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NOVEL 6,8-DIBROMO-4(3H)-QUINAZOLINONE DERIVATIVES OF PROMISING ANTI-INFLAMMATORY AND ANALGESIC PROPERTIES

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Abstract: A new series of the title compounds incorporated into diverse N and O heterocyclic moieties of pharmacoavailability as anti-inflammatory and analgesic agents, were synthesized starting with 6,8-dibromo-2-phenyl-4H-3,1-benzoxazin-4-one (**I**) by its fusion with *p*-aminoacetophenone to give the new intermediate compound, 6,8-dibromo-2-phenyl-3-(4-acetylphenyl)-4(3H)-quinazolinone (**II**). The one pot reaction of **II** with the appropriate aromatic aldehydes and anhyd. ammonium acetate in the presence of either ethyl cyanoacetate or malononitrile afforded the corresponding 2(1H)-pyridones **III** or 2(1H)-iminopyridines **IV,** respectively, while its reaction with malononitrile and aromatic aldehydes in piperidine gave 2-aminopyrans **V**. Also, reaction of the acetyl derivative **II** with aromatic aldehydes afforded the corresponding 1,3-propen-1-one derivatives **VI** which underwent cyclization with hydrazine to give the corresponding pyrazolines **VII** and with urea and/or thiourea to give the corresponding tetrahydropyrimidin-2-ones and/or tetrahydropyrimidin-2-thiones **VIII** . Some representative examples of the new compounds showed promising anti-inflammatory and analgesic activities in experimental animals.

Keywords: 6,8-dibromo-2-phenylbenzoxazin-4-one, 6,8-dibromo-2-phenyl-quinazolin-4-one, pyridine-2(1H)-ones, 2-iminopyridines, 2-aminopyrans, 1,3-propen-1-ones, pyrazolines, pyrimidinones, pyrimidine-thiones, anti-inflammatory and analgesic activities

In continuation of our drug research program and our previous efforts directed towards developing a facile synthesis of heterocycles incorporated into quinazolinone nucleus (1), which have anti-inflammatory and analgesic effect and in continuation of our recent work (2), concerning synthesis of monobromoquinazolinone derivatives that showed potent anti-inflammatory and analgesic effect sometimes higher than that of indomethacin with minimal ulcerogenic effect, it was of our interest to synthesize third safer series of new dibromoquinazolin-4-one derivatives to be evaluated for its anti-inflammatory and analgesic effect using the same technique in experimental animals to be compared with monobromo derivatives (2), to study structure activity relationship.

This work was based on the fact that several quinazoline derivatives (1-7), have potent anti-inflammatory and analgesic effect.

It is well known that the most common method to obtain substituted 3H-quinazolin-4-one derivatives is based on the aminolysis of the corresponding benzoxazin-4-ones (2). Synthesis of the starting compound, namely, 6,8-dibromo-2-phenyl-3-(4-acetylphenyl)-4(3H)-quinazolinone **(II)** was achieved by fusion of the known, 6,8-dibromo-2-phenyl-4H-3,1-benzoxazin-4-one **(I)** with *p*-aminoacetophenone. The facile one pot reaction of the ketone **II** with the appropriate aromatic aldehyde, namely, benzaldehyde, *p*-anisaldehyde, *p*-tolualdehyde, *p*-chlorobenzaldehyde, 3,4-dichlorobenzaldehyde, *o*-hydroxybenzaldehyde, naphthalene-2-carboxaldehyde and/or furfural, with ethyl cyanoacetate in the presence of anhyd. ammonium acetate in n-butanol afforded the corresponding pyridine-2(1H)-ones, namely, 6-{4-[6,8-dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-oxo-4-aryl or [4-(2-furyl)]-1,2-dihydropyridine-3-carbonitriles **(IIIa-h),** respectively, according to our recent reported method (2). In the same manner, the one pot reaction of **II** with the same aldehydes and malononitrile in the presence of anhyd. ammonium acetate in n-butanol afforded the corresponding 2(1H)-iminopyridine derivatives, namely, 6-{4-[6,8-dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-aryl or [4-(2-furyl)]-1,2-dihy-

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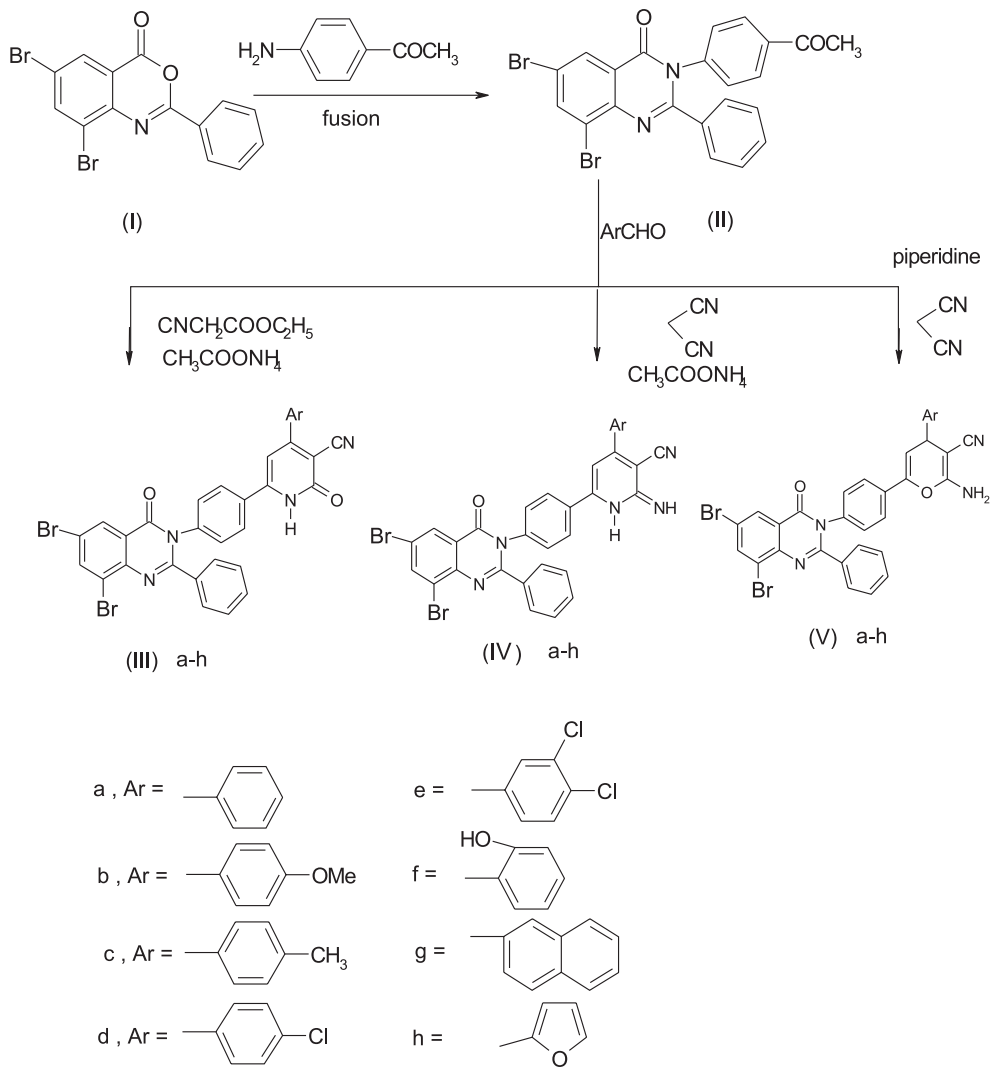
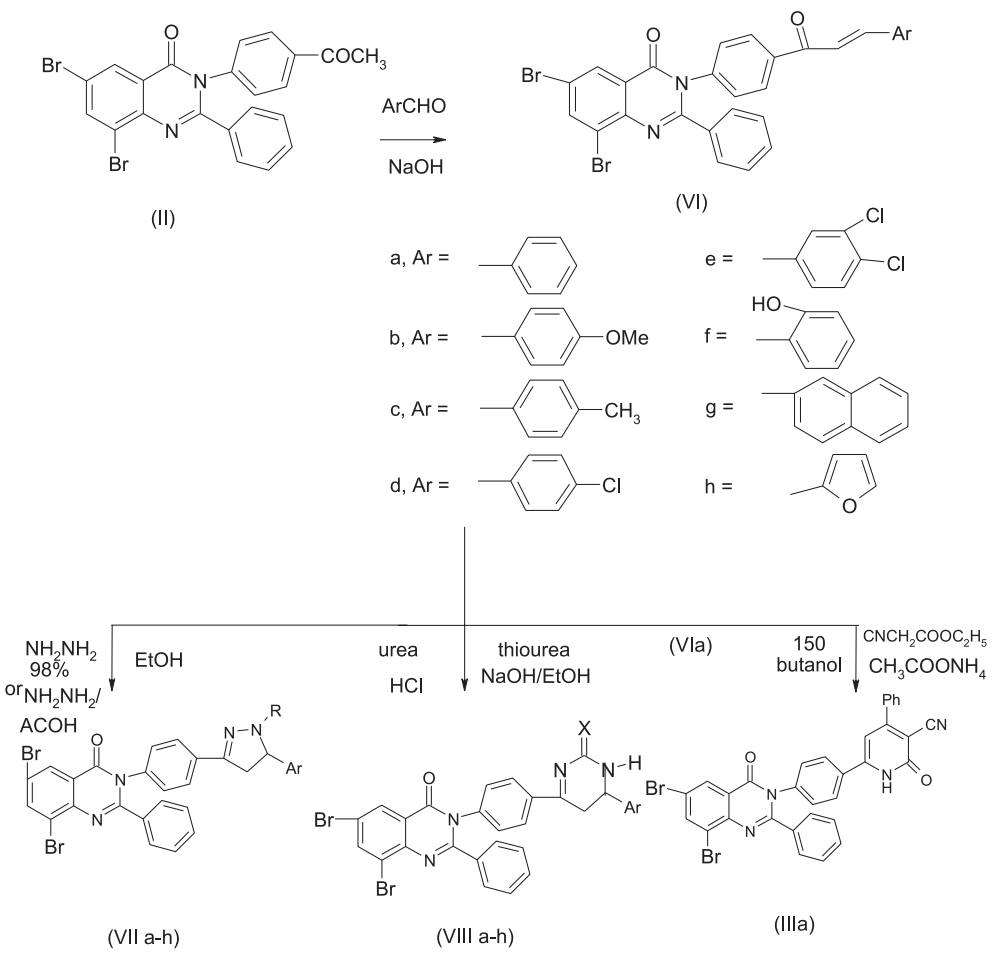
dropyridine-3-carbonitriles **(IV a-h)**, respectively, while the same one pot reaction of **II** with aromatic aldehydes and malononitrile in piperidine, gave the corresponding 2-aminopyrans, namely, 6-{4-[6-bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-amino-4-aryl-4,4-dihydropyran-3-carbonitriles **(Va-h)** (Scheme 1)

