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Der Pharma Chemica, 2011, 3(3):1-12
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis of some quinazolin-4-one derivatives carrying ibuprofenyl moiety and their antiinflammatory activity

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ABSTRACT

*A new series of antiinflammatory active Ibuprofen derivatives comprises quinazolinone moiety was synthesized. Ibuprofen was converted into its acid chloride **1** and reacted with anthranilic acid to give the anilide **2**. The anilide **2** was refluxed with acetic anhydride to form benzoxazinone **3**. The later on reaction with nitrogen nucleophile such as hydrazine hydrate, gave 3-aminoquinazolinone **4**. The compound **4** was used as key starting material to synthesize twelve quinazolinone derivatives **5**, **6**, **7a-c**, **8a-c**, **9a-c**, and **10**. The structures of the synthesized compounds have been established on the basis of spectral and analytical data. All the synthesized compounds have been estimated as anti-inflammatory with minimal ulceroginc effect.*

Keywords: ibuprofen, quinazolinone, antiinflammatory, ulceroginc activity.

INTRODUCTION

NSAIDs, Nonsteroidal antiinflammatory drugs, are the primary selection of treatments in curing of inflammatory and rheumatic disorders. Ibuprofen (2-*RS*-(4-Isobutylphenyl)propanoic acid), a famous NSAID, is the active ingredient in a number of counter pain relievers, e.g. Advil, Motrin, and Nuprin. Ibuprofen is one of the top-ten drugs sold worldwide. Despite the efficiently defeating pain and inflammation, NSAIDs, including ibuprofen, have disadvantageous side effects such as; dyspepsia, symptomatic and complicated gastric, and duodenal ulcers. Long-term use of these drugs has been associated with gastro-intestinal (GI) ulceration, bleeding, and nephrotoxicity [1]. It is known that most of NSAIDs inhibit the enzyme COX and production of prostaglandins. Traditional NSAIDs differ in their relative inhibitory potency against two iso-forms of COX: COX-1 and COX-2 [2]. The maximum extent of damage is generally caused by NSAIDs that are favored COX-1 inhibitors and include a free carboxylic group such as aspirin, ibuprofen, and indomethacin [3]. A widespread approach in medicinal chemistry research is based on utilization of well-known medicines as key compounds to design new drugs with better

therapeutic properties. These new drugs show comparable anti-inflammatory activity and lesser ulcerogenicity in comparison to the parent drug [4]. It is intended to exploit biochemical differences between the two COX enzymes by conversion of carboxylate-containing NSAID Ibuprofen into gastro-protective amide pro-drugs of ibuprofen. This can be achieved by masking the free carboxylic group and may shift its enzyme selectivity from COX-1 towards COX-2. The free carboxylic acid group found in NSAIDs such as flurbiprofen and ibuprofen forms critical interactions with residues Arg-120, Glu-524, and Tyr-355 within the cyclooxygenase active site [5]. The masking of the ibuprofen-free carboxylic group seems to be principally the basis of this reduced topical irritant action [6]. Ibuprofen has been modified into various heterocyclic amide derivatives having improved analgesic activity and lower ulcerogenic effects, as aminoprofen, an amide derivative of ibuprofen has been used for its topical anti-inflammatory activity [7]. Quinazolinone derivatives have attracted a considerable attention in recent years due to their wide range pharmaceutical applications. Quinazolin-4-one represents a useful nucleus for preparation of some new tranquilizer, hypnotic and anticonvulsant agents [8]. It was reported that the 2,3-disubstituted quinazolinones exhibited fascinating pharmaceutical behavior such as analgesic [9], antiinflammatory [10], antimicrobial [11], and antihypertensive activities [12]. Due to these important biological properties of both ibuprofens and quinazolinones, herein, ibuprofen is modified through building up of a quinazolinone nucleus. The new ibuprofenylquinazolinone and its derivatives are examined for their anti-inflammatory and ulcerogenesis activities.

MATERIALS AND METHODS

All melting points are uncorrected and determined by the open capillary method using Stuart SMP-10 apparatus. Microanalyses were carried out by the Micro Analytical Center at Cairo University. IR spectra were recorded on FT-IR-300E Jasco spectrophotometer in KBr discs. The ^{1}H NMR spectra were measured on a Varian Gemini 200 MHz instrument with chemical shifts (δ). Mass spectra were recorded on Shimadzu GC-MS instrument model QP-1000EX, operating at 70 eV. All reactions were monitored by thin-layer chromatography (TLC) on 0.2-mm silica gel F-254 (Merck) plates, using UV light (254 and 366 nm) for detection. 2-(4-Isobutylphenyl)propanoyl chloride (**1**) was prepared according to described procedure in literature [2].

2-{[2-(4-Isobutylphenyl)propanoyl]amino}benzoic acid (2)

2-(4-Isobutylphenyl)propanoyl chloride (1) (22.47 g, 100 mmol) was portion-wise added to a stirred solution of anthranilic acid (13.7 g, 100 mmol), in dry pyridine (150 mL) during 10 min. The mixture was stirred at room temperature for 3 h then poured into ice-cold water (250 mL), acidified with hydrochloric acid (2N) up to complete precipitation. The crude solid product was filtered, washed thoroughly with cold water, and crystallized from benzene. Yield 23.40 g (72 %); m. p. 118-119^{o}C. IR (KBr), ν (cm^{-1}): 3400 (O–H, N–H), 3055 (C–H$_{arom}$), 2965, 2935, 2875 (C–H$_{aliph}$), 1735 (C=O), 1646 (C=O), 1614 (bending N–H). ^{1}H NMR ($CDCl_3$) δ: 1.10 (d, *J* = 6.4 Hz, 6H, $CH_2CH(CH_3)_2$), 1.52 (d, *J* = 7.2 Hz, 3H, $CHCH_3$), 2.22 (m, 1H, $CH_2CH(CH_3)_2$), 2.51 (d, *J* = 7.1 Hz, 2H, $CH_2CH(CH_3)_2$), 3.89 (q, *J* = 7.2 Hz, H, $CHCH_3$), 7.24-7.78 (m, 7H, H$_{arom}$), 8.08 (d, *J* = 8.1 Hz, 1H, H$_{arom}$), 8.90 (bs, 1H exchangeable with D_2O, NH) , 12.85 (bs, 1H exchangeable with D_2O, OH). MS, *m/z* (I_{rel} (%)): 325 (36). Found (%): C, 73.60; H, 7.00; N, 4.20. $C_{20}H_{23}NO_3$ (325.41). Calculated (%): C, 73.82; H, 7.12; N, 4.30.

