International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

International Journal of Pharmacology 1 (3): 261-266, 2005
ISSN 1811-7775

Synthesis and Anti-inflammatory Evaluation of Some New Quinazoline Derivatives

[1]Mosaad Sayed Mohamed, [2]Mohamed Kamal Ibrahim, [2]Ahmed Mahmoud Alafify,
[2]Sami Gaber Abdel-Hamide and [3]Adel M. Mostafa
[1]Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Helwan University Cairo, Egypt
[2]Department of Pharmaceutical Chemistry, [3]Department of Pharmacology,
Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt

Abstract: A series of new 5-(4-chlorophenyl)-9-iodo-3-substituted-1,2,4-triazolo[4,3-c]quinazoline and 2- (4-chlorophenyl)-6-iodo-4-substituted-quinazoline was prepared via several synthetic routes. Some of the compounds were prepared by cyclization of 2-(4-chlorophenyl)-4-chloro-6-iodoquinazoline with semicarbazide or acid hydrazide; other compounds were obtained from reaction of 2-(4-chlorophenyl)-4-chloro-6-iodoquinazoline with some amines and amino acid esters. The synthesized compounds were evaluated as anti-inflammatory agents through the carrageenin-induced paw edema test. The screening data revealed that nine of the tested compounds have activity comparable to indomethacin.

Key words: 1,2,4-triazolo[4,3-c] quinazoline, synthesis, anti-inflammatory, nonsteroidal, analgesic

INTRODUCTION

Inflammation is a normal protective response to tissue injury caused by physical trauma, noxious chemical or microbiological agents, it is the body's effort to inactivate or destroy invading organism, remove irritants and set the stage for tissue repair[1]. Inflammation is triggered by the release of chemical mediators from the injured tissue and migrating cells where prostaglandins appear to play a major role. The specific chemical mediator vary with the type of inflammatory process and include amines such as histamine and 5-hydroxytryptamine, lipids such as the prostaglandins, small peptides such as bradykinine and large peptides such as interleukine-1[2]. Almost all classes of nonsteroidal anti-inflammatory drugs (NSAIDs) strongly inhibit the conversion of arachidonic acid into prostaglandin E_2 (PGE_2) and other prostaglandins through inhibition of cyclooxygenase enzyme. This effect of NSAIDs parallels their relative potency in various tests. The carrageenin-induced rat hind paw edema test is a common model for evaluating anti-inflammatory drugs. There a good correlation between efficacy in this model and activity in humans[3]. In the paw edema model, cyclooxygenase-2 (COX-2) levels are elevated with a concomitant increase in PGE_2 production.

Long term therapy with corticosteroids is often accompanied by various side effects. Considerable research has continued in an effort to find new NSAIDs. Imidazo [1,2-c] quinazoline[4],1,2,4-triazolo[4,3-c]quinazolines[5], pyrroloquinazoline[6], 4-phenethylamino-quinazolines[7-9] and other related derivatives were recently reported to show interesting anti-inflammatory, analgesic and antipyretic properties[10-13].

In the present contribution, we describe the synthesis of novel 1,2,4-triazolo[4,3-c]quinazoline and 4-alkyl, 4-cycloalkyl and 4-heteroaryl-amino-quinazoline derivatives together with their screening as anti-inflammatory agents.

RESULTS AND DISCUSSION

Chemistry: The preparation of compounds 3-27 (Scheme 1 and 2) necessitates the use of 2-(4-chlorophenyl)-4-chloro-6-iodoquinazoline 2 as a suitable starting material. Compound 2 and 3 were recently prepared in our laboratory[14] (2 is obtained by allowing 2-(4-chlorophenyl)-6-iodoquinazoline 1 to react with a mixture of phosphorus oxychloride ($POCl_3$) and phosphorus pentachloride (PCl_5) which was then treated with hydrazine hydrate in ethanol to afford 3). Treating the 4-hydrazino derivative 3 with carbon disulfide in ethanolic potassium hydroxide afforded 3-mercapto-5-(4-chlorophenyl)-9-iodo-1,2,4-triazolo[4,3-c]quinazoline 4. Heating compound 2 under reflux with aliphatic carbohydrazideds in *n*-butanol, yielded the corresponding

