Synthesis and Radiation Stability of Some New Biologically Active Hydroquinoline and Pyrimido[4,5-*b*]quinoline Derivatives

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A new series of hydroquinolines **6a-d**, **10**, **12**, **15**, **17b**, **20** and pyrimidoquinolines **7**, **8**, **9a**, **11**, **14** and **16** were synthesized starting from 2-amino-4-(3-bromo-phenyl)-7,7-dimethyl-1-naphthalen-1-yl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carbonitrile **6b**. The structures of the synthesized compounds were elucidated by elemental analyses and spectral data. Compounds **6a**, **10**, **11** and **18** exhibited a remarkable antifungal activity compared with fungicide Mycostatine. Radiosterilization of the biologically active compounds **6a**, **10** and **11** in the dry state may prove to be applicable [retaining their structures unchanged up to (40 kGy)].

Keywords: Hydroquinoline; Pyrimido[4,5-b]quinoline and radiation stability.

INTRODUCTION

The chemistry of hydroquinoline derivatives has been increasing in interest because many of these compounds have useful applications as chemotherapeutic agents against malarial parasites and microbes.[1-5] Encouraged by the above observations and as a further probe in this direction, we undertook a study in which the aromatic system (α-naphthyl) with a bromo group has been incorporated into a quinoline or pyrimidoquinoline, all present in one molecule, with a view to explore the possibility of achieving better antimicrobial effects.[6] In recent years, considerable interest has been developed regarding the radiation sensitivity of various antibiotics[7-10] and synthetic biologically active heterocyclic compounds.[11-16] Studies, for the most part, have focused on the correlation between chemical structure and biological function. Generally, data of these compounds indicate that, even at a dose of 25 KGy, radiosterilization may be feasible.[17,18]

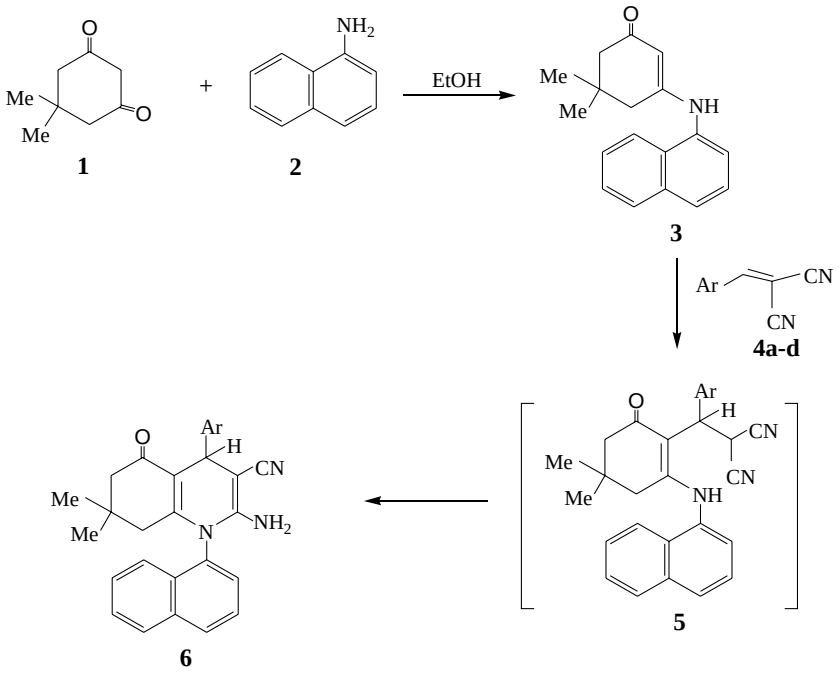
CHEMISTRY

Enaminones are versatile reagents for the synthesis of quinoline and pyrimidine derivatives.[19-21] As a part of a program directed towards the synthesis of new suitably functionalised quinolines of potential biological activity, we report here the possible utility of 5,5-dimethyl-3-(naphthalen-1-ylamino)-cyclohex-2-enone (enaminone) **3** with its bulky naphthyl moiety in the synthesis of N-Naphthylquinoline systems. Enaminone[22] **3** was obtained from condensation of 5,5-dimethyl-1,3-cyclohexandione **1** with α-naphthylamine **2**. Treatment of enaminone **3** with cinnamonitriles **4a-d** in the presence of a catalytic amount of triethylamine resulted in cycloaddition affording the hexahydroquinolines **6a-d**, presumably via Michael type product **5**.

N-aryl substituent (α-naphthyl) decreases the nucleophilicity of enaminoketone **3** toward 2-arylidenemalononitrile **4a-d**; a base catalyst was required to achieve the formation of N-α-naphthyl substituted hexahydroquinolines **6a-d**. Presumably, the base generates the anion of the 3-aminocyclohex-2-en-1-one **3**, thus facilitating the addition to the unsaturated nitrile **4a-d** (Scheme II).

The IR spectrum of compound **6a** showed bands at 3430, 3330 (NH_2), 2920 (CH aliph.), 2190 (C≡N), 1650 cm^{-1} (C=O). The mass spectrum of **6a** exhibited a molecular ion peak *m/z* at 339 (M^+-NH_2, 5.03%), with a base peak at 342, and other significant peaks appeared at 343 (24.08%), 257 (5.09%), 207 (3.55%), 169 (4.28%), 127 (22.70%), 55 (10.24%). UV Spectrum of **6a** showed λ_{max} at 282 nm and Log ε at 3.64. The IR spectrum of **6b** revealed bands at 3470, 3360 (NH_2), 3090 (CH arom.), 2930 (CH aliph.), 2200 (C≡N) and 1650 cm^{-1} (C=O). ^{1}H NMR spectrum of (**6b** in DMSO-d_6) showed signals at δ 0.8, 1.3 [2s, 6H, $2CH_3$], 2.1, 2.3 [2s, 4H, $2CH_2$ cyclo], 4.6 [s, 1H, 4H pyridine], 5.6 [s, 2H, NH_2 exchangeable D_2O], and 7.4-8.3 [m, 11H, Ar-H]. The mass spectrum of **6b** revealed a molecular ion peak *m/z* at 498 (M^+, 3.15%), with a base peak at 342, and other significant peaks appeared at 497 (M-1, 8.15%), 499 (M+1, 5.84%), 500 (M+2,

