New Quinolones and Naphthyridinones Bearing Heterocyclic Rings

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The behaviour of some α,β -unsaturated ketones or β -diketones, derived from quinolones, naphthyridinones or a combination of both of them, towards amines, diamines, and other ammonia derivatives at different ratios and conditions had been studied; the result were many interesting polyheterocyclic compounds containing either quinolone, naphthyridinone or both as the main moiety besides the recently formed hetero rings as: diazepine, oxazepine, thiazepine, triazepine, thiazole, thiazoline, pyrazoline, isooxazoline, pyrimidine, indole, triazinoindole, and quinoxaline. The structures of the resulting new polyheterocyclic compounds were established by chemical reactions, elemental analysis, and spectral data.

Quinolones and naphthyridinones are famous categories of compounds known by their intensive biological activity and vital important medicinal and pharmaceutical applications [1-4]. This prompted us long ago to carry out intensive research work on these classes of organic compounds [5-8].

In our previous publication [9] the action of primary amines on the 3-acryloyl-4-hydroxy-2-oxoquinoline I was studied at the mole ratio (x_r) 1:1, and the products were found to be the 1,4-Michael type adducts II (Scheme 1). In the present work the study is extended by carrying out the reaction at the mole ratio 2:1. The IR spectra of the products revealed the absence of the C=O absorption peak of the side chain, indicating that it is captured in the reaction course, which means that the reaction products are the amino-imino compounds III, where one molecule of the amine underwent Michael type addition, while the other condensed to the carbonyl side chain, many supports had been done for that result, among them is microelemental analysis, NMR spectral data and producing compound III directly from the reaction of compounds II with one mole of the same primary amine.

Diamines and other bifunctional reagents such as o-phenylenediamine, o-aminothiophenol, ethylenediamine, and ethanolamine, when subjected to react with the α,β -unsaturated ketones I, cycloadditioncondensation reaction took place giving rise to the novel heterocyclic compounds of expected biological importance: benzodiazepine IV, benzothiazepine V, diazepine VIa and oxazepine VIb derivatives, the structures of which found good supports from spectral data and elemental analysis.

The study of action of amines and diamino reagents was extended to the β -diketones VII [6] (Scheme 2), where primary, secondary, aliphatic, aromatic or heterocyclic amines condense with the ω -enolized carbonyl group to give the α,β -unsaturated oxoenamines VIIIa-VIIIm, these structures were inferred from their analytical and spectral data as well as similarity to the well-known reactions, cited in the literature [10]. The bifunctional amonia derivatives such as ethylenediamine, semicarbazide, thiosemicarbazide, and aminoguanidine furnished the diazepine IX, triazepinone, triazepinthione, and iminotriazepine Xa-Xc, respectively. The structures of these compounds were deduced from their correct elemental analysis and spectroscopic studies.

Insertion of heterocyclic rings, of known biological activity, such as thiazole, pyrazole, and pyrimidine to the quinolone moiety was achieved by reacting the acetyl compound XI (Scheme 3) with 2-cyanomethylbenzothiazole, 2-phenylimino-4-thiazolidinone, 3-methyl-5-pyrazolinone, 3-phenyl-5-pyrazolinone, and barbituric acid, where the carbonyl of the acetylquinolinone XI condenses with the active methylene of the reagents giving rise to the novel compounds XII—XVI, which are characterized by elemental analysis and their IR and ¹H NMR data are in good accordance with the suggested formula.

Reaction of the acetylquinolinone XI with some carbohydrazide derivatives produced new compounds XVIIa—XVIId, having the corresponding hydrazones as substituents to the quinolinone skeleton at position 3. These substituents may induce good pharmaceutical properties to the newly synthesized compounds. The acid hydrazides used were: cyanoacetylhydrazine, p-methoxybenzoylhydrazine, p-chlorobenzoylhydrazine, and o-carbohydrazinopyridine. The structures of the compounds XVIIa—XVIId were elucidated using different physical and chemical tools where the data





of their elemental and spectral analysis are coincident with the proposed formula. In a similar manner the acetyl compound XI reacts with potassium hydrazinecarbodithioate to give potassium (3-acetyl-4hydroxy-1-methyl-2(1H)-quinolone)hydrazonocarbodithioate XVIII (Scheme 4), the structure of which is found to be in agreement with spectral data and microanalysis. The quinoxaline substructure is one of heterocyclic systems known by its biological activity, suitable to be immersed as a substituent to quinolone; compound XI was reacted with 2,3dihydrazinoquinoxaline at the mole ratio 1:1, where the product obtained was identified as the hydrazone XIX. The presence of the hydrazine substrate in XIX was checked up by its reaction with benzaldehyde, affording the dihydrazone compound XX, furthermore XIX is highly affected by glacial acetic acid, giving rise to its acetyl derivative XXI. Another new biologically promising quinolone substituted by further heterocyclic system was obtained by reacting the acetylquinolone XI with isatine-3-hydrazone to produce 4-hydroxy-1-methyl-3-(2'-oxo-1H-indol-3ylidenehydrazonoacetyl)-2(1H)-quinolone XXII.

