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Synthesis and Antiinflammatory Screening of Some Quinazoline and Quinazolyl-4-oxoquinazoline Derivatives

Synthesis of some new derivatives of 2-aryl-4-oxo-1-(4-quinazolyl)quinazolines is described. Methyl *N*-(4-quinazolyl)anthranilate was allowed to react with phenyl iso(thio)cyanate to give 3-phenyl-1-(4-quinazolyl)-1,2,3,4-tetrahydro-2,4-dioxo- and 4-oxo-2-thioxoquinazolines (**3 a** and **3 b**, respectively) Alternatively, anthranilic acid amide derivatives were subjected to cyclization with aromatic aldehydes to give 2-aryl-4-oxo-1-(4-quinazolyl)-1,2,3,4-tetrahydroquinazolines **5**. On the other hand, 2-chloro-4-(4-substituted 1-piperazinyl)quinazoline derivatives were subjected to the same type of reactions at the 2-position to afford the corresponding quinazoline derivatives **8** and **10**, respectively. Furthermore, the acid amide **4 b** was cyclized with acid chlorides to give the corresponding 2-aryl-1-(2-chloro-4-quinazolyl)-4-oxo-1,4-dihydroquinazolines **11**, from which the triazoloquinazoline derivatives **13** and **15** were synthesized through the intermediate hydrazine derivatives **12**. Most of the newly synthesized compounds were tested for their antiinflammatory activities. However, some of the novel compounds were found to exhibit good antiinflammatory potencies.

Keywords: 4-Oxoquinazolines; Triazolo[4,3-*a*]quinazolines; Antiinflammatory activity

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Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are among the most widely used of all therapeutic agents. The fact that so many new compounds have been produced and are still being produced is a reflection of the fact that none is ideal in controlling and modifying the signs and symptoms of inflammation. A particular problem is that virtually all NSAIDs can have significant side effects. Therefore, there is a great deal of research going on into antiinflammatory and immunosuppressant agents. A major mechanism of action of NSAIDs is lowering prostaglandin production through inhibition of cyclooxygenase (COX), which has dual functions, mediation of inflammation [1] and cytoprotection of the stomach and intestine [2]. Thus, long-term therapy with NSAIDs will cause gastrointestinal damage and ulceration. However, it was discovered that COX exists in two isoforms, COX-1 and COX-2, which are encoded by two distinct genes [3]. COX-1 is expressed constitutively providing cytoprotection while COX-2 is transiently upregulated by proinflammatory mediators [4]. This regulated expression suggests that a selective inhibitor of COX-2 may have antiinflammatory properties and lack the ulcerogenic side effects. This hypothesis has been supported by several *in vivo* studies with selective COX-2 inhibitors [5, 6]. Among the many reported classes of antiinflammatory agents, 4-oxoquinazolines possess good activity [7, 8]. Moreover, 4-anilinoquinazoline derivatives were reported to exhibit protein kinase inhibitor activity, which is of therapeutic value in a wide range of disease states, such as cancer and arthritis [9]. Furthermore, we had reported some 1,2,4-triazolo[4,3-*c*] and [1,5-*c*]quinazoline derivatives of potent and selective COX-2 inhibition properties [10]. Directed by these findings, we here report the synthesis of 4-oxoquinazoline derivatives of potential antiinflammatory activity.

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Results and discussion

Chemistry

All the compounds synthesized in the current work were derived from 4-chloro- and 2,4-dichloroquinazoline (**1 a** and **1 b**, respectively) as exemplified in Schemes 1–3. The presence of a chloro group at C-4 of the quinazoline

