A Convenient Route for Synthesis of 1,2,4-Triazolines as Substituents to Benzo[*f*]-4-hydroxy-1,2-dihydro-2-quinolone

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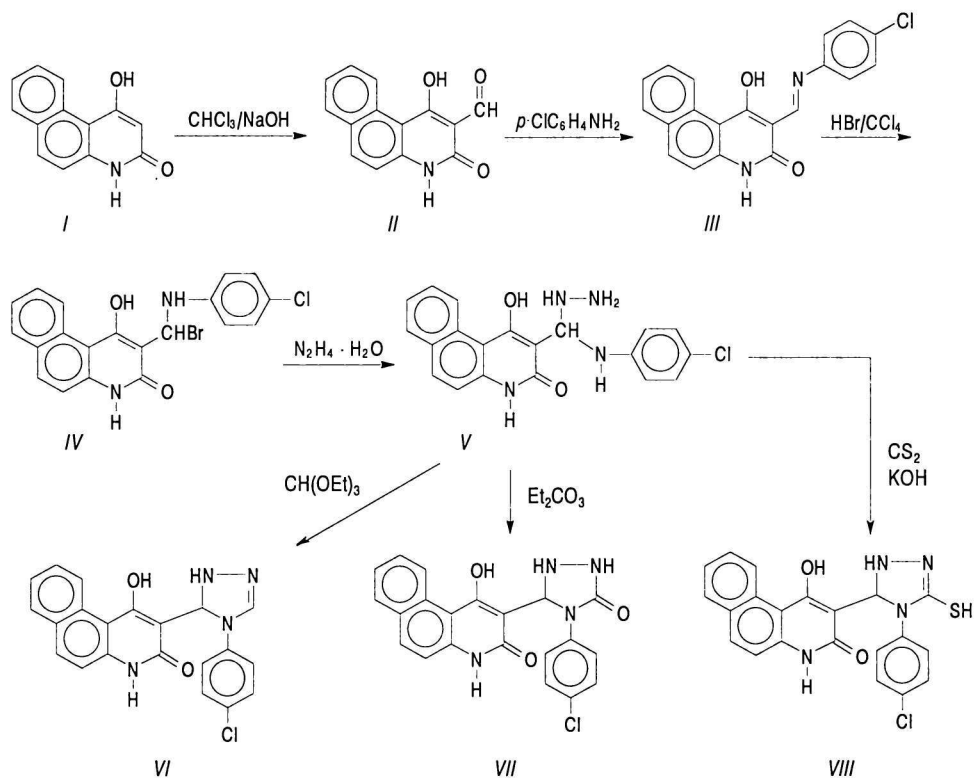
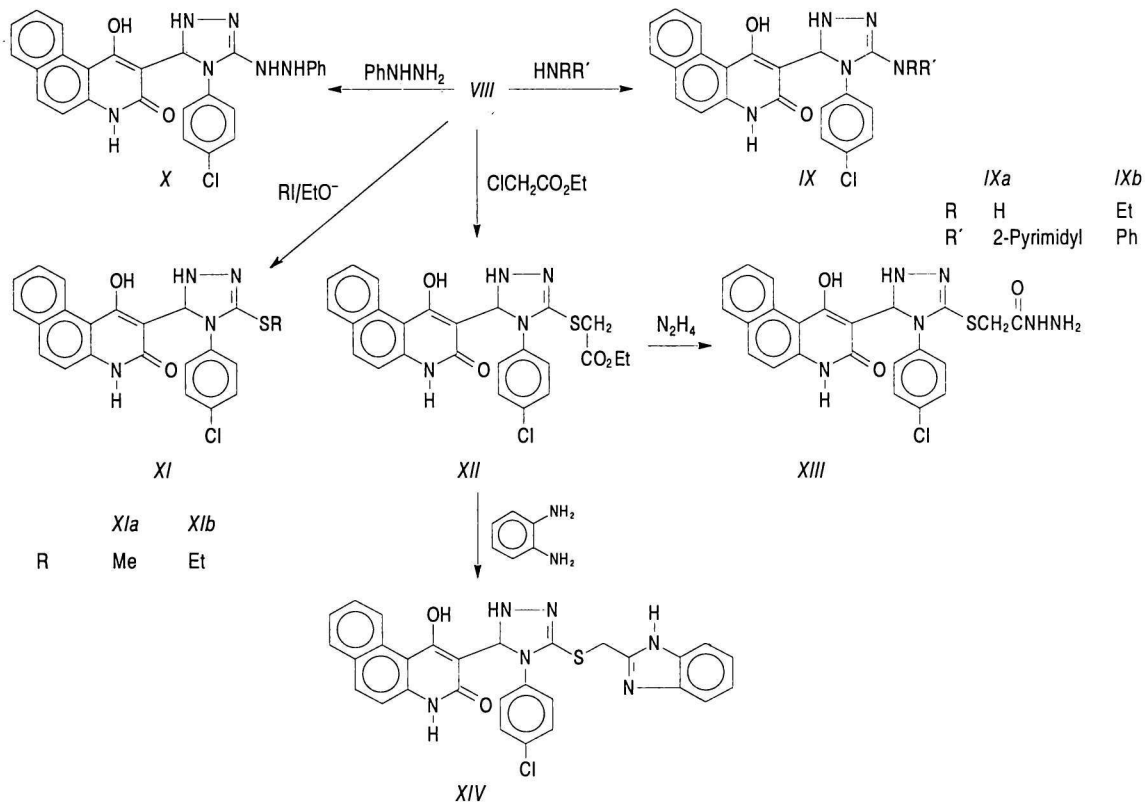
Benzo[*f*]-3-[(*p*-chlorophenylamino)(hydrazino)methyl]-4-hydroxy-1,2-dihydro-2-quinolone was prepared by the addition of HBr on —CH=N bond of the Schiff base followed by condensation with hydrazine and was used in the synthesis of different substituted triazolines borne on a quinolone moiety giving rise to a system of high probability to be of great biological importance. Some other derivatives of this class of compounds of expected pharmaceutical importance were obtained by the action of certain nucleophiles as well as by alkylation of the respective triazoline. The structures of the obtained compounds were elucidated by IR and ^{1}H NMR spectroscopy.

