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New Quinazolinone Derivatives: Synthesis, Anti-inflammatory and Antitumor Activities

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Abstract: Quinazolinones represent a class of drugs of diverse biological activities, including antimicrobial, anti-inflammatory, anticonvulsant, antitumor, in addition to other activities. In this work, we have focused on the antitumor and anti-inflammatory activities of 2, 3-disubstituted-4(3H) quinazolinone.
New quinazolinone derivatives **IVa-c**, **VII**, **VIIIa-c, IXa-d, Xa-d, XIa-d, XIIa-d, XVa-f, XVIIa,b, XIX, XXa-d, XXIa-c, XXIIa-f, XXVa-j,** and **XVIII** were prepared according to the adopted procedures in schemes 1, 2, 3 and 4.
Twenty two representative compounds have been tested for cytotoxic activity against human mammary carcinoma cell line (MCF7) using doxorubicin as a reference standard. Furthermore, Fourteen compounds were evaluated for their anti-inflammatory activity by applying the method of "carrageenan rat paw oedema" using ibuprofen as a standard drug. Then, ulcerogenic liability was applied for the active derivatives.
Results revealed that sixteen derivatives are active as antitumor. Also, all the tested compounds revealed variable anti-inflammatory activity and four of them demonstrated superior anti-inflammatory activity with lower ulcer liability than the reference standard.
Key words: Quinazolinone, anti-inflammatory activity, antitumor activity.

Introduction

Quinazolinone scaffold has been gaining prominence due to the fact that its derivatives have been known to possess significant anticancer activity.

Additionally, some researches reported the importance of quinazolinone derivatives as potent analgesic and anti-inflammatory activities with nearly negligible ulcer index unlike other non steroidal anti-inflammatory drugs. [18-24, 35] Based on the foregoing, it became interestingly to synthesize some 3-substituted quinazolinone having a phenoxymethyl moiety at position 2 **IVa-c, IXa-d, Ia-d** with a hope to develop new derivatives that would be active as anti-inflammatory agents.

Also, it was considered of interest to synthesize some hybrid molecules by incorporation of an anti-inflammatory nucleus through an amide linkage to obtain **(VIIIa-c)** or an ester linkage to get **(XXIIIa-f)** aiming to generate derivatives to be tested for their anti-inflammatory activity.

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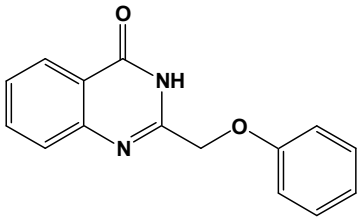
one (PMQ) **(1)** is a promising anticancer agent. [31] Accordingly, our objective was focused on 2-phenoxymethyl-quinazolin-4(3*H*)-one as the main nucleus for the synthesis of some new quinazolinone derivatives. Literature survey indicated that quinazolinones bearing thioureido,[29] thiazolidinone, [32, 33] or arylideneamino, [34] showed antitumor activity. Therefore, it seemed of interest to synthesize compounds of the general formula **XIIa-d**, **XIIIa,b**, and **XVa-f**. Further studies were applied by directing our attention to perform isosteric substitution of the thiazolidinone by imidazolinone moiety or further incorporation of benzylidne moiety on the thiazolidinone to obtain derivatives **XVIII** and **XXIa-d**, respectively. However, for further exploration of novel anticancer agents, the authors thought that it would be worthwhile to prepare two series **XXa-c** and **XXIa-d** based on the reactivity of the methylene functionality of **XIX** aiming to obtain derivatives with



1

Experimental

Remarks

Melting points were carried out by the open capillary tube method using Galenkamp digital melting points apparatus and they are uncorrected. IR spectra were made on Bruker Vector 22 (Germany) Perken Elmer 1600 series (Chain) KBr disc. Proton magnetic resonance ^{1}H-NMR spectra were carried out using Fourier transforms NMR spectrometer 200MHZ and Fourier transform EM -290, 300 MHz NMR spectrometer. Mass spectra were carried out using Finnigan SSQ 7000, mass spectrometer, Electron Impact at ei at 70 eV. Elemental analysis was carried out using Heraew and Vario EL III (elemntar), C,H,N,S analyzer (Germany) at the microanalytical Center, Faculty of Science, Cairo University. Compounds **II**, [36] **IV**, [12] **VII**, [37] **X**, [38] **XVIIa,b**, [12] **XXIIIa-e**. [39] were prepared as reported.

2-Phenoxymethyl-3-(4-substituted-phenyl)-quinazolin-4(3*H*)-one (IVa-c).

A mixture of 2-(2-phenoxy-acetylamino)-benzoic acid **(II)** (2.71 g, 10 mmol) and 4-substituted aniline (10 mmol) in dry benzene (15 mL) was stirred and treated dropwise with a solution phosphorus oxychloride (5 mL) in benzene (10 mL) over a period of 15 minutes, then refluxed for 2 hours. Excess benzene was distilled under reduced pressure and the mixture was treated with 10 % sodium carbonate solution (20 mL). The precipitated solid was filtered, washed with water, dried, and recrystallized from ethanol Table 1.^{1}H NMR (DMSO- d_6) of **IVa**: δ=2.33 (s, 3H, CH_3), 4.75(s, 2H, OCH_2), 6.84-7.87 (m, 12H, aromatic CH), 8.16 (d, 1H, C_5-H, J=6 Hz). Mass Spectrum of **IVa:** m/z (%): M^+ =342 (34.0 %); **IVb:** m/z (%): M+1 = 363 (4.67 %) M+2 = 364 (0.34%); **IVc:** m/z (%): M^+ =407 (0.8 %)

***N*-(4-Oxo-2-phenoxymethyl-quinazolin-3(4*H*)-yl)-amide derivatives (VIIIa-c).**

The appropriate acyl chloride (10 mmol) was added dropwise to the 3-amino-4(3*H*)-quinazolinone **VII** (2.67g, 10 mmol) in dimethylformamide (15 mL), stirring was continued for an hour at room temperature. The reaction mixture was poured onto ice, the separated solid was filtered, washed with water, dried then recrystallized from ethanol Table 1. ^{1}H NMR (DMSO- d_6) of **VIIIa**: δ= 5.17 (s, 2H, OCH_2), 6.94-7.95(m, 13H, aromatic CH), 8.15(d, 1H, C_5-H, J=5.4 Hz), 11.52(s, 1H, NH; D_2O exchange). Mass Spectrum of **VIIIb**: m/z (%): M^+ =479 (3.5 %)

3-Substituted-2-phenoxymethyl-quinazolin-4(3*H*)-one (IXa-d).

Procedure for IXa, b:

A mixture of 3-amino-quinazolin-4(3*H*)-one **VII** (2.67g, 10 mmol) and acetic anhydride (5 mL) was refluxed for an hour for **IXa** or 3 hours for **IXb**. The obtained solid was filtered, dried and recrystallized from ethanol Table 1. ^{1}H NMR (DMSO- d_6) of **IXa**: δ = 3.28 (s, 3H, CH_3), 4.99(d, 2H, CH_2O, J=11.7), 6.95-8.17(m, 9H, aromatic CH), 11.05(s, 1H, NH (D_2O exchange). Mass Spectrum of **IXa:** m/z (%): M^+ = 309 (5.4 %); **IXb:** m/z (%): M^+ = 351 (12.0 %)

Procedure for IXc, d:

A mixture of 3-amino-quinazolin-4(3*H*)-one **VII** (2.67g, 10 mmol) and succinic anhydride or maleic anhydride (10 mmol) was fused in a sand bath for an hour, the reaction mixture was diluted with water and filtered off. The obtained solid was recrystallized from ethanol to give compounds **IXc, d** Table 1.^{1}H NMR (DMSO- d_6) of **IXc**: δ= 2.89 (t, 4H, CH_2CH_2), 5.32 (s, 2H, OCH_2), 6.95-8.12(m, 8H, aromatic CH), 8.14 (d, 1H, C_5-H, J=4.4).

Mass Spectrum **of IXc:** m/z (%): M^+ = 349 (68.55 %).

3-(4-(4-Substituted)benzylidene-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl)-2-phenoxymethyl-quinazolin-4(3*H*)-one (XIa-d).

A mixture of 3-amino-4(3*H*)-quinazolinone **VII** (2.67g, 10 mmol) and 4-benzylidene-2-phenyl-4*H*-oxazol-5-one **Xa-d** (10 mmol) was fused at 150ºC in a sand bath for an hour. The reaction mixture was diluted with water and filtered off. The obtained solid was recrystallized from ethanol to give compounds **XIa-d** Table 1. ^{1}H NMR (DMSO- d_6) of **XIa**: δ= 5.35 (s, 2H, OCH_2), 6.87-8.14 (m, 19, aromatic CH), 8.28 (s, 1H, CH of benzylidene).Mass Spectrum **XIa**: m/z (%): M-2 = 496 (31.06 %); **XIb**: m/z (%): M^+ = 532 (0.61 %).

1-Substituted-3-(4-oxo-2-(phenoxymethyl) quinazoline-3(4*H*)-yl)thiourea XIIa-d.