Scheme I



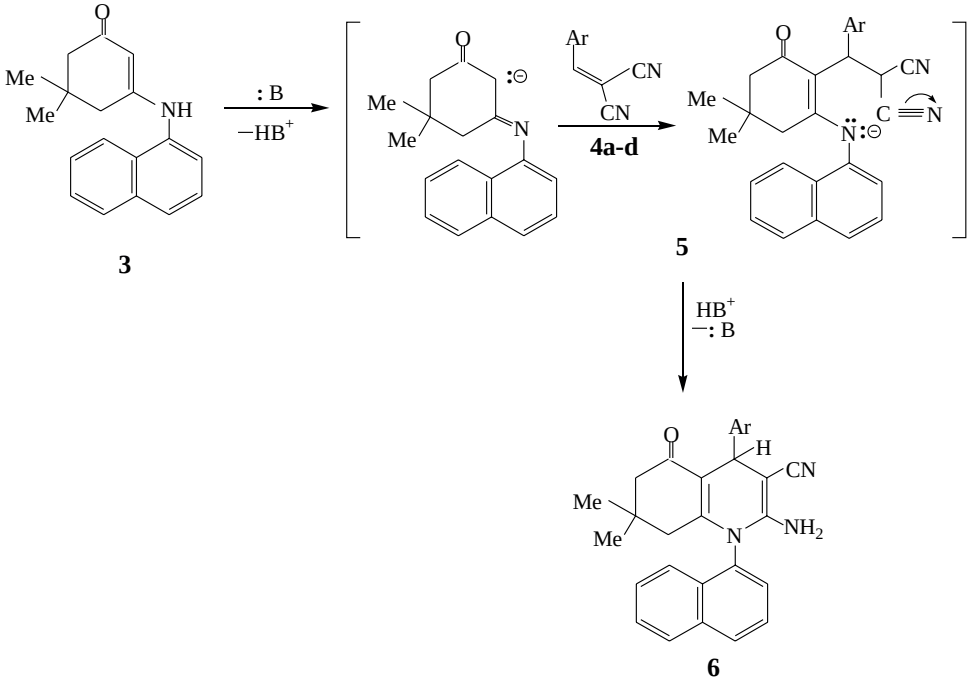
6a, Ar = $C_6H_3F_2$ - 2, 4

6b, Ar = C_6H_4Br - 3

6c, Ar = C_6H_2 (OCH_3)-3,4,5

6d, Ar = 

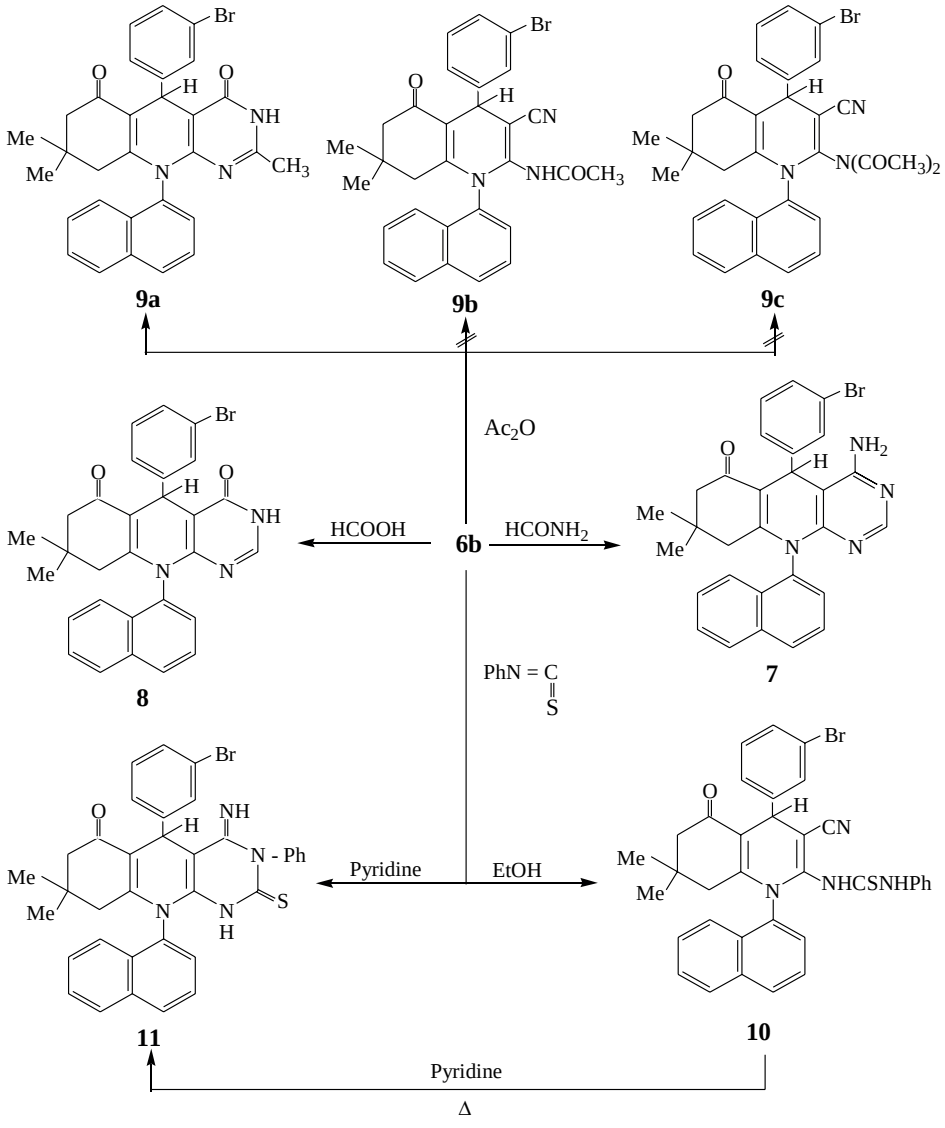
Scheme II



1.80%), 414 (0.88%), 258 (4.35%), 231 (1.03%), 127 (8.20%), and 76 (2.14%). UV spectrum of **6b** revealed λ_{max} at 266, 327 nm and Log ε at 3.86, 3.46. The IR spectrum of **6c** exhibited bands at 3480, 3370 (NH_2), 3060 (CH arom.), 2950 (CH aliph.), 2200 (C≡N), 1660 cm^{-1} (C=O). ^1H NMR spectrum of (**6c** in DMSO-d_6) revealed signals at δ 0.8, 0.9 [2s, 6H, $2CH_3$], 2.1, 2.2 [2s, 4H, $2CH_2$ cyclo], 4.6 [s, lH, 4H pyridine], 5.5 [s, 2H, NH_2, exchangeable D_2O], and 6.6-8.2 [m, 9H, Ar-H]. UV spectrum of **6c** exhibited λ_{max} at 283 nm and Log ε at 3.74. The IR spectrum of **6d** showed bands at 3340, 3200 (NH_2), 2200 (C≡N), 1650 cm^{-1} (C=O). UV spectrum of **6d** revealed λ_{max} at 291 nm and Log ε at 3.56.

The pyrimidoquinoline derivative **7** was obtained by the reaction of **6b** with formamide. The structure of **7** was established through microanalyses and its IR spectrum, which showed the absence of (C≡N) and presence of (NH_2) at 3340, 3200, (CH arom.) at 3100, (CH aliph.) at 2960, and (C=O) at 1630 cm^{-1}. The mass spectrum of **7** exhibited a molecular ion peak *m/z* at 525 (M^+, 3.14%), with a base peak at 369, and other significant peaks appeared at 526 (M+1, 8.86%), 527 (M+2, 2.38%), 441 (2.87%), 355 (10.75%), 285 (3.82%), 194 (8.55%), 143 (2.22%), 127 (10.38%), 77 (2.45%). UV spectrum of **7** showed λ_{max} at 286 nm and Log ε at 4.09. The behaviour of compound **6b** towards acid derivatives was also investigated. Thus, heating compound **6b** with formic acid caused cyclization to give pyrimidoquinoline derivative **8** (Scheme III). The IR spectrum of **8** showed the absence of (C≡N) band and presence of band at 3100 (NH), 2940 (CH