Corresponding Authors: Mosaad Sayed Mohamed, Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Helwan University, Cairo, Egypt E-mail: eisa1424@yahoo.com
Sami Gaber Abdel-Hamide, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt

Scheme 1:

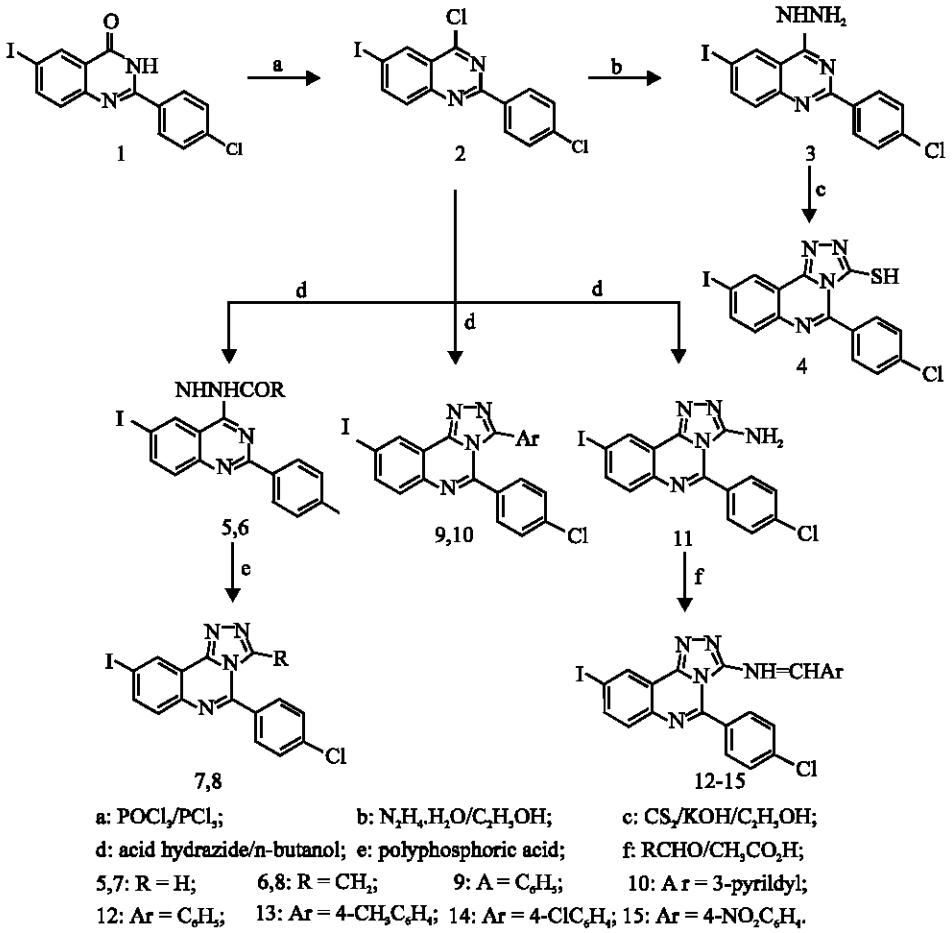


Table 1: Anti-inflammatory activity of the tested compounds evaluated in parallel with indomethacine as a reference standard

Comp. No.	Mean% increase in paw wt.±SE	Reduction of paw edema from the control group (%)
Control	33.2±2.3	---
4	20.3±1.1	33.4
7	23.8±2.1	10.8
8	26.8±1.5	18.3
9	22.2±1.5	31.3
10	24.1±1.7*	17.5
11	29.1±2.0	12.34
12	21.0±1.1*	36.1
15	28.0±1.7	11.6
16	26.1±1.8	21.4
19	30.0±1.4	19.6
21	22.1±1.6	20.1
23	22.1±1.2	18.8
24	21.4±1.2	27.4
25	22.1±1.2*	30.7
26	23.8±2.1	12.34
27	21.2±1.1*	13.1
Indomethacine	20.1±0.8*	39.5