A mixture of 3-amino-2-(phenoxymethyl) quinazoline-4(3*H*)-one **(VII)** (2.67 gm, 10 mmol), the appropriate isothiocyanate (10 mmol) in absolute ethanol (15 mL) and 5 drops triethylamine was refluxed for 12 hours. The separated solid was filtered,

washed with water, dried and recrystallized from DMF/water to give compounds **XIIa-d** Table 1.^{1}H NMR (DMSO- d_6) of **XIIb**: δ=1.46(t, 3H, CH_2CH_3), 4.88 (q, 2H, CH_2CH_3), 5.66 (s, 2H, OCH_2), 6.97-8.11(m, 10H, 2H NH (D_2O exchange) and 8H aromatic.CH), 8.58(d, 1H, C_5-H, J=8.1). ^{1}H NMR (DMSO- d_6) of **XIId**: δ= 5.75(s, 2H, CH_2O), 6.99-8.08(m, 14H, aromatic CH), 12.60(s, 2H, NH (D_2O exchange). Mass Spectrum **XIIa**: m/z (%): M^+ = 340 (3.13 %); **XIIb**: m/z (%): M^+ = 354 (0.26 %); **XIIc**: m/z (%): M-1 = 367 (0.36 %).

3-(3-Substituted-4-oxo-thiazolidin-2-ylideneamino)-2-phenoxymethyl-quinazolin-4(3*H*)-one XIIIa,b.

A mixture of thiourea derivative **XIIb** or **XIId** (10 mmol), chloroacetic acid (0.95 gm, 10 mmol) and anhydrous sodium acetate (3.28 gm, 40 mmol) was refluxed in glacial acetic acid (10 mL) for 16 hours. The mixture was poured onto ice water, the separated solid was filtered, washed with water, dried and recrystallized from ethanol to give compounds **XIIIa,b** Table 1. ^{1}H NMR (DMSO- d_6) of **XIIIa**: δ= 1.12 (t, 3H, CH_2CH_3), 4.04 (q, 2H, CH_2CH_3), 4.08 (s, 2H, CH_2-S), 4.62 (s, 2H, OCH_2), 6.92-7.51(m, 8H, arom. CH), 8.21(d, 1H, C_5-H, J= 8.1). Mass Spectrum **XIIIb**: m/z (%): M^+ = 442 (0.70 %).

3-Substituted-4-hydroxy-2-(4-oxo-2-phenoxymethyl-quinazolin-3(4*H*)-ylimino)-thiazolidine-5-carboxylic acid ethyl ester (XIVa-b).

A mixture of thiourea derivatives **XIIa-d** (10 mmol) diethyl bromomalonate (2.35 gm, 10 mmol) and anhydrous sodium acetate (3.28 gm, 40 mmol) was refluxed in glacial acetic acid (10 mL) for 16 hours. The mixture was poured onto ice water, the precipitated solid was filtered, washed with water and recrystallized from ethanol to give compound **XIVa,b** Table 1. ^{1}H NMR (DMSO- d_6) of **XIVb**: δ=1.25(t, 3H, CH_2CH_3), 4.19 (q, 2H, CH_2CH_3), 4.70(s, 2H, OCH_2), 6.95-7.56(m, 13H, aromatic CH), 8.37-8.40 (d, 1H, C_5-H, J=8.2), 11.15(s, 1H, OH). Mass Spectrum of **XIVb:** m/z (%): M-3 = 511 (0.49 %).

3-(4-Substitutedbenzylideneamino)-2-(phenoxymethyl)quinazoline-4(3*H*)-one XVa-f

A mixture of 3-amino-2-(phenoxymethyl) quinazoline-4(3*H*)-one **VII** (2.67 gm, 10 mmol) and 4-substituted aromatic aldehyde (10 mmol) in ethanol (20 ml) and piperidine (1 mL) was heated under reflux for 8 hours. The reaction mixture was concentrated, the obtained solid was filtered, washed with aqueous ethanol, dried and recrystallized from ethanol Table 1. ^{1}H NMR (DMSO- d_6) of **XVc**: δ= 2.10(s, 3H, CH_3), 5.31(s, 2H, OCH_2), 6.98-7.88(m, 12H, aromatic CH), 8.25 (d, 1H, C_5-H, J=7.2 Hz), 9.14(s, 1H, N=CH). Mass spectrum **XVb**: m/z (%): M+ = 389 (5.4 %) M+2= 391(2.1). Mass Spectrum **XVc**: m/z (%): M^+ = 369 (11.2%). Mass Spectrum **XVd**: m/z (%): M^{+1} = 386 (11.2%).

3-(4-Oxo-2-phenoxymethyl-quinazolin-3(4*H*)-yl)-imidazole-2,5-dione XVIII.

A suspension of the chloroacetamide derivative **XVIIa, n=1** (3.48g, 10 mmol) and potassium cyanate (0.81 gm, 10 mmol) in absolute ethanol (20 mL) was refluxed for 6 hours. The solvent was concentrated, the obtained precipitate was filtered, washed with water, dried and recrystallized from ethanol, yield 75%, m.p.218-220ºC.
IR (KBr) cm^{-1}: 3055(arom. CH), 2954, 2884(aliph. CH), 1729, 1688(C=O), 1608, 1540(C=C, C=N).^{1}H NMR (DMSO- d_6): δ = 5.35 (s, 2H, OCH_2), 6.99-8.29 (m, 10H, 9H aromatic CH, 1H, CH=N). Mass Spectrum: m/z (%): M^+ = 348 (0.40 %). Anal. Calc. for $C_{18}H_{12}N_4O_4$ (348): Calculated: C, 62.07; H, 3.47; N, 16.09. Found C, 62.00; H, 3.80; N, 16.56%.

3-(4-Oxo-4,5-dihydro-thiazol-2-ylamino)-2-phenoxymethyl-quinazolin-4(3*H*)-one XIX.

A solution of the chloroacetamide derivative **XVIIa, n=1** (3.48g, 10 mmol) and ammonium thiocyanate (0.76 gm, 10 mmol) in absolute ethanol (20 mL) was refluxed for 6 hours and allowed to stand overnight at room temperature. The obtained precipitate was filtered, washed with water, dried and recrystallized from ethanol, yield 70 %, m.p.198-200ºC. IR (KBr) cm^{-1}: 3363(NH), 3067(arom. CH), 2950, 2890(aliph. CH), 1730, 1655(C=O), 1599, 1574(C=C, C=N).^{1}H NMR (DMSO- d_6): δ = 4.11 (s, 2H, CH_2-S), 5.12 (s, 2H, OCH_2), 7.02-8.18 (m, 9H, arom.CH), 12.48 (s, 1H, NH (D_2O exchange). Mass Spectrum: m/z (%): M^+ = 366 (11.54 %). Anal. Calc. for $C_{18}H_{14}N_4O_3S$ (366.39). Calculated: C, 59.01; H, 3.85; N, 15.29. Found: C, 59.29; H, 4.02; N, 15.51%.

3-[5-(4-Substituted-benzylidene)-4-oxo-4,5-dihydro-thiazol-2-ylamino]-2-phenoxymethyl-quinazolin-4(3*H*)-one XXa-d.

A mixture of 3-(4-oxo-4,5-dihydro-thiazol-2-ylamino)-2-phenoxy methyl-3*H*-quinazolin-4-one **XIX** (3.66g, 10 mmol), 4-substituted benzaldehyde (10 mmol) and anhydrous sodium acetate (3.28 gm, 40 mmol) in glacial acetic acid (15 mL) was refluxed for 24 hours then allowed to cool. The solid product was collected, dried and recrystallized from acetic acid Table 1. ^{1}H NMR (DMSO- d_6) of **XXb**: δ= 5.14(s, 2H, OCH_2), 6.82-8.11 (m, 13H, arom. CH), 8.09(s, 1H, CH=), 13.10 (s, 1H, NH (D_2O exchange). Mass

Spectrum of **XXb**: m/z (%): M^+ = 488 (9.25) M+2 = 490 (3.79 %).

3-(5-Substituted-methyl-4-oxo-thiazolidin-2-ylamino)-2-phenoxymethylquinazolin-4(3*H*)-one XXIa-c.

To a solution of 3-(4-oxo-4,5-dihydro-thiazol-2-ylamino)-2-phenoxymethyl-3*H*-quinazolin-4-one **XIX** (3.66g, 10 mmol) in absolute ethanol (10 mL) and formaldehyde (1 mL, 37%) the appropriate secondary amine (10 mmol) was added. The reaction mixture was refluxed for 4 hours. Upon cooling, the crude compound was precipitated, filtered, dried, and recrystallized from ethanol Table 1. ^{1}H NMR (DMSO- d_6) of **XXIa**: δ= 2.50 (t, 4H, CH_2NCH_2 of morhpoline), 3.48(d, 2H, CH_2-N, J=8.15), 3.74-3.85(m, 5H, CH thiazolidinone, CH_2OCH_2 of morhpoline), 4.705(d, 2H, CH_2O J =11.7), 6.90-8.12(m, 9H, aromatic CH), 11.96(s, 1H, NH D_2O exchange). Mass Spectrum **XXIa**: m/z (%): M-1 = 464 (0.40 %).