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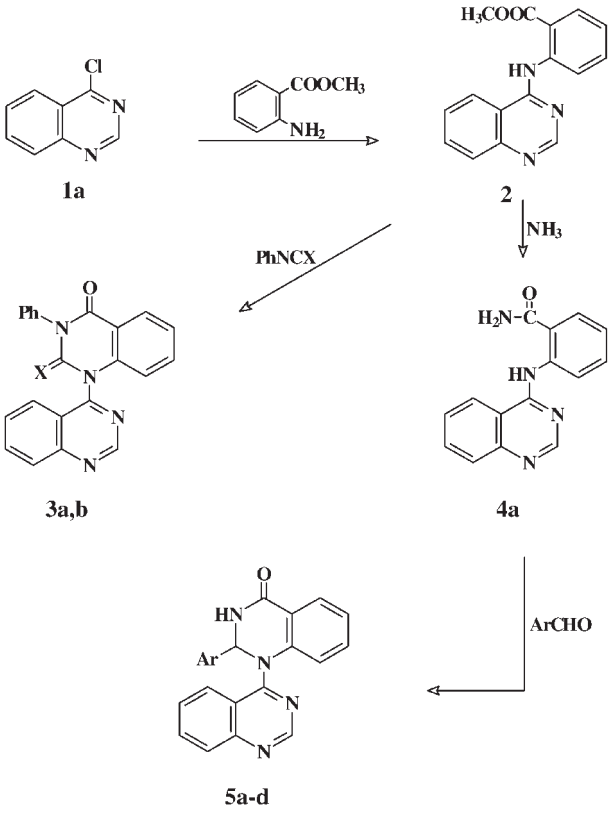
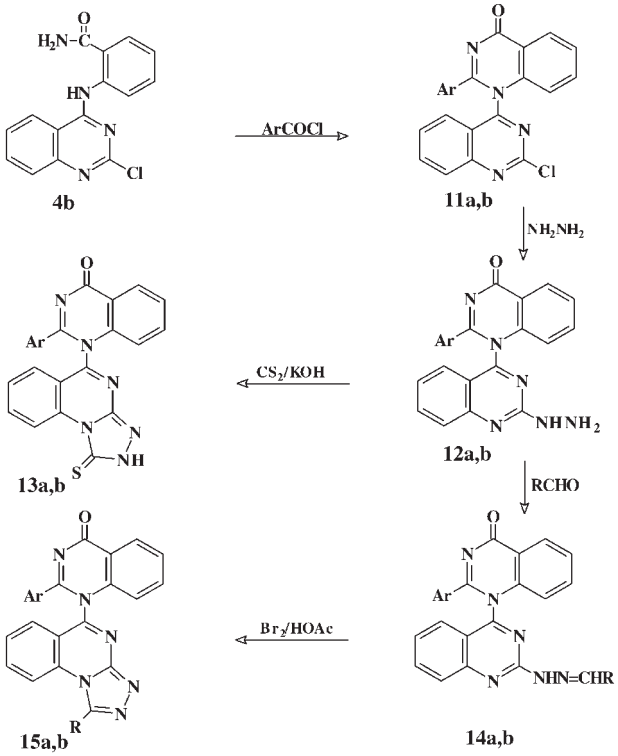
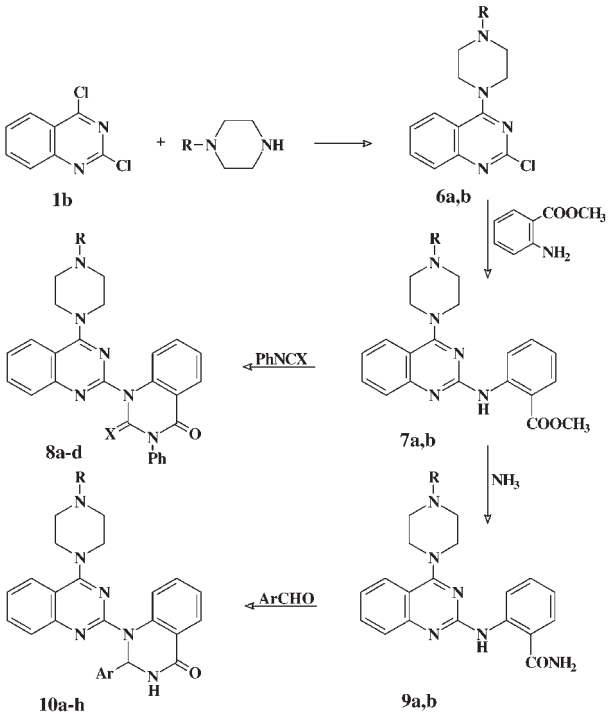


Scheme 1



Scheme 3



Scheme 2

ring provided a functionalizable handle from which various moieties could be obtained. A facile reaction of methyl ester of anthranilic acid takes place with 4-chloroquinazoline (**1 a**) through a nucleophilic substitution mechanism to give compound **2**. The 4-oxoquinazoline derivatives utilized in this study were prepared by different synthetic methods according to the type of cyclizing agent as shown in Schemes 1–3. Thus, 1-(4-quinazolyl)-4-oxoquinazolines **3** and **5** were prepared from compound **2** using the routes depicted in Scheme 1 (Table 1). These compounds were prepared essentially following two procedures for cyclization of anthranilic acid derivatives. The first procedure involves the reaction of a solution of methyl ester of *N*-substituted anthranilic acid **2** and sodium hydride in tetrahydrofuran (THF) with a solution of phenyl iso(thio)cyanate in THF to give compounds **3**. In the second cyclization procedure, the *N*-substituted anthranilic acid amide **4 a** was used. Compound **4 a** was previously reported [11], however, in the current work it was prepared by ammonolysis of the ester **2**, and then allowed to react with an ethanolic solution of the appropriate aromatic aldehyde in basic medium to give **5**. However, similar reactions were applied with 2,4-dichloroquinazoline (**1 b**). Under all reaction conditions, equimolar amounts of several nucleophiles attack exclusively at the C-4 of quinazoline ring, which is of preferential