The knowledge of the serious medicinal importance of naphthyridinones [11] prompted us to synthesize new members of this class of compounds,





where 3-formyl-4-hydroxy-1,8-naphthyridinone XXIII (Scheme 5) was prepared and used as starting material for the preparation of new naphthyridinone derivatives. Condensation of the aldehyde XXIII with different acetyl derivatives (such as acetophenones and acetylquinolones) gave rise to new α,β -unsaturated ketones, which in turn converted to new pyrazolines and isooxazolines when reacted with hydrazines and/or hydroxylamine. The reaction of XXIII with acetophenone and/or 4-N-acetylaminoacetophenone was carried out, at the mole ratio 1:1, in the presence of piperidine as catalyst to afford α,β -unsaturated ketones XXIVa, XXIVb.

Another interesting α,β -unsaturated ketone XXV

derived by combination of both quinolone and naphthyridinone skeletons was achieved by reacting the acetoacetylquinolone VII with the formylnaphthyridinone XXIII in the presence of piperidine as catalyst.

To facilitate the following study of additive effect of linking quinolone and naphthyridinone moieties on the biological activity of the combine we had reacted the formylnaphthyridinone XXIII with 3acetyl-1-butyl-4-hydroxy-2(1H)-quinolinone XXVI to give α,β -unsaturated ketone XXVII. Elemental analysis and spectral data of compound XXVII are coincident with the proposed structure. The effect of hydrazine on each of α,β -unsaturated compounds XXIV, XXV, and XXVII was studied. Thus treatment of





compound XXIVa with hydrazine hydrate gave the pyrazoline XXVIII. Elemental analysis of the latter compound was found in good accordance with the predicted structure which is formed by condensation of one molecule of hydrazine with the carbonyl group followed by intermolecular addition to the α , β -double bond giving rise to the new pyrazolinylnaphthyridinone XXVIII.

As mentioned before XXV is considered as α,β unsaturated ketone, therefore it was expected that XXV may react with hydrazine at the mole ratio 1:1 to produce the pyrazoline XXIX or XXX. The actual product was neither of them, it was found that it does not react any more with an extra amount of hydrazine, which means that all the active carbonyl groups had been consumed in the reaction with the first mole of hydrazine. Therefore, the structure proposed for the product is XXXI, which found supports by its correct elemental analysis, IR and ¹H NMR spectra. IR spectrum gave good indication for the pyrazole structure where the characteristic bands for the two (C==O) groups of the acetoacrylyl moiety disappeared. On the other hand, the α,β -unsaturated ketone derivative of the combined naphthyridinone-quinolinone XXVII underwent normal cyclocondensation with hydrazine to produce the pyrazoline derivative XXXIIa and similar cyclocondensation took place when XXVII reacted with phenylhydrazine and hydroxylamine to afford the phenylpyrazoline and isoxazoline XXXIIb and XXXIIc, respectively. The structures of compounds XXXIIa, XXXIIb were established on the basis of their correct elemental analyses and spectral data.

The reaction of the aldehyde XXIII with 2,3dihydrazinoquinoxaline was studied at different mole ratios. It was found that when the reaction was carried out at the mole ratio 1:1, the product was found to be the monohydrazone XXXIII, while at the mole ratio (formyl:reagent) 2:1, the product was identified as the dihydrazone XXXIV (Scheme 6). The compounds XXXIII and XXXIV were characterized by their correct elemental analyses and spectral data.

A strong evidence for the correctness of the structure proposed for compound XXXIII was attained by its successful condensation with benzaldehyde to form benzalazino derivative XXXV indicating the presence of a free hydrazino group in XXXIII. The structure



Scheme 4

XXXV was inferred from its correct elemental analysis and its IR spectral data.

In order to have more and more of the biologically promising naphthyridinone derivatives, the aldehyde XXIII was reacted with some ammonia derivatives (some amines and acid hydrazides). Thus, XXIII was subjected to react with *p*-aminoacetophenone to produce the imine XXXVI, the structure of which was easily inferred from its correct elemental analysis as well as spectral data.

One more interesting naphthyridinone derivative XXXVII bearing multiaza hetero rings, was obtained by refluxing the aldehyde XXIII in ethanol with 3-hydrazino-1,2,4-triazinoindole. Structure XXXVII was supported by its correct elemental analysis and spectral data.

The formation of further derivatives of naphthyridinones was performed by reacting *XXIII* with some acid hydrazides, to give the corresponding acylhydrazones XXXVIIIa—XXXVIIIe, the structures of which were fortified by correct elemental analysis and studying their spectra.

EXPERIMENTAL

Melting points were determined in open capillary using Gallenkamp melting point apparatus MFB-595. Infrared spectra were recorded on a Perkin—Elmer 598 spectrophotometer using samples in KBr discs. ¹H NMR spectra were taken on a Jeol FX-90 NMR spectrometer (90 MHz) and a Varian EM-390 NMR spectrometer, using DMSO- d_6 as the solvent and TMS as the internal standard. Elemental microanalyses were performed at the Microanalytical Centre, Cairo University. All compounds gave satisfactory values for w_i (found) (i: C, H, N (Cl and S)) within $\pm 0.4 \%$ of the calculated values. Characterizations of the new compounds are listed in Tables 1—6.



