J*=7.5 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.70-1.76 (m, 2H, -$CH_2\underline{CH_2}CH_3$), 2.61 (t, *J*=7.5 Hz, 2H, -$\underline{CH_2}CH_2CH_3$), 4.2 (s, 1H, OH), 6.6-7.6 (dd, *J*=5 Hz, 4H, Ar-H), 7.3 (d, *J*=8.5 Hz, 1H, quinazoline-H_8), 8.02-8.07 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7), 8.15 (s, 1H, $\underline{CH}$=N), 8.34 (d, *J*=2.5 Hz, 1H, quinazoline-H_5).	m/z 433 (M^+ 2.81), 313 (5.9%).
28		0.9 (t, *J*=7.5 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.70-1.76 (m, 2H, -$CH_2\underline{CH_2}CH_3$), 2.56 (t, *J*=7.5 Hz, 2H, -$\underline{CH_2}CH_2CH_3$), 4.0 (s, 1H, OH), 4.3 (s, 1H, OH), 6.3-6.9 (m, 3H, Ar-H), 7.34 (d, *J*=8.5 Hz, 1H, quinazoline-H_8), 8.01-8.07 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7), 8.13 (s, 1H, $\underline{CH}$=N), 8.31 (d, *J*=2.5 Hz, 1H, quinazoline-H_5).	m/z 449 (M^+, 6.11%), 313 (15.31%), 284 (9.3%).

Table 2: (*Continued…*)
Spectral data for the prepared compounds.

Compd	IR (V_{max}/cm^{-1}	^{1}H NMR (δ, ppm)	MS (relative intensity %)
29		0.92 (t, *J*=7.5 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.70-1.76 (m, 2H, -$CH_2\underline{CH_2}CH_3$), 2.6 (t, *J*=7.5 Hz, 2H, -$\underline{CH_2}CH_2CH_3$), 3.34 (s, 2H, S$\underline{CH_2}$CO), 3.75 (s, 3H, OCH_3), 5.92 (s, 1H, C$\underline{H}$), 6.61-6.95 (dd, *J*=5 Hz, 4H, Ar-H), 7.34 (d, *J*=8.5 Hz, 1H, quinazoline-H_8), 8.01-8.08 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7), 8.3 (d, *J*=2.5 Hz, 1H, quinazoline-H_5)	
30	3550-3450 (OH), 3040 (CH-Ar), 2950 (CH, aliph.), 1760-1680 (2C=O), 1620 (C=N).	0.91 (t, *J*=7.5 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.70-1.76 (m, 2H, -$CH_2\underline{CH_2}CH_3$), 2.61 (t, *J*=7.5 Hz, $\underline{CH_2}CH_2CH_3$), 4.4 (s, 1H, OH), 5.94 (s, 1H, $\underline{CH}$), 6.61-6.89 (dd, *J*=6 Hz, 4H, Ar-H), 7.31 (d, *J*=8.5 Hz, 1H, quinazoline-H_8), 8.03-8.08 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7) and 8.34 (d, *J*=2.5 Hz, 1H, quinazoline-H_5).	
31		0.9 (t, *J*=7.5 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.10-1.77 (m, 2H, -$\underline{CH_2}CH_2CH_3$), 2.56 (t, *J*=7.5 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 3.33 (s, 2H, SCH_2CO), 4.1 (s, 1H, OH), 4.3 (s, 1H, OH), 5.93 (s, 1H, $\underline{CH}$), 6.17-6.73 (m, 3H, Ar-H), 7.34 (d, *J*=8.5 Hz, 1H, quinazoine-H_8), 8.02-8.08 (dd, *J*=8.5, 2.5 Hz, 1H, quinazoline-H_7) and 8.34 (d, *J*=2.5 Hz, 1H, quinazoline-H_5).	m/z 523 (M^+, 10.11%), 313 (47.7%), 122 (30.43%).

Table 3: Iodoquinazolines derivatives and their lipophilicity constants (log ko) and the inhibition constant of aldehyde oxidase.

Compound No.	Log Ko lipophilicity	Inhibitory constant (μM) with aldehyde oxidase
4	3.40	420
5	2.54	225
6	5.17	—
7	3.57	340
9	3.89	230
10	3.16	250
11	7.74	245
12	5.67	690
13	5.77	<700
14	4.77	330
15	4.38	550
16	6.61	580
17	5.30	370
18	4.50	330
19	3.97	485
20	3.30	170
21	3.30	140
24	2.45	210
25	5.12	—
26	6.32	265
27	5.44	640
28	5.05	570
29	5.25	600
30	4.37	430
31	3.98	465

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