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NOVEL 3-(P-SUBSTITUTED PHENYL)-6-BROMO-4(3H)-QUINAZOLINONE DERIVATIVES OF PROMISING ANTIINFLAMMATORY 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 or analgesic agents, were synthesized starting with 6-bromo-2-phenyl-4H-3,1-benzoxazin-4-one **(I)** by its fusion with *p*-aminoacetophenone to give the intermediate compound, 6-bromo-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)-pyridone derivatives **III** or 2(1H)- iminopyridine derivatives **IV,** respectively, while its reaction with malononitrile and aromatic aldehydes in piperdine gave the 2-aminopyrans **V**. Also reaction of the acetyl derivative **II** with different aromatic aldehydes afforded the corresponding 1,3-propen-1-one derivatives **VI** which underwent cyclization with hydrazines to give the corresponding pyrazoline derivatives **VII** and with urea or thiourea to give the pyrimidones or pyrimidinethiones **VIII** . Some representative examples of the new compounds showed promising anti-inflammatory and analgesic activities in experimental animals.

Keywords : 6-bromo-2-phenylbenzoxazin-4-one, 6-bromo-2-phenylquinazolin-4-one, pyridine-2(1H)-one, 2-iminopyridines, 2-aminopyrans, 1,3-propen-1-ones, pyrazolines, pyrimidones, pyrimidinethiones, antiinflammatory and analgesic activities evaluation.

Quinazolines and quinazolinone derivatives have diverse medicinal applications as chemotherapeutic agents (1-4). 3H-Quinazolin-4-one moiety is a frequently encountered unit in natural products (5), such as the alkaloids L-Vasicinone **1** (6), Chrysogine **2** (7) and drugs such as the sedative hypnotic methaqualone **3** (8), the diuretic and antihypertensive quinethazone **4** and metolazone **5** (9, 10). Besides, several other quinazolinone derivatives exhibit a multitude of interesting pharmacological activities including anticonvulsant, antidiabetic (11, 12), analgesic (13), sedative (14) and antiinflammatory activities (15, 16). Some other quinazoline derivatives display a wide diversity of enzyme inhibitory activity, and so many publications expected them to be useful for patients with acquired immune deficiency syndrome (AIDS), cancer chemotherapy and organ transplantation (17-19).

Besides the diverse biological activity ascribed to quinazolinone derivatives (13, 14) and enzyme inhibitory effect of several 6-bromoquinazolinones (20, 21) and based on continuation of our drug research program on the development of safe quinazolinone antiinflammatory agents (16), it was of interest to synthesize a novel series of 6-bromoquinazolin-4(3H)-ones incorporated into other heterocyclic moieties such as pyridine, pyran, pyrazoline, pyrimidone and/or pyrimidinethione ring systems to be evaluated for their antiinflammatory and analgesic activities.

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 (16).

The synthesis of a starting compound, namely, 6-bromo-2-phenyl-3-(4-acetylphenyl)-4(3H)quinazolinone **(II)** was achieved by fusion of 6-bromo-2-phenyl-4H-benz[3,1]oxazin-4-one **(I)** (21) with *p*-aminoacetophenone. The one pot reaction of ketone **II** with the appropriate aromatic aldehydes, namely, benzaldehyde, *p*-anisaldehyde, *p*-tolualdehyde, *p*-chlorobenzaldehyde, 3,4-dichlorobenzaldehyde, *o*-hydroxybenzaldehyde, naphthalene-2-carboxaldehyde and/or furfural, with ethyl cyanoacetate in the

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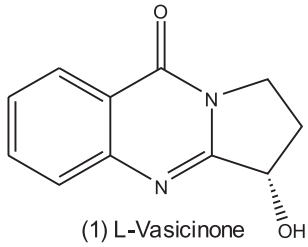
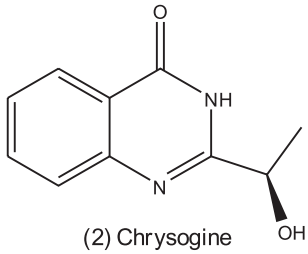
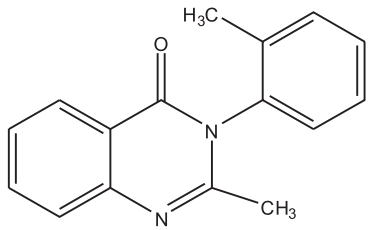


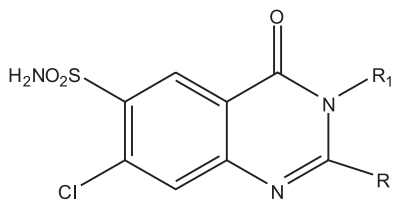
(1) L-Vasicinone



(2) Chrysogine



(3) Methaqualone



(4) quinethazone, R= ethyl; R_1= H

(5) metolazone R= methyl; R_1= o-tolyl

presence of anhydrous ammonium acetate, afforded the corresponding pyridin-2(1H)-ones, namely, 6-[4-(6-bromo-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. In the same manner, the one pot reaction of **II** with the same aldehydes and malononitrile in the presence of anhydrous ammonium acetate afforded the corresponding 2(1H)-iminopyridine derivatives, namely, 6-[4-(6-bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl]-2-imino-4-aryl or [4-(2-furyl)]-1,2-dihydropyridine-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-c)** (Scheme 1).

On the other hand, α,β-unsaturated ketones (chalcones), represent active intermediates for several heterocyclic ring systems, such as pyrazolines, pyridones and pyrimidone or pyrimidine-thiones, of biological importance (15). 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-bromo-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 hydrazine hydrate 98% in ethanol or with hydrazine hydrate in the presence of acetic acid to give the corresponding pyrazolines and N-acetylpyrazolines, namely, 6-bromo-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-bromo-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).

Also, cyclocondensation of the chalcones **VIa-c** with urea in the presence of HCl or with thiourea in the presence of NaOH afforded the corresponding pyrimidones or pyrimidinethiones, namely, 3-{4[6-aryl-2-oxo (or thioxo)-1,2-dihydropyrimidin-4-yl]-phenyl}6-bromo-2-phenyl-3H-quinazolin-4-ones **(VIIIa-d**), respectively (Scheme 2).

