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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization, and evaluation of some novel 4(3*H*)-quinazolinone derivatives as anti-inflammatory and analgesic agents

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Abstract Some of new 3-(4-chlorophenyl or 4-fluorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazoline derivatives having a Schiff bases, oxazolone, imidazolidine, pyrazolidine, pyridine, pyrimidine, and various substituted C-2 have been synthesized. Screening for some selected compounds was carried out for their potential anti-inflammatory and analgesic activity.

Keywords 4(3*H*)-quinazolinone · Imidazolidine · Pyrazolidine · Pyridine · Pyrimidine · Anti-inflammatory · Analgesic agent

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are useful tools in the treatment of acute and chronic inflammation (Sng and Schug, 2009), pain (Chou *et al.*, 2009) and fever (Eccles, 2006). However, long-term clinical usage of NSAIDs is associated with significant side effects of gastrointestinal lesions, bleeding, and nephrotoxicity (Rathee *et al.*, 2009). Therefore, the discovery of new and safer anti-inflammatory drugs represents a challenging goal for such a research area. In general quinazoline derivatives are known to possess remarkable anti-inflammatory activity as NOS-II (Harris *et al.*, 2000), TNF-a (Tobe *et al.*, 2001), IMPDH-II (Buckley *et al.*, 2005), MAPK (Schlapbach *et al.*, 2004), PDE-3 (Piaz and Giovannoni, 2000), and PDE-4 (Chandrika *et al.*, 2008) inhibitors. Furthermore, imidazo[1,2-c]quinazolines (Balakumar *et al.*, 2010), pyrroloquinazolines (Rioja *et al.*, 2002), 4-phenethylaminoquinazolines (Tobe *et al.*, 2003), 2,3,6-trisubstituted quinazolines (Kumar *et al.*, 2003), 2-substituted aminoquinazolinones (Alagarsamy and Murugesan, 2007) and benzothiazolylquinazolinones (Laddha *et al.*, 2006) were reported to have significant anti-inflammatory, analgesic and antipyretic properties (Chao *et al.*, 1999; Balakumar *et al.*, 2010). A recent literature survey revealed that many of the halogen containing heterocyclic moiety have attracted attention due to the ability of halogen to act as polar hydrogen or hydroxyl mimic. Substitution of hydrogen by halogen has been a strategy in designing molecules for biological studies (Karegoudar *et al.*, 2008; Alafeefy *et al.*, 2010). Based on the above observations and in continuation of our drug research program, it was of interest to synthesize a novel series of quinazolinone derivatives with structure modifications involving incorporation of the iodine atom at position 6, aryl halogen at position 3, and a heterocyclic moiety at position 2 of 4(3*H*)-quinazolinone moiety as a trial to obtain safer and potent anti-inflammatory and analgesic agents.

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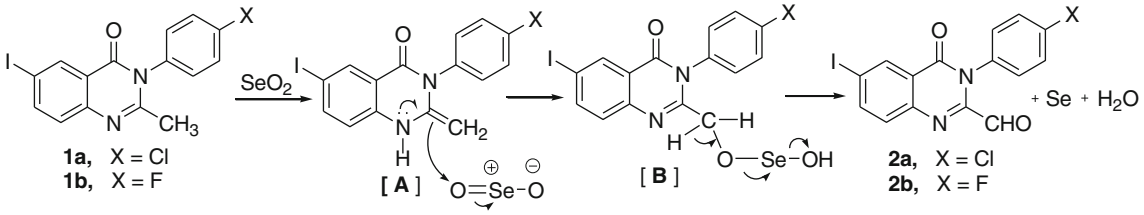
Discussion

Chemistry

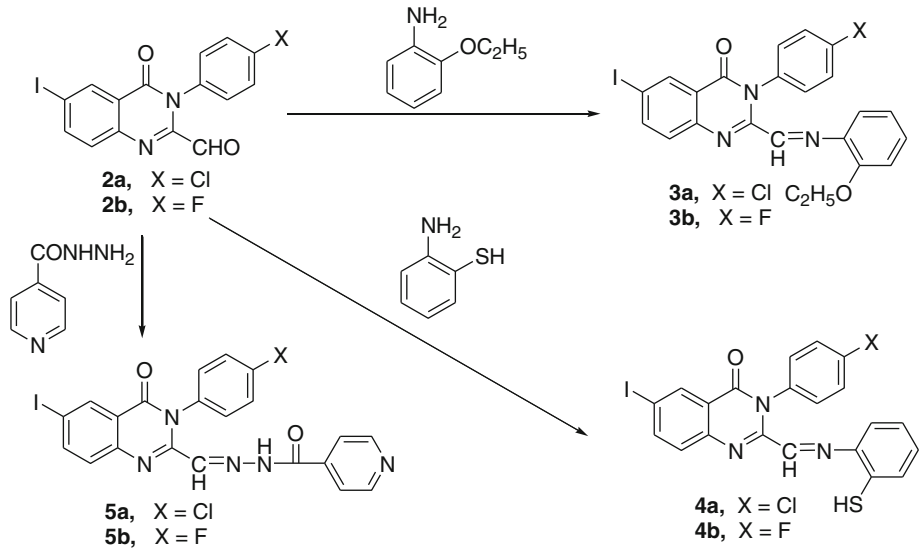
In this investigation, 2-methyl-4(3*H*) quinazolinones **1a**,**b** were synthesized according to a previously reported method (Rajendra and Bhaduri, 1979). One of the reasons for the interest in 2-methyl-4(3*H*) quinazolinones **1a**,**b** relates to the possibility of oxidation of the methyl group in their structure with the possibility that further useful functionalization might be generated at this position. Therefore, oxidation of the methyl group in products **1a**,**b** to a formyl group using SeO_2 was carried out, and the novel 4(3*H*)-quinazolinone-2-carboxaldehyde derivatives **2a**,**b** were furnished. Presumably, the oxidizing agent (SeO_2) acts as an electrophile and initially attacks the methyl group. So, the reaction probably proceeds by a mechanism similar to that proposed by Sokai *et al.*, (1972) involving direct oxidation of methyl group via intermediates **A** and **B** to give the proposed structure **2a**,**b** (Scheme 1). The structural elucidation of the 4(3*H*)-quinazolinone-2-carboxaldehydes **2a**,**b** was inferred from correct elemental analysis and carful inspection of their spectral data.

The scope of the reaction of aldehydes **2a**,**b** with various nitrogen nucleophile was studied with the objective of obtaining biologically active compounds. Thus, the reaction of aldehydes **2a**,**b** with the selected amines, *o*-phenetidine, *o*-aminothiophenol and isonicotinic hydrazide, in dioxane led to the formation of Schiff's bases **3**, **4** and the hydrazone derivative **5** in high yield (Scheme 2). The formation of **3**–**5** may be interpreted through correct elemental analysis and spectral data. ^{1}H NMR spectrum of compound **3a** displayed one triplet signal at 1.35 and one quartet signal at 4.04 equivalents to five protons of OC_2H_5 group, also, its ^{13}C NMR revealed signals at 15.43 (CH_3) and 67.45 (CH_2) due to OC_2H_5 group.

Five-membered heterocycles are ideal representatives of a recurring core structure that is found in numerous biologically active compounds. Thus, condensation of the aldehydes **2a**,**b** with 2-thioxothiazolidin-4-one afforded the corresponding thioxothiazolidinone derivatives **6a**,**b**. In addition, the oxazolone derivatives **7a**,**b** were produced upon cyclocondensation of the aldehydes **2a**,**b** with hippuric acid. When, the oxazolone derivatives **7a**,**b** were subjected to react with *o*-phenetidine in acetic acid containing sodium acetate afforded the corresponding imidazole derivatives **8a**,**b**. Anti-inflammatory of pyrazole motivated us to synthesize a novel