(4-Oxo-2-phenoxymethyl-quinazolin-3(4*H*)-ylcarbamoyl)methyl or ethyl ester (XXIIa-f).

A mixture of 2-chloro-*N*-(4-oxo-2-phenoxymethyl-4*H*-quinazolin-3-yl)-acetamide **XVIIa,b** (10 mmol) and sodium salt of salicylic acid, ibuprofen, diclofenac or naproxen (10 mmol) in dimethylformamide (5 mL) was heated in a water bath for 3 hours. The resulting solution was cooled and poured onto crushed ice, the separated solid was filtered, dried and recrystallized from ethanol Table 1. ^{1}H NMR (DMSO- d_6) of **XXIIa**: δ= 5.14(s, 2H, CH_2OCO), 5.19 (s, 2H, CH_2O), 6.99-8.26 (m, 13H, aromatic CH), 10.33(s, 1H, NH (D_2O exchange), 11.62 (s, 1H, OH (D_2O exchange). ^{1}H NMR (DMSO- d_6) of **XXIIf**: δ = 2.90 (s, 2H, CH_2), 3.87(t, 2H, CH_2CH_2O), 5.01(s, 2H, CH_2O), 5.16(t, 2H, CH_2CH_2O), 6.80-8.16(m, 16 H, aromatic CH), 8.63(s, 2H, NH (D_2O exchange). Mass Spectrum **XXIIa**: m/z (%): M^+ = 445 (10.8 %). Mass Spectrum **XXIIb**: m/z (%): M-1 = 536 (5.80 %); **XXIIf**: m/z (%): M^+ = 617 (5.80 %).

2-[4-(4-Substituted-phenyl)-5-cyano-6-oxo-1,6-dihydro-pyrimidin-2-ylsulfanyl]-*N*-(4-oxo-2-phenoxymethyl-quinazolin-3(4*H*)-yl)-acetamide or propamide (XXIVa-j).

A mixture of 2-thiouracil derivatives **XXIIa-e** (10 mmol) and 2-chloro-*N*-(4-oxo-2-phenoxymethyl-4*H*-quinazolin-3-yl) acetamide **XVIIa,b** (10 mmol) in acetone (15 mL) containing anhydrous potassium carbonate (1.37g, 10 mmol) was refluxed for 8 hours. The reaction mixture was poured onto ice water; the precipitated solid was filtered, washed with water, dried and recrystallized from ethanol Table 1. ^{1}H NMR (DMSO- d_6) of **XXIVa**: δ= 4.35(s, 2H, CH_2S), 4.80(s, 2H, CH_2O), 6.62-8.15(m, 13H, aromatic CH), 8.18(d, 1H, C_5H J=7.4) 11.48(s, 2H, NH (D_2O exchange).^{1}H NMR (DMSO- d_6) of **XXIVc**: δ= 2.35(s, 3H, CH_3), 4.38 (s, 2H, CH_2S), 4.80-4.851(d, 2H, CH_2O), 6.84-7.92(m, 12H, aromatic CH), 8.21 (d, 1H, C_5H J=7.4), 11.50 (s, 2H, NH (D_2O exchange). ^{1}H NMR (DMSO- d_6) of **XXIVf**: δ= 2.87 (t, 2H, CH_2CH_2), 5.05 (t, 2H, CH_2CH_2), 5.21(s, 2H, OCH_2), 6.93-7.90(m, 13H, aromatic CH), 8.19(d, 1H, C_5H J=6.2) 11.27 (s, 2H, NH (D_2O exchange). Mass Spectrum **XXIVa**: m/z (%): M-1 = 537 (5.2 %). Mass Spectrum **XXIVc**: m/z (%): M^+ = 550 (1.39 %).; Mass **XXIVf**: m/z (%): M^+ = 550 (1.07 %).

Antitumor Activity. [40]

Cells were plated in 96-multiwell plate (10^4 cells/well) for 24 hours before treatment with the compounds to allow attachment of cell to the wall of the plate. Different concentrations of compound under test (0.0, 1.0, 2.5, 5.0 and 10.0 μg/ml) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 hours at 37ºC and in atmosphere of 5 % CO_2. After 48 hours, cells were fixed, washed and stained with Sulforhodamine B stain. Excess stain was washed with acetic acid and attached stain was recovered with tri EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve of the tumor cell line after the specified compound.

Anti-inflammatory Activity. [41]

Adult albino rats of both sexes weighing between 120-150 g were used. Rats were uniformly hydrated by giving 3 ml water/rat through gastric inoculation to reduce variability to oedema response. Animals were divided into 16 groups each of five animals. The control group was given saline solution containing few drops of Tween 80, ibuprofen (50 mg /kg) was taken as standard drug for comparison and compounds under examination (50mg/kg) were suspended in distilled water by the aid of few drops of Tween 80 and were given interaperitoneally one hour before induction of inflammation. Induction of inflammation was performed by subcutaneous injection of 0.1 ml of 1% carrageenan-sodium gel (Sigma-Aldrich, USA), into the sub-plantar region of the right hind paw. The dorso-ventral diameter (thickness) of the right of each rat was measured using a pair of dial thickness gauge calipers accurate to

0.001 cm^3 1h, 2h, 3h and 4h after induction of inflammation.

The percentage of anti-inflammatory activity (% inhibition of inflammation) was calculated after 4 hours according to the following equation

$$\% \text{ inhibition} = (L_c - L_t / L_c) \times 100$$

L_t is the mean increase in paw thickness in rats treated with the tested compounds.

L_c is the mean increase in paw thickness in control group.

Data were collected, checked, revised and fed in the computer and then analyzed by one-way ANOVA (F test) followed by Dunnett's t test at $p<0.05$ was used to tabulate the results (table 19, 20) and represent them graphically.

Acute ulcerogenic liability [42, 43]

Adult albino rats of both sexes weighing between 120-150 g were used. Animals were divided into 6 groups each of five animals. Rats were fasted 20 hours before drug administration. The four tested compounds **IXc, XXIIb**, **XXIIc**, **XXIIf** and ibuprofen were given orally in a dose of 50mg/kg suspended in 1% tween while one group received vehicle (1% tween). Rats were fasted for 2 hours, allowed to feed for 2 hours then fasted for another 20 hours. Rats were given another two doses in the second and third days. In the fourth day, rats were sacrificed, the stomach was removed, opened along with the greater curvature and rinsed with 0.9% saline. The number of mucosal damage (red spots) were counted using magnifying lens and their severity (ulcerogenic severity) was graded by mean from 0 (no lesion) to 4 (exceptional sever lesions). The following figures were calculated:

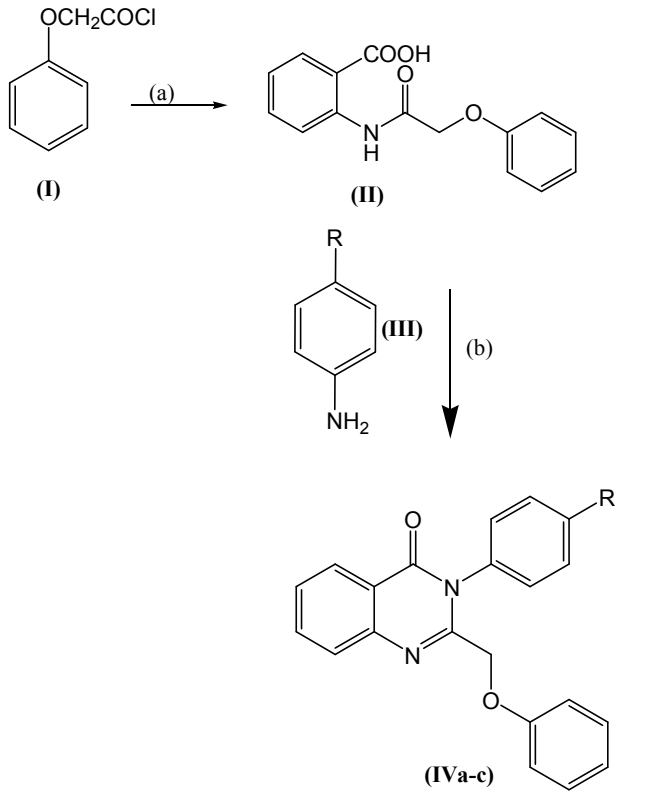
1-% Incidence /10 = [number of rats showing ulcer divided by total number of rats in the group x 100] / 10

2-Average number of ulcer: number of ulcers in the group/ total number of rats in the group.

3-Average severity: sum (each ulcer x score of severity)/ number of ulcers.

