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Synthesis, Characterization and Evaluation of Anti-Inflammatory and Analgesic Activity of Some Novel Quinoline Based Thiazolidinone Heterocycles

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IN this paper we report the synthesis of some quinoline based thiazolidinone derivatives **(13–22)** in a three-step process. Condensation of 2-hydrazinylquinoline **2** with different aromatic aldehydes gave the corresponding Schiff bases **3-10** which in turn were reacted with thioglycolic acid to furnish the corresponding thiazolidinone derivatives **13-20**. Reaction of compound **2** with isatin or methyl isatin gave 1-sustituted-3-(2-(quinolin-2-yl)hydrazono) indolin-2-ones **11** and **12**, which were converted to 1-substituted 3'-(quinolin-2-ylamino) spiro[indoline-3,2'-thiazolidine]-2,4'-dione **21** and **22** by cyclocondensation with thioglycolic acid. All newly synthesized compounds have been characterized by means of elemental analyses, IR, ^{1}H NMR and MS. Furthermore, all new thiazolidinone derivatives were evaluated for their anti-inflammatory and analgesic activity. The Study results revealed that the highest anti-inflammatory potency was gained by 6 derivatives according to the following order **22** > **17** >**13** > **14** > **21** > **15**, showing a good edema inhibition compared to the reference drug indomethacin. Compound **22** carrying indole ring system inhibited the edema volume significantly at the 1st h post administration, and the activity was enhanced up to the 4th h giving a promising edema volume inhibition compared to that produced by indomethacin. The longest duration of analgesic action up to 90 min post compounds administration was obtained by the compounds **13**, **17** and **22**, they exhibited potent analgesia compared to that obtained by aspirin.

Keywords: Quinoline, Thiazolidinone, spiro[indoline-3,2'-thiazolidine]-2,4'-dione, Synthesis, Anti-inflammatory and analgesic activity.

Introduction

The chemistry of quinoline derivatives has been of increasing interest due to their vast chemical reactivity, biological and pharmaceutical activities [1–5]. It has been reported that these derivatives possesses anti-tuberculosis [6,7], Antiplasmodial [4], Antibacterial [5], antihistamine [6], anticancer [11–14], anti-hypertensive [9], antifungal [10], antimalarial [11], anti-HIV [12] and antioxidant activities [13]. On the other hand, thiazole and thiazolidinone derivatives are known to exhibit diverse biological activities[14–16], they have anti-inflammatory [20, 21], anticancer, antimicrobial [19], anti-tuberculosis [20] and antioxidant activity [21]. Inflammation is a fundamental physiological process that is not only essential for survival but also at the same time is one of the major causes of human mortality [25, 26]. It's known that, non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat a wide variety of illnesses and diseases, such as inflammation [24], cancers [25] and the peripheral and central nervous system diseases [26]. The anti-inflammatory effect of NSAIDs arises from their ability to inhibit both COX-1 and COX-2 isoforms of cyclooxygenase (COX) enzyme[27]. Literature survey revealed that some of the synthesized derivatives having quinoline ring or bearing thiazole ring have significant anti-inflammatory and analgesic activity [31–33, 20, 21]. In the light of above mentioned facts and our interest in designing new biologically active molecules, our efforts were directed towards

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the synthesis of new heterocyclic compounds containing quinoline moiety with anticipated biological activities. In this paper, we report synthesis of novel quinoline based thiazolidinone derivatives as anti-inflammatory and analgesic agents.

Material and Methods

General

All melting points were determined in open-glass capillaries and are uncorrected. IR spectra were recorded on a BRUKER Vector 22 Germany spectrometer (KBr). ^{1}H NMR spectra were recorded on (Bruker) 400 MHz spectrometer using TMS as an internal reference. The Electron Impact mass spectra were obtained at 70 eV using Shimadzu QP-2010 Plus mass spectrometer. The reactions were followed up by thin-layer chromatography (TLC) on silica gel F254 aluminum sheets (Merck), and the spots were detected by UV lamp at 254–365 nm.

*Preparation of 2-hydrazinylquinoline (**2**)*

2-Chloroquinoline **1** (1.0 g, 6.1 mmol) and hydrazine monohydrate (3 mL) in n-butanol (10 ml) were refluxed for 6 h. The solvent was removed under reduced pressure giving a brownish orange residue, the residue was triturated with ethanol then filtered to give compound **2**, orange crystals, yield 86.5 %; mp 140–142 °C; IR (KBr, cm-1): 3282, 3188 (NH), 3042 (CH_{arom}), 1621(C=N).

*General procedure for the synthesis of (E)-2-(2-arylidenehydrazinyl)quinoline (**3–9**)*

A mixture of compound **2** (1.0 g, 6.3 mmol) and the substituted aldehydes (6.3 mmol), were refluxed in ethanol (20 mL) containing few drops of glacial acetic acid for 3 h. The solvent was reduced to its half, and allowed to cool. The separated solid was filtered, dried, and recrystallized from ethanol.

*(E)-2-(2-(4-chlorobenzylidene)hydrazinyl) quinoline (**3**)*

Pale yellow solid; yield 85.5 %; mp 123–125 °C; IR (KBr, cm^{-1}): 3429 (NH), 3045 (CH_{arom}),1621 (CH=N); MS (m/z): 281 [M^+ , 0.21 %], 247 [M^+–Cl, 0.15 %], 171 [M^+–PhCl, 7.24 %], 69 [base peak, 100 %]; ^{1}H NMR (DMSO-d_6): δ (ppm) = 13.3 (s, 1H, NH), 8.6 (s, 1H, CH=N), 8.13–7.36 (m, 10H, Ar-H). Anal. Calcd for $C_{16}H_{12}ClN_3$ (281.74): C, 68.21; H, 4.29; N, 14.91. Found: C, 68.06; H, 4.13; N, 14.75.