Scheme 1 Synthesis of aldehydes



Scheme 2 Synthesis of Schiff's bases derivatives

series of 4(3*H*)-quinazoline derivatives containing pyrazole moiety. The Schiff's base derivatives **9a**,**b** were obtained via the reaction of the aldehydes **2a**,**b** with 4-aminoantipyrene. The ^{1}H NMR spectrum of **9a** revealed the appearance of characteristic singlet at $\delta = 2.03$ and 3.20 ppm assigned to CH_3 and N-CH_3 protons, while its ^{13}C NMR exhibited the carbon of these groups at 18.98 and 34.42. Also, the pyrazoline derivatives **11a**,**b** were obtained through the condensation of the compounds **2a**,**b** with ethyl acetoacetate to give **10a**,**b** followed by reaction with hydrazine hydrate in ethanol. Structures of compounds **10a**,**b** and **11a**,**b** were elucidated on the basis of elemental analysis and spectral data. The ^{1}H NMR spectrum compound **10a** as example revealed triplet and quartet signals at: $\delta = 1.18$, 4.15 due to ethyl protons in addition to singlet signal at $\delta = 2.44$ due to acetyl group. On the other hand, ^{1}H NMR spectrum of compound **11a** displayed signal at: $\delta = 2.27$ due to methyl group, aromatic multiplet in the region $\delta = 7.23$–8.56, in addition to two singlets at: 9.45, 9.87 due to two NH groups and revealed the lack of signals characteristic for ethyl group. The lack of carbonyl ester in the IR spectra supported the formation of structure **11**. In this paper, the synthesis of the chalcone derivatives **12a**,**b** were accomplished according to the Claisen-Schmidt condensation of the corresponding quinazoline-2-aldehydes **2a**,**b** with acetophenone. Cyclocondensation of the chalcone derivatives **12a**,**b** with hydrazine hydrate affording the corresponding pyrazoline derivatives **13a**,**b**. Structures of compounds **12**, **13** were inferred from their correct elemental analyses and spectral data. Thus, IR spectrum of **12a** showed bands at: 1708, 1682 cm^{-1} attributed to the C=O groups. ^{1}H NMR spectra of the compounds **12**, **13** were compatible with the assigned structure (Scheme 3).

The synthesis of pyridine derivatives was carried out aiming to develop new drugs. Condensation of the quinazoline-2-aldehyde derivatives **2a**,**b** with malononitrile afforded the corresponding arylidene derivatives **14a**,**b**. These arylidene derivatives were used as intermediates in the synthesis of 4(3*H*)-quinazolinone containing pyridine moiety **15a**,**b** upon reaction with *N*-(*o*-ethoxyphenyl) cyanoactanilide in the presence of ethanolic piperidine. An important evidence for the latter products was arrived from their synthesis via another synthetic route. Thus, multicomponent reaction of the aldehyde derivatives **2a**,**b** with malononitrile and *N*-(*o*-ethoxyphenyl) cyanoactanilide in the presence of few drops of piperidine gave **15a**,**b**. (m.p. and mixed m.p.). The IR spectrum of the compound **15a** revealed two sharp strong absorption bands at: 3247, 3234 cm^{-1} for NH_2 group. Further, ^{1}H NMR spectrum of **15a** exhibited a triplet and quartet at 1.55 and 4.21 for ethoxy group. It is of great interest that specifically functionalized pyrimidinones may possess specific biological properties. Thus, condensation of the aldehyde derivatives **2a**,**b** with barbituric acid furnished pyrimidine 2,4,6-trione **16a**,**b**. In addition, multicomponent Biginelli reaction was occurred via the reaction of the aldehyde derivatives **2a**,**b** with ethyl acetoacetate and thiourea in the presence of hydrochloric acid to get pyrimidine derivatives **17a**,**b**. The arylidene derivatives **10a**,**b** were used as intermediates in the synthesis of pyrimidine derivatives **17a**,**b** upon reaction with thiourea (Scheme 4). The identity of the products was determined by spectral studies. The IR spectrum of compound **17a** revealed a sharp strong absorption band above 1,720 cm^{-1} due to the presence of the ester function in the structure. The characteristic signals of an ester moiety confirm the presence of ester group in the structure by resonating as triplet and quartet for CH_2 and CH_3 at $\delta = 1.54$, 4.23 ppm, respectively, and a doublet at: 4.77 attributed for H-4 of pyrimidine ring. The aromatic protons resonate as multiplets at δ 7.32–8.43 ppm.

Biological activity

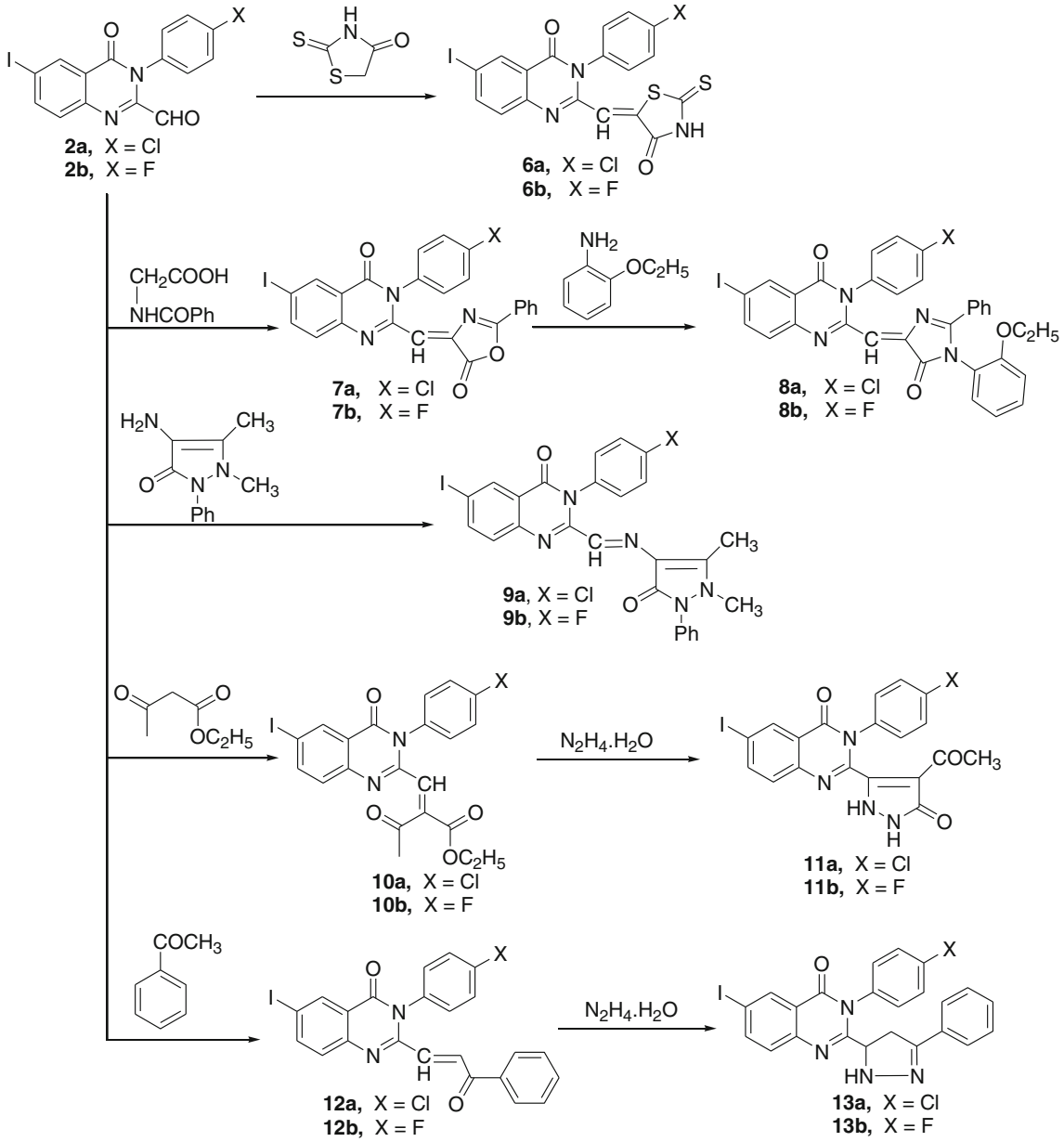
Some new selected synthesized 4(3*H*)-quinazolinone derivatives **3b**, **5b**, **6b**, **7a**, **9a**, **9b**, **11a**, **12b**, **13a**, and **15b** (10 compounds) were screened for anti-inflammatory and analgesic activities. Adult albino rats of both sexes weighting 120–150 gm were divided into 12 groups, one group as control, 10 groups for the test compounds and one group receiving the reference standard. Each group consists of 6 animals. They were housed in colony rooms with 12/12 light/dark cycle at 21 ± 2 °C room temperature and had free access to cubed dry food and water. The test compounds and the reference standards were prepared as suspensions in 2 % tween 80 while the negative control groups received 1 ml of water suspended in tween 80 (vehicle). Doses of the tested compounds (100 mg/kg body weight) and the reference standards were calculated according to the reported method (Sastry *et al.*, 1989).

Anti-inflammatory studies

The anti-inflammatory activity was investigated through acute and chronic model.