4-Ulcer index = the sum of the three figures

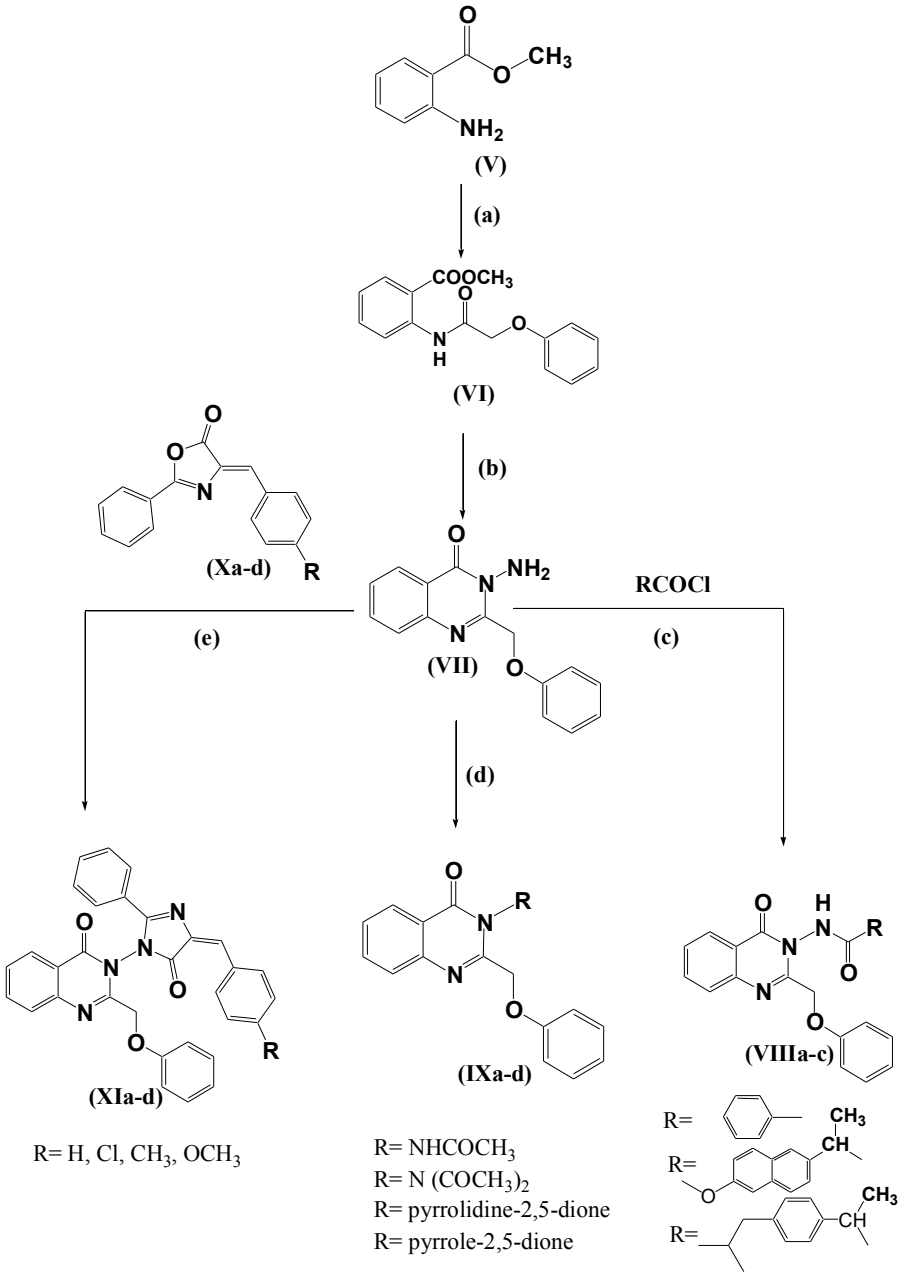
Scheme 1



R=CH_3, Cl, SO_2NH_2

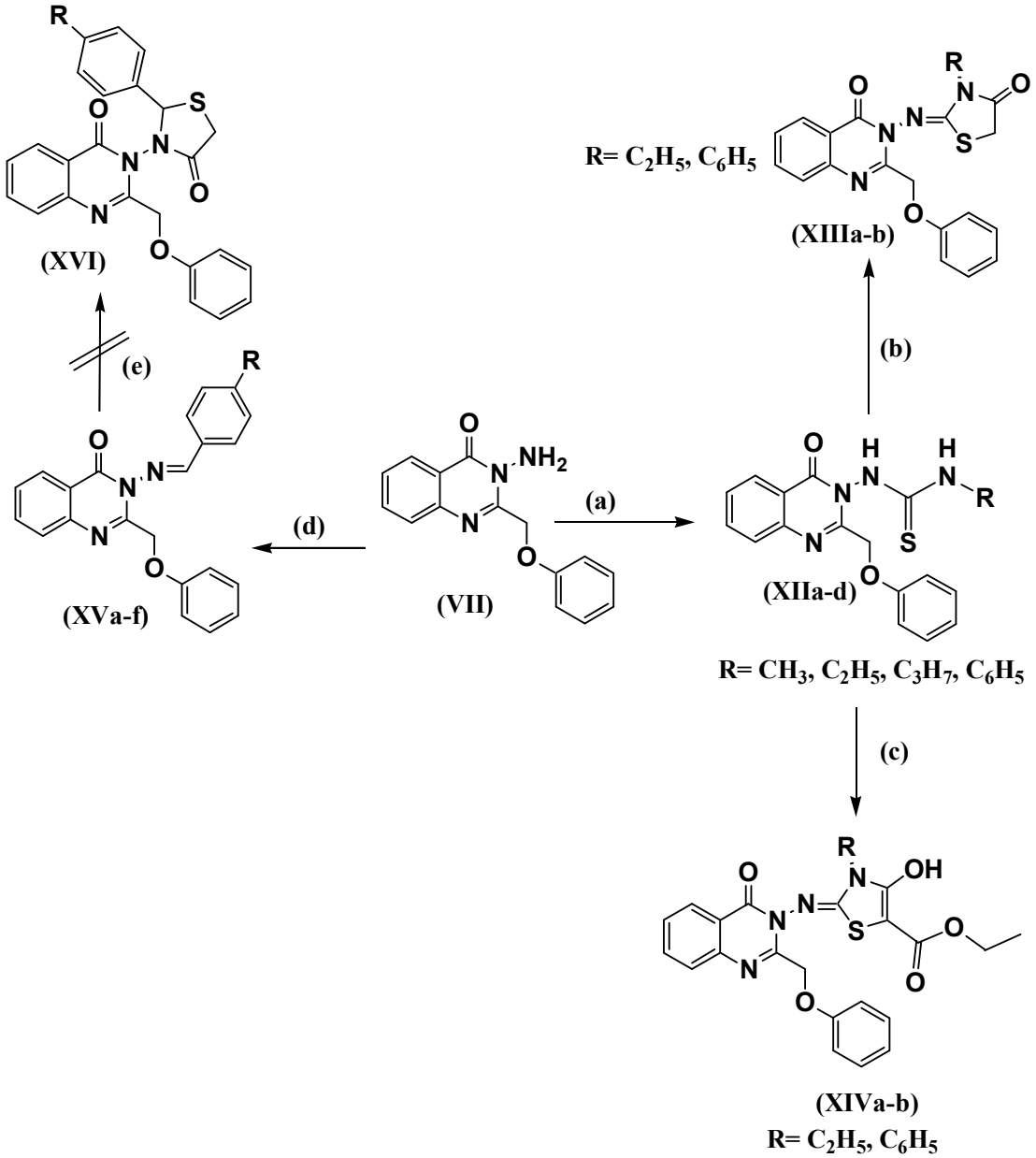
Reaction Condition: a) anthranilic acid, dry dimethylformamide, 3 h. b) substituted aniline $POCl_3$, dry benzene, reflux, 5 h.