*(E)-2-(2-(4-methoxybenzylidene)hydrazinyl) quinoline (**4**)*

Yellow solid; yield 86 %; mp 155–157 °C; IR (KBr, cm-1): 3431 (NH), 3106 (CH_{arom}), 2966 (CH_{aliph}),1599 (CH=N), 1023 (OCH_3); MS (m/z): 277 [M^+, 3.33 %], 247 [M^+–OCH_3, 1.05%], 69 [base peak, 100 %]; ^{1}H NMR (DMSO-d_6): δ (ppm) = 11.2 (s, 1H, NH), 8.6 (s, 1H, CH=N), 7.82–7.04 (m, 10H, Ar-H), 3.8 (s, 3H, OCH_3). Anal. Calcd for $C_{17}H_{15}N_3O$ (277.33): C, 73.63; H, 5.45; N, 15.15. Found: C, 73.50; H, 5.32; N, 15.02.

*(E)-N,N-dimethyl-4-((2-(quinolin-2-yl) hydrazono)methyl)aniline (**5**)* [30]

Yellow solid, yield 65.5%; mp 260–262 °C; IR (KBr, cm^{-1}): 3428 (NH), 3045 (CH_{arom}), 2911 (CH_{aliph}), 1651 (CH=N); MS (m/z): 290 [M^+ , 0.85 %], 262 [M^+–$2CH_3$, 0.65 %], 247 [M^+–$N(CH_3)2$,0.36 %], 170 [base peak, 100 %]; ^{1}H NMR (DMSO-d_6): δ (ppm) = 13.2 (s, 1H, NH), 8.55 (s, 1H, CH=N), 8.20 – 7.45 (m, 10H, Ar-H), 3.02 (s, 6H, $2CH_3$). Anal. Calcd for $C_{18}H_{18}N_4$ (290.37): C, 74.46; H, 6.25; N, 19.30. Found: C, 74.31; H, 6.09; N, 19.14.

*(E)-2-(2-(2-chlorobenzylidene)hydrazinyl) quinoline (**6**)*

Yellow solid; yield 77 %; mp 278–280 °C; IR (KBr, cm^{-1}): 3393 (NH), 3063 (CH_{arom}), 1647 (CH=N); MS (m/z): 281 [M^+ , 0.34 %], 247 [M^+–Cl, 1.05 %], 171 [M^+–PhCl, 8.73 %], 69 [base peak, 100 %]; ^{1}H NMR (DMSO-d_6): δ (ppm) = 13.6 (s, 1H, NH), 8.9 (s, 1H, CH=N), 8.83–7.46 (m, 10H, Ar-H). Anal. Calcd for $C_{16}H_{12}ClN_3$ (281.74): C, 68.21; H, 4.29; N, 14.91. Found: C, 68.06; H, 4.13; N, 14.75.

*(E)-2-(2-benzylidenehydrazinyl)quinoline (**7**)*

Yellow solid; yield 73.5 %; mp 105–107 °C; IR (KBr, cm^{-1}): 3425 (NH), 3046 (CH_{arom}), 1663, (CH=N); MS (m/z): 247 [M^+ , 1.05 %], 171 [M^+–Ph, 8.73 %], 69 [base peak, 100 %]; ^{1}H NMR (DMSO-d_6): δ (ppm) = 11.2 (s, 1H, NH), 8.72 (s, 1H, CH=N), 7.8 – 7.35 (m, 11H, Ar-H). Anal. Calcd for $C_{16}H_{13}N_3$ (247.30): C, 77.71; H, 5.30; N, 16.99. Found: C, 77.56; H, 5.16; N, 16.84.

*(E)-2-((2-(quinolin-2-yl)hydrazono)methyl) phenol (**8**)*

Yellow solid; yield 79 %; mp 220–222 °C; IR (KBr, cm^{-1}): 3752 (OH), 3425 (NH), 3043 (CH_{arom}), 2916 (CH_{aliph}),1621 (CH=N); MS (m/z): 263 [M^+ , 0.44 %], 247 [M^+–OH, 2.23 %]; ^{1}H NMR (DMSO-d_6): δ (ppm) = 13.2 (s, 1H, NH), 11.2 (s, 1H, OH), 9.0 (s, 1H, CH=N), 7.70 – 6.9 (m, 10H, Ar-H). Anal. Calcd for $C_{16}H_{13}N_3O$ (263.30): C, 72.99; H, 4.98; N, 15.96. Found: C,

72.84; H, 4.82; N, 15.80.

*(E)-2-(2-(3-nitrobenzylidene)hydrazinyl) quinoline (**9**)*

Yellow solid; yield 79 %; mp 132–134 °C; IR (KBr, cm^{-1}): 3426 (NH), 3046 (CH_{arom}), 1617 (CH=N), 1518, 1347 (NO_2); MS (m/z): 292 [M+ , 27.69 %], 247 [M^+–NO_2, 0.06 %], 170 [base peak ,100 %]; ^1H NMR (DMSO-d_6): δ (ppm) = 11.8 (s, 1H, NH), 8.49 (s, 1H, CH=N), 8.22 – 7.29 (m, 10H, Ar-H). Anal. Calcd for $C_{16}H_{12}N_4O_2$ (292.30): C, 65.75; H, 4.14; N, 19.17. Found: C, 65.60; H, 3.99; N, 19.01.

*Synthesis of (E)-2-(2-(naphthalen-1-ylmethylene) hydrazinyl)quinoline (**10**)*

To a solution of compound **2** (1.0 g, 6.3 mmol) and 1-naphthaldehyde (6.3 mmol), in ethanol (20 mL) few drops of glacial acetic acid were added, and the mixture was refluxed for 3 h. The solvent was reduced to its half, and allowed to cool. The separated solid was filtered, dried, and recrystallized from ethanol.

Yellow solid; yield 82 %; mp 280–282 °C; IR (KBr, cm^{-1}): 3426 (NH), 3057 (CH_{arom}), 1644 (CH=N); MS (m/z): 297 [M^+ 0.15 %], 259 [base peak, 100]; ^1H NMR (DMSO-d_6): δ (ppm) = 9.54 (s, 1H, NH), 8.54 (s, 1H, CH=N), 8.20 – 7.49 (m, 13H, Ar-H). Anal. Calcd for $C_{20}H_{15}N_3$ (297.36): C, 80.78; H, 5.08; N, 14.13. Found: C, 80.63; H, 4.92; N, 13.98.