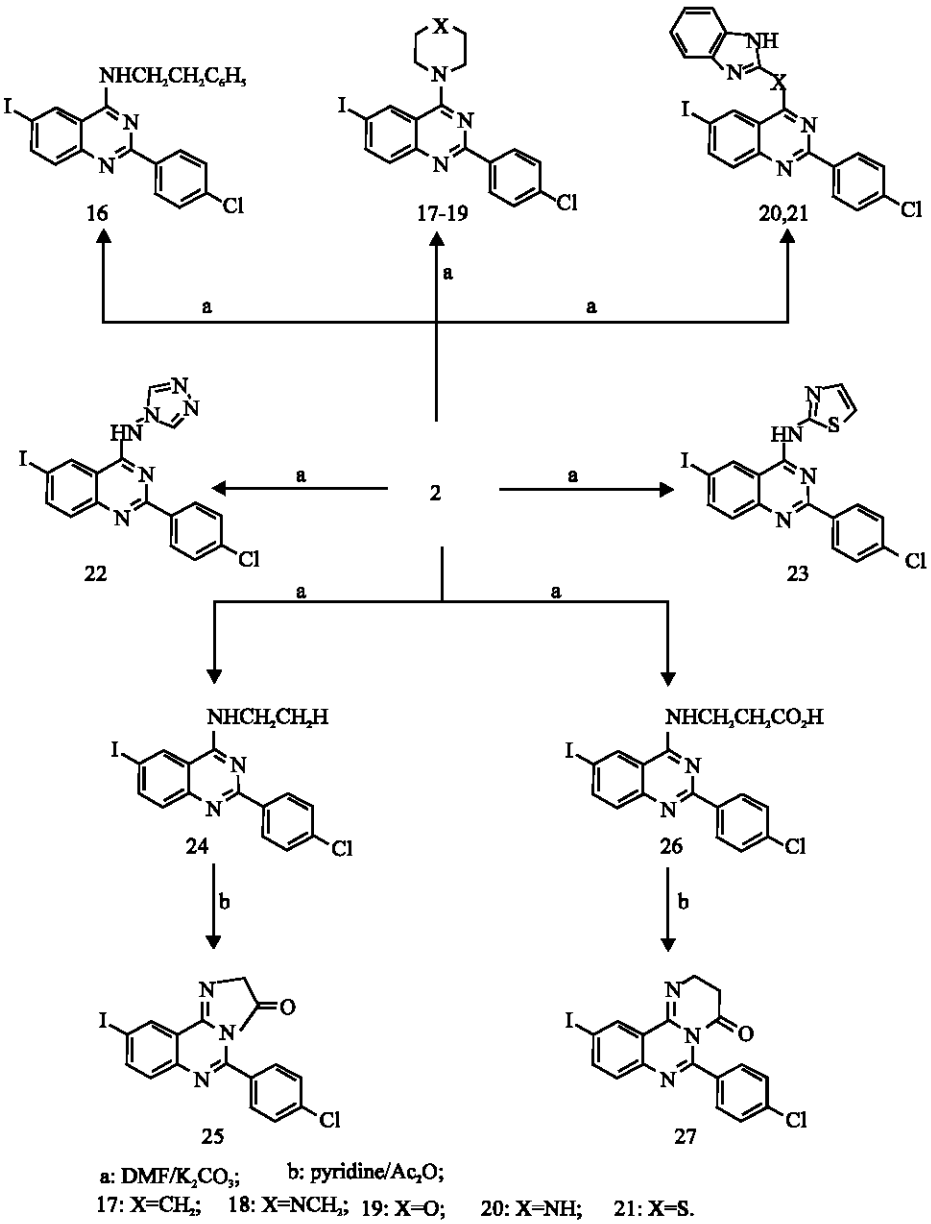
All the test compounds and indomethacine were given orally in a dose of 100 mg kg^{-1}. *Significantly different from the control group using student t test ($p<0.05$).