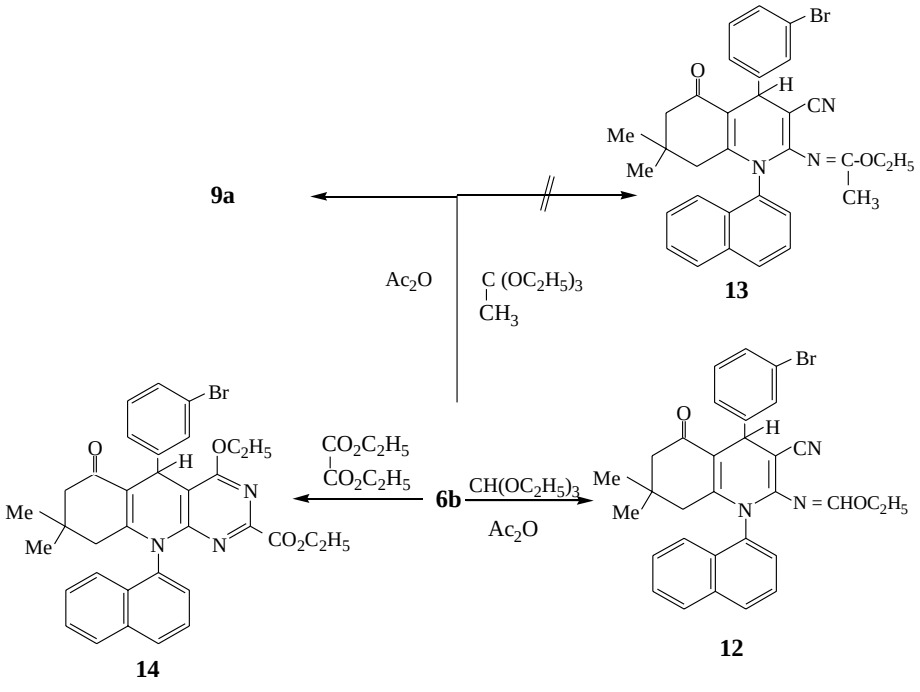
Scheme III



aliph.), 1720, 1650 (2C=O), and 1620 cm^{-1} (C=N). The mass spectrum of **8** revealed a molecular ion peak *m/z* at 526 (M^+, 1.20%), with a base peak at 472, and other significant peaks appeared at 518 (1.88%), 500 (47.73%), 446 (20.01%), 389 (1.12%), 290 (34.73%), 176 (52.39%), 127 (90.08%), and 77 (18.85%). UV spectrum of **8** showed λ_{max} at 272, 281 nm and Log ε at 3.99, 3.94. When compound **6b** was made to react with acetic anhydride, the fused system pyrimidoquinoline **9a** was isolated and the monoacetyl **9b** or diacetyl derivative **9c** was eliminated from consideration on the basis of elemental analyses and ^{1}H-NMR spectroscopy. The IR spectrum of **9a** showed the disappearance of (C≡N) band and presence of bands at 3100 (NH), 2930 (CH aliph.), 1700, 1650 (2C=O), and 1600 cm^{-1} (C=N). ^{1}H NMR spectrum of (**9a** in DMSO-d_6) showed signals at δ 0.7, 0.8 [2s, 6H, $2CH_3$], 1.8 [s, 3H, CH_3], 1.9, 2.0 [2s, 4H, $2CH_2$ cyclo], 5.1 [s, 1H, CH pyridine], 7.2-7.6 [m, 11H, Ar-H], and 12.2 [s, 1H, NH]. Mass spectrum of compound **9a** revealed a molecular ion peak *m/z* 540 (M^+, 1.84%), 541 (M+1, 4.41%), 542 (M+2, 1.50%) with a base peak at 384 and other significant peaks appeared at 456 (0.31%), 328 (2.58%), 300 (5.04%), 201 (2.76%), 180 (0.42%), 127 (5.85%), and 77 (1.12%). UV spectrum of **9a** exhibited λ_{max} at 278, 288 nm and Log ε at 4.24, 4.26.