On the other hand, α,β-unsaturated ketones (chalcones), represent active intermediates for several heterocyclic ring systems of biological importance, such as pyrazolines, pyridones and pyrimidone or pyrimidine-thiones (3). So, Claisen-Schmidt condensation of ketone **II** with the same aromatic aldehydes as in Scheme 1, in the presence of NaOH, afforded the corresponding 1,3-propen-1-one derivatives (chalcones), namely, 6,8-dibromo-2-phenyl-3-{4-[(E)-3-aryl-[or 3-(2-furyl)]-acryloyl]-phenyl}-3H-quinazolin-4-ones (**VIa-h**)**,** respectively. Compounds **VIa-c** were allowed to condense with 98% hydrazine hydrate in ethanol or with hydrazine hydrate in the presence of acetic acid, to give the corresponding pyrazolines and N-acetylpyrazolines, namely, 6,8-dibromo-2-phenyl-3-{4-[5-phenyl or 5-(p-anisyl)-4,5-dihydro-1H-pyrazol-3-yl]-phenyl}-3H-quinazolin-4-ones (**VIIa,b**), respectively, or 6,8-dibromo-2-phenyl-3-{4-[5-(p-anisyl or 5-(p-tolyl)-4,5-dihydro-1-acetyl-pyrazol-3-yl]-phenyl}-3H-quinazolin-4-ones (**VIIc,d**), respectively (Scheme 2).



Scheme 1.



a R = H, Ar = Ph
b R = H, Ar = *p*-anisyl
c R = H, Ar = *p*-tolyl
d R = H, Ar = *p*-chlorophenyl
e R = $COCH_3$, Ar = Ph
f R = $COCH_3$, Ar = *p*-anisyl
g R = $COCH_3$, Ar = *p*-tolyl
h R = $COCH_3$, Ar = *p*-chlorophenyl

a X = O, Ar = Ph
b X = O, Ar = *p*-anisyl
c X = O, Ar = *p*-tolyl
d X = O, Ar = *p*-chlorophenyl
e X = S, Ar = Ph
f X = S, Ar = *p*-anisyl
g X = S, Ar = *p*-tolyl
h X = S, Ar = *p*-chlorophenyl

Scheme 2.

Also, cyclocondensation of the chalcones **VIa-c** with urea in presence of HCl or with thiourea in presence of NaOH according to a reported method (2), afforded the corresponding tetrahydropyrimidinone or tetrahydropyrimidine-thione derivatives, namely, 3-{4[6-aryl-2-oxo (or thioxo)-1,2,5,6-tetrahydropyrimidin-4-yl]-phenyl}-6,8-dibromo-2-phenyl-3H-quinazolin-4-ones (**VIIIa-h**), respectively (Scheme 2).

As a chemical investigation of the one pot reaction to obtain the 2(1H)-pyridine carbonitriles **III**, the reaction of the α,β -unsaturated ketone **VIa** with ethyl cyanoacetate in the presence of anhyd. ammonium acetate in n-butanol, afforded pyridone **IIIa** with the same melting point (288°C), and mixed melting point with that obtained by the one pot reaction, but with overall yield percentage = 55%, while the one pot reaction gave 70% yield (Scheme 2).

BIOLOGICAL EVALUATION
MATERIALS AND METHODS

Animals

Adult albino (Sprague-Dawley) rats of both sexes weighing 150-200 g and adult Swiss male albino mice weighing 20-25 g were used in the experiments. Animals were housed under standardized conditions for light and temperature and received standard rat chow and tap water *and libitum*. The animals were randomly assigned to different experimental groups, each kept in separate cage. All animal procedures were performed after approval from the Ethics Committee of the National Research Centre and in accordance with the recommendations for the proper care and use of laboratory animals (NIH publication No. 85-23, revised 1985).

Drugs and chemicals

Carrageenan lambda, Sigma-Aldrich Chemical Co. (USA) indomethacin , Khahira Pharmaceutical and Chemical Co. (Cairo, Egypt).

Anti-inflammatory effect

The carrageenan rat paw edema model of inflammation was used to evaluate the anti-inflammatory properties of the tested compounds (8). Rats were randomly assigned to treatment groups and sterile carrageenan lambda (100 mL of a 1% solution in saline) was injected sub-plantar into the right hind paw of the rat. The contralateral hind paw received the same volume of saline and served as a normal control. Carrageenan caused visible redness and pronounced swelling that was well developed by 4 h and persisted for more than 48 h (9). Hind foot-pad thickness was measured with a micrometer caliber (10, 11) , before and at 1, 2, 3 and 4 h after carrageenan injection. Eight groups of rats each of six animals were administered either saline (1 mL) and served as control or the tested compounds (10 mg/100 g b. w., orally) or indomethacin (2 mg/100 g b. w.) Different compound or indomethacin were given 1 h before the carrageenan injection.

Test on analgesia – hot plate test

The hot-plate test was performed on rats by using an electronically controlled hot-plate (Ugo Basile, Italy) heated to 52^{o}C (± 0.1^{o}C) for possible centrally mediated analgesic effect of the drugs (12). Eight groups of 6 rats each were given vehicle and/or the different compounds and the last group received indomethacin (2 mg/100 g b. w.) 60 min prior to testing. Latency to lick a hind paw (13) was recorded sequentially before and at 1 and 2 h after treatment.