Acute model (carrageenan hind paw edema assay)

The procedure of Winter et al. (1962) was adopted, all the tested compounds and the reference drug (indomathacin; 5 mg/kg body weight) were administered orally for each rat. 1 h later, the hind paw edema was induced by injecting 0.05 ml of 1 % carrageenan sodium into the subplantar region of the right hind paw of each rat. The initial hind paw volume was measured immediately following carrageenan injection. The edema in each test group of animals after 3 h of carrageenan administration was measured, using mercury plethysmography, to calculate the percent

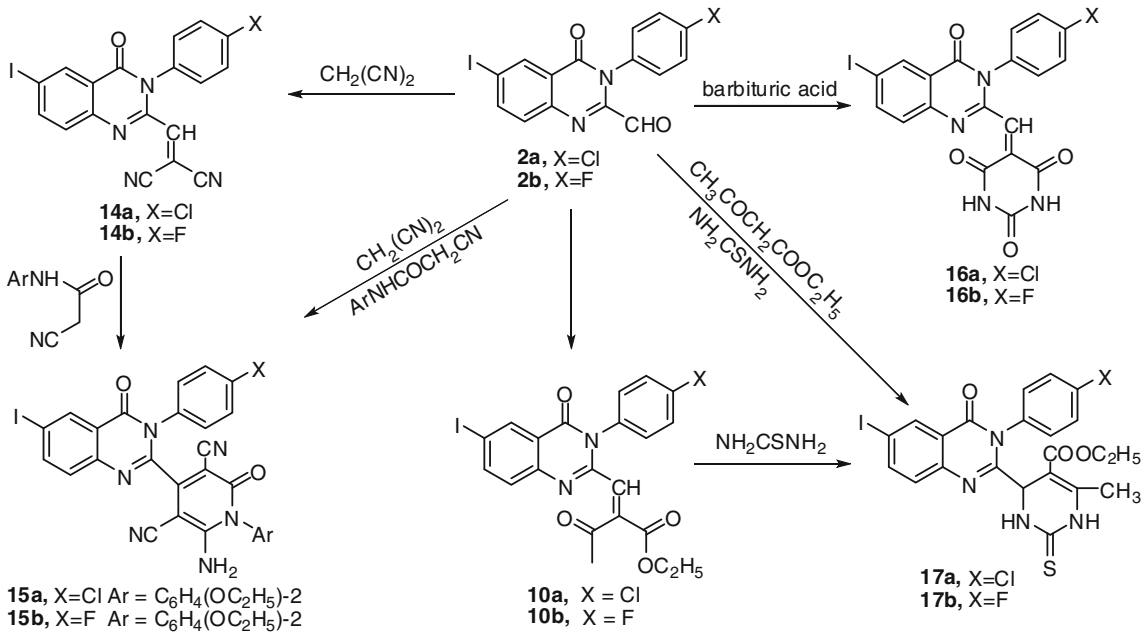


Scheme 3 Synthesis of the arylidene, oxazolone, imidazolidine, and pyrazole derivatives

edema achieved by the reference drug and the tested compounds (Table 1).

Chronic model

The procedure of Meier et al. (1950) was followed; rats were divided into 12 groups, each of 6 animals, where 4 cotton pellets weighting 30–35 mg were channeled subcutaneously to the pectoral area of each rat. Daily oral doses of the tested compounds (100 mg/kg) and the reference drug (Indomethacin; 5 mg/kg) were given for seven successive days. The rats were killed in following day and the cotton pellets with the surrounding granulomatous tissues were removed. The pellets were dried overnight to have a constant weight. The gain in pellets weight were calculated for both the tested compounds and the Indomethacin and compared to the control group (Table 1). The screening of the anti-inflammatory activity (chronic model) of the tested 4(*3H*)-quinazlinone compounds revealed that, the 3-(4-fluorophenyl)-2-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylimino)-methyl]-6-iodo-3*H*-quinazolin-4-one (**9b**), which has azomethine side chain at C-2 position ending with a pyrazole moiety and chlorophenyl at position 3, showed strong anti-inflammatory activity. When the chlorophenyl at position 3 of this compound was replaced by fluorophenyl moiety in case of



Scheme 4 Synthesis of pyridinone and pyrimidine derivatives

Table 1 Anti-inflammatory activity of the tested compounds and indomethacin

Compd. no.	Anti-inflammatory activity					
	Acute model			Chronic model		
	X ± S.E.	Change %	Potency	X ± S.E.	Change %	Potency
Control	57.6 ± 1.1	–	–	112.4 ± 5.5	–	–
3b	35.2 ± 0.8	38.9	0.5	55.9 ± 2.2	50.2	0.6
5b	31.5 ± 1.2	45.3	0.6	37.4 ± 2.2	66.7	0.8
6b	31.8 ± 1.8	44.8	0.6	36.8 ± 1.8	67.3	0.8
7a	29.4 ± 2.1	49.6	0,6	30.8 ± 3.1	72.6	0.9
9a	30.3 ± 1.7	47.4	0.6	44.2 ± 1.7	60.7	0.8
9b	26.8 ± 1.8	53.5	0.7	29.8 ± 1.8	73.5	1.0
11a	29.8 ± 3.1	48.3	0.6	31.2 ± 2.3	72.2	0.9
12b	41.3 ± 2.8	28.3	0.4	65.4 ± 3.8	41.8	0.5
13a	28.6 ± 3.6	50.4	0.7	31.5 ± 2.6	71.9	0.9
15b	45.7 ± 1.8	20.7	0.3	53.7 ± 1.8	52.2	0.7
Indomethacin	12.4 ± 1.1	78.3	1.0	27.9 ± 2.6	75.2	1.0

compound **9a**, the potency was dropped to 0.8 potency. Compound **11a** incorporating pyrazole moiety at C-2 showed strong anti-inflammatory activity (0.9 potency); Also, compound **13a** showed strong anti-inflammatory activities (0.9 potency), the activity showed by compound **13a** may be due to the presence of pyrazoline moiety at C-2. On the other hand, compounds **5b**, **6b**, and **7a** (which have hydrazone, thiazole, and oxazole at C-2 position, respectively) exhibited strong anti-inflammatory activities, ranged from 0.8 to 0.9 potencies comparable to the reference drug. Compound **15b** with pyridine moiety at position 2 showed moderate activities (0.7 potency). While mild effects were exerted by compounds **3b** and **12b** which have at C-2 position 2-ethoxyphenyl azomethine and chalcone moieties, respectively (Table 1).

Analgesic activity

The analgesic activity was evaluated according to the reported method of Charlier et al. (1961) Electric current as noxious stimulus was used as described by Charlier et al. and the minimum voltage that caused the rat to emit a cry was determined. Electrical stimulation of the tail was applied by means of 515 master Schoker (Lafayette Inst. Indiana, USA). The minimum

Table 2 The analgesic activities of the tested compounds and novalgin

Compd. no.	Voltage needed after treatment					
	1 h			2 h		
	X ± S.E.	Change %	Potency	X ± S.E.	Change %	Potency
Control	79.9 ± 3.7	–	–	80.6 ± 3.2	–	–
3b	111.3 ± 2.8	39.3	0.5	125.8 ± 3.5	56.1	0.7
5b	125.5 ± 2.9	57.1	0.7	132.4 ± 2.6	64.3	0.8
6b	126.2 ± 3.2	57.9	0.7	130.0 ± 2.7	61.3	0.7
7a	128.6 ± 2.1	60.9	0.7	131.6 ± 2.2	63.3	0.7
9a	122.8 ± 3.2	53.7	0.6	124.3 ± 2.3	54.2	0.6
9b	131.7 ± 2.2	64.8	0.8	133.5 ± 1.8	65.6	0.8
11a	118.2 ± 2.2	47.9	0.6	130.5 ± 3.7	61.9	0.7
12b	117.4 ± 2.6	46.9	0.6	124.2 ± 3.4	54.1	0.6
13a	124.2 ± 3.8	55.4	0.7	128.3 ± 1.5	59.2	0.7
15b	115.9 ± 3.6	45.1	0.5	123.4 ± 2.8	53.1	0.6
Novalgin	146.2 ± 1.6	82.9	1.0	149.7 ± 1.5	85.7	1.0

voltage required for the animal to emit a cry was recorded for the control and treated groups with the tested compounds (dose; 100 mg/kg body weight) and Novalgin as a reference standard (dose; 5 mg/kg body weight). The mean voltage for each group was obtained. Analgesic activity was measured for the tested compounds and the reference (Table 2). The screening of the analgesic activity of the tested 4(*3H*)-quinazlinone compounds revealed that, the activity was nearly increased by time and all compounds showed moderate analgesic activity compared to that of novalgin except the 3-(4-fluorophenyl)-2-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylimino)-methyl]-6-iodo-3*H*-quinazolin-4-one **(9b)** exhibited strong analgesic activities.