In addition, the behaviour of **6b** towards phenyl isothiocyanate under different conditions was also studied. Thus, reaction of **6b** with phenyl isothiocyanate in boiling ethanol afforded a product ($C_{35}H_{29}N_4OSBr$) for which two structures **10** and **11** seemed possible. Structure **10** was established for the reaction product on the basis of its IR spectrum, which showed the presence of (C≡N) band. Compound **6b** was also reacted with phenyl isothiocyanate in pyridine to give pyrimidoquinoline derivative **11**. Compound **11** was also obtained by heating **10** in pyridine (Scheme III). The IR spectrum of **10** showed bands at 3400, 3300 (2NH), 3070 (CH arom.), 2960 (CH aliph.), 2200 (C≡N), and 1650 cm^{-1} (C=O). ^{1}H NMR spectrum of (**10** in DMSO-d_6) revealed signals at δ 0.6, 0.7 [2s, 6H, $2CH_3$], 0.8, 1.2 [2s, 4H, $2CH_2$ cyclo], 4.6 [s, 1H, CH pyridine], 7.3-7.8 [m, 16H, Ar-H], 8.1, and 8.2 [2s, 2H, 2NH]. UV spectrum of **10** showed λ_{max} at 276, 284 nm and Log ε at 3.74, 3.75. The IR spectrum of **11** showed the absence of (C≡N) band and presence of bands at 3210 (NH), 3070 (CH arom.), 2950 (CH aliph.), 1630 (C=O), and 1600 cm^{-1} (C=N). Mass spectrum of **11** revealed a molecular ion peak *m/z* at 633 (M^+, 12.43%), with a base peak at 127, and other significant peaks appeared at 617 (17.01%), 538 (13.51%), 460 (28.85%), 347 (37.84%), 294 (48.73%), 230 (57.03%), and 86 (34.58%). UV spectrum of **11** showed λ_{max} at 270, 290 nm and Log ε at 3.78. The enaminonitrile **6b** was reacted with triethylorthoformate in acetic anhydride to yield the ethoxymethylideneamino derivative **12**. On using triethylorthoformate only without acetic anhydride the same product **12** was obtained in good yield. The IR spectrum of **12** showed bands at 3080 (CH arom.), 2970 (CH aliph.), 2210 (C≡N), 1680 (C=O), and 1620 cm^{-1} (C=N). ^{1}H NMR spec-

Scheme IV

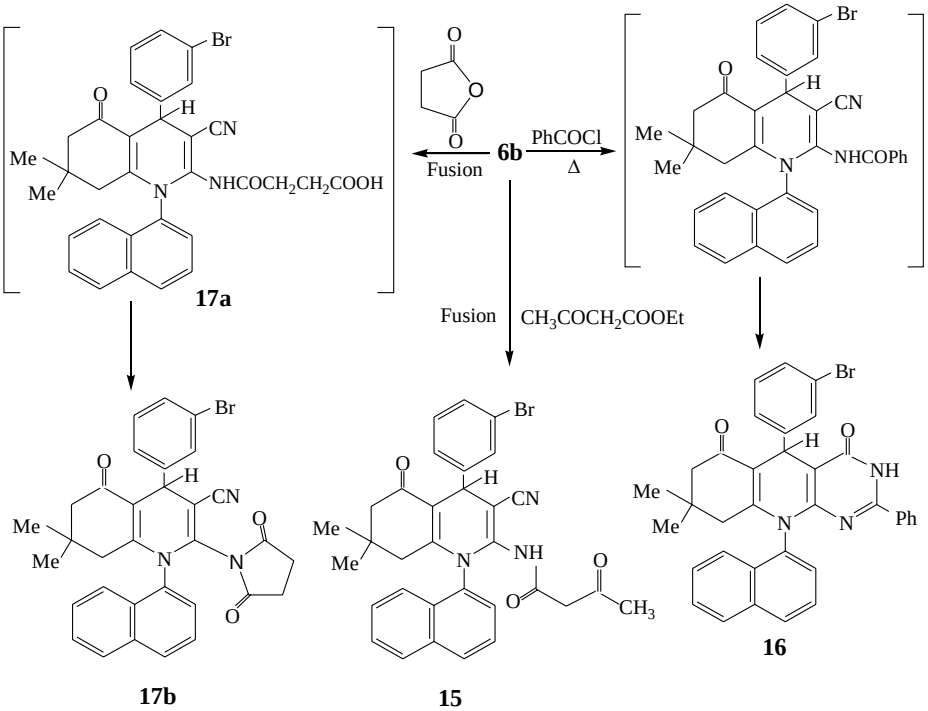


trum of (**12** in DMSO-d_6) revealed signals at 0.65, 0.8 [2s, 6H, $2CH_3$ cyclo], 0.9 [t, 3H, CH_3 ethyl], 2.1, 2.5 [2s, 4H, $2CH_2$ cyclo], 4.8 [q, 2H, CH_2 ethyl], 5.1 [s, 1H, CH pyridine], 7.4-7.8 [m, 11H, Ar-H], and 8.1 [s, 1H, N=CH]. UV spectrum of **12** revealed λ_{max} at 270 nm and Log ε at 3.97.