Scheme 2



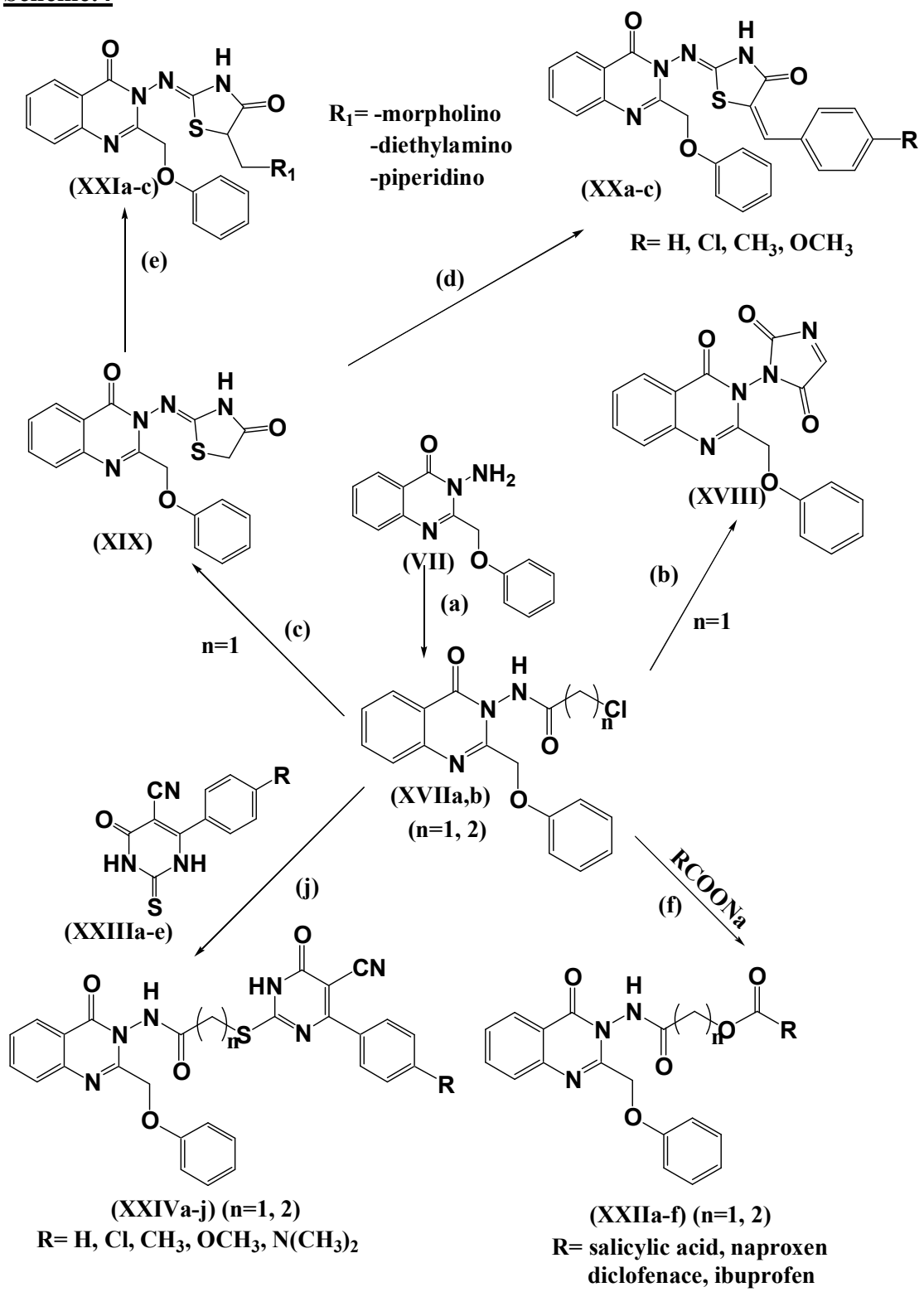
Reaction Condition: a) Phenoxyacetyl chloride, dry benzene, stirring over night, r. t b) hydrazine hydrate, Butanol, reflux, 8 h, c) sub. acyl chloride, dry DMF, 3 h, d) acetic anhydride, reflux, 2 h, 4 h or fusion with succinic anhydride, 1 h, e) oxazolinone, fusion 3 h.

Scheme 3



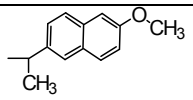
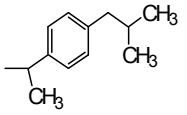
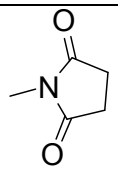
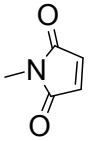
Reaction Condition: a) RNCS, ethanol, drops triethylamine, 12 h. b) $ClCH_2COOH$, sodium acetate, acetic acid, 24 h, c) diethylbromomalonate, anhydrous sodium acetate, acetic acid, 24 h. d) RCHO, ethanol, acetic acid, 8 h, e) $HSCH_2COOH$, dry benzene 24 h.

Scheme:4

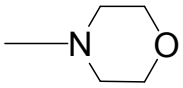
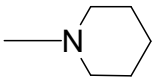
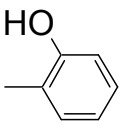
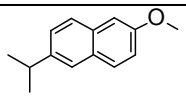


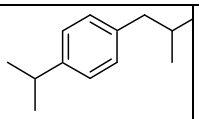
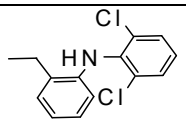
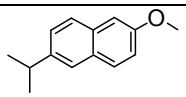
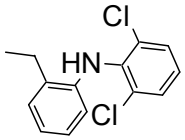
Reaction Condition: a) Chloroacetylchloride or chloropropionyl chloride dry DMF, stirr over night. r. t. b) Potassium cyanate, ethanol, 6 h. c) NH_4SCN, ethanol, 6 h. d) Ar-CHO, ethanol, 24 h. e) HCHO, secondary .amine, 4 h. f) Sodium salt of acid, DMF, 80ºC, 3 h. j) 2-Thiouracil der., K_2CO_3 , acetone, 8

Table (1): Physical, microanalytical and IR data for the newly synthesized compounds

Cpd.No	R	Mol. formula Mol.wt	m.p °C Yield %	calc	found	IR cm^{-1}
IV a	CH_3	$C_{22}H_{18}N_2O_2$ 342.39	183-2 30	C=77.1 H=5.30 N=8.18	77.31 5.23 8.50	3064-3008(arom. CH), 2949, 2920 (aliph. CH), 1676(C=O), 1586, 1570(C=C, C=N).
IV b	Cl	$C_{21}H_{15}ClN_2O_2$ 362.81	203-5 35	C=69.52 H=4.17 N=7.72	69.90 4.77 7.72	3074 (arom. CH), 2949(aliph. CH), 1680 (C=O), 1587, 1494 (C=C, C=N).
IV c	SO_2NH_2	$C_{21}H_{17}N_3O_4S$ 407.44	175-8 33	C=61.90 H=4.21 N=10.31	61.95 4.40 10.21	3421,3234(NH_2), 3066, 2926 (arom. aliph. CH), 1681(C=O), 1587, 1525, 1492(C=C, C=N).
VIIIa	$-C_6H_5$	$C_{22}H_{17}N_3O_3$ 371.39	150-152 51	C=71.15 H=4.61 N=11.31	70.99 4.81 11.58	3458(NH), 3064, 2945(arom. aliph. CH), 1710, 1681(C=O), 1622, 1593, 1487(C=C, C=O).
VIIIb		$C_{29}H_{25}N_3O_4$ 479.53	144-146 49	C=72.64 H=5.25 N=8.76	72.34 5.13 9.00	3323(NH), 3062, 3920, 2848(arom. aliph. CH), 1728, 1674(C=O), 1622, 1596, 1496(NH, C=C, C=O)
VIIIc		$C_{28}H_{29}N_3O_3$ 455.55	195-197 37	C=73.82 H=6.42 N=9.22	74.17 5.99 8.99	.3188(NH), 3062, 2976, 2841 (arom. aliph. CH), 1728, 1681 (C=O), 1597, 1587, 1494(NH, C=C, C=O).
IXa	$NHCOCH_3$	$C_{17}H_{15}N_3O_3$ 309.32	162-4 63	C=66.01 H=4.89 N=13.58	66.12 4.96 13.95	3304 (NH), 3022, 2974 (arom. aliph. CH), 1735, 1681(C=O), 1068, 1597, 1496(NH, C=C, C=N).
IXb	$N(COCH_3)_2$	$C_{19}H_{17}N_3O_4$ 351.36	183-5 75	C=64.95 H=4.88 N=11.96	65.19 4.59 11.76	3010, 2935 (arom. aliph. CH), 1741, 1722, 1697 (C=O), 1618, 1597, 1489 (C=C, C=N).
IXc		$C_{19}H_{15}N_3O_4$ 349.34	154-6 35	C=65.32 H=4.33 N=12.03	65.29 4.31 11.83	3040, 2939(arom. aliph. CH), 1743, 1712 (C=O), 1609, 1597, 1492 (C=C, C=N).
IXd		$C_{19}H_{13}N_3O_4$ 347.32	195-6 33	C=65.70 H=3.77 N=12.10	65.57 4.24 11.91	3066(arom. CH), 2939(aliph. CH), 1741, 1712(C=O), 1608, 1587, 1490(C=C, C=N).
XIa	H	$C_{31}H_{22}N_4O_3$ 498.53	176-179 35	C=74.69 H=4.45 N=11.24	74.79 4.59 11.18	3062, 3032 (arom. CH), 2980 (aliph. CH), 1697 (C=O), 1604, 1577 (C=C, C=N).