Conclusions

In summary, a series of new 4(3*H*)-quinazolinone derivatives carrying many heterocyclic rings could be synthesized and evaluated for their anti-inflammatory and analgesic activities. Some of 4(3*H*)-quinazolinones which contain pyrazole moiety showed highly significant anti-inflammatory effect, as compounds **9b**, **11a**, **13a** comparable to the standard (Indomethacin).

Experimental

General

All melting points are recorded on digital Gallen Kamp MFB-595 instrument and are uncorrected. The IR spectra (KBr) (cm^{-1}) were measured on a Shimadzu 440 spectrophotometer. NMR spectra (δ, ppm) were obtained in deutrated dimethyl sulfoxide on a Varian Gemini 200 (200 MHz) spectrometer, using TMS as an internal standard; chemical shifts are reported as δ_{ppm} units. Mass spectra (*m/z*, %) were obtained on GC MS-QP 100 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at Microanalytical Unit, Cairo University, Cairo, Egypt.

*Synthesis of 3-(4-chlorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazoline-2-carbaldehyde (**2a**)*

2-Methyl-3(4*H*)-quinazolinone **1a** (0.01 mol) was dissolved in hot dioxane (50 ml), powdered selenium dioxide (0.02 mol) was added portion-wise while stirring. After complete addition, the reaction mixture was boiled with stirring for 6 h.The reaction mixture was then filtered off. The filtrate was poured onto crushed ice, the solid product obtained was filtered and crystallized from benzene to give **2a** as beige crystals, mp 217–218 °C. Yield 65 %. IR: υ/cm^{-1}: 1719, 1687 (C=O). ^{1}H NMR: δ/ppm: 7.32–7.51 (m, 4H, ArH), 7.73 (d, 1H, Ar–H at C_8–H quinazoline), 8.29 (d, 1H, ArH at C_7–H quinazoline), 8.49 (s, 1H, ArH at C_5–H quinazoline), 9.43 (s, 1H, CHO); MS, m/z (%): 410 (M^+; 100 %), 411 (M + 1; 25.2 %), 412 (M + 2; 32.9 %), 409 (M-1; 18.1 %), 382 (M-CO; 35.6 %), 381 (M-CHO; 69.2 %), 270 (M-[C_6H_4Cl + CHO]; 14.8 %), 255 (M-[I + CO]; 33.9 %), 227 (M-[I + 2CO]; 32.3 %), 76 (phenylene moiety; 66.3 %). Anal. Calcd for $C_{15}H_8ClIN_2O_2$ (410.59): C, 43.88; H, 1.96; N, 6.82; Found: C, 43.90; H, 2.00; N, 6.70.

*Synthesis of 3-(4-fluorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazoline-2-carbaldehyde (**2b**)*

It was synthesized according to our reported method (Aly *et al.*, 2010).

*Synthesis of Schiff's bases derivatives **3a**,**b***

A mixture of 4(3*H*)-quinazolinone-2-carboxaldehydes **2a**,**b** (0.01 mol) and *o*-phenetidine (0.01 mol) in dioxane (30 ml) was heated under reflux for 1 h. The reaction mixture was concentrated under vacuum, left to cool and then cold ethanol was added. The solid product obtained was filtered off and crystallized from ethanol to give the final products.

*3-(4-Chlorophenyl)-2-((2-ethoxyphenylimino)methyl)-6-iodoquinazolin-4(3H)-one (**3a**)*

mp 215–216 °C. Yield 85 %. IR: υ/cm^{-1}: 1686 (C=O), 1610 (CH=N); ^{1}H NMR: δ/ppm: 1.35 (t, 3H, CH_3), 4.04 (q, 2H, CH_2), 6.65–8.25 (m, 11H, ArH), 8.76 (s, 1H, CH=N); ^{13}C NMR: 15.43(CH_3), 67.45(CH_2), 100.20, 116.43, 120.78, 121.32, 121.54, 122.43, 123.85, 123.95, 126.43, 128.54, 129.43, 129.68, 131.32, 132.43, 139.54, 146.65, 147.43, 148.54 (18C–Ar), 164.49, 166.64 (2C=N) and 173.06 (C=O); Anal. Calcd for $C_{23}H_{17}ClIN_3O_2$ (529.76): C, 52.15; H, 3.23; N, 7.93; Found: C, 52.30; H, 3.10; N, 7.70.

*3-(4-Fluorophenyl)-2-((2-ethoxyphenylimino)methyl)-6-iodoquinazolin-4(3H)-one (**3b**)*

mp 212–214 °C. Yield 78 %. IR: υ/cm^{-1}: 1672 (C=O), 1607(CH=N); ^{1}H NMR: δ/ppm: 1.36 (t, 3H, CH_3), 4.08 (q, 2H, CH_2), 6.87–8.34 (m, 11H, ArH), 8.66 (s, 1H, CH=N), ^{13}C NMR: 14.83(CH_3), 66.76 (CH_2), 104.10, 116.14, 116.63, 120.58, 121.43, 121.63, 123.76, 123.98, 126.43, 128.56, 129.63, 129.98, 132.65, 139.48, 146.54, 147.43, 153.54, 156.23 (18C–Ar), 164.29, 166.54 (2C=N) and 167.34 (C=O); Anal. Calcd for $C_{23}H_{17}FIN_3O_2$ (513.30): C, 53.82; H, 3.34; N, 8.19; Found: C, 53.70; H, 3.20; N, 8.30.

*Synthesis of Schiff's bases derivatives **4a**,**b***

A mixture of 4(3*H*)-quinazolinone-2-carboxaldehydes **2a**,**b** (0.01 mol) and *o*-aminothiophenol (0.01 mol) in dioxane (30 ml) was heated under reflux for 1 h. The reaction mixture was concentrated under vacuum, left to cool and then cold ethanol was added. The solid product obtained was filtered off and crystallized from ethanol to give the final products.

*3-(4-Chlorophenyl)-6-iodo-2-((2-mercaptophenylimino)methyl)quinazolin-4(3H)-one (**4a**)*

mp 253–255 °C. Yield 73 %. IR: υ/cm^{-1}: 3251 (SH), 1685 (C=O), 1612 (CH=N); ^{1}H NMR: δ/ppm: 4.20 (bs, 1H, SH), 6.79–8.36 (m, 11H, ArH), 8.68 (s, 1H, CH=N); ^{13}C NMR: 99.65, 115.54, 115.96, 118.23, 122.97, 123.76, 123.98, 125.12, 126.43, 128.56, 129.63, 129.98, 132.65, 139.48, 146.54, 147.43, 153.54, 156.23 (18C–Ar), 163.29, 164.54 (2C=N) and 168.35 (C=O); Anal. Calcd for $C_{21}H_{13}ClIN_3OS$ (517.77): C, 48.71; H, 2.53; N, 8.12; Found: C, 49.00; H, 2.60; N, 8.10.

*3-(4-Fluorophenyl)-6-iodo-2-((2-mercaptophenylimino)methyl)quinazolin-4(3H)-one (**4b**)*

mp 230–232 °C. Yield 73 %. IR: υ/cm^{-1}: 3253 (SH), 1682 (C=O), 1604(CH=N); ^{1}H NMR: δ/ppm: 4.34 (bs, 1H, SH), 6.74–8.23 (m, 11H, ArH), 8.24 (s, 1H, CH=N); ^{13}C NMR: 99.23, 115.56, 115.82, 118.45, 122.56, 123.56, 123.87, 125.24, 126.54, 128.34, 129.56, 129.79, 132.67, 139.40, 146.23, 147.54, 149.12, 156.45 (18C–Ar), 163.12, 164.87 (2C=N) and 167.34 (C=O); Anal. Calcd for $C_{21}H_{13}FIN_3OS$ (501.32): C, 50.31; H, 2.61; N, 8.38; Found: C, 50.50; H, 2.70; N, 8.50.

*Synthesis of hydrazide derivatives **5a**,**b***

A mixture of 4(3*H*)-quinazolinone-2-carboxaldehydes **2a**,**b** (0.01 mol) and isonicotinic hydrazide (0.01 mol) in dioxane (30 ml) was heated under reflux for 1 h. The reaction mixture was concentrated under vacuum, left to cool. The solid product obtained was filtered off and crystallized from ethanol to give the final products.