N substituted hydrazides 5, 6 which were subsequently cyclized by acetic acid/sodium acetate to afford the corresponding 1,2,4-triazolo[4,3-c]quinazoline derivatives 7, 8. However, aromatic acid hydrazides yielded the corresponding triazolo[4,3-c]quinazoline 9, 10 directly when heated under reflux with 2 in *n*-butanol. Heating 2 under reflux with semicarbazide in *n*-butanol afforded 3-amino derivative 11. Compound 11 was allowed to react with differently substituted aldehydes to afford the corresponding 3-arylidene-amino-5-(4-chlorophenyl)-9-iodo-1,2,4-triazolo[4,3-c]quinazoline (12-15).

Scheme 2 shows the preparation of the target compounds (16-27) by heating 4-chloroquinazoline derivative 2 under reflux with the appropriate amine in dimethylformamide in presence of potassium carbonate. Subsequent cyclization of *N*-[2-(4-chlorophenyl)-6-iodoquinazolin-4-yl]amino acid derivatives 24 and 26 was achieved by heating in pyridine in presence of acetic anhydride to obtain the desired imidazoquinazoline derivatives 25 and 27.

Pharmacology: Most of the newly synthesized compounds were subjected to anti-inflammatory testing by means of the carrageenin-induced paw edema assay in

Scheme 2:



rats as described by Winter *et al.*[15]. It has been reported that the edema induced in rat paw by carrageenin injection is mediated by histamine and serotonin during the first hour, after which the increase in vascular permeability is maintained by kinin release up to 2.5 h[5]. From 2.5-6 h, the mediator appears to be prostaglandins. Therefore, the anti-inflammatory activity that depends mainly on inhibition of prostaglandin synthesis was tested 4 h after carrageenin injection. Indomethacin® was used as a reference standard being one of the potent NSAIDs with wide margin of safety and minimal side effects.

From the screening results (Table 1), it is clear that six of the tested compounds possess significant anti-inflammatory activity. Among these inflammation suppressants four compounds, namely, compounds 4, 9, 12 and 25 showed the highest activity. The othercompounds were far less effective, however, non of the tested compounds were found to be as potent as the reference drug which exhibited 39.5% reduction of the carrageenin-induced edema at a dose of 5 mg kg^{-1}.

Structural activity correlation of the obtained results revealed that, the phenethylamine moiety at position 4 in

the quinazoline nucleus improves the activity. This observation is in accord with the results obtained concerning quinazoline derivatives, where this moiety at this position yielded very potent inhibitors of NF-κB activation as mentioned in the literature.

Also, it was found that glycine moiety at position 4 compound 24 is more potent than its β-alanine analogue 26. Cyclization of the active compound 24 into imidazo[4,5-c]quinazoline 25 tend somewhat to improve the activity. On the other hand, the 3-substituted-1,2,4-triazolo[4,3-c]quinazoline synthons (compounds 4, 9 and 12) proved to be the most active. Comparing the effect of the 3-substituent on the activity of triazolo[4,3-c]quinazoline revealed that, mercapto group enhances the activity. Planar lipophilic moiety like phenyl group, tends to improve the activity. On the other hand compounds 7, 8 and 11, which lacks the aryl substituent on the triazole ring, showed poor anti-inflammatory activity. The foregoing results point to the significance of the phenyl ring to bring about a good biological effect, it might play a role in fitting with a hydrophobic site in the receptor. Incorporation of arylideneamine moiety at position 3 yielded the most active derivative in this series.

The overall results reflects the necessity of having a fused 1,2,4-triazole ring bearing a lipophilic substituent to obtain the required activity.

Experimental

Synthesis: Melting points (°C) were determined on a Koffler apparatus and are uncorrected. IR spectra were obtained on a Pye Unicam SP 1200 spectrophotometer using Kbr wafer technique (v, cm^{-1}). ^1H NMR spectra were recorded on a varian Gimine 200 MHz, Brucker AC 200-MHz and Brucker MAX 400 MHz using TMS as an internal standard (chemical shifts δ, ppm). The reactions and the purity of all compounds were checked by TLC using chloroform:*n*-hexane (9:1) as eluent.