Also, interaction of **6b** with triethylorthoacetate in acetic anhydride produced compound **9a**, instead of the expected product **13**. This result was proved using IR spectrum which showed the absence of (C≡N) band, and, ^{1}H NMR data, which exhibited the absence of a triplet and a quartet due to the ethyl group. Cyclocondensation of **6b** with diethyloxalate in ethanol containing sodium ethoxide yielded the corresponding pyrimidoquinoline derivative **14**; its IR spectrum showed bands at 1760, 1720 (2C=O), and 1660 cm^{-1} (C=N). ^{1}H NMR spectrum of (**14** in DMSO-d_6) revealed signals at δ 0.6, 0.8 [2s, 6H, $2CH_3$], 1.1 [m, 6H, $2CH_3$ ethyl], 2.1, 2.3 [2s, 4H, $2CH_2$ cyclo], 4.0, 4.4 [m, 4H, $2CH_2$ ethyl], 5.0 [s, 1H, CH pyridine], and 7.4-8.1 [m, 11H, Ar-H]. Mass spectrum of compound **14** exhibited a molecular ion peak *m/z* at 626 (M^+, 0.9%), with a base peak at 368 and other significant peaks appeared at 599 (9.17%), 499 (3.37%), 442 (35.12%), 342 (17.88%), 256 (4.48%), 155 (7.81%), 127 (22.03%), and 77 (2.88%). UV spectrum of **14** revealed λ_{max} at 285 nm and Log ε at 4.10. This work was extended to cover the reactivity of compound **6b** toward carbonyl compounds. Thus, condensation of **6b** with ethylacetoacetate under conditions of fusion gave a product which was formulated as quinoline derivative **15** (Scheme V). The IR spectrum of **15** showed bands at 3380 (NH), 3100 (CH arom.), 2940 (CH aliph.), 2220 (C≡N), 1710, 1700, 1680 cm^{-1} (3C=O). ^{1}H NMR spectrum of (**15** in DMSO-d_6) exhibited signals at δ 0.7, 0.8 [2s, 6H, $2CH_3$], 2.1, 2.2 [2s, 4H, $2CH_2$], 2.5 [s, 3H, $COCH_3$], 4.6 [s, 1H, CH pyridine], 5.6 [s, 2H, CH_2CO], 7.4-8.1 [m, 11H, Ar-H], and 8.4 [s, 1H, NH]. UV spectrum of **15** revealed λ_{max} at 273, 285 nm and Log ε at 4.19, 4.24. Interaction of compound **6b** with benzoylchloride afforded the pyrimido-quinoline derivative **16** (Scheme V). The IR spectrum showed the absence of (C≡N) band and presence of bands at 3100 (NH), 3080 (CH arom.), 2930 (CH aliph.), 1690, 1660 cm^{-1} (2C=O). ^{1}H NMR spectrum of compound (**16** in DMSO-d_6) exhibited signals at δ 0.8, 0.9 [2s, 6H, $2CH_3$], 2.3, 2.4 [2s, 4H, $2CH_2$], 5.4 [s, 1H, CH pyridine], 7.4-8.2 [m, 17H, Ar-H+NH]. UV spectrum of **16** showed λ_{max} at 286 nm and Log ε at 4.17.

Fusion of compound **6b** with succinic anhydride yielded the unexpected pyrrolidine derivative **17b** through the initial formation of the expected intermediate **17a** based on elemental analysis and IR spectrum which showed the absence of (NH) band and presence of bands at 3070 (CH arom.), 2960 (CH aliph.), 2220 (C≡N), 1750, 1700, 1670 (3C=O), and 1620 cm^{-1} (C=N). Mass spectrum of compound **17b** exhibited