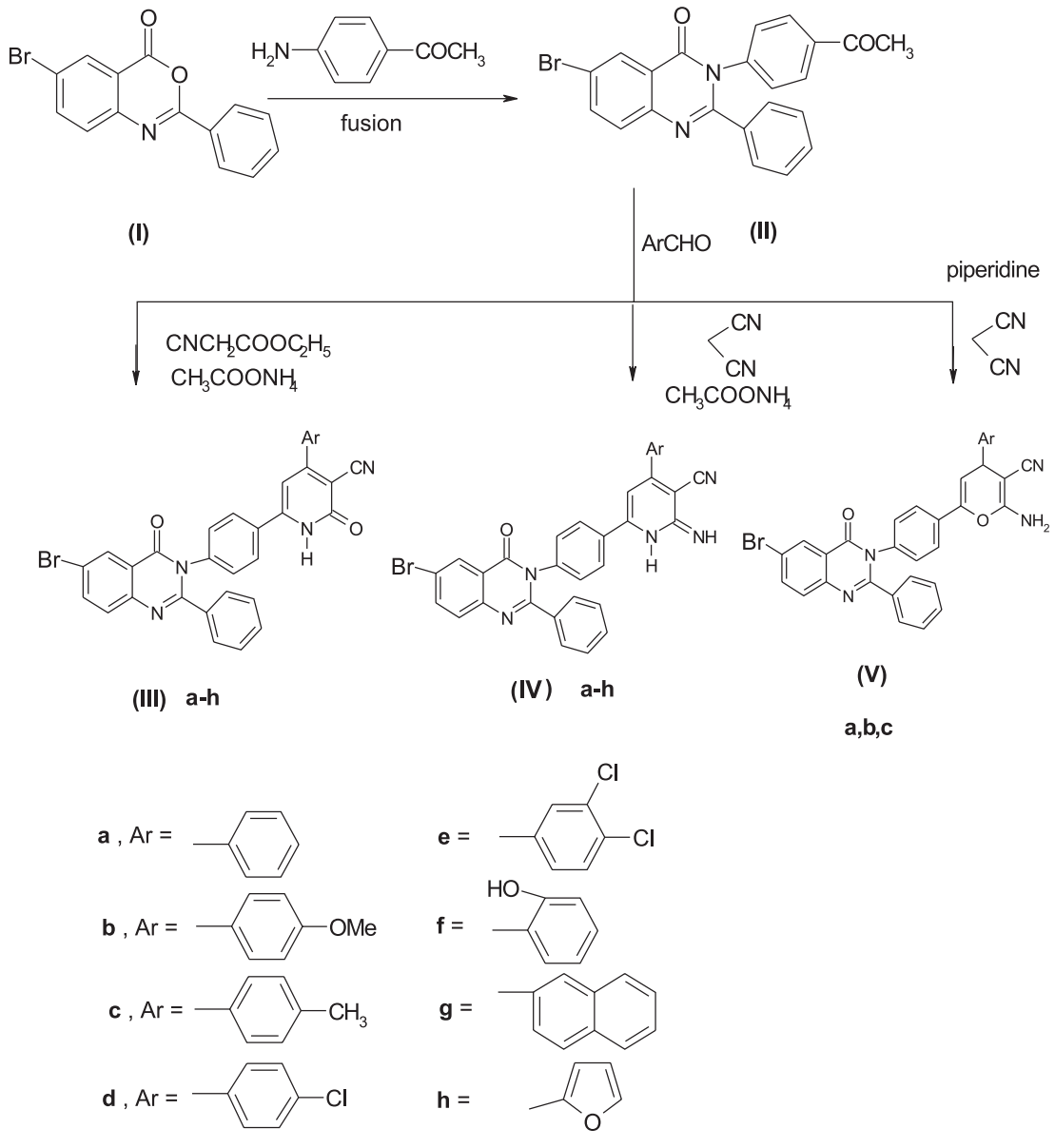
In the same manner, as a chemical investigation of the one pot reaction to obtain the 2(1H)-pyridine carbonitriles **III**, the reaction of the α,β -unsaturated ketone **VIa** with ethyl cyano acetate in the presence of anhydrous ammonium acetate in butanol afforded pyridone **IIIa** with the same melting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

Biological evaluation

Materials and methods

Animals

Adult albino rats (Sprague-Dacoley) 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 differ-



Scheme 1.

ent 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

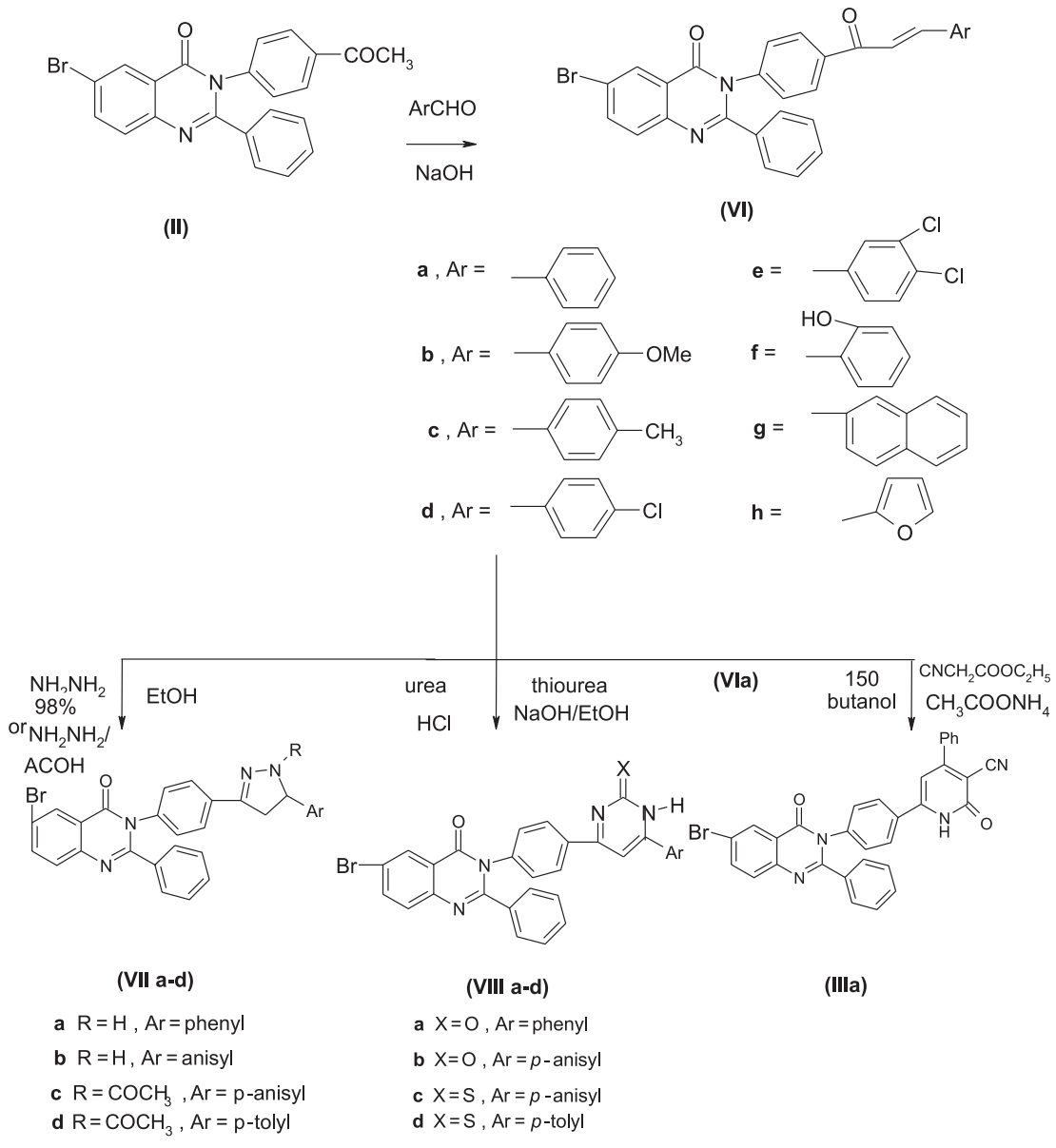
1-Carrageenan lambda, Sigma – Aldrich Chemical Company (USA). 2-Indomethacin, Kahira Pharmaceutical and Chemical Company (Cairo, Egypt).