XIb	Cl	$C_{31}H_{21}ClN_4O_3$ 532.98	181-183 40	C=69.86 H=3.97 N=10.51	70.11 3.91 10.60	3064, 2654(arom. Aliph. CH), 1699 (broad C=O), 1604, 1543, 1489 (C=C, C=O).
XIc	CH_3	$C_{32}H_{24}N_4O_3$ 512.56	231-233 34	C=74.99 H=4.72 N=10.93	75.16 44.81 10.52	3062, 2922(arom. aliph. CH), 1705, , 1654(broad C=O), 1064, 1516, 1489 (C=C, C=N).
XId	OCH_3	$C_{32}H_{24}N_4O_4$ 528.56	242-244 37	C=72.72 H=4.58 N=10.60	73.03 4.50 10.32	3064, 2924(arom. aliph. CH), 1670 (broad, C=O), 1608, 1508, 1425 (C=O, C=N).
XIIa	CH_3	$C_{17}H_{16}N_4O_2S$ 340.40	280-282 51	C=59.98 H=4.74 N=16.46	60.09 4.87 16.73	3176.3132(NH), 3052, 2926 (arom. aliph. CH), 1682(C=O). 1613, 1595, 1445(NH, C=C, C=N).
XIIb	C_2H_5	$C_{18}H_{18}N_4O_2S$ 354.43	289-290 63	C=61.00 H=5.12 N=15.81	61.32 4.82 16.31	3447 (NH), 3049, 2920 (arom. aliph. CH), 1982(C=O), 1631(NH), 1562, 1536, 1485(C=C, C=O).
XIIc	C_3H_9	$C_{19}H_{20}N_4O_2S$ 368.45	280-282 38	C=61.94 H=5.47 N=15.21	61.89 5.07 15.46	3346, 3186(NH), 3038, 2923 (arom. aliph. CH), 1681(C=O), 1600, 1497, 1497 (NH, C=C, C=O).
XIId	C_6H_5	$C_{22}H_{18}N_4O_2S$ 402.47	293-295 59	C=65.65 H=4.51 N=13.92	66.07 4.99 14.22	3261, 3185(NH), 3061, 2928 (arom. aliph. CH), 1681(C=O), 1601, 1493, 1472 (NH, C=C, C=N).
XIIIa	C_2H_5	$C_{20}H_{18}N_4O_3S$ 394.45	182-184 47	C=60.90 H=4.60 N=14.20	60.97 4.21 13.90	3056, 2976(arom. aliph. CH), 1739, 1693(C=O), 1610, 1587, 1485 (C=C, C=N).
XIIIb	C_6H_5	$C_{24}H_{18}N_4O_3S$ 442.49	190-193 39	C=65.14 H=4.10 N=12.66	64.90 4.32 12.56	3057, 2976(arom. aliph. CH), 1730, 1695(C=O), 1583, 1533, 1496 (C=C, C=N).
XIVa	C_2H_5	$C_{23}H_{22}N_4O_3S$ 466.13	154-56 52	C=59.22 H=4.75 N=12.01	59.50 4.77 12.36	3106(OH), 2961, 2922, 2851 (arom. aliph. CH). 1726, 1650 (C=O), 1584, 1542, 1487(C=C, C=N).
XIVb	C_6H_5	$C_{27}H_{22}N_4O_3S$ 514.55	142-44 67	C=63.02 H=4.13 N=10.89	63.30 4.30 10.62	3272(OH), 3051, 2920, 2851 (arom. aliph. CH), 1730, 1660 (C=O), 1583, 1543, 1494(C=C, C=N).
XVa	H	$C_{22}H_{17}N_3O_2$ 355.39	130-133 71	C=74.39 H=4.82 N=11.82	74.44 5.10 11.55	3040(arom. CH), 2920(aliph. CH), 1678(C=O), 1581, 1496 (C=C, C=N).
XVb	Cl	$C_{22}H_{16}ClN_3O_2$ 389.83	160-162 80	C=67.78 H=4.14 N=10.78	68.01 4.30 10.77	3028(arom. CH), 2923, 2887(aliph. CH), 1674(C=O), 1597, 1493, 1461 (C=C, C=N).

XVc	CH_3	$C_{23}H_{19}N_3O_2$ 369.42	175-177 75	C=74.78 H=5.18 N=11.37	75.13 5.10 11.00	3059, 3030(arom. CH), 2918(aliph. CH), 1681(C=O), 1587, 1496 (C=C, C=N).
XVd	OCH_3	$C_{23}H_{19}N_3O_3$ 385.42	153-156 60	C=71.67 H=4.97 N=10.90	7189 4.89 10.66	3040, 2912(arom. aliph. CH), 1680 (C=O), 1597, 1587, 1496 (C=C, C=N).
XXa	H	$C_{25}H_{18}N_4O_3S$ 454.50	150-151 62	C=66.07 H=3.99 N=12.33	66.21 4.06 12.56	3309(NH), 3064, 2926(arom. aliph. CH), 1701, 1643(C=O), 1604(NH), 1543, 1489(C=C, C=N).
XXb	Cl	$C_{25}H_{17}ClN_4O_3S$ 488.95	185-186 53	C=61.41 H=3.50 N=11.46	61.73 3.85 11.41	3363(NH), 3062, 2978(arom. aliph. CH), 1732, 1653(C=O), 1605(NH), 1597, 1583, 1489(C=C, C=N).
XXc	CH_3	$C_{26}H_{20}N_4O_3S$ 468.53	161-163 59	C=66.65 H=4.30 N=11.96	66.46 4.63 12.26	3361(NH), 3062, 2964(arom. aliph. CH), 1732, 1683(C=O), 1605(NH), 1597, 1489, 1493(C=C, C=N).
XXd	OCH_3	$C_{26}H_{20}N_4O_4S$ 484.53	155-157 43	C=64.45 H=4.16 N=11.56	63.90 4.25 11.64	3361(NH), 3062, 2978(arom. aliph. CH), 1732, 1654 (C=O), 1612(NH), 1597, 1489(C=C, C=N).
XXIa		$C_{23}H_{23}N_5O_4S$ 465.53	186-188 33	C=59.34 H=4.98 N=15.04	59.69 4.72 15.02	3367(NH), 3040, 2919(arom. aliph. CH), 1735, 1685(C=O), 1587(NH), 1535, 1492(C=C, C=N).
XXIb	$N(C_2H_5)_2$	$C_{23}H_{25}N_5O_3S$ 451.54	183-185 39	C=61.18 H=5.58 N=15.51	61.39 5.32 16.12	3255(NH), 3064, 2943(arom, aliph, CH), 1739, 1695(C=O), 1587(NH), 1492, 1473(C=C, C=N).
XXIc		$C_{24}H_{25}N_5O_3S$ 463.55	194-196 32	C=62.18 H=5.44 N=15.11	62.52 5.29 15.64	3273(NH), 3064, 2933(arom. aliph. CH), 1732, 1683(C=O), 1587(NH), 1558, 1494(C=C, C=N).
XXIIa n=1		$C_{24}H_{19}N_3O_6$ 445.42	150-154 53	C=64.72 H=4.30 N=9.43	64.60 4..20 9.29	3474(OH), 3183(NH), 3057, 3010 (arom. CH), 2903, 2845 (aliph.CH), 1715, 1686(C=O), 1605, 1498 (NH, C=C,C=N)
XXIIb n=1		$C_{31}H_{27}N_3O_6$ 537.56	133-135 61	C=69.26 H=5.06 N=7.82	68.93 4.79 8.08	3236(NH), 3061, 2982(arom. aliph. CH), 1729, 1689(C=O), 1611, 1500, 1468(NH, C=C, C=O).

XXIIc n=1		$C_{30}H_{31}N_3O_5$ 513	155-157 35	C=70.16 H=6.08 N=8.18	70.00 5.82 8.35	3194(NH), 2992, 2860(arom. aliph. CH), 1716, 1684(C=O), 1610, 1481, 1443(NH, C=C, C=N).
XXIId n=1		$C_{31}H_{24}Cl_2N_4O_5$ 603.45	142-144 57	C=61.70 H=4.01 N=11.75	61.49 3.92 11.45	3279, 3446(NH), 3084,2917(arom. aliph. (CH), 1731, 1682(C=O), 1612, 1565, 149(NH, C=C, C=N).
XXIIe n=2		$C_{32}H_{29}N_3O_6$ 551.59	135-137 37	C=69.68 H=5.30 N=7.62	69.03 4,98 7.41	3348(NH), 3060(arom.CH), 2941 (aliph. CH), 1691(broad C=O), 1606, 1587, 1496(C=C, C=N).
XXIIf n=2		$C_{32}H_{26}Cl_2N_4O_3$ 617.48	144-146 33	C=62.24 H=4.24 N=9.07	62.52 4.49 9.37	3273(NH), 3053(arom. CH), 2926 (aliph. CH), 1732, 189 (C=O), 1583, 1543 (C=C, C=N).
XXIVa n=1	H	$C_{28}H_{20}N_6O_4S$ 536.56	258-60 56	C=62.68 H=3.76 N=15.66	62.60 3.60 16.00	3188(NH), 2995(arom.CH), 2202 (CN), 1716, 1697(C=O), 1612, 1597, 1544(NH, C=C, C=N).
XXIVb n=1	Cl	$C_{28}H_{19}ClN_6O_4S$ 571.01	280-282 43	C=58.90 H=3.35 N=14.72	58.79 3.20 14.67	3161(NH), 3022, 2897(arom. aliph. CH), 2220(CN), 1720, 1660 (C=O), 1609(NH), 1539,1523(C=C, C=N).
XXIVc n=1	CH_3	$C_{29}H_{22}N_6O_4S$ 550.59	235-238 61	C=63.26 H=4.03 N=15.26	63.10 3.90 15.33	3151(NH), 2997, 2854(arom.aliph. CH),2216(CN), 1722, 1668 (C=O), 1651,1539,1525 (NH, C=C, C=N).
XXIVd n=1	OCH_3	$C_{29}H_{22}N_6O_5S$ 566.59	225-227 49	C=61.48 H=3.91 N=14.12	61.30 3.80 13.95	3160(NH), 2929, 2841(arom. aliph. CH),2218(CN), 1685, 1654(C=O), 1600, 1543,1529(NH, C=C, C=N).
XXIVe n=1	$N(CH_3)_2$	$C_{30}H_{25}N_7O_4S$ 579.63	200-201 67	C=62.16 H=4.35 N=16.92	62.00 4.20 16.87	3304(NH), 2922, 252(arom. aliph. CH), 2216(CN), 1681, 1666(C=O), 161, 1566, 1521(NH, C=C, C=N).
XXIVf n=2	H	$C_{29}H_{22}N_6O_4S$ 550.59	219-220 53	C=63.26 H=4.01 N=15.26	63.31 4.31 14.97	3350(NH), 2924, 2858(arom. aliph. CH), 2214(CN), 1662(broad C=O), 1610, 1566, 1521(NH, C=C, C=N).
XXIVg n=2	Cl	$C_{29}H_{21}ClN_6O_4S$ 585.03	172-173 64	C=59.54 H=3.62 N=14.37	59.28 3.79 14.06	3188(NH), 3010, 2924(arom. aliph. CH), 2223(CN), 1681(broad C=O), 1608, 1598, 1537(NH, C=C, C=N).