Scheme 5

3-(3-Aryl-3-arylamino-1-aryliminopropan-1-yl)-4-hydroxy-1-methyl(1*H*)-quinolin-2-ones *IIIa*— *IIIf*

Method A

To a solution or suspension of each of compounds

IIa—IIf (0.01 mol) in absolute ethanol (50 cm³), the appropriate arylamine was added. The reaction mixture was heated under reflux for 4 h, then cooled to room temperature and the solid that deposited was filtered off and recrystallized to give the corresponding products.



Scheme 6

Method B

A mixture of compound I (0.01 mol), the proper primary arylamine (0.02 mol), and one drop of piperidine was heated on boiling water bath for 2 h. The solid mass so formed was triturated with cold methanol (20 cm³), filtered off and crystallized. IR spectrum (KBr), $\tilde{\nu}(IIIa)/\text{cm}^{-1}$: 1610 (C=N), 1650 (C=O_{quinolone}), 2700-3000 (OH), 3400-3600 (NH).

3-(2-Aryl- Δ^4 -benzo[b]-1,5-diazepin-4-yl)-4hydroxy-1-methyl(1H)-quinolin-2-ones IVa—IVd and 4-Hydroxy-1-methyl-3-(7-styryl- Δ^4 -1,4-diazepine/1,4-oxazepin-5-yl)-(1H)-quinolin-2-ones VIa and VIb

To a solution of compound I (0.01 mol) in glacial acetic acid (5 cm³) the appropriate amine was added. The reaction mixture was refluxed for 4 h, cooled and

| Table 1. | Characterization | of the Ne | w Compounds | III—VI |
|----------|------------------|-----------|-------------|--------|
| | <u></u> | 2 23 Y X | | |

| Compound | Yield | M.p. | Solvent |
|----------|-------|------|---------|
| | % | °C | |
| IIIa | 74 | 192 | MeOH |
| IIIb | 96 | 150 | MeOH |
| IIIc | 84 | 218 | EtOH |
| IIId | 73 | 180 | EtOH |
| IIIe | 68 | 146 | EtOH |
| IIIf | 77 | 171 | Dioxane |
| IVa | 72 | 258 | Dioxane |
| IVb | 76 | 220 | Dioxane |
| IVc | 82 | 249 | Dioxane |
| IVd | 81 | 186 | Dioxane |
| V | 71 | 130 | Benzene |
| VIa | 66 | 162 | DMF |
| VIb | 58 | 210 | MeOH |

Table 3. Characterization of the New Compounds XII- XVI

| Compound | Yield % | M.p. ℃ | Solvent |
|----------|------------|-----------|---------|
| | | | |
| XIII | 78 | 122 | MeOH |
| XIV | 77 | 172 | MeOH |
| XV | 93 | 134 | MeOH |
| XVI | 93 | 290 | DMF |

 Table 4. Characterization of the New Compounds XVII—

 XXII

| Compound | Yield % | <u>M.p.</u> ℃ | Solvent |
|----------|------------|------------------|---------|
| | | | |
| XVIIb | 63 | 279 | AcOH |
| XVIIc | 88 | 238 | Dioxane |
| XVIId | 67 | 242 | AcOH |
| XVIII | 71 | 283 | AcOH |
| XIX | 89 | 231 | Dioxane |
| XX | 69 | 242 | Dioxane |
| XXI | 78 | 182 | Dioxane |
| XXII | 93 | 242 | AcOH |

M.p.

°C

210

300

252

260

292

272

292

294

281

A suspension of the compound I (0.01 mol) in methanol (20 cm³) was treated with o-aminothiophe-

nol (0.01 mol) and one drop of piperidine, shaken for

15 min at room temperature. The solid product so ob-

tained was filtered off, washed with diethyl ether (20

that of VI with the exception of the last peak.

3-(3-Arylaminobut-2-enoyl)-4-hydroxy-

1-methyl(1H)-quinolin-2-ones VIIIa-VIIIm

IR spectrum of compound V is nearly the same as

Table 5. Characterization of the New Compounds

Yield

%

66

63

58

56

65

60 65

63

62

Compound

XXIVa

XXIVb

XXV

XXVII

XXVIII

XXXI

XXXIIa XXXIIb

XXXIIc

 cm^3) and crystallized.

Table 2. Characterization of the New Compounds VIII-X

| Compound | Yield | M.p. | Solvent |
|-----------|---|-------|---------|
| | ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ | °C | |
| 3 | 70 | 0 | |
| VIIIa | 71 | 140 | MeOH |
| VIIIb | 69 | 192 | EtOH |
| VIIIc | 81 | 116 | MeOH |
| VIIId | 76 | 162 | MeOH |
| VIIIe | 72 | 204 | EtOH |
| VIIIf | 69 | 105 | MeOH |
| VIIIg | 82 | 179 | EtOH |
| VIIIh | 79 | 275 | DMF |
| VIIIi | 82 | 213 | MeOH |
| VIIIj | 77 | 167 | AcOH |
| VIIIk | 80 | 116 | MeOH |
| VIIIl | 78 | 182 | EtOH |
| VIIIm | 88 | 110 | EtOH |
| IX | 83 | 243 | AcOH |
| Xa | 77 | > 300 | AcOH |
| Xb | 69 | 141 | EtOH |
| Xc | 78 | 254 | MeOH |

poured into water. The solid precipitate was filtered off and crystallized.