Determination of median lethal dose (LD_{50})

The approximate LD_{50} of the different compounds were determined using mice. Compounds were dissolved in distilled water and given orally to groups of 6 mice each. Each group was given a different dose of each compound. The animals were observed for any toxic signs and the percentage mortality for each group was recorded after 24 h.

Antiinflammatory effect:

The carrageenan rat paw edema model of inflammation was used to evaluate the antiinflam-



Scheme 2.

matory properties of the tested compounds (22). Rats were randomly assigned to treatment groups and sterile carrageenan lambda (100 mL of a 1% solution in saline) was injected under the sub-plantar skin of 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 (23). Hind foot-pad thickness was measured with a micrometer caliber (24, 25), 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 a control or the tested compounds (10 mg/100 g body weight, orally) or indomethacin (2 mg/100 g body weight) given 1 h before the carrageenan injection.

Tests 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°C (± 0.1°C). For possible

centrally mediated analgesic effect of the drugs (26), eight groups of 6 rats each were given vehicle and/or the different compounds and the last group received indomethacin (2 mg/100 g body weight) 60 min prior to testing. Latency to lick a hind paw or jumping (27) was recorded sequentially before and at 1 and 2 h post treatment.

Acetic acid-induced writhing

Eight separate groups of 6 mice each were administered the vehicle and/or the different compounds (10 mg/100 g body weight). After 60 min interval, an *i.p.* injection of 0.6% acetic acid was administered (28, 29). Each mice was then placed in an individual clear plastic observational chamber and the total number of writhes made by the animal was counted for 20 min.

Gastric ulcerogenic studies

Gastric lesions were induced in rats by absolute ethanol (1 mL of 100 %, orally) (30). Animals were fasted for 24 h and then divided into seven groups; one group received ethanol and served as a control and the remaining groups received 10 mg/100 g body weight 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 (31).

Statistical analysis

Results are expressed as the mean ± S.E. 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 done according to Armitage et al. (32).

Toxicological study

Oral administration to mice of different doses of compounds **IIIh,VIg,VIIc, Vc, IVf and II** up to 1 g/kg body weight induced no obvious toxic effects and all the treated animals were still alive after 24 h.

RESULTS

Effect of the tested compounds on carrageenan induced paw edema

Administration of the tested compounds 60 min prior to carrageenan injection at a dose of 10 mg/100 g body weight significantly inhibited the paw edema response (Table 1). The percentages of inhibition were 30.6, 26.2, 16.4, 19.1, 11.7 and 21.4 after one hour of treatment, respectively, in comparison to control group, the positive control, indomethacin, markedly and significantly inhibited the paw edema response by 43.2%, after one hour of carrageenan injection. All compounds have an anti-inflammatory activity. 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**, **VIg**, **VIIc**, **Vc**, **IVf** and **II** with the percent of change 14.7, 12.5, 26.7, 59.3 and 33.3 after 1 h, respectively, and by 13.3, 15, 50, 28.8 and 50.0 after 2 h. Indomethacin showed a significant delay by 51.1 and 78.9 percent of change after 1 and 2 h, respectively, indicating a central analgesic effect (Table 2a).

Acetic acid induced writhing

Acetic acid induced writhing was significantly reduced in mice receiving all tested compounds. The antinociceptive activity of the tested compounds was maximal for the reduction of the writhing score by 80.4 and 80.2% for compounds **Vc** and **IVf**, respectively, indicating peripheral analgesic effect. The positive control, indomethacin, inhibited the writhing response by 77.8% i.e. the analgesic effect of compounds **Vc** , **IVf** was higher than that of indomethacin (Table 2-b).

Gastric ulcerogenic studies

In the ethyl alcohol control group, the number and severity of gastric mucosal lesions were 35.5 + 2.0 and 80.2 + 2.0, respectively. This was significantly reduced by the newly synthesized compounds and compounds **IIIh, VIg, Vc, and II** were the most potent with 93.8, 91.2 92.1 and 91.6%, respectively, 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 to the release of histamine

and serotonin and the edema is maintained during the plateau phase by kinin like substance (33) 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 studies using hot plate method and peripheral activity in acetic acid induced writhing test. The compounds significantly increased the reaction time in hot-plate test and also reduced the writhing response in mice injected with acetic acid, indicating their ability to inhibit the permeability of the small blood vessels (34). 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 antiinflammatory drugs is their ability to produce gastric lesions (35). The synthetic new quinazolone compounds under investigation inhibited the development of gastric lesions Therefore, the potential medicinal value of these compounds may be as antiinflammatory and analgesic agents which affects without side effects on gastric mucosa.

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}H NMR spectra were determined on a Varian-Gemmini-300 MHz. and Joel-Ex 270 MHz NMR spectrometer 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) plates.

6-Bromo-2-phenyl-4H-3,1 benzoxazin-4-one (I)

Compound prepared according to the reported method, m.p 180^{o}C (21).

6-Bromo-2-phenyl-3-(4-acetylphenyl)-4(3H)-quinazolinone (II)

A mixture of compound **I** (2.9 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 from ethanol twice to give dark brown crystals of **II**, m.p. 215^{o}C in 82% yield.