Scheme V

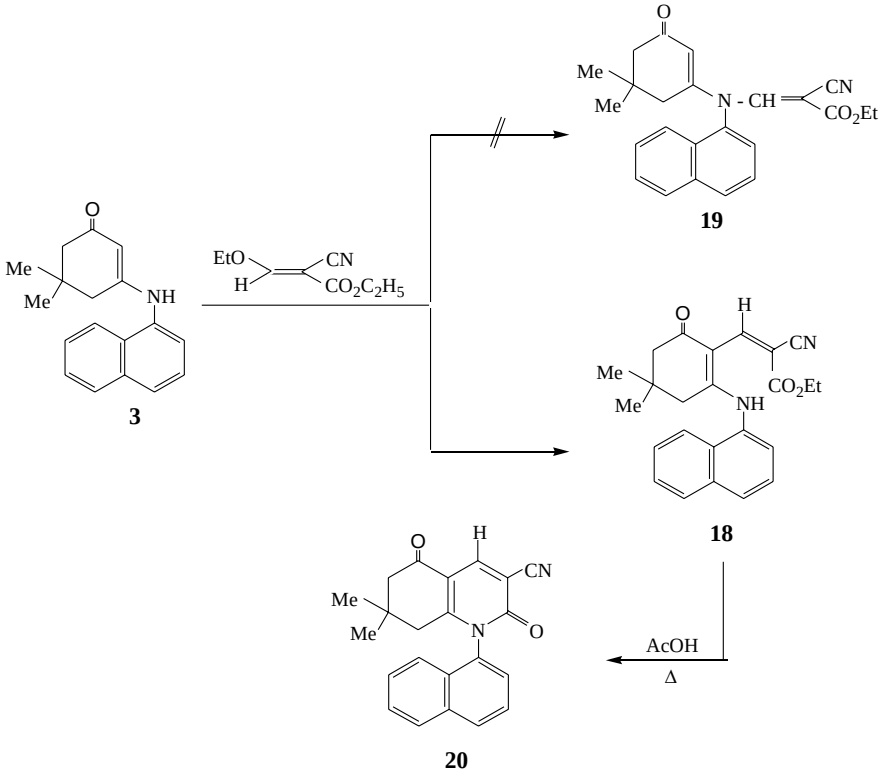


a molecular ion peak *m/z* at 580 (M^+, 4.33%), 581 (M+1, 9.51%), 582 (M+2, 4.01%) with a base peak at 424, and other significant peaks appeared at 579 (M-1, 10.04%), 479 (8.14%), 312 (3.63%), 290 (20.83%), 207 (11.32%), 127 (83.82%), and 55 (34.58%). UV spectrum of **17b** showed λ_{max} at 274, 282 nm and Log ε at 4.23, 4.24. The reaction of enaminone **3** with ethyl-α-cyano-β-ethoxyacrylate by refluxing in ethanol afforded a high yield of 2-cyano-3-[4,4-dimethyl-2-(naphthalen-1-ylamino)-6-oxo-cyclohex-1-enyl]-acrylic acid ethyl ester **18** instead of its expected isomer **19** (Scheme VI). The structure of **18** was established by elemental analysis and IR spectrum which showed the presence of (NH) band at 3220 cm^{-1} and (CH aliph.) at 2940 cm^{-1}, (C≡N) at 2210 cm^{-1}, and (2C=O) at 1690, 1640 cm^{-1}. ^{1}H NMR spectrum of compound (**18** in DMSO-d_6) showed signals at δ 1.0 [s, 6H, $2CH_3$], 1.2 [t, 3H, CH_3 ethyl], 2.1, 2.5 [2s, 4H, $2CH_2$ cyclo], 4.2 [q, 2H, CH_2 ethyl], 7.3-8.0 [m, 7H, Ar-H], 8.2 [s, 1H, NH], and 9.1 [s, 1H, CH]. Mass spectrum of compound **18** exhibited a molecular ion peak *m/z* at 388 (M^+, 1.85%) with a base peak at 180, and other significant peaks appeared at 341 (0.24%), 314 (0.31%), 265 (71.70%), 209 (83.50%), 127 (38.27%), and 77 (17.39%). UV spectrum of **18** showed λ_{max} at 327 nm and Log ε at 4.02. The structure of compound **18** was further confirmed upon conducting it to an intramolecular cyclization reaction. Thus, when compound **18** was heated in glacial acetic acid, cyclization occured and the corresponding quinoline **20** was obtained. The IR spectrum of **20** showed bands at 3050 (CH arom.), 2960 (CH aliph.), 2210 (C≡N), 1680, 1660 cm^{-1} (2C=O). Mass spectrum of compound **20** exhibited a molecular ion peak *m/z* at 342 (M^+, 2.54%), with a base peak at 265 and other significant peaks appeared at 333 (4.70%), 313 (8.23%), 295 (3.53%), 209 (87.57%), 180 (74.84%), 127 (28.58%), 115 (23.21%), and 55 (23.21%). UV spectrum of **20** showed λ_{max} at 274 nm and Log ε at 3.77.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Stuart melting point apparatus. IR spectra were recorded on a Pye-Unicam SP 3-100 spectrophotometer using the KBr technique. ^{1}H NMR spectra were recorded on a BRUKER proton NMR-Avance 300 (300 MHz), in DMSO-d_6 as a solvent, using tetramethylsilane (TMS) as internal standard. Mass spectra were run on an HP Model MS-5988. Elemental analyses were carried out at the microanalytical laboratories of the Faculty of Science, Cairo University. The samples

Scheme VI



were irradiated with gamma radiation (^{60}Co) at the National Center for Radiation Research and Technology. Powder samples were irradiated at room temperature conditions in polycarbonate vials at a dose rate of (10 KGy/h). UV spectra were recorded using an ATI unicam. UV/Vis AURORA SCAN.

2-Amino-4-substituted-7,7-dimethyl-1-naphthalen-1-yl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carbonitrile (6a-d)

A mixture of **3** (2.63 g, 0.01 mol), appropriate cinnamonitrile **4a-d** (0.01 mol) and triethylamine (3 drops) in ethanol (15 mL) was refluxed for 30 min. The solid obtained upon cooling was crystallized from ethanol to give **6a-d**.

4-Amino-5-(3-bromo-phenyl)-8,8-dimethyl-10-naphthalen-1-yl-5,8,9,10-tetrahydro-7H-pyrimido[4,5-b]quinolin-6-one (7)

A solution of **6b** (4.98 g, 0.01 mol) in formamide (5 mL) was refluxed for 5 h. The solid obtained was crystallized from dioxane to give **7**.

5-(3-Bromo-phenyl)-8,8-dimethyl-10-naphthalen-1-yl-5,8,9,10-tetrahydro-3H,7H-pyrimido[4,5-b]quinoline-4,6-dione (8)

A solution of **6b** (4.98 g, 0.01 mol) in formic acid (5 mL), was refluxed for 4 h. The solid obtained was crystallized from ethanol to give **8**.

5-(3-Bromo-phenyl)-2,8,8-trimethyl-10-naphthalen-1-yl-5,8,9,10-tetrahydro-3H,7H-pyrimido[4,5-b]quinolin-4,6-dione (9a)

A solution of **6b** (4.98 g, 0.01 mol) in acetic anhydride (10 mL) was refluxed for 3 h. After cooling the solid obtained was crystallized from ethanol to give **9a**.

1-[4-(3-Bromo-phenyl)-3-cyano-7,7-dimethyl-1-naphthalen-1-yl-5-oxo-1,4,5,6,7,8-hexahydro-quinolin-2-yl]-3-phenyl-thiourea (10)

A mixture of **6b** (4.98 g, 0.01 mol), phenyl isothiocyanate (1.35 g, 0.01 mol) and absolute ethanol (10 mL) was refluxed for 5 h. The solid obtained was crystallized from ethanol to give **10**.