XXYIVh n=2	CH_3	$C_{30}H_{24}N_6O_4S$ 564.62	174-175 42	C=63.82 H=4.28 N=14.88	64,02 4.48 14.70	3211(NH), 3064, 2922(arom.aliph. CH), 2216(CN), 1693(broad C=O), 1606, 1533, 1494(NH, C=C, C=N).
XXIVi n=2	OCH_3	$C_{30}H_{24}N_6O_4S$ 580.62	166-168 38	C=62.06 H=4.17 N=14.47	62.20 4.31 14.06	3169(NH), 3039, 2962(arom. aliph. CH), 2214(CN), 1681(broad C=O), 1606, 1535, 1465(NH, C=C, C=N).
XXIVj n=2	$N(CH_3)_2$	$C_{31}H_{27}N_7O_4S$ 593.66	220-223 46	C=62.72 H=4.58 N=16.52	63.06 4.78 16..86	3165(NH), 3072, 2956(arom. aliph. CH), 2216(CN), 1681(broad C=O), 1606, 1589, 1531(NH, C=C, C=N).

Table 2: Cytotoxic activity of the newly synthesized compounds (IC_{50}) (against MCF7 cell line)

Figure.	Comp. No	IC_{50}	Figure.	Comp. No	IC_{50}
1	**VII**	**3.57**	13	**XXIa**	**4.69**
2	**XVIIa**	**--**	14	**XXa**	**--**
3	**XVIIb**	**--**	15	**XXb**	**4.46**
4	**XIIb**	**2.34**	16	**XXd**	**--**
5	**XIId**	**1.84**	17	**XXIVa**	**--**
6	**XIIIa**	**3.34**	18	**XXIVb**	**3.61**
7	**XIIIb**	**2.19**	19	**XXIVd**	**2.04**
8	**XIX**	**--**	20	**XXIVf**	**0.85**
9	**XVa**	**2.3**	21	**XXIVg**	**4.15**
10	**XVb**	**2.3**	22	**XXIVi**	**3.96**
11	**XVd**	**4.72**	23	**DOX.**	**0.70**
12	**XVIII**	**4.46**			

Table 3: Oedema thickness of control, ibuprofen and the tested compounds

Comp.	Dose mg/kg	Oedema (mm)			
		1h	**2h**	**3h**	**4h**
control	0	1.92 ± 0.276	3.31 ± 0.450	3.87 ± 0.274	3.82 ± 0.151^{a}
ibuprofen	50	0.54 ± 0.137	0.95 ± 0.190	0.90 ± 0.080	0.95 ± 0.215^{a}
IVa	50	1.33 ± 0.426^{ab}	1.76 ± 0.629^{ab}	1.91 ± 0.627^{ab}	1.46 ± 0.492^{a}
VII	50	1.52 ± 0.021^{ab}	1.39 ± 0.052^{a}	2.07 ± 0.125^{ab}	1.98 ± 0.175^{ab}
VIIIb	50	0.79 ± 0.262^{a}	1.84 ± 0.140^{ab}	1.84 ± 0.205^{ab}	1.42 ± 0.297^{a}
VIIIc	50	1.12 ± 0.330^{a}	1.52 ± 0.228^{ab}	1.54 ± 0.178^{ab}	1.87 ± 0.302^{ab}
IXc	50	0.92 ± 0.119^{a}	0.85 ± 0.157^{a}	0.43 ± 0.234^{a}	0.16 ± 0.043^{ab}
IXd	50	1.82 ± 0.105^{a}	1.75 ± 0.474^{ab}	2.03 ± 0.253^{ab}	1.23 ± 0.278^{a}
XIb	50	0.89 ± 0.336^{a}	2.03 ± 0.276^{ab}	2.46 ± 0.330^{ab}	2.67 ± 0.232^{ab}
$XVII_a$	50	1.41 ± 0.094^{ab}	1.54 ± 0.329^{ab}	1.31 ± 0.337^{a}	1.27 ± 0.403^{a}
$XVII_b$	50	1.50 ± 0.119^{ab}	1.17 ± 0.277^{a}	1.17 ± 0.403^{a}	0.77 ± 0.291^{a}
$XXII_b$	50	1.63 ± 0.343^{ab}	0.82 ± 0.325^{a}	0.15 ± 0.167^{ab}	0.21 ± 0.227^{ab}
$XXII_c$	50	1.65 ± 0.200^{ab}	0.86 ± 0.204^{a}	0.15 ± 0.354^{ab}	0.21 ± 0.339^{ab}
$XXII_d$	50	1.18 ± 0.120^{ab}	1.29 ± 0.270^{a}	1.16 ± 0.367^{a}	1.02 ± 0.486^{a}
$XXII_e$	50	0.89 ± 0.139^{ab}	0.69 ± 0.201^{a}	1.09 ± 0.369^{a}	1.23 ± 0.440^{a}
$XXII_f$	50	1.04 ± 0.189^{ab}	0.55 ± 0.226^{a}	0.82 ± 0.153^{a}	0.72 ± 0.218^{a}

Statistical analysis was carried out by one-way ANOVA test.

[a] significant difference from reference value at $p<0.05$.

[b] significant difference from reference value at $p<0.01$.

Table 4: % inhibition of oedema of tested compounds and ibuprofen.

Comp.	Dose mg/kg	% protection			
		1h	2h	3h	4h
control	**00**	0	0	0	0
Ibuprofen	**50**	71.88	71.29	76.74	75.13
IVa	**50**	30.73^{a}	46.82^{ab}	50.65^{ab}	61.78^{a}
VII	**50**	20.83^{a}	58.00^{a}	46.51^{ab}	48.17^{ab}
VIIIb	**50**	58.85^{a}	44.41^{ab}	52.45^{ab}	62.83^{a}
VIIIc	**50**	41.66^{a}	54.08^{ab}	60.20^{ab}	51.08^{ab}
IXc	**50**	52.08^{a}	74.32^{a}	88.88^{a}	95.81^{ab}
IXd	**50**	5.21^{a}	47.13^{ab}	47.54^{ab}	67.80^{a}
XIb	**50**	53.46^{a}	38.67^{ab}	36.43^{ab}	30.10^{ab}
$XVII_a$	**50**	26.56^{ab}	$53.4a7^{ab}$	66.15^{a}	66.75^{a}
$XVII_b$	**50**	21.87^{ab}	64.65^{a}	69.76^{a}	79.84^{a}
XXIIb	**50**	15.10^{ab}	75.23^{a}	96.12^{ab}	94.50^{ab}
XXIIc	**50**	14.06^{ab}	74.02a	77.00^{ab}	94.50^{ab}
XXIId	**50**	38.54^{ab}	61.03^{a}	70.03^{a}	73.20^{a}
XXIIe	**50**	53.64^{ab}	79.15^{a}	71.83^{a}	67.80^{a}
XXIIf	**50**	45.83^{ab}	83.38^{a}	78.81^{a}	81.15^{a}

Statistical analysis was carried out by one-way ANOVA test.
[a] significant difference from reference value at $p<0.05$.
[b] significant difference from reference value at $p<0.01$

Table 5: The ulcerogenic liability of the most active compounds

compound	Number of animals with ulcer	% incidence divided by 10	Average of ulcers number	Average severity	Ulcer index
Control	0/5	0.00	0.00	0.00	0.00
Ibuprofen	5/5	10	10.80	1.80	22.60
IXc	4/5	8	2.6	1.15	11.75
XXIIb	5/5	10	5.4	1.22	16.62
XXIIc	4/5	8	3.20	1.13	12.33
XXIIf	5/5	10	4.8	1.58	16.30

Result and Discussion

Chemistry

The present work involves the synthesis of the target quinazolin-4(3*H*)-one derivatives. Schemes 1-4 summarize the steps followed in the synthesis of the key intermediate and the final compounds.