*General procedure for the synthesis of (Z)-1-sustituted-3-(2-(quinolin-2-yl)hydrazono)indolin-2-one (**11**) and (**12**)*

A mixture of compound **2** (1.0 g, 6.3 mmol) and isatin or methyl isatin (6.3 mmol), was refluxed in ethanol (20 mL) containing few drops of glacial acetic acid for 3 h. The solvent was reduced to its half, and allowed to cool. The separated solid was filtered, dried, and recrystallized from ethanol.

*(Z)-3-(2-(quinolin-2-yl)hydrazono)indolin-2-on (**11**)*[31]

Pale orange solid; yield 81%; mp 278–280 °C; IR (KBr, cm^{-1}): 3431 (NH), 3090 (CH_{arom}), 1646 (C=O), 1616 (CH=N); MS (m/z): 288 [M^+ , 9.01 %], 262 [M^+–CO, 0.35 %], 259 [base peak, 100 %]; ^1H NMR (DMSO-d_6): δ (ppm) = 13.2 (s, 1H, NH), 11.2 (s, 1H, NH, indole), 7.99– 6.79 (m, 10H, Ar-H). Anal. Calcd for $C_{17}H_{12}N_4O$ (288.31): C, 70.82; H, 4.20; N, 19.43 Found: C, 70.68; H, 4.04; N, 19.29.

*(Z)-1-methyl-3-(2-(quinolin-2-yl)hydrazono) indolin-2-one (**12**)*

Orange solid; yield 77.5 %; mp 190–192 °C; IR (KBr, cm^{-1}): 3430 (NH), 3051 (CH_{arom}), 2927 (CH_{aliph}),1674 (C=O), 1606 (CH=N); MS (m/z): 302 [M^+ , 0.3 %], 288 [M^+ -CH3, 8.86 %], 262 [M^+–CH_3 and CO, 0.67 %], 69 [base peak, 100 %]; ^1H NMR (DMSO-d_6): δ (ppm) = 12.97 (s, 1H, NH), 8.43– 7.16 (m, 10H, Ar-H), 3.31 (s, 3H, CH_3). Anal. Calcd for $C_{18}H_{14}N_4O$ (302.34): C, 71.51; H, 4.67; N, 18.53. Found: C, 71.36; H, 4.52; N, 18.40.

*General procedures for the synthesis of 2-substituted-3-(quinolin-2-ylamino)thiazolidin-4-one (**13–20**)*

***Methode A**:* A mixture of compounds (**3–10**) (1.0 mmol) and thioglycolic acid (1.0 mmol) in dry dioxane (20 mL) was refluxed for 24h. The volume was reduced to its half, and was left to cool. The formed precipitate was filtered off, dried and recrystallized from appropriate solvent to give target compounds. In case of no precipitate formed upon cooling, the solution was added to water and neutralized using Na_2CO_3 solution, the formed precipitate was filtered, dried and recrystallized to obtain the expected thiazolidinone products (**13–20**), respectively.

***Method B**:* A mixture of 2-hydrazinylquinoline **2** (5 mmol, 0.796 g), substituted aldehydes (5 mmol) and thioglycolic acid (5 mmol; 0.460 g) was taken in a round bottom flask containing 1,4-dioxane (30 mL) and equipped with a reflux condenser. The reaction mixture was refluxed for 24 h (monitored by TLC). The mixture was cooled to room temperature and the formed precipitate was filtered off and recrystalized from ethanol to give the expected thiazolidinone derivatives (**13–20**).

2-(4-chlorophenyl)-3-(quinolin-2-ylamino) thiazolidin-4-one (13)

Pale orange solid; yield 82.5 %; mp 178–180 °C; IR (KBr, cm^{-1}): 3433 (NH), 3050 (CH_{arom}), 2921 ($CH_{streching}$), 1705 (C=O), 1607 (C=N); MS (m/z): 355 [M^+, 0.05 %], 321 [M^+–Cl, 0.12 %], 245 [M^+–PhCl,0.17 %], 213 [m^+–$C_9H_8N_2$, 0.20 %], 144 [Base peak, 100 %]; ^1H NMR (DMSO-d_6): δ (ppm) = 13.86 (s,1H, NH), 8.93 (s, 1H, CH, thiazolidinone), 8.2 (s, 1H, 4-H, quinoline), 8.54, 8.52 and 7.86–7.47 (m, 9H, Ar-H), 3.47 (s, 2H, CH_2, thiazolidinone). Anal. Calcd for $C_{18}H_{14}ClN_3OS$ (355.84): C, 60.76; H, 3.97; N, 11.81 Found: C, 60.61; H, 3.82; N, 11.66.

*2-(4-methoxyphenyl)-3-(quinolin-2-ylamino) thiazolidin-4-one (**14**)*

Yellow solid; yield 74.5 %; mp 120–122 °C; IR (KBr, cm^{-1}):): 3430 (NH), 3049 (CH_{arom}), 2932 ($CH_{streching}$), 2834 (CH_3) 1673 (C=O), 1610 (C=N); MS (m/z): 351 [M^+, 1.7 %], 337 [M^+–CH_3, 2.82 %], 245 [M^+–Ph-O-CH_3, 2.54 %], 274 [Base peak, 100 %]; ^{1}H NMR (DMSO-d_6): δ (ppm) = 13.78 (s, 1H, NH), 8.91 (s, 1H, CH, thiazolidinone), 8.3 (s, 1H, 4-H, quinoline), 7.96–7.43 (m, 9H, Ar-H), 3.45 (s, 2H, CH_2, thiazolidinone). Anal. Calcd for $C_{19}H_{17}N_3O_2S$ (351.42): C, 64.94; H, 4.88; N, 11.96.Found: C, 64.79; H, 4.73; N, 11.81.