5-(3-Bromo-phenyl)-4-imino-8,8-dimethyl-2-thioxo-10-naphthalen-1-yl-3-phenyl-2,3,4,5,7,8,9,10-octahydro-1H-pyrimido[4,5-b]quinolin-6-one (11)

Method (A):

A mixture of **6b** (4.98 g, 0.01 mol), phenyl isothiocyanate (1.35 g, 0.01 mol) and pyridine (20 mL) was refluxed in an oil bath for 6 h. The reaction mixture was cooled, diluted with ethanol and the resulting solid was crystallized from dioxane to give **11**.

Method (B):

A solution of **10** (6.33 g, 0.01 mol) in pyridine (5 mL) was refluxed for 5 h. The reaction mixture was then cooled and diluted with ethanol/H_2O to give **11**.

N-[4-(3-Bromo-phenyl)-3-cyano-7,7-dimethyl-1-naphthalen-1-yl-5-oxo-1,4,5,6,7,8-hexahydro-quinolin-2-yl]formimidic acid ethyl ester (12)

A mixture of **6b** (4.98 g, 0.01 mol), triethylorthoformate (2 mL) and acetic anhydride (10 mL) was refluxed for 8 h. The reaction mixture was left to cool overnight and the solid formed was crystallized from ethanol to give **12**.

5-(3-Bromo-phenyl)-4-ethoxy-8,8-dimethyl-10-naphthalen-1-yl-6-oxo-5,6,7,8,9,10-hexahydro-pyrimido[4,5-b]quinoline-2-carboxylic acid ethyl ester (14)

A mixture of **6b** (4.98 g, 0.01 mol) and diethyloxalate (0.01 mol) in ethanol containing (0.01 mol) sodium ethoxide was refluxed for 3 h. The obtained product was crystallized from ethanol to give **14**.

N-[4-(3-Bromo-phenyl)-3-cyano-7,7-dimethyl-1-naphthalen-1-yl-5-oxo-1,4,5,6,7,8-hexahydro-quinolin-2-yl]-3-oxo-butyramide (15)

A mixture of **6b** (4.98 g, 0.01 mol) and ethylacetoacetate (15 mL) was fused at 180 °C for 1 h. The obtained solid was crystallized from acetic acid to give **15**.

5-(3-Bromo-phenyl)-8,8-dimethyl-10-naphthalen-1-yl-2-phenyl-5,8,9,10-tetrahydro-3H,7H-pyrimido-[4,5-b]quinoline-4,6-dione (16)

A mixture of **6b** (4.98 g, 0.01 mol) and benzoylchloride (1.40 g, 0.01 mol) in pyridine (20 mL) was refluxed for 12 h. The obtained product was crystallized from dioxane to give **16**.

4-(3-Bromo-phenyl)-2-(2,5-dioxo-pyrrolidin-1-yl)-7,7-dimethyl-1-naphthalen-1-yl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carbonitrile (17)

A mixture of **6b** (4.98 g, 0.01 mol) and succinic anhydride (1 g, 0.01 mol) was fused at 220 °C for 15 min. The obtained product was cooled, ground to a fine powder in an mortar to give **17**, and treated with NaOH (4%, 100 mL); the filtrate was acidified with dil HCl. The obtained product was crystallized from acetic acid to give **17**.

2-Cyano-3-[4,4-dimethyl-2-(naphthalen-1-yl-amino)-6-oxo-cyclohex-1-enyl]acrylic acid ethyl ester (18)

A mixture of **3** (2.63 g, 0.01 mol) and ethyl-α-cyano-β-ethoxyacrylate (1.69 g, 0.01 mol) in ethanol (30 mL) was refluxed for 5 h. The precipitate that separated after cooling was collected and crystallized from ethanol to give **18**.

Cyclization of 18: formation of 7,7-dimethyl-1-naphthalen-1-yl-2,5-dioxo-1,2,5,6,7,8-hexahydro-quinoline-3-carbonitrile (20)

A solution of **18** (3.88 g, 0.01 mol) in glacial acetic acid (15 mL) was heated under reflux for 4 h. The solid that separated after cooling was collected by filtration and crystallized from acetic acid to give **20**.

ANTIMICROBIAL ACTIVITY

Fourteen compounds were screened in vitro for their antimicrobial activities against Gram positive bacteria *Staphylococcus aureus* [29213], Gram negative bacteria *Escherichia coli (ATCC 25922)* and one yeast fungus *Saccharomyces Cerevisiae* by the agar diffusion technique.[22] A 1 mg/mL solution in dimethylformamide was used. The bacteria and fungi were maintained on nutrient agar and Czapek's-Dox agar media, respectively. DMF showed no inhibition zones. The agar media were inoculated with different microorganism's culture tested after 24 hrs. of incubation at 30 °C for bacteria and 48 hrs. of incubation at 28 °C for fungi; the diameter of inhibition zone (mm) was measured (Table 2). Ofloxacin

Table 1. Characterization data for newly synthesized compounds (**6a-20**)