2-[1-(4-Isobutylphenyl)ethyl]-4H-3,1-benzoxazin-4-one (3)

A mixture of the anilide **2** (3.25 g, 10 mmol) and acetic anhydride (50 mL) was heated under reflux for 4 h and then concentrated. The residue was crystallized from petroleum ether 40-60 ^{o}C, giving colorless crystals. Yield 2.09 g (68 %); m. p. 69-70^{o}C. IR (KBr), ν (cm^{-1}): 3058 (C–H$_{arom}$), 2964, 2936, 2872 (C–H$_{aliph}$), 1760 (C=O), 1624-1614 (C=N), 1161 (C–O–C). ^{1}H NMR

($CDCl_3$) δ: 1.04 (d, *J* = 6.2 Hz, 6H, $CH_2CH(CH_3)_2$), 1.45 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 1.88 (m, 1H, $CH_2CH(CH_3)_2$), 2.45 (d, *J* = 6.6 Hz, 2H, $CH_2CH(CH_3)_2$), 3.85 (q, *J* = 6.8 Hz, H, $CHCH_3$), 7.35-7.84 (m, 7H, H_{arom}), 8.18 (d, *J* = 8.2 Hz, 1H, H_{arom}). MS, *m/z* (I_{rel} (%)): 307 (62). Found (%): C, 78.00; H, 6.60; N, 4.40. $C_{20}H_{21}NO_2$ (307.40). Calculated (%): C, 78.15; H, 6.89; N, 4.56.

3-Amino-2-[1-(4-isobutylphenyl)ethyl]quinazolin-4(3H)-one (4)

Mixture of the benzoxazinone **3** (3.07 g, 10 mmol) and hydrazine hydrate (0.6 mL, 11 mmol, 100%) was heated under reflux on a boiling-water bath for 30 min, then ethanol (50 mL) was added and the mixture was refluxed for 2 h. The precipitate that formed was collected by filtration during hot, dried and crystallized from petroleum ether (60-80^oC). Yield 2.60 g (81 %); m. p. 128-129^oC. IR (KBr), ν (cm^{-1}): 3360, 3280 (NH_2), 3054 (C–H_{arom}), 2974, 2938, 2876 (C–H_{aliph}), 1668 (C=O), 1618–1605 (C=N, N–H). ^1H NMR ($CDCl_3$) δ: 1.09 (d, *J* = 6.2 Hz, 6H, $CH_2CH(CH_3)_2$), 1.33 (d, *J* = 6.6 Hz, 3H, $CHCH_3$), 2.22 (m, 1H, $CH_2CH(CH_3)_2$), 2.51 (d, *J* = 6.4 Hz, 2H, $CH_2CH(CH_3)_2$), 3.68 (q, *J* = 6.6 Hz, H, $CHCH_3$), 6.20 (bs, 2H exchangeable with D_2O, NH_2), 7.38–7.84 (m, 7H, H_{arom}), 8.20 (d, *J* = 8.4 Hz, 1H, H_{arom}). MS, *m/z* (I_{rel} (%)): 321 (65). Found (%): C, 74.70; H, 7.20; N, 12.80. $C_{20}H_{23}N_3O$ (321.43). Calculated (%): C, 74.74; H, 7.21; N, 13.07.

N-{2-[1-(4-Isobutylphenyl)ethyl]-4-oxo-4H-quinazolin-3-yl}acetamide (5)

A mixture of the amine **4** (3.21 g, 10 mmol) and acetic anhydride (10 mL) was heated under reflux for 1 h. Then, the excess acetic anhydride was evaporated under reduced pressure. The pasty residue that obtained was triturated with cold methanol (5 mL). The solid material that formed was filtered and crystallized from methanol. Yield 3.19 g (88 %); m. p. 178-179 ^oC. IR (KBr), ν (cm^{-1}): 3268 (N–H), 3055 (C–H_{arom}), 2976, 2939, 2876 (C–H_{aliph}), 1675 (C=O), 1643 (C=O), 1614 (C=N, N–H). ^1H NMR ($CDCl_3$) δ: 1.11 (d, *J* = 6.2 Hz, 6H, $CH_2CH(CH_3)_2$), 1.38 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 2.22 (m, 1H, $CH_2CH(CH_3)_2$), 2.31 (s, 3H, CH_3C=O), 2.51 (d, *J* = 6.4 Hz, 2H, $CH_2CH(CH_3)_2$), 3.70 (q, *J* = 6.4 Hz, H, $CHCH_3$), 7.22–7.87 (m, 7H, H_{arom}), 8.20 (d, *J* = 8.2 Hz, 1H, H_{arom}), 11.02 (bs, 1H exchangeable with D_2O, CON–H). MS, *m/z* (I_{rel} (%)): 363 (45). Found (%): C, 72.50; H, 6.70; N, 11.40. $C_{22}H_{25}N_3O_2$ (363.46). Calculated (%): C, 72.70; H, 6.93; N, 11.56.

Methyl {2-[1-(4-isobutylphenyl)ethyl]-4-oxo-4H-quinazolin-3-yl}dithiocarbamate (6)

An aqueous solution of sodium hydroxide (12 mL, 24 mmol, 2 N) was drop-wise added to a stirred mixture of the amine **4** (6.42 g, 20 mmol) and carbon disulfide (1.5 mL, 24 mmol), in DMSO (10 mL), in an ice bath, over a period of 30 min. Then the reaction mixture was stirred for additional 2 h, afterwards, dimethyl sulphate (1.9 mL, 20 mmol) was gradually added with continuous stirring in for 2 h. Then the reaction mixture was diluted with ice-cold water (50 mL) to give solid deposits which were filtered, washed with water, dried and crystallized from acetonitrile. Yield 3.53 g (43 %); m. p. 142-143^oC. IR (KBr), ν (cm^{-1}): 3288 (N–H), 3058 (C–H_{arom}), 2984, 2945, 2882 (C–H_{aliph}), 1645 (C=O), 1612 (C=N, N–H), 1050 (C=S). ^1H NMR ($CDCl_3$) δ: 1.09 (d, *J* = 6.2 Hz, 6H, $CH_2CH(CH_3)_2$), 1.32 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 2.21 (m, 1H, $CH_2CH(CH_3)_2$), 2.43 (d, *J* = 6.4 Hz, 2H, $CH_2CH(CH_3)_2$), 2.54 (s, 3H, SCH_3), 3.65 (q, *J* = 6.4 Hz, H, $CHCH_3$), 7.24–7.89 (m, 7H, H_{arom}), 8.19 (d, *J* = 8.2 Hz, 1H, H_{arom}), 8.92 (bs, 1H exchangeable with D_2O, CSN–H). MS, *m/z* (I_{rel} (%)):411 (36). Found (%): C, 64.30; H, 6.00; N, 10.10. $C_{22}H_{25}N_3OS_2$ (411.59). Calculated (%): C, 64.20; H, 6.12; N, 10.21.

General Procedure for Preparation of Carbothioamides 7a-c.