*2-(4-(dimethylamino)phenyl)-3-(quinolin-2-ylamino)thiazolidin-4-one (**15**)*

Dark orange solid; yield 78.1 %; mp 180–182 °C; IR (KBr, cm^{-1}): 3429 (NH), 3050 (CH_{arom}), 2921 ($CH_{streching}$), 2855 ($2CH_3$), 1649 (C=O), 1605 (C=N); MS (m/z): 364 [M^+, 0.13 %], 365 [M^++1, 0.06 %], 144 [Base peak, 100 %]. Anal. Calcd for $C_{20}H_{20}N_4OS$ (364.47): C, 65.91; H, 5.53; N, 15.37. Found: C, 65.76; H, 5.38; N, 15.22.

*2-(2-chlorophenyl)-3-(quinolin-2-ylamino) thiazolidin-4-one (**16**)*

Pale yellow solid; yield 59.6 %; mp 298–300 °C; IR (KBr, cm^{-1}): 3407 (NH), 3048 (CH_{arom}), 2909 ($CH_{streching}$), 1650 (C=O), 1607 (C=N); MS (m/z): : 355 [M^+ 0.42 %], 321 [M^+–Cl, 0.13 %], 245 [M^+–PhCl, 2.31 %], 213 [m^+–$C_9H_8N_2$, 0.74 %], 144 [Base peak, 100 %]; ^{1}H NMR (DMSO-d_6): δ (ppm) = 13.86 (s, 1H, NH), 8.93 (s, 1H, CH, thiazolidinone), 8.2 (s, 1H, 4-H, quinoline), 8.56, 8.53 and 7.87–7.45 (m, 10H, Ar-H), 3.45 (s, 2H, CH_2, thiazolidinone). Anal. Calcd for $C_{18}H_{14}ClN_3OS$ (355.84): C, 60.76; H, 3.97; N, 11.81. Found: C, 60.61; H, 3.82; N, 11.66.

*2-phenyl-3-(quinolin-2-ylamino)thiazolidin-4-one (**17**)*

Yellow solid; yield 62.5 %; mp 140–142 °C; IR (KBr, cm^{-1}): 3438 (NH), 3050 (CH_{arom}), 2921 ($CH_{streching}$), 1695 (C=O), 1605 (C=N); MS (m/z): 321 [M^+ , 0.07 %], 320 [M^+–1, 0.26 %], 245 [M^+–Ph, 1.53 %], 179 [M^+–$C_9H_8N_2$, 1.53 %], 144 [Base peak, 100 %]; ^{1}H NMR (DMSO-d_6): δ (ppm) = 12.02 (s, 1H, NH), 8.2 (s, 1H, 4-H, quinoline), 8.11 (s, 1H, CH, thiazolidinone) 7.79–7.27 (m, 9H, Ar-H), 3.67 (s, 2H, CH_2, thiazolidinone). Anal. Calcd for $C_{18}H_{15}N_3OS$ (321.40): C, 67.27; H, 4.70; N, 13.07. Found: C, 67.12; H, 4.55; N, 12.92.

*2-(2-hydroxyphenyl)-3-(quinolin-2-ylamino) thiazolidin-4-one (**18**)*

brown solid; yield 68.3 %; mp 263–265 °C; IR (KBr, cm^{-1}): 3652 (OH), 3427 (NH), 3072 (CH_{arom}), 2979 ($CH_{streching}$),1644 (C=O), 1605 (C=N); MS (m/z): 336 [M^+ -1, 0.06 %], 320 [M^+- OH, 0.10 %], 245 [M^+–PhOH, 2.95 %], 144 [Base peak, 100 %]; ^{1}H NMR (DMSO-d_6): δ (ppm) = 13.86 (s, 1H, NH), 11.4 (s, 1H, OH), 8.93 (s, 1H, CH, thiazolidinone), 8.2 (s, 1H, 4-H, quinoline), 8.56, 8.53 and 7.87–7.45 (m, 9H, Ar-H), 3.45 (s, 2H, CH_2, thiazolidinone). Anal. Calcd for $C_{18}H_{15}N_3O_2S$ (337.40): C, 64.08; H, 4.48; N, 12.45. Found: C, 63.92; H, 4.33; N, 12.32.

*2-(3-nitrophenyl)-3-(quinolin-2-ylamino) thiazolidin-4-one (**19**)*

Yellow solid; yield 74.05 %; mp 255–257 °C; IR (KBr, cm^{-1}): 3431 (NH), 3012 (CH_{arom}), 2902 ($CH_{streching}$),1722 (C=O), 1647 (C=N), 1514, 1342 (NO_2); MS (m/z): 366 [M^+, 0.05 %], 322 [M^+–NO_2, 0.03%,], 355 [M^+–PhNO_2, 0.08 %],76 [Base peak, 100 %]; ^{1}H NMR (DMSO-d_6): δ (ppm) = 12.02 (s, 1H, NH), 8.3 (s, 1H, 4-H, quinoline), 8.2 (s, 1H, CH, thiazolidinone) 8.1–7.22 (m, 9H, Ar-H), 3.7 (s, 2H, CH_2, thiazolidinone). Anal. Calcd for $C_{18}H_{14}N_4O_3S$ (366.40): 59.01; H, 3.85; N, 15.29. Found: 58.87; H, 3.725; N, 15.13.

*2-(naphthalen-1-yl)-3-(quinolin-2-ylamino) thiazolidin-4-one (**20**)*

Pale yellow solid; yield 72.6 %; mp 260–262 °C; IR (KBr, cm^{-1}): 3426 (NH), 3048 (CH_{arom}), 2917 ($CH_{streching}$), 1648 (C=O), 1605 (C=N); MS (m/z): 369 [M^+ - 2, 0.05 %], 144 [Base peak, 100 %]. Anal. Calcd for $C_{22}H_{17}N_3OS$ (371.46): C, 71.14; H, 4.61; N, 11.31. Found: C, 71.01; H, 4.48; N, 11.18.