2-(2-phenoxy-acetylamino)-benzoic acid **II** was prepared through the reaction of phenoxyacetyl chloride with anthranilic acid in dry DMF using sodium hydroxide according to the reported method. [37] It was then cyclized to **IVa-c** via reaction with the appropriate 4-substituted aniline in presence of phosphorus oxychloride in dry benzene.(Scheme 1). Reaction of phenoxyacetyl chloride with methyl anthranilate **V** in dry ether afforded the corresponding methyl 2-(2-phenoxy)acetamido) benzoate **VI**, [12] which was reacted with hydrazine hydrate to give **VII** [37]. Stirring of **VII** with the acid chloride of benzoic acid, ibuprofen or naproxen in dry dimethyl formamide at room temperature afforded compounds **VIIIa-c**. Reaction of **VII** with acetic anhydride afforded two products according to the time of reaction. Heating for an hour gave the mono substituted 3-acetamido derivative **IXa,** while heating for three hours gave the diacetamido derivative **IXb**.

Attempt to synthesize **IXc,d** via the reaction of 3-aminoquinazolinone **VII** with succinic or maleic anhydride in glacial acetic acid containing sodium acetate failed to give the desired products. Unfortunately, deamination of **VII** occurred to give 1, which was confirmed by IR spectrum that revealed the disappearance of amino group. Mass spectrum revealed m/z = 251 that is in concordance with the deaminated structure. Compounds **IXc,d** were prepared by fusion of **VII** with the appropriate acid anhydride.

Refluxing **VII** with oxazol-5(4*H*)-one derivatives **Xa-d** in glacial acetic acid in presence of anhydrous sodium acetate didn't afforded the expected imidazolone derivatives **XIa-d** and also deamination of **VII** is produced (confirmed as previously mentioned). The target derivatives **XIa-d** were also obtained by fusion of **VII** and the appropriate oxazol-5(4*H*)-one **Xa-d** (Scheme 2).

As shown in scheme 3, thiourea derivatives **XIIa-d** were synthesized by refluxing **VII** with the appropriate isothiocyanate derivatives in ethanol in presence of triethylamine in which **XIIa,b** were cyclized to the thiazolidinone derivatives **XIIIa,b** or 2,3-dihydrothiazol-4-ol derivatives **XIVa,b** by reaction with monochloroacetic acid or diethylbromomalonate, respectively. Alternatively, reaction of **VII** with aromatic aldehyde in ethanol containing few drops of piperidine afforded **XVa-f** that were failed to be cyclized into the target compound **XVI** using thioglycolic acid.

Compounds **XVIIa,b** were prepared by reaction of chloroacetyl chloride or chloropropionyl chloride with 3-aminoquinazolinone derivatives **VII** at room temperature in dimethylformamide according to the reported procedure. [12] Cyclization of **XVIIa** with potassium cyanate or ammonium thiocyanate yielded **XVIII** or **XIX**, respectively. Reaction on the active methylene group of **XIX** with aromatic aldehyde or secondary amine in presence of HCHO under Mannich reaction condition afforded **XXa-c** or **XXa-c**, respectively.

Reaction of chloroacetyl or chloropropionyl derivatives **XVIIa,b** with sodium or potassium salt of some organic acid in DMF yielded **XXIIa-f**. Moreover, reaction of **XVIIa,b** with 6-(4-substituted-phenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile **XXIIIa-e** [44-48] produced **XXIVa-j**.

Antitumor activity

Twenty two representative compounds have been tested for cytotoxic activity against human mammary carcinoma cell line (MCF7) in the National Cancer Institute, Cairo University. The screening involves calculation of the percentage growth or surviving fraction of the drug treated cell lines compared by untreated control using Sulforhodamine B (SRB) colorimetric assay. [40] Culture fixed with (TCA) were stained for 30 minutes with 0.4 % w/v Sulforhodamine B dissolved in 1 % acetic acid, and protein bound dye was extracted with 10mM tris base [tris(hydroxymetyl) aminomethane] for determination of optical density in a computer-interfaced, 96-well microtiter plate reader. The optical density measured is linear with cell number of the survival fraction. Therefore, the assay is a sensitive measure of drug induced cytotoxicity with the best signal to noise ratio. The assay also, provides a colorimetric end point that is nondestructive, indefinite stable and visible to naked eye. [40]

Data were presented in table 2 revealed the IC_{50} of the newly synthesized compounds. On testing compounds **VII, XIIa,b, XIIIb,d, XVa,b,d, XVIIa,b, XVIII, XIX, XXIa, XXa,b,d, XXIVa,b,d,f,g,i**, it was found that sixteen derivatives **VII, XIIa,b, XIIIa,b, XVa,b,c, XVIII, XXa, XXIb, XXIV,b,c, XXIVf,g,h** were active as antitumor, while the rest compounds were inactive **XVII1,2, XIX, , XXIa,c, XXIVa**. Also, the antitumor screening of the reported compound **VII** showed activity as antitumor agent and this activity is decreased upon acylating its amino group with either chloroacetylchloride in compound **XVIIIa** or chloropropionylchloride in compound **XVIIb.** Furthermore, the replacement of the 3-amino group of **VII** by thiourea moiety led to an increase in the activity as shown in derivatives **XIIb,d**. On the other hand, comparing their cytotoxic activities indicated that, the phenyl thiourea derivative **XIId** showed increased activity than the ethyl one **XIIb**. The cytotoxic screening of the thiazolidinone derivatives **XIIIa,b** obtained by cyclization of **XIIb,d** with chloroacetic acid revealed that they still active as cytotoxic agent but to a lesser extent than their precursors thiourea. Also, **XIIIb** bearing phenyl substituent was more active than ethyl derivative **XIIIa**, whereas the unsubstituted thiazolidinone **XIX** prepared by reacting **XVIIa** with ammonium thiocyanate showed no activity. The benzylidene derivatives of the thiazolidinone **XXa,b,d** produced variable cytotoxicity ranging from abolishing the activity as in compounds **XXa,d** to restoring the activity to a certain limit as in **XXb**. Also, the incorporation of the benzylidene moiety at position 3 of quinazolinone gave compounds with varied antitumor activity. Furthermore, the unsubstituted benzylidene **XVa** and 4-chloro benzylidene derivatives **XVb** showed nearly equal antitumor activity, while

that containing 4-methoxy substituent was less active. Moreover, on studying the antitumor activity of the thiouracil containing compounds **XXIV**, it was found that the unsubstituted derivatives **XXIVa** was inactive while the substituted derivatives 4-methoxy **XXIVd** and 4-chloro **XXIVb** were active in the following order **XXIVd > XXIVb**. Furthermore, by increasing the spacer between the thiouracil and the quinazolinone ring by one carbon atom as in **XXIVf-j**, the same pattern of activity order was obtained and 4-methoxy derivatives **XXIVi** is more active than 4-chloro derivatives **XXIVg**. The only exception is that the unsubstituted derivative **XXIVf** was the most active one and nearly as active as doxorubicin.

Anti-inflammatory screening

The anti-inflammatory activity of the newly synthesized compounds **IVa**, **IXc,d, XIb, VIII b,c, XXII b-d (n =1)**, **XXII e, f (n = 2)** and the reported ones **VII**, **XVIIa,b** were evaluated using ibuprofen as standard drug and applying the method of "carrageenan rat paw oedema" that had been described by Winter *et al*. [41]

Data represented in table 3 and 4 revealed that, they showed considerable anti-inflammatory activity. The chloroacetylamino derivatives **XVIIa** showed moderate anti-inflammatory activity (66.7% protection) whereas its chloropropionyl analog **XVIIb** exhibited slight increase in activity (79.84% protection) than the reference drug (75.13% protection).

The anti-inflammatory activity of **XVIIa,b** increased by the incorporation of the anti-inflammatory drugs (naproxen, ibuprofen, diclofenac) through an ester link to afford **XXIIb-f** that produced percentage inhibition of odema ranging from (67-94.5%). Unfortunately, the hybridization of the previously mentioned biologically active drugs with **VII** through an amide link produced **VIII** that showed percentage inhibition of odema **of (51.08-62.83%)** lower than that of the reference drug**.**

The anti-inflammatory activity of pyrrole-2,5-dione derivatives **IXd**, (67.80%) was lower than its pyrrolidine-2,5-dione **IXc**, (95.81%). Finally, 3-(4-tolyl) derivatives **IVa** demonstrated moderate anti-inflammatory activity with (61.78 %) inhibition of oedema. Unfortunately, the anti-inflammatory activity of **XIb** is contradicted with the result obtained by the molecular modeling study.

Acute ulcerogenic liability

The ulcerogenic activity was performed for compounds **IXc**, **XXIIb,c** and **f** that exhibited marked anti-inflammatory activity (95.81, 94.50, 94.50, 81.15) % inhibition of oedema respectively according to the reported method.[42, 43] From the obtained Data (table 5) it has been noticed that all the tested derivatives **IXc, XXIIb, XXIIc** and **XXIIf** possess less ulcerogenic potentialities comparable with that of ibuprofen (used as a reference standard). These results will bring a conclusion that oral administration of the tested compounds pyrrolidine-2, 5-dione **(IXc)** and ester of 3-chloroacetylamino-ibuprofen **(XXIIc)** were found to be safer than ibuprofen with respect to ulcerogenic liability.

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