A mixture of dithiocarbamate **6** (2.06 g, 5 mmol) and the appropriate amine (15 mmol); namely piperidine (1.5 mL), morpholine (1.3 mL), and anhydrous piperazine (1.30 g), in absolute

ethanol (20 mL), was heated under refluxed for 3 h. After cooling, the produced precipitate was filtered, washed with cold methanol (10 mL), and crystallized from the proper solvent.

N-{2-[1-(4-Isobutylphenyl)ethyl]-4-oxo-4H-quinazolin-3-yl}piperidine-1-carbothioamide (7a). This compound was obtained from piperidine and crystallized from methanol. Yield 1.30 g (58 %); m. p. 280-282^{o}C. IR (KBr), ν (cm^{-1}): 3288 (N–H), 3053 (C–H_{arom}), 2977, 2928, 2878 (C–H_{aliph}), 1665 (C=O), 1614–1602 (C=N, N–H), 1150 (N–C=S). ^{1}H NMR ($CDCl_3$) δ: 1.10 (d, *J* = 6.4 Hz, 6H, $CH_2CH(CH_3)_2$), 1.31 (d, *J* = 6.2 Hz, 3H, $CHCH_3$), 1.50-1.62 (m, 6H, β-$CH_{2piperidine}$ + γ-$H_{2piperidine}$), 2.22 (m, 1H, $CH_2CH(CH_3)_2$), 2.52 (d, *J* = 6.4 Hz, 2H, $CH_2CH(CH_3)_2$), 3.07 (t, *J* = 6.6 Hz, 4H, α-$CH_{2piperidine}$), 3.40 (q, *J* = 6.2 Hz, 1H, $CHCH_3$), 7.24–7.84 (m, 7H, H_{arom}), 8.20 (d, *J* = 8.2 Hz, 1H, H_{arom}), 9.00 (bs, 1H exchangeable with D_2O, N–H). MS, *m/z* (I_{rel} (%)):448 (27). Found (%): C, 69.50; H, 6.90; N, 12.20. $C_{26}H_{32}N_4OS$ (448.64). Calculated (%): C, 69.61; H, 7.19; N, 12.49.

N-{2-[1-(4-Isobutylphenyl)ethyl]-4-oxo-4H-quinazolin-3-yl}morpholine-4-carbothioamide (7b). This compound was obtained from morpholine and crystallized from methanol. Yield 1.05 g (47 %); m. p. 287-289 ^{o}C. IR (KBr), ν (cm^{-1}): 3282 (N–H), 3050 (C–H_{arom}), 2975, 2939, 2885 (C–H_{aliph}), 1665 (C=O), 1612–1600 (C=N, N–H), 1145 (N–C=S). ^{1}H NMR ($CDCl_3$) δ: 1.11 (d, *J* = 6.4 Hz, 6H, $CH_2CH(CH_3)_2$), 1.30 (d, *J* = 6.2 Hz, 3H, $CHCH_3$), 2.22 (m, 1H, $CH_2CH(CH_3)_2$), 2.51 (d, *J* = 6.4 Hz, 2H, $CH_2CH(CH_3)_2$), 3.30 (q, *J* = 6.4 Hz, 1H, $CHCH_3$), 3.48 (t, *J* = 6.8 Hz, 4H, β-$CH_{2morpholine}$), 3.77 (t, *J* = 6.8 Hz, 4H, α-$CH_{2morpholine}$), 7.20–7.87 (m, 7H, H_{arom}), 8.18 (d, *J* = 8.2 Hz, 1H, H_{arom}), 8.98 (bs, 1H exchangeable with D_2O, N–H). MS, *m/z* (I_{rel} (%)): 450 (32). Found (%): C, 66.40; H, 6.80; N, 12.30. $C_{25}H_{30}N_4O_2S$ (450.61). Calculated (%): C, 66.64; H, 6.71; N, 12.43.

N-{2-[1-(4-Isobutylphenyl)ethyl]-4-oxo-4H-quinazolin-3-yl}piperazine-1-carbothioamide (7c). This compound was obtained from piperazine and crystallized from DMF. Yield 1.46 g (65 %); m. p. 295-297^{o}C. IR (KBr), ν (cm^{-1}): 3348, 3279 (N–H), 3055 (C–H_{arom}), 2978, 2932, 2887 (C–H_{aliph}), 1665 (C=O), 1616–1605 (C=N, N–H), 1148 (N–C=S). ^{1}H NMR (DMSO-d_6) δ: 1.08 (d, *J* = 6.2 Hz, 6H, $CH_2CH(CH_3)_2$), 1.37 (d, *J* = 6.6 Hz, 3H, $CHCH_3$), 2.12 (m, 1H, $CH_2CH(CH_3)_2$), 2.58 (d, *J* = 6.4 Hz, 2H, $CH_2CH(CH_3)_2$), 3.20–3.38 (m, 5H, $CHCH_3$ and β-$CH_{2piperazine}$), 3.72 (t, *J* = 6.2 Hz, 4H, α-$CH_{2piperazine}$), 7.18–7.80 (m, 7H, H_{arom}), 8.08 (d, *J* = 8.2 Hz, 1H, H_{arom}), 8.90 (bs, 1H exchangeable with D_2O, N–H). MS, *m/z* (I_{rel} (%)):449 (26). Found (%): C, 66.60; H, 6.80; N, 15.20. $C_{25}H_{31}N_5OS$ (449.62). Calculated (%): C, 66.78; H, 6.95; N, 15.58.

General Procedure for Preparation of Schiff's Bases 8a-c.

A mixture of the amine **4** (3.21 g, 10 mmol) and the appropriate aldehyde (10 mmol); namely, 4-(*N*,*N*-dimethylamino)benzaldehyde (1.5 g), 3,4-dimethoxybenzaldehyde (1.68 g), and 1,3-benzodioxole-5-carboxaldehyde (1.52 g), in absolute ethanol (50 mL), was heated under reflux for 4 h. Then produced solid material was filtered and crystallized from the proper solvent.

3-[(4-N,N-Dimethylaminobenzylidene)amino]-2-[1-(4-isobutylphenyl)ethyl]-quinazolin-4(3H)-one (8a). This compound was obtained from 4-(*N*,*N*-dimethylamino)-benzaldehyde and crystallized from ethanol. Yield 3.35 g (74 %); m. p. 200-201^{o}C. IR (KBr), ν (cm^{-1}): 3052 (C–H_{arom}), 2980, 2878 (C–H_{aliph}), 1674 (C=O), 1620 (C=N). ^{1}H NMR ($CDCl_3$) δ: 0.98 (d, *J* = 6.2 Hz, 6H, $CH_2CH(CH_3)_2$), 1.62 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 1.89 (m, 1H, $CH_2CH(CH_3)_2$), 2.22 (d, *J* = 6.4 Hz, 2H, $CH_2CH(CH_3)_2$), 3.34 (q, *J* = 6.2 Hz, 1H, $CHCH_3$), 3.68 (s, 6H, $N(CH_3)_2$), 6.97–7.22 (m, 4H, H_{arom}), 7.48–7.87 (m, 7H, H_{arom}), 8.18 (d, *J* = 8.2 Hz, 1H, H_{arom}), 8.85 (s, 1H, N=C*H*).