3-Mercapto-5-(4-chlorophenyl)-9-iodo-1,2,4-triazolo [4,3-c]quinazoline (4): A mixture of 2-(4-chlorophenyl)-4-chloro-6-iodoquinazoline 27 (0.2 g, 0.0005 mol), potassium hydroxide (0.057 g, 0.001 mol) and carbon disulphide (0.76 g, 0.01 mol) in methanol (10 mL) was heated under reflux for 4 h. On cooling, the solvent was removed under reduced pressure and the residue was dissolved in 10% aqueous potassium hydroxide solution (50 mL). After filtration, the filtrate was neutralized with dilute hydrochloric acid and the solid separated was filtered, washed with water, dried and crystallized from ethanol to yield 0.09 g, (43%) M. P. 242-244°C. Compound (4): Yield: 66%, mp: 230-232°C. Analysis for $C_{15}H_8ClIN_4S$: % Calc. (Found); C: 41.07 (40.9), H: 1.86(2.1), N: 12.77(12.8), S: 7.31 (7.5).

Preparation of compounds (5), (6),(9) and (10)

General procedure: A mixture of 2-(4-chlorophenyl)-4-chloro-6-iodoquinazoline 2 (0.2 g, 0.0005 mol) and the appropriate acid hydrazide (0.0005 mol) in *n*-butanol (10 mL) was heated under reflux for 1 h. The solvent was removed under vacuum and the separated solid was filtered, washed with water, dried and crystallized from ethanol. Compound (5): Yield: 88%, mp 192-94. Analysis for $C_{15}H_{10}ClIN_4O$: % Calc. (Found); C: 42.43 (42.22), H: 2.37 (2.40), N: 13.19 (13.18). IR (KBr): 3330 (N*H*), 1680 (*CO*).^1H NMR (DMSO-d_6, δ ppm): 3.4-3.5 (m, 2H, CH_2), 5.1 (bs, 1H, N*H*, D_2O exchangeable), 7.1-8.1 (m, 7H, Ar-*H*). Compound (6): Yield: 90%, mp 212-214. Analysis for $C_{16}H_{12}ClIN_4O$: % Calc. (Found); C: 43.81 (43.76), H: 2.76 (2.66), N: 12.77 (12.09). IR (KBr): 3340 (N*H*), 1680 (*CO*). Compound (9): Yield: 90%, mp >300°C. Analysis for $C_{21}H_{12}ClIN_4$: % Calc. (Found); C: 52.25 (52.28), H: 2.51 (2.48), N: 11.61 (11.64).^1H NMR (DMSO-d_6): 7.1-8.1 (m, 12H, Ar-*H*). Compound (10): Yield: 85%, mp >300°C. Analysis for $C_{20}H_{11}ClIN_5$: % Calc. (Found); C: 49.66 (49.80), H: 2.29 (2.34), N: 14.48 (14.21).

5-(4-Chlorophenyl)-9-iodo-1,2,4-triazolo[4,3-c]quinazoline (7) and 3-methyl-5-(4-Chlorophenyl)-9-iodo-1,2,4-triazolo[4,3-c]quinazoline (8): A mixture of compound (5) or (6) (0.01 mol) and polyphosphoric acid (10 mL) was heated at 100°C for 2 h. After cooling, the reaction mixture was poured onto ice water (100 mL) and neutralized by addition ammonia solution. The separated solid was then filtered, washed with water and crystallized from ethanol. Compound (7): Yield: 45%, mp >267-69°C. Analysis for $C_{15}H_8ClIN_4$: % Calc. (Found); C: 44.31 (44.37), H: 1.98 (2.15), N: 13.78 (13.51).^1H NMR (DMSO-d_6): 7.1-8.3 (m, 8H, Ar-*H*). Compound (8): Yield: 45%, mp >290-93°C. Analysis for $C_{16}H_{10}ClIN_4$ % Calc. (Found); C: 45.69 (46.14), H: 2.41 (2.44), N: 13.32 (13.28). ^1H NMR (DMSO-d_6): 2.3 (s, 3H, CH_3), 7.1-8.2 (m, 7H, Ar-*H*).

