Some Reactions with 4-(p-Cinnamoylanilino)quinolines

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p-Cinnamoylanilinoquinolines, Pyrazolinylanilinoquinolines, Isoxazolinylanilinoquinolines, Tetrahydro-oxopyrimidinylanilinoquinoline, Tetrahydro-thioxopyrimidinylanilinoquinoline

For possible biological activity, the title compounds were prepared and allowed to condense with hydrazine hydrate, phenyl hydrazine, hydroxylamine HCl, urea and thiourea to give the pyrazolines 3, isoxazolines 4, oxo and thioxopyrimidines 5, respectively.

The chemistry of quinoline derivatives has been of increasing interest, since many of these compounds have found useful applications as chemotherapeutic agents especially against malaria parasites and cancer [1–3]. On the other hand, it has been reported that certain α,β-unsaturated ketones and chalcones have bacteriostatic and fungistatic action [4, 5]. Also, several pyrazoles, isoxazoles and pyrimidines have been reported to possess biological activity as antimetabolites [6, 7] and as antiinflammatory agents [8].

Based on these findings, it was of interest to synthesize some new heterocycles, namely, pyrazolines, isoxazolines, pyrimidines and pyrimidinethiones incorporated to a quinoline moiety at position 4 through a para-iminophenyl side chain in a trial to obtain compounds of anticipated biological value.

For this purpose, the key intermediate, 4-(p-acetylaniino)-7-chloroquinoline (1) was prepared by the reaction of 4,7-dichloroquinoline with p-amino-benzaldehyde. Claisen-Schmidt condensation of 1 with appropriate aromatic aldehydes, namely, benzaldehyde, p-anisaldehyde, p-dimethylaminobenzaldehyde, 2-thienyl-2-carboxaldehyde and pyridine-2-carboxaldehyde in presence of sodium hydroxide gave the corresponding α,β-unsaturated ketones 2a–f, respectively.

Condensation of 2a, e with hydrazine hydrate (98%) in ethanol afforded the pyrazolines 3a, b, respectively. In this way both 2c, d were condensed with phenyl hydrazine to give the N-phenylpyrazoline derivatives 3c, d, respectively.

Treatment of both 2a and 2b with hydroxylamine hydrochloride in ethanolic sodium hydroxide solution afforded the corresponding 4-[p-(2-isoxazolin-3-yl)anilino]quinolines (4a and 4b), respectively.

The reaction of 2b with urea in presence of ethanolic hydrogen chloride gave the pyrimidine derivative 5a. Also, reaction of 2b with thiourea in presence of ethanolic sodium hydroxide afforded the corresponding pyrimidine-2-thione derivative 5b (Scheme).

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The structures of the newly prepared compounds were inferred from their analytical data and IR spectra.

**Biology**

Representative examples of these compounds are under biological evaluation as anticancer agents in experimental animals. The preliminary results revealed that 2d and 2e were found to be inactive towards P388 mouse Leukemia tumor at the doses of 100, 200 and 400 mg/kg, while 2c was toxic at the dose of 100 mg/kg.

**Experimental**

Melting points are uncorrected and were taken on Boetius melting point microscope. The IR spectra were taken on Unicam Sp 1000 infracord Spectrophotometer. Compound purity was routinely checked by TLC using 5x10 cm plates coated with silica gel G. One solvent system was employed: Benzene/ethyl acetate/methanol (9:2:1). Coloured spots appeared after spraying with iodine.

**7-Chloro-4-(p-acetylanilino)quinoline (1)**

A mixture of 9.8 g (0.05 mole) of 4,7-dichloroquinoline and 6.7 g (0.05 mole) of p-aminoacetophenone was dissolved in 80 ml of absolute ethanol and few drops of HCl were added. The reaction mixture was gently refluxed for 1 h to give yellow precipitate. It was filtered off, washed with cold dilute NH₄OH solution followed with water and crystallized from ethanol to give 1 in 85% yield, m.p. 270–271 °C.

Analysis: C₇H₁₃ClN₂O (296.7)
Calcd C 68.80 H 4.41 N 9.44,
Found C 69.12 H 4.55 N 9.32.

**Condensation of 1 with aromatic aldehydes: Synthesis of 7-chloro-4-(p-cinnamoylanilino)quinolines (2a–f)**

A mixture of 1 (0.01 mole) and 0.012 mole of the appropriate aldehyde (a: benzaldehyde, b: p-anisaldehyde, c: p-dimethylaminobenzaldehyde, d: 3,4,5-trimethoxybenzaldehyde, e: thiophene-2-carboxaldehyde, f: pyridine-2-carboxaldehyde) in 40 ml (5%) ethanolic NaOH was refluxed for 2 h, then cooled and filtered. The precipitate was crystallized from ethanol/water (20:1) to give the corresponding chalcone analogues (2a–f) respectively in 70–75% yield (Table).