*General procedures for the synthesis of 1-substituted 3'-(quinolin-2-ylamino) spiro[indoline-3,2'-thiazolidine]-2,4'-diones (**21, 22**)*

Method A: a mixture of compound **11** or **12** (1.0 mmol) and thioglycolic acid (1.0 mmol) in dry dioxane (20 mL) was refluxed for 24h. The volume was reduced to its half, and was left to cool. The formed precipitate was filtered off, dried and recrystallized from appropriate solvent to give target compounds **21** and **22**.

Method B: A mixture of 2-hydrazinylquinoline **2** (5 mmol, 0.796 g), isatin or methyl isatin (5 mmol) and thioglycolic acid (5 mmol; 0.460 g) was taken in a round bottom flask containing 1,4-dioxane (30 mL) and equipped with a reflux condenser. The reaction mixture was refluxed for 24 h (monitored by TLC). The mixture was cooled

to room temperature and the formed precipitate was filtered off and recrystallized from ethanol to give 1-substituted 3'-(quinolin-2-ylamino) spiro[indoline-3,2'-thiazolidine]-2,4'-dione **21** and **22**.

*3'-(quinolin-2-ylamino)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (**21**)*

Brown solid; yield 69.8 %; mp 298–300 °C; IR (KBr, cm^{-1}): 3439 ($NH_{hydrazone}$), 3217 (NH_{indole}), 3059 (CH_{arom}), 2923 ($CH_{streching}$), 1701 ($C=O_{thiazole}$),1645 ($C=O_{indole}$), 1605 (C=N); MS (m/z): 361 [M^+ -1, 0.08 %], 363 [M^+ +1, 0.23 %], 259 [Base peak, 100 %]; ^{1}H NMR (DMSO-d_6): δ (ppm) = 13.01 (s,1H, NH), 12.4 (s, 1H, NH indole), 8.4 (s, 1H, 4-H, quinoline), 7.9–7.1 (m, 9H, Ar-H), 3.64 (m, 2H, CH_2, thiazolidinone). Anal. Calcd for $C_{19}H_{14}N_4O_2S$ (362.41): C, 62.97; H, 3.89; N, 15.46. Found: C, 62.82; H, 3.74; N, 15.31.

*1-methyl-3'-(quinolin-2-ylamino) spiro[indoline-3,2'-thiazolidine]-2,4'-dione (**22**)*

Orange solid; yield 72.2 %; mp 196–198 °C; IR (KBr, cm^{-1}): 3432 ($NH_{hydrazone}$), 3050 (CH_{arom}), 2923 ($CH_{streching}$), 1728 ($C=O_{thiazole}$), 1677 ($C=O_{indole}$), 1604 (C=N); MS (m/z): 376 [M^+, 0.09 %], 273 [Base peak, 100 %]; ^{1}H NMR (DMSO-d_6): δ (ppm) = 13.01 (s, 1H, NH), 8.4 (s, 1H, 4-H, quinoline), 7.94–7.07 (m, 9H, Ar-H), 3.66 (m, 2H, CH_2, thiazolidinone), 3.45 (s, 3H, CH_3). Anal. Calcd for $C_{20}H_{16}N_4O_2S$ (376.43): C, 63.81; H, 4.28; N, 14.88. Found: C, 63.66; H, 4.13; N, 14.73.

Pharmacology

Anti-inflammatory activity

Male Wistar rats weighing (120–150 g) were used throughout the assay. Animals were housed under standardized conditions of light and temperature and received standard rat chow and tap water *ad libitum*. Animals were randomly assigned to different experimental groups, each of six rats and kept in separate cages. One group of six rats was kept as a control group and another group received the standard drug indomethacin. All animal procedures were performed after an approval from the Ethics Committee of the National Research Centre and in accordance with the recommendations for the proper care and use of laboratory animals (NIH publication No. 85-23, revised 1985). Carrageenan lambda from Sigma Aldrich Chemical Co. (USA), indomethacin from Khahira Pharmaceutical, and Chemical Co. (Cairo, Egypt). Paw edema was induced by subplantar injection of 100 µL of 1 % sterile carrageenan in saline into the right hind paw (1 % suspension of carrageenan in sterile saline was prepared, the suspension was placed in a refrigerator (4 ºC) overnight to allow complete hydration of the carrageenan [32]. Twelve groups of rats, each of six animals, were used. One group received saline and served as control. Indomethacin (10 mg/kg) was administered to a group of rats that served as a positive control. Tested groups received the compounds in a dose of (10 mg/kg). All the tested compounds and indomethacin were orally administered 1 h before induction of inflammation. The right hind paw volume was measured immediately before carrageenan injection and at selected times (1, 2, 3, and 4 h) thereafter by planimeter [33].

Analgesic activity

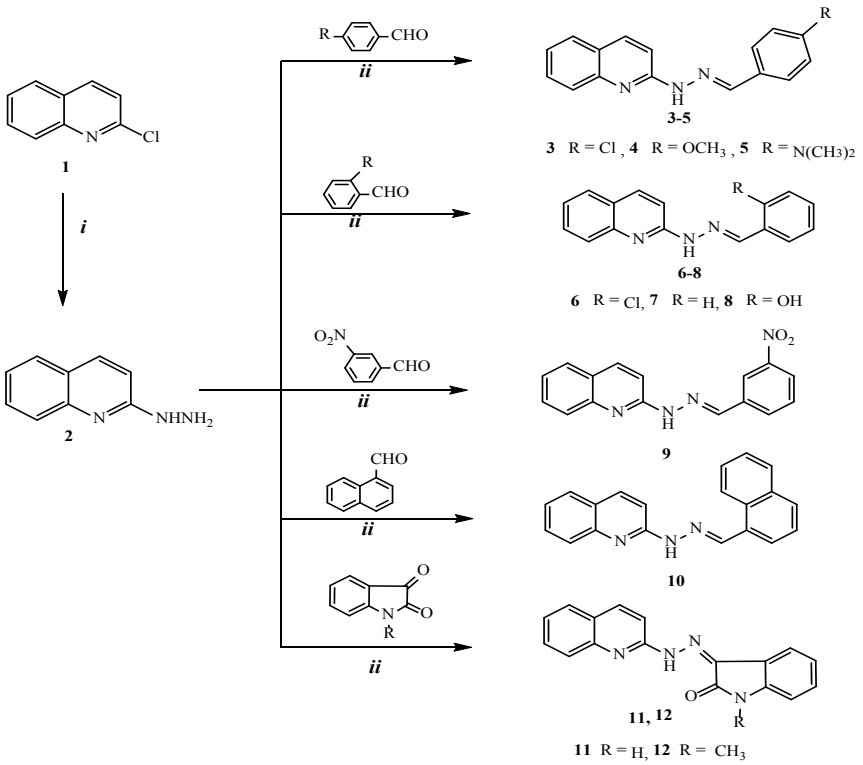
Each animal was placed gently on a hot plate at 50ºC. Latency to exhibit nociceptive responses, such as licking paws or jumping off the hot plate was determined 30, 60, 90 min after administration of test substances or saline [34]. All drugs were injected orally (100 mg/kg) 30 minutes before placing the animal on the hot plate. Aspirin (100 mg/kg) was administered to a group of rats that served as a positive control.