3-Amino-5-(4-chlorophenyl)-9-iodo-1,2,4-triazolo[4,3-c]quinazoline (11): A mixture of 2-(4-chlorophenyl)-4-chloro-6-iodoquinazoline 2 (1.0 g, 0.0025 mol), semicarbazide hydrochloride (0.27 g, 0.0025 mol) and *n*-butanol (10 mL) containing few drops pyridine was heated under reflux for 1 h. The product obtained was collected by filtration, dried and crystallized from ethanol to give 0.8 g, (80%) of 11:mp >300°C; Analysis for $C_{15}H_9ClIN_5$: % Calc. (Found); C: 42.73 (42.71), H: 2.15 (2.44), N: 16.61 (16.99). ^1H NMR (DMSO-d_6): 4.85 (bs, 2H, NH_2; D_2O exchangeable), 7.64-8.71 (m, 7H, Ar-*H*).

3-Arylideneamino-5-(4-chlorophenyl)-9-iodo-1,2,4-triazolo[4,3-c]quinazolines (12-15): A mixture of compound (11) (0.25 g, 0.0006 mol), the appropriate aldehyde (0.006 mol) and absolute ethanol (10 mL) was

refluxed for 5 h. The solid separated was collected by filtration, dried and crystallized from ethanol. Compound (12): Yield: 75%, mp: 273-75°C. Analysis for $C_{22}H_{13}ClIN_5$: % Calc. (Found); C: 51.84 (51.91), H: 2.57 (2.19), N: 13.74 (13.84) ^{1}H NMR (DMSO-d_6, δ ppm), 7.1-8.4 (m, 13H, Ar-H and Ar-CH=N). Compound (13): Yield: 75%, mp: 274-76°C. Analysis for $C_{23}H_{15}ClIN_5$: % Calc. (Found); C: 52.74 (52.71), H: 2.89 (3.05), N: 13.37 (13.40). ^{1}H NMR (DMSO-d_6, δ ppm), 2.35(s, 3H, CH_3), 7.22-8.54 (m, 12H, Ar-H and Ar-C*H*=N). Compound (14): Yield: 68%, mp >300°C. Analysis for $C_{22}H_{12}Cl_2IN_5$: % Calc. (Found); C: 48.56 (48.60), H: 2.23 (2.42), N: 12.78 (12.57). ^{1}H NMR (DMSO-d_6, δ ppm), 7.1-8.3 (m, 12H, Ar-*H* and Ar-C*H*=N). Compound (15): Yield: 55%, mp >300°C. Analysis for $C_{22}H_{16}ClIN_6O_2$: % Calc. (Found); C: 47.63 (47.93), H: 2.18 (1.99), N; 15.15 (15.22). ^{1}H NMR (DMSO-d_6, δ ppm), 7.2-8.3 (m, 12H, Ar-*H* and Ar-C*H*=N).