**7-Chloro-4-[p-(5-phenyl-2-pyrazolin-3-yl)anilino]quinoline (3a)**

A mixture of 2a (or 2e) (0.005 mole), 98% hydrazine hydrate (0.2 g; 0.005 mole) and ethanol (25 ml) was refluxed for 8 h, then cooled and filtered to give either 3a or 3b as yellow precipitates in 65% and 55% yields, respectively.

3a: m.p. 213–215 °C (EtOH/H₂O). IR: 3280 cm⁻¹ (NH), 1580 cm⁻¹ (C=N) and 790 cm⁻¹ (C–Cl).

Analysis: C₂₄H₂₇ClN₄ (398.8)
Calcd C 72.26 H 4.80 N 14.04,
Found C 71.77 H 5.00 N 13.65.

**Table. Preparation of 2.**
3b: m.p. 137–139 °C (EtOH).
Analysis: C_{22}H_{17}ClN_{4}S (404.92)
   Calcd N 13.83,
   Found N 13.60.

7-Chloro-4-[p-[1-phenyl-5-(p-dimethylaminophenyl)-
2-pyrazolin-3-yl]anilino]quinoline (3c) and
7-chloro-4-[p-[1-phenyl-5-(3,4,5-trimethoxyphenyl)-
2-pyrazolin-3-yl]anilino]quinoline (3d)

A mixture of 2c (or 2d) (0.005 mole) and phenyl
hydrazine (0.6 ml; 0.0055 mole) in acetic acid
(15 ml) was refluxed for 4 h, cooled, poured over ice
cold water (200 ml) and filtered. The product was
crystallized from absolute ethanol to give 3c and 3d,
respectively in 60% yield.
3c: m.p. 142–144 °C (EtOH).
Analysis: C_{32}H_{28}ClN_{5} (518.04)
   Calcd N 13.52,
   Found N 13.88.
3d: m.p. 175–177 °C (EtOH/H_{2}O)
Analysis: C_{33}H_{29}ClN_{4}O_{3} (565.05)
   Calcd C 70.14 H 5.17,
   Found C 69.88 H 4.77.

7-Chloro-4-[2-(5-phenyl-2-isoxazolin-3-yl)anilino]-
quinoline (4a) and 7-chloro-4-[2-[5-(p-methoxy-
phenyl)-2-isoxazolin-3-yl]anilino]quinoline (4b)

A mixture of 2a (or 2b) (0.005 mole), hydroxylamine
hydrochloride (0.35 g; 0.005 mole), and NaOH (0.5 g) in EtOH (60 ml) was refluxed for 5 h, cooled and poured into 150 ml of cold water.
The yellow precipitate was filtered off and crystal-
lized to give 4 in about 55% yield.
4a: m.p. 250–262 °C (MeOH). IR: 3285 cm^{-1} (NH), 1600 cm^{-1} (C=N), 1550 cm^{-1} (C=C aromatic) and 790 cm^{-1} (C=Cl).
Analysis: C_{24}H_{18}ClN_{4}O (399.8)
   Calcd C 70.04 H 4.53,
   Found C 71.66 H 4.84.
4b: m.p. 295–297 °C (EtOH/H_{2}O)
Analysis: C_{25}H_{20}ClN_{4}O_{2} (429.9)
   Calcd C 69.84 H 4.68 N 9.77,
   Found C 70.33 H 5.00 N 9.39.

7-Chloro-4-[p-[1,2,5,6-tetrahydro-2-oxo-6-(p-methoxyphenyl)-4-pyrimidinyl]anilino]-
quinoline (5a)

To 0.1 g (0.0015 mole) of urea in 20 ml ethanol,
5 ml of conc. HCl was added. To the formed solution,
2b (0.42 g; 0.001 mole) was added, and the mixture was heated at reflux temperature for 8 h
then concentrated in vacuo to 1/3 its volume and cooled. The mixture was neutralized with cold
NH_{4}OH and the precipitated material was crystal-
lized from ethyl alcohol to give 5a in 45% yield, m.p.
210–212 °C. IR: 3280 cm^{-1} (NH), 1660 cm^{-1} (C=O)
and 1590 cm^{-1} (C=N).
Analysis: C_{26}H_{21}ClN_{4}O_{2} (456.9)
   Calcd N 12.26,
   Found N 11.88.

7-Chloro-4-[p-[1,2,5,6-tetrahydro-2-thioxo-
6-(p-methoxyphenyl)-4-pyrimidinyl]anilino]-
quinoline (5b)

A mixture of 2b (0.42 g; 0.001 mole); thiourea
(0.11 g; 0.0014 mole); NaOH (0.1 g); and 30 ml of
80% ethanol was refluxed for 5 h, then concen-
trated, cooled and filtered. The precipitate was crys-
tallized from abs. EtOH to give 5b, m.p.
225–226 °C (d).
Analysis: C_{26}H_{21}ClN_{4}OS (472.9)
   Calcd N 12.26,
   Found N 11.88.

The biological data are the results of screening
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