Gastric ulcerogenic studies

Gastric lesions were induced in rats by absolute ethanol (1 mL of 100% ethanol orally) (14). Animals were fasted for 24 h and then divided into seven groups, one group received ethanol and served as control, and the remaining groups received 10 mg/100 g b. w. of different compounds 1 h before the ethanol was given. Rats were killed 1 h after ethanol administration by cervical dislocation after being lightly anesthetized with ether and the stomach was excised, opened along the greater curvature, rinsed with saline, extended on a plastic board and examined for mucosal lesions. The number and severity of mucosal lesions were noted and lesions were scaled as follows: petechial lesions = 1, lesions less than 1 mm = 2, lesion between 1 and 2 mm = 3, lesions between 2 and 4 mm = 4, lesions more than 4 mm = 5. A total lesion score for each animal is calculated as the total number of lesions multiplied by the respective severity scores. The results are expressed as the severity of lesions/rat (15)**.**

Statistical analysis

Results are expressed as the mean ± SE. Differences between vehicle control and treatment groups were tested using one-way ANOVA followed by the least significant difference (L.S.D.). Methods of statistical analysis were used according to (16).

RESULTS

Effect of the tested compound on carrageenan induced paw edema:

Administration of the tested compounds 60 min. prior to the carrageenan injection at a dose of 10 mg/100 g b. w. significantly inhibited the paw edema response (Table 1). The percentages of inhibition were 19.9, 16.1, 9.2, 12.6, 23.8 and 0.4 after 1 h of treatment, respectively, in comparison to control group. The positive control, indomethacin, markedly and significantly inhibited the paw edema response by 35.8, after 1 h of carrageenan injection. All compounds have an anti-inflammatory activity, except compound **VIIIc**. Compound **VIg** was the most potent one.

Effect on analgesia – hot plate test

The mean reaction time on the hot plate was significantly delayed after the administration of compounds **IIIh**, **IVf**, **Va**, and **VIg**, with a percent of

Table 1. Anti-inflammatory effects of selected investigated compounds.

Group	Dose mg/100 g b. w.	Time			
		1 h	2 h	3 h	4 h
Control	1 mL saline	82.4 ± 1.4	86.0 ± 0.97	84.4 ± 1.3	83.8 ± 1.5
II	10	66.0 ± 1.8*** (-19.9)	75.5 ± 1.5*** (-12.2)	74.5 ± 2.5* (-11.7)	73.9 ± 2.5* (-11.8)
IIIh	10	69.1 ± 3.1*** (-16.1)	73.5 ± 1.9*** (-22.1)	81.1 ± 1.2 (-3.9)	79.6 ± 2.8 (-5.0)
IVf	10	74.8 ± 4.2* (-9.2)	77.2 ± 2.4* (-10.2)	80.7 ± 2.9 (-4.4)	81.3 ± 4.9 (-3)
Va	10	72.0 ± 1.1*** (-12.6)	77.3 ± 0.9***(-10.1)	77.3 ± 0.9** (-8.4)	76.7 ± 2.1* (-8.4)
VI g	10	62.8 ± 2.4*** (-23.8)	61.6 ± 2.8*** (-28.4)	60.5 ± 2.4*** (-28.3)	63.1 ± 1.2*** (-24.7)
VIIIc	10	82.1 ± 3.0 (0.4)	79.8 ±2.9 (-7.2)	78.2 ± 2.9 (-7.3)	79.7 ± 1.8 (-4.9)
Indo.	2	52.9 ± 3.3*** (35.8)	54.2 ± 2.6*** (37.0)	57.3 ± 3.6*** (32.0)	59.0. ± 3.4*** (29.6)

Each group represents the mean ± SE of six animals; significant *vs*. control group at the corresponding hour * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; % of change from control group at the corresponding hour. Indo. = indomethacin

Table 2. Analgesic effect; hot-plate test.

Group	Dose mg/100 g b. w.	Pre-drug value	1 h		2 h	
		X^- ± SE	X^- ± SE	% of change	X^- ± SE	% of change
Control	1 mL saline	10.7 ± 0.7	10.6 ± 0.9	-	8.9 ± 0.4	-
II	10	11.5 ± 0.7	11.7 ± 0.6	1.7	12.2 ± 0.9	6.1
IIIh	10	10.1 ± 0.6	12.2 ± 1.1*	20.8	13.5 ± 0.9*	33.7
IVf	10	9.1 ± 0.3	12.2 ± 0.4**	34.1	13.5 ± 1.2*	48.4
Va	10	8.9 ± 0.4	11.6 ± 0.4**	30.3	12.0 ± 0.3**	34.8
VIg	10	9.9 ± 0.0.7	12.6 ± 0.8*	27.3	13.1 ± 1.1*	32.1
VIIIc	10	10.4 ± 0.5	10.2 ± 0.7	-1.9	11.1 ± 0.7	6.7
Indo.	2	10.2 ± 0.5	12.5 ± 0.6*	22.5	13.5 ± 0.5**	32.4

Data are presented as the mean ± SE. % of change from basal (pre-drug) value for each group.
Values are denoted by * $p < 0.05$, ** $p < 0.01$. Indo. = imdomethacin

Table 3. Effect of newly synthesized compounds II, IIIh, IVf, Va, VIg and VIIIc on gastric mucosal injury induced by ethanol on rats.

Treatment group	Number of lesions/rat X^- ± SE	% of change	Severity of lesions/rat X^- ± SE	% of change
control	11.0 ± 0.9	-	25.8 ± 3.3	-
II	8.7 ± 1.1	20.9	19.7 ± 0.3***	23.6
IIIh	10.0 ± 0.5	9.1	26.3 ± 2.2	1.9
IVf	6.0 ±0.7***	45.5	9.5 ± 1.5***	63.2
Va	3.2 ± 0.4***	70.9	4.5 ± 0.5***	82.6
VIg	2.3 ± 0.5***	79.1	8.2 ± 1.7***	68.2
VIIIc	1.5 ± 0.3***	86.4	5.3 ± 1.2***	79.5

Statistical comparison of the difference between the control group and treated groups is indicated by asterisks, *** $p < 0.001$ (Student's *t*-test)

change 20.8 , 34.1 30.3, and 27.3 after 1 h, respectively, and by 33.7, 48.4, 34.8, and 32.0 after 2 h. Indomethacin showed a significant delay by a percent of change 22.5 and 32.4 after 1, and 2 h indicating a central analgesic effect (Table 2).

Gastric ulcerogenic studies

In the ethanol control group, the number and severity of gastric mucosal lesions were 11.0 ± 0.9 and 25.8 ± 3.3, respectively. This was significantly reduced by the newly synthesized compounds compound **IVf**, **Va**, **VIg** and **VIIIc** with 45.5, 70.9, 79.1, 86.4, respectively, for the number and by 63.2, 82.6, 68.2, 79.5% for severity, as shown in Table 3.

Discussion

The development of edema in the paw of the rat after injection of carrageenan is a biphasic event.The initial of the edema is due the release of histamine and serotonin and the edema is maintained during the plateau phase by kinin like substance (17) and the second accelerating phase of swelling due to the release of prostaglandin like substances. Inhibition of edema observed in carrageenan models may be due to the ability of the different compounds to inhibit these chemical mediators of inflammation, or a stabilizating effect on lysosomal membranes.The central analgesic activity of the synthetic compounds were studied using hot plate method, and significantly increased the reaction time in hot plate test Hence, it is speculated that apart from inhibition of chemical mediators of inflammation, they may also modulate the pain response in the central nervous system.The main side effect of non-steroidal anti-inflammatory drugs is their ability to produce gastric lesions (18). Synthetic compounds under investigation inhibited the development of gastric lesions Therefore, there is a potential medicinal value of this compounds as producing anti-inflammatory and analgesic effects without side effects on gastric mucosa.

CONCLUSION

We can conclude from the results of this paper and the results of monobromoquinazolinone derivatives (2), that both mono and dibromoquinazolinone derivatives have significant anti-inflammatory and analgesic effect with minimal ulcerogenic effect. We can also conclude that monobromoquinazolinone derivatives have higher anti-inflammatory and analgesic effect with minimal ulcerogenic effect than dibromo quinazolinone derivatives.