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Table 1. Physicochemical data of the new compounds.

	Ar	R(X)	Mp [°C]	Rec. Sol.[a]	Yield [%]	Mol. Formula
3 a	–	(O)	>300	E/C	65	$C_{22}H_{14}N_4O_2$
3 b	–	(S)	277–279	E/C	72	$C_{22}H_{14}N_4OS$
5 a	Ph	–	>300	E/B	57	$C_{22}H_{16}N_4O$
5 b	4-Cl-Ph	-	>300	E/B	65	$C_{22}H_{15}ClN_4O$
5 c	3,4-$(OMe)_2$-Ph	–	263–265	E	71	$C_{24}H_{20}N_4O_3$
5 d	3-NO_2-Ph	–	>300	E	62	$C_{22}H_{15}N_5O_3$
6 a	–	Me	185–187	M	87	$C_{13}H_{15}ClN_4$
6 b	–	Ph	191–193	M	91	$C_{18}H_{17}ClN_4$
7 a	–	Me	214–216	M/C	76	$C_{21}H_{23}N_5O_2$
7 b	–	Ph	232–234	M/C	72	$C_{26}H_{25}N_5O_2$
8 a	–	Me(O)	>300	A	64	$C_{27}H_{24}N_6O_2$
8 b	–	Me(S)	281–283	A	69	$C_{27}H_{24}N_6OS$
8 c	–	Ph(O)	>300	A	75	$C_{32}H_{26}N_6O_2$
8 d	–	Ph(S)	295–297	A	62	$C_{32}H_{26}N_6OS$
9 a	–	Me	232–234	M	51	$C_{20}H_{22}N_6O$
9 b	–	Ph	263–265	M	54	$C_{25}H_{24}N_6O$
10 a	Ph	Me	282–284	M	74	$C_{27}H_{26}N_6O$
10 b	4-Cl-Ph	Me	287–289	M	62	$C_{27}H_{25}ClN_6O$
10 c	3,4-$(OMe)_2$-Ph	Me	265–267	M/C	67	$C_{29}H_{30}N_6O_3$
10 d	3-NO_2-Ph	Me	>300	M/C	61	$C_{27}H_{25}N_7O_3$
10 e	Ph	Ph	277–279	E	68	$C_{32}H_{28}N_6O$
10 f	4-Cl-Ph	Ph	294–296	E	80	$C_{32}H_{27}ClN_6O$
10 g	3,4-$(OMe)_2$-Ph	Ph	271–273	E	67	$C_{34}H_{32}N_6O_3$
10 h	3-NO_2-Ph	Ph	>300	E	72	$C_{32}H_{27}N_7O_3$
11 a	3-Cl-Ph	–	>300	E/C	62	$C_{22}H_{12}Cl_2N_4O$
11 b	4-Br-Ph	–	>300	E/C	56	$C_{22}H_{12}BrClN_4O$
12 a	3-Cl-Ph	–	>300	E	90	$C_{22}H_{15}ClN_6O$
12 b	4-Br-Ph	–	>300	E	82	$C_{22}H_{15}BrN_6O$
13 a	3-Cl-Ph	–	291–293	E	52	$C_{23}H_{13}ClN_6OS$
13 b	4-Br-Ph	–	>300	M	46	$C_{23}H_{13}BrN_6OS$
14 a	3-Cl-Ph	3-NO_2-Ph	281–283	E	64	$C_{29}H_{18}ClN_7O_3$
14 b	4-Br-Ph	3-NO_2-Ph	278–280	E	73	$C_{29}H_{18}BrN_7O_3$
15 a	3-Cl-Ph	3-NO_2-Ph	265–267	M	58	$C_{29}H_{16}ClN_7O_3$
15 b	4-Br-Ph	3-NO_2-Ph	283–285	M	87	$C_{29}H_{16}BrN_7O_3$