It is well known that triazoles are of biological importance [1—4], it is also reported in the literature that quinolones have many pharmaceutical applications [5—10]. This prompted us to design and synthesize novel compounds, in which both the triazoline and quinolone moieties are coupled, aiming to improve the medicinal importance of this class of compounds.

The target compounds having both quinolone and triazoline skeletons *VI*—*VIII* were obtained by cyclization of the hydrazino derivative *V*, using different reagents and different cyclization reactions (Scheme 1). Thus compound *I* was formylated by heating with chloroform and sodium hydroxide, affording benzo[*f*]-4-hydroxy-1,2-dihydro-2-quinolone-3-carbaldehyde (*II*). The latter compound upon treatment with *p*-chloroaniline gave benzo[*f*]-4-hydroxy-3-(*p*-chlorophenyliminomethine)-1,2-dihydro-2-quinolone (*III*), which readily added HBr to produce benzo[*f*]-3-[(bromo)(*p*-chlorophenylamino)methyl]-4-hydroxy-1,2-dihydro-2-quinolone (*IV*). Substitution of



Scheme 1



Scheme 2

the bromine atom of compound *IV* by a hydrazino group was achieved by refluxing *IV* with hydrazine hydrate, affording the halfway compound *V*.

Compound *V* was cyclized by reacting it with triethyl orthoformate to produce benzo[*f*]-3-[4-(*p*-chlorophenyl)-Δ^2-1,2,4-triazolin-5-yl]-4-hydroxy-1,2-dihydro-2-quinolone (*VI*), whereas cyclization of *V* using diethyl carbonate produced benzo[*f*]-3-[4-(*p*-chlorophenyl)-1,2,4-triazolidin-3-one-5-yl]-4-hydroxy-1,2-dihydro-2-quinolone (*VII*). On the other hand, reaction of *V* with carbon disulfide in the presence of potassium hydroxide promoted the cyclization to benzo[*f*]-3-[4-(*p*-chlorophenyl)-1,2,4-triazolidin-3-thione-5-yl]-4-hydroxy-1,2-dihydro-2-quinolone (*VIII*).