EXPERIMENTAL

All melting points are uncorrected, elemental analyses were carried out in the microanalytical unit of National Research Centre and Cairo University, Egypt. IR spectra were recroded on FT-IR spectrophotometer-Nexus 670-Nicolet, USA and Perkin Elmer-9712 spectrophotometer. ^{1}HNMR spectra were determined on a Varian Gemini-300 MHz. and Joel-Ex270 MHz NMR spectrometers using TMS as an internal standard. Mass spectra were determined on Finnigan Mat SSQ 7000 mode, EI 70 eV (Thermo Inst. Sys. Inc. USA). Thin layer chromatography was carried out on silica gel 60 F254 (Merck) TLC plates using a chloroform, petroleum ether and methanol mixture (7 : 4 : 1, v/v/v) as the mobile phase.

6,8-Dibromo-2-phenyl-4H-3,1- benzoxazin-4-one **(I)**

This compound was prepared according to the reported method (19).

6,8-Dibromo-2-phenyl-3-(4-acetylphenyl)-4(3H) quinazolinone **(II)**

A mixture of benzoxazine **I** (19) (3.8 g, 0.01 mol) and *p*-aminoacetophenone (1.35 g, 0.01 mol) was heated together upon fusion at 150^{o}C on sand bath for 2 h. After cooling, the crude mass was crystallized twice from ethanol to give dark brown crystals of **II**, m.p. 240^{o}C, 85% yield. Analysis: for $C_{22}H_{14}Br_2N_2O_2$ (m. w. 498.17); calcd.: C, 53.04; H 2.83; N, 5.62%; found: C, 52.99; H, 3.63; N, 5.55%. IR (KBr, cm^{-1}): 3302 (C-H aromatic), 1736 (C=O of acetyl), 1685 (C=O of quinazolinone), 1633 (C=N), 1590 (C=C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.5 (3H, s, $COCH_3$), 7.5-7.8 (m, 9H, Ar-H), 8.1, 8.44 (2 s, 7-H, 5-H, quinazolinone ring). MS (m/z): 495, 497, 499 (71%, base, 69%) [M$^+$ -1], isotope abundances corresponding to its molecular formula (20).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-oxo-4-substituted aryl (or 2-furyl)]1,2-dihydropyridine-3-carbonitriles (IIIa-h)

General method

A mixture of ketone **II** (0.99 g; 0.002 mol), ethyl cyanoacetate (0.23 mL, 0.002 mol), anhyd. ammonium acetate (1.24 g; 0.016 mol) and the appropriate aldehydes namely, dichlorobenzaldehde, *p*-hydroxybenzaldehyde, naphthalene-2-carboxaldehyde and/or furan-2-carboxaldehyde (0.002 mol) in 10 mL n-butanol was refluxed for 6 h. The reaction mixture was concentrated to half of its vol-

ume under reduced pressure. After cooling, the formed precipitatet was filtered off, air dried, and recrystallized from the proper solvent to give compounds **IIIa-h,** respectively**.**

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-oxo-4-phenyl]1,2-dihydropyridine-3-carbonitrile **(IIIa)**

Crystallized from glacial acetic acid, yellow crystals, m.p. 316-318°C, yield 0.91 g (75%). Analysis: for $C_{32}H_{18}Br_2N_4O_2$, m.w. 650.32, calcd.: C, 59.10; H, 2.79; N, 8.62%; found: C, 59.00; H, 2.68; N, 8.43%. IR: (KBr, cm^{-1}): 3362 (NH), 2219 (-CN), 1737 (C=O, pyridone), 1680 (C=O, quinazolinone), and 1598 (C=C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 7.15-8.12 (17H, m, Ar-H including 1 H of pyridine), 9.45 (1 H, s, NH). MS (m/z): 647, 649, 651 (1.33%, 1.83%, 1.1%) [M^+ -1], 69 (100%).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-oxo-4-(4-methoxyphenyl)]1,2-dihydropyridine-3-carbonitrile **(IIIb)**

Crystallized from acetic acid, light brown crystals, m.p. 310-312°C, yield 1.1g (80%). Analysis: for $C_{33}H_{20}Br_2N_4O_3$, m.w. 680.34, calcd.: C, 58.26; H, 2.96, N, 8.24%; found: C, 58.00; H, 2.88; N, 8.20%. IR (KBr, cm^{-1}): 3365 (NH), 2220 (-CN), 1725 (C=O, pyridone), 1680 (C=O quinazolinone), 1595 (C=C). ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.83 (3H, s, OCH_3), 7.4-8.4 (15H, m, Ar-H including 1 H of pyridone), 9.45 (1 H, s, NH). MS (m/z): 681, 679, 677 (3.2%, 5.8%, 3.4%) [M^+ -1], 57 (100%).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-oxo-4-*p*-tolyl]1,2-dihydropyridine-3-carbonitrile **(IIIc)**

Crystallized from acetic, brown crystals, m.p. 290-292°C, yield 1.1 g (83%). Analysis: for $C_{33}H_{20}Br_2N_4O_2$, m.w. 664.35, calcd.: C, 59.66; H, 3.03; N, 8.43%; found: C, 59.60; H, 3.00; N, 8.33%. IR (KBr, cm^{-1}): 3360 (NH), 2219 (-CN), 1722 (C=O of pyridone), 1680 (C=O quinazolinone), 1595 (C=C).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-oxo-4-(4-chlorophenyl)]1,2-dihydropyridine-3-carbonitrile **(IIId)**

Crystallized from ethanol, yellow crystals, m.p. 295-297°C, yield 0.95 g (70%). Analysis: for $C_{32}H_{17}Br_2ClN_4O_2$, m .w. 684.7, calcd.: C, 56.13; H, 2.50; N, 8.18%; found: C, 56.00; H, 2.45; N, 8.02%. IR (KBr, cm^{-1}): 3352 (NH), 2217 (-CN), 1730 (C=O, pyridone), 1685 (C=O, quinazolinone), 1580 (C=C).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-oxo-4-(3,4-dichlorophenyl)]1,2-dihydropyridine-3-carbonitrile **(IIIe)**

Crystallized from ethanol, reddish brown crystals, m.p.330-332°C, yield 1 g, (72%). Analysis: for $C_{32}H_{16}Br_2Cl_2N_4O_2$, m.w. 719.21, calcd.: C, 53.44; H, 2.24; N, 7.79%; found: C, 53.39; H, 2.20; N, 7.70. IR (KBr, cm^{-1}): 3362 (NH), 2210 (-CN), 1740 (C=O, pyridone), 1684 (C=O, quinazolinone), 1593 (C=C).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-oxo-4-(2-hydroxyphenyl)]1,2-dihydropyridine-3-carbonitrile **(IIIf)**

Crystallized from acetic acid, brown crystals, m.p. 287-289°C, yield 1.1 g (80%). Analysis: for $C_{32}H_{18}Br_2N_4O_3$, m.w. 666.32, calcd.: C, 57.68; H, 2.72; N, 8.41%; found: C, 57.64; H, 2.62; N, 8.31%. IR (KBr, cm^{-1}): 3346 (NH), 3310-3240 (OH), 2200 (-CN), 1740 (C=O pyridone), 1685 (C=O, quinazolinone), 1580 (C=C).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-oxo-4-(naphthalen-2-yl)]1,2-dihydropyridine-3-carbonitrile **(IIIg)**

Crystallized from acetic acid, dark brown crystals, m.p. 318-320°C, yield 1.2 g (85%). Analysis: for $C_{36}H_{20}Br_2N_4O_2$, m.w. 700.38, calcd.: C, 61.74; H, 2.88; N, 8.00%; found: C, 61.61; H, 2.83; N, 7.99%. IR (KBr, cm^{-1}): 3352 (NH), 2218 (-CN), 1744, 1688 (C=O, pyridone and quinazolinone), 1590 (C=C).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-oxo-4-(furan-2-yl)]1,2-dihydropyridine-3-carbonitrile **(IIIh)**

Crystallized from acetic acid, dark brown crystals, m.p. 275-277°C, yield 0.95 g (75%). Analysis: for $C_{30}H_{16}Br_2N_4O_3$, m.w. 637.96, calcd.: C, 56.28; H, 2.52; N, 8.75%; found: C, 56.20; H, 2.49; N, 8.71%. IR (KBr, cm^{-1}): 3350 (NH), 2204 (-CN), 1722, 1678 (2 C=O groups), 1580 (C=C).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]phenyl}-2-imino-4-substituted aryl(or 2-furyl)-1,2-dihydropyridine-3-carbonitriles (IVa-h)

General method

A mixture of compound **II** (0.99 g, 0.002 mol), malononitrile (0.12 mL, 0.002 mol), anhyd. ammonium acetate (1.24 g, 0.016 mol) and the appropriate aldehydes which are in the same sequence as in compounds **IIIa-h**, was refluxed for 5 h. After cooling, the reaction mixture was filtered and the precipitate crystallized from the proper solvent to give the

iminopyridines **IV a-h**, respectively, in 70-80% yields.