Analysis: for $C_{22}H_{15}BrN_2O_2$ (M. w. 419.2) Calcd.: %C, 63.0, %H 3.6. %N 6.7. Found: %C, 63.32, %H 3.63, %N 6.55.

IR (KBr, cm^{-1}): 3302 (C-H aromatic), 1762 (C=O of quinazolone), 1685 (C=O of acetyl), 1633 (C=N) and at 1590 (C=C). ^{1}H NMR (DMSO-d_6, δ, ppm): 2.45 (s, 3H, $COCH_3$), 7.4-7.7 (m, 9H, Ar-H), 7.9-8.4 (m, 3H, quinazoline ring). MS (m/e): M^+

Table 1. Antiinflammatory effects

Group	Dose mg/100 g b. w.	1 h	2 h	3 h	4 h
Control		74.2 ± 5.0	80.4 ± 3.6	95.2 ± 2.8	95.8 ± 2.7
IIIh	10	51.5 ± 0.7** (-30.6)	67.3 ± 3.4* (-19.5)	81.9 ±1.5** (-14)	80.9 ± 1.1*** (-15.6)
VIg	10	58.8 ± 1.3* (-26.2)	62.6 ± 2.2** (-22.1)	62.4 ± 1.5*** (-34. 5)	61.7 ± 2.1*** (-35.6)
VIIc	10	62.0 ± 0.6* (-16.4)	66.3 ± 3.6** (-17.5)	78.9 ± 1.4** (-17.1)	68.7 ± 1.8*** (-28.3)
Vc	10	60.0 ± 1.1* (-19.1)	68.3 ± 0.6* (-15.0)	71.2 ± 2.9*** (-25.2)	85.4 ± 1.9* (-10.9)
IVf	10	65.5 ± 1.6 (-11.7)	80.9 ± 1.5 (0.6)	85.9 ± 3.6* (-9.8)	69.3 ± 2.5*** (-27.7)
II	10	58. 3 ± 2.4* (21.4)	60.7 ± 1.4** (-25.4)	80.4 ± 1.7** (-15.5)	78.2 ± 2.9** (-18.4)
Indo.	2	43.2 ± 7.1* (41.8)	58.0 ± 5.0* (27.9)	65.0 ± 6.0** (31.7)	65.2 ± 6.2** (31.9)

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

Table 2. Analgesic effect determinations
2a. hot-plate test

Group	Dose mg/100g b. w.	Pre-drug value	1 h		2 h	
		$X^- \pm$ S.E	$X^- \pm$ S.E	% of change[a]	$X^- \pm$ S.E	% of change[a]
Control	1 mL saline	6.4 ± 0.16	6.8 ± 0.2	-	7.3 ± 0.5	-
IIIh	10	7.5 ± 0.4	8.6 ± 0.2*	14.7	8.5 ± 0.3*	13.3
VIg	10	8.0 ± 0.6	9.0 ± 0.6*	12.5	9.2 ± 0,3**	15
VIIc	10	6.0 ± 0.3	7.6 ± 0.2**	26.7	9.0 ± 0.7**	50
Vc	10	7.9 ± 0.2	9.0 ± 0.5	13.9	9.0 ± 0.4	13.9
IVf	10	5.9 ± 0.2	9.4 ± 0.6**	59.3	7.6 ± 0.3**	28.8
II	10	6.0 ± 0.3	8.0 ± 0.6*	33.3	9.0 ± 0.6**	50.0
Indo.	2	9.0 ± 0.3	13.6 ± 1.0**	51.1	16.1 ± 0.9**	78.9

Data are presented as the mean ± S.E.; a % of change from basal (pre-drug) value for each group.
Significance: * $p < 0.05$, ** $p < 0.01$. Indo. = indomethacin

2b. Acetic acid-induced writhing

Group	Dose mg/100 g b. w.	Number of contractions $X^- \pm$ S.E	% of change[a]
Control	1 mL saline	99.3 ± 1.7	-
IIIh	10	55.7 ± 1.4***	-43.9
VIg	10	30.7 ± 1.4***	-69.1
VIIc	10	21.5 ± 0.9***	-78.3
Vc	10	19.50 ± 0.8***	-80.4
IVf	10	19.7 ± 0.8***	-80.2
II	10	28.5 ± 0.8***	-71.2
Indo.	2	22.0 ± 1.2***	-77.8

Data are presented as the mean ± S.E.; [a] % of change from control value. Significant change from control group is denoted by *** $p < 0.001$. Indo. = indomethacin

418, 420 (75%, 73%). $(M^+ - H)^+$ 417, 419 (100% and 97.3%), $(M^+ - CH_3)^+$ 403, 405 (11.3%, 12.6%). $M^+ - COCH_3)^+$ 375, 377 (16%, 18.3%), $(M^+ - Br)^+$ 339 (5%).

6-[4-(6-Bromo-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** (0.84 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, benzaldehyde, *p*-anisaldehyde, *p*-tolualdehyde, *p*-chlorobenzaldehyde, 3,4-dichlorobenzaldehde, *p*-hydroxybenzaldehyde, naphthalene-2-carboxaldehyde and/or furan-2-carboxaldehyde (0.002 mol) in 10 mL of *n*-butanol was refluxed for 6 h. The reaction mixture was concentrated to half of its volume under reduced pressure. After cooling, the formed precipitate was filtered, air dried and recrystallized from the proper solvent to give compounds **IIIa-h**, respectively**.**

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl]-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (IIIa)

Crystallized from acetic acid to give brown crystals , m.p. 300-302°C, yield 0.79 g (70%).
Analysis: for $C_{32}H_{19}BrN_4O_2$ (M. w. 571.42) Calcd.: %C 67.26, %H 3.35, %N 9.80. Found: %C 67.24, %H 3.31, %N 9.6.

IR (KBr, cm^{-1}): 3360 (NH), 2216 (CN),1737 (C=O of quinazolone), 1671 (C=O pyridone), 1598

Table 3. Effect of newly synthesized compounds **IIIh**, **VIg**, **VIIc**, **Vc**, **IVf** and **II** on gastric mucosal injury induced by ethyl alcohol in rats

Treatment group	Number of lesions/rat $X^- \pm$ S.E.	% of change	Severity of lesions/rat $X^- \pm$ S.E.	% of change
Control	35.5 ± 2.0	-	80.20 ± 2.0	-
IIIh	2.8 ± 0.6***	-92.1	5.0 ± 0.8***	-93.8
VIg	5.2 ± 04***	-85.4	7.0 ± 0.5***	-91.2
VIIc	7.8 ± 1.8***	-78.0	15.8 ± 1.8***	-80.3
Vc	4.3 ± 0.7 ***	-87.9	6.3 ± 0.8***	-92.1
IVf	7.6 ± 0.2***	-78.6	10.8 ± 0.9***	-86.5
II	7.5 ± 1.4***	-78.9	6.7 ± 0.8***	-91.6

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

(C=C). ^{1}H NMR (DMSO-d_6, δ ppm): 7.15-8.12 (m, 14H, aromatic protons including 1 H of pyridine), 9.45 (s, 1H, NH). MS (m/e): M^+ 570, 572 (0.11%,0.12%), 376, 374 (33%, 3.2%), 253 (100%), 195 (4.2%).