The latter compound was aminated and/or alkylated at the purpose of preparing some of its derivatives having Ar—N(R)—, —NH—, —NH(Ph) and/or —SR substrates which may positively affect the biological activity of this class of compounds.

So, when *VIII* was subjected to react with 2-aminopyrimidine (Scheme 2), it gave benzo[*f*]-3-[4-(*p*-chlorophenyl)-3-(2-pyrimidylamino)-Δ^2-1,2,4-triazolin-5-yl]-4-hydroxy-1,2-dihydro-2-quinolone (*IXa*). On the other hand, similar reaction of *VIII* with *N*-ethylaniline led to the formation of benzo[*f*]-3-[4-(*p*-chlorophenyl)-3-(*N*-ethyl-*N*-phenylamino)-Δ^2-1,2,4-triazolin-5-yl]-4-hydroxy-1,2-dihydro-2-quinolone (*IXb*). Similarly, *VIII* reacted with phenyl hydrazine giving rise to benzo[*f*]-3-[4-(*p*-chlorophenyl)-3-(phenylhydrazino)-Δ^2-1,2,4-triazolin-5-yl]-4-hydroxy-1,2-dihydro-2-quinolone (*X*).

Compound *VIII* underwent *S*-alkylation, when subjected to react with alkyl halides (namely: methyl iodide and ethyl iodide) in the presence of sodium ethoxide to afford benzo[*f*]-3-[4-(*p*-chlorophenyl)-3-(methylthio)-Δ^2-1,2,4-triazolin-5-yl]-4-hydroxy-1,2-dihydro-2-quinolone (*XIa*) and benzo[*f*]-3-[4-(*p*-chlorophenyl)-3-(ethylthio)-Δ^2-1,2,4-triazolin-5-yl]-4-hydroxy-1,2-dihydro-2-quinolone (*XIb*), respectively. Ethyl chloroacetate reacted with *VIII* in the presence of potassium carbonate in acetone to produce benzo[*f*]-3-[4-(*p*-chlorophenyl)-3-ethoxycarbonylmethylthio)-Δ^2-1,2,4-triazolin-5-yl]-4-hydroxy-1,2-dihydro-2-quinolone (*XII*), which upon condensation with hydrazine hydrate gave benzo[*f*]-3-[4-(*p*-chlorophenyl)-3-(thiomethyleneoxyhydrazido)-Δ^2-1,2,4-triazolin-5-yl]-4-hydroxy-1,2-dihydro-2-quinolone (*XIII*).

Finally, the thioethereal ester *XII* condensed with *o*-phenylene diamine, to give the cyclocondensation product: benzo[*f*]-3-[4-(*p*-chlorophenyl)-3-(2-benzoimidazolylmethylthio)-Δ^2-1,2,4-triazolin-5-yl]-4-hydroxy-1,2-dihydro-2-quinolone (*XIV*).

EXPERIMENTAL

Melting points are reported uncorrected, IR spectra were taken on a Pye—Unicam SP 1100 spectrophotometer and ^{1}H NMR spectra (DMSO-d_6)

on an EM 390 (90 MHz) spectrometer using TMS as internal standard. Benzo[*f*]-4-hydroxy-1,2-dihydro-2-quinolone (*I*) was prepared according to the method described by *Mohamed* [11]. Benzo[*f*]-4-hydroxy-1,2-dihydro-2-quinolone-3-carbaldehyde (*II*) was prepared following the method reported by *Brown et al.*[12].

Condensation of the Formyl Compound *II* with *p*-Chloroaniline: Formation of *III*

A suspension of *II* (2.39 g; 0.01 mol) in ethanol (10 cm^3) was heated with *p*-chloroaniline (1.28 g; 0.01 mol). The reaction mixture was refluxed for 4 h, then cooled and the solid obtained was filtered off and crystallized (*cf.* Table 1).