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]phenyl}-2-imino-4-phenyl-1,2-dihydropyridine-3-carbonitrile **(IVa)**

Crystallized from ethanol, yellow crystals, m.p. 177-179°C, yield 1 g (80%). Analysis: for $C_{32}H_{19}Br_2N_5O$, m. w. 649.33, calcd.: C, 59.19, H, 2.95, N, 10.79%; found: C, 59.10, H, 2.90, N, 10.75%. IR (KBr, cm^{-1}): 3335-3225 (NH, =NH), 2200 (C=N), 1700 (C=O, quinazolinone), 1600 (C=N). MS (m/z): 649, 651, 653(1.55%, 2.4%, 1.1%) [M^+ -1], 380 (100%).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]phenyl}-2-imino-4-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbonitrile **(IVb)**

Crystallized from acetic acid, pale yellow crystals, m.p. 160-162°C, yield 1 g (76%). Analysis: for $C_{33}H_{21}Br_2N_5O_2$, m.w. 679.36, calcd.: C, 58.34, H, 3.12, N, 10.31%; found: C, 58.31, H, 3.00, N, 10.29%. IR (KBr, cm^{-1}): 3340 (NH), 2205 (C=N), 1685 (C=O, quinazolinone), 1600 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.84 (3H, s, OCH_3), 7.1-8.4 (16H, m, Ar-H), 9.60, 11.70 (2H, 2s, 2NH). MS (m/z): 677, 679, 681 (2.5% , 5.4%, 2.1%) [M^+], 187 (100%).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]phenyl}-2-imino-4-p-tolyl-1,2-dihydropyridine-3-carbonitrile **(IVc)**

Crystallized from ethanol, yellow crystals, m.p. 200-202°C, yield 0.98 g (74%). Analysis: for $C_{33}H_{21}Br_2N_5O$, m. w. 663.36, calcd.: C, 59.75, H, 3.19, N, 10.56%; found: C, 65.71, H, 3.10, N, 10.52%. IR (KBr, cm^{-1}): 3335 (NH), 2200 (C=N), 1680 (C=O, quinazolone), 1610 (C=N).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]phenyl}-2-imino-4-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile **(IVd)**

Crystallized from acetic acid, pale brown crystals, m.p. 165-167°C, yield 0.98 g (72%). Analysis: for $C_{32}H_{18}Br_2ClN_5O$, m. w. 683.78, calcd.: C, 56.21, H, 2.65, N, 10.24%; found: C, 56.00, H, 2.62, N, 10.20%. IR (KBr, cm^{-1}): 3346 (NH), 2208 (C=N), 1690 (C=O, quinazolinone), 1600(C=N).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-(3,4-dichlorophenyl)-1,2-dihydropyridine-3-carbonitrile **(IVe)**

Crystallized from ethanol, brown crystals, m.p. 270-272°C yield 1 g (70%). Analysis: for $C_{32}H_{17}Br_2Cl_2N_5O$, m.w. 718.22, calcd.: C, 53.51, H, 2.39, N, 9.75%; found: C, 53.41, H, 2.34, N, 9.70%. IR (KBr, cm^{-1}): 3360 (NH), 2210 (-CN), 1688 (C=O), 1605 (C=N), 1580 (C=C).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-(2-hydroxyphenyl)-1,2-dihydropyridine-3-carbonitrile **(IVf)**

Crystallized from ethanol, reddish brown crystals, m.p. 190-192°C, yield 0.93 g (70%). Analysis: for $C_{32}H_{19}Br_2N_5O_2$, m. w. 665.33, calcd.: C, 57.77, H, 2.88, N, 10.53%; found: C, 57.73, H, 2.84, N, 10.50%. IR (KBr, cm^{-1}): 3345 (NH), 3340-3240 (OH), 2205 (-CN), 1690 (C=O, quinazolinone), 1600 (C=N).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-(naphthalen-2-yl-)-1,2-dihydropyridine-3-carbonitrile **(IVg)**

Crystallized from ethanol, brown crystals, m.p. 290°C, yield 1 g (73%). Analysis: for $C_{36}H_{21}Br_2N_5O$, m. w. 699.39, calcd.: C, 61.82, H, 3.03, N, 10.01%; found, C, 61.80, H, 3.00, N, 9.99%. IR (KBr, cm^{-1}): 3340 (NH), 2208 (C=N), 1685 (C=O, quinazolinone), 1600 (C=N).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-(furan-2-yl)-1,2-dihydropyridine-3-carbonitrile **(IVh)**

Crystallized from ethanol, dark brown crystals, m.p. 225-227°C, yield 0.89 g (70%). Analysis: for $C_{30}H_{17}Br_2N_5O_2$, m. w. 639.30, calcd.: C, 56.36, H, 2.68, N, 10.95%; found: C, 56.30, H, 2.63, N, 10.90%. IR (KBr, cm^{-1}): 3342 (NH), 2208 (-CN), 1690 (C=O), 1600 (C=N).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-substituted aryl-4,4-dihydropyran-3-carbonitriles (Va-h)

General method

A mixture of compound **II** (0.99 g, 0.002 mol), malononitrile (0.12 mL, 0.002 mol), and the appropriate aromatic aldehyde (benzaldehyde, *p*-anisaldehyde and/or *p*-tolualdehyde) in a few drops of piperidine was refluxed for 4 h. The reaction mixture was reduced to half of its volume under reduced pressure, and cooled. The precipitate was filtered, washed with cold water, and crystallized from the proper solvent to give the aminopyrans **Va-c,** respectively, in 60-65% yields.

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-phenyl-4,4-dihydropyran-3-carbonitrile **(Va)**

Crystallized from ethanol to give brown crystals, m.p. 150-152°C, yield 0.8 g (60%). Analysis: for $C_{32}H_{20}Br_2N_4O_2$, m. w. 652.33, calcd.: C, 58.92, H, 3.09, N, 8.59%; found: C, 58.89, H, 2.99, N, 8.53%. IR (KBr, cm^{-1}): 3430-3347 (NH_2), 2220 (-CN), 1680 (C=O quinazolinone), 1600 (C=N).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-(4-methoxyphenyl)-4,4-dihydropyran-3-carbonitrile **(Vb)**

Crystallized from ethanol, reddishbrown crystals, m.p. 180-182°C. Analysis for $C_{33}H_{22}Br_2N_4O_3$, m. w. 682.36, calcd.: C, 58.09, H, 3.25, N, 8.21%; found: C, 58.00, H, 3.21, N, 8.00%. IR (KBr, cm^{-1}): 3435-3347 (NH_2), 2220 (-CN), 1685 (C=O quinazolinone), 1600 (C=N).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-(*p*-tolyl)-4,4-dihydropyran-3-carbonitrile **(Vc)**

Crystallized from glacial acetic acid, dark brown crystals, m.p. 188-190°C. Analysis: for $C_{33}H_{22}Br_2N_4O_2$, m. w. 666.36, calcd.: C, 59.48, H, 3.33, N, 8.41%; found: C, 59.42, H, 3.29, N, 8.39%. IR (KBr, cm^{-1}): 3430-3340 (NH_2), 2218 (C=N), 1690 (C=O quinazolinone), 1600 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.50 (3H, s, C-CH_3) 7.25-8.4 (17H, m, Ar-H including that of pyran ring), 9.6 (2H, s, NH_2). MS (m/z): 665, 667, 669 (3.1%, 6.2%, 2.8%) [M^+ 1], 189.39 (100%).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-(4-chlorophenyl)-4,4-dihydropyran-3-carbonitrile **(Vd)**