2-(4-Chlorophenyl)-4-substituted-6-iodoquinazoline(16-24 and 26): A mixture of 2-(4-chlorophenyl)-4-chloro-6-iodoquinazoline 2 (0.4 g, 0.001 mol), the appropriate reagent (0.001 mol) and potassium carbonate (0.276 g, 0.002 mol) in DMF (10 mL) was heated at 100°C for 5 h. After cooling to room temperature, the mixture was acidified with acetic acid and the precipitated solid was filtered, washed with water and crystallized from ethanol to afford the products in yields ranging from 60-65%. Compound (16): mp 282-284°C. Analysis for $C_{22}H_{17}ClIN_3$: % Calc. (Found); C: 50.74 (50.77), H: 3.53 (3.56), N: 8.56 (8.62). IR: 3350 (*NH*). ^{1}H NMR (CD_3OD, δ ppm):2.7-2.8 (m, 2H, CH_2), 2.9-3.0 (m, 2H, CH_2), 5.7 (bs, 1H, N*H*), 7.2-8.3 (m, 12H, Ar-*H*). Compound (24): mp 282-284°C. Analysis for $C_{16}H_{11}ClIN_3O_2$: % Calc. (Found); C: 43.71 (44.1), H: 2.52(2.6), N: 9.56 (9.8). IR: 3300-2500 (*OH*), 1730 (*C=O*). ^{1}H NMR (DMSO-d_6, δ ppm): 3.1-3.2 (m, 2H, CH_2) 7.2-8.3 (m, 7H, Ar-H), 9.5-9.6 (bs, 1H, N*H*), 10.3-10.4 (s, 1H, O*H*). Compound (26): Yield: 61%, mp 294-296°C. Analysis for $C_{17}H_{13}ClIN_3O_2$: % Calc. (Found); C: 45.01 (44.9), H: 2.89(3.1), N: 9.26 (8.9). IR: 3300-2400 (OH), 1730(*C=O*). ^{1}H NMR (DMSO-d_6, δ ppm): 2.4-2.5 (m, 2H, CH_2CH_2), 2.9-3.0 (m, 2H, CH_2NH), 7.2-8.3 (m, 7H, Ar-*H*), 9.4-9.5 (bs, 1H, N*H*), 10.3-10.4 (s, 1H, OH).

5-(4-Chlorophenyl)]-9-iodo-2H-imidazo[1,2-c]quinazolin-3-one (25) and 6-iodo-10-(4-chlorophenyl)-2,3-dihydro-4,9,10a-triazaphenanthren-1-one (27): Acetic anhydride (5 ml) was added to a solution of 24 or 26 (0.001 mol) in pyridine (10 mL). The mixture was stirred for 2 h at 100°C. Most of the solvent was removed in vacuum and the residue was triturated with water. The formed solid product was collected by filtration, washed with water and crystallized from ethanol. Compound (25): Yield: 43%, mp 201-203°C. Analysis for $C_{16}H_{19}ClIN_3O$: % Calc. (Found); C: 45.58 (45.8), H: 2.15 (2.4), N: 9.97 (9.9). IR (KBr): 1670 (*CO*). ^{1}HNMR: 4.34 (s, 2H, CH_2), 7.1-8.2 (m, 7H, Ar-*H*). Compound (27): Yield: 40%, mp 225-227°C. Analysis for $C_{17}H_{11}ClIN_3O$: % Calc. (Found) C: 46.87 (46.8), H: 2.55 (2.45), N: 9.65 (9.8). IR (Kbr): 1675 (*CO*). ^{1}H N MR: 2.4-2.5 (t, 2H, CH_2CO), 3.8-3.9 (t, 2H, CH_2N), 7.2-8.2 (m, 7H, Ar-*H*).

Biological Screening

Anti-inflammatory screening: The anti-inflammatory activity was carried out by means of the carrageenin-induced rat hind paw edema test following the procedures of Winter *et al.*[15], using groups of male albino rats weighing 100-120 g each, 6 rats in each group. A 1% suspension of the test compound in 0.05% aqueous Carboxy Methyl Cellulose (CMC) was administered to the rats by oral intubations (10 mL kg^{-1}). Indomethacin® was used as positive control (reference standard) given orally in a dose of 100 mg kg^{-1}. A control group has received only equivalent amount of solvent. One hour later, carrageenin (1% solution, 100 mg kg^{-1}) was injected S.C. into the planar tissue of the right hind paw. Four hours post carrageenin injections, the animals were sacrificed by cervical dislocation, the right and left paws were cut at a standard 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.

REFERENCES

1. Mycek, M.J., R.A. Harrey and P.C. Champe, 1987. Pharmacology Lippincott's Illustrated Reviews. 2nd Edn., Chap. 39, pp: 401.
2. Evans, D. and W.R. Nigel, 1987. Clinical Pharmacology. Vol. 9 Chap. 7, Anti-inflammatory Compounds, 1st Edn., Williamson, W.R., Edn., Marcel Decker Inc., New York.
3. Huslisson, E.C., 1983. Clinical Pharmacology and Therapeutics Series, Vol. 3, Chap. 1. Antirheumatic Drugs (Huskisson, E.C.,) Praeger New York.
4. El-Kerdawy, M.M., M.B. El-Ashmawy, I.A. Shehata, A.M. Bargash, E.R. El-Bendary and H.A. El-Kashef, 1997. Fused pyrimidines synthesis and anti-inflammatory testing of certain novel imidazo[1,2-c]quinazoline, pyrazolo[3,4-d]triazole[3,4-b]pyrimidine and pyrimido[2,1-a]phthalazine derivatives. Saudi Pharm. J., 5: 46-55.

5. Gineinah, M.M., M.N. Nasr, A.M. Abdelal, A.A. El-Emam and S.A. Said, 2000. Synthesis and anti-inflammatory evaluation of new 2- and 3-substituted 1,2,4-triazolo[4,3-c] and [1,5-c]quinazoline derivatives. Med. Chem. Res., 10: 243-254
6. Inmaculada, R., T. Carmen, U. Amalia, M. Pedro, T. Alberto, G.T. Antonia and M.A. Jose, 2002. A pyrroloquinazoline derivative with anti-inflammatory and analgesic activity by dual inhibition of cyclo-oxygenase-2 and 5-lipoxygenase. Eur. J. Pharmacol., 434: 177-185
7. Masanori, T., I. Yoshiali, T. Hideyuki, N. Takahiro, T. Hirotada, F. Tominaga and H. Hideya, 2003. Discovery of quinazolines as a novel structural class of potent inhibitors of NF-κB activation. Bioorg. Med. Chem., 11: 383-391.
8. Masanori, T., I. Yoshiali, T. Hideyuki, N. Takahiro, T. Hirotada, F. Tominaga and H. Hideya, 2003. Structural activity relationship of 6-fluoroquinazolines: dual acting compounds with inhibitory activities toward both TNF-α production and T cell proliferation. Bioorg. Med. Chem., 11: 609-616.
9. Masanori, T., I. Yoshiali, T. Hideyuki, N. Takahiro, T. Hirotada, F. Tominaga and H. Hideya, 2003. A novel structural class of potent inhibitors of NF-κB activation: Structural activity relationship and biological effects of 6-aminoquinazoline derivatives. Bioorg. Med. Chem., 11: 3869-3878.
10. Sadanadam, Y.S., K.R.M. Reddy and A.B. Rao, 1987. Synthesis of substituted 2,3-dihydro-1-(β-phenethyl)-2-aryl and 2,3-diaryl-4-(1*H*)-quinazolines and their pharmacological activities. Eur. J. Med. Chem., 22: 169-73.
11. Perrin, J.W., W.J. Houlihan and E.I. Takesue, 1984. Anti-inflammatory and other pharmacodynamic properties of five members of the 4-aryl-1-isopropyl-2(1*H*)-quinazoline series. Arzeneim-Forsch, 34: 879-85.
12. Chao, Q., L. Deny, H. Shib, L.M. Leoni, D. Genini, D.A. Carson and H.B. Cottam, 2001. Synthesis and pharmacological study of 1-methyl-5-(substituted 3,4-dihydro-4-oxoquinazolin-3-yl)-1H-pyrazole-4-actetates. J. Med. Chem., 36: 737.
13. Maggio, M.M., G. Daidone, D. Raffa, S. Plesica, V.H.C. Manitone, N.G. Cutuli, G. Mangano and A. Caruso, 2001. Substituted isoquinolines and quinazolines as potential antiinflammatory agents. Synthesis and biological evaluation of inhibitors of tumor necrosis factor. J. Med. Chem., 42: 3860.
14. Mohamed, S.M., K.I. Mohammed, M.A. Ahmed and S.G. Abdel-Hamide, 2004. Quinazoline related derivatives with antimicrobial activities: Part II. J. Biol. Sci., 4: 504-509.
15. Winter, C.A., E.A. Risely and G.W. Nuss, 1962. Carrageenin-induced edema in the hind paw of the rat as an assay for anti-inflammatory drugs. Proc. Soc. Exp. Biol. Med., III: 544-47.