*N'-((3-(4-chlorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)methylene)isonicotinohydrazide (**5a**)*

mp > 300 °C. Yield 74 %. IR: υ/cm^{-1}: 3241(NH), 1698, 1675 (C=O). ^{1}H NMR: δ/ppm: 7.59–8.32 (m, 11H, ArH), 8.50 (s, 1H, CH=N), 8.90 (s, 1H, NH); ^{13}C NMR, 94.50, 116.54, 122.59, 123.76, 126.32, 128.12, 129.54, 129.78, 131.13, 131.34, 132.23, 134.65, 135.34, 136.75, 139.45, 146.34, 146.12 (17C–Ar), 159.22, 163.12 (2C=N) and 170.34, 173.56 (2C=O); MS, m/z (%): 529 (M^+, 3.87), 426 (9.61), 423 (M-nicotinoyl moiety; 38.05), 360 (M-$C_6H_5ClN_3O$; 52.58), 233 ($C_{15}H_9N_2O$; 13.77), 127 (I, 9.12), 106 (nicotinoyl moiety; 100), 103 (C_7H_3O; 30.73), 78 (pyridine moiety; 88.14); Anal. Calcd for $C_{21}H_{13}ClIN_5O_2$ (529.72): C, 47.61; H, 2.47; N, 13.22; Found: C, 47.48; H, 2.65; N, 13.34.

*N'-((3-(4-Fluorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)methylene)isonicotinohydrazide (**5b**)*

mp 280–282 °C. Yield 73 %. IR: υ/cm^{-1}: 3232(NH), 1687, 1675 (2C=O). ^{1}H NMR: δ/ppm: 7.60–8.33 (m, 11H, ArH),

8.49 (s, 1H, CH=N), 8.90 (s, 1H, NH), ^{13}C NMR, 94.35, 116.93, 122.98, 123.89, 126.45, 128.32, 129.08, 129.54, 131.04, 131.34, 132.23, 134.79, 135.65, 136.87, 139.75, 146.45, 151.43, 150.88 (17C–Ar), 159.33, 163.38 (2C=N) and 170.32, 173.00 (2C=O); Anal. Calcd for $C_{21}H_{13}FIN_5O_2$ (513.72): C, 49.14; H, 2.55; N, 13.64. Found: C, 49.20; H, 2.60; N, 13.30.

*Synthesis of the arylidene derivatives **6a**,**b***

To equimolar amount of the aldehyde derivatives **2a**,**b** and 2-thioxothiazolidin-4-one (0.01 mol) in dioxane (30 ml), few drops of piperidine was added. The reaction mixture was heated under reflux for 2 h., then allowed to cool. The obtained product was collected by filtration and crystallized from dioxane.

*5-((3-(4-Chlorophenyl)-6-iodo-4-oxo-3, 4-dihydroquinazolin-2-yl)methylene)-2-thioxothiazolidin-4-one (**6a**)*

mp > 300 °C. Yield 72 %. IR: υ/cm^{-1}: 3342 (NH), 1682, 1667 (2C=O). ^{1}H NMR: δ/ppm: 5.6 (s, 1H, CH = thiazolidine), 7.28–7.54 (m, 4H, ArH), 7.64 (d, 1H, C_8–H quinazoline), 8.00 (d, 1H, C_7-quinazoline), 8.43 (s, 1H, C_5-quinazoline), 13.40 (s, 1H, NH); ^{13}C NMR: 97.32, 122.21, 123.66, 125.32, 126.43, 128.54, 129.76, 130.43, 136.32, 137.87, 139.54, 140.45, 142.32, 148.54, (12C–Ar + C=C), 164.49, (C=N), 165.60, 170.45 (2C=O), 197.06 (C=S); Anal. Calcd for $C_{18}H_9ClIN_3O_2S_2$ (525.77): C, 41.12; H, 1.73; N, 7.99; Found: C, 41.30; H, 1.60; N, 7.80.

*5-((3-(4-Fluorophenyl)-6-iodo-4-oxo-3, 4-dihydroquinazolin-2-yl)methylene)-2-thioxothiazolidin-4-one (**6b**)*

mp > 300 °C. Yield 70 %. IR: υ/cm^{-1}: 3233 (NH), 1676, 1664 (C=O). ^{1}H NMR: δ/ppm: 5.52 (s, 1H, CH = thiazolidine), 7.25–7.65 (m, 4H, ArH), 7.74 (d, 1H, C_8-H quinazoline), 8.06 (d, 1H, C_7-quinazoline), 8.32 (s, 1H, C_5-quinazoline), 13.45 (s, 1H, NH); ^{13}C NMR: 99.34, 121.22, 122.67, 124.35, 126.54, 127.34, 129.56, 130.46, 136.43, 137.77, 139.64, 140.23, 142.43, 156.89, (12C–Ar + C=C), 164.56, (C=N), 165.89, 172.43 (2C=O), 197.45 (C=S); Anal. Calcd for $C_{18}H_9FIN_3O_2S_2$ (509.32): C, 42.45; H, 1.78; N, 8.25; Found: C, 42.30; H, 1.60; N, 8.10.

*Synthesis of the oxazolone derivatives **7a**,**b***

A mixture of 4(3*H*)-quinazolinone-2-carboxaldehydes **2a**,**b** (0.01 mol), hippuric acid (0.01 mol) and fused sodium acetate (0.5 gm) in acetic anhydride (30 ml) was heated under reflux for 1 h.The reaction, left to cool. The solid product obtained was filtered off and recrystallized from toluene to give **7a**,**b**.

*4-((3-(4-Chlorophenyl)-6-iodo-4-oxo-3, 4-dihydroquinazolin-2-yl)methylene)-2-phenyloxazol-5(4H)-one (**7a**)*

mp 176–177 °C, Yield 75 %. IR: υ/cm^{-1}: 1723, 1686 (C=O); ^{1}H NMR: δ/ppm: 5.52 (s, 1H, CH = oxazolone), 7.43–8.56 (m, 12H, Ar–H); ^{13}C NMR: 96.95, 122.43, 122.56, 123.67, 124.23, 126.45, 128.89, 129.23, 129.71, 130.32, 130.56, 131.23, 131,45, 132.45, 134.77, 137.65, 139.37, 142.32, 146.54, 148.38, (18C–Ar + C=C), 164.89, 165.32 (2C=N), 166.84, 170.32 (2C=O); MS, m/z (%): 553 (M^+, 0.11), 427 (M-C_7H_5NO; 0.41), 398 (0.57), 382 (M-$C_{10}H_6NO_2$; 32.51), 245 (C_7H_4INO; 6.42), 169 (33.19), 171($C_{10}H_5NO_2$; 33.19), 127 (I; 100), 110 (21.48), 98 (16.84), 76 (phenylene moiety; 30.18), 61 (42.78); Anal. Calcd for $C_{24}H_{13}ClIN_3O_2$ (553.74): C, 52.06; H, 2.37; N, 7.59, Found: C, 52.20; H, 2.50; N, 7.30.

*4-((3-(4-Fluorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)methylene)-2-phenyloxazol-5(4H)-one (**7b**)*

mp 156–157 °C, Yield 71 %. IR: υ/cm^{-1}: 1714, 1687 (C=O). ^{1}H NMR: δ/ppm: 5.45 (s, 1H, CH = oxazolone), 7.45–8.53 (m, 12H, Ar–H); ^{13}C NMR: 96.95, 116.32, 116.56, 122.43, 123.67, 124.23, 128.89, 129.23, 129.71, 130.32, 130.56, 131.23, 131,45, 132.45, 134.77, 137.65, 142.32, 146.54, 148.38, 156.32 (18C–Ar + C=C), 164.65, 165.76 (2C=N), 166.76, 170.87 (2C=O); Anal. Calcd for $C_{24}H_{13}FIN_3O_2$ (537.28): C, 53.65; H, 2.44; N, 7.82; Found: C, 53.50; H, 2.50; N, 7.70.

*Synthesis of imidazolidine derivatives **8a**,**b***

To a solution of the oxazolone derivatives **7a** or **7b** in acetic acid (20 ml) containing sodium acetate (0.5 gm), *o*-phenetidine (0.01 mol) was added. The reaction mixture was heated under reflux for 3 h, left to cool, then poured into crushed ice. The resulting precipitate was filtrated off, dried, and crystallized from ethanol to give **8a**,**b**.

*3-(4-Chlorophenyl)-2-((1-(2-ethoxyphenyl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)methyl)-6-iodoquinazolin-4(3H)-one (**8a**)*

mp 282–283 °C, Yield 75 %. IR: υ/cm^{-1}: 1695, 1682 (C=O); ^{1}H NMR: δ/ppm: 1.26 (t, 3H, CH_3), 4.14 (q, 2H, CH_2), 5.64 (s, 1H, CH = imidazolidine), 6.83–8.54 (m, 16H, Ar–H); ^{13}C NMR: 14.67(CH_3), 66.54(CH_2), 96.94, 115.34, 120.32, 120.89, 121.47, 121.87, 122.43, 123.67,

124.23, 125.98, 126.45, 128.89, 129.23, 129.71, 130.32, 130.56, 131,45, 132.45, 134.77, 137.65, 139.37, 142.32, 143.56, 146.54, 148.38, 150.43 (24C–Ar + C=C), 164.45, 165.67 (2C=N), 166.84, 167.23 (2C=O); Anal. Calcd for $C_{32}H_{22}ClIN_4O_3$ (672.90): C, 57.12; H, 3.30; N, 8.33; Found: C, 57.20; H, 3.40; N, 8.40.