Crystallized from ethanol, brown crystals, m.p. 228-230°C. Analysis: for $C_{32}H_{19}Br_2ClN_4O_2$, m. w. 686.78, calcd.: C, 55.96, H, 2.79, N, 8.16%; found, C, 55.91, H, 2.72, N, 8.11%. IR (KBr, cm^{-1}): 3432-3345 (NH_2), 2215 (C=N), 1685 (C=O quinazolinone), 1600 (C=N).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-(3,4-dichlorophenyl)-4,4-dihydropyran-3-carbonitrile **(Ve)**

Crystallized from ethanol, brown crystals with m.p. 186-188°C. Analysis: for $C_{32}H_{18}Br_2Cl_2N_4O_2$, m. w. 721.22. calcd.: C, 53.29, H, 2.52, N, 7.77%; found, C, 53.24, H, 2.49, N, 7.71%. IR (KBr, cm^{-1}): 3430-3340 (NH_2), 2218 (-CN), 1695 (C=O quinazolinone), 1600 (C=N).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-(2-hydroxyphenyl)-4,4-dihydropyran-3-carbonitrile **(Vf)**

Crystallized from acetic acid, brown crystals, m.p. 179°C. Analysis: for $C_{32}H_{20}Br_2N_4O_3$, m. w. 668.33, calcd.: C, 57.51, H, 3.02, N, 8.38%; found: C, 57.48, H, 3.00, N, 8.35%. IR (KBr, cm^{-1}): 3410-3330 (NH_2), 2210 (-CN), 1688 (C=O quinazolinone), 1600 (C=N).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-(4-(naphthalene-2-yl-)-4,4-dihydropyran-3-carbonitrile **(Vg)**

Crystallized from ethanol, brown crystals, m.p. 240-242°C. Analysis: for $C_{36}H_{22}Br_2N_4O_2$, m. w. 702.39, calcd.: C, 61.56, H, 3.16, N, 7.98%; found: C, 65.50, H, 3.10, N, 7.93%; IR (KBr, cm^{-1}): 3425-3334 (NH_2), 2215 (-CN), 1690 (C=O quinazolone), 1600 (C=N).

6-{4-[6,8-Dibromo-2-phenyl-4-oxo-4H-quinazolin-3-yl]-phenyl}-2-imino-4-(furan-2-yl)-4,4-dihydropyran-3-carbonitrile **(Vh)**

Crystallized from ethanol, brown crystals, m.p. 178-180°C. Analysis: for $C_{30}H_{18}Br_2N_4O_3$, m. w. 642.30, calcd.: C, 56.10, H, 2.82, N, 8.72%; found: C, 56.05, H, 2.78, N, 8.67%, IR (KBr, cm^{-1}): 3362-3333 (NH_2), 2204 (-CN), 1690 (C=O quinazolinone), 1590 (C=N).

6,8-Dibromo-2-phenyl-3-{4-[(E)-3-substituted aryl-acryloyl]-phenyl}-3H-quinazolin-4-ones (VIa-h) (Chalcones)

General method

To a mixture of ketone **II** (0.002 mol) and the appropriate aromatic aldehyde, (0.002 mol) in ethanol (10 mL) 5% NaOH in ethyl alcohol (10 mL) was added dropwise within 15 min. The reaction mixture was refluxed for 3 h then cooled and the precipitated material was filtered, air dried and then crystallized from the proper solvent to give the chalcones **VIa-h,** respectively.

6,8-Dibromo-2-phenyl-3-{4-[(E)-3-phenyl-acryloyl]-phenyl}-3H-quinazolin-4-one **(VIa)**

Crystallized from glacial acetic acid, yellow crystals, m.p. > 342°C, yield 0.84 g (72%). Analysis: for $C_{29}H_{18}Br_2N_2O_2$, m. w. 586.27, calcd.: C, 59.41; H, 3.09; N, 4.78%; found: C, 59.38; H, 2.99, N, 4.74%. IR (KBr, cm^{-1}): 1690 (C=O quinazolinone), 1665 (C=O α,β-unsaturated ketone), 1600 (C=N).

6,8-Dibromo-2-phenyl-3-{4-[(E)-3-(4-methoxyphenyl-acryloyl]-phenyl}-3H-quinazolin-4-one **(VIb)**

Crystallized from ethanol, brown crystals, m.p. 250-252°C, yield 0.9 g (75%). Analysis: for

$C_{30}H_{20}Br_2N_2O_3$, m. w. 616.30, calcd.: C, 58.47; H, 3.27; N, 4.55%; found: C, 58.43; H, 3.23, N, 4.51%. IR (KBr, cm^{-1}): 1685 (C=O quinazolinone), 1670 (C=O of α,β-unsaturated ketone), 1610 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.80 (3H, s, OCH_3), 6.6-6.8 (2H, dd, CH=CH), 7.4-8.4 (15H, m, Ar-H including that of CH-5, CH-7 of the quinazoline ring).

6,8-Dibromo-2-phenyl-3-{4-[(E)-3-(*p*-tolyl-acryloyl]-phenyl}-3H-quinazolin-4-one **(VIc)**

Crystallized from ethanol, yellowish brown crystals, m.p. 280-282°C, yield 0.9 g (75%). Analysis: for $C_{30}H_{20}BrN_2O_2$, m. w. 600.30, calcd.: C, 60.02; H, 3.36; N, 4.67%; found: C, 60.00; H, 3.31, N, 4.63%. IR (KBr, cm^{-1}): 1685 (C=O quinazolinone), 1674 (C=O of α,β-unsaturated ketone), 1610 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.34 (3H, s, C-CH_3), 6.6-6.80 (2H, dd, CH=CH), 7.4-8.6 (15H, m, Ar-H including that of quinazoline ring). MS (m/z): at m/z 594, 596, 598 (3.1%, 5.2%, 3.8%) [M^+ -2], 429 (100%).

6,8-Dibromo-2-phenyl-3-{4-[(E)-3-(4-chlorophenyl-acryloyl]-phenyl}-3H-quinazolin-4-one **(VId)**

Crystallized from methanol, dark brown crystals, m.p. > 330°C, yield 0.86 g (70%). Analysis: for $C_{29}H_{17}Br_2ClN_2O_2$, m. w. 620.72, calcd.: C, 56.11; H, 2.76; N, 4.51%; found: C, 56.06; H, 2.73, N, 4.32%. IR (KBr, cm^{-1}): 1692 (C=O quinazolinone), 1675 (C=O of α,β-unsaturated ketone), at 1612 (C=N).

6,8-Dibromo-2-phenyl-3-{4-[(E)-3-(3,4-chlorophenyl-acryloyl]-phenyl}-3H-quinazolin-4-one **(VIe)**

Crystallized from acetic acid, yellow crystals, m.p. 292-294°C, yield 0.9 g, (69%). Analysis: for $C_{29}H_{16}Br_2Cl_2N_2O_2$, m. w. 655.16, calcd.: C, 53.16; H, 2.46; N, 4.28%; found: C, 53.12; H, 2.42, N, 4.21%. IR (KBr, cm^{-1}): 1685 (C=O quinazolinone), 1672 (C=O of α,β-unsaturated ketone), 1615 (C=N).

6,8-Dibromo-2-phenyl-3-{4-[(E)-3-(2-hydroxyphenyl-acryloyl]-phenyl}-3H-quinazolin-4-one **(VIf)**

Crystallized from methanol, dark brown crystals, m.p. 300-302°C, yield 0.95 g (79%). Analysis: for $C_{29}H_{18}Br_2N_2O_3$, m. w. 602.27, calcd.: C, 57.83; H, 3.01; N, 4.65%; found: C, 57.80; H, 2.98, N, 4.60%. IR (KBr, cm^{-1}): 1692 (C=O quinazolone), 1670 (C=O of α,β-unsaturated ketone), 1610 (C=N).