Addition of HBr to *III*: Formation of *IV*

To a suspension of the Schiff base *III* (3.48 g; 0.01 mol) in CCl_4 (15 cm^3), hydrobromic acid (63 mass %) (0.74 cm^3, 0.01 mol) was added with vigorous shaking, the reaction mixture was stirred well for 2 h and then the solvent was distilled off in vacuum. The residue was washed with cold water and cold methanol, dried and crystallized from the proper solvent (*cf.* Table 1).

Action of Hydrazine Hydrate on *IV*: Formation of *V*

A mixture of *IV* (4.3 g; 0.01 mol) and hydrazine hydrate (98 mass %) (0.75 cm^3, 0.015 mol) in absolute ethanol (20 cm^3) was heated under reflux for 2 h, cooled and the solid that separated was filtered off and crystallized from the appropriate solvent (*cf.* Table 1).

Cyclization of Compound *V* by Triethyl Orthoformate and/or Diethyl Carbonate: Formation of Compounds *VI* and *VII*

A mixture of compound *V* (3.81 g; 0.01 mol) with either triethyl orthoformate or diethyl carbonate (10 cm^3) was heated at the boiling point of the mixture for 8 h, using a short air condenser so that ethanol formed escaped freely. The precipitate formed was treated with cold methanol (20 cm^3), filtered off and the brown solid products were crystallized from the suitable solvent (*cf.* Table 1).

Cyclization of Compound *V* by CS_2: Formation of Compound *VIII*

An alcoholic potassium hydroxide solution (1.12 g; 0.02 mol) in water (5 cm^3) and ethanol (30 cm^3) was added to a mixture of *V* (3.81 g; 0.01 mol) and CS_2 (15 cm^3). The reaction mixture was refluxed on a water bath for 4 h and the excess CS_2 was then evaporated. The solid obtained was dissolved in H_2O, filtered off from any insoluble material and acidified. The yellowish precipitate that formed was filtered off and crystallized from the appropriate solvent (*cf.* Table 1).

Action of Amines Resp. Phenylhydrazine on *VIII*: Formation of *IXa*, *IXb*, and *X*

A suspension of compound *VIII* (4.23 g; 0.01 mol) in ethanol (10 cm^3) was treated with an excess of 2-aminopyrimidine, *N*-ethylaniline resp. phenylhydrazine (0.013 mol) and the reaction mixture was refluxed for 4 h. The resulting products deposited upon treatment with cold dilute acetic acid were filtered off and crystallized from the appropriate solvent (*cf.* Table 1).

S-Alkylation of Compound *VIII*: Formation of *XIa*, *XIb*

A mixture of *VIII* (4.23 g; 0.01 mol), alkyl halides, namely methyl iodide and ethyl iodide (0.01 mol), and sodium (0.46 g; 0.02 mol) in absolute ethanol (50 cm^3) was heated for 6 h. The reaction mixture was cooled and acidified with dilute hydrochloric acid. The solid products that precipitated were filtered off, washed several times with cold water, dried and crystallized from the proper solvent (*cf.* Table 1).

Action of Ethyl Chloroacetate on *VIII*: Formation of *XII*

A mixture of *VIII* (4.23 g; 0.01 mol), ethyl chloroacetate (1.85 g; 0.015 mol), and anhydrous potassium carbonate (15 g) in dry acetone (200 cm^3) was refluxed on a water bath for 24 h. The reaction mixture was cooled and poured into water. The resultant solid was filtered off, dried and crystallized from the appropriate solvent (*cf.* Table 1).

Formation of the Acid Hydrazide Derivative *XIII*

A mixture of *XII* (5.09 g; 0.01 mol) and hydrazine hydrate (98 mass %) (0.5 cm^3, 0.01 mol) in ethanol (30 cm^3) was refluxed for 6 h. The solid that separated upon cooling was crystallized from the proper solvent (*cf.* Table 1).