*3-(4-Fluorophenyl)-2-((1-(2-ethoxyphenyl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)methyl)-6-iodoquinazolin-4(3H)-one (**8b**)*

mp 282–283 °C, Yield 75 %. IR: υ/cm^{-1}: 1696, 1684 (C=O). ^1H NMR: δ/ppm: 1.33 (t, 3H, CH_3), 4.05 (q, 2H, CH_2), 5.74 (s, 1H, CH = imidazolidine), 6.80–8.45 (m, 16H, Ar–H); ^{13}C NMR: 14.68(CH_3), 66.34(CH_2), 96.93, 115.12, 115.78, 120.81, 121.34, 122.67, 123.45, 124.32, 125.67, 126.42, 128.80, 129.56, 130.34, 130.76, 131.32, 131.52, 132.45, 134.67, 137.57, 139.43, 142.12, 143.74, 146.82, 148.32, 150.43, 156.32(24C–Ar + C=C), 164.23, 165.45 (2C=N), 166.34, 167.46 (2C=O); Anal. Calcd. for $C_{32}H_{22}FIN_4O_3$ (656.44): C, 58.55; H, 3.38; N, 8.53; Found: C, 58.40; H, 3.40; N, 8.60.

*Synthesis of Schiff's bases derivatives **9a**,**b***

A mixture of 4(3*H*)-quinazolinone-2-carboxaldehydes **2a**,**b** (0.01 mol) and 4-aminoantipyrene (0.01 mol) in dioxane (30 ml) was heated under reflux for 1 h. The reaction mixture was concentrated under vacuum, left to cool and then cold ethanol was added. The solid product obtained was filtered off and crystallized from dioxane to give the final products.

*3-(4-Chlorophenyl)-2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylimino)methyl)-6-iodoquinazolin-4(3H)-one (**9a**)*

mp 269–271 °C. Yield 72 %. IR: υ/cm^{-1}: 2898 (CH-aliph), 1685, 1678 (2C=O), 1614 (CH=N); ^1H NMR: δ/ppm: 2.03 (s, 3H, CH_3), 3.20 (s, 3H, N–CH_3), 7.43-8.41 (m, 12H, ArH), 9.15 (s, 1H, CH=N); ^{13}C NMR: 18.98 (CH_3), 34.42 (N–CH_3), 92.72, 114.14, 114.14, 122.54, 124.54, 125.90, 125.90, 127.78, 128.97, 129.23, 129.75, 130.60, 132.97, 133.70, 134.68, 136.71, 143.20, 146.50, 146.58, 146.89 (18C–Ar + C=C), 150.78, 151.75 (2C=N) and 157.99, 160.22 (2C=O); Anal. Calcd for $C_{26}H_{19}ClIN_5O_2$ (595.82): C, 52.41; H, 3.21; N, 11.75. Found: C, 52.10; H, 3.30; N, 11.60.

*3-(4-Fluorophenyl)-2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylimino)methyl)-6-iodoquinazolin-4(3H)-one (**9b**)*

mp 275–277 °C. Yield 70 %. IR: υ/cm^{-1}: 2930 (CH-aliph), 1671, 1654 (2C=O), 1598 (CH=N); ^1H NMR: δ/ppm: 2.06 (s, 3H, CH_3), 3.24 (s, 3H, N–CH_3), 7.47-8.53 (m, 12H, ArH), 9.05 (s, 1H, CH=N); ^{13}C NMR: 19.04 (CH_3), 34.98 (N–CH_3), 92.98, 114.15, 114.15, 122.65, 124.59, 125.98, 125.98, 127.83, 128.87, 129.45, 129.89, 130.97, 132.87, 133.45, 134.76, 136.54, 143.34, 146.65, 146.87, 146.97 (18C–Ar + C=C), 150.56, 151.98 (2C=N) and 157.78, 160.76 (2C=O); Anal. Calcd for $C_{26}H_{19}FIN_5O_2$ (579.36): C, 53.90; H, 3.31; N, 12.09; Found: C, 53.70; H, 3.40; N, 12.20.

*Synthesis of the arylidene derivatives (**10a**,**b**)*

To equimolar amount of the aldehyde derivatives **2a**,**b** and ethyl acetoacetate (0.01 mol) in dioxane (30 ml), few drops of piperidine was added. The reaction mixture was heated under reflux for 2 h., then allowed to cool. The obtained product was collected by filtration and crystallized from dioxane.

*Ethyl 2-((3-(4-chlorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)methylene)-3-oxobutanoate (**10a**)*

mp 240–241 °C, Yield 78 %. IR: υ/cm^{-1}: 2876 (CH-aliph.), 1732, 1703, 1679 (3C=O); ^1H NMR: δ/ppm: 1.18 (t, $J = 7.3$ Hz 3H, CH_3-ester), 2.44 (s, 3H, CH_3), 4.15 (q, $J = 7.2$ Hz 2H, CH_2), 6.38 (s, 1H, CH=), 7.28–7.54 (m, 4H, ArH), 7.64 (d, 1H, C_8-H quinazoline), 8.00 (d, 1H, C_7-quinazoline); 8.43 (s, 1H, C_5-quinazoline); ^{13}C NMR: 13.8 (CH_3-ester), 28.21(CH_3), 60.34 (CH_2), 99.05, 122.21, 122.54, 123.66, 126.23, 128.34, 129.76, 130.45, 136.32, 137.87, 139.54, 140.45, 142.32, 148.54, (12C–Ar + C=C), 164.49, (C=N), 165.60, 166.45 (2C=O), 197.12 ($COCH_3$); Anal. Calcd for $C_{21}H_{16}ClIN_2O_4$ (522.72): C, 48.25; H, 3.09; N, 5.36. Found: C, 48.30; H, 3.20; N, 5.50.

*Ethyl 2-((3-(4- fluorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)methylene)-3-oxobutanoate (**10b**)*

mp 200–201 °C, Yield 75 %. IR: υ/cm^{-1}: 2876 (CH-aliph.), 1728, 1700, 1684 (3C=O); ^1H NMR: δ/ppm: 1.15 (t, $J = 7.2$ Hz 3H, CH_3-ester), 2.51 (s, 3H, CH_3), 4.15 (q, $J = 7.3$ Hz, 2H, CH_2), 6.56 (s, 1H, CH=), 7.41–7.59 (m, 4H, ArH), 7.67 (d, 1H, C_8–H quinazoline), 8.12 (d, 1H, C_7-quinazoline); 8.47 (s, 1H, C_5-quinazoline); ^{13}C NMR: 13.68 (CH_3-ester), 26.72 (CH_3), 61.15 (CH_2-ester), 93.75, 115.97, 116.63, 122.65, 123.79, 126.23, 129.71, 130.99, 133.60, 134.70, 134.77, 139.37, 145.38, 158.81 (12C–Ar + C=C), 160.89, (C=N), 161.30, 162.84 (2C=O), 199.58 ($COCH_3$); MS, m/z (%): 506 (M^+; 0.26), 491 (M-CH_3; 2.42;), 435 (M-$COCH_3$; 0.33), 366 (M-$C_7H_8O_3$; 100), 245 (9.79), 234 (M-$C_7H_8IO_3$; 10.07), 183 (18.01), 122 (10.72), 95 (C_6H_4F; 86.38), 88 (22.84), 74 (89.35), 62 (43.27); Anal. Calcd for $C_{21}H_{16}FIN_2O_4$ (506.27): C, 49.82; H, 3.19; N, 5.53. Found: C, 49.80; H, 3.20; N, 5.60.

*Synthesis of the pyrazole derivatives **11a,b***

A solution of the arylidene derivatives **10a** or **10b** (0.01 mol) in ethanol (20 ml) was treated with hydrazine hydrate (0.012 mol). The reaction mixture was heated under reflux for 4 h, left to cool. The solid product obtained was filtered off and crystallized from ethanol to give **11a**,**b**.