6,8-Dibromo-2-phenyl-3-{4-[(E)-3-(naphth-2-yl)-acryloyl]-phenyl}-3H-quinazolin-4-one **(VIg)**

Crystallized from ethanol, dark brown crystals, m.p. 265-267şC, yield 0.8 g (65%). Analysis: for $C_{33}H_{20}Br_2N_2O_2$, m. w. 636.33, calcd.: C, 62.29; H, 3.17; N, 4.40%; found: C, 62.23; H, 3.12, N, 4.30%. IR (KBr, cm^{-1}): 1690 (C=O quinazolone), 1670 (C=O of α,β-unsaturated ketone), 1612 (C=N). MS (m/z): 639, 637, 635(6.1%, 10.2%, 5.9%) [M^++1] 429 (100%).

6,8-Dibromo-2-phenyl-3-{4-[(E)-3-(furan-2-yl)-acryloyl]-phenyl}-3H-quinazolin-4-one **(VIh)**

Crystallized from glacial acetic acid, dark brown crystals, m.p. 254-256°C, yield 0.78 g (68%). Analysis: for $C_{27}H_{16}Br_2N_2O_3$, m. w. 576.24, calcd.: C, 56.28; H, 2.80; N, 4.86; found: C, 56.24; H, 2.72, N, 4.83%. IR (KBr, cm^{-1}): 1684 (C=O quinazolinone), 1670 (C=O of α,β-unsaturated ketone), 1618 (C=N).

5-Aryl-pyrazole derivatives (VIIa-d)

A mixture of the chalcone **VIa-d** (0.005 mol) and hydrazine hydrate (2.5 mL, 0.005 mol, 98%) in absol. ethanol (25 mL) was heated under reflux for 10 h. After cooling, the separated material was filtered, air dried and crystallized from ethanol to give **VIIa-d,** respectively.

6,8-Dibromo-2-phenyl-3-{4-[5-phenyl-4,5-dihydro-1H-pyrazol-3-yl]-phenyl}-3H-quinazolin-4-one **(VIIa)**

Crystallized from methanol, yellow crystals, m.p. 242-244°C, yield 1.8 g (60%). Analysis: for $C_{29}H_{20}Br_2N_4O$, m. w. 600.30, calcd.: C, 58.02; H, 3.36; N, 9.33%; found: C, 57.98; H, 3.32; N,9.30%. IR (KBr, cm^{-1}): 3360 (NH), disappearance of the (C=O, of chalcone) at 1660 and the presence of the characteristic band of C=O (quinazolinone) at 1690, 1600 (C=N). MS (m/z): 598, 600, 602 (7.3%, 16.1%, 8.2%) [M^+], 105 (100%).

6,8-Dibromo-2-phenyl-3-{4-[5-(*p*-anisyl)-4,5-dihydro-1H-pyrazol-3-yl]-phenyl}-3H-quinazolin-4-one **(VII b)**

Crystallized from ethanol, yellow crystals, m.p. 239-240°C, yield 1.8 g (58%). Analysis: for $C_{30}H_{22}Br_2N_4O_2$, m. w. 630.33, calcd.: C, 57.16; H, 3.52; N, 8.89%; found: C, 57.12; H, 3.50; N,8.83%. IR (KBr, cm^{-1}): 3350 (NH), 1685 (C=O, quinazolinone), 1625 (C=N). ^{1}H-NMR (DMSO, d_6, δ, ppm): 3.5, 4.4 (2H, dd, dd, CH_2 of pyrazoline), 3.8 (3H, s, OCH_3), 4.0 (1H, dd , CH of pyrazoline), 7.4-8.4 (15H, m, Ar-H).

6,8-Dibromo-2-phenyl-3-{4-[5-(*p*-tolyl)-4,5-dihydro-1H-pyrazol-3-yl]-phenyl}-3H-quinazolin-4-one **(VIIc)**

Crystallized from ethanol, brown crystals, m.p. 210-212°C, yield 1.8 g (60%). Analysis: for $C_{30}H_{22}Br_2N_4O$, m. w. 614.33, calcd.: C, 58.65; H, 3.61; N, 9.12%; found: C, 58.60; H, 3.54; N, 9.10%. IR (KBr, cm^{-1}): 3360 (NH), disappearance 1670 (C=O of chalcone), 1690 (quinazolone), 1635 (C=N) .

6,8-Dibromo-2-phenyl-3-{4-[5-(*p*-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl]-phenyl}-3H-quinazolin-4-one **(VIId)**

Crystallized from ethanol, dark brown crystals, m.p. 250-252°C, yield 1.8 g (58%). Analysis: for $C_{29}H_{19}Br_2ClN_4O$, m. w. 634.75, calcd.: C, 54.87; H, 3.02; N, 8.83%; found: C, 54.82; H, 2.97; N, 8.80%. IR (KBr, cm^{-1}): 3360 (NH), 1685 (C=O of quinazolinone), 1635 (C=N) .

5-(Aryl)-N-acetylpyrazole derivatives (VIIe-h)

The foregoing procedure was repeated using the chalcones **VIe-h** and hydrazine hydrate in the presence of glacial acetic acid (10 mL) upon refluxing for 6 h to give the N-acetylpyrazolines **VIIe-h**, respectively.

6,8-Dibromo-2-phenyl-3-{4-[5-phenyl-4,5-dihydro-1-acetyl-1H-pyrazol-3-yl]-phenyl}-3H-quinazolin-4-one **(VIIe)**

Crystallized from ethanol, yellowish brown crystals, m.p. 100-102°C, yield 1.7 g (55%). Analysis: for $C_{31}H_{22}Br_2N_4O_2$, m. w. 642.34, calcd.: C, 57.96; H, 3.45 ; N, 8.72%, found: C, 57.91; H, 3.40; N, 8.65%. IR (KBr, cm^{-1}): 1688 (C=O quinazolinone), 1670 (C=O, acetyl), 1635 (C=N). MS (m/z): 640.3, 642.4, 644.4 (9.5%, 20.3%, 10.2%) [M^+], 321 (100%).

6,8-Dibromo-2-phenyl-3-{4-[5-(*p*-anisyl)-4,5-dihydro-1-acetyl-1H-pyrazol-3-yl]-phenyl}-3H-quinazolin-4-one **(VIIf)**

Crystallized from methanol, pale yellow crystals, m.p. 110-112°C, yield 1.8 g (54%). Analysis: for $C_{32}H_{24}Br_2N_4O_3$, m. w. 672.37, calcd.: C, 57.16; H, 3.60; N, 8.33%; found: C, 57.10; H, 3.55; N,8.30%. IR (KBr, cm^{-1}): 1678 (C=O quinazolinone), 1668 (C=O, acetyl), 1635 (C=N). MS (m/z): 670, 672, 674 (1.3%, 2.4%, 1.1%) [M^+], 395 (100%).

6,8-Dibromo-2-phenyl-3-{4-[5-(p-tolyl)-4,5-dihydro-1-acetyl-1H-pyrazol-3-yl]-phenyl}-3H-quinazolin-4-one **(VIIg)**

Crystallized from ethanol, dark brown crystals, m.p. 105-107°C, yield 1.7 g (54%). Analysis: for $C_{32}H_{24}Br_2N_4O_2$, m. w. 656.37, calcd.: C, 58.56; H, 3.69 ; N, 8.54%; found: C, 58.51; H, 3.62; N,8.52%. IR (KBr, cm^{-1}): 1685 (C=O quinazolinone), 1670 (C=O, acetyl), 1635 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.1 (3H, s , $COCH_3$), 2.32 (3H, s, CH_3), 3.88, 4.4 (2H, dd, dd, CH_2 of pyrazoline), at 4.1 (1H, dd, CH of pyrazoline), 7.28-8.2(15H, m, Ar-H including those of quinazolinone ring).