IR spectrum (KBr), $\tilde{\nu}(IVa)/cm^{-1}$: 1605—1620 (C=N_{diazepine}), 1645 (C=O_{quinolone}), 2640 (H-bonded OH), 3150 (NH). ¹H NMR spectrum (DMSO- d_6), $\delta(IVa)$: 3.24 (d, 2H, CH_{2 diazepine}), 3.65 (s, 3H, NCH₃), 3.85–3.90 (m, 1H, CH_{diazepine}), 4.82 (b, 1H, NH), 6.92–8.17 (m, 14H_{arom}), 11.70–11.75 (b, 2H, 2OH exchangeable with D₂O). IR spectrum (KBr), $\tilde{\nu}(IVa)/cm^{-1}$: 1580–1600 (C=C), 1600– 1615 (C=N_{diazepine}), 1645 (C=O_{quinolone}), 2625 (Hbonded OH), 3125–3250 (NH).

4-Hydroxy-1-methyl-3-(2-styryl- Δ^4 -1,5-benzo-[b]thiazepin-4-yl)(1H)-quinolin-2-one (V)

Solvent

DMF

DMF

DMF

DMF

DMF

DMF

AcOH

DMF

MeOH

 Table 6. Characterization of the New Compounds XXXIII— XXXVIII

| Compound | Yield | M.p. | Solvent |
|----------|-------|------|---------|
| | % | °C | |
| XXXIII | 84 | 302 | EtOH |
| XXXIV | 70 | 278 | DMF |
| XXXV | 75 | 234 | EtOH |
| XXXVI | 62 | 305 | DMF |
| XXXVII | 85 | 270 | DMF |
| XXXVIIIa | 92 | 252 | DMF |
| XXXVIIIb | 90 | 240 | MeOH |
| XXXVIIIc | 78 | 255 | DMF |
| XXXVIIId | 75 | 291 | Anisole |
| XXXVIIIe | 78 | 200 | DMF |

A solution of the acetoacetyl derivative VII (0.02 mol) in ethanol (5 cm³) was treated with the appropriate amine (0.02 mol) and kept at room temperature overnight. The crystalline solid deposited was filtered off and crystallized.

¹H NMR spectrum (DMSO- d_6), δ (VIIIa): 2.27 (d, 3H, CH₃—C=), 3.7 (s, 3H, N—CH₃), 5.7 (s, 1H, CH=C), 6.35—6.75 (m, 4H_{arom}), 7.1—7.8 (m, 4H_{quinolone}), 8.0 (b, 3H, NH₂ + NH exchangeable with D₂O), 11.7 (b, 1H, OH exchangeable with D₂O).

3-(7-Methyl-2,3-dihydro-1*H*-1,4-diazepin-5-yl)-4-hydroxy-1-methyl(1*H*)-quinolin-2-one (*IX*)

To a solution of the compound VII (0.01 mol) in ethanol (25 cm³), ethylenediamine (0.01 mol) was added and the mixture was refluxed for 2 h. The solid that deposited was filtered off and crystallized to afford IX.

IR spectrum (KBr), $\tilde{\nu}(IX)/\text{cm}^{-1}$: 1590—1600 (C=C), 1620 (C=N_{diazepine}), 1640 (C=O_{quinolone}), 2925—3126 (H-bonded OH), 3150—3300 (NH).

3-(7-Methyl-3-oxo-, -thioxo- or -imino-2,3dihydro-1H-1,2,4-triazepin-5-yl)-4-hydroxy-1-methyl(1H)-quinolin-2-one Xa—Xc

A mixture of the acetoacetyl derivative VII (0.01 mol) and semicarbazide, thiosemicarbazide or aminoguanidine (0.012 mol) in ethanol (30 cm³) was refluxed on a water bath for 2 h. The yellowish solid that formed was filtered off and crystallized to give Xa-Xc.

IR spectrum (KBr), $\tilde{\nu}(Xb)/cm^{-1}$: 1215—1340 (C=S), 1575 (C=N_{triazepine}), 1625 (C=O_{quinoIone}), 2550 (H-bonded OH), 3230 (NH). ¹H NMR spectrum (DMSO-d₆), $\delta(Xa)$: 2.10 (s, 3H, CH₃), 3.70 (s, 3H, NCH₃), 3.85—3.95 (m, 1H, CH_{diazepine}), 7.10—8.00 (m, 4H, H_{arom}), 10.70—11.00 (b, 2H, 2NH exchangeable with D₂O), 11.6 (b, 1H, OH exchangeable with D₂O).

2-(2-Benzothiazolyl)-3-methyl-3-(4-hydroxy-1-methyl-2-oxo(1H)-quinolin-3-yl)acrylonitrile (XII)

A mixture of the acetyl derivative XI(0.01 mol), 2cyanomethylbenzothiazole (0.01 mol), and few drops of piperidine was heated on a boiling water bath for 4 h. The reaction mixture was triturated with ethanol and the solid so obtained was filtered off, washed with diethyl ether and crystallized.