Results and Discussion

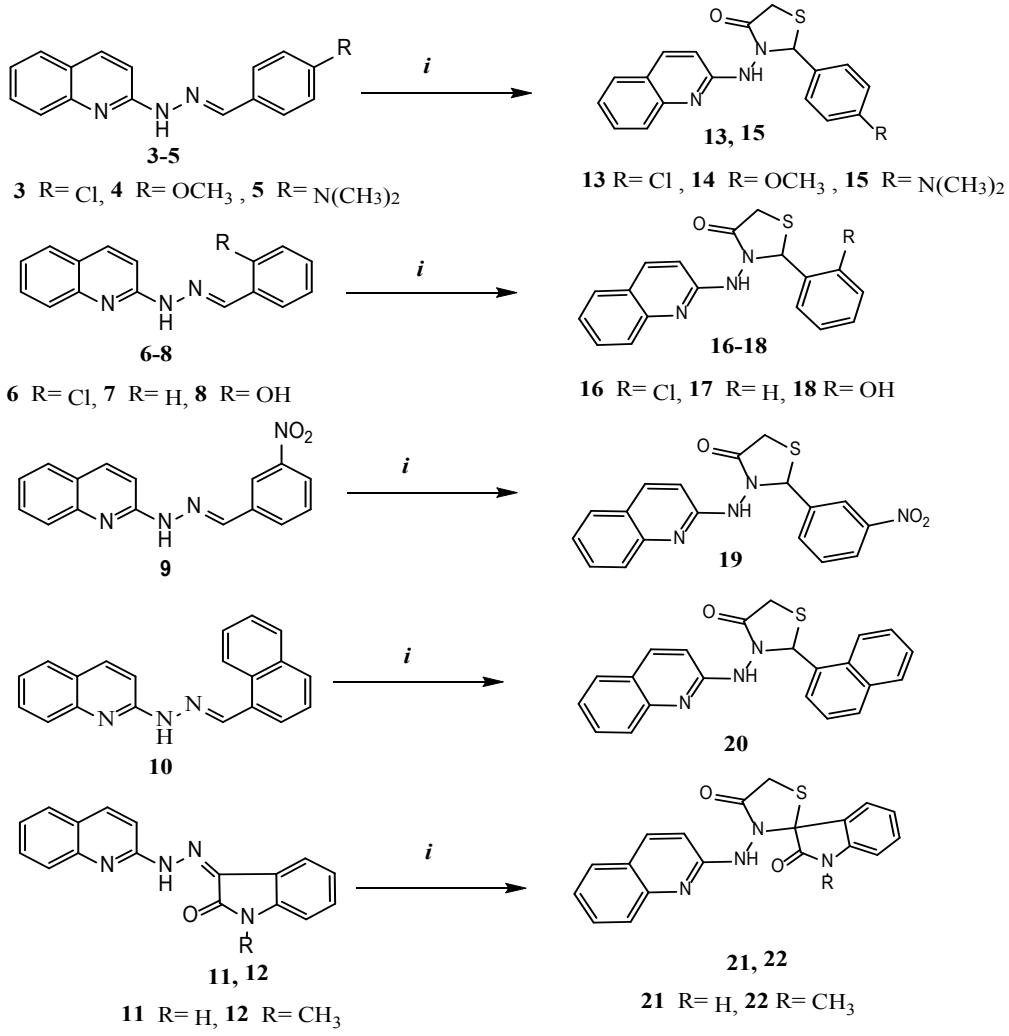
Synthesis of target compounds (**13–22**) was achieved as outlined in Schemes 1 and 2. The starting material 2-hydrazinylquinoline **2** was synthesized in a high yield from the reaction of hydrazine hydrate with 2-chloroquinoline **1** in refluxing n-butanol, through procedures previously reported [35]. Reaction of compound **2** with substituted aldehydes in (1:1) molar ratio with elimination of water afforded the corresponding arylidenehydrazinyl quinoline derivatives **3–10** in a good yield. Structures of compounds **3–10** were supported by their elemental analysis and spectral data. ^{1}HNMR spectra of compounds **3–10** showed the presence of the (NH) proton and azomethine (CH═N) proton signals at the expected regions. ^{1}HNMR spectra of compounds **3–10** Showed singlet signals at the ranges δ 13.3–11.2 ppm corresponding to NH protons and singlet signals at the ranges δ 9.0–8.49 ppm corresponding to the azomthine protons. Furthermore, derivatives **4, 5,** and **12** showed singlet signals at the ranges δ 3.02–3.8 ppm due to methyl group protons. Derivative **8** showed a singlet signal at 11.2 ppm corresponding to the hydroxyl group proton.