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl]-2-oxo-4-(4-methoxyphenyl)]-1,2-dihydropyridine-3-carbonitrile (IIIb)

Crystallized from acetic acid to give brown crystals , m.p. 320-322°C, yield 1 g (83%).
Analysis: for $C_{33}H_{21}BrN_4O_3$ (M. w. 601.45) Calcd.: %C 65.90, %H 3.52; %N 9.32. Found: %C 65.80, %H 3.31, %N 9.22.

IR (KBr, cm^{-1}): 3360 (NH), 2216 (CN), 1720 (C=O of quinazolone), 1660 (C=O pyridone), 1593 (C=C). ^{1}H NMR (DMSO-d_6, δ ppm): 3.83 (s, 3H, OCH_3), 7.15-8.12 (m, 13H, aromatic protons including 1 H of pyridine), 9.45 (s, 1 H, NH).

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

Crystallized from ethanol to give yellow crystals, m.p. 310-312°C, yield 1g (85%).
Analysis: for $C_{33}H_{21}BrN_4O_2$ (M. w. 585.45)
Calcd.: %C 67.70, %H 3.62, %N 9.57. Found: %C 67.50, %H 3.51, %N 9.54.

^{1}H NMR (DMSO-d_6, δ ppm): 2.34 (s, 3H, C-CH_3), 7.15-8.12 (m, 14H, aromatic protons including 1 H of pyridine), 9.45 (s, 1H, NH).

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl]-2-oxo-4-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (IIId)

Crystallized from ethanol to give reddish brown crystals, m.p. 325-327°C, yield 0.8 g; (66%).
Analysis: for $C_{32}H_{18}BrClN_4O_2$, (M. w. 605.87)
Calcd.: %C 63.44, %H 2.99, %N 9.25. Found: %C 63.40, %H 2.97, %N 9.21.

IR (KBr, cm^{-1}): 3350 (NH), 2208 (CN), 1720 (C=O), 1660 (C=O pyridone), 1580(C=C).

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl]-2-oxo-4-(3,4-dichlorophenyl)-1,2-dihydropyridine-3-carbonitrile (IIIe)

Crystallized from acetic acid to give yellow crystals, m.p. 335-337°C, yield 0.9 g, (70%).
Analysis: for $C_{32}H_{17}BrCl_2N_4O_2$, (M. w. 640.31)
Calcd.: %C 60.02, %H 2.68, %N 8.75. Found: %C 60.00, %H 2.62, %N 8.71.

IR (KBr, cm^{-1}): 3364 (NH), 2208 (CN), 1740 (C=O of quinazolone), 1674 (C=O pyridone), 1593 (C=C).

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl]-2-oxo-4-(2-hydroxyphenyl)]-1,2-dihydropyridine-3-carbonitrile (IIIf)

Crystallized from glacial acetic acid to give brown crystals, m.p.285-287°C, yield 0.9 g (76%).
Analysis: for $C_{36}H_{21}BrN_4O_2$ (M. w. 621.48) Calcd.: %C 69.57, %H 3.41, %N 9.02. Found: %C 69.52, %H 3.23, %N 9.00.

IR (KBr, cm^{-1}): 3346 (NH), 3300-3240 (OH), 2201 (CN), 1675 (C=O pyridone), 1580 (C=C).

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl)-2-oxo-4-(naphthalene-2-yl)]-1,2-dihydropyridine-3-carbonitrile (IIIg)

Crystallized from ethanol to give dark brown crystals, m.p.340-342°C, yield 1g (85%).

Analysis: for $C_{32}H_{19}BrN_4O_3$ (M. w. 587.42) Calcd.: %C 65.43, %H 3.26, %N 9.54. Found: %C 65.41, %H 3.23, %N 9.52.

IR (KBr, cm^{-1}): 3357 (NH), 2205 (CN), 1677 (C=O pyridone), 1590 (C=C).

6-[4-(6-Bromo-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 to give brown crystals, m.p. 295-297°C, yield 0.8 g (71%).
Analysis for $C_{30}H_{17}BrN_4O_3$ (M. w. 561.38) Calcd.: %C 64.18, %H 3.05, %N 9.98. Found: %C 64.15, %H 3.11, %N 9.95.

IR (KBr, cm_{-1}): 3360 (NH), 2200 (CN), 1720 (C=O of quinazolone), 1660 (C=O pyridone), 1580 (C=C). MS (m/e): the molecular ion peak is unstable toward electron impact, 301, 303 (50.8%, 55.3%) of 6-bromo-2-phenylquinazolone $[C_{14}H_8BrN_{2O}+1]^+$, 258 (4.8%) $C_9H_7N_2O^+$, 105 (100%).

6-[4-(6-Bromo-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** (0.84 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 rection mixture was filtered and the precipitate crystallized from the proper solvent to give the iminopyridines **IV a-h**, respectively, in 61-70 % yields.

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)phenyl]-2-imino-4-phenyl-1,2-dihydropyridine-3-carbonitrile (IVa)

Crystallized from ethanol to give pale yellow crystals with m.p. 290-292°C, yield 0.7g, (61%).
Analysis: for $C_{32}H_{20}BrN_5O$ (M. w. 570.44) Calcd.: %C 67.38, %H 3,53, %N 12.28. Found: %C 67.34, %H 3.50, %N 12.25.

IR (KBr, cm^{-1}): 3333-3220 (NH, =NH), 2200 (C=N), 1730 (C=O, quinazolone), 1600 (C=N).

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)phenyl]-2-imino-4-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbonitrile (IVb)

Crystallized from glacial acetic acid to give pale brown crystals with m.p. 270-272°C, yield 0.75 g, (62%).
Analysis: for $C_{33}H_{22}BrN_5O_2$ (M. w. 600.46) Calcd.: %C 66.01, %H 3.69, %N 11.66. Found: %C 65.99, %H 3.67, %N 11.64.

IR (KBr, cm^{-1}): 3350 (NH), 2202 (C=N), 1725 (C=O, quinazolone), 1600 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 3.75 (s, 3H, OCH_3), 7.28-8.2 (m, 17H, aromatic protons including those of quinazolone ring), 9.60, 11.70 (2s, 2H, 2 × NH).