IR spectrum (KBr), $\tilde{\nu}(XII)/\text{cm}^{-1}$: 720 (cyclic C— S—C), 1600 (C=C), 1620 (C=N), 1650 (C=O_{quinolone}), 2210 (C=N), 2650–2930 (H-bonded OH). ¹H NMR spectrum (DMSO- d_6), $\delta(XII)$: 2.5 (s, 3H, CH₃), 3.65 (s, 3H, NCH₃), 7.12–8.15 (m, 8H, H_{arom}), 10.85 (b, 1H, OH exchangeable with D₂O).

5-[1-(4-hydroxy-1-methyl-2-oxo(1*H*)-quinolin-3-yl)ethylidene]-2-phenyliminothiazolidin-4-one (*XIII*)

Similar method to that used to obtain XII was followed using 2-phenyliminothiazolidin-4-one with the acetyl derivative XI.

IR spectrum (KBr), $\tilde{\nu}(XIII)/cm^{-1}$: 1180, 1200, 1330 (N=C-S), 1600 (C=C), 1620 (C=N), 1650 (C=O_{quinolone}), 1700 (C=O_{thiazolidinone}), 2620-3200 (H-bonded OH), 3150 (NH). ¹H NMR spectrum (DMSO- d_6), $\delta(XIII)$: 2.5 (s, 3H, CH₃), 3.70 (s, 3H, NCH₃), 7.2-8.00 (m, 9H, H_{arom}), 9.80 (b, 1H, NH exchangeable with D₂O), 10.85 (b, 1H, OH exchangeable with D₂O).

4-[1-(4-Hydroxy-1-methyl-2-oxo(1H)-quinolin-3-yl)ethylidene]-3-methyl/phenylpyrazolin-5one XIV and XV

A procedure similar to that used for compound XII was utilized to obtain XIV and XV from the acetyl derivative XI with 3-methyl or -phenylpyrazolinones.

5-[1-(4-Hydroxy-1-methyl-2-oxo(1H)-quinolin-3-yl)ethylidene]barbituric Acid (XVI)

The above compound was prepared from compound XI and barbituric acid using the same method described for the synthesis of compound XII.

3-Aroylhydrazonoacetyl-4-hydroxy-1-methyl-(1H)-quinolin-2-ones XVIIa—XVIId

To a solution of the acetyl derivative XI (0.01 mol) in ethanol (25 cm³) the appropriate acid hydrazide (cyanoacetylhydrazine, *p*-methoxybenzoylhydrazine, *p*-chlorobenzoylhydrazine or 2-pyridylcarbohydrazine) (0.01 mol) was added. The reaction mixture was then heated under reflux for 2 h and the solid deposited was filtered off and crystallized. IR spectrum (KBr), $\tilde{\nu}(XVIIa)/\text{cm}^{-1}$: 1610 (C=N), 1650 (C=O_{quinolone}), 1760 (C=O_{cyanoacety}), 2257 (CN), 2800-3000 (H-bonded OH), 3220 (NH). ¹H NMR spectrum (DMSO- d_6), $\delta(XVIIa)$: 2.30 (s, 3H, CH₃), 3.56 (s, 3H, NCH₃), 6.49 (s, 2H, COCH₂CN), 7.00-8.00 (m, 4H, H_{arom}), 9.40 (b, 1H, NH exchangeable with D₂O), 11.45 (b, 1H, OH exchangeable with D₂O).

Potassium 3-[1-(4-Hydroxy-1-methyl-2-oxo-(1H)-quinolin-3-yl)ethylidene]hydrazinecarbodithioate (XVIII)

A solution of the acetyl derivative XI (0.01 mol) in ethanol (25 cm³) was treated with potassium hydrazinecarbodithioate (0.01 mol), and the mixture was refluxed for 2 h on a water bath. The separated organic solid mass was filtered off and recrystallized affording compound XVIII.

IR spectrum (KBr), $\tilde{\nu}(XVIII)/cm^{-1}$: 660 (C—S—C), 1190—1270 (NHC—S), 1525, 1565 (CN), 1595, 1620 (C—N), 1635—1650 (C—O_{quinolone}), 2600—2750 (H-bonded OH), 3220 (NH). ¹H NMR spectrum (DMSO- d_6), $\delta(XVIII)$: 2.30 (s, 3H, NC—CH₃), 3.56 (s, 3H, NCH₃), 7.10—8.30 (m, 4H, H_{arom}), 9.30 (b, 1H, NH exchangeable with D₂O), 11.20 (b, 1H, OH exchangeable with D₂O).

3-(3-Hydrazino-2-quinoxalinylhydrazono)acetyl-4-hydroxy-1-methyl(1*H*)-quinolin-2-one (*XIX*)

A mixture of XI (0.01 mol) and 2,3-dihydrazinoquinoxaline (0.01 mol) in ethanol (10 cm³) was refluxed for 2 h. The yellow precipitate that formed was filtered off and crystallized to give XIX.