IR spectra of compounds **3–12** revealed the presence of absorption bands at 3431–3393 cm^{-1} due to NH, 3106–3043 cm^{-1} corresponding to CH Aromatic and 1663–1599 cm^{-1} corresponding to C=N. Furthermore, IR spectrum of compound **4** and **5** showed the presence of CH aliphatic at 2966 and 2911 cm^{-1} respectively. Also, IR spectrum of compound **8** showed the presence of OH group at 3752 cm^{-1}. On the other hand IR spectrum of compound **9** showed presence of NO_2 at 1518 and 1347 cm^{-1}. IR spectra of compounds **11** and **12** showed additional absorption bands at 1646 and 1674 cm^{-1} respectively, due to C=O groups. Mass spectra of all compounds showed the molecular ion peaks which were in agreement with their molecular formulae.

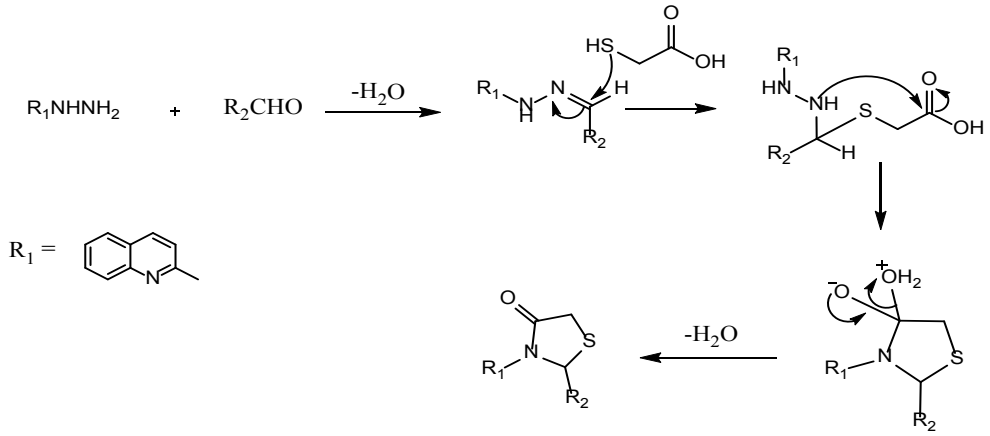
Condensation of derivatives **3–12** with thioglycolic acid in dry dioxane led to the formation of the corresponding thiazolidinone derivatives **13–22**. IR spectra of the thiazolidinone compounds **13–20**, revealed the appearance of new absorption bands at 1722–1644 cm^{-1} attributed to C=O functionalities, while their ^{1}H NMR spectra showed singlet signals at the ranges of δ 3.7- 3.45 ppm and δ 8.93–8.11, representing the corresponding methylene protons (-CH_2-) and the methine protons (N-CH-S) of the new formed thiazolidinone ring. On the other hand, IR spectra of derivatives **21** and **22** showed absorption bands at 1701 and 1028 cm^{-1} due to presence of carbonyl groups, and their ^{1}HNMR spectra showed multiplet signals at δ 3.64 ppm and δ 3.66 representing the corresponding methylene protons (-CH_2-) and there were no signals due to the methine protons (N-CH-S) of the new formed spiro[indoline-3,2'-thiazolidine]-2,4'-dione derivatives. Mass spectra of the compounds showed the molecular ion peaks which were in agreement with their molecular formula. One-pot three component reaction was adopted for synthesis of the target compound **13–22** involving 2-hydrazinylquinoline, aromatic aldehyde or isatin derivatives and thioglycolic acid. The reaction has been suggested to proceed via imine formation followed by the attack of the sulfur nucleophile on the imine carbon, followed by intramolecular cyclization with the elimination of water to give thiazolidin-4-one derivatives as discussed in Scheme 3 [36]. The one-pot reaction gives a satisfactory yield compared to the multistep reaction and have the merit of saving more time in the synthesis process.



Scheme 1 Synthesis of derivatives **2-12**.
Reagents and conditions ***i*** BuOH/$NH_2NH_2.H_2O$/Reflux, 6h, ***ii*** EtOH/Acetic acid/reflux 3h



Scheme 2 Synthesis of derivatives **13-22**.
Reagents and conditions *i* $SHCH_2COOH$/1,4-Dioxane/Reflux, 24h



Scheme 3 formation of compounds **13 - 22**

Anti-inflammatory activity

In this study, 10 newly synthesized derivatives were evaluated for their anti-inflammatory activity by using carrageenan-induced paw edema bioassay in rats [32] using indomethacin as a reference standard. Results were expressed as mean ± SE. The difference between control and treated groups were tested using Two way Anova followed by LST test. The anti-inflammatory results (Table 1) revealed that the highest anti-inflammatory potency at 4 h was gained by **6** derivatives according to the following order **22** > **17** >**13** > **14** > **21** > **15**. It has been noticed that they exhibited early action showing good percentages of edema inhibition relative to the reference drug indomethacin. Compound **22** carrying indole ring system inhibited the edema volume significantly at the [1]st h post administration, and the activity was enhanced up to the 4th h giving promising edema volume inhibition compared to that produced by indomethacin. Also, significant edema inhibition at the first hour post compounds administration was observed by derivatives **22**, **17**, **21**, **16** and **15**, respectively. Regarding Structure activity relationship (SAR), it is clear that presence of –Cl at position 4 of the phenyl ring of compound **13** has a significant effect on edema inhibition more than that of (-OCH_3) and -$N(CH_3)_2$ in compounds **14** and **15** respectively. On the other hand, absence of substitution on the phenyl ring of compound **17** leads to higher level of edema inhibition more than compounds **16** and **18**. It can be noticed that presence of (NO_2) group at position 2 of the phenyl ring of compound **19** has no significant effect on level of edema inhibition. A good inhibition level relative to the reference drug indomethacin was observed by the N-methyl indole derivative **22**.