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

Crystallized from ethanol to give yellowish brown crystals with m.p. 320-322°C, yield 0.8 g, (68%).
Analysis: for $C_{33}H_{22}BrN_5O$ (M. w. 584.46) Calcd.: %C 67.81, %H 3.79, %N 11.98. Found: %C 67.79, %H 3.75, %N 11.95.

IR (KBr, cm^{-1}): 3345 (NH), 2200 (C=N), 1730 (C=O, quinazolone), 1610 (C=N).

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)phenyl]-2-imino-4-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (IVd)

Crystallized from ethanol to give pale brown crystals with m.p. 275-277°C, yield 0.85 g, (70%).
Analysis: for $C_{32}H_{19}BrClN_5O$ (M. w. 604.88) Calcd.: %C 63.54, %H 3,17, %N 11.58. Found: %C 63.50, %H 3.14, %N 11.54.

^{1}H NMR (DMSO-d_6, δ ppm): 7.30-8.2 (m, 17H, aromatic protons including those of quinazoline and pyridine ring systems), 9.5-11.5(2s, 2H, 2 × NH).

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl]-2-imino-4-(3,4-dichlorophenyl)-1,2-dihydropyridine-3-carbonitrile (IVe)

Crystallized from ethanol to give yellowish brown crystals with m.p. 315-317°C, yield 0.85 g (66%).
Analysis for $C_{32}H_{18}BrCl_2N_5O$ (M. w. 639.33) Calcd.: %C 60.12, %H 2.84, %N 10.95. Found: %C 60.00, %H 2.81, %N 10.90.

IR (KBr, cm^{-1}): 3365 (NH), 2200 (CN), 1738 (C=O), 1605 (C=N), 1580(C=C).

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl]-2-imino-4-(2-hydroxyphenyl)-1,2-dihydropyridine-3-carbonitrile (IVf)

Crystallized from acetic acid to give reddish brown crystals with m.p. 330-332°C, yield 0.75 g (63%).
Analysis: for $C_{32}H_{20}BrN_5O_2$ (M. w. 586.44) Calcd.: %C 65.54, %H 3.44, %N 11.94. Found: %C 65.50, %H 3.40, %N 11.91.

IR (KBr, cm^{-1}): 3350 (NH), 3345-3240 (OH), 2205 (CN), 1730 (C=O, quinazolone), 1606 (C=N).

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl]-2-imino-4-(naphthalen-2-yl-)-1,2-dihydropyridine-3-carbonitrile (IVg)

Crystallized from ethanol to give dark brown crystals with m.p. higher than 340°C, yield 0.8 g (64%).

Analysis: for $C_{36}H_{22}BrN_5O$ (M. w. 620.50) Calcd.: %C 69.68, %H 3.57, %N 11.29. Found: %C 69.60, %H 3.52, %N 11.23.

IR (KBr, cm^{-1}): 3345 (NH), 2202 (C=N), 1725 (C=O, quinazolone), 1600 (C=N).

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl]-2-imino-4-(furan-2-yl)-1,2-dihydropyridine-3-carbonitrile (IVh)

Crystallized from ethanol to give greenish brown crystals with m.p. 288-300°C, yield 0.69 g (61%).

Analysis: for $C_{30}H_{18}BrN_5O_2$ (M. w. 560.40) Calcd.: %C 64.30, %H 3.24, %N 12.50. Found: %C 64.26, %H 3.20, %N 12.43.

IR (KBr, cm^{-1}): 3336 (NH), 2200 (CN), 1730 (C=O, quinazolone), 1620 (C=N). MS (m/e): 459, 461 (5.2%, 5.0%).

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl]-2-imino-4-substituted aryl-4,4-dihydropyran-3-carbonitriles (Va-c)

General method

A mixture of compound **II** (2.1 g, 0.005 mol), malononitrile (0.3 mL, 0.005 mol), and the appropriate aromatic aldehydes, namely, benzaldehyde, *p*-anisaldehyde and/or *p*-tolualdehyde in 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 precipitated crude product 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-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl]-2-imino-4-phenyl-4,4-dihydropyran-3-carbonitrile (Va)

Crystallized from acetic acid to give dark brown crystals with m.p.174-176°C, yield 0.7 g (61%).

Analysis: for $C_{32}H_{21}BrN_4O_2$ (M. w. 573.44) Calcd.: %C 67.02, %H 3.69, %N 9.77. Found: %C 67.00, %H 3.66, %N 11.74.

IR (KBr, cm^{-1}): 3362-3342 (NH2), 2202 (C=N), 1730 (C=O quinazolone), 1600 (C=N). MS (m/e): M^+ 572, 574 (26%, 23.2%), [($M^+ - C_{12}H_9N_2O$, the substituted pyran ring]$^+$ 375, 377 (3%, 2.5%).

6-[4-(6-Bromo-2-phenyl-4-oxo-4H-quinazolin-3-yl)-phenyl]-2-imino-4-(4-methoxyphenyl)-4,4-dihydropyran-3-carbonitrile (Vb)

Crystallized from ethanol to give brown crystals with m.p. 190°C, yield 0.73 g, (61%).

Analysis for $C_{33}H_{23}BrN_4O_3$ (M. w. 603.46) Calcd.: %C 65.68, %H 3.84, %N 9.28. Found: %C 65.65, %H 3.81, %N 9.25.

IR (KBr, cm^{-1}): 3362-3342 (NH2), 2210 (C=N), 1735 (C=O quinazolone), 1600 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 3.83 (s, 3H, OCH_3), 7.25-8.00 (m, 13H, aromatic protons including those of the pyran ring), 9.6 (s, 2H, NH_2).

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

Crystallized from ethanol to give dark brown crystals with m.p. 200-202°C, yield 0.8 g, 62%).

Analysis: for $C_{33}H_{23}BrN_4O_2$ (M. w. 587.47) Calcd.: %C 67.47, %H 3.95, %N 9.54. Found: %C 67.42, %H 3.93, %N 9.51.

IR (KBr, cm^{-1}): 3362-3342 (NH_2), 2205 (C=N), 1730 (C=O quinazolone), 1600 (C=N).

^{1}H NMR (DMSO-d_6, δ ppm): 2.34 (s, 3H, C-CH_3), 7.25-8.00 (m, 13H, aromatic protons including those of pyran ring), 9.6 (2H,s, NH_2). MS (m/e): M^+ 586, 588 (20.1%, 19.2%).

6-Bromo-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 ethyl alcohol (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 crude precipitated material was filtered, air dried and crystallized from the proper solvent to give chalcones **VIa-h**, respectively.