Formation of the Benzoimidazole Derivative *XIV*

A mixture of *XII* (5.09 g; 0.01 mol) and *o*-phenylenediamine (1.08 g; 0.01 mol) was heated at 150 °C for 6 h, then the temperature was raised to

Table 1. Physical, Analytical, and Spectral Data of the New Compounds

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	S	Cl	Yield %	M.p./°C Solvent	IR $\tilde{\nu}$/cm^{-1}	^{1}H NMR δ
III	$C_{20}H_{13}N_2O_2Cl$ 348.5	68.87 69.00	3.73 3.90	8.03 8.20		10.19 10.00	90	155—156 EtOH	3420, 3290, 2800 br, 1635, 1590, 740, 700	7.3—8.1 (m, 11H, H_{arom} + —HC=N—), 10.2 (br, 1H, NH), 11.7 (br, 1H, OH)
IV	$C_{20}H_{14}N_2O_2BrCl$ 429.5	55.88 55.60	3.20 3.00	6.52 6.80			70	165—167 EtOH	3390, 2700 br, 1630, 740, 700, 685	3.1 (d, 1H, CH), 4.9 (br, 1H, NH_{amino}), 7.5—8.3 (m, 10H, H_{arom}), 10.0 (br, 1H, $NH_{quinolone}$), 11.9 (br, 1H, OH)
V	$C_{20}H_{17}N_4O_2Cl$ 380.5	63.07 63.30	4.47 4.70	14.72 14.90		9.33 9.33	83	> 300 DMF	3500—2500 br, 1645, 740, 700	
VI	$C_{21}H_{15}N_4O_2Cl$ 390.5	64.53 64.70	3.84 3.50	14.34 14.50		9.09 9.40	55	> 300 DMF	3500—2500, 1650, 1615, 1580	4.5 (br, 1H, CH-$5_{triazoline}$), 7.3—8.5 (m, 11H, H_{arom} + CH-$3_{triazoline}$), 9.9 (br, 1H, $NH_{quinolone}$), 10.8 (br, 1H, $NH_{quinolone}$), 11.9 (br, 1H, OH)
VII	$C_{22}H_{15}N_4O_3Cl$ 406.5	61.99 62.30	3.69 3.40	13.78 13.50		8.73 8.90	65	> 300 DMF	3500—2500 br, 1660, 1635, 1590	
VIII	$C_{22}H_{15}N_4O_2SCl$ 422.5	59.64 59.40	3.55 3.80	13.25 13.00	7.57 7.60	8.40 8.90	45	> 300 DMF	3300, 3280, 2850 br, 2550 w, 1640, 1595, 1180	4.9 (d, 1H, CH-$5_{triazoline}$), 7.2—8.2 (m, 10H, H_{arom}), 9.9 (br, 1H, NH-$1_{triazoline}$), 10.8 (br, 1H, $NH_{quinolone}$), 11.6 (br, 1H, OH), 12.1 (br, 1H, NH--$2_{triazoline}$)
IXa	$C_{25}H_{18}N_7O_2Cl$ 483.5	62.05 62.30	3.72 3.40	20.27 20.00		7.34 7.60	66	> 300 DMF	3350—2500 br, 1650, 1615, 1580	
IXb	$C_{29}H_{24}N_5O_2Cl$ 509.5	68.30 68.70	4.71 4.80	13.74 13.80		6.97 7.20	71	> 300 DMF		
X	$C_{27}H_{21}N_6O_2Cl$ 496.5	65.26 65.40	4.23 4.10	16.92 17.30		7.15 7.00	70	290—292 EtOH	3570—2500 br, 1640, 1600, 1585	4.8 (d, 1H, CH-$5_{triazoline}$), 6.2 (br, 1H, NHPh), 7.2—8.2 (m, 15H, H_{arom}), 10.1 (br, 1H, $NH_{triazoline}$), 10.8 (br, 1H, $NH_{quinolone}$), 11.7 (br, 1H, OH), 12.3 (br, 1H, $NH_{hydrazino}$)
XIa	$C_{22}H_{17}N_4O_2SCl$ 436.5	60.48 60.60	3.89 4.10	12.83 12.60	7.33 7.30	8.13 8.60	55	232—233 Acetone	3500—2500 br, 1645, 1610, 1580, 1180	
XIb	$C_{23}H_{19}N_4O_2SCl$ 450.5	61.27 61.00	4.22 4.40	12.43 12.40	7.10 7.50	7.88 7.60	63	240—241 Acetone		1.5 (t, 3H, CH_3), 3.00 (q, 2H, CH_2), 4.8 (d, 1H, CH-$5_{triazoline}$), 7.2—8.1 (m, 10H, H_{arom}), 9.9 (br, 1H, $NH_{triazoline}$), 10.8 (br, 1H, NH), 11.9 (br, 1H, OH)
XII	$C_{25}H_{22}N_4O_4SCl$ 508.5	59.00 58.00	4.13 4.00	11.01 10.90	6.29 6.00	6.98 7.20	60	278—279 DMF	3600—2500 br, 1725, 1650, 1620, 1080	1.9 (t, 3H, CH_3), 3.6 (q, 2H, OCH_2), 4.0 (s, 2H, S—CH_2), 4.8 (d, 1H, CH-$5_{triazoline}$), 7.1—8.2 (m, 10H, H_{arom}), 9.9 (br, 1H, $NH_{triazoline}$), 10.6 (br, 1H, $NH_{quinolone}$), 11.7 (br, 1H, OH)
XIII	$C_{23}H_{19}N_6O_3SCl$ 494.5	55.81 56.10	3.84 3.50	16.99 17.30	6.47 6.70	7.18 6.90	44	258—259 AcOH	3400, 3200, 3150, 2500 br, 1655, 1645, 1615, 1585	4.1 (s, 2H, S—CH_2), 4.3 (br, 2H, NH_2), 4.8 (d, 1H, CH-$5_{triazoline}$), 7.2—8.1 (m,10H, H_{arom}), 9.5 (br, 1H, NHCO), 9.9 (br,1H, $NH_{triazoline}$), 10.9 (br,1H, $NH_{quinolone}$), 11.9 (br, 1H, OH)
XIV	$C_{29}H_{22}N_6O_2SCl$ 552.5	62.99 62.90	3.80 3.80	15.20 15.00	5.79 5.70	6.43 6.40	35	249—251 AcOH	3600—3400 br, 3300—2500 br, 1645, 1620—1580	4.2 (s, 2H, S—CH_2), 4.8 (d, 1H, CH-$5_{triazoline}$), 7.2—8.5 (m, 14H, H_{arom}), 9.9—10.1 (br, 2H, 2 × $NH_{triazoline + imidazole}$), 10.9 (br, 1H, $NH_{quinolone}$), 11.65 (br, 1H, OH)