IR spectrum (KBr), $\tilde{\nu}(XIX)/\text{cm}^{-1}$: 1610 (C=N), 1645 (C=O_{quinolone}), 2500–3190 (b, NH and OH), 3284 (NH₂). ¹H NMR spectrum (DMSO-*d*₆), $\delta(XIX)$: 2.60 (s, 3H, NC–CH₃), 3.50 (s, 3H, NCH₃), 4.30 (s, 2H, NH₂ exchangeable with D₂O), 7.00–8.10 (m, -8H, H_{arom}), 9.30–9.60 (b, 2H, NH exchangeable with D₂O), 10.80 (b, 1H, OH exchangeable with D₂O).

3-(3-Benzalhydrazino-2-quinoxalinylhydrazono)acetyl-4-hydroxy-1-methyl(1H)quinolin-2-one (XX)

Using the same method as for preparation of XIX, treatment of compound XIX with benzaldehyde yielded the compound XX.

3-[(3-Acetylhydrazino-2-quinoxalinylhydrazono)acetyl]-4-hydroxy-1-methyl(1*H*)quinolin-2-one (*XXI*)

Compound XIX (0.005 mol) was dissolved in glacial acetic acid (25 cm^3) and heated under reflux for

4 h and left to cool to room temperature. The crystallized material so obtained was filtered off and washed with absolute ethanol (5 cm³) and diethyl ether (20 cm³).

4-Hydroxy-1-methyl-3-(2-oxoindol-3-ylidene)hydrazonoacetyl(1H)-quinolin-2-one (XXII)

A solution of the acetyl derivative XI (0.01 mol) in ethanol (25 cm³) was treated with isatine-3-hydrazone (0.01 mol) and the mixture was refluxed for 2 h on a water bath. The separated organic solid mass was filtered off and recrystallized affording compound XXII.

IR spectrum (KBr), $\tilde{\nu}(XXII)/\text{cm}^{-1}$: 1610 (C=N), 1675 (C=O_{quinolone}), 1690–1710 (C=O_{indolinone}), 2650–2700 (H-bonded OH), 3120–3200 (NH). ¹H NMR spectrum (DMSO- d_6), $\delta(XXII)$: 2.55 (s, 3H, NCH₃), 3.56 (s, 3H, NCH₃), 7.10–8.50 (m, 8H, H_{arom}), 11.00 (b, 1H, NH exchangeable with D₂O), 11.85 (b, 1H, OH exchangeable with D₂O).

3-(4-R-phenacylidene)methyl-4-hydroxy-1,8(1H)-naphthyridin-2-ones XXIVa, XXIVb

A mixture of the aldehyde XXIII (0.01 mol), acetophenone, resp. *p*-acetylaminoacetophenone, and one drop of piperidine was heated at 90 °C for 4 h. The reaction mixture was then cooled, triturated with methanol (10 cm³), and the formed deposits were filtered off, washed with diethyl ether and crystallized.

IR spectrum (KBr), $\tilde{\nu}(XXIVa)/cm^{-1}$: 1600 (C=C), 1630 (C=O_{quinolone}), 1700 (C=O_{side chain}), 2500 (Hbonded OH), 3218 (NH). ¹H NMR spectrum (DMSO d_6), $\delta(XXIVa)$: 6.2 (d, 2H, CH=CH), 7.10-8.30 (m, 8H, H_{arom}), 8.90 (s, 1H, NH exchangeable with D₂O), 11.60 (s, 1H, OH exchangeable with D₂O).

3-[3-(4-Hydroxy-2-oxo-1-methyl(1H)quinoline-3-carbonyl)-2-oxo-3-buten-4-yl]-4-hydroxy-1,8(1H)-naphthyridin-2-one (XXV) and 1-Butyl-3-[β -(4-hydroxy-2-oxo-1,8(1H)naphthyridin-3-yl)-acryloyl]-4-hydroxy(1H)quinolin-2-one (XXVII)

A procedure similar to that described for compound XXIV was utilized to obtain compounds XXV and XXVII from the aldehyde XXIII and 3acetoacetylquinolinone VII resp. 3-acetylquinolinone XXVI.

IR spectrum (KBr), $\tilde{\nu}(XXV)/\text{cm}^{-1}$: 1600 (C=C), 1635 (C=O_{naphthyridinone}), 1650 (C=O_{quinolinone}), 1730 (C=O_{α,β -unsat.}), 2900–3000 (H-bonded OH), 3286 (NH). ¹H NMR spectrum (DMSO- d_6), $\delta(XXV)$: 2.40 (s, 3H, COCH₃), 3.80 (s, 3H, NCH₃), 6.50–6.70 (s, 1H, CH=C), 7.50–8.90 (m, 7H, H_{arom}), 9.2 (s, 1H, NH), 11.80 (b, 2H, 2OH exchangeable with D₂O).

IR spectrum (KBr), $\tilde{\nu}(XXVII)/\text{cm}^{-1}$: 1590—1610 (C=C), 1630 (C=O_{naphthyridinone}), 1650

(C=O_{quinolinone}), 1700 (C=O_{α,β -unsat.}), 2600–2900 (H-bonded OH), 3280 (NH). ¹H NMR spectrum (DMSO- d_6), $\delta(XXVII$): 0.91 (t, 3H, CH₃), 1.32–1.81 (m, 4H, 2CH₂), 4.40 (t, 2H, α -CH₂), 6.20–6.52 (m, 2H, CH=CH), 7.05–8.16 (m, 7H, H_{arom}), 9.10 (s, 1H, NH exchangeable with D₂O), 11.20 (b, 2H, 2OH exchangeable with D₂O).