*2-(4-Acetyl-5-oxo-2,5-dihydro-1H-pyrazol-3-yl)-3-(4-chlorophenyl)-6-iodoquinazolin-4(3H)-one (**11a**)*

mp 282–283 °C, Yield 75 %. IR: υ/cm^{-1}: 3453, 3376, (NH), 1708, 1695, 1667 (3C=O); ^{1}H NMR: δ/ppm: 2.27 (s, 3H, CH_3), 7.23–8.56 (m, 7H, Ar–H), 9.45, 9.87 (2s, 2H, 2NH); ^{13}C NMR: 24.34 (CH_3), 96.34, 118.34, 121.89, 121.97, 123.67, 125.98, 128.89, 129.23, 129.71, 131,45, 134.77, 137.45, 146.54, 148.38 (12C–Ar + C=C), 164.46 (C=N), 166.84, 167.23, 198.23 (3C=O); Anal. Calcd for $C_{19}H_{12}ClIN_4O_3$ (506.68): C, 45.04; H, 2.39; N, 11.06; Found: C, 45.20; H, 2.40; N, 11.20.

*2-(4-Acetyl-5-oxo-2,5-dihydro-1H-pyrazol-3-yl)-3-(4-fluorophenyl)-6-iodoquinazolin-4(3H)-one (**11b**)*

mp 276–278 °C, Yield 71 %. IR: υ/cm^{-1}: 3565, 3399, (NH), 1698, 1687, 1664 (3C=O); ^{1}H NMR: δ/ppm: 2.34 (s, 3H, CH_3), 7.20–8.45 (m, 7H, Ar–H), 9.43, 9.80 (2s, 2H, 2NH); ^{13}C NMR: 24.62 (CH_3), 96.30, 116.45, 116.89, 121.89, 123.56, 125.64, 128.82, 129.78, 129.97, 131,23, 134.56, 137.43, 146.34, 156.43 (12C–Ar + C=C), 164.23 (C=N), 166.56, 167.45, 198.12 (3C=O); Anal. Calcd for $C_{19}H_{12}FIN_4O_3$ (490.23): C, 46.55; H, 2.47; N, 11.43; Found: C, 46.30; H, 2.30; N, 11.20.

*Synthesis of the chalcone derivatives **12a,b***

A mixture of the aldehyde derivatives **2a**,**b** (0.01 mol), acetophenone (0.01 mol) and piperidine (1 ml) in dioxane (20 ml) was heated under reflux for 4 h, left to cool. The solid product obtained was filtered off and crystallized from ethanol to give **12a**,**b**.

*3-(4-Chlorophenyl)-6-iodo-2-(3-oxo-3-phenylprop-1-enyl)quinazolin-4(3H)-one (**12a**)*

mp 232–234 °C, Yield 73 %. IR: υ/cm^{-1}: 1708, 1682 (2C=O); ^{1}H NMR: δ/ppm: 7.46–7.59 (2d, 2H, CH=CH), 7.60-8.46 (m, 12H, Ar–H); ^{13}C NMR: 95.79, 123.60, 128.03, 128.44, 128.57, 128.82, 129.12, 129.30, 129.51, 130.18, 131.18, 132.14, 133.37, 133.42, 134.52, 134.64, 136.10, 142.97, 143.67, 145.24, (18C–Ar + C=C), 147.48 (C=N), 158.59, 185.87 (2C=O); Calcd for $C_{23}H_{14}ClIN_2O_2$ (512.73): C, 53.88; H, 2.75; N, 5.46, Found: C, 53.60; H, 2.40; N, 5.30.

*3-(4-Fluorophenyl)-6-iodo-2-(3-oxo-3-phenylprop-1-enyl)quinazolin-4(3H)-one (**12b**)*

mp 242–244 °C, Yield 75 %. IR: υ/cm^{-1}: 1707, 1695 (2C=O); ^{1}H NMR: δ/ppm: 6.85–6.94 (2d, 2H, CH=CH), 7.22–8.48 (m, 12H, Ar–H); ^{13}C NMR: 96.97, 116.32, 116.67, 121.65, 123.32, 124.76, 128.87, 129.23, 129.57, 130.12, 130.87, 131.12, 131.32, 132.43, 137.75, 139.56, 142.23, 143.86, 148.34, 156.54 (18C–Ar + C=C), 165.12 (C=N), 166.34, 168.56 (2C=O); Calcd for $C_{23}H_{14}FIN_2O_2$ (496.27): C, 55.66; H, 2.84; N, 5.64; Found: C, 55.40; H, 2.50; N, 5.70.

*Synthesis of the pyrazoline derivatives **13a,b***

A solution of the chalcone derivatives **(12a**,**b)** (0.01 mol) and hydrazine hydrate (0.012 mol) in ethanol (20 ml) was heated under reflux for 4 h, left to cool. The solid product obtained was filtered off and crystallized from ethanol to give **13a**,**b**.

*3-(4-Chlorophenyl)-6-iodo-2-(3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)quinazolin-4(3H)-one (**13a**)*

mp 254–255 °C, Yield 67 %. IR: υ/cm^{-1}: 3241 (NH), 1676 (C=O); ^{1}H NMR: δ/ppm: 3.10 (dd, 1H, H-pyrazoline), 3.77 (dd, 1H, H-pyrazoline), 5.53 (dd, 1H, H-pyrazoline), 7.32–8.43 (m, 12H, Ar–H), 12.32(s, 1H, NH); Calcd for $C_{23}H_{16}ClIN_4O$ (526.76): C, 52.44; H, 3.06; N, 10.64; Found: C, 52.50; H, 3.00; N, 10.50.

*3-(4-Fluorophenyl)-6-iodo-2-(3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)quinazolin-4(3H)-one (**13b**)*

mp 277–278 °C, yield 69 %. IR: υ/cm^{-1}: 3254 (NH), 1674 (C=O); ^{1}H NMR: δ/ppm: 3.13 (dd, 1H, H-pyrazoline), 3.76 (dd, 1H, H-pyrazoline), 5.66 (dd,1H, H-pyrazoline), 7.24–8.46 (m, 12H, Ar–H), 12.56 (s, 1H, NH); Calcd for $C_{23}H_{16}FIN_4O$ (510.30): C, 54.13; H, 3.16; N, 10.98, Found: C, 54.30; H, 2.90; N, 11.10.

*Synthesis of arylidene derivatives **14a,b***

To equimolar amount of the aldehyde derivatives **2a**,**b** and malononitrile (0.01 mol) in dioxane (30 ml), few drops of piperidine was added. The reaction mixture was heated under reflux for 2 h. then allowed to cool, the obtained product was collected by filtration and crystallized from dioxane.

*2-((3-(4-Chlorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)methylene)malononitrile (**14a**)*

mp 256–258 °C, yield 76 %. IR: υ/cm^{-1}: 2223 (CN), 1689 (C=O); ^{1}H NMR: δ/ppm: 7.76–8.65 (m, 8H, ArH + CH=); ^{13}C NMR: 91.34, 95.98, 111.87, 113.23, 116.56, 116.75, 123.54, 129.98, 131.23, 131.56, 131.78, 134.98, 143.87, 144.87, 146.99, 150.98 (12C–Ar + C=C + 2CN), 161.87 (C=N), 163.98, (C=O); Anal. Calcd. for $C_{18}H_8ClIN_4O$ (458.64): C, 47.14; H, 1.76; N, 12.22; Found: C, 47.20; H, 1.80; N, 12.30.

*2-((3-(4-Fluorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)methylene)malononitrile (**14b**)*

mp 246–247 °C Yield 77 %. IR: υ/cm^{-1}: 2218(CN), 1687(C=O). ^{1}H NMR: δ/ppm: 7.46–8.48 (m, 8H, ArH + CH=); ^{13}C NMR: 91.15, 95.45, 111.82, 113.08, 116.67, 116.86, 123.46, 129.66, 131.16, 131.24, 134.97, 143.81, 144.93, 146.99, 150.42, 159.18 (12C–Ar + C=C + 2CN), 161.55 (C=N), 163.52(C=O); Anal. Calcd. for $C_{18}H_8FIN_4O$ (442.19): C, 48.89; H, 1.82; N, 12.67; Found: C, 48.70; H, 1.90; N, 12.40.

*Synthesis of pyridinone derivatives **15a**,**b***

Method A: to a mixture of the arylidene derivatives **14a**,**b** (0.01 mol) and *N*-ethoxyphenylcyanoacetanilide (0.01 mol) in ethanol (20 ml), piperidine (0.5 ml) was added. The reaction mixture was heated under reflux for 3 h, left to cool and the obtained product was filtered off, crystallized from ethanol to give (**15a**,**b**).

Method B: A mixture of the aldehyde derivatives **2a**,**b**, malononitrile (0.01 mol), *N*-ethoxyphenyl cyanoacetanilide (0.01 mol) and piperidine (0.5 ml) in dioxane (20 ml), was heated under reflux for 3 h, left to cool. The solid product obtained was filtered off and crystallized to give **15a**,**b**.