[a] Recrystallization solvent; A: acetonitrile, B: benzene, C: chloroform, E: ethanol, M: methanol.

reactivity over the C-2 position. Synthesis of 4-oxo-1-[4-(4-substituted 1-piperazinyl)-2-quinazolyl]-2-substitutedquinazolines **8** and **10** is outlined in Scheme 2. The synthesis began with selective nucleophilic substitution of the 4-chloro group of **1 b**. Incorporation of a piperazinyl residue into the 4-position of **1 b** was accomplished by refluxing in ethanol in presence of sodium carbonate to give **6**. Now, compounds **6** have the C-2 as the only available position for nucleophilic attack. Therefore, **6** was refluxed with an ethanolic solution of methyl anthranilate to give **7**. The 3-phenyl-1-substituted quinazolyl-2,4-dioxo- and 4-oxo-2-thioxoquinazoline derivatives **8** were prepared from **7** applying the same procedure used for preparation of **3**. Moreover, 2-aryl-4-oxo-1-substituted quinazolylquinazolines **10** were prepared from **7** (Scheme 2), which was transformed into **9** using the same procedure as was applied for the preparation of **4**, as outlined earlier (Scheme 1). However, insertion of the

4-oxoquinazoline moiety at the 4-position of **1 b** ensured that **4 b** [11] was cyclized using benzoyl chloride derivatives to yield **11** (Scheme 3). Refluxing **11** with hydrazine formed **12**, which upon cyclization under standard conditions provided the desired triazolo[4,3-*a*]quinazoline skeleton **13** and **15**. Two potential strategies were applied for construction of the fused triazole ring. The first methodology involves the reaction of **12** with carbon disulfide under basic conditions to afford a fused thioxotriazole structure **13**. The second method relies upon condensation of the aromatic aldehyde with **12** to give the corresponding arylidene derivatives of the hydrazines **14**. Formation of **15** was achieved following a published procedure [12] by treating **14** with an acetic acid solution of bromine followed by pouring onto sodium hydroxide solution.

Biological screening

Most of the newly synthesized compounds were tested for their antiinflammatory activity against carrageenin-induced edema at dose of 100 mg/kg using ketoprofen as a reference standard (Table 2). With the objective of identifying compounds with selective COX-2 inhibition, we distinguished the selective compounds of the present study by assessing their *in vivo* ulcerogenic effects. Our initial screening efforts were directed towards the evaluation of the antiinflammatory activities of the quinazolyl-4-oxoquinazoline derivatives with interchange of the position of attachment of both nuclei. Most of these analogs exhibit good activity ranging from 60 to 88 % edema reduction, as shown in Table 2. The major exception proved to be the 3,4-dimethoxyphenyl derivatives **5 c** and **10 c** with 45 % and 32 % edema reduction, respectively. As a general rule, the non-cyclized *N*-substituted anthranilic acid derivatives were found to be less potent than the cyclized analogs. Thus, compounds **4 a**, **7 a**, and **7 b** possess the lowest antiinflammatory activities. Regarding compounds **3** and **8**, with the exception of **8 d**, the isosteric replacement of the oxygen atom at the 2-position of 2,4-dioxoquinazoline analogs with a sulfur atom gave compounds with 4-oxo-2-thioxoquinazoline structure characterized by better antiinflammatory activities. With the 4-oxoquinazoline moiety in compounds **5** and **10**, we investigated the effect of the 2-aryl group in detail. When the group on the phenyl ring was changed to a number of substituents ranging from electron-donating to electron-withdrawing groups, it was found to correlate quite well with the antiinflammatory activity. Thus, insertion of a 3-nitro group as in **5 d** provided a substantial improvement in activity. Moreover, COX-2 selectivity, as indicated by minimal ulcerogenic effect, was significantly improved. On the other hand, the 3,4-dimethoxy substituent in **5 c** showed relatively poor activity. However, the 4-chloro group in **5 b** led to an activity intermediate between **5 d** and **5 c**. As can be seen in Table 2, this trend generally held true in the 4-oxo-1-(4-substituted piperazinyl-2-quinazolyl)quinazoline series **10**. However, a change of substituent on the piperazine nucleus in compounds **8** and **10** did not appreciably affect the potency. On the contrary, cyclization of **12** to give thioxotriazoloquinazoline derivatives resulted in a significant increase in potency. Moreover, the potency of **12** was increased again by the formation of the corresponding arylidene derivatives **14**. However, cyclization of compound **14** gave the triazolo derivatives **15** characterized by a decrease in antiinflammatory activity.