4-Hydroxy-2-oxo-3-(3-phenyl- Δ^2 -pyrazolin-5-yl)-1,8(1*H*)-naphthyridine (XXVIII)

A suspension of the compound XXIVa (0.01 mol) in absolute ethanol (30 cm³) containing DMF (5 cm³) was treated with hydrazine hydrate (0.012 mol). The reaction mixture was heated under reflux for 2 h, then cooled and filtered off. The solid so obtained was crystallized to give compound XXVIII.

IR spectrum (KBr), $\tilde{\nu}(XXVIII)/cm^{-1}$: 1618 (C=N), 1627 (C=O), 2800 (H-bonded OH), 3480 (NH). ¹H NMR spectrum (DMSO- d_6), $\delta(XXVIII)$: 4.21 (b, 1H, NH_{pyrazoline} exchangeable with D₂O), 6.21 (d, 2H, CH_{2 pyrazoline}), 7.23–8.13 (m, 8H, H_{arom}), 8.6 (s, 1H, NH exchangeable with D₂O), 10.50 (b, 1H, OH exchangeable with D₂O).

3-(4-Hydroxy-1-methyl-2-oxo(1*H*)-quinolin-3-yl)-4-(4-hydroxy-2-oxo-1,8(1*H*)naphthyridine-3-methylene)-5-methylpyrazole (*XXXI*) and 3-(1-Butyl-4-hydroxy-2-oxo(1*H*)quinolin-3-yl)-5-(4-hydroxy-2-oxo-1,8(1*H*)naphthyridin-3-yl)- Δ^2 -pyrazolines or $-\Delta^2$ isooxazoline *XXXIIa*—*XXXIIc*

A mixture of the compound XXV (0.01 mol) and hydrazine hydrate (0.012 mol) in absolute ethanol (25 cm³) was refluxed for 3 h. The reaction mixture was then cooled and poured into cold water. The solid so obtained was filtered off, washed with cold methanol (15 cm³) and crystallized.

IR spectrum (KBr), $\tilde{\nu}(XXXI)/cm^{-1}$: 1600 (C=C), 1614 (C=N), 1630 (C=O_{naphthyridinone}), 1645 (C=O_{quinolinone}), 2600—2900 (H-bonded OH), 3156 (NH). ¹H NMR spectrum (DMSO- d_6), $\delta(XXXI)$: 2.65 (s, 3H, CH₃), 3.65 (s, 3H, NCH₃), 6.20 (s, 1H, CH=C), 7.10—8.32 (m, 7H, H_{arom}), 8.85 (b, 1H, NH exchangeable with D₂O), 10.85—11.05 (b, 2H, 2OH exchangeable with D₂O).

IR spectrum (KBr), $\tilde{\nu}(XXXIIa)/\text{cm}^{-1}$: 1375 (CH_{pyrazoline}), 1624 (C=N), 1630

 $\begin{array}{l} (C = O_{naphthyridinone}), \ 1650 \ (C = O_{quinolinone}), \ 2500 - \\ 3200 \ (NH \ and \ H-bonded \ OH). \ ^1H \ NMR \ spectrum \\ (DMSO-d_6), \ \delta(XXXIIa): \ 0.95 \ (t, \ 3H, \ CH_{3 \ butyl}), \ 1.65 \\ -1.82 \ (m, \ 4H, \ 2CH_{2 \ butyl}), \ 4.15 \ (t, \ 1H, \ CH_{pyrazoline}), \\ 4. \ 43 \ (t, \ 2H, \ NCH_{2 \ butyl}), \ 6.32 \ (d, \ 2H, \ CH_{2 \ pyrazoline}), \\ 6.50 \ (b, \ 1H, \ NH_{pyrazoline} \ exchangeable \ with \ D_2O), \\ 7.15 - 8.12 \ (m, \ 7H, \ H_{arom}), \ 8.50 \ (b, \ 1H, \ NH_{naphthyridine} \\ exchangeable \ with \ D_2O). \end{array}$

4-Hydroxy-2-oxo-1,8(1*H*)-naphthyridine-3-carbaldehyde 3-Hydrazinoquinoxalin-2-ylhydrazone (*XXXIII*) and Bis-(4-hydroxy-2oxo-1,8(1*H*)-naphthyridine-3-carbaldehyde)quinoxaline-2,3-diylhydrazone (*XXXIV*)

A mixture of the aldehyde XXIII (0.01 mol) and 2,3-dihydrazinoquinoxaline (0.01 mol) in absolute ethanol (10 cm³) was refluxed for 2 h. The solid product that formed after cooling was filtered off, washed with cold methanol and crystallized to give XXXIII.

IR spectrum (KBr), $\tilde{\nu}(XXXIII)/cm^{-1}$: 1610 (C—N), 1630 (C—O_{naphthyridinone}), 2500—3200 (NH and H-bonded OH), 3290 (NH₂). ¹H NMR spectrum (DMSO- d_6), $\delta(XXXIII)$: 4.50 (s, 2H, NH₂ exchangeable with D₂O), 7.18—8.10 (m, 7H, H_{arom}), 8.52 (s, 1H, CH_{azomethine}), 8.95—9.30 (b, 3H, 3NH exchangeable with D₂O), 11.03 (b, 1H, OH exchangeable with D₂O).