Compound No.	M.P. (°C)	Yield (%)	Mol. Formula (Mol.Wt)	Elemental Analyses Calculated /Found.		
				C %	H %	N %
6a	262-264	91	$C_{28}H_{23}N_3OF_2$	73.85	5.05	9.23
			(455)	73.60	4.90	9.50
6b	266-268	63	$C_{28}H_{24}N_3OBr$	67.47	4.82	8.43
			(498)	67.80	4.60	8.20
6c	216-218	59	$C_{31}H_{31}N_3O_4$	73.08	6.09	8.25
			(509)	73.30	6.30	8.50
6d	279-281	55	$C_{27}H_{24}N_4O$	77.14	5.71	13.33
			(420)	77.40	5.50	13.10
7	170-172	57	$C_{29}H_{25}N_4OBr$	66.29	4.76	10.67
			(525)	66.50	4.40	10.40
8	98-100	76	$C_{29}H_{24}N_3O_2Br$	66.16	4.56	7.98
			(526)	66.40	4.70	7.70
9a	334-336	68	$C_{30}H_{26}N_3O_2Br$	66.67	4.81	7.78
			(540)	66.40	4.90	7.50
10	113-115	74	$C_{35}H_{29}N_4OSBr$	66.35	4.58	8.85
			(633)	66.60	4.80	8.60
11	166-168	81	$C_{35}H_{29}N_4OSBr$	66.35	4.58	8.85
			(633)	66.10	4.30	9.10
12	218-220	76	$C_{31}H_{28}N_3O_2Br$	67.15	5.05	7.58
			(554)	67.30	5.30	7.80
14	200-202	79	$C_{34}H_{32}N_3O_4Br$	65.18	5.11	6.71
			(626)	65.50	5.30	6.40
15	153-155	69	$C_{32}H_{28}N_3O_3Br$	65.98	4.81	7.22
			(582)	65.70	4.60	7.50
16	91-93	75	$C_{35}H_{28}N_3O_2Br$	69.77	4.65	6.98
			(602)	69.90	4.80	6.70
17b	213-215	81	$C_{32}H_{26}N_3O_3Br$	66.21	4.48	7.24
			(580)	66.50	4.70	7.50
18	128-130	77	$C_{24}H_{24}N_2O_3$	74.23	6.19	7.22
			(388)	74.50	6.40	7.10
20	158-160	72	$C_{22}H_{18}N_2O_2$	77.19	5.26	8.19
			(342)	77.50	5.50	8.40

Table 2. Antimicrobial activity of the newly synthesized compounds

Compound No.	*Staphylococcus aureus (29213)*	*Escherichia coli (ATCC 25922)*	*Saccharomyces Cerevisiae*
6a	++	0	+++
6b	0	+	0
6c	0	0	0
6d	+	0	0
7	+	0	+
8	++	0	+
9a	+	0	0
10	0	0	+++
11	0	0	++++
12	0	0	+
14	+	0	+
15	0	0	++
16	0	+	+
18	++	0	+++
Ofloxacin[a] (Tarivid)	++++	+++	0
SXT[a]	++++	+++	0
Mycostatine[b]	0	0	+++
DMF	0	0	0

[a] Ofloxacin and SXT (Trimethoprime + Sulfamethoxazole) were supplied from Oxoid Lab., England.
[b] Manufactured by Bristol Myers Squibb, Giza, Egypt.
Well diameter 1 cm
Inhibition values = 0.1-0.5 cm beyond control = +,
Inhibition values = 0.6-1.0 cm beyond control = ++,
Inhibition values = 1.1-1.5 cm beyond control = +++,
Inhibition values = 1.6-2.0 cm beyond control = ++++,
0 = Not detected.

Table 3. UV data of biologically active compounds before and after gamma-irradiation

Compound	Dose (KGy)	Conc. (Mol)	$\lambda max_{(1)}$	Abs. (O.D.)	$\lambda max_{(2)}$	Abs. (O.D.)
6a	Control	5×10^{-5}	282	0.892	-	-
	5		282	0.938	-	-
	10		282	0.982	-	-
	15		282	1.041	-	-
	20		282	1.042	-	-
	25		282	1.072	-	-
	30		282	1.081	-	-
	40		282	1.086	-	-
10	Control	5×10^{-5}	276	1.101	284	1.142
	5		276	1.107	284	1.163
	10		276	1.123	284	1.212
	15		276	1.128	284	1.230
	20		276	1.134	284	1.274
	25		276	1.152	284	1.249
	30		276	1.156	284	1.250
	40		276	1.150	284	1.255
11	Control	5×10^{-5}	270	1.214	290	1.209
	5		270	1.218	290	1.211
	10		270	1.231	290	1.222
	15		270	1.236	290	1.225
	20		270	1.238	290	1.220
	25		270	1.230	290	1.234
	30		270	1.248	290	1.241
	40		270	1.256	290	1.244

Abs. = Absorbance.

and SXT in a concentration of 30 μg mL^{-1} and Mycostatine 30 μg mL^{-1} were used as a reference for antibacterial and antifungal activities, respectively. The minimal inhibitory concentration (MIC) of the biologically active compounds was measured by a two fold serial dilution method. The data obtained are summarized in Table 2. The quinoline derivative **6a** containing 2,4-difluorophenyl in position four, quinoline derivative **10** having thiourea and 3-bromophenyl moieties and quinolinopyrimidine derivative **11** containing thioxo moiety and cyclo derivative **18** were found to be the most active compounds against *Saccharomyces Cerevisiae,* whereas compounds **6a**, **8** and **18** showed a moderate activity against *Staphylococcus aureus (29213).* From these results it can be concluded that the biologically active compounds **6a**, **10**, **11** and **18** (MIC values were < 50 μg/mL) are nearly as active as the standared Mycostatine.

RADIOSTABILITY OF THE BIOLOGICALLY ACTIVE COMPOUNDS

The aim of the present work is to investigate the stability of the chemical structure of the biologically active compounds **6a**, **10** and **11** after irradiation. These compounds, in the dry state, were exposed to doses of gamma irradiation ranging from 5-40 KGy. Ultraviolet measurements (UV spectra) and thin layer chromatography (TLC) were run before and after irradiation to probe any change after irradiation. The UV spectra of unirradiated (control) and irradiated compounds in DMF as solvent are listed in Table 3. The results showed that all of the biologically active compounds **6a**, **10** and **11** remain radioresistant, retaining their structure unchanged up to 40 KGy (Table 3).

Further, thin layer chromatographic analyses (R_f) were made on precoated silica gel G sheets 1B-F and were detected by use of a UV Lamp at 254 nm. The R_f values of the unirradiated compounds **6a**, **10** and **11** were 0.37, 0.46 and 0.39, respectively [eluent benzene/ethylacetate 8.5/1.5]. After irradiation, the irradiated compounds gave identical R_f values as before irradiation. This means that the structures of these compounds remain radioresistant, and sterilization of these compounds in dry form by gamma irradiation may prove to be applicable.

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