Table 2. Antiinflammatory activity of the tested compounds assessed in parallel with ketoprofen as a reference standard.

Comp.	Mean % increase in paw weight ± SE	% Reduction of paw edema from control group
Control	52.73 ± 4.54	–
3 a	11.84 ± 1.21[a]	77.54
3 b	8.64 ± 1.34[a]	83.61
4 a	40.33 ± 3.26	23.52
5 a	20.79 ± 3.17[a]	60.57
5 b	17.16 ± 2.38[a]	67.46
5 c	28.57 ± 1.76[a]	45.82
5 d	13.51 ± 2.28[a]	74.38
7 a	43.00 ± 4.26	18.45
7 b	37.34 ± 2.94	29.19
8 a	8.35 ± 1.28[a]	84.16
8 b	6.13 ± 1.67[a]	88.37
8 c	8.85 ± 1.17[a]	83.22
8 d	12.35 ± 1.59[a]	76.58
9 a	33.62 ± 2.31[a]	36.24
10 c	35.56 ± 1.93[a]	32.56
10 d	11.16 ± 0.97[a]	78.83
10 h	12.18 ± 1.19[a]	76.90
512 a	19.65 ± 2.29[a]	62.73
13 a	11.34 ± 1.12[a]	78.49
14 a	13.89 ± 2.45[a]	73.66
14 b	12.01 ± 1.19[a]	77.22
15 a	20.54 ± 2.17[a]	61.05
15 b	18.29 ± 1.29[a]	65.31
Ketopr.	9.14 ± 2.45[a]	82.67

All the test compounds and ketoprofen were given orally at a dose of 100 mg/kg.

[a] Significantly different from the control group using the student “t” test

Table 3. Potential ulcerogenic effect of the test compounds compared with ketoprofen and indomethacin.

Comp.	Dose [mg/kg]	Mean ulcer index ± S.E.
Control	Vehicle	0
Ketoprofen	50	3.2 ± 0.3[a]
Indomethacin	5	10.1 ± 0.7
3 b	50	1.7 ± 0.2[b]
5 a	50	4.3 ± 0.4[a]
5 d	50	1.8 ± 0.2[b]
8 a	50	2.7 ± 0.3[a]
8 b	50	3.9 ± 0.3[a]
8 c	50	1.5 ± 0.1[b]
10 d	50	2.8 ± 0.3[a]
13 a	50	2.4 ± 0.3[a]
14 b	50	3.8 ± 0.4[a]

[a] ($p < 0.05$) significantly different from indomethacin-treated group using the student "t" test.

[b] ($p < 0.05$) significantly different from ketoprofen-treated group.

The ulcerogenicity testing data are compiled in Table 3. The selected compounds, which are the most active in edema reduction, were tested against ketoprofen and indomethacin. The latter was used as a potent antiinflammatory drug with substantial ulcerogenic effect. As shown in Table 3, it is obvious that indomethacin produces high incidence of gastric ulceration while ketoprofen produces much less ulcerogenic effect. On the other hand, with the exception of compounds **5 a**, **8 b**, and **14 b**, the tested compounds revealed less ulcerogenic effect than ketoprofen. Moreover, compound **8 c** gave minimal gastric ulceration. Meanwhile, this compound is almost equipotent with ketoprofen. Thus, it is considered to be a lead compound with high antiinflammatory activity and insignificant ulcerogenic effect. In other words, compound **8 c** is a potent antiinflammatory agent with selective COX-2 inhibitory activity.

In conclusion, the quinazoline ring system provided a useful scaffold for attaching different heterocyclic moieties to obtain potent and selective COX-2 inhibitors. The 2-oxo and 2-thioxo groups in **3** and **8** provide enhancement of the potency of the 4-oxoquinazoline series relative to 2-aryl groups as in **5** and **10**. However, in accordance with the conclusion of such comparisons, the 3-thioxotriazolo moiety in **13** was found to be superior in activity to the 3-aryl substituent in **15**, as shown in Table 2. Moreover, in agreement with the findings in the 2-aryl-4-oxo-1-(4-quinazolyl)quinazoline series represented by **5**, the 3-nitrophenyl substituent manifested better activity in compounds **10**. It is noteworthy that the displacement of the 4-oxoquinazoline residue from the 4-position to the 2-position of the quinazoline nucleus increased the antiinflammatory activity.