Similarly compound XXXIV was obtained using the aldehyde XXIII (0.01 mol) and 2,3-dihydrazinoquinoxaline (0.005 mol), and the reaction was carried out under the same conditions.

IR spectrum (KBr), $\tilde{\nu}(XXXIV)/\text{cm}^{-1}$: 1610— 1615 (C=N), 1635 (C=O_{naphthyridinone}), 2500—3100 (NH and H-bonded OH). ¹H NMR spectrum (DMSO d_6), $\delta(XXXIV)$: 7.18—8.15 (m, 10H, H_{arom}), 8.52 (s, 1H, CH_{azomethine}), 8.90—9.19 (b, 4H, 4NH exchangeable with D₂O), 11.23 (b, 2H, 2OH exchangeable with D₂O).

4-Hydroxy-2-oxo-1,8(1*H*)-naphthyridine-3-carbaldehyde 3-Benzalhydrazinoquinoxalin-2-ylhydrazone (*XXXV*)

To a suspension of compound XXXIII (0.005 mol) in methanol (25 cm³) benzaldehyde (0.005 mol) was added and the reaction mixture was refluxed for 1 h.The mixture was left to cool to room temperature and the precipitate so obtained was collected by filtration, washed thoroughly with cold methanol (10 cm³) and crystallized.

IR spectrum (KBr), $\tilde{\nu}(XXXV)/\text{cm}^{-1}$: 1600—1620 (C=N), 1635 (C=O_{naphthyridinone}), 2600—3100 (NH and H-bonded OH).

3-(4-Acetylphenylimino)methyl-4-hydroxy-1,8(1*H*)-naphthyridin-2-one (*XXXVI*)

A mixture of the aldehyde XXIII (0.01 mol) and 4-aminoacetophenone (0.01 mol) in absolute ethanol (10 cm³) was warmed at 55—60 °C for 2 h, then the reaction mixture was left to cool to room temperature and the solid so resulted was filtered off, dried and crystallized to give the imine XXXVI.

IR spectrum (KBr), $\tilde{\nu}(XXXVI)/\text{cm}^{-1}$: 1610 (C=N), 1629 (C=O_{naphthyridinone}), 1675 (C=O_{acetyl}), 2500-2700 (H-bonded OH).

4-Hydroxy-2-oxo-1,8(1*H*)-naphthyridine-3-carbaldehyde 5*H*-1,2,4-Triazino[5,6-*b*]indol-3-ylhydrazone (*XXXVII*)

A mixture of the aldehyde XXIII (0.01 mol) and 3-hydrazino-1,2,4(5*H*)-triazino[5,6-*b*]indole (0.01 mol) in ethanol (50 cm³) containing DMF (5 cm³) was refluxed for 4 h. The solid mass that formed was filtered off, washed thoroughly with cold ethanol (10 cm³) and recrystallized.

IR spectrum (KBr), $\tilde{\nu}(XXXVII)/\text{cm}^{-1}$: 1610 (C=N), 1630 (C=O_{naphthyridinone}), 2500-2773 (Hbonded OH), 3080, 3110, 3200 (NH). ¹H NMR spectrum (DMSO- d_6), $\delta(XXXVII)$: 7.32-8.12 (m, 7H, H_{arom}), 8.61 (s, 1H, CH_{azomethine}), 8.90 (s, 1H, NH_{naphthyridine} exchangeable with D₂O), 9.80 (s, 1H, NH_{hydrazone} exchangeable with D₂O), 11.25 (s, 1H, NH_{indole} exchangeable with D₂O), 11.65 (s, 1H, OH exchangeable with D₂O).

4-Hydroxy-2-oxo-1,8(1*H*)-naphthyridine-3-carbaldehyde Acyl/Aroylhydrazones *XXXVIIIa*—*XXXVIIIe*

To a suspension of the aldehyde XXIII (0.01 mol) in ethanol (25 cm³) the appropriate acylhydrazide (namely cyanoacetylhydrazide, 4-methoxybenzoylhydrazide, 2-*N*-phenyluriedobenzoylhydrazide, 4-chlorobenzoylhydrazide, 2,4-dichlorobenzoylhydrazide) (0.01 mol) was added and the reaction mixture was heated under reflux for 2 h. The solid deposits were filtered off and crystallized to give XXXVIIIa— XXXVIIIe. IR spectrum (KBr), $\tilde{\nu}(XXXVIIIa)/cm^{-1}$: 1608 (C=N), 1629 (C=O_{naphthyridinone}), 2229 (C=N), 2500-3200 (b, NH and H-bonded OH). ¹H NMR spectrum (DMSO- d_6), $\delta(XXXVIIIa)$: 6.47 (s, 2H, COCH₂CN), 7.00-8.20 (m, 3H, H_{arom}), 8.80 (s, 1H, NH_{naphthyridine} exchangeable with D₂O), 9.50 (s, 1H, NH_{acylhydrazone} exchangeable with D₂O), 11.50 (b, 1H, OH exchangeable with D₂O).

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