*6-Amino-4-(3-(4-chlorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)-1-(2-ethoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**15a**)*

mp 265–266 °C, Yield 66 %. IR: υ/cm^{-1}: 3247, 3234 (NH_2), 2223, 2218(2CN), 1698, 1676 (2C=O); ^{1}H NMR: δ/ppm: 1.55 (t, 3H, CH_3-ethoxy), 4.21(q, 2H, CH_2-ethoxy), 7.12–8.48(m, 11H, Ar–H), 8.90(s, 2H, NH_2); ^{13}C NMR: 15.01 (CH_3-ethoxy), 58.41 (CH_2-ethoxy), 116.87, 116.98 (2CN), 76.34, 96.25, 110.32, 115.43, 119.56, 120.12, 120.87, 121.37, 121.78, 124.34, 124.87, 126.23, 129.43, 129.23, 130.34, 131.34, 137.59, 142.23, 143.89, 148.45, 150,56, 158.43 (18C-Ar + 4C-pyridyl), 163.13 (C=N), 166.34, 167.43 (2C=O); Calcd for $C_{29}H_{18}ClIN_6O_3$ (660.85): C, 52.71; H, 2.75; N, 12.72, Found: C, 52.60; H, 2.50; N, 12.50.

*6-Amino-4-(3-(4-fluorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)-1-(2-ethoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**15b**)*

mp 245–246 °C, yield 68 %. IR: υ/cm^{-1}: 3257, 3241 (NH_2), 2222, 2216(2CN), 1696, 1674 (2C=O); ^{1}H NMR: δ/ppm: 1.33 (t, 3H, CH_3-ethoxy), 4.34(q, 2H, CH_2-ethoxy), 6.78-8.54(m, 11H, Ar–H), 913 (s, 2H, NH_2); ^{13}C NMR: 15.01 (CH_3-ethoxy), 58.41 (CH_2-ethoxy), 117.12, 117.76 (2CN), 76.38, 96.67, 110.45, 115.46, 119.77, 120.34, 120.87, 121.39, 121.98, 124.12, 124.76, 126.67, 129.23, 129.56, 130.67, 131.34, 137.56, 142.12, 143.56, 148.45, 154.34, 158.56 (18C–Ar + 4C-pyridyl), 163.34 (C=N), 166.56, 167.78 (2C=O); Calcd for $C_{29}H_{18}FIN_6O_3$ (644.39): C, 54.03; H, 2.82; N, 13.04, Found: C, 54.20; H, 2.50; N, 13.10.

*Synthesis of arylidene derivatives **16a**,**b***

To equimolar amount of the aldehyde derivatives **2a**,**b** and barbituric acid (0.01 mol) in dioxane (30 ml), few drops of piperidine was added. The reaction mixture was heated under reflux for 2 h. then allowed to cool. The obtained product was collected by filtration and crystallized from dioxane.

*5-((3-(4-Chlorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (**16a**)*

mp 225–227 °C, Yield 78 %. IR: υ/cm^{-1}: 3343, 3227 (2NH), 1683, 1676, 1664 (C=O). ^{1}H NMR: δ/ppm: 6.78 (s, 1H, CH=), 7.56-8.45 (m, 7H, ArH), 10.23, 10.56 (2s, 2H, 2NH); ^{13}C NMR: 95.98, 122.45, 122.76, 123.79, 126.23, 129.71, 130.99, 133.60, 134.70, 134.77, 137.65, 138,34, 139.37, 145.38, (12C–Ar + C=C), 152.58 (C=O); 164.89, (C=N); 165.84, 167.43, 167.87 (3C=O); MS, *m/z* (%): 520 (M^+, 5.13), 522 (M + 2, 3.47), 410 (2.92), 382 (M-$C_5H_2N_2O_3$; 23.32), 354 (3.15), 245 (6.75), 190 (3.14), 128 (barbituric acid; 100), 110 (25.79), 100 (31.03), 85 (84.38), 74 (22.94); Anal. Calcd for $C_{19}H_{10}ClIN_4O_4$ (520.66): C, 43.83; H, 1.94; N, 10.76; Found: C, 43.70; H, 1.70; N, 10.60.

*5-((3-(4-Fluorophenyl)-6-iodo-4-oxo-3,4-dihydroquinazolin-2-yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (**16b**)*

mp 213–215 °C, Yield 78 %. IR: υ/cm^{-1}: 3319, 3228 (2NH), 1687, 1672, 1660 (C=O). ^{1}H NMR: δ/ppm: 6.45 (s,

1H, CH=), 7.45-8.34 (m, 7H, Ar–H), 10.45, 10.98 (2s, 2H, 2NH); ^{13}C NMR: 96.56, 116.12, 116.45, 123.79, 126.23, 129.71, 130.99, 133.60, 134.70, 134.77, 137.65, 138,34, 139.37, 156.43, 157.32 (12C–Ar + C=C + C=O), 164.76, (C=N), 165.76, 167.44, 167.89 (3C=O); Anal. Calcd for $C_{19}H_{10}FIN_4O_4$ (504.21): C, 45.26; H, 2.00; N, 11.11; Found: C, 45.40; H, 1.90; N, 11.00.

*Synthesis of pyrimidine derivatives **17a**,**b***

Method A: a mixture of the aldehyde derivatives **2a**,**b** (0.01 mol), thiourea (0.01 mol), ethyl acetoacetate (0.01 mol) and few drops of conc. HCl in dioxane (20 ml) was heated under reflux for 3 h, left to cool. The solid product obtained was filtered off and crystallized from dioxane to give **17a**,**b**.

Method B: a mixture of the arylidene derivatives **10a**,**b** (0.01 mol), thiourea (0.01 mol) and few drops of conc. HCl in ethanol (20 ml) was heated under reflux for 3 h, left to cool. The solid product obtained was filtered off and crystallized from dioxane to give **17a**,**b**.

*Ethyl 4-(3-(4-chlorophenyl)-6-iodo-4-oxo-3, 4-dihydroquinazolin-2-yl)-6-methyl-2-thioxo-1,2,3, 4-tetrahydropyrimidine-5-carboxylate (**17a**)*

mp 243–244 °C, Yield 62 %. IR: υ/cm^{-1}: 3241, 3214 (2NH), 1723, 1675 (2C=O); ^{1}H NMR: δ/ppm: 1.54 (t, $J = 7.2$ Hz, 3H, CH_3-ester), 1.89 (s, 3H, CH_3), 4.23(q, $J = 7.3$ Hz, 2H, CH_2-ester), 4.77(d, 1H, CH), 7.32-8.43(m, 7H, Ar–H), 10.13, 10.54(2 s, 2H, 2NH); ^{13}C NMR: 18.34 (CH_3-ester), 18.43 (CH_3), 58.43 (CH_2-ester), 54.43 (C_4-pyrimidine), 104.54, 154.45(C_5-, C_6-pyrimidine), 96.43, 121.35, 121.68, 124.34, 129.43, 129.23, 130.34, 131.34, 137.59, 142.23, 143.89, 148.45 (12C–Ar), 163.13 (C=N), 166.34 (C=O), 167.12 (C=O), 178.32 (C=S); Calcd for $C_{22}H_{18}ClIN_4O_3S$ (580.83): C, 45.49; H, 3.12; N, 9.65; Found: C, 45.60; H, 3.22; N, 9.48.

*Ethyl 4-(3-(4-fluorophenyl)-6-iodo-4-oxo-3, 4-dihydroquinazolin-2-yl)-6-methyl-2-thioxo-1,2,3, 4-tetrahydropyrimidine-5-carboxylate (**17b**)*

mp 263–264 °C, Yield 62 %. IR: υ/cm^{-1}: 3245, 3234 (2NH), 1714, 16765 (2C=O); ^{1}H NMR: δ/ppm: 1.54 (t, 3H, CH_3-ester), 1.90 (s, 3H, CH_3), 4.54(q, 2H, CH_2-ester), 4.75(d, 1H, CH), 7.13–8.23 (m, 7H, Ar–H), 10.34, 10.65(2s, 2H, 2NH); ^{13}C NMR: 18.30 (CH_3-ester), 18.41 (CH_3), 58.48 (CH_2-ester), 54.12 (C_4-pyrimidine), 104.52, 154.40(C_5-, C_6-pyrimidine), 96.43, 115.34, 115.98, 121.35, 124.34, 129.23, 130.34, 131.34, 137.59, 142.23, 143.89, 154.32 (12C-Ar), 163.24 (C=N), 166.56 (C=O), 167.08 (C=O), 178.76 (C=S); Calcd for $C_{22}H_{18}ClFN_4O_3S$ (564.37): C, 46.82; H, 3.21; N, 9.93, Found: C, 46.60; H, 3.30; N, 9.70.

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