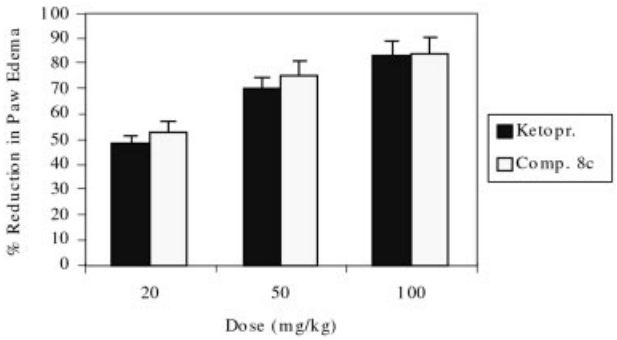

Figure 1. The antiinflammatory activity of ketoprofen and compound **8 c** at three different dose levels (20, 50, and 100 mg/kg) expressed as % reduction in paw edema ± SE. No significant difference between **8 c**- and ketoprofen-treated groups using student "t" test.

Nevertheless, compound **8 c**, as a promising antiinflammatory agent, was subjected to antiinflammatory testing at different dose levels in parallel with ketoprofen (Figure 1). It was found that compound **8** c has more or less comparable efficacy with that of ketoprofen.

Acknowledgement

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Experimental

Chemistry

Melting points were determined on a Fischer-Johns apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian EM-360 (90 MHz) instrument using TMS as internal standard (chemical shifts in ppm, δ units). The results of elemental analyses (C,H,N) were within ± 0.4 % of the theoretical values. Thin-layer chromatography was performed on silica gel GLF plates, 250 µm using chloroform/methanol (9/1) as a mobile phase.

4-(2-Methoxycarbonylphenylamino)quinazoline (**2**)

A mixture of 4-chloroquinazoline (**1 a**) (1.65 g, 10 mmol), methyl anthranilate (1.5 g, 10 mmol), pyridine (0.5 mL), and absolute ethanol (40 mL) was heated under reflux for 5 h. On cooling, the product obtained was collected by filtration, dried, and recrystallized from methanol to give 2 g (72 %) of **2**, mp 171–173 °C. ^{1}H-NMR (DMSO-d_6): 3.88 (s, 3 H, CH_3), 7.11–8.12 (m, 8 H, Ar-H), 8.53 (s, 1 H, Ar-H), 10.14 (s, 1 H, NH; D_2O exchangeable).

2,4-Dioxo- and 4-oxo-2-thioxo-3-phenyl-1-(4-quinazolyl)-1,2,3,4-tetrahydroquinazolines (**3 a, b**)

A mixture of **2** (0.28 g, 1 mmol), sodium hydride (60 %, 0.04 g, 1 mmol), and THF (10 mL) was stirred at room temperature for 15 min. A solution of phenyl iso(thio)cyanate (1.5 mmol) in THF (5 mL) was added while cooling in an ice bath to the reaction mixture, which was then stirred for 1 h at room temperature. The product was collected by filtration, washed with cold water, dried, and recrystallized. ^{1}H-NMR (DMSO-d_6), **3a**: 7.21–8.14 (m, 13 H, Ar-H), 8.81 (s, 1 H, Ar-H).

4-(2-Aminocarbonylphenylamino)quinazoline (**4 a**)

A mixture of **2** (0.56 g, 2 mmol) and methanolic solution of ammonia saturated at 0 °C (40 mL) was stirred at room temperature for 24 h. The product obtained was collected by filtration, washed with methanol, dried, and recrystallized from DMF/H_2O to give 0.36 g (68 %) of **4 a**, mp 217–219 °C as reported [11].

2-Aryl-4-oxo-1-(4-quinazolyl)-1,2,3,4-tetrahydroquinazolines (**5 a**–**d**)

A mixture of **4 a** (0.53 g, 2 mmol), the appropriate aldehyde (2 mmol), and an ethanolic solution of NaOH (5 %, 30 mL) was heated at reflux for 8 h. After cooling, the product was collected by filtration, dried, and recrystallized. ^{1}H-NMR (DMSO-d_6), **5 b**: 7.18–8.21 (m, 13 H, Ar-H and H-2), 8.62 (s, 1 H, Ar-H), 10.68 (s, 1 H, NH; D_2O exchangeable). **5 d**: 6.94–8.33 (m, 13 H, Ar-H and H-2), 8.73 (s, 1 H, Ar-H), 10.72 (s, 1 H, NH; D_2O exchangeable).