MS, *m/z* (I_{rel} (%)): 452 (88). Found (%): C, 76.70; H, 6.90; N, 12.10. $C_{29}H_{32}N_4O$ (452.60). Calculated (%): C, 76.96; H, 7.13; N, 12.38.

3-[(3,4-Dimethoxybenzylidene)amino]-2-[1-(4-isobutylphenyl)-ethyl]quinazolin-4(3H)-one (8b). This compound was obtained from 3,4-dimethoxybenzaldehyde and crystallized from methanol. Yield 3.56 g (76 %); m. p. 208-209^{o}C. IR (KBr), ν (cm^{-1}): 3055 (C–H_{arom}), 2975, 2870 (C–H_{aliph}), 1672 (C=O), 1622 (C=N), 1120 (C–O–C). ^{1}H NMR ($CDCl_3$) δ: 1.08 (d, *J* = 6.2 Hz, 6H, $CH_2CH(CH_3)_2$), 1.58 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 1.90 (m, 1H, $CH_2CH(CH_3)_2$), 2.12 (d, *J* = 6.4 Hz, 2H, $CH_2CH(CH_3)_2$), 3.32 (q, *J* = 6.2 Hz, 1H, $CHCH_3$), 3.86 (s, 6H, $(OCH_3)_2$), 7.05–7.28 (m, 5H, H_{arom}), 7.44–7.88 (m, 5H, H_{arom}), 8.16 (d, *J* = 8.4 Hz, 1H, H_{arom}), 8.88 (s, 1H, N=C*H*). MS, *m/z* (I_{rel} (%)): 469 (100). Found (%): C, 74.00; H, 6.40; N, 8.70. $C_{29}H_{31}N_3O_3$ (469.59). Calculated (%): C, 74.18; H, 6.65; N, 8.95.

3-{[(1,3-Benzodioxole-5-yl)methylidene]amino}-2-[1-(4-isobutylphenyl)ethyl]-quinazolin-4(3H)-one (8c). This compound was obtained from 1,3-benzodioxole-5-carboxaldehyde and crystallized from benzene. Yield 3.26 g (72 %); m. p. 130-131^{o}C. IR (KBr), ν (cm^{-1}): 3048 (C–H_{arom}), 2985, 2825 (C–H_{aliph}), 1674 (C=O), 1620 (C=N), 1126 (C–O–C). ^{1}H NMR ($CDCl_3$) δ: 1.01 (d, *J* = 6.2 Hz, 6H, $CH_2CH(CH_3)_2$), 1.58 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 1.95 (m, 1H, $CH_2CH(CH_3)_2$), 2.28 (d, *J* = 6.4 Hz, 2H, $CH_2CH(CH_3)_2$), 3.38 (q, *J* = 6.2 Hz, 1H, $CHCH_3$), 6.27 (s, 4H, OCH_2O), 7.00–7.24 (m, 5H, H_{arom}), 7.40–7.83 (m, 5H, H_{arom}), 8.17 (d, *J* = 8.2 Hz, 1H, H_{arom}), 8.82 (s, 1H, N=C*H*). MS, *m/z* (I_{rel} (%)): 453 (86). Found (%): C, 73.80; H, 5.80; N, 9.10. $C_{28}H_{27}N_3O_3$ (453.55). Calculated (%): C, 74.15; H, 6.00; N, 9.26.

General Procedure for Preparation of Thiazolidinones 9a-c.

An equimolar amount (5 mmol) of mercaptoacetic acid (0.5 mL, 98%) and the proper *Schiff*'s bases; **8a** (2.26 g), **8b** (2.35 g) and/or **8c** (2.27 g), in dry benzene (50 mL), was heated under reflux for 10-12 h. The solvent was then evaporated in vacuum. The solid residue was washed with diethyl ether (50 mL), filtered, and crystallized from the proper solvent.

3-[2-(4-Dimethylaminophenyl)-4-oxo-thiazolidin-3-yl]-2-[1-(4-isobutylphenyl)ethyl]quinazolin-4(3H)-one (9a). This compound was obtained from *Schiff*'s base **8a** and crystallized from methanol. Yield 0.95 g (36 %); m. p. 224-226^{o}C. IR (KBr), ν (cm^{-1}): 3052 (C–H_{arom}), 2984, 2829 (C–H_{aliph}), 1688 (C=$O_{thiazolidinone}$), 1665 (C=$O_{quinazolinone}$), 1608 (C=N). ^{1}H NMR ($CDCl_3$) δ: 0.99 (d, *J* = 6.2 Hz, 6H, $CH_2CH(CH_3)_2$), 1.48 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 1.86 (m, 1H, $CH_2CH(CH_3)_2$), 2.41 (d, *J* = 6.4 Hz, 2H, $CH_2CH(CH_3)_2$), 3.35 (q, *J* = 6.2 Hz, 1H, $CHCH_3$), 3.66 (s, 6H, $N(CH_3)_2$), 4.02 (s, 2H, $CH_{2thiazolidinone}$), 5.65 (1H, s, $CH_{thiazolidinone}$), 6.98–7.24 (m, 4H, H_{arom}), 7.48–7.88 (m, 7H, H_{arom}), 8.23 (d, *J* = 8.2 Hz, 1H, H_{arom}). MS, *m/z* (I_{rel} (%)): 526 (10). Found (%): C, 70.50; H, 6.40; N, 10.40. $C_{31}H_{34}N_4O_2S$ (526.71). Calculated (%): C, 70.69; H, 6.51; N, 10. 46.

3-[2-(3,4-Dimethoxyphenyl)-4-oxo-thiazolidin-3-yl]-2-[1-(4-isobutylphenyl)ethyl]quinazolin-4(3H)-one (9b). This compound was obtained from *Schiff*'s base **8b** and crystallized from ethanol. Yield 1.03 g (38 %); m. p. 237-239^{o}C. IR (KBr), ν (cm^{-1}): 3052 (C–H_{arom}), 2984, 2829 (C–H_{aliph}), 1674 (C=$O_{thiazolidinone}$), 1662 (C=$O_{quinazolinone}$), 1608 (C=N). ^{1}H NMR ($CDCl_3$) δ: 1.04 (d, *J* = 6.2 Hz, 6H, $CH_2CH(CH_3)_2$), 1.42 (d, *J* = 6.3 Hz, 3H, $CHCH_3$), 1.89 (m, 1H, $CH_2CH(CH_3)_2$), 2.30 (d, *J* = 6.4 Hz, 2H, $CH_2CH(CH_3)_2$), 3.33 (q, *J* = 6.3 Hz, 1H, $CHCH_3$), 4.04 (s, 2H, $CH_{2thiazolidinone}$), 3.85 (s, 6H, $(OCH_3)_2$), 5.65 (1H, s, $CH_{thiazolidinone}$), 7.06–7.27 (m, 5H, H_{arom}), 7.40–7.85 (m, 5H, H_{arom}), 8.16 (d, *J* = 8.2 Hz, 1H, H_{arom}). MS, *m/z* (I_{rel} (%)): 543 (14). Found (%): C, 68.30; H, 6.00; N, 7.60. $C_{31}H_{33}N_3O_4S$ (543.69). Calculated (%): C, 68.48; H, 6.12; N, 7.73.