6-Bromo-2-phenyl-3-{4-[(E)-3-phenyl-acryloyl]-phenyl}-3H-quinazolin-4-one (VIa)

Crystallized from ethanol to give yellow crystals with m.p.160-162°C, yield 0.7 g (68%).

Analysis: for $C_{29}H_{19}BrN_2O_2$ (M. w. 507.38) Calcd.: %C 68.65, %H 3.77; %N 5.52. Found: %C 68.60, %H 3.54, %N 5.40.

IR (KBr, cm^{-1}): 1724 (C=O quinazolone), 1670 (C=O of the α,β-unsaturated ketone), 1610 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 6.60-6,80 (dd, 2H, CH=CH), 7.3-8.6 (m, 12H, aromatic protons includ-

ing those of quinazoline ring). MS (m/e): M^+ 506, 508 (1.3 %, 1.29%), 105 (100%).

6-Bromo-2-phenyl-3-{4-[(E)-3-(4-methoxyphenyl)-acryloyl]-phenyl}-3H-quinazolin-4-one (VIb)

Crystallized from ethanol to give yellowish brown crystals with m.p. 150-151°C, yield 0.8 g (74%).

Analysis: for $C_{30}H_{21}BrN_2O_3$ (M. w. 537.40) Calcd.: %C 67.05, %H 3.94, %N 5.51. Found: %C 67.00, %H 3.89, %N 5.40.

IR (KBr, cm^{-1}): 1725 (C=O quinazolone), 1670 (C=O of the α,β-unsaturated ketone), 1610 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 3.83 (s, 3H, OCH_3), 6.60-6,80 (dd, 2H, CH=CH), 7.3-8.6 (m, 12H, aromatic protons including those of the quinazoline ring). MS (m/e): M^+ 536, 538 (0.1 %, 0.09%), 301, 303 (50.8%, 55.3%), 224, 226 (5%,5%), 106 (9%), 105 (100%).

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

Crystallized from methanol to give brown crystals with m.p. 170-172°C, yield 0.75 g (72%).

Analysis: for $C_{30}H_{21}BrN_2O_2$ (M. w. 521.40) Calcd.: %C 69.11, %H 4.06, %N 5.37. Found: %C 68.99, %H 4.00, %N 5.32.

IR (KBr, cm^{-1}): 1730 (C=O quinazolone), 1672 (C=O of the α,β-unsaturated ketone), 1610 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.34 (s, 3H, C-CH_3), 6.60-6.80 (dd, 2H, CH=CH), 7.3-8.6 (m, 12H, aromatic protons including those of quinazoline ring).

6-Bromo-2-phenyl-3-{4-[(E)-3-(4-chlorophenyl)-acryloyl]-phenyl}-3H-quinazolin-4-one (VId)

Crystallized from ethanol to give brown crystals with m.p. 165-167°C, yield 0.7 g (65%).

Analysis: for $C_{29}H_{18}BrClN_2O_2$ (M. w. 541.82). Calcd.: %C 64.28, %H 3.35, %N 5.17. Found: %C 64.00, %H 3.30, %N 5.12.

IR (KBr, cm^{-1}): 1734 (C=O quinazolone), 1673 (C=O of the α,β-unsaturated ketone), 1612 (C=N).

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

Crystallized from acetic acid to give yellow crystals with m.p. 169-171°C, yield 0.76 g (66%).

Analysis: for $C_{29}H_{17}BrCl_2N_2O_2$ (M. w. 576.27). Calcd.: %C 60.44, %H 2.97, %N 4.86. Found: %C 60.40, %H 2.92, %N 4.82.

IR (KBr, cm^{-1}): 1732 (C=O quinazolone), 1670 (C=O of the α,β-unsaturated ketone), 1615 (C=N).

6-Bromo-2-phenyl-3-{4-[(E)-3-(2-hydroxyphenyl)-acryloyl]-phenyl}-3H-quinazolin-4-one (VIf)

Crystallized from ethanol to give dark brown crystals with m.p.155-157°C, yield 0.8 g (76%).

Analysis: for $C_{29}H_{19}BrN_2O_3$ (M. w. 523.38) Calcd.: %C 66.55, %H 3.66, %N 5.35. Found: %C 66.50, %H 3.62, %N 5.30.

IR (KBr, cm^{-1}): 1735 (C=O quinazolone), 1671 (C=O of the α,β-unsaturated ketone), 1610 (C=N).

6-Bromo-2-phenyl-3-{4-[(E)-3-(naphthalen-2-yl)-acryloyl]-phenyl}-3H-quinazolin-4-one (VIg)

Crystallized from methanol to give brown crystals with m.p. 190-192°C, yield 0.75 g (67%).

Analysis: for $C_{33}H_{21}BrN_2O_2$ (M. w. 556.08) Calcd.: %C 71.10, %H 3.80, %N 5.03. Found: %C 70.99, %H 3.76, %N 5.00.

IR (KBr, cm^{-1}): 1733 (C=O quinazolone), 1665 (C=O of the α,β-unsaturated ketone), 1610 (C=N).

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

Crystallized from acetic acid to give dark brown crystals with m.p. 182-184°C, yield 0.68 g (68%).

Analysis: for $C_{27}H_{17}BrN_2O_3$ (M. w. 497.34) Calcd.: %C 65.20, %H 3.45, %N 5.63. Found: %C 65.00, %H 3.42, %N, 5.60.

IR (KBr, cm^{-1}): 1732 (C=O quinazolone), 1675 (C=O of the α,β-unsaturated ketone), 1610 (C=N).

5-Aryl-pyrazole derivatives (VIIa, b)

A mixture of the chalcone **VIa** (or **VIb**) (0.005 mol) and hydrazine hydrate (2.5 mL, 0.005 mol, 98%) in absolute 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** and **VIIb,** respectively.

6-Bromo-2-phenyl-3-[4-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]-3H-quinazolin-4-one (VIIa)

Crystallized from ethanol to give yellow crystals with m.p 202-204°C, yield 1.5 g (58%).

Analysis: for $C_{29}H_{21}BrN_4O$ (M. w. 521.41) Calcd.: %C, 66.80, %H 4.06, %N 10.75.

Found: %C 66.50, %H 4.03, %N 10.44.

IR (KBr, cm^{-1}): 3360 (NH), the disappearance of (C=O, of chalcone) at 1670, characteristic band of quinazolone at 1750, 1635 (C=N) .

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

Crystallized from methanol to give dark brown crystals with m.p 220-222°C, yield 1.6 g (58%). Analysis: for $C_{30}H_{23}BrN_4O_2$ (M. w. 551.43) Calcd.: %C 65.34, %H 4.20, %N 10.16. Found: %C 65.30, %H 4.00, %N 10.12.