TABLE 1. Anti-inflammatory effect of the tested compounds on carrageenan-induced rat paw edema (mL)

Group no.	Paw edema volume (mL)			
	1h	2h	3h	4h
Control	142.9±13.31	99.09±3.23	79.83±1.94	60.07±6.98
Indomethacin 10 mg/kg	42.69±6.66*	38.02±4.01*	34.70±3.94*	26.06±4.11*
13	74.81±7.75*	62.16±6.04*	57.61±2.96*	33.45±7.32
14	79.10±5.23*	69.63±2.93*	51.36±2.68*	31.82±2.23*
15	82.67±11.11*	64.88±6.28*	59.23±3.03*	29.58±3.44*
16	103.3±6.08	71.44±3.16	52.90±4.43*	28.59±2.23*
17	59.95±2.57*	52.42±2.62*	39.24±4.03*	24.29±3.86*
18	108.4±6.72	88.16±5.03	63.50±4.12	33.04±2.94*
19	119.8±8.49	90.63±6.22	72.99±2.87	36.66±2.98
20	112.3±9.89	86.64±8.26	68.66±2.08	38.9±3.14
21	79.60±5.66*	60.49±5.99*	47.72±5.23*	26.50±3.14*
22	42.85±5.94*	36.26±4.11*	30.54±1.85*	18.09±2.01*

The data represent the mean ± standard error of the mean (n = 6).
Values represent the mean ± S.E. of six animals for each group.
* P< 0.05: Statistically significant from Control. (Two way Anova followed by LST test).

Analgesic activity

The analgesic activity of the above mentioned derivatives was also evaluated in comparison with aspirin as a standard reference drug (100 mg/kg) by applying hot plate test [34]. The results were expressed as mean ± SE. The difference between the control and treatment groups was tested using two way ANOVA followed by LST test. The analgesic activity expressed in Table 2 showed that the longest duration of action up to 90 min post compounds administration was obtained by the compounds **13**, **17** and **22**. They exhibited good analgesia relative to that obtained by aspirin. Unsubstituted phenyl ring in case of compound **17** has a noticeable effect on analgesic activity more than that having –Cl at position 4 in compound **13**. It is clear that the presence of N-methyl group on the indole ring give higher activity, this in turn reveals that there is a significant relation between activity and substituent on the nitrogen atom of indole nucleus.

Conclusion

In summary, we have discussed the synthesis of some quinoline based thiazolidinone derivatives in a three-step process. All newly synthesized compounds have been fully characterized. Furthermore, all new thiazolidinone derivatives were evaluated for their anti-inflammatory and analgesic activity. The Study results revealed that the highest anti-inflammatory potency was gained by **6** derivatives, showing a good edema inhibition compared to the reference drug indomethacin. The longest duration of analgesic action up to 90 min post compounds administration was obtained by three compounds, they exhibited potent analgesia compared to that obtained by aspirin.

TABLE 2. Analgesic activity of the tested compounds by hot plate method.

Group no.	Reaction time (sec.)			
	0 min	30 min	60 min	90 min
Control	5.122±0.37	5.520±0.22	5.240±0.45	5.040±0.41
Aspirin 100 mg/kg	5.100±0.58	11.56±0.69*	14.98±1.41	13.64±1.36
13	5.000±0.36	6.525±0.68	10.44±0.80*	12.33±0.85*
14	4.100±0.29	5.320±0.14	7.880±0.54	9.280±0.97
15	5.075±0.4	6.000±0.70	6.825±0.55	7.850±1.02
16	4.875±0.16	5.425±0.52	6.253±0.71	6.575±0.96
17	4.550±0.44	8.240±0.94	10.47±0.97*	10.38±1.13*
18	4.775±0.35	5.475±0.44	5.750±0.63	6.000±0.76
19	4.050±0.37	4.775±0.51	6.775±0.6	7.700±0.58
20	3.750±0.49	5.350±0.26	5.850±0.68	6.675±0.53
21	4.625±0.46	5.775±0.51	7.100±0.62	8.275±0.57
22	5.525±0.6	10.55±0.76*	10.10±1.10*	10.50±0.86*

The data represent the mean ± standard error of the mean (n = 6).
Values represent the mean ± S.E. of six animals for each group.
* P< 0.05: Statistically significant from control. (Two way Anova followed by LST test).

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تحضير وتوصيف وتقييم النشاط المضاد للالتهابات والمسكن للآلام لبعض مشتقات الثيازوليدون المتصلة بحلقة الكينولين

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يتناول هذا البحث طريقة تحضير بعض مشتقات الثيازوليدون المتصلة بنواة الكينولين (**١٣** إلى **٢٢**) من خلال عملية مكونة من ثلاث خطوات. فعند تكاثُف ٢-هيدرازينيل كينولين **٢** مع عدد من الألدهيدات الأروماتية تكونت قواعد شيف المناظرة **٣** إلى **١٠** والتي تفاعلت بدورها مع حمض ثيوجليكوليك لتعطي مشتقات الثيازوليدون المناظرة **١٣** إلى **٢٠**. وعند مفاعلة المركب **٢** مع إيزاتين أو مع ميثيل إيزاتين فإنه ينتج مشتقات ٣-(كينولين-٢- يل أمينو) سبيرو] اندولين-٢،٣-ثيازوليدين]-٤،٢-دايون **٢١** و **٢٢** من خلال تفاعل الحولقة التكاثفية مع حمض ثيوجليكوليك. تم إثبات تركيب جميع المركبات الجديدة عن طريق التحليل العنصري للكربون والهيدروجين والنيتروجين وطيف الأشعة تحت الحمراء وكذلك الرنين النووي المغناطيسي لنواة ذرة الهيدروجين إضافةً إلى تحليل طيف الكتلة لجميع المركبات. تم تقييم النشاط المضاد للالتهابات والمُسكن للآلام لجميع مشتقات الثيازوليدون الجديدة، وأوضحت الدراسة أن أعلى قيمة للفاعلية كمضاد للالتهابات أظهرته ستة مركبات بالترتيب التالي **٢٢**>**١٧**>**١٣**>**١٤**>**٢١**>**١٥** وذلك عند مقارنتها بالإندوميثاسين. كما أظهرت المشتقات **١٣**و**١٧**و**٢١** فاعلية ملحوظة كمسكن للآلام وذلك مقارنةً بالأسبيرين.