6,8-Dibromo-2-phenyl-3-{4-[5-(*p*-chlorophenyl)-4,5-dihydro-1-acetyl-1H-pyrazol-3-yl]-phenyl}-3H-quinazolin-4-one **(VIIh)**

Crystallized from ethanol, reddish brown crystals, m.p.140-142°C, yield 1.7 g (52%). Analysis: for $C_{31}H_{21}Br_2ClN_4O_2$, m. w. 676.79, calcd.: C, 55.01; H, 3.13 ; N, 8.28%; found: C, 54.98; H, 3.09; N, 8.24%. IR (KBr, cm^{-1}): 1690 (C=O quinazolinone), 1685 (C=O, acetyl), 1635 (C=N).

6-Phenyl-1,2,5,6-tetyrahydropyrimidone derivatives (VIIIa-d)

A mixture of the chalcone **VIa-d** (0.005 mol) and urea (0.5 g, 0.005 mol) in ethanol (20 mL) and conc. HCl (5 mL) was refluxed for 7 h. The reaction mixture was concentrated to half of its volume, cooled and neutralized with NH_4OH solution. The precipitated solid was filtered, washed with water, air dried and crystallized from the proper solvent to give compounds **VIIIa-d**.

3-{4-[6-Phenyl-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl]-phenyl}-6,8-dibromo-2-phenyl-3H-quinazolin-4-one **(VIIIa)**

Crystallized from acetic acid, yellow crystals, m.p. 108-110°C, yield 2.1 g (70%). Analysis: for $C_{30}H_{20}Br_2N_4O_2$ m. w. 628.31, calcd.: C, 57.35; H, 3.21; N, 8.92%; found: C, 57.30; H, 3.14; N,8.89%. IR (KBr, cm^{-1}): 3200-3600 (br, OH enolic of pyrimidine), 1688 (C=O quinazolinone), 1618 (C=N).

3-{4-[6-(*p*-Anisyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl]-phenyl}-6,8-dibromo-2-phenyl-3H-quinazolin-4-one **(VIIIb)**

Crystallized from ethanol, brown crystals, m.p. 100-102°C, yield 1.97 g (60%). Analysis: for $C_{31}H_{22}Br_2N_4O_3$, m. w. 658.34, calcd.: C , 56.56; H, 3.37; N, 8.51%; found: C, 56.51; H, 3.34; N,8.45%. ^{1}H-NMR spectrum (DMSO-d_6, δ, ppm): 3.5 (2H, d, CH_2 of pyrimidinone), 3.9 (3H, s, OCH_3), 5.1 (1H, t, CH of pyrimidinone), 7.2-8.5 (16H, m, Ar-H including that of pyrimidone and quinazolone rings). MS (m/z): 656.6, 658.6, 660.6 (5.30%, 10.2%, 6.1%) [M^+], 339 (100%).

3-{4-[6-(*p*-Tolyl)-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl]-phenyl}-6,8-dibromo-2-phenyl-3H-quinazolin-4-one **(VIIIc)**

Crystallized from ethanol, yellowish brown crystals, m.p. 112-114°C, yield 2.24 g (70%). Analysis: for $C_{31}H_{22}Br_2N_4O_2$, m. w. 642.34, calcd.: C, 57.96; H, 3.45; N, 8.72%; found: , C, 57.93; H, 3.41; N,8.69%. IR (KBr, cm^{-1}): 3200-3600 (br, OH enolic of pyrimidine), 1685 (C=O quinazolinone), 1618 (C=N). MS (m/z): 625, 627, 629 (4.6%, 10.1%, 5.3%) [M^+- CH_3], 339 (100%).

3-{4-[6-(*p*-Chlorophenyl-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl]-phenyl}-6,8-dibromo-2-phenyl-3H-quinazolin-4-one **(VIIId)**

Crystallized from ethanol, dark brown crystals, m.p. 107-109°C, yield 2.31 g (70%). Analysis: for $C_{30}H_{19}Br_2ClN_4O_2$ m. w. 662.76, calcd.: C, 54.37; H, 2.89; N, 8.45%; found: C, 54.30; H, 2.82; N,8.40%. IR (KBr, cm^{-1}): 3200-3600(br, OH enolic of pyrimidine), 1685 (C=O quinazolone), 1618 (C=N).

Preparation of 6-(p-aryl)-1,2,5,6-tetrahydropyrimidine-thione derivatives (VIIIe-h)

The foregoing procedure was carried out using ketone **VIe-h** and thiourea in the presence of 0.5 g of NaOH in 5 mL of water, instead of urea. The mixture was refluxed in ethanol (25 mL) for 6 h, then concentrated under vaccum and neutralized with dilute HCl. The precipitated material was filtered, washed with water, dried and crystallized from the proper solvent to give compounds **VIIIe-h,** respectively.

3-{4-[6-Phenyl-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl]phenyl-6,8-dibromo-2-phenyl-3H-quinazolin-4-one **(VIIIe)**

Crystallized from ethanol, yellow crystals, m.p. 150-152°C, yield 2 g (65%). Analysis: for $C_{30}H_{20}Br_2N_4OS$, m. w. 644.38, calcd.: C, 55.92; H, 3.13; N, 8.69%; found: C, 55.90; H, 3.10; N, 8.65I%. IR (KBr, cm^{-1}): 3220 (NH), 1680 (C=O, quinazolinone), 1640 (C=N), 1275 (C=S).

3-{4-[6-(*p*-Anisyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl]phenyl-6,8-dibromo-2-phenyl-3H-quinazolin-4-ones **(VIIIf)**

Crystallized from ethanol, brown crystals, m.p. 147-14°C, yield 2.35 g (70%). Analysis: for $C_{31}H_{22}Br_2N_4O_2S$, m. w. 674.40, calcd.: C, 55.21; H, 3.29; N, 8.31%; found: C, 55.16; H, 3.25; N,8.28%. IR (KBr, cm^{-1}): 3220 (NH), 1690 (C=O, quinazolinone), 1640 (C=N), 1275 (C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.34 (3H, s, CH_3), 3.70 (2H, d, CH_2 of pyrimidine), 5.1 (1H, t, CH of pyrimidinone), 7.0-8.4 (16H, m, Ar-H including 1H of pyrimidone). MS (m/z): 674, 676, 678 (2.4%, 4.4%, 2.8%) [M^+ +2], 220 (100%).

3-{4-[6-(*p*-Tolyl-2-thioxo-1,2-dihydropyrimidin-4-yl]phenyl-6,8-dibromo-2-phenyl-3H-quinazolin-4-one **(VIIIg)**

Crystallized from ethanol, brown crystals, m.p. 118-120°C, yield 2 g (62%). Analysis: for $C_{31}H_{22}Br_2N_4OS$, m. w. 658.41, calcd.: C, 56.55; H, 3.37; N, 8.51%; found: C, 56.51; H, 3.32; N, 8.45%. IR (KBr, cm^{-1}): 3220 (NH), 1688 (C=O, quinazolone), 1640 (C=N), 1275 (C=S). MS (M/z): 643.1, 645.3, 647.15 (1.3%, 2.11%, 1.4%) [M^+-CH_3], 23 (100%).

3-{4-[6-(*p*-Chlorophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl]phenyl-6,8-dibromo-2-phenyl-3H-quinazolin-4-one **(VIIIh)**

Crystallized from ethanol, dark brown crystals, m.p. 130-132°C, yield 2 g (62%). Analysis: for $C_{30}H_{19}Br_2ClN_4OS$, m. w. 678.82, calcd.: %C, 53.08; H, 2.82; N, 8.25%; found: C, 52.59; H, 2.79; N, 8.20%. IR (KBr, cm^{-1}): 3220 (NH), 1690 (C=O, quinazolinone), 1640(C=N), 1275(C=S).

Preparation of the pyridone-carbonitrile IIIa (from chalcone VIa)

A mixture of chalcone **VIa** (1.17 g, 0.002 mol), ethyl cyanoacetate (0.23 mL, 0.002 mol) and anhyd. ammonium acetate (1.24 g, 0.016 mol) was refluxed in n-butanol at 150°C for 4 h to give 55% yield of compound **IIIa** with the same m.p. 300-302°C as obtained by the one pot synthesis of compound **III**a, mixed m.p. 302°C. This indicates that the one pot reaction gives better yields (72%) of the pyridone carbonitriles than for those obtained from chalcones.

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