180 °C for another 1 h. The mixture was cooled and the solid obtained was crystallized (*cf.* Table 1).

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Some New Quinolones of Expected Pharmaceutical Importance Derived from 1,2-Dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde

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The title compound was condensed with various amino derivatives giving rise to new quinolones of expected biological activity, especially the condensation products of thiosemicarbazide and its derivatives. For the purpose of inducing and/or improving the pharmaceutical importance of the latter products, they were subjected to certain cyclization reactions, affording new quinolones substituted with heterocyclic rings. The structures of certain other new quinolones were elucidated by preparing them by two different routes, using interesting reagents. Condensation of 1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline with certain compounds having active methylene groups was also studied.

It is reported in the literature that 1,2-dihydro-4-hydroxy-2-oxoquinolines are of great medicinal importance [1—6]. On the other hand, thiosemicarbazones, triazinoindoles, barbituric acid, thiobarbituric acid, and pyrazolones show antimicrobial, antitumour activities and possess a wide spectrum of medicinal properties [7—10]. This led to the decision to combine quinoline with each of these mentioned and some other heterocyclic substrates with the aim to obtain new compounds of higher and modified biological activities.

In order to achieve this purpose, it was necessary to synthesize a formyl derivative of quinolone and condense it with thiosemicarbazides and other reagents. Thus 1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline (*I*, Scheme 1), which was synthesized according to the novel method described by the author [11], was formylated following the procedure, reported by *Tomita* [1] to give 1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde (*II*).

This aldehyde *II* condensed readily with thiosemicarbazide, phenyl, *p*-anisyl, and allylthiosemicarbazide to afford the desired thiosemicarbazones *IIIa—IIId*, which were also obtained when the hydrazone *IV* (preliminarily produced by condensing the aldehyde *II* with excess hydrazine hydrate) was