2-Chloro-4-(4-substituted 1-piperazinyl)quinazolines (**6 a, b**)

A mixture of 2,4-dichloroquinazoline (**1 b**) (0.2 g, 1 mmol), 1-substituted piperazine (1 mmol), anhydrous sodium carbonate (0.2 g), and absolute ethanol (25 mL) was heated under reflux for 2–4 h. The product obtained after cooling was collected by filtration, washed with water, dried, and recrystallized. ^{1}H-NMR (DMSO-d_6), **6 a**: 2.24 (t, 4 H, piperazine-H), 2.41 (s, 3 H, CH_3), 3.19 (t, 4 H, piperazine-H), 7.12–8.14 (m, 4 H, Ar-H). **6 b**: 2.26 (t, 4 H, piperazine-H), 3.24 (t, 4 H, piperazine-H), 7.10–8.22 (m, 9 H, Ar-H).

2-(2-Methoxycarbonylphenylamino)-4-(4-substituted 1-piperazinyl)quinazolines (**7 a, b**)

These compounds were prepared from **6** following the same procedure applied for preparation of **2**. ^{1}H-NMR (DMSO-d_6), **7 a**: 2.22 (t, 4 H, piperazine-H), 2.43 (s, 3 H, CH_3), 3.21 (t, 4 H, piperazine-H), 3.92 (s, 3 H, OCH_3), 7.03–8.16 (m, 8 H, Ar-H), 10.2 (s, 1 H, NH; D_2O exchangeable).

2,4-Dioxo- and 4-oxo-2-thioxo-3-phenyl-1-[4-(4-substituted 1-piperazinyl)-2-quinazolyl]-1,2,3,4-tetrahydroquinazolines (**8 a**–**d**)

These compounds were prepared from **7** applying the procedure used for preparation of compounds **3**. ^{1}H-NMR (DMSO-d_6), **8 a**: 2.19 (t, 4 H, piperazine-H), 2.39 (s, 3 H, CH_3), 3.22 (t, 4 H, piperazine-H), 7.21–8.33 (m, 13 H, Ar-H), **8 c**: 2.18 (t, 4 H, piperazine-H), 3.24 (t, 4 H, piperazine-H), 7.19–8.25 (m, 18 H, Ar-H).

2-(2-Aminocarbonylphenylamino)-4-(4-substituted 1-piperazinyl)quinazolines (**9 a, b**)

These two compounds were prepared from **7** following the procedure used for preparation of compound **4 a**. ^{1}H-NMR (DMSO-d_6), **9 b**: 2.21 (t, 4 H, piperazine-H), 3.24 (t, 4 H, piperazine-H), 7.31–8.27 (m, 13 H, Ar-H), 8.51 (br s, 2 H, NH_2; D_2O exchangeable), 10.12 (br s, 1 H, NH; D_2O exchangeable).

2-Aryl-4-oxo-1-[4-(4-substituted 1-piperazinyl)-2-quinazolyl]-1,2,3,4-tetrahydroquinazolines (**10 a**–**h**)

Compounds **10** were prepared from **9** applying the same procedure as used for preparation of **5**. ^{1}H-NMR (DMSO-d_6), **10 a**: 2.18 (t, 4 H, piperazine-H), 2.41 (s, 3 H, CH_3), 3.24 (t, 4 H, piperazine-H), 7.32–8.19 (m, 14 H, Ar-H and H-2), 10.82 (br s, 1 H, NH; D_2O exchangeable). **10 c**: 2.20 (t, 4 H, piperazine-H), 2.38 (s, 3 H, CH_3), 3.25 (t, 4 H, piperazine-H), 4.35 (s, 6 H, 2 OCH_3), 7.21–8.25 (m, 12 H, Ar-H and H-2), 10.76 (br s, 1 H, NH; D_2O exchangeable). **10 e**: 2.24 (t, 4 H, piperazine-H), 3.31 (t, 4 H, piperazine-H), 7.12–8.24 (m, 19 H, Ar-H), 10.83 (br s, 1 H, NH; D_2O exchangeable). **10 h**: 2.19 (t, 4 H, piperazine-H), 3.25 (t, 4 H, piperazine-H), 7.33–8.25 (m, 18 H, Ar-H and H-2), 10.74 (br s, 1 H, NH; D_2O exchangeable).

2-Aryl-1-(2-chloro-4-quinazolyl)-4-oxo-1,4-dihydroquinazolines (**11 a, b**)

A mixture of **4 b** (0.6 g, 2 mmol), substituted benzoyl chloride (5 mmol), and chloroform (20 mL) was heated under reflux for 24 h. The solvent was evaporated under reduced pressure, the residue was neutralized with aqueous sodium carbonate, collected by filtration, washed with water, dried, and recrystallized. ^{1}H-NMR (DMSO-d_6), **11 a**: 7.24–8.31 (m, 12 H, Ar-H).