IR (KBr, cm^{-1}): 3360 (NH), characteristic band at 1750 (C=O quinazolone), 1625 (C=N) . ^{1}H NMR (DMSO-d_6, δ ppm): 2.6 (d, J = 8.0 Hz, 2H, CH_2 of pyrazoline), 3.77 (s, 3H, OCH_3), 4.2-4.5 (2dd, ax, aq, J =7.9, 7.3 Hz, 1H, CH of pyrazoline), 7.4-8.4 (m, 17H, aromatic protons).

5-(Aryl)-N-acetylpyrazole derivatives (VIIc, d)

The foregoing procedure was repeated using the chalcones **VIb (or VIc)** and hydrazine hydrate in the presence of glacial acetic acid (10 mL) upon reflux for 6 h to give the N-acetylpyrazolines **VIIc** and **VIId**, respectively.

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

Crystallized from ethanol to give yellow crystals with m.p. 142-144°C, yield 1.6 g (54%). Analysis: for $C_{32}H_{25}BrN_4O_3$ (M. w. 593.47) Calcd.: %C 64.76, %H 4.25, %N, 9.44. Found: %C 64.63, %H 4.11, %N 9.32.

IR (KBr, cm^{-1}): 1750 (C=O quinazolone), 1685 (C=O, acetyl), 1635(C=N). MS (m/e): molecular ion peak is unstable toward electron impact, $[M^+ - C_8H_{10}O_2]^+$ 452, 454 (9.4%, 9.2%), 77 (100%).

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

Crystallized from ethanol to give brown crystals with m.p. 146-148°C, yield 1.5 g (52%). Analysis: for $C_{32}H_{25}BrN_4O_2$ (M. w. 577.47) Calcd.: %C 66.56, %H 4.36, %N 9.70. Found: %C 66.42, %H 4.10, %N,9.52.

R (KBr, cm^{-1}): 1750 (C=O, quinazolone), 1685 (C=O, acetyl), 1635 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 1.37 (d, 2H, CH_2 of pyrazoline), 2.04 (s, 3H, $COCH_3$), 2.34 (s, 3H, CH_3), 4.9 (m, 1H, CH), 7.28-8.2 (m, 11H, aromatic protons including those of quinazolone ring)

6-Phenylpyrimidone derivatives (VIIIa, b)

A mixture of chalcone **VIa** or **VIb** (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 compound **VIIIa** or **VIIIb**.

3-[4-(6-Phenyl -2-oxo-1,2-dihydropyrimidin-4-yl)-phenyl]-6-bromo-2-phenyl-3H-quinazolin-4-one (VIIIa)

Crystallized from ethanol to give dark brown crystals with m.p. 120-122°C, yield 2 g (73%). Analysis: for $C_{30}H_{19}BrN_4O_2$ (M. w. 547.40) Calcd.: %C 65.82, %H 3.50, %N 10.24. Found: %C 65.76, %H 3.30, %N 10.10.

IR (KBr, cm^{-1}): 3200-3600 (OH enolic of pyrimidine), 1725 (C=O, quinazolone),1618 (C=N). ^{1}HNMR spectrum (DMSO-d_6, δ ppm): showed signals at 7.00-8.4(m, 18H, aromatic protons including 1H of pyrimidone and 3H of quinazolone), 12.60 (s, 1H, OH). MS (m/e): (M^+ – OH) 529, 531 (55.5 %, 57 %)

3-{4-[6-(*p*-Anisyl)-2-oxo-1,2-dihydropyrimidin-4-yl]-phenyl}-6-bromo-2-phenyl-3H-quinazolin-4-one (VIIIb)

Crystallized from ethanol to give dark brown crystals with m.p. 130-132°C, yield 1.75 g (61%). Analysis: for $C_{31}H_{21}BrN_4O_3$ (M. w. 577.1) Calcd.: %C 64.45, %H 3.76, %N 9.71. Found: %C 64.20, %H 3.39, %N 9.50.

^{1}H NMR (DMSO-d_6, δ ppm): 3.80 (s, 3H, OCH_3), 7.2-8.5 (m, 17H, aromatic protons including those of pyrimidone and quinazolone rings).

6-(*p*-Substituted aryl)-pyrimidinethione derivatives (VIIIc, d)

The foregoing procedure was carried out using ketone **VIb** (or **VIc**) 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 **VIIIc or VIIId**, respectively.

3-{4-[6-(p-Anisyl)-2-thioxo-1,2-dihydropyrimidin-4-yl]phenyl-6-bromo-2-phenyl-3H-quinazolin-4-one (VIIIc)

Crystallized from acetic acid to give brown crystals with m.p. 206-208°C, yield 1.75 g (60%). Analysis: for $C_{31}H_{21}BrN_4O_2S$ (M. w. 583.1) Calcd.: %C 63.80, %H, 3.60, %N 9.60. Found: %C 63.60, %H 3.53, %N 9.40.

IR (KBr, cm^{-1}): 3220 (NH), 1750 (C=O, quina-

zolone), 1640 (C=N), 1275 (C=S). MS (m/e): (M^+ – $C_{16}H_{11}N_2S$) 320, 322 (1.9 %, 1.2%), (p-anisyl – 1)$^+$ 105 (100%).

3-{4-[6-(*p*-tolyl)-2-thioxo-1,2-dihydropyrimidin-4-yl]phenyl-6-bromo-2-phenyl-3H-quinazolin-4-ones (VIIId)

Crystallized from ethanol to give dark brown crystals with m.p. 215-217°C, yield 2 g (69%). Analysis: for $C_{31}H_{21}BrN_4OS$ (M. w. 577) Calcd.: %C 64.45, %H 3.76, %N 9.71. Found: %C 64.23, %H 3.55, %N 9.52.

IR (KBr, cm^{-1}): 3220 (NH), 1750 (C=O, quinazolone), 1640 (C=N), 1275 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 2.34 (s, 3H, CH_3), 7.00-8.4 (m, 18H, aromatic protons including 1H of pyrimidone and 3H of quinazolone).

The pyridone-carbonitrile IIIa (from chalcone VIa)

A mixture of chalcone **VIa** (1.014 g, 0.002 mol), ethyl cyanoacetate (0.23 mL, 0.002 mol) and anhydrous ammonium acetate (1.24 g, 0.016 mol) was refluxed in 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 **IIIa**, mixed m.p. 302°C. This indicates that the one pot reaction gives better yields (70%) of the pyridone carbonitriles than for those obtained from chalcones.

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