3-[2-(Benzo[1,3]dioxol-5-yl)-4-oxothiazolidin-3-yl]-2-[1-(4-isobutylphenyl)ethyl]-quinazolin-4(3H)-one (9c). This compound was obtained from *Schiff*'s base **8c** and crystallized from ethanol. Yield 1.03 g (40 %); m. p. 242-244^{o}C. IR (KBr), ν (cm^{-1}): 3050 ($C–H_{arom}$), 2989, 2846 ($C–H_{aliph}$), 1677 ($C=O_{thiazolidinone}$), 1660 ($C=O_{quinazolinone}$), 1618 (C=N). ^{1}H NMR ($CDCl_3$) δ: 1.08 (d, *J* = 6.2 Hz, 6H, $CH_2CH(CH_3)_2$), 1.38 (d, *J* = 6.3 Hz, 3H, $CHCH_3$), 1.94 (m, 1H, $CH_2CH(CH_3)_2$), 2.38 (d, *J* = 6.4 Hz, 2H, $CH_2CH(CH_3)_2$), 3.28 (q, *J* = 6.3 Hz, 1H, $CHCH_3$), 4.05 (s, 2H, $CH_{2thiazolidinone}$), 3.85 (s, 6H, $(OCH_3)_2$), 5.65 (1H, s, $CH_{thiazolidinone}$), 6.28 (s, 4H, OCH_2O), 7.08–7.22 (m, 5H, H_{arom}), 7.40–7.86 (m, 5H, H_{arom}), 8.12 (d, *J* = 8.0 Hz, 1H, H_{arom}). MS, *m/z* (I_{rel} (%)): 527 (15). Found (%): C, 68.10; H, 5.40; N, 7.80. $C_{30}H_{29}N_3O_4S$ (527.65). Calculated (%): C, 68.29; H, 5.54; N, 7.96.

3-Hydroxy-2-[1-(4-isobutylphenyl)ethyl]quinazolin-4(3H)-one (10)

Procedure A

To a solution of the amine **4** (1.61 g, 5 mmol), in hydrochloric acid (10 mL, 10 mmol, 1N), sodium nitrite solution (13.8 mL, 10 mmol, 5 %) was added with continuous stirring, in an ice bath at 0-5^{o}C. The reaction mixture was stirred for an hour then boiled for 5 minutes, cooled and extracted with chloroform (3x10 mL). The combined organic extract solutions was collected and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the separated solid was crystallized from ethanol. Yield 1.09 g (68 %); m. p. 180-182^{o}C.

Procedure B

An equimolar amounts (5 mmol) of benzoxazinone **3** (1.54 g) and hydroxylamine hydrochloride (0.35 g) in 10 mL of dry pyridine was heated under reflux for 6 h. The reaction mixture was then left to cool and poured into cold water with constant stirring. The solid product that separated out was filtered, washed with water, dried and then crystallized from ethanol. Yield 1.01 g (63 %); m. p. 180-182^{o}C. IR (KBr), ν (cm^{-1}): 3460 (O–H), 3055 ($C–H_{arom}$), 2976, 2935, 2874 ($C–H_{aliph}$), 1668 (C=O), 1618 (C=N). ^{1}H NMR ($CDCl_3$) δ: 1.12 (d, *J* = 6.2 Hz, 6H, $CH_2CH(CH_3)_2$), 1.37 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 2.21 (m, 1H, $CH_2CH(CH_3)_2$), 2.48 (d, *J* = 6.4 Hz, 2H, $CH_2CH(CH_3)_2$), 3.62 (q, *J* = 6.4 Hz, H, $CHCH_3$), 7.29–7.85 (m, 7H, H_{arom}), 8.24 (d, *J* = 8.2 Hz, 1H, H_{arom}), 9.38 (bs, 1H exchangeable with D_2O, O–H). MS, *m/z* (I_{rel} (%)): 322 (64). Found (%): C, 74.40; H, 6.60; N, 8.50. $C_{20}H_{22}N_2O_2$ (322.41). Calculated (%): C, 74.51; H, 6.88; N, 8.69.

Antiinflammatory Evaluation

Westar rats and albino mice of either sex were used in the present study. Animal weighting 180-200g (12 weeks) and 22-25g (8 weeks) were used. The animals were housed in groups of six and acclimatized to room conditions for at least 2 days before the experiments. Food and water were freely available up to the time of experiments. The food was withdrawn on the day before the experiment, but free access to water was allowed. All compounds and reference ibuprofen (70 mg/kg body mass) were suspended in 1% carboxymethyl cellulose (CMC) and administrated orally using an animal feeding needle. The control groups received appropriate a volume of vehicle (1.0% CMC, oral) only. This activity was performed by the following procedure of Winter *et al.* [14] on groups of six animals each. A freshly prepared suspension carrageenin (1% m/v, 0.1 ml) was injected in the planter region of the right hind paw of each rat. One group each kept as control and the animals of the other groups were pretreated with the test drugs (70 mg/kg body mass) suspended in 1.0 % CMC given orally 1 hour before the carrageenin treatment. The volume was before and after 4 hours the carrageenin treatment measured using pleytheysmometer.

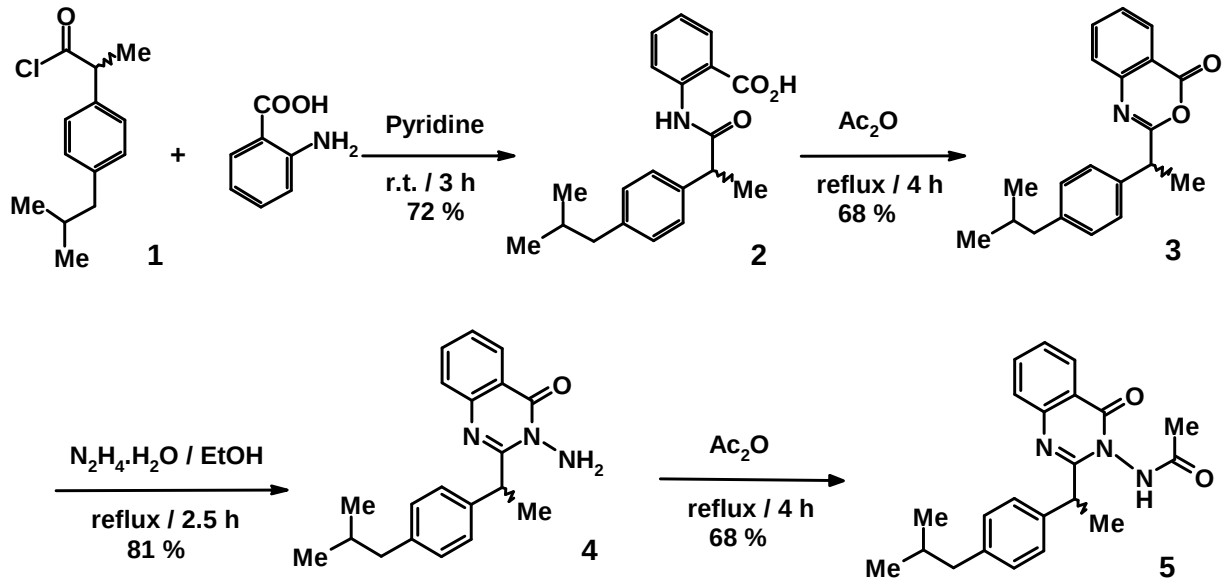
Acute Ulcerogenesis Test

Acute ulcerogenesis test was done according to *Cioli et al.* [15] rats were divided into different groups consisting of six animals each. Ulcerogenic activity was evaluated after 2 weeks administration of test compounds or ibuprofen at the dose of 200 mg/kg body mass. Food but not water was removed 24 h before administration of the test compounds. After the drug treatment, the rats were fed normal diet for 17 h and were then sacrificed. The stomach was removed and opens along the greater curvature, washed with distilled water and cleaned gently by dipping in saline. The mucosal damage was examined by means of magnifying glass. For each stomach the mucosal damage was assessed according to the following scoring system: 0.5 redness; 1.0 spot ulcer; 1.5 hemorrhagic streaks; 2.0 ulcer.

RESULTS AND DISSOCIATION

Chemistry

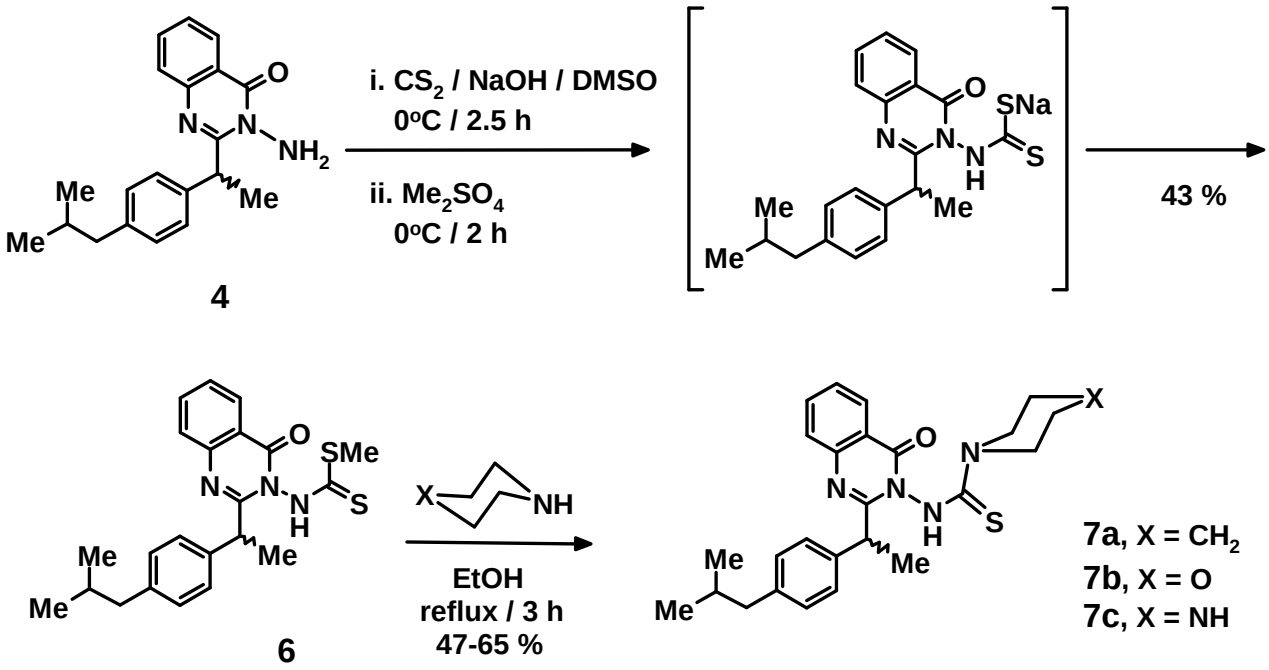
2-(4-Isobutylphenyl)propanoyl chloride (**1**) was prepared by treatment of (*RS*)-ibuprofen with thionyl chloride [2]. The reaction of the acid chloride **1** with anthranilic acid, in dry pyridine, afforded the corresponding anilide **2** (Scheme 1). The structure of the anilide **2** was inferred from its microanalytical and spectral data. Thus, its IR spectrum showed characteristic absorption stretching bands due to C=O of both carboxylic acid and amide functions at ν 1735 and 1646 cm^{-1}, respectively. ^{1}H NMR spectrum of the anilide **2** revealed the presence of two, deuterium-exchangeable, protons at δ 8.08 and 12.85 related to N–H and CO_2H. Intramolecular dehydration of the anilide **2**, using acetic anhydride, led to cyclization giving rise the benzoxazinone **3** (Scheme 2).



Scheme 1.

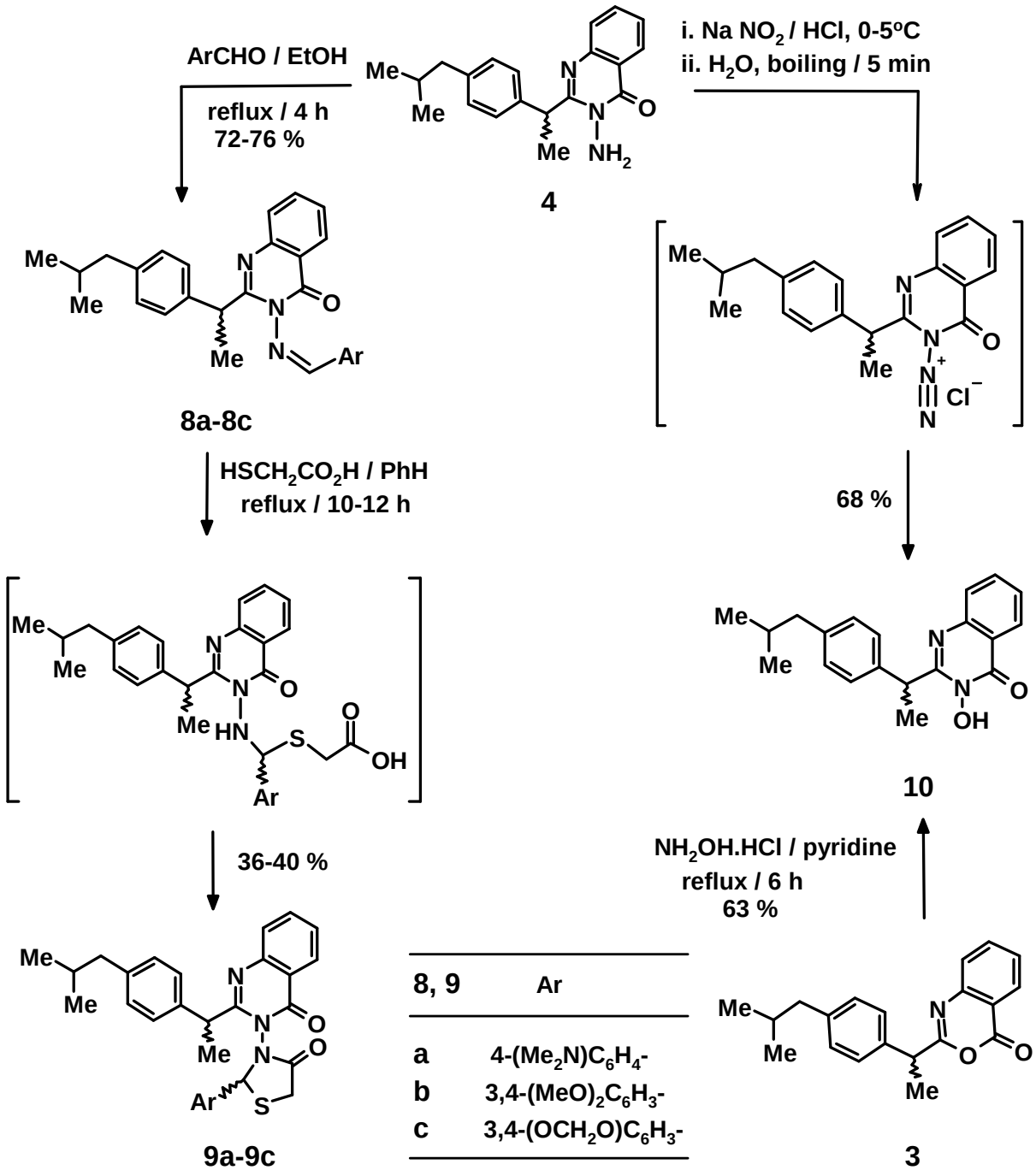
IR and ^{1}H NMR spectra of compound **3** indicated the absence of both carboxylic and amide functions. A different absorption band was observed at ν 1760 cm^{-1} which is characteristic for C=O function of 3,1-benzoxazin-4-ones. Mass spectrum exhibited a molecular ion peak at *m/z* 307 which is coincident with the expected molecular formula obtained *via* loss of a water molecule from the anilide **2**. These results are considered confirmatory for the postulation that cyclization process involved both carboxylic and amidic functions. The benzoxazinone **3** was

subjected to react with hydrazine hydrate to give the 3-aminoquinazolinone **4**, in 81 % yield (Scheme 1). It is expected that this reaction proceeds *via* nucleophilic ring-opening ring closure (RORC) process, replacing ring oxygen with nitrogen bearing amino group. IR spectrum of the amine **4** showed specific stretching bands at ν 3360 and 3280 cm^{-1} due to symmetric and asymmetric vibrations of NH_2 function. The absorption band due to C=O function, for typical quinazolin-4-ones, was noticed at ν 1668 cm^{-1}. These results are in conformity with ^1H NMR spectral data of compound **4** which indicated a broad singlet chemical shift at δ 6.20 due to two deuterium-exchangeable protons of NH_2. Acetylation of the amine **4** with acetic anhydride furnished the acetamide **5** (Scheme 1). IR spectrum of the acetamide **5** showed the presence of two absorption bands due amidic C=O functions at ν 1675 and 1634 cm^{-1}. ^1H NMR spectrum showed singlet chemical shift at δ 2.31 due to three protons of acetyl group beside a deuterium-exchangeable signal at δ 11.02 due the acidic proton of acetamide N–H. There is no indication for obtaining a N,N-diacteylation product even if high excess of acetylating agent was used. This may be attributed to steric hindrance due crowding of neighboring ibuprofenyl grouping.



Scheme 2.

The carbothioamides **7a–c** were targeted because of their expected biological activity. A convenient and efficient path-way was utilized to prepare the desired structures **7a–c** (Scheme 2). Thus, treatment of the amine **4** with carbon disulfide, in presence of sodium hydroxide as base catalyst, and *in situ* methylation of the not separated sodium dithiocarbamide salt, using dimethyl sulfate, gave the methyl dithiocarbamate **6**, in overall 43% yield (Scheme 2). ^1H NMR spectrum of the product revealed a singlet chemical shift at δ 2.54 due three protons of SCH_3. Mass spectrum showed a molecular ion peak at *m/z* 411, confirming the suggested molecular formula of the product. Treatment of the methyl dithiocarbamate **6** with some secondary cyclic amines, namely; piperidine, morpholine, and piperazine furnished the consequent carbothioamides **7a–c**, in 47-65 % yields (Scheme 2). A nucleophilic addition-elimination took place with removal of methanethiol which was detected during the course of reaction.



Scheme 3.

Condensation of the amine **4** with certain aromatic aldehydes, namely; 4-(N,N-dimethylamino)benzaldehyde, 3,4-dimethoxybenzaldehyde (veratraldehyde), and 1,3-benzodioxole-5-carboxaldehyde (piperonaldehyde), gave the corresponding *Schiff*'s bases **8a–c** (Scheme 3). Spectral data of the products **8a–c** pointed to the absence of NH_2 function, indicating its inclusion in the condensation reaction. ^1H NMR spectrum of the trio showed specific chemical shift signals of azomethine proton (N=C–H) observed at δ 8.85 (±0.03). Heterocyclization of the *Schiff*'s bases **8a–c** with mercaptoacetic acid was performed, in boiling dry benzene, affording the thiazolidinones **9a–c** (Scheme 3). It is thought that mercaptoacetic acid underwent nucleophilic addition reaction to the azomethine double bond. Consequently, intermolecular cyclo-condensation reaction took place accompanied by removal of a water molecule [13]. The structure of the thiazolidinones **9a–c** was distinguished *via* integration of

both spectral and analytical data of these compounds. Thus, IR spectra of the thiazolidinones **9a–c** represented strong absorption band at ν 1688–1674 cm^{-1}, due to stretching vibration of C=O. ^1H NMR spectra revealed characteristic chemical shifts of thiazolidinones C–H at position 2 which was observed as singlet peak at δ 5.65 while the CH_2 at position 5 of thiazolidinones appeared at δ 4.02–4.05.

The amino group in compound **4** was converted into a hydroxyl one *via* diazotization, using in situ freshly prepared nitrous acid, followed by hydrolysis by boiling for only five minutes. The structure of the product; 3-hydroxyquinazolin-4-one **10**, was established on basis of its spectral as well as analytical results. Furthermore, this structure received a good synthetic elucidation when the same compound **10** was prepared *via* condensation reaction of the benzoxazinone **3** with hydroxylamine hydrochloride, in a RORC process (Scheme 3).

Table 1. The Anti-inflammatory activity and ulcerogenic activity of ibuprofen derivatives.

Compd. No.	Anti-inflammatory activity[†] (Mean inhibition, %)	Ulcerogenic activity[‡] (Mean severity)
2	84	1.9
3	85	1.8
4	78	0.5
5	80	-
6	77	-
7a	54	-
7b	83	0.6
7c	94	0.5
8a	84	0.8
8b	82	-
8c	83	-
9a	90	0.6
9b	88	-
9c	85	0.5
10	83	-
Ibuprofen	91	1.9
control	-	-

[†]*Dose 70 mg/kg body mass.*
[‡]*Dose 200 mg/kg body mass.*

Antiinflammatory activity

All the synthesized compounds were evaluated as antiinflammatory activity at an oral dose of 70 mg/kg body mass and were compared with the standard drug ibuprofen at the same oral dose. The tested compounds showed antiinflammatory activity ranging from 57-94 % (Table 1) and the standard drug ibuprofen showed 91% inhibition after 4 hours.

Structure activity relationship (SAR) in the series of compounds **7a-c** revealed that increase in polarity, H-bonding and basicity of structure is associated with increase in mean inhibition behavior of compound (Figure 1). Thus the carbothioamide derivative **7c** having piperazine group showed the maximum activity 94% whereas when this group was replaced piperidine group **7a** the activity was found to be minimal 54%. Also it was observed that thiazole derivatives **9a-c** showed high anti-inflammatory activity ranged 85-90 %. The tested compounds show mean severity ranged between 0.5–1.9, a comparatively improved ulcerogenic activity with respect to ibuprofen itself (Figure 2).

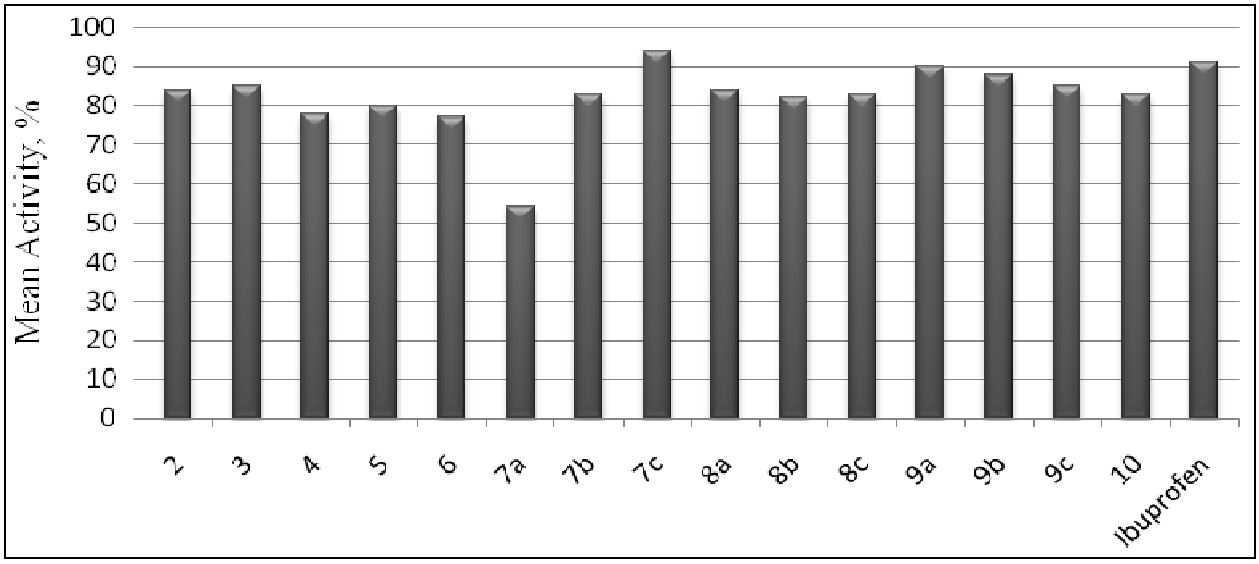


Figure 1. The Antiinflammatory activity of new ibuprofen derivatives.

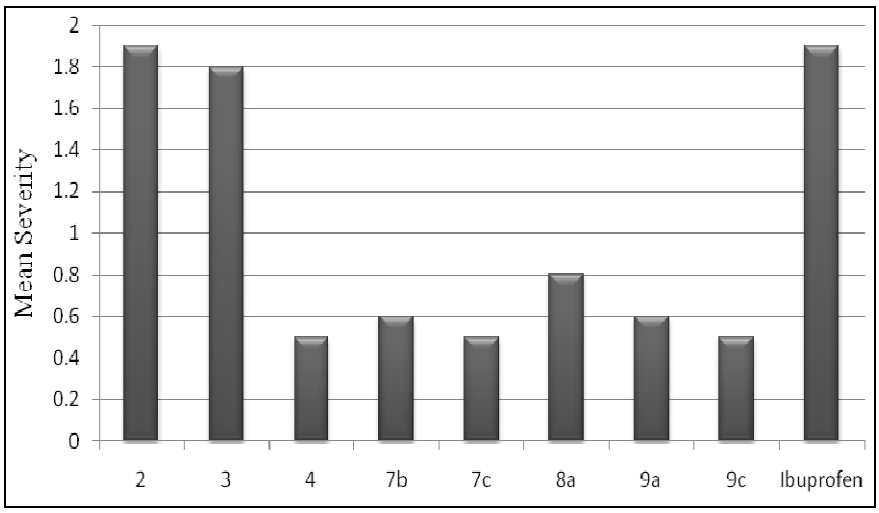


Figure 2. The ulcerogenic activity of the new ibuprofen derivatives.

CONCLUSION

Various quinazolinone derivatives of ibuprofen were prepared with the objective of developing better anti-inflammatory compounds with minimal ulcerogenic activity estimated as anti-inflammatory with minimal ulcerogine effect. The carbothioamide **7c** and 3-thiazolidinylquinazolinone **9a** derivatives of ibuprofen, showed maximum activity 94% and 90%, respectively. In the same time these two compounds showed the lowest ulcerogenic activity (mean severity 0.5). Also, many products showed significant antiinflammatory activities (78-94 %) along with maximum reduction of the severity index (0.5-1.9).

Acknowledgements
Authors are thankful to National Organization for Drug Control and Research, Egypt for providing all the necessary facilities for carrying out biological evaluation.

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