2-Aryl-1-(2-hydrazino-4-quinazolyl)-4-oxo-1,4-dihydroquinazolines (**12 a, b**)

A mixture of **11** (2 mmol), hydrazine hydrate (99 %, 2 mL), and absolute ethanol (20 mL) was heated under reflux for 4 h. The product was collected by filtration, washed with ethanol, dried, and recrystallized. ^{1}H-NMR (DMSO-d_6), **12 b**: 4.81 (br s, 2 H, NH; D_2O exchangeable), 7.31–8.35 (m, 12 H, Ar-H), 10.11 (br s, 1 H, NH; D_2O exchangeable).

9-(2-Aryl-4-oxo-1,4-dihydro-1-quinazolyl)-3-thioxo-2H-1,2,4-triazolo[4,3-a]quinazolines (**13 a, b**)

A mixture of **12** (2 mmol), potassium hydroxide (0.2 g), carbon disulfide (1.5 mL), and methanol (25 mL) was heated under reflux for 8 h. The solvent was removed under reduced pressure, the residue obtained was dissolved in 10 % aqueous solution of potassium hydroxide, the solution was filtered and neutralized with dilute solution of hydrochloric acid. The product was collected by filtration, washed with water, dried, and recrystallized. ^{1}H-NMR (DMSO-d_6), **13 b**: 7.41–8.53 (m, 12 H, Ar-H), 12.11 (s, 1 H, NH; D_2O exchangeable).

2-Aryl-1-(2-arylidenehydrazino-4-quinazolyl)-4-oxo-1,4-dihydroquinazolines (**14 a, b**)

A mixture of **12** (2 mmol), the appropriate aldehyde (2.2 mmol), and absolute ethanol (30 mL) was heated under reflux for 2 h. The product was collected by filtration, dried, and recrystallized. ^{1}H-NMR (DMSO-d_6), **14 a**: 7.51–8.49 (m, 17 H, Ar-H, and Ar-CH=N), 12.15 (s, 1 H, NH; D_2O exchangeable).

3-Aryl-9-(2-aryl-4-oxo-1,4-dihydroquinazolyl)-1,2,4-triazolo-[4,3-a]quinazolines (**15 a, b**)

A solution of bromine (0.1 mL) in glacial acetic acid (0.5 mL) was added to a suspension of **14** (2 mmol) and anhydrous sodium acetate (1.5 g) in acetic acid (5 mL). The reaction mixture was stirred for 30 min at room temperature and then poured onto ice-cooled sodium hydroxide (5 %, 100 mL). The product was collected by filtration, washed with water, dried, and recrystallized. ^{1}H-NMR (DMSO-d_6), **15 a**: 7.42–8.41 (m, 16 H, Ar-H).

Biological screening

Antiinflammatory screening

The preliminary screening was accomplished by applying the procedure of Winter et al. [13] using groups of albino rats weighing 100–120 g each, with 6 rats in each group. The compounds were suspended in 0.5 % carboxymethylcellulose (CMC) and given to the rats orally in a dose of 100 mg/kg. Ketoprofen was used as a positive control (reference standard) given orally in a dose of 100 mg/kg. Another animal group serving as a negative control received equivalent volume of the vehicle (0.5 % CMC) orally. One hour after drug administration, each rat was injected with 0.05 mL of 1 % carrageenin solution into the plantar tissue of the right hind paw. Four hours after carrageenin injection, the animals were killed by cervical dislocation and both the right and left hind paws were cut at a standard point and weighed. The difference in weight between right and left paws was recorded for each animal. The percentage increase in weight of the carrageenin-injected paw over the other paw was calculated and percentage reduction of edema from the control group was calculated as a measure of activity.

Ulcerogenicity determination

Male albino rats weighing 150–180 g, divided into 4 groups of 6 rats each, were fasted for 12 h while allowing free access to water. Indomethacin suspended in 0.5 % CMC was given orally at a dose of 5 mg/kg whereas ketoprofen and other compounds were administered at a dose of 50 mg/kg. The dose was repeated daily for 5 days. Eight hours after the last dose, the animals were killed by an overdose of ether. The stomach was removed, rinsed with physiological saline, opened along the greater curvature, and studied with hand lens (×10 magnification). The ulcer index of each animal was expressed according to the sum of the length of lesions on according to